

# 10° CONGRESSO NAZIONALE



*Quello che le Linee  
Guida Non Dicono*

Napoli  
Hotel Excelsior  
14-15 aprile 2023

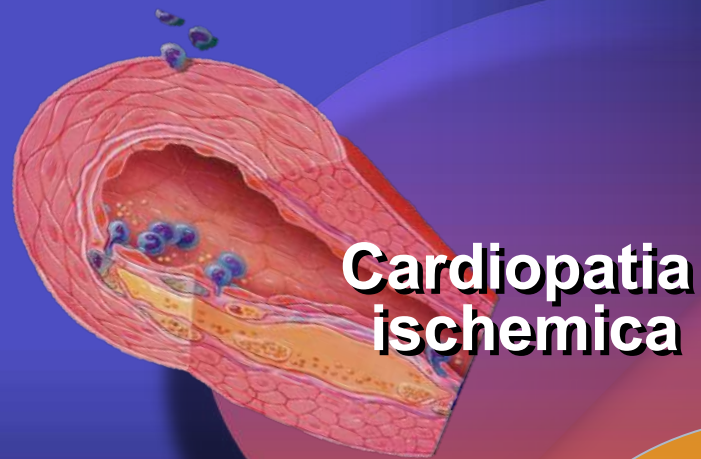
**SGLT2i nel trattamento del paziente con HFpEF**

Pierfranco Terrosu

## SGLT2i nel trattamento del paziente con HFpEF

- **Eterogeneità e fenotipi della HFpEF**
- **Studi clinici nella HFpEF**
- **Risultati in base alla Frazione di eiezione**

# Insufficienza cardiaca Frazione di eiezione preservata Fenotipi



**Malattia  
Cardio  
Metabolica**

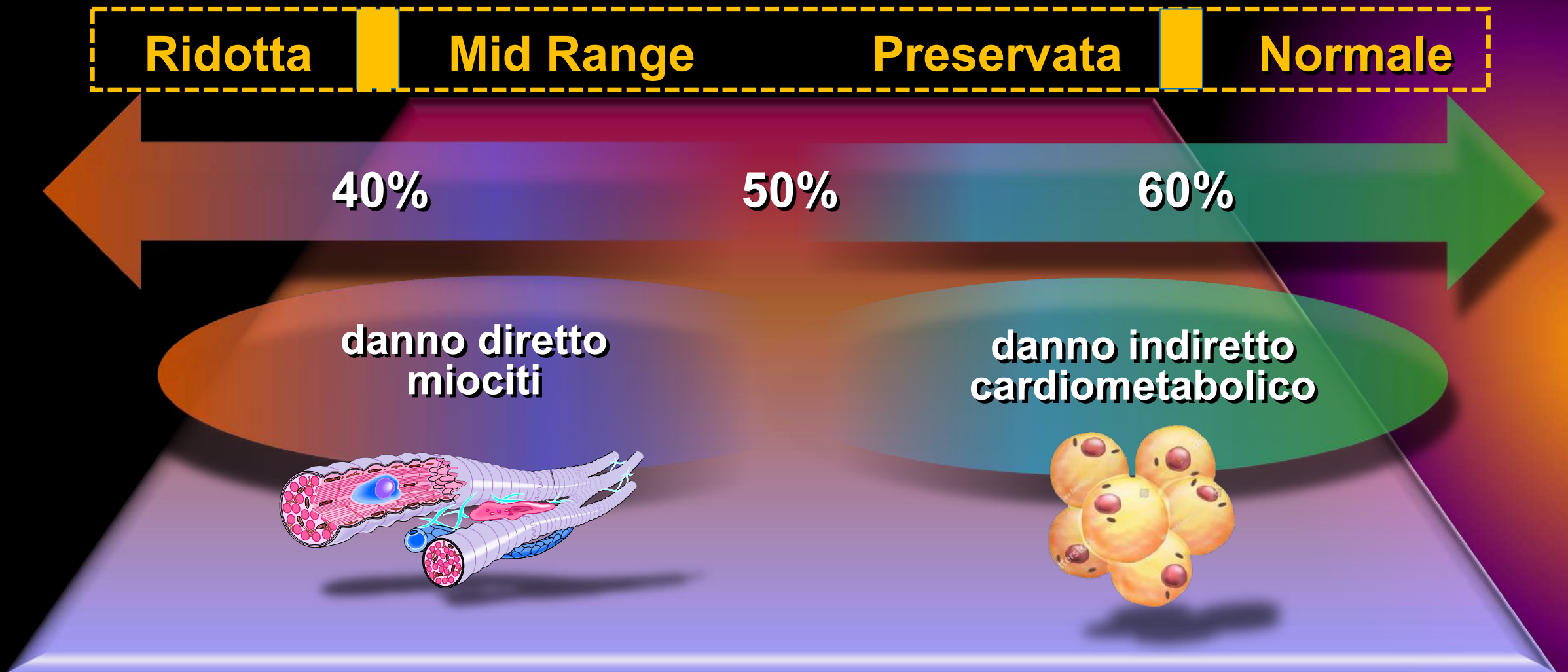


**Miopatia  
Atriale**

**Insufficienza  
renale**

# Insufficienza cardiaca cronica

## Frazione di eiezione





# FE Preservata

40%

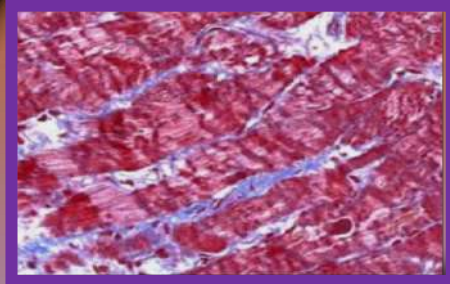
50%

60%

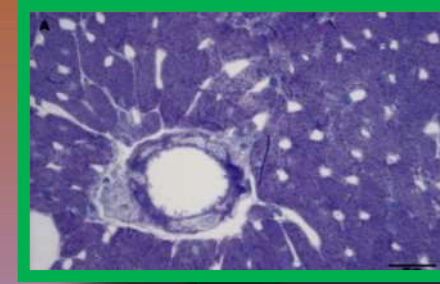
danno diretto  
miociti

danno indiretto  
cardiometabolico

fibrosi



ipertrofia



Rigidità  
interstiziale

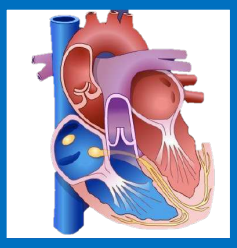
disfunzione  
diastolica

Rigidità  
sarcomeri

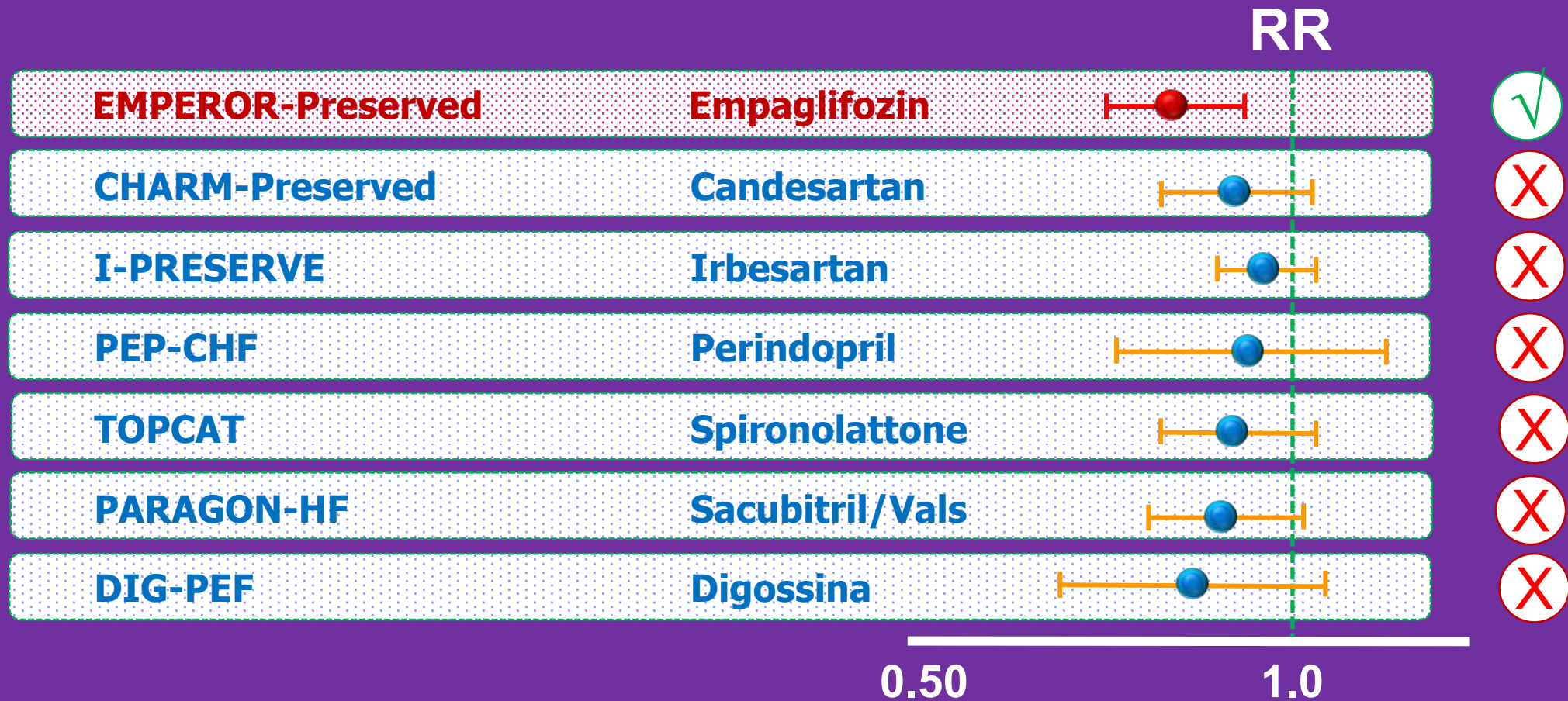


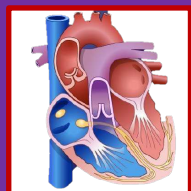
## SGLT2i nel trattamento del paziente con HFpEF

- **Eterogeneità e fenotipi della HFpEF**
- **Studi clinici nella HFpEF**
- **Risultati in base alla Frazione di eiezione**



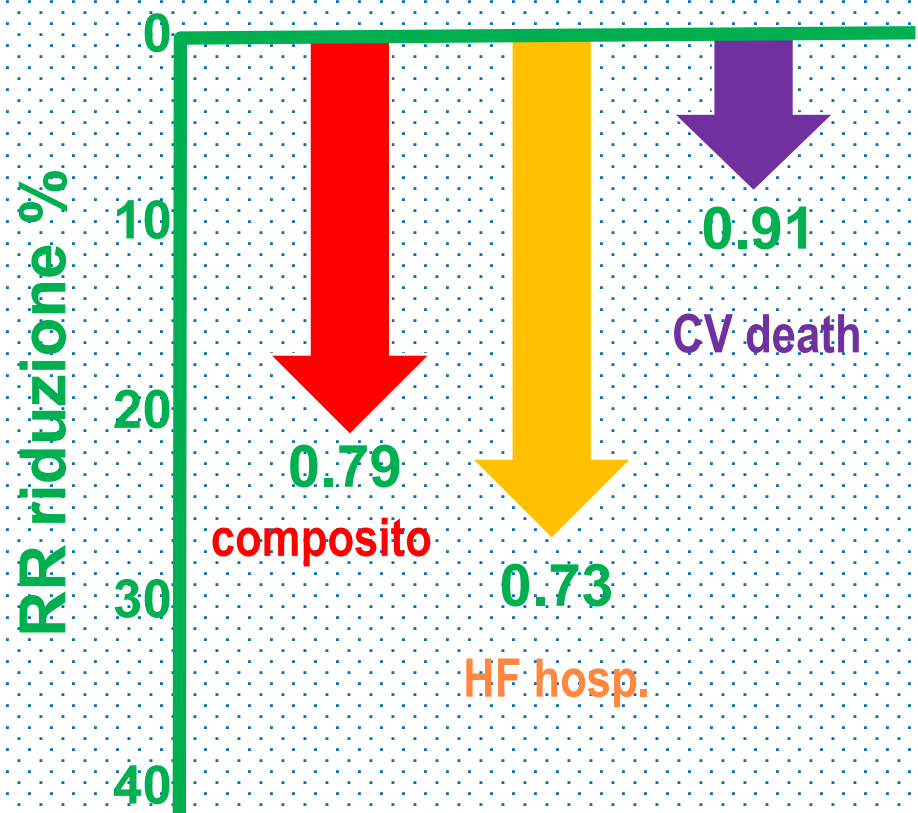
# Studi clinici nella insuff. Cardiaca a FE preservata



