Actotalk In Tabriz

Sept, 2021

ACTOVERCO

Together for a healthy future

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Case (1)

- 48 y/o woman
- Admitted to the hospital
- CC: Chest pain
- Middle income
- **PMHx:**
  - Smoker
  - History of gestational diabetes
  - Positive family history of T2DM, MI, and Stroke

- **PE: On the day of admission**
  - BP: 198/101 mmHg
  - HR: 122 bpm
  - Oral temp.: 37.4 °C
  - BW: 116 kg
  - BH: 167 cm
  - BMI: 41.4
  - Electrocardiogram (-) for MI
  - (-) cardiac enzymes

Lab test on admission day

Lab Test
HbA1c: 9.5%; Random Blood Glu: 310 mg/dL
Cr: 1.5 mg/dl
LFT: AST: 19 - ALT: 26
TSH : Normal
TG:250 mg/dl , LDL: 141 mg/dl HDL: 22 mg/dl
BUN: 35 mg/dL, U/A Albumin: negative

Blood Glucose Follow-up

- Patient is admitted for a cardiac catheterization and further cardiac work-up. Her blood glucose was controlled by insulin (rapid acting). She stayed for 4 day. On hospital day 3, the patient awakened with a blood glucose level of 248 mg/dL. Her physician initiated basal insulin to obtain better glucose control.Her angiogram showed normal epicardial coronary artery and she was cleared for discharge by her cardiologist, but her primary care physician would prefer to monitor her glucose levels for one more day, including her two-hour postprandial level after her evening meal. Throughout the day, the following blood glucose levels were documented:
  - 7 a.m.: 248 mg/dL
  - 11 a.m.: 121 mg/dL
  - 5 p.m.: 118 mg/dL
  - 7 p.m. (two-hour postprandial): 210 mg/dL
  - 9 p.m.: 178 mg/dL
- The following morning, the patient was discharged to home with prescription on oral antidiabetics.

A1C Goal of Therapy

10-year risk of heart disease or stroke

43.7%

What antidiabetic(s) should be started in the first place?

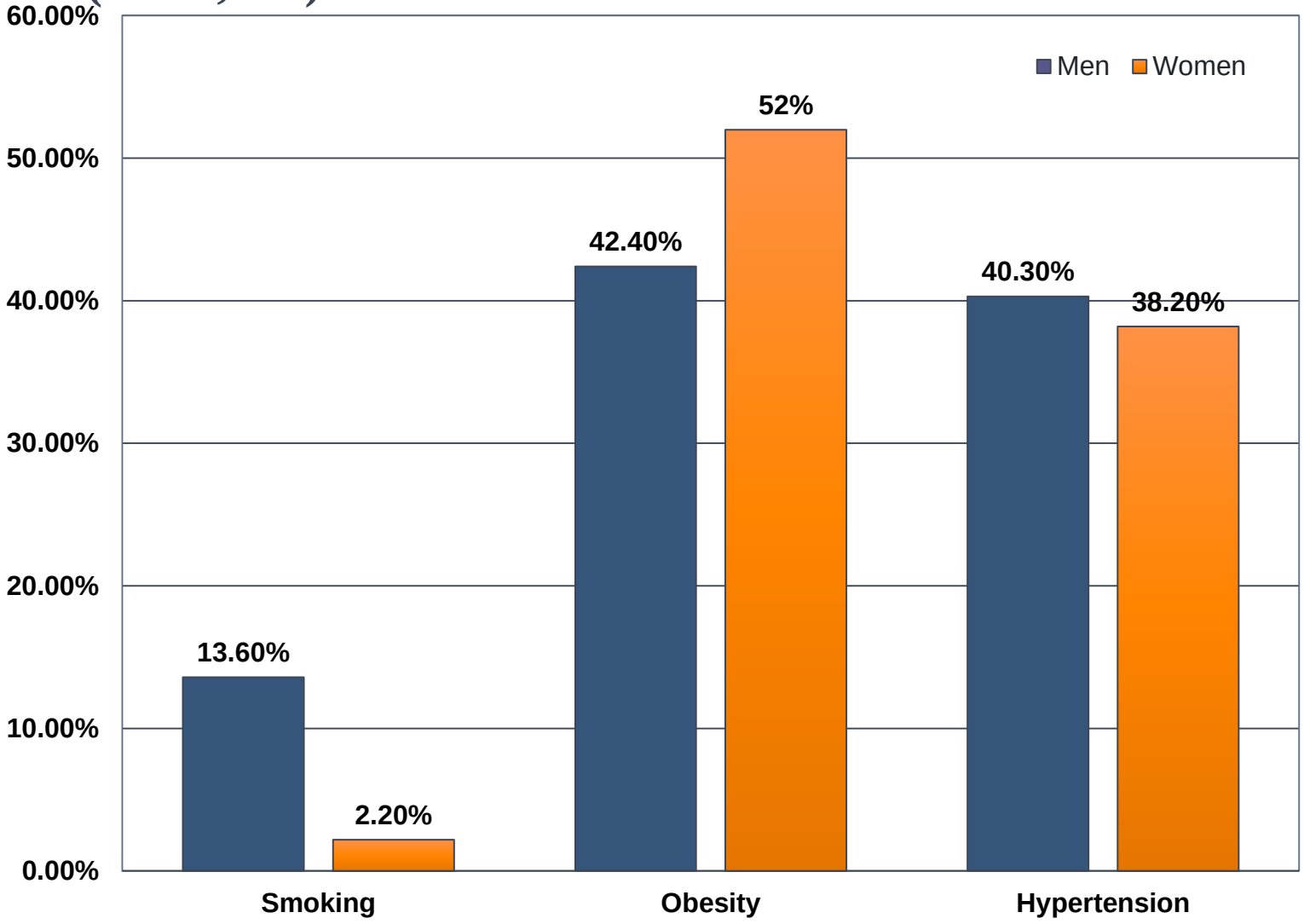
Which one?

