SGLT2i: IL PUNTO DI VISTA DEL CARDIOLOGO

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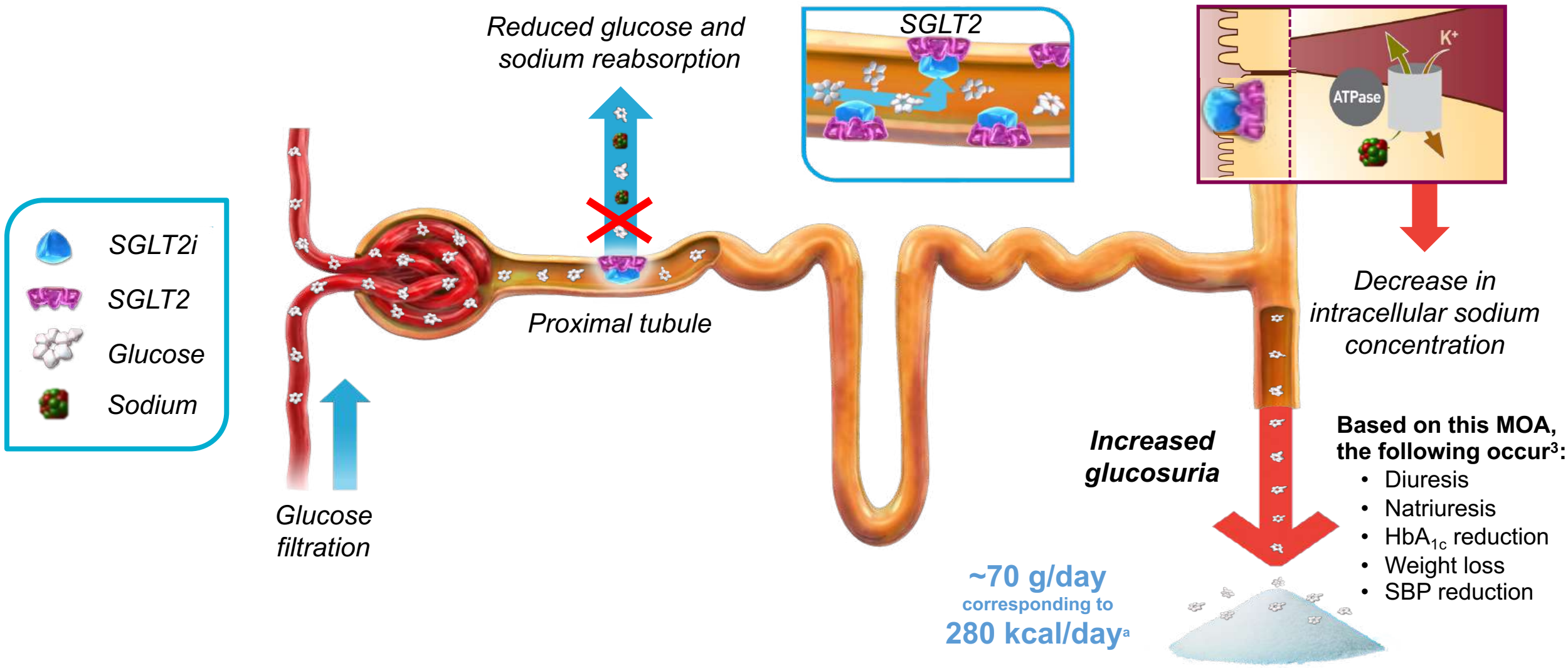
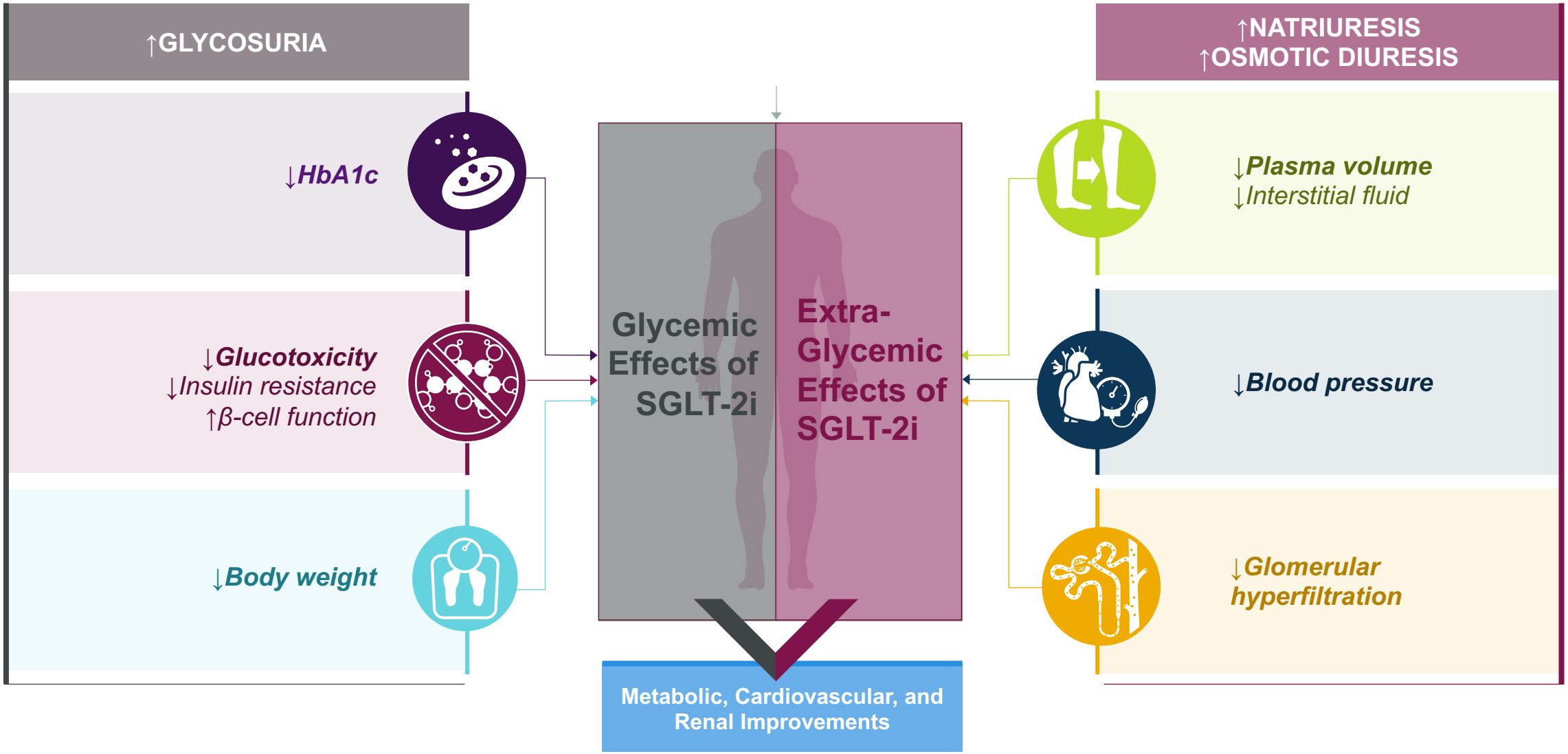
SGLT2 inhibition: An insulin-independent approach to remove excess glucose by reducing the renal threshold[1–3]



SGLT2i, sodium–glucose co-transporter 2 inhibitor

1. Marsenic O. *Am J Kidney Dis* 2009;53:875–885; 2. Dapagliflozin Summary of Product Characteristics; 3. Mudaliar S, et al. *Diabetes Care* 2016;39:1115–1122

Key Physiological Effects of SGLT-2 Inhibition

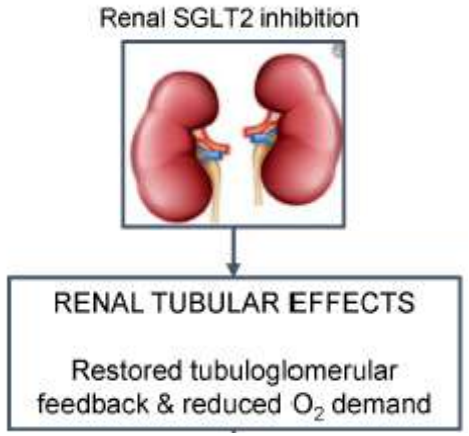


HbA1C=hemoglobin A1C; SGLT-2=sodium-glucose co-transporter 2; SGLT-2i=sodium-glucose co-transporter 2 inhibitor.

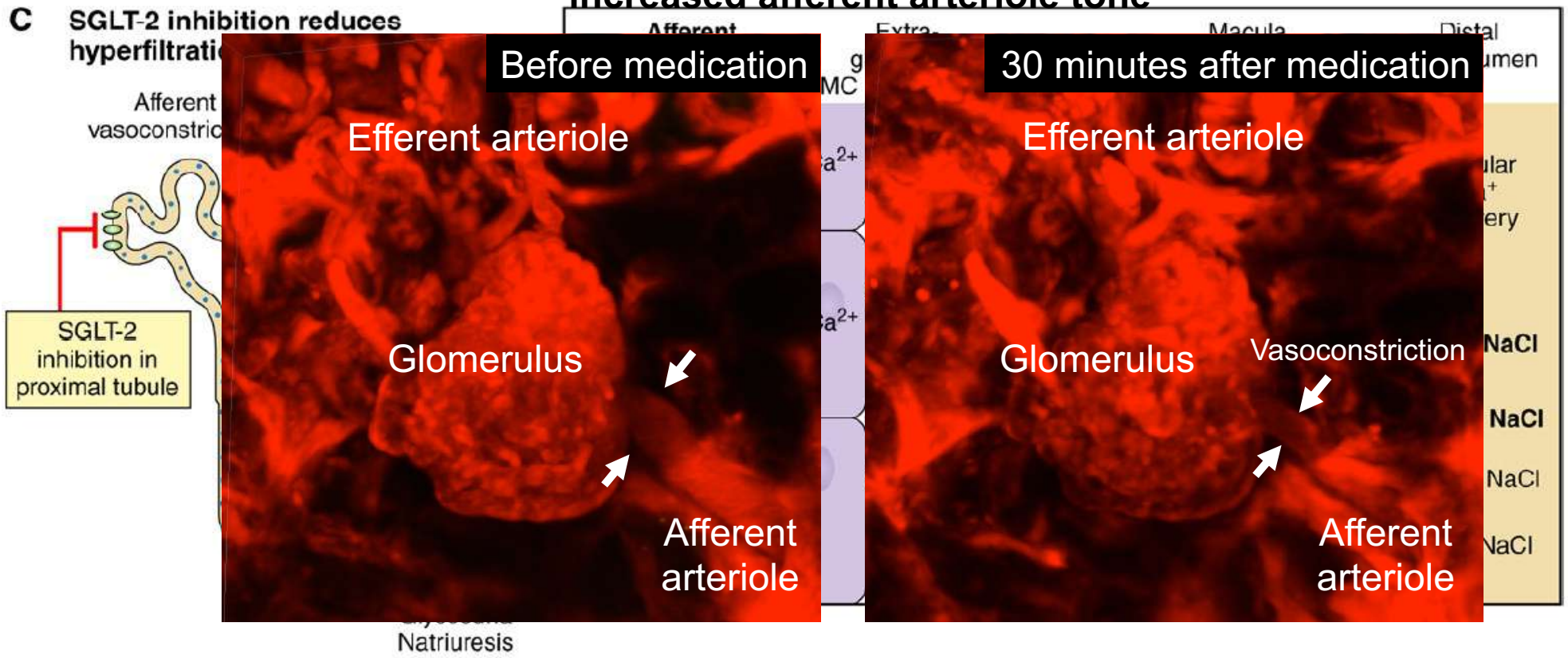
1. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 2. van Baar MJB, et al. *Diabetes Care*. 2018;41(8):1543-1556. 3. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32.

