

Gian Piero Perna

**Come armonizzare le complessità cliniche
con le semplicità farmacologiche nello
scompenso cardiaco cronico**

17° Meeting

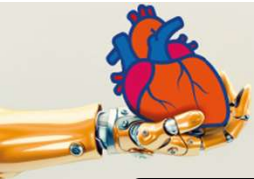


CardioLucca
Heart Brings Heart 2023

Lucca, 22-24 Giugno 2023

Centro Congressi Auditorium San Francesco





17° Meeting
CardioLucca
Heart Brings Heart 2023



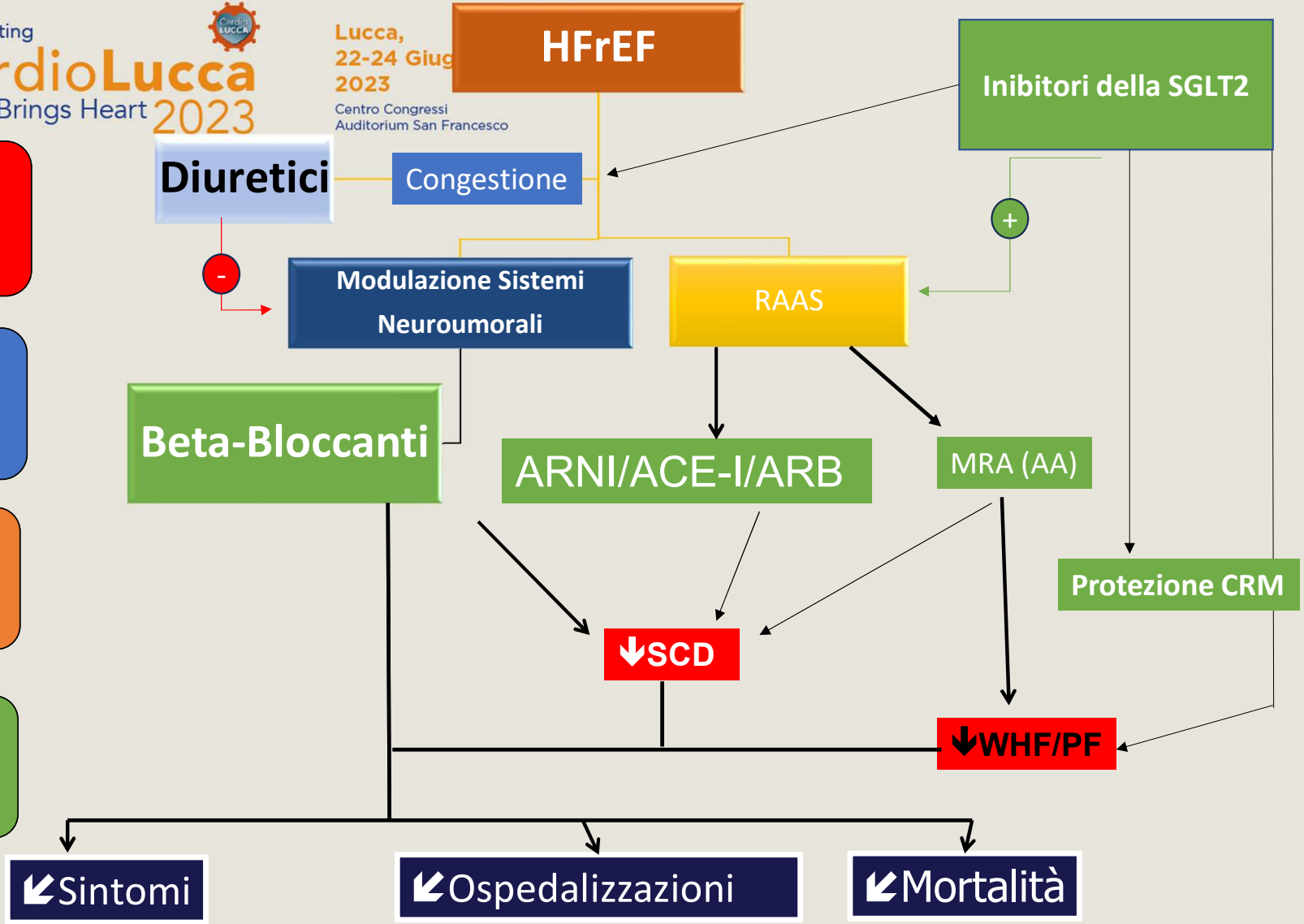
Lucca,
22-24 Giug
2023
Centro Congressi
Auditorium San Francesco

Marker di rischio
↓
Target di terapia

LV-Reverse
Remodeling
↓
MVO₂

Mecc. di Azione ≠
↓
Somma effetti

Nefroprotezione
(↓WRF)



↙ Sintomi

↙ Ospedalizzazioni

↙ Mortalità



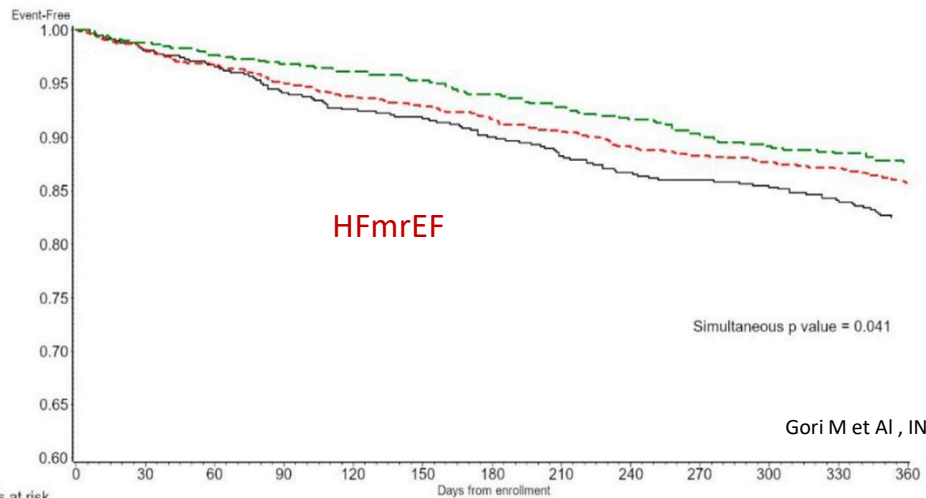
Recommendations	Class ^a	Level ^b
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. ¹³⁷	I	C

137. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002;**82**:149–158.

Mortality : 3trials, 221 pts (OR 0.25) ; WHF : 4 trials, 444pts (OR = 0.32)

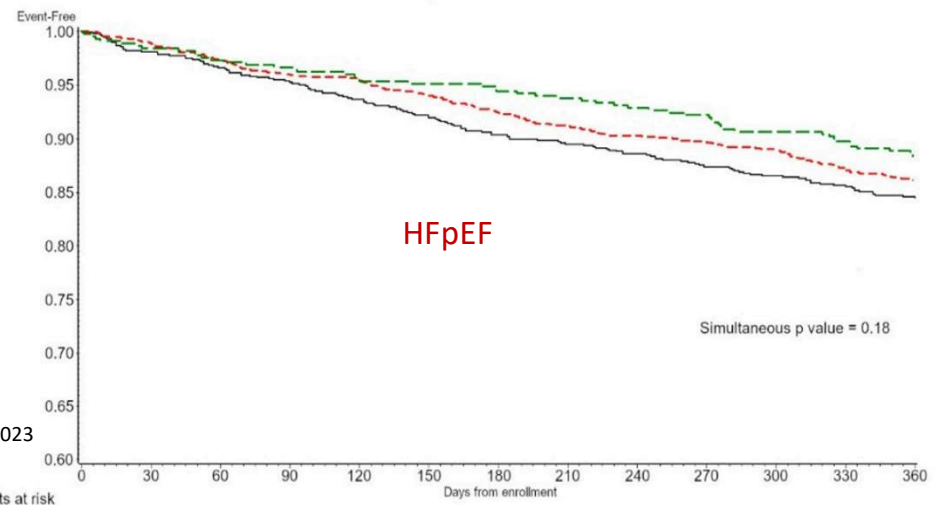
Drug	Guideline	HFrEF (EF ≤ 40%)	HFmrEF (EF 41-49%)	HFpEF (EF ≥ 50%)
ARNI	ESC 2021	I	IIb	
	ACC/AHA/HFSA 2022	I	IIb	IIb**
BB	ESC 2021	I	IIb	
	ACC/AHA/HFSA 2022	I	IIb	
MRA	ESC 2021	I	IIb	
	ACC/AHA/HFSA 2022	I	IIb	IIb*
SGLT2i	ESC 2021	I		
	ACC/AHA/HFSA 2022	I	IIa	

