Informing Clinical Practice Guideline Development and Implementation: Prevalence of Coexisting Conditions Among Adults with Coronary Heart Disease

Cynthia M. Boyd, MD, MPH,[*†‡§] Bruce Leff, MD,*[*†‡§] Jennifer L. Wolff, PhD,*[*†‡§] Qilu Yu, PhD,*[*†] Jing Zhou, MS,[‖] Cynthia Rand, PhD,[#] and Carlos O. Weiss, MD, MHS*[*†]*

OBJECTIVES: To describe the prevalence of coexisting conditions that affect clinical decision-making in adults with coronary heart disease (CHD).

DESIGN: Cross-sectional.

SETTING: National Health and Nutrition Examination Survey, 1999 to 2004.

PARTICIPANTS: Eight thousand six hundred fifty-four people aged 45 and older; 1,259 with CHD.

MEASUREMENTS: Coexisting conditions relevant to clinical decision-making and implementing therapy for CHD across three domains: chronic diseases, self-reported and laboratory-based clinical measures, and health status factors of self-reported and observed function. Prevalence was estimated according to sex and age, mutually exclusive patterns were examined, and the odds ratios (OR) of having incurred repeated hospitalization in the last year of participants with CHD and each complexity pattern versus CHD alone were modeled.

RESULTS: The prevalence of comorbid chronic diseases in subjects with CHD was 56.7% for arthritis, 29.0% for congestive heart failure, 25.5% for chronic lower respiratory tract disease, 24.8% for diabetes mellitus, and 13.8% for stroke. Clinical factors adding to complexity of clinical decision-making for CHD were use of more than four medications (54.5%), urinary incontinence (48.6%), dizziness or falls (34.8%), low glomerular filtration rate (24.4%), anemia (10.1%), high alanine aminotransferase (5.9%), use of warfarin (10.2%), and health status factors were cognitive impairment (29.9%), mobility difficulty (40.4%), frequent mental distress (14.3%), visual impairment (16.7%), and hearing impairment (17.9%). Several comorbidity patterns were associated with high odds of hospitalization.

CONCLUSION: Coexisting conditions that may modify the effectiveness of or interact with CHD therapies, influence the feasibility of CHD therapies, or alter patients' priorities concerning their health care should be considered in the development of trials and guidelines to better inform real-world clinical decision-making. **J Am Geriatr Soc 59:797–805, 2011.**

Key words: comorbidity; heart disease; guideline; prevalence

Coronary heart disease (CHD) is a common disease in older adults, with a prevalence of 37% in men and 26% in women aged 65 and older in the United States.[1] It is negatively associated with quality of life and is the leading cause of death in this country.[2,3] In older adults with CHD, 79% of women and 69% of men have at least one additional major chronic disease.[4] There is increasing recognition that people with CHD and additional chronic conditions experience high levels of healthcare use and poor outcomes.[5,6]

Prior work in the Medicare population has found that select noncardiac comorbidities increase the risk of preventable hospitalizations and death in people with CHD.[7] Conditions that worsen the specific pathophysiology of CHD; reduce the person's physiological ability to compensate for CHD and thereby worsen its effects; interact with CHD therapies to alter their actions, both beneficial and unintended; affect patients' or physicians' priorities for treatment; or function as competing demands may cause these adverse outcomes. In this respect, CHD is typical, rather than an exception, among major chronic diseases,

From the Divisions of *Geriatric Medicine and Gerontology and [#]Pulmonary Medicine, School of Medicine and, [‡]Department of Health Policy and Management and [§]Roger C. Lipitz Center for Integrated Health Care, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, Maryland; [†]Center on Aging and Health, Johns Hopkins Medical Institutions, Baltimore, Maryland; and [‖]United States Military Cancer Institute, Walter Reed Army Medical Center, Bethesda, Maryland.

Address correspondence to Cynthia M. Boyd, Division of Geriatric Medicine and Gerontology and the Center on Aging and Health, Johns Hopkins University School of Medicine, Mason F. Lord Building, Center Tower, Seventh Floor, 5200 Eastern Avenue, Johns Hopkins Bayview Medical Campus, Baltimore, MD 21224. E-mail: cboyd1@jhmi.edu

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although which comorbidities are important to consider in patients with CHD is unknown, and prevalence and the potential for the condition to affect real-world clinical decision-making are likely to determine the highest priorities. Comorbidity has been defined as "any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study."[8] Comorbidity has been studied for the purposes of prognostication, risk adjustment, and more recently, understanding heterogeneity of treatment effect,[9,10] but there has been little work to frame how comorbidities that may confer health status complexity at the patient level affect clinical decision-making.[11,12] Thus, which comorbid conditions should be considered in the development of more-relevant clinical practice guidelines (CPGs) and their implementation is unknown. Such a framework would help establish priorities for their development, so this study sought to describe the prevalence of coexisting factors in nationally representative data with the specific purpose of articulating influential factors that affect clinical decision-making and that might potentially inform the development and implementation of clinical guidelines for CHD. This article draws from a nationally representative data set, the National Health and Nutrition Survey (NHANES), to estimate the prevalence and effect of patterns of chronic diseases, clinical factors, and health status factors that increase the complexity of management of CHD as a basis for deciding which clinically important factors should be studied and incorporated into management for people with CHD. The cross-sectional relationship between these factors and healthcare use, specifically repeated hospitalization in the past year, is then modeled, comparing the most common mutually exclusive patterns of these factors plus CHD with CHD alone.