Effects of SGLT2 inhibition on cardiorenal pathophysiology

1) RENAL TUBULAR EFFECTS



In vivo imaging showed that SGLT2i therapy increased afferent arteriole tone



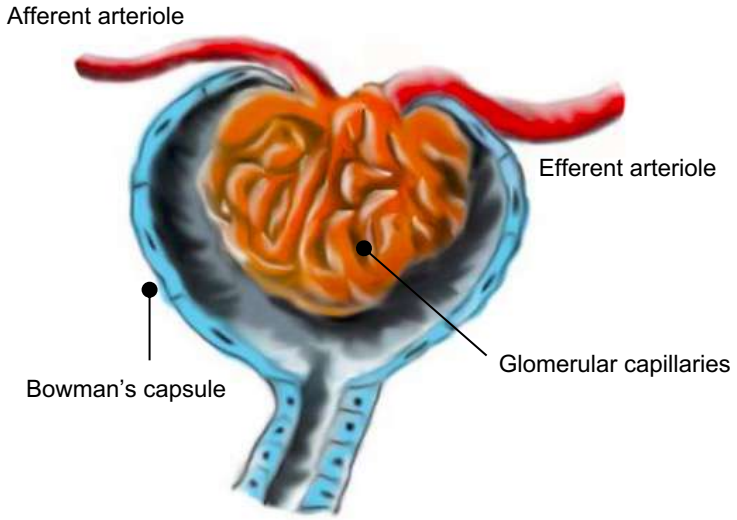
W.G. Herrington et al., European Journal of Heart Failure (2021) doi:10.1002/ejhf.2286; Heerspink et al., Circulation. 2016;134:752–772. DOI: 10.1161/CIRCULATIONAHA.116.021887; Kidokoro K, et al. Circulation 2019;140:303–315

SGLT2 inhibition and RAAS blockade both reduce glomerular hyperfiltration by complimentary mechanisms[1-3]

SGLT2 inhibitors

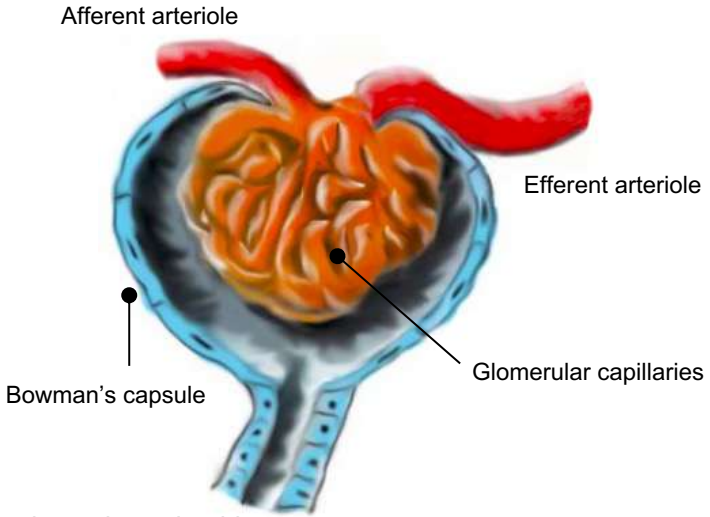
Afferent constriction[1-3]

Due to increased Na+ delivery to the macula densa[1-3]



RAAS blockade

Efferent vasodilation[1]



CLINICAL IMPLICATIONS

- **Decreased glomerular pressure[1,3]**
- **Reduction in albuminuria[1,2]**

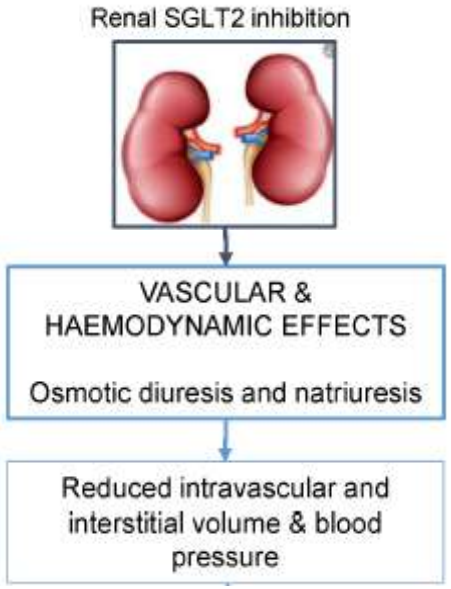
- **Decreased glomerular pressure[1,3]**
- **Reduction in albuminuria[4]**

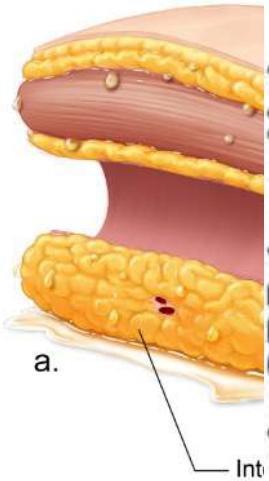
SGLT2, sodium-glucose cotransporter 2; Na, sodium; RAAS, renin-angiotensin-aldosterone system.

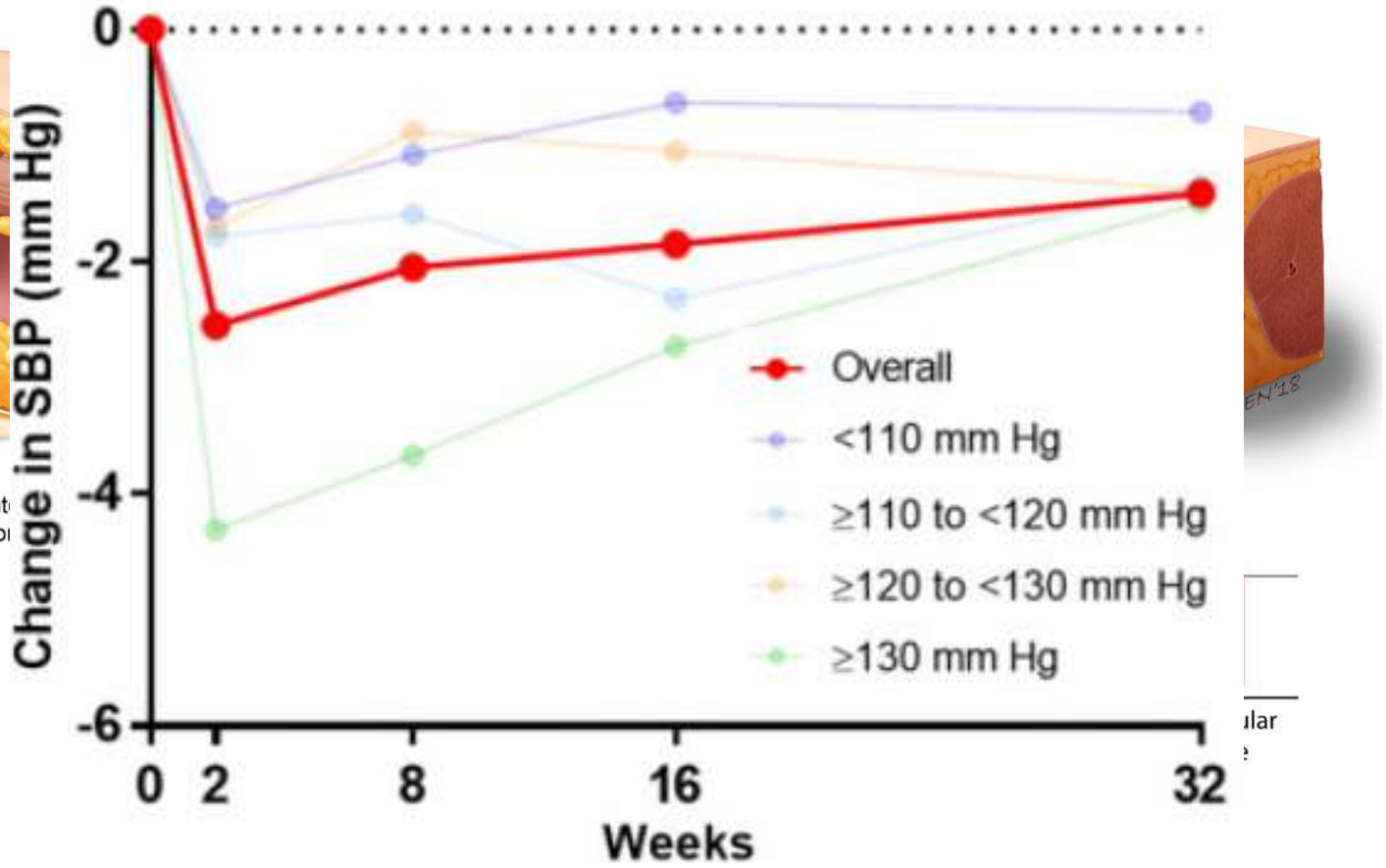
1. Van Bommel EJ, et al. *Clin J Am Soc Nephrol*. 2017;12(4):700-710. 2. Seidu S, et al. *Prim Care Diabetes*. 2018;12(3):265-283. 3. Cherney DZ, et. al. *Circulation*. 2014 Feb 4;129(5):587-97. 4. Heerspink HJ, et al. *Diabetes Care*. 2011;34 Suppl 2:S325-9. 5. Adapted from: Shiraishi M, et al. *FASEB J*. 2003;17(15):2284-6.

Effects of SGLT2 inhibition on cardiorenal pathophysiology

2) VASCULAR & HAEMODYNAMIC EFFECTS



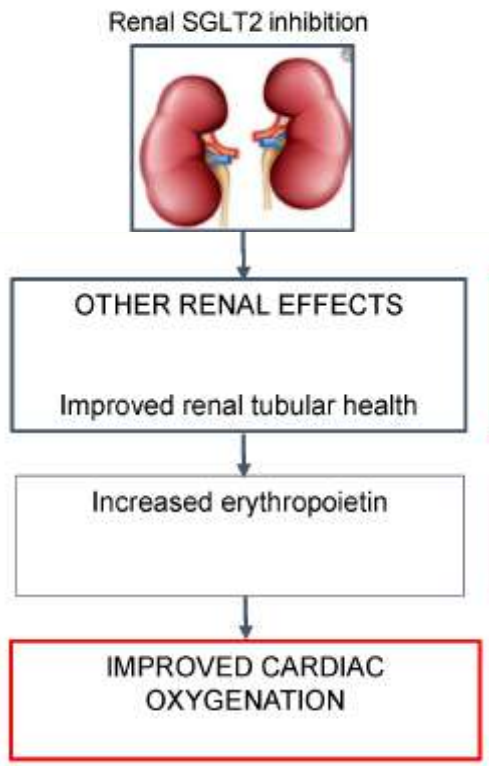


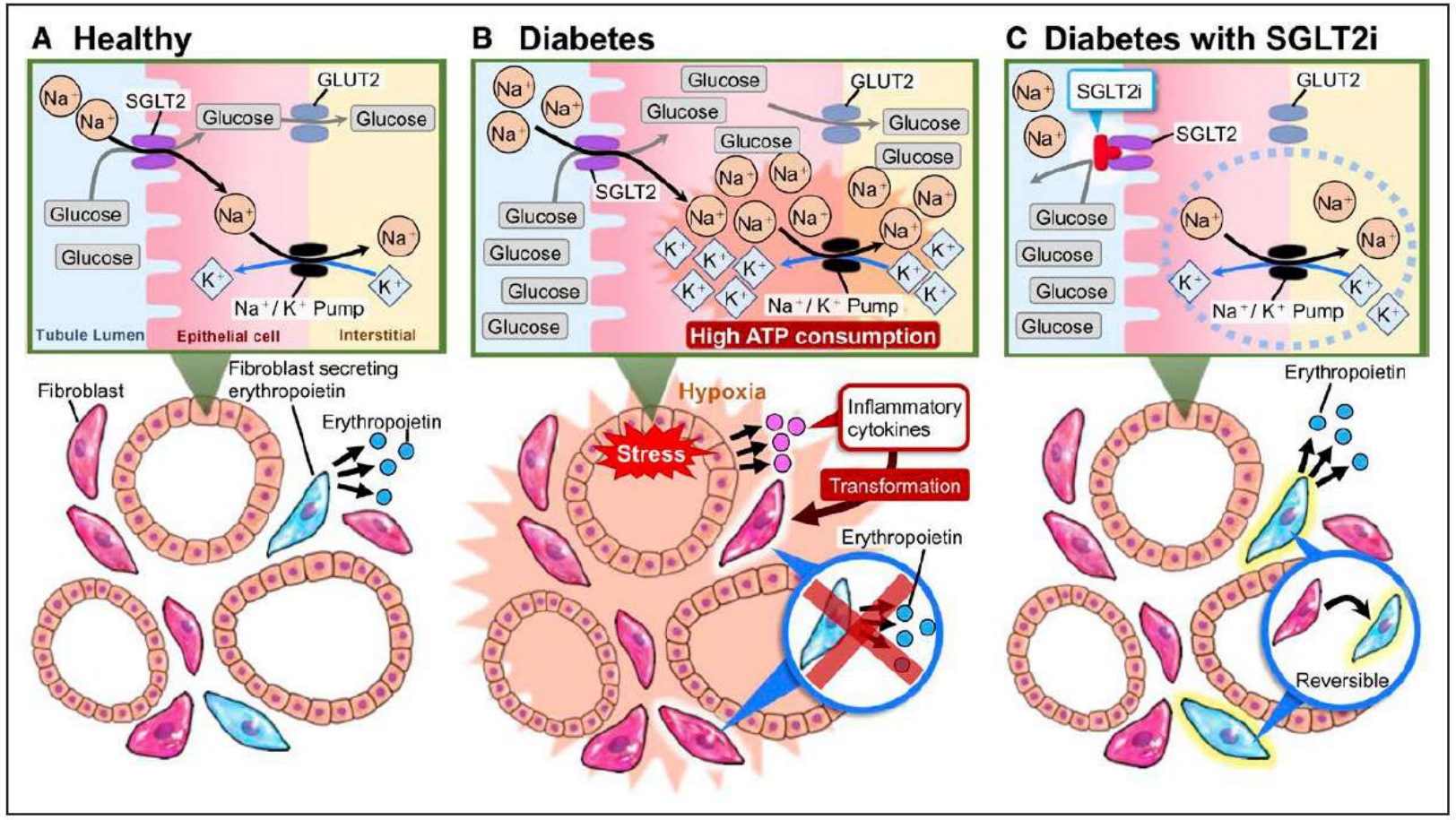


W.G. Herrington et al., European Journal of Heart Failure (2021) doi:10.1002/ejhf.2286; Verma S, McMurray JJV. Diabetologia. 2018;61:2108-2117; Serenelli M et al. Eur Heart J. 2020;41:3402-3418.