No/Single: None or Single (RASi or BB or MRA) — Double: RASi+BB or RASi+MRA or BB+MRA - - Triple: RASi+BB+MRA - - -



Pts at risk	0	30	60	90	120	150	180	210	240	270	300	330	360
No/Single	578	568	559	544	535	531	520	512	501	497	494	486	459
Double	613	606	599	595	590	585	577	570	564	555	549	328	458
Triple	1107	1088	1073	1053	1039	1030	1016	1004	988	979	972	966	873

No/Single: None or Single (RASi or BB or MRA) — Double: RASi+BB or RASi+MRA or BB+MRA - - Triple: RASi+BB+MRA - - -



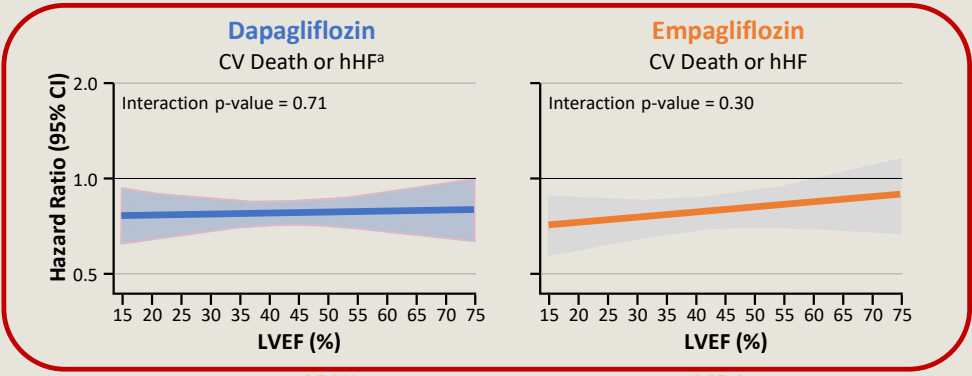
Pts at risk	0	30	60	90	120	150	180	210	240	270	300	330	360
No/Single	880	863	851	839	824	811	797	788	779	770	761	753	682
Double	430	424	418	415	410	409	407	403	399	395	389	384	328
Triple	1099	1087	1069	1054	1049	1032	1014	1000	989	983	974	955	842



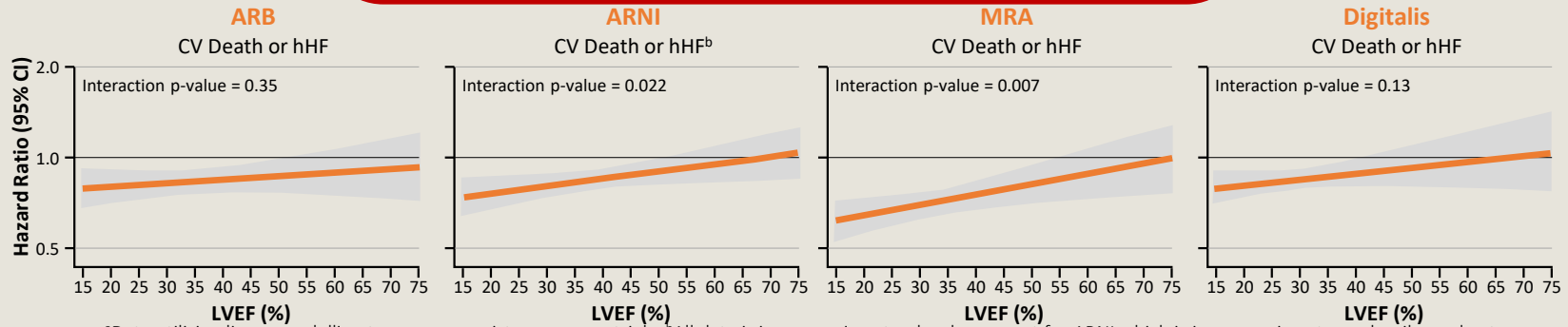


Benefit of SGLT2i is Consistent, With no Attenuation, Across LVEF^{1,2}

**DAPA-HF
 +
 DELIVER**



**EMPEROR REDUCED
 +
 EMPEROR PRESERVED**



^aData utilizing linear modelling to ensure consistency across trials; ^bAll data is in comparison to placebo, except for ARNI which is in comparison to enalapril or valsartan.

1. Kondo T et al. *Eur Heart J.* 2022;43(5):427-429; 2. In House Data, AstraZeneca.

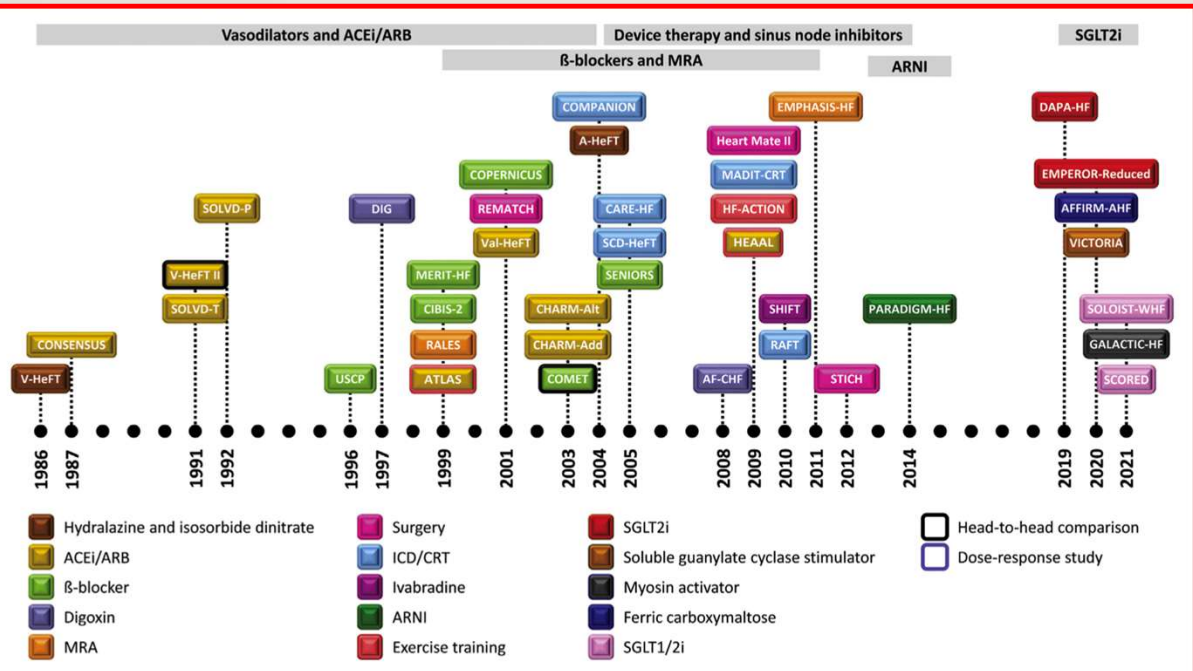
Differences among trial design, patient population, and treatment groups impact ability to directly compare results across different trials.



17th Meeting
CardioLucca
 Heart Brings Heart 2023



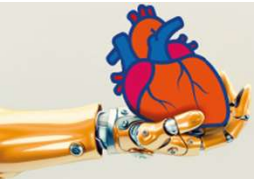
Lucca,
 22-24 Giugno
 2023
 Centro Congressi
 Auditorium San Francesco



Management of HFrEF

To reduce mortality - for all patients			
ACE-I/ARNI	BB	MRA	SGLT2i
To reduce HF hospitalization/mortality - for selected patients			
Volume overload Diuretics			
SR with LBBB ≥ 150 ms CRT-P/D		SR with LBBB 130-149 ms or non LBBB ≥ 150 ms CRT-P/D	
Ischaemic aetiology ICD		Non-ischaemic aetiology ICD	
Atrial fibrillation Anticoagulation	Atrial fibrillation Digoxin	Coronary artery disease CABG	Iron deficiency Ferric carboxymaltose
Aortic stenosis SAVR/TAVI	Mitral regurgitation TEE MV Repair	Heart rate SR>70 bpm Ivabradine	Black Race Hydralazine/ISDN
		ACE-I/ARNI intolerance ARB	
For selected advanced HF patients			
Heart transplantation	MCS as BTT/BTC	Long-term MCS as DT	
To reduce HF hospitalization and improve QOL - for all patients			
Exercise rehabilitation			
Multi-professional disease management			