METHODS

Study Population

NHANES is a nationally representative study of noninstitutionalized civilians that employs a complex multistage probability design to oversample persons aged 60 and older. Collection of information occurs through home interviews or examinations in mobile centers. Study details, including operations manuals, are publicly available.[13] To ensure adequate sample size in age and sex strata, three survey waves (1999–2000, 2001–2002, and 2003–2004) were joined to create an analytical sample of 8,654 observations of people aged 45 and older, including 1,259 with CHD. NHANES interview response rates ranged from 76% to 80% for the three waves.

Choice of Conditions

Conditions that are likely to alter the clinical course or ability to treat CHD were considered, focusing on intrinsic conditions that are relevant when making decisions related to prescribing medications or other treatments or achieving adherence. Although health system and societal factors are also significant, these factors were beyond the scope of this study. Specifically, the clinician authors created a consensus list of conditions that physiologically interact with recommended therapies or that alter a patient's ability to achieve treatment benefit. These factors were grouped into disease, clinical, and health status domains to reflect a progressively widening scope from classic disease definitions to conditions and finally to whole-person relevance (Table 1). The disease domain encompassed other traditional chronic diseases that are considered of major importance because they are established as leading causes of death or morbidity and because there are known interactions between each disease and CHD, between CHD treatments and each disease, between one of their treatments and CHD, or between treatments for both conditions. The clinical domain consisted of physiological conditions and factors that should be weighed when prescribing therapies because they may be a contraindication or relative contraindication (e.g., the presence of high liver enzymes when considering the use of statin drugs or complaints of dizziness when considering the use and dose of therapy to lower blood pressure). The health status domain was reserved for conditions that affect function and quality of life, are likely to affect a person's ability to adhere to therapy, and are often caused by several processes in older adults.

Diseases

Comorbid disease status was ascertained through NHANES questions asking "Has a doctor or other health professional ever told you had [disease]?" Arthritis, congestive heart failure (CHF), and stroke were identified in this manner through single questions. Persons with CHD were those who responded affirmatively to any of three questions about CHD, angina pectoris, or a heart attack. Likewise, chronic lower respiratory tract disease included emphysema, chronic bronchitis, or current asthma or a history of asthma and refused to answer if they still had it. Apart from this exception, individuals were counted as disease-free only if they responded no to relevant questions. Participants were able to answer that they had borderline diabetes mellitus. Of those reporting borderline diabetes, individuals were counted as having diabetes mellitus if they took insulin or a pill for diabetes mellitus or had retinopathy, a lower extremity ulcer that took more than 4 weeks to heal, or numbness or tingling in the hands or feet due to diabetes mellitus.

Clinical Factors

Low glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease equation based on serum creatinine, age, race and gender as <60 mL/min.[14] Low hemoglobin was defined as <12 g/dL in women and <13 g/dL in men.[15] High alanine aminotransferase was defined as a serum level greater than 40 u/L in women and greater than 45 u/L in men. Urinary incontinence (UI) was ascertained according to self-report of leaking urine at least a few times a month. Individuals who reported dizziness or imbalance lasting at least 2 weeks or for an unknown duration or having fallen in the last year were counted as having problems with dizziness or falls. Using more than four medications was defined following a previously established cutpoint[16] and from inspection of prescribed medications and over-the-counter analgesics used daily. Supplements, vitamins, and minerals were not counted as medications. Use of warfarin was defined after inspection of prescribed medications.

Table 1. Definitions of Factors Adding to Complexity

Condition	Measure	Ascertainment Method
Index disease		
Coronary heart disease: coronary heart disease, angina pectoris, or heart attack		
Complexity in three domains		
I. Chronic disease domain		
Arthritis	Arthritis	▼
Chronic lower respiratory tract	Emphysema	▼
	Chronic bronchitis	▼
Disease	Asthma now or had in past and refused to say	▼
Congestive heart failure	Congestive heart failure	▼
Diabetes mellitus	Diabetes mellitus	▼
	Borderline diabetes mellitus and take a pill or insulin	▼
	Borderline diabetes mellitus and retinopathy, leg ulcer, or numbness or tingling due to diabetes mellitus	▼
Stroke	Stroke	▼
II. Clinical domain		
High alanine aminotransferase	>40 u/L in women and ≥45 in men	•
Anemia	Hemoglobin <12 g/dL in women and <13 g/dL in men	•
Dizziness or falls	Dizziness or imbalance lasting >2 weeks or do not know how long or difficulty falling in past year	▼
Low glomerular filtration rate	<60 mL/min according Modified Diet in Renal Disease based on serum creatinine, age, race, and sex	•
>4 Medications	Inspection of prescribed medications and over-the-counter analgesics used daily	■
Urinary incontinence	Leak urine a few times a month or more	▼
Warfarin use	Inspection of medications	■
III. Health status domain		
Cognitive impairment	Lowest quintile Digit Symbol Substitution Test or refused or unable to complete practice test	■
Hearing impairment	A lot of trouble hearing or use hearing aid	▼
Frequent mental distress	≥14 of past 30 days "mental health not good"	▼
Mobility difficulty	Difficulty walking one-quarter of a mile or up 10 steps without equipment	▼
Visual impairment	Extreme difficulty reading newsprint or seeing up close or vision >20/50 in better eye	▼ ■

■ = performance; • = laboratory; ▼ = self-report.