Effects of SGLT2 inhibition on cardiorenal pathophysiology

3) OTHER RENAL EFFECTS



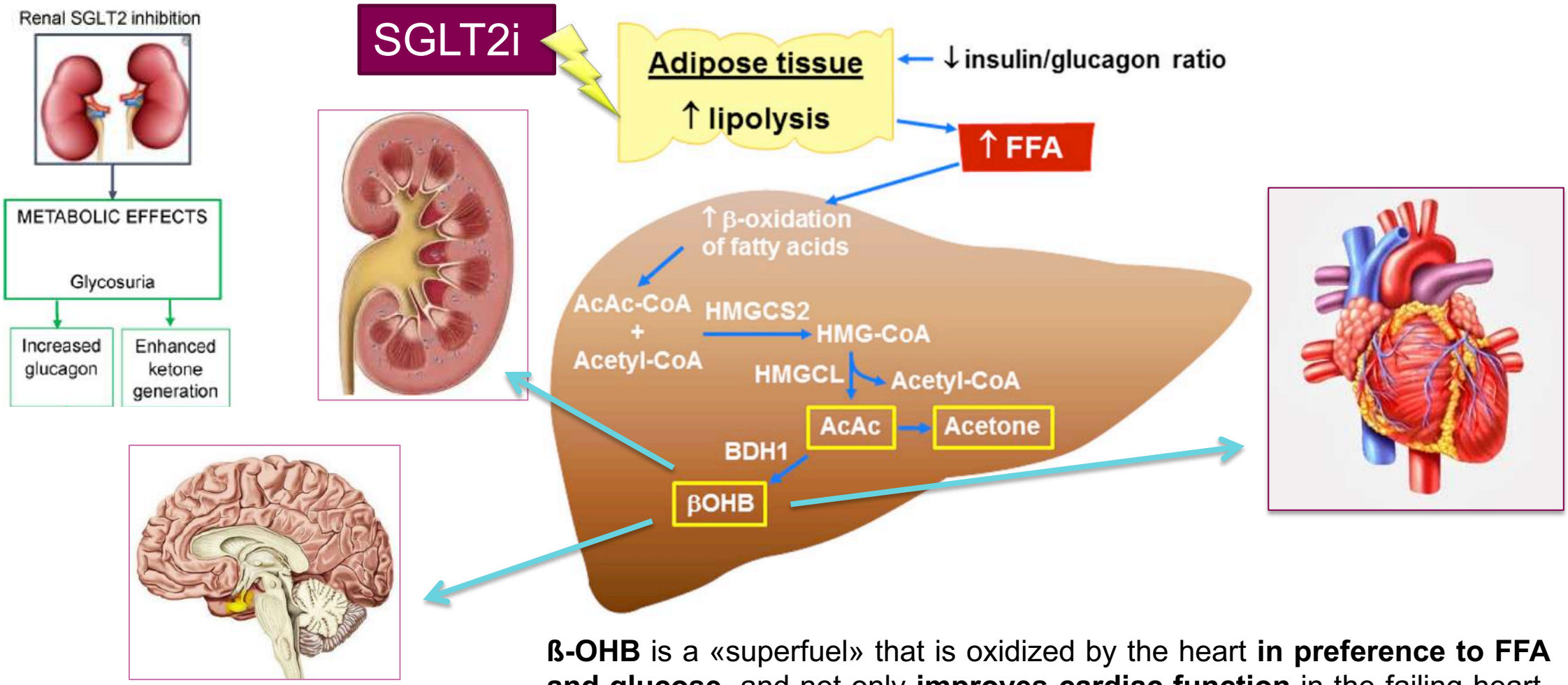


1. ↑ HIF-1 -> ↑ Erythropoietin
2. Reduced inflammatory cytokines
3. Reduced ATP consumption

W.G. Herrington et al., European Journal of Heart Failure (2021) doi:10.1002/ejhf.2286

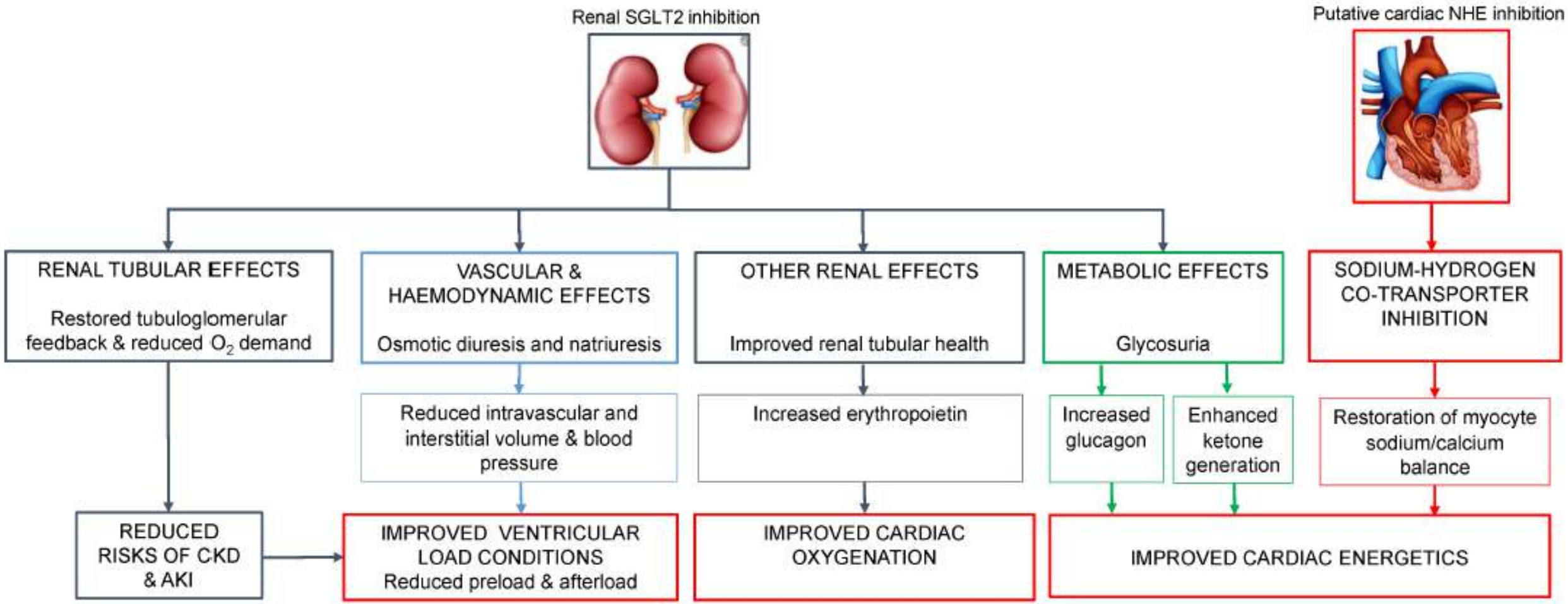
Effects of SGLT2 inhibition on cardiorenal pathophysiology

4) METABOLIC EFFECTS



ß-OHB is a «superfuel» that is oxidized by the heart **in preference to FFA and glucose**, and not only **improves cardiac function** in the failing heart, but also **increases mechanical efficiency**.

Effects of SGLT2 inhibition on cardiorenal pathophysiology



W.G. Herrington et al., European Journal of Heart Failure (2021) doi:10.1002/ejhf.2286

What Is Heart Failure?

Proposed Universal Definition of HF[1]

Clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.

HF Categories According to LVEF

ESC[2]

HFrEF	HFmrEF	HFpEF
HF with reduced EF	**HF with mildly reduced EF**	**HF with preserved EF**
LVEF ≤40%	LVEF 41-49%	LVEF ≥50%

AHA/ACC/HFSA[3]

HFrEF	HFmrEF	HFpEF	HFimpEF
HF with reduced EF	**HF with mildly reduced EF**	**HF with preserved EF**	**HF with improved EF**
LVEF ≤40%	LVEF 41-49%	LVEF ≥50%	Previous LVEF ≤40% and follow-up LVEF >40%

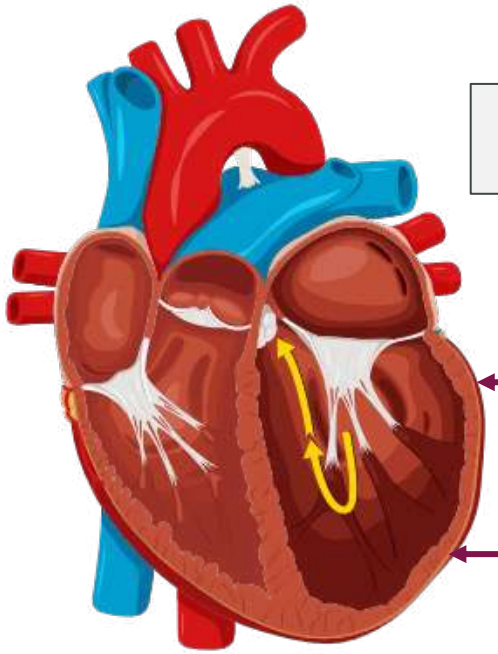
ACC = American College of Cardiology; AHA = American Heart Association; EF = ejection fraction; ESC = European Society of Cardiology; HF = heart failure; HFimpEF = heart failure with improved ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; LVEF = left ventricular ejection fraction.

1. Bozkurt B et al. *Eur J Heart Fail*. 2021;23(3):352-380; 2. McDonagh TA et al. *Eur Heart J*. 2021;42(36):3599-3726; 3. Heidenreich PA et al. *J Am Coll Cardiol.* 2022;79(17):e263-e421.

Differences in HF Pathophysiology[1-3]

HFrEF

LV contraction is reduced resulting in inadequate cardiac output.



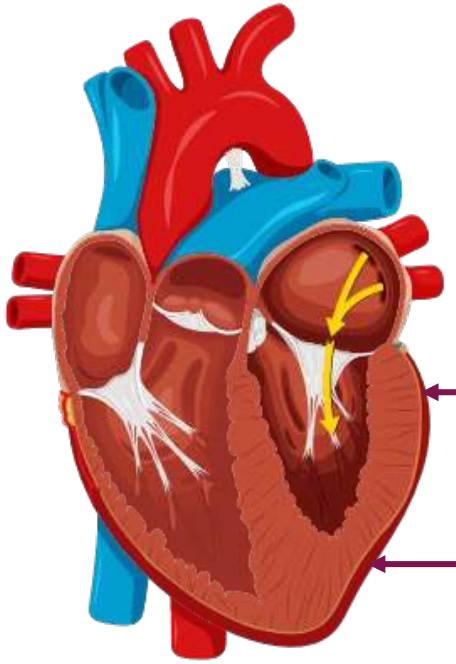
~2/3 of cases are due to CAD

- **LVEF ≤40%**
- **LV dilation**

- **Abnormal contractility**
- **LV remodeling**

HFpEF

LV filling is reduced so that, even though LVEF is normal, cardiac output is reduced.



Substantial pathophysiologic heterogeneity

- **Normal LVEF (≥50%)**
- **No LV dilation**

- **Stiff, thickened walls**
- **Normal contractility**
- **Concentric LV hypertrophy**

CAD = coronary artery disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction.

