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Acute heart failure syndromes: the 'Cinderella' of heart failure research

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Acute heart failure syndromes (AHFS) comprises a heterogeneous set of conditions, which has received relatively little clinical attention, despite being one of the most commonly encountered syndromes in emergency medicine. The condition is one of the most common reasons for hospitalization in the developed world and is associated with substantial costs, in terms of morbidity, mortality, days spent in hospital, and financial expenditure. When compared with acute myocardial infarction, which accounts for a similar number of hospitalizations each year, the low number and small scale of clinical studies of AHFS is striking. This has resulted in a relative lack of progress in developing new therapies and in establishing optimal treatment strategies. New studies are exigently needed to address these needs. In the setting of this requirement for a greater understanding of AHFS, several population-based studies are in progress, with the aim of collecting epidemiological data on the condition. One such study is the EFICA observational cohort study of patients hospitalized with AHFS in France. This will provide information on the clinical and aetiological features, management, and outcomes of AHFS, which should steer the design of treatment strategies and clinical trials that are essential to improve management of this condition.

Introduction

Heart failure is a significant burden on healthcare services in developed countries, with a worse prognosis than that of many major cancers or myocardial infarction.[1] Acute heart failure is often perceived as an extension of chronic heart failure (CHF), but it is increasingly being regarded as a standalone disease. The syndrome encompasses a broad spectrum of heterogeneous conditions including pulmonary oedema, hypertensive crisis, exacerbated CHF, and cardiogenic shock—and therefore may be more accurately described as a set of syndromes (termed as acute heart failure syndromes, AHFS).[2] Not surprisingly, therefore, clinical presentation, heart failure history, aetiology, pathophysiology, and subsequent disease outcome vary considerably among patients.

Although AHFS is one of the most commonly encountered syndromes in emergency medicine,[2] it has received relatively little clinical attention when compared with both CHF and other acute cardiac conditions, such as acute myocardial infarction (AMI; *Table 1*). Furthermore, the lack of progress, until recently, in developing new therapies for AHFS is striking when compared with the significant treatment advances for other cardiovascular diseases, such as thrombolytic agents for AMI and GPIIb/IIIa inhibitors for acute coronary syndromes.

Specific epidemiological data for AHFS are scarce; most data are derived from hospital discharge records corresponding to the general heart failure code. Several recent initiatives are beginning to address this issue, including the French EFICA (Epidémiologie Francaise de l'Insuffisance Cardiaque Aiguë)[3] and EPICAL

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(Epidémiologie de l'Insuffisance Cardiaque Avancée en Lorraine)[4] observational cohort studies, the EuroHeart Failure Survey covering 24 European countries,[5] and the ADHERE (Acute Decompensated Heart Failure National Registry) database in the USA.[6] The shortage of epidemiological data, together with the heterogeneity and confusing nomenclature of this syndrome, partly explains why the disease remains relatively poorly understood and undefined. This paper considers the epidemiology and disease burden of AHFS, as well as the clinical attention the syndrome has received in comparison with AMI.

Epidemiology

Heart failure is a common cardiac condition with an estimated prevalence of $\sim$1–2% in both Europe and USA.[7–9] Population-based studies of AHFS are lacking and, although data are published for heart failure, comparisons are difficult, because no universally agreed definition for AHFS exists, and differing methodologies have been used to assess the extent of the disease.[10] Hospital epidemiological data for heart failure are the most widely available, but even these should be interpreted with caution due to the range of syndromes covered and the uncertainty of diagnosis.

In the USA, 550 000 new cases of CHF were recorded in 2001, and its prevalence in the total population was estimated at 2.2%.[8] Although Europe-wide data for heart failure are scarce, most studies suggest that heart failure is also a significant and growing problem throughout this continent, particularly in the elderly. According to the European Society of Cardiology estimates, there are at least 10 million patients with heart failure in Europe.[11]

The incidence and prevalence of heart failure increases dramatically with age: 1 in 35 people aged 65–74 years has heart failure; this increases to 1 in 15 for people aged 75–84 years and 1 in 7 for those aged $\geq$85 years.[12] The increased prevalence of heart failure among the elderly, together with the progressive ageing of the general population and increased survival of patients, will undoubtedly result in a continued increase in prevalence and greater healthcare burden.

Table 1 A comparison of the burden and clinical attention for acute heart failure with AMI

	Acute heart failure	Acute myocardial infarction
Number of hospitalizations (USA)	995 000	795 000
Readmission rate	High	Low
Placebo-controlled trials	2	>100
Medline citations (2001–July 2004)	172	5113
European guidelines	Pending	Yes

Adapted from Felker *et al.*[26]

