KGP Biel/Bienne
Kardiologische Gemeinschaftspraxis AG
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HIRSLANDEN
KLINIK LINDE
CLINIQUE DES TILLEULS

KARDIOLOGIE

DONNERSTAG, 9. NOVEMBER 2023, 16.00 – 19.30 UHR
AMAG LOUNGE, TISSOT ARENA, BIEL

«MANAGEMENT DER HFpEF»

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Professor emer. (Universität Bern)
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HerzGefässZentrum Im Park, Zürich

Ehem. Chefarzt & Extraordinarius für Herzinsuffizienz (1993 – 2017), Kardiologie, Inselspital Bern

Topics

1) History & Relevance of HFpEF
2) Definitions
3) Management of HFpEF
4) It works „why“ ?

Classification of Heart Failure

HF with reduced EF (HFrEF):

- HF with LVEF ≤ 40%

HF with mildly reduced EF (HFmrEF):

- HF with LVEF 41-49%

HF with preserved EF (HFpEF):

- HF with LVEF ≥ 50%

HF with improved EF (HFimpEF):

- HF with a baseline LVEF ≤ 40%, a ≥ 10 point increase from baseline LVEF, and a second measurement of LVEF > 40%

M. Wallner, Q. Zhou, Zirlik, Mohacsi P. SMF 2022, submitted

Life expectancy in Switzerland

smw · swiss medical weekly

Original article | Published 17 February 2023 | doi:10.57187/smw.2023.40043
Cite this as: Swiss Med Wkly. 2023;153:40043

Trends in the disability-free life expectancy in Switzerland over a 10-year period: an analysis of survey-based data

Laurence Seematter-Bagnoud[ab], Giulia Belloni[a], Jonathan Zufferey[c], Sonia Pellegrini[c], Christophe Bula[b], Isabelle Peytremann-Bridevaux[a]

[a] Centre for Primary Care and Public Health (Unisanté), Department of Epidemiology and Health Systems, University of Lausanne, Switzerland
[b] Service of Geriatric Medicine and Geriatric Rehabilitation, Lausanne University Hospital, Lausanne, Switzerland
[c] Swiss Health Observatory (Obsan), Neuchâtel, Switzerland

2021 :

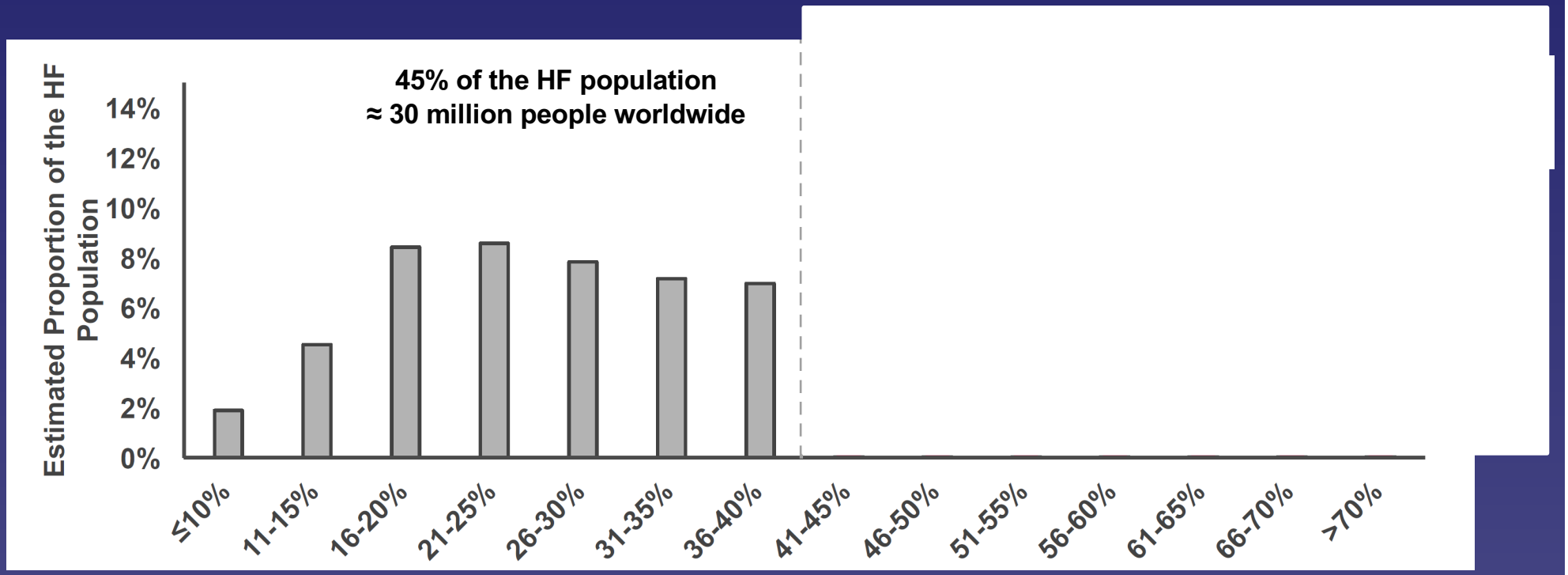
for women → 85.7 years

for men → 81.6 years

Early years of the 20th century :

< 50 years

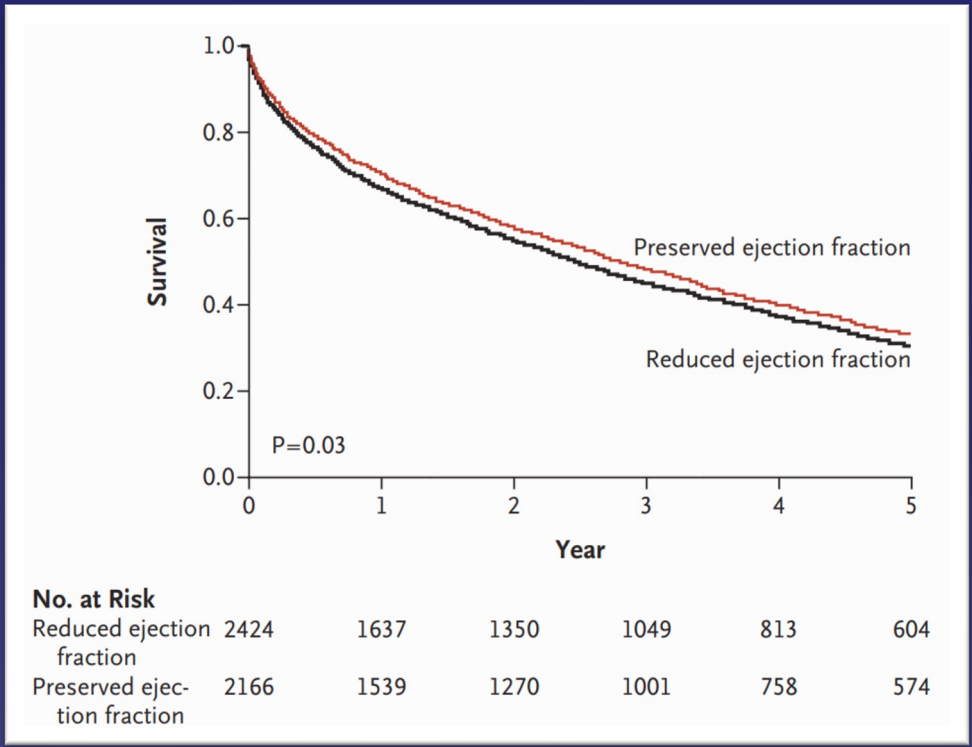
Häufig



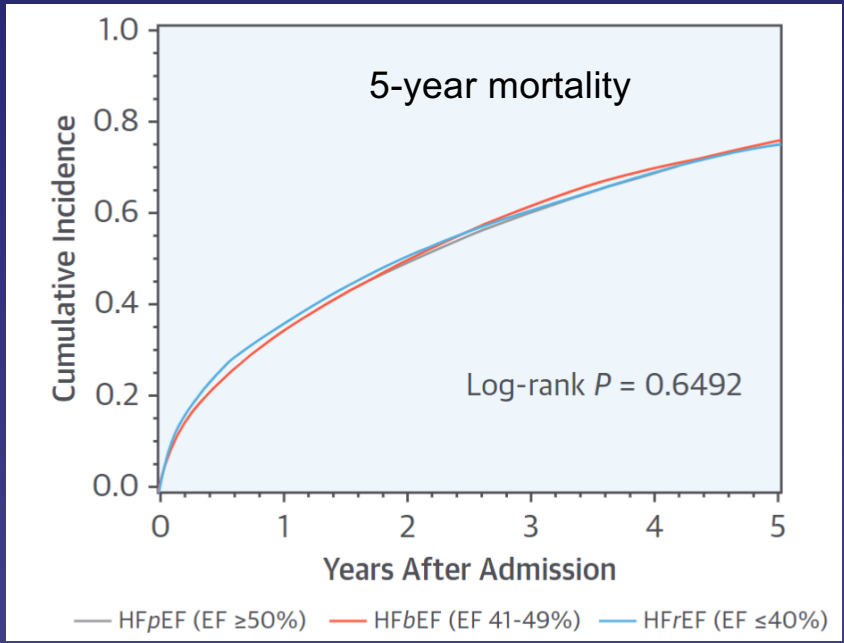
GWTG-HF registry

Vaduganathan M et al., JAMA Cardiology, 2021

Schlechte Prognose



Olmsted County, Minnesota:1987 – 2001 (n=4.596)

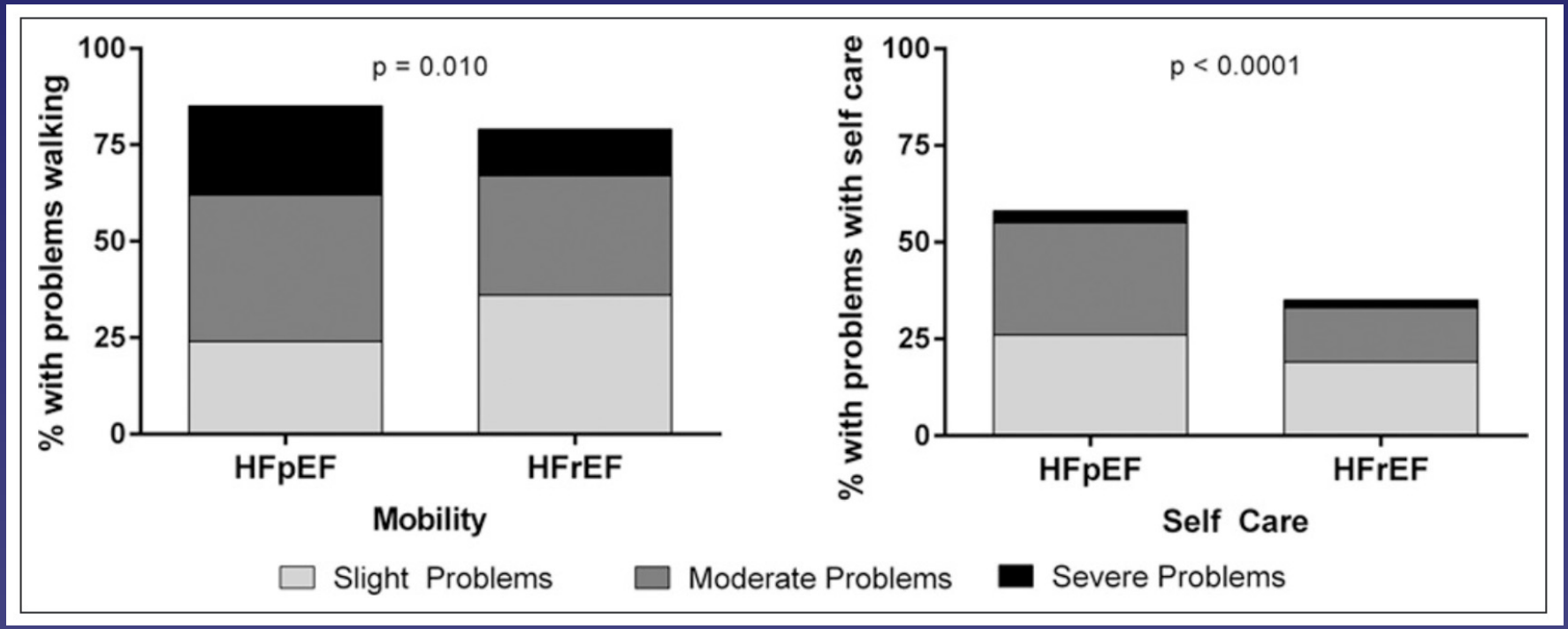


GWTG-HF: 2005 – 2009 (n=39.982)

Owan et al., NEJM, 2006
KS Shah et al., JACC, 2017

Schlechte Lebensqualität

≥ 60a, hospitalized with ADHF, n=202

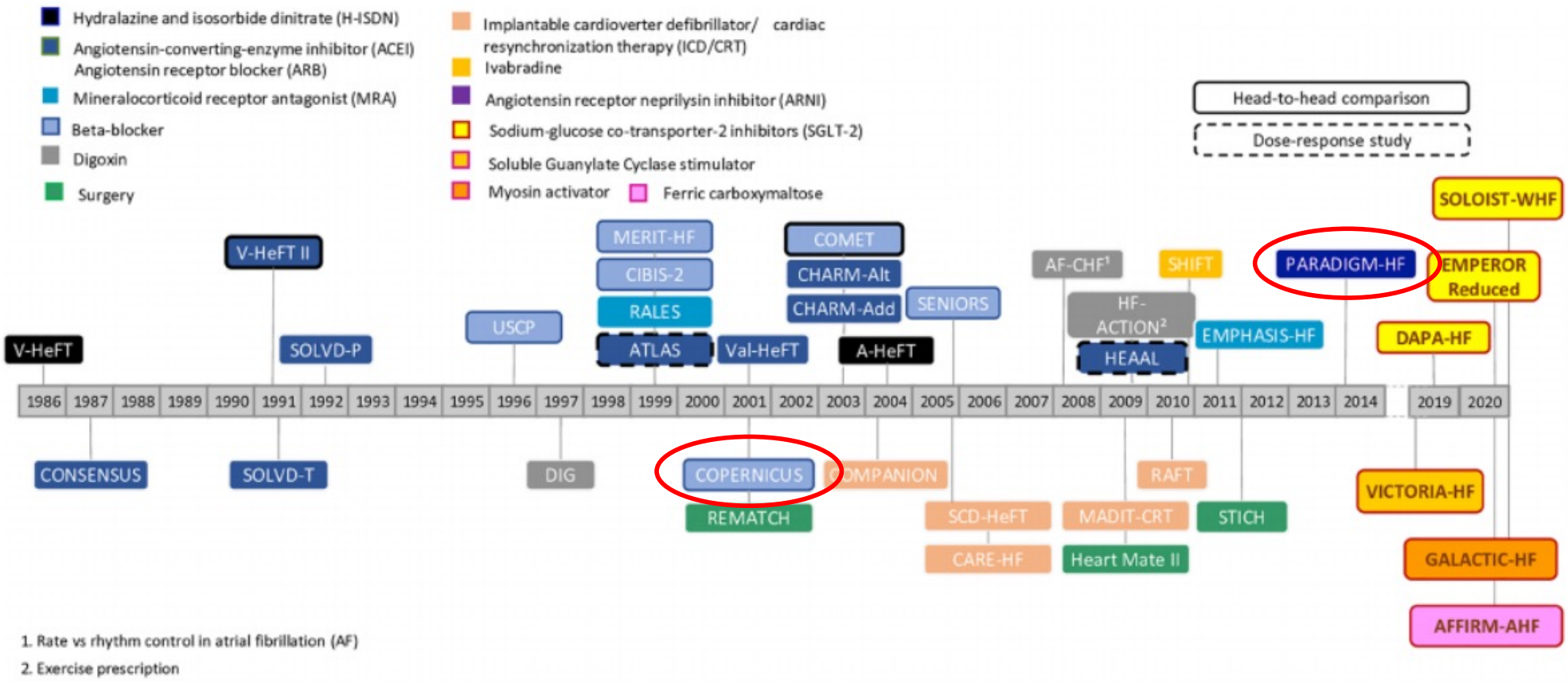


HJ Warraich et al., Circ Heart Fail.,2018

Heart failure in the last year: progress and perspective

Daniela Tomasoni[1,2], Marianna Adamo[1,2], Markus S. Anker[3,4,5,6], Stephan von Haehling[7,8], Andrew J. S. Coats[9] and Marco Metra[1,2]*

Figure 3 Positive trials in the treatment of heart failure with reduced ejection fraction from 1986 to 2020. Modified from McMurray. [168]



ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 3505–3530
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13124

Negative RCTs for HFpEF

PEP-CHF	Perindopril
CHARM-Preserved	Candesartan
I-PRESERVE	Irbesartan
TOPCAT	Spironolacton
DIG-Preserved	Digoxin
PARAGON	Valsartan/Sacubitril

ESC-Guidelines 2021

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Table 9 **Objective evidence of cardiac structural, functional and serological abnormalities consistent with the presence of left ventricular diastolic dysfunction/raised left ventricular filling pressures**[259,261]

Parameter[a]	Threshold	Comments
LV mass index **Relative wall thickness**	≥**95** g/m^2 (Female), ≥**115** g/m^2 (Male) >**0.42**	Although the presence of concentric LV remodelling or hypertrophy is supportive, the absence of LV hypertrophy does not exclude the diagnosis of HFpEF
LA volume index[a]	>**34** mL/m^2 (SR)	In the absence of AF or valve disease, LA enlargement reflects chronically elevated LV filling pressure (in the presence of AF, the threshold is >40 mL/m^2)
E/e' ratio at rest[a]	>**9**	Sensitivity 78%, specificity 59% for the presence of HFpEF by invasive exercise testing, although reported accuracy has varied. A higher cut-off of 13 had lower sensitivity (46%) but higher specificity (86%).[71,259,274]
NT-proBNP **BNP**	>**125** (SR) or >**365** (AF) pg/mL >**35** (SR) or >**105** (AF) pg/mL	Up to 20% of patients with invasively proven HFpEF have NPs below diagnostic thresholds, particularly in the presence of obesity
PA systolic pressure **TR velocity at rest**[a]	>**35** mmHg >**2.8** m/s	Sensitivity 54%, specificity 85% for the presence of HFpEF by invasive exercise testing[259,261]

AF = atrial fibrillation; BNP = B-type natriuretic peptide; E/e'ratio = early filling velocity on transmitral Doppler/early relaxation velocity on tissue Doppler; HFpEF = heart failure with preserved ejection fraction; LA = left atrial; LV = left ventricular; NP = natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PA = pulmonary artery; SR = sinus rhythm; TR = tricuspid regurgitation.