1. Bloom MW et al. *Nat Rev Dis Primers.* 2017;3:17058; 2. Borlaug BA. *Nat Rev Cardiol*. 2014;11:507-515; 3. Redfield MM. *N Engl J Med*. 2016;375:1868-1877.

HF is a growing public health problem, with high morbidity and mortality

BURDEN

HF affects

~64 million

people worldwide[1]

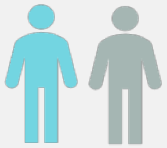
Over 50% of patients with HF have **HFpEF**[2]

HOSPITALIZATION

HF is the **number one cause of hospitalization** in people >65 years[2,a]

hHF is **projected to rise by ~50%** over the next 25 years[3]

MORTALITY



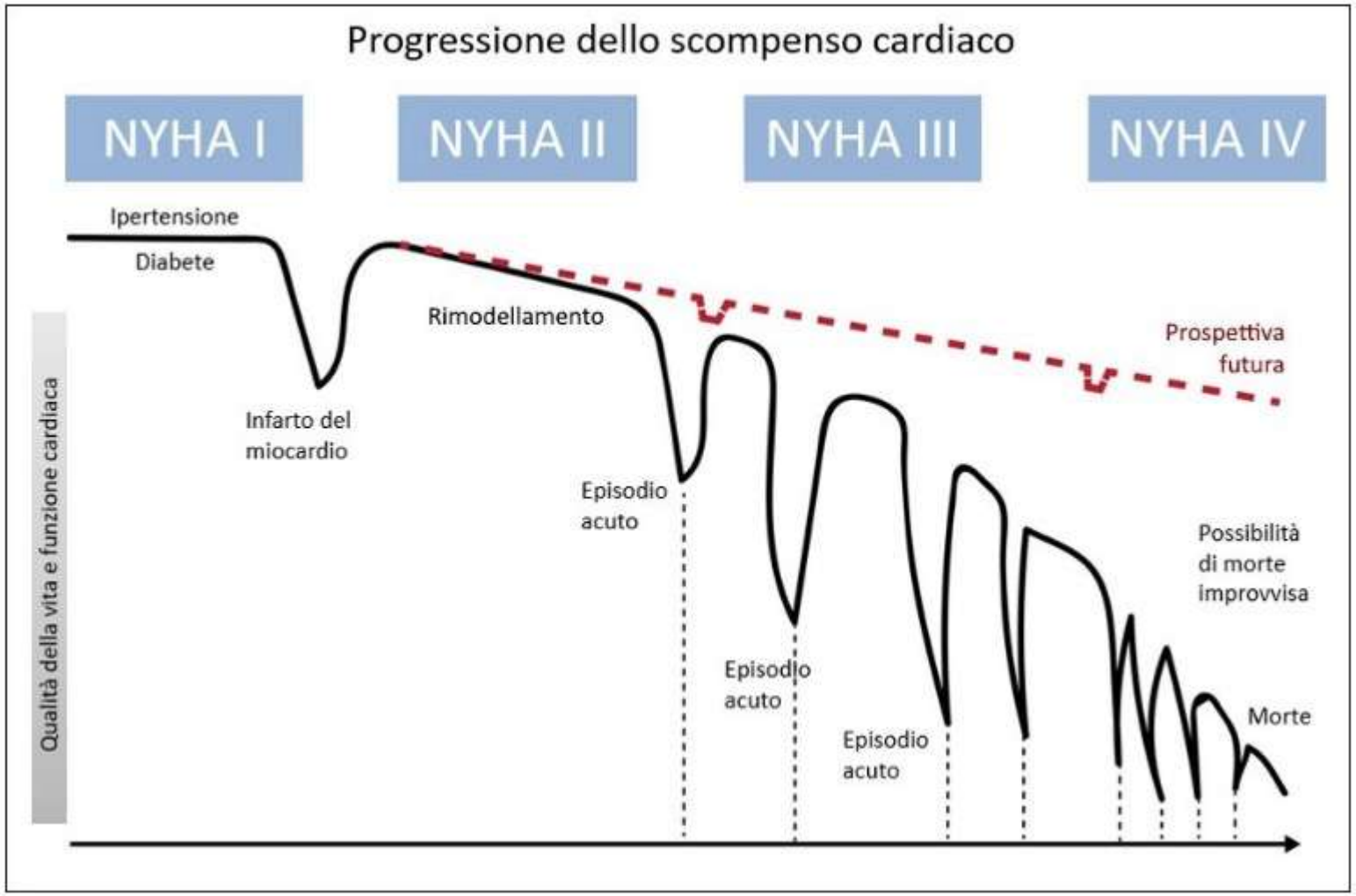
The 5-year mortality rate for patients with HF is **~50%**[4]

Mortality significantly increases after each HF readmission[5]

[a]In developed countries.

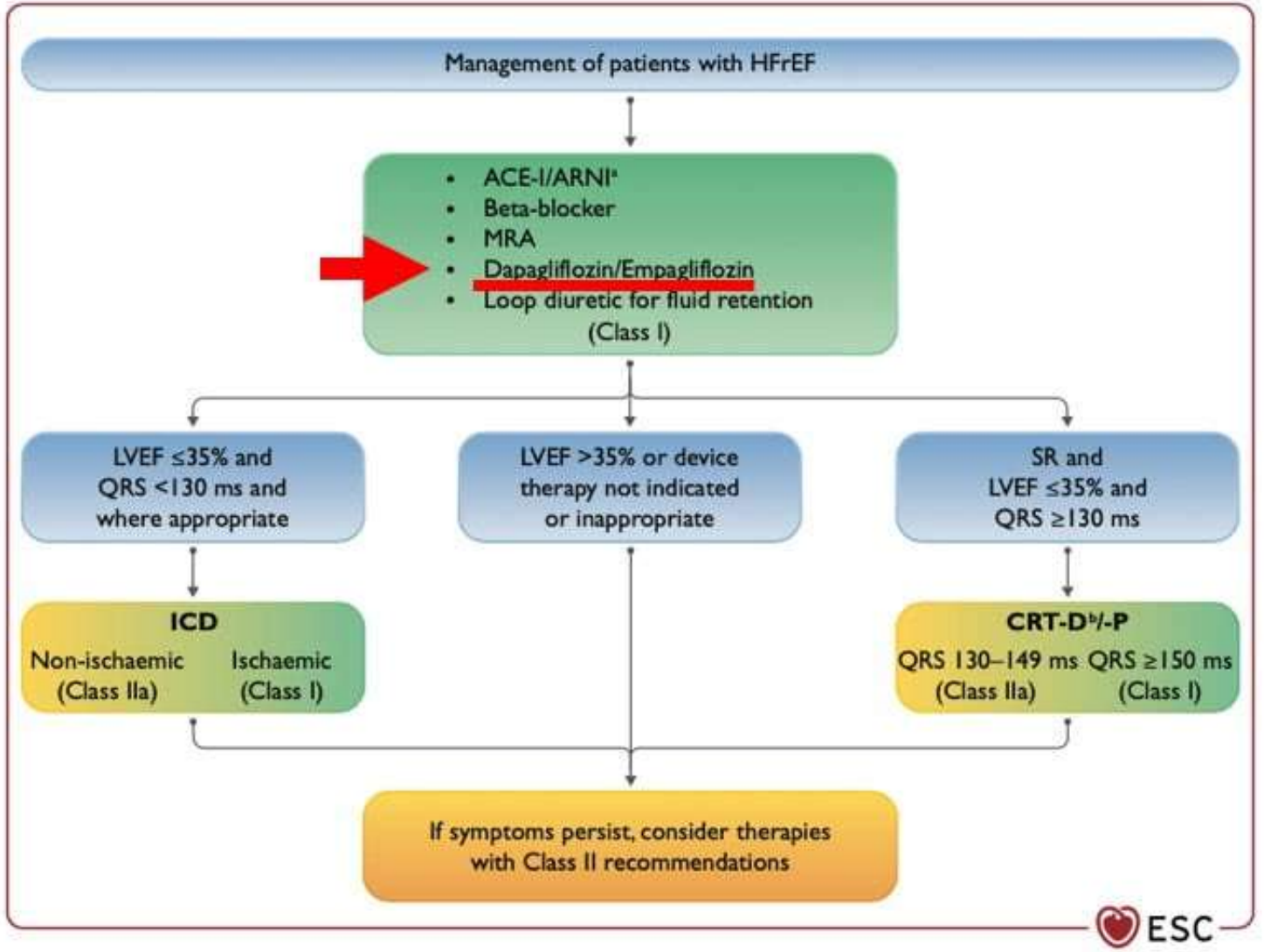
1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Lancet. 2018;392(10159):1789-1858; 2. Cowie MR et al. ESC Heart Fail. 2014;1(2):110-145;
3. Groenewegen A et al. Eur J Heart Fail. 2020;22(8):1342-1356; 55; 4. Jones NR et al. Eur J Heart Fail. 2019;21(11):1306-1325; 5. Setoguchi S et al. Am Heart J. 2007;154(2):260-266;

Progressione dello scompenso cardiaco



Modificato da Georghiade et al. 2005.

ESC 2021 Guidelines HFrEF



ESC 2021 Heart Failure Guidelines: Dapagliflozin is Recommended in Patients with HFrEF to Reduce the Risk of HF Hospitalization and Mortality

Recommendations	Class[a]	Level[b]
An ACEI is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEI in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

[a]Class of recommendation; [b]Level of evidence.

ACEI = angiotensin-converting enzyme inhibitor; ESC = European Society of Cardiology; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.

McDonagh TA et al. Online ahead of print. *Eur Heart J*. 2021.

I pilastri della terapia HFrEF 2021

ACE i/ARB	Neprilysin inhibitor	Beta-blocker	MRA	SGLT2 inhibitor

ESC European Society of Cardiology
European Heart Journal (2021) 42, 681–683
doi:10.1093/eurheartj/ehaa1012

EDITORIAL

Heart failure drug treatment: the fantastic four

Johann Bauersachs *

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Online publish-ahead-of-print 11 January 2021

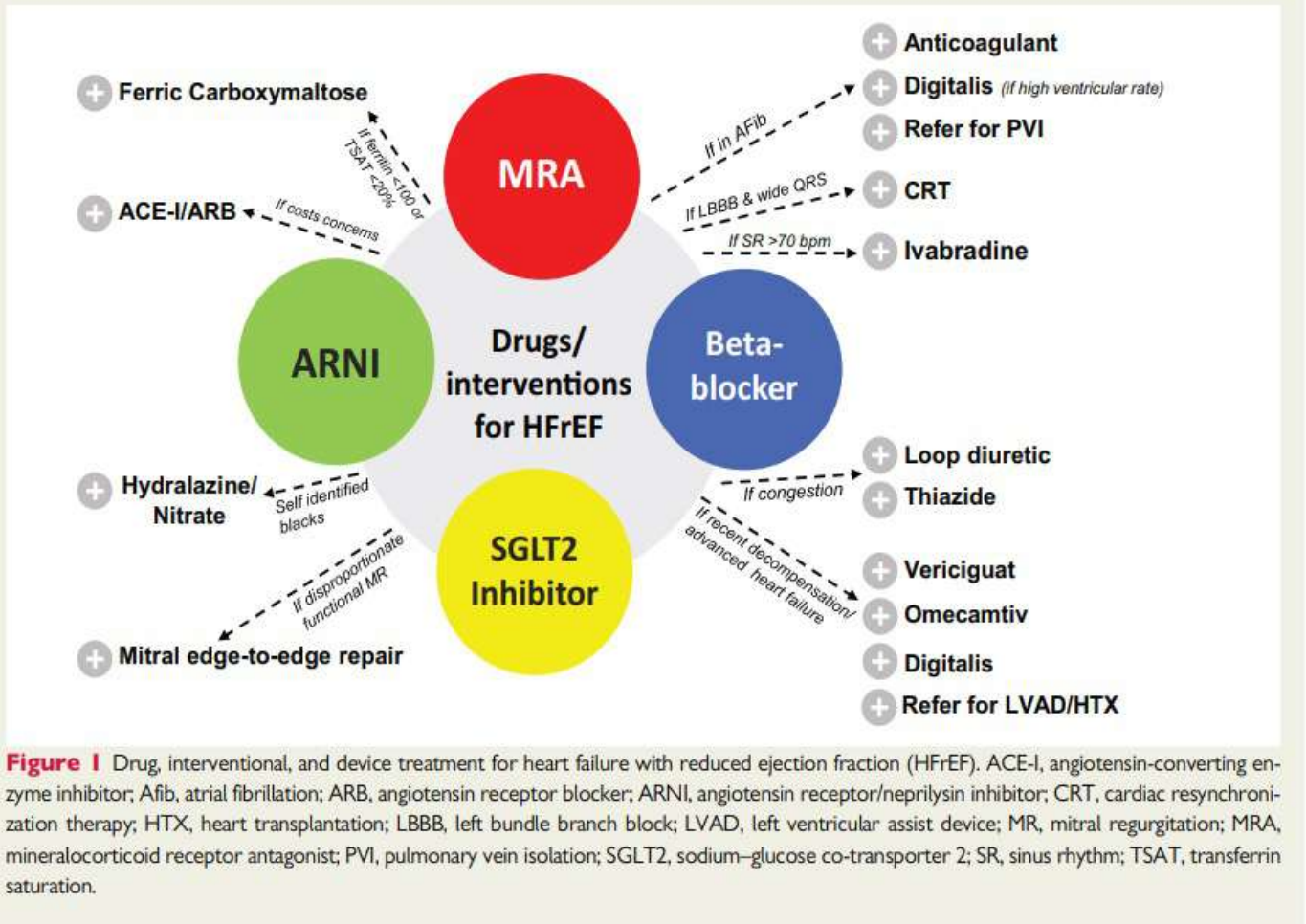


Figure 1 Drug, interventional, and device treatment for heart failure with reduced ejection fraction (HFrEF). ACE-I, angiotensin-converting enzyme inhibitor; Afib, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CRT, cardiac resynchronization therapy; HTX, heart transplantation; LBBB, left bundle branch block; LVAD, left ventricular assist device; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; PVI, pulmonary vein isolation; SGLT2, sodium–glucose co-transporter 2; SR, sinus rhythm; TSAT, transferrin saturation.