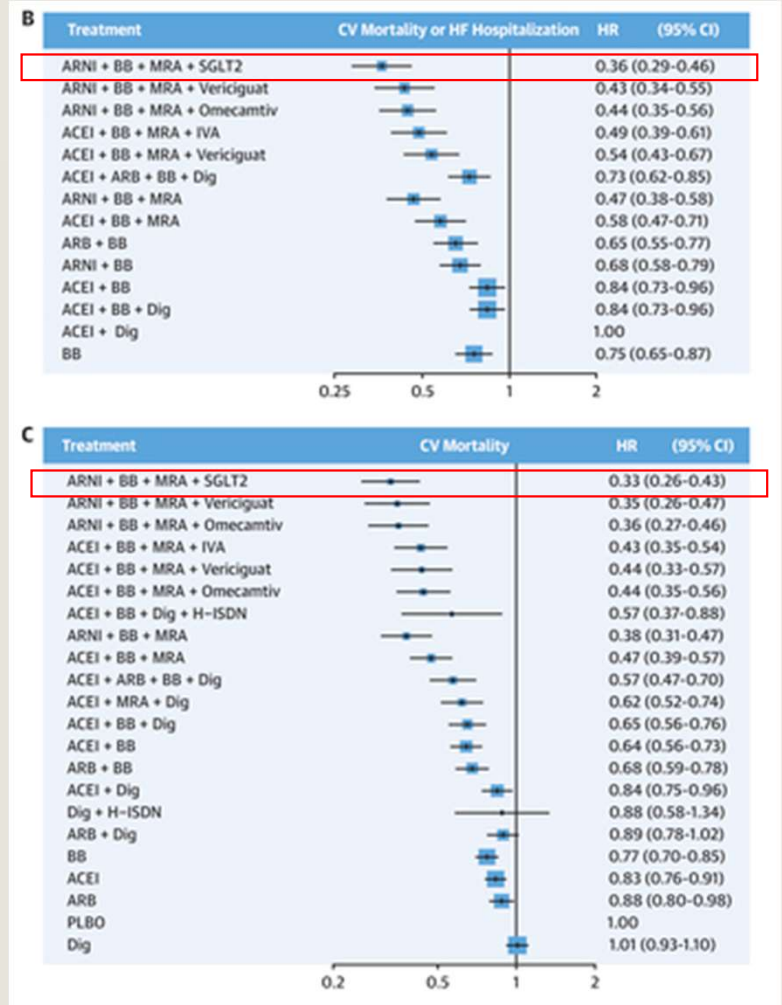
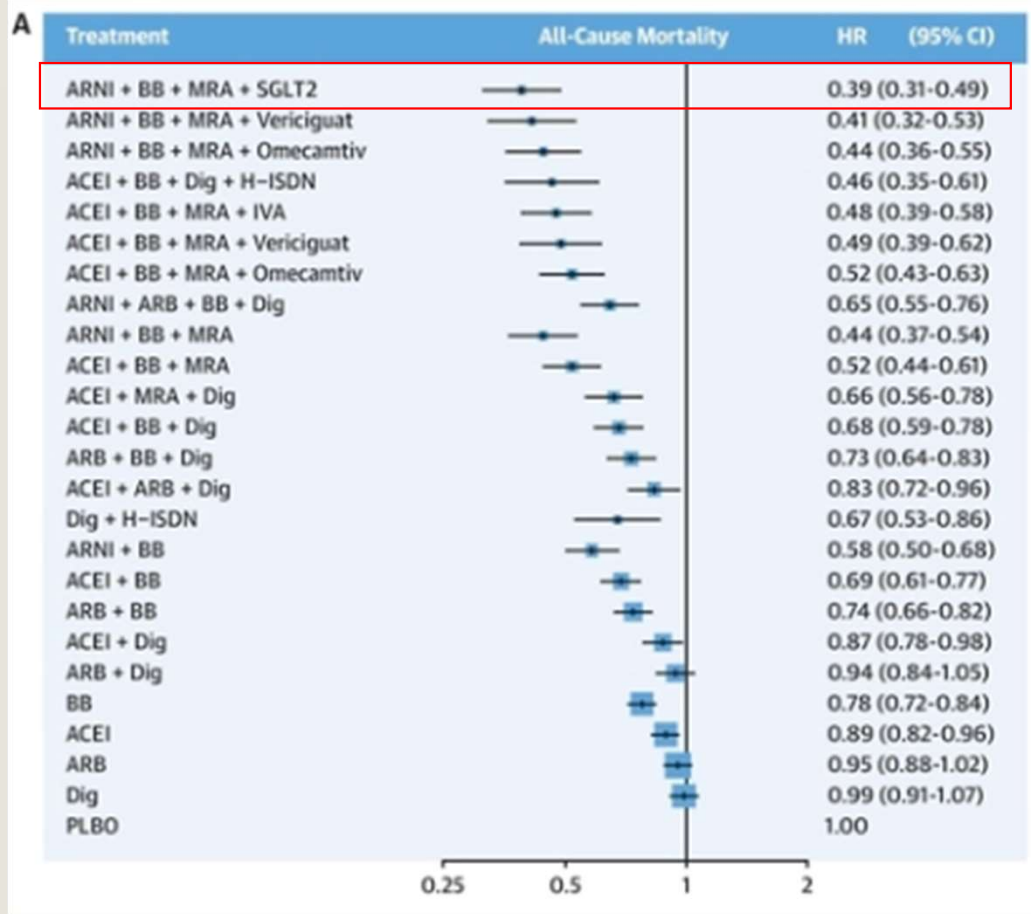
Tutti comunque ?
 In quale sequenza ?
 Quando e dove fare la «titolazione» ?
 Con quali parametri seguire la titolazione ?
 Sempre e comunque le dosi target ?

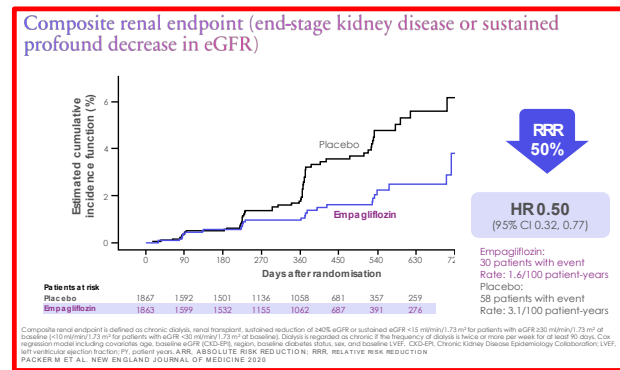
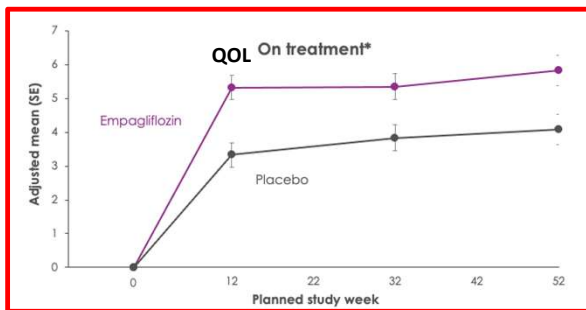
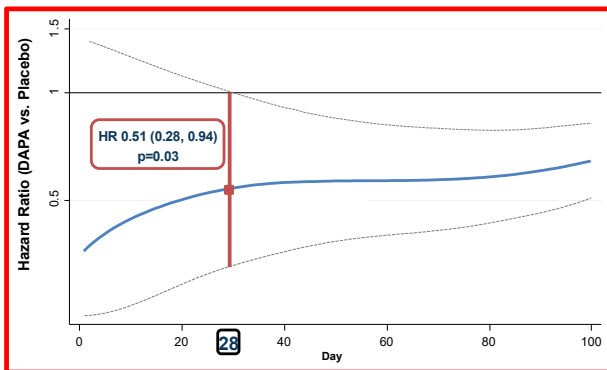


Relative Risk Reduction for All-Cause Mortality of Different Pharmacologic Treatment Combinations for Heart Failure Derived From Studies With High Quality : A systematic network meta-analysis

Heart Brings Heart 2023

Centro Congressi Auditorium San Francesco





Unico dosaggio

Tutti i pazienti con HF dovrebbero essere trattati con Glifozine ; nei pazienti «naive» sono i farmaci con cui iniziare

