PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA
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di Confindustria
Auditorium
della Tecnica

9ª Edizione

30 Settembre
1 Ottobre
2022

Gliflozine ed incretine: da farmaci antidiabetici a farmaci cardiovascolari

Strategie di utilizzo delle gliflozine: perché? quando? come? a chi?

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HoT
HEART FAILURE SPECIALISTS OF TOMORROW

Disclosures

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- Novartis

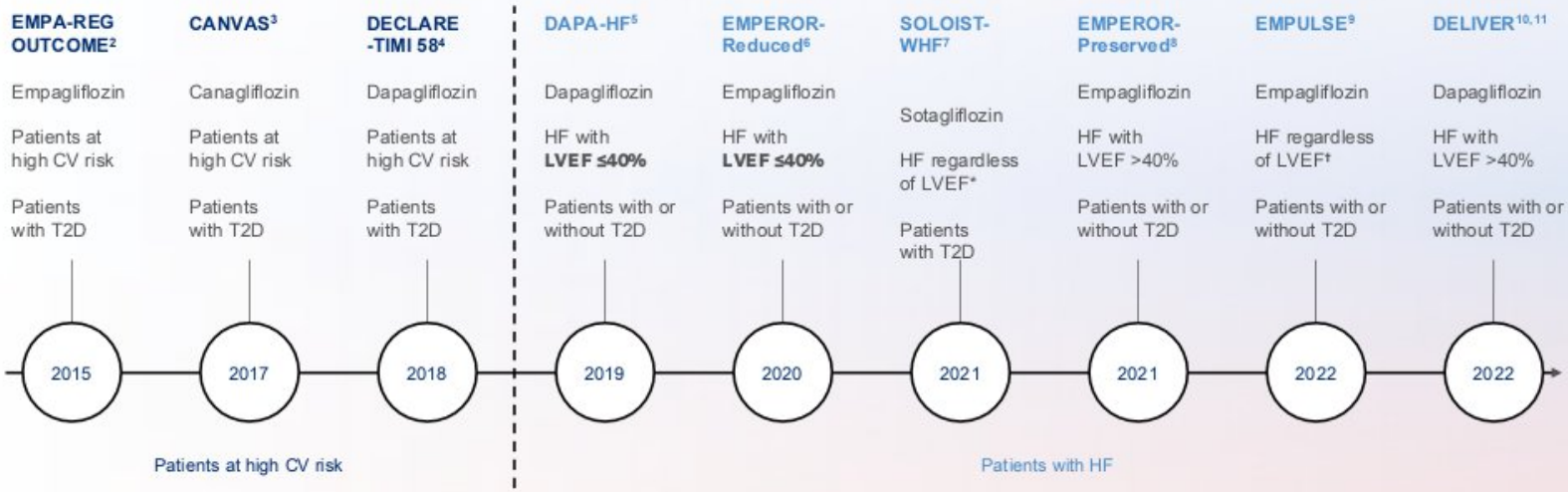
Speaker fees:

- AstraZeneca, Vifor Pharma, Amgen, Sanofi, Neopharmed Gentili

No other conflicts of interest relevant to this presentation.

Strategie di utilizzo delle gliflozine: **perché?** quando? come? a chi?

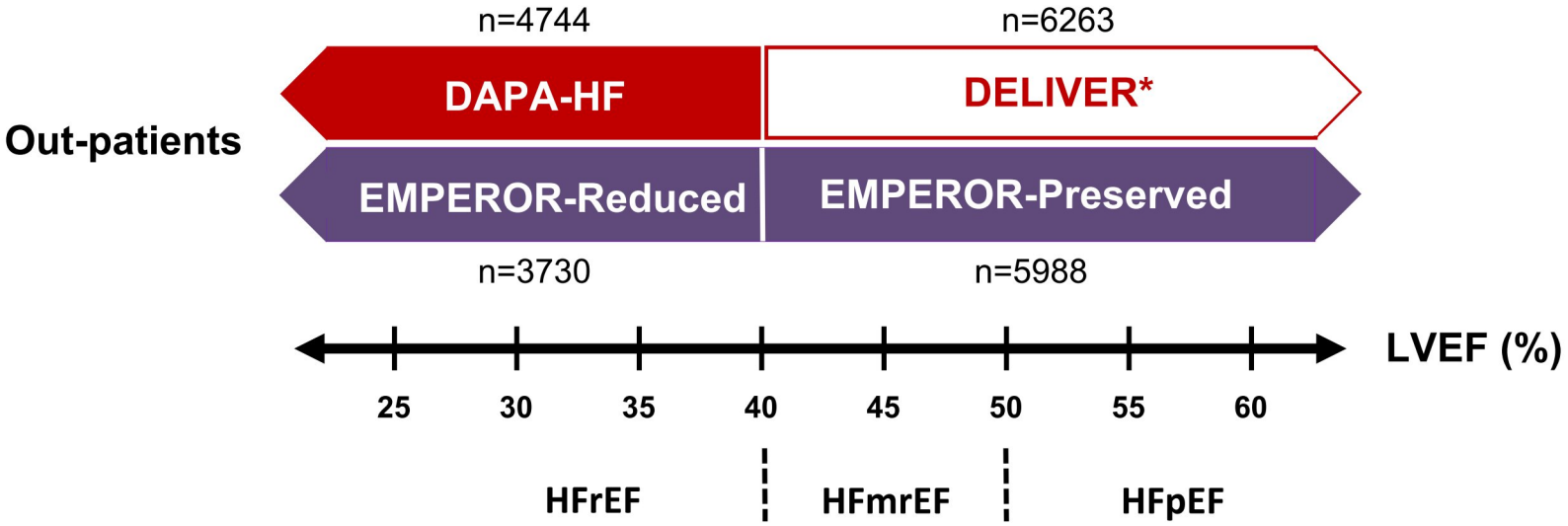
Growing evidence from RCTs demonstrates the favourable profile of SGLT2 inhibitors on CV outcomes and mortality in patients with HF



*In patients hospitalized for worsening HF. †In patients hospitalized for acute HF, once stabilized. CV, cardiovascular; HF, heart failure; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes.

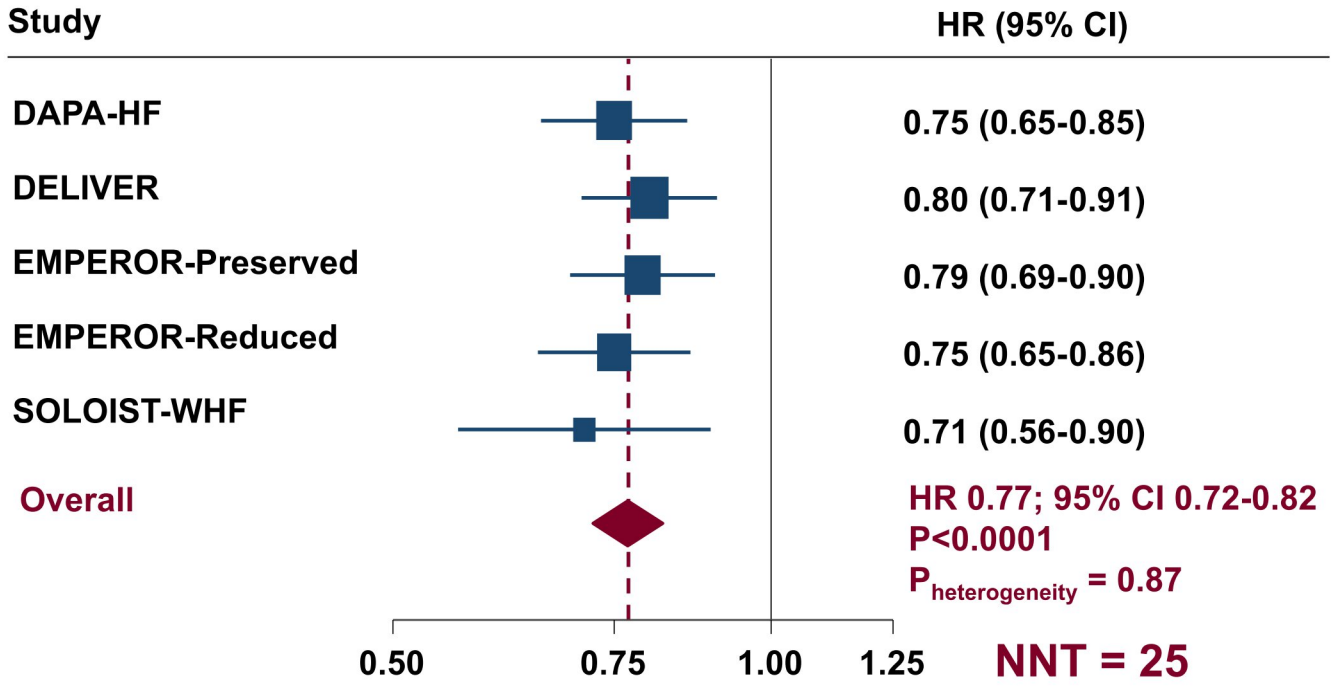
1. Tsampasian V *et al. Cardiol Res Pract.* 2021;2021:9927533; 2. Zinman B *et al. N Engl J Med.* 2015;373:2117; 3. Neal B *et al. N Engl J Med.* 2017;377:644; 4. Wiviott SP *et al. N Engl J Med.* 2019;380:347; 5. McMurray J *et al. N Engl J Med.* 2019;381:1995; 6. Packer M *et al. N Engl J Med.* 2020;383:1413; 7. Bhatt DL *et al. N Engl J Med.* 2021;384:117; 8. Anker SD *et al. N Engl J Med.* 2021;385:1451; 9. Voors AA *et al. Nat Med.* 2022;28:568; 10. AstraZeneca. Press release, 2022. Available at: https://www.astrazeneca-us.com/content/az-us/media/press-releases/2022/farxiga-met-primary-endpoint-in-deliver-phase-III-trial.html (accessed August 2022); 11. Solomon SD *et al. Eur J Heart Fail.* 2021;23:1217.

