



SOCIETÀ ITALIANA DI TERAPIA CLINICA E SPERIMENTALE



CardioVascular Outcome Trials e SGLT2-i: aggiornamenti della letteratura

Dott. Emanuele Spreafico

S.S.D. Endocrinologia e Diabetologia

ASST di Monza

Presidio di Desio e Poliambulatorio di Muggiò

DICHIARAZIONE CONFLITTO DI INTERESSI

DOTT. EMANUELE SPREAFICO

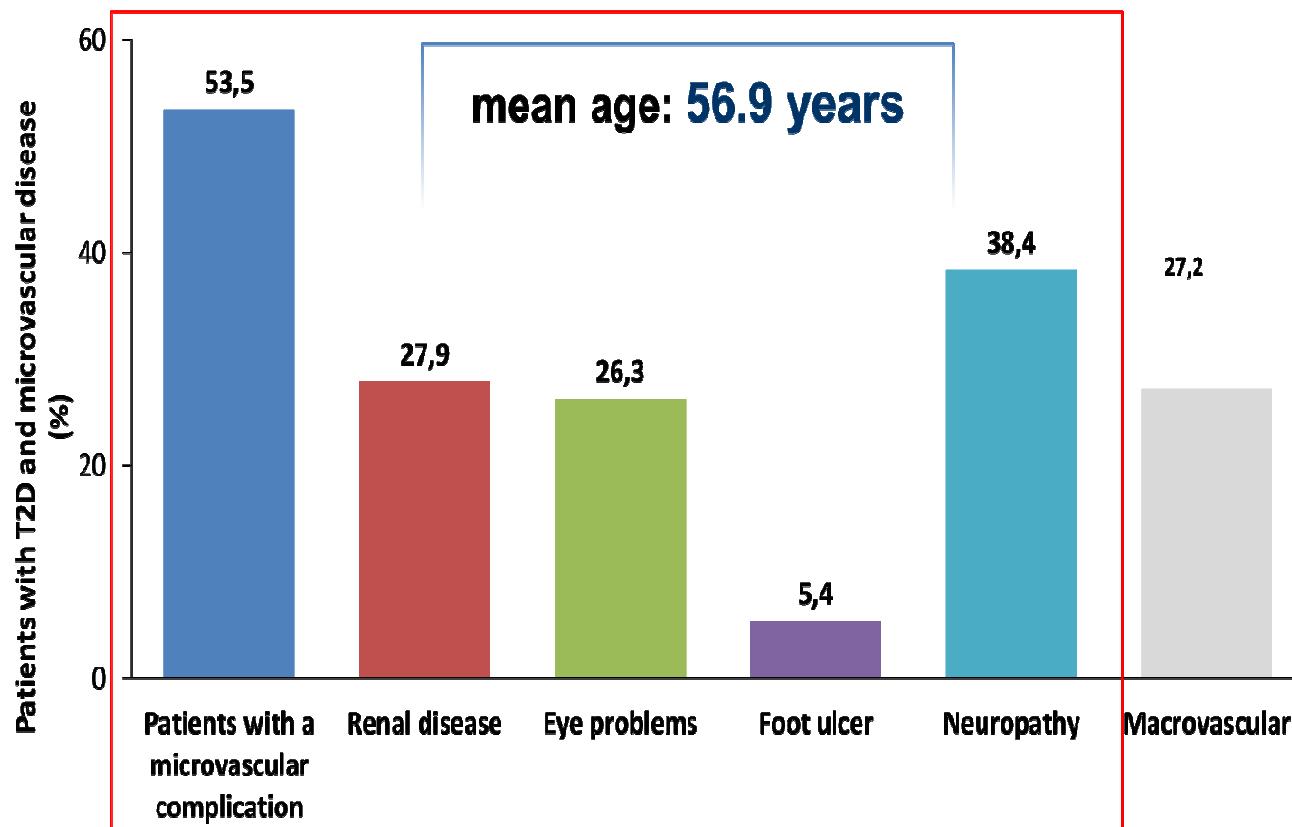
Ai sensi del Regolamento applicativo dell'Accordo Stato-Regioni 02.02.2017, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- ***ELI-LILLY***
- ***GUIDOTTI***
- ***MUNDIPHARMA***
- ***NOVONORDISK***

DIABETE MELLITO E RISCHIO CARDIONEFROVASCOLARE

Type 2 diabetes is a major cause of mortality and morbidity

Patients with type 2 diabetes and microvascular complications: A₁chieve study (N=66,276)^{2,a}

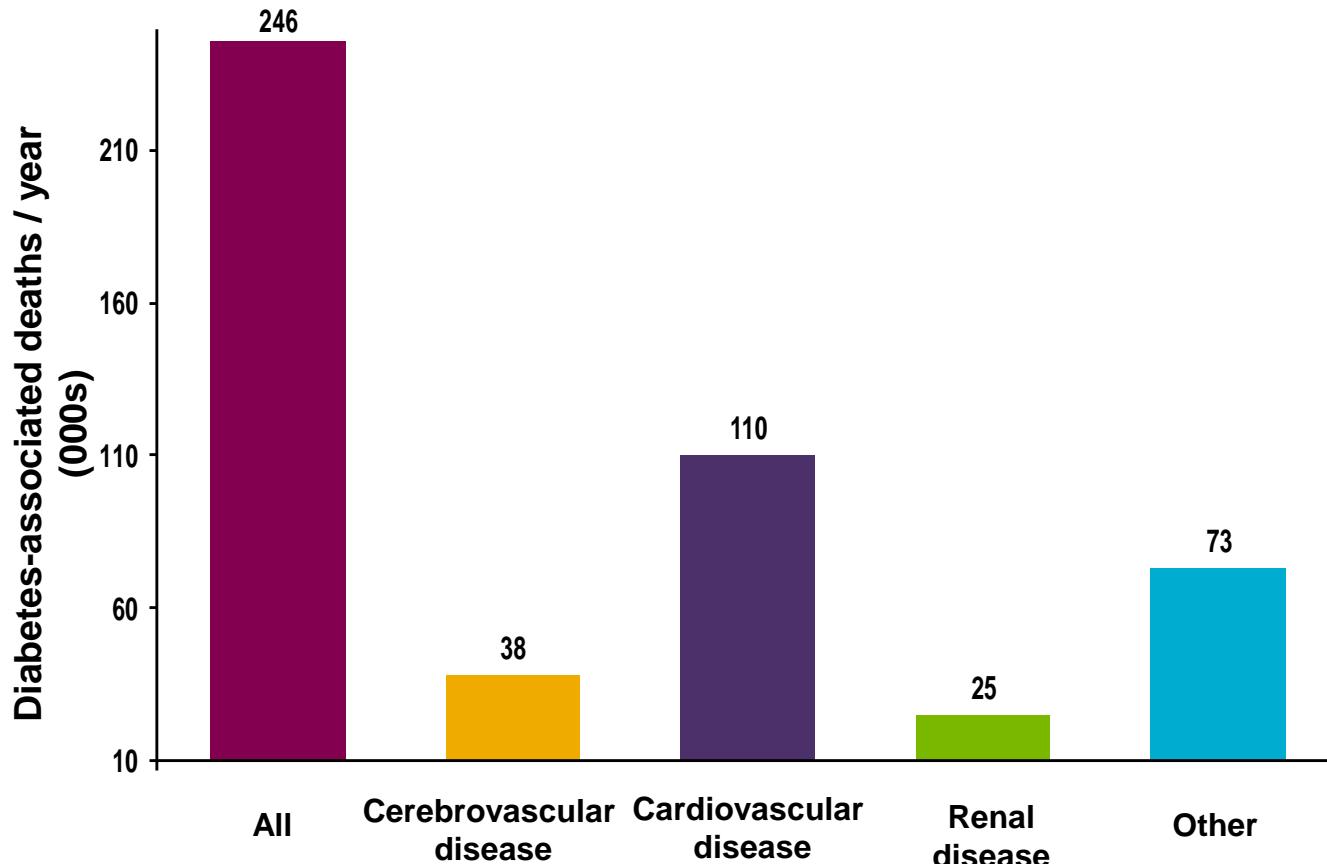


^aDue to the observational nature of this study, not all baseline data were recorded.

1. World Health Organization. 2016. <https://www.who.int/diabetes/global-report> Accessed October 2017;

2. Litwak L, et al. *Diabetol Metab Syndr* 2013;5:57.

~50% of Diabetes-associated Deaths Are Attributable to CV Disease



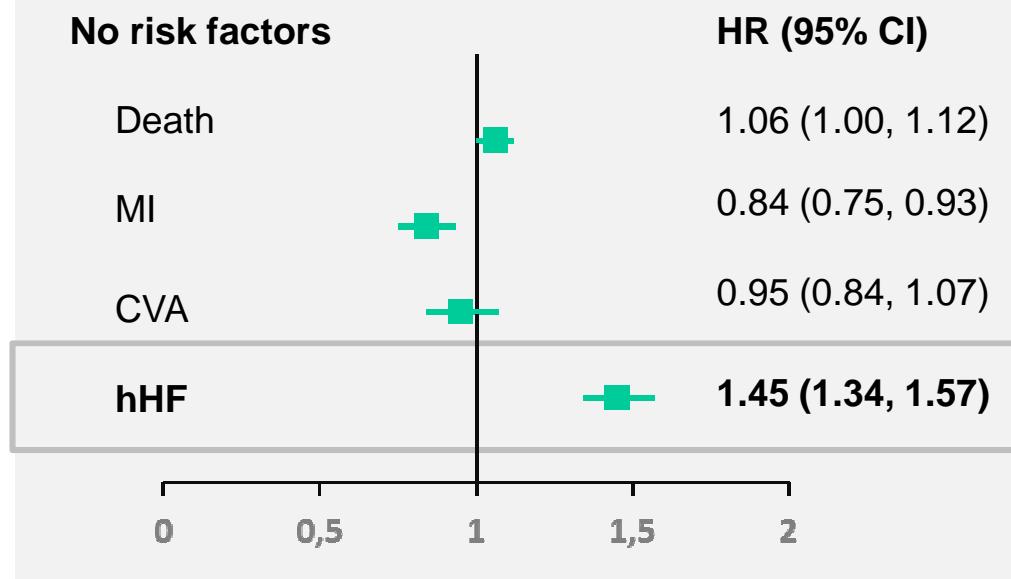
Data source: USA Centers for Disease Control and Prevention National Vital Statistics Reports for total deaths in 2009 by primary cause of death, scaled to 2012 using the annual diabetes population growth rate from 2009 to 2012 for each age, sex, and race/ethnicity group

CV, cardiovascular

ADA. *Diabetes Care* 2013;36:1033–1046

Despite control of known CV risk factors, patients with T2D remain at elevated risk of developing HF

Risk of event in patients with T2D with no other risk factors out of range compared to patients without diabetes



- In this analysis the risk of hHF in patients with T2D ($n=271,174$) was compared to those without T2D ($n=1,355,870$)
- The following risk factors were either not present or within guideline range: systolic and diastolic BP, LDL-C, albuminuria and tobacco use
- A substantial risk for hHF remained among patients who had all the variables within target range

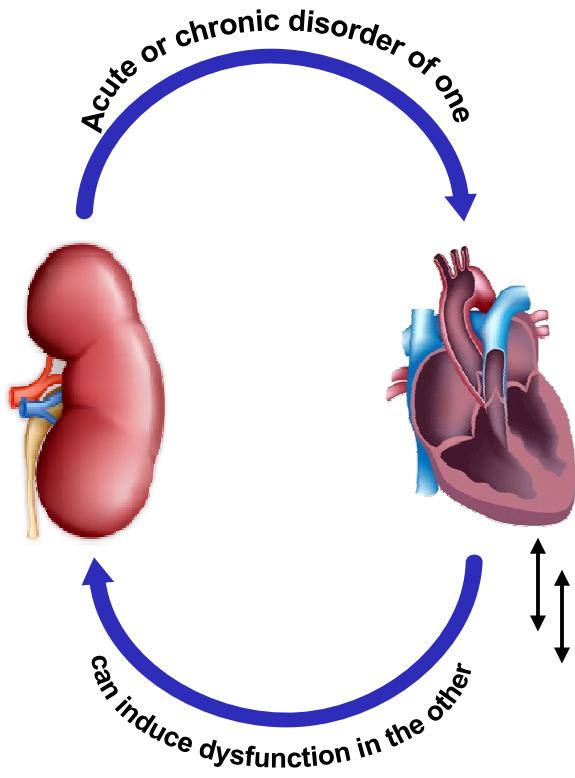
On average, the patients with T2D had a 45% increase in the risk of hHF, despite other major risk factors in guideline recommended range or absent

BP, blood pressure; CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; hHF, hospitalisation for HF; HR, hazard ratio; LDL-C, low density-lipoprotein cholesterol; MI, myocardial infarction; T2D, type 2 diabetes.

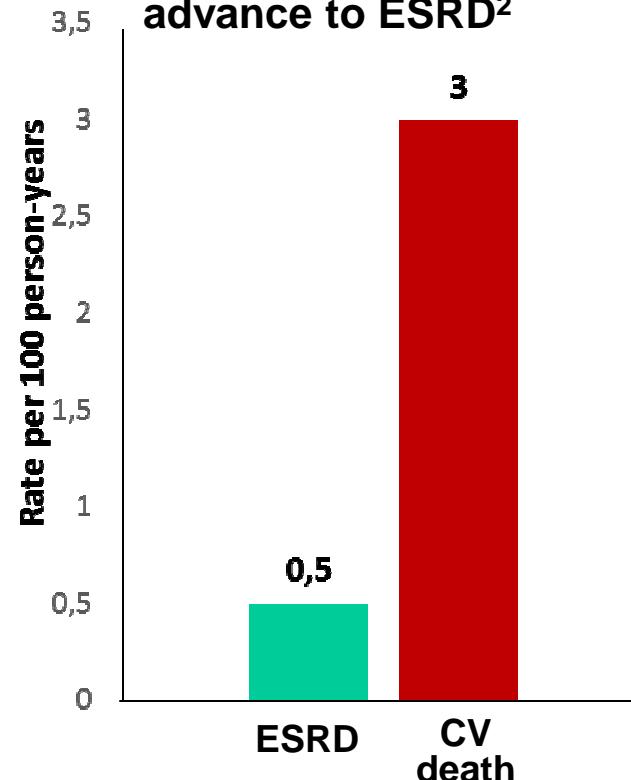
Rawshani A, et al. *N Engl J Med*. 2018;379:633-644.

Renal and cardiovascular disease are interconnected

Renal and cardiac systems are linked¹



CKD patients are more likely to die of heart disease than advance to ESRD²



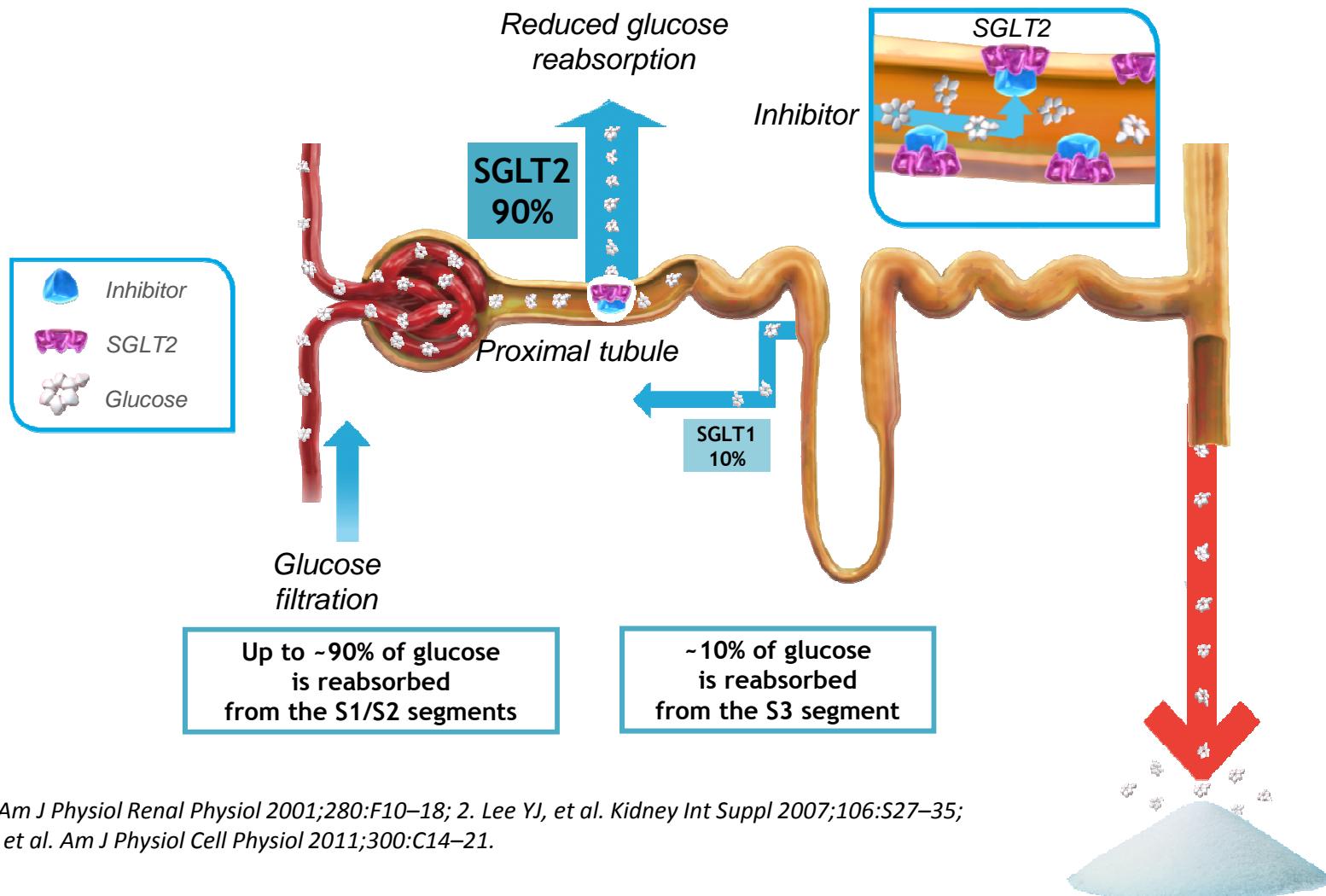
Therefore renal and cardiac systems and outcomes should be considered together

CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease.