Along side of life style modification (calorie restriction and increasing physical activity):

1. **Start with Metformin 500 mg BD then add Empagliflozin 10 mg/day or change to Metformin/Empagliflozin (500/5) BD**
2. **Start with Empagliflozin Plus (500/5) BD then increase to Empagliflozin Plus (1000/5) BD**
3. **Start with Empagliflozin plus (500/5) BD then add Sitagliptin 50 mg/day**
4. **Start with Metformin 500 mg BD and Liraglutide**
5. **Start with Metformin 500 mg BD and Liraglutide then add Empagliflozin 10 mg/day**
6. **Start with Glibenclamide 5 mg/day**
7. **Start with Gliclazide MR 30 mg/day then increase the dose or add Metformin**
8. **Other options?**

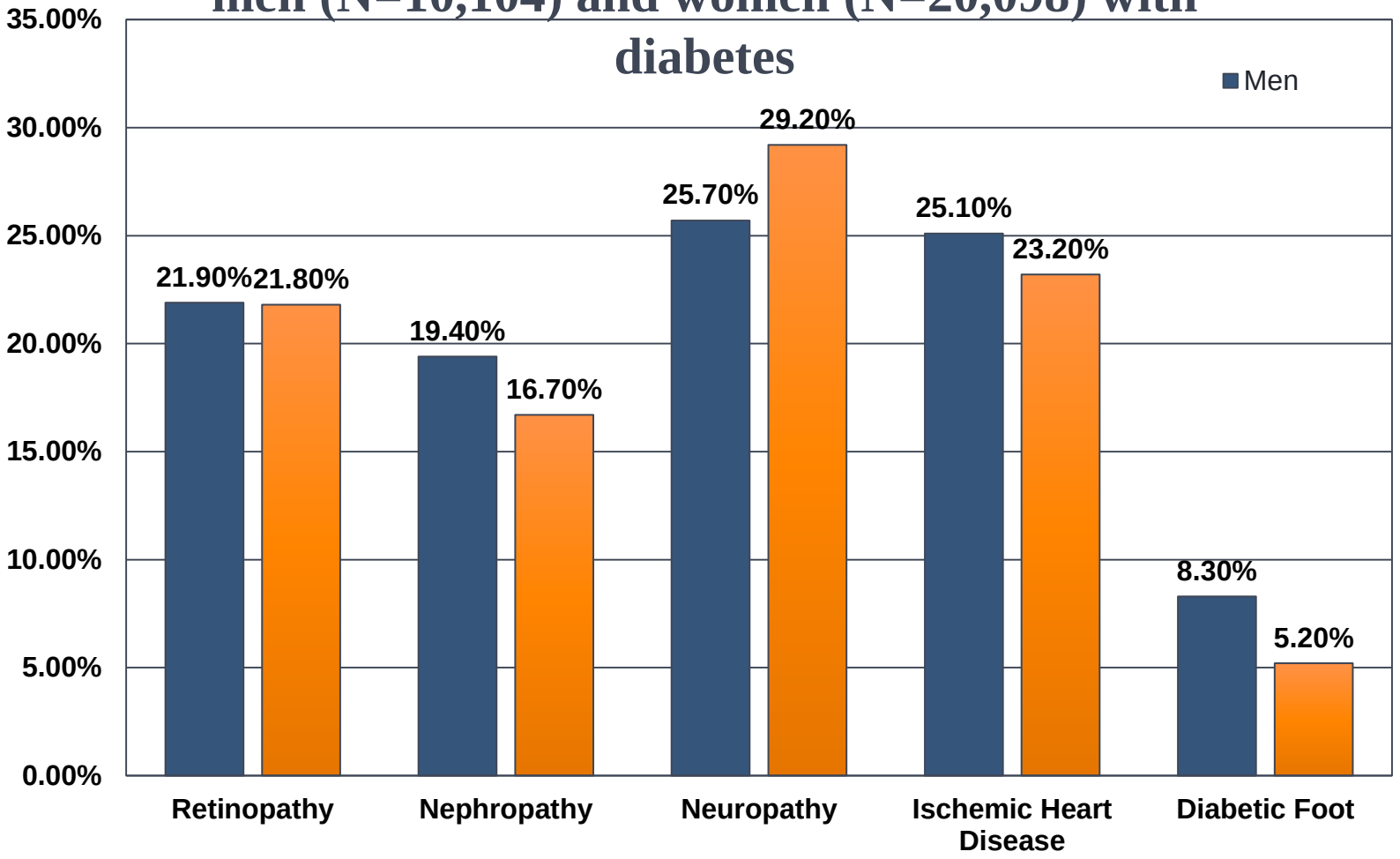
The Status of SGLT2-I in Primary Prevention of Cardio-renal Complication Among Patient With Diabetes