SGLT2 inhibitors heart failure trials: Out-patients



SGLT2 inhibitors in out-patients with HF

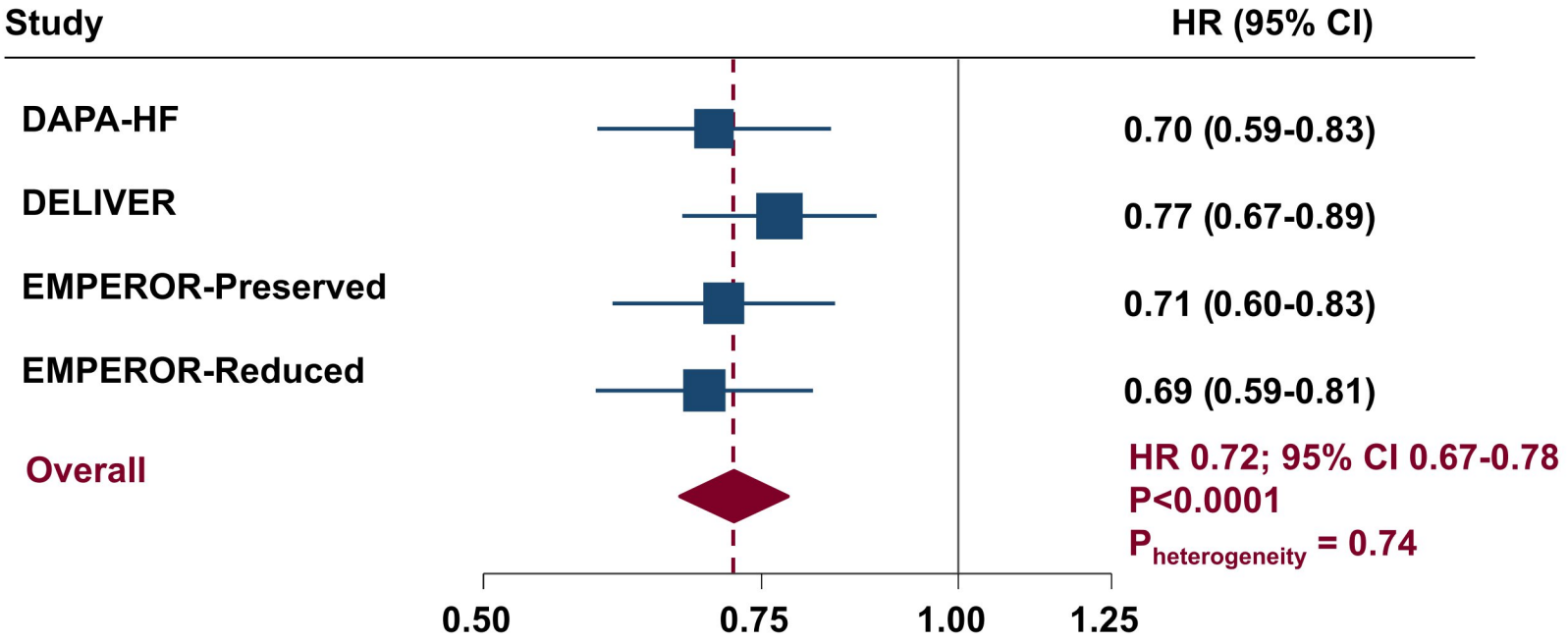
↓ 23% (18-28%) RRR of Primary Endpoint (CV Death or HF Hospitalization)



Vaduganathan M et al. ESC Congress 2022

SGLT2 inhibitors in out-patients with HF

↓ 28% (22-33%) Relative Risk Reduction of HF Hospitalisation



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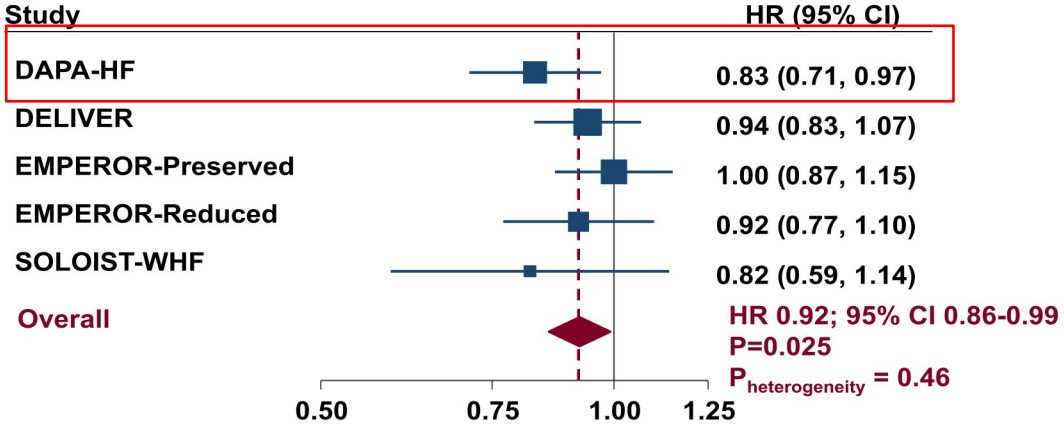
SGLT2 inhibitors in out-patients with HF

Cardiovascular death

All cause death

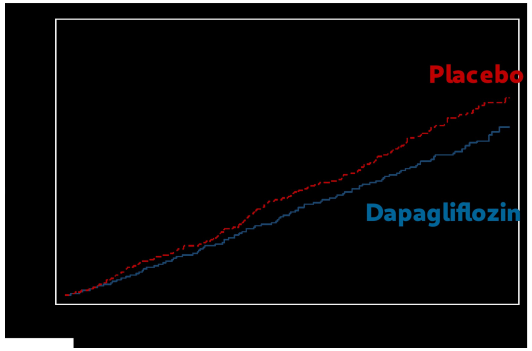


ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Cardiovascular death

HR 0.82 (0.69, 0.98); p=0.029



Vaduganathan M et al. ESC Congress 2022

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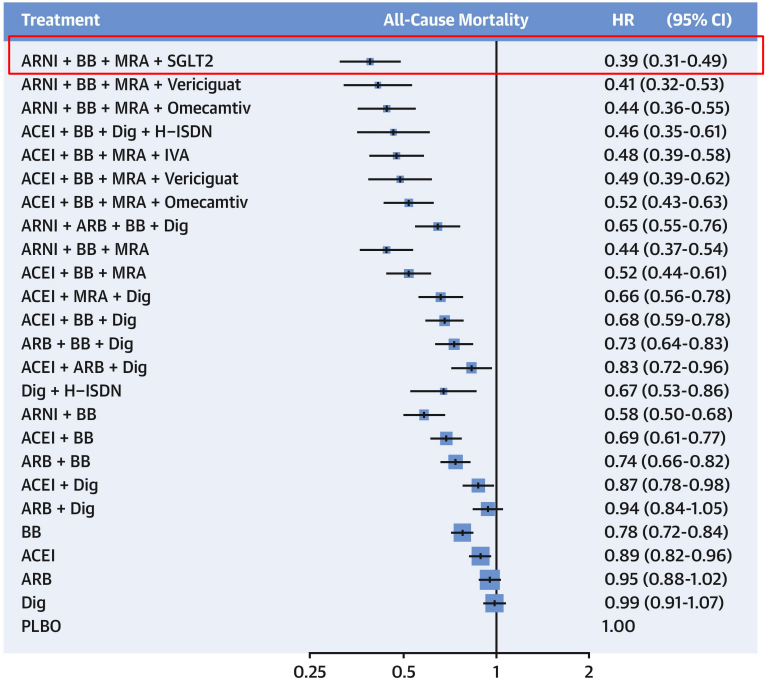
CENTRAL ILLUSTRATION: Relative Risk Reduction of Different Pharmacological Treatment Combinations for Heart Failure

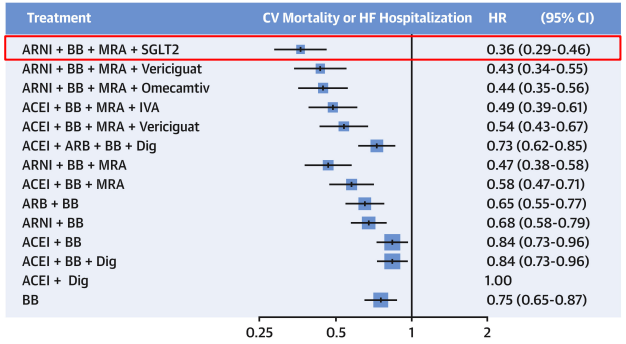
A



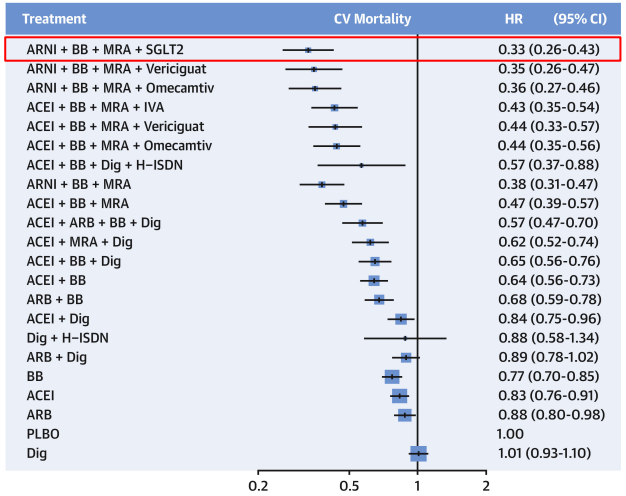
Tromp, J. et al. J Am Coll Cardiol HF. 2022;10(2):73-84.

CENTRAL ILLUSTRATION: Continued

B



C

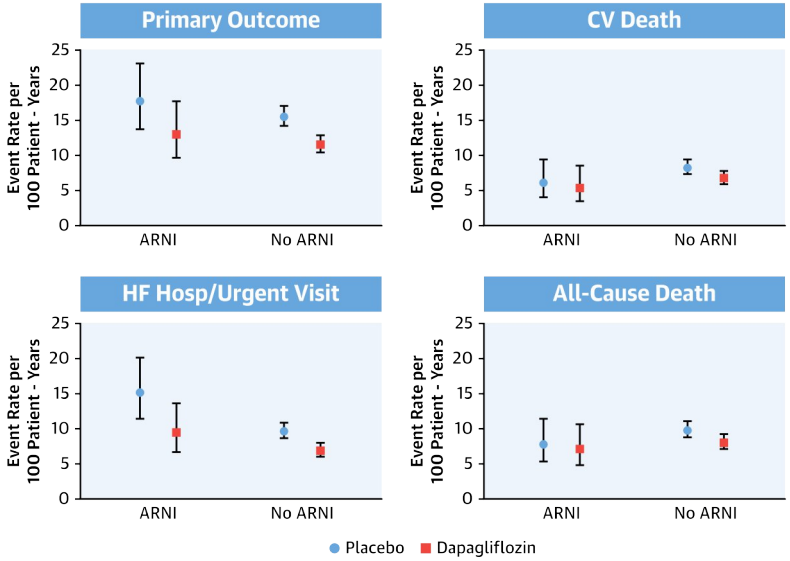


Tromp, J. et al. J Am Coll Cardiol HF. 2022;10(2):73-84.

