Chelanti del K+ e Vericiguat
Nuove terapie nello Scompenso Cardiaco

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Cardiologia 2

Ospedale San Giovanni Bosco - ASL città di Torino

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IL PAZIENTE
FRAGILE IN CARDIOLOGIA
VI Edizione

CHELANTI DEL POTASSIO

HF and hyperkalaemia

Physiological

Chronic kidney disease

In CKD, K^+ homeostasis, established mostly by excretion of K^+ via urine, is deregulated and up to 73% of patients have hyperkalaemia

Heart failure

In HF, RAASi is up-regulated, renal perfusion is reduced and Na^+ is often excreted due to usage of diuretics.

Diabetes mellitus

Due to the lack of insulin-stimulated Na^+-K^+ pump mediated K^+ uptake in skeletal muscles

Age

Age-dependent reduction in the availability of nephrons further increases the risk for hyperkalaem

Environmental

Medication

Background use of RAASi, BB and AA are associated with an increase in K^+ levels

Exercise

Because skeletal muscles constitute the major reservoir for K^+ in the body, K^+ levels may increase markedly and reach values up to ~8 mEq/L during exercise

- *Kjeldsen KP and Schmidt TA. Eur Heart J Suppl. 2019;2*

Patients (%) with new hyperkalaemia event during follow-up

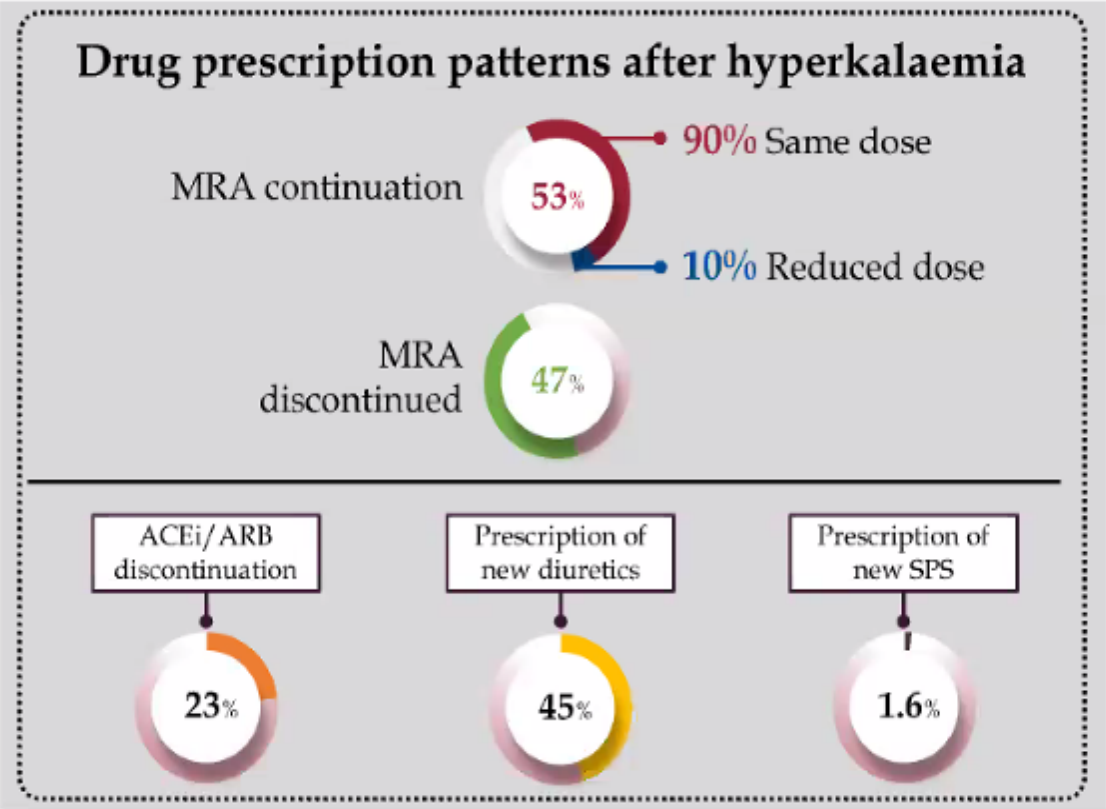
Population-based cohort study linking individual data from mandatory hospital, prescription and laboratory databases in patients with first-time diagnosis of HF from the Danish National Patient Registry in northern Denmark (population 1.8 million) during 2000–2012 (N=31,649)

20% severe hyperkalaemia

Patients with heart failure have recurrent HK episodes, with successively shorter time between the episodes

Thomsen RW et al. J Am Heart Assoc. 2018;7:e008912

RAASi discontinuation or reduction in patient with HF after a hyperkalemia event



Observational study including 13,726 Swedish patients initiating MRA therapy during 2007–2010

1 year follow-up

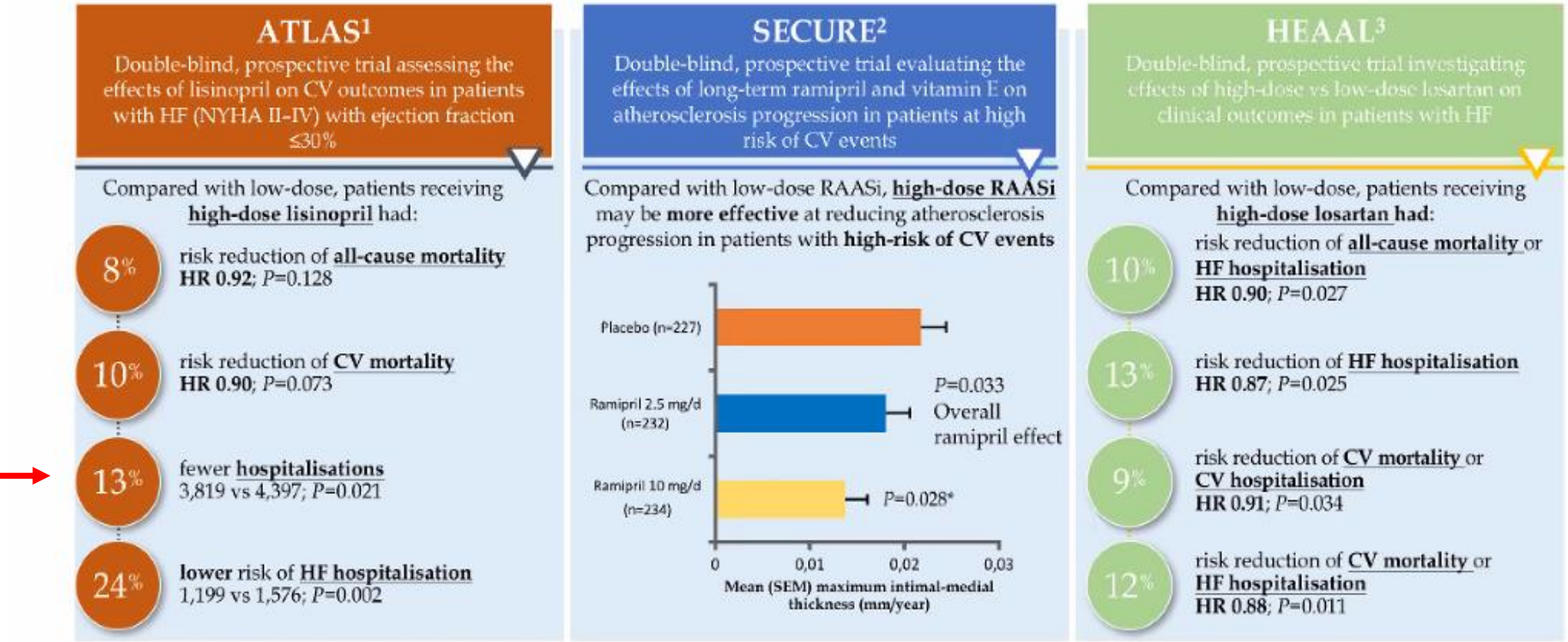
18.5% hyperkalaemia

MRA discontinuation

- Discontinuation rates were higher after moderate/severe (K^+ >5.5 mEq/L) and < 3 months from MRA initiation
- Participants with CKD carried the highest risk of MRA discontinuation

Trevisan M, et al. Eur J Heart Fail. 2018;20:1217–26

High RAASi doses and better CV outcome in HF



Packer M, et al. Circulation. 1999;100:2312–18; 2. Lonn EM, et al. Circulation. 2001;103:919–25; 3. Konstam MA, et al. Lancet 9;374:1840–8

MRA doses and prognostic impact in chronic HFrEF

SPIRONOLACTONE
RALES TRIAL

junction with an ACE inhibitor.[17] We found that spironolactone at a dose of 12.5 to 25 mg daily was pharmacologically effective in blocking the aldosterone receptors and decreasing atrial natriuretic peptide concentrations and that serious hyperkalemia occurred most frequently with daily doses of 50 mg or greater.[17] In the present study, therefore, spironolactone therapy was initiated at a daily dose of 25 mg, and physicians were given the option of reducing the dose to 25 mg every other day if serum potassium concentrations started to rise to a hyperkalemic level or of increasing the dose to 50 mg daily after eight weeks in patients who had symptoms or signs of worsening heart failure but no evidence of hyperkalemia. It should be emphasized, however,

