Novità terapeutiche: Sacubitril-Valsartan…

Pierluigi Sbarra
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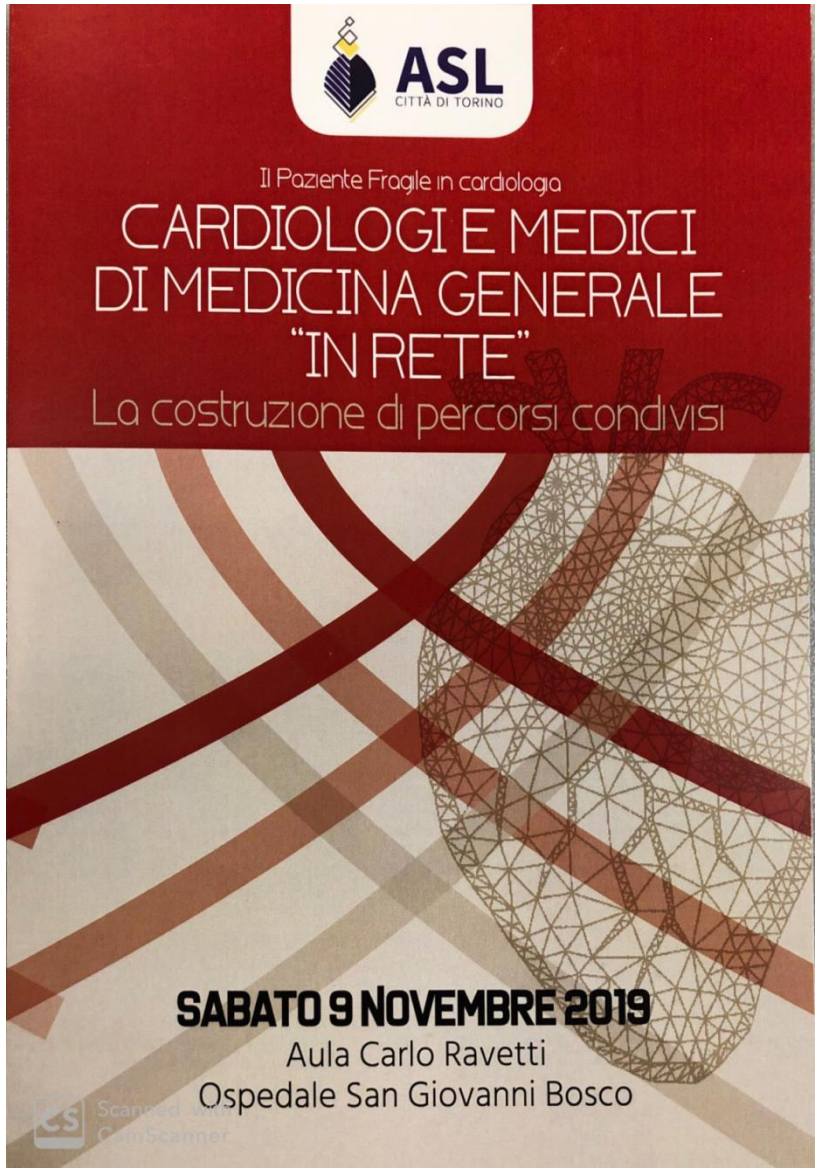
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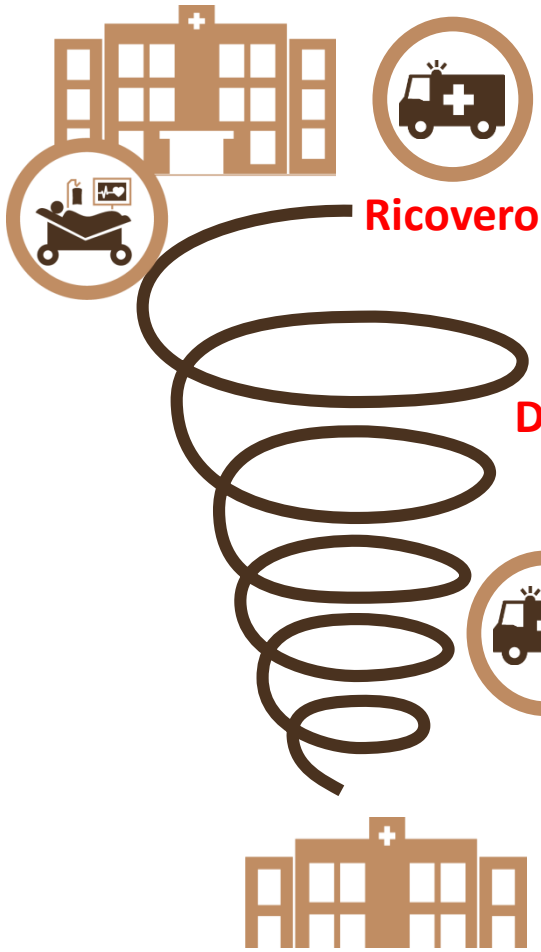
Il Paziente Fragile in cardiologia
CARDIOLOGI E MEDICI
DI MEDICINA GENERALE
"IN RETE"
La costruzione di percorsi condivisi
SABATO 9 NOVEMBRE 2019
Aula Carlo Ravetti
Ospedale San Giovanni Bosco

Lo Scompenso Cardiaco (SC) è la prima causa di ospedalizzazione

Nei paesi sviluppati, **l' HF è la prima causa di ospedalizzazione** nei pazienti di età >65 anni



Tutti i pazienti con HF sono a rischio aumentato di frequenti **ospedalizzazioni ripetute**

30 giorni

1 su 4 pazienti di età ≥65 richiede la riospedalizzazione[6]