Effect of Dapagliflozin in Patients With HFrEF Treated With Sacubitril/Valsartan

The DAPA-HF Trial

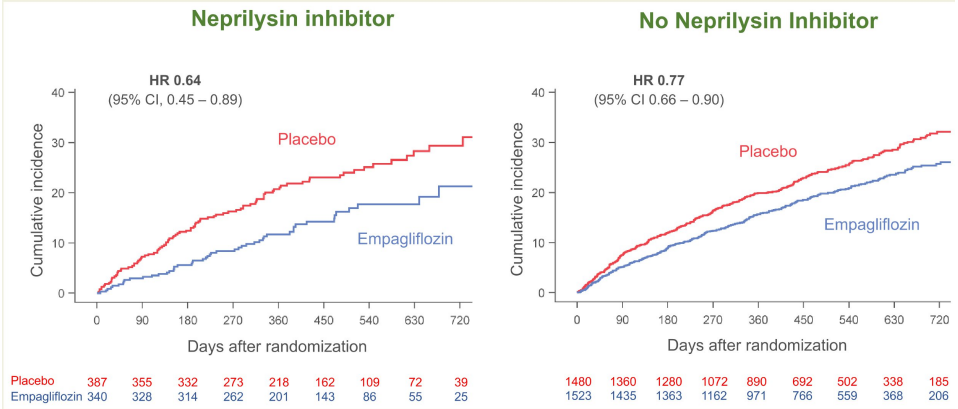
Scott D. Solomon, MD,[a] Pardeep S. Jhund, MBChB, PhD,[b] Brian L. Claggett, PhD,[a] Pooja Dewan, MBBS,[b] Lars Køber, MD,[c] Mikhail N. Kosiborod, MD,[d] Felipe A. Martinez, MD,[e] Piotr Ponikowski, MD,[f] Marc S. Sabatine, MD,[g] Silvio E. Inzucchi, MD,[h] Akshay S. Desai, MD,[a] Olof Bengtsson, PhD,[i] Daniel Lindholm, MD,[b] Mikaela Sjostrand, MD, PhD,[a] Anna Maria Langkilde, MD,[i] John J.V. McMurray, MD[b]



Solomon, S.D. et al. J Am Coll Cardiol HF. 2020;8(10):811-8.

Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial

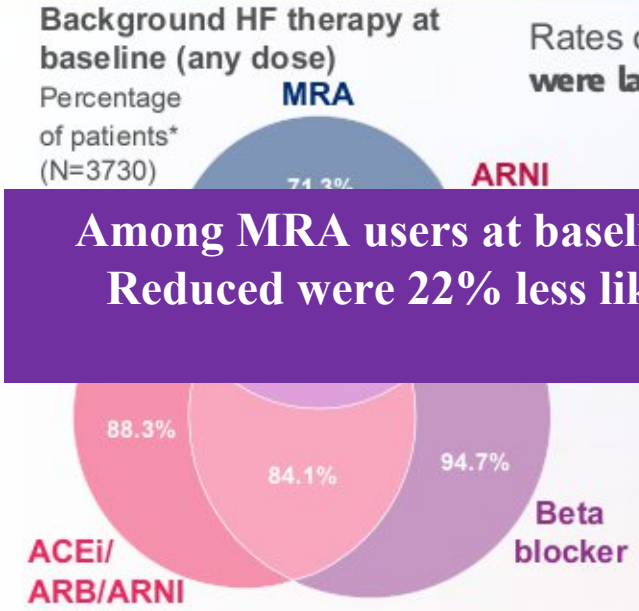
Milton Packer [1,2]*, Stefan D. Anker [3], Javed Butler[4], Gerasimos Filippatos[5], Joao Pedro Ferreira[6], Stuart J. Pocock [7], Hans-Peter Brunner-La Rocca[8], Stefan Janssens[9], Hiroyuki Tsutsui[10], Jian Zhang[11], Martina Brueckmann[12], Waheed Jamal [13], Daniel Cotton [14], Tomoko Iwata[15], Janet Schnee [14], and Faiez Zannad [6]; for the EMPEROR-Reduced Trial Committees and Investigators

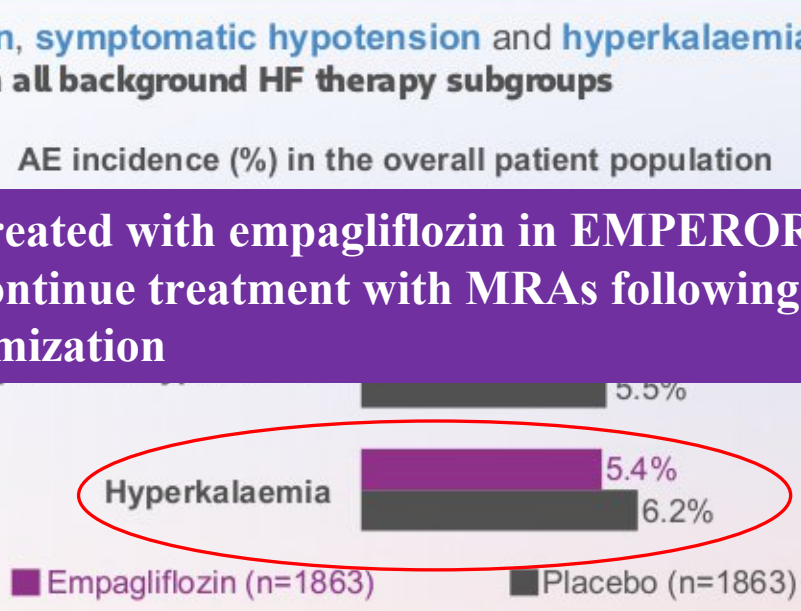


Packer M et al. EHJ 2021

EMPEROR-Reduced showed empagliflozin can be combined with other foundational HFrEF therapies with no impact on safety profile

Among MRA users at baseline, those treated with empagliflozin in EMPEROR-Reduced were 22% less likely to discontinue treatment with MRAs following randomization





*Percentages were calculated based on the number of patients receiving a specified HF therapy or combination of HF therapies at baseline.
ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

Verma S *et al. Lancet Diabetes Endocrinol.* 2022

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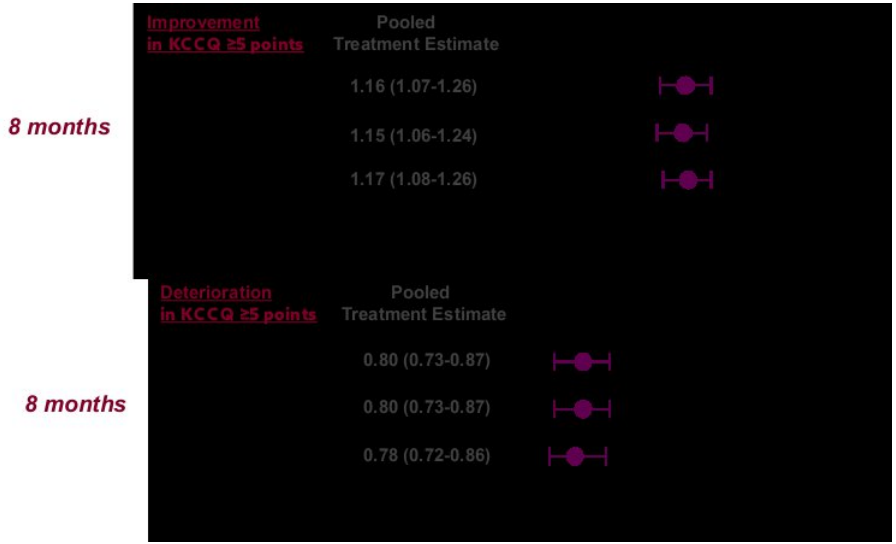
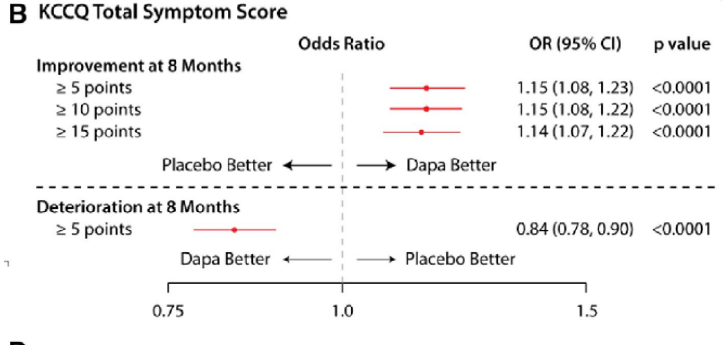
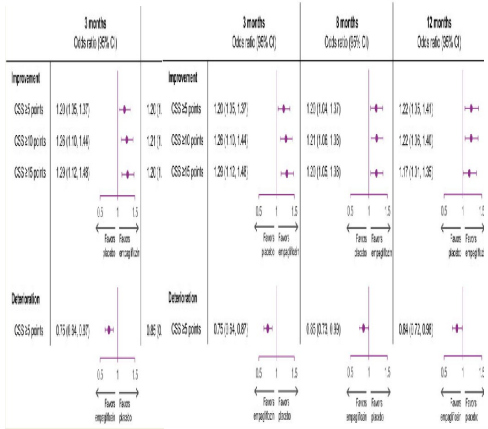
Greater Clinically Meaningful Improvement and Lesser Deterioration in Multiple Domains of Health Status with SGLT2i







Butler J et al. EJHF 2021
Kosiborod MN et al. Circulation 2020
Vaduganathan M et al. ESC Congress 2022

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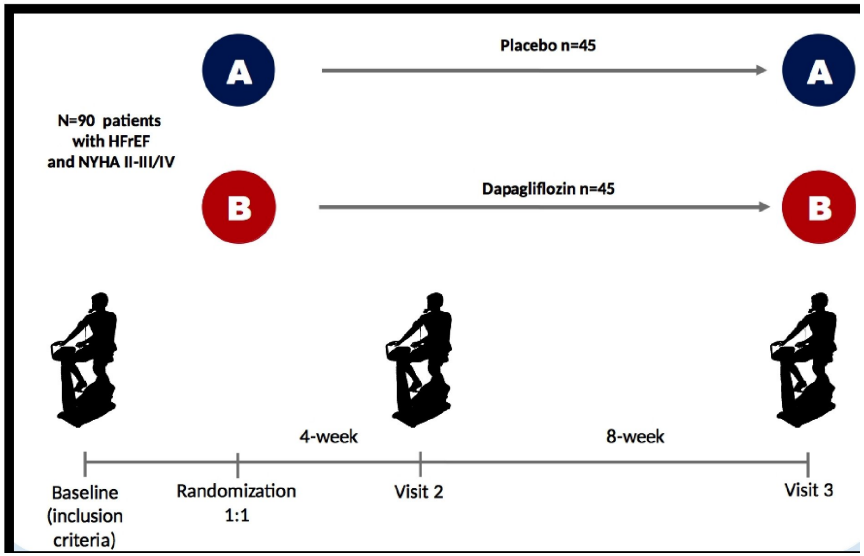
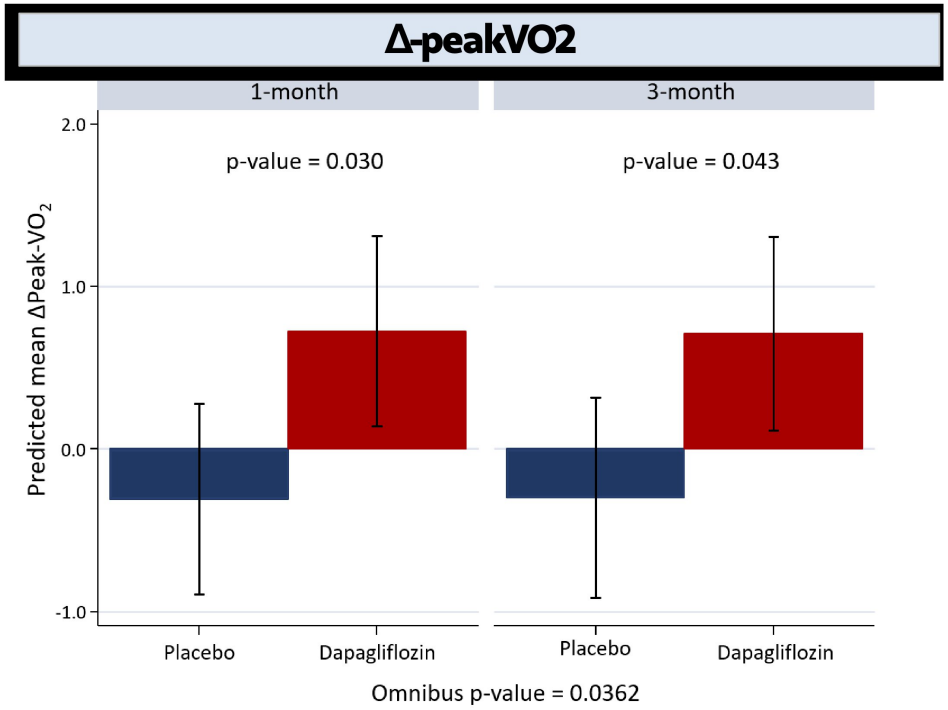
Short-term Effects of Dapagliflozin on Peak VO2 in Heart failure and Reduced Ejection Fraction (DAPA-VO2): a Randomized Clinical Trial





