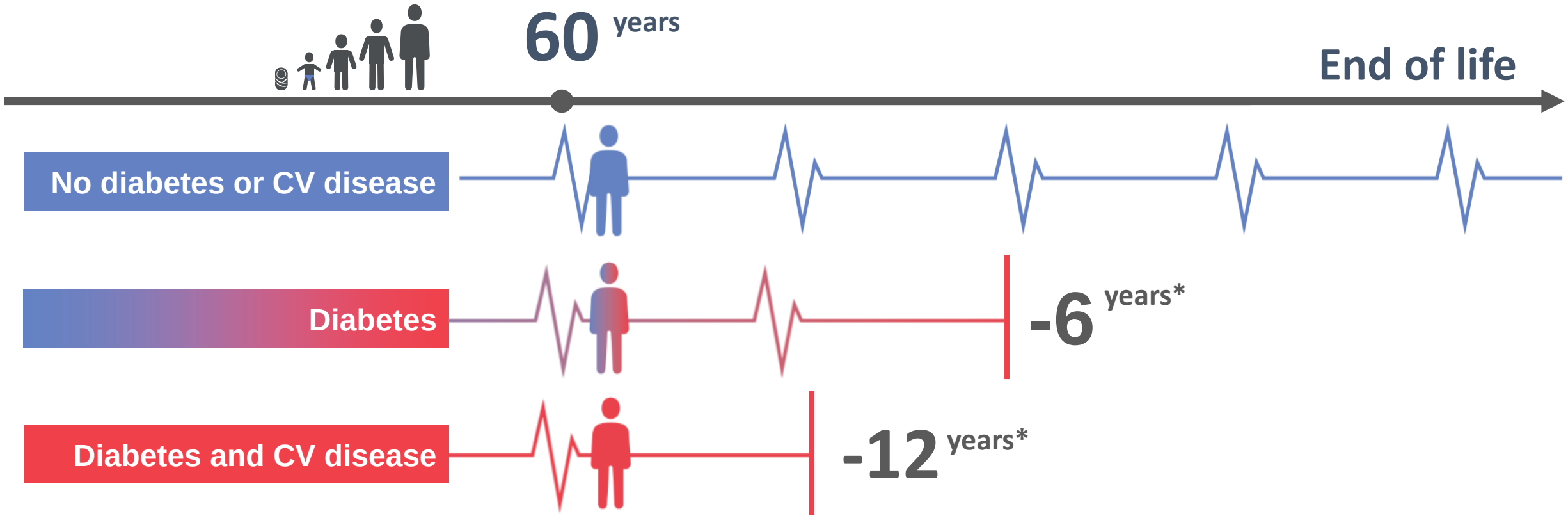
Life expectancy is reduced by ~12 years in patients with diabetes and CV disease [1]

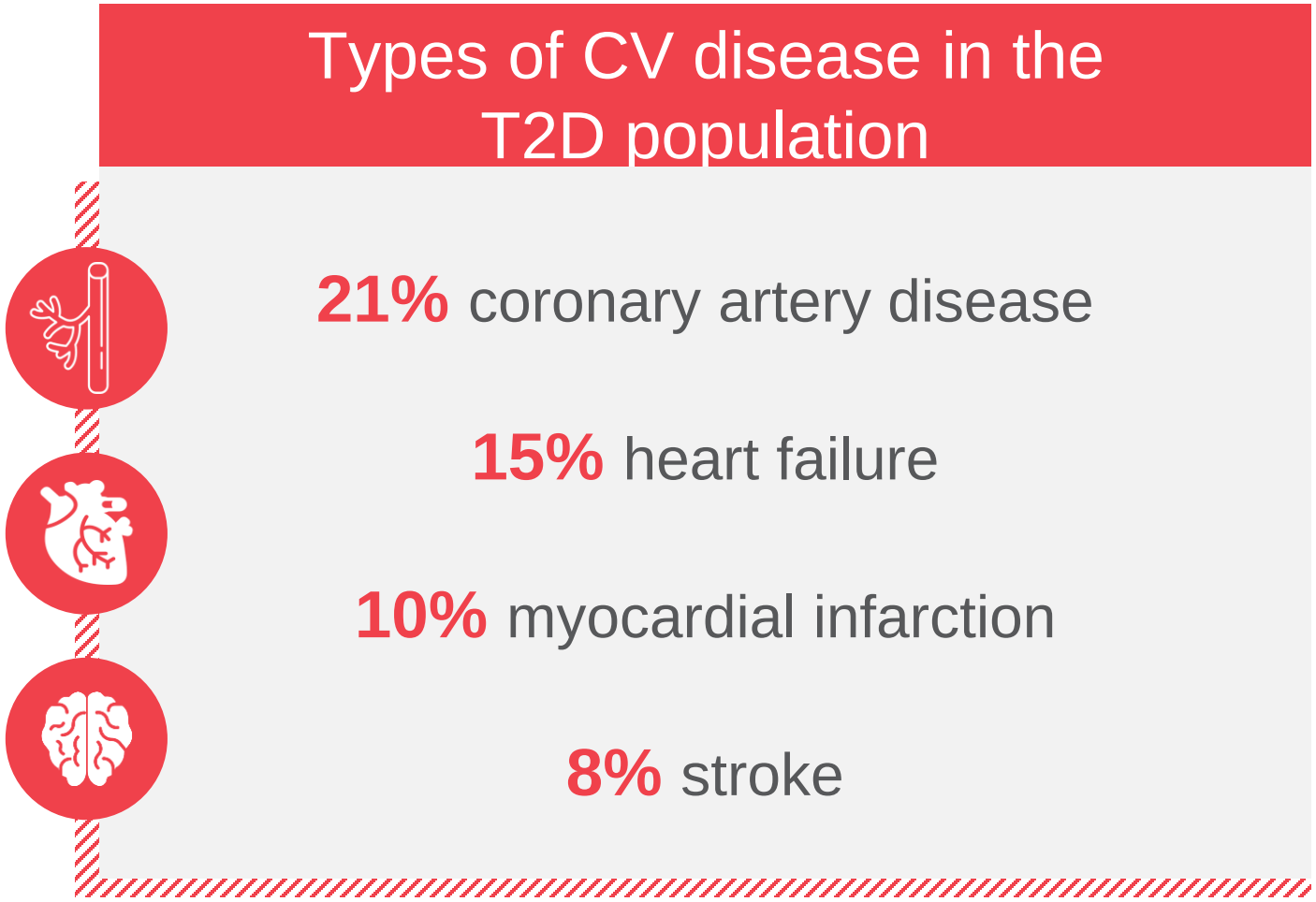
A 60-year-old patient with diabetes and CV disease dies, on average, 12 years earlier than a person without diabetes or CV disease



In this case, CV disease is represented by MI or stroke
*Average for men and women
CV, cardiovascular, MI, myocardial infarction

1 The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52

CV disease can manifest as atherosclerotic events, arterial disease or heart failure [1]



Analysis of 57 studies with 4,549,481 patients with T2D
CV, cardiovascular; T2D, type 2 diabetes
1-Einarson TR *et al. Cardiovasc Diabetol* 2018;17:83

Guidelines Recommendations

Diabetes guidelines and societies now recommend a cardioprotective glucose-lowering agent for patients with T2D and CV disease[1,2,3]

American Diabetes Association®

*"…therapy should […] incorporate an **agent proven to reduce major adverse CV events and CV mortality** (currently empagliflozin and liraglutide)..."* [1]

DIABETES CANADA

*"…an antihyperglycemic agent with **demonstrated CV outcome benefit** should be added to **reduce the risk of major CV events**."* [2]

American Diabetes Association®

EASD

*"…Among patients with T2D who have **established ASCVD**, **SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended** as part of glycaemic management."* [3]

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes

1. American Diabetes Association. *Diabetes Care* 2018;41:S1; 2. Diabetes Canada. *Can J Diabetes* 2018;42:S162; 3. Davies MJ *et al. Diabetes Care* 2018;41:2669

abidi DIABETES

Cardiology guidelines[1] now recommend a cardioprotective glucose-lowering agent for patients with T2D and CV disease[1,2,3]

EUROPEAN SOCIETY OF CARDIOLOGY®

*"In patients with **T2D and CV disease**, the use of an **SGLT2 inhibitor** should be considered early in the course of the disease to **reduce CV and total mortality.**"* [1]

AMERICAN COLLEGE *of* CARDIOLOGY

*"CV specialists should be aware of the **evidence supporting the use of novel therapies, SGLT2 inhibitors and GLP-1 RAs**, to reduce risk in patients with T2D and ASCVD"* [2]

HEART FAILURE ASSOCIATION OF THE ESC

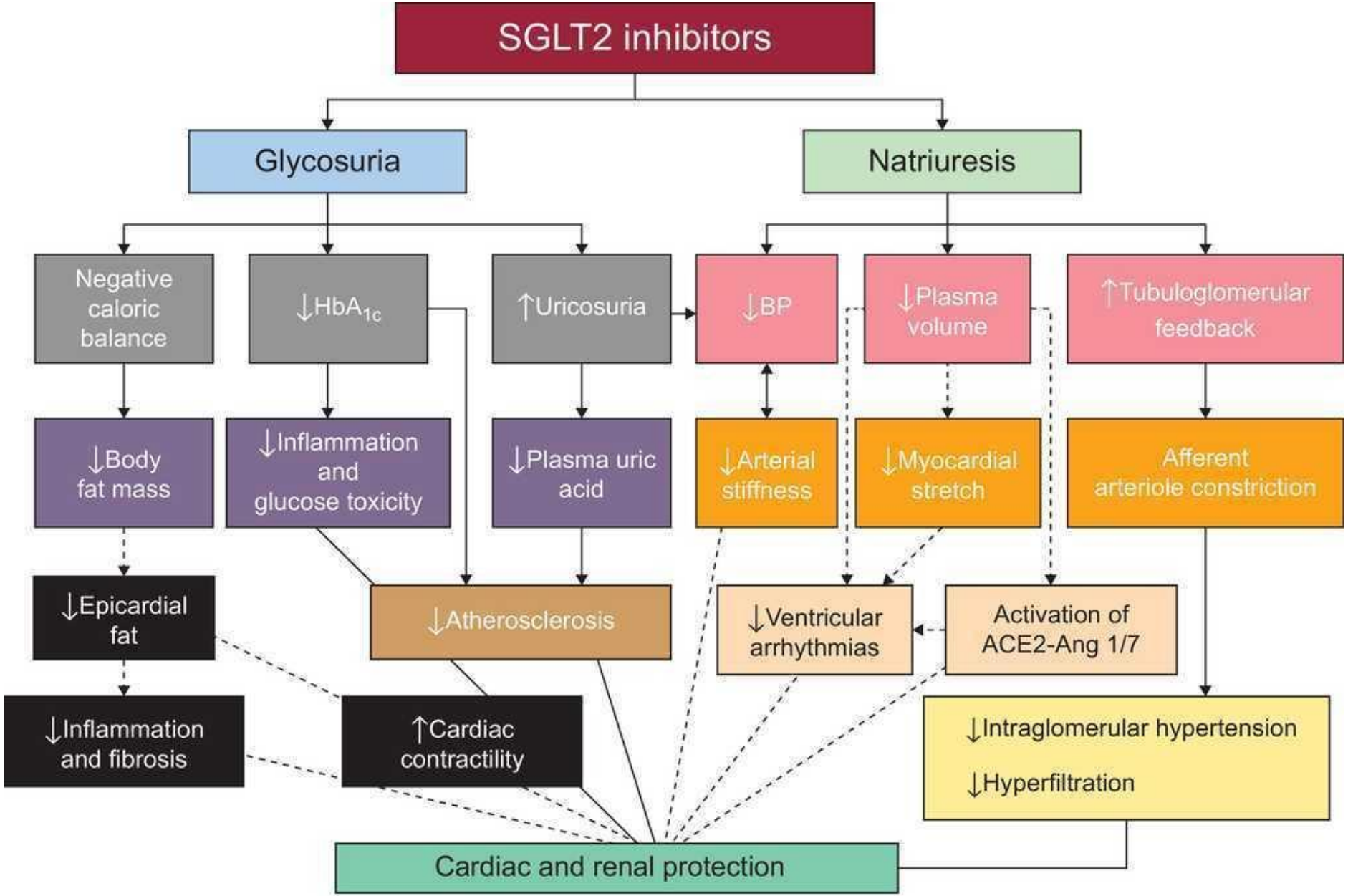
EUROPEAN SOCIETY OF CARDIOLOGY®

*"**Empagliflozin** should be considered in patients with T2D in order to **prevent or delay the onset of HF and prolong life.**"* [3]