Comorbidities among men (N=10,104) and women (N=20,098) with diabetes



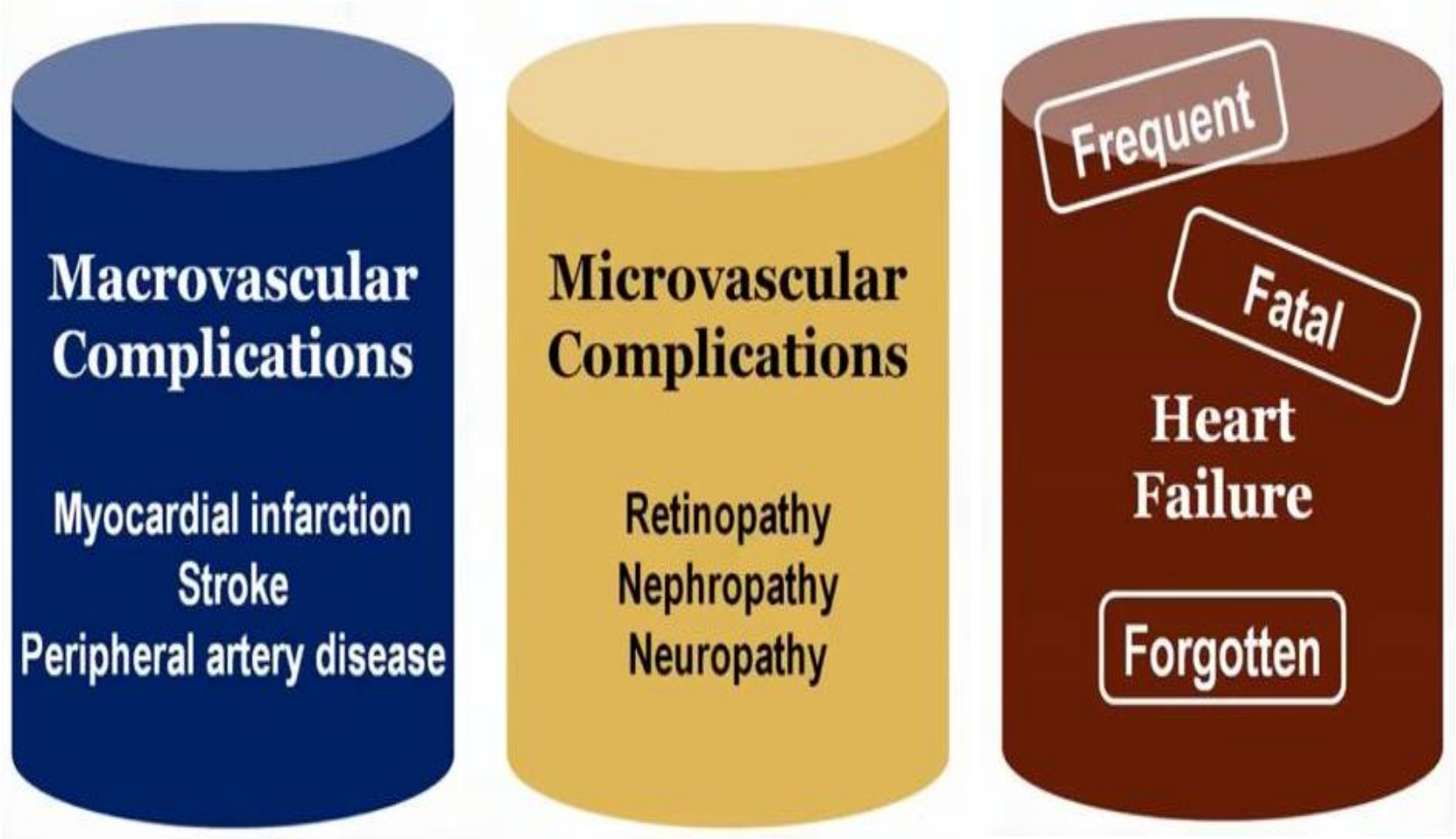
Diabetes in Iran: Prospective Analysis from First Nationwide Diabetes Report of National Program for Prevention and Control of Diabetes (NPPCD-2016). Sci Rep . 2017 Oct 18;7(1):13461.