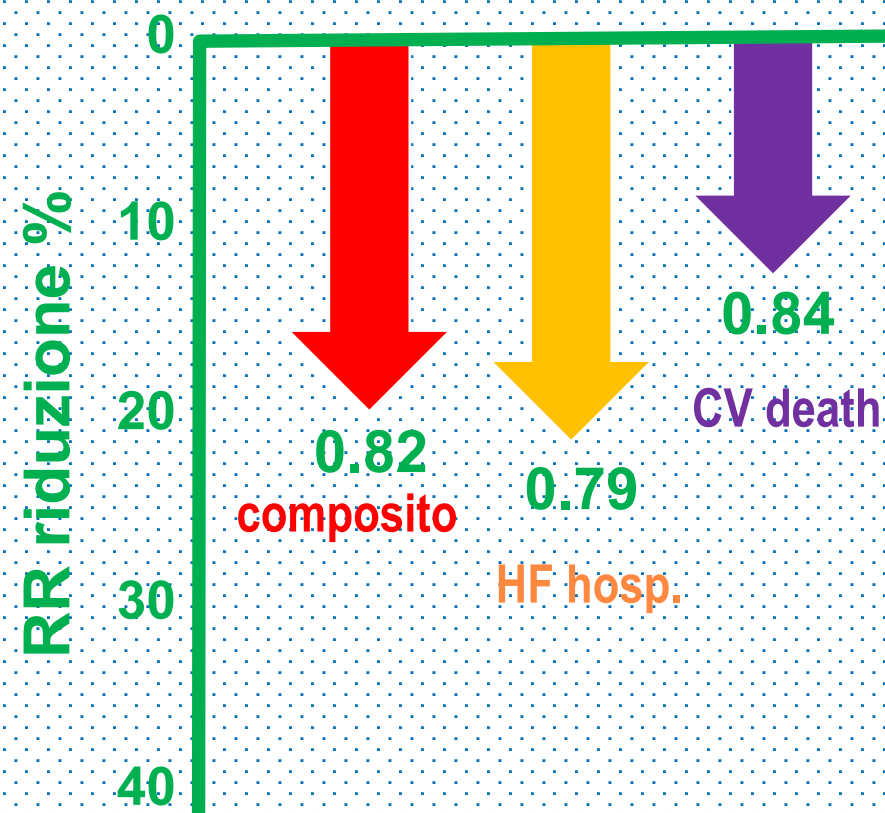


# Studi clinici nella insuff. Cardiaca a FE preservata

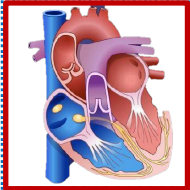
## EMPEROR-Preserved Empaglifozin



## DELIVER Dapaglifozin



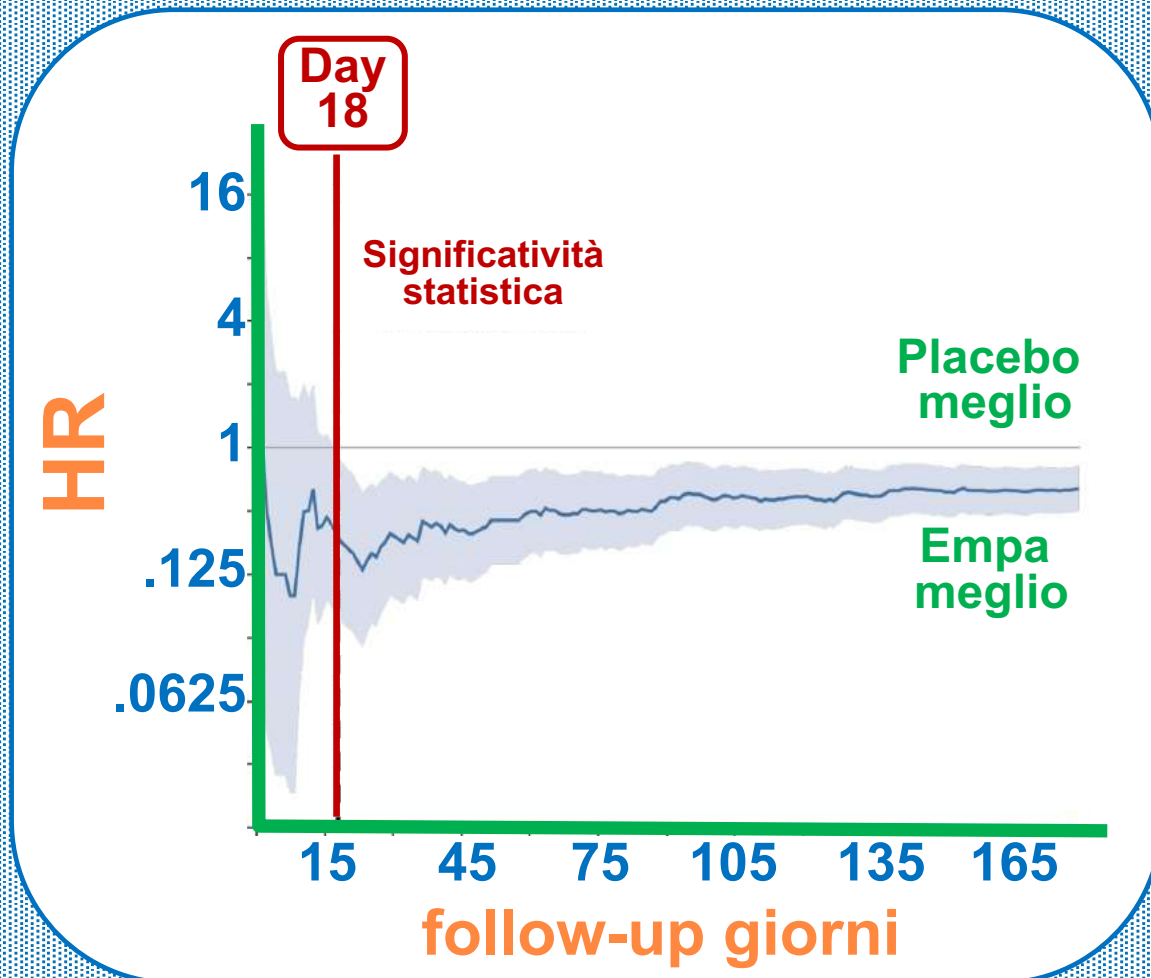




# Efficacia rapida e precoce delle glifozine

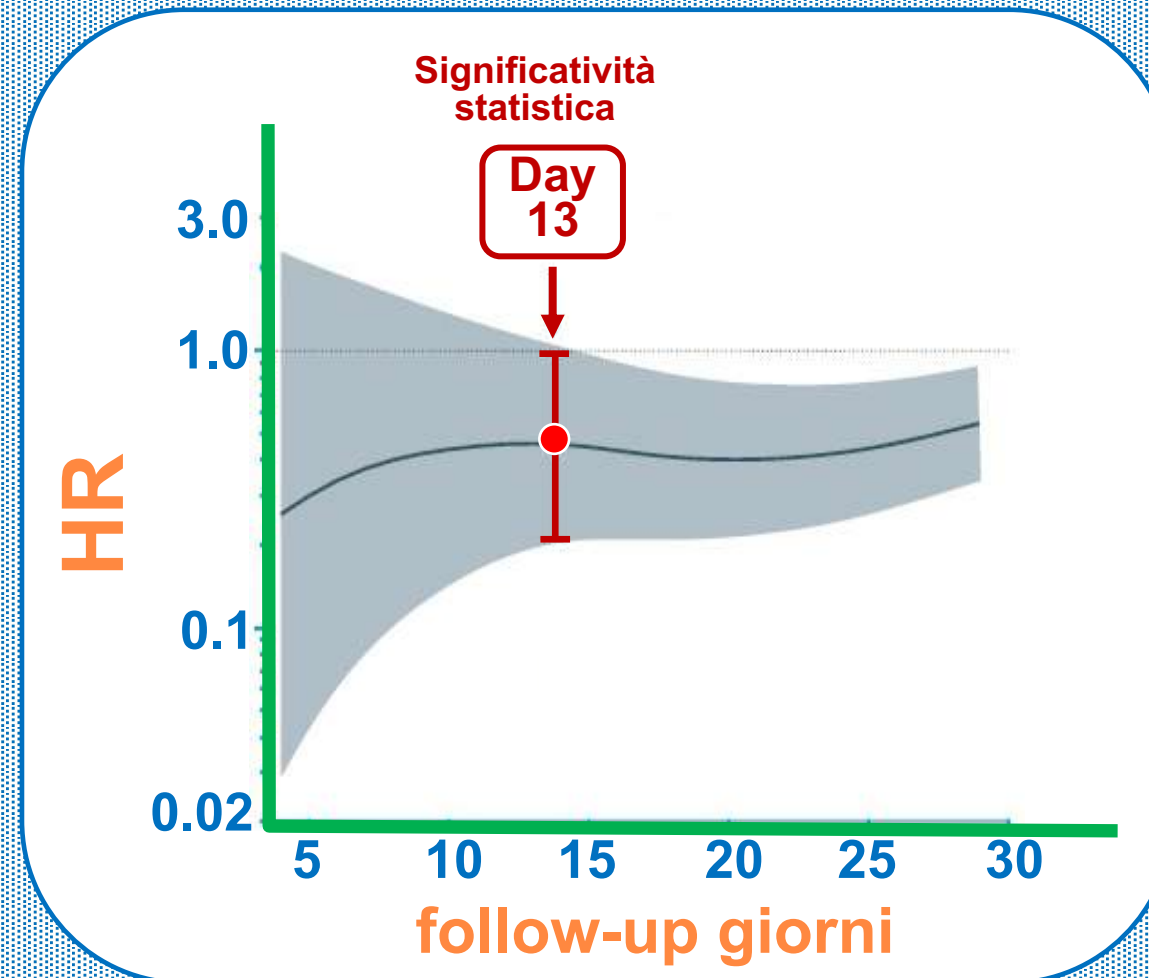
## EMPEROR-Reduced

Packer Circulation 2021

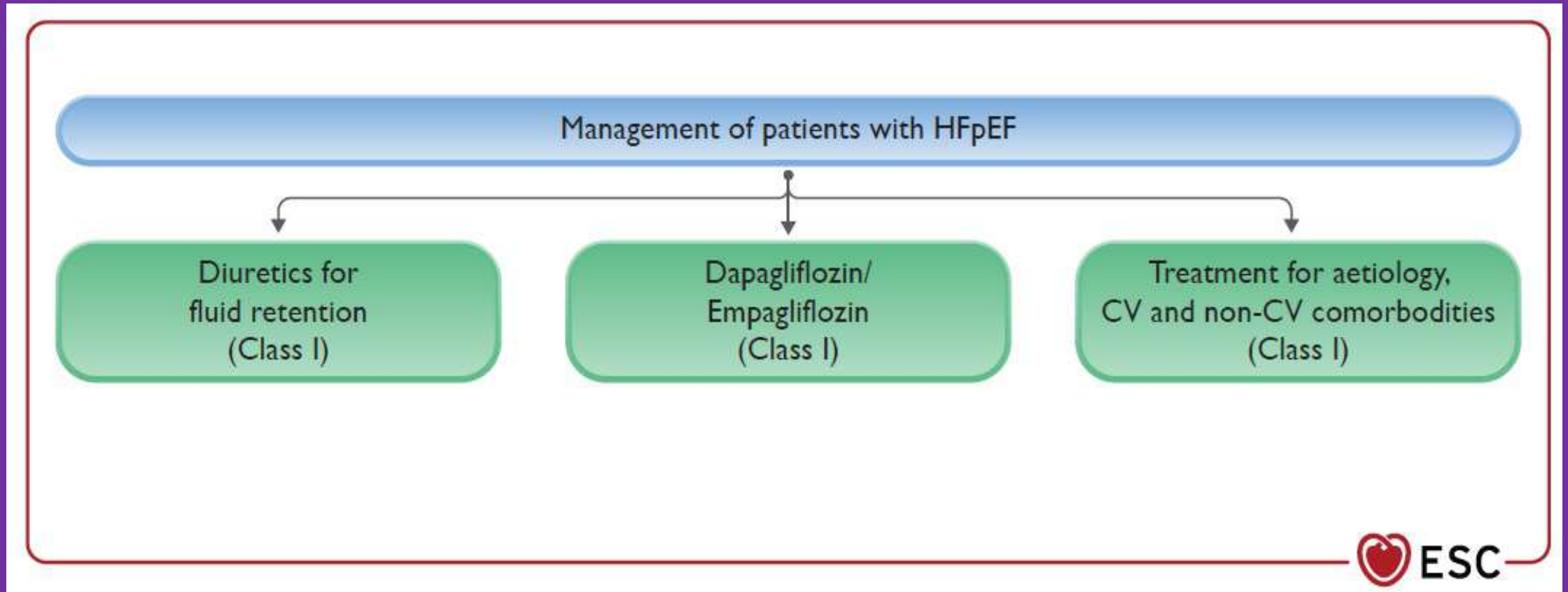


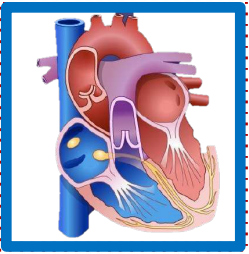
## DELIVER

Vaduganathan JAMA Cardiol 2022



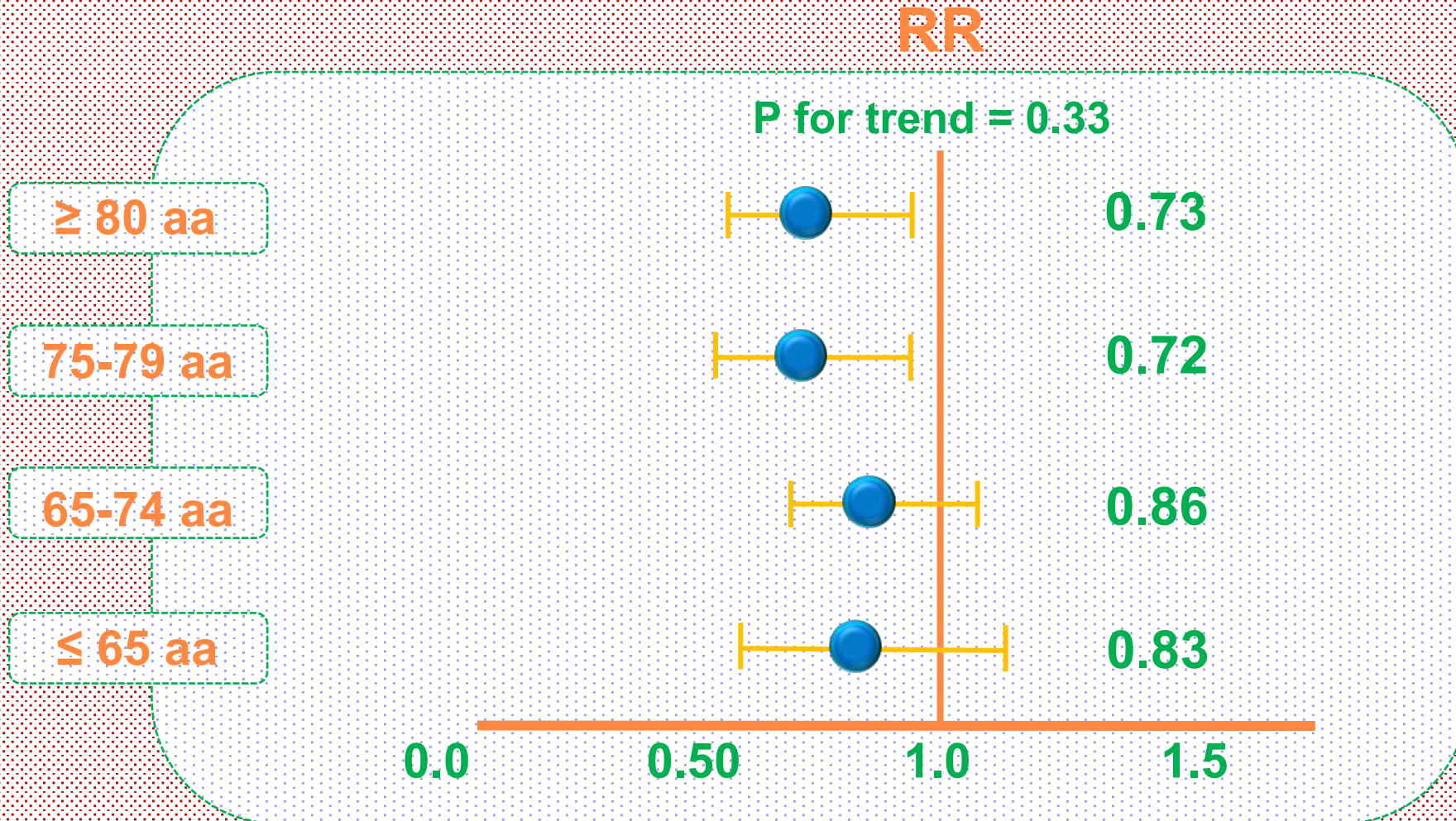
# Guidelines ESC 2023 Focused Update FE $\geq 50\%$

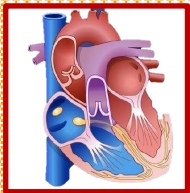




# Empagliflozin Improves Outcomes Irrespective of Age

(EMPEROR Preserved – Bohm JACC 2022)

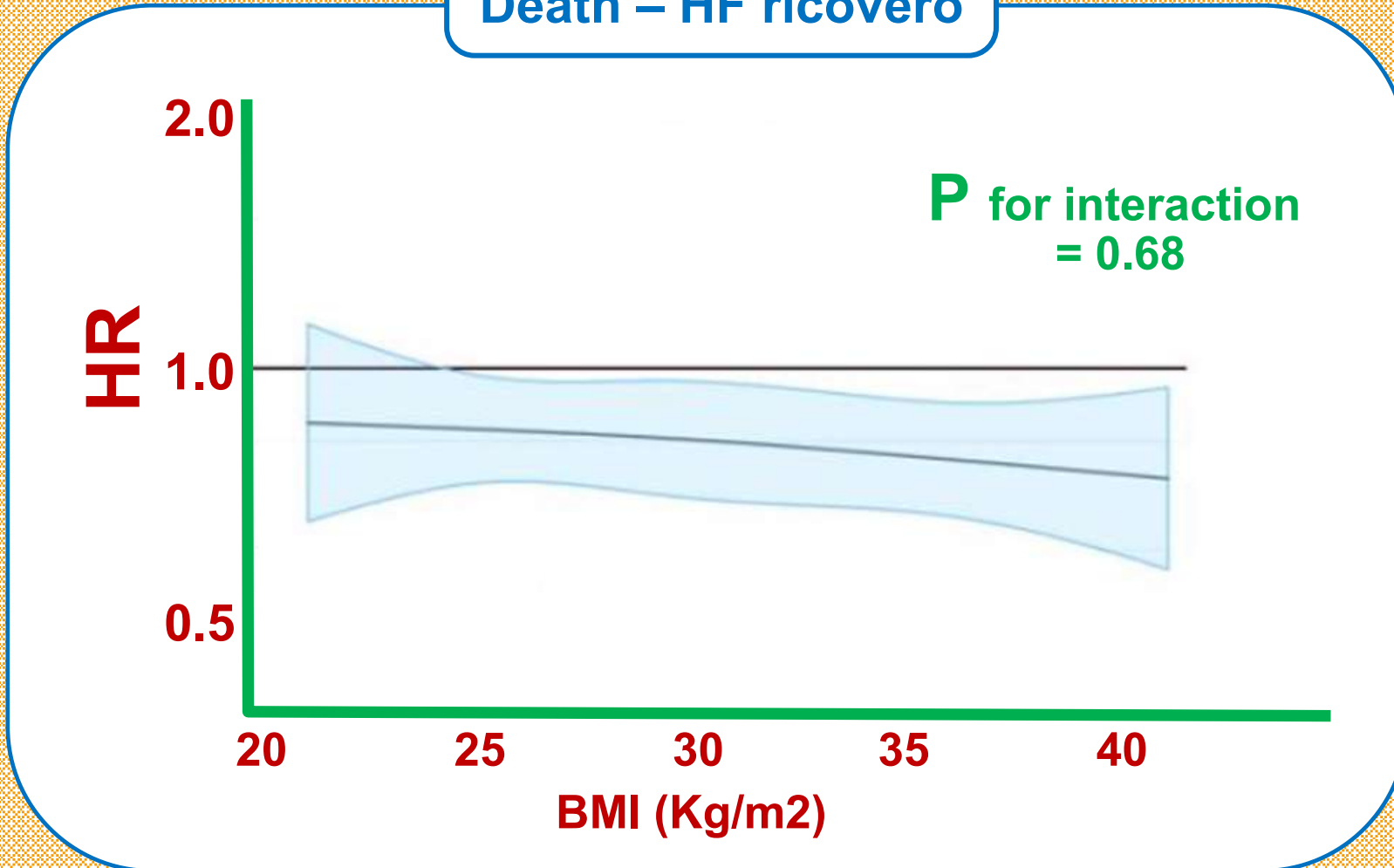


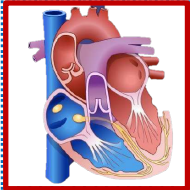


# Trial DELIVER sottoanalisi Dapaglifozin

(Adamson, Eur Heart J 2023)

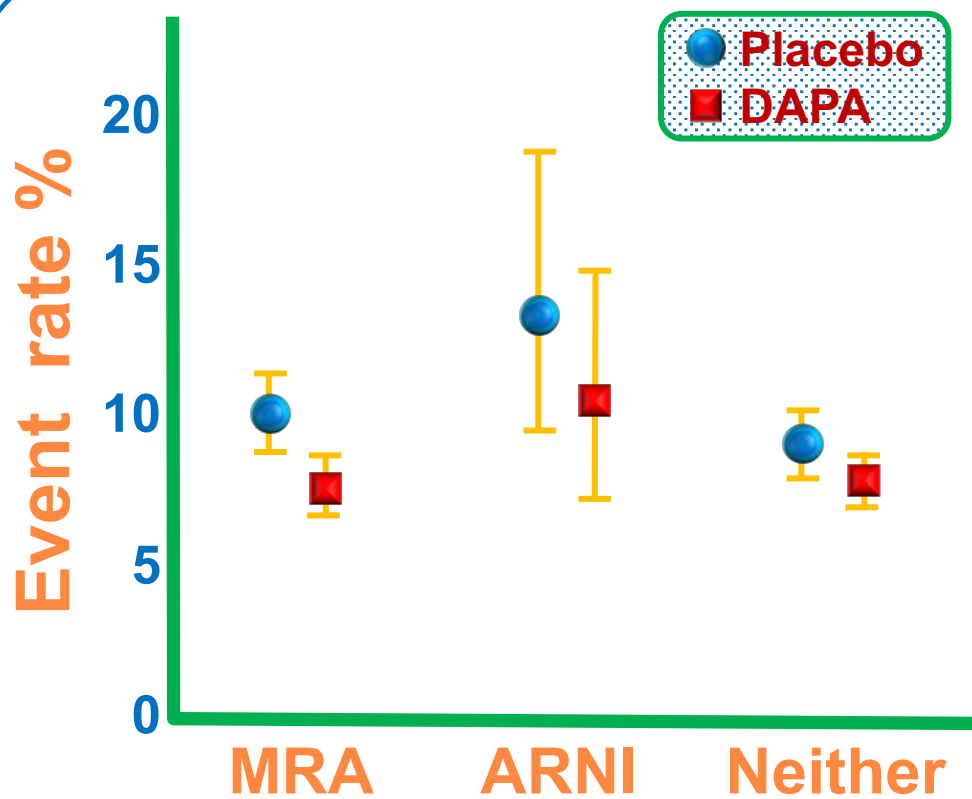
Death – HF ricovero



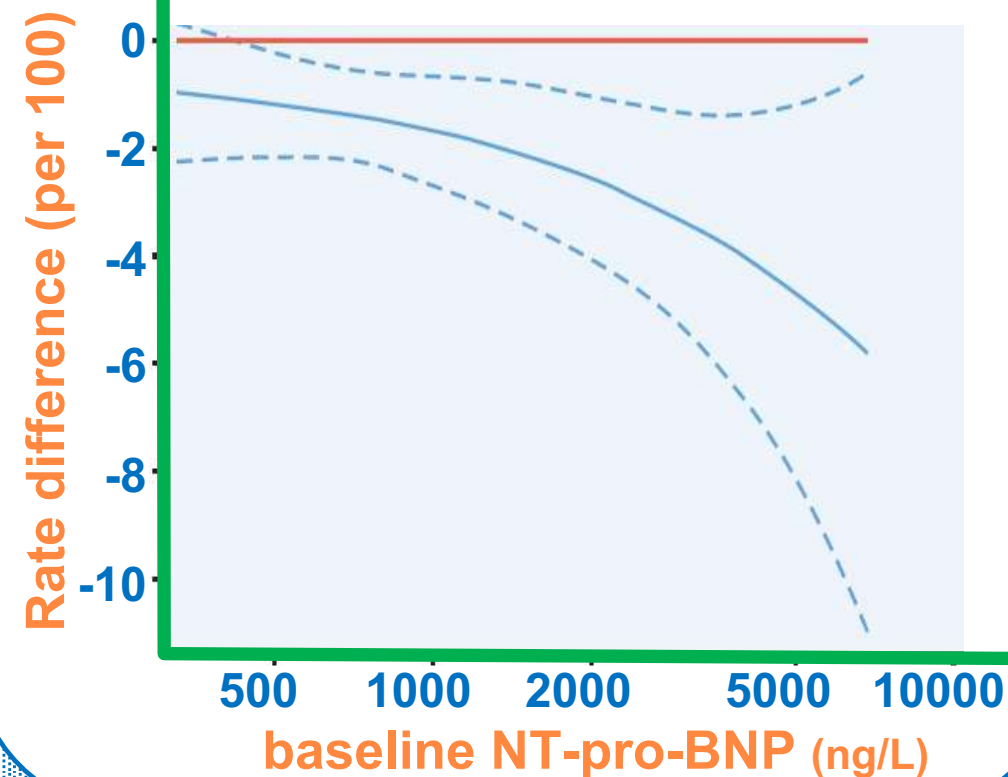


# Trial DELIVER sottoanalisi Dapaglifozin

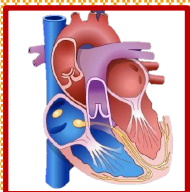
## CV death – Worsening HF Yang Eur J Heart Fail 2022