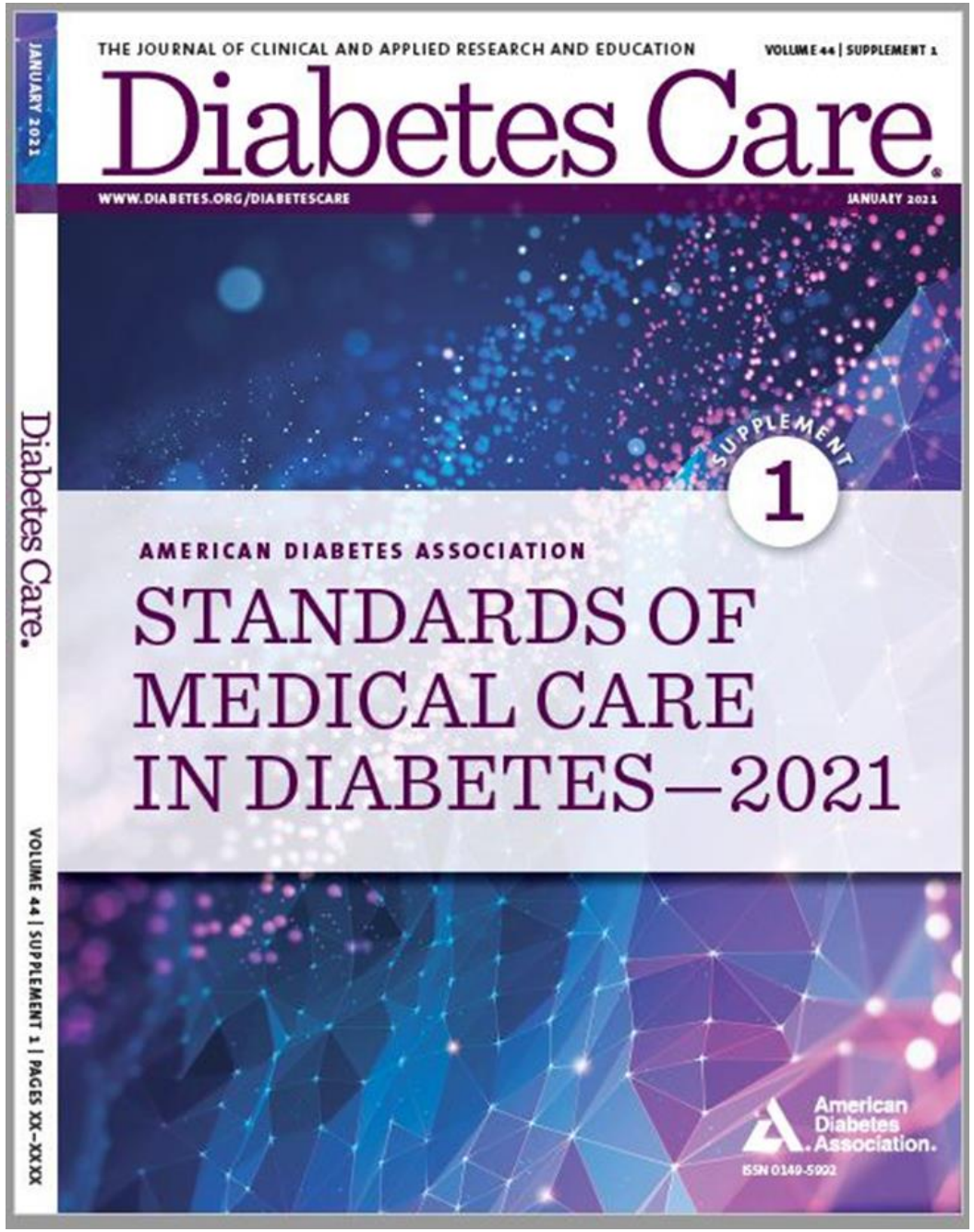
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes

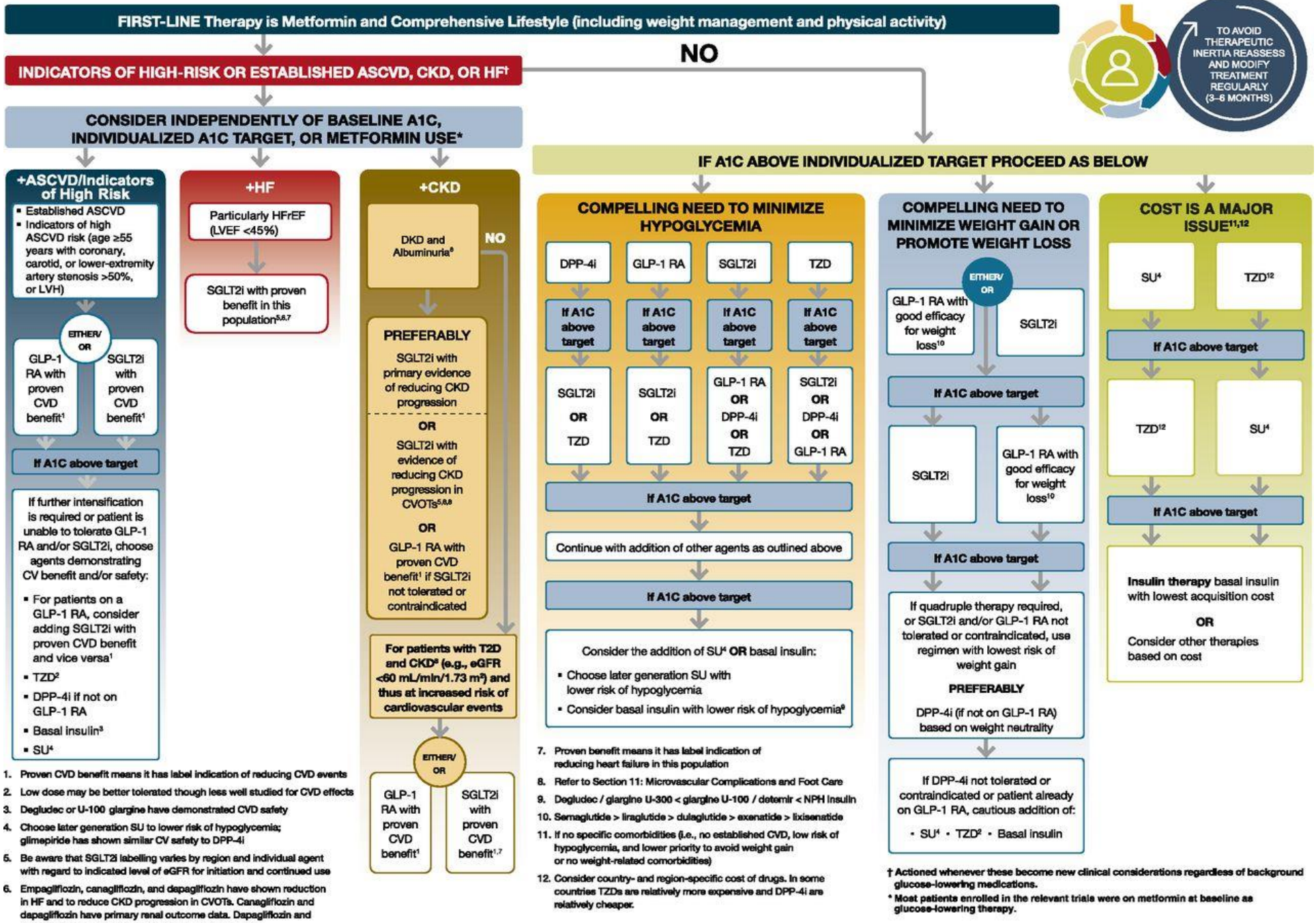
1. Piepoli MF *et al. Eur Heart J* 2016;37:2315; 2. Das SR *et al. J Am Coll Cardiol* 2018;72:3200; 3. Ponikowski P *et al. Eur Heart J* 2016;37:2129

abidi DIABETES



Rev Esp Cardiol. 2016;69:1088–97

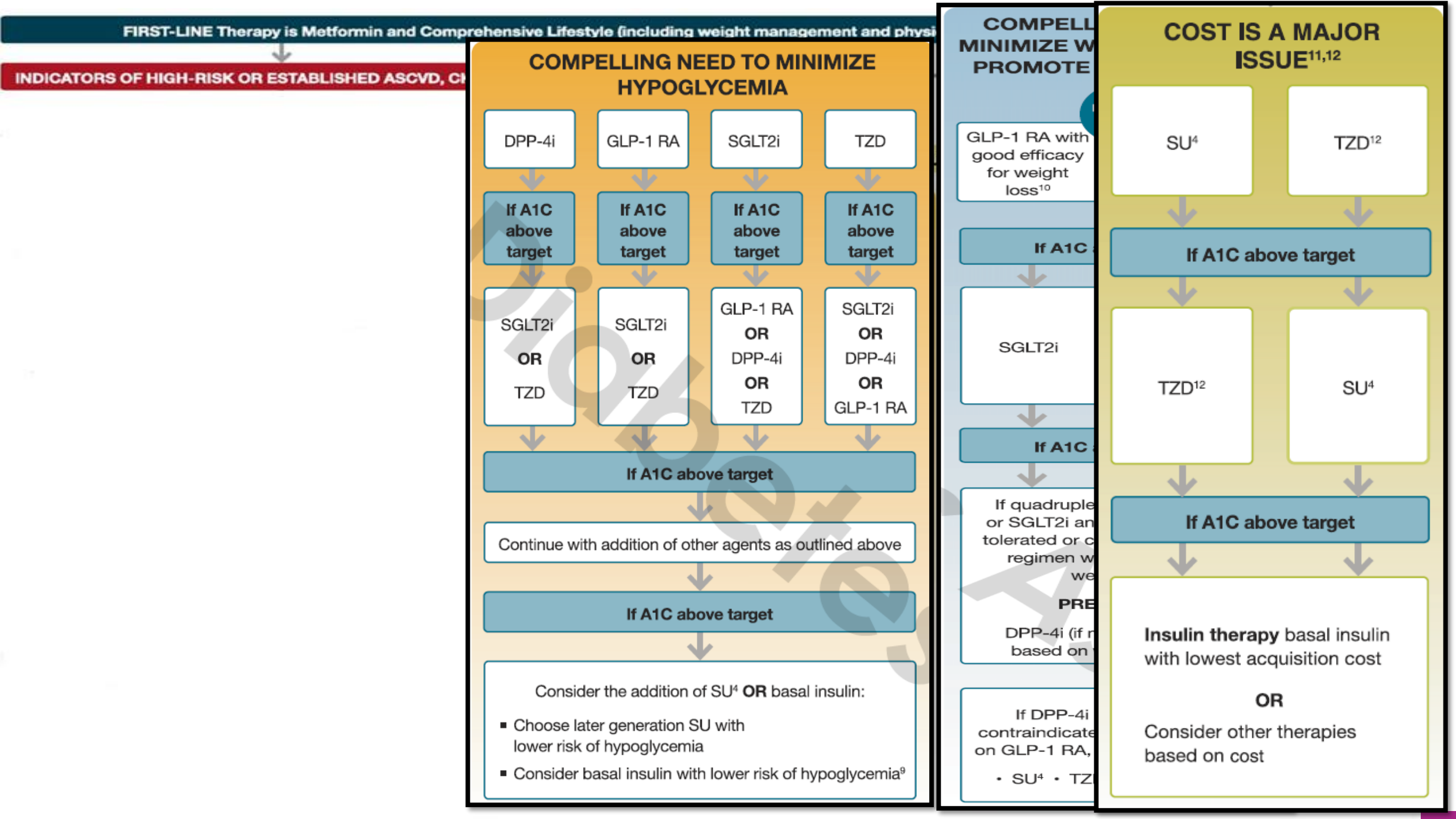

JANUARY 2021
THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION
VOLUME 44 | SUPPLEMENT 1
Diabetes Care
WWW.DIABETES.ORG/DIABETESCARE
JANUARY 2021
SUPPLEMENT
1
AMERICAN DIABETES ASSOCIATION
STANDARDS OF MEDICAL CARE IN DIABETES—2021
Diabetes Care
VOLUME 44 | SUPPLEMENT 1 | PAGES XX–XXXX
American Diabetes Association.
ISSN 0149-5992



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Diabetes Care 2021; 44(Suppl. 1):S111-S124.


FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physi
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CI
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i
TZD
If A1C above target
If A1C above target
If A1C above target
If A1C above target
SGLT2i OR TZD
SGLT2i OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i OR DPP-4i OR GLP-1 RA
If A1C above target
Continue with addition of other agents as outlined above
If A1C above target
Consider the addition of SU[4] OR basal insulin:
Choose later generation SU with lower risk of hypoglycemia
Consider basal insulin with lower risk of hypoglycemia[9]
COMPELL
MINIMIZE W
PROMOTE
GLP-1 RA with good efficacy for weight loss[10]
If A1C
SGLT2i
If A1C
If quadruple
or SGLT2i an
tolerated or c
regimen w
we
PRE
DPP-4i (if r
based on
If DPP-4i
contraindicate
on GLP-1 RA,
• SU[4] • TZ
COST IS A MAJOR ISSUE[11,12]
SU[4]
TZD[12]
If A1C above target
TZD[12]
SU[4]
If A1C above target
Insulin therapy basal insulin with lowest acquisition cost
OR
Consider other therapies based on cost

ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

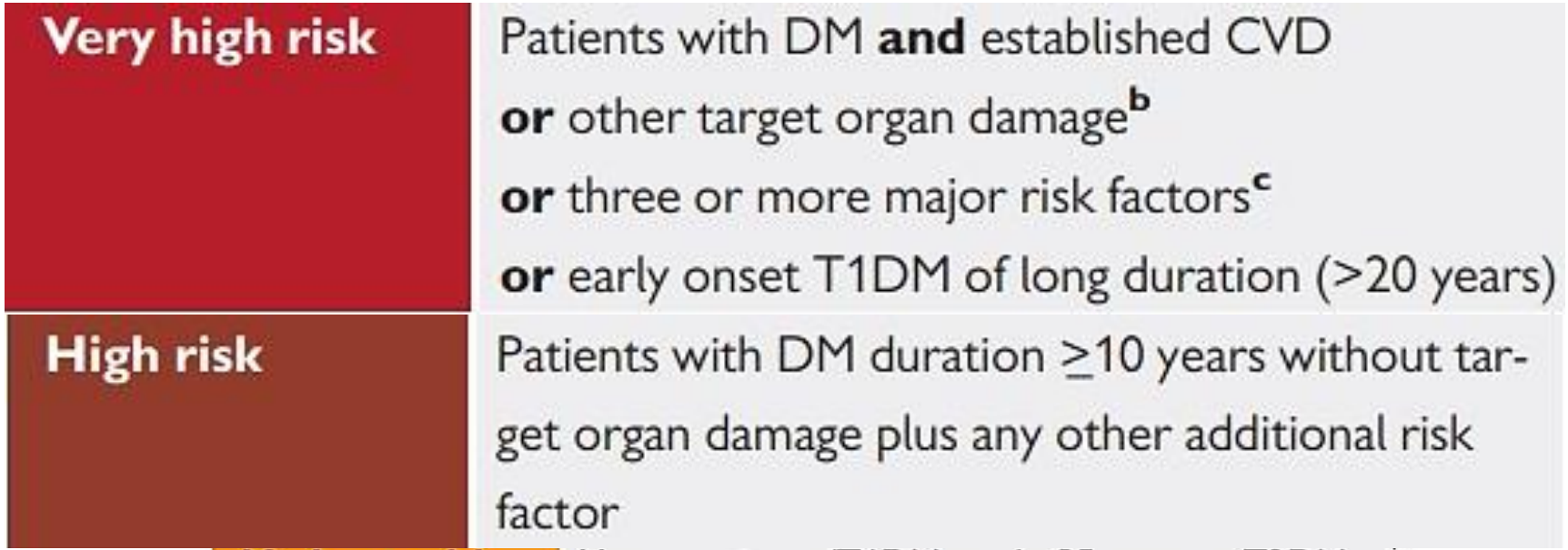
ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