Health Status Factors

Cognitive impairment for those aged 60 and older was ascertained through performance on the Digit Symbol Substitution Test.[17] People who refused or were unable to perform the practice test for cognitive reasons or performed in the lowest quintile (<30 correct answers in 120 seconds) were counted as cognitively impaired. Mobility difficulty was defined as present if the individual reported difficulty walking one-quarter of a mile or up 10 steps without equipment.[18] Frequent mental distress was present if participants reported that for at least 14 of the past 30 days mental health was not good.[19,20] Visual impairment was ascertained through self-reported extreme difficulty reading newsprint or seeing up close or examined visual acuity score greater than 20/50 in the better eye. Hearing impairment was defined according to self-reporting a lot of trouble hearing or use of a hearing aid.

Additional Variables

The effects of age, sex, education, income, having health insurance, and race were examined using self-reported responses to questions. Access to care was defined as self-report of two or more physician visits in the last year.

Repeated Hospitalization Outcome

Study participants were asked whether they experienced an overnight hospital stay in the last year, not including spending a night in an emergency department. Those who replied affirmatively were also asked how many times this had occurred in the last year. The outcome was categorized as at least two hospitalizations in the last year. Sensitivity analyses were performed with alternative outcomes of more than one hospitalization in the last year, more than three hospitalizations in the last year, and a continuous outcome analyzed through negative binomial regression.

Analytic Plan

The National Center for Health Statistics (NCHS) provides sampling weights that account for sampling strategy and survey nonresponse. Using methods provided by NCHS, the original weights in the combined sample were modified to maintain national representation. Protocols for each wave

were compared to detect changes. No changes in protocol were observed for the variables used in these analyses, although revisions were made for inconsistencies in naming and coding. Analyses were performed with statistical software designed to conduct subpopulation analyses using masked variance units to estimate appropriate standard errors. Baseline characteristics were summarized using means and standard deviations. Differences in these variables between subjects with and without CHD were compared using a two-sided *t*-test for continuous variables and the a chi-square test for categorical data.

The decision to group age into categories of 45 to 64 and 65 and older was made following convention and after confirming that the small number of people aged 85 and older limited analyses in that group. Prevalence was estimated using binomial Wald 95% confidence intervals for the complexity factors in disease, clinical, and health status domains in older adults with CHD for different sex and age groups. The effect of these factors on the outcome of repeated hospitalization was then estimated and tested using a logistic regression model. Age and access to care ($\geq$2 physician visits in the last year) were adjusted for in the model. In each domain (disease, clinical, and health status factors), the five most common mutually exclusive complexity patterns were identified, taking into account the presence or absence of conditions in a domain. For the clinical domain, six patterns were examined because there was not a substantial drop in prevalence between the fifth and sixth most common patterns. Interactive terms were employed as appropriate to model odds ratios (ORs) for at least two hospitalizations in adults aged 45 and older with CHD plus a complexity pattern versus CHD alone. The effects of age, access to care, sex, education, income, and race were examined through multivariate models accounting for complexity factors. All analyses were conducted in SAS version 9.1 (SAS Institute, Inc., Cary, NC) and Stata version 9.2 (Stata Corp, College Station, TX). The Johns Hopkins University School of Medicine institutional review board approved the study protocol.

RESULTS

Table 2 describes the baseline demographic and complexity factors according to CHD status. People with CHD were more likely to be older, male, white, and less educated and to have health insurance and lower household income. Complexity factors across all three domains were all statistically significant and more prevalent for participants with CHD than for their counterparts without CHD, except for high alanine aminotransferase.

The prevalence of comorbid chronic diseases in subjects with CHD was 56.7% for arthritis, 29.0% for congestive heart failure, 25.5% for chronic lower respiratory tract disease, 24.8% for diabetes mellitus, and 13.8% for stroke; clinical factors adding to complexity of clinical decision-making for CHD were use of more than four medications (54.5%), UI (48.6%), dizziness or falls (34.8%), low GFR (24.4%), anemia (10.1%), high alanine aminotransferase (5.9%), use of warfarin (10.2%), and health status factors were cognitive impairment (29.9%), mobility difficulty (40.4%), frequent mental distress (14.3%), visual impairment (16.7%), and hearing impairment (17.9%).

Figure 1A–C depicts prevalence rates of chronic disease, clinical, and health status complexity in people with CHD. Although some conditions were significantly more common in the population aged 65 and older (UI, low GFR, anemia, mobility difficulty, visual and hearing impairment), many were equally common in those aged 45 to 64 (>4 medications, dizziness or falls, arthritis).

Table 3 depicts the prevalence of mutually exclusive patterns of the presence of CHD alone versus CHD with other specific complexity patterns of disease, clinical factors, or health status factors and the ORs and 95% CIs of experiencing at least two hospitalizations in the prior year. The six most prevalent complexity disease patterns captured 70.4% of people with CHD, the seven most prevalent clinical complexity patterns captured 58.1%, and the six most prevalent health status patterns captured 44.2% of people with CHD (Table 3).