The social and financial burden of disease

Heart failure is one of the most common reasons for hospitalization in the developed world, and is responsible for $\sim$5% of acute medical admissions in Europe.[13,14] In England, 107 471 hospitalizations with heart failure as the primary diagnosis were recorded in National Health Service hospitals in 2002–03.[12] Comparable figures were reported for AMI: a total of 105 476 inpatient cases with a primary diagnosis of AMI were recorded over the same period.[9] In contrast, in France, the number of admissions for heart failure is estimated at twice that for AMI (*Table 2*).[15] In the USA, hospital discharge rates for heart failure are broadly comparable to those reported for AMI: 995 000 patients were discharged with a diagnosis of AHFS and 795 000 with AMI, during 2001 (*Table 1*).[8] Although few European data exist, discharge rates are generally believed to be similar to those observed in the USA. Hospitalizations for heart failure are most common among the elderly: the admission rate in Spain was estimated at 2.5 per 1000 adults and 26.5 per 1000 adults aged $\geq$80 years.[16]

Although recent European clinical data suggest that age-adjusted hospitalization rates for heart failure are now decreasing,[17] the burden of hospitalization remains significant. There is some evidence to suggest a trend towards decreasing hospitalization rates for AMI and increasing rates for heart failure. In the last decade, the discharge rate in Scotland for AMI decreased by one-third, from 260 to 173 per 100 000 population.[18] Decreased AMI hospitalization rates have also been observed in other European countries and the USA.[19–21] In contrast, over the last 20 years, the discharge rate for heart failure in the USA doubled from 168 to 349 discharges per 100 000 population.[8] Similarly, annual admission rates have increased by 4–5% over the last decade in the UK, with numbers projected to increase from 78 200 in 2000–01 to 113 100 by 2027 in patients aged $\geq$45 years.[22] These data may reflect a relative lack of progress in patient management and treatment for AHFS when compared with AMI.

AHFS is associated with substantial morbidity and mortality in most developed countries. The mortality rate due to AHFS is usually an underestimate because guidance on death certificates discourages citation of heart failure as the cause of death, preferring physicians to code the underlying aetiology (e.g. coronary artery disease).[10] In the UK, around 11 500

Table 2 Clinical and societal impact of acute heart failure compared with AMI, during 1999[15]

	Acute heart failure	Acute myocardial infarction
Number of admissions	142 421	77 325
Length of stay (days)	10.2	8.0
In-hospital mortality (%)	11	8.7

deaths due to heart failure were officially recorded in 2001, but the true number (derived from incidence and survival data) is estimated to be closer to 24 000 deaths.[9] The significant morbidity associated with heart failure is reflected in hospital readmission rates, which are also higher than those observed for AMI (*Table 1*). Estimates of risk of death or readmission vary, but the largest randomized trial in patients hospitalized with decompensated heart failure found the 60 day mortality rate to be 9.6% and the combined 60 day mortality or readmission rate to be 35.2%.[23] The Euro-Heart Failure Survey programme found that 24% of patients with heart failure were readmitted within 12 weeks of discharge.[5] In other studies, almost one-third of heart failure patients in the USA and 16% of patients in The Netherlands were readmitted within 6 months.[24,25] Additionally, in a population-based survey in London, UK, >50% of patients with a new diagnosis of heart failure were subsequently hospitalized at least once over a period of 19 months.[7] In comparison, available data suggest that the mortality and readmission rates for AMI are lower: the 30 day mortality rate has been estimated at 3–9%[26] and the 6 month mortality or readmission rate for AMI across four hospitals in Spain was ~24%.[27] A population-based analysis in Canada found that 7.7% of patients with AMI were readmitted with a second AMI within 1 year.[28]

Each year heart failure accounts for 6.5 million days spent in hospital in the USA, 1.4 million days in France, and about 1 million days in the UK.[12,15,26] This is nearly twice the total number of days spent in hospital for AMI in France.[15]

The overall costs for managing heart failure are staggering. The annual cost is nearly $25.8 billion in the USA (*Figure 1*) and £625 million in the UK.[8,12] In Sweden, the annual expenditure for heart failure is ~217–282 million Euros (exchange rate: 1 € = 9.21 SEK), which corresponds to 2% of the total Swedish healthcare budget. Hospital care accounts for >60% of the total healthcare expenditure for managing patients with heart failure.[7,29] Improving management and treatment of patients could considerably reduce hospitalization rates and result in a significant saving in terms of healthcare expenditure.

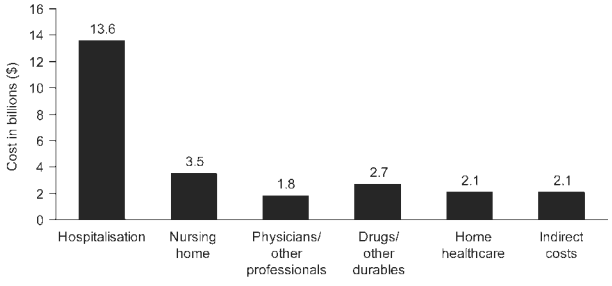

Figure 1 Estimated costs associated with heart failure in the USA in 2004.[8]

Clinical attention

Despite the increasing prevalence and healthcare burden associated with AHFS, clinical attention has been considerably lower than that for AMI (*Table 1*). Hundreds of studies have been conducted and thousands of citations exist for AMI, whereas research into AHFS has been far less active to date. For example, a MEDLINE search of articles published from January 2001 to July 2004 retrieved 5113 articles for AMI, but only 172 for AHFS. Large differences also exist in the quality of studies conducted for these two conditions. Many large, multicentre, international studies involving thousands of patients have been conducted for AMI, whereas placebo-controlled, randomized trials for AHFS are few and have only recently been reported—notably, OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure), involving 949 patients,[30] and a study comparing intravenous nesiritide and nitroglycerin, involving 489 patients.[31] In addition to the lack of clinical research on AHFS, European guidelines for patient management in this area have only recently been developed and are yet to be published (*Table 1*).