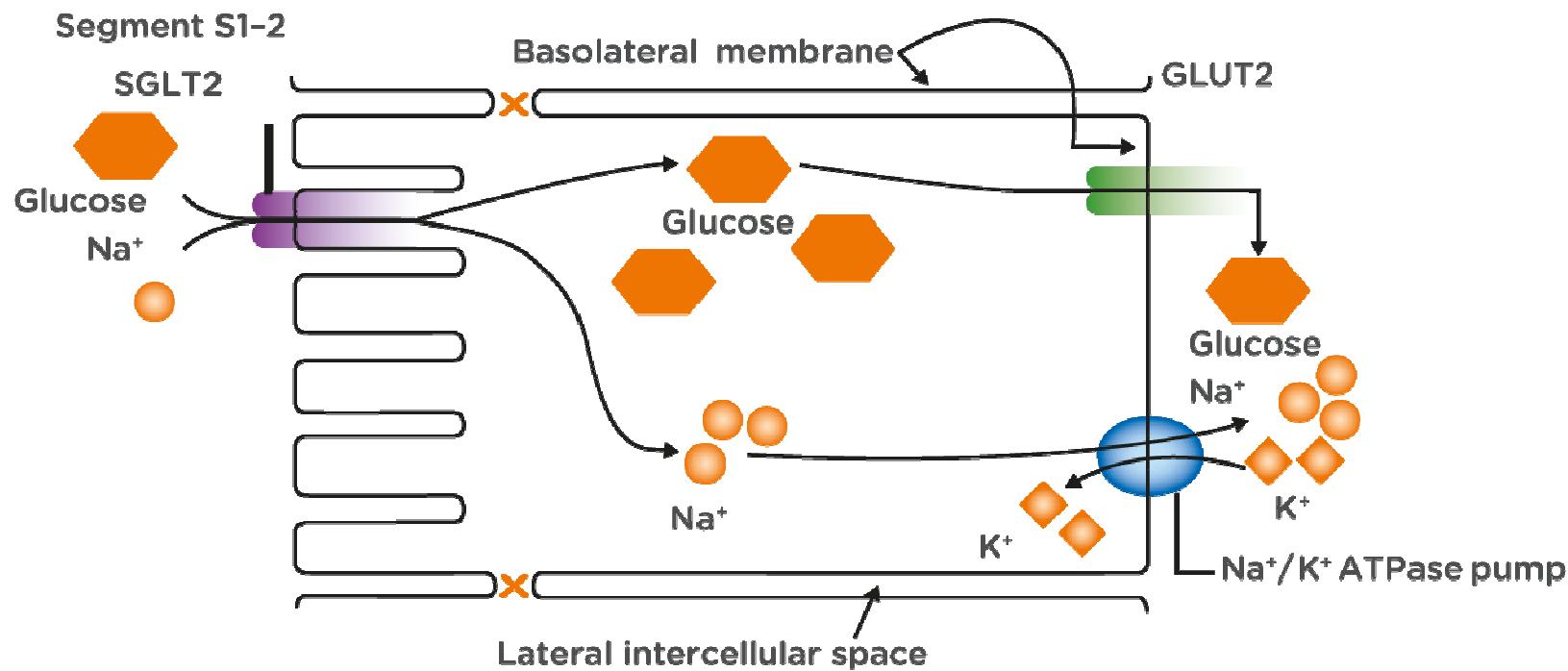
1. Ronco C, et al. *J Am Coll Cardiol.* 2008;52:1527. 2. Dalrymple L, et al. *J Gen Intern Med.* 2011;26:379.

SGLT2-i: MECCANISMO DI AZIONE

SGLT2-i: MECCANISMO DI AZIONE



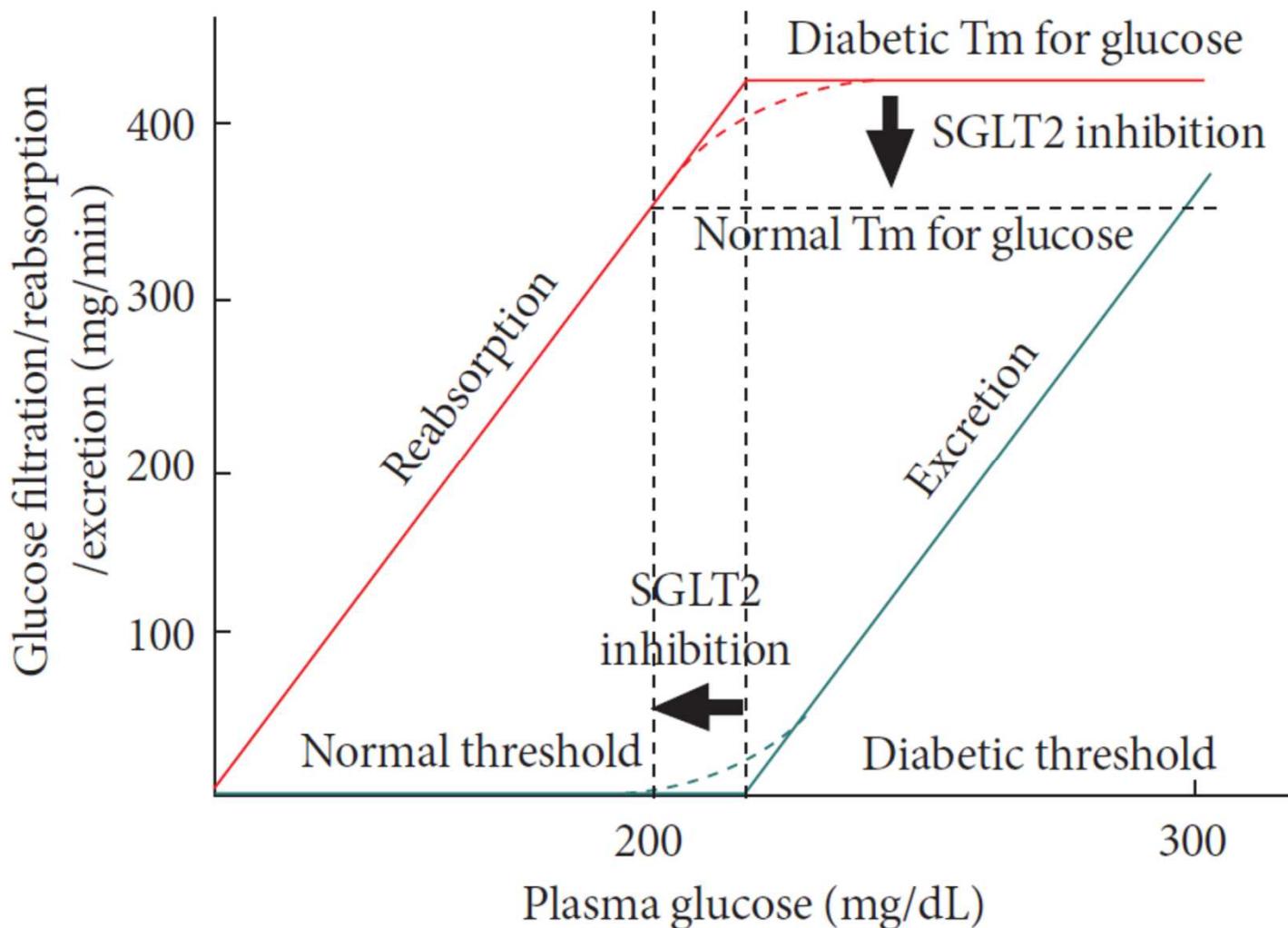
SGLT2-i: MECCANISMO DI AZIONE



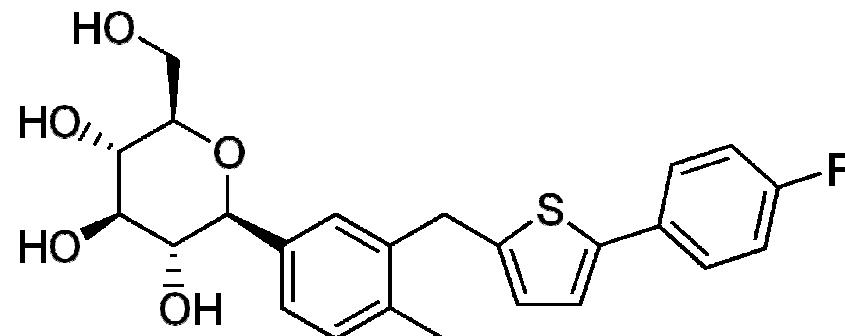
- SGLTs transfer glucose and sodium from the lumen into the cytoplasm of tubular cells through a secondary active transport mechanism
- At the basolateral membrane GLUT2 transfers the intracellular glucose to the interstitium and plasma by a facilitated transport process (via a Na^+/K^+ ATPase)

Adapted from: Wright EM, et al. *Physiology* 2004;19:370–76;
Bakris GL, et al. *Kidney Int* 2009;75:1272–1277.

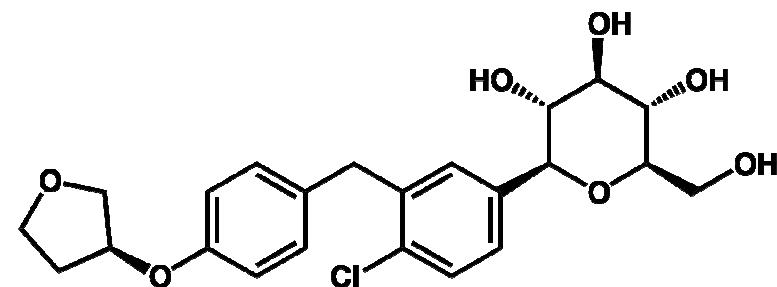
SGLT2-i: MECCANISMO DI AZIONE



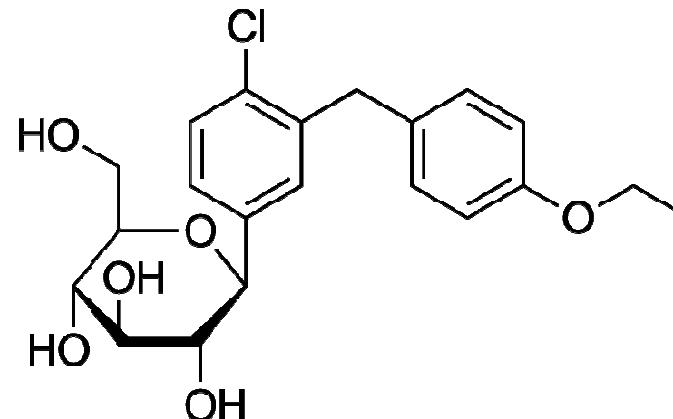
SGLT2-i



Canagliflozin

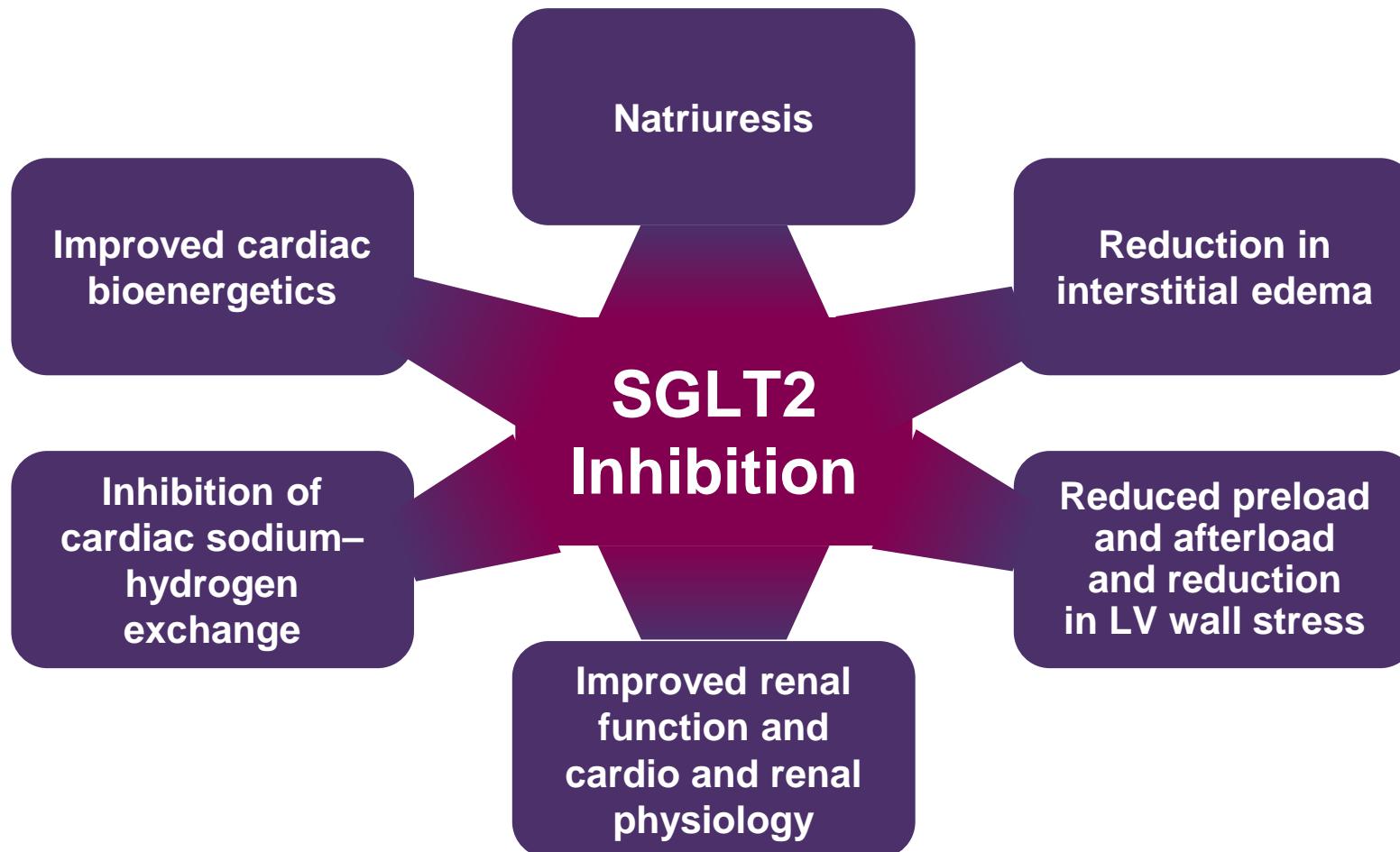


Empagliflozin

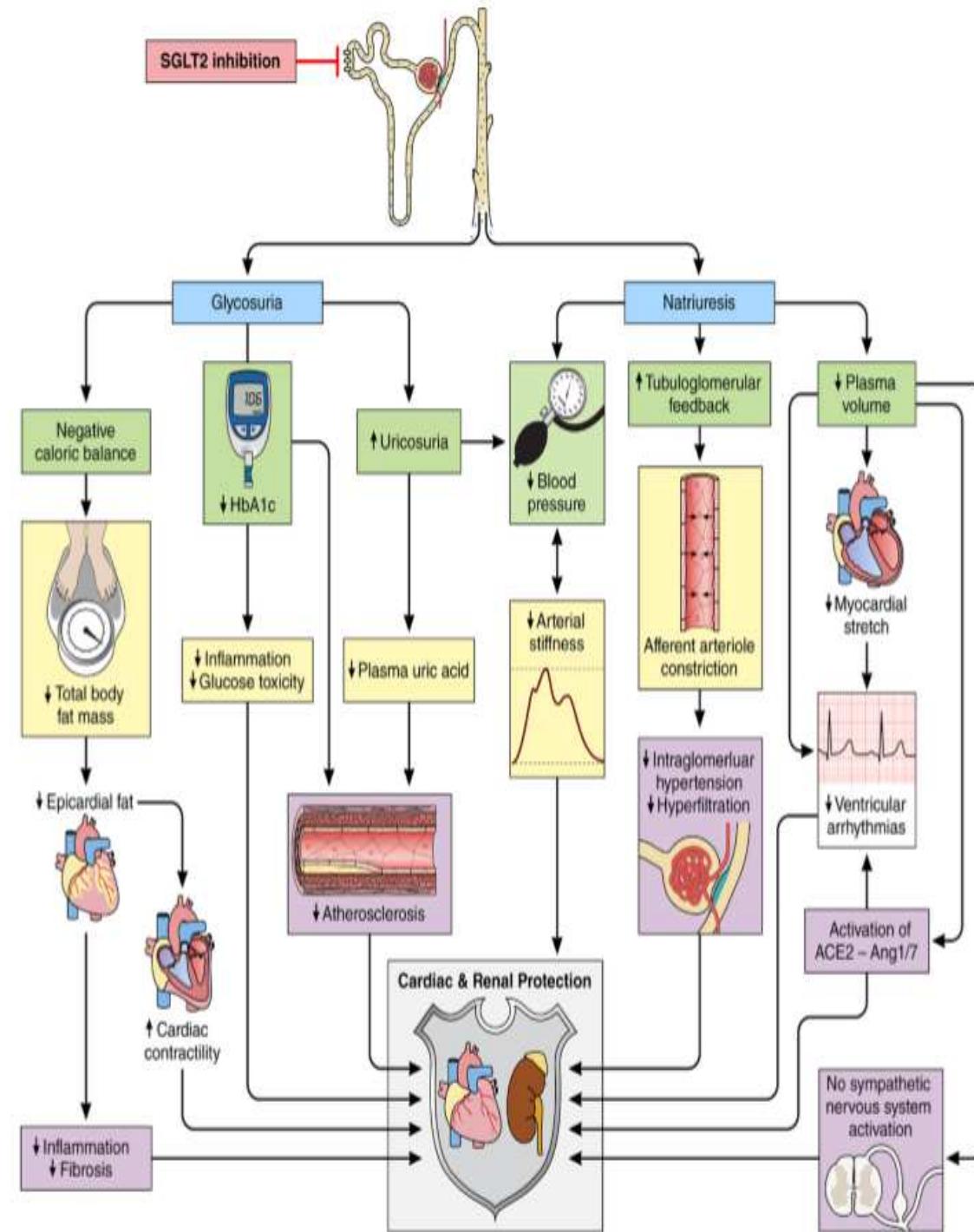


Dapagliflozin

The cardiorenal benefits likely result from different but yet to be confirmed mechanisms for SGLT2 inhibitors