Note: The greater the number of abnormalities present, the higher the likelihood of HFpEF.

[a]Only commonly used indices are listed in the table; for less commonly used indices refer to the consensus document of the ESC/HFA.[259]

LA size > 32 ml/m2
Mitral E velocity < 90 cm/s
Septal e‘ velocity < 9 cm/s
E/e‘ ratio > 9

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Europäische HFpEF Koryphäen

Burkert Pieske

Michal Tendera

Michael Böhm

Otto Hess †
1946 - 2011

Diastolische Dysfunktion (Therapie vor 5 Jahren)

- Weitgehend empirisch -> Symptomatik
  - Empfehlungen IIa, Evidenz C
- Ursachensuche (HTN, Hypertrophie, Ischämie, myokardiale, perikardiale Erkrankung)
- Kontrolle der Herzfrequenz
- Diuretika (cave preload-Senkung -> CO)

Diastolische Herzinsuffizienz

- **Therapie der Grunderkrankung (z.B. HTN mittels ACE-Inh, ARB; Ischämie führt zu Relaxations- und Compliance-störung), diesbezüglich viele Studien.**
- **Basiert auf empirischer symptomatischer Behandlung und pathophysiologischen Ueberlegungen (wenige Studien)**
  - **Behandlung der HTN**
  - **Erhaltung des SR**
  - **Betablockergabe (HR-Reduktion, Verlängerung der Diastole), SENIORS**
  - **Reduktion des Preloads (vorsichtig Diuretika, Nitrate)**
  - **ACE-Inh (PEP-CHF Studie mit Perindopril)**
  - **ARB (CHARM-Preserved mit Candesartan)**

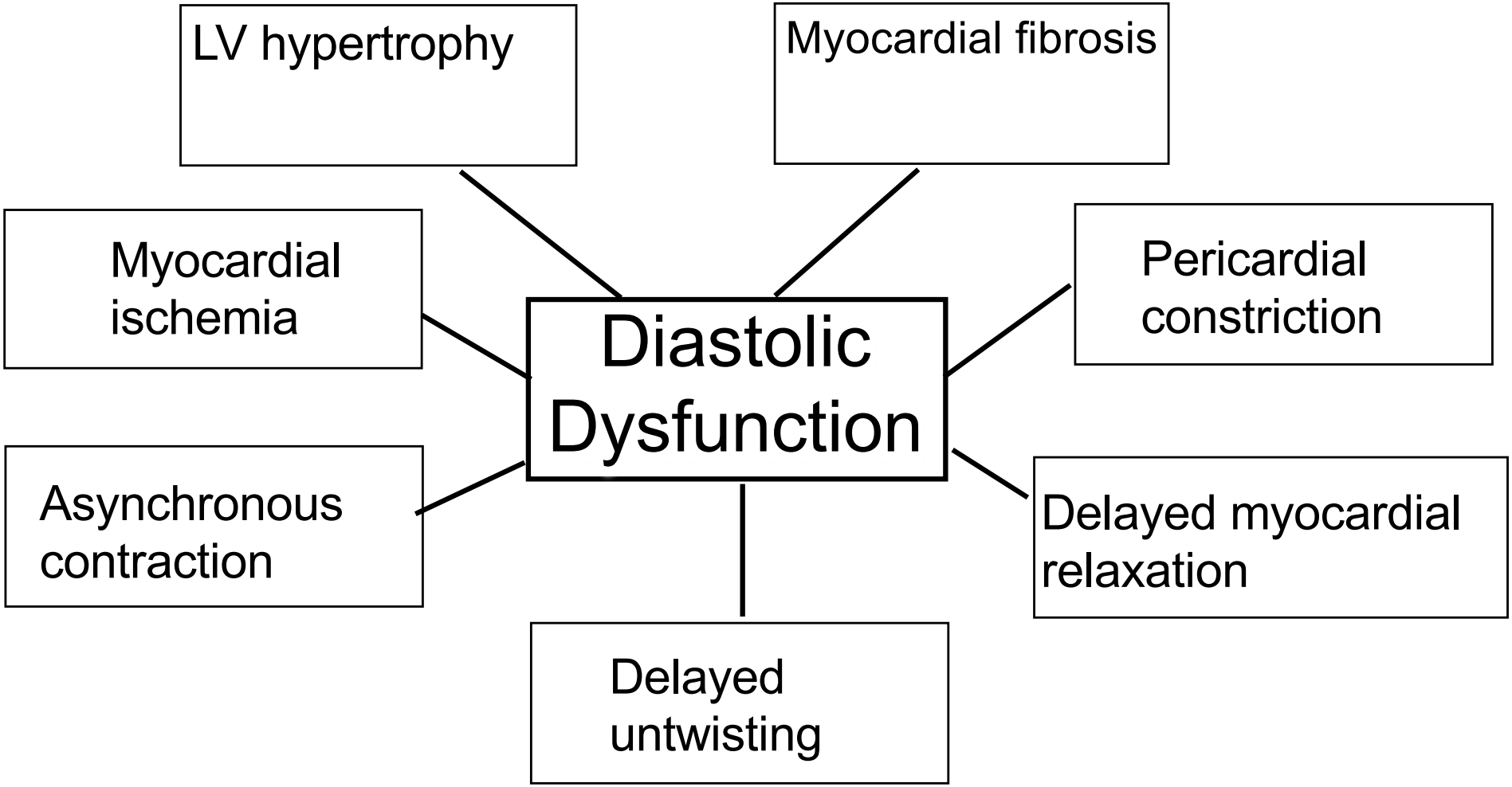
Lusitropie

- ist die Beeinflussung der Myokardfähigkeit zur schnellen und vollständigen Erschlaffung
- Funktioneller Gegensatz zur Inotropie (Kontraktilität)
- Ist für die mechanische Pumpwirkung des Herzens genau so wichtig
- Positive Lusitropie = Steigerung der Relaxationsfähigkeit
- Positive Lusitrope Medikamente = A/NA, PDE-3-Inhib
- Negativ lusitrope Medikamente = Herzglykoside zwar pos inotrop (erhöhte Ca-Aufnahme), jedoch auch negativ lusitrop

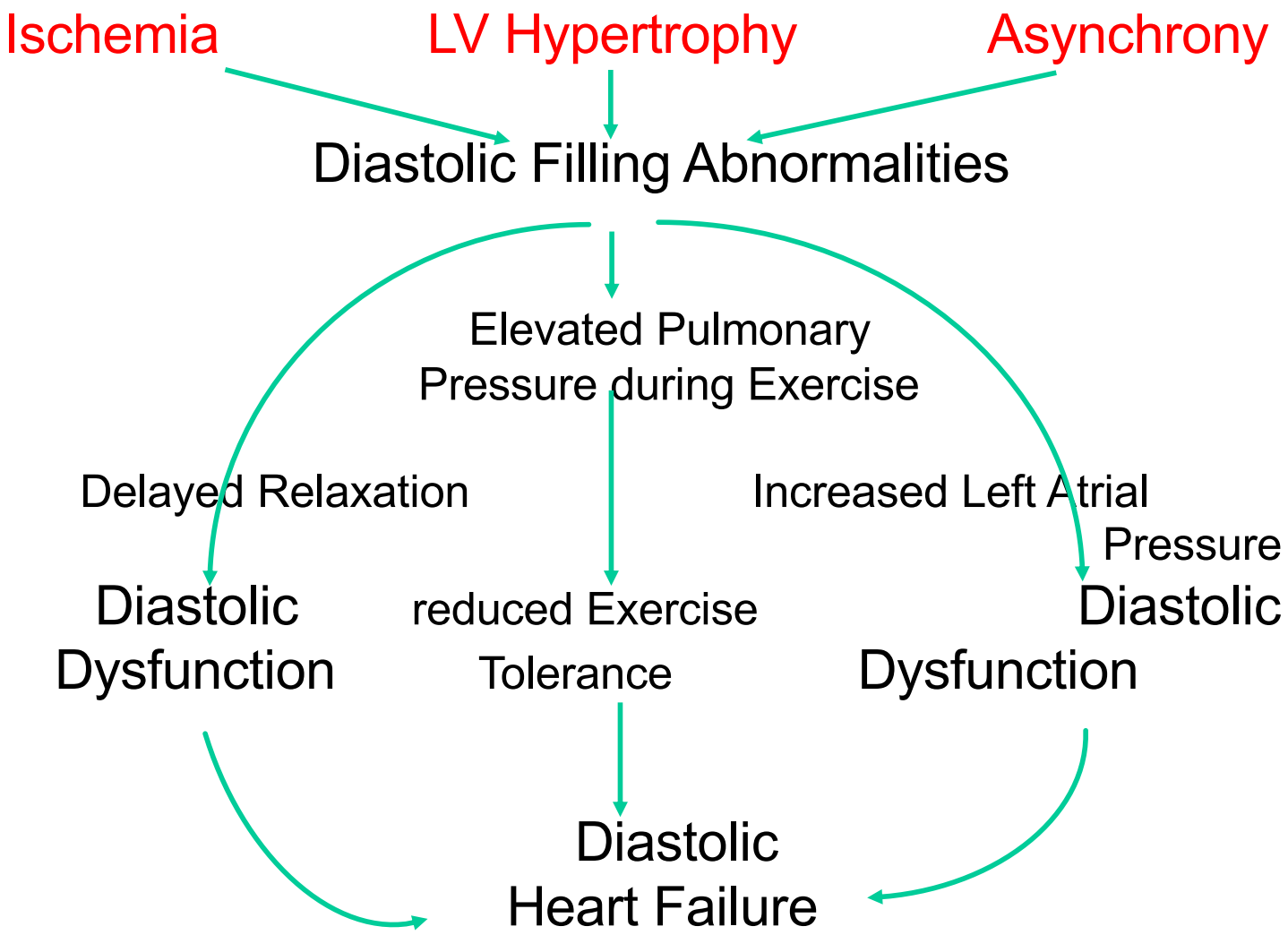
Therapie der Diast Herzinsuffizienz ?

Pathophysiologische Ueberlegungen

Factors Contributing to Diastolic Dysfunction



Transition from LV Dysfunction to Diastolic Failure



Pharmakologische Behandlung der diastol. Dysfunktion

- **Diuretika sind die Eckpfeiler in der Behandlung der diastolischen Dysfunktion, aber sie können das Schlagvolumen und das Herzminutenvolumen kritisch vermindern („volume sensitivity“)**
- **art. Vasodilatatoren werden oft schlecht vertragen**
- **Kalziumantagonisten können theoretisch die Kammerrelaxation verbessern, aber interferieren mit der Pumpfunktion des Herzens (kontraindiziert bei syst. Dysfunktion)**
- **Digitalis ist kontraindiziert, ausser zur Frequenzkontrolle bei Vfli**
- **ACE-Inhibitoren verbessern die diastolische Funktion, dienen aber vor allem zur Verbesserung der systol. Pumpfunktion; sie weisen einen günstigen Effekt auf das ventrikuläre Remodeling auf.**

European Heart Journal (2005) **26**, 1115–1140
doi:10.1093/eurheartj/ehi204

ESC Guidelines

Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005)

The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology

Authors/Task Force Members: Karl Swedberg, Chairperson,* Göteborg (Sweden) *Writing Committee:* John Cleland, Hull (UK), Henry Dargie, Glasgow (UK), Helmut Drexler, Hannover (Germany), Ferenc Follath, Zurich (Switzerland), Michel Komajda, Paris (France), Luigi Tavazzi, Pavia (Italy), Otto A. Smiseth, Oslo (Norway).
Other Contributors: Antonello Gavazzi, Bergamo (Italy), Axel Haverich, Hannover (Germany), Arno Hoes, Utrecht (The Netherlands), Tiny Jaarsma, Gronigen (The Netherlands), Jerzy Korewicki, Warsaw (Poland), Samuel Lévy, Marseille (France), Cecilia Linde, Stockholm (Sweden), José-Luis Lopez-Sendon, Madrid (Spain), Markku S. Nieminen, Helsinki (Finland), Luc Piérard, Liège (Belgium), Willem J. Remme, Rhoon (The Netherlands)

European Heart Journal (2012) **33**, 1787–1847
doi:10.1093/eurheartj/ehs104

ESC GUIDELINES

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: John J.V. McMurray (Chairperson) (UK)* Stamatis Adamopoulos (Greece), Stefan D. Anker (Germa (Switzerland), Michael Böhm (Germany), Kenneth Dickstei Volkmar Falk (Switzerland), Gerasimos Filippatos (Greece) (Portugal), Miguel Angel Gomez-Sanchez (Spain), Tiny Jaa Lars Køber (Denmark), Gregory Y.H. Lip (UK), Aldo Pietr Alexander Parkhomenko (Ukraine), Burkert M. Pieske (Aus (Romania), Per K. Rønnevik (Norway), Frans H. Rutten (TI Juerg Schwitter (Switzerland), Petar Seferovic (Serbia), Jar Pedro T. Trindade (Switzerland), Adriaan A. Voors (The Ne (France), Andreas Zeiher (Germany).

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

European Heart Journal (2021) **00**, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

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

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans

European Heart Journal (2005) 26, 1115–1140
doi:10.1093/eurheartj/ehi204

European Heart Journal (2012) 33, 1787–1847
doi:10.1093/eurheartj/ehs104

ESC GUIDELINES

ESC Guidelines for the diagnosis and treatment

ESC European Society of Cardiology

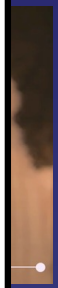
European Heart Journal (2023) 44, 3627–3639
https://doi.org/10.1093/eurheartj/ehad195

ESC GUIDELINES

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC



Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans

ESC European Society of Cardiology
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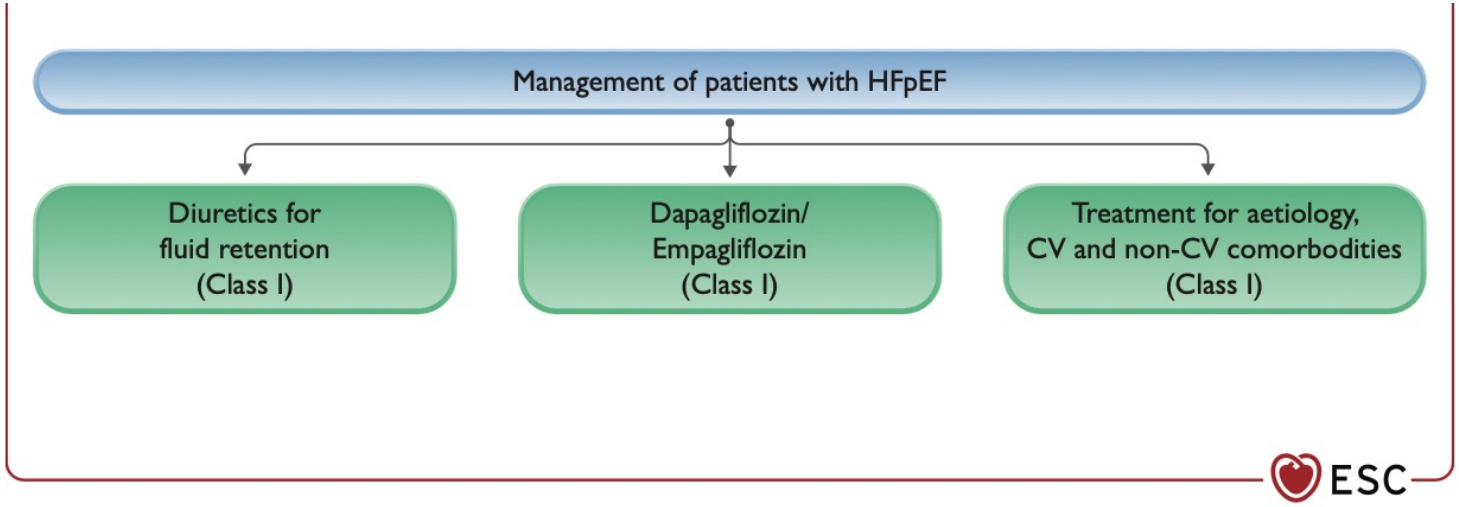
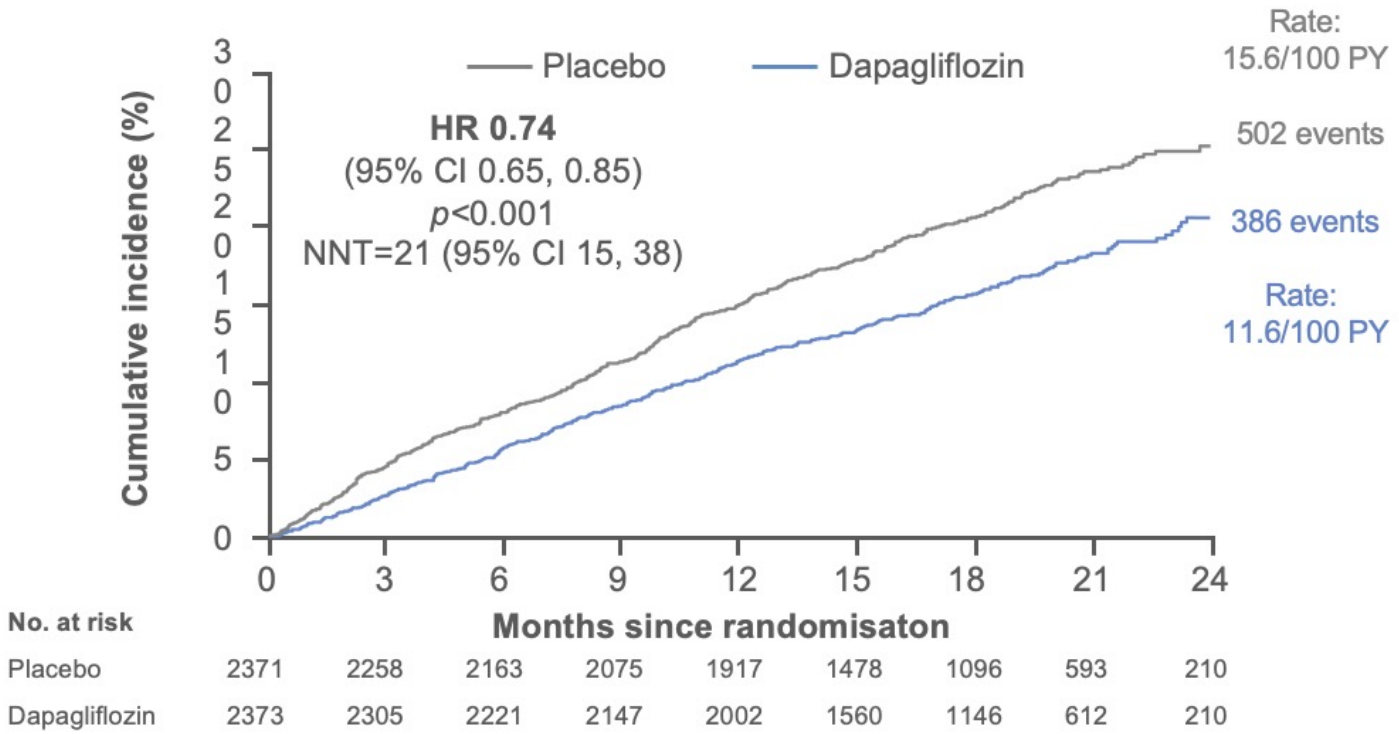


Figure 2 Management of patients with heart failure with preserved ejection fraction. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction.

