

**Chart 14-17. Age-standardized global mortality rates of subarachnoid hemorrhage (SAH) per 100 000, both sexes, 2017.**

Mortality attributable to SAH is highest in Southeast Asia and Mongolia.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>375</sup> Printed with permission. Copyright © 2018, University of Washington.

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## 15. CONGENITAL CARDIOVASCULAR DEFECTS AND KAWASAKI DISEASE

**ICD-9 745 to 747; ICD-10 Q20 to Q28. See Tables 15-1 through 15-3 and Charts 15-1 through 15-7**

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CCDs arise from abnormal or incomplete formation of the heart and blood vessels. CCDs range in severity from minor abnormalities not requiring treatment to complex malformations, including absent, hypoplastic,

### Abbreviations Used in Chapter 15

ACS	acute coronary syndrome
AHA	American Heart Association
AMI	acute myocardial infarction
ASD	atrial septal defect
AV	atrioventricular
CABG	coronary artery bypass graft
CCD	congenital cardiovascular defect
CDC	Centers for Disease Control and Prevention
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CI	confidence interval
DM	diabetes mellitus
GBD	Global Burden of Disease
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HLHS	hypoplastic left heart syndrome
HR	hazard ratio
ICD-9	<i>International Classification of Diseases, 9th Revision</i>
ICD-10	<i>International Classification of Diseases, 10th Revision</i>
ICU	intensive care unit
IHD	ischemic heart disease
IQR	interquartile range
IRR	incidence rate ratio
IVIG	intravenous immunoglobulin
KD	Kawasaki disease
NH	non-Hispanic
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
PAH	pulmonary arterial hypertension
RR	relative risk
RV	right ventricle
STS	Society of Thoracic Surgeons
TGA	transposition of the great arteries
TOF	tetralogy of Fallot
UI	uncertainty interval
VSD	ventricular septal defect

or atretic portions of the heart, valves, or vessels that could require multiple surgeries and interventions, including cardiac transplantation. Thus, there is significant variability in their presentation and requirements for care that can have a significant impact on morbidity, mortality, and healthcare costs both in children and adults.<sup>1</sup> Some types of CCDs are associated with diminished quality of life,<sup>2</sup> on par with what is seen in other chronic pediatric health conditions,<sup>3</sup> as well as deficits in cognitive functioning<sup>4</sup> and neurodevelopmental outcomes.<sup>5</sup> Health outcomes generally continue to improve for CCDs, including survival, which has led to a population shift into adulthood. There is a growing population of adults with both congenital heart defects and the more usual adult medical diagnoses,<sup>6</sup> which adds to the management complexity of this group of patients<sup>7,8</sup> and emphasizes the importance of specialty care by adult congenital HD specialists.<sup>9</sup>

### Overall Lifespan Prevalence (See Tables 15-1 through 15-3)

The 32nd Bethesda Conference estimated that the total number of adults living with CCDs in the United States in 2000 was 800 000.<sup>1</sup> In 2010, the estimated prevalence of CCDs in all age groups was 2.4 million (Table 15-1). The annual birth prevalence of CCDs ranged from 2.4 to 13.7 per 1000 live births (Table 15-2). In the United States, 1 in 150 adults is expected to have some form of congenital heart defect, including minor lesions such as bicuspid aortic valve and severe CCD such as HLHS.<sup>7</sup> The estimated prevalence of CCDs ranges from 2.5% for hypoplastic right heart syndrome to 20.1% for VSD in children and from 1.8% for TGA to 20.1% for VSD in adults (Table 15-3). In population data from Canada, the measured prevalence of CCDs in the general population was 13.11 per 1000 children and 6.12 per 1000 adults in the year 2010.<sup>10</sup> The expected growth rates of the congenital heart defects population vary from 1% to 5% per year depending on age and the distribution of lesions.<sup>11</sup>

Estimates of the distribution of lesions in the CCD population using available data vary based on proposed assumptions. If all those born with CCDs between 1940 and 2002 were treated, there would be  $\approx$ 750 000 survivors with simple lesions, 400 000 with moderate lesions, and 180 000 with complex lesions; in addition, there would be 3.0 million people alive with bicuspid aortic valves.<sup>11</sup> Without treatment, the number of survivors in each group would be 400 000, 220 000, and 30 000, respectively. The actual numbers surviving were projected to be between these 2 sets of estimates as of more than a decade ago.<sup>11</sup> The most common types of defects in children are VSD, 620 000 people; ASD, 235 000 people; valvar pulmonary stenosis, 185 000 people; and patent ductus arteriosus,

173 000 people.<sup>11</sup> The most common lesions seen in adults are ASD and TOF.<sup>12</sup>

## Birth Prevalence

The incidence of disorders present before birth, such as CCDs, is generally described as the *birth prevalence*. The birth prevalence of CCDs is reported as 6.9 per 1000 live births in North America, 8.2 per 1000 live births in Europe, and 9.3 per 1000 live births in Asia.<sup>13</sup> The overall birth prevalence of CCDs at the Bhabha Atomic Research Centre Hospital in Mumbai, India, from 2006 through 2011 was 13.28 per 1000 live births.<sup>14</sup>

Variations in birth prevalence rates may be related to the age at detection; major defects can be identified in the prenatal or neonatal period, but minor defects might not be detected until later in childhood or, in fact, adulthood, which makes it challenging to estimate birth prevalence and population prevalence. To distinguish more serious defects, some studies report the number of new cases of sufficient severity to result in death or an invasive procedure within the first year of life (in addition to the overall birth prevalence). Birth prevalence rates are likely to increase over time because of improved technological advancements in diagnosis and screening, particularly fetal cardiac ultrasound,<sup>15</sup> pulse oximetry,<sup>16</sup> and echocardiography during infancy.

### **Overall Birth Prevalence**

(See Table 15-2)

- According to population-based data from the Metropolitan Atlanta Congenital Defects Program (Atlanta, GA), a CCD occurred in 1 of every 111 to 125 births (live, still, or >20 weeks' gestation) from 1995 to 1997 and from 1998 to 2005. Some defects showed variations by sex and racial distribution.<sup>17</sup>
- According to population-based data from Alberta, Canada, there was a total birth prevalence of 12.42 per 1000 total births (live, still, or >20 weeks' gestation).<sup>18</sup>
- An estimated minimum of 40 000 infants are expected to be affected by CCDs each year in the United States. Of these, ≈25%, or 2.4 per 1000 live births, require invasive treatment in the first year of life (Table 15-2).

### **Birth Prevalence of Specific Defects**

- The National Birth Defects Prevention Network showed the average birth prevalence of 21 selected major birth defects for 13 states in the United States from 2004 to 2006. These data indicated that there are >6100 estimated annual cases of 5 CCDs: truncus arteriosus (0.07 per 1000 births), TGA (0.3 per 1000 births), TOF (0.4

per 1000 births), AV septal defect (0.47 per 1000 births), and HLHS (0.23 per 1000 births).<sup>19,20</sup>

- Metropolitan Atlanta Congenital Defects Program data for specific defects at birth showed the following: VSD, 4.2 per 1000 births; ASD, 1.3 per 1000 births; valvar pulmonic stenosis, 0.6 per 1000 births; TOF, 0.5 per 1000 births; aortic coarctation, 0.4 per 1000 births; AV septal defect, 0.4 per 1000 births; and TGA (0.2 per 1000 births).<sup>17</sup>
- Bicuspid aortic valve occurs in 13.7 of every 1000 people; these defects might not require treatment in infancy or childhood but could require care later in adulthood.<sup>21</sup>

## Risk Factors

- Numerous intrinsic and extrinsic nongenetic risk factors, as well as genetic factors, are thought to contribute to CCDs.<sup>22,23</sup>
- Intrinsic risk factors for CCDs can include various genetic syndromes. Twins are at higher risk for CCDs<sup>24</sup>; one report from Kaiser Permanente data showed monochorionic twins were at particular risk (RR, 11.6 [95% CI, 9.2–14.5]).<sup>25</sup> Known risks generally focus on maternal exposures, but a study of paternal occupational exposure documented a higher incidence of CCDs with paternal exposure to phthalates.<sup>26</sup>
- Other paternal exposures that increase risk for CCDs include paternal anesthesia, which has been implicated in TOF (3.6%); sympathomimetic medication and coarctation of the aorta (5.8%); pesticides and VSDs (5.5%); and solvents and HLHS (4.6%).<sup>27</sup>
- Known maternal risks include smoking<sup>28,29</sup> during the first trimester of pregnancy, which has also been associated with a ≥30% increased risk of the following lesions in the fetus: ASD, pulmonary valvar stenosis, truncus arteriosus, TGA,<sup>30</sup> and septal defects (particularly for heavy smokers [ $\geq$ 25 cigarettes daily]).<sup>31</sup> Maternal smoking might account for 1.4% of all congenital heart defects.
- Exposure to secondhand smoke has also been implicated as a risk factor.<sup>32</sup>
- Air pollutants can also increase the risk of CCDs. In a retrospective review of singleton infants born in Florida from 2000 to 2009, maternal exposure during pregnancy to the air pollutant benzene was associated with an increased risk in the fetus of critical and noncritical CCDs (1.33 [95% CI, 1.07–1.65]).<sup>33</sup>
- Maternal binge drinking<sup>34</sup> is also associated with an increased risk of CCDs, and the combination of binge drinking and smoking can be particularly deleterious: Mothers who smoke and report any binge drinking in the 3 months before pregnancy

- are at an increased risk of giving birth to a child with a CCD (adjusted OR, 12.65).<sup>34</sup>
- Maternal obesity is associated with CCDs. A meta-analysis of 14 studies of females without gestational DM showed infants born to mothers who were moderately and severely obese, respectively, had 1.1 and 1.4 times greater risk of CCDs than infants born to normal-weight mothers.<sup>35–37</sup> The risk of TOF was 1.9 times higher among infants born to mothers with severe obesity than among infants born to normal-weight mothers.<sup>36</sup>
  - Maternal DM, including gestational DM, has also been associated with CCDs, both isolated (CCD[s] as the only major congenital anomaly) and multiple (CCD[s] plus ≥1 noncardiac major congenital anomalies).<sup>38,39</sup> Pregestational DM has been associated with CCDs, specifically TOF.<sup>40</sup>
  - Preeclampsia is considered a risk factor for CCDs, although not critical defects.<sup>41</sup>
  - Folate deficiency is a well-documented risk for congenital malformations, including CCDs, and folic acid supplementation is routinely recommended during pregnancy.<sup>22</sup> An observational study of folic acid supplementation in Hungarian females showed a decrease in the incidence of CCDs, including VSD (OR, 0.57 [95% CI, 0.45–0.73]), TOF (OR, 0.53 [95% CI, 0.17–0.94]), dextro-TGA (OR, 0.47 [95% CI, 0.26–0.86]), and ASD secundum (OR, 0.63 [95% CI, 0.40–0.98]).<sup>41</sup> A US population-based case-control study showed an inverse relationship between folic acid use and the risk of TGA (Baltimore-Washington Infant Study, 1981–1989).<sup>42</sup>
  - An observational study from Quebec, Canada, of 1.3 million births from 1990 to 2005 found a 6% per year reduction in severe congenital heart defects using a time-trend analysis before and after public health measures were instituted that mandated folic acid fortification of grain and flour products in Canada.<sup>43</sup>
  - Maternal infections, including rubella and chlamydia, have been associated with congenital heart defects.<sup>44,45</sup>
  - High altitude has also been described as a risk factor for CCDs. Tibetan children living at 4200 to 4900 m had a higher prevalence of congenital heart defects (12.09 per 1000) than those living at lower altitudes of 3500 to 4100 m (4.32 per 1000); patent ductus arteriosus and ASD contributed to the increased prevalence.<sup>46</sup>

## Screening

Pulse oximetry screening for CCDs was incorporated as part of the US recommended uniform screening panel for newborns in 2011 and has been endorsed by the

AHA and the American Academy of Pediatrics.<sup>47</sup> At present, all 50 states and the District of Columbia have laws or regulations mandating newborn screening for identification of previously unidentified (by fetal cardiac ultrasound) newborn CCDs,<sup>48</sup> and several studies have demonstrated the benefit of such screening.<sup>49–51</sup>

- Several key factors contribute to effective screening, including probe placement (postductal), oximetry cutoff (<95%), timing (>24 hours of life), and altitude (<2643 ft [806 m]).
- If fully implemented, screening would predict identification of 1189 additional infants with critical congenital heart defects and yield 1975 false-positive results.<sup>52</sup>
- A simulation model estimates that screening the entire United States for critical CCDs with pulse oximetry would uncover 875 infants (95% UI, 705–1060) who truly have nonsyndromic CCDs versus 880 (95% UI, 700–1080) false-negative screenings (no CCDs).<sup>53</sup>
- It has been estimated that 29.5% (95% CI, 28.1%–31.0%) of nonsyndromic children with critical CCDs are diagnosed after 3 days and thus might benefit from pulse oximetry screening.<sup>54</sup>
- A meta-analysis of 13 studies that included 229 421 newborns found pulse oximetry had a sensitivity of 76.5% (95% CI, 67.7%–83.5%) for detection of critical CCDs and a specificity of 99.9% (95% CI, 99.7%–99.9%), with a false-positive rate of 0.14% (95% CI, 0.06%–0.33%).<sup>55</sup>
- A recent observational study demonstrated that statewide implementation of mandatory policies for newborn screening for critical CCDs was associated with a significant decrease (33.4% [95% CI, 10.6%–50.3%]) in infant cardiac deaths between 2007 and 2013 compared with states without such policies.<sup>56</sup>
- The cost of identifying a newborn with a critical CCD has been estimated at \$20 862 per newborn detected and \$40 385 per life-year gained (2011 US dollars).<sup>53</sup>
- Reports outside of the United States have shown similar performance of pulse oximetry screening in identifying critical CCDs,<sup>57</sup> with a sensitivity and specificity of pulse oximetry screening for critical congenital heart defects of 100% and 99.7%, respectively.

## Social Determinants

Recently, several studies have demonstrated there can be variations in CCD outcomes based on factors such as ethnicity, race, and socioeconomic status.<sup>58–62</sup>

- In a review of 15 533 infants with CCD born between 2004 and 2013, survival among infants with univentricular CCDs was improved for those

whose fathers were >35 years of age (71.6% [95% CI, 63.8%–80.3%]) compared with those who were younger (59.7% [95% CI, 54.6%–65.2%]), and factors associated with survival in biventricular CCDs included maternal education, race or ethnicity, and marital status.<sup>58</sup>

- All infants undergoing cardiac intervention in England and Wales from 2005 to 2010 were identified through a national registry, and CCD incidence was shown to be higher in Asian and black ethnic groups than in the Caucasian reference population (IRR 1.5 for Asians [95% CI, 1.4–1.7] and 1.4 for blacks [95% CI, 1.3–1.6]).<sup>59</sup>

## Genetics and Family History

- CCDs can have a heritable component. There is a greater concordance of CCDs in monozygotic than dizygotic twins.<sup>63</sup> Among parents with ASD or VSD, 2.6% and 3.7%, respectively, have children who are similarly affected, 21 times the estimated population frequency.<sup>64</sup> However, the majority of CCDs occur in families with no other history of CCDs, which supports the possibility of de novo genetic events.
- Large chromosomal abnormalities are associated with some CCDs. For example, aneuploidies such as trisomy 13, 18, and 21 account for 9% to 18% of CCDs.<sup>54</sup> The specific genes responsible for CCDs that are disrupted by these abnormalities are difficult to identify. There are studies that suggest that *DSCAM* and *COL6A* contribute to Down syndrome–associated CCDs.<sup>65</sup>
- Copy number variants also contribute to CCDs and have been shown to be overrepresented in larger cohorts of patients with specific forms of CCDs.<sup>66</sup> The most common copy number variant is del22q11, which encompasses the T-box transcription factor (*TBX1*) gene and presents as DiGeorge syndrome and velocardiofacial syndrome. Others include del17q11, which causes William syndrome.<sup>67</sup>
- Single point mutations are also a cause of CCDs and include mutations in a core group of cardiac transcription factors (*NKX2.5*, *TBX1*, *TBX2*, *TBX3*, *TBX5*, and *MEF2*),<sup>67,68</sup> *ZIC3*, and the *NOTCH1* gene (dominantly inherited and found in ≈5% of cases of bicuspid aortic valve) and related *NOTCH* signaling genes.<sup>69</sup>
- Advances in whole-exome sequencing have suggested that 10% of sporadic severe cases of CCDs are caused by de novo mutations,<sup>70</sup> particularly in chromatin-regulating genes.
- Rare monogenic CCDs also exist, including monogenic forms of ASD, heterotaxy, severe mitral valve prolapse, and bicuspid aortic valve.<sup>67</sup>

- Complications related to CCD may also have a genetic component; a recent whole-exome sequence study identified *SOX17* as a novel candidate gene for PAH in patients with CCD patients.<sup>71</sup>
- There is no exact consensus currently on the role, type, and utility of clinical genetic testing in people with CCDs,<sup>67</sup> but it should be offered to patients with multiple congenital abnormalities or congenital syndromes (including CCD lesions associated with a high prevalence of 22q11 deletion or DiGeorge syndrome), and it can be considered in patients with a family history, in those with developmental delay, and in patients with left-sided obstructive lesions.<sup>1</sup>
- The diagnostic yield for CCD genetic panels in familial, nonsyndromic cases is 31% to 46% and is even lower in nonfamilial disease.<sup>72,73</sup> Use of whole-exome genetic testing has been shown to improve rates of detection.<sup>74</sup>
- A Pediatric Cardiac Genomics Consortium has been developed to provide and better understand phenotype and genotype data from large cohorts of patients with CCDs.<sup>75</sup>

## Mortality

### (See Tables 15-1 and 15-4 and Charts 15-1 through 15-5)

Overall mortality attributable to CCDs:

- In 2017:
  - Mortality related to CCDs was 2906 deaths (Table 15-1), an 18.1% decrease from 2007 (unpublished NHLBI tabulation using NVSS<sup>76</sup>).
  - CCDs (*ICD-10* Q20–Q28) were the most common cause of infant deaths resulting from birth defects (*ICD-10* Q00–Q99); 22.5% of infants who died of a birth defect had a heart defect (*ICD-10* Q20–Q24; unpublished NHLBI tabulation using NVSS<sup>76</sup>).
  - The age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 0.9, a 25.0% decrease from 2007 (unpublished NHLBI tabulation using CDC WONDER<sup>77</sup>).
- According to a review of Norwegian national mortality data in live-born children with CCDs from 1994 to 2009, the all-cause mortality rate was 17.4% for children with severe congenital heart defects and 3.0% for children with milder forms of CCDs, with declining mortality rates over the analysis period related to declining operative mortality and more frequent pregnancy terminations.<sup>78</sup>
- Death rates attributed to CCDs decrease as gestational age advances toward 40 weeks.<sup>79</sup> In-hospital mortality of infants with major CCDs is independently associated with late-preterm birth (OR, 2.70

- [95% CI, 1.69–4.33]) compared with delivery at later gestational ages.<sup>80,81</sup>
- Similarly, postoperative mortality of infants with CCDs born near term (37 weeks) is 1.34 (95% CI, 1.05–1.71;  $P=0.02$ ) higher than for those born full term, with higher complication rates and longer lengths of stay.<sup>82</sup> The presence of CCDs substantially increases mortality of very low-birth-weight infants; in a study of very low-birth-weight infants, the mortality rate with serious congenital heart defects was 44% compared with 12.7% in very low-birth-weight infants without serious CCDs.<sup>83</sup>
  - Analysis of the STS Congenital Heart Surgery Database, a voluntary registry with self-reported data for a 3-year cycle (2013–2016) from 116 centers performing CCD surgery (112 based in 40 US states, 3 in Canada, and 1 in Turkey),<sup>84</sup> showed that of 122 193 total patients who underwent an operation with analyzable data, the aggregate hospital discharge mortality rate was 3.0% (95% CI, 2.9%–3.1%).<sup>85</sup> The mortality rate was 8.6% (95% CI, 8.2%–9.1%) for neonates, 2.8% (95% CI, 2.6%–3.0%) for infants, 1.0% (95% CI, 0.9%–1.1%) for children (>1 year to 18 years of age), and 1.5% (95% CI, 1.3%–1.8%) for adults (>18 years of age).<sup>85</sup>
  - Another recent analysis of mortality after CCD surgery, culled from the Pediatric Cardiac Care Consortium's US-based multicenter data registry, demonstrated that although standardized mortality ratios continue to decrease, there remains increased mortality in CCD patients compared with the general population. The data included 35 998 patients with median follow-up of 18 years and an overall standardized mortality ratio of 8.3% (95% CI, 8.0%–8.7%).<sup>86</sup>
  - The Japan Congenital Cardiovascular Surgery Database reported similar surgical outcomes for congenital HD from 28 810 patients operated on between 2008 and 2012, with 2.3% and 3.5% mortality at 30 and 90 days, respectively.<sup>87</sup>
  - In Mexico, there were 70 741 deaths attributed to CCD during the years 2000 to 2015, with the standardized mortality rates increased from 3.3 to 4 per 100 000 individuals, and an increase in mortality rates in the age group <1 year of age from 114.4 to 146.4 per 100 000 live births.<sup>88</sup>
  - In population-based data from Canada, 8123 deaths occurred among 71 686 patients with CCDs followed up for nearly 1 million patient-years.<sup>7</sup>
  - Among 12 644 adults with CCDs followed up at a single Canadian center from 1980 to 2009, 308 patients in the study cohorts (19%) died.<sup>89</sup>
  - Trends in age-adjusted death rates attributable to CCD mortality showed a decline from 1999 to

- 2017 (Chart 15-1); this varied by race/ethnicity and sex (Charts 15-2 and 15-3).
- From 1999 to 2017, there was a decline in the age-adjusted death rates attributable to CCDs in black, white, and Hispanic people (Chart 15-2), in both males and females (Chart 15-3), and in age groups 1 to 4 years, 5 to 14 years, 15 to 24 years, and ≥25 years (Chart 15-4) in the United States.
  - CCD-related mortality varies substantially by age, with 1- to 4-year-old children demonstrating higher mortality rates than any age group other than infants from 1999 to 2017 (Chart 15-4).
  - The US 2017 age-adjusted death rate (deaths per 100 000 people) attributable to CCDs was 1.01 for NH white males, 1.28 for NH black males, 0.91 for Hispanic males, 0.77 for NH white females, 1.03 for NH black females, and 0.73 for Hispanic females (Chart 15-5). Infant (<1 year of age) mortality rates were 27.4 for NH white infants, 38.6 for NH black infants, and 30.0 for Hispanic infants (unpublished NHLBI tabulation using CDC WONDER<sup>77</sup>).
  - Mortality after congenital heart surgery also differs between races/ethnicities, even after adjustment for access to care. One study found that a higher risk of in-hospital mortality was associated with nonwhite race (OR, 1.36 [95% CI, 1.19–1.54]) and Medicaid insurance (OR, 1.26 [95% CI, 1.09–1.46]).<sup>90</sup> One center's experience suggested race was independently associated with neonatal surgical outcomes only in patients with less complex CCDs.<sup>91</sup> Another center found that a home monitoring program can reduce mortality even in this vulnerable population.<sup>92</sup>
  - Data from the HCUP's Kids' Inpatient Database from 2000, 2003, and 2006 show male children had more CCD surgeries in infancy, more high-risk surgeries, and more procedures to correct multiple cardiac defects. Female infants with high-risk CCDs had a 39% higher adjusted mortality than males.<sup>92,93</sup> According to CDC multiple-cause death data from 1999 to 2006, sex differences in mortality over time varied with age. Between the ages of 18 and 34 years, mortality over time decreased significantly in females but not in males.<sup>94</sup>
  - In studies that examined trends since 1979, age-adjusted death rates declined 22% for critical CCDs<sup>95</sup> and 39% for all CCDs,<sup>96</sup> and deaths tended to occur at progressively older ages. Population-based data from Canada showed overall mortality decreased by 31% and the median age of death increased from 2 to 23 years between 1987 and 2005.<sup>7</sup>
  - Further analysis of the Kids' Inpatient Database from 2000 to 2009 showed a decrease in HLHS stage 3 mortality by 14% and a decrease in stage 1 mortality by 6%.<sup>97</sup> Surgical interventions are the primary treatment for reducing mortality. A Pediatric

Heart Network study of 15 North American centers revealed that even in lesions associated with the highest mortality, such as HLHS, aggressive palliation can lead to an increase in the 12-month survival rate, from 64% to 74%.<sup>98</sup>

- Surgical interventions are common in adults with CCDs. Mortality rates for 12 CCD procedures were examined with data from 1988 to 2003 reported in the NIS. A total of 30 250 operations were identified, which yielded a national estimate of  $152\,277 \pm 7875$  operations. Of these, 27% were performed in patients  $\geq 18$  years of age. The overall in-hospital mortality rate for adult patients with CCDs was 4.71% (95% CI, 4.19%–5.23%), with a significant reduction in mortality observed when surgery was performed on such adult patients by pediatric versus non-pediatric heart surgeons (1.87% versus 4.84%;  $P < 0.0001$ ).<sup>99</sup> For adults with CCDs, specialist care is a key determinant of mortality and morbidity. In a single-center report of 4461 adult patients with CCDs with 48 828 patient-years of follow-up, missed appointments and delay in care were predictors of mortality.<sup>100</sup>

## Hospitalizations (See Table 15-1)

- In 2016, the total number of hospital discharges for CCDs for all ages was 45 000 (Table 15-1).
- Hospitalization of infants with CCDs is common; one-third of patients with congenital heart defects require hospitalization during infancy,<sup>101,102</sup> often in an ICU.

## Cost

- Using HCUP 2013 NIS data, one study noted that hospitalization costs for individuals of all ages with CCDs exceeded \$6.1 billion in 2013, which represents 27% of all birth defect-associated hospital costs.<sup>103</sup>
- Among pediatric hospitalizations (0–20 years of age) in the HCUP 2012 Kids' Inpatient Database<sup>104</sup>:
  - Pediatric hospitalizations with CCDs (4.4% of total pediatric hospitalizations) accounted for \$6.6 billion in hospitalization spending (23% of total pediatric hospitalization costs).
  - 26.7% of all CCD costs were attributed to critical CCDs, with the highest costs attributable to HLHS, coarctation of the aorta, and TOF.
  - Median (IQR) hospital cost was \$51 302 (\$32 088–\$100 058) in children who underwent cardiac surgery, \$21 920 (\$13 068–\$51 609) in children who underwent cardiac catheterization, \$4134 (\$1771–\$10 253) in

children who underwent noncardiac surgery, and \$23 062 (\$5529–\$71 887) in children admitted for medical treatments.

- The mean cost of CCDs was higher in infancy (\$36 601) than in older ages and in those with critical congenital heart defects (\$52 899).
- Other studies confirm the high cost of HLHS. An analysis of 1941 neonates with HLHS showed a median cost of \$99 070 for stage 1 palliation (Norwood or Sano procedure), \$35 674 for stage 2 palliation (Glenn procedure), \$36 928 for stage 3 palliation (Fontan procedure), and \$289 292 for transplantation.<sup>105</sup>
- Other CCD lesions, often which are either less complex or preserve a biventricular circulation, are less costly. In 2124 patients undergoing congenital heart operations between 2001 and 2007, total costs for the other surgeries were \$12 761 (ASD repair), \$18 834 (VSD repair), \$28 223 (TOF repair), and \$55 430 (arterial switch operation).<sup>106</sup>
- A Canadian study published in 2017 demonstrated increasing hospitalization costs for children and adults with CCDs, particularly those with complex lesions, which appeared to be independent from inflation or length of stay.<sup>107</sup>
- A recent US study evaluating cost and length of stay in neonates with HLHS revealed significant regional differences in cost, length of stay, and mortality.<sup>108</sup>

## Global Burden of CCDs (See Charts 15-6 and 15-7)

- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.<sup>109</sup> In 2017:
  - Prevalence of congenital heart anomalies was an estimated 12.0 million people.
  - There were 300 000 deaths attributed to congenital heart anomalies worldwide.
  - Age-standardized mortality rates of congenital heart anomalies are lowest in high-income countries and several African nations (Chart 15-6).
  - The age-standardized prevalence of congenital heart anomalies is highest in Central Europe (Chart 15-7).

## Kawasaki Disease **ICD-9 446.1; ICD-10 M30.3.**

KD is an acute inflammatory illness characterized by fever, rash, nonexudative limbal-sparing conjunctivitis, extremity changes, red lips and strawberry tongue, and

a swollen lymph node. In areas where bacille Calmette-Guerin vaccination is common, the site can reactivate in KD.<sup>110</sup> The most feared consequence of this vasculitis is coronary artery aneurysms, which can result in coronary ischemic events and other cardiovascular outcomes in the acute period or years later.<sup>111</sup> The cause of KD is unknown, but it could be an immune response to an acute infectious illness based in part on genetic susceptibilities.<sup>112,113</sup> This is supported by the occurrence of epidemics and variation in incidence by age, geography, and season, but also by race/ethnicity, sex, and family history.<sup>113,114</sup> The Nationwide Longitudinal Survey in Japan has shown that breastfeeding is protective against developing KD.<sup>115</sup>

### Prevalence

- KD is the most common cause of acquired HD in children in the United States and other developed countries.<sup>114</sup>

### Incidence

- The incidence was 20.8 per 100 000 US children <5 years of age in 2006.<sup>116</sup> This is the most recent national estimate available and is limited by reliance on weighted hospitalization data from 38 states.
- Boys have a 1.5-fold higher incidence of KD than girls.<sup>116</sup>
- Although KD can occur into adolescence (and rarely beyond), 76.8% of US children with KD are <5 years of age.<sup>116</sup>
- Race-specific incidence rates indicate that KD is most common among Americans of Asian and Pacific Island descent (30.3 per 100 000 children <5 years of age), occurs with intermediate frequency in NH blacks (17.5 per 100 000 children <5 years of age) and Hispanics (15.7 per 100 000 children <5 years of age), and is least common in whites (12.0 per 100 000 children <5 years of age).<sup>116</sup>
- There is also geographic variation in KD incidence within the United States. States with higher Asian American populations have higher rates of KD; for example, rates are 2.5-fold higher in Hawaii (50.4 per 100 000 children <5 years of age) than in the continental United States.<sup>117</sup> Within Hawaii, the race-specific rates of KD per 100 000 children <5 years of age in 1996 to 2006 were 210.5 for Japanese, 86.9 for Native Hawaiian, 83.2 for Chinese, 64.5 for Filipino, and 13.7 for white children.<sup>117</sup>
- There are seasonal variations in KD; KD is more common during the winter and early spring months, except in Hawaii, where no clear seasonal trend is seen.<sup>116,117</sup>
- KD can recur. Recurrences constitute 2% to 4% of total KD cases in both the United States and Japan,<sup>118</sup> and incidence of first recurrence among

children with a history of KD has been reported as 6.5 per 1000 person-years in Japan (2007–2010) and 2.6 per 1000 person-years in Canada (2004–2014).<sup>119,120</sup>

### Secular Trends

- Although the incidence of KD is rising worldwide, there has been no clear secular trend in the United States, but recent data are lacking. US hospitalizations for KD were 17.5 and 20.8 per 100 000 children <5 years of age in 1997 and 2006, respectively, but the test for linear trend was not significant.<sup>116</sup>

### Genetics/Family History

- Approximately 1% of KD cases have a positive family history of KD. Among siblings of KD patients, the RR of KD is ≈10-fold compared with the general population (2.1% rate within 1 year of index case onset). Among identical twins, concordance is ≈13 percent.<sup>114</sup>
- A variety of genetic variants have been associated with KD susceptibility or development of coronary artery lesions in KD; however, thus far these have not explained differences in incidence between ancestry groups (eg, Japanese versus European).<sup>112,121</sup>

### Treatment and Control

- Treatment of acute KD rests on diminishing the inflammatory response with IVIG, which clearly reduces the incidence of coronary artery aneurysms (from 25% to ≈4% for aneurysms defined by absolute dimensions).<sup>114</sup> Aspirin is routinely used for its anti-inflammatory and antiplatelet effects, but it does not reduce the incidence of coronary artery aneurysms.
  - On the basis of a Cochrane review, addition of prednisolone to the standard IVIG regimen could further reduce the incidence of coronary artery abnormalities (RR, 0.29 [95% CI, 0.18–0.46]), but the applicability of these data to non-Asian and less severe KD cases is not certain.<sup>122</sup>
  - On the basis of limited data, other anti-inflammatory treatments have also been used, and several clinical trials are under way.<sup>123</sup>
  - Resistance to IVIG, defined as recurrent or persistent fever ≥36 hours after completion of IVIG infusion, occurs in 10% to 20% of KD patients. Predictive models for IVIG resistance have been developed in Asian populations but have not been useful in North American patients. Treatment of IVIG resistance is currently not standardized.<sup>114</sup>
- Management of established coronary artery aneurysms in the short and long term is centered on

thromboprophylaxis. Successful coronary intervention for late coronary stenosis or thrombosis has been accomplished percutaneously and surgically (eg, CABG).<sup>124,125</sup>

### Complications of KD

- In the acute phase (up to ≈6 weeks from fever onset), several important cardiovascular complications can occur.
  - KD shock syndrome, with variable contributions from myocardial dysfunction and decreased peripheral resistance, occurs in 5% to 7% of KD cases and is associated with higher risk of coronary arterial dilation, resistance to IVIG treatment, and rarely, long-term myocardial dysfunction or death.<sup>114,126</sup>
  - It is estimated that even with current therapy (high-dose IVIG within the first 10 days of illness), 20% of children develop transient coronary artery dilation ( $Z$  score >2), 5% develop coronary artery aneurysms ( $Z$  score  $\geq 2.5$ ), and 1% develop giant aneurysms ( $Z$  score  $\geq 10$  or >8 mm).<sup>114</sup> Estimates are complicated by variability in ascertainment method (administrative codes or research measurement), size criteria, timing (because the majority of dilated segments and approximately half of aneurysms reduce to normal dimensions over time), and therapeutic regimens in the underlying studies. In the most recent US data from 2 centers in 2004 to 2008, maximal coronary artery dimensions reached  $Z$  scores  $\geq 2.5$  in 30% of KD cases up to 12 weeks from fever onset, including medium ( $Z$  score  $\geq 5$  to <10) and giant aneurysms in ≈6% and ≈3% of KD cases, respectively.<sup>127</sup> Risk factors for coronary artery abnormalities include younger age, male sex, late treatment, and failure to respond to initial IVIG with defervescence.<sup>127–130</sup>
  - Peak KD-associated mortality occurs during the acute phase but is rare, estimated at 0% to 0.17% in older US data and 0.03% in recent data from Japan.<sup>131–133</sup> Mortality is related to thrombosis or rupture of rapidly expanding aneurysms, or less commonly, shock or macrophage activation syndrome with multiorgan failure.<sup>114,133,134</sup>
  - Long term, IHD and death are related to coronary artery stenosis or thrombosis.
    - Prognosis is predicted largely by coronary artery size 1 month from illness onset. In a Taiwanese study of 1073 KD cases from 1980 to 2012, coronary artery aneurysms were present in 18.3% beyond 1 month, including 11.6% with small, 4.1% with medium, and

2.5% with giant aneurysms. Among those with persistent aneurysms beyond 1 month, IHD death occurred in 2%, nonfatal AMI occurred in another 2%, and myocardial ischemia occurred in another 3%, for a total 7% ischemic event rate during 1 to 46 years of follow-up. Nearly all events occurred in those with giant aneurysms, for whom the ischemia event-free survival rates were 0.63 and 0.36 at 10 and 20 years, respectively, after KD onset.<sup>135</sup> Findings were similar in a Japanese study of 76 patients with giant aneurysms diagnosed since 1972 and followed up through 2011 and in a Canadian study of 1356 KD patients diagnosed in 1990 to 2007 and followed up for up to 15 years.<sup>124,136</sup>

- A recent Japanese multicenter cohort study of 1006 individuals identified risk factors for 10-year incidence of coronary events (thrombosis, stenosis, obstruction, acute ischemic events, or coronary intervention).<sup>137</sup> Significant risk factors included giant-sized aneurysm (HR, 8.9 [95% CI, 5.1–15.4]), male sex (HR, 2.8 [95% CI, 1.7–4.8]), and resistance to IVIG therapy (HR, 2.2 [95% CI, 1.4–3.6]).
- Among 261 adults <40 years of age with ACS who underwent coronary angiography for suspected myocardial ischemia in San Diego, CA, from 2005 to 2009, 5% had aneurysms consistent with late sequelae of KD.<sup>138</sup>
- In 2017, US mortality attributable to KD was 5 patients for underlying mortality and 10 patients for all-cause mortality (unpublished NHLBI tabulation using CDC WONDER<sup>77</sup>).

### Healthcare Utilization

- In 2016, there were 6000 all-listed diagnoses hospital discharges for KD, with 4000 males and 2000 females (HCUP,<sup>139</sup> unpublished NHLBI tabulation).

### Global Burden of KD

- The annual incidence of KD is highest in Japan, at 308.0 per 100 000 children <5 years of age in 2014, followed by South Korea at 194.7 per 100 000 children <5 years of age in 2014 and Taiwan at 55.9 per 100 000 in children <5 years of age for the period 2000 to 2014.<sup>133,140,141</sup> National incidence data are lacking for China, but the most recent estimates for Shanghai are 55.5 per 100 000 children <5 years of age in 2012.<sup>142</sup>
- In Japan, the cumulative incidence of KD at 10 years of age has been calculated with national survey data as >1%, at 1.5 per 100 boys and 1.2 per 100 girls for 2007 to 2010.<sup>143</sup> Using different methodology with complete capture of cases through the national health insurance program,

- Taiwan recorded a cumulative incidence of 2.8% by 5 years of age in 2014.<sup>141</sup>
- The incidence of KD is lower in Canada, at 19.6 per 100 000 children <5 years of age for the period 2004 to 2014, and in European countries, such as Italy with 14.7 per 100 000 children <5 years of age in 2008 to 2013, Spain with 8 per 100 000 children <5 years of age in 2004 to 2014,

Germany with 7.2 per 100 000 children <5 years of age in 2011 to 2012, and the United Kingdom and Ireland with 4.6 per 100 000 children <5 years of age in 2014 to 2015.<sup>120,144–148</sup>

- The incidence of KD is rising worldwide, with potential contributions from improved recognition, diagnosis of incomplete KD more often, and true increasing incidence.<sup>133,141,145,148</sup>

**Table 15-1.** CCDs in the United States

Population Group	Estimated Prevalence, 2010, All Ages	Mortality, 2017, All Ages*	Hospital Discharges, 2016, All Ages
Both sexes	2.4 million	2906	45 000
Males	...	1583 (54.5%)†	25 000
Females	...	1323 (45.5%)†	20 000
NH white males	...	923	...
NH white females	...	779	...
NH black males	...	273	...
NH black females	...	225	...
Hispanic males	...	301	...
Hispanic females	...	239	...
NH Asian or Pacific Islander males	...	62	...
NH Asian or Pacific Islander females	...	59	...
NH American Indian or Alaska Native	...	31	...

CCD indicates congenital cardiovascular defect; ellipses (...), data not available; and NH, non-Hispanic.

\*Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.

Sources: Prevalence: Gilboa et al.<sup>149</sup> Mortality: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System.<sup>76</sup> These data represent underlying cause of death only. Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016.<sup>139</sup> Data include those inpatients discharged alive, dead, or status unknown.

**Table 15-2.** Annual Birth Prevalence of CCDs in the United States, 1930 to 2010

Type of Presentation	Rate per 1000 Live Births	Estimated Number (Variable With Yearly Birth Rate)
Fetal loss	Unknown	Unknown
Invasive procedure during the first year	2.4	9200
Detected during first year*	8	36 000
Bicuspid aortic valve	13.7	54 800

CCD indicates congenital cardiovascular defect.

\*Includes stillbirths and pregnancy termination at <20 weeks' gestation; includes some defects that resolve spontaneously or do not require treatment.

Source: Data derived from van der Linde et al<sup>13</sup> and Parker et al.<sup>19</sup>

**Table 15-3.** Estimated US Prevalence of CCDs and Percent Distribution by Type, 2002\* (in Thousands)

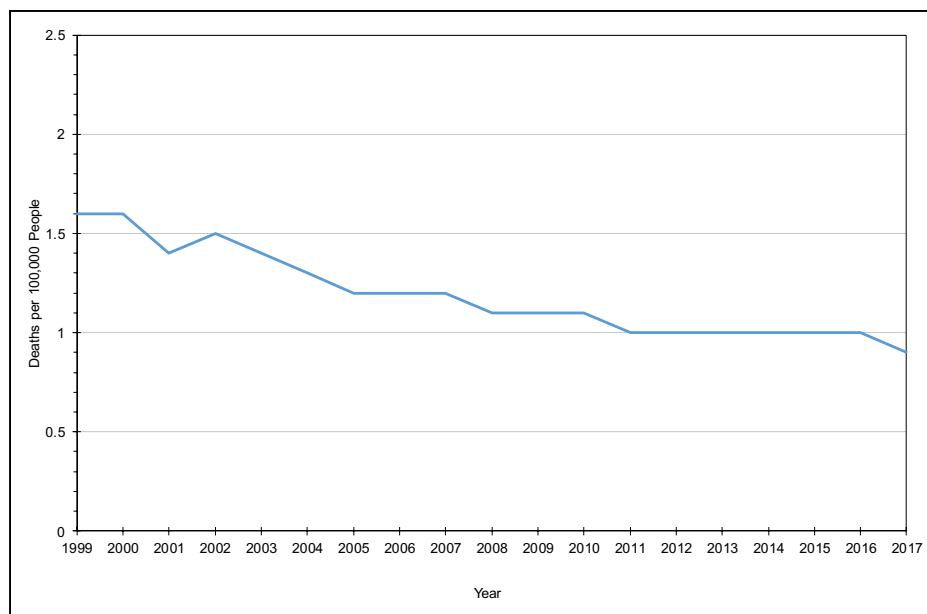
Type	Prevalence, N			Percent of Total		
	Total	Children	Adults	Total	Children	Adults
Total	994	463	526	100	100	100
VSD†	199	93	106	20.1	20.1	20.1
ASD	187	78	109	18.8	16.8	20.6
Patent ductus arteriosus	144	58	86	14.2	12.4	16.3
Valvular pulmonic stenosis	134	58	76	13.5	12.6	14.4
Coarctation of aorta	76	31	44	7.6	6.8	8.4
Valvular aortic stenosis	54	25	28	5.4	5.5	5.2
TOF	61	32	28	6.1	7	5.4
AV septal defect	31	18	13	3.1	3.9	2.5
TGA	26	17	9	2.6	3.6	1.8
Hypoplastic right heart syndrome	22	12	10	2.2	2.5	1.9
Double-outlet RV	9	9	0	0.9	1.9	0.1
Single ventricle	8	6	2	0.8	1.4	0.3
Anomalous pulmonary venous connection	9	5	3	0.9	1.2	0.6
Truncus arteriosus	9	6	2	0.7	1.3	0.5
HLHS	3	3	0	0.3	0.7	0
Other	22	12	10	2.1	2.6	1.9

ASD indicates atrial septal defect; AV, atrioventricular; CCD, congenital cardiovascular defect; HLHS, hypoplastic left heart syndrome; RV, right ventricle; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

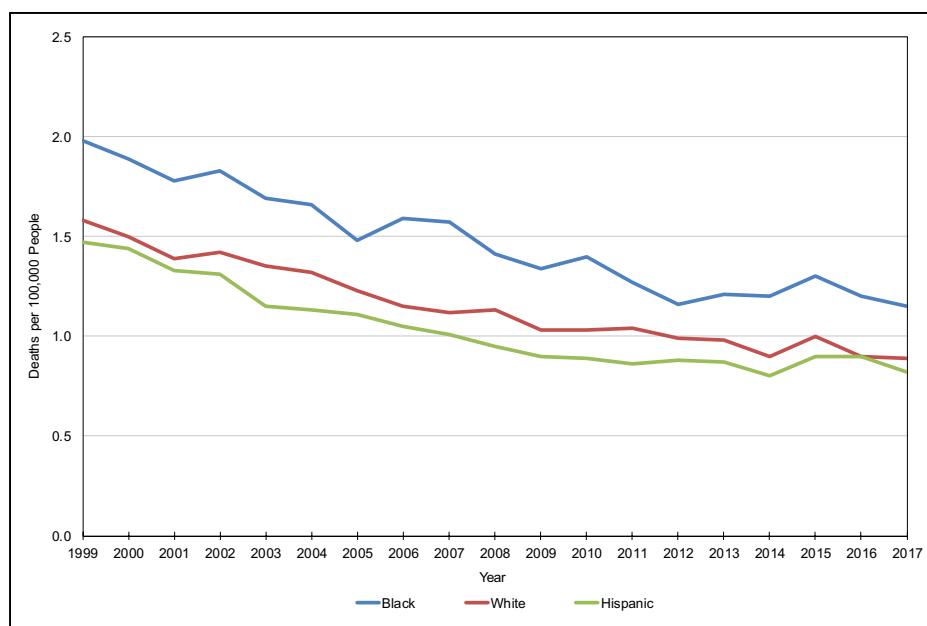
\*Excludes an estimated 3 million bicuspid aortic valve prevalence (2 million in adults and 1 million in children).

†Small VSD, 117 000 (65 000 adults and 52 000 children); large VSD, 82 000 (41 000 adults and 41 000 children).

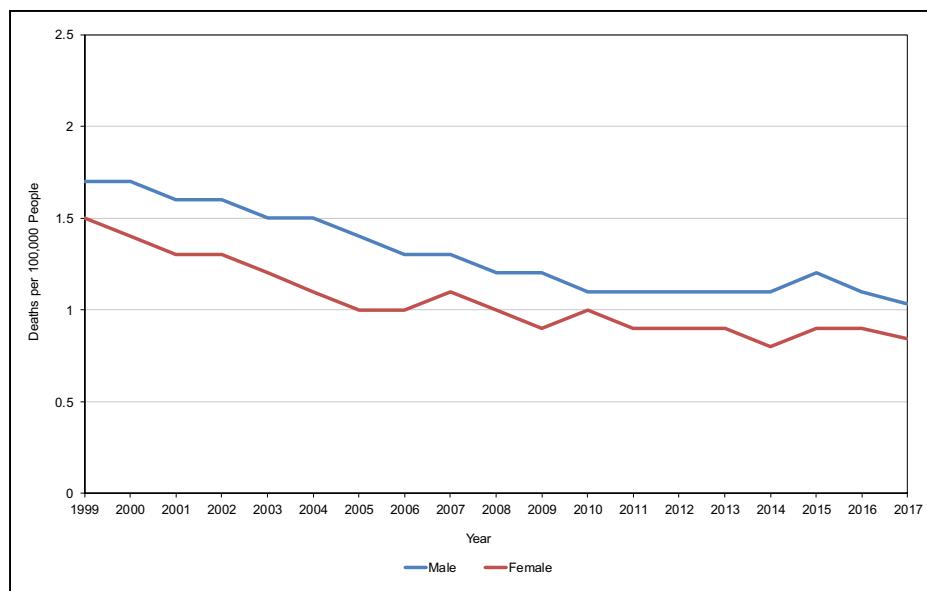
Source: Data derived from Hoffman et al.<sup>11</sup>

**Chart 15-1.** Trends in age-adjusted death rates attributable to congenital cardiovascular defects, United States, 1999 to 2017.

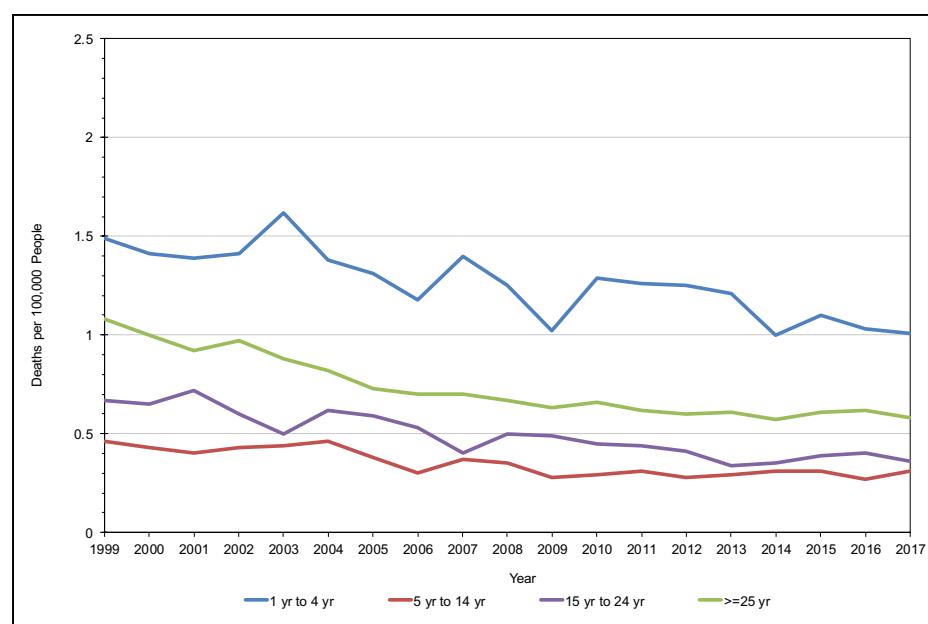
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.<sup>77</sup>

**Chart 15-2. Trends in age-adjusted death rates attributable to congenital cardiovascular defects by race/ethnicity, United States, 1999 to 2017.**

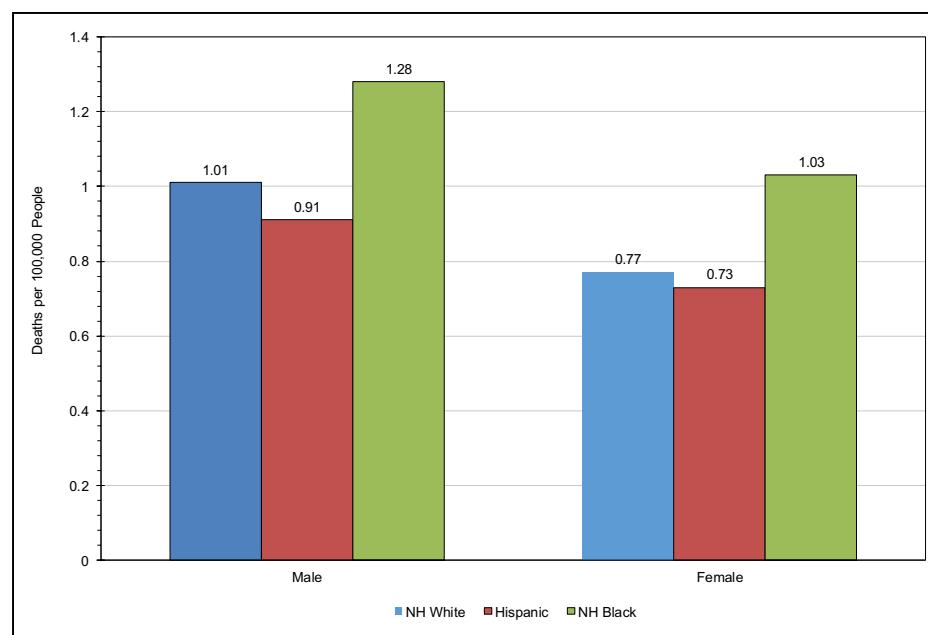
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.<sup>77</sup>

**Chart 15-3. Trends in age-adjusted death rates attributable to congenital cardiovascular defects by sex, United States, 1999 to 2017.**

Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.<sup>77</sup>

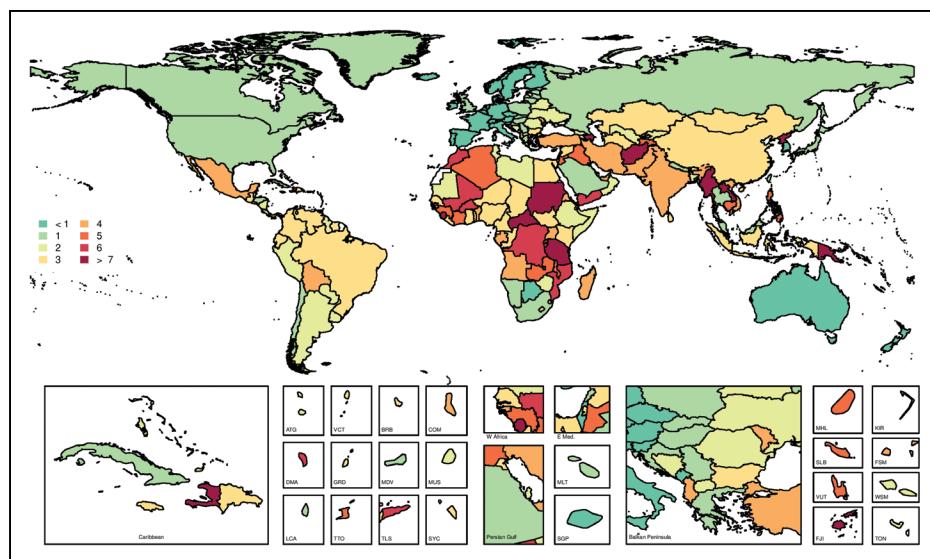
**Chart 15-4.** Trends in age-specific death rates attributable to congenital cardiovascular defects by age at death, United States, 1999 to 2017.

Yr indicates year.

Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.<sup>77</sup>**Chart 15-5.** Age-adjusted death rates attributable to congenital cardiovascular defects, by sex and race/ethnicity, United States, 2017.

NH indicates non-Hispanic.

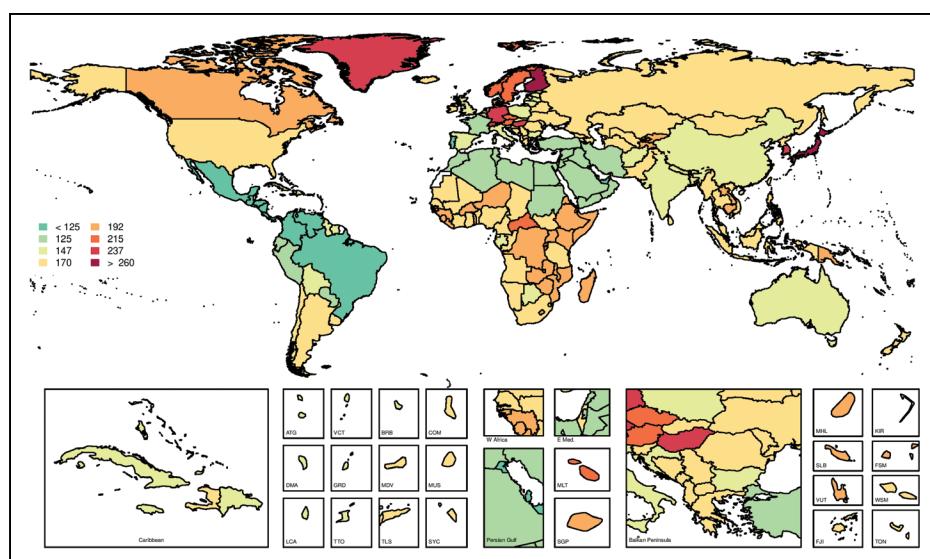
Source: Unpublished National Heart Lung and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research.<sup>77</sup>



Age-standardized mortality rates of congenital heart anomalies are lowest in high-income countries and several African nations.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>109</sup> Printed with permission. Copyright © 2018, University of Washington.



The age-standardized prevalence of congenital heart anomalies is highest in Central Europe.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>109</sup> Printed with permission. Copyright © 2018, University of Washington.

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## 16. DISORDERS OF HEART RHYTHM

See Table 16-1 and Charts 16-1 through 16-10

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### Arrhythmias (Disorders of Heart Rhythm)

2017: Mortality—54 145. Any-mention mortality—558 408.

### Bradyarrhythmias

**ICD-9 426.0, 426.1, 427.81; ICD-10 I44.0 to I44.3, I49.5**

2017: Mortality—1327. Any-mention mortality—7018.

2016: Hospital discharges—97 000.

Mean hospital charges: \$74 846; in-hospital death rate: 1.15%; mean length of stay: 3.9 days.

### Abbreviations Used in Chapter 16

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
AF	atrial fibrillation
AMI	acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities
AV	atrioventricular
BiomarCaRE	Biomarker for Cardiovascular Risk Assessment in Europe
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHA <sub>2</sub> DS <sub>2</sub> -VASc	Clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, diabetes mellitus, and sex (1 point each); age ≥75 y and stroke/transient ischemic attack/thromboembolism (2 points each); plus history of vascular disease, age 65–74 y, and (female) sex category
CHADS <sub>2</sub>	Clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, age ≥75 y, diabetes mellitus (1 point each), and prior stroke/transient ischemic attack/thromboembolism (2 points)
CHARGE-AF	Cohorts for Heart and Aging Research in Genomic Epidemiology—Atrial Fibrillation
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CPAP	continuous positive airway pressure
CVD	cardiovascular disease
CVH	cardiovascular health
DALY	disability-adjusted life-year
DM	diabetes mellitus

(Continued)

### Abbreviations Used in Chapter 16 Continued

DNA	deoxyribonucleic acid
DOAC	direct oral anticoagulant
ECG	Electrocardiogram
ED	emergency department
EF	ejection fraction
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPIC	European Prospective Investigation Into Cancer and Nutrition
ESRD	end-stage renal disease
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GLORIA-AF	Global Registry on Long-term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation
GRS	genetic risk score
GWAS	genome-wide association study
GWTG	Get With The Guidelines
HbA <sub>1c</sub>	hemoglobin A <sub>1c</sub> (glycosylated hemoglobin)
HCM	hypertrophic cardiomyopathy
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HR	hazard ratio
ICD-9	<i>International Classification of Diseases, 9th Revision</i>
ICD-10	<i>International Classification of Diseases, 10th Revision</i>
ICU	intensive care unit
IQR	interquartile range
IRR	incidence rate ratio
Look AHEAD	Look: Action for Health in Diabetes
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MESA	Multi-Ethnic Study of Atherosclerosis
MET	metabolic equivalent
MI	myocardial infarction
MRI	magnetic resonance imaging
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
NCHS	National Center for Health Statistics
NEDS	Nationwide Emergency Department Sample
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHDS	National Hospital Discharge Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NSTEMI	non-ST-segment-elevation myocardial infarction
NVSS	National Vital Statistics System
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
OSA	obstructive sleep apnea

(Continued)

**Abbreviations Used in Chapter 16 Continued**

PA	physical activity
PAD	peripheral artery disease
PAF	population attributable fraction
PAR	population attributable risk
PCI	percutaneous coronary intervention
PINNACLE	Practice Innovation and Clinical Excellence
PREDIMED	Prevención con Dieta Mediterránea
PREVEND	Prevention of Renal and Vascular End-Stage Disease
QALY	quality-adjusted life-year
RACE 3	Routine vs. Aggressive Risk Factor Driven Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RE-LY	Randomized Evaluation of Long-term Anticoagulant Therapy
RR	relative risk
SBP	systolic blood pressure
SCD	sudden cardiac death
SES	socioeconomic status
SNP	single-nucleotide polymorphism
STEMI	ST-segment–elevation myocardial infarction
STROKESTOP	Systematic ECG Screening for Atrial Fibrillation Among 75-Year-Old Subjects in the Region of Stockholm and Halland, Sweden
SVT	supraventricular tachycardia
TIA	transient ischemic attack
UI	uncertainty interval
USD	US dollars
VF	ventricular fibrillation
WHS	Women's Health Study
WPW	Wolff-Parkinson-White

**AV Block****Prevalence and Incidence**

- In a healthy sample of participants from the ARIC study (mean age 53 years), the prevalence of first-degree AV block was 7.8% in black males, 3.0% in black females, 2.1% in white males, and 1.3% in white females.<sup>1</sup> Lower prevalence estimates were noted in the relatively younger population (mean age 45 years) of the CARDIA study at its year 20 follow-up examination: 2.6% in black males, 1.9% in black females, 1.2% in white males, and 0.1% in white females.<sup>2</sup>
- The prevalence of PR-interval prolongation was observed to be 2.1% in Finnish middle-aged adults, but the authors noted that the PR interval normalized in follow-up in 30% of these people.<sup>3</sup>
- No population-based studies have reported the prevalence of second-degree AV block. On the basis of results from clinical series, Mobitz II second-degree AV block is rare in healthy individuals ( $\approx 0.003\%$ ), whereas Mobitz I (Wenckebach) is

observed in 1% to 2% of healthy individuals <20 years of age, especially during sleep.<sup>4</sup>

- The prevalence of third-degree AV block in the general adult population is very low. The prevalence was 0.04% in the Icelandic Reykjavik Study<sup>5</sup> and 0.6% in a large sample of people with hypertension and without DM enrolled with Veterans Health Administration hospitals.<sup>6</sup>
- In an analysis of standard 12-lead ECGs from 264 324 Brazilian primary care patients, prevalence of complete AV block was 0.05%, ranging from 0.02% in individuals 20 to <40 years of age to 0.3% in persons  $\geq 80$  years of age.<sup>7</sup>
- In 122 815 recordings from 122 454 unique patients prescribed 14-day continuous single-lead electrocardiographic monitoring with the Zio patch device between 2011 and 2013, prevalence of high-grade AV block (defined as either Mobitz II or complete heart block) was 1.2% (1486 of all tracings).<sup>8</sup>
- An English registry study estimated the incidence of infant complete AV block as 2.1 per 100 000 live births.<sup>9</sup> Congenital complete heart block could be attributable to transplacental transfer of maternal anti-SSA/Ro or SSB/La antibodies.<sup>10</sup>

**Risk Factors**

- In healthy individuals from MESA without CVD or its risk factors, PR interval was longer with advancing age, in males compared with females, and in blacks compared with whites.<sup>11</sup>
- Although first-degree AV block and Mobitz type I second-degree AV block can occur in apparently healthy people, presence of Mobitz II second- or third-degree AV block usually indicates underlying HD, including CHD, and HF.<sup>4</sup>
- Reversible causes of AV block include electrolyte abnormalities, drug-induced AV block, perioperative AV block attributable to hypothermia, or inflammation near the AV conduction system after surgery in this region. Some conditions may warrant pacemaker implantation because of the potential for disease progression even if the AV block reverses transiently (eg, sarcoidosis, amyloidosis, and neuromuscular diseases).<sup>12</sup>
- Long sinus pauses and AV block can occur during sleep apnea. In the absence of symptoms, these abnormalities are reversible and do not require pacing.<sup>12,13</sup>
- Although the majority of determinants of heart rate are acquired, there are genetic components that are associated with heart rate. For example, a GWAS has identified 21 genetic loci associated with heart rate.<sup>14</sup>

**Prevention**

- Detection and correction of reversible causes of acquired AV block could be of potential importance

in preventing symptomatic bradycardia and other complications of AV block.<sup>12</sup>

### **Complications** **(See Chart 16-1)**

- In the FHS, PR-interval prolongation (>200 ms) was associated with increased risk of AF (HR, 2.06 [95% CI, 1.36–3.12]), pacemaker implantation (HR, 2.89 [95% CI, 1.83–4.57]), and all-cause mortality (HR, 1.44 [95% CI, 1.09–1.91]).<sup>15</sup> Compared with people with a PR interval ≤200 ms, those with a PR interval >200 ms had an absolute increased risk per year of 1.0% for AF, 0.5% for pacemaker implantation, and 2.1% for death (Chart 16-1).
- Decisions about the need for a pacemaker are influenced by the presence or absence of symptoms directly attributable to bradycardia and the likelihood of the arrhythmia progressing to complete heart block. Permanent pacing improves survival in patients with third-degree AV block, especially if syncope has occurred.<sup>12</sup>
- In a large, prospective, regional French registry of 6662 STEMI patients (2006–2013), high-degree AV block was noted in 3.5% of individuals. In 64% of cases, high-degree AV block was present on admission. Although patients with high-degree AV block on admission or occurring during the first 24 hours of hospitalization had higher in-hospital mortality rates than patients without heart block, it was not an independent predictor of mortality after multivariable analysis (OR, 0.99 [95% CI, 0.60–1.66]).<sup>16</sup>
- Little evidence exists to suggest that pacemakers improve survival in patients with isolated first-degree AV block.<sup>17</sup> However, marked first-degree AV block (PR >300 ms) can lead to symptoms even in the absence of higher degrees of AV block, with uncontrolled studies suggesting that those patients benefit from pacemaker implantation.<sup>12,18</sup>

## **Sinus Node Dysfunction**

### **Prevalence and Incidence**

- There are no accurate estimates of the prevalence of sinus node dysfunction in the general population.
- According to a survey of members of the North American Society of Pacing and Electrophysiology, sick sinus syndrome accounted for 48% of implantations of first permanent pacemakers in the United States in 1997.<sup>19,20</sup>
- Sinus node dysfunction is commonly present with other causes of bradyarrhythmias (carotid sinus hypersensitivity in 42% of patients and advanced AV conduction abnormalities in 17%).<sup>21,22</sup>
- Incidence rates of sinus node dysfunction hospitalization among Medicare beneficiaries >65 years of age were 207 per 100 000 person-years in 1998.

Rates increased with age and were higher in males than females and in whites than blacks.<sup>23</sup>

- The incidence rate of sick sinus syndrome was 0.8 per 1000 person-years of follow-up in 2 US cohorts that included whites and blacks, ARIC and CHS.<sup>24</sup> The incidence increased with advancing age (HR, 1.73 [95% CI, 1.47–2.05] per 5-year increment), and blacks were at 41% lower risk of sick sinus syndrome than their white counterparts (HR, 0.59 [95% CI, 0.37–0.98]). Investigators projected that in the United States, the number of new cases of sick sinus syndrome per year would rise from 78 000 in 2012 to 172 000 in 2060.<sup>24</sup>

### **Risk Factors**

- The causes of sinus node dysfunction can be classified as intrinsic (secondary to pathological conditions involving the sinus node) or extrinsic (caused by depression of sinus node function by external factors such as drugs or autonomic influences).<sup>25</sup>
- Idiopathic degenerative disease is probably the most common cause of sinus node dysfunction.<sup>26</sup>
- Investigators collected data from 28 different studies on atrial pacing for sinus node dysfunction that showed a median annual incidence of second- and third-degree AV block of 0.6% (range, 0%–4.5%) and an overall prevalence of 2.1% (range, 0%–11.9%). This suggests that the degenerative process also affects the specialized conduction system, although the rate of progression is slow and does not dominate the clinical course of disease.<sup>27</sup>
- In the CHS and ARIC studies, factors associated with incident sick sinus syndrome included white (versus black) race, higher mean BMI, height, prevalent hypertension, lower heart rate, right bundle-branch block, N-terminal pro-BNP, cystatin C, and history of a major cardiovascular event.<sup>24</sup>

### **Complications**

#### **(See Chart 16-2)**

- The survival of patients with sinus node dysfunction appears to depend primarily on the severity of underlying cardiac disease, is not different from survival in the general population when treated with pacemaker, and is not significantly changed by type of pacemaker therapy.<sup>28–30</sup>
- In a retrospective study<sup>31</sup> of patients with sinus node dysfunction who had pacemaker therapy, mortality among those with ventricular pacing only was 63% compared with 40% among those with DDD pacing at 7-year follow-up.
- In 19893 males and females >45 years of age from the ARIC and CHS cohorts, incidence of sick sinus syndrome was associated with increased mortality (HR, 1.4 [95% CI, 1.1–1.7]), CHD (HR, 1.7 [95% CI, 1.1–2.7]), HF (HR, 2.9 [95% CI, 2.2–3.8]), stroke (HR, 1.6 [95% CI, 1.0–2.5]), AF (HR, 5.8

- [95% CI, 4.4–7.5]), and pacemaker implantation (HR, 53.7 [95% CI, 42.9–67.2]).<sup>32</sup>
- In a multicenter study from the Netherlands of people with bradycardia treated with pacemaker implantation, the actuarial 1-, 3-, 5-, and 7-year survival rates were 93%, 81%, 69%, and 61%, respectively. Individuals without CVD at baseline had similar survival rates as age- and sex-matched control subjects.<sup>33</sup>
  - With sinus node dysfunction, the incidence of sudden death is extremely low, and pacemaker implantation does not appear to alter longevity.<sup>12,34</sup> SVT including AF was prevalent in 53% of patients with sinus node dysfunction.<sup>29</sup>
  - On the basis of records from the NIS, pacemaker implantation rates per million increased from 467 in 1993 to 616 in 2009, although overall use plateaued in 2001. The patients' mean age and number of comorbidities at implantation increased over time. Total hospital charges associated with pacemaker implantation increased 45% from \$53 693 in 1993 to \$78 015 in 2009 (in 2011 dollars).<sup>35</sup>
  - On the basis of NHDS data, the escalating implantation rate was attributable to increasing implantation for isolated sinus node dysfunction; implantation for sinus node dysfunction increased by 102%, whereas implantation for all other indications did not increase (Chart 16-2).<sup>36</sup>
  - In 5831 participants of the MESA cohort, a heart rate <50 beats per minute was not associated with mortality or incident CVD among individuals not taking heart rate-modifying drugs compared with those with heart rate between 50 and 59 beats per minute.<sup>37</sup>

## SVT (Excluding AF and Atrial Flutter)

**ICD-9 427.0; ICD-10 I47.1.**

2017: Mortality—179. Any-mention mortality—1511.

2016: Hospital discharges—40 000 (18 000 male; 22 000 female).

### Prevalence and Incidence

(See Chart 16-3)

- Data from the Marshfield Epidemiologic Study Area in Wisconsin suggested the incidence of documented paroxysmal SVT was 35 per 100 000 person-years, whereas the prevalence was 225 per 100 000 people. The mean age at SVT onset was 57 years, and both female sex (RR, 2.0) and age ≥65 years (versus <65 years: RR, 5.3) were significant risk factors (Chart 16-3).<sup>38</sup>
- A review of ED visits in US hospitals using NHAMCS data from 1993 to 2003 revealed that an estimated 550 000 visits were for SVT (0.05% of all visits [95% CI, 0.04%–0.06%]), or ≈50 000 visits

per year (incidence rate of 1.8 ED visits per 10 000 person-years [95% CI, 1.4–2.3]). Of these patients, 24% (95% CI, 15%–34%) were admitted to the hospital, and 44% (95% CI, 32%–56%) were discharged without specific follow-up.<sup>39</sup> Rates were higher in individuals ≥65 years of age than in those <65 years of age (3.9 versus 1.5 per 10 000 person-years) and lower in males than in females (1.1 versus 2.6 per 10 000 person-years).

- The prevalence of SVT that is clinically undetected is likely much greater than the estimates from ED visits and electrophysiology procedures would suggest. Among 26 751 individual patients receiving a Zio Patch monitor for clinical indications, prevalence of SVT (defined as at least a single run of ≥8 beats) was 31%.<sup>40</sup>
- Of 1383 participants in the Baltimore Longitudinal Study of Aging undergoing maximal exercise testing, 6% exhibited SVT during the test; increasing age was a significant risk factor. Only 16% exhibited >10 beats of SVT, and only 4% were symptomatic. Over an average of 6 years of follow-up, people with exercise-induced SVT were more likely to develop SVT or AF.<sup>41</sup>
- In a study of 3554 consecutive males 17 to 21 years of age applying for a pilot's license and 3700 symptomatic arrhythmia patients, the surface ECG revealed that the prevalence of ectopic atrial tachycardia was estimated to be 0.34% in asymptomatic applicants and 0.46% in symptomatic applicants.<sup>42</sup>

### Complications

- Rare cases of incessant SVT can lead to a tachycardia-induced cardiomyopathy,<sup>43</sup> and rare cases of sudden death attributed to SVT as a trigger have been described.<sup>44</sup>
- Among 2 350 328 pregnancies included in Taiwan's national insurance database between 2001 and 2012, 769 females experienced paroxysmal SVT during pregnancy. Compared with those females without paroxysmal SVT during pregnancy, paroxysmal SVT during pregnancy was associated with a higher risk for poor maternal outcomes (severe morbidity and cesarean delivery) and poor fetal outcomes (low birth weight, preterm labor, fetal stress, and obvious fetal abnormalities).<sup>45</sup>
- A California administrative database study of almost 5 million patients suggested that after the exclusion of people with diagnosed AF, SVT was associated with an adjusted doubling of the risk of stroke in follow-up (HR, 2.10 [95% CI, 1.69–2.62]). The absolute stroke rate was low, however. The cumulative stroke rate was 0.94% (95% CI, 0.76%–1.16%) over 1 year in patients with SVT

versus 0.21% (95% CI, 0.21%–0.22%;  $P<0.001$ , log-rank test) in those without SVT.<sup>46</sup>

- In a Swedish study of 214 patients (51% females) with paroxysmal SVT undergoing ablation, females had a longer history of symptomatic arrhythmia ( $16.2\pm14.6$  versus  $9.9\pm13.1$  years), were more likely to report not being taken seriously when consulting for their symptoms (17% versus 7%), and were more symptomatic after 6 months of ablation than males.<sup>47</sup>

### Specific Types

- Among those presenting for invasive electrophysiological study and ablation, AV nodal reentrant tachycardia (a circuit that requires 2 AV nodal pathways) is the most common mechanism of SVT<sup>48,49</sup> and usually represents the majority of cases (56% in one series of 1754 cases).<sup>49</sup>
- AV reentrant tachycardia (an arrhythmia that requires the presence of an extranodal connection between the atria and ventricles or specialized conduction tissue) is the second most common type of SVT (27% in a study by Porter et al<sup>49</sup>), and atrial tachycardia is the third most common (17% in a series of 1754 SVT cases from Porter et al<sup>49</sup>).
- In a US-based national pediatric electrophysiology registry study, AV reentrant tachycardia was the most common SVT mechanism (68%), whereas the remainder of the patients had AV nodal reentrant tachycardia (32%).<sup>50</sup>
- AV reentrant tachycardia prevalence decreases with age, whereas AV nodal reentrant tachycardia and atrial tachycardia prevalence increase with advancing age.<sup>49</sup>
- The majority of patients with AV reentrant tachycardia were males (55%), whereas females constituted the majority with AV nodal reentrant tachycardia (70%) or atrial tachycardia (62%) in the study by Porter et al.<sup>49</sup>
- Multifocal atrial tachycardia is an arrhythmia that is commonly confused with AF and is characterized by 3 distinct P-wave morphologies, irregular R-R intervals, and a rate >100 beats per minute. It is uncommon in both children<sup>51</sup> and adults,<sup>52</sup> with a prevalence in hospitalized adults estimated at 0.05% to 0.32%.<sup>52</sup> The average age of onset in adults is 72 years. Adults with multifocal atrial tachycardia have a high mortality rate, with estimates around 45%, but this is generally ascribed to the underlying condition(s).<sup>52</sup> In a study of older ambulatory adults in Greece, the mortality in follow-up did not differ by whether or not multifocal atrial rhythms were detected on baseline ECG.<sup>53</sup>

### WPW Syndrome

#### Prevalence

- A WPW electrocardiographic pattern was observed in 0.11% of males and 0.04% of females among

47358 ECGs from adults participating in 4 large Belgian epidemiological studies.<sup>54</sup> In a study of 32837 Japanese students who were required by law to receive ECGs before entering school, a WPW electrocardiographic pattern was reported in 0.07%, 0.07%, and 0.17% of elementary, junior high, and high school students, respectively.<sup>55</sup>

#### Complications

- WPW syndrome, a diagnosis reserved for those with both ventricular preexcitation (evidence of an anterograde conducting AV accessory pathway on a 12-lead ECG) and tachyarrhythmias, deserves special attention because of the associated risk of sudden death. Sudden death is generally attributed to rapid heart rates in AF conducting down an accessory pathway and leading to VF.<sup>56</sup>
- A cohort study from Intermountain Healthcare with ≈8 years of follow-up reported that rates of cardiac arrest were low and similar between WPW and control patients without WPW. In follow-up, WPW was associated with a significantly higher risk of AF (HR, 1.55 [95% CI, 1.29–1.87]); 7.0% of the WPW patients developed AF compared with 3.8% of those without WPW.<sup>57</sup>
- Asymptomatic adults with ventricular preexcitation appear to be at no increased risk of sudden death compared with the general population.<sup>58,59</sup>
- In a single-center prospective registry study of 2169 patients who agreed to undergo an electrophysiology study for WPW syndrome from 2005 to 2010, 1168 patients (206 asymptomatic) underwent radiofrequency ablation, none of whom had malignant arrhythmias or VF in up to 8 years of follow-up. Of those who did not receive radiofrequency ablation (n=1001; 550 asymptomatic) in follow-up, 1.5% had VF, most of whom (13 of 15) were children. The authors noted that poor prognosis was related to accessory pathway electrophysiological properties rather than patient symptoms.<sup>60</sup>
- In a meta-analysis of 20 studies involving 1869 asymptomatic patients with a WPW electrocardiographic pattern followed up for a total of 11722 person-years, the rate of sudden death in a random effects model that was used because of heterogeneity across studies was estimated to be 1.25 (95% CI, 0.57–2.19) per 1000 person-years. Risk factors for sudden death included male sex, inclusion in a study of children (<18 years of age), and inclusion in an Italian study.<sup>61</sup>
- Several studies in asymptomatic children with ventricular preexcitation detected by screening suggested a benign prognosis.<sup>59,62</sup> A referral-based registry study reported that electrophysiological testing can identify a group of asymptomatic

children with a risk of sudden death or VF as high as 11% over 19 months of follow-up.<sup>63</sup> In a pediatric hospital retrospective review of 446 children with WPW syndrome, 64% were symptomatic at presentation, and 20% had onset of symptoms during a median of 3 years of follow-up. The incidence of sudden death was 1.1 per 1000 person-years in patients without structural HD.<sup>64</sup>

## AF and Atrial Flutter

### Prevalence

- The prevalence of AF in the United States was estimated to rise from ≈5.2 million in 2010 to 12.1 million in 2030.<sup>65</sup>
- In the European Union, the prevalence of AF in adults >55 years of age was estimated to be 8.8 million (95% CI, 6.5–12.3 million) in 2010 and was projected to rise to 17.9 million in 2060 (95% CI, 13.6–23.7 million).<sup>66</sup>
- Data from a California health plan suggested that compared with whites, blacks (OR, 0.49 [95% CI, 0.47–0.52]), Asians (OR, 0.68 [95% CI, 0.64–0.72]), and Hispanics (OR, 0.58 [95% CI, 0.55–0.61]) have a significantly lower adjusted prevalence of AF.<sup>67</sup>
- Among Medicare patients ≥65 years of age who were diagnosed from 1993 to 2007, the prevalence of AF increased ≈5% per year, from 41.1 per 1000 beneficiaries to 85.5 per 1000 beneficiaries.<sup>68</sup>
  - In 2007 in the 5% Medicare sample, there were 105 701 older adults with AF: 3.7% were black, 93.8% were white, and 2.6% were other/unknown race.<sup>68</sup>
  - The prevalence rate per 1000 beneficiaries was 46.3 in blacks, 90.8 in whites, and 47.5 in other/unknown race.<sup>68</sup>
- In an analysis involving the entire South Korean population, prevalence of AF more than doubled, from 0.73% in 2006 to 1.53% in 2015, and was estimated to reach 5.81% in 2060.<sup>69</sup>

### Incidence

#### (See Table 16-1 and Chart 16-4)

- In a Medicare sample, per 1000 person-years, the age- and sex-standardized incidence of AF was 27.3 in 1993 and 28.3 in 2007, representing a 0.2% mean annual increase ( $P=0.02$ ).<sup>68</sup>
- Investigators from MESA estimated the age- and sex-adjusted incidence rate of hospitalized AF per 1000 person-years (95% CI) as 11.2 (9.8–12.8) in NH whites, 6.1 (4.7–7.8) in Hispanics, 5.8 (4.8–7.0) in NH blacks, and 3.9 (2.5–6.1) in Chinese.<sup>70</sup>
- Data from California administrative databases were analyzed with regard to racial variation in incidence of AF. After adjustment for AF risk factors, compared with their white counterparts,

lower incidence rates were found in blacks (HR, 0.84 [95% CI, 0.82–0.85];  $P<0.001$ ), Hispanics (HR, 0.78 [95% CI, 0.77–0.79];  $P<0.001$ ), and Asians (HR, 0.78 [95% CI, 0.77–0.79];  $P<0.001$ ; Chart 16-4).<sup>71</sup>

- Racial variation in AF incidence is also observed in other countries. For instance, in a study of the UK Clinical Practice Research Datalink cohort ≥45 years of age, the incidence rates per 1000 person-years standardized to the UK population were 8.1 (95% CI, 8.1–8.2) in whites versus 5.4 (95% CI, 4.6–6.3) in Asians and 4.6 (95% CI, 4.0–5.3) in black patients.<sup>72</sup>
- Using data from a health insurance claims database covering 5% of the United States, the incidence of AF was estimated at 1.2 million new cases in 2010 and was projected to increase to 2.6 million new cases in 2030.<sup>65</sup>
- In an analysis involving the entire South Korean population, incidence of AF between 2006 and 2015 has remained flat, with an overall incidence during this period of 1.77 new cases per 1000 person-years.<sup>69</sup>

### Lifetime Risk and Cumulative Risk

#### (See Chart 16-5)

- In studies from FHS and the BiomarCaRE Consortium, the lifetime risk for AF in individuals of European ancestry was estimated to be ≈1 in 3.
  - In the BiomarCaRE study based on 4 European community-based studies, the incidence increased after 50 years of age in males and 60 years in females, but the cumulative incidence of AF was similar, at >30%, by 90 years of age.<sup>73</sup>
  - In an FHS report based on participants with DNA collected after 1980, the lifetime risk of AF after 55 years of age was 37.1%, which was influenced by both clinical and genetic risk.<sup>74</sup> In a subsequent study from FHS, the lifetime risk of AF varied by risk factor burden. In individuals with optimal risk profile, the lifetime risk was 23.4% (95% CI, 12.8%–34.5%), whereas the risk was 33.4% (95% CI, 27.9%–38.9%) with a borderline risk profile and 38.4% (95% CI, 35.5%–41.4%) with an elevated risk profile (Chart 16-5).<sup>75</sup>
- In a medical insurance database study from the Yunnan Province in China, the estimated lifetime risk of AF at 55 years of age was 21.1% (95% CI, 19.3%–23.0%) for females and 16.7% (95% CI, 15.4%–18.0%) for males.<sup>76</sup> In a Taiwanese study, the lifetime risk of AF was estimated to be 16.9% (95% CI, 16.7%–14.2%) in males and 14.6% (95% CI, 14.4%–14.9%) in females.<sup>77</sup>
- Investigators from the NHLBI-sponsored ARIC study observed that the lifetime risk of AF was 36% in

white males (95% CI, 32%–38%), 30% in white females (95% CI, 26%–32%), 21% in black males (95% CI, 13%–24%), and 22% in black females (95% CI, 16%–25%).<sup>78</sup>

### **Secular Trends**

- During 50 years of observation of the FHS (1958–1967 to 1998–2007), the age-adjusted prevalence and incidence of AF approximately quadrupled. However, when only AF that was ascertained on ECGs routinely collected in the FHS was considered, the prevalence but not the incidence increased, which suggests that part of the changing epidemiology was attributable to enhanced surveillance. Although the prevalence of most risk factors changed over time, the hazards associated with specific risk factors did not change. Hence, the PAR associated with BMI, hypertension treatment, and DM increased (consistent with increasing prevalence). Over time, the multivariable-adjusted hazards of stroke and mortality associated with AF declined by 74% and 25%, respectively.<sup>79</sup>
- Between 2000 and 2010 in Olmsted County, MN, age- and sex-adjusted incidence rates and survival did not change over time.<sup>80</sup> However, over a similar time frame in the United Kingdom (2001–2013), the incidence of nonvalvular AF in people  $\geq 45$  years of age increased modestly from 5.9 (95% CI, 5.8–6.1) to 6.9 (95% CI, 6.8–7.1) per 1000 patient-years, with the largest increase observed in those  $>80$  years of age.<sup>72</sup>
- In data from the ARIC study, the prevalence of AF in the setting of MI increased slightly, from 11% to 15%, between 1987 and 2009; however, the increased risk of death (OR, 1.47 [95% CI, 1.07–2.01]) in the year after MI accompanied by AF did not change over time.<sup>81</sup>
- Between 1999 and 2013, among Medicare fee-for-service beneficiaries, rates of hospitalization for AF increased  $\approx 1\%$  per year. Although the median hospital length of stay, 3 days (IQR, 2.0–5.0 days), did not change, the mortality declined by 4% per year, and hospital readmissions at 30 days declined by 1% per year. During the same years, median Medicare inpatient costs per hospitalization increased substantially, from \$2932 (IQR, \$2232–\$3870) to \$4719 (IQR, \$3124–\$7209).<sup>82</sup>
- Similar trends have been observed globally. For instance, on the basis of data from a national health insurance database, in Korea between 2006 and 2015 the prevalence of AF increased 2.10-fold, and the incidence remained flat (1.8 per 1000 person-years), whereas the mortality rate (HR, 0.70 [95% CI, 0.68–0.93]) and ischemic stroke rate (HR, 0.91 [95% CI, 0.88–0.93]) after

AF declined. Investigators projected that the adult prevalence of AF would reach 5.8% in 2060.<sup>69</sup>

### **Risk Factors (See Chart 16-6)**

- The highest PAF for AF was hypertension, followed by BMI, smoking, cardiac disease, and DM in ARIC (Chart 16-6).

