AZIENDA OSPEDALIERA SAN PIO
BENEVENTO
UOC CARDIOLOGIA INTERVENTISTICA
Unità di Terapia Intensiva Cardiologica
Direttore: Dr. Marino SCHERILLO

AORN "SAN PIO" di Benevento

Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione

Unità Operativa Complessa

Cardiologia Interventistica e UTIC

Centro HUB I Livello – Centrale Cardiologica Regionale

Direttore : Dr. Marino Scherillo

Trattamento Precoce Con ARNI Nel Paziente Con Scompenso Cardiaco

Il Problema

Antonio Parente

Campus Cuore SUMMIT
Napoli, 2 ottobre 2021

Tweet 1

ARNI in CHF:

(r)EVOLUTION IS NOW

2014

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

PARADIGM-HF: dimostrata superiorità di Sacubitril/Valsartan vs Enalapril nel migliorare la prognosi dell' HFrEF

20% RRR morte CV o prima ospedalizzazione per HF [1]

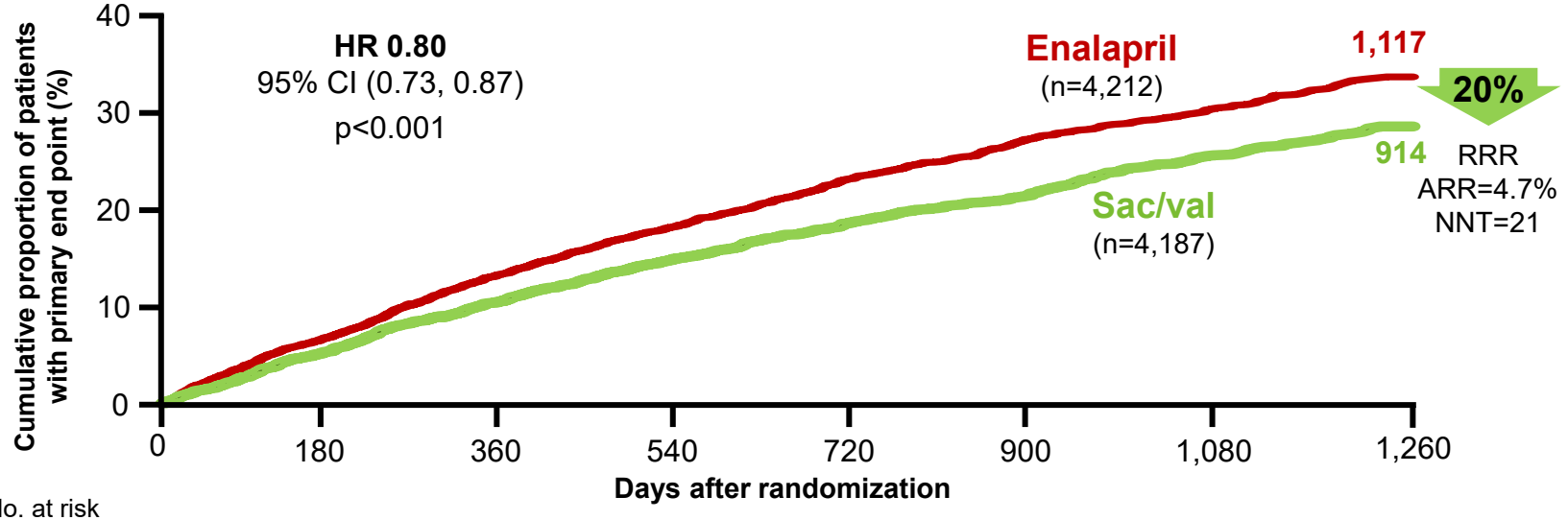
20% RRR morte cardiaca improvvisa[2]

16% RRR di morte per tutte le cause[1]

23% RRR di ricoveri per HF[3]

18% RRR di permanenza in terapia intensiva[3]

PARADIGM-HF Riduzione di morte CV o prima ospedalizzazione per HF[1]



No. at risk

Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236
Sac/val	4,187	3,922	3,663	3,018	2,257	1,544	896	249

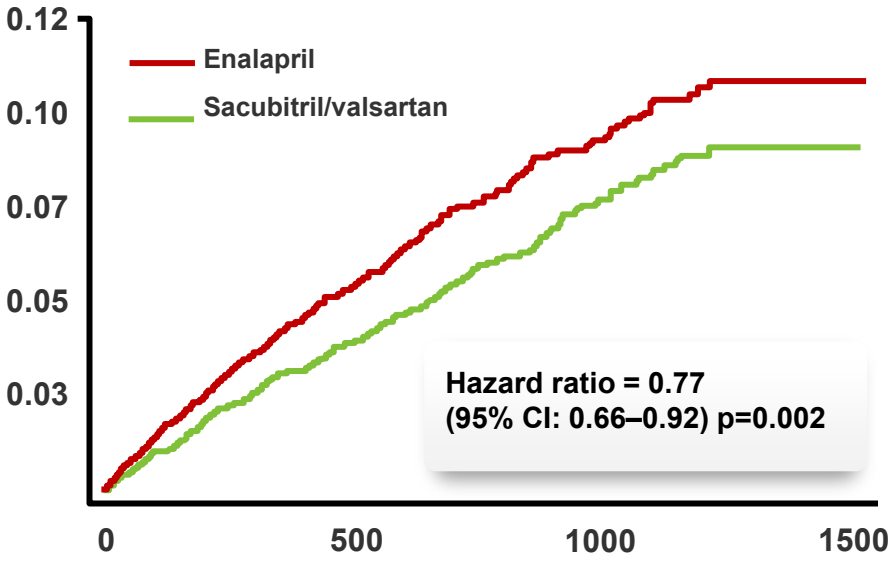
ACEi, angiotensin converting enzyme inhibitor; ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFrEF, HF with reduced ejection fraction; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction; QoL, quality of life

1. McMurray et al. N Engl J Med 2014;371(11):993-1004; 2. Desai et al. Eur Heart J 2015;36(30):1990-7; 3. Packer et al. Circulation 2015;131(1):54-61

La superiorità di Sacubitril/Valsartan vs Enalapril nel ridurre la Morte Cardiaca Improvvisa e l'Arresto Cardiaco è indipendente dalla presenza di ICD

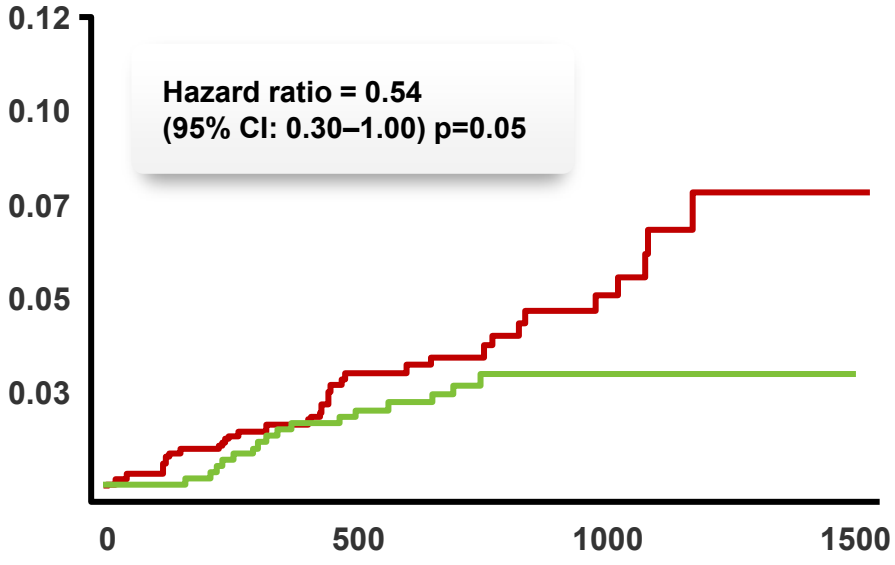
RRR - 23%

Morte Improvvisa o Arresto Cardiaco in pazienti senza ICD



RRR - 56%

Morte Improvvisa o Arresto Cardiaco in pazienti con ICD

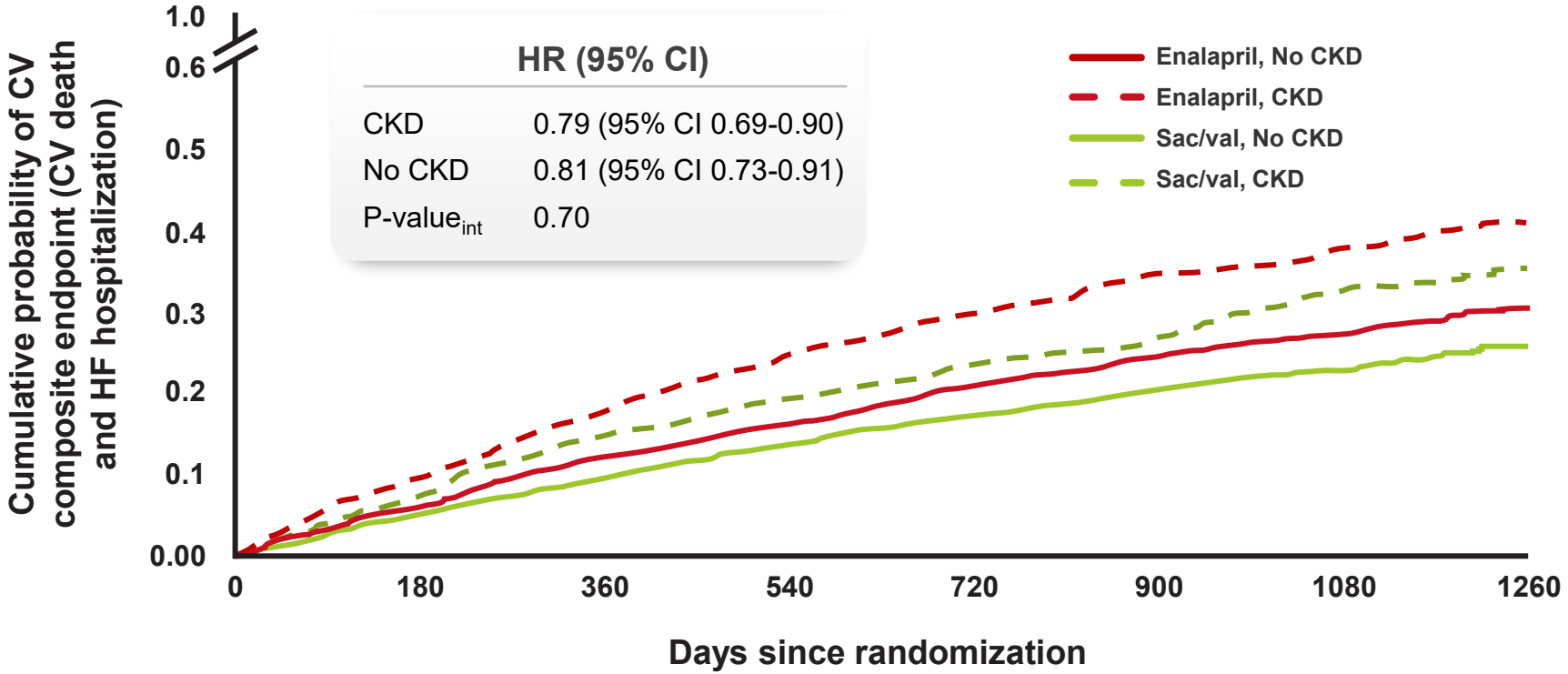


P-interazione in termini di efficacia di sacubitril/valsartan e ICD = 0,21

Novartis data on file

Sacubitril/Valsartan è significativamente superiore ad Enalapril indipendentemente dalla presenza di CKD