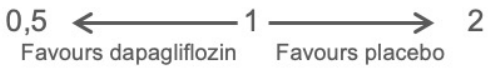
DAPA-HF: dapagliflozin reduces HF worsening and CV death



Mac Murray JJV et al. 2019;381:1995-2008.

…irrespective of presence of diabetes

	Dapagliflozin	Placebo	
	n with event/N analysed	n with event/N analysed	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
T2D at baseline			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



Mac Murray JJV et al. 2019;381:1995-2008.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

This article was published on August 27, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2107038

Table 1. Characteristics of the Patients at Baseline.*

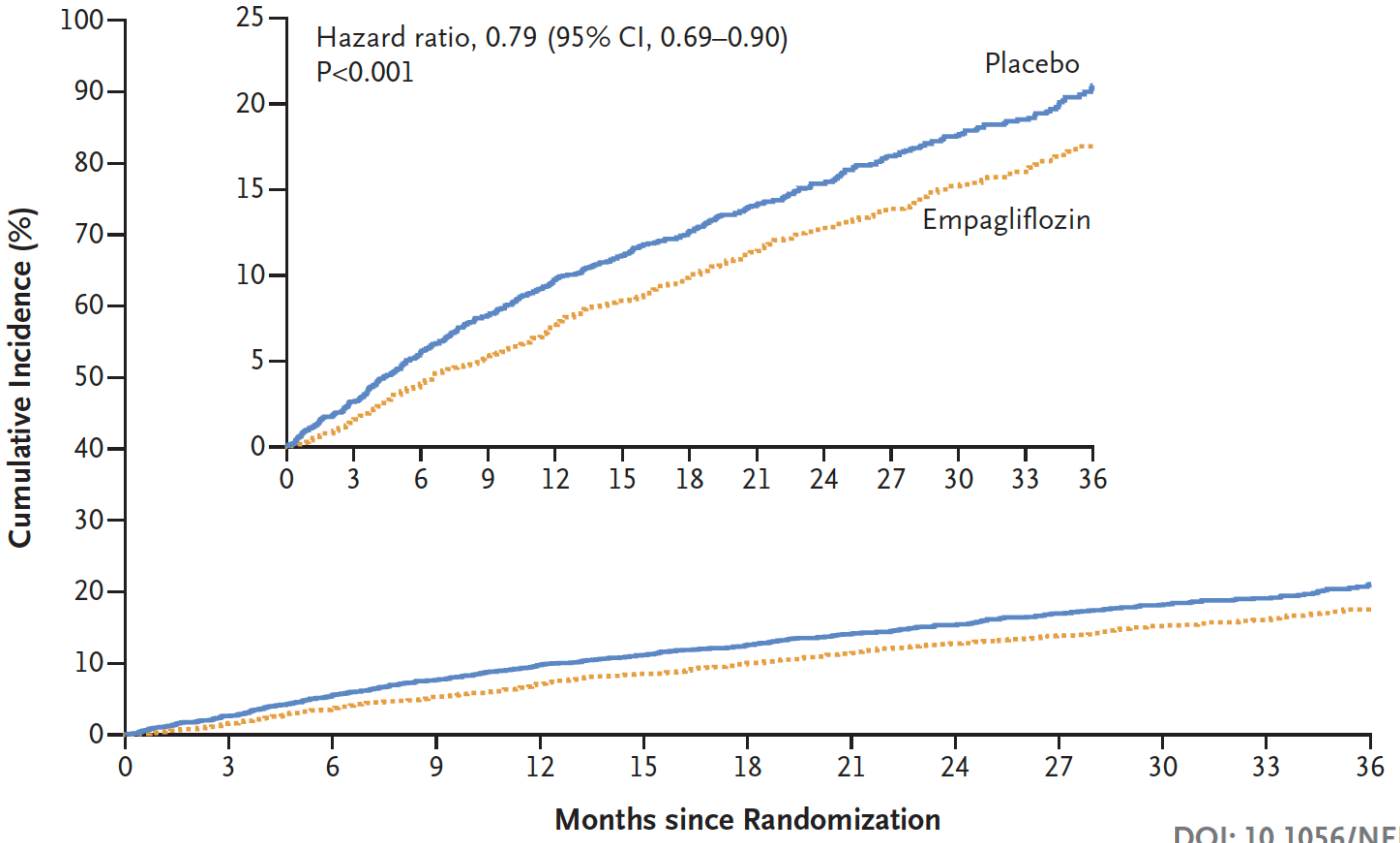
Characteristic	Empagliflozin (N=2997)	Placebo (N=2991)
Age — yr	71.8±9.3	71.9±9.6
Female sex — no. (%)	1338 (44.6)	1338 (44.7)
Race — no. (%)†		
White	2286 (76.3)	2256 (75.4)
Black	133 (4.4)	125 (4.2)
Asian	413 (13.8)	411 (13.7)
Other or missing	165 (5.5)	199 (6.7)
Geographic region — no. (%)		
North America	360 (12.0)	359 (12.0)
Latin America	758 (25.3)	757 (25.3)
Europe	1346 (44.9)	1343 (44.9)
Asia	343 (11.4)	343 (11.5)
Other	190 (6.3)	189 (6.3)
NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Body-mass index‡	29.77±5.8	29.90±5.9
Heart rate — beats per minute	70.4±12.0	70.3±11.80
Systolic blood pressure — mm Hg	131.8±15.6	131.9±15.7
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)
Mean eGFR — ml/min/1.73 m^2	60.6±19.8	60.6±19.9
eGFR <60 ml/min/1.73 m^2 — no./total no. (%)	1504/2997 (50.2)	1484/2989 (49.6)

* Plus–minus values are means ±SD. The abbreviation eGFR denotes estimated glomerular filtration rate, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.
† Race was reported by the patient; patients who identified with more than one race or with no race were classified as other.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Two patients with an ejection fraction of exactly 40% underwent randomization and were included in the analysis.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

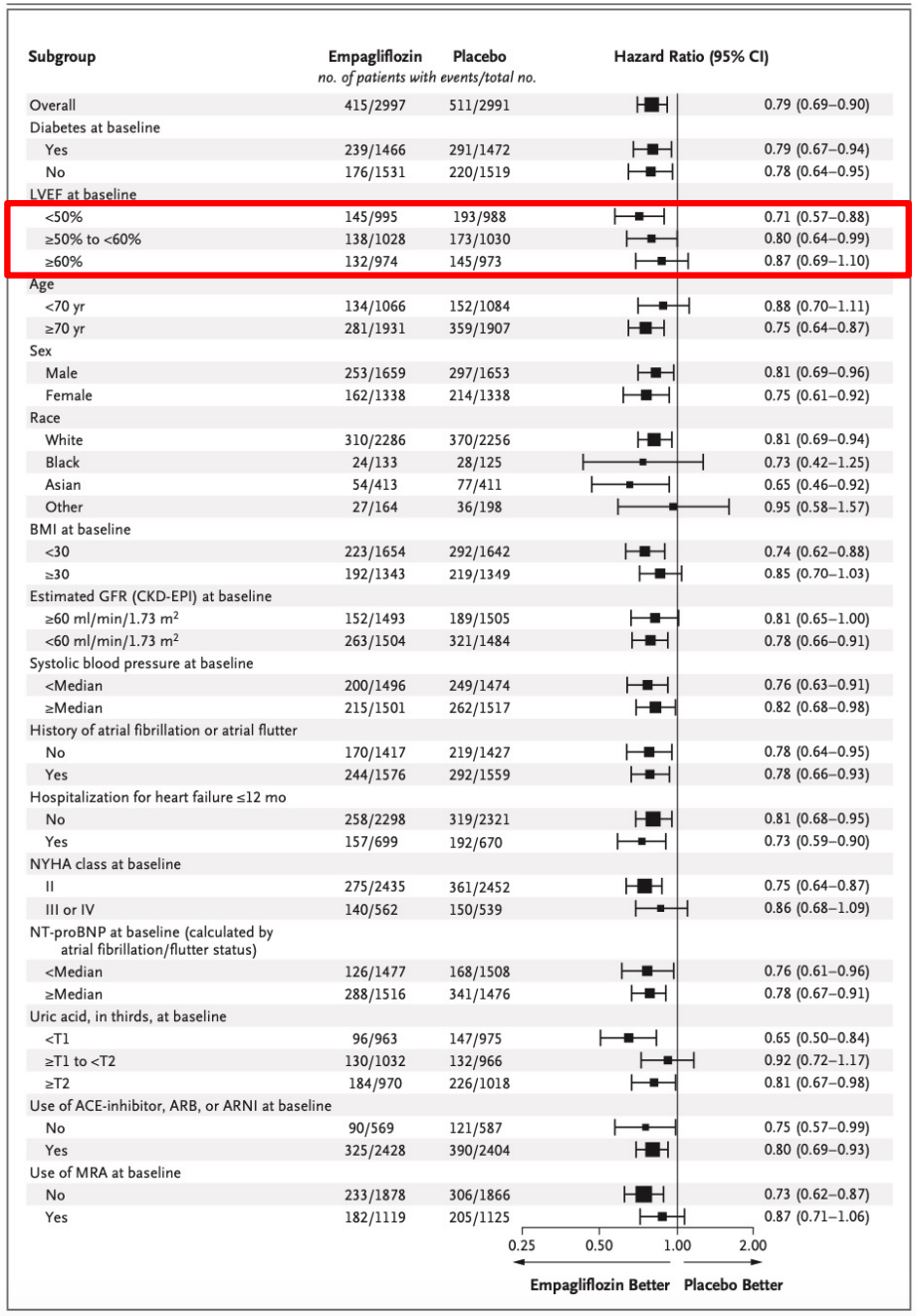
Empagliflozin in Heart Failure with a Preserved Ejection Fraction



DOI: 10.1056/NEJMoa2107038

Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Empagliflozin (N=2997)		Placebo (N=2991)		Hazard Ratio or Difference (95% CI)	P Value
		events per 100 patient-yr		*events per 100 patient-yr*		
Primary composite outcome — no. (%)	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90)	<0.001
Hospitalization for heart failure	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83)	
Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09)	
Secondary outcomes specified in hierarchical testing procedure						
Total no. of hospitalizations for heart failure	407	—	541	—	0.73 (0.61–0.88)	<0.001
eGFR (CKD-EPI) mean slope change per year — ml/min/1.73 m^2†	−1.25±0.11	—	−2.62±0.11	—	1.36 (1.06–1.66)	<0.001
Other prespecified analyses						
Change in KCCQ clinical summary score at 52 wk‡	4.51±0.31	—	3.18±0.31	—	1.32 (0.45–2.19)	
Total no. of hospitalizations for any cause	2566	—	2769	—	0.93 (0.85–1.01)	
Composite renal outcome — no. (%)	108 (3.6)	2.1	112 (3.7)	2.2	0.95 (0.73–1.24)	
Onset of new diabetes in patients with prediabetes — no. (%)	120 (12.0)	6.1	137 (14.0)	7.4	0.84 (0.65–1.07)	
Death from any cause — no. (%)	422 (14.1)	6.6	427 (14.3)	6.7	1.00 (0.87–1.15)	


Subgroup
Empagliflozin
Placebo
no. of patients with events/total no.
Hazard Ratio (95% CI)
Overall 415/2997 511/2991 0.79 (0.69–0.90)
Diabetes at baseline
Yes 239/1466 291/1472 0.79 (0.67–0.94)
No 176/1531 220/1519 0.78 (0.64–0.95)
LVEF at baseline
<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)
Age
<70 yr 134/1066 152/1084 0.88 (0.70–1.11)
≥70 yr 281/1931 359/1907 0.75 (0.64–0.87)
Sex
Male 253/1659 297/1653 0.81 (0.69–0.96)
Female 162/1338 214/1338 0.75 (0.61–0.92)
Race
White 310/2286 370/2256 0.81 (0.69–0.94)
Black 24/133 28/125 0.73 (0.42–1.25)
Asian 54/413 77/411 0.65 (0.46–0.92)
Other 27/164 36/198 0.95 (0.58–1.57)
BMI at baseline
<30 223/1654 292/1642 0.74 (0.62–0.88)
≥30 192/1343 219/1349 0.85 (0.70–1.03)
Estimated GFR (CKD-EPI) at baseline
≥60 ml/min/1.73 m2 152/1493 189/1505 0.81 (0.65–1.00)
<60 ml/min/1.73 m2 263/1504 321/1484 0.78 (0.66–0.91)
Systolic blood pressure at baseline
<Median 200/1496 249/1474 0.76 (0.63–0.91)
≥Median 215/1501 262/1517 0.82 (0.68–0.98)
History of atrial fibrillation or atrial flutter
No 170/1417 219/1427 0.78 (0.64–0.95)
Yes 244/1576 292/1559 0.78 (0.66–0.93)
Hospitalization for heart failure ≤12 mo
No 258/2298 319/2321 0.81 (0.68–0.95)
Yes 157/699 192/670 0.73 (0.59–0.90)
NYHA class at baseline
II 275/2435 361/2452 0.75 (0.64–0.87)
III or IV 140/562 150/539 0.86 (0.68–1.09)
NT-proBNP at baseline (calculated by atrial fibrillation/flutter status)
<Median 126/1477 168/1508 0.76 (0.61–0.96)
≥Median 288/1516 341/1476 0.78 (0.67–0.91)
Uric acid, in thirds, at baseline
<T1 96/963 147/975 0.65 (0.50–0.84)
≥T1 to <T2 130/1032 132/966 0.92 (0.72–1.17)
≥T2 184/970 226/1018 0.81 (0.67–0.98)
Use of ACE-inhibitor, ARB, or ARNI at baseline
No 90/569 121/587 0.75 (0.57–0.99)
Yes 325/2428 390/2404 0.80 (0.69–0.93)
Use of MRA at baseline
No 233/1878 306/1866 0.73 (0.62–0.87)
Yes 182/1119 205/1125 0.87 (0.71–1.06)
0.25
0.50
1.00
2.00
Empagliflozin Better
Placebo Better

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*

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dapagliflozin (N=3131)	Placebo (N=3132)
Age — yr	71.8±9.6	71.5±9.5
Female sex — no. (%)	1364 (43.6)	1383 (44.2)
Race — no. (%)†		
Asian	630 (20.1)	644 (20.6)
Black	81 (2.6)	78 (2.5)
White	2214 (70.7)	2225 (71.0)
Other	206 (6.6)	185 (5.9)
Geographic region — no. (%)		
North America	428 (13.7)	423 (13.5)
Latin America	602 (19.2)	579 (18.5)
Europe or Saudi Arabia	1494 (47.7)	1511 (48.2)
Asia	607 (19.4)	619 (19.8)
NYHA class — no. (%)‡		
II	2314 (73.9)	2399 (76.6)
III	807 (25.8)	724 (23.1)
IV	10 (0.3)	8 (0.3)
Left ventricular ejection fraction		
Mean — %	54.0±8.6	54.3±8.9
Distribution — no. (%)		
≤49%	1067 (34.1)	1049 (33.5)
50–59%	1133 (36.2)	1123 (35.9)
≥60%	931 (29.7)	960 (30.7)
Medical history — no. (%)		
Type 2 diabetes mellitus	1401 (44.7)	1405 (44.9)
Hypertension	2755 (88.0)	2798 (89.3)
Previous left ventricular ejection fraction ≤40%	572 (18.3)	579 (18.5)
Estimated GFR — ml/min/1.73 m²	61±19	61±19

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. GFR denotes glomerular filtration rate.
† Race was reported by the investigators.
‡ One patient in the placebo group who had New York Heart Association (NYHA) class I disease at baseline was not included in the analysis of this variable.