## Primary Endpoint Myhre JACC HF 2022



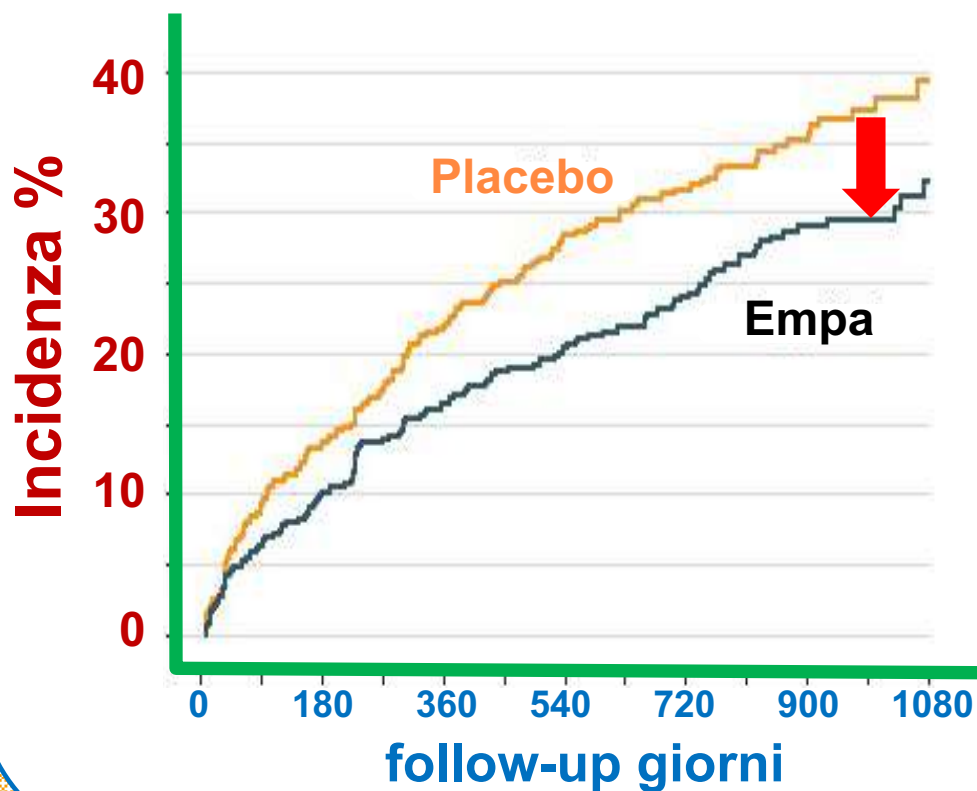




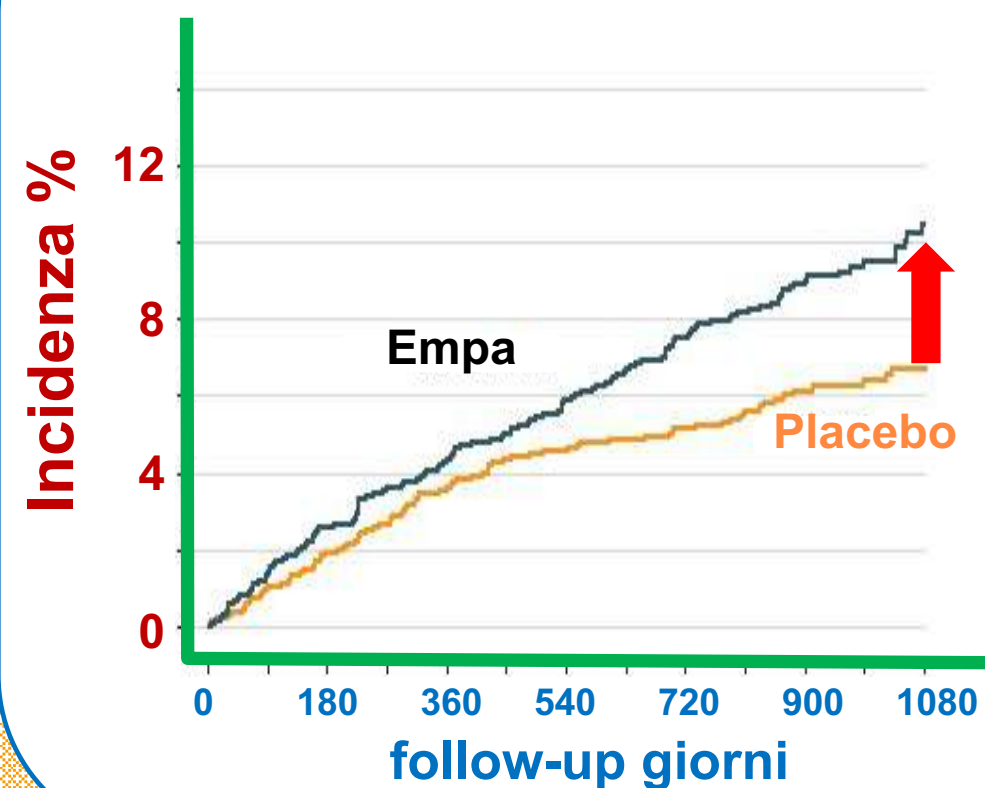
# Efficacia di Empaglifozin e uso dei diuretici

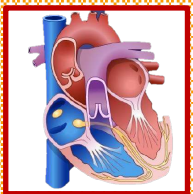
(Post Hoc Analysis EMPEROR Preserved - Butler, JAMA Cardiol 2023)

Inizio diuretici



sospensione diuretici

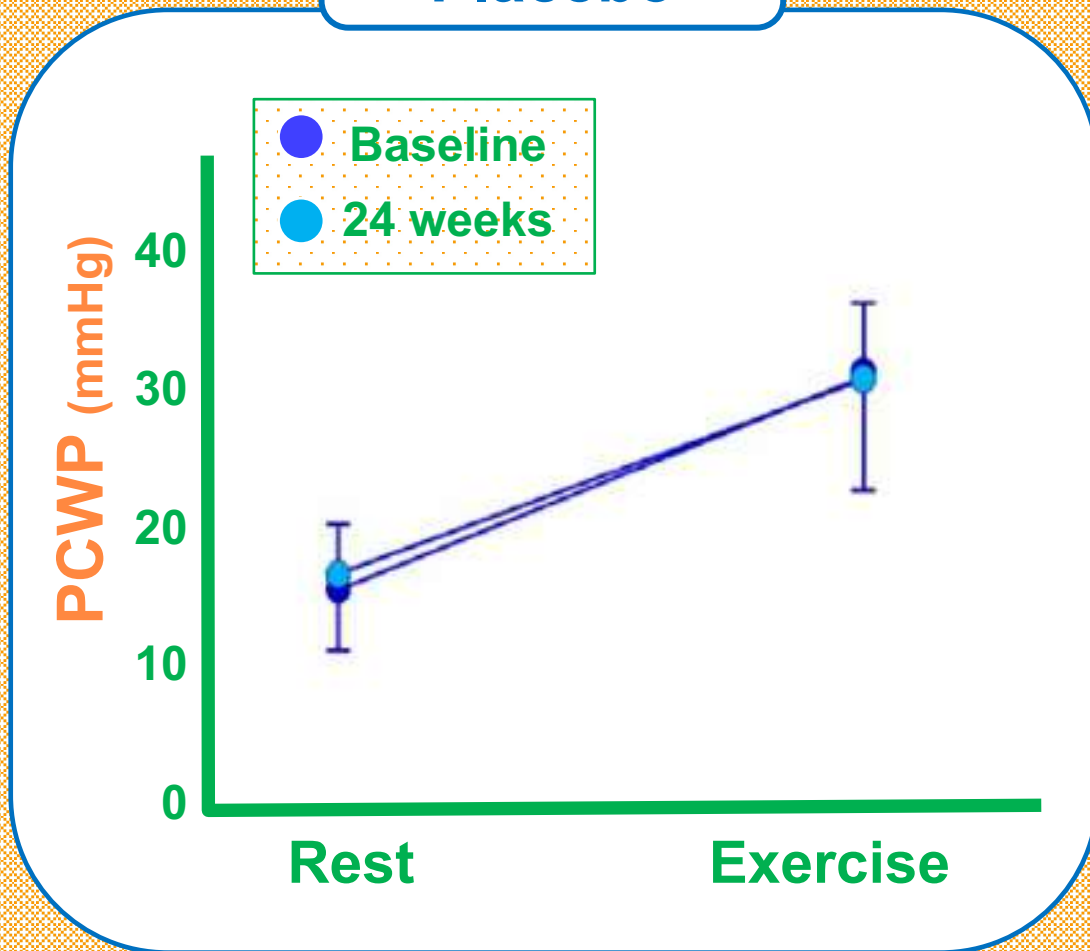




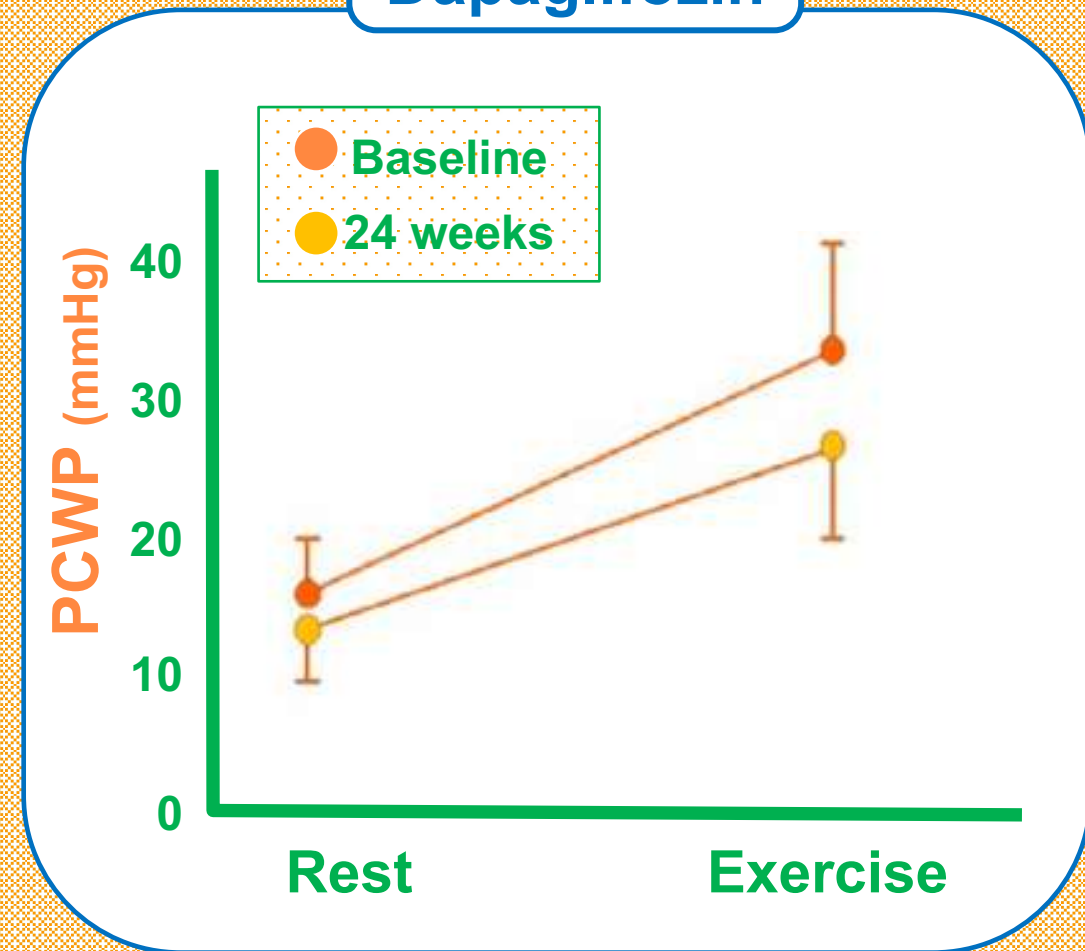
# Effetto emodinamico del Dapaglifozin

(Borlaug, Circulation 2023)

## Placebo

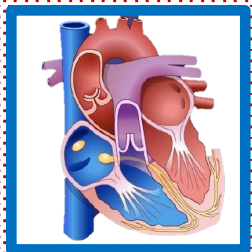


## Dapaglifozin



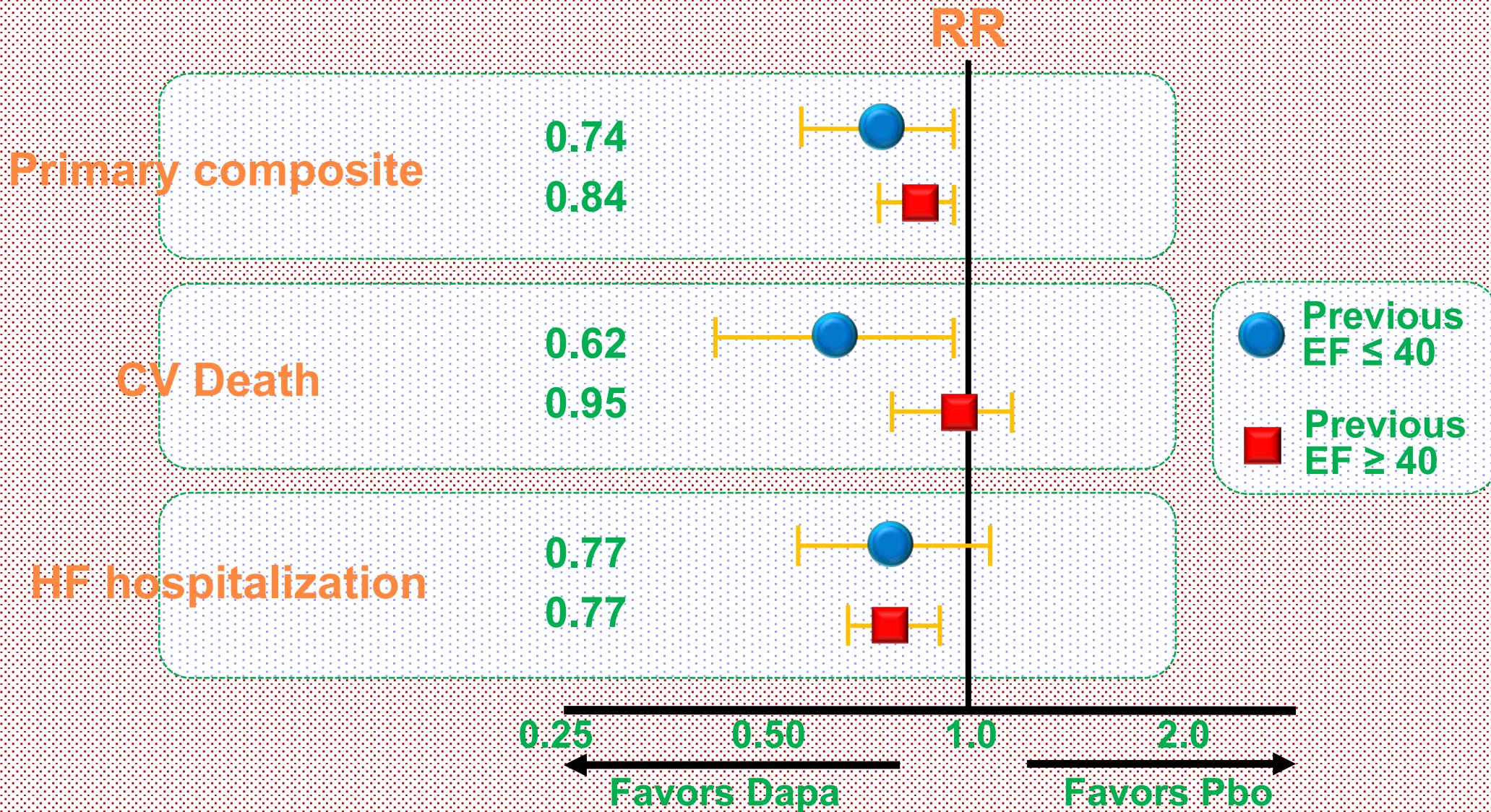
## **SGLT2i nel trattamento del paziente con HFpEF**

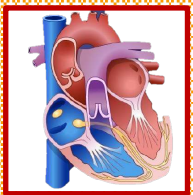
- **Eterogeneità e fenotipi della HFpEF**
- **Studi clinici nella HFpEF**
- **Risultati in base alla Frazione di eiezione**



# Dapagliflozin in heart failure with improved EF

(DELIVER Trial - Vardeny Nat Med 2022)

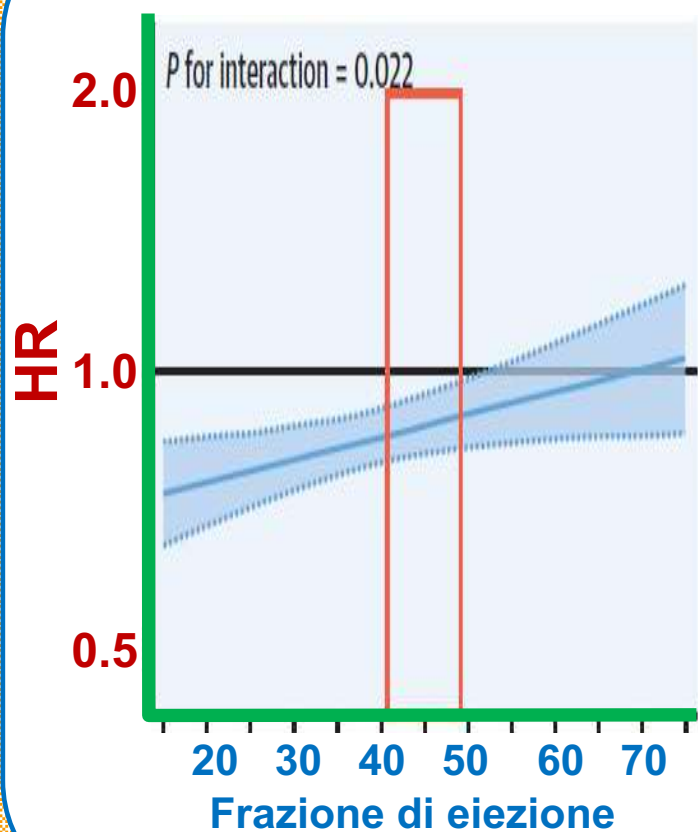




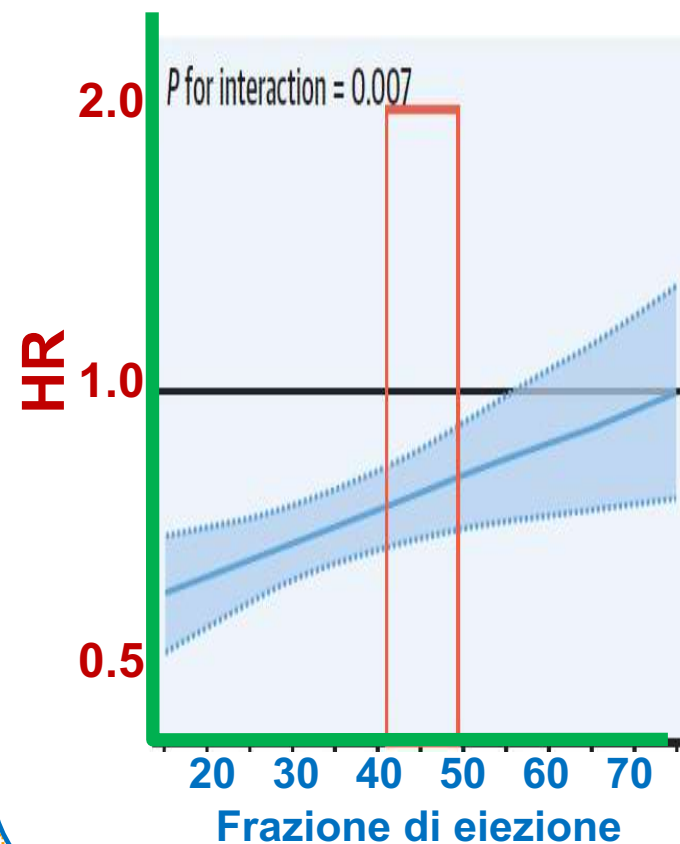
# Frazione di eiezione e terapie anti-scompenso