EPLERENONE
Emphasis- HF trial

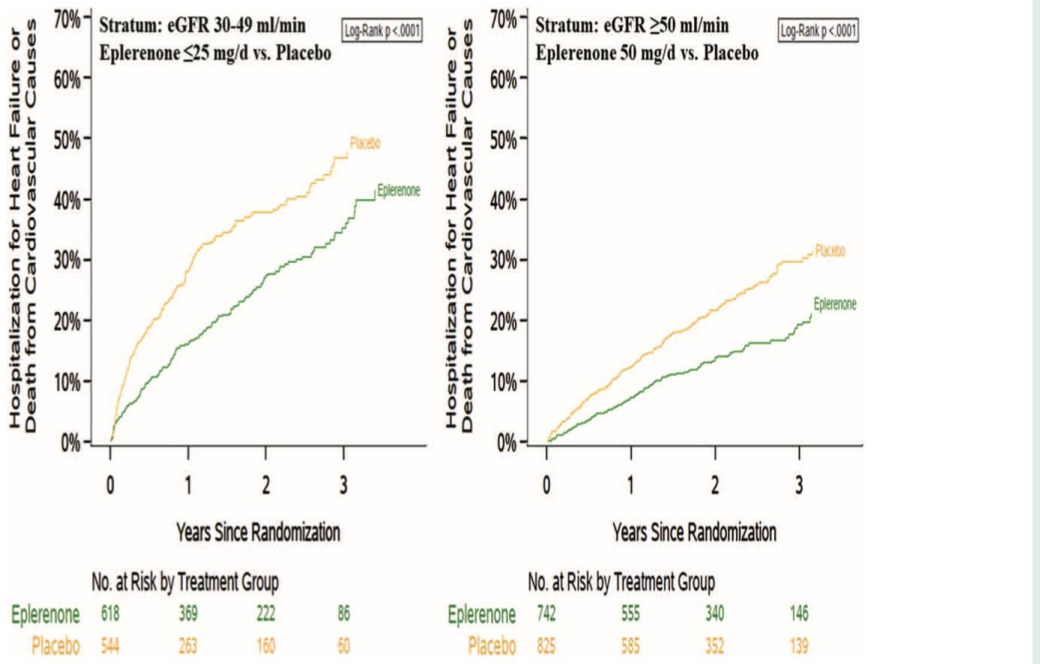


Table 3 Adjusted hazard ratio within each estimated glomerular filtration rate strata

Study outcomes	eGFR stratum										
	≥ 50 mL/min/1.73 m²: high-dose eplerenone vs. placebo					30–49 mL/min/1.73 m²: low-dose eplerenone vs. placebo					$P_{interaction}$
	Events, *n* (%)		ARD (%)	HR (95% CI)[a]	*P*-value	Events, *n* (%)		ARD (%)	HR (95% CI)[a]	*P*-value	
	Eplerenone	Placebo				Eplerenone	Placebo				
HFH/CVM	100 (13.5)	178 (21.6)	−8.1	0.58 (0.45–0.74)	<0.001	149 (24.1)	177 (32.5)	−8.4	0.62 (0.49–0.78)	<0.001	0.89
CVM	51 (6.9)	89 (10.8)	−3.9	0.61 (0.43–0.86)	0.004	96 (15.5)	95 (17.5)	−1.9	0.77 (0.58–1.04)	0.084	
HFH[b]	69 (9.3)	126 (15.3)	−6.0	0.56 (0.42–0.76)	<0.001	95 (15.4)	127 (23.3)	−8.0	0.55 (0.41–0.72)	<0.001	

Ferreira et al European Journal of Heart Failure (2019) ***21****, 345–351*

ESC European Society of Cardiology
European Heart Journal (2017) 38, 2890–2896
doi:10.1093/eurheartj/ehx460

CLINICAL RESEA
Heart failure/cardiomy

Associations of serum potassium levels with mortality in chronic heart failure patients

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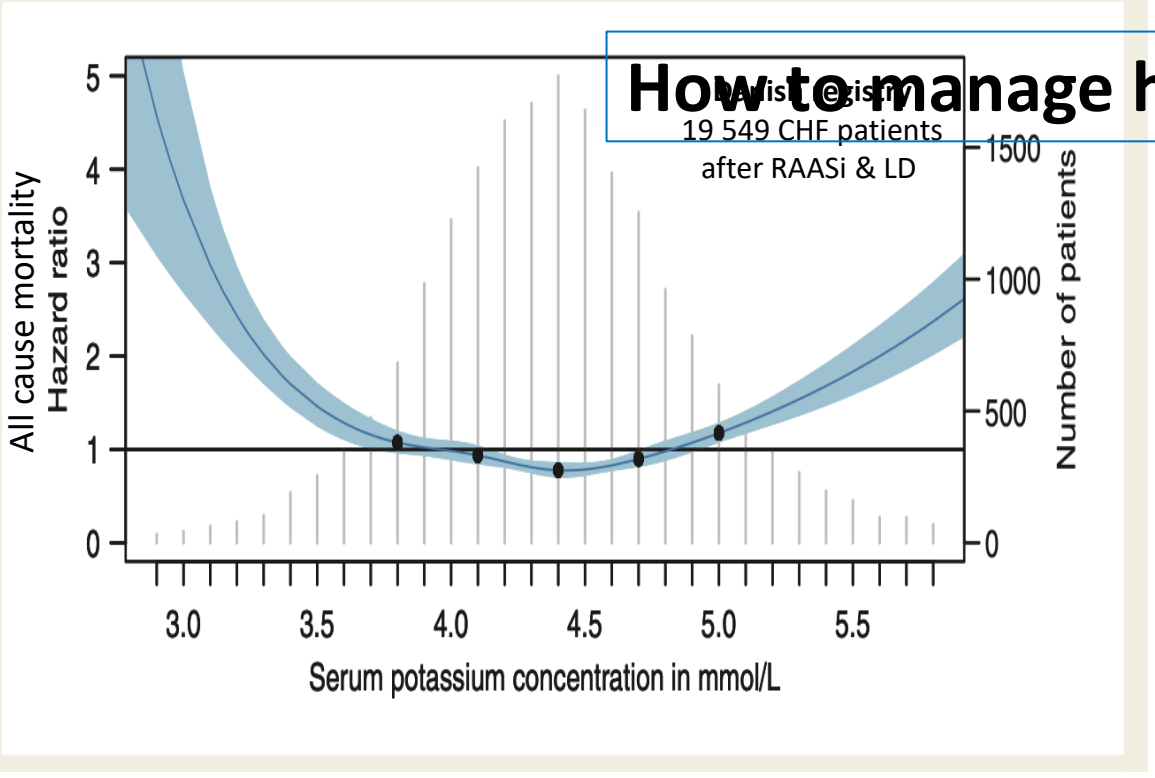


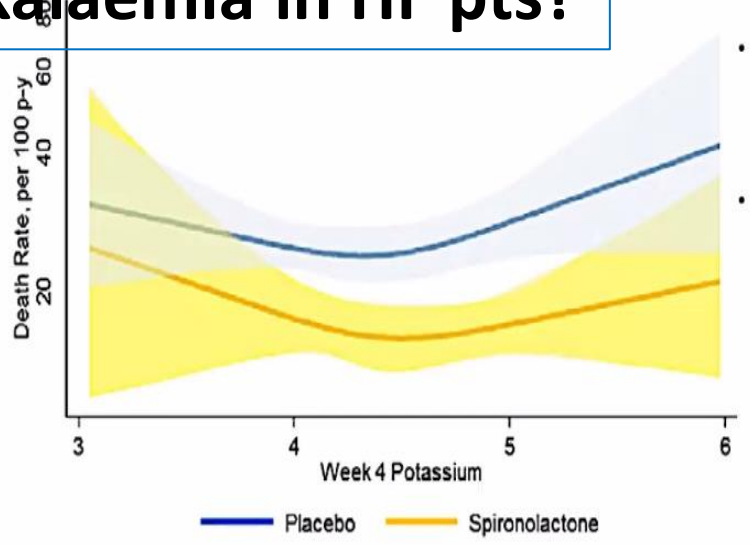
Danish Register
19 549 CHF patients
after RAASi & LD

How to manage hyperkalaemia in HF pts?

RAASi reduce mortality irrespective of K level

Rales trial

1663 patients with class III or IV, LVEF<35, spironolactone 25 mg vs placebo



- Hyperkalaemia is associated with higher incidence of mortality
- Significantly lower mortality in pts receiving active treattment than those receving placebo ($p < 0.0001$)

Circ Heart Fail. 2014;7:573-579

SODIO POLISTIRENE SULFONATO (SPS) ?

	Sodio polistirene sulfonato
Meccanismo d'azione	Resina contenente Na che viene scambiato con un altro catione (K, Ca o Mg)
Formulazione	Polvere per sospensione orale e rettale
Dosaggi	Per os: 15 g 1-4 volte/die Per via rettale: 30 g 1-2 volte/die
Temperatura di conservazione	Temperatura ambiente
Inizio d'azione	1-2 h
Proprietà farmacocinetiche	Non assorbito nel tratto GI Eliminato con le feci
Effetti collaterali	Disturbi GI: anoressia, nausea, vomito, stipsi, diarrea Disturbi elettrolitici: ritenzione sodica, ipopotassiemia e ipocalcemia
Effetti collaterali gravi	Ischemia GI

As recommended by several regulatory agencies, the chronic use of SPS alone or in conjunction with sorbitol should be avoided because its prolonged use may be associated with severe gastrointestinal side effects such as bowel necrosis.[56] Sodium polystyrene sulfonate has never undergone rigorous testing in placebo-controlled clinical trials to prove its efficacy and safety for treatment of acute or chronic hyperkalaemia.[57,59] In addition, because Na^+ is the counter exchange ion in SPS, caution is advised if it is administered to patients who do not tolerate even a small increase in Na^+ load (i.e. those with HF, severe hyper-

2018 ESC consensus on hyperkalemia treatemnt in patients with cv disease treated with RAASi

(patiromer) for oral suspension

sodium zirconium cyclosilicate powder for oral suspension

	Patiromer calcio sorbitolo	**Sodio zirconio ciclosilicato**
Meccanismo d'azione	Resina contenente Ca che viene scambiato col K	Composto inorganico non polimerico che agisce come scambiatore Na-K
Formulazione	Polvere per sospensione orale	Polvere per sospensione orale
Dosaggi	Dose iniziale: 8.4 g/die Dose massima: 25.2 g/die	Dose iniziale: 10 g 3 volte/die per max 3 giorni Dose di mantenimento: max 10 g/die
Temperatura di conservazione	2-8°C	Temperatura ambiente
Inizio d'azione	4-7 h	1 h
Proprietà farmacocinetiche	Non assorbito nel tratto GI Eliminato con le feci	Non assorbito nel tratto GI Eliminato con le feci
Effetti collaterali	Disturbi GI: stipsi (6.2%) diarrea (3%), dolore addominale (2.9%) Disturbi elettrolitici: ipomagnesemia (5.3%) Ipopotassiemia (4.5%)	Disturbi elettrolitici: ipopotassiemia (2.3%) Edema (5.7%): ritenzione di liquidi, edema generalizzato o localizzato, ipervolemia
Effetti collaterali gravi	Nessuno	Nessuno