LA CARDIO- NEFROPROTEZIONE



SGLT2-i: CARDIONEFROPROTEZIONE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE-TIMI 58 Investigators*

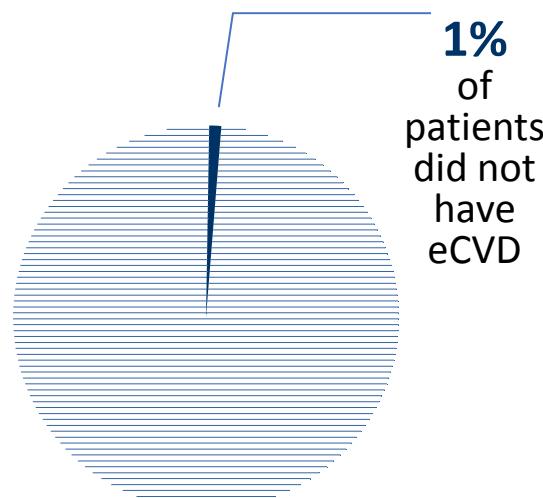
SGLT2-i: CARDIONEFROPROTEZIONE

	DECLARE-TIMI 58 ^{1,2,3}	CANVAS Program ⁴	EMPA-REG OUTCOME ⁵
Number of patients	17,160	10,142 (CANVAS: 4330; CANVAS-R: 5812)	7020
Key inclusion criteria	<ul style="list-style-type: none"> HbA1c ≥6.5% and <12%^a CrCl^b ≥60 mL/min 	<ul style="list-style-type: none"> HbA1c ≥7% and ≤10.5% eGFR^c >30 mL/min/1.73 m² 	<ul style="list-style-type: none"> HbA1c ≥7% and ≤10% eGFR^c ≥30 mL/min/1.73 m²
Study population	MRF: 59.4%; ECVD: 40.6%	MRF: 34.4%; ECVD: 65.6%	ECVD: >99%
Interventions (randomization ratio)	DAPA 10 mg or PBO (1:1)	CANVAS: CANA 100 mg, CANA 300 mg, or PBO (1:1:1) CANVAS-R: CANA 100 mg with optional increase to 300 mg or PBO (1:1)	EMPA 10 mg, EMPA 25 mg, or PBO (1:1:1)
Number of events	1559 (Actual)	CANVAS: 658; CANVAS-R: 353 (Actual)	772 (Actual)
Median follow-up	4.2 years	2.4 years (CANVAS: 5.7 years; CANVAS-R: 2.1 years)	3.1 years
Primary endpoint	Primary safety endpoint: MACE (composite of CV death, nonfatal MI, or nonfatal ischemic stroke). Primary efficacy endpoints: <ul style="list-style-type: none"> MACE Composite of CV death or hHF 	Pooled MACE (composite of CV death, nonfatal MI, or nonfatal stroke) from CANVAS & CANVAS-R	Pooled MACE (composite of CV death, nonfatal MI, or nonfatal stroke) from 2 doses
Important secondary endpoints	Renal composite endpoint (sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m ² and/or ESRD and/or renal or CV death), all-cause mortality	All-cause mortality, CV death, albuminuria progression (>30% increase in albuminuria and change in category), composite of CV mortality or hHF	Composite of MACE or hospitalization for UA, silent MI, hHF, microvascular composite, new onset microalbuminuria, new onset macroalbuminuria

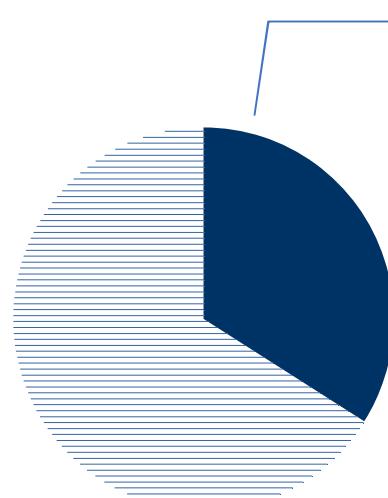
SGLT2-i: CARDIONEFROPROTEZIONE

The proportion of patients with and without established CV disease varied across the three SGLT2 CV outcome studies

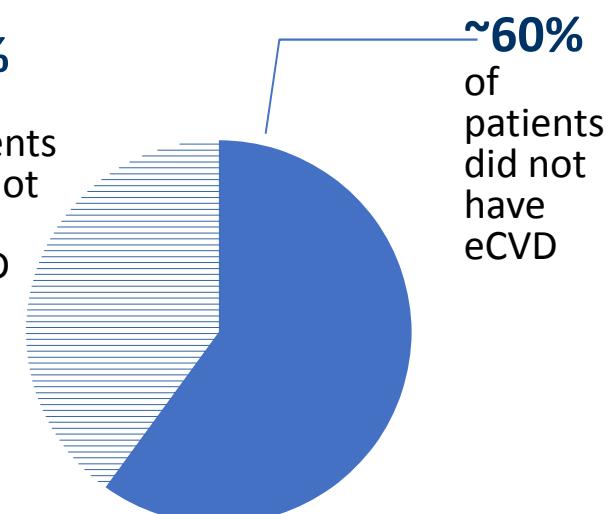
EMPA-REG OUTCOME
(N=7,020)



CANVAS
(N=10,142)



DECLARE
(N=17,160)



CV, cardiovascular; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes; eCVD, established CV disease.

1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128.; 2. Neal B, et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1611925;3. Sattar Diabetologia (2013) 56:686–695 4. Raz I, et al. *Diabetes Obes Metab* 2018. <http://dx.doi.org/10.1111/dom.13217>

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

MACE

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kata, Avivit Cahn

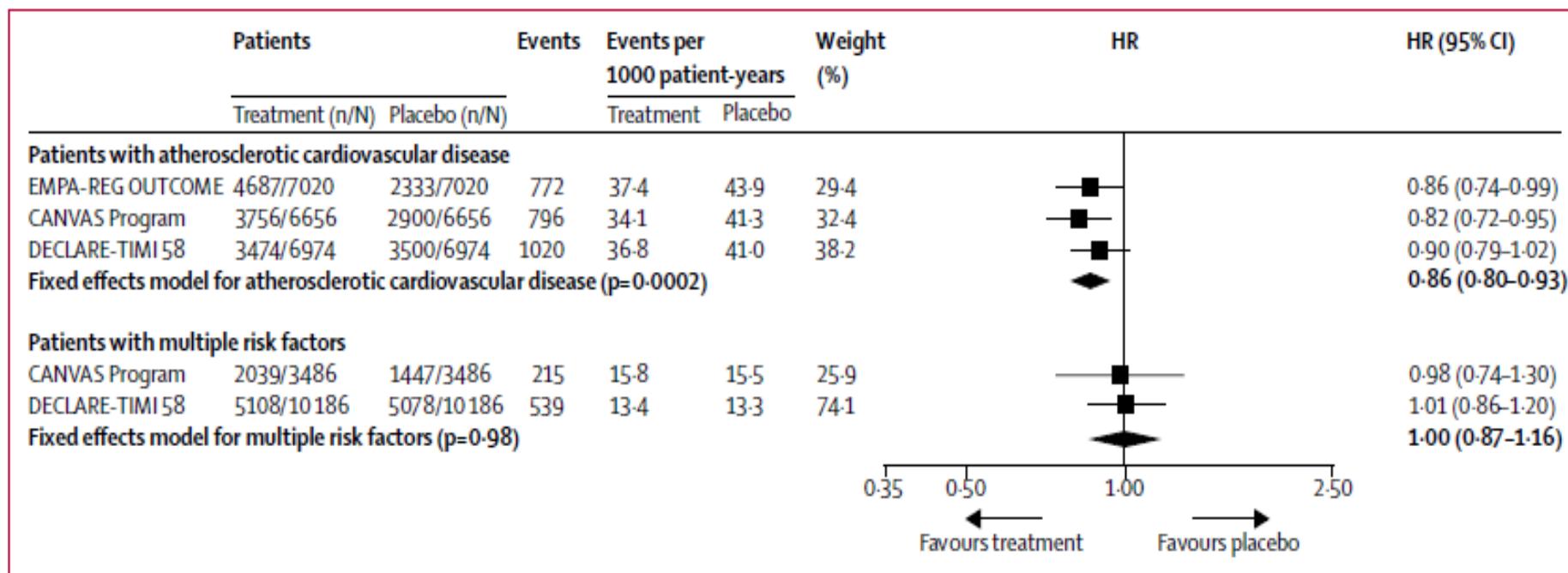


Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

No heterogeneity was found in terms of between-study variance in the subgroups (atherosclerotic cardiovascular disease: Q statistic=0.94, p=0.63, $I^2=0\%$; multiple risk factors: Q statistic=0.03, p=0.86, $I^2=0\%$). Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. The p value for subgroup differences was 0.0501. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Zelniker TA et al Lancet 2018

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

HHF

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo HM Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P Wilding, Marc S Sabatine

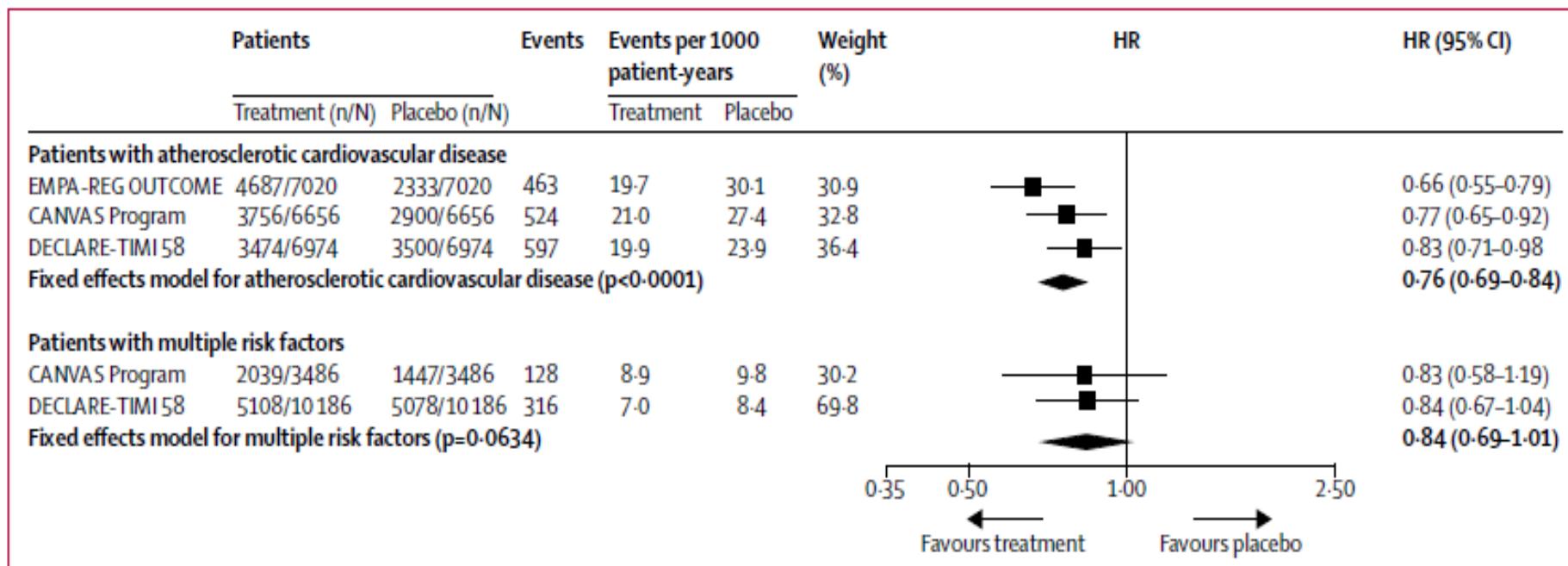


Figure 2: Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease

Atherosclerotic cardiovascular disease: Q statistic=3.49, p=0.17, $I^2=42.7\%$; multiple risk factors: Q statistic=0.00, p=0.96, $I^2=0\%$. The p value for subgroup differences was 0.41. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Zelniker TA et al Lancet 2018

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

CKD

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo HM Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John PH Wilding, Marc S Sabatine

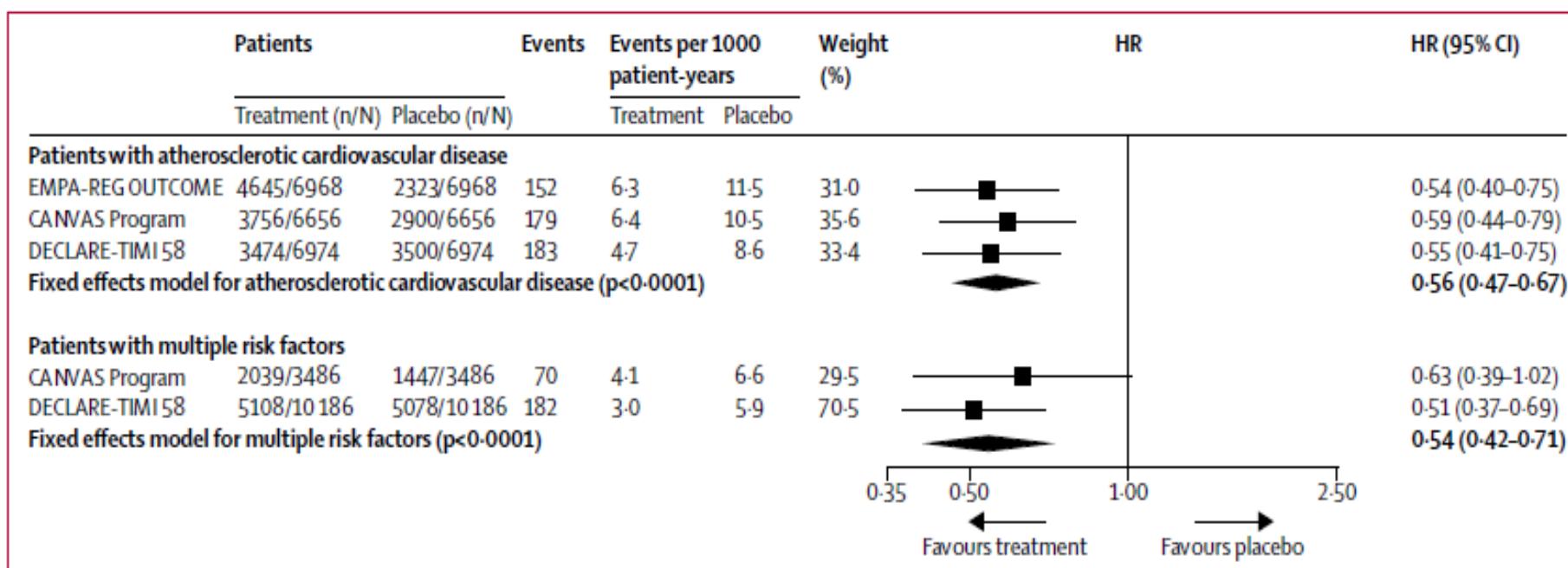


Figure 4: Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease

Atherosclerotic cardiovascular disease: Q statistic=0.19, p=0.91, $I^2=0\%$; multiple risk factors: Q statistic=0.52, p=0.47, $I^2=0\%$. The p value for subgroup differences was 0.71. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Zelniker TA et al Lancet 2018

Primary vs. tertiary CVD prevention ?

Comment

Pump, pipes, and filter: do SGLT2 inhibitors cover it all?