Prevalence of chronic vascular complications among men (N=10,104) and women (N=20,098) with diabetes



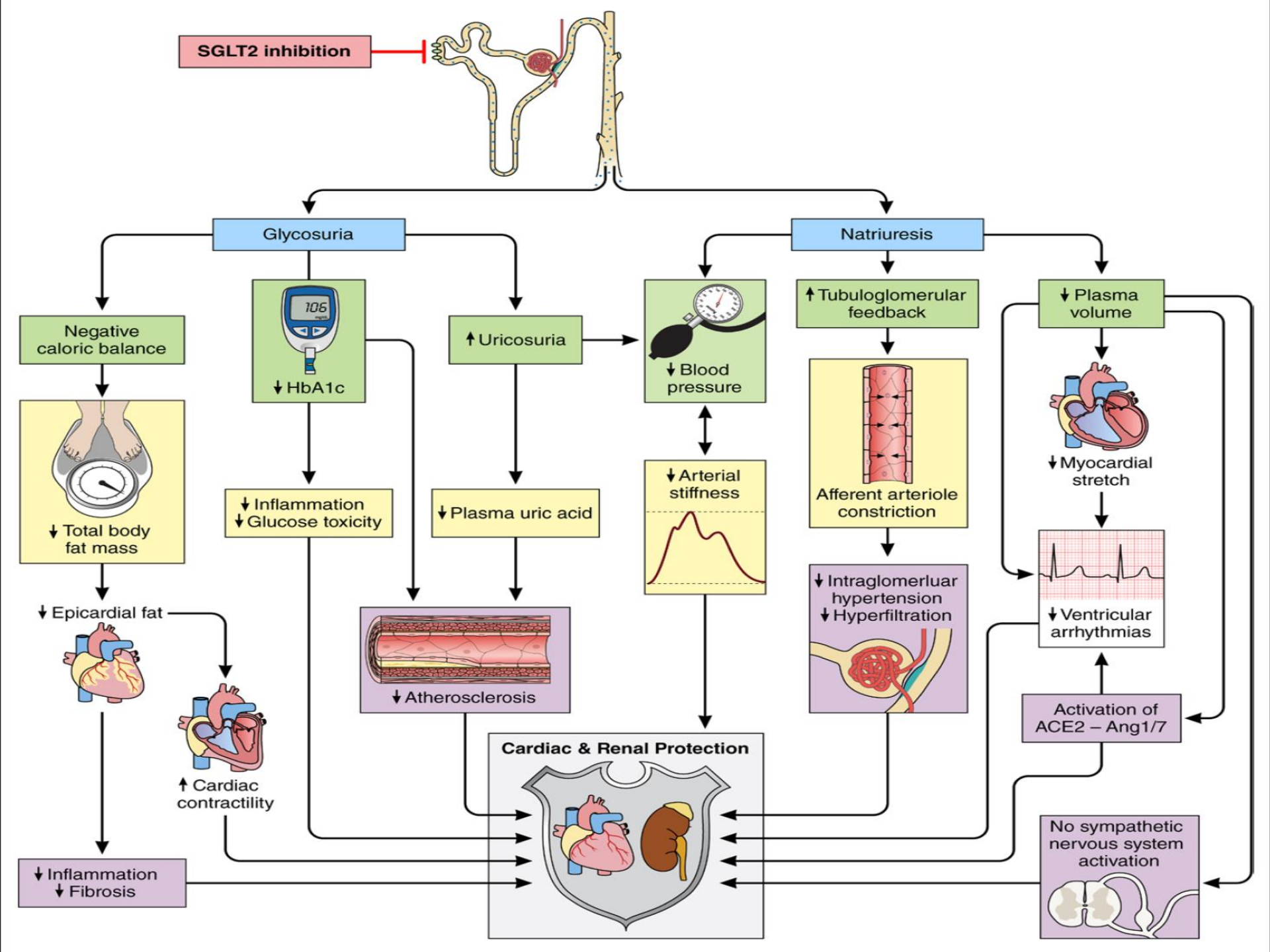
Diabetes in Iran: Prospective Analysis from First Nationwide Diabetes Report of National Program for Prevention and Control of Diabetes (NPPCD-2016). Sci Rep . 2017 Oct 18;7(1):13461.