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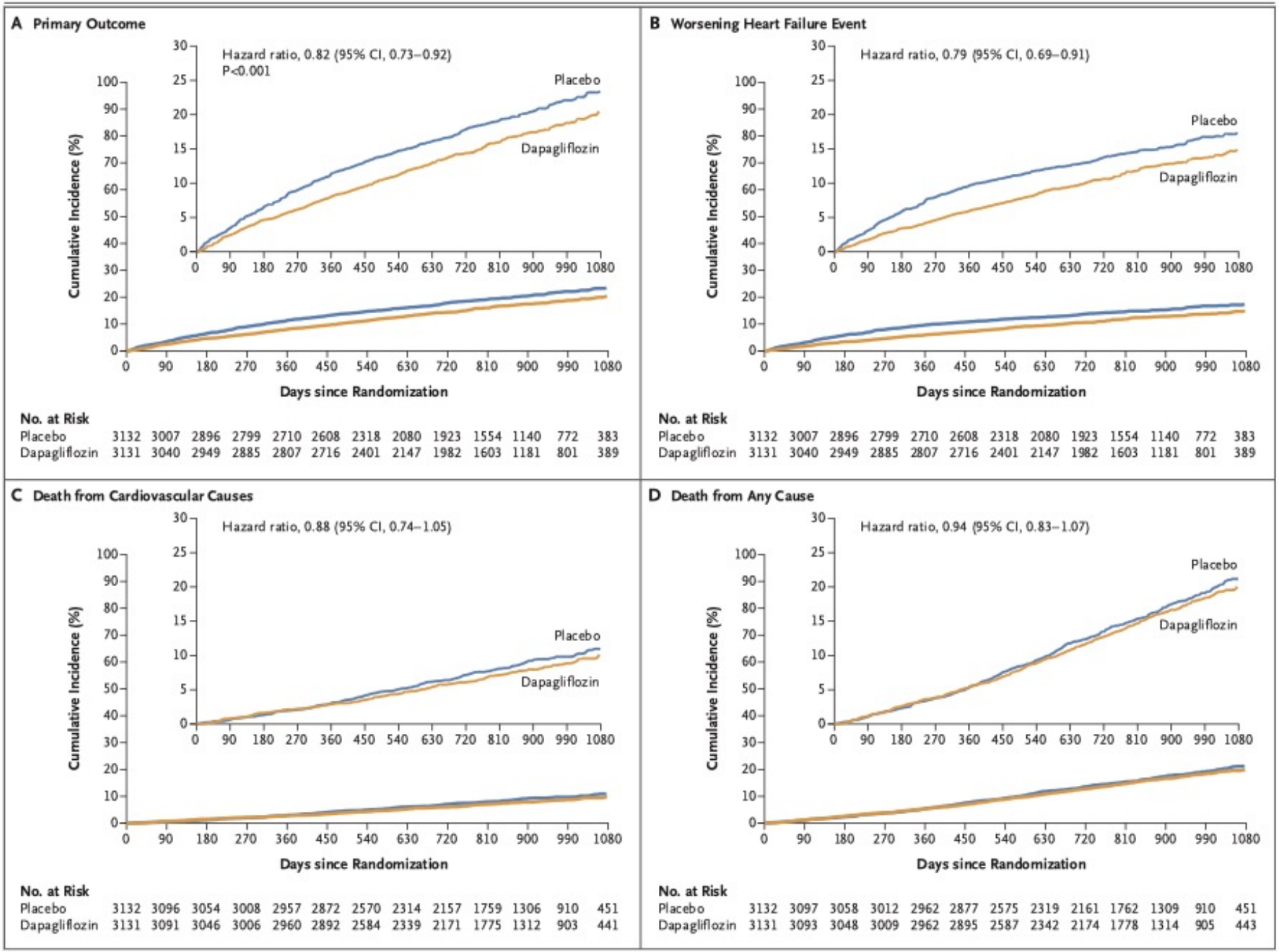
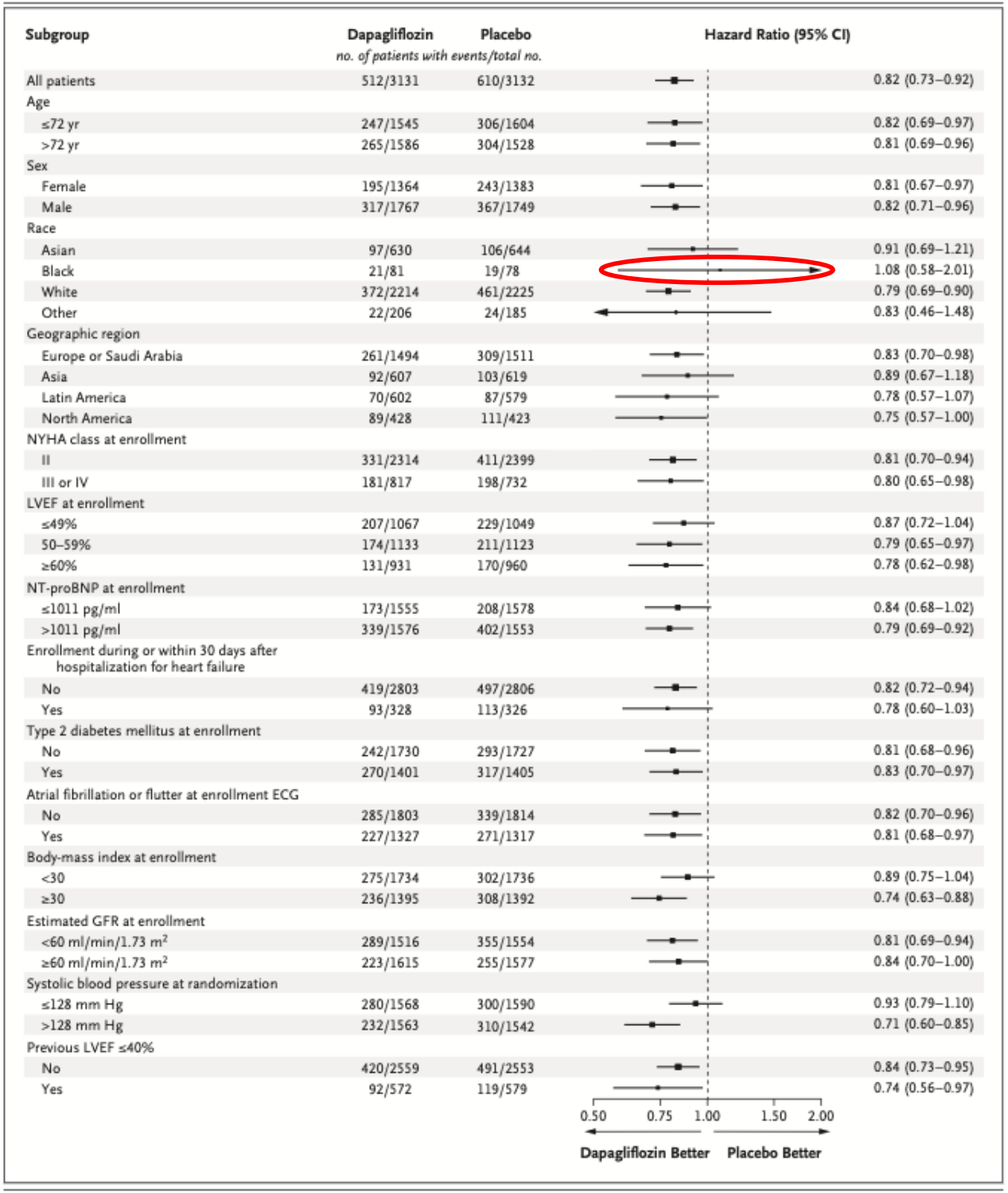
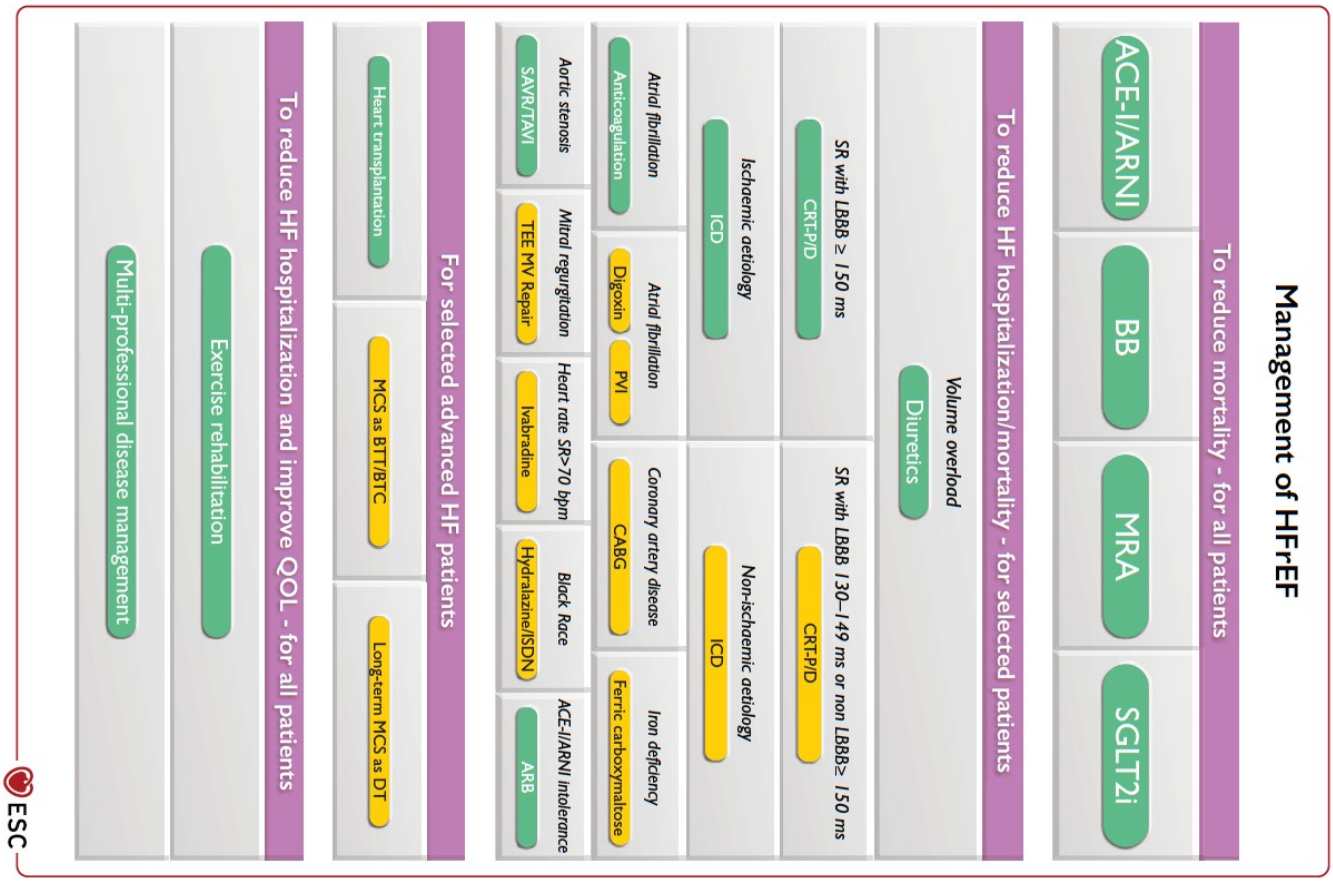
Table 2. Primary and Secondary Cardiovascular Outcomes and Safety Outcomes in the Overall Population.*

Variable	Dapagliflozin (N=3131)		Placebo (N=3132)		Hazard or Rate Ratio or Win Ratio (95% CI)	P Value
	values	*events/ 100 patient-yr*	*values*	*events/ 100 patient-yr*		
Efficacy outcomes						
Primary composite outcome — no. (%)	512 (16.4)	7.8	610 (19.5)	9.6	0.82 (0.73–0.92)	<0.001
Hospitalization for heart failure or an urgent visit for heart failure	368 (11.8)	5.6	455 (14.5)	7.2	0.79 (0.69–0.91)	NA
Hospitalization for heart failure	329 (10.5)	5.0	418 (13.3)	6.5	0.77 (0.67–0.89)	NA
Urgent visit for heart failure	60 (1.9)	0.9	78 (2.5)	1.1	0.76 (0.55–1.07)	NA
Cardiovascular death†	231 (7.4)	3.3	261 (8.3)	3.8	0.88 (0.74–1.05)	NA
Secondary outcomes						
Total no. of worsening heart failure events and cardiovascular deaths‡	815	11.8	1057	15.3	0.77 (0.67–0.89)	<0.001
Change in KCCQ total symptom score at mo 8§	—	—	—	—	1.11 (1.03–1.21)	0.009
Mean change in KCCQ total symptom score at mo 8 among survivors	—	—	—	—	2.4 (1.5–3.4)	NA
Death from any cause — no. (%)	497 (15.9)	7.2	526 (16.8)	7.6	0.94 (0.83–1.07)	NA
Safety outcomes — no./total no. (%)¶						
Any serious adverse event	1361/3126 (43.5)	—	1423/3127 (45.5)	—	—	—
Any adverse event that led to discontinuation of dapagliflozin or placebo	182/3126 (5.8)	—	181/3127 (5.8)	—	—	—
Any adverse event that led to interruption of dapagliflozin or placebo	436/3126 (13.9)	—	494/3127 (15.8)	—	—	—
Any amputation	19/3126 (0.6)	—	25/3127 (0.8)	—	—	—
Any adverse event that potentially placed a patient at risk for a lower-limb amputation	188/3126 (6.0)	—	199/3127 (6.4)	—	—	—
Any definite or probable diabetic ketoacidosis	2/3126 (0.1)	—	0	—	—	—
Any major hypoglycemic event‖	6/3126 (0.2)	—	7/3127 (0.2)	—	—	—
Any serious adverse event or adverse event that led to discontinuation of dapagliflozin or placebo that was suggestive of volume depletion	42/3126 (1.3)	—	32/3127 (1.0)	—	—	—
Any renal serious adverse event or adverse event that led to discontinuation of dapagliflozin or placebo	73/3126 (2.3)	—	79/3127 (2.5)	—	—	—
Fournier's gangrene	0	—	0	—	—	—


A Primary Outcome
Hazard ratio, 0.82 (95% CI, 0.73–0.92)
P<0.001
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days since Randomization
No. at Risk
Placebo 3132 3007 2896 2799 2710 2608 2318 2080 1923 1554 1140 772 383
Dapagliflozin 3131 3040 2949 2885 2807 2716 2401 2147 1982 1603 1181 801 389
B Worsening Heart Failure Event
Hazard ratio, 0.79 (95% CI, 0.69–0.91)
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days since Randomization
No. at Risk
Placebo 3132 3007 2896 2799 2710 2608 2318 2080 1923 1554 1140 772 383
Dapagliflozin 3131 3040 2949 2885 2807 2716 2401 2147 1982 1603 1181 801 389
C Death from Cardiovascular Causes
Hazard ratio, 0.88 (95% CI, 0.74–1.05)
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days since Randomization
No. at Risk
Placebo 3132 3096 3054 3008 2957 2872 2570 2314 2157 1759 1306 910 451
Dapagliflozin 3131 3091 3046 3006 2960 2892 2584 2339 2171 1775 1312 903 441
D Death from Any Cause
Hazard ratio, 0.94 (95% CI, 0.83–1.07)
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days since Randomization
No. at Risk
Placebo 3132 3097 3058 3012 2962 2877 2575 2319 2161 1762 1309 910 451
Dapagliflozin 3131 3093 3048 3009 2962 2895 2587 2342 2174 1778 1314 905 443


Subgroup
Dapagliflozin
Placebo
no. of patients with events/total no.
Hazard Ratio (95% CI)
All patients 512/3131 610/3132 0.82 (0.73–0.92)
Age
≤72 yr 247/1545 306/1604 0.82 (0.69–0.97)
>72 yr 265/1586 304/1528 0.81 (0.69–0.96)
Sex
Female 195/1364 243/1383 0.81 (0.67–0.97)
Male 317/1767 367/1749 0.82 (0.71–0.96)
Race
Asian 97/630 106/644 0.91 (0.69–1.21)
Black 21/81 19/78 1.08 (0.58–2.01)
White 372/2214 461/2225 0.79 (0.69–0.90)
Other 22/206 24/185 0.83 (0.46–1.48)
Geographic region
Europe or Saudi Arabia 261/1494 309/1511 0.83 (0.70–0.98)
Asia 92/607 103/619 0.89 (0.67–1.18)
Latin America 70/602 87/579 0.78 (0.57–1.07)
North America 89/428 111/423 0.75 (0.57–1.00)
NYHA class at enrollment
II 331/2314 411/2399 0.81 (0.70–0.94)
III or IV 181/817 198/732 0.80 (0.65–0.98)
LVEF at enrollment
≤49% 207/1067 229/1049 0.87 (0.72–1.04)
50–59% 174/1133 211/1123 0.79 (0.65–0.97)
≥60% 131/931 170/960 0.78 (0.62–0.98)
NT-proBNP at enrollment
≤1011 pg/ml 173/1555 208/1578 0.84 (0.68–1.02)
>1011 pg/ml 339/1576 402/1553 0.79 (0.69–0.92)
Enrollment during or within 30 days after hospitalization for heart failure
No 419/2803 497/2806 0.82 (0.72–0.94)
Yes 93/328 113/326 0.78 (0.60–1.03)
Type 2 diabetes mellitus at enrollment
No 242/1730 293/1727 0.81 (0.68–0.96)
Yes 270/1401 317/1405 0.83 (0.70–0.97)
Atrial fibrillation or flutter at enrollment ECG
No 285/1803 339/1814 0.82 (0.70–0.96)
Yes 227/1327 271/1317 0.81 (0.68–0.97)
Body-mass index at enrollment
<30 275/1734 302/1736 0.89 (0.75–1.04)
≥30 236/1395 308/1392 0.74 (0.63–0.88)
Estimated GFR at enrollment
<60 ml/min/1.73 m² 289/1516 355/1554 0.81 (0.69–0.94)
≥60 ml/min/1.73 m² 223/1615 255/1577 0.84 (0.70–1.00)
Systolic blood pressure at randomization
≤128 mm Hg 280/1568 300/1590 0.93 (0.79–1.10)
>128 mm Hg 232/1563 310/1542 0.71 (0.60–0.85)
Previous LVEF ≤40%
No 420/2559 491/2553 0.84 (0.73–0.95)
Yes 92/572 119/579 0.74 (0.56–0.97)
0.50
0.75
1.00
1.50
2.00
Dapagliflozin Better
Placebo Better