1-European Heart Journal 2019; 00, 169

Cardiovascular risk categories in patients with diabetes[1]



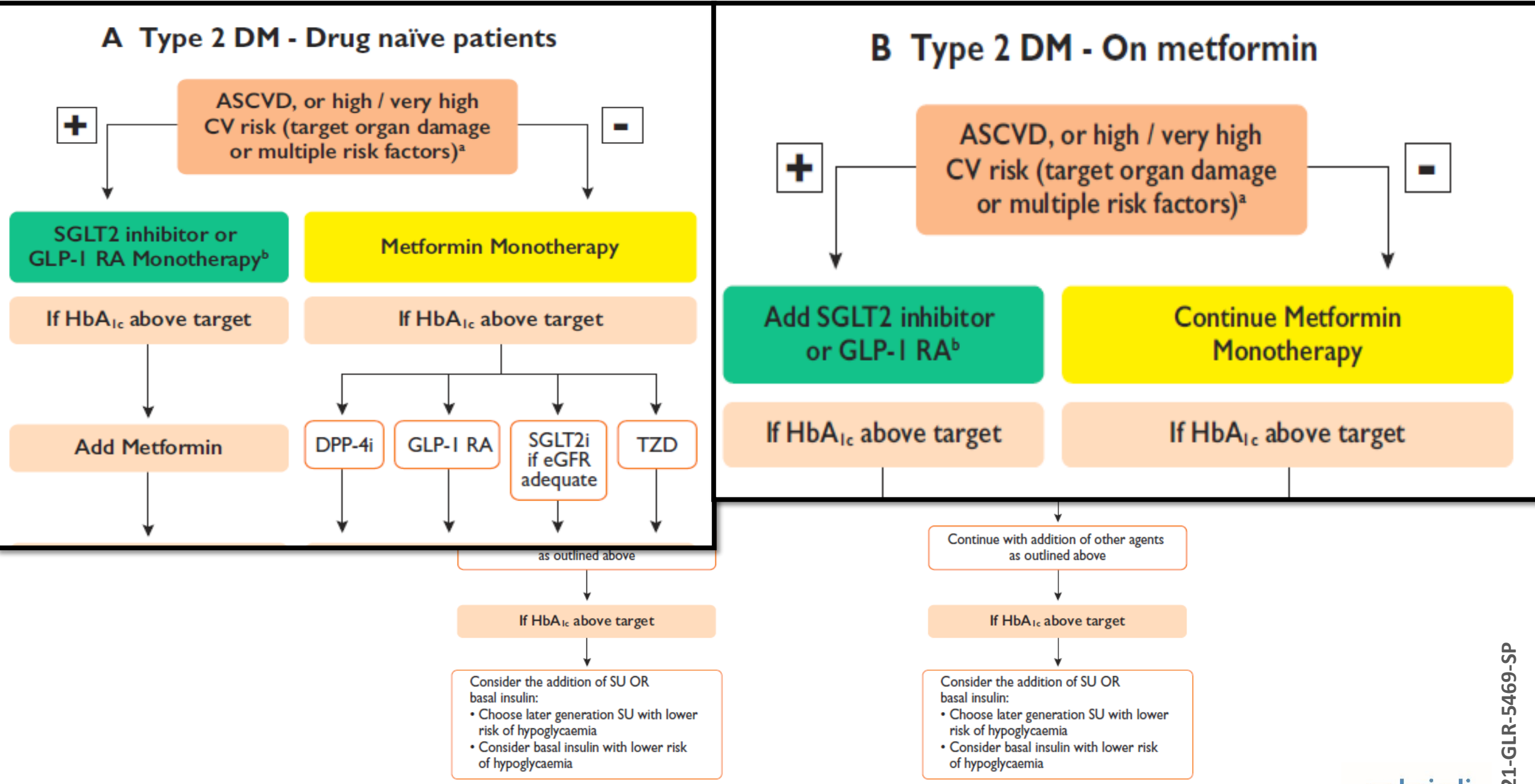
CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

[c]Age, hypertension, dyslipidemia, smoking, obesity.

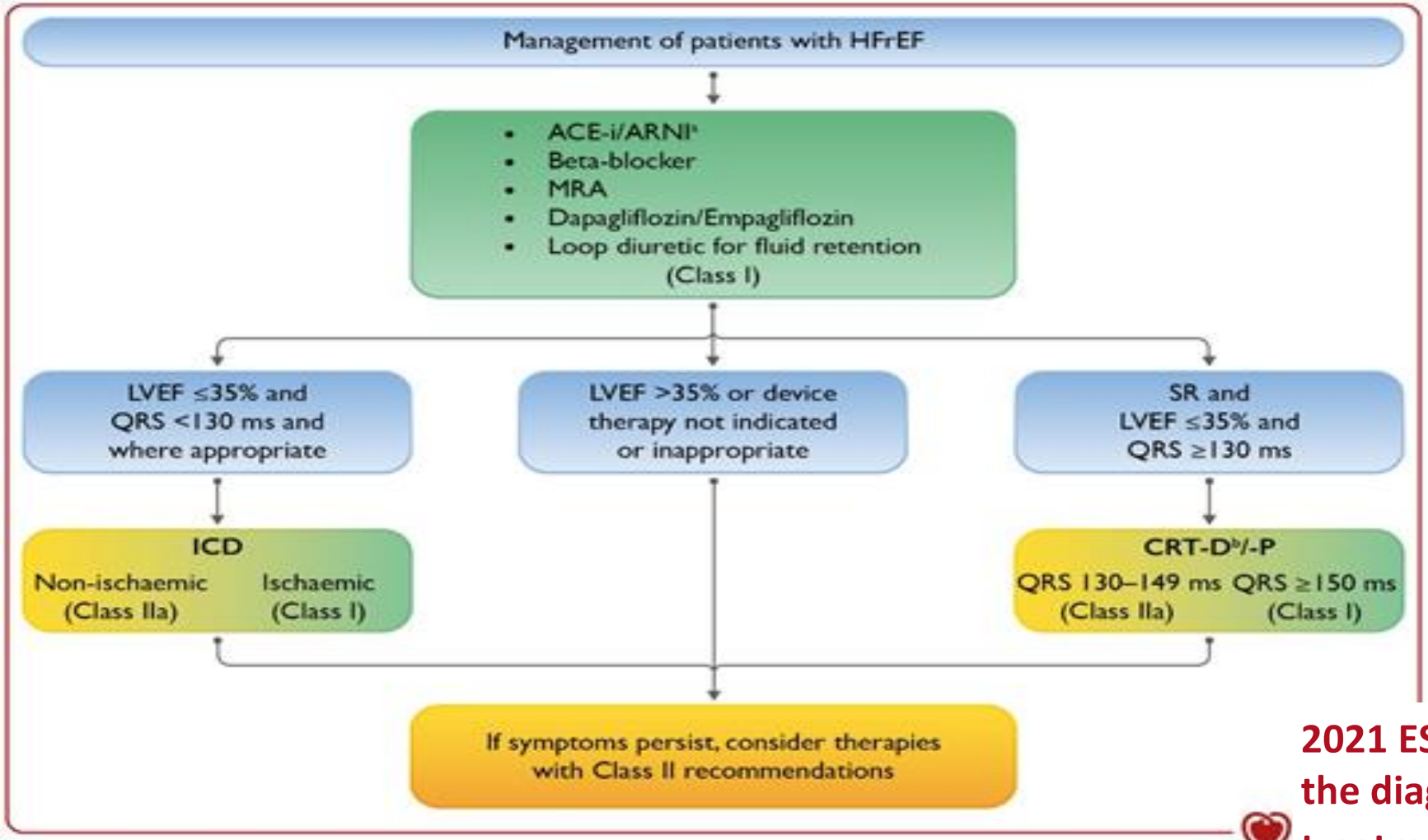
1-Piepoli, Massimo F., et al. "2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)." *European heart journal* 37.29 (2016): 2315-2381.



European Heart Journal 2019; 00, 169

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

Therapeutic algorithm in HF with reduced EF



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

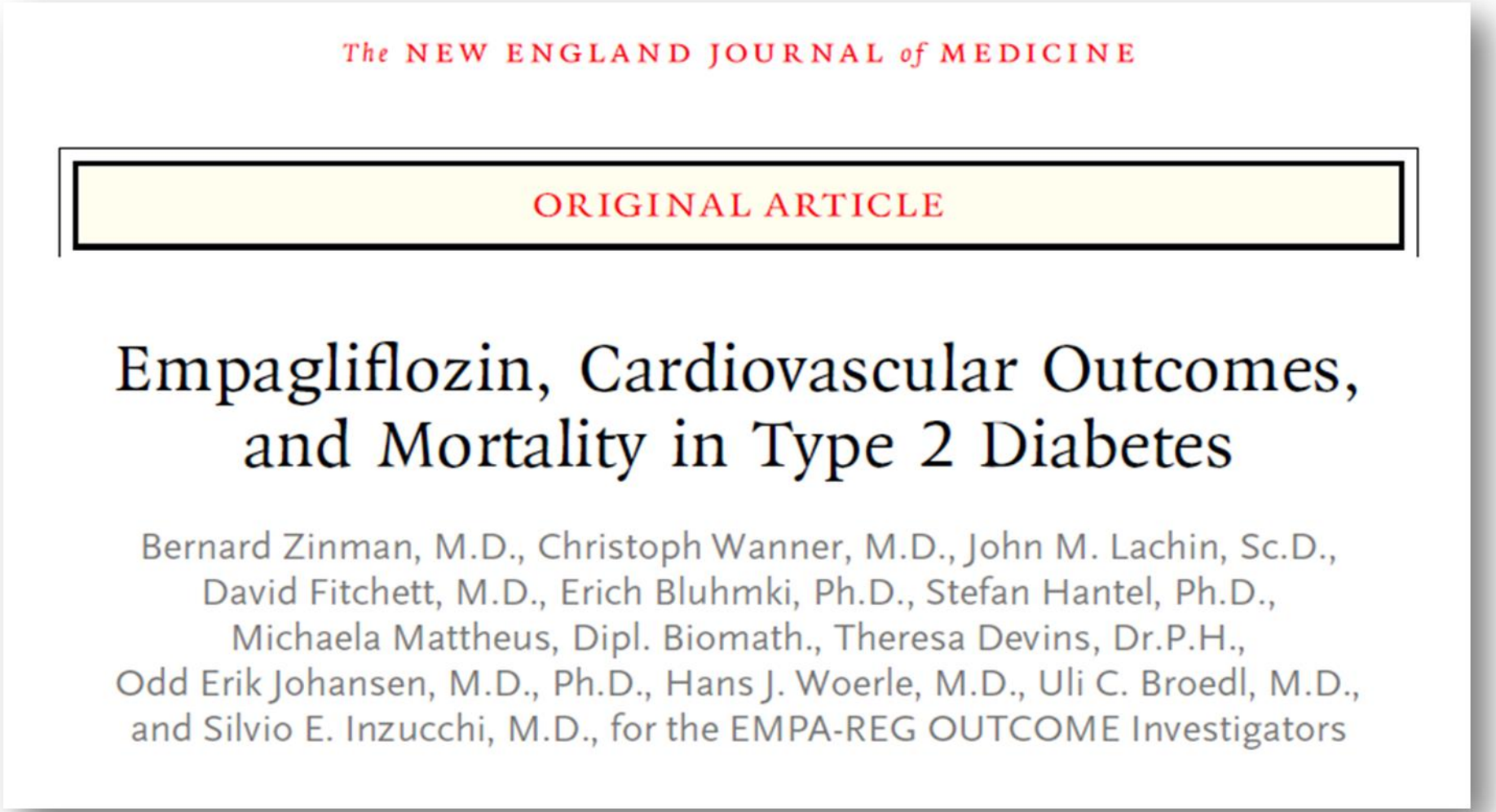
Pharmacological treatments indicated in patients with (NYHA class II - IV) heartfailure with reduced ejection fraction(LVEF≤ 40%)

Recommendations	Class	Level
An ACE-I 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 ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA= New York Heart Association.