Diabetes-associated Complication

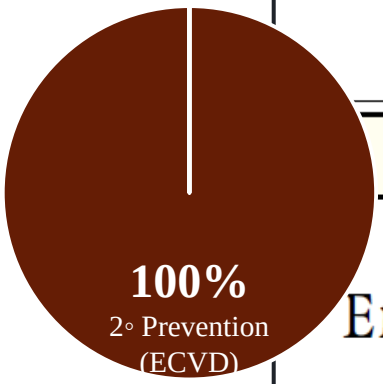


Heart failure: the frequent, forgotten, and often fatal complication of diabetes. Diabetes Care. 2003 Aug;26(8):2433-41.

Physiologic mechanisms implicated in the cardiovascular and renal protection with SGLT2 inhibition


SGLT2 inhibition
Glycosuria
Natriuresis
Negative caloric balance
↓ HbA1c
↑ Uricosuria
↓ Blood pressure
↑ Tubuloglomerular feedback
↓ Plasma volume
↓ Total body fat mass
↓ Inflammation
↓ Glucose toxicity
↓ Plasma uric acid
↓ Arterial stiffness
Afferent arteriole constriction
↓ Myocardial stretch
↓ Epicardial fat
↓ Atherosclerosis
↓ Intraglomerluar hypertension
↓ Hyperfiltration
↓ Ventricular arrhythmias
↑ Cardiac contractility
Cardiac & Renal Protection
Activation of ACE2 – Ang1/7
↓ Inflammation
↓ Fibrosis
No sympathetic nervous system activation

Cardiovascular Outcomes Trials



The NEW ENGLAND JOURNAL of MEDICINE

NOVEMBER 26, 2015

IF: 91.24

ORIGINAL ARTICLE

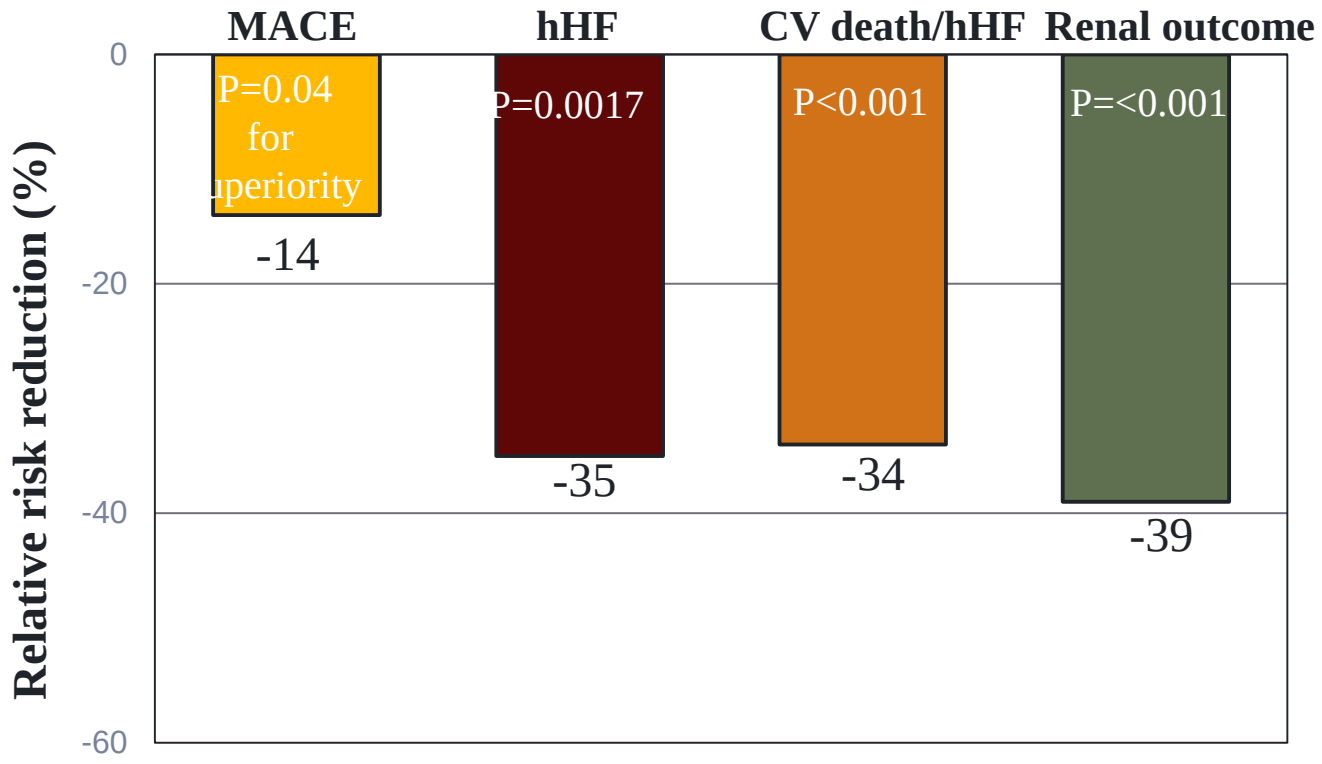
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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