RRR - 21% CKD
RRR - 19% No CKD



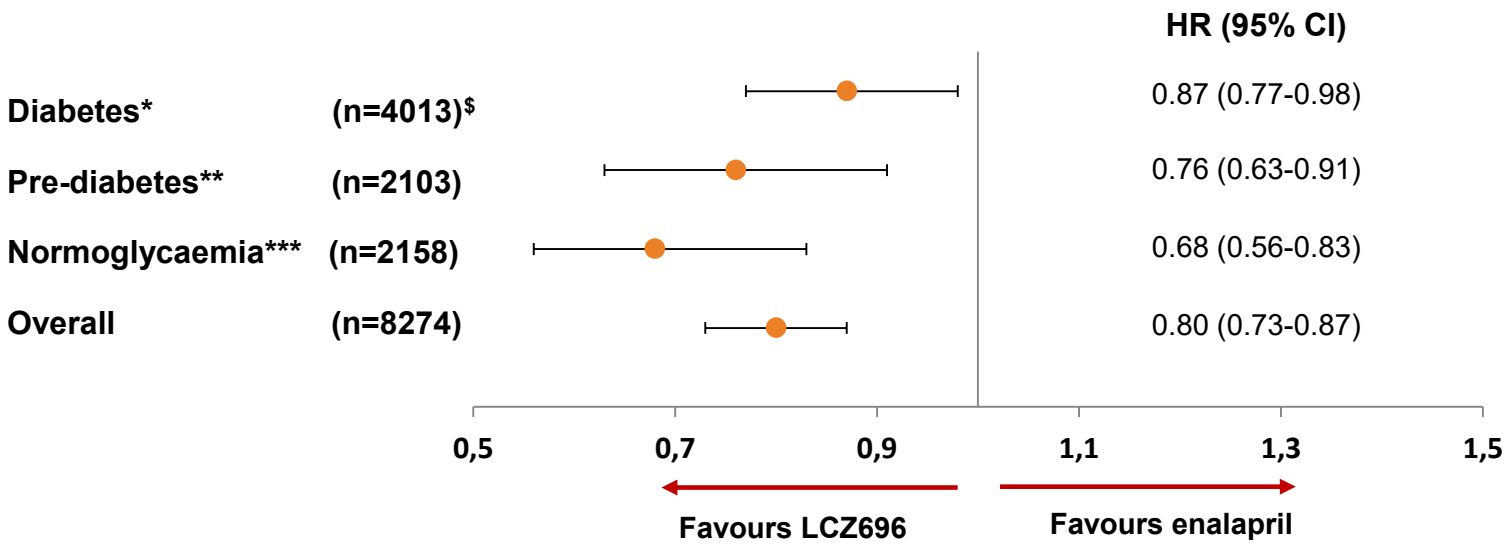
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; HR, hazard ratio; int, interaction; sac/val, sacubitril/valsartan

Damman et al., JACC Heart Fail. 2018 DOI: 10.1016/j.jchf.2018.02.004

Sacubitril/Valsartan è significativamente superiore ad Enalapril, indipendentemente dallo Stato Glicemico

Sia il diabete che il pre-diabete sono risultati associati ad aumentato rischio di mortalità CV o di ospedalizzazione per HF, rispetto ai pazienti non diabetici con HbA_{1c} <6,0%

Effetto del trattamento sac/val sull'endpoint composito primario in funzione dello stato glicemico#



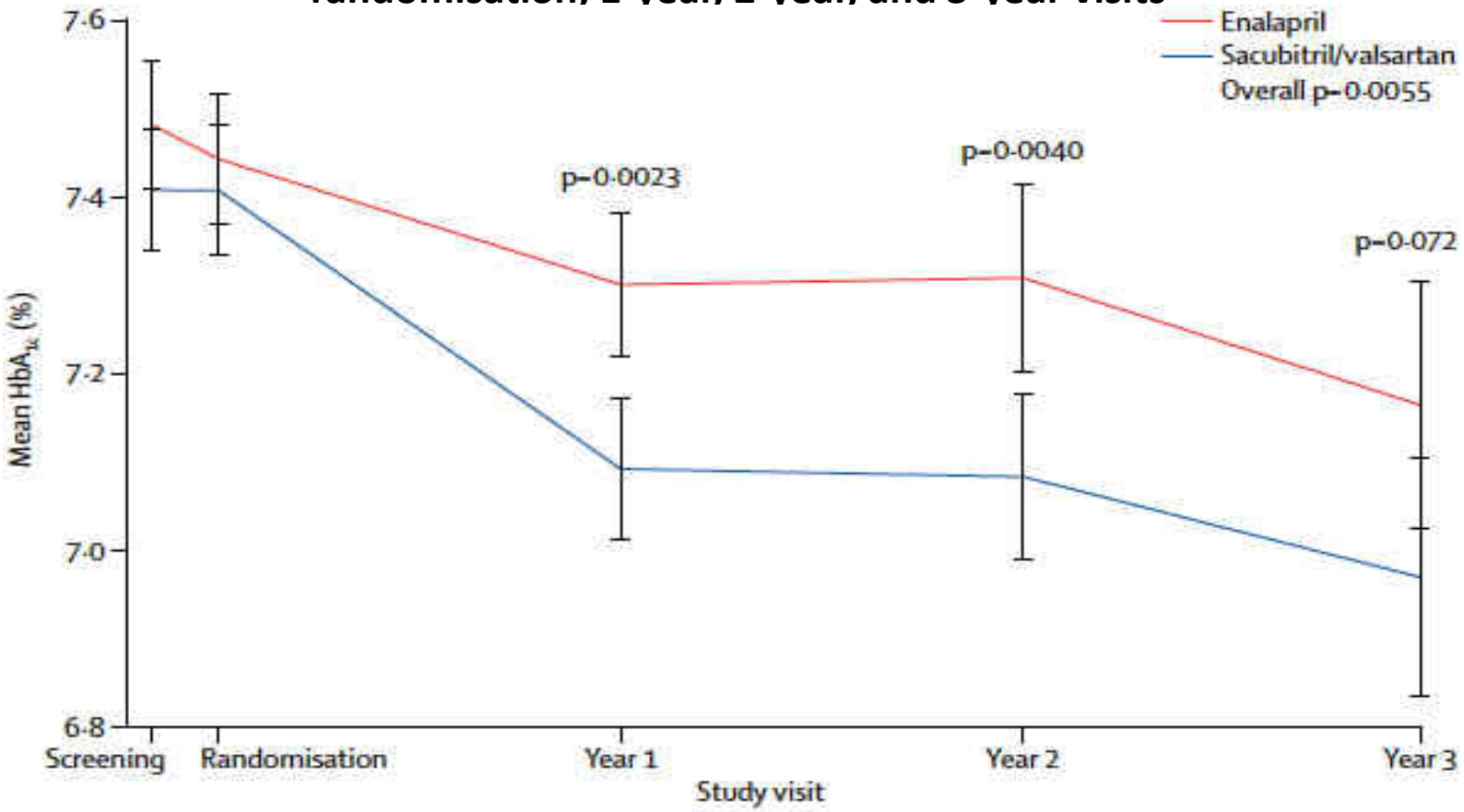
#The primary composite endpoint of CV mortality or HF hospitalisation. *A history of diabetes or HbA1c≥6.5% ; **No history of diabetes and HbA1c=6.0-6.4% ; ***No history of diabetes and HbA1c<6.0%. $Includes both patients with a history of diabetes (n=2907) and patients with undiagnosed diabetes (n=1106)

CI=confidence interval; CV=cardiovascular; HbA1c=hemoglobin A1c; HF=heart failure; HF-REF=heart failure with reduced ejection fraction; HR=hazard ratio

Kristensen et al. Eur Heart J 2015; 36(Suppl):875(P5031)

Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial

Changes in mean HbA1c and confidence intervals by treatment group at screening, randomisation, 1-year, 2-year, and 3-year visits