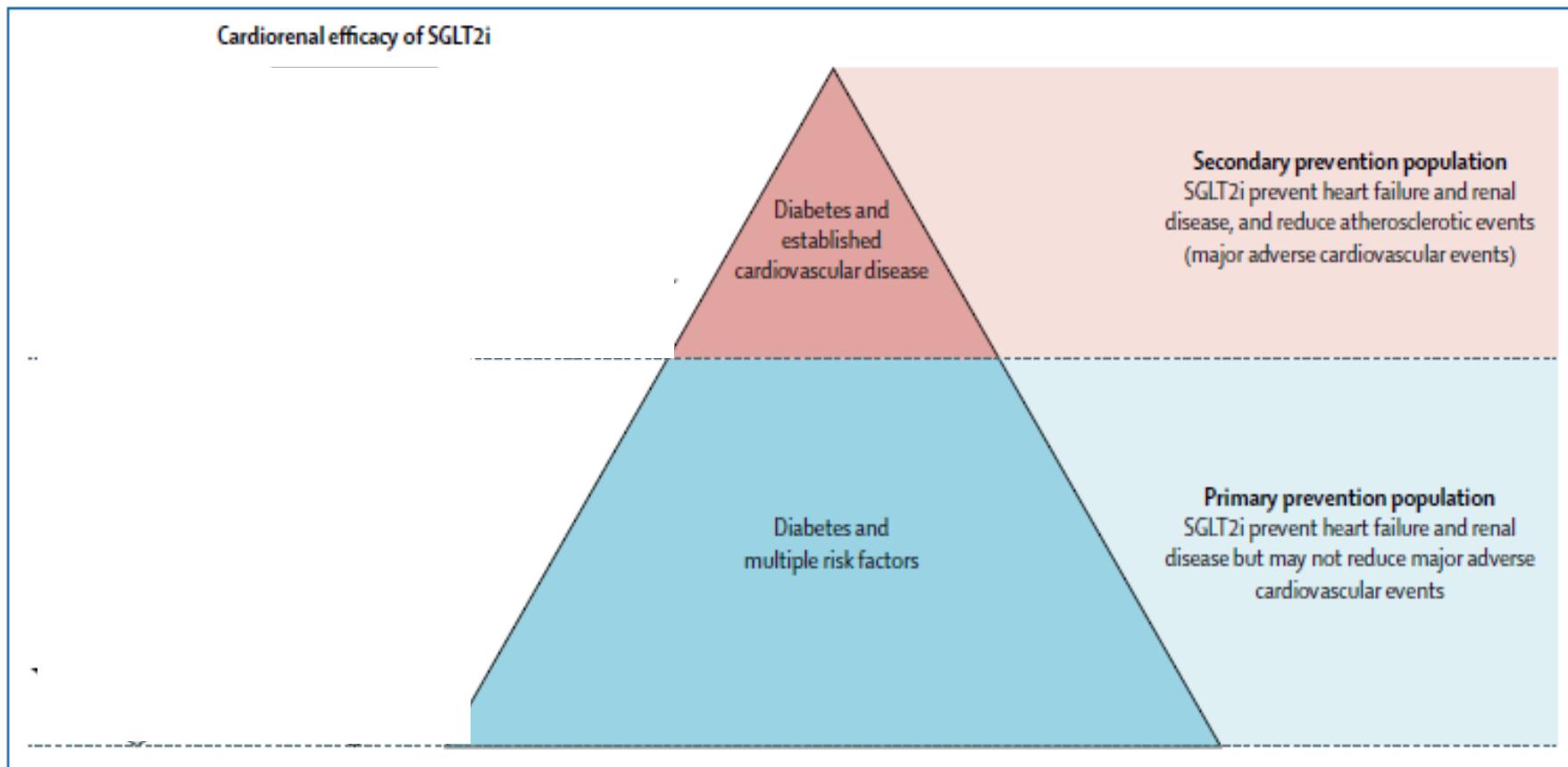


Figure: Cardiorenal benefits of SGLT2i in different patient populations
SGLT2i=sodium-glucose cotransporter-2 inhibitors.

Primary vs. tertiary CVD prevention ?

Comment

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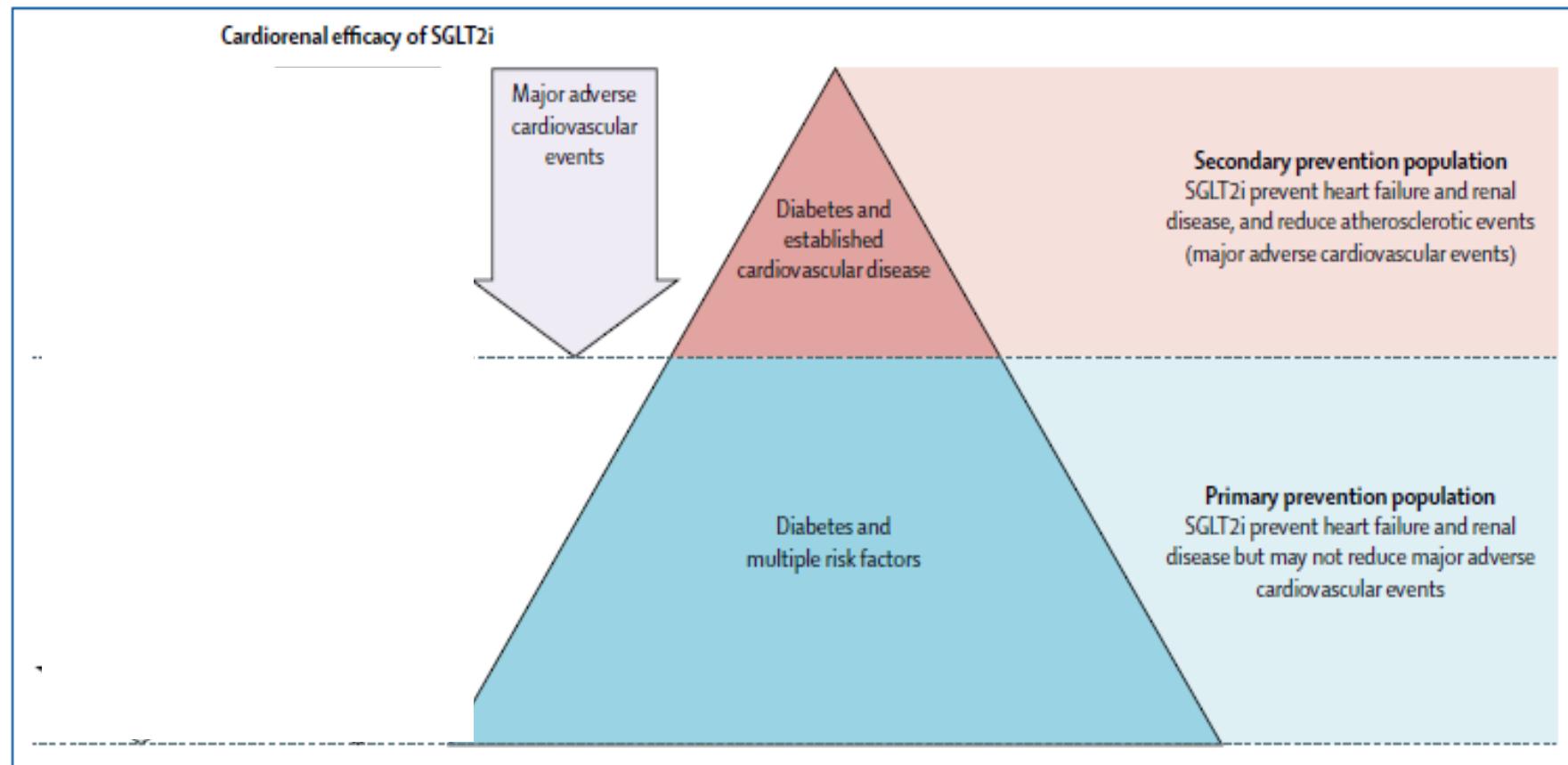


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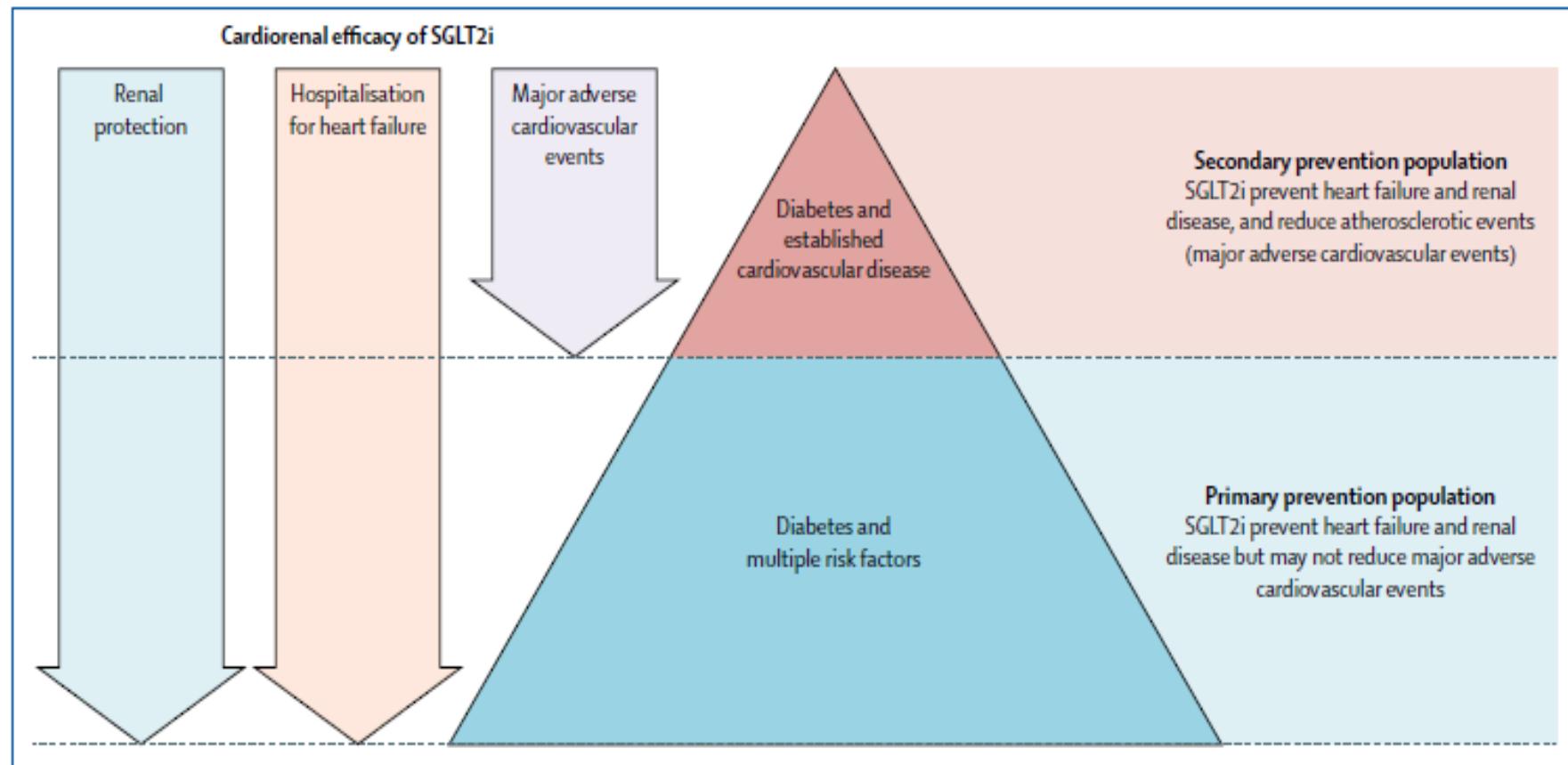


Figure: Cardiorenal benefits of SGLT2i in different patient populations

SGLT2i=sodium-glucose cotransporter-2 inhibitors.

LE NOVITÀ IN LETTERATURA

SGLT2-i e MALATTIA RENALE

CREDENCE STUDY

Original Report: Patient-Oriented, Translational Research



Am J Nephrol 2017;46:462–472
DOI: 10.1159/000484633

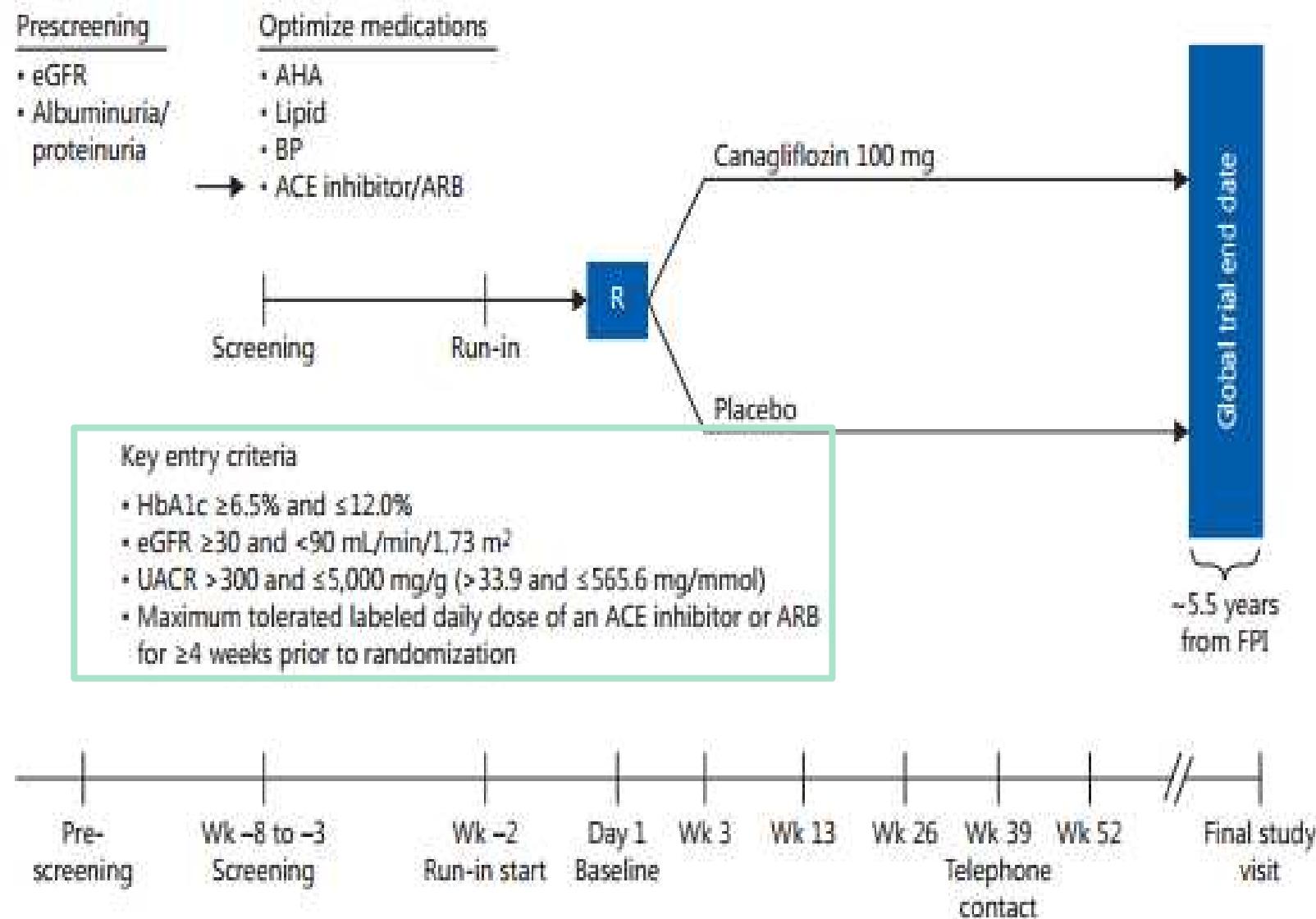
Received: September 22, 2017
Accepted: October 27, 2017
Published online: December 1, 2017

The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics

Meg J. Jardine^{a, b} Kenneth W. Mahaffey^c Bruce Neal^{a, d-f} Rajiv Agarwal^g
George L. Bakris^h Barry M. Brennerⁱ Scott Bull^j Christopher P. Cannon^k
David M. Charytan^l Dick de Zeeuw^m Robert Edwards^j Tom Greeneⁿ
Hiddo J.L. Heerspink^m Adeera Levin^o Carol Pollock^p David C. Wheeler^q
John Xie^j Hong Zhang^r Bernard Zinman^s Mehul Desai^j Vlado Perkovic^a
on behalf of the CREDENCE study investigators

- Studio randomizzato, doppio cieco, event-driven, placebo-controllato
- 695 centri diabetologici in 34 Paesi
- **4.401 T2DM**
- **Esclusi:** diabetici con nefropatia non diabetica, precedentemente trattati con immunosoppressori, dializzati o con precedente trapianto renale.
- **FU 5.5 anni**

CREDENCE STUDY



Telephone contact was made at midpoint between office visits after Wk 52.
Site visits were conducted at 26-week intervals after Wk 52.

