

CLINICAL EPIDEMIOLOGY OF HEART FAILURE

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The aim of this paper is to review the clinical epidemiology of heart failure. The last paper comprehensively addressing the epidemiology of heart failure in *Heart* appeared in 2000.^{w1} Despite an increase in manuscripts describing epidemiological aspects of heart failure since the 1990s,¹ additional information is still needed, as indicated by various editorials.^{w2 w3}

The evaluation and management of heart failure is schematically depicted in fig 1. Following some methodological considerations, most issues indicated in fig 1 (risk factors, aetiology, prevalence, incidence, prognosis, prevention) will be discussed.

The therapeutic management of patients diagnosed with heart failure is beyond the scope of this paper, as is detailed information about the possible diagnostic tests and strategies to establish or rule out heart failure, although the prevailing definitions and categorisations of the syndrome will be discussed. The guidelines of the European Society of Cardiology and selected reviews provide up to date information on the diagnosis and therapeutic management of heart failure.^{2 w4 w5}

DEFINITION AND CLASSIFICATION OF HEART FAILURE

Heart failure is a syndrome with symptoms and signs caused by cardiac dysfunction, resulting in reduced longevity. To establish a diagnosis of heart failure, the European Society of Cardiology guidelines warrant the presence of symptoms and signs (tables 1 and 2), objective evidence of cardiac dysfunction (preferably by echocardiography), and, in case of remaining doubt, a favourable response to treatment directed towards heart failure.^{w5} To support the failing heart numerous compensatory mechanisms occur, including activation of the neurohormonal system.² An increase in natriuretic peptide concentrations (particularly B type natriuretic peptide) is considered a hallmark of heart failure.

The diagnosis of heart failure, especially when relying solely on symptoms and signs (which is often the case in primary care), is fraught with difficulties.³ Many patients deemed to have heart failure will simply be found to be obese, have a poor physical condition, pulmonary disease, or ischaemia on further examination. Evidence is accumulating that normal natriuretic peptide levels and a normal electrocardiogram should lead to a reconsideration of a diagnosis of heart failure.^{4 w6}

Acute versus chronic heart failure

Heart failure generally is a chronic condition (chronic heart failure—CHF) in which bouts of worsening symptoms and signs can occur that may require hospitalisation or more frequent doctor visits (decompensation of CHF). Alternatively, heart failure may present acutely, with occurrence of severe symptoms and signs within 24 h. Acute heart failure clinically presents in several forms:

- ▶ acute pulmonary oedema secondary to cardiac dysfunction
- ▶ cardiogenic shock, usually in the setting of an acute coronary syndrome, characterised by hypotension, oliguria, and peripheral vasoconstriction
- ▶ acute worsening (decompensation) of CHF.

Systolic versus diastolic heart failure, impaired versus preserved left ventricular ejection fraction

Heart failure traditionally was seen to result from impairment in ability of the heart to pump sufficient amounts of blood into the circulation during systole—that is, left ventricular systolic dysfunction. Echocardiography is most often employed to assess left ventricular systolic function, an ejection fraction of $\leq 40\%$ indicating impaired left ventricular systolic function. Heart failure can also occur in patients with normal left ventricular systolic function in whom higher filling pressures are needed to obtain a normal end-diastolic volume of the left ventricle, so called heart failure with preserved left ventricular ejection fraction (PLVEF) or “diastolic” heart failure.^{w7}

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Establish the presence or absence of heart failure in patients suspected of the syndrome

Does my patient have heart failure (diagnosis)?
(risk factors, incidence, prevalence)



No: prevention of heart failure
(prevention)

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Yes:

Identify type of heart failure, cause and contributing factors

Why does my patient have (worsening) heart failure (aetiology)?

What will happen to my heart failure patient (prognosis)?

Initiate treatment

Can I improve the prognosis (ie reduce mortality, morbidity, hospitalisations, complaints or increase quality of life) of my heart failure patient (therapeutic management)?

