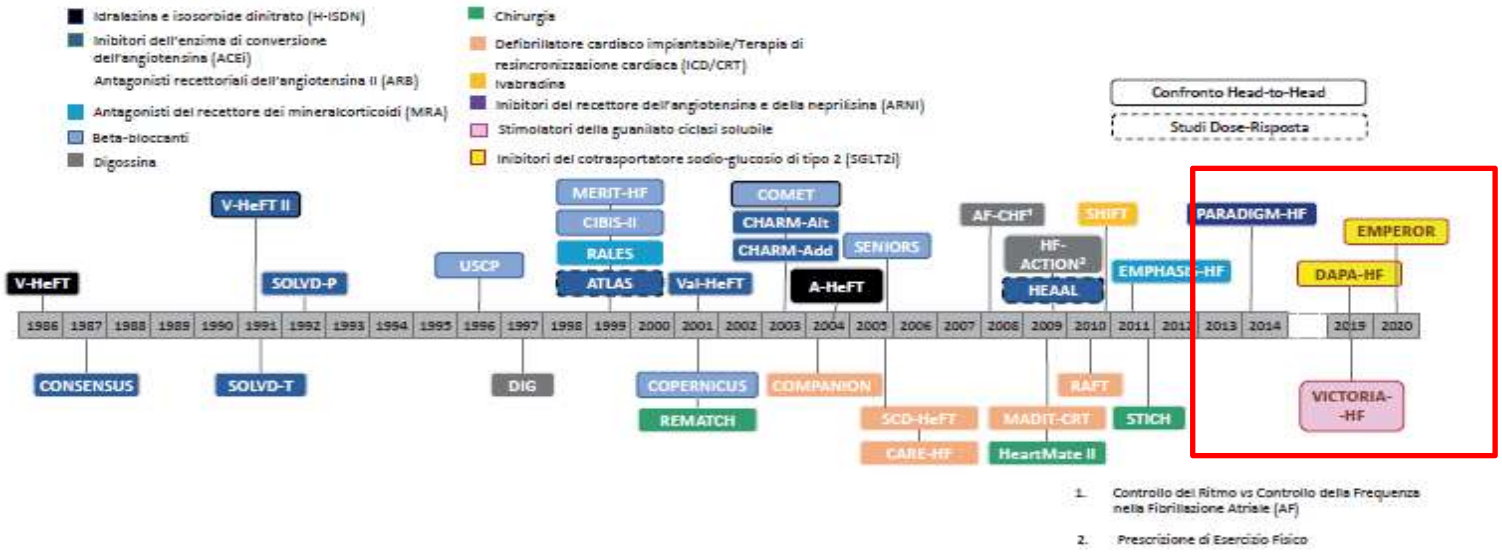
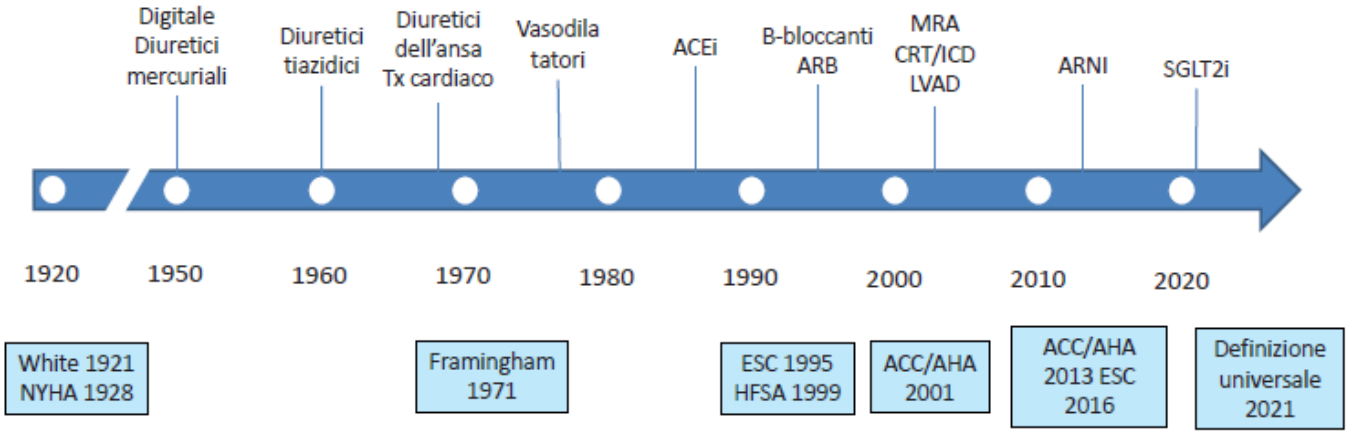
Scompenso Cardiaco: Terapia Medica

Dr. Michele Bianconcini

Cardiologia UTIC- Azienda Ospedaliero Universitaria di Parma


Idralazina e isosorbide dinitrato (H-ISDN)
Inibitori dell'enzima di conversione dell'angiotensina (ACEi)
Antagonisti recettoriali dell'angiotensina II (ARB)
Antagonisti del recettore dei mineralcorticoidi (MRA)
Beta-bloccanti
Digossina
Chirurgia
Defibrillatore cardiaco impiantabile/Terapia di resincronizzazione cardiaca (ICD/CRT)
Ivabradina
Inibitori del recettore dell'angiotensina e della neprilisina (ARNI)
Stimolatori della guanilato ciclasi solubile
Inibitori del cotrasportatore sodio-glucosio di tipo 2 (SGLT2i)
Confronto Head-to-Head
Studi Dose-Risposta
V-HeFT
V-HeFT II
SOLVD-P
SOLVD-T
CONSENSUS
USCP
DIG
MERIT-HF
CIBIS-II
RALES
ATLAS
Val-HeFT
COPERNICUS
REMATCH
COMET
CHARM-Alt
CHARM-Add
SENIORS
A-HeFT
COMPANION
SCD-HeFT
CAFE-HF
AF-CHF[1]
HF-ACTION[2]
HEAAL
SHIFT
EMPHASIS-HF
RAFT
MADIT-CRT
HeartMate II
STICH
PARADIGM-HF
EMPEROR
DAPA-HF
VICTORIA-HF
1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2020
1. Controllo del Ritmo vs Controllo della Frequenza nella Fibrillazione Atriale (AF)
2. Prescrizione di Esercizio Fisico


Digitale
Diuretici mercuriali
Diuretici tiazidici
Diuretici dell'ansa
Tx cardiaco
Vasodilatatori
ACEi
B-bloccanti
ARB
MRA
CRT/ICD
LVAD
ARNI
SGLT2i
1920
1950
1960
1970
1980
1990
2000
2010
2020
White 1921
NYHA 1928
Framingham 1971
ESC 1995
HFSA 1999
ACC/AHA 2001
ACC/AHA 2013 ESC 2016
Definizione universale 2021

- La terapia farmacologica è la pietra angolare della gestione, e deve essere ottimizzata prima di considerare device.

- Tre principali obiettivi:

1. ridurre la mortalità,
2. prevenzione delle riospedalizzazioni
3. miglioramento dello stato clinico, della capacità funzionale e della qualità di vita.

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

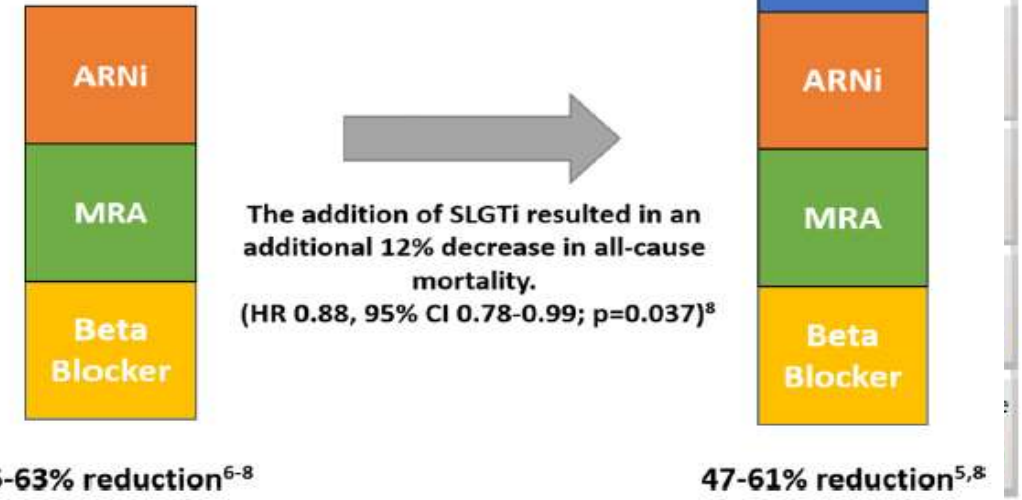
	Starting dose	Target dose
ACE-I		
Captopril[a]	6.25 mg t.i.d.	50 mg t.i.d.
Enalapril	2.5 mg b.i.d.	10–20 mg b.i.d.
Lisinopril[b]	2.5–5 mg o.d.	20–35 mg o.d.
Ramipril	2.5 mg b.i.d.	5 mg b.i.d.
Trandolapril[a]	0.5 mg o.d.	4 mg o.d.
ARNI		
Sacubitril/valsartan	49/51 mg b.i.d.[c]	97/103 mg b.i.d.
Beta-blockers		
Bisoprolol	1.25 mg o.d.	10 mg o.d.
Carvedilol	3.125 mg b.i.d.	25 mg b.i.d.[e]
Metoprolol succinate (CR/XL)	12.5–25 mg o.d.	200 mg o.d.
Nebivolol[d]	1.25 mg o.d.	10 mg o.d.
MRA		
Eplerenone	25 mg o.d.	50 mg o.d.
Spironolactone	25 mg o.d.[f]	50 mg o.d.
SGLT2 inhibitor		
Dapagliflozin	10 mg o.d.	10 mg o.d.
Empagliflozin	10 mg o.d.	10 mg o.d.
Other agents		
Candesartan	4 mg o.d.	32 mg o.d.
Losartan	50 mg o.d.	150 mg o.d.
Valsartan	40 mg b.i.d.	160 mg b.i.d.
Ivabradine	5 mg b.i.d.	7.5 mg b.i.d.
Vericiguat	2.5 mg o.d.	10 mg o.d.
Digoxin	62.5 µg o.d.	250 µg o.d.
Hydralazine/ Isosorbide dinitrate	37.5 mg t.i.d./20 mg t.i.d.	75 mg t.i.d./40 mg t.i.d.