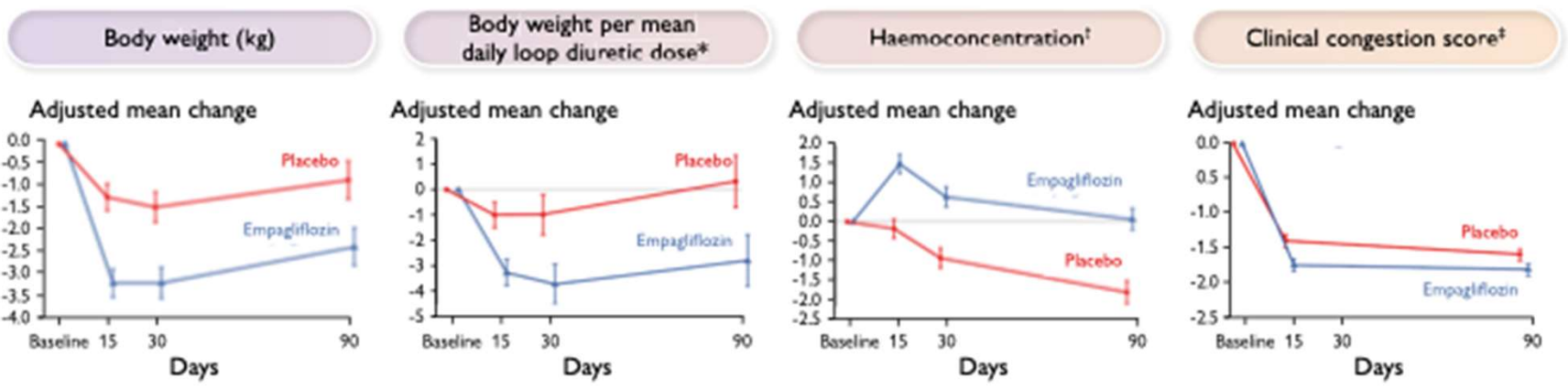
Evidence-based therapy	Relative risk reduction in all-cause mortality, %	Mortality at 24 mo, %	Absolute reduction in all-cause mortality, %
None	NA	35	NA
ARNI (vs imputed placebo)	28	25	10
β -Blocker	35	16	9
Aldosterone antagonist	30	12	5
SGLT2-i	17	10	2
Quadruple therapy ^b	73	10	26

The NNT for 24 months with all 4 medical therapies to prevent 1 death = 3.9

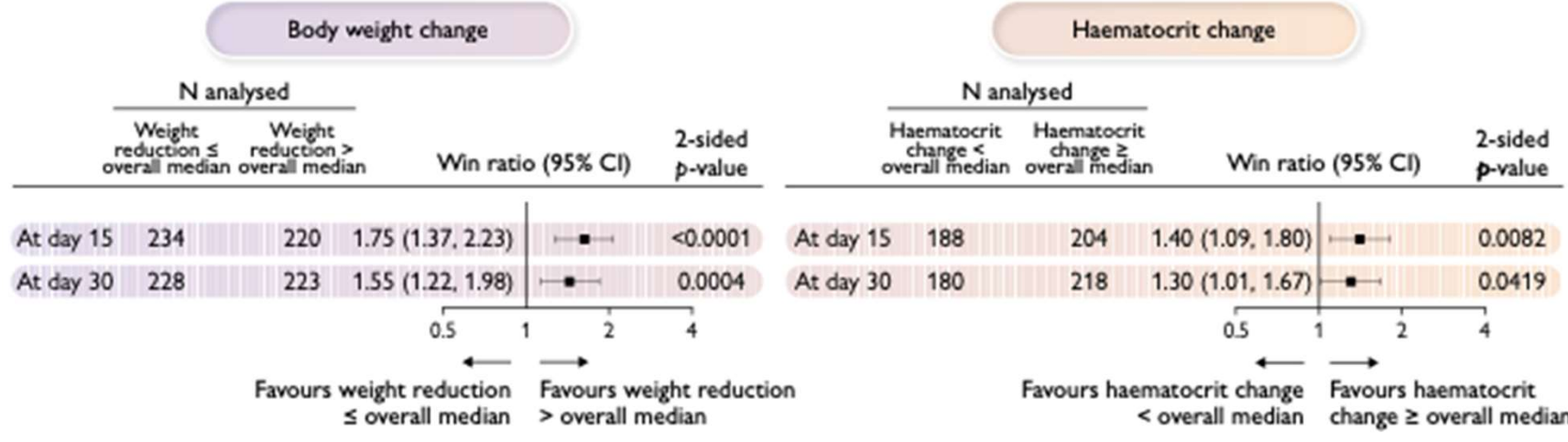


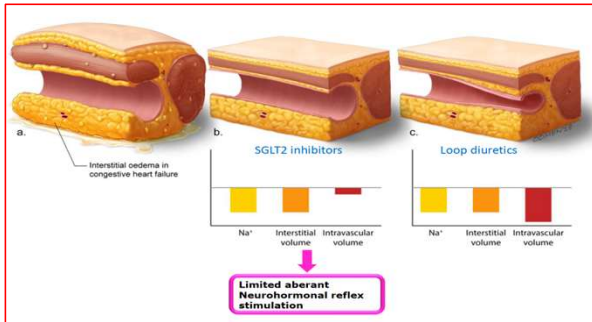
EMPULSE trial (AHF)

Treatment effect



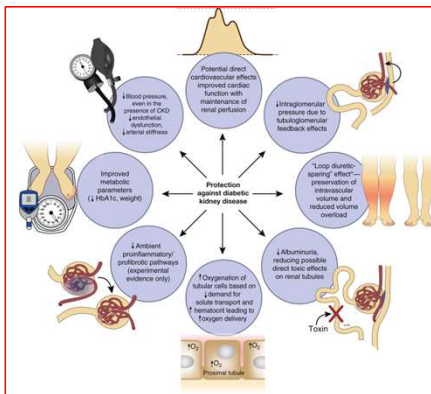
Clinical benefit at day 90§



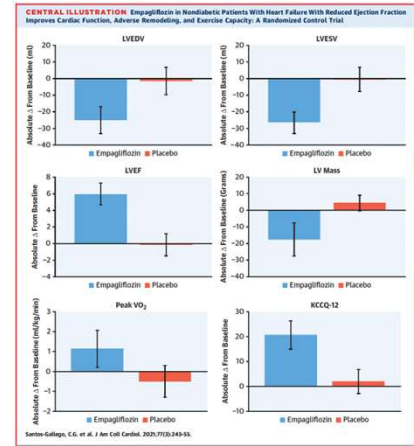
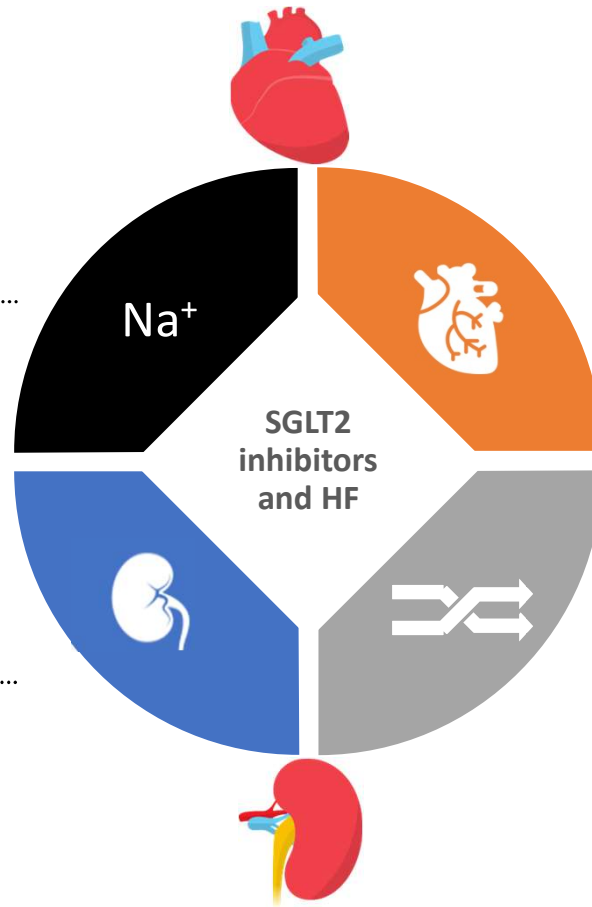