### **BP and Hypertension**

- Hypertension accounted for  $\approx 22\%$ <sup>83</sup> of AF cases.
- In MESA, the PAF of AF attributable to hypertension appeared to be higher in US NH blacks (33.1%), Chinese (46.3%), and Hispanics (43.9%) than in NH whites (22.2%).<sup>70</sup>

### **BMI and Obesity**

- In a meta-analysis of 16 studies involving >580 000 individuals, of whom  $\approx 91 000$  had obesity, AF developed in 6.3% of those who had obesity and 3.1% of those without it. Individuals with obesity had an RR of 1.51 for developing AF (95% CI, 1.35–1.68) compared with those without obesity.<sup>84</sup>
- Another meta-analysis of 29 studies examined various anthropometric components in relation to incident AF. A 5 kg/m<sup>2</sup> increment in BMI was associated with an RR of 1.28 (95% CI, 1.20–1.38) in relation to AF. The risk was nonlinear ( $P<0.0001$ ), with stronger associations observed at higher BMIs, but a BMI of 22 to 24 kg/m<sup>2</sup> was still associated with excess risk compared with a BMI of 20 kg/m<sup>2</sup>. Waist, waist-hip ratio, fat mass, and waist gain were also associated with increased risk of AF.<sup>85</sup>
- A causal relationship between higher BMI and incident AF gained further support from a genetic mendelian randomization study, which observed that a BMI GRS that included 39 SNPs was associated with a higher risk of AF.<sup>86</sup>

### **Smoking**

- A meta-analysis of 29 studies from 22 publications revealed that smoking was associated with an increased risk of AF. Compared to never-smokers, the RR of current smoking was 1.32 (95% CI, 1.12–1.56), former smoking was 1.09 (95% CI, 1.00–1.18), and ever smoking was 1.21 (95% CI, 1.12–1.31). There appeared to be a dose-response relationship such that the RR per 10 cigarettes per day was 1.14 (95% CI 1.10–1.20), and the RR per 10 pack-years was 1.16 (95% CI, 1.09–1.25).<sup>87</sup>

### **DM and HbA<sub>1c</sub>**

- In a meta-analysis restricted to prospective studies, HbA<sub>1c</sub> was associated with an increased risk of AF when analyzed as a continuous (RR, 1.11 [95% CI, 1.06–1.16]) or categorical (RR, 1.09 [95% CI, 1.00–1.18]) variable.<sup>88</sup>

- In a meta-analysis of observational studies (excluding a large outlier study) the RR of incident AF was 1.28 (31 cohort studies [95% CI, 1.22–1.35]) for DM and 1.20 (4 studies [95% CI, 1.03–1.39]) for prediabetes.<sup>89</sup>
- A machine learning meta-analysis reported similar risks of incident AF in individuals with type 1 and type 2 DM. However, compared with males with DM (RR, 1.11 [95% CI, 1.01–1.22]), females with DM appeared to have a higher risk (RR, 1.38 [95% CI, 1.19–1.60]) of incident AF.<sup>90</sup>

### *Activity and Exercise*

- A multiracial longitudinal study from Detroit, MI, reported a dose-response relation between objectively assessed exercise capacity and lower risk of new-onset AF.<sup>91</sup> In unadjusted analyses, the incidence rates of AF over 5 years were 3.7%, 5.0%, 9.5%, and 18.8% for >11, 10 to 11, 6 to 9, and <6 METs, respectively. Every 1-higher peak MET was associated with an adjusted 7% lower risk of AF (HR, 0.93 [95% CI, 0.92–0.94]). The protective association of fitness was observed in all subgroups examined but was particularly beneficial in obese individuals.
- Whereas regular PA is associated with lower risk of AF, a meta-analysis of 9 studies supports that athletes have a higher risk of AF than the general population (OR, 2.34 [95% CI, 1.04–5.28]). However, the investigators reported substantial heterogeneity in the data, with the highest risks observed among males and individuals <60 years of age.<sup>92</sup>

### *Miscellaneous Risk Factors*

- Other consistently reported risk factors for AF include clinical and subclinical hyperthyroidism,<sup>93</sup> CKD,<sup>94,95</sup> and moderate<sup>96</sup> or heavy alcohol consumption.<sup>97</sup>
- In a meta-analysis of 8 studies, the sleep apnea-hypopnea syndrome was associated with an increased risk of AF after adjustment for confounders (RR, 1.40 [95% CI, 1.12–1.74];  $P<0.001$ ).<sup>98</sup> A meta-analysis of 3 studies of sleep quality also reported an association between insomnia and increased odds of AF (OR, 1.30 [95% CI, 1.26–1.35]) of AF.<sup>99</sup>
- Air pollution:
  - Investigators from the Danish Diet, Cancer, and Health cohort reported that individuals with higher exposure to NO<sub>2</sub>, a traffic-related air pollutant, had higher risk of AF (adjusted IRR, 1.08 [95% CI, 1.01–1.14] per 10  $\mu\text{g}/\text{m}^3$  higher 10-year time-weighted mean exposure to NO<sub>2</sub>).<sup>100</sup>
  - Using the Korean National Health Insurance Service investigators similarly reported that

per 10  $\mu\text{g}/\text{m}^3$  increments, both fine particles (PM<sub>2.5</sub>, or those  $\leq 2.5 \mu\text{m}$  in diameter; HR, 1.179 [95% CI, 1.176–1.183]) and coarse dust particles (PM<sub>10</sub>, or those 2.5–10  $\mu\text{m}$  in diameter; HR, 1.034 [95% CI, 1.033–1.036]) were associated with incident AF.<sup>101</sup>

- There is increasing research on the relation between social determinants of health and AF risk. In a study from REGARDS, involuntary unemployment was associated with increased risk of prevalent (OR, 1.60 [95% CI, 1.24–2.07]) and incident (OR, 1.54 [95% CI, 1.04–2.37]) AF.<sup>102</sup>
- AF frequently occurs secondary to other comorbidities.
  - In the FHS, 31% of AF was diagnosed in the context of a secondary, reversible condition. The most common triggers of AF were cardiothoracic surgery (30%), infection (23%), and AMI (18%). Paroxysmal AF in the context of a secondary precipitant frequently recurred over follow-up.<sup>103</sup>
  - Sepsis is associated with an increased risk of AF. In a Medicare sample, 25.5% of patients with sepsis had AF; 18.3% of AF was pre-existing, and 7.2% was newly diagnosed.<sup>104</sup> AF occurring in the context of sepsis is associated with an increased risk of stroke and death.<sup>105</sup>
  - A meta-analysis reported that new-onset AF has been observed in 10.9% of patients undergoing noncardiac general surgery.<sup>106</sup>
  - AF also occurs after CABG, with a risk-adjusted incidence of 33.1%, which has not varied over time.<sup>107</sup>
- Prevalence of AF is particularly elevated in adults with congenital HD.<sup>108</sup>

### *Risk Prediction of AF*

- Life's Simple 7:
  - In the biracial REGARDS study, better CVH, as classified by Life's Simple 7, predicted decreased risk of AF similarly between sexes and in blacks and whites. Individuals with optimal CVH (score 10–14 points) had an adjusted 32% lower risk of AF (OR, 0.68 [95% CI, 0.47–0.99]).<sup>109</sup>
  - The ARIC study, which includes white and black participants, also observed that patients with average (HR, 0.59 [95% CI, 0.51–0.67]) and optimal (HR, 0.38 [95% CI, 0.32–0.44]) CVH had a lower risk of incident AF. For every 1-point higher Life's Simple 7 score, the risk of AF was 12% lower (HR, 0.88 [95% CI, 0.86–0.89]).<sup>110</sup>
- ARIC,<sup>111</sup> the FHS,<sup>112</sup> and the WHS<sup>113</sup> have developed risk prediction models to predict new-onset

AF. Predictors of increased risk of new-onset AF include advancing age, European ancestry, body size (greater height and BMI), electrocardiographic features (LVH, left atrial enlargement), DM, BP (SBP and hypertension treatment), and presence of CVD (CHD, HF, valvular HD).

- More recently, the ARIC, CHS, and FHS investigators developed and validated a risk prediction model for AF in blacks and whites, which was replicated in 2 European cohorts.<sup>114</sup> The CHARGE-AF model has been validated in US multiethnic cohorts including Hispanics,<sup>115</sup> in MESA,<sup>116</sup> in a UK cohort (EPIC Norfolk),<sup>117</sup> and in a post-CABG cohort.<sup>118</sup>

### **Borderline Risk Factors**

- Data from the ARIC study indicated that having at least 1 elevated risk factor explained 50% and having at least 1 borderline risk factor explained 6.5% of incident AF cases. The estimated overall incidence rate per 1000 person-years at a mean of 54.2 years of age was 2.19 for those with optimal risk, 3.68 for those with borderline risk, and 6.59 for those with elevated risk factors.<sup>83</sup>

### **Subclinical Atrial Tachyarrhythmias, Unrecognized AF, Screening for AF**

#### **Device-Detected AF**

- Cardiac implantable electronic devices (eg, pacemakers and defibrillators) have increased clinician awareness of the frequency of subclinical AF and atrial high-rate episodes in people without a documented history of AF.
- In a meta-analysis of 28 studies including patients with pacemakers or defibrillators followed up for a mean of 22 months, new-onset device-detected atrial tachyarrhythmias were observed in 23% of patients. In 9 studies, device-detected atrial tachyarrhythmias were associated with a 2.88 (95% CI, 1.79–4.64;  $P<0.001$ ) RR of thromboembolism, which was higher with longer duration ( $\geq 5$  minutes RR, 3.86 versus <1 minute RR, 1.77).<sup>119</sup>
- Another meta-analysis reported that high atrial rate episodes detected by cardiac implantable electronic devices were associated with higher risk of clinical AF (n=2 studies, including 2892 participants; OR, 5.7 [95% CI, 4.0–8.0];  $P<0.001$ ) and a higher risk of stroke (n=7 studies, including 17247 participants; OR, 2.4 [95% CI, 1.8–3.3];  $P<0.001$ ). The annual stroke rate was 1.89 with versus 0.93/100 person-years without high atrial rate episodes.<sup>120</sup>
- The temporal association of AF and stroke risk was evaluated in a case-crossover analysis among 9850 patients with cardiac implantable electronic devices enrolled in the Veterans Health Administration healthcare system. The OR for an acute ischemic

stroke was the highest within a 5-day period after a qualifying AF episode, which was defined as at least 5.5 hours of AF on a given day. This estimate reduced as the period after the AF occurrence extended beyond 30 days.<sup>121</sup>

#### **Community Screening**

- The prevalence of undiagnosed AF in the community is unknown. Using Medicare and commercials claims data, investigators have estimated that in 2009,  $\approx 0.7$  million (13.1%) of the  $\approx 5.3$  million AF cases in the United States were undiagnosed. Of the undiagnosed AF cases, investigators estimated 535 400 (95% CI, 331 900–804 400; 1.3%) were in individuals  $\geq 65$  years of age, and 163 500 (95% CI, 17 700–400 000; 0.09%) were in individuals 18 to 64 years of age.<sup>122</sup>
- The incidence of detecting previously undiagnosed AF by screening depends on the underlying risk of AF in the population studied, the intensity and duration of screening, and the method used to detect AF.<sup>123</sup>
- Methods vary in their sensitivity and specificity in the detection of undiagnosed AF, increasing from palpation, to devices such as handheld single-lead ECGs, modified BP devices, and plethysmographs.<sup>123</sup>
- There has been increasing interest in the use of smart phone technology to aid in community screening.<sup>124,125</sup>
- In a community-based study in Sweden (STROKESTOP), half of the population 75 to 76 years of age were invited to a stepwise screening program for AF, and 7173 participated in the screening, of whom 218 had newly diagnosed AF (3.0% [95% CI, 2.7%–3.5%]) and an additional 666 (9.3% [95% CI, 8.6%–10.0%]) had previously diagnosed AF. Of the 218 newly diagnosed AF cases, only 37 were diagnosed by initial screening electrocardiography, whereas intermittent monitoring detected 4 times as many cases. Of those individuals with newly diagnosed AF, 93% initiated treatment with oral anticoagulant drugs.<sup>126</sup>
- There have been several systematic reviews regarding the effectiveness of screening to detect unknown AF.
  - Lowres et al<sup>127</sup> identified 30 separate studies that included outpatient clinics or community screening. In individuals without a prior diagnosis of AF, they observed that 1.0% (95% CI, 0.89%–1.04%) of those screened had AF (14 studies, N=67 772), whereas among those individuals  $\geq 65$  years of age, 1.4% (95% CI, 1.2%–1.6%; 8 studies, N=18 189) had AF.
  - Another systematic review by Moran et al<sup>128</sup> observed that in individuals  $>65$  years of

age, systematic screening (OR, 1.57 [95% CI, 1.08–2.26]) and opportunistic screening (OR, 1.58 [95% CI, 1.10–2.29]) were associated with enhanced detection of AF. The number needed to screen by either method was ≈170 individuals.

- A systematic review by the US Preventive Services Task Force of asymptomatic adults at least 65 years of age included 17 studies (135 300 individuals). Compared with no screening, systematic screening with ECG detected more new cases of AF (over 1 year, absolute increase from 0.6% [95% CI, 0.1%–0.9%] to 2.8% [95% CI, 0.9%–4.7%]). However, the systematic ECGs did not detect more cases than pulse palpation. Furthermore, none of the studies compared systematic screening versus usual care, and none examined health outcomes.<sup>129</sup>
- At present, the detection of AF, even in an asymptomatic stage, is the basis for risk stratification for stroke and appropriate decision making on the need for anticoagulant drugs. Ongoing trials are evaluating the risks and benefits of anticoagulation among patients at high risk for stroke but without a prior history of AF. The findings from these studies will help to determine optimal strategies for subclinical AF screening and treatment.<sup>123</sup> To date, no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications.

### **Family History and Genetics**

- Although unusual, early-onset lone AF has long been recognized to cluster in families.<sup>12,130</sup> In the past decade, the heritability of AF in the community has been appreciated.
- In studies from the FHS:
  - Adjusted for coexistent risk factors, having at least 1 parent with AF was associated with a 1.85-fold increased risk of AF in the adult offspring (multivariable-adjusted 95% CI, 1.12–3.06;  $P=0.02$ ).<sup>131</sup>
  - A history of a first-degree relative with AF also was associated with an increased risk of AF (HR, 1.40 [95% CI, 1.13–1.74]). The risk was greater if the first-degree relative's age of onset was  $\leq 65$  years (HR, 2.01 [95% CI, 1.49–2.71]) and with each additional affected first-degree relative (HR, 1.24 [95% CI, 1.05–1.46]).<sup>132</sup> Similar findings were reported from Sweden.<sup>133</sup>
- A prospectively enrolled University of Illinois at Chicago AF Registry revealed that individuals with early-onset AF in the absence of structural HD had a 3-fold adjusted odds of having a first-degree

relative with AF (adjusted OR, 3.02 [95% CI, 1.82–4.95];  $P<.001$ ) compared with individuals with AF without early-onset AF. Higher odds of having a proband with AF in the setting of early-onset AF were observed in individuals of African (OR, 2.69), Hispanic (OR, 9.25), and European (OR, 2.51) descent.<sup>134</sup>

- A Taiwanese population-based study reported that a history of a first-degree relative with AF was associated with a 1.92-fold (95% CI, 1.84–1.99) increased risk of newly diagnosed AF. They estimated that 19.9% of the increased risk was attributable to genetic (heritability) factors, with the remaining risk related to shared (3.5%) and non-shared (76.5%) environmental factors.<sup>135</sup>
- A study from the UK Biobank estimated that the heritability of AF was 22.1% (95% CI, 15.6%–28.5%). The heritability was similar by sex and in older ( $>65$  years) versus younger ( $\leq 65$  years) people. Most of the variation was explained by common (minor allele frequency  $\geq 5\%$ ) genetic variation.<sup>136</sup>
- Racial variation in AF incidence is complex and not fully understood. One study of blacks and whites from CHS and ARIC suggested that genetic markers of European ancestry were associated with an increased risk of incident AF.<sup>137</sup>
- A GWAS that included  $>65\,000$  patients with AF reported 97 AF-associated loci, 67 of which were novel in combined-ancestry analyses.<sup>138</sup> Another recent GWAS of  $>1\,000\,000$  individuals identified 111 independent genes associated with AF, many of which are near deleterious mutations that cause more serious heart defects or genes important for striated muscle function and integrity.<sup>139</sup>
- Whole exome/genome sequencing studies have identified rare mutations in additional genes, including *MYL4*.<sup>140</sup>
- Additional rare mutations identified from other studies include *SCN4B* and *KCNA5*, a conserved gene that encodes the voltage-gated Kv1.5 potassium channel; loss-of-function mutations in these genes have been shown to be associated with AF.<sup>141,142</sup> Recently, loss-of-function variants in the titin gene have been associated with early-onset AF.<sup>143,144</sup>
- Investigators in the FHS examined the lifetime risk of AF at 55 years of age using both clinical and genetic risk factors. They derived polygenic risk scores of 1000 variants (many were subthreshold hits) associated with AF in the UK Biobank. They divided participants into tertiles of clinical and genetic risk and reported that individuals within the lowest tertile of clinical and of polygenic risk had a lifetime risk of AF of 22.3% (95% CI, 15.4%–29.1%), whereas those in the highest

- tertile of clinical and polygenic risk had a lifetime risk of 48.2% (95% CI, 41.3%–55.1%).<sup>74</sup>
- Some studies suggest that genetic markers of AF could improve risk prediction for AF over models that include clinical factors.<sup>113</sup>
  - GRS could also identify patients at higher risk of cardioembolic stroke<sup>145</sup>; however, the utility of clinical genetic testing for AF-related genetic variants is currently unclear.
  - SNPs associated with increased risk of AF are also associated with increased risk of AF recurrence after catheter ablation<sup>146</sup> and after CABG.<sup>147</sup>

### **Prevention: Observational Data**

#### *Primary Prevention of AF: Observational Data*

- An observational prospective Swedish study revealed that individuals having bariatric surgery had a 29% lower risk (HR, 0.71 [95% CI, 0.60–0.83];  $P<0.001$ ) of developing AF in 19 years of median follow-up than matched referents.<sup>148</sup>

#### *Secondary Prevention of AF: Observational Data*

- There are increasingly more data supporting the importance of risk factor modification for secondary prevention of AF recurrence and improved symptoms.
  - In individuals referred for catheter ablation, those who agreed to aggressive risk factor modification had lower symptom burden in follow-up and higher adjusted AF-free survival (HR, 4.8 [95% CI, 2.0–11.4];  $P<0.001$ ).<sup>149</sup>
  - The same Australian investigators reported that overweight and obese individuals with symptomatic AF who opted to participate in weight loss and aggressive risk factor management interventions had fewer hospitalizations, cardioversions, and ablation procedures than their counterparts who declined enrollment. The risk factor management group was associated with a predicted 10-year cost savings of \$12 094 per patient.<sup>150</sup>
  - In adjusted analyses, overweight and obese individuals with paroxysmal or persistent AF who achieved at least 10% weight loss were 6-fold more likely to be AF free (86.2% AF free; HR, 5.9 [95% CI, 3.4–10.3];  $P<0.001$ ) than those with <3% weight loss (39.6% AF free). In addition, individuals losing at least 10% weight reported fewer symptoms.<sup>151</sup>
  - The same Australian group also reported that among consecutive overweight and obese patients with AF who agreed to participate in an exercise program, those who achieved less improvement in cardiorespiratory fitness (<2 METs gained) had lower AF-free survival (40%; HR, 3.9 [95% CI, 2.1–7.3];  $P<0.001$ )

than those with greater improvement in fitness ( $\geq 2$  METs gained, 89% AF free).<sup>152</sup>

- Treatment of OSA has been noted to decrease risk of progression to permanent AF.<sup>153</sup> In a meta-analysis, CPAP was reported to be associated with a reduced risk of recurrent AF after ablation.<sup>154</sup> However, there is a lack of robust randomized data supporting the role of CPAP in the primary and secondary prevention of AF in individuals with sleep-disordered breathing.
- In a national outpatient registry of AF patients (ORBIT-AF), 94% had indications for guideline-based primary or secondary prevention in addition to oral anticoagulant drugs; however, only 47% received all guideline-indicated therapies, consistent with an underutilization of evidence-based preventive therapies for comorbid conditions in individuals with AF.<sup>155</sup>
- Predictors of not receiving all guideline-indicated therapies included frailty, comorbid illness, geographic region, and antiarrhythmic drug therapy. Factors most strongly associated with the 17% warfarin discontinuation rate in the first year prescribed included hospitalization because of bleeding (OR, 10.9 [95% CI, 7.9–15.0]), prior catheter ablation (OR, 1.8 [95% CI, 1.4–2.4]), noncardiovascular/nonbleeding hospitalization (OR, 1.8 [95% CI, 1.4–2.2]), cardiovascular hospitalization (OR, 1.6 [95% CI, 1.3–2.0]), and permanent AF (OR, 0.25 [95% CI, 0.17–0.36]).<sup>156</sup>
- A study of 2 national Canadian primary care audits similarly observed that 84.3% of individuals enrolled were eligible for at least 1 cardiovascular evidence-based therapy. The proportions receiving evidence-based therapy varied by diagnosis, at 40.8% of those with CAD, 48.9% of those with DM, 40.2% of those with HF, and 96.7% of those with hypertension.<sup>157</sup>

### **Prevention: Randomized Data**

#### *Primary Prevention of AF: Randomized Data*

- Intensive glycemic control was not found to prevent incident AF in the ACCORD study.<sup>158</sup>
- In the Look AHEAD randomized trial of individuals with type 2 DM who were overweight to obese, an intensive lifestyle intervention associated with modest weight loss did not significantly affect the rate of incident AF (6.1 versus 6.7 cases per 1000 person-years of follow-up; multivariable HR, 0.99 [95% CI, 0.77–1.28]); however, AF was not prespecified as a primary or secondary outcome.<sup>159</sup>
- Meta-analyses have suggested that BP lowering might be useful in prevention of AF in trials of hypertension, after MI, in HF, and after cardioversion.<sup>160,161</sup> However, the studies were primarily

secondary or post hoc analyses, the intervention duration was modest, and the results were fairly heterogeneous.

- Recently, in an analysis of the EMPHASIS-HF trial, in one of many secondary outcomes, eplerenone was nominally observed to reduce the incidence of new-onset AF. However, the number of AF events was modest.<sup>162</sup>
- A post hoc analysis of the PREDIMED randomized primary prevention study suggested a significant reduction in incident AF with the Mediterranean diet that included extra-virgin olive oil (HR, 0.62 [95% CI, 0.45–0.85]).<sup>163</sup>
- Although heterogeneous in their findings, modest-sized short-term studies suggested that the use of statins might prevent AF; however, larger longer-term studies do not provide support for the concept that statins are effective in AF prevention.<sup>164</sup>

#### *Secondary Prevention of AF: Randomized Data*

- Randomized trials of overweight or obese patients referred to an Adelaide, Australia, arrhythmia clinic for management of symptomatic paroxysmal or persistent AF demonstrated that individuals randomized to a weight loss intervention reported lower symptom burden.<sup>165</sup>
- The RACE 3 study randomized individuals with early persistent AF and mild to moderate HF to conventional therapy or targeted therapy, which comprised mineralocorticoid receptor antagonists, statins, ACE inhibitors or angiotensin receptor blockers, and cardiac rehabilitation (counseling, PA, dietary counseling). At 1 year, individuals in the intervention group had higher prevalence of sinus rhythm (75%) than those in the conventional treatment group (63%; OR, 1.77 [95% CI, 1.02–3.05];  $P=0.04$ ).<sup>166</sup>

#### *Awareness*

- In REGARDS, a US national biracial study, compared with whites, blacks had approximately one-third the likelihood (OR, 0.32 [95% CI, 0.20–0.52]) of being aware that they had AF.<sup>167</sup> The REGARDS investigators also reported that compared with individuals aware of their diagnosis, individuals who were unaware of their AF had a 94% higher risk of mortality in follow-up.<sup>168</sup>
- A study from Kaiser Permanente in California examined the relation between AF diagnosis (2006–2009) and self-report questionnaire data (2010). Of the >12 000 individuals with diagnosed AF, 14.5% were unaware of their diagnosis and 20.4% had inadequate health literacy. In adjusted analyses, low health literacy was associated with a lack of awareness of their AF diagnosis (literacy prevalence ratio, 0.96 [95% CI, 0.94–0.98]).<sup>169</sup>

#### **Treatment and Control**

##### *Anticoagulation Undertreatment*

- Studies have demonstrated underutilization of oral anticoagulation therapy. In a meta-analysis, males and individuals with prior stroke were more likely to receive warfarin, whereas factors associated with lower use included alcohol and substance use disorder, noncompliance, warfarin contraindications, dementia, falls, both gastrointestinal and intracranial hemorrhage, renal impairment, and advancing age.<sup>170</sup> The underutilization of anticoagulation in AF has been demonstrated to be a global problem.<sup>171</sup>
- The GWTG-Stroke program conducted a retrospective analysis consisting of 1622 hospitals and 94 474 patients with acute ischemic stroke in the setting of known AF from 2012 to 2015. In that analysis, 79 008 patients (83.6%) were not receiving therapeutic anticoagulation: 13.5% had a subtherapeutic international normalized ratio, 39.9% were receiving antiplatelet treatment only, and 30.3% were not receiving any antithrombotic therapy. In adjusted analyses, versus patients receiving no antithrombotic medications, patients receiving antecedent therapeutic warfarin, non-vitamin K antagonist oral anticoagulant drugs, or antiplatelet therapy had lower odds of moderate or severe stroke (adjusted OR, 0.56 [95% CI, 0.51–0.60], 0.65 [95% CI, 0.61–0.71], and 0.88 [95% CI, 0.84–0.92], respectively) and lower in-hospital mortality.<sup>172</sup>
- In the NCDR PINNACLE registry of outpatients with AF:
  - Less than half of high-risk patients, defined as those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 4$ , were receiving an oral anticoagulant prescription.<sup>173</sup>
  - Between 2008 and 2014, in individuals with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $>1$ , direct anticoagulant use increased from 0% to 24.8%, and use of warfarin decreased from 52.4% to 34.8%. Although over the time period, the prevalence of oral anticoagulation treatment increased from 52.4% to 60.7%, substantive gaps remain.<sup>174</sup>
  - In the PINNACLE registry, females were significantly less likely to receive oral anticoagulant drugs at all levels of CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (56.7% versus 61.3%;  $P<0.001$ ).<sup>175</sup>
  - The PINNACLE registry investigators also reported that receipt of warfarin versus a DOAC varied significantly by type of insurance, with military, private, and Medicare insured patients more likely to receive newer anticoagulants than individuals with Medicaid and other insurance.<sup>176</sup>

- The GLORIA-AF Registry reported North American anticoagulation patterns in 3320 patients with AF between 2011 and 2014, observing that factors associated with increased likelihood of receiving indicated oral anticoagulant prescription included nonparoxysmal AF (OR, 2.02), prior stroke/TIA (OR, 2.00), specialist care (OR, 1.50), more concomitant medications (OR, 1.47), commercial insurance (OR, 1.41), and HF (OR, 1.44), whereas factors inversely related were antiplatelet drugs (OR, 0.18), prior falls (OR, 0.41), and prior bleeding (OR, 0.50).<sup>177</sup>

### *Disparities in Treatment*

- In the ORBIT AF II US-based registry study of outpatients with nontransient AF, black individuals were less likely than their white counterparts to receive DOACs if an anticoagulant was prescribed, after adjustment for socioeconomic and clinical factors, (adjusted OR, 0.73 [95% CI, 0.55–0.95]); there were no significant differences in DOAC use for AF between white and Hispanic groups. However, black and Hispanic patients were more likely than their white counterparts to receive inappropriate doses of DOACs.<sup>178</sup>
- Disparities in treatment patterns have also been observed in Sweden. In adjusted analyses, compared with individuals with AF living in middle-income neighborhoods, those living in high-SES neighborhoods were more likely to be prescribed warfarin (males: OR, 1.44 [95% CI, 1.27–1.67]; females: OR, 1.19 [95% CI, 1.05–1.36]).<sup>179</sup>

### *Role of Coordinated Care*

- A systematic review and meta-analysis identified 3 studies of coordinated systems of care that included 1383 patients.<sup>180</sup> The investigators reported that AF integrated care approaches were associated with reduced all-cause mortality (OR, 0.51 [95% CI, 0.32–0.80];  $P=0.003$ ) and cardiovascular hospitalizations (OR, 0.58 [95% CI, 0.44–0.77];  $P=0.0002$ ).

### *Mortality*

(See Chart 16-7)

**2016 ICD-9 427.3; ICD-10 I48.**

In 2017, AF was the underlying cause of death in 26 077 people and was listed on 166 793 US death certificates (any-mention mortality; unpublished NHLBI tabulation using NVSS<sup>181</sup> and CDC Wonder<sup>182</sup>).

- The age-adjusted mortality rate from AF was 6.6 per 100 000 people in 2017 (unpublished NHLBI tabulation using CDC WONDER<sup>182</sup>).
- In adjusted analyses from the FHS, AF was associated with an increased risk of death in both males (OR, 1.5 [95% CI, 1.2–1.8]) and females (OR, 1.9 [95% CI, 1.5–2.2]).<sup>183</sup> Furthermore, there was an interaction with sex, such that AF appeared to

diminish the survival advantage typically observed in females.

- Although there was significant between-study heterogeneity ( $P<0.001$ ), a meta-analysis confirmed that the adjusted risk of death was significantly higher in females than in males with AF (RR, 1.12 [95% CI, 1.07–1.17]).<sup>184</sup>
- An observational study of Olmsted County, MN, residents with first diagnosis of AF or atrial flutter between 2000 and 2010 reported a high early mortality compared with individuals of similar age and sex; the standardized mortality ratio was 19.4 (95% CI, 17.3–21.7) in the first 30 days and 4.2 (95% CI, 3.5–5.0) for days 31 to 90. Survival within the first 90 days did not change over time (adjusted HR, 0.96 [95% CI, 0.85–1.31] for 2010 versus 2000).<sup>80</sup>
- Although stroke is the most feared complication of AF, the RE-LY clinical trial reported that stroke accounted for only ≈7.0% of deaths in AF, with SCD (22.25%), progressive HF (15.1%), and non-cardiovascular death (35.8%) accounting for the majority of deaths.<sup>185</sup>
- AF is also associated with increased mortality in subgroups of individuals, including the following:
  - Individuals with other cardiovascular conditions and procedures, including HCM,<sup>186</sup> MI,<sup>187,188</sup> pre-CABG,<sup>189</sup> post-CABG<sup>187,188,190,191</sup> (both short-term<sup>190</sup> and long-term<sup>190,191</sup>), post-transcatheter aortic valve implantation,<sup>192</sup> PAD,<sup>193</sup> and stroke.<sup>194</sup>
  - Individuals with AF have increased mortality with concomitant HF,<sup>195,196</sup> including HF with preserved EF,<sup>197,198</sup> and HF with reduced EF.<sup>197</sup> In a meta-analysis that examined the timing of AF in relation to HF onset with regard to mortality, the risk of death associated with incident AF was higher (RR, 2.21 [95% CI, 1.96–2.49]) than with prevalent AF (RR, 1.19 [95% CI, 1.03–1.38];  $P_{\text{interaction}}<0.001$ ).<sup>199</sup>
  - AF is also associated with an increased risk of death in other conditions, including DM,<sup>158,200</sup> ESRD,<sup>201</sup> sepsis,<sup>105,202</sup> critically ill patients in the ICU,<sup>203</sup> after primary PCI,<sup>204</sup> and noncardiac surgery.<sup>205</sup>
- In a Medicare unadjusted analysis, blacks and Hispanics had a higher risk of death than their white counterparts with AF; however, after adjustment for comorbidities, blacks (HR, 0.95 [95% CI, 0.93–0.96];  $P<0.001$ ) and Hispanics (HR, 0.82 [95% CI, 0.80–0.84];  $P<0.001$ ) had a lower risk of death than whites with AF.<sup>206</sup> In contrast, in the population-based ARIC study, the rate difference for all-cause mortality for individuals with versus without AF per 1000 person-years was 106.0 (95% CI, 86.0–125.9)<sup>200</sup> in blacks, which was

- higher than the 55.9 (95% CI, 48.1–63.7) rate difference in mortality observed for whites.<sup>207</sup>
- In a US-based study, there was substantial variation in mortality with AF in US counties from 1980 to 2014.<sup>208</sup> Investigators estimated there were ≈22 700 (95% UI, 19 300–26 300) deaths attributable to AF in 2014 and 191 500 (95% UI, 168 000–215 300) years of life lost. In an examination of county-level data, the age-standardized AF mortality rates were 5.6 per 100 000 for the 10th percentile and 9.7 per 100 000 for the 90th percentile. The counties with age-standardized death rates greater than the 90th percentile were clustered in Oregon, California, Utah, Idaho, northeastern Montana, areas east of Kansas City, MO, and southwest West Virginia.<sup>208</sup>
- In a study using the NIS for the period 2010 to 2015, adjusted in-hospital mortality in the setting of AF was higher (4.8% vs 4.3%;  $P=0.02$ ) among Medicaid beneficiaries than among patients with private insurance.<sup>209</sup>
- Investigators conducted multivariable cross-sectional analyses of the NIS between 2012 and 2014 and observed that patients admitted to rural hospitals had a 17% higher risk of death than those admitted to urban hospitals (OR, 1.17 [95% CI, 1.04–1.32]).<sup>210</sup>
- In a Swedish study based on 75 primary care centers, an adjusted analysis of patients diagnosed with AF revealed that males living in low SES neighborhoods were 49% (HR, 1.49 [95% CI, 1.13–1.96]) more likely to die than their counterparts living in middle-income neighborhoods. The results were similar in models that additionally adjusted for anticoagulant and statin treatment (HR, 1.39 [95% CI, 1.05–1.83]).<sup>211</sup> In another study from the same group, unmarried and divorced males and males with lower educational levels with AF had higher risk of mortality than their married and better-educated male counterparts.<sup>212</sup>

### Complications

- Five years after diagnosis with AF, the cumulative incidence rate of mortality, HF, MI, stroke, and gastrointestinal bleeding was higher in older age groups (80–84, 85–89, and ≥90 years of age) than in younger age groups (67–69, 70–74, and 75–79 years of age; Table 16-1).

### Extracranial Systemic Embolic Events

- In a Danish population-based registry of individuals 50 to 89 years of age discharged from the hospital, individuals with new-onset AF had an elevated risk of thromboembolic events to the aorta and renal mesenteric, pelvic, and peripheral arteries. The excess thromboembolic event rate was 3.6 in males and 6.3 in females per 1000 person-years of

follow-up. Compared with referents in the Danish population, the RR of diagnosed extracranial embolism was 4.0 (95% CI, 3.5–4.6) in males and 5.7 (95% CI, 5.1–6.3) in females.<sup>213</sup>

- Investigators pooled data from 4 large, contemporary, randomized anticoagulation trials and observed 221 systemic emboli in 91 746 person-years of follow-up. The systemic embolic event rate was 0.24 versus a stroke rate of 1.92 per 100 person-years. Compared with individuals experiencing stroke, patients experiencing systemic emboli were more likely to be females (56% versus 47%;  $P=0.01$ ) but had similar mean age and CHADS<sub>2</sub> score as those with stroke. Both stroke (RR, 6.79 [95% CI, 6.22–7.41]) and systemic emboli (RR, 4.33 [95% CI, 3.29–5.70]) were associated with an increased risk of death compared with patients with neither event.<sup>214</sup>

### Stroke

(See Chart 16-7)

- A systematic review of prospective studies found wide variability in stroke risk between studies and between AF patients, ranging between 0.5% and 9.3% per year.<sup>215</sup>
- Before the widespread use of anticoagulant drugs, after accounting for standard stroke risk factors, AF was associated with a 4- to 5-fold increased risk of ischemic stroke. Although the RR of stroke associated with AF ( $\approx$ 3- to 5-fold increased risk) did not vary substantively with advancing age, the proportion of strokes attributable to AF increased significantly. In the FHS, AF accounted for  $\approx$ 1.5% of strokes in individuals 50 to 59 years of age and  $\approx$ 23.5% in those 80 to 89 years of age.<sup>216</sup>
- AF was also an independent risk factor for ischemic stroke severity, recurrence, and mortality.<sup>194</sup> In an observational study, at 5 years, only 39.2% (95% CI, 31.5%–46.8%) of ischemic stroke patients with AF were alive, and 21.5% (95% CI, 14.5%–31.3%) had experienced recurrent stroke.<sup>217</sup>
- In Medicare analyses that were adjusted for comorbidities, blacks (HR, 1.46 [95% CI, 1.38–1.55];  $P<0.001$ ) and Hispanics (HR, 1.11 [95% CI, 1.03–1.18];  $P<0.001$ ) had a higher risk of stroke than whites with AF.<sup>206</sup> The increased risk persisted in analyses adjusted for anticoagulant therapy status.<sup>206</sup> Additional analyses from the Medicare registry demonstrated that the addition of black race to the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system significantly improved the prediction of stroke events among newly diagnosed AF patients  $\geq$ 65 years of age.<sup>218</sup>
- In a University of Pennsylvania AF inception cohort without a history of remote stroke, compared with whites, blacks with AF were more likely to be younger and female and to have more

cardiovascular risk factors. In addition, in adjusted analyses, compared with whites with AF, blacks with new-onset AF were more likely to have an ischemic stroke precede (OR, 1.37 [95% CI, 1.03–1.81]) or follow (HR, 1.67 [95% CI, 1.30–2.14]) the diagnosis of AF. The rate of ischemic stroke per year after AF diagnosis was 1.5% (95% CI, 1.3%–1.8%) in whites and 2.5% (95% CI, 2.1%–2.9%) in blacks.<sup>219</sup>

- A meta-analysis that examined stroke risk by sex and presence of AF reported that AF conferred a multivariable-adjusted 2-fold stroke risk in females compared with males (RR, 1.99 [95% CI, 1.46–2.71]); however, the studies were noted to have significant heterogeneity.<sup>184</sup>

### Cognition

- A meta-analysis of 21 studies indicated that AF was associated with increased risk of cognitive impairment in patients with (RR, 2.70 [95% CI, 1.82–4.00]) and without (RR 1.37 [95% CI, 1.08–1.73]) a history of stroke. The risk of dementia was similarly increased (RR, 1.38 [95% CI, 1.22–1.56]).<sup>220</sup>
- In individuals with AF without evidence of cognitive dysfunction or stroke from Olmsted County, MN, the cumulative rate of dementia at 1 and 5 years was 2.7% and 10.5%, respectively.<sup>221</sup>
- In a multicenter study of individuals with diagnosed AF (mean age 73 years) from Switzerland, among 1390 patients without a history of stroke or TIA, clinically silent infarcts were observed in 245 patients (18%) with small noncortical infarcts and 201 (15%) with large noncortical or cortical infarcts based on brain MRIs.<sup>222</sup> Furthermore, in adjusted analyses of all the vascular brain features, large noncortical or cortical infarcts had the strongest association with reduced Montreal Cognitive Assessment ( $\beta=-0.26$  [95% CI, –0.40 to –0.13];  $P<0.001$ ), even when restricted to individuals with clinically silent infarcts.

### Physical Disability and Subjective Health

- AF has been associated with physical disability, poor subjective health,<sup>223,224</sup> and diminished quality of life.<sup>225</sup> A recent systematic review suggested that among people with AF, moderate-intensity activity improved exercise capacity and quality of life.<sup>226</sup>

### Falls

- In the REGARDS study, AF was significantly associated with an adjusted higher risk of falls (10%) than among those without AF (6.6%; OR, 1.22 [95% CI, 1.04–1.44]). The presence of a history of both AF and falls was associated with a significantly higher risk of mortality (per 1000 person-years: AF plus falls, 51.2; AF and no falls, 34.4; no AF and

falls, 29.8; no AF and no falls, 15.6). Compared with those with neither AF nor falls, those with both conditions had an adjusted 2-fold increased risk of death (HR, 2.12 [95% CI, 1.64–2.74]).<sup>227</sup>

- A systematic review and Markov decision analytic modeling report focused on people with AF  $\geq 65$  years of age noted that warfarin treatment was associated with 12.9 QALYs per patient with typical risks of stroke and falls versus 10.2 QALYs for those treated with neither warfarin nor aspirin. Of interest, sensitivity analyses of the probability of falls or stroke did not substantively influence the results.<sup>228</sup>
- A Medicare study noted that patients at high risk for falls with a CHADS<sub>2</sub> score of at least 2 who had been prescribed warfarin had a 25% lower risk (HR, 0.75 [95% CI, 0.61–0.91];  $P=0.004$ ) of a composite cardiovascular outcome (out-of-hospital death or hospitalization for stroke, MI, or hemorrhage) than those who did not receive anti-coagulant drugs.<sup>229</sup>

### Heart Failure

(See Chart 16-7)

- AF and HF share many antecedent risk factors, and  $\approx 40\%$  of people with either AF or HF will develop the other condition.<sup>196</sup>
- In the community, estimates of the incidence of HF in individuals with AF ranged from 3.3<sup>196</sup> to 5.8<sup>230</sup> per 100 person-years of follow-up. In Olmsted County, MN, in individuals with AF, per 100 person-years of follow-up, the incidence of HF with preserved EF was 3.3 (95% CI, 3.0–3.7), which was more common than HF with reduced EF (2.1 [95% CI, 1.9–2.4]).<sup>230</sup>
- Among older adults with AF in Medicare, the 5-year event rate was high, with rates of death and HF exceeding those for stroke (Chart 16-7). Higher event rates after new-onset AF were associated with older age and higher mean CHADS<sub>2</sub> score.<sup>231</sup>
- Investigators examined the incidence rate of HF with systolic dysfunction versus preserved LVEF (<40% versus >50%, respectively) in a Netherlands community-based cohort study (PREVEND) by AF status. Per 1000 person-years, the incidence rate of systolic HF was 12.75 versus 1.99 for those with versus those without AF, with a multivariable-adjusted HR of AF of 5.79 (95% CI, 2.40–13.98). Corresponding numbers for preserved EF were 4.90 versus 0.85 with and without AF, with a multivariable-adjusted HR of AF of 4.80 (95% CI, 1.30–17.70).<sup>232</sup>
- A meta-analysis of 9 studies reported that individuals with AF have a 5-fold increased risk of HF (RR, 4.62 [95% CI, 3.13–6.83]).<sup>233</sup>

## Myocardial Infarction (See Chart 16-7)

- A meta-analysis of 16 cohort studies reported that AF was associated with a 1.54 (95% CI, 1.26–1.85) increased risk of MI in follow-up.<sup>233</sup>
- In the REGARDS study in individuals with AF, the age-adjusted MI incidence rate per 1000 person-years was 12.0 (95% CI, 9.6–14.9) in those with AF compared with 6.0 (95% CI, 5.6–6.6) in those without AF.<sup>234</sup>
- Both REGARDS<sup>234</sup> and the ARIC study<sup>235</sup> observed that the risk of MI after AF was higher in females than in males.
- For individuals with AF in both REGARDS<sup>234</sup> and the CHS,<sup>236</sup> a higher risk of MI was observed in blacks than whites. For instance, the CHS observed that individuals with AF who were black had a higher risk of MI (HR, 3.1 [95% CI, 1.7–5.6]) than whites (HR, 1.6 [95% CI, 1.2–2.1];  $P_{\text{interaction}}=0.03$ ).<sup>236</sup>
- In ARIC, AF was associated with an adjusted increased risk of NSTEMI (HR, 1.80 [95% CI, 1.39–2.31]) but not STEMI (HR, 0.49 [95% CI, 0.18–0.34];  $P$  for comparison of HR=0.004).<sup>235</sup>

## Chronic Kidney Disease

- In a Japanese community-based study, individuals with AF had approximately a doubling in increased risk of developing kidney dysfunction or proteinuria, even in those without baseline DM or hypertension. Per 1000 person-years of follow-up, the incidence of kidney dysfunction was 6.8 in those without and 18.2 in those with AF at baseline.<sup>237</sup>
- In a Kaiser Permanente study of people with CKD, new-onset AF was associated with an adjusted 1.67-fold increased risk of developing ESRD compared with those without AF (74 versus 64 per 1000 person-years of follow-up).<sup>238</sup>

## SCD and VF

- In a study that examined data from 2 population-based studies, AF was associated with a doubling in the risk of SCD after accounting for baseline and time-varying confounders. In ARIC, the unadjusted incidence rate per 1000 person-years was 1.30 (95% CI, 1.14–1.47) in those without AF and 2.89 (95% CI, 2.00–4.05) in those with AF; corresponding rates in CHS were 3.82 (95% CI, 3.35–4.35) and 12.00 (95% CI, 9.45–15.25). The multivariable-adjusted HR associated with AF for sudden death was 2.47 (95% CI, 1.95–3.13).<sup>239</sup>
- An increased risk of VF was observed in a community-based case-control study from the Netherlands. Individuals with ECG-documented VF during OHCA were matched with non-VF community control subjects. The prevalence of AF in the 1397 VF cases was 15.4% versus 2.6% in the community referents. Individuals with AF had

an overall adjusted 3-fold increased risk of VF (adjusted OR, 3.1 [95% CI, 2.1–4.5]). The association was similar across age and sex categories and was observed in analyses of individuals without comorbidities, without AMI, and not using antiarrhythmic or QT-prolonging drugs.<sup>240</sup>

- In a meta-analysis of 27 studies, AF was associated with a doubling in risk of sudden death (pooled RR, 2.02 [95% CI, 1.77–2.35];  $P<0.01$ ). When restricted to 7 studies that conducted multivariable analyses, AF remained associated with an increased risk of sudden death (pooled RR, 2.22 [95% CI, 1.59–3.09];  $P<0.01$ ).<sup>241</sup>

## AF Type and Complications

- A meta-analysis of 12 studies reported that compared with paroxysmal AF, nonparoxysmal AF was associated with a multivariable-adjusted increased risk of thromboembolism (HR, 1.38 [95% CI, 1.19–1.61];  $P<0.001$ ) and death (HR, 1.22 [95% CI, 1.09–1.37];  $P<0.001$ ).<sup>242</sup>
- In the Canadian Registry of AF, 755 patients with paroxysmal AF were followed up for a median of 6.35 years. At 1, 5, and 10 years, 8.6%, 24.3%, and 36.3% had progressed to persistent AF. Within 10 years, >50% of the patients had progressed to persistent AF or had died.<sup>243</sup>

## Atrial Flutter Versus AF

- Using a 5% Medicare sample from 2008 to 2014, investigators reported the annual stroke rate to be 2.02% (95% CI, 1.99%–2.05%) in patients with AF and 1.38% (95% CI, 1.22%–1.57%) in patients with atrial flutter. After adjustment for demographics and vascular risk factors, the risk of stroke was significantly lower in patients with atrial flutter than in those with AF (HR, 0.69 [95% CI, 0.61–0.79]).<sup>244</sup>
- A national Taiwanese study compared the prognosis of 175 420 patients with AF and 6239 patients with atrial flutter. Using propensity scoring, they observed that compared with atrial flutter, individuals with AF had significantly higher incidences of ischemic stroke (1.63-fold), HF hospitalization (1.70-fold), and all-cause mortality (1.08-fold).<sup>245</sup>

## Hospitalizations and Ambulatory Care Visits

- According to HCUP data,<sup>246</sup> in 2016, there were 465 000 hospital discharges with AF and atrial flutter as the principal diagnosis; ≈50.4% were males (unpublished NHLBI tabulation).
  - The rate per 100 000 discharges increased with advancing age, from 15.1 in those 18 to 44 years of age, 149.2 in those 45 to 64 years, and 577.5 in those 65 to 84 years, to 1158.6 in individuals ≥85 years of age; however, 53.2% of all hospital discharges

for AF occurred in patients 65 to 84 years of age.

- In 2016, there were 7 042 000 physician office visits and 647 000 ED visits for AF (NAMCS, NHAMCS, unpublished NHLBI tabulation).<sup>247,248</sup>
- Using cross-sectional data (2006–2014) from the HCUP's NEDS, the NIS, and the NVSS, investigators estimated that in 2014, AF listed as a primary diagnosis accounted for ≈599 790 ED visits and 453 060 hospitalizations, with a mean length of stay of 3.5 days. Including AF listed as a comorbid condition, there were ≈4 million (3.6% of total) ED visits and 3.5 million (12.0% of total) hospitalizations.<sup>249</sup>
- On the basis of Medicare and MarketScan databases, annually, people with AF (37.5%) are approximately twice as likely to be hospitalized as age- and sex-matched referents (17.5%).<sup>250</sup>

### Cost

#### (See Chart 16-8)

- Investigators examined Medicare and Optum Touchstone databases (2004–2010) to estimate costs attributed to nonvalvular AF versus propensity-matched control subjects in 2014 US dollars<sup>251</sup>:
  - For patients 18 to 64 years of age, average per capita medical spending was \$38 861 (95% CI, \$35 781–\$41 950) versus \$28 506 (95% CI, \$28 409–\$28 603) for matched patients without AF. Corresponding numbers for patients ≥65 years of age were \$25 322 for those with AF (95% CI, \$25 049–\$25 595) versus \$21 706 (95% CI, \$21 563–\$21 849) for matched non-AF patients.
  - The authors estimated that the incremental cost of AF was \$10 355 for commercially insured patients and \$3616 for Medicare patients.
  - Estimating that the prevalence of diagnosed versus undiagnosed nonvalvular AF, respectively, was 0.83% versus 0.07% for individuals 18 to 64 years of age and 8.8% versus 1.1% for those ≥65 years of age, the investigators estimated that the incremental cost of undiagnosed AF was \$3.1 billion (95% CI, \$2.7–3.7 billion).
- Investigators examined Medicare and MarketScan databases (2004–2006) to estimate costs attributed to AF in 2008 US dollars (Chart 16-8)<sup>250</sup>:
  - Extrapolating to the US population, it was estimated that the incremental cost of AF was ≈\$26 billion, of which \$6 billion was attributed to AF, \$9.9 billion to other cardiovascular expenses, and \$10.1 billion to noncardiovascular expenses.

— Using cross-sectional data (2006–2014) from the HCUP's NEDS, the NIS, and the NVSS, investigators estimated that in 2014, for AF listed as a primary diagnosis, the mean charge for ED visits was ≈\$4000, and the mean cost of hospitalizations was ≈\$8819.<sup>249</sup>

- A systematic review that examined costs of ischemic stroke in individuals with AF included 16 studies from 9 countries. In international dollars adjusted to 2015 values, they estimated that stroke-related healthcare costs were \$8184, \$12 895, and \$41 420 for lower middle-, middle-, and high-income economies, respectively.<sup>252</sup>
- Costs of AF have been estimated for many other countries. Investigators estimated that the 3-year societal costs of AF were ≈€20 403 to €26 544 per person and €219 to 295 million for Denmark as a whole.<sup>253</sup>

### Global Burden of AF

#### (See Charts 16-9 and 16-10)

- The vast majority of research studies on the epidemiology of AF have been conducted in Europe and North America. Investigators from the GBD project noted that the global prevalence, incidence, mortality, and DALYs associated with AF increased from 1990 to 2010.<sup>254</sup>
- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.<sup>255</sup>
  - Total number of global deaths attributable to AF/atrial flutter was ≈300 000 in 2017 (200 000 females and 100 000 males).
  - Globally, 37.6 million individuals had prevalent AF/atrial flutter in 2017 (17.8 million females and 19.8 million males).
  - Age-standardized mortality attributable to AF is highest in Northern Europe and Australasia and lowest in parts of sub-Saharan Africa and Western and Central Asia (Chart 16-9).
  - Age-standardized prevalence of AF is highest in Northern Europe, Central Europe, Australasia, and the United States (Chart 16-10).
- Investigators conducted a prospective registry of >15 000 AF patients presenting to EDs in 47 countries. They observed substantial regional variability in annual AF mortality: South America (17%) and Africa (20%) had double the mortality rate of North America, Western Europe, and Australia (10%;  $P<0.001$ ). HF deaths (30%) exceeded deaths attributable to stroke (8%).<sup>256</sup>

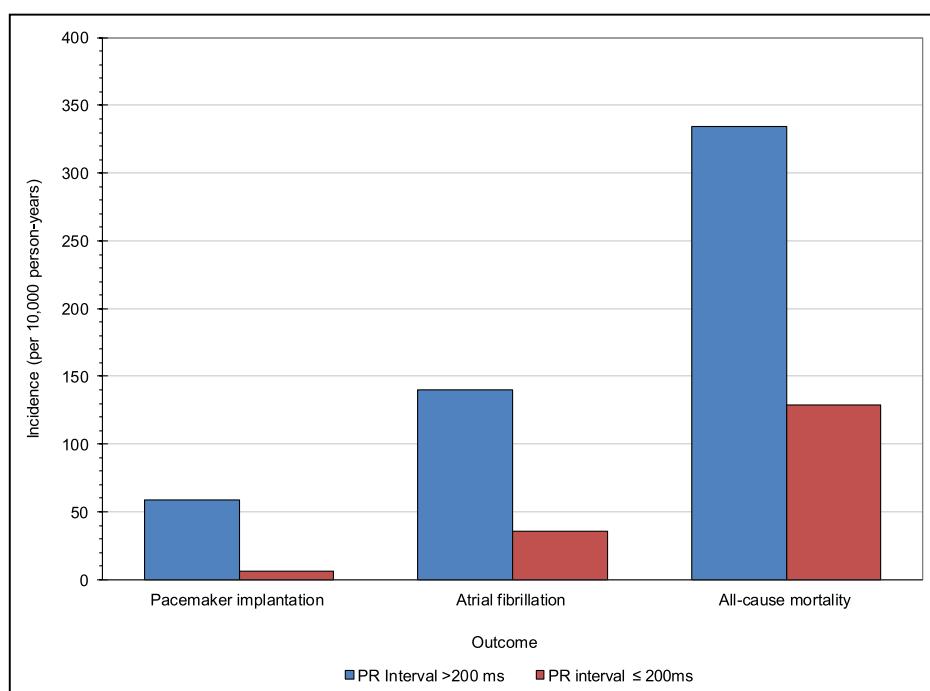
**Table 16-1.** Cumulative Incidence Rate Over 5 Years After AF Diagnosis, by Age,\* United States, Diagnosed 1999 to 2007

Age Group, y	Mortality	HF	MI	Stroke	Gastrointestinal Bleeding
67–69	28.8	11.0	3.3	5.0	4.4
70–74	32.3	12.1	3.6	5.7	4.9
75–79	40.1	13.3	3.9	6.9	5.9
80–84	52.1	15.1	4.3	8.1	6.4
85–89	67.0	15.8	4.4	8.9	6.6
≥90	84.3	13.7	3.6	6.9	5.4

All values are percentages. AF indicates atrial fibrillation; HF, heart failure; and MI, myocardial infarction.

\*See Chart 16-7.

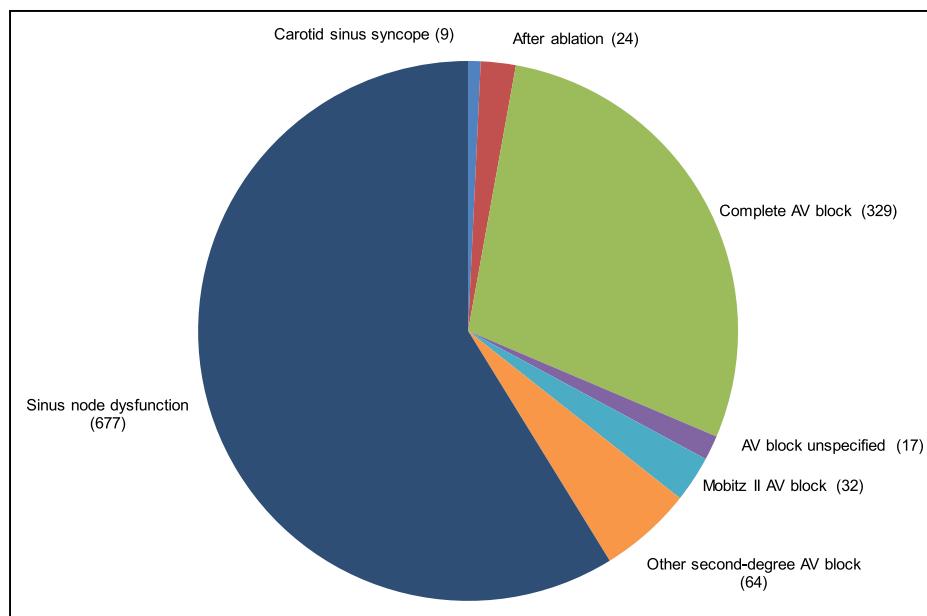
Source: Adapted from Piccini et al<sup>231</sup> by permission of the European Society of Cardiology. Copyright © 2013, The Authors.



**Chart 16-1.** Long-term outcomes in individuals with prolonged PR interval (>200 ms; first-degree atrioventricular block) compared with individuals with normal PR interval in the FHS, 1968 to 2007.

FHS indicates Framingham Heart Study.

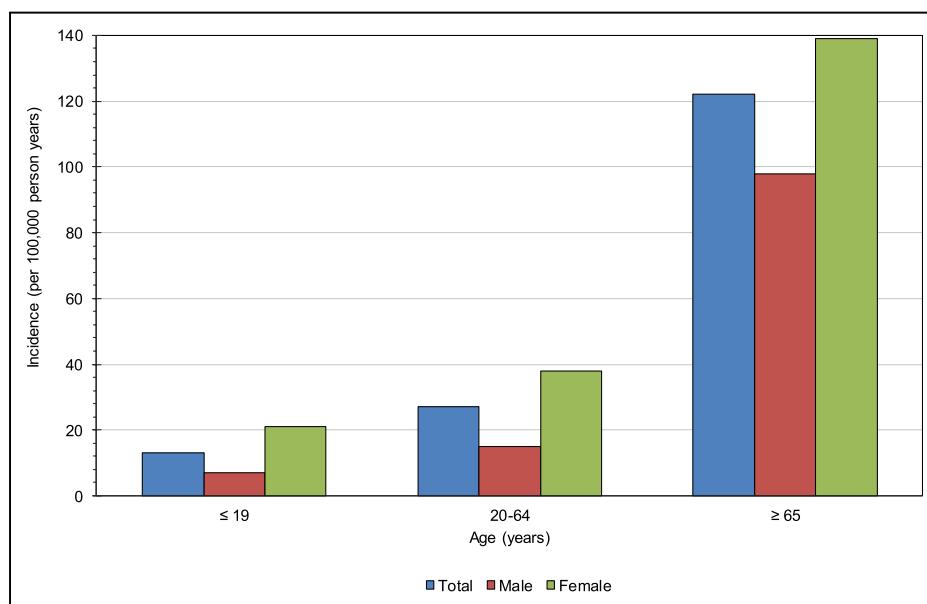
Source: Data derived from Cheng et al.<sup>15</sup>



**Chart 16-2. Primary indications (in thousands) for pacemaker placement between 1990 and 2002, United States (NHDS, NCHS).**

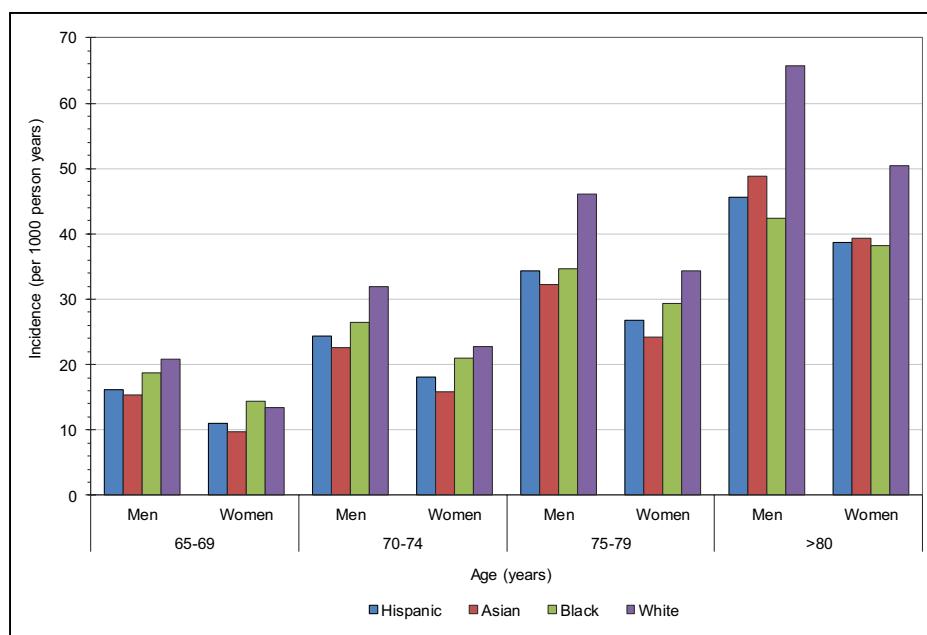
AV indicates atrioventricular; NCHS, National Center for Health Statistics; NHDS, National Hospital Discharge Survey.

Source: Data derived from Birnie et al.<sup>36</sup>

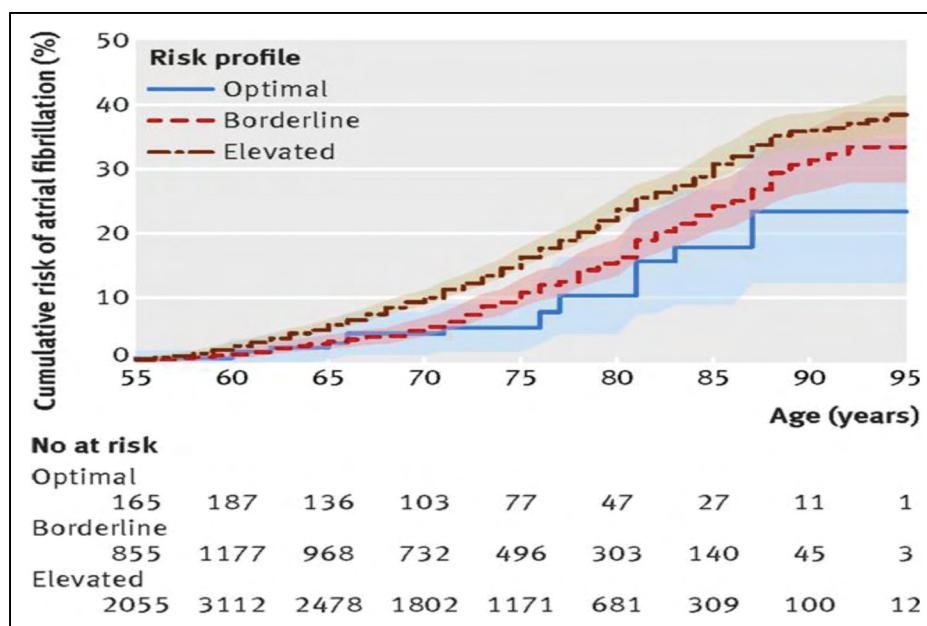


**Chart 16-3. Incidence rate of paroxysmal supraventricular tachycardia per 100 000 person-years by age and sex, Marshfield Area, Wisconsin, July 1, 1991, to June 30, 1993.**

Source: Data derived from Orejarena et al.<sup>38</sup>

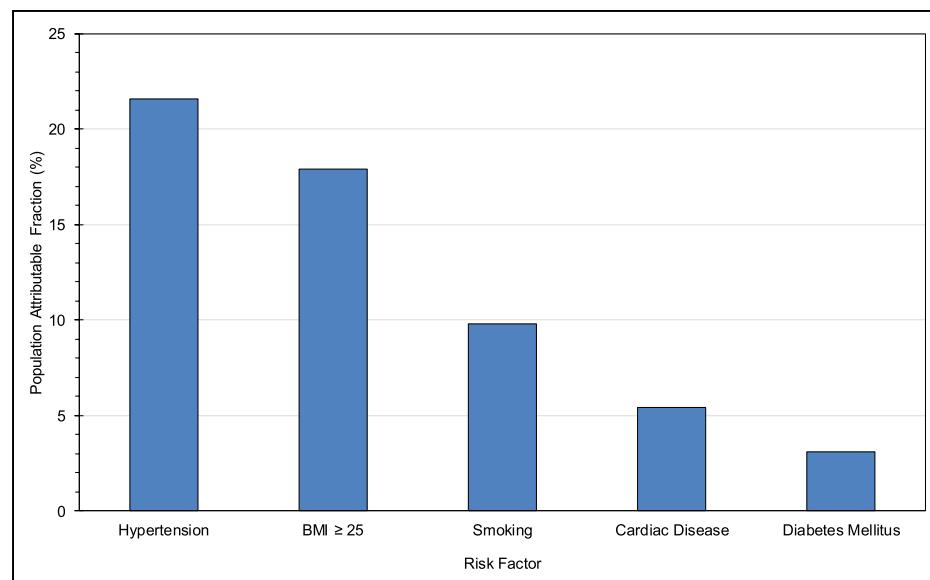
**Chart 16-4.** Atrial fibrillation incidence by race, 2005 to 2009.

Incidence increased with advancing age among different races and sexes in California.

Source: Data derived from Dewland et al.<sup>71</sup>**Chart 16-5.** Lifetime risk (cumulative incidence at 95 years of age) for atrial fibrillation at different ages (through 94 years of age) by sex in the FHS, 1968 to 2014.

FHS indicates Framingham Heart Study.

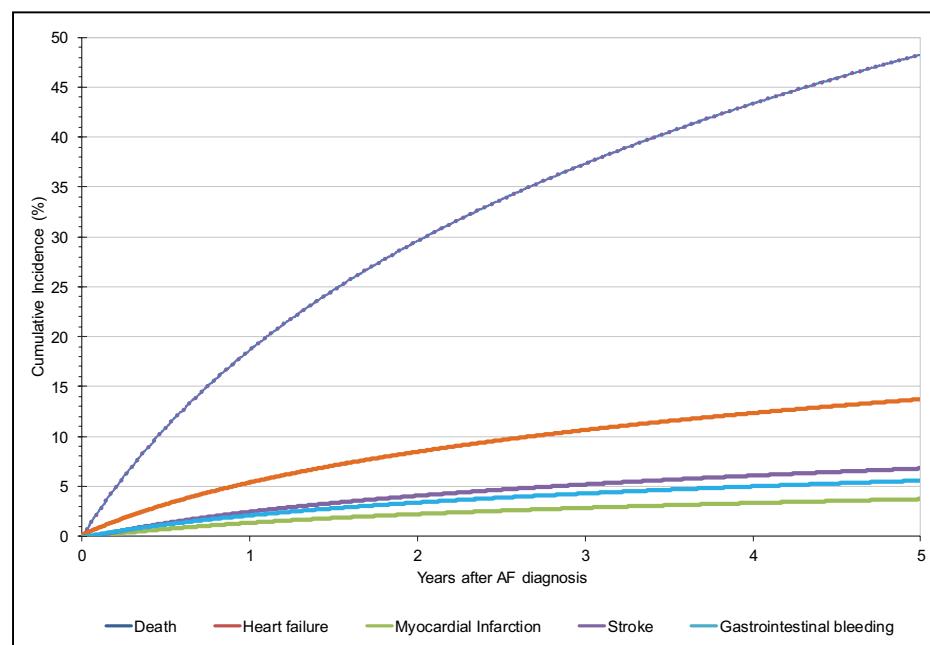
Source: Reprinted from Staerk et al.<sup>75</sup> Copyright © 2018, The Authors. Published on behalf of the Authors by the British Medical Group. This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.



**Chart 16-6. Population attributable fraction of major risk factors for atrial fibrillation in the ARIC study, 1987 to 2007.**

ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index (in kg/m<sup>2</sup>); cardiac disease, patients with history of coronary artery disease or heart failure; and smoking, current smoker.

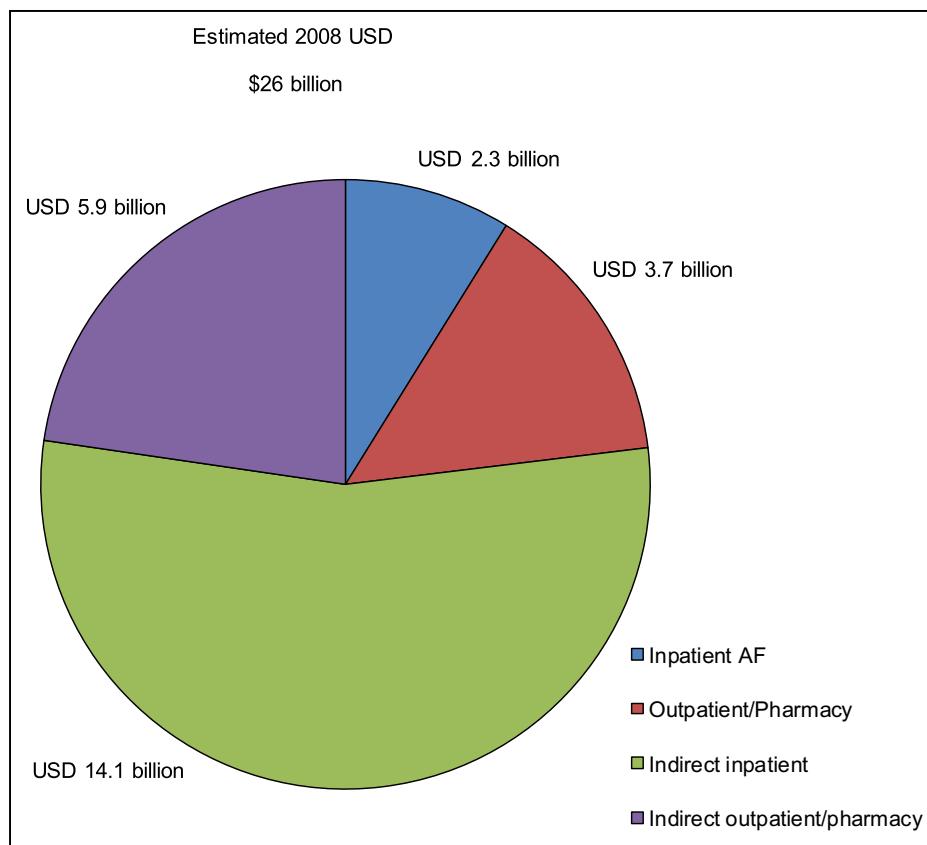
Source: Data derived from Huxley et al.<sup>83</sup>



**Chart 16-7. Cumulative incidence of events in the 5 years after diagnosis of incident AF in Medicare patients in the United States, diagnosed 1999 to 2007.**

AF indicates atrial fibrillation.

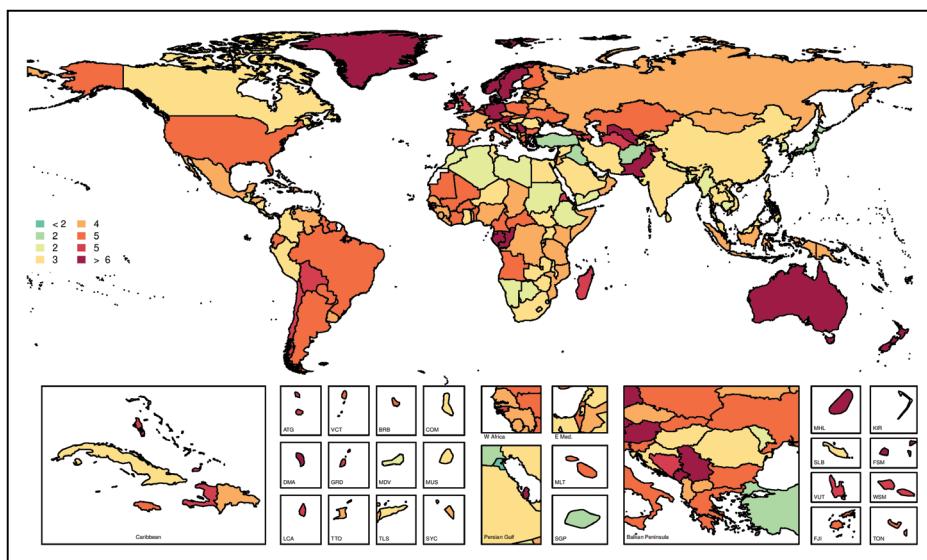
Source: Reprinted from Piccini et al<sup>231</sup> by permission of the European Society of Cardiology. Copyright © 2013, The Authors.



**Chart 16-8.** AF cost estimates in 2008 USD, in which AF is diagnosed in inpatient and outpatient encounters, United States, 2004 to 2006.

Indirect costs are incremental costs of inpatient and outpatient visits. AF indicates atrial fibrillation; and USD, US dollars.

Adapted from Kim et al.<sup>250</sup> Copyright © 2011, American Heart Association, Inc.

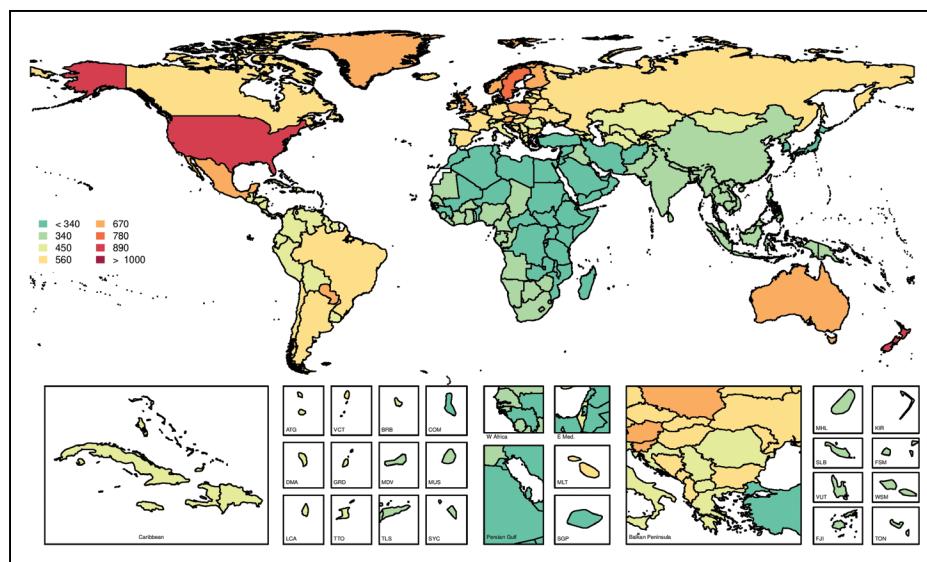


**Chart 16-9.** Age-standardized global mortality rates of atrial fibrillation (AF) and atrial flutter per 100 000, both sexes, 2017.

Age-standardized mortality attributable to AF is highest in Northern Europe and Australasia and lowest in parts of sub-Saharan Africa and Western and Central Asia.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>255</sup> Printed with permission. Copyright © 2018, University of Washington.



**Chart 16-10. Age-standardized global prevalence rates of atrial fibrillation (AF) per 100 000, both sexes, 2017.**

Age-standardized prevalence of AF is highest in Northern Europe, Central Europe, Australasia, and the United States.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>255</sup> Printed with permission. Copyright © 2018, University of Washington.

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## 17. SUDDEN CARDIAC ARREST, VENTRICULAR ARRHYTHMIAS, AND INHERITED CHANNELOPATHIES

**See Tables 17-1 through 17-7 and Charts 17-1 through 17-4**

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### Cardiac Arrest (Including VF and Ventricular Flutter)

**ICD-9 427.4, 427.5; ICD-10 I46.0, I46.1, I46.9, I49.0.**

2017: Mortality—18 835. Any-mention mortality—379 133.

### Abbreviations Used in Chapter 17

ACS	acute coronary syndrome
AED	automated external defibrillator
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities
ARVC	arrhythmogenic right ventricular cardiomyopathy
AV	atrioventricular
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CARES	Cardiac Arrest Registry to Enhance Survival
CASQ2	calsequestrin 2
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CLRD	chronic lower respiratory disease
CPC	Cerebral Performance Index
CPR	cardiopulmonary resuscitation
CPVT	catecholaminergic polymorphic ventricular tachycardia
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
DM	diabetes mellitus
DVT	deep vein thrombosis
ECG	electrocardiogram
ED	emergency department
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EMS	emergency medical services
ERP	early repolarization pattern
GWAS	genome-wide association study
GWTG	Get With The Guidelines
HCM	hypertrophic cardiomyopathy
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio

(Continued)

### Abbreviations Used in Chapter 17 Continued

ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision
ICU	intensive care unit
IHCA	in-hospital cardiac arrest
IQR	interquartile range
IRR	incidence rate ratio
LQTS	long-QT syndrome
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
METs	metabolic equivalents
MI	myocardial infarction
NEDS	Nationwide Emergency Department Sample
NH	non-Hispanic
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
PA	physical activity
PE	pulmonary embolism
PEA	pulseless electrical activity
PVC	premature ventricular contraction
PVT	polymorphic ventricular tachycardia
QTc	corrected QT interval
ROC	Resuscitation Outcomes Consortium
RR	relative risk
RV	right ventricular
RYR2	ryanodine receptor 2
SBP	systolic blood pressure
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SD	standard deviation
STEMI	ST-segment-elevation myocardial infarction
SUDS	Sudden Unexpected Death Study
TdP	torsade de pointes
VF	ventricular fibrillation
VT	ventricular tachycardia
WPW	Wolff-Parkinson-White

### Tachycardia

**ICD-9 427.0, 427.1, 427.2; ICD-10 I47.1, I47.2, I47.9.**

2017: Mortality—997. Any-mention mortality—8035.

Cardiac arrest is the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation.<sup>1</sup> An operational definition of SCA is unexpected cardiac arrest that results in attempts to restore circulation. If resuscitation attempts are unsuccessful, this situation is referred to as SCD. SCA results from many disease processes; a consensus statement by the International Liaison Committee on Resuscitation recommends categorizing cardiac arrest into events with external causes (drowning, trauma, asphyxia, electrocution, and drug overdose) or medical causes.<sup>2</sup> Because of fundamental differences in underlying pathogenesis

and the system of care, epidemiological data for OHCA and IHCA are collected and reported separately. For similar reasons, data for infants (<1 year of age), children (1–18 years of age), and adults are reported separately.

- In a Swedish registry of 70 846 OHCA from 1992 to 2014, 92% of cases had medical causes. Among nonmedical cases, trauma was the most common cause.<sup>3</sup>
- Adjudication of cause of death in 179 cases of SCA in middle school, high school, college, and professional athletes from 2014 to 2016 identified a cause in 117 (65.4%): HCM (16.2%), coronary artery anomalies (13.7%), idiopathic cardiomyopathy (11.1%), autopsy-negative sudden unexplained death (6.8%), WPW syndrome (6.8%), and LQTS (6.0%).<sup>4</sup>

## Incidence (See Tables 17-1 through 17-3)

- The ROC clinical trial network maintained a registry of EMS-assessed and EMS-treated OHCA in multiple regions of the United States from 2005 to 2015 (Table 17-1).
- The ongoing CARES registry<sup>5</sup> estimates the incidence of EMS-treated OHCA among individuals of any age in >1400 EMS agencies in the United States (Table 17-1).
- Incidence of EMS-assessed OHCA for 2015 in people of any age is 110.8 individuals per 100 000 population (95% CI, 108.9–112.6), or 356 461 people (quasi CI, 350 349–362 252), based on extrapolation from the ROC registry of OHCA (ROC Investigators, unpublished data, July 7, 2016) to the total population of the United States (325 193 000 as of June 9, 2017).<sup>6</sup>
- Incidence of EMS-treated OHCA in people of any age is 57 individuals per 100 000 population based on the 2013 CARES registry of EMS-treated OHCA and 63.8 individuals per 100 000 population based on the 2013 ROC registry.<sup>7</sup>
- Incidence of EMS-treated OHCA in people of any age is 74.3 individuals per 100 000 population based on the 2018 CARES registry, with >2-fold variation between states (range, 51.6–128.3; Table 17-2).
- Of the 3 686 296 hospital discharges from academic medical centers in 2012, 33 700 (0.91%) included a cardiac arrest diagnosis.<sup>8</sup>
- In the NIS for 2016:
  - “Cardiac arrest” or “VF/flutter” was included in 273 295 hospital discharges (rate of 84.6 per 100 000 people). For 9.5% (26 040) this was the principal diagnosis for hospital admission.

- ICD-10 codes for CPR or defibrillation were included in 286 945 hospital discharges (rate of 88.8 per 100 000 people).<sup>9</sup>
- In the NEDS for 2016:
  - The weighted national estimate of ED visits with a principal diagnosis of “cardiac arrest” or “VF/flutter” was 183 629 (rate of 56.8 per 100 000 people). Of these, 15.8% (29 096) were admitted to the same hospital or transferred to another hospital (Table 17-3).
  - “Cardiac arrest” or “VF/flutter” was estimated at 404 691 visits among all listed diagnoses, but this larger number may include patients with cardiac arrest after hospital admission (Table 17-3).
  - The weighted national estimate of ED visits including ICD-10 codes for CPR or defibrillation was 187 097 (rate of 57.9 per 100 000 people; unpublished tabulation using HCUP<sup>9</sup> 2016).

### OHCA: Adults (See Table 17-4)

- Incidence of EMS-assessed OHCA for 2015 in adults was 140.7 individuals per 100 000 population (95% CI, 138.3–143.1), or 347 322 adults (95% CI, 341 397–353 246) based on extrapolation from the ROC registry of OHCA to the total population of the United States (ROC Investigators, unpublished data, July 7, 2016).<sup>5</sup>
- Incidence of EMS-treated OHCA in adults for 2015 was 73.0 individuals per 100 000 population (95% CI, 71.2–74.7), or 180 202 adults (95% CI, 175 759–184 399) in the ROC registry. Approximately 52% of EMS-assessed adult OHCA had resuscitation attempted (ROC Investigators, unpublished data, July 7, 2016).
- In 2015, the incidence of EMS-treated OHCA in adults was 66 per 100 000. Incidence of EMS-treated OHCA with initial shockable rhythm was 13.5 per 100 000 (ROC Investigators, unpublished data, July 7, 2016).
- Ten ambulance services serving almost 54 000 000 residents of England attended 28 729 EMS-treated cardiac arrests in 2014 (annual incidence 53 per 100 000 residents).<sup>10</sup>
- In 2018, location of OHCA in adults was most often a home or residence (69.8%), followed by public settings (18.8%) and nursing homes (11.5%; Table 17-4). OHCA in adults was witnessed by a layperson in 37.7% of cases or by an EMS provider in 12.7% of cases. For 49.6% of cases, collapse was not witnessed.<sup>5</sup>
- Initial recorded cardiac rhythm was VF or VT or shockable by an AED in 18.7% of EMS-treated OHCA in 2018 (Table 17-4).