A subset of complexity factors across domains was associated with repeated hospitalizations. For example, the 22.2% of participants with CHD who also had arthritis were not at significantly greater risk for repeated hospitalization than people with CHD alone (OR = 1.36, 95% CI = 0.77–2.38). In contrast, the 7.7% of participants with CHD who also had arthritis and diabetes mellitus were more than twice as likely to have been hospitalized at least twice (OR = 2.33, 95% CI = 1.18–4.62). In the clinical domain, the 13.1% with CHD also taking more than four medications (OR = 3.15, 95% CI = 1.75–5.66) and the 7.0% with CHD taking more than four medications and experiencing dizziness and UI (OR = 4.65, 95% CI = 1.37–15.79) were at greater risk for repeated hospitalization than those with CHD alone; those with UI were not. In the health status domain, mobility difficulty was consistently associated with repeated hospitalization; 11.4% with CHD and mobility difficulty (OR = 2.05, 95% CI = 1.15–3.67), 3.3% with CHD and mobility difficulty and hearing impairment (OR = 2.11, 95% CI = 0.87–5.16), and 2.4% with CHD mobility difficulty and visual impairment (OR = 3.24, 95% CI = 1.65–6.38) were at high risk.

DISCUSSION

This article describes a novel and replicable approach to considering clinical complexity that may assist in choosing conditions to be considered in clinical trials, guideline development and implementation, and therefore eventually in clinical decision-making with multimorbid patients. It found that three-quarters of adults with CHD have at least one condition contributing to complexity and that many people have several. The high prevalence of complexity of health status in people with CHD, which has not been previously identified or quantified, underscores the importance of recognizing these coexisting conditions in the conduct of research and clinical practice and the development and application of clinical practice guidelines for adults with CHD. Clinical and health factors that are not disease specific were as prevalent as, and sometimes more strongly associated with repeated hospitalization than, major chronic diseases. These findings suggest that efforts to reduce hospitalizations of people with CHD should potentially target interventions at conditions that classic disease

Table 2. Baseline Characteristics (Demographics and Complexity Factors) in Adults Aged ≥45, Overall and According to Coronary Heart Disease Status: National Health and Nutrition Examination Survey 1999–2004

Characteristic	Overall Sample (N = 8,654)	Subjects without CHD (n = 7,306)	Subjects with CHD (n = 1,259)	*P*-Value
Demographic variables				
Age, mean ± standard deviation	60.3 ± 0.2	59.3 ± 0.2	67.6 ± 0.6	<.001
Age, n (%)				
45–64		3,925 (69.4)	355 (39.4)	
65–74		1,688 (17.4)	1,693 (28.7)	
≥75		366 (13.2)	538 (31.8)	
Sex, n (%)				
Male	4,212 (46.1)	3,444 (44.8)	731 (56.1)	<.001
Female	4,442 (53.9)	3,862 (55.2)	528 (43.9)	
Race or ethnicity, n (%)				
White	4,846 (80.6)	3,981 (80.0)	829 (85.6)	<.001
Black	1,544 (10.0)	1,352 (10.2)	172 (8.2)	
Hispanic	2,031 (9.4)	1,781 (9.8)	224 (6.2)	
≥High school education, n (%)	5,350 (76.7)	4,583 (78.1)	727 (66.9)	<.001
Has health insurance, n (%)	7,578 (90.6)	6,328 (90.1)	1,175 (94.7)	<.001
Household income <$20,000, n (%)	2,368 (21.6)	1,888 (19.8)	449 (33.3)	<.001
Disease variables, n (%)				
Arthritis	3,517 (37.3)	2,767 (34.6)	703 (56.7)	<.001
Chronic lower respiratory tract disease	1,254 (15.4)	950 (14.0)	287 (25.5)	<.001
Diabetes mellitus	1,443 (12.5)	1,063 (10.6)	347 (24.8)	<.001
Stroke	568 (4.5)	357 (3.2)	199 (13.8)	<.001
Congestive heart failure	530 (4.5)	173 (1.7)	343 (29.0)	<.001
Clinical factors, n (%)				
Urinary incontinence	2,127 (42.8)	1,698 (41.8)	394 (48.5)	.003
Dizziness or falls	2,034 (20.9)	1,552 (18.8)	447 (34.8)	<.001
Use of >4 medications	1,961 (20.8)	1,258 (16.0)	671 (54.5)	<.001
Low glomerular filtration rate	915 (10.0)	626 (8.0)	278 (24.4)	<.001
Anemia	636 (5.9)	487 (5.2)	137 (10.1)	<.001
High alanine transferase	503 (7.3)	451 (7.5)	49 (5.9)	.16
Warfarin use	300 (2.7)	152 (1.6)	138 (10.2)	<.001
Health status factors, n (%)				
Cognitive impairment	813 (23.9)	619 (22.2)	178 (29.9)	.002
Mobility difficulty	2,035 (20.0)	1,561 (17.5)	447 (40.4)	<.001
Frequent mental distress	504 (10.4)	401 (10.0)	98 (14.3)	.002
Visual impairment	989 (10.3)	751 (9.0)	215 (16.7)	<.001
Hearing impairment	1,134 (9.8)	848 (8.6)	265 (17.9)	<.001

labels do not capture and focus on other clinical and health status factors.

