Terapia dello scompenso cardiaco a frazione di eiezione ridotta: oltre i 4 pilastri

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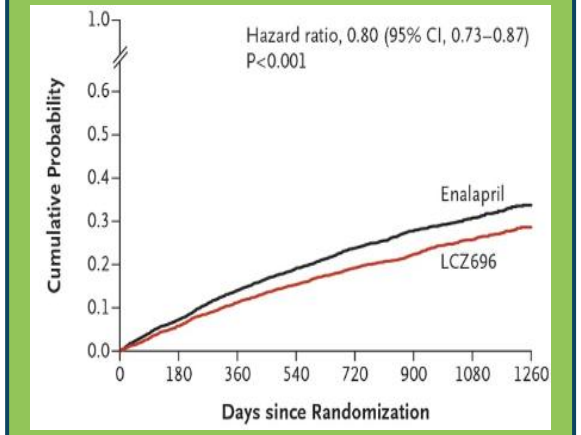
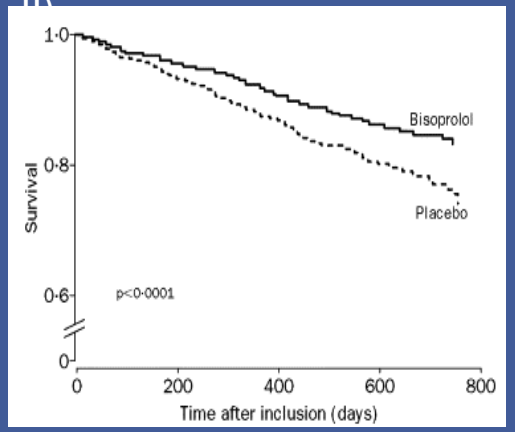
Background: terapia cardine dell'insufficienza cardiaca

ARNi (PARADIGM-HF)



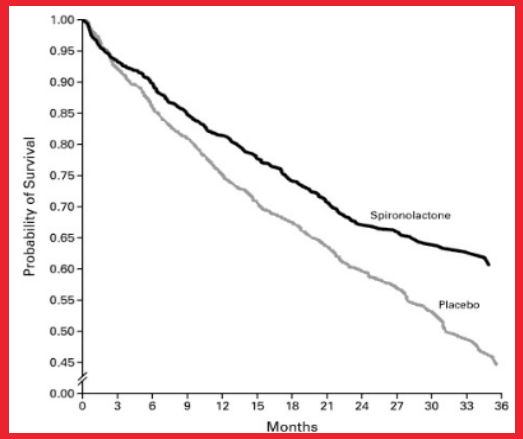
ARNi riduce la mortalità

BETABLOCCANTI (CIBIS-II)



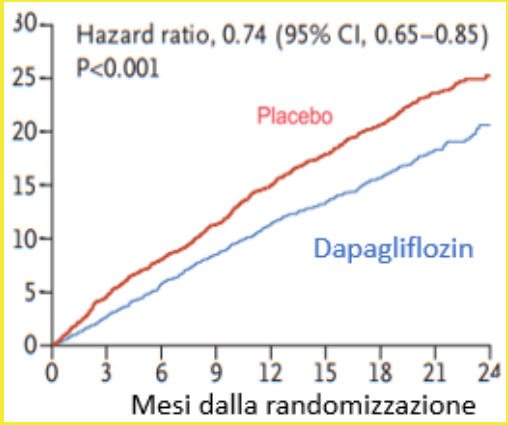
I betabloccanti riducono la mortalità

MRA (RALES)

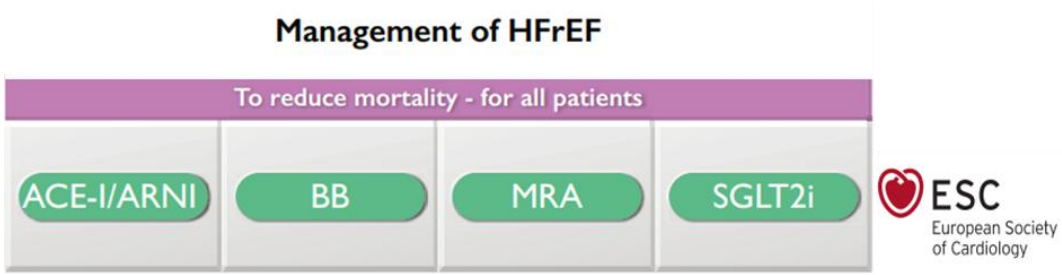


MRA riducono la mortalità

SGLT2i (DAPA-HF)



SGLT2i riducono la mortalità



McMurray JJ et al. *N Engl J Med*. 2014;371(11):993-1004.

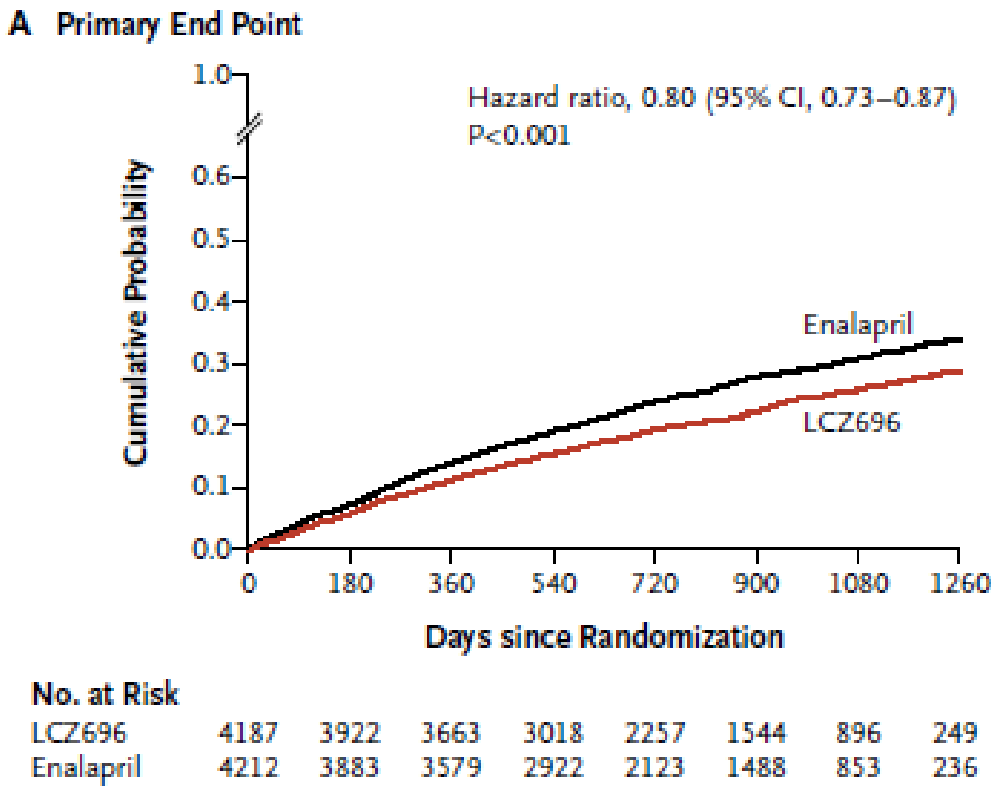
The Cardiac Insufficiency *Lancet*. 1999;353(9146):9-13.

Pitt B et al. *N Engl J Med*. 1999;341(10):709-717.

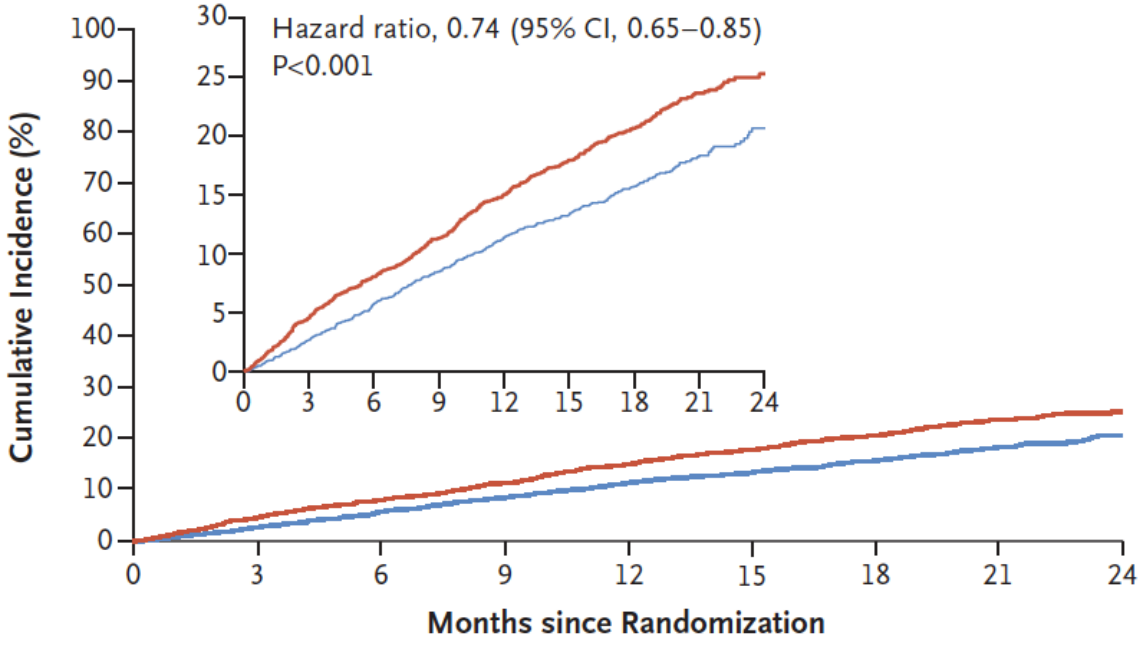
Zannad F et al.. Lancet. 2020;396(10254):819-829.

Beneficio precoce

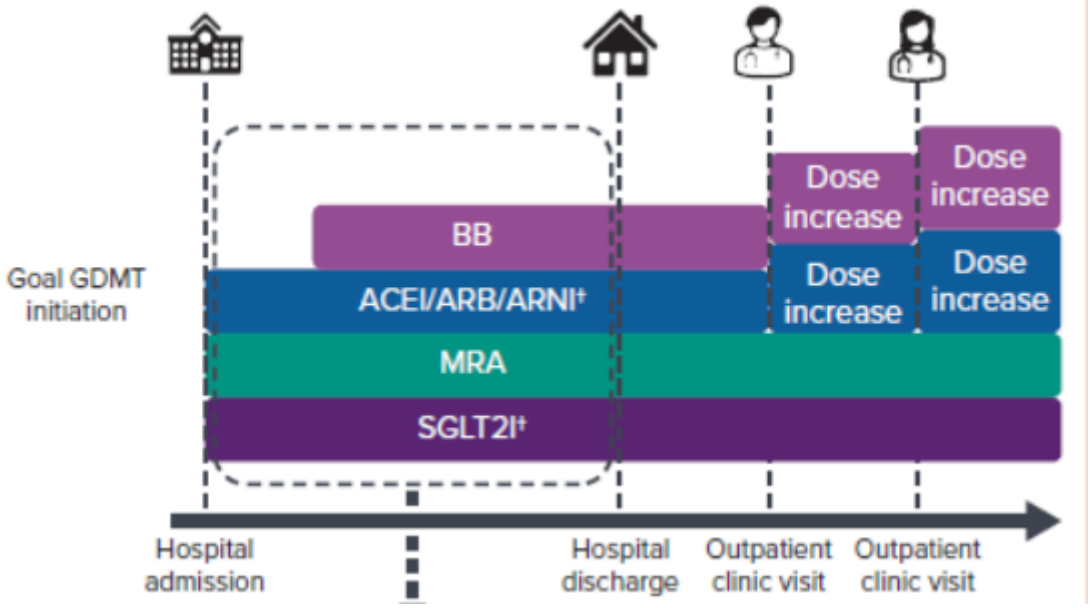
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

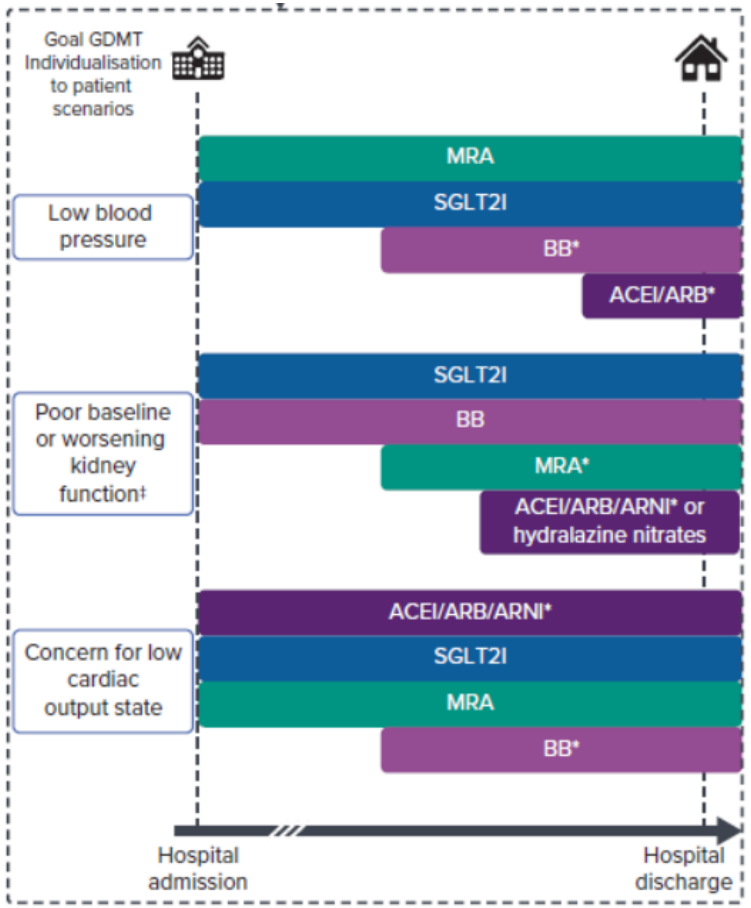


Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

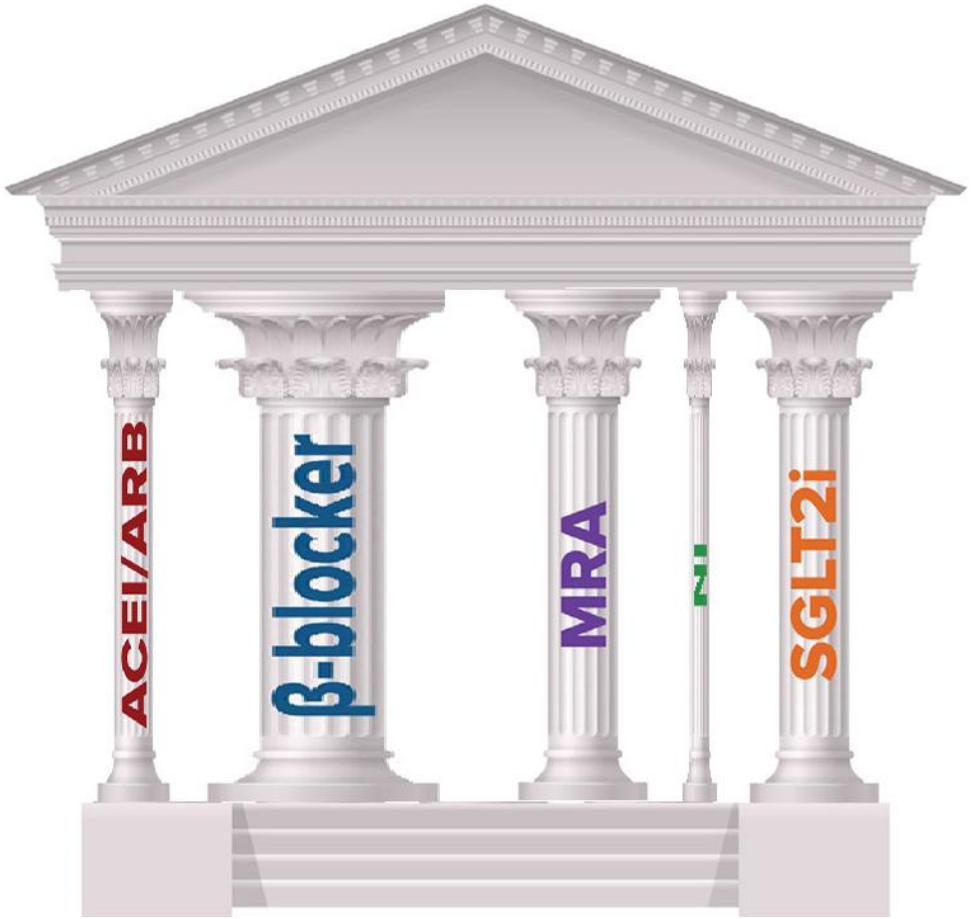


Tailored sequencing in GDMT

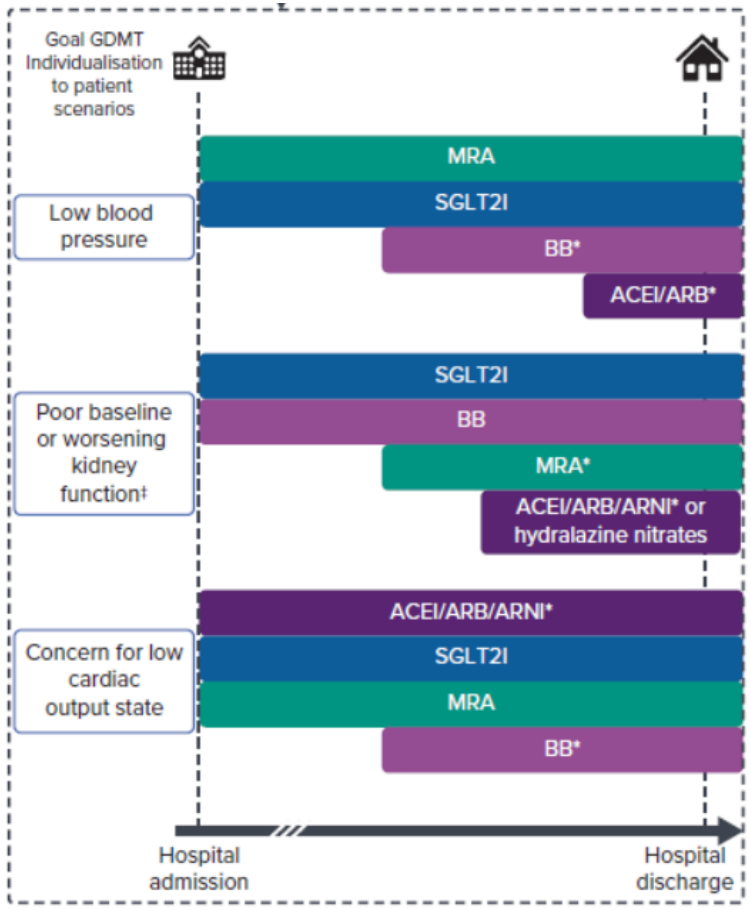


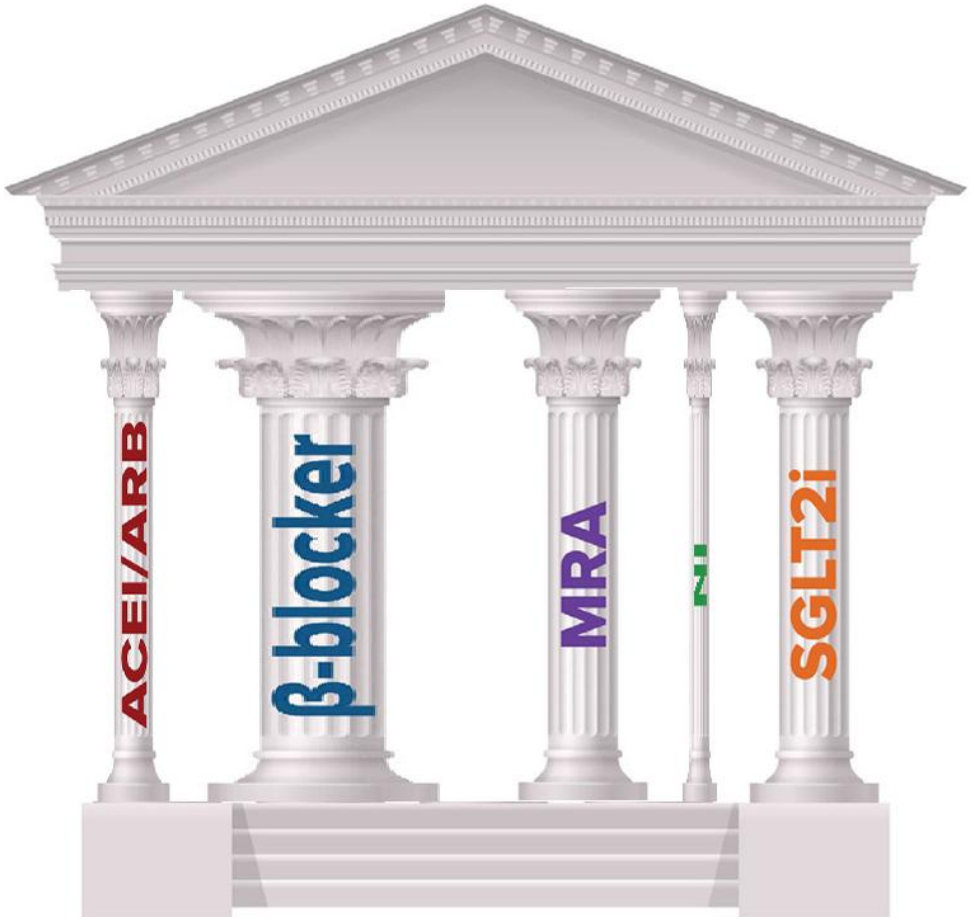


Not only sequencing…



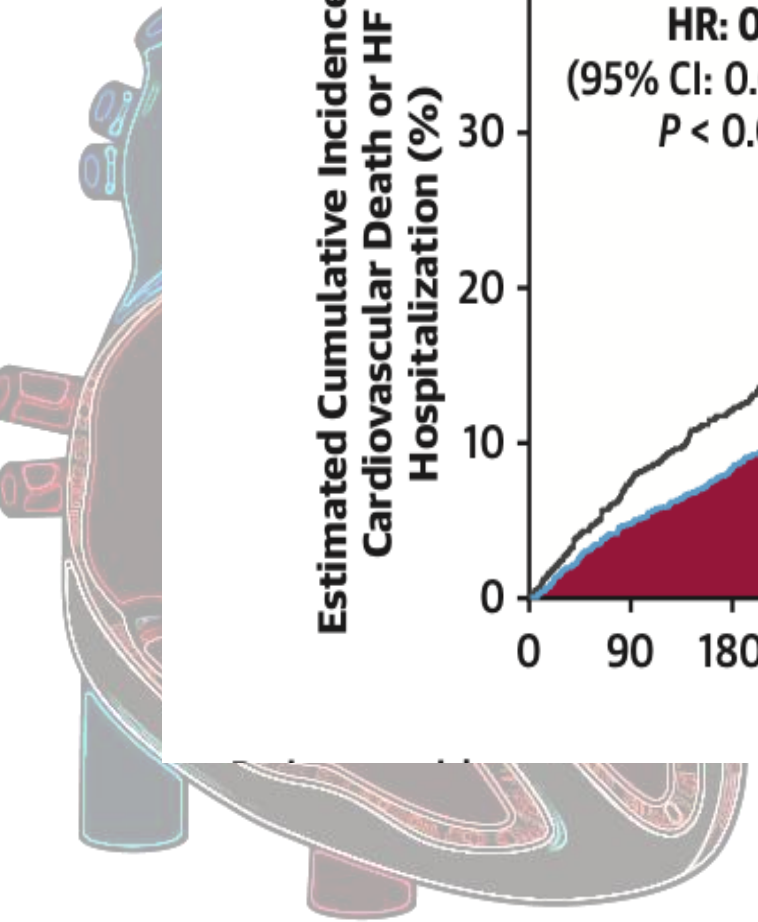
Not only sequencing…

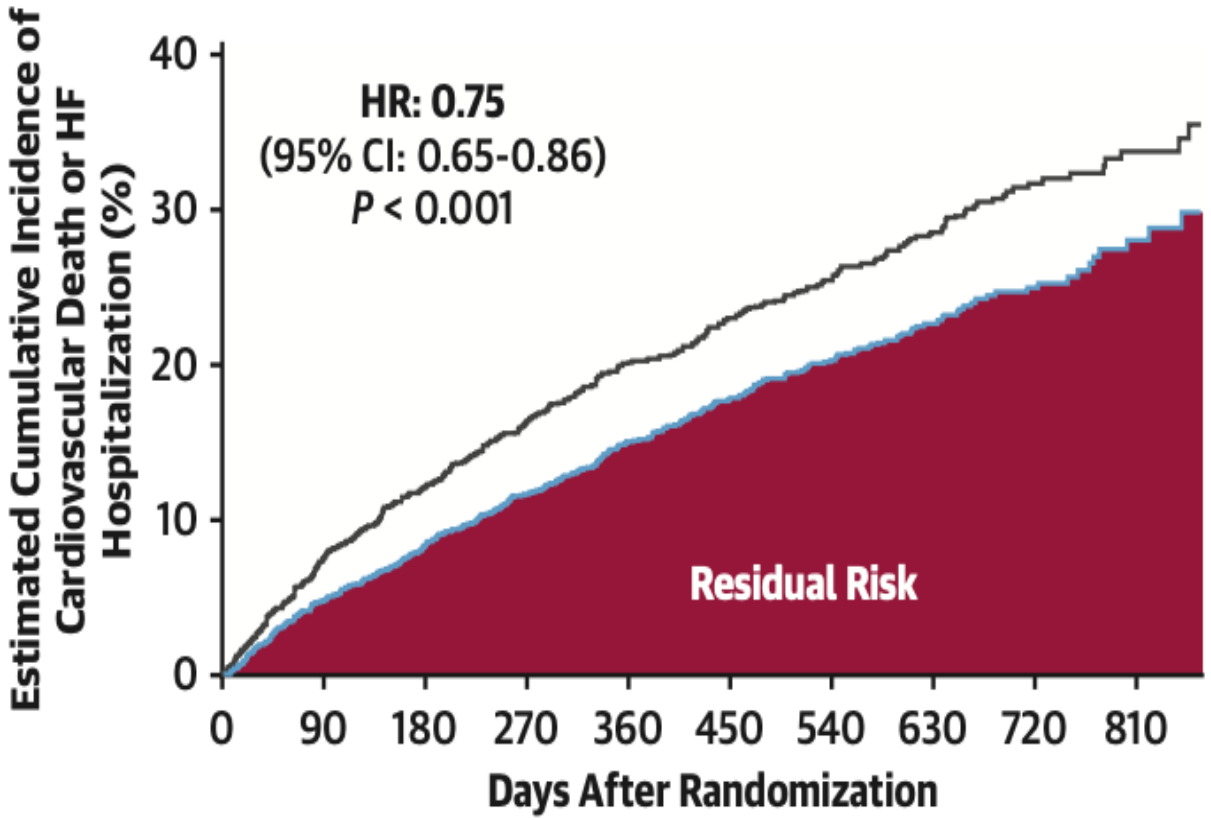




I 4 pilastri: abbiamo raggiunto il massimo?

