Il punto sullo scompenso cardiaco

Brescia 12 Settembre 2014

Marco Ferri
Aspetti epidemiologici
Chart 13-5. Percentage breakdown of deaths attributable to cardiovascular disease (United States: 2009). Source: National Heart, Lung, and Blood Institute from National Center for Health Statistics reports and data sets. *Not a true underlying cause. With any-mention deaths, heart failure accounts for 35% of cardiovascular disease deaths. Total may not add to 100 because of rounding. Coronary heart disease includes International Classification of Diseases, 10th Revision (ICD-10) codes I20 to I25; stroke, I60 to I69; heart failure, I50; high blood pressure, I10 to I15; diseases of the arteries, I70 to I78; and Other, all remaining ICD-10 categories.

Note: Hospital discharges include people discharged alive, dead, and status unknown. Source: National Hospital Discharge Survey/National Center for Health Statistics and National Heart, Lung, and Blood Institute.
Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND

Frank P. Brouwers¹*,†, Rudolf A. de Boer¹, Pim van der Harst¹, Adriaan A. Voors¹, Ron T. Gansevoort², Stephan J. Bakker², Hans L. Hillege¹, Dirk J. van Veldhuisen¹, and Wiek H. van Gilst¹
Figure 2  Cumulative incidence of new onset heart failure, divided by total new onset heart failure, heart failure with reduced ejection fraction, and heart failure with preserved ejection fraction. Incidence of heart failure is adjusted for mortality during follow-up.
Figure 3  Five-year survival curve after diagnosis of new onset heart failure with reduced ejection fraction and heart failure with preserved ejection fraction.
<table>
<thead>
<tr>
<th></th>
<th>Adjusted for age and sex</th>
<th>Mutually adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HFrEF</th>
<th>HFP EF</th>
<th>$P_{cr}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>–</td>
<td>–</td>
<td>1.81 (1.47–2.24)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>–</td>
<td>–</td>
<td>1.48 (1.03–2.13)</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>1.93 (1.37–2.73)</td>
<td>&lt;0.001</td>
<td>1.62 (1.10–2.37)</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>Heart rate (per 5 b.p.m.)</td>
<td>1.05 (0.98–1.13)</td>
<td>0.155</td>
<td>–</td>
<td>–</td>
<td>0.750</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.99 (1.37–2.89)</td>
<td>&lt;0.001</td>
<td>1.17 (0.77–1.77)</td>
<td>0.458</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.45 (2.38–4.99)</td>
<td>&lt;0.001</td>
<td>2.27 (1.54–3.34)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Smoking or quit smoking &lt;1 year</td>
<td>1.31 (0.96–1.79)</td>
<td>0.087</td>
<td>1.24 (0.87–1.77)</td>
<td>0.228</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.64 (1.23–5.66)</td>
<td>0.013</td>
<td>1.10 (0.55–2.19)</td>
<td>0.787</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.41 (1.51–3.85)</td>
<td>&lt;0.001</td>
<td>1.66 (0.99–2.78)</td>
<td>0.056</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolaemia (mmol/L)</td>
<td>1.65 (1.21–2.26)</td>
<td>0.002</td>
<td>1.34 (0.95–1.88)</td>
<td>0.096</td>
<td></td>
</tr>
<tr>
<td>Log Creatinine (per doubling)</td>
<td>1.00 (0.84–1.20)</td>
<td>0.973</td>
<td>–</td>
<td>–</td>
<td>0.713</td>
</tr>
<tr>
<td>eGFR &gt;60 mL/min/kg</td>
<td>1.07 (0.66–1.74)</td>
<td>0.782</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Log Cystatine C (per doubling)</td>
<td>1.43 (1.23–1.68)</td>
<td>&lt;0.001</td>
<td>1.08 (0.94–1.24)</td>
<td>0.295</td>
<td></td>
</tr>
<tr>
<td>Log UAE (per doubling)</td>
<td>1.35 (1.22–1.50)</td>
<td>&lt;0.001</td>
<td>1.01 (0.91–1.14)</td>
<td>0.798</td>
<td></td>
</tr>
<tr>
<td>Log hs-C-reactive protein (per doubling)</td>
<td>1.41 (1.17–1.70)</td>
<td>&lt;0.001</td>
<td>1.14 (0.92–1.41)</td>
<td>0.228</td>
<td></td>
</tr>
<tr>
<td>Log NT-proBNP (per doubling)</td>
<td>2.11 (1.79–2.49)</td>
<td>&lt;0.001</td>
<td>1.68 (1.39–2.04)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Log hs-TnT (per doubling)</td>
<td>1.67 (1.51–1.86)</td>
<td>&lt;0.001</td>
<td>1.33 (1.17–1.52)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
I progressi terapeutici farmacologici e non hanno comportato negli ultimi decenni:

Mortalità: relativamente bassa (7%) con trend in riduzione.