1. escardio.org/guidelines

EMPA-REG OUTCOME



Objective[1]

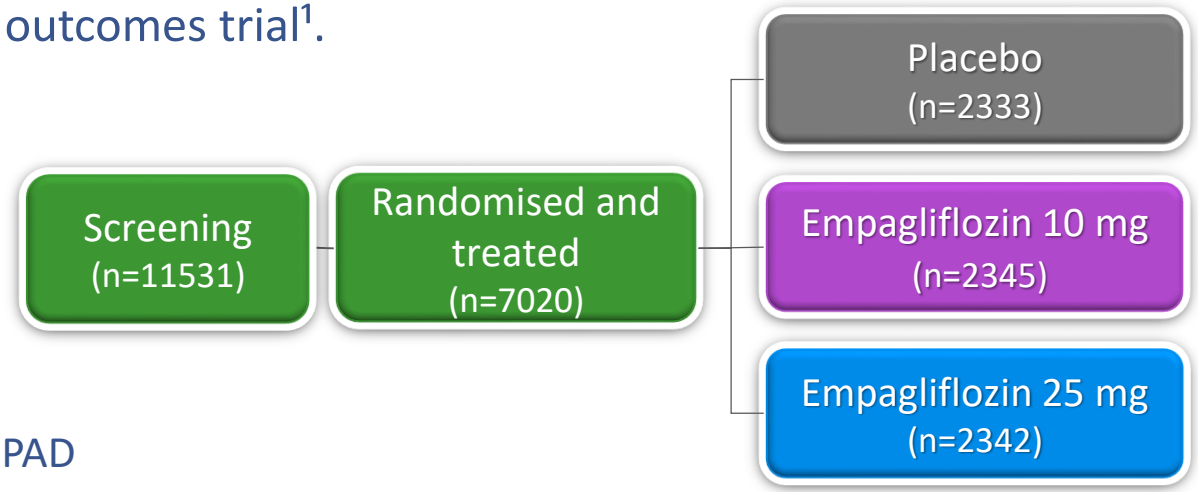
To examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV morbidity and mortality in patients with type 2 diabetes and high risk of CV events

1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Trial Design[1]

EMPA-REG OUTCOME

- **Design**
  - Randomized, double-blind, placebo-controlled CV outcomes trial[1].
- **Key inclusion criteria**
  - Adults with T_2DM
  - BMI ≤45 *kg/m2*
  - HbA_{1c} 7–10%*
  - Established cardiovascular disease
    - Prior MI, CAD, stroke, unstable angina or occlusive PAD
- **Key exclusion criteria**
  - eGFR <30 *mL/min/1.73m²* (MDRD)

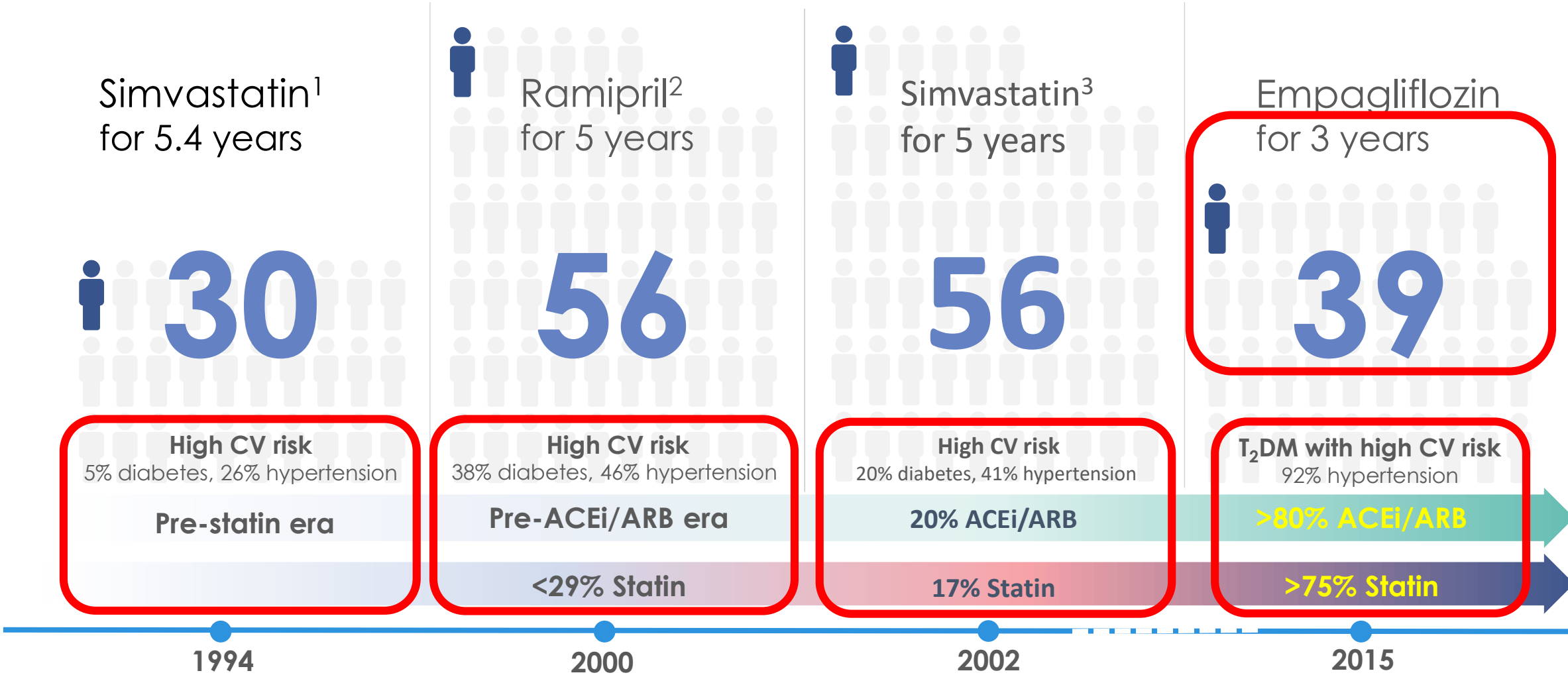


✓ The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event.

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease
*No glucose-lowering therapy for ≥12 weeks prior to randomisation or no change in dose for ≥12 weeks prior to randomisation or, in the case of insulin, unchanged by >10% compared to the dose at randomisation

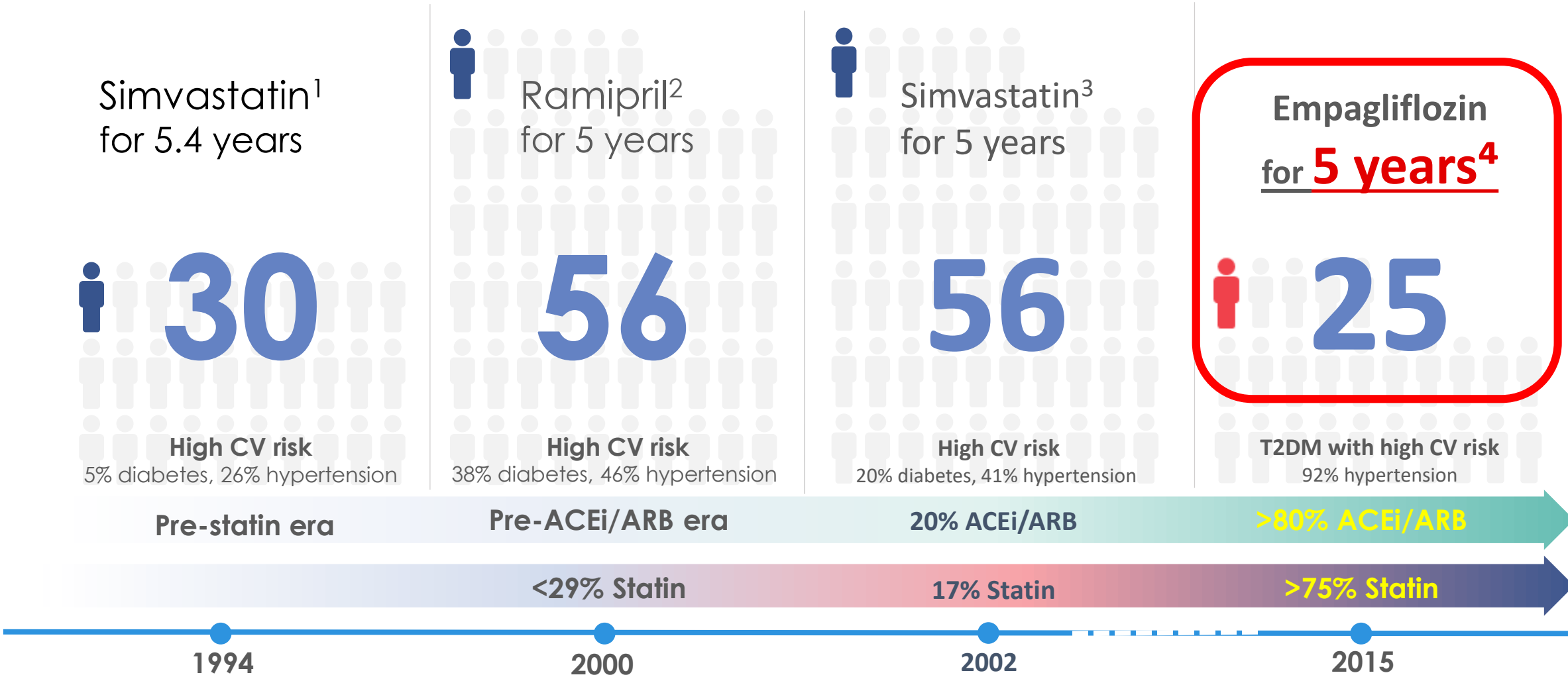
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

NNT to Prevent One Death Across Major Trials in Patients with High CV Risk



1. 4S investigators. Lancet 1994; 344: 1383-89. 2. HOPE investigators. N Engl J Med 2000;342:145-53, EBM2000;5:47; HOPE investigators. Evid Based Med 2000;5:47.
3. HPS group Lancet 2002; 360: 7–22.
4. Zinman B et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

NNT to Prevent One Death Across Major Trials in Patients with High CV Risk

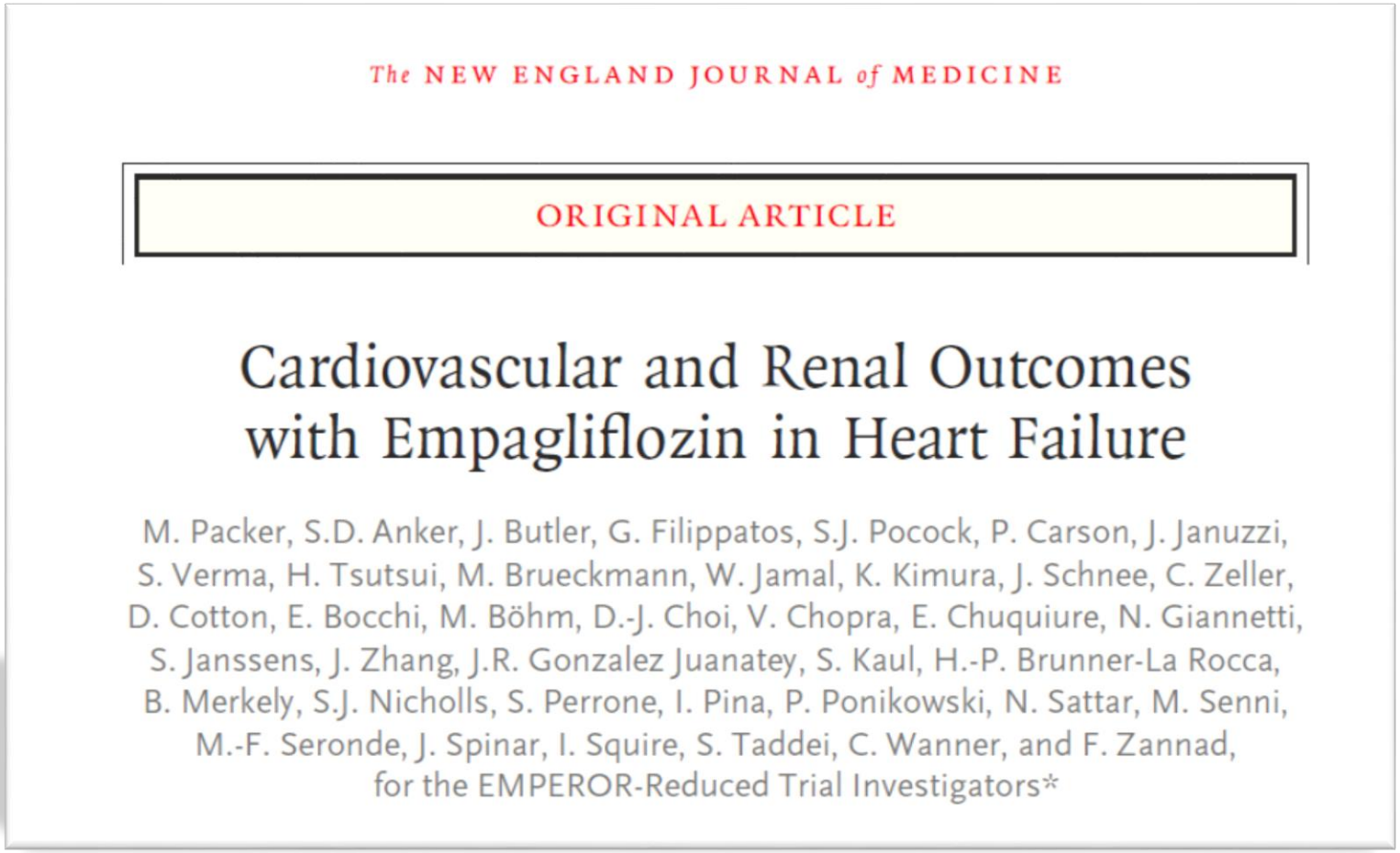


1. 4S investigators. Lancet 1994; 344: 1383-89.
2. HOPE investigators. N Engl J Med 2000;342:145-53, EBM2000;5:47; HOPE investigators. Evid Based Med 2000;5:47.
3. HPS group Lancet 2002; 360: 7–22.
4. Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

EMPEROR-Reduced Background

- ✓SGLT2 inhibitors may prevent the onset of HF in high-risk patients, but can these drugs ***treat*** **HF** in those with an established diagnosis?
- ✓If the benefits are unrelated to blood glucose, could these drugs exert favorable effects in patients who ***have HF*** but ***who do not have diabetes***?
- ✓Would such benefits be seen in those who are ***already receiving appropriate drug treatments for HF***?