- Of 4729 patients with STEMI in Los Angeles County, CA, from 2011 to 2014, 422 (9%) had OHCA.<sup>11</sup>
- In a clinical trial of a wearable defibrillator in 2302 patients with reduced EF (<35%) after AMI, 44 patients (1.9%) had arrhythmic sudden death, 21 (0.9%) had appropriate defibrillator shock, and 86 (3.7%) had death attributable to any cause during the first 90 days.<sup>12</sup>

### IHCA: Adults

(See Table 17-4)

- Incidence of adult IHCA was a mean of 10.16 (SD, 26.08) per 1000 hospital admissions and 1.99 (SD, 1.57) per 1000 inpatient days in the 2018 GWTG data (GWTG—Resuscitation, unpublished data, 2019).
- Incidence of IHCA was 4.0 per 1000 hospitalizations (range, 1.4–11.8 per 1000 hospitalizations) based on 2 205 123 hospitalizations at 101 Veterans Health Administration hospitals between 2008 and 2012.<sup>13</sup>
- Incidence of IHCA was 1.7 per 1000 hospital admissions based on 18 069 patients with IHCA in the Swedish Register of CPR.<sup>14</sup>
- Incidence of IHCA was 1.6 per 1000 hospital admissions, with a median across hospitals of 1.5 (IQR, 1.2–2.2) in the UK National Cardiac Arrest Audit database between 2011 and 2013 (144 hospitals and 22 628 patients ≥16 years of age).<sup>15</sup>
- According to 2018 GWTG data, location of adult IHCA was 54.2% in the ICU, operating room, or ED and 45.8% in noncritical care areas among 26 742 events at 319 hospitals (Table 17-4).
- Initial recorded cardiac rhythm was VF or VT or shockable in 15.3% of adult IHCAs in 2018 GWTG data (GWTG—Resuscitation, unpublished data, 2019; Table 17-4).

### OHCA: Children

- Incidence of EMS-assessed OHCA in children in 2015 was 7037 (quasi CI, 6214–7861) in the United States based on extrapolation from ROC for individuals <18 years of age (ROC Investigators, unpublished data, July 7, 2016).
- In 2018, location of EMS-treated OHCA was at home for 92.1% of children ≤1 year old, 81.2% of children 1 to 12 years of age, and 75.7% of children 13 to 18 years of age in the CARES 2018 data. Location was in a public place for 7.8% of children ≤1 year old, 18.8% of children 1 to 12 years of age, and 23.1% of children 13 to 18 years of age.<sup>5</sup>
- Annual incidence of pediatric OHCA was 8.7 per 100 000 population in Western Australia from 2011 to 2014.<sup>16</sup>

### Sports-Related SCA/SCD

- Sports-related SCA accounted for 39% of SCAs among those ≤18 years of age, 13% for those

19 to 25 years of age, and 7% for those 25 to 34 years of age in a prospective registry of 3775 SCAs in Portland, OR, between 2002 and 2015 that included 186 SCAs in young people (5–34 years of age).<sup>17</sup>

- Incidence of SCA or SCD was 1 per 44 832 athlete-years for males and 1 per 237 510 athlete-years for females based on a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes.<sup>18</sup>
- Incidence of SCA during competitive sports in people 12 to 45 years of age was 0.76 per 100 000 athlete-years in a population-based registry of all paramedic responses in Toronto, Canada, from 2009 to 2014.<sup>19</sup>
- Studies that included >14 million participants in long-distance or marathon running events from 1976 to 2009 reported race-related incidence of SCA or SCD ranging from 0.6 to 1.9 per 100 000 runners using various methods to ascertain events.<sup>20</sup> Only 2 deaths were reported among 1 156 271 participants in half or full marathons in Sweden from 2007 to 2016, yielding an estimated SCD incidence of 0.24 (95% CI, 0.04–0.79) per 100 000 runners.<sup>21</sup>
- In a 2007 to 2013 registry of 104 cases of SCA and SCD in high school athletes, adjudication revealed a cause of death in 50 cases (73%): idiopathic LVH or possible cardiomyopathy (26%), autopsy-negative sudden unexplained death (18%), HCM (14%), and myocarditis (14%).<sup>18</sup>
- Adjudication of cause of death in 179 cases of SCA in middle school, high school, college, and professional athletes from 2014 to 2016 identified a cause in 117 (65.4%): HCM (16.2%), coronary artery anomalies (13.7%), idiopathic cardiomyopathy (11.1%), autopsy-negative sudden unexplained death (6.8%), WPW (6.8%), and LQTS (6.0%).<sup>4</sup>
- Among 55 patients admitted to 8 Spanish hospitals with SCA during or within 1 hour of vigorous sport activities between 2007 and 2016, 90.9% were male, mean (SD) age was 47 (15) years, and 96.4% presented with shockable rhythm. The cause of SCA varied by age: 25% cardiomyopathy, 63% idiopathic VF, and 13% AMI for those <35 years of age; 9% cardiomyopathy, 18% idiopathic VF, 67% AMI, and 7% unknown for those ≥35 years of age.<sup>22</sup>
- Preparticipation screening of 5169 middle and high-school students (mean [SD] age 13.06 [1.78] years) from 2010 to 2017 revealed high-risk cardiovascular conditions in 1.47%.<sup>23</sup> Anatomic findings included DCM (n=11), nonobstructive HCM (n=3), and anomalous coronary artery origins (n=23). Electrocardiographic findings included WPW (n=4), prolonged QT intervals (n=34), and Brugada pattern (n=1).

### IHCA: Children (See Table 17-4)

- Incidence of IHCA for children (30 days to 18 years of age) was a mean 12.66 (SD, 41.04) per 1000 admissions and 1.89 (SD, 4.99) per 1000 inpatient days for 810 events from 92 hospitals per 2018 GWTG data (GWTG—Resuscitation, unpublished data, 2019).
- Of 810 events of IHCA in children (30 days to 18 years of age) at 92 hospitals, 87% occurred in the ICU, operating room, or ED and 13% in noncritical care areas per 2018 GWTG data (Table 17-4).
- Incidence of IHCA was 1.8 CPR events per 100 pediatric (<18 years of age) ICU admissions (sites ranged from 0.6 to 2.3 per 100 ICU admissions) in the Collaborative Pediatric Critical Care Research Network data set of 10 078 pediatric ICU admissions from 2011 to 2013.<sup>24</sup>
- In a registry of 23 cardiac ICUs in the Pediatric Critical Care Consortium that included 15 098 children between 2014 and 2016, 3.1% of children in ICUs had a cardiac arrest, with substantial variation between centers (range, 1%–5.5%), for a mean incidence of 4.8 cardiac arrests per 1000 cardiac ICU days (range, 1.1–10.4 per 1000 cardiac ICU days).<sup>25</sup>
- Initial recorded cardiac arrest rhythm was VF or VT or shockable in 9.0% of 571 events at 90 hospitals in GWTG—Resuscitation in 2018 (Table 17-4).

### Lifetime Risk and Cumulative Incidence (See Table 17-5 and Chart 17-1)

- SCD appeared among the multiple causes of death on 13.5% of death certificates in 2017 (379 133 of 2 813 503), which suggests that 1 of every 7.4 people in the United States died of SCD (Table 17-5). Because some people survive SCA, the lifetime risk of cardiac arrest is even higher.
- In 2017, infants had a higher incidence of SCD (11.2 per 100 000) than older children (1.2–2.2 per 100 000). Among adults, risk of SCD increased exponentially with age, surpassing the risk for infants by 35 to 39 years of age (13.3 per 100 000; Chart 17-1).
- Of 2656 Finnish males 42 to 60 years of age randomly selected from 1984 to 1989 and prospectively followed up until 2008, a total of 193 (7.3%) had SCD.<sup>26</sup>

### Secular Trends (See Table 17-1 and Charts 17-2 and 17-3)

- Incidence of EMS-treated OHCA increased from 47 per 100 000 to 66 per 100 000 between 2008 and 2015 in the ROC Epistry (ROC Investigators, unpublished data, July 7, 2016; Table 17-1).

- The annual rate of SCD among patients with HF with reduced EF has declined from 6.5% to 3.3%, based on analysis of 3583 cases of SCD among 40 195 patients enrolled in 12 clinical trials in which enrollment started between 1995 and 2010.<sup>27</sup> This analysis estimates the current cumulative incidence of SCD in patients with HF with reduced EF is 1% by 3 months, <2% by 6 months, and 8.8% by 3 years.
- Incidence of pediatric OHCA declined from 1997 to 2014 in Perth, Western Australia, particularly among children <1 year old.<sup>16</sup>
- Incidence of pediatric (<16 years of age) OHCA that was EMS attended (6.7 per 100 000) or EMS treated (4.9 per 100 000) did not change from 2000 to 2016 in Victoria, Australia.<sup>28</sup> Survival to hospital discharge increased from 9.4% to 17.7%.
- Age-adjusted death rates for any mention of SCD declined from 138 per 100 000 person-years in 1999 to 97.1 per 100 000 person-years by 2017 (Chart 17-2).
- Unadjusted survival to hospital discharge after EMS-treated OHCA increased from 10.2% in 2006 to 12.4% in 2015 in the ROC Epistry (Table 17-1).
- Survival after IHCA increased from 28.5% to 53.8% between 2000 and 2016 and then declined to 48.7% by 2018 in GWTG data (Chart 17-3).
- A national database of 120 365 adult, medical OHCAs in the Republic of Korea from 2006 to 2015 reported increases over time in layperson CPR (1.2% to 17.0%), age- and sex-adjusted survival (3.0% to 8.0%), and good functional recovery (0.9% to 5.8%).<sup>29</sup> Layperson CPR rates increased more in the highest socioeconomic quintile (1.6% to 32.5%) than in the lowest socioeconomic quintile (1.6% to 15.3%)

### Risk Factors (See Charts 17-1 and 17-4)

- SCA and SCD result from many different disease processes, each of which can have different risk factors. Among patients with OHCA resuscitated and hospitalized from 2012 to 2016, ACS and other cardiac causes accounted for the largest proportion of causes. Among patients with IHCA, respiratory failure was the most common cause (Chart 17-4).<sup>30</sup>

#### Age

- In 2017, mortality rates for any mention of SCD decreased for those from 0 to 9 years of age, stayed stable from 10 to 14 years of age, and increased from 15 years of age onward (Chart 17-1).

#### Sex

- According to multiple studies, females with OHCA are older, less likely to present with shockable rhythms, and less likely to collapse in public.

Despite these factors that would reduce survival, females have equivalent or higher rates of survival to hospital discharge or to 30 days relative to males.<sup>31</sup>

- In an EMS-based registry of 3862 OHCA from 2013 to 2015 that includes 90% of the population of New Zealand, OHCA was more common in males (69%) than females (31%).<sup>32</sup> Females were older, collapsed unwitnessed at home, were considered to have a noncardiac cause, presented in a nonshockable rhythm, and less often received layperson CPR. There was no difference between sexes in survival of the event or 30-day survival after adjustment for age, rhythm, location of arrest, and witnessed collapse.
- In a registry that included 40 159 OHCA from 2009 to 2012 in Singapore, Japan, Republic of Korea, Malaysia, Thailand, Taiwan, and United Arab Emirates, OHCA was more common in males (60%) than females (40%).<sup>33</sup> Females were older, more often presented in a nonshockable rhythm, and more often received layperson CPR, but less often collapsed in public. There was no difference between sexes in survival of the event or survival to hospital discharge after adjustment for these factors.

### Race

- In patients with implanted defibrillators, rate of first ventricular dysrhythmia or death within 4 years was higher among black patients (42%) than whites (34%; adjusted HR, 1.60 [95% CI, 1.18–2.17]).<sup>34</sup>
- A study in New York, NY, found the age-adjusted incidence of OHCA per 10 000 adults was 10.1 among blacks, 6.5 among Hispanics, and 5.8 among whites.<sup>35</sup>

### Socioeconomic Factors

- OHCA rates were higher in census tracts from the lowest socioeconomic quartile relative to the highest socioeconomic quartile (IRR, 1.9 [95% CI, 1.8–2.0]) in 9235 cases from the ROC Epistry (from 2006 to 2007).<sup>36</sup>
- In King County, WA, SCA was more common in census tracts with more pharmacies or other medical facilities (OR 1.28 [95% CI, 1.03–1.59]).<sup>37</sup>
- In a national database of 120 365 adult, medical OHCA in the Republic of Korea from 2006 to 2015, there were differences from the lowest to highest socioeconomic quintiles for layperson CPR (5.5% to 11.4%), survival to hospital discharge (3.8% to 6.1%), and good functional recovery (1.9% to 2.9%).<sup>29</sup>

### HD, Cardiac Risk Factors, and Other Comorbidities

- Among 2656 Finnish males 42 to 60 years of age randomly selected from 1984 to 1989 and

prospectively followed up until 2008, the hazard for SCD increased with below-median (7.9 METs) baseline cardiopulmonary fitness (HR, 1.6 [95% CI, 1.1–2.3]) and below-median (191 kcal/d) leisure-time PA (HR, 1.4 [95% CI, 1.0–2.0]).<sup>26</sup>

- In a cohort of 233 970 patients from the United Kingdom, resting heart rate >90 beats per minute was associated with an increased hazard of SCD or cardiac arrest as initial presentation of HD (adjusted HR, 2.71 [95% CI, 1.90–3.83]).<sup>38</sup>
- In a cohort of 1937 360 patients from the United Kingdom registered between 1997 and 2010, smoking was not associated with hazard of SCD or cardiac arrest as the initial presentation of HD (age-adjusted HR, 1.04 [95% CI, 0.91–1.09]), but it was associated with increased risk of unheralded death caused by CHD (age-adjusted HR, 2.70 [95% CI, 2.27–3.21]), a phenotype that may overlap with SCD.<sup>39</sup>
- In a cohort of 1937 360 patients from the United Kingdom registered between 1997 and 2010, heavy drinking (adjusted HR, 1.50 [95% CI, 1.26–1.77]) and former drinking (adjusted HR, 1.37 [95% CI, 1.12–1.67]) were associated with increased hazard of SCD or cardiac arrest as the initial presentation of HD.<sup>40</sup>
- Among 7011 patients admitted to the hospital with acute HF, the 30-day rate of SCD, SCA, or VT/VF was 1.8% (n=121).<sup>41</sup> Events were associated with male sex (adjusted OR, 1.73 [95% CI, 1.07–2.49]), history of VT (adjusted OR, 2.11 [95% CI, 1.30–3.42]), chronic obstructive pulmonary disease (adjusted OR, 1.63 [95% CI, 1.07–2.49]), or prolonged QRS interval (adjusted OR, 1.10 [95% CI, 1.03–1.17] per 10% increase from baseline).
- Analysis of 76 009 patients including 8401 with AF from 21 studies between 1991 and 2017 found that patients with AF had higher risk of incident SCD/SCA or VF/VT (RR, 2.04 [95% CI, 1.77–2.35]).<sup>42</sup>
- Among 21 105 patients with AF followed up for a median of 2.8 years, SCD accounted for 31.7% of all deaths, with an incidence of 12.9 per 1000 patient-years.<sup>43</sup>
- Risk of SCD in prospective cohorts who were initially free of CVD when recruited in 1987 to 1993 was associated with male sex, black race, DM, current smoking, and SBP.<sup>44</sup>
- A logistic model incorporating age, sex, race, current smoking, SBP, use of antihypertensive medication, DM, serum potassium, serum albumin, HDL-C, eGFR, and QTc interval, derived in 13 677 adults, correctly stratified 10-year risk of SCD in a separate cohort of 4207 adults (C statistic, 0.820 in ARIC and 0.745 in CHS).<sup>44</sup>

- A meta-analysis of 24 trials of statins in patients with HF, which included a total of 11 463 patients, concluded that statins did not reduce the risk of SCD (RR, 0.92 [95% CI, 0.70–1.21]).<sup>45</sup>
- In a registry of 2119 SCAs in Portland, OR, from 2002 to 2015, prior syncope was present in 6.8% of cases, and history of syncope was associated with increased risk of SCA relative to 746 geographically matched control subjects (OR, 2.8 [95% CI, 1.68–4.85]).<sup>46</sup>
- In a cohort of 5211 Finnish people >30 years of age in 2000 to 2001 followed up for a median of 13.2 years, high baseline thyroid-stimulating hormone was independently associated with greater risk of SCD (HR, 2.28 [95% CI, 1.13–4.60]).<sup>47</sup>
- In a meta-analysis that included 17 studies with 118 954 subjects, presence of depression or depressive symptoms was associated with increased risk of SCD (HR, 1.62 [95% CI, 1.37–1.92]), and specifically for VT/VF (HR, 1.47 [95% CI, 1.23–1.76]).<sup>48</sup>

## Risk Prediction

### *Prodromal Symptoms*

- Abnormal vital signs during the 4 hours preceding IHCA occurred in 59.4% and at least 1 severely abnormal vital sign occurred in 13.4% of 7851 patients in the 2007 to 2010 GWTG data.<sup>49</sup>
- Early warning score systems using both clinical criteria and vital signs identified hospital patients with a higher risk of IHCA.<sup>50</sup>
- A comparison using receiver-operator curves of early warning score accuracy for predicting risk of IHCA and other serious events for individual patients in the hospital had areas under the curve of 0.663 to 0.801.<sup>51</sup>
- Among 1352 surgical patients with postoperative IHCA within 30 days, 746 (55%) had developed a postoperative complication (acute kidney injury, acute respiratory failure, DVT/PE, MI, sepsis/septic shock, stroke, transfusion) before the arrest.<sup>52</sup>

### *ECG Abnormalities*

- Among 12 241 subjects from the ARIC study, in which 346 subjects had SCD during a median follow-up of 23.6 years, prolongation of the QT interval at baseline was associated with risk of SCD (HR, 1.49 [95% CI, 1.01–2.18]), and this association was driven specifically by the T-wave onset to T-peak component of the total interval.<sup>53</sup>
- In a cohort of 4176 subjects with no known HD, 687 (16.5%) had early repolarization with terminal J wave, but this pattern had no association with cardiac deaths (0.8%) over 6 years of follow-up compared with matched control subjects.<sup>54</sup>

- Among 11 956 residents of rural Liaoning Province, China, who were ≥35 years of age, 1.3% had ERP, with higher prevalence in males (2.6%) than females (0.2%).<sup>55</sup>
- In an Italian public health screening project, 24% of 13 016 students 16 to 19 years of age had at least 1 of the following electrocardiographic abnormalities: ventricular ectopic beats, AV block, Brugada-like ECG pattern, left anterior/posterior fascicular block, LVH/RV hypertrophy, long/short QT interval, left atrial enlargement, right atrial enlargement, short PQ interval, and ventricular pre-excitation WPW syndrome.<sup>56</sup>

## Genetics and Family History Associated With SCD

- Age- and sex-adjusted prevalence of electrocardiographic abnormalities associated with SCD was 0.6% to 1.1% in a sample of 7889 Spanish citizens ≥40 years of age, including Brugada syndrome in 0.13%, QTc <340 ms in 0.18%, and QTc ≥480 ms in 0.42%.<sup>57</sup>
- Exome sequencing in younger (<51 years of age) decedents who died of sudden unexplained death or suspected arrhythmic death revealed likely pathogenic variants in channelopathy- or cardiomyopathy-related genes for 29% to 34% of cases.<sup>58,59</sup> Among children with exertion-related deaths, pathogenic mutations were present in 10 of 11 decedents (91%) 1 to 10 years of age and 4 of 21 decedents (19%) 11 to 19 years of age.<sup>60</sup>
- Screening of 398 first-degree relatives of 186 unexplained SCA and 212 unexplained SCD probands revealed cardiac abnormalities in 30.2%: LQTS (13%), CPVT (4%), ARVC (4%), and Brugada syndrome (3%).<sup>61</sup>
- In a registry of 109 families of probands with unexplained SCD from 2007 to 2012, screening of 411 relatives revealed a diagnosis in 18% of families: LQTS (15%), Brugada syndrome (3%), and CPVT (1%).<sup>62</sup>
- In a registry of families of probands with unexplained SCD before 45 years of age from 2009 to 2014, screening of 230 people from 64 families revealed a diagnosis in 25% of families: Brugada syndrome (11%), LQTS (7.8%), DCM (3.1%), and HCM (3.1%).<sup>63</sup>
- Screening of 292 relatives of 56 probands with SCD revealed a diagnosis in 47 (16.1%) relatives: LQTS (12.7%), CPVT (0.3%), DCM (0.7%), ARVC (0.3%), and thoracic aortic dilation (0.3%). Among relatives completing follow-up, 3.3% had a cardiac event within 3 years and 7.2% within 5 years.<sup>64</sup>
- Prevalence of genetic HD declines with increasing age according to a screening of 180 survivors of

SCA, who represented 5.9% of 3037 referrals to a genetic heart rhythm clinic from 1999 to 2017.<sup>65</sup> Among 127 adults, diagnoses included idiopathic VF (44.1%), arrhythmogenic bileaflet mitral valve (14.2%), acquired LQTS (9.4%), LQTS (7.9%), and J-wave syndromes such as Brugada (3.9%). Among 53 children, diagnoses included LQTS (28.3%), CPVT (20.8%), idiopathic VF (20.8%), HCM (5.7%), and triadin knockout syndrome (5.7%).

### Genome-Wide Association Studies

- GWASs on cases of arrhythmic death attempt to identify previously unidentified genetic variants and biological pathways associated with potentially lethal ventricular arrhythmias and risk of sudden death. Limitations of these studies are the small number of samples available for analysis and the heterogeneity of case definition. The number of loci uniquely associated with SCD is much smaller than for other complex diseases. For example, a recent GWAS of 3939 cases with SCA found no variants associated with SCD at genomewide significance, which suggests that common genetic variation is not a significant risk factor for SCD.<sup>66</sup>
- In addition, studies do not consistently identify the same variants. A pooled analysis of case-control and cohort GWASs identified a rare (1.4% minor allele frequency) novel marker at the *BAZ2B* locus (bromodomain adjacent zinc finger domain 2B) that was associated with a risk of arrhythmic death (OR, 1.9 [95% CI, 1.6–2.3]), but inconsistent relationships for alleles associated with QRS and QT prolongation.<sup>67</sup>

### Long-QT Syndrome

- Hereditary LQTS is a genetic channelopathy characterized by prolongation of the QT interval (QTc typically >460 ms) and susceptibility to ventricular tachyarrhythmias that lead to syncope and SCD. Investigators have identified mutations in 15 genes leading to this phenotype (*LQT1* through *LQT15*).<sup>68,69</sup> *LQT1* (*KCNQ1*), *LQT2* (*KCNH2*), and *LQT3* (*SCN5A*) mutations account for the majority (≈80%) of the typed mutations.<sup>70,71</sup>
- Approximately 5% of sudden infant death syndrome and some cases of intrauterine fetal death could be attributable to LQTS.<sup>72,73</sup>
- Acquired prolongation of the QT interval is common. Prevalence of prolonged QTc was 115 of 412 (27.9%) among adults admitted to an ICU from 2014 to 2016 in Brazil.<sup>74</sup> At least 1 drug known to prolong QT interval was present in 70.4% of these cases.
- Prevalence of prolonged QTc interval was 251 of 900 patients (27.9%) admitted to a cardiac care unit from 2008 to 2009.<sup>75</sup>

- Prevalence of prolonged QTc interval was 50 of 712 patients (7%) admitted to a short-stay medical unit in the United Kingdom.<sup>76</sup>
- Prevalence of prolonged QTc interval was 95 of 7522 patients (1.9%) with ECG in the ED from 2010 to 2011, and these prolongations were attributable individually or in combination to electrolyte disturbances (51%), QT-prolonging medical conditions (56%), or QT-prolonging medications (77%).<sup>77</sup>

### Short-QT Syndrome

#### Prevalence and Incidence

- Short-QT syndrome is an inherited mendelian condition characterized by shortening of the QT interval (typically QT <320 ms) and predisposition to AF, ventricular tachyarrhythmias, and sudden death. Mutations in 5 ion channel genes have been described (*SQT1*–*SQT5*).<sup>78</sup>
- Prevalence of a QTc interval shorter than 320 ms in a population of 41 767 young, predominantly male Swiss conscripts was 0.02%,<sup>79</sup> which was identical to prevalence from a Portugal sudden death registry.<sup>80</sup>
- Prevalence of QT interval ≤320 ms in 18 825 apparently healthy people from the United Kingdom 14 to 35 years of age between 2005 and 2013 was 0.1%.<sup>81</sup> Short QT intervals were associated with male sex and Afro-Caribbean ethnicity.
- Prevalence of QT interval ≤340 ms in 99 380 unique patients ≤21 years of age at Cincinnati Children's Hospital between 1993 and 2013 was 0.05%.<sup>82</sup> Of these children, 15 of 45 (33%) were symptomatic.<sup>82</sup>
- In an international case series of 15 centers that included 25 patients ≤21 years of age with short-QT syndrome who were followed up for 5.9 years (IQR, 4–7.1 years), 6 patients had aborted sudden death (24%) and 4 (16%) had syncope.<sup>83</sup> Sixteen patients (84%) had a familial or personal history of cardiac arrest. A gene mutation associated with short-QT syndrome was identified in 5 of 21 probands (24%).

### Brugada Syndrome

#### Prevalence and Incidence

- Brugada syndrome is an acquired or inherited channelopathy characterized by persistent ST-segment elevation in the precordial leads ( $V_1$ – $V_3$ ), right bundle-branch block, and susceptibility to ventricular arrhythmias and SCD.<sup>84</sup> Brugada syndrome is associated with mutations in at least 12 ion channel-related genes.<sup>84,85</sup>
- In a meta-analysis of 24 studies, prevalence was estimated at 0.4% worldwide, with regional

prevalence of 0.9%, 0.3%, and 0.2% in Asia, Europe, and North America, respectively.<sup>86</sup> Prevalence was higher in males (0.9%) than in females (0.1%).<sup>84,87-89</sup>

### Complications

- Cardiac event rates for Brugada syndrome patients followed up prospectively in Northern Europe (31.9 months) and Japan (48.7 months) were similar: 8% to 10% in patients with prior aborted sudden death, 1% to 2% in those with history of syncope, and 0.5% in asymptomatic patients. Predictors of poor outcome included clinical history of syncope or ventricular tachyarrhythmias, family history of sudden death, and a spontaneous ERP on ECG.<sup>87,90,91</sup>
- Among patients with Brugada syndrome, first-degree AV block, syncope, and spontaneous type 1 ST-segment elevation were independently associated with risk of sudden death or implantable cardioverter-defibrillator-appropriate therapies.<sup>92,93</sup>
- Among 678 patients with Brugada syndrome from 23 centers in 14 countries, patients whose first documented arrhythmic event was SCA had a mean (SD) age of 39 (15) years, whereas patients with prophylactic defibrillator implantation first documented arrhythmic event was 46 (13) years.<sup>94</sup>

## Catecholaminergic PVT

### Prevalence and Incidence

- CPVT is a familial condition characterized by adrenergically induced ventricular arrhythmias associated with syncope and sudden death. Arrhythmias include frequent ectopy, bidirectional VT, and PVT with exercise or catecholaminergic stimulation (such as emotion, or medicines such as isoproterenol). Mutations in genes encoding RYR2 (*CPVT1*) are found in the majority of patients and result in a dominant pattern of inheritance.<sup>95</sup> Mutations in genes encoding CASQ2 (*CPVT2*) are found in a small minority and result in a recessive pattern of inheritance. Mutations have also been described in *KCNJ2* (*CPVT3*), *TRDN*, *ANK2*, and *CALM1*.<sup>95</sup>
- Prevalence of CPVT is estimated at 1:5000 to 1:10 000, but this could be an underestimate, because childhood cases were excluded.<sup>95</sup>
- Analysis of 171 probands with CPVT who were <19 years of age and 65 adult relatives described clinical presentations and prevalence of genotypes.<sup>96</sup> The presenting symptom was cardiac arrest for 28% of cases and syncope/seizure in 58%. Genetic testing of 194 subjects identified variants in *RYR2* (60%), *CASQ2* (5%), *KCNJ2* (1%), and >1 gene

in 17 cases (9%). For 23 cases (12%), no genetic variant was identified.

### Complications

- Risk factors for cardiac events included younger age at diagnosis and absence of β-blocker therapy. A history of aborted cardiac arrest and absence of β-blocker therapy were risk factors for fatal or near-fatal events.<sup>97</sup>
- In a cohort of 34 patients with CPVT, 20.6% developed fatal cardiac events during 7.4 years of follow up.<sup>98</sup>
- Incidence of SCA in children with ≥2 CPVT gene variants was 11 of 15 (73%).<sup>99</sup> VT or exertional syncope occurred in 3 of the children (20%), and only 1 (7%) was asymptomatic.

## Arrhythmogenic RV Dysplasia/ Cardiomyopathy

### Complications

- During a median follow-up of 100 patients with arrhythmogenic RV dysplasia for 6 years, 47 patients received an implantable cardioverter-defibrillator, 29 of whom received appropriate implantable cardioverter-defibrillator shocks. At the end of follow-up, 66 patients were alive. Twenty-three patients died at study entry, and 11 died during follow-up (91% of deaths were attributable to SCA).<sup>100</sup> Similarly, the annual mortality rate was 2.3% for 130 patients with ARVC from Paris, France, who were followed up for a mean of 8.1 years.<sup>101</sup>
- In a cohort of 301 patients with ARVC from a single center in Italy, probability of a first life-threatening arrhythmic event was 14% at 5 years, 23% at 10 years, and 30% at 15 years.<sup>102</sup>
- In a cohort of 502 patients with ARVC, younger patients (<50 years of age versus >50 years of age) were more likely to present with SCA (5% versus 2%) or SCD (7% versus 6%).<sup>103</sup>

## Hypertrophic Cardiomyopathy

(Please refer to Chapter 20, Cardiomyopathy and Heart Failure, for statistics regarding the general epidemiology of HCM.)

### Complications

- Among 1436 SCA cases in individuals 5 to 59 years of age between 2002 and 2015, HCM was present in 3.2% of those 5 to 34 years of age and 2.2% of those 35 to 59 years of age. This study noted the difficulty of distinguishing HCM from secondary LVH in older patients, who were excluded from the analysis.<sup>104</sup>

## Early Repolarization Syndrome

### Prevalence and Incidence

- There is no single electrocardiographic definition or set of criteria for ERP. Studies have used a range of criteria including ST elevation, terminal QRS slurring, terminal QRS notching, J-point elevation, J waves, and other variations. Although the Brugada ECG pattern is considered an early repolarization variant, it is generally not included in epidemiology assessments of ERP or early repolarization syndrome.<sup>105</sup>
- ERP was observed in 4% to 19% of the population (more commonly in young males and in athletes) and conventionally has been considered a benign finding.<sup>105–109</sup>
- In CARDIA, 18.6% of 5069 participants had early repolarization restricted to the inferior and lateral leads at baseline; by year 20, only 4.8% exhibited an ERP.<sup>109</sup> Younger age, black race, male sex, longer exercise duration and QRS duration, and lower BMI, heart rate, QT index, and Cornell voltage were associated with the presence of baseline early repolarization. Persistence of the electrocardiographic pattern from baseline to year 20 was associated with black race (OR, 2.62 [95% CI, 1.61–4.25]), BMI (OR, 0.62 per 1 SD [95% CI, 0.40–0.94]), serum triglyceride levels (OR, 0.66 per 1 SD [95% CI, 0.45–0.98]), and QRS duration (OR, 1.68 per 1 SD [95% CI, 1.37–2.06]) at baseline.<sup>109</sup>

### Complications

- Shocks from an automatic implantable cardioverter-defibrillator occur more often and earlier in survivors of idiopathic VF with inferolateral early repolarization syndrome.<sup>110,111</sup>
- In an analysis of the Social Insurance Institution's Coronary Disease Study in Finland, J-point elevation was identified in 5.8% of 10 864 people.<sup>108</sup> Those with inferior lead J-point elevation more often were male and more often were smokers; had a lower resting heart rate, lower BMI, lower BP, shorter QTc, and longer QRS duration; and were more likely to have electrocardiographic evidence of CAD. Those with lateral J-point elevation were more likely to have LVH. Before and after multivariable adjustment, subjects with J-point elevation  $\geq 1$  mm in the inferior leads ( $n=384$ ) had a higher risk of cardiac death (adjusted RR, 1.28 [95% CI, 1.04–1.59]) and arrhythmic death (adjusted RR, 1.43 [95% CI, 1.06–1.94]); however, these patients did not have a significantly higher rate of all-cause mortality. Before and after multivariable adjustment, subjects with J-point elevation  $>2$  mm ( $n=36$ ) had an increased risk of cardiac death (adjusted RR, 2.98 [95% CI, 1.85–4.92]), arrhythmic death (adjusted RR, 3.94 [95% CI,

1.96–7.90]), and death of any cause (adjusted RR, 1.54 [95% CI, 1.06–2.24]).

- Evidence from families with a high penetrance of the early repolarization syndrome associated with a high risk of sudden death suggests that the syndrome can be inherited in an autosomal dominant fashion.<sup>112</sup>

## Premature Ventricular Contractions

- In a study of 1139 older adults in the CHS without HF or systolic dysfunction studied by Holter monitor (median duration, 22.2 hours), 0.011% of all heartbeats were PVCs, and 5.5% of participants had nonsustained VT. Over follow-up, the highest quartile of ambulatory ECG PVC burden was associated with an adjusted odds of decreased LVEF (OR, 1.13 [95% CI, 1.05–1.21]) and incident HF (HR, 1.06 [95% CI, 1.02–1.09]) and death (HR, 1.04 [95% CI, 1.02–1.06]).<sup>113</sup> Although PVC ablation has been shown to improve cardiomyopathy, the association with death may be complex, representing both a potential cause and a noncausal marker for coronary or structural HD.
- Among 698 patients with cardiac resynchronization therapy, 3-year risk of VT/VF was higher in patients with  $>10$  PVCs/h (24%) than in patients with  $<10$  PVCs/h (8%; adjusted HR, 2.79 [95% CI, 1.69–4.58]).<sup>114</sup>

## Monomorphic VT

### Prevalence and Incidence

- Among 2099 subjects (mean age 52 years; 52.2% male) without known CVD, exercise-induced nonsustained VT occurred in 3.7% and was not independently associated with total mortality.<sup>115</sup>

## Polymorphic VT

### Prevalence and Incidence

- In the setting of AMI, the prevalence of PVT was 4.4%.<sup>116</sup>

### Complications

- In the setting of AMI, PVT is associated with increased mortality (17.8%).<sup>116</sup>

### Risk Factors

- PVT in the setting of a normal QT interval is most frequently seen in the context of acute ischemia or MI.<sup>117</sup>

## Torsade de Pointes

### Prevalence and Incidence

- Among 14 756 patients exposed to QT-prolonging drugs in 36 studies, 6.3% developed QT prolongation, and 0.33% developed TdP.<sup>118</sup>

- A prospective, active surveillance, Berlin-based registry of 51 hospitals observed that the annual incidence of symptomatic drug-induced QT prolongation in adults was 2.5 per million males and 4.0 per million females. The authors reported 42 potentially associated drugs, including metoclopramide, amiodarone, melperone, citalopram, and levomethadone. The mean age of patients with QT prolongation/TdP was  $57 \pm 20$  years, and the majority of the cases occurred in females (66%) and out of the hospital (60%).<sup>119</sup>
- The prevalence of drug-induced prolongation of QT interval and TdP is 2 to 3 times higher in females than in males.<sup>120,121</sup>

### Complications

- In a cohort of 459 614 Medicaid and Medicare enrollees 30 to 75 years of age who were taking antipsychotic medications, the incidence of sudden death was 3.4 per 1000 person-years, and the incidence of ventricular arrhythmia was 35.1 per 1000 person-years.<sup>122</sup>

### Risk Factors

- An up-to-date list of drugs with the potential to cause TdP is available at a website maintained by the University of Arizona Center for Education and Research on Therapeutics.<sup>123</sup>
- Specific risk factors for drug-induced TdP include prolonged QT interval, female sex, advanced age, bradycardia, hypokalemia, hypomagnesemia, LV systolic dysfunction, and conditions that lead to elevated plasma concentrations of causative drugs, such as kidney disease, liver disease, drug interactions, or some combination of these.<sup>121,124,125</sup>
- Drug-induced TdP rarely occurs in patients without concomitant risk factors. An analysis of 144 published articles describing TdP associated with non-cardiac drugs revealed that 100% of the patients had at least 1 risk factor, and 71% had at least 2 risk factors.<sup>121</sup>

## Awareness and Treatment (See Table 17-1)

- Median annual CPR training rate for US counties was 2.39% (25th–75th percentiles, 0.88%–5.31%) based on training data from the AHA, the American Red Cross, and the Health & Safety Institute, the largest providers of CPR training in the United States.<sup>126</sup> Training rates were lower in rural areas, counties with high proportions of black or Hispanic residents, and counties with lower median household income.
- Prevalence of reported current training in CPR was 18% and prevalence of having CPR training at some point was 65% in a survey of 9022 people

in the United States in 2015.<sup>127</sup> The prevalence of CPR training was lower in Hispanic/Latino people, older people, people with less formal education, and lower-income groups.

- Those with prior CPR training include 90% of citizens in Norway,<sup>128</sup> 68% of citizens in Victoria, Australia,<sup>129</sup> 61.1% of laypeople in the United Kingdom,<sup>130</sup> and 49% of people in the Republic of Korea,<sup>131</sup> according to surveys.
- Laypeople with knowledge of AEDs include 69.3% of people in the United Kingdom, 66% in Philadelphia, PA, and 32.6% in the Republic of Korea.<sup>130–132</sup> A total of 58% of Philadelphia respondents<sup>132</sup> but only 2.1% of UK respondents<sup>130</sup> reported that they would actually use an AED during a cardiac arrest.
- A survey of 5456 households in Beijing, China, Shanghai, China, and Bangalore, India, found that 26%, 15%, and 3% of respondents, respectively, were trained in CPR.<sup>133</sup>
- A survey of 501 inhabitants of Vienna, Austria, found that 52% would recognize cardiac arrest, 50% were willing to use an AED, and 33% were willing to do CPR.<sup>134</sup>
- Laypeople in the United States initiated CPR in 39.2% of OHCA in CARES 2018 data (Table 17-1).
- Layperson CPR rates in Asian countries range from 10.5% to 40.9%.<sup>135</sup>
- Laypeople in the United States were less likely to initiate CPR for people with OHCA in low-income black neighborhoods (OR, 0.49 [95% CI, 0.41–0.58])<sup>136</sup> or in predominantly Hispanic neighborhoods (OR, 0.62 [95% CI, 0.44–0.89]) than in high-income white neighborhoods.<sup>137</sup>
- Laypeople from Hispanic and Latino neighborhoods in Denver, CO, reported that barriers to learning or providing CPR include lack of recognition of cardiac arrest events and lack of understanding about what a cardiac arrest is and how CPR can save a life, as well as fear of becoming involved with law enforcement.<sup>138</sup>

## Mortality (See Tables 17-2 and 17-5 and Chart 17-1)

- In 2017, primary-cause SCD mortality was 18 835, and any-mention SCD mortality in the United States was 379 133 (Table 17-5). The any-mention age-adjusted annual rate is 97.1 (95% CI, 96.8–97.4) SCDs per 100 000 population.<sup>139</sup>
- Survival of hospitalization after cardiac arrest varied between academic medical centers and was higher in hospitals with higher cardiac arrest volume, higher surgical volume, greater availability of invasive cardiac services, and more affluent catchment areas.<sup>8</sup>

- Survival after OHCA varied between US regions (4.2%–19.8%) in the ROC Epistry from 2011 to 2015.<sup>140</sup> This variation was more marked at the level of EMS agencies (0%–28.9%) and persisted after adjustment for multiple patient, resuscitation, and hospital variables.<sup>141</sup>
- Survival after EMS-treated OHCA was 10.4% in the 2018 CARES registry, with variation between states reporting data (range, 7.8%–15.3%; Table 17-2).
- Of 1452808 death certificates from 1999 to 2015 for US residents 1 to 34 years of age, 31492 listed SCD (2%) as the cause of death, for an SCD rate of 1.32 per 100 000 individuals.<sup>142</sup>
  - SCD rate varied by age, from 0.49 per 100 000 (1–10 years) to 2.76 per 100 000 (26–34 years).
  - The rate of SCD declined from 1999 to 2015, from 1.48 to 1.13 per 100 000 individuals.
- Mortality rates for any mention of SCD by age are provided in Chart 17-1.

### **OHCA: Adults**

(See Tables 17-1 and 17-6)

- Survival to hospital discharge after EMS-treated OHCA was 10.4%, and survival with good functional status was 8.2% based on 73 910 cases in CARES for 2018.<sup>5</sup>
- Survival to hospital discharge after EMS-treated cardiac arrest in 2018 was 10.4% for patients of any age and 10.4% for adults in the CARES registry (Tables 17-1 and 17-6).
- Survival to hospital admission after EMS-treated nontraumatic OHCA in 2018 was 28.2% for all presentations, with higher survival rates in public places (40.9%) and lower survival rates in homes/residences (26.4%) and nursing homes (18.5%) in the 2018 CARES registry (Table 17-6).
- Survival to hospital discharge varied between regions of the United States, being higher in the Midwest (adjusted OR, 1.16 [95% CI, 1.02–1.32]) and the South (adjusted OR, 1.24 [95% CI, 1.09–1.40]) relative to the Northeast, in 154 177 patients hospitalized after OHCA in the NIS (2002–2013).<sup>143</sup>
- Survival at 1, 5, 10, and 15 years, respectively, was 92.2%, 81.4%, 70.1%, and 62.3% among 3449 patients surviving to hospital discharge after OHCA from 2000 to 2014 in Victoria, Australia.<sup>144</sup>
- Patients with STEMI who had OHCA had higher in-hospital mortality (38%) than STEMI patients without OHCA (6%) in a Los Angeles, CA, registry of 4729 STEMI patients from 2011 to 2014.<sup>11</sup>
- Survival to 30 days was lower for 2516 patients in nursing homes (1.7% [95% CI, 1.2%–2.2%]) than for 24483 patients in private homes (4.9%

[95% CI, 4.6%–5.2%]) in a national database in Denmark from 2001 to 2014.<sup>145</sup>

### **Sports-Related SCA/SCD**

- In a population-based registry of all paramedic responses for SCA from 2009 to 2014, 43.8% of athletes with SCA during competitive sports survived to hospital discharge.<sup>19</sup>

### **IHCA: Adults**

(See Table 17-4 and Chart 17-3)

- Survival to hospital discharge was 25.8% of 26 742 adult IHCAAs at 319 hospitals in GWTG 2018 data (Table 17-4, Chart 17-3). Among survivors, 82% had good functional status (cerebral performance category 1 or 2) at hospital discharge.
- Unadjusted survival rate after IHCA was 18.4% in the UK National Cardiac Arrest Audit database between 2011 and 2013. Survival was 49% when the initial rhythm was shockable and 10.5% when the initial rhythm was not shockable.<sup>15</sup>
- Unadjusted survival to 30 days after IHCA was 28.3% and survival to 1 year was 25.0% in 18 069 patients from 66 hospitals between 2006 and 2015 in the Swedish Register of CPR.<sup>14</sup>
- Survival to hospital discharge after IHCA was lower for males than for females (adjusted OR, 0.90 [95% CI, 0.83–0.99]) in a Swedish registry of 14 933 cases of IHCA from 2007 to 2014.<sup>146</sup>
- Mortality was lower among 348 368 patients with IHCA managed in teaching hospitals (55.3%) than among 376 035 managed in nonteaching hospitals (58.8%), even after adjustment for baseline patient and hospital characteristics (adjusted OR, 0.92 [95% CI, 0.90–0.94]).<sup>147</sup>

### **OHCA: Children**

(See Table 17-7)

- Survival to hospital discharge after EMS-treated nontraumatic cardiac arrest in 2015 was 13.2% (95% CI, 7.0%–19.4%) for children in the ROC Epistry (ROC Investigators, unpublished data, July 7, 2016).
- Survival to hospital discharge was 6.7% for 1280 children ≤1 year old, 16.2% for 560 children 1 to 12 years of age, and 19.2% for 416 children 13 to 18 years of age in CARES 2018 data (Table 17-7).
- Mortality was lower in teaching hospitals (OR, 0.57 [95% CI, 0.50–0.66]), trauma centers (OR, 0.76 [95% CI, 0.67–0.86]), and urban hospitals (OR, 0.78 [95% CI, 0.63–0.97]) relative to nonteaching, nontrauma, or rural hospitals, respectively, among 42 036 presentations of children 0 to 18 years of age for cardiac or respiratory failure in the HCUP NEDS.<sup>148</sup>
- In a registry including 974 children with OHCA from 2009 to 2012 in Singapore, Japan, Republic

of Korea, Malaysia, Thailand, Taiwan, and United Arab Emirates, 8.6% (range, 0%–9.7%) of children survived to hospital discharge.<sup>149</sup>

### IHCA: Children

(See Table 17-4)

- Survival to hospital discharge after pulseless IHCA was 41.1% in 571 children 0 to 18 years of age and 38.2% in 159 neonates (0–30 days old) per 2018 GWTG data (Table 17-4).
- Survival to hospital discharge for children with IHCA in the ICU was 45% in the Collaborative Pediatric Critical Care Research Network from 2011 to 2013.<sup>24</sup>

### Complications

(See Tables 17-6 and 17-7)

- Survivors of cardiac arrest experience multiple medical problems related to critical illness, including impaired consciousness and cognitive deficits (Tables 17-6 and 17-7).
- Functional impairments are associated with reduced function, reduced quality of life, and shortened lifespan.<sup>150,151</sup>
- Functional recovery continues over at least the first 12 months after OHCA in children and over the first 6 to 12 months after OHCA in adults.<sup>152,153</sup>
- Among 366 patients discharged after IHCA in a Veterans Administration hospital between 2014 and 2015, 55 (15%) endorsed suicidal ideation during the first 12 months.<sup>154</sup>
- Serial testing in a cohort of 141 people who survived hospitalization after SCA revealed severe cognitive deficits in 14 (13%), anxiety and depression in 16 (15%), posttraumatic stress symptoms in 29 (28%), and severe fatigue in 55 (52%).<sup>155</sup> Subjective symptoms declined over time after SCA, although 10% to 22% had cognitive impairments at 12 months, with executive functioning being most affected.<sup>156</sup>
- Of 141 individuals who survived hospitalization after SCA, 41 (72%) returned to work by 12 months.<sup>155</sup>
- Of 287 people who survived hospitalization after OHCA, 47% had reduced participation in pre-morbid activities, and 27% of those who were working before the OHCA were on sick leave at 6 months.<sup>157</sup>
- Of 153 survivors of OHCA 18 to 65 years of age in Paris, France, between 2000 and 2013, 96 (63%) returned to work after a mean (SD) of 714 (1013) days.<sup>158</sup> Younger patients with a higher-level job and for whom cardiac arrest occurred in the workplace were more likely to return to work.
- Of 206 patients who survived to 1 year after OHCA in Finland, 188 (91.3%) were living at home.<sup>159</sup>

Among 95 patients who were employed before the arrest, 69 (72.6%) had returned to work, whereas 23 (24.2) had stopped work specifically because of their medical condition.

- Among 195 family caregivers of cardiac arrest survivors, anxiety was present in 33 caregivers (25%) and depression in 18 caregivers (14%) at 12 months.<sup>160</sup>
- Among 57 437 patients discharged from the hospital after cardiac arrest identified from 2008 to 2015 Medicare claims data, unadjusted annual incidence of seizures was 1.26% (95% CI, 1.20%–1.33%), which is higher than for other Medicare patients (0.61% [95% CI, 0.61%–0.62%]).<sup>161</sup> Cardiac arrest survivors had no increased hazard for seizures after adjustment for demographics and comorbidities (HR, 0.9 [95% CI, 0.9–1.0]).

### Healthcare Utilization and Cost

- In the Oregon SUDS, the estimated societal burden of SCD in the United States was 2 million years of potential life lost for males and 1.3 million years of potential life lost for females, accounting for 40% to 50% of the years of potential life lost from all cardiac disease.<sup>162</sup>
- Among 138 children surviving IHCA, caregiver burden increased at baseline and at 3 and 12 months as measured by the Infant Toddler Quality of Life Questionnaire (<5 years) or the Child Health Questionnaire (children >5 years).<sup>163</sup>
- Among males, estimated deaths attributable to SCD exceeded all other individual causes of death, including lung cancer, accidents, CLRD, cerebrovascular disease, DM, prostate cancer, and colorectal cancer.<sup>162</sup>

### Global Burden

- International comparisons of cardiac arrest epidemiology must take into account differences in case ascertainment. OHCA usually is identified through EMS systems, and regional and cultural differences in use of EMS affect results.<sup>164</sup>
- A systematic review of the international epidemiology of OHCA from 1991 to 2007 included 30 studies from Europe, 24 from North America, 7 from Asia, and 6 from Australia.<sup>165</sup> Estimated incidence per 100 000 population of EMS-assessed OHCA was 86.4 in Europe, 98.1 in North America, 52.5 in Asia, and 112.9 in Australia. Estimated incidence per 100 000 population of EMS-treated OHCA was 40.6 in Europe, 47.3 in North America, 45.9 in Asia, and 51.1 in Australia. The proportion of cases

- with VF was highest in Europe (35.2%) and lowest in Asia (11.2%).
- A prospective data collection concerning 10 682 OHCA cases from 27 European countries in October 2014 found an incidence of 84 per 100 000 people, with CPR attempted in 19 to 104 cases per 100 000 people.<sup>166</sup> Return of pulse occurred in 28.6% (range for countries, 9%–50%), with 10.3% (range, 1.1%–30.8%) of people on whom CPR was attempted surviving to hospital discharge or 30 days.

- Western Australia reports an age- and sex-adjusted incidence of 65.9 EMS-attended cardiac arrests per 100 000 population, with resuscitation attempted in 43%.<sup>167</sup> Survival to hospital discharge was 8.7%. Among children (<18 years of age), crude incidence was 5.6 per 100 000.<sup>16</sup>
- Hospitals in Beijing, China, reported IHCA incidence of 17.5 events per 1000 admissions.<sup>168</sup>
- Among 353 adults after IHCA in 6 Kenyan hospitals in 2014 to 2016, 16 (4.2%) survived to hospital discharge.<sup>169</sup>

**Table 17-1.** Trends in Layperson Response and Outcomes for EMS-Treated OHCA, 2006 to 2018

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Survival to hospital discharge													
ROC	10.2	10.1	11.9	10.3	11.1	11.3	12.4	11.9	12.7	12.4	...	...	...
CARES	...	...	...	...	...	10.5	10	10.6	10.8	10.6	10.8	10.5	10.4
Survival if first rhythm shockable													
ROC	25.9	29	33.6	27.8	30.1	30.9	34.1	32.7	33.5	30.2	...	...	...
CARES	...	...	...	...	...	...	...	...	29.3	29.1	29.5	29.3	29.5
First rhythm shockable													
ROC	23.7	21.7	21.9	20.9	20.8	21.4	21.7	20.2	20.8	21.3	...	...	...
CARES	...	...	...	...	...	23.2	23.1	23.2	20.4	20.1	19.8	18.4	18.4
Layperson-initiated CPR													
ROC	36.5	37.9	37.4	39.1	38.6	38.6	42.8	43	44.5	43.6	...	...	...
CARES	...	...	...	...	...	38	37.8	40.4	40.4	40.6	40.7	39.4	39.2
Layperson use of AED													
ROC	3.2	3.3	3.9	4.5	4	3.9	5.1	6	6.6	6.7	...	...	...
CARES	...	...	...	...	...	4.4	4	4.6	4.9	5.4	5.7	6.0	7.3
AED shock by layperson													
ROC	2	1.6	1.8	1.8	2	1.8	2	2.2	2.2	2.3	...	...	...
CARES	...	...	...	...	...	1.7	1.6	1.6	1.6	1.7	1.7	1.6	1.7

Values are percentages. AED indicates automated external defibrillator; CARES, Cardiac Arrest Registry to Enhance Survival; CPR, cardiopulmonary resuscitation; ellipses (...), data not available; EMS, emergency medical services, OHCA, out-of-hospital cardiac arrest; and ROC, Resuscitation Outcomes Consortium.

Source: Data reported by ROC (ROC Investigators, unpublished data, July 7, 2016) and CARES.<sup>5</sup>

**Table 17-2.** Regional Variation in EMS-Treated OHCA, 2018

	Percent of Population Reporting Data	EMS-Treated OHCA Cases	Rate per 100 000 persons	Layperson-Initiated CPR, %	Public Use of AED, %	Survival to Hospital Discharge if Witnessed Collapse and Shockable Rhythm, %	Overall Survival to Hospital Discharge, %
United States	33.7	81 864	74.3	39.2	11.9	33.3	10.4
Alaska	83.2	410	66.8	70.7	14.9	35.1	12.9
District of Columbia	100.0	793	112.9	31.4	8.5	37.5	7.8
Delaware	100.0	1241	128.3	32.1	9.0	32.5	14.3
Hawaii	100.0	1348	94.9	47.8	9.9	33.2	10.7
Michigan	81.9	7451	91.0	37.6	14.5	29.9	8.4
Minnesota	85.6	2478	51.6	37.4	13.0	36.2	13.1
Montana	60.5	375	58.4	50.3	9.1	27.5	11.5
North Carolina	68.9	5420	75.7	36.3	11.8	34.7	12.5
Oregon	85.6	2300	64.1	55.0	13.3	39.0	14.5
Pennsylvania	70.4	7254	80.5	33.3	12.9	33.9	9.4
Vermont	100.0	507	81.0	46.2	9.2	25.6	11.6
Washington	84.4	4051	63.7	57.3	14.5	42.1	15.3

Population reporting data indicates percentage of region's population within geographic footprint of EMS agencies contributing data. Layperson CPR rate excludes EMS witnessed, nursing home, and healthcare facility events. Public AED use rate excludes EMS witnessed, home/residence, nursing home, and healthcare facility events. AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services, and OHCA, out-of-hospital cardiac arrest.

Source: Cardiac Arrest Registry to Enhance Survival 2018 data from states with ≥50% population reporting data and voluntarily sharing data.<sup>5</sup>

**Table 17-3.** SCA Diagnoses Among ED Visits in the United States, 2016

	Adult (≥18 y)	Child (1–17 y)	Infant (<1 y)	Total	Rate per 100 000 People
Any listed diagnosis, n	393 872	6510	3961	404 691	125.2
CPR or defibrillation procedure code, n	185 509	969	559	187 097	88.8
Principal diagnosis, n	177 052	3406	3027	183 629	56.8
Died in ED, %	77.1	70.0	80.8	77.0	...
Transferred to another hospital, %	5.1	15.0	8.4	5.3	...
Admitted to same hospital, %	10.8	5.2	2.1	10.5	...
Died in same hospital, %	5.6	2.1	1.9	5.5	...
Discharged from same hospital, %	4.9	2.7	...	5.0	...

CPR indicates cardiopulmonary resuscitation; ED, emergency department; ellipses (...), data not reported; and SCA, sudden cardiac arrest. Source: Unpublished tabulation using Healthcare Cost and Utilization Project, 2016.<sup>9</sup>

**Table 17-4.** Characteristics of and Outcomes for OHCA and IHCA, 2018

	OHCA		IHCA	
	Adults	Children	Adults	Children
Survival to hospital discharge	10.4	11.4	25.8	41.1
Good functional status at hospital discharge	8.2	9.2	21.2	14.2
VF/VT/shockable	18.7	7.6	15.3	9.0
PEA	...	...	53.9	48.4
Asystole	...	...	22.7	28.5
Unknown	...	...	8.1	14.2
Public setting	18.8	13.3	...	...
Home	69.8	86.4	...	...
Nursing home	11.5	0.3	...	...
Arrest in ICU, operating room, or ED	...	...	54.2	87.0
Noncritical care area	...	...	45.8	13.0

Values are percentages. ED indicates emergency department; ellipses (...), data not available; EMS, emergency medical services; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Source: OHCA data derived from the Cardiac Arrest Registry to Enhance Survival,<sup>5</sup> based on 79 356 EMS-treated OHCA adult cases and 2256 EMS-treated OHCA child cases in 2018. IHCA data are from Get With The Guidelines (unpublished AHA tabulation) 2018, based on 26 742 pulseless adult IHCAs in 319 hospitals and 571 pulseless child IHCAs in 90 hospitals.

**Table 17-5.** SCA Mortality, 2017 (ICD-10 Codes 146.0, 146.1, 146.9, 149.0)

Population Group	Number of Deaths as Underlying Cause, 2017, All Ages	Number of Deaths as Any-Mention Cause, 2017, All Ages
Both sexes	18835	379 133
Males	10 144	195 227
Females	8691	183 906
NH white males	7623	140 039
NH white females	6554	130 378
NH black males	1748	26 213
NH black females	1506	26 815
Hispanic males	456	18 823
Hispanic females	355	17 596
NH Asian/Pacific Islander males	252	7 913
NH Asian/Pacific Islander females	220	7 416
NH American Indian/Alaska Natives	87	2 502

Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses. *ICD-10* indicates *International Classification of Diseases, 10th Revision*; NH, non-Hispanic; and SCA, sudden cardiac arrest.

Sources: Underlying cause data derived from unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System, 2017.<sup>170</sup> Any-mention cause data derived from unpublished NHLBI tabulation using Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database, 2017.<sup>139</sup>

**Table 17-6.** Outcomes of EMS-Treated Nontraumatic OHCA in Adults (Age ≥18 Years), CARES, 2018

Presenting Characteristics (N)	Survival to Hospital Admission	Survival to Hospital Discharge	Survival With Good Neurological Function (CPC 1 or 2)	In-Hospital Mortality*
All presentations (79 356)	28.2	10.4	8.2	63.3
Home/residence (55 358)	26.4	8.5	6.6	67.9
Nursing home (9105)	18.5	4.3	1.9	76.9
Public setting (14 893)	40.9	21.0	18.1	48.7
Unwitnessed (39 378)	17.9	4.4	3.2	75.4
Bystander witnessed (29 887)	37.3	15.6	12.7	58.1
EMS provider witnessed (10 089)	41.7	17.9	14.3	57.1
Shockable presenting rhythm (14 867)	48.2	29.2	25.7	39.3
Nonshockable presenting rhythm (64 477)	23.6	6.0	4.1	74.7
Layperson CPR (22 707)	31.2	13.6	11.6	56.2
No layperson CPR (35 706)	24.6	7.3	5.5	70.5

Values are percentages. CARES indicates Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Index; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

\*Percentage of patients admitted to hospital who died before hospital discharge.

Source: Data derived from CARES.<sup>5</sup>

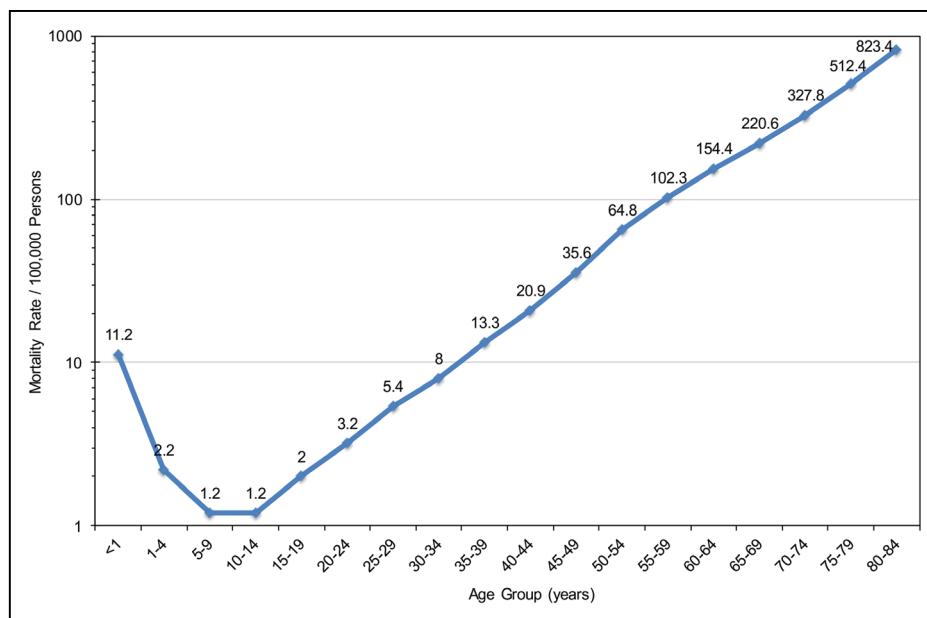
**Table 17-7.** Outcomes of EMS-Treated Nontraumatic OHCA in Children, CARES, 2018

Age Group (N)	Survival to Hospital Admission	Survival to Hospital Discharge	Survival With Good Neurological Function (CPC 1 or 2)	In-Hospital Mortality*
<1 y (1280)	19.2	6.7	4.9	65.0
1–12 y (560)	37.9	16.2	13.2	57.1
13–18 y (416)	41.1	19.2	17.1	53.2

Values are percentages. CARES indicates Cardiac Arrest Registry to Enhance Survival; CPC, Cerebral Performance Category; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

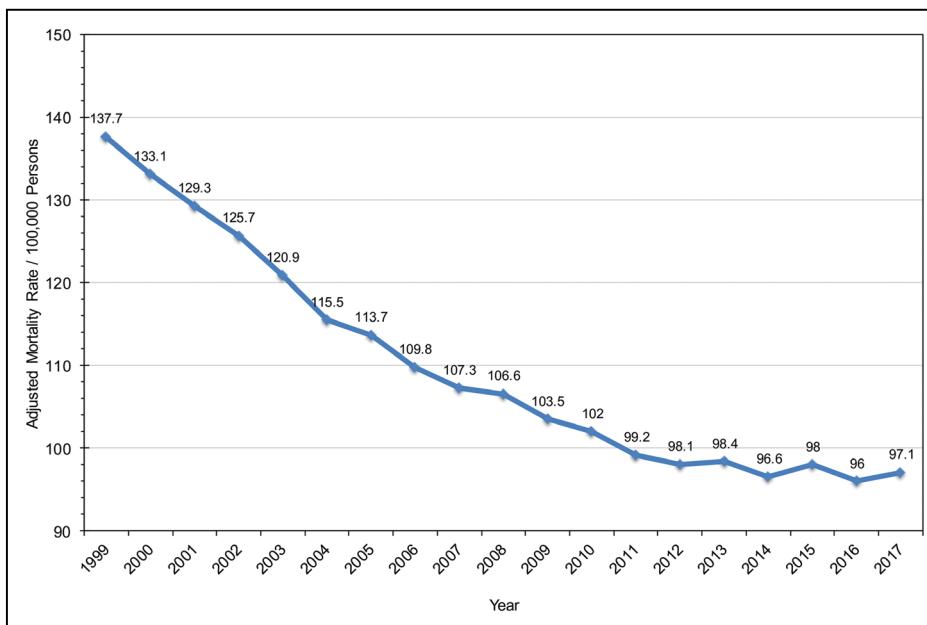
\*Percentage of patients admitted to hospital who died before hospital discharge.

Source: Data derived from CARES.<sup>5</sup>



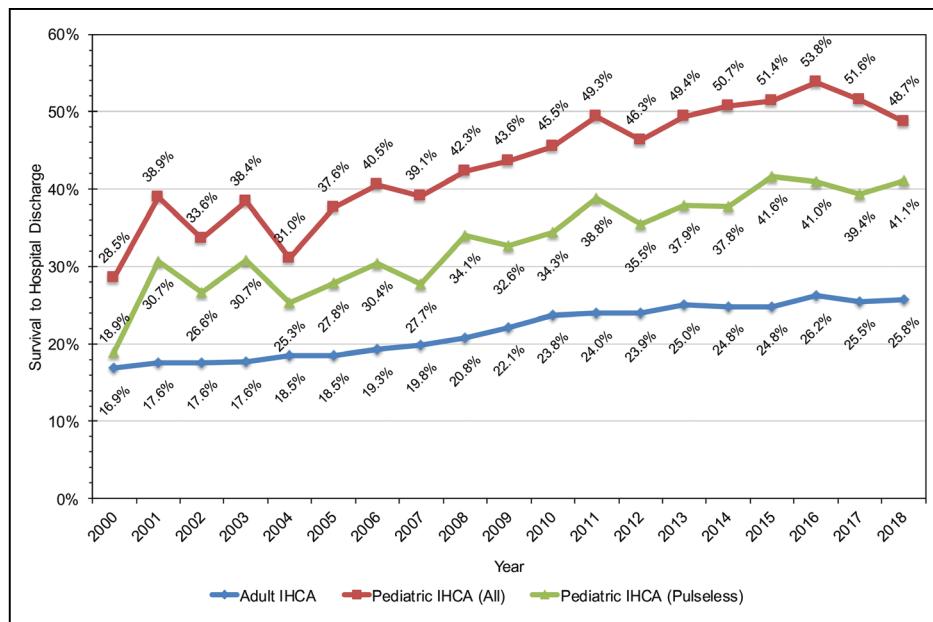
**Chart 17-1. Age-specific mortality rates for any mention of sudden cardiac death by age, United States, 2017.**

Source: Data derived from Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research database. Accessed June 7, 2018.<sup>139</sup>



**Chart 17-2. Age-adjusted mortality rates for any mention of sudden cardiac death, United States, 1999 to 2017.**

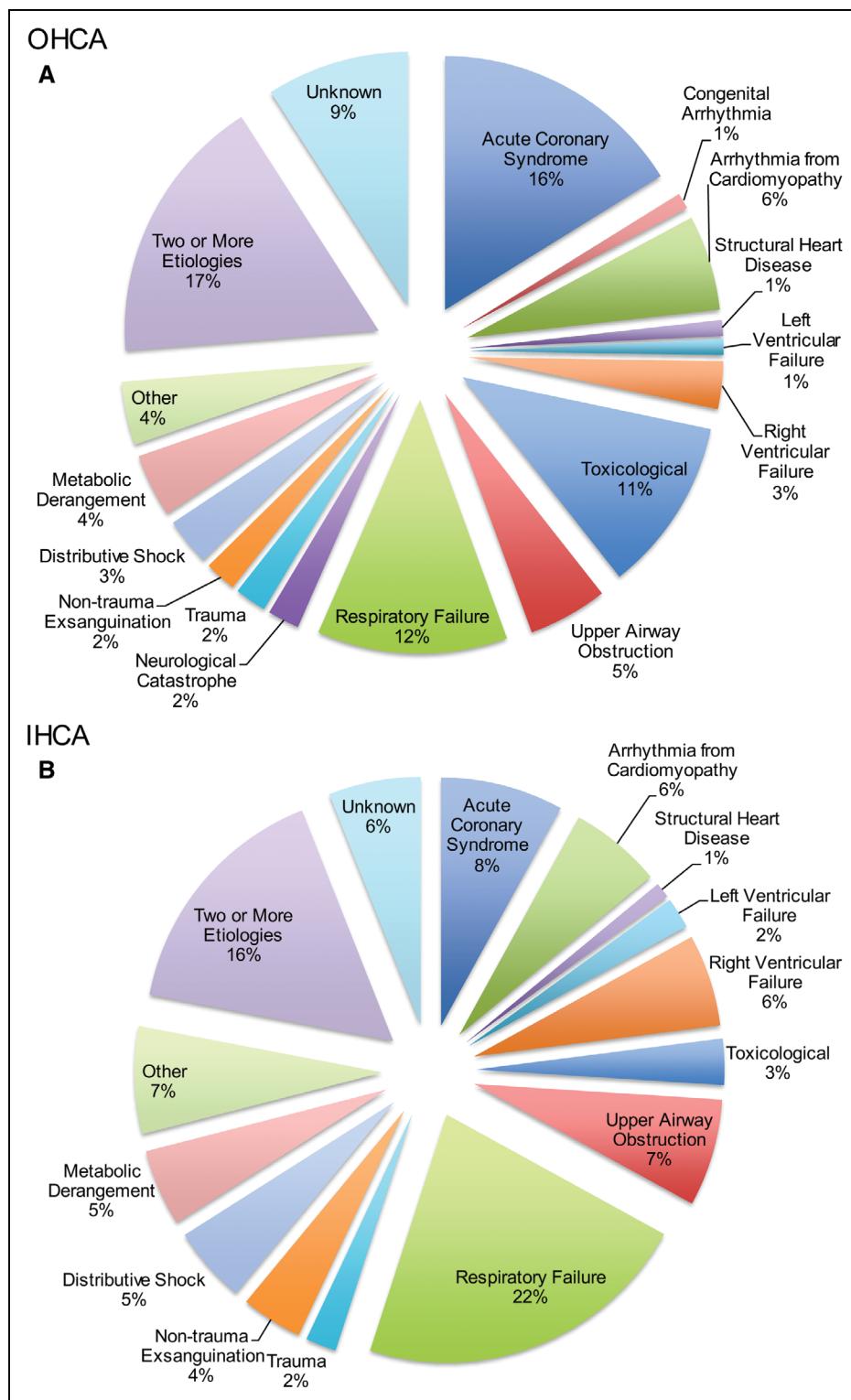
Source: Data derived from Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research. Accessed June 7, 2018.<sup>139</sup>



**Chart 17-3. Temporal trends in survival to hospital discharge after IHCA in adults and children in GWTG—Resuscitation from 2000 to 2018.**

GWTG indicates Get With The Guidelines; and IHCA, in-hospital cardiac arrest.

Source: GWTG—Resuscitation; unpublished American Heart Association data, 2017.



**Chart 17-4. Detailed causes of OHCA and IHCA among patients surviving to hospital admission.**

**A.** Proportion of hospitalized patients with each cause after OHCA. **B.** Proportion of hospitalized patients with each cause after IHCA. Pathogenesis based on testing and evaluation in the hospital. “Other” corresponds to all other causes. IHCA, in-hospital cardiac arrest; and OHCA, out-of-hospital cardiac arrest.

Source: Data derived from Chen et al.<sup>30</sup>

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## 18. SUBCLINICAL ATHEROSCLEROSIS

**See Charts 18-1 through 18-4**

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Multiple complementary imaging modalities allow detection and quantification of atherosclerosis through its stages in different vascular beds. Early identification of subclinical atherosclerosis can guide preventive care, including lifestyle modifications and medical treatment (eg, aspirin, antihypertensive therapy, lipid-lowering therapy) to prevent clinical manifestations of atherosclerosis such as MI, stroke, or PAD. Several modalities

### Abbreviations Used in Chapter 18

ABI	ankle-brachial index
ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
ASCVD	atherosclerotic cardiovascular disease
AWHS	Aragon Workers' Health Study
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CAC	coronary artery calcification
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CONFIRM	Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry
CRP	C-reactive protein
CT	computed tomography
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
EF	ejection fraction
ESRD	end-stage renal disease
FHS	Framingham Heart Study
FMD	flow-mediated dilation
FRS	Framingham Risk Score
HANDLS	Healthy Aging in Neighborhoods of Diversity Across the Life Span
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
IMPROVE	Carotid Intima Media Thickness (IMT) and IMT Progression as Predictors of Vascular Events in a High Risk European Population
IMT	intima-media thickness
JHS	Jackson Heart Study
JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)

(Continued)

### Abbreviations Used in Chapter 18 Continued

LV	left ventricular
LVH	left ventricular hypertrophy
MACE	major adverse cardiovascular events
MASALA	Mediators of Atherosclerosis in South Asians Living in America
MESA	Multi-Ethnic Study of Atherosclerosis
MetS	metabolic syndrome
MI	myocardial infarction
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NHLBI	National Heart, Lung, and Blood Institute
NNT <sub>5</sub>	5-year number needed to treat
OR	odds ratio
PA	physical activity
PAD	peripheral artery disease
PESA	Progression of Early Subclinical Atherosclerosis
PREDIMED	Prevención con Dieta Mediterránea
PWV	pulse-wave velocity
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SES	socioeconomic status
SWAN	Study of Women's Health Across the Nation
TC	total cholesterol
TIA	transient ischemic attack
TIPS	The Indian Polycap Study

can be used for imaging atherosclerosis, including CT of the chest for evaluation of CAC, B-mode ultrasound of the neck for evaluation of carotid artery IMT or plaque, brachial artery reactivity testing, aortic and carotid MRI, and tonometric methods of measuring vascular compliance or microvascular reactivity. Among these modalities, the role of CAC in cardiovascular risk assessment is particularly well defined. According to the 2018 Cholesterol Clinical Practice Guideline<sup>1</sup> and the 2019 CVD Primary Prevention Clinical Practice Guidelines,<sup>2</sup> in intermediate-risk or selected borderline-risk adults, if the decision about statin therapy remains uncertain after 10-year ASCVD risk calculation and after accounting for risk enhancers, it is reasonable to use a CAC score in the decision to withhold, postpone, or initiate statin therapy.<sup>1</sup>

### Coronary Artery Calcification Background

- CAC measures the burden of atherosclerosis in the coronary arteries by CT. Other components of the atherosclerotic plaque, including fatty (eg, cholesterol-rich components) and fibrotic components, often accompany CAC and can be present even in the absence of CAC.
- The presence of any CAC, which indicates that at least some atherosclerotic plaque is present, is defined by an Agatston score >0. The Agatston score is calculated as a sum of scores for each calcification in a coronary artery, assigning a weighted

value to the highest density of calcification and multiplying this by the area of calcification. Scores can be reported in both age, sex, and race percentile units and in absolute units; absolute CAC cutoffs offer more prognostic information across all age groups in both males and females.<sup>3</sup> An absolute score of 1 to 99 may favor statin therapy, especially among individuals  $\geq 55$  years of age, and a score of  $\geq 100$  is a stronger indication for statin therapy, with the choice made in the context of shared decision making.<sup>1,2</sup>

### **Prevalence and Risk Factors (See Charts 18-1 through 18-3)**

- The NHLBI's FHS reported CAC measured in 3238 white adults in age groups ranging from  $<45$  to  $\geq 75$  years of age.<sup>4</sup>
  - Overall, 32.0% of females and 52.9% of males had prevalent CAC.
  - Among participants at intermediate risk according to the FRS, 58% of females and 67% of males had prevalent CAC.
- The NHLBI's CARDIA study measured CAC in 3043 black and white adults 33 to 45 years of age (at the CARDIA year 15 examination).<sup>5</sup>
  - Overall, 15.0% of males, 5.1% of females, 5.5% of those 33 to 39 years of age, and 13.3% of those 40 to 45 years of age had prevalent CAC. Overall, 1.6% of participants had an Agatston score  $>100$ .
- Chart 18-1 shows the prevalence of CAC by ethnicity and sex in adults 33 to 45 years of age. The prevalence of CAC was lower in black versus white males but was similar in black versus white females at these ages.
- The NHLBI's JHS assessed the prevalence of elevated CAC in 4416 black participants (mean age 54 years; 64% females).<sup>6</sup>
  - CAC  $>100$  was noted in 14% of those without any MetS or DM, 26% of those with MetS, and 41% of those with DM.
- The NHLBI's MESA, a study of white, black, Chinese, and Hispanic adults, measured CAC in 6814 participants 45 to 84 years of age (mean 63 years), including white (n=2619), black (n=1898), Hispanic (n=1494), and Chinese (n=803) males and females.<sup>7</sup>
  - The overall prevalence of CAC in these 4 ethnic groups was 70.4%, 52.1%, 56.5%, and 59.2%, respectively, among men and was 44.6%, 36.5%, 34.9%, and 41.9%, respectively, among women.
  - The prevalence and 75th percentile levels of CAC were highest in white males and lowest in black and Hispanic females. Significant ethnic differences persisted after adjustment

for risk factors, with the prevalence of coronary calcium being 22% lower in blacks, 15% lower in Hispanics, and 8% lower in Chinese than in whites.

- Compared with MESA, the MASALA study is a community-based cohort of South Asians in the United States and on average 5 years younger than in MESA.<sup>8</sup>
  - The age-adjusted prevalence of CAC was similar among white (68.8%) and South Asian (67.9%) males, with these groups having a greater prevalence of CAC than Chinese (57.8%), black (51.2%), and Hispanic (57.9%) males.
  - In contrast, the age-adjusted prevalence of CAC was lower in South Asian females (36.8%) than in white females (42.6%) and females of other races/ethnicities.
- Further illustrating the variability of CAC based on population and habits, a forager-horticulturalist population of 705 individuals living in the Bolivian Amazon had the lowest reported levels of CAC of any population recorded to date.<sup>9</sup>
  - Overall in the population (mean age 58 years; 50% females), 85% of individuals were free from any CAC, and even in individuals  $>75$  years of age, 65% remained free of CAC. These unique data indicate that coronary atherosclerosis can typically be avoided by maintaining a low lifetime burden of CAD risk factors.<sup>9</sup>
- The prevalence of CAC varies according to baseline traditional risk factor profile. In recent studies from MESA, the prevalence of CAC in those with no lipid abnormalities was 42% versus 50% in those with 3 lipid abnormalities,<sup>10</sup> and 32% of people in MESA with no known traditional CVD risk factors had presence of CAC versus 65% of those with 3 risk factors.<sup>11</sup>
- The duration of risk factor exposure is associated with CAC, as exemplified in an analysis of exposure to DM and prediabetes in 3628 participants in CARDIA.<sup>12</sup>
  - For each additional 5 years of exposure to DM and prediabetes, the adjusted HR for CAC was 1.15 (95% CI, 1.06–1.25) and 1.07 (95% CI, 1.01–1.13), respectively.
- Beyond traditional cardiovascular risk factors, recent studies have identified obesity, NAFLD, and elevated Lp(a) as being associated with CAC.
  - Considering 1585 participants free of CHD and free of MetS, those who were obese had a higher prevalence of CAC than individuals with a normal weight, with a prevalence ratio of 1.59 (95% CI, 1.38–1.84).<sup>13</sup>

- In a meta-analysis of 42 410 individuals, including 16 883 with NAFLD, CAC scores were higher in those with NAFLD (OR, 1.64 [95% CI, 1.42–1.89]).<sup>14</sup>
- In 937 apparently healthy asymptomatic family members of individuals with premature ASCVD, high Lp(a) levels were associated with CAC  $\geq 100$  (OR, 1.79 [95% CI, 1.13–2.83]).<sup>15</sup>
- In a cohort of 428 HIV-positive and 276 HIV-negative individuals concurrently referred for clinically indicated cardiac CT, those who were HIV positive had less calcified plaque than those who were HIV negative (adjusted OR, 0.57 [95% CI, 0.40–0.82]).<sup>16</sup>
- The 10-year trends in CAC among individuals without clinical CVD in MESA were assessed (Chart 18-2).
  - The mean age at the baseline examination was 67 years, with 47.4% men. Detectable CAC was evaluated in whites, African American, Hispanic, and Chinese participants, with >50% prevalence at baseline.
  - Ten-year trends in CAC prevalence among the 4 racial/ethnic groups revealed a significant trend toward increased prevalence of CAC in blacks but not in any other group (Chart 18-2). Among blacks, the CAC prevalence ratio (year 10 versus baseline) was 1.27 ( $P<0.001$  for test for trend).<sup>17</sup>
  - The severity of CAC was also evaluated at baseline and 10 years (Chart 18-3). After adjustment for age, sex, ethnicity, and type of CT scanner, the proportion of participants with no CAC decreased over time from 40.7% to 32.6% ( $P=0.007$ ), and the proportions increased from 29.9% to 37.0% ( $P=0.01$ ) for those with a CAC score ranging from 1 to 99 and from 14.7% to 17.7% ( $P=0.14$ ) for those with a CAC score of 100 to 399, whereas the proportion with a CAC score  $\geq 400$  decreased from 9.1% to 7.2% ( $P=0.11$ ).

### CAC and Incidence of ASCVD Events (CHD and Stroke)

#### (See Chart 18-4)

- In a landmark study, the NHLBI's MESA reported on the association of CAC scores with first CHD events over a median follow-up of 3.9 years among a population-based sample of 6722 individuals (39% white, 27% black, 22% Hispanic, and 12% Chinese).<sup>18</sup>
- Chart 18-4 shows the HRs associated with CAC scores of 1 to 100, 101 to 300, and  $>300$  compared with those without CAC (score=0), after adjustment for standard risk factors. People with CAC scores of 1 to 100

had  $\approx 4$  times greater risk and those with CAC scores  $>100$  were 7 to 10 times more likely to experience a coronary event than those without CAC.

- CAC provided similar predictive value for coronary events in whites, Chinese, blacks, and Hispanics (HRs ranging from 1.15–1.39 for each doubling of coronary calcium).
- In a more recent MESA analysis with 12-year follow-up, machine learning was used to assess predictors of cardiovascular events.
  - Among 735 variables from imaging and non-invasive tests, questionnaires, and biomarker panels, CAC emerged as the strongest predictor of CHD and ASCVD events.<sup>19</sup>
- CAC was highly predictive of CHD event risk in both young and elderly MESA participants in a follow-up that extended to 8.5 years, which suggests that once CAC is known, chronological age has less importance.<sup>20</sup>
  - Compared with a CAC score of 0, CAC  $>100$  was associated with an increased multivariable-adjusted CHD event risk in the younger individuals (45–54 years of age), with an HR of 12.4 (95% CI, 5.1–30.0).
  - The respective risk was similar even in the very elderly (75–84 years of age), with an HR of 12.1 (95% CI, 2.9–50.2).
- The prospective Dallas Heart Study reported the prognostic value of CAC scores in a relatively younger cohort (44.4 $\pm$ 9.0 years of age) of 2084 participants who were followed up for a median of 9 years.<sup>21</sup>
  - Compared with individuals with CAC=0, those with CAC scores of 10 to 100 and  $>100$  were associated with an HR of 3.43 (95% CI, 1.36–8.56) and 5.64 (95% CI, 2.28–13.97) for CHD events, respectively.
  - The addition of CAC to the traditional risk factor model resulted in significant improvement in the C statistic ( $\Delta=0.03$ ;  $P=0.003$ ), as well as a net correct reclassification of 22%.
- In the Heinz Nixdorf Recall Study of 4180 individuals, CAC independently predicted stroke during a mean follow-up of 7.9 years.<sup>22</sup> Cox proportional hazards regressions were used to examine CAC as a predictor of stroke in addition to established vascular risk factors (age, sex, SBP, LDL-C, HDL-C, DM, smoking, and AF).
  - Study participants who had a stroke had significantly higher CAC values at baseline than the remaining participants (median 104.8 [quartile 1, 14.0; quartile 3, 482.2] versus 11.2 [quartile 1, 0; quartile 3, 106.2];  $P<0.001$ ).
  - In a multivariable Cox regression, log10(CAC + 1) was a stroke predictor (HR, 1.52 [95% CI,

1.19–1.92];  $P=0.001$ ) independent of traditional risk factors in low- and intermediate-risk individuals.

- A recent meta-analysis that pooled data from 3 studies evaluated 13 262 asymptomatic individuals (mean age 60 years, 50% males) without apparent CVD.<sup>23</sup>
  - During a mean follow-up of 7.2 years, the pooled RR of incident stroke with CAC >0 was 2.95 (95% CI, 2.18–4.01;  $P<0.001$ ) compared with CAC=0.
  - Furthermore, there was an increasing risk with higher CAC score (0.12% per year for CAC=0, 0.26% per year for CAC 1–99, 0.41% per year for CAC 100–399, and 0.70% per year for CAC ≥400).

### CAC and Incidence of HF, AF, and Noncardiovascular Outcomes

- In the Rotterdam Study, CAC independently predicted incident HF during a median follow-up of 6.8 years.<sup>24</sup>
  - After adjustment for risk factors, those with severe CAC (>400) had a 4.1-fold higher risk (95% CI, 1.7–10.1) of HF than those with CAC scores of 0 to 10.
  - In addition, CAC substantially improved the risk classification (net reclassification index, 34.0%).
- A recent MESA analysis examining prediction of HF with preserved EF found that CAC >300 was a significant independent predictor in females (HR, 2.82 [95% CI, 1.32–6.00]) but not in males (HR, 0.91 [95% CI, 0.46–1.82]).<sup>25</sup>
- In MESA, during a median follow-up of 8.5 years, after accounting for risk factors, higher CAC scores were associated with increased risk for AF (CAC=0: HR, 1.0 [referent]; CAC=1–100: HR, 1.4 [95% CI, 1.01–2.0]; CAC=101–300: HR, 1.6 [95% CI, 1.1–2.4]; CAC >300: HR, 2.1 [95% CI, 1.4–2.9]).<sup>26</sup> The addition of CAC to a risk score yielded relative integrated discrimination improvement of 0.10 (95% CI, 0.061–0.15).
- A MESA analysis also showed that a higher CAC burden was associated with noncardiovascular outcomes.<sup>27</sup>
  - During a median follow-up of 10.2 years, accounting for demographics and traditional risk factors, participants with severe CAC (>400) were at an increased risk of cancer (HR, 1.53 [95% CI, 1.18–1.99]), CKD (HR, 1.70 [95% CI, 1.21–2.39]), pneumonia (HR, 1.97 [95% CI, 1.37–2.82]), chronic obstructive pulmonary disease (HR, 2.71 [95% CI, 1.60–4.57]), and hip fracture (HR, 4.29 [95% CI, 1.47–12.50]) compared with those with CAC=0.