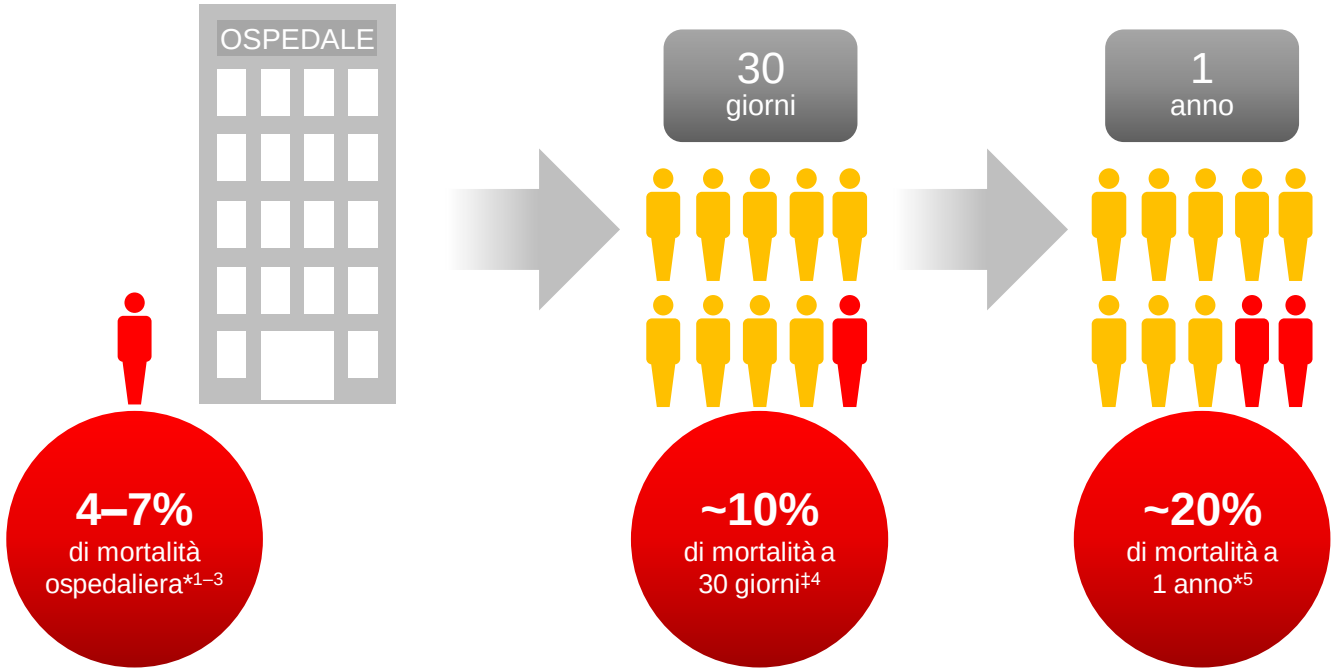
1 anno

~44% dei pazienti sarà riospedalizzato almeno una volta[3]

1. Cowie et al. ESC Heart Failure 2014;1:110–45;
2. 2. Healthcare Cost and Utilization Project 2009. Available at: http://www.hcup-
3. us.ahrq.gov/reports/factsandfigures/2009/pdfs/FF_2009_exhibit2;
4. 3. Maggioni. Eur J Heart Fail 2013;15:808–17;

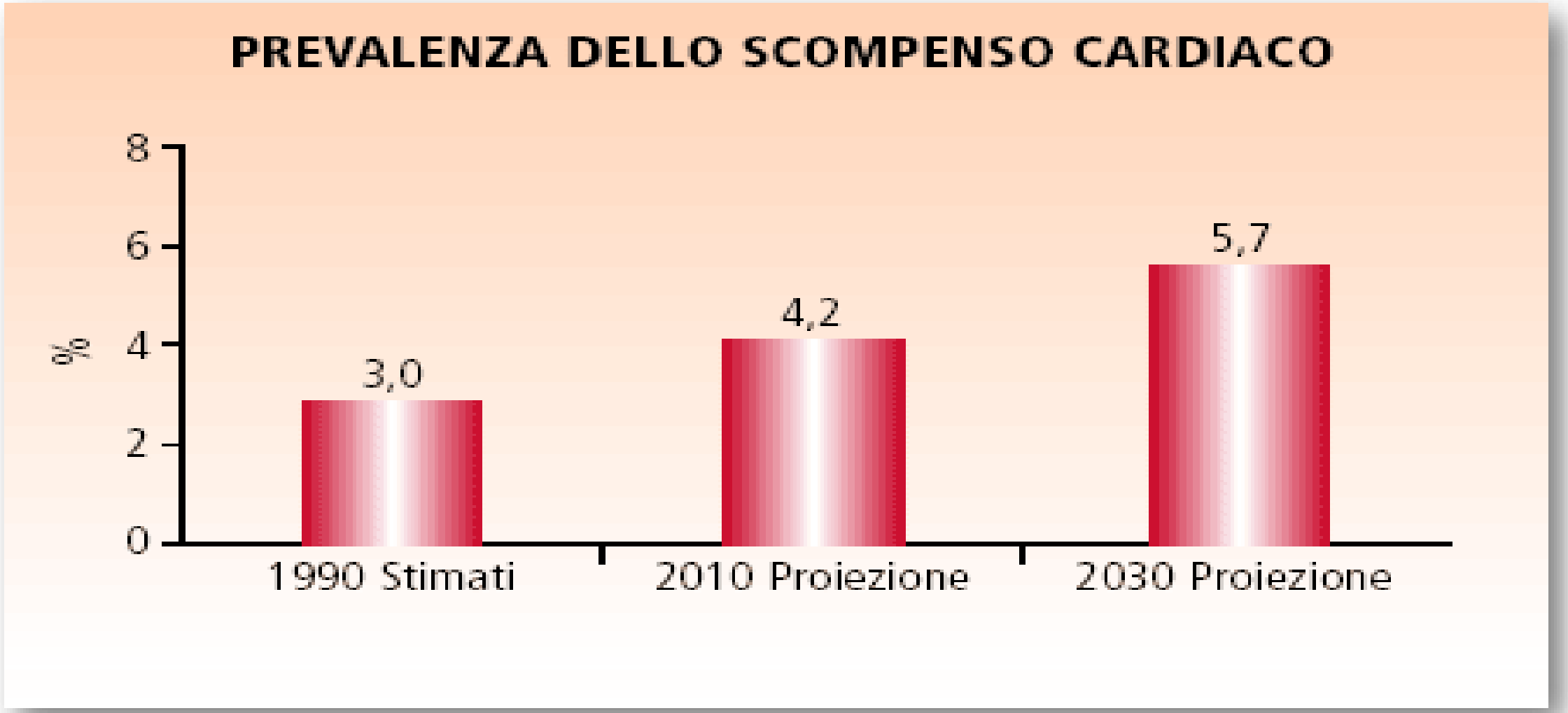
4. Lee et al. Am J Med 2009;122:162–95; 6. Krumholz et al. Circ Cardiovasc Qual Outcomes 2009;2:407–13