1-N. Engl. J. Med 2020.8;383(15)1413-1424

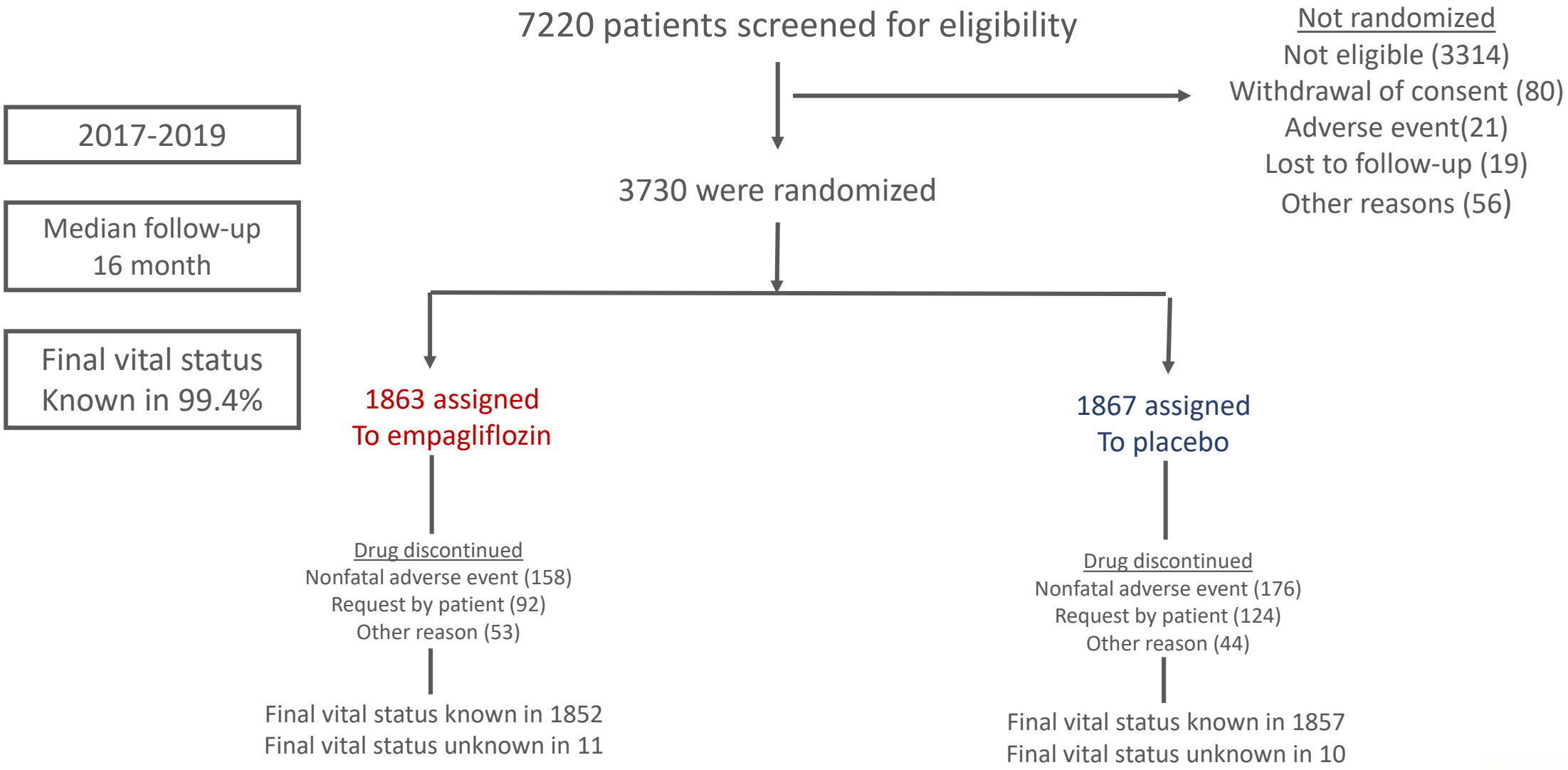


Objective[1]:

The **EMPEROR-Reduced trial** was designed to evaluate the effects of empagliflozin 10 mg once daily (as compared with placebo) in patients with heart failure and a **reduced** ejection fraction, with or without diabetes, who were already receiving all appropriate treatments for heart failure.

1-N Engl J Med. 2020 Oct 8;383(15)1413-1424

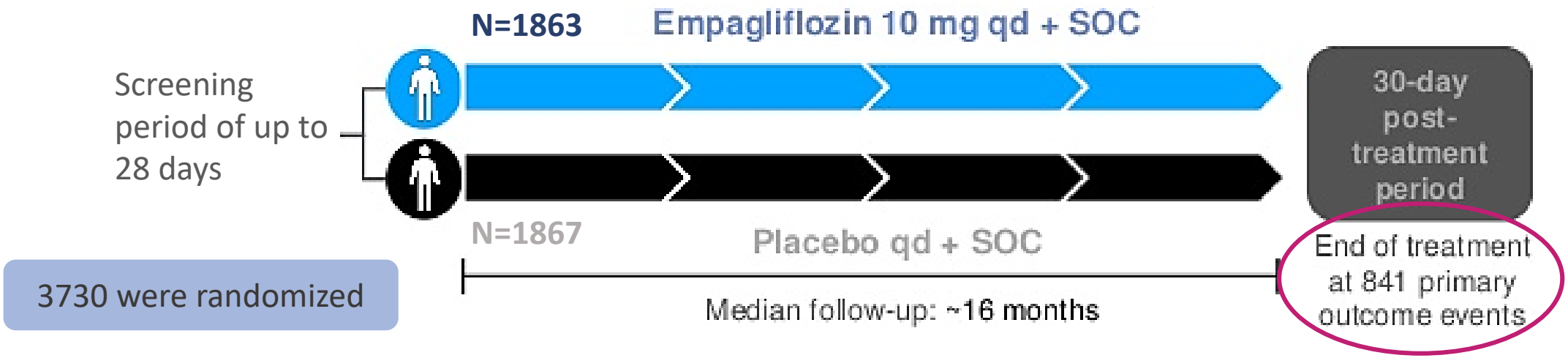
EMPEROR-Reduced: Patient Disposition[1]



1-N. Engl. J. Med 2020.8;383(15)1413-1424

Trial Design[1]

Patients must be receiving all appropriate treatments for HF



3730 were randomized

SOC; Standard Of Care

1-N. Engl. J. Med 2020.8;383(15)1413-1424

EMPEROR-Reduced trial specified only three endpoints

✓ Primary End point

Composite of cardiovascular death Or heart failure hospitalization

✓ First Secondary End point

Total (first and recurrent) heart failure hospitalization

✓ Second Secondary End point

Slope of decline in glomerular Filtration rate over time

1-N. Engl. J. Med 2020.8;383(15)1413-1424

Inclusion criteria

patients with **Chronic HF** with reduced ejection fraction

Key inclusion criteria:

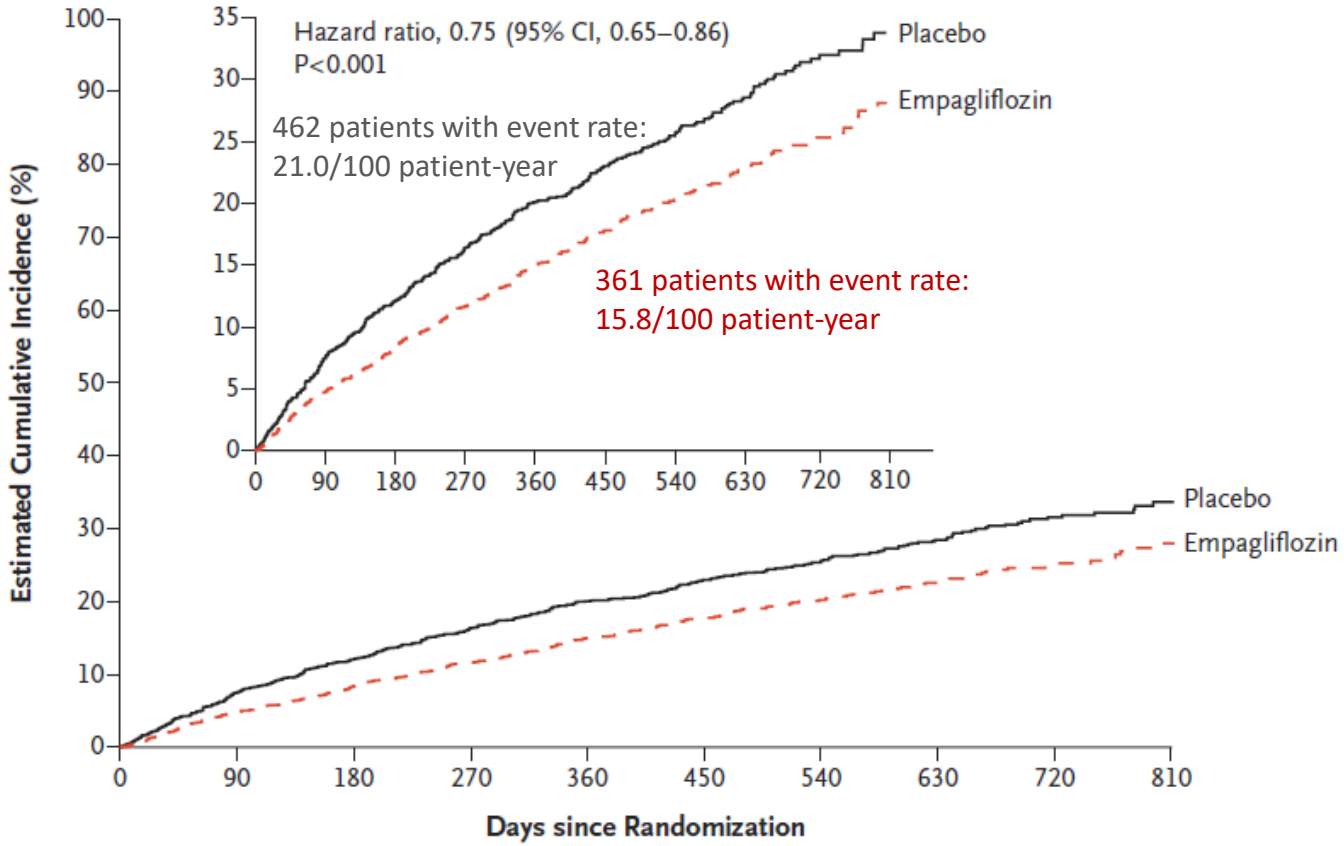
- NYHA class II-IV
- Elevated NT-pro BNP
- Guideline recommendation medication stable ≥1 week prior to first visit
- eGFR ≥20 ml/min/1.73 m^2

EF%	NT-proBNP (pg/ml) Patients without AF	NT-proBNP (pg/ml) Patients with AF
≥36 to ≤40	≥2500	≥5000
≥31 to ≤35	≥1000	≥2000
≤30	≥600	≥1200
> 40+HHF within 12 months	≥600	≥1200

1-N. Engl. J. Med 2020.8;383(15)1413-1424

Empagliflozin Group Had Lower Incidence of Cardiovascular Death or Hospitalization for Heart Failure[1]

A Primary Outcome



No. at Risk

Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

25% RRR

p<0.001

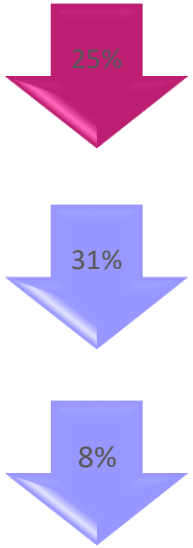
19.4% vs 24.7%

HR = 0.75 (0.65-0.86)

1-N. Engl. J. Med 2020.8;383(15)1413-1424

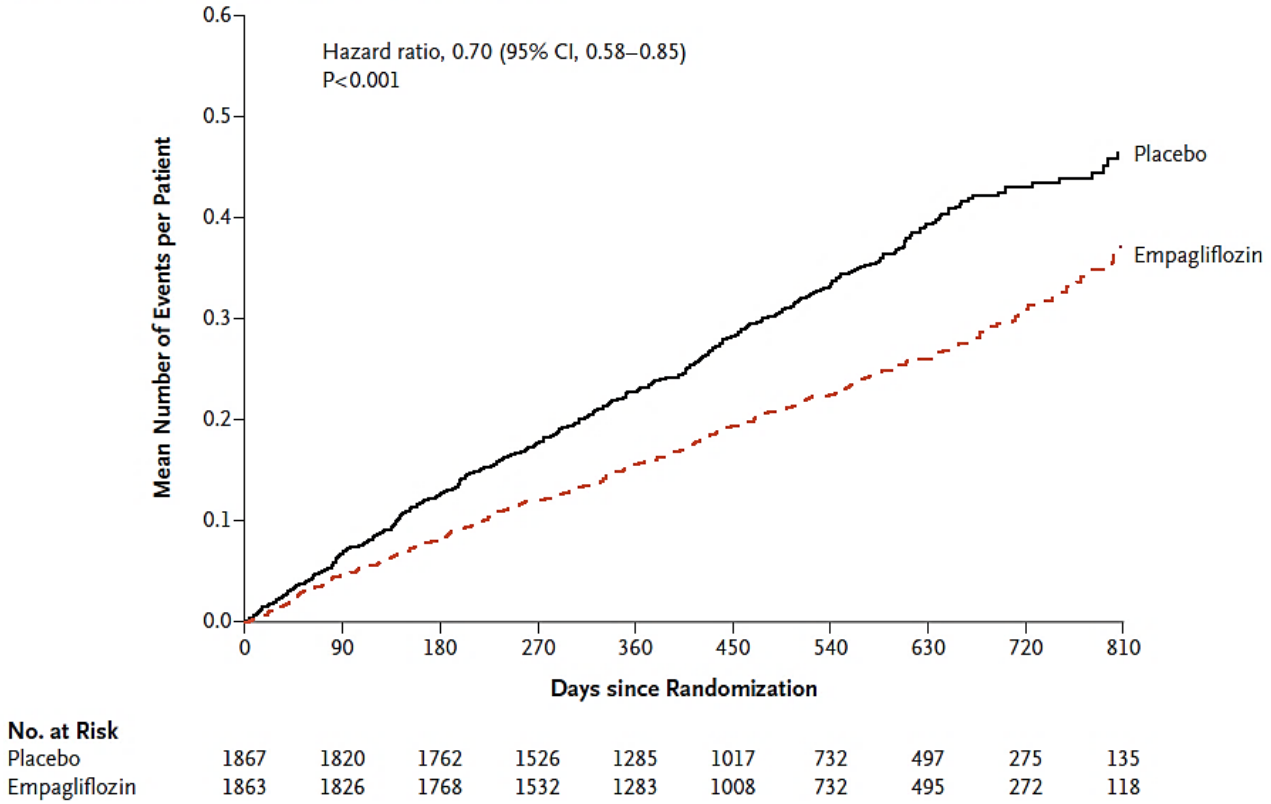
Effect on individual components of the primary endpoint[1]