(Dimond, JACC HF 2024)

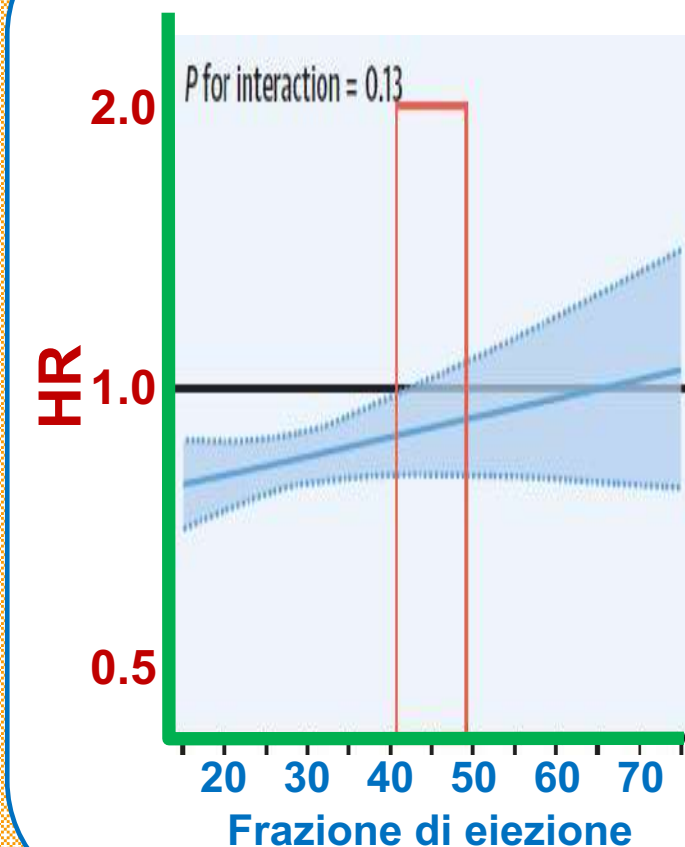
**ANRI**  
CV Death – HF hosp



**Anti-aldosteronici**  
CV Death – HF hosp



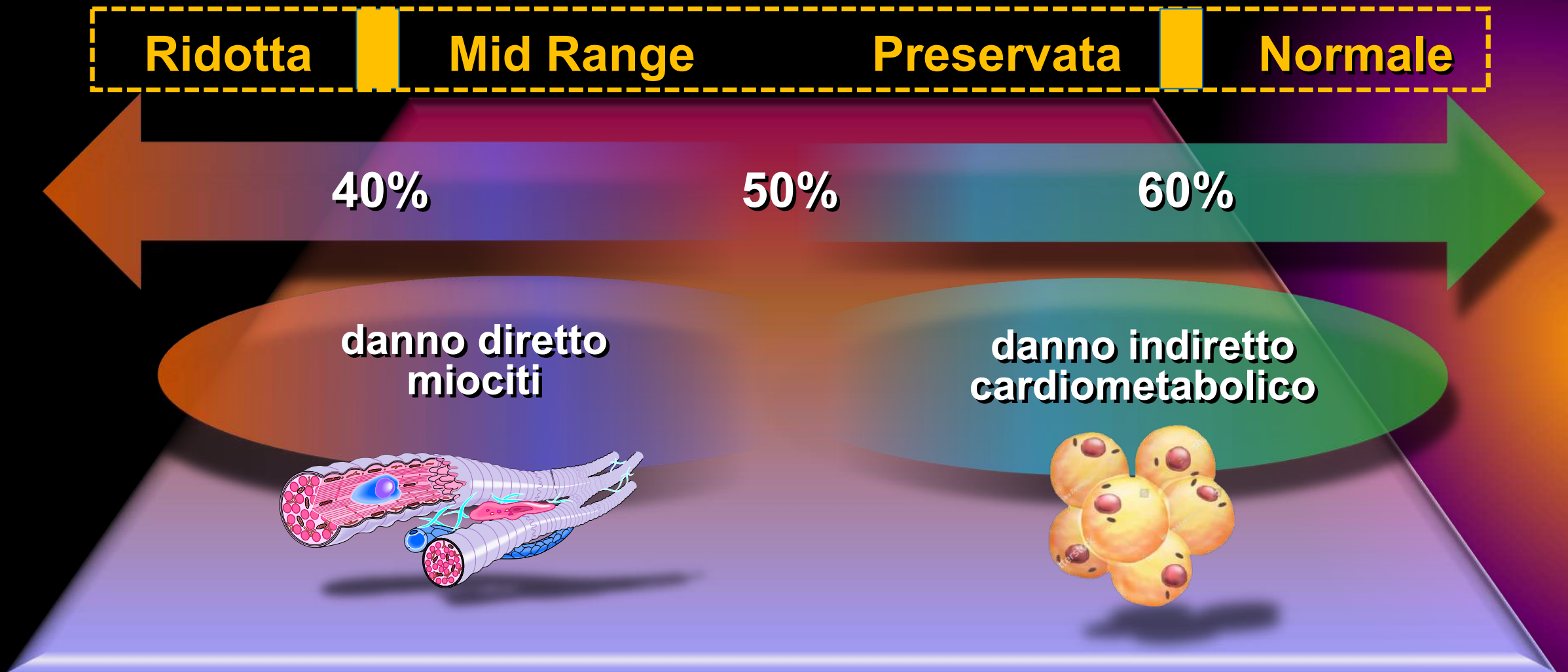
**Digitale**  
CV Death – HF hosp



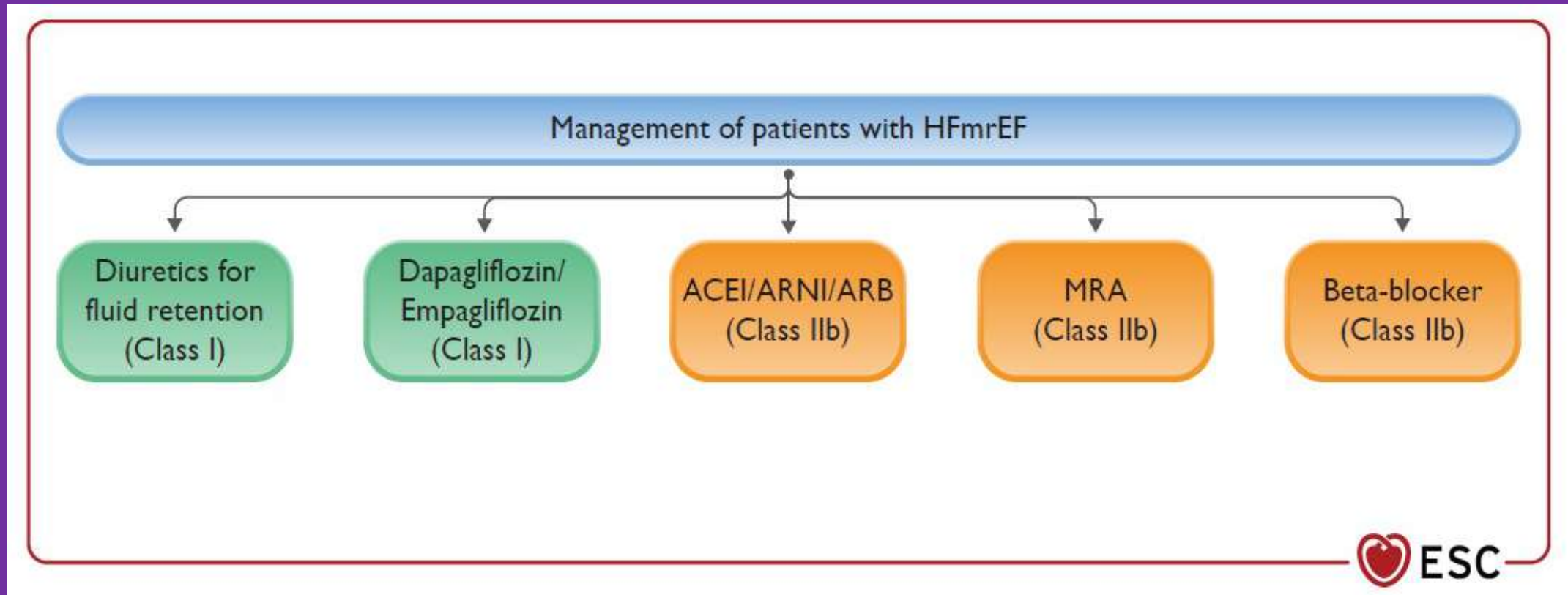


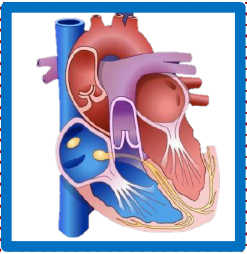
# Insufficienza cardiaca cronica

## Frazione di eiezione



# Guidelines ESC 2023 Focused Update FE 40-50 %



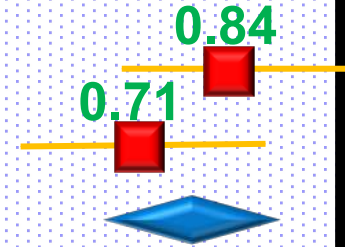


# Relazione tra glifozine e frazione di eiezione

(Kotit, Global Cardiol Sci Pract 2023)

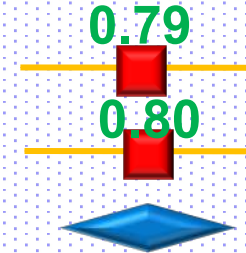
FE 41-49%

DELIVER  
EMPEROR-Preserved  
totale



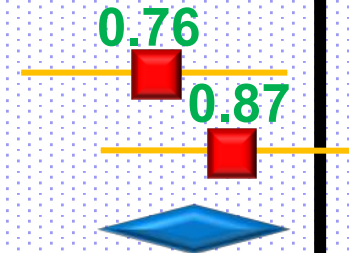
FE 50-59%

DELIVER  
EMPEROR-Preserved  
totale



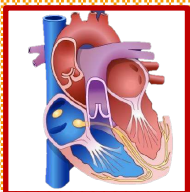
FE ≥ 60%

DELIVER  
EMPEROR-Preserved  
totale



0.50 0.75 1.0 1.25

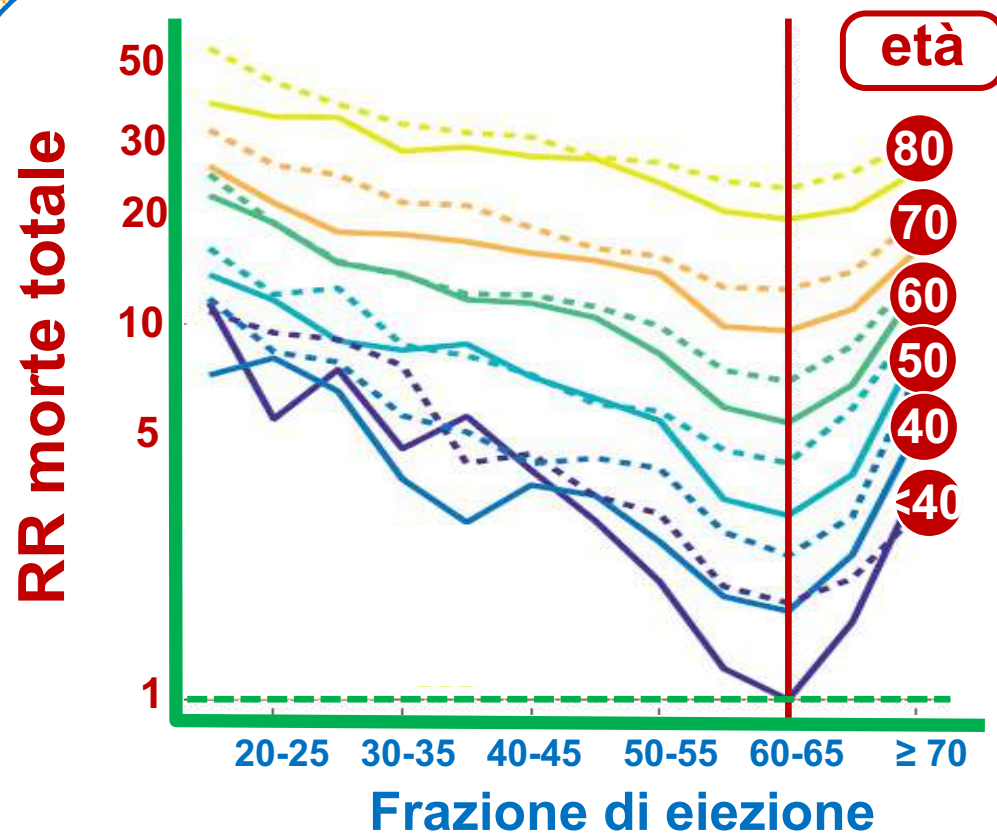
$P_{\text{eterogenicity}} = 0.42$



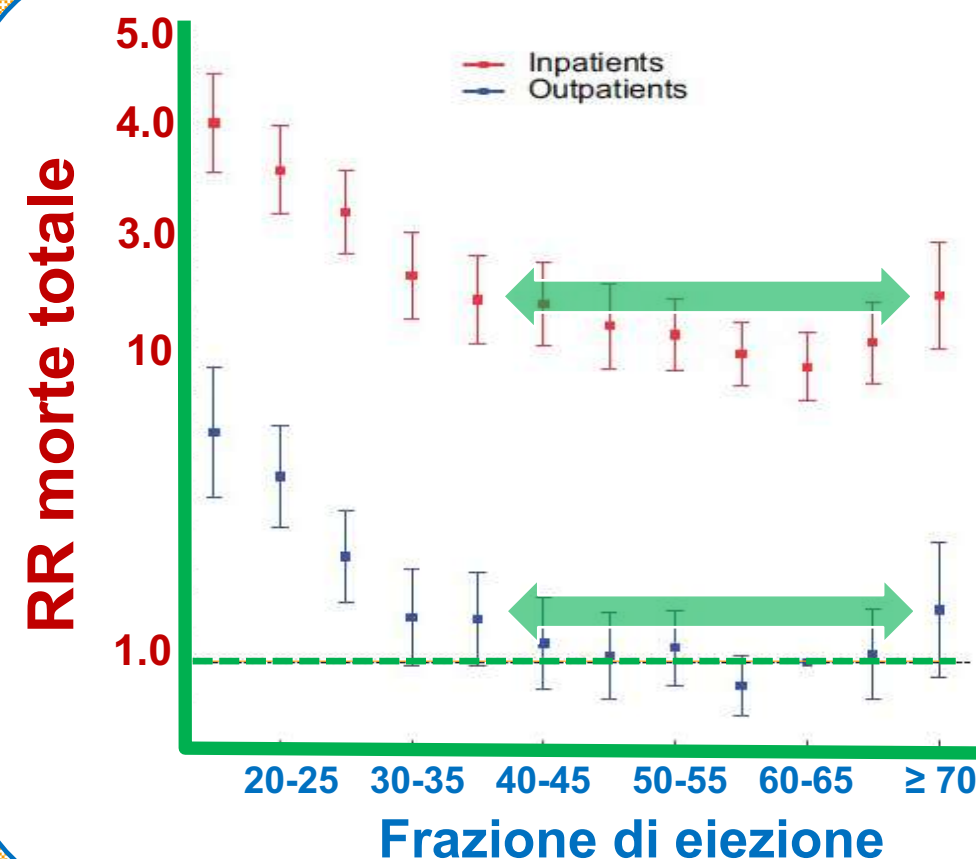
# Frazione di eiezione e mortalità: dove sta il nadir?