«If you use all of these drugs correctly there will be no progression of heart failure…»?





Placebo
N = 462
Event rate = 21.0/100 patient-years

Empagliflozin
N = 361
Event rate = 15.8/100 patient-years

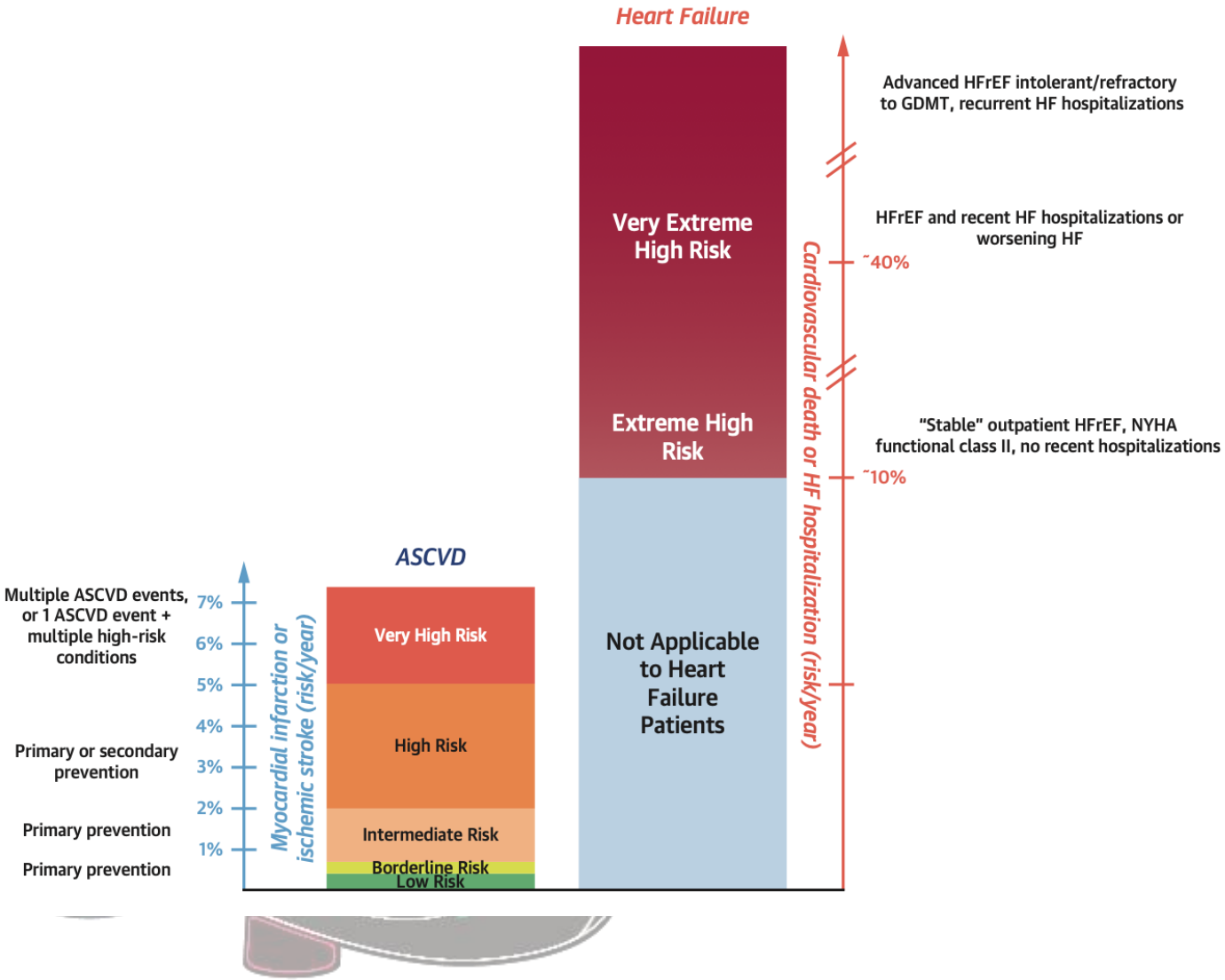
Rate of CV Death or HF Hospitalization: 15.8/100 patient-years

Despite Background Quadruple Therapy

100% SGLT2 inhibitor
95% BB
89% ACE inhibitor/ARB/ARNI
71% MRA

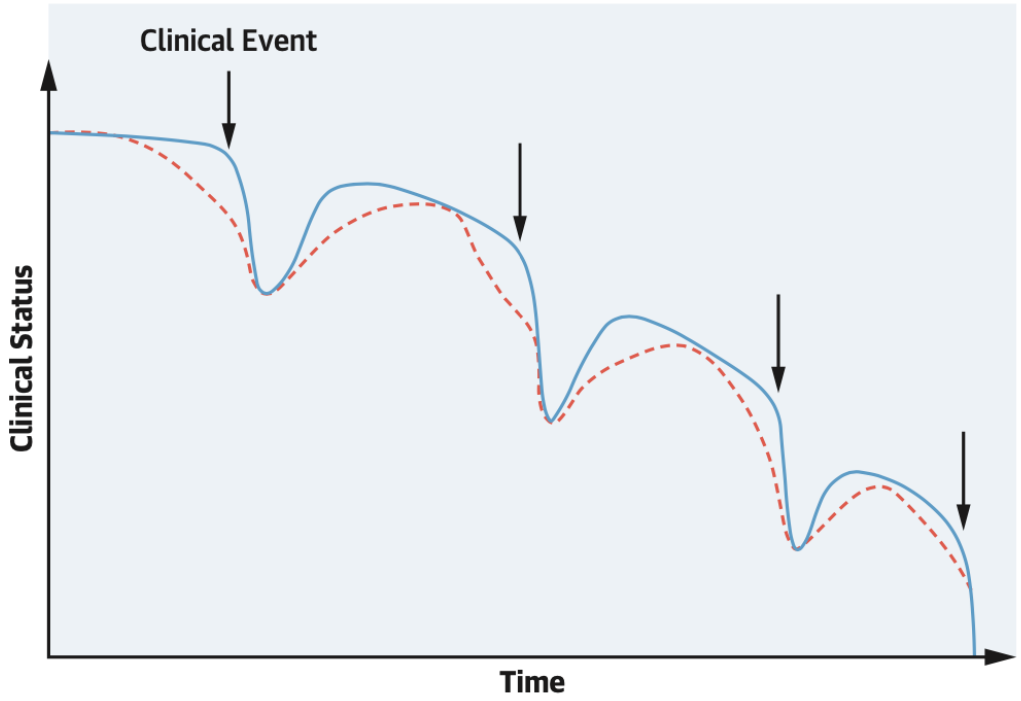
Packer, J Am Heart Assoc. 2020 Greene, JACC 2023

I 4 pilastri: abbiamo raggiunto il massimo?



The misperception of 'stable' heart failure

Domingo Pascual-Figal ✉, Antoni Bayes-Genis



Greene, JACC 2023

Worsening heart failure

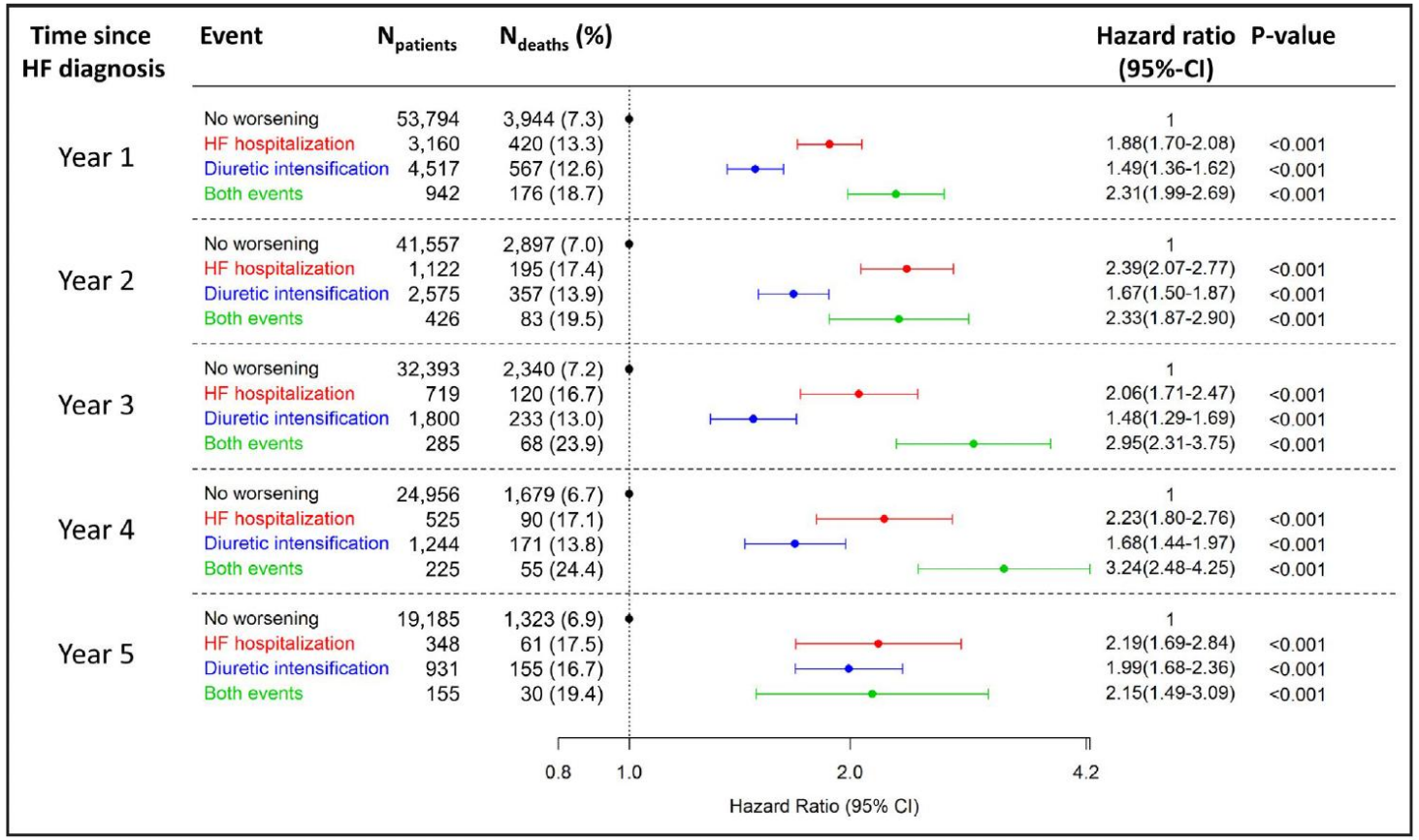
What it is and why it matters

Generally defined by the need for increased oral or diuretic therapy.

- 6% of outpatient events and 4.2% of HF hospitalizations
- One-year mortality:
  - 18.0% after an intensification event
  - 22.6% after HF hospitalization
  - 10.4% for matched controls with neither

ORIGINAL RESEARCH

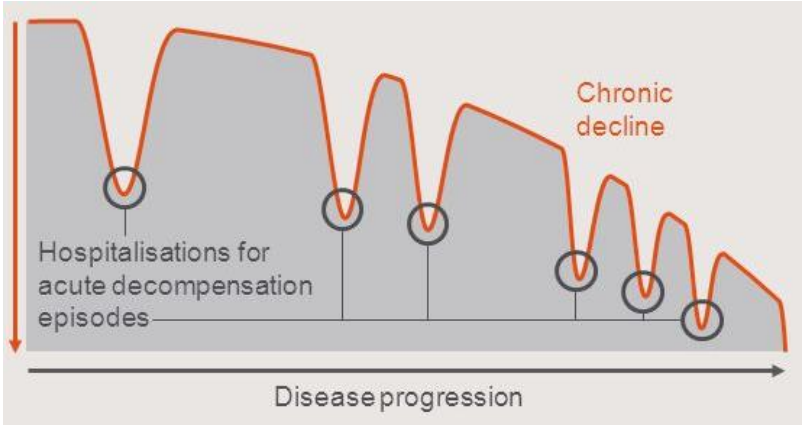
One-Year Mortality After Intensification of Outpatient Diuretic Therapy



Madelaire et al. J Am Heart Assoc. 2020;9:e016010. DOI: 10.1161/JAHA.119.016010

Worsening heart failure

Instruction for use: where is my patient?



Clinical elements

- De novo vs chronic HF
- HF duration
- Medical therapy naive vs optimized medical therapy
- Chronic functional class
- High chronic diuretic dose
- *Triggers*
  - Extra-cardiac triggers (infection, COPD, PE, AKI…)
  - Cardiac triggers (rapid AF, MR, coronary ischemia, drugs….) -> NB always try to understand whether it is a trigger or a consequence of disease progression
  - No triggers (worst case!)
- Actionable treatment targets (AF, MR, coronary ischemia, LBBB, CVP)

Tachicardiomiopatie

Electrical management of heart failure: from pathophysiology to treatment

Frits W. Prinzen [1]*, Angelo Auricchio[2], Wilfried Mullens[3,4], Cecilia Linde [5,6], and Jose F. Huizar[7,8]

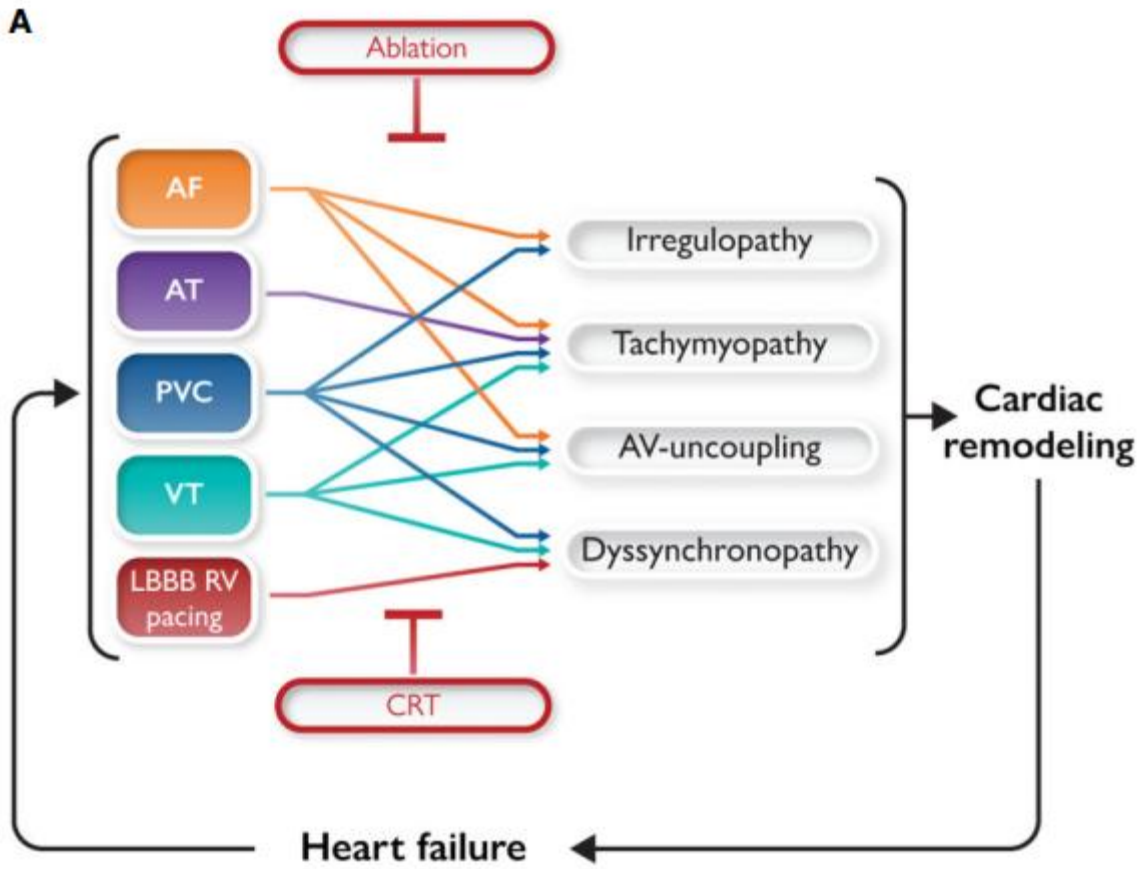
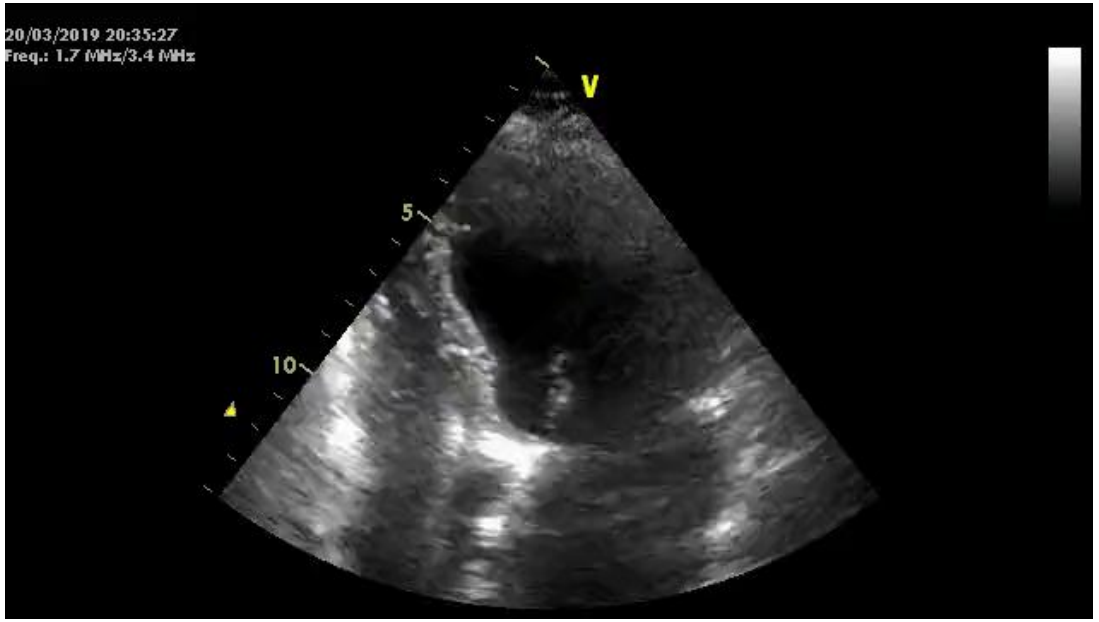
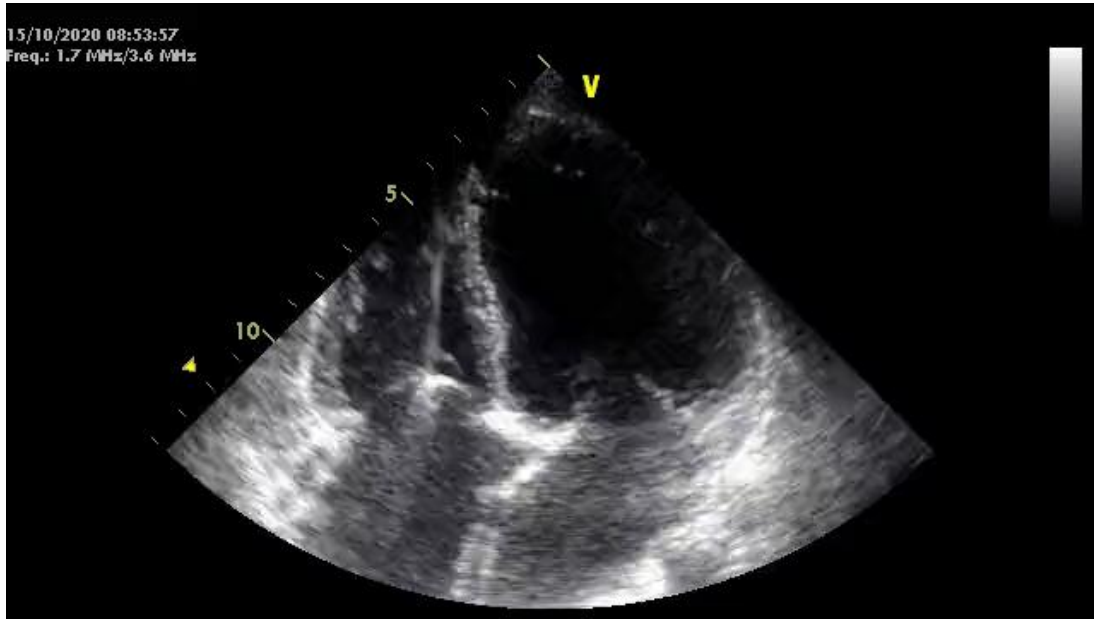


Table 2 Clinical and premature ventricular contraction features to identify premature ventricular contraction-mediated cardiomyopathy

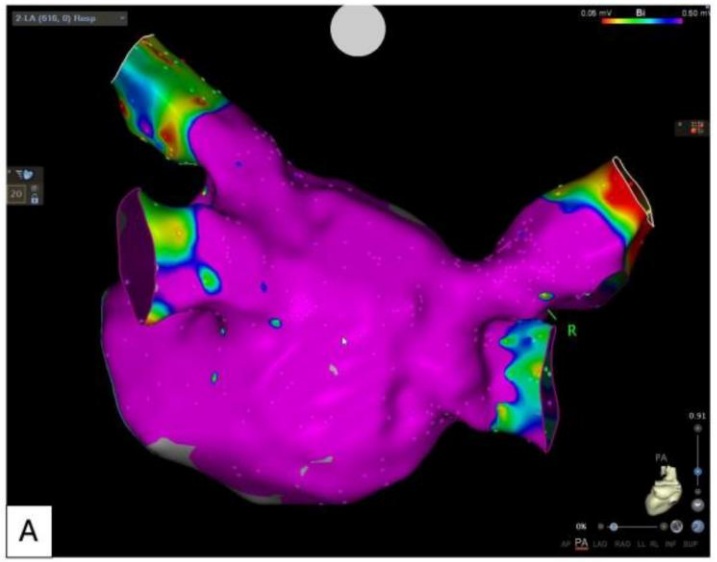
	CM resulting in PVCs	PVCs causing CM
Patient characteristics	Older with known heart disease	Healthy otherwise
Comorbidities	CAD, myocarditis, RV dysplasia[a]	No prior cardiac hx
Echocardiogram	Segmental hypokinesis, LVEF <25%	Global hypokinesis, LVEF 35 ± 10%[b]
Cardiac MRI (late gadolinium enhancement)	Significant scar	Absence or minimal scar burden (≤9 g)
PVC frequency	<5000/24 h (<5%)	≥10 000/24 h (≥10%)
PVC pattern	Multifocal	Monomorphic
QRS morphology	Non-specific	RVOT/LVOT/ epicardial
Response to PVC suppression	No change in LV function	Improvement of LV function

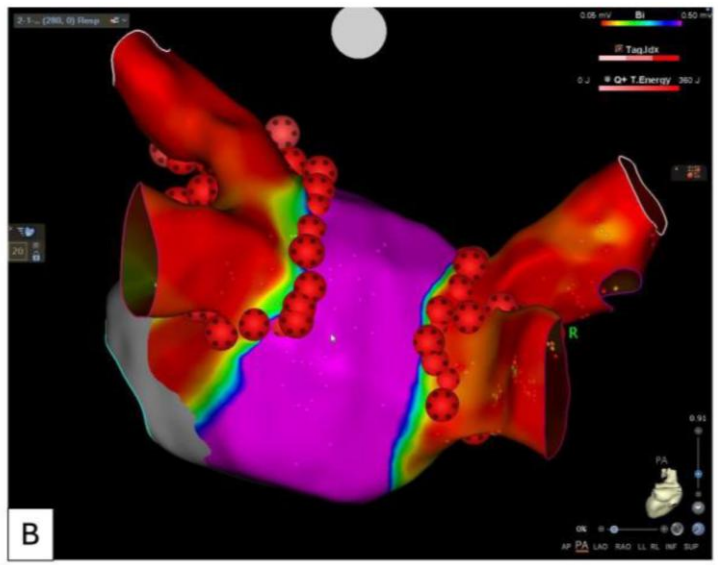
Tachicardiomiopatia (fibrillazione atriale)