Study Patients: Eligible patients with type 2 diabetes were adults (≥18 years of age) with a BMI 45 or less and an eGFR of at least 30 ml per minute per 1.73 m2 of body-surface area, All the patients had established cardiovascular disease and had a HbA1c of at least 7.0% and no more than 9.0%.

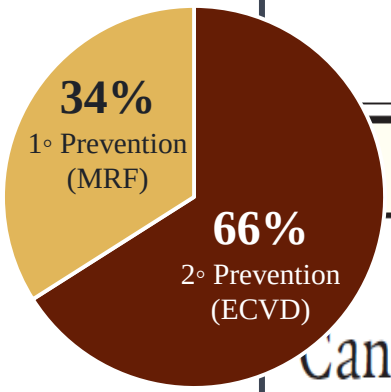
The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Key CV Outcomes from EMPA-REG Outcome



CV, cardiovascular; ECVD, established cardiovascular disease; hHF, hospitalization for heart failure; MACE, major adverse cardiovascular events.
Composite renal outcome was progression to macroalbuminuria (urinary albumin-to-creatinine ratio>300mg/g); a doubling of the serum creatinine level, accompanied by an estimated glomerular filtration rate of ≤45mL/min/1.73m^2; the initiation of renal-replacement therapy; or death from renal disease.

Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N. Engl. J. Med. 373, 2117–2128 (2015).



The NEW ENGLAND JOURNAL of MEDICINE
2017;377:644-57

IF: 91.24

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*

METHODS

The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks.