- Pharmacological
- Non-pharmacological: diet, fluid restriction, exercise, quit smoking
- Correct ischaemia, valvular heart disease, eliminate contributing factors (fever, use of non-steroidal anti-inflammatory drugs, anaemia, alcohol excess, thyroid dysfunction, poor drug compliance, etc)
- Consider device therapy (implantable cardioverter-defibrillator and/or cardiac resynchronisation)
- Inform and instruct patient and his/her relatives
- Coordinate care

As the terms systolic and diastolic heart failure are not mutually exclusive—in heart failure patients with impaired left ventricular systolic function, diastolic abnormalities are often found as well—it is more appropriate to distinguish between heart failure with normal/preserved and impaired left ventricular ejection fraction. The occurrence of heart failure with PLVEF has been documented in numerous population-based studies,^{5,6} as well as in studies of patients presenting to the hospital with acute pulmonary oedema.^{w8} Heart failure with PLVEF is more common in women, at a higher age, and in persons with longstanding hypertension, and carries a better prognosis than heart failure caused by impaired left ventricular systolic function. A recent hospital-based study among 2802 patients admitted with heart failure in Ontario, Canada, reported similar 1 year mortality rates in patients with preserved ejection fraction (>50%) and those with an ejection fraction <40%: 22% versus 26% ($p=0.07$).^{w9} The hospital based nature of this study with its inherent biases of patient inclusion, selection for echocardiography and coding of heart failure is likely to account for the relatively poor prognosis in patients with preserved left ventricular function. Although the importance of heart failure with PLVEF is undisputed, there is no consensus on the exact definition of this entity and some researchers even argue that the prevalence of “diastolic heart failure” is grossly overestimated.^{w10–12}

Table 1 European Society of Cardiology definition of heart failure

- I. Symptoms of heart failure (at rest or during exercise)
and
- II. Objective evidence (preferably by echocardiography) of cardiac dysfunction (systolic and/or diastolic) (at rest)
and (in cases where the diagnosis is in doubt)
- III. Response to treatment directed towards heart failure

Criteria I and II should be fulfilled in all cases.

Figure 1 The evaluation and management of heart failure.

Asymptomatic versus symptomatic left ventricular dysfunction

Population-based echocardiographic studies have demonstrated that more than 50% of participants with left ventricular systolic dysfunction (generally defined as LVEF <35–40%) have no symptoms or signs of heart failure.^{7,8,w13} Asymptomatic left ventricular systolic dysfunction is found more frequently in person with coronary artery disease (relative risk (RR) 12.5, 95% confidence interval (CI) 4.5 to 33.3), hypertension (RR 3.5, 95% CI 1.4 to 8.5) or an abnormal ECG (RR 7.1, 95% CI 2.8 to 16.7). Asymptomatic left ventricular dysfunction is an important precursor of heart failure and other cardiovascular events.⁹ ^{w14} By definition heart failure is characterised by symptoms and signs and as such asymptomatic left ventricular systolic dysfunction is not equivalent to heart failure.

NYHA classification versus AHA/ACC staging

The New York Heart Association (NYHA) classification has traditionally been used to classify severity of heart failure and indicate prognosis and, thus, to guide patient management. The severity of heart failure ranges from essentially asymptomatic—well treated patients in whom symptoms have been relieved (NYHA I)—to mild (NYHA II, slight limitation in physical activity), to moderate (NYHA III, symptoms while walking on

Table 2 Heart failure: symptoms and signs

Symptoms	Signs
Dyspnoea (on exertion, nocturnal)	Oedema, ascites
Reduced exercise tolerance	Elevated jugular venous pressure
Fatigue, lethargy	Crepitations or wheeze
Orthopnoea	Tachycardia
Nocturnal cough	Third heart sound, murmurs
Wheeze	Hepatomegaly
Anorexia	Displaced apex beat
Confusion/delirium (elderly)	Cachexia and muscle wasting

Table 3 American College of Cardiology/American Heart Association stages of heart failure^{w15}

Stage	Description	Example
A	High risk, no symptoms	Hypertension, coronary artery disease, diabetes mellitus
B	Structural heart disease, no symptoms	Left ventricular hypertrophy, asymptomatic left ventricular systolic dysfunction
C	Structural heart disease, previous or current symptoms	Dyspnoea or fatigue due to heart failure
D	Structural heart disease, refractory symptoms	Patients with end stage heart failure

the flat), to severe heart failure (NYHA IV, breathless at rest and essentially housebound). An NYHA III class patient may improve to class II upon initiation of treatment, indicating that the NYHA classification is essentially a functional/symptomatic score, not taking into account the underlying cardiac disorder that will almost inevitably progress.