Incidenza: in aumento con l’età dei pazienti e complessivamente

Trend di ricovero:

  in relativo aumento.

Miglioramento della sopravvivenza

“Cronicizzazione” della patologia
“Cronicizzazione” della patologia:

Terapie:
- sostenibili (economicamente-socialmente)
- proporzionate ("cost-effective" non in senso economico).

Organizzazione:
- rapporti ospedale territorio
- riospedalizzazioni (è un problema clinico?)
- gestione della terminalità (hospice?)

Gestione:
- patologia d’organo o sindromica?
Spunti di fisiopatologia
MECHANISMS OF DISEASE

Proteotoxicity and Cardiac Dysfunction — Alzheimer’s Disease of the Heart?

Monte S. Willis, M.D., Ph.D., and Cam Patterson, M.D., M.B.A.
Figure 1. Association of the Development of Cardiac Atrophy and Hypertrophy with Changes in the Balance between Protein Synthesis and Protein Degradation.

The development of cardiac atrophy involves both the inhibition of protein synthesis and a simultaneous increase in the rates of protein degradation (Panel A), resulting in shorter half-lives of individual cardiac proteins, as compared with the half-lives of proteins in a steady state, when protein synthesis and degradation are balanced (Panel B). The development of cardiac hypertrophy involves both an increased fractional synthesis rate of proteins and the suppression of protein degradation (Panel C), resulting in longer half-lives of cardiac proteins.7-10
**Figure 2. Cellular Stress as a Cause of Protein Misfolding.**

Molecular chaperones stabilize and fold newly synthesized proteins and play a role in refolding proteins that undergo stress (unfolding). The continuous wear and tear eventually causes damage that the chaperone system cannot correct. These proteins may then be recognized by the ubiquitin–proteasome system (UPS) involving ubiquitin (Ub) ligases that target specific proteins for degradation by the 26S proteasome. Deubiquitinating enzymes act to counter the UPS ubiquitinylation for fine control of the degradation process.
The accumulation of misfolded proteins (either soluble oligomers or protein aggregates) in the pathogenesis of neurodegenerative diseases such as Huntington’s disease, Parkinson’s disease, and Alzheimer’s disease parallels new findings in heart failure that misfolded proteins accumulate and form aggregates, or preamyloid inclusions. The proteasome appears to be able to degrade misfolded proteins early in the process of misfolding; such proteins are soluble oligomers (also known as preamyloid oligomers). Alternative protein-degradation pathways through lysosomes that involve a process called “autophagy” mainly remove aggregates.

Recent studies in the CryABR120G mouse model, resulting from a misfolded-prone CryAB mutation, illustrate the importance of removing misfolded proteins in the pathogenesis of heart disease. In these studies, increasing expression of the 11S subunit of the proteasome by transgenic overexpression of the cardiac proteasome 28 subunit α reduces CryAB-positive protein aggregates. Enhancing proteasome activity may be a method for reducing proteotoxicity in vivo, in addition to targeting the formation of toxic soluble oligomers.
Figure 1. Phases of the Autophagic Pathway.
The autophagic pathway proceeds through several phases, including initiation (formation of a preautophagosomal structure leading to an isolation membrane, or phagophore), vesicle elongation, autophagosome maturation and cargo sequestration, and autophagosome-lysosome fusion. In the final stage, autophagosomal contents are degraded by lysosomal acid hydrolases and the contents of the autolysosome are released for metabolic recycling.
CARDIOVASCULAR DISEASES

Modulations in autophagy have been associated with diseases of the heart, including cardiomyopathies, cardiac hypertrophy, ischemic heart disease, heart failure, and ischemia–reperfusion injury. Genetic X-linked deficiency in lysosome-associated membrane protein 2 (LAMP2), which assists in autophagosome–lysosome fusion, causes cardiomyopathy known as Danon’s disease. In patients with this disease, cardiomyocytes with evidence of mitochondrial dysfunction have an increased number of autophagosomes, as does cardiac tissue from patients with heart failure. In a mouse model of desmin-related cardiomyopathy, autophagic activity was shown to provide cardioprotection.

