



9^a Edizione

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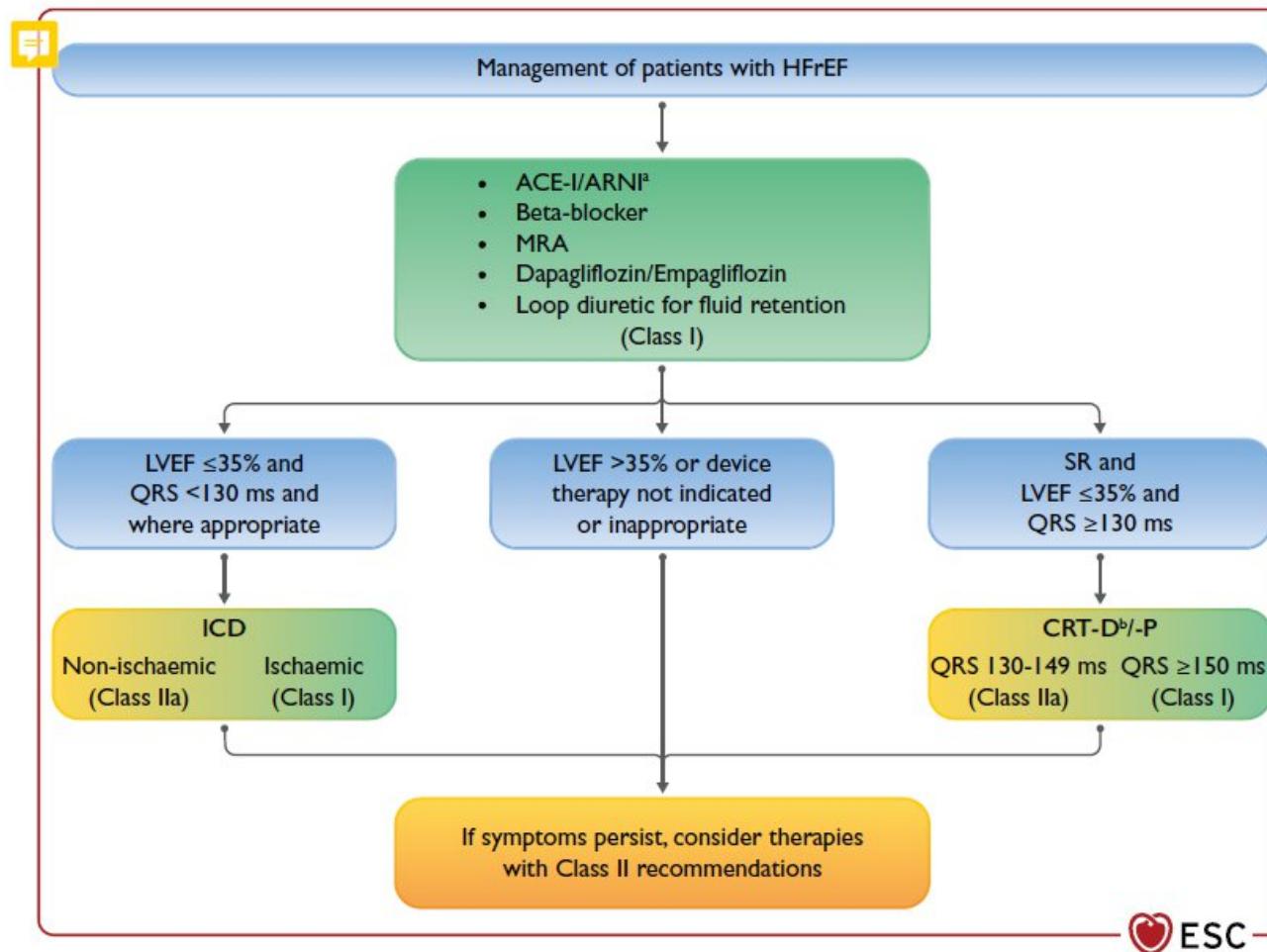
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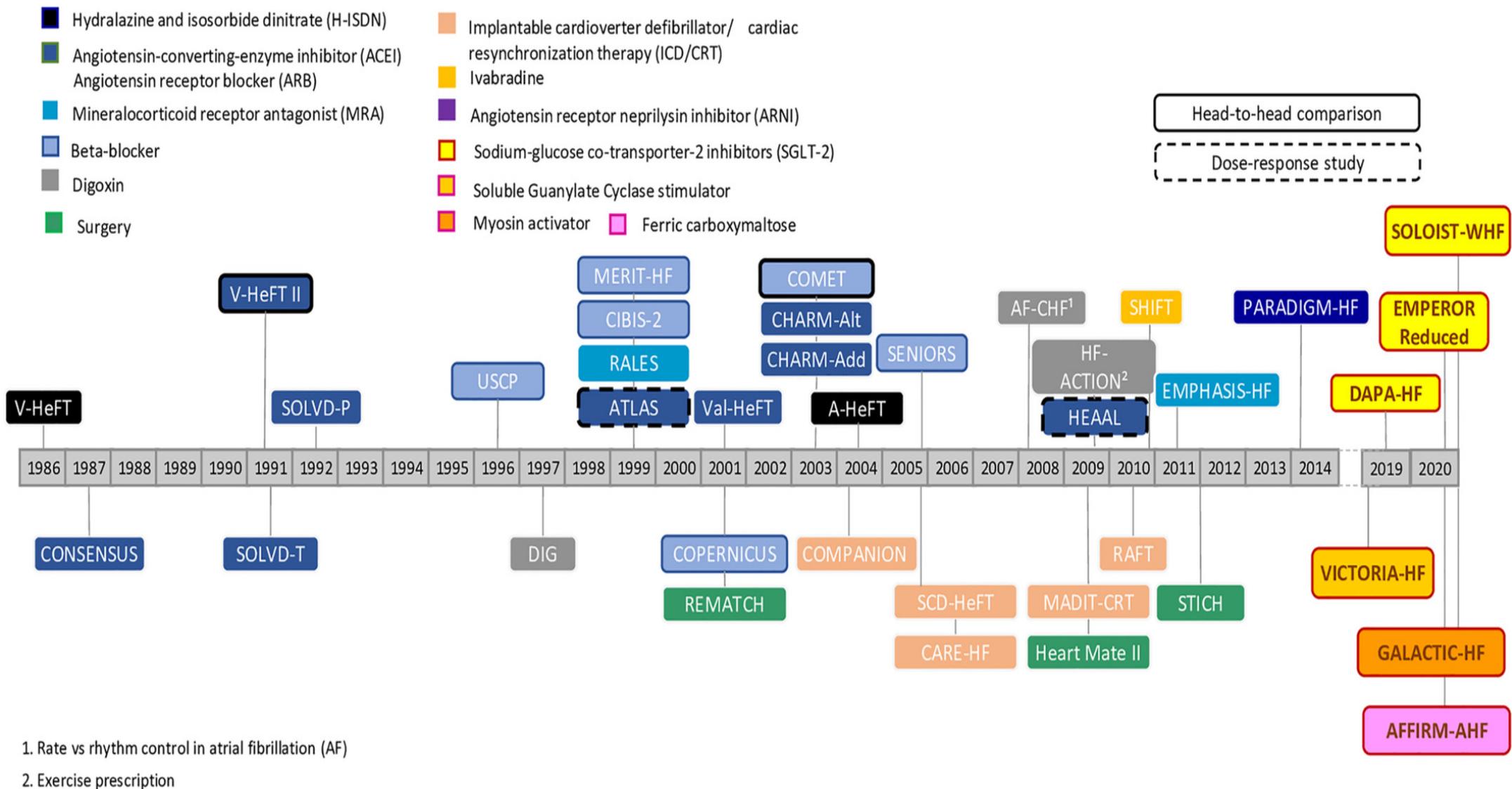