(Wehner, Eur Heart J 2020)

## Popolazione Generale

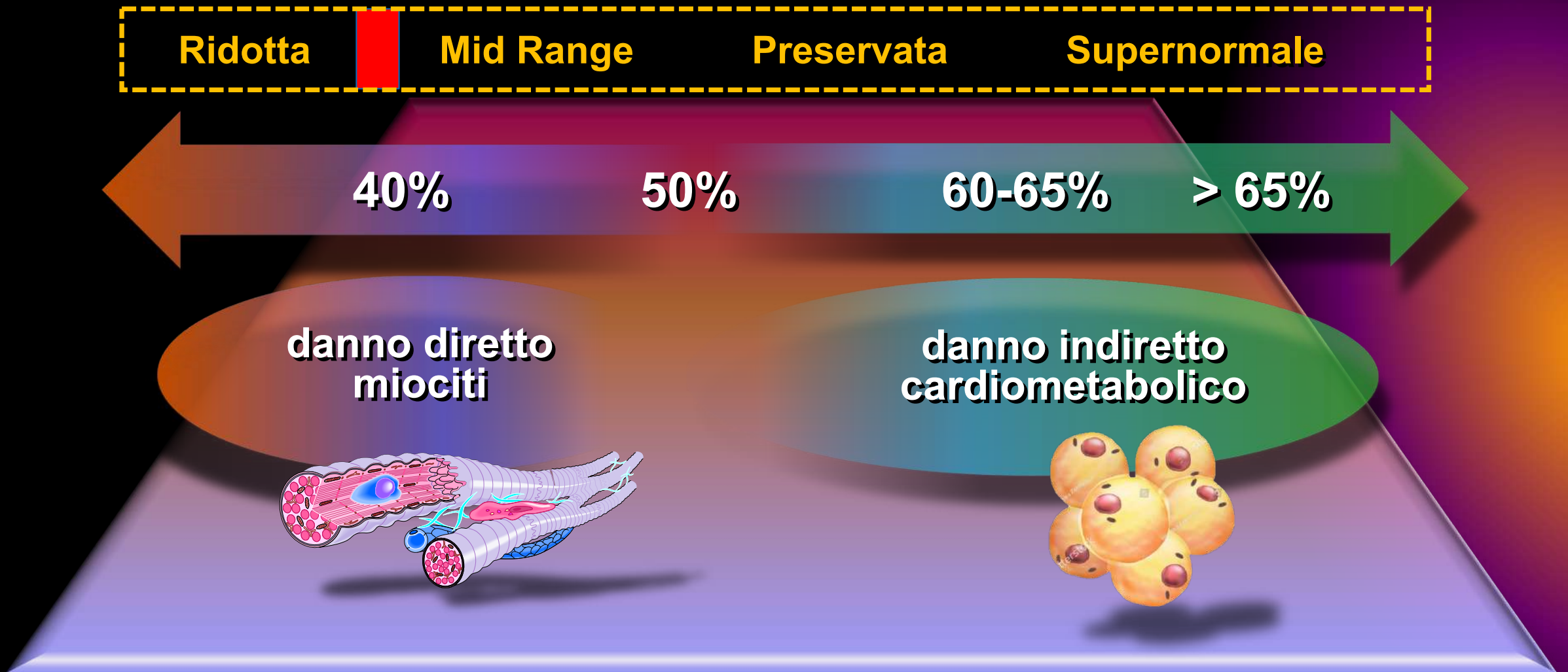


## Insufficienza Cardiaca



# Insufficienza cardiaca cronica

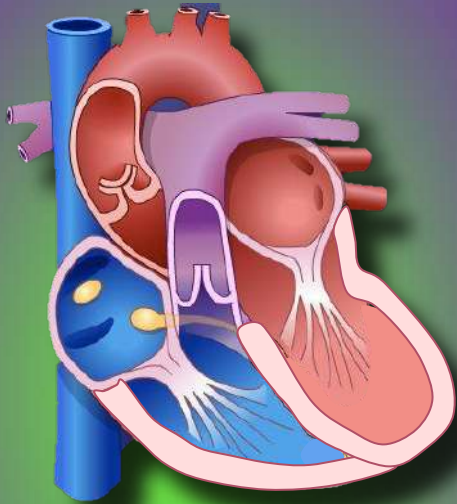
## Frazione di eiezione





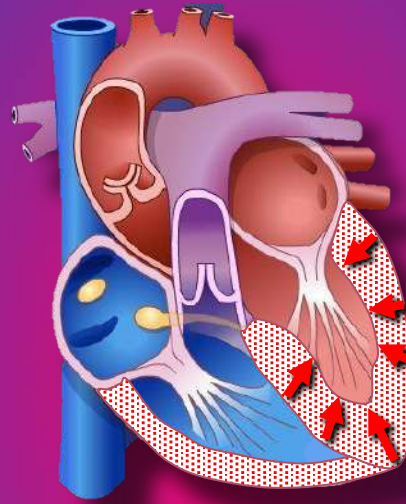
# Mortalità insufficienza cardiaca FE supernormale (Teramoto, JACC Asia 2023)

**VS normale  
Strain normale**



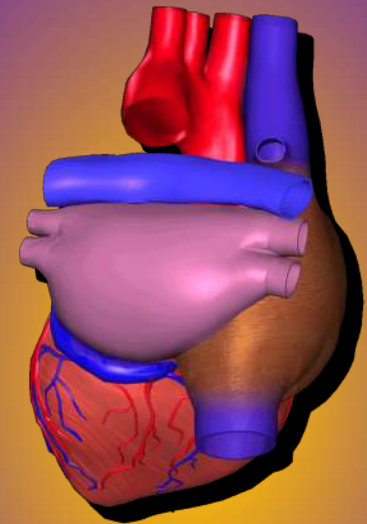
**2 y mortalità  
4.3 %**

**rimodellamento  
concentrico**



**2y mortalità  
10.3 %**

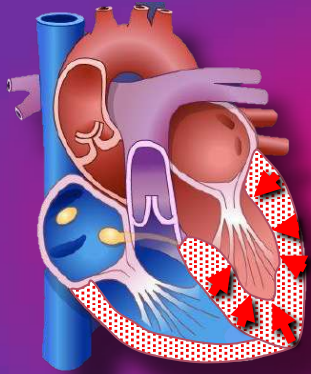
**miopatia atriale  
prevalente**



**2y mortalità  
10.1 %**

# FE supernormale donne anziane con ipertrofia del VS

**rimodellamento  
concentrico**



**FE ↑↑↑**

**contrazione  
prolungata**

**rigidità  
arterie**

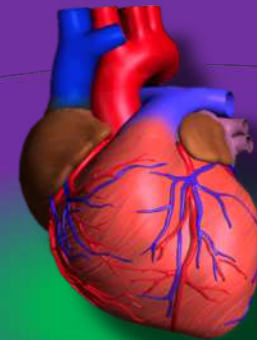


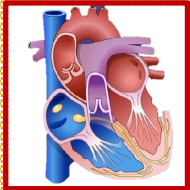
**accoppiamento  
ventricolo  
arterioso**

**post-carico ↑↑**

**rigidità  
diastole**

**insufficienza cardiaca  
FE supernormale**

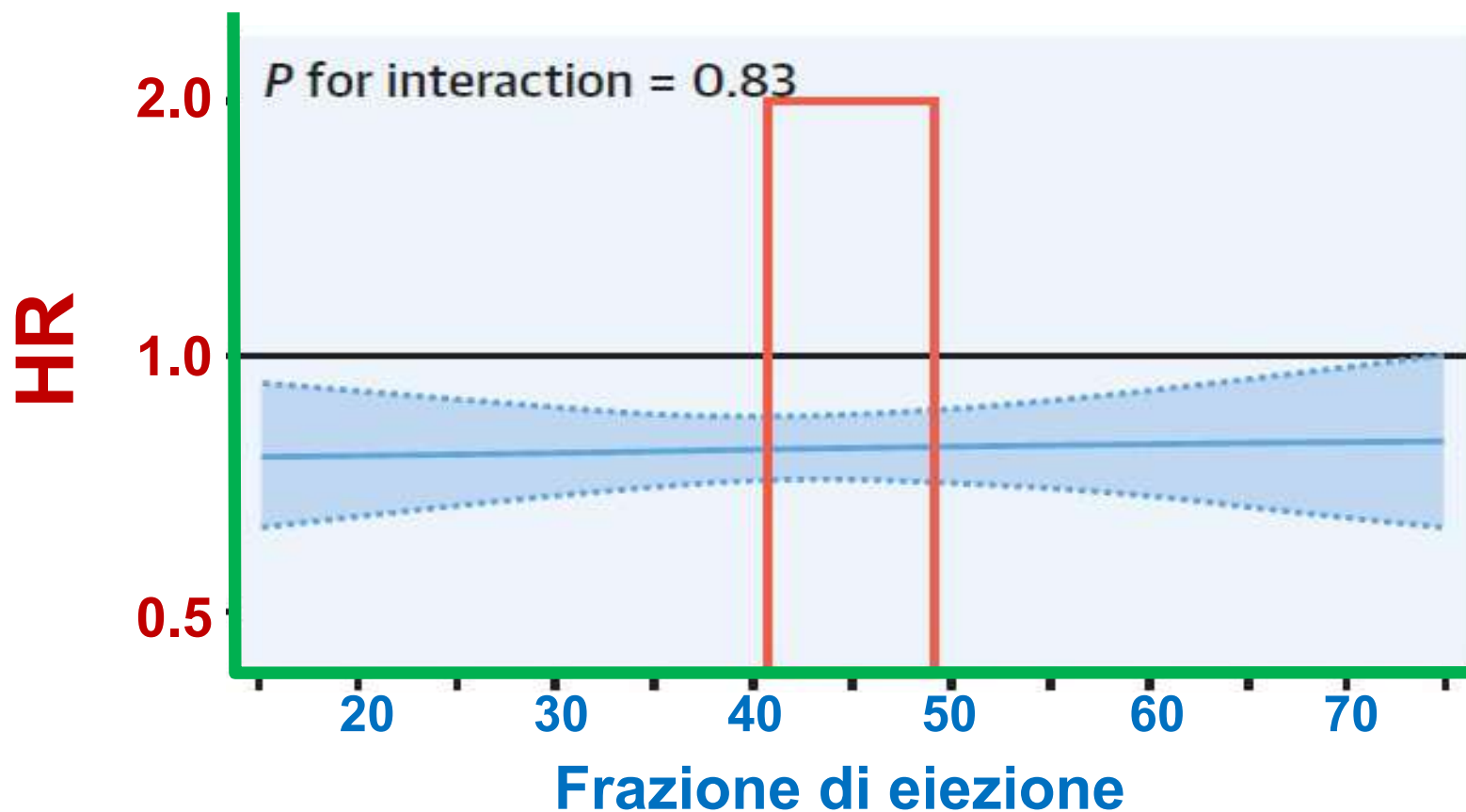


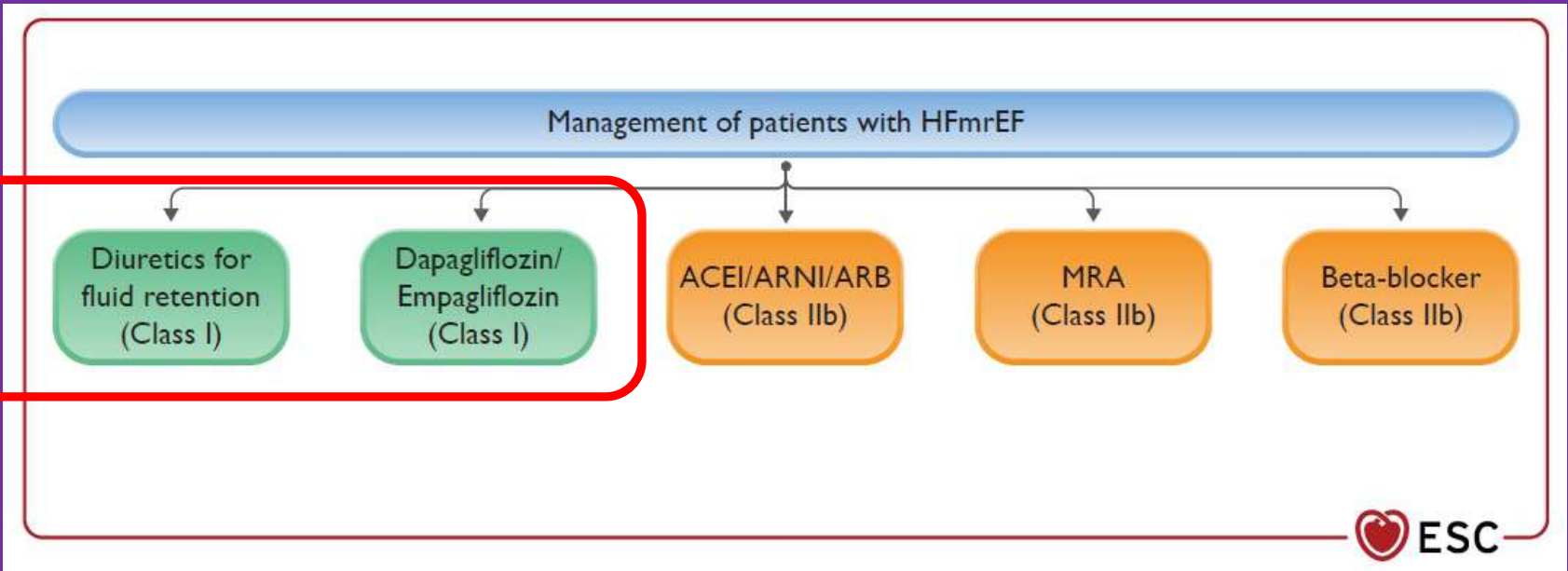


# Frazione di eiezione e terapie anti-scompenso

(Dimond, JACC HF 2024)