The staged American College of Cardiology/American Heart Association (ACC/AHA) heart failure classification acknowledges that heart failure is largely preventable (by control of blood pressure and other risk factors), is generally preceded by asymptomatic structural and functional cardiovascular abnormalities, and when present generally progresses (table 3).^{w15} Neurohormonal activation, as measured by natriuretic peptide values, in persons without heart failure increases the risk of heart failure.^{w16}

Although the ACC/AHA classification emphasises the importance of recognising patients at high risk of developing heart failure and of correcting/treating major risk factors for the condition, the categorisation of these determinants—for example, diabetes or hypertension as “stage A heart failure”—is unjustified, if not misleading, since the criteria included in the definition of heart failure (that is, ventricular dysfunction and accompanying symptoms) are not fulfilled. For similar reasons, we prefer the term “asymptomatic left ventricular dysfunction” to the term “stage B heart failure”.

OCCURRENCE OF HEART FAILURE
Heart failure in the real world

Since the review by Cowie *et al.*¹ which provides an extensive overview of studies published until 1995, numerous papers have been published addressing aspects of the heart failure epidemic from patients in population based cohorts to the highly selected groups of participants in clinical trials. The estimates vary considerably owing to a lack of uniformity in the definition and assessment of heart failure, that can be attributed to the absence of a gold standard for heart failure.^{w17} In addition, non-cardiac conditions (chronic obstructive pulmonary disease (COPD), obesity or a poor physical condition) may mimic heart failure.^{w12} If heart failure is deemed present on clinical grounds (medical history, signs and symptoms) heart failure with PLVEF (“diastolic heart failure”) is hard to tell apart from heart failure caused by impaired LVEF without the use of Doppler echocardiography or invasive measurements, although some features may point to heart failure with PLVEF (table 4).^{w18}

Ideally, estimates of the “true” prevalence and incidence of heart failure should be based on surveys in random samples of

the general population, using validated questionnaires and properly conducted physical examinations (to document symptoms and signs of heart failure as well as medication use), and objective methods (echocardiography, electrocardiography, neurohormones) to demonstrate cardiac dysfunction, thus allowing an expert panel to classify patients as (not) having heart failure. In this way the presence of systolic and diastolic dysfunction in relation to the symptoms and signs of heart failure can be determined. Only a limited number of population based studies have used this approach.

The majority of patients with heart failure are managed by general practitioners rather than by cardiologists—the typical heart failure patient in general practice being an elderly woman with longstanding hypertension (more often suffering from “diastolic” heart failure)—whereas cardiologists tend to see men in their 60s who have had a myocardial infarction (having systolic heart failure). Heart failure patients in general practice are generally 15 years older (79 vs 64 years), more often women (58% vs 22%), more often have (a history of) hypertension, and are less likely to have had a myocardial infarction (15% vs 43%) than heart failure patients seen by cardiologists.¹⁰ The average age of heart failure patients in general practice in the UK is 77 years.^{w19}

These differences are important to bear in mind when interpreting the results of randomised clinical trials in heart failure; such trials have only recently begun to include patients older than 75–80 years and patients with heart failure with preserved left ventricular systolic function.^{w20}

Prevalence and incidence of heart failure

Generally speaking, the prevalence of heart failure can be estimated at 1–2% in the western world and the incidence approaches 5–10 per 1000 persons per year. Estimates of the occurrence of heart failure in the developing world are largely absent.^{11 w21}

Prevalence of heart failure

Persons younger than 50 years are hardly ever found to have heart failure, but in those older than 50 years the prevalence and incidence increase progressively with age. In a recent US population-based study the prevalence of heart failure was 2.2% (95 CI 1.6% to 2.8%), increasing from 0.7% in persons aged 45 through 54 years to 8.4% for those aged 75 years or older.⁸ Congestive heart failure was found to be more common in women. These figures are highly comparable to previous studies, such as the Rotterdam study (prevalence of heart failure being 1% in age group 55–64 years, 3% in age group 65–74 years, 7% in age group 75–84 years, and over 10% in those aged ≥85 years).^{w13}