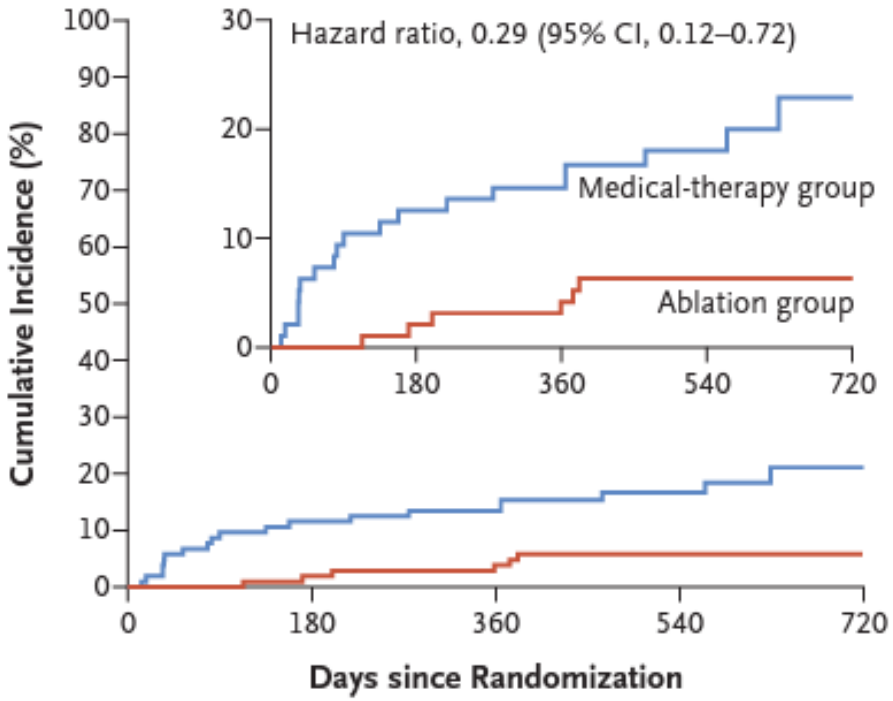


Catheter Ablation in End-Stage Heart Failure with Atrial Fibrillation





B **Death from Any Cause**

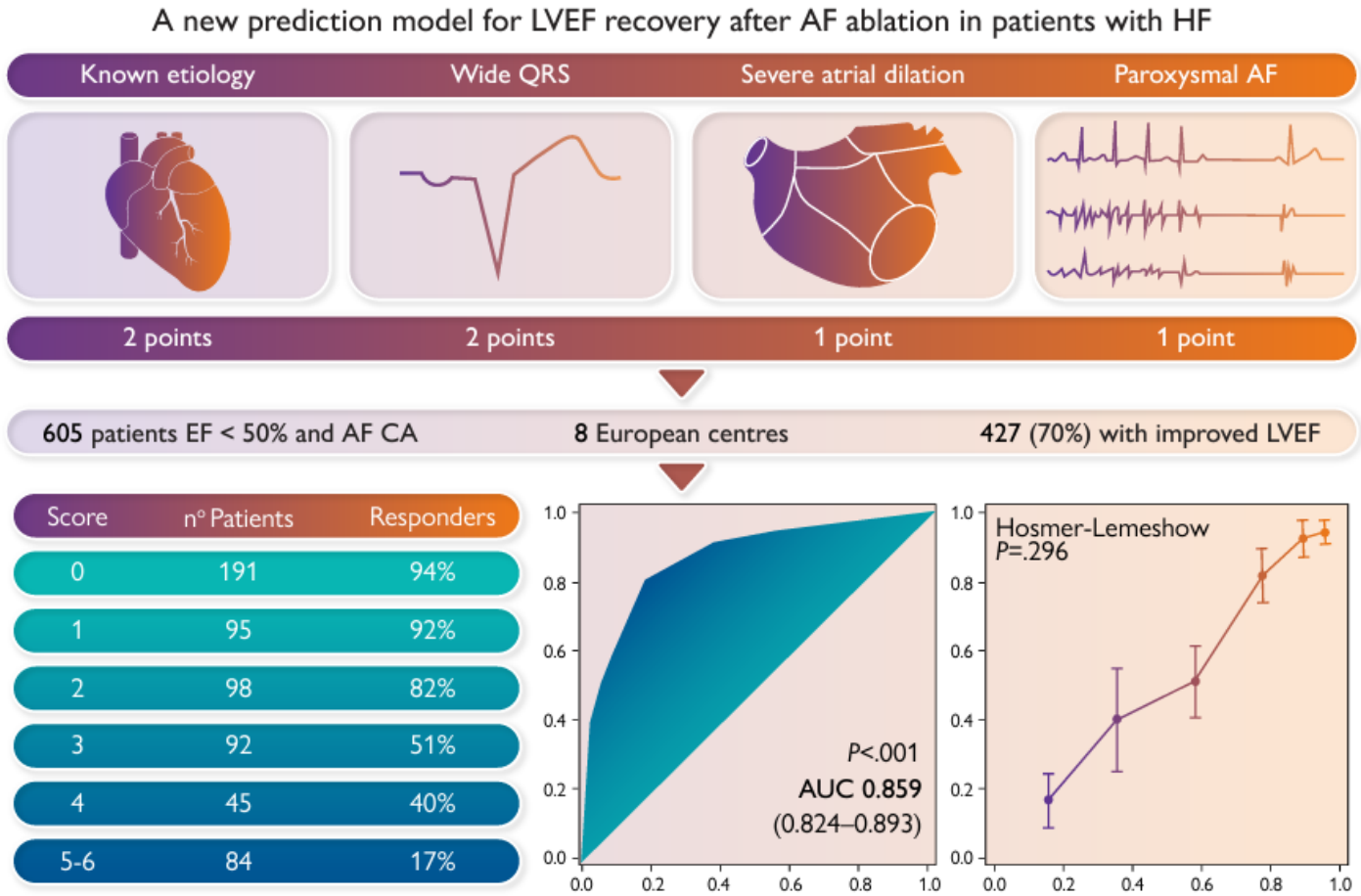


No. at Risk

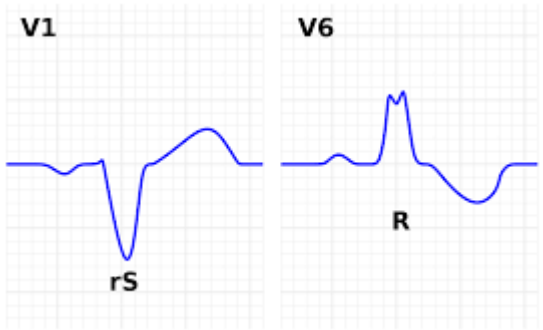
Medical-therapy group	97	85	83	45	13
Ablation group	97	95	93	51	20

N Engl J Med. 2023 Aug 27. doi: 10.1056/NEJMoa2306037.

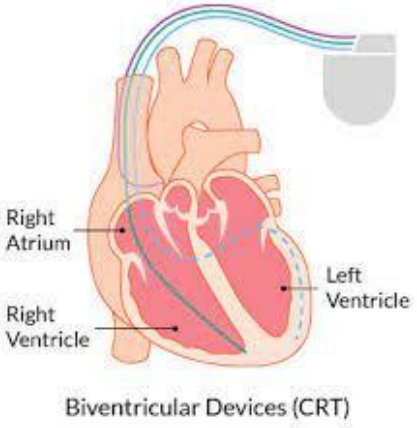
Left ventricular functional recovery after atrial fibrillation catheter ablation in heart failure: a prediction model



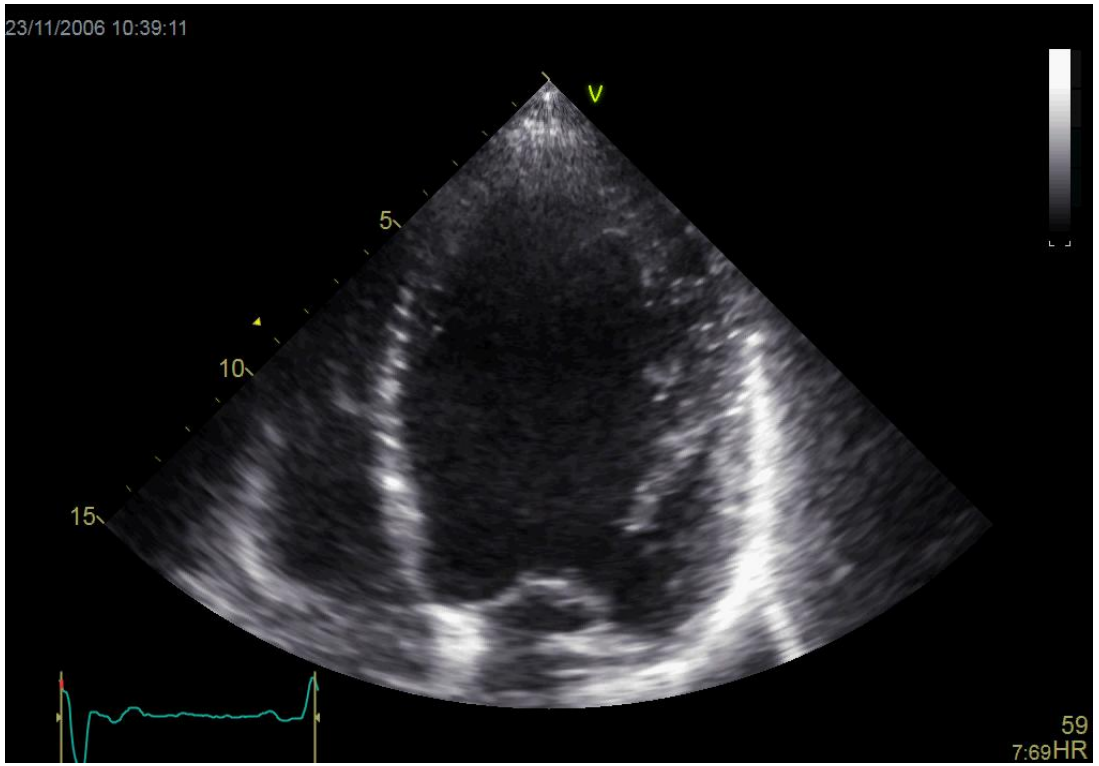
2023 Sep 14;44(35):3327-3335. doi: 10.1093/eurheartj/ehad428



LBBB-cardiomyopathy



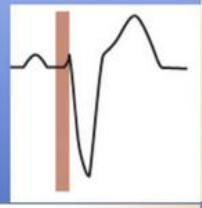
Biventricular Devices (CRT)



Early diagnostic work-up of LBBB-induced cardiomyopathy: Red-Flags

ECG

. Typical LBBB
Wide QRS (> 140 msec) with notching in lateral leads and QS or rS in V2-V3
. No pseudonecrosis

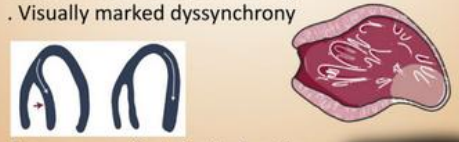


Medical history/genetics

. No family history for DCM
. Exclusion of:
- coronary artery disease
- toxic causes of LV dysfunction (e.g. alcohol)
- peripartum
- thyroid disorders
- sustained supraventricular arrhythmias
- frequent premature ventricular contractions
- inflammatory cardiomyopathy*
- genetic mutations specific for DCM (e.g. Lamin)**

Echocardiography

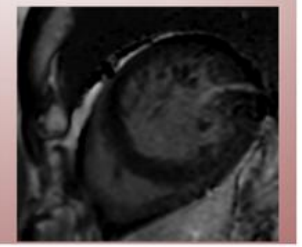
. Usually non severe left ventricular dilatation
. Normal wall thickness
. Septal flash and apical rocking
. Visually marked dyssynchrony



. Non-severe diastolic dysfunction
. Mild left atrial dilatation
. Mild functional mitral regurgitation
. Usually normal right ventricle

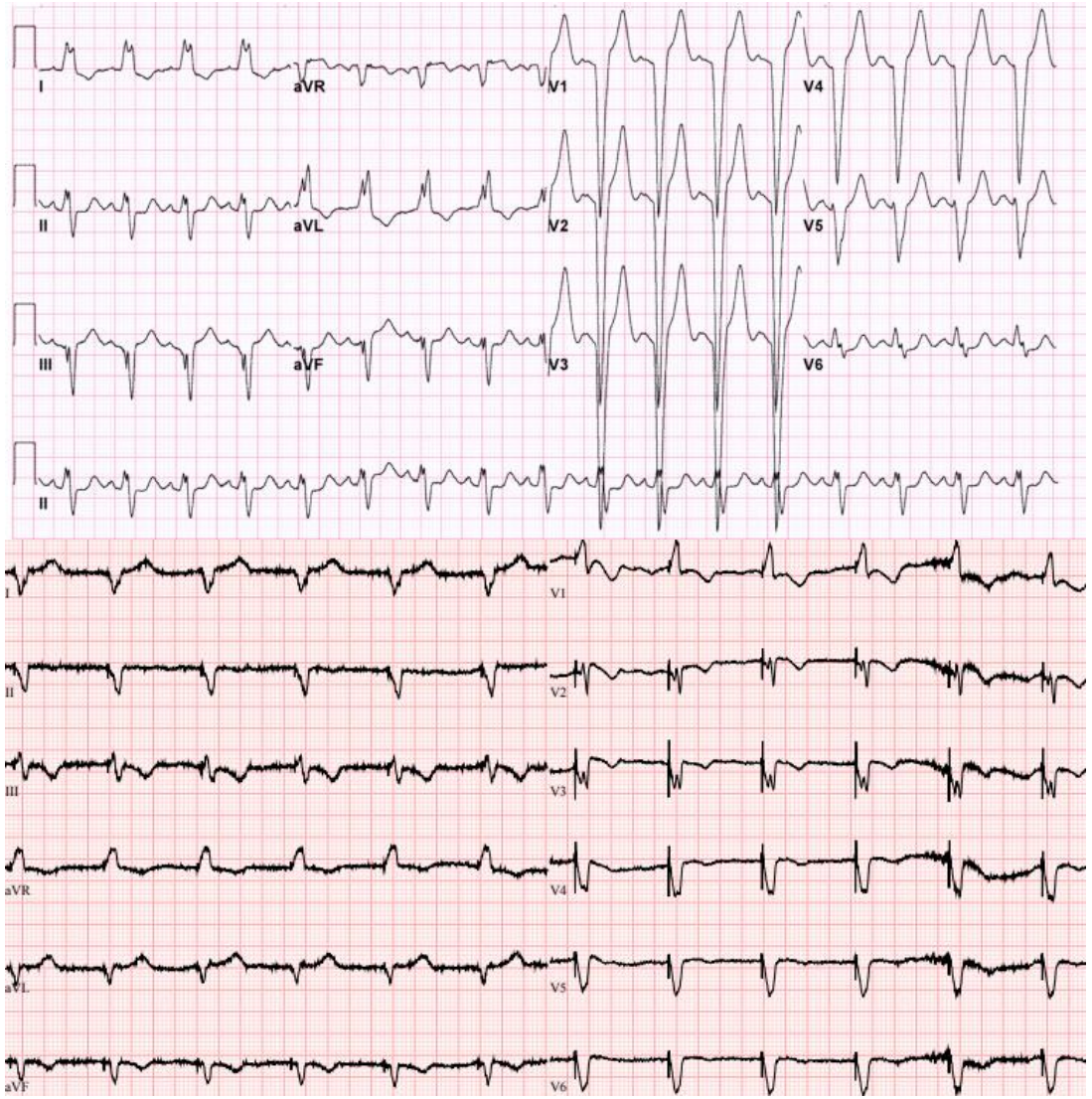
CMR

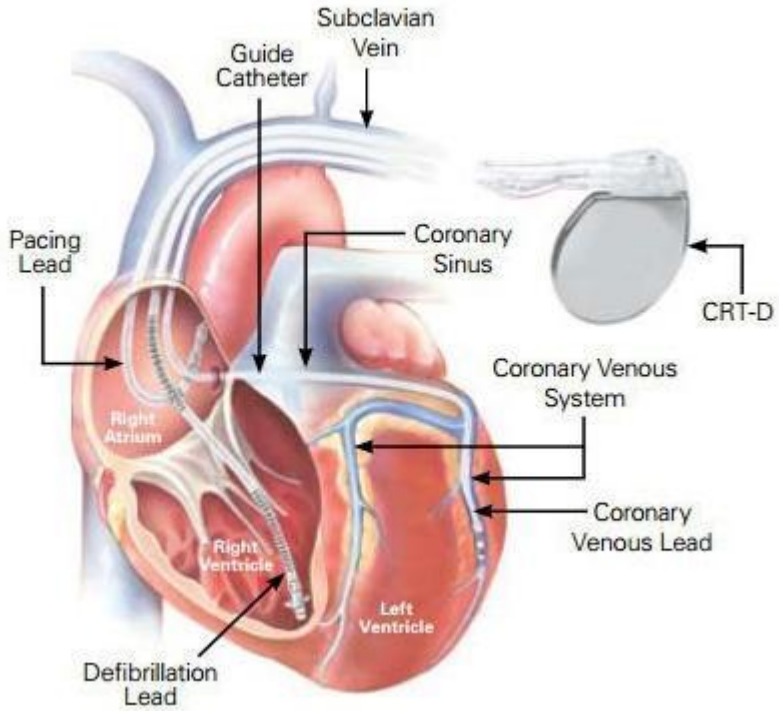
. Tissue characterization unremarkable (i.e. no or non-significant scar or fibrosis – usually no LGE, T1 and T2 mapping within normal limits)



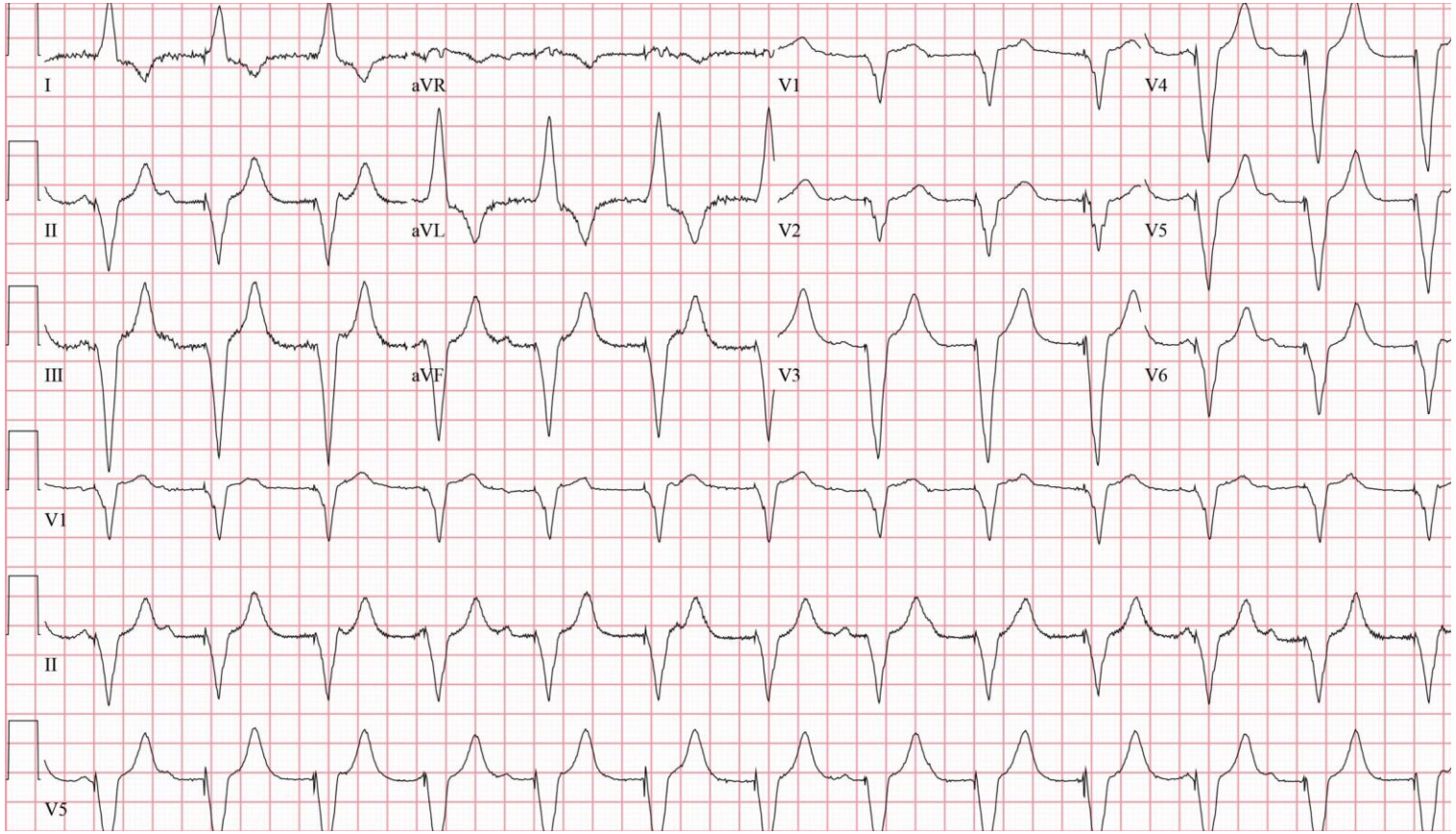
Left bundle branch block-induced cardiomyopathy: a diagnostic proposal for a poorly explored pathological entity☆,☆☆

