HFA Heart Failure Association
European Society of Cardiology
САНУ СРПСКА АКАДЕМИЈА НАУКА И УМЕТНОСТИ
УНИВЕРЗИТЕТ У БЕОГРАДУ МЕДИЦИНСКИ ФАКУЛТЕТ
KLINIČKI CENTAR SRBIJE
Heart failure Society of Serbia

Prof. dr Petar M. Seferovic, MD, PhD, FESC, FACC

Chair, ESC Task force on Eastern Countries

Co-Editor for Eastern Europe, European Heart Journal

Vice-president, European Society of Cardiology (2020-2022)

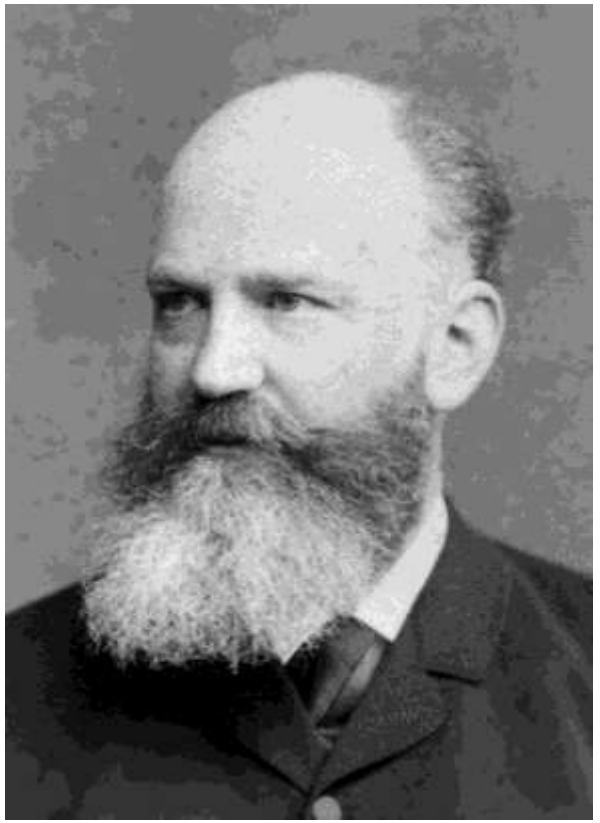
Type 2 diabetes and heart failure: Effect of the SGLT2 inhibitors

Academician, Serbian Academy of Sciences and Arts

Professor of Cardiology, Belgrade University School of Medicine

President, Heart failure Society of Serbia

Old disease, new threats:
Dark past and brighter future ?

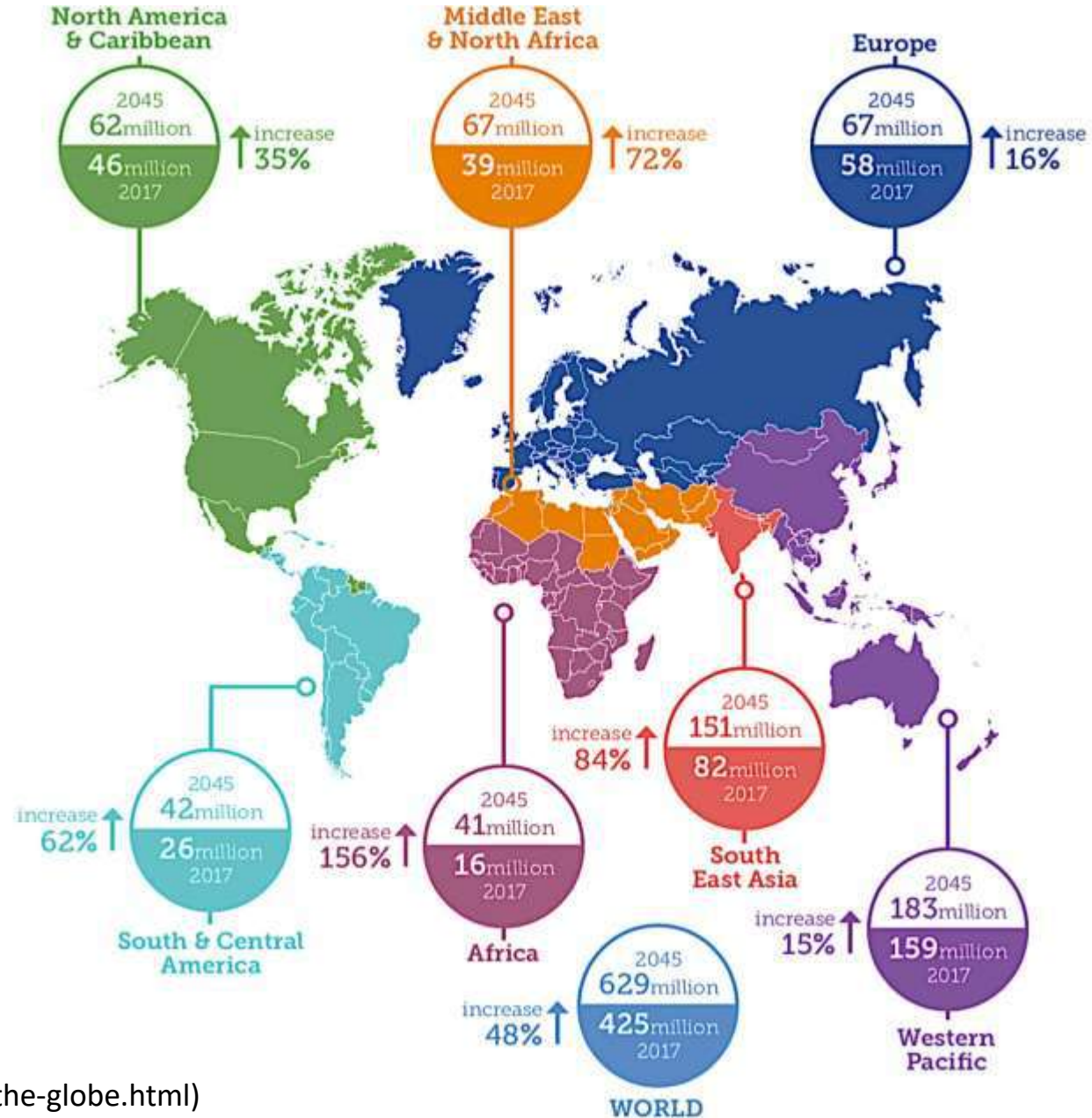


Ebers papyrus (1550 BC), Egyptian medical report on a condition of "passing too much urine"

Global epidemy of diabetes: worrisome predictions

- **Prevalence, n= 424.9 million (8.8% of adults).**
- **Expected to rise to 1.5x by 2045.**
- **Undiagnosed diabetes, 50% of all patients.**
- **Responsible for 10.7% of all-cause mortality.**
- **T2DM: the most common type of diabetes (90% of all patients).**

Number of people with diabetes in 2017 and estimates for 2045



Source: IDF Diabetes Atlas - 8th edition (http://www.diabetesatlas.org/across-the-globe.html)

DIABETIC ANGIOPATHY

A SPECIFIC VASCULAR DISEASE

KNUD LUNDBÆK
M.D. Copenhagen
PROFESSOR OF INTERNAL MEDICINE IN THE UNIVERSITY OF AARHUS, DENMARK

From the Second University Clinic of Internal Medicine, Kommunehospitalet, Aarhus

IT has been known for many years that vascular diseases are more common among diabetics than among non-diabetics. In the last few years evidence has accumulated indicating that some, at least, of these vascular anomalies are closely related to the duration of diabetes mellitus. True diabetic retinopathy, for instance, is very unusual after a few years of diabetic life, but ten years after the diagnosis has been made ophthalmoscopy will reveal retinopathy in some patients, and after fifteen years it will do so in the great majority.

Before the introduction of insulin and for some years thereafter the number of diabetics with vascular diseases was still relatively insignificant. During the last decennium, however, thanks to the survival of the many patients who would have succumbed without the help of insulin, vascular disease in diabetes mellitus has become a major problem. Today we are faced with a rather characteristic syndrome affecting patients who have had diabetes for more than fifteen years.

This clinical syndrome is composed of four important organ lesions retinopathy nephropathy coronary

be regarded as "complicating disease"—arteriosclerosis, atherosclerosis, medial sclerosis, diffuse arteriolar sclerosis, or any other more or less well-known and more or less well-defined vascular disease?

Until recently the vascular diseases in diabetes mellitus were usually classified as arteriosclerosis, and the high incidence of these anomalies was usually dealt with only by stating that diabetes mellitus promotes the development of arteriosclerosis.

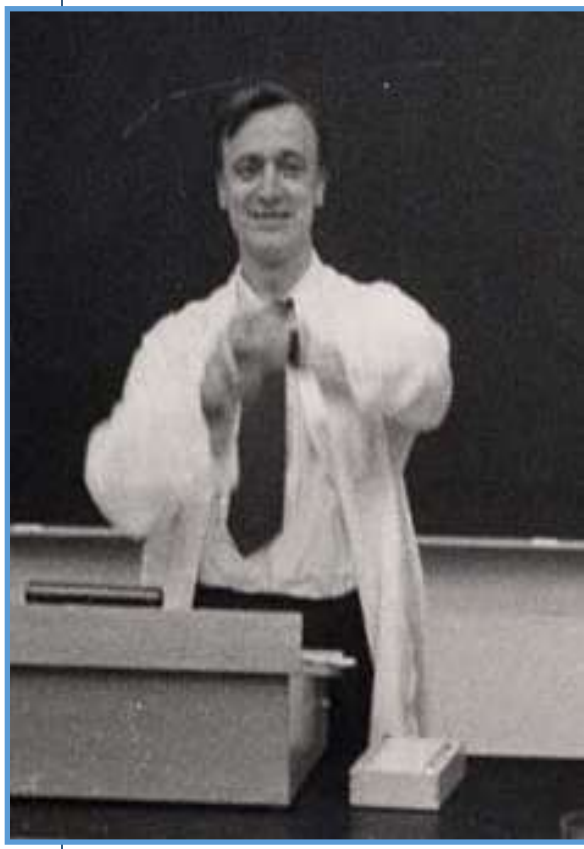
Joslin et al. (1940) wrote: ". . . the development of arteriosclerosis is excessive and has become the major cause of death among diabetics generally."

Keiding et al. (1952) write: "These patients (long-term diabetics) offer an unusual opportunity for the study of the nature of arteriosclerosis. . . ."

In latter years many workers seem either to have abandoned the term arteriosclerosis or to use it as a generic term to cover any kind of arterial hardening. With the growth of the study of intimal lesions in large and middle-sized arteries, the vascular anomalies in diabetics have come to be regarded as atherosclerosis—e.g., Warren and LeCompte (1952) and Katz and Stamler (1953). Barach and Lowy (1952) say:

"What we know is that atherosclerosis is a characteristic lesion in diabetes and that it occurs more frequently in diabetes than in other diseases."

I give below the salient points which favour the hypothesis of a generalised specific diabetic vascular disease, a diabetic angiopathy, not identical with any of the above-mentioned nosological entities.

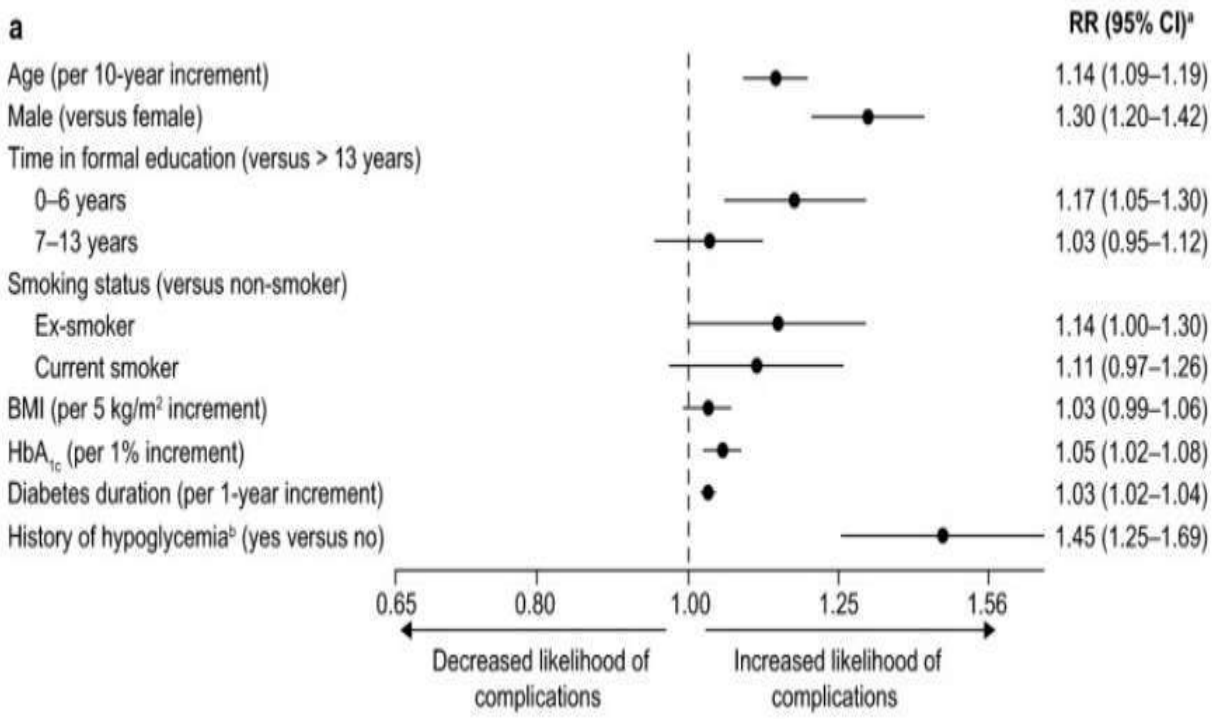


Knud Lundbæk (1912-1995)