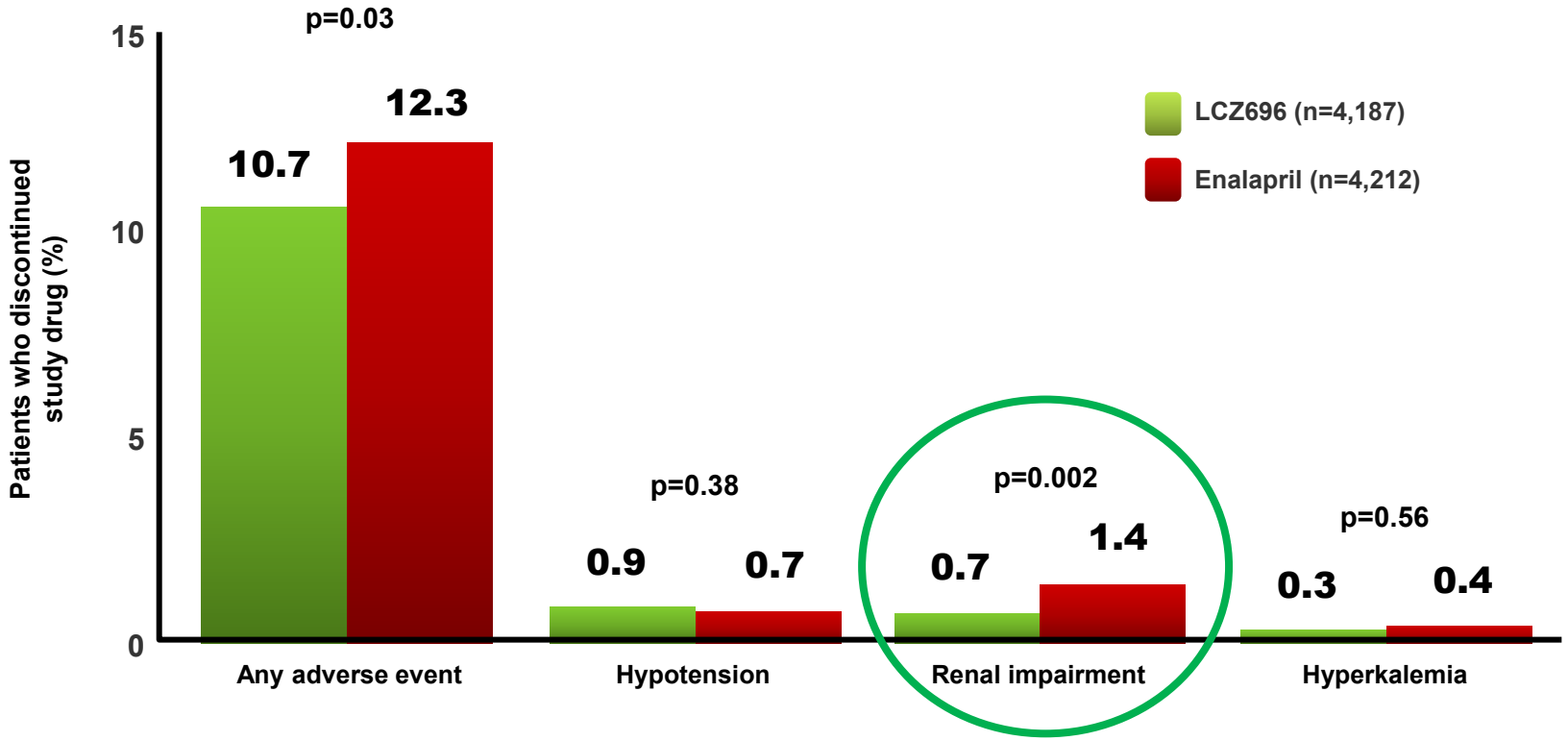


Interpretation Patients with diabetes and HFrEF enrolled in PARADIGM-HF who received sacubitril/valsartan had a greater long-term reduction in HbA_{1c} than those receiving enalapril. These data suggest that sacubitril/valsartan might enhance glycaemic control in patients with diabetes and HFrEF.

Seferovic et al. *Lancet Diabetes Endocrinol* 2017

Meno pazienti con Sacubitril/Valsartan sviluppano Eventi Avversi rispetto ad Enalapril

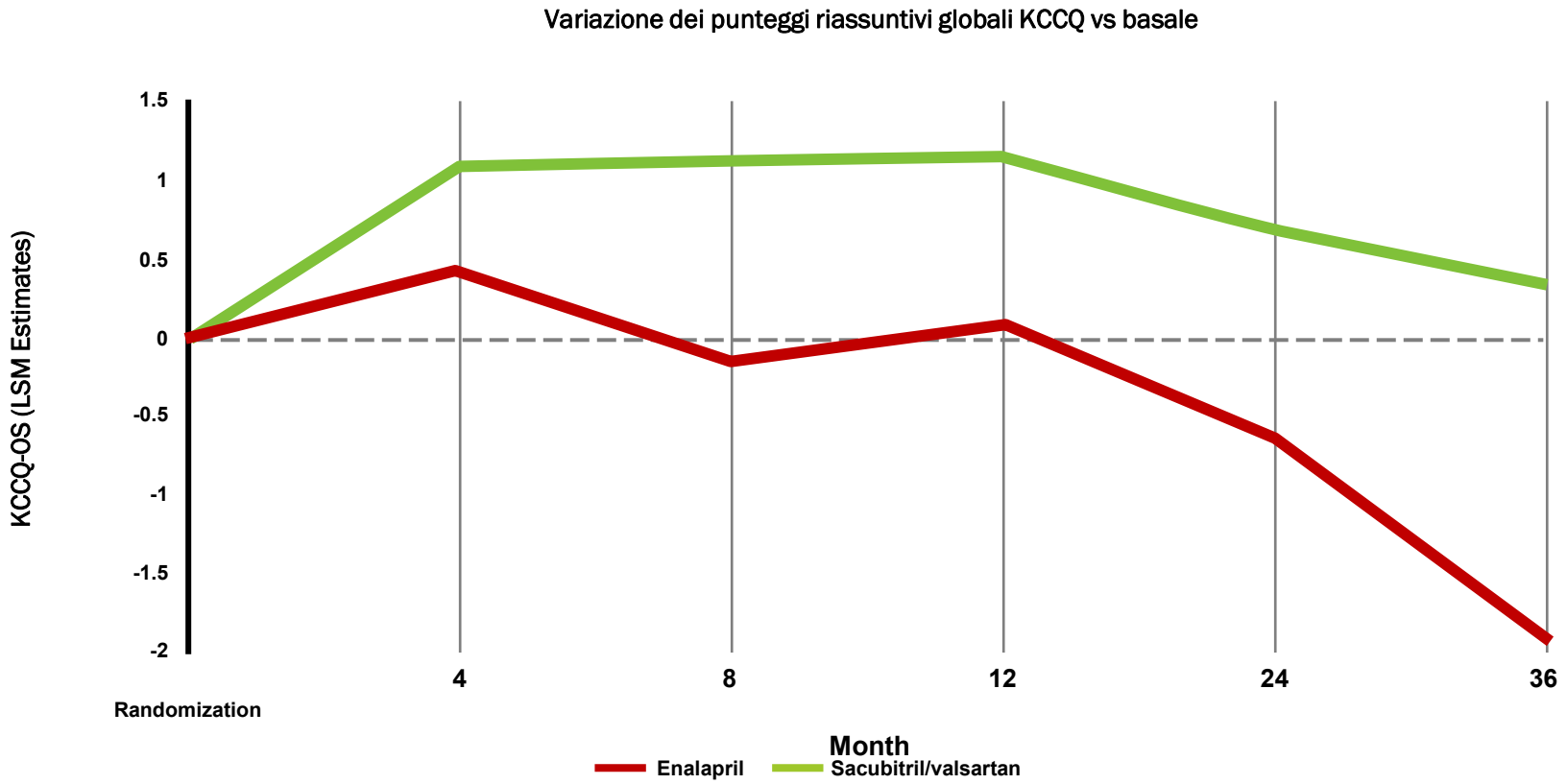
Un numero inferiore di pazienti trattati con Sac-Val rispetto ai pazienti trattati con enalapril ha interrotto lo studio a causa degli eventi avversi (10,7% vs 12,3%; p=0,03)



McMurray et al. N Engl J Med 2014;371:993–1004

Sacubitril/Valsartan determina un miglioramento persistente della Qualità della Vita dai 4 ai 36 mesi, vs Enalapril

il KCCQ valuta l'attività fisica, sintomi, attività sociale, autonomia, apprendimento e QoL



KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-OS, KCCQ-Overall Summary; LSM, least squares mean; SE, standard error

Lewis EF et al. Circ Heart Fail 2017;10(8):e003430. doi: 10.1161/CIRCHEARTFAILURE.116.003430

ESC European Society of Cardiology
European Heart Journal (2021) 42, 3599 – 3726
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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

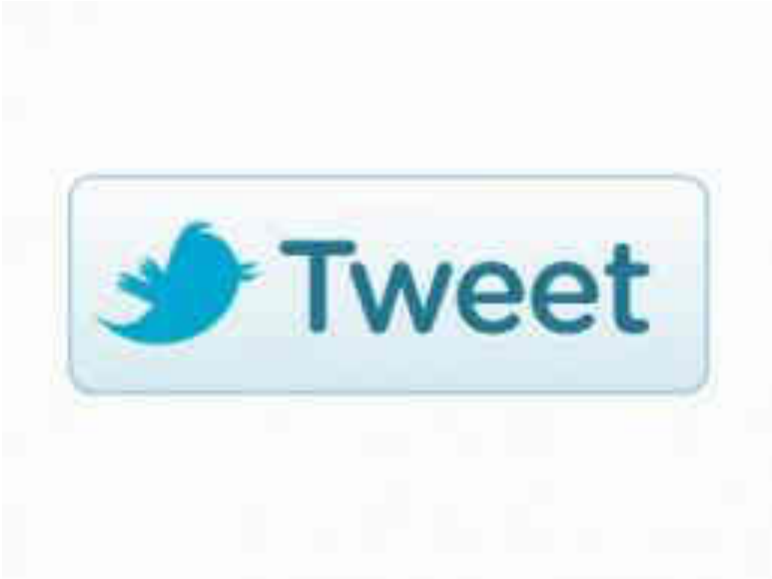
Management of patients with HFrEF

- ACE-I/ARNI[a]
- Beta-blocker
- MRA
- Dapagliflozin/Empagliflozin
- Loop diuretic for fluid retention

(Class I)

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

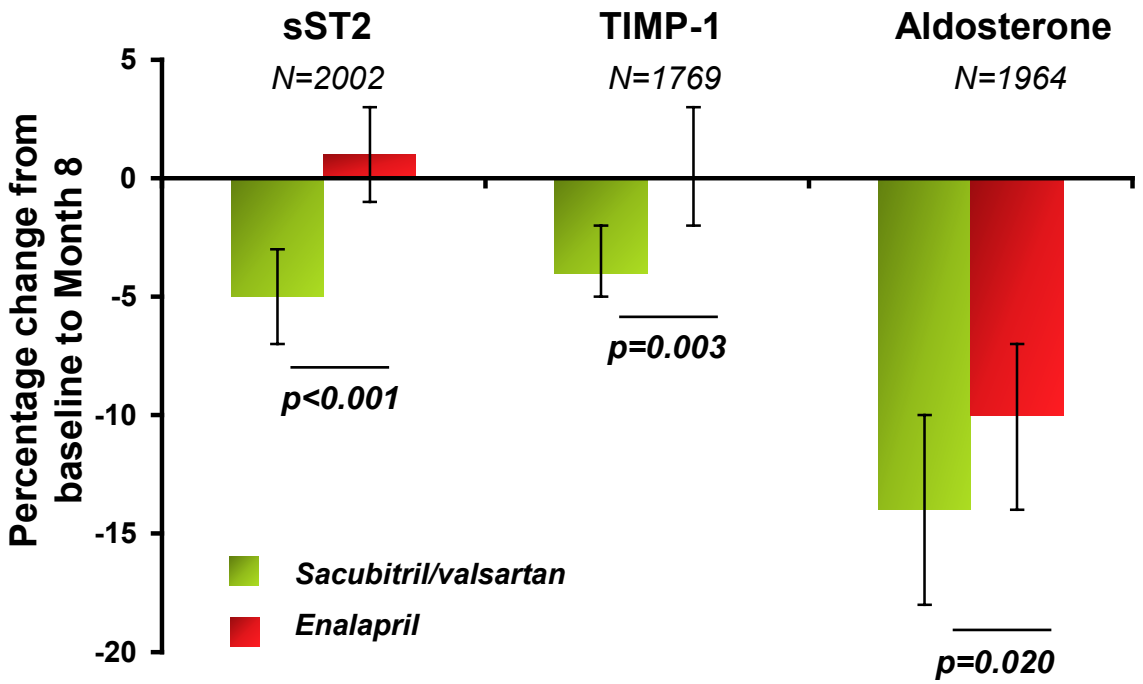


2

ARNI ha un

EFFETTO BIOLOGICO

Sacubitril/Valsartan riduce i Biomarkers di Fibrosi Cardiaca: sST2, TIMP-1 ed Aldosterone