G Ital Cardiol 2019;20(10):543-551

Chelanti e interazioni farmacologiche

- **Patiromer** è in grado di legarsi ad alcuni farmaci somministrati contemporaneamente per via orale, riducendo il loro assorbimento gastrointestinale, per questa ragione deve essere somministrato ad almeno **3 h di distanza** da altri farmaci assunti per via orale.
- **ZS-9** può aumentare temporaneamente il pH gastrico rilasciando ioni idrogeno e può causare alterazioni dell'assorbimento di medicinali con solubilità pH-dipendente, per cui dovrebbe essere somministrato a **2h di distanza** da questo tipo di farmaci (es. antimicotici azolici, inibitori delle tirosin-chinasi, farmaci antiretrovirali)

Patiromer- evidenze

DIAMOND RCT

Due to slov
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Patiromer use in patients with heart failure and reduced ejection fraction (HFrEF) with hyperkalemia (HK)

Table 4 Patients experiencing adverse events during the randomized phase

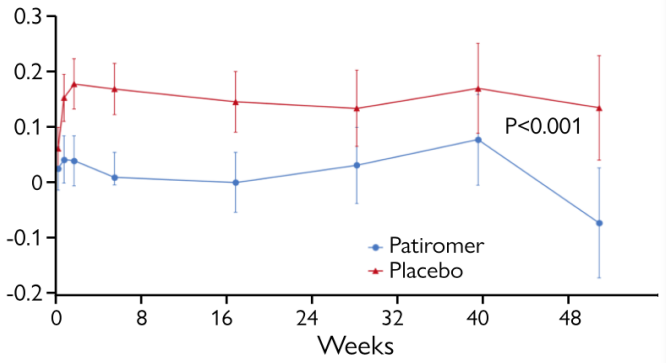
Variable	Patiromer (*n* = 439)	Placebo (*n* = 439)
Any adverse events, *n* (%)	320 (72.9)	325 (74.0)
Hypokalemia	66 (15.0)	47 (10.7)
Mild	57 (13.0)	42 (9.6)
Moderate	8 (1.8)	4 (0.9)
Severe	1 (0.2)	1 (0.2)
Hypomagnesemia	19 (4.3)	22 (5.0)
Diarrhea	19 (4.3)	15 (3.4)
Constipation	11 (2.5)	5 (1.1)
Nausea	4 (0.9)	4 (0.9)
Adverse events leading to withdrawal, *n* (%)	12 (2.7)	11 (2.5)
Any serious adverse event, *n* (%)	54 (12.3)	58 (13.2)

Placebo Patiromer

Primary endpoint

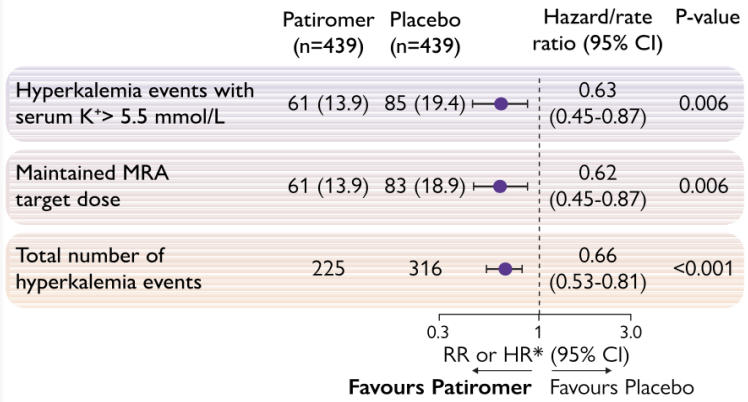
Median duration of FU 27 (13-43 weeks)

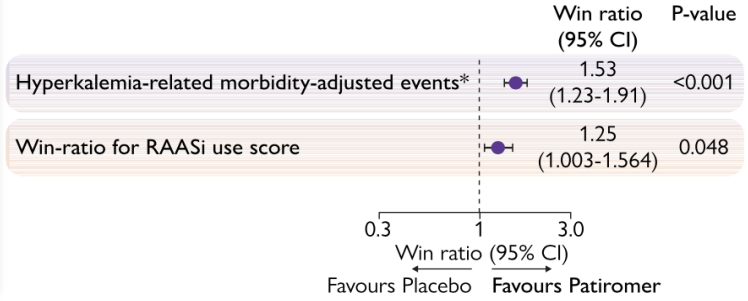
Mean change in serum potassium (mmol/L) from baseline (95% confidence interval (CI))



	Day 3	Weeks 1	2	6	18	30	42	54
Patiromer	409	406	402	376	273	183	104	66
Placebo	416	409	397	361	270	184	106	74

Secondary endpoints





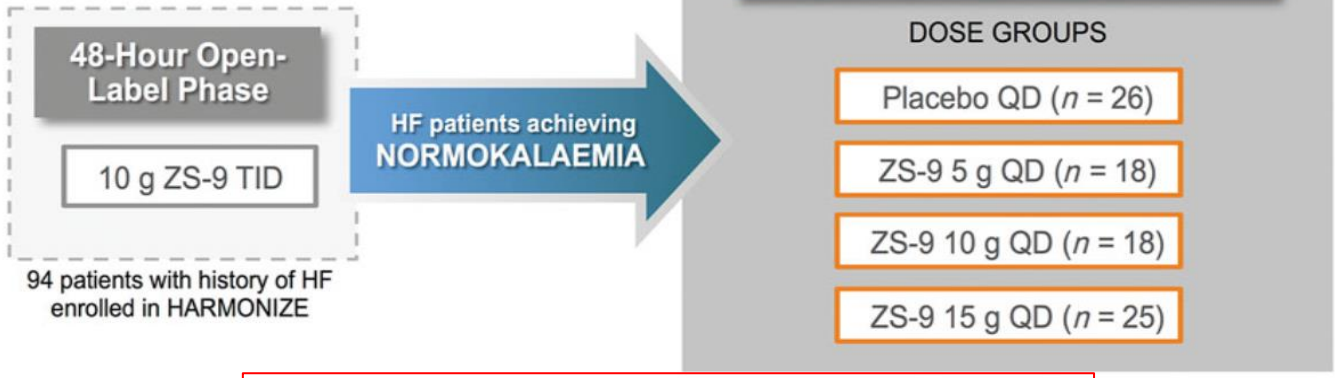
*Morbidity-adjusted hyperkalemia-related outcomes were tested in a hierarchical manner with the following sequence: cardiovascular death, cardiovascular hospitalization, total hyperkalemia events >6.5 mmol/L, >6.0–6.5 mmol/L, and >5.0–6.0 mmol/L

Szc Evidenze

Harmonize RCT – subanalysis on HF pts

USA, Australia, and South Africa

Harmonize RCT:
258 ambulatory pts with HK



without adjustment of their RAASi dose

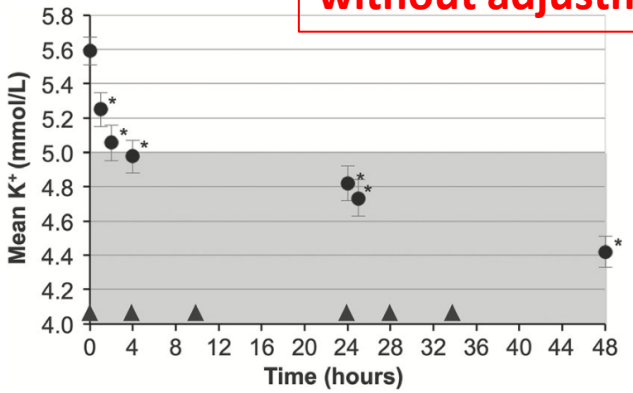


Figure 2 Mean serum potassium over time in patients treated with ZS-9 10 g three times daily (circles) for 48 h during the open-label phase. The shaded portion represents normal potassium levels. Bars indicate 95% confidence intervals. Triangles indicate administration of ZS-9 dose. *$P < 0.001$ for comparisons against placebo.

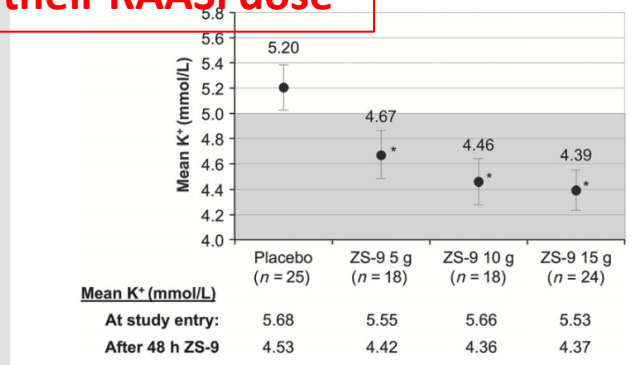


Figure 3 Mean serum potassium, days 8–29 after randomization, placebo vs. ZS-9 5 g, 10 g, and 15 g dose groups. Mean baseline serum potassium values before and after 48 h of ZS-9 treatment are shown below the graph for each dose group. The shaded portion represents normal potassium levels. Bars indicate 95% confidence interval. *$P < 0.001$ for comparisons against placebo.

Overall Harmonize cohort

	No. (%)				
	Open-Label Phase (Zirconium Cyclosilicate, 10 g) (n = 258)	Randomized Phase			
		Placebo Group (n = 85)	Zirconium Cyclosilicate Dose Group		
			5 g (n = 45)	10 g (n = 51)	15 g (n = 56)
Gastrointestinal disorders					
Constipation	2 (0.8)	6 (7.1)	0	1 (2.0)	1 (1.8)
General disorders and administration site conditions					
Edema[a]	0	2 (2.4)	1 (2.2)	3 (5.9)	8 (14.3)
Metabolism and nutrition disorders					
Hypokalemia (all)	0	0	0	5 (9.8)	6 (10.7)
Hypokalemia (reported as adverse event)	0	0	0	0	1 (1.8)

Results confirmed in Harmonize-global study
(Japan, Russia, South Korea, and Taiwan)

OPRA-HF RCT ongoing…

PIANO TERAPEUTICO AIFA DI PRESCRIVIBILITÀ PER PATIROMER E SODIO ZIRCONIO CICLOSILICATO

La prescrivibilità di questi medicinali è consentita ai soli medici appartenenti a centri ospedalieri o specialisti nefrologo, cardiologo, internista . Validità del piano 6 mesi

CRITERI DI ELEGGIBILITÀ AL TRATTAMENTO (devono essere soddisfatti entrambi i punti 1 e 2)

1) Diagnosi: Iperkaliemia persistente (livello di potassiemia >5.5mmol/L) in pazienti con risposta insufficiente o controindicazione alle resine (calcio polistirene sulfonato/sodio polistirene sulfonato).