**La quadrupla terapia antineuroromonale
nello scompenso cardiaco a frazione
d'eliezione ridotta: criticità**

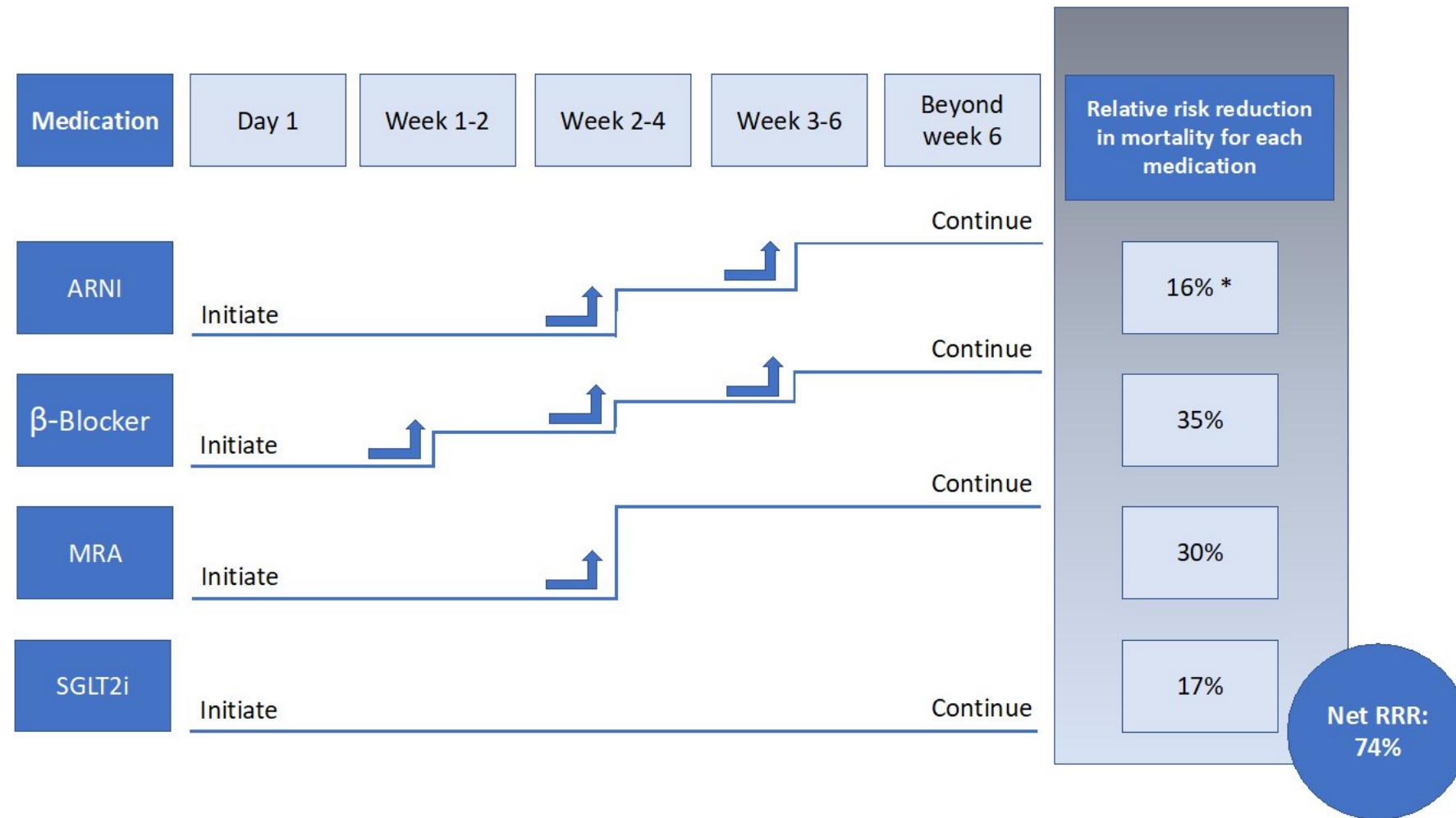
Claudia Tota

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





Quadrupla terapia e riduzione del rischio relativo di mortalità'