Experimental ischemia–reperfusion injury also causes morphologic indicators of autophagy to increase in response to stress signals, including depleted ATP, hypoxia, and altered Ca^{2+} balance and may play various roles, depending on the phase of the injury. Increased numbers of autophagosomes are evident in macrophages from atherosclerotic plaques. Autophagy may stabilize atherosclerotic plaques by preventing macrophage apoptosis and plaque necrosis and by preserving efferocytosis.
Autophagy

Cancer
- Lipophagy
- Mitophagy
- Xenophagy

Vascular disease
- Plaque stabilization and regulation of proliferation

Infectious diseases
- Antigen presentation, pathogen removal, and regulation of inflammation

Neurodegenerative disease and aging
- Aggregate clearance and mitochondrial preservation

Pulmonary disease

Metabolic disease
- Cell survival, energy maintenance, and metabolite generation

Cell death, chemosensitization, and tumor suppression
- Chemoresistance, radioresistance, and tumor growth

Apoptosis
La scoperta degli intimi meccanismi delle patologie:

Elemento fondamentale per la strategia terapeutica...
Elemento fondamentale del metodo scientifico...
Elemento basilare per affrontare con consapevolezza la patologia...

Fondamento per attuare la strategia di Cura...senza dimenticare la Care.
Fondamento per considerare la patologia senza un atteggiamento riduzionistico...
Affrontare il problema
Spunti dall’epidemiologia (Heart centered)
Fattori considerati per il corretto profilo cardiovascolare

1. Current smoking
2. BMI*
3. PA (Physical Activity)
4. Healthy diet pattern
5. Total cholesterol
6. Blood pressure
7. Fasting plasma glucose
Incidence of cardiovascular disease according to the number of ideal health behaviors and health factors.
Affrontare il problema

Spunti dall’epidemiologia
(comorbididity perspective)
Table 31. Ten Most Common Co-Occurring Chronic Conditions Among Medicare Beneficiaries With HF (N=4,947,918), 2011

<table>
<thead>
<tr>
<th>Chronic Condition</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>3,685,373</td>
<td>84.2</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3,145,718</td>
<td>71.9</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2,623,601</td>
<td>60.0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2,200,674</td>
<td>50.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2,027,875</td>
<td>46.3</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1,901,447</td>
<td>43.5</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1,851,812</td>
<td>42.3</td>
</tr>
<tr>
<td>COPD</td>
<td>1,311,118</td>
<td>30.0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1,247,748</td>
<td>28.5</td>
</tr>
<tr>
<td>Alzheimer’s disease/dementia</td>
<td>1,207,704</td>
<td>27.6</td>
</tr>
</tbody>
</table>
Distribution of COPD stages according to NYHA class.

$P$ (trend) = .02
### Associazione multivariata fra i livelli di emoglobina, mortalità e riospedalizzazione

<table>
<thead>
<tr>
<th>Emoglobina (g/dl)</th>
<th>Mortalità “per ogni causa”</th>
<th>Riospedalizzazione per scompenso cardiaco</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥17</td>
<td>1.42(1.24-1.63)</td>
<td>1.14(1.03)</td>
</tr>
<tr>
<td>14.0-14.9</td>
<td>0.92(0.88-0.97)</td>
<td>0.98(0.94-1.01)</td>
</tr>
<tr>
<td>13.0-13.9</td>
<td>Int di riferimento</td>
<td>Int di riferimento</td>
</tr>
<tr>
<td>12.0-12.9</td>
<td>1.16(1.11-1.21)</td>
<td>1.12(1.09-1.16)</td>
</tr>
<tr>
<td>11.0-11.9</td>
<td>1.50(1.44-1.57)</td>
<td>1.33(1.28-1.38)</td>
</tr>
<tr>
<td>10-10.9</td>
<td>1.89(1.80-1.98)</td>
<td>1.64(1.58-1.71)</td>
</tr>
<tr>
<td>9.0-9.9</td>
<td>2.31(2.18-2.45)</td>
<td>1.89(1.80-1.99)</td>
</tr>
<tr>
<td>&lt;9.0</td>
<td>3.48(3.25-3.73)</td>
<td>1.99(1.86-2.13)</td>
</tr>
</tbody>
</table>
### Associazione multivariata fra la funzione renale e mortalità e riospedalizzazione