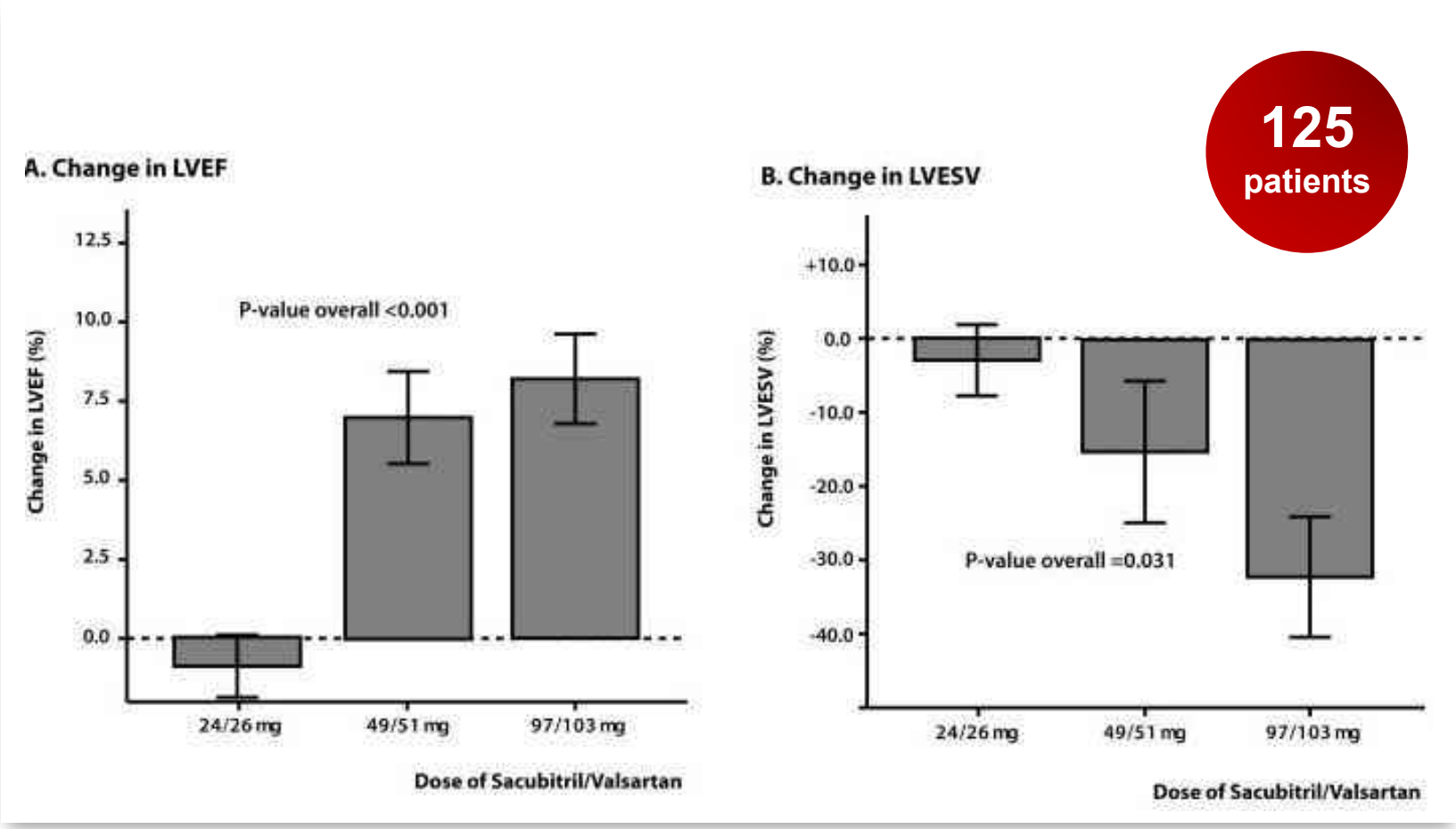


- Sacubitril/valsartan reduced the levels of sST2, TIMP-1, and aldosterone, known biomarkers of ECM homeostasis and myocardial fibrosis, which are shown to be associated with CV death and HF hospitalization in this sub-analysis of PARADIGM-HF.
- Compared with enalapril, sacubitril/valsartan significantly reduced sST2 (% change: -5% versus +1%; p<0.001) and TIMP-1 levels (-4% versus 0%; p=0.003) from baseline to Month 8 in patients with HFrEF.

CV, cardiovascular; ECM, extracellular matrix; HF, heart failure; HFrEF, HF with reduced ejection fraction; sST2, soluble ST2; TIMP-1, tissue inhibitor of matrix metalloproteinase 1

O'Meara et al. Eur Heart J. 2016;37 (Abstract Supplement):1022 Presentation FP Number 5126 at ESC2016, Rome

Sacubitril/Valsartan
promuove il Rimodellamento Cardiaco Inverso
in pazienti con HFrEF, in un f-up medio di 4 mesi



Martens et al; Cardiovascular Therapeutics. 2018;36:e12435. wileyonlinelibrary.com/journal/cdr https://doi.org/10.1111/1755-5922.12435

Lo studio PROVE-HF

PROVE-HF

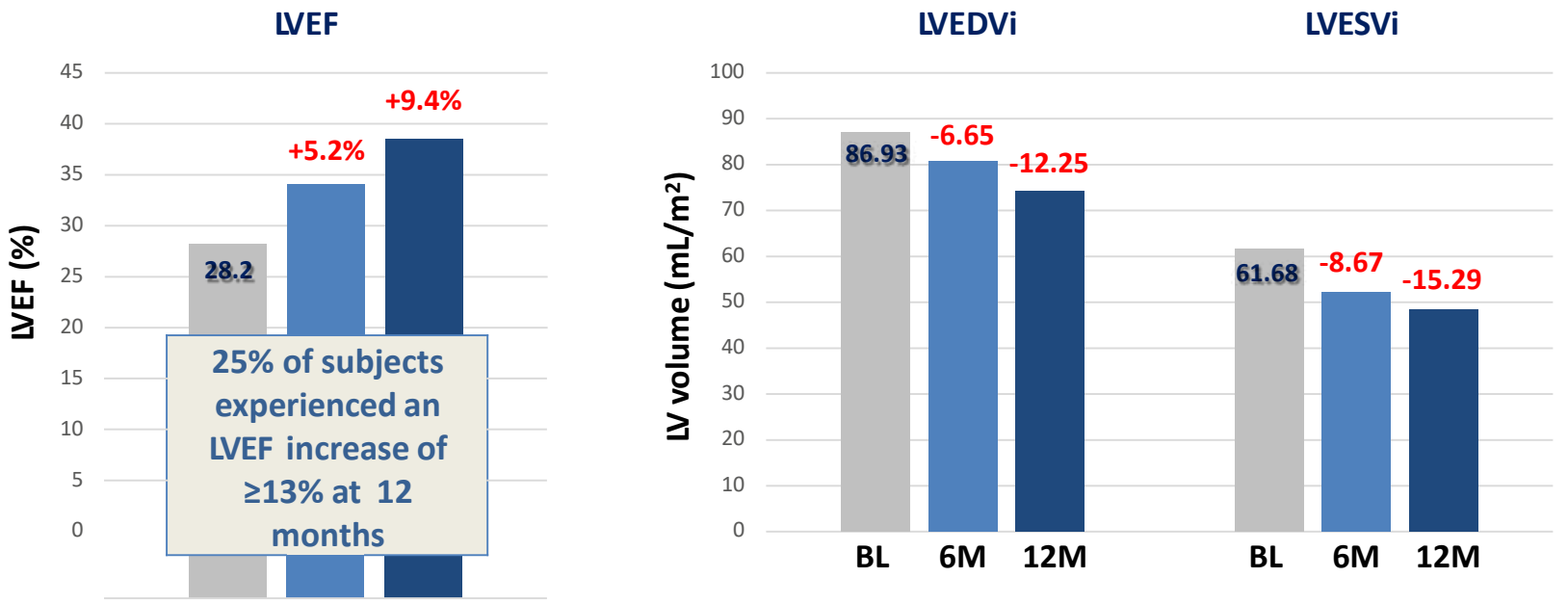
Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure *(PROVE-HF; NCT02887183)*

James L. Januzzi MD[1,2], Margaret F. Prescott PhD[3], Javed Butler MD MPH MBA[4], G. Michael Felker MD MHS[5], Alan S. Maisel MD[6], Kevin McCague MA[3], Alexander Camacho PhD[1], Ileana L. Piña MD MPH[7], Ricardo A. Rocha MD[3], Amil M. Shah MD MPH[8], Kristin M. Williamson PharmD[3], and Scott D. Solomon MD[8] on behalf of the PROVE-HF Investigators

[1]Massachusetts General Hospital, [2]Baim Institute for Clinical Research, Boston, MA, USA; [3]Novartis Pharmaceuticals, East Hanover, NJ, USA; [4]University of Mississippi Medical Center, Jackson, MS, USA; [5]Duke University Medical Center and Duke Clinical Research Institute, Durham, NC, USA; [6]University of California, San Diego School of Medicine, San Diego, CA, USA; [7]Detroit Medical Center, Detroit, MI, USA; [8]Brigham and Women's Hospital, Boston, MA, USA

Effetto di S\V sul Rimodellamento Cardiaco Inverso (1)

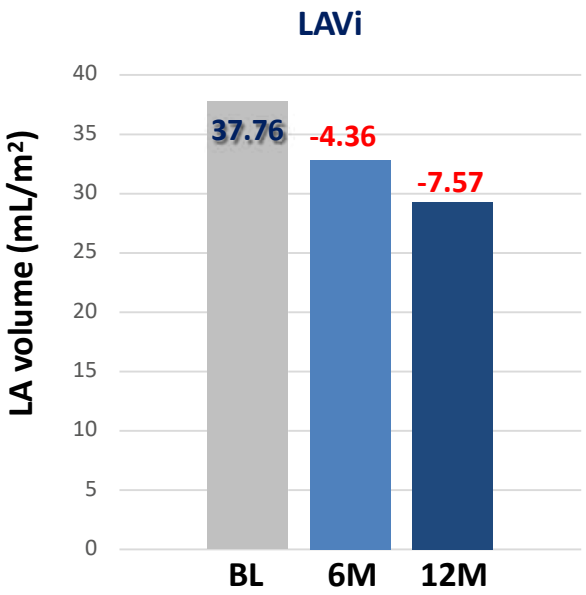
Baseline to 12 months: all P <.001

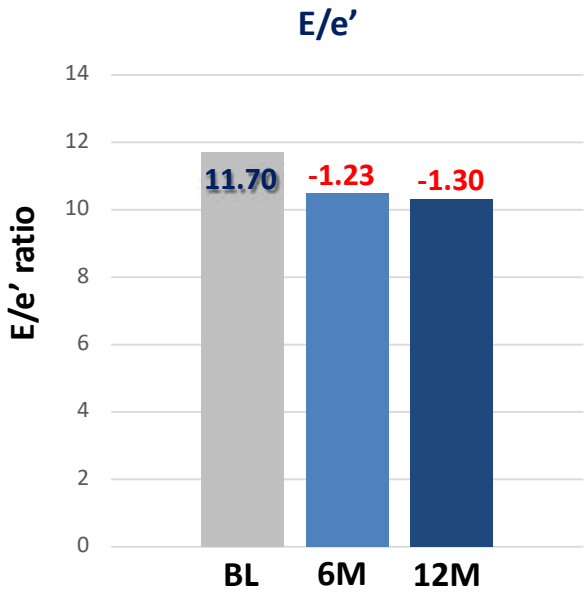


BL, baseline; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index

Effetto di S\V sul Rimodellamento Cardiaco Inverso (2)