	Empagliflozin (n=1863)		Placebo (n=1867)		Hazard Ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yr	Number of events (%)	Events/100 patient-yr		
Primary composite outcome	361 (19.4%)	15.8	462 (24.7%)	21.0	0.75 (0.65 – 0.86)	<0.001
First hospitalization for heart failure	246 (13.2%)	10.7	342 (18.3%)	15.5	0.69 (0.59 – 0.81)	
Cardiovascular death	187 (10.0%)	7.6	202 (10.8%)	8.1	0.92 (0.75 – 1.12)	



1-N. Engl. J. Med 2020.8;383(15)1413-1424

Empagliflozin-Treated Patients Had lower Risk of Hospitalization for Heart Failure[1]



30% RRR

p<0.001

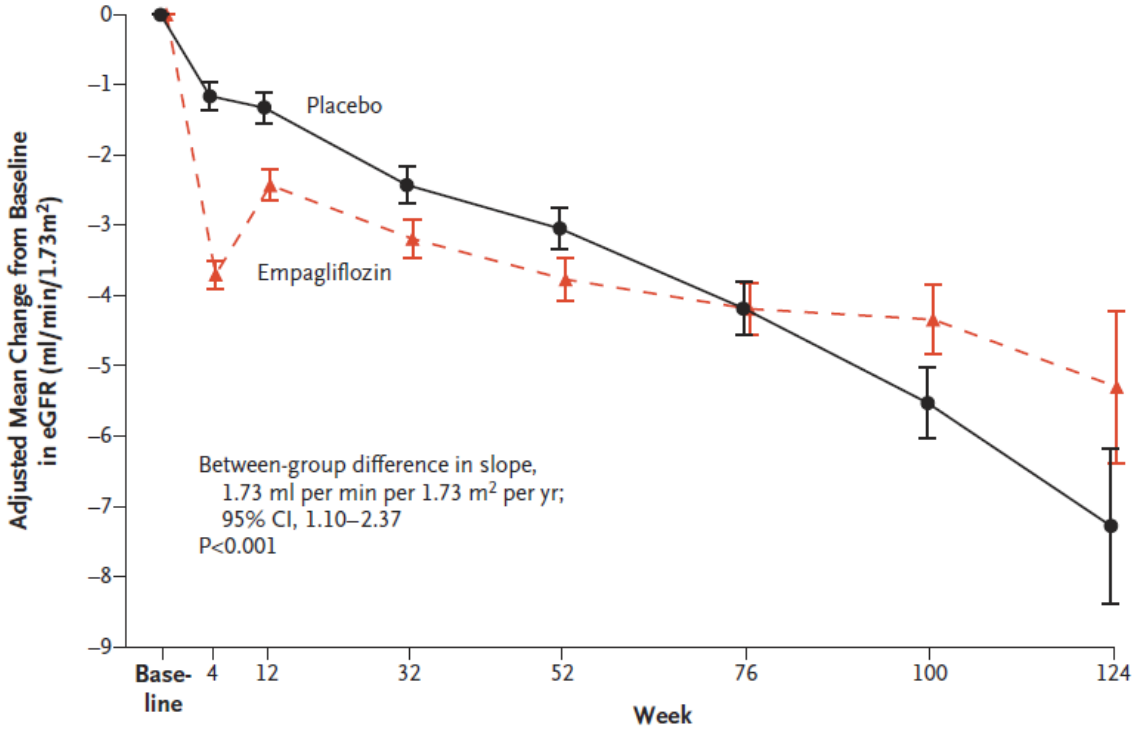
٣٨٨ Vs 553

HR=0.70 (0.58-0.85)

✓ The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group, with 388 events and 553 events, respectively (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001)

1-N. Engl. J. Med 2020. 8;383(15):1413-1424

Empagliflozin Decreased the slope of eGFR Reduction Significantly Over the Time vs Placebo[1]



No. at Risk								
Placebo	1792	1765	1683	1500	1146	745	343	76
Empagliflozin	1799	1782	1720	1554	1166	753	356	80

–2.28 ml / min / 1.73 m2 / year
On placebo

– 0.55 ml /min/1.73 m2 / year
On Empagliflozin

1.73 ml / min / 1.73 m2 / year

P < 0.001

✓ Empagliflozin was associated with a slower progressive decline in renal function in patients with chronic HF and a reduced EF, regardless of the presence or absence of diabetes[2].

1-N. Engl. J. Med 2020. 8;383(15):1413-1424

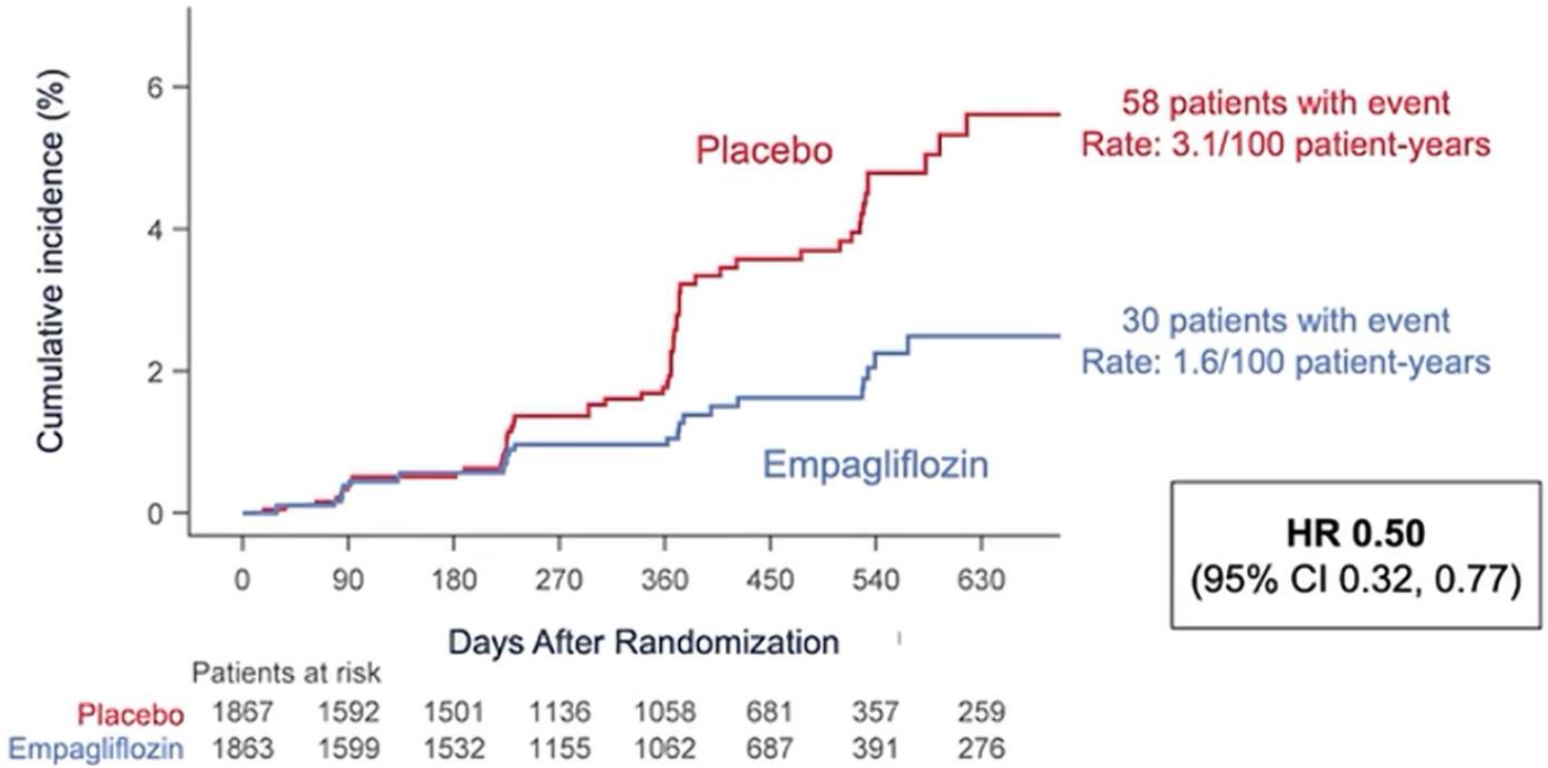
achieved all three endpoints at p<0.001

	**Primary Endpoint** Composite of cardiovascular death or heart failure hospitalization	**Achieved** **P < 0.001**
	**First Secondary Endpoint** Total (first and recurrent heart failure hospitalizations)	**Achieved** **P < 0.001**
	**Second Secondary Endpoint** Slope of decline in glomerular filtration rate over time	**Achieved** **P < 0.001**

Also achieved success on composite renal endpoint, KCCQ clinical summary score, and total number of hospitalizations for any reason (all nominal P < 0.01)

1-N. Engl. J. Med 2020. 8;383(15):1413-1424

Empagliflozin reduced composite renal endpoint by 50%[1]



50%
30 on Empagliflozin
58 on Placebo
HR= 0.50 (0.32-0.77)

- ✓ a composite renal outcome:
    1. chronic dialysis or renal transplantation
    2. profound, sustained reduction in the estimated GFR.

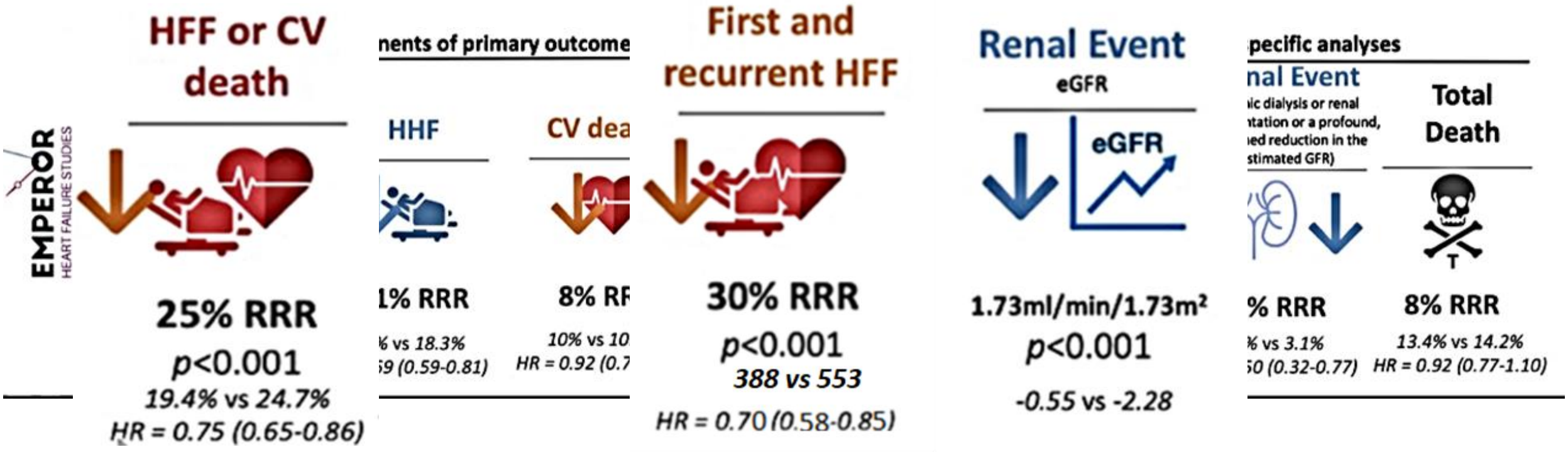
EMPEROR-Reduced: Adverse events[1]

- ✓ Uncomplicated genital tract infection was reported more frequently with empagliflozin than with placebo[2].
- ✓ Safety concerns that have been seen with other drugs for heart failure (e.g., hypotension, volume depletion, renal dysfunction, bradycardia, and hyperkalemia) were not evident with empagliflozin[2].