LBBB-cardiomyopathy

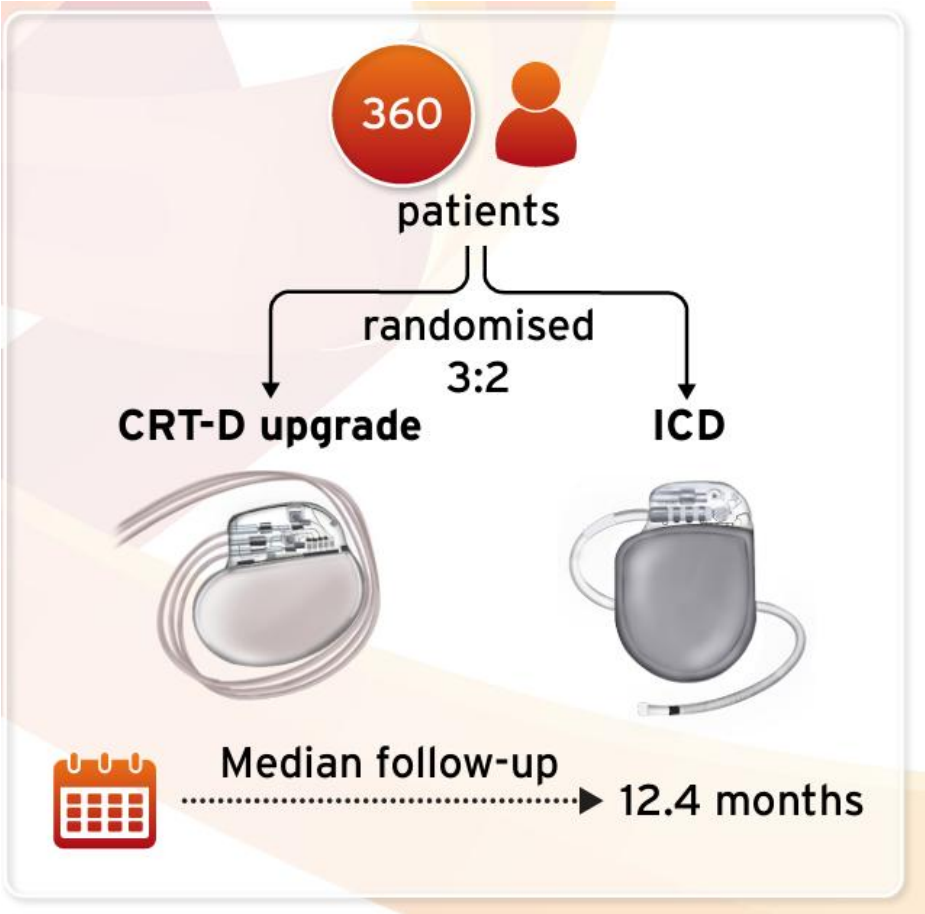


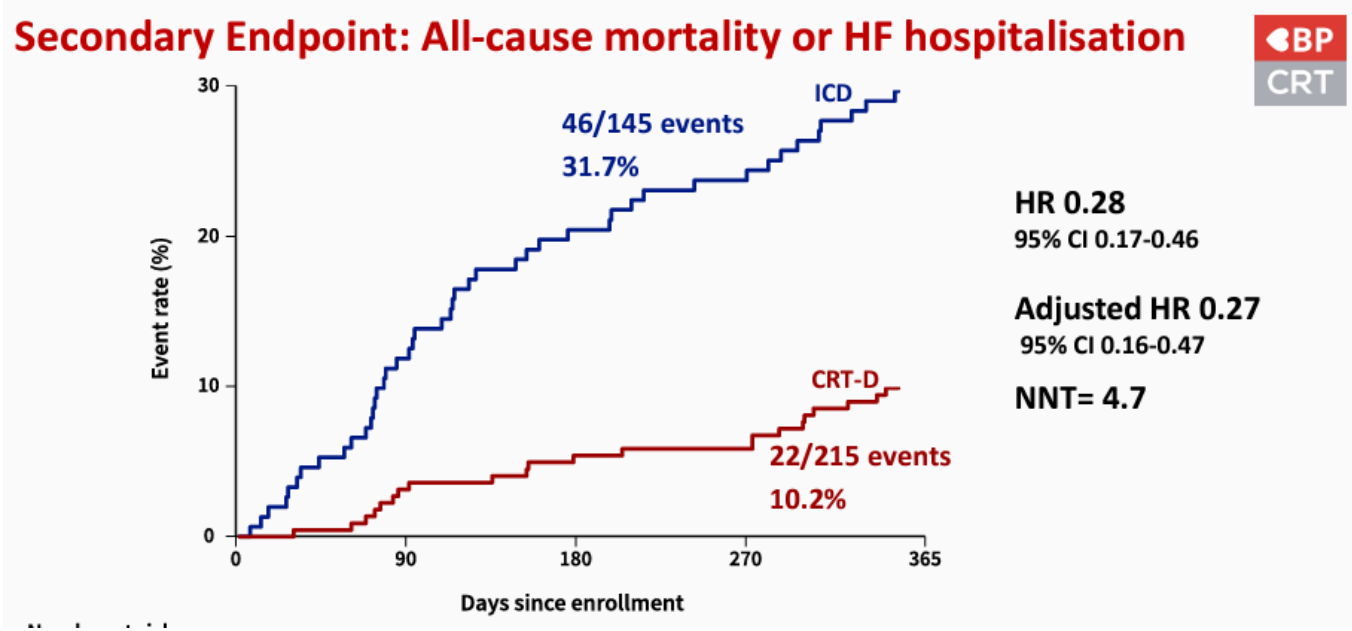


RV pacing



RV pacing



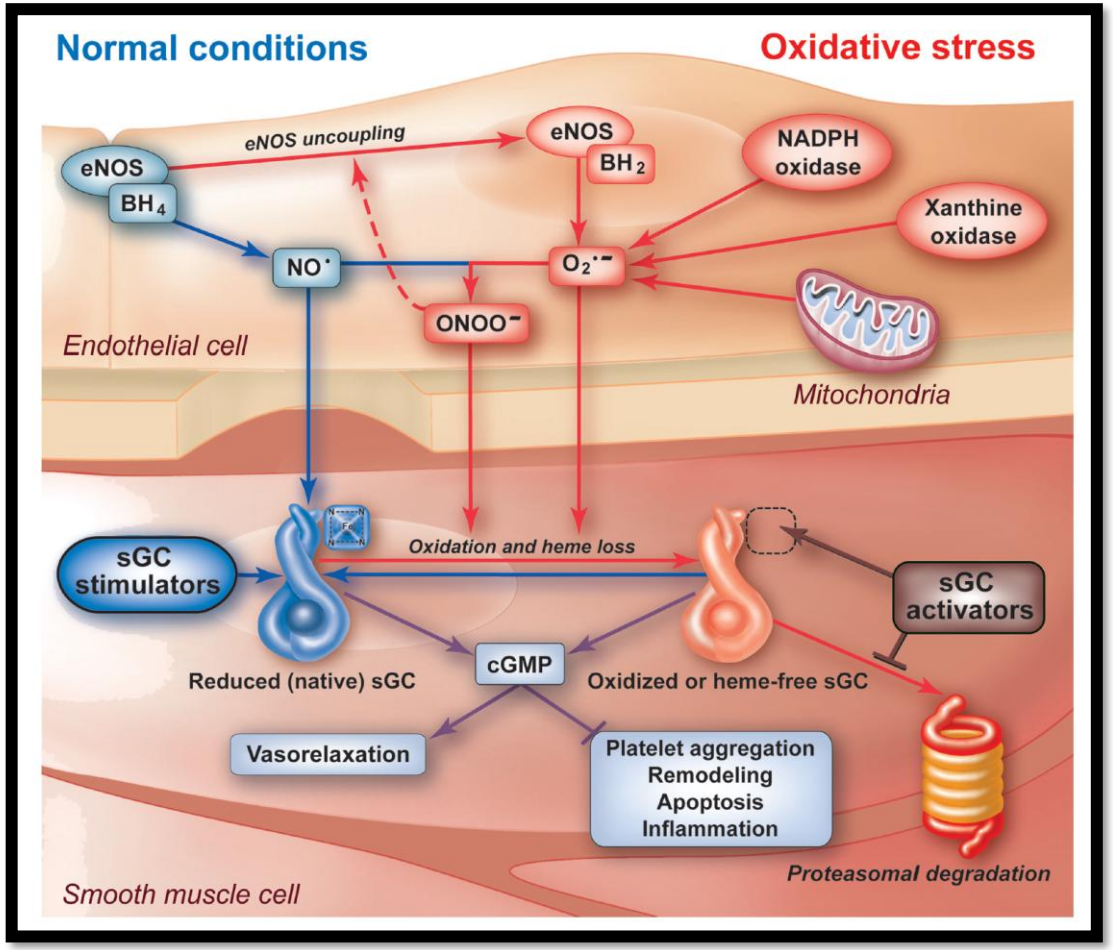


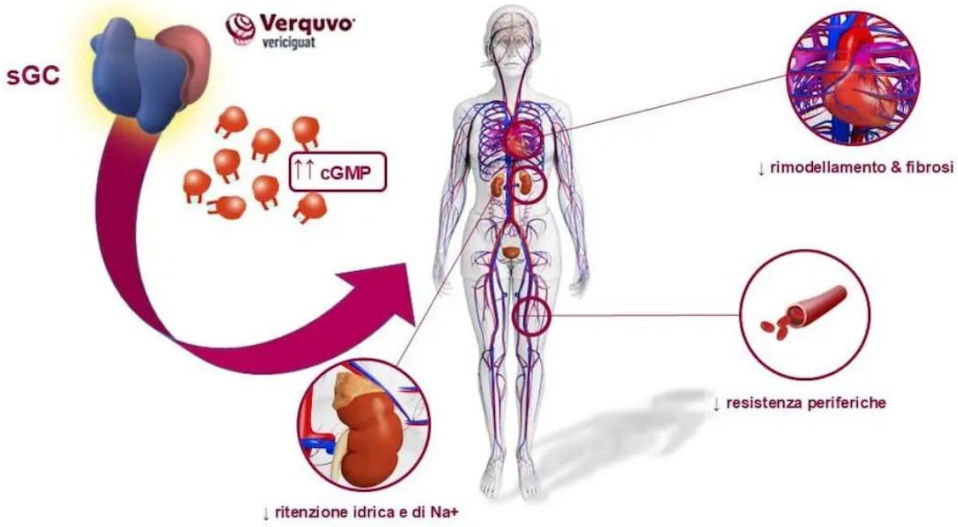
RV pacing 20-100%, QRS > 150 msec

2023 Aug 26;ehad591. doi: 10.1093/eurheartj/ehad591

A new pillar?

sGC stimulators





1. **Vasodilatazione**: Il cGMP induce il rilassamento della muscolatura liscia vascolare, portando alla vasodilatazione e alla riduzione della resistenza vascolare periferica.
2. **Inotropismo positivo**: A livello miocardico, il cGMP migliora la contrattilità cardiaca (inotropismo positivo) attraverso il miglioramento del ciclo di rilascio del calcio e della sensibilità al calcio.

History first!

Riociguat for Patients With Pulmonary Hypertension Caused by Systolic Left Ventricular Dysfunction

A Phase IIb Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Hemodynamic Study

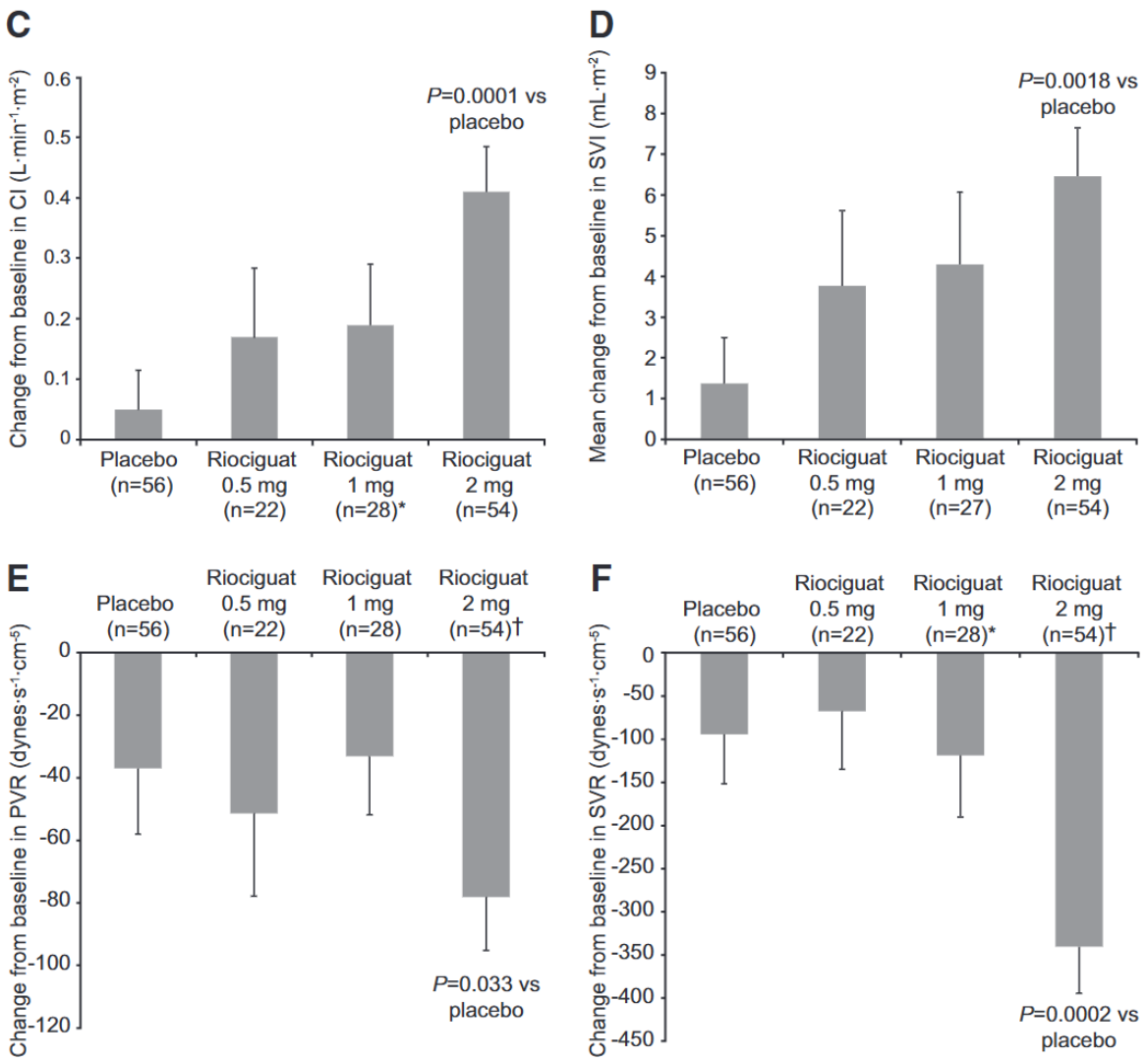
Parameter	Placebo (n=69)	Riociguat 0.5 mg (n=32)	Riociguat 1 mg (n=33)	Riociguat 2 mg (n=67)	Total (n=201)
Male sex, n (%)	61 (88)	26 (81)	30 (91)	55 (82)	172 (86)
Mean age (range), y	58.9 (25–79)	57.2 (36–78)	55.1 (28–74)	59.3 (26–76)	58.1 (25–79)
Mean (SEM) body mass index, $kg \cdot m^{-2}$	28.7 (0.7)	29.2 (1.0)	28.2 (0.8)	28.9 (0.6)	…
6-min walking distance (SEM), m	382.1 (14.9)	416.6 (16.9)	401.9 (17.7)	380.9 (15.4)	…
LVEF (SEM), %	27.1 (0.6)	27.0 (0.9)	28.8 (0.8)	28.4 (0.7)	…

Table 2. Hemodynamic Results From Right Heart Catheterization (Per-Protocol Population)

Parameter	Placebo (n=56)	Riociguat 0.5 mg (n=22)	Riociguat 1 mg (n=28)	Riociguat 2 mg (n=54)	Placebo-Corrected LS Mean Difference (95% CI), Riociguat 2 mg vs Placebo	*P* Value, Riociguat 2 mg vs Placebo*
Mean pulmonary artery pressure, mm Hg						
Baseline	40.4±1.2	37.9±2.2	35.2±1.8	38.1±1.3	–2.7 (–6.0 to 0.6)	0.10
Week 16	36.4±1.4	33.4±2.4	34.5±2.2	32.0±1.6		

Bonderman D, et al. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. Circulation. 2013 Jul 30;128(5):502-11

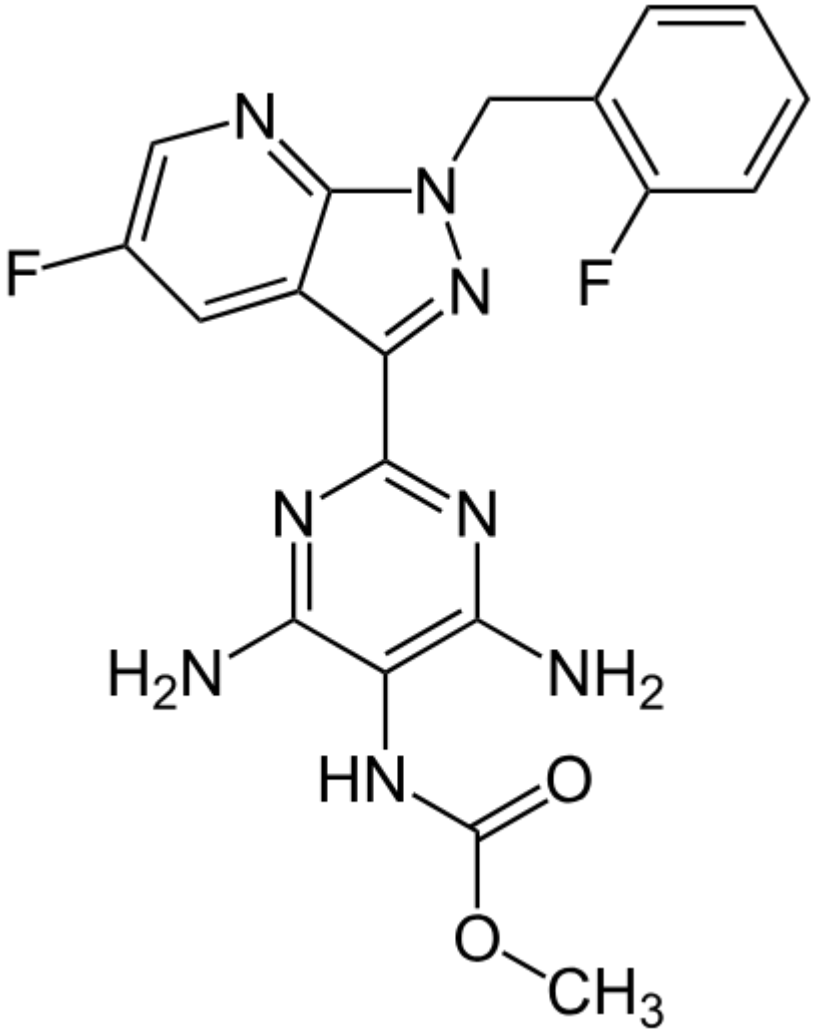
History first!



Bonderman D, et al. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study. Circulation. 2013 Jul 30;128(5):502-11

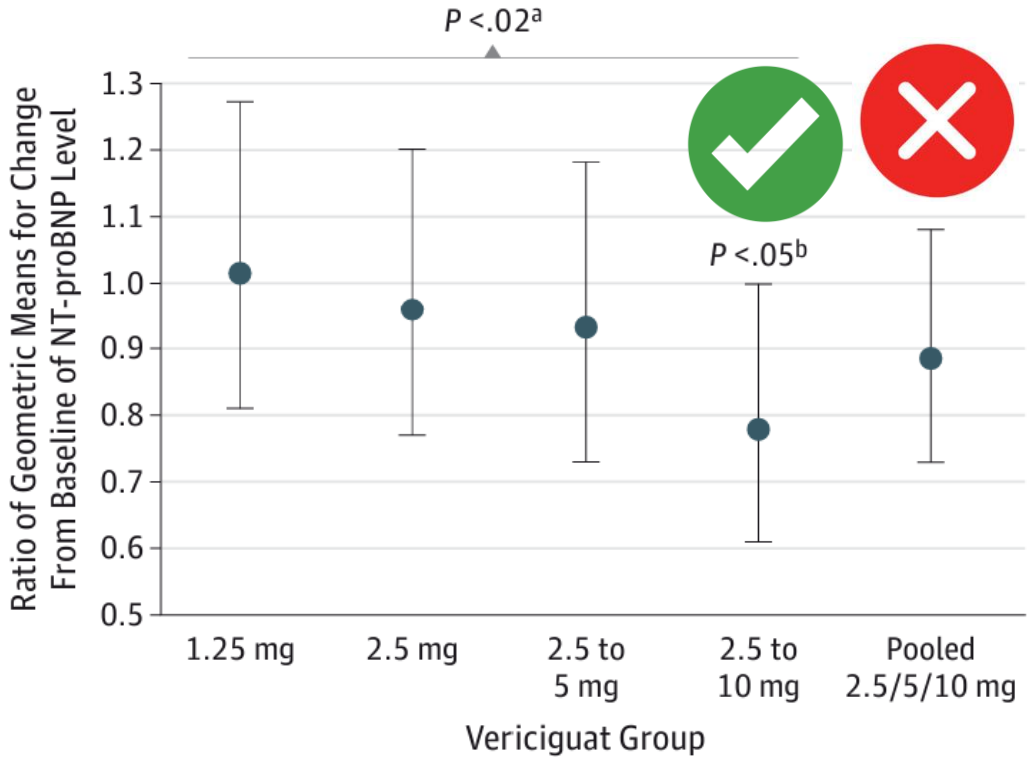
Vericiguat

- Stimulator of the soluble guanylate cyclase.
- Longer half-life compared to riociguat.
- It can be administered once daily.



SOCRATES-REDUCED

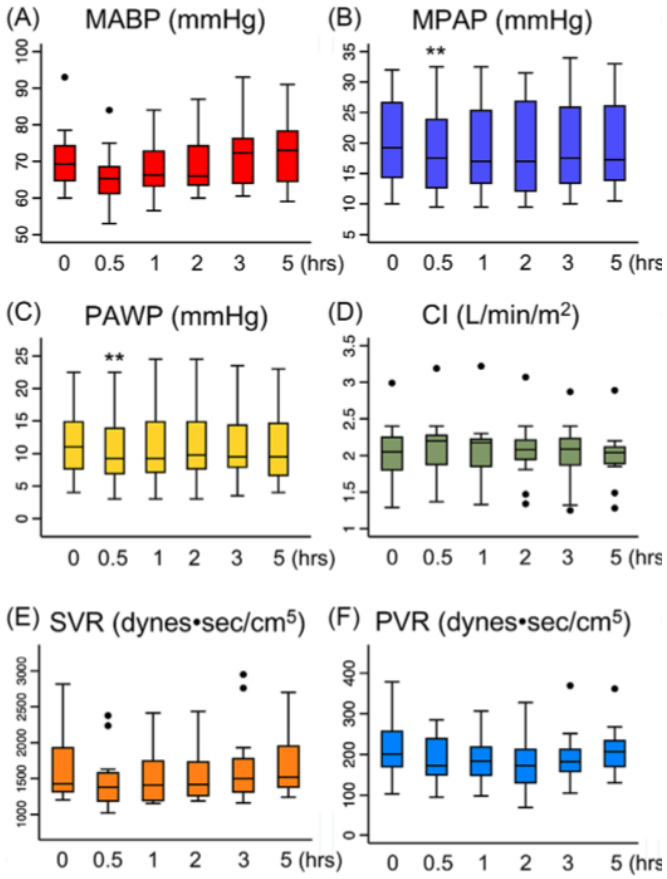
Figure 2. Change From Baseline in NT-proBNP Level for Vericiguat Dose Groups Compared With Placebo (Per-Protocol Set)



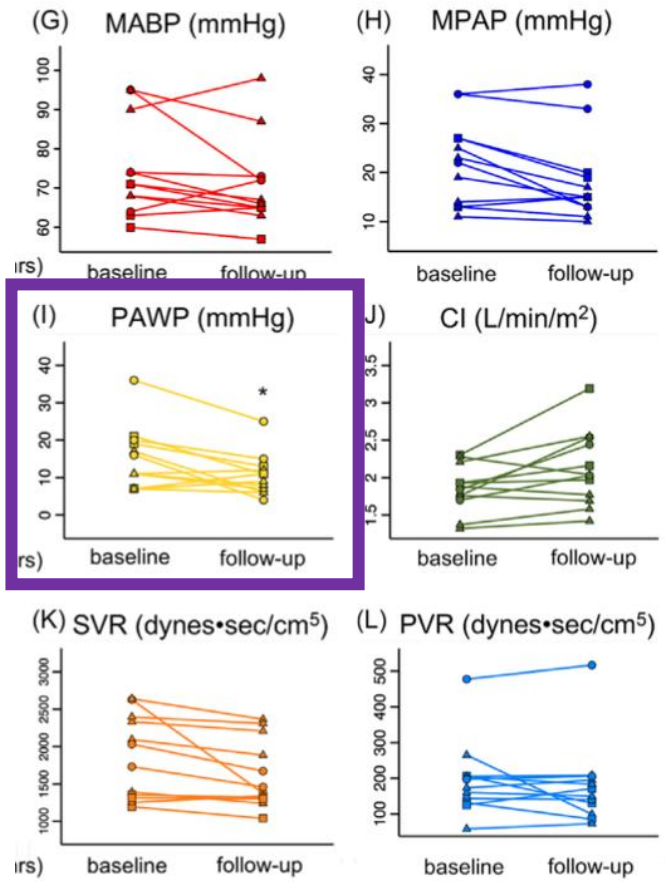
Gheorghiade M. Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction: The SOCRATES-REDUCED Randomized Trial. JAMA. 2015 Dec 1;314(21):2251-62

Vericiguat – hemodynamic effects (12 pts)

ACUTE EFFECTS



CHRONIC EFFECTS (105 days)



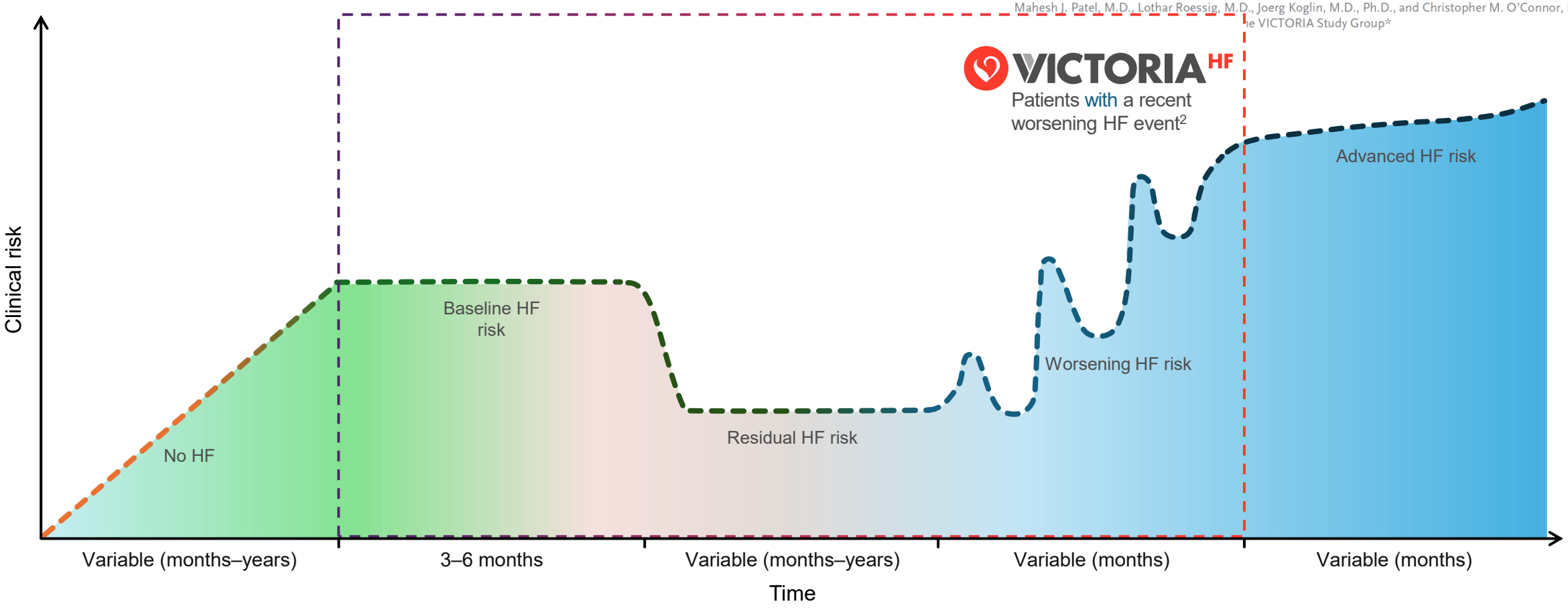
Suzuki et al. ESC Heart Fail. 2024 Aug;11(4):2451-2454.