Benefici a breve termine della quadrupla terapia

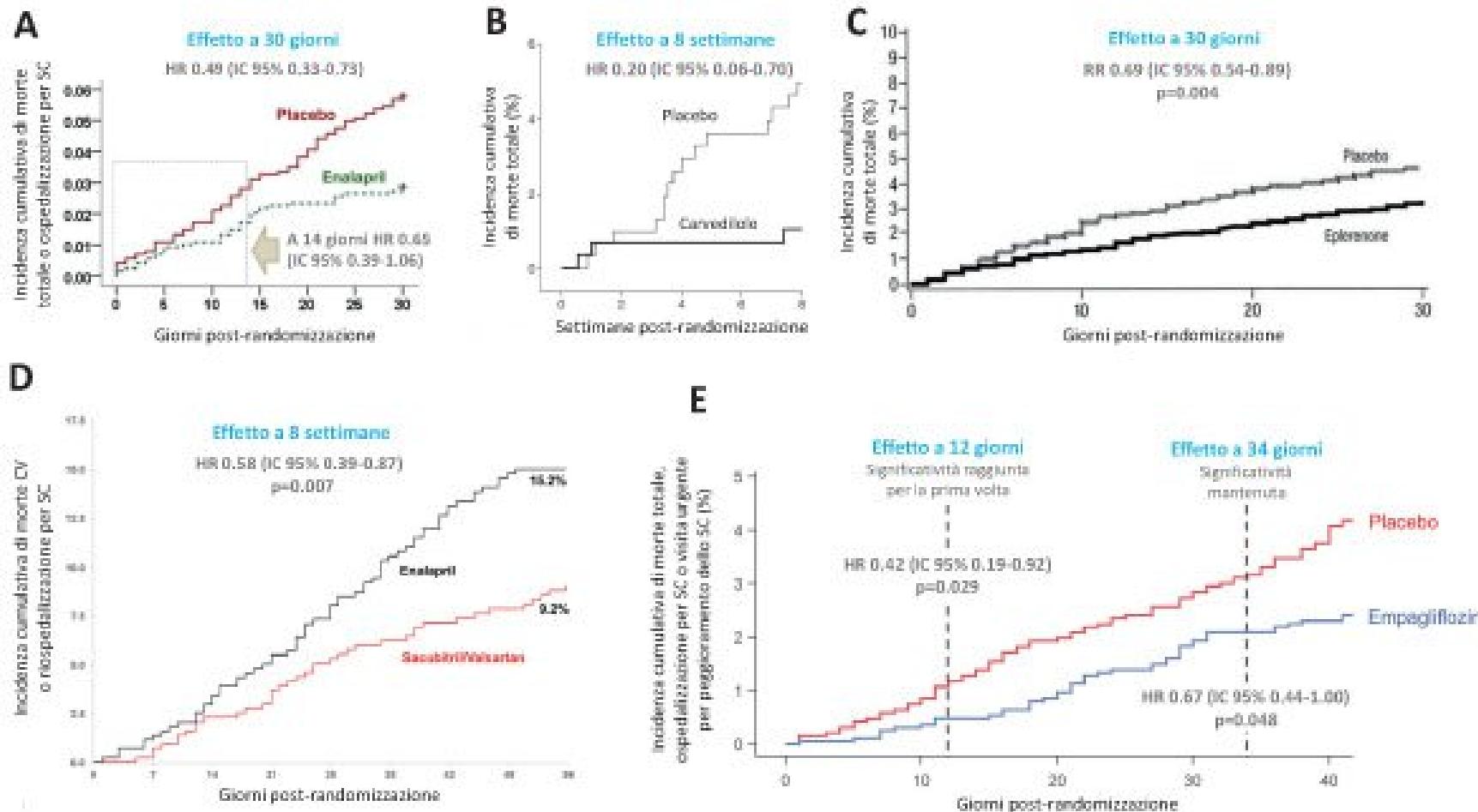
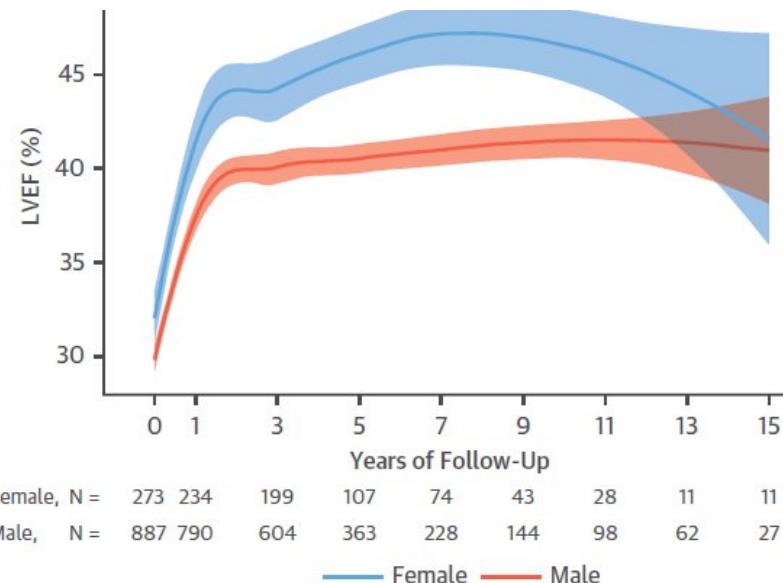
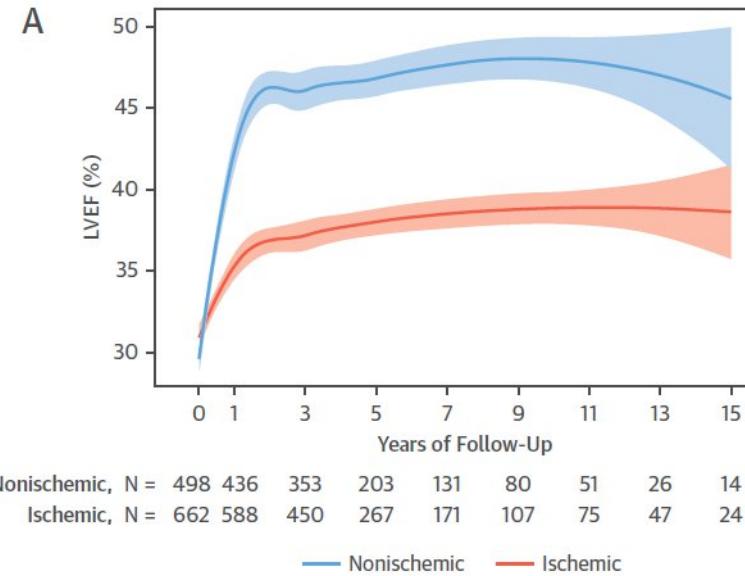
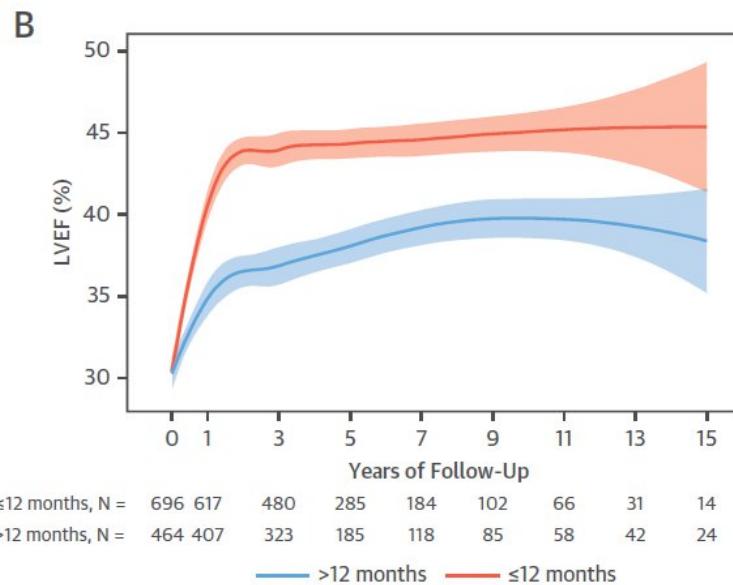
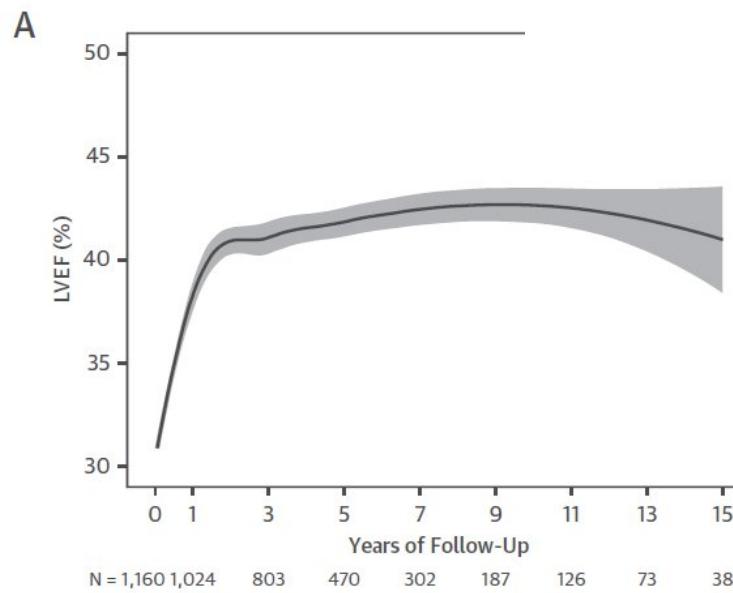