Ricovero per SC: alta mortalità



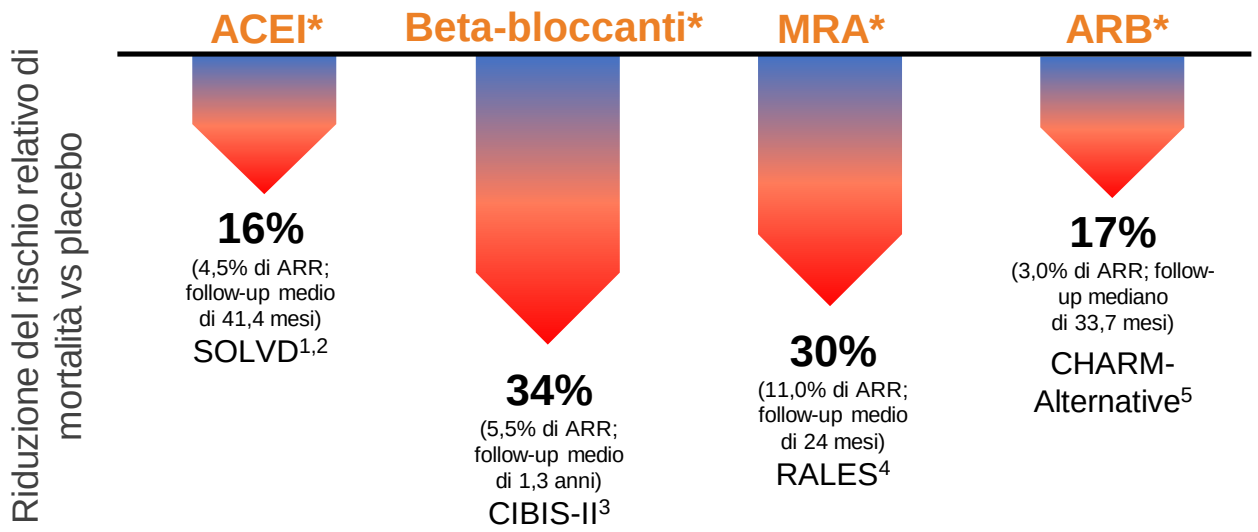
1. Maggioni et al. Eur J Heart Fail 2010;12:1076–84; 2. Nieminen et al. Eur Heart J 2006;27:2725–36; 3. Cleland et al. Eur Heart J 2003;24:442–636; 4. Loehr et al. Am J Cardiol 2008;101:1016–22; 5. Maggioni et al. Eur J Heart Fail 2013;15:808–17

Proiezione per l'anno 2030 negli USA



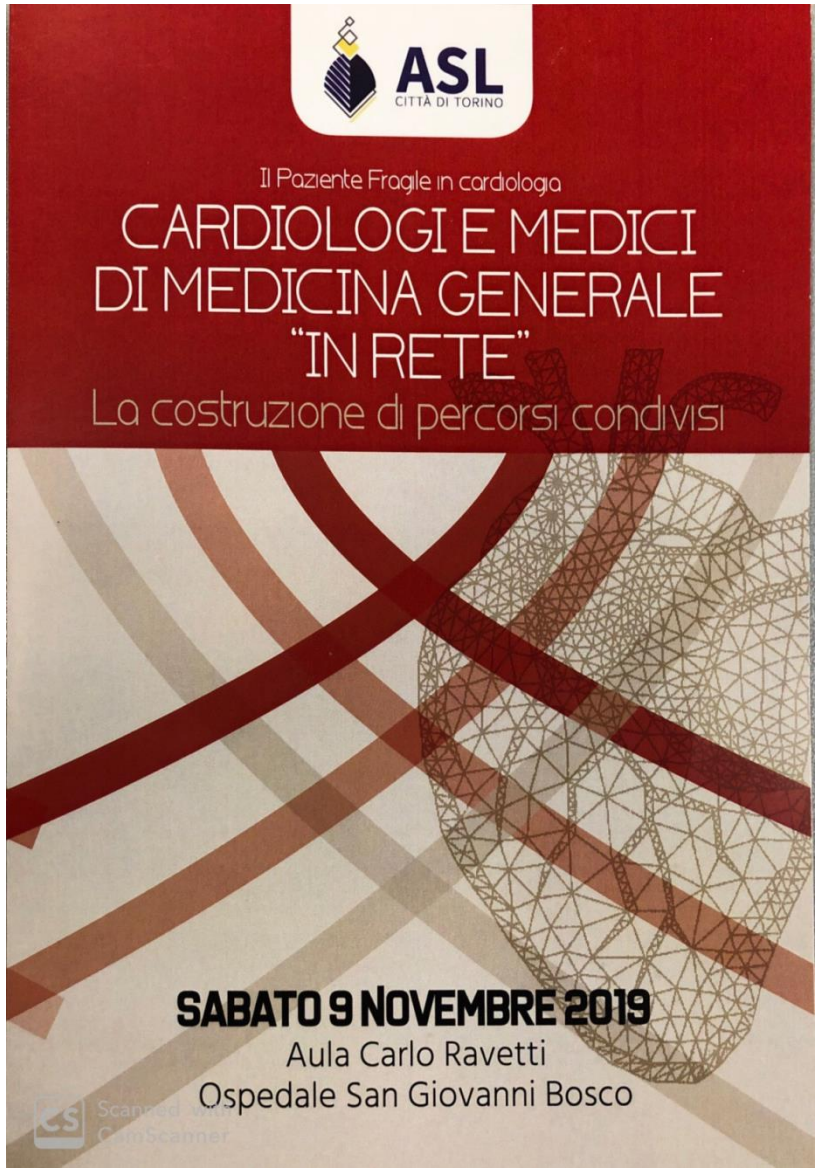
Scompenso Cardiaco: la mortalità resta elevata

