

# Clinical burden and health service challenges of chronic heart failure

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## SIR JAMES MACKENZIE MD FRS

A remarkable figure during his professional career, which spanned time as a regular GP, a consulting physician, and early cardiologist in London, Mackenzie lived from 1853 to 1925. He was a Burnley GP for 28 years from 1879, before moving to London in 1907 as a visiting consultant, attempting to buck the opposition from his more esteemed colleagues over his admitting rights. He gave up the struggle for appropriate recognition just as it was tantalisingly close, and 'retired' from practice to establish the GP Academic Centre, at St Andrews in 1919. He died in 1925, having ironically suffered angina for years. He was an extraordinary figure, publishing 50 papers and seven textbooks despite a copious caseload. He was the first to fully describe

arrhythmias, the benign nature of ventricular ectopics, and auricular (atrial) fibrillation. To cap it all, he invented the polygraph, the precursor of the electrocardiogram (ECG). I hope he would have approved of this talk, a description of a decade of research in an interlinked and explanatory programme around a better understanding of heart failure, its diagnosis, and better management.

## INTRODUCTION

Heart failure and left ventricular systolic dysfunction (LVSD) are increasingly important chronic disease syndromes, associated with poor prognosis, very poor quality of life for patients, and among the highest healthcare costs for a single condition.<sup>1,2</sup> Annual mortality in severe heart failure is around 60%.<sup>3</sup> In the general population, where all grades of heart failure are represented, 5-year mortality is around 42%,<sup>4</sup> but where the diagnosis is established during a hospital admission, 5-year mortality is between 50% and 75%.<sup>5,6</sup>

## PREVALENCE OF HEART FAILURE

Earlier studies of heart failure prevalence used clinical diagnostic criteria, which are known to be inaccurate,<sup>7</sup> particularly early in the disease process.<sup>8,9</sup> More recent studies of LVSD prevalence included objective assessment of left ventricular function, usually using echocardiography,<sup>10,11</sup> indicate a prevalence of LVSD of 2.9% in patients under 75 years,<sup>10</sup> and up to 7.5% in 75–84 year olds.<sup>11</sup> However, limitations of these studies include not screening all adult age groups,<sup>10</sup> with data particularly lacking in older people in whom LVSD is more common, or not examining representative populations.<sup>11</sup> Furthermore, heart failure is a complex syndrome with multiple causes,<sup>12</sup> including aetiologies where systolic function is preserved,<sup>13</sup> as well as LVSD which is the principal cause in around half of cases. To add to the complication, LVSD is defined mainly on echocardiographic criteria (a semi-quantitative imaging assessment) where the main measure, left ventricular ejection fraction (LVEF), is a continuous variable, and the conventional cut-off that defines caseness, an LVEF below 40%, is proposed to change to below 50%.

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## How this fits in

Heart failure is common and on the increase. It remains one of the most damaging diseases for patients in terms of shortening life, serious symptoms, and very poor quality of life. Heart failure has a high cost to many healthcare systems (the most common cause of hospital readmission). The syndrome is difficult to diagnose accurately and needs high index of suspicion in people with recent onset of breathlessness (especially if they have suffered prior myocardial infarction) and prompt access to investigations especially natriuretic peptide assay and echocardiograph. There are many evidence-based interventions that improve symptoms and survival, especially angiotensin-converting enzyme inhibitors and beta blockers, which should be titrated to maximum doses. Specialist nurse outreach programmes, and advice to patients and carers on regular weighing and looking for signs of decompensation, improve outcomes. Palliative care should be considered in late-stage disease where the priority is breathing not pain.

In the largest recent prospective evaluation of heart failure in the community (ECHOES), asymptomatic and symptomatic LVSD (symptomatic LVSD also meets diagnostic criteria for heart failure) was found in 1.8% (95% confidence interval [CI] = 1.4 to 2.3%) of the population over 45 years; borderline left ventricular dysfunction, defined as LVEF between 40–50%, in a further 3.5%; and definite heart failure in 2.3% (95% CI = 1.9 to 2.8%) of the population (with LVEF <40% in 41% cases); and using an LVEF cut-off of <50% rather than 40%, 3.1% (95% CI = 2.6 to 3.7%) of people aged 45 years or over had heart failure.<sup>14</sup>

### INCIDENCE OF HEART FAILURE

Estimates of heart failure incidence are less available, and vary from 0.915 to 2.26 cases per 1000 population per annum in females aged 45–74 years, and 1.613 to 4.66 cases per 1000 population per annum in men aged 45–74 years.<sup>15</sup> Incidence rises rapidly in older people; however, with 1% of men per year developing heart failure after 75 years and almost 2% per year in those aged over 85 years.<sup>16</sup>