Baseline to 12 months: all P <.001

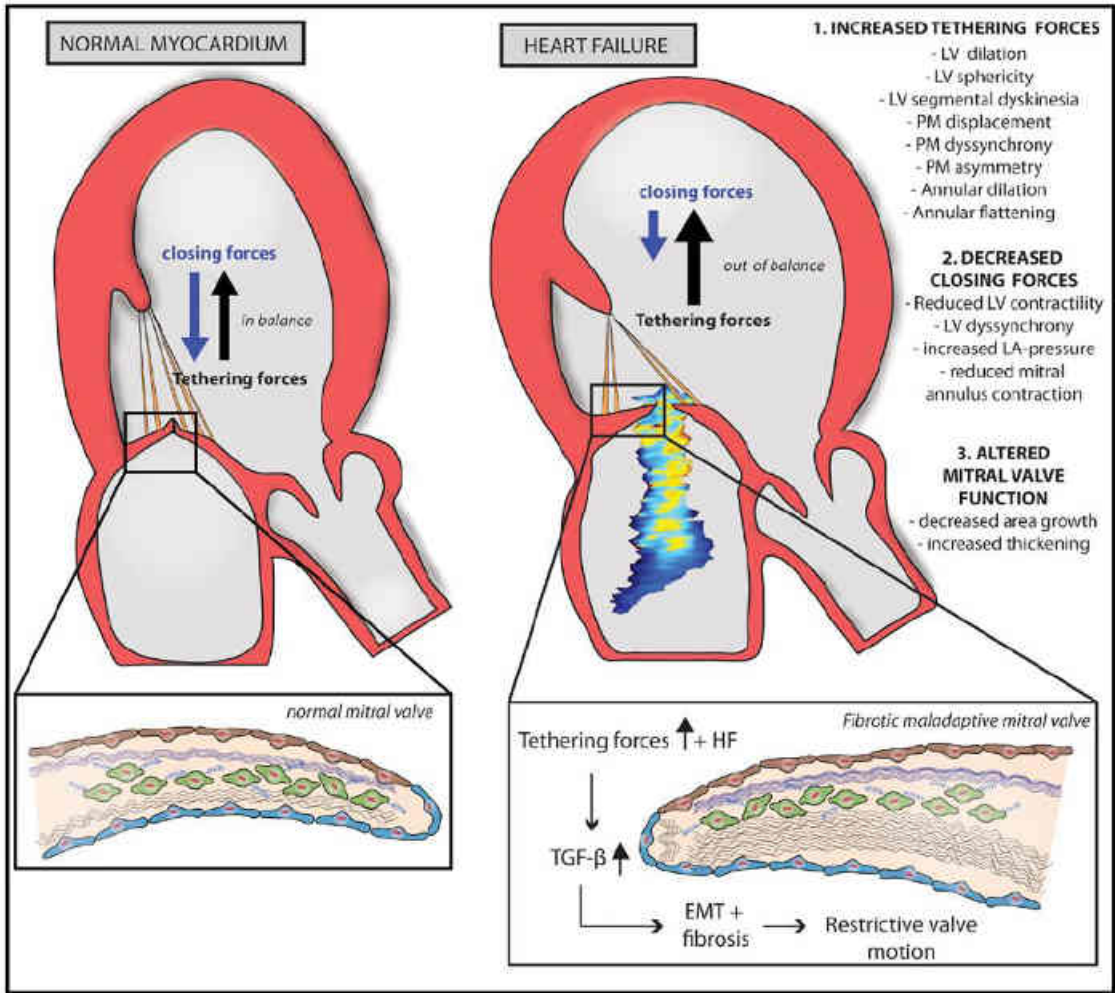




LVMi fell from 124.77 to 107.82 g/m²
(mean -16.00 g/m²; P <.001)

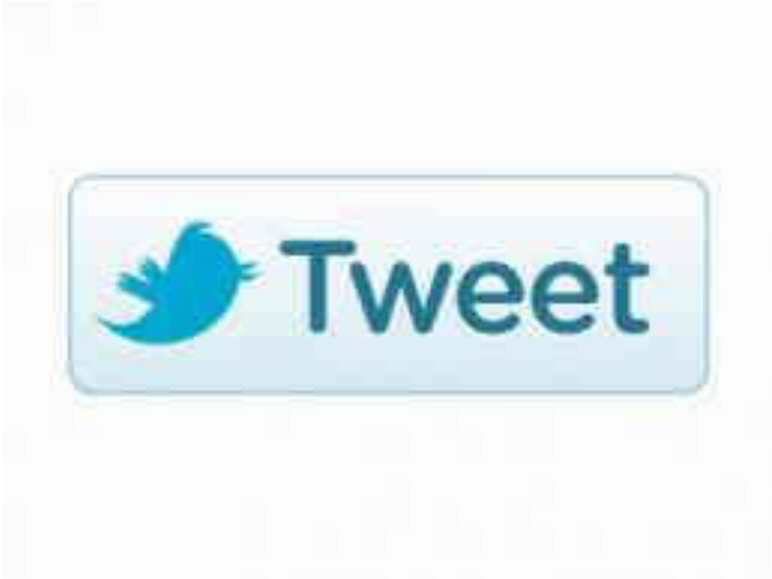
BL, baseline; mL, milliliter; LA, left atrial; LAVi, left atrial volume index; E/e', ratio of early diastolic filling velocity and early diastolic mitral annular velocity; LVMi, left ventricular mass index.

L'ottimizzazione del trattamento con Sacubitril/Valsartan migliora il Deficit Funzionale Mitralico



perhaps indicate that patient selection (severe MR without advanced LV dilation) is important (see Figure B).[9] Indeed, once the LV has remodeled significantly, it is well established that the presence of severe MR loses its prognostic relation with poor outcome.[15] As such, percutaneous interventions targeting secondary MR in that setting might be futile in reverting the progressed disease, thereby underscoring the importance of adequate follow-up of patients under uptitration of guideline-directed medical therapy and assessment of eligibility for additional percutaneous interventions. Clearly, further analysis of the COAPT and MITRA-FR trials and the finalization of the RESHAPE-HF2 trial (A Clinical Evaluation of the Safety and Effectivieness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation; NCT02444338) will help to understand the precise place of percutaneous techniques to reduce the degree of MR and improve clinical outcome. However, for now, it is clear that, before contemplating these percutaneous interventions, guideline-directed medical therapy should always be optimized first. This intrinsically includes the prescription of the class I lifesaving therapy sacubitril/valsartan.

D. Kang- S. Park Circulation. 2019;139:1354–1365. DOI: 10.1161/CIRCULATIONAHA.118.037077



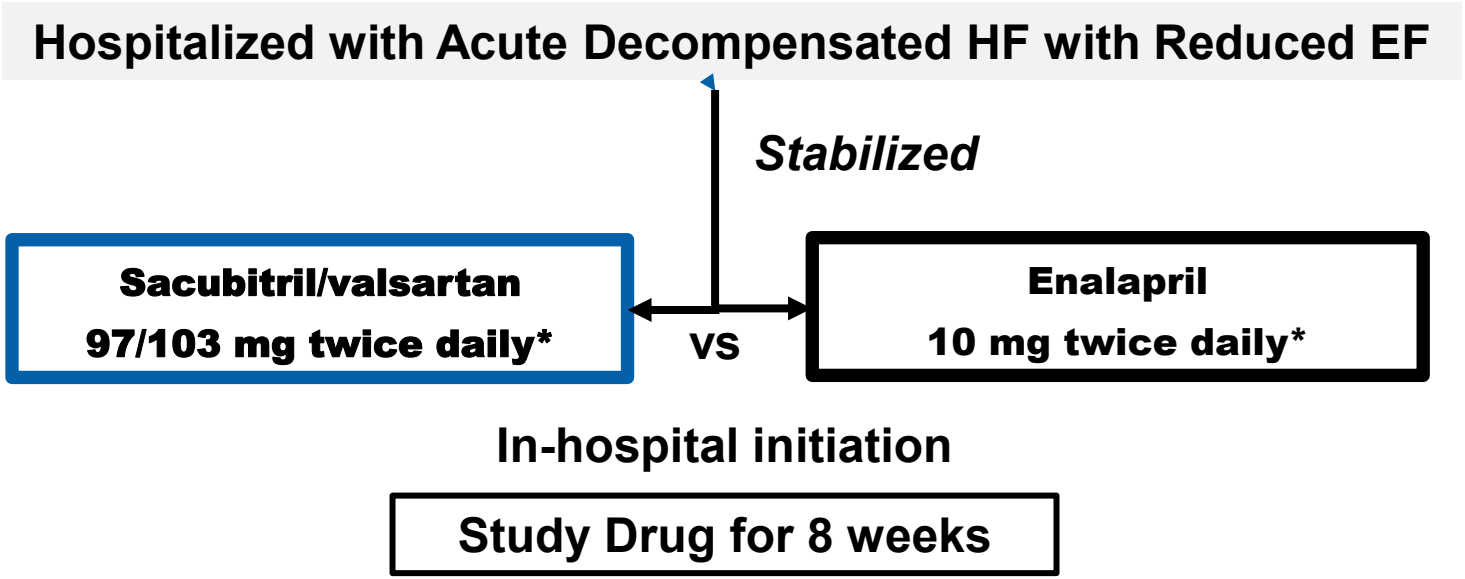
3

ARNI nello

SC Acuto Stabilizzato:

……Si può fare

PIONEER-HF : disegno dello studio



- Evaluate biomarker surrogates of efficacy
- Evaluate safety and tolerability
- Explore clinical outcomes

*Target Dose HF, Heart Failure. EF, Ejection Fraction

Velazquez E J et al Am Heart J. 2018 Apr;198:145-151

PIONEER-HF Study

Key Entry Criteria

- **Hospitalized for Acute Decompensated Heart Failure (ADHF)**
- **LVEF ≤40% within the last 6 months**
- **NT-proBNP ≥1600pg/mL or BNP ≥400 pg/mL***
- **Stabilized while hospitalized**
  - **SBP ≥100 mmHg in prior 6h; no symptomatic hypotension**
  - **No increase in IV diuretics in prior 6h**
  - **No IV vasodilators in prior 6h**
  - **No IV inotropes in prior 24h**