In clinical practice, patients without contraindications appear to **gain most benefit from combined treatment with the 'fantastic four':** an ARNI, a beta-blocker, an MRA, and an SGLT2 inhibitor.

J.bauersachs; European Heart Journal (2021) 42,681-683

DAPA-HF: First and Largest SGLT2i HFrEF Trial to Successfully Improve Outcomes and Symptoms[2,5]

DAPA-HF Overview[5]

N=4744

- 45% T2D
- 55% No T2D

1:1 Double-blind

- **DAPA 10 mg n=2373**
- **Placebo n=2371**

Inclusion Criteria: ≥18 years with or without T2D, LVEF ≤40%, NYHA class II-IV, elevated NT-proBNP, eGFR ≥30 mL/min/1.73 m^2, stable SoC HFrEF treatment

Significant Reduction in Composite of CV Death or Worsening HF[5,b]

26% RRR

HR 0.74 (0.65-0.85)
p<0.001

NNT=21

CV Death[6]

18% RRR
p=0.029

hHF[6]

30% RRR
p=0.00003
[Includes urgent HF visits]

Consistent Benefit Across a Broad and Representative Population

- T2D/No T2D[7]
- Background HF therapy[8]
- Diuretic use and dose[9]
- Baseline LVEF[10]
- NT-proBNP[11]
- eGFR[12]

Risk of both **first and recurrent hHF events**[13]

Reduction in **all-cause mortality** (p=0.022[c])[6]

HF symptom improvement more common and deterioration less common[14]

Significantly reduced risk of CV death or worsening HF[b] **as early as**[15]

DAPA-HF Safety[5,7]

DAPA was well-tolerated in patients with and without T2D

Adverse events rarely led to discontinuation of treatment

No events of major hypoglycemia or DKA in patients without T2D

Overview of results from EMPEROR-Reduced[1]

Primary outcome

HHF or CV death

↓ 25% RRR
p<0.001

Secondary outcomes

Total HHF*

↓ 30% RRR
p<0.001

eGFR slope†

+1.73
difference
p<0.001

Exploratory outcomes

Composite kidney outcome‡

HR 0.50
(95% CI 0.32, 0.77)
NA

KCCQ clinical summary score

1.75 rate ratio
p=0.0058

The rates of AEs were similar between empagliflozin and placebo[1]

Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR Reduced trial

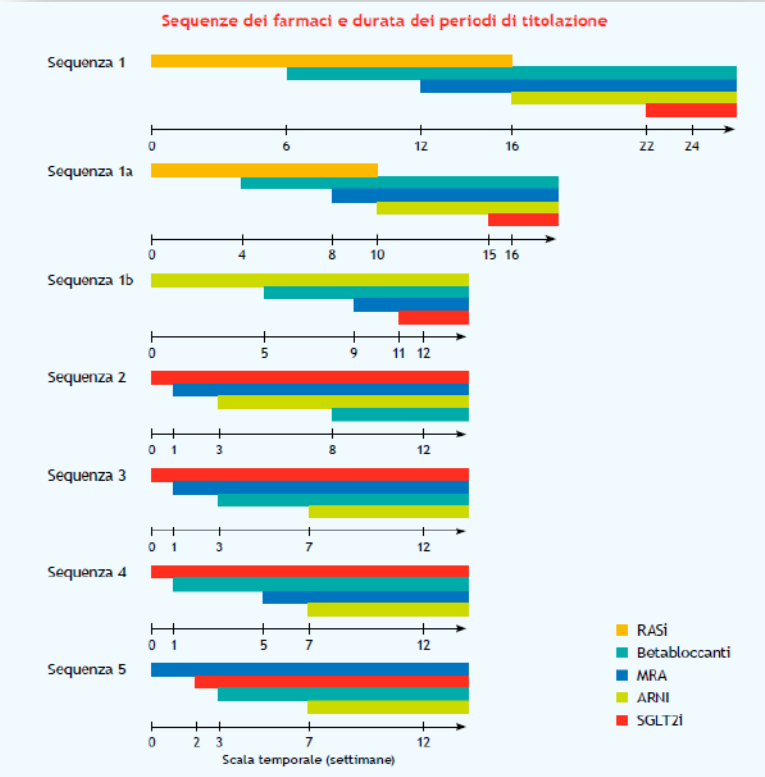
European Heart Journal (2021) 42, 1203–1212 CLINICAL RESEARCH doi:10.1093/eurheartj/ehaa1007

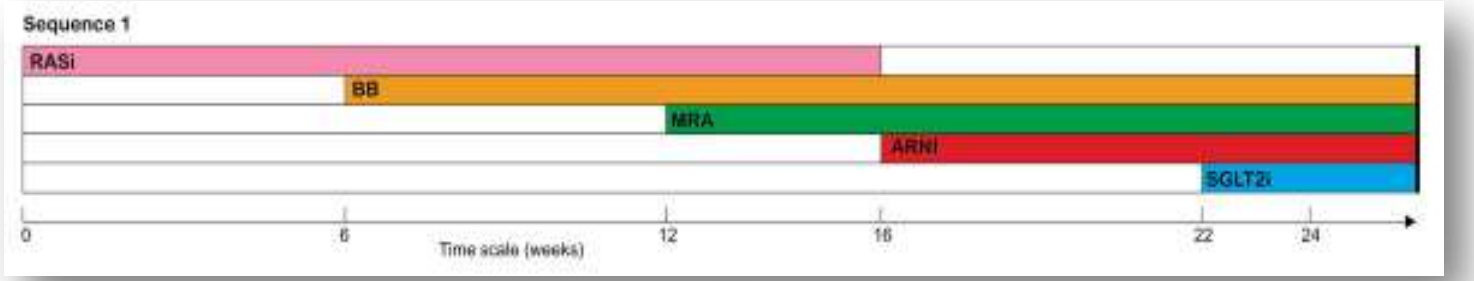
SGLT2i Early Use

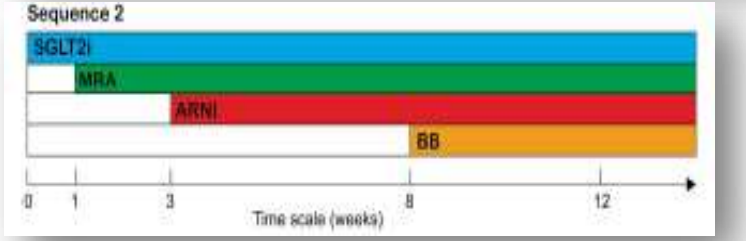
ESC European Society of Cardiology
European Heart Journal (2022) 43, 2573–2587
https://doi.org/10.1093/eurheartj/ehac210
CLINICAL RESEARCH
Heart failure and cardiomyopathies

Accelerated and personalized therapy for heart failure with reduced ejection fraction

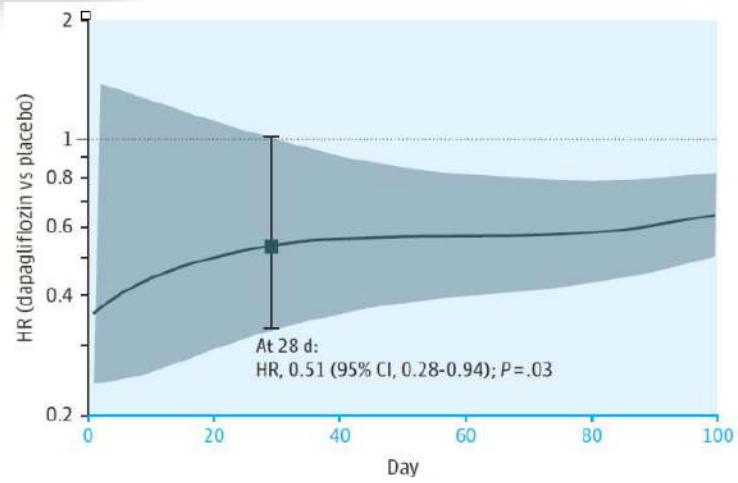
Li Shen[1,2], Pardeep Singh Jhund[2], Kieran Francis Docherty[2], Muthiah Vaduganathan[3], Mark Colquhoun Petrie[2], Akshay Suvas Desai[3], Lars Køber[4], Morten Schou[5], Milton Packer[6,7], Scott David Solomon[3], Xingwei Zhang[1], and John Joseph Valentine McMurray[2]*







«When Sequence 2 was compared with the standard approach (Sequence 1), the number of patients who could have avoided an event* was almost doubled, thanks to increased titration rate and drug order modification.



** CV death or hospitalization for HF*

Li Shen et Al. European Heart Journal (2022) 43 2573-2587

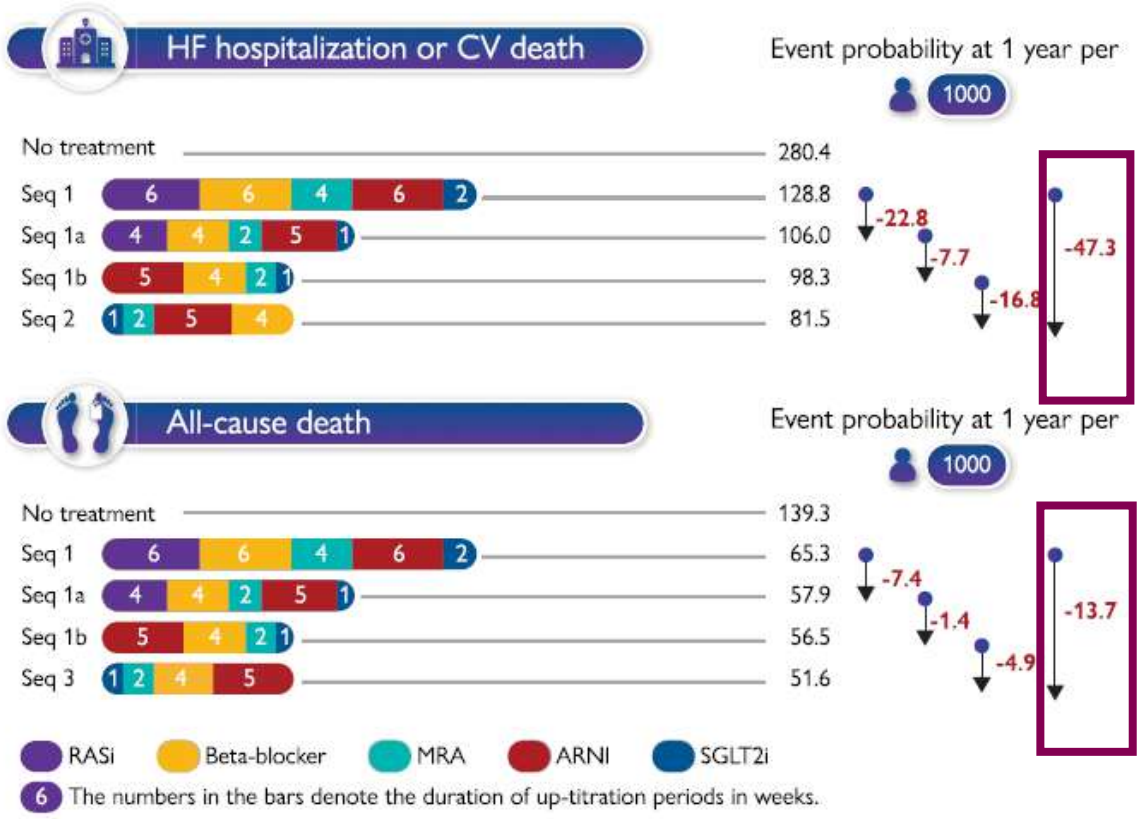
SGLT2i Early Use

ESC European Society of Cardiology
European Heart Journal (2022) **00**, 1–15
https://doi.org/10.1093/eurheartj/ehac210

