

Il punto sullo scompenso cardiaco

Brescia 12 Settembre 2014

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Aspetti epidemiologici

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association

Circulation. 2013;127:e6-e245; originally published online December 12, 2012;
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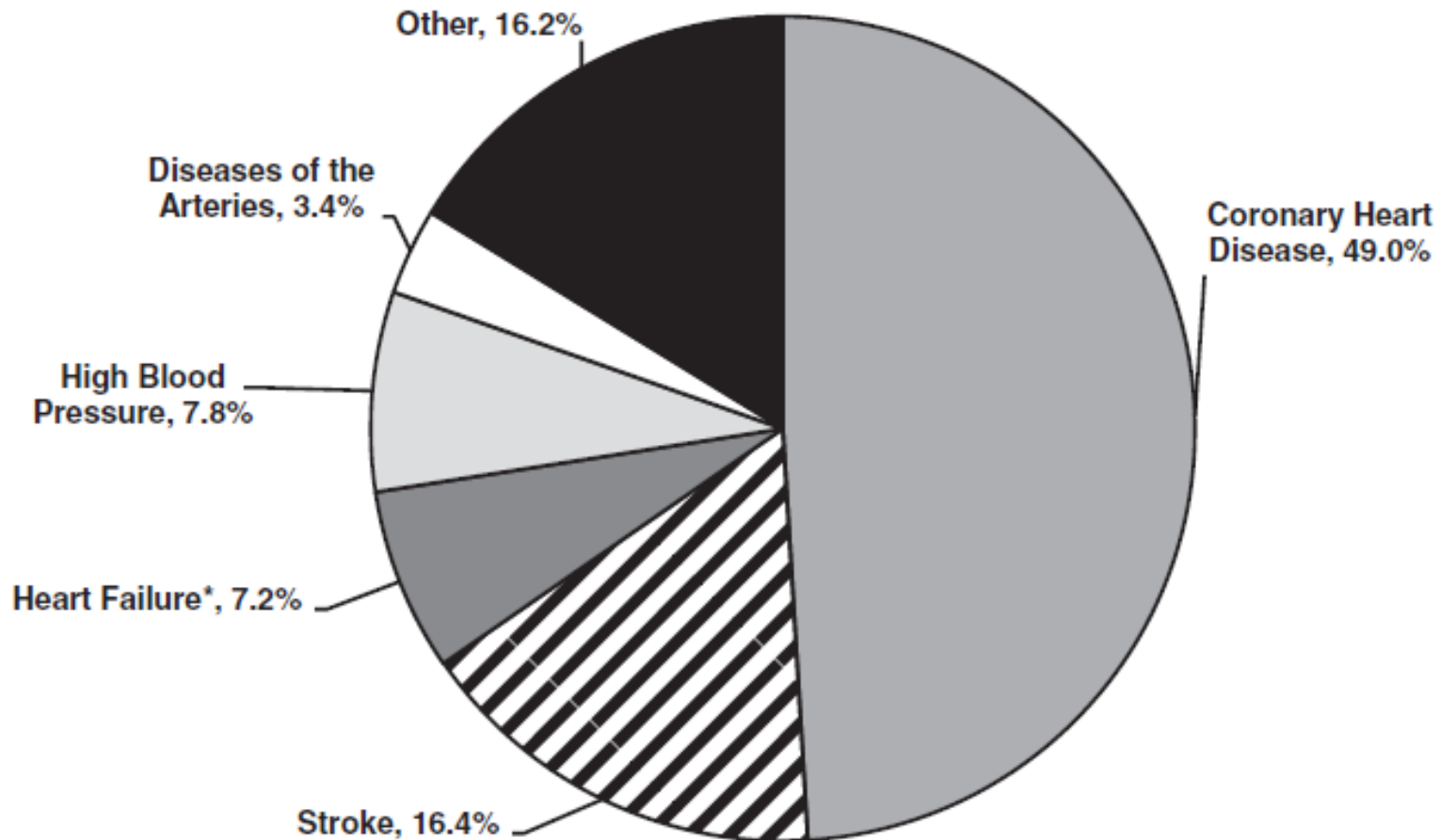


Chart 13-5. Percentage breakdown of deaths attributable to cardiovascular disease (United States: 2009). Source: National Heart, Lung, and Blood Institute from National Center for Health Statistics reports and data sets. *Not a true underlying cause. With any-mention deaths, heart failure accounts for 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* I categories.

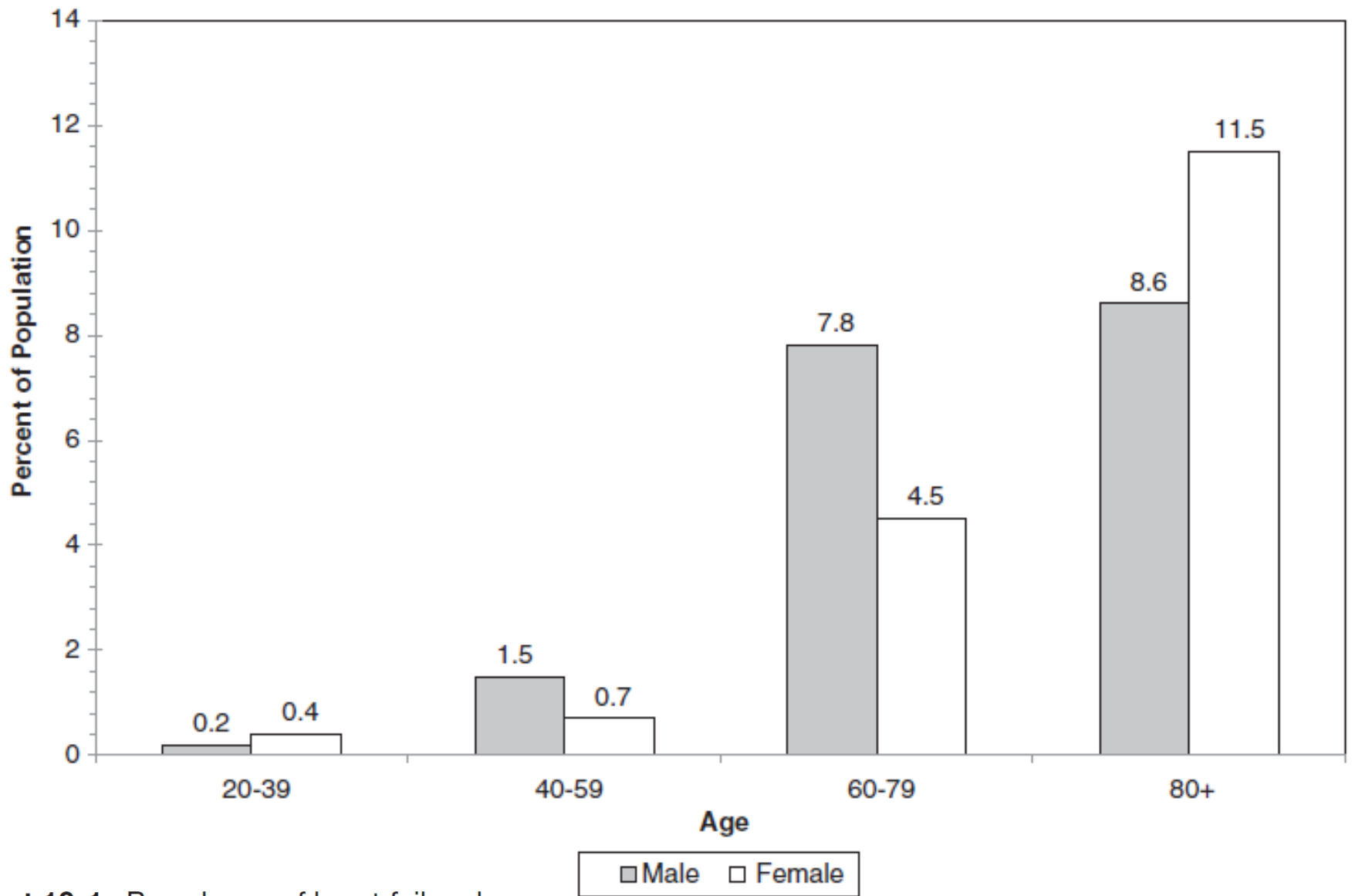


Chart 19-1. Prevalence of heart failure by sex and age (National Health and Nutrition Examination Survey: 2007–2010). Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

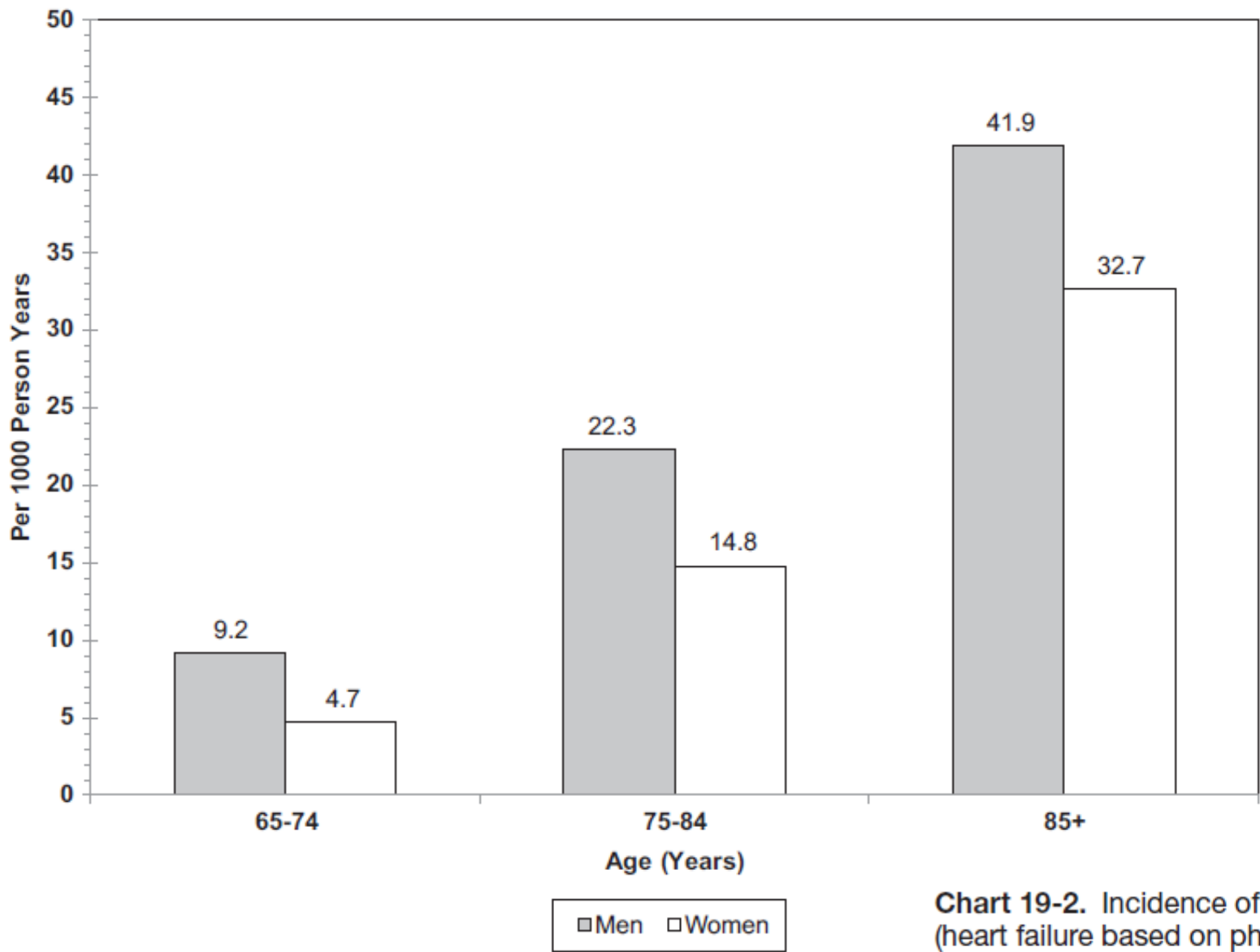


Chart 19-2. Incidence of heart failure (heart failure based on physician review of medical records and strict diagnostic criteria) by age and sex (Framingham Heart Study: 1980–2003). Source: National Heart, Lung, and Blood Institute.

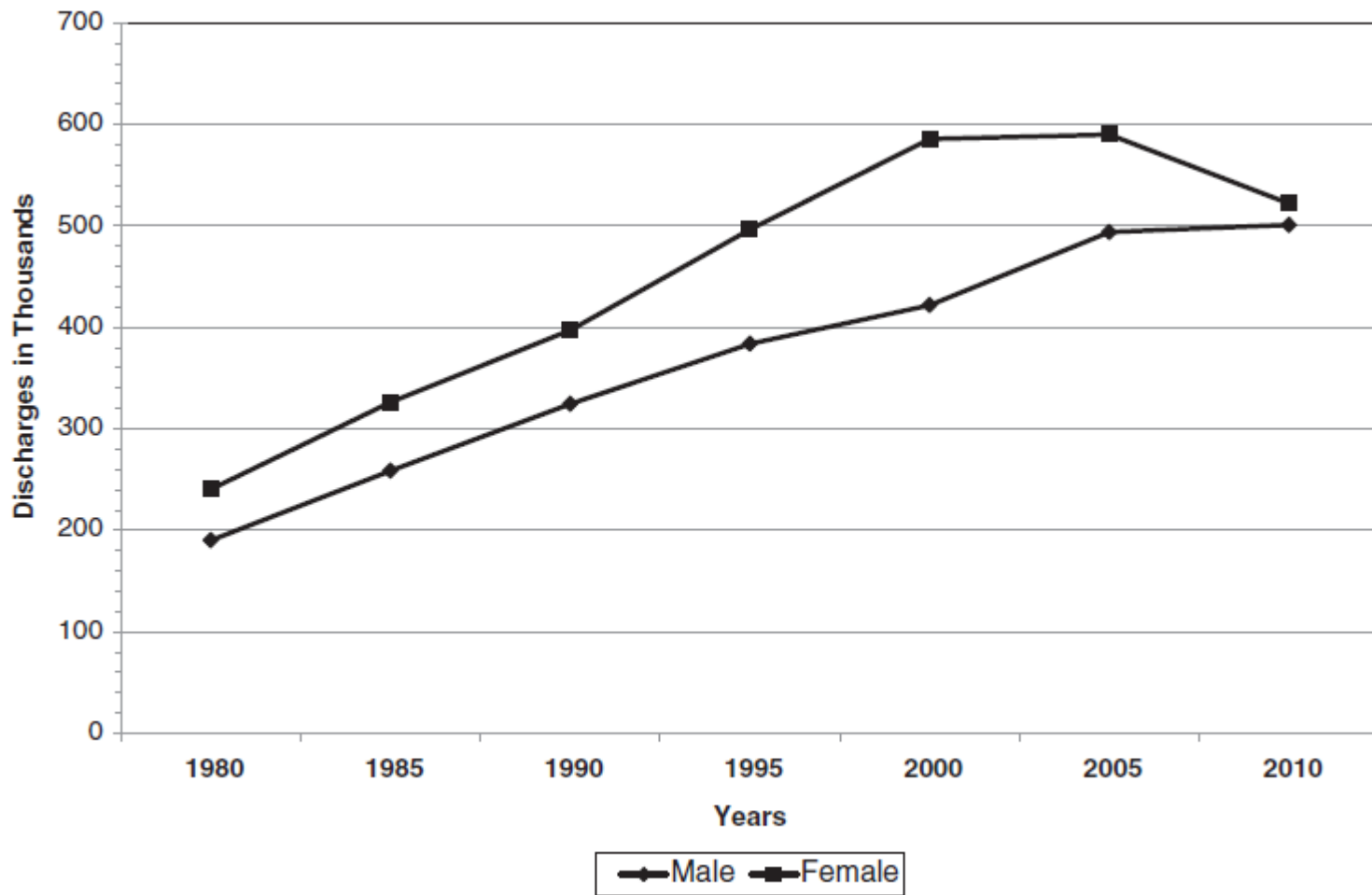


Chart 19-3. Hospital discharges for heart failure by sex (United States: 1980–2010). Note: Hospital discharges include people discharged alive, dead, and status unknown. Source: National Hospital Discharge Survey/National Center for Health Statistics and National Heart, Lung, and Blood Institute.