*At screening
A complete list of inclusion and exclusion criteria has been previously published at Velazquez et al. Am Heart J 198 (2018) 145-151
LVEF, Left Ventricular Ejection Fraction. NT-proBNP N-terminal pro–Brain Natriuretic Peptide. BNP, Brain Natriuretic Peptide. SBP, Systolic Blood Pressure. IV, Intravenous

Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018

PIONEER-HF

*Study Endpoints**

Primary endpoint:

- **Time-averaged proportional change in NT-proBNP from baseline at 4 and 8 weeks**

Safety

- **Worsening renal function**
- **Hyperkalemia**
- **Symptomatic hypotension**
- **Angioedema**

Exploratory Clinical Outcomes

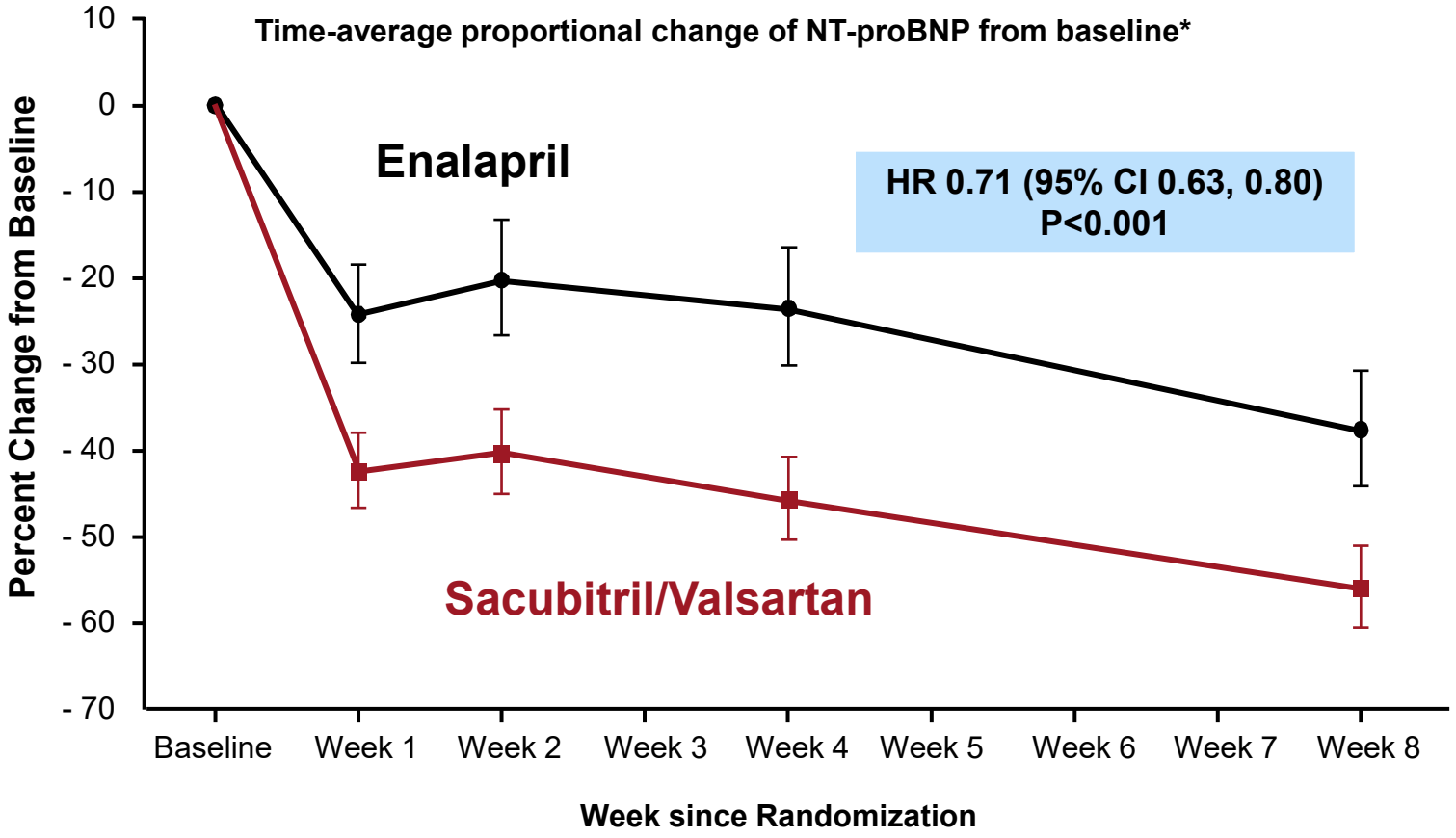
- **Serious Clinical Composite: Death, Hospitalization for HF, LVAD or listing for cardiac transplant**

*A more complete list of PIONEER study endpoints has been previously published at Velazquez et al. Am Heart J 198 (2018) 145-151
NT-proBNP N-terminal pro–Brain Natriuretic Peptide. HF, Heart Failure. LVAD, Left Ventricular Assist Device. HF, Heart Failure
Data on File: PIONEER-HF Protocol, Novartis Pharmaceutical Corp; October 2018

Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018

PIONEER-HF : risultati

Sac-Val è superiore ad enalapril nel ridurre i livelli di NT-proBNP e questa riduzione è evidente già dopo la prima settimana

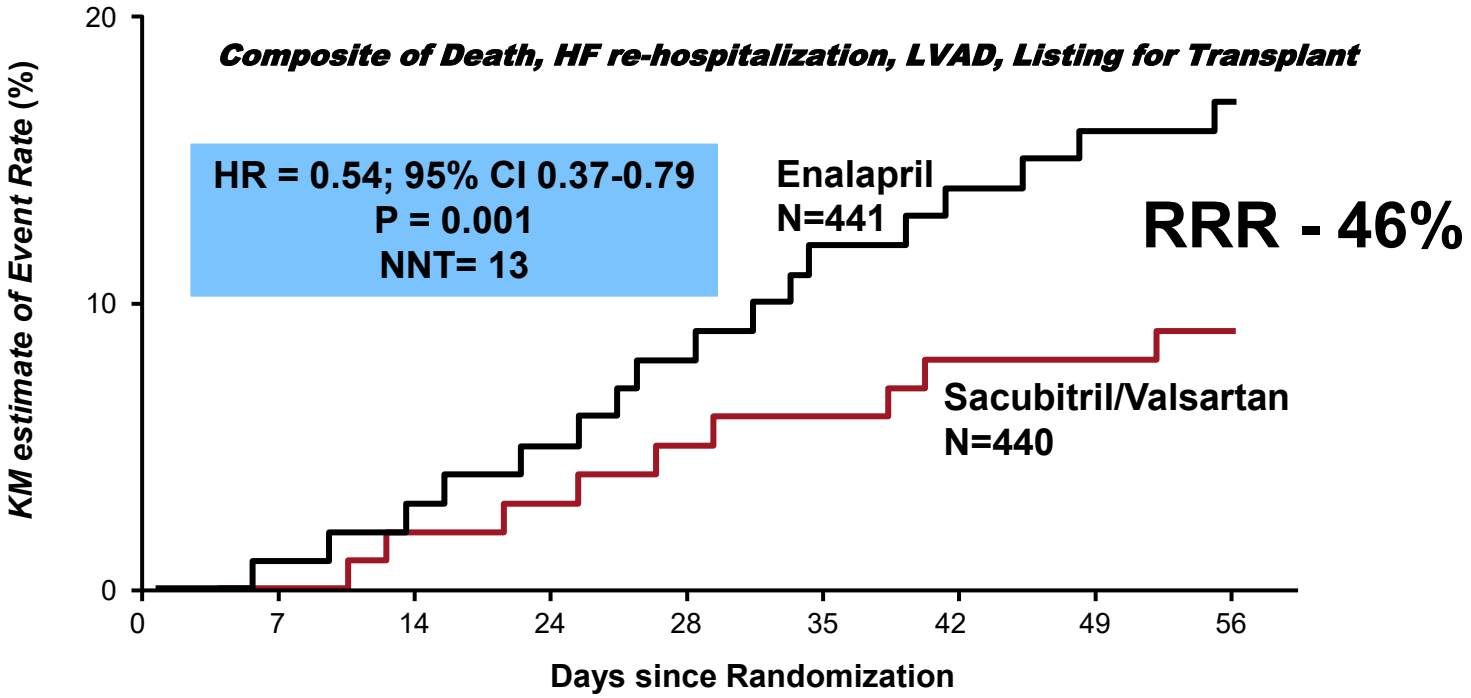


*Percentage (%) change from baseline to mean of weeks 4 and 8

Velazquez E J et al Am Heart J. 2018 Apr;198:145-151

PIONEER-HF

Exploratory Serious Clinical Composite Endpoint



- Exploratory Serious Clinical Composite endpoint was driven by the reduction of risk of death and HF re-hospitalizations

Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018

PIONEER-HF

Additional Clinical Endpoints

	Sacubitril/ Valsartan (n=440)	Enalapril (n=441)	HR	P-value
Serious Composite, %	**9.3**	**16.8**	**0.54**	**0.001**
Death, %	**2.3**	**3.4**	**0.66**	**0.311**
Re-hospitalization for HF, %	**8.0**	**13.8**	**0.56**	**0.005**
Requirement of LVAD, %	**0.2**	**0.2**	**0.99**	**0.999**
Cardiac Transplant, %	**0**	**0**	**-**	**-**

- Exploratory Serious Clinical Composite endpoint was driven by the reduction of risk of death and HF

Data on File: PIONEER-HF Protocol, Novartis Pharmaceutical Corp; October 2018

PIONEER-HF

Safety

Safety Events (%)	Sacubitril/ Valsartan (n=440) (%)	Enalapril (n=441) (%)	RR (95% CI)
Worsening renal function[a]	13.6	14.7	0.93 (0.67-1.28)
Hyperkalemia	11.6	9.3	1.25 (0.84-1.84)
Symptomatic hypotension	15.0	12.7	1.18 (0.85-1.64)
Angioedema events[b]	0.2	1.4	0.17 (0.02-1.38)

[a] SCr ≥0.5 with simultaneous eGFR reduction of ≥25%
[b] Positively adjudicated angioedema cases.
RR, Relative risk

Data on File: PIONEER-HF Protocol, Novartis Pharmaceutical Corp; October 2018

ESC European Society of Cardiology
European Heart Journal (2021) 42, 3599 – 3726
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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