### CAC Progression and Risk

- Data from 6778 people in MESA showed annual CAC progression averaged 25±65 Agatston units, and among those without CAC at baseline, a 5-U annual change in CAC was associated with HRs of 1.4 and 1.5 for total and hard CHD events, respectively.<sup>28</sup>
  - Among those with CAC >0 at baseline, HRs per 100-U annual change in CAC were 1.2 and 1.3, respectively, and for those with annual progression ≥300 versus no progression, HRs were 3.8 and 6.3, respectively.
- Furthermore, in MESA, CAC progression was associated with incident AF. Presence of any CAC progression (>0 per year) in the 5-year follow-up was associated with 1.55-fold higher risk for AF (95% CI, 1.10–2.19).<sup>26</sup>
  - The risk of AF increased with higher levels of CAC progression: (1–100 per year: HR, 1.47 [95% CI, 1.03–2.09]; 101–300 per year: HR, 1.92 [95% CI, 1.15–3.20]; >300 per year: HR, 3.23 [95% CI, 1.48–7.05]).
- In a MESA study of 2759 postmenopausal females, despite no association between sex hormones and prevalent CAC, an association emerged between sex hormones and CAC progression over a median of 4.7 years.<sup>29</sup>
  - Females with higher free testosterone showed greater CAC progression (RR, 1.26 [95% CI, 1.01–1.56]), and those with higher sex hormone binding globulin had lower progression (0.80 [5% CI, 0.64–0.99]).

### Social Determinants of CAC

- Addressing individuals living in the rural United States, a study reported the distribution of CAC scores among 1607 (mean age 56 years; 56% females) community-dwelling asymptomatic individuals from central Appalachia.<sup>30</sup>
  - Overall, 44% had a CAC score of 0, whereas the prevalence of those with mild (1–99), moderate (100–399), and severe (≥400) CAC was 29%, 15%, and 11%, respectively.
- Schmidt et al<sup>31</sup> examined the interaction of SES and a common variant in chromosome 9p21.3 in association with CAC and incident events in the Heinz Nixdorf Recall Study. In the 4116 participants in the analysis, SES was examined by education and income.
  - Genotype-income interaction, but not genotype-education interaction, was observed for CAC and events.
  - The lowest tertile of income had the strongest genetic effect, a 53.1% (95% CI, 30.6%–79.6%;  $P=1.8\times10^{-7}$ ) increase in CAC and an HR of 1.44 (95% CI, 1.01–2.07;

$P=0.049$ ) for incident coronary events per additional risk allele.

- This suggests that lower income may be a determinant of increased expression of genetic susceptibility to CAD.

## Carotid IMT

### Background

- Carotid IMT measures the thickness of 2 layers (the intima and media) of the wall of the carotid arteries, the largest conduits of blood going to the brain. Carotid IMT is thought to be an earlier manifestation of atherosclerosis than CAC, because thickening precedes the development of frank atherosclerotic plaque. Carotid IMT methods may vary by part of the artery measured (common carotid, internal carotid, or bulb), measurement of near and far walls, and reporting of average (more common) or maximum thickness.
- Carotid IMT is greater with age and in males. Thus, high-risk levels of thickening might be considered as those in the highest quartile or quintile for one's age and sex, or  $\geq 1$  mm. Carotid ultrasound can also detect plaques and percent stenosis, although primary prevention guidelines have not recommended screening of asymptomatic people using either the presence of atherosclerotic plaque or carotid IMT to quantify atherosclerosis or predict risk.<sup>32,33</sup>
- In the CHS, mean maximal common carotid IMT was  $1.03 \pm 0.20$  mm, and mean internal carotid IMT was  $1.37 \pm 0.55$  mm.<sup>34</sup>

### Risk Factors

- In participants in the Bogalusa Heart Study (mean age of  $32 \pm 3$  years), after adjustment for age, race, and sex, carotid IMT was associated significantly and positively with waist circumference, SBP, DBP, and LDL-C. Carotid IMT was inversely correlated with HDL-C levels. Participants with greater numbers of adverse risk factors (0, 1, 2, 3, or more) had stepwise increases in mean carotid IMT levels.<sup>35</sup>
- Additionally, the Bogalusa Heart Study investigated the association between risk factors measured in childhood with carotid IMT measured in these young adults.<sup>36</sup> Higher BMI and LDL-C levels measured at 4 to 7 years of age were associated with increased risk for being >75th percentile for carotid IMT in young adulthood. Higher SBP and LDL-C and lower HDL-C in young adulthood were also associated with having high carotid IMT.
- A similar pattern of association between risk factors at a younger age and carotid IMT in adulthood was demonstrated in a large Finnish cohort study.<sup>37</sup> These data highlight the importance of adverse risk factor levels in early

childhood and young adulthood in the early development of atherosclerosis.

- Two large, population-based prospective studies have investigated the association of carotid ultrasound findings with outcomes with shared pathogenesis of atherosclerosis.<sup>38,39</sup>
- In 1243 FHS participants ( $57 \pm 9$  years of age; 53% females), the degree of carotid stenotic burden on carotid ultrasound was predictive of cerebral microbleeds on brain MRI, a marker of stroke and dementia. Carotid stenosis  $\geq 25\%$  was associated with a 2.2-fold (95% CI, 1.10–4.40) increased risk of cerebral microbleed, whereas no association was noted with carotid IMT.<sup>38</sup>
- Among 13 197 individuals 45 to 64 years of age (26% blacks, 56% females) followed up for a median of 22.7 years, mean carotid IMT in the fourth quartile ( $\geq 0.81$  mm) versus first quartile ( $< 0.62$ ) was significantly associated with ESRD.<sup>39</sup>
- Recent evidence suggests that sleep patterns and duration, which are associated with CVD, are associated with subclinical atherosclerosis.<sup>40</sup> In nearly 4000 asymptomatic middle-aged individuals in the PESA Study, individuals with very short (<6 hours) sleep and highest quintile of sleep fragmentation had the greatest odds of subclinical atherosclerosis defined by carotid and femoral ultrasound imaging.<sup>40</sup> Compared with those who slept 7 to 8 hours per night, and with adjustment for conventional risk factors, those who slept <6 hours per night had a 1.27 greater odds of noncoronary atherosclerosis.
- In the Bogalusa Heart Study,<sup>35</sup> carotid IMT was measured in 518 black and white males and females at a mean age of  $32 \pm 3$  years. These males and females were healthy but overweight.
  - Males had significantly higher carotid IMT in all segments than females, and blacks had higher common carotid and carotid bulb IMT than whites.
- Updates from an individual-participant meta-analysis involving 15 population-based cohorts worldwide that included 60 211 individuals (46 788 whites, 7200 blacks, 3816 Asians, and 2407 Hispanics) demonstrated differing associations between risk factors and burden of carotid IMT according to racial/ethnic groups.<sup>41</sup> Specifically, the association between age and carotid IMT was weaker in blacks and Hispanics, SBP was more strongly associated with carotid IMT in Asians, and HDL-C and smoking were less associated with carotid IMT in blacks.
- Among both females and males in the NHLBI's MESA, blacks had the highest common carotid

IMT, but they were similar to whites and Hispanics in internal carotid IMT. Chinese participants had the lowest carotid IMT, in particular in the internal carotid, of the 4 ethnic groups.<sup>42</sup>

- In MESA, carotid IMT and CAC were found to be commonly associated, but patterns of association differed somewhat by sex and race.<sup>42</sup>
  - Common and internal carotid IMT were greater in females and males who had CAC than in those who did not, regardless of ethnicity.
  - Overall, CAC prevalence and scores were associated with carotid IMT, but associations were somewhat weaker in blacks than in other ethnic groups.
  - In general, blacks had the thickest carotid IMT of all 4 ethnic groups, regardless of the presence of CAC.
  - Common carotid IMT differed little by race/ethnicity in females with any CAC, but among females with no CAC, IMT was higher among blacks (0.86 mm) than in the other 3 groups (0.76–0.80 mm).

### **Social Determinants of Carotid IMT and Vascular Disease**

- The IMPROVE study cohort of 3703 Europeans studied the relation of SES with carotid IMT. Manual laborers had higher carotid IMT than white collar workers, a finding that was independent of sex, age groups, and education and was only partially mediated by risk factors.<sup>43</sup>
- In the biracial HANDLS study of 2270 adults, interaction analyses demonstrated a race × SES effect whereby blacks with high (rather than low) SES had higher carotid IMT and PWV (aortic stiffness) than other groups, suggesting a group with greater subclinical CVD.<sup>44</sup>
- In the Young Finns Study of 1813 adults 27 to 39 years of age followed up for >20 years, SES indexed to education was inversely associated with CVD risk factors including obesity, glycemic level, and smoking and was directly associated with PA.<sup>45</sup> Individuals with higher education had lower progression in IMT in follow-up.

### **Risk Prediction**

- A study from 3 population-based cohorts (ARIC, N=13 907; MESA, N=6640; and the Rotterdam Study, N=5220) demonstrated that both a higher carotid IMT and presence of carotid plaque were independently associated with an increased risk of incident AF.<sup>46</sup> In this study, a 1-SD increase in carotid IMT and presence of carotid plaque were associated with a meta-analyzed HR of 1.12 (95% CI, 1.08–1.16) and 1.30 (95% CI, 1.19–1.42), respectively.

- The CHS reported follow-up of 4476 males and females ≥65 years of age (mean age 72 years) who were free of CVD at baseline.<sup>34</sup> After a mean follow-up of 6.2 years, those with maximal combined carotid IMT in the highest quintile had a 4-fold greater risk for incident heart attack or stroke than those in the bottom quintile. After adjustment for other risk factors, a 3-fold greater risk for the top versus the bottom quintile remained.

- In one of the largest studies to date evaluating both prediction and reclassification from carotid IMT and presence of carotid plaque, ARIC investigators found that the addition of carotid IMT and plaque to traditional risk factors improved prediction of CHD risk.<sup>47</sup> In particular, among 13 145 participants (5682 men, 7463 women), ≈23% were reclassified by adding carotid IMT and plaque data to traditional risk factors. The area under the curve improved from 0.742 to 0.755 (95% CI for difference in adjusted area under the curve, 0.008–0.017).
- In MESA, during a median follow-up of 3.3 years, an IMT rate of change of 0.5 mm per year was associated with an HR of 1.23 (95% CI, 1.02–1.48) for incident stroke.<sup>48</sup> The upper quartile of IMT rate of change had an HR of 2.18 (95% CI, 1.07–4.46) compared with the lower 3 quartiles combined.
- Despite this evidence, conflicting data have been reported on the contribution of carotid IMT to risk prediction. A consortium of 14 population-based cohorts consisting of 45 828 individuals followed up for a median of 11 years demonstrated little additive value of common carotid IMT to FRS for purposes of discrimination and reclassification of incident MI and stroke (95% CI, 2.7%–4.6%).<sup>49</sup> The C statistics of the model with FRS alone (0.757 [95% CI, 0.749–0.764]) and with addition of common carotid IMT (0.759 [95% CI, 0.752–0.766]) were similar. The net reclassification improvement with the addition of common carotid IMT was small (0.8% [95% CI, 0.1%–1.6%]). In those at intermediate risk, the net reclassification improvement was 3.6% among all individuals.

- Interestingly, the ability of carotid IMT to predict incident CVD events might also depend on how the data are modeled. In MESA, the use of an age-, sex-, and race-adjusted carotid IMT score that combined data from both the internal and common carotid artery resulted in a significant improvement in the net reclassification improvement of 4.9% ( $P=0.024$ ), with a particularly higher impact in individuals with an intermediate FRS, in whom the net reclassification improvement was 11.5%.<sup>50</sup>
- Among 13 590 participants in ARIC who were 45 to 64 years of age, each 1-SD increase in carotid

IMT was associated with incident HF (HR, 1.20 [95% CI, 1.16–1.25]) in a 20-year follow-up after accounting for major CVD risk factors and CHD.<sup>51</sup> Similar associations were also noted across all race and sex groups. This relationship was found to be much stronger among those without established DM.

- A study from a consortium of population-based cohorts reported no added value of measurement of mean common carotid IMT in individuals with high BP for improving cardiovascular risk prediction.<sup>52</sup> For those at intermediate risk, the addition of mean common carotid IMT to an existing cardiovascular risk score resulted in a small but statistically significant improvement in risk prediction.
- In a recent study, however, carotid plaque burden measured via 3-dimensional carotid ultrasound showed promise in improving CVD risk prediction.<sup>53</sup> The prospective Biolmage Study enrolled 5808 asymptomatic US adults (mean age 69 years; 56.5% females). Carotid plaque areas from both carotid arteries were summed as the carotid plaque burden. The primary end point was the composite of MACE (cardiovascular death, MI, and ischemic stroke). After adjustment for risk factors, the HRs for MACE were 1.45 (95% CI, 0.67–3.14) and 2.36 (95% CI, 1.13–4.92) with increasing carotid plaque burden tertile. Net reclassification improved significantly with carotid plaque burden (0.23).
- To date, few studies have comprehensively studied the association of carotid IMT progression with CVD outcomes. Data from a comprehensive meta-analysis of individual participant data demonstrated that common carotid artery IMT progression in people with DM ranged between –0.09 and 0.04 mm per year in a follow-up of 3.6 years; however, this change was not associated with cardiovascular outcomes.<sup>54</sup> The HR for a 1-SD increase in common carotid artery IMT progression was 0.99 (95% CI, 0.91–1.08).

## CAC, Carotid IMT, CT Angiography, and Risk Prediction

- In MESA, the investigators reported on follow-up of 6779 males and females in 4 ethnic groups over 9.5 years and compared the predictive utility of carotid IMT, carotid plaque, and CAC (presence and burden).<sup>55</sup>
  - CAC presence was a stronger predictor of incident CVD and CHD than carotid ultrasound measures.
  - Mean IMT  $\geq$ 75th percentile (for age, sex, and race) alone did not predict events. Compared with traditional risk factors, C statistics for CVD ( $C=0.756$ ) and CHD ( $C=0.752$ ) increased

the most by the addition of CAC presence (CVD,  $C=0.776$ ; CHD,  $C=0.784$ ;  $P<0.001$ ), followed by carotid plaque presence (CVD,  $C=0.760$ ; CHD,  $C=0.757$ ;  $P<0.05$ ).

- Compared with risk factors ( $C=0.782$ ), carotid plaque presence ( $C=0.787$ ;  $P=0.045$ ) but not CAC ( $C=0.785$ ;  $P=0.438$ ) improved prediction of stroke/TIA.
- Investigators from the NHLBI's CARDIA and MESA studies examined the burden and progression of subclinical atherosclerosis among adults <50 years of age.<sup>56</sup> Ten-year and lifetime risks for CVD were estimated for each participant, and the participants were stratified into 3 groups of predicted CVD risk: (1) low 10-year (<10%)/low lifetime (<39%) risk; (2) low 10-year (<10%)/high lifetime ( $\geq$ 39%) risk; and (3) high 10-year risk ( $>$ 10%). The final group had the highest burden and greatest progression of subclinical atherosclerosis. Given the young age of those studied,  $\approx$ 90% of participants were at low 10-year risk, but of these, half had high predicted lifetime risk. Compared with those with low short-term/low lifetime predicted risks, those with low short-term/high lifetime predicted risk had significantly greater burden and progression of CAC and significantly greater burden of carotid IMT, even at these younger ages. These data confirm the importance of early exposure to risk factors for the onset and progression of subclinical atherosclerosis.
- Although CAC and carotid ultrasound have been used more commonly in epidemiological studies, CT angiography has been examined for its potential role in detection, quantitation, and characterization of atherosclerotic coronary plaques that might make them prone to rupture, such as positive remodeling, low attenuation, and spotty calcifications.<sup>57</sup>
- However, limited impact on the prediction of outcomes in asymptomatic individuals has been shown, and thus, guidelines have not recommended its use as a screening tool for assessment of cardiovascular risk in asymptomatic individuals.<sup>2,32,33,58</sup> In the CONFIRM study, although CT angiography presence, extent, and severity of CAD improved risk prediction over traditional risk factors, no additional prognostic value for all-cause death was conferred once traditional risk factors and CAC scores were included in the model.<sup>59</sup> In another analysis of the CONFIRM data, it was noted that coronary CT angiography only provided incremental prognostic utility for prediction of mortality and nonfatal MI for asymptomatic individuals with moderately high CAC scores, but not for those with lower or higher CAC scores.<sup>60</sup>

## Genetics/Family History

- There is evidence for genetic control of subclinical atherosclerosis, with several loci identified that associate with CAC and carotid artery IMT in multiethnic and racial populations.<sup>61–64</sup> On the basis of the identified genes and variants, there are considerable shared genetic components to subclinical disease and other risk factors (such as blood lipids) and incident disease.
- Recently, investigators identified 8 unique genetic loci that contribute to carotid IMT in 71 128 individuals and 1 novel locus for carotid plaque in 48 434 individuals.<sup>65</sup> Genetic correlations with CHD and stroke using linkage disequilibrium score regression analysis were observed, which suggests the connection between genetic susceptibility to subclinical atherosclerosis and overt CVD.

## Treatment: Healthy Lifestyle and Preventive Medications

- A healthy lifestyle is the foundation of preventive treatment. Diets high in vegetables and fruits are associated with lower risk for CVD. PREDIMED, a small, randomized cohort study, demonstrated delayed progression of carotid IMT and carotid plaque after a median of 2.4 years in those randomized to a Mediterranean diet with nuts versus controls.<sup>66</sup>
- Recently, a study examining the relation of different vegetables to carotid IMT in a cohort of older females showed that a diet high in vegetables, particularly cruciferous vegetables, was associated with lower carotid IMT.<sup>67</sup> Consuming ≥3 servings of vegetables each day was associated with an ≈5% lower amount of carotid atherosclerosis compared with consuming <2 servings of vegetables.
- SWAN examined the association of a 10-component Healthy Lifestyle Score using self-reported data regarding smoking, diet, and PA with carotid atherosclerosis in females during midlife. After 14 years of follow up, individuals with a healthier lifestyle, particularly the abstinence of smoking, had lower carotid IMT, which emphasizes the role of optimal lifestyle habits on subclinical atherosclerosis.<sup>68</sup> Similar results of lifestyle habits including Mediterranean diet, abstinence from smoking, and moderate alcohol intake were associated with lower subclinical atherosclerosis in nearly 2000 individuals in the Spanish AWHS.<sup>69</sup>
- CAC has been examined in multiple studies for its potential to identify those most likely and not likely to benefit from pharmacological treatment for the primary prevention of CVD.
- A total of 950 participants from MESA who met JUPITER clinical trial entry criteria (risk factors plus

LDL-C <130 mg/dL and high-sensitivity CRP ≥2 mg/L) were identified and stratified according to CAC scores of 0, 1 to 100, or >100; CHD event rates were calculated, and the NNT<sub>5</sub> was calculated by applying the benefit found in JUPITER to the event rates found in each of these groups.<sup>70</sup> For CHD, the predicted NNT<sub>5</sub> was 549 for those with CAC of 0, 94 for scores of 1 to 100, and 24 for scores >100.

- In a similar fashion, 2 studies extrapolated the NNT<sub>5</sub> for LDL-C lowering by statins, applying the 30% RR reduction associated with a 1 mmol/L (39 mg/dL) reduction in LDL-C from a Cochrane meta-analysis of statin therapy in primary prevention across the spectrum of lipid abnormalities (LDL-C ≥130 mg/dL, HDL-C <40 mg/dL for males or <50 mg/dL for females, and triglycerides ≥150 mg/dL), as well as across 10-year FRS categories (0%–6%, 6%–10%, 10%–20%, and >20%).<sup>10,71</sup>
  - The estimated NNT<sub>5</sub> for preventing 1 CVD event across dyslipidemia categories in the MESA cohort ranged from 23 to 30 in those with CAC ≥100.<sup>10</sup> The NNT<sub>5</sub> was 30 in participants with no lipid abnormality and CAC >100, whereas it was 154 in those with 3 lipid abnormalities and CAC of 0. A very high NNT<sub>5</sub> of 186 and 222, respectively, was estimated to prevent 1 CHD event in the absence of CAC among those with 10-year FRS of 11% to 20% and >20%. The respective estimated NNT<sub>5</sub> was as low as 36 and 50 with the presence of a very high CAC score (>300) among those with 10-year FRS of 0% to 6% and 6% to 10%, respectively. These collective data show the utility of CAC in identifying those most likely to benefit from statin treatment across the spectrum of risk profiles with an appropriate NNT<sub>5</sub>.
  - Similarly, CAC testing also identified appropriate candidates who might derive the highest benefit with aspirin therapy. In MESA, individuals with CAC ≥100 had an estimated net benefit with aspirin regardless of their traditional risk status; the estimated NNT<sub>5</sub> was 173 for individuals classified as having <10% FRS and 92 for individuals with ≥10% FRS, and the estimated 5-year number needed to harm was 442 for a major bleed.<sup>71</sup> Conversely, individuals with zero CAC had unfavorable estimates (estimated NNT<sub>5</sub> of 2036 for individuals with <10% FRS and 808 for individuals with ≥10% FRS; estimated 5-year number needed to harm of 442 for a major bleed). Sex-specific and age-stratified analyses showed similar results.
  - A study from MESA also examined the role of CAC testing to define the target population to treat with a polypill.<sup>72</sup> The NNT<sub>5</sub> to prevent 1 event

was estimated by applying the expected 62% CHD event reduction associated with the use of the polypill (based on TIPS). The estimated NNT<sub>5</sub> to prevent 1 CHD event ranged from 170 to 269 for patients with CAC=0, from 58 to 79 for those with CAC scores from 1 to 100, and from 25 to 27 for those with CAC scores >100, which enabled significant reductions in the population considered for treatment with more selective use of the polypill and, as a result, avoidance of treatment of those who were unlikely to benefit.

- Within the scope of the 2013 ACC/AHA guideline on the treatment of blood cholesterol, data from MESA demonstrated that among those for whom statins were recommended, 41% had CAC=0 and had 5.2 ASCVD events per 1000 person-years.<sup>73</sup> Among 589 participants (12%) considered for moderate-intensity statin treatment, 338 (57%) had CAC=0, with an ASCVD event rate of 1.5 per 1000 person-years. Of participants eligible (recommended or considered) for statins, 44% (1316 of 2966) had CAC=0 at baseline and an observed 10-year ASCVD event rate of 4.2 per 1000 person-years. The study results highlighted that among the intermediate-risk range of 5% to 20%, nearly half (48%) had CAC=0, and their 10-year ASCVD risk was below the threshold recommended for statin therapy (4.5%).
- These findings were recently confirmed in the JHS.<sup>74</sup> Among 2812 black individuals 40 to 75 years of age without prevalent ASCVD followed up for a median of 10 years, participants who were statin eligible by the 2013 ACC/AHA guideline on the treatment of blood cholesterol experienced a 10-year ASCVD event rate of 8.1 per 1000 person-years. However, in the absence of CAC, the 10-year observed ASCVD risk was below the threshold of statin recommendation set by the guidelines, at 3.1 per 1000 person-years.

## Measures of Vascular Function and Incident CVD Events

### Background

- Measures of arterial tonometry (stiffness) are based on the concept that pulse pressure has been shown to be an important risk factor for CVD. Arterial tonometry offers the ability to directly and noninvasively measure central PWV in the thoracic and abdominal aorta.
- BP and its variability are related to CVD events. Greater home BP variability was associated with higher carotid IMT, aortic calcification, and lower ABI in 1033 Japanese males and females.<sup>75</sup>
- Brachial FMD is a marker for nitric oxide release from the endothelium that can be measured by ultrasound. Impaired FMD is an early marker of CVD.

- Recommendations have not been specific, however, as to which, if any, measures of vascular function might be useful for CVD risk stratification in selected patient subgroups. Because of the absence of significant prospective data relating these measures to outcomes, the guidelines do not recommend measuring either FMD or arterial stiffness for cardiovascular risk assessment in asymptomatic adults.<sup>58</sup>

### **Arterial Stiffness and CVD**

- The Rotterdam Study measured arterial stiffness in 2835 elderly participants (mean age 71 years).<sup>76</sup> They found that as aortic PWV increased, the RR of CHD was 1.72 (second versus first tertile) and 2.45 (third versus first tertile). Results remained robust even after accounting for carotid IMT, ABI, and pulse pressure.
- A study from Denmark of 1678 individuals 40 to 70 years of age found that each 1-SD increment in aortic PWV (3.4 m/s) increased CVD risk by 16% to 20%.<sup>77</sup>
- The FHS studied several indices of arterial stiffness, including PWV, wave reflection, and central pulse pressure.<sup>78</sup> Higher PWV was associated with a 48% increased risk of incident CVD events, and PWV improved CVD risk prediction (integrated discrimination improvement of 0.7%,  $P<0.05$ ).
- An analysis from the JHS suggested peripheral arterial tonometry is associated with LVH.<sup>79</sup> A total of 440 black participants (mean age  $59\pm10$  years, 60% females) underwent both peripheral arterial tonometry and cardiac MRI evaluations between 2007 and 2013. Age- and sex-adjusted Pearson correlation analysis suggested that natural log-transformed LV mass index measured by MRI was negatively correlated with reactive hyperemia index (coefficient  $-0.114$ ;  $P=0.02$ ) after accounting for age, sex, BMI, DM, hypertension, ratio of TC and HDL-C, smoking, and history of CVD.
- Evidence suggests that arterial stiffness has negative impacts on brain health across the life spectrum. In 5853 children in the Generation R study, DBP was related to nonverbal intelligence, and in 5187 adults in the Rotterdam study, cognition was linearly related to SBP, PWV, and pulse pressure, and nonlinearly with DBP.<sup>80</sup> In the ARIC–Neurocognitive and positron emission tomography study, higher arterial stiffness measured by heart-carotid PWV was associated with greater  $\beta$ -amyloid deposition in the brain defined by positron emission tomography imaging, and carotid femoral PWV was associated with lower brain volumes and with higher white matter hyperintensity burden.<sup>81</sup> FHS investigators also previously demonstrated findings of arterial stiffness with brain aging and similar brain structural abnormalities and progression of these abnormalities in regions implicated in Alzheimer disease.<sup>82–86</sup>

### FMD and CVD

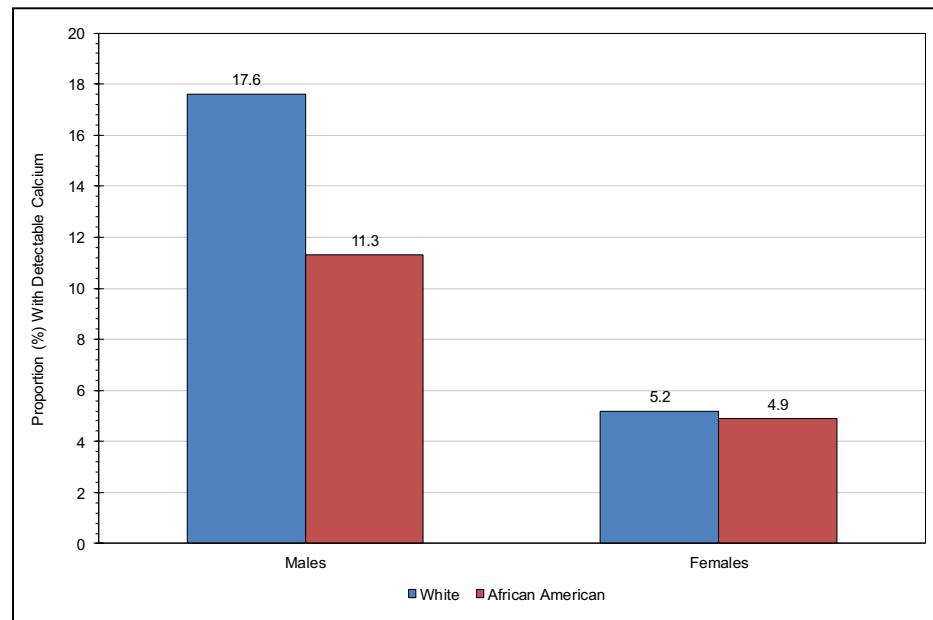
- A recent meta-analysis assessed the relation of FMD with CVD events. Thirteen studies involving 11 516 individuals without established CVD, with a mean duration of 2 to 7.2 years and adjusted for age, sex, and risk factors, reported a multivariate RR of 0.93 (95% CI, 0.90–0.96) per 1% increase in brachial FMD.<sup>87</sup>

### Comparison of Measures

- In MESA, a comparison of 6 risk markers—CAC, ABI, high-sensitivity CRP, carotid IMT, brachial FMD, and family history of CHD—and their clinical utility over FRS was evaluated in 1330 intermediate-risk individuals.<sup>88</sup> After 7.6 years of follow-up, CAC, ABI, high-sensitivity CRP, and family history were independently associated with incident CHD in multivariable analyses (HRs of 2.6, 0.79, 1.28, and 2.18, respectively), but carotid IMT and brachial FMD were not. CAC provided the highest incremental improvement over the FRS (0.784 for both CAC and FRS versus 0.623 for FRS alone), as well as the greatest net reclassification improvement (0.659).
- Additionally, in MESA, the values of 12 negative markers (CAC score of 0, carotid IMT <25th percentile, absence of carotid plaque, brachial FMD >5% change, ABI >0.9 and <1.3, high-sensitivity CRP <2 mg/L, homocysteine <10 μmol/L, N-terminal

pro-BNP <100 pg/mL, no microalbuminuria, no family history of CHD [any/premature], absence of MetS, and healthy lifestyle) were compared for all and hard CHD and for all CVD events over the 10-year follow-up.<sup>89</sup> After accounting for CVD risk factors, absence of CAC had the strongest negative predictive value, with an adjusted mean diagnostic likelihood ratio of 0.41 (SD, 0.12) for all CHD and 0.54 (SD, 0.12) for CVD, followed by carotid IMT <25th percentile (diagnostic likelihood ratio, 0.65 [SD, 0.04] and 0.75 [SD, 0.04], respectively).

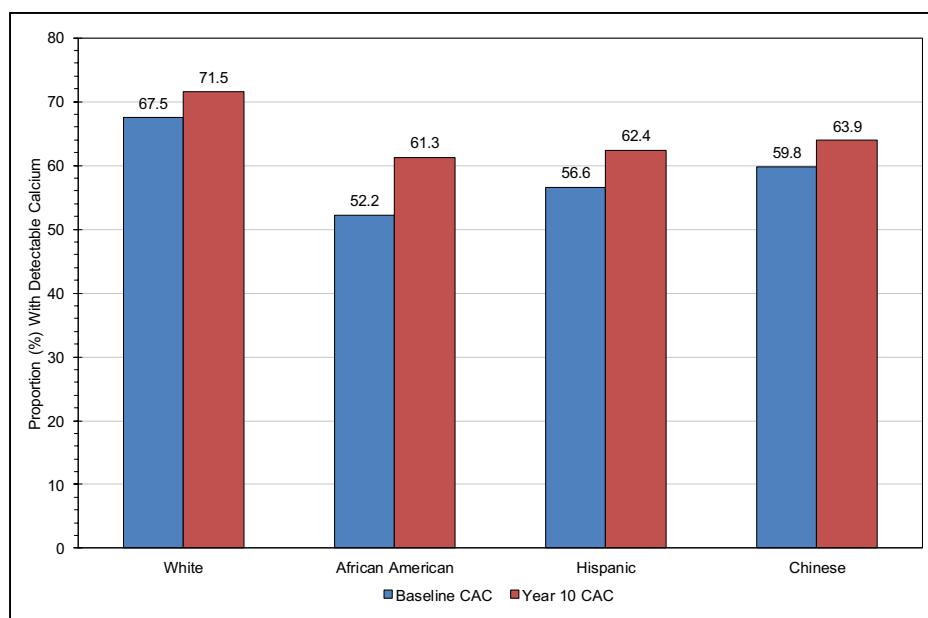
- Similar findings were also noted in the Rotterdam Study, in which among 12 CHD risk markers, improvements in FRS predictions were most statistically and clinically significant with the addition of CAC scores.<sup>90</sup>
- The pooled cohort ASCVD risk estimator was recently compared against the FRS for prediction of subclinical atherosclerosis measured by carotid IMT and vascular dysfunction measured by carotid femoral PWV, central pulse pressure, and augmentation index in a cohort of 1231 individuals free of prevalent CVD.<sup>91</sup> Not surprisingly, given that the FRS was based on individuals of northern European descent, the pooled cohort risk equations were suggested to better identify the significance of race in subclinical atherosclerosis and vascular dysfunction.



**Chart 18-1. Prevalence (%) of detectable coronary calcium in the CARDIA study: US adults 33 to 45 years of age (2000 to 2001).**

*P*<0.0001 across race-sex groups. CARDIA indicates Coronary Artery Risk Development in Young Adults.

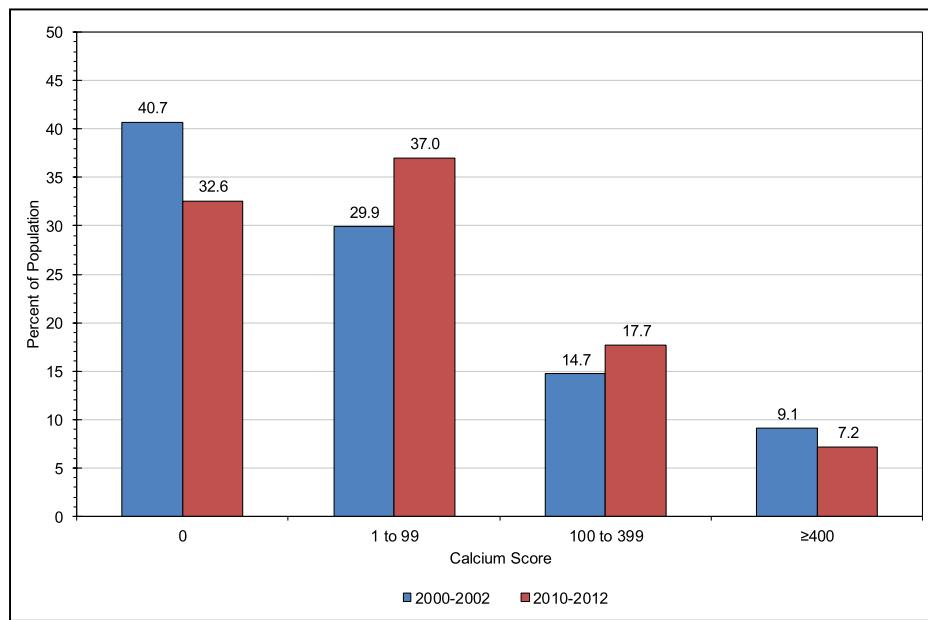
Source: Data derived from Loria et al.<sup>5</sup>



**Chart 18-2.** Prevalence by ethnicity of detectable CAC at baseline (2000–2002) and year 10 (2010–2012) among US adults 55 to 84 years of age without cardiovascular disease in MESA.

CAC indicates coronary artery calcification; and MESA, Multi-Ethnic Study of Atherosclerosis.

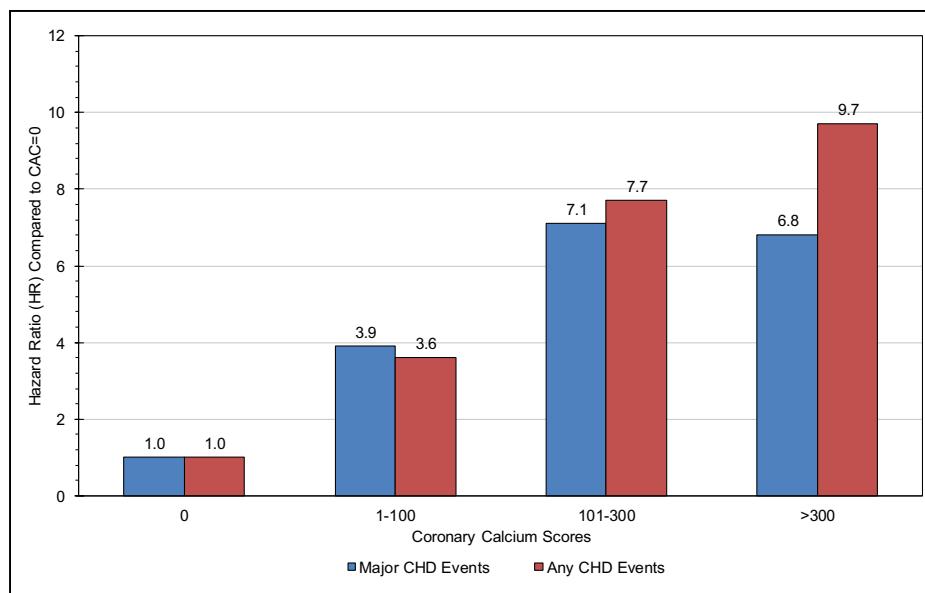
Source: Data derived from Bild et al.<sup>7,17</sup>



**Chart 18-3.** Ten-year trends in severity of coronary artery calcification in US individuals without clinical cardiovascular disease in MESA, baseline examination 2000 to 2002.

Data adjusted to the average baseline age (67 years), sex (47% male), race/ethnicity (39% white, 28% African American, 21% Hispanic, and 12% Chinese), and scanner (electron-beam computed tomography vs other). MESA indicates Multi-Ethnic Study of Atherosclerosis.

Source: Adapted from Bild et al.<sup>17</sup>



**Chart 18-4.** HRs for CHD events associated with CAC scores: US adults 45 to 84 years of age (reference group, CAC=0) in MESA, baseline examination 2000 to 2002.

Baseline examination 2000 to 2002 with median of 3.9 years of follow-up (maximum 5.3 years). All HRs  $P<0.0001$ . Major CHD events included myocardial infarction and death attributable to CHD; any CHD events included major CHD events plus definite angina or definite or probable angina followed by revascularization. CAC indicates coronary artery calcification; CHD, coronary heart disease; HR, hazard ratio; and MESA, Multi-Ethnic Study of Atherosclerosis.

Source: Data derived from Detrano et al.<sup>18</sup>

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## 19. CORONARY HEART DISEASE, ACUTE CORONARY SYNDROME, AND ANGINA PECTORIS

**See Tables 19-1 through 19-3 and Charts 19-1 through 19-11**

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### Coronary Heart Disease

**ICD-9 410 to 414, 429.2; ICD-10 I20 to I25 (includes MI) ICD-10 I21 to I22).**

#### Prevalence

**(See Tables 19-1 and 19-2 and Charts 19-1 through 19-4)**

- On the basis of data from NHANES 2013 to 2016,<sup>1</sup> an estimated 18.2 million Americans ≥20 years of age have CHD (Table 19-1). The prevalence of CHD was higher for males than females ≥60 years of age (Chart 19-1).

### Abbreviations Used in Chapter 19

ACS	acute coronary syndrome
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AHA	American Heart Association
AMI	acute myocardial infarction
AP	angina pectoris
ARIC	Atherosclerosis Risk in Communities
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASCVD	atherosclerotic cardiovascular disease
BEST	Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease
BRFSS	Behavioral Risk Factor Surveillance System
CABG	coronary artery bypass graft
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults
CARDIoGRAM	Coronary Artery Disease Genome-Wide Replication and Meta-Analysis
CARDIoGRAMplusC4D	Coronary Artery Disease Genome-Wide Replication and Meta-Analysis (CARDIoGRAM) plus the Coronary Artery Disease Genetics (C4D)
CARE	Cholesterol and Recurrent Events
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CMS	Centers for Medicare & Medicaid Services

### Abbreviations Used in Chapter 19 Continued

CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patient Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
EMS	emergency medical services
FH	familial hypercholesterolemia
FHS	Framingham Heart Study
FINRISK	Finnish population survey on risk factors for chronic, noncommunicable diseases
FRS	Framingham Risk Score
GBD	Global Burden of Disease
GRS	genetic risk score
GWAS	genome-wide association study
GTWTG	Get With The Guidelines
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HCUP	Healthcare Cost and Utilization Project
HDL-C	high-density lipoprotein cholesterol
HD	heart disease
HF	heart failure
HR	hazard ratio
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision
IHD	ischemic heart disease
JHS	Jackson Heart Study
JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin
LDL-C	low-density lipoprotein cholesterol
LV	left ventricular
MEPS	Medical Expenditure Panel Survey
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
MI-GENES	Myocardial Infarction Genes Study
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Study
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NSTEMI	non-ST-segment-elevation myocardial infarction
NYHA	New York Heart Association
OR	odds ratio
PCI	percutaneous coronary intervention

(Continued)

(Continued)

**Abbreviations Used in Chapter 19 Continued**

PHS	Physicians' Health Study
PRECOMBAT	Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus Stents in Patients With Left Main Coronary Artery Disease
PROVE IT-TIMI 22	Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22
RCT	randomized controlled trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SES	socioeconomic status
SHS	Strong Heart Study
SNP	single-nucleotide polymorphism
STEMI	ST-segment–elevation myocardial infarction
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
TC	total cholesterol
TRACE-CORE	Transitions, Risks, and Actions in Coronary Events—Center for Outcomes Research and Education
UA	unstable angina
UI	uncertainty interval
WHI	Women's Health Initiative
WHS	Women's Health Study

- Total CHD prevalence is 6.7% in US adults  $\geq 20$  years of age. CHD prevalence is 7.4% for males and 6.2% for females. CHD prevalence by sex and ethnicity is shown in Table 19-1.
- On the basis of data from the 2017 NHIS, the CHD prevalence estimates are 5.6% among whites, 5.9% among blacks, 2.7% among American Indian/Alaska Natives, and 4.3% among Asians  $\geq 18$  years of age.<sup>2</sup>
- According to data from NHANES 2013 to 2016 (unpublished NHLBI tabulation),<sup>1</sup> the overall prevalence for MI is 3.0% in US adults  $\geq 20$  years of age. Males have a higher prevalence of MI than females for all age groups except 20 to 39 years (Chart 19-2). MI prevalence is 4.0% for males and 2.3% for females. MI prevalence by sex and ethnicity is shown in Table 19-1.
- According to data from NHANES 2013 to 2016,<sup>1</sup> the overall prevalence for angina is 3.6% in US adults  $\geq 20$  years of age (Table 19-2).
- According to data from NHANES for the period 1988 to 2012, angina prevalence declined substantially in NH whites (from 4.0% to 2.1%) but not in NH blacks (from 4.9% to 4.4%). Angina prevalence declined in both males and females

$\geq 65$  years of age (males from 5.1% to 2.9%, females from 5.6% to 2.4%).<sup>3</sup>

- Data from the BRFSS 2017 survey indicated that 4.2% of respondents had been told that they had had an MI. The highest prevalence was in West Virginia (6.0%) and the lowest was in Hawaii (2.6%; age-adjusted; Chart 19-3).<sup>4</sup>
- In the same survey, 3.9% of respondents had been told that they had angina or CHD. The highest prevalence was in Puerto Rico (6.6%) and West Virginia (6.0%), and the lowest was in the District of Columbia (2.1%) and Hawaii (2.2%; age-adjusted; Chart 19-4).<sup>4</sup>

**Incidence****(See Charts 19-5 through 19-7)**

- Approximately every 40 seconds, an American will have an MI (AHA computation based on incidence data from the ARIC study of the NHLBI<sup>5</sup>).
- On the basis of data tabulated by NHLBI from the 2005 to 2014 ARIC study of the NHLBI<sup>5</sup>:
  - This year,  $\approx 720\ 000$  Americans will have a new coronary event (defined as first hospitalized MI or CHD death), and  $\approx 335\ 000$  will have a recurrent event.
  - The estimated annual incidence of MI is 605 000 new attacks and 200 000 recurrent attacks. Of these 805 000 first and recurrent events, it is estimated that 170 000 are silent.
  - Average age at first MI is 65.6 years for males and 72.0 years for females.
- In the REGARDS study, 37% of adjudicated MIs had a primary hospital discharge diagnosis of MI, whereas 63% had a primary hospital discharge diagnosis other than MI, which suggests that most MIs that result in hospitalization might be occurring during hospitalization for other acute illnesses.<sup>6</sup>
- Self-reported income and education were associated with incident CHD (defined as definite or probable MI or acute CHD death) in the REGARDS study. Those reporting low income and low education had twice the incidence of CHD as those reporting high income and high education (10.1 versus 5.2 per 1000 person-years, respectively).<sup>7</sup>
- Annual numbers for MI or fatal CHD in the NHLBI-sponsored ARIC study and the CHS stratified by age and sex are displayed in Chart 19-5. Incidence of heart attacks or fatal CHD stratified by age, race, and sex is displayed in Chart 19-6.
- Incidence of MI by age, sex, and race in the NHLBI-sponsored ARIC study is displayed in Chart 19-7. Black males have a higher incidence of MI in all age groups.
- HRs for incident fatal CHD were higher for black males than for white males 45 to 65 years of age

(ARIC: 2.09 [95% CI, 1.42–3.06]; REGARDS: 2.11 [95% CI, 1.32–3.38]). Nonfatal CHD risk was lower (ARIC: 0.82 [95% CI, 0.64–1.05]; REGARDS: 0.94 [95% CI, 0.69–1.28]). However, after adjustment for social determinants of health and cardiovascular risk factors, black males and females have similar risk for fatal CHD but lower risk for nonfatal CHD.<sup>8</sup>

- In 9498 participants in the ARIC study, whites had a higher rate of clinically recognized MI than blacks (5.04 versus 3.24 per 1000 person-years,  $P=0.002$ ).<sup>9</sup>

### **Secular Trends**

- The overall body of literature suggests that the incidence of MI in the United States has declined significantly over time.<sup>10</sup>
- In Olmsted County, MN, between 1995 and 2012, the population rate of MI declined 3.3% per year; however, these declines varied among types of MI, with the greatest declines occurring for prehospital fatal MI.<sup>11</sup>
- Among Medicare beneficiaries between 2002 and 2011, the rates of MI hospitalization declined from 1485 to 1122 per 100 000 person-years. The rates of MI as the primary reason for hospitalization decreased over time (from 1063 to 677 per 100 000 person-years between 2002 and 2011), whereas the rates of MI as a secondary reason for hospitalization increased (from 190 to 245 per 100 000 person-years). The percentage of MIs that were attributable to a secondary diagnosis increased from 28% to 40%.<sup>12</sup>
- Among Medicare beneficiaries, the rates of primary hospitalization for MI between 2002 and 2011 declined by 36.6% among NH whites (from 1057 to 670 per 100 000 person-years between 2002 and 2011) and by 26.4% among NH blacks (from 966 to 711 per 100 000 person-years between 2002 and 2011).<sup>13</sup>

### **Social Determinants**

- In an analysis of a population-based register sample of adults 40 to 60 years of age in Finland in 1995 ( $N=302\,885$ ) followed up until the end of 2007, MI incidence and mortality were examined in relation to living arrangements (living with a marital partner was contrasted to 3 alternatives: cohabiting with nonmarital partner, coresidence with people other than a partner, and living alone). Living arrangements were strong determinants for survival after MI independent of other sociodemographic factors. The results demonstrated greater fatality associated with living alone in males (HR, 1.50 [95% CI, 1.29–1.75]) and suggested that cohabitation in midlife might be associated with

a greater fatality risk in females (HR, 2.00 [95% CI 1.26–3.17]).<sup>14</sup>

- In an analysis of nationally representative longitudinal register data in Finnish adults ( $N = 94\,501$ ) for the period 1988 to 2010, household crowding during childhood increased the risk of MI incidence in adulthood by 16% (95% CI, 5%–29%) in males and 25% (95% CI, 3%–50%) in females. Most aspects of childhood circumstances did not strongly influence long-term fatality risk. Income and education remained associated with MI incidence when adjusted for unobserved shared family factors in siblings. Low adult socioeconomic resources remained a strong determinant of MI incidence and fatality.<sup>15</sup>
- Among US adults 45 to 74 years of age in 2009 to 2013, factors accounting for the US county variation in CVD mortality included demographic composition (36% of the variation in county CVD); economic/social conditions (32%); and healthcare utilization, features of the environment, and health indicators (6%).<sup>16</sup>

### **Risk Prediction**

- The percentage of US adults with a 10-year predicted ASCVD risk (using the Pooled Cohort risk equations)  $\geq 20\%$  decreased from 13.0% in 1999 to 2000 to 9.4% in 2011 to 2012. The proportion of US adults with 10-year predicted ASCVD risk of 7.5% to  $<20\%$  was 23.9% in 1999 to 2000 and 26.8% in 2011 to 2012.<sup>17</sup>
- For adults with optimal risk factors (TC of 170 mg/dL, HDL-C of 50 mg/dL, SBP of 110 mmHg without antihypertensive medication use, no DM, and not a smoker), 10-year CVD risk  $\geq 7.5\%$  will occur at 65 years of age for white males, 70 years of age for black males and females, and 75 years of age for white females.<sup>18</sup>
- The ASCVD tool might overestimate risk across all strata of risk compared with external contemporary cohorts (PHS, WHS, and WHI Observational Study), as well as in reanalysis of the original validation cohorts. However, some of the subsequent analyses were not conducted in comparable populations as the original study cohorts.<sup>19</sup>
- In 9066 participants 45 to 79 years of age from the REGARDS study, the observed and predicted ASCVD risk using the Pooled Cohort risk equations were similar in people with high social deprivation, although ASCVD risk was overestimated in those with low social deprivation.<sup>20</sup>
- In the WHI, although the risk of ASCVD was overestimated using the Pooled Cohort risk equations, adding additional ASCVD events identified through linkage with CMS claims that were not self-reported resulted in alignment of the observed and predicted risks.<sup>21</sup>

## Genetics and Family History

### Family History as a Risk Factor

- Among adults ≥20 years of age, 12.4% (SE, 0.5%) reported having a parent or sibling with a heart attack or angina before 50 years of age. The racial/ethnic breakdown from NHANES 2013 to 2016 is as follows (unpublished NHLBI tabulation)<sup>1</sup>:
  - For NH whites, 12.2% (SE 1.0%) for males, 15.0% (SE 0.9%) for females.
  - For NH blacks, 7.1% (SE 0.9%) for males, 14.0% (SE 1.3%) for females.
  - For Hispanics, 7.7% (SE 0.6%) for males, 10.7% (SE 0.5%) for females.
  - For NH Asians, 6.3% (SE 0.9%) for males, 4.6% (SE 0.8%) for females.
- HD occurs as people age, so the prevalence of family history will vary depending on the age at which it is assessed. The breakdown of reported family history of heart attack by age of survey respondent in the US population as measured by NHANES 2013 to 2016 is as follows (unpublished NHLBI tabulation)<sup>1</sup>:
  - 20 to 39 years of age, 8.5% (SE 1.0%) for males, 9.9% (SE 0.6%) for females.
  - 40 to 59 years of age, 11.4% (SE 1.4%) for males, 16.9% (SE 1.2%) for females.
  - 60 to 79 years of age, 13.6% (SE 1.7%) for males, 16.6% (SE 1.6%) for females.
  - ≥80 years of age, 12.5% (SE 2.7%) for males, 13.6% (SE 2.6%) for females.
- Family history of premature angina, MI, angioplasty, or bypass surgery increases lifetime risk by ≈50% for both HD (from 8.9% to 13.7%) and CVD mortality (from 14.1% to 21%).<sup>22</sup>
- In premature ACS (≤55 years of age), a greater percentage of females (28%) than males (20%) have a family history of CAD ( $P=0.008$ ). Compared with patients without a family history, patients with a family history of CAD have a higher prevalence of traditional CVD risk factors.<sup>23</sup>
- Among patients with STEMI in the NIS between 2003 and 2011, those with a family history of CAD were more likely to undergo coronary intervention and had lower in-hospital mortality than patients without a family history (OR, 0.45 [95% CI, 0.43–0.47];  $P<0.001$ ).<sup>24</sup>

### Genetic Predictors of CHD

- For the past decades, candidate gene studies have been conducted to identify the genetic variants underlying the heritability of CHD, but very few have identified consistent, replicated, and independent genetic variants, and all have had small effect sizes.
- Over the past decade, the application of GWASs to large cohorts of CHD case and control subjects

has identified many consistent genetic variants associated with CHD. The total number of CAD-associated regions identified in GWASs is 73, with 15 novel CAD associations related to atherosclerosis and traditional risk factors but also highlighting the importance of key biological process in the arterial wall.<sup>25</sup>

- The first GWAS identified the now most consistently replicated genetic marker for CHD and MI in European-derived populations, on chromosome 9p21.3.<sup>26</sup> The frequency of the primary SNP is very common (50% of the white population is estimated to harbor 1 risk allele, and 23% harbors 2 risk alleles).<sup>27</sup>
  - The 10-year HD risk for a 65-year-old male with 2 risk alleles at 9p21.3 and no other traditional risk factors is ≈13.2%, whereas a similar male with 0 alleles would have a 10-year risk of ≈9.2%. The 10-year HD risk for a 40-year-old female with 2 alleles and no other traditional risk factors is ≈2.4%, whereas a similar female with 0 alleles would have a 10-year risk of ≈1.7%.<sup>27</sup>
- The association of SNPs with incident CHD was investigated in a large multiethnic study of multiple cohorts in the United States (including NHANES, WHI, the Multiethnic Cohort Study, CHS, ARIC, CARDIA, HCHS/SOL, and SHS). SNPs, including in 9p21, APOE, and LPL, were associated with incident CHD in individuals of European ancestry but not blacks. Effect sizes were greater for those ≤55 years of age and in females.<sup>28</sup>
- More recently, genetic studies of CHD have focused on the coding regions of the genome (exons) and have identified additional genes and SNPs for CHD, including loss-of-function mutations in the angiopoietin-like 4 gene (ANGPTL4), which is an inhibitor of lipoprotein lipase. These mutations are associated with low plasma triglycerides and high HDL-C.<sup>29</sup>
- In a discovery analysis of common SNPs (minor allele frequency of >5%) on an exome array, 6 new loci associated with CAD were identified, including SNPs on the KCNJ13-G/GYF2, C2, MRVI1-CTR9, LRP1, SCARB1, and CETP genes.<sup>30</sup>
- In the DiscovEHR study, loss-of-function variants in the angiopoietin-like 3 gene (ANGPTL3) were less common in patients with CAD than in control subjects (0.33% versus 0.45%) and were associated with 27% lower triglyceride levels, 9% lower LDL-C, and 4% lower HDL-C.<sup>31</sup>
- Protein-truncating variants at the CETP gene are associated with increased HDL-C and lower LDL-C and triglycerides. Compared with noncarriers, carriers of protein-truncating variants at CETP had a

lower risk of CHD (OR, 0.70 [95% CI, 0.54–0.90];  $P=5.1\times10^{-3}$ ).<sup>32</sup>

- Using a network mendelian randomization analysis, a 1-U longer genetically determined telomere length was associated with a lower risk of CHD in the CARDIoGRAM Consortium (OR, 0.79 [95% CI, 0.65–0.97];  $P=0.016$ ) and the CARDIoGRAMplusC4D 1000 Genome Consortium (OR, 0.89 [95% CI, 0.79–1.00];  $P=0.052$ ). Fasting insulin can partially mediate the association of telomere length with CHD, accounting for 18.4% of the effect of telomere length on CHD.<sup>33</sup>
- Whole-genome sequencing studies, which offer a deeper and more comprehensive coverage of the genome, have recently identified 13 variants with large effects on blood lipids. Five variants within *PCSK9*, *APOA1*, *ANGPTL4*, and *LDLR* are associated with CHD.<sup>34</sup>

### Clinical Utility of Genetic Markers

- Recent advances have demonstrated the utility of genetics in CAD risk prediction. In 48 421 individuals enrolled in the Malmo Diet and Cancer Study and 2 primary prevention trials (JUPITER, ASCOT) and 2 secondary prevention trials of lipid lowering (CARE, PROVE IT-TIMI22), a GRS consisting of 27 variants of genetic risk for CAD improved risk prediction above models that incorporated traditional risk factors and family history.<sup>35</sup> In the Malmo Diet and Cancer Study, application of an additional 23 SNPs known to be associated with CAD resulted in greater discrimination and reclassification (both  $P<0.0001$ ).<sup>36</sup>
- In the FINRISK and FHS cohorts, with a sample size of 16 082 individuals, a GRS incorporating 49 310 SNPs based on the CARDIoGRAMplusC4D Consortium data showed that the combination of GRS with the FRS improved 10-year cardiac risk prediction, particularly in those  $\geq60$  years of age.<sup>37</sup>
- Studies have also shown that patients with early-onset MI have a higher proportion of very high polygenic GRS than of FH mutations; for example,  $\approx2\%$  carry a rare FH genetic mutation, whereas  $\approx17\%$  have a high polygenic risk score.<sup>38</sup>
- In the MI-GENES trial of intermediate-risk patients, patient knowledge of their GRS resulted in lower levels of LDL-C than in a control group managed by conventional risk factors alone, which suggests the influence of GRS in risk prevention.<sup>39</sup>
- Even in individuals with high genetic risk, prevention strategies have added benefit. For example, in 4 studies across 55 685 participants, genetic and lifestyle factors were independently associated with CHD, but even in participants at high genetic risk, a favorable lifestyle was associated

with a nearly 50% lower RR of CHD than was an unfavorable lifestyle.<sup>40</sup>

- A novel genomic risk score for CAD including 1.7 million genetic variants was associated with increased risk of CAD in the UK Biobank (HR, 1.71 [95% CI, 1.68–1.73] per SD increase in the score). Compared with individuals in the bottom quintile of the score, the HR of CAD for those in the top quintile was 4.17 (95% CI, 3.97–4.38). However, adding the genetic score to conventional risk factors only resulted in a small increase in predictive ability (C-statistic changing from 0.670 to 0.696).<sup>41</sup>

### **Awareness, Treatment, Control**

#### *Awareness of Warning Signs and Risk for HD*

- In 2012, NH black and Hispanic females had lower awareness than white females that HD/heart attack is the leading cause of death for females.<sup>42</sup>
- The percentages of females in 2012 identifying warning signs for a heart attack were as follows: pain in the chest—56%; pain that spreads to the shoulder, neck, or arm—60%; shortness of breath—38%; chest tightness—17%; nausea—18%; and fatigue—10%.<sup>42</sup>
- Among online survey participants, 21% responded that their doctor had talked to them about HD risk. Rates were lower among Hispanic females (12%) than whites (22%) or blacks (22%) and increased with age from 6% (25–34 years) to 33% ( $\geq65$  years).<sup>42</sup>
- Among 2009 females and 976 males  $<55$  years of age hospitalized for MI, only 48.7% of females and 52.9% of males reported having been told they were at risk for HD or a heart problem. Also, 50.3% of females and 59.7% of males reported their healthcare provider had discussed HD and things they could do to take care of their heart.<sup>43</sup> Data from the NHIS indicate that awareness of 5 common heart attack symptoms (jaw, neck, or back discomfort; weakness or lightheadedness; chest discomfort; arm or shoulder discomfort; and shortness of breath) increased from 39.6% in 2008 to 50.0% in 2014 and 50.2% in 2017. In 2017, knowledge of the 5 symptoms was higher in females than in males (54.4% versus 45.6%) and differed by race/ethnicity (whites, 54.8%; blacks, 43.1%; Asians, 33.5%; Hispanics, 38.9%).<sup>44</sup>

#### *Time of Symptom Onset and Arrival at Hospital*

- Data from Worcester, MA, indicate that the median time from symptom onset to hospital arrival did not improve from 2001 through 2011. In 2009 to 2011, 48.9% of patients reached the hospital within 2 hours of symptom onset, compared with 45.8% in 2001 to 2003.<sup>45</sup>
- A retrospective analysis of the NHAMCS data from 2004 to 2011 that reviewed 15 438 hospital visits

related to ACS symptoms suggested that blacks have a 30% longer waiting time than whites, the reasons for which are unclear.<sup>46</sup>

- The timing of hospital admission influences management of MI. A study of the NIS database from 2003 to 2011 indicated that admission on a weekend for NSTEMI was associated with a significantly reduced odds for coronary angiography (OR, 0.88 [95% CI, 0.89–0.90];  $P<0.001$ ) and early invasive strategy (OR, 0.48 [95% CI, 0.47–0.48];  $P<0.001$ ), resulting in greater mortality.<sup>47</sup>
- Among patients hospitalized for ACS between 2001 and 2011 in the NIS, those with STEMI admitted on the weekend versus on a weekday had a 3% higher odds of in-hospital mortality.<sup>48</sup>
- In a meta-analysis including 57 136 patients from 10 studies, door-to-balloon time of >90 minutes versus ≤90 minutes was associated with higher in-hospital or 30-day mortality (OR, 1.52 [95% CI, 1.40–1.65]). An increased risk of 6-month to 12-month mortality was also observed for >90 minute door-to-balloon delay in 14 261 patients from 8 studies (OR, 1.53 [95% CI, 1.13–2.06]).<sup>49</sup>

### *Operations and Procedures*

- In 2014, an estimated 480 000 percutaneous transluminal coronary angioplasties, 371 000 inpatient bypass procedures, 1 016 000 inpatient diagnostic cardiac catheterizations, 86 000 carotid endarterectomies, and 351 000 pacemaker procedures were performed for inpatients in the United States (unpublished NHLBI tabulation using HCUP<sup>50</sup>).
- In an analysis of the BEST, PRECOMBAT, and SYNTAX trials comparing individuals with MI and who had left main or multivessel CAD, the outcomes of CABG versus PCI were examined. CABG was associated with a lower risk of recurrent MI and repeat revascularizations.<sup>51</sup> In patients with multivessel CAD, CABG was associated with lower all-cause and cardiovascular mortality; however, no differences in all-cause and cardiovascular mortality between CABG and PCI were observed among patients with multivessel plus left main CAD.<sup>52</sup>
- In a meta-analysis of 6 randomized trials that included 4686 patients with unprotected left main CAD, no significant differences in all-cause and cardiovascular mortality or a composite outcome of death, MI, or stroke were observed between patients treated with PCI versus CABG. However, PCI was associated with a lower risk of the composite outcome within the first 30 days of follow-up (OR, 0.62 [95% CI, 0.45–0.86]).<sup>53</sup>
- In 5-year follow-up of the SYNTAX trial, greater MI-related death in PCI-treated patients was associated with the presence of DM, 3-vessel disease, or high SYNTAX scores.<sup>54</sup>

- At 5 years of follow-up in the SYNTAX and BEST randomized trials, among patients with multivessel CAD involving the proximal left anterior descending coronary artery, PCI was associated with increased composite outcome of all-cause death, MI, or stroke (HR, 1.43 [95% CI, 1.05–1.95];  $P=0.026$ ), cardiovascular death (HR, 2.17 [95% CI, 1.24–3.81];  $P=0.007$ ), and major adverse cardiovascular and cerebrovascular events (HR, 1.68 [95% CI, 1.31–2.15];  $P<0.001$ ).<sup>55</sup>
- In 27 840 STEMI patients transported via EMS to 744 hospitals in the ACTION registry, preactivation of the catheterization laboratory >10 minutes before hospital arrival compared with no preactivation was associated with shorter times to the catheterization laboratory (median of 17 minutes versus 28 minutes), shorter door-to-device time (median of 40 minutes versus 52 minutes), and lower in-hospital mortality (2.8% versus 3.4%;  $P=0.01$ ).<sup>56</sup>
- In the NIS, isolated CABG procedures decreased by 25.4% from 2007 to 2011 (326 to 243 cases per million adults), particularly at higher-volume centers. Low-volume centers were associated with greater risk of all-cause in-hospital mortality in multivariable analysis (OR, 1.39 [95% CI, 1.24–1.56];  $P<0.001$ ).<sup>57</sup>
- According to the NIS, the number of PCI procedures declined by 38% between 2006 and 2011. Among patients with stable IHD, a 61% decline in PCI occurred over this time period.<sup>58</sup>
- In Washington State, the overall number of PCIs decreased by 6.8% between 2010 and 2013, with a 43% decline in the number of PCIs performed for elective indications.<sup>59</sup>
- Among Medicare fee-for-service beneficiaries, the total number of revascularization procedures performed peaked in 2010 and declined by >4% per year through 2012. In-hospital and 90-day mortality rates declined after CABG surgery overall, as well as among patients presenting for elective CABG or CABG after NSTEMI.<sup>60</sup>
- Between 2011 and 2014, the use of femoral access declined (from 88.8% to 74.5%) and radial access increased (from 10.9% to 25.2%).<sup>61</sup>
- In a meta-analysis of 13 observational studies and 3 RCTs, a transradial approach for PCI was associated with a reduction in vascular complications (OR, 0.36 [95% CI, 0.30–43]) and stroke (OR, 0.79 [95% CI, 0.64–0.97]) compared with a transfemoral approach. A transradial approach was also associated with a reduced risk of death (OR, 0.56 [95% CI, 0.45–0.69]), although this was driven by the observational studies, because no association with death was observed in the randomized trials.<sup>62</sup>

- In 2014, from the CathPCI registry, median door-to-balloon time for primary PCI for STEMI was 59 minutes for patients receiving PCI in the presenting hospital and 105 minutes for patients transferred from another facility for therapy.<sup>61</sup>
- The importance of adherence to optimal medical therapy was highlighted in an 8-hospital study of NSTEMI patients, in which medication nonadherence was associated with a composite outcome of all-cause mortality, nonfatal MI, and reintervention (HR, 2.79 [95% CI, 2.19–3.54];  $P<0.001$ ). In propensity-matched analysis, CABG outcomes were favorable compared with PCI in patients nonadherent to medical therapy ( $P=0.001$ ), but outcomes were similar in medicine-adherent patients ( $P=0.574$ ).<sup>63</sup>

### **Cardiac Rehabilitation**

- In the NCDR ACTION Registry—GWTG, cardiac rehabilitation referral after patients were admitted with a primary diagnosis of STEMI or NSTEMI increased from 72.9% to 80.7% between 2007 and 2012.<sup>64</sup>
- In the NCDR between 2009 and 2012, 59% of individuals were referred to cardiac rehabilitation after PCI, with significant site-specific variation.<sup>65</sup>
- In the BRFSS from 2005 to 2015, <40% of patients self-reported participation in cardiac rehabilitation after AMI. Between 2011 and 2015, patients who declared participation in cardiac rehabilitation were less likely to be female (OR, 0.76 [95% CI, 0.65–0.90];  $P=0.002$ ) or black (OR, 0.70 [95% CI, 0.53–0.93];  $P=0.014$ ); were less well educated (high school versus college graduate: OR, 0.69 [95% CI, 0.59–0.81];  $P<0.001$ ; less than high school versus college graduate: OR, 0.47 [95% CI 0.37–0.61];  $P<0.001$ ); and were more likely to be retired or self-employed (OR, 1.39 [95% CI, 1.24–1.73];  $P=0.003$ ) than patients who did not participate in cardiac rehabilitation.<sup>66</sup>
- In a randomized trial in patients undergoing cardiac rehabilitation after ACS with PCI, patients receiving digital health interventions (consisting of an online and smartphone-based platform by which patients reported dietary and exercise habits and received educational information geared toward a healthy lifestyle) had more weight loss at 90 days than the control group (mean $\pm$ SD of  $-5.1\pm6.5$  kg versus  $-0.8\pm3.8$  kg;  $P=0.02$ ) and reduced cardiovascular-related rehospitalizations and ED visits at 180 days (8.1% versus 26.6%; RR, 0.30 [95% CI, 0.08–1.10];  $P=0.054$ ).<sup>67</sup>

### **Mortality**

(See Table 19-1)

- On the basis of 2017 mortality data<sup>68</sup>:
  - CHD mortality was 365 914, and CHD any-mention mortality was 541 008 (Table 19-1).

- MI mortality was 110 346. MI any-mention mortality was 149 028 (Table 19-1).
- From 2007 to 2017, the annual death rate attributable to CHD declined 28.1% and the actual number of deaths declined 10.0% (unpublished NHLBI tabulation using CDC WONDER<sup>69</sup>).
- CHD age-adjusted death rates per 100 000 were 131.1 for NH white males, 142.2 for NH black males, and 93.9 for Hispanic males; for NH white females, the rate was 66.7; for NH black females, it was 81.8; and for Hispanic females, it was 52.4 (unpublished NHLBI tabulation using CDC WONDER<sup>69</sup>).
- 77% of CHD deaths occurred out of the hospital. According to US mortality data, 281 792 CHD deaths occur out of the hospital or in hospital EDs annually (unpublished NHLBI tabulation using CDC WONDER<sup>69</sup>).
- The estimated average number of years of life lost because of an MI death is 16.1 (unpublished NHLBI tabulation using CDC WONDER<sup>69</sup>).
- Approximately 35% of the people who experience a coronary event in a given year will die as a result of it, and  $\approx$ 14% who experience an MI will die of it (unpublished NHLBI tabulation using ARIC Community Surveillance [2005–2014]).<sup>5</sup>
- Life expectancy after AMI treated in hospitals with high performance on 30-day mortality measures compared with low-performing hospitals was on average between 0.74 and 1.14 years longer.<sup>70</sup>
- In-hospital mortality is higher in females than in males with STEMI (7.4% versus 4.6%) and NSTEMI (4.8% versus 3.9%).<sup>71,72</sup> Females experience longer door-to-balloon times and lower rates of guideline-directed medical therapy than males; however, a 4-step systems-based approach to minimize STEMI care variability at the Cleveland Clinic resulted in reduced sex disparities and improved care and outcomes in females.<sup>73</sup>
- Among 194 071 adults who were hospitalized for an AMI in the 2009 to 2010 NIS, in-hospital mortality for those <65 years of age was higher for Hispanic females (3.7%) than for black females (3.1%) and white females (2.5%). Differences were smaller for males <65 years of age. Among older adults ( $\geq$ 65 years), in-hospital mortality was 8.0% for white females and between 6% and 8% for other race-sex groups.<sup>74</sup>
- In a study using data from the Cooperative Cardiovascular Project, survival and life expectancy after AMI were higher in whites than in blacks (7.4% versus 5.7%). White patients living in high SES areas showed the longest life expectancy. Gaps in life expectancy between white and black patients were largest among high SES areas, with smaller differences in medium and low SES areas.

These differences were attenuated but did not disappear after adjustment for patient and treatment characteristics.<sup>75</sup>

- Among patients hospitalized for STEMI between 2003 and 2014 in the NIS database, lack of health insurance (OR, 1.77 [95% CI, 1.72–1.82];  $P<0.001$ ) and below-median income (OR, 1.08 [95% CI, 1.07–1.09];  $P<0.001$ ) were independent predictors of in-hospital mortality.<sup>76</sup>
- Compared with nonparticipants, participants in the Supplemental Nutrition Assistance Program have twice the risk of CVD mortality, which likely reflects differences in socioeconomic, environmental, and behavioral characteristics.<sup>77</sup>
- In the CRUSADE study including 22 295 patients  $\geq 65$  years of age treated for STEMI or NSTEMI at 344 hospitals in the United States between 2004 and 2006, in-hospital mortality was 7%. Mortality was 24% at 1 year, 51% at 5 years, and 65% at 8 years. Eight-year mortality was higher for NSTEMI (67%) than for STEMI (53%), although the difference was attenuated after adjustment for demographics and comorbidities (HR, 0.94 [95% CI, 0.88–1.00]).<sup>78</sup>
- Among Medicare fee-for-service beneficiaries, between 1999 and 2011, the 30-day mortality rate after hospitalized MI declined by 29.4%.<sup>79</sup>
- In a community-based study of Worcester, MA, the percentage of patients dying after cardiogenic shock during their hospitalization for MI declined from 47.1% in 2001 to 2003 to 28.6% in 2009 to 2011.<sup>80</sup>
- Between 2001 and 2011 in the NIS, in-hospital mortality did not change for patients with STEMI with a PCI (3.40% and 3.52% in 2001 and 2011, respectively) or CABG (5.79% and 5.70% in 2001 and 2011, respectively) and increased for patients with no intervention (12.43% and 14.91% in 2001 and 2011, respectively). In-hospital mortality declined for patients with NSTEMI undergoing CABG (from 4.97% to 2.91%) or no procedure (from 8.87% to 6.26%) but did not change for patients with NSTEMI undergoing PCI (1.73% and 1.45%).<sup>81</sup>
- Among US males  $<55$  years of age, CHD mortality declined 5.5% per year between 1979 and 1989; a smaller decline was present in 1990 to 1999 (1.2% per year) and in 2000 to 2011 (1.8% per year). Among US females  $<55$  years of age, CHD mortality declined 4.6% per year in 1979 to 1989, with no decline between 1990 and 1999 and a decline of 1.0% in 2000 to 2011.<sup>82</sup>
- Taking into account past trends in CHD mortality from 1980, and considering age period and cohort effects, CHD mortality is likely to continue its decades-long decline, with a reduction in deaths

by 2030 of 27%; however, race disparities will persist.<sup>83</sup> Recent reports have suggested a slowing down of all CVD and HD mortality in recent years.<sup>84,85</sup>

### Complications

- In a pooled analysis of individuals after PCI in 5 RCTs, those with STEMI had a greater risk of death within the first 30 days after PCI than those with stable IHD, whereas those with NSTEMI had a greater risk of death during the entire 2 years of follow up.<sup>86</sup>
- From the NCDR CathPCI registry, in 2014 the unadjusted rates of various events were as follows: acute kidney injury, 2.6% (versus 2.3% in 2011); blood transfusion, 1.4% (versus 1.9% in 2011); postprocedural stroke, 0.2% (versus 0.2% in 2011); emergency CABG surgery, 0.2% (versus 0.3% in 2011); and vascular access site injury, 1.3% (versus 1.2% in 2011).<sup>61</sup>
- STEMI confers greater in-hospital risks than NSTEMI, including death (6.4% for STEMI, 3.4% for NSTEMI), cardiogenic shock (4.4% versus 1.6%, respectively), and bleeding (8.5% versus 5.5%, respectively).<sup>61</sup> In the NCDR ACTION Registry—GWTG, a measure of neighborhood SES was associated with in-hospital deaths and major bleeding in patients with AMI. Compared with those in the highest quintile of neighborhood SES, those residing in the most disadvantaged quintile experienced higher rates of in-hospital death (OR, 1.10 [95% CI, 1.02–1.18]) and major bleeding (OR, 1.10 [95% CI, 1.05–1.15]).<sup>87</sup>
- Among females with AMI, those with spontaneous coronary artery dissection had higher odds of in-hospital mortality (6.8%) than females without spontaneous coronary artery dissection (3.8%; OR, 1.87 [95% CI, 1.65–2.11];  $P<0.001$ ).<sup>88</sup>
- In the NCDR ACTION Registry—GWTG, patients with STEMI or NSTEMI with nonobstructive coronary arteries (<50% stenosis) had lower in-hospital mortality than patients with obstructive CAD (1.1% versus 2.9%;  $P<0.001$ ). Nonobstructive coronary arteries were more common in females than males (10.5% versus 3.4%;  $P<0.001$ ), but no difference in in-hospital mortality was observed between females and males with nonobstructive coronary arteries ( $P=0.84$ ).<sup>89</sup>
- Patients with LV thrombosis complicating anterior STEMI had longer hospital stays, higher hospitalization-related costs, and higher risk of thromboembolic events than those without LV thrombosis (7.3% versus 2.1%; OR, 3.65 [95% CI, 1.95–6.84];  $P<0.001$ ).<sup>90</sup>
- In a propensity score–matched analysis from the NIS HCUP that included discharges with MI as the

- principal diagnosis from 2012 to 2014, patients with delirium had higher rates of in-hospital mortality than those without delirium (10.5% versus 7.6%; RR, 1.39 [95% CI, 1.2–1.6];  $P<0.001$ ).<sup>91</sup>
- Individuals with HF symptoms (NYHA functional class  $\geq 2$ ) within 30 days after PCI for STEMI experience increased risk of death or hospitalization for HF within 1 year compared with those without HF symptoms (HR, 3.78 [95% CI, 1.16–12.22];  $P=0.03$ ).<sup>92</sup>
  - On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012), within 1 year after a first MI (unpublished NHLBI tabulation):
    - At  $\geq 45$  years of age, 18% of males and 23% of females will die.
    - At 45 to 64 years of age, 3% of white males, 5% of white females, 9% of black males, and 10% of black females will die.
    - At 65 to 74 years of age, 14% of white males, 18% of white females, 22% of black males, and 21% of black females will die.
    - At  $\geq 75$  years of age, 27% of white males, 29% of white females, 19% of black males, and 31% of black females will die.
  - In part because females have MIs at older ages than males, they are more likely to die of MI within a few weeks.
  - Within 5 years after a first MI:
    - At  $\geq 45$  years of age, 36% of males and 47% of females will die.
    - At 45 to 64 years of age, 11% of white males, 17% of white females, 16% of black males, and 28% of black females will die.
    - At 65 to 74 years of age, 25% of white males, 30% of white females, 33% of black males, and 44% of black females will die.
    - At  $\geq 75$  years of age, 55% of white males, 60% of white females, 61% of black males, and 64% of black females will die.
  - Of those who have a first MI, the percentage with a recurrent MI or fatal CHD within 5 years is as follows:
    - At  $\geq 45$  years of age, 17% of males and 21% of females.
    - At 45 to 64 years of age, 11% of white males, 15% of white females, 22% of black males, and 32% of black females.
    - At 65 to 74 years of age, 12% of white males, 17% of white females, 30% of black males, and 30% of black females.
    - At  $\geq 75$  years of age, 21% of white males, 20% of white females, 45% of black males, and 20% of black females.
  - The percentage of people with a first MI who will have HF in 5 years is as follows:

- At  $\geq 45$  years of age, 16% of males and 22% of females.
- At 45 to 64 years of age, 6% of white males, 10% of white females, 13% of black males, and 25% of black females.
- At 65 to 74 years of age, 12% of white males, 16% of white females, 20% of black males, and 32% of black females.
- At  $\geq 75$  years of age, 25% of white males, 27% of white females, 23% of black males, and 19% of NH black females.
- The percentage of people with a first MI who will have an incident stroke within 5 years is as follows:
  - At  $\geq 45$  years of age, 4% of males and 7% of females.
  - At  $\geq 45$  years of age, 5% of white males, 6% of white females, 4% of black males, and 10% of black females.
- The median survival time (in years) after a first MI is as follows:
  - At  $\geq 45$  years of age, 8.2 for males and 5.5 for females.
  - At  $\geq 45$  years of age, 8.4 for white males, 5.6 for white females, 7.0 for black males, and 5.5 for black females.
- The burden of rehospitalizations for AMI may be substantial: A retrospective cohort study of 78 085 Medicare beneficiaries  $\geq 66$  years of age without recent CHD history who were hospitalized for AMI in 2000 to 2010 reported that 20.6% had at least 1 rehospitalization during the 10 years after the index MI. Among patients with a CHD rehospitalization, 35.9% had  $\geq 2$  CHD rehospitalizations. Males and patients  $\geq 85$  years of age had greater rate ratios for first rehospitalization.<sup>93</sup>
- A study of 3 250 194 Medicare beneficiaries admitted for PCI found that readmission rates declined slightly from 16.1% in 2000 to 15.4% in 2012. The majority of readmissions were because of chronic IHD (26.6%), HF (12%), and chest pain/angina (7.9%). A minority (<8%) of total readmissions were for AMI, UA, or cardiac arrest/cardio-genic shock.<sup>94</sup>
- Rehospitalization can be influenced by clinical, psychosocial, and sociodemographic characteristics not accounted for in traditional CMS claims-based models, including prior PCI, CKD, low health literacy, lower serum sodium levels, and lack of cigarette smoking.<sup>95</sup>
- In a study of 3 central Massachusetts hospitals, the 90-day rehospitalization rate declined from 31.5% in 2001 to 2003 to 27.3% in 2009 to 2011.<sup>96</sup> Crude 30-day rehospitalization rates decreased from 20.5% in 2001 to 2003 to 15.8% in 2009 to 2011.<sup>97</sup>

## Hospital Discharges and Ambulatory Care Visits (See Table 19-1 and Chart 19-8)

- From 2006 to 2016, the number of inpatient discharges from short-stay hospitals with CHD as the first-listed diagnosis decreased from 1857 000 to 1 045 000 (Table 19-1).
- From 1997 through 2016, the number of hospital discharges for CHD was higher for males than females (Chart 19-8).
- In 2016, there were 11 072 000 physician office visits for CHD (unpublished NHLBI tabulation using NAMCS<sup>98</sup>). In 2016, there were 469 000 ED visits with a primary diagnosis of CHD (unpublished NHLBI tabulation using NHAMCS<sup>99</sup>).
- In the NIS, the mean length of hospital stay for STEMI patients with primary PCI declined from 3.3 days in 2005 to 2.7 days in 2014; the proportion of hospitalizations with length of stay >3 days declined from 31.9% in 2005 to 16.9% in 2014.<sup>100</sup>
- In the CathPCI registry, a composite of use of evidence-based medical therapies, including aspirin, P2Y12 inhibitors, and statins, was high (89.1% in 2011 and 93.5% in 2014). However, in the ACTION-GWTG registry, metrics that were shown to need improvement were defect-free care (median hospital performance rate of 78.4% in 2014), P2Y12 inhibitor use in eligible medically treated patients with AMI (56.7%), and the use of aldosterone antagonists in patients with LV systolic dysfunction and either DM or HF (12.8%).<sup>61</sup>

### Cost

- The estimated direct costs of HD in 2014 to 2015 (average annual) were \$109.4 billion (MEPS,<sup>101</sup> unpublished NHLBI tabulation).
- The estimated direct and indirect cost of HD in 2014 to 2015 (average annual) was \$218.7 billion (MEPS,<sup>101</sup> unpublished NHLBI tabulation).
- MI (\$12.1 billion) and CHD (\$9.0 billion) were 2 of the 10 most expensive conditions treated in US hospitals in 2013.<sup>102</sup>
- In 642 105 Medicare beneficiaries hospitalized for AMI between 2011 and 2014, 30-day episode payments averaged \$22 128 but varied 2-fold across hospitals. Median costs were \$20 207 in the lowest quartile versus \$24 174 in the highest quartile of hospitals.<sup>103</sup>
- In Medicare beneficiaries hospitalized with AMI, the 180-day expenditures increased from an average of \$32 182 per person in 1999 to 2000 to \$36 836 in 2008 and remained relatively stable thereafter, with expenditures of \$36 668 in 2013 to 2014.<sup>104</sup>
- In a multipayer administrative claims database of patients with incident inpatient PCI admissions between 2008 and 2011, post-PCI angina and

chest pain were common and costly (\$32 437 versus \$17 913;  $P<0.001$  at 1 year comparing those with and without angina or chest pain).<sup>105</sup>

- Among Medicare beneficiaries linked to the NCDR CathPCI Registry with inpatient or outpatient PCI between July 2009 and December 2012, costs were \$3502 (95% CI, \$3347–\$3648;  $P<0.001$ ) lower for patients with same-day discharge than for those not discharged the same day. Although a minority of patients receive transradial intervention and same-day discharge (1.2%), a cost savings of \$3689 (95% CI, \$3486–\$3902;  $P<0.001$ ) was observed compared with patients with transfemoral intervention not discharged the same day.<sup>106</sup>

### Global Burden

#### (See Table 19-3 and Charts 19-9 and 19-10)

- The GBD 2017 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.<sup>107</sup> Globally, it is estimated that in 2017, 126.5 million people live with IHD, and it is more prevalent in males than in females (68.5 and 57.9 million people, respectively). The number of people with IHD increased by 74.9% from 1990 to 2017, although the age-standardized rate per 100 000 decreased 11.8% over the same time period (Table 19-3).
  - IHD mortality rates are generally lower than 150 per 100 000 for most of the world but exceed 280 per 100 000 in Eastern Europe and Central Asia (Chart 19-9).
  - Eastern Europe, North Africa, and the Middle East have the highest prevalence rates of IHD in the world (Chart 19-10).