ESC Guidelines on Heart Failure 2021



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SGLT2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials

Muthiah Vaduganathan, Kieran F Docherty*, Brian L Claggett, Pardeep S Jhund, Rudolf A de Boer, Adrian F Hernandez, Silvio E Inzucchi, Mikhail N Kosiborod, Carolyn S P Lam, Felipe Martinez, Sanjiv J Shah, Akshay S Desai, John J V McMurray†, Scott D Solomon†*

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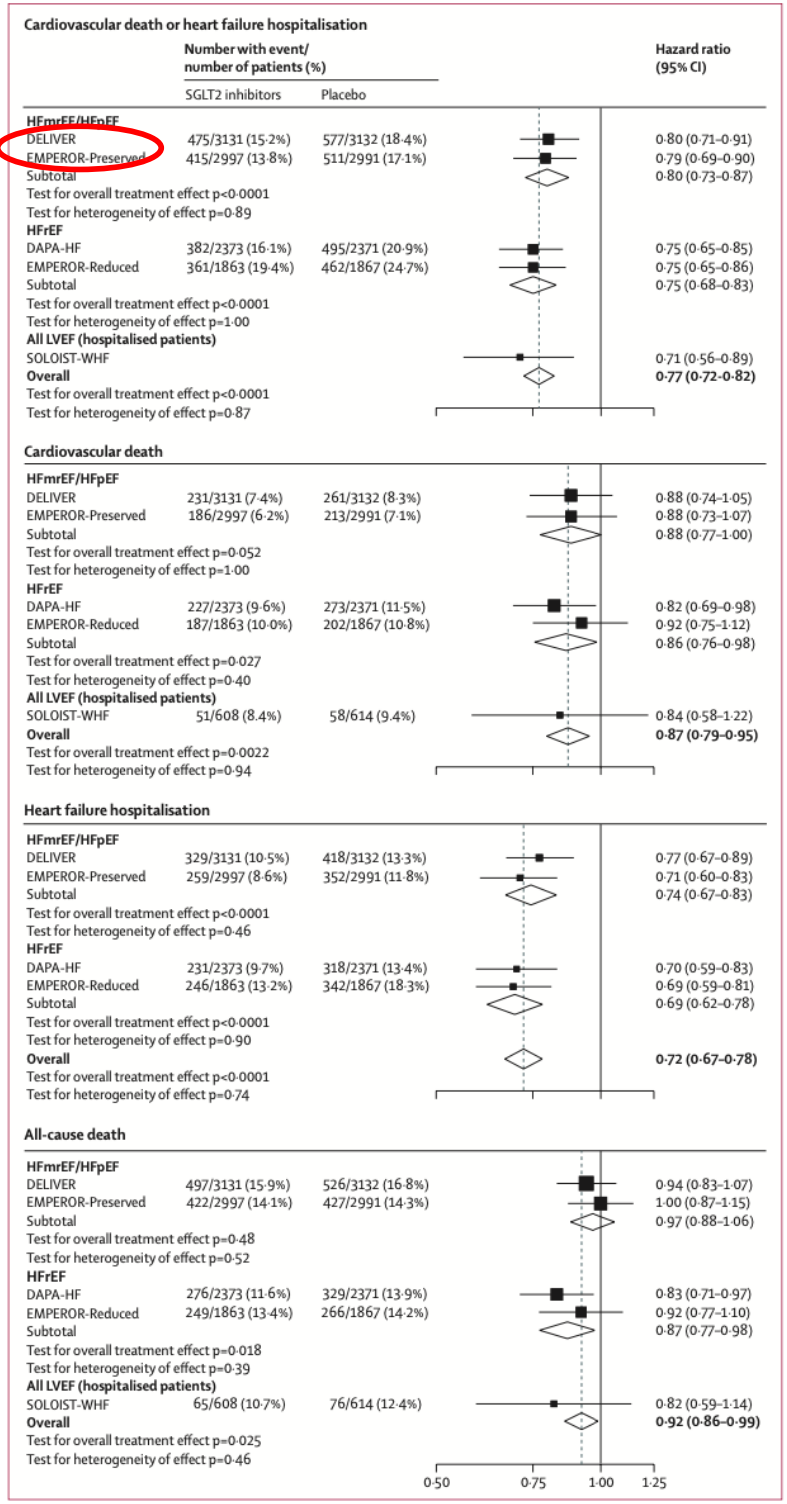
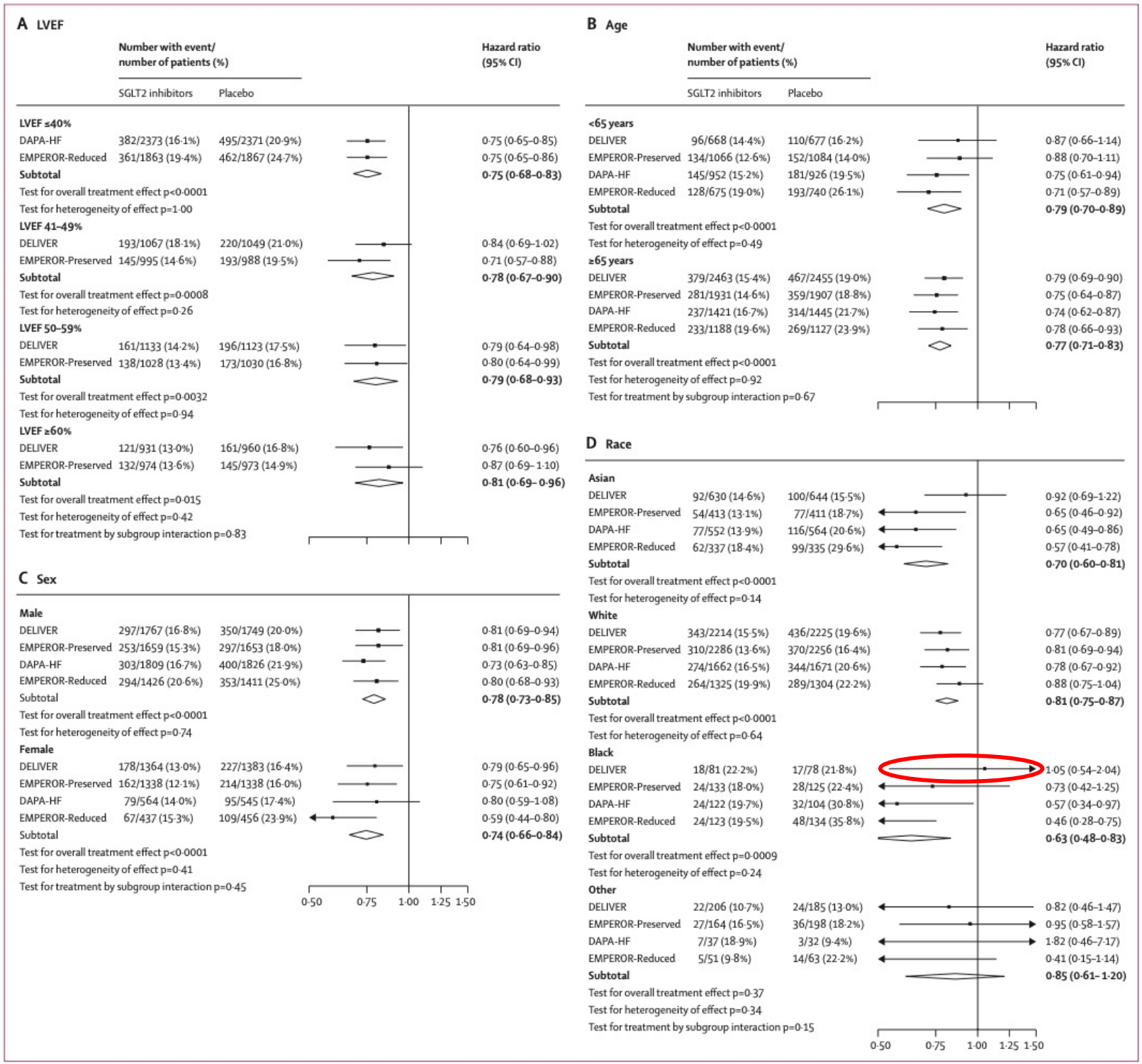
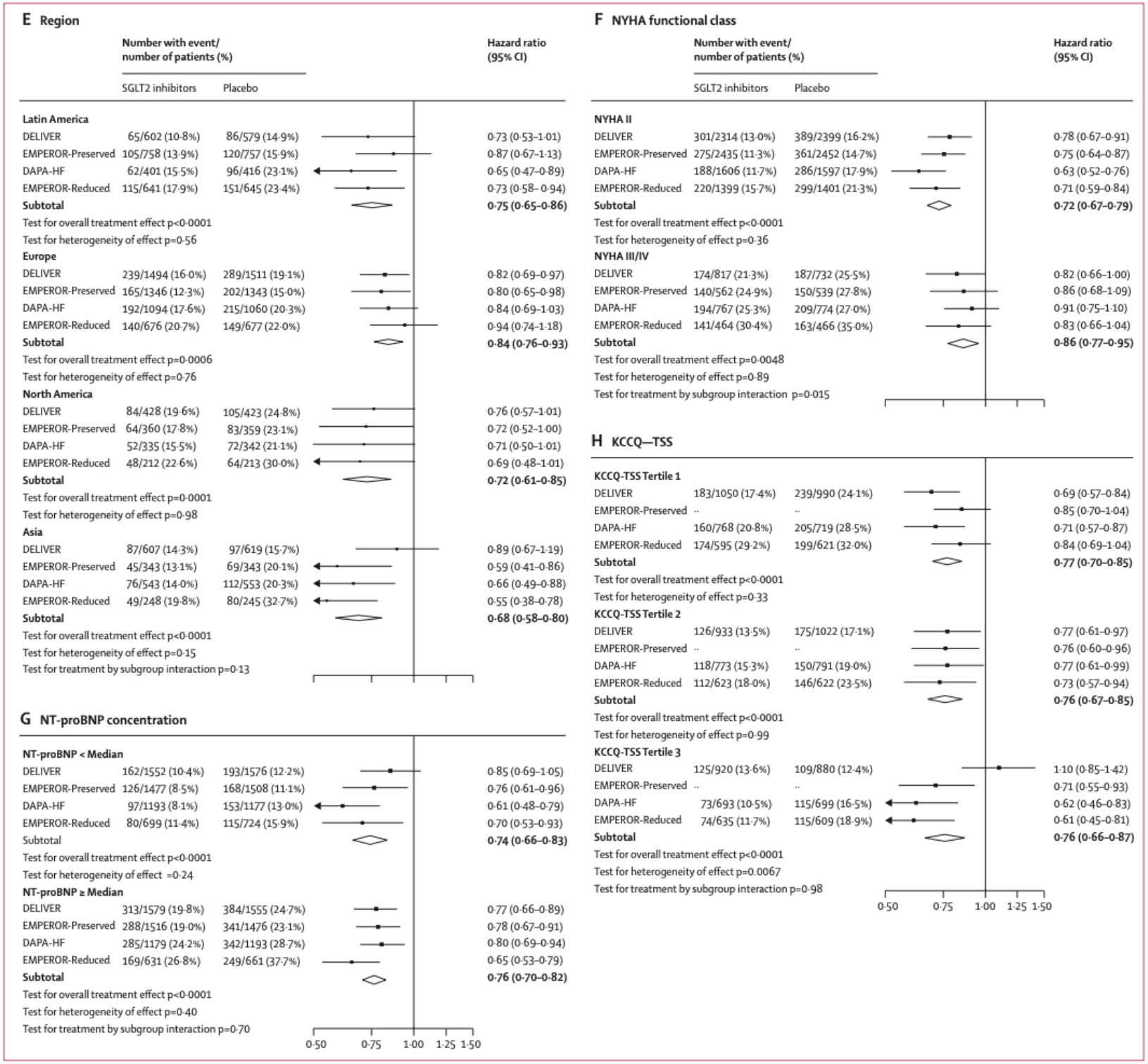


	DELIVER		EMPEROR-Preserved	
	Dapagliflozin (n=3126)	Placebo (n=3127)	Empagliflozin (n=2996)	Placebo (n=2989)
Any serious adverse event	1361 (43·5%)	1423 (45·5%)	1436 (47·9%)	1543 (51·6%)
Amputation	19 (0·6%)	25 (0·8 %)	16 (0·5%)	23 (0·8%)
Diabetic ketoacidosis	2 (0·1%)	0 (0·0 %)	4 (0·1%)	5 (0·2%)
Hypoglycaemia	6 (0·2 %)	7 (0·2 %)	73 (2·4%)	78 (2·6%)
Renal	73 (2·3 %)	79 (2·5 %)	363 (12·1%)	384 (12·8%)

Adverse events were not directly compared or meta-analysed because of differential data capture and exact definitions for these safety events in both trials. In both trials, the safety analyses were done in treated patients who received at least a single dose of the study medication. In EMPEROR-Preserved, although limb amputations were reported through the end of the trial, other adverse events were only reported up to 7 days after discontinuation of study medication. Similarly, in DELIVER, all reported adverse events were on-treatment or within 30 days of discontinuation of study medication. In DELIVER, diabetes ketoacidosis includes events that were adjudicated as definite or probable cases, and hypoglycaemic events represent major hypoglycaemia. DELIVER collected adverse event data from serious adverse events, adverse events leading to drug discontinuation or interruption, and selected adverse events, except in select countries that required reporting of all adverse events. The appendix (p 2) juxtaposes the relevant definitions for these adverse events in both trials.

Table 2: **Adverse events in DELIVER and EMPEROR-Preserved**


A LVEF
Number with event/ number of patients (%)
SGLT2 inhibitors
Placebo
Hazard ratio (95% CI)
LVEF ≤40%
DAPA-HF 382/2373 (16·1%) 495/2371 (20·9%) 0·75 (0·65–0·85)
EMPEROR-Reduced 361/1863 (19·4%) 462/1867 (24·7%) 0·75 (0·65–0·86)
Subtotal 0·75 (0·68–0·83)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=1·00
LVEF 41–49%
DELIVER 193/1067 (18·1%) 220/1049 (21·0%) 0·84 (0·69–1·02)
EMPEROR-Preserved 145/995 (14·6%) 193/988 (19·5%) 0·71 (0·57–0·88)
Subtotal 0·78 (0·67–0·90)
Test for overall treatment effect p=0·0008
Test for heterogeneity of effect p=0·26
LVEF 50–59%
DELIVER 161/1133 (14·2%) 196/1123 (17·5%) 0·79 (0·64–0·98)
EMPEROR-Preserved 138/1028 (13·4%) 173/1030 (16·8%) 0·80 (0·64–0·99)
Subtotal 0·79 (0·68–0·93)
Test for overall treatment effect p=0·0032
Test for heterogeneity of effect p=0·94
LVEF ≥60%
DELIVER 121/931 (13·0%) 161/960 (16·8%) 0·76 (0·60–0·96)
EMPEROR-Preserved 132/974 (13·6%) 145/973 (14·9%) 0·87 (0·69–1·10)
Subtotal 0·81 (0·69–0·96)
Test for overall treatment effect p=0·015
Test for heterogeneity of effect p=0·42
Test for treatment by subgroup interaction p=0·83
B Age
Number with event/ number of patients (%)
SGLT2 inhibitors
Placebo
Hazard ratio (95% CI)
<65 years
DELIVER 96/668 (14·4%) 110/677 (16·2%) 0·87 (0·66–1·14)
EMPEROR-Preserved 134/1066 (12·6%) 152/1084 (14·0%) 0·88 (0·70–1·11)
DAPA-HF 145/952 (15·2%) 181/926 (19·5%) 0·75 (0·61–0·94)
EMPEROR-Reduced 128/675 (19·0%) 193/740 (26·1%) 0·71 (0·57–0·89)
Subtotal 0·79 (0·70–0·89)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·49
≥65 years
DELIVER 379/2463 (15·4%) 467/2455 (19·0%) 0·79 (0·69–0·90)
EMPEROR-Preserved 281/1931 (14·6%) 359/1907 (18·8%) 0·75 (0·64–0·87)
DAPA-HF 237/1421 (16·7%) 314/1445 (21·7%) 0·74 (0·62–0·87)
EMPEROR-Reduced 233/1188 (19·6%) 269/1127 (23·9%) 0·78 (0·66–0·93)
Subtotal 0·77 (0·71–0·83)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·92
Test for treatment by subgroup interaction p=0·67
C Sex
Male
DELIVER 297/1767 (16·8%) 350/1749 (20·0%) 0·81 (0·69–0·94)
EMPEROR-Preserved 253/1659 (15·3%) 297/1653 (18·0%) 0·81 (0·69–0·96)
DAPA-HF 303/1809 (16·7%) 400/1826 (21·9%) 0·73 (0·63–0·85)
EMPEROR-Reduced 294/1426 (20·6%) 353/1411 (25·0%) 0·80 (0·68–0·93)
Subtotal 0·78 (0·73–0·85)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·74
Female
DELIVER 178/1364 (13·0%) 227/1383 (16·4%) 0·79 (0·65–0·96)
EMPEROR-Preserved 162/1338 (12·1%) 214/1338 (16·0%) 0·75 (0·61–0·92)
DAPA-HF 79/564 (14·0%) 95/545 (17·4%) 0·80 (0·59–1·08)
EMPEROR-Reduced 67/437 (15·3%) 109/456 (23·9%) 0·59 (0·44–0·80)
Subtotal 0·74 (0·66–0·84)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·41
Test for treatment by subgroup interaction p=0·45
0·50
0·75
1·00
1·25
1·50
D Race
Asian
DELIVER 92/630 (14·6%) 100/644 (15·5%) 0·92 (0·69–1·22)
EMPEROR-Preserved 54/413 (13·1%) 77/411 (18·7%) 0·65 (0·46–0·92)
DAPA-HF 77/552 (13·9%) 116/564 (20·6%) 0·65 (0·49–0·86)
EMPEROR-Reduced 62/337 (18·4%) 99/335 (29·6%) 0·57 (0·41–0·78)
Subtotal 0·70 (0·60–0·81)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·14
White
DELIVER 343/2214 (15·5%) 436/2225 (19·6%) 0·77 (0·67–0·89)
EMPEROR-Preserved 310/2286 (13·6%) 370/2256 (16·4%) 0·81 (0·69–0·94)
DAPA-HF 274/1662 (16·5%) 344/1671 (20·6%) 0·78 (0·67–0·92)
EMPEROR-Reduced 264/1325 (19·9%) 289/1304 (22·2%) 0·88 (0·75–1·04)
Subtotal 0·81 (0·75–0·87)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·64
Black
DELIVER 18/81 (22·2%) 17/78 (21·8%) 1·05 (0·54–2·04)
EMPEROR-Preserved 24/133 (18·0%) 28/125 (22·4%) 0·73 (0·42–1·25)
DAPA-HF 24/122 (19·7%) 32/104 (30·8%) 0·57 (0·34–0·97)
EMPEROR-Reduced 24/123 (19·5%) 48/134 (35·8%) 0·46 (0·28–0·75)
Subtotal 0·63 (0·48–0·83)
Test for overall treatment effect p=0·0009
Test for heterogeneity of effect p=0·24
Other
DELIVER 22/206 (10·7%) 24/185 (13·0%) 0·82 (0·46–1·47)
EMPEROR-Preserved 27/164 (16·5%) 36/198 (18·2%) 0·95 (0·58–1·57)
DAPA-HF 7/37 (18·9%) 3/32 (9·4%) 1·82 (0·46–7·17)
EMPEROR-Reduced 5/51 (9·8%) 14/63 (22·2%) 0·41 (0·15–1·14)
Subtotal 0·85 (0·61–1·20)
Test for overall treatment effect p=0·37
Test for heterogeneity of effect p=0·34
Test for treatment by subgroup interaction p=0·15
0·50
0·75
1·00
1·25
1·50