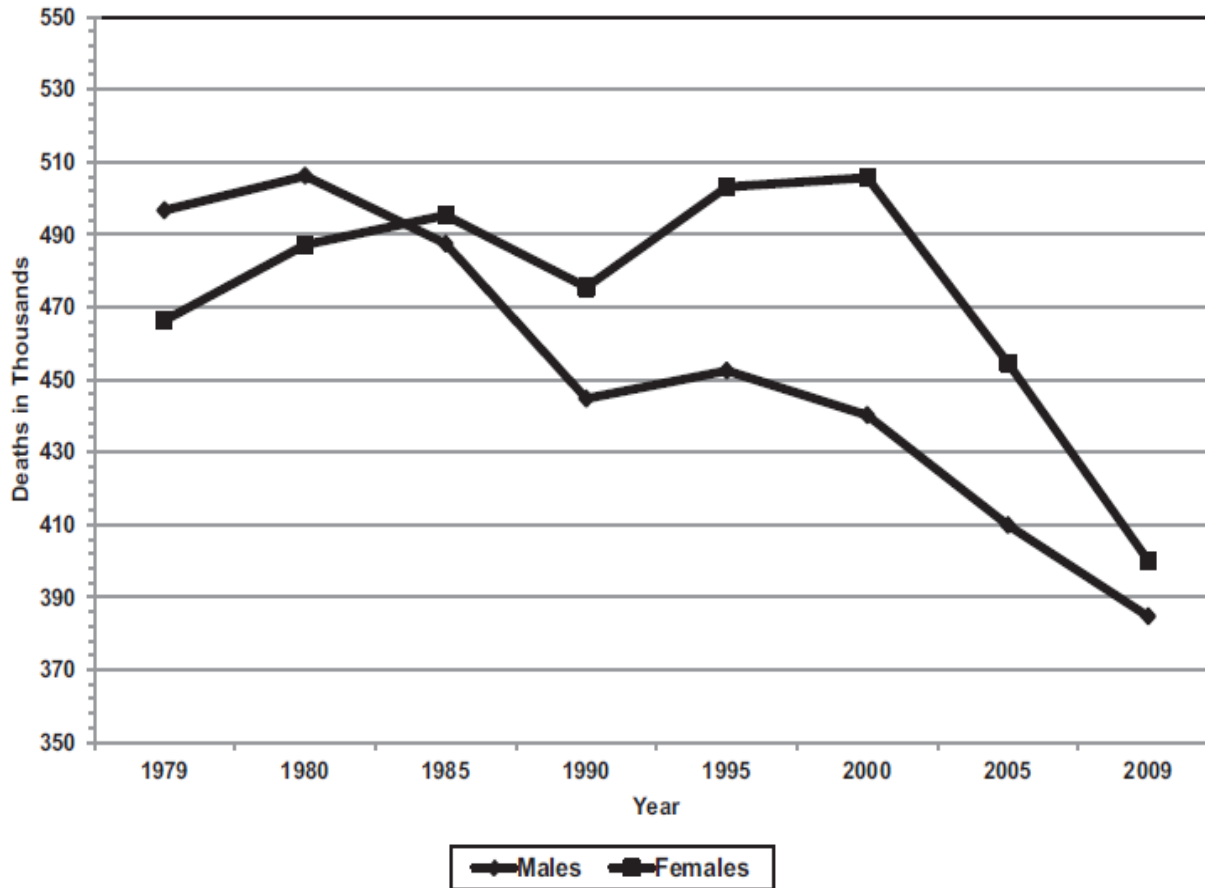
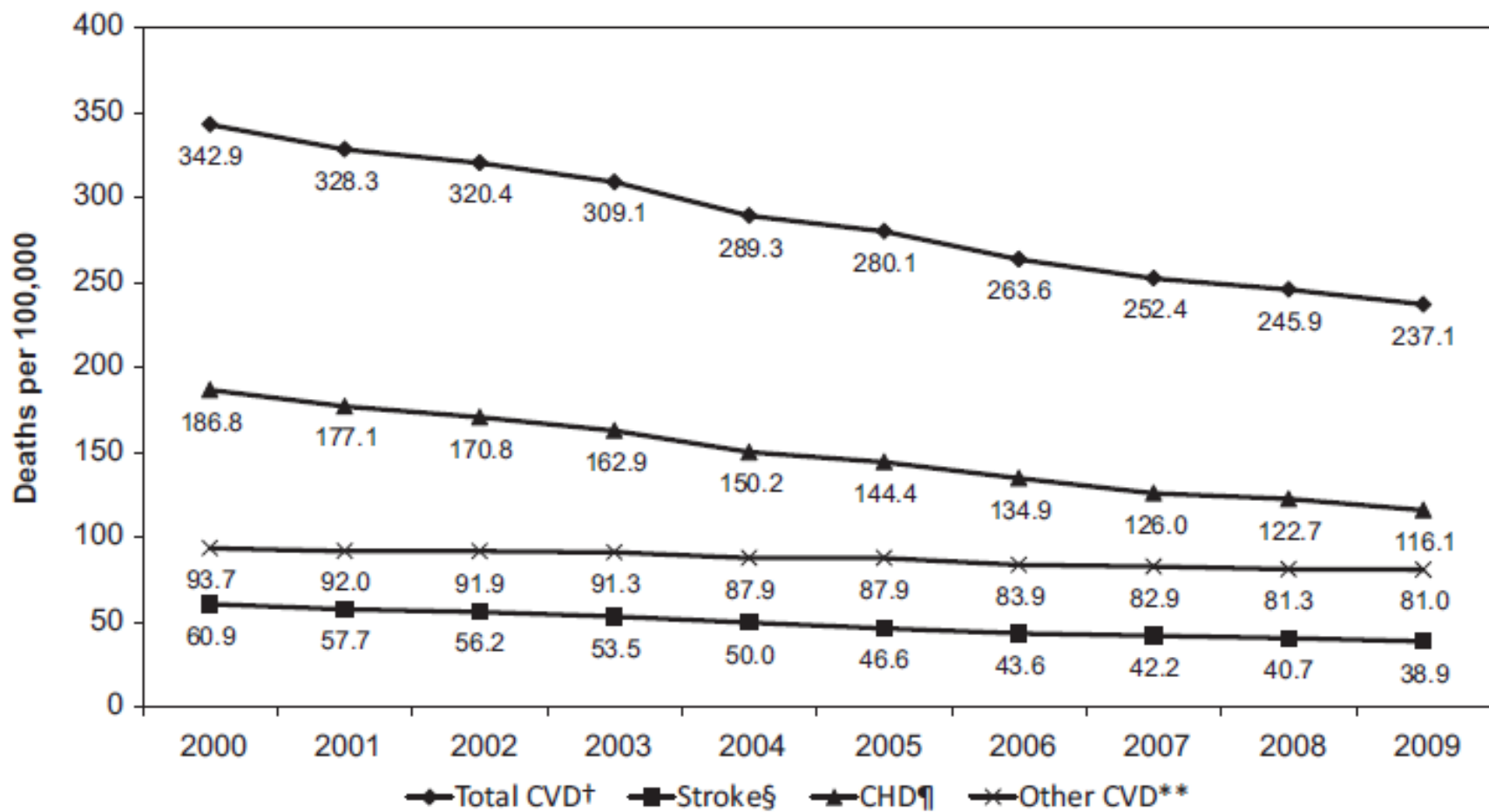


Chart 13-17. Cardiovascular disease mortality trends for males and females (United States: 1979–2009). CVD excludes congenital cardiovascular defects (*International Classification of Diseases, 10th Revision* codes I00–I99). The overall comparability for cardiovascular disease between the *International Classification of Diseases, 9th Revision* (1979–1998) and *International Classification of Diseases, 10th Revision* (1999–2009) is 0.9962. No comparability ratios were applied. Source: National Center for Health Statistics.



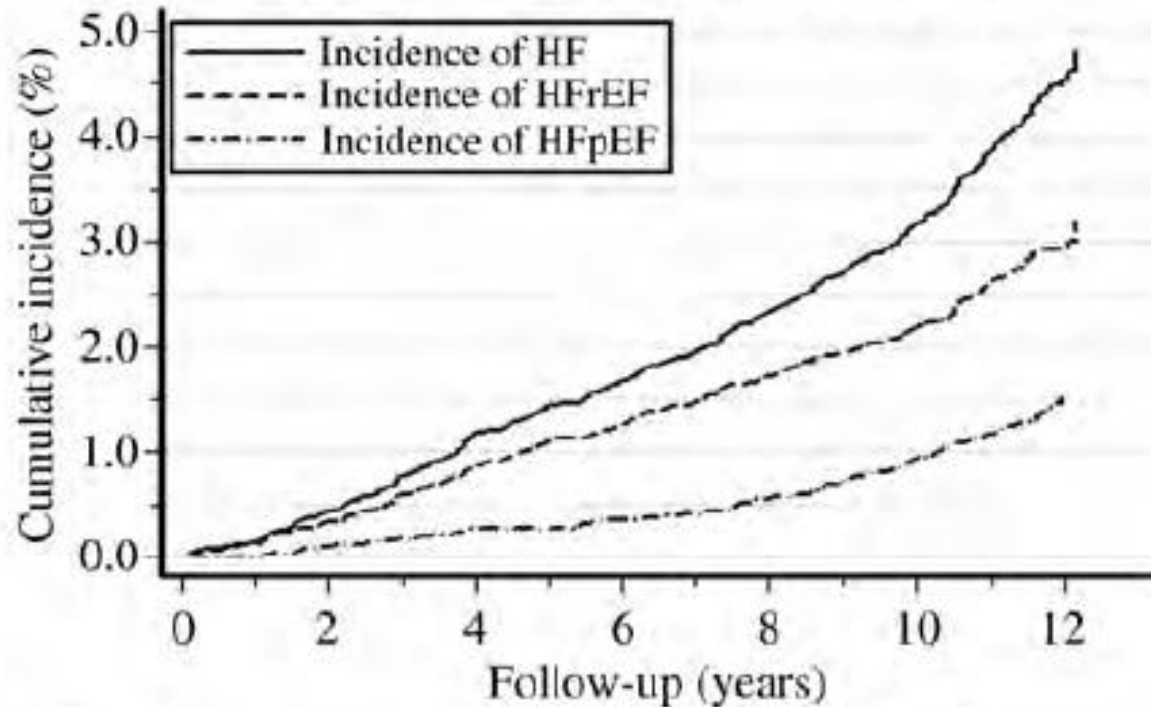


European Heart Journal (2013) **34**, 1424–1431
doi:10.1093/eurheartj/eh066

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

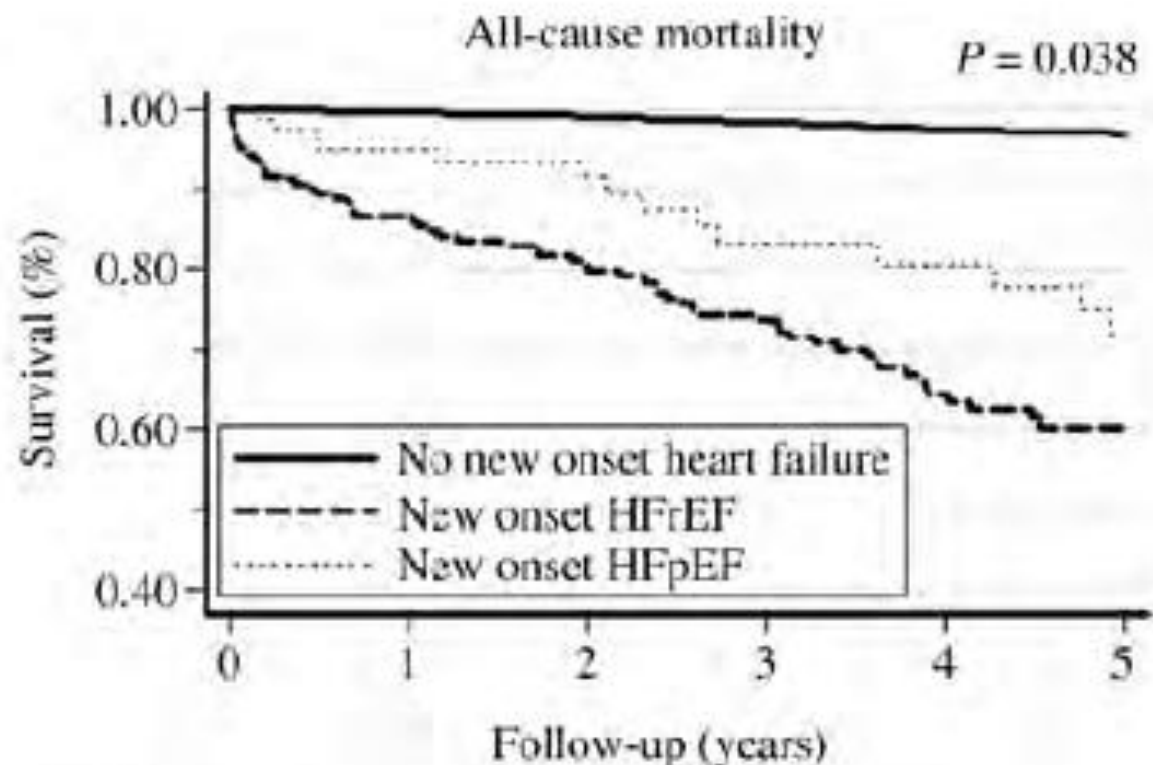
Frank P. Brouwers^{1*†}, Rudolf A. de Boer¹, Pim van der Harst¹, Adriaan A. Voors¹, Ron T. Gansevoort², Stephan J. Bakker², Hans L. Hillege¹, Dirk J. van Veldhuisen¹, and Wiek H. van Gilst¹

Heart failure incidence; Total, HFrEF, and HFpEF



Total HF	8569	8313	7966	7638	7312	6633	1273
HFrEF	8569	8322	7991	7669	7351	6693	1287
HFpEF	8569	8336	8031	7721	7412	6747	1306

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.