It is likely that the mechanism by which coexisting diseases, clinical conditions, or health status conditions influence an outcome such as repeated hospitalization is complex, dependent on specific diseases and conditions, and influenced by social and health system factors that were not examined here. Not all clinical patterns of complexity were associated with risk of repeated hospitalization. Specific combinations of coexisting conditions influenced the outcome of repeated hospitalization, underscoring that not only the number of conditions, but also the specific conditions a person has, influences health status complexity. Many of the coexisting conditions may function as competing demands for physicians, patients, and family or friends.[21,22] Some studies suggest that having more chronic conditions is not associated with worse performance on disease-specific process measures, perhaps in part because of more-frequent contact with the health system.[23–25] Although disease-specific process measures are commonly used in patients with multimorbidity, there is no consensus on what the best quality measures for the population with multimorbidity are.[26] Considering whether coexisting conditions are concordant (sharing pathophysiology and likely to have an overlapping management plan) or discordant (not directly related in their pathogenesis or management and not sharing an underlying predisposing factor) illustrates that the relationship may be more complex.[27,28] For example, conditions that are discordant with diabetes mellitus decrease the likelihood of intensification of

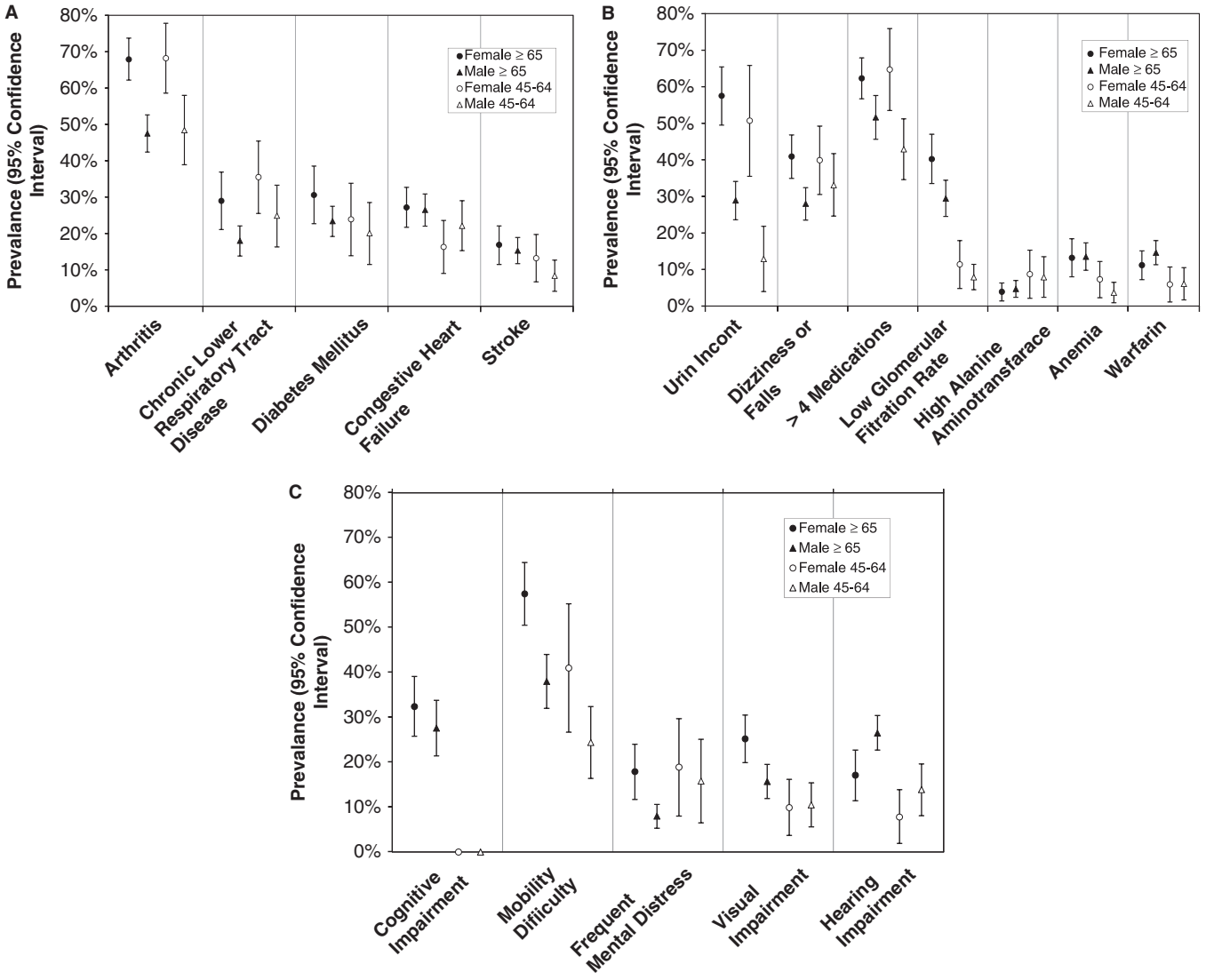

Figure 1. Prevalence of (A) diseases, (B) clinical factors, and (C) health status factors in people with coronary heart disease stratified according to age and sex.

hypertension management.[27,29–31] The acuity, severity, or dominance of comorbid conditions may be most important at a particular point in time.[29,32,33]