E Region
Number with event/ number of patients (%)
SGLT2 inhibitors
Placebo
Hazard ratio (95% CI)
Latin America
DELIVER 65/602 (10·8%) 86/579 (14·9%) 0·73 (0·53–1·01)
EMPEROR-Preserved 105/758 (13·9%) 120/757 (15·9%) 0·87 (0·67–1·13)
DAPA-HF 62/401 (15·5%) 96/416 (23·1%) 0·65 (0·47–0·89)
EMPEROR-Reduced 115/641 (17·9%) 151/645 (23·4%) 0·73 (0·58–0·94)
Subtotal 0·75 (0·65–0·86)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·56
Europe
DELIVER 239/1494 (16·0%) 289/1511 (19·1%) 0·82 (0·69–0·97)
EMPEROR-Preserved 165/1346 (12·3%) 202/1343 (15·0%) 0·80 (0·65–0·98)
DAPA-HF 192/1094 (17·6%) 215/1060 (20·3%) 0·84 (0·69–1·03)
EMPEROR-Reduced 140/676 (20·7%) 149/677 (22·0%) 0·94 (0·74–1·18)
Subtotal 0·84 (0·76–0·93)
Test for overall treatment effect p=0·0006
Test for heterogeneity of effect p=0·76
North America
DELIVER 84/428 (19·6%) 105/423 (24·8%) 0·76 (0·57–1·01)
EMPEROR-Preserved 64/360 (17·8%) 83/359 (23·1%) 0·72 (0·52–1·00)
DAPA-HF 52/335 (15·5%) 72/342 (21·1%) 0·71 (0·50–1·01)
EMPEROR-Reduced 48/212 (22·6%) 64/213 (30·0%) 0·69 (0·48–1·01)
Subtotal 0·72 (0·61–0·85)
Test for overall treatment effect p=0·0001
Test for heterogeneity of effect p=0·98
Asia
DELIVER 87/607 (14·3%) 97/619 (15·7%) 0·89 (0·67–1·19)
EMPEROR-Preserved 45/343 (13·1%) 69/343 (20·1%) 0·59 (0·41–0·86)
DAPA-HF 76/543 (14·0%) 112/553 (20·3%) 0·66 (0·49–0·88)
EMPEROR-Reduced 49/248 (19·8%) 80/245 (32·7%) 0·55 (0·38–0·78)
Subtotal 0·68 (0·58–0·80)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·15
Test for treatment by subgroup interaction p=0·13
G NT-proBNP concentration
NT-proBNP < Median
DELIVER 162/1552 (10·4%) 193/1576 (12·2%) 0·85 (0·69–1·05)
EMPEROR-Preserved 126/1477 (8·5%) 168/1508 (11·1%) 0·76 (0·61–0·96)
DAPA-HF 97/1193 (8·1%) 153/1177 (13·0%) 0·61 (0·48–0·79)
EMPEROR-Reduced 80/699 (11·4%) 115/724 (15·9%) 0·70 (0·53–0·93)
Subtotal 0·74 (0·66–0·83)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect =0·24
NT-proBNP ≥ Median
DELIVER 313/1579 (19·8%) 384/1555 (24·7%) 0·77 (0·66–0·89)
EMPEROR-Preserved 288/1516 (19·0%) 341/1476 (23·1%) 0·78 (0·67–0·91)
DAPA-HF 285/1179 (24·2%) 342/1193 (28·7%) 0·80 (0·69–0·94)
EMPEROR-Reduced 169/631 (26·8%) 249/661 (37·7%) 0·65 (0·53–0·79)
Subtotal 0·76 (0·70–0·82)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·40
Test for treatment by subgroup interaction p=0·70
0·50 0·75 1·00 1·25 1·50
F NYHA functional class
Number with event/ number of patients (%)
SGLT2 inhibitors
Placebo
Hazard ratio (95% CI)
NYHA II
DELIVER 301/2314 (13·0%) 389/2399 (16·2%) 0·78 (0·67–0·91)
EMPEROR-Preserved 275/2435 (11·3%) 361/2452 (14·7%) 0·75 (0·64–0·87)
DAPA-HF 188/1606 (11·7%) 286/1597 (17·9%) 0·63 (0·52–0·76)
EMPEROR-Reduced 220/1399 (15·7%) 299/1401 (21·3%) 0·71 (0·59–0·84)
Subtotal 0·72 (0·67–0·79)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·36
NYHA III/IV
DELIVER 174/817 (21·3%) 187/732 (25·5%) 0·82 (0·66–1·00)
EMPEROR-Preserved 140/562 (24·9%) 150/539 (27·8%) 0·86 (0·68–1·09)
DAPA-HF 194/767 (25·3%) 209/774 (27·0%) 0·91 (0·75–1·10)
EMPEROR-Reduced 141/464 (30·4%) 163/466 (35·0%) 0·83 (0·66–1·04)
Subtotal 0·86 (0·77–0·95)
Test for overall treatment effect p=0·0048
Test for heterogeneity of effect p=0·89
Test for treatment by subgroup interaction p=0·015
H KCCQ—TSS
KCCQ-TSS Tertile 1
DELIVER 183/1050 (17·4%) 239/990 (24·1%) 0·69 (0·57–0·84)
EMPEROR-Preserved .. .. 0·85 (0·70–1·04)
DAPA-HF 160/768 (20·8%) 205/719 (28·5%) 0·71 (0·57–0·87)
EMPEROR-Reduced 174/595 (29·2%) 199/621 (32·0%) 0·84 (0·69–1·04)
Subtotal 0·77 (0·70–0·85)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·33
KCCQ-TSS Tertile 2
DELIVER 126/933 (13·5%) 175/1022 (17·1%) 0·77 (0·61–0·97)
EMPEROR-Preserved .. .. 0·76 (0·60–0·96)
DAPA-HF 118/773 (15·3%) 150/791 (19·0%) 0·77 (0·61–0·99)
EMPEROR-Reduced 112/623 (18·0%) 146/622 (23·5%) 0·73 (0·57–0·94)
Subtotal 0·76 (0·67–0·85)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·99
KCCQ-TSS Tertile 3
DELIVER 125/920 (13·6%) 109/880 (12·4%) 1·10 (0·85–1·42)
EMPEROR-Preserved .. .. 0·71 (0·55–0·93)
DAPA-HF 73/693 (10·5%) 115/699 (16·5%) 0·62 (0·46–0·83)
EMPEROR-Reduced 74/635 (11·7%) 115/609 (18·9%) 0·61 (0·45–0·81)
Subtotal 0·76 (0·66–0·87)
Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·0067
Test for treatment by subgroup interaction p=0·98
0·50 0·75 1·00 1·25 1·50

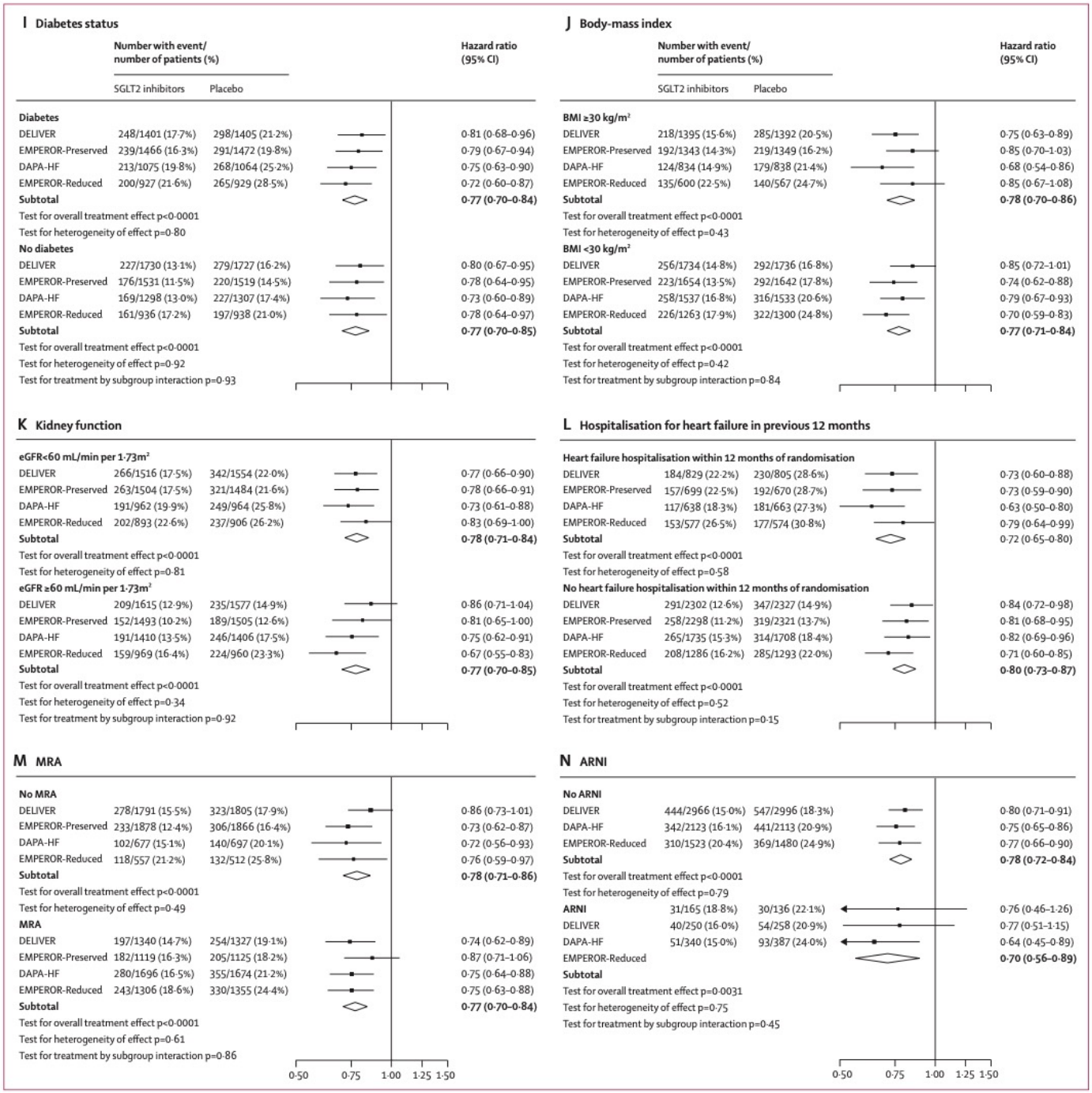
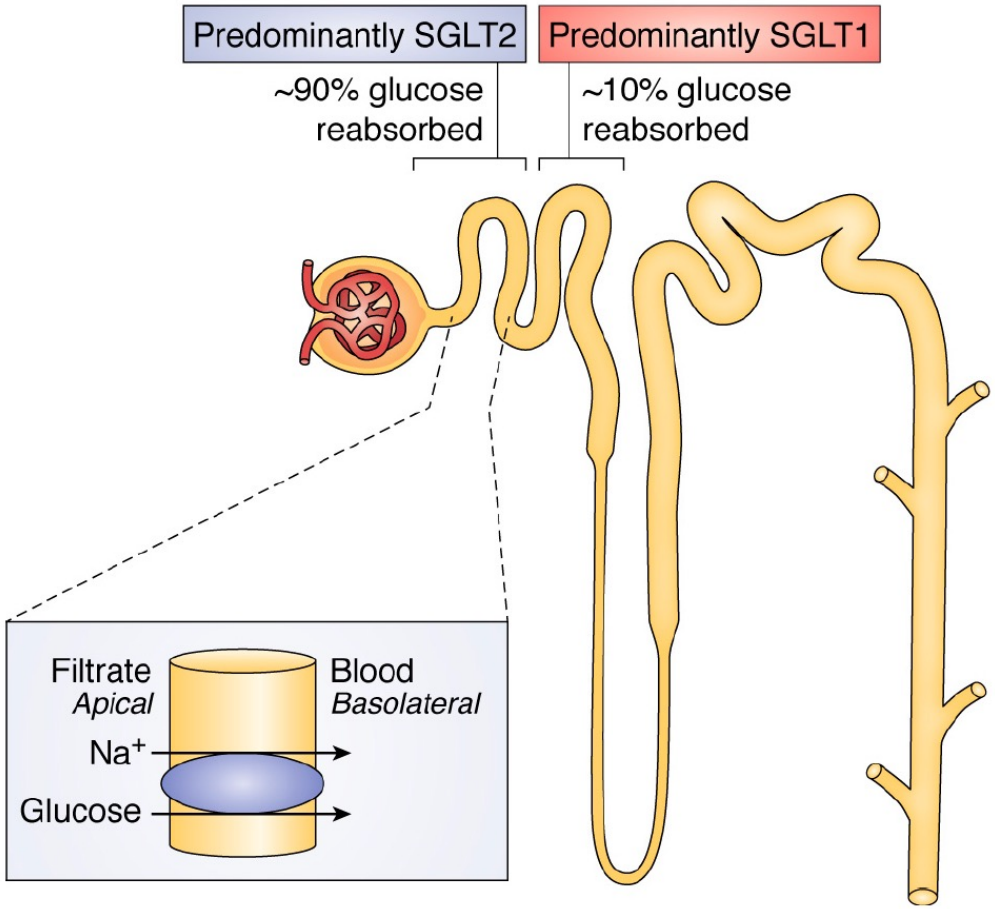


Figure 2: **Treatment effects of SGLT2 inhibitors on the composite of cardiovascular death or first hospitalisation for heart failure across 14 clinically relevant subgroups**
The age-based subgroup for EMPEROR-Preserved was dichotomised at 70 years. In the DELIVER trial, Saudi Arabia was included in the Europe region. The NT-proBNP-based median concentration was calculated on the basis of atrial fibrillation or flutter status in EMPEROR-Preserved. ARNI=angiotensin receptor neprilysin inhibitor. eGFR=estimated glomerular filtration rate. KCCQ-TSS=Kansas City Cardiomyopathy Questionnaire—Total Symptom Score. MRA=mineralocorticoid receptor antagonists. NT-proBNP=N-terminal prohormone of B-type natriuretic peptide. NYHA=New York Heart Association.

Topics

1) History & Relevance of HFpEF
2) Definitions
3) Management of HFpEF
4) It works „why“ ?