## Acute Coronary Syndrome

### **ICD-9 410, 411; ICD-10 I20.0, I21, I22.**

- In 2016, there were 661 000 ACS principal diagnosis discharges. Of these, an estimated 409 000 were males, and 252 000 were females. This estimate was derived by adding the principal diagnoses for MI (651 000) to those for UA (10 000; unpublished NHLBI tabulation using HCUP<sup>50</sup>).
- When all listed discharge diagnoses in 2016 were included, the corresponding number of inpatient hospital discharges was 1 045 000 unique hospitalizations for ACS; 615 000 were males, and 430 000 were females. Of the total, 1 022 000 were for MI alone, and 23 000 were for UA alone (HCUP<sup>50</sup> unpublished NHLBI tabulation).
- In a study using the NIS and the State Inpatient Databases for the year 2009, mean charge per

ACS discharge was \$63 578 (median \$41 816). Mean charges, however, were greater for the first compared with the second admission (\$71 336 versus \$53 290, respectively).<sup>108</sup>

- On the basis of medical, pharmacy, and disability insurance claims data from 2007 to 2010, short-term productivity losses associated with ACS were estimated at \$7943 per disability claim, with long-term productivity losses of \$52 473 per disability claim. ACS also resulted in substantial wage losses, from \$2263 to \$20 609 per disability claim for short- and long-term disability, respectively.<sup>109</sup>
- According to data from the NIS, between 2001 and 2011, the use of PCI for patients with ACS declined by 15%.<sup>58</sup>
- In a report from the TRACE-CORE study, persons with recurrent ACS were more likely to report anxiety, depression, higher perceived stress, and lower mental and physical quality of life; were more likely to have impaired cognition; and had lower levels of health literacy and health numeracy than individuals with a first ACS.<sup>110</sup>
- In the NIS from 2012 to 2013, females with non-ST-elevation ACS treated with an early invasive strategy had lower in-hospital mortality than females treated conservatively (2.1% versus 3.8%). However, the survival advantage for invasive management was restricted to females with NSTEMI (OR, 0.52 [95% CI, 0.46–0.58]), and no differences in in-hospital survival for invasive versus conservative treatment were observed among females with UA.<sup>111</sup>
- In a meta-analysis of 8 randomized trials, the risk of long-term all-cause mortality at a mean of 10.3 years of follow-up was similar for non-ST-elevation ACS patients treated with a routine strategy (coronary angiography within 24 to 96 hours of presentation) versus a selective invasive strategy (medical

stabilization with or without coronary angiography in those who demonstrated evidence of ischemia on noninvasive stress test or with ongoing symptoms), at 28.5% for both strategies.<sup>112</sup>

## Stable AP

### ***ICD-9 413; ICD-10 I20.1 to I20.9.***

#### **Prevalence**

(See Table 19-2 and Chart 19-11)

- According to data from NHANES 2013 to 2016, the prevalence of AP among adults ( $\geq 20$  years of age) is 3.6% (9.4 million adults; Table 19-2).
- On the basis of NHANES 2013 to 2016, the prevalence of AP increased with age from <1% among males and females 20 to 39 years of age to >10% among males and females  $\geq 80$  years of age (Chart 19-11).
- On the basis of data from NHANES in 2009 to 2012, there were an average of 3.4 million people  $\geq 40$  years of age in the United States with angina each year, compared with 4 million in 1988 to 1994. Declines in angina symptoms have occurred for NH whites but not for NH blacks.<sup>3</sup>
- In Americans  $\geq 40$  years of age with health insurance, age-adjusted angina prevalence declined from 7.6% in 2001 to 2002 to 5.2% in 2011 to 2012 ( $P$  for trend<0.001), whereas in those without health insurance, there was an increase from 4.7% to 7.6% ( $P$  for trend=0.4).<sup>113</sup>
- Among patients with a history of CAD (ACS, prior coronary revascularization procedure, or stable angina), 32.7% self-reported at least 1 episode of angina over the past month. Of those reporting angina, 23.3% reported daily or weekly symptoms of angina, and 56.3% of these patients with daily or weekly angina were taking at least 2 antianginal medications.<sup>114</sup>

**Table 19-1.** CHD in the United States

Population Group	Prevalence, CHD, 2013–2016 Age ≥20 y	Prevalence, MI, 2013–2016 Age ≥20 y	New and Recurrent MI and Fatal CHD, 2005–2014 Age ≥35 y	New and Recurrent MI, 2005–2014 Age ≥35 y	Mortality,* CHD, 2017 All Ages	Mortality,* MI, 2017 All Ages	Hospital Discharges: CHD, 2016 All Ages
Both sexes	18 200 000 (6.7%)	8 400 000 (3.0%)	1 055 000	805 000	365 914	110 346	1 045 000
Males	9 400 000 (7.4%)	5 100 000 (4.0%)	610 000	470 000	213 295 (58.3%)†	64 436 (58.4%)†	664 000
Females	8 800 000 (6.2%)	3 300 000 (2.3%)	445 000	335 000	152 619 (41.7%)†	45 910 (41.6%)†	381 000
NH white males	7.7%	4.0%	520 000‡	...	168 868	51 155	...
NH white females	6.1%	2.2%	370 000‡	...	119 151	35 720	...
NH black males	7.2%	4.0%	90 000‡	...	22 167	6595	...
NH black females	6.5%	2.2%	75 000‡	...	18 055	5458	...
Hispanic males	6.0%	3.4%	...	...	14 195	4437	...
Hispanic females	6.0%	2.0%	...	...	10 041	3113	...
NH Asian males	4.8%	2.4%	...	...	5721	1693§	...
NH Asian females	3.2%	1.0%	...	...	4103	1271§	...
NH American Indian or Alaska Native	...	...	...	...	2032	593	...

CHD includes people who responded “yes” to at least 1 of the questions in “Has a doctor or other health professional ever told you that you had CHD, angina or angina pectoris, heart attack, or MI?” Those who answered “no” but were diagnosed with Rose angina are also included (the Rose questionnaire is only administered to survey participants >40 years of age). CHD indicates coronary heart disease; ellipses (...), data not available; MI, myocardial infarction; and NH, non-Hispanic.

\*Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total CHD and MI mortality that is for males vs females.

‡Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

§Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey 2013 to 2016.<sup>1</sup> Percentages for racial/ethnic groups are age adjusted for Americans ≥20 years of age. Age-specific percentages are extrapolated to the 2016 US population estimates. These data are based on self-reports. Incidence: Atherosclerosis Risk in Communities study (2005–2014),<sup>5</sup> unpublished tabulation by NHLBI, extrapolated to the 2014 US population. Mortality: unpublished NHLBI tabulation using National Vital Statistics System, 2017.<sup>68</sup> Mortality for NH Asians includes Pacific Islanders. Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016<sup>50</sup> (data include those inpatients discharged alive, dead, or status unknown).

**Table 19-2.** AP\* in the United States

Population Group	Prevalence, 2013–2016, Age ≥20 y	Hospital Discharges, 2016, All Ages
Both sexes	9 400 000 (3.6%)	18 000
Males	4 300 000 (3.5%)	9000
Females	5 100 000 (3.7%)	9000
NH white males	3.8%	...
NH white females	3.8%	...
NH black males	3.6%	...
NH black females	3.8%	...
Hispanic males	2.6%	...
Hispanic females	3.6%	...
NH Asian or Pacific Islander males	2.0%	...
NH Asian or Pacific Islander females	1.6%	...

AP includes people who either answered “yes” to the question of ever having angina or angina pectoris or who were diagnosed with Rose angina (the Rose questionnaire is only administered to survey participants >40 years of age). AP indicates angina pectoris; ellipses (...), data not available; and NH, non-Hispanic.

\*AP is chest pain or discomfort that results from insufficient blood flow to the heart muscle. Stable AP is predictable chest pain on exertion or under mental or emotional stress. The incidence estimate is for AP without myocardial infarction.

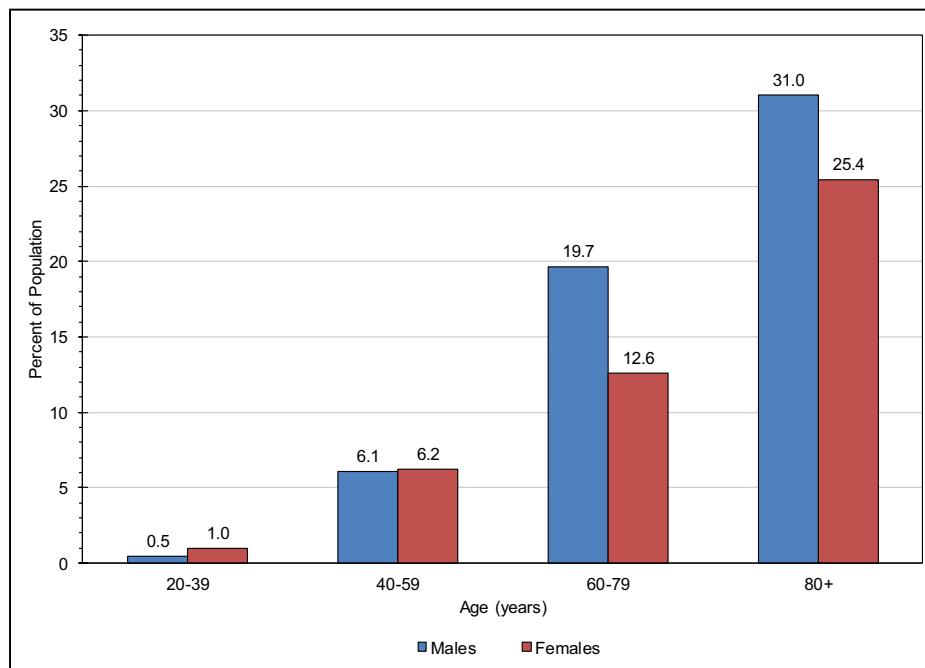
Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey (NHANES), 2013 to 2016.<sup>1</sup> Percentages for racial/ethnic groups are age adjusted for US adults ≥20 years of age. Estimates from NHANES 2013 to 2016 were applied to 2016 population estimates (≥20 years of age). Hospital discharges: unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016<sup>50</sup>; data include those inpatients discharged alive, dead, or status unknown.

**Table 19-3.** Global Burden of IHD and Trends, 2017

	Both Sexes		Male		Female	
	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)	Deaths (95% UI)	Prevalence (95% UI)
Total number (millions)	8.9 (8.8 to 9.1)	126.5 (118.6 to 134.7)	4.9 (4.8 to 5.0)	68.5 (64.3 to 73.2)	4.0 (3.9 to 4.1)	57.9 (54.3 to 61.9)
Percent change total number 1990 to 2017	52.3 (49.1 to 55.0)	74.9 (71.8 to 78.6)	58.3 (53.9 to 62.0)	73.6 (70.4 to 77.2)	45.5 (41.7 to 49.0)	76.6 (73.1 to 80.5)
Percent change total number 2007 to 2017	22.3 (20.6 to 23.8)	24.0 (21.7 to 26.5)	23.1 (21.1 to 25.2)	22.8 (20.5 to 25.4)	21.3 (19.1 to 23.4)	25.5 (23.3 to 27.9)
Rate per 100 000	116.9 (115.1 to 119.7)	1583.7 (1484.5 to 1691.1)	144.4 (141.5 to 147.9)	1835.8 (1720.7 to 1962.2)	93.3 (91.2 to 96.1)	1361.3 (1274.8 to 1453.4)
Percent change rate 2007 to 2017	-9.7 (-11.0 to -8.7)	-5.1 (-6.8 to -3.2)	-9.0 (-10.5 to -7.6)	-6.5 (-8.3 to -4.5)	-10.8 (-12.4 to -9.2)	-3.7 (-5.4 to -1.9)
Percent change rate 1990 to 2017	-30.0 (-31.3 to -28.8)	-11.8 (-13.5 to -9.9)	-27.8 (-29.7 to -26.2)	-14.3 (-16.0 to -12.5)	-33.2 (-34.9 to -31.6)	-9.8 (-11.5 to -7.8)

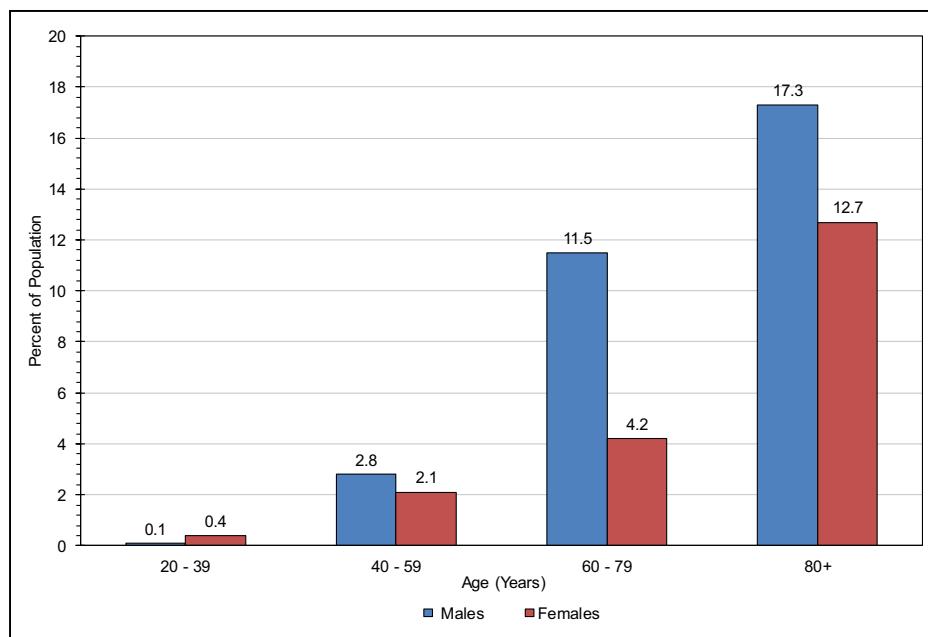
IHD indicates ischemic heart disease; and UI, uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>107</sup> Printed with permission. Copyright © 2018, University of Washington.

**Chart 19-1.** Prevalence of coronary heart disease by age and sex, United States (NHANES, 2013–2016).

NHANES indicates National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.<sup>1</sup>

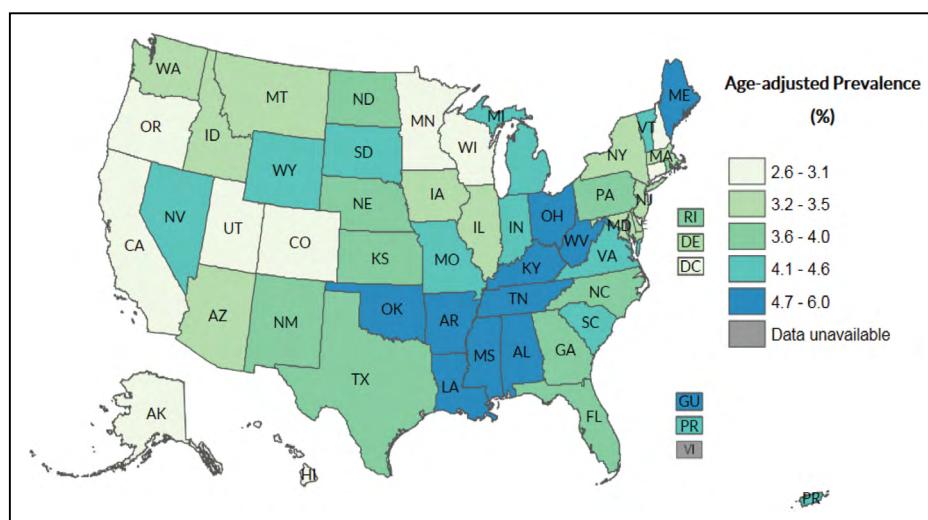


**Chart 19-2. Prevalence of myocardial infarction (MI) by age and sex, United States (NHANES, 2013–2016).**

MI includes people who answered “yes” to the question of ever having had a heart attack or MI.

NHANES indicates National Health and Nutrition Examination Survey.

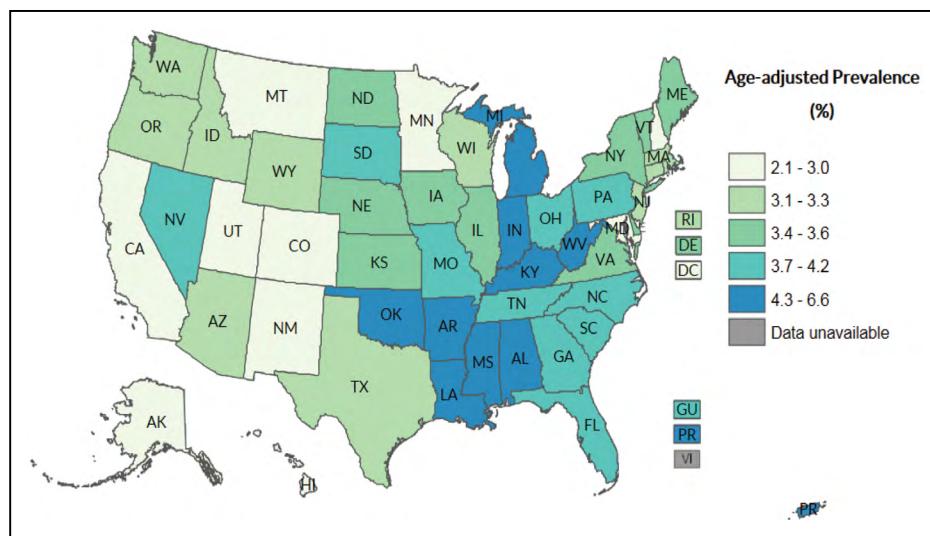
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.<sup>1</sup>



**Chart 19-3. “Ever told you had a heart attack (myocardial infarction)?” Age-adjusted US prevalence by state (BRFSS Prevalence and Trends Data, 2017).**

BRFSS indicates Behavioral Risk Factor Surveillance System.

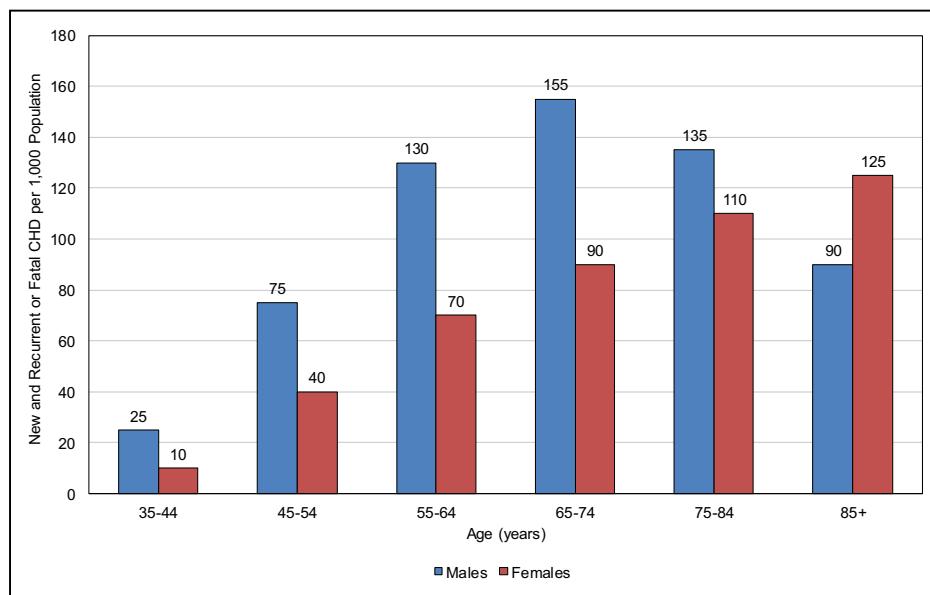
Source: BRFSS Prevalence and Trends Data, 2017.<sup>4</sup>



**Chart 19-4.** "Ever told you had angina or coronary heart disease?" Age-adjusted US prevalence by state (BRFSS Prevalence and Trends Data, 2017).

BRFSS indicates Behavioral Risk Factor Surveillance System.

Source: BRFSS Prevalence and Trends Data, 2017.<sup>4</sup>

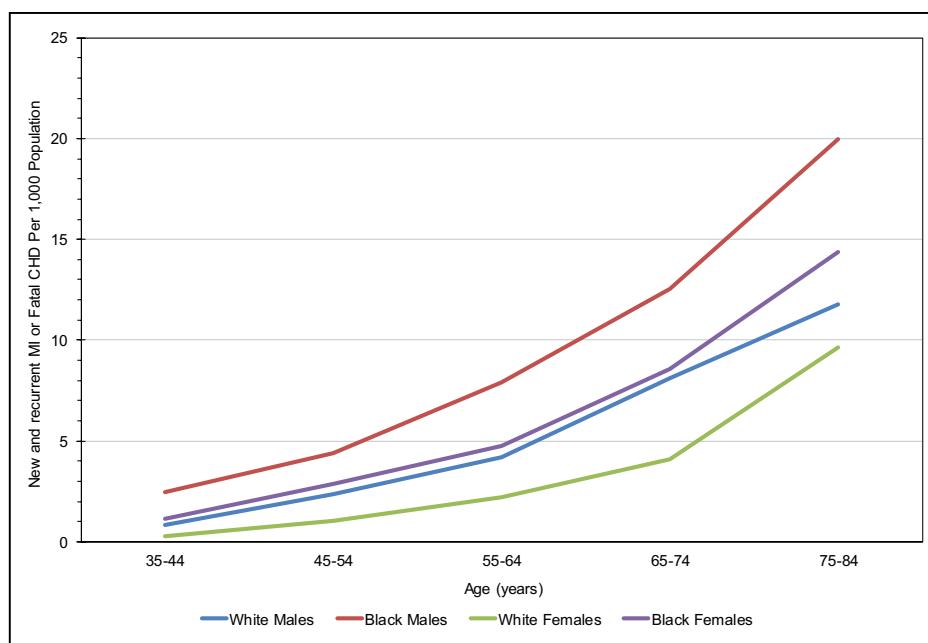


**Chart 19-5.** Annual number of US adults per 1000 having diagnosed heart attack or fatal CHD by age and sex (ARIC surveillance, 2005–2014 and CHS).

These data include myocardial infarction (MI) and fatal CHD but not silent MI.

ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; and CHS, Cardiovascular Health Study.

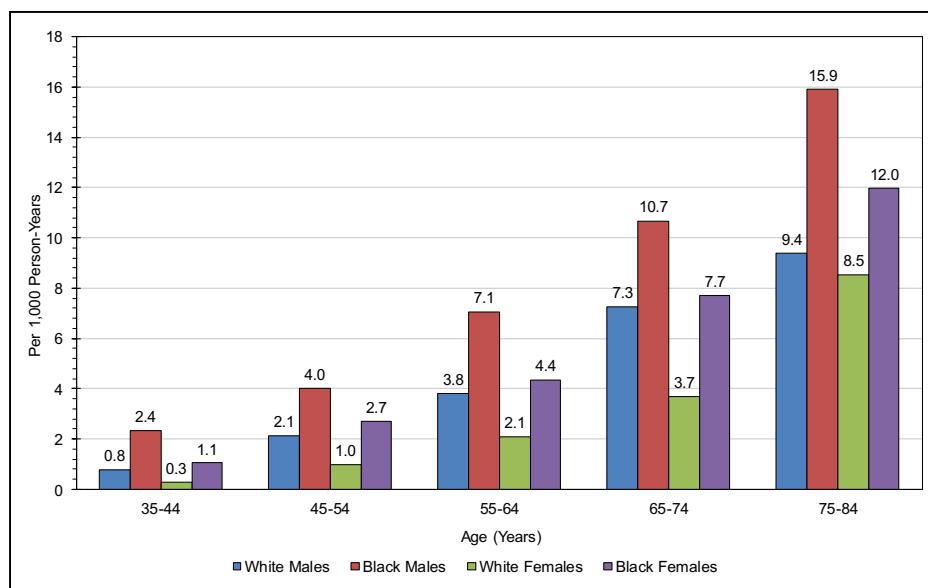
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC, 2005 to 2014<sup>5</sup> and CHS.<sup>115</sup>



**Chart 19-6. Incidence of heart attack or fatal CHD by age, sex, and race, United States (ARIC Surveillance, 2005–2014).**

ARIC indicates Atherosclerosis Risk in Communities; CHD, coronary heart disease; and MI, myocardial infarction.

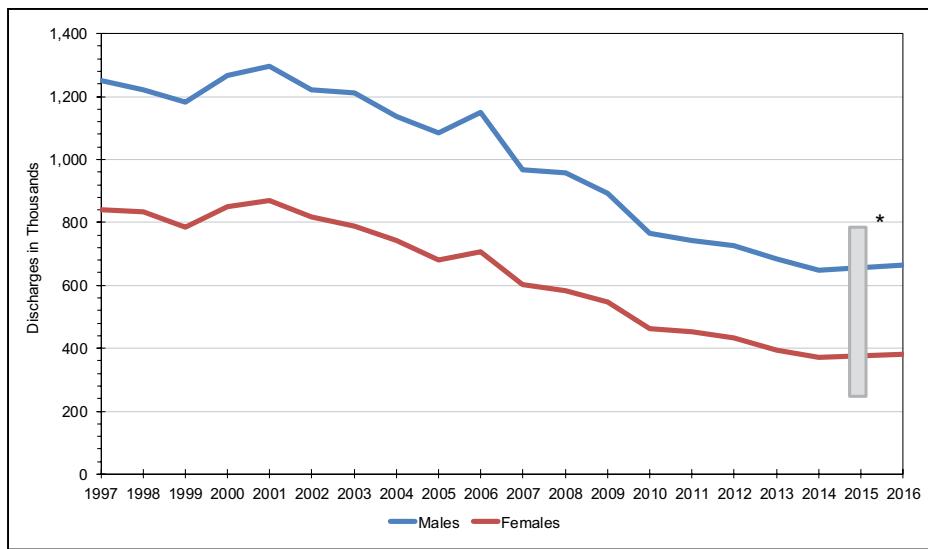
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC, 2005 to 2014.<sup>5</sup>



**Chart 19-7. Incidence of myocardial infarction by age, sex, and race, United States (ARIC Surveillance, 2005–2014).**

ARIC indicates Atherosclerosis Risk in Communities.

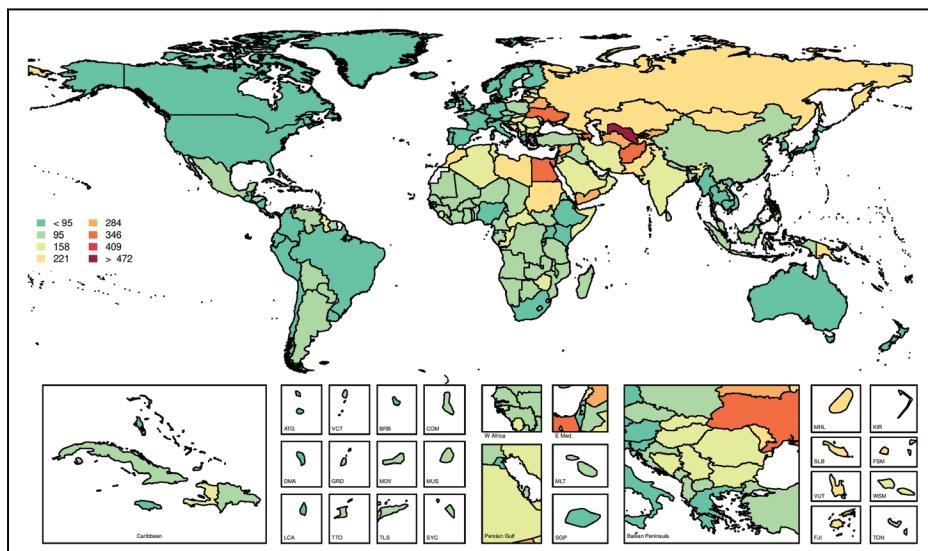
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC, 2005 to 2014.<sup>5</sup>

**Chart 19-8. Hospital discharges for coronary heart disease by sex, United States (HCUP, 1997–2016).**

Hospital discharges include people discharged alive, dead, and status unknown. HCUP indicates Healthcare Cost and Utilization Project.

\*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

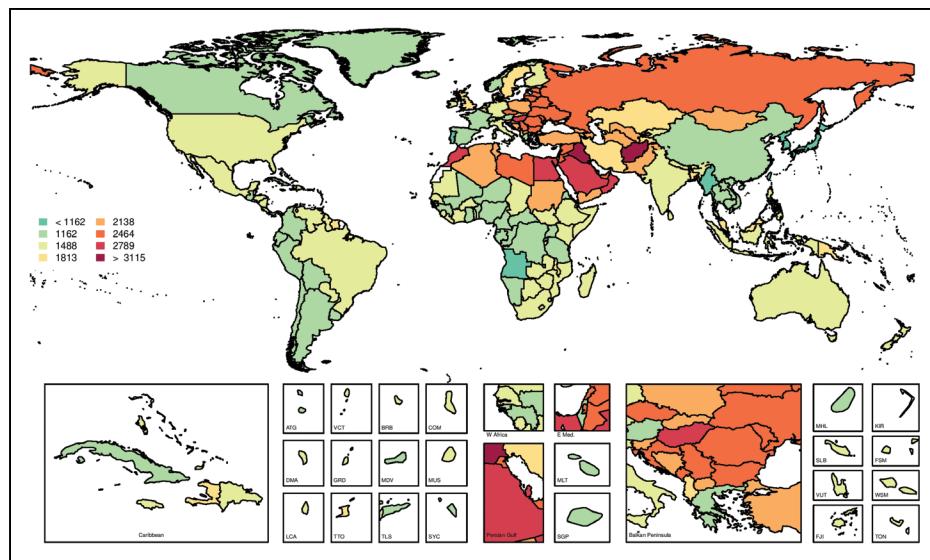
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using HCUP.<sup>50</sup>

**Chart 19-9. Age-standardized global mortality rates of ischemic heart disease (IHD) per 100 000, both sexes, 2017.**

IHD mortality rates are generally lower than 150 per 100 000 for most of the world but exceed 280 per 100 000 in Eastern Europe and Central Asia.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa. IHD indicates ischemic heart disease.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>107</sup> Printed with permission. Copyright © 2018, University of Washington.

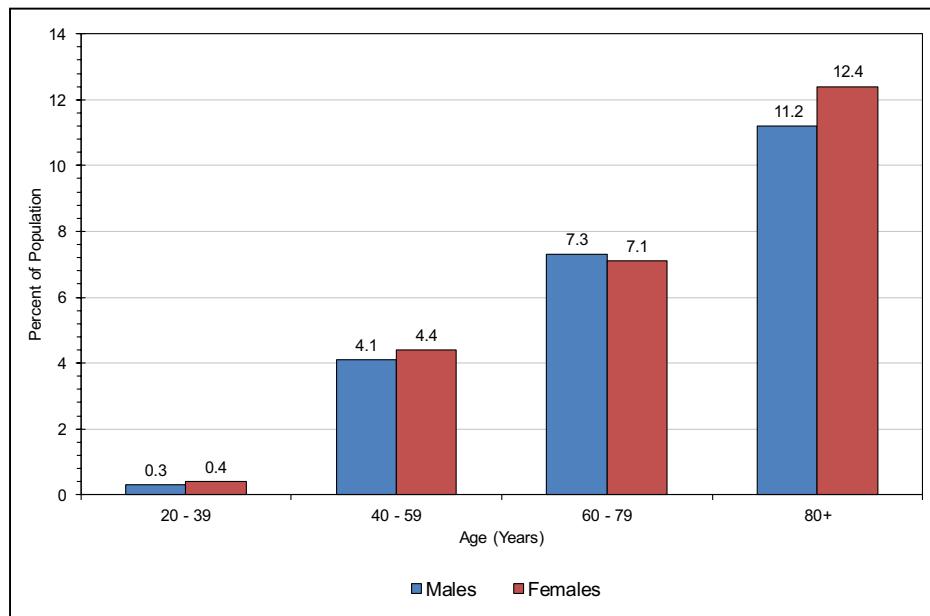


**Chart 19-10. Age-standardized global prevalence rates of ischemic heart disease (IHD) per 100 000, both sexes, 2017.**

Eastern Europe, North Africa, and the Middle East have the highest prevalence rates of IHD.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>107</sup> Printed with permission. Copyright © 2018, University of Washington.



**Chart 19-11. Prevalence of angina pectoris by age and sex (NHANES, 2013–2016).**

Angina pectoris includes people who either answered “yes” to the question of ever having angina or angina pectoris or were diagnosed with Rose angina. NHANES indicates National Health and Nutrition Examination Survey.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.<sup>1</sup>

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## 20. CARDIOMYOPATHY AND HEART FAILURE

**See Tables 20-1 and 20-2 and Charts 20-1 through 20-7**

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### Cardiomyopathy

**ICD-9 425; ICD-10 I42.**

2017: Mortality—21427. Any-mention mortality—42937.

Cardiomyopathy diagnoses account for a substantial number of inpatient and outpatient encounters annually. Using HCUP data<sup>1</sup> for cardiomyopathy in 2016, there were 19 000 inpatient hospitalizations for which cardiomyopathy was the principal diagnosis (11 000 for men; 8 000 for women) and 994 000 where it was included among all-listed diagnoses (NHLBI unpublished tabulation).

### Abbreviations Used in Chapter 20

ACE	angiotensin-converting enzyme
ACR	albumin-to-creatinine ratio
AF	atrial fibrillation
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CAD	coronary artery disease
CARDIA	Coronary Artery Risk Development in Young Adults Study
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHD	coronary heart disease
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CRP	C-reactive protein
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
DM	diabetes mellitus
ED	emergency department
EF	ejection fraction
ESRD	end-stage renal disease
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GWAS	genome-wide association study
GWTG	Get With The Guidelines
HbA <sub>1c</sub>	hemoglobin A <sub>1c</sub> (glycosylated hemoglobin)
HCM	hypertrophic cardiomyopathy
HCUP	Healthcare Cost and Utilization Project

(Continued)

### Abbreviations Used in Chapter 20 Continued

HD	heart disease
Health ABC	Health, Aging, and Body Composition
HF	heart failure
HR	hazard ratio
ICD-9	<i>International Classification of Diseases, 9th Revision</i>
ICD-10	<i>International Classification of Diseases, 10th Revision</i>
IHD	ischemic heart disease
IL	interleukin
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MedaMACS	Medical Arm of Mechanically Assisted Circulatory Support
MESA	Multi-Ethnic Study of Atherosclerosis
MII	myocardial infarction
MRI	magnetic resonance imaging
NAMCS	National Ambulatory Medical Care Survey
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
PA	physical activity
PAR	population attributable risk
PHS	Physicians' Health Study
PPCM	peripartum cardiomyopathy
PVC	premature ventricular contraction
QALY	quality-adjusted life-year
ROADMAP	Randomized Olmesartan and Diabetes Microalbuminuria Prevention
RR	relative risk
RV	right ventricular
SBP	systolic blood pressure
SCD	sudden cardiac death
SES	socioeconomic status
UI	uncertainty interval

### Hypertrophic Cardiomyopathy

- The prevalence of unexplained LVH has been estimated at 0.2% and up to 1.4% in the community.<sup>2</sup>
- Of persons with unexplained LVH, ≈20% to 30% are likely to have a sarcomere mutation that suggests clinically expressed HCM; however, not all people with sarcomere mutations manifest clinical HCM, because of incomplete penetrance, even among members of the same family (see Family History and Genetics for more details).<sup>3</sup>

- The Sarcomeric Human Cardiomyopathy Registry studied 4591 patients with HCM, contributing >24 000 person-years of follow-up, and observed ≈3-fold higher mortality risk in patients with HCM compared with similarly aged individuals in the US general population. Risk for adverse events (ie, any ventricular arrhythmia, HF, AF, stroke, or death) was highest in patients diagnosed before 40 years of age versus after 60 years of age (77% [95% CI, 72%–80%] versus 32% [95% CI, 29%–36%] cumulative incidence). Adverse events were also 2-fold higher in patients with versus without sarcomere mutations. AF and HF accounted for a substantial proportion of the adverse events, despite not typically manifesting until years to decades after initial diagnosis.<sup>4</sup>

### Dilated Cardiomyopathy

- Commonly recognized causes of chronic DCM are mutations in a diverse group of genes that are inherited in an autosomal dominant fashion with age-dependent penetrance and variable clinical expression (see Family History and Genetics for more details). Other causes of DCM of variable chronicity and reversibility include cardiomyopathies that can develop after an identifiable exposure such as tachyarrhythmia, stress, neurohormonal disorder, alcoholism, chemotherapy, infection, or pregnancy (see Peripartum Cardiomyopathy).<sup>5</sup> The annual incidence of chronic idiopathic DCM has been reported as between 5 and 8 cases per 100 000, although these estimates might be low because of underrecognition, especially in light of prevalent asymptomatic LV dysfunction observed in community-based studies (see LV Function).<sup>6,7</sup>

### Peripartum Cardiomyopathy

- Data from the NIS databases indicate that the incidence of PPCM increased between 2004 and 2011 from 8.5 to 11.8 per 10 000 live births ( $P_{\text{trend}}<0.001$ ), likely related to rising average maternal age and prevalence of PPCM risk factors such as obesity, hypertension, pregnancy-related hypertension, and DM.<sup>8</sup>
- The NIS data also show that maternal age has increased in all racial/ethnic groups, except Hispanics and Asians/Pacific Islanders, and across all census regions in the United States. When stratified by race/ethnicity, incidence of PPCM was lowest in Hispanics and highest in blacks. When stratified by region, incidence was lowest in the West (6.5 [95% CI, 6.3–6.7] per 10 000 live births) and highest in the South (13.1 [95% CI, 12.9–13.1] per 10 000 live births).<sup>8</sup>
- In females diagnosed with PPCM, data from a prospective cohort indicate that 13% had major events (death, cardiac transplantation, or implantation of

an LVAD) or persistent severe cardiomyopathy at 12 months. Black females had worse LV dysfunction at presentation and at 6 and 12 months postpartum than nonblack females.<sup>9</sup>

- For a majority of females with PPCM (50%–80%), LVEF recovers to at least a near-normal range (≥50%), with many achieving this recovery within the first 6 months; however, a substantial proportion remain affected by overtly impaired cardiac function.<sup>9–12</sup>

### Youth

- Since 1996, the NHLBI-sponsored Pediatric Cardiomyopathy Registry has collected data on children with newly diagnosed cardiomyopathy in New England and the central Southwest (Texas, Oklahoma, and Arkansas).<sup>13</sup>
  - The overall incidence of cardiomyopathy is 1.13 cases per 100 000 among children <18 years of age.
  - Among children <1 year of age, the incidence is 8.34, and among children 1 to 18 years of age, it is 0.70 per 100 000.
  - The annual incidence is higher in black children than in white children, in boys than in girls, and in New England (1.44 per 100 000) than in the central Southwest (0.98 per 100 000).
- The estimated annual incidence of HCM in children was 4.7 per 1 million children, with higher incidence in New England than in the central Southwest region and higher incidence in boys than in girls.<sup>14</sup> Long-term outcomes of children with HCM suggest that 9% progress to HF and 12% to SCD.<sup>15</sup> See Chapter 16 (Disorders of Heart Rhythm) for statistics regarding sudden death in HCM.
- The estimated annual incidence of DCM in children <18 years of age is 0.57 per 100 000 overall, with higher incidence in boys than girls (0.66 versus 0.47 cases per 100 000, respectively) and blacks than whites (0.98 versus 0.46 cases per 100 000, respectively). The most commonly recognized causes of DCM were myocarditis (46%) and neuromuscular disease (26%).<sup>16</sup> The 5-year incidence rate of SCD is 3% among children <18 years of age at the time of DCM diagnosis.<sup>17</sup>
- Data from the Childhood Cancer Survivor Study cohort of 14 358 survivors of childhood or adolescent cancers show that these individuals are at 6-fold increased risk for future HF,<sup>18</sup> usually preceded by asymptomatic cardiomyopathy. This risk is especially pronounced for individuals who were treated with chest radiation or anthracycline chemotherapy and persists up to 30 years after the original cancer diagnosis.

### **Global Burden of Cardiomyopathy (See Table 20-1 and Charts 20-1 through 20-3)**

- Chart 20-1 shows temporal trends in the incidence of PPCM in the United States.
- The GBD 2017 Study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.<sup>19</sup>
  - Between 1990 and 2017, the global number of deaths attributable to cardiomyopathy and myocarditis increased 54.5%. In 2017, the age-adjusted death rate was 4.8 per 100 000, a 25.8% decrease in the rate from 1990 (Table 20-1).
  - The highest age-standardized mortality rates attributable to cardiomyopathy and myocarditis are in Eastern Europe (Chart 20-2).
  - Age-standardized prevalence of cardiomyopathy and myocarditis is highest in Central Europe (Chart 20-3).

## **Heart Failure**

### **ICD-9 428; ICD-10 I50.**

2017: Mortality—80 480. Any-mention mortality—352 119. 2016: Hospital discharges—809 000.

#### **Prevalence**

##### **(See Table 20-2 and Chart 20-4)**

- Based on data from NHANES 2013 to 2016, an estimated 6.2 million Americans ≥20 years of age had HF (Table 20-2; Chart 20-4). This represents an increase from an estimated 5.7 million US adults with HF based on NHANES 2009 to 2012 (NHLBI unpublished tabulation using NHANES<sup>20</sup>).
- Projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in >8 million people ≥18 years of age with HF. Additionally, the total percentage of the population with HF is predicted to increase from 2.42% in 2012 to 2.97% in 2030.<sup>21</sup>

#### **Incidence**

##### **(See Table 20-2 and Chart 20-5)**

- Based on ARIC Community Surveillance data, the incidence of HF in persons ≥55 years of age was ≈1 000 000 in 2014, with a slightly higher number of new-onset cases observed in women than in men (Table 20-2) and a greater burden seen in blacks than in whites (Chart 20-5).
- Data from the NHLBI-sponsored Chicago Heart Association Detection Project in Industry, ARIC, and CHS cohorts indicate that HF incidence approaches 21 per 1000 population after 65 years of age.<sup>22</sup>

- Data from Kaiser Permanente indicated a 14% increase in the incidence of HF among the elderly (from the 1970s to the 1990s) along with improved HF survival, which resulted in increased HF prevalence, with both trends being more pronounced in males.<sup>23</sup>
- Data from Olmsted County, MN, indicate that the age- and sex-adjusted incidence of HF declined substantially, from 315.8 per 100 000 in 2000 to 219.3 per 100 000 in 2010, with a greater rate reduction for HF with reduced EF (−45.1% [95% CI, −33.0% to −55.0%]) than for HF with preserved EF (−27.9% [95% CI, −12.9% to −40.3%]).<sup>24</sup>
- In the CARDIA study, HF before 50 years of age was more common among blacks than whites. Hypertension, obesity, and systolic dysfunction were important risk factors that may be targets for prevention.<sup>25</sup>
- In MESA, blacks had the highest risk of developing HF, followed by Hispanic, white, and Chinese Americans (4.6, 3.5, 2.4, and 1.0 per 1000 person-years, respectively). This higher risk reflected differences in the prevalence of hypertension, DM, and low SES.<sup>26</sup> Blacks had the highest proportion of incident HF not preceded by clinical MI (75%).<sup>26</sup>
- Data from the 2005 to 2014 community surveillance component of the ARIC study indicate that rates of hospitalizations for HF are increasing over time, apparently driven by rises in HF with preserved EF. Overall events included 50% HF with reduced EF and 39% HF with preserved EF, where the former was more common in black males and white males and the latter was most common in white females. Other events may be attributable to intermediate or recovered EF. Age-adjusted rates of HF hospitalization were highest in blacks (38 per 1000 black males, 31 per 1000 black females).<sup>27</sup>

#### **Lifetime Risk**

- Because most forms of HF tend to present in older age, lifetime risk for HF in the community is high with an aging population. Data from the NHLBI-sponsored Chicago Heart Association Detection Project in Industry, ARIC, and CHS cohorts indicated the following<sup>22</sup>:
  - Overall, at 45 years of age through 95 years of age, lifetime risks for HF were high (20%–45%).
  - Lifetime risks for HF were 30% to 42% in white males, 20% to 29% in black males, 32% to 39% in white females, and 24% to 46% in black females. The lower lifetime risk in black males appears likely to be attributable to competing risks.
  - Lifetime risk for HF was higher with higher BP and BMI at all ages.

- The lifetime risk of HF occurring for people with BMI  $\geq 30 \text{ kg/m}^2$  was approximately double that of those with BMI  $< 25 \text{ kg/m}^2$ .
- The lifetime risk of HF occurring for people with BP  $> 160/90 \text{ mm Hg}$  was 1.6 times that of those with BP  $< 120/90 \text{ mm Hg}$ .

### Risk Factors

- Traditional factors account for a considerable proportion of HF risk. Data from Olmsted County, MN, indicate that CHD, hypertension, DM, obesity, and smoking are responsible for 52% of incident HF cases in the population, with ORs or RRs and their PARs as follows<sup>28</sup>: CHD OR, 3.1 and overall PAR, 20% (highest in males, 23% versus 16% in females); cigarette smoking RR, 1.4 and PAR, 14%; hypertension RR, 1.4 and PAR, 20% (highest in females, 28% versus 13% in males); obesity RR, 2.0 and PAR, 12%; and DM OR, 2.7 and PAR, 12%.
- Traditional risk factors for HF are common in the US adult population. Data from NHANES indicate that at least 1 HF risk factor is present in up to one-third of the US adult population.<sup>29</sup>
- Racial disparities in risks for HF persist, as shown in the Health ABC Study, a US cohort of 2934 adults 70 to 79 years of age followed up for 7 years.<sup>30</sup> Among blacks, a greater proportion of HF risk (68% versus 49% among whites) was attributable to modifiable risk factors, including elevated SBP, elevated fasting glucose level, CHD, LVH, and smoking. LVH was 3-fold more prevalent in blacks than in whites. CHD (PAR, 23.9% for white participants, 29.5% for black participants) and uncontrolled BP (PAR, 21.3% for white participants, 30.1% for black participants) had the highest PARs in both races.<sup>30</sup> Hispanics carry a predominance of HF risk factors and healthcare disparities, which suggests a relatively elevated HF risk in this population as well.<sup>31</sup>
- Risk factors appear to differ by HF subtype. As a group, patients with HF with preserved EF are older, are more likely to be female, and have greater prevalence of hypertension, obesity, and anemia than those with HF with reduced EF.<sup>32</sup>
- Dietary and lifestyle factors also impact HF risk. Among 20900 male physicians in the PHS, the lifetime risk of HF was higher in males with hypertension, whereas healthy lifestyle factors (normal weight, not smoking, regular PA, moderate alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables) were related to lower risk of HF.<sup>33</sup>
- In the ARIC study, greater adherence to the AHA's Life's Simple 7 guidelines (better profiles in smoking, BMI, PA, diet, cholesterol, BP, and glucose) was

associated with a lower lifetime risk of HF, as well as more optimal echocardiographic parameters of cardiac structure and function.<sup>34</sup>

- Multiple nontraditional risk factors for HF have been identified.
  - In the FHS, circulating BNP, urinary ACR, elevated serum  $\gamma$ -glutamyl transferase, and higher levels of hematocrit were identified as risk factors for incident HF.<sup>35–37</sup> Circulating concentrations of resistin were also associated with incident HF independent of prevalent coronary disease, obesity, insulin resistance, and inflammation.<sup>38</sup> Circulating adiponectin concentrations were also related to incident HF, with a J-shaped relationship.<sup>39</sup> Inflammatory markers (IL-6 and tumor necrosis factor- $\alpha$ ), serum albumin levels, and cigarette smoking exposure additionally were associated with increased HF risk.<sup>40–42</sup>
  - In the CHS, baseline cardiac high-sensitivity troponin and changes in high-sensitivity troponin levels were significantly associated with incident HF.<sup>43</sup> Conversely, circulating individual and total omega-3 fatty acid concentrations were associated with lower incidence of HF.<sup>44</sup>
  - In the ARIC study, white blood cell count, CRP, albuminuria, HbA<sub>1c</sub> among individuals without DM, cardiac troponin, PVCs, and socioeconomic position over the life course were all identified as risk factors for HF.<sup>45–50</sup>
  - In MESA, plasma N-terminal pro-BNP provided incremental prognostic information beyond the traditional risk factors and the MRI-determined LV mass index for incident symptomatic HF.<sup>51</sup>
  - In the FHS, measures of major organ system dysfunction (higher serum creatinine, lower ratios of forced expiratory volume in 1 second to forced vital capacity, and lower hemoglobin concentrations) were also associated with an adjusted increased risk of new-onset HF.<sup>52</sup>

### LV Function

- Measures of impaired systolic or diastolic LV function are common precursors to clinical HF.
  - In the FHS, the prevalence of asymptomatic LV systolic dysfunction was 5% and that of diastolic dysfunction was 36%. LV systolic and diastolic dysfunction were associated with increased risk of incident HF.
  - In Olmsted County, MN, diastolic dysfunction (HR, 1.81 [95% CI, 1.01–3.48]) was observed to progress with advancing age and was associated with an increased risk of incident clinical HF during 6 years of subsequent follow-up

after adjustment for age, hypertension, DM, and CAD.<sup>53</sup>

- With respect to variation by race/ethnicity, presence of asymptomatic LV systolic dysfunction in MESA was higher in blacks than in whites, Chinese, and Hispanics (1.7% overall and 2.7% in blacks). After 9 years of follow-up, asymptomatic LV dysfunction was associated with increased risk of overt HF (HR, 8.69 [95% CI, 4.89–15.45]), as well as CVD and all-cause mortality.<sup>6</sup>
- In the Echocardiographic Study of Hispanic/Latinos, almost half (49.7%) of middle-aged or older Hispanics had some form of cardiac dysfunction (systolic, diastolic, or both), although fewer than 1 in 20 Hispanic/Latinos had symptomatic or clinically recognized HF.<sup>54</sup>
- LV function is variably abnormal in the setting of clinically overt HF.
- GWTG-HF data from 2005 to 2010 indicate that of 110621 patients hospitalized with HF, half had a reduced EF (<40%), 14% had an EF that was ≥40% and <50%, and 36% had an EF of ≥50%.<sup>32</sup>
- Data collected between 1985 and 2014 from 12 857 person-observations in the FHS showed that the frequency of HF with reduced EF (EF <40%) decreased over time, whereas HF with mid-range EF (40%–<50%) remained stable, and HF with preserved EF (EF ≥50%) increased over time. These findings appeared attributable to trends in risk factors, especially a decrease in prevalent CHD among people with HF.<sup>55</sup>

### **Family History and Genetics**

- HCM and familial DCM are the most common mendelian cardiomyopathies, with autosomal dominant or recessive transmission, in addition to X-linked and mitochondrial inheritance.
- Familial DCM accounts for up to 50% of cases of DCM, with a prevalence of 1 in 2500, but is likely underestimated.<sup>56</sup> Familial DCM often displays an age-dependent penetrance.<sup>57</sup> Up to 40% of cases have an identifiable genetic cause.<sup>56</sup>
- Given the heterogeneous nature of the underlying genetics, manifestation of the disease is highly variable, even in cases for which the causal mutation has been identified.<sup>58</sup> Variants in the β-myosin heavy chain gene (*MYH7*) were some of the earliest to be associated with familial HCM,<sup>59,60</sup> with >30 other genes implicated since, each accounting for <5% of cases, as reviewed elsewhere.<sup>57,61,62</sup> The considerable variability in the penetrance and pathogenicity of specific mutations makes

clinical interpretation of sequence data particularly challenging.

- Missense and truncating variants in the titin gene have been linked to autosomal dominant cardiomyopathy,<sup>63</sup> as well as to DCM, with incomplete penetrance in the general population.<sup>63</sup> Analysis of sequence data in 7855 cardiomyopathy case subjects and >60 000 control subjects revealed the variance in penetrance of putative disease variants, which further highlights the challenges in clinical interpretation of variation in mendelian disease genes.<sup>64</sup>
- Several GWASs have been conducted to identify common variations associated with cardiomyopathy and HF in the general population, albeit with modest results,<sup>57,60</sup> highlighting a small number of putative loci, including *HSPB7*<sup>65–67</sup> and *CACNB4*.<sup>68</sup> Given the heterogeneous multifactorial nature of common HF, identification of causal genetic loci remains a challenge.
- Genetic variation within subjects with HF may determine outcomes, with a locus on chromosome 5q22 associated with mortality in HF patients.<sup>69</sup> A large meta-analysis of >73 000 subjects identified 52 loci associated with myocardial mass.<sup>70</sup> The clinical utility of genetic testing for variants associated with common HF and related phenotypes remains unclear.
- HCM is a monogenic disorder with primarily autosomal dominant inheritance and is caused by one of hundreds of mutations in up to 18 genes that primarily encode components of the sarcomere, with mutations in *MYH7* and cardiac myosin-binding protein C (*MYBPC3*) being the most common, with each having 40 HCM cases attributed to it.<sup>71</sup> A mutation is identifiable in 50% to 75% of cases of familial HCM.
- Clinical genetic testing is recommended for patients with DCM with significant conduction system disease or a family history of SCD, as well as in patients with a strong clinical index of suspicion for HCM. It can be considered in other forms of DCM and restrictive cardiomyopathy and in LV noncompaction.<sup>72</sup>
- Genetic testing is also recommended in family members of patients with DCM, HCM, restrictive cardiomyopathy, and LV noncompaction.<sup>72</sup>

### **Mortality (See Table 20-2)**

- Survival after the onset of HF in older adults has improved, as indicated by data from Kaiser Permanente<sup>23</sup>; however, improvements in HF survival have not been even across all demographics. Among Medicare beneficiaries, the overall 1-year HF mortality rate declined slightly from 1998 to

2008 but remained high at 29.6%, and rates of decline were uneven across states.<sup>73,74</sup> In the NHLBI's ARIC study, the 30-day, 1-year, and 5-year case fatality rates after hospitalization for HF were 10.4%, 22%, and 42.3%, respectively, and blacks had a greater 5-year case fatality rate than whites ( $P<0.05$ ).<sup>75</sup>

- Observed mortality declines have been primarily attributed to evidence-based approaches to treat HF risk factors and the implementation of treatment with ACE inhibitors,  $\beta$ -blockers, coronary revascularization, implantable cardioverter-defibrillators, and cardiac resynchronization therapies.<sup>76</sup> Contemporary evidence from the GWTG-HF registry suggests that  $\approx$ 47% of individuals admitted to the hospital with HF should have had initiation of  $\geq 1$  new medication on discharge;  $\approx$ 24% need to start  $\geq 1$  new medication and  $\approx$ 14% need to start  $\geq 3$  new medications to be in compliance with current guidelines.<sup>77</sup>
- In a large Swedish registry of patients with HF with preserved EF, statins improved 1-year cardiovascular hospitalization, mortality, and cardiovascular mortality.<sup>78</sup> Accordingly, 5-year survival of HF diagnosis after an MI in Olmsted County, MN, improved in 2001 to 2010 versus 1990 to 2000, from 54% to 61%.<sup>79</sup>
- Some data suggest that improvements in survival could be leveling off over time. Data from the Rochester Epidemiology Project in Olmsted County, MN, showed improved survival after HF diagnosis between 1979 and 2000<sup>80</sup>; however, 5-year mortality did not decline from 2000 to 2010 and remained high at  $\approx$ 50% (52.6% overall; 24.4% for 60-year-olds and 54.4% for 80-year-olds). Importantly, mortality was more frequently ascribed to noncardiovascular causes (54.3%), and the risk of noncardiovascular death was greater in HF with preserved EF than in HF with reduced EF.<sup>24</sup>
- Given improvements in HF survival overall, the number of individuals carrying a diagnosis of HF at death has increased. Mortality associated with HF is substantial, such that 1 in 8 deaths has HF mentioned on the death certificate (unpublished NHLBI tabulation).<sup>81</sup>
- In 2017, HF was the underlying cause in 80 480 deaths (36 824 males and 43 656 females; Table 20-2). Table 20-2 shows the numbers of these deaths that were coded for HF as the underlying cause.
- The number of underlying causes of deaths attributable to HF was 42.3% higher in 2017 (80 480) than it was in 2007 (56 565; unpublished NHLBI tabulation using NVSS<sup>81</sup>).

- In 2017, the overall any-mention age-adjusted death rate for HF was 89.7 per 100 000, with variation across racial/ethnic groups: in males, the rates were 111.3 for NH whites, 118.2 for NH blacks, 46.9 for NH Asians or Pacific Islanders, 95.0 for NH American Indians or Alaska Natives, and 69.2 for Hispanics; in females, the respective rates were 80.4 for NH whites, 86.0 for NH blacks, 34.7 for NH Asians or Pacific Islanders, 80.6 for NH American Indians or Alaska Natives, and 49.7 for Hispanics (unpublished NHLBI tabulation using CDC WONDER<sup>82</sup>).

### Healthcare Utilization: Hospital Discharges

#### Ambulatory Care Visits

(See Table 20-2 and Chart 20-6)

- Hospital discharges for HF (including discharged alive, dead, and status unknown) are shown for the United States (1997–2016) by sex in Chart 20-6. Discharges for HF decreased from 2006 to 2016, with principal diagnosis discharges of 1020 000 and 809 000, respectively (Table 20-2).
- In 2016, there were 1932 000 physician office visits with a primary diagnosis of HF (NAMCS,<sup>83</sup> unpublished NHLBI tabulation). In 2016, there were 414 000 ED visits for HF (NHAMCS,<sup>84</sup> NHLBI unpublished tabulation).
- Among 1077 patients with HF in Olmsted County, MN, hospitalizations were common after HF diagnosis, with 83% of patients hospitalized at least once and 43% hospitalized at least 4 times. More than one-half of all hospitalizations were related to noncardiovascular causes.<sup>85</sup>
- Among Medicare beneficiaries, the overall HF hospitalization rate declined substantially from 1998 to 2008 but at a lower rate for black males,<sup>74</sup> and the temporal trend findings were uneven across states.
- In the GWTG-HF Registry, only one-tenth of eligible HF patients received cardiac rehabilitation referral at discharge after hospitalization for HF.<sup>86</sup>
- Among Medicare part D coverage beneficiaries, HF medication adherence (ACE inhibitors/angiotensin receptor blockers,  $\beta$ -blockers, and diuretic agents) after HF hospitalization discharge decreased over 2 to 4 months after discharge, followed by a plateau over the subsequent year for all 3 medication classes.<sup>87</sup>
- Rates of HF rehospitalization or cardiovascular death were greatest for those previously hospitalized for HF.<sup>88</sup>
- Although Hispanic patients hospitalized with HF were significantly younger than NH whites, the prevalence of DM, hypertension, and overweight/obesity was higher among them. In multivariate analysis, a 45% lower in-hospital mortality risk was

observed among Hispanics with HF with preserved EF compared with NH whites but not among those with HF with reduced EF.<sup>89</sup>

- On the basis of data from the community surveillance component of the ARIC study of the NHLBI<sup>90</sup>:
  - The average incidence of hospitalized HF for those  $\geq 55$  years of age was 11.6 per 1000 people per year; incidence of recurrent hospitalized HF was 6.6 per 1000 people per year.
  - Age-adjusted annual hospitalized HF incidence was highest for black males (15.7 per 1000), followed by black females (13.3 per 1000), white males (12.3 per 1000), and white females (9.9 per 1000).
  - Of incident hospitalized HF events, 53% had HF with reduced EF and 47% had preserved EF. Black males had the highest proportion of hospitalized HF with reduced EF (70%); white females had the highest proportion of hospitalized HF with preserved EF (59%).
  - Age-adjusted 28-day and 1-year case fatality after hospitalized HF was 10.4% and 29.5%, respectively, and did not differ by race or sex.
- Data from the Health and Retirement Study from 1998 to 2014 show racial/ethnic differences in hospitalization trajectories over 24 months after HF diagnosis.<sup>91</sup> Compared with NH males, Hispanic males have declines in hospitalization after initial diagnosis but then increases in hospitalizations in later stages of disease. Among females, compared with whites, blacks had significantly more hospitalizations throughout the follow-up period.
- Data from Olmsted County, MN, indicate that among those with HF, hospitalizations were particularly common among males and did not differ by HF with reduced EF versus preserved EF, with 63% of hospitalizations for noncardiovascular causes. Among those with HF, hospitalization rates for cardiovascular causes did not change over time, whereas those for noncardiovascular causes increased from 2000 to 2010.<sup>24</sup>

### Cost

The overall cost of HF continues to rise. See Chapter 26 (Economic Cost of Cardiovascular Disease) for further statistics.

- In 2012, total cost for HF was estimated to be \$30.7 billion (2010\$), of which more than two-thirds was attributable to direct medical costs.<sup>21</sup> Projections suggest that by 2030, the total cost of HF will increase by 127%, to \$69.8 billion, amounting to  $\approx \$244$  for every US adult.<sup>21</sup>
- Implantable cardioverter-defibrillators could be cost-effective in the guideline-recommended groups of individuals with HF with reduced EF; however, the benefit might not be as great in those

with high overall mortality risk (eg, age  $\geq 75$  years, New York Heart Association functional class III, LVEF  $\leq 20\%$ , BNP  $\geq 700$  pg/mL, SBP  $\leq 120$  mm Hg, AF, DM, chronic lung disease, and CKD).<sup>92,93</sup>

- The costs associated with treating HF comorbidities and HF exacerbations in youths are significant, totaling nearly \$1 billion in inpatient costs, and may be rising. The associated cost burden of HF is anticipated to constitute a large portion of total pediatric healthcare costs.<sup>94</sup>

### **Open Heart Transplantation and Mechanical Circulatory Support Device Placement in the United States (See Chart 20-7)**

From September 1987 to December 2012, 40 253 people were waiting for heart transplants, with a median survival of 2.3 years; 26 943 received transplants, with median survival of 9.5 years. Life-years saved were 465 296; life-years saved per patient were 5.0.<sup>95</sup>

- Among other causes, heart transplant patients die of SCD at a rate of 1.3% per year, particularly those with a history of allograft vasculopathy, although other risk factors have been described in a meta-analysis of >47 000 individuals.<sup>96</sup>
- According to a study based on the NIS, the outcomes after admission for HF are similar in patients with a prior history of heart transplant and those without previous transplants.<sup>97</sup>
- In the MedaMACS study, from May 2013 to October 2015, 161 patients with advanced HF were included, and 47% died within 2 years of follow-up. Although survival was similar to that of patients with an LVAD in the overall INTERMACS cohort, in individuals with HF of greater severity, survival was lower in the INTERMACS cohort.<sup>98</sup>
- In the ROADMAP study, among 195 patients with advanced ambulatory non-inotrope-dependent HF, only those with higher severity of HF (defined as INTERMACS profile 4) benefitted from LVAD implantation compared with optimal medical management, despite increased complications. In individuals with INTERMACS profiles 5 through 7, no benefit of LVADs was noted.<sup>99</sup>
- In 2019, INTERMACS reported >25 000 mechanical circulatory support device implantations from June 2006 to December 2017, of which >20 000 were primary left mechanical circulatory support devices, including total artificial hearts (339), pulsatile-flow LVADs (923), and continuous-flow LVADs (19 206), including axial and centrifugal pumps. This includes both isolated LVAD and combined left and right ventricular assist devices. As of 2017, 51% of the LVADs were centrifugal and 49% were axial-flow devices.<sup>100</sup>

- The 1-year LVAD survival rate has now reached 83%, with a median survival of 5 years among patients with isolated continuous-flow LVADs. When an additional RV assist device is needed, the 1-year survival is only 58% and the median survival is limited to 31%.<sup>100</sup>
- The proportion of LVADs implanted as destination therapy increased from 2% in 2008 to 49% in 2017 for continuous-flow LVADs, with an overall decline in those in whom the LVAD was implanted as a bridge to decision or transplantation over this time period (Chart 20-7).<sup>100</sup> However, a substantial difference in indications exists across device type, with 73% of axial-flow pump-type LVADs being used as destination therapy in 2017 versus only 27% of centrifugal-flow LVADs.
- The 1-year survival of individuals with an LVAD implanted as a bridge to transplantation was 88%; for those with a bridge-to-decision implantation, survival was 85%; and for those with an LVAD as destination therapy, survival was 80%.<sup>100</sup>
- From 2006 to April 2017, 450 individuals in INTERMACS underwent a total artificial heart implantation. Among those, 266 underwent transplantation and 162 died on support. The 1-year survival rate was 53%, with most deaths occurring because of multiorgan failure. At 12 months, 52% of the patients had undergone transplantation, 34% had died, and 13% were still alive and with the device.<sup>101</sup>
- According to an NIS study, there is no difference in outcomes after ventricular assist device implantation across geographic areas in the United States, despite differences in cost and length of stay.<sup>102</sup>
- In 2011, in-hospital mortality with LVAD implantation decreased significantly, from 47.2% in 2005 to 12.7%, among Medicare beneficiaries. An inflection point was seen, with a sharp rise in LVAD implantation and decrease in the in-hospital mortality rate in 2008. Average hospital length of stay decreased from the pulsatile LVAD (pre-2008) to the continuous-flow LVAD (2008–2011) eras.<sup>103</sup> The mean cost of LVAD-related hospitalization increased from \$194 380 in 2005 to \$234 808 in 2011.<sup>104</sup>
- In a comparable cost-effectiveness analysis in the French healthcare system, LVAD implants were associated with improved survival at a high cost, exceeding €100 000 per QALY, and were not considered cost-effective.<sup>105</sup>
- In a meta-analysis of 8 studies (7957 patients total) comparing mortality rates in patients treated with heart transplantation versus bridge-to-transplantation LVAD or LVAD as destination therapy, there was no difference in late (>6 months) all-cause mortality between heart transplantation and LVAD

(pooled OR, 0.91 [95% CI, 0.62–1.32] for transplantation versus bridge-to-transplantation LVAD; pooled OR, 1.49 [95% CI, 0.48–4.66] for transplantation versus destination therapy LVAD).<sup>106</sup>

- In a Markov model analysis, LVADs in patients with non-inotrope-dependent HF improved quality of life, at a substantial increase in costs, mostly attributable to frequent readmissions and cost of follow-up care. The gain in quality of life was from 2.67 to 4.41 QALYs. However, the incremental cost-effectiveness ratio was US \$209 400 per QALY gained and US \$597 400 per life-year gained. Moreover, those results were sensitive to readmission rates and outpatient care costs.<sup>107</sup>
- Elevated LVAD index admission costs could be related to procurement costs and length of stay. Hospital readmissions also contribute significantly to overall cost of LVAD therapy: in a retrospective study with continuous-flow LVAD, 44% of patients were readmitted within 30 days of discharge, with a median cost of \$7546. The most common causes of readmission were gastrointestinal bleeding, infection, and stroke, with device malfunction and arrhythmias the costliest causes of readmission. There was no difference in survival between patients who were and were not readmitted, although median follow-up was only 11 months.<sup>108</sup>
- In a study that used the United Network for Organ Sharing registry between 2006 and 2015 and addressed insurance status, among those with bridge-to-transplantation LVADs, Medicaid insurance was associated with worse survival of patients on the heart transplant waiting list compared with patients with private insurance, although access to transplantation was not different.<sup>109</sup>
- Among Medicare beneficiaries undergoing LVAD implantation, the outcomes vary widely according to the presence of ESRD. During a median follow-up of 762 days, 82% of individuals with ESRD died, whereas only 36% of those without ESRD died. Even after adjustment for confounding, the OR for mortality was 36.3 for the presence of ESRD.

#### **LVAD and Open-Heart Transplantation Disparities**

- The 2019 INTERMACS report did not specifically address the influence of sex or race/ethnicity on mortality after LVAD procedures, although a higher mortality was seen in females in prior reports (HR, 1.16;  $P=0.005$ ).<sup>110</sup>
- In a study that included 111 patients with ventricular assist devices, SES was not associated with adverse prognosis or complications after implantation.<sup>111</sup>
- In the United Network for Organ Sharing database of 18085 patients who had open heart

transplantation performed at 102 centers, blacks had a higher adjusted 1-year mortality, particularly at poor-performing centers (observed-to-expected mortality ratio >1.2; OR, 1.37 [95% CI, 1.12–1.69];  $P=0.002$ ).<sup>112</sup> Compared with whites and Hispanics, a higher proportion of blacks were treated at centers with higher than expected mortality, which persisted after adjustment for insurance type and education level.

### Global Burden of HF

- HF prevalence was lowest in west sub-Saharan Africa (0.74 [95% CI, 0.58–0.98] per 1000 in males and 0.57 [95% CI, 0.44–0.76] per 1000 in females).<sup>113</sup> HF made the largest contribution to age-standardized years lived with disability among males in high-income North America, Oceania, Eastern and Western Europe, southern Latin America, and Central Asia.<sup>113</sup>
- HF risk factors vary substantially across world regions, with hypertension being highly associated with HF in all regions but most commonly in Latin America, the Caribbean, Eastern Europe, and sub-Saharan Africa, and with a minimal association of IHD with HF in sub-Saharan Africa.<sup>114</sup> IHD prevalence among HF patients is highest in Europe and North America but rare in sub-Saharan Africa, whereas hypertension prevalence among HF patients was highest in Eastern Europe and sub-Saharan Africa; valvular and rheumatic HD

prevalence among HF patients was highest in East Asia and Asia-Pacific countries.<sup>114</sup> Follow-up from a multiethnic cohort composed of individuals from low- to middle-income countries in Africa, Asia, the Middle East, and South America will provide additional data regarding the global burden of HF.<sup>115</sup> HF is common throughout sub-Saharan Africa. According to a meta-analysis, the most common pathogenesis is hypertensive HD in 39.2% (95% CI, 32.6%–45.9%), followed by cardiomyopathies in 21.4% (95% CI, 16.0%–27.2%) and rheumatic HD in 14.1% (95% CI, 10.0%–18.8%), whereas IHD was reported in only 7.2% of cases (95% CI, 4.1%–11.0%). However, there was important variability in the prevalence according to the region of the continent.<sup>116</sup>

- The prevalence estimates for HF across Asia range from 1.26% to 6.7%. Rheumatic HD is a major contributor to HF in certain parts of South Asia, such as India, but recently, trends toward an ischemic cause for HF have been observed in Asia, such as in China and Japan.<sup>117</sup>
- Ischemic HF prevalence in 2010 was highest (>5 per 1000) in high-income North America, Oceania, and Eastern Europe. In particular, HF prevalence in 2010 was highest in Oceania (4.53 [95% CI, 3.19–6.29] per 1000 in females; 5.22 [95% CI, 3.84–7.08] per 1000 in males), followed by high-income North America and North Africa/Middle East.<sup>113</sup>

**Table 20-1. Global Prevalence and Mortality of Cardiomyopathy and Myocarditis, 2017**

	Both Sexes Combined		Males		Females	
	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)
Total number (millions)	0.4 (0.3 to 0.4)	5.4 (4.7 to 6.3)	0.2 (0.2 to 0.2)	2.7 (2.4 to 3.2)	0.2 (0.1 to 0.2)	2.7 (2.3 to 3.1)
Percent change total number, 1990 to 2017	54.5 (46.4 to 64.1)	57.5 (52.5 to 63.0)	74.9 (62.3 to 92.2)	65.9 (60.0 to 73.1)	33.2 (26.5 to 43.4)	49.8 (44.7 to 55.3)
Percent change total number, 2007 to 2017	8.1 (3.8 to 18.2)	24.5 (22.5 to 26.5)	6.7 (0.7 to 23.9)	26.1 (23.5 to 28.8)	10.0 (7.0 to 14.3)	22.8 (20.3 to 25.3)
Rate per 100 000	4.8 (4.5 to 5.0)	68.7 (59.6 to 79.1)	6.0 (5.2 to 6.4)	74.0 (64.0 to 85.4)	3.7 (3.5 to 3.9)	63.4 (54.8 to 72.9)
Percent change rate, 2007 to 2017	-16.6 (-19.8 to -9.4)	-5.8 (-7.1 to -4.5)	-15.9 (-20.3 to -2.8)	-4.2 (-6.1 to -2.5)	-17.1 (-19.3 to -14.0)	-6.9 (-8.6 to -5.2)
Percent change rate, 1990 to 2017	-25.8 (-29.4 to -20.6)	-21.7 (-24.1 to -19.2)	-16.0 (-21.8 to 0.6)	-17.2 (-19.9 to -14.0)	-36.1 (-38.9 to -31.9)	-25.0 (-27.5 to -22.5)

UI indicates uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>19</sup> Printed with permission. Copyright © 2018, University of Washington.

**Table 20-2.** HF in the United States

Population Group	Prevalence, 2013–2016, Age $\geq 20$ y	Incidence, 2014, Age $\geq 55$ y	Mortality, 2017, All Ages*	Hospital Discharges, 2016, All Ages	Cost, 2012†
Both sexes	6 200 000 (2.2%)	1 000 000	80 480	809 000	\$30.7 billion
Males	3 000 000 (2.4%)	495 000	36 824 (45.8%)‡	415 000	...
Females	3 200 000 (2.1%)	505 000	43 656 (54.2%)‡	394 000	...
NH white males	2.2%	430 000§	30 076	...	...
NH white females	1.9%	425 000§	36 004	...	...
NH black males	3.5%	65 000§	4 068	...	...
NH black females	3.9%	80 000§	4 683	...	...
Hispanic males	2.5%	...	1 820	...	...
Hispanic females	2.1%	...	1 960	...	...
NH Asian males	1.7%	...	633	...	...
NH Asian females	0.7%	...	752	...	...
NH American Indian or Alaska Native	...	...	339	...	...

HF includes people who answered “yes” to the question of ever having congestive heart failure. Ellipses (...) indicates data not available; HF, heart failure; and NH, non-Hispanic.

\*Mortality data for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

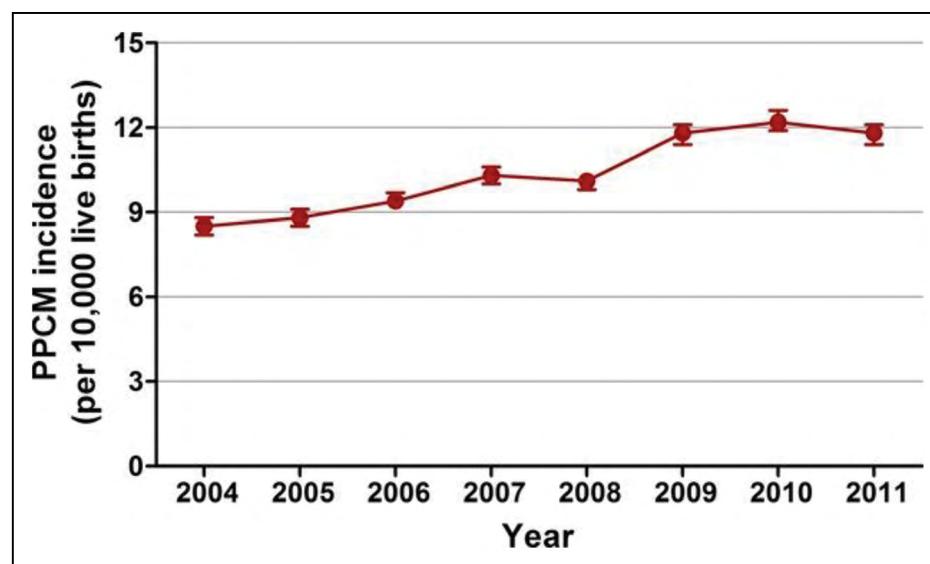
†Cost data are from Heidenreich et al.<sup>21</sup>

‡These percentages represent the portion of total mortality attributable to HF that is for males vs females.

§Estimates for whites include other nonblack races.

||Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

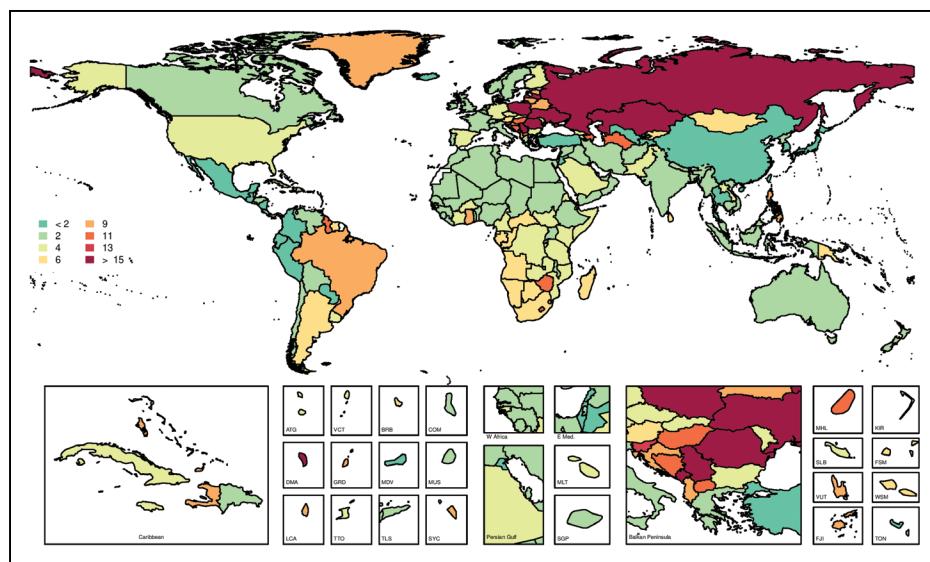
Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey 2013 to 2016.<sup>20</sup> Percentages are age adjusted for Americans  $\geq 20$  years of age. Age-specific percentages are extrapolated to the 2016 US population estimates. These data are based on self-reports. Incidence: Unpublished NHLBI tabulation using Atherosclerosis Risk in Communities study Community Surveillance, 2005 to 2014.<sup>118</sup> Mortality: Unpublished NHLBI tabulation using National Vital Statistics System, 2017.<sup>81</sup> Mortality for NH Asians includes Pacific Islanders. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016 (data include those inpatients discharged alive, dead, or status unknown).<sup>1</sup>

**Chart 20-1.** Temporal trends in PPCM incidence rate per 10 000 live births, United States, 2004 to 2011.

PPCM incidence rate per 10 000 live births per calendar year was calculated with the numerator representing the number of women 15 to 54 years of age with PPCM in that calendar year and the denominator representing the number of live births in women 15 to 54 years of age for the same calendar year.  $P_{trend} < 0.001$ . Error bars represent 95% CI.

PPCM indicates peripartum cardiomyopathy.

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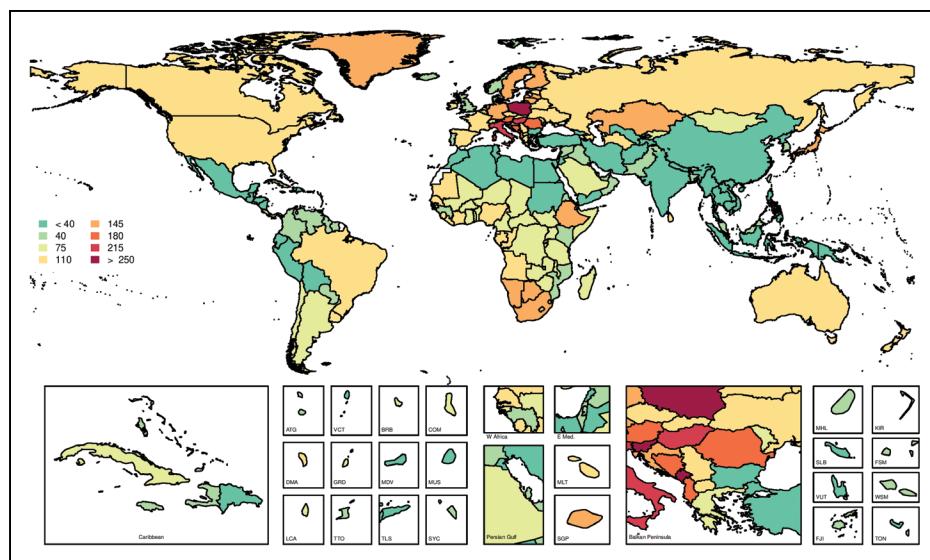


**Chart 20-2. Age-standardized global mortality rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2017.**

The highest age-standardized mortality rates attributable to cardiomyopathy and myocarditis are in Eastern Europe.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>19</sup> Printed with permission. Copyright © 2018, University of Washington.

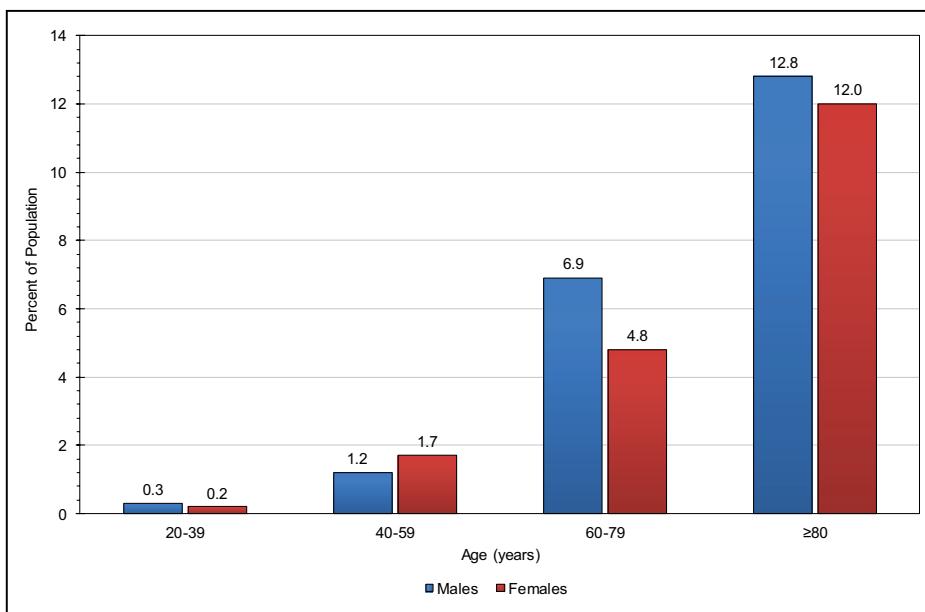


**Chart 20-3. Age-standardized global prevalence rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2017.**

Age-standardized prevalence of cardiomyopathy and myocarditis is highest in Central Europe.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

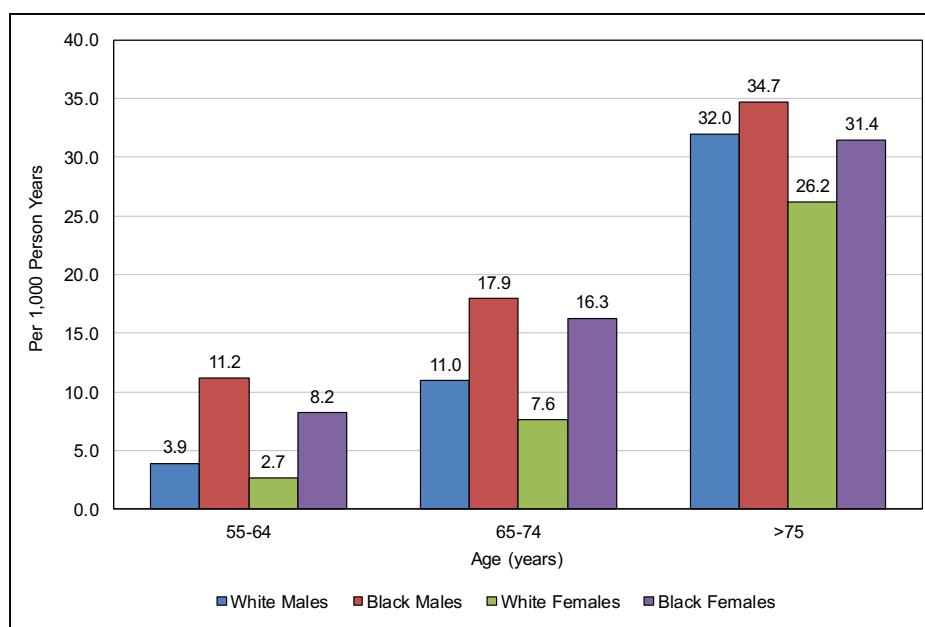
Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>19</sup> Printed with permission. Copyright © 2018, University of Washington.



**Chart 20-4. Prevalence of heart failure among US adults  $\geq 20$  years of age, by sex and age (NHANES, 2013–2016).**

NHANES indicates National Health and Nutrition Examination Survey.