This study is particularly important in the context of the use of CPGs, which are used to guide management of chronic medical conditions. Translation of CPGs into practice can be difficult, but payers and others often use them to define quality standards and provide focus for quality improvement efforts.[34,35] Historically, CPGs have been developed with a focus on specific chronic conditions,[36] but little has been known about how or whether CPGs can be applied to the management of people with multimorbidity.[28,37–39] The data from the current study suggest that strict provider adherence to CPGs in complex adults with CHD may be associated with harm. For example, following the recommendations in a CPG for CHD may lead to taking more medications and could result in medication side effects such as dizziness or falls, all factors demonstrated to be associated with repeated hospitalization. In addition, taking more medications can lead to poorer adherence and influence patient safety and clinical outcomes.[40] CPG use in the clinical setting requires a substantial effort by the clinician to prioritize and make choices about all possible recommendations for CHD and other conditions.[39,41–44] Clinicians are without explicit guidance or evidence as to how to approach care decisions for such patients. A first step toward developing such guidance is to understand the common patterns of coexisting conditions relevant to clinical decision-making for adults with CHD.

These results also have implications for adults with CHD who do not have coexisting factors in any domain. Of this subpopulation, those who do not receive proven therapies may represent a prime opportunity to increase effectiveness given that they have fewer likely treatment interactions and contraindications to therapies and may have fewer barriers to adherence.

Neglect of these coexisting factors that may add to complexity of clinical decision-making in the design, conduct, and reporting of clinical and health services trials raises serious concerns about external validity of most CPGs. The patients studied in clinical trials that form the basis of CPGs do not adequately reflect the true population

Table 3. Likelihood of Reporting at Least Two Hospitalizations in Last Year in People with Coronary Heart Disease (CHD) Plus Multimorbidity Pattern Versus CHD Alone in Adults Aged ≥45: National Health and Nutrition Examination Survey 1999–2004

Multimorbidity Pattern	%	OR (95% Confidence Interval)
None (only CHD)	22.7	Reference
Arthritis	22.2	1.36 (0.77–2.38)
Arthritis and diabetes mellitus	7.7	2.33 (1.18–4.62)*
Arthritis and chronic lower respiratory tract disease	7.1	1.48 (0.84–2.59)
Arthritis and congestive heart failure	5.5	2.20 (1.04–4.63)*
Diabetes mellitus	5.2	1.72 (1.16–2.55)*
CHD and . . .		
No clinical factors	24.1	ref.
>4 medications	13.1	3.15 (1.75–5.66)*
>4 medications and dizziness or falls and UI	7.0	4.65 (1.37–15.79)*
>4 medications and UI	6.0	3.51 (1.32–9.32)*
UI	4.5	1.11 (0.53–2.33)
>4 medications and low glomerular filtration rate and UI	3.4	4.44 (1.28–15.44)*
Dizziness or falls and UI	2.9	1.48 (0.59–3.70)
CHD and . . .		
No functional factors	22.4	ref.
Mobility difficulty	11.4	2.05 (1.15–3.67)*
Mobility difficulty and hearing impairment	3.3	2.11 (0.87–5.16)
Hearing impairment	2.8	1.03 (0.52–2.05)
Mobility difficulty and visual impairment	2.4	3.24 (1.65–6.38)*
Visual impairment	1.9	1.58 (0.84–2.99)

Odds ratio (OR) using adults with CHD as referent (odds if have CHD and multimorbidity pattern/odds if have CHD). Models adjusted for age (continuous) and access to care (≥2 physician visits in last year). Sex, education, income, and race were not significant predictors after accounting for complexity factors, age, and access to care.

* Statistically significant.

UI = urinary incontinence.

in terms of burden of comorbidity, due in part to emphasis on efficacy by funding and regulatory agencies and perceived barriers to the participation of older adults in clinical trials.[45–47] Many older patients and patients with major comorbidities are still excluded from many clinical trials.[45,48] Although the number of trials with age exclusions has decreased, the number of heart failure trials excluding participants with specific comorbidities increased from 1985 to 1999, with more than half of such trials excluding people with major hepatic, renal, or hematological comorbidities.[49] By providing a framework for evaluating complexity along with empirical data for CHD, it may be possible to find a balance between trial safety and the need to include adequate representation of the targeted population. As a first step toward improving the ability to assess external validity, this study has provided nationally representative estimates for CHD and factors that may add to the complexity of clinical decision-making. If patients with multiple morbidities are to be enrolled in more pragmatic trials, new analytical techniques that account for heterogeneity of treatment effects, as opposed to emphasizing a single overall "average," should be explored.[50]

Studies of CHD report on the prevalence of a small number of conditions. To develop CPGs more relevant to people with CHD (or any index condition) and comorbidities, first it must be decided what the common and clinically relevant conditions to consider are. The current study has considered these on two levels: conditions and treatments that interact with CHD or its treatments and conditions that may make the implementation of guidelines more challenging. It described how common these conditions are in people with CHD to have this inform the processes that CHD guideline developers will undertake during development of new or revised CHD guidelines. This article does not mandate a specific set of conditions that should be considered in the development of CPGs. This choice will need to be part of priority setting at the outset of CPG development; the results reported here are necessary for a thoughtful deliberation.