Management of HFrEF

To reduce mortality - for all patients

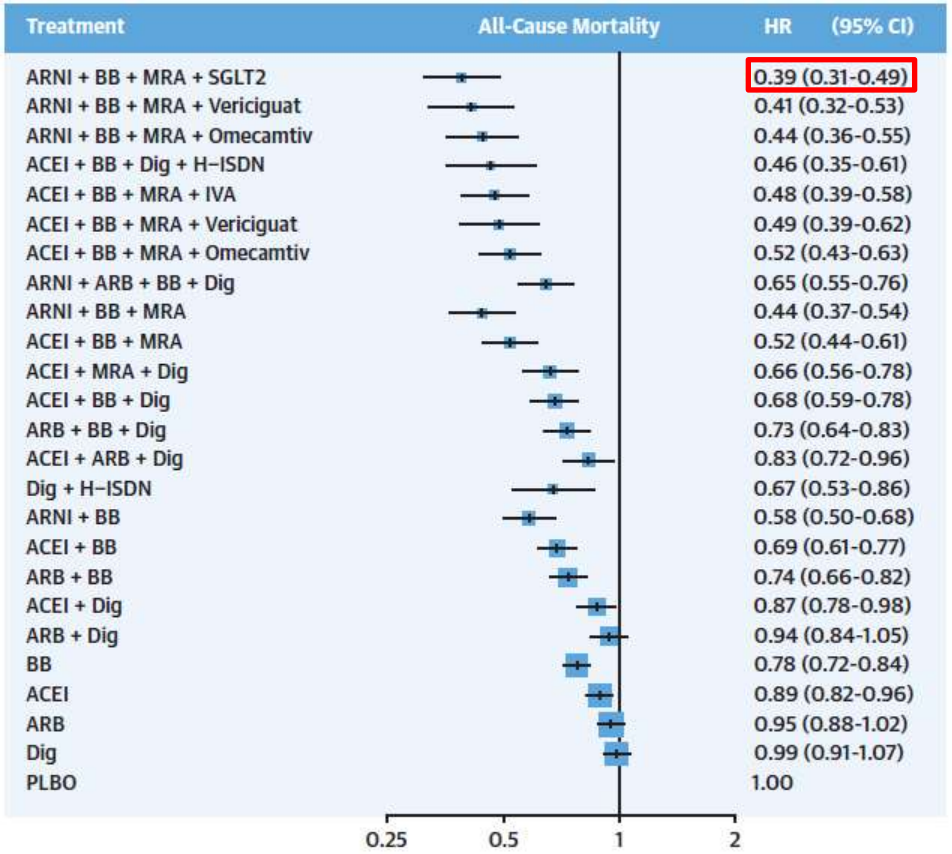
ACE-I/ARNI | BB | MRA | SGLT2i

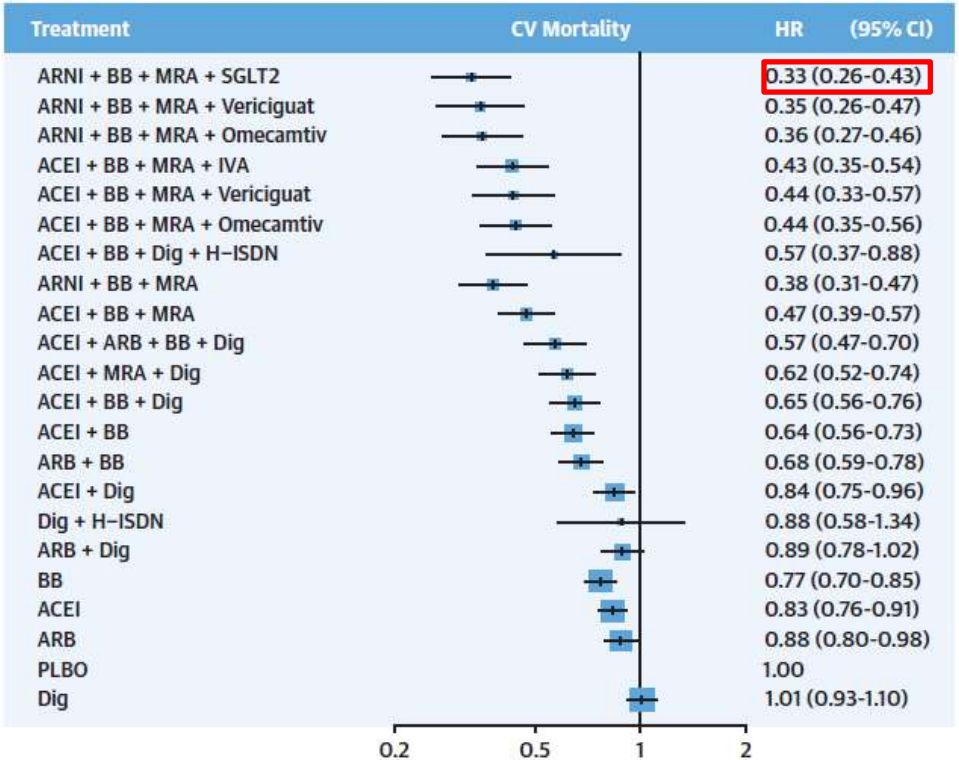
To reduce HF hospitalization/mortality - for selected patients



CENTRAL ILLUSTRATION Relative Risk Reduction of Different Pharmacological Treatment Combinations for Heart Failure

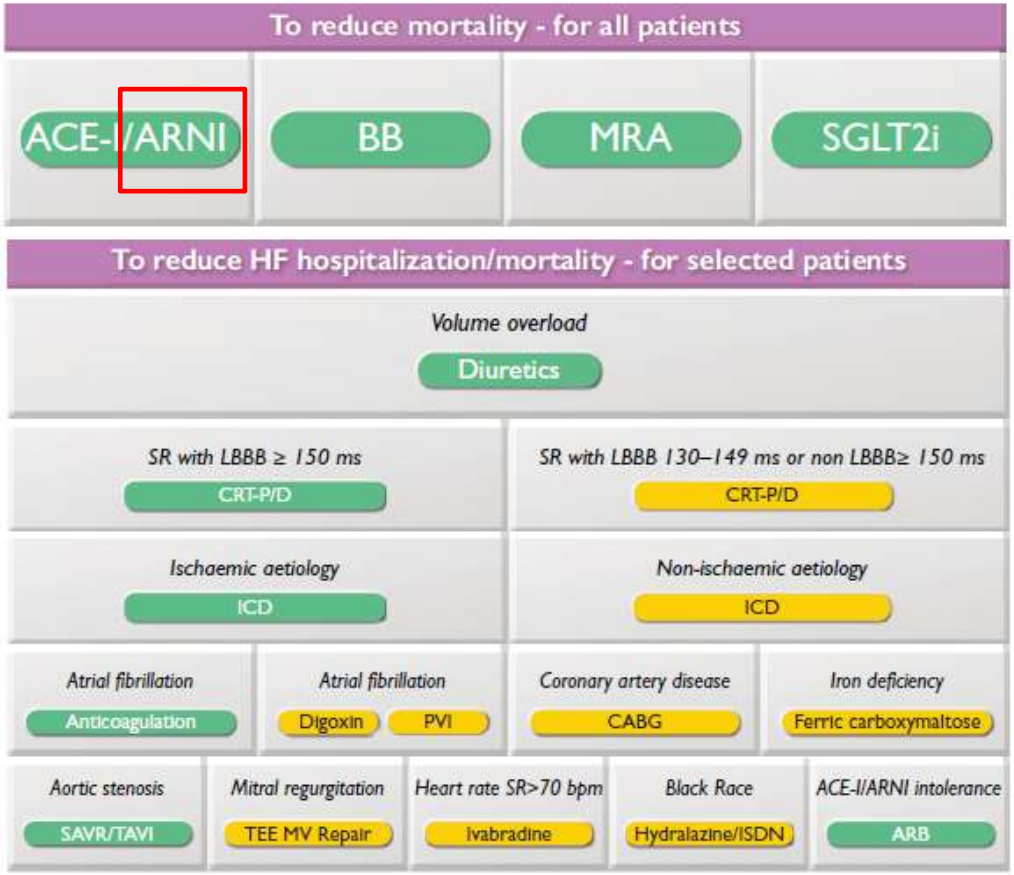
Tromp, J. et al. J Am Coll Cardiol HF. 2022;10(2):73-84.



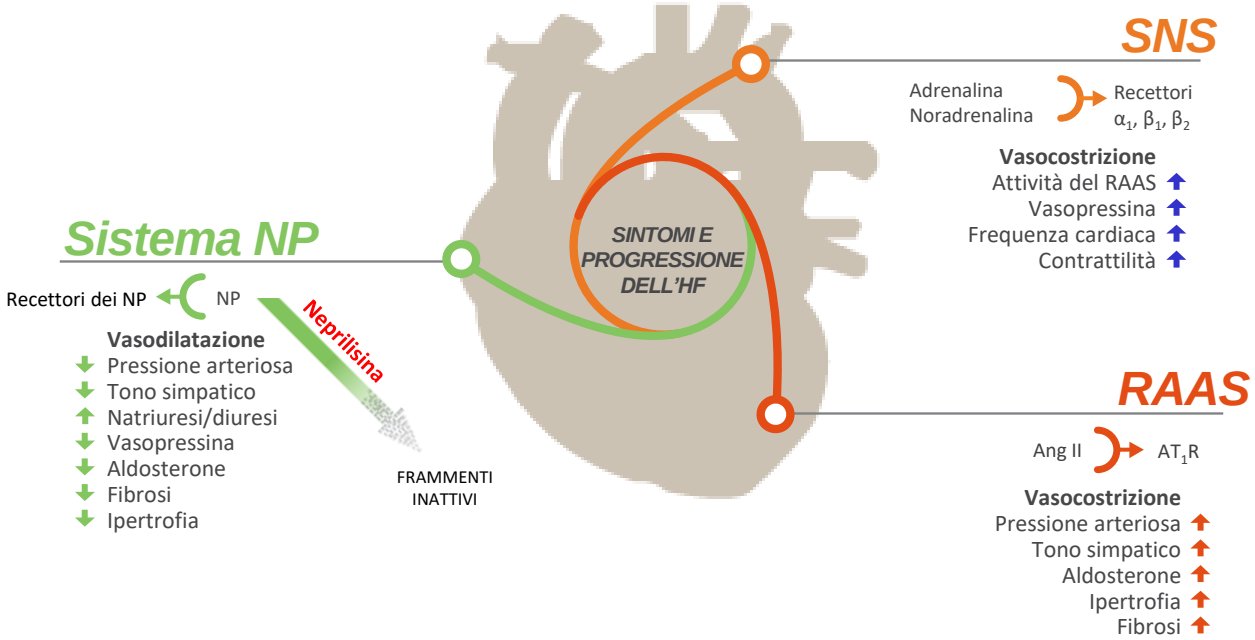


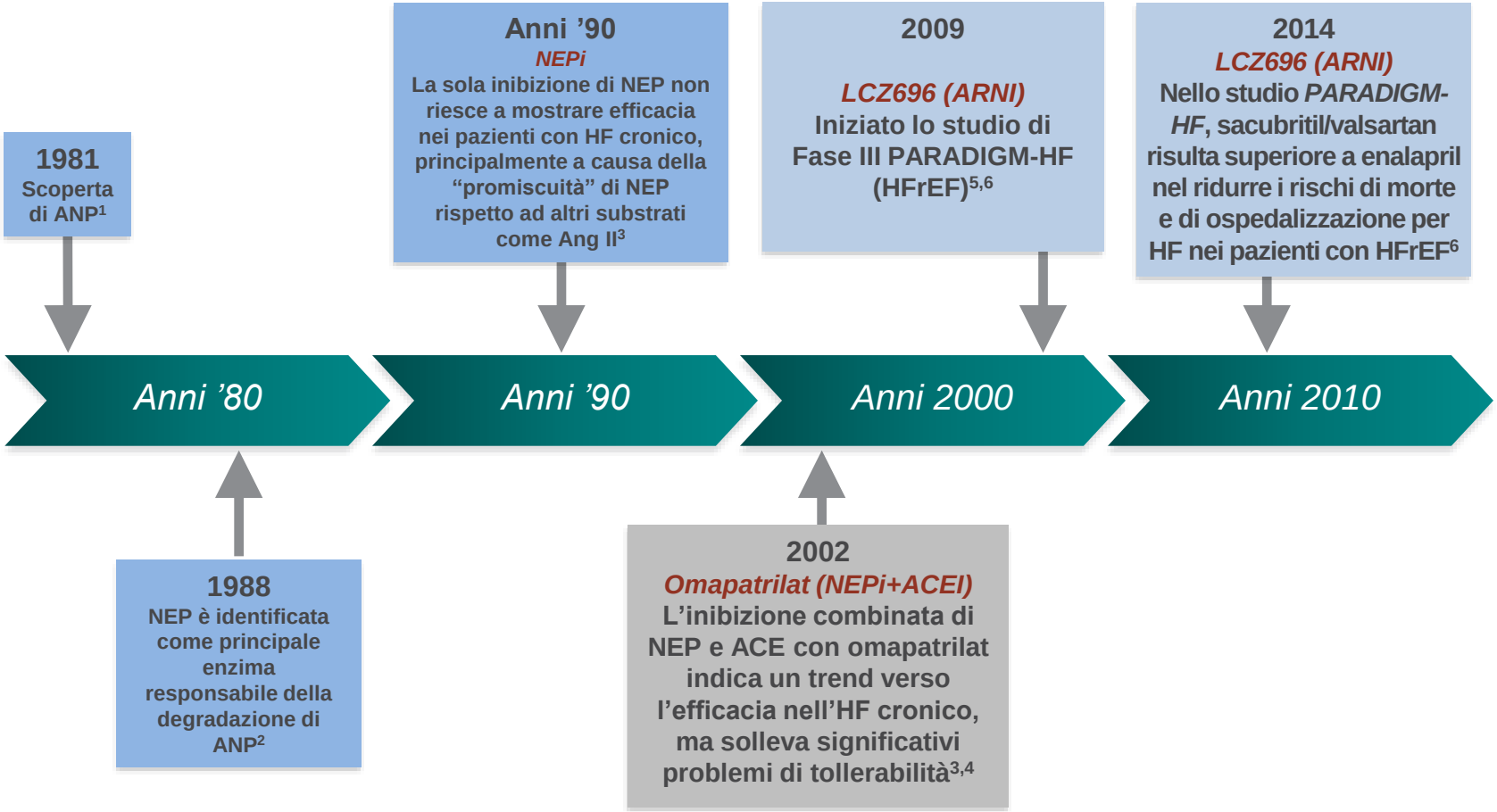
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Management of HFrEF