Figura 1. Effetto precoce (4-8 settimane) della quadruplice terapia dello scompenso sistolico. (A) Mortalità totale e ospedalizzazione per scompenso cardiaco (SC) a 30 giorni con enalapril vs placebo¹³. (B) Mortalità totale a 8 settimane in pazienti ad alto rischio con carvedilolo vs placebo¹⁴. (C) Mortalità totale a 30 giorni con eplerenone vs placebo¹⁵. (D) Mortalità cardiovascolare (CV) e ospedalizzazione per SC a 8 settimane con sacubitril/Valsartan vs placebo¹⁷. (E) Mortalità totale, ospedalizzazione per SC o visita urgente per peggioramento dello SC a 40 giorni con empagliflozin vs placebo¹⁸.

IC, intervallo di confidenza; HR, hazard ratio; RR, rischio relativo.

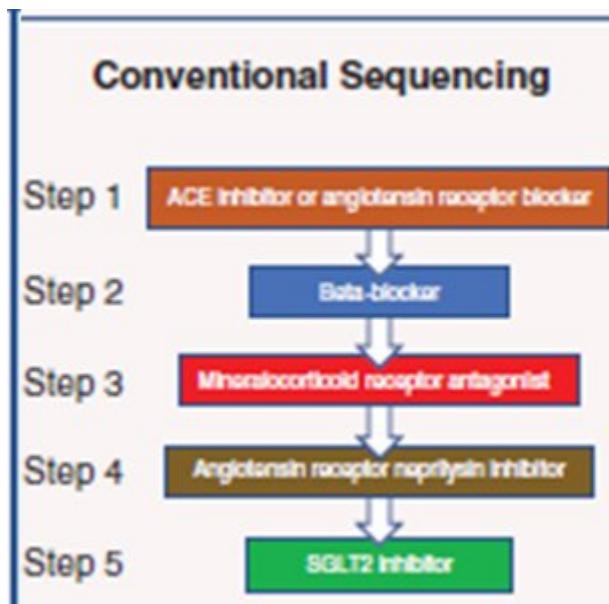
Dynamic Trajectories of left ventricular ejection fraction in heart failure



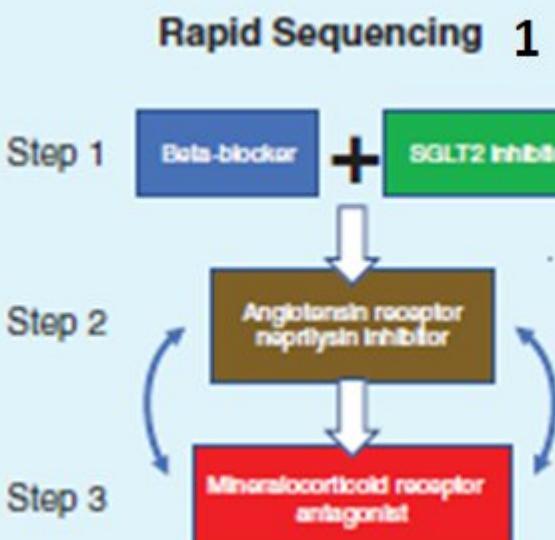
1160 included patients with reduced LVEF (<40%) and mid-range LVEF (40% to 49%)

Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction

SEQUENZA RAPIDA 1
PAZIENTI ACE-I/SARTANO
NAIVE

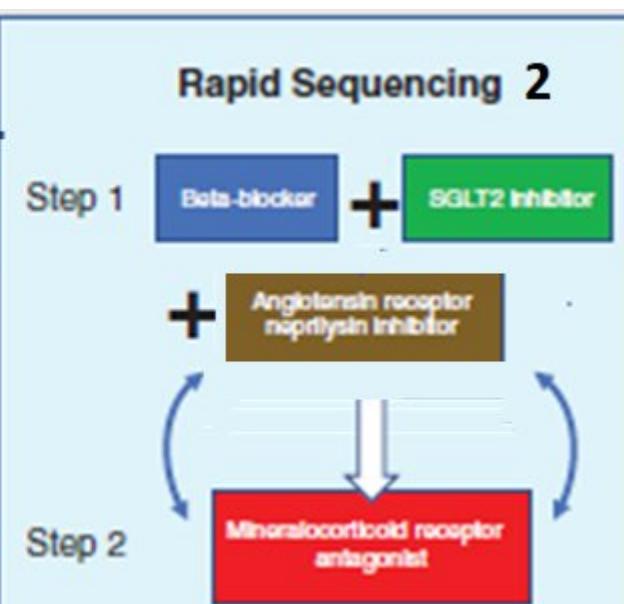


Uptitration to target doses at each step
Typically requires 6 months or more



All 3 steps achieved within 4 weeks
Uptitration to target doses thereafter

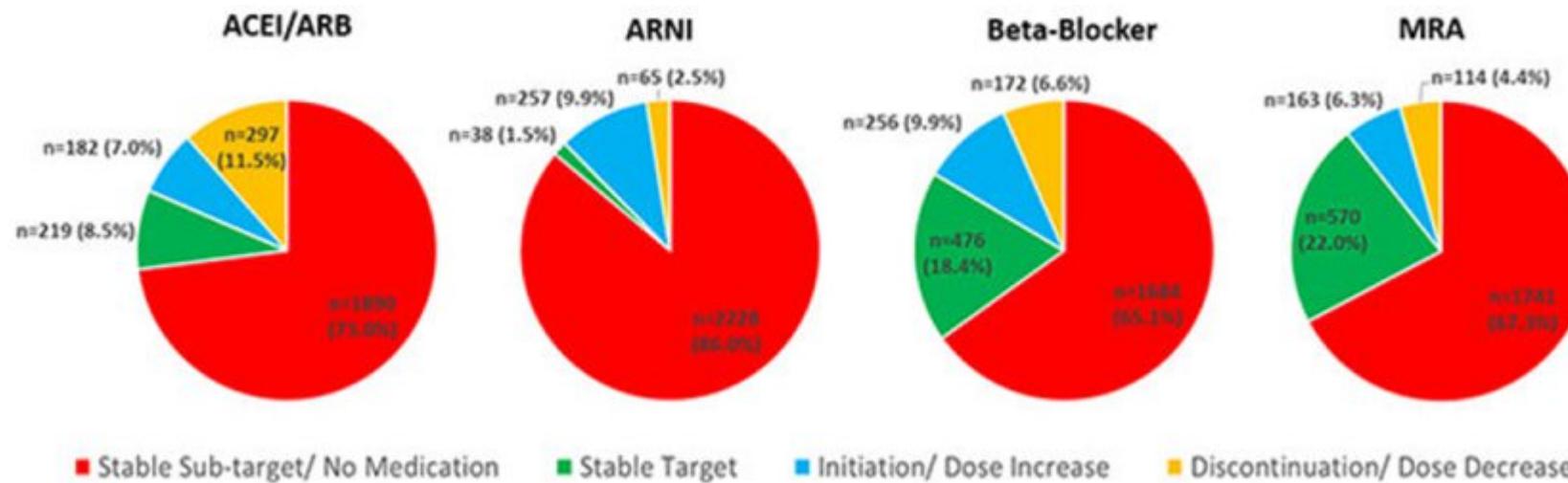
SEQUENZA RAPIDA 2
PAZIENTI IN TERAPIA CON
ACE-I/SARTANO



All 2 steps achieved within 2 weeks
Uptitration to target doses thereafter

Longitudinal Titration of Medical Therapy for Heart Failure with Reduced Ejection Fraction: The CHAMP-HF Registry

Dose of Medication at 12-month Follow-up Compared with Baseline



At baseline 80.2%, 66.3%, 33.7% and 13.6% patients were treated with beta-blocker, ACEI/ARB, MRA, and ARNI therapy respectively

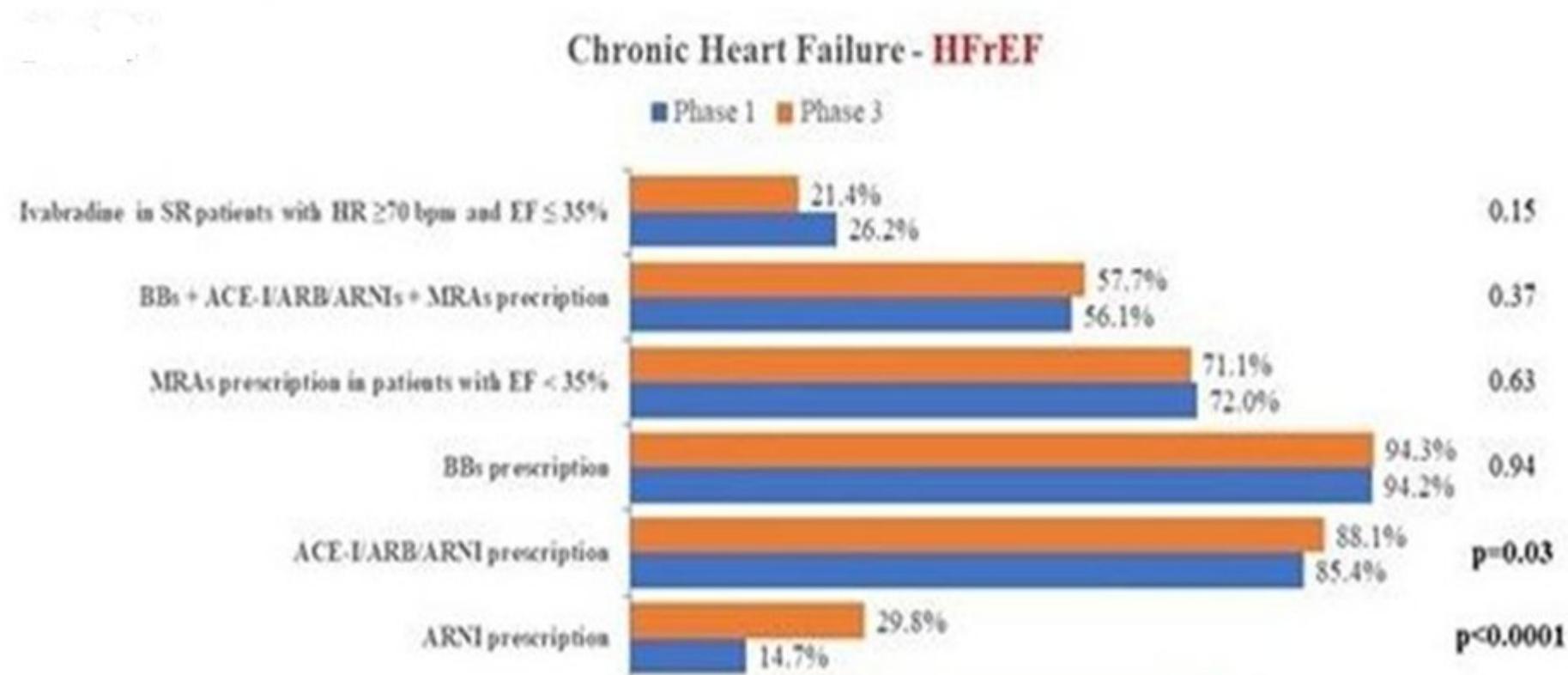
22.3% patients were simultaneously treated with any dose of ACEI/ARB/ARNI, beta-blocker, and MRA at baseline and 12 months

The median percent of $\geq 50\%$ target dose achieved at 12 months was 39.6% and ranged from 10.0% to 66.7%

For all therapies the majority of patients (> 80%) remained on stable sub-target doses of medication

The target dosing of simultaneous therapy with ACE/ARNI/ARB, beta blocker and MRA is achieved in 3.4% at 12 months.