<table>
<thead>
<tr>
<th>Filtrato glomerulare (ml/min-1.73m-2)</th>
<th>Mortalità “per ogni causa”</th>
<th>Riospedalizzazione per scompenso cardiaco</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>Int di riferimento</td>
<td>Int di riferimento</td>
</tr>
<tr>
<td>45-59</td>
<td>1.01(0.97-1.05)</td>
<td>1.11(1.08-1.14)</td>
</tr>
<tr>
<td>30-44</td>
<td>1.39(1.34-1.44)</td>
<td>1.44(1.40-1.49)</td>
</tr>
<tr>
<td>15-29</td>
<td>2.28(2.19-2.39)</td>
<td>1.97(1.90-2.05)</td>
</tr>
<tr>
<td>&lt;15</td>
<td>3.26(3.05-3.49)</td>
<td>1.89(1.79-2.01)</td>
</tr>
</tbody>
</table>
In CHF patients, the prevalence of major depression – i.e., the full clinical picture of major depression – develops in 14–26%. However, single depressive symptoms can be detected in 24–85% of CHF patients. The prevalence of depression in CHF patients also seems to increase with age, but is clearly aggravated by the presence of CHF compared to patients with other forms of or without any organic heart disease. First and foremost, patients with CHF and depressive disorder have a 2–3 times higher mortality. Readmission rates are also 3 times higher, and over a third of CHF patient's depression does not remit within one year after discharge. Comorbid depression and CHF raise medical costs by 25–40% as well as hospitalisation rates, impairment of the NYHA status and daily activities.

J Cardiol (2007), doi:10.1016/j.ijcard.2007.05.020
Body Mass Index and Prognosis in Patients With Chronic Heart Failure: Insights From the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program

![Graph showing cumulative incidence of all-cause death across different BMI categories]

Log-Rank p-value < 0.0001

<table>
<thead>
<tr>
<th>BMI Categories</th>
<th>No. at risk</th>
<th>Time (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 22.5</td>
<td>889</td>
<td></td>
</tr>
<tr>
<td>22.5 to 24.9</td>
<td>1277</td>
<td></td>
</tr>
<tr>
<td>25 to 29.9</td>
<td>3063</td>
<td></td>
</tr>
<tr>
<td>30 to 34.9</td>
<td>1579</td>
<td></td>
</tr>
<tr>
<td>≥ 35</td>
<td>791</td>
<td></td>
</tr>
</tbody>
</table>

*Circulation* 2007:116:627-636
L’epidemiologia:
Ci aiuta a capire l’entità dei problemi ma, soprattutto a vedere le relazioni che legano le dinamiche delle patologie. Tali osservazioni ci aiutano a **mirare** le strategie terapeutiche e gli strumenti apppropriati.

Esempi?
- Miglioramento degli stili di vita nella popolazione anziana con scompenso
- Maggiore focalizzazione sulla comorbosità
- Evitamento di test inappropriati....siamo tutti unici ma condividiamo molti meccanismi fisiopatologici.
Affrontare il problema
Staging and treatment
At Risk for Heart Failure

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF
- e.g., Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome
  - Using cardiotoxins
  - With family history of cardiomypathy

**STAGE B**
Structural heart disease but without signs or symptoms of HF
- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**STAGE C**
Structural heart disease with prior or current symptoms of HF
- e.g., Patients with:
  - Known structural heart disease and HF signs and symptoms

**STAGE D**
Refractory HF
- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

---

**THERAPY**
**STAGE A**
- Goals:
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities
- Drugs:
  - ACEI or ARB in appropriate patients for vascular disease or DM
  - Statins as appropriate

**THERAPY**
**STAGE B**
- Goals:
  - Prevent HF symptoms
  - Prevent further cardiac remodeling
- Drugs:
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
- In selected patients:
  - ICD
  - Revascularization or valvular surgery as appropriate

**THERAPY**
**STAGE C**
- Goals:
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality
- Drugs for routine use:
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
- Drugs for use in selected patients:
  - Hydralazine/isosorbide dinitrate
  - ACEI and ARB
  - Digitalis
- In selected patients:
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

**THERAPY**
**STAGE D**
- Goals:
  - Control symptoms
  - Improve HRQOL
  - Reduce hospital readmissions
  - Establish patient's end-of-life goals
- Options:
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative surgery or drugs
  - Palliative care and hospice
  - ICD deactivation
Avere un atteggiamento legato alla "targeted-therapy":

- Ci obbliga ad una maggiore attenzione al singolo paziente
- Ci obbliga ad un atteggiamento più competente e attento alla valutazione di parametri che dobbiamo considerare
- Ci permette di utilizzare gli strumenti, tecnologici e non, in modo maggiormente appropriato e sostenibile
Affrontare il problema

Instruments.. “On the go”
Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis
We did, however, observe a significant interaction with age, the allcause mortality benefit being seen in patients <75 years but not in those aged ≥75 years. One explanation for the lack of mortality benefit in the older cohort could be that increases in the dose of some drugs were less overall than in <75 year old patients. It is conceivable, based on results from the PROTECT study, that elderly patients will exhibit benefit with more gradual, careful up-titration of medications according to BNP/NT-proBNP levels than younger patients.
6.3. Biomarkers: Recommendations