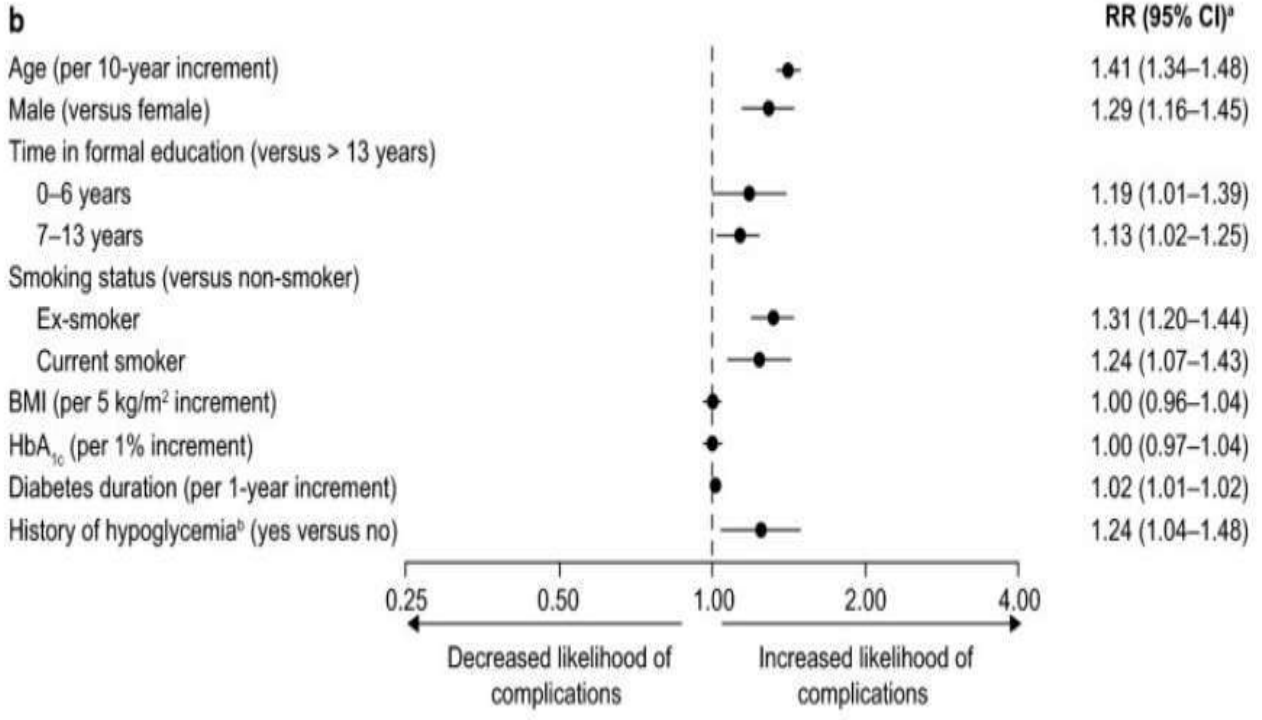
Lundbaek K. Lancet 1954

Multivariable analysis of risk factors associated with microvascular and macrovascular complications

Microvascular complications



Macrovascular complications

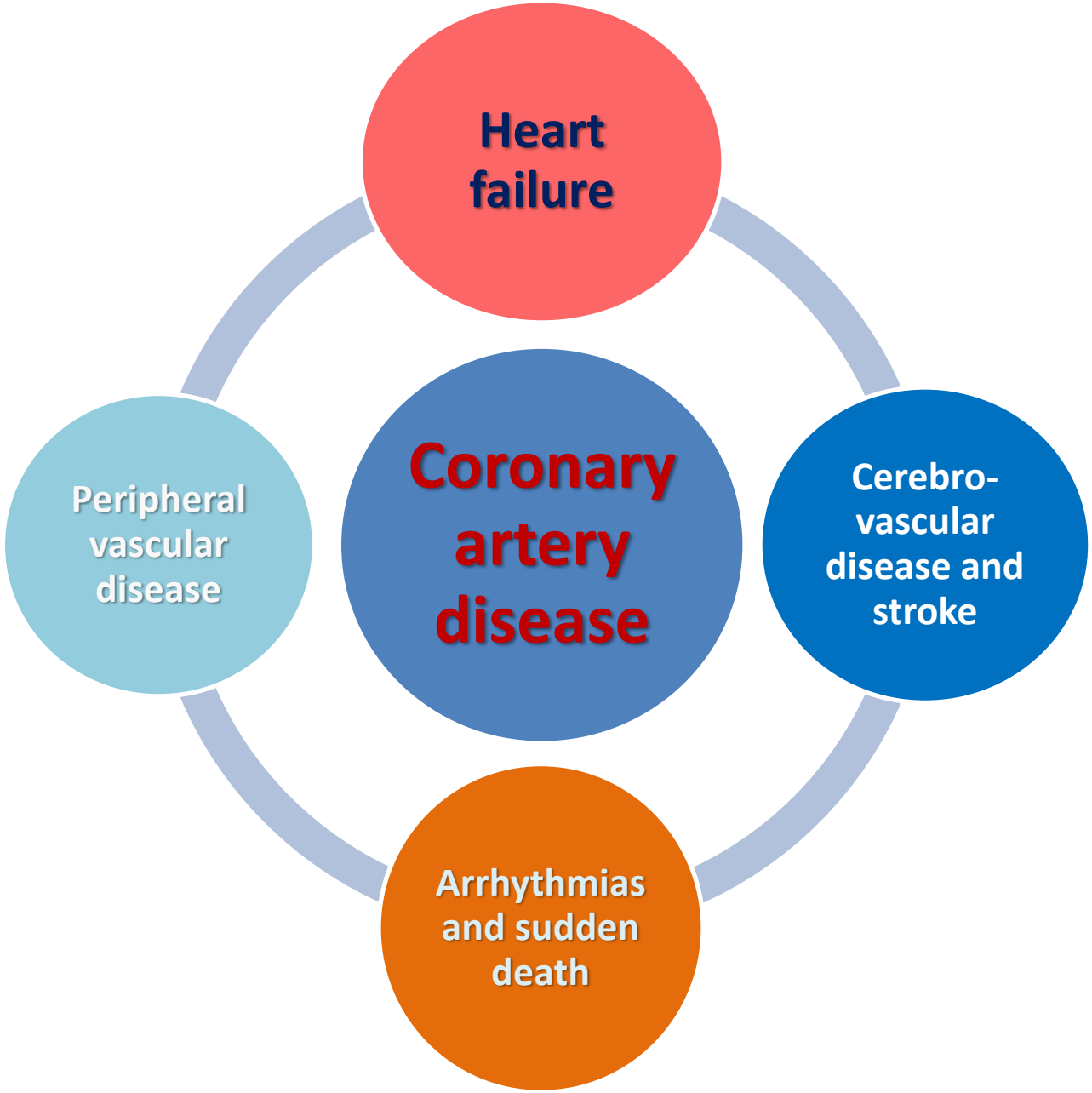


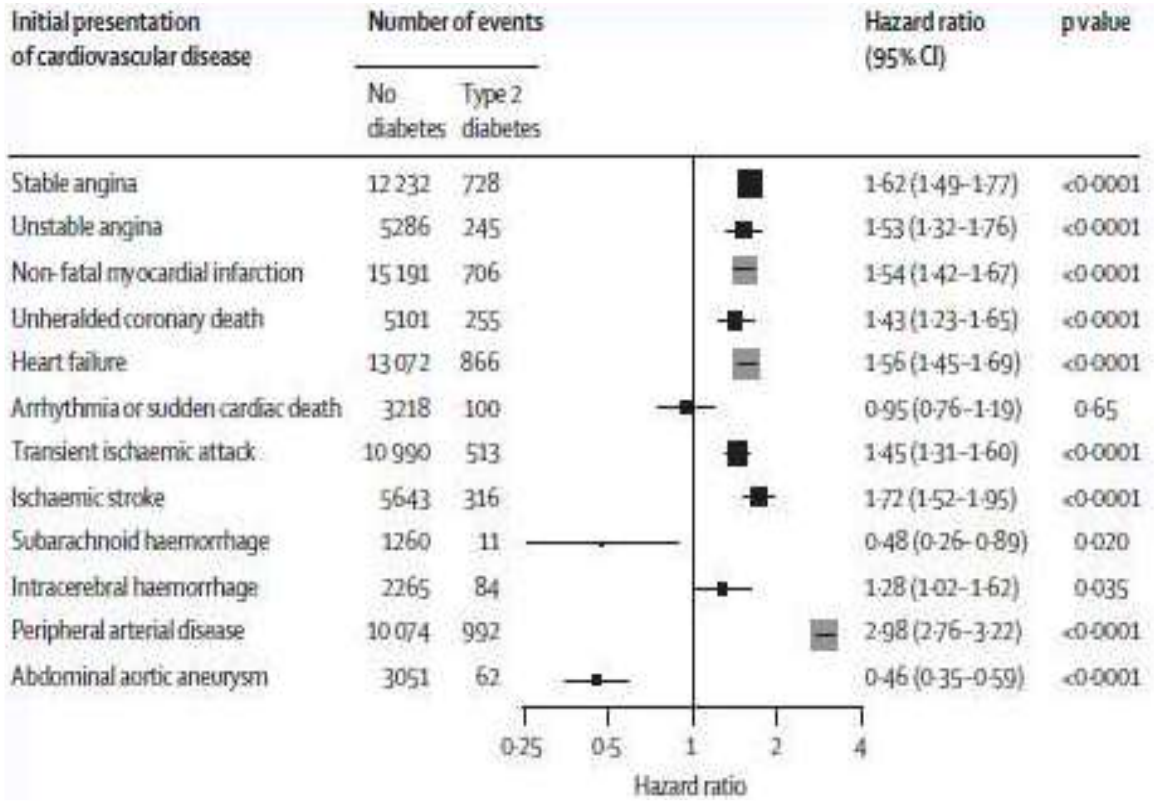
- **Microvascular and macrovascular complications in type 2 diabetes develop relatively early in the disease process.**

DISCOVER-global, prospective, observational study program of 15,992 pts with type 2 diabetes initiating second-line therapy, conducted across 38 countries

Cardiovasc Diabetol. 2018; 17: 150

Cardiovascular disease in diabetes



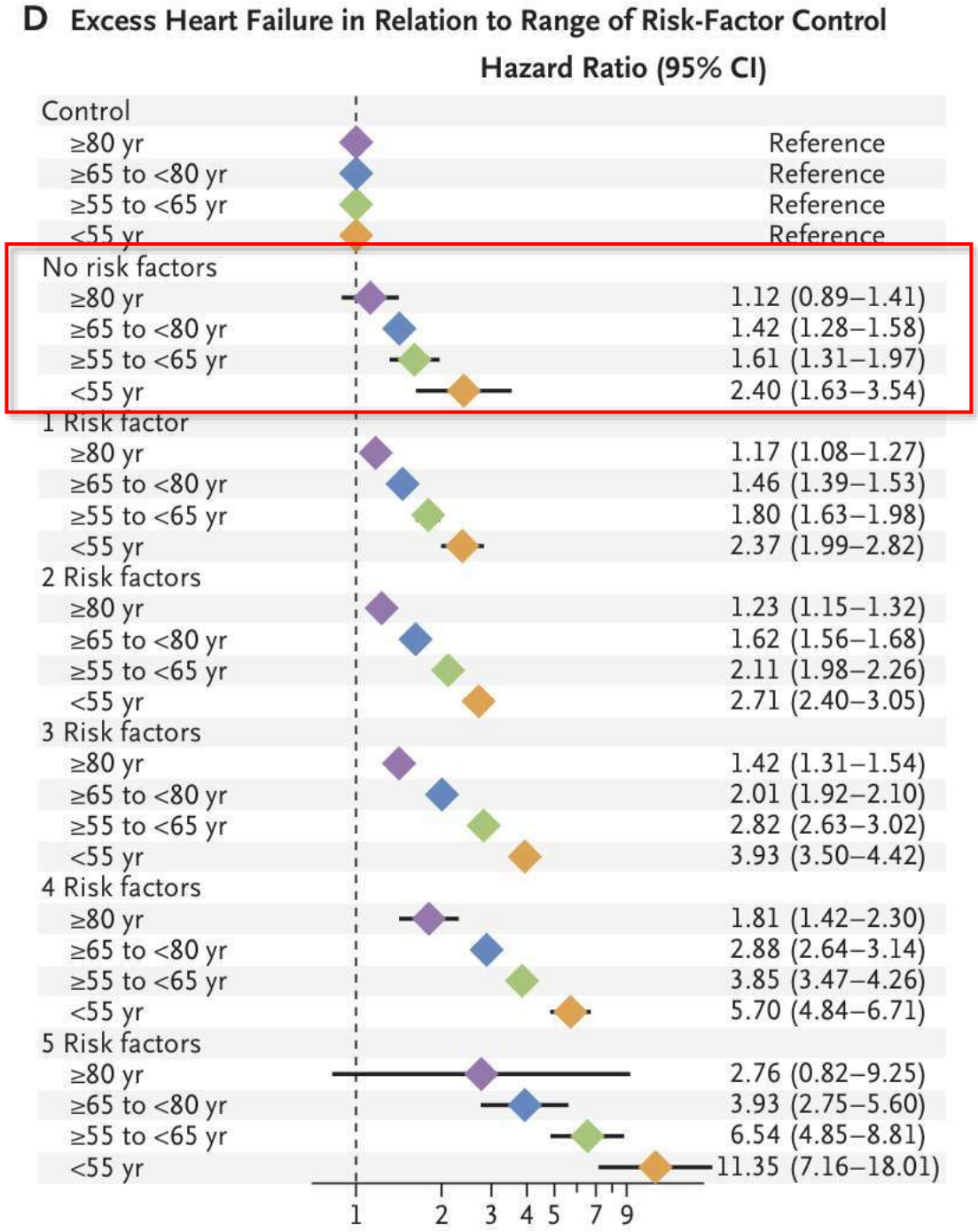


- **1,921.260 individuals, 34.198 (1,8%) with T2DM, follow-up 5.5 years**
- **Adjusted hazard ratios (HRs) for CVD initial presentations in T2DM**

Shah AD et al. Lancet Diabetes Endocrinol. 2015;3(2):105-13.

Diabetes confers an excess risk of heart failure regardless of other risk factors

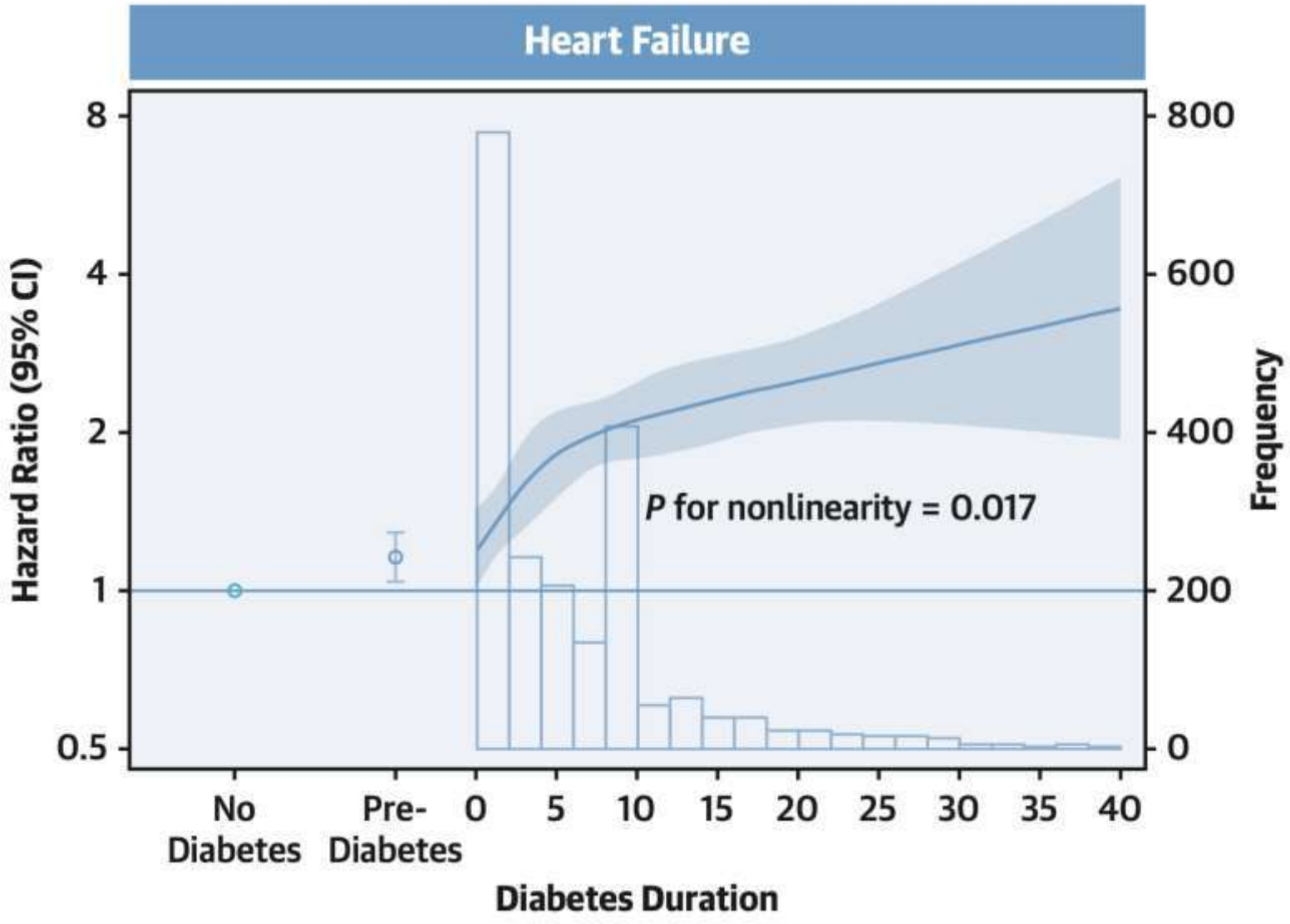
- N=271,174 pts with T2DM from the Swedish National Diabetes Register and n=1,355,870 matched controls without T2DM.
- Unlike other CV complications, the risk of developing HF in patients with T2DM remains high even after controlling multiple risk factors.
- The risk appears to be particularly high in younger patients with T2DM.



