Challenges and opportunities in heart failure: unmet clinical needs, economic burden, and impact on society

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Milan, Italy
Clinical unmet needs in heart failure treatment

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Ireland
Agenda

• Incidence and mortality of HF
• HF clinical needs
  – early diagnosis
  – HF-PEF treatment
  – HF-REF treatment
• Where to next?
What is it?

• Heart failure (HF) is defined, clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function.

• It is a chronic condition with episodes of acute decompensation.

### Two main types

<table>
<thead>
<tr>
<th>HF with preserved ejection fraction (HF-PEF)</th>
<th>HF with reduced ejection fraction (HF-REF)</th>
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<tbody>
<tr>
<td><strong>Diastolic HF</strong></td>
<td><strong>Systolic HF</strong></td>
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<tr>
<td>Thicker and stiff heart muscle</td>
<td>Thinner and weak heart muscle</td>
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<tr>
<td>Aorta</td>
<td>Aorta</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>Right ventricle</td>
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</tbody>
</table>

Incidence

Prevalence\(^1\)

\(~2\%\) of the population in Europe have HF

As many as **1 in 5** people aged 70–80 years have HF

\(~15\) million

Growth\(^2\)

Increasing prevalence of risk factors

HF PREVALENCE

An aging population

Improved post-MI survival


MI, myocardial infarction.
Quality of life similar in HF and dialysis patients

BP, bodily pain; CHF, congestive heart failure; GH, general health perceptions; MH, mental health; PF, physical functioning; pop., population; RE, role limitations caused by emotional problems; RP, role limitations due to physical limitations; SF, social functioning; SF-36, Short Form 36 health survey; VT, vitality.

Acute HF is associated with a lengthy hospital stay

Median length of hospitalization is 8 days

48% of hospitalized patients will require admission to the ICU for a median period of 4 days

Data from 1,892 European patients with acute HF in the European Society of Cardiology Heart Failure (ESC-HF) pilot study

ICU, intensive care unit.

Data from 1,433 patients with ACC/AHA chronic “Stage D” HF (persistent symptoms and high risk of hospitalization despite maximum medical therapy) enrolled in ADHERE LM. Data presented show time from entry in ADHERE LM for 50% of patients to be rehospitalized or die in 3 cohorts of patients defined by the number of hospitalizations experienced in the 6-months prior to registry entry.

ACC, American College of Cardiology; ADHERE LM, Acute Decompensated Heart Failure National Registry Longitudinal Module; AHA, American Heart Association.

HF is as “malignant” as many cancer types

More ‘malignant’ than cancer? Five-year survival following a first admission for heart failure

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poorest 5-year survival rate (approximately 25% for both sexes). On an adjusted basis, heart failure was associated with worse long-term survival than bowel cancer in men (adjusted odds ratio, 0.89; 95% CI, 0.82–0.97; \( P < 0.01 \)) and breast cancer in women (odds ratio, 0.59; 95% CI, 0.55–0.64; \( P < 0.001 \)). The overall population rate of expected life-years lost due to heart life-years lost. © 2001 European Society of Cardiology. All rights reserved.
Hospitalized HF patients have a 10% mortality by 30 days post discharge.

- 3.8% in-hospital mortality rate
- ~10% mortality after 30 days

### HF patients in the community have only 50% survival at 5 years

<table>
<thead>
<tr>
<th>Study</th>
<th>Survival rates (%)</th>
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<tbody>
<tr>
<td>Hillingdon Study (2000)¹</td>
<td>18-month survival: 57</td>
</tr>
<tr>
<td>Framingham (2002)²</td>
<td>5-year survival: males 41; females 55</td>
</tr>
<tr>
<td>Mayo Clinic (2004)³</td>
<td>5-year survival: 52</td>
</tr>
<tr>
<td>ECHOES study (2007, 2012)⁴,⁵</td>
<td>5-year survival: 53⁴</td>
</tr>
<tr>
<td></td>
<td>10-year survival: 26.7⁵</td>
</tr>
<tr>
<td>Olmsted County Study (2008)⁶</td>
<td>5-year survival: 45</td>
</tr>
<tr>
<td>Sweden (2013)⁷</td>
<td>5-year survival: 48</td>
</tr>
</tbody>
</table>

HF is a progressive disease

“The very essence of cardiovascular medicine is the recognition of early heart failure”

Sir Thomas Lewis (1933)
Diagnosis problems

- 34% of patients with an existing clinical label of HF in general practice records had this diagnosis confirmed by echocardiography\(^1\)
- Most patients are diagnosed based on symptoms and signs alone, with only 32% having further investigations or referral\(^2\)

Missed diagnosis in primary care

1. Pneumonia (6.7%)
2. ** Decompensated HF (5.7%)**
3. Acute renal failure (5.3%)
4. Cancer (primary) (5.3%)
5. Urinary tract infection or pyelonephritis (4.8%)

In Scotland, most people with any long-term condition have comorbidities.

COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack.
Clinical trials show reduced risk of mortality with HF medications

**In addition to standard of care at the time of study. Patient populations varied between trials; therefore RRR between trials cannot be directly compared. SOLVD (Studies of Left Ventricular Dysfunction), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II), and RALES (Randomized Aldactone Evaluation Study) enrolled chronic HF patients with left ventricular ejection fraction ≤ 35%.**

**Analysis of HF data from 1,282 incident cases of HF in the Atherosclerosis Risk in Communities (ARIC) population-based study of 15,792 individuals from 4 communities in the USA (1987–2002).**

ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; RRR, relative risk reduction.

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No treatment has yet been shown, convincingly, to reduce morbidity and mortality in patients with HF-PEF. Diuretics are used to control sodium and water retention and relieve breathlessness and oedema as in HF-REF. Adequate treatment of hypertension and myocardial ischaemia is also considered to be important, as is control of the ventricular rate in patients with AF (see Section 11). Two very small studies (<30 patients each) have shown that the heart rate-limiting calcium-channel blocker (CCB) verapamil may improve exercise capacity and symptoms in these patients. Rate-limiting CCBs may also be useful for ventricular rate control in patients with AF and in the treatment of hypertension and myocardial ischaemia (which is not the case in patients with HF-REF where their negative inotropic action can be dangerous). Beta-blockers may also be used to control the ventricular rate in patients with HF-PEF and AF.

The drugs that should be avoided in HF-REF (see Section 7.4) should also be avoided in HF-PEF, with the exception of CCBs. The key mortality–morbidity trials to date are:

- The 3023-patient Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial, which showed no reduction in the primary composite endpoint (cardiovascular death or HF hospitalization).
- The 850-patient Perindopril for Elderly People with Chronic Heart failure trial (PEP-CHF), which showed no reduction in the primary composite endpoint of death or HF hospitalization.
- The 4128 patient Irbesartan in heart failure with preserved systolic function trial (I-Preserve) which showed no reduction in the primary composite outcome of death or cardiovascular
Do we need new therapy?

• Mortality rates are still high – approx. 50% at 5 years\textsuperscript{1–5}
• No disease-modifying treatments are available for HF-PEF\textsuperscript{6}
• There is a new therapeutic option targeting the natriuretic peptide system
• PARADIGM-HF prospectively compared ARNI and ACEI to determine the impact on global mortality and morbidity in HF\textsuperscript{7}
  – LCZ696, compared with a target-dose enalapril-based regimen, significantly reduced the rates of death from any cause and from cardiovascular causes and the rates of hospitalizations for worsening HF in patients with HF-REF
  – Quality of life was significantly improved
• PARAGON-HF is an ongoing study comparing LCZ696 with valsartan in patients with HF-PEF\textsuperscript{8}

Where to next?
Life-years gained from early application of therapy in HF-REF

<table>
<thead>
<tr>
<th>Time horizon (years)</th>
<th>Life-years gained (years)</th>
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<th></th>
<th>Overall</th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACEI</td>
<td>ACEI + BB</td>
<td>ACEI</td>
<td>ACEI + BB</td>
</tr>
<tr>
<td>3</td>
<td>0.104</td>
<td>0.307</td>
<td>0.113</td>
<td>0.326</td>
</tr>
<tr>
<td>5</td>
<td>0.150</td>
<td>0.459</td>
<td>0.174</td>
<td>0.511</td>
</tr>
<tr>
<td>10</td>
<td>0.218</td>
<td>0.697</td>
<td>0.278</td>
<td>0.854</td>
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</tbody>
</table>

“This year, the [clinical practice guidelines] reflect the increasing use of evidence-based recommendations in addition to the recognition that the population-based evidence derived from studies needs to be tailored to the individual patient”

Richard Grant, MD, MPH, incoming chair of the American Diabetic Association Professional Practice Committee 2013
Personalized HF prevention

- Use natriuretic peptides to identify patients at highest risk of developing HF and to target care to this group
- **STOP HF study**¹
  - HF and LV dysfunction (odds ratio [OR] 0.55, 95% CI 0.37–0.82; p = 0.003)
  - Hospitalization for major cardiac events (incidence rate ratio 0.60, 95% CI 0.45–0.81; p = 0.002)
- **PONTIAC study**²
  - Hospitalization for major cardiac event or cardiac death (hazard ratio [HR] 0.351, 95% CI 0.127–0.975; p = 0.044)
- Will be further explored in the PARABLE study using LCZ696 in those patients with mildly elevated natriuretic peptide levels and cardiovascular risk factors³

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CI, confidence interval; LV left ventricular.
One-size-fits-all approach

Group of patients with the same syndrome

Targeted therapy

The definition of insanity is repeating the same behaviors and expecting a different outcome.

Albert Einstein
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