A. Ambulatory/Outpatient

Class I
1. In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty. *(Level of Evidence: A)*
2. Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF. *(Level of Evidence: A)*

Class IIa
1. BNP- or NT-proBNP–guided HF therapy can be useful to achieve optimal dosing of GDMT in select clinically euvoletic patients followed in a wellstructured HF disease management program. *(Level of Evidence: B)*

Class IIb
1. The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established. *(Level of Evidence: B)*
2. Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF. *(Level of Evidence: B)*

B. Hospitalized/Acute

Class I
1. Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis. *(Level of Evidence: A)*
2. Measurement of BNP or NT-proBNP and/or cardiac troponin is useful for establishing prognosis or disease severity in acutely decompensated HF. *(Level of Evidence: A)*

Class IIb
1. The usefulness of BNP- or NT-proBNP–guided therapy for acutely decompensated HF is not well established. *(Level of Evidence: C)*
2. Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with acutely decompensated HF. *(Level of Evidence: A)*
### Table 10. Recommendations for Noninvasive Cardiac Imaging

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with suspected, acute, or new-onset HF should undergo a chest x-ray</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>A 2-dimensional echocardiogram with Doppler should be performed for initial evaluation of HF</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Repeat measurement of EF is useful in patients with HF who have had a significant change in clinical status or received treatment that might affect cardiac function or for consideration of device therapy</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Noninvasive imaging to detect myocardial ischemia and viability is reasonable in HF and CAD</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Viability assessment is reasonable before revascularization in HF patients with CAD</td>
<td>IIa</td>
<td>B&lt;sup&gt;281–285&lt;/sup&gt;</td>
</tr>
<tr>
<td>Radionuclide ventriculography or MRI can be useful to assess LVEF and volume</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>MRI is reasonable when assessing myocardial infiltration or scar</td>
<td>IIa</td>
<td>B&lt;sup&gt;286–288&lt;/sup&gt;</td>
</tr>
<tr>
<td>Routine repeat measurement of LV function assessment should not be performed</td>
<td>III: No Benefit</td>
<td>B&lt;sup&gt;289,290&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; COR, Class of Recommendation; EF, ejection fraction; HF, heart failure; LOE, Level of Evidence; LV, left ventricular; LVEF, left ventricular ejection fraction; and MRI, magnetic resonance imaging.
Nonpharmacologic interventions

Class IIa
Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms. *(Level of Evidence: C)*

Class IIa
Continuous positive airway pressure can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea.393–396 *(Level of Evidence: B)*

Class I
Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status. *(Level of Evidence: A)*

Class IIa
Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, HRQOL, and mortality.404,406–411 *(Level of Evidence: B)*
Affrontare il problema
Treatment in time
Decision Making in Advanced Heart Failure: A Scientific Statement From the American Heart Association

*Circulation.* 2012;125:1928-1952; originally published online March 5, 2012; doi: 10.1161/CIR.0b013e31824f2173
Table 2. European Society of Cardiology Criteria for Advanced Chronic Heart Failure

1. Moderate to severe symptoms of dyspnea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV)
2. Episodes of fluid retention and/or reduced cardiac output
3. Objective evidence of severe cardiac dysfunction demonstrated by at least 1 of the following:
   - Left ventricular ejection fraction <30%
   - Pseudonormal or restrictive mitral inflow pattern by Doppler
   - High left and/or right ventricular filling pressures, or
   - Elevated B-type natriuretic peptide
4. Severe impairment of functional capacity as demonstrated by either inability to exercise, 6-min walk distance <300 m, or peak oxygen uptake <12 to 14 mL·g⁻¹·min⁻¹
5. History of at least 1 hospitalization in the past 6 mo
6. Characteristics should be present despite optimal medical therapy
Transition to Advanced Heart Failure:

- Oral therapies failing
- A time for many major decisions
- Consider MCS and/or transplantation, if eligible
- Consider inversion of care plan to one dominated by a palliative approach, which may involve formal hospice
Affrontare il problema

Prognosis...heart perspective
The Seattle Heart Failure Model: Prediction of Survival in Heart Failure

*Circulation*. 2006;113:1424-1433; originally published online March 13, 2006;
Predicting survival in heart failure: a risk score based on 39,372 patients from 30 studies