	Number at risk					
No new onset heart failure	8195	8139	7977	7842	7696	7547
New onset HFrEF	196	144	122	104	75	62
New onset HFpEF	86	64	48	36	28	23

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 2 Cox regression: cause-specific hazard (risk) ratios

	Adjusted for age and sex		Mutually adjusted ^a		HFrEF	HFpEF	<i>P</i> _{Cr} ^b
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value	HR (95% CI)	HR (95% CI)	
Age (per 10 years)	–	–	1.81 (1.47–2.24)	<0.001	1.61 (1.24–2.09)	2.53 (1.93–3.30)	0.018
Males	–	–	1.48 (1.03–2.13)	0.035	2.43 (1.49–3.95)	0.56 (0.31–1.01)	<0.001
Obesity	→ 1.93 (1.37–2.73)	<0.001	1.62 (1.10–2.37)	0.014	–	–	0.750
Heart rate (per 5 b.p.m.)	1.05 (0.98–1.13)	0.155					
Hypertension	1.99 (1.37–2.89)	<0.001	1.17 (0.77–1.77)	0.458	–	–	0.288
Myocardial infarction	→ 3.45 (2.38–4.99)	<0.001	2.27 (1.54–3.34)	<0.001	2.77 (1.73–4.43)	1.25 (0.64–2.45)	0.058
Smoking or quit smoking <1 year	1.31 (0.96–1.79)	0.087	1.24 (0.87–1.77)	0.228	1.51 (0.96–2.36)	0.80 (0.46–1.41)	0.086
Atrial fibrillation	→ 2.64 (1.23–5.66)	0.013	1.10 (0.55–2.19)	0.787	0.42 (0.19–0.93)	3.79 (1.64–8.77)	<0.001
Diabetes mellitus	→ 2.41 (1.51–3.85)	<0.001	1.66 (0.99–2.78)	0.056	–	–	0.794
Hypercholesterolaemia (mmol/L)	1.65 (1.21–2.26)	0.002	1.34 (0.95–1.88)	0.096	–	–	0.713
Log Creatinine (per doubling)	1.00 (0.84–1.20)	0.973					
eGFR >60 mL/min/kg	1.07 (0.66–1.74)	0.782					
Log Cystatine C (per doubling)	1.43 (1.23–1.68)	<0.001	1.08 (0.94–1.24)	0.295	0.98 (0.86–1.11)	1.45 (1.03–2.04)	0.033
Log UAE (per doubling)	1.35 (1.22–1.50)	<0.001	1.01 (0.91–1.14)	0.798	0.96 (0.84–1.09)	1.21 (0.98–1.48)	0.061
Log hs-C-reactive protein (per doubling)	1.41 (1.17–1.70)	<0.001	1.14 (0.92–1.41)	0.228	–	–	0.230
Log NT-proBNP (per doubling)	2.11 (1.79–2.49)	<0.001	1.68 (1.39–2.04)	<0.001	1.85 (1.42–2.41)	1.35 (1.06–1.72)	0.082
Log hs-TnT (per doubling)	1.67 (1.51–1.86)	<0.001	1.33 (1.17–1.52)	<0.001	1.38 (1.18–1.60)	1.10 (0.90–1.36)	0.091

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

REVIEW ARTICLE

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.

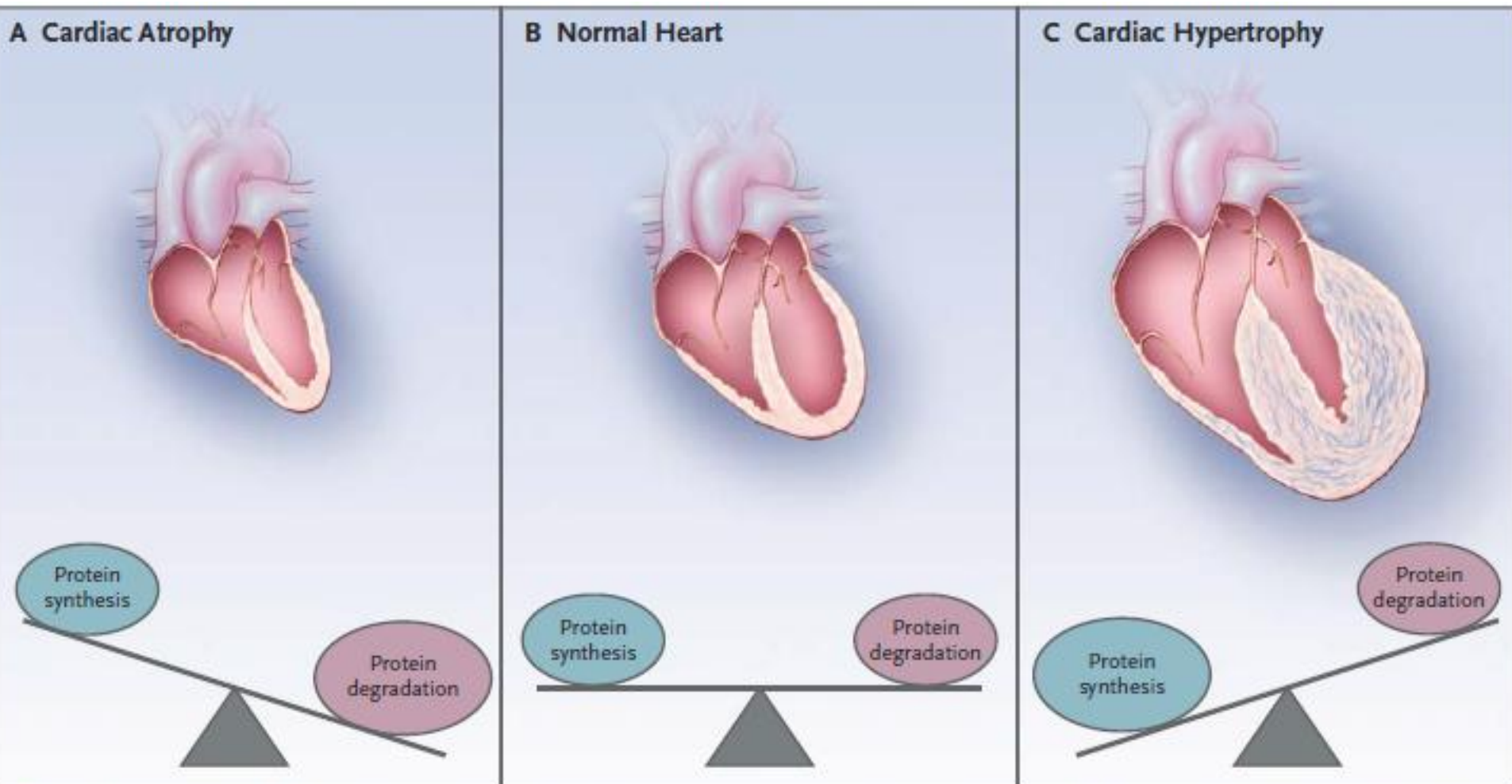


Figure 1. Association of the Development of Cardiac Atrophy and Hypertrophy with Changes in the Balance between Protein Synthesis and Protein Degradation.

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

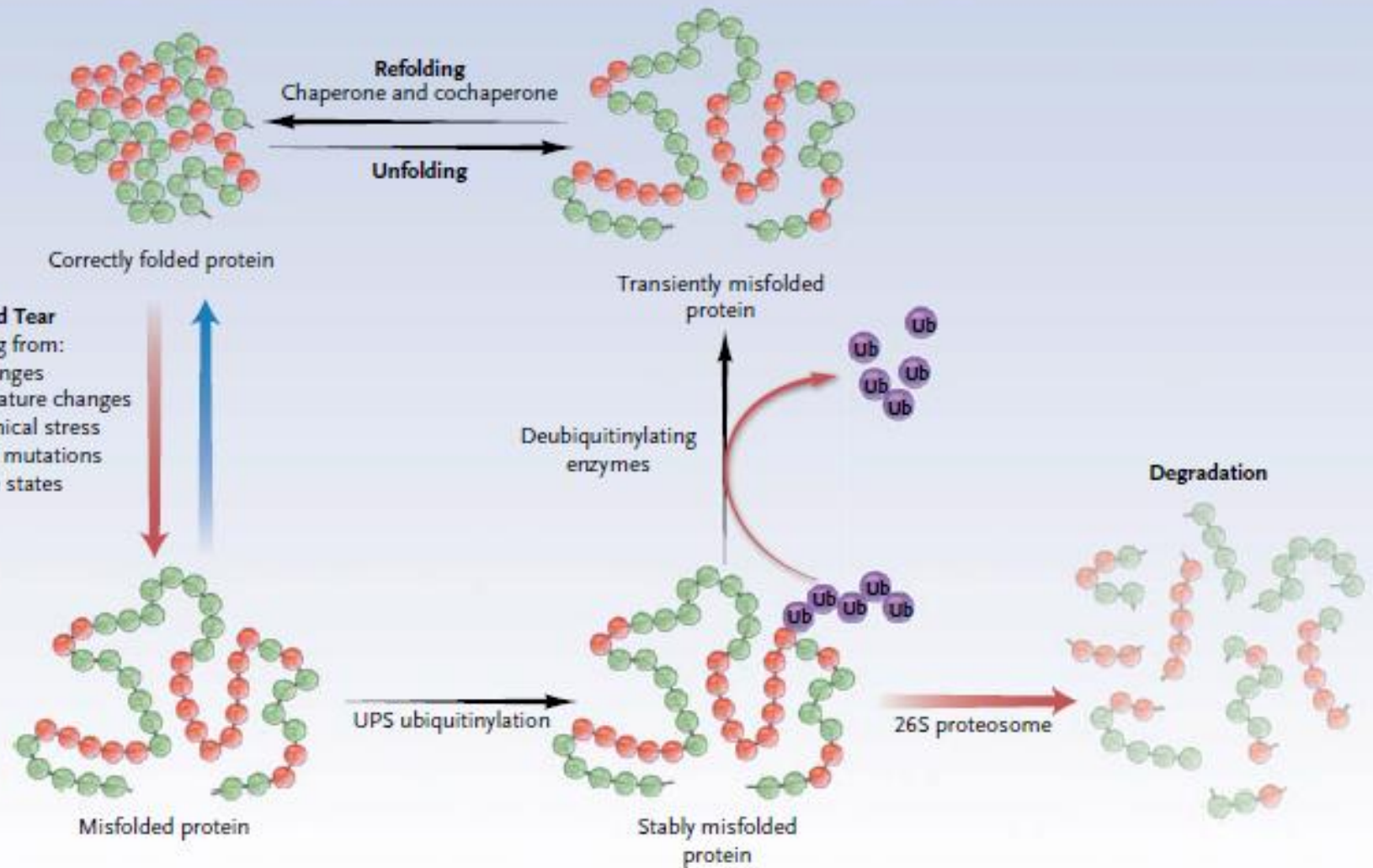


Figure 2. Cellular Stress as a Cause of Protein Misfolding.

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. Deubiquitylating enzymes act to counter the UPS ubiquitylation for fine control of the degradation process.

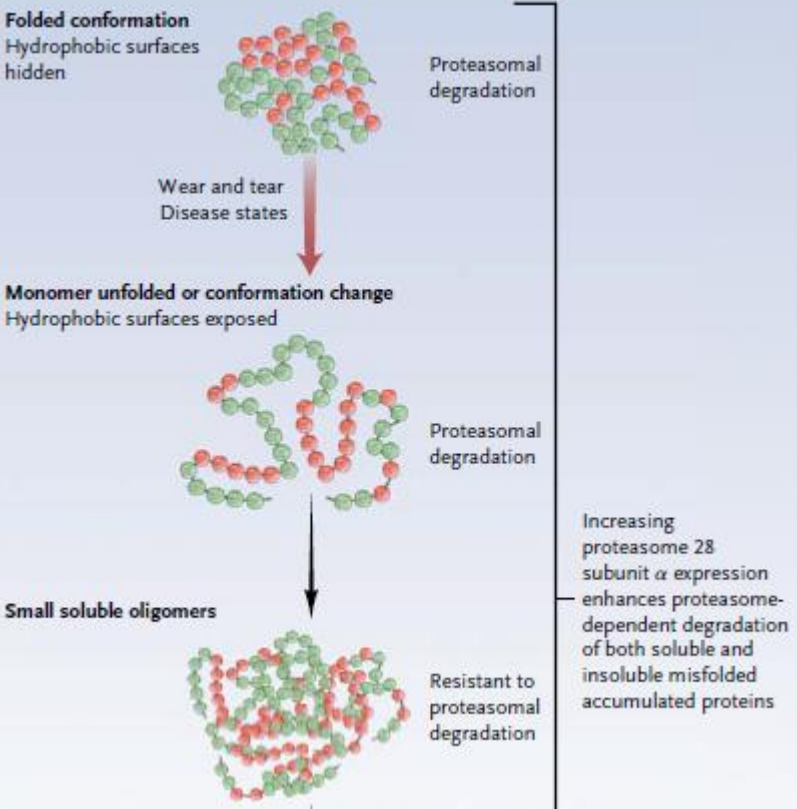
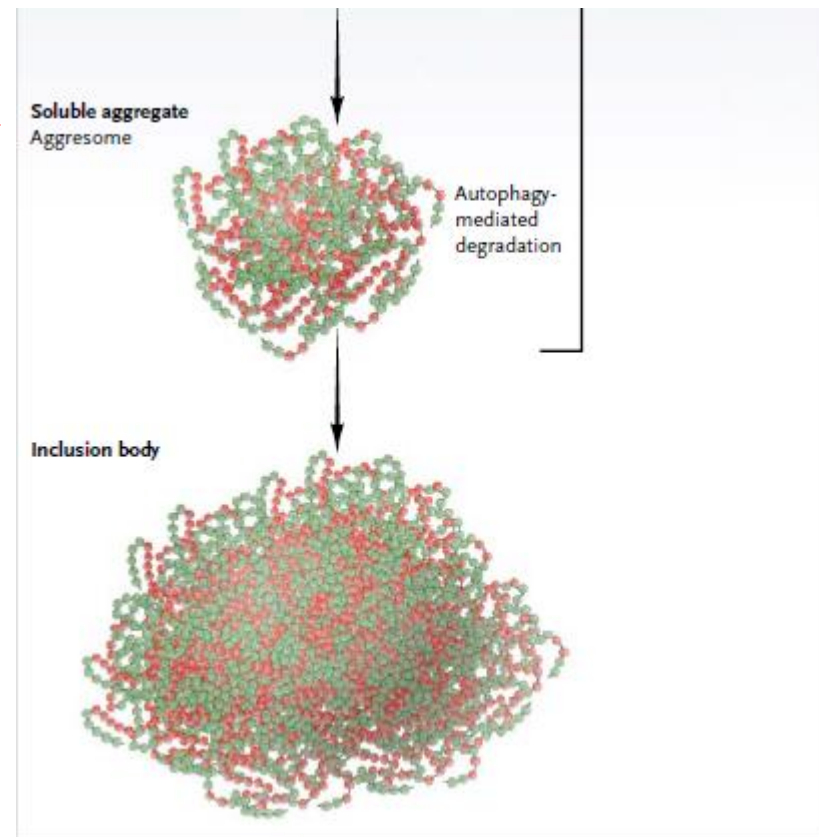


Figure 3. Parallel Mechanisms Underlying the Accumulation of Misfolded Proteins

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.⁴⁴ Enhancing proteasome activity may be a method for reducing proteotoxicity in vivo, in addition to targeting the formation of toxic soluble oligomers.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Autophagy in Human Health and Disease