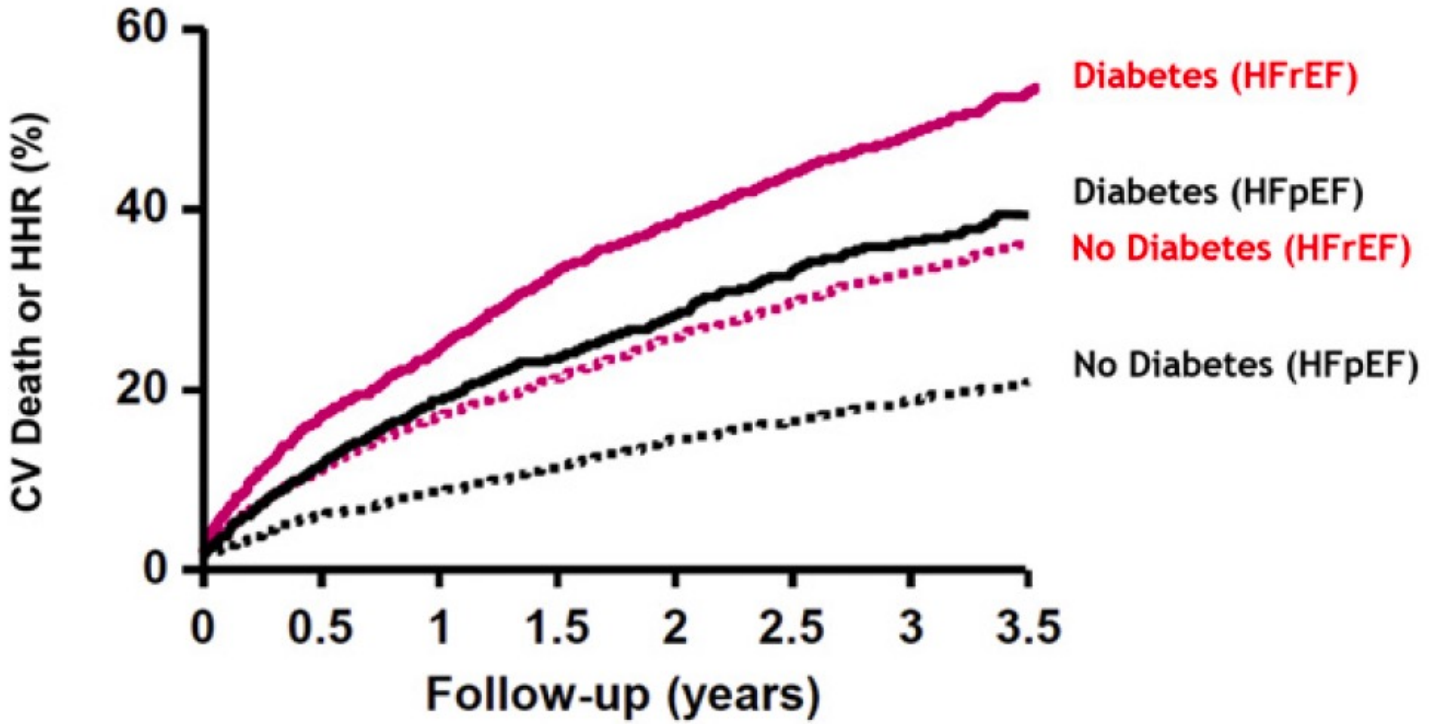
SGLT-2i: principle of glucose lowering



Perry RJ et al. J Biol Chem 2020; 295(42):14379-142390.

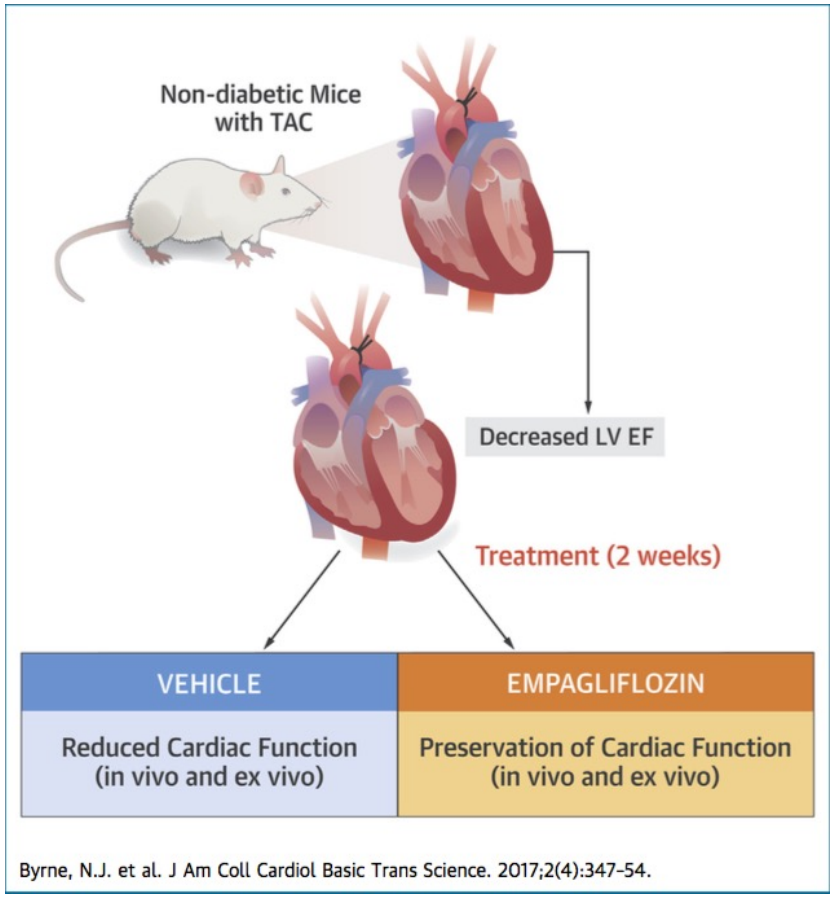
Diabetes worsens outcome of HErEF and HFpEF

Analysis of 7599 patients included in CHARM trial program with symptomatic HF and a broad range of EF

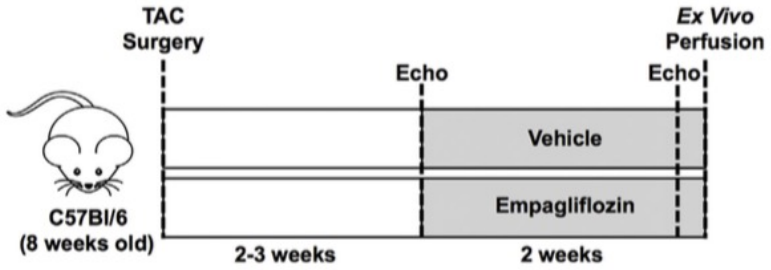


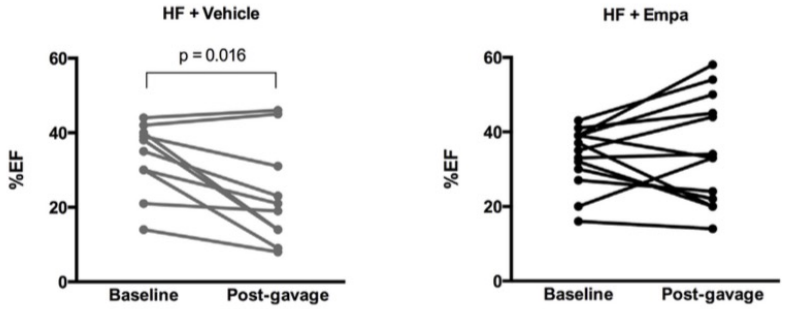
MacDonald MR et al. Eur Heart J 2008;28:1377-1385.

SGLT-2i prevents worsening of experimental HF

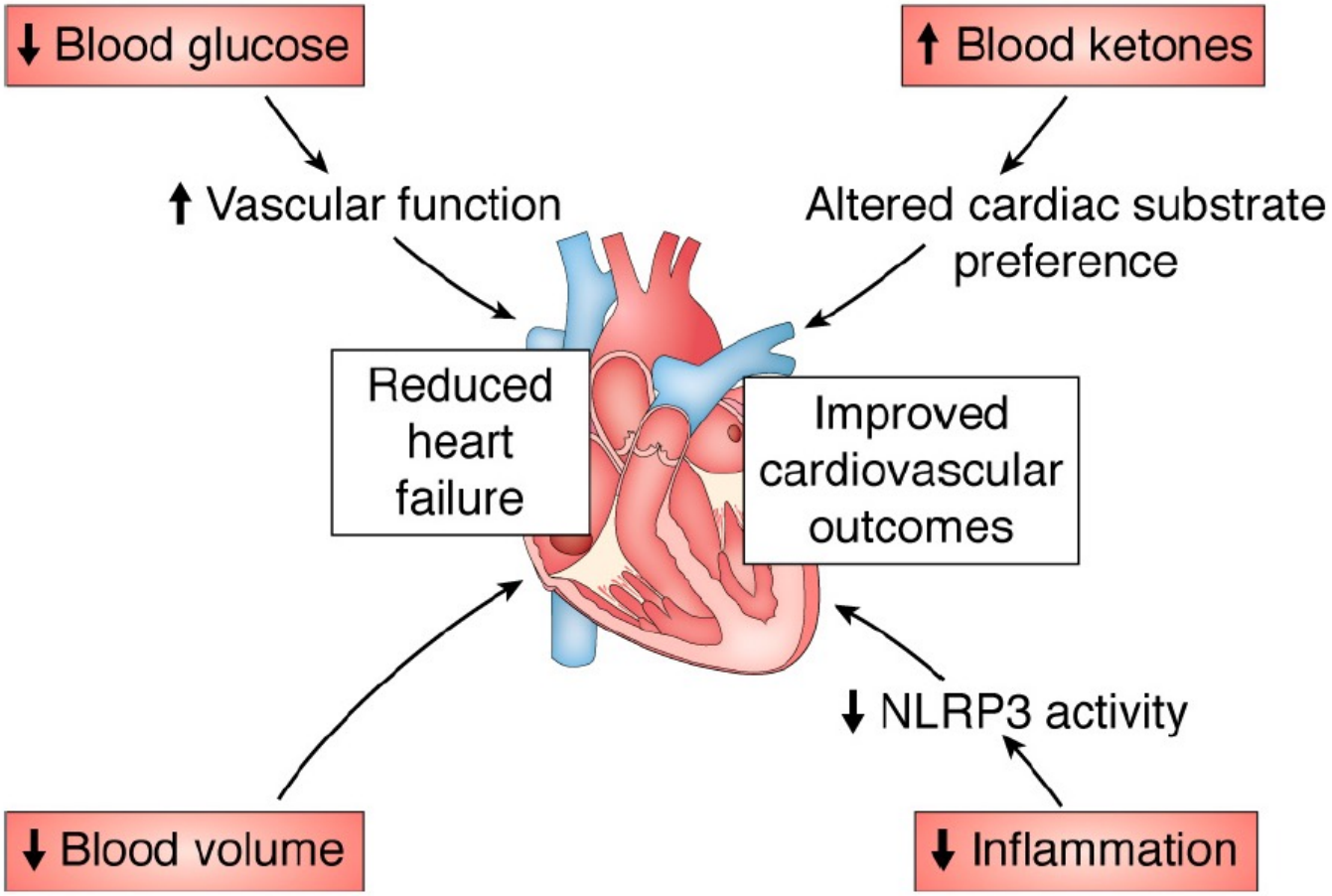


Byrne, N.J. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(4):347-54.



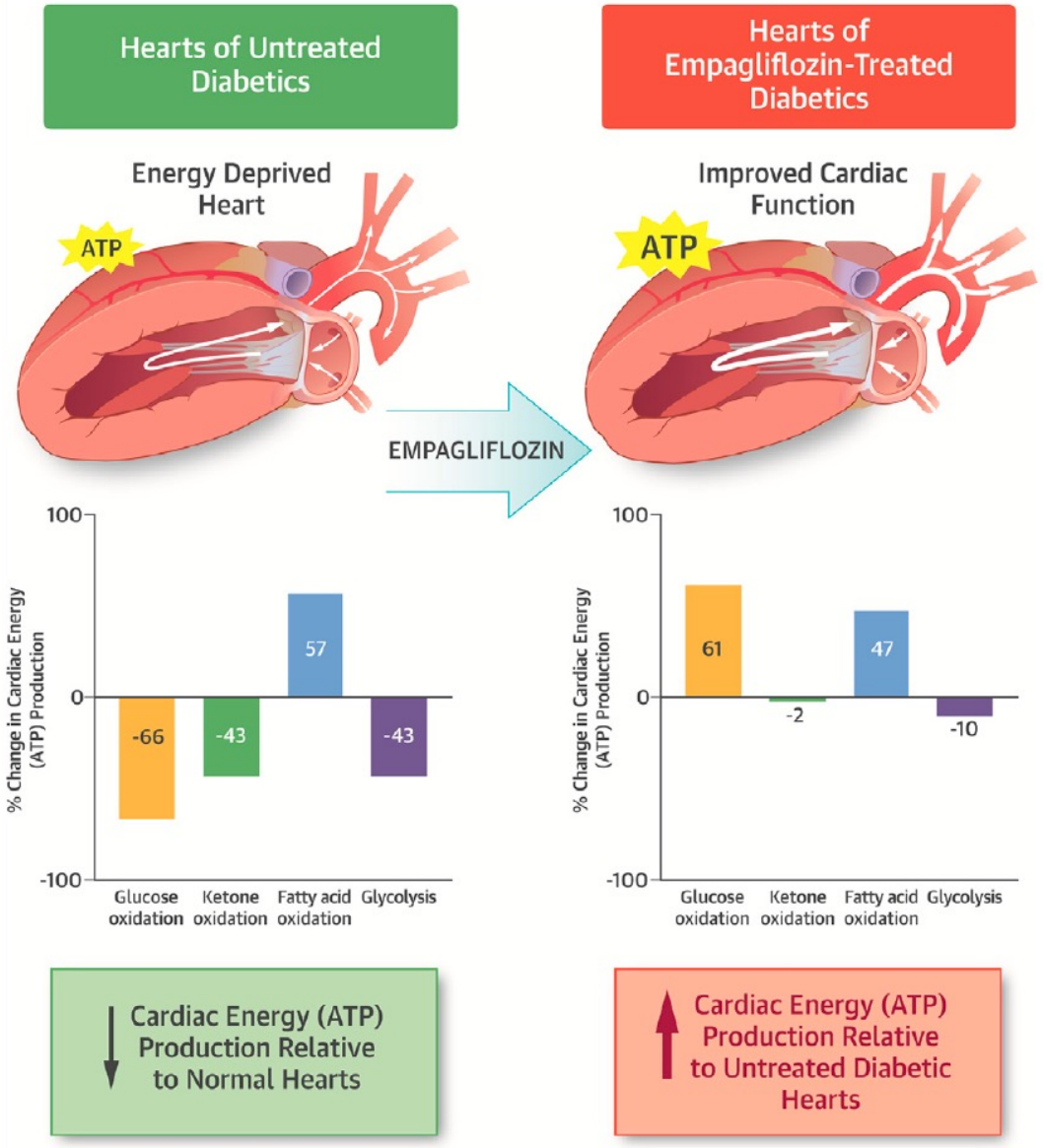


SGLT-2i: cardiac effects



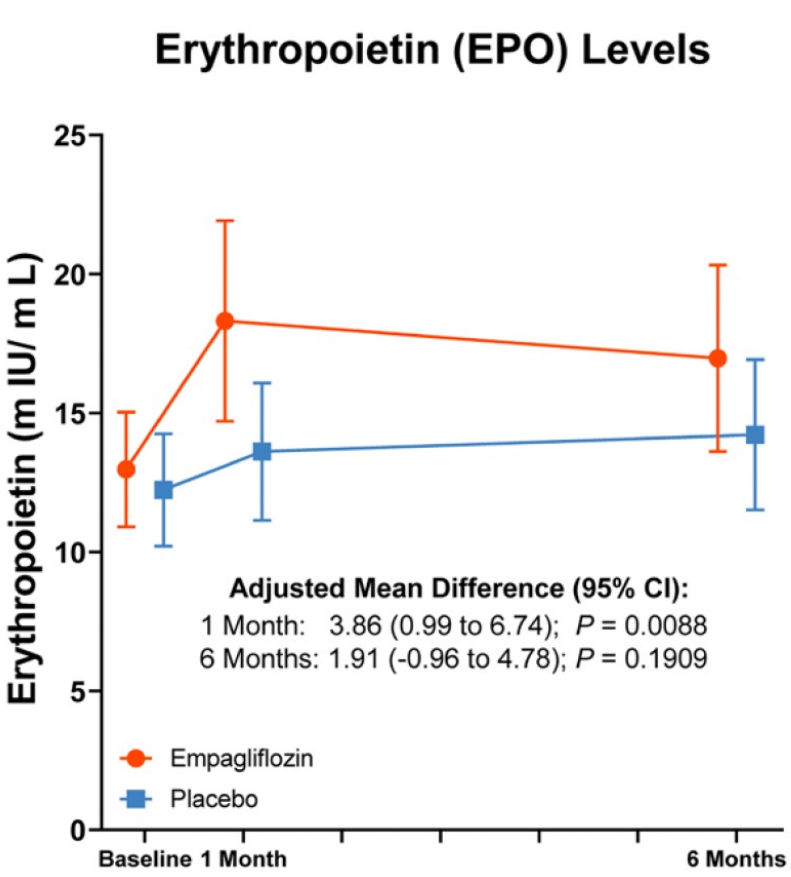
Perry RJ et al. J Biol Chem 2020; 295(42):14379-142390.