Relazione tra SNS RAAS e Sistema NP



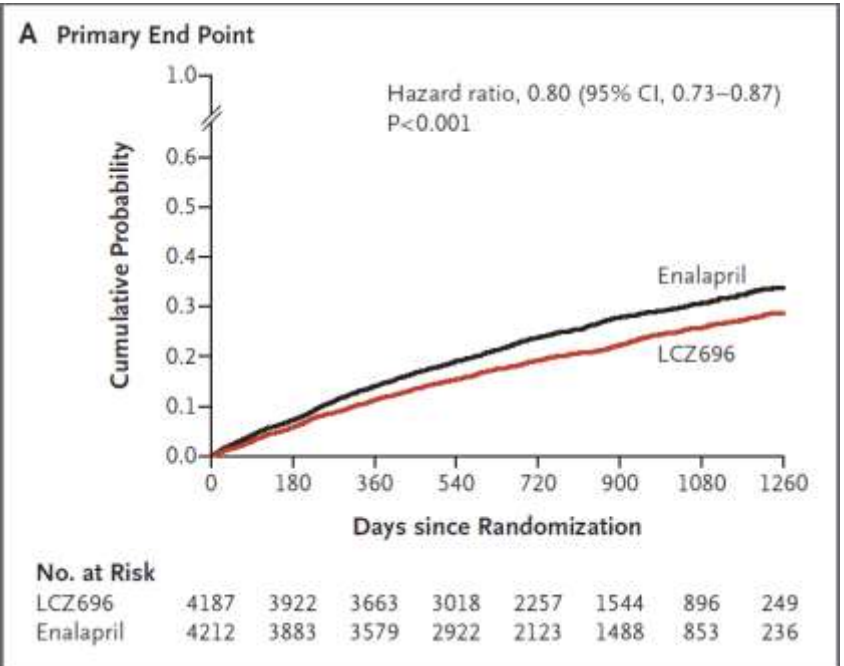

1981
Scoperta di ANP[1]
1988
NEP è identificata come principale enzima responsabile della degradazione di ANP[2]
Anni ’90
NEPi
La sola inibizione di NEP non riesce a mostrare efficacia nei pazienti con HF cronico, principalmente a causa della “promiscuità” di NEP rispetto ad altri substrati come Ang II[3]
2002
Omapatrilat (NEPi+ACEI)
L’inibizione combinata di NEP e ACE con omapatrilat indica un trend verso l’efficacia nell’HF cronico, ma solleva significativi problemi di tollerabilità[3,4]
2009
LCZ696 (ARNI)
Iniziato lo studio di Fase III PARADIGM-HF (HFrEF)[5,6]
2014
LCZ696 (ARNI)
Nello studio PARADIGM-HF, sacubritil/valsartan risulta superiore a enalapril nel ridurre i rischi di morte e di ospedalizzazione per HF nei pazienti con HFrEF[6]
Anni ’80
Anni ’90
Anni 2000
Anni 2010

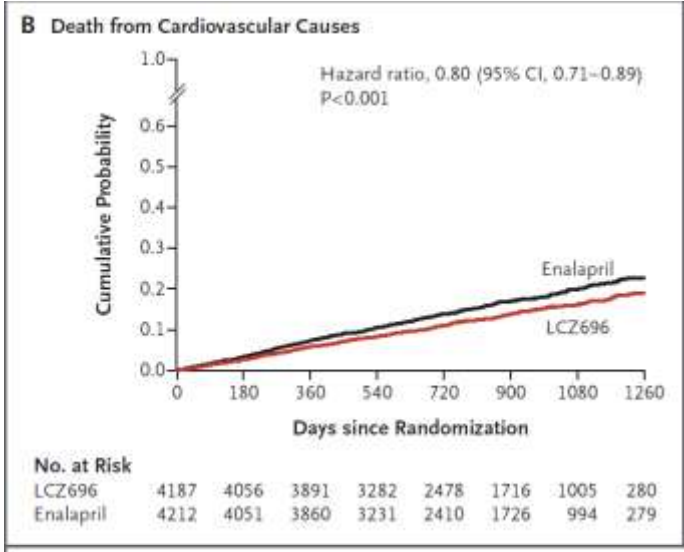
The NEW ENGLAND JOURNAL of MEDICINE

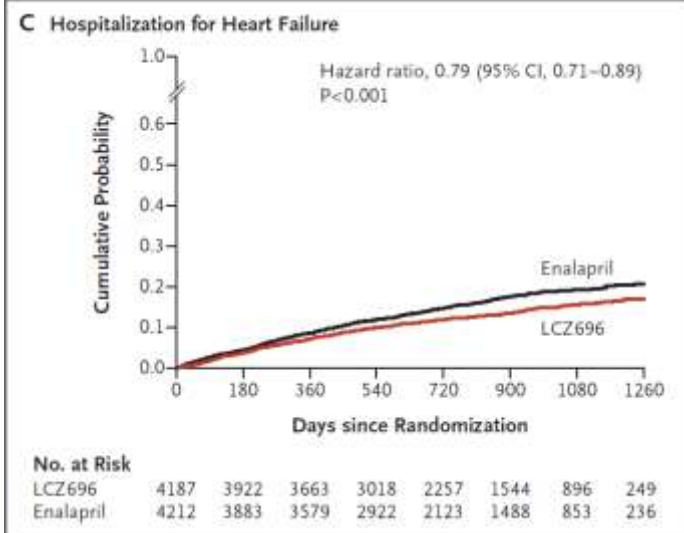
ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