N ENGL J MED 368;7 NEJM.ORG FEBRUARY 14, 2013

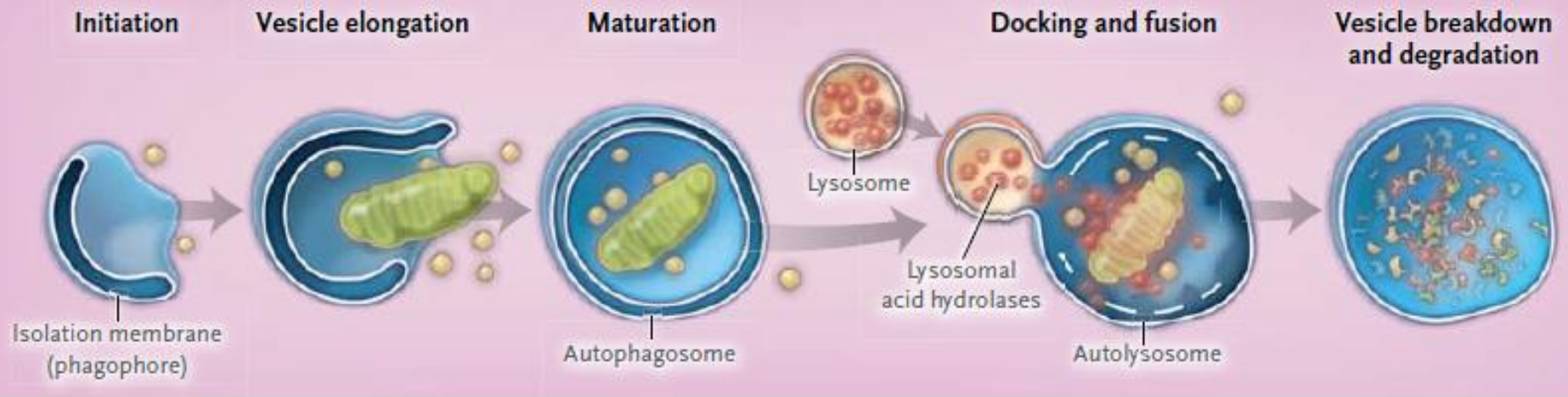


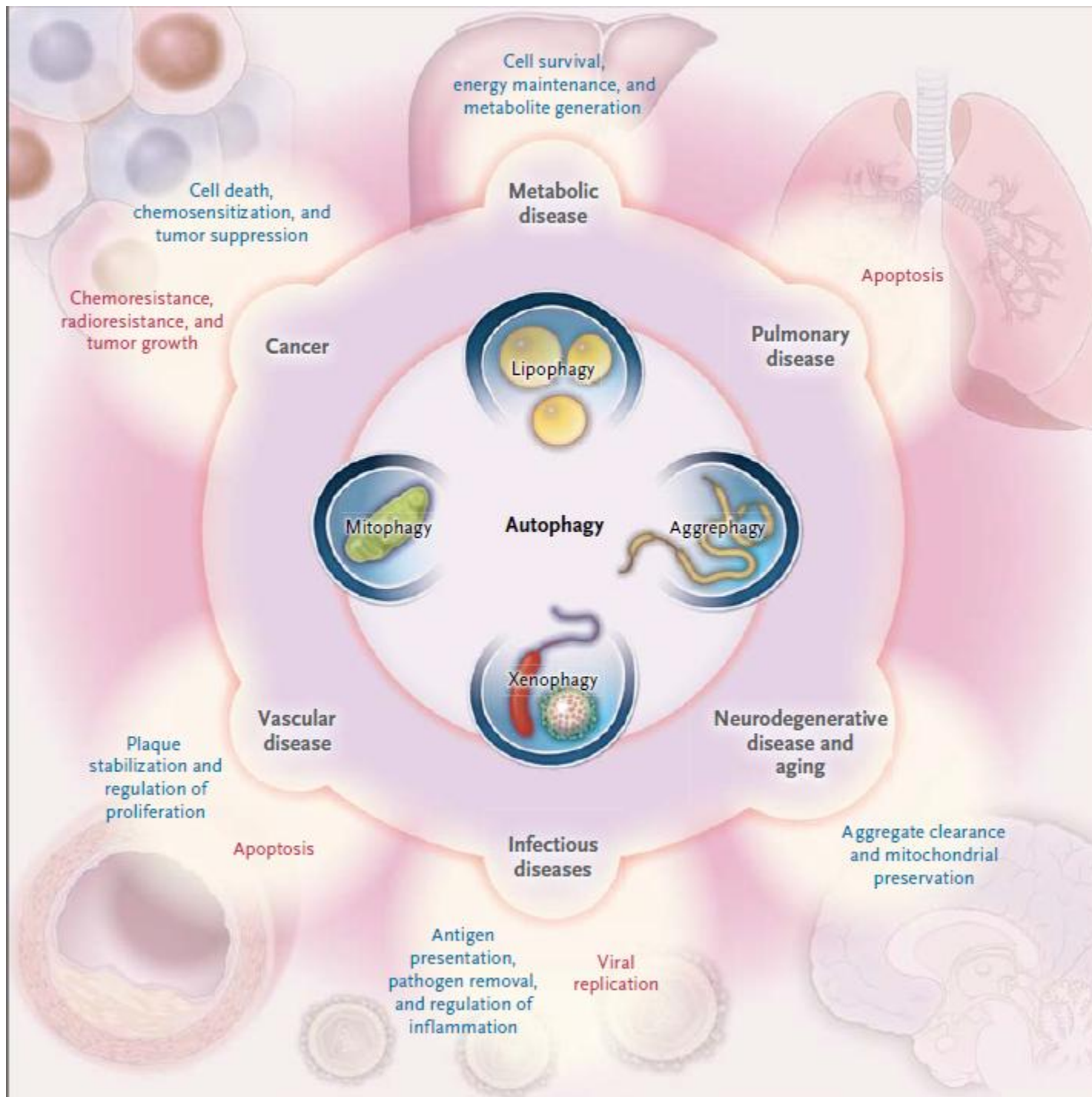
Figure 1. Phases of the Autophagic Pathway.

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.⁷⁹ Genetic X-linked deficiency in lysosome-associated membrane protein 2 (LAMP2), which assists in autophagosome–lysosome fusion, causes cardiomyopathy known as Danon’s disease.²³ In patients with this disease, cardiomyocytes with evidence of mitochondrial dysfunction have an increased number of autophagosomes,²³ as does cardiac tissue from patients with heart failure.^{80,81} In a mouse model of desmin-related cardiomyopathy, autophagic activity was shown to provide cardioprotection.⁸²

Experimental ischemia–reperfusion injury also causes morphologic indicators of autophagy to increase in response to stress signals, including depleted ATP, hypoxia, and altered Ca²⁺ balance and may play various roles, depending on the phase of the injury.⁸³ Increased numbers of autophagosomes are evident in macrophages from atherosclerotic plaques.⁸⁴ Autophagy may stabilize atherosclerotic plaques by preventing macrophage apoptosis and plaque necrosis and by preserving efferocytosis.⁸⁵



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 Cure.

Fondamento per considerare la patologia senza un atteggiamento riduzionistico...

Affrontare il problema

Spunti dall'epidemiologia
(Heart centered)

Table 2-2. Prevalence of US Population With Ideal Cardiovascular Health and With Components of Ideal Cardiovascular Health, Overall and in Selected Age Strata From NHANES 2007–2008 and 2009–2010

	Prevalence, %				
	Ages 12–19 y	Ages ≥20 y*	Ages 20–39 y	Ages 40–59 y	Ages ≥60 y
2007–2008 (baseline)					
Ideal CV health profile (composite—all 7)	0.0	0.0	0.0	0.0	0.0
≥6 Ideal CV health composite score	8.2	3.6	7.1	2.1	0.1
≥5 Ideal CV health composite score	39.8	15.8	29.7	9.7	2.9
Ideal health factors index (composite—all 4)	35.5	13.9	27.7	7.3	1.0

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

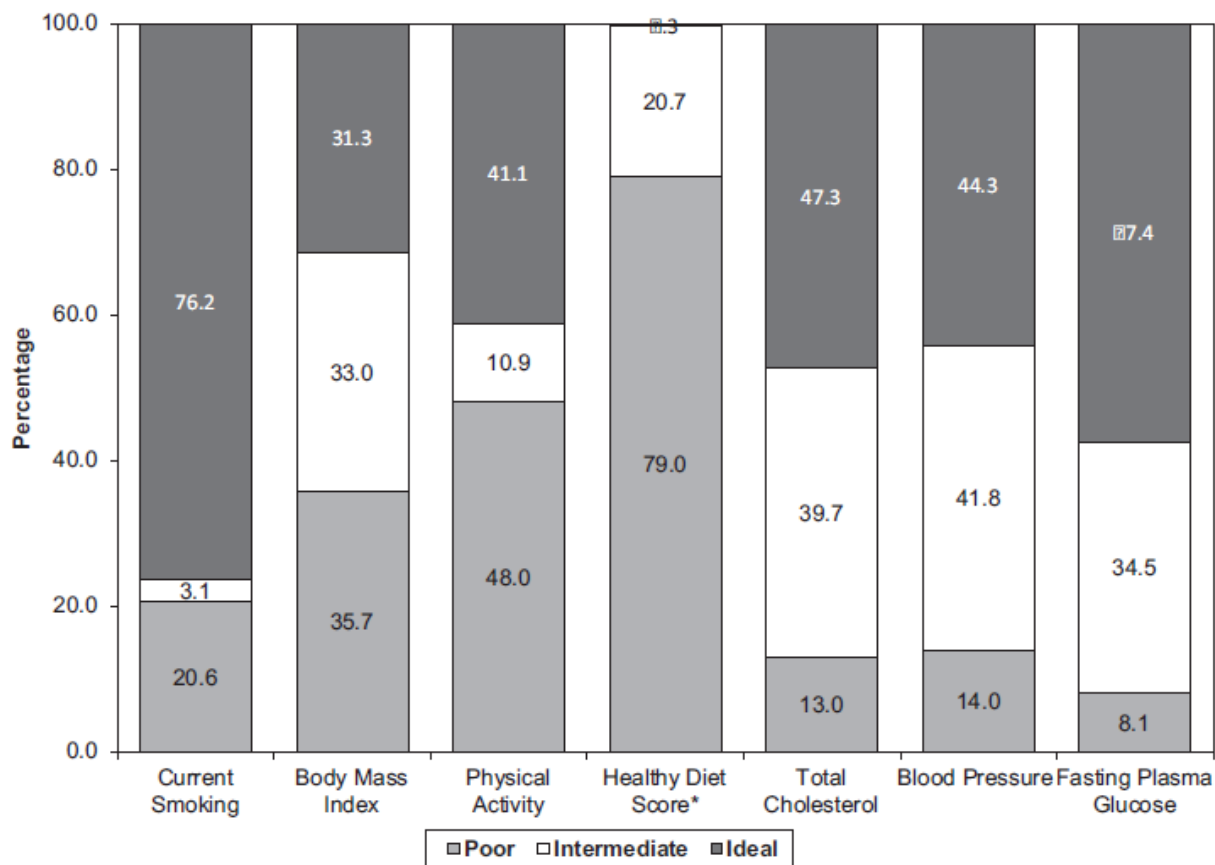
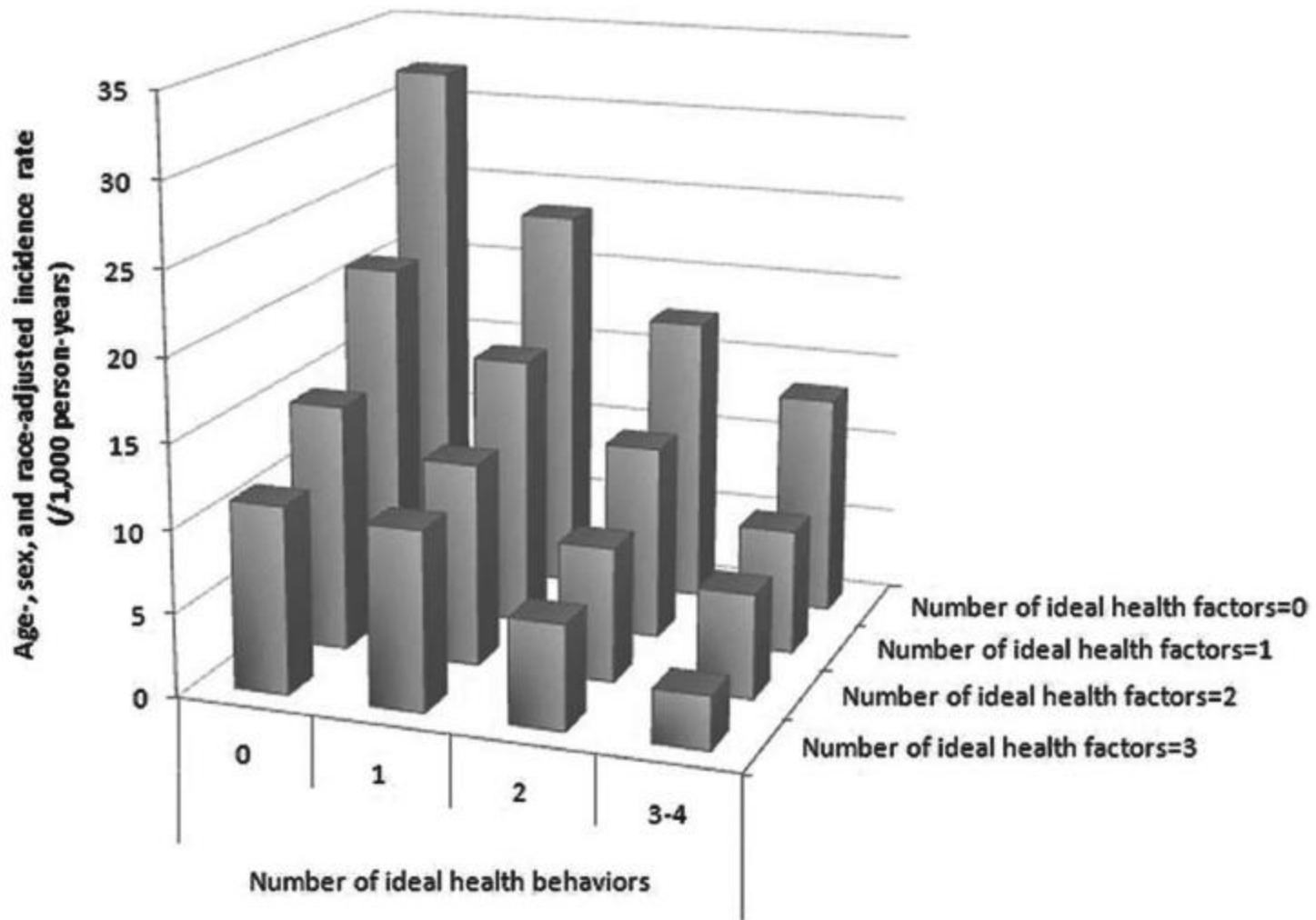


Chart 2-2. Age-standardized prevalence estimates for poor, intermediate, and ideal cardiovascular health for each of the 7 metrics of cardiovascular health in the American Heart Association 2020 goals, among US adults aged ≥ 20 years, National Health and Nutrition Examination Survey (NHANES) 2009-2010* (available data as of June 1, 2012). *Healthy Diet Score reflects 2007-2008 NHANES data



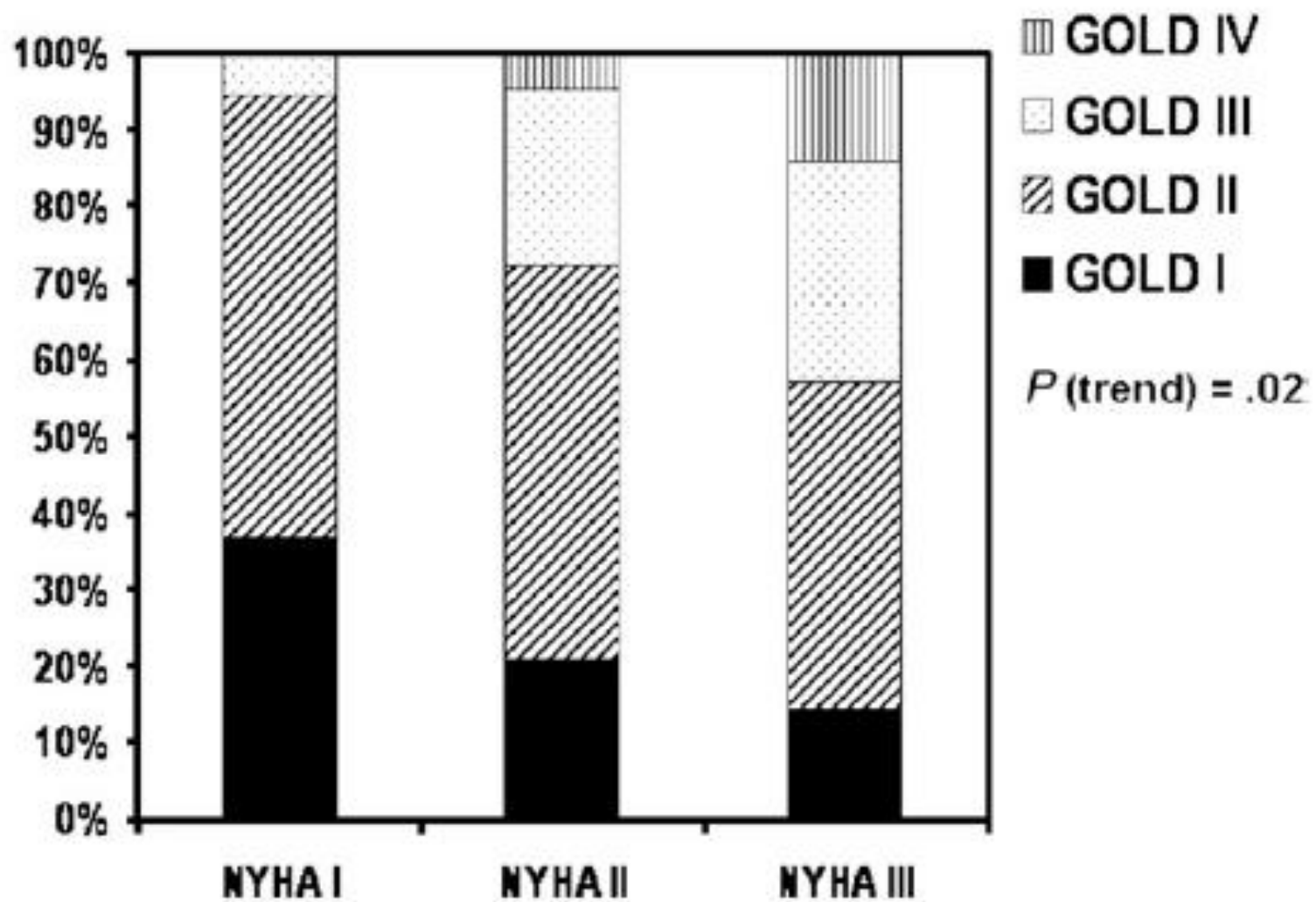
Incidence of cardiovascular disease according to the number of ideal health behaviors and health factors.