Rawshani A et al. N Engl J Med 2018;379:633-44.

Diabetes duration is important determinant of HF risk

- 9,734 participants (mean age 63 years, 58% women) from the ARIC study without HF or coronary heart disease.
- In patients with T2DM, duration of T2DM was calculated.
- Each 5-year increase in T2DM duration was associated with a 17% (95% CI: 11-22) relative increase in HF risk.



Echouffo-Tcheugui, J.B. et al. J Am Coll Cardiol HF. 2021;9(8):594–603.

European Heart Journal (2015) **36**, 1718–1727
doi:10.1093/eurheartj/ehv134

REVIEW

Clinical update

Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes

Petar M. Seferović[1] and Walter J. Paulus[2]*

[1]University Medical Center, Belgrade, Serbia; and [2]Institute for Cardiovascular Research VU (ICaR-VU), VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands

Received 28 October 2014; revised 1 April 2015; accepted 2 April 2015; online publish-ahead-of-print 17 April 2015

Diabetes mellitus-related cardiomyopathy (DMCMP) was originally described as a dilated phenotype with eccentric left ventricular (LV) remodelling and systolic LV dysfunction. Recently however, clinical studies on DMCMP mainly describe a restrictive phenotype with concentric LV remodelling and diastolic LV dysfunction. Both phenotypes are not successive stages of DMCMP but evolve independently to respectively heart failure with preserved left ventricular ejection fraction (HFPEF) or reduced left ventricular ejection fraction (HFREF). Phenotype-specific patho-

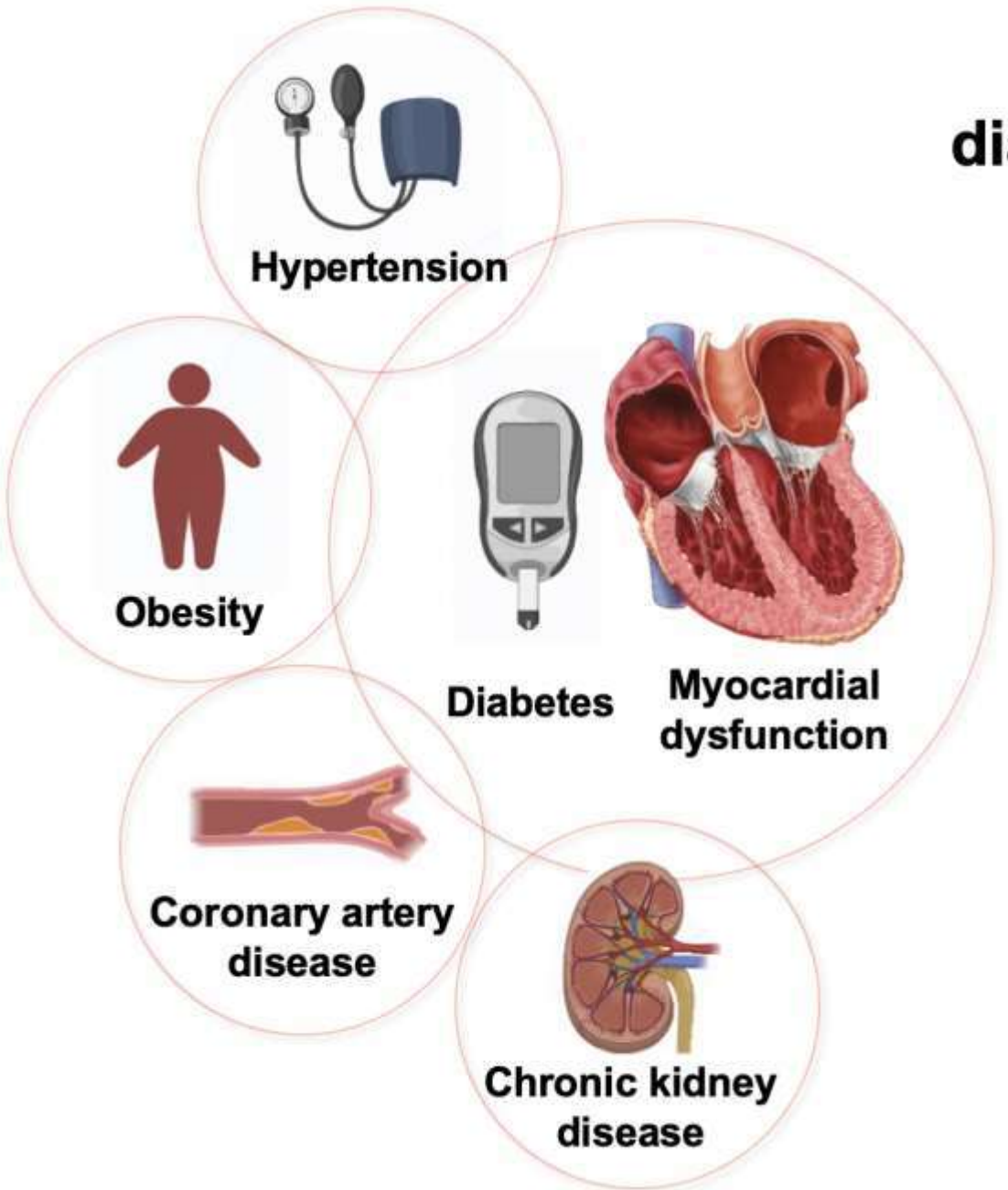
ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3347

POSITION PAPER

Diabetic myocardial disorder. A clinical consensus statement of the Heart Failure Association of the ESC and the ESC Working Group on Myocardial & Pericardial Diseases

Petar M. Seferović[1,2*], Walter J. Paulus[3], Giuseppe Rosano[4,5], Marija Polovina[1,6], Mark C. Petrie[7], Pardeep S. Jhund[7], Carsten Tschöpe[8,9], Naveed Sattar[7], Massimo Piepoli[10,11], Zoltán Papp[12], Eberhard Standl[13], Mamas A. Mamas[14], Paul Valensi[15], Ales Linhart[16], Nebojša Lalić[1,2,17], Antonio Ceriello[18], Wolfram Döhner[8,9,19], Arsen Ristić[1,6], Ivan Milinković[1,6], Jelena Seferović[1,17], Francesco Cosentino[20], Marco Metra[21], and Andrew J.S. Coats[22]



New proposed definition of diabetic myocardial disorder by the HFA of the ESC and the ESC WG on Myocardial & Pericardial Disorders

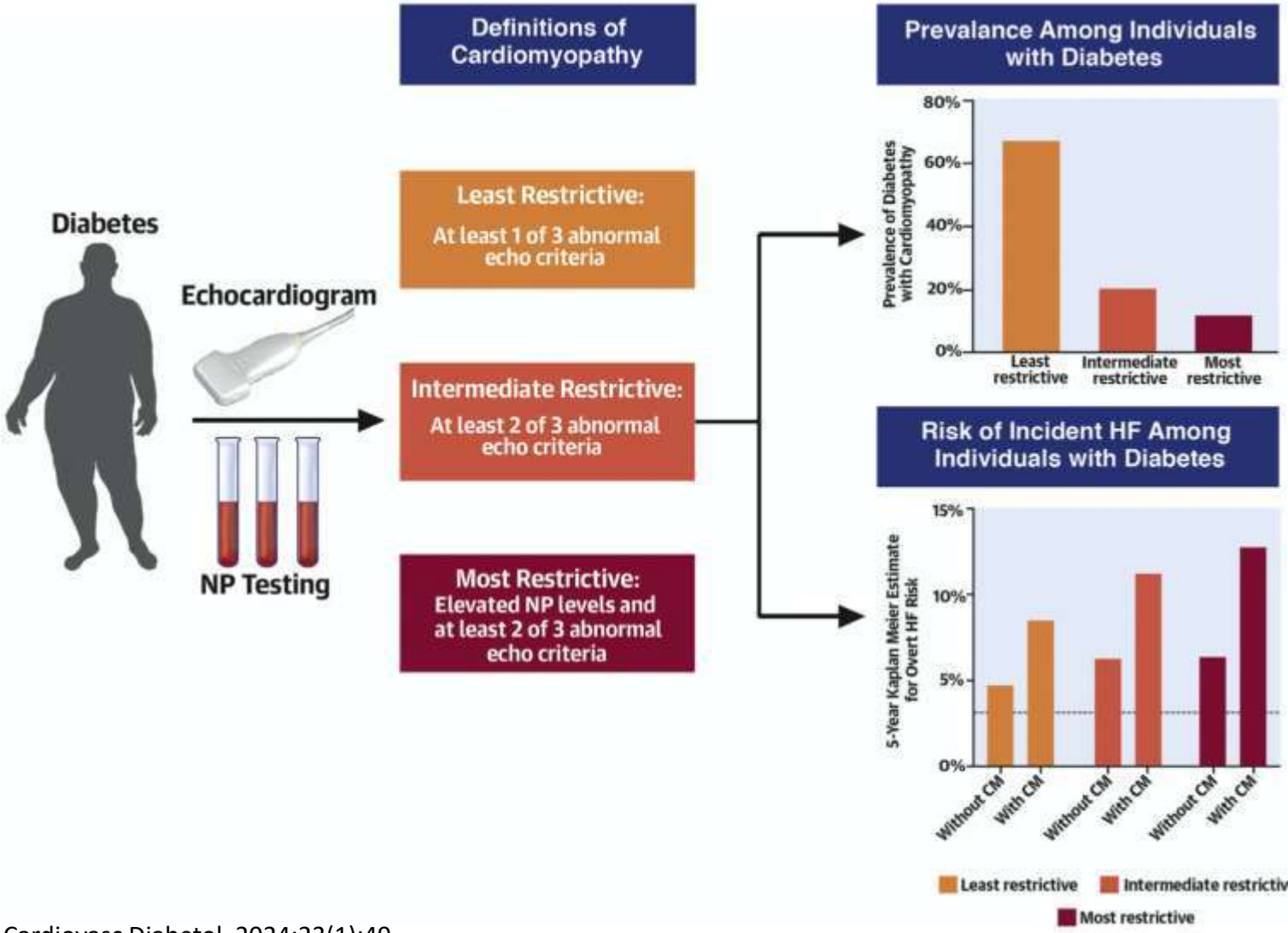
Diabetic myocardial disorder is defined as systolic and/or diastolic myocardial dysfunction in the presence of diabetes. Diabetes is rarely exclusively responsible for myocardial dysfunction, but usually acts in association with obesity, arterial hypertension, chronic kidney disease and/or coronary artery disease, causing additive myocardial impairment.

Seferović P et al. Eur J Heart Fail. 2024 Sep;26(9):1893-1903

Diabetic myocardial disorder is highly prevalent in patients with diabetes without ACVD

- **US observational data**: T2DM without ACVD or HF (n=2900) - the prevalence diabetic myocardial disorder **12% to 67%** depending upon the criteria used.

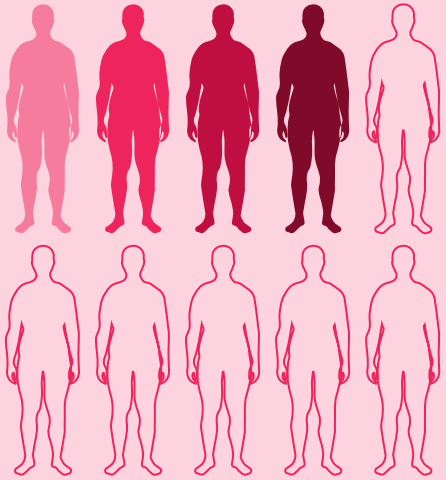
- **ARISE-HF trial** - most frequently observed abnormalities:
  - ✓ Impaired GLS (25.3%)
  - ✓ Diastolic dysfunction (17.7%),
  - ✓ Left atrial enlargement (11.9%),
  - ✓ LVH (11.9%)
  - ✓ Increased RV systolic pressure(3.9%),
  - ✓ ↑ NP (26.6%) and hs-Tn (20.4%) levels.

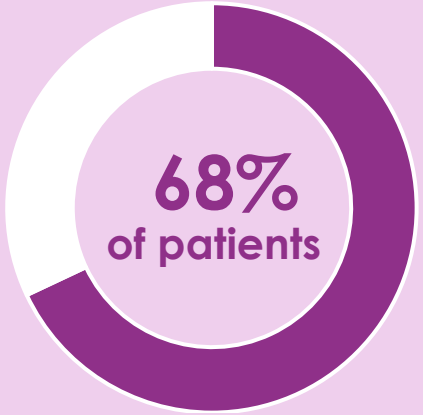


Segar, M.W. et al. J Am Coll Cardiol. 2021;78(16):1587–1598. Januzzi JL, et al. Cardiovasc Diabetol. 2024;23(1):49.