	Empagliflozin (n=1863)	Placebo (n=1863)
Serious adverse events	772 (41.4)	896 (48.1)
Related to cardiac disorder	**500 (26.8)**	**634 (34.0)**
Related to worsening renal function	**59 (3.2)**	**95 (5.1)**
Selected adverse events of special interest		
Volume depletion	197 (10.6)	184 (9.9)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Hypoglycemia	27 (1.4)	28 (1.5)
Ketoacidosis	0 (0.0)	0 (0.0)
Urinary tract infections	91 (4.9)	83 (4.5)
Genital tract infections	31 (1.7)	12 (0.6)
Bone fractures	45 (2.4)	42 (2.3)
Lower limb amputations	13 (0.7)	10 (0.5)

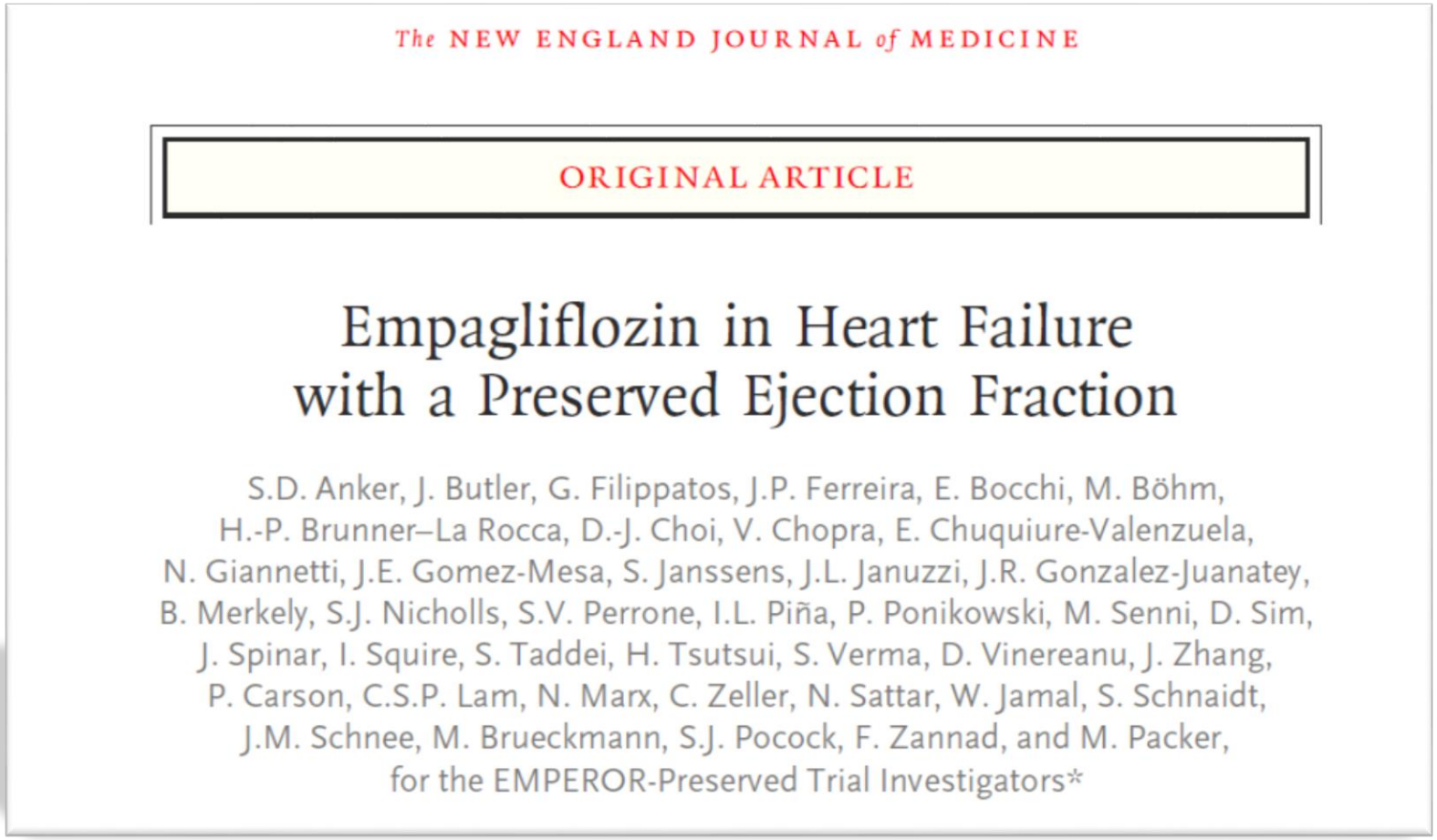
1-N. Engl. J. Med 2020. 8;383(15):1413-1424

Conclusion[1]



- ✓ Overall, in this trial, empagliflozin was associated with a lower combined risk of cardiovascular death or hospitalization for heart failure than placebo and with a slower progressive decline in renal function in patients with chronic heart failure and a reduced ejection fraction, regardless of the presence or absence of diabetes.

1-N. Engl. J. Med 2020. 8;383(15):1413-1424



Objective[1]:

To evaluate the effects of SGLT2 inhibition with empagliflozin on major heart failure outcomes in patients with heart failure and a **preserved ejection fraction**, irrespective of diabetes status.[1]

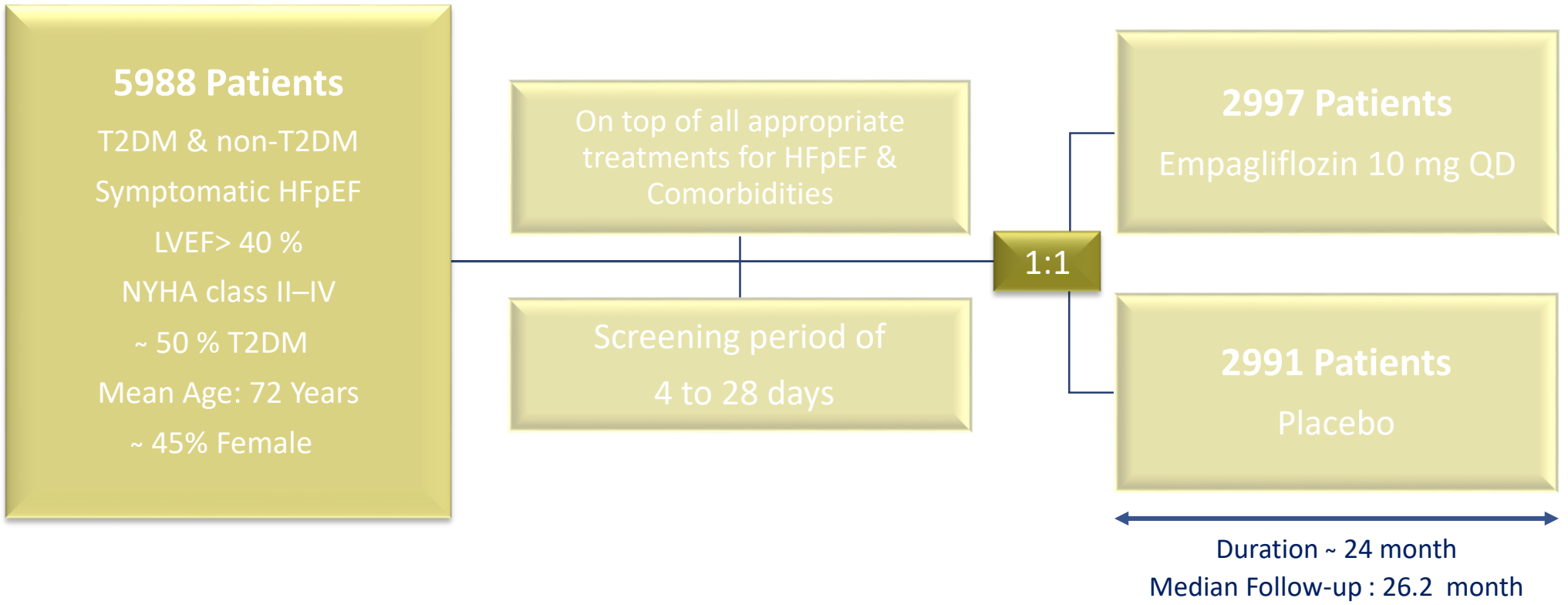
1- N Eng J Med. 2021 Oct 14;385(16):1451-1461 SGLT2: sodium-glucose co-transporter 2

EMPEROR-Preserved Trial Design[1]

Phase **III** randomized, double blind, parallel-group, placebo-controlled, event driven trial[1]

23 Countries, **622** Sites

11,583 Patients screened , **5988** Patients randomized



1- N Eng J Med. 2021 Oct 14;385(16):1451-1461 LVEF: left ventricular ejection fraction NYHA:New York Heart Association T2DM: type 2 diabetes mellitus
HFpEF: heart failure with preserved ejection fraction

Patients' Criteria[1]

Inclusion criteria

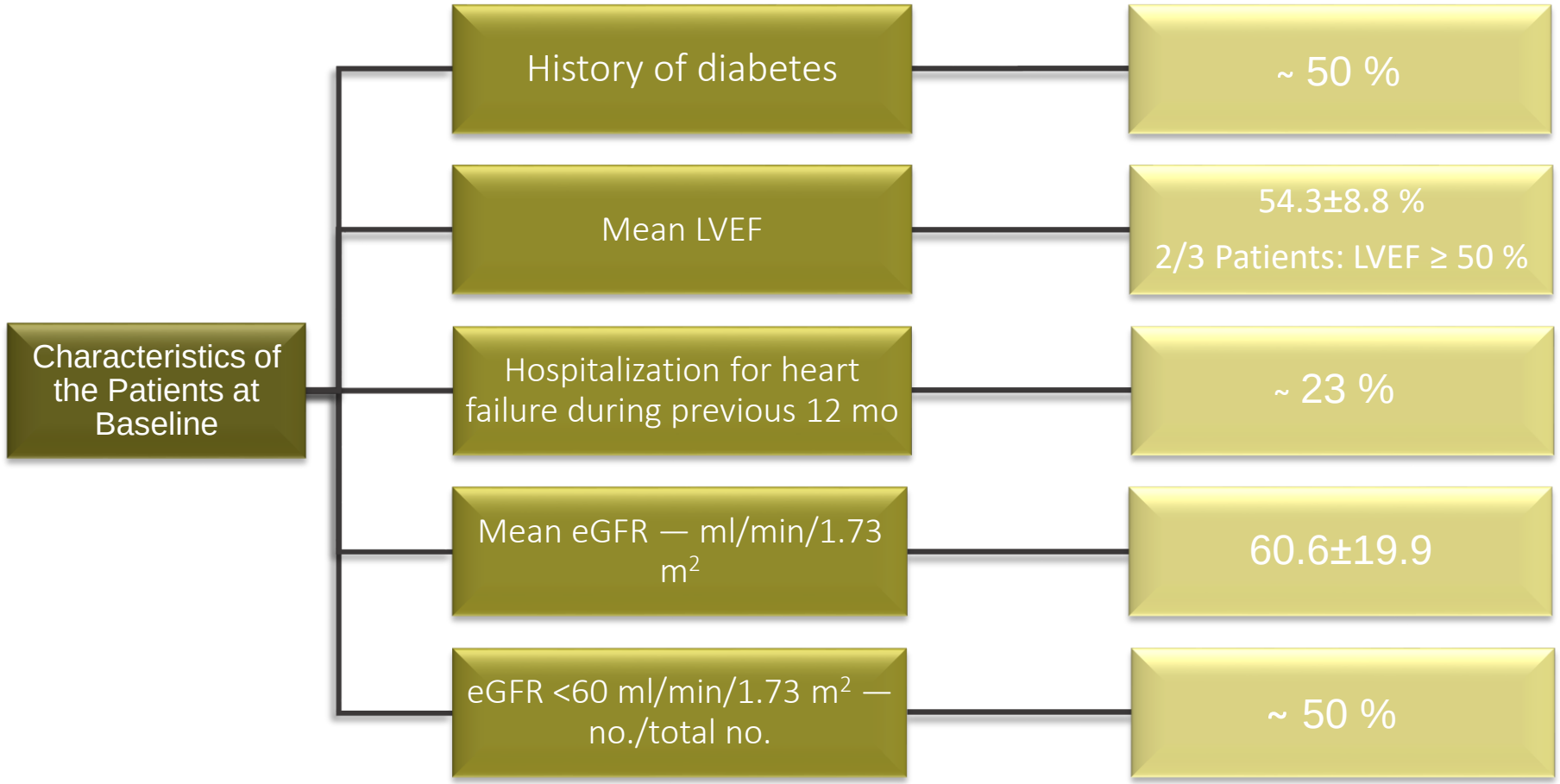
- Age ≥ 18 Years
- LVEF > 40%
- NYHA functional class II–IV chronic heart failure
- (NT-proBNP) level of more than 300 pg per milliliter or, for patients with atrial fibrillation at baseline, an NT-proBNP level of more than 900 pg per milliliter.
- Structural heart changes within 6 month
- Hospitalization for heart failure within 12 month
- Stable dose of oral diuretics

Exclusion criteria

- Liver or kidney disease eGFR< 20 ml/min/1.73 m^2
- Symptomatic hypotension
- Acute coronary syndrome or TIA within 90 days
- SBP ≥ 180

1- N Eng J Med. 2021 Oct 14;385(16):1451-1461 LVEF: left ventricular ejection fraction NYHA:New York Heart Association T2DM: type 2 diabetes mellitus HFpEF: heart failure with preserved ejection fraction NT-pro BNP: N-terminal prohormone of brain natriuretic peptide TIA: transient ischemic attack SBP: systolic blood pressure

Base-Line Characteristic of Patients[1]



1- N Eng J Med. 2021 Oct 14;385(16):1451-1461 LVEF: left ventricular ejection fraction eGFR: estimated glomerular filtration rate

EMPEROR-Preserved trial specified only three endpoints to be tested in hierarchical manner[1]

✓ Primary End point

A Composite of Cardiovascular Death or Hospitalization for Heart Failure.