Palau et al. EJHF 2022

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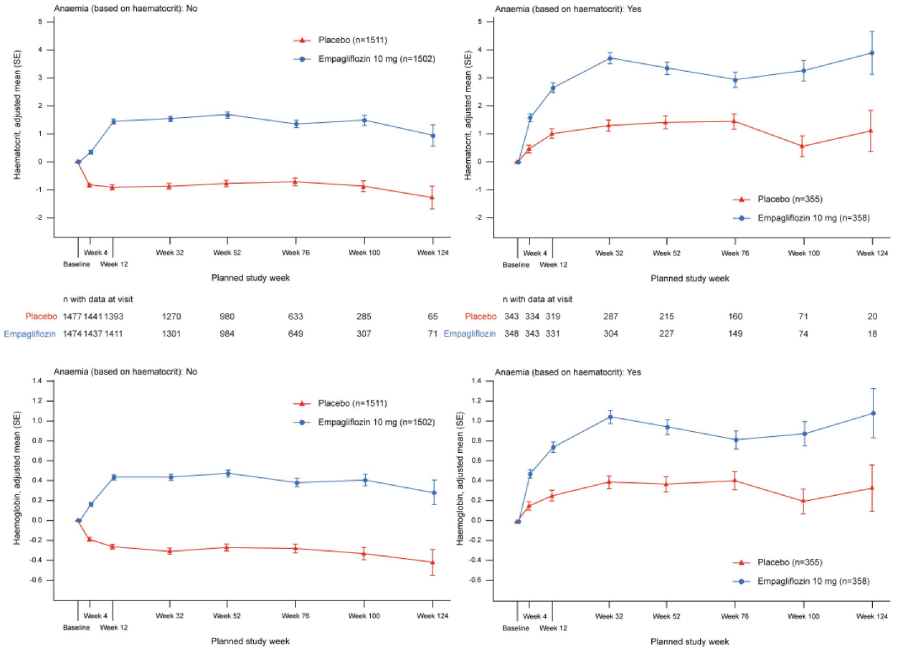
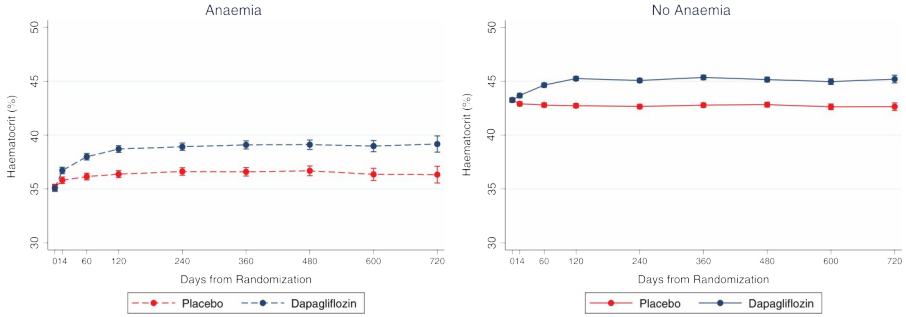
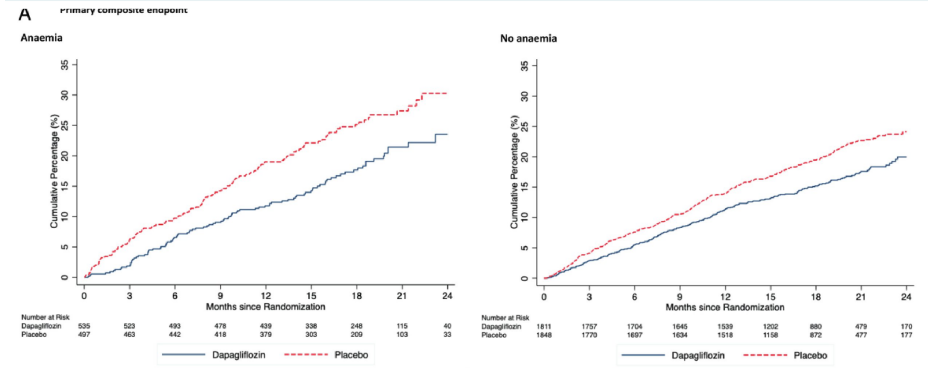
Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: findings from EMPEROR-Reduced

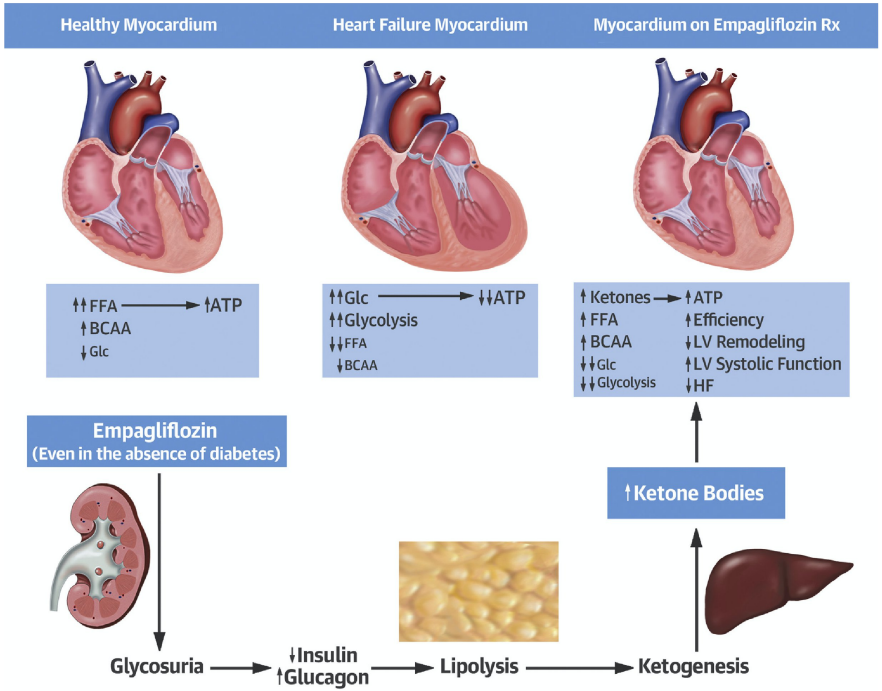


Dockerty KF et al. EJHF 2021
Ferreira JP et al. EJHF 2022

Effect of dapagliflozin on anaemia in DAPA-HF



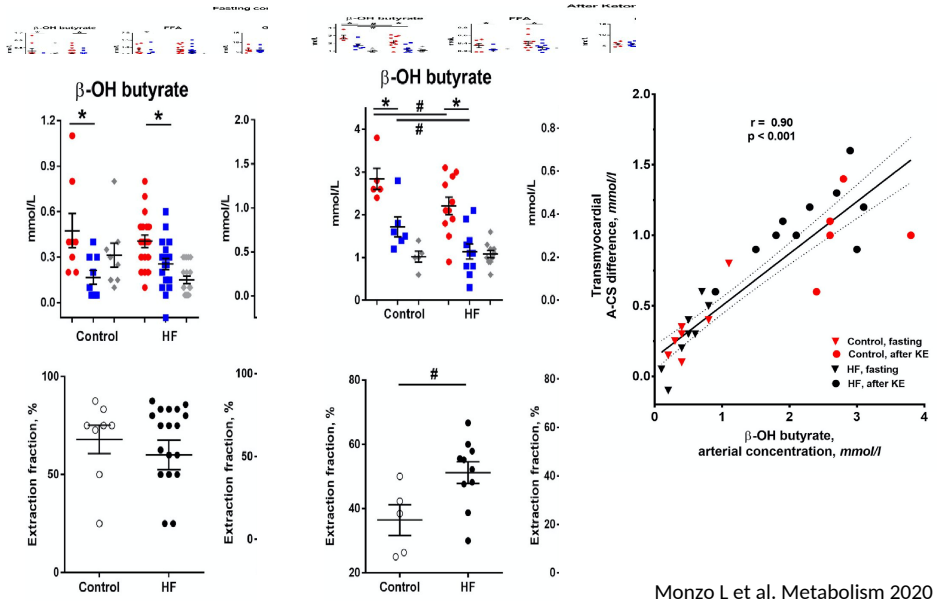




Santos-Gallego, C.G. et al. J Am Coll Cardiol. 2019;73(15):1931-44.