2) Almeno una delle seguenti condizioni (possibilità di scelta multipla):

☐ Insufficienza renale: stadio 3b-CKD in pazienti **con** concomitante terapia con RAASi

☐ Insufficienza renale: stadio 4 o 5-CKD **non in dialisi**, in pazienti **con o senza** concomitante terapia con RAASi

☐ Insufficienza renale: stadio 5-CKD **in dialisi** (solo per sodio zirconio ciclosilicato) DIALIZE study

☐ Scompenso cardiaco (frazione di eiezione ≤40%) in pazienti **con** concomitante terapia con RAASi in dose giudicata subottimale.

2021 ESC HF GL
HK management in HF pts in RAASi

→ Possono essere considerati i nuovi chelanti del K+ in pazienti con iperK+ cronica o episodi ricorrenti in terapia con RAASi non appena si riscontrino livelli ***> 5 meq/l.*** *Va* ***ottimizzata la terapia con RAASi*** *non appena K+ < 5 meq/L.*

- in pazienti con **K>6.5** mEq/l → Sospendere farmaci RAASi indipendentemente dal fatto che siano a dose target o meno, e iniziare farmaci che abbassano i valori di potassio. Solo se il potassio torna a valori <5 mEq/l nel f-up si può valutare la reintroduzione graduale.

- In pazienti con **K compreso tra 5-6.5** mEq/l e **dose target** massima tollerata di RAASi→ avviare farmaci che diminuiscono livelli di potassio mantenendo posologia RAASi inalterata.

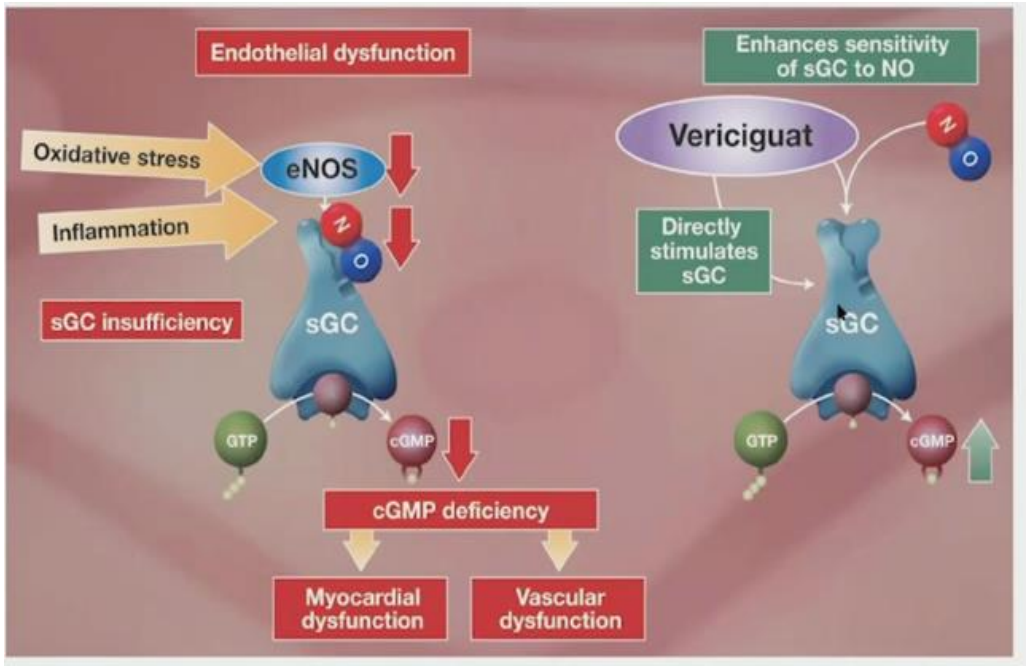
- In pazienti con **K compreso tra 5-6.5** mEq/l e **NON dose target** massima tollerata di RAASi → avviare farmaci che diminuiscono livelli di potassio, e se K<5 mEq/l al f-UP si può procedere a titolazione dei RAASi.

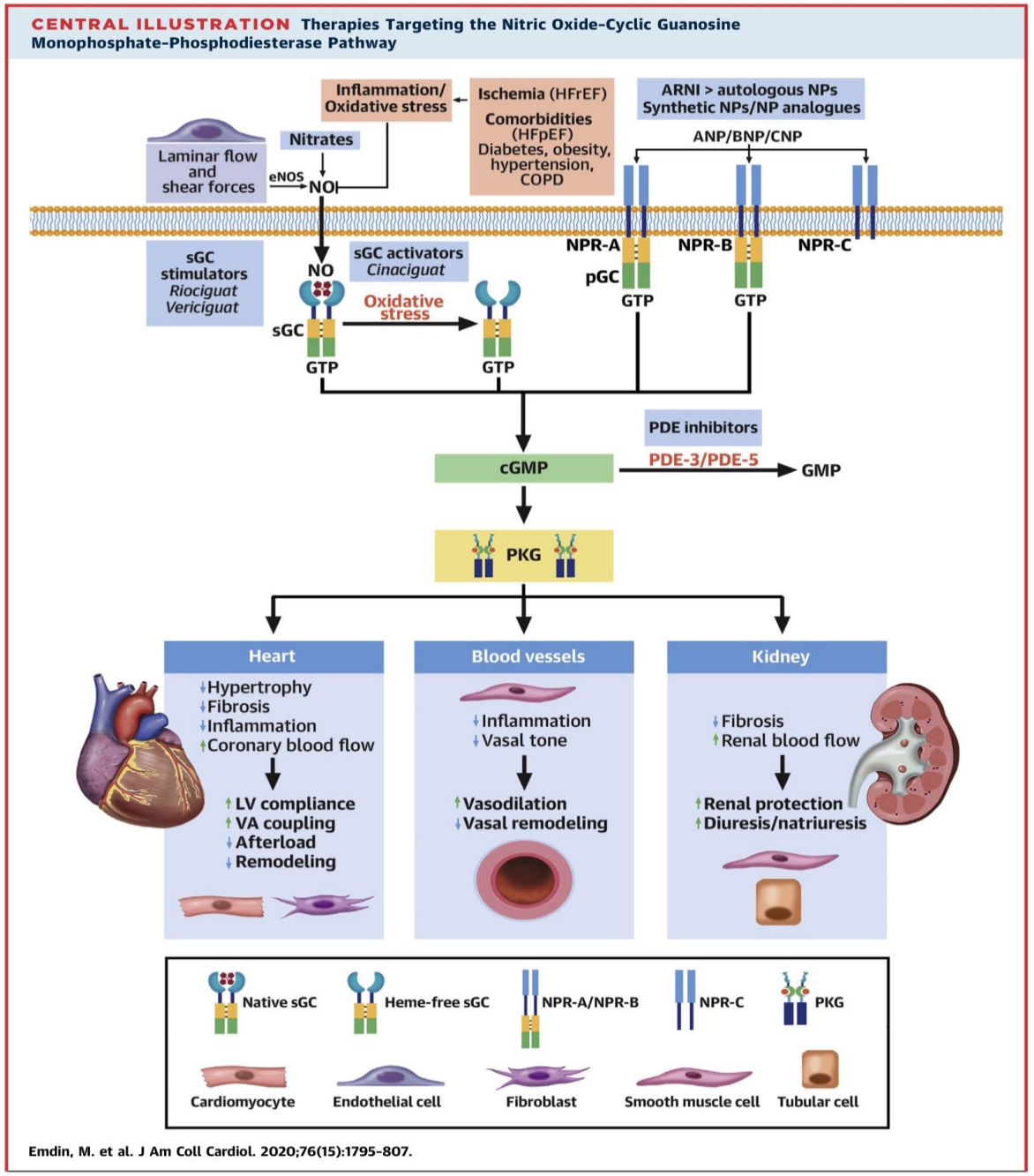
- In pazienti con **K compreso tra 4.5-5** mEq/l e **NON dose target** massima tollerata di RAASi→ titolare RAASi monitorando attentamente kaliemia, e aggiungere farmaci che diminuiscono livelli di potassio solo se K>5 mEq/l.

VERICIGUAT

Vericiguat
ESC HF GL 2021

Recommendations	Class	Level
Soluble guanylate cyclase receptor stimulator		
Vericiguat may be considered in patients in NYHA Class II–IV who have had **worsening HF** despite treatment with an **ACEi (or ARNi), a beta blocker and an MRA** to reduce the risk of CV mortality or HFH	IIb	B





Emdin, M. et al. J Am Coll Cardiol. 2020;76(15):1795–807.

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The NEW ENGLAND JOURNAL of MEDICINE

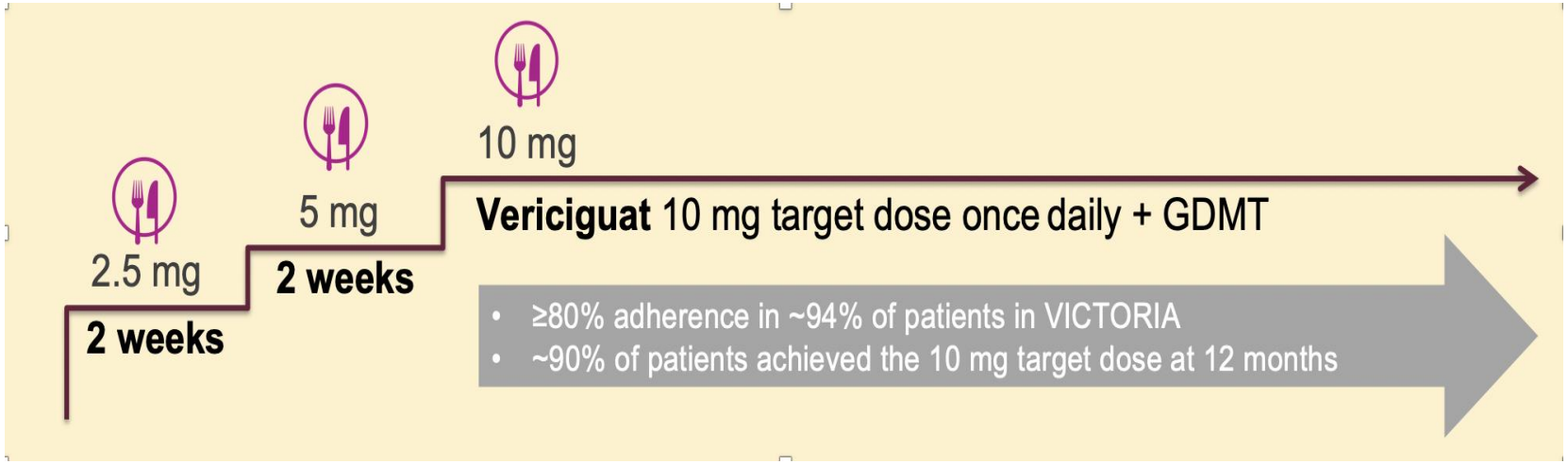
ORIGINAL ARTICLE

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., for the VICTORIA Study Group*