CREDENCE STUDY – Baseline

Characteristic	Canagliflozin (N = 2202)	Placebo (N = 2199)	All Patients (N = 4401)
Age—yr	62.9±9.2	63.2±9.2	63.0±9.2
Female sex—no. (%)	762 (34.6)	732 (33.3)	1494 (33.9)
Hypertension—no. (%)	2131 (96.8)	2129 (96.8)	4260 (96.8)
Heart failure—no. (%)	329 (14.9)	323 (14.7)	652 (14.8)
Duration of diabetes—yr	15.5±8.7	16.0±8.6	15.8±8.6
Cardiovascular disease—no. (%)	1113 (50.5)	1107 (50.3)	2220 (50.4)
Blood pressure—mm Hg			
Systolic	139.8±15.6	140.2±15.6	140.0±15.6
Diastolic	78.2±9.4	78.4±9.4	78.3±9.4
Glycated hemoglobin—%	8.3±1.3	8.3±1.3	8.3±1.3
Estimated GFR—ml/min/1.73 m ²	56.3±18.2	56.0±18.3	56.2±18.2
Median urinary albumin-to-creatinine ratio (IQR)	923(459–1794)	931 (473–1868)	927 (463–1833)

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Median urinary albumin-to-creatinine ratio (IQR)	923(459–1794)	931 (473–1868)	927 (463–1833)

CREDENCE STUDY - Endpoint

Table 1. Prespecified efficacy and safety endpoints and evaluations of the CREDENCE study

<i>Primary and secondary efficacy endpoints</i>	
Primary endpoint	Composite of ESKD, doubling of serum creatinine, and renal or cardiovascular death
Secondary endpoints	Composite of cardiovascular death and hospitalized congestive heart failure Cardiovascular death All-cause death Renal composite endpoint of ESKD, doubling of serum creatinine, and renal death Cardiovascular composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalized congestive heart failure, and hospitalized unstable angina
Additional exploratory endpoints	Composite endpoint of ESKD and renal or cardiovascular death Individual components of the composite endpoints ESKD Doubling of serum creatinine Renal death Cardiovascular death Fatal and nonfatal MI Fatal and nonfatal stroke Hospitalized congestive heart failure Hospitalized unstable angina Change in eGFR over time Change in albuminuria over time

CREDENCE STUDY

Phase 3 CREDENCE Renal Outcomes Trial of INVOKANA® (canagliflozin) is Being Stopped Early for Positive Efficacy Findings

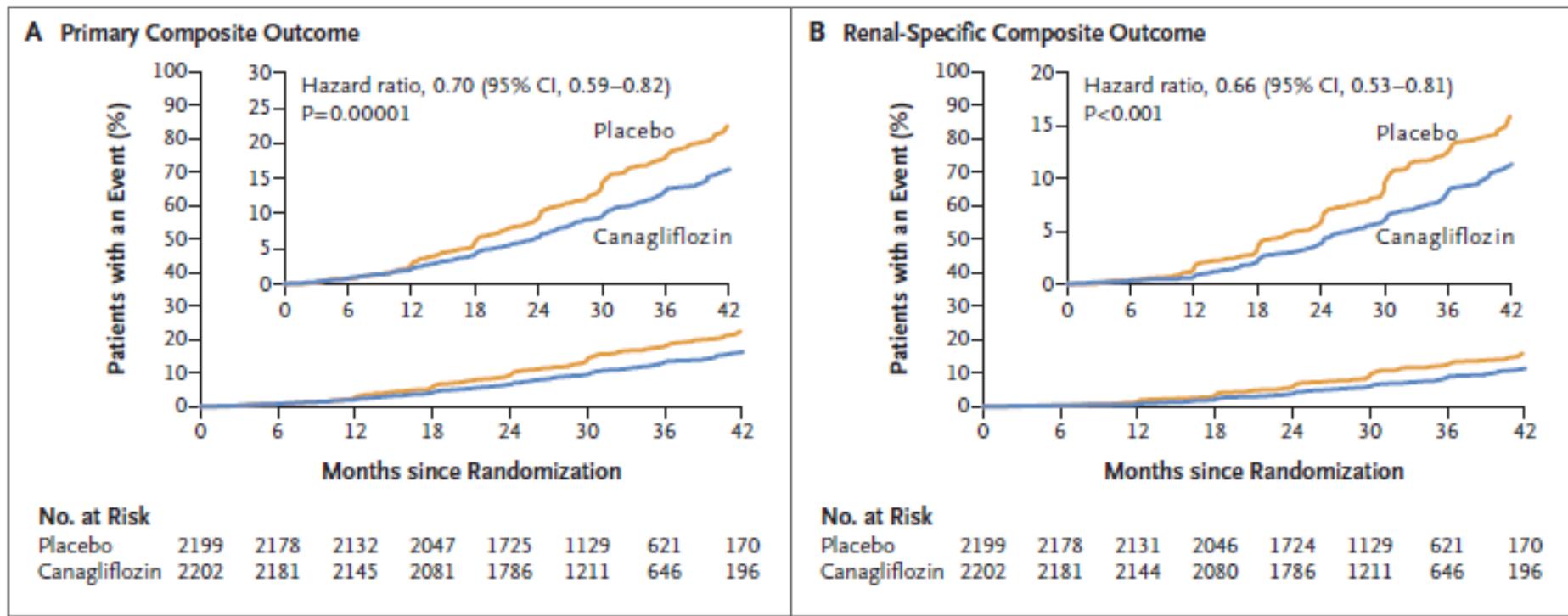
Published: Jul 16, 2018

- INVOKANA® has the potential to be the first new therapy in more than 15 years for slowing the progression of chronic kidney disease in patients with type 2 diabetes
- Worldwide, 160 million patients with type 2 diabetes are at risk for developing chronic kidney disease[i]
- CREDENCE assessed INVOKANA® for renal protection by evaluating the risk reduction of the composite endpoint of time to dialysis or kidney transplantation, doubling of serum creatinine and renal or cardiovascular death, when used in addition to standard of care

RARITAN, N.J., July 16, 2018 /PRNewswire/ -- The **Janssen Pharmaceutical Companies of Johnson & Johnson** today announced that the Phase 3 CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) clinical trial, evaluating the efficacy and safety of INVOKANA® (canagliflozin) versus placebo when used in addition to standard of care for patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), is being stopped early based on the achievement of pre-specified efficacy criteria.

The decision is based on a recommendation from the study's Independent Data Monitoring Committee (IDMC) that met to review the data during a planned interim analysis. This recommendation was based on demonstration of efficacy, as the trial had achieved pre-specified criteria for the primary composite endpoint of end-stage kidney disease (time to dialysis or kidney

CREDENCE STUDY - Results



-30%

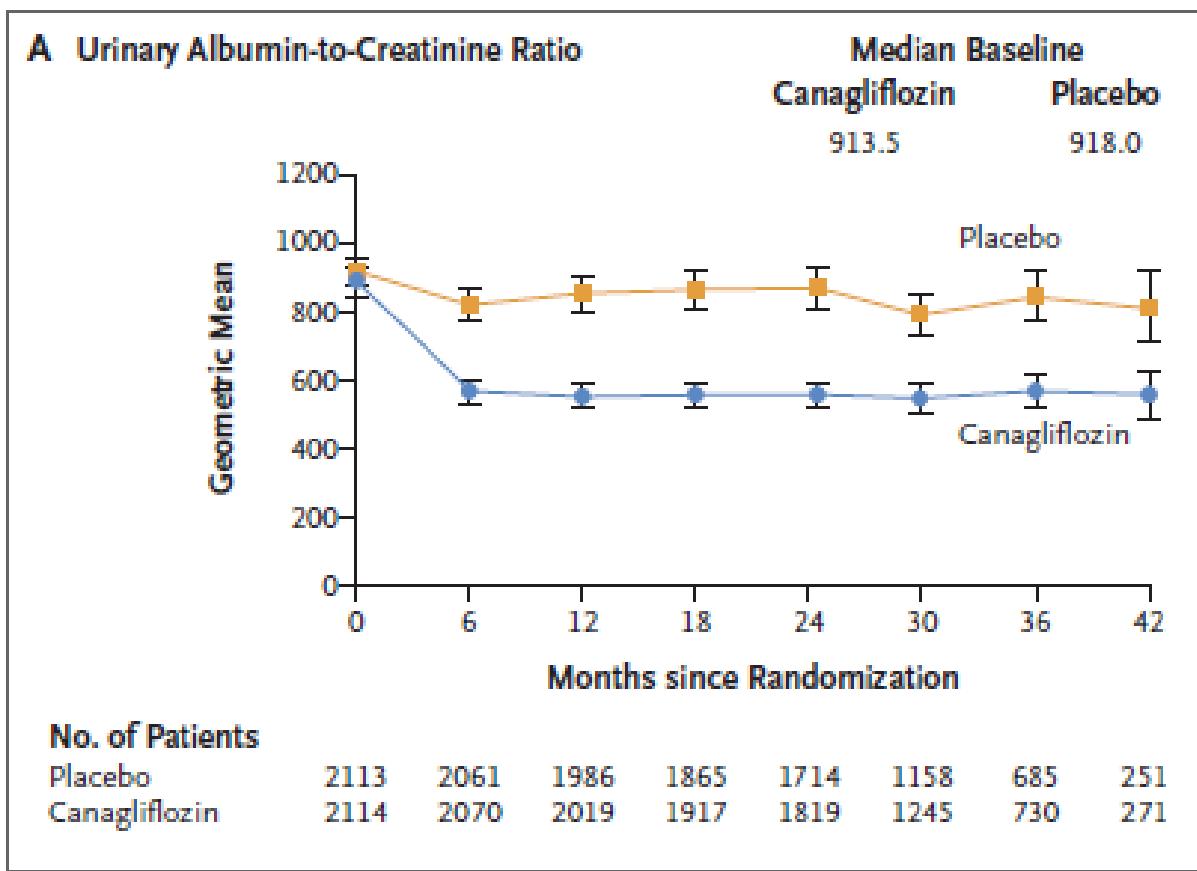
composite outcome of end-stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular

-34%

endstage kidney disease, doubling of serum creatinine level, or renal death.

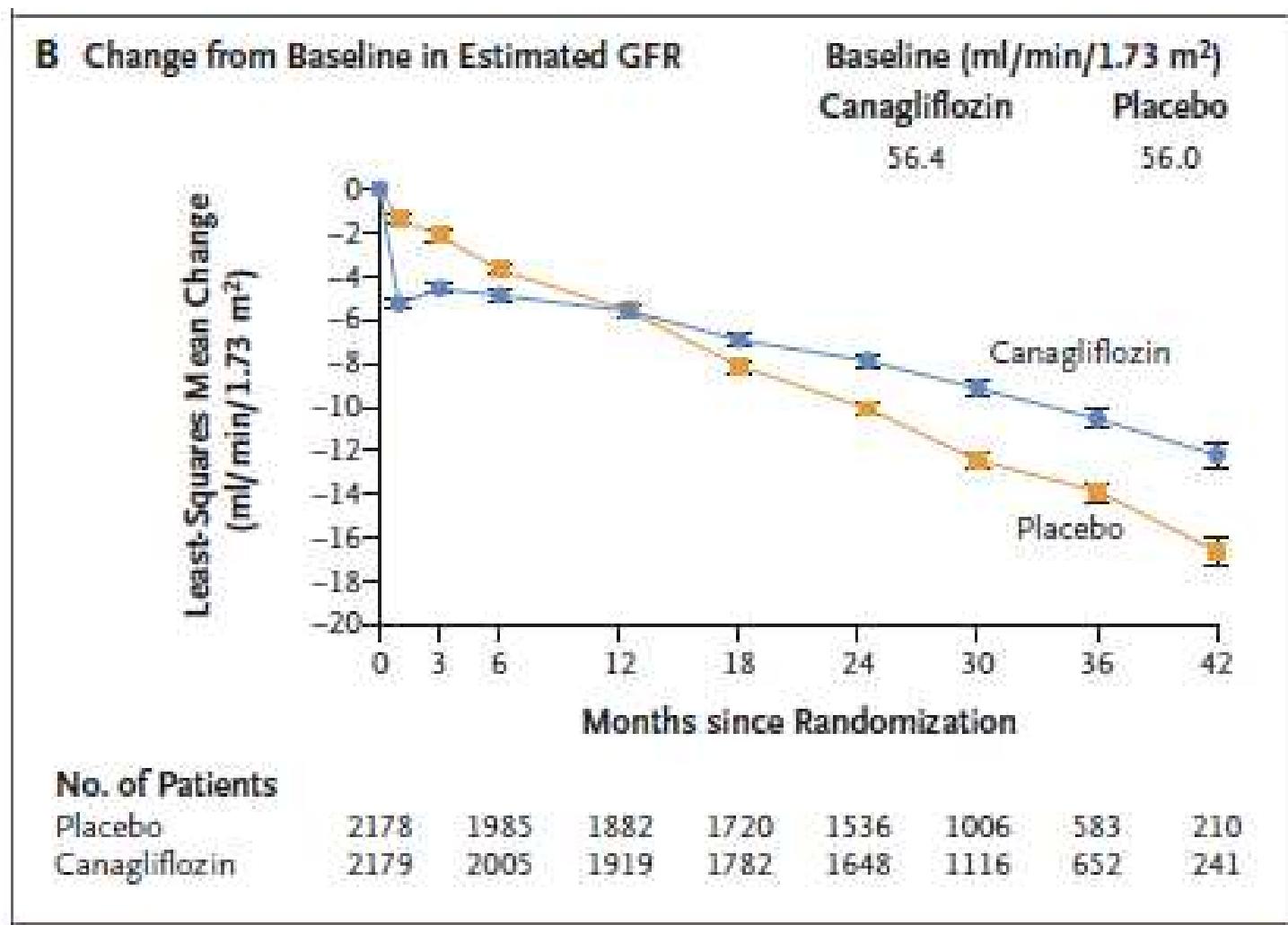
CREDENCE STUDY - Results

Effects on Albuminuria and Estimated GFR

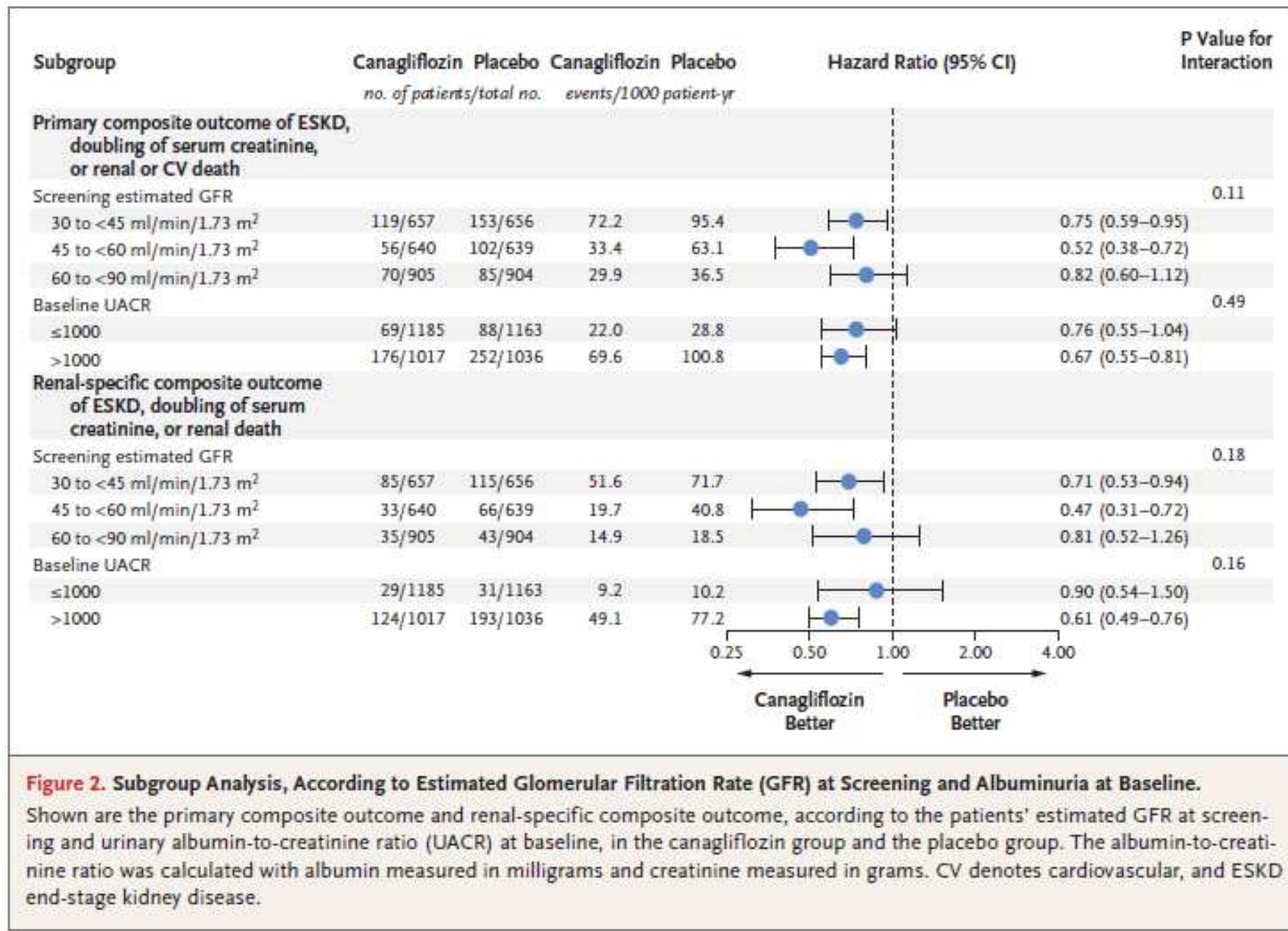


CREDENCE STUDY - Results

Effects on Albuminuria and Estimated GFR

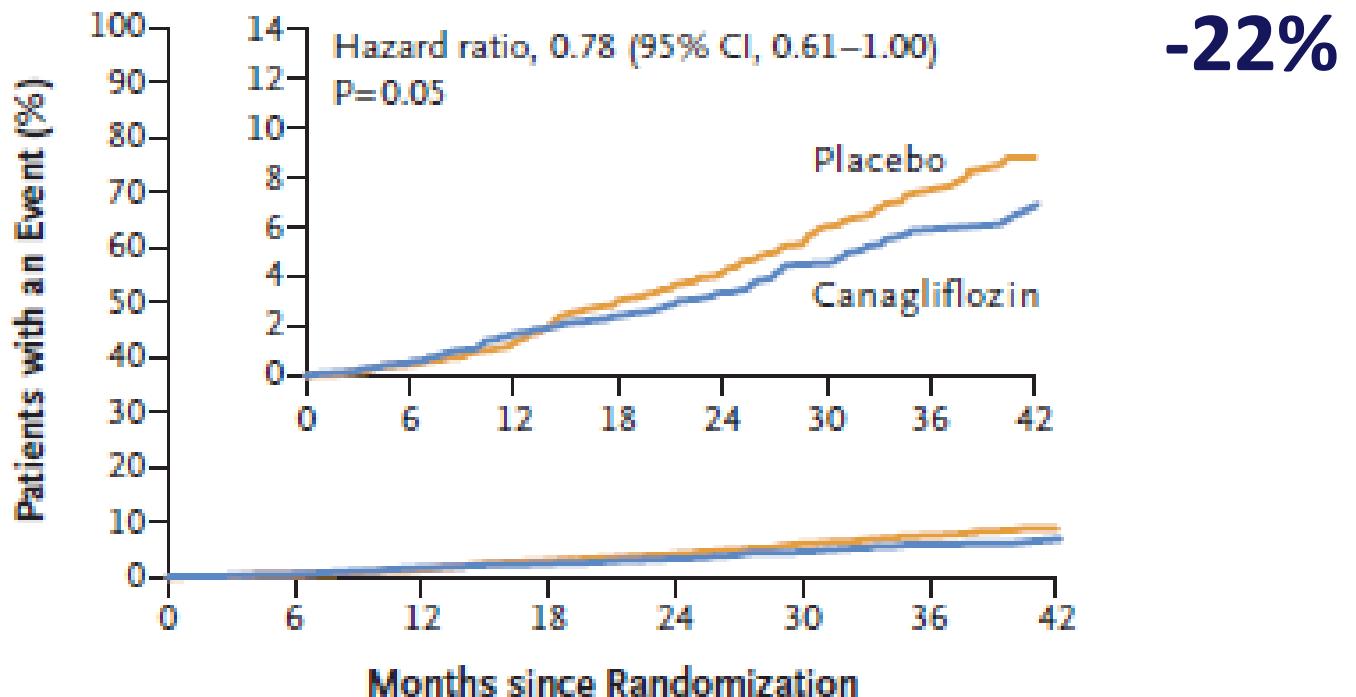


CREDENCE STUDY - Results



CREDENCE STUDY - Results

E Death from Cardiovascular Cause



No. at Risk

	Placebo	2199	2185	2160	2106	1818	1220	688	189
Canagliflozin	2202	2187	2155	2120	1835	1263	687	212	