The first prevalence study to use two-dimensional echocardiography in the population at large took place in Glasgow (1647 participants, 48% men, mean age 50 years), deeming heart failure present if LVEF was <30% in persons having cardiac shortness of breath or using loop diuretics. The prevalence of heart failure was 1.5% (1.6% in men, 1.4% in women). Interestingly asymptomatic left ventricular systolic dysfunction was found to occur very frequently (overall 1.4%, men 2.4%, women 0.5%). The Rotterdam study (using M-mode echocardiography in a subgroup of 2267 participants, aged 55 years or older) also found left ventricular systolic dysfunction to

Table 4 Findings suggestive of diastolic heart failure^{w18}

- ▶ Pronounced hypertension during episode of heart failure (systolic blood pressure >160 mm Hg, diastolic blood pressure >100 mm Hg)
- ▶ Echocardiography: concentric left ventricular hypertrophy without wall motion abnormalities, increased relative wall thickness, normal end diastolic volume
- ▶ Tachycardia with a shortened diastolic filling period (for example, rapid atrial fibrillation)
- ▶ Precipitation of heart failure by the infusion of a small amount of intravenous fluid
- ▶ Clinical improvement in response to treatment directed at the cause of diastolic dysfunction (such as lowering blood pressure, reducing heart rate, or restoring the atrial "kick")

occur more frequently in men than in women (5.5% vs 2.2%).^{w13} Subsequent studies have confirmed these earlier data and confirmed that many persons (more than half) with impaired left ventricular systolic function have no symptoms or signs of heart failure at all.⁸

Only a few epidemiological studies have used echocardiography to investigate diastolic dysfunction specifically, other studies defining diastolic heart failure as symptoms and signs of heart failure in the presence of a normal left ventricular ejection fraction (that is heart failure with preserved left ventricular systolic function).^{5 6 8 w22 w23} The MONICA Augsburg study (1274 persons, aged 25 to 75 years) found a high prevalence of diastolic function abnormalities, assessed by Doppler echocardiography, increasing from 2.8% in persons aged 25–35 years to 15.8% in those over 65 years.^{w23} Interestingly, in participants without left ventricular hypertrophy, hypertension, coronary artery disease, obesity or diabetes, diastolic function abnormalities were largely absent.

The most all inclusive epidemiologic study of heart failure prevalence in the population is from Olmsted County, Minnesota, USA.⁸ In 2042 persons older than 45 years the presence of heart failure was established and Doppler echocardiography was used to assess left ventricular systolic and diastolic dysfunction in great detail. In addition to measuring standard transmitral flow parameters, pulmonary venous flow, mitral inflow at peak Valsalva manoeuvre and Doppler tissue imaging of mitral annular motion were used to characterise diastolic function. The prevalence of heart failure was 2.2%, 44% having an ejection fraction higher than 50%; 7.3% were found to have moderate or severe diastolic dysfunction, generally (75%) with normal ejection fraction. Moderate to severe systolic dysfunction (ejection fraction <40%) was found in 2.0%. Less than half of those having moderate or severe diastolic or systolic dysfunction had heart failure.

Incidence of heart failure

Reliable estimates of the incidence of heart failure are available from the Rotterdam and Hillingdon heart failure studies.^{w24 w25} Both studies are population based and used an expert panel to establish the presence or absence of heart failure. In the Hillingdon study the incidence of heart failure increased from 0.2/1000 person years in those aged 45–55 years to 12.4/1000 person years in those aged >85 years. In Rotterdam the incidence increased from 2.5/1000 person years (age 55–64 years) to 44/1000 person years (>85 years or older). Heart

- ▶ **Prevalence:** The number of persons having heart failure at a certain moment in time (generally expressed as a percentage).
- ▶ **Incidence:** The number of persons newly diagnosed with heart failure during a certain time period (generally expressed as the number of new cases of heart failure per 1000 persons per year—the incidence rate—and sometimes expressed as a proportion of those free from the disease that develops the disease within a specified time period—for example, the 5 year cumulative incidence).