Heart failure is an early, highly prevalent and often asymptomatic complication in patients with T2D[1,2]

Between **25% and 40%** of patients with diabetes have HF[1]





who had T2D for 5 years* (N=386) showed signs of asymptomatic LV dysfunction†[2]

Undiagnosed HF was detected in **28% of patients with T2D** aged ≥60 years (N=581) during cardiac screening‡[3]

*Median value (interquartile range 2–10 years across patient groups); †Patients had no evidence of cardiac disease at baseline. Asymptomatic LV dysfunction comprised combined asymptomatic LV systolic and/or diastolic dysfunction, which are foundational indications of early HF; ‡Western European cohort

HF, heart failure; LV, left ventricular; T2D, type 2 diabetes

1. Rosano G *et al*. *Cardiac Failure Rev* 2017;3:52; 2. Faden G *et al. Diabetes Res Clin Pract* 2013;101:309; 3. Boonman-de Winter LJ *et al*. *Diabetologia* 2012;55:2154

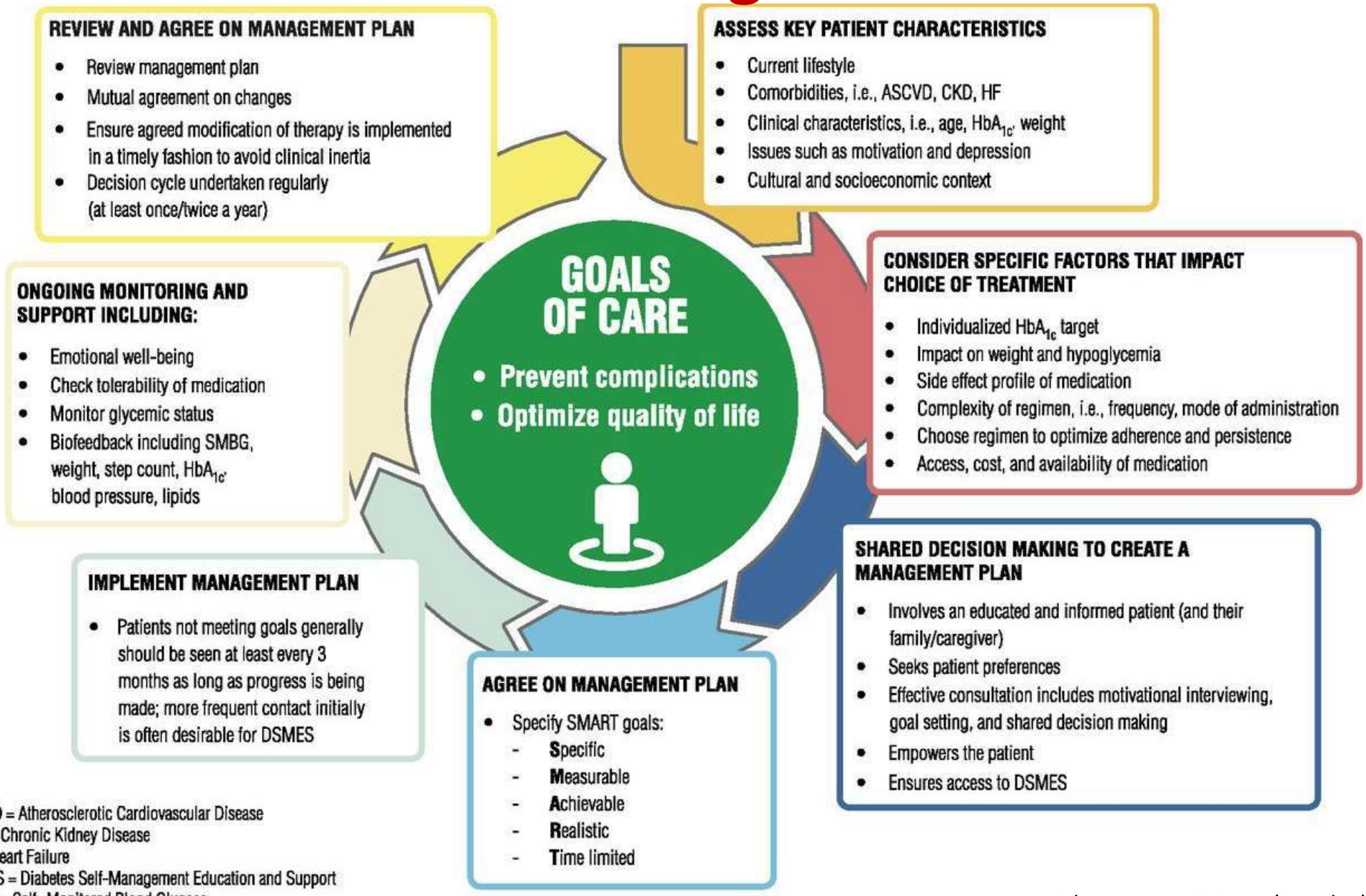
European Journal of Heart Failure (2018) **20**, 853–872
doi:10.1002/ejhf.1170

HFA POSITION STATEMENT

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

Petar M. Seferović[1]*, Mark C. Petrie[2], Gerasimos S. Filippatos[3], Stefan D. Anker[4], Giuseppe Rosano[5], Johann Bauersachs[6], Walter J. Paulus[7], Michel Komajda[8], Francesco Cosentino[9], Rudolf A. de Boer[10], Dimitrios Farmakis[2], Wolfram Doehner[11], Ekaterini Lambrinou[12], Yuri Lopatin[13], Massimo F. Piepoli[14], Michael J. Theodorakis[15], Henrik Wiggers[16], John Lekakis[2], Alexandre Mebazaa[17], Mamas A. Mamas[18], Carsten Tschöpe[19], Arno W. Hoes[20], Jelena P. Seferović[21], Jennifer Logue[22], Theresa McDonagh[23], Jillian P. Riley[24], Ivan Milinković[1], Marija Polovina[1], Dirk J. van Veldhuisen[25], Mitja Lainscak[26], Aldo P. Maggioni[27], Frank Ruschitzka[28], and John J.V. McMurray[29]

Patient centered management of T2DM

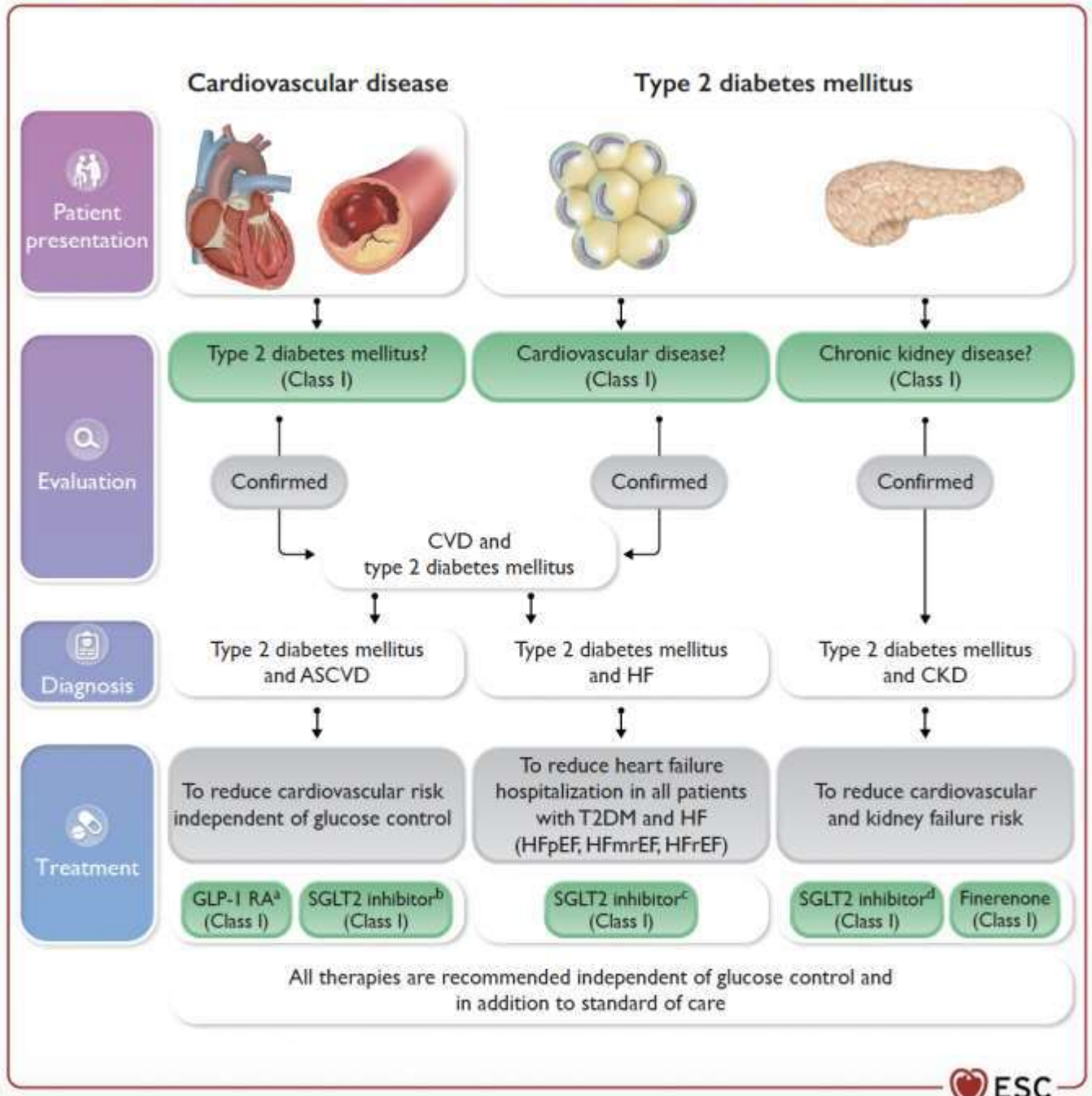


ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self- Monitored Blood Glucose

Diabetes Care 2021;44(Suppl. 1):S40-S52

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Management of cardiovascular disease in patients with T2DM: clinical approach and key recommendations



Marx N et al. European Heart Journal (2023) 00, 1–98

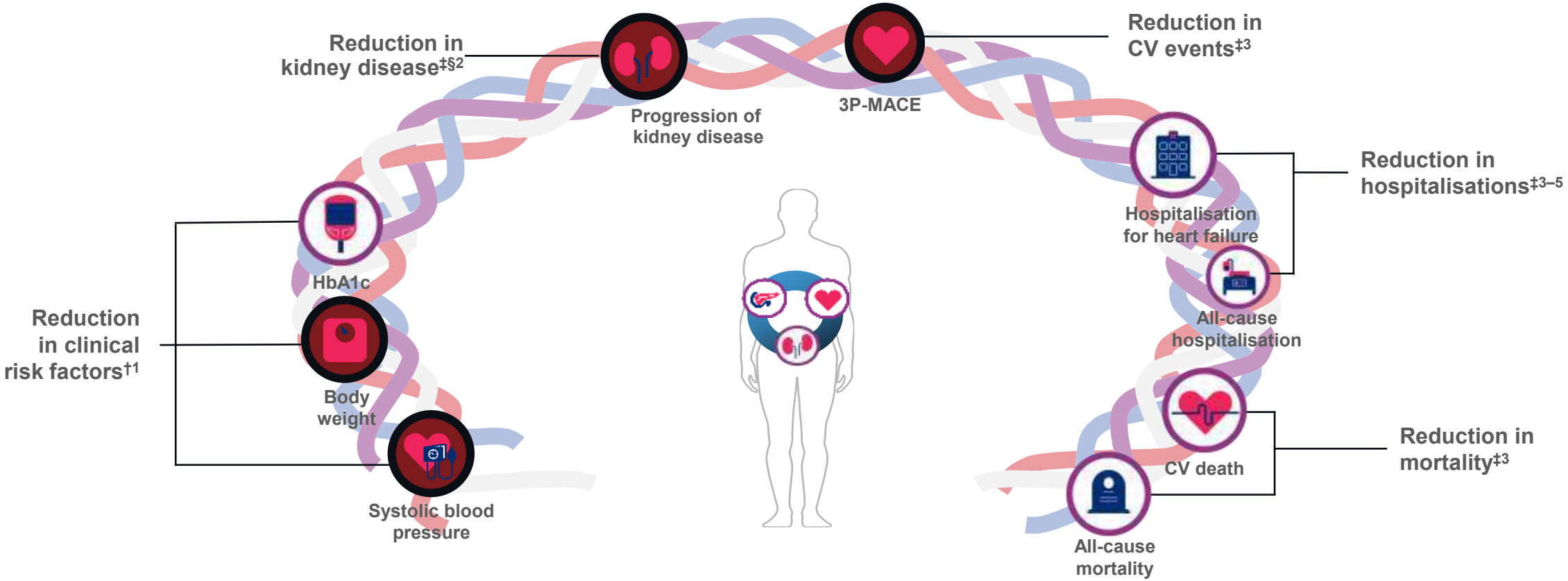
2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Special considerations for the glucose-lowering medication in patients with T2DM, with and without CV disease

Special considerations for glucose-lowering medications in patients with T2DM with and without HF		
It is recommended to switch glucose-lowering treatment from agents without proven CV benefit or proven safety to agents with proven CV benefit.	I	C

Marx N et al. European Heart Journal (2023) 00, 1–98

SGLT2 inhibitors has early beneficial effects in preventing cardio-renal complications in T2D*



*The cardiovascular and renal benefits are observed in patients with T2D with CV disease or high CV risk. †Empagliflozin as add-on to metformin; ‡Empagliflozin on top of standard of care in patients with T2D and established CV disease; §Empagliflozin is not indicated for the treatment of chronic kidney disease or diabetic kidney disease. 3P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; HbA1c, glycated haemoglobin; T2D, type 2 diabetes

1. Häring H-U *et al. Diabetes Care* 2014;37:1650; 2. Wanner C *et al. N Engl J Med* 2016;375:323; 3. Zinman B *et al. N Engl J Med* 2015:373:2117; 4. Fitchett D *et al. Eur Heart J* 2016;37:1526; 5. Patorno E *et al. Circulation* 2019;139:2822