CREDENCE STUDY - Summary

Primary	Hazard ratio (95% CI)	P value	
1. ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59–0.82)	0.00001	✓
Secondary			
2. CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001	✓
3. CV death, MI, or stroke	0.80 (0.67–0.95)	0.01	✓
4. Hospitalization for heart failure	0.61 (0.47–0.80)	<0.001	✓
5. ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001	✓
6. CV death	0.78 (0.61–1.00)	0.0502	Not significant
7. All-cause mortality	0.83 (0.68–1.02)	–	Not formally tested
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	–	Not formally tested

CREDENCE STUDY - Results

Table 2. NNT for the Primary Composite Outcome and Select Cardiovascular Outcomes in the Primary and Secondary Prevention Cohorts and Overall Population

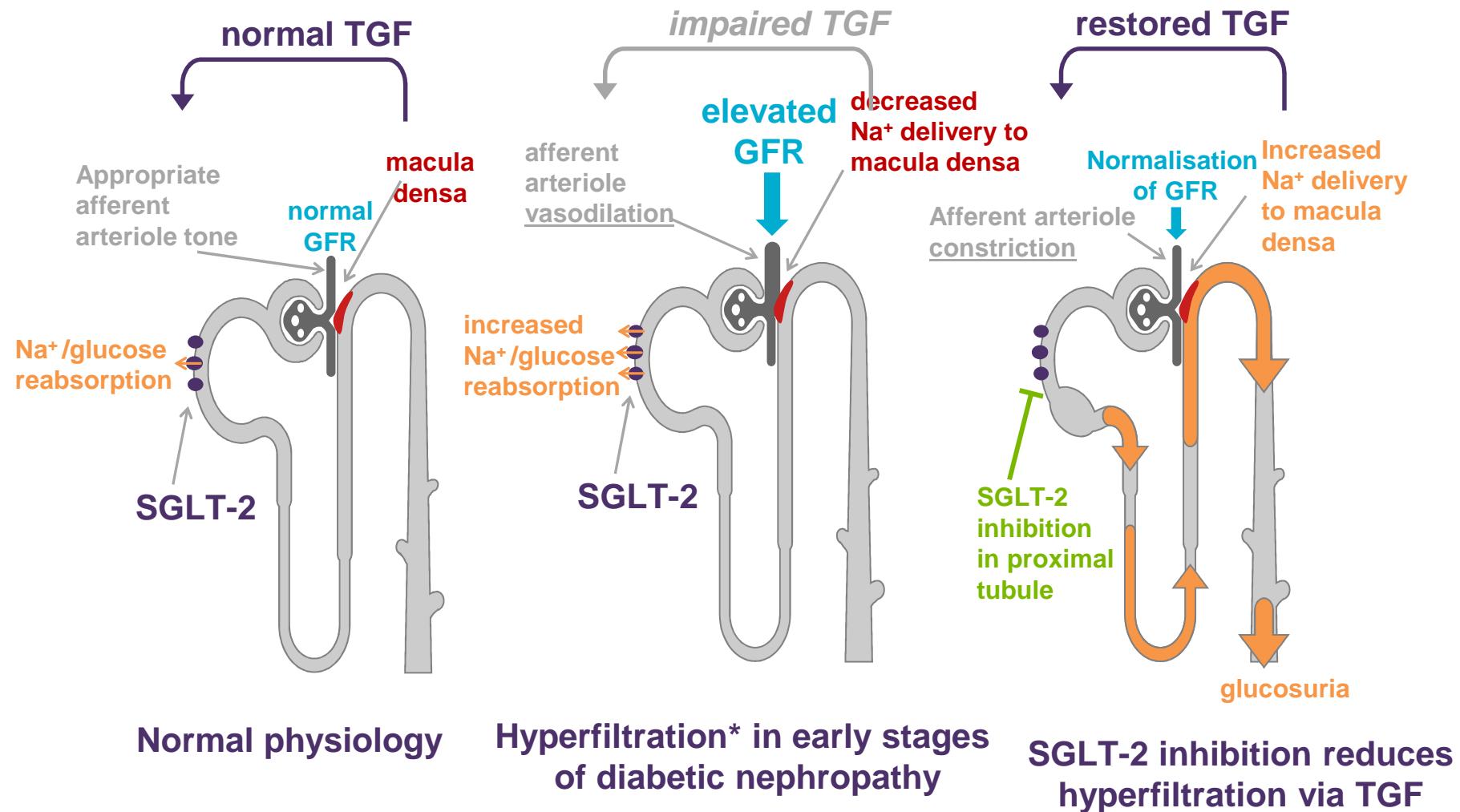
	NNT for 2.5 y (95% CI)		
	Primary Prevention	Secondary Prevention	Overall
End-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death	19 (12–40)	26 (15–96)	22 (15–38)
Cardiovascular death or hospitalization for heart failure	53*	21 (13–47)	29 (20–61)
Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	36 (20–186)	44*	40 (23–165)

NNT indicates number needed to treat.

*The 95% CI for NNT is not provided when the 95% CI for absolute risk reduction at 2.5 years includes 0.

- 2181 participants (49.6%) had no history of documented cardiovascular disease at entry (the primary prevention group),
- 2220 participants (50.4%) were in the secondary prevention group.

Regularization of the tubuloglomerular feedback and hyperfiltration reduction with SGLT2i



*Renal hyperfiltration: $\text{GFR} \geq 135 \text{ mL/min}/1.73\text{m}^2$. GFR, glomerular filtration rate; TGF, tubuloglomerular feedback mechanism.

Modified from: Cherney DZ, et al. Circulation 2014; 129:587-97

DAPA-HF STUDY

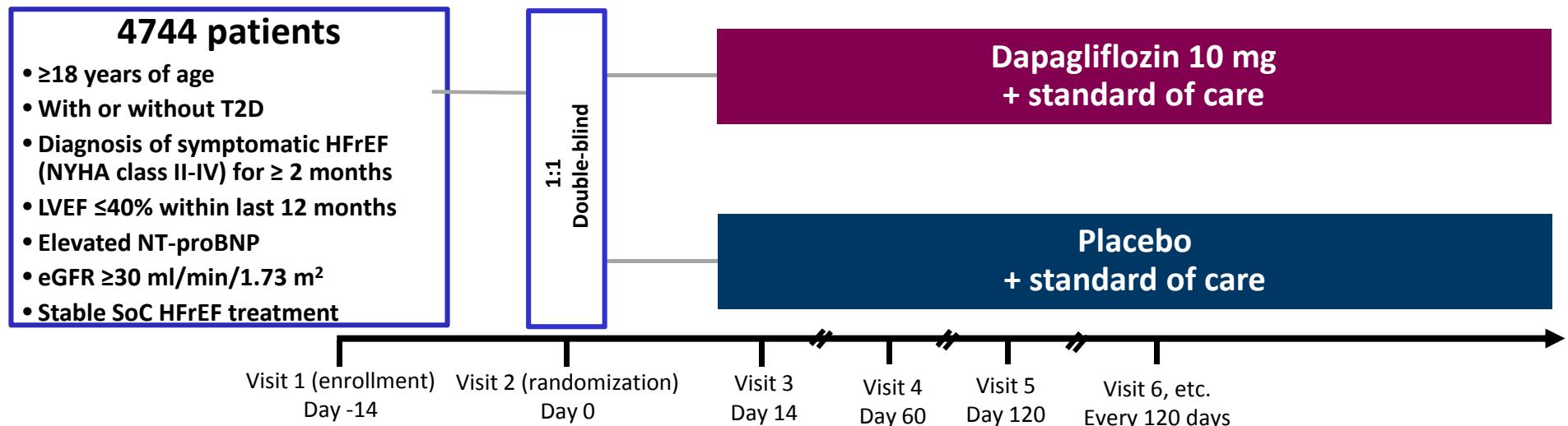
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod,
F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm,
C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozd, A. Dukát,
J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau,
E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma,
C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand,
and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

DAPA-HF STUDY



Primary Endpoint

- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit

Target primary endpoint events: 844¹
Median follow-up: 18.2 months²
Completion: July 2019³

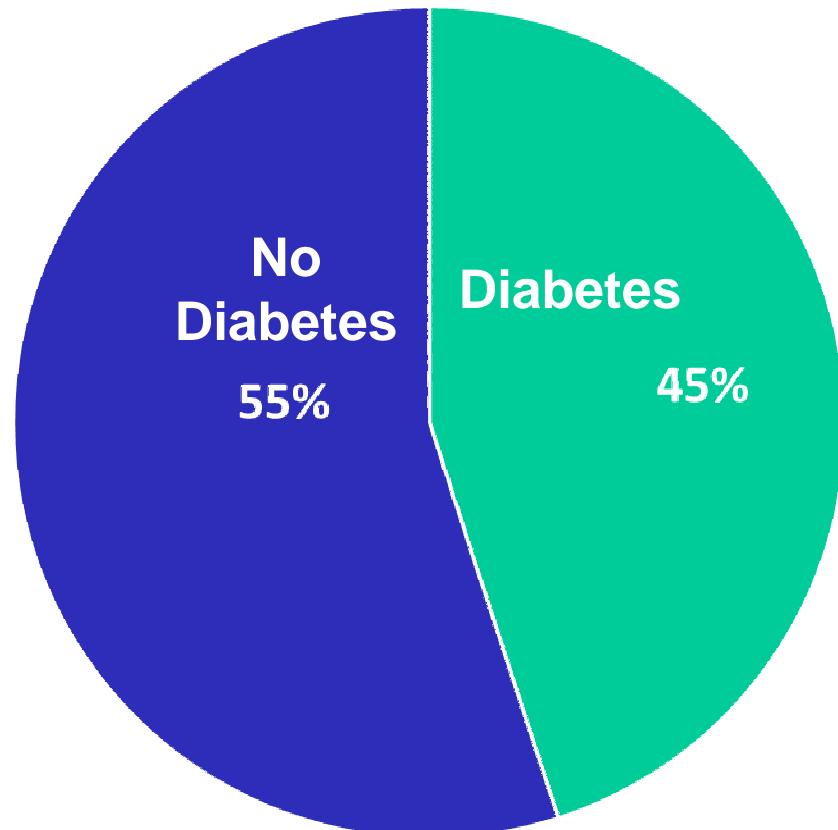
Secondary Endpoints

- Time to first occurrence of either of the components of the composite: CV death or hHF
- Total number of (first and recurrent) hHF and CV death
- Change from baseline measured at 8 months in the total symptom score of the KCCQ
- Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD or renal death
- Time to death from any cause

DAPA-HF STUDY

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/mL)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (mL/min/1.73m ²)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%) ^a	45	45

Majority of Patients in DAPA-HF did not have Type 2 Diabetes



N=4744

History of Diabetes (n=2137)

- Pre-existing diagnosis of T2D: (42%; n=1983)
- Previously undiagnosed T2D: HbA1c $\geq 6.5\%$ at Visits 1 and 2 (3%; n=154)

No Diabetes (n=2607)

- Prediabetes: HbA1c ($\geq 5.7^*$ to $<6.5\%$) at Visits 1 and 2 (37%; n=1750)
- Euglycemic: HbA1c $<5.7\%$ at Visits 1 and 2 (18%; n=857)

*ADA guidelines define prediabetes as A1C 5.7 to 6.4%²

HbA1c = glycated hemoglobin; T2D = type 2 diabetes.

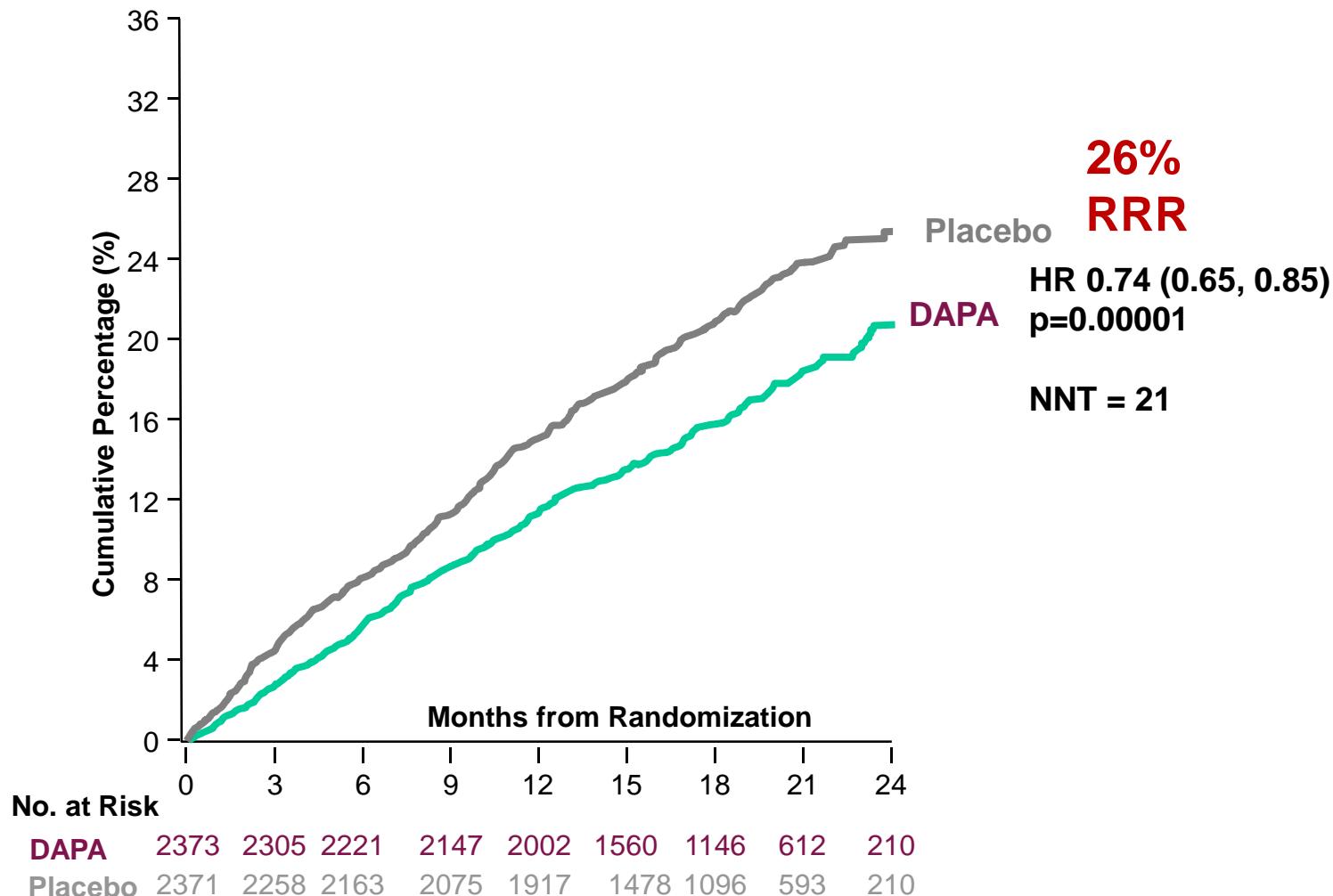
1. McMurray J JV et al. Article and supplementary appendix. *Eur J Heart Fail.* 2019;doi: 10.1002/ejhf.1548. Accessed August 21, 2019. 2. ADA Standards of Care. *Diabetes Care.* 2019; 42(Supplement 1):S1-S193.