- I tassi di sopravvivenza nell'HF cronico sono migliorati con l'introduzione di nuove terapie[1]



- **Resta tuttavia una mortalità significativa: ~50% dei pazienti muore entro 5 anni dalla diagnosi[6–9] (ARR=absolute risk reduction)**

1. McMurray et al. Eur Heart J 2012;33:1787–847; 2. SOLVD Investigators. N Engl J Med 1991;325:293–302; 3. CIBIS-II Investigators. Lancet 1999;353:9–13; 4. Pitt et al. N Engl J Med 1999;341:709-17; 5. Granger et al. Lancet 2003;362:772–66; 6. Go et al. Circulation 2014;129:e28-e292; 7. Yancy et al. Circulation 2013;128:e240–327; 8. Levy et al. N Engl J Med 2002;347:1397–402; 9. Roger et al. JAMA 2004;292:344–50



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Paradigm-HF

The NEW ENGLAND JOURNAL of MEDICINE

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Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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ABSTRACT

BACKGROUND

We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS

In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

RESULTS

The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

CONCLUSIONS

LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

From the British Heart Foundation (BHF) Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.V.M.); the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (M.P.); the Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston (A.S.D., S.D.S.); Novartis Pharmaceuticals, East Hanover, NJ (J.G., M.P.L., A.R.R., V.C.S.); Institut de Cardiologie de Montréal, Université de Montréal, Montreal (J.L.R.); the Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden (K.S.); National Heart and Lung Institute, Imperial College London, London (K.S.); and the Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston (M.R.Z.). Address reprint requests to Dr. Packer at the Department of Clinical Sciences, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, or at milton.packer@utsouthwestern.edu; or to Dr. McMurray at the BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland G12 8QQ, United Kingdom, or at john.mcmurray@glasgow.ac.uk.

*A complete list of the investigators in the Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) is provided in the Supplementary Appendix, available at NEJM.org.

Drs. McMurray and Packer contributed equally to this article.

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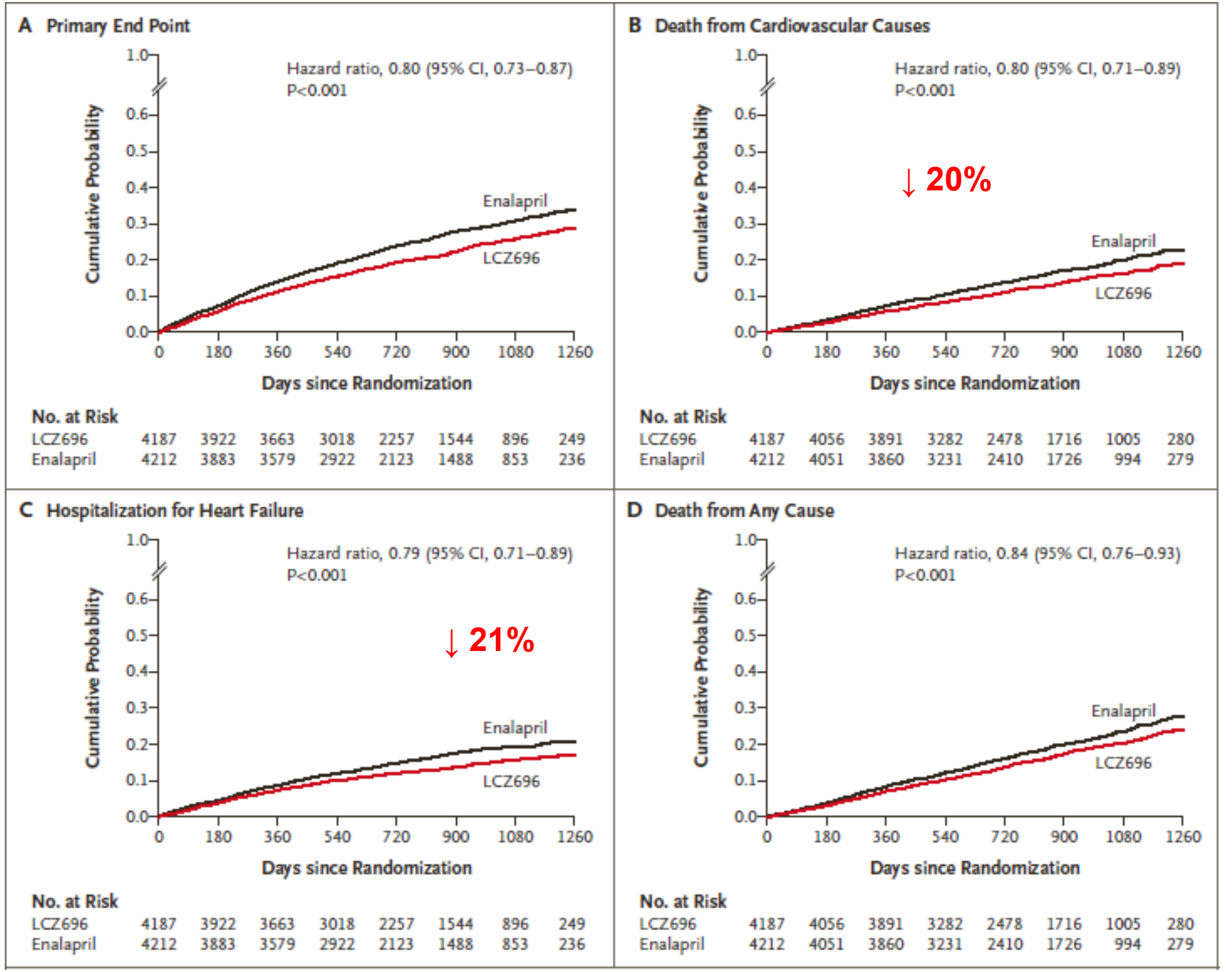
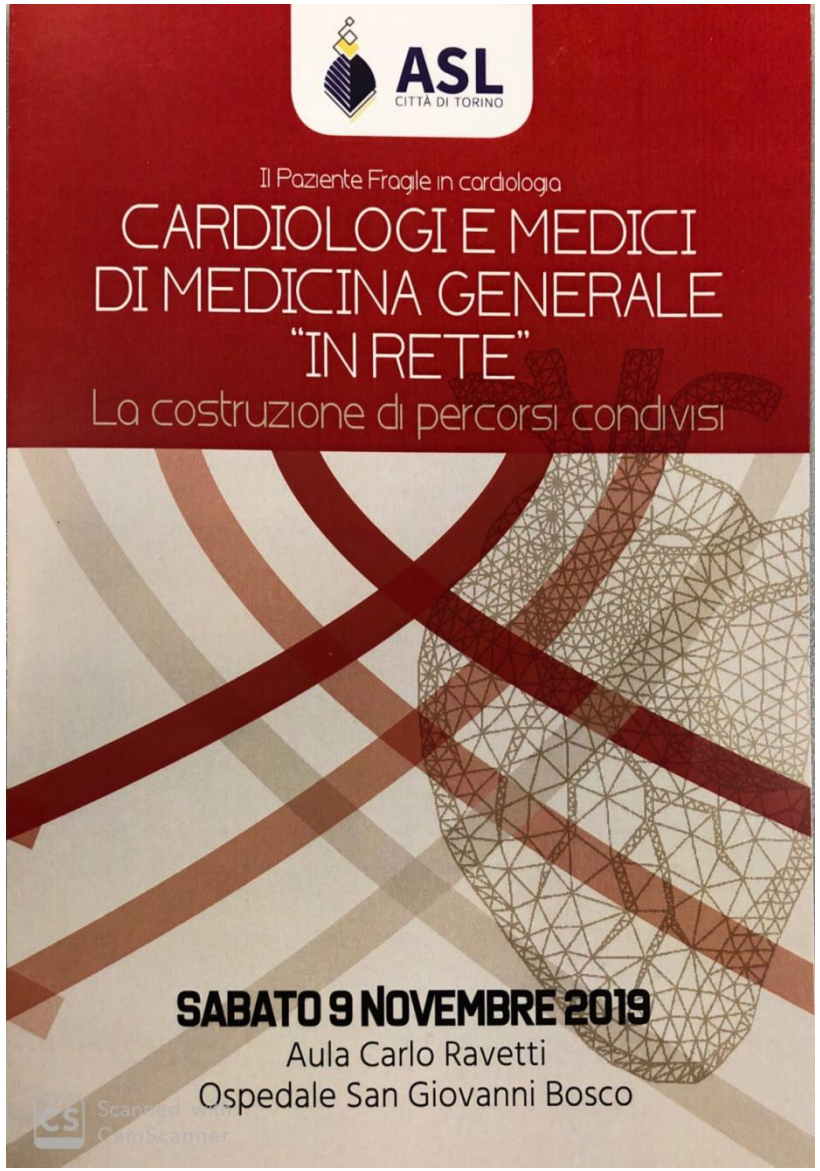
DOI: 10.1056/NEJMoa1409077