### BURDEN OF HEART FAILURE ON PATIENTS: MORTALITY, MORBIDITY, AND QUALITY OF LIFE

Mortality rates in heart failure are high. Conventionally, rates are often quoted based on New York Heart Association (NYHA) classification, which is a simple symptomatic rating or staging scale of the severity of breathlessness, from NYHA I (no shortness of breath) to IV (shortness of breath at rest). Annual mortality in the placebo arms of recent trials, against the background of angiotensin-converting enzyme (ACE) inhibitors, have ranged from 7% in mild heart failure (NYHA II), to 11%,<sup>17</sup> to 13%,<sup>12</sup> in moderate cases (NYHA III), and 20%,<sup>5</sup> 23%,<sup>18</sup> or 28%<sup>19</sup> in severe heart failure. By

comparison, the Framingham cohort showed an overall 1-year heart failure (defined initially on ECG criteria, but latterly on echocardiography) mortality rate of 17%, a 2-year mortality rate of 30%, and a 10-year mortality of 78%.<sup>20</sup> The National Health and Nutrition Examination Survey study, conducted from 1971 to 1986 in the US, revealed 10-year mortality rates of 43% in patients who self-reported heart failure, and 38% in patients who had heart failure defined by a clinical score.<sup>21</sup>

Mortality data from more recent epidemiological studies provide more reliable case definitions, but mainly report on only LVSD heart failure, younger patients only,<sup>22</sup> or patients presenting to hospital, usually with incident symptomatic heart failure.<sup>23,24</sup> In the latter studies, mortality is particularly high, with 50% 2-year mortality, probably representing late presentations — rates that equate to the prognosis of newly diagnosed colorectal cancer in men or ovarian cancer in women.

A more accurate estimate of prognosis of prevalent heart failure, across all ages and stages, is available from follow-up of the ECHOES cohort.<sup>4</sup> The 5-year survival rate of the general population was 93% compared to 58% of those with a prevalent diagnosis of LVSD, and 58% for those with prevalent definite heart failure. The median survival time of definite heart failure was 7 years 7 months. Those with a prior diagnostic label of heart failure had the lowest survival compared with the general population, and survival improved significantly with increasing ejection fraction. Importantly, significantly worse mortality rates were seen among patients with 'borderline' ejection fraction levels of between 40% and 50%. Indeed, people identified with this degree of 'minor' systolic impairment suffered mortality rates over 1.5 times higher than people with ejection fractions over 50%. Those persons with multiple causes of heart failure had the poorest survival. The ECHOES mortality data provide recent confirmation of the poor prognosis of patients suffering heart failure across the community, providing a generalisable mortality risk estimate of 8–9% per year.<sup>4</sup> Importantly, outcomes in heart failure are improving, presumed to be due to better initiation and maintenance of evidence-based therapies.<sup>25</sup>

Morbidity in heart failure is considerable, whether measured by symptom severity, quality of life, or need for consultation, treatment, or hospital admission. Studies with comparative normative data are few and suggest that heart failure worsens quality of life more than other chronic diseases (although heart failure diagnosis in this study was not determined on the basis of objective tests),<sup>26</sup> and that women may suffer worse impairment.<sup>27</sup> Other studies have shown heart failure is associated with depressive illness,<sup>28</sup> and

further that this is then linked to a worse prognosis.<sup>29</sup> Those with heart failure had significant impairment of all the measured aspects of physical and mental health, not only physical functioning. Significantly worse impairment was found in those with more severe heart failure by NYHA class. Patients with asymptomatic left ventricular dysfunction, and patients rendered asymptomatic by treatment had similar scores to the random population sample. Those with heart failure reported more severe impairment of quality of life than people giving a history of chronic lung disease or arthritis, with a similar impact to patients reporting depression.

ACE inhibitors<sup>30</sup> and beta-blockers<sup>31</sup> have been shown to improve exercise tolerance and symptoms (as assessed by the NYHA functional class) in patients with heart failure due to LVSD, as well as significantly prolonging survival and reducing hospitalisation rates. These drugs have also been shown to improve global quality of life in sufferers,<sup>32,33</sup> as have other interventions producing symptom gains, such as exercise training<sup>34</sup> and intensive nurse-led discharge and outreach programmes.<sup>35</sup>

Access to palliative care services should be considered in end-stage heart failure. Community-based research has highlighted that patients with end-stage disease have a poorer understanding of the illness and prognosis, and less opportunity to address end-of-life issues than patients with cancer.<sup>36</sup>

### **BURDEN OF HEART FAILURE ON HEALTHCARE PROVIDERS: HEALTH-SYSTEM COSTS**

Chronic heart failure remains one of the most costly conditions to manage in many health systems. This is principally because the syndrome is common, it frequently results in hospital admission (which is the disproportionate driver of healthcare expenditure), mean admissions are prolonged (averaging 11 days in Europe), and readmission is frequent (nearly 25% of patients are readmitted within 12 weeks of discharge).<sup>37</sup> In the UK, 4.9% of admissions to one hospital were for heart failure, extrapolating to up to 120 000 admissions per year nationally.<sup>38</sup> Admissions continue to rise.<sup>39,40</sup>

As a consequence, heart failure accounts for at least 2% of total healthcare expenditure,<sup>41</sup> namely €26 million per million population in the UK, €37 million per million population in Germany, €39 million per million population in France, and €70 million per million population in the US. The average cost per hospital admission in Europe is €10 000.<sup>36</sup> The burden of heart failure is expected to rise as prevalence rises, presumed to be due to improved survival of patients post myocardial infarction, and better treatment of heart failure once developed.<sup>42</sup>