BLITZ-HF study: a nationwide initiative to assess and improve guideline recommendations adherence in cardiology centers managing patients with acute and chronic heart failure



BLITZ-HF was a prospective study based on a web based recording system used during two enrollment periods (phase 1 and 3), interspersed by face-to-face macro-regional benchmark analysis and educational meetings (phase 2).

7218 patients with acute and chronic HF were enrolled at 106 sites in Italy.

Barriers to implementation of medical therapy

Table 1 Common side effects of guideline-directed medical therapy

Drug	Common side effects
Diuretics	Hypotension; hypokalaemia; hypomagnesaemia; hyponatraemia; hyperuricemia; hypovolaemia/dehydration; rise in creatinine, urea
ACEi/ARB	Cough; hypotension; rise in urea, creatinine, potassium
ARNI	Hypotension; rise in creatinine, potassium; angioedema
Beta-blockers	Worsening HF; low heart rate; hypotension
Ivabradine	Low heart rate; visual phenomena
MRA	Rise in creatinine, potassium; breast discomfort or gynaecomastia
SGLT2i	Genital infection (in diabetic patients)

Table 2 Common comorbidities seen in heart failure and impact on use of guideline-directed medical therapy

Comorbidity	GDMT	Precaution	Comment
Coronary artery disease and angina	✓		Beta-blockers and ivabradine may help control symptoms
Diabetes	✓		GDMT have shown similar benefits in diabetic patients
Lung disease		Asthma is a relative contraindication to beta-blocker; starting with low doses of cardio-selective beta-blocker may allow its use	Beta-blockers can be given in COPD
Depression	✓		Depression is associated with low adherence to medication
Erectile dysfunction	✓		Thiazides, spironolactone and beta-blockers (nebivolol preferred) may aggravate erectile dysfunction
Iron deficiency/anaemia			
Kidney dysfunction		ACEi, ARB, ARNI, MRA may have some limitations (see text)	Diuretics may need higher doses to be effective
Cachexia		ACEi, ARB, ARNI should be up-titrated carefully because of orthostatic hypotension	

3) Scarsa aderenza alla terapia del paziente (barriere sociali, decadimento cognitivo, disturbi psichiatrici.....)

4) Inerzia prescrittiva del clinico

Patient profiling in heart failure for tailoring medical therapy. A consensus document of HFA of ESC
G.M.C. Rosano et al.
European J Heart Failure (2021) 23, 872-881

Drug therapy for heart failure with reduced ejection fraction: what is the 'right dose'?

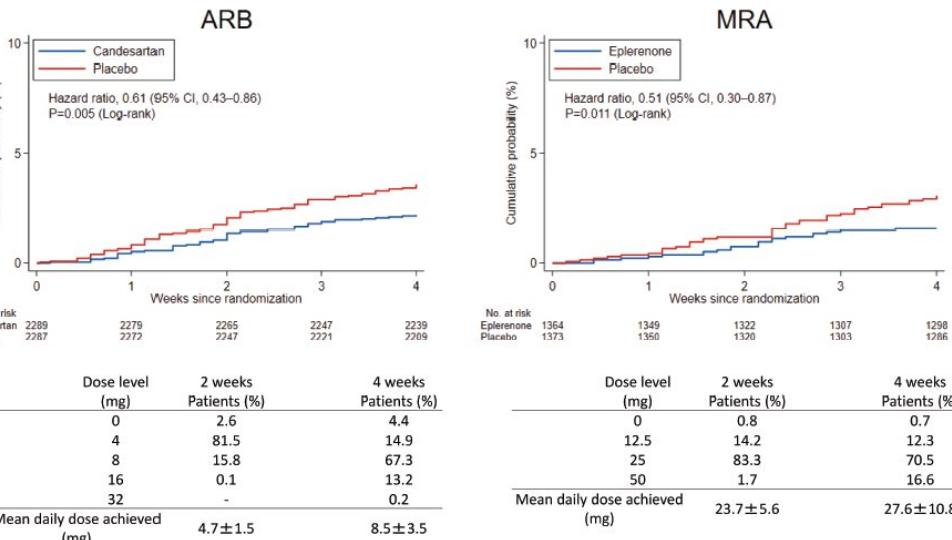


Figure 1 Kaplan–Meier analysis for the composite of all-cause death or hospitalization for heart failure up to 4 weeks in trials using an angiotensin receptor blocker (ARB) (CHARM-HFrEF trials) and a mineralocorticoid receptor antagonist (MRA) (EMPHASIS-HF). CI, confidence interval.

Table 4 Randomized clinical outcome trials comparing effects of low and high-dose renin–angiotensin system blockers in patients with heart failure and reduced ejection fraction