CLINICAL RESEARCH
Heart failure and cardiomyopathies

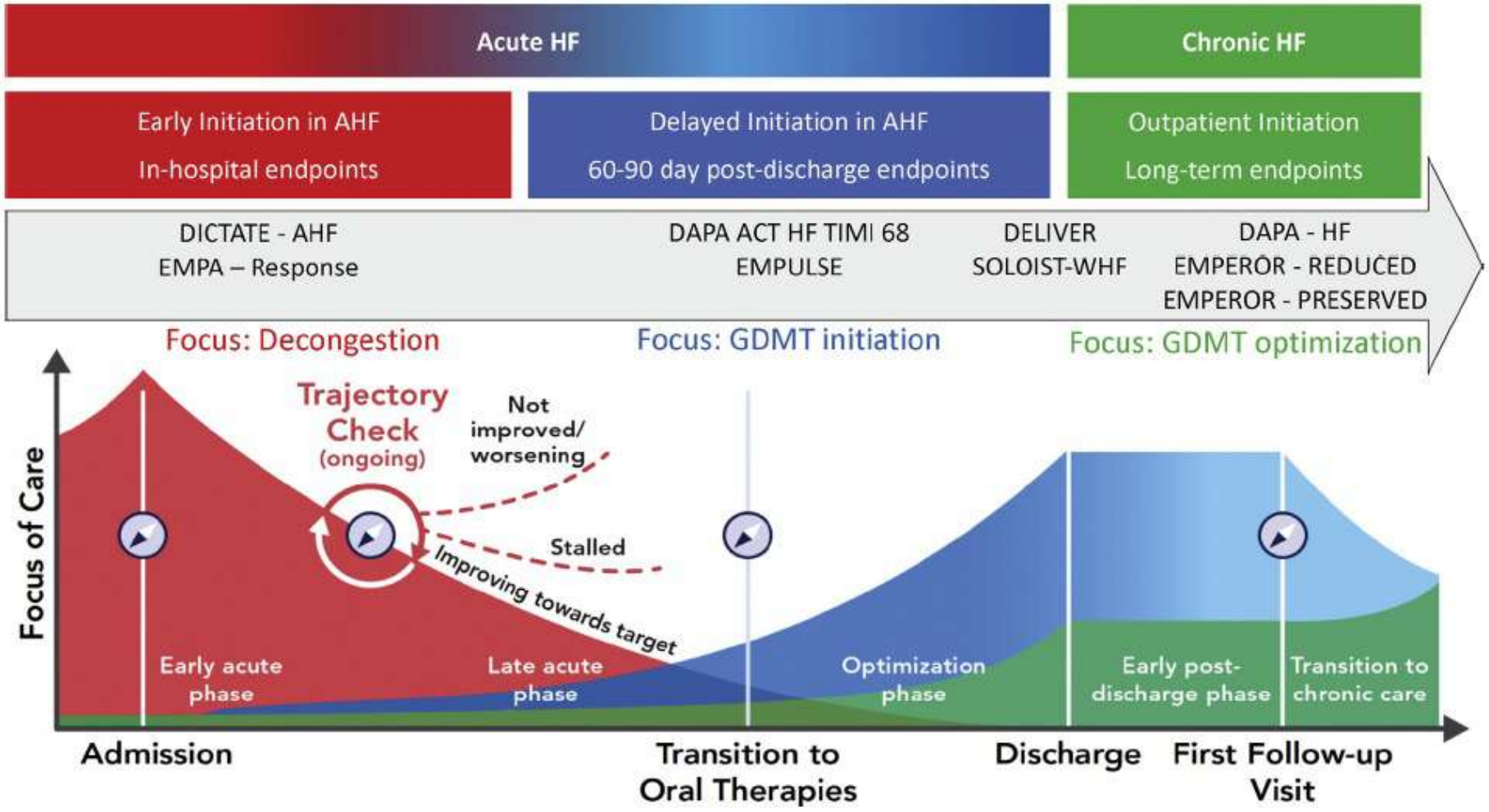
Accelerated and personalized therapy for heart failure with reduced ejection fraction

Li Shen[1,2], Pardeep Singh Jhund[2], Kieran Francis Docherty[2], Muthiah Vaduganathan[3], Mark Colquhoun Petrie[2], Akshay Suvas Desai[3], Lars Køber[4], Morten Schou[5], Milton Packer[6,7], Scott David Solomon[3], Xingwei Zhang[1], and John Joseph Valentine McMurray[2]*



Li Shen et Al. European Heart Journal (2022) 43 2573-2587

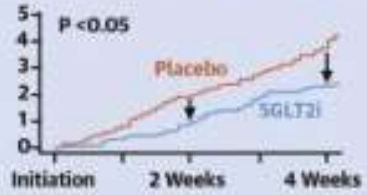
SGLT2i use in acute and chronic HF



In-Hospital Initiation of SGLT2i for HFrEF

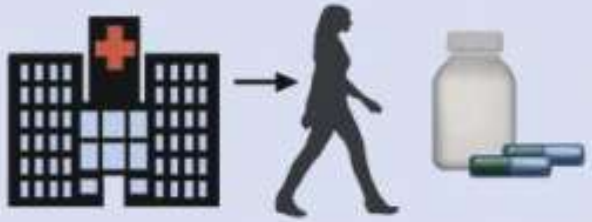
Patients-centered benefits

Early clinical benefit within days to weeks of initiation



Deferring in-hospital initiation exposes patients to excess risk of early post-discharge clinical worsening, readmission, and death.

Deferred in-hospital initiation of GDMT is associated with never initiating



Among patients eligible for therapy, discharging without medication associated with >75% chance will not be started within 1 year.

Potential improved tolerance to other evidence-based therapies

Hospitalized population vulnerable to in-hospital and post-discharge discontinuation of GDMT may particularly benefit from ↓risk of hyperkalemia and worsening renal function.

Safety and Tolerability

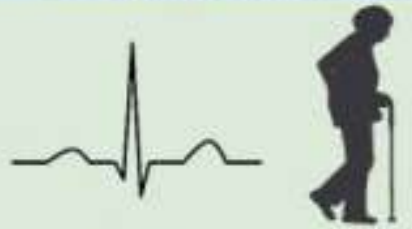
Favorable blood pressure and kidney profile

Minimal to no effect on blood pressure, and no excess risk of symptomatic hypotension. No adverse renal effects (instead preserves kidney function and prevents dialysis).

Favorable glycemic safety profile

No excess risk of hypoglycemia in clinical trials. No excess risk of DKA in HFrEF trials (↑absolute risk of DKA <0.2% across all SGLT2i trials).

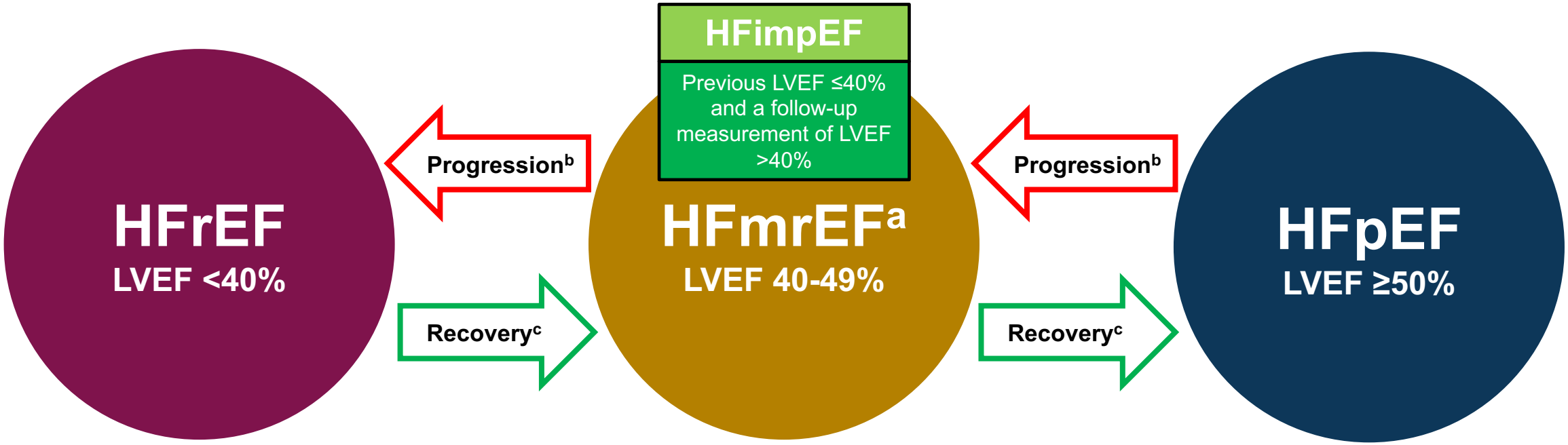
Well-tolerated and safe, including among high-risk subgroups



Numerically fewer serious adverse events than placebo. Rarely symptomatic side effects and well tolerated among older patients.

2021 Rao et al., J AM Coll Cardiol. 2021;78(20):2004-2012

Changes in LVEF Occur Over Time and Are Associated With Specific Patient Characteristics



Factors associated with progression[b]:

Diabetes, ischemic heart disease, lack of specialized HF follow-up, higher NT-proBNP levels

Factors associated with recovery[c]:

Younger age, female, lower HF severity, shorter HF duration, fewer comorbidities

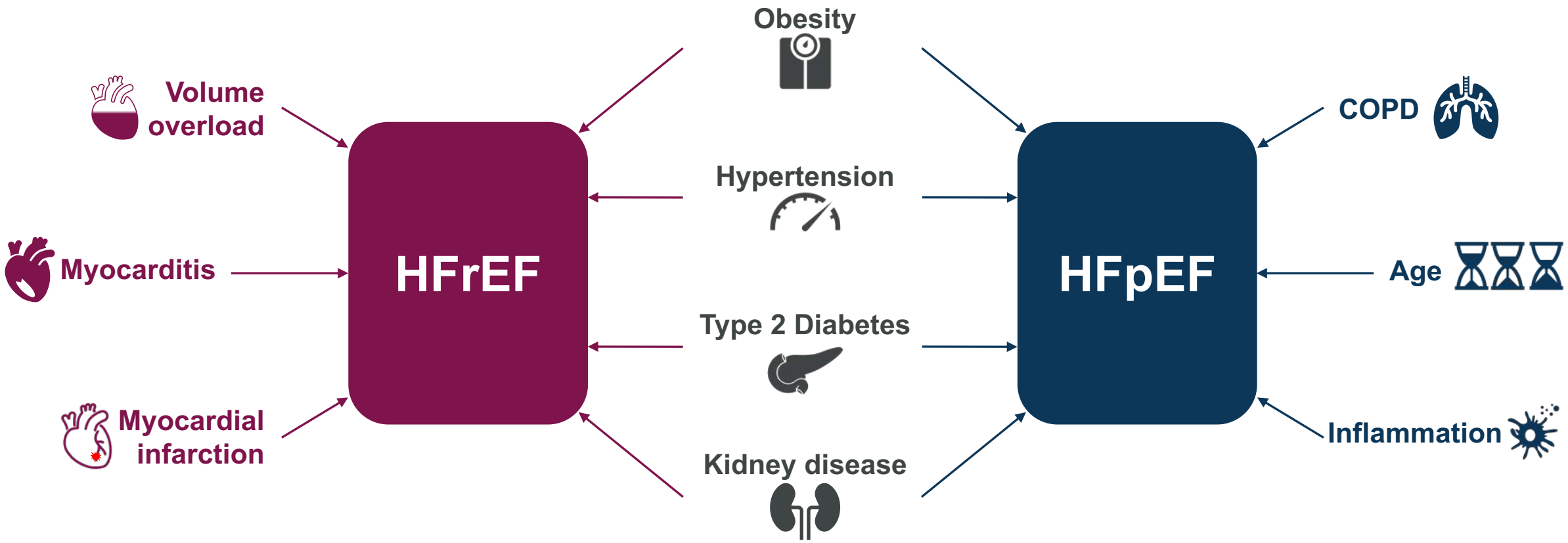
Data from patients with ≥2 EF measurements in the SwedeHF study (N=4942) between May 2000 and December 2012.