Myocardial ketone body utilization in patients with heart failure: The impact of oral ketone ester

Luca Monzo [a,b], Kamil Sedlacek [a], Katarina Hromanikova [a], Lucie Tomanova [a], Barry A. Borlaug [c], Antonin Jabor [a], Josef Kautzner [a], Vojtech Melenovsky [a,*]



Monzo L et al. Metabolism 2020

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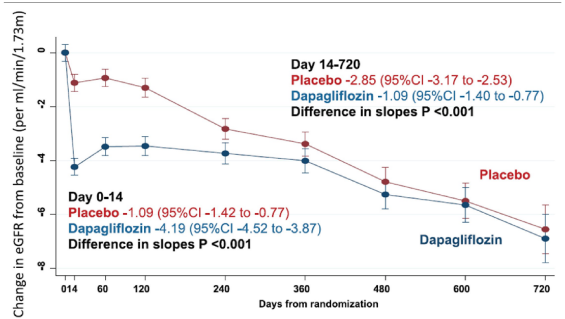
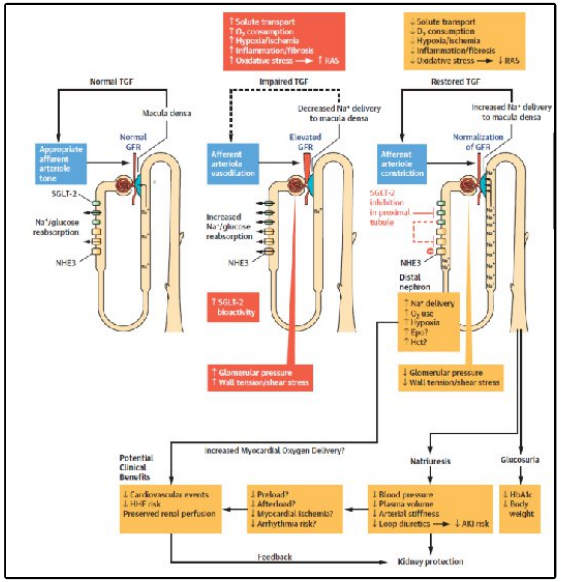
Effect of SGLT2i on renal function in chronic HF

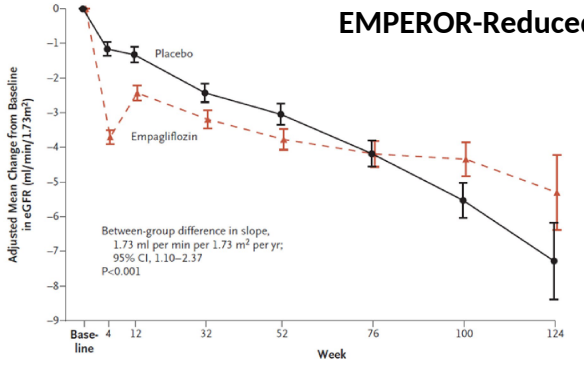
DAPA-HF



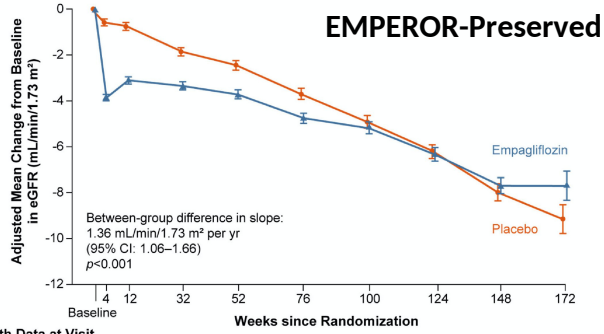


Cherney et al JACC HF 2019

EMPEROR-Reduced

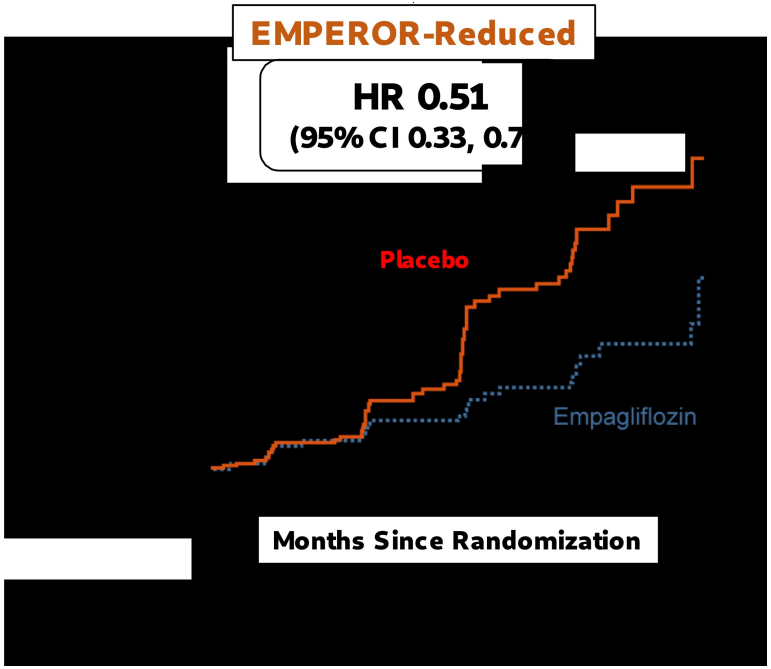


EMPEROR-Preserved

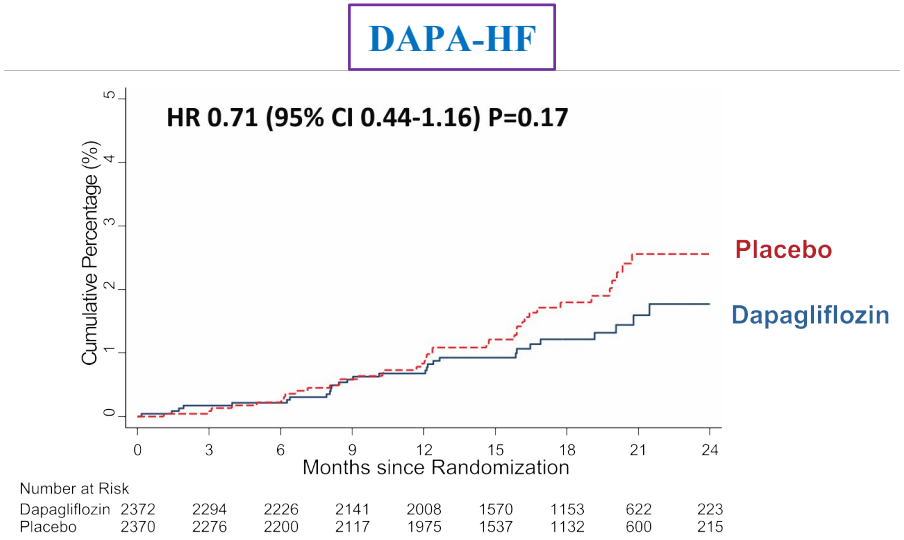


Jhund et al Circulation 2021
Zannad et al Circulation 2021
Anker SD et al N Engl J Med. 2021

SGLT2i improve renal outcomes in chronic HF



Prespecified renal composite outcome was a composite of **≥40%** sustained decline eGFR or end-stage renal disease

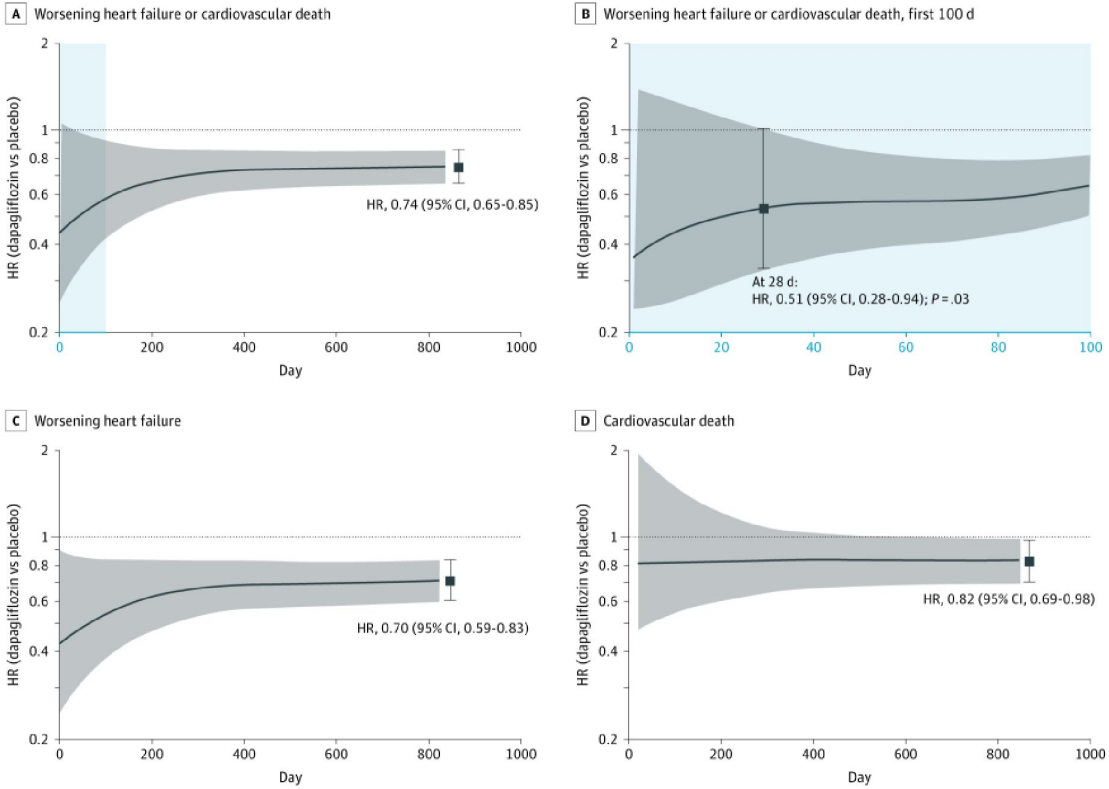


Prespecified renal composite outcome was a composite of **≥50%** sustained decline eGFR or end-stage renal disease **or renal death**

Zannad et al Circulation 2021
Jhund et al Circulation 2021

Strategie di utilizzo delle gliflozine: perché? **quando?** come? a chi?

Setting: out-patients with HFrEF



JAMA Cardiology | Original Investigation

Time to Clinical Benefit of Dapagliflozin and Significance of Prior Heart Failure Hospitalization in Patients With Heart Failure With Reduced Ejection Fraction

The earlier, the better !!!