### **DIAGNOSTIC AND MANAGEMENT ISSUES IN HEART FAILURE**

An essential element for treatment success is the reliable and precise diagnosis of heart failure. The major issue in the diagnosis of the disease relates to the criteria definitions. Guidelines for the evaluation and management of heart failure are established in both the US (American College of Cardiology/American Heart Association and Consensus Recommendations)<sup>43</sup> and Europe (European Society of Cardiology).<sup>25</sup> These state that the diagnosis of heart failure is justified when there are typical signs and symptoms of heart failure and myocardial dysfunction, confirmed by the objective evidence of cardiac dysfunction at rest. In case of diagnostic uncertainty, a clinical response to treatment directed at heart failure is helpful in establishing the diagnosis. Simple and reliable diagnostic procedures are very important for primary care physicians, who are responsible for the early diagnosis of heart failure and implementation of adequate therapy.

Unfortunately, primary care physicians in Europe have variable and often delayed access to the most appropriate objective test, namely echocardiography. As a consequence, doctors believe they need to rely on alternatives to echocardiography, such as the ECG or chest X-ray; both tests being perceived to be used in most cases of heart failure in the IMPROVEMENT study.<sup>44</sup> A normal ECG recording will, if read by a specialist, in most cases exclude left ventricular dysfunction.<sup>45,46</sup> However, changes may be subtle and interpretation requires expert opinion. Chest X-rays are often cited as useful in diagnosis, but a normal result does not exclude heart failure.<sup>47,48</sup> Furthermore, symptoms and signs may indicate the possibility of heart failure, but are not reliable for establishing the diagnosis.<sup>49</sup> It is therefore not surprising that studies exploring the validity of a clinical diagnosis of heart failure in primary care report high rates of misdiagnosis when patients are assessed against objective criteria (rates of 25–50% accuracy reported in different series).<sup>50–52</sup> Furthermore, under-investigation of heart failure is not confined to primary care,<sup>53</sup> with only 31% of patients in one study being offered echocardiography by hospital physicians following referral with possible heart failure.<sup>54</sup>

In this context, the potential role of natriuretic peptides in diagnosing heart failure on the basis of a simple and inexpensive blood test has emerged. Numerous studies have confirmed the stability and feasibility of natriuretic peptide testing, although there are relatively few data testing the peptides in the clinical setting where they would be most used, that is, in adults in the community presenting with persisting breathlessness. However, what is clear is that maximising the cut-off values to ensure high negative

predictive value, which is important in a primary care setting, reduces the specificity of the test. For example, both NT-proBNP and BNP assays set at cut-offs to achieve a sensitivity of 100%, showed a specificity of 70%, a positive predictive value of 7%, a negative predictive value of 100%, and an area under receiver operator characteristic curve of 0.92 (95% CI = 0.82 to 1.0) for diagnosing heart failure in the general population.<sup>55</sup> Performance of the assays was similar whatever the cause of heart failure and similar negative predictive values were also shown for diagnosing LVSD.<sup>56</sup> These data should be interpreted as showing that a normal level of natriuretic peptides virtually guarantees that heart failure is not present, but that confirmatory echocardiography is needed in patients with elevated peptides to confirm the diagnosis. The cost-effectiveness of natriuretic peptides versus standard diagnostic triage is not established. However, they may also have an important role in guiding therapy, at least in specialist settings,<sup>57</sup> on the basis of small follow-up studies.

ACE inhibitors improve both morbidity and mortality in all grades of symptomatic heart failure due to LVSD, and, in patients with asymptomatic LVSD, can delay or prevent progression to symptomatic heart failure.<sup>33,58</sup> Beta-blocker therapy in heart failure due to LVSD has also been demonstrated to improve prognosis and reduce admission rates,<sup>59,60</sup> although these agents have to be introduced slowly and are associated with slight worsening of symptoms initially in a proportion of patients. Aldosterone blockers reduce hospitalisation and mortality in severely symptomatic (NYHA grade II and IV) patients,<sup>18</sup> or in post-myocardial infarction LVSD.<sup>61</sup> However, in the older community care is needed with these agents, as they may be associated with increasing mortality if not used carefully in routine practice (only in low doses and withdrawn during periods of illness especially when dehydrated).<sup>62</sup> Recent data have demonstrated the general utility of angiotensin receptor blockers in patients who are intolerant of ACE inhibitors, or in addition to ACE inhibitors and beta-blockers in those with impaired left ventricular function.<sup>63</sup> However, heart failure remains suboptimally diagnosed and treated in many countries.<sup>64,65</sup>

## CONCLUSIONS

Heart failure is a common disorder, especially in older people, with major and increasing significance for patients and healthcare systems. We need better identification of patients and more intensive attempts to introduce and maintain the large evidence base for therapies. However, given the burden of disease, prevention of heart failure is a priority, and this requires formalised programmes of cardiovascular disease prevention.

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