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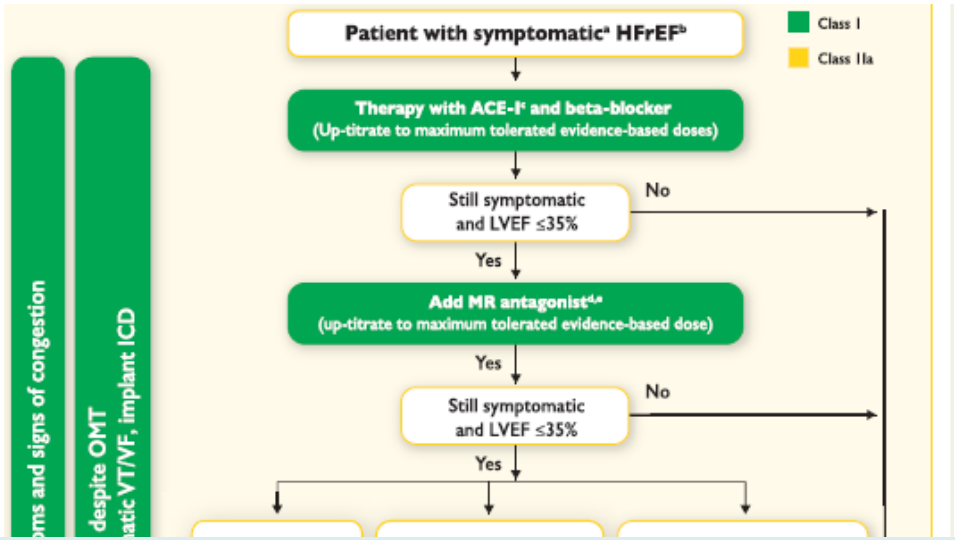
European Heart Journal
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

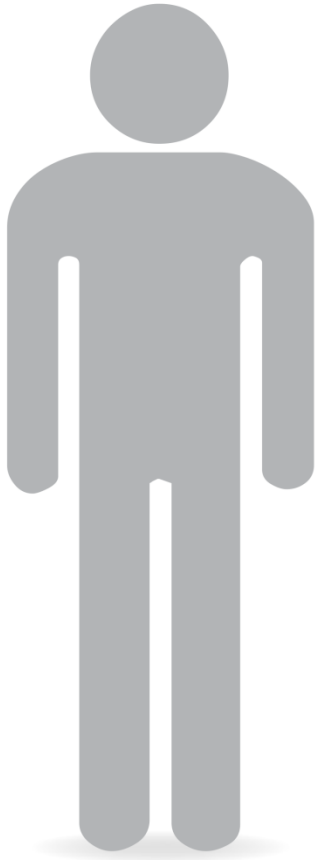
The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)



Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class[a]	Level[b]	Ref[c]
Diuretics			
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.	I	B	178, 179
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.	IIa	B	178, 179
Angiotensin receptor neprilysin inhibitor			
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B	162