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*

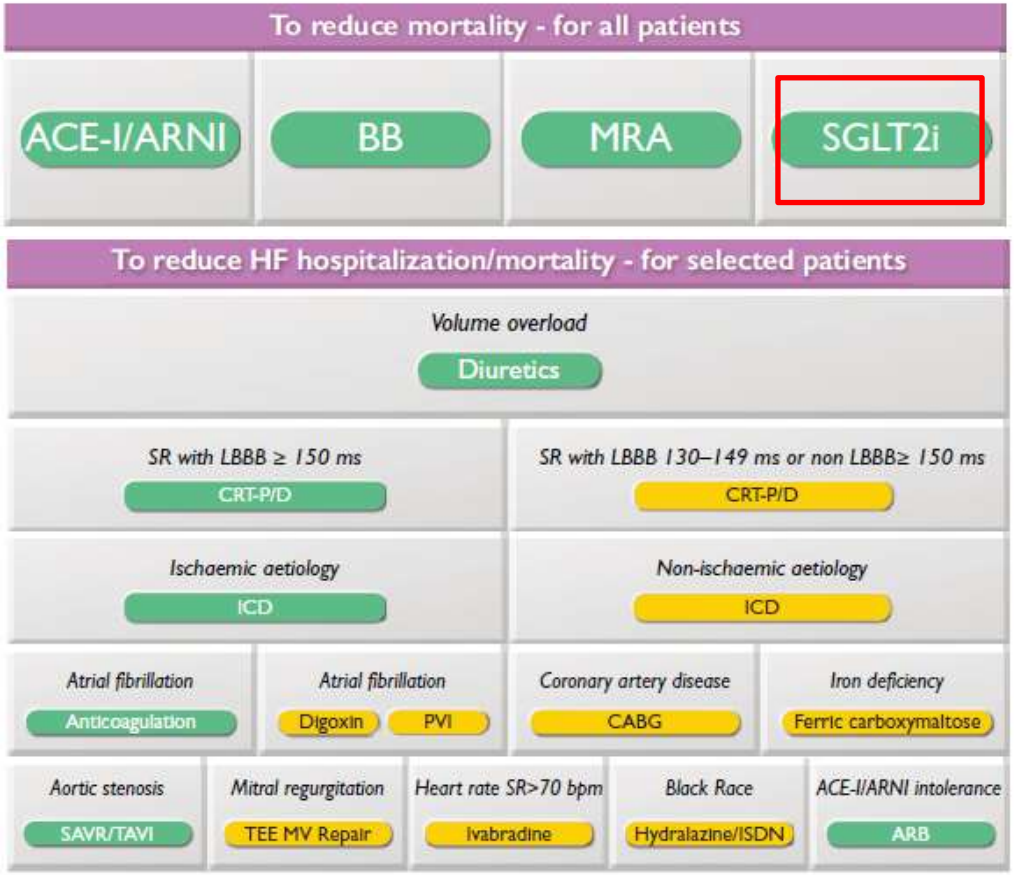




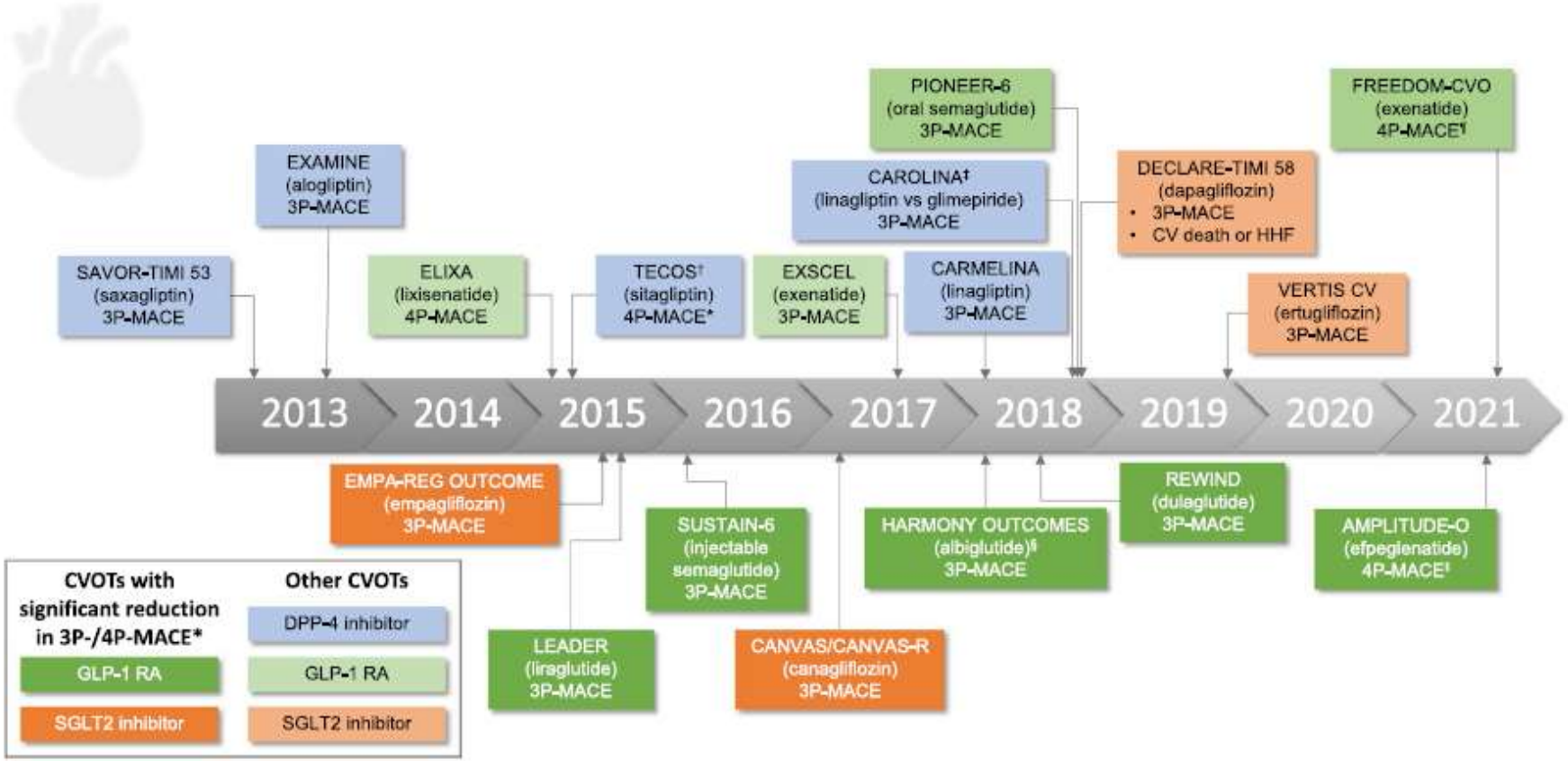


2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Management of HFrEF



Cardiovascular Outcome Trials



Davies *et al. Cardiovascular Diabetology* (2022) 21:144


EMPA-REG OUTCOME
CANVAS/ CANVAS-R (canagliflozin)
DECLARE-TIMI 58 (dapagliflozin)
VERTIS CV (ertugliflozin)
SGLT2i
Patients with T2D and established CVD
Patients with T2D and CVD or CV risk
Patients with T2D and CKD
Patients with HFrEF +/- T2D
Empagliflozin
EMPA-REG OUTCOME
Canagliflozin
CANVAS Program
CREDENCE
Dapagliflozin
DECLARE-TIMI 58
DAPA-HF
Ertugliflozin
VERTIS-CV
Key
benefit observed for...
3P-MACE
CV death
HHF
Renal outcomes
All death
progression 38%†
progression 42%†
progression 16%†
progression 31%†
progression not reported
progression 21%*

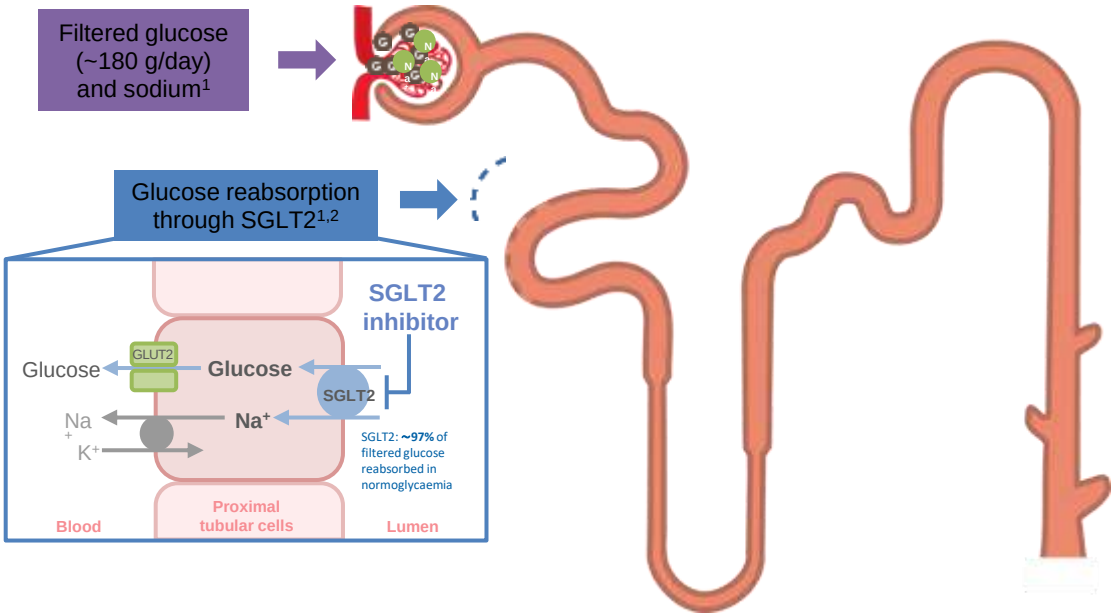
Insulin-independent glucose excretion mode of action: SGLT2 inhibitors facilitate the renal excretion of excess glucose

↓ Insulin
↑ Glucagon

↓HbA1c 0,7%

Filtered glucose (~180 g/day) and sodium[1]

Glucose reabsorption through SGLT2[1,2]



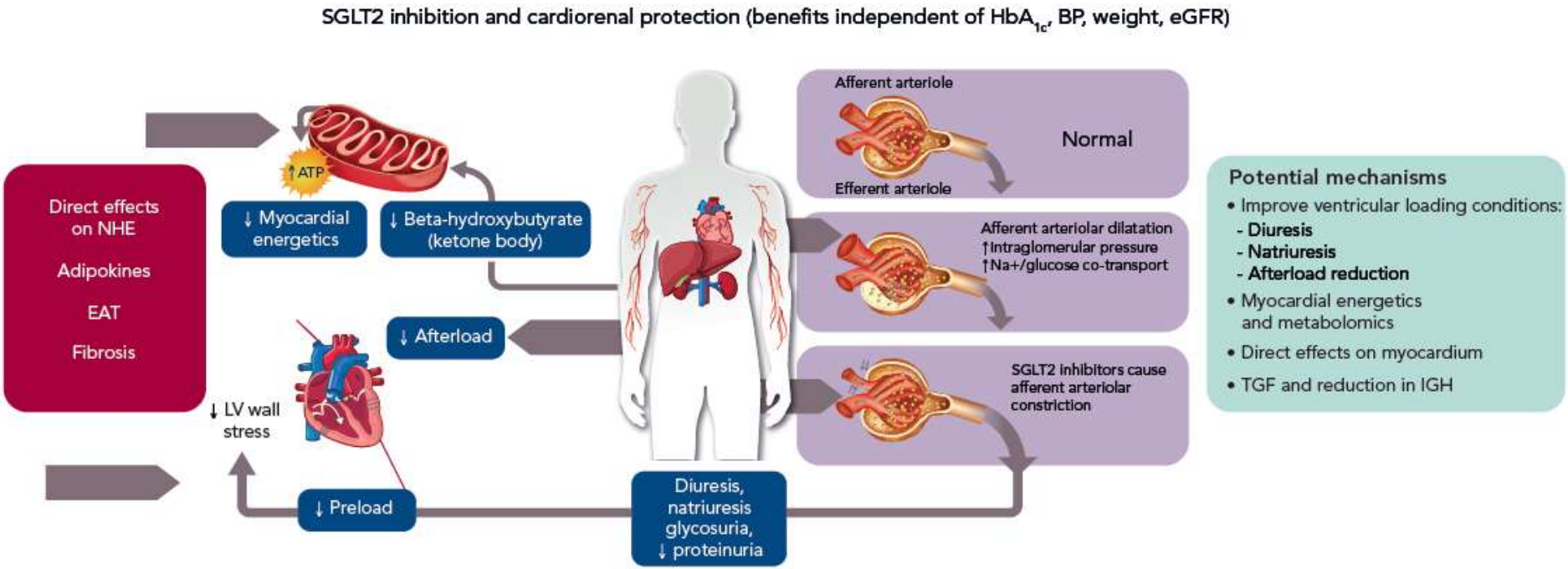
SGLT2 inhibitors **reduce glucose and sodium reabsorption** in the proximal tubule[3] leading to:

- **Diuresis[3]**
- **Glucose excretion[2,3]**
- **Natriuresis[3]**

Urinary glucose excretion:
78 g/day[4]

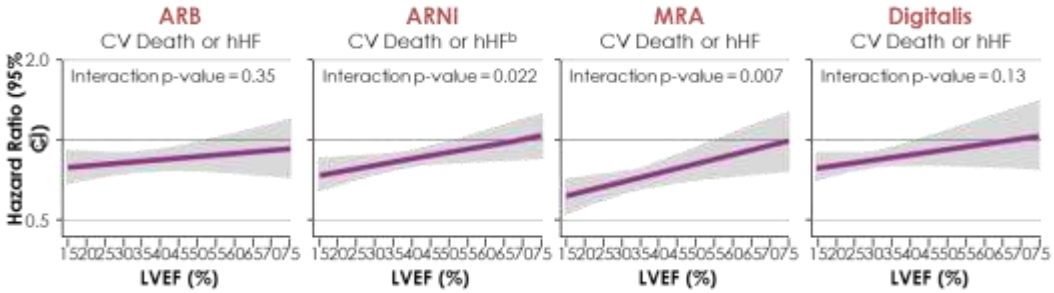
1. Bakris GL *et al. Kidney Int* 2009;75:1272; 2. Vallon V & Thomson SC. *Diabetologia* 2017;60:215; 3. Heise T *et al. Clin Ther* 2016;38:2265;
4. Boehringer Ingelheim Pharmaceuticals, Inc. Jardiance® (empagliflozin) summary of product characteristics. Jan 2020

Figure 3: Proposed Mechanism of Cardiovascular Benefits of SGLT2 Inhibitors



ATP = adenosine triphosphate; BP = blood pressure; EAT = epicardial adipose tissue; eGFR = estimated glomerular filtration rate; IGH = intraglomerular hypertension; LV = left ventricular; NHE = sodium-hydrogen exchanger; SGLT2 = sodium–glucose co-transporter 2; TGF = tubuloglomerular feedback. Source: Verma et al. 2017.[37] Adapted with permission from the American Medical Association.

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± signs[a]	Symptoms ± signs[a]	Symptoms ± signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]



Kondo T et al. Eur Heart J. 2022;43(5):427-429

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

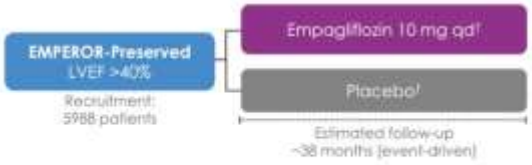
Recommendations	Class[a]	Level[b]
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.[137]	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[11]	IIb	C
An ARB may be considered for patients 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

EMPEROR-Preserved

Phase III randomised double-blind placebo-controlled event driven trial

Key Inclusion Criteria: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II-IV) with LVEF >40%, elevated NT-proBNP concentrations and structural heart changes or documented HHF within 12 months.

Key Exclusion Criteria: Symptomatic hypotension and eGFR <20 mL/min/1.73m2.