VICTORIA trial

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 14, 2020 VOL. 382 NO. 20

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D., Justin Ezekowitz, M.B., B.Ch., Adrian F. Hernandez, M.D., M.H.S., Javed Butler, M.D., M.P.H., M.B.A., Carolyn S.P. Lam, M.B., B.S., Ph.D., Piotr Ponikowski, M.D., Adriaan A. Voors, M.D., Ph.D., Gang Jia, Ph.D., Steven E. McNulty, M.S., Mahesh J. Patel, M.D., Lothar Roessig, M.D., Joerg Koglin, M.D., Ph.D., and Christopher M. O'Connor, M.D., ...e VICTORIA Study Group*

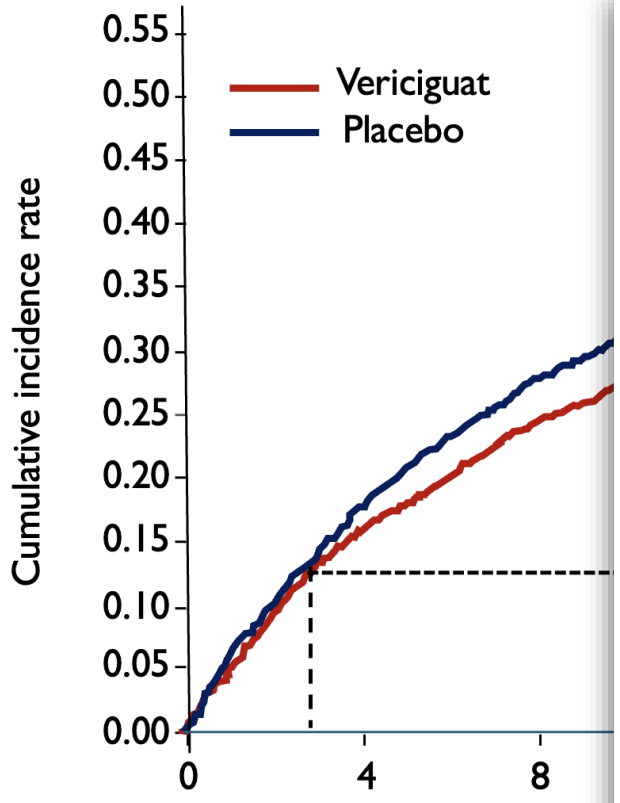


VICTORIA trial

N=5050

Symptomatic chronic HFrEF population:

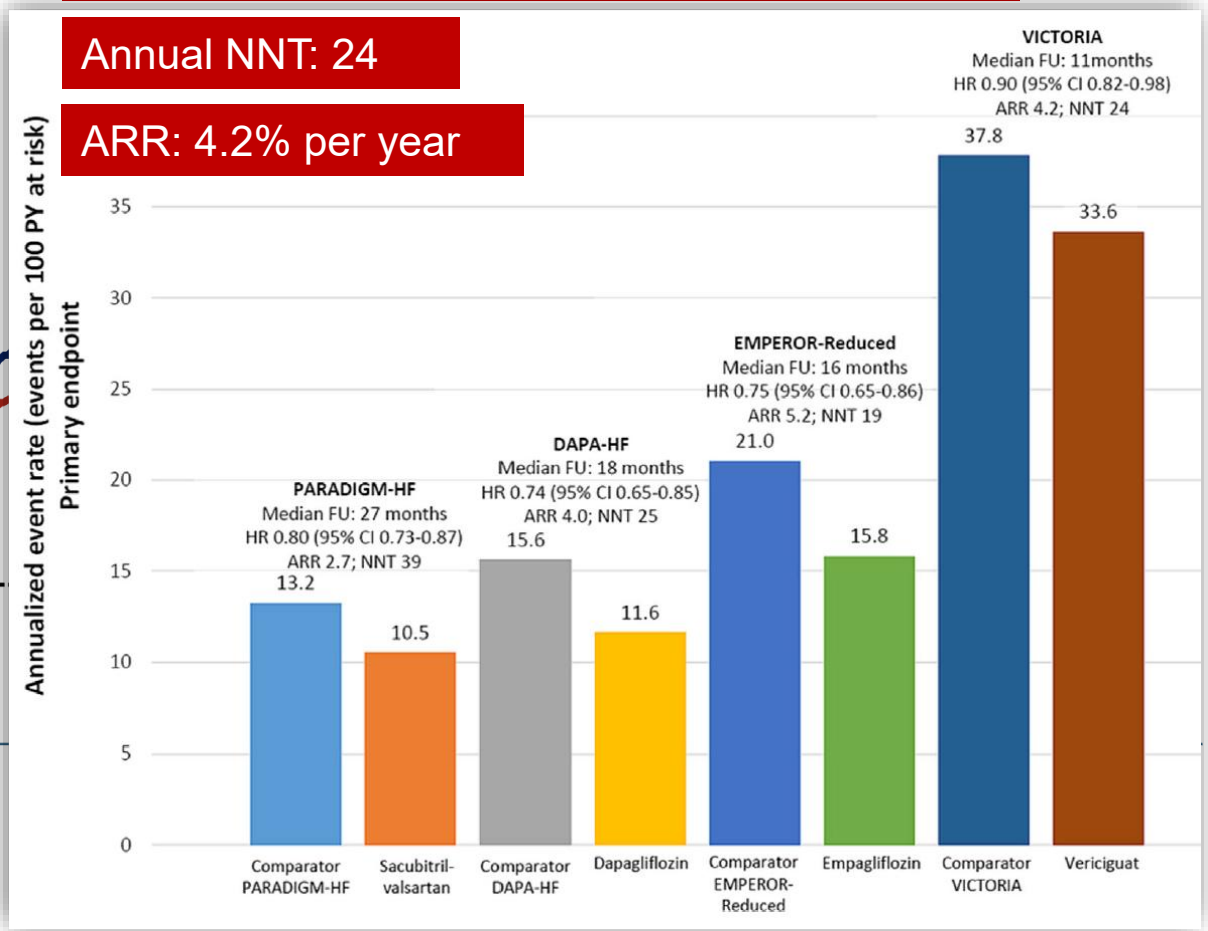
- HFrEF <45%
- NYHA II–IV
- Receiving HF SOC
- Prior HFH within 6 months or outpatient IV diuretic for HF within 3 months
- Elevated NP*
- SBP >100
- eGFR>15 ml/min/1.73 m^2



HR=0.90 (95% CI 0.82–0.98) P=0.02

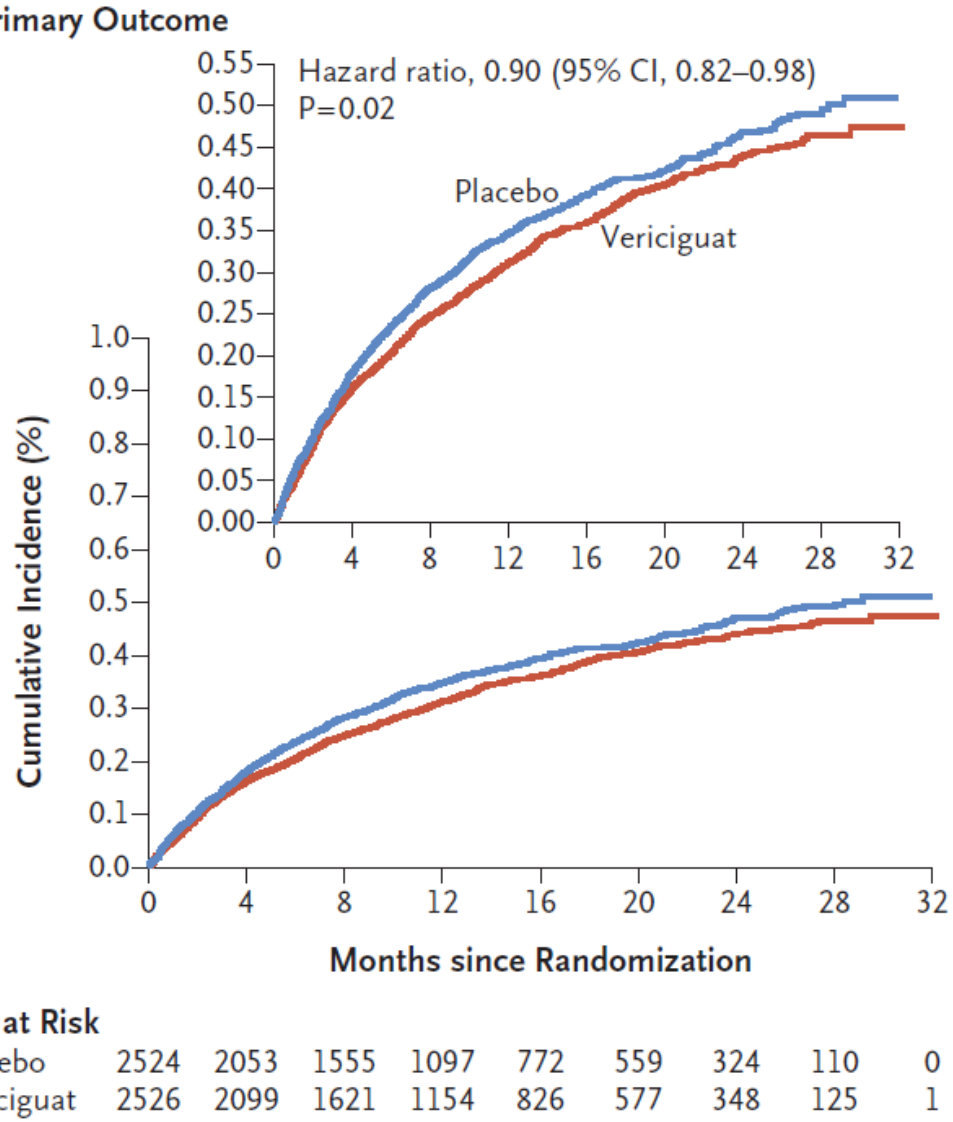
Annual NNT: 24

ARR: 4.2% per year



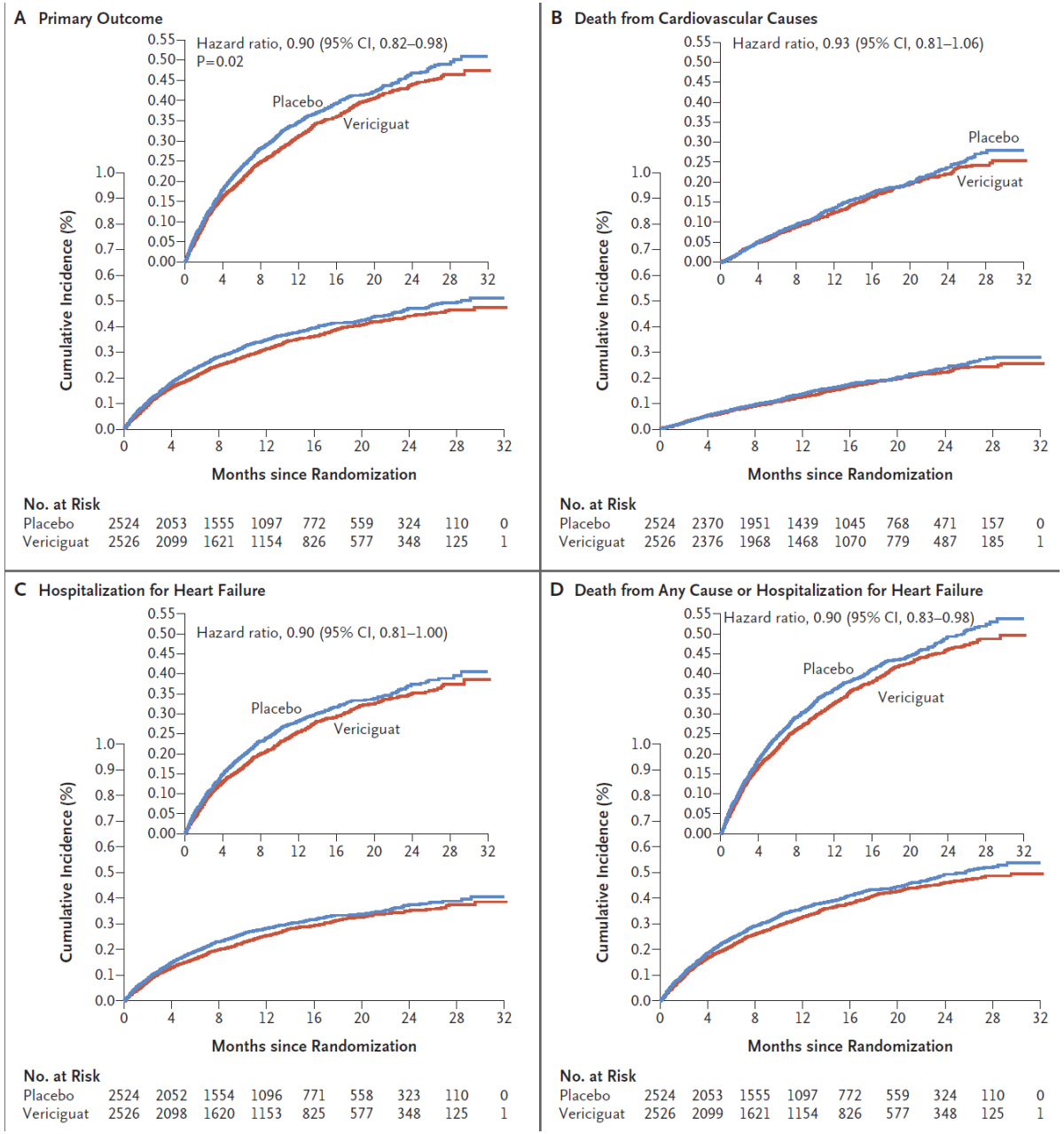
*Natriuretic peptides cut off: BNP level > 300 pg/mL (>500 if AF) - NT-proBNP > 1000 pg/mL (>1600 if AF)

VICTORIA trial



Armstrong PW, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020 May 14;382(20):1883-1893

VICTORIA trial



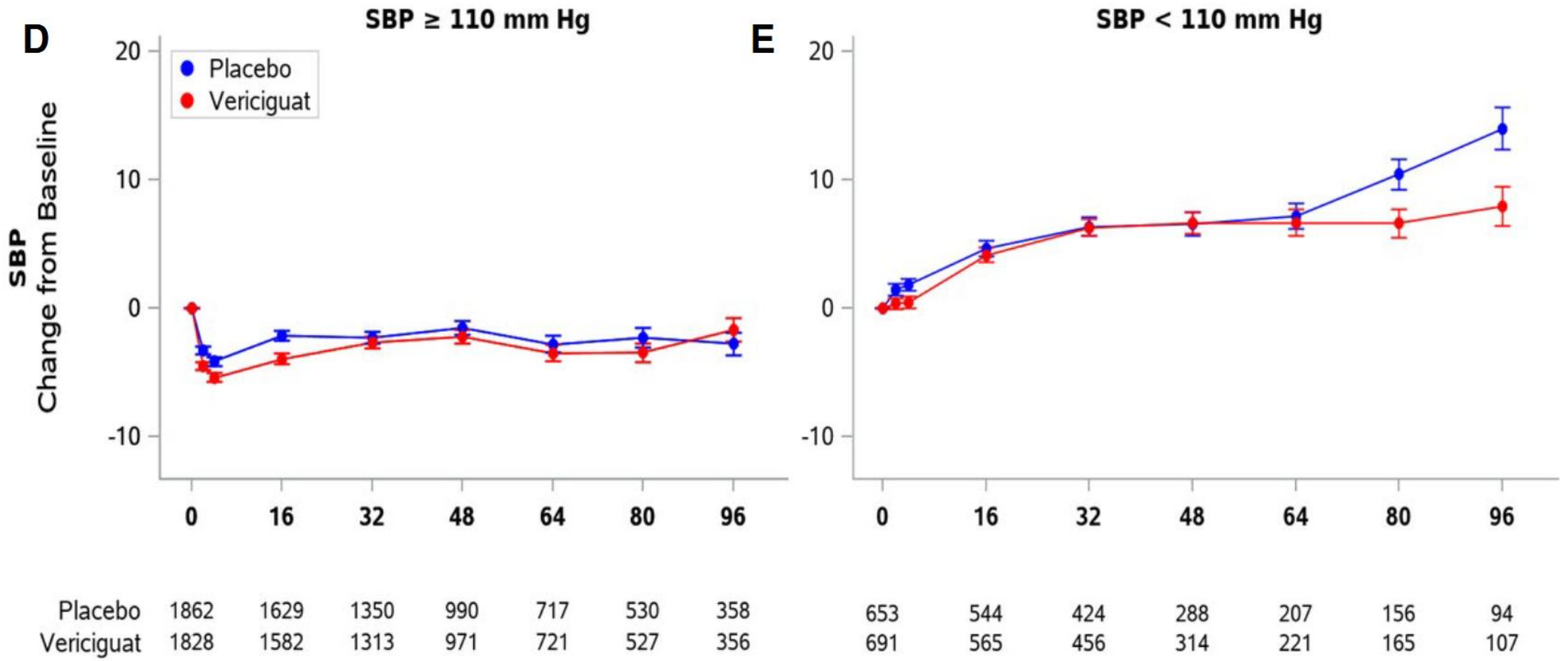
Armstrong PW, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020 May 14;382(20):1883-1893

Vericiguat: is it safe?

Three main concerns when starting a new drug:

- Blood pressure lowering
- Worsening renal function
- Hyperkalemia

Vericiguat – blood pressure



Lam CSP. Blood Pressure and Safety Events With Vericiguat in the VICTORIA Trial. J Am Heart Assoc. 2021 Nov 16;10(22):e021094

Vericiguat –renal function

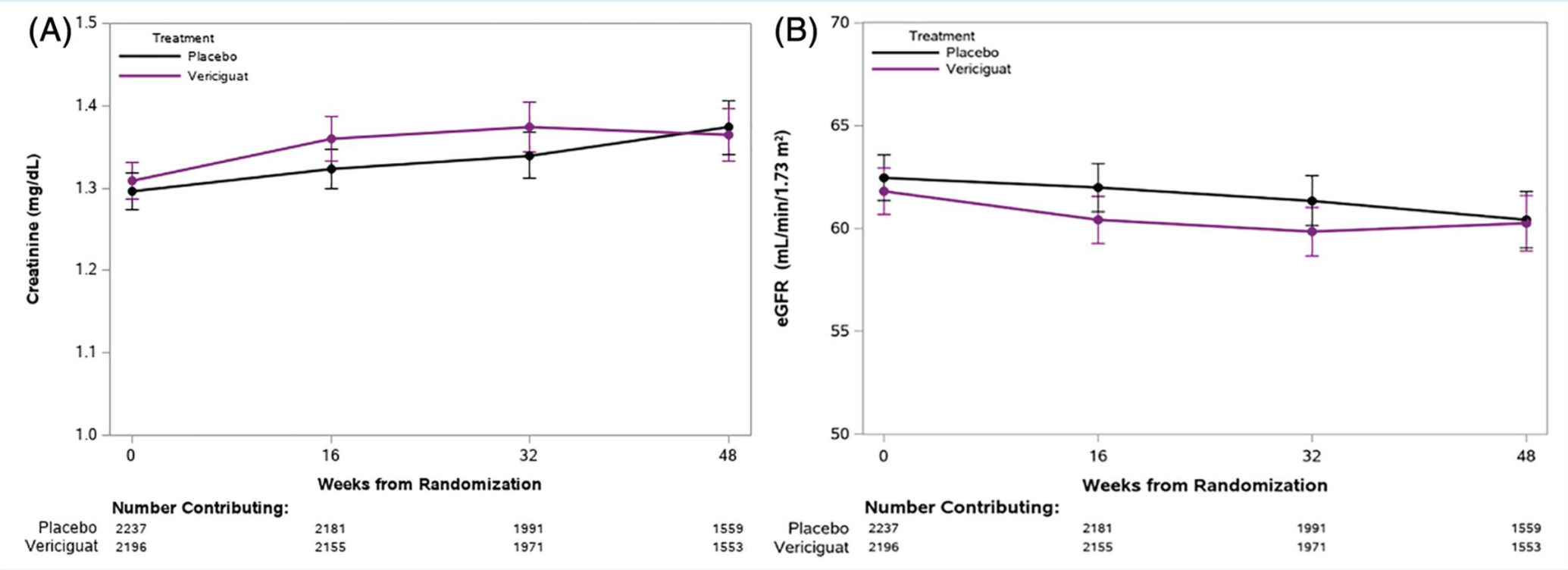


Figure 1 Change in serum creatinine (*A*) and estimated glomerular filtration rate (eGFR, *B*) over time in vericiguat- and placebo-treated patients was assessed with a linear mixed model. This figure shows no differences in the change in creatinine ($P = 0.18$) and eGFR ($P = 0.50$) between the vericiguat and placebo groups, as evaluated by the interaction between treatment and study visit in the model.

Voors AA. Renal function and the effects of vericiguat in patients with worsening heart failure with reduced ejection fraction: insights from the VICTORIA (Vericiguat Global Study in Subjects with HFrEF) trial. Eur J Heart Fail. 2021 Aug;23(8):1313-1321

Vericiguat – hyperkalemia

Table 2 Safety outcomes by treatment and estimated glomerular filtration rate category

	eGFR ≤30 mL/min/1.73 m²		30 < eGFR ≤60 mL/min/1.73 m²		eGFR >60 mL/min/1.73 m²		Overall (*n* = 4956)
	Vericiguat (*n* = 261)	Placebo (*n* = 246)	Vericiguat (*n* = 1060)	Placebo (*n* = 1070)	Vericiguat (*n* = 1153)	Placebo (*n* = 1166)	
Syncope	11 (4.2)	10 (4.1)	48 (4.5)	38 (3.6)	41 (3.6)	37 (3.2)	185 (3.7)
Symptomatic hypotension	29 (11.1)	22 (8.9)	109 (10.3)	98 (9.2)	86 (7.5)	72 (6.2)	416 (8.4)
Hyperkalaemia	21 (8.0)	25 (10.2)	71 (6.7)	84 (7.9)	29 (2.5)	39 (3.3)	269 (5.4)
Treatment discontinuation	144 (55.2)	138 (56.1)	436 (41.1)	435 (40.7)	371 (32.2)	368 (31.6)	1892 (38.2)
Reason for discontinuation							
Adverse event	30 (20.8)	32 (23.2)	83 (19.0)	75 (17.2)	59 (15.9)	50 (13.6)	329 (17.4)
Death	55 (38.2)	57 ((41.3)	156 (35.8)	173 (39.8)	141 (38.0)	149 (40.5)	731 (38.6)
Lost to follow-up	2 (1.4)	2 (1.4)	2 (0.5)	2 (0.5)	4 (1.1)	7 (1.9)	19 (1.0)
Non-compliance with study drug	2 (1.4)	6 (4.3)	23 (5.3)	24 (5.5)	22 (5.9)	19 (5.2)	96 (5.1)
Physician decision	30 (20.8)	22 (15.9)	78 (17.9)	70 (16.1)	65 (17.5)	62 (16.8)	327 (17.3)
Protocol deviation	1 (0.7)	1 (0.7)	4 (0.9)	1 (0.2)	3 (0.8)	0 (0.0)	10 (0.5)
Withdrawal by patient	24 (16.7)	18 (13.0)	90 (20.6)	90 (20.7)	77 (20.8)	81 (22.0)	380 (20.1)
Worsening renal function by 16 weeks	47/210 (22.4)	35/184 (19.0)	183/892 (20.5)	173/921 (18.8)	116/1016 (11.4)	92/1041 (8.8)	646/4264 (15.2)

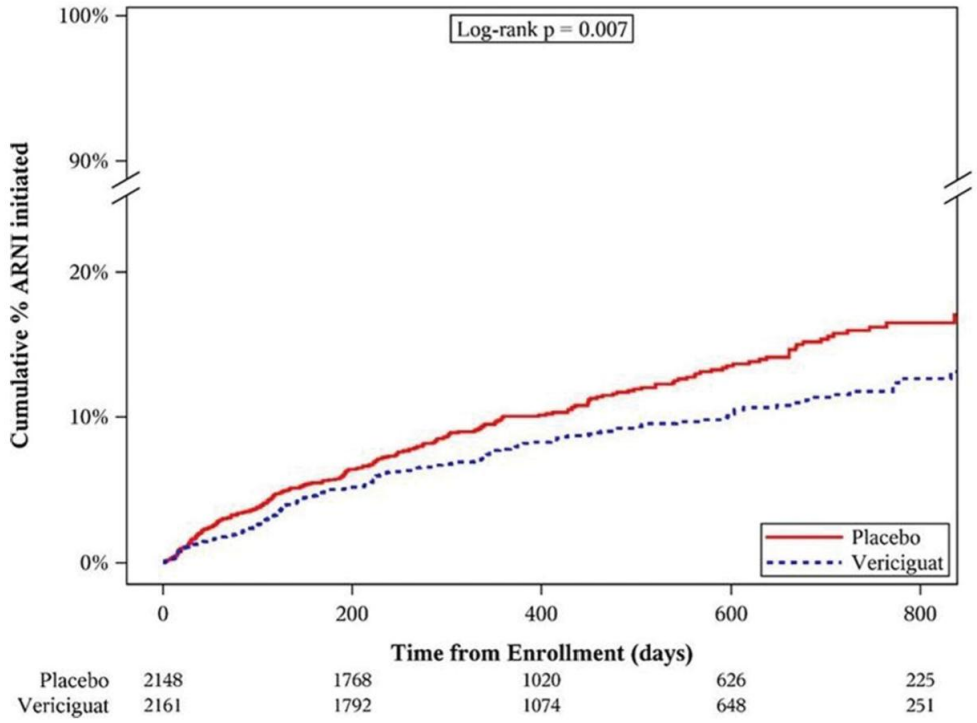
Voors AA. Renal function and the effects of vericiguat in patients with worsening heart failure with reduced ejection fraction: insights from the VICTORIA (Vericiguat Global Study in Subjects with HFrEF) trial. Eur J Heart Fail. 2021 Aug;23(8):1313-1321

Vericiguat – more room for ARNI?