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

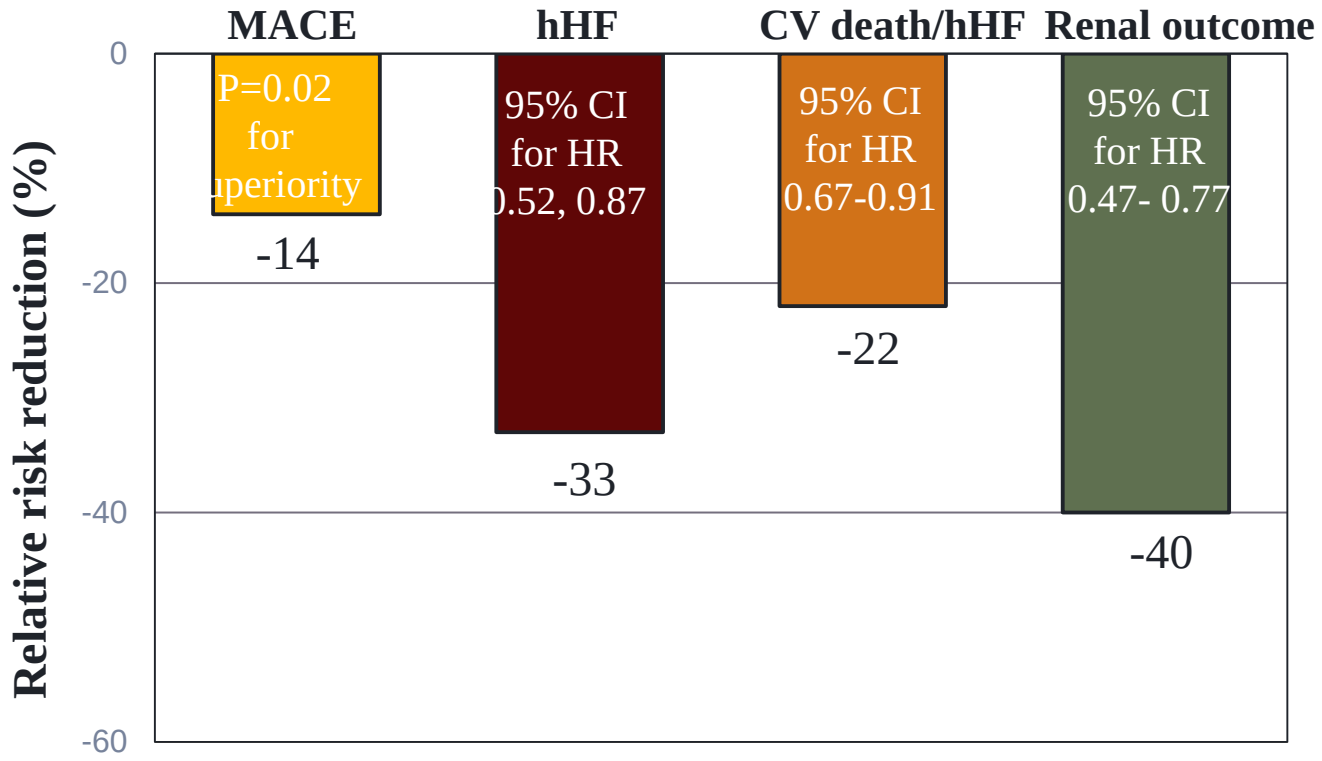
Participant

Participants were men and women with type 2 diabetes (HbA1c ≥7.0% and ≤10.5%) and were either 30 years of age or older with a history of symptomatic atherosclerotic cardiovascular disease or **50 years** of age or older **with two or more of the following risk factors for cardiovascular disease**:

- ✓ duration of diabetes of at least 10 years,
- ✓ SBP higher than 140 mm Hg while they were receiving one or more antihypertensive agents,
- ✓ current smoking,
- ✓ microalbuminuria or macroalbuminuria,
- ✓ or HDL cholesterol level of less than 38.7 mg per deciliter.

Canagliflozin and cardiovascular and renal events in type 2 diabetes. N. Engl. J. Med. 377, 644–657 (2017).

Key CV Outcomes from CANVAS Program



CV, cardiovascular; ECVD, established cardiovascular disease; hHF, hospitalization for heart failure; MACE, major adverse cardiovascular events.

Composite renal outcome was sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death for renal cases.

Canagliflozin and cardiovascular and renal events in type 2 diabetes. N. Engl. J. Med. 377, 644–657 (2017).

Conclusion

In two trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal (6.3 vs. 3.4 participants per 1000 patient-years; hazard ratio, 1.97; 95% CI, 1.41 to 2.75).

Canagliflozin and cardiovascular and renal events in type 2 diabetes. N. Engl. J. Med. 377, 644–657 (2017).

Real-World Data, Top of Metformin, SUL vs. DPP4I vs. SGL2-I

SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

IF: 24.09

ORIGINAL INVESTIGATIONS

J Am Coll Cardiol. 2018 Jun 5;71(22):2497-2506.