Natriuresis → Decongestion

Improved kidney function and cardio-renal physiology



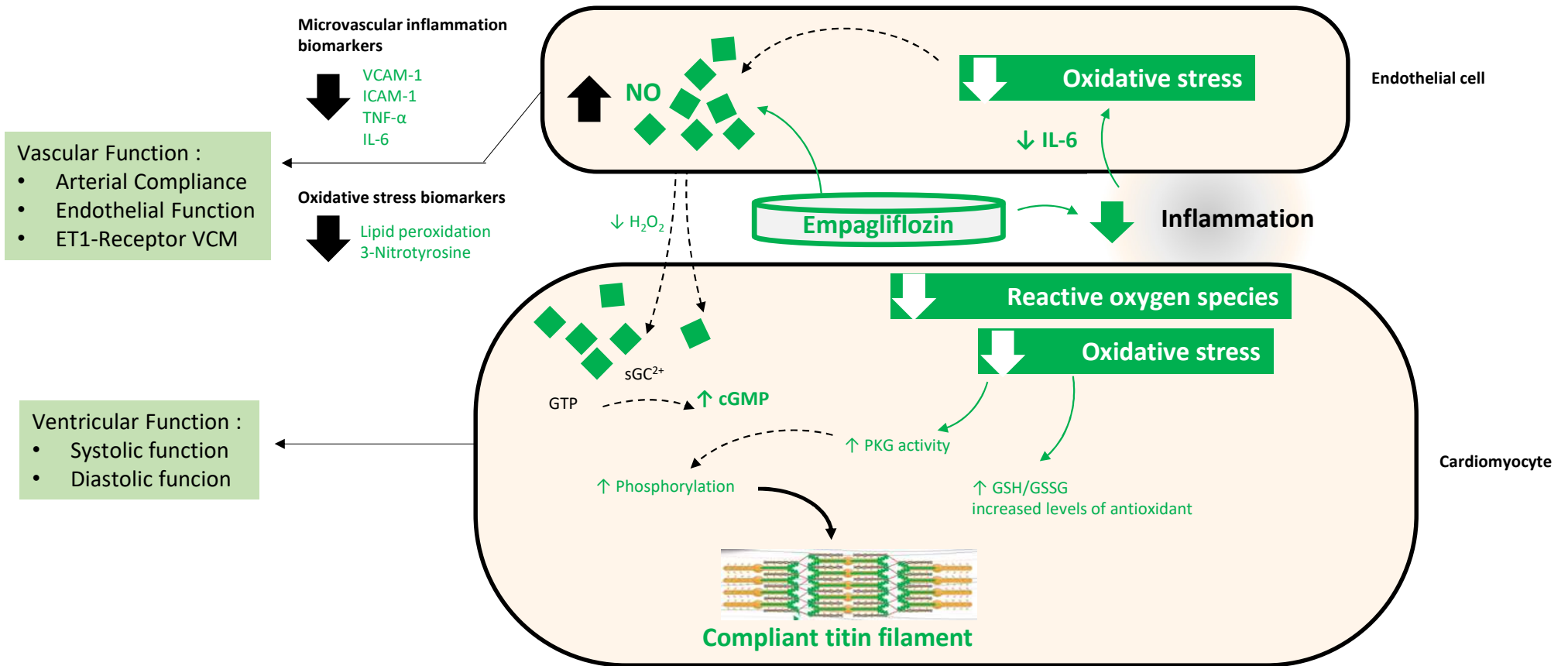
Farkouh ME & Verma S. *J Am Coll Cardiol* 2018;71:2507 (Modified)

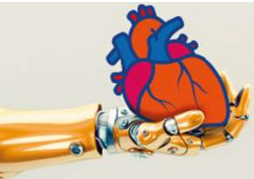


BONE MARROW

- ↑ Erythropoiesis
- ↑ Iron utilisation
- ↑ Oxygen delivery

Empagliflozin treatment reduces inflammation & oxidative stress, improving endothelial & cardiomyocyte fx





17° Meeting

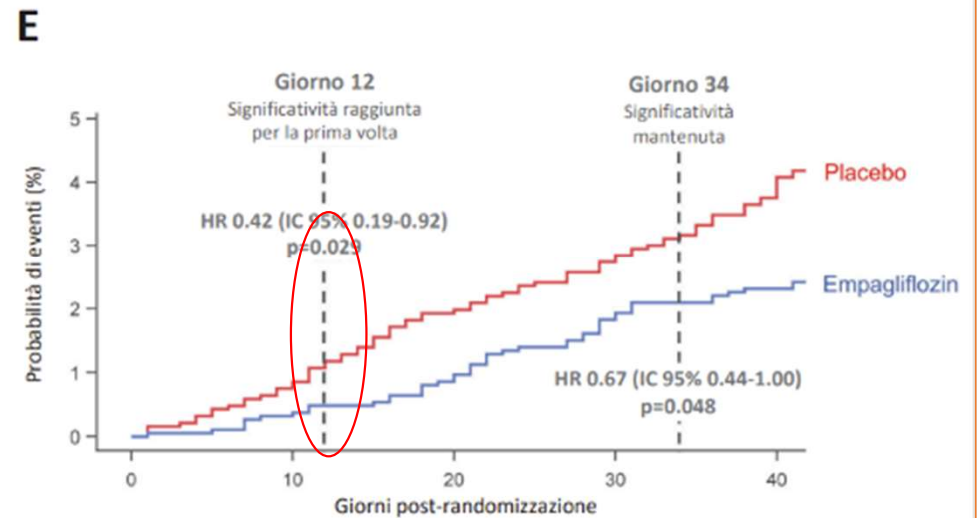
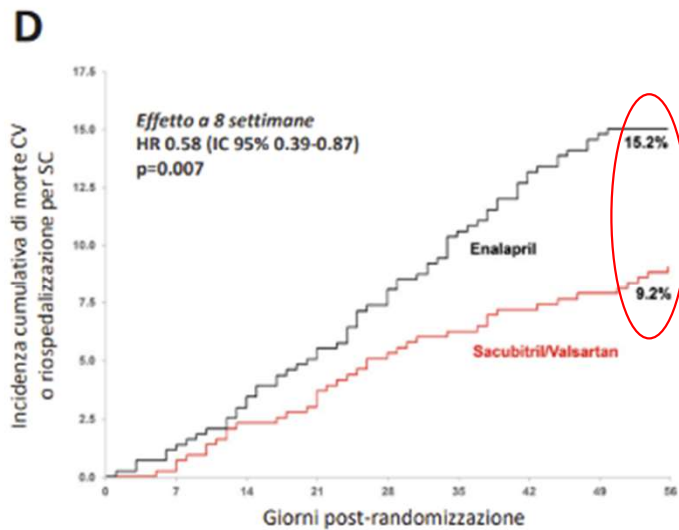
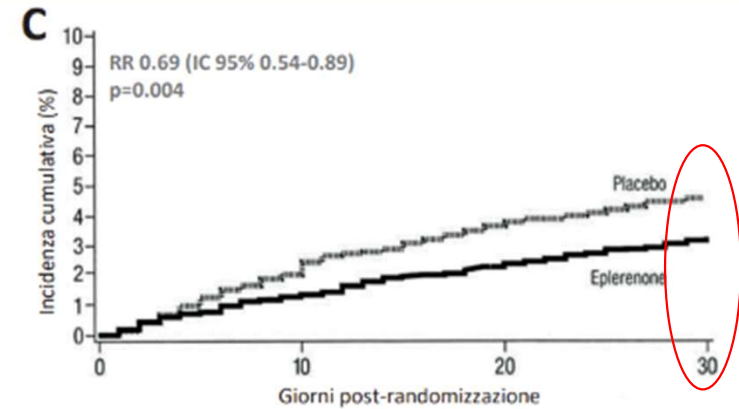
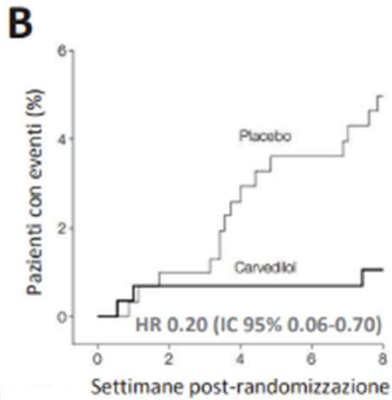
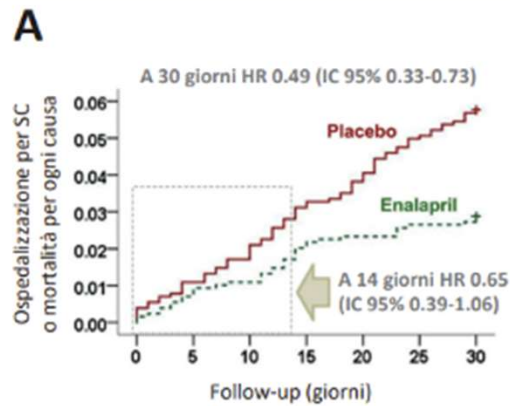
CardioLucca