Tabella 1. Criteri di inclusione ed esclusione nello studio VICTORIA

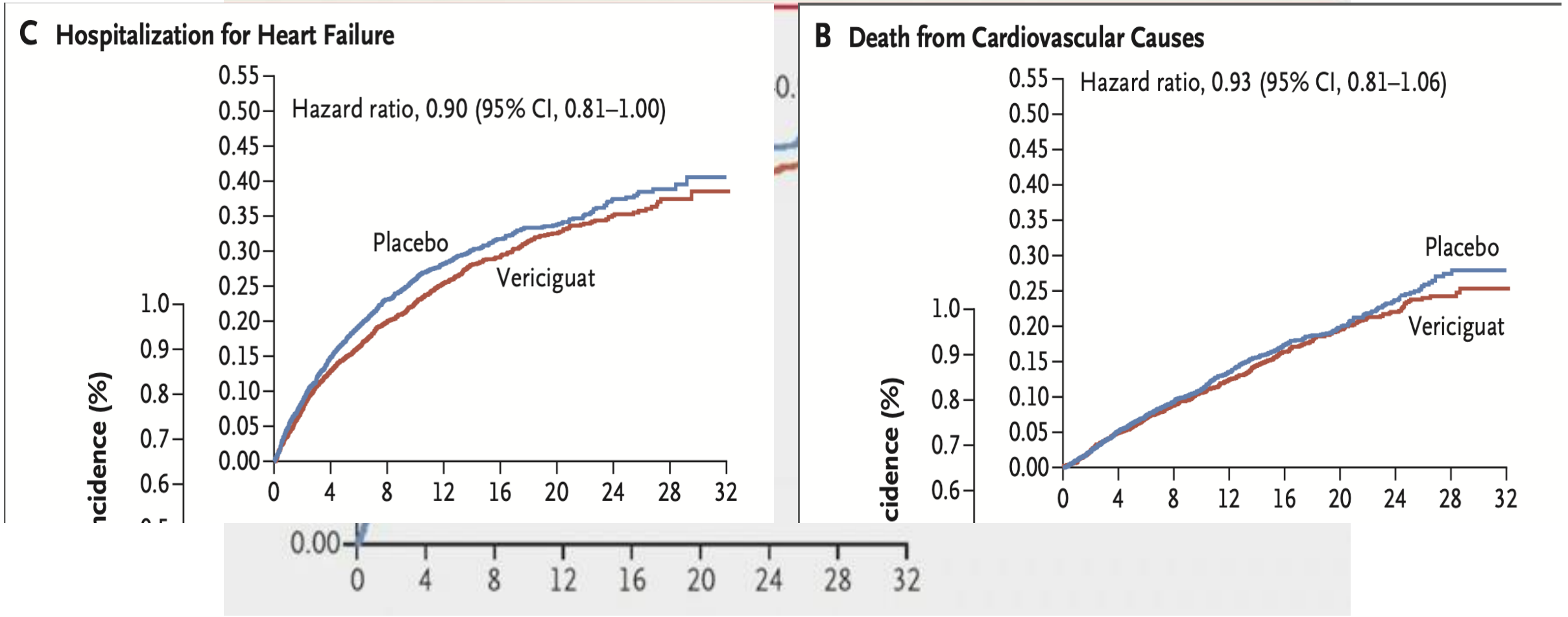
Criteri di inclusione	Criteri di esclusione
· FE < 45% valutata nei 12 mesi precedenti la randomizzazione · NT-proBNP> 1,000 pg/ml se RS, > 1,600 pg/ml se FA (misurato entro 30 giorni prima dalla randomizzazione) · Precedente ospedalizzazione per SC nei 6 mesi precedenti (con tetto del 20% per il numero di pazienti arruolati con ospedalizzazione > 3 mesi) o necessità di terapia diuretica endovena per peggioramento dello SC nei 3 mesi precedenti la randomizzazione	· Paziente clinicamente instabile · PAS < 100 mmHg · Uso concomitante o previsto di nitrati a lunga durata d'azione o stimolatori della sGC o inibitori della PDE5 · In terapia con inotropi, portatori di LVAD o in attesa di trapianto cardiaco · Comorbidità cardiache complesse, correggibili o clinicamente attive · Recente intervento di correzione di vizio valvolare (< 3 mesi) o rivascolarizzazione coronarica (< 60 giorni) · Incapace di fornire il consenso informato · Donne in età fertile non facenti uso di contraccettivo efficace



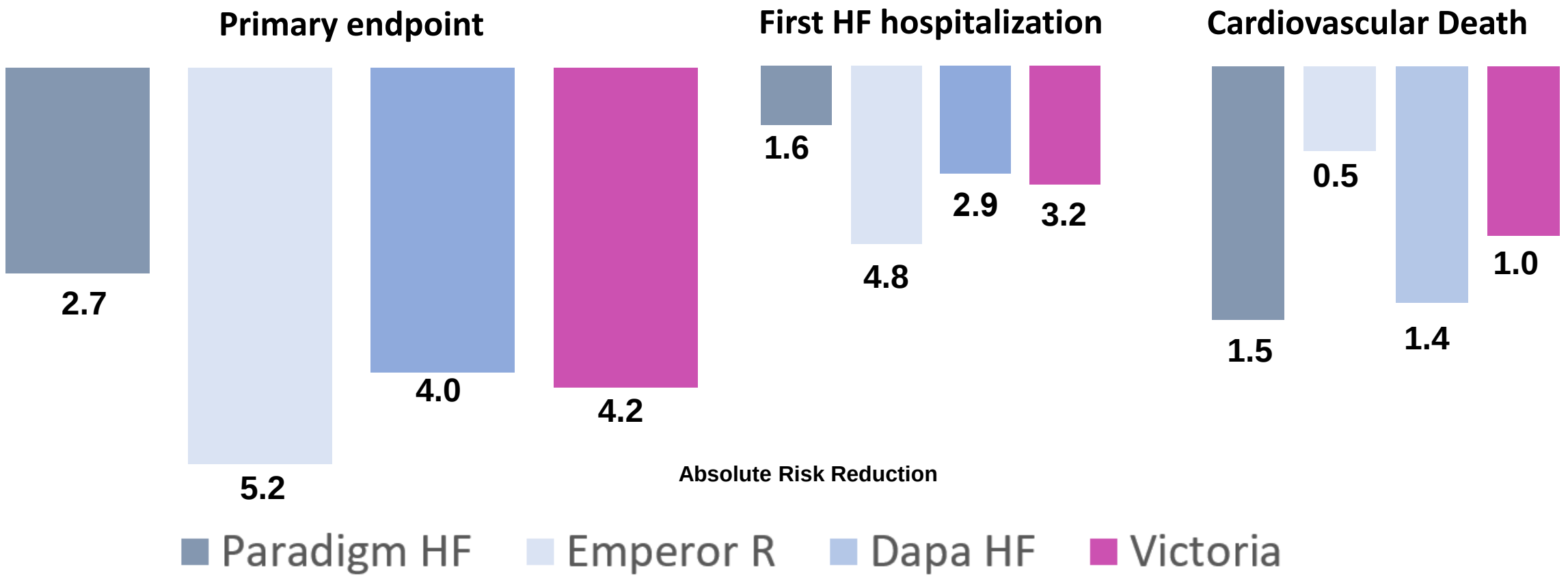
- One tablet per day with meal/food
- Titration guided by evaluation of blood pressure and clinical symptoms
- No dosage adjustment for geriatric patients or patients with moderate renal or hepatic impairment

Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893.