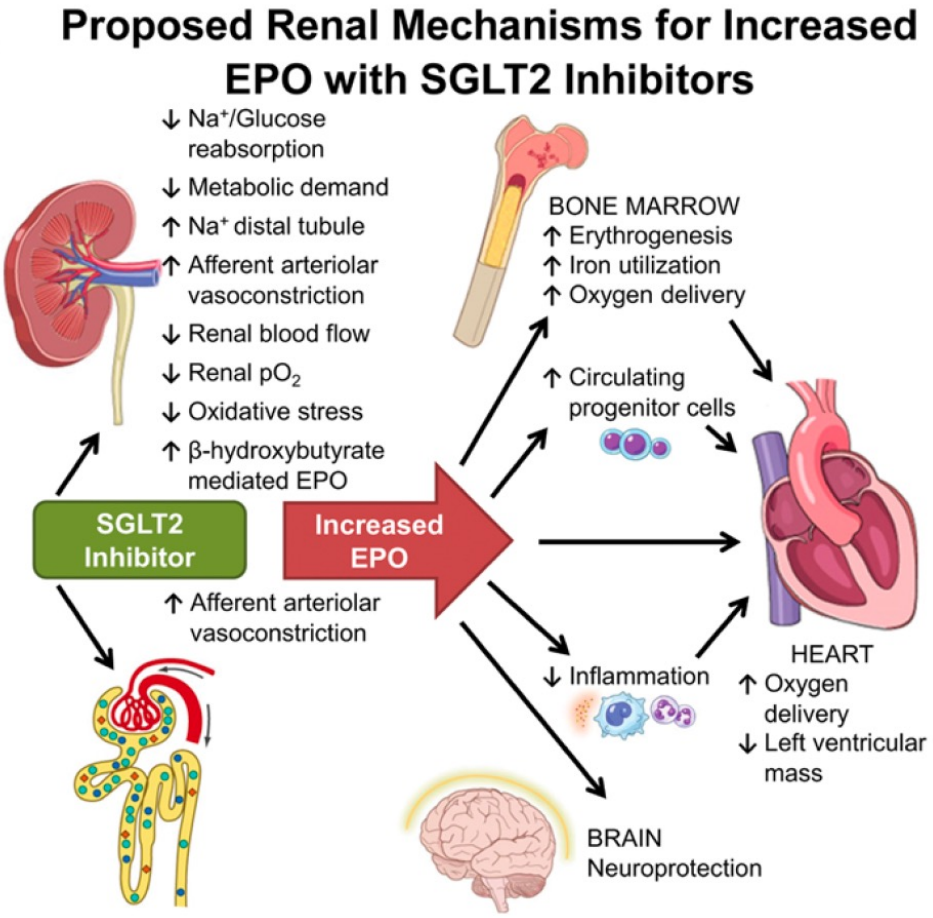
SGLT-2i increase energy production and balance



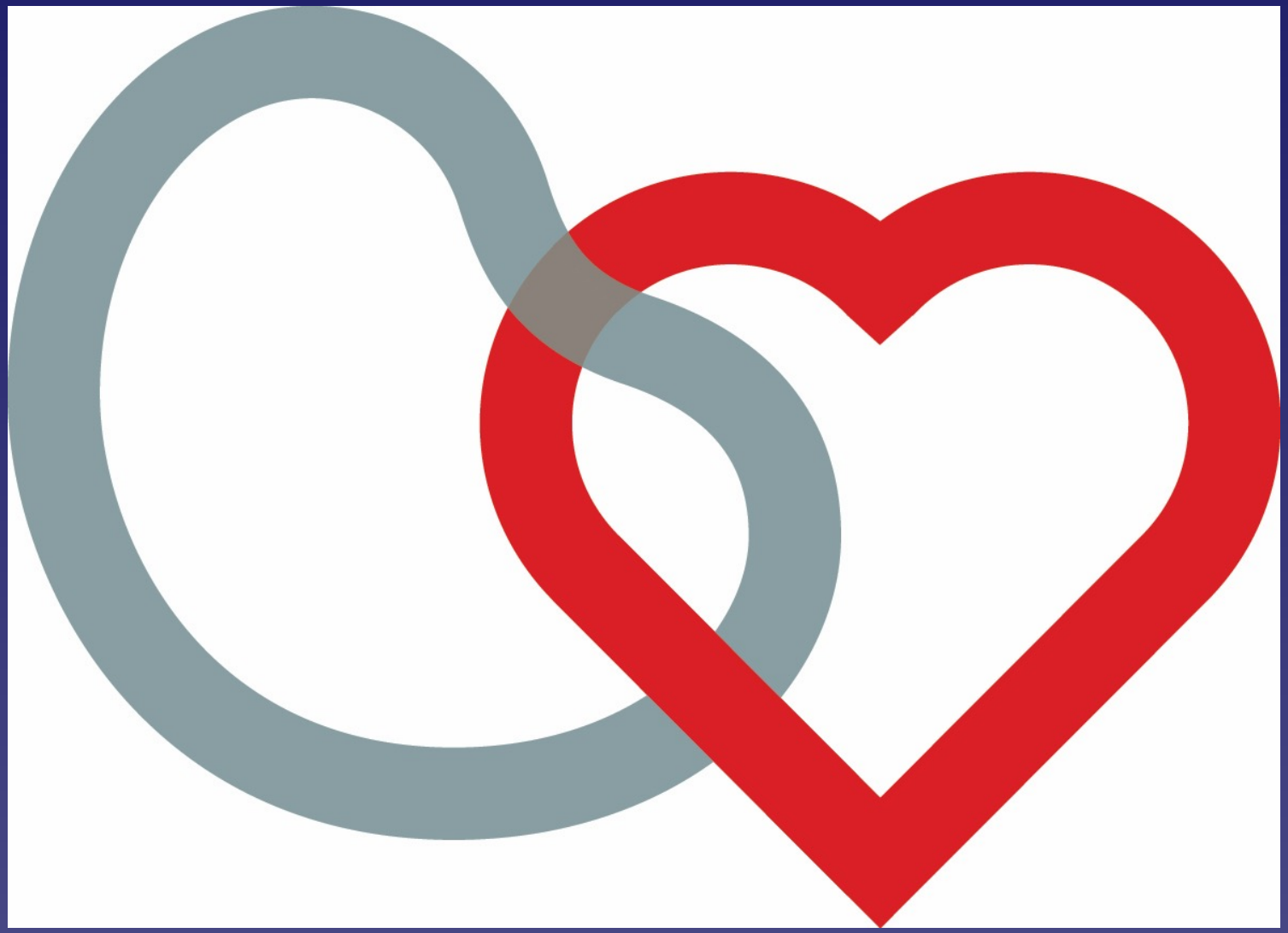
Verma, S. et al. J Am Coll Cardiol Basic Trans Science. 2018;3(5):575-87.

Empagliflozin therapy stimulates Erythropoetin expression

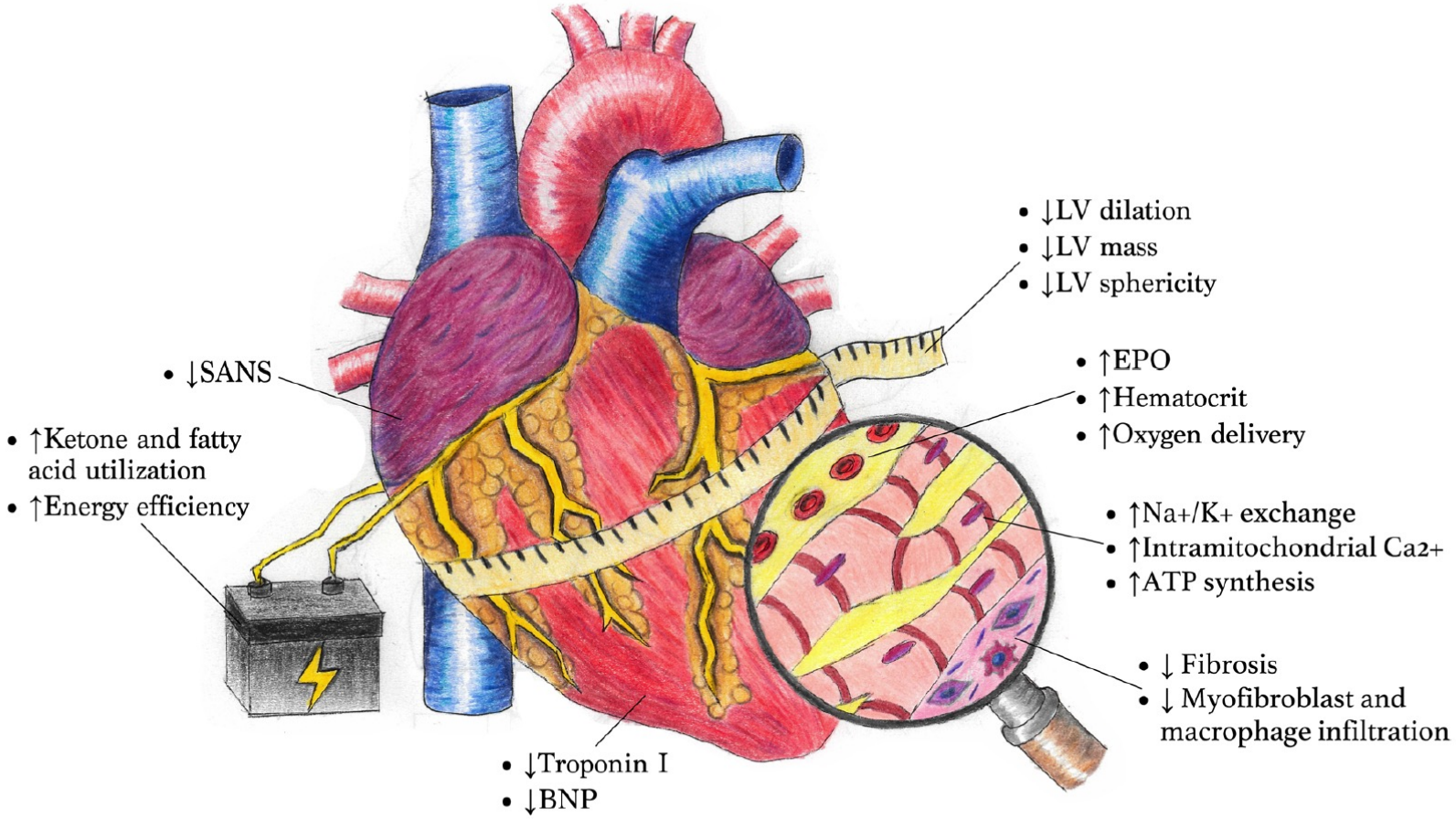




Mazer CD et al. Circulation. 2020:141:704-707.



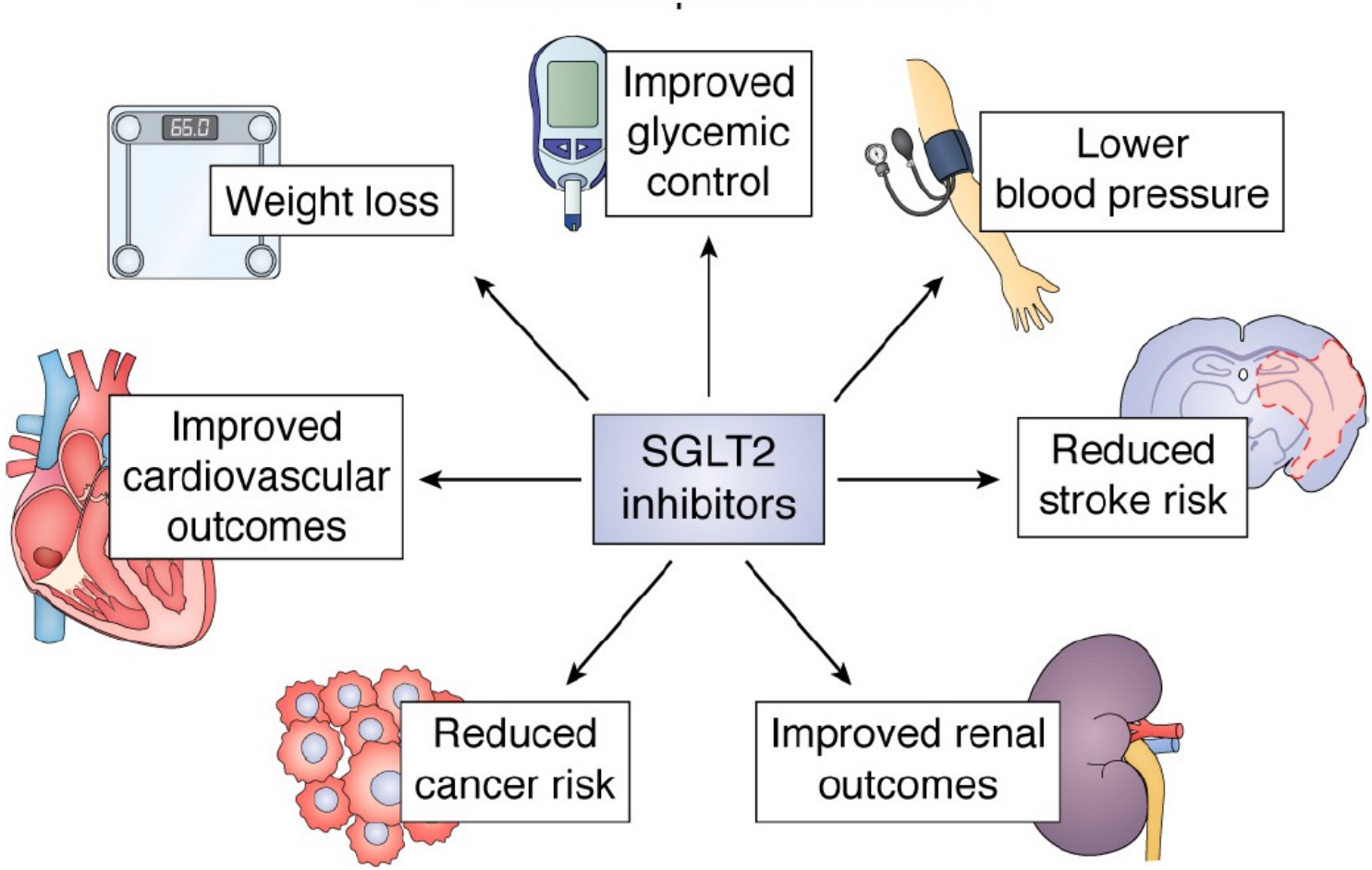
SGLT-2i and the HEART



EPO= Erythropoietin, LV= Left ventricular, SANS= Sympathetic autonomic nervous system

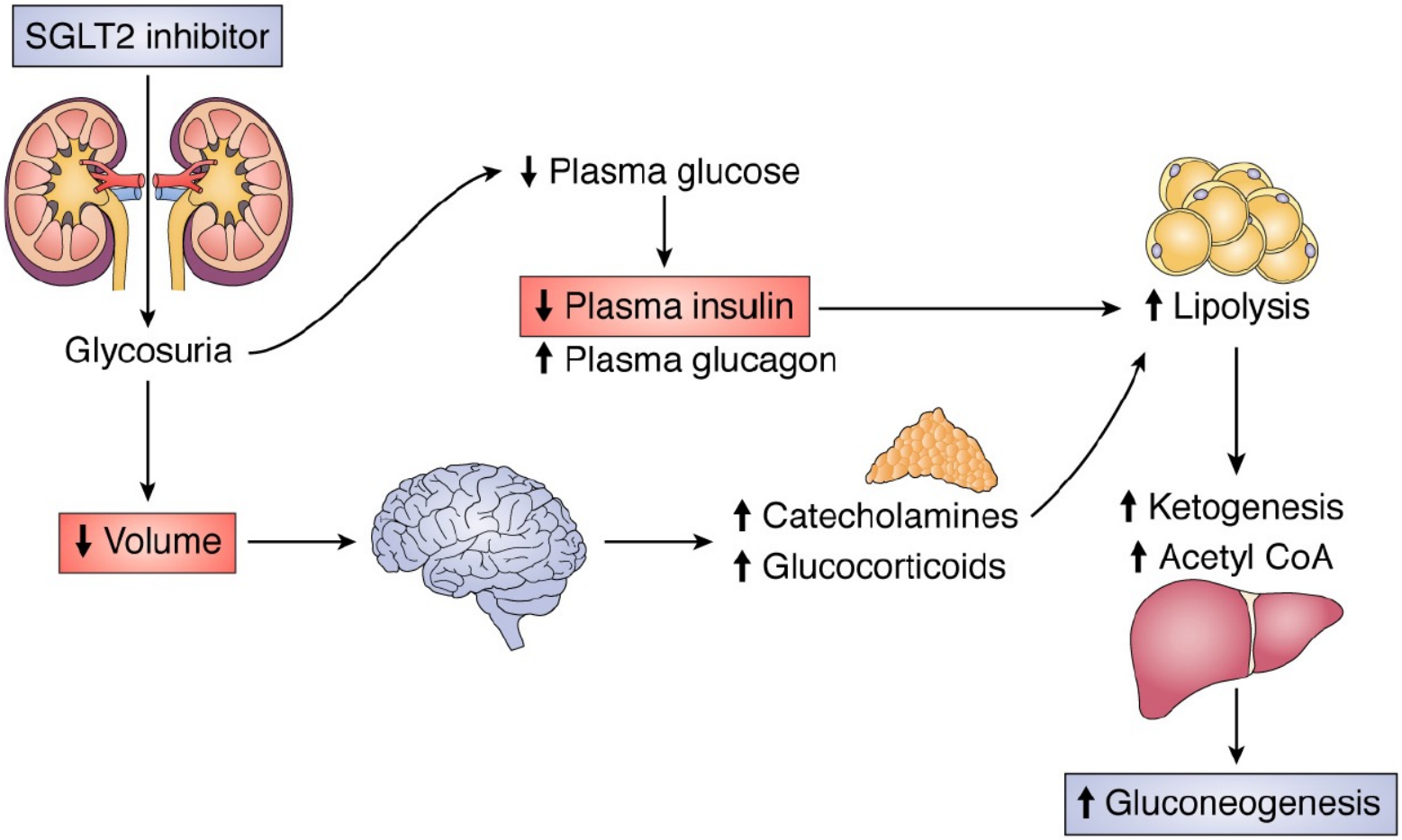
Aguilar-Gallardo JS, Correa A, Contreras P . 2021; 0:1-11.

SGLT-2i: Benefits



Perry RJ et al. J Biol Chem 2020; 295(42):14379-142390.

SGLT-2i: systemic effects



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