COMPOSITE PRIMARY ENDPOINT
Time to first event of adjudicated CV death or adjudicated HHF

CONFIRMATORY KEY SECONDARY ENDPOINTS
- First and recurrent adjudicated HHF events
- Slope of change in eGFR (CKD-EPI) from baseline

†Guideline-directed medical therapy

CV Death or HF Hospitalisation (Primary endpoint)	**21%** Relative Risk-reduction **3.3%** Absolute Risk Reduction NNT of **31 over 26-months**	**HR 0.79** (95% CI 0.69, 0.90) ***p*<0.001**
First and Recurrent HF Hospitalisations (Key secondary endpoint)	**27%** Relative Risk-reduction	**HR 0.73** (95% CI 0.61, 0.88) ***p*<0.001**
eGFR slope (Key secondary endpoint)	Stabilization of decline in eGFR, improved kidney outcomes	Slope difference per year **1.36** ml/min/1.73 m² ***p*<0.001**

DELIVER: The largest and broadest trial to date in patients with LVEF >40%[1]

Primary endpoint[2]

Composite of CV death or worsening HF (hHF or an urgent HF visit):
- Full patient population
- Patients with LVEF <60%

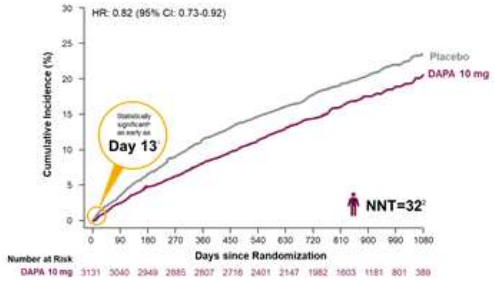
Secondary endpoints[2]
- Total number of hHF (first and recurrent) and CV death
- Change in KCCQ-TSS from baseline to 32 weeks
- CV death
- All-cause mortality

Baseline characteristics[1,2]

72 years Mean Age	75% NYHA class II
1011 pg/mL Median NT-proBNP	54% Average LVEF
55% Without T2D	50% With an eGFR <60 mL/min/1.73 m²
16% Hospitalized or discharged <90 days	~18% With prior LVEF ≤40%

1. Solomon SD et al. *JACC Heart Fail*. 2022;10(3):184-197; 2. Solomon SD et al. *N Engl J Med*. 2022.

Dapagliflozin significantly reduced the risk of CV death and worsening HF[a] in patients with HFmrEF and HFpEF[1]



CV Death or Worsening HF[a]
18% RRR
3.1% ARR
p=0.0008

CV death
12% RRR
1% ARR
0.88 (0.74, 1.05)

Worsening HF[a]
21% RRR
3.7% ARR
0.79 (0.69, 0.91)

Consistent benefit in the primary endpoint across key subgroups

All-cause mortality was also reduced in the dapagliflozin group

All-cause mortality 6% RRR
~1% ARR
0.94 (0.83, 1.07)

Quality of life
2.4 Points TSS-KCCQ
P<0.001

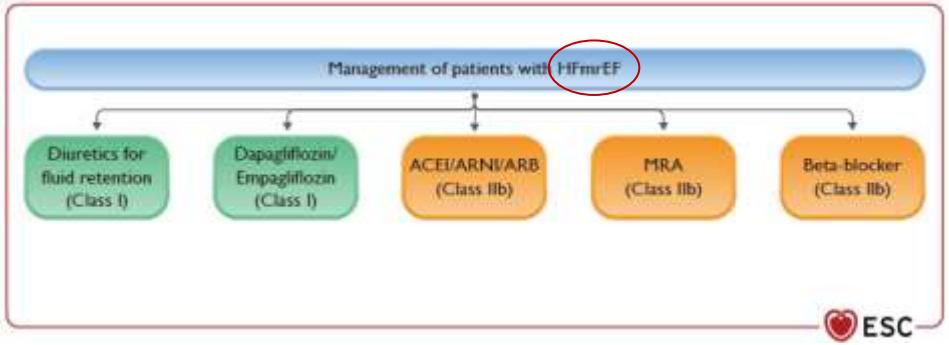
[a]Nominal significance at Day 13 (HR, 0.46; 95% CI, 0.20-0.99; p=0.046), with sustained statistical significance starting at Day 15.
1. Solomon SD et al. *N Engl J Med*. 2022;387(12):1089-1098.

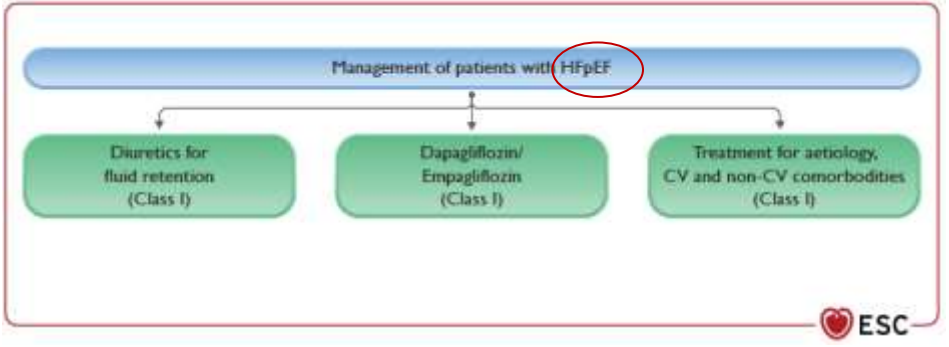
Recommendation Table 1 — Recommendation for the treatment of patients with symptomatic heart failure with mildly reduced ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

Recommendation Table 2 — Recommendation for the treatment of patients with symptomatic heart failure with preserved ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

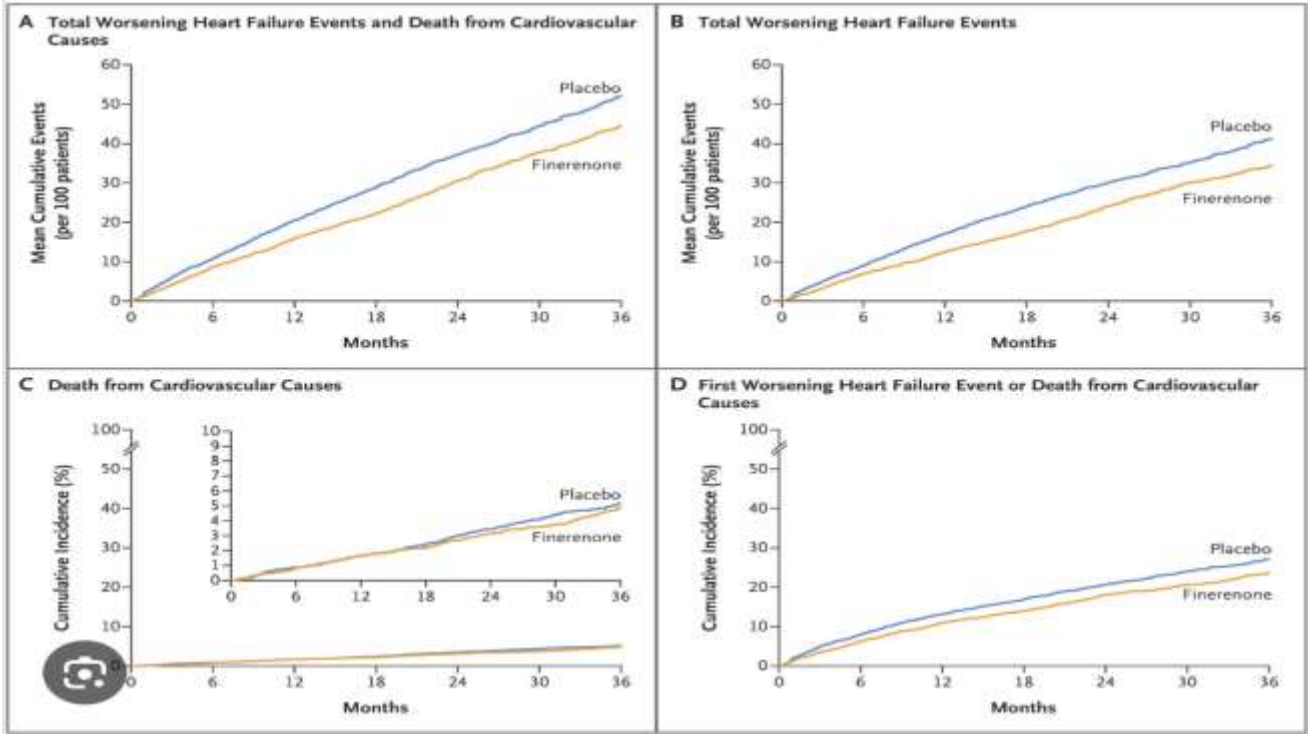
Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Authors: Scott D. Solomon, M.D., John J.V. McMurray, M.D., Muthiah Vaduganathan, M.D., M.P.H., Brian Claggett, Ph.D., Pardeep S. Jhund, M.B., Ch.B., Ph.D., Akshay S. Desai, M.D., M.P.H., Alasdair D. Henderson, Ph.D., et al., for the FINEARTS-HF Committees and Investigators* Author Info & Affiliations