Berg D et al. JAMA Cardiol. 2021

Substantial benefit in patients at higher risk

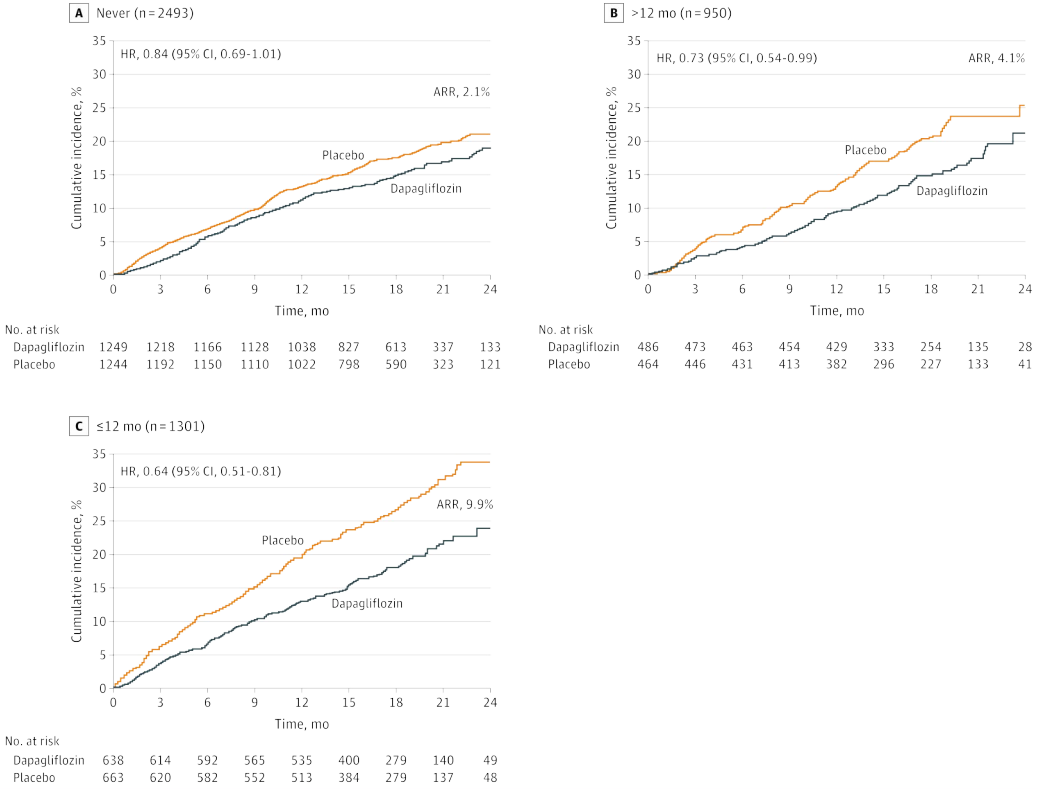
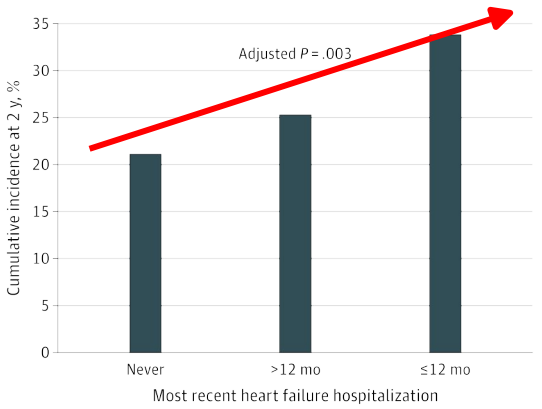


Figure 2. Cumulative Incidence of Cardiovascular Death or Worsening Heart Failure Event at 2 Years by Timing of Most Recent Heart Failure Hospitalization Relative to Trial Enrollment



Berg D et al. JAMA Cardiol. 2021

SOLOIST-WHF

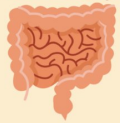
All T2DM. Hospitalized for HF (or within 3 days of discharge) or urgent HF visit. Not required to have reduced LVEF (stratified by LVEF <50%/≥50%) – but 75% patients LVEF <50%. Elevated BNP/NT-proBNP. Median FU 9 mo.

SOTAGLIFLOZIN

inhibits

SGLT-2 ▼ increases urinary glucose excretion

SGLT-1 ▼ delays intestinal glucose absorption



QUESTION

In patients with diabetes and recently worsening HF, does SOTAGLIFLOZIN:
↓ CV mortality?
↓ HF urgent visits?
↓ HF hospitalizations?

INCLUSION

18 - 85 yo patients with diabetes hospitalized for signs or symptoms of HF and treatment with IV diuretics

1222 patients ▼

	PRIMARY OUTCOME	SECONDARY OUTCOMES	
TOTAL NO. OF EVENTS (RATE PER 100 PATIENT YEARS)	HF urgent visits HF hospitalizations CV Death	HF urgent visits HF hospitalizations	CV Death
Sotagliflozin n=608	245 (51)	194 (40)	51 (11)
	HR 0.67 95% CI 0.52-0.85 p<0.001	HR 0.64 95% CI 0.49-0.83 p<0.001	HR 0.84 95% CI 0.58-1.22 p=0.36
Placebo n=614	355 (76)	297 (64)	58 (13)

CONCLUSION

In patients with diabetes with worsening HF, sotagliflozin significantly decreased CV deaths, HF urgent visits, and HF hospitalizations

Bhatt DL et al. NEJM , 2021

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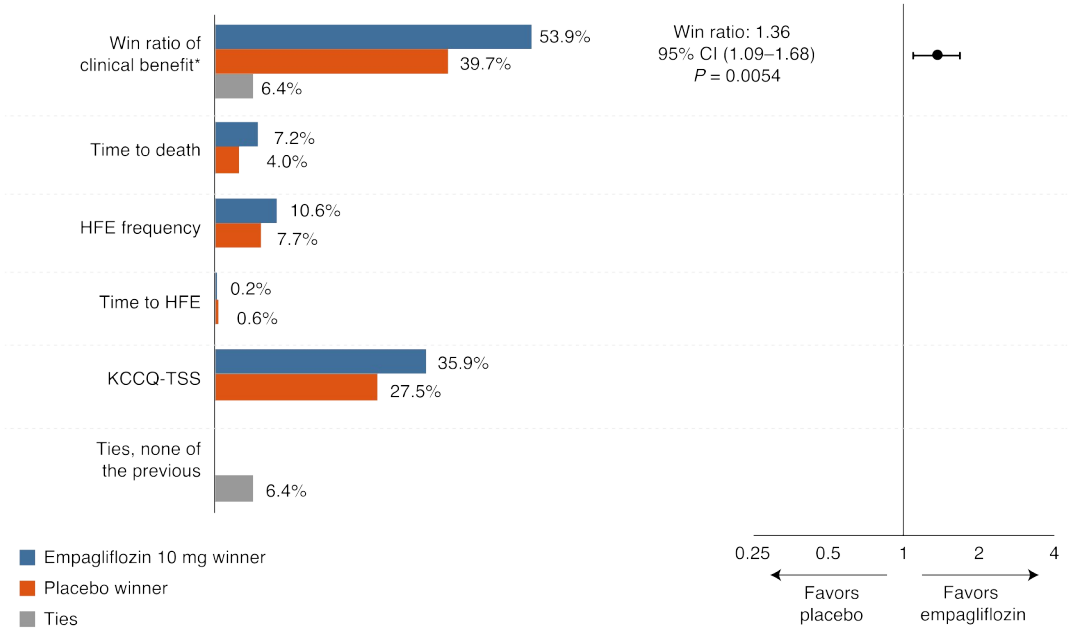
EMPULSE

Empagliflozin in patients hospitalized for acute heart failure

EMPULSE[1]

- 530 patients with of acute de novo or decompensated HF (rEF 67%; pEF 33%) randomized to empagliflozin 10 mg OD or placebo
- median time from hospital admission to randomization, 3 days
- primary outcome: clinical benefit (composite of death any cause, heart failure events and time to first heart failure event, or ≥5 point change in KCCQ) at 90 days FU, as assessed using a win ratio



Voors A. et al. Nature Medicine, March 2022

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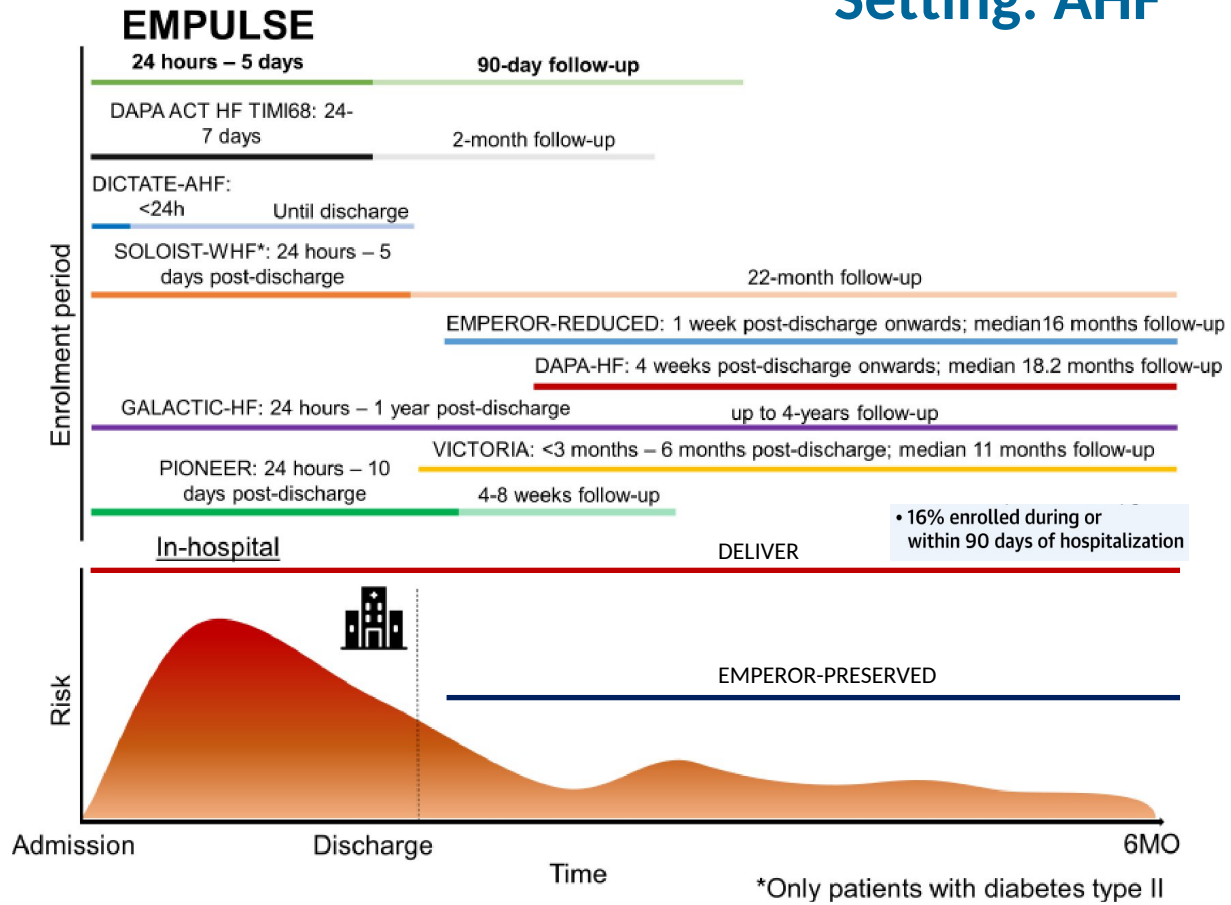
Setting: AHF



Modified from: Tromp et al. EJHF 2021

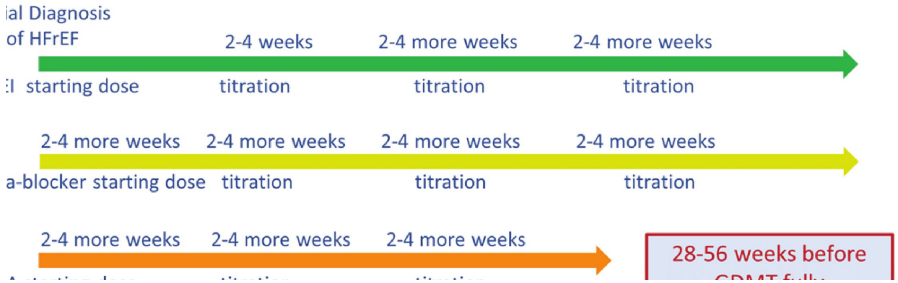
Strategie di utilizzo delle gliflozine: perché? quando? **come?** a chi?