VICTORIA – CV death & HF hospitalisation

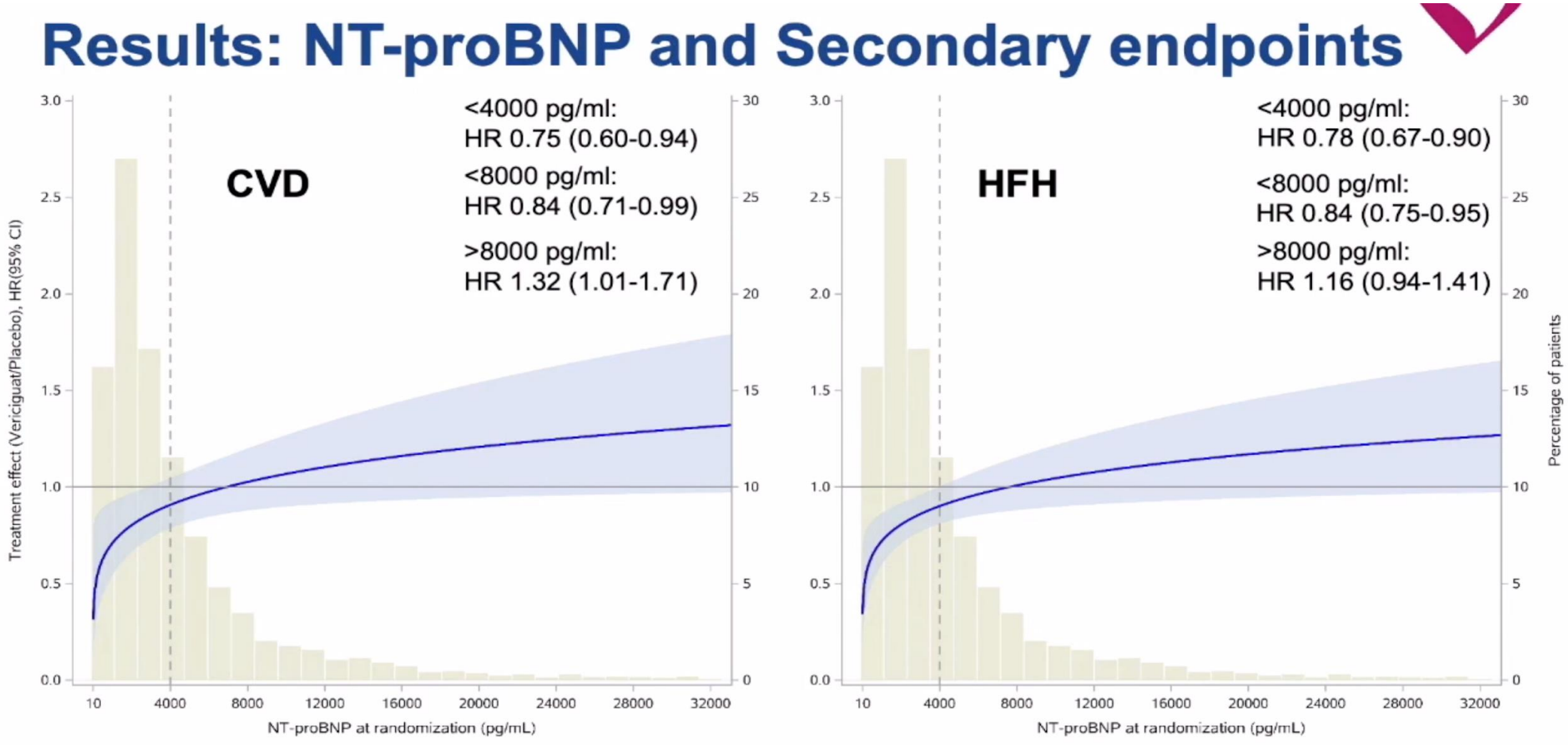


	Primary endpoint	Comparator	Treatment	NNT
ARNI	Paradigm HF	13.2	10.5	**37**
Dapaglifozin	Dapa HF	15.6	11.6	**25**
Empaglifozin	Emperor R	21.0	15.8	**19**
Vericiguat	**Victoria**	**37.8**	**33.6**	**24**



1. McMurray JJV et al. *N Engl J Med.* 2014;371:993–1004; 2. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008; 3. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 4 . Packer M et al. *N Engl J Med.* 2020;383:1413–1424.

Vericiguat & baseline NTproBNP: subanalysis

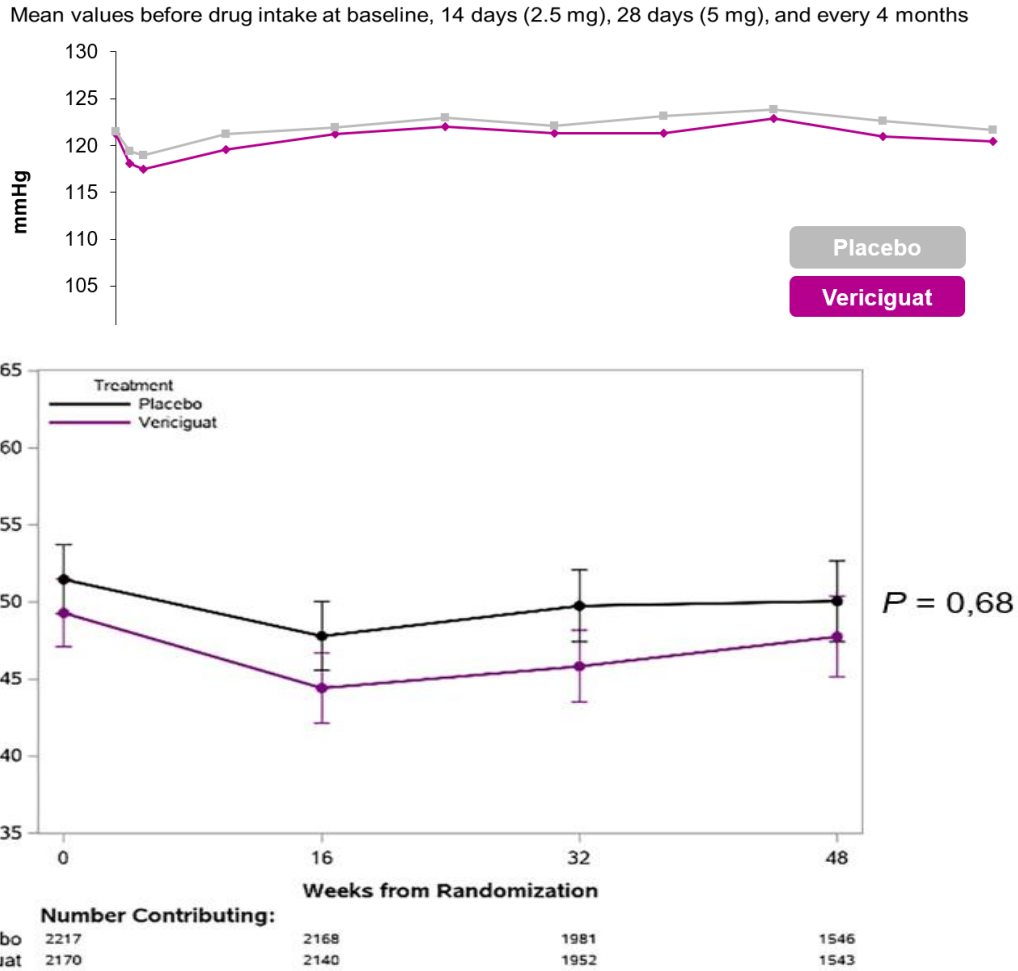


JACC Heart Fail 2020;8:931-939

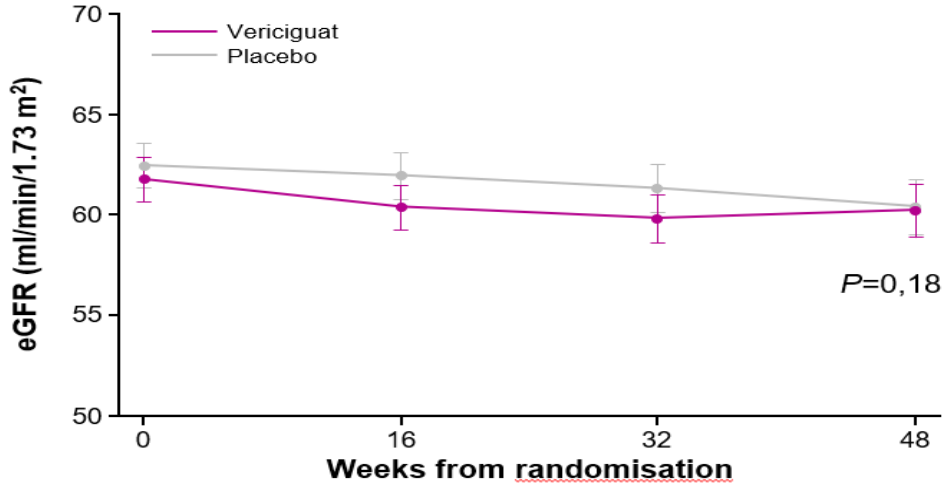
Safety Profile

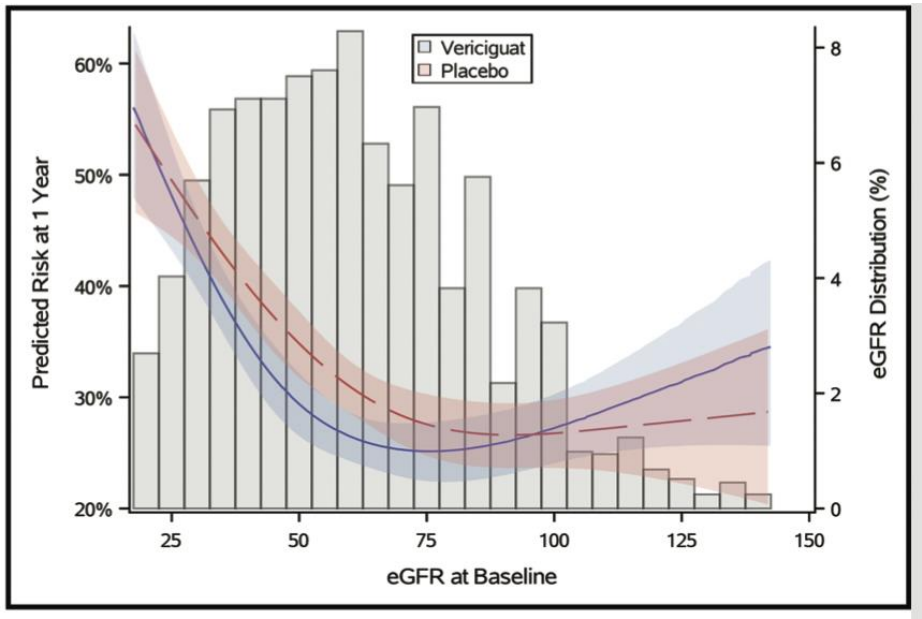
Systolic Blood Pressure Over Time[1,2]

Decrease in BP occurred early and very small differences in mean values between vericiguat and placebo arm (1 to ~1.5 mmHg)



Change in eGFR over time





Voors et al EurJHF 2021

Vericiguat

2,5 - 5 - 10 mg compresse (frantumabili) assunte con il cibo

- FDA approval: 01- 2021
- EMEA approval: 07-2021
- AIFA approval: 10-2021

“per il trattamento dell’insufficienza cardiaca sintomatica cronica in pazienti adulti con ridotta frazione di eiezione stabilizzati dopo un recente evento di riacutizzazione che abbia richiesto una terapia per via endovenosa”

… aspettando rimborsabilità e piano terapeutico.