LIMITATIONS

Although this work is generalizable to the community-dwelling population of the United States, it was limited to factors included in the NHANES data set, and it was not possible to assess fully all factors that would add to complexity of management of CHD, including depression and other diagnosed mental illnesses.[51] It is likely that frequent mental distress is associated with true mental illness but is not identical. It was not possible to address the perceived treatment burden that patients and their families and friends experience from therapies for CHD and coexisting conditions. It was possible to assess cognitive impairment only in those aged 65 and older, and visual impairment was fully measured only in participants aged 50 and older. It was not possible to assess health literacy, language barriers, or neighborhood characteristics. The institutional population is not represented in NHANES. Similarly, there are many conditions that would greatly add to complexity of management of a person with CHD that NHANES did not assess, including active cancer, aspirin sensitivity, and many others. It was not possible to ascertain the length of stay or cause of hospitalization. The hospitalizations occurred in the year before the NHANES assessment. Self-report of conditions was relied on for many of the assessed conditions, and although agreement between self-report of chronic conditions and a thorough adjudication process has been demonstrated to be reasonably good in community-dwelling disabled women, there is still some misclassification.[52] Despite these limitations, the empirical data on the burden of complexity experienced by adults with CHD provided is useful and is more than has been previously recognized in clinical practice, CPGs, and clinical and health services research.

CONCLUSION

Complexity of clinical management for people with CHD is the rule, not the exception. Although half of older adults have three or more chronic conditions, the current

paradigm of evidence-based medicine and healthcare quality focuses largely on single diseases.[35,39,53–55] Data are limited, so there is a limited knowledge base to guide clinicians on how to deliver the best-quality care to these patients.[39,41–44] CPGs focused on single diseases do not apply well to those with multimorbidity.[39] Describing the complexity of patients with CHD is a necessary first step toward developing evidence and strategies to guide the care of these patients. The findings presented here support the idea that the complexity of a persons' health status can be better understood using a framework that incorporates disease, clinical, and health status domains. Understanding how to best care for patients with CHD in terms of all of their health needs may lead to improvements in quality of life, use of health care, safety, morbidity, and mortality.

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REFERENCES

1. Federal Interagency Forum on Aging-Related Statistics. Older Americans 2008: Key Indicators of Well-Being. Washington, DC: US Govt. Printing Office, 2008.
2. Gijsen R, Hoeymans N, Schellevis FG et al. Causes and consequences of comorbidity: A review. J Clin Epidemiol 2001;54:661–674.
3. Jemal A, Ward E, Hao Y et al. Trends in the leading causes of death in the United States, 1970–2002. JAMA 2005;294:1255–1259.
4. Weiss CO, Boyd CM, Yu Q et al. Patterns of prevalent major chronic disease among older adults in the United States. JAMA 2007;298:1160–1162.
5. Glynn LG, Buckley B, Reddan D et al. Multimorbidity and risk among patients with established cardiovascular disease: A cohort study. Br J Gen Pract 2008;58:488–494.
6. Ritchie C, Ekundayo OJ, Muchimba M et al. Effects of diabetes mellitus in patients with heart failure and chronic kidney disease: A propensity-matched study of multimorbidity in chronic heart failure. Int J Cardiol 2009;134:330–335.
7. Braunstein JB, Anderson GF, Gerstenblith G et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. J Am Coll Cardiol 2003;42:1226–1233.
8. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. J Chronic Dis 1970;23:455–468.
9. Charlson ME, Pompei P, Ales KL et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–383.
10. Greenfield S, Billimek J, Pellegrini F et al. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes: A cohort study. Ann Intern Med 2009;151:854–860.
11. Yancik R, Ershler W, Satariano W et al. Report of the National Institute on Aging Task Force on Comorbidity. J Gerontol A Biol Sci Med Sci 2007;62A:275–280.
12. Boyd CM, Ritchie CS, Tipton EF et al. From Bedside to Bench: Summary from the American Geriatrics Society/National Institute on Aging Research Conference on Comorbidity and Multiple Morbidity in Older Adults. Aging Clin Exp Res 2008;20:181–188.
13. National Center for Health Statistics. National Health and Nutrition Examination Survey. Volume 2008 [on-line]. Available at http://www.cdc.gov/nchs/nhanes.htm Accessed August 14, 2008.
14. Stevens LA, Coresh J, Greene T et al. Assessing kidney function–measured and estimated glomerular filtration rate. N Engl J Med 2006;354:2473–2483.
15. Woodman R, Ferrucci L, Guralnik J. Anemia in older adults. Curr Opin Hematol 2005;12:123–128.
16. Hanlon JT, Weinberger M, Samsa GP et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. Am J Med 1996;100:428–437.
17. Wechsler D. WAIS-R Manual. San Antonio, TX: The Psychological Corporation, 1981.
18. Chaves PH, Ashar B, Guralnik JM et al. Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women. Should the criteria currently used to define anemia in older people be reevaluated? J Am Geriatr Soc 2002;50:1257–1264.
19. Centers for Disease Control and Prevention. Self-reported frequent mental distress among adults–United States, 1993–1996. JAMA 1998;279:1772–1773.
20. Strine TW, Greenlund KJ, Brown DW et al. Characteristics of people aged 45 years or older with heart disease by frequent mental distress status, 2001. Prev Med 2004;39:191–196.
21. Yarnall KS, Pollak KI, Ostbye T et al. Primary care: Is there enough time for prevention? Am J Public Health 2003;93:635–641.
22. Ostbye T, Yarnall KS, Krause KM et al. Is there time for management of patients with chronic diseases in primary care? Ann Fam Med 2005;3:209–214.
23. Min LC, Reuben DB, MacLean CH et al. Predictors of overall quality of care provided to vulnerable older people. J Am Geriatr Soc 2005;53:1705–1711.
24. Min LC, Wenger NS, Fung C et al. Multimorbidity is associated with better quality of care among vulnerable elders. Med Care 2007;45:480–488.
25. Higashi T, Wenger NS, Adams JL et al. Relationship between number of medical conditions and quality of care. N Engl J Med 2007;356:2496–2504.
26. Forum NQ. Volume 2010, 2010 [on-line]. Available at http://www.qualityforum.org/Projects/i-m/Multiple_Chronic_Conditions/Multiple_Chronic_Conditions_Measurement_Framework.aspx Accessed August 14, 2008.
27. Piette JD, Kerr EA. The impact of comorbid chronic conditions on diabetes care. Diabetes Care 2006;29:725–731.
28. Sales AE, Tipton EF, Levine DA et al. Are co-morbidities associated with guideline adherence? The MI-Plus study of Medicare patients. J Gen Intern Med 2009;24:1205–1210.