Foundational therapy[1,2]

ARNI/ACEi*	Beta blocker	MRA	SGLT2 inhibitor

- **Initiation** and **titration** of medications should be adapted and **optimized to meet the patient's individual need**[1,2]
- If **initiated simultaneously, low starting doses** are recommended[1]
- If **initiated sequentially, no need to achieve target doses** before initiating next medication[1]

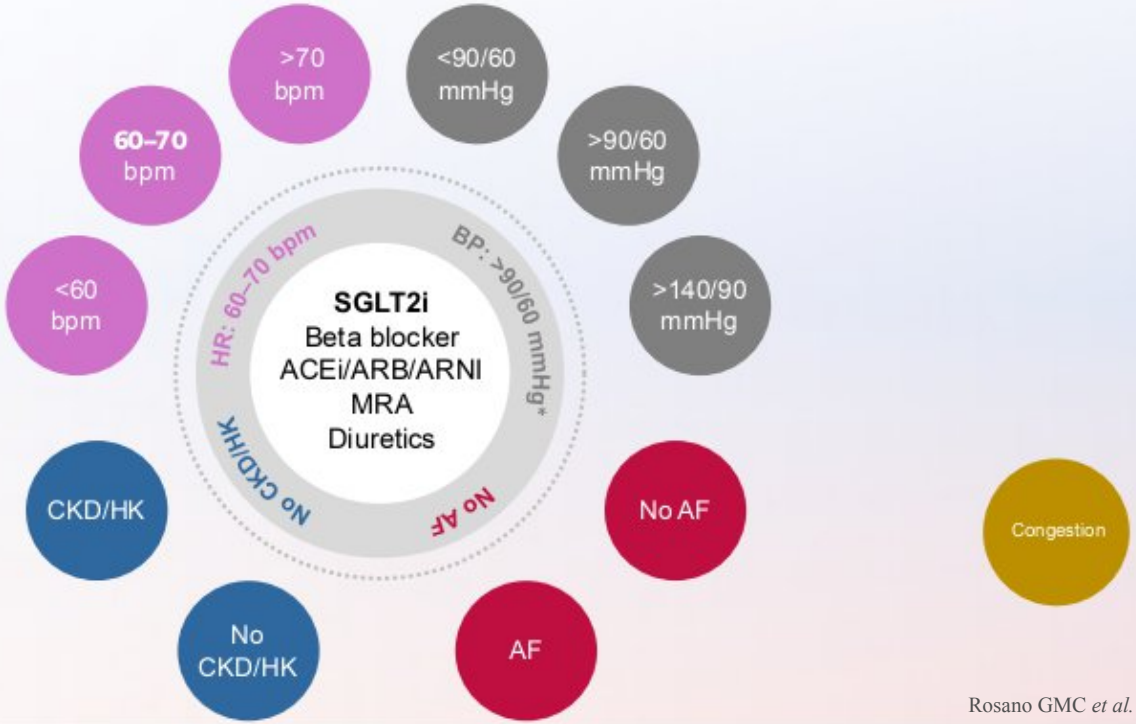
Traditional Serial Strategy



Anker S. ESC meeting, Barcelona, August 2022
Khan MS et al. EJHF (2021) 23, 1514–1517

The HFA-ESC consensus document highlights key characteristics that should be considered in the management of HFrEF

The HFA-ESC consensus document recommends **maintaining SGLT2i** across all phenotypes listed



*In patients with predominant chronic coronary syndrome, blood pressure threshold is 120/80 mmHg.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, **angiotensin receptor–neprilysin inhibitor; BP, blood pressure;** bpm, beats per minute; CKD, chronic kidney disease; HFA-ESC, Heart Failure Association of the European Society of Cardiology; HFrEF, heart failure with reduced ejection fraction; HK, hyperkalaemia; HR, heart rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

Rosano GMC *et al. EJHF*. 2021

When and how to initiate SGLT2 inhibitors?

Based on EMPULSE trial

- No increase in diuretic dose in prior 6 hours
- No intravenous vasodilators or inotropic agents in prior 24 hours
- Systolic blood pressure ≥ 100 mmHg
- eGFR ≥ 20 mL/min/1.73 m^2

Based on DAPA-HF and EMPEROR-Reduced trials

- Symptomatic HFrEF regardless of background therapy
- Systolic blood pressure > 100 mmHg (empaglifozin) or ≥95 mmHg (dapaglifozin)
- eGFR ≥20 mL/min/1.73 (empagliflozin) or ≥25 mL/min/1.73 (dapagliflozin)

Contraindications:

- Type 1 diabetes
- DKA history
- eGFR <20-25 ml/min
- Volume depletion/hypotension
- Pregnancy and lactation

Which drug? Dapagliflozin 10 mg daily or Empagliflozin 10 mg daily

Advices. Monitor renal function at 1-2 weeks if low eGFR at baseline although initial 10-15% declines are common/expected, do not reflect acute kidney injury and therapy should be continued unless major fall in eGFR. Prevention of genital tract infection or mycosis.

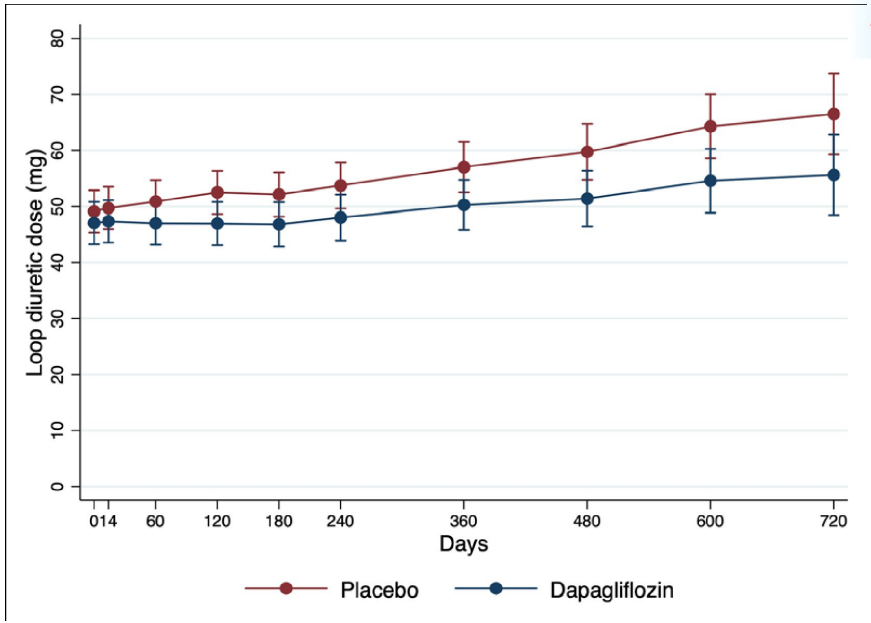
Follow-up: Encourage adherence to guideline-recommended therapies. Adjust diuretic therapy based on volume status.

Tomasoni D et al. EJHF 2022

PLACE 9ª Edizione

ORIGINAL RESEARCH ARTICLE

Dapagliflozin and Diuretic Use in Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF



	No Diuretic (n=736)		Furosemide-Equivalent Dose			
			<40 mg* (n=1311)		40 mg (n=1365)	
	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin
Safety						
Discontinuation because of adverse event, n (%)	19 (5.2)	12 (3.3)	25 (3.9)	26 (3.9)	20 (3.0)	29 (4.2)
Volume depletion, n (%)	31 (8.5)	16 (4.3)	34 (5.3)	37 (5.5)	33 (4.9)	55 (8.0)
Renal adverse event, n (%)	21 (5.8)	8 (2.2)	31 (4.8)	27 (4.0)	46 (6.8)	44 (6.4)

Jackson AM et al. Circulation. 2020 Sep 15

Counselling for patients on SGLT2i

TOP TIPS!

- Educate patients on bioparameters to regularly monitor: blood pressure, body weight, blood glucose if gliflozin is used in association with anti-diabetic drugs.
- Educate patients on appropriate personal hygiene: keeping the genital region clean and dry.
- Advise patients about the need to withhold gliflozin in case of prolonged fasting, 2-3 days before and on the day of the elective surgery that requires fasting (sick-day rule).
- Advise patients about the need to avoid low carbohydrate diets and excessive alcohol consumption
- Inform patients about the symptoms of volume depletion: weakness, orthostatic hypotension, weight decrease >1 kg over 24 h or >2 kg in 1 week.
- Inform patients about symptoms and signs of uro-genital infections: pain or burning on urination; redness, swelling, or itching in the genital area; nasty-smelling vaginal or penile secretion
- Inform patients about symptoms of diabetic ketoacidosis: excessive thirst, sweet-smelling breath, a change in urine or sweat odour, nausea, vomiting, abdominal pain, confusion, weakness, and fever.