[a]Reference uses the term HF with midrange EF (EF 40-49%) for this group; [b]EF decrease; [c]EF increase.

EF = ejection fraction; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Savarese G et al. *JACC Heart Fail*. 2019;7:306-317.

HFrEF and HFpEF Share Many Comorbidities and Risk Factors, While Others Differ



COPD = chronic obstructive pulmonary disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

Simmonds SJ et al. *Cells*. 2020;9:242.

Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class	Level
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.	I	C

HFpEF = heart failure with preserved ejection fraction.

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab368)

Guidelines Consistently Recommend SGLT2i as Class 1A Therapy for HFrEF[1,2]

	ESC European Society of Cardiology	American Heart Association. / AMERICAN COLLEGE of CARDIOLOGY / HFSA HEART FAILURE SOCIETY OF AMERICA
Class 1A recommendation to **reduce hospitalization for HF and mortality**[a]	✓	✓
First Line Therapy with ACEI/ARNI[b], beta-blockers and MRA	✓	✓
Initiate during hospitalization and **promptly optimize**	✓	✓

2022 AHA/ACC/HFSA Guidelines also **recommend SGLT2i** for the treatment of **HFmrEF and HFpEF**

[a]AHA/ACC/HFSA guidelines recommend SGT2i to reduce the risk of hospitalization for HF and CV mortality; [b]AHA/ACC/HFSA guidelines also recommend ARB to reduce morbidity and mortality in patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEI because of cough or angioedema and when the use of ARNI is not feasible.

ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitor; AHA = American Heart Association; ARB = angiotensin-receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; CV = cardiovascular; ESC = European Society of Cardiology; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

1. McDonagh TA et al. *Eur Heart J*. 2021;42:3599-3726; 2. Heidenreich PA et al. *J Am Coll Cardiol.* 2022;79(17):e263-e421.

EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart failure with Preserved Ejection Fraction

Purpose:

Evaluate the effects of SGLT2 inhibitor (Empagliflozin) on cardiovascular death and heart failure hospitalizations in patients with heart failure with a preserved ejection fraction (HFpEF), with or without diabetes.

Trial Design: N=5998, International multicenter (622 centers in 23 countries) randomized placebo controlled, double-blind, event-driven study. Symptomatic HFpEF patients (LVEF>40%) received empagliflozin (10mg once daily) or placebo, in addition to usual therapy. Median follow up period was 26 months.

Primary Endpoint: Composite of CV death or heart failure hospitalization.

Secondary Endpoints: Heart Failure hospitalizations(including first and recurrent events), rate of decline in eGFR during treatment.

	Empagliflozin n=2997	Placebo n=2991	HR (95% CI)	P-value
Primary Composite Outcome: Composite of CV death or HF hospitalization	415 (13.8%)	511 (17.1%)	0.79 (0.69-0.90)	< 0.001
HF hospitalization	259 (8.6%)	352 (11.8%)	0.71 (0.60-0.83)	
Cardiovascular Death	219 (7.3%)	244 (8.2%)	0.91 (0.76-1.09)	
Secondary Outcomes specified in hierarchical testing procedure				
Total number of HF hospitalizations	407	541	0.73 (0.61-0.88)	< 0.001
eGR mean slope change per year (ml/min/1.73m^2)	-1.25±0.11	-2.62±0.11	1.36 (1.06-1.66)	< 0.0001

Results: Empagliflozin reduced the combined risk of cardiovascular death or heart failure hospitalization in patients with HFpEF by 21%, regardless of the presence or absence of diabetes. This benefit was consistent across pre-specified EF subgroups. Empagliflozin reduced total (first and recurrent) hospitalizations for HF by 27%.

Results reflect the data available at the time of presentation.

Presented by: Stefan Anker ESC 2021, The Digital Experience

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

DELIVER[1,2]

N=6263

- LVEF >40% and evidence of structural heart disease
- Elevated NT-proBNP
- Ambulatory or hospitalized
- eGFR ≥25 mL/min/1.73 m^2

1:1 randomization

DAPA 10 mg | **Placebo**

Median follow-up: 2.3 years

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

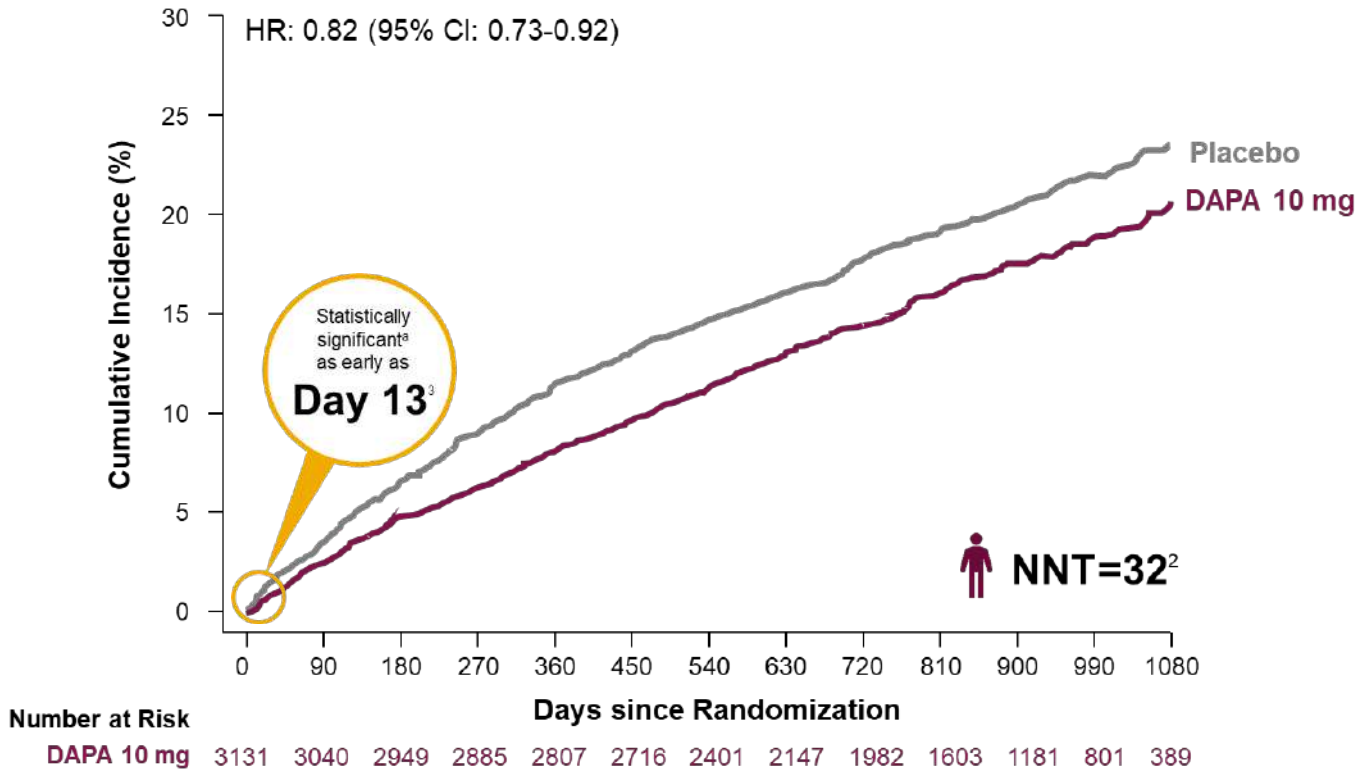
50%
With an eGFR <60 mL/min/1.73 m^2

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.

DELIVER: 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, 0.45; 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

Major guidelines recommend SGLT2 inhibitors across HFrEF, HFmrEF, and HFpEF to reduce hHF and CV mortality[1,2]

ESC[a] European Society of Cardiology

HF type	COR	LOE
HFrEF (LVEF ≤40%)	I	A

American Heart Association. / AMERICAN COLLEGE of CARDIOLOGY / HFSA HEART FAILURE SOCIETY OF AMERICA

HF type	COR	LOE
HFrEF (LVEF ≤40%)	1	A
HFmrEF (LVEF 41-49%)	2a	B-R
HFpEF (LVEF ≥50%)	2a	B-R

GDMT use, including SGLT2 inhibitors, is suboptimal[3]

[a]2021 ESC HF guidelines recommend dapagliflozin or empagliflozin in patients with HFrEF to reduce the risk of hHF and death. These guidelines were released before full results of SGLT2 inhibitor trials in patients with HFmrEF or HFpEF, with or without T2D, were available.[1,4-6]

1. McDonagh TA et al. *Eur Heart J*. 2021;42(36):3599-3726; 2. Heidenreich PA et al. *J Am Coll Cardiol*. 2022;79(17):e263-e421; 3. Ghazi L et al. *J Am Coll Cardiol*. 2022;79(22):2203-2213; 4. Anker SD et al. *N Engl J Med*. 2021;385:1451-1461; 5. Nassif ME et al. *Nat Med*. 2021;27:1954-1960; 6. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022.

Guida pratica ANMCO all'impiego degli inibitori del cotrasportatore sodio-glucosio di tipo 2 nei pazienti con scompenso cardiaco

Stefania Angela Di Fusco[1], Antonella Spinelli[1], Stefano Aquilani[1], Michele Massimo Gulizia[2], Domenico Gabrielli[3,4], Fabrizio Oliva[5], Furio Colivicchi[1]

Tabella 3. Considerazioni pratiche per l'impiego degli inibitori del cotrasportatore sodio-glucosio di tipo 2 nei pazienti con scompenso cardiaco e frazione di eiezione ridotta.

In chi e quando?	Indicazioni	Pazienti con HFrEF indipendentemente dalla presenza di DM2
	Controindicazioni	Gravidanza o allattamento eGFR <20 o 25 mL/min/1.73 m² per empagliflozin e dapagliflozin rispettivamente Ipovolemia o PAS <95 mmHg DM1 per mancanza di dati su efficacia e sicurezza Storia di chetoacidosi
Quale dosaggio?	Dapagliflozin	Dose iniziale/di mantenimento 10 mg/die
	Empagliflozin	Dose iniziale/di mantenimento 10 mg/die
Come usarli?		Definire la funzione renale all'inizio della terapia e monitorarla regolarmente Monitorare la glicemia (soprattutto nei pazienti diabetici) Identificare eventuali fattori di rischio per chetoacidosi ed eliminarli Monitorare regolarmente il bilancio di liquidi, particolarmente se il paziente assume diuretici, se è anziano o fragile
Effetti collaterali		Glicosuria: predisposizione ad infezioni fungine genito-urinarie Ipoglicemia: usare con cautela in associazione a insulina, sulfoniluree e altri insulino-secretagoghi Ipotensione: valutare lo stato di idratazione e ridurre o sospendere eventuale terapia diuretica in atto Chetoacidosi: da sospettare in caso di nausea, vomito, anoressia, dolore addominale, sete eccessiva, difficoltà a respirare, confusione, insolita fatica Fascite necrotizzante del perineo o gangrena di Fournier

DM1, diabete mellito di tipo 1; DM2, diabete mellito di tipo 2; eGFR, filtrato glomerulare stimato; HFrEF, scompenso cardiaco con frazione di eiezione ridotta; PAS, pressione arteriosa sistolica.