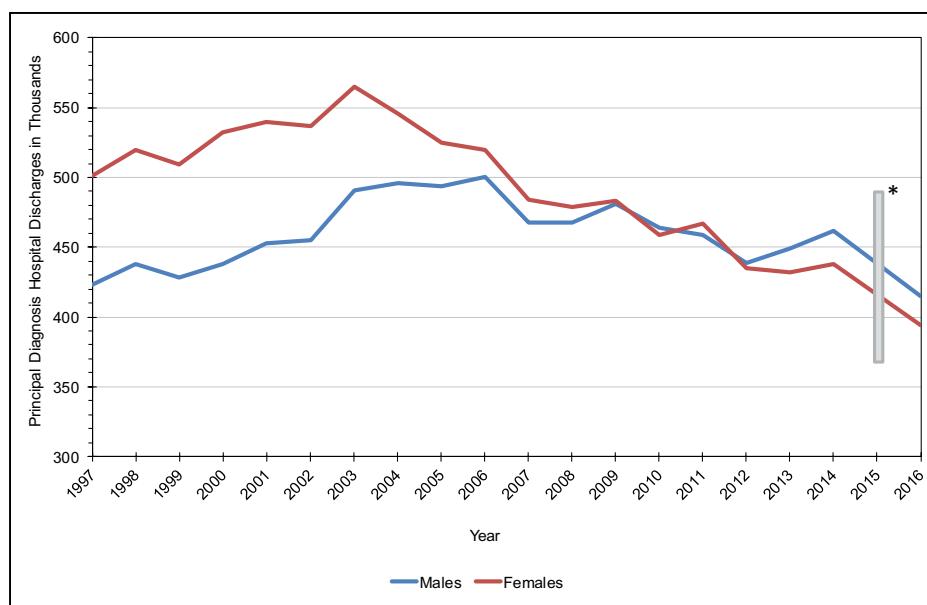
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES, 2013 to 2016.<sup>20</sup>



**Chart 20-5. First acute decompensated heart failure annual event rates per 1000 from ARIC Community Surveillance by sex and race, United States, 2005 to 2014.**

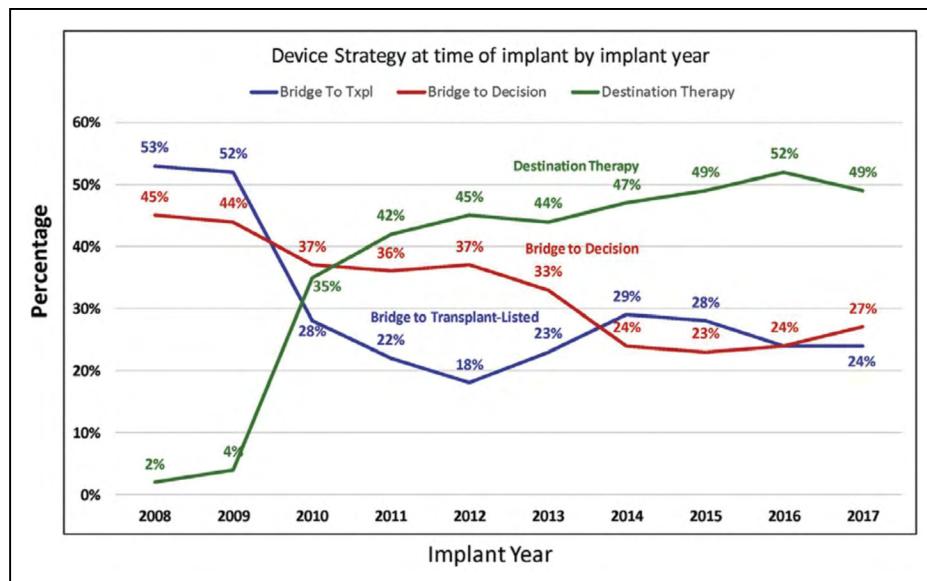
ARIC indicates Atherosclerosis Risk in Communities.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using ARIC Community Surveillance, 2005 to 2014.<sup>118</sup>

**Chart 20-6. Hospital discharges for heart failure by sex, United States, 1997 to 2016.**

Hospital discharges include people discharged alive, dead, and status unknown.

\*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 1997 to 2016.<sup>1</sup>**Chart 20-7. Device strategy at the time of implantation by year, United States, 2008 to 2017.**

Implantations are continuous-flow left ventricular assist devices, April 2008 to December 2017. N=18359.

Txpl indicates transplant.

Source: Reprinted from Kormos et al<sup>100</sup> with permission from The Society of Thoracic Surgeons. Copyright © 2019, The Society of Thoracic Surgeons. Published by Elsevier Inc. on behalf of International Society for Heart and Lung Transplantation.

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## 21. VALVULAR DISEASES

**See Tables 21-1 and 21-2 and Charts 21-1 through 21-6**

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Mortality and any-mention mortality in this section are for 2017 based on unpublished NHLBI tabulations using the NVSS and CDC WONDER.<sup>1,2</sup> “Mortality” is the number of deaths in 2017 for the given underlying cause based on *ICD-10*. Prevalence data are for 2016 and 2017. Hospital discharge data are from HCUP<sup>3</sup> (2016); data included are for inpatients discharged alive, dead, or status unknown. Hospital discharge data for 2016 are based on *ICD-10* codes.

### Abbreviations Used in Chapter 21

ACC	American College of Cardiology
AF	atrial fibrillation
AGES	Age, Gene/Environment Susceptibility
AHA	American Heart Association
APAC	Asia-Pacific
CABG	coronary artery bypass graft
CALA	Caribbean and Latin America
CANHEART	Cardiovascular Health in Ambulatory Care Research Team
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CER	cost-effectiveness ratio
CI	confidence interval
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation
DALY	disability-adjusted life-year
DCM	dilated cardiomyopathy
DM	diabetes mellitus
EF	ejection fraction
EVEREST	Endovascular Valve Edge-to-Edge Repair
EVEREST II HRS	Endovascular Valve Edge-to-Edge Repair High-Risk Study
FHS	Framingham Heart Study
GBD	Global Burden of Disease
GRS	genetic risk score
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
ICD	<i>International Classification of Diseases</i>
ICD-9	<i>International Classification of Diseases, 9th Revision</i>
ICD-10	<i>International Classification of Diseases, 10th Revision</i>
ICE-PCS	International Collaboration on Endocarditis—Prospective Cohort Study

(Continued)

### Abbreviations Used in Chapter 21 Continued

ICE-PLUS	International Collaboration on Endocarditis—PLUS
IE	infective endocarditis
IHD	ischemic heart disease
IQR	interquartile range
iSAVR	isolated surgical aortic valve replacement
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
LV	left ventricular
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MITRA-FR	Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation
MR	mitral regurgitation
NH	non-Hispanic
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
NYHA	New York Heart Association
OR	odds ratio
PAR	population attributable risk
PARTNER	Placement of Aortic Transcatheter Valve
QALY	quality-adjusted life-year
REMEDY	Global Rheumatic Heart Disease Registry
RR	relative risk
RV	right ventricular
SAVR	surgical aortic valve replacement
SD	standard deviation
SNP	single-nucleotide polymorphism
STS	Society of Thoracic Surgeons
SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation
SVT	supraventricular tachycardia
TA	transapical
TAVR	transcatheter aortic valve replacement
TIA	transient ischemic attack
TOF	tetralogy of Fallot
TV	transvascular
TVT	Transcatheter Valve Therapy
VT	ventricular tachycardia

### Valvular Heart Disease *ICD-9 424; ICD-10 I34 to I38.*

2017: Mortality—24811. Any-mention mortality—52939. 2016: Hospital discharges—120 000.

#### Prevalence

- Previously undiagnosed, predominantly mild valvular HD was found in 51% of 2500 individuals ≥65 years of age from a primary care population screened using transthoracic echocardiography.

The prevalence of undiagnosed moderate or severe valvular HD was 6.4%.<sup>4</sup>

### Incidence

- In a recent report using a Swedish nationwide register to identify all patients with a first diagnosis of valvular HD at Swedish hospitals between 2003 and 2010 (N=10 164 211), the incidence of valvular HD was 63.9 per 100 000 person-years, with aortic stenosis (47.2%), MR (24.2%), and aortic regurgitation (18.0%) contributing most of the valvular diagnoses. The majority of valvulopathies were diagnosed in the elderly (68.9% in subjects ≥65 years of age). Incidences of aortic regurgitation, aortic stenosis, and MR were higher in males, who were also more frequently diagnosed at an earlier age. Mitral stenosis incidence was higher in females.<sup>5</sup>

## Aortic Valve Disorders

### (See Chart 21-1)

### **ICD-9 424.1; ICD-10 I35.**

2017: Mortality—16 827. Any-mention mortality 35 434.

2016: Hospital discharges—91 000.

### Prevalence

- Prevalence of aortic stenosis by echocardiography was 4.3% among individuals ≥70 years of age in the Icelandic AGES-Reykjavik cohort.<sup>6</sup>
- In younger age groups, the most prevalent cause of aortic stenosis is bicuspid aortic valve, the most common form of congenital HD. In an Italian study of 817 primary school students, the prevalence of bicuspid aortic valve was 0.5% (95% CI, 0.13%–1.2%).<sup>7</sup>

### Incidence

- Nationally representative data from Sweden demonstrate an age-adjusted incidence of aortic stenosis from 15.0 to 11.4 per 100 000 males and from 9.8 to 7.1 per 100 000 females, between the years 1989 to 1991 and 2007 to 2009.<sup>8</sup>
- In the Norwegian Tromsø study, the incidence of new aortic stenosis was 5 per 1000 per year, with the initial mean age of participants being 60 years.<sup>9</sup>
- In the Canadian CANHEART aortic stenosis study, absolute incidence of severe aortic stenosis among individuals >65 years of age was 144 per 100 000 person-years (169 and 127 per 100 000 person-years in males and females, respectively).<sup>10</sup>

### Lifetime Risk and Cumulative Incidence

- The number of elderly patients with calcific aortic stenosis is projected to more than double by 2050 in both the United States and Europe based on a simulation model in 7 decision analysis studies.

In the Icelandic AGES-Reykjavik study alone, projections suggest a doubling in prevalence among those with severe aortic stenosis who are ≥70 years of age by 2040 and a tripling by 2060.<sup>6</sup>

### Risk Factors

- In the Canadian CANHEART study, among 1.12 million individuals >65 years of age followed up for a median of 13 years, 20995 subjects developed severe aortic stenosis. Hypertension (adjusted HR, 1.71 [95% CI, 1.66–1.76]), DM (HR, 1.49 [95% CI, 1.44–1.54]), and dyslipidemia (HR, 1.17 [95% CI, 1.14–1.21]) were the strongest predictors of development of severe aortic stenosis (all  $P<0.001$ ).<sup>10</sup>
- In a retrospective analysis of predictors of cardiac outcomes in 227 ambulatory adults with bicuspid aortic valve, independent predictors of the composite end point (need for surgery, death, aortic dissection, endocarditis, HF, arrhythmias, or IHD) were baseline moderate to severe aortic valve dysfunction (HR, 3.19 [95% CI, 1.35–7.54];  $P<0.01$ ) and aortic valve leaflet calcification (HR, 4.72 [95% CI, 1.91–11.64];  $P<0.005$ ).<sup>11</sup>

### Genetics and Family History

- A GWAS in 6942 individuals identified an SNP located in an intron of the Lp(a) gene that was significantly associated with the presence of aortic calcification (OR per allele, 2.05), circulating Lp(a) levels, and the development of aortic stenosis.<sup>12</sup>
- Multiple SNPs that encode for LDL-C have been combined to form a GRS that has been associated with prevalent aortic valve calcification (OR, 1.38 [95% CI, 1.09–1.74] per GRS increment) and incident aortic valve stenosis (HR, 2.78 [95% CI, 1.22–6.37] per GRS increment) by use of a mendelian randomization design.<sup>13</sup>
- The heritability of bicuspid aortic valve has been estimated at 89% ( $0.89\pm0.06$ ;  $P<0.001$ ), which suggests that most cases are familial.<sup>14</sup> Bicuspid aortic valve has been linked to mutations of NOTCH1, GATA5, and more recently GATA4.<sup>15–17</sup>
- GWASs and transcriptome studies of aortic valve stenosis have identified several loci, including *LPA*, *PALMD*, and *TEX41*.<sup>12,18,19</sup>
- In a nationwide Swedish study comprising 6 117 263 siblings (13 442 with aortic stenosis), having at least 1 sibling with aortic stenosis was associated with an HR of 3.41 (95% CI, 2.23–5.21) for being diagnosed with aortic stenosis. These findings indicate an overall familial aggregation of this disease beyond bicuspid aortic valve alone.<sup>20</sup>

### Awareness, Treatment, and Control

- After the US Food and Drug Administration approved TAVR for patients with severe aortic

stenosis at high surgical risk in 2011, implantation numbers have increased steeply. From 2011 through 2014, the STS/ACC TVT Registry recorded 26414 TAVR procedures performed at 348 centers in 48 US states.<sup>21</sup> Sixty-eight percent of patients were  $\geq 80$  years of age, median STS risk was 6.7%, and 95% of patients were deemed to be at extreme or high risk. The number of patients receiving commercially approved devices from 2012 through 2015 increased to 54 782 in a recent report from the same registry.<sup>22</sup>

- Despite the increase in TAVR procedures, the percentage of black patients undergoing TAVR was 3.8% compared with 93% among Caucasians in the STS/ACC TVT Registry.<sup>21,23</sup>
- The 54 782 patients with TAVR who entered the STS/ACC TVT Registry between 2012 and 2015 demonstrated decreases in expected risk of 30-day operative mortality (STS Predicted Risk of Mortality score) from 7% to 6% and in TVT Registry–predicted risk of mortality from 4% to 3% (both  $P<0.0001$ ) from 2012 to 2015. Observed in-hospital mortality decreased from 5.7% to 2.9%, and 1-year mortality decreased from 25.8% to 21.6%. However, 30-day postprocedure pacemaker insertion increased from 8.8% in 2013 to 12.0% in 2015.<sup>22</sup>
- In Germany, >15 000 TAVR procedures were performed in 2016, a number 3 times higher than in 2011 based on data from the German Institute for Quality Assurance and Transparency in Healthcare. Over the same period (2011 to 2016), the number of SAVR procedures remained relatively stable at  $\approx 10 000$  per year, a lower number than for TAVR (Chart 21-1). In the same European registry, mortality decreased continuously, with overall in-hospital mortality being similar for TAVR and SAVR (2.6% versus 2.9%,  $P=0.19$ , respectively) in 2016 despite the higher risk profile in TAVR patients (Chart 21-1).
- On the basis of a retrospective study of 8210 patients using the NIS (2012 to 2014), females with severe aortic stenosis undergoing TAVR experienced similar mortality (4.7% versus 3.9%,  $P=0.15$ ) as males; however, females had higher rates of stroke (3% versus 2%,  $P=0.04$ ), hemorrhage requiring transfusion (28% versus 20%,  $P<0.0001$ ), and pericardial complications (1.3% versus 0.5%,  $P=0.0009$ ).<sup>24</sup>
- Two randomized controlled trials (PARTNER 1A and US CoreValve High Risk) using balloon-expandable and self-expanding devices, respectively, have shown that TAVR is able to compete with SAVR in terms of mortality in high-risk patients at 1 and 5 years.<sup>25,26</sup>
- In a cohort of 1746 patients with severe aortic stenosis at intermediate surgical risk in the SURTAVI

trial, the estimated incidence of the primary end point (death attributable to any cause or debilitating stroke) was 12.6% in the TAVR group (in whom a balloon-expandable device was used) and 14.0% in the SAVR group (95% credible interval [bayesian analysis] for difference, -5.2 to 2.3%; posterior probability of noninferiority,  $>0.999$ ) at 24 months. In the PARTNER 2 trial using a self-expanding device, the Kaplan-Meier event rates of the same end point were 19.3% in the TAVR group and 21.1% in the SAVR group (HR in the TAVR group, 0.89 [95% CI, 0.73–1.09];  $P=0.25$ ) at 2-year follow-up. These findings demonstrate that TAVR is a noninferior alternative to SAVR in patients with severe aortic stenosis at intermediate surgical risk.<sup>27,28</sup>

- In 1000 patients with severe aortic stenosis at low surgical risk randomized in the PARTNER 3 trial<sup>29</sup> to either balloon-expandable TAVR or SAVR, the Kaplan-Meier estimate of the rate of the primary composite end point (death, stroke, or rehospitalization) was significantly lower in the TAVR group than in the SAVR group (8.5% versus 15.1%; absolute difference, -6.6 percentage points [95% CI, -10.8 to -2.5];  $P<0.001$  for noninferiority; HR, 0.54 [95% CI, 0.37–0.79];  $P=0.001$  for superiority). Similar results were obtained in the Evolut Low Risk trial<sup>30</sup> using a self-expanding valve in low-risk patients with severe aortic stenosis. Among the 1403 patients randomized to either TAVR or SAVR, the 24-month incidence of composite death or disabling stroke was 5.3% in the TAVR group and 6.7% in the SAVR group (difference, -1.4 percentage points [95% Bayesian credible interval for difference, -4.9 to 2.1]; posterior probability of noninferiority  $>0.999$ ).

### Mortality

- On the basis of ICD-10 (with data coded from 1999 to 2009), there were 146 304 deaths over 10 years in the aortic valve disease category in the United States. Of these, 82.7% were attributed to aortic stenosis, 4.0% to aortic insufficiency, and 0.6% to aortic stenosis with insufficiency, whereas 11.9% were unspecified or coded as attributed to other aortic valve disease and 0.7% to congenital aortic valve disease (assumed to be predominantly bicuspid aortic valve). The age- and sex-adjusted mortality rate increased over time by 1.56% (95% CI, 1.52%–1.61%;  $P<0.001$ ) per year for nonrheumatic aortic valve disease.<sup>31</sup>
- In the community, morbidity related to bicuspid aortic valve is higher in males than in females, with a total combined risk of aortic regurgitation, surgery, and IE of  $52\pm 4\%$  versus  $35\pm 6\%$  in females ( $P=0.01$ ).<sup>32</sup> Nevertheless, females have a

significantly higher RR of death in tertiary and surgical referral cohorts, with an age-adjusted relative death risk of 1.63 (95% CI, 1.40–1.89) for females versus 1.34 (95% CI, 1.22–1.47) for males ( $P=0.026$ ).<sup>32</sup> The risk of death is independently associated with aortic regurgitation ( $P\leq0.04$ ).

### Complications

- In a cohort of 416 community-based participants from Olmsted County, MN, with bicuspid aortic valve followed up for a mean (SD) of 16 (7) years, the incidence of aortic dissection in individuals  $\geq$ 50 years of age at baseline was 17.4 (95% CI, 2.9–53.6) cases per 10 000 patient-years. For patients  $\geq$ 50 years of age with a bicuspid valve and a baseline aortic aneurysm, the incidence of aortic dissection was 44.9 (95% CI, 7.5–138.5) cases per 10 000 patient-years. In the remaining participants without baseline aortic aneurysm, the incidence of aneurysm was 84.9 (95% CI, 63.3–110.9) cases per 10 000 patient-years, for an age-adjusted RR of 86.2 (95% CI, 65.1–114) compared with the general population.<sup>33</sup>

### Cost

- Initial length of stay was an average of 4.4 days shorter for patients at high surgical risk who were treated with TAVR than for those who underwent SAVR. TAVR also reduced the need for rehabilitation services at discharge and was associated with improved 1-month quality of life. TAVR had higher index admission and projected lifetime costs than SAVR (differences of \$11 260 and \$17 849 per patient, respectively). However, TAVR was estimated to provide a lifetime gain of 0.32 QALYs (0.41) with 3% discounting. Lifetime incremental CERs were \$55 090 per QALY gained and \$43 114 per life-year gained. On the basis of sensitivity analyses, a reduction in the initial cost of TAVR by  $\approx$ \$1650 was expected to lead to an incremental CER of  $<$ \$50 000 per QALY gained.<sup>34</sup>
- In a European study of patients at intermediate surgical risk with severe aortic stenosis, TAVR was associated with an increase of 0.42 years and 0.41 QALYs and lifetime cost savings of €439 compared with SAVR.<sup>35</sup>

## Mitral Valve Disorders

### ICD-9 424.0; ICD-10 I34.

2017: Mortality—2719. Any-mention mortality—6274. 2016: Hospital discharges—26 000.

### Prevalence

- A systematic review by de Marchena et al<sup>36</sup> found that in the US population, the prevalence of MR according to the Carpentier functional classification system was as follows:

- Type I (congenital MR [ $<$ 10 per million] and endocarditis [3–7 per million]): <20 per 1 million
- Type II (MR associated with mitral valve prolapse): 15 170.5 per 1 million
- Type IIIa (rheumatic HD, systemic lupus erythematosus, antiphospholipid syndrome, and rare diseases): 10 520 per 1 million
- Type IIIb (ischemic MR, LV dysfunction, DCM): 16 250 per 1 million
- Unclassified: 9530 per 1 million

Primary MR includes Carpentier types I, II, and IIIa, with the most common cause being mitral valve prolapse (type II MR). Secondary MR is associated with ischemic cardiomyopathy, LV dysfunction, or DCM (type IIIb MR).

### Subclinical Disease

- Milder, nondiagnostic forms of mitral valve prolapse, first described in the familial context, are also present in the community and are associated with higher likelihood of mitral valve prolapse in offspring (OR, 2.52 [95% CI, 1.25–5.10];  $P=0.01$ ). Up to 80% of nondiagnostic morphologies can progress to diagnostic mitral valve prolapse.<sup>37–39</sup>

### Genetics and Family History

- Among 3679 generation 3 participants in the FHS (53% female; mean age  $40\pm9$  years) with available parental data, 49 (1%) had mitral valve prolapse. Parental mitral valve prolapse was associated with a higher prevalence of mitral valve prolapse in offspring (10/186 [5.4%]) compared with no parental mitral valve prolapse (39/3493 [1.1%]; adjusted OR, 4.51 [95% CI, 2.13–9.54];  $P<0.0001$ ).<sup>40</sup> A number of genetic variants have been identified for the rare X-linked valvular dystrophy and the most common form of autosomal dominant mitral valve prolapse through pedigree investigations and GWASs. Genes implicated in mitral valve prolapse include *FLNA*, *DCHS1*, *DZIP1*, *TNS1*, and *LMCD1*.<sup>41–44</sup>
- Familial clustering exists across different MR subtypes, including both primary (ie, related to mitral valve prolapse) and nonprimary MR. In a recent study, heritability of MR in the FHS was estimated at 15% (95% CI, 7%–23%), 12% (95% CI, 4%–20%) excluding mitral valve prolapse, and 44% (95% CI, 15%–73%) for moderate or greater MR only (all  $P<0.05$ ).<sup>45</sup> In Sweden, sibling MR was associated with an HR of 3.57 (95% CI, 2.21–5.76;  $P<0.001$ ) for development of MR.

### Awareness, Treatment, and Control (See Charts 21-2 and 21-3)

- The treatment of mitral valve prolapse remains largely surgical and based on valve repair. Nevertheless, percutaneous mitral valve repair techniques are becoming a common treatment

option for high-risk patients not deemed candidates for surgical repair. Data from the STS/ACC TVT Registry on patients commercially treated with the MitraClip percutaneous mitral valve repair device showed the following: of 564 patients (56% male, median age 83 years), 473 (86%) were severely symptomatic. The median STS Predicted Risk of Mortality scores for mitral valve repair and replacement were 7.9% (IQR, 4.7%–12.2%) and 10% (IQR, 6.3%–14.5%), respectively.<sup>46</sup> Most of the patients undergoing transcatheter mitral valve repair (90.8%) had degenerative disease, and the procedure was successful in reducing MR to moderate levels in 93% of cases. In the EVEREST II trial, which included mostly primary MR (73%) and compared MitraClip with surgical mitral valve repair, the respective rates of the components of the primary end point at 12 months were as follows: death, 6% in each group; surgery for mitral valve dysfunction, 20% versus 2%; and grade 3+ or 4+ MR, 21% versus 20%.<sup>47</sup>

- Worldwide, the number of MitraClip procedures has increased progressively since 2008, especially in Western Europe. In the United States, the commercial use of the MitraClip started in 2014, with a steadily growing number of procedures performed (Chart 21-2).
- The role of MitraClip in secondary MR has been investigated in 2 recently published randomized clinical trials with divergent results (Chart 21-3).<sup>48–50</sup> MITRA-FR included 304 patients with HF, severe secondary MR, and LVEF 15% to 40% on optimal medical therapy and cardiac resynchronization therapy as indicated. There was no difference in the combined end point of death or rehospitalization for HF at 12 months (83 of 152 patients or 54.6% versus 78 of 152 or 51.3% for interventional and conservative management, respectively). The COAPT trial included 614 patients with HF and moderate-severe or severe secondary MR who were symptomatic (NYHA functional class II–IV) despite optimal medical therapy and cardiac resynchronization therapy. There was a significant reduction of the primary end point of rehospitalization because of HF at 2 years (35.8% versus 67.9%; HR, 0.53 [95% CI, 0.40–0.70];  $P<0.001$ ). There was also a significant reduction of all-cause mortality at 2 years (29% versus 46.1%; HR, 0.62 [95% CI, 0.46–0.82];  $P<0.001$ ). The divergent results of the 2 trials may be related to differences in sample characteristics, sample size, duration of follow-up and primary end point. Further studies are needed to solve this controversy.
- In patients with severe chronic MR secondary to ischemic cardiomyopathy undergoing CABG surgery, survival rates were not significantly different

after bypass alone compared with bypass combined with mitral valve repair (1-, 5-, and 10-year survival of 88%, 75%, and 47% versus 92%, 74%, and 39%, respectively;  $P=0.6$ ).<sup>51</sup> In patients with moderate secondary MR, the rate of death was 6.7% in the combined-surgery group and 7.3% in the CABG-alone group (HR with mitral valve repair, 0.90 [95% CI, 0.38–2.12];  $P=0.81$ ).<sup>52</sup>

- Despite the poor prognosis associated with severe MR, only a small minority of affected patients meeting criteria for surgical intervention undergo mitral surgery (29% for mitral valve prolapse–related MR and 5% for secondary MR), even in the Olmsted County community with advanced and readily accessible means of diagnosis and treatment.<sup>53</sup>

### Mortality

- Secondary MR (or Carpentier type IIIb) is associated with 47% mortality over 5 years in patients with HF and is a predictor of long-term mortality (HR, 1.61 [95% CI, 1.22–2.12],  $P=0.001$  after adjustment for clinical variables, and HR, 1.38 [95% CI, 1.03–1.84],  $P=0.03$  after adjustment for echocardiographic parameters).<sup>54</sup>

### Complications

- In the Olmsted County, MN, population, characterized by a mixed spectrum of community-dwelling and referred patients, females were diagnosed with mitral valve prolapse more often than males and at a younger age<sup>55</sup>; however, females had fewer complications (flail leaflet occurred in 2% versus 8% in males and severe regurgitation in 10% versus 23%; all  $P<0.001$ ). At 15 years of follow-up, females with no or mild MR had better survival than males (87% versus 77%; adjusted RR, 0.82 [95% CI, 0.76–0.89]). In contrast, in individuals with severe MR, females had worse survival than males (60% versus 68%; adjusted RR, 1.13 [95% CI, 1.01–1.26]). Survival 10 years after surgery was similar in females and males (77% versus 79%;  $P=0.14$ ).<sup>56</sup>

### Cost

- Lifetime costs, life-years, QALYs, and incremental cost per life-year and QALY gained were estimated for patients receiving MitraClip therapy compared with standard of care.<sup>57</sup> The EVEREST II HRS provided data on treatment-specific overall survival, risk of clinical events, quality of life, and resource utilization. The published literature was reviewed to obtain health utility and unit costs (Canadian 2013 dollars). The incremental cost per QALY gained was \$23 433. On the basis of sensitivity analysis, MitraClip therapy had a 92% chance of being cost-effective compared with standard of care at a \$50 000 per QALY willingness-to-pay threshold.

## Pulmonary Valve Disorders

### *ICD-9 424.3; ICD-10 I37.*

2017: Mortality—19. Any-mention mortality—49.

- Pulmonic valve stenosis is a relatively common congenital defect, occurring in ≈10% of children with congenital HD.<sup>58</sup> Among 44 neonates with critical pulmonic stenosis who underwent balloon pulmonary valvuloplasty from 1990 to 2017, 15 (34.1%) needed reintervention. At a median follow-up of 8.2 years (IQR, 3.4–13.1 years), moderate or severe pulmonary regurgitation was seen in 22 children (half of the sample), 3 of whom required pulmonary valve repair/replacement.<sup>59</sup>
- The most common cause of severe pulmonic regurgitation is iatrogenic, caused by surgical valvotomy/valvectomy or balloon pulmonary valvuloplasty performed for RV outflow tract obstruction as part of TOF repair.<sup>60</sup> Percutaneous pulmonic valve implantation of either a Melody or a SAPIEN valve is an effective and relatively safe option in patients with prosthetic pulmonic valve regurgitation, including those with a pulmonary artery conduit with regurgitant prosthetic valve.<sup>60–62</sup> In a study using the NIS database and including 57 percutaneous pulmonic valve implantation procedures performed in 2012, vascular complications occurred in 8 (14%), but serious complications occurred only in 3 patients (1 died, and 2 required surgical intervention).<sup>63</sup> Surgical pulmonary valve replacement is preferred for native pulmonic valve regurgitation (caused by endocarditis, carcinoid, etc) and is associated with <1% periprocedural mortality and excellent long-term outcome, with >60% freedom from reoperation at 10 years.<sup>64</sup>
- In a large multicenter cohort of 977 patients with repaired TOF, those treated with a pulmonary valve replacement had a similar risk of (aborted) death and sustained VT (41 subjects; HR, 0.65 [95% CI, 0.31–1.36];  $P=0.25$ ) and combined HF, nonsustained VT, and sustained SVT (88 subjects; HR, 1.43 [95% CI, 0.83–2.46];  $P=0.19$ ) compared with those without surgical treatment at an average follow-up of 5.3 years.<sup>65</sup>

## Tricuspid Valve Disorders

### *ICD-9 424.2; ICD-10 I36.*

2017: Mortality—71. Any-mention mortality—239.

- The frequency of tricuspid regurgitation and valvular pathology was evaluated in a study of 5223 adults (predominantly males, with a mean age of 67 years) who underwent echocardiography at 3 Veterans Affairs medical centers.<sup>66</sup> Moderate to severe tricuspid regurgitation was present in

819 (16%), but only 8% had primary tricuspid valve pathology. In the same study, moderate or greater tricuspid regurgitation was associated with increased mortality regardless of pulmonary artery systolic pressure (HR, 1.31 [95% CI, 1.16–1.49] for pulmonary artery systolic pressure >40 mm Hg; HR, 1.32 [95% CI, 1.05–1.62] for pulmonary artery systolic pressure ≤40 mm Hg) and LVEF (HR, 1.49 [95% CI, 1.34–1.66] for EF <50%; HR, 1.54 [95% CI, 1.37–1.71] for EF ≥50%).<sup>66</sup>

- Patients with rapid development of significant tricuspid regurgitation have worse survival than patients in whom severe tricuspid regurgitation develops more slowly (log rank  $P=0.001$ ). Fast development of severe tricuspid regurgitation is the most powerful predictor of all-cause mortality (HR per preceding year of development, 0.92 [95% CI, 0.90–0.94];  $P<0.001$ ).<sup>67</sup>
- An analysis of the NIS demonstrated an increase in the number of isolated tricuspid valve surgeries performed over a 10-year period, from 290 in 2004 to 780 in 2013. In-hospital mortality was consistent over this time period at 8.8%.<sup>68</sup>
- In a cohort of 64 consecutive patients (mean age  $76.6\pm10$  years) at excessive surgical risk who underwent compassionate MitraClip treatment of chronic, severe tricuspid regurgitation, tricuspid regurgitation was reduced by at least 1 grade in 91% of the patients at a mean of  $14\pm18$  days. There were no intraprocedural deaths, cardiac tamponade, emergency surgeries, strokes, MIs, or major vascular complications. There was a significant improvement of NYHA class ( $P<0.001$ ) and 6-minute walking distance ( $177.4\pm103.0$  m versus  $193.5\pm115.9$  m;  $P=0.007$ ).<sup>69</sup>

## Rheumatic Fever/Rheumatic HD

### (See Table 21-1 and Charts 21-4 through 21-6)

### *ICD-9 390 to 398; ICD-10 I00 to I09.*

2017: Mortality—3320. Any-mention mortality—6668.

2016: Hospital discharges—26 000.

#### Prevalence

- Rheumatic HD is uncommon in high-income countries such as the United States but remains endemic in some low- and middle-income countries.<sup>70</sup>

#### Subclinical Disease

- The prevalence of subclinical or latent rheumatic HD among children is estimated by echocardiography and can be classified as definite or borderline.<sup>71</sup> The prevalence of combined definite and borderline disease ranges between 10 and 45 per 1000 in recent studies from endemic countries (eg,

Nepal, Brazil, and Uganda) compared with <8 per 1000 in low-risk populations.<sup>72–75</sup>

- The natural history of latent rheumatic HD detected by echocardiography is not clear. Emerging data suggest that up to 20% to 30% of children with definite rheumatic HD may have progression of disease, but 30% to 50% of those with borderline rheumatic HD may return to normal over 2 to 8 years of follow-up.<sup>76–79</sup>
- Few echocardiographic screening studies for rheumatic HD have been conducted in adults, for whom the criteria are not well validated. In a study from Uganda, the prevalence of rheumatic HD in adults >20 years of age was 2.34% (95% CI, 1.49%–3.49%).<sup>80</sup>
- Latent rheumatic HD appears to be half as common among HIV-infected youth compared with the general Uganda population (1.5% [95% CI, 0.88%–2.54%] versus 3% [95% CI, 2.7%–3.24%]), possibly related to improved access to preventive care or nearly universal trimethoprim-sulfamethoxazole prophylaxis among HIV-infected youth.<sup>81</sup>

### Awareness, Treatment, and Control

- The REMEDY study highlighted consistently poor access to recommended therapies among people living with rheumatic HD: only 55% were taking penicillin prophylaxis, and only 3.6% of females of childbearing age were using contraception. Although 70% of those with indications (mechanical valve, AF, or severe mitral stenosis) were appropriately prescribed anticoagulant drugs, only a quarter of these had therapeutic international normalized ratios.<sup>82</sup>
- In Uganda, retention in care over time is poor (56.9% [95% CI, 54.1%–59.7%] seen in clinic in the past 12 months), but among those retained in care, optimal adherence to benzathine penicillin G is high (91.4% [95% CI, 88.7%–93.5%]).<sup>83</sup>

### Mortality

- In the United States in 2017, mortality attributable to rheumatic fever/rheumatic HD was 3320 for all ages (2217 females and 1103 males; Table 21-1).
- Mortality attributable to rheumatic HD varies widely across the United States, with the highest rates clustered in Alaska, Mississippi, Alabama, Kentucky, and Utah, where age-standardized mortality rates were estimated to be 5 to 10 per 100 000 population in 2014.<sup>84</sup>
- In 1950, ≈15 000 Americans (adjusted for changes in ICD codes) died of rheumatic fever/rheumatic HD compared with ≈3300 annually in the present era (Table 21-1). Recent declines in mortality have been slowest in the South compared with other regions.<sup>84</sup>

### Complications

- People living with rheumatic HD experience high rates of morbid complications. In the international REMEDY cohort study, 33% had HF, 22% had AF, 7% had prior stroke, and 4% had prior endocarditis at baseline.<sup>82</sup> After 2 years of follow-up, the incidence of new events was 38 per 1000 patient-years for HF, 8.5 per 1000 patient-years for stroke or TIA, and 3.7 per 1000 patient-years for endocarditis.<sup>85</sup>
- Prognosis after development of complications is also worse for people living with rheumatic HD. In Thailand, patients with rheumatic mitral valve disease who had ischemic stroke had a higher risk of cardiac arrest (OR, 2.1), shock (OR, 2.1), arrhythmias (OR, 1.7), respiratory failure (OR, 2.1), pneumonia (OR, 2.0), and sepsis (OR, 1.4) after controlling for age, sex, and other comorbid chronic diseases.<sup>86</sup>
- The PAR of rheumatic HD for maternal mortality may approach 10% in sub-Saharan Africa.<sup>87</sup>

### Global Burden of Rheumatic HD

(See Charts 21-4 through 21-6)

- In 2015, 33.4 million people were estimated to be living with rheumatic HD around the world, with sub-Saharan Africa and Oceania having the highest concentration of DALYs attributable to rheumatic HD.<sup>70</sup>
- Globally, age-standardized mortality from rheumatic HD was estimated to have declined 47.8% from 1990 to 2015; however, the prevalence of HF attributable to rheumatic HD increased by 88% in the same time period.<sup>70</sup>
- The REMEDY study is a prospective registry of 3343 patients with rheumatic HD from 25 hospitals in 12 African countries, India, and Yemen. The age and sex distribution of the subjects are shown in Chart 21-4. Rheumatic HD was twice as common among females, a finding consistent with prior studies across a variety of populations.<sup>82</sup>
- Mortality attributable to rheumatic HD remains exceptionally high in endemic settings. In a study from Fiji of 2619 people followed up during 2008 to 2012, the age-standardized death rate was 9.9 (95% CI, 9.8–10.0) per 100 000, or more than twice the GBD estimates.<sup>88</sup> Prognosis is exceptionally poor in sub-Saharan Africa, as highlighted by a follow-up study of REMEDY, which had a mortality rate of 116 per 1000 patient-years in the first year and 65 per 1000 patient-years in the second year.<sup>85</sup>
- The GBD 2017 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.<sup>89</sup>

- Age-standardized mortality attributable to rheumatic HD is highest in South Asia, sub-Saharan Africa, and Oceania (Chart 21-5).
- Rheumatic HD prevalence is generally highest in sub-Saharan Africa and Oceania (Chart 21-6).

## Infective Endocarditis (See Table 21-2) **ICD-9 421.0; ICD-10 I33.0.**

2017: Mortality—1464. Any-mention mortality—3303.  
2016: Hospital discharges—12 000.

### **Prevalence and Incidence**

- In 2011, there were 47 134 cases of IE and valve replacement in the United States (Table 21-2).
- Data from the NIS (2000–2011)<sup>90</sup> suggested no change in temporal trends in the incidence of IE before and after publication of the 2007 AHA guideline for antibiotic prophylaxis before dental procedures.<sup>91</sup> These findings from referral centers were corroborated by a community-based review of adults in Olmsted County, MN.<sup>92</sup> In the Olmsted County study, age- and sex-adjusted incidence of IE was 7.4 (95% CI, 5.3–9.4) cases per 100 000 person-years. In addition, these guideline changes do not appear to have altered rates of pediatric endocarditis. Using 2003 to 2010 data from 37 centers in the Pediatric Health Information Systems Database, Pasquali and colleagues<sup>93</sup> did not demonstrate a significant difference in the number of IE hospitalizations after the guidelines were implemented in 2007 (1.6% difference after versus before guideline implementation [95% CI, –6.4% to 10.3%];  $P=0.7$ ).
- A systematic review that included 160 studies and 27 083 patients from 1960 to 2011 demonstrated that in hospital-based studies (142 studies; 23 606 patients), staphylococcal endocarditis has increased over time (coagulase-negative *Staphylococcus* 2% to 10%,  $P<0.001$ ), with recent increases in *S aureus* IE (21% to 30%;  $P<0.05$ ) and enterococcal IE (6.8% to 10.5%;  $P<0.001$ ) over the past decade and a corresponding decrease in streptococcal endocarditis (32% to 17%) over the same time period.<sup>94</sup>

### **Risk Factors**

- The 15-year cohort risk (through 2006) of IE after diagnosis of mitral valve prolapse (between 1989 to 1998) among Olmsted County, MN, residents was  $1.1\pm0.4\%$  (incidence, 86.6 cases per 100 000 person-years [95% CI, 43.3–173.2 cases per 100 000 person-years]); there was a higher age- and sex-adjusted risk of IE in patients with mitral valve prolapse (RR, 8.1 [95% CI, 3.6–18.0])

compared with the general population of Olmsted County ( $P<0.001$ ). No IE cases were identified among patients without previously diagnosed MR. Conversely, there was a higher incidence of IE in patients with mitral valve prolapse and moderate, moderate-severe, or severe MR (289.5 cases per 100 000 person-years [95% CI, 108.7–771.2 cases per 100 000 person-years];  $P=0.02$  compared with trivial, mild, or mild-moderate MR) and in patients with a flail mitral leaflet (715.5 cases per 100 000 person-years [95% CI, 178.9–2861.0 cases per 100 000 person-years];  $P=0.02$  compared with no flail mitral leaflet).<sup>95</sup>

- Admissions for endocarditis related to injection drug use have risen in recent years in parallel with the opioid drug crisis. The prevalence of documented intravenous drug use among patients admitted for endocarditis in the NIS rose from 4.3% in 2008 to 10% in 2014. This trend was accentuated among the young (<30 years of age) and among whites (compared with blacks and other races).<sup>96</sup>
- Cardiac device IE appears to be present in 6.4% (95% CI, 5.5%–7.4%) of patients with definite IE, according to data from ICE-PCS (2000–2006). Nearly half (45.8% [95% CI, 38.3%–53.4%]) of such cases were related to healthcare-associated infection. In-hospital and 1-year mortality rates for these patients were 14.7% (26 of 177 [95% CI, 9.8%–20.8%]) and 23.2% (41 of 177 [95% CI, 17.2%–30.1%]), respectively. Although not based on randomized data, compared with individuals without initial hospitalization device removal, there appeared to be a 1-year survival benefit in individuals undergoing device explantation during the index hospitalization (HR, 0.42 [95% CI, 0.22–0.82]).<sup>97</sup>
- Prosthetic valve IE continues to be associated with high in-hospital and 1-year mortality, although early surgery is associated with improved outcomes compared with medical therapy alone (1-year mortality 22% versus 27%; HR, 0.68 [95% CI, 0.53–0.87]), even in propensity-adjusted analyses (HR, 0.57 [95% CI, 0.49–0.67]).<sup>98</sup>
- Antibiotic prophylaxis is currently not recommended for bicuspid aortic valve and mitral valve prolapse.<sup>91</sup> However, in a Spanish registry of 3208 consecutive patients with IE, subjects with these conditions had a higher incidence of viridans group streptococci IE than did a high-risk group with an antibiotic prophylaxis indication and patients in a low- to moderate-risk group without an antibiotic prophylaxis indication (35.2% and 39.3% versus 12.1% and 15.0%, respectively; all  $P<0.01$ ). Subjects with bicuspid aortic valve and mitral valve prolapse had more intracardiac complications than

did those at low or moderate risk (50% and 47.2% versus 30.6%; both  $P<0.01$ ) and were similar to patients in the high-risk group.<sup>99</sup>

### Awareness, Treatment, and Control

- Surgery was performed in 47% of cases of definite left-sided, non-cardiac device-related IE in the ICE-PLUS registry of 1296 patients from 16 countries.<sup>100</sup>
- In a randomized, noninferiority multicenter trial of 400 stable cases with left-sided native IE, the combined outcome of all-cause mortality, unplanned surgery, embolic events, or relapse of bacteremia was similar in those treated with continuous intravenous antibiotic drugs compared with those switched from intravenous to oral antibiotic drugs after 10 days (24 cases or 12.1% versus 18 cases or 9%; between-group difference, 3.1 percentage points [95% CI, -3.4 to 9.6];  $P=0.40$ ).<sup>101</sup>

### Mortality

- According to the 2015 GBD study, the age-standardized death rate attributable to IE in 2015 was 1.3 per 100 000.<sup>102</sup>
- Data collected between 2004 and 2010 from the Pediatric Health Information System database from 37 centers that included 1033 cases of IE demonstrated a mortality rate of 6.7% ( $n=45$ ) and 3.5% ( $n=13$ ) among children (0–19 years of age) with and without congenital HD, respectively.<sup>103</sup>

### Complications

- Among 162 cases of left-sided native-valve *S aureus* IE retrospectively identified in 1254 patients hospitalized between 1990 and 2010 for IE, *Staphylococcus* represented 18% of all IE cases

and 23% of native-valve IE cases. HF occurred in 45% of IE cases, acute renal failure in 23%, sepsis in 29%, neurological events in 36%, systemic embolic events in 55%, and in-hospital mortality in 25%. The risk of in-hospital mortality was higher in patients with HF (OR, 2.5;  $P=0.04$ ) and sepsis (OR, 5.3;  $P=0.001$ ). Long-term 5-year survival was  $49.6\pm4.9\%$ . There was higher long-term risk of death among individuals with HF (OR, 1.7;  $P=0.03$ ), sepsis (OR, 3.0;  $P=0.0001$ ), and delayed surgery (OR, 0.43;  $P=0.003$ ). When the authors compared 2 study periods, 1990 to 2000 and 2001 to 2010, there was a significant increase in bivalvular involvement, valvular insufficiency, and acute renal failure from 2001 to 2010. In-hospital mortality rates and long-term 5-year survival were not significantly different between the 2 study periods (28.1% versus 23.5%;  $P=0.58$ ).<sup>104</sup>

### Heart Valve Procedure Costs

- In 2013, for heart valve procedures<sup>105</sup>:
  - The mean inflation-adjusted cost per hospitalization in 2013 dollars was \$51 415, compared with \$53 711 in 2005 and \$43 829 in 2000.
  - The number of discharges for which heart valve surgery was the principal operating room procedure was 102 425, which was an increase from 93 802 in 2005 and 79 719 in 2000.
- Total inflation-adjusted national cost in 2013 dollars (in millions) was \$5264, which was an increase from the mean cost (in millions) of \$5058 in 2005 and \$3488 in 2000.<sup>105</sup>

**Table 21-1.** Rheumatic Fever/Rheumatic HD in the United States

Population Group	Mortality, 2017: All Ages*	Hospital Discharges, 2016: All Ages
Both sexes	3320	26 000
Males	1103 (33.2%)†	11 000
Females	2217 (66.8%)†	15 000
NH white males	887	...
NH white females	1791	...
NH black males	95	...
NH black females	176	...
Hispanic males	72	...
Hispanic females	155	...
NH Asian or Pacific Islander males	38‡	...
NH Asian or Pacific Islander females	75‡	...
NH American Indian or Alaska Native	25	...

Ellipses (...) indicate data not available; HD, heart disease; and NH, non-Hispanic.

\*Mortality for American Indian or Alaska Native and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total mortality that is for males vs females.

‡Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

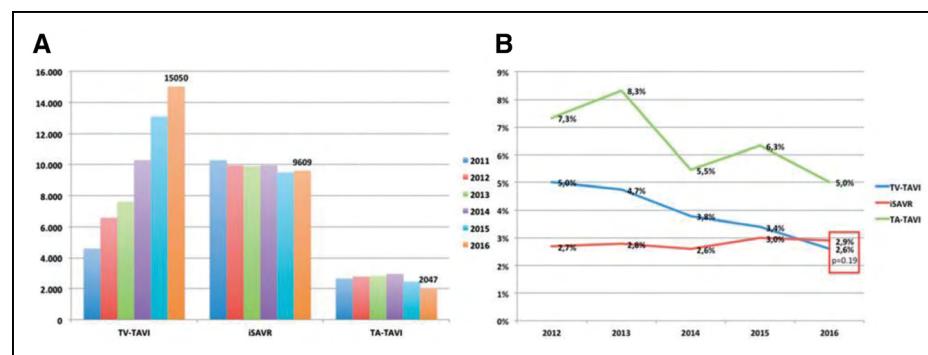
Sources: Mortality: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System, 2017<sup>1</sup>; data represent underlying cause of death only. Hospital discharges: Unpublished NHLBI tabulation using Healthcare Cost and Utilization Project, 2016<sup>3</sup>; data include those inpatients discharged alive, dead, or of unknown status.

**Table 21-2.** Incidence of IE and Valve Replacement, United States, 2000 to 2011

Year	Total IE Cases	IE Incidence per 100 000	Valve Replacement per 1000 IE Cases
2000	29 820	11	14
2001	31 526	11	16
2002	32 229	11	19
2003	35 190	12	18
2004	36 660	13	19
2005	37 508	13	23
2006	40 573	14	23
2007	38 207	12	30
2008	41 143	14	19
2009	43 502	14	27
2010	43 560	14	27
2011	47 134	15	26

IE indicates infective endocarditis.

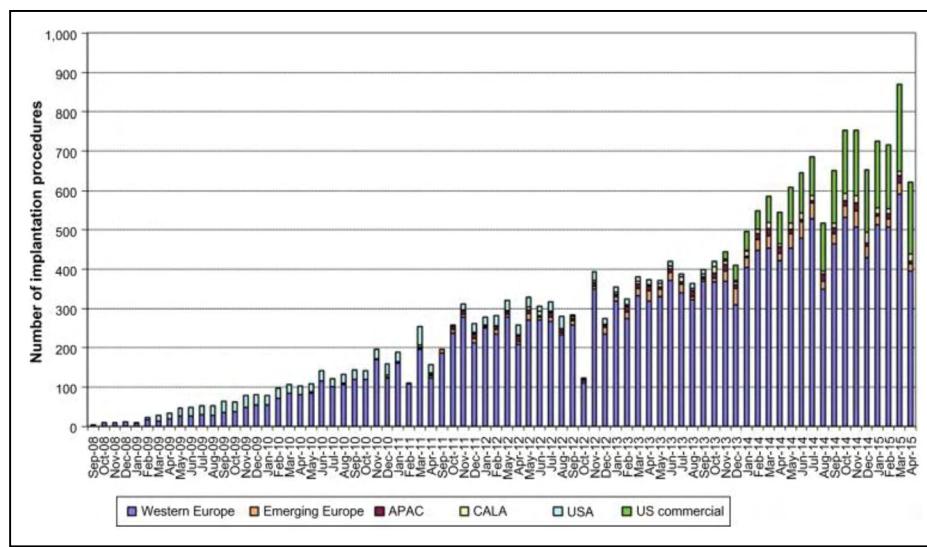
Source: Reprinted from Pant et al<sup>90</sup> with permission from The American College of Cardiology Foundation. Copyright © 2015, The American College of Cardiology Foundation.

**Chart 21-1.** Number of TAVI and surgical aortic valve replacement (SAVR) procedures performed and in-hospital mortality according to type of procedure, Germany, 2011 to 2016.

A, Number of TAVI and SAVR procedures. B, In-hospital mortality.

iSAVR indicates isolated SAVR; TA, transapical; TAVI, transcatheter aortic valve implantation; and TV, transvascular.

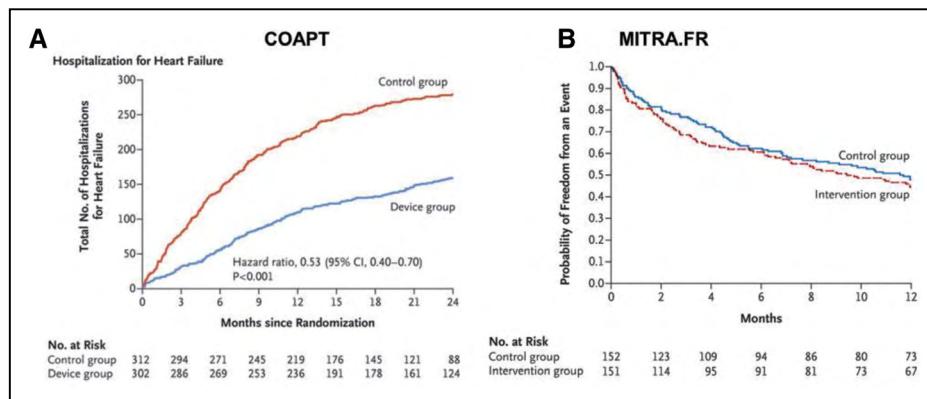
Source: Reprinted from Gaede et al.<sup>106</sup> Copyright © 2017, The Author. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited.



**Chart 21-2. Worldwide experience with the MitraClip procedure from September 2008 until April 2015.**

APAC indicates Asia-Pacific; and CALA, Caribbean and Latin America.

Source: Figure courtesy of Abbott Laboratories.

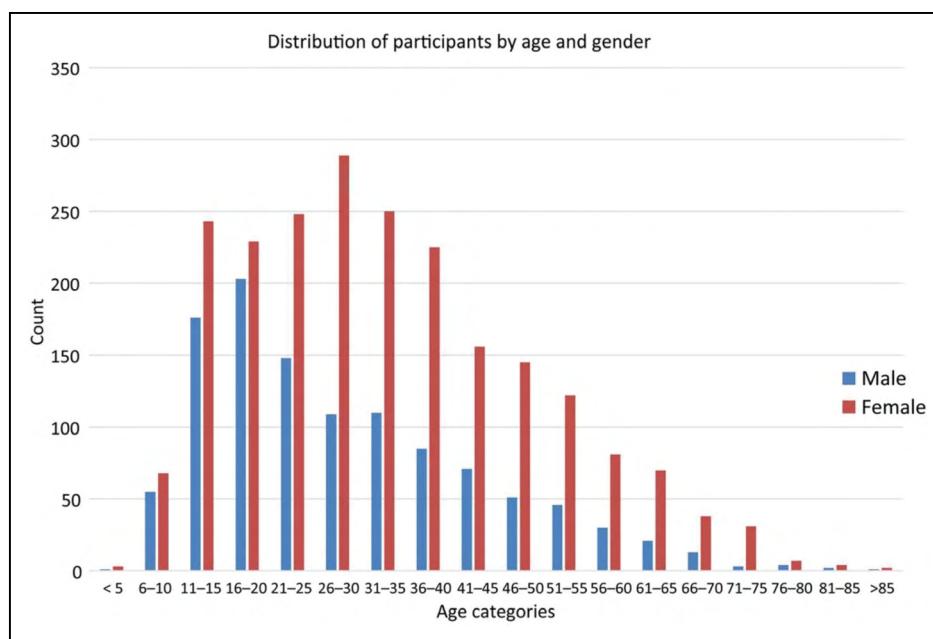


**Chart 21-3. Comparison of primary outcomes after MitraClip implantation for secondary mitral regurgitation in COAPT and MITRA-FR trials.**

**A**, COAPT trial; **(B)** MITRA-FR trial.

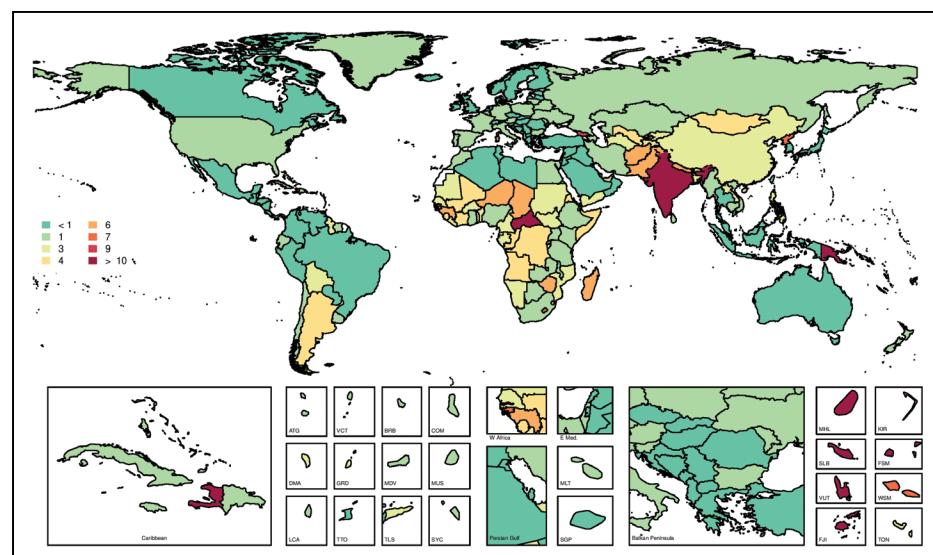
COAPT indicates Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; and MITRA-FR, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation.

Source: **A**, Reprinted from Stone et al<sup>49</sup> with permission from the Massachusetts Medical Society. Copyright © 2018, Massachusetts Medical Society. **B**, Reprinted from Obadia et al<sup>50</sup> with permission from the Massachusetts Medical Society. Copyright © 2018, Massachusetts Medical Society.



**Chart 21-4.** Age and sex distribution of 3343 subjects with rheumatic heart disease participating in the REMEDY (Global Rheumatic Heart Disease Registry) study, 2010 to 2012.

Source: Reprinted from Zühlke et al<sup>82</sup> by permission of the European Society of Cardiology. Copyright © 2014, The Authors.

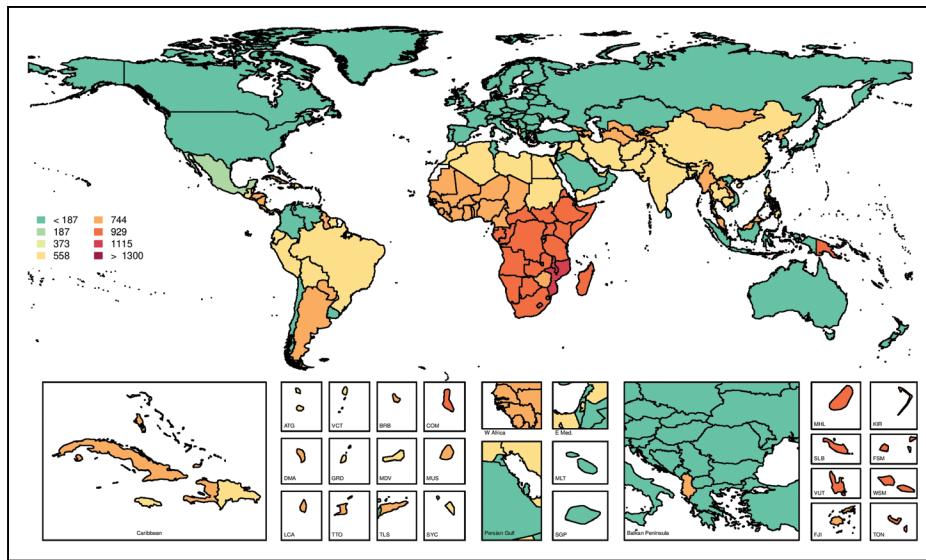


**Chart 21-5.** Age-standardized global mortality rates of rheumatic heart disease (HD) per 100,000, both sexes, 2017.

Age-standardized mortality attributable to rheumatic HD is highest in South Asia, sub-Saharan Africa, and Oceania.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>89</sup> Printed with permission. Copyright © 2018, University of Washington.



**Chart 21-6. Age-standardized global prevalence rates of rheumatic heart disease (HD) per 100000, both sexes, 2016.**

Rheumatic HD prevalence is generally highest in sub-Saharan Africa and Oceania.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>89</sup> Printed with permission. Copyright © 2018, University of Washington.

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## 22. VENOUS THROMBOEMBOLISM (DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM), CHRONIC VENOUS INSUFFICIENCY, PULMONARY HYPERTENSION

**See Charts 22-1 and 22-2**

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In this chapter, 2017 mortality data come from unpublished NHLBI tabulations using the NVSS<sup>1</sup> and CDC WONDER.<sup>2</sup> Hospital discharge data come from unpublished NHLBI tabulations using the HCUP.<sup>3</sup>

### Abbreviations Used in Chapter 22

AF	atrial fibrillation
ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
BNP	B-type natriuretic peptide
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CI	confidence interval
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CVI	chronic venous insufficiency
DM	diabetes mellitus
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ED	emergency department
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FHS	Framingham Heart Study
FVL	factor V Leiden
GRS	genetic risk score(s)
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HD	heart disease
HF	heart failure
HIV	human immunodeficiency virus
HR	hazard ratio
ICD-9	<i>International Classification of Diseases, 9th Revision</i>
ICD-10	<i>International Classification of Diseases, 10th Revision</i>
NAMCS	National Ambulatory Medical Care Survey
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHDS	National Hospital Discharge Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	National (Nationwide) Inpatient Sample
NVSS	National Vital Statistics System
NYHA	New York Heart Association
OR	odds ratio
PAH	pulmonary arterial hypertension
PE	pulmonary embolism
PH	pulmonary hypertension
PTS	postthrombotic syndrome
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RCT	randomized controlled trial
RR	relative risk
RV	right ventricular
VTE	venous thromboembolism
WHO	World Health Organization

## Pulmonary Embolism *ICD-9 415.1; ICD-10 I26.*

Mortality—8704. Any-mention mortality—35605. Hospital discharges—185 000 (principal diagnosis), 367 000 (all-listed diagnoses).

### Deep Vein Thrombosis

*ICD-9 451.1, 451.2, 451.81, 451.9, 453.0, 453.1, 453.2, 453.3, 453.4, 453.5, 453.9; ICD-10 I80.1, I80.2, I80.3, I80.9, I82.0, I82.1, I82.2, I82.3, I82.4, I82.5, I82.9.*

Mortality—3172. Any-mention mortality—17006. Hospital discharges—102 000 (principal diagnosis), 602 000 (all-listed diagnoses).

## Venous Thromboembolism

### Incidence

(Charts 22-1 and 22-2)

- VTE includes both DVT and PE. The HCUP NIS (Charts 22-1 and 22-2) shows increasing numbers of hospitalized cases for PE from 1996 to 2016. Focusing on all-listed diagnoses, the number of hospitalized DVT cases also increased from 2005 to 2016. Extrapolating from these data and using all-listed diagnoses, if we assume 30% of DVTs were treated in the outpatient setting, we estimate that in 2016 there were ≈857 000 DVTs, ≈370 000 PEs, and ≈1 220 000 total VTE events in the United States (US population was 323 million in 2016).
- In 2016, there were 1 001 000 physician office visits and 211 000 ED visits with a principal diagnosis of DVT (unpublished NHLBI tabulation using NAMCS<sup>4</sup> and NHAMCS<sup>5</sup>).
- Interpretation of the HCUP NIS, as well as most other sources of VTE incidence data, should be viewed in light of secular trends and data characteristics that could have resulted in an increase in VTE diagnosis that might overstate changes in VTE incidence (eg, advances in PE imaging, which enable the detection of smaller PEs,<sup>6</sup> increased the use of full leg ultrasound, which detects distal DVT; the co-occurrence of codes for DVT and PE in the same patient) and other factors that could lead to underestimation of VTE incidence (eg, outpatient management of ≈35% of DVT cases<sup>7</sup> and a smaller portion of PE cases,<sup>8,9</sup> misdiagnosis of VTE events, and failure to ascertain fatal PEs because of low autopsy rates).
- Using administrative data in the United States, the estimated admissions for PE increased from 23 per 100 000 in 1993 to 65 per 100 000 in 2012.<sup>10</sup> Trends in DVT incidence were not reported.

- Incidence rates for PE and DVT increase exponentially with advancing age for both males and females.<sup>11–13</sup>
- VTE incidence varies by race/ethnicity.<sup>14–17</sup> Blacks appear to be at greatest risk, followed by whites, Hispanics, and Asians, respectively.
- Educational attainment has been inversely associated with VTE risk.<sup>18</sup>

### Lifetime Risk

- The remaining lifetime risk of VTE at 45 years of age was 8.1% (95% CI, 7.1%–8.7%) overall, 11.5% in blacks, 10.9% in those with obesity, 17.1% in individuals with the FVL genetic mutation, and 18.2% in people with sickle cell trait or disease, using data derived from nearly 20 000 participants of 2 US cohorts who were 45 to 99 years of age.<sup>19</sup>

### Risk Factors

- Approximately 50% of VTEs are provoked because of immobilization, trauma, surgery, or hospitalization in the antecedent 3 months; 20% are associated with cancer; and 30% are unprovoked.<sup>20–22</sup>
- Independent VTE risk factors include increasing age, obesity, family history or personal history of thrombosis, recent surgery, trauma/fracture, hospitalization, prolonged immobility, nursing home residence, active cancer, indwelling central venous catheter or transvenous pacemaker, prior superficial vein thrombosis, infection, inherited or acquired thrombophilia, kidney disease, neurological disease with leg paresis, sickle cell anemia and sickle cell trait, and long-distance travel.<sup>23–25</sup> Autoimmune diseases, such as lupus and Sjögren syndrome, and acute infection have also been associated with elevated VTE risk.<sup>26–31</sup>
- Among females, VTE risk is elevated among those using estrogen-based contraceptives, hormone therapy, or infertility treatment.<sup>32</sup> Risk is also elevated in pregnancy and the postpartum period. Pregnancy-associated VTE has an incidence of 1 to 2 per 1000 person-years; compared with nonpregnant females of childbearing age, the RR for VTE is increased 4-fold.<sup>33–35</sup> VTE risk is higher for pregnancies after in vitro fertilization than for natural pregnancies,<sup>36</sup> and with multiple gestation, cesarean delivery, or other pregnancy complications.<sup>37,38</sup> Risk factors associated with VTE in the general population (eg, obesity) are also associated with pregnancy-associated VTE.
- Traditional atherosclerotic risk factors, including hypertension, hyperlipidemia, and DM, were not associated with VTE risk in a 2017 individual-level meta-analysis of >240 000 participants from 9 cohorts.<sup>39</sup> Cigarette smoking was associated with provoked but not with unprovoked VTE events.

Similar findings were reported in a 2019 publication combining data from the Emerging Risk Factors Collaboration and UK Biobank whereby there was no association with hypertension and dyslipidemia, although for DM, the association was inconsistent. Age and obesity were associated with greater risk in this analysis.<sup>40</sup>

### Family History and Genetics

- VTE is highly heritable.<sup>41,42</sup>
- FVL is the most common inherited thrombophilia in populations of European descent but is rare in African and Asian populations.<sup>43</sup> In ARIC, ≈5% of Caucasians and <1% of African Americans are heterozygous carriers of FVL, and lifetime risk of VTE was 17.1% in individuals with the FVL genetic mutation.<sup>19</sup> Pooling data from 36 epidemiological studies, Simone et al<sup>44</sup> found that risk of VTE was increased 4-fold in heterozygous FVL (OR, 4.2 [95% CI, 3.4–5.3]) and 11-fold in homozygous FVL (OR, 11.4 [95% CI, 6.8–19.3]) compared with noncarriers.
- Antithrombin deficiency is a rare mutation that is associated with greatly increased risk of incident VTE (OR ≈14).<sup>45</sup> A bayesian meta-analysis found that for childbearing females with this mutation, VTE risk was 7% in the antepartum period and 11% postpartum.<sup>46</sup> The authors suggested that thrombosis prophylaxis should be considered for childbearing females with this mutation.
- More common genetic variants associated with VTE have a lesser risk of VTE than rare mutations and include non-O blood group, prothrombin 20210A, and sickle cell disease and trait.<sup>47</sup> GWASs have identified additional common genetic variants associated with VTE risk, including variants in *F5*, *F2*, *F11*, *FGG*, and *ZFPM2*.<sup>48</sup> These common variants individually increase the risk of VTE to a small extent, but a GRS composed of a combination of these variants yielded an OR for VTE risk of 7.5.<sup>49</sup> Exome-wide analysis of rare variants in >24 000 individuals of European ancestry and 1858 individuals of African ancestry confirmed previously implicated loci but did not uncover novel rare variants associated with VTE.<sup>50</sup> Similarly, targeted sequencing efforts did not uncover novel rare variants for DVT.<sup>51</sup>

### Treatment

- In the latter half of the past decade, substantial progress has been made in the management of patients with suspected VTE. This includes patient-tailored diagnostic and therapeutic strategies because of the confluence of refined use of biomarkers (eg age-adjusted D-dimer threshold), risk prediction algorithms (PE Rule-Out Criteria), and the introduction of DOACs.<sup>52</sup>

- VTE is generally treated for 3 to 6 months with anticoagulation (primary treatment), at which point the risks and benefits of continued anticoagulation should be assessed (secondary prevention).<sup>53</sup> When oral anticoagulation is contraindicated or ineffective, inferior vena cava filters can be used. However, in general they should be avoided.<sup>52</sup> Thrombolysis is generally reserved for patients with massive PE or those with DVT that is threatening to result in limb loss.<sup>52</sup>
- Current treatment guidelines consider anticoagulation with either warfarin or DOAC drugs (ie, apixaban, rivaroxaban, dabigatran, edoxaban) as the standard of care.<sup>53</sup> In phase III RCTs of VTE primary treatment,<sup>54–57</sup> the DOAC drugs were each shown to be as effective as warfarin in the prevention of recurrent VTE and VTE-related death. A meta-analysis<sup>58</sup> of these trials suggested that DOAC drugs have a lower risk of bleeding complications than warfarin.
- Observational studies have also indicated that statins reduce the risk of recurrent VTE. An RCT published in 2018 demonstrated that among VTE patients, randomization to rosuvastatin was associated with improved coagulation profiles relative to those not randomized to a statin.<sup>59</sup>

### Mortality

- Among Medicare beneficiaries with DVT, the 30-day mortality rate was 5.1% and the 1-year mortality rate was 19.6% in 2010.<sup>60</sup> These rates were similar to those in 1999 (5.0% and 21.5%, respectively).
- Among Medicare beneficiaries with PE, the 30-day mortality rate was 9.1% and the 6-month mortality rate was 19.6% in 2010.<sup>61</sup> These rates only showed slight improvements from rates in 1999 (12.3% and 23.0%, respectively).
- An analysis using administrative data for first-time VTE in Quebec, Canada, reported that the 1-year survival rate for VTE was 77% overall, but when stratified by VTE-provoking status, it was 47% for cancer-associated VTE, 84% for provoked VTE, and 93% for unprovoked VTE.<sup>62</sup>
- Asymptomatic DVTs diagnosed with compression ultrasound were associated with a 3-fold increased risk of short-term all-cause mortality in patients with acute medical illness relative to those with no evidence of DVT.<sup>63</sup>

### Complications

- VTE is a chronic disease with episodic recurrence; in the absence of long-term anticoagulation, ≈30% of patients develop recurrence within the next 10 years.<sup>18,23,64</sup>
- Independent predictors of recurrence within 180 days include active cancer and inadequate

anticoagulation. Two-week case-fatality rates are 2% for recurrent DVT alone and 11% for recurrent PE with or without DVT.<sup>65</sup>

- Because of the use of anticoagulant therapy to treat VTE, bleeding is a major potential complication. Data from phase III RCTs suggest that use of DOACs, instead of warfarin, for VTE primary treatment could further reduce bleeding risk.<sup>58</sup>
- PTS/venous stasis syndrome and venous stasis ulcers are important complications of proximal lower-extremity DVT, which are discussed in greater depth in the Chronic Venous Insufficiency section of this chapter. After proximal lower-extremity DVT, the 20-year cumulative incidences of PTS/venous stasis syndrome and venous stasis ulcers are 30% and 3.7%, respectively.<sup>66</sup>
- CTEPH affects ≈4% of patients with PE within 2 years of their initial PE event.<sup>67</sup>

### Costs

- A literature review estimated incremental direct medical costs (2014 US dollars) per case among 1-year survivors of acute VTE at \$12 000 to \$15 000 and the cost of complications, including recurrent VTE, PTS, CTEPH, and anticoagulation-related adverse events, at \$18 000 to \$23 000 per case. This review assumed 375 000 to 425 000 new cases in the United States annually and estimated the annual overall cost at \$7 billion to \$10 billion.<sup>68</sup>

## Chronic Venous Insufficiency ICD-10 I87.2.

Mortality—57. Any-mention mortality—543.

### Prevalence

- Varicose veins are a common manifestation of CVI. In the San Diego Population Study (mean age, 59 years), visible disease was common; 6.2% had trophic changes (eg, hyperpigmentation, edema, ulcers), 23.3% had varicose veins, and 51.9% had spider veins.<sup>69</sup>
- PTS is a common complication of DVT that develops in 20% to 50% of cases after proximal DVT and is severe in 5% to 10% of cases.<sup>70</sup> Approximately 4% of patients with DVT experience venous stasis ulcers.<sup>67</sup>

### Incidence

- The FHS reported an annual incidence of varicose veins of 2.6% in females and 1.9% in males.<sup>71</sup>

### Risk Factors

- The prevalence of moderate CVI increases with advancing age, family history, hernia surgery, obesity, number of births, and presence of flat feet in females and is less likely in those with hypertension;

risk factors for more severe CVI include smoking in males and leg injury in females.<sup>72</sup> Inflammation, endothelial dysfunction, and blood coagulation disorders are all thought to predispose to CVI.<sup>73,74</sup>

- PTS, a subset of CVI, has specific risk factors that can be identified at the time of or after DVT: recurrent ipsilateral DVT, obesity, more extensive DVT, poor quality of initial anticoagulation, ongoing symptoms or signs of DVT 1 month after diagnosis, and elevated D-dimer at 1 month.<sup>70,75,76</sup>
- Using data from 762 DVT patients, Rabinovich et al<sup>77</sup> developed a clinical prediction model for PTS. High-risk predictors were index DVT in the iliac vein; BMI of  $\geq 35$  kg/m<sup>2</sup>; and moderate to severe Villalta (PTS severity) score at DVT diagnosis.
- In a meta-analysis of DVT patients who underwent ultrasonography at least 6 weeks after their DVT, 2 ultrasound parameters were predictive of PTS: residual vein thrombosis (pooled OR, 2.17 [95% CI, 1.79–2.63]) and venous reflux at the popliteal level (pooled OR, 1.34 [95% CI, 1.03–1.75]).<sup>78</sup>
- Data from 2018 demonstrated that among DVT patients, initial compression with either compression hosiery or multilayer bandaging was associated with fewer irreversible skin signs, edema, and pain on calf compression versus no compression.<sup>79</sup> Multilayer bandaging was slightly more effective than hosiery but has substantially higher costs, without a gain in health-related quality of life.
- For patients with DVT, use of compression stockings for 24 months is standard therapy for the prevention of PTS. In a 2018 RCT, a total of 865 patients were randomized to either standard duration or individualized therapy length.<sup>80</sup> Individualized therapy was noninferior to standard duration of therapy of 24 months. Individualization of therapy duration may potentially enhance patients' well-being.
- Rabinovich and Kahn described the best means to prevent PTS as prevention of future DVT and appropriate anticoagulation of existing DVT.<sup>81</sup>

### **Family History and Genetics**

- Varicose veins are more likely to occur in the setting of a positive family history, consistent with a heritable component. Although a number of genes have been implicated,<sup>82</sup> the genetic factors predisposing to varicose veins have not been definitively identified.<sup>83</sup>

### **Complications**

- More severe venous disease often includes manifestations such as hyperpigmentation, venous eczema, lipodermatosclerosis, atrophie blanche, and healed or active venous ulcers.<sup>84</sup>
- Analysis of NIS data for black and white Americans demonstrated declines in ulcer debridement, vein stripping, and sclerotherapy procedures from 1998

to 2011. Blacks presented at younger ages and more often had ulcer debridement and history of DVT than whites.<sup>85</sup>

- A 2017 publication that used a database of 300 patients treated for advanced CVI with radiofrequency ablation procedures showed that blacks presented with higher-severity CVI and had less improvement with ablation.<sup>86</sup>

### **Cost**

- The estimated cost in the United States to treat venous ulcers is \$1 billion annually.<sup>84</sup>

## **Pulmonary Hypertension**

### **ICD-10 I27.0, I27.2.**

Mortality—7618. Any-mention mortality—24 584.

### **Incidence**

- In the United States, between 2001 and 2010, hospitalization rates for PH increased significantly, and among those  $\geq 85$  years of age, hospitalization rates nearly doubled.<sup>87</sup> In 2010, the age-adjusted rate of hospitalization associated with PH was 131 per 100 000 discharges overall and 1527 per 100 000 for those  $\geq 85$  years of age.<sup>87</sup>
- The WHO classifies PH into 5 groups (described below) according to underlying pathogenesis. Limited information is available on prevalence of PH subtypes in nonreferral settings. In one study conducted in Armadale, Australia, the most commonly identified PH subtypes were left-sided HD (WHO group 2: 68%); lung disease (WHO group 3: 9%); WHO group 1, underlying causes combined (3%); and CTEPH (WHO group 4: 2%). Fifteen percent were unclassifiable.<sup>88</sup>
- The prevalence of WHO group 1 PH (idiopathic, heritable, drug/toxin induced, or associated with other factors including connective tissue disease, infections [HIV, schistosomiasis], portal hypertension, and congenital HD) is estimated at 6.6 to 26.0 per million adults and the incidence at 1.1 to 7.6 per million adults annually.<sup>89</sup>
- WHO group 2 PH is attributable to left-sided HD. Estimates of the incidence and prevalence are difficult to ascertain but most likely would track with HF prevalence rates.<sup>89</sup>
- The prevalence and incidence of WHO group 3 PH (attributable to lung disease or hypoxia) is difficult to estimate but likely would track with lung disease prevalence.<sup>89</sup>
- The prevalence of WHO group 4 PH (CTEPH and other pulmonary obstructions) ranges from 1.0% to 8.8% among those with PE.<sup>89</sup> CTEPH incidence, however, may be underestimated based on general population data; in a 2017 modeling study, only 7% to 29% of CTEPH cases were diagnosed.<sup>90</sup>

- WHO group 5 PH has multifactorial mechanisms. When it accompanies sickle cell disease, the prevalence is 6% to 10% and increases with advancing age. When it accompanies thalassemia, the prevalence is 2.1%.<sup>89,91</sup>

### Risk Factors

- Risk factors are implicit in the WHO disease classification of the 5 mechanistic subtypes of PH described above. The most common risk factors are left-sided HD and lung disease.
- In a cohort of 23 329 patients with first VTE (mean follow-up, 3.5 years) 283 patients were diagnosed with CTEPH. Cumulative incidence was 1.3% and 3.3% at 2 and 10 years after PE and 0.3% and 1.3% after DVT, respectively. Risk factors for CTEPH included age >70 years, being female, chronic obstructive pulmonary disease, HF, and AF.<sup>92</sup>
- In a study of 772 consecutive PE patients without major comorbidities such as cancer, the risk factors for CTEPH were unprovoked PE, hypothyroidism, symptom onset >2 weeks before PE diagnosis, RV dysfunction on CT or echocardiography, DM, and thrombolytic therapy or embolectomy; a risk prediction score that included these factors was able to predict a group with a CTEPH incidence of 10% (95% CI, 6.5%–15%).<sup>93</sup> It is not clear to what extent these factors may be affected by the possibility that the index presentation was caused by worsening RV failure in the setting of CTEPH rather than acute PE. Higher BMI also has been associated with CTEPH risk after PE.<sup>94</sup>
- A 2018 analysis of 2368 REVEAL registry patients with PH reported that patients with a ≥10% decline in eGFR from baseline over ≥1 year had a significantly increased risk of death (HR, 1.66;  $P<0.0001$ ) and the composite of all-cause hospitalization and death (HR, 1.33;  $P=0.002$ ).<sup>95</sup> This decline predicted survival independently of changes in 6-minute walk distance and functional class. Likewise, using PH patients from the same registry, both baseline and change in concentrations of plasma BNP were associated with increased risk of death. Comparing those with high (>340 pg/mL) versus low ( $\leq 340$  pg/mL) baseline BNP, the HR was 3.6 (95% CI, 3.0–4.2).<sup>96</sup>
- Among patients with ESRD, PH is associated with a 2-fold increased risk of all-cause mortality for both patients receiving maintenance dialysis and those with a functioning kidney transplant.<sup>97</sup>

### Family History and Genetics

- A 2018 study reported clustering of CTEPH in families, providing novel evidence that heritable genetic factors influence an individual's risk of developing CTEPH.<sup>98</sup>

- A Japanese family study also identified the bone morphogenetic protein type 2 receptor gene (*BMPR2*) as a risk factor for PAH.<sup>99</sup>

### Treatment

- Galiè and colleagues<sup>100</sup> performed a double-blind RCT of 500 treatment-naïve patients with WHO group 2 or 3 PH, randomizing them to ambrisentan, tadalafil, or both in combination. The combination group (versus the pooled monotherapy groups) was at lower risk for the composite primary end point of death, PAH hospitalization, or clinical disease progression (HR, 0.50 [95% CI, 0.35–0.72]).
- In a large, placebo-controlled, double-blind RCT of 1156 patients with PAH randomized to selexipag, an oral selective IP prostacyclin receptor agonist, versus placebo, Sitbon and colleagues<sup>101</sup> found a significant reduction in the primary composite end point of death attributable to any cause or PAH-related complication (HR, 0.60 [99% CI, 0.46–0.78]). This observed benefit was driven by differences in disease progression and hospitalization; no significant difference in mortality was seen between selexipag and placebo.
- Pulido and colleagues<sup>102</sup> performed a 250-patient RCT of 3 mg or 10 mg of macitentan, a dual endothelin receptor antagonist, versus placebo, with a primary end point composite of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of PAH. Macitentan was shown to have statistically and clinically significant benefit at either tested dose; the HR for 3 mg of macitentan versus placebo was 0.70 (97.5% CI, 0.52–0.96), and for 10 mg of macitentan versus placebo, the HR was 0.55 (97.5% CI, 0.39–0.76).<sup>102</sup>

### Mortality

Mortality of PH depends on the cause and treatment. On the basis of 2010 NHDS data, the death rate for PH as a contributing cause of death was 6.5 per 100 000.<sup>87</sup>

- Five-year survival was 61.2% to 65.4% in the US-based REVEAL registry of patients with group 1 PH. Lower 5-year survival was strongly and directly associated with worse functional class at presentation.<sup>103</sup> In an earlier study from this registry, 6-minute walk distance was also shown to be a strong predictor, with 97%, 90%, and 68% 1-year survival for patients with >440, 165 to 440, and <165 meter walk distances, respectively. A decline of >15% over time also predicted a significantly worse outcome compared with a stable or improving 6-minute walk distance.<sup>104</sup>
- A German single-center registry study reported 5-year survival rates of 65.3% for patients with idiopathic PH, 50.9% for those with PH associated with connective tissue disease, 74.5% for those with PH

caused by congenital HD, and 18.7% for those with pulmonary venous occlusive disease, respectively.<sup>105</sup>

- In a French registry study of 981 patients with idiopathic, heritable, or drug-induced PAH enrolled between 2006 and 2016, survival at 1 and 3 years was 90% and 73%, respectively.<sup>106</sup>
- In sickle cell disease–related PH, the 5-year survival rate in one study was 63% with and 83% without PH.<sup>107</sup>
- An international prospective registry that included 679 patients with CTEPH estimated that the 3-year survival was 89% with and 70% without pulmonary thromboendarterectomy.<sup>108</sup> Among the patients with CTEPH, treatments for PH did not affect survival. High NYHA functional class, increased right atrial pressure, and history of cancer were associated with mortality regardless of surgery.