SGLT-2 Inhibitors and Cardiovascular Risk

An Analysis of CVD-REAL

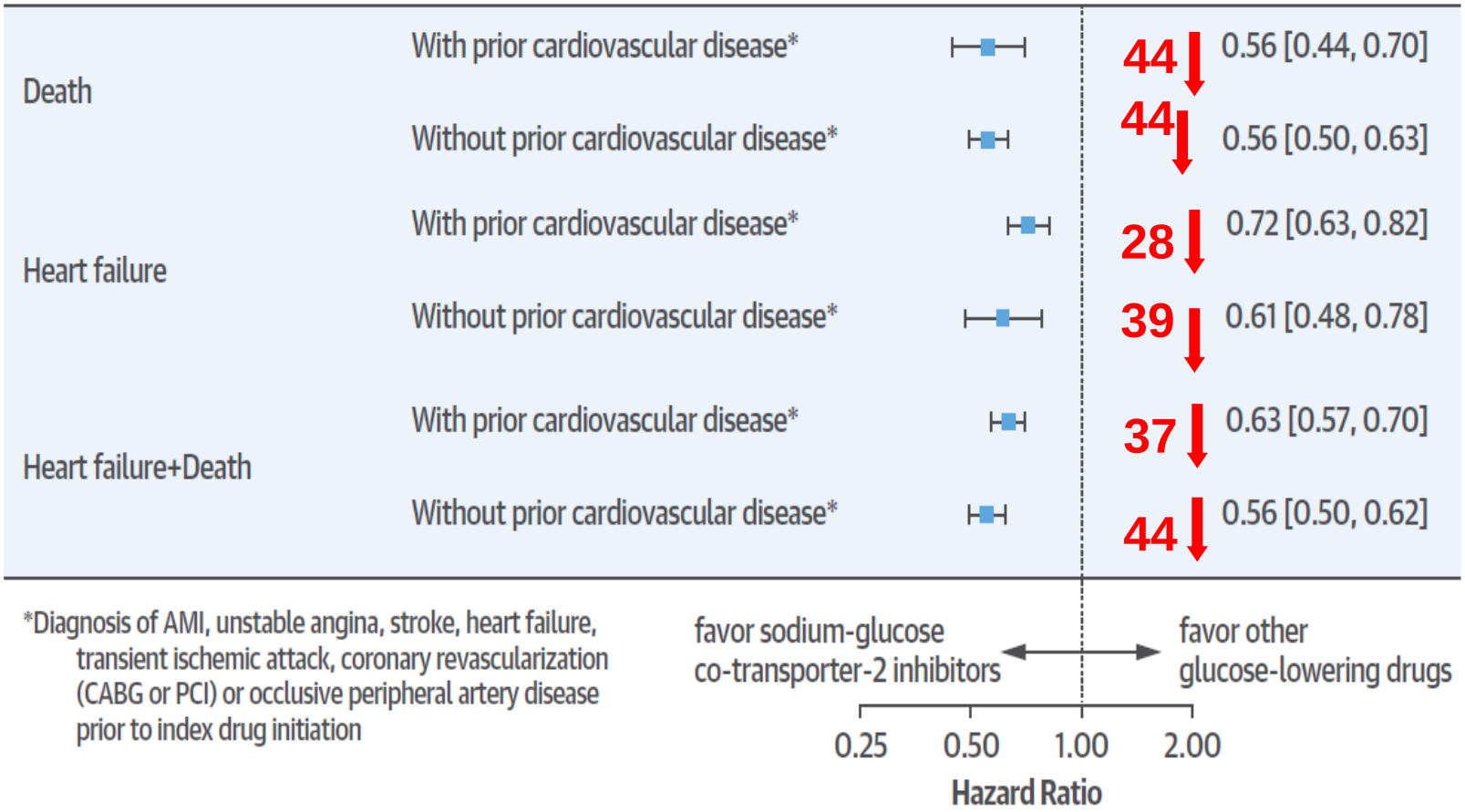
Matthew A. Cavender, MD, MPH,[a,b] Anna Norhammar, MD,[c] Kåre I. Birkeland, MD,[d] Marit Eika Jørgensen, MD,[e,f] John P. Wilding, MD,[g] Kamlesh Khunti, MD,[h] Alex Z. Fu, PhD,[i] Johan Bodegård, MD,[j] Betina T. Blak, PhD,[k] Eric Wittbrodt, PharmD, MPH,[l] Marcus Thuresson, PhD,[m] Peter Fenici, MD,[n] Niklas Hammar, PhD,[c,o] Mikhail Kosiborod, MD,[p] on behalf of the CVD-REAL Investigators and Study Group

Background: Prior studies found patients treated with sodium-glucose co-transporter-2 inhibitors (SGLT-2i) had lower rates of death and heart failure (HF). Whether the benefits of SGLT-2i vary based upon the presence of cardiovascular disease (CVD) is unknown.

Objectives: This study sought to determine the association between initiation of SGLT-2i therapy and HF or death in patients with and without CVD.

Methods: The CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) study was a multinational, observational study in which adults with type 2 diabetes were identified. Patients prescribed an SGLT-2i or other glucose-lowering drugs (GLDs) were matched based on a propensity score for initiation of an SGLT-2i. Hazard ratios (HRs) for the risk of death, HF, and HF or death in patients with and without established CVD were estimated for each country and pooled

CENTRAL ILLUSTRATION **Sodium-Glucose Co-Transporter-2 Inhibitors in Patients With and Without Cardiovascular Disease**



Cavender, M.A. et al. J Am Coll Cardiol. 2018;71(22):2497-506.

Pooled adjusted hazard ratios from meta-analyses for death, heart failure, and heart failure or death in patients with and without cardiovascular disease at initiation of the index drug in the intention-to-treat cohort. AMI = acute myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

BMJ. 2020 Sep 23;370:m3342. IF: 39.89

Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study

Kristian B Filion,[1,2] Lisa M Lix,[3] Oriana HY Yu,[1,4] Sophie Dell'Aniello,[1] Antonios Douros,[1,2,5] Baiju R Shah