✓ First Secondary End point

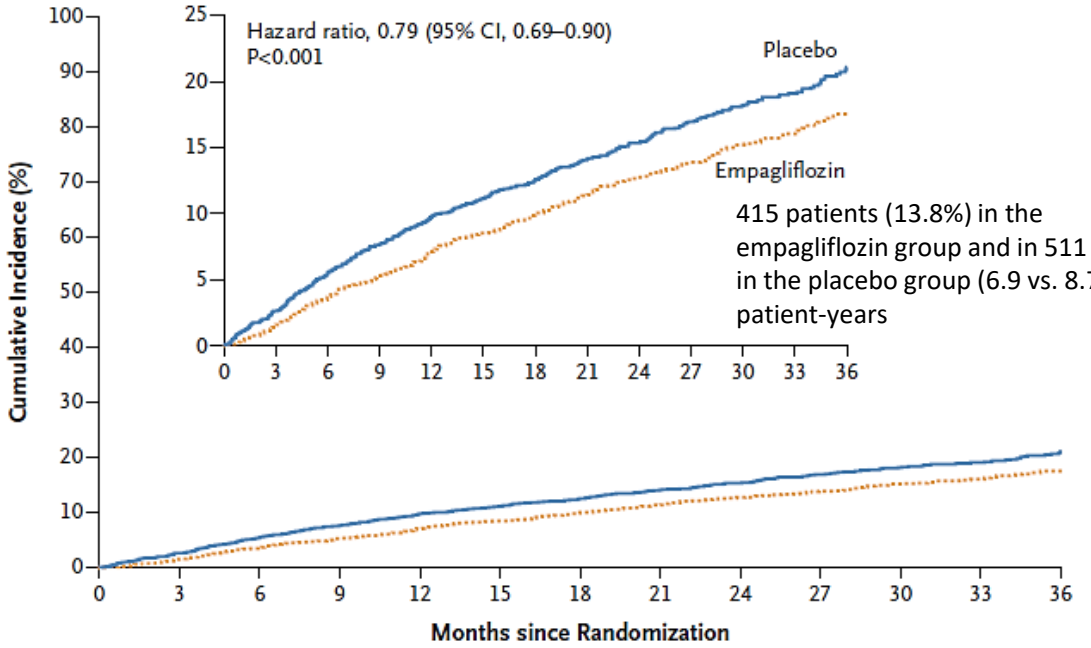
Total (first and recurrent) heart failure hospitalization

✓ Second Secondary End point

The rate of decline in the eGFR during double blind treatment

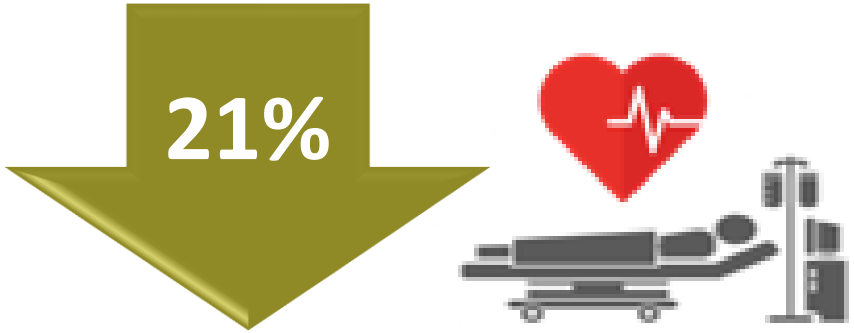
1- N Eng J Med. 2021 Oct 14;385(16):1451-1461 eGFR: estimated glomerular filtration rate

Empagliflozin Group Had Lower Incidence of Cardiovascular Death or Hospitalization for Heart Failure[1]



415 patients (13.8%) in the empagliflozin group and in 511 patients (17.1%) in the placebo group (6.9 vs. 8.7 events per 100 patient-years

No. 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



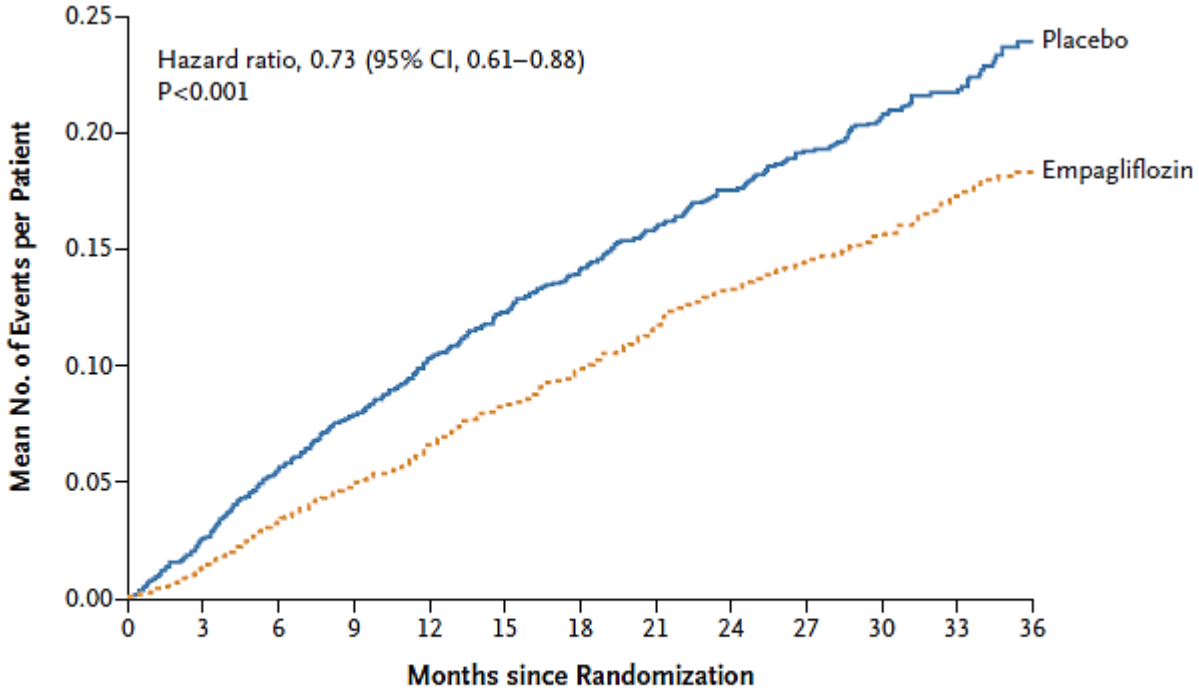
P<0.001

hazard ratio, 0.79; 95% CI, 0.69 to 0.90

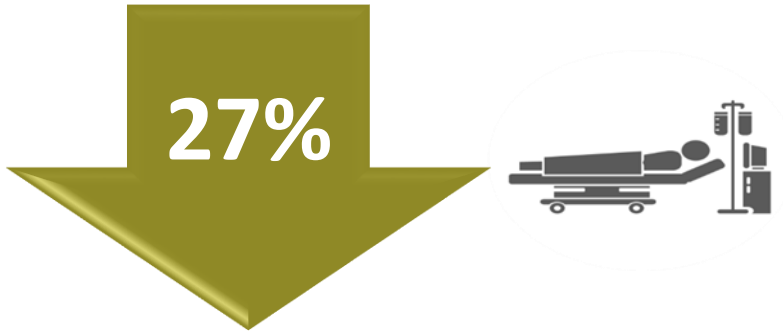
- ✓ In patients with heart failure and a preserved ejection fraction, SGLT2 inhibition with Empagliflozin led to a 21% lower relative risk in the composite of cardiovascular death or hospitalization for heart failure, which was mainly related to a 29% lower risk of hospitalization for heart failure with Empagliflozin.[1]

1- N Eng J Med. 2021 Oct 14;385(16):1451-1461 HR: hazard ratio CI: confidence interval SGLT2: sodium-glucose co-transporter 2

Empagliflozin Also Led to a Lower Total Number of HHF And a Longer Time to First HHF[1]



No. at Risk													
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446



P<0.001

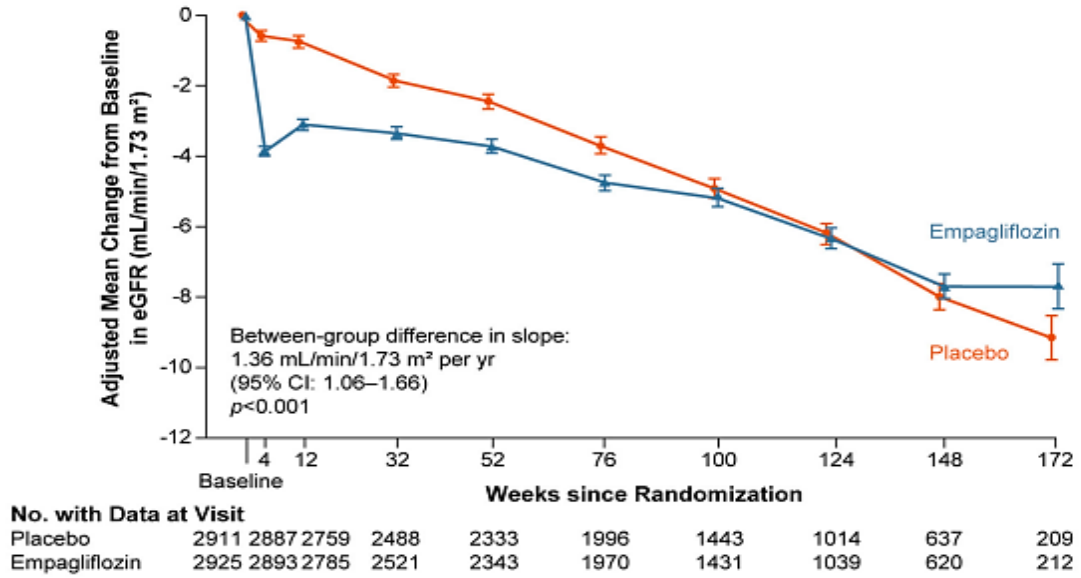
407 vs 541

hazard ratio, 0.73; 95% CI, 0.61 to 0.88

✓ The total number of hospitalizations for heart failure was lower in the Empagliflozin group than in the placebo group, with 407 events and 541 events, respectively (hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001).[1]

1- N Eng J Med. 2021 Oct 14;385(16):1451-1461 HR: hazard ratio CI: confidence interval HHF: hospitalization for heart failure

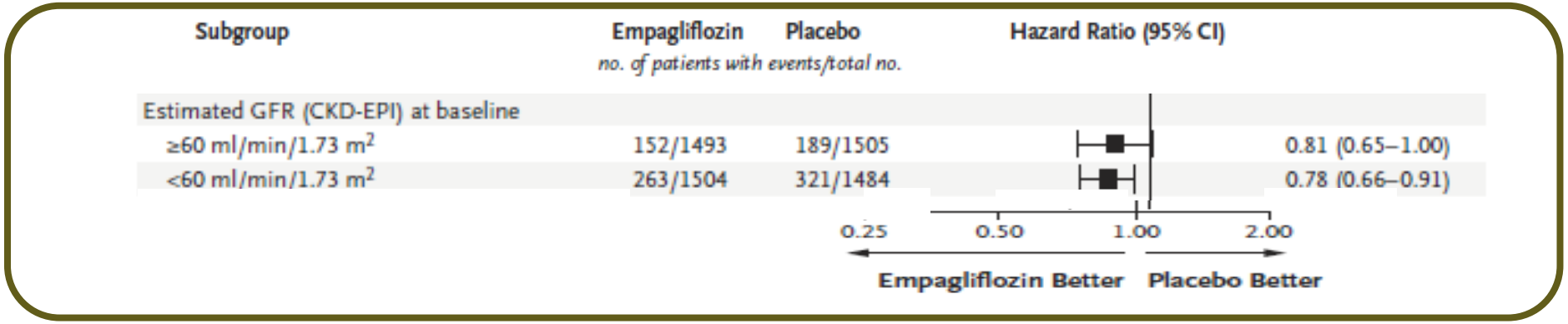
Empagliflozin Significantly Slowed Kidney Function Decline[1]



P<0.001

(–1.25 vs. –2.62)

ml per minute per 1.73 m^2 per year



- ✓ Empagliflozin was associated with a slower progressive decline in renal function in patients with chronic HF and a Preserved EF, regardless of the presence or absence of diabetes.[1]

1- N Eng J Med. 2021 Oct 14;385(16):1451-1461 HF: heart failure EF: ejection fraction CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

EMPEROR-Preserved: Adverse Events[1]

	Empagliflozin (N=2996) n(%)	Placebo (N=2989) n(%)
Serious adverse events	**1436 (47.9)**	**1543 (51.6)**
Selected Adverse events of special interest		
Hypotension	311 (10.4)	257 (8.6)
Symptomatic hypotension	197 (6.6)	156 (5.2)
Hypoglycemia	73 (2.4)	78 (2.6)
Ketoacidosis	4 (0.1)	5 (0.2)
Bone fracture	134 (4.5)	126 (4.2)
Lower limb amputation	12 (0.4)	17 (0.6)
Urinary tract infection	297 (9.9)	243 (8.1)
Genital tract infection	67 (2.2)	22 (0.7)

✓ Uncomplicated genital and urinary tract infections and hypotension were more common in patients treated with Empagliflozin.[1]

1- N Eng J Med. 2021 Oct 14;385(16):1451-1461

Conclusion[1]

Primary outcomes

HHF or CV death

21% RRR

P <0.001

13.8% vs 17.1%

(HR= 0.79; 95% CI, 0.69 to 0.90;)

Components of primary outcomes

HHF

29% RRR

P > 0.05

8.6% vs 11.8%

(HR= 0.71; 95% CI, 0.60 to 0.83)

CV death

9% RRR

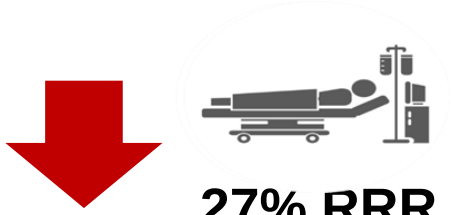
P > 0.05

7.3% vs 8.2%

(HR=0.91; 95% CI, 0.76 to 1.09)

Secondary outcomes

First and recurrent HHF



27% RRR

P <0.001

407 vs 541

(HR= 0.73; 95% CI, 0.61 to 0.88)

Renal event

P <0.0001

(–1.25 vs. –2.62)

ml per minute per 1.73 m2 per year

- ✓ Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes.[1]
- ✓ Landmark trial demonstrates empagliflozin is the first therapy to show statistically significant improvement in heart failure outcomes in adults with preserved ejection fraction[2]
- ✓ Empagliflozin as the first and only treatment to significantly improve outcomes for the full spectrum of heart failure patients[2]

1- N Eng J Med. 2021 Oct 14;385(16):1451-1461. 2- https://www.boehringer-ingelheim.com/press-release/emperor-preserved-heart-failure-full-data