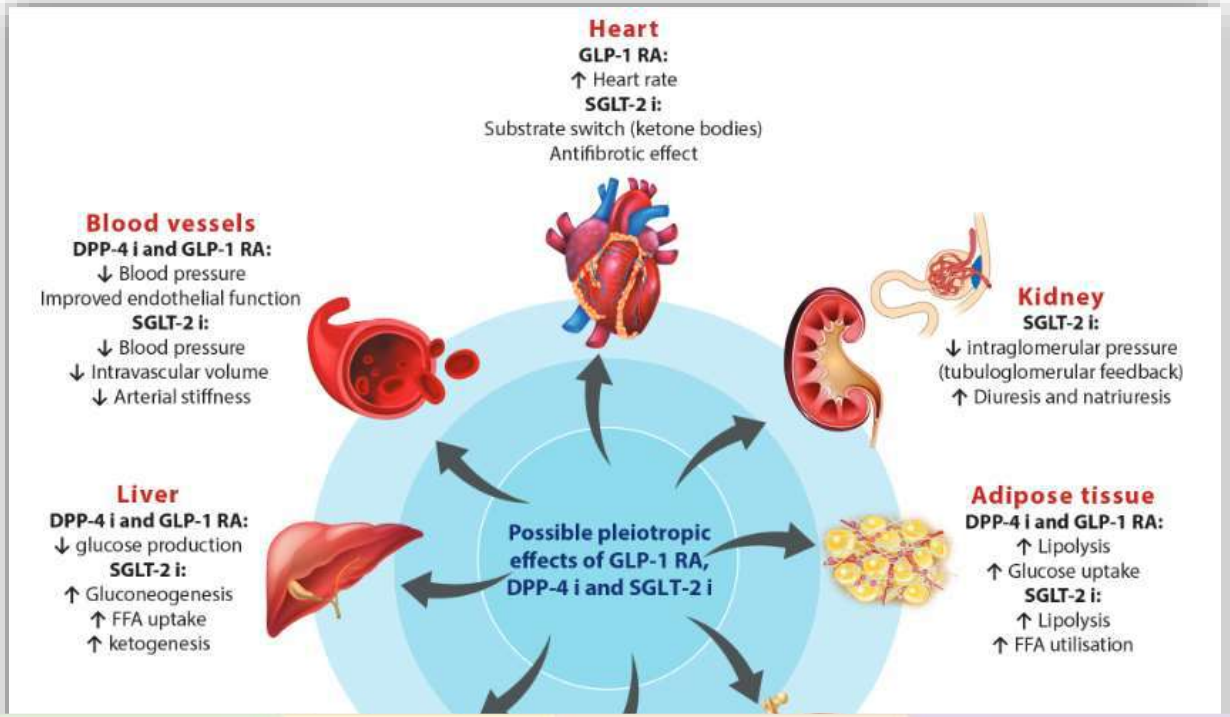
ESC European Society of Cardiology

European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1673

POSITION PAPER

European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure

Petar M. Seferović[1,2]*, Andrew J.S. Coats[3], Piotr Ponikowski[4], Gerasimos Filippatos[5,6], Martin Huelsmann[7], Pardeep S. Jhund[8], Marija M. Polovina[1,9], Michel Komajda[10], Jelena Seferović[1,11], Ibrahim Sari[12], Francesco Cosentino[13], Giuseppe Ambrosio[14], Marco Metra[15], Massimo Piepoli[16], Ovidiu Chioncel[17,18], Lars H. Lund[19], Thomas Thum[20], Rudolf A. De Boer[21], Wilfried Mullens[22,23], Yuri Lopatin[24], Maurizio Volterrani[25], Loreena Hill[26], Johann Bauersachs[27], Alexander Lyon[28], Mark C. Petrie[29], Stefan Anker[30], and Giuseppe M.C. Rosano[31]



Effect of new glucose lowering drugs on cardiovascular outcomes in placebo-controlled trials

	3-point MACE	CV death	Myocardial infarction	Stroke	HF hospitalisation
DPP-4 inhibitors Saxagliptin Alogliptin Sitagliptin Vildagliptin Linagliptin	Neutral effect	Neutral effect	Neutral effect	Neutral effect	↑ Risk Saxagliptin: 27% Neutral effect: Alogliptin, Sitagliptin, Vildagliptin Linagliptin
GLP-1 RA Lixisenatide Liraglutide Semaglutide Albiglutide Exenatide	↓ Risk Liraglutide: 13%, Semaglutide: 26% Albiglutide: 22% Neutral effect: Lixisenatide, Exenatide	↓ Risk Liraglutide:22%. Neutral effect: Albiglutide, Semaglutide, Lixisenatide, Exenatide	↓ Risk Albiglutide:25% Neutral effect: Liraglutide, Semaglutide, Exenatide, Lixisenatide	↓ Risk Semaglutide: 39% Neutral effect: Liraglutide, Exenatide Albiglutide, Lixisenatide	Neutral effect: All GLP-1 RA
SGLT-2 inhibitors Empagliflozin Canagliflozin Dapagliflozin	↓ Risk Empagliflozin:14% Canagliflozin: 14% Dapagliflozin: 17%*	↓ Risk Empagliflozin:32% Neutral effect: Canagliflozin, Dapagliflozin	Neutral effect: All SGLT-2 inhibitors	Neutral effect: All SGLT-2 inhibitors	↓ Risk Empagliflozin:35% Canagliflozin: 33% Dapagliflozin: 27%

SGLT-2 inhibitor	Recommended dose	Dose adjustment
Empagliflozin	10 mg per os OD 25 mg per os OD	**Impaired renal function:** ▪ eGFR <30 ml/min/1.73 m²: **discontinue**
Canagliflozin	100 mg per os OD 300 mg per os OD	**Impaired renal function:** ▪ eGFR <30 ml/min/1.73 m²: **discontinue**
Dapagliflozin	10 mg per os OD	**Impaired renal function:** ▪ eGFR <30 ml/min/1.73 m²: **discontinue** **Hepatic impairment:** ▪ Starting dose, **5 mg**

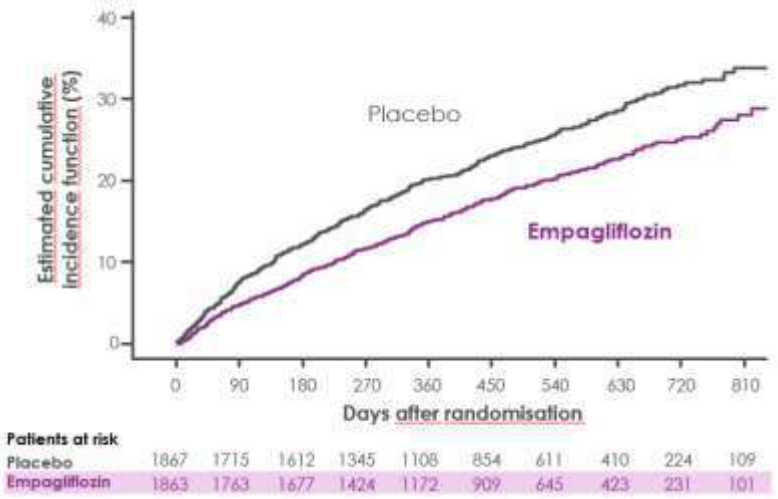
Precautions and warnings

All SGLT-2 inhibitors

- Diabetic ketoacidosis
- Hepatic injury
- Volume depletion
- Hypotension
- Critical illness
- Emergency surgery
- Recurrent genital mycotic infections
- Lower limb amputation
- Electrolyte imbalance

EMPEROR Reduced

Primary endpoint: First adjudicated CV death or HF hospitalisation



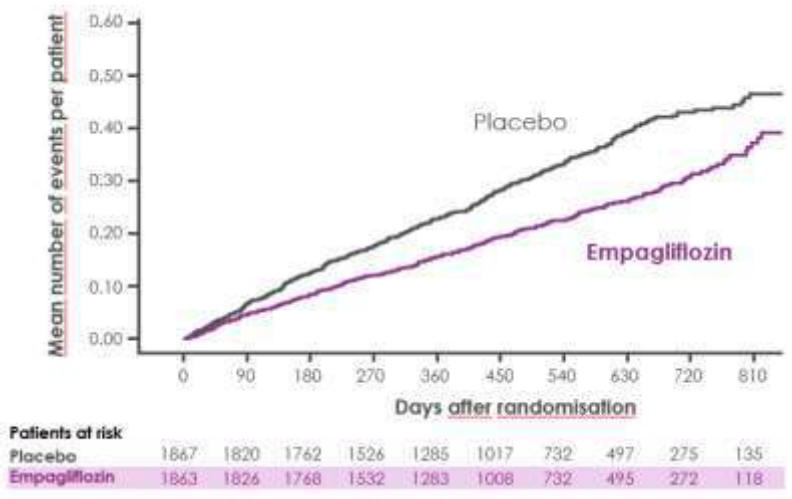
RRR 25%

ARR 5.2%

NNT = 19

HR 0.75
(95% CI 0.65, 0.86)
p<0.001

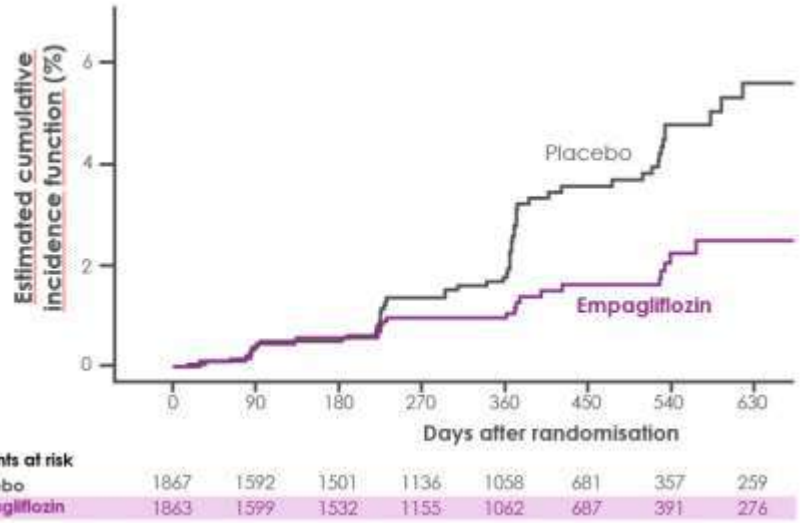
Key secondary: Adjudicated total HF hospitalisations (first and recurrent)



RRR 30%

HR 0.70
(95% CI 0.58, 0.85)
p<0.001

Composite renal endpoint (ESKD or sustained profound decrease in eGFR)



RRR 50%

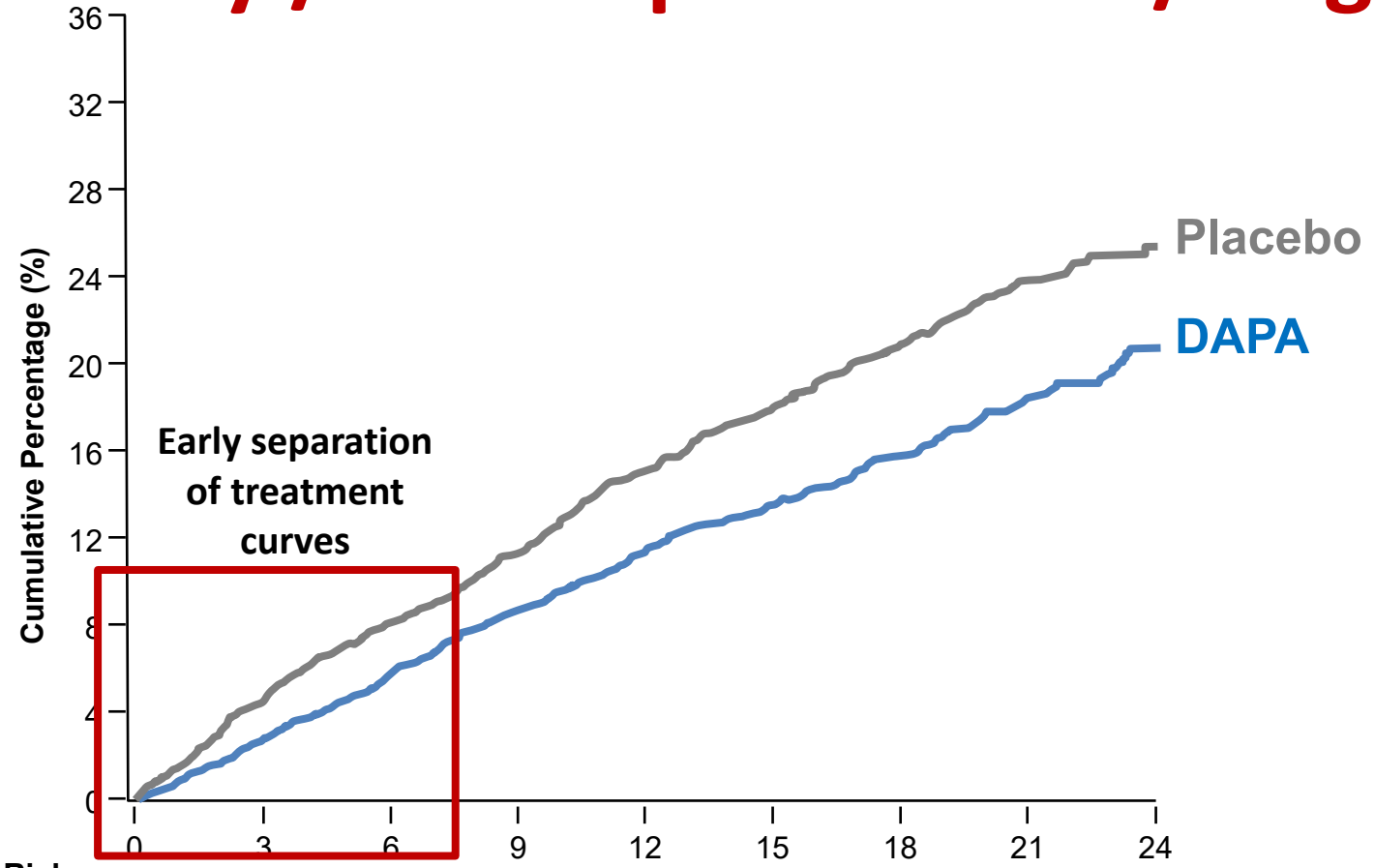
ARR 1.5%

HR 0.50
(95% CI 0.32, 0.77)

N Engl J Med 2020; 383:1413-1424

DAPA-HF: primary composite outcome

CV mortality / HF hospitalisation / Urgent HF visit



HR 0.74 (0.65, 0.85)
p=0.00001

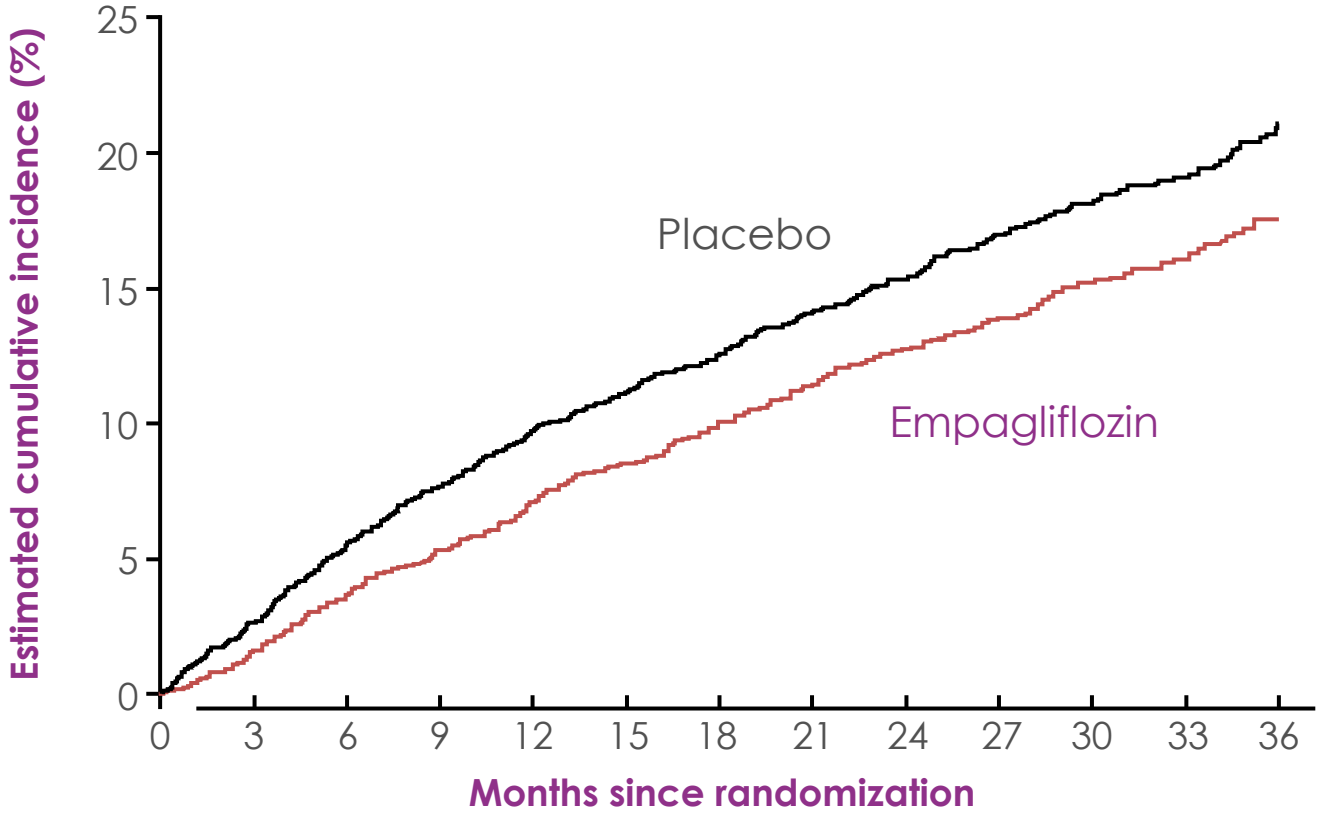
26% RRR

NNT = 21

DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat.

1. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

EMPEROR-preserved: Reduction of composite primary endpoint of CV death/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

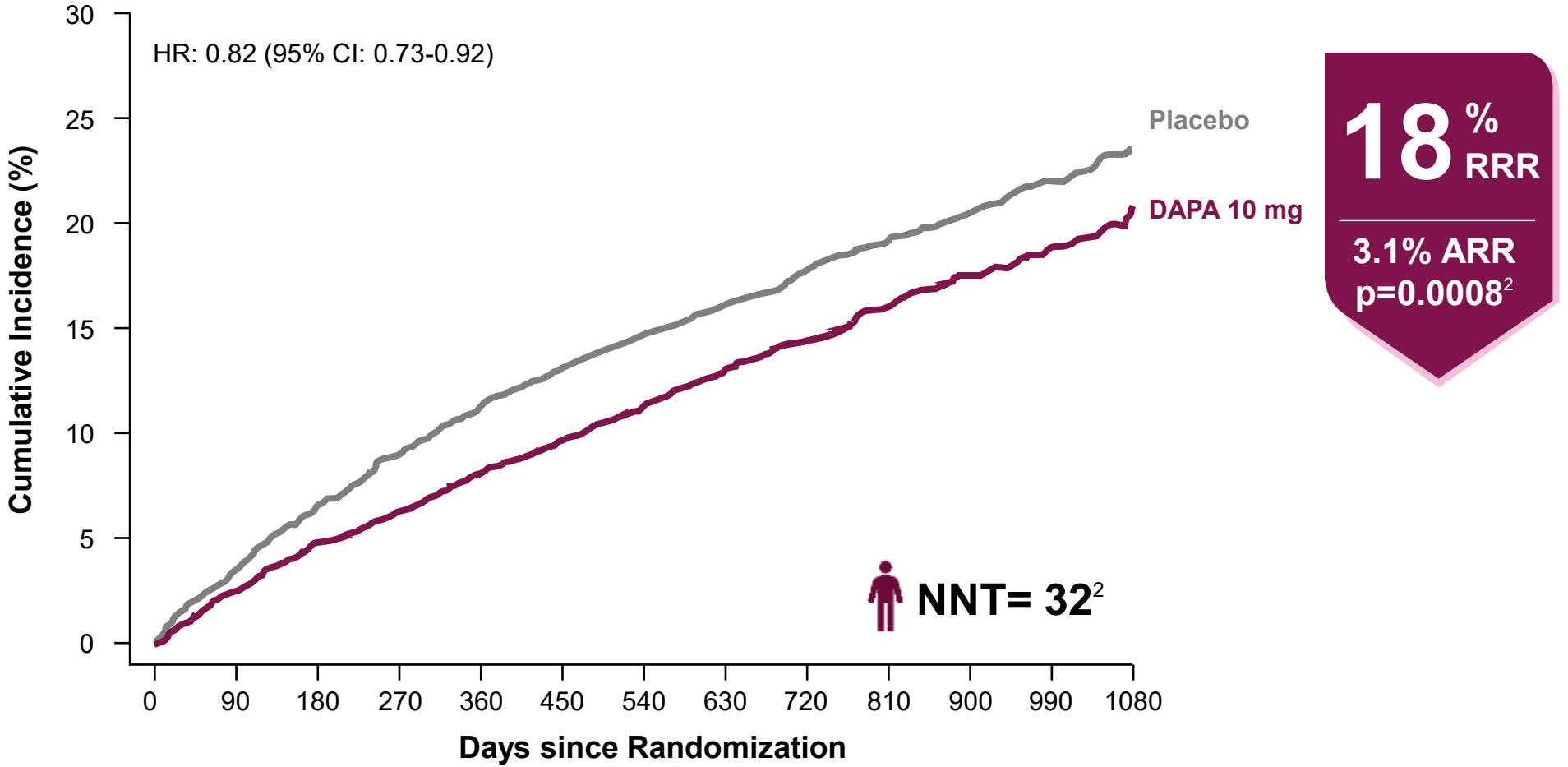
*During a median trial period of 26 months. ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction. Anker S *et al. N Engl J Med*. 2021 Aug 27. doi: 10.1056/NEJMoa2107038.

Dapagliflozin significantly reduced the risk of CV death or worsening HF[a] in patients with LVEF >40%[1]

DELIVER

Primary Endpoint

Composite of CV Death or Worsening HF[a]



[a]hHF or an urgent HF visit.

Solomon SD et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Aug 27.

DAPA-HF + DELIVER Pooled Analysis

Pre-specified, patient-level pooled analysis

Study Design[1-3]

DAPA-HF
LVEF ≤40%; N=4744
+
DELIVER
LVEF >40%; N=6263

N=11,007

DAPA 10 mg n=5504

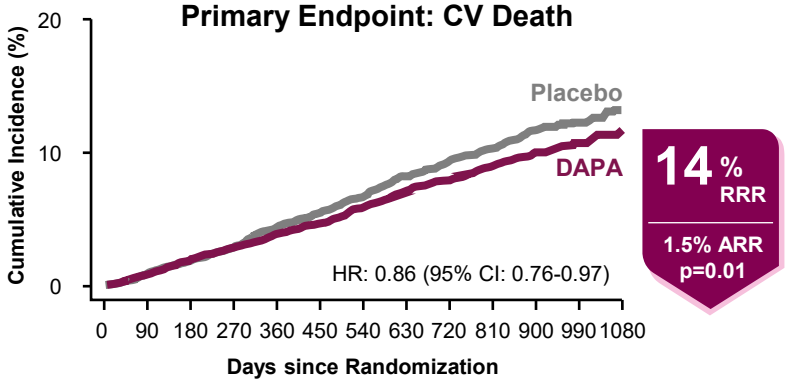
Placebo n=5503

Median Follow-up: 22 months

Purpose[1]

- Examine the effect of DAPA across the LVEF range given the attenuation seen in patients with higher LVEFs in other HF medication trials
- Prespecified outcomes:
  - ❖CV death
  - ❖Total[a] hHF
  - ❖CV death or hHF
  - ❖All-cause death
  - ❖MACE[b]

DAPA significantly reduced the risk of death and hHF across the LVEF range[1]



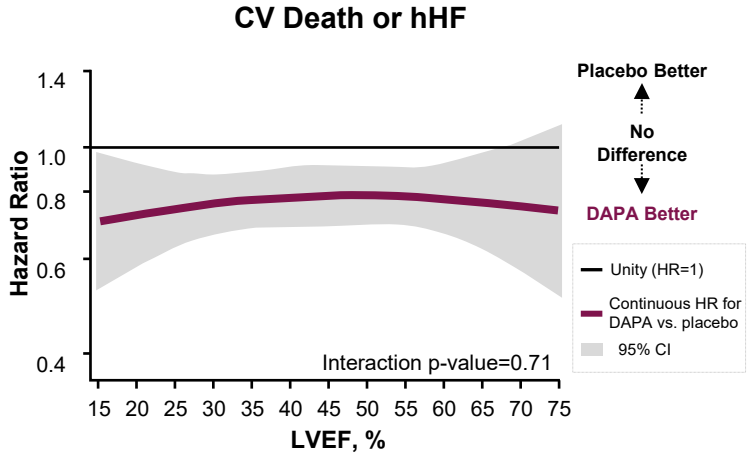
14 % RRR
1.5% ARR
p=0.01

All-cause death
10 % RRR
1.5% ARR
p=0.03
HR: 0.90
95% CI: 0.82-0.99

Total[a] hHF
29 % reduction
6.0% ARR
p<0.001
RR: 0.71
95% CI: 0.65-0.78

First hHF
26 % RRR
3.2% ARR
p<0.001
HR: 0.74
95% CI: 0.66-0.82

DAPA significantly reduced the risk of CV death or hHF across the LVEF range[1]



DAPA reduced the risk of CV death or hHF by 22%
HR: 0.78 (95% CI: 0.72-0.86); p<0.001

SGLT2 inhibitors are **recommended in patients with HF regardless of LVEF** in Treatment Guidelines[4]

[a]First and recurrent; [b]Composite of CV death, MI, or stroke.

1. Jhund PS et al. *Nat Med*. 2022 Aug 27; *2.* McMurray JJV et al. *N Engl J Med*. 2019;381(21):1995-2008; 3. Solomon SD et al. *N Engl J Med*. 2022 Aug 27.; 4. Heidenreich PA et al. *J Am Coll Cardiol*. 2022;79(17):e263-e421.

The prevention of HF hospitalisation

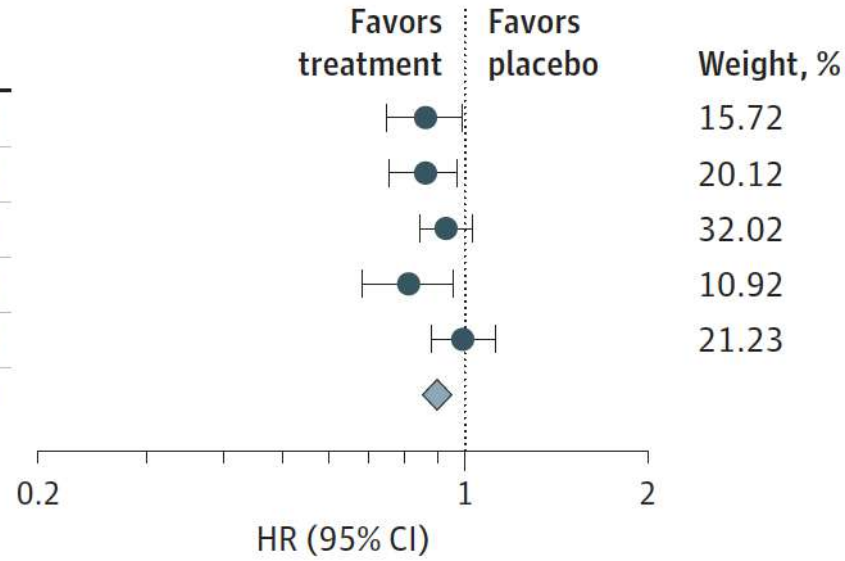
The integrity of clinical decision making

- Primary prevention
- In type 2 diabetes, with or without atherosclerotic CV disease (EMPA-REG OUTCOME, CANVAS, VERITIS-CV)
- In chronic kidney disease, with or
- without diabetes (CREDENCE,
- DAPA-CKD, SCORED)
- Secundary prevention
- HFrEF (EMPEROR-reduced, DAPA-HF)
- HFpEF (EMPEROR-preserved)

SGLT2 inhibitors: impact on major cardiovascular outcomes in type 2 diabetes

Meta-analysis, 4 different SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin), n=46,969 pts with T2DM (66% with CVD)

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 5.22; *df* = 4; *P* = .27; I^2 = 23.4%)					0.90 (0.85-0.95)



Reduction in the risk of MACE without evidence of a considerable heterogeneity between the trials

McGuire DK, Shih WJ, Cosentino F et al. JAMA Cardiol. 2021;6(2):148-158.

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Recommendations for the management of patients with HFrEF and T2DM

Pharmacological treatment indicated in patients with HFrEF (NYHA class II–IV) and diabetes		
SGLT2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended in all patients with HFrEF and T2DM to reduce the risk of HF hospitalization and CV death.	I	A
An intensive strategy of early initiation of evidence-based treatment (SGLT2 inhibitors, ARNI/ACE-Is, beta-blockers, and MRAs), with rapid up-titration to trial-defined target doses starting before discharge and with frequent follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce re-admissions or mortality.	I	B

Other treatments indicated in selected patients with HFrEF (NYHA class II–IV) and diabetes		
Hydralazine and isosorbide dinitrate should be considered in self-identified Black patients with diabetes and LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA class III–IV despite treatment with an ACE-I (or ARNI), a beta-blocker, and an MRA, to reduce the risk of HF hospitalization and death.	IIa	B
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with sacubitril/valsartan or an ACE-I, a beta-blocker, and an MRA, to reduce the risk of hospitalization.	IIb	B

Marx N et al. European Heart Journal (2023) 00, 1–98

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Recommendations for the management of diabetic patients with HFmrEF and HFpEF

Heart failure treatments in patients with diabetes and LVEF >40%		
Empagliflozin or dapagliflozin are recommended in patients with T2DM and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death.	I	A

Marx N et al. European Heart Journal (2023) 00, 1–98

Dapagliflozin and risk of new-onset diabetes

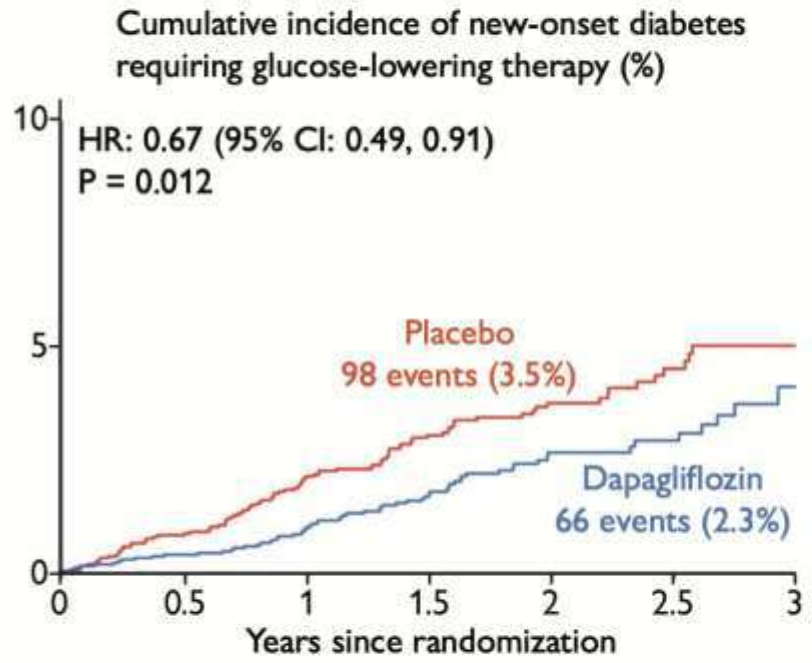
SGLT2i and new-onset diabetes in patients with cardiovascular or kidney disease