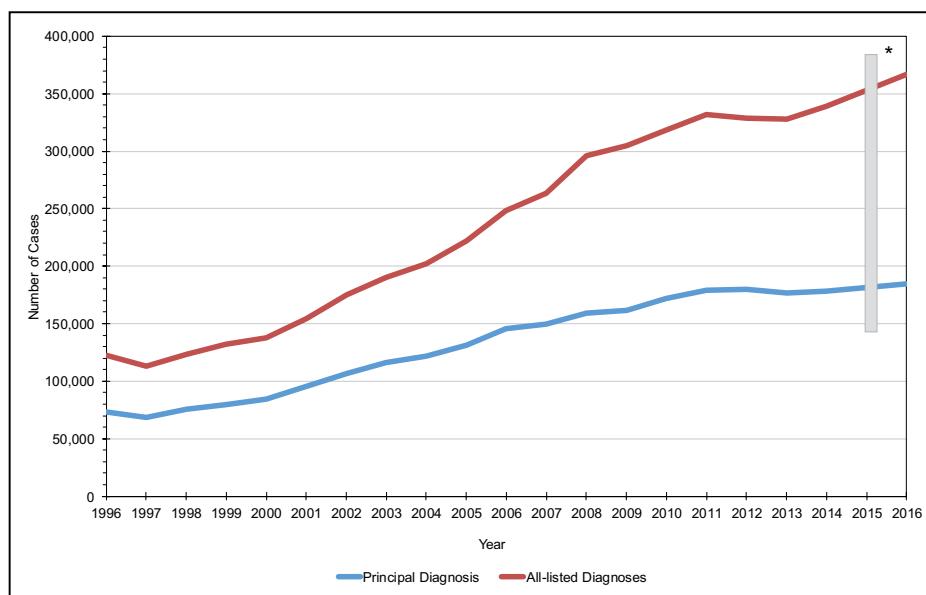
### Costs

- Healthcare costs associated with PH are substantial. In an analysis of administrative data, the

per-patient per-month total all-cause healthcare costs for patients with PH who were commercially insured was \$9503 for those on monotherapy and \$16 240 for those on combination therapy. Among PH patients with Medicare Advantage and Part D, the monthly costs for patients on monotherapy and combination therapy were \$6271 and \$14 340, respectively.<sup>109</sup>

### Global Burden

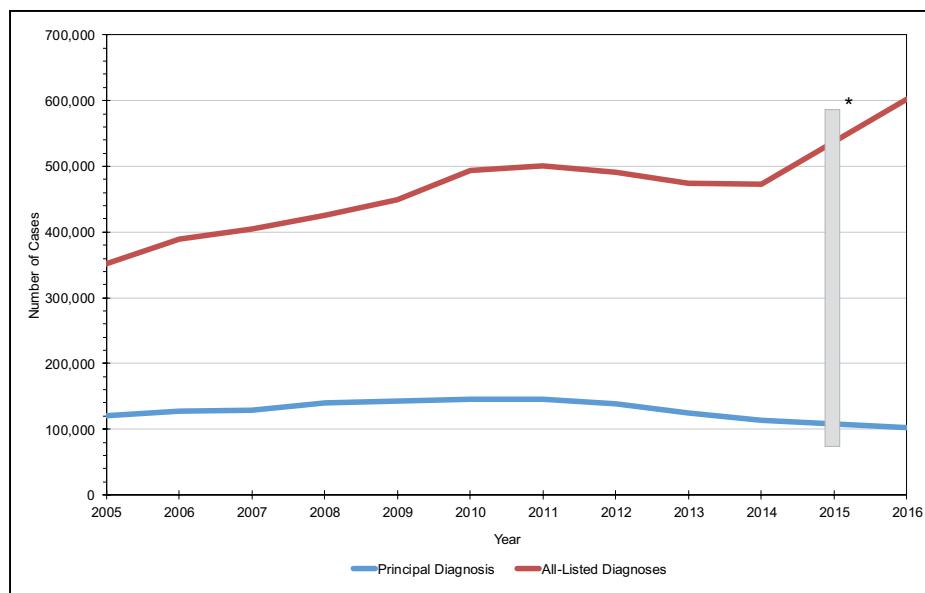
- 80% of patients with PH live in developing countries, and the cause of their PH is primarily HD and lung disease, but schistosomiasis, rheumatic HD, HIV, and sickle cell disease remain prominent compared with developed countries. In these countries, younger people are more often affected (average age of onset <40 years).<sup>89</sup>
- In high-income countries, rates of CTEPH are believed to be lower in Japan than in the United States and Europe.<sup>90</sup>



**Chart 22-1. Trends in hospitalized pulmonary embolism, United States, 1996 to 2016.**

\*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>3</sup>



**Chart 22-2. Trends in hospitalized deep vein thrombosis, United States, 2005 to 2016.**

\*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>3</sup>

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## 23. PERIPHERAL ARTERY DISEASE AND AORTIC DISEASES

**ICD-9 440.20 to 440.24, 440.30 to 440.32, 440.4, 440.9, 443.9, 445.02; ICD-10 I70.2, I70.9, I73.9, I74.3, I74.4. See Tables 23-1 through 23-3 and Charts 23-1 through 23-9**

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### Abbreviations Used in Chapter 23

AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
ACC	American College of Cardiology
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
CDC WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
FH	familial hypercholesterolemia
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
GBD	Global Burden of Disease
GWAS	genome-wide association study
HCUP	Healthcare Cost and Utilization Project
HF	heart failure
HR	hazard ratio
ICD	<i>International Classification of Diseases</i>
ICD-9	<i>International Classification of Diseases, 9th Revision</i>
ICD-10	<i>International Classification of Diseases, 10th Revision</i>
IRAD	International Registry of Acute Aortic Dissection
KD	Kawasaki disease
LDL	low-density lipoprotein
MACE	major adverse cardiovascular event
MI	myocardial infarction
NAMCS	National Ambulatory Medical Care Survey
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHLBI	National Heart, Lung, and Blood Institute
NIS	Nationwide Inpatient Sample
NVSS	National Vital Statistics System
OR	odds ratio
OVER	Open Versus Endovascular Repair
PA	physical activity
PAD	peripheral artery disease
PCSK9	proprotein convertase subtilisin/kexin type 9
RR	relative risk
SBP	systolic blood pressure
SES	socioeconomic status
SNP	single-nucleotide polymorphism
TGF	transforming growth factor
UI	uncertainty interval

## Peripheral Artery Disease

### Prevalence and Incidence (Charts 23-1 and 23-2)

- On the basis of data from several US cohorts during the 1970s to 2000s and the 2000 US Census, 6.5 million Americans ≥40 years of age (5.8%) are estimated to have low ABI (<0.9).<sup>1</sup>
- Further accounting for PAD cases with ABI >0.9 (after revascularization or false-negative results with ABI), in 2000, PAD was estimated to affect ≈8.5 million Americans ≥40 years of age (7.2%).<sup>1</sup>
- Estimates of PAD prevalence in males and females by age and ethnicity are shown in Charts 23-1 and 23-2.
- The highest prevalence of low ABI (<0.9) has been observed among older adults (22.7% among individuals ≥80 years of age versus 1.6% among those 40–49 years of age) and NH blacks (≈11.6% in NH blacks versus ≈5.5% in whites).<sup>1</sup> The prevalence of low ABI (<0.9) is similar between females (5.9%) and males (5.0%).
- Only ≈10% of people with PAD have the classic symptom of intermittent claudication. Approximately 40% do not complain of leg pain, whereas the remaining 50% have a variety of leg symptoms different from classic claudication (ie, exertional pain that either did not stop the individual from walking or did stop the individual from walking but did not involve the calves or did not resolve within 10 minutes of rest).<sup>2,3</sup>
- On the basis of *ICD* codes in nationwide claims data from large employers' health plans and from Medicare and Medicaid programs between 2003 and 2008, among adults >40 years of age, the annual incidence and prevalence of PAD were 2.69% and 12.02%, respectively.<sup>4</sup> The corresponding estimates for critical limb ischemia, the most severe form of PAD, were 0.35% and 1.33%, respectively.
- Data from the NIS demonstrate that admission rates because of critical limb ischemia remained constant from 2003 to 2011.<sup>5</sup>

### Risk Factors

- The risk factors for PAD are similar but not identical to those for CHD. Cigarette smoking is a stronger risk factor for PAD than for CHD.<sup>6</sup> The age- and sex-adjusted OR for heavy smoking was 3.94 for symptomatic PAD and 1.66 for CHD.<sup>6</sup>
- Among males in the Health Professionals Follow-up Study, smoking, type 2 DM, hypertension, and hypercholesterolemia accounted for 75% (95% CI, 64%–87%) of risk associated with development of clinical PAD.<sup>7</sup>
- In a meta-analysis of 34 studies from high-income countries and low- to middle-income

countries, respectively, important risk factors for PAD included cigarette smoking (OR, 2.72 versus 1.42), DM (OR, 1.88 versus 1.47), hypertension (OR, 1.55 versus 1.36), and hypercholesterolemia (OR, 1.19 versus 1.14).<sup>8</sup>

- A study of 3.3 million people 40 to 99 years of age primarily self-referring for vascular screening tests in the United States showed that risk factor burden was associated with increased prevalence of PAD, and there was a graded relationship between the number of traditional risk factors and the prevalence of PAD.<sup>9</sup>
- Other risk factors for PAD include sedentary lifestyle, elevated inflammation markers, hypertension in pregnancy, and CKD.<sup>9–12</sup>
- Blacks have a 37% higher amputation risk than whites (HR, 1.37 [95% CI, 1.30–1.45]). Lower SES is an independent predictor for amputation (HR, 1.12 [95% CI, 1.06–1.17]).<sup>13</sup>
- A secondary analysis of a randomized feeding trial showed reduced risk of incident PAD with the Mediterranean diet compared with a control diet.<sup>14</sup>
- In the ARIC study, the incidence of PAD was higher among participants with lower household income and educational attainment.<sup>15</sup>

### Genetics

- Atherosclerotic PAD is heritable, even independent of risk factors for PAD which themselves are heritable.
- In the ethnically diverse San Diego Population Study, a family history of PAD was independently associated with a 1.83-fold higher odds of PAD.<sup>16</sup> In the Swedish Twin Registry, the OR of PAD in a monozygotic twin was 17.7, and 5.7 in dizygotic twins; estimated genetic effects accounted for 58% and nonshared environmental effects for 42% of the phenotypic variance between twins.<sup>17</sup> The NHLBI Twin Study found that 48% of the variability in ABI with similar environmental risk factors could be attributed to additive genetic effects.<sup>18</sup>
- There are monogenic (mendelian) diseases that result in PAD, including familial lipoprotein disorders such as chylomicronemia and FH, hyperhomocysteinemia, and pseudoxanthoma elasticum.<sup>19</sup>
- GWASs have identified genetic loci associated with atherosclerotic PAD, including the CHD-associated chromosome 9p21 genetic locus, which has been shown to be associated with PAD, AAA, and intracranial aneurysm.<sup>20</sup> Other PAD-associated genetic loci found through GWASs include SNPs in chromosome 9 near *CDKN2B*, *DAB2* interaction protein (*DAB2IP*), and cytochrome B-245 α-chain (*CYBA*) genes.<sup>21</sup>

- GWASs have also identified genetic variants associated with inflammatory forms of PAD such as KD.<sup>22</sup>

### Awareness, Treatment, and Control

- A US survey of >2500 adults ≥50 years of age found that 25% expressed familiarity with PAD in contrast to >65% for CHD, stroke, and HF. Only 50% of the population were aware that DM and smoking are risk factors of PAD. One in 4 knew that PAD is associated with increased risk of MI and stroke, and only 14% were aware that PAD could result in amputation. Lower income and education levels were related to lower levels of all knowledge domains.<sup>23</sup>
- In data concerning people ≥70 years of age or those 50 to 69 years of age with a history of DM or smoking, as well as their physicians, 83% of patients with a previous diagnosis of PAD recognized the diagnosis, but only half of their physicians were aware of the diagnosis.<sup>2</sup>
- A 2011 systematic review evaluated lower-extremity aerobic exercise against usual care and demonstrated a range of benefits, including the following<sup>24</sup>:
  - Increased time to claudication by 71 seconds (79%), to 918 seconds (422%)
  - Increased distance before claudication by 15 m (5.6%), to 232 m (200%)
  - Increased walking distance/time by 67% to 101% after 40 minutes of walking 2 to 3 times per week
- Observational studies have found that the risks of death,<sup>25</sup> MI,<sup>26</sup> and amputation<sup>25</sup> are substantially greater in individuals with PAD who continue to smoke than in those who have stopped smoking.
- The “2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease” noted that several randomized and observational studies demonstrated that statins reduced the risk of MACE and amputation among people with PAD.<sup>27</sup>
- A few studies have reported that statin therapy may reduce the risk of adverse leg outcomes among patients with PAD.<sup>28,29</sup>
- The FOURIER trial demonstrated that a PCSK9 inhibitor, evolocumab, reduced the risk of major adverse limb events, including acute limb ischemia, major amputation, and urgent revascularization (HR 0.58 [95% CI, 0.38–0.88]), among patients with a history of MI, stroke, or PAD.<sup>30</sup>
- A few novel antithrombotic medications (rivaroxaban and vorapaxar) have been shown to reduce the risk of adverse limb outcomes (eg, revascularization or amputation) among patients with PAD.<sup>31,32</sup>

- A recent Danish trial in males 65 to 74 years of age reported that screening of PAD (with ABI), AAA (with abdominal ultrasound), and hypertension followed by optimal care resulted in 7% lower risk of 5-year mortality compared with no screening.<sup>33</sup>
- Data from the US Department of Veterans Affairs during 2013 to 2014 demonstrate that patients with PAD alone receive optimal medical therapy less frequently than patients with CHD (including those with concomitant PAD; statin use 59% versus 72% and antiplatelet use 66% versus 84%, respectively).<sup>34</sup>
- In a study that randomized patients with PAD to 3 groups (optimal medical care, supervised exercise training, and iliac artery stent placement), supervised exercise resulted in superior treadmill walking distance compared with stenting. Results in the exercise group and stent group were superior to optimal medical care alone.<sup>35</sup>
- In 2017, the Centers for Medicare & Medicaid Services decided to cover supervised exercise therapy (up to 36 sessions over 12 weeks) for eligible symptomatic PAD patients with intermittent claudication.<sup>36</sup>
- Endovascular therapies for critical limb ischemia are being used with greater frequency in the United States. From 2003 to 2011, there was a significant increase in endovascular treatment of critical limb ischemia (from 5.1% to 11.0%), which was accompanied by lower rates of in-hospital mortality and major amputation, as well as shorter length of stay.<sup>5</sup>

### Mortality

#### (See Chart 23-3)

- In 2017, the overall any-mention age-adjusted death rate for PAD was 14.4 per 100 000. Any-mention death rates in males were 17.8 for NH whites, 22.1 for NH blacks, 7.3 for NH Asians or Pacific Islanders, 17.1 for NH American Indians or Alaska Natives, and 13.4 for Hispanic males. In females, rates were 12.4 for NH whites, 14.8 for NH blacks, 5.3 for NH Asians or Pacific Islanders, 13.1 for NH American Indians or Alaska Natives, and 9.1 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER<sup>37</sup>).
- In 2017, PAD was the underlying cause in 12 805 deaths. The number of any-mention deaths attributable to PAD was 56 938 in 2017 (unpublished NHLBI tabulation using NVSS<sup>38</sup> and CDC WONDER<sup>37</sup>).
- A 2008 meta-analysis of 24 955 males and 23 339 females from 16 cohorts demonstrated a reverse-J-shaped association between ABI and mortality in which participants with an ABI of 1.11 to 1.40 were at lowest risk for mortality. In males, low ABI ( $\leq 0.9$ )

carried a 3-fold (RR, 3.33 [95% CI, 2.74–4.06]) risk of all-cause death compared with a normal ABI (1.11–1.40), and a similar risk was observed in females (RR, 2.71 [95% CI, 2.03–3.62]).<sup>38</sup> A similar reverse-J-shaped association between ABI and cardiovascular mortality was observed (Chart 23-3).

- In-hospital mortality was higher in females than males, regardless of disease severity or types of procedure, even after adjustment for age and comorbidities: 0.5% versus 0.2% after percutaneous revascularization for intermittent claudication; 1.0% versus 0.7% after surgical revascularization for intermittent claudication; 2.3% versus 1.6% after percutaneous revascularization for critical limb ischemia; and 2.7% versus 2.2% after surgical revascularization for critical limb ischemia ( $P<0.01$  for all comparisons).<sup>39</sup>

### Complications

- PAD is a marker for systemic atherosclerotic disease, and thus, people with PAD are more likely to have atherosclerosis in other vascular beds (eg, coronary, carotid, and renal arteries and abdominal aorta).<sup>40–43</sup>
- Pooled data from 11 studies in 6 countries found that the pooled age-, sex-, risk factor-, and CVD-adjusted RRs in people with PAD (defined by ABI  $<0.9$ ) versus those without were 1.45 (95% CI, 1.08–1.93) for CHD and 1.35 (95% CI, 1.10–1.65) for stroke.<sup>44</sup>
- A recent study with  $\approx 28\ 000$  patients with a history of CVD demonstrated that patients with symptomatic PAD but no prior MI or stroke had  $\approx 2$  times higher risk of CVD events than those with prior MI or stroke but no symptomatic PAD.<sup>30</sup>
- From 2000 to 2008, the overall rate of lower-extremity amputation decreased significantly, from 7258 to 5790 per 100 000 Medicare beneficiaries with PAD. Patients with PAD who underwent major lower-extremity amputation were more likely to have DM (60.3% versus 35.7% with PAD without amputation;  $P<0.001$ ).<sup>45</sup>
- However, a recent report from the NIS demonstrated that after declining trends, the rate of nontraumatic lower-extremity amputation increased by 50% between 2009 and 2015 in adults with DM.<sup>46</sup>
- Significant geographic variation in the rate of lower-extremity amputation within the United States was reported, from 5500 amputations per 100 000 PAD patients in the Mountain region to 8400 amputations per 100 000 PAD patients in the East South Central region. Lower-extremity amputation was performed more frequently in the East South Central region (adjusted OR, 1.152 [95% CI, 1.131–1.174];  $P<0.001$ ) and West South Central

region (adjusted OR, 1.115 [95% CI, 1.097–1.133];  $P<0.001$ ) and less in the Middle Atlantic region (OR, 0.833 [95% CI, 0.820–0.847];  $P<0.001$ ) versus the South Atlantic reference region.<sup>45</sup>

- Among 186 338 older Medicare PAD patients undergoing major lower-extremity amputation, mortality was found to be 48.3% at 1 year.<sup>47</sup>
- A study of Medicare beneficiaries reported that between 2006 and 2011, 39 339 required revascularization for PAD, and the annual rate of peripheral vascular intervention increased slightly from 401.4 to 419.6 per 100 000 people.<sup>48</sup>
- Among 6391 patients with PAD in the COMPASS trial, 128 (2.0%) experienced leg revascularization or amputation during a median follow-up of 21 months. PAD patients who experienced leg revascularization or amputation had higher risk of adverse outcomes such as all-cause mortality (HR, 3.23 [95% CI, 1.87–5.56]) and any subsequent hospitalization (HR, 7.21 [95% CI, 5.51–9.43]).<sup>31</sup>
- People with PAD have impaired function and quality of life, regardless of whether or not they report leg symptoms. Furthermore, patients with PAD, including those who are asymptomatic, experience a significant decline in lower-extremity function over time.<sup>49–51</sup> A few recent studies have demonstrated that even individuals with low-normal ABI (0.91–0.99) have reduced physical function compared with those with normal ABI.<sup>52</sup>
- Among patients with established PAD, higher PA levels during daily life are associated with better overall survival rate, a lower risk of death because of CVD, and slower rates of functional decline.<sup>53,54</sup> In addition, better 6-minute walk performance and faster walking speed are associated with lower rates of all-cause mortality, cardiovascular mortality, and mobility loss.<sup>55,56</sup>

### **Healthcare Utilization: Hospital Discharges and Ambulatory Care Visits (See Table 23-1)**

- Principal diagnosis discharges for PAD decreased from 2006 to 2016, with first-listed discharges of 156 000 and 111 000, respectively (HCUP,<sup>57</sup> unpublished NHLBI tabulation; Table 23-1).
- In 2016, there were 1 600 000 physician office visits and 11 000 ED visits with a primary diagnosis of PAD (NAMCS<sup>58</sup>/NHAMCS,<sup>59</sup> unpublished NHLBI tabulation).

### **Global Burden (See Table 23-2 and Charts 23-4 through 23-6)**

- A systematic review of 34 studies reported that globally, 202 million people have PAD, and during 2000 to 2010, the number of people with PAD increased by 28.7% in low- to middle-income countries and by 13.1% in high-income countries.<sup>8</sup>

The prevalence of PAD increased with age in both men and women and in both low/middle- and high-income countries (Chart 23-4).

- Global mortality attributable to PAD and global prevalence of PAD by sex from the GBD 2017 study are shown in Table 23-2.<sup>60</sup> The GBD 2017 study used statistical models and data on incidence, prevalence, case fatality, excess mortality, and cause-specific mortality to estimate disease burden for 359 diseases and injuries in 195 countries and territories.
  - PAD mortality is highest in Eastern Europe (Chart 23-5).
  - PAD prevalence is highest in North America, Southeast Asia, and Oceania (Chart 23-6).

### **Aortic Diseases**

#### **ICD-9 440, 441, 444, and 447; ICD-10 I70, I71, I74, I77, and I79.**

##### **Aortic Aneurysm and Acute Aortic Dissection**

**(See Charts 23-7 and 23-8)**

##### **ICD-9 441; ICD-10 I71.**

##### **Prevalence and Incidence**

- The prevalence of AAAs that are 2.9 to 4.9 cm in diameter ranges from 1.3% in males 45 to 54 years of age to 12.5% in males 75 to 84 years of age. For females, the prevalence ranges from 0% in the youngest to 5.2% in the oldest age groups.<sup>61</sup>
- A meta-analysis of 15 475 individuals from 18 studies on small AAAs (3.0–5.4 cm) demonstrated that mean aneurysm growth rate was 2.21 mm per year and did not vary significantly by age and sex. Growth rates were higher in smokers versus former or never smokers (by 0.35 mm/y) and lower in people with DM than in those without DM (by 0.51 mm/y).<sup>62</sup>
- A study from Olmsted County, MN,<sup>63</sup> demonstrated annual age- and sex-adjusted incidences per 100 000 people of 3.5 (95% CI, 2.2–4.9) for thoracic aortic aneurysm rupture and 3.5 (95% CI, 2.4–4.6) for acute aortic dissection.

##### **Risk Factors**

- Many risk factors for atherosclerosis are also associated with increased risk for AAAs.<sup>64</sup> Of these, smoking is the most important modifiable risk factor for AAAs.<sup>65</sup>
- A 2014 systematic review of 17 community-based observational studies demonstrated a consistent, inverse association between DM and prevalent AAAs (OR, 0.80 [95% CI, 0.70–0.90]).<sup>66</sup>
- On the basis of nationally representative data from the United Kingdom, giant cell arteritis has been demonstrated to be associated with a 2-fold

higher risk (sub-HR, 1.92 [95% CI, 1.52–2.41]) after adjustment for competing risks for developing an AAA.<sup>67</sup>

### Genetics

- Monogenic diseases that cause thoracic aortic disease include Marfan syndrome (caused by fibrillin gene mutations), Loeys-Dietz syndrome (*TGFB1*, *TGFB2*, *SMAD3*, *TGFB3* gene mutations, all within the TGF- $\beta$  pathway), vascular Ehlers-Danlos syndrome (*COL3A1* mutations), arterial tortuosity syndrome (*SLC2A10* mutations), and familial thoracic aortic aneurysm syndrome (*ACTA2*, *TGBR2*, and mutations in several other genes).
  - Mutations in the genes causing these disorders significantly increase the risk of developing vascular aneurysms. If these disorders are suspected (eg, because of strong family history or co-occurrence of nonaortic features typical of the disease), referral to a specialty clinic for genetic testing can be useful for diagnosis, treatment, and cascade screening in family members. The identification of a genetic cause of thoracic aortic disease can influence treatment decisions, including need for screening for aneurysms in other vascular beds and a lower threshold for aneurysm diameter for consideration of surgical repair.
- GWASs have identified genetic variants associated with nonfamilial forms of thoracic aortic aneurysm/dissection, including common variants in the fibrillin gene (*FBN1*; rare mutations in this gene cause Marfan syndrome) and variants in the LDL receptor protein-related 1 (*LRP1*) and unc-51-like kinase 4 (*ULK4*) genes.<sup>68,69</sup>
- AAA is heritable; a family history of AAA is a risk factor for AAA, particularly in male siblings of male patients, for whom the RR for AAA is as high as 18.<sup>70,71</sup>
- GWASs and other studies have identified genetic variants associated with AAA, including a locus on chromosome 3p12.3 and SNPs in *DAB2IP*, *LDLR*, *LRP1*, *MMP3*, *TGFB2*, and *SORT1*.<sup>72,73</sup>
- A GWAS has also identified common genetic variants for intracranial aneurysms.<sup>74</sup> In addition, rare variants in *ANGPTL6* are associated with increased risk of intracranial aneurysms.<sup>75</sup>
- Despite the co-occurrence of different types of aneurysms, a meta-analysis has found no shared genetic variants for intracranial, thoracic, and aortic aneurysms.<sup>70</sup>
- Nonatherosclerotic forms of arterial disease such as fibromuscular dysplasia and spontaneous coronary artery dissection are more difficult to evaluate for genetic components given their lesser prevalence and heterogeneous nature, but studies of these

diseases are ongoing. A recent study has identified a noncoding SNP in the phosphatase and actin regulator 1 gene (*PHACTR1*) as being associated with fibromuscular dysplasia.<sup>76</sup>

### Awareness, Treatment, and Control

- Results from 4 trials (N=3314 participants) evaluating the effect of open or endovascular repair of small AAAs (4.0–5.5 cm) did not demonstrate an advantage to earlier intervention compared with routine ultrasound surveillance.<sup>77</sup>
- Data from 23 838 patients with ruptured AAAs collected through the NIS (2005–2010) demonstrated in-hospital mortality of 53.1% (95% CI, 51.3%–54.9%), with 80.4% of patients (95% CI, 79.0%–81.9%) undergoing intervention for repair. Of individuals who underwent repair, 20.9% (95% CI, 18.6%–23.2%) underwent endovascular repair, with a 26.8% (95% CI, 23.7%–30.0%) postintervention mortality rate, and 79.1% (95% CI, 76.8%–81.4%) underwent open repair, with a 45.6% (95% CI, 43.6%–47.5%) postintervention mortality rate.<sup>78</sup>
- Data from the NIS suggest that the use of endovascular repair of AAAs rose substantially between 2000 and 2010 (5% versus 74% of all AAA repairs, respectively), whereas the overall number of AAAs ( $\approx$ 45 000 per year) remained stable. In-hospital mortality and length of stay declined during this period, but costs rose.<sup>79</sup>
- At least for the first 3 years after elective repair of an AAA, individuals who have endovascular repair may have better outcomes than those who undergo open repair. After multivariable adjustment, Medicare patients who underwent open AAA repair had a higher risk of all-cause mortality (HR, 1.24 [95% CI, 1.05–1.47]), AAA-related mortality (HR, 4.37 [95% CI, 2.51–7.66]), and complications at 1 year than patients who underwent endovascular repair.<sup>80</sup> However, after 8 years of follow-up, survival in the open repair group was similar to that in the endovascular repair group. Of note, individuals in the endovascular repair group had a higher rate of eventual aneurysm rupture (5.4%) than patients who underwent open repair (1.4%).<sup>81</sup> Similar findings were observed in the OVER Veterans Affairs Cooperative trial, which compared open AAA repair to endovascular repair in 881 patients and demonstrated reductions in mortality from endovascular repair at 2 years (HR, 0.63 [95% CI, 0.40–0.98]) and 3 years (HR, 0.72 [95% CI, 0.51–1.00]).<sup>82</sup> However, there was no survival difference between open and endovascular repair in individuals followed up for up to 9 years (mean, 5 years; HR, 0.97 [95% CI, 0.77–1.22]).<sup>82</sup>
- In comparisons of the United States and the United Kingdom, the United States demonstrated

a higher rate of AAA repair, smaller AAA diameter at the time of repair, and lower rates of AAA rupture and AAA-related death.<sup>83</sup>

- In ruptured AAAs, implementation of an endovascular-first protocol was associated with decreased perioperative adverse outcomes and improved long-term prognosis in a retrospective analysis of 88 consecutive patients seen at an academic medical center.<sup>84</sup>
- Perioperative mortality of endovascular aneurysm repair was not related to surgeon case volume but was lower in hospitals with higher volume (eg, 1.9% in hospitals with <10 cases a year versus 1.4% in those with 49–198 cases;  $P<0.01$ ). Perioperative mortality after open repair was inversely related to both surgeon case volume (6.4% in ≤3 cases versus 3.8% in 14–62 cases;  $P<0.01$ ) and hospital case volume (6.3% in ≤5 cases versus 3.8% in 14–62 cases;  $P<0.01$ ).<sup>85</sup>
- The data for surgery in thoracic aortic aneurysms are more mixed between open and endovascular repair. A sample of 12 573 and 2732 Medicare patients who underwent open thoracic aortic aneurysm and endovascular repair from 1998 to 2007 demonstrated higher perioperative mortality for open repair in both intact (7.1% versus 6.1%;  $P=0.56$ ) and ruptured (45% versus 28%;  $P<0.001$ ) thoracic aortic aneurysms but higher 5-year survival rates (70% versus 56%;  $P<0.001$ ).<sup>86</sup> Perioperative mortality rates for open repair of thoracic aortic aneurysms were higher for NH black Medicare patients than for white Medicare patients (14% versus 7%;  $P<0.001$ ), but rates were similar for endovascular repair (7% versus 6%;  $P=0.54$ ).<sup>87</sup> On the basis of data from the NIS (N=1400), weekend repair for thoracic aortic aneurysm rupture (n=322) was associated with higher mortality than weekday repair (n=1078; OR, 2.55 [95% CI, 1.77–3.68]), likely because of delays in surgical intervention.<sup>88</sup>
- Seventeen-year trends in the IRAD database (1996–2013) demonstrate an increase in surgical repair of type A thoracic dissections (from 79% to 90%) and a significant decrease in in-hospital and surgical mortality for type A dissections (from 31% to 22% [ $P<0.001$ ] and from 25% to 18% [ $P=0.003$ ], respectively). Type B dissections were more likely to be treated with endovascular therapies, but no significant changes in mortality were observed.<sup>89</sup>

### Mortality

2017: Mortality—9928. Any-mention mortality—16954.

### Complications

(See Charts 23-7 and 23-8)

- Rates of rupture of small AAAs (3.0–5.4 cm in diameter) range from 0.71 to 11.03 per 1000

person-years, with higher rupture rates in smokers (pooled HR, 2.02 [95% CI, 1.33–3.06]) and females (pooled HR, 3.76 [95% CI, 2.58–5.47];  $P<0.001$ ).<sup>62</sup>

- There is a dose-response association between the diameter and the minimum and maximum risk of AAA rupture per year (Chart 23-7).<sup>90</sup>
- A 2015 systematic review that included 4 randomized trials of ultrasound screening demonstrated lower AAA-associated mortality, emergency operations, and rupture with screening, but with higher AAA-associated elective repair rates; however, there was no effect on all-cause mortality (Chart 23-8).<sup>91</sup> Similar results were reported in a systematic review report prepared for the US Preventive Services Task Force<sup>87</sup> and in a 2016 Swedish study evaluating a nationwide screening program targeting 65-year-old males.<sup>92</sup>
- Data from IRAD demonstrated that the rate of mesenteric malperfusion in 1809 patients with type A acute dissections was 3.7%, with a higher mortality rate than for patients without malperfusion (63.2% versus 23.8%;  $P<0.001$ ).<sup>93</sup>
- Data from IRAD demonstrated that patients with acute type B aortic dissection have heterogeneous in-hospital outcomes. In-hospital mortality in patients with and without complications (such as mesenteric ischemia, renal failure, limb ischemia, or refractory pain) was 20.0% and 6.1%, respectively. In patients with complications, in-hospital mortality associated with surgical and endovascular repair was 28.6% and 10.1% ( $P=0.006$ ), respectively.<sup>94</sup>

### Healthcare Utilization: Hospital Discharges

- In 2016, there were 68 000 hospital discharges with aortic aneurysm as principal diagnoses, of which 49 000 were males and 19 000 were females (HCUP,<sup>57</sup> unpublished NHLBI tabulation).

### Global Burden

(See Table 23-3 and Chart 23-9)

- Global mortality attributable to and prevalence of aortic aneurysm by sex are shown in Table 23-3. The highest age-standardized mortality rates attributable to aortic aneurysm are reported in Northern Europe, southern Latin America, New Zealand, and Fiji (Chart 23-9).

### Atherosclerotic Renal Artery Stenosis

**ICD-9 440.1; ICD-10 I70.1.**

#### Prevalence and Incidence

- A US community-based cohort of older adults (≥65 years of age) reported the prevalence of renal artery disease as 6.8%.<sup>95</sup> Among those with renal

artery stenoses, 88% were unilateral and 12% were bilateral.

- A US study using Medicare data reported that the incidence rate of renal artery stenosis was 3.1 per 1000 patient-years.<sup>96</sup> The incidence of renal artery stenosis increased by ≈5-fold from 1992 to 2004.

### Risk Factors

- Traditional atherosclerotic risk factors such as advanced age, DM, smoking, and hypertension are associated with higher prevalence of atherosclerotic renal artery stenosis.<sup>97</sup>

### Awareness, Treatment, and Control

- The CORAL study compared medical therapy alone versus medical therapy plus renal artery

stenting in patients with atherosclerotic renal artery stenosis and hypertension. Although there was a significant difference in SBP favoring the stent group (−2.3 mm Hg [95% CI, −4.4 to −0.2 mm Hg]), there was no difference in the primary end point of major cardiovascular or kidney event.<sup>98</sup>

### Complications

- Atherosclerotic renal artery stenosis is often a cause of drug-resistant hypertension.<sup>97</sup>
- An Irish study reported that among a total of 3987 patients undergoing coronary angiography, the presence of renal artery stenosis conferred 2 times higher mortality risk.<sup>99</sup>

**Table 23-1. PAD in the United States**

Population Group	Prevalence, 2000, Age $\geq 40$ y	Mortality, 2017, All Ages*	Hospital Discharges, 2016, All Ages
Both sexes	≥6.5 Million	12 805	111 000
Males	2.8 Million	5764 (45.0%)†	66 000
Females	3.7 Million	7041 (55.0%)†	45 000
NH white males	2.1 Million	4594	...
NH white females	3.0 Million	5658	...
NH black males	0.5 Million	696	...
NH black females	0.1 Million	811	...
Hispanic males	0.1 Million	333	...
Hispanic females	0.1 Million	364	...
NH Asian or Pacific Islander males	...	99‡	...
NH Asian or Pacific Islander females	...	140‡	...
NH American Indian/Alaska Native	...	61	...

Ellipses (...) indicate data not available; NH, non-Hispanic; and PAD, peripheral artery disease.

\*Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total mortality attributable to PAD that is for males vs females.

‡Includes Chinese, Filipino, Hawaiian, Japanese, and Other Asian or Pacific Islander.

Sources: Prevalence: Data derived from Allison et al.<sup>1</sup> Prevalence of PAD is based on an ankle-brachial index <0.9 or a previous revascularization for PAD. Mortality: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Vital Statistics System, 2017.<sup>100</sup> Hospital Discharges: Unpublished NHLBI tabulation using Hospital Cost and Utilization Project, 2017.<sup>57</sup>

**Table 23-2.** Global Mortality From and Prevalence of PAD by Sex, 2017

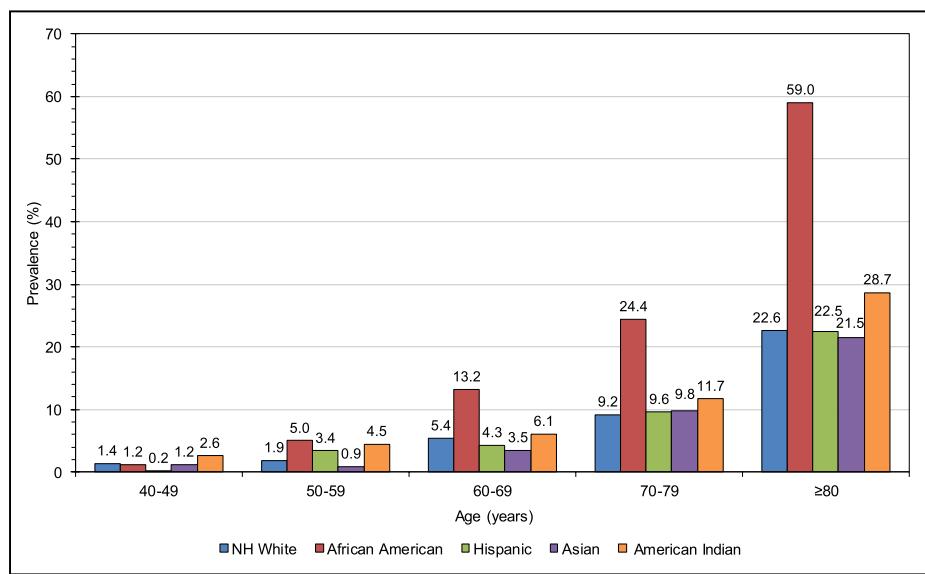
	Both Sexes Combined		Males		Females	
	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)	Death (95% UI)	Prevalence (95% UI)
Total number (millions)	0.1 (0.0 to 0.1)	118.1 (102.7 to 134.4)	0.0 (0.0 to 0.1)	53.1 (46.1 to 60.7)	0.0 (0.0 to 0.1)	65.0 (56.7 to 73.8)
Percent change total number, 2007 to 2017	55.7 (31.0 to 74.2)	30.0 (29.1 to 30.8)	55.6 (27.1 to 72.6)	29.9 (28.8 to 30.9)	55.8 (25.6 to 79.9)	30.1 (29.2 to 30.9)
Percent change total number, 1990 to 2017	251.2 (118.8 to 411.1)	91.5 (90.1 to 93.0)	236.8 (89.7 to 361.1)	94.3 (92.2 to 96.6)	265.7 (100.5 to 483.2)	89.2 (87.6 to 90.8)
Rate per 100 000	1.0 (0.6 to 1.7)	1,480.4 (1290.2 to 1681.9)	1.1 (0.6 to 2.0)	1,438.5 (1251.7 to 1637.9)	0.8 (0.4 to 1.9)	1,520.0 (1326.0 to 1727.2)
Percent change rate, 2007 to 2017	10.5 (−6.8 to 24.1)	−1.7 (−2.2 to −1.2)	11.1 (−8.7 to 23.8)	−2.3 (−3.0 to −1.7)	10.2 (−11.1 to 27.4)	−1.1 (−1.7 to −0.6)
Percent change rate, 1990 to 2017	50.3 (−6.3 to 117.8)	−5.5 (−6.1 to −4.9)	45.6 (−19.0 to 99.8)	−6.4 (−7.2 to −5.6)	53.1 (−16.2 to 143.6)	−4.9 (−5.5 to −4.2)

PAD indicates peripheral artery disease; and UI, uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>60</sup> Printed with permission. Copyright © 2018, University of Washington.**Table 23-3.** Global Mortality From and Prevalence of Aortic Aneurysm by Sex, 2017

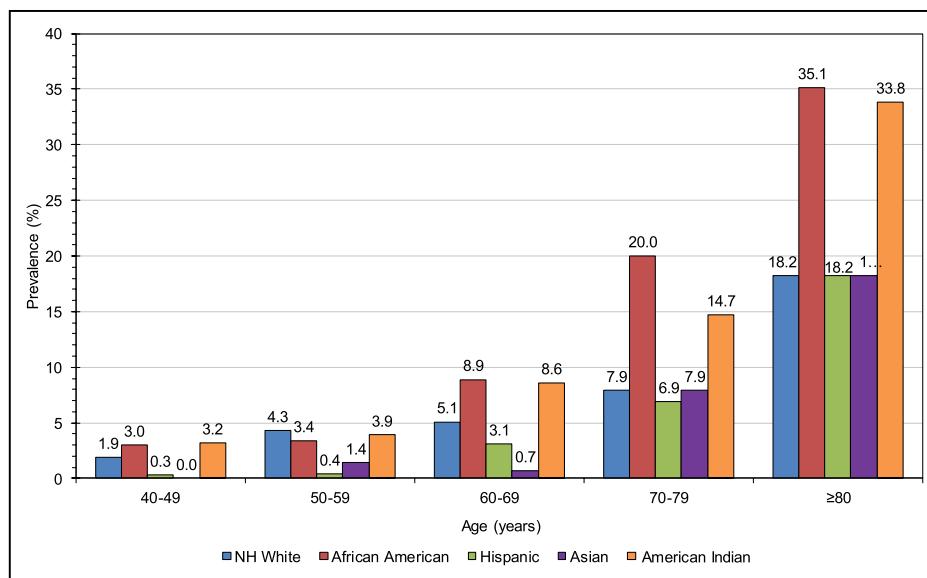
	Both Sexes (95% UI)	Males (95% UI)	Females (95% UI)
Total number (millions)	0.2 (0.2 to 0.2)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)
Percent change total number, 1990 to 2017	59.6 (52.2 to 66.1)	53.3 (45.5 to 61.8)	71.8 (60.1 to 81.7)
Percent change total number, 2007 to 2017	23.7 (19.9 to 27.6)	22.0 (17.5 to 27.0)	26.8 (22.2 to 30.7)
Rate per 100 000	2.2 (2.1 to 2.3)	3.1 (3.0 to 3.4)	1.4 (1.4 to 1.5)
Percent change rate, 2007 to 2017	−8.5 (−11.2 to −5.8)	−10.5 (−13.6 to −7.0)	−6.6 (−10.0 to −3.8)
Percent change rate, 1990 to 2017	−24.1 (−27.4 to −21.4)	−28.9 (−32.3 to −25.4)	−19.4 (−24.7 to −15.0)

UI indicates uncertainty interval.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>60</sup> Printed with permission. Copyright © 2018, University of Washington.**Chart 23-1.** Estimates of prevalence of peripheral artery disease in males by age and ethnicity, United States, 2000.

NH indicates non-Hispanic.

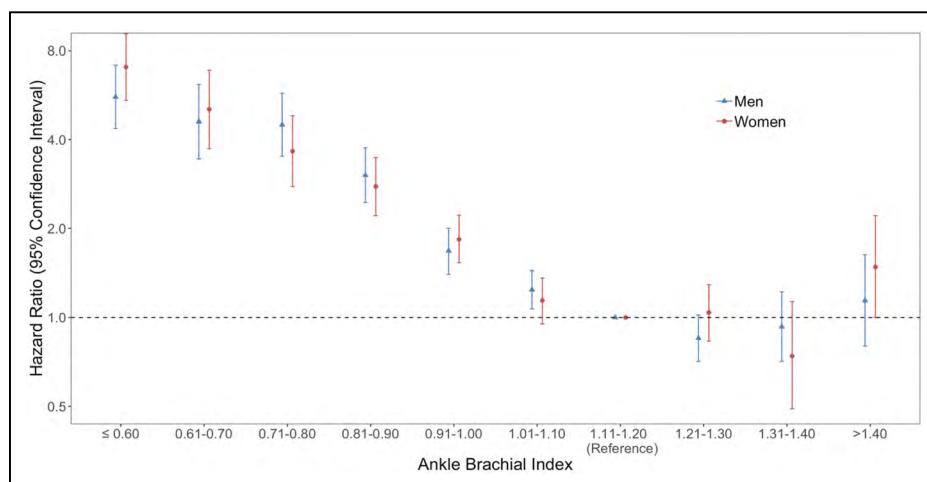
Source: Data derived from Allison et al.<sup>1</sup>



**Chart 23-2. Estimates of prevalence of peripheral artery disease in females by age and ethnicity, United States, 2000.**

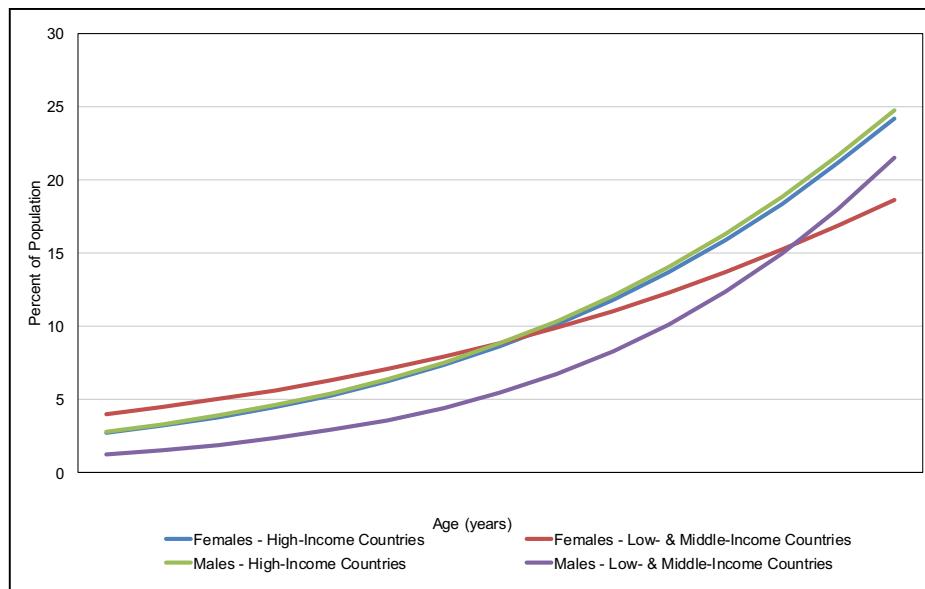
NH indicates non-Hispanic.

Source: Data derived from Allison et al.<sup>1</sup>



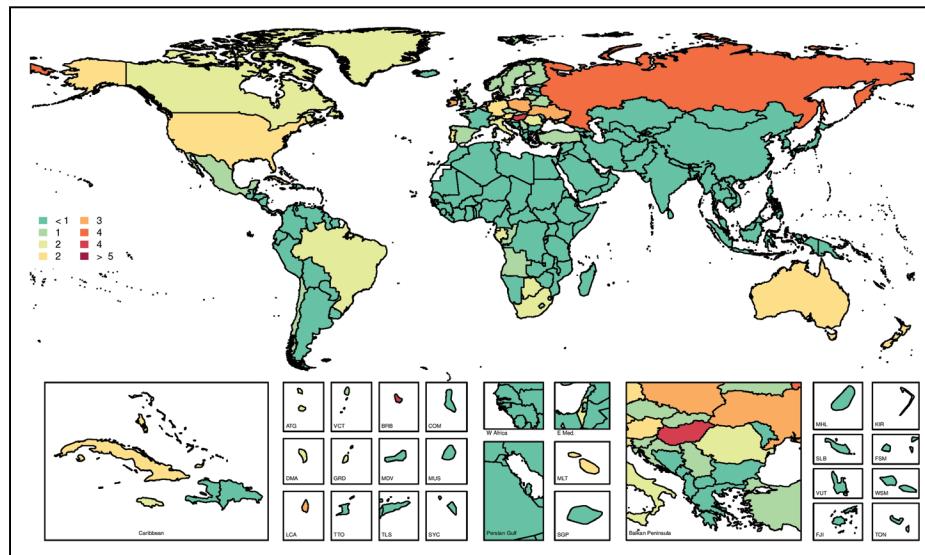
**Chart 23-3. Hazard ratios of global cardiovascular mortality with 95% CI by ankle-brachial index categories, 1976 to 2000 (baseline years).**

Source: Data derived from Fowkes et al.<sup>38</sup>



**Chart 23-4. Global prevalence of peripheral artery disease by age in males and females in high-income countries and low-income or middle-income countries, 1995 to 2009.**

Source: Adapted from *The Lancet* (Fowkes et al<sup>8</sup>) with permission from Elsevier. Copyright © 2013, Elsevier Ltd.

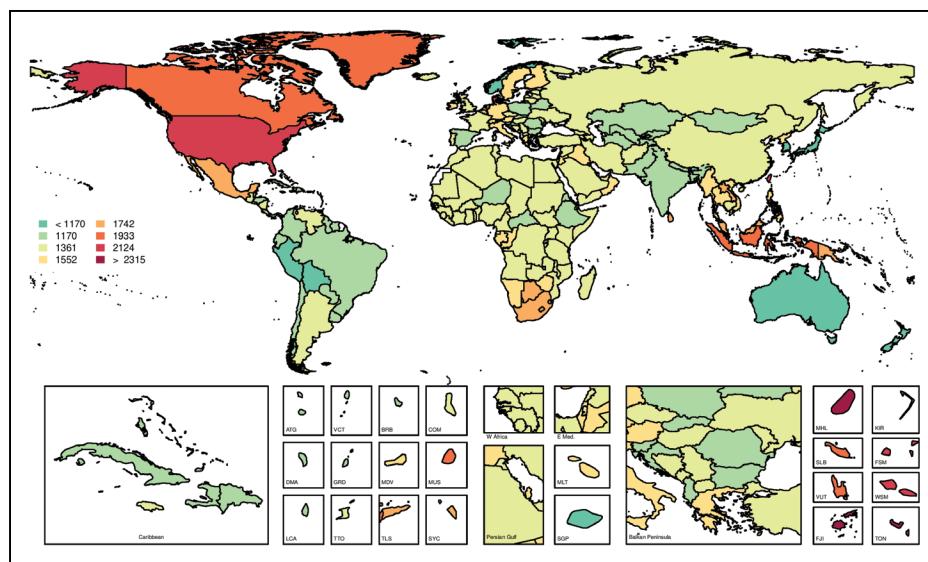


**Chart 23-5. Age-standardized mortality rates of peripheral artery disease per 100 000, both sexes, 2017.**

Peripheral artery disease mortality is highest in Eastern Europe.

Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>60</sup> Printed with permission. Copyright © 2018, University of Washington

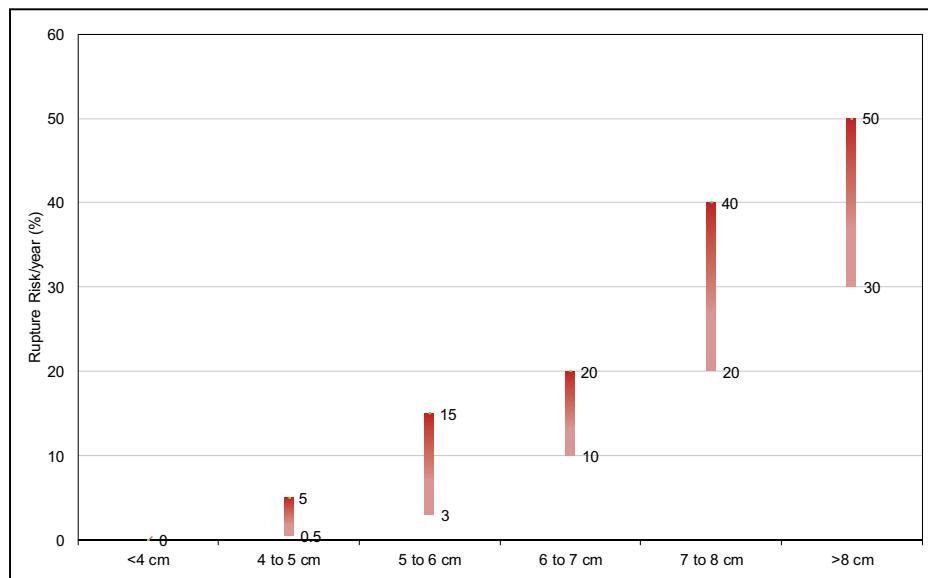


**Chart 23-6. Age-standardized prevalence of peripheral artery disease per 100 000, both sexes, 2017.**

Peripheral artery disease prevalence is highest in North America, Southeast Asia, and Oceania.

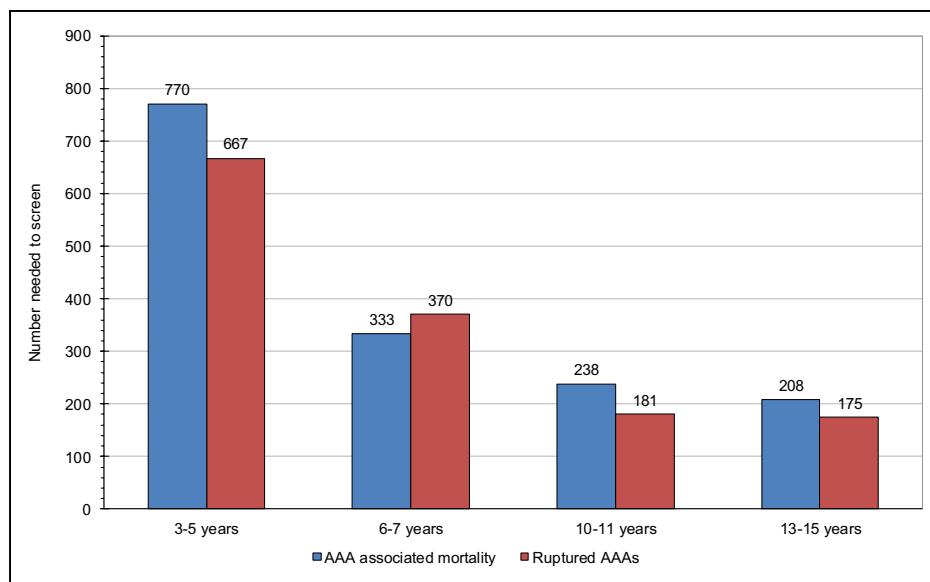
Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TON, Tonga; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>60</sup> Printed with permission. Copyright © 2018, University of Washington



**Chart 23-7. Association between diameter and minimum and maximum risk of abdominal aortic aneurysm rupture per year.**

Source: Data derived from Brewster et al.<sup>90</sup>

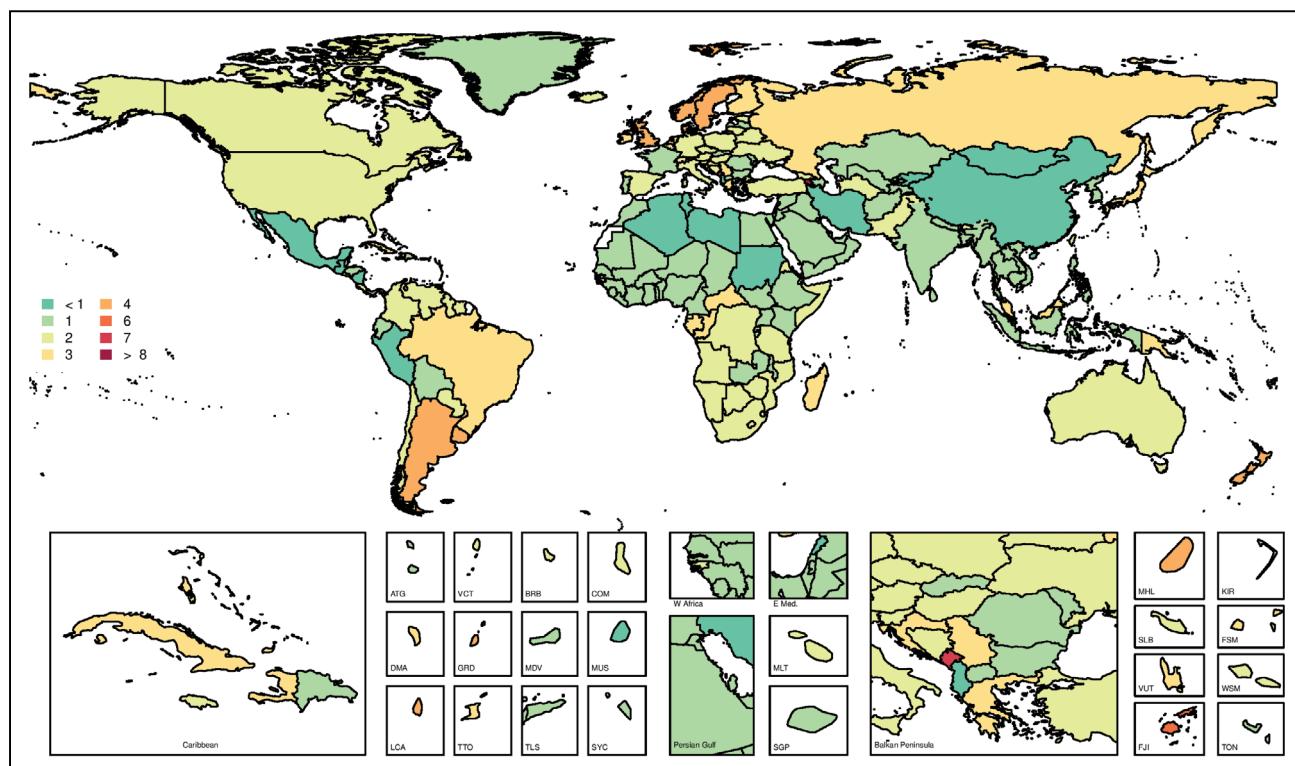


**Chart 23-8. Numbers needed to screen to avoid an AAA-associated death and a ruptured AAA, 1988 to 1999 (baseline years) with average follow-up of 4 to 15 years.**

Global data.

AAA indicates abdominal aortic aneurysm.

Source: Data derived from Eckstein et al.<sup>91</sup>



**Chart 23-9. Age-standardized mortality rates of aortic aneurysm per 100 000, both sexes, 2017.**

The highest age-standardized mortality rates attributable to aortic aneurysm are reported in Northern Europe, Southern Latin America, New Zealand, and Fiji. Country codes: ATG, Antigua and Barbuda; BRB, Barbados; COM, Comoros; DMA, Dominica; E Med., Eastern Mediterranean; FJI, Fiji; FSM, Federated States of Micronesia; GRD, Grenada; KIR, Kiribati; LCA, Saint Lucia; MDV, Maldives; MHL, Marshall Islands; MLT, Malta; MUS, Mauritius; SGP, Singapore; SLB, Solomon Islands; SYC, Seychelles; TLS, Timor-Leste; TTO, Trinidad and Tobago; VCT, Saint Vincent and the Grenadines; VUT, Vanuatu; W Africa, West Africa; and WSM, Samoa.

Source: Data derived from Global Burden of Disease Study 2017, Institute for Health Metrics and Evaluation, University of Washington.<sup>60</sup> Printed with permission. Copyright © 2018, University of Washington.

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## 24. QUALITY OF CARE

See Tables 24-1 through 24-9

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The Institute of Medicine defines quality of care as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge,”<sup>1</sup> identifying 6 specific domains for improving health care: safety, effectiveness, patient or people-centeredness, timeliness, efficiency, and equity.

### Abbreviations Used in Chapter 24

ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
AVAIL	Adherence Evaluation After Ischemic Stroke Longitudinal
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CHA <sub>2</sub> DS <sub>2</sub> -VASc	Clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, diabetes mellitus, and sex (1 point each); age ≥75 y and stroke/transient ischemic attack/thromboembolism (2 points each); plus history of vascular disease, age 65–74 y, and (female) sex category
CHD	coronary heart disease
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
CPR	cardiopulmonary resuscitation
CVD	cardiovascular disease
DM	diabetes mellitus
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ECG	electrocardiogram
ED	emergency department
EMS	emergency medical services
ERR	excess readmission ratio
GLORIA-AF	Global Registry on Long-term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation
GWTG	Get With The Guidelines
HbA <sub>1c</sub>	hemoglobin A <sub>1c</sub> (glycosylated hemoglobin)
HF	heart failure
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HMO	health maintenance organization
HR	hazard ratio
HRRP	Hospital Readmissions Reduction Program
ICD-10	<i>International Classification of Diseases, 10th Revision</i>
IHCA	in-hospital cardiac arrest
IQR	interquartile range
IV	intravenous
LDL-C	low-density lipoprotein cholesterol

(Continued)

### Abbreviations Used in Chapter 24 Continued

LV	left ventricular
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MEPS	Medical Expenditure Panel Survey
MI	myocardial infarction
N/A	not available or not applicable
NCDR	National Cardiovascular Data Registry
NIHSS	National Institutes of Health Stroke Scale
NIS	National (Nationwide) Inpatient Sample
NSTEMI	non-ST-segment-elevation myocardial infarction
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
PA	physical activity
PCI	percutaneous coronary intervention
PINNACLE	Practice Innovation and Clinical Excellence
PPO	preferred provider organization
RR	relative risk
RSMR	risk-standardized mortality rate
SES	socioeconomic status
STEMI	ST-segment-elevation myocardial infarction
TIA	transient ischemic stroke
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist
tPA	tissue-type plasminogen activator
UA	unstable angina
UFH	unfractionated heparin

Assessing care quality requires the development and implementation of performance measures, explicit standards or metrics of care against which care delivery can be judged.<sup>2</sup> This differs from guidelines, which provide clinical recommendations to inform usual clinical scenarios but ultimately leave decisions to reasonable clinician discretion. Measuring performance requires a robust process for data collection across care facilities and clinicians, data transfer, analysis, and dissemination.

Over the past decades, clinical registries in the United States and worldwide have helped to better understand and improve quality, performance, and outcomes. Early registries focused on the inpatient setting (MI, HF, stroke) or discrete procedures (PCI, defibrillator implantation, peripheral vascular interventions, cardiothoracic surgery). In the United States, these have been principally run by the ACC's NCDR<sup>3</sup> and the AHA's GWTG Program.<sup>4</sup> Elective procedural registries were also developed by the AHA and ACC, such as those for AF ablation and left atrial appendage occlusion. Additionally, outpatient registries such as the ACC's PINNACLE Registry use electronic health record data transfer rather than case report form data entry to examine performance measures across a wide range of cardiovascular conditions. Increasingly, outpatient post-marketing registries have been sponsored by pharmaceutical or device companies and managed by contract research organizations, such as for anticoagulation in AF. Finally, medical claims data from payers (Medicare,

commercial claims) or integrated healthcare systems (Veterans Affairs) have also examined quality.

In the following sections, data on quality of care will be presented across these 6 domains, grouped by disease or therapeutic area. Where possible, data are reported from recently published literature or as standardized quality indicators drawn from quality-improvement registries whose methods are consistent with performance measures endorsed by the ACC and the AHA.<sup>2,5,6</sup>

Additional data on adherence to ACC/AHA clinical practice guidelines are also included to supplement performance measures data. The select data presented are meant to provide illustrative examples of quality of care and are not meant to be comprehensive given the sheer volume of quality data published each year.

## Acute Myocardial Infarction (See Tables 24-1 through 24-4)

- The ACC's Chest Pain – MI Registry (formerly the ACTION Registry)<sup>7</sup> is currently the largest US-based hospital registry of inpatient AMI care (Tables 24-1 through 24-4).
- Wadhera and colleagues<sup>5</sup> examined a large cohort of Medicare beneficiaries with 642 105 index hospitalizations for AMI and showed that higher 30-day payments were associated with lower 30-day mortality after adjustment for patient characteristics and comorbidities (adjusted OR for additional \$1000 payments, 0.986 [95% CI, 0.979–0.992];  $P<0.001$ ). This could have implications for payment programs incentivizing reduction in payments without considering value.
- The association of state Medicaid expansion with quality of AMI care and outcomes was investigated in 55 737 low-income patients <65 years of age across 765 sites using NCDR data from January 1, 2012, to December 31, 2016.<sup>8</sup> During this study period, Medicaid coverage increased from 7.5% to 14.4% in expansion states, compared with 6.2% to 6.6% in nonexpansion states ( $P<0.001$ ). In expansion compared with nonexpansion states, there was no change in use of procedures such as PCI for NSTEMI, and delivery of defect-free care increased to a lesser extent in expansion states. In-hospital mortality improved to a similar extent in expansion and nonexpansion states: 3.2% to 2.8% (adjusted OR, 0.93 [95% CI, 0.77–1.12]) versus 3.3% to 3.0% (adjusted OR, 0.85 [95% CI, 0.73–0.99];  $P_{\text{interaction}}=0.48$ ).
- Chatterjee and Joynt Maddox<sup>6</sup> examined patterns in 30-day mortality from AMI in relation to public outcome reporting from 2009 to 2015 across 2751 hospitals. They showed that 30-day mortality was highest among baseline poor performers (worst quartile in 2009 and 2010 in public reporting, before value-based payment) but improved more over time compared with other hospitals (from 18.6% in 2009 to 14.6% in 2015 [ $-0.74\%$  per year;  $P<0.001$ ] versus from 15.7% in 2009 to 14.0% in 2015 [ $-0.26\%$  per year;  $P<0.001$ ];  $P_{\text{interaction}}<0.001$ ).
- Examining hospitals with higher-than-expected risk-adjusted 30-day readmission rates ( $\text{ERR}>1$ ) after AMI, Pandey and colleagues<sup>9</sup> showed that risk-adjusted 30-day readmission rates were not associated with in-hospital quality of AMI care (adjusted OR, 0.94 [95% CI, 0.81–1.08] per 0.1-unit increase in AMI ERR for overall defect-free care). Among 51 453 patients with 1-year outcomes data, higher AMI ERR was associated with higher all-cause readmission within 1 year of discharge; however, this association was largely driven by readmissions early after discharge and was not significant in landmark analyses beginning 30 days after discharge. The AMI ERR was not associated with risk for mortality within 1 year of discharge.
- In 119 735 patients with AMI who were admitted to 1824 hospitals, Bucholz and colleagues<sup>10</sup> showed that patients admitted to high-performing hospitals after AMI had longer life expectancies than patients treated at low-performing hospitals. This signal appeared in the first 30 days and persisted over 17 years of follow-up. Patients treated at high-performing hospitals lived on average 0.74 to 1.14 years longer than patients treated at low-performing hospitals.
- Makam and Nguyen<sup>11</sup> showed cardiac biomarker testing in the ED is common even among those without symptoms suggestive of ACS. Biomarker testing occurred in 8.2% of visits in the absence of symptoms related to ACS, representing 8.5 million visits. Among individuals who were subsequently hospitalized, cardiac biomarkers were tested in 47% of all visits. Biomarkers were tested in 35.4% of visits in this group despite the absence of ACS-related symptoms.
- If patients who have cardiac biomarker testing without ACS symptoms are misclassified as having AMI, this could have negative implications for value-based programs focused on AMI care. A single-center study by McCarthy et al<sup>12</sup> of 633 patients spanning 2017 to 2018 examined whether patients with nonischemic myocardial injury may be miscoded as having type 2 MI (demand ischemia) using the new ICD-10 system. After adjudication using the fourth universal definition of MI, 56.7% had type 2 MI, 41.9% had myocardial injury, 0.9% had type 1 MI, and 0.5% had UA. Patients with type 2 MI and patients with

myocardial injury each had high 30-day readmission and mortality rates.

- The CMS and Hospital Quality Alliance started to publicly report 30-day mortality measures for AMI and HF in 2007, subsequently expanding to include 30-day readmission rates. According to national Medicare data from July 2015 through June 2016, the median (IQR) hospital RSMR for MI was 13.1% (12.6%, 13.5%), and the median (IQR) risk-standardized 30-day readmission rate was 15.8% (15.5%, 16.2%).<sup>13</sup>
- Mathews and colleagues<sup>14</sup> examined post-MI medication adherence as a hospital-level variable using data from 347 US hospitals participating in the ACTION Registry—GWTG. They observed that postdischarge use of secondary prevention medications varied significantly across US hospitals and was inversely associated with 2-year outcomes at the hospital level.
- Two recent studies examined the association of the HRRP with mortality among Medicare fee-for-service beneficiaries ≥65 years of age and hospitalized with AMI.
  - The study by Khera et al<sup>15</sup> spanned 2006 to 2014 and included 1.7 million hospitalizations for AMI. Before the HRRP announcement, monthly postdischarge mortality was stable for AMI (slope for monthly change, 0.002% [95% CI, -0.001% to 0.006% per month]), with no change inflection in slope around HRRP announcement or implementation ( $P>0.05$ ). In-hospital mortality decreased for AMI from 10.4% to 9.7%, and 30-day postdischarge mortality decreased from 7.4% to 7.0% ( $P$  for trend<0.001).
  - The study by Wadhera et al<sup>16</sup> spanned 2005 to 2015 and included 1.8 million hospitalizations for AMI. Evaluating outcomes in relation to announcement and implementation of the HRRP, the study evaluated 4 time periods. Periods 1 and 2 were before the HRRP: April 2005 to September 2007 and October 2007 to March 2010. Periods 3 and 4 were after HRRP announcement (April 2010 to September 2012) and HRRP implementation (October 2012 to March 2015). The HRRP announcement was associated with a reduction in 30-day postdischarge mortality in patients with AMI (0.18% pre-HRRP increase versus 0.08% post-HRRP announcement decrease; difference in change, -0.26%;  $P=0.01$ ) and did not significantly change after HRRP implementation.
- A 20-year evaluation from January 1, 1995, to December 31, 2014, evaluated AMI outcomes in older adults.<sup>17</sup> The sample included 4367485

Medicare fee-for-service beneficiaries ≥65 years of age cared for at 5680 US hospitals. The rate of AMI hospitalization decreased from 914 to 566 per 100 000 beneficiary-years, with improvements in 30-day mortality from 20.0% to 12.4%, 30-day all-cause readmissions from 21.0% to 15.3%, and 1-year recurrent AMI from 7.1% to 5.1%.

## Heart Failure (See Tables 24-5 and 24-6)

- Current US HF quality data are best captured by the widespread but voluntary GWTG–HF program (Tables 24-5 and 24-6).
- In a study based on the GWTG–HF program linked with Medicare data, the association between 30-day readmission rates and 3-year mortality and median survival was not significant at the hospital level. The HR for 3-year mortality comparing the top and bottom quartiles for readmission was 0.9 (95% CI, 0.90–1.01), whereas median survival time was highest for the bottom quartile.<sup>18</sup>
- In an evaluation of the validity of use of hospital volume as a structural metric for quality of HF care, Kumbhani and colleagues<sup>19</sup> examined the relationship between admission volume, process-of-care metrics, and short- and long-term outcomes in patients admitted with acute HF in the GWTG–HF registry with linked Medicare inpatient data. In their cohort of 125 595 patients at 342 hospitals, they found that hospital volume correlated with process measures but not with 30-day outcomes and only marginally with outcomes up to 6 months of follow-up. Lower-volume hospitals were significantly less likely to be adherent to HF process measures than higher-volume hospitals. On multivariable modeling, higher hospital volume was not associated with a difference in the in-hospital mortality (OR, 0.99 [95% CI, 0.94–1.05];  $P=0.78$ ), 30-day mortality (HR, 0.99 [95% CI, 0.97–1.01];  $P=0.26$ ), or 30-day readmissions (HR, 0.99 [95% CI, 0.97–1.00];  $P=0.10$ ).
- In a national cohort study including 241 533 patients admitted with HF at all 591 acute care institutions in Canada, authors found inverse associations between in-patient mortality and hospital volume, with 11.3% mortality in low-volume centers versus 17.3% in high-volume centers, with an adjusted OR of 0.90 (95% CI, 0.80–1.00) and with a similar trend for 30-day readmissions (OR, 0.91 [95% CI, 0.85–0.97]).<sup>20</sup>
- Gupta and colleagues<sup>21</sup> examined the association of the HRRP with readmission and mortality outcomes among patients hospitalized with HF. Among a cohort of 115 245 fee-for-service Medicare beneficiaries discharged after HF

hospitalizations, the 1-year risk-adjusted readmission rate declined from 57.2% to 56.3% (HR, 0.92 [95% CI, 0.89–0.96]), and the 1-year risk-adjusted mortality rate increased from 31.3% to 36.3% (HR, 1.10 [95% CI, 1.06–1.14]) after the HRRP implementation.

- However, in an interrupted time-series analysis of the HRRP evaluating the changes in slope for HF-related mortality from 2006 to 2014, no significant increase in in-hospital mortality was noted, despite a reduction in readmissions after HRRP implementation.<sup>15</sup>
- In a longitudinal cohort study of 48 million hospitalizations among 20 million Medicare fee-for-service patients across 3497 hospitals, Desai and colleagues<sup>22</sup> showed that patients at hospitals subject to penalties under the HRRP had greater reductions in readmission rates than those at non-penalized hospitals. Reductions in readmission rates were greater for target versus nontarget conditions for patients at the penalized hospitals but not at nonpenalized hospitals.
- Chatterjee and Joynt-Maddox<sup>6</sup> examined patterns in 30-day mortality from HF as they relate to public reporting of these outcomes. In data from 2009 to 2015 from 3796 hospitals with publicly reported mortality data for HF, they showed baseline poor performers (worst quartile in 2009 and 2010 in public reporting, before value-based payment) improved over time (from 13.5% to 13.0%; −0.12% per year;  $P<0.001$ ), but mean mortality among all other HF hospitals increased during the study period (from 10.9% to 12.0%; 0.17% per year;  $P<0.001$ ,  $P_{\text{interaction}}<0.001$ ).
- Yet another evaluation of the HRRP among Medicare beneficiaries suggested an increase in 30-day mortality after hospitalization after HF but no association between HRRP and mortality within 45 days of admission. The authors concluded that further research is needed to better understand whether the increase in 30-day mortality is related to the implementation of the HRRP.<sup>16</sup>
- In a secondary analysis of the TOPCAT and HF-ACTION trials focused on patient-reported outcomes, Pokharel and colleagues<sup>23</sup> observed that the most recent of a series of Kansas City Cardiomyopathy Questionnaire scores was most strongly associated with subsequent death and cardiovascular hospitalization.
- Among 106 304 patients hospitalized with HF at 317 centers in the GWTG-HF registry, there was a graded inverse association between 30-day RSMR and long-term mortality (quartile 1 versus quartile 4: 5-year mortality, 73.7% versus 76.8%). Lower hospital-level 30-day RSMR was associated with greater 1-, 3-, and 5-year survival for patients with

HF. These differences in 30-day survival continued to accrue beyond 30 days and persisted long term, which suggests that 30-day RSMR could be a useful HF performance metric.<sup>24</sup>

- Pandey et al<sup>9</sup> reported results from the GWTG-HF registry evaluating the association between HF ERR and performance measures, as well as in-hospital and 1-year clinical outcomes. They stratified participating centers into groups with low (HF ERR ≤1) versus high (HF ERR >1) risk-adjusted readmission rates. There were no differences between the low and high risk-adjusted 30-day readmission groups in median adherence rate to all performance measures (95.7% versus 96.5%,  $P=0.37$ ) or median percentage of defect-free care (90.0% versus 91.1%,  $P=0.47$ ). The composite 1-year outcome of death or all-cause readmission rates was also not different between the 2 groups (median 62.9% versus 65.3%;  $P=0.10$ ). The high HF ERR group had higher 1-year all-cause readmission rates (median 59.1% versus 54.7%;  $P=0.01$ ); however, 1-year mortality rates were lower among the high versus low group, with a trend toward statistical significance (median 28.2% versus 31.7%;  $P=0.07$ ). The authors concluded that the quality of care and clinical outcomes were comparable among hospitals with high versus low risk-adjusted 30-day HF readmission rates.
- According to national Medicare data from July 2015 through June 2016, the median (IQR) hospital RSMR for HF was 11.6% (10.8%, 12.4%), and the median (IQR) risk-standardized 30-day readmission rate was 21.4% (20.8%, 22.1%).<sup>13</sup>
- Krumholz and colleagues<sup>25</sup> examined readmission outcomes among patients who had multiple admissions at >1 hospital within a given year to attempt to separate hospital from patient effects. They found the observed readmission rate to be consistently higher among patients admitted to hospitals in a worse-performing quartile than among those admitted to hospitals in a better-performing quartile, but the only statistically significant difference was observed when one was in the best-performing quartile and the other was in the worst (absolute difference in readmission rate 2.0 percentage points [95% CI, 0.4–3.5]).
- In a Medicare cohort comprising almost 3 million admissions for HF and 1.2 million for MI, Dharmarajan and colleagues<sup>26</sup> studied the association between changes in hospital readmission rates and changes in mortality rates. They observed that among Medicare fee-for-service beneficiaries hospitalized for HF and AMI, reductions in hospital 30-day readmission rates were weakly but significantly correlated with reductions in hospital 30-day mortality rates after discharge.

- Home time after admission for HF may be calculated as the time spent alive outside a hospital, skilled nursing facility, or rehabilitation facility after discharge. In a study using GWTG-HF data between 2011 and 2014, home time 30 days and 1-year after discharge was highly correlated with survival and survival free from HF readmissions.<sup>27</sup>
- In the GWTG-HF registry, discharge to hospice after HF admissions increased from 2.0% in 2005 to 4.9% in 2014. For individuals discharged to hospice, the median postdischarge survival was 11 days, with 34.1% mortality within 3 days and a 15.0% survival after 6 months. Among those discharged to hospice, the readmission rate (4.1%) was significantly lower than for other patients with advanced HF (27.2%) or other HF in the registry (22.2%).<sup>28</sup>

## Prevention and Risk Factor Modification (See Table 24-7)

- The National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set consists of established measures of quality of care related to CVD prevention in the United States (Table 24-7).<sup>29</sup>
- Pokharel and colleagues<sup>30</sup> examined practice-level variation in statin therapy among patients 40 to 75 years of age with DM and no CVD between May 2008 and October 2013 from the ACC's PINNACLE Registry. Among 215 193 patients (582 048 encounters) from 204 cardiology practices, statins were prescribed in 61.6% of patients with DM. Among 182 practices with ≥30 patients with DM, the median practice statin prescription rate was 62.3%, with no noticeable change over time. There was a 57% practice-level variation in statin use for 2 similar patients that was not affected by adjustment for patient-related variables, which suggests that practice- or clinician-related factors primarily determined variation in statin use.
- Using data from the PINNACLE Registry, Hira and colleagues<sup>31</sup> showed that among 27 533 patients receiving prasugrel, 13.9% (n=3824) had a contraindication to prasugrel use (ie, history of TIA or stroke). This was considered inappropriate prasugrel use. A further 4.4% of patients (n=1210) were receiving it for a nonrecommended indication (>75 years of age without history of DM or MI or weight <60 kg). Both inappropriate and nonrecommended prasugrel use showed wide practice-level variation (median rate ratio of 2.89 [95% CI, 2.75–3.03] and 2.29 [95% CI, 2.05–2.51], respectively).
- In an analysis from the PINNACLE Registry, Hira and colleagues<sup>32</sup> showed that among 68 808 patients receiving aspirin therapy for primary prevention, roughly 11.6% (7972 of 68 808) were receiving

inappropriate therapy (10-year risk of CVD <6%). There was significant practice-level variation in inappropriate aspirin use (range, 0%–71.8%; median, 10.1%; IQR, 6.4%) for practices with an adjusted median rate ratio of 1.63 (95% CI, 1.47–1.77).

- Using aspirin dosing data from 221 199 patients with MI enrolled in the ACTION Registry-GWTG, Hall and colleagues<sup>33</sup> showed a 25-fold variation in the use of high-dose aspirin (325 mg/d) across participating centers. Overall, 60.9% of patients were discharged on high-dose aspirin. High-dose aspirin was prescribed to 73% of patients treated with PCI and 44.6% of patients managed medically; 56.7% of patients with an in-hospital bleeding event were also discharged on high-dose aspirin. Among 9075 patients discharged on aspirin, thienopyridine, and warfarin, 44.0% were prescribed high-dose aspirin therapy. Given the increased risk of bleeding with high-dose aspirin and its unclear benefit, these findings may have implications for future quality improvement efforts.
- Data from the PINNACLE Registry showed that among 156 145 patients with CAD in 58 practices, just over two-thirds (n=103 830, or 66.5%) of patients were prescribed the optimal combination of medications ( $\beta$ -blockers, ACE inhibitors or angiotensin receptor blockers, statins) for which they were eligible. After adjustment for patient factors, the practice median rate ratio for prescription was 1.25 (95% CI, 1.20–1.32), which indicates a 25% likelihood that any 2 practices would differ in treating identical CAD patients.<sup>34</sup>
- Using data from MEPS, Salami and colleagues<sup>35</sup> described trends in statin use and related out-of-pocket expense from 2002 to 2013. Although statin use increased overall and among those with established ASCVD, use in higher-risk groups was suboptimal. Statin use was significantly lower in females (OR, 0.81 [95% CI, 0.79–0.85]) and racial/ethnic minorities (OR, 0.65 [95% CI, 0.61–0.70]). Gross domestic product-adjusted total cost for statins decreased from \$17.2 billion (out-of-pocket cost, \$7.6 billion) in 2002 to 2003 to \$16.9 billion (out-of-pocket cost, \$3.9 billion) in 2012 to 2013, and the mean annual out-of-pocket costs for patients decreased from \$348 to \$94.

## Atrial Fibrillation

- Of all CVD, AF may have the largest quantity of registries, with at least 10 non-industry-funded and 6 industry-funded registries.<sup>36</sup> These largely emerged after the introduction of DOACs, and performance measures and use of anticoagulation have been a major focus.
- In 2016, the ACC and AHA revised the clinical performance and quality measures for AF and atrial

flutter.<sup>37</sup> The 3 pairs of inpatient and outpatient performance measures include documentation of CHA<sub>2</sub>DS<sub>2</sub>-VASc score, oral anticoagulant prescription, and planned or monthly international normalized ratio testing for warfarin. The 18 quality measures reflect metrics for appropriate medications for comorbidities (HF), inappropriate prescription of specific anticoagulant drugs and antiarrhythmic drugs in specific clinical scenarios, and documentation of shared decision making.

- Over the past decade, the proportion of patients with AF receiving oral anticoagulants has increased from ~67% to >80%.<sup>36</sup> The highest uptake is reported in US and European registries (90%) and the lowest in Asia (58%). However, methodological factors are likely a major source of difference in estimates, including selection bias of both numerator and denominator (patient, clinician, site, and in some registries, requirement of informed consent), patient characteristics, and oral anticoagulant ascertainment methodology. For example, in the outpatient, electronic health record-based PINNACLE-AF US registry, oral anticoagulant prescription for those with CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2 in 2014 was 48%. In the industry-funded, informed-consent, postmarketing GLORIA-AF international registry, oral anticoagulant prescription between 2011 and 2014 was 80%.<sup>38</sup> The AHA GWTG-AF program has been designed to track the 2016 performance measures.<sup>39</sup> An analysis of data from the AHA GWTG-AF program examined prescription of oral anticoagulation therapy at discharge in 33 235 patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2 hospitalized for AF at one of 115 sites from 2013 to 2017. Oral anticoagulation use increased consistently over time, and there was a high level of adherence, with 93.5% of eligible patients without contraindications being prescribed oral anticoagulation therapy for stroke prevention in AF.<sup>40</sup>
- Potential overuse in low-risk patients remains a concern, with oral anticoagulants administered to AF patients with no stroke risk factors.<sup>36</sup> Methodological limitations of comorbidity ascertainment could lead to overestimation of overuse.
- Inappropriate use of aspirin for patients at moderate to high risk of stroke remains a concern. In PINNACLE-AF, which examined the use of aspirin rather than guideline-recommended oral anticoagulants for patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2, 40% of patients were treated with aspirin alone, and this was influenced by CHD comorbidities.<sup>41</sup>
- Treating specialty can influence likelihood of therapy and resultant outcomes. In the Veterans Health Administration, the largest integrated healthcare system in the United States, provision of cardiology outpatient care within 90 days of newly diagnosed

AF was associated with a reduced adjusted risk of stroke (HR, 0.91 [95% CI, 0.86–0.96]) and death (HR, 0.89 [95% CI, 0.88–0.91]), although with an increased risk of arrhythmia-related hospitalization (HR, 1.38 [95% CI, 1.35–1.42]).<sup>42</sup> This finding was statistically mediated by an increase in 90-day oral anticoagulant prescription.

### Other Treatments

Data from AHA GWTG-AF on use of rate versus rhythm control, appropriate and inappropriate use of antiarrhythmic drugs, and procedural factors related to catheter ablation are expected to be forthcoming. The NCDR AF ablation and left atrial appendage occlusion registries have also not yet published data.