Caratteristiche del paziente ideale per Sacubitril/Valsartan



Classe NYHA: **II-III**
FE: **≤35%***

PAS: **≥100** mmHg

eGFR: **≥30** ml/min/1,73m²

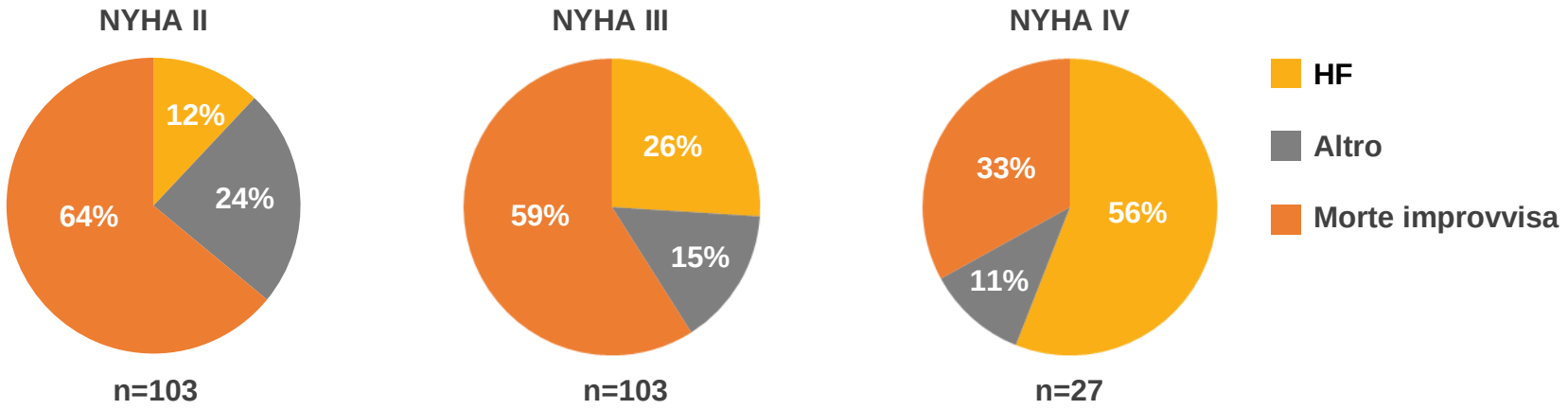
Potassio sierico: **≤5,4** mmol/l

In trattamento con dosi stabili di **ACE-I** o **sartani**

Morte improvvisa e SC

- La morte cardiaca improvvisa è responsabile della metà circa dei decessi nei pazienti con HF[1–3]
- L'incidenza delle morti cardiache improvvise varia in funzione della classe NYHA ed è maggiore nei pazienti con sintomi da lievi a moderati (classi NYHA II–III)[2,3]

Gravità dell'HF e modalità di decesso nella sperimentazione MERIT-HF[2]



1. McMurray et al. Eur Heart J 2012;33:1787–847; 2. MERIT-HF. Lancet 1999;353:2001–7; 3. Desai et al. Eur Heart J 2015;36:1990–7

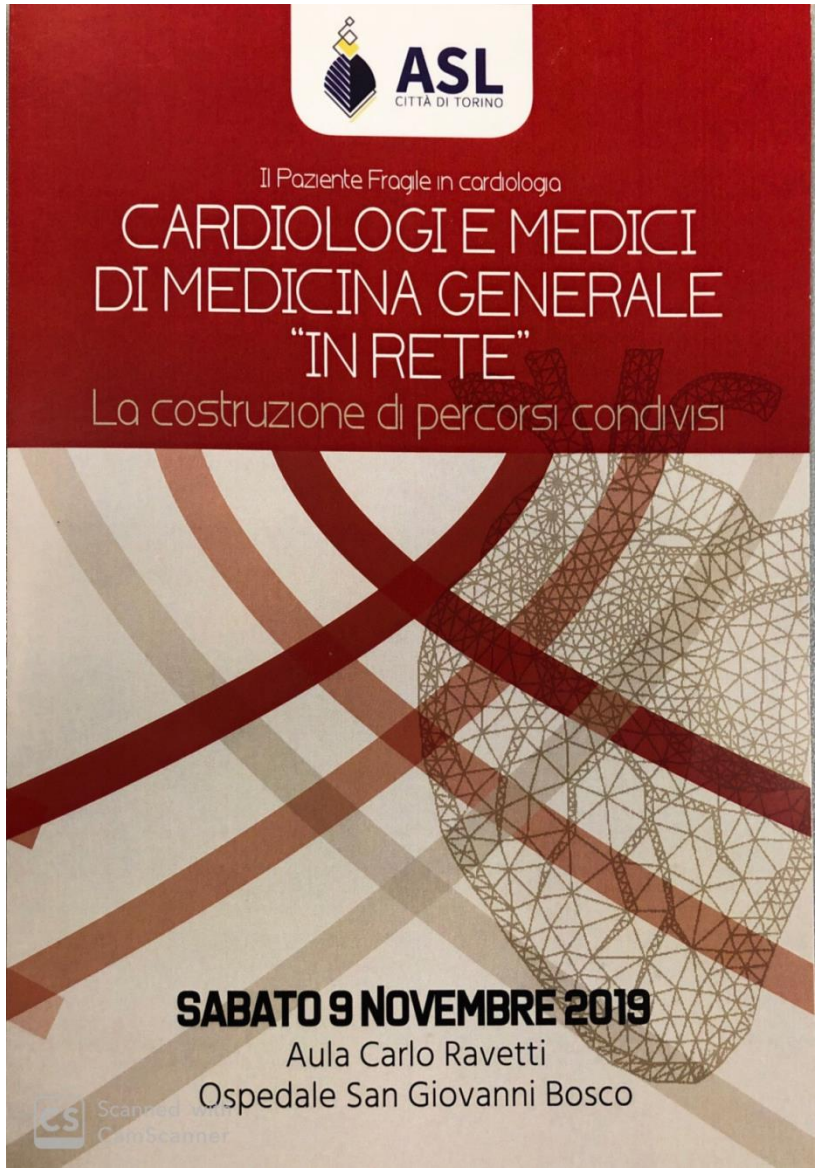
European Heart Journal
doi:10.1093/eurheartj/ehw128