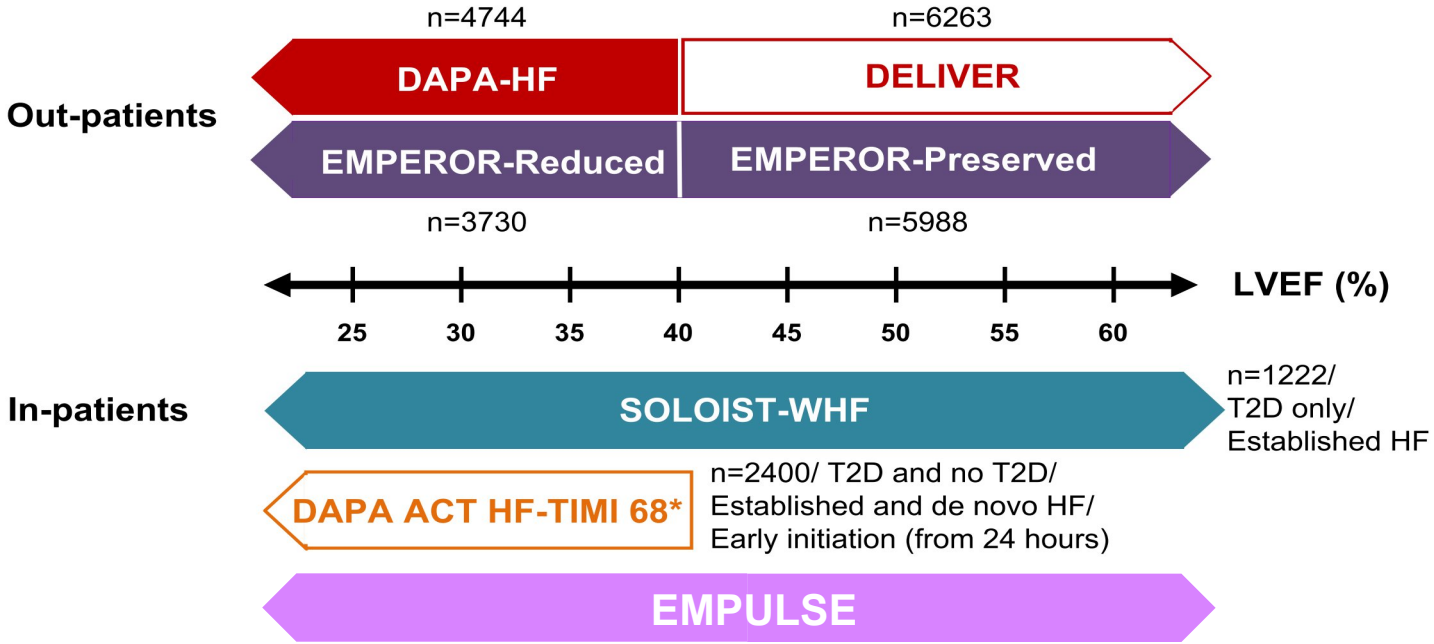
Communicate with GPs

- No panic if mild reduction in eGFR
- No panic if high glucose in the urine sample

Strategie di utilizzo delle gliflozine:

perché? quando? come? **a chi?**

The totality of evidence supports prioritizing the use of SGLT2 inhibitors in all patients with heart failure, irrespective of patient phenotype or care setting



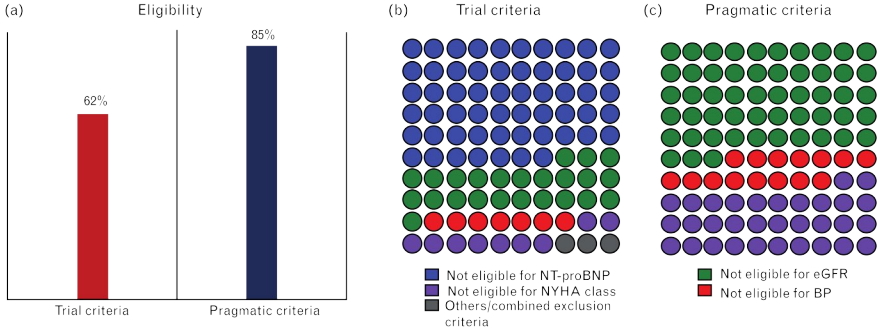
PLACE 9ª Edizione

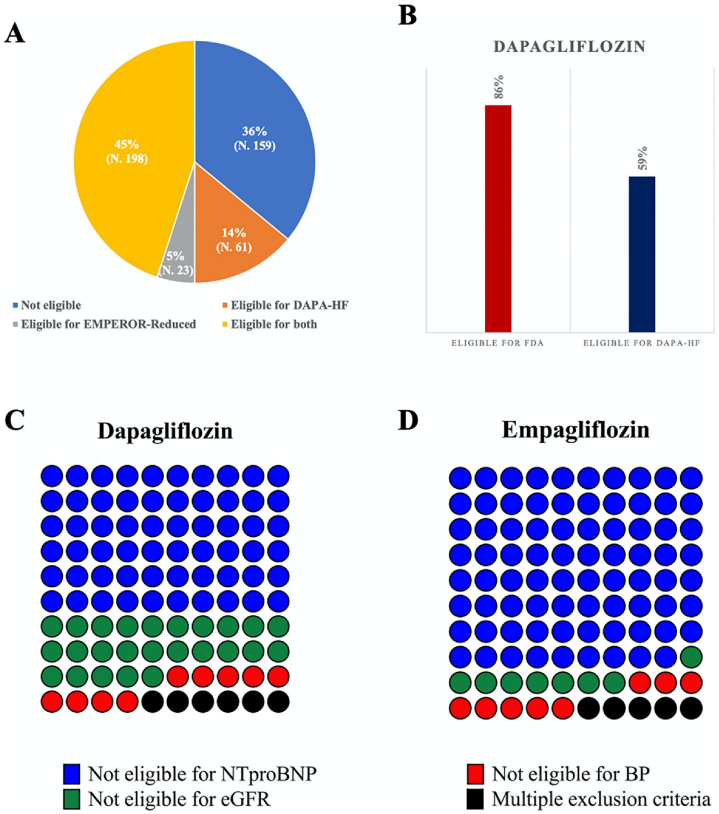
Sodium–glucose co-transporter-2 inhibitors eligibility in patients with heart failure with reduced ejection fraction☆

Luca Monzo [a,b,*], Ilaria Ferrari [b], Francesco Cicogna [a], Claudia Tota [a], Leonardo Calò [a]

What proportion of patients with heart failure and preserved ejection fraction are eligible for empagliflozin?

Luca Monzo[a,b], Ilaria Ferrari[b], Francesco Cicogna[a], Claudia Tota[a] and Leonardo Calò[a]



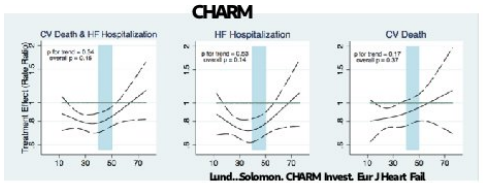


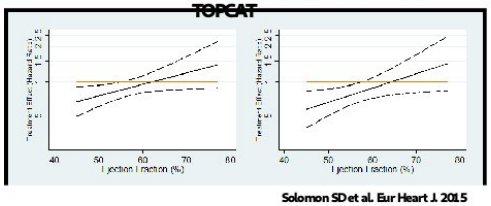
Monzo et al. J Cardiov Med, Aug 2022
Monzo et al. Int J Cardiol Aug 2021

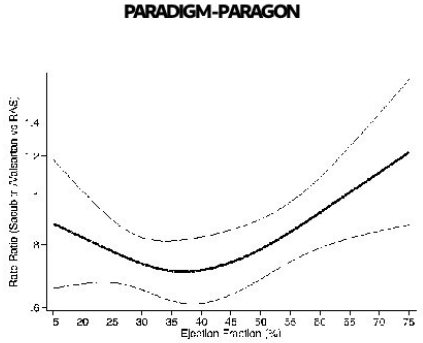
New data DELIVERed!!

EMPEROR-Preserved

	Empagliflozin	Placebo	HR (95% CI)	HR (95% CI)
	n with event/N analysed			
Baseline LVEF				
<50%	145/995	193/988		0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030		0.80 (0.64–0.99)
≥60%	132/974	145/973		0.87 (0.69–1.10)





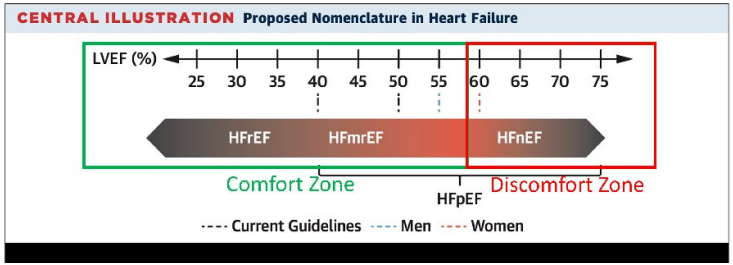


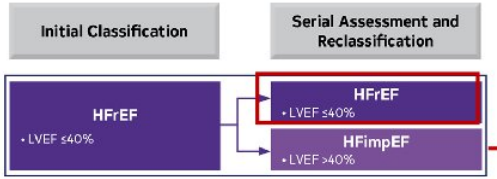
Solomon et al. Circulation 2019

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, B. Claggett, R.A. de Boer, D. DeMets, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, F. Martinez, S.J. Shah, A.S. Desai, P.S. Jhund, J. Belohlavek, C.-E. Chiang, C.J.W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J.C. Fang, M.A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J.W. Cabrera Honorio, S.P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J.F.K. Saraiva, S.N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V.N. Pham, U. Wilderäng, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, and A.M. Langkilde, for the DELIVER Trial Committees and Investigators*





Recognizing LVEF is dynamic, the AHA/ACC/HFSA 2022 Guidelines define HFimpEF as: "Previous LVEF ≤40% and a follow-up measurement of LVEF >40%"
(as defined in the DELIVER trial)

Solomon S et al N Engl J Med. 2022

New data DELIVERed!!

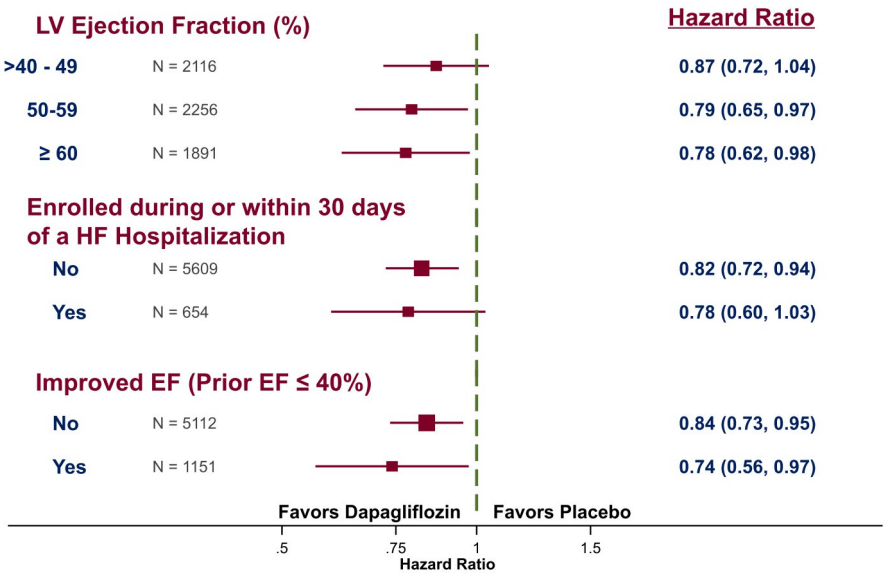
- **Clear signal of benefit across LVEF categories**
- **Efficacy in those with improved/recovered LVEF (previously <40%)**

HFimpEF
Dapagliflozin

HFrEF
Dapagliflozin
Empagliflozin

HFmrEF
Dapagliflozin
Empagliflozin

HFpEF
Dapagliflozin
Empagliflozin



Solomon S et al N Engl J Med. 2022