## Stroke

### (See Tables 24-4 and 24-8)

- The AHA GWTG-Stroke program (Tables 24-4 and 24-8) remains the largest stroke quality improvement program. The US-based program is an ongoing, voluntary hospital registry and performance improvement initiative for acute stroke and supplies most of the quality data for acute stroke care.
- Care processes that would lead to best functional outcomes after acute stroke are poorly understood. A study of 2083 patients with ischemic stroke from 82 hospitals with data in both the AVAIL registry and GWTG-Stroke found that one-third of patients with acute stroke were functionally dependent or dead at 3 months after stroke. Functional rates varied considerably across hospitals, which indicates the need to understand which process measures could be targeted to minimize hospital variation and improve poststroke functional outcomes.<sup>43</sup>
- Door-to-needle time for tPA administration decreased on average by 10 minutes, from 77 minutes (IQR, 60–98 minutes) to 67 minutes (IQR, 51–87 minutes), after implementation of Target: Stroke Phase I, the first stage of the AHA's GWTG-Stroke quality improvement program. During this period, in-hospital all-cause mortality declined (from 9.93% to 8.25%; adjusted OR, 0.89 [95% CI, 0.83–0.94]), and discharge to home became more frequent (37.6% versus 42.7%; adjusted OR, 1.14 [95% CI, 1.09–1.19];  $P<.0001$ ).<sup>44</sup>
- Target: Stroke Phase II was launched in April 2014 to promote further reduction in door-to-needle time. There was significant site variation in door-to-needle time, and 16 strategies were identified that were significantly associated with reduced door-to-needle time. It was estimated that door-to-needle time could be reduced on average by an additional 20 minutes if all strategies were implemented.<sup>45</sup>

- A study of 204 591 patients with ischemic and hemorrhagic strokes admitted to 1563 GWTG—Stroke participating hospitals between April 1, 2003, and June 30, 2010, showed that 63.7% of the patients arrived at the hospital by EMS. Older patients, those with Medicaid and Medicare, and those with severe strokes were more likely to activate EMS. Conversely, minority race/ethnicity (black, Hispanic, Asian) and living in rural communities were associated with a lower likelihood of EMS use. EMS transport was independently associated with an onset-to-door time  $\leq 3$  hours, a higher proportion of patients meeting door-to-imaging time of  $\leq 25$  minutes, more patients meeting a door-to-needle time of  $\leq 60$  minutes, and more eligible patients being treated with tPA if onset of symptoms was  $\leq 2$  hours. The authors concluded that although EMS use was associated with rapid evaluation and treatment of stroke, more than one-third of stroke patients fail to use EMS.<sup>46</sup>
- Because of the poor survival after stroke, interventions related to improvement in end-of-life care are desirable to improve quality of care for those patients. In a study using GWTG—Stroke data, it was demonstrated that discharge from a Medicare Shared Savings Program hospital or alignment with a related organization was associated with a 16% increase in the odds of hospice enrollment (OR, 1.16 [95% CI, 1.06–1.26]) for patients with high mortality risk, with absolute rates of 20% versus 22%. However, a reduction in patient conform measures or hospice enrollment in individuals at lower mortality risk was noted in the same organizations, from 9% to 8% (OR, 0.82 [95% CI, 0.74–0.91]).<sup>47</sup>
- In an analysis comparing individuals presenting with stroke at institutions participating in the GWTG—Stroke program versus institutions not enrolled in the program, those in the GWTG—Stroke program were more likely to receive intravenous tPA (RR, 3.74 [95% CI, 1.65–8.50]), to receive education on risk factors (RR, 1.54 [95% CI, 1.16–2.05]), to be evaluated for swallowing (RR, 1.25 [95% CI, 1.04–1.50]), to receive a lipid evaluation (RR, 1.18 [95% CI, 1.05–1.32]), and to be evaluated by a neurologist (RR, 1.12 [95% CI, 1.05–1.20]).<sup>48</sup>

## Implantable Defibrillators

- In a comparative effectiveness study of single- versus dual-chamber implantable cardioverter-defibrillators using data from the ACC's Implantable Cardioverter Defibrillator Registry, Peterson and colleagues<sup>49</sup> found that among patients receiving an implantable cardioverter-defibrillator for primary prevention without indications for pacing, the use of a dual-chamber device compared with a

single-chamber device was associated with a higher risk of device-related complications and similar 1-year mortality and hospitalization outcomes. In a propensity-matched cohort, rates of complications were lower for single-chamber devices (3.51% versus 4.72%;  $P<0.001$ ; risk difference, -1.20 [95% CI, -1.72 to -0.69]), but device type was not significantly associated with 1-year mortality (unadjusted rate, 9.85% versus 9.77%; HR, 0.99 [95% CI, 0.91–1.07];  $P=0.79$ ), 1-year all-cause hospitalization (unadjusted rate, 43.86% versus 44.83%; HR, 1.00 [95% CI, 0.97–1.04];  $P=0.82$ ), or hospitalization for HF (unadjusted rate, 14.73% versus 15.38%; HR, 1.05 [95% CI, 0.99–1.12];  $P=0.19$ ).

## Resuscitation (See Table 24-9)

- Quality measures in resuscitation have targeted inpatient care settings. Started in 1999, the AHA GWTG—Resuscitation Registry remains the dominant source of US quality improvement data (Table 24-9). GWTG—Resuscitation is a voluntary hospital registry and performance improvement initiative for IHCA.
- Process measures for in-hospital resuscitation are generally based on time to correct administration of specific resuscitation and postresuscitation procedures, drugs, or therapies. Recent findings are discussed here.
- Among Medicare beneficiaries participating in GWTG—Resuscitation, 1-year survival after IHCA has increased modestly over the past decade<sup>50</sup>. However, despite an overall improvement in survival, there remains lower survival in IHCA during off-hours (nights and weekends) compared with on-hours events.<sup>51</sup>
- Of 103 932 IHCAs between 2000 and 2014, 12.7% had delays to epinephrine administration, with marked variation across hospitals. The delay was inversely correlated to risk-standardized survival. Whether reduction in this process measure could improve outcomes has not yet been demonstrated.<sup>52</sup>
- A composite performance score for in-hospital arrest varied significantly across hospitals (89.7% [IQR, 85.4%–93.1%]). Hospital process composite quality performance was associated with risk-standardized discharge rates and favorable neurological status at discharge.<sup>53</sup>
- Stub et al<sup>54</sup> reported a post hoc secondary analysis of a large, partial factorial trial of interventions for patients with OHCA. The quality of hospital-based postresuscitation care given to each patient was assigned an evidence-based quality score that considered (1) initiation of temperature management; (2) achievement of target temperature 32°C to

34°C; (3) continuation of temperature management for >12 hours; (4) performance of coronary angiography within 24 hours; and (5) no withdrawal of life-sustaining treatment before day 3. These were aggregated as hospital-level composite performance scores, which varied widely (median [IQR] scores from lowest to highest hospital quartiles, 21% [20%–25%] versus 59% [55%–64%]). Adjusted survival to discharge increased with each quartile of composite performance score (from lowest to highest: 16.2%, 20.8%, 28.5%, and 34.8%;  $P<0.01$ ). Adjusted rates of favorable neurological outcome also increased (from lowest quartile to highest: 8.3%, 13.8%, 22.2%, and 25.9%;  $P<0.01$ ). Hospital score was significantly associated with outcome after risk adjustment for established baseline factors (highest versus lowest adherence quartile: adjusted OR of survival, 1.64 [95% CI, 1.13–2.38]).<sup>54</sup>

## Social Determinants

- In NCDR data collected at 586 hospitals from July 2008 to December 2013, Udell et al<sup>55</sup> examined AMI care in 390 692 patients stratified by neighborhood SES. They reported longer median arrival-to-angiography time in lower SES neighborhoods (lowest, 8.0 hours; low, 5.5 hours; medium, 4.8 hours; high, 4.5 hours; and highest, 3.4 hours;  $P<0.0001$ ), and a higher proportion of patients with STEMI treated with fibrinolysis (lowest, 23.1%; low, 20.2%; medium, 18.0%; high, 14.2%; and highest, 5.9%;  $P<0.0001$ ). Although overall defect-free acute care appeared similar after controlling for covariates, patients from lower SES neighborhoods had greater independent risk of in-hospital mortality, major bleeding, and a lower quality of discharge care. These results indicate further opportunities to improve the quality of AMI care in patients from the most disadvantaged neighborhoods.
- Graham et al<sup>56</sup> assessed the degree to which non-race characteristics explain survival differences between white and black patients with AMI in a prospective registry study across 31 US hospitals from 2003 to 2008. Propensity scores associated with black race were calculated using 8 domains of patient characteristics. Among 6402 patients with AMI, 5-year mortality occurred in 28.9% of black patients (476 of 1648) and 18.0% of white patients (856 of 4754; HR, 1.72 [95% CI, 1.54–1.92];  $P<0.001$ ). Controlling for propensity associated with being a black patient, no difference in mortality by race was observed (adjusted HR, 1.09 [95% CI, 0.93–1.26];  $P=.37$ ). These findings suggest that most of the mortality rate difference between black and white patients is mediated by patient characteristics.

- Healthcare insurance coverage may influence oral anticoagulant and novel oral anticoagulant use. An analysis of 363 309 patients with prevalent AF from the PINNACLE-AF outpatient registry found considerable variation in oral anticoagulant use across insurance plans.<sup>57</sup> Relative to Medicare, Medicaid insurance was associated with a lower odds of oral anticoagulant prescription and of novel oral anticoagulant use.
- Before HRRP implementation, there was a continuous trend in the reduction of racial disparities for MI and HF, particularly in safety-net hospitals. For example, although blacks had 13% higher odds of readmission if treated in safety-net hospitals in 2007, this difference decreased to 5% in 2010. Data suggest those improvements persisted after HRRP implementation.<sup>58</sup>
- Using NIS data, Ziaeian and colleagues<sup>59</sup> showed HF hospitalization rates decreased 30.8% between 2002 and 2013. The ratio of males to females increased from 20% greater to 39% greater ( $P_{trend}=0.002$ ) over that time. Black males and black females had hospitalization rates that were 229% ( $P_{trend}=0.141$ ) and 240% ( $P_{trend}=0.725$ ) those of whites in 2013. Hispanic males had rates that were 32% greater in 2002, and the difference narrowed to 4% greater ( $P_{trend}=0.047$ ) in 2013 relative to whites. For Hispanic females, the rate was 55% greater in 2002 and narrowed to 8% greater ( $P_{trend}=0.004$ ) in 2013 relative to whites. Asian/Pacific Islander males had a 27% lower hospitalization rate in 2002, which improved to 43% lower ( $P_{trend}=0.040$ ) in 2013 relative to whites. For Asian/Pacific Islander females, the hospitalization rate was 24% lower in 2002 and improved to 43% lower ( $P_{trend}=0.021$ ) in 2013 relative to whites.
- In an analysis from GWTG-Stroke, Asian American individuals presented with more severe strokes, with an OR of 1.35 (95% CI, 1.30–1.40;  $P<0.001$ ) for an NIHSS score >16, and were less likely to receive intravenous tPA (OR, 0.95 [95% CI, 0.91–0.91];  $P=0.003$ ). They also had higher in-hospital mortality (OR, 1.14 [95% CI, 1.09–1.19];  $P<0.001$ ) and more symptomatic hemorrhage after tPA (OR, 1.36 [95% CI, 1.20–1.55];  $P<0.001$ ) than white patients, although the mortality was in fact lower after adjustment for stroke severity (OR, 0.95 [95% CI, 0.91–0.99];  $P=0.008$ ). Additionally, Asian American patients had better adherence to rehabilitation (OR, 1.27 [95% CI, 1.18–1.36];  $P<0.001$ ) and intensive statin therapy (OR, 1.14 [95% CI, 1.10–1.18];  $P<0.001$ ).<sup>60</sup>
- In a temporal trend evaluation of survival to discharge after IHCA across races, there was a significant increase in survival in blacks (11.3% in 2000 versus 21.4% in 2014) and in whites (15.8% versus 23.2%), although a reduction in the difference between races was noted ( $P_{interaction}<0.001$ ).<sup>61</sup>

**Table 24-1.** AMI Quality-of-Care Measures, 2018

Quality-of-Care Measure	Chest Pain – MI Registry*	
	STEMI	NSTEMI
Aspirin within 24 h of arrival†	98.5	98.0
Aspirin at discharge‡	99.3	98.7
β-Blockers at discharge	98.1	97.0
Lipid-lowering medication at discharge§	99.7	99.3
ARB/ACE inhibitor at discharge for patients with LVEF <40%	92.4	89.6
ACE inhibitor at discharge for AMI patients	58.6	46.5
ARB at discharge for AMI patients	16.6	20.0
Adult smoking cessation advice/counseling	98.2	98.1
Cardiac rehabilitation referral for AMI patients	87.8	80.5

Values are percentages. ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; and STEMI, ST-segment-elevation myocardial infarction.

\*Chest Pain – MI Registry: STEMI and NSTEMI patients are reported separately. Patients must be admitted with acute ischemic symptoms within the previous 24 hours, typically reflected by a primary diagnosis of STEMI or NSTEMI. Patients who are admitted for any other clinical condition are not eligible. Data reported include data from the first quarter of 2018 to the fourth quarter of 2018.

†Effective January 1, 2015, this measure was updated in the Chest Pain – MI Registry to exclude patients who were taking dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at home.

‡Effective January 1, 2015, this measure was updated in the Chest Pain – MI Registry to exclude patients who were prescribed dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at discharge.

§Denotes statin use at discharge. Use of nonstatin lipid-lowering agent was 3.4% for STEMI patients and 5.9% for NSTEMI patients in the Chest Pain – MI Registry.

Source: Data from the American College of Cardiology's Chest Pain - MI Registry.<sup>7</sup>

**Table 24-2.** Time Trends in the Chest Pain – MI Registry's CAD Quality-of-Care Measures, 2010 to 2018

Quality-of-Care Measure	2010	2011	2012	2013	2014	2015	2016	2017	2018
Aspirin within 24 h of arrival*	97	97.6	97.8	95.4	98.1	98.6	98.5	98.5	98.7
Aspirin at discharge†	98	98.3	98.4	98.4	98.7	98.7	98.7	98.7	98.9
β-Blockers at discharge	96	96.7	97.1	97.1	97.6	97.5	97.5	97.4	97.4
Statin use at discharge	92	98.4	98.8	98.8	99.1	99.2	99.4	99.4	99.5
ARB/ACE inhibitor at discharge for patients with LVEF <40%	86	87.8	89.7	90.0	91.2	90.2	91.0	90.3	90.9
Adult smoking cessation advice/counseling	98	98.4	98.4	98.4	98.6	98.0	98.1	98.0	98.2
Cardiac rehabilitation referral for AMI patients	75	76.5	77.3	77.2	79.4	77.8	78.6	80.4	83.3

Values are percentages. ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

\*Effective January 1, 2015, this measure was updated in the Chest Pain – MI Registry to exclude patients taking dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at home.

†Effective January 1, 2015, this measure was updated in the Chest Pain – MI Registry to exclude patients who were prescribed dabigatran, rivaroxaban, or apixaban (novel oral anticoagulant medications) at discharge.

Source: Data from the American College of Cardiology's Chest Pain – MI Registry.<sup>7</sup>

**Table 24-3.** Additional Chest Pain – MI Registry Quality-of-Care Metrics for AMI Care, 2018

Quality Metrics	Overall	STEMI	NSTEMI
ECG within 10 min of arrival	68.6	77.3	65.1
Aspirin within 24 h of arrival	98.7	98.5	98.0
Any anticoagulant use*	96.1	97.3	95.3
Dosing errors			
UFH dose	43.2	41.2	43.3
Enoxaparin dose	9.8	7.3	10.0
Glycoprotein IIb/IIIa inhibitor dose	4.3	4.5	3.8
Discharge			
Aspirin at discharge	98.9	99.3	98.7
Prescribed statins on discharge	99.5	99.7	99.3
Adult smoking cessation advice/counseling	98.2	98.2	98.1
Cardiac rehabilitation referral	83.3	87.8	80.5
In-hospital mortality† (95% CI)	4.12 (3.96–4.39)	6.30 (5.96–6.97)	2.65 (2.51–2.88)

Values are percentages. Data reported include data from the first quarter of 2018 to the fourth quarter of 2018. AMI indicates acute myocardial infarction; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; and UFH, unfractionated heparin.

\*Includes UFH, low-molecular-weight heparin, or direct thrombin inhibitor use.

†Includes all patients.

Source: Data from the American College of Cardiology's Chest Pain – MI Registry.<sup>7</sup>

**Table 24-4.** Timely Reperfusion for AMI and Stroke

Quality-of-Care Measure	GWTG—Stroke (for Stroke) 7/1/2017–6/30/2018	Chest Pain – MI Registry: STEMI, 2018
STEMI		
Thrombolytic agents within 30 min	N/A	56.1
PCI within 90 min*	N/A	96.0
Stroke		
IV tPA in patients who arrived <2 h after symptom onset, treated ≤3 h	89.8†	N/A
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h	83.7‡	N/A
IV tPA door-to-needle time ≤60 min	82.4†	N/A

Values are percentages. AMI indicates acute myocardial infarction; IV, intravenous; MI, myocardial infarction; N/A, not applicable; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; and tPA, tissue plasminogen activator.

\*Excludes transfers.

†Reflects analysis performed for the Heart Disease and Stroke Statistics—2020 Update.

‡The “IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h” measure was changed in 2016 to include in-hospital strokes in the denominator.

Source: Chest pain data from the American College of Cardiology's Chest Pain – MI Registry.<sup>7</sup> Stroke data from unpublished data, Get With The Guidelines—Stroke, July 1, 2017, to June 30, 2018.

**Table 24-5.** HF Quality-of-Care Measures, July 1, 2017, to June 30, 2018

Quality-of-Care Measure	AHA GWTG—HF
LVEF assessment	98.6
ARB/ACE inhibitor at discharge for patients with LVSD	92.4
Complete discharge instructions	93.4
β-Blockers at discharge for patients with LVSD, no contraindications	98.0
Anticoagulation for AF or atrial flutter, no contraindications	87.6

Values are percentages. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin receptor blocker; GWTG—HF, Get With The Guidelines—Heart Failure; HF, heart failure; LVEF, left ventricular ejection fraction; and LVSD, left ventricular systolic dysfunction.

Source: Unpublished American Heart Association tabulation, GWTG—HF, July 1, 2017, to June 30, 2018.

**Table 24-6.** Quality of Care by Race/Ethnicity and Sex in the GWTG-HF Program, July 1, 2017, to June 30, 2018

Quality-of-Care Measure	Race/Ethnicity			Sex	
	White	Black	Hispanic	Males	Females
Postdischarge appointment*	82.42	79.96	78.82	80.95	81.21
Complete set of discharge instructions	92.07	93.75	94.07	93.41	91.67
Measure of LV function*	99.14	98.98	98.62	98.96	98.80
ACE inhibitor or ARB at discharge for patients with LVSD, no contraindications*	92.21	92.97	92.23	92.58	92.06
Smoking cessation counseling, current smokers	91.36	92.96	91.01	91.83	91.79
Evidence-based specific β-blockers*	93.01	95.20	93.40	94.01	93.11
β-Blockers at discharge for patients with LVSD, no contraindications	98.03	97.96	97.47	98.04	97.74
Hydralazine/nitrates at discharge for patients with LVSD, no contraindications†	0.00	32.49	0.00	34.07	29.42
Anticoagulation for AF or atrial flutter, no contraindications	87.96	85.78	85.23	87.65	87.19
Composite quality-of-care measure (using discharge instructions and β-blocker at discharge)	96.09	96.15	96.07	96.08	95.76

Values are percentages. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; GWTG-HF, Get With The Guidelines—Heart Failure; LV, left ventricular; and LVSD, left ventricular systolic dysfunction.

\*Indicates the 4 key achievement measures targeted in GWTG-HF.

†For black patients only.

Source: Unpublished American Heart Association tabulation, GWTG-HF, July 1, 2017, to June 30, 2018.

**Table 24-7.** National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set on CVD, DM, Tobacco, Nutrition, and Lifestyle, 2017

	Commercial		Medicare		Medicaid
	HMO	PPO	HMO	PPO	HMO
<b>CVD</b>					
β-Blocker persistence after MI*	85.4	84.0	90.0	90.7	78.5
BP control†	62.2	54.4	70.9	72.0	56.9
Statin therapy for patients with CVD	80.4	80.9	79.0	79.1	76.1
<b>DM</b>					
HbA <sub>1c</sub> testing	91.2	89.8	93.7	93.5	87.6
HbA <sub>1c</sub> >9.0%	31.7	41.2	25.4	22.3	40.5
Eye examination performed	55.0	49.0	71.9	71.1	57.2
Monitoring nephropathy	90.4	88.2	95.7	95.1	90.1
BP <140/90 mmHg	62.2	50.3	67.4	63.6	62.7
Statin therapy for patients with DM	61.5	60.1	72.3	69.6	61.4
<b>Tobacco, nutrition, and lifestyle</b>					
Advising smokers and tobacco users to quit	75.9	72.5	86.2	84.5	77.0
BMI percentile assessment in children and adolescents (3–17 y of age)	70.3	56.6	N/A	N/A	72.5
Nutrition counseling (children and adolescents [3–17 y of age])	64.3	52.9	N/A	N/A	67.1
Counseling for PA (children and adolescents [3–17 y of age])	59.5	47.8	N/A	N/A	60.6
BMI assessment for adults 18–74 y of age	80.3	67.1	95.0	94.6	84.5
PA discussion in older adults (≥65 y of age) (2016 data)	N/A		55.1	58.4	N/A
PA advice in older adults (≥65 y of age) (2016 data)	N/A		52.0	51.2	N/A

Values are percentages. BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HMO, health maintenance organization; MI, myocardial infarction; N/A, not available or not applicable; PA, physical activity; and PPO, preferred provider organization.

\*β-Blocker persistence: received persistent β-blocker treatment for 6 months after hospital discharge for acute myocardial infarction.

†Adults 18 to 59 years of age with BP <140/90 mmHg, adults 60 to 85 years of age with a diagnosis of DM and BP <140/90 mmHg, and adults 60 to 85 years of age without a diagnosis of DM and BP <150/90 mmHg.

Source: Healthcare Effectiveness Data and Information Set, 2017.<sup>29</sup>

**Table 24-8.** Quality of Care by Race/Ethnicity and Sex in the GWTG-Stroke Program, July 1, 2017, to June 30, 2018

Quality-of-Care Measure	Race/Ethnicity			Sex	
	White	Black	Hispanic	Males	Females
IV tPA in patients who arrived ≤2 h after symptom onset, treated ≤3 h*	87.17	86.57	87.55	87.85	86.62
IV tPA in patients who arrived <3.5 h after symptom onset, treated ≤4.5 h†	81.28	81.30	83.23	82.14	81.04
IV tPA door-to-needle time ≤60 min	83.91	83.50	83.24	84.64	83.14
Thrombolytic complications: IV tPA and life-threatening, serious systemic hemorrhage	9.17	10.78	7.18	9.81	8.35
Antithrombotic agents <48 h after admission*	97.21	96.76	96.48	97.25	96.80
DVT prophylaxis by second hospital day*	99.25	99.27	98.99	99.24	99.21
Antithrombotic agents at discharge*	98.90	98.72	98.26	98.89	98.64
Anticoagulation for AF at discharge*	96.43	95.55	96.92	96.58	96.20
Therapy at discharge if LDL-C >100 mg/dL or LDL-C not measured or on therapy at admission*	98.44	98.78	98.26	98.75	98.24
Counseling for smoking cessation*	97.33	97.01	96.69	97.11	97.19
Lifestyle changes recommended for BMI >25 kg/m <sup>2</sup>	50.81	53.79	55.11	52.00	51.88
Composite quality-of-care measure	97.95	97.91	97.50	98.04	97.72

Values are percentages. AF indicates atrial fibrillation; BMI, body mass index; DVT, deep vein thrombosis; GWTG, Get With The Guidelines; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; and tPA, tissue-type plasminogen activator.

\*Indicates the 7 key achievement measures targeted in GWTG-Stroke.

†This measure was changed in 2016 to include in-hospital strokes in the denominator.

Source: Unpublished American Heart Association tabulation, GWTG-Stroke, July 1, 2017, to June 30, 2018.

**Table 24-9.** Quality of Care of Patients With IHCA Among GWTG-Resuscitation Hospitals, 2018

	Adults	Children
Event outside critical care setting	45.8	13.0
All objective CPR data collected	99.0	99.6
End-tidal CO <sub>2</sub> monitoring used during arrest	11.6	40.3
Induced hypothermia after resuscitation from shockable rhythm	7.8	8.8

Values are mean percentages. CPR indicates cardiopulmonary resuscitation; GWTG, Get With The Guidelines; and IHCA, in-hospital cardiac arrest.

Source: GWTG-Resuscitation Registry unpublished data, 2018.

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## 25. MEDICAL PROCEDURES

**See Tables 25-1 and 25-2 and Charts 25-1 through 25-4**

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### Trends in Operations and Procedures (See Tables 25-1 and 25-2 and Charts 25-1 and 25-2)

- The mean hospital charges for cardiovascular procedures in 2014 ranged from \$43 484 for CEA to \$808 770 for heart transplantations (Table 25-1).
- The trends in the numbers of 5 common cardiovascular procedures in the United States from 1993 to 2014 are presented in Chart 25-1. Of the 5 procedures, cardiac catheterization was the most common procedure for all years presented (Chart 25-1).
- Of the 10 leading diagnostic groups in the United States, the greatest number of surgical procedures were cardiovascular and obstetric procedures (Chart 25-2).
- The total number of inpatient cardiovascular operations and procedures decreased 6%, from 8 461 000 in 2004 to 7 971 000 in 2014 (Table 25-2).
- Data from the HCUP were examined by the NHLBI for trends from 1997 to 2014 for use of PCI and CABG,<sup>1</sup> as discussed in this chapter.

### Coronary Artery Bypass Grafting

- The number of inpatient discharges for CABG decreased from 683 000 in 1997 to 371 000 in 2014 (Chart 25-1).
- In 1997, the number of inpatient discharges for CABG was 484 000 for males and 199 000 for females; these numbers declined to 276 000 and 94 000, respectively, in 2014 (Table 25-2).<sup>1</sup>

### Abbreviations Used in Chapter 25

ASD	atrial septal defect
AV	atrioventricular
CABG	coronary artery bypass graft
CEA	carotid endarterectomy
HCUP	Healthcare Cost and Utilization Project
HLHS	hypoplastic left heart syndrome
ICD-9-CM	<i>International Classification of Diseases, 9th Revision, Clinical Modification</i>
NHLBI	National Heart, Lung, and Blood Institute
PCI	percutaneous coronary intervention
STS	Society of Thoracic Surgeons
VSD	ventricular septal defect

### Inpatient Cardiac Catheterization and PCI (See Tables 25-1 and 25-2 and Chart 25-1)

- Inpatient PCI discharges decreased from 359 000 for males and 190 000 for females in 1997 to 325 000 and 155 000, respectively, by 2014 (Table 25-2).
- Data on Medicare beneficiaries undergoing a coronary revascularization procedure between 2008 and 2012 indicate that the rapid growth in non-admission PCIs (from 60 405 to 106 495) has been more than offset by the decrease in PCI admissions (from 363 384 to 295 434).<sup>2</sup>
- In 2014, the mean inpatient hospital charge for PCI was \$84 813 (Table 25-1).
- From 2004 to 2014, the number of inpatient cardiac catheterizations decreased from 1 486 000 to 1 016 000 annually (Chart 25-1).
- In 2014, an estimated 480 000 inpatient PCIs (previously referred to as percutaneous transluminal coronary angioplasty) procedures were performed in the United States (Chart 25-1).
- In 2014, ≈68% of PCI procedures were performed on males, and ≈50% were performed on people ≥65 years of age (Table 25-2).
- Inpatient hospital deaths for PCI increased from 0.8% in 2004 to 2.1% in 2014 (Table 25-1). In 2014, ≈82% of stents implanted during PCI were drug-eluting stents compared with 18% that were bare-metal stents.
- The rate of any cardiac stent procedure per 10 000 population rose by 61% from 1999 to 2006, then declined by 27% between 2006 and 2009.<sup>3</sup>

### Cardiac Open Heart Surgery

- Data from the STS Adult Cardiac Surgery Database, which voluntarily collects data from ≈80% of all hospitals that perform CABG in the United States, indicate that a total of 159 869 procedures involved isolated CABG in 2016.<sup>4</sup>
- Among other major procedures in 2016, there were 28 493 isolated aortic valve replacements and 7 706 isolated mitral valve replacements; 17 507 procedures involved both aortic valve replacement and CABG, whereas 2 935 procedures involved both mitral valve replacement and CABG.<sup>4</sup>

### Congenital Heart Surgery, 2013 to 2016

According to data from the STS Congenital Heart Surgery Database<sup>5</sup>:

- There were 122 459 congenital heart surgeries performed from July 2014 to June 2018. The in-hospital mortality rate was 2.9% during that time period. The 5 most common diagnoses were

type 2 VSD (6.3%), open sternum with open skin (5.9%), HLHS (5.8%), patent ductus arteriosus (4.2%), and secundum ASD (4.0%).

- The 5 most common primary procedures were delayed sternal closure (8.3%), patch VSD repair (6.3%), mediastinal exploration (3.5%), patch ASD repair (3.2%), and complete AV canal (ASD) repair (2.8%).

## Heart Transplantations (See Charts 25-3 and 25-4)

According to data from the Organ Procurement and Transplantation Network<sup>6</sup>:

- In 2018, 3408 heart transplantations were performed in the United States (Chart 25-3). There are 256 transplantation hospitals in the United States, 143 of which performed heart transplantations in 2018.

- Of the recipients in 2018, 69.8% were male, and 62.6% were white; 21.6% were black, 10.4% were Hispanic, and 3.9% were Asian. Heart transplantations by recipient age are shown in Chart 25-4.
- For transplantations that occurred between 2008 and 2015, the 1-year survival rate was 90.5% for males and 91.1% for females; the 5-year survival rates based on 2008 to 2015 transplantations were 78.4% for males and 77.7% for females. The 1- and 5-year survival rates for white cardiac transplantation patients were 90.7% and 79.1%, respectively. For black patients, they were 90.7% and 74.1%, respectively. For Hispanic patients, they were 90.1% and 80.0%, respectively. For Asian patients, they were 91.4% and 80.1%, respectively.
- As of July 22, 2019, 3779 patients were on the transplant waiting list for a heart transplant, and 46 patients were on the list for a heart/lung transplant.

**Table 25-1. Mean Hospital Charges, In-Hospital Death Rates, and Mean Length of Stay for Various Cardiovascular Procedures, United States, 2014**

Procedure	Mean Hospital Charges, \$	In-Hospital Death Rate, %	Mean Length of Stay, d	ICD-9-CM Procedure Codes
Total vascular and cardiac surgery and procedures	90215	3.34	6.3	35–39, 00.50–00.51, 00.53–00.55, 00.61–00.66
CABG	168541	1.78	9.3	36.1–36.3
PCI	84813	2.07	3.5	00.66, 17.55, 36.01, 36.02, 36.05
Cardiac catheterization	57494	1.42	4.2	37.21–37.23
Pacemakers	83521	1.46	5.1	37.7–37.8, 00.50, 00.53
Implantable defibrillators	171476	0.69	6.3	37.94–37.99, 00.51, 00.54
CEA	43484	0.27	2.6	38.12
Heart valves	201557	3.36	9.7	35.00–35.14, 35.20–35.28, 35.96, 35.97, 35.99
Heart transplantations	808770	7.84	45.4	37.51

Principal procedure only. CABG indicates coronary artery bypass graft; CEA, carotid endarterectomy; ICD-9-CM, International Classification of Diseases, Clinical Modification, 9th Revision; and PCI, percutaneous coronary intervention.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 2014.<sup>1</sup>

**Table 25-2.** Estimated\* Inpatient Cardiovascular Operations, Procedures, and Patient Data by Sex and Age (in Thousands), United States, 2014

Operation/Procedure/ Patients	ICD-9-CM Procedure Codes	All	Sex		Age, y			
			Male	Female	18–44	45–64	65–84	≥85
Heart valves	35.00–35.14, 35.20–35.28, 35.96, 35.97, 35.99	156	92	63	11	40	83	16
PCI	00.66, 17.55, 36.01, 36.02, 36.05	480	325	155	26	213	212	28
PCI with stents	36.06, 36.07	434	294	140	24	194	191	25
CABG	36.1–36.3	371	276	94	10	148	204	9
Cardiac catheterization	37.21–37.23	1016	625	391	68	432	455	54
Pacemakers	37.7, 37.8, 00.50, 00.53	351	185	166	9	57	197	85
Pacemaker devices	37.8, 00.53	141	72	69	3	19	80	38
Pacemaker leads	37.7, 00.50	210	114	97	7	38	117	47
Implantable defibrillators	37.94–37.99, 00.51, 00.54	60	43	17	4	21	30	3
CEA	38.12	86	51	35	0	20	60	6
Total vascular and cardiac surgery and procedures†‡	35–39, 00.50–00.51, 00.53–00.55, 00.61–00.66	7971	4602	3368	777	2860	3402	558

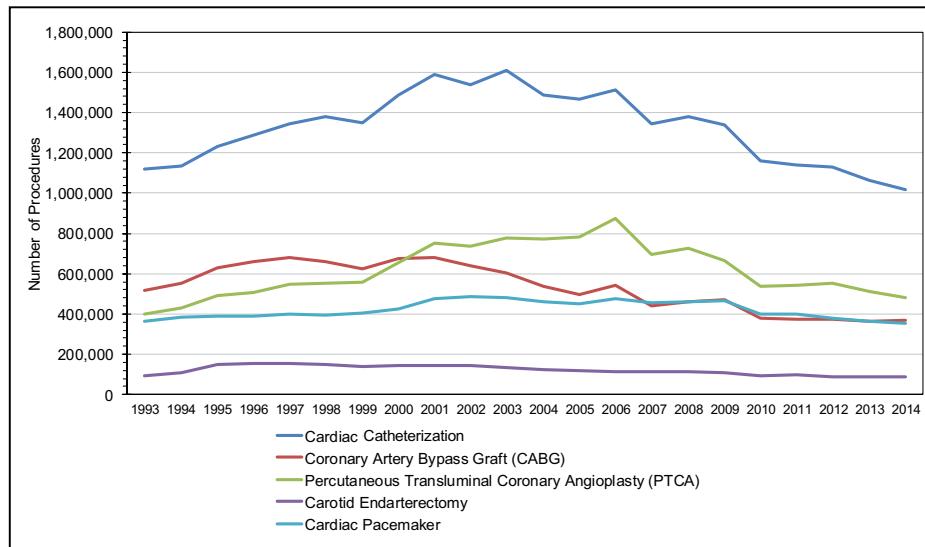
These data do not reflect any procedures performed on an outpatient basis. Many more procedures are being performed on an outpatient basis. Some of the lower numbers in this table compared with 2006 probably reflect this trend. Data include procedures performed on newborn infants. Some of the ICD-9-CM procedure codes may have changed over the years. CABG indicates coronary artery bypass graft; CEA, carotid endarterectomy; ICD-9-CM, International Classification of Diseases, Clinical Modification, 9th Revision; and PCI, percutaneous coronary intervention.

\*Breakdowns are not available for some procedures, so entries for some categories do not add to totals. These data include codes for which the estimated number of procedures is <5000. Categories with such small numbers are considered unreliable by the National Center for Health Statistics and in some cases may have been omitted.

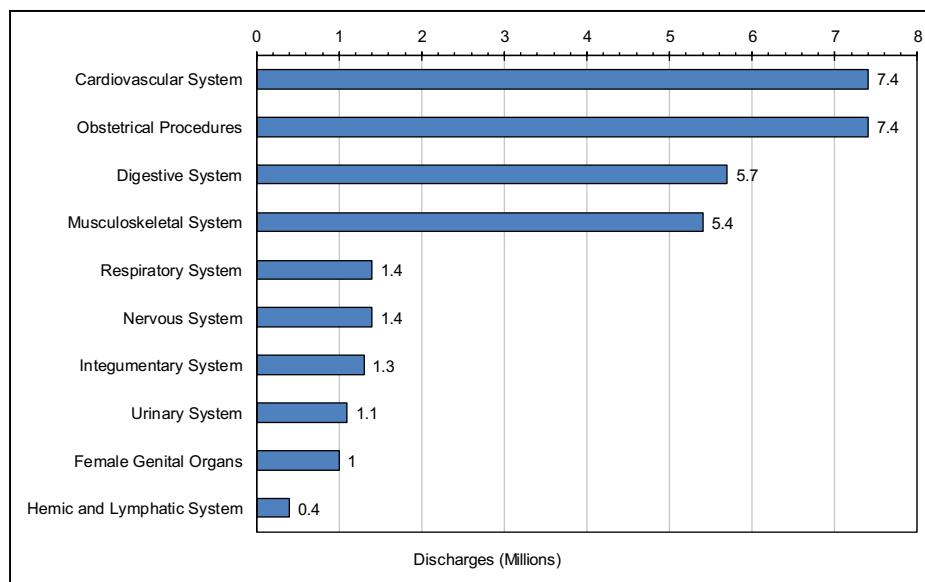
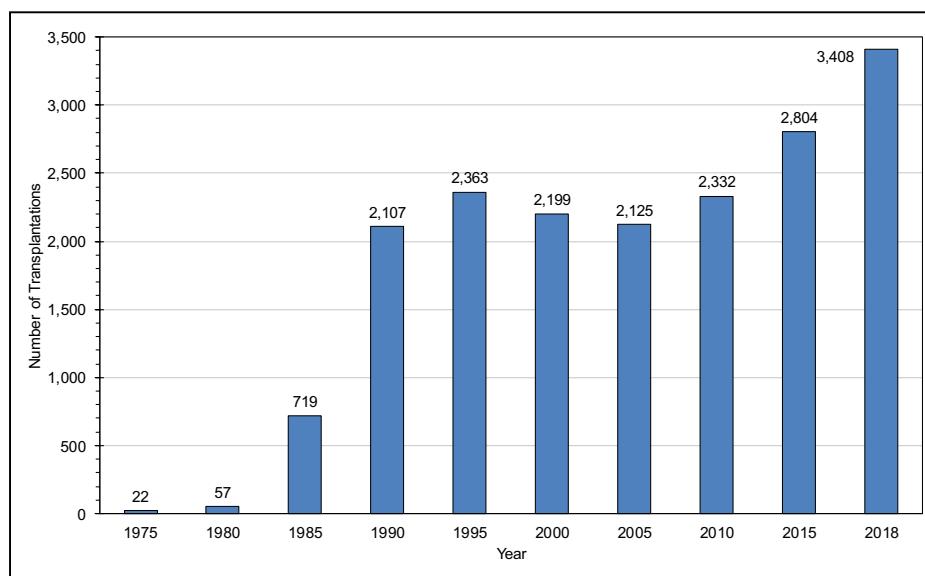
†Totals include procedures not shown here.

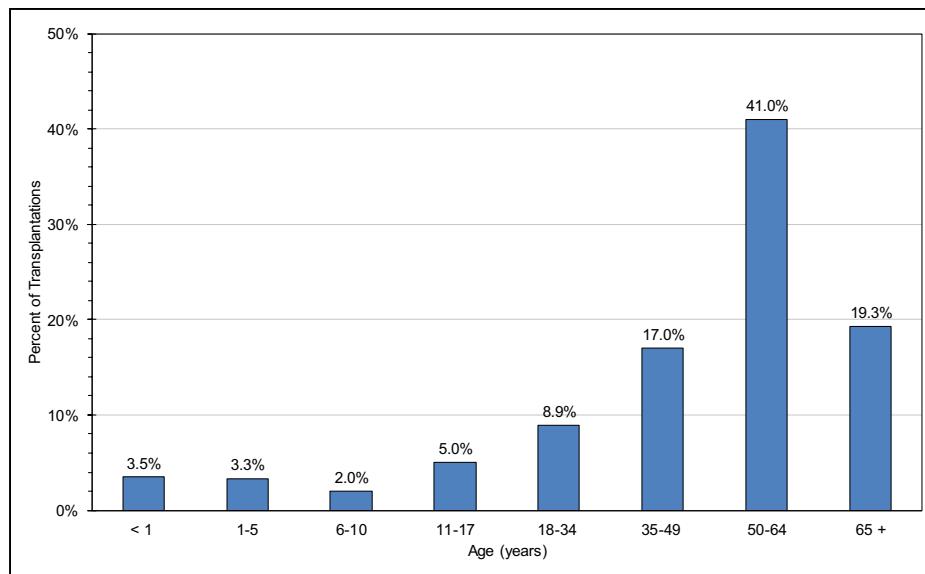
‡This estimate includes angioplasty and stent insertions for noncoronary arteries.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 2014.<sup>1</sup>

**Chart 25-1.** Trends in cardiovascular procedures, United States, 1993 to 2014; inpatient procedures only.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 1993 to 2014.<sup>1</sup>

**Chart 25-2.** Number of surgical procedures in the 10 leading diagnostic groups, United States, 2014.Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project, 2014.<sup>1</sup>**Chart 25-3.** Trends in heart transplantations, United States, 1975 to 2018.Source: Data derived from the Organ Procurement and Transplantation Network, 1975 to 2018.<sup>6</sup>

**Chart 25-4.** Heart transplantations by recipient age, United States, 2018.Source: Data derived from the Organ Procurement and Transplantation Network, 2018.<sup>6</sup>

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## 26. ECONOMIC COST OF CARDIOVASCULAR DISEASE

**See Tables 26-1 and 26-2 and Charts 26-1 through 26-6**

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Using data from MEPS (2014–2015),<sup>1</sup> the annual direct and indirect cost of CVD in the United States is an estimated \$351.3 billion (Table 26-1 and Chart 26-1). This figure includes \$213.8 billion in expenditures (direct costs, which include the cost of physicians and other professionals, hospital services, prescribed medications, and home health care, but not the cost of nursing home care) and \$137.5 billion in lost future productivity (indirect costs) attributed to premature CVD and stroke mortality in 2014 to 2015.

The direct costs for CVD and stroke for 2014 to 2015 (average annual) are available on the website of the nationally representative MEPS of the Agency for Healthcare Research and Quality.<sup>1</sup> Details on the advantages or disadvantages of using MEPS data are provided in the “Heart Disease and Stroke Statistics—2011 Update.”<sup>2</sup> Indirect mortality costs are estimated for 2014 to 2015 (average annual) by multiplying the number of deaths for those years attributable to CVD and stroke, in age and sex groups, by estimates of the present value of lifetime earnings for those age and sex groups as of 2014 to 2015. Mortality data are from the NVSS of the NCHS.<sup>3</sup> The present values of lifetime earnings are unpublished estimates furnished by the Institute for Health and Aging, University of California, San Francisco, by Wendy Max, PhD, on April 4, 2018. Those estimates incorporate a 3% discount rate, which is the recommended percentage.<sup>4</sup> The discount rate removes the effect of inflation in income over the lifetime of earnings. The estimate is for 2014, inflated to 2015 to account for the 2014 to 2015 change in hourly worker compensation in the business sector reported by the US Bureau of Labor Statistics.<sup>5</sup>

### Abbreviations Used in Chapter 26

AHA	American Heart Association
CHD	coronary heart disease
CHF	congestive heart failure
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
DM	diabetes mellitus
ED	emergency department
GI	gastrointestinal (tract)
HBP	high blood pressure
HD	heart disease
HF	heart failure
MEPS	Medical Expenditure Panel Survey
NCHS	National Center for Health Statistics
NVSS	National Vital Statistics System

The indirect costs exclude lost productivity costs attributable to chronic, prevalent nonfatal CVD and stroke illness during 2014 to 2015 among workers, people keeping house, people in institutions, and people unable to work. Those morbidity costs were substantial in very old studies, but because of the lack of contemporary data, an adequate update could not be made.

### Most Costly Diseases (See Tables 26-1 and 26-2 and Charts 26-2 and 26-3)

CVD accounted for 14% of total US health expenditures in 2014 to 2015, more than any major diagnostic group.<sup>1</sup> By way of comparison, CVD total direct costs shown in Table 26-1 are higher than the 2014 to 2015 Agency for Healthcare Research and Quality estimates for cancer, which were \$84.0 billion (55% for outpatient or doctor office visits, 32% for inpatient care, and 9% for prescription drugs).<sup>1</sup>

Table 26-2 shows direct and indirect costs for CVD by sex and by 2 broad age groups. Chart 26-2 shows total direct costs for the 21 leading chronic diseases on the MEPS list. HD is the most costly condition.<sup>6</sup>

The estimated direct costs of CVD in the United States increased from \$103.5 billion in 1996 to 1997 to \$213.8 billion in 2014 to 2015 (Chart 26-3).

### Economic Value of CVD Risk Factor Control

Cutler et al<sup>7</sup> analyzed individual-level Medicare and non-Medicare healthcare spending captured by Medicare Current Beneficiary Survey data from 1999 to 2012. Overall, increased use of lipid-lowering, antihypertensive, and anti-DM medications over time accounted for a combined 51% of the reduction in individual spending on CVD.<sup>7</sup>

### Projections (See Charts 26-4 through 26-6)

- The AHA developed methodology to project future costs of care for HBP, CHD, HF, stroke, and all other CVD.<sup>8</sup> The methods used for the projections are very different from those used to derive the other direct and indirect costs in this chapter. For example, the projections estimates include the direct costs of nursing home care and the indirect costs of CVD morbidity.
- By 2035, 45.1% of the US population is projected to have some form of CVD.<sup>8</sup>
- Between 2015 and 2035, total direct medical costs of CVD are projected to increase from \$318 billion to \$749 billion (2015 dollars in billions). Of this total in 2035, 55.5% will be attributable to hospital costs, 15.3% to medications, 15.0% to

physicians, 7.2% to nursing home care, 5.5% to home health care, and 1.5% to other costs.<sup>8</sup>

- Indirect costs (attributable to lost productivity) for all fatal and nonfatal CVDs are estimated to increase from \$237 billion in 2015 to \$368 billion in 2035 (2015 dollars in billions), an increase of 55%.<sup>8</sup>
- Between 2015 and 2035, the total costs are expected to increase for total CVD, HBP and HBP as a risk factor, CHD, CHF, stroke, and other CVDs (Chart 26-4).
- Between 2015 and 2035, the projected total (direct and indirect) costs of total CVD are estimated to remain relatively stable for 18- to 44-year-olds,

increase slightly for 45- to 64-year-olds, and increase sharply for 65- to 79-year-olds and adults ≥80 years of age (Chart 26-5).

- Whereas the direct costs of CVD for home health care, nursing homes, healthcare professionals, and medications are estimated to rise steadily between 2015 and 2035, projected hospital costs are estimated to more than double in this same time frame (Chart 26-6).
- These data indicate that CVD prevalence and costs are projected to increase substantially unless CVD incidence is reduced or short-term and long-term CVD care costs are better controlled.

**Table 26-1. Estimated Direct and Indirect Costs (in Billions of Dollars) of CVD and Stroke, United States, Average Annual, 2014 to 2015**

	HD*	Stroke	Hypertensive Disease†	Other Circulatory Conditions‡	Total CVD
<b>Direct costs§</b>					
Hospital inpatient stays	59.4	17.4	7.9	12.8	97.5
Hospital ED visits	6.3	0.8	1.3	1.0	9.4
Hospital outpatient or office-based provider visits	22.6	2.4	13.7	7.9	46.6
Home health care	11.1	6.6	8.2	1.6	27.5
Prescribed medicines	10.0	0.8	20.2	1.8	32.8
<b>Total expenditures</b>	<b>109.4</b>	<b>28.0</b>	<b>51.3</b>	<b>25.1</b>	<b>213.8</b>
<b>Indirect costs  </b>					
Lost productivity/mortality	109.3	17.5	4.6	6.1	137.5
<b>Grand totals</b>	<b>218.7</b>	<b>45.5</b>	<b>55.9</b>	<b>31.2</b>	<b>351.3</b>

Numbers do not add to total because of rounding. CVD indicates cardiovascular disease; ED, emergency department; and HD, heart disease.

\*This category includes coronary HD, heart failure, part of hypertensive disease, cardiac dysrhythmias, rheumatic HD; cardiomyopathy, pulmonary HD, and other or ill-defined HDs.

†Costs attributable to hypertensive disease are limited to hypertension without HD.

‡Other circulatory conditions include arteries, veins, and lymphatics.

§Medical Expenditure Panel Survey (MEPS) healthcare expenditures are estimates of direct payments for care of a patient with the given disease provided during the year, including out-of-pocket payments and payments by private insurance, Medicaid, Medicare, and other sources. Payments for over-the-counter drugs are not included. These estimates of direct costs do not include payments attributed to comorbidities. Total CVD costs are the sum of costs for the 4 diseases but with some duplication.

||The Statistics Committee agreed to suspend presenting estimates of lost productivity attributable to morbidity until a better estimating method can be developed. Lost future earnings of people who died in 2015 to 2016, discounted at 3%.

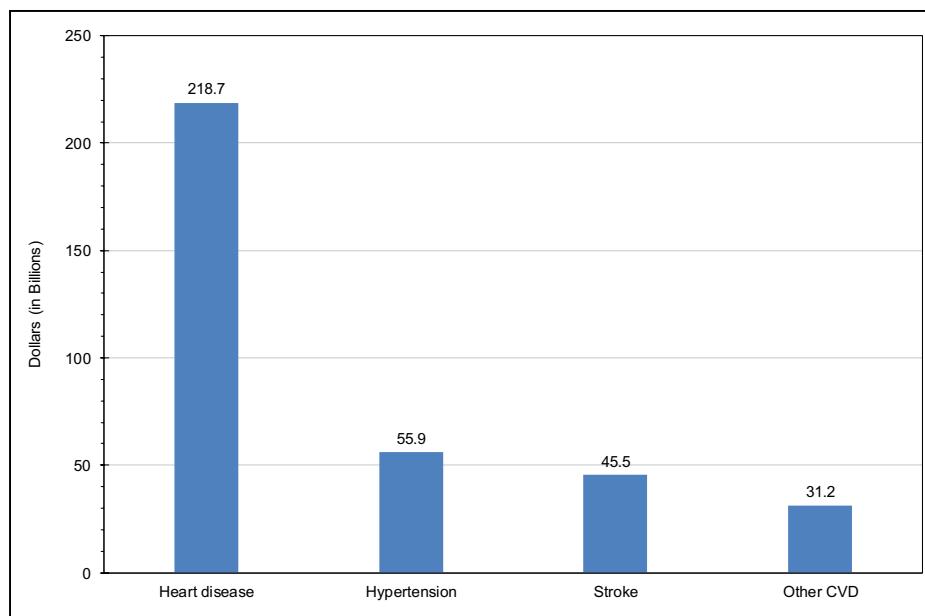
Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using Household Component of the MEPS for direct costs (average annual 2014 to 2015).<sup>6</sup> Indirect mortality costs are based on 2014 to 2015 counts of deaths by the National Center for Health Statistics and an estimated present value of lifetime earnings furnished for 2014 by Wendy Max (Institute for Health and Aging, University of California, San Francisco, April 4, 2018) and inflated to 2015 from change in worker compensation reported by the US Bureau of Labor Statistics.<sup>5</sup>

**Table 26-2. Costs of Total CVD and Stroke in Billions of Dollars by Age and Sex, United States, Average Annual, 2014 to 2015**

	Total	Males	Females	Age <65 y	Age ≥65 y
All direct	213.8	122.4	91.4	85.5	128.3
Indirect: mortality only	137.5	102.3	35.2	115.6	21.9
<b>Total</b>	<b>351.3</b>	<b>224.7</b>	<b>126.6</b>	<b>201.1</b>	<b>150.2</b>

Numbers may not add to total because of rounding. CVD indicates cardiovascular disease.

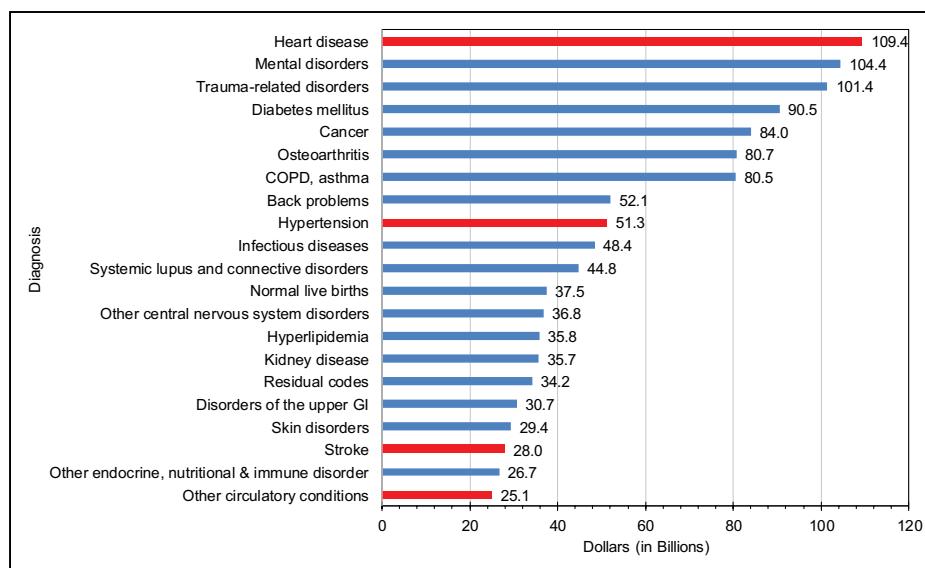
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey, average annual 2014 to 2015 (direct costs) and mortality data from the National Vital Statistics System and present value of lifetime earnings from the Institute for Health and Aging, University of California, San Francisco (indirect costs).<sup>3,6</sup>



**Chart 26-1. Direct and indirect costs of CVD (in billions of dollars), United States, average annual 2014 to 2015.**

CVD indicates cardiovascular disease.

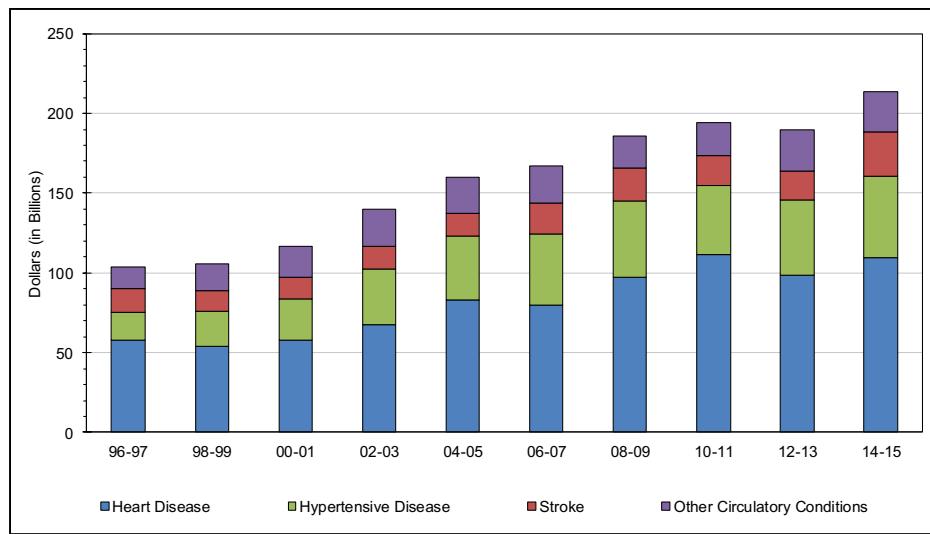
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and mortality data from the National Vital Statistics System.<sup>1,3</sup>



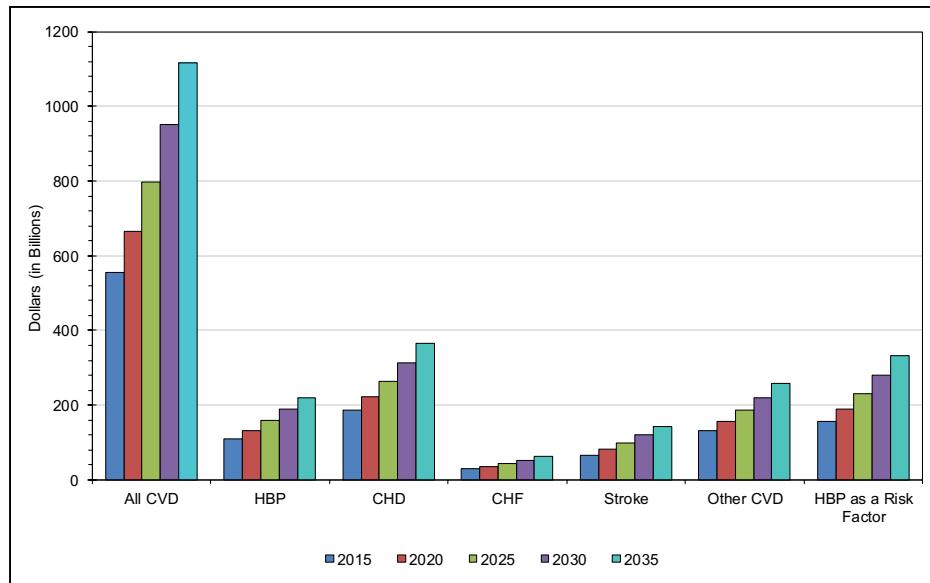
**Chart 26-2. The 21 leading diagnoses for direct health expenditures, United States, average annual 2014 to 2015 (in billions of dollars).**

COPD indicates chronic obstructive pulmonary disease; and GI, gastrointestinal (tract).

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and excluding nursing home costs.<sup>1</sup>

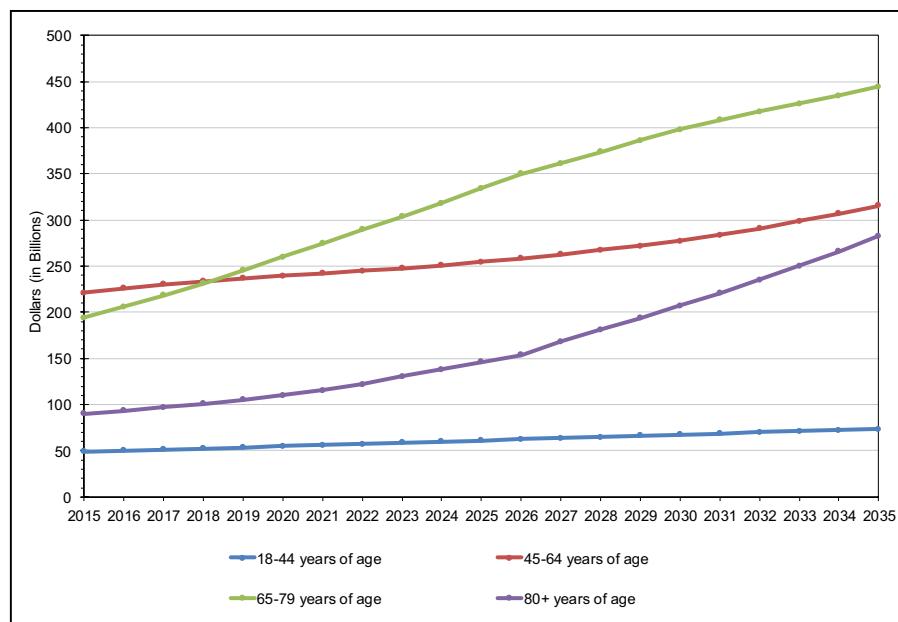
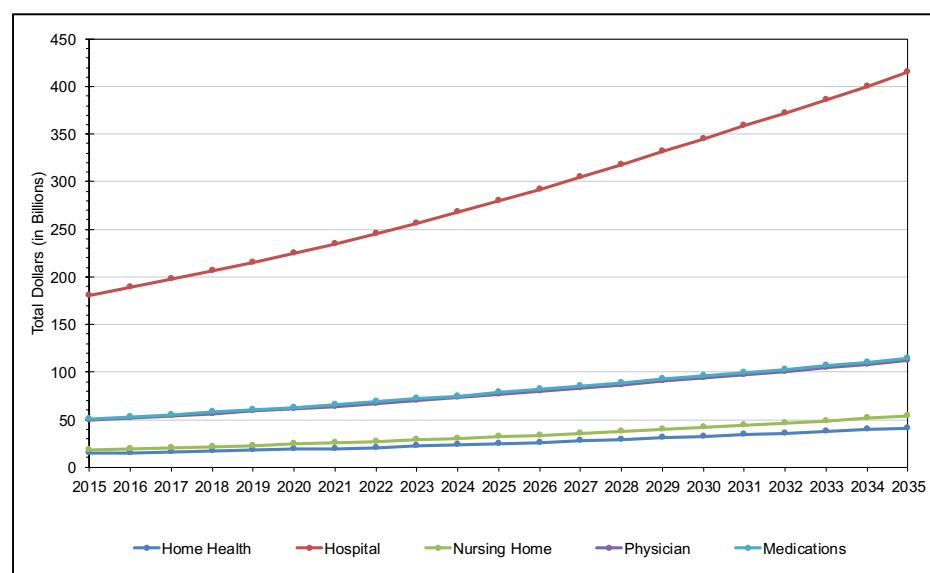
**Chart 26-3. Estimated direct cost (in billions of dollars) of cardiovascular disease, United States, average annual (1996–1997 to 2014–2015).**

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey for direct costs (average annual 1996–1997 to 2014–2015).<sup>1</sup>

**Chart 26-4. Projected total costs of CVD, United States, 2015 to 2035 (2015 dollars in billions).**

CHD indicates coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; and HBP, high blood pressure.

Source: Data from RTI International.<sup>8</sup> Copyright © 2016, American Heart Association, Inc.

**Chart 26-5. Projected total (direct and indirect) costs of total cardiovascular disease by age, United States, 2015 to 2035 (2015 dollars in billions).**Source: Data from RTI International.<sup>8</sup> Copyright © 2016, American Heart Association, Inc.**Chart 26-6. Projected direct costs of total cardiovascular disease by type of cost, United States, 2015 to 2035 (2015 dollars in billions).**Source: Data from RTI International.<sup>8</sup> Copyright © 2016, American Heart Association, Inc.

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## 27. AT-A-GLANCE SUMMARY TABLES

**See Tables 27-1 through 27-3**

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Sources: See the following summary tables for complete details:

- Prevalence of Overweight, Obesity, and Severe Obesity in Youth and Adults, United States, 2013 to 2016—Table 6-1

- High TC and LDL-C and Low HDL-C, United States, 2013 to 2016 (Age ≥20 Years)—Table 7-1
- HBP in the United States—Table 8-1
- DM in the United States—Table 9-1
- CVDs in the United States—Table 13-1
- Stroke in the United States—Table 14-1
- CCDs in the United States—Table 15-1
- CHD in the United States—Table 19-1; AP in the United States—Table 19-2
- HF in the United States —Table 20-2

**Table 27-1. Males and CVD: At-a-Glance Table**

Diseases and Risk Factors	Both Sexes	Total Males	NH White Males	NH Black Males	Hispanic Males	NH Asian Males	NH American Indian/Alaska Native*
Overweight and obesity							
Prevalence, 2013–2016							
Overweight and obesity, BMI ≥25.0 kg/m <sup>2</sup> †	168.1 M (71.1%)	85.3 M (74.3%)	75.6%	69.8%	81.3%	49.5%	...
Obesity, BMI ≥30.0 kg/m <sup>2</sup> †	73.8 M (31.2%)	35.7 M (31.1%)	31.3%	30.1%	35.3%	11.3%	...
Blood cholesterol							
Prevalence, 2013–2016							
Total cholesterol ≥200 mg/dL‡	92.8 M (38.2%)	41.2 M (35.4%)	35.4%	29.8%	39.9%	38.7%	...
Total cholesterol ≥240 mg/dL‡	28.5 M (11.7%)	12.4 M (10.7%)	10.5%	8.9%	13.0%	11.7%	...
LDL-C ≥130 mg/dL‡	69.6 M (28.9%)	34.8 M (30.1%)	29.4%	29.5%	33.5%	32.2%	...
HDL-C <40 mg/dL‡	45.6 M (19.2%)	33.7 M (29.0%)	29.7%	19.8%	32.6%	25.9%	...
HBP							
Prevalence, 2013–2016†	116.4 M (46.0%)	58.7 M (49.0%)	48.2%	58.6%	47.4%	46.4%	...
Mortality, 2017§	90 098	43 127 (47.9%)¶	29 086	8 690	3 478	1 269#	568
DM							
Prevalence, 2013–2016							
Diagnosed DMT†	26.0 M (9.8%)	13.7 M (10.9%)	9.4%	14.7%	15.1%	12.8%	...
Undiagnosed DMT†	9.4 M (3.7%)	5.5 M (4.6%)	4.7%	1.7%	6.3%	6.1%	...
Prediabetes†	91.8 M (37.6%)	51.7 M (44.0%)	43.7%	31.9%	48.1%	47.1%	...
Incidence, diagnosed DM, 2015**	1.5 M	...	...	...	...	...	...
Mortality, 2017§	83 564	46 302 (55.4%)¶	31 343	7 494	5 054	1 612#	1 114
Total CVD							
Prevalence, 2013–2016†	121.5 M (48.0%)	61.5 M (51.2%)	50.6%	60.1%	49.0%	47.4%	...
Mortality, 2017§	859 125	440 460 (51.3%)¶	340 026	54 780	29 366	11 891#	4 554
Stroke							
Prevalence, 2013–2016†	7.0 M (2.5%)	3.2 M (2.5%)	2.4%	3.1%	2.0%	1.1%	...
New and recurrent strokes§	795.0 K	370.0 K (46.5%)¶	325.0 K††	45.0 K††	...	...	...
Mortality, 2017§	146 383	61 645 (42.1%)¶	45 078	8 566	5 073	2 442#	737##
CHD							
Prevalence, CHD, 2013–2016†	18.2 M (6.7%)	9.4 M (7.4%)	7.7%	7.2%	6.0%	4.8%	...
Prevalence, MI, 2013–2016†	8.4 M (3.0%)	5.1 M (4.0%)	4.0%	4.0%	3.4%	2.4%	...
Prevalence, AP, 2013–2016†	9.4 M (3.6%)	4.3 M (3.5%)	3.8%	3.6%	2.6%	2.0%	...
New and recurrent MI and fatal CHD§§	1.05 M	610.0 K	520.0 K††	90.0 K††	...	...	...
New and recurrent MI§§	805.0 K	470.0 K	...	...	...	...	...

(Continued)

**Table 27-1.** Continued

Diseases and Risk Factors	Both Sexes	Total Males	NH White Males	NH Black Males	Hispanic Males	NH Asian Males	NH American Indian/Alaska Native*
Mortality, 2017, CHD§	365 914	213 295 (58.3%)¶	168 868	22 167	14 195	5721	2032
Mortality, 2017, MI§	110 346	64 436 (58.4%)¶	51 155	6595	4437	1693#	593
HF							
Prevalence, 2013–2016†	6.2 M (2.2%)	3.0 M (2.4%)	2.2%	3.5%	2.5%	1.7%	...
Incidence, 2014	1.0 M	495.0 K	430.0 K††	65.0 K††	...	...	...
Mortality, 2017§	80 480	36 824 (45.8%)¶	30 076	4068	1820	633#	339

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; DM, diabetes mellitus; ellipses (...), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); and NH, non-Hispanic.

\*Both sexes.

†Age ≥20 years.

‡Total data for total cholesterol are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial/ethnic groups are age adjusted for age ≥20 years.

§All ages.

||Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

\*\*Age ≥18 years.

††Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

††Estimate considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

||Age ≥55 years.

**Table 27-2.** Females and CVD: At-a-Glance Table

Diseases and Risk Factors	Both Sexes	Total Females	NH White Females	NH Black Females	Hispanic Females	NH Asian Females	NH American Indian/Alaska Native*
Overweight and obesity							
Prevalence, 2011–2014							
Overweight and obesity, BMI ≥25.0 kg/m <sup>2</sup> †	168.1 M (71.1%)	82.8 M (68.1%)	66.3%	80.5%	77.8%	36.5%	...
Obesity, BMI ≥30.0 kg/m <sup>2</sup> †	73.8 M (31.2%)	38.1 M (31.3%)	29.6%	40.6%	37.8%	13.3%	...
Blood cholesterol							
Prevalence, 2013–2016							
Total cholesterol ≥200 mg/dL‡	92.8 M (38.2%)	51.6 M (40.4%)	41.8%	33.1%	38.9%	39.6%	...
Total cholesterol ≥240 mg/dL‡	28.5 M (11.7%)	16.1 M (12.4%)	13.6%	9.0%	10.1%	10.8%	...
LDL-C ≥130 mg/dL, 2011–2014‡	69.6 M (28.9%)	34.8 M (27.6%)	29.7%	23.4%	23.8%	25.1%	...
HDL-C <40 mg/dL, 2013–2016‡	45.6 M (19.2%)	11.9 M (9.9%)	9.3%	8.1%	13.1%	7.9%	...
HBP							
Prevalence, 2013–2016†	116.4 M (46.0%)	57.7 M (42.8%)	41.3%	56.0%	40.8%	36.4%	...
Mortality, 2017§	90 098	46 971 (52.1%)¶	33 396	8387	3282	1538#	568
DM							
Prevalence, 2013–2016							
Diagnosed DM†	26.0 M (9.8%)	12.3 M (8.9%)	7.3%	13.4%	14.1%	9.9%	...
Undiagnosed DM†	9.4 M (3.7%)	3.9 M (2.8%)	2.6%	3.3%	4.0%	2.1%	...
Prediabetes†	91.8 M (37.6%)	40.1 M (31.3%)	32.2%	24.0%	31.7%	29.4%	...
Incidence, diagnosed DM, 2015**	1.5 M	...	...	...	...	...	...
Mortality, 2017§	83 564	37 262 (44.6%)¶	23 773	7304	4162	1435#	1114
Total CVD							
Prevalence, 2013–2016†	121.5 M (48.0%)	60.0 M (44.7%)	43.4%	57.1%	42.6%	37.2%	...
Mortality, 2017§	859 125	418 665 (48.7%)¶	326 447	52 528	25 309	11 242#	4554

(Continued)

**Table 27-2.** Continued

Diseases and Risk Factors	Both Sexes	Total Females	NH White Females	NH Black Females	Hispanic Females	NH Asian Females	NH American Indian/Alaska Native*
<b>Stroke</b>							
Prevalence, 2013–2016†	7.0 M (2.5%)	3.8 M (2.6%)	2.5%	3.8%	2.2%	1.6%	...
New and recurrent strokes§	795.0 K	425.0 K (53.5%)¶	365.0 K††	60.0 K††	...	...	...
Mortality, 2017§	146 383	84 738 (57.9%)¶	64 960	10 522	5 702	2 988#	737‡‡
<b>CHD</b>							
Prevalence, CHD, 2013–2016†	18.2 M (6.7%)	8.8 M (6.2%)	6.1%	6.5%	6.0%	3.2%	...
Prevalence, MI, 2013–2016†	8.4 M (3.0%)	3.3 M (2.3%)	2.2%	2.2%	2.0%	1.0%	...
Prevalence, AP, 2013–2016†	9.4 M (3.6%)	5.1 M (3.7%)	3.8%	3.8%	3.6%	1.6%	...
New and recurrent MI and fatal CHD§§	1.05 M	445.0 K	370.0 K††	75.0 K††	...	...	...
New and recurrent MI§§	805.0 K	335.0 K	...	...	...	...	...
Mortality, 2017, CHD§¶	365 914	152 619 (41.7%)¶	119 151	18 055	10 041	4 103	2 032
Mortality, 2017, MI§¶	110 346	45 910 (41.6%)¶	35 720	5 458	3 113	1 271#	593
<b>HF</b>							
Prevalence, 2013–2016†	6.2 M (2.2%)	3.2 M (2.1%)	1.9%	3.9%	2.1%	0.7%	...
Incidence, 2014¶¶	1.0 M	505.0 K	425.0 K‡‡	80.0 K‡‡	...	...	...
Mortality, 2017§¶	80 480	43 656 (54.2%)¶	36 004	4 683	1 960	752#	339

AP indicates angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes MI, AP, or both); CVD, cardiovascular disease; DM, diabetes mellitus; ellipses (...), data not available; HBP, high blood pressure; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, thousands; LDL-C, low-density lipoprotein cholesterol; M, millions; MI, myocardial infarction (heart attack); and NH, non-Hispanic.

\*Both sexes.

†Age ≥20 years.

‡Total data for total cholesterol are for Americans ≥20 years of age. Data for LDL-C, HDL-C, and all racial/ethnic groups are age adjusted for age ≥20 years.

§All ages.

¶Mortality for Hispanic, NH American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese, Filipino, Hawaiian, Japanese, and other Asian or Pacific Islander.

\*\*Age ≥18 years.

††Estimates include Hispanics and non-Hispanics. Estimates for whites include other nonblack races.

‡‡Estimate considered unreliable or does not meet standards of reliability or precision.

§§Age ≥35 years.

¶¶Age ≥55 years.

**Table 27-3.** Children, Youth, and CVD: At-a-Glance Table

Diseases and Risk Factors	Both Sexes	Total Males	Total Females	NH Whites		NH Blacks		Hispanic		NH Asian				
				Males	Females	Males	Females	Males	Females	Males	Females			
Overweight and obesity														
Prevalence, 2011–2014														
Overweight and obesity, ages 2–19 y*	25.4 M (34.2%)	13.0 M (34.2%)	12.5 M (34.3%)	30.9%	28.5%	32.4%	42.2%	43.8%	43.8%	24.2%	19.2%			
Obesity, ages 2–19 y*	13.2 M (17.8%)	6.9 M (18.1%)	6.4 M (17.5%)	15.3%	14.1%	17.9%	23.0%	24.3%	22.9%	11.9%	7.4%			
Blood cholesterol, 2013–2016														
Mean total cholesterol, mg/dL														
Ages 6–11 y	157.8	157.9	157.7	157.1	159.1	158.8	158.2	158.7	153.9	160.1	161.5			
Ages 12–19 y	154.4	151.6	157.5	150.6	157.2	150.8	156.0	152.7	156.0	155.4	170.2			
Mean HDL-C, mg/dL														
Ages 6–11 y	56.0	57.4	54.5	56.6	54.7	62.5	58.1	55.9	52.2	58.1	54.4			
Ages 12–19 y	51.8	49.9	53.8	49.2	53.5	54.4	56.9	49.6	52.2	52.8	56.6			
Mean LDL-C, mg/dL														
Ages 12–19 y	86.7	85.6	87.8	86.7	87.9	81.7	88.4	85.0	84.2	81.7	103.3			
Congenital cardiovascular defects (all age groups: children and adults)														
Mortality, 2017†‡§¶	2906	1583 (54.5%)§	1323 (45.5%)§	923	779	273	225	301	239	62	59			

CVD indicates cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, millions; and NH, non-Hispanic.

\*In children, overweight and obesity are based on body mass index (BMI)-for-age values at or above the 85th percentile of the 2000 Centers for Disease Control and Prevention (CDC) growth charts. Obesity is based on BMI-for-age values at or above the 95th percentile of the CDC growth charts.

†All ages.

‡Mortality for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

§These percentages represent the portion of total congenital cardiovascular mortality that is for males vs females.

¶NH American Indian/Alaska Native, Mortality: 38.

## 28. GLOSSARY

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- **Age-adjusted rates**—Used mainly to compare the rates of ≥2 communities or population groups or the nation as a whole over time. The American Heart Association (AHA) uses a standard population (2000), so these rates are not affected by changes or differences in the age composition of the population. Unless otherwise noted, all death rates in this publication are age adjusted per 100 000 population and are based on underlying cause of death.
- **Agency for Healthcare Research and Quality (AHRQ)**—A part of the US Department of Health and Human Services, this is the lead agency charged with supporting research designed to improve the quality of health care, reduce the cost of health care, improve patient safety, decrease the number of medical errors, and broaden access to essential services. The AHRQ sponsors and conducts research that provides evidence-based information on healthcare outcomes, quality, cost, use, and access. The information helps healthcare decision makers (patients, clinicians, health system leaders, and policy makers) make more informed decisions and improve the quality of healthcare services. The AHRQ conducts the Medical Expenditure Panel Survey (MEPS; ongoing).
- **Body mass index (BMI)**—A mathematical formula to assess body weight relative to height. The measure correlates highly with body fat. It is calculated as weight in kilograms divided by the square of the height in meters ( $\text{kg}/\text{m}^2$ ).
- **Centers for Disease Control and Prevention/National Center for Health Statistics (CDC/NCHS)**—The CDC is an agency within the US Department of Health and Human Services. The CDC conducts the Behavioral Risk Factor Surveillance System (BRFSS), an ongoing survey. The CDC/NCHS conducts or has conducted these surveys (among others):
  - National Health Examination Survey (NHES I, 1960–1962; NHES II, 1963–1965; NHES III, 1966–1970)
  - National Health and Nutrition Examination Survey I (NHANES I; 1971–1975)
  - National Health and Nutrition Examination Survey II (NHANES II; 1976–1980)
  - National Health and Nutrition Examination Survey III (NHANES III; 1988–1994)
  - National Health and Nutrition Examination Survey (NHANES; 1999 to ...) (ongoing)
  - National Health Interview Survey (NHIS; ongoing)
- National Hospital Discharge Survey (NHDS; 1965–2010)
- National Ambulatory Medical Care Survey (NAMCS; ongoing)
- National Hospital Ambulatory Medical Care Survey (NHAMCS; ongoing)
- National Nursing Home Survey (periodic)
- National Home and Hospice Care Survey (periodic)
- National Vital Statistics System (ongoing)
- **Centers for Medicare & Medicaid Services**—The federal agency that administers the Medicare, Medicaid, and Child Health Insurance programs.
- **Comparability ratio**—Provided by the NCHS to allow time-trend analysis from one *International Classification of Diseases (ICD)* revision to another. It compensates for the “shifting” of deaths from one causal code number to another. Its application to mortality based on one *ICD* revision means that mortality is “comparability modified” to be more comparable to mortality coded to the other *ICD* revision.
- **Coronary heart disease (CHD) (ICD-10 codes I20–I25)**—This category includes acute myocardial infarction (I21–I22); certain current complications following acute myocardial infarction (I23); other acute ischemic (coronary) heart disease (I24); angina pectoris (I20); atherosclerotic cardiovascular disease (I25.0); and all other forms of chronic ischemic (coronary) heart disease (I25.1–I25.9).
- **Death rate**—The relative frequency with which death occurs within some specified interval of time in a population. National death rates are computed per 100 000 population. Dividing the total number of deaths by the total population gives a crude death rate for the total population. Rates calculated within specific subgroups, such as age-specific or sex-specific rates, are often more meaningful and informative. They allow well-defined subgroups of the total population to be examined. Unless otherwise stated, all death rates in this publication are age adjusted and are per 100 000 population.
- **Diseases of the circulatory system (ICD-10 codes I00–I99)**—Included as part of what the AHA calls “cardiovascular disease” (“Total cardiovascular disease” in this Glossary).
- **Diseases of the heart (ICD-10 codes I00–I09, 111, 113, 120–151)**—Classification the NCHS uses in compiling the leading causes of death. Includes acute rheumatic fever/chronic rheumatic heart diseases (I00–I09); hypertensive heart disease (I11); hypertensive heart and renal disease (I13); CHD (I20–I25); pulmonary heart disease and diseases of pulmonary circulation (I26–I28); heart failure (I50); and other forms of heart disease

(I30–I49, I51). “Diseases of the heart” are not equivalent to “total cardiovascular disease,” which the AHA prefers to use to describe the leading causes of death.

- **Hispanic origin**—In US government statistics, “Hispanic” includes people who trace their ancestry to Mexico, Puerto Rico, Cuba, Spain, the Spanish-speaking countries of Central or South America, the Dominican Republic, or other Spanish cultures, regardless of race. It does not include people from Brazil, Guyana, Suriname, Trinidad, Belize, or Portugal, because Spanish is not the first language in those countries. Most of the data in this update are for all Hispanics, as reported by government agencies or specific studies. In certain time-trend charts and tables, data for Mexican Americans are shown because data are not available for all Hispanics.
- **Hospital discharges**—The number of inpatients (including newborn infants) discharged from short-stay hospitals for whom some type of disease was the principal diagnosis. Discharges include those discharged alive, dead, or “status unknown.”
- **International Classification of Diseases (ICD) codes**—A classification system in standard use in the United States. The *ICD* is published by the World Health Organization. This system is reviewed and revised approximately every 10 to 20 years to ensure its continued flexibility and feasibility. The 10th revision (*ICD-10*) began with the release of 1999 final mortality data. The *ICD* revisions can cause considerable change in the number of deaths reported for a given disease. The NCHS provides “comparability ratios” to compensate for the “shifting” of deaths from one *ICD* code to another. To compare the number or rate of deaths with that of an earlier year, the “comparability-modified” number or rate is used.
- **Incidence**—An estimate of the number of new cases of a disease that develop in a population, usually in a 1-year period. For some statistics, new and recurrent attacks, or cases, are combined. The incidence of a specific disease is estimated by multiplying the incidence rates reported in community- or hospital-based studies by the US population. The rates in this report change only when new data are available; they are not computed annually.
- **Infective endocarditis**—An infection of the heart’s inner lining (endocardium) or of the heart valves. The bacteria that most often cause endocarditis are streptococci, staphylococci, and enterococci.
- **Major cardiovascular diseases**—Disease classification commonly reported by the NCHS; represents *ICD-10* codes I00 to I78. The AHA does not use “major cardiovascular diseases” for any

calculations. See “Total cardiovascular disease” in this Glossary.

- **Metabolic syndrome**—Metabolic syndrome is defined as the presence of any 3 of the following 5 diagnostic measures: Elevated waist circumference (>102 cm in males or >88 cm in females), elevated triglycerides ( $\geq 150 \text{ mg/dL}$  [1.7 mmol/L] or drug treatment for elevated triglycerides), reduced high-density lipoprotein cholesterol ( $<40 \text{ mg/dL}$  [0.9 mmol/L] in males,  $<50 \text{ mg/dL}$  [1.1 mmol/L] in females, or drug treatment for reduced high-density lipoprotein cholesterol), elevated blood pressure ( $\geq 130 \text{ mmHg}$  systolic blood pressure,  $\geq 85 \text{ mmHg}$  diastolic blood pressure, or drug treatment for hypertension), and elevated fasting glucose ( $\geq 100 \text{ mg/dL}$  or drug treatment for elevated glucose).
- **Morbidity**—Incidence and prevalence rates are both measures of morbidity (ie, measures of various effects of disease on a population).
- **Mortality**—Mortality data for states can be obtained from the NCHS website (<http://cdc.gov/nchs/>), by direct communication with the CDC/NCHS, or from the AHA on request. The total number of deaths attributable to a given disease in a population during a specific interval of time, usually 1 year, are reported. These data are compiled from death certificates and sent by state health agencies to the NCHS. The process of verifying and tabulating the data takes  $\approx 2$  years.
- **National Heart, Lung, and Blood Institute (NHLBI)**—An institute in the National Institutes of Health in the US Department of Health and Human Services. The NHLBI conducts such studies as the following:
  - Framingham Heart Study (FHS; 1948 to ...) (ongoing)
  - Honolulu Heart Program (HHP; 1965–2002)
  - Cardiovascular Health Study (CHS; 1989 to ...) (ongoing)
  - Atherosclerosis Risk in Communities (ARIC) study (1987 to ...) (ongoing)
  - Strong Heart Study (SHS; 1989 to ...) (ongoing)
  - Multi-Ethnic Study of Atherosclerosis (MESA; 2000 to ...) (ongoing)
- **National Institute of Neurological Disorders and Stroke (NINDS)**—An institute in the National Institutes of Health of the US Department of Health and Human Services. The NINDS sponsors and conducts research studies such as these:
  - Greater Cincinnati/Northern Kentucky Stroke Study (GCNKS)
  - Rochester (Minnesota) Stroke Epidemiology Project
  - Northern Manhattan Study (NOMAS)
  - Brain Attack Surveillance in Corpus Christi (BASIC) Project

- **Physical activity**—Any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level.
- **Physical fitness**—The ability to perform daily tasks with vigor and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and respond to emergencies. Physical fitness includes a number of components consisting of cardiorespiratory endurance (aerobic power), skeletal muscle endurance, skeletal muscle strength, skeletal muscle power, flexibility, balance, speed of movement, reaction time, and body composition.
- **Prevalence**—An estimate of the total number of cases of a disease existing in a population during a specified period. Prevalence is sometimes expressed as a percentage of population. Rates for specific diseases are calculated from periodic health examination surveys that government agencies conduct. Annual changes in prevalence as reported in this Statistical Update reflect changes in the population size. Changes in rates can be evaluated only by comparing prevalence rates estimated from surveys conducted in different years. Note: In the data tables, which are located in the different disease and risk factor chapters, if the percentages shown are age adjusted, they will not add to the total.
- **Race and Hispanic origin**—Race and Hispanic origin are reported separately on death certificates. In this publication, unless otherwise specified, deaths of people of Hispanic origin are included in the totals for whites, blacks, American Indians or Alaska Natives, and Asian or Pacific Islanders according to the race listed on the decedent's death certificate. Data for Hispanic people include all people of Hispanic origin of any race. See "Hispanic origin" in this Glossary.
- **Stroke (ICD-10 codes I60–I69)**—This category includes subarachnoid hemorrhage (I60); intracerebral hemorrhage (I61); other nontraumatic intracranial hemorrhage (I62); cerebral infarction (I63); stroke, not specified as hemorrhage or infarction (I64); occlusion and stenosis of precerebral arteries not resulting in cerebral infarction (I65); occlusion and stenosis of cerebral arteries not resulting in cerebral infarction (I66); other cerebrovascular diseases (I67); cerebrovascular disorders in diseases classified elsewhere (I68); and sequelae of cerebrovascular disease (I69).
- **Total cardiovascular disease (ICD-10 codes I00–I99)**—This category includes rheumatic fever/rheumatic heart disease (I00–I09); hypertensive diseases (I10–I15); ischemic (coronary) heart disease (I20–I25); pulmonary heart disease and diseases of pulmonary circulation (I26–I28); other forms of heart disease (I30–I52); cerebrovascular disease (stroke) (I60–I69); atherosclerosis (I70); other diseases of arteries, arterioles, and capillaries (I71–I79); diseases of veins, lymphatics, and lymph nodes not classified elsewhere (I80–I89); and other and unspecified disorders of the circulatory system (I95–I99).
- **Underlying cause of death or any-mention cause of death**—These terms are used by the NCHS when defining mortality. Underlying cause of death is defined by the World Health Organization as "the disease or injury which initiated the chain of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." Any-mention cause of death includes the underlying cause of death and up to 20 additional multiple causes listed on the death certificate.