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Recommendations for the management of ventricular tachyarrhythmias in heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Potential aggravating/precipitating factors (e.g. low serum potassium/ magnesium, ongoing ischaemia) should be sought and corrected in patients with ventricular arrhythmias.	IIa	C	
Treatment with beta-blocker, MRA and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias (as for other patients)(see Section 7).	I	A	162, 170–175
Implantation of an ICD or CRT-D device is recommended for selected patients with HFrEF (see Section 8).	I	A	223–226, 388
Several strategies should be considered to reduce recurrent symptomatic arrhythmias in patients with an ICD (or in those who are not eligible for ICD), including attention to risk factors and optimal pharmacological treatment of HF, amiodarone, catheter ablation and CRT.	IIa	C	
Routine use of antiarrhythmic agents is not recommended in patients with HF and asymptomatic ventricular arrhythmias because of safety concerns (worsening HF, proarrhythmia, and death).	III	A	247, 248, 364, 365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Future
Present
Past

Myocardial Fibrosis as a Key Determinant of Left Ventricular Remodeling in Idiopathic Dilated Cardiomyopathy

A

Pier Giorgic
Michele
Claud

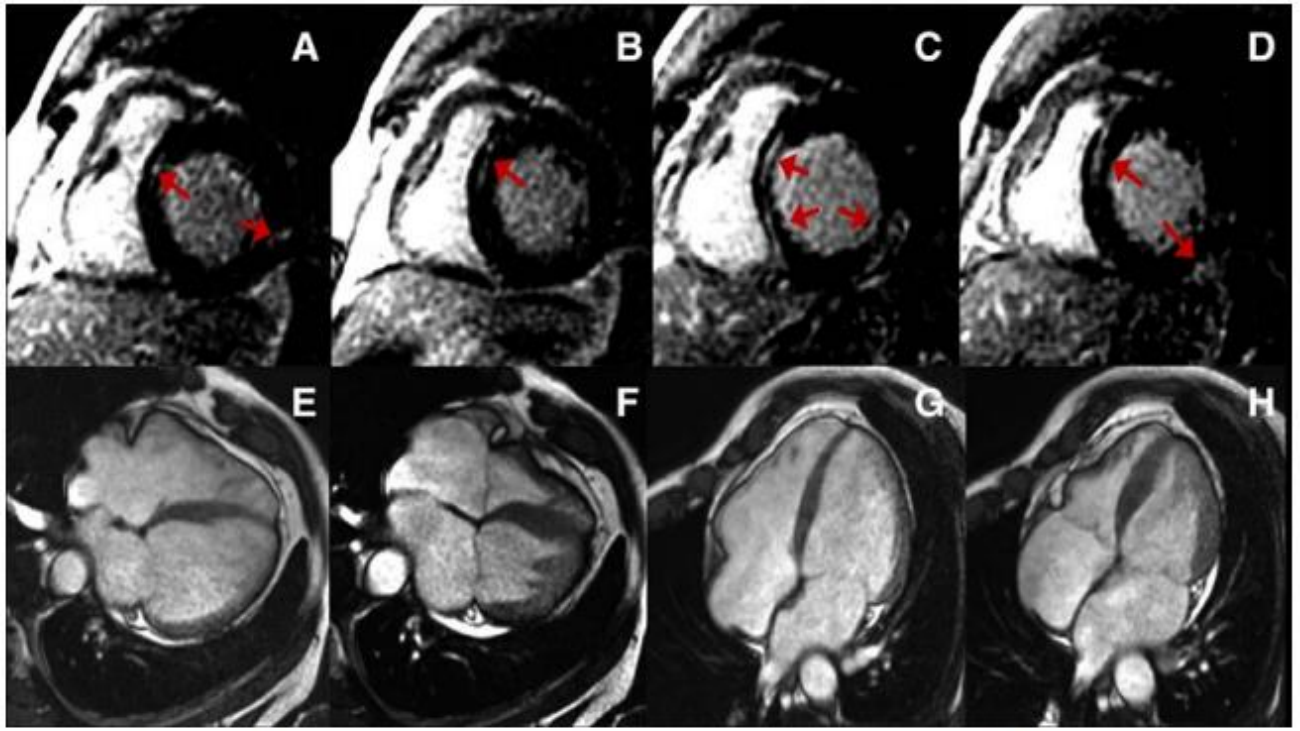

Figure 3. A 51-year-old man with 11-month history of idiopathic dilated cardiomyopathy complaining of episodes of palpitation and asthenia. Baseline postcontrast basal (**A**) and midventricular (**B**) short-axis images showed late gadolinium enhancement (LGE) of the septum and left ventricular (LV) inferolateral wall (arrows). At follow-up, postcontrast basal (**C**) and midventricular (**D**) short-axis images showed an increase in LGE extent (from 4.43% to 7.52%; Δ value, 3.09%). End-diastolic (**E** and **G**) and end-systolic (**F** and **H**) horizontal long-axis images at baseline (**E** and **F**; Movie III in the online-only Data Supplement) and follow-up (**G** and **H**; Movie IV in the online-only Data Supplement) showed no significant changes in LV volumes (end-diastolic volume from 108 to 107 mL/m^2; end-systolic volume from 55 to 54 mL/m^2) and function (ejection fraction 49% at baseline and follow-up).

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Basic Science and Experimental Studies

LCZ696 (Sacubitril/Valsartan), an Angiotensin-Receptor Neprilysin Inhibitor, Attenuates Cardiac Hypertrophy, Fibrosis, and Vasculopathy in a Rat Model of Chronic Kidney Disease