DAPA-HF STUDY

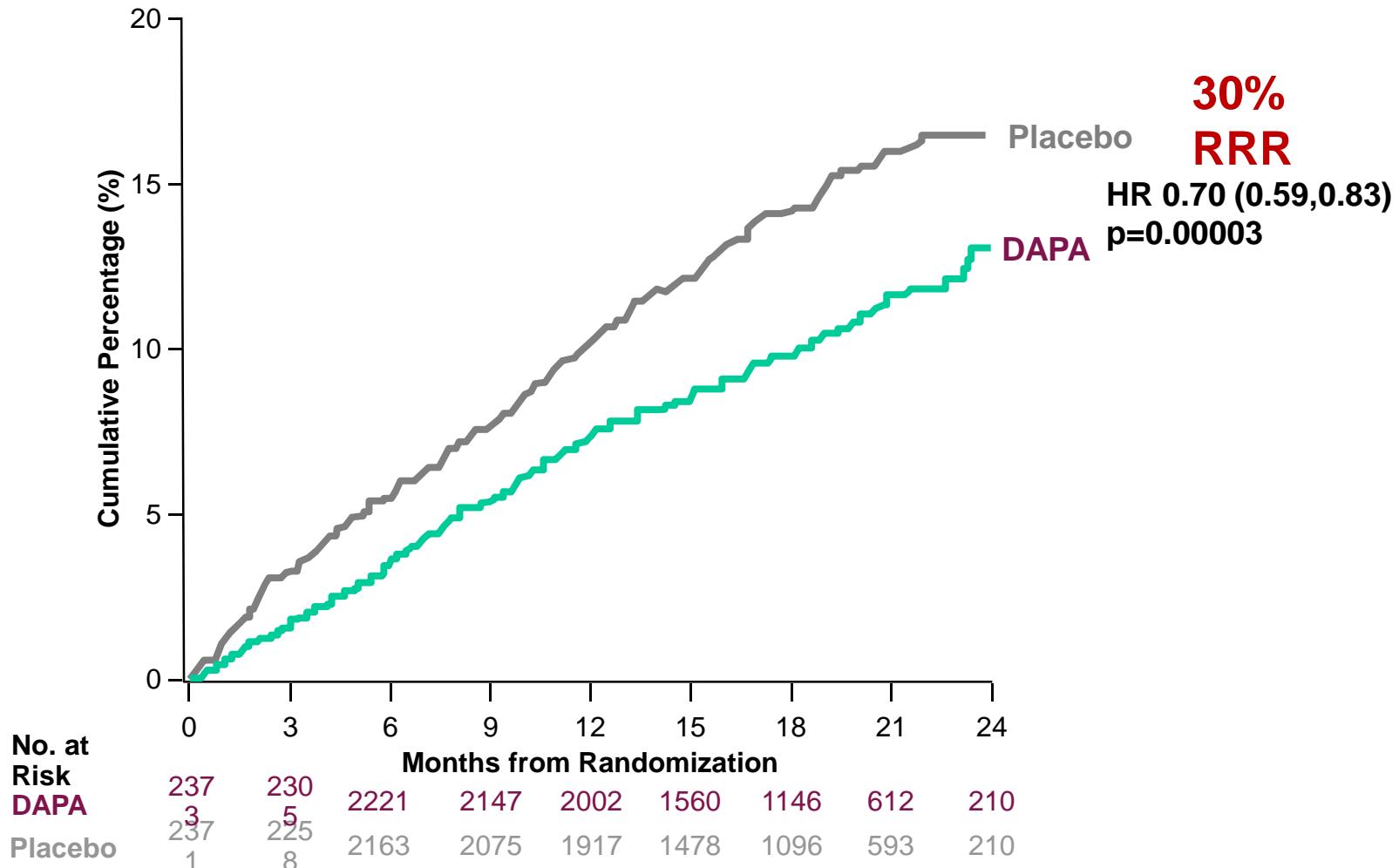
Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

Primary Endpoint: CV Death or hHF or an Urgent HF Visit¹



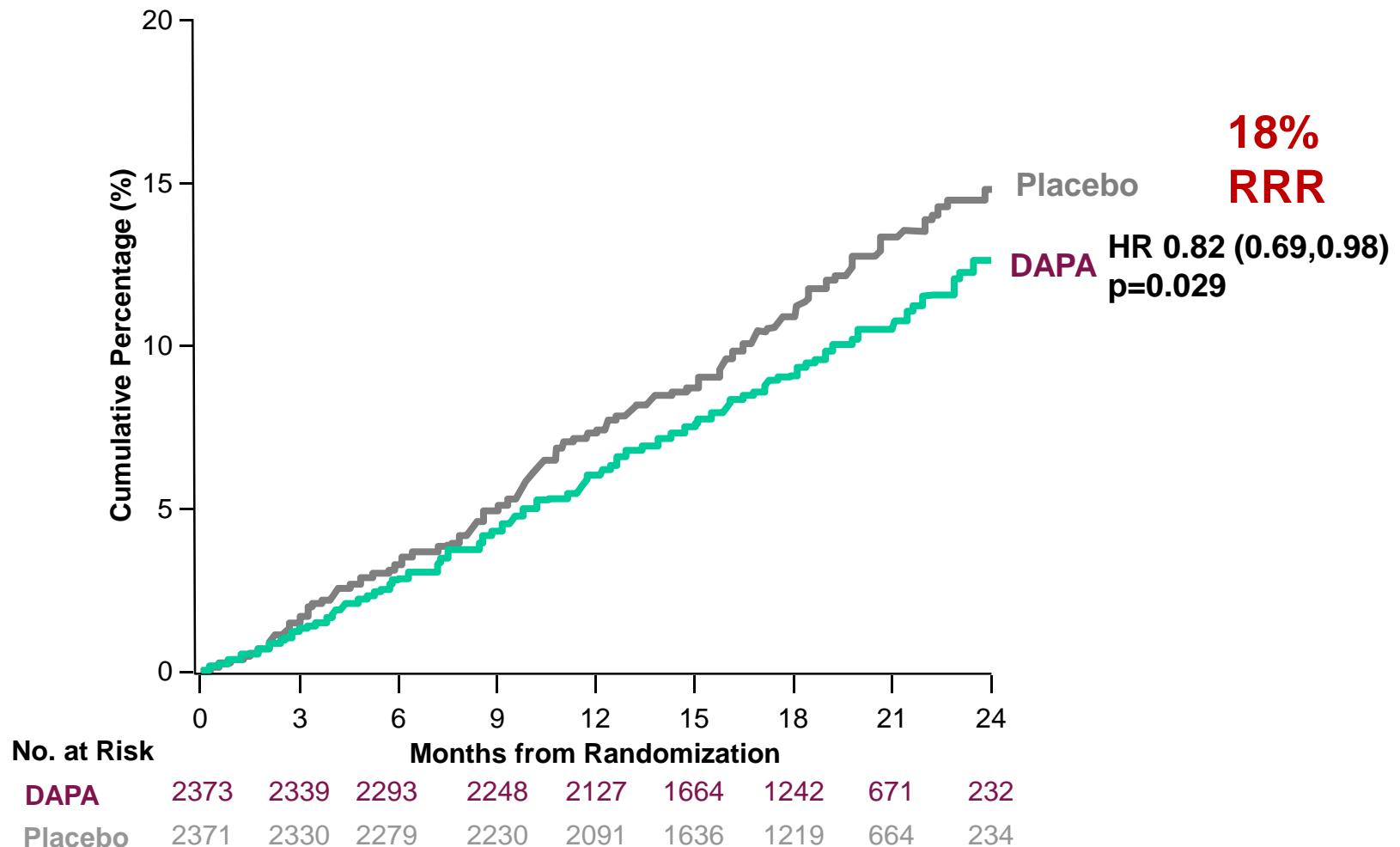
DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat.

Component of Primary Endpoint: Worsening HF Event



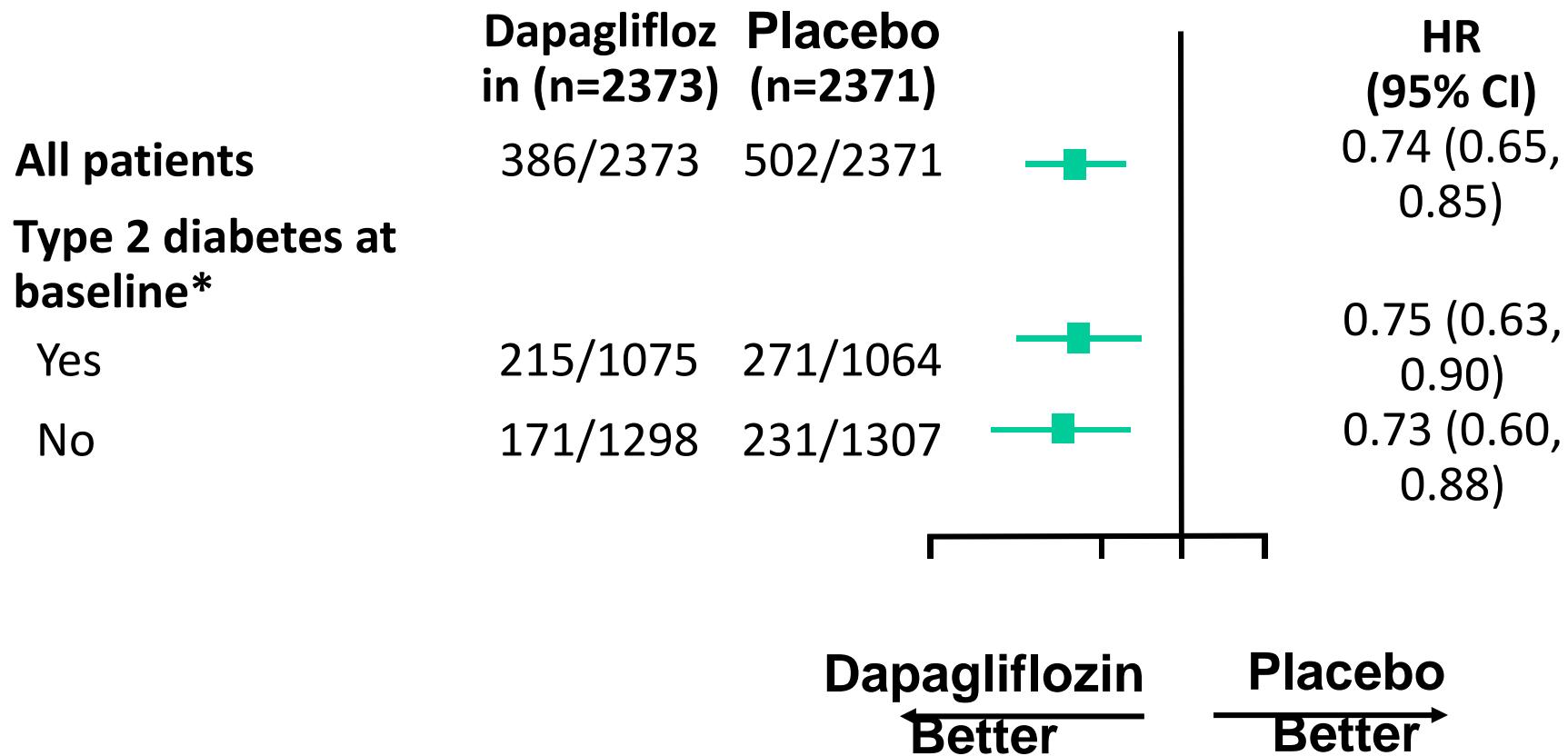
DAPA = Dapagliflozin; HF = Heart failure; HR = Hazard ratio.

Component of Primary Endpoint: Cardiovascular Death



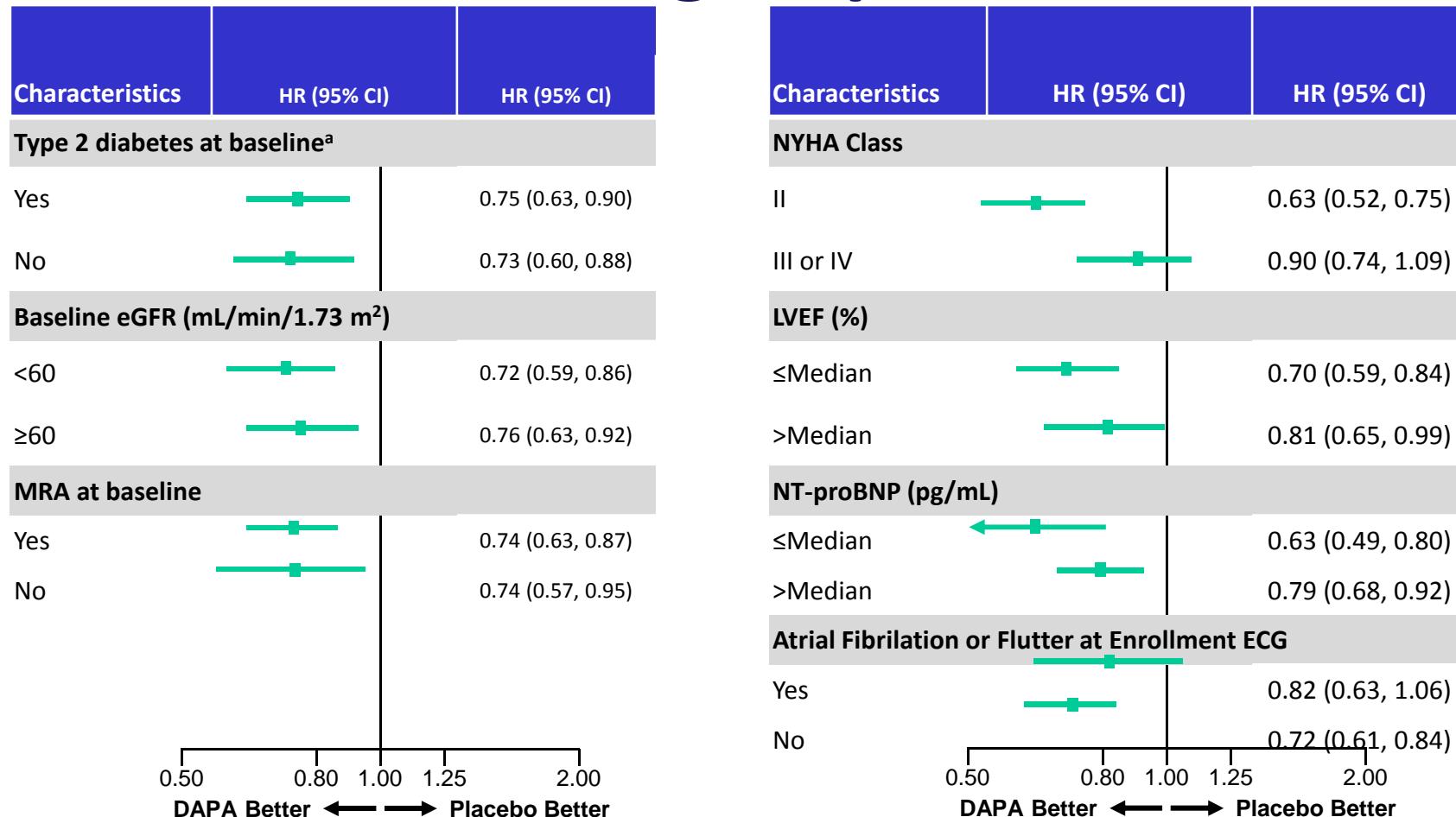
DAPA = Dapagliflozin; HR = Hazard ratio.

Primary Endpoint: Subgroup of Patients with and without T2D



*Prespecified subgroup; defined as history of type 2 diabetes or HbA1c $\geq 6.5\%$ at both enrollment and randomization visits

Primary Endpoint: Prespecified Subgroups



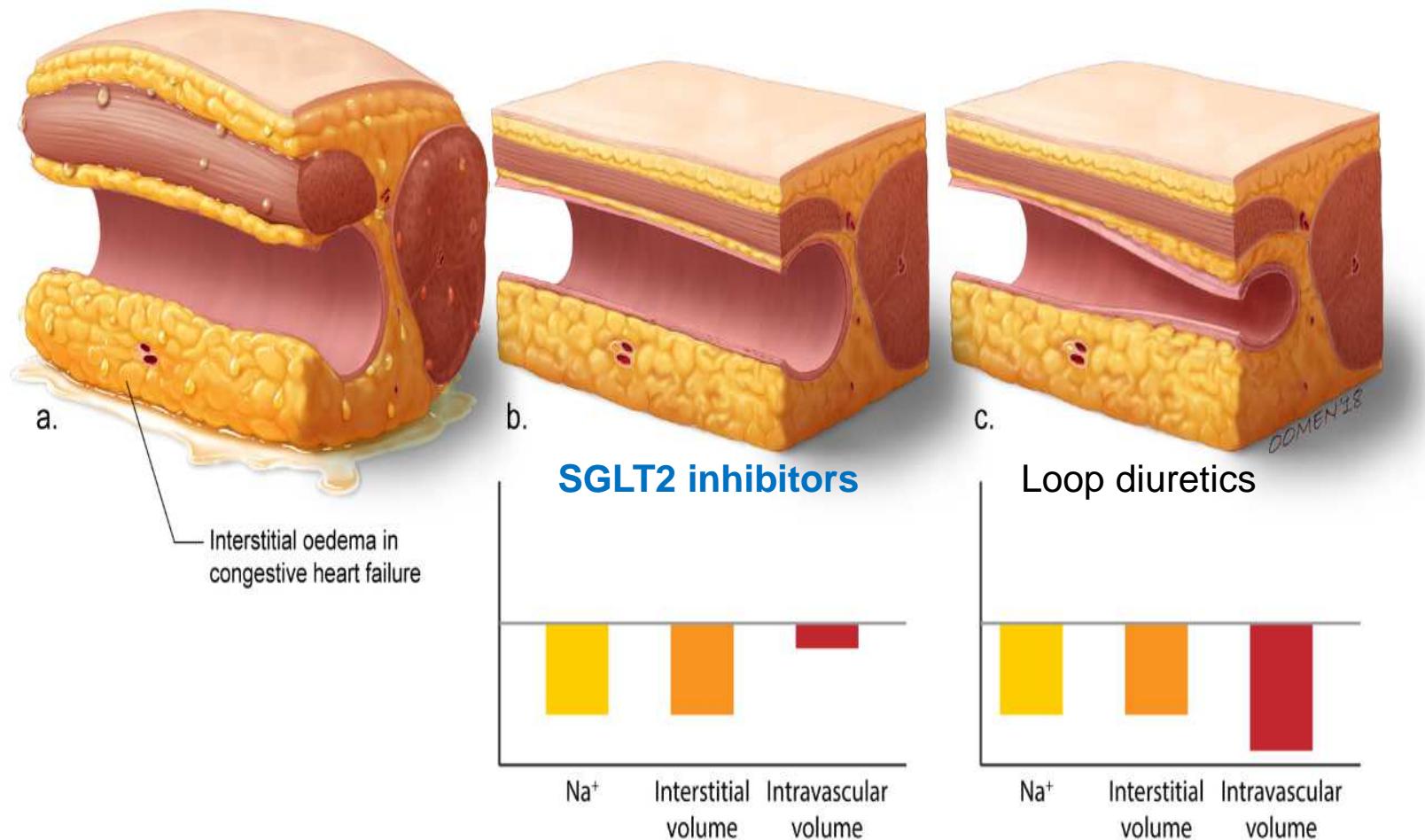
A selection of subgroups is presented above.