Real-world eligibility for vericiguat according to trial, guideline, and labelling eligibility criteria: data from the Swedish Heart Failure Registry

V.N. Nguyen[1], F. Lindberg[1], U. Dahlstrom[2], L.H. Lund[1], G. Savarese[1]

[1]*Karolinska Institutet, Division of Cardiology, Department of Medicine, Stockholm, Sweden;* [2]*Linkoping University, Department of Cardiology and Department of Health, Medicine and Caring Sciences, Linkoping, Sweden*

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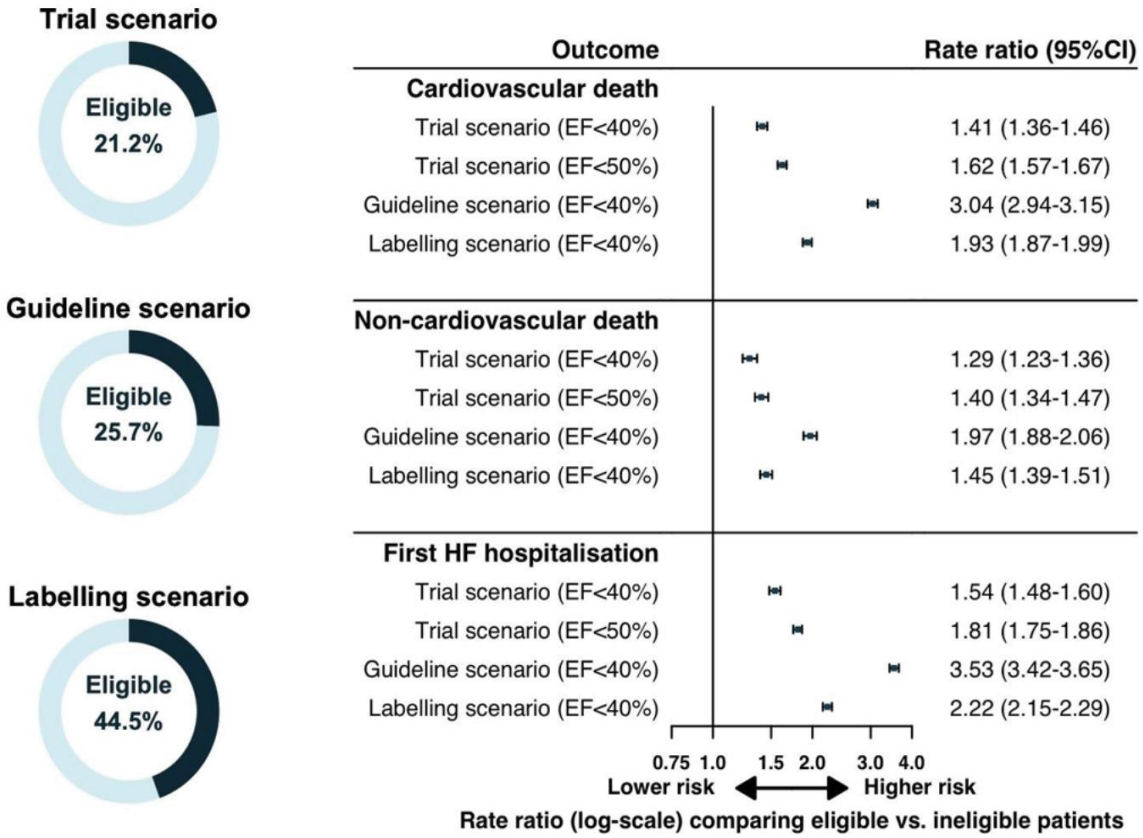


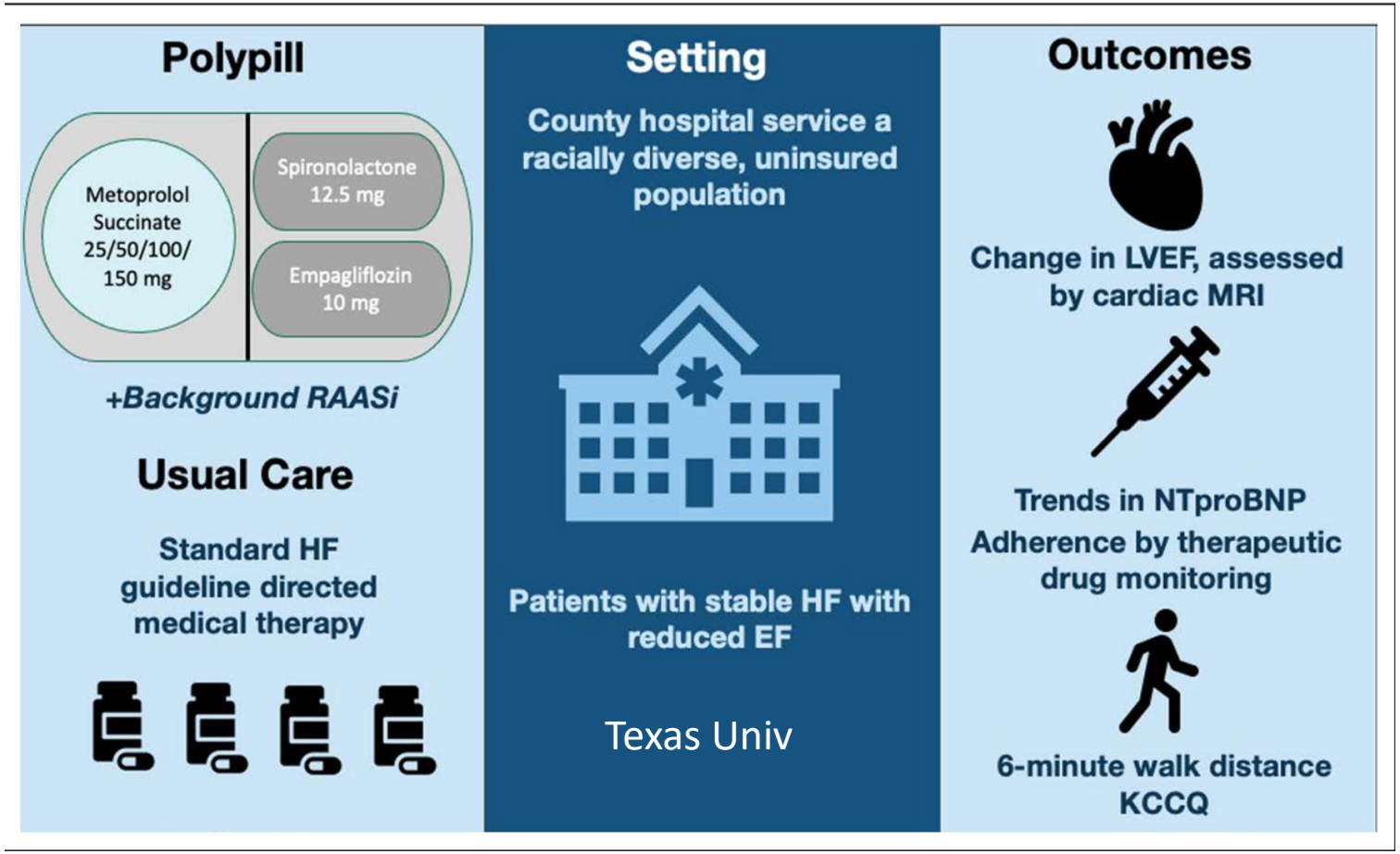
Figure 1

The 2023 HF patients' therapy

- SGL2 inhibitors (qd)
- Betablocker (qd/bid)
- ARNI (bid)
- MRA (qd)
- Furosemide (qd/bid/tid)
- Patiromer/ZS-9 (qd)
- Vericiguat (qd)
- NOAC? SAPT? DAPT?
- Statin therapy (qd) ?

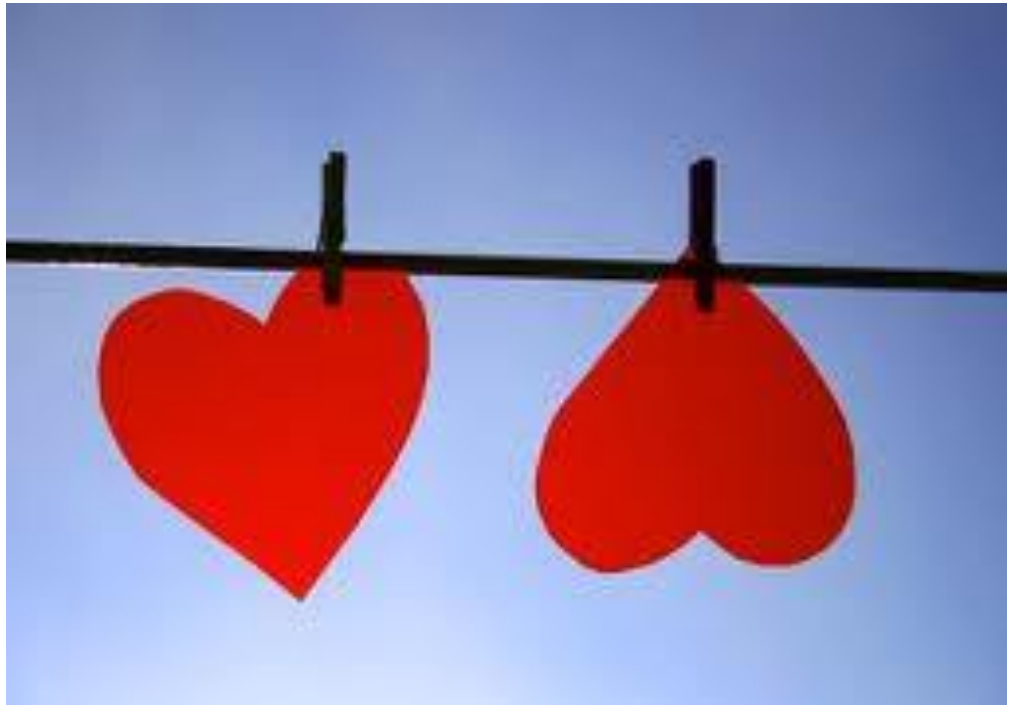
Should Polypills Be Used for Heart Failure With Reduced Ejection Fraction?