Guida pratica ANMCO all'impiego degli inibitori del cotrasportatore sodio-glucosio di tipo 2 nei pazienti con scompenso cardiaco

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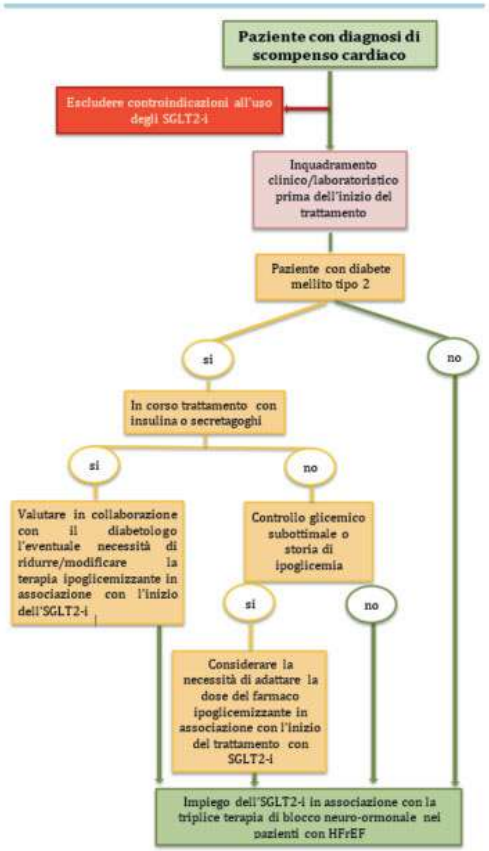
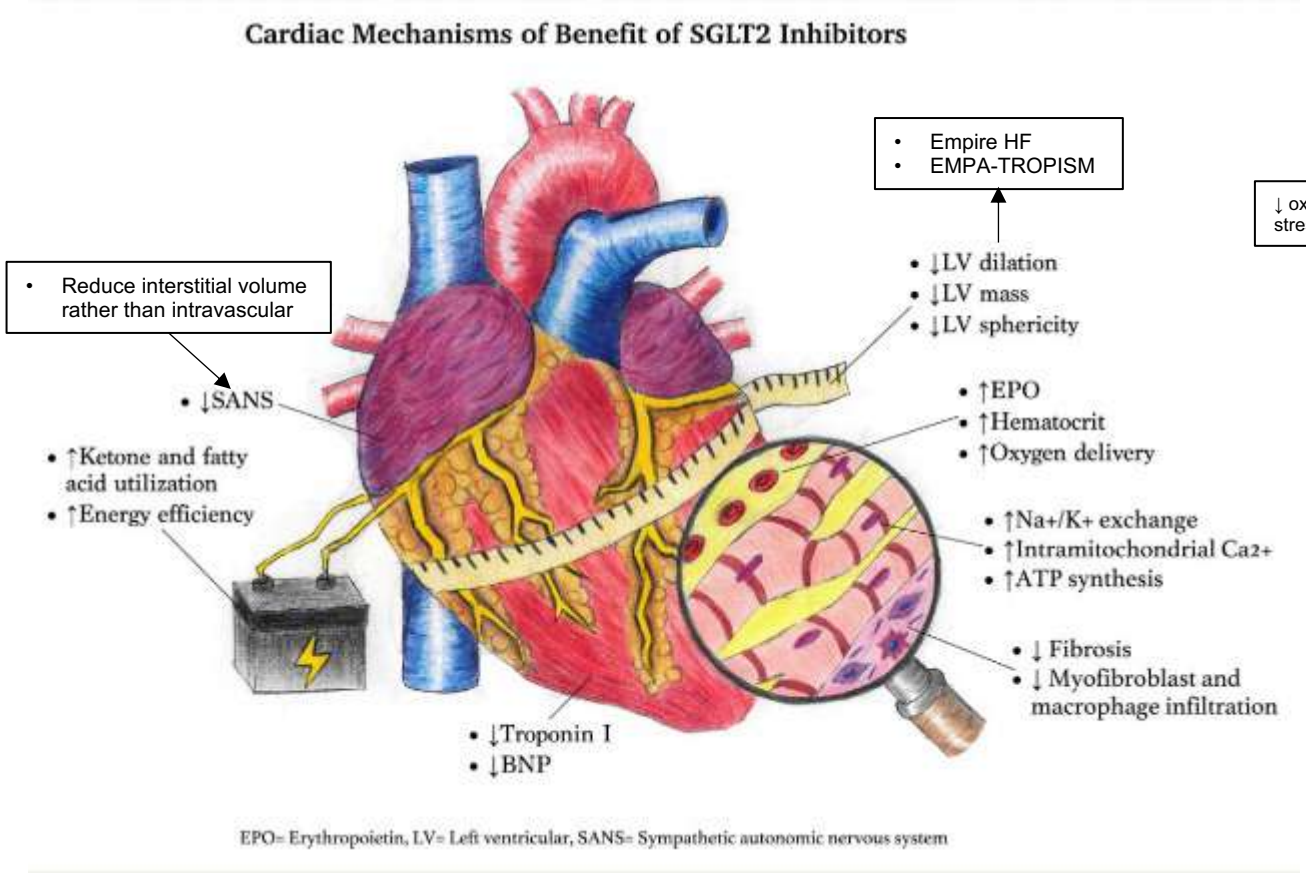
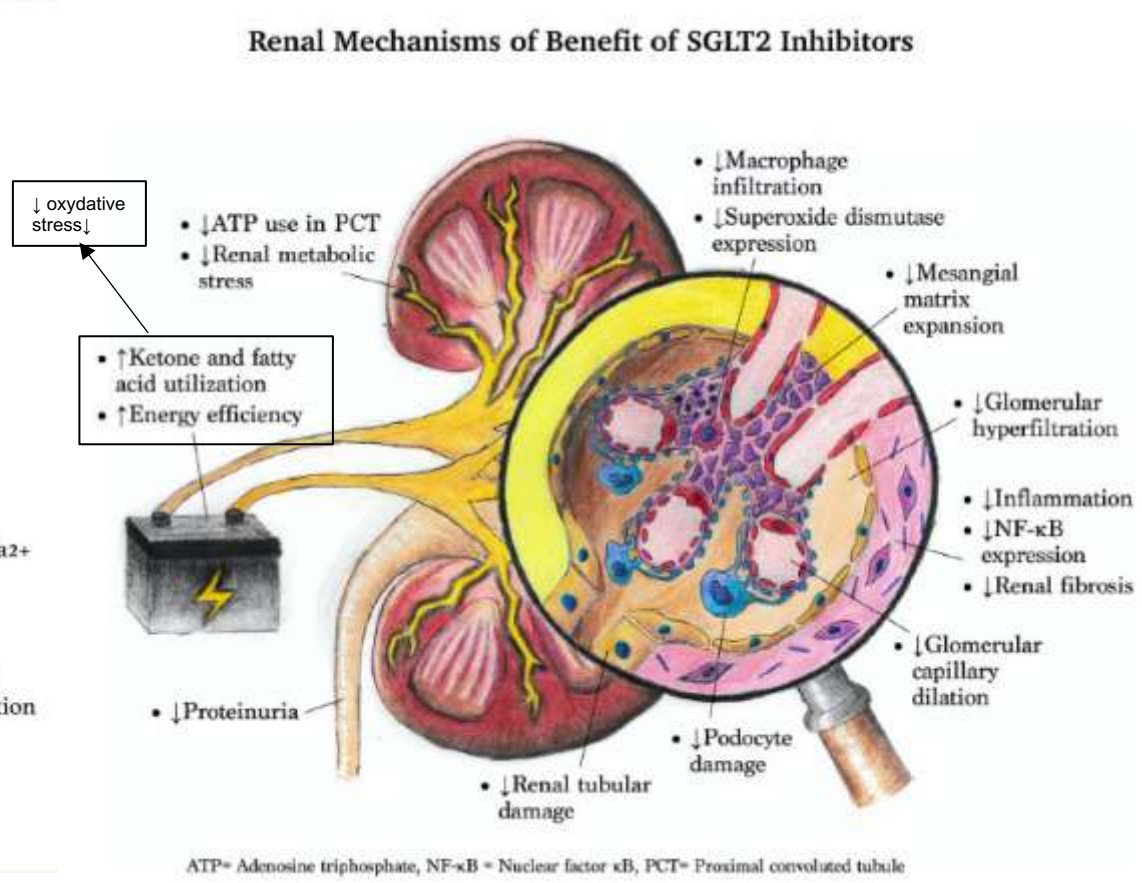


Figura 2. Algoritmo per l'impiego degli inibitori del cotrasportatore sodio-glucosio di tipo 2 (SGLT2-i) nei pazienti con scompenso cardiaco.
HFrEF, scompenso cardiaco con frazione di eiezione ridotta (<40%).
Modificata da Di Fusco et al.[22]

G Ital Cardiol 2023;24(1):66-74

Cardio-Renal Mechanisms of benefit of SGLT2 inhibitors





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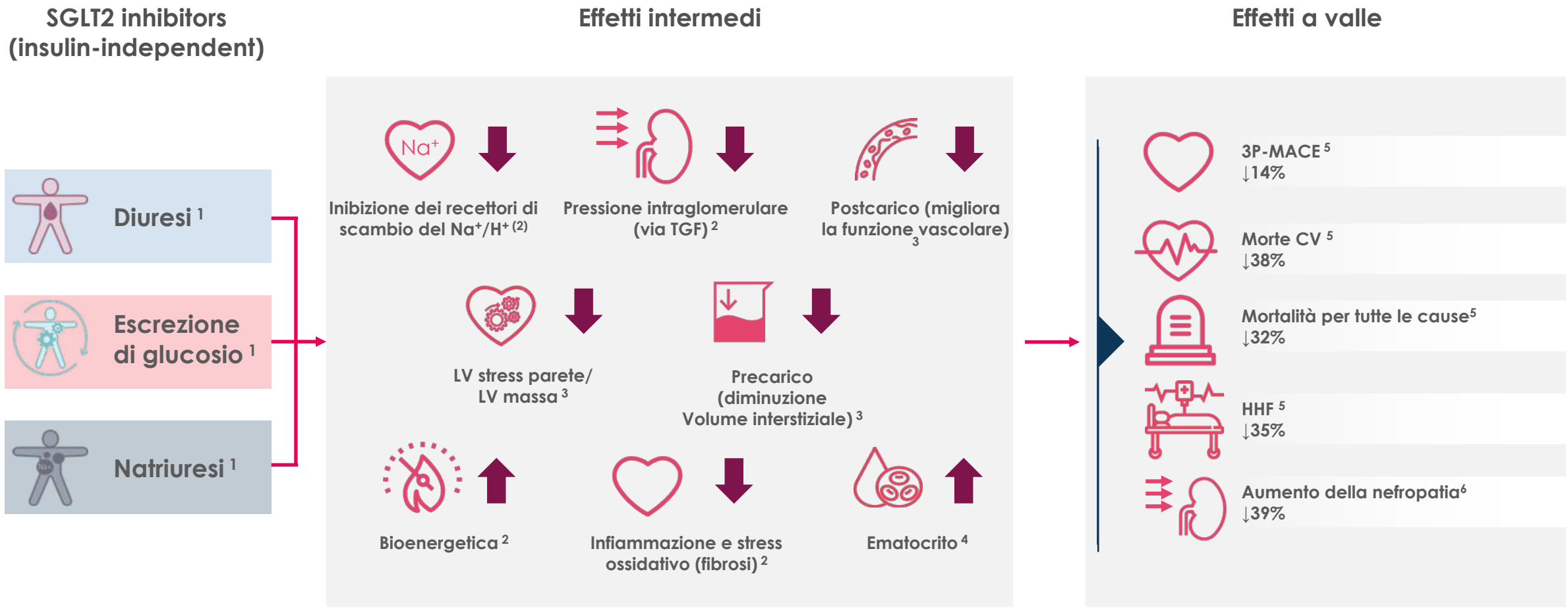
https://doi.org/10.1093/ehjcvp/pvab056

Gli effetti degli inibitori SGLT2 sul sistema cardio-renale-metabolici possono essere mediati da molteplici meccanismi



SGLT2: sodium-glucose cotransporter 2, LV: left ventricular; HHF: hospitalisation for heart failure; TGF: tubuloglomerular feedback

1. Giugliano et al. Cardiovasc Diabetol (2021) 20:17; 2. Barutta et al., Diabetes Metab Res Rev. 2019;e3171; 3. Margonato D et al., Heart Failure Reviews (2021) 26:337–345; 4. Sano M et al., J Clin Med Res. 2016;8(12):844-847,
5. Zinman B et al. N Engl J Med 2015:373:2117; 6. Wanner C et al. N Engl J Med 2016;375:323

ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–2
doi:10.1093/eurheartj/ehab765

Braunwald's Corner

SGLT2 inhibitors: the statins of the 21st century

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A relatively small number of drugs have been responsible for major advances in medical practice. The discovery, development, and elucidation of the mechanisms of action of aspirin, penicillin, and statins are remarkable success stories, each with some surprises and each crowned by a Nobel Prize. The sodium glucose co-transporter inhibitors have been proven effective in the treatment of type 2 diabetes mellitus, various forms of heart failure, and kidney failure and represent *the, or one of the* major pharmacological advances in cardiovascular medicine in the 21st century.

Grazie