Stuart J. Pocock¹*, Cono A. Ariti¹, John J.V. McMurray², Aldo Maggioni³, Lars Køber⁴, Iain B. Squire⁵, Karl Swedberg⁶, Joanna Dobson¹, Katrina K. Poppe⁷, Gillian A. Whalley⁷, and Rob N. Doughty⁷, on behalf of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Addition to risk score</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td>&lt;20  20-24  25-29  30-34  35-39  40+</td>
<td>7  6  5  3  2  0</td>
</tr>
<tr>
<td>Extra for age (years)</td>
<td>&lt;55  56-59  60-64  65-69  70-74  75-79  80+</td>
<td>0  1  2  4  6  8  10</td>
</tr>
<tr>
<td>EF &lt; 30</td>
<td>0  1  2  4  6  8  10</td>
<td></td>
</tr>
<tr>
<td>EF 30 - 39</td>
<td>0  2  4  6  8  10  13</td>
<td></td>
</tr>
<tr>
<td>EF 40 +</td>
<td>0  3  5  7  9  12  15</td>
<td></td>
</tr>
<tr>
<td>Extra for Systolic blood pressure (mm Hg)</td>
<td>&lt;110  110-119  120-129  130-139  140-149  150+</td>
<td>5  4  3  2  1  0</td>
</tr>
<tr>
<td>EF &lt; 30</td>
<td>5  4  3  2  1  0</td>
<td></td>
</tr>
<tr>
<td>EF 30 - 39</td>
<td>3  2  1  0  0  0</td>
<td></td>
</tr>
<tr>
<td>EF 40 +</td>
<td>2  1  0  0  0  0</td>
<td></td>
</tr>
<tr>
<td>BMI (kg / m²)</td>
<td>&lt;15  15-19  20-24  25-29  30+</td>
<td>6  5  3  2  0</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>&lt;90  90-109  110-129  130-149  150-169  170-209  210-249  250+</td>
<td>0  1  2  3  4  5  6  8</td>
</tr>
<tr>
<td>NYHA Class</td>
<td>1  2  3  4  8</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of COPD</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>First diagnosis of heart failure in the past 18 months</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>Not on beta blocker</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>Not on ACEI/ARB</td>
<td>+1</td>
<td></td>
</tr>
</tbody>
</table>

Total risk score =
Affrontare il problema
Prognosis...geriatric perspective
Multidimensional Prognostic Index Based on a Comprehensive Geriatric Assessment Predicts Short-Term Mortality in Older Patients With Heart Failure
Alberto Pilotto, Filomena Addante, Marilisa Franceschi, Gioacchino Leandro, Giuseppe Rengo, Piero D'Ambrosio, Maria Grazia Longo, Franco Rengo, Fabio Pellegrini, Bruno Dallapiccola and Luigi Ferrucci
Table 1. MPI Score Assigned to Each Domain Based on the Severity of the Problems

<table>
<thead>
<tr>
<th></th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Assessment</td>
<td>(Value = 0)</td>
</tr>
<tr>
<td>ADL*</td>
<td>6–5</td>
</tr>
<tr>
<td>Instrumental ADL*</td>
<td>8–6</td>
</tr>
<tr>
<td>Short portable mental status questionnaire†</td>
<td>0–3</td>
</tr>
<tr>
<td>Comorbidity index (cumulative illness rating scale-Cl)‡</td>
<td>0</td>
</tr>
<tr>
<td>Mini nutritional assessment§</td>
<td>≥24</td>
</tr>
<tr>
<td>Exton-Smith scale¶</td>
<td>16–20</td>
</tr>
<tr>
<td>No. of medications</td>
<td>0–3</td>
</tr>
<tr>
<td>Social support</td>
<td>Living with family</td>
</tr>
<tr>
<td>network</td>
<td></td>
</tr>
</tbody>
</table>

*No. of active functional activities.
†No. of errors.
‡No. of diseases.
§Mini Nutritional Assessment score: ≥24, satisfactory nutritional status; 17–23.5, at risk of malnutrition; <17, malnutrition.
¶Exton-Smith Scale score: 16–20, minimum risk; 10–15, moderate risk; 5–9 high risk of developing scores.
Figure. ROC curves for the MPI, NYHA, EFFECT, and ADHERE risk scores at 30 days of follow-up in men (right) and women (left).
Senza dimenticare...