ARNI in AHF

Studies have shown that such optimization of medical treatment is associated with a lower risk of 30-day readmission, although prospective randomized trials have not been performed, to date.[103,467,513] Retrospective analyses show that discontinuation or dose reduction of beta-blocker therapy during an AHF hospitalization is associated with worse outcomes.[514] Initiation of ARNI in recently hospitalized stable patients with HFrEF, including those who are ACE-I/ARB naïve, is safe and may be considered in this setting.[106,107] Safety and better outcome have also been recently shown in a prospective randomized trial with sotagliflozin in diabetic patients hospitalized for HF, irrespective of their LVEF.[136]

Tweet

4

ARNI in HF-pEF & HF-mrEF: .....Si può fare

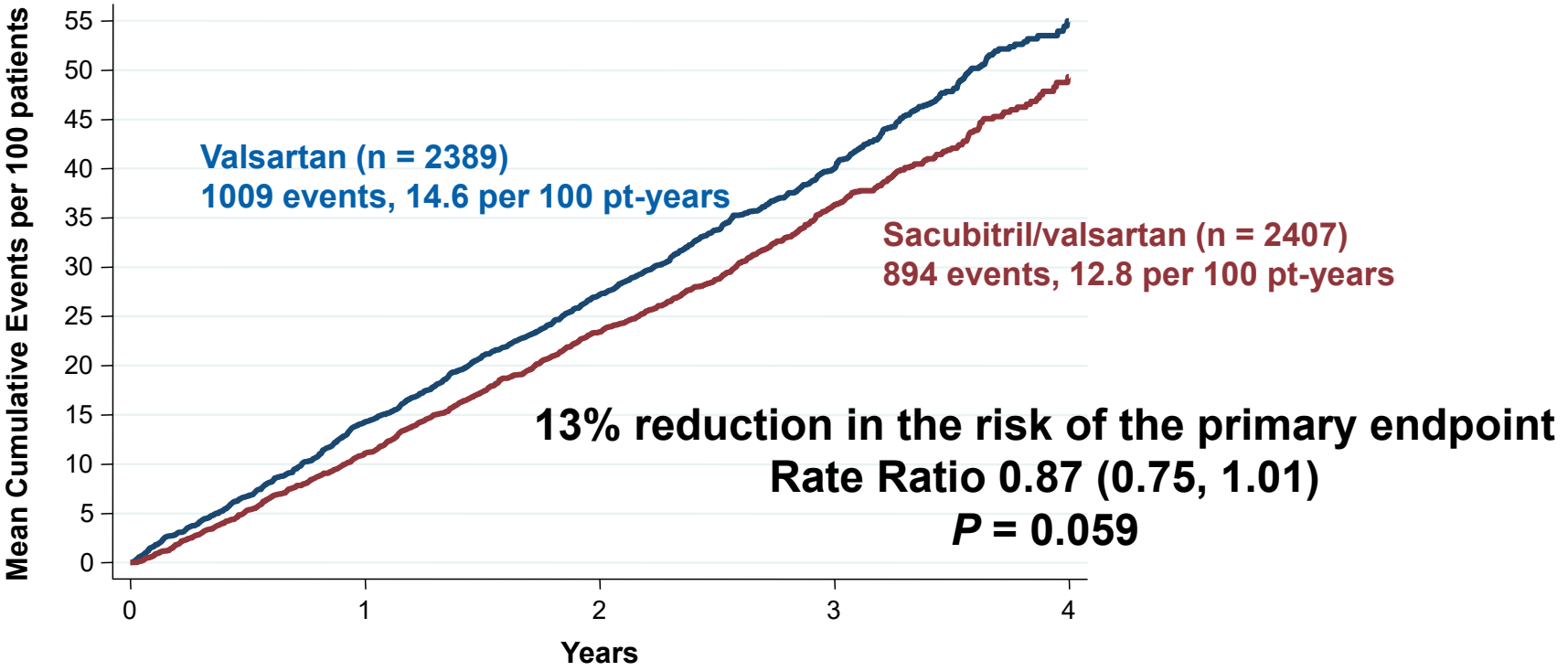
PARAGONHF

EF ≥ 45%

PARALLAXHF

EF > 40%

Primary endpoint: ospedalizzazioni totali per HF e morte CV



*Semiparametric LWYY method.

CV, cardiovascular; HF, heart failure

Solomon S, et al. N Engl J Med. 2019 (In press)

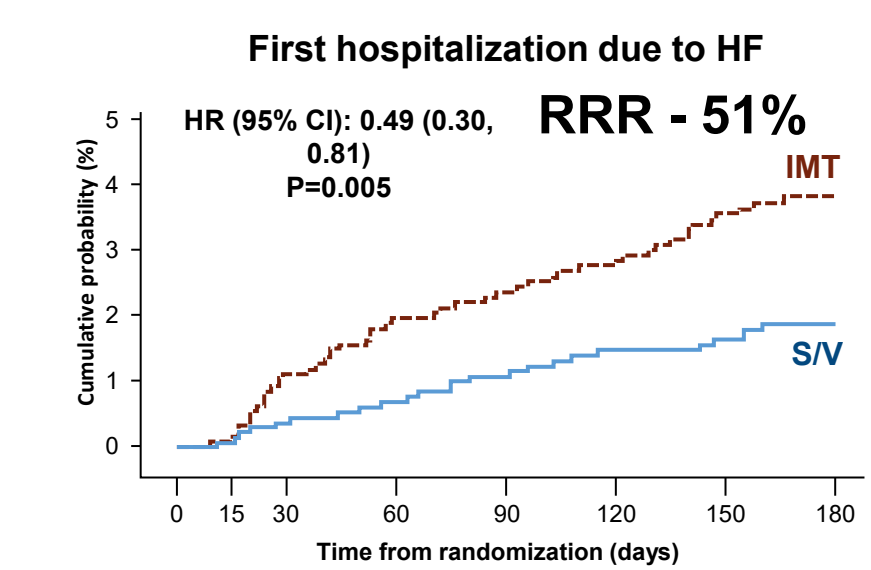
Endpoint primario: Conclusioni

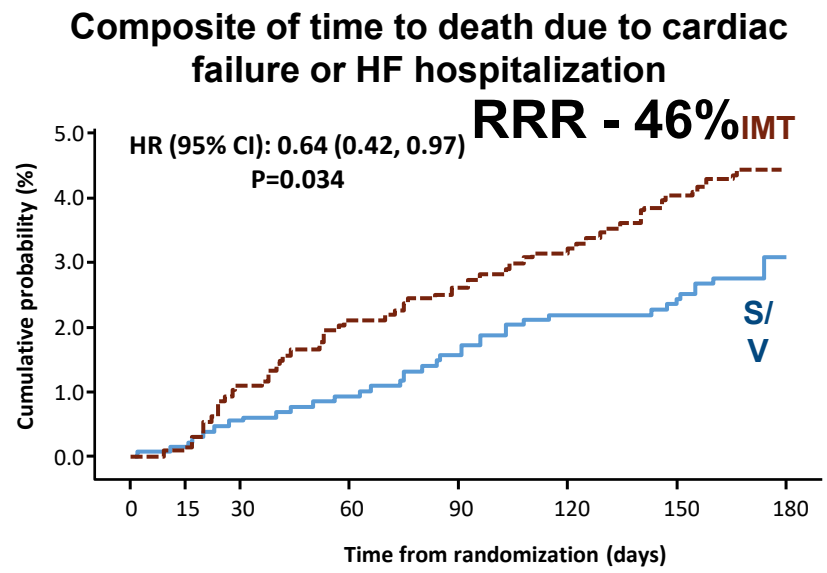
- **More pronounced effects** on the primary endpoint were observed for:
  - Investigator-reported (non-adjudicated) events (16% reduction; RR=0.84; 95% CI: 0.74, 0.96; p=0.015)
  - Pre-defined subgroups, with notable interaction p-values <0.1
    - **Women: 27% reduction; RR=0.73; 95% CI: 0.59, 0.90**
    - **Individuals with lower ejection fraction (< median of 57): 22% reduction; RR=0.78; 95% CI: 0.64, 0.95**

CI, confidence intervals; CV, cardiovascular; HF, heart failure; RR, rate ratio

Solomon S, et al. N Engl J Med. 2019 (In press)

Cardiac failure events leading to death or hospitalization*





No. at risk

S/V	1281	1277	1272	1258	1247	1232	1219	128
IMT	1285	1281	1260	1238	1229	1216	1198	118

No. at risk

S/V	1281	1277	1272	1258	1245	1232	1219	128
IMT	1285	1281	1260	1238	1229	1216	1198	118

**Post-hoc* analysis of cardiac failure events leading to hospitalization and/or death that were documented as adverse events and were not adjudicated

S/V, sacubitril/valsartan, IMT, individualized medical therapy

Conclusions

JACC: HEART FAILURE
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STATE-OF-THE-ART REVIEW

Sacubitril/Valsartan

Neprilysin Inhibition 5 Years After PARADIGM-HF

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CONCLUSIONS

Sacubitril/valsartan is an efficacious, safe, and cost-effective therapy that improves quality of life and longevity in patients with chronic HFrEF and reduces hospital admission. An in-hospital initiation strategy offers a potentially new avenue to improve the clinical uptake of sacubitril/valsartan.

The recently completed PARAGON-HF trial showed that sacubitril/valsartan modestly reduced the risks of total heart failure hospitalizations and cardiovascular death than valsartan in patients with HFpEF, although this finding narrowly missed statistical significance (18), Clinical benefits were observed in secondary endpoints including quality of life and kidney endpoints; women and patients at the lower end of the LVEF spectrum appeared to preferentially benefit. The safety profile of sacubitril/valsartan was largely consistent with prior trial experiences. Regulatory review of sacubitril/valsartan for the treatment of HFpEF is currently under way. Ongoing trials are evaluating the clinical utility of sacubitril/valsartan among patients with HFpEF (PARALLAX) and acute myocardial infarction (PARADISE-MI) (Supplemental Table 1).

In the last 5 years, sacubitril/valsartan has been established as a cornerstone component of comprehensive disease-modifying medical therapy in the management of chronic HFrEF. The next 5 years should see its wider implementation in practice and potential expansion of its therapeutic indications.