Efficacy and safety of vericiguat in patients with HFrEF treated with sacubitril/valsartan: results from the VICTORIA trial

M. Senni[1], W. Alemayehu[2], D. Sim[3], F. Edelmann[4], J. Butler[5], J.A. Ezekowitz[2], A.F. Hernandez[6], C.S.P. Lam[3], C.M. O'Connor[7], B. Pieske[4], P. Ponikowski[8], L. Roessig[9], A.A. Voors[10], C. McMullan[11], P.W. Armstrong[2]

Figure. Time to initiation of ARNI in patients who were not already on ARNI at randomization (n=4309).



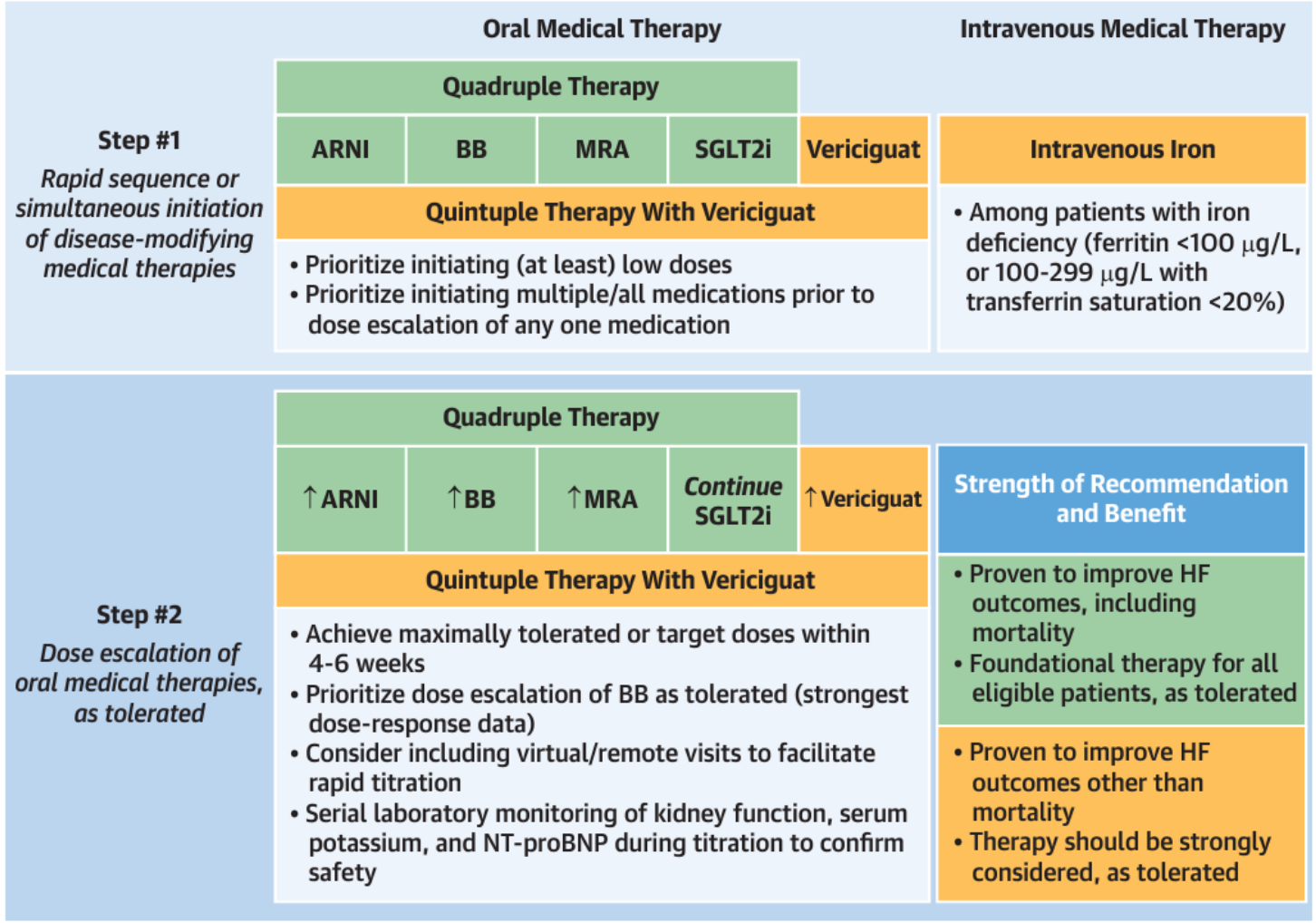
2021, ESC Congress

Vericiguat – real-world data from Germany (1416 pts)

	Prior to vericiguat initiation (n = 1416)	After to vericiguat initiation (n = 1416)
HF co-medication		
BB	1113 (78.6%)	1202 (84.9%)
ACEi	236 (16.7%)	204 (14.4%)
ARB	179 (12.6%)	168 (11.9%)
ARNi	801 (56.6%)	949 (67.0%)
Any RASi	1113 (78.6%)	1193 (84.3%)
MRA	769 (54.3%)	943 (66.6%)
SGLT2i	724 (51.1%)	1040 (73.4%)
Diuretic medication	1124 (79.4%)	1243 (87.8%)
Digitalis	141 (10.0%)	175 (12.4%)
Ivabradine	82 (5.8%)	104 (7.3%)
HF drug combinations		
≤ 1 drug class	252 (17.8%)	103 (7.3%)
2 drug classes	381 (26.9%)	319 (22.5%)
3 drug classes	375 (26.5%)	375 (26.5%)
4 drug classes	408 (28.8%)	619 (43.7%)

Kerwagen F, et al. Real-world characteristics and use patterns of patients treated with vericiguat: A nationwide longitudinal cohort study in Germany. Eur J Clin Pharmacol. 2024;80(6):931-940.

Quintuple therapy for heart failure?

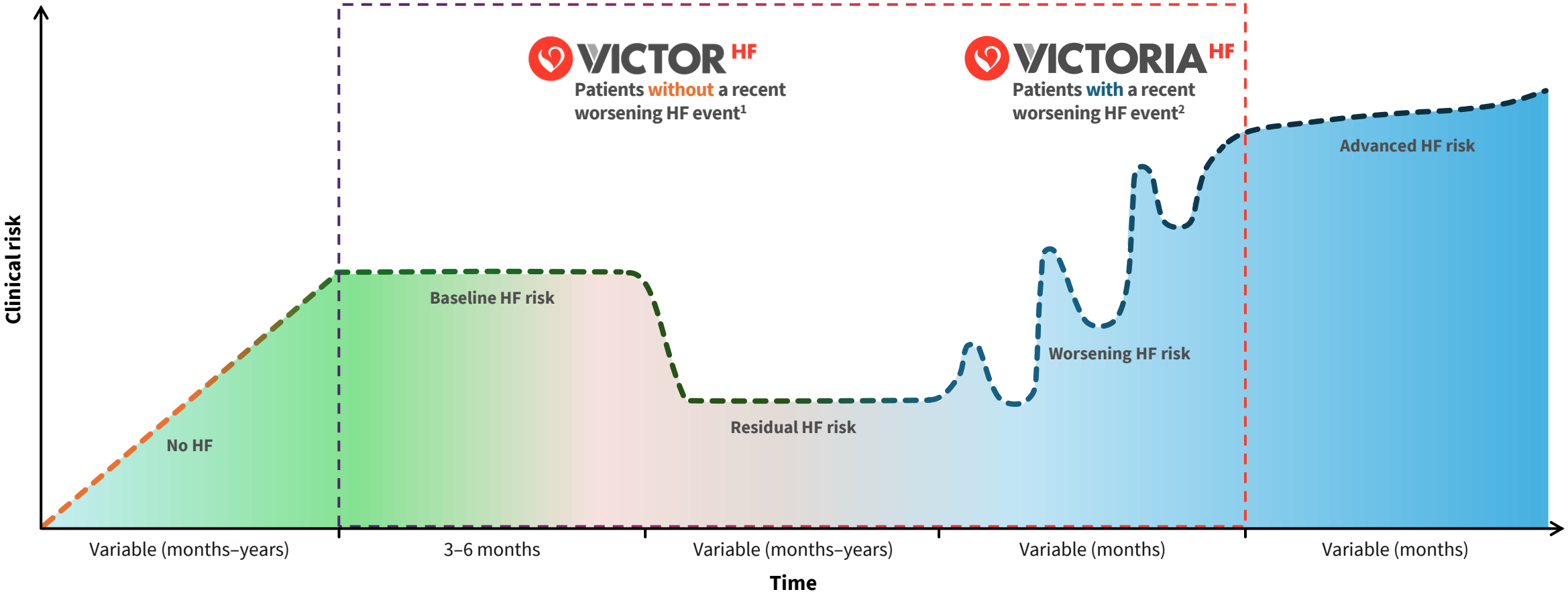


Greene SJ, et al. J Am Coll Cardiol. 2023;82(6):559-571.

VICTOR trial

Vericiguat in patients with chronic heart failure and reduced ejection fraction (VICTOR): a double-blind, placebo-controlled, randomised, phase 3 trial

*Javed Butler, Ciaran J McMullan, Kevin J Anstrom, Irina Barash, Marc P Bonaca, Maria Borentain, Stefano Corda, Justin A Ezekowitz, G Michael Felker, Davis Gates, Carolyn S P Lam, Eldrin F Lewis, JoAnn Lindenfeld, Robert J Mentz, Christopher M O'Connor, Piotr Ponikowski, Yogesh N V Reddy, Giuseppe M C Rosano, Clara Saldarriaga, Michele Senni, Lilin She, Pedro Pinto Teixeira, James Udelson, Alessia Urbinati, Vanja Vlajnic, Adriaan A Voors, Aiwen Xing, Mahesh J Patel, Faiez Zannad, for the VICTOR Study Group**



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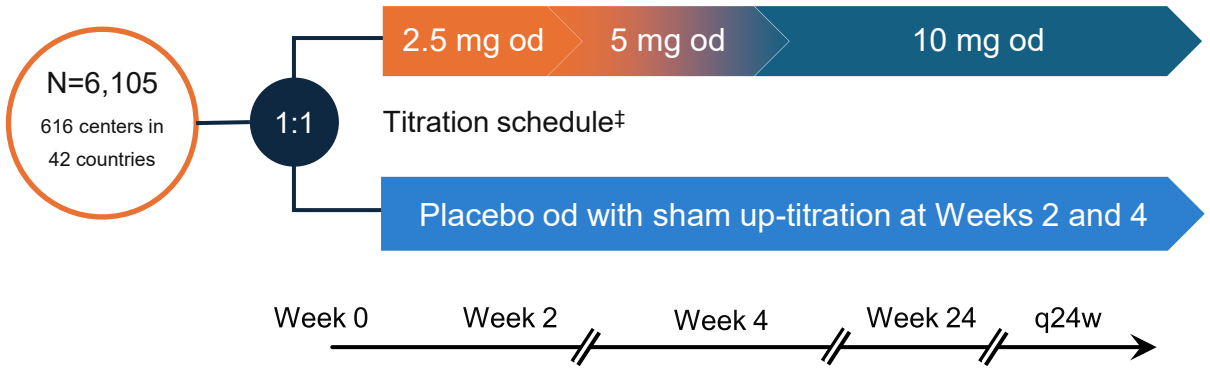
Phase 3, double-blind, placebo-controlled, 1:1 randomized, event-driven trial

Key eligibility criteria

- LVEF ≤40% within 12 months
- NYHA class II–IV on GDMT
- No HFH within 6 months or outpatient i.v. diuretic use within 3 months
- NT-proBNP level within 30 days
  - SR: 600–6,000 pg/ml; AF: 900–6,000 pg/ml
- eGFR ≥15 ml/min/1.73 m^2 and not on chronic dialysis



Follow-up continued until target number of CV death events was reached (n=590)

Composite primary endpoint

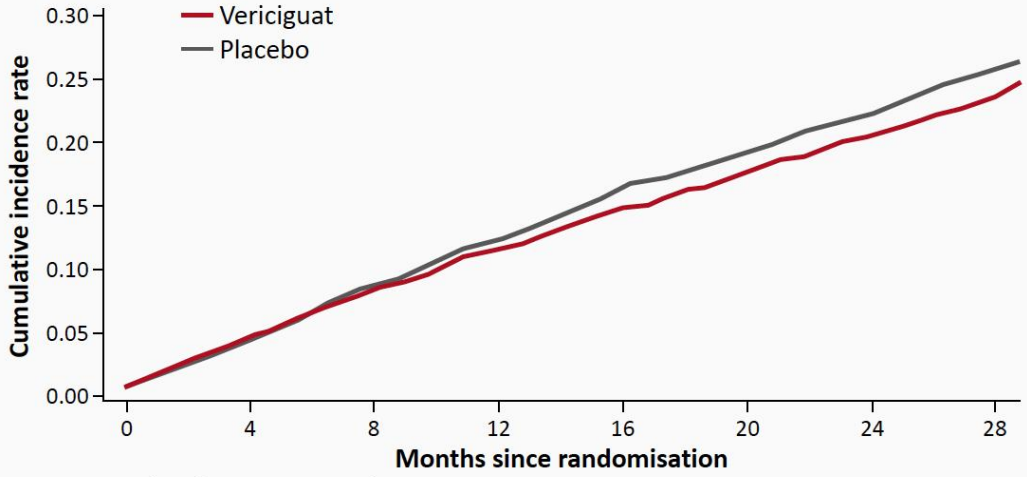
Time to first occurrence of HFH or CV death

Key secondary endpoint

Time to CV death

VICTOR results in practice

Primary outcome results: Time to CV death or first HHF



	Number of participants at risk							
Vericiguat	3053	2927	2797	2581	1917	1352	849	459
Placebo	3052	2929	2771	2543	1879	1314	823	442
	Cumulative number of events up to the time point							
Vericiguat	0	109	228	333	409	462	505	527
Placebo	0	108	242	355	442	506	547	574

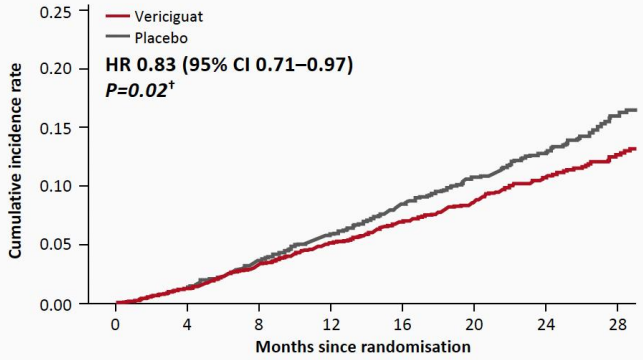
Vericiguat: 549 (**18.0%**)
Placebo: 584 (**19.1%**)

HR 0.93 (95% CI 0.83 – 1.04); P=0.22

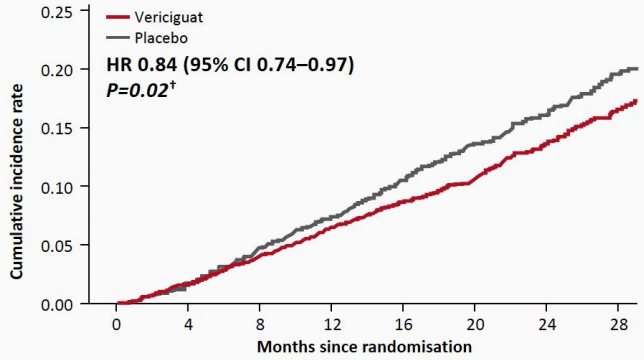
Effects of vericiguat on mortality

CV death[1,2]

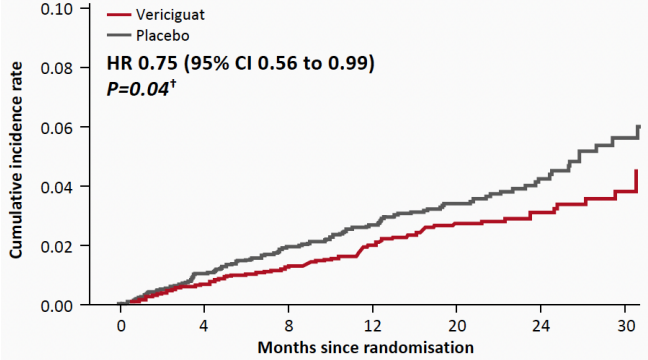
Prespecified powered secondary endpoint



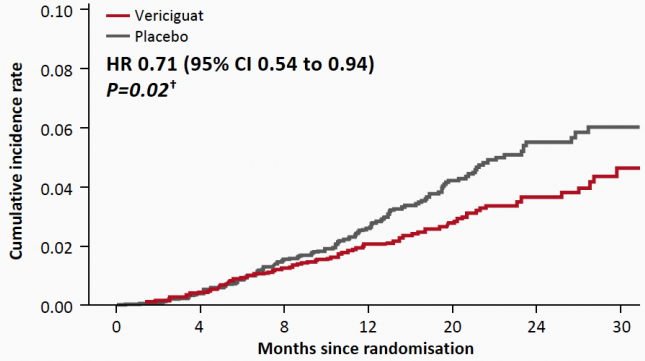
All-cause death[1,2]



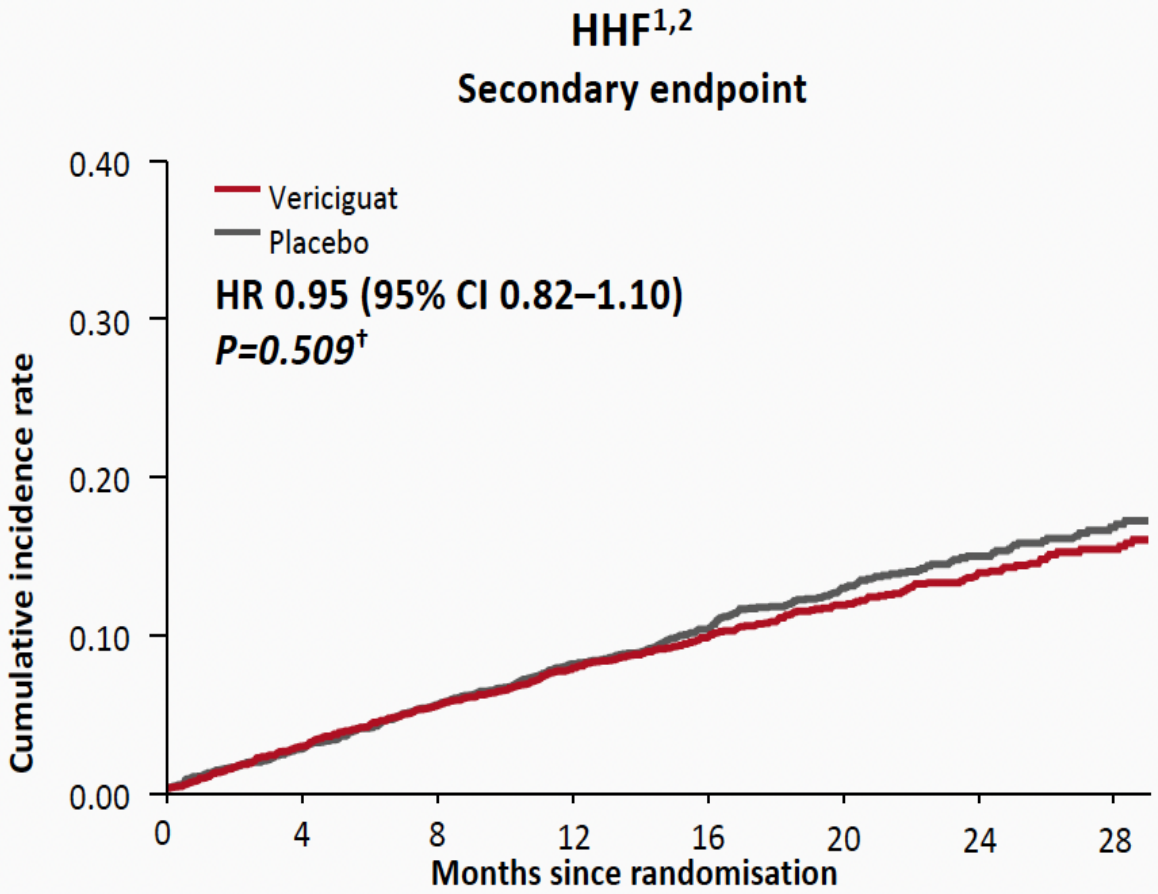
Sudden cardiac death[1,2]

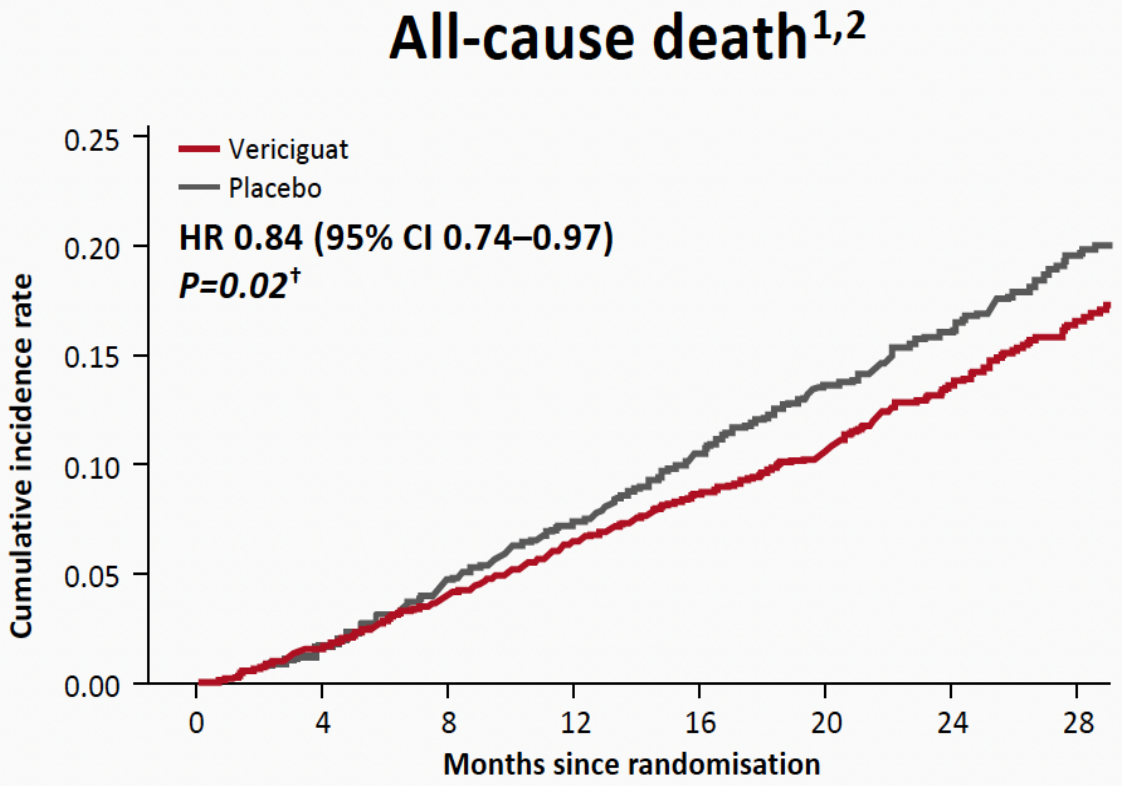


HF-related death[1,2]