failure occurs more frequently in men than in women (15 and 12 per 1000 person years, respectively). The higher figures in Rotterdam most probably reflect differences in methodology (including evaluation of all patients being prescribed diuretics or angiotensin converting enzyme (ACE) inhibitors in Rotterdam) rather than true differences in the incidence of heart failure. Interestingly, a more recent analysis from the Rotterdam study, although using a somewhat different methodology to identify incident heart failure, produced remarkably similar results.^{w26}

Hospitalisations for heart failure

The number of hospitalisations for heart failure (usually expressed as a number per 1000 patients per year) and the change in this measure provide useful information on the epidemic of heart failure. It should be emphasised, however, that hospitalisation rates result from a complex interaction of multiple determinants, including the prevalence, incidence and survival of the disease, referral patterns and treatment possibilities in primary care as well as discharge diagnosis coding practices. Consequently, time trends in hospitalisation rates are often difficult to interpret.

Age adjusted hospitalisation rates increased considerably throughout the western world in the 1980s and early 1990s, as documented by reports from New Zealand, the USA, Sweden, Scotland, and the Netherlands.^{1 w27} Recent reports have suggested that admission numbers have peaked in the 1990s (at least in Scotland, the Netherlands and Sweden) and that the prognosis of hospitalised heart failure patients has improved (fig 2).^{12 w28–30}

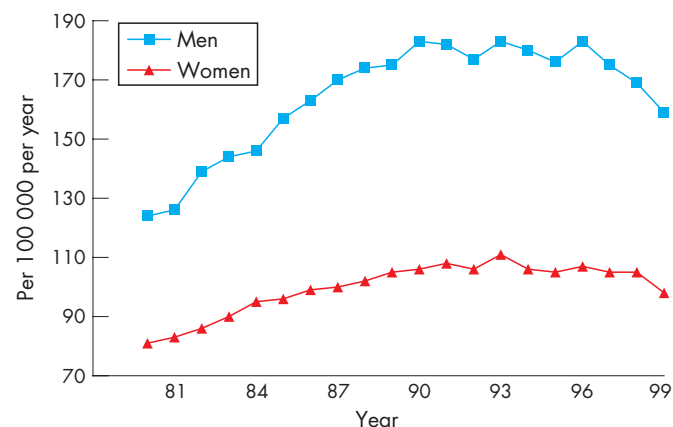


Figure 2 Admissions for heart failure in Dutch hospitals, 1980–1999.^{w29}

In the Netherlands the total number of hospitalisations for heart failure increased by 72% between 1980 (14 441) and 1999 (24 868). Part of this increase is explained by the ageing of the population, the mean age of patients admitted with heart failure increasing from 71.2 to 72.9 years in men and from 75.0 to 77.7 years in women during the same period. After reaching a peak in 1992 (men) and 1993 (women), age adjusted hospitalisation rates for heart failure started to decline by 1.0–1.5% per year. Concomitantly, the average duration of hospitalisation declined from 21.1 days in 1980 to 12.9 days in 1999. In-hospital mortality declined from 18.6% to 13.5%.^{w29}

One hospital based study specifically addressed secular trends in prevalence and prognosis of heart failure patients with or without PLVEF.¹³ The prevalence of heart failure with PLVEF in patients admitted to the Mayo Clinics increased from 38% to 54% between 1987 to 2001, concomitant with an increase in prevalence of hypertension, atrial fibrillation and diabetes. In this time frame survival improved significantly for patients with impaired left ventricular systolic function, but did not change in those with preserved left ventricular systolic function.

In the face of the predicted increase in age adjusted prevalence of heart failure,¹⁴ the observed decline in hospitalisation rates may come as a surprise. However, hospitalisations for heart failure do not reflect the occurrence and prognosis of heart failure in the community, as they relate only to the more severe stages of heart failure warranting in-hospital evaluation and treatment. The decline in hospitalisation rates may well be due to improved treatment and management of heart failure patients—for example, by means of dedicated heart failure clinics. In addition, it is conceivable that an increasing number of patients with terminal heart failure are being cared for in a home-based setting by their general practitioner, rather than being admitted to hospital.