Affrontare il problema

Spunti dall'epidemiologia
(comorbidity perspective)

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

Beneficiaries Age ≥ 65 y (N=4 376 150)*		
	N	%
Hypertension	3 685 373	84.2
Ischemic heart disease	3 145 718	71.9
Hyperlipidemia	2 623 601	60.0
Anemia	2 200 674	50.3
Diabetes	2 027 875	46.3
Arthritis	1 901 447	43.5
Chronic kidney disease	1 851 812	42.3
COPD	1 311 118	30.0
Atrial fibrillation	1 247 748	28.5
Alzheimer's disease/dementia	1 207 704	27.6



Distribution of COPD stages according to NYHA class.

Associazione multivariata fra i livelli di emoglobina, mortalità e riospedalizzazione

	Mortalità "per ogni causa"	Riospedalizzazione per scompenso cardiaco
<i>Emoglobina (g/dl)</i>		
≥17	1.42(1.24-1.63)	1.14(1.03)
14.0-14.9	0.92(0.88-0.97)	0.98(0.94-1.01)
13.0-13.9	Int di riferimento	Int di riferimento
12.0-12.9	1.16(1.11-1.21)	1.12(1.09-1.16)
11.0-11.9	1.50(1.44-1.57)	1.33(1.28-1.38)
10-10.9	1.89(1.80-1.98)	1.64(1.58-1.71)
9.0-9.9	2.31(2.18-2.45)	1.89(1.80-1.99)
<9.0	3.48(3.25-3.73)	1.99(1.86-2.13)

Associazione multivariata fra la funzione renale e mortalità e riospedalizzazione

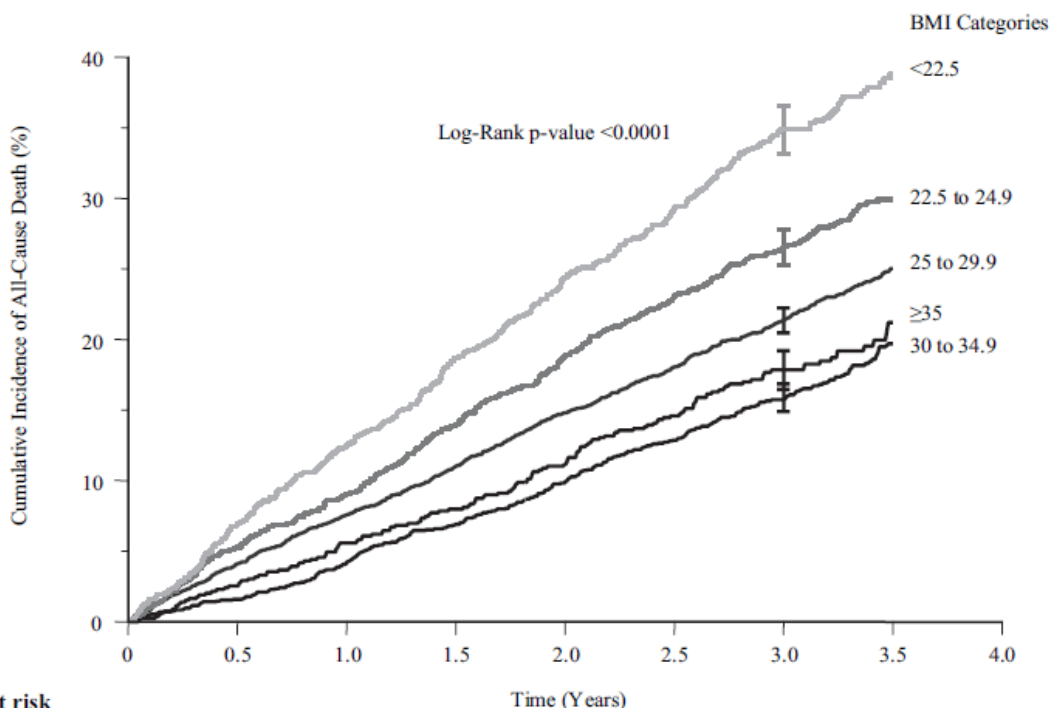
Filtrato glomerulare (ml.min-1.1.73m-2)	Mortalità "per ogni causa"	Riospedalizzazione per scompenso cardiaco
≥60	Int di riferimento	Int di riferimento
45-59	1.01(0.97-1.05)	1.11(1.08-1.14)
30-44	1.39(1.34-1.44)	1.44(1.40-1.49)
15-29	2.28(2.19-2.39)	1.97(1.90-2.05)
<15	3.26(3.05-3.49)	1.89(1.79-2.01)



High impact of depression in heart failure: Early diagnosis and treatment options

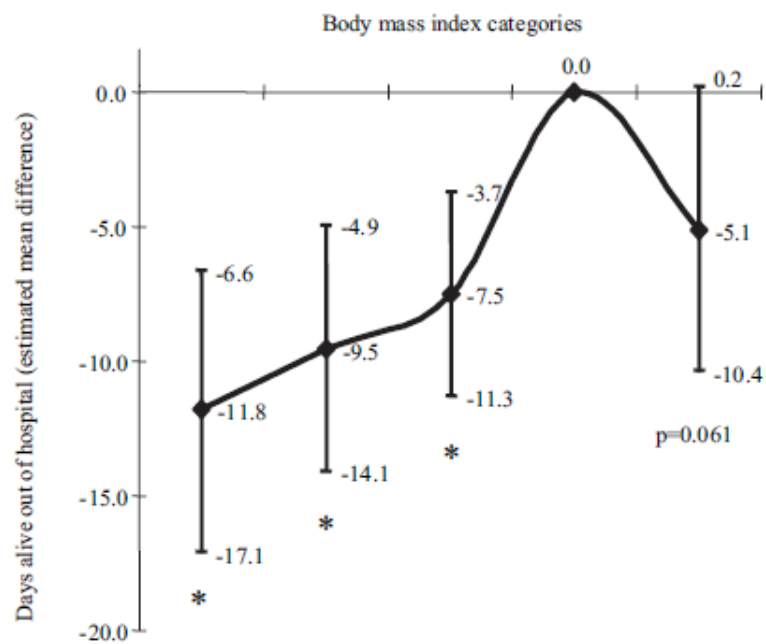
In CHF patients, the prevalence of major depression – i.e., the full clinical picture of major depression – develops in 14–26%. However, single depressive symptoms can be detected in 24–85% of CHF patients. The prevalence of depression in CHF patients also seems to increase with age, but is clearly aggravated 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.

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

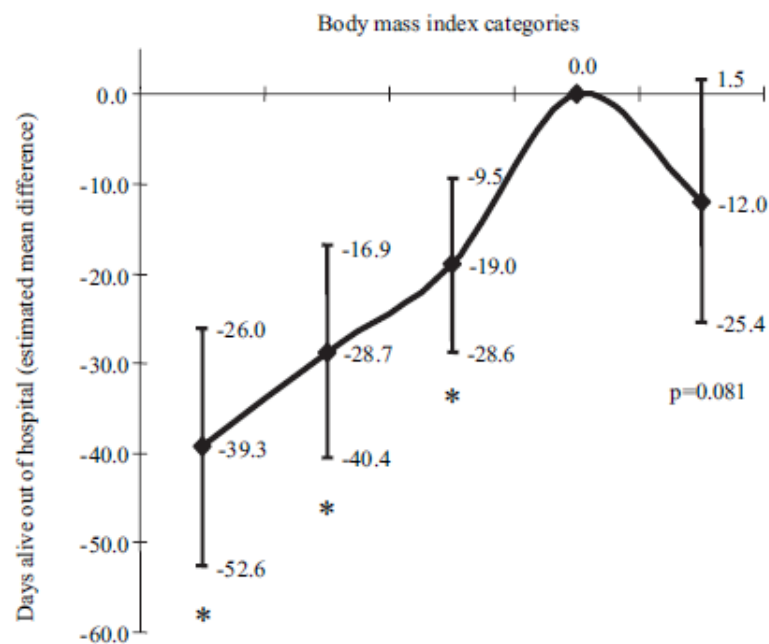


No. at risk								
BMI categories								
<22.5	889	828	777	722	672	597	448	157
22.5 to 24.9	1277	1210	1162	1100	1037	923	700	263
25 to 29.9	3063	2934	2828	2722	2605	2384	1802	647
30 to 34.9	1579	1554	1513	1470	1424	1311	974	329
≥35	791	771	747	728	703	659	448	109

During 1 year of follow-up



During 2 years of follow-up



Body mass index	<22.5	22.5-24.9	25-29.9	30-34.9	≥35
No of patients	889	1277	3063	1579	791
Days alive out of hospital (Mean±SD)	334.1 ±76.7	339.8 ±70.7	343.5 ±65.3	352.8 ±43.7	348.9 ±53.1

Body mass index	<22.5	22.5-24.9	25-29.9	30-34.9	≥35
No of patients	889	1277	3063	1579	791
Days alive out of hospital (Mean±SD)	626.4 ±196.2	646.7 ±179.4	661.5 ±164.4	686.4 ±123.6	677.8 ±140.6

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 appropriati.

Esempi?

- Miglioramento degli stili di vita nella popolazione anziana con scompenso
- Maggiore focalizzazione sulla comorbidità
- Evitamento di test inappropriati....siamo tutti unici ma condividiamo molti meccanismi fisiopatologici.

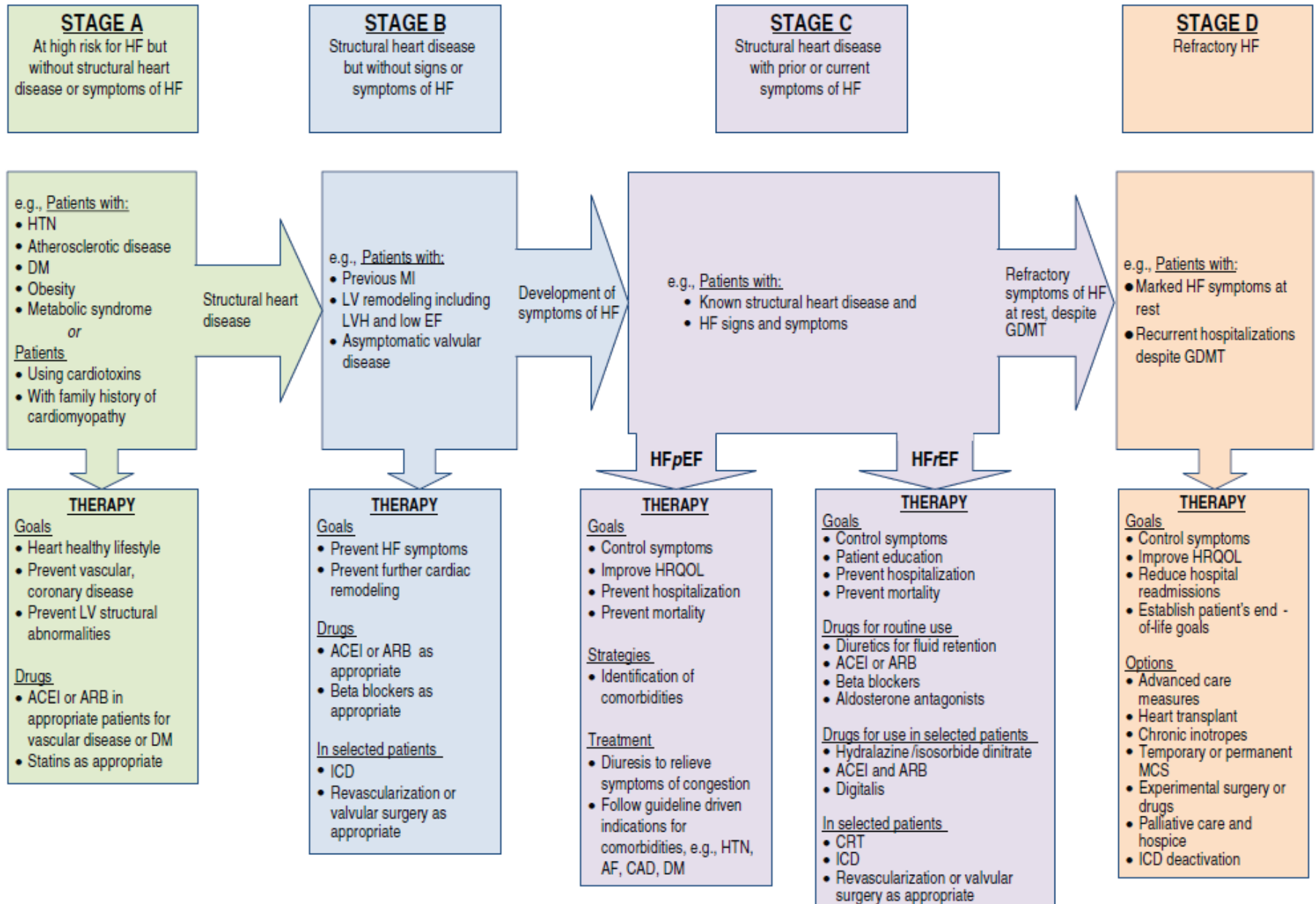


Affrontare il problema

Staging and treatment

At Risk for Heart Failure

Heart Failure



Avere un atteggiamento legato alla “targeted-therapy”:

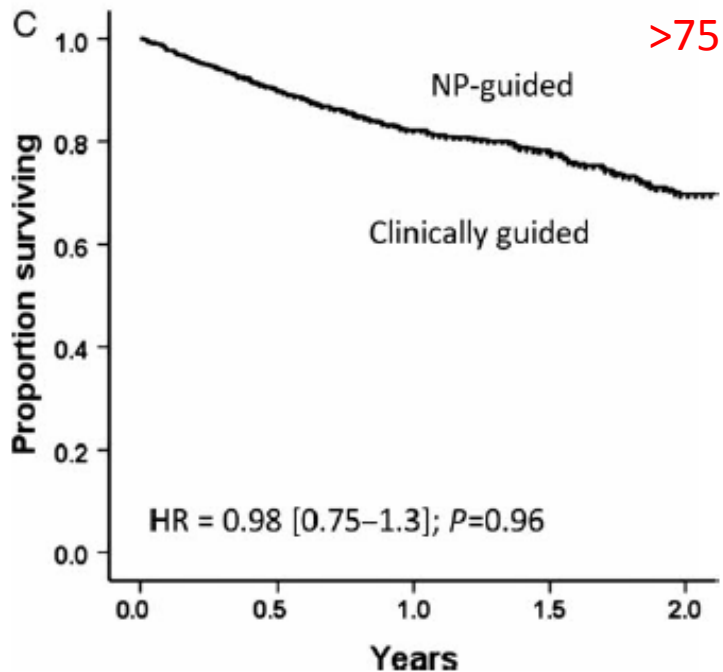
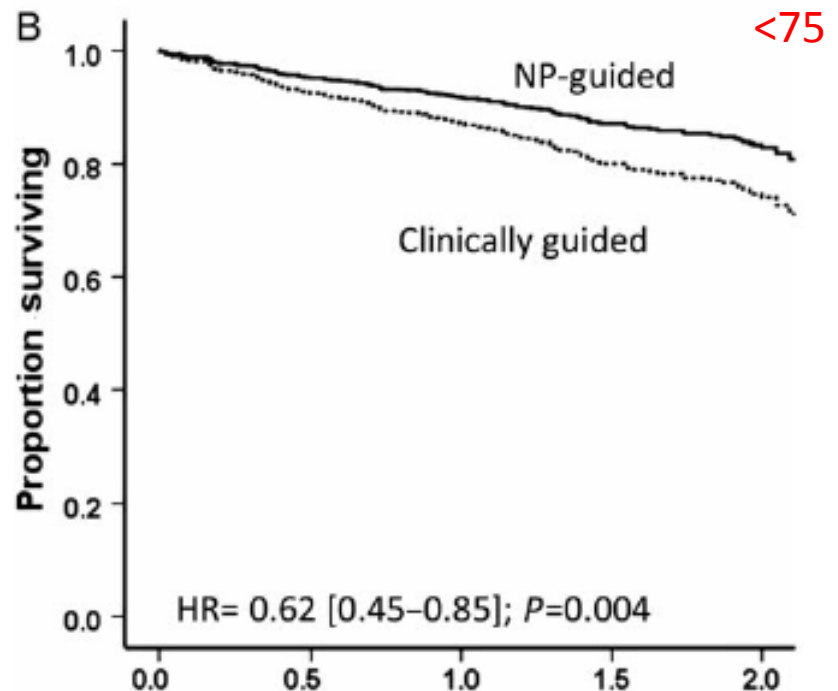
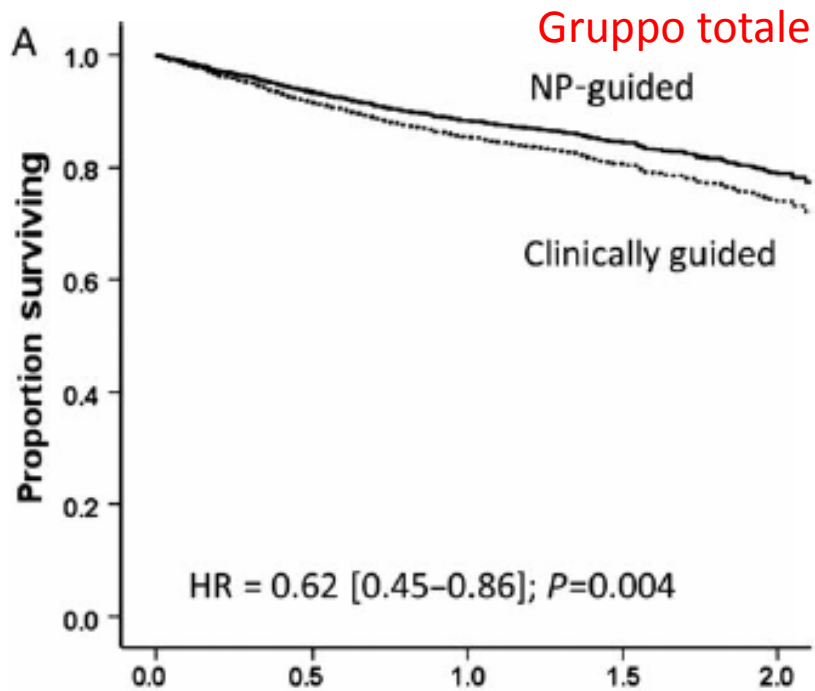
- Ci obbliga ad una maggiore attenzione al singolo paziente
- Ci obbliga ad un atteggiamento più competente e attento alla valutazione di parametri che dobbiamo considerare
- Ci permette di utilizzare gli strumenti, tecnologici e non, in modo maggiormente appropriato e sostenibile



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 euvolemic** 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)*

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION



Non invasive imaging

Table 10. Recommendations for Noninvasive Cardiac Imaging

Recommendations	COR	LOE
Patients with suspected, acute, or new-onset HF should undergo a chest x-ray	I	C
A 2-dimensional echocardiogram with Doppler should be performed for initial evaluation of HF	I	C
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	I	C
Noninvasive imaging to detect myocardial ischemia and viability is reasonable in HF and CAD	IIa	C
Viability assessment is reasonable before revascularization in HF patients with CAD	IIa	B ²⁸¹⁻²⁸⁵
Radionuclide ventriculography or MRI can be useful to assess LVEF and volume	IIa	C
MRI is reasonable when assessing myocardial infiltration or scar	IIa	B ²⁸⁶⁻²⁸⁸
Routine repeat measurement of LV function assessment should not be performed	III: No Benefit	B ^{289,290}

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

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

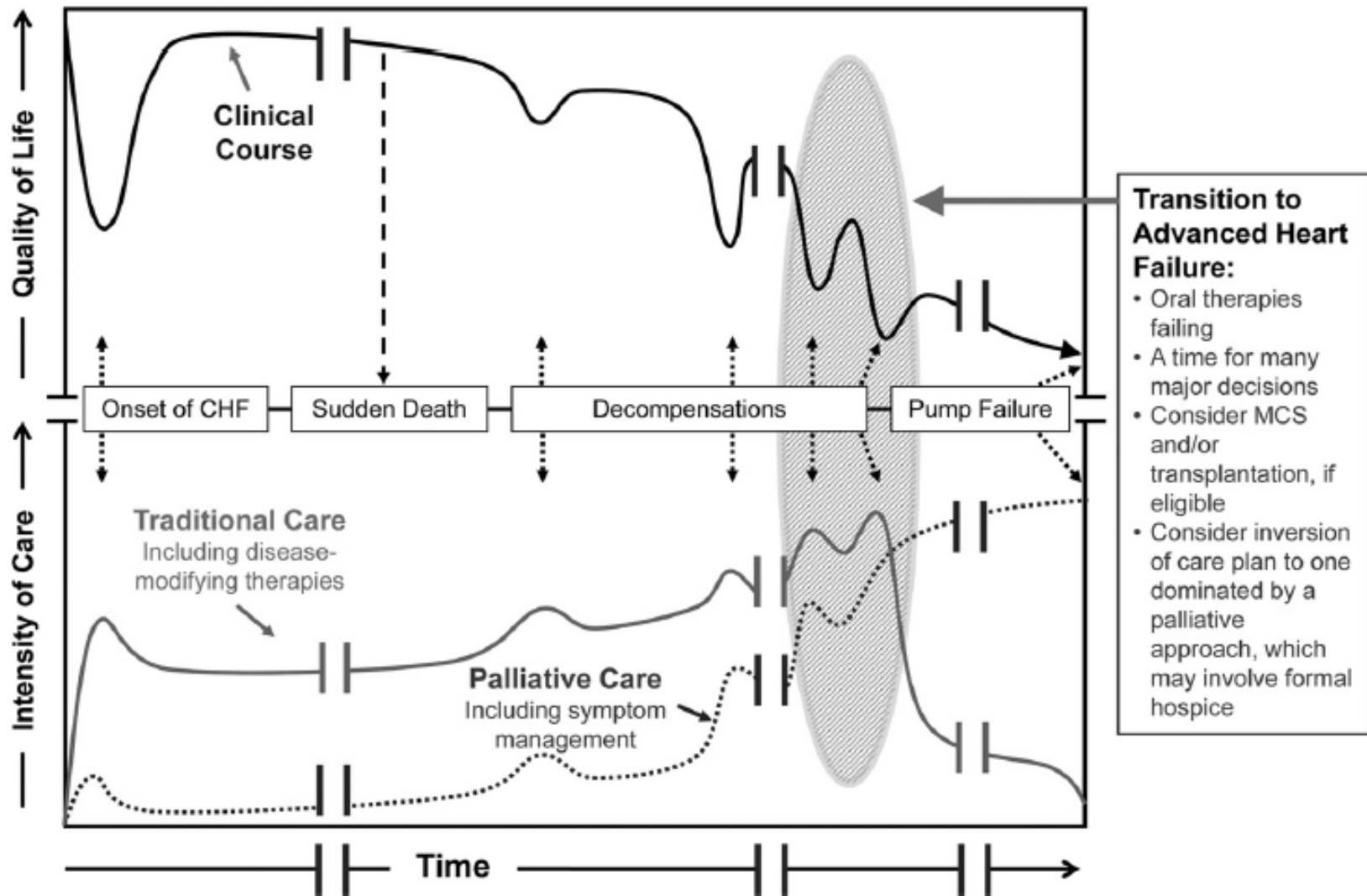


Decision Making in Advanced Heart Failure: A Scientific Statement From the American Heart Association

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 $14 \text{ mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$
 5. History of at least 1 hospitalization in the past 6 mo
 6. Characteristics should be present despite optimal medical therapy
-



Affrontare il problema

Prognosis...heart perspective

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



American
Heart
Association®

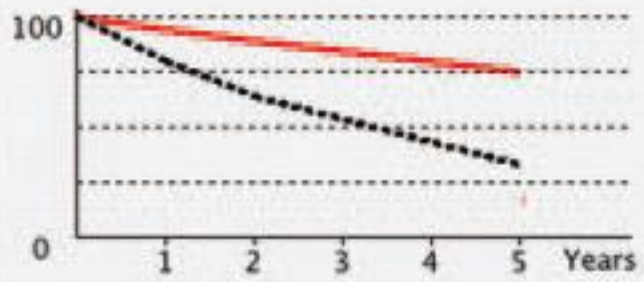
The Seattle Heart Failure Model: Prediction of Survival in Heart Failure

Wayne C. Levy, Dariush Mozaffarian, David T. Linker, Santosh C. Sutradhar, Stefan D. Anker, Anne B. Cropp, Inder Anand, Aldo Maggioni, Paul Burton, Mark D. Sullivan, Bertram Pitt, Philip A. Poole-Wilson, Douglas L. Mann and Milton Packer

Circulation. 2006;113:1424-1433; originally published online March 13, 2006;

	Baseline		
	1 year	2 year	5 year
Survival	80 %	64 %	33 %
Mortality	20 %	36 %	67 %
Mean life expectancy	4.1 years		

	Post-intervention		
	1 year	2 year	5 year
Survival	84 %	69 %	75 %
Mortality	6 %	11 %	25 %
Mean life expectancy	3.7 years		



Baseline Characteristics

Clinical

Age: 65

Gender: Male

NYHA Class: 3

Weight (kg): 80

EF: 20

Syst BP: 120

Ischemic

Medications

ACE-I

Beta-blocker

ARB

Statin

Allopurinol

Aldosterone blocker

Diuretics

Lasix: 40

Bumex: 0

Demadex: 0

Metolazone: 0

HCTZ: 0

Lab Data

Hgb: 13.4

Lymphocytes: 24

Uric Acid: 7

Total Chol: 190

Sodium: 137

QRS > 120 msec

Devices

None

BiV Pacer

ICD

BiV ICD

Defaults

Interventions

ACE-I ARB Beta-blocker

Statin Aldosterone Blocker

Devices

None

BiV Pacer BiV ICD

ICD LVAD



European Heart Journal
doi:10.1093/eurheartj/ehs337

Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies

**Stuart J. Pocock^{1*}, 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)**

Risk factor	Addition to risk score								Risk score
Ejection fraction (%)	<20 +7	20–24 +6	25–29 +5	30–34 +3	35–39 +2	40+ 0			
Extra for age (years)	<55	56–59	60–64	65–69	70–74	75–79	80+		
EF < 30	0	+1	+2	+4	+6	+8	+10		
EF 30 - 39	0	+2	+4	+6	+8	+10	+13		
EF 40 +	0	+3	+5	+7	+9	+12	+15		
Extra for Systolic blood pressure (mm Hg)	<110	110–119	120–129	130–139	140–149	150+			
EF < 30	+5	+4	+3	+2	+1	0			
EF 30 - 39	+3	+2	+1	+1	0	0			
EF 40 +	+2	+1	+1	0	0	0			
BMI (kg / m ²)	<15 +6	15–19 +5	20–24 +3	25–29 +2	30+ 0				
Creatinine (μmol/l)	<90 0	90–109 +1	110–129 +2	130–149 +3	150–169 +4	170–209 +5	210–249 +6	250+ +8	
NYHA Class	1 0	2 +2	3 +6	4 +8					
Male				+1					
Current smoker				+1					
Diabetic				+3					
Diagnosis of COPD				+2					
First diagnosis of heart failure in the past 18 months				+2					
Not on beta blocker				+3					
Not on ACEI/ARB				+1					
Total risk score =									

Affrontare il problema

Prognosis...geriatric perspective

Circulation

Heart Failure



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

	Problems		
	No	Minor	Severe
Assessment	(Value=0)	(Value=0.5)	(Value=1)
ADL*	6–5	4–3	2–0
Instrumental ADL*	8–6	5–4	3–0
Short portable mental status questionnaire†	0–3	4–7	8–10
Comorbidity index (cumulative illness rating scale-CI)‡	0	1–2	≥3
Mini nutritional assessment§	≥24	17–23.5	<17
Exton-smith scale¶	16–20	10–15	5–9
No. of medications	0–3	4–6	≥7
Social support network	Living with family	Institutionalized	Living alone

*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.