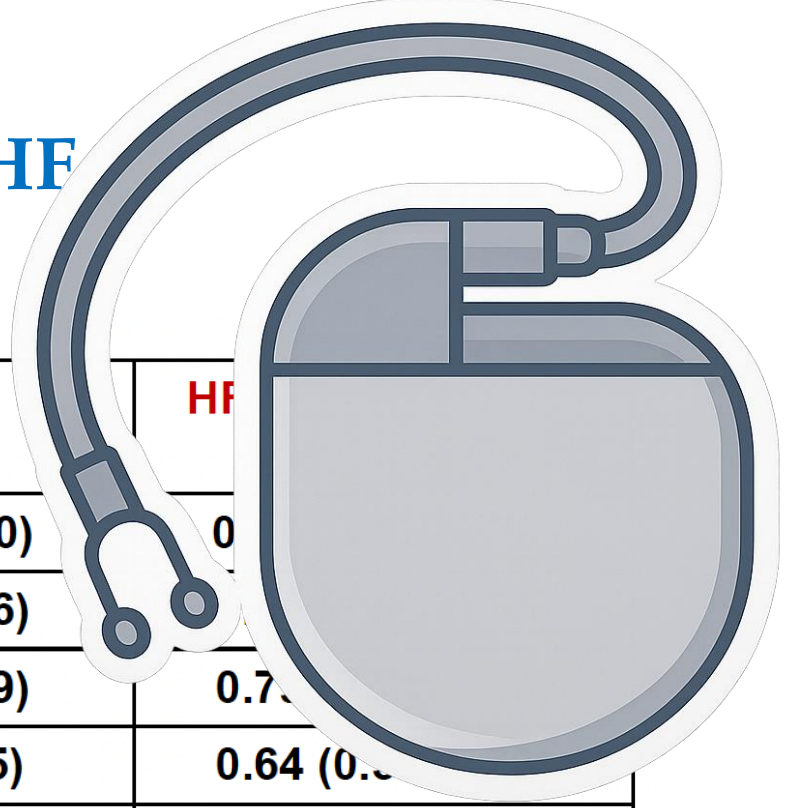


VICTOR results in practice





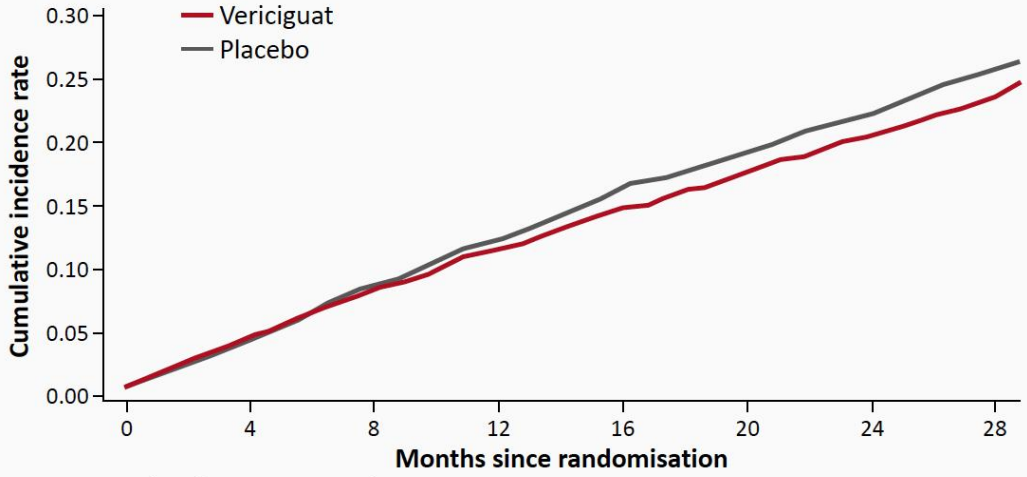
Effect of HF treatment on CV death and HHF



	CV death HR (95% CI)	HF
Beta-blocker (CIBIS-2, bisoprolol)	**0·71 (0·56–0·90)**	**0**
MRA (EMPHASIS-HF, eplerenone)	**0.77 (0.62–0.96)**	
Sacubitril/valsartan (PARADIGM-HF)	**0.80 (0.71–0.89)**	**0.7**
ACE inhibitor (SOLVD-T, enalapril)	**0.83 (0.73,0.95)**	**0.64 (0.**
Soluble guanylate cyclase stimulator (VICTOR, vericiguat)	**0.83 (0.71, 0.97)**	**0·95 (0·82–1·10)**
ARB (CHARM-HFrEF, candesartan)	**0.84 (0.75–0.95)**	**0.76 (0.68–0.85)**
SGLT2 inhibitor (meta-analysis)	**0·86 (0·76–0·98)**	**0·69 (0·62–0·78)**
Sinus node inhibition (SHIFT, ivabradine)	**0·91 (0·80–1·03)**	**0·74 (0·66–0·83)**
Digitalis glycoside (DIG, digoxin)	**1.01 (0.93–1.10)**	**0.72 (0.66–0.79)**

VICTOR results in practice

Primary outcome results: Time to CV death or first HHF



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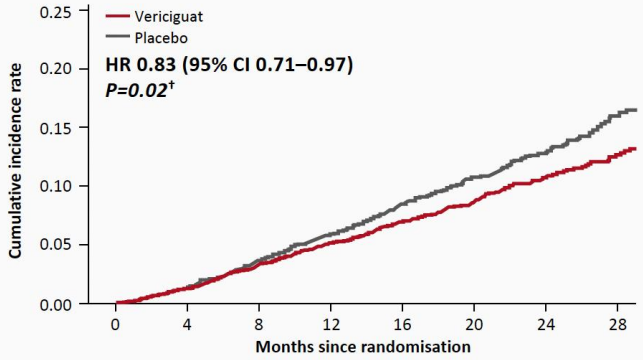
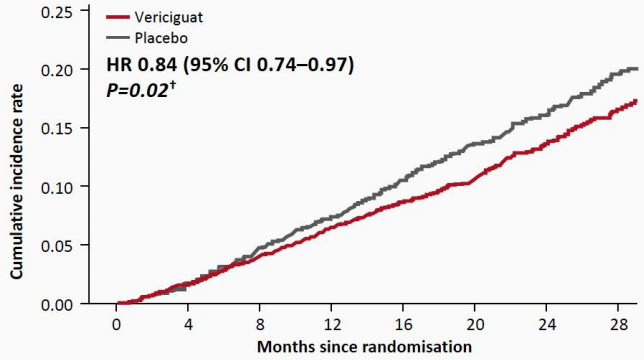
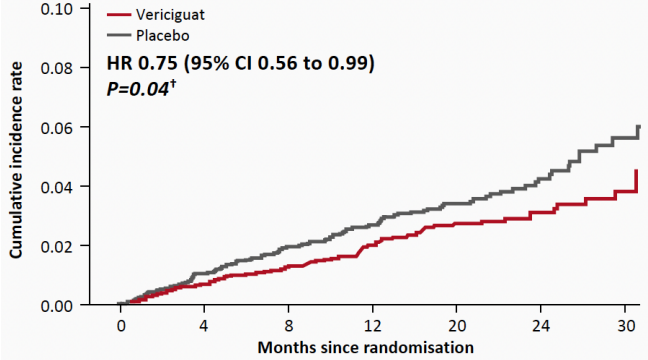
Prespecified powered secondary endpoint



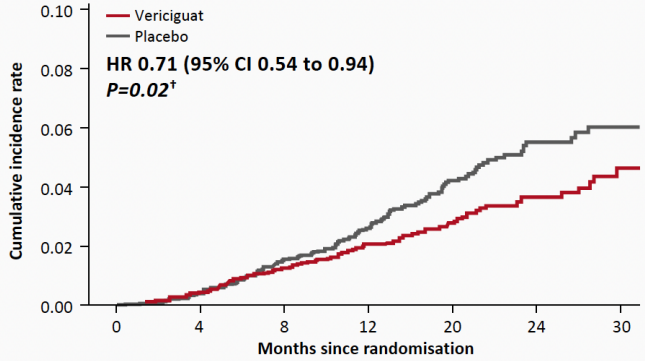
All-cause death[1,2]



Sudden cardiac death[1,2]



HF-related death[1,2]



VICTOR placebo group treatment

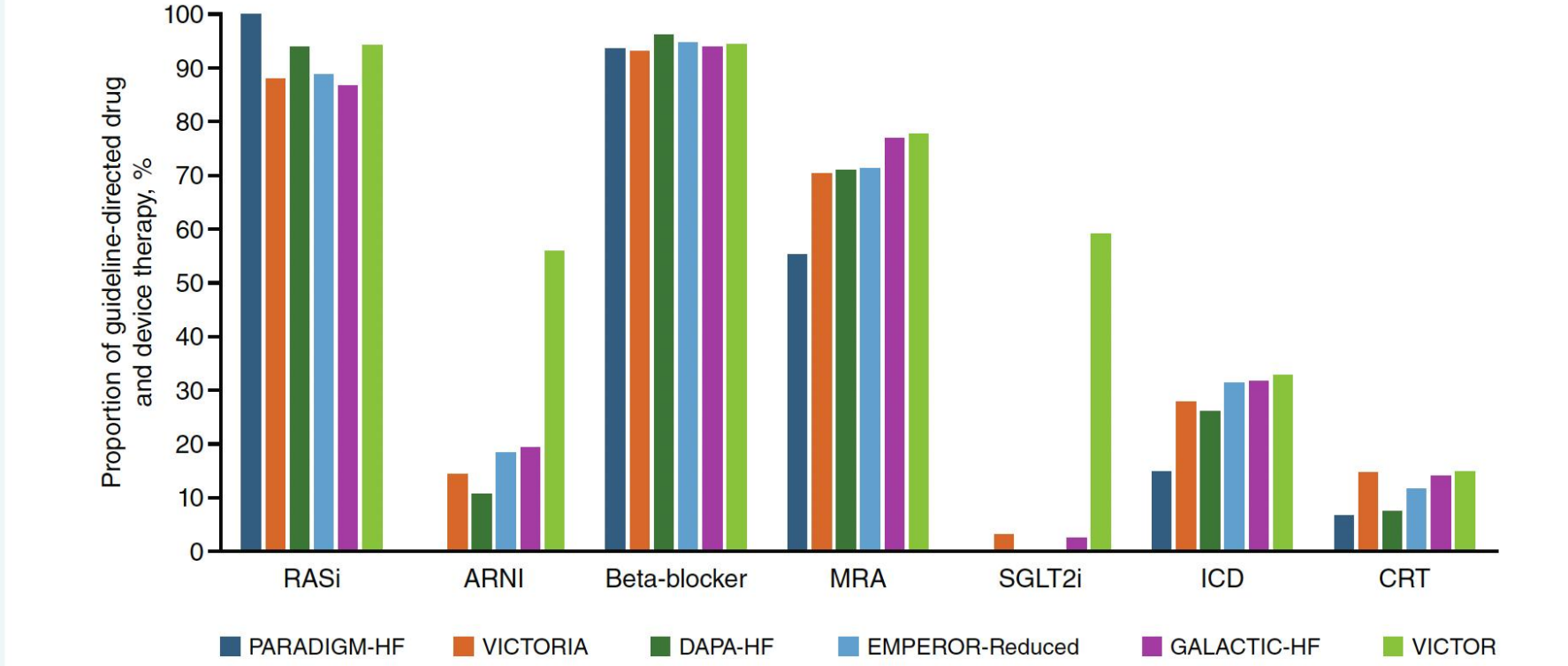
ESC European Society of Cardiology
European Journal of Heart Failure (2025) 27, 1426–1435
doi:10.1002/ejhf.3598
RESEARCH ARTICLE

Baseline characteristics of contemporary trial participants with heart failure and reduced ejection fraction: The VICTOR trial

Clara I. Saldarriaga[1], Faiez Zannad[2]*, Ciaran J. McMullan[3], Aiwen Xing[3],

Phase III trial

Baseline characteristics of contemporary trial participants with heart failure and reduced ejection fraction. The VICTOR trial



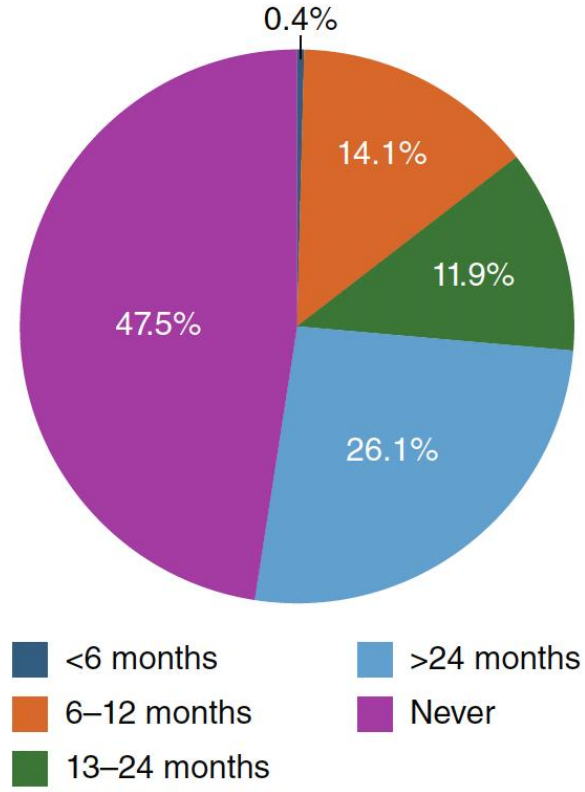


Figure 2 Proportion of guideline-directed drug and device therapy across contemporary heart failure with reduced ejection fraction trials. ARNI, angiotensin receptor–neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

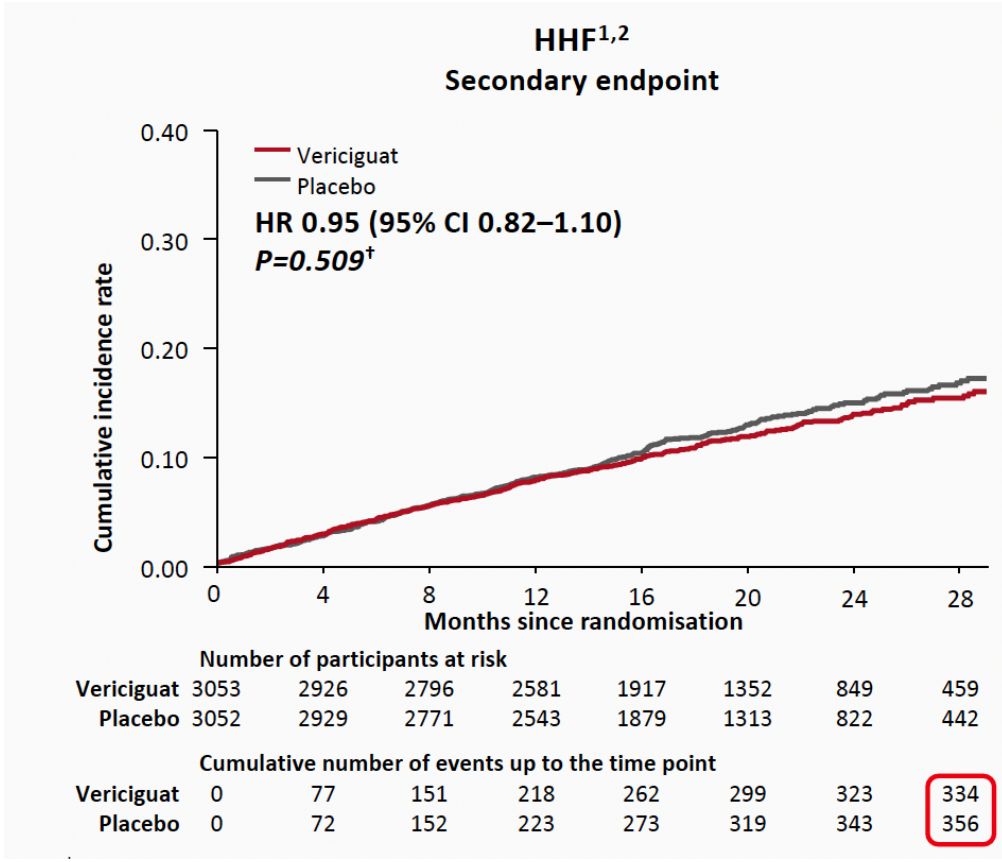
VICTOR results in practice

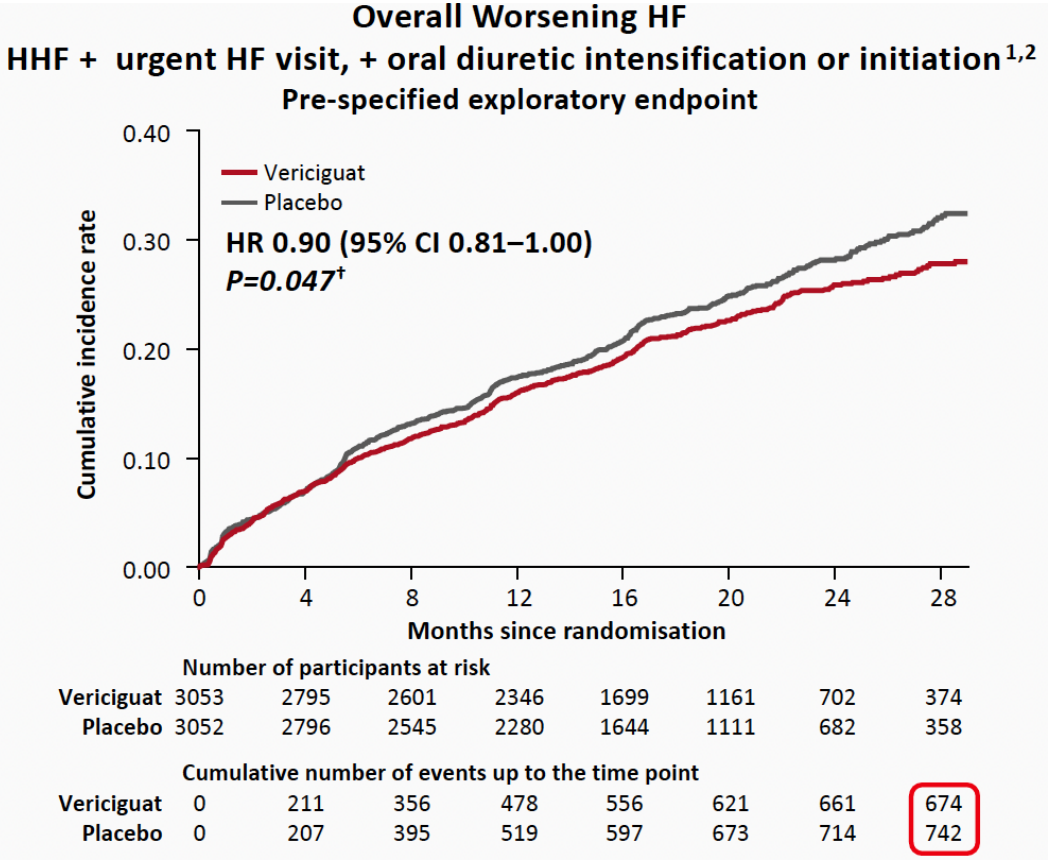
Effects of Vericiguat on total HF events

Effect of Vericiguat on Total Heart Failure Events in Compensated Outpatients With HFrEF

Insights From VICTOR

Faiez Zannad, MD, PhD,[a] Yogesh N.V. Reddy, MBBS,[b] Irina Barash, MD, MS, MD,[c] Kevin J. Anstrom, PhD,[d]



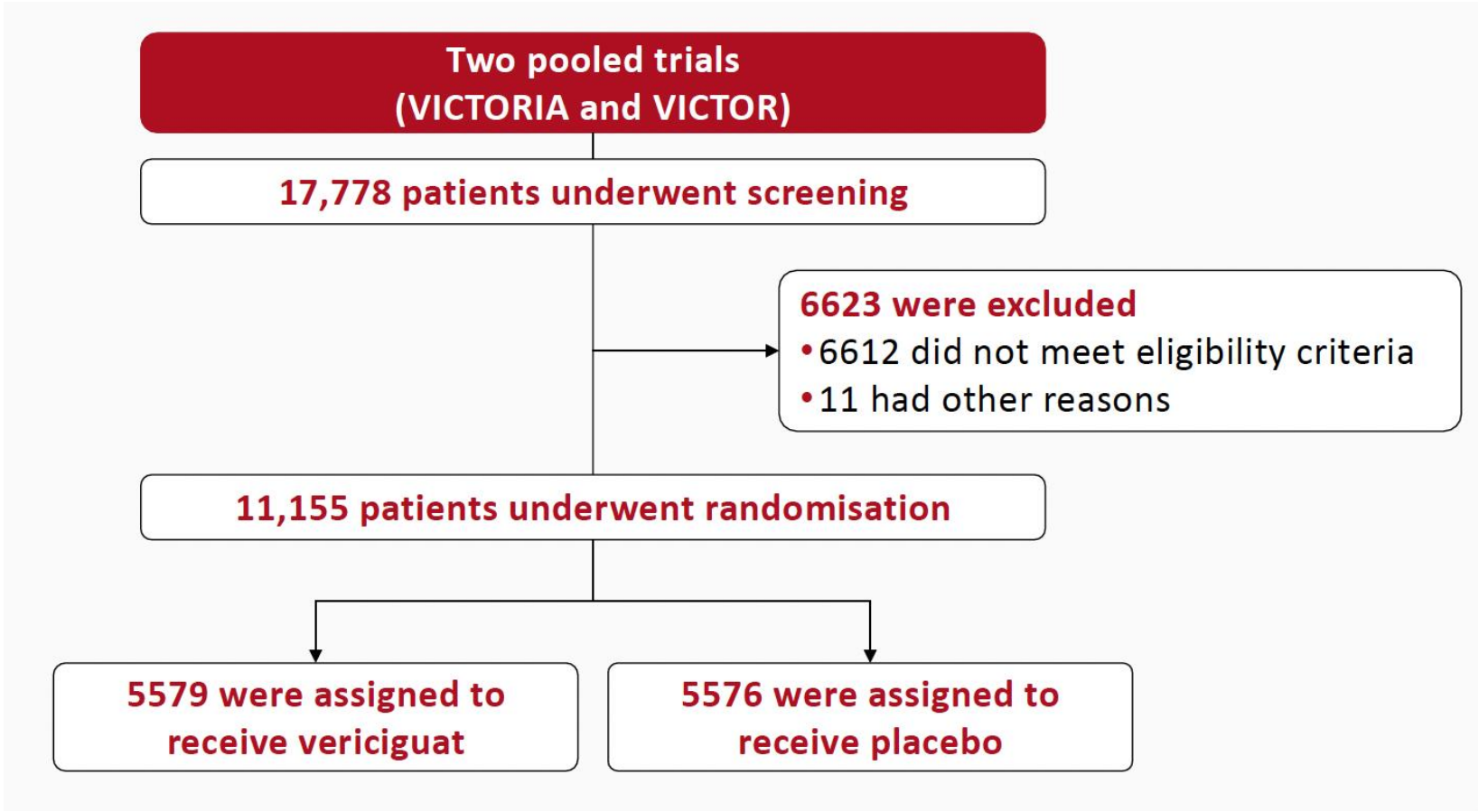


N eventi di HFH (pochi, probabilmente non sufficiente per evidenziare un effect size basso) vs eventi HF complessivi sufficientemente alti per evidenziare riduzione significativa

VICTORIA/VICTOR pooled analysis

Vericiguat for patients with heart failure and reduced ejection fraction across the risk spectrum: an individual participant data analysis of the VICTORIA and VICTOR trials

Faiez Zannad, Christopher M O'Connor, Javed Butler, Ciaran J McMullan, Kevin J Anstrom, Irina Barash, Marc P Bonaca, Maria Borentain, Stefano Corda, Davis Gates, Justin A Ezekowitz, Adrian F Hernandez, Carolyn S P Lam, Eldrin F Lewis, JoAnn Lindenfeld, Robert J Mentz, Piotr Ponikowski, Yogesh N V Reddy, Giuseppe M C Rosano, Clara Saldarriaga, Michele Senni, Pedro P Teixeira, James Udelson, Alessia Urbinati, Vanja Vlajnic, Adriaan A Voors, Aiwen Xing, Mahesh J Patel, Paul W Armstrong, for the VICTORIA and VICTOR Study Groups



Largest contemporary HF dataset

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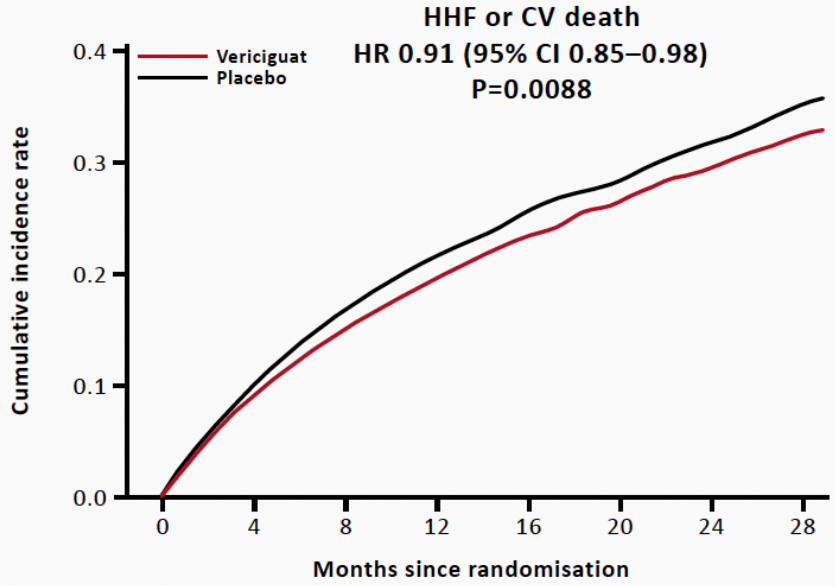
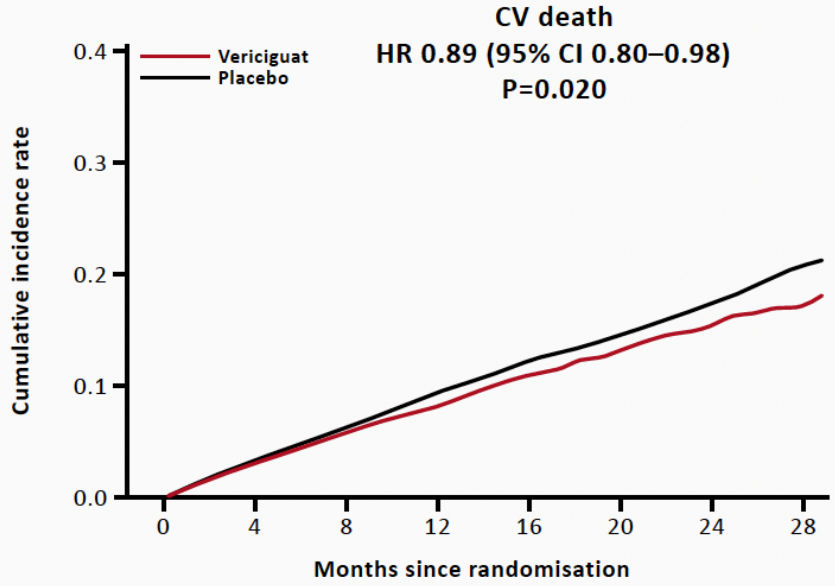
Primary composite endpoint and CV death (VICTORIA/VICTOR pooled)