Published September 1, 2024 | DOI: 10.1056/NEJMoa2407107

- 16%

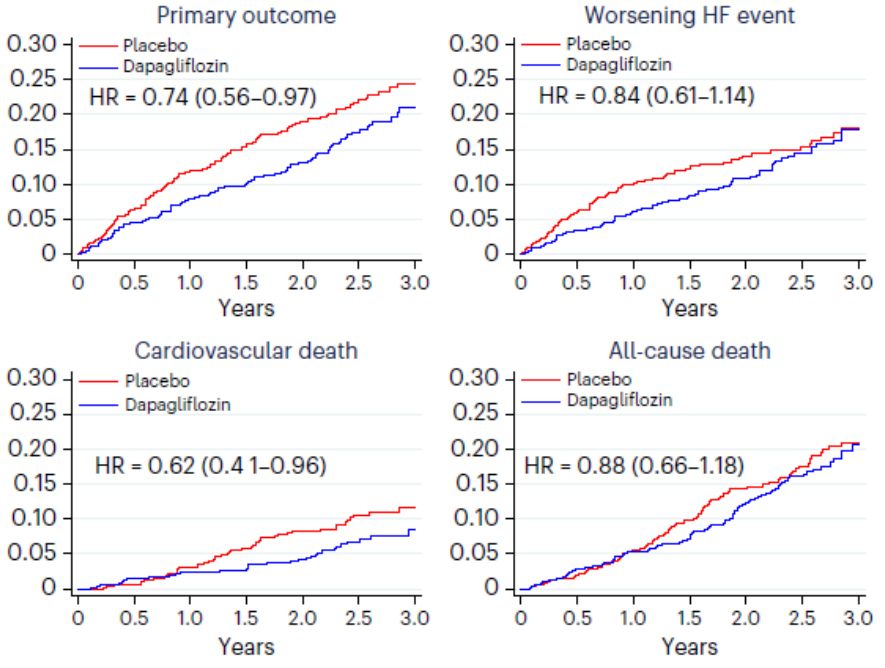
- 18%

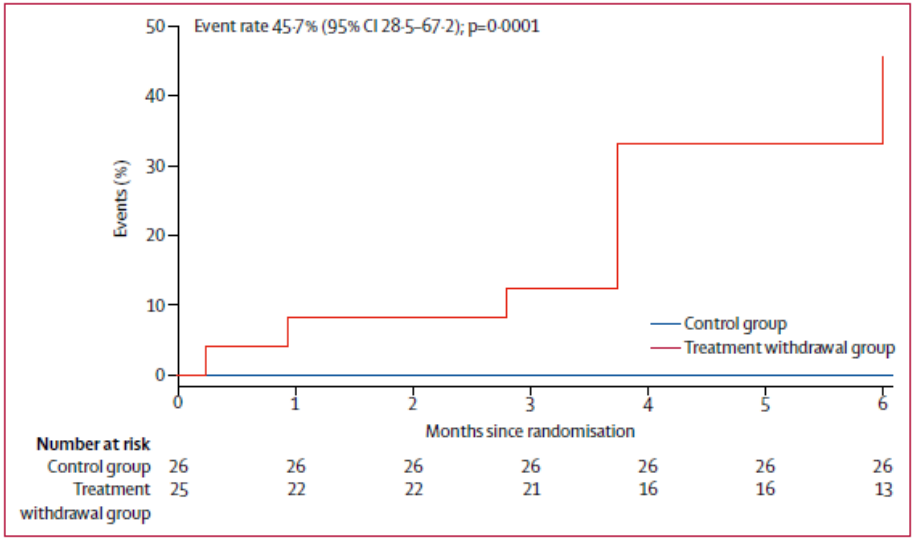


Nature Medicine | Volume 28 | December 2022 | 2504–2511

Lancet 2019; 393: 61–73

a





• CV death

55% Without T2D

50% With an eGFR <60 mL/min/1.73 m²

~18% With prior LVEF ≤40%

Median follow-

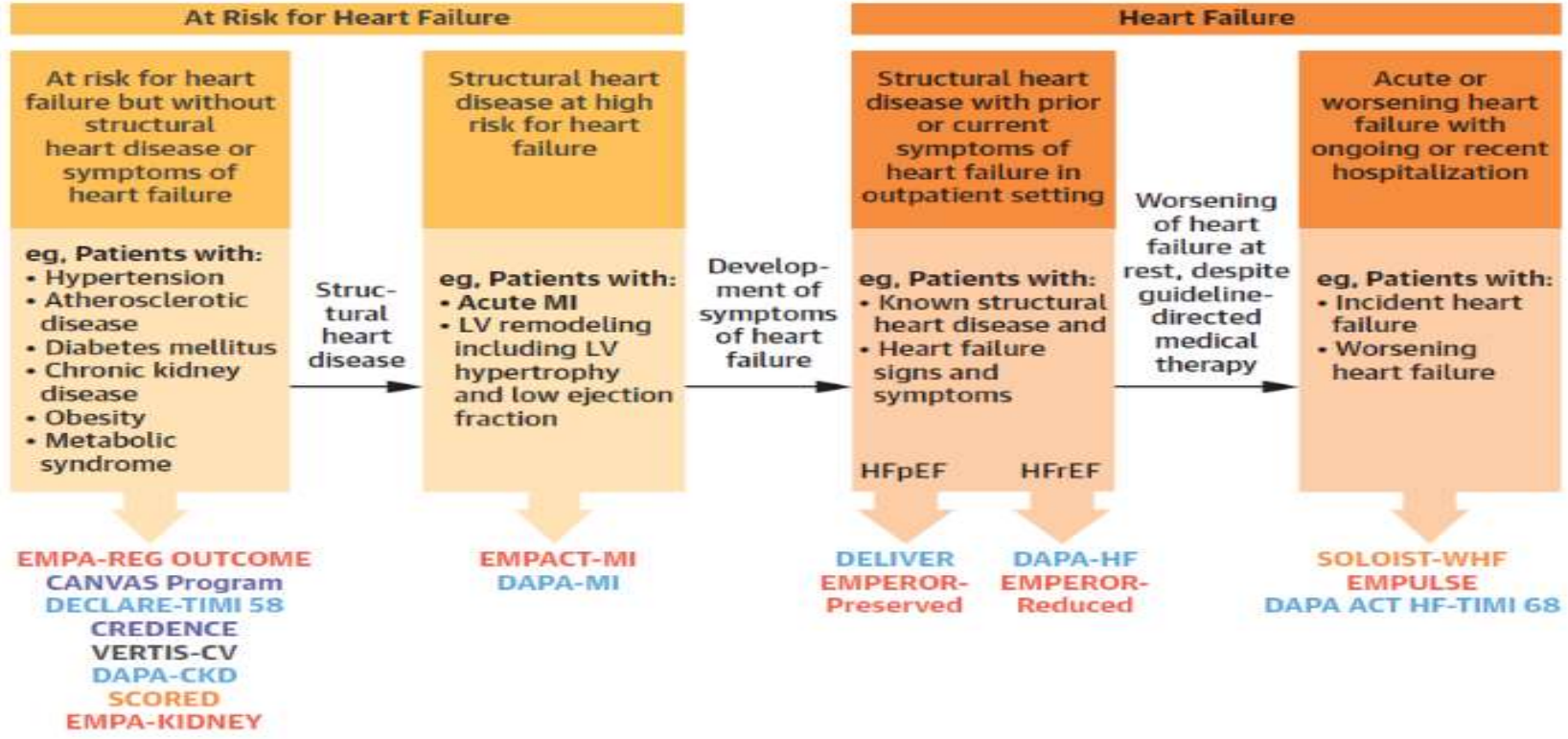
1. Solomon SD et al. *JACC Hf*

Recommendation for HF With Improved EF (HFimpEF)
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

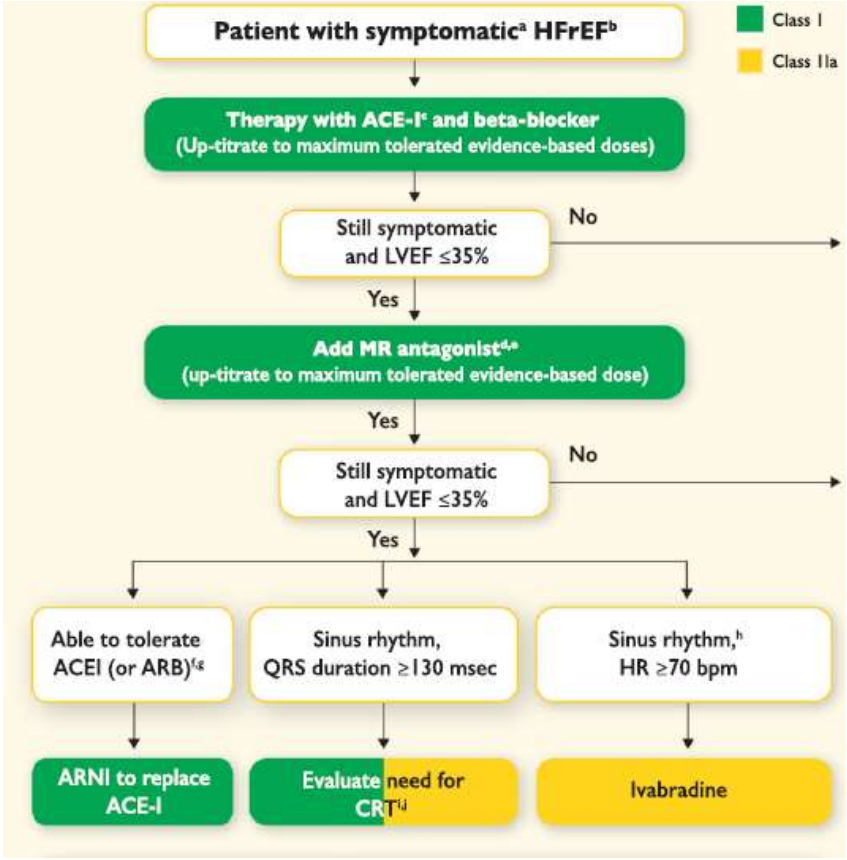
COR	LOE	Recommendation
1	B-R	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and left ventricular dysfunction, even in patients who may become asymptomatic.[38]

Circulation. 2022;145:e876–e894.

CENTRAL ILLUSTRATION Sodium Glucose Cotransporter-2 Inhibition Across the Spectrum of Cardiovascular Risk



Udell JA, et al. J Am Coll Cardiol. 2022;79(20):2058–2068.



European Heart Journal (2016) **37**, 2129–2200

Management of HFrEF

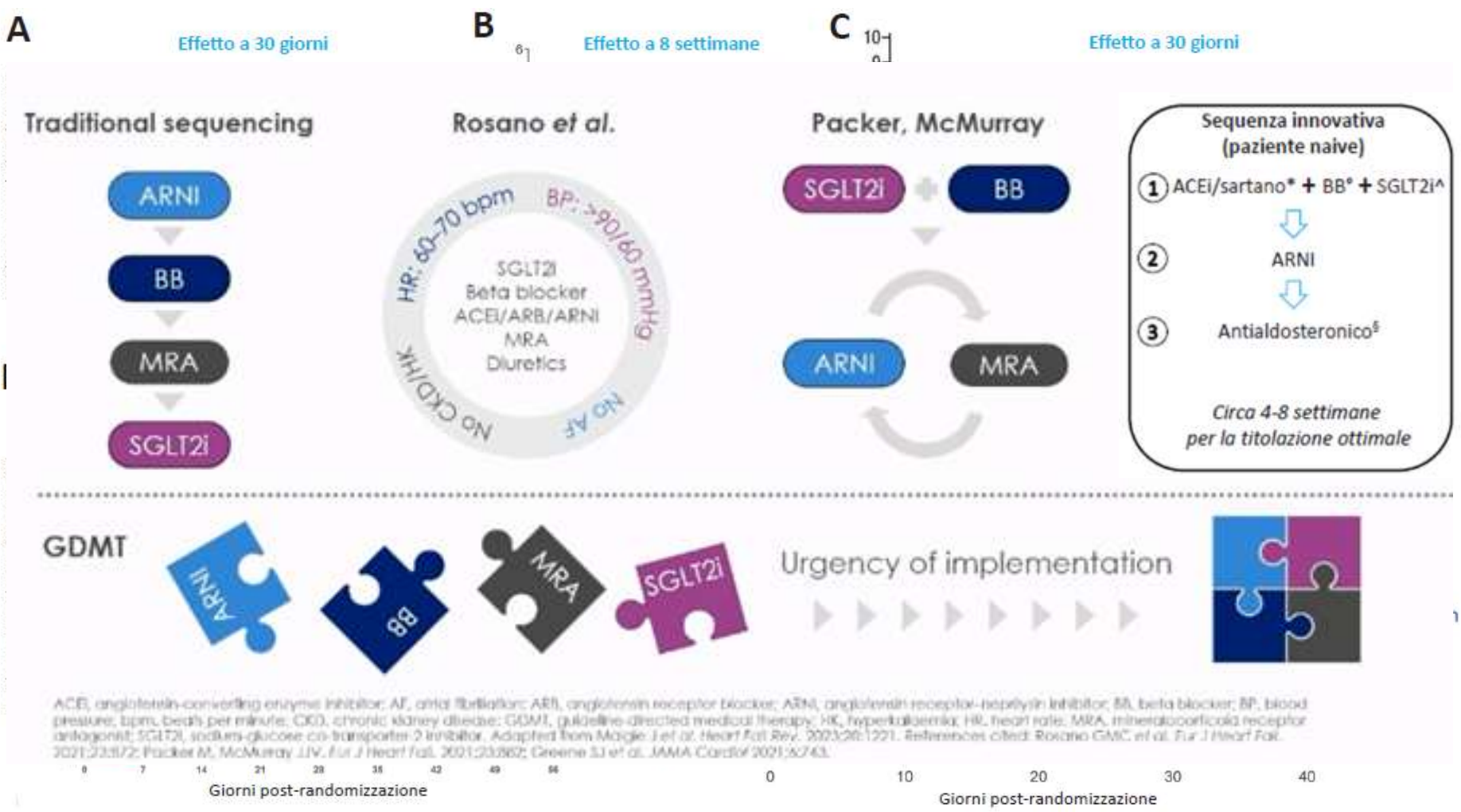
European Heart Journal (2021) **42**, 3599–3726