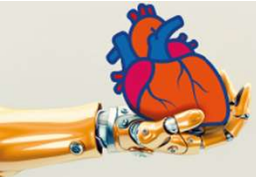
Heart Brings Heart 2023



Lucca,
22-24 Giugno
2023

Centro Congressi
Auditorium San Francesco





17^o Meeting

CardioLucca

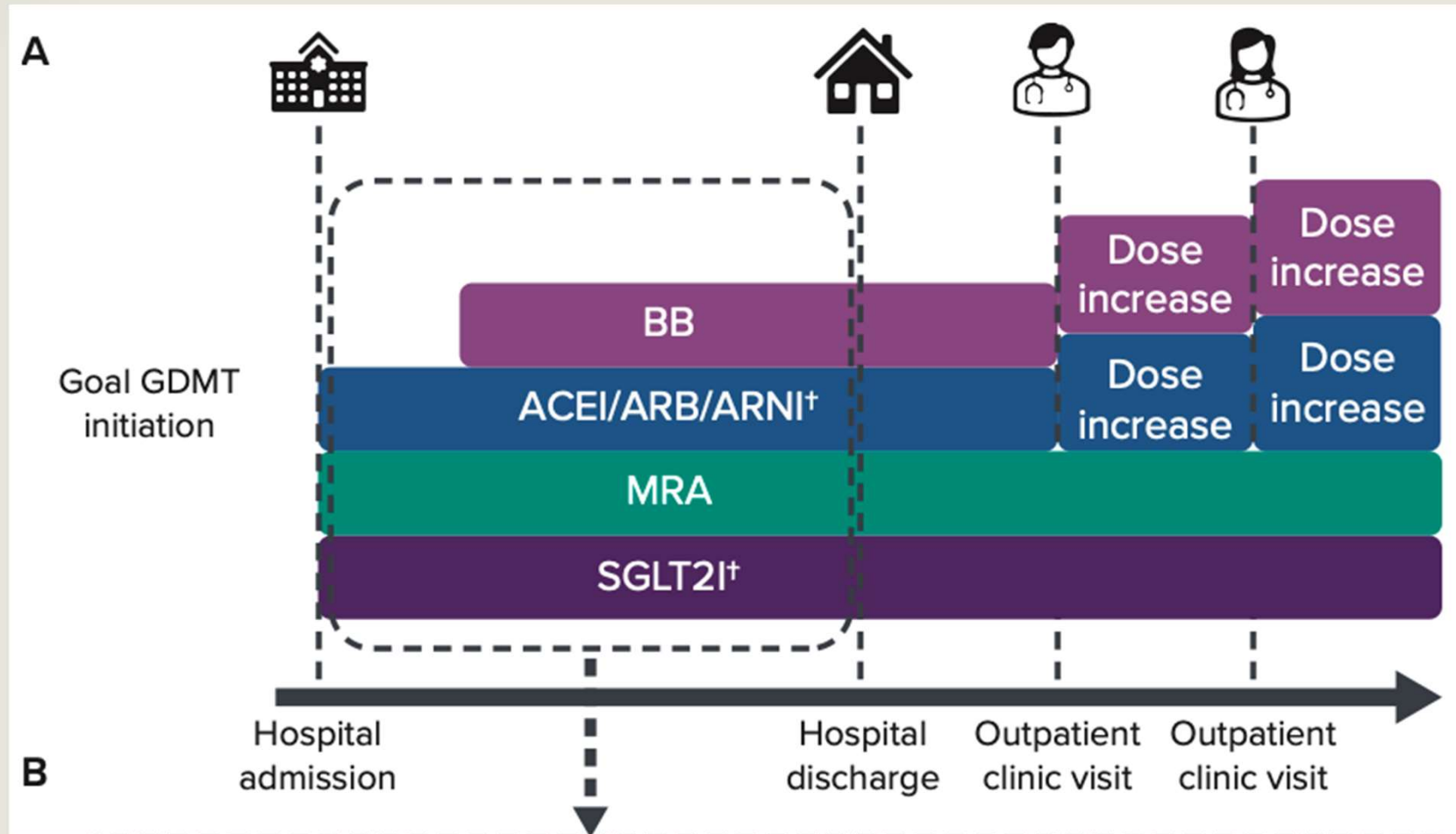
Heart Brings Heart 2023



Lucca,
22-24 Giugno
2023

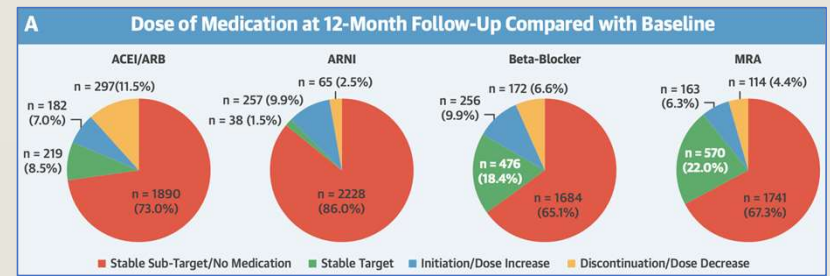
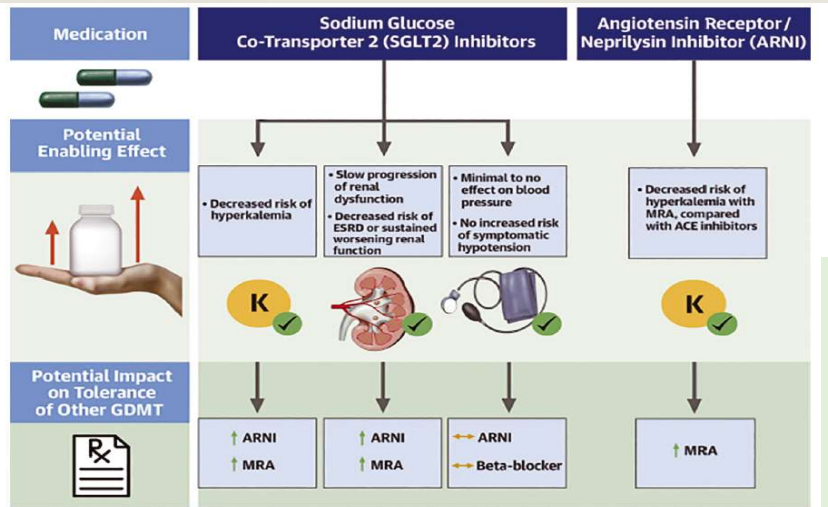
Centro Congressi
Auditorium San Francesco

Cardiac Failure Review 2022;8:e21





Teamwork between heart failure medications



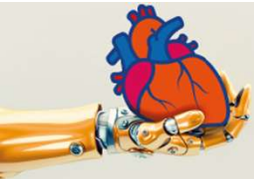
Inserimento di almeno 3 dei 4 farmaci è la regola nei pts ricoverati
Glifozine ben tollerate e unico dosaggio (no aggiustamenti di dose)
 Bassi dosaggi di farmaci in up-titration rimangono efficaci
 I parametri da seguire sono PA, fc, Clinica, Creatinina, Elettroliti
 Inizio terapia in Ospedale fidelizza i pazienti alla terapia

Effetto su	ACE-I/ARB	ARNI	BB	MRA	SGLT2-i
Riduzione della pressione arteriosa	+	++	+	-	-
Peggioramento della funzione renale	+	-	=	+	-
Iperkaliemia	+	-	=	++	-

ACE-I, inibitore dell'enzima di conversione dell'angiotensina; ARB, antagonista recettoriale dell'angiotensina; ARNI, antagonista del recettore dell'angiotensina e della neprilisina; BB, betabloccante; MRA, antagonista del recettore dei mineralcorticoidi; SGLT2-i, inibitore del cotrasportatore sodio-glucosio di tipo 2.

Per l'effetto su rene e potassio di ARNI e SGLT2-i, vedi testo e relativa bibliografia.

Impegno clinico/organizzativo	+	++	+	++	=



Association between dosing and combination use of medications and outcomes in heart failure with reduced ejection fraction: data from the Swedish Heart Failure Registry

Domenico D'Amario^{1,2,3}, Daniele Rodolico^{1,3}, Giuseppe M.C. Rosano⁴, Ulf Dahlström⁵, Filippo Crea^{2,3}, Lars H. Lund^{1,6†}, and Gianluigi Savarese^{1,6*†}

European Journal of Heart Failure (2022) 24, 871–884

Key questions

There is an emerging consensus that **low dose of multiple drugs** is better than **high dose of few drugs** in HFrEF.