Number of participants at risk

Vericiguat	5579	5026	4418	3735	2743	1929	1197	584
Placebo	5576	4982	4326	3640	2651	1873	1147	552



Number of participants at risk

Vericiguat	5579	5376	4896	4220	3162	2295	1455	721
Placebo	5576	5373	4861	4167	3095	2224	1411	671

Vericiguat significantly reduced the risk of the primary composite and the CV death, with treatment effects emerging at around 4 months and around 8 months, respectively

VICTORIA/VICTOR pooled analysis

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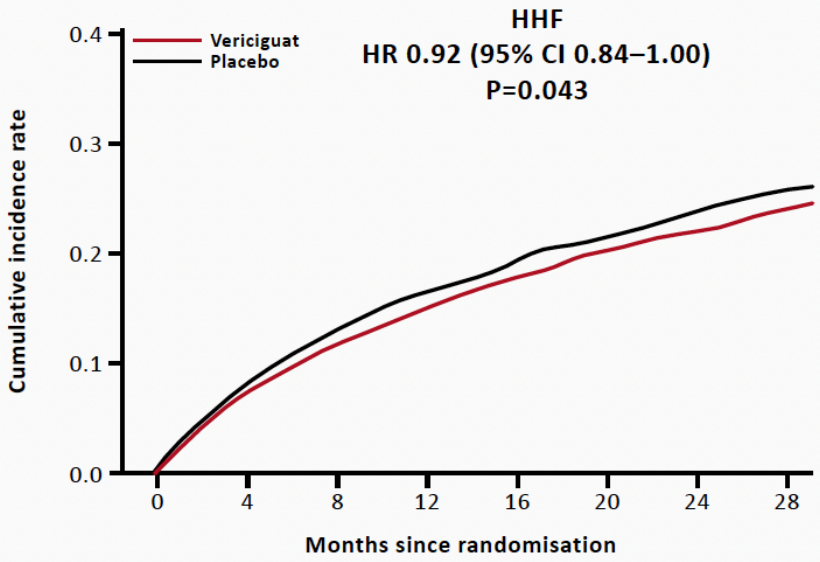
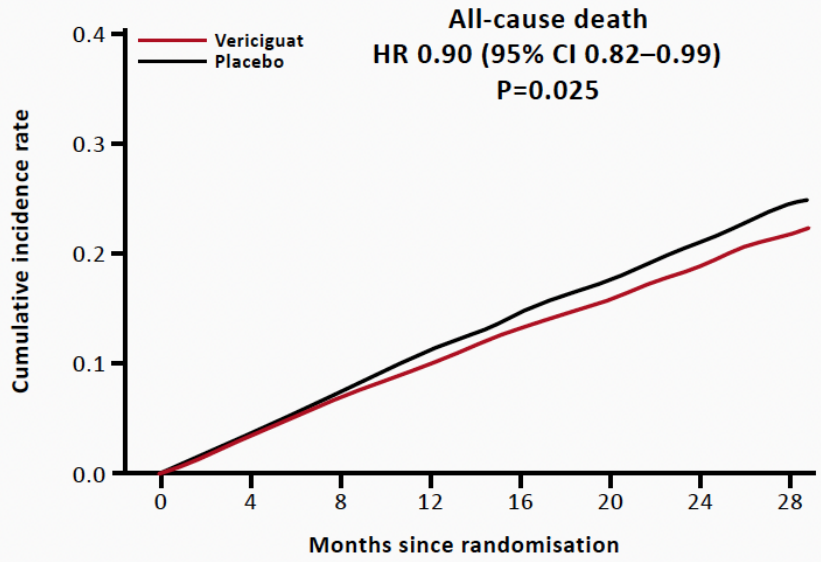
HHF and all-cause death (VICTORIA/VICTOR pooled)



Number of participants at risk

Vericiguat	5579	5024	4416	3734	2742	1929	1197	584
Placebo	5576	4981	4325	3639	2650	1871	1145	552

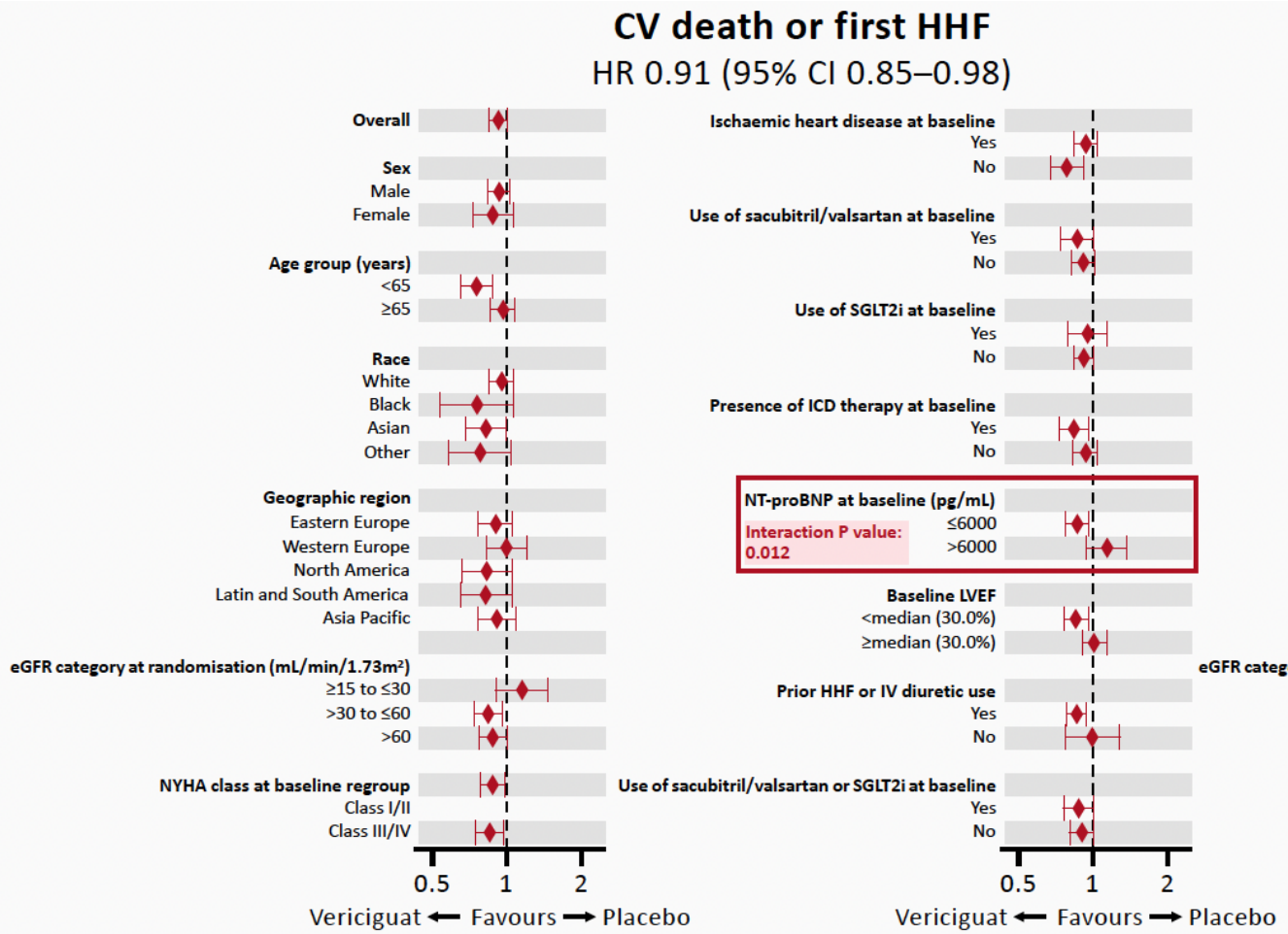


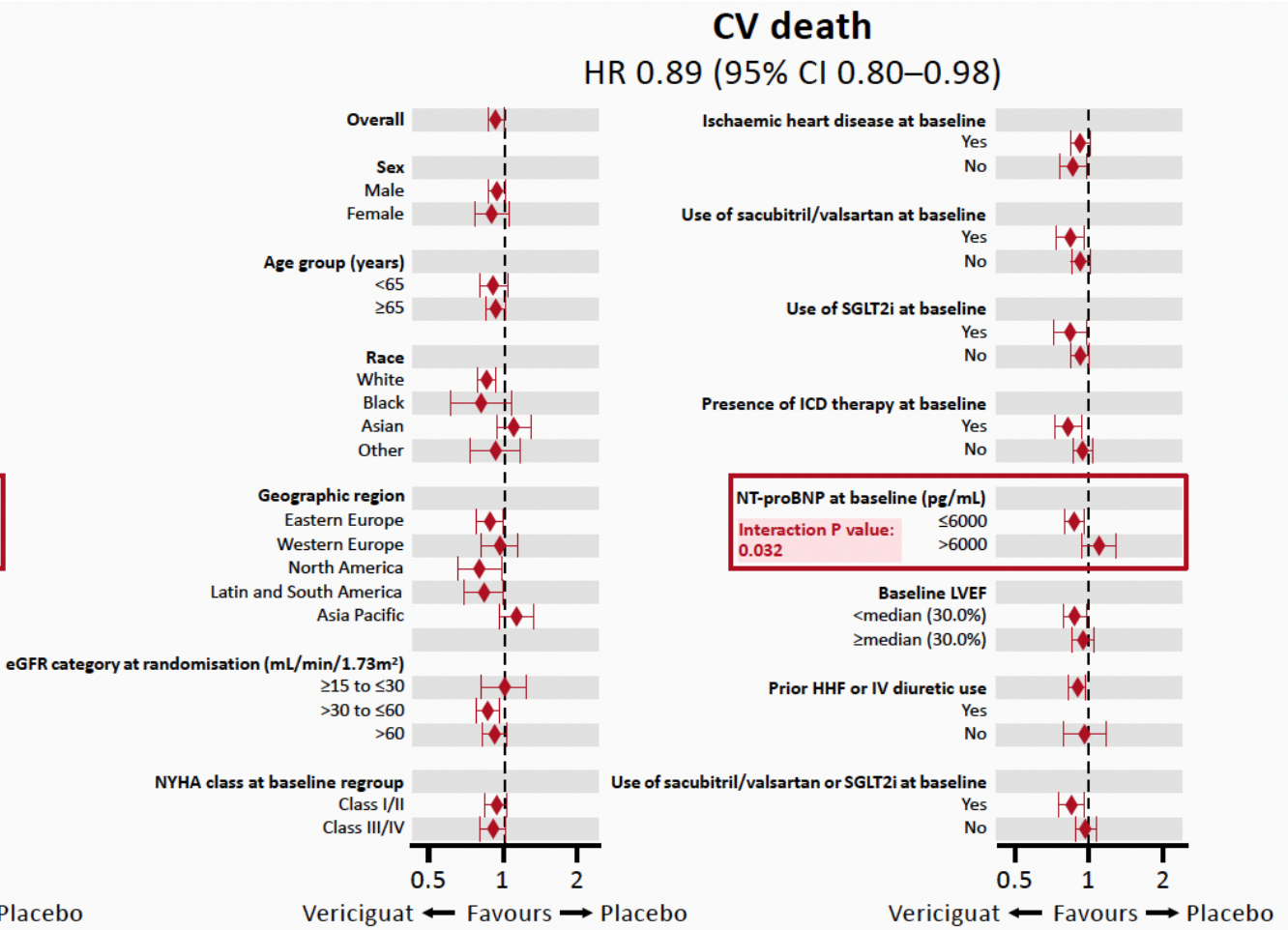
Number of participants at risk

Vericiguat	5579	5376	4896	4220	3162	2295	1455	721
Placebo	5576	5373	4861	4167	3095	2224	1411	671

- Vericiguat significantly reduced the risk of first HHF and all-cause death, with treatment effects emerging at around 4 months and around 8 months, respectively
- No evidence of treatment by trial interaction (P=0.586 for HHF or CV death; P=0.318 for CV death; P=0.510 for HHF; P=0.235 for all-cause death)

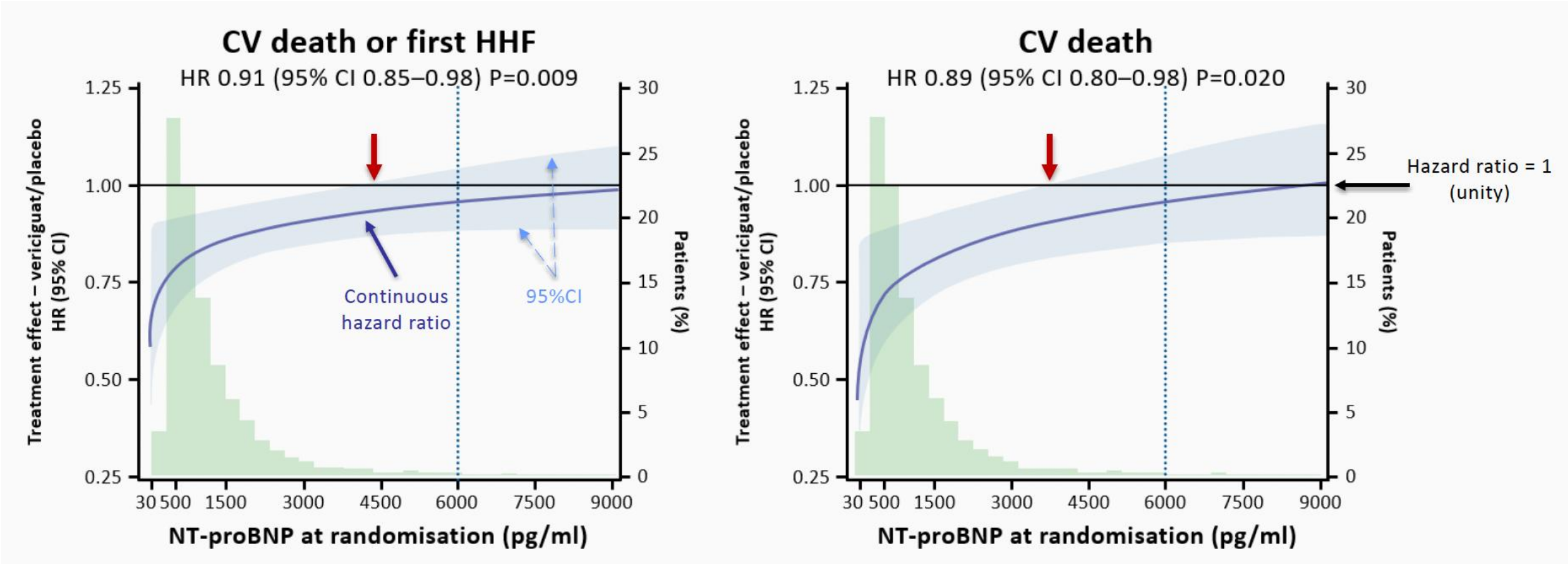
VICTORIA/VICTOR pooled subgroups analysis





The only subgroup showing significant and consistent interaction with treatment effect was baseline NT-proBNP ≤6000 pg/mL

Vericiguat and NTproBNP interaction

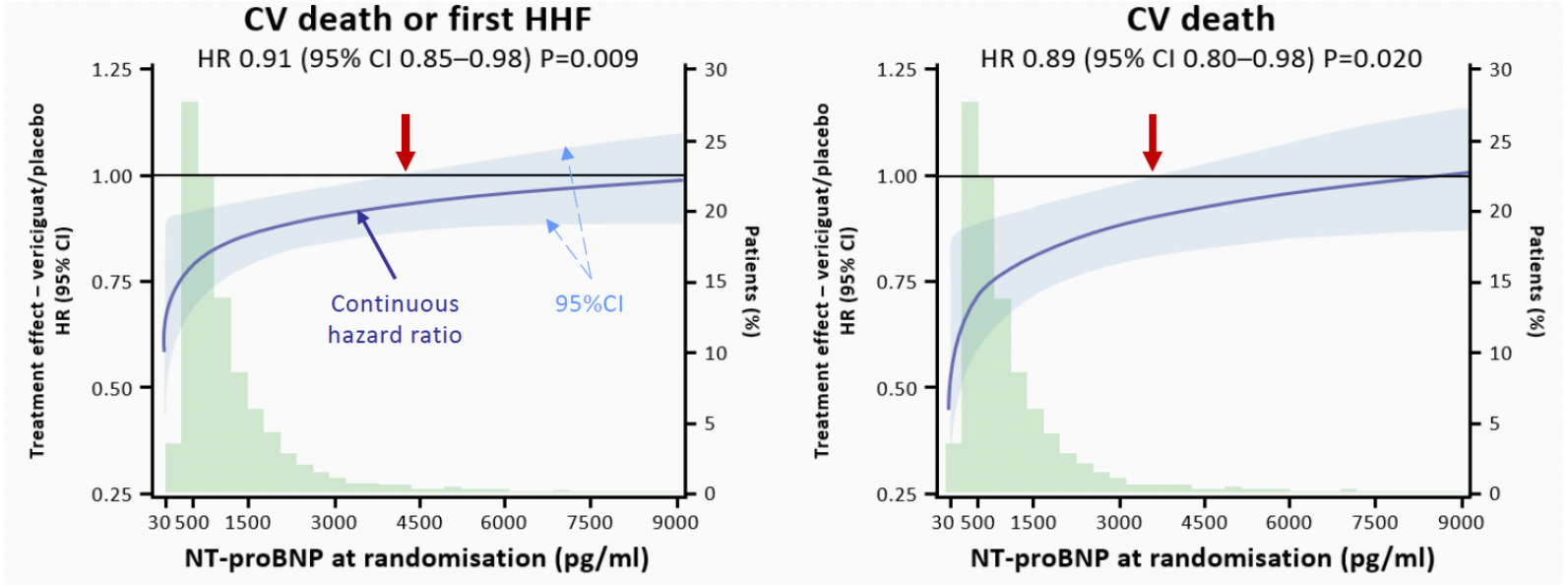


Is there any plausible biological explanation for this interaction? Natriuretic peptides act through increasing cGMP, as does vericiguat (but different cGMP pathways – particulate vs. soluble guanylate cyclase).

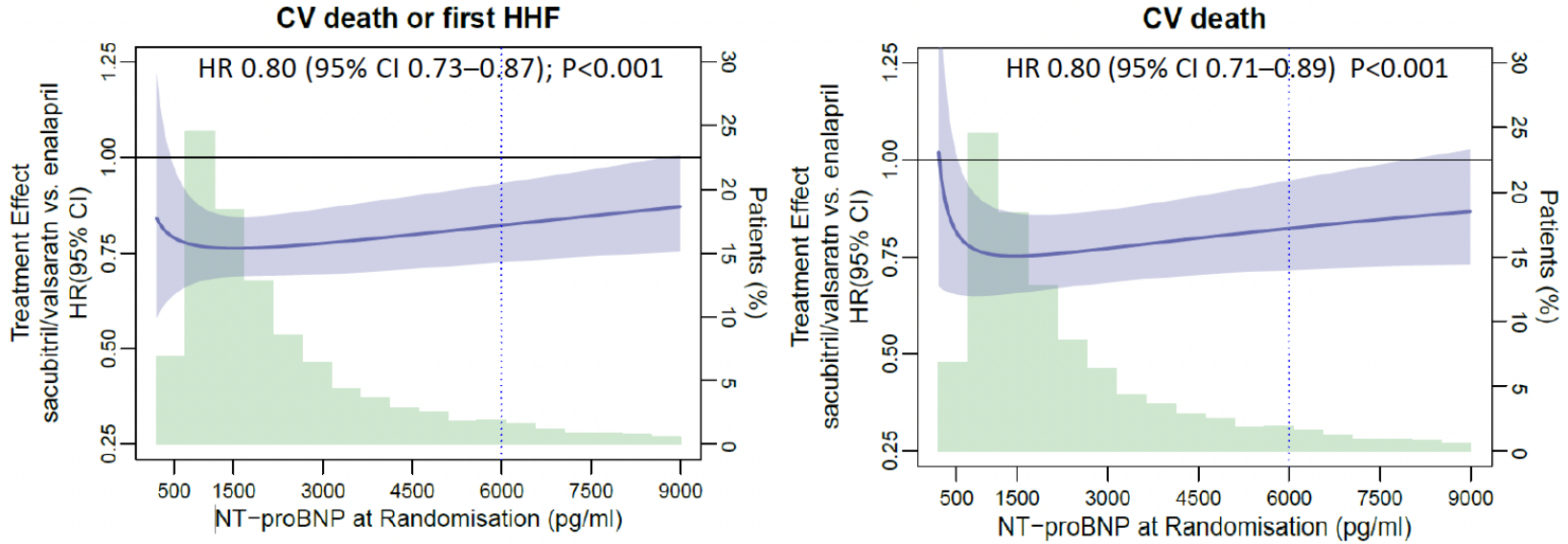
Need a better understanding of this interaction, if it is true.
Who are people with higher NT-proBNP?
Older, thinner, lower LVEF, AF, CKD, worse HF, poorer treatment.

Vericiguat and NTproBNP interaction

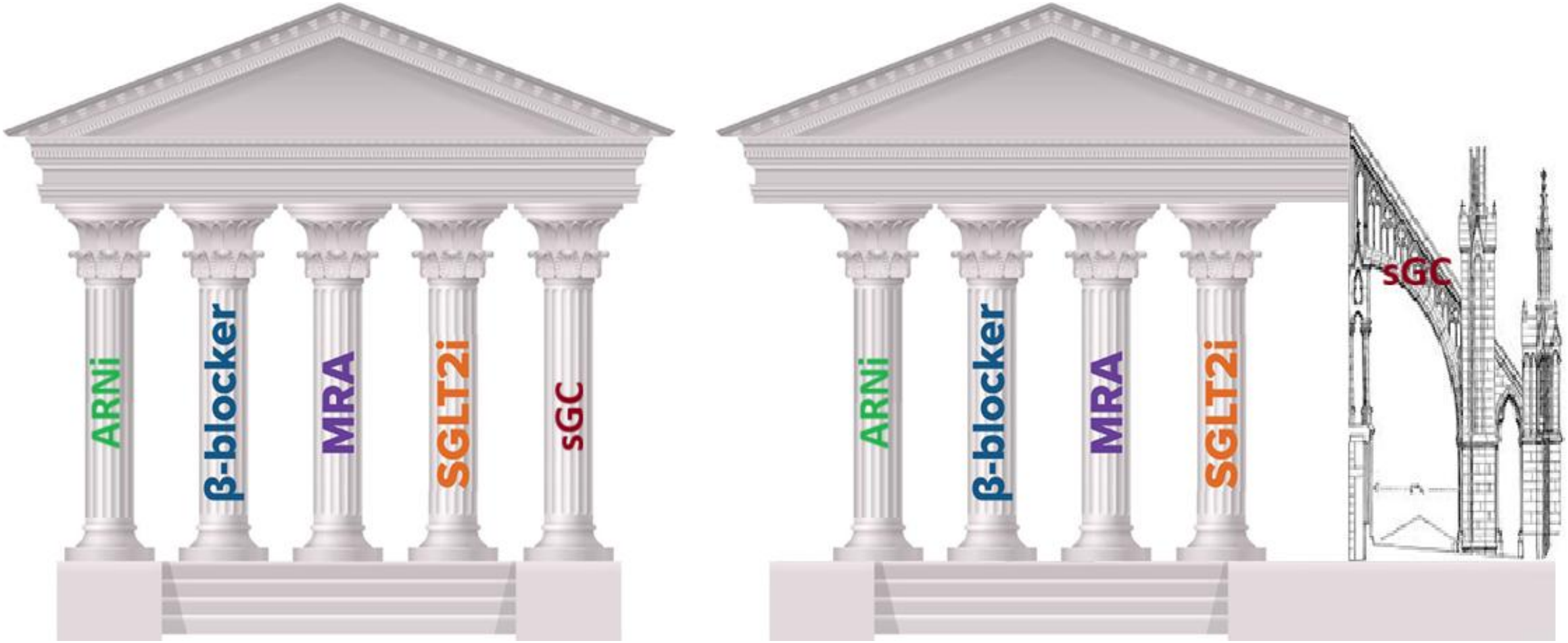
VICTOR and VICTORIA



PARADIGM-HF



A new pillar?



TAKE HOME MESSAGES

1. **VICTOR demonstrated a significative reduction of mortality and total HF events in patients with stable chronic heart failure.**

2. **Vericiguat benefit, despite a limited effect size, was additive on top of highly optimized medical therapy, adding evidence for routine use in HF ambulatory patients.**

3. **Favourable safety profile and ease in up titration make Vericiguat an appealing treatment option in complex patients.**


Thank you!