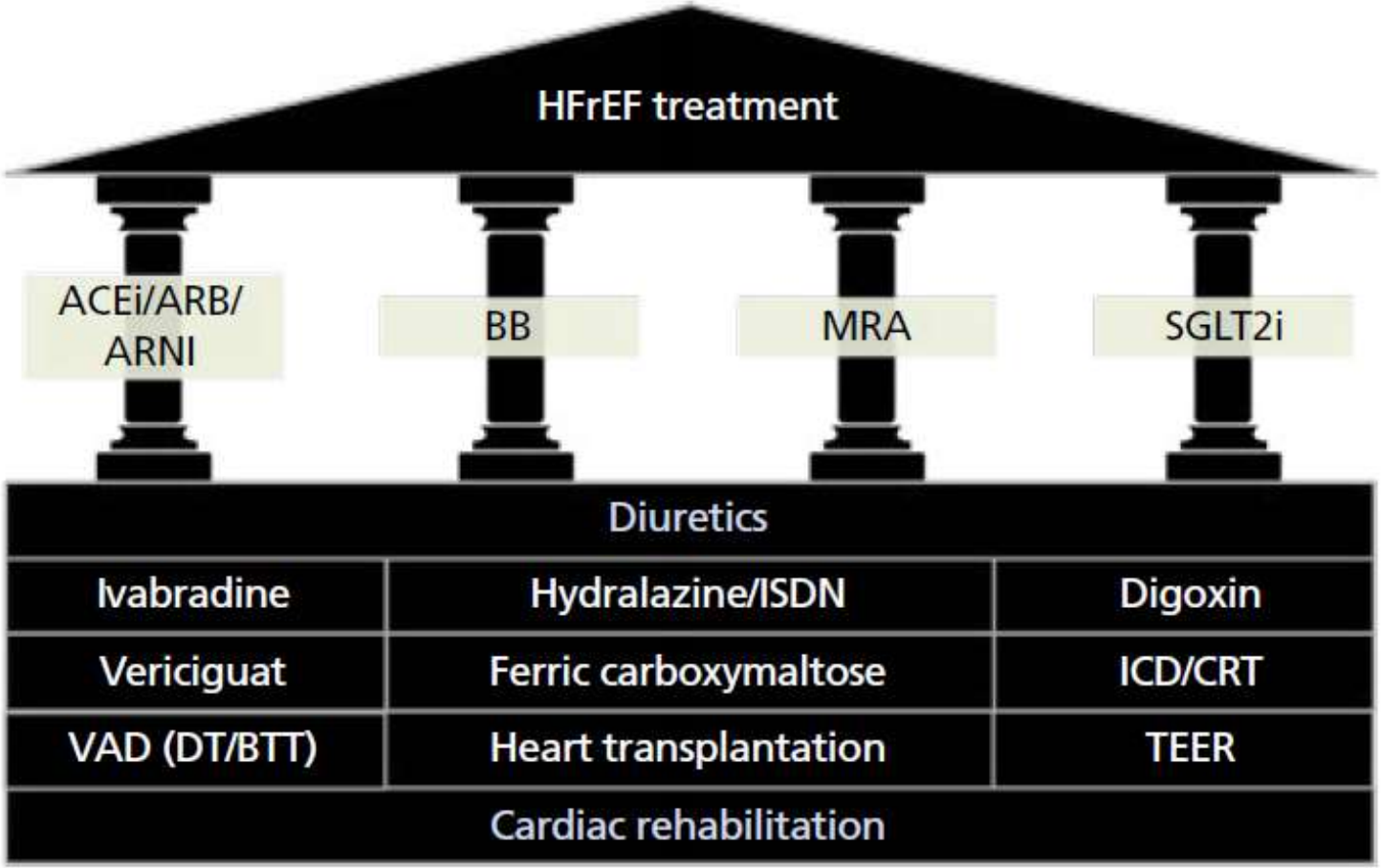
Sequenza convenzionale

1. ACEi/sartano
2. BB
3. Antialdosteronico
4. ARNI
5. SGLT2i

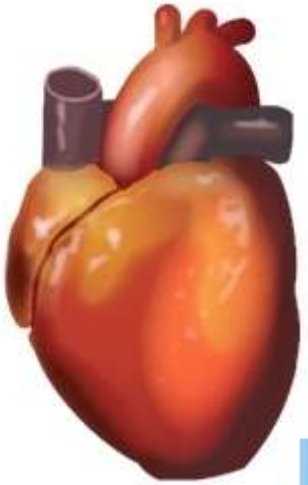
Circa 6 mesi per la titolazione ottimale

G Ital Cardiol 2021;22(10):861-868


A
Effetto a 30 giorni
B
Effetto a 8 settimane
C
Effetto a 30 giorni
Traditional sequencing
ARNI
BB
MRA
SGLT2i
Rosano et al.
HR: 60–70 bpm
BP: >90/60 mmHg
No CKD/HK
No AF
SGLT2i
Beta blocker
ACEI/ARB/ARNI
MRA
Diuretics
Packer, McMurray
SGLT2i
BB
ARNI
MRA
Sequenza innovativa
(paziente naive)
1 ACEi/sartano* + BB° + SGLT2i^
2 ARNI
3 Antialdosteronico§
Circa 4-8 settimane
per la titolazione ottimale
GDMT
ARNI
BB
MRA
SGLT2i
Urgency of implementation
ACE, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta blocker; BP, blood pressure; bpm, beats per minute; CKD, chronic kidney disease; GDMT, guideline-directed medical therapy; HK, hyperkalaemia; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose co-transporter 2 inhibitor. Adapted from Maggioni et al. Heart Fail Rev. 2023;28:1221. References cited: Rosano GMC et al. Eur J Heart Fail. 2021;23:872; Packer M, McMurray JJV. Eur J Heart Fail. 2021;23:882; Greene SJ et al. JAMA Cardiol 2021;6:743.
0 7 14 21 28 35 42 49 56
Giorni post-randomizzazione
0 10 20 30 40
Giorni post-randomizzazione


HFrEF treatment
ACEi/ARB/
ARNI
BB
MRA
SGLT2i
Diuretics
Ivabradine
Hydralazine/ISDN
Digoxin
Vericiguat
Ferric carboxymaltose
ICD/CRT
VAD (DT/BTT)
Heart transplantation
TEER
Cardiac rehabilitation

Low NO bioavailability may lead to insufficient sGC activity and reduced cGMP production

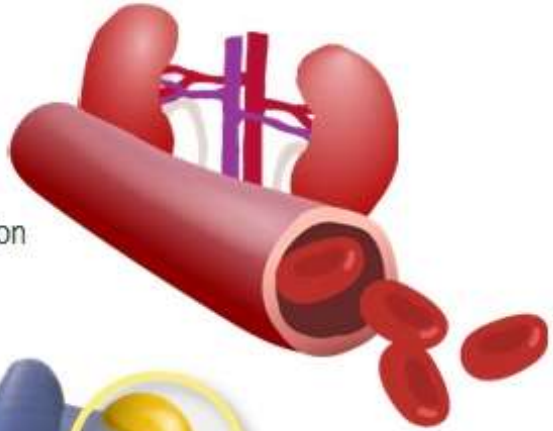


Ventricular Dysfunction

- Hypertrophy
- Fibrosis

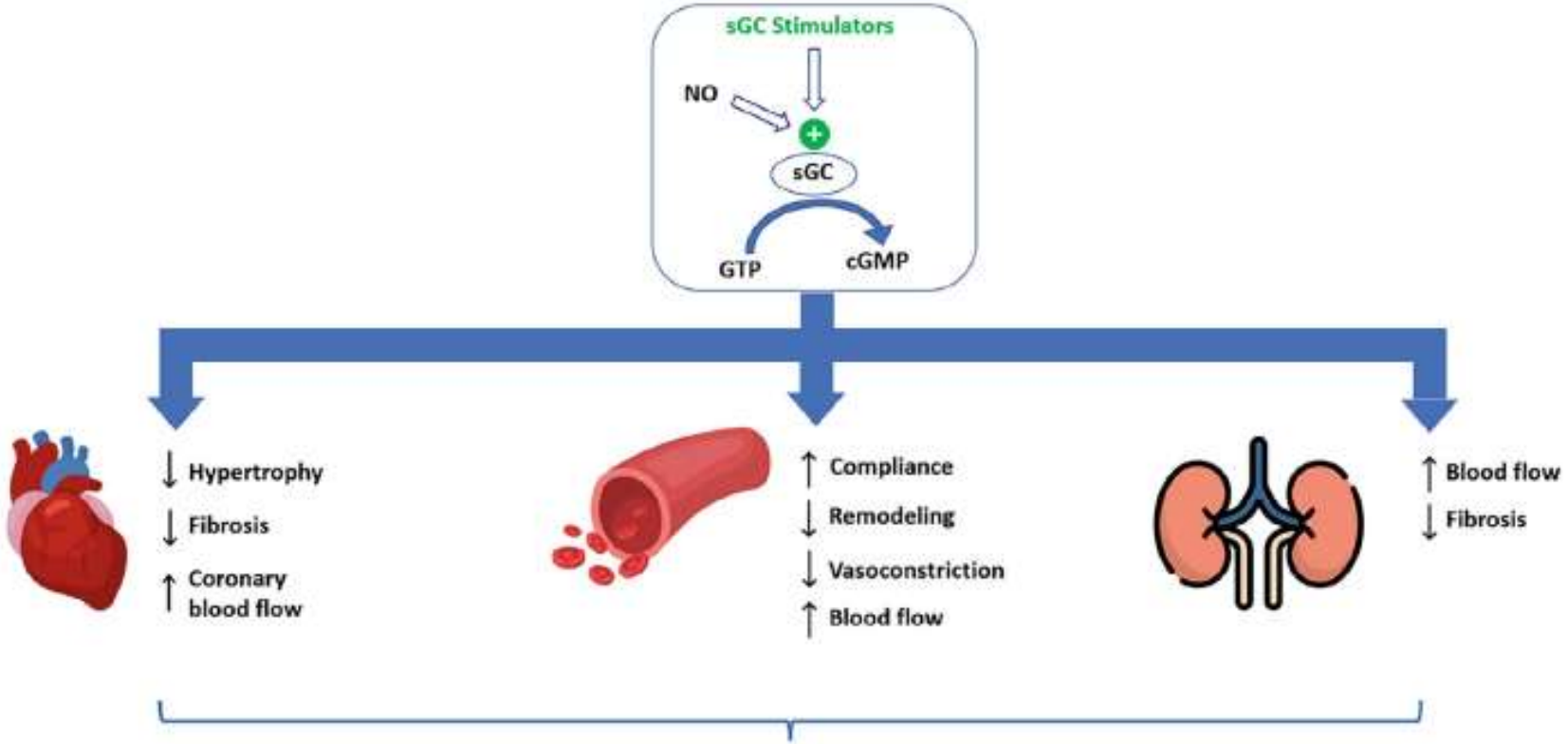
Vascular Dysfunction

- Endothelial dysfunction
- Vascular stiffness



Direct sGC stimulation could restore impaired NO–sGC–cGMP signaling in HF

Gheorghiade M et al. *Heart Fail Rev*. 2013;18:123; Breitenstein S et al. *Handb Exp Pharmacol*. 2017;243:225.



European Journal of Heart Failure (2022) 24, 2029–2036

HFrEF
(FE < 40%)

+

Terapia ottimizzata

(ACEi/sartano/sacubitril+valsartan, beta-bloccante, MRA al dosaggio raccomandato o massimo tollerato, SGLT2-inibitore)

+

Rischio di riospedalizzazione persistentemente elevato

(BNP ≥300 ng/L o NT-proBNP ≥1000 ng/L in RS, BNP ≥500 ng/L o NT-proBNP ≥1600 ng/L in FA)

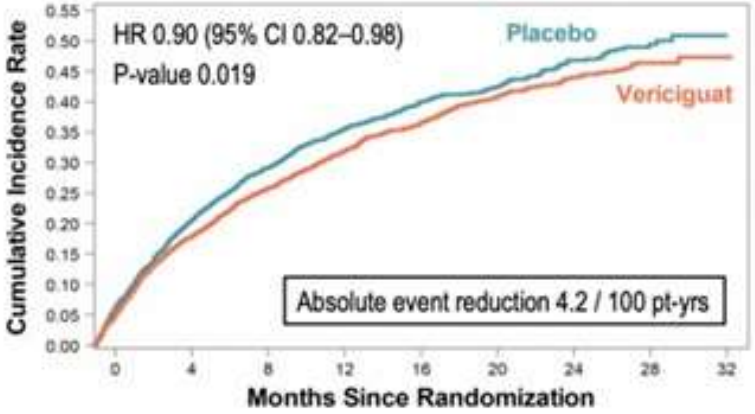
+

Ospedalizzazione nei 6 mesi precedenti

o

Necessità di diuretici ev nei 3 mesi precedenti

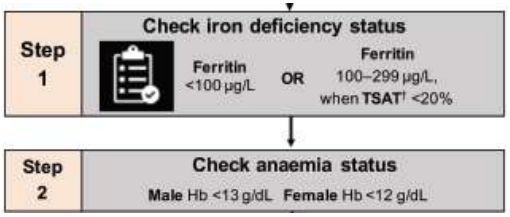
G Ital Cardiol 2023;24(4):323-331



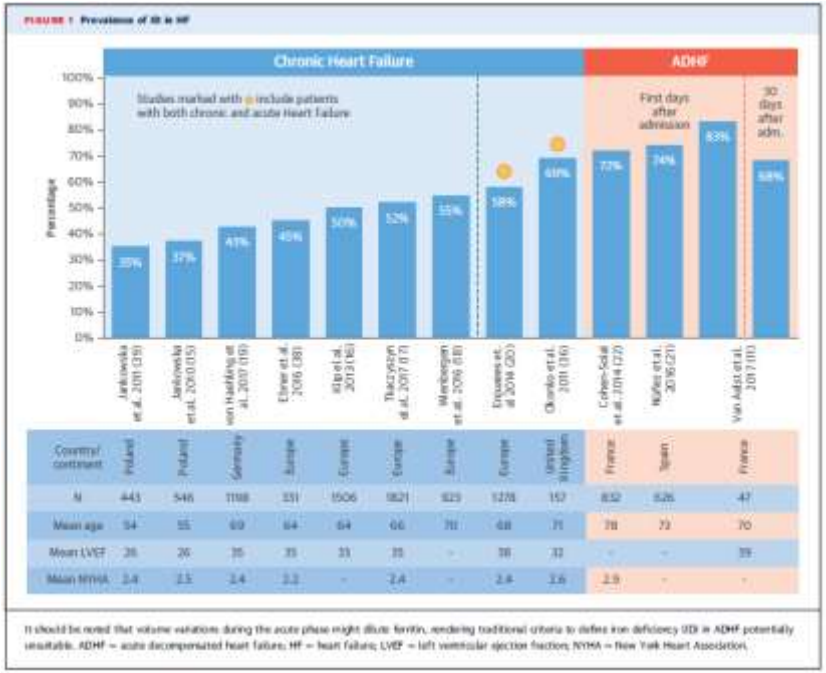
Soluble guanylate cyclase stimulator

Vericiguat may be considered in patients in NYHA class II – IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.[141]	IIb	B