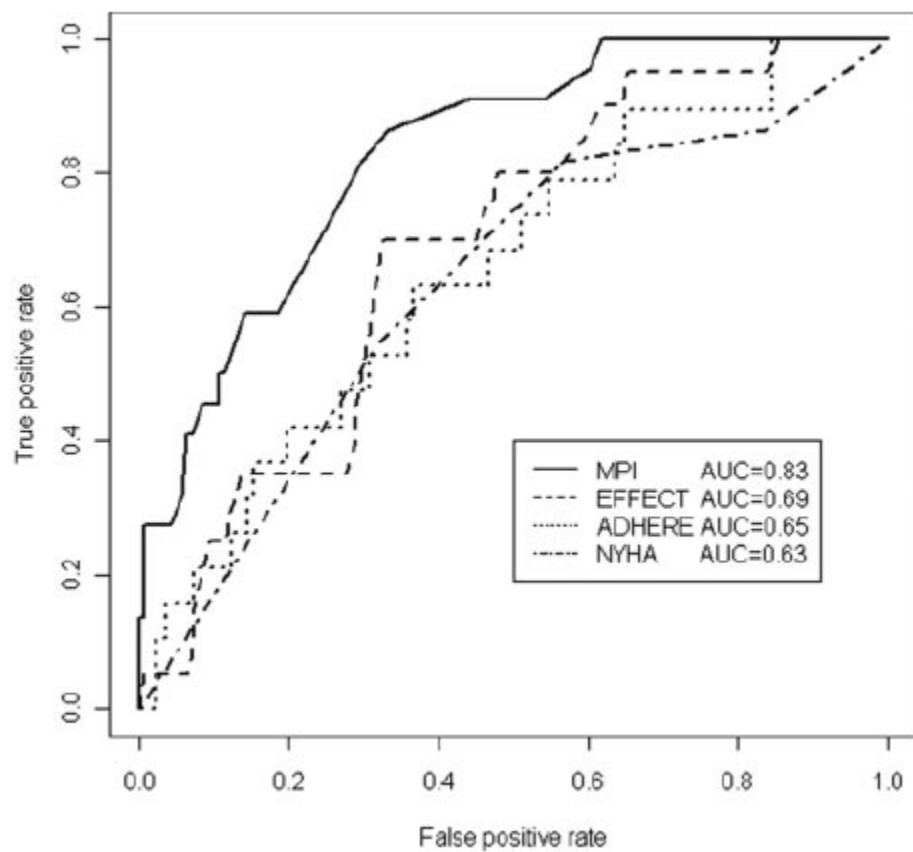
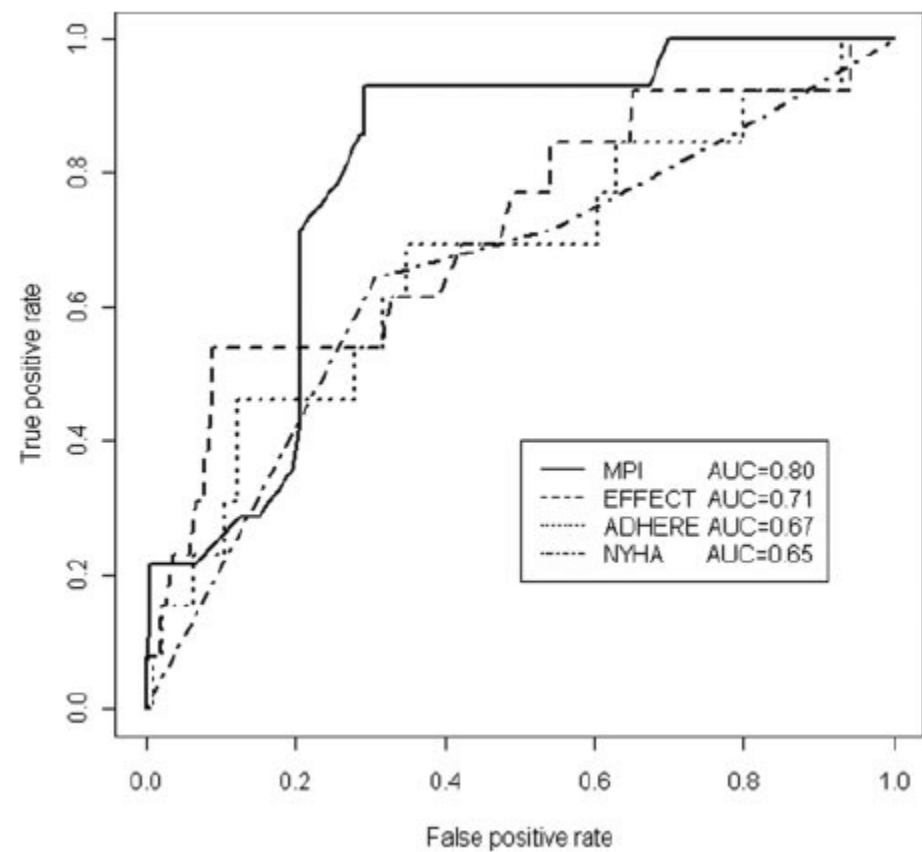


Figure. ROC curves for the MPI, NYHA, EFFECT, and ADHERE risk scores at 30 days of follow-up in men (right) and women (left).

Senza dimenticare...

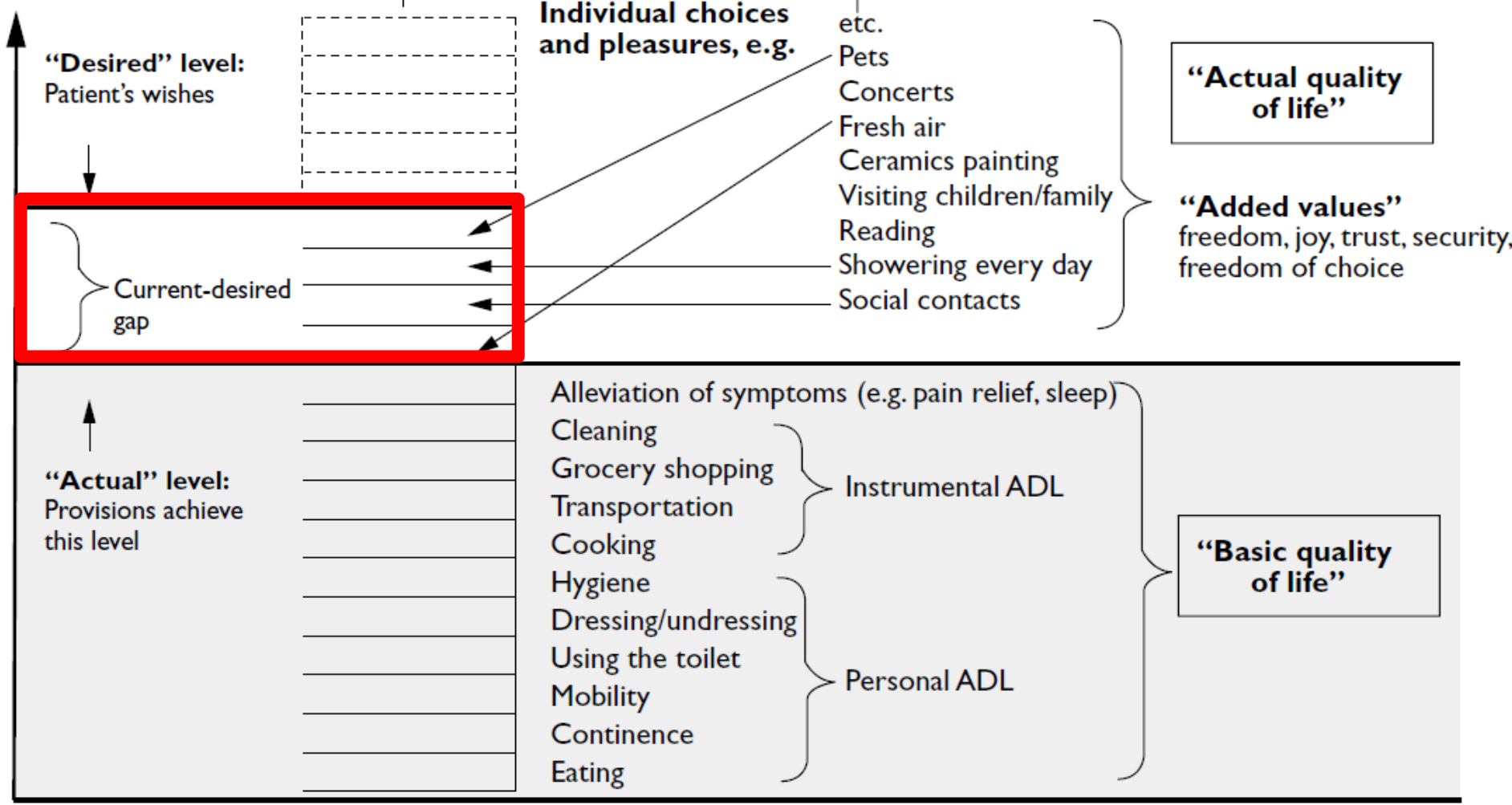
...se possibile

Geriatric Care and Treatment

A systematic compilation of existing scientific literature



Quality of life



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



EUROPEAN
SOCIETY OF
CARDIOLOGY®

European Journal of Heart Failure (2014) 16, 494–508

doi:10.1002/ejhf.62

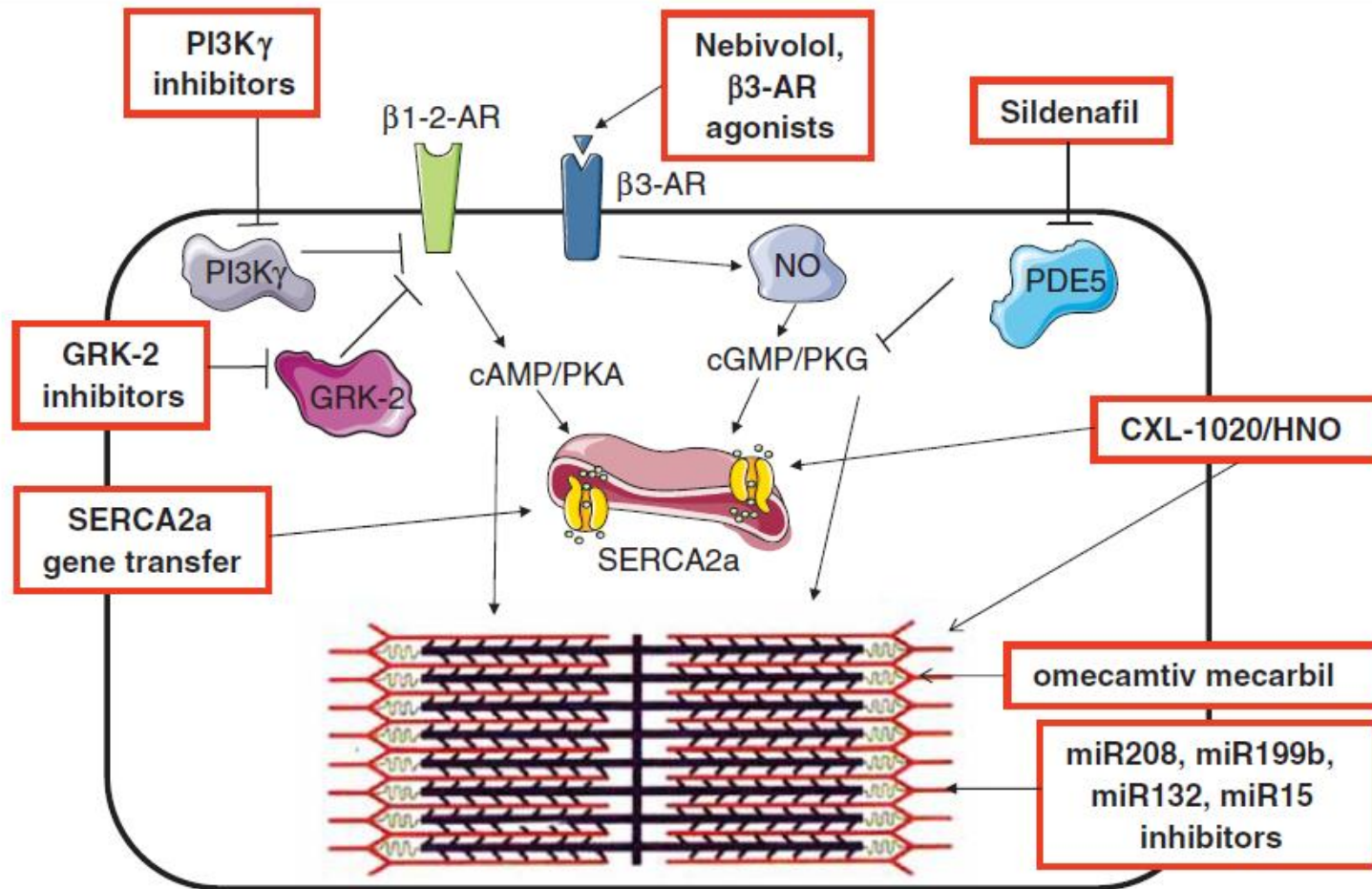


Figure 1 Therapeutic strategies to improve cardiomyocyte function. Red boxes identify molecules capable of improving cardiomyocyte function by acting on the indicated targets. GRK2, G protein-coupled receptor kinase 2; PI3K, Phosphoinositide 3 kinase gamma; SERCA2a, sarco/endoplasmic reticulum Ca²⁺-ATPase 2a; $\beta 3$ -AR, beta3 adrenergic receptor.

Table 1 Molecular targets and drugs with therapeutic potential on myocardial remodelling in heart failure

Drug/target	Mechanism of action	Experimental stage	References
Improving myocyte function			
GRK2	Prevent β -AR desensitization	Pre-clinical	Ciccarelli et al. ⁴
PI3K γ	Normalization of β -AR density and contractility	Clinical	NCT00103350
Sildenafil	Increase GMP/PKG signalling	Clinical	NCT00763867 ²³
CXL-1020	HNO donor	Clinical (NCT01092325, NCT01096043)	25, 116
β_3 AR agonists (e.g. nebivolol)		Pre-clinical/clinical	16–19
SERCA2a	\uparrow Ca ²⁺ SR uptake	Clinical (NCT0045481, NCT01643330)	29
Omecamtiv mecarbil	Myosin activator	Clinical (NCT00624442)	32
miR-208, miR-199a-5p, miR-199b, miR-212/132, miR15	Inhibit maladaptive hypertrophy	Pre-clinical	34–38, 40, 117
Preventing myocyte death			
Necrostatin-1	Inhibit RIPK1 and necroptosis	Pre-clinical	44, 45
Cyclosporin A	Inhibit MPTP opening and cell death	Clinical (NCT01650662, bNCT01502774)	48, 49
Neuregulin 1	Enhance protective signalling	Clinical (NCT01251406)	52, 53
HSPB5, HSPB6, HSPB8, BAG3, Melusin	Promote protein folding and enhance protective signalling	Pre-clinical	56, 58, 59, 61, 63, 64, 118, 119
CHIP, Atrogin1, MuRF1, Telethonin	Control of protein degradation	Pre-clinical	65, 120
Boosting angiogenesis in the heart			
VEGF-A	Promote endothelial cell growth and migration	Clinical	82–85, 121
VEGF-B	Promote endothelial cell growth and migration; enhance myocyte survival	Pre-clinical	89
PLGF	Promote endothelial cell growth and migration; regulate inflammation	Pre-clinical	87, 88
miR-126, miR-210	Promote endothelial cell growth and migration	Pre-clinical	90–92
Bromocriptine	Inhibit prolactin release and protect in PPCM	Pre-clinical/clinical	94, 95
miR146, miR92a, miR-24	Protection in PPCM and MI	Pre-clinical	96–99
Erythropoietin	Protection in anthracycline- induced myopathy	Pre-clinical	100
Regulating interstitial remodelling			
Thrombospondins, SPARC, syndecans	Promote favourable matrix remodelling; reduce inflammation	Pre-clinical	40, 104, 106, 122, 123
Torsemide	Diuretic, indirectly reduces fibrosis	Clinical	108, 109
miR-21 inhibitor	Inhibit fibroblast proliferation and secretion of ECM	Pre-clinical	110, 111, 124
miR-101, miR-29	Down-regulate ECM transcripts	Pre-clinical	112

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.