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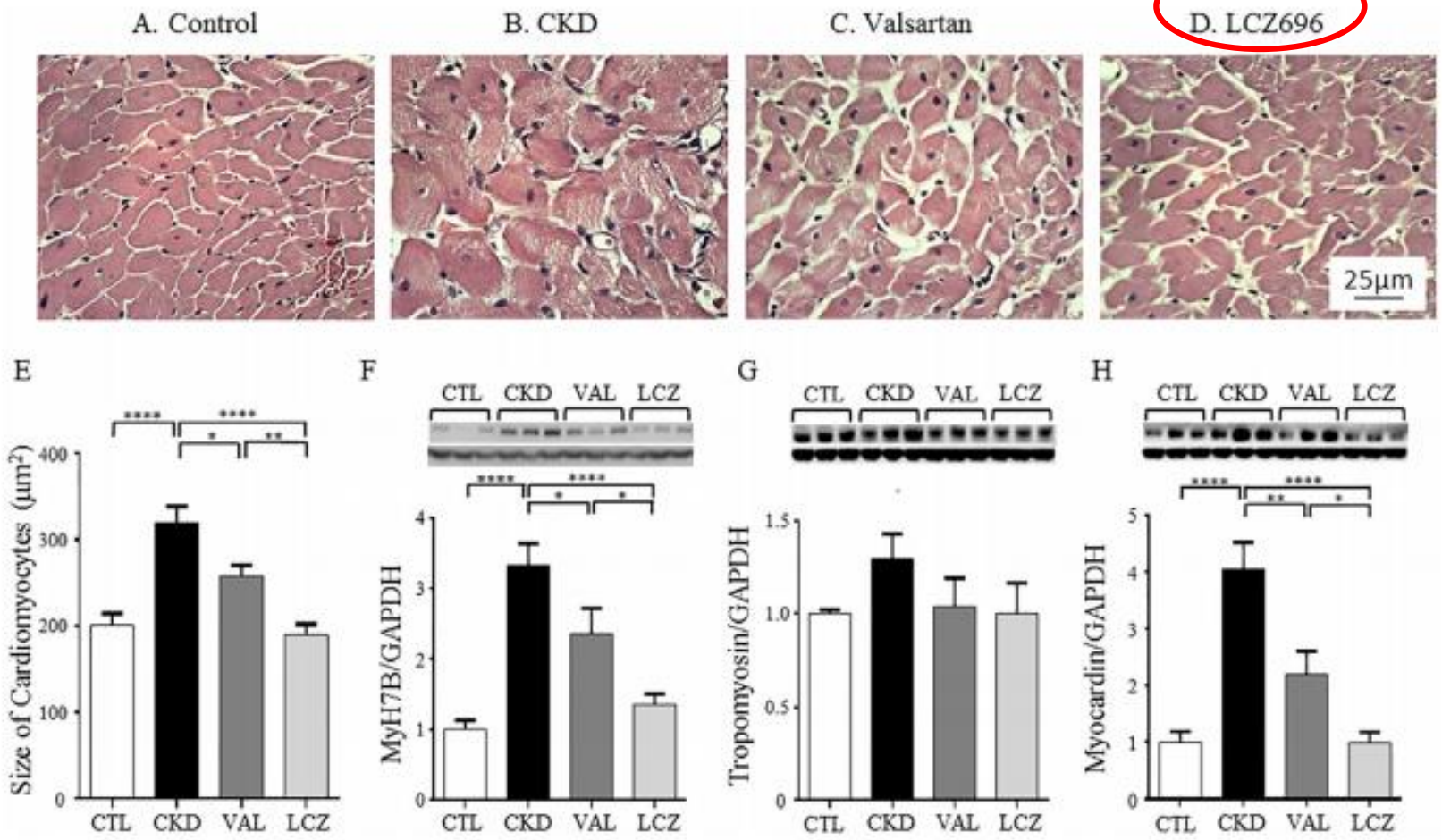
Irvine, and California; and Xi'an, People's Republic of China



American Heart Journal 199 (2018) 130–136

Contents lists available at ScienceDirect

American Heart Journal

Trial Design

Rationale and methods of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF)

James L. Januzzi, MD, FACC, FESC [a,b,*], Javed Butler, MD [c], Emmanuel Fombu, MD [d], Alan Maisel, MD [e], Kevin McCague, MA [d], Ileana L. Piña, MD [f], Margaret F. Prescott, PhD [d], Jerome B. Riebman, MD [d], Scott Solomon, MD [g]

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Ruolo del MMG?

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PRESCRIZIONE DI SACUBITRIL/VALSARTAN

INDICAZIONI
Paziente ambulatoriale in terapia medica ottimizzata (beta-bloccante, ACEI o ARBI, MRA)
Pazienti sintomatici per dispnea da sforzo (NYHA II-->IV)
Frazione di eizione ≤ 35%
Aumento di NT-proBNP e BNP

CONTROINDICAZIONI
Pressione Arteriosa < 100mmHg
Insufficienza epatica severa, colestasi, cirrosi biliare
Iperpotassiemia > 5.4 mEq/L
Angioedema
Secondo e terzo trimestre di gravidanza

Usare con cautela
NYHA IV
Insufficienza epatica moderata
Stenosi dell'arteria renale
Insufficienza renale severa (eGFR <30)

INTRODUZIONE DI SACUBITRIL/VALSARTAN
STOP ACE-I , iniziare SAcubitril/Valsartan solo dopo 36ore
STOP Sartano: sostituzione diretta

TITOLAZIONE
OGNI 2-4 SETTIMANE FINO AL DOSAGGIO MASSIMO (97/103mg x2) TOLLERATO

RICORDA CHE NON E' NECESSARIO VARIARE IL PIANO TERAPEUTICO QUANDO SI AUMENTA IL DOSAGGIO
Consigli pratici (in caso di ipotensione, PA< 100mmHg)
Prima di sospendere il Sacubitril/Valsartan:
Riduzione dosaggio del diuretico (dimezza o sospendi)
Sospensione dei farmaci antiipertensivi

MONITORAGGIO
Controllo ogni 6 mesi (creatinina,ast,alt, sodio, potassio, NT-proBNP)

Position paper ANMCO sull'utilizzo della terapia con sacubitril/valsartan nel paziente con scompenso cardiaco

Giuseppe Di Tano[1] (Coordinatore), Andrea Di Lenarda[2] (Coordinatore), Domenico Gabrielli[3] (Coordinatore), Nadia Aspromonte[4], Renata De Maria[5], Maria Frigerio[6], Massimo Iacoviello[7], Andrea Mortara[8], Adriano Murrone[9], Federico Nardi[10], Fabrizio Oliva[6], Roberto Pontremoli[11], Marino Scherillo[12], Michele Senni[13], Stefano Urbinati[14], Michele Massimo Gulizia[15] (Coordinatore)

Ruolo del MMG

- **Eleggibile a trattamento < 20% dei pazienti con SC**
- **Stimolo per rivalutazione terapia in corso**
- **Consulenza cardiologica per rivalutazione in ACE/ARB**
- **Conoscenza profilo clinico e sociale per aderenza terapeutica**
- **Formazione locale: confronto MMG e cardiologi**
- **Dinamiche comunicative**

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Grazie per l'attenzione!