HF trials

33%

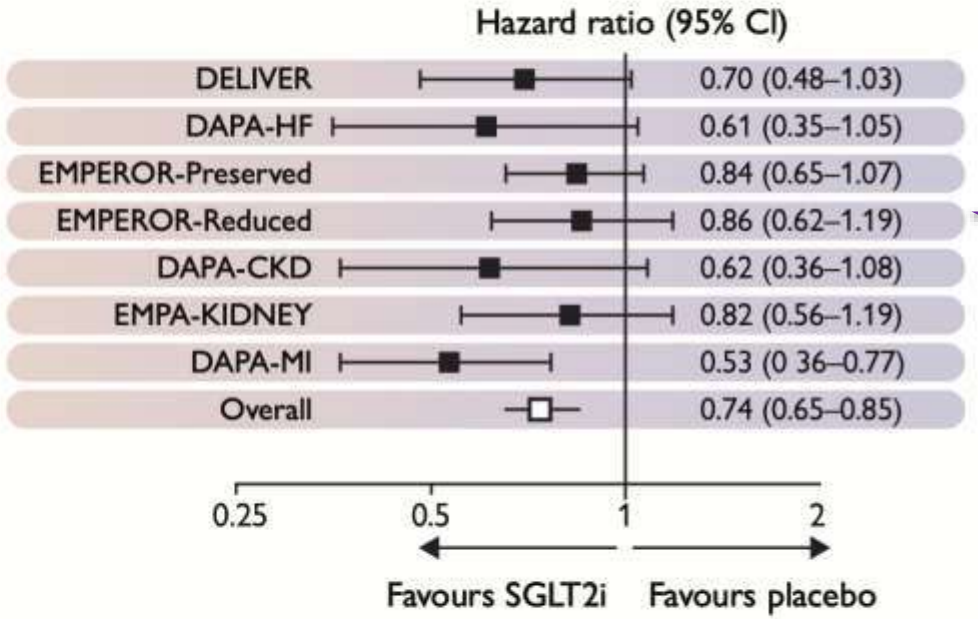
Lower risk of new-onset T2DM

Participant-level pooled analysis of DAPA-HF and DELIVER (n = 5623)



33% Reduction in the rate of new-onset diabetes requiring new glucose-lowering therapy with dapagliflozin vs placebo, with consistent findings across the LVEF spectrum and key subgroups

Fixed-effects meta-analysis of 7 cardiovascular and kidney trials (n = 17 855)



26% Reduction in the rate of new-onset diabetes with SGLT2i vs placebo (test for overall treatment effect: P < 0.001), without heterogeneity in treatment effects across trials

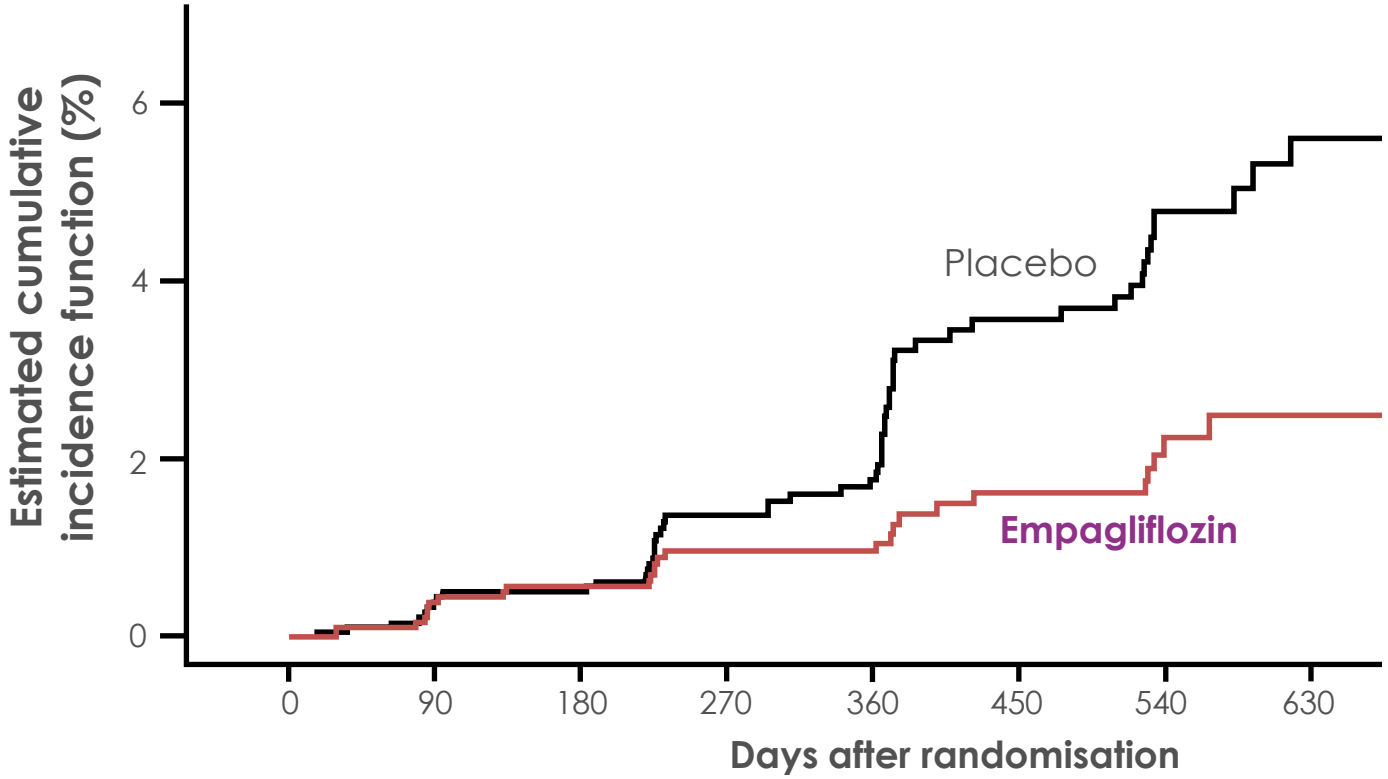
All CV trials

26%

Lower risk of new-onset T2DM

Ostrominski J et al. European Heart Journal (2024) 00, 1–11

Composite renal endpoint (end-stage kidney disease/sustained profound decrease in eGFR)



Patients at risk								
Placebo	1867	1592	1501	1136	1058	681	357	259
Empagliflozin	1863	1599	1532	1155	1062	687	391	276

RRR 50%

ARR 1.5%

HR 0.50
(95% CI 0.32, 0.77)

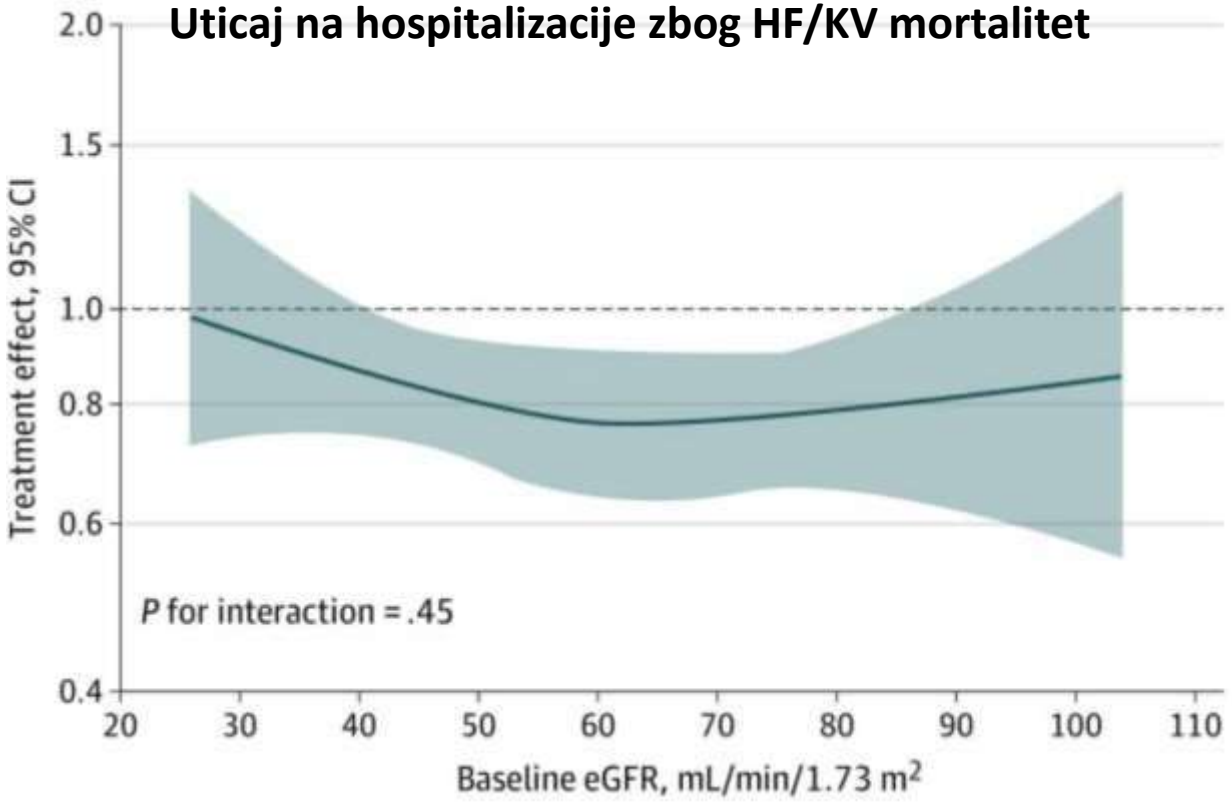
Empagliflozin:
30 patients with event
Rate: 1.6/100 patient-years
Placebo:
58 patients with event
Rate: 3.1/100 patient-years

Composite renal endpoint is defined as chronic dialysis, renal transplant, sustained reduction of ≥40% eGFR or sustained eGFR <15 ml/min/1.73 m^2 for patients with eGFR ≥30 ml/min/1.73 m^2 at baseline (<10 ml/min/1.73 m^2 for patients with eGFR <30 ml/min/1.73 m^2 at baseline). Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. Cox regression model including covariates age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, and baseline LVEF. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR,

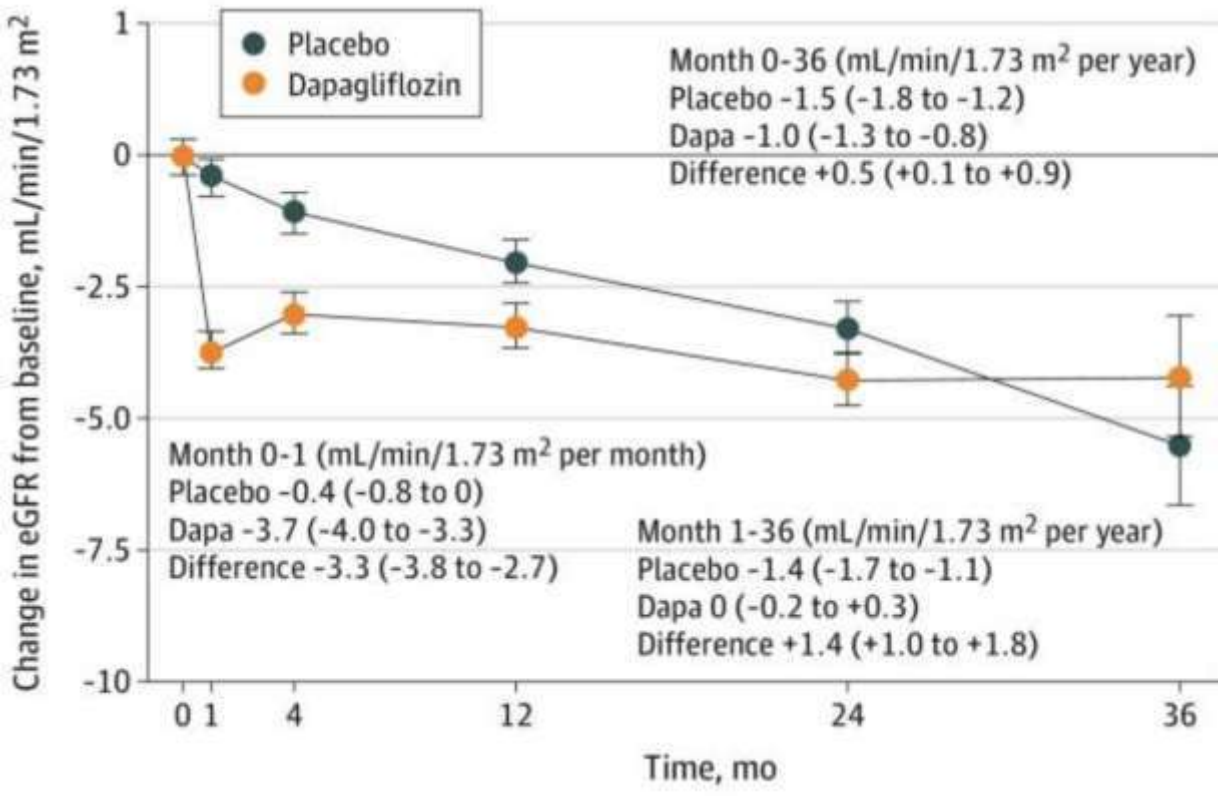
Dapagliflozin and renal function: DELIVER

1. **Therapeutic efficacy of dapagliflozin is preserved across a wide range of eGFR (25 to >100 mL/min/1,73 m$^{2)}$.**

Uticaj na hospitalizacije zbog HF/KV mortalitet



2. **Dapagliflozin is associated with slower decline in eGFR over time vs. placebo.**