29. Kerr EA, Zikmund-Fisher BJ, Klamerus ML et al. The role of clinical uncertainty in treatment decisions for diabetic patients with uncontrolled blood pressure. Ann Intern Med 2008;148:717–727.
30. Turner BJ, Hollenbeak CS, Weiner M et al. Effect of unrelated comorbid conditions on hypertension management. Ann Intern Med 2008;148:578–586.
31. Lagu T, Weiner MG, Hollenbeak CS et al. The impact of concordant and discordant conditions on the quality of care for hyperlipidemia. J Gen Intern Med 2008;23:1208–1213.
32. Kerr EA, Heisler M, Krein SL et al. Beyond comorbidity counts: How do comorbidity type and severity influence diabetes patients' treatment priorities and self-management? J Gen Intern Med 2007;22:1635–1640.
33. Bolen SD, Samuels TA, Yeh HC et al. Failure to intensify antihypertensive treatment by primary care providers: A cohort study in adults with diabetes mellitus and hypertension. J Gen Intern Med 2008;23:543–550.
34. Casalino L, Gillies RR, Shortell SM et al. External incentives, information technology, and organized processes to improve health care quality for patients with chronic diseases. JAMA 2003;289:434–441.
35. Garber AM. Evidence-based guidelines as a foundation for performance incentives. Health Aff (Millwood) 2005;24:174–179.
36. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), Volume 2005.
37. Schellevis FG, van der Velden J, van de Lisdonk E et al. Comorbidity of chronic diseases in general practice. J Clin Epidemiol 1993;46:469–473.
38. Tinetti ME, Bogardus ST Jr., Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. N Engl J Med 2004;351: 2870–2874.
39. Boyd CM, Darer J, Boult C et al. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: Implications for pay for performance. JAMA 2005;294:716–724.
40. May C, Montori VM, Mair FS. We need minimally disruptive medicine. BMJ 2009;339:b2803.
41. Kravitz RL, Duan N, Braslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. Milbank Q 2004;82:661–687.
42. Greenfield S, Kravitz R, Duan N et al. Heterogeneity of treatment effects: Implications for guidelines, payment, and quality assessment. Am J Med 2007; 120:S3–S9.
43. Fortin M, Soubhi H, Hudon C et al. Multimorbidity's many challenges. BMJ 2007;334:1016–1017.
44. Fortin M, Dionne J, Pinho G et al. Randomized controlled trials: Do they have external validity for patients with multiple comorbidities? Ann Fam Med 2006;4:104–108.
45. Van Spall HG, Toren A, Kiss A et al. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: A systematic sampling review. JAMA 2007;297:1233–1240.
46. Mody L, Miller DK, McGloin JM et al. Recruitment and retention of older adults in aging research. J Am Geriatr Soc 2008;56:2340–2348.
47. Kitzman DW, Rich MW. Age disparities in heart failure research. JAMA 2010;304:1950–1951.
48. Wedzicha JA, Calverley PM, Seemungal TA et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008;177:19–26.
49. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. Arch Intern Med 2002;162:1682–1688.
50. Kent DM, Kitsios G. Against pragmatism: On efficacy, effectiveness and the real world. Trials 2009;10:48.
51. Safford MM, Allison JJ, Kiefe CI. Patient complexity: More than comorbidity. The vector model of complexity. J Gen Intern Med 2007;22(Suppl 3):382–390.
52. Simpson CF, Boyd CM, Carlson MC et al. Agreement between self-report of disease diagnoses and medical record validation in disabled older women: Factors that modify agreement. J Am Geriatr Soc 2004;52:123–127.
53. Anderson G, Horvath J. Chronic Conditions: Making the Case for Ongoing Care: Partnership for Solutions, 2002 [on-line]. Available at http://www.rwjf.org/files/research/chronicbook2002.pdf Accessed November 14, 2010.
54. Marengoni A, Rizzuto D, Wang HX et al. Patterns of chronic multimorbidity in the elderly population. J Am Geriatr Soc 2009;57:225–230.
55. Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: The Health and Retirement Study. J Am Geriatr Soc 2009;57:511–516.