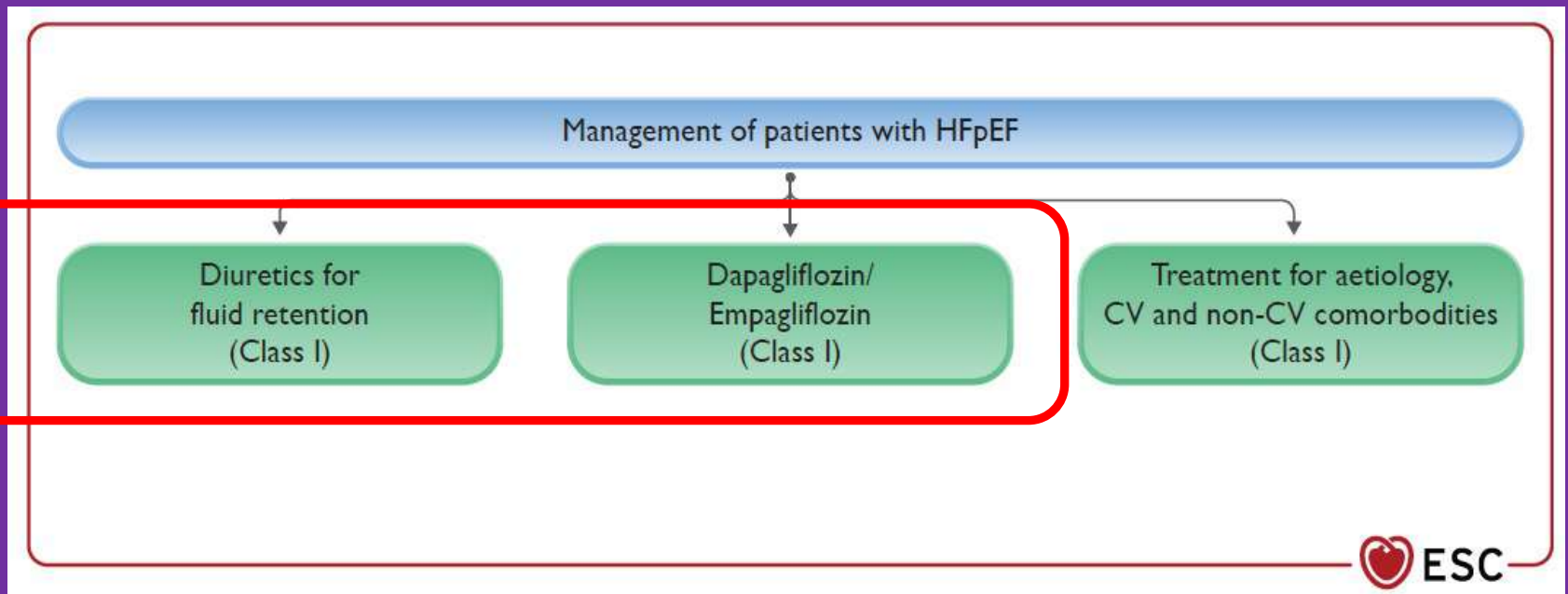
## Glifozine Death – HF ricovero



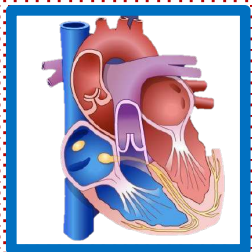


FE 40-50%

Guidelines ESC  
2023  
Focused Update

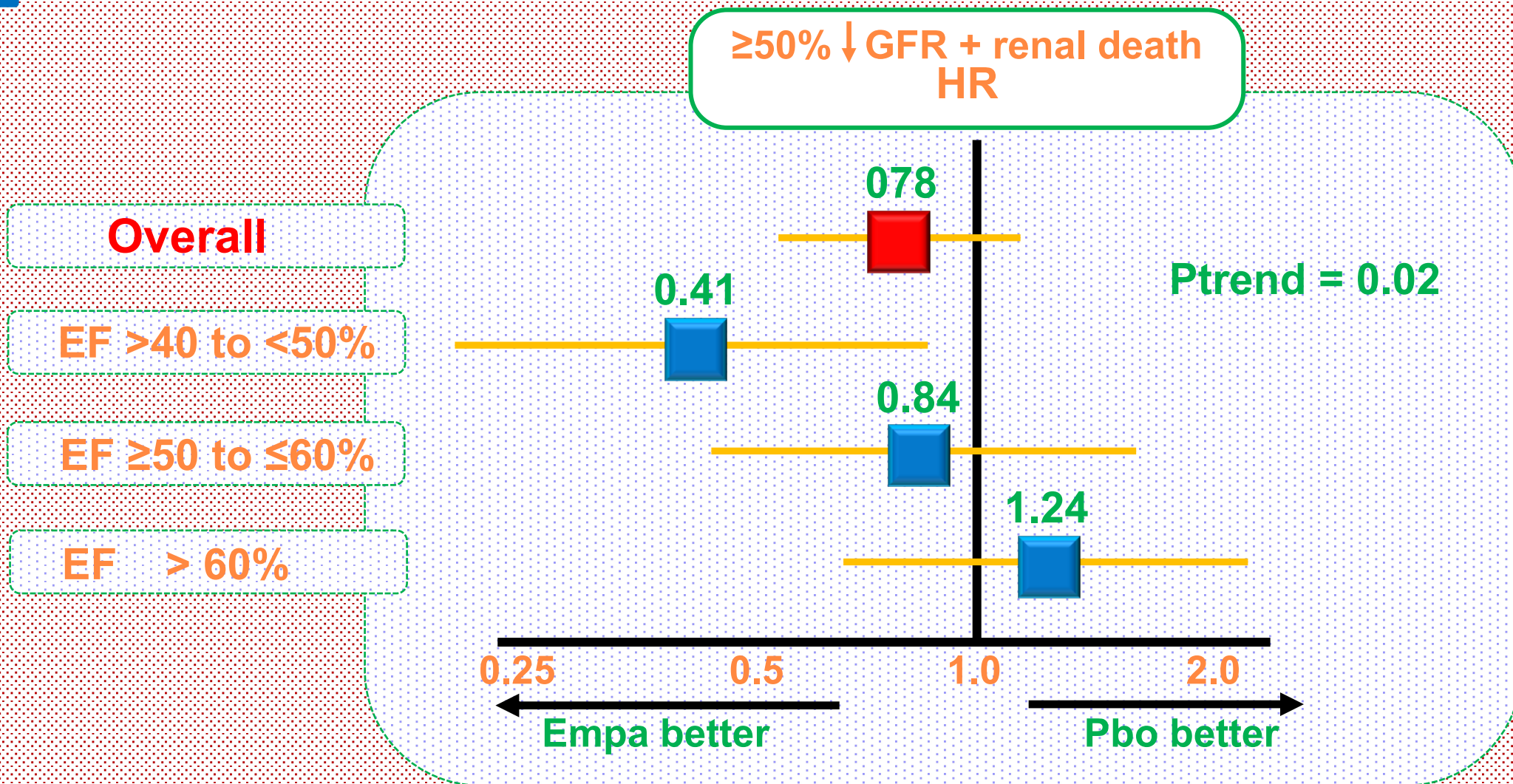


FE > 50%



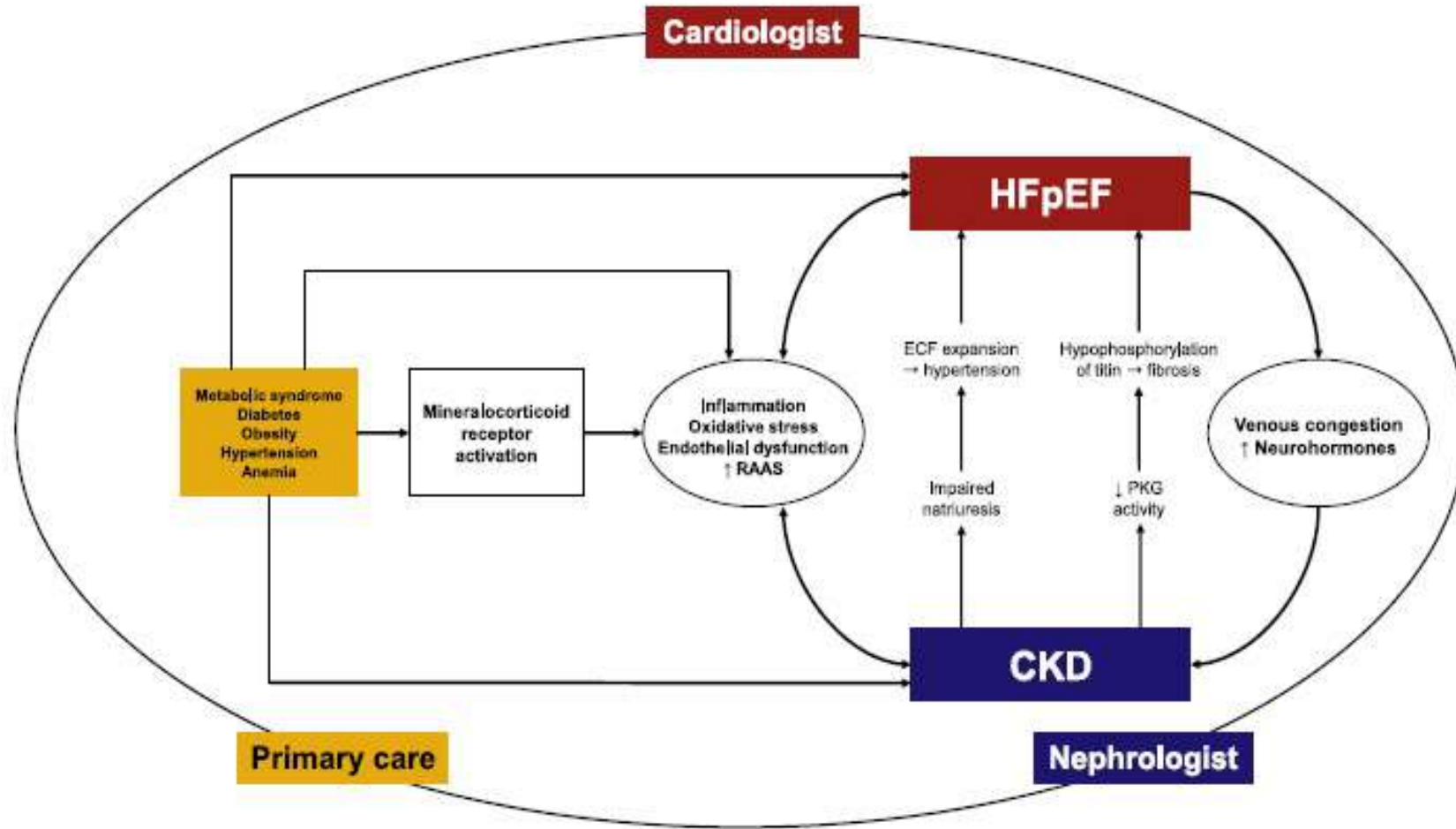
# Empaglifozin effetti renali e frazione di eiezione

(EMPEROR-Preserved, Packer Eur J Heart Fail 2021)

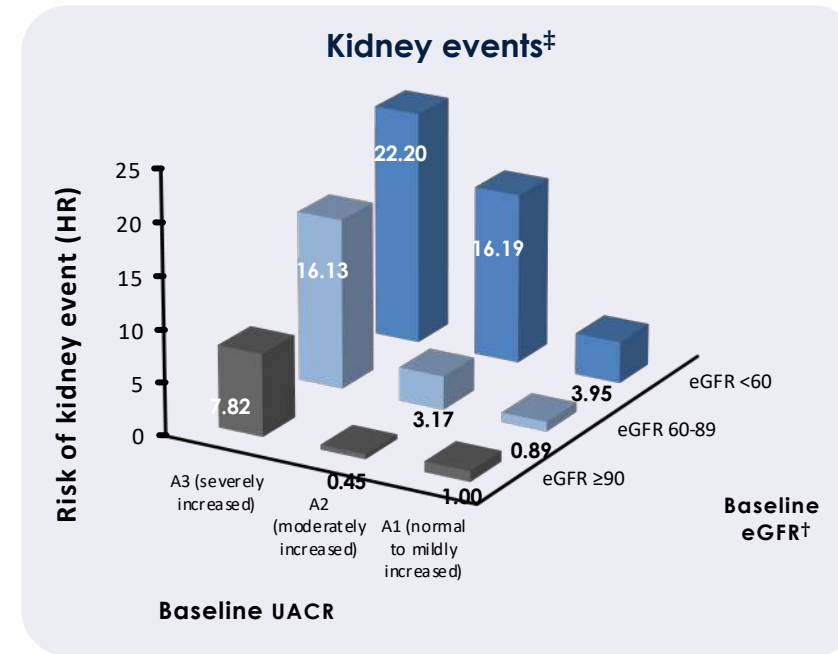
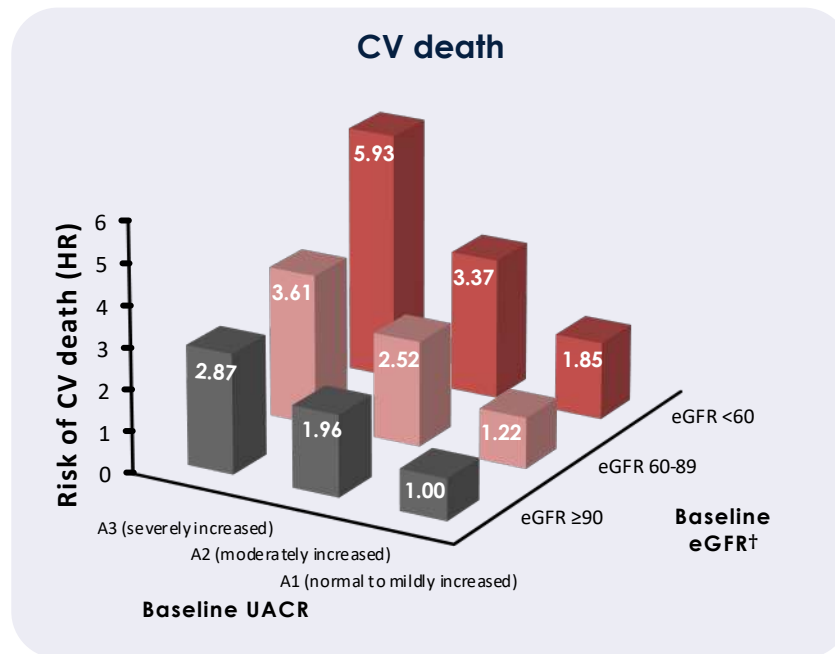




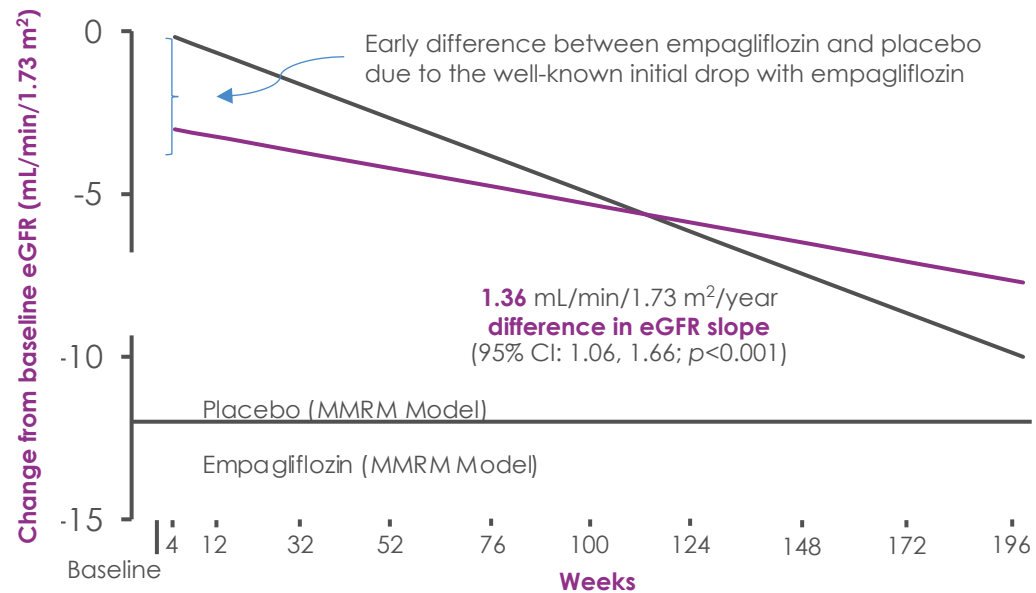
# Patel



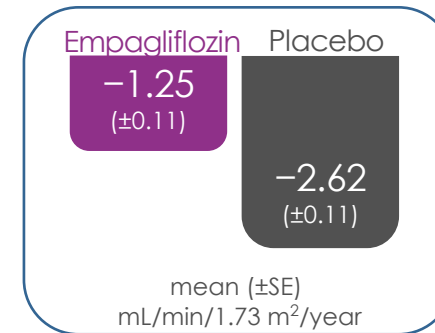
Reduced eGFR and increased albuminuria are independently associated with increased risk of CV death and kidney events



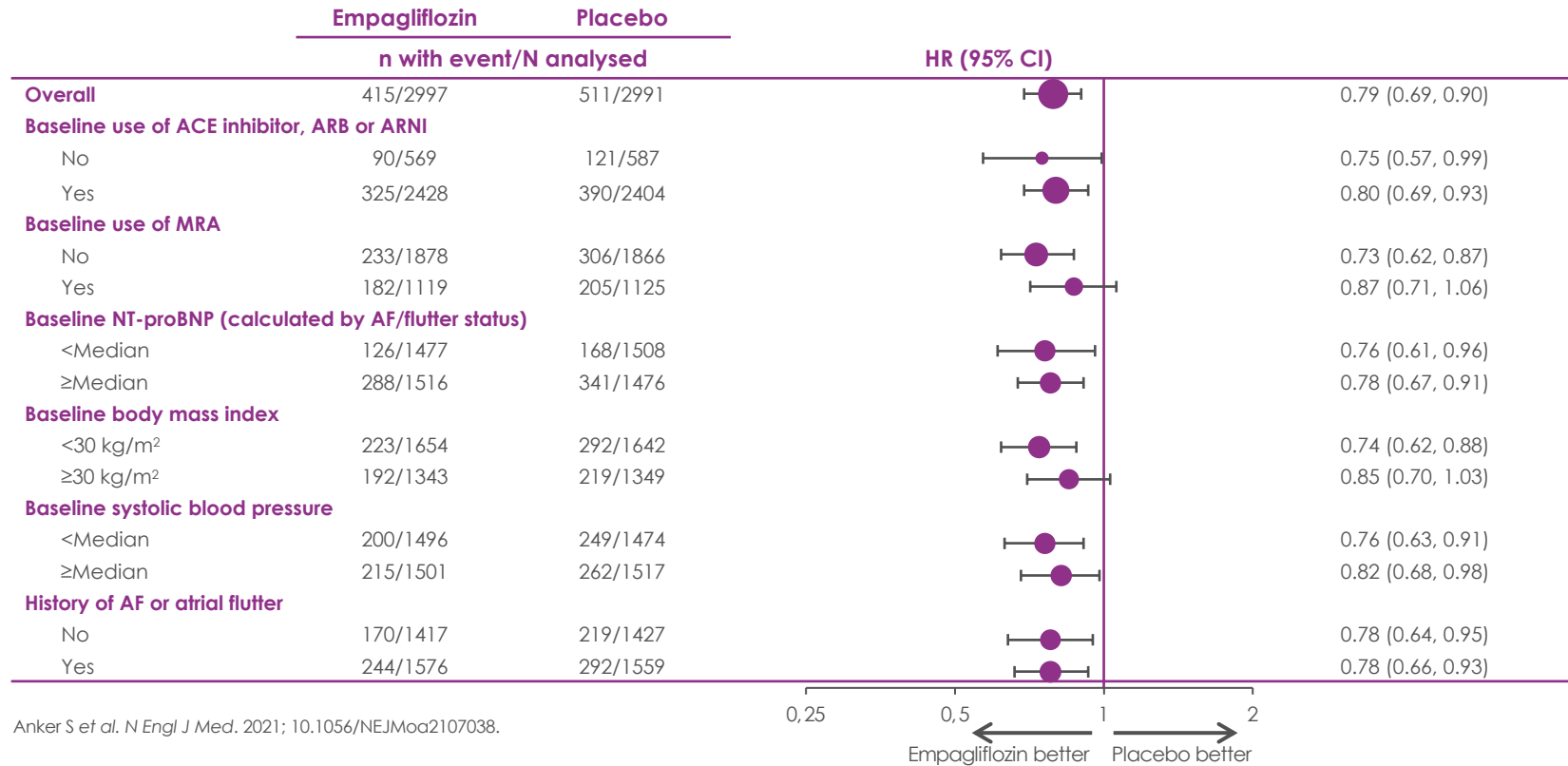
# Empagliflozin protected the kidney by significantly slowing the decline in kidney function



The rate of eGFR decline in patients treated with empagliflozin was half that of patients treated with placebo

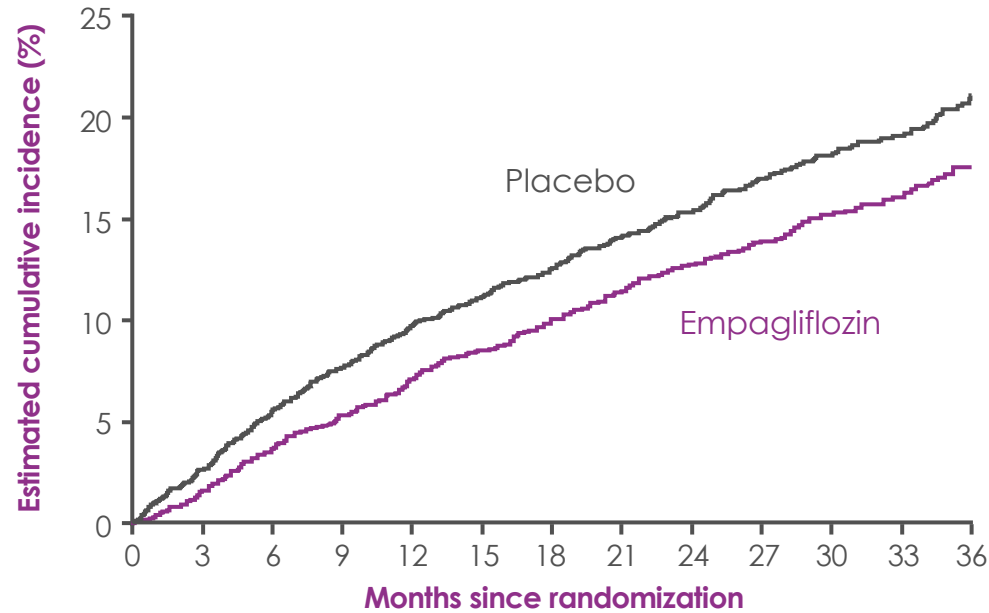


# EMPEROR-Preserved: Primary endpoint Subgroup analysis (3 of 3)



Anker S et al. *N Engl J Med.* 2021; 10.1056/NEJMoa2107038.

# Empagliflozin demonstrated a clinically meaningful 21% RRR in the composite primary endpoint of CV death or HHF



#### Patients at risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

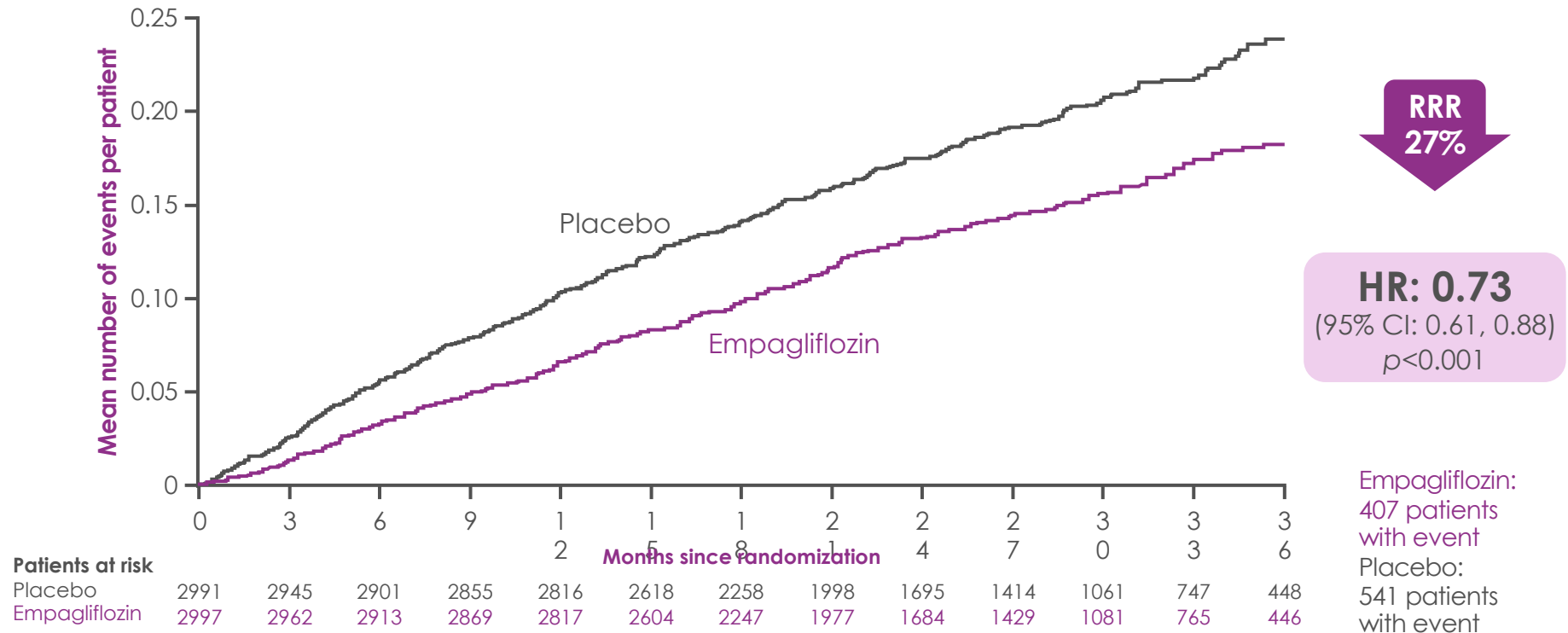
**RRR 21%**      **ARR 3.3%**      **NNT\*=31**

**HR: 0.79**  
(95% CI: 0.69, 0.90)  
*p* < 0.001

Empagliflozin:  
415 (13.8%) patients with event  
Rate: 6.9/100 patient-years  
Placebo:  
511 (17.1%) patients with event  
Rate: 8.7/100 patient-years

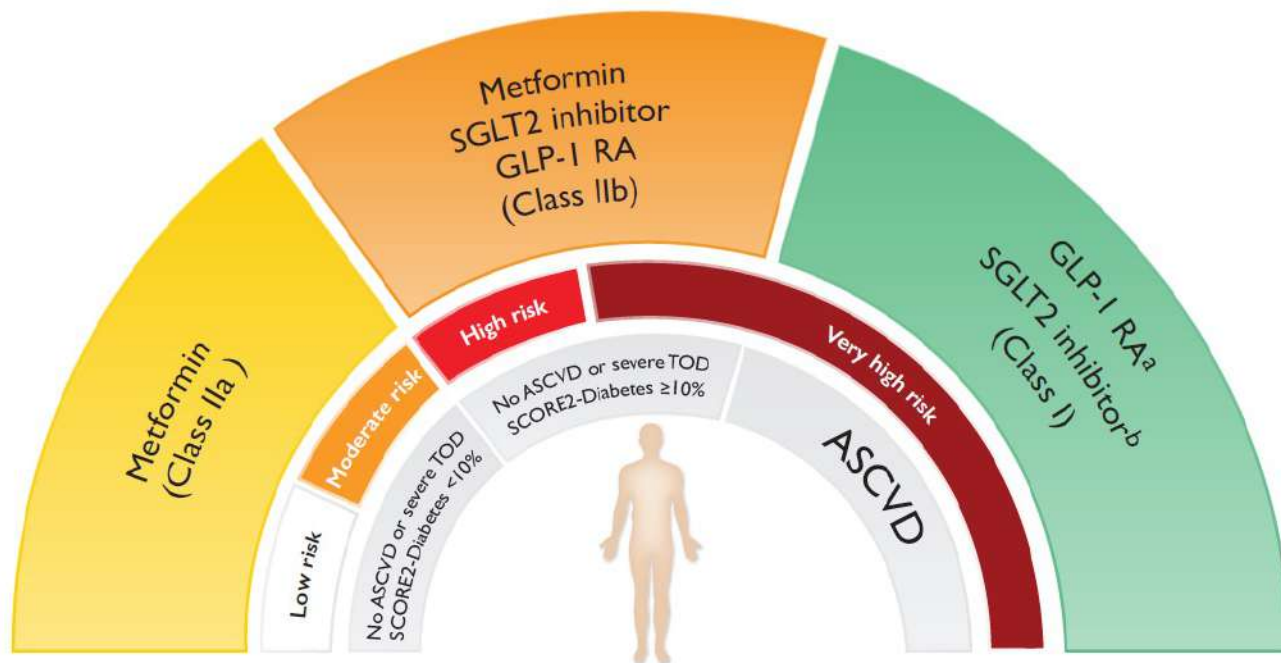
. Anker S et al. *N Engl J Med.* 2021; 10.1056/NEJMoa2107038.