...se possibile
Geriatric Care and Treatment

A systematic compilation of existing scientific literature

SBU • Statens beredning för medicinsk utvärdering
The Swedish Council on Technology Assessment in Health Care
Quality of life

“Desired” level:
Patient’s wishes

Current-desired gap

“Actual” level:
Provisions achieve this level

Individual choices and pleasures, e.g.
- Pets
- Concerts
- Fresh air
- Ceramics painting
- Visiting children/family
- Reading
- Showering every day
- Social contacts

“Actual quality of life”

“Added values”
freedom, joy, trust, security, freedom of choice

Alleviation of symptoms (e.g. pain relief, sleep)
- Cleaning
- Grocery shopping
- Transportation
- Cooking
- Hygiene
- Dressing/undressing
- Using the toilet
- Mobility
- Continence
- Eating

“Basic quality of life”

Instrumental ADL

Personal ADL
Affrontare il problema

Ipotesi prossime
Targeting myocardial remodelling to develop novel therapies for heart failure

A position paper from the Working Group on Myocardial Function of the European Society of Cardiology
Figure 1 Therapeutic strategies to improve cardiomyocyte function. Red boxes identify molecules capable of improving cardiomyocyte function by acting on the indicated targets. GRK2, G protein-coupled receptor kinase 2; PI3K, Phosphoinositol 3 kinase gamma; SERCA2a, sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a; b3-AR, beta3 adrenergic receptor.
Table 1 Molecular targets and drugs with therapeutic potential on myocardial remodelling in heart failure

<table>
<thead>
<tr>
<th>Drug/target</th>
<th>Mechanism of action</th>
<th>Experimental stage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improving myocyte function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRK2</td>
<td>Prevent β-AR desensitization</td>
<td>Pre-clinical</td>
<td>Ciccarelli et al.⁴</td>
</tr>
<tr>
<td>PI3Kγ</td>
<td>Normalization of β-AR density and contractility</td>
<td>Clinical</td>
<td>NCT0103350</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Increase GMP/PKG signalling</td>
<td>Clinical</td>
<td>NCT00763867²³</td>
</tr>
<tr>
<td>CXL-1020</td>
<td>HNO donor</td>
<td>Clinical</td>
<td>25, 116</td>
</tr>
<tr>
<td>β₂-AR agonists (e.g. nebivolol)</td>
<td></td>
<td>Pre-clinical/clinical</td>
<td>16–19</td>
</tr>
<tr>
<td>SERCA2a</td>
<td>1Ca²⁺ SR uptake</td>
<td>Clinical</td>
<td>NCT0045481, NCT01643330</td>
</tr>
<tr>
<td>Omeprazole mecarbil</td>
<td>Myosin activator</td>
<td>Clinical</td>
<td>32</td>
</tr>
<tr>
<td>miR-208, miR-199a-5p, miR-199b, miR-212/132, miR15</td>
<td>Inhibit maladaptive hypertrophy</td>
<td>Pre-clinical</td>
<td>34–38, 40, 117</td>
</tr>
<tr>
<td>Preventing myocyte death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrostatin-1</td>
<td>Inhibit RIPK1 and necroptosis</td>
<td>Pre-clinical</td>
<td>44, 45</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>Inhibit MPTP opening and cell death</td>
<td>Clinical</td>
<td>48, 49</td>
</tr>
<tr>
<td>Neuregulin 1</td>
<td>Enhance protective signalling</td>
<td>Clinical</td>
<td>NCT01251406, bNCT01502774</td>
</tr>
<tr>
<td>HSPB5, HSPB6, HSPB8, BAG3, Melusin</td>
<td>Promote protein folding and enhance protective signalling</td>
<td>Pre-clinical</td>
<td>52, 53</td>
</tr>
<tr>
<td>CHIP, Atrogin1, MuRF1, Telethonin</td>
<td>Control of protein degradation</td>
<td>Pre-clinical</td>
<td>56, 58, 59, 61, 63, 64, 118, 119</td>
</tr>
<tr>
<td>Boosting angiogenesis in the heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF-A</td>
<td>Promote endothelial cell growth and migration</td>
<td>Clinical</td>
<td>82–85, 121</td>
</tr>
<tr>
<td>VEGF-B</td>
<td>Promote endothelial cell growth and migration; enhance myocyte survival</td>
<td>Pre-clinical</td>
<td>89</td>
</tr>
<tr>
<td>PLGF</td>
<td>Promote endothelial cell growth and migration; regulate inflammation</td>
<td>Clinical</td>
<td>87, 88</td>
</tr>
<tr>
<td>miR-126, miR-210</td>
<td>Promote endothelial cell growth and migration</td>
<td>Pre-clinical</td>
<td>90–92</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Inhibit prolactin release and protect in PPCM</td>
<td>Pre-clinical/clinical</td>
<td>94, 95</td>
</tr>
<tr>
<td>mir146, mir92a, mir-24</td>
<td>Protection in PPCM and MI</td>
<td>Pre-clinical</td>
<td>96–99</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Protection in anthraceline-induced myopathy</td>
<td>Pre-clinical</td>
<td>100</td>
</tr>
<tr>
<td>Regulating interstitial remodelling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombospondins, SPARC, syndecans</td>
<td>Promote favourable matrix remodelling; reduce inflammation</td>
<td>Pre-clinical</td>
<td>40, 104, 106, 122, 123</td>
</tr>
<tr>
<td>Torasemide</td>
<td>Diuretic, indirectly reduces fibrosis</td>
<td>Clinical</td>
<td>108, 109</td>
</tr>
<tr>
<td>miR-21 inhibitor</td>
<td>Inhibit fibroblast proliferation and secretion of ECM</td>
<td>Pre-clinical</td>
<td>110, 111, 124</td>
</tr>
<tr>
<td>miR-101, miR-29</td>
<td>Down-regulate ECM transcripts</td>
<td>Pre-clinical</td>
<td>112</td>
</tr>
</tbody>
</table>