Aetiology and risk factors for heart failure

Aetiology of heart failure

Although many conditions can cause heart failure (coronary artery disease, hypertension, cardiomyopathies, valvular and congenital heart disease, arrhythmias, pericardial disease, myocarditis, pulmonary hypertension, and cardiotoxic substances—including alcohol), the predominant cause of heart failure in the western world is ischaemic heart disease (table 5).^{15 16 w24} The variation in frequencies of causes of heart failure reported in different studies can be explained by differences in study population, from the highly selected group of participants in clinical trials to relatively unselected participants in population-based studies, differences in definitions, and time differences (the Framingham heart study originated in 1948). In addition, it has become clear that using non-invasive methods the precise aetiology of heart failure cannot always be determined accurately. In the Bromley heart failure study the percentage of heart failure with unknown cause declined from 42% to 10% after nuclear testing and cardiac catheterisation, while the percentage of patients with ischaemic heart failure increased from 29% to 52%.¹⁶

Risk factors for heart failure

Various (population-based) studies have addressed risk factors for the occurrence of heart failure.^{1 15 17 w31–34} Coronary artery disease notably increases the chance of developing heart

failure; in 7–8 years after myocardial infarction up to 36% of patients will experience heart failure, especially those with left ventricular systolic dysfunction documented during admission.¹⁸

Although the risk of heart failure associated with hypertension (systolic blood pressure >140 mm Hg, or diastolic blood pressure >90 mm Hg, or treatment with antihypertensive medication) is smaller than that associated with myocardial infarction, hypertension contributes considerably to the population burden of heart failure as it occurs more frequently than myocardial infarction (table 6).¹⁵ Obesity (body mass index >30 kg/m²), increasingly present in western societies, doubles the risk of heart failure after adjustment for associated risk factors.¹⁹ Valvular abnormalities, factors indicative of heart disease (left ventricular hypertrophy, left ventricular dilatation), a parental history of heart failure, conventional risk factors (such as smoking, diabetes, obesity), as well extra-cardiac conditions (renal dysfunction, obstructive pulmonary disease) all increase the risk of heart failure (table 6).^{17 w35 w36}

The relation of obesity, increased cholesterol values and hypertension to cardiovascular morbidity and mortality is undisputed. In patients with CHF considerable evidence exists that obesity, hypercholesterolaemia and hypertension are “protective”. This phenomenon has been termed “reverse epidemiology” for which a comprehensive explanation is still lacking.²⁰ Proposed explanations are the syndrome of cardiac cachexia, reverse causation (the underlying cause of hypotension—that is, pump failure—being detrimental rather than hypotension per se) and time discrepancies among competitive risk factors. The reverse epidemiology does not hold for all conventional risk factors, as quitting smoking is associated with a better prognosis in heart failure patients.²¹

Comorbidity in heart failure

Heart failure, being a common disease in the elderly, should not be viewed in isolation: anemia, cachexia, renal impairment, obstructive sleep apnoea, chronic pulmonary disease and diabetes mellitus are conditions frequently observed in heart failure patients and unfavourably affect prognosis.² Comorbidity was found to be one of the prime determinants of prognosis in a study of patients admitted with heart failure and contributes to the poor quality of life as perceived by heart failure patients.^{w37 w38} The complex interplay between diseases previously perceived as entities on their own, such as COPD, renal disease, obstructive sleep apnoea on the one hand and heart failure on the other, is increasingly acknowledged.

Patients with chronic kidney disease constitute a group of patients at high risk for having or developing cardiovascular disease, including heart failure.^{w39} Heart failure in these patients may result from coronary heart disease, longstanding hypertension resulting in concentric hypertrophy, or volume overload due to anaemia, fluid overload and arteriovenous fistulas leading to left ventricular dilatation. The prevalence of heart failure increases with severity of renal impairment; approximately 20% of patients with a glomerular filtration rate <30 ml/min/1.73 m² (not on dialysis) have heart failure.^{w40 w41} Along similar lines, heart failure appears to be frequently present in patients with COPD; in a recent Dutch study of 405 patients older than 65 years with a diagnosis of COPD, 20.5% were found to have previously unrecognised heart failure.²²