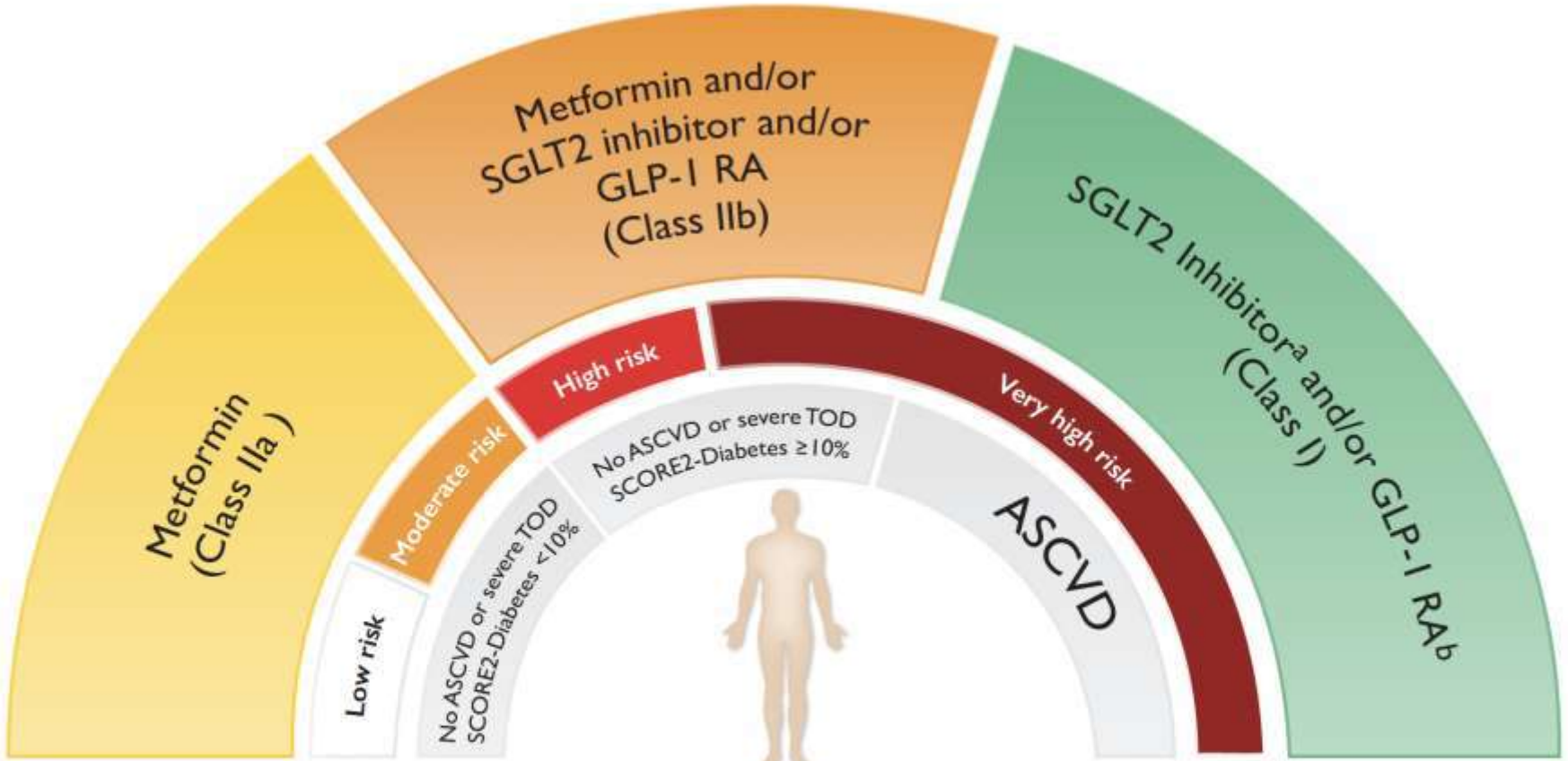
Mc Causland F et al. JAMA Cardiol. 2022 Nov 3;8(1):56–65

Treatment targets for the management of patients with diabetes

Risk factor	Target
BP	• Target SBP 130 mmHg for most adults, <130 mmHg if tolerated, but not <120 mmHg • Less-stringent targets, SBP 130 - 139 in older patients (aged >65 years)
Glycaemic control: HbA1c	• HbA1c target for most adults is <7.0% (<53 mmol/mol) • More-stringent HbA1c goals of <6.5% (48 mmol/mol) may be suggested on a personalized basis if this can be achieved without significant hypoglycaemia or other adverse effects of treatment • Less-stringent HbA1c goals of <8% (64 mmol/mol) or ≤9% (75 mmol/mol) may be adequate for elderly patients (see *section 6.2.1*)
Lipid profile: LDL-C	• In patients with DM at very high CV risk,[a] target LDL-C to <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50%. • In patients with DM at high risk,[a] target LDL-C to <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50%. • In patients with DM at moderate CV risk,[a] aim for an LDL-C target of <2.6 mmol/L (<100 mg/dL)
Platelet inhibition	In DM patients at high/very high CV risk
Smoking	Cessation obligatory
Physical activity	Moderate-to-vigorous, ≥150 min/week, combined aerobic and resistance training
Weight	Aim for weight stabilization in overweight or obese patients with DM, based on calorie balance, and weight reduction in subjects with IGT, to prevent the development of DM.
Dietary habits	Reduction of caloric intake is recommended in obese patients with T2DM to lower body weight; there is no ideal percentage of calories from carbohydrate, protein, and fat for all people with DM.

European Heart Journal (2023) 41, 255-323

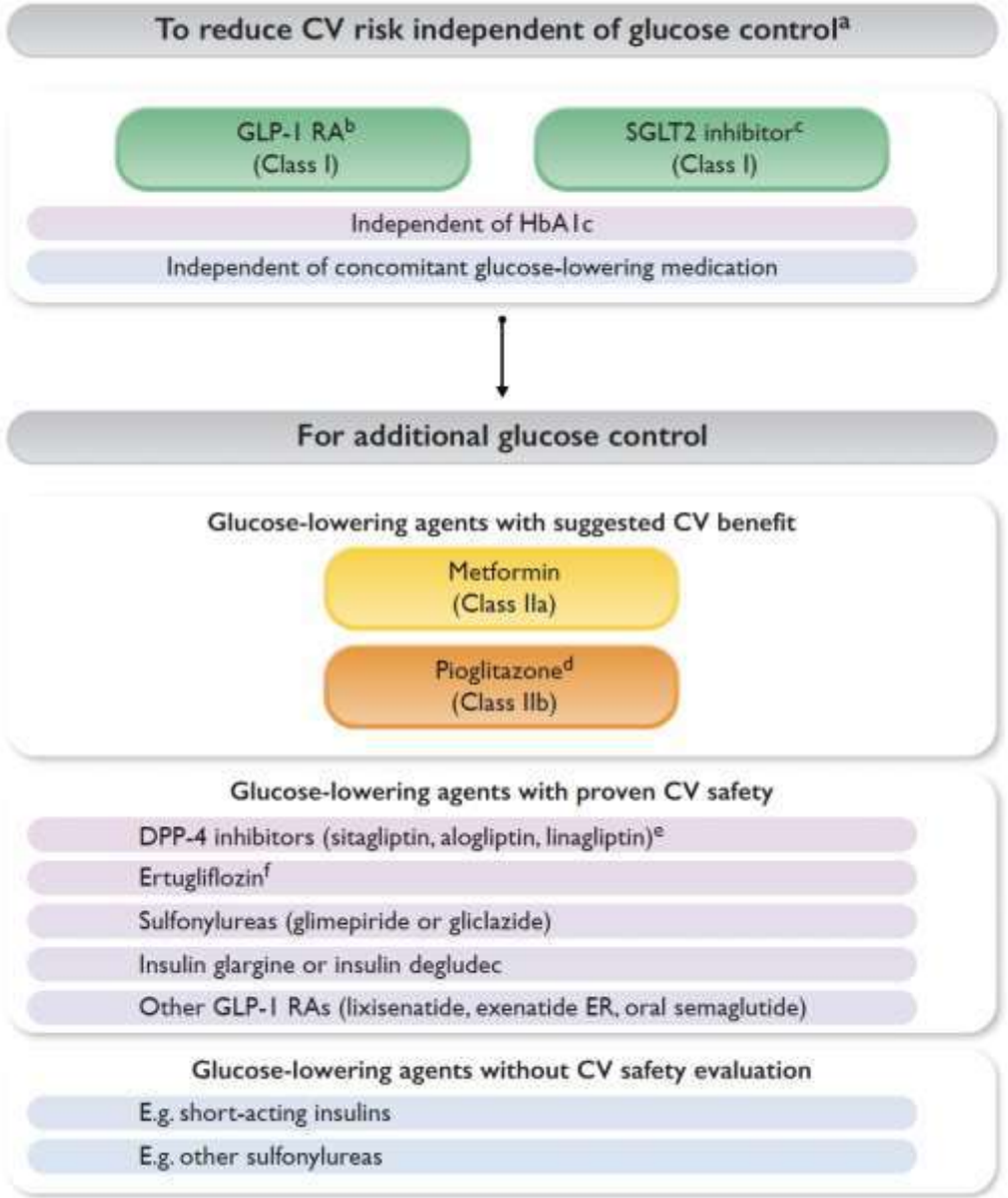
Reduction of CV risk in type 2 diabetes: Glucose-lowering treatment



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

Marx N et al. European Heart Journal 2023, 44: 4043–4140

Reduction of CV risk in type 2 diabetes and atherosclerotic disease: Glucose lowering treatment



Marx N et al. European Heart Journal 2023, 44: 4043–4140

Recommendations for glucose-lowering treatment for patients with diabetes

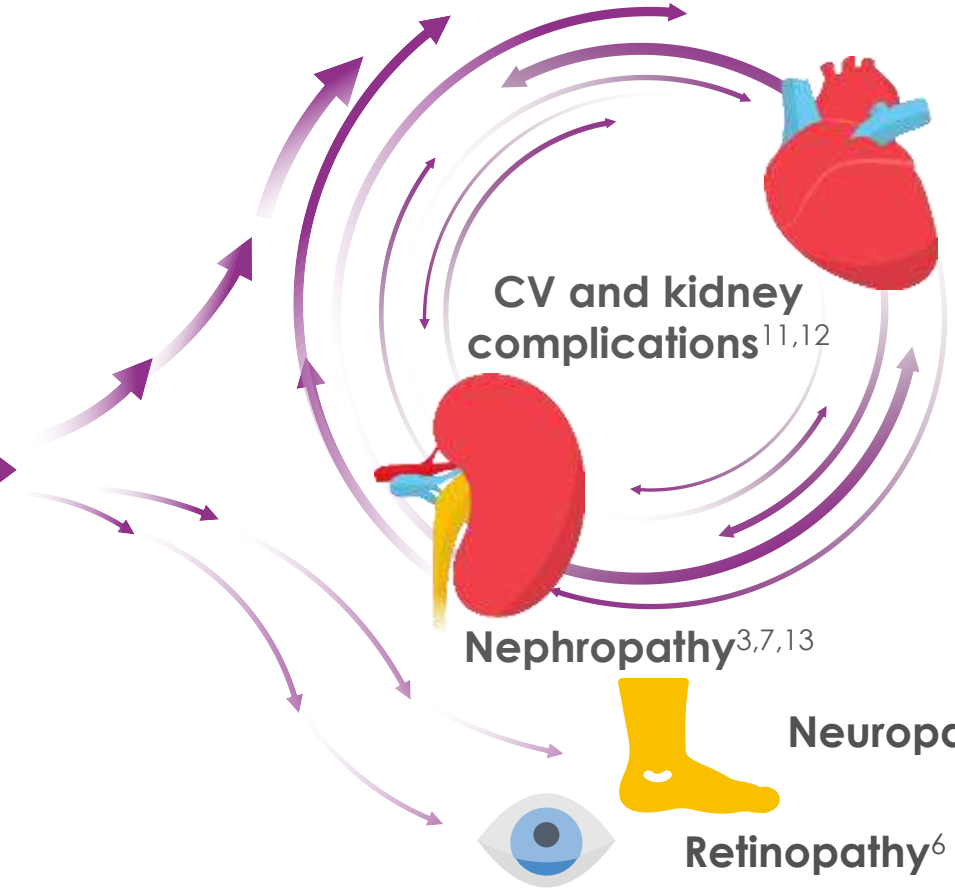
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B
GLP1-RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[176,299–300,302–303]	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce the risk of death.[176]	I	B
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.[146,149]	IIa	C
Insulin		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities.[260–262]	IIa	C
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF.	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF.[291]	III	B

European Heart Journal (2023) 41, 255-323

Cardiovascular complications in T2DM can be prevented and treated

- Obesity
- Hypertension
- Dyslipidaemia
- Smoking[1–3]

- β-cell-dysfunction
- Insulin resistance
- Hyperglycaemia[4,5,9]



Leading hypotheses shown; additional factors may contribute to progression of complications. CV, cardiovascular; T2D, type 2 diabetes; MI, myocardial infarction

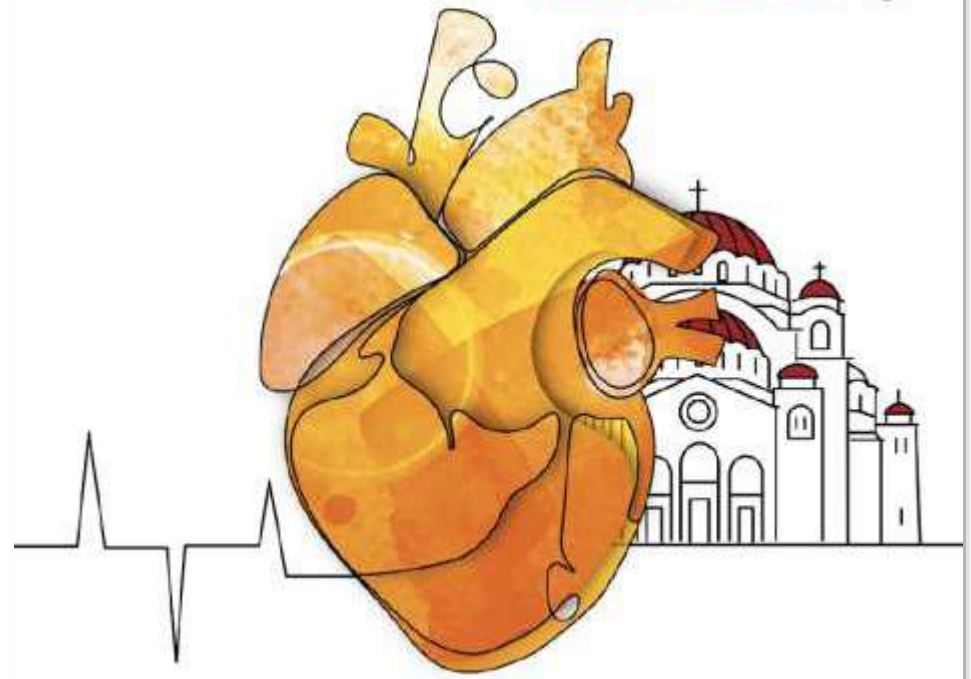
1. Leon BM & Maddox TM. *World J Diabetes* 2015;6:1246; 2. Sposito AC *et al. Cardiovasc Diabetol* 2018;17:157; 3. Cade WT. *Phys Ther* 2008;88:1322; 4. Marwick TH *et al. J Am Coll Cardiol* 2018;71:339; 5. DeFronzo RA *et al. Diabetes* 2009;58:773; 6. Fowler MJ. *Clinical Diabetes* 2011;29:116; 7. Song MK *et al. J Diabetes Res* 2014;2014:e313718; 8. Bugger H & Abel ED. *Diabetologia* 2014;57:660; 9. Galicia-Garcia U *et al.* Int *J Mol Sci* 2020;21:6275; 10. Hayden MR *et al. Cardiorenal Med* 2013;3:265; 11. Ronco C *et al. J Am Coll Cardiol* 2008;52:1527; 12. McCullough PA *et al. Contrib Nephrol* 2013;182:82; 13. Chen Y *et al. Kidney Dis* 2020;6:225

Manuel Jimenez Prieto: Martin Charcot visits a patient, 1897

Heart Failure 2012

HFA
Heart Failure
Association

Heart Failure & World Congress on Acute Heart Failure 2025



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