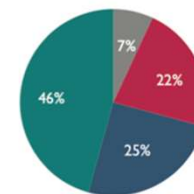
Key findings

Use of 2 drug classes at 50%-99% of target dose was associated with lower risk than 1 drug class at 100% of target dose.

Take-home message

Our data support using **lower doses of multiple drugs** instead of **up-titrating only one pharmacological class**.

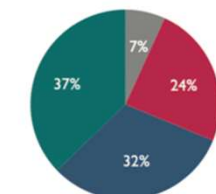
Target dose achievement for HF medications in SwedeHF 17 809 outpatients (2000-2018)



Legend:
 No use of drug (grey)
 1-49% of TD (red)
 50-99% of TD (blue)
 ≥100% of TD (green)

TD: target dose

ACEi/ARB/ARNi



β-blocker

Median follow-up 2.06 years (IQR 0.87-4.65)

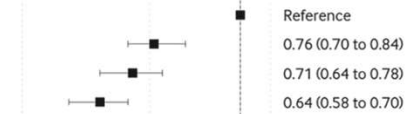
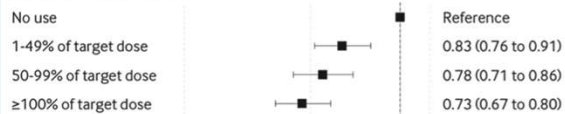
CV death or HF hospitalization

All-cause death

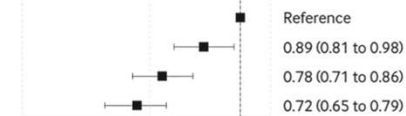
Adjusted HR (95% CI)

Adjusted HR (95% CI)

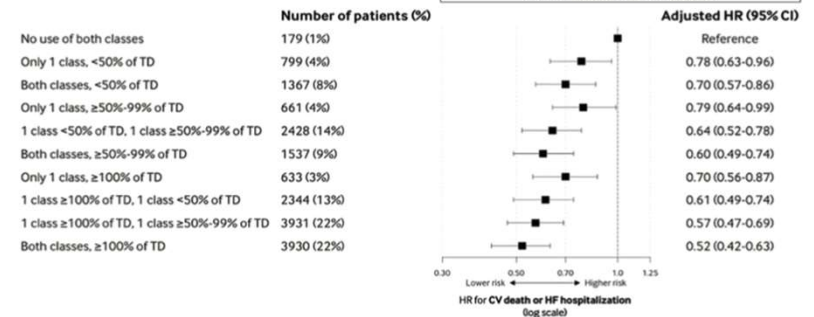
ACEi/ARB/ARNi use



Beta-blocker use



CV death or HF hospitalization



2 pharmacological classes at 50-99% of target dose

associated with lower risk of cardiovascular death or heart failure hospitalization [HR (95% CI) 0.86 (0.74-0.99), p-value <0.05]

1 pharmacological class at 100% of target dose



Routine-care Databases

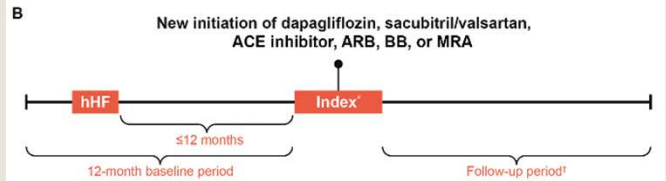
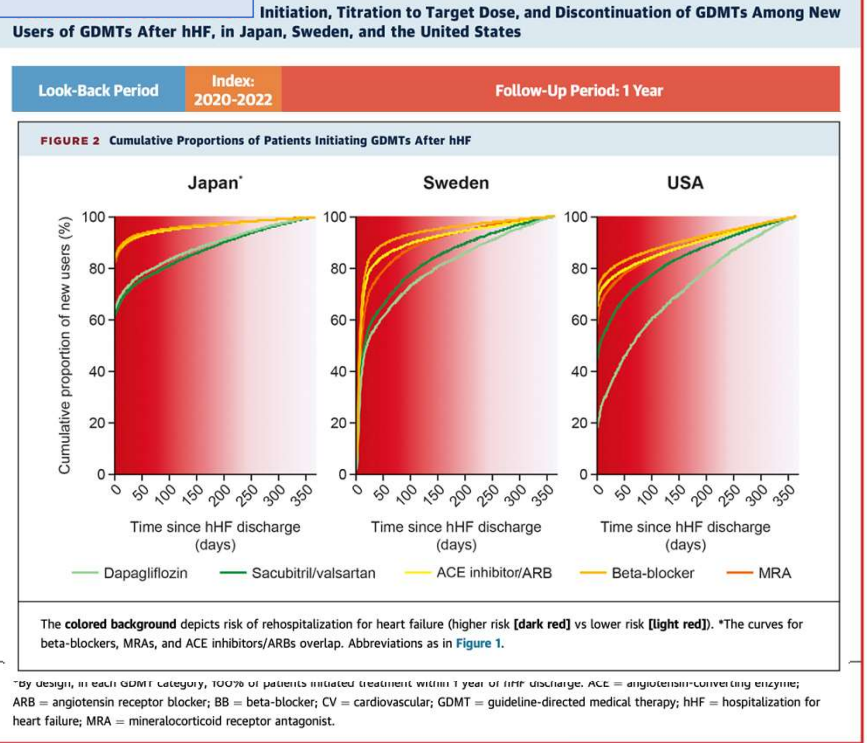
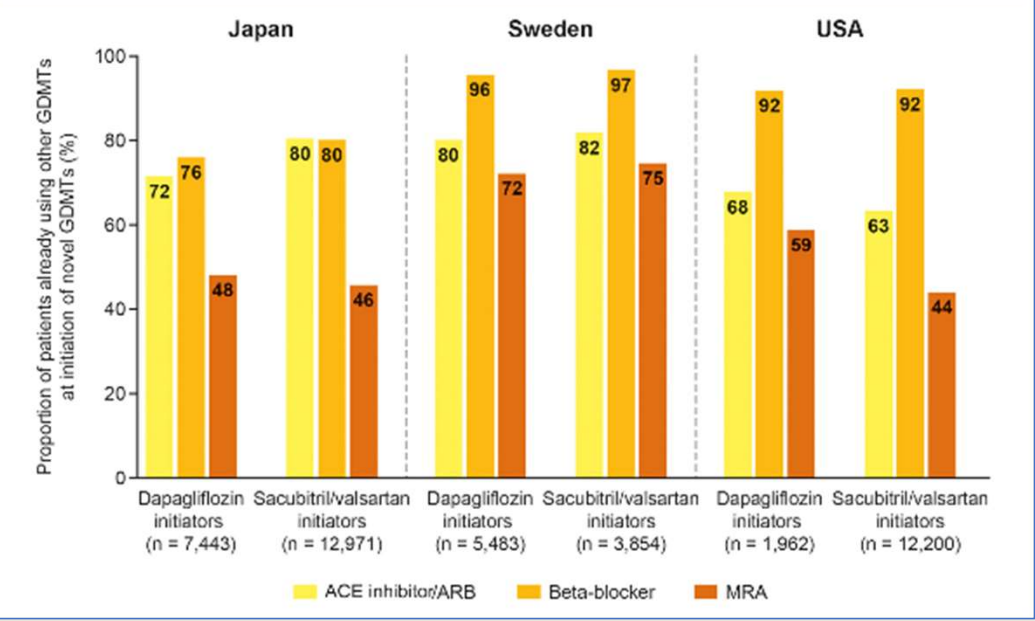
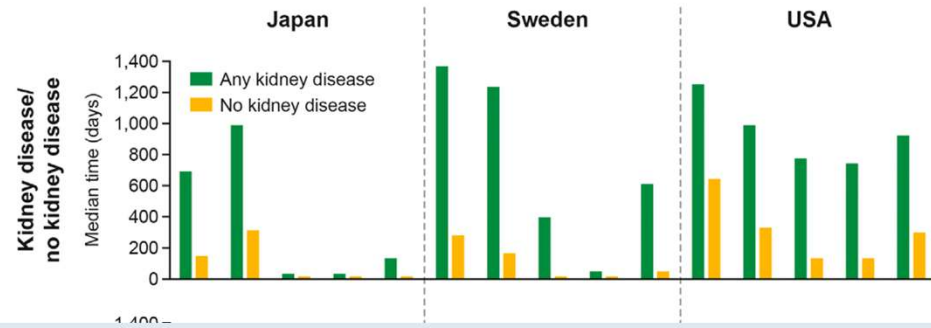


FIGURE 3 Proportions of Patients Already Using ACE Inhibitor/ARB, Beta-Blocker, or MRA at Initiation of Novel GDMTs (Dapagliflozin and Sacubitril/Valsartan)