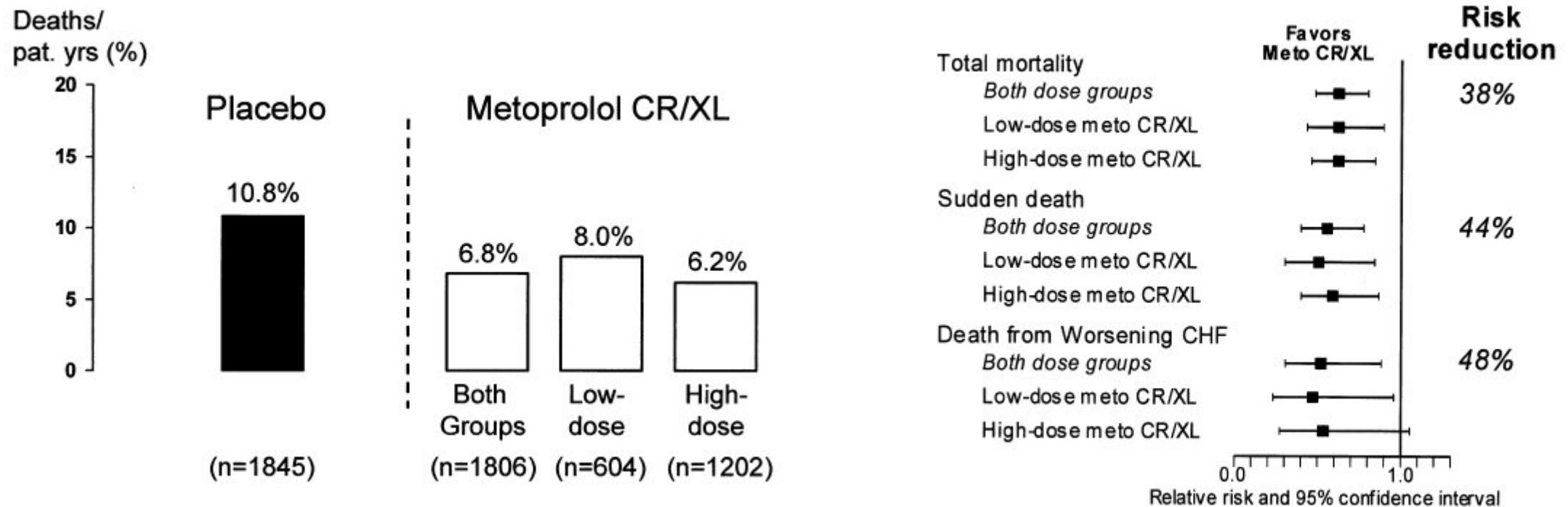
	Treatments (n)	Median trial duration (months)	Target dose	Mean daily dose achieved	All-cause mortality or HF hospitalization, HR (95% CI)	All-cause mortality, HR (95% CI)	Cardiovascular mortality, HR (95% CI)
ATLAS	Lisinopril-low (1596)	46	2.5–5.0 mg qd	4.5 mg ^a	0.85 (0.78–0.93)	0.92 (0.82–1.03)	0.90 (0.81–1.01)
	Lisinopril-high (1568)		32.5–35 mg qd	33.2 mg ^a	p = 0.002	p = 0.128	p = 0.073
HEAAL	Losartan-low (1919)	56.4	50 mg qd	46 mg ^b	0.90 (0.82–0.99) ^b	0.94 (0.84–1.04)	0.92 (0.81–1.05)
	Losartan- high (1927)		150 mg qd	129 mg ^b	p = 0.027	p = 0.24	p = 0.20

CI, confidence interval; HF, heart failure; HR, hazard ratio; qd, once daily; SD, standard deviation.

^aAt the end of dose titration. Over the whole duration of the trial, the mean (SD) daily dose of lisinopril in the high-dose group was 22.5 (15.7) mg compared to 3.2 (2.5) mg in the low-dose group.

^bFrom the time of follow-up to the time of a primary endpoint or study end, the mean daily losartan doses administered were 129 mg (SD 39) for the 150 mg group and 46 mg (SD 11) for the 50 mg treatment group. For the composite of cardiovascular death or heart failure hospitalization, the HR was 0.88 (95% CI 0.79–0.97; p = 0.011).

Dose of Metoprolol CR/XL and Clinical Outcomes in Patients with Heart Failure Analysis of the MERIT-HF trial



Heart rate was reduced to a similar degree in the two dose groups

Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial

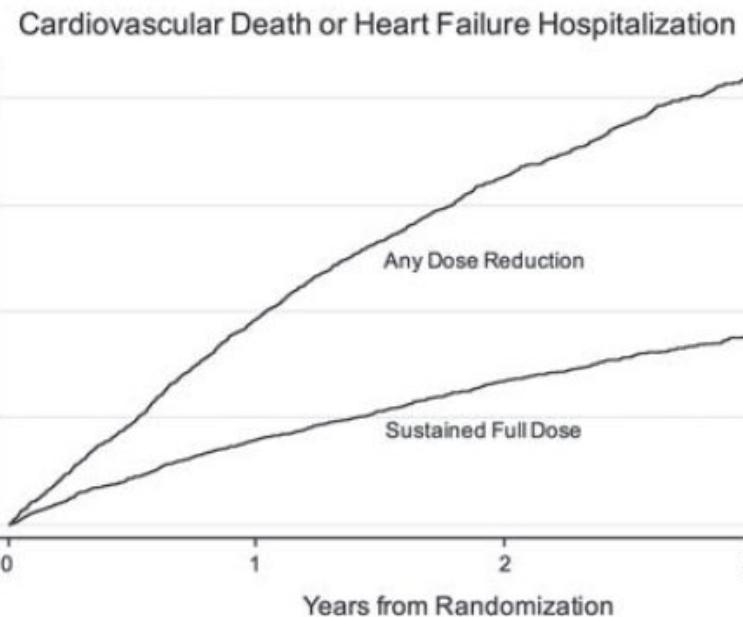


Figure 1 Kaplan–Meier curves showing primary outcome events by dose reduction status. Participants with a dose reduction had a higher risk of the primary event compared with those who remained on full study medication doses.