Ambarish Pandey, MD, MSCS; Neil Keshvani, MD; Thomas J. Wang, MD



Circulation. 2022;146:276–278. DOI: 10.1161/CIRCULATIONAHA.122.059661

GRAZIE PER L'ATTENZIONE



maurizio.bertaina@aslcittaditorino.it

Backup slides

Patiromer- evidenze

DIAMOND RCT

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Patiromer use in patients with heart failure and reduced ejection fraction (HFrEF) with hyperkalemia (HK)

Table 4 Patients experiencing adverse events during the randomized phase

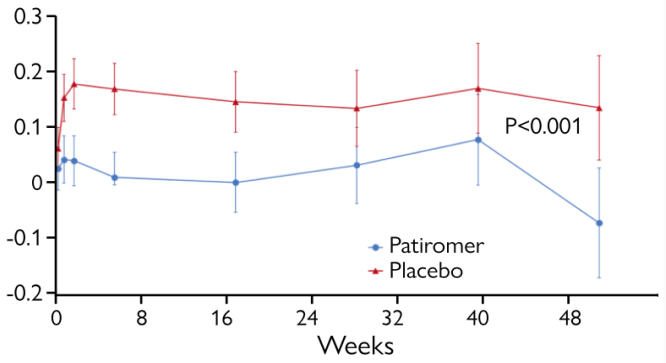
Variable	Patiromer (*n* = 439)	Placebo (*n* = 439)
Any adverse events, *n* (%)	320 (72.9)	325 (74.0)
Hypokalemia	66 (15.0)	47 (10.7)
Mild	57 (13.0)	42 (9.6)
Moderate	8 (1.8)	4 (0.9)
Severe	1 (0.2)	1 (0.2)
Hypomagnesemia	19 (4.3)	22 (5.0)
Diarrhea	19 (4.3)	15 (3.4)
Constipation	11 (2.5)	5 (1.1)
Nausea	4 (0.9)	4 (0.9)
Adverse events leading to withdrawal, *n* (%)	12 (2.7)	11 (2.5)
Any serious adverse event, *n* (%)	54 (12.3)	58 (13.2)

Placebo Patiromer

Primary endpoint

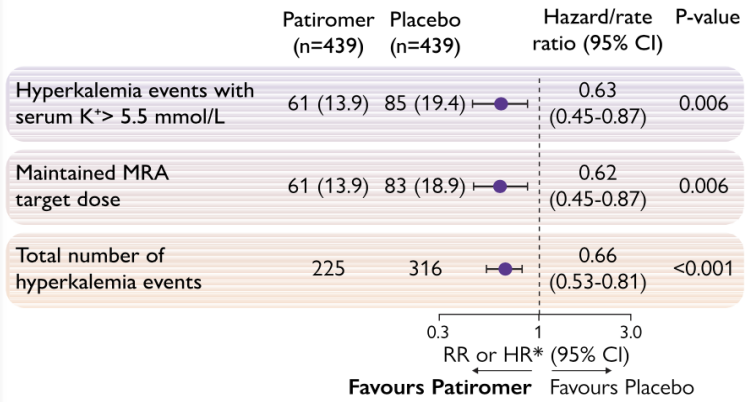
Median duration of FU 27 (13-43 weeks)

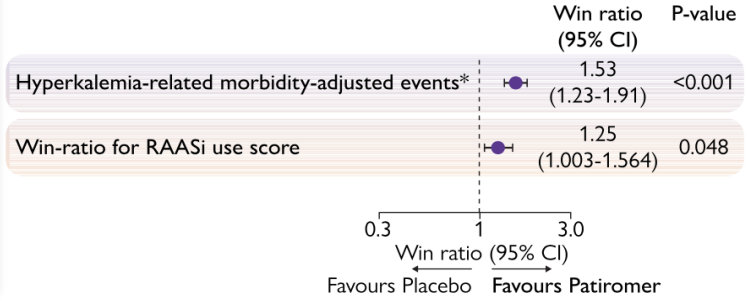
Mean change in serum potassium (mmol/L) from baseline (95% confidence interval (CI))



	Day 3	Weeks 1	2	6	18	30	42	54
Patiromer	409	406	402	376	273	183	104	66
Placebo	416	409	397	361	270	184	106	74

Secondary endpoints

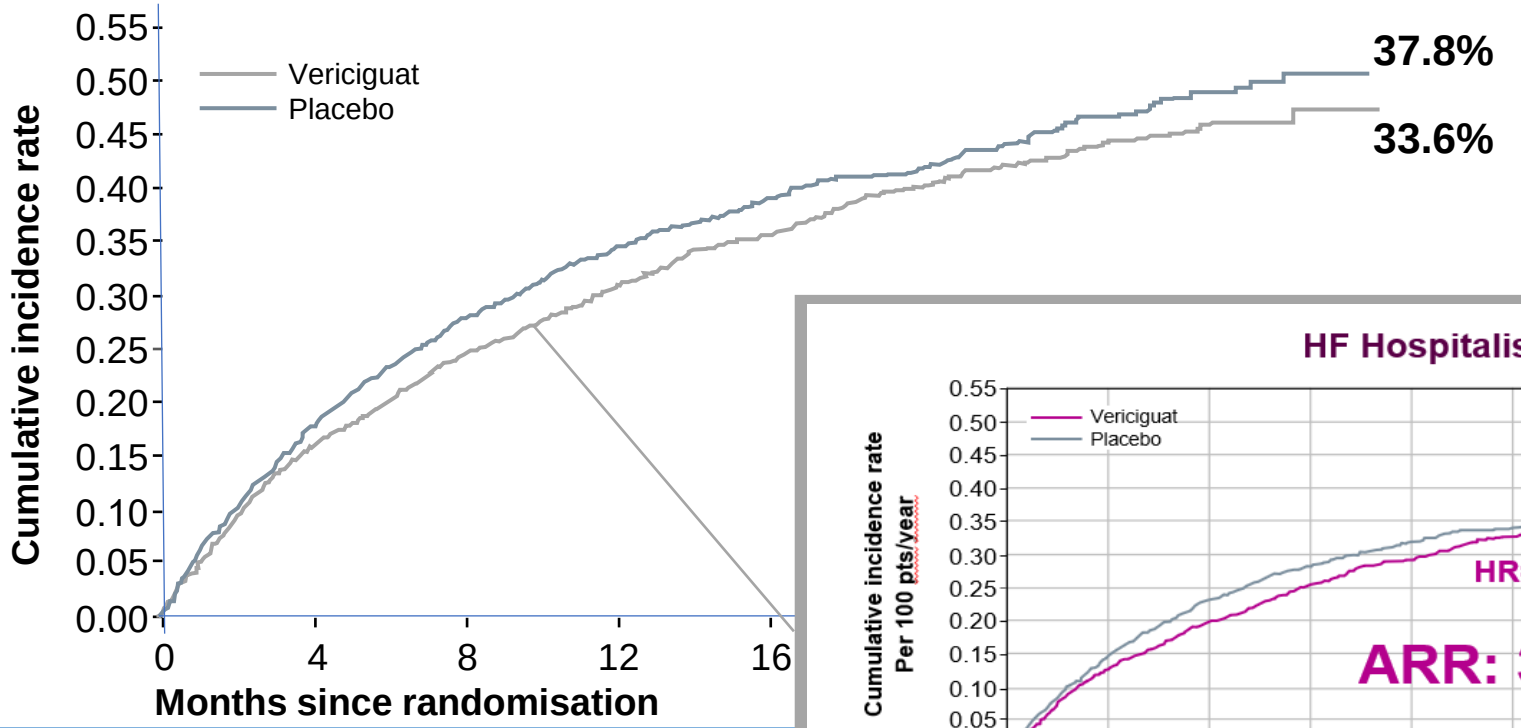




*Morbidity-adjusted hyperkalemia-related outcomes were tested in a hierarchical manner with the following sequence: cardiovascular death, cardiovascular hospitalization, total hyperkalemia events >6.5 mmol/L, >6.0–6.5 mmol/L, and >5.0–6.0 mmol/L

Vericiguat reduced HFH by means 3.2% (ARR)

Time to CV death or first HFH



HR=0.90 (95% CI 0.82–0.98)
P=0.02

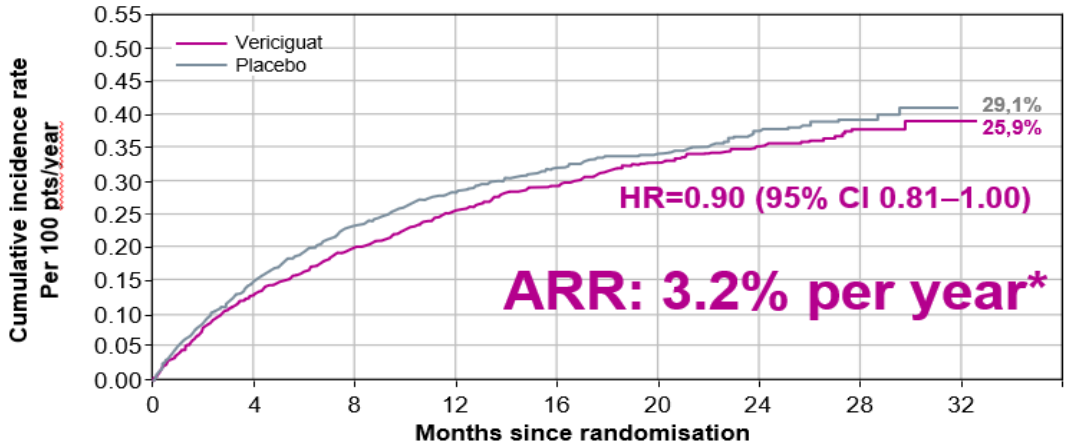
Annual NNT: 24#

ARR: 4.2% per year*

Number of subjects at risk					
Vericiguat	2526	2099	1621	1154	826
Placebo	2524	2053	1555	1097	772

Armstrong PW et al. *N Engl J Med*. 2020;382:1883–1893

HF Hospitalisation



Number of subjects at risk									
Vericiguat	2526	2098	1620	1153	825	577	348	125	1
Placebo	2524	2052	1554	1096	771	558	323	110	0

*Annual ARR: 29.1–25.9=3.2%.
ARR, absolute risk reduction; CI, confidence interval; HF, heart failure; HFH, heart failure hospitalisation; HR, hazard ratio.
1. Armstrong PW et al. *N Engl J Med.* 2020; doi:10.1056/NEJMoa1915928.

Background HF th in Victoria trial

Standard of care treatment			
ACE inhibitor or ARB, no./No. (%)	1847/2521 (73.3%)	1853/2519 (73.6%)	3700/5040 (73.4%)
Beta blocker, no./No. (%)	2349/2521 (93.2%)	2342/2519 (93.0%)	4691/5040 (93.1%)
MRA, no./No. (%)	1747/2521 (69.3%)	1798/2519 (71.4%)	3545/5040 (70.3%)
Angiotensin receptor–neprilysin inhibitor (Sacubitril/Valsartan), no./No. (%)	360/2521 (14.3%)	371/2519 (14.7%)	731/5040 (14.5%)