Public awareness and perception of heart failure is also low. A pan-European public survey of 7958 individuals demonstrated that only 3% could correctly identify heart failure from a description of typical signs and symptoms, whereas nearly one-third of subjects could identify a description of angina and about half could identify stroke.[32] Furthermore, only one-third of surveyed individuals believed heart failure signs and symptoms were a severe complaint. Programmes to increase public knowledge and awareness of the importance of heart failure are exigently required and could help obtain more funding and improved management for heart failure healthcare.

Encouragingly, however, interest in this area is being stimulated as the understanding of this complex disease continues to grow and potential new therapies emerge.

AHFS study design

Community-based study populations, generally, have a higher mean age and a larger proportion of women than patient populations currently included in most heart failure clinical trials. A national survey of heart failure in French hospitals found substantial differences between populations in heart failure clinical trials and those in routine clinical practice. The median age of patients hospitalized for heart failure was 76 years in this survey; most patients would have been too old to be eligible for large heart failure studies.[33]

New therapies for both heart failure and AHFS should be developed, where possible, with clear clinical benefit demonstrated in well designed, randomized, controlled trials involving an appropriate patient population. Patient eligibility criteria should be carefully considered and clearly defined to obtain the most representative patient population possible. The approach to design of

trials in AHFS is also important and should be different to that taken for CHF.[34] The goal of AHFS therapy is not only to prevent disease progression but also to have a beneficial effect on an acute event that worsens disease progression.

The efficacy variables to be employed in a study need careful consideration and validation. Mortality is traditionally used as an endpoint in heart failure studies, but large reductions (such as that originally observed with beta-blockers) are becoming increasingly difficult to demonstrate as therapies have to be studied against a background of ACE inhibitors, beta-blockers, diuretics, and digoxin.[34] A combined endpoint assessing survival and rehospitalization rates is becoming increasingly popular for acute therapies.

Data from patient registries and epidemiological studies of AHFS will make this task much easier, enabling the design of clinical trials that more closely represent the community-based population.

EFICA: an observational cohort study in AHFS

Clinicians increasingly recognize the need to enhance their understanding of AHFS, improve their knowledge of patient outcomes, and address some of the outstanding questions. With this in mind, a French group designed EFICA—an observational cohort study of patients with AHFS.[3]

The study evaluated patients with AHFS admitted consecutively from May to December 2001 to 60 intensive care units (ICUs) or coronary care units (CCUs) in France. Selection criteria included hospitalization following emergency admission with symptoms of AHFS. Patient characteristics and medical history, along with therapeutic measures performed during hospitalization in ICU or CCU, were recorded. The number of patients who died in the emergency department before admission to ICU/CCU was obtained from 34 out of 60 centres.

A total of 599 patients were enrolled, and presenting patients' profiles were diverse. Two-thirds of patients had been previously diagnosed with CHF, and one-third of patients had been previously admitted for AHFS. On admission, 82% of patients had pulmonary oedema and 29% had cardiogenic shock. The most frequent cause of AHFS was ischaemic heart disease (*Figure 2*). Median left ventricular ejection fraction, measured in 322 patients, was 35%.

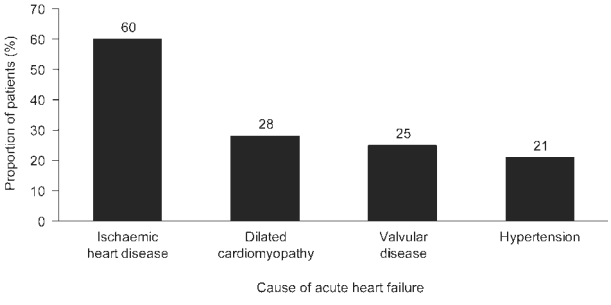

Figure 2 Most frequent causes of acute heart failure in patients enrolled in the EFICA study.[3]

The median length of stay in ICU was 4 days, and total length of hospital stay was 12 days. In-hospital mortality was 29%, and 75% of these deaths were related to cardiogenic shock, 25% to AMI, and 12% to ventricular arrhythmias. More detailed results along with 6 month outcome data and prognostic analyses will be published shortly.

EFICA and similar databases provide information on clinical and aetiological features, management, and outcomes of AHFS, which are critical for designing new patient management programmes and clinical trials specific to this acute condition.

Conclusion

AHFS is a heterogeneous set of clinical syndromes associated with a high mortality and hospitalization rates and a consequent heavy healthcare burden. Further epidemiological and clinical research is needed to improve our understanding and knowledge of the syndromes, thereby enhancing patient care.

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