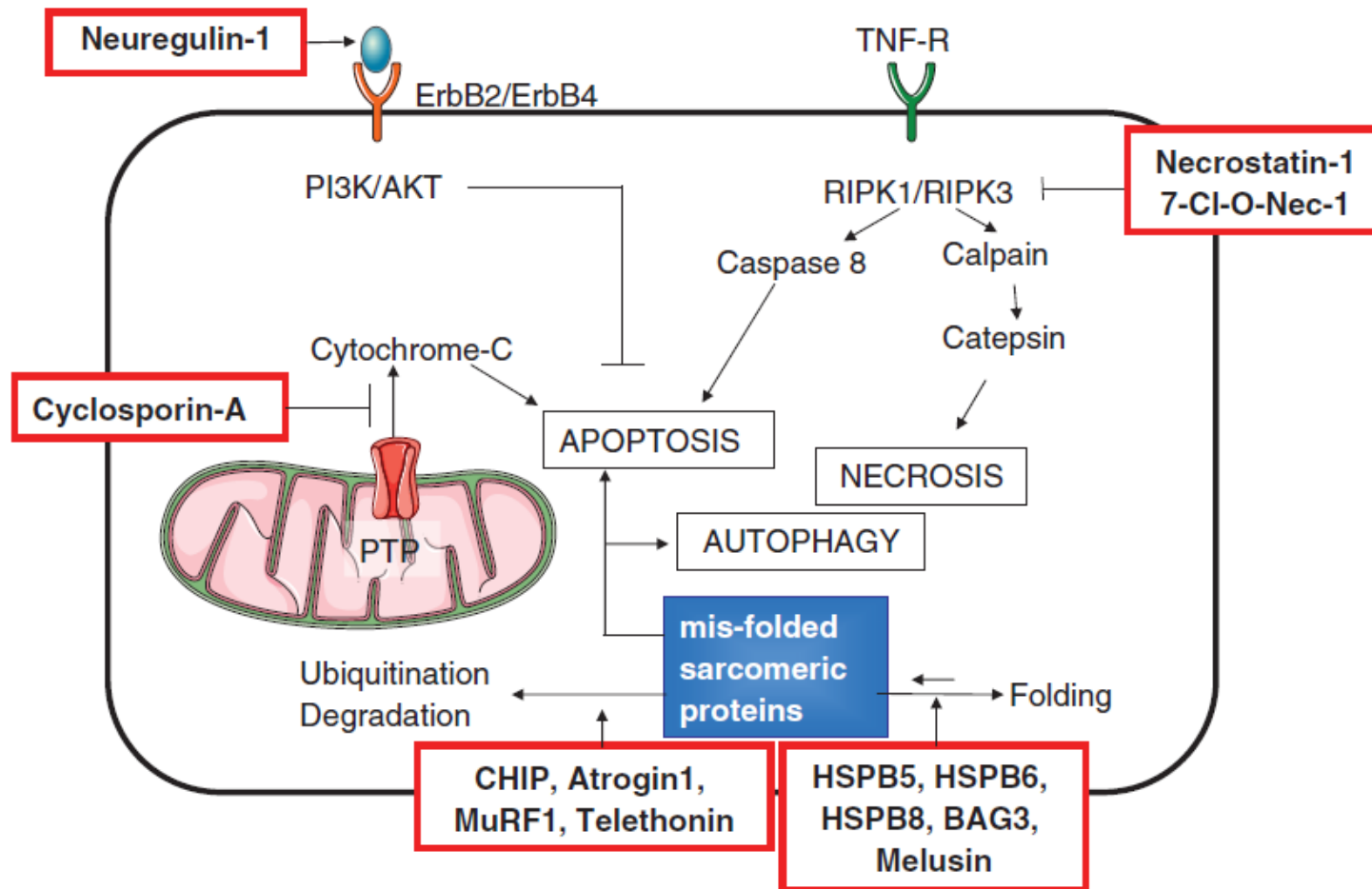


Figure 2 Therapeutic strategies to prevent cardiomyocyte death. Red boxes identify molecules capable of preventing cardiomyocyte death by acting on the indicated targets and processes. CHIP, Carboxy terminus of Hsp70-interacting protein–ubiquitin ligase; MURF1, Muscle-specific RING finger protein 1–ubiquitin ligase; BAG3, Bcl-2-associated athanogene 3.

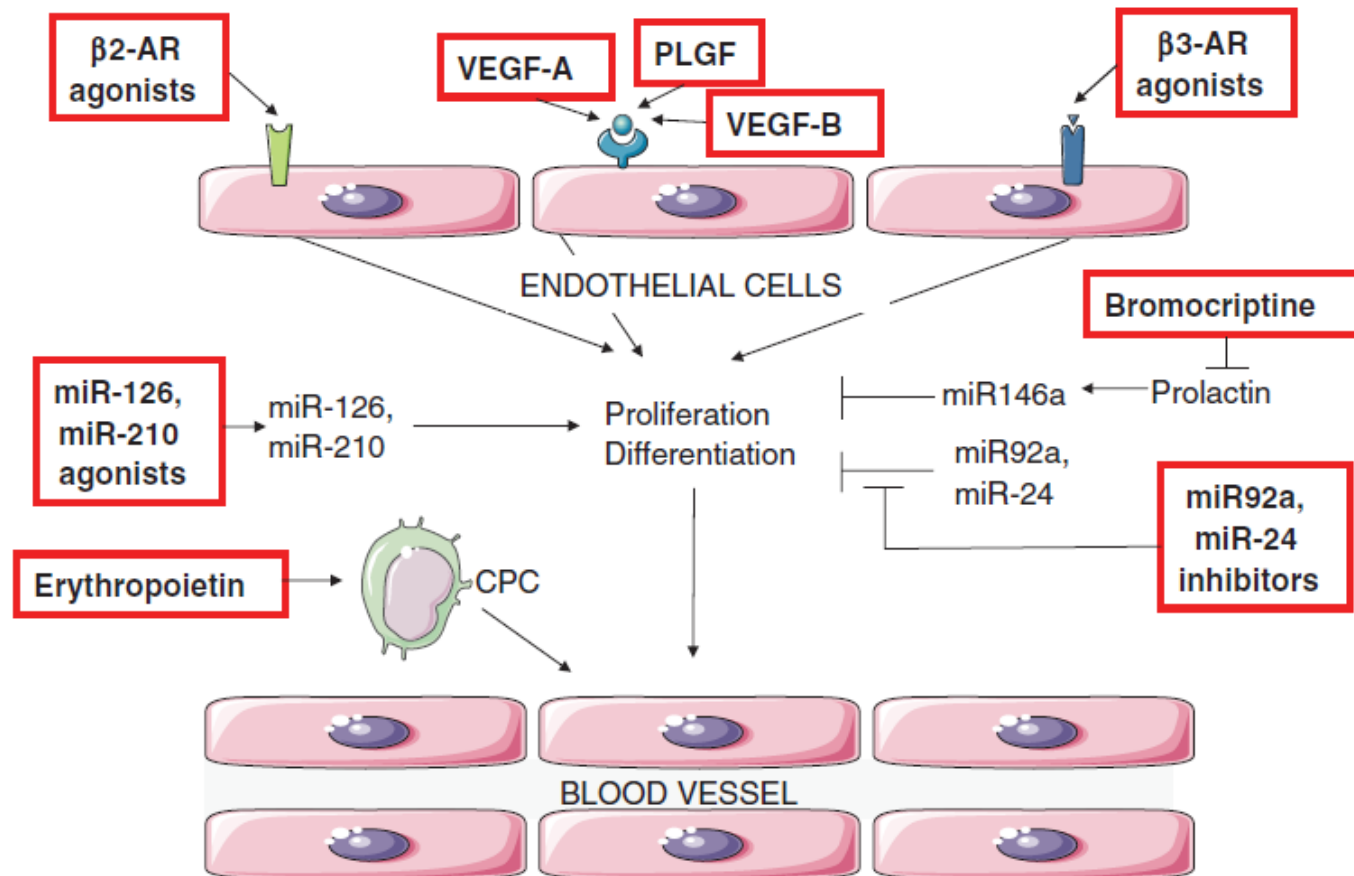


Figure 3 Therapeutic strategies to promote growth of blood vessels. Red boxes identify molecules capable of boosting growth of novel blood vessels by acting on the indicated targets and processes. β 3-AR, beta3 adrenergic receptor; β 2-AR, beta2 adrenergic receptor; VEGF-A, vascular endothelial growth factor A; VEGF-B, vascular endothelial growth factor B; PLGF, placenta growth factor.

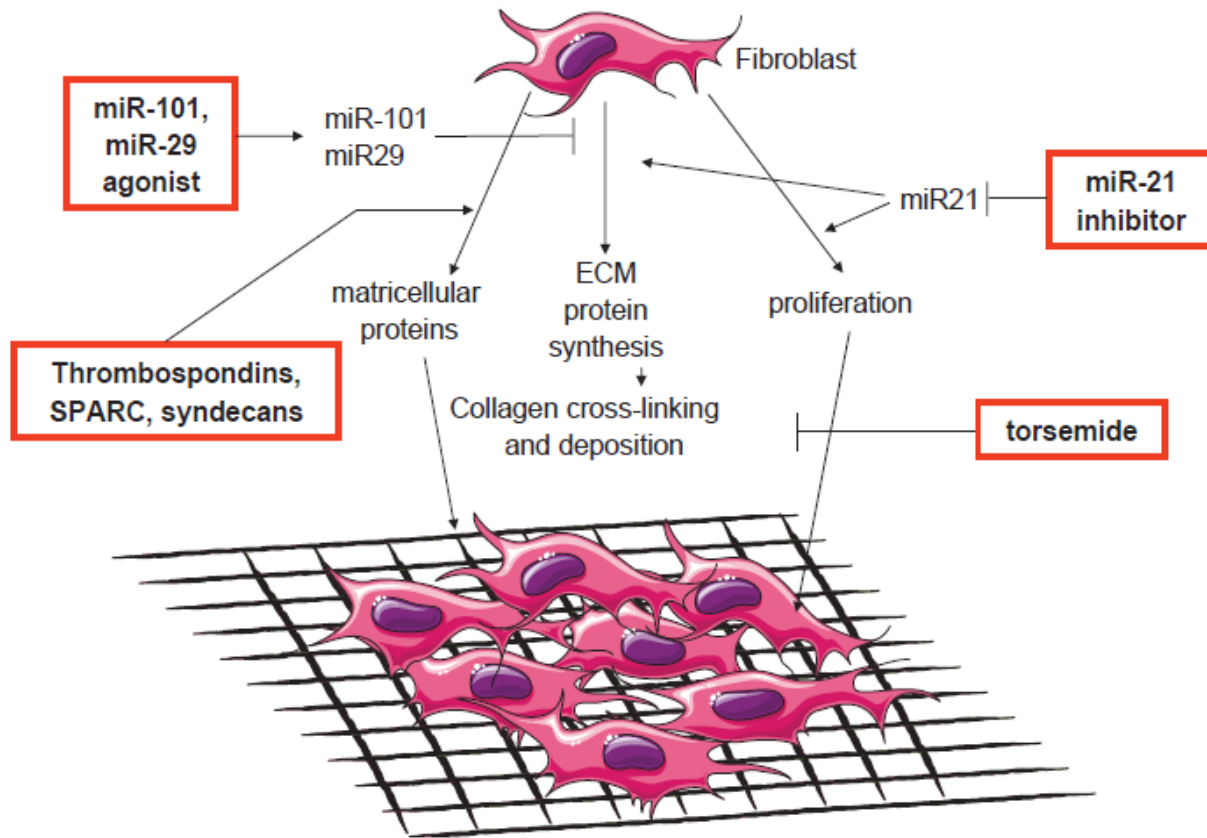


Figure 4 Therapeutic strategies to regulate extracellular matrix deposition. Red boxes identify molecules capable of impacting on extracellular matrix protein synthesis/deposition and fibroblast proliferation by acting on the indicated targets and processes. SPARC, Secreted protein acidic and rich in cysteine.

Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Gene Therapy for Heart Failure

Lisa Tilemann, Kiyotake Ishikawa, Thomas Weber and Roger J. Hajjar

Circ Res. 2012;110:777-793

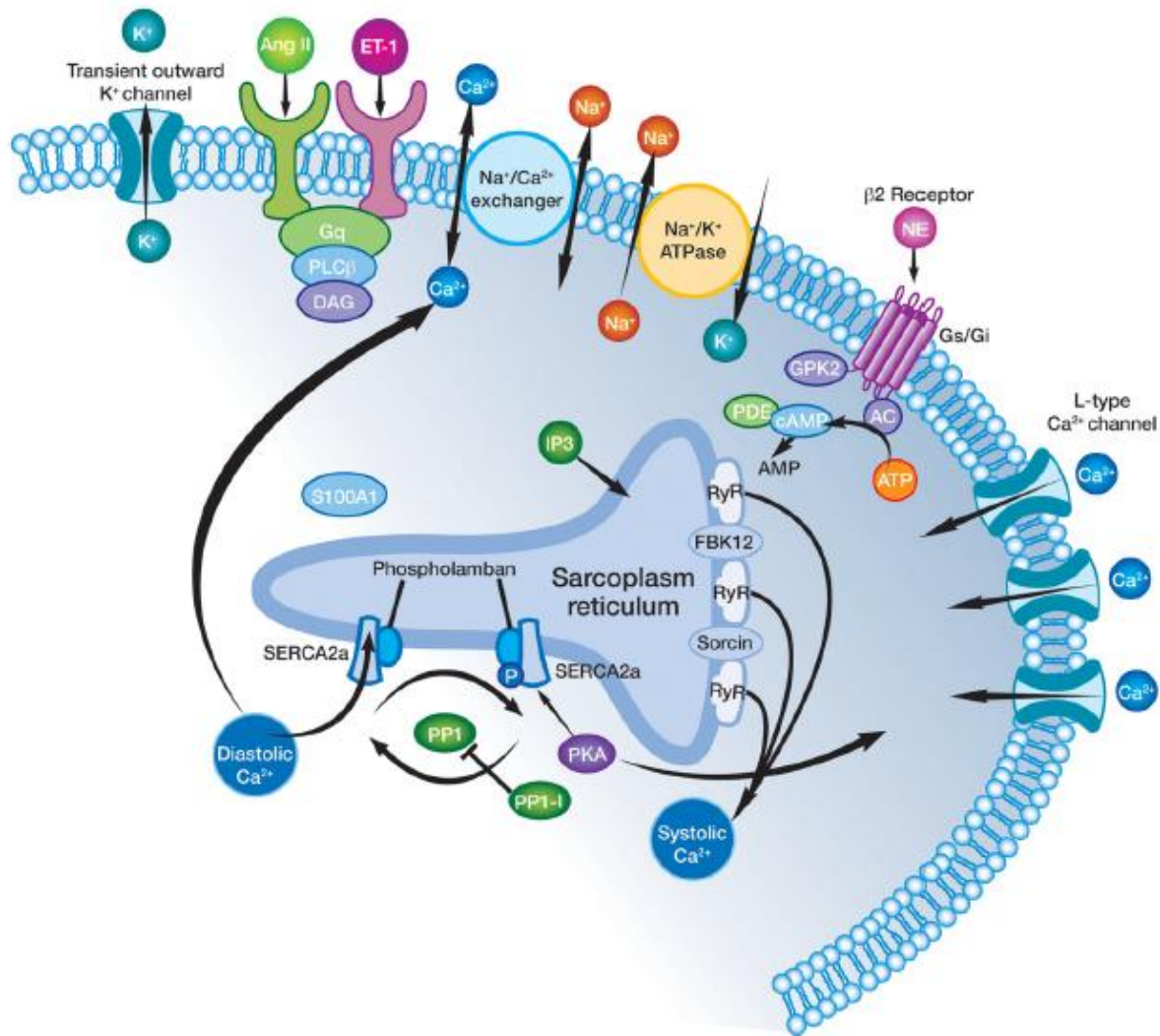


Figure 6. Excitation-contraction coupling in cardiac myocytes provides multiple targets for gene therapy.

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.



Stem cell therapy for chronic ischaemic heart disease and congestive heart failure (Review)

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 4

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.