AR, adrenergic receptor; ECM, extracellular matrix; MI, myocardial infarction; MPTP, mitochondrial permeability transition pore; PI3K, phosphoinositide 3-kinase; PKG, protein kinase G; PPCM, peripartum cardiomyopathy; RIPK1, receptor-interacting serine/threonine-protein kinase 1; SERCA2a, sarcoplasmic/endoplasmic Ca²⁺ ATPase 2a; SPARC, secreted protein acidic and rich in cysteine; SR, sarcoplasmic reticulum; VEGF, vascular endothelial growth factor.
Figure 2 Therapeutic strategies to prevent cardiomyocyte death. Red boxes identify molecules capable of preventing cardiomyocyte death by acting on the indicated targets and processes. CHIP, Carboxy terminus of Hsp70-interacting protein—ubiquitin ligase; MURF1, Muscle-specific RING finger protein 1—ubiquitin ligase; BAG3, Bcl-2-associated athanogene 3.
Figure 3 Therapeutic strategies to promote growth of blood vessels. Red boxes identify molecules capable of boosting growth of novel blood vessels by acting on the indicated targets and processes. β3-AR, beta3 adrenergic receptor; β2-AR, beta2 adrenergic receptor; VEGF-A, vascular endothelial growth factor A; VEGF-B, vascular endothelial growth factor B; PLGF, placenta growth factor.
Figure 4 Therapeutic strategies to regulate extracellular matrix deposition. Red boxes identify molecules capable of impacting extracellular matrix protein synthesis/deposition and fibroblast proliferation by acting on the indicated targets and processes. SPARC, Secreted protein acidic and rich in cysteine.
Figure 6. Excitation-contraction coupling in cardiac myocytes provides multiple targets for gene therapy.
Ipotesi prossime...

...ricordando la prudenza
Discrepancies in autologous bone marrow stem cell trials and enhancement of ejection fraction (DAMASCENE): weighted regression and meta-analysis

Abstract

Objective To investigate whether discrepancies in trials of use of bone marrow stem cells in patients with heart disease account for the variation in reported effect size in improvement of left ventricular function.

Design Identification and counting of factual discrepancies in trial reports, and sample size weighted regression against therapeutic effect size. Meta-analysis of trials that provided sufficient information.

Data sources PubMed and Embase from inception to April 2013.

Eligibility for selecting studies Randomised controlled trials evaluating the effect of autologous bone marrow stem cells for heart disease on mean left ventricular ejection fraction.

Results There were over 600 discrepancies in 133 reports from 49 trials. There was a significant association between the number of discrepancies and the reported increment in EF with bone marrow stem cell therapy (Spearman’s r=0.4, P=0.005). Trials with no discrepancies were a small minority (five trials) and showed a mean EF effect size of −0.4%. The 24 trials with 1-10 discrepancies showed a mean effect size of 2.1%. The 12 with 11-20 discrepancies showed a mean effect of size 3.0%. The three with 21-30 discrepancies showed a mean effect size of 5.7%. The high discrepancy group, comprising five trials with over 30 discrepancies each, showed a mean effect size of 7.7%.

Conclusions Avoiding discrepancies is difficult but is important because discrepancy count is related to effect size. The mechanism is unknown but should be explored in the design of future trials because in the five trials without discrepancies the effect of bone marrow stem cell therapy on ejection fraction is zero.
Authors’ conclusions

This systematic review and meta-analysis found moderate quality evidence that BMSC treatment improves LVEF. Unlike in trials where BMSC were administered following acute myocardial infarction (AMI), we found some evidence for a potential beneficial clinical effect in terms of mortality and performance status in the long term (after at least one year) in people who suffer from chronic IHD and heart failure, although the quality of evidence was low.