ESC European Society of Cardiology
European Heart Journal (2021) 42, 3599 – 3726
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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

Pharmacological treatments to be considered in patients with (NYHA class II–IV) heart failure with mildly reduced ejection fraction

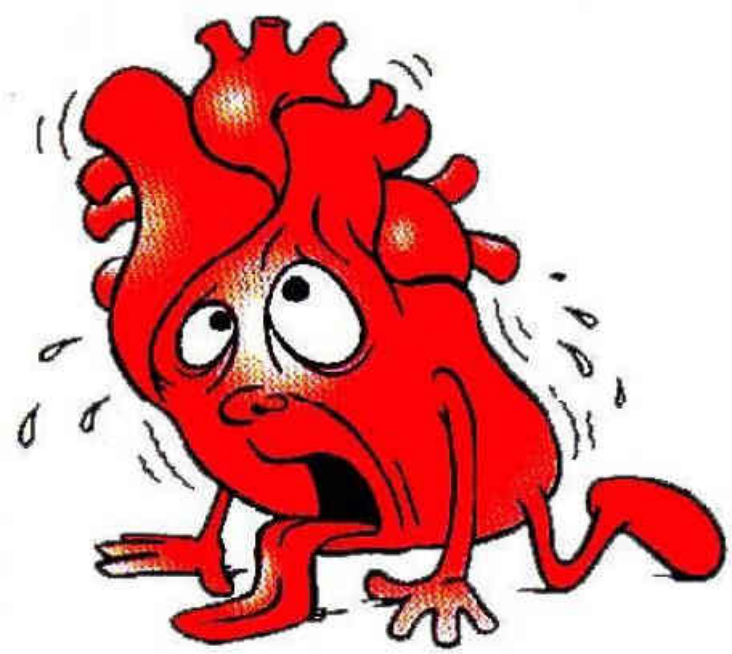
Recommendations	Class[a]	Level[b]
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.[137]	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[11]	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[245]	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[12,119]	IIb	C
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[246]	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[13,247]	IIb	C

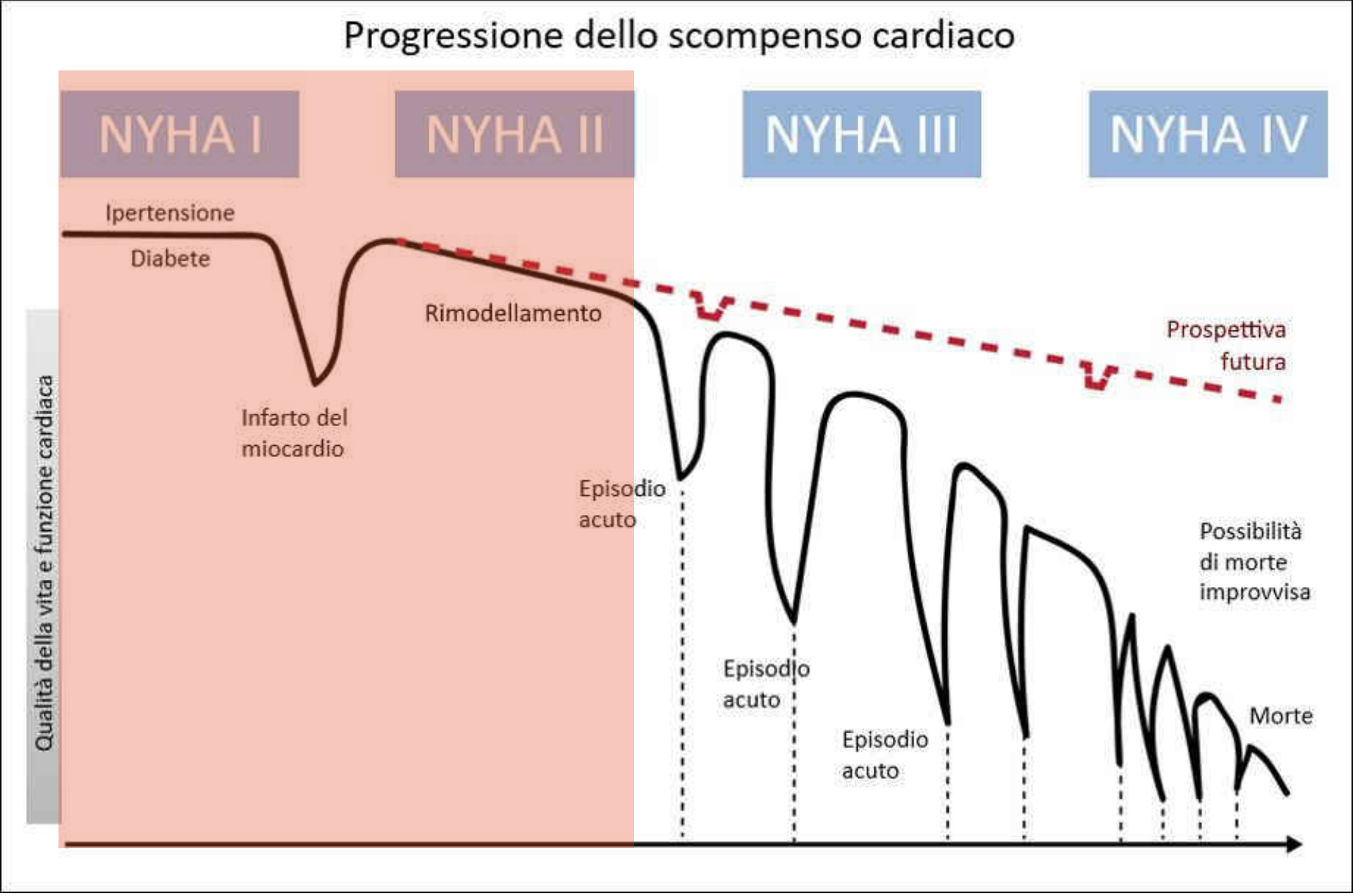
LVEF 41 – 49%

ESC
European Society
of Cardiology

AIFA

“ From Paper to Patient ”

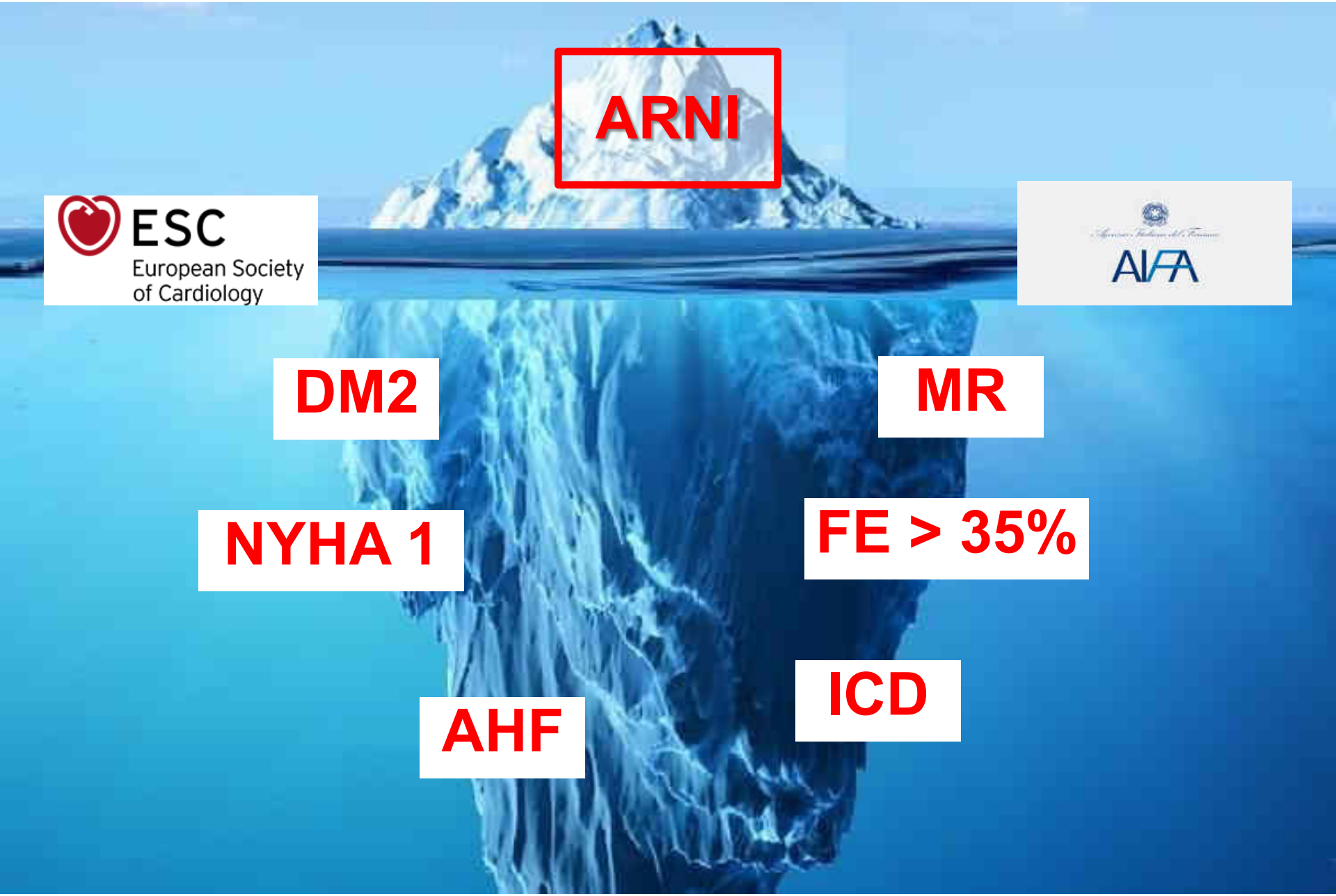




STADIO PRE-CLINICO → **EXITUS**

NYHA II-III
FE ≤ 35%
ACE-I / ARB

2- Eleggibilità e Dati Clinici (EDC)			
Entresto è indicato in pazienti adulti per il trattamento dell'insufficienza cardiaca sintomatica cronica con ridotta frazione di eiezione			
Per i pazienti già in trattamento (risposta 'Si' alla domanda 'Paziente già in trattamento con sacubitril valsartan ed eleggibile secondo i criteri specificatamente individuati in questa scheda AIFA di monitoraggio?') l'eleggibilità è riferita all'inizio reale del trattamento con il medicinale. La raccolta delle informazioni è necessaria ai fini del proseguimento del trattamento e follow up (inserimento delle Rivalutazioni stato di malattia obbligatorie) a carico SSN.			
Si prega di prendere visione di RCP per le informazioni complete sull'utilizzo di Entresto.			
E	Insufficienza cardiaca sintomatica cronica di classe NYHA:	I	*blocco*
		II	
		III	
		IV	*blocco*
E	Frazione di eiezione ventricolare (%)	...	*blocco se >35%*
O	Marker dello scompenso cardiaco:	Peptide natriuretico tipo B (BNP)	*scelta multipla. È sufficiente uno dei due markers*
		Pro-BNP (NT-proBNP)	
O	Per ognuno indicare il valore in pg/mL	...	
O	Il paziente è portatore di defibrillatore impiantabile	Si	
		No	
E	Il paziente è stato sottoposto al miglior trattamento farmacologico tollerato che comprende un ACE inibitore o un bloccante del recettore dell'angiotensina II a dose terapeutica e somministrato per almeno 6 mesi?	*Si*	
		No	*blocco*


ARNI
ESC
European Society
of Cardiology
AIFA
DM2
MR
NYHA 1
FE > 35%
ICD
AHF

Trattamento precoce con ARNI nel Paziente con Scompenso Cardiaco

- **Paziente ambulatoriale stabile, NYHA 1, FEVS > 35%**
- **Paziente con recente AHF, pre-dimissione**
- **Paziente con FE < 35% prima di impianto ICD**