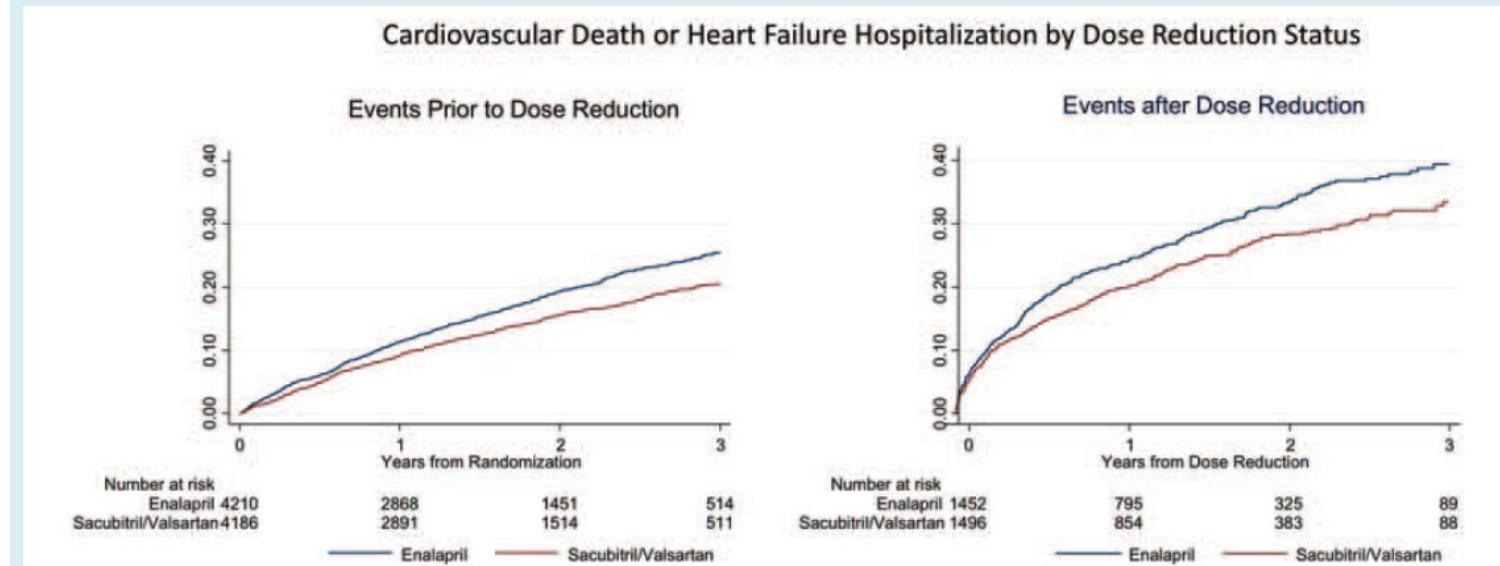
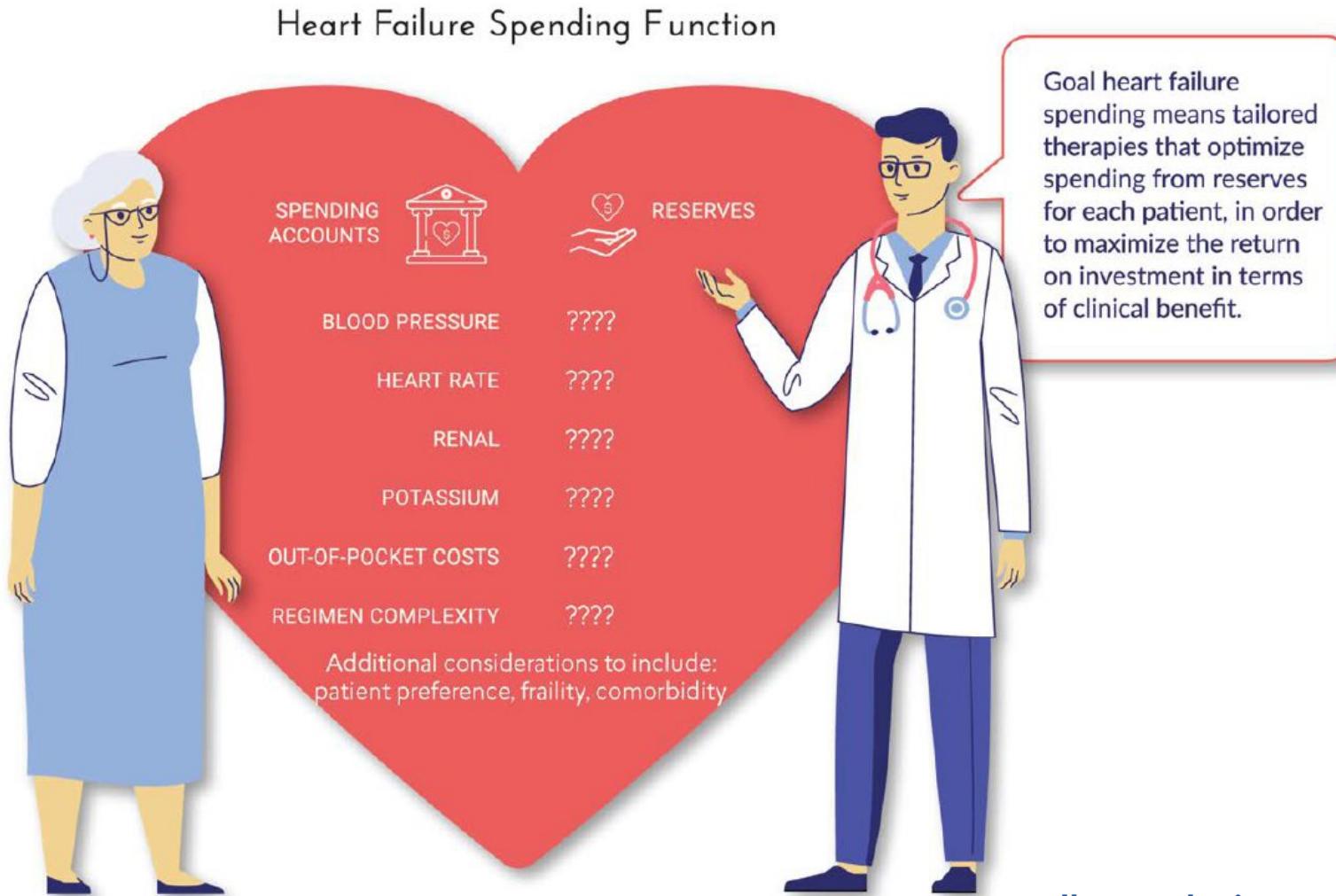


Figure 2 (A) Kaplan–Meier curves showing primary outcome events censored at dose reduction by treatment assignment. Individuals taking sacubitril/valsartan had fewer events compared with the enalapril group [hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.71–0.88]. (B) Kaplan–Meier curves showing primary outcome events following dose reduction by treatment assignment. Individuals randomized to sacubitril/valsartan had fewer events relative to enalapril after dose reduction (HR 0.80, 95% CI 0.70–0.93).

Patient profiling in heart failure for tailoring medical therapy. A consensus document of HFA of ESC



Heart Failure Spending Function: An Investment Framework for Sequencing and Intensification of Guideline-Directed Medical Therapies



Scompenso cardiaco con ridotta frazione d'eiezione, la terapia ottimale?

Deve essere quadrupla, rapida e personalizzata
'start-four-at-once'



- Nei trial clinici di registrazione dei farmaci è stato dimostrato che i pazienti ottengono benefici in termini di riduzione dello ospedalizzazioni e della mortalità da ciascuna di queste classi di farmaci entro poche settimane rispetto ai pazienti nei bracci di controllo.
- Dopo 30 giorni di trattamento quadruplo il rischio relativo di morte di un paziente diminuisce di oltre tre quarti.
- I benefici di ciascuna delle quattro classi coinvolgono percorsi fisiologici distinti e quindi derivano maggiori benefici dal trattamento simultaneo .
- La tolleranza dei vari trattamenti può essere favorita dall'inizio contemporaneo a basso dosaggio , adattando la terapia allo specifico profilo del paziente.
- L'inizio immediato e contemporaneo riduce anche il rischio di inerzia prescrittiva da parte del clinico.