# EMPEROR-Preserved: Key secondary endpoint – adjudicated total HHF (first and recurrent)

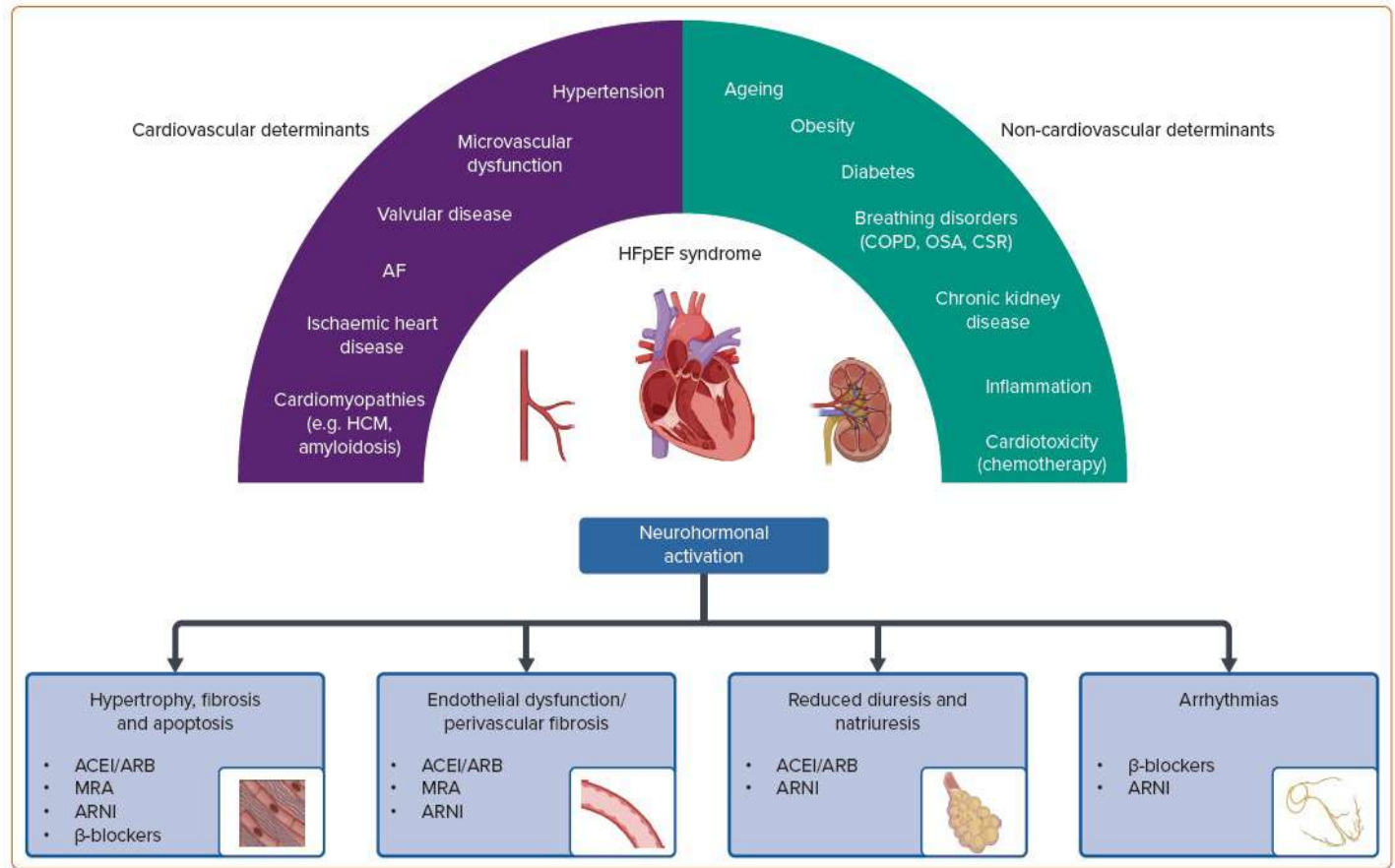


Anker S et al. N Engl J Med. 2021; 10.1056/NEJMoa2107038.



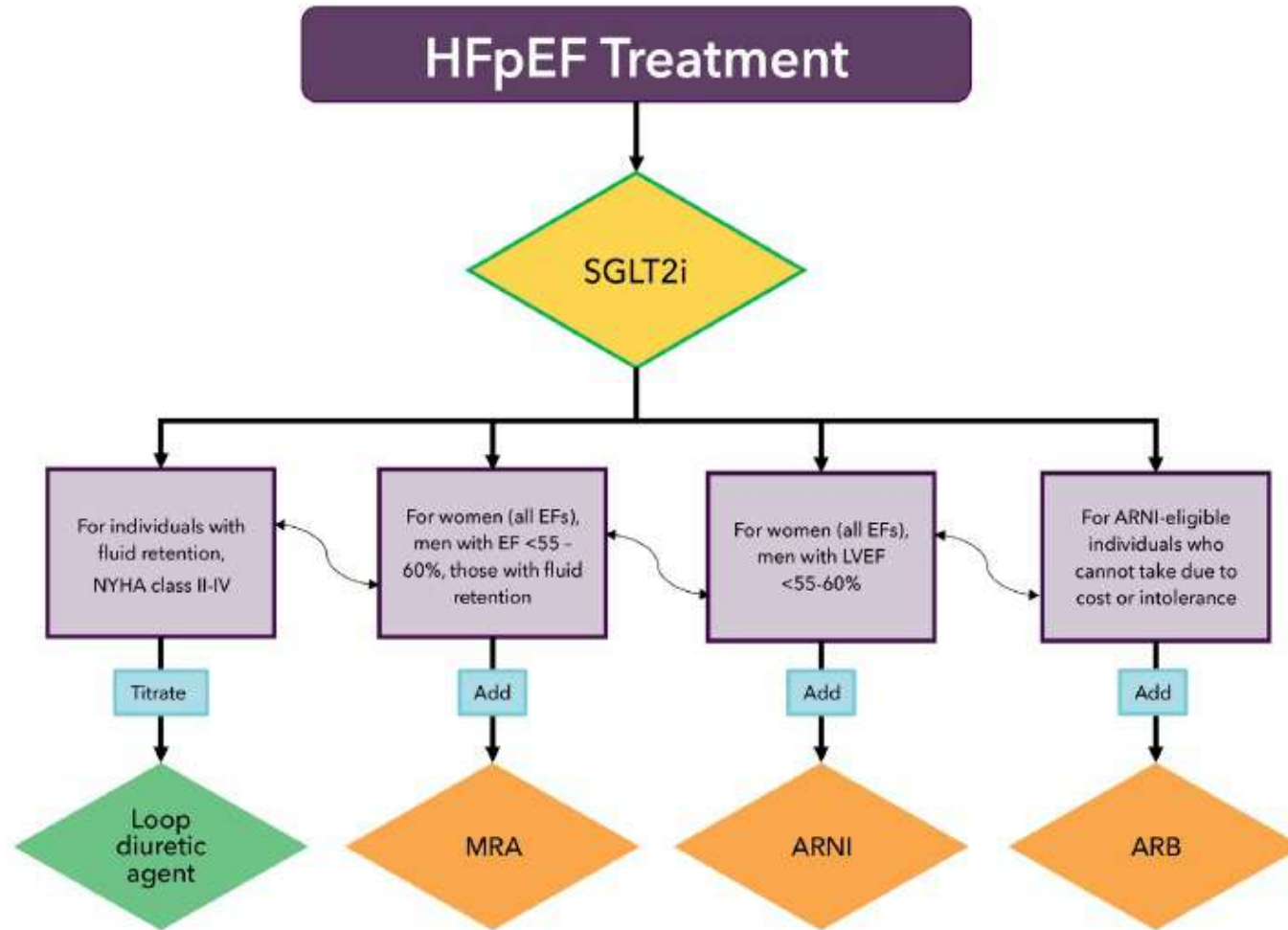


Risk assessment for patients with type 2 diabetes based on the presence of ASCVD/severe TOD and 10-year CVD risk estimation via SCORE2-Diabetes

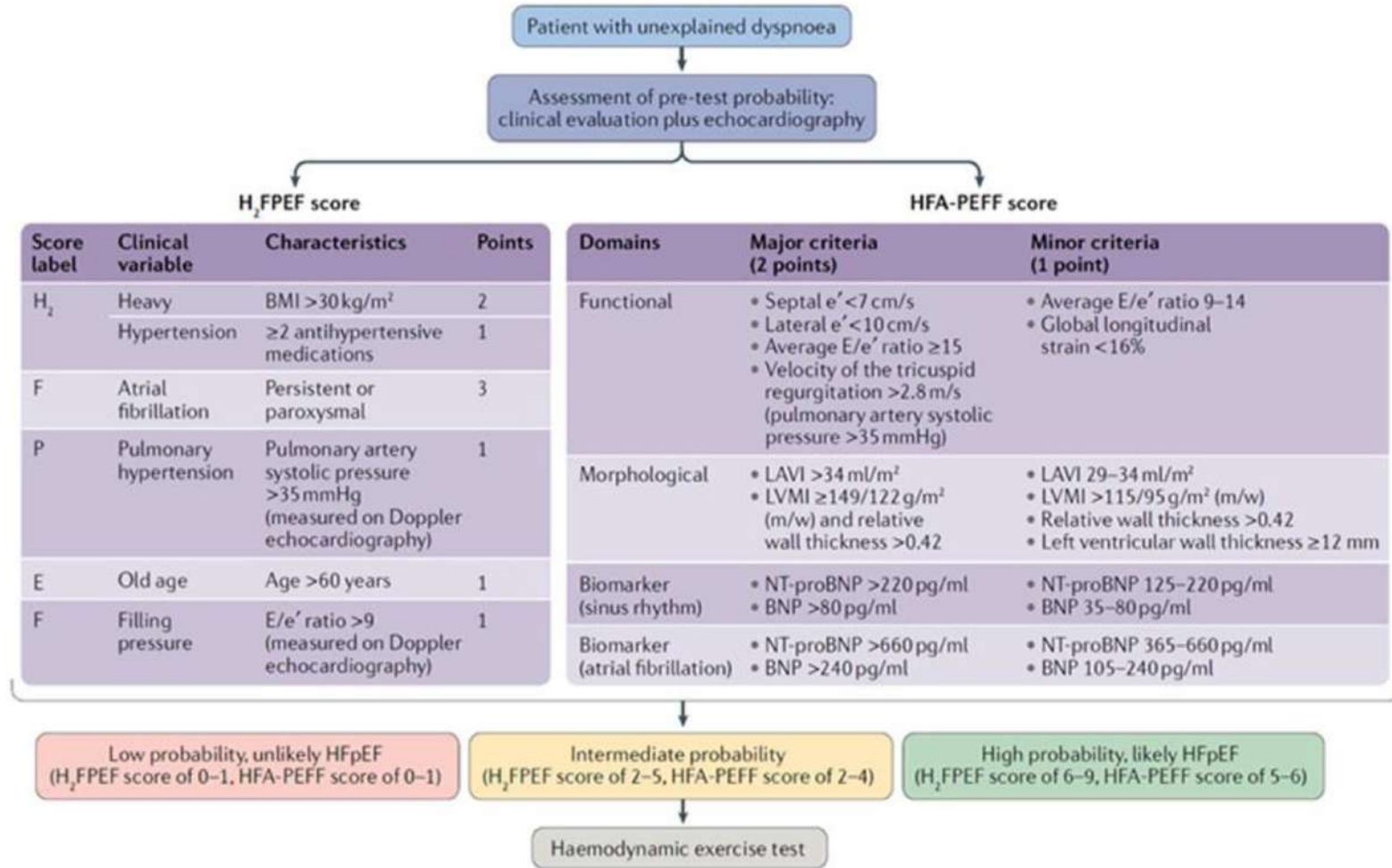


# 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction JACC 2023

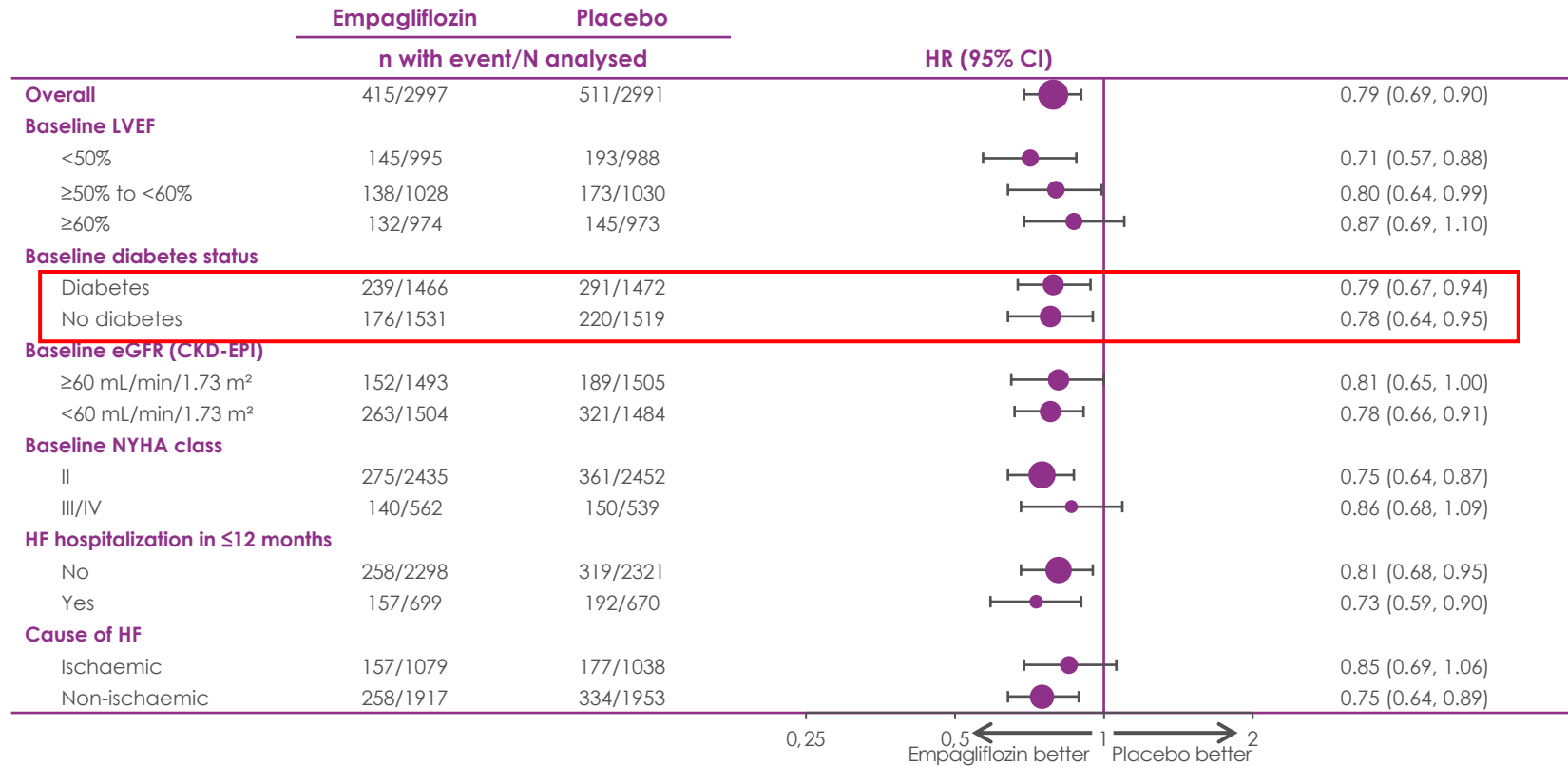
FIGURE 9 Treatment Algorithm for Guideline-Directed Medical Therapy in HFpEF\*