Un elevato numero di pazienti inizia con BB e ACE-I/ARB
 Gli ARNI vengono implementati «per sostituzione» ACE/ARB
 Le Glifozine vengono implementate in add-on
 Comunque SGLT2-I e ARNI non vengono usati x primi
 Gli antialdosteronici sono utilizzati solo in circa il 50% dei pts

FIGURE 6 Median Time from First HF Diagnosis to GDMT Initiation for Subgroups of New Users of GDMTs After hHF

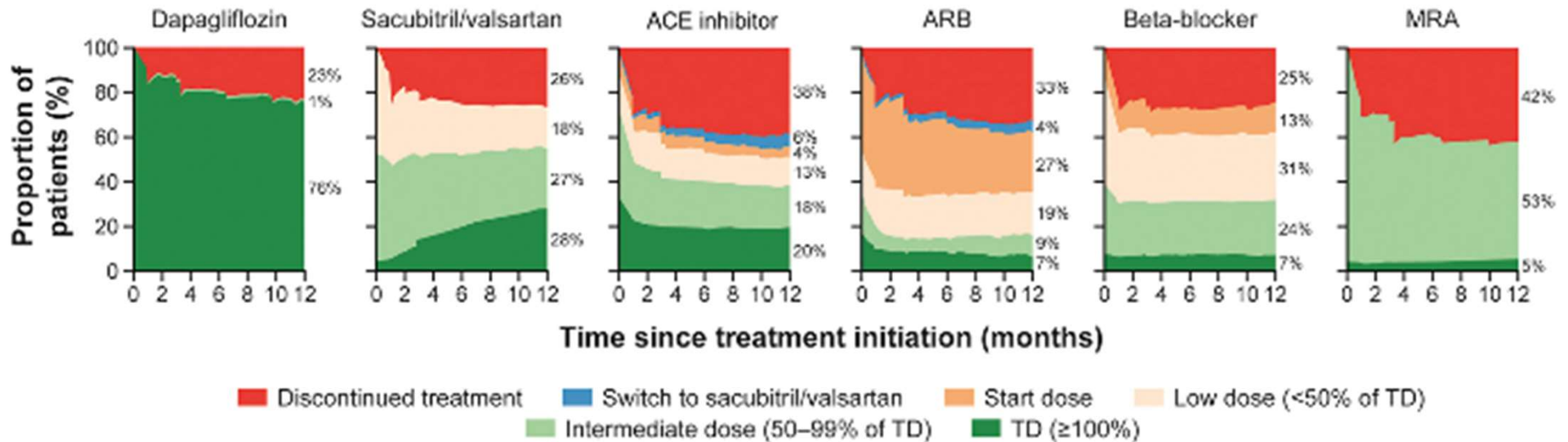


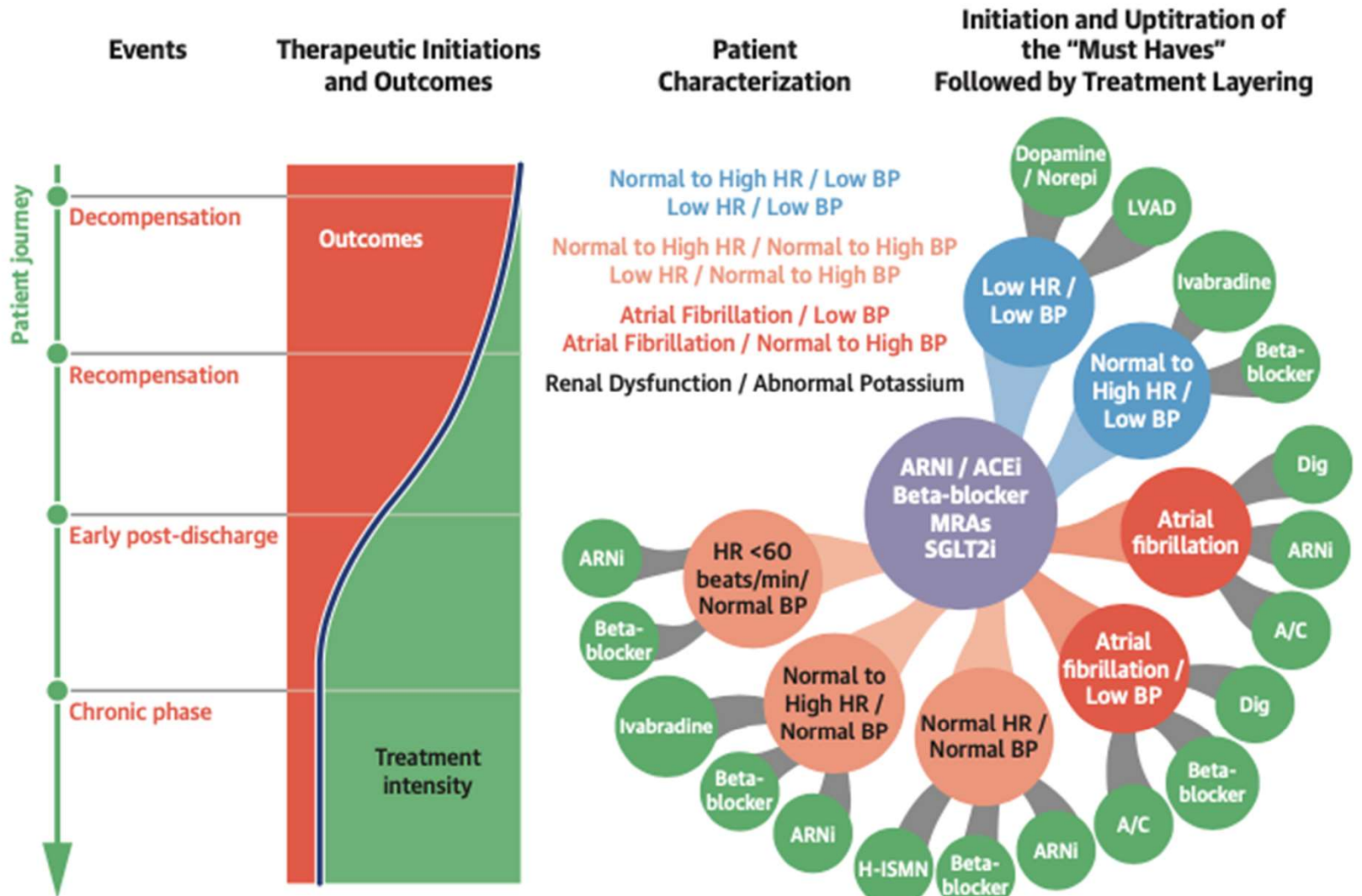
For GDMTs requiring uptitration, few patients received the target dose in the 12 months after initiation, and many discontinued treatment.

Conversely, dapagliflozin was associated with relatively low rates of discontinuation.

The delay in novel GDMT initiation was more

FIGURE 5 Titration to Target Dose and Discontinuation of the Most Frequently Used Treatments in Each GDMT Class Among New Users of GDMTs After hHF, Pooled Across Japan, Sweden, and the United States





Rosano, G.M.C. et al. J Am Coll Cardiol HF. 2021;9(11):775-783.

Conclusioni - 1



17° Meeting

CardioLucca
Heart Brings Heart 2023



Lucca,
22-24 Giugno
2023

Centro Congressi
Auditorium San F

Conclusioni - 2

Paziente con HF-rEF
(out-patient)

Stabilità Clinica e
laboratoristica

Paziente non trattato
con diuretici
(naive)

Paziente già trattato
con diuretici
(MMG)

Paziente già trattato
con diuretici e ACE-I
(MMG, Card Terr.)

FAB-4

Ridurre§ il diuretico
FAB-4

Shift ad ARNI
Ridurre il Diuretico

UP titration
* ARNI
* BB

UP Titration
* ARNI
* BB

Implementa SGLT-2I
Ridurre§ Diuretico

UP Titration
* ARNI
* BB

§ Sospendere se possibile

ICD
(GL)

FEVS < 35%
Ausilio per Up-Titration
AIV presenti
CAD

CRTD indicata (GL)
(BBS, QRS > 150msec)

FEVS < 35%
Ausilio per Up-Titration
IM, CAD
AIV presenti
CRT-D score favorevole

CRTD

L' unico vero problema complesso
per ARNI e Glifozine ? I costi !!!!!

Un approccio pragmatico per i FAB-4



17° Meeting

CardioLucca

Heart Brings Heart 2023



Lucca,
22-24 Giugno
2023

Centro Congressi
Auditorium San Francesco