^aDefined as history of T2DM or HbA1c ≥6.5% at both enrollment and randomization visits.

DAPA = dapagliflozin; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MRA = mineralocorticoid receptor antagonist; NT pro BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction.

McMurray JJV et al. *N Engl J Med*. 2019. <https://doi.org/10.1056/NEJMoa1911303>. Accessed September 19, 2019.

In contrast to loop diuretics, SGLT2 inhibitors reduce interstitial volume more than intravascular volume

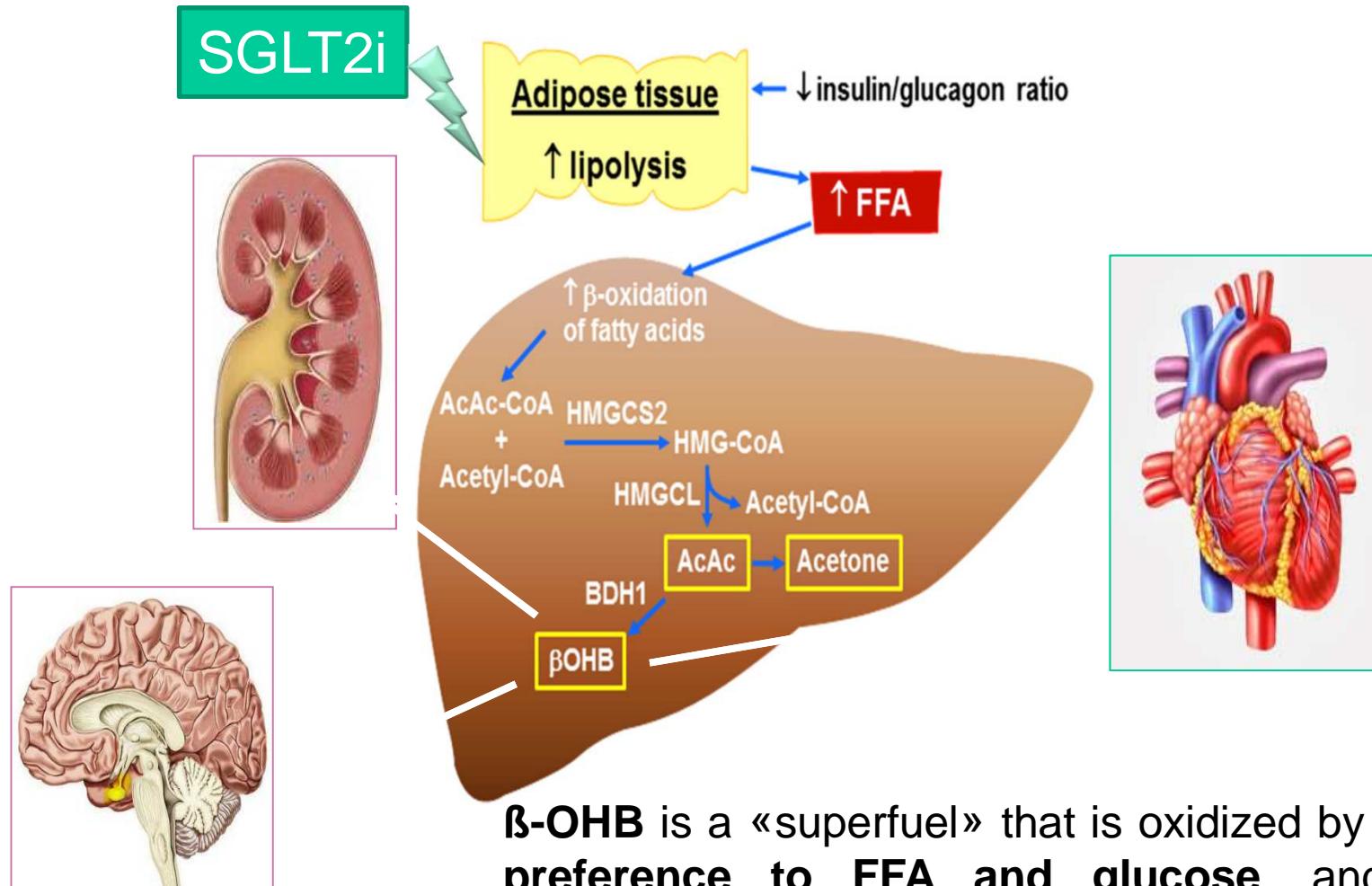


SGLT2, sodium-glucose cotransporter 2.

Verma S, McMurray JJV. *Diabetologia*. 2018;61:2108-2117.

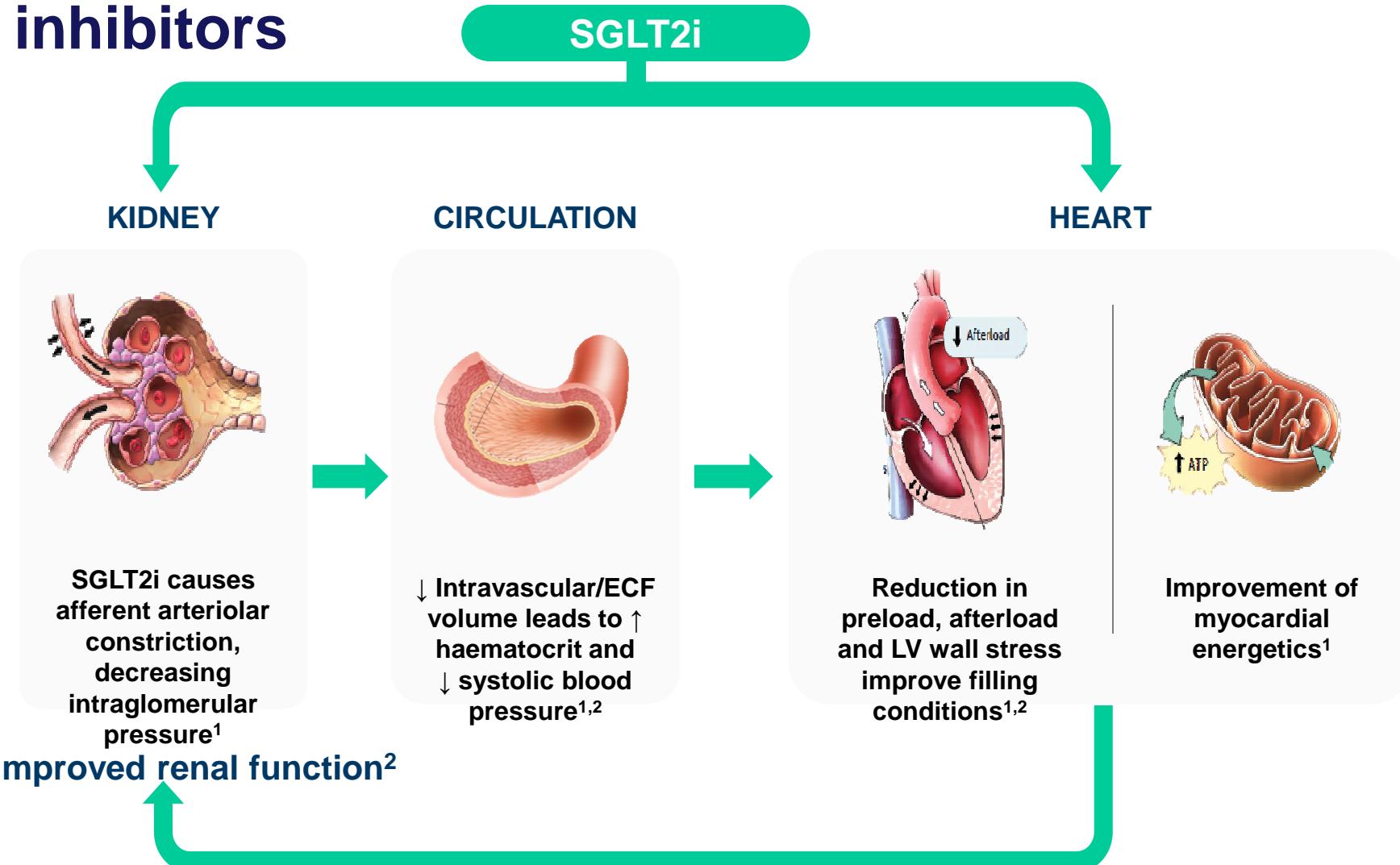
The Thrifty Substrate Hypothesis

(Ferrannini et al. 2016; Mudaliar et al., 2016)



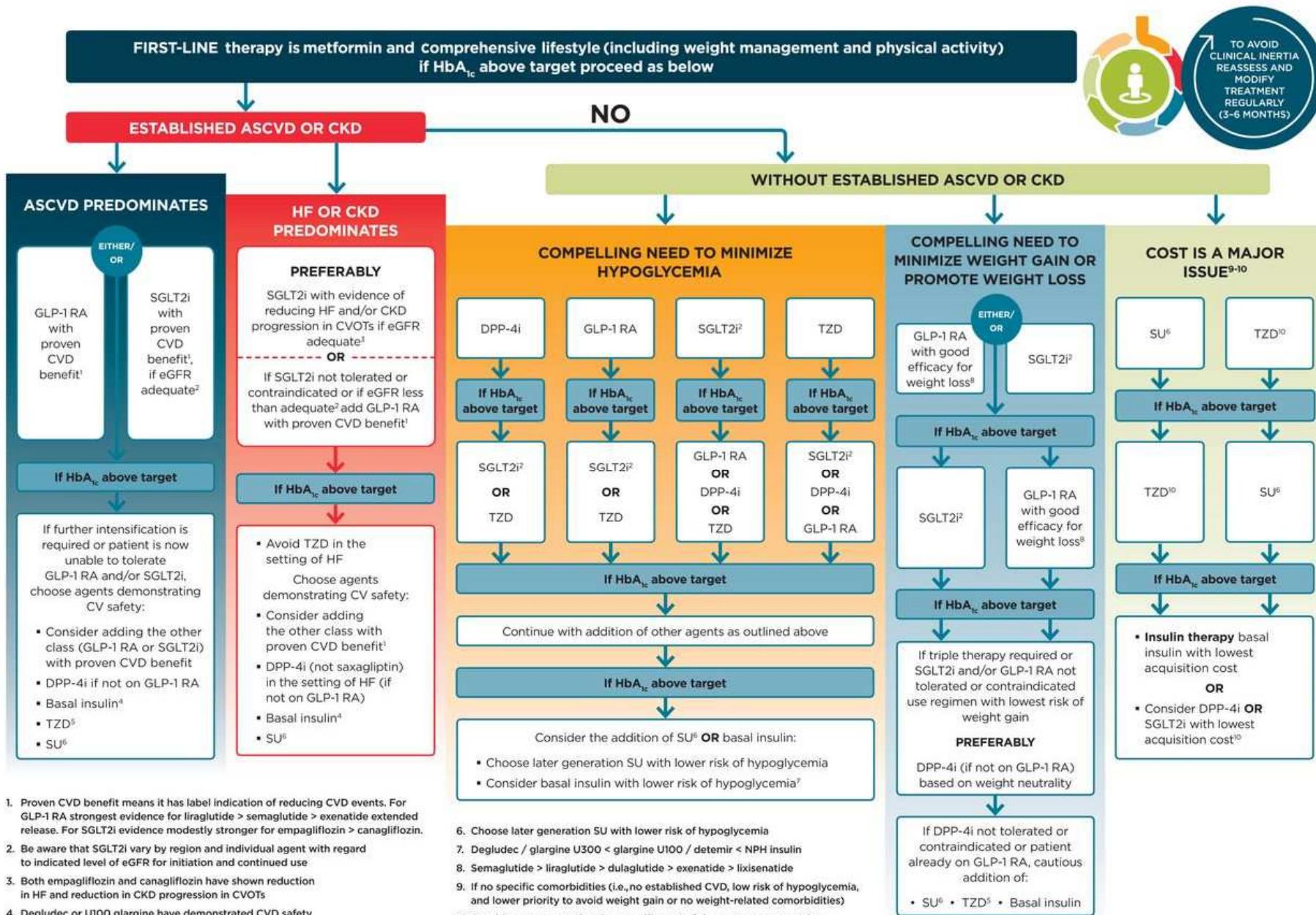
β-OHB is a «superfuel» that is oxidized by the heart **in preference to FFA and glucose**, and not only improves cardiac function in the failing heart, but also increases mechanical efficiency.

There are a number of putative mechanisms to explain cardiorenal protection with SGLT2 inhibitors



ECF, extracellular fluid; LV, left ventricular; SGLT2, sodium-glucose cotransporter 2.

1. Verma S, et al. *JAMA Cardiol*. 2017;2:939-940. 2. Sattar N, et al. *Diabetologia*. 2016;59:1333-1339.



2019 ESC/EASD Guidelines on diabetes and CVD

Target 1

Target 2

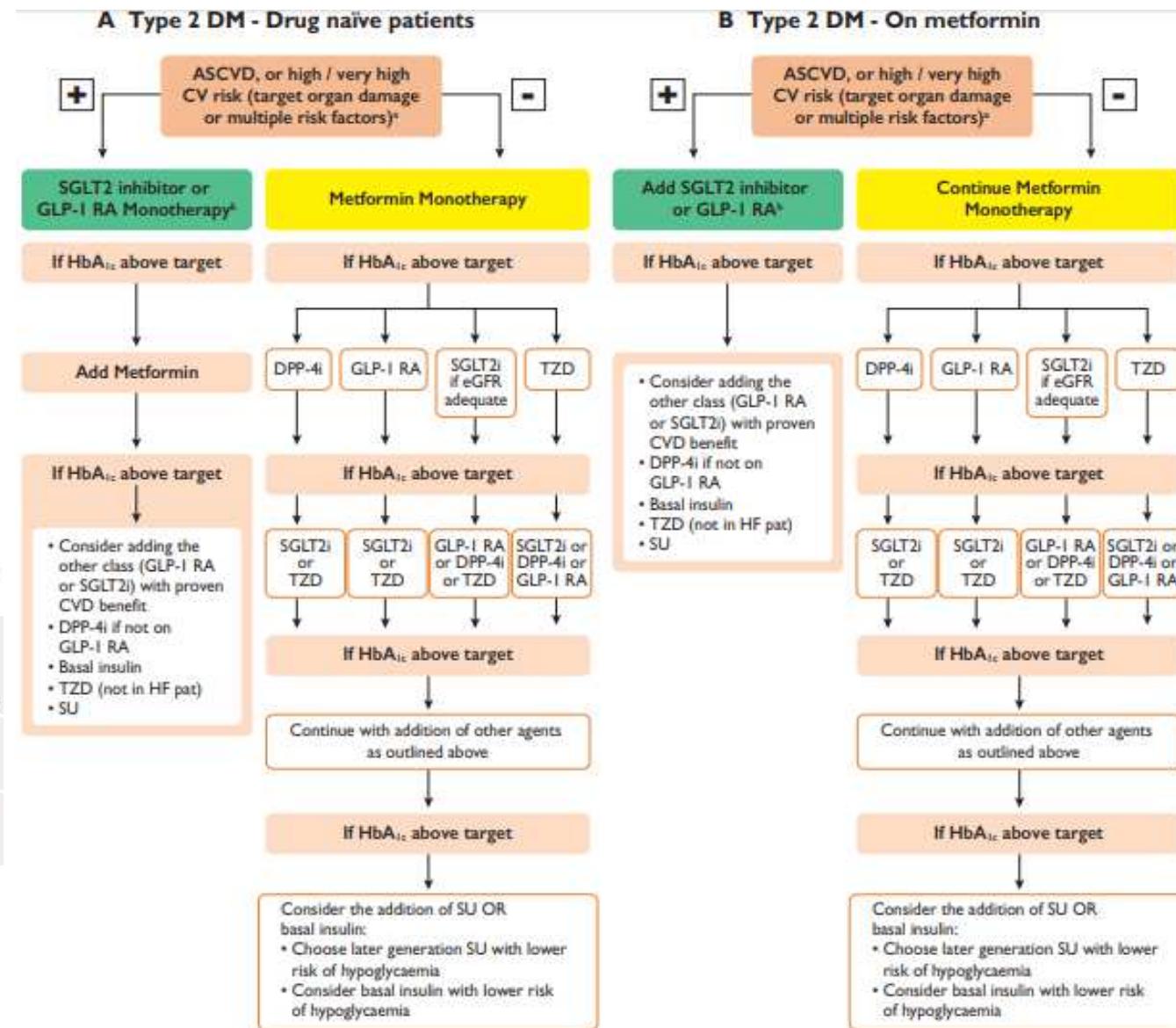


Table 7 Cardiovascular risk categories in patients with diabetes^a

Very high risk	Patients with DM and established CVD or other target organ damage ^b or three or more major risk factors ^c or early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration \geq 10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

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

^aModified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.²⁷

^bProteinuria, renal impairment defined as eGFR \geq 30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy.

^cAge, hypertension, dyslipidemia, smoking, obesity.

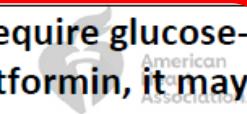
Treatment DM2 in primary prevention of CVD

Recommendations for Adults With Type 2 Diabetes Mellitus

Referenced studies that support recommendations are summarized in [Online Data Supplement 10](#).

COR	LOE	Recommendations
I	A	<ol style="list-style-type: none">1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-1, S4.2-2).
I	A	<ol style="list-style-type: none">2. Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-3, S4.2-4).
IIa	B-R	<ol style="list-style-type: none">3. For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk (S4.2-5–S4.2-8).
IIb	B-R	<ol style="list-style-type: none">4. For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk (S4.2-9–S4.2-14).

Arnett et al. 2019 ACC/AHA Guideline
on the Primary Prevention of Cardiovascular Disease



FINE



*«La medicina è la sola professione che lotta
incessantemente per distruggere la ragione della
propria esistenza»*

Attribuita a
James Bryce (1838 – 1922),
giurista, storico e politico britannico