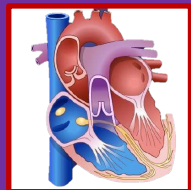


# Patel



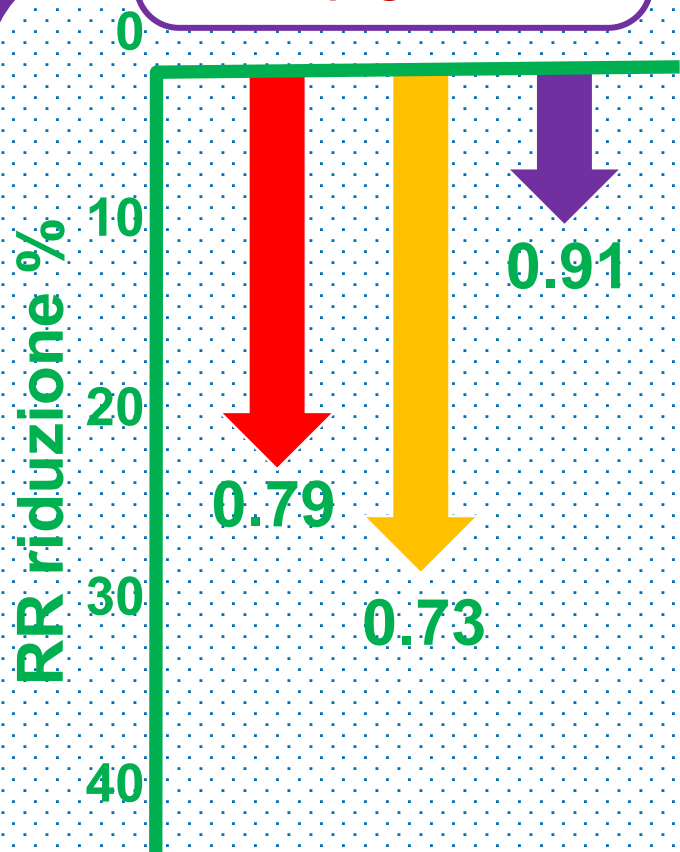
# EMPEROR-Preserved: Primary endpoint Subgroup analysis (2 of 3)



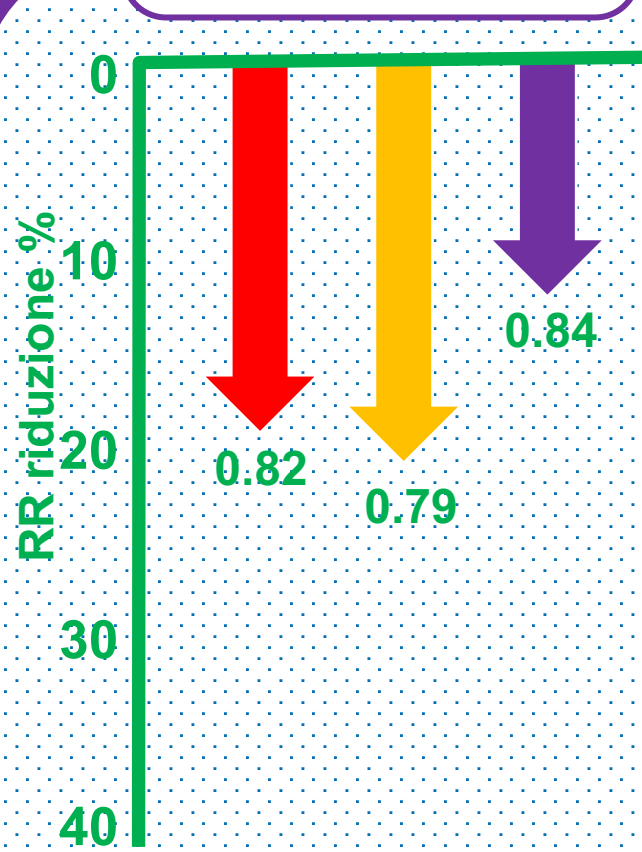


# Studi clinici nella insuff. Cardiaca a FE preservata

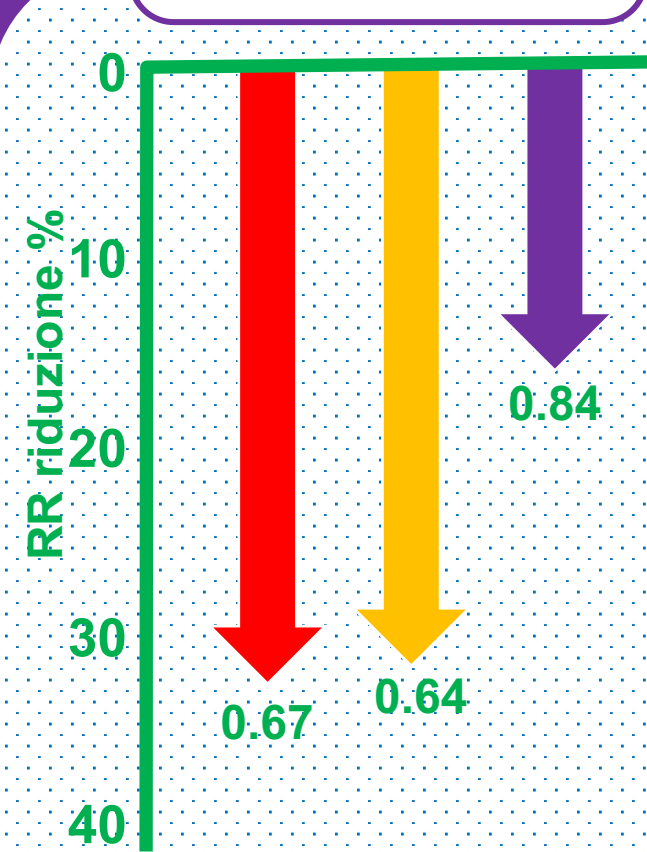
**EMPEROR-Preserved**  
Empaglifozin



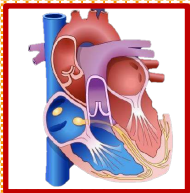
**DELIVER**  
Dapaglifozin



**SOLOIST-WHF**  
Sotaglifozin



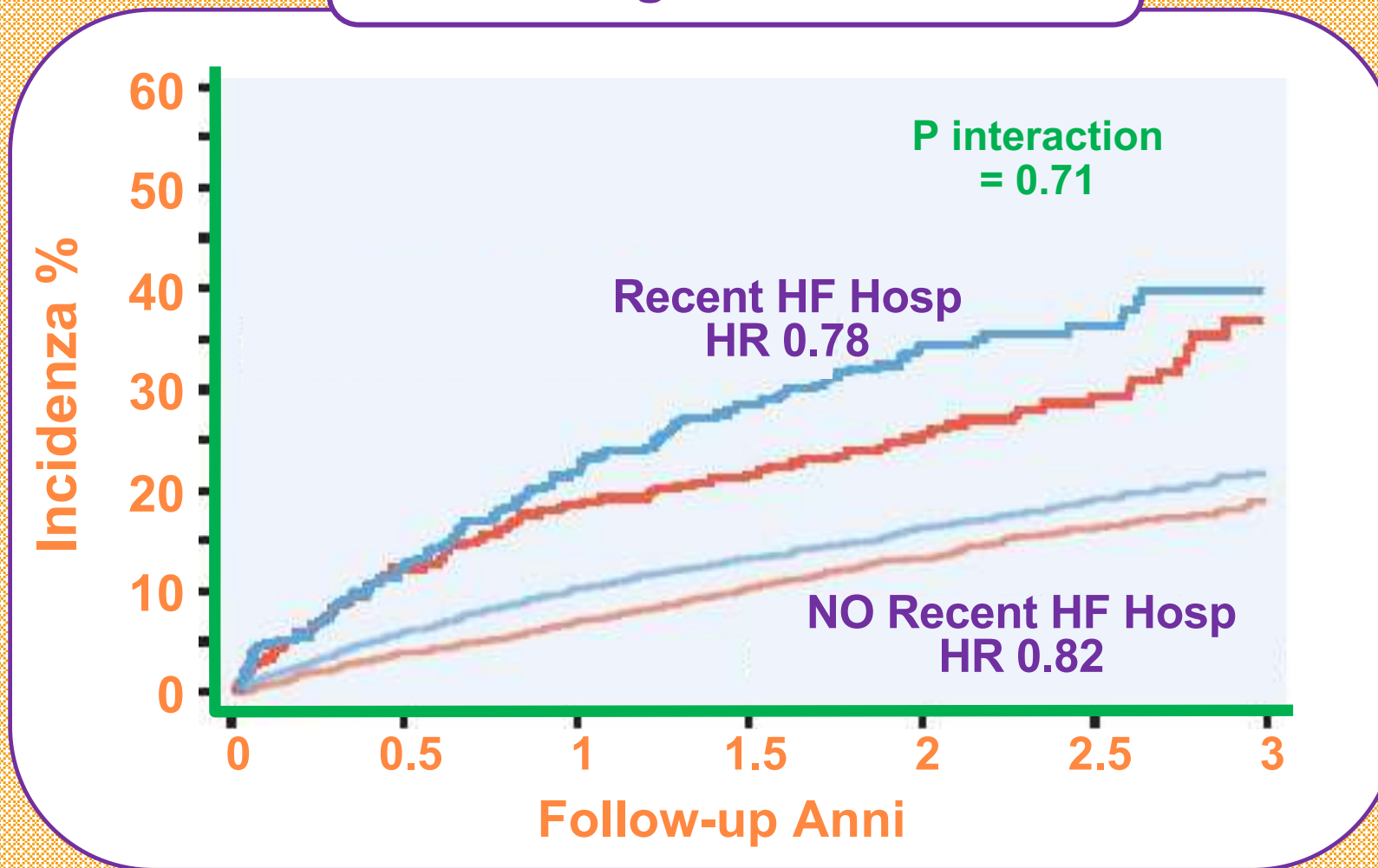




# Dapaglifozin nella ospedalizzazione recente

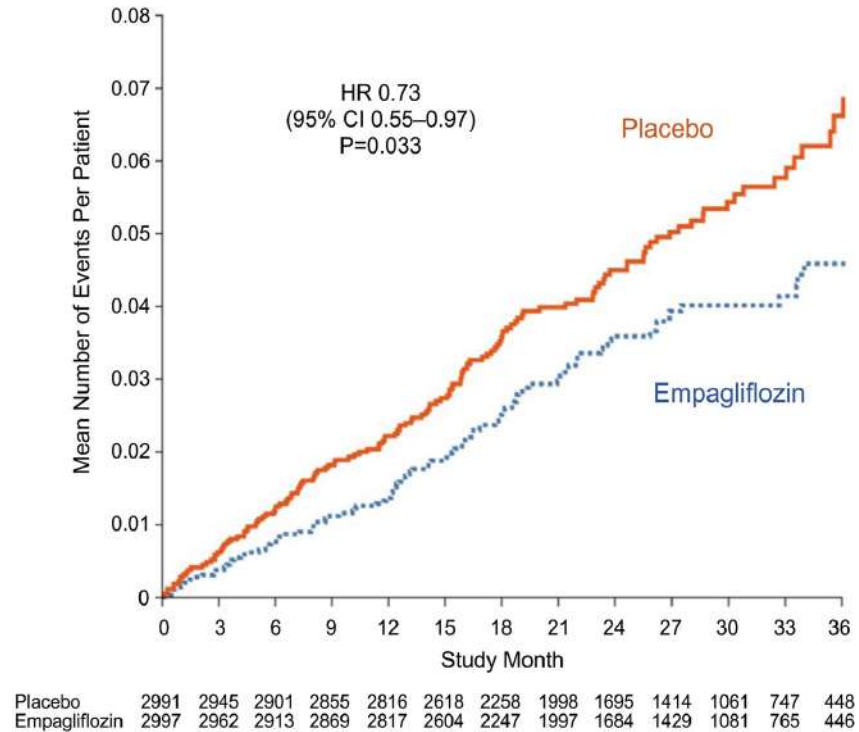
(Cunnungham, JACC 2022)

## Worsening HF or CV Death

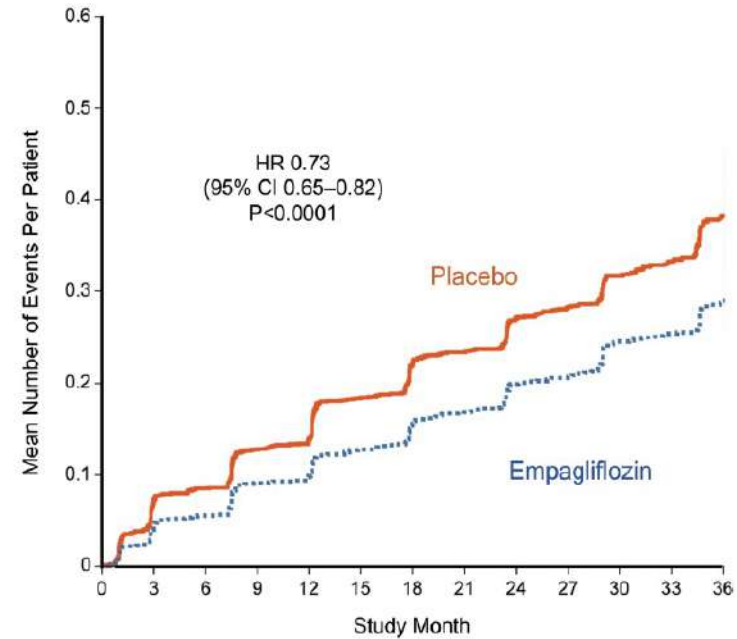


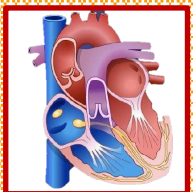
**Figure 1. Total (first and recurrent) hospitalizations for any reason that required intravenous vasopressors or positive inotropic agents.**

Shown are mean cumulative function curves for placebo (shown in red) and for empagliflozin (shown in blue). HR indicates hazard ratio.



**Figure 4. Total number of outpatient visits reporting interval intensification of diuretics for worsening heart failure.**

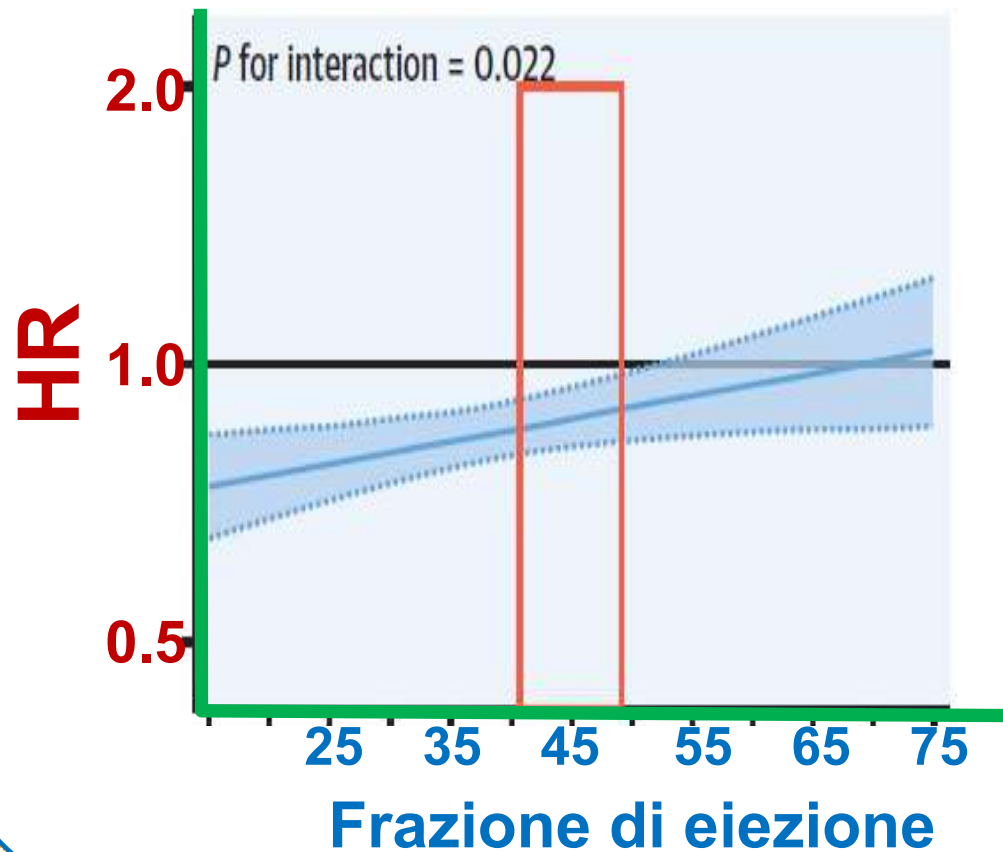




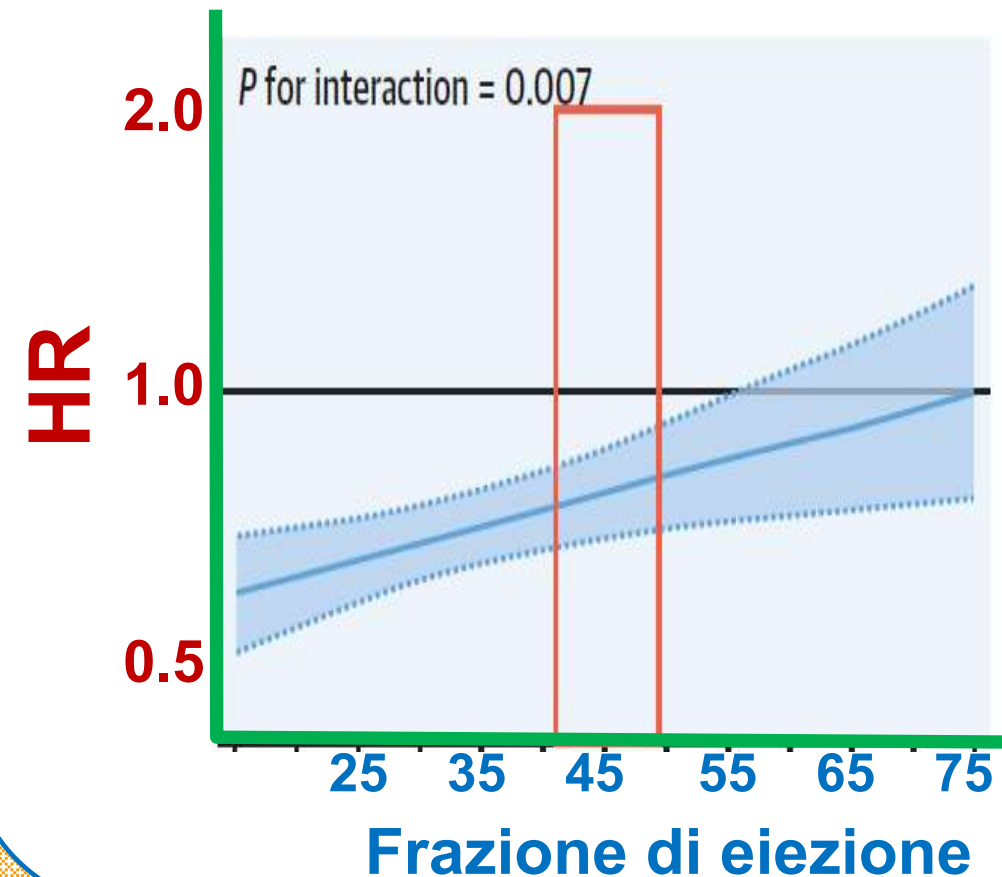
# Frazione di eiezione e terapie anti-scompenso

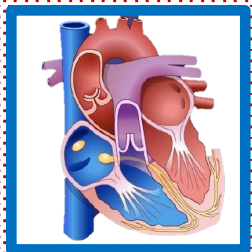
(Dimond, JACC HF 2024)

### ANRI Death – HF ricovero



### Anti-aldosteronici Death – HF ricovero





# Empaglifozin effetti renali e frazione di eiezione

(EMPEROR-Preserved, Packer Eur J Heart Fail 2021)

RR

≥40% ↓GFR

Overall

EF >40 to <50%

EF ≥50 to ≤60%

EF > 60%

≥50% ↓GFR  
renal death

Overall

EF >40 to <50%

EF ≥50 to ≤60%

EF > 60%

0.25  
Empa better

0.5

1.0

2.0  
Pbo better

Ptrend = 0.02