European Heart Journal (2021) **42**, 3599 – 3726

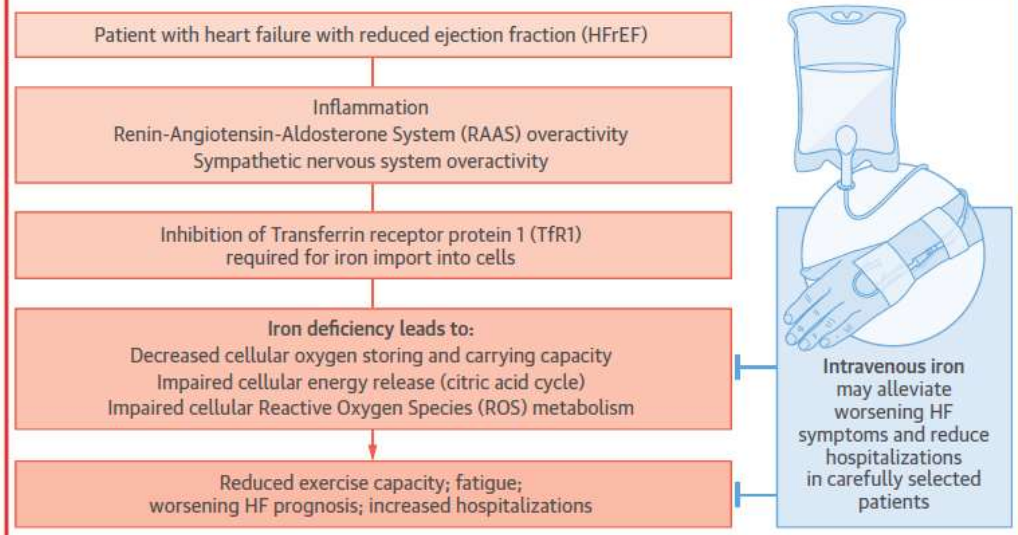


European Journal of Heart Failure (2018) 20, 1661–1672



It should be noted that volume variations during the acute phase might dilute ferritin, rendering traditional criteria to define iron deficiency (ID) in ADHF potentially unsuitable. ADHF = acute decompensated heart failure; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

CENTRAL ILLUSTRATION Pathophysiology of ID in HF



Rocha, B.M.L. et al. J Am Coll Cardiol. 2018;71(7):782–93.

Contrary to oral formulations, intravenous iron bypasses intestinal absorption. The pathophysiology of heart failure (HF) intertwines with that of iron deficiency (ID), as inflammation and overactivity of both the RAAS and sympathetic nervous system may inhibit iron cellular uptake by blocking transferrin receptor. Iron scarcity in both myocyte and erythroid cells lead to symptoms similar to those of HF. RAAS = renin-angiotensin-aldosterone system; ROS = reactive-oxygen species.

Step 3	Iron deficiency treatment Note: if Hb >15 g/dL do not administer IV iron

Consider single doses of ferric carboxymaltose **(500–1000 mg iron)** to correct iron deficiency*

Calculate total iron need using the table:

Haemoglobin		Patient body weight		
g/dL	mmol/L	<35 kg	35 kg to <70 kg	≥70 kg
<10	<6.2	500 mg	1500 mg	2000 mg
10 to <14	6.2 to <8.7	500 mg	1000 mg	1500 mg
≥14 to 15	≥8.7 to 9.3	500 mg	500 mg	500 mg

Table 1 Dilution plan for ferric carboxymaltose for intravenous infusion

Equivalent iron dose to be replaced	Volume of FCM required	Maximum amount of sterile 0.9% m/V sodium chloride solution	Minimum administration time
500 mg	10 mL	100 mL	6 min
1000 mg	20 mL	250 mL	15 min

FCM, ferric carboxymaltose; m/V, mass/volume %.

European Journal of Heart Failure (2018) **20**, 1664–1672

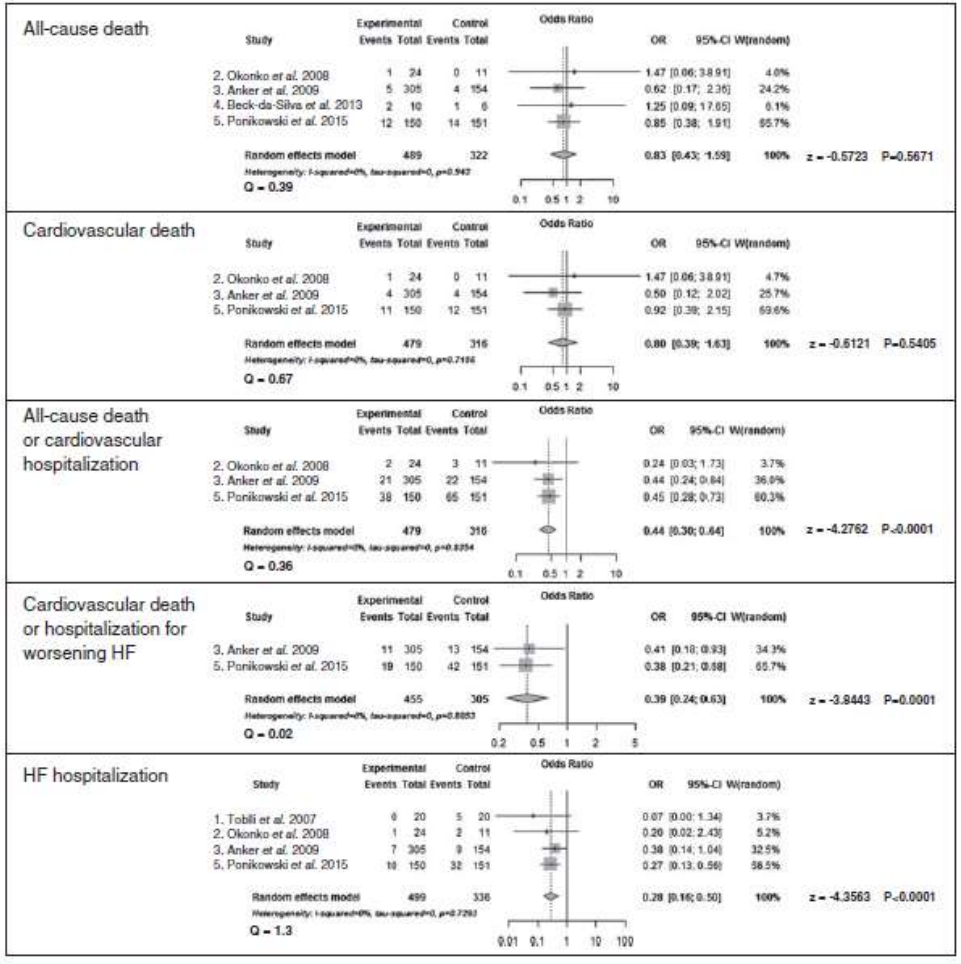
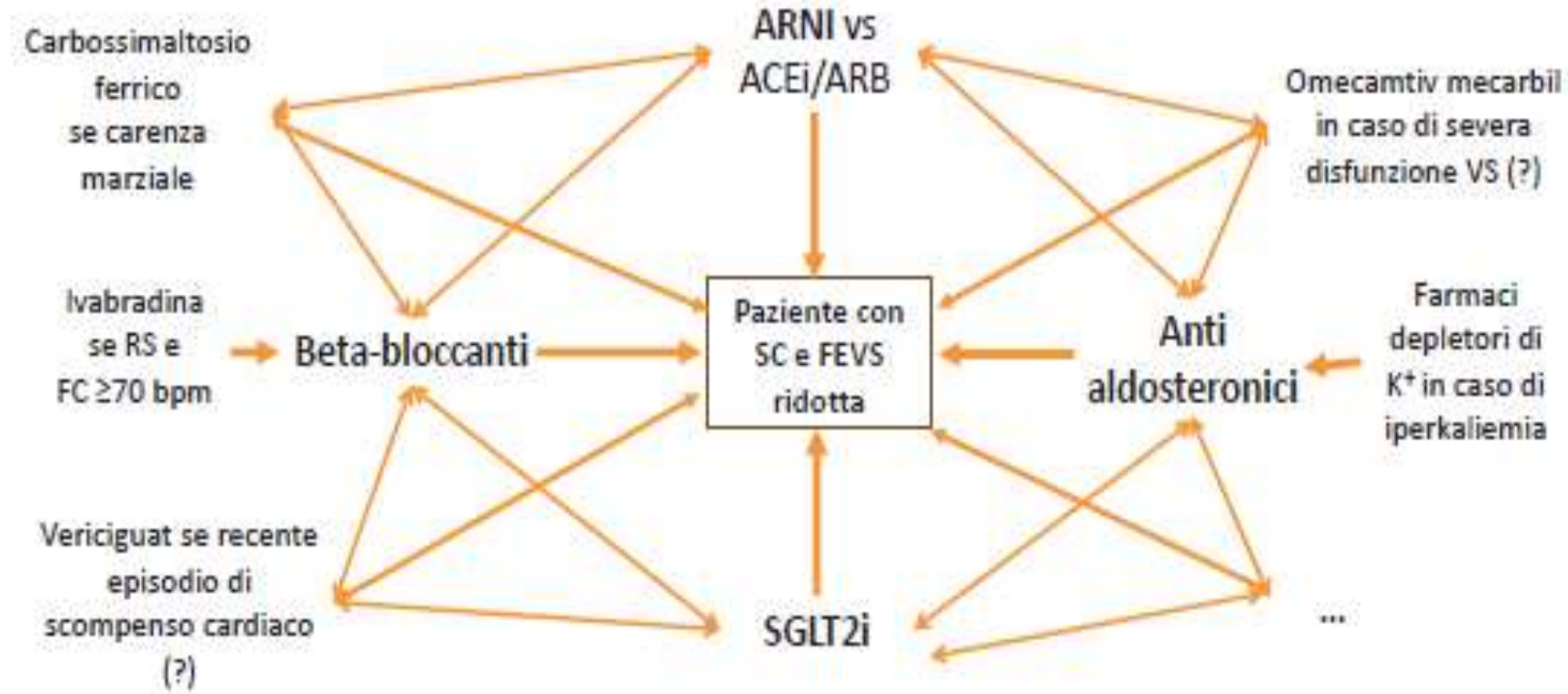


Figure 2 Effects of intravenous iron therapy on outcomes in patients with systolic heart failure (HF) and iron deficiency. CI, confidence interval, HF, heart failure; OR, odds ratio.

European Journal of Heart Failure (2016) **18**, 786–795



G Ital Cardiol 2022;23(8):571-584

Venerdì 25 e Sabato 26 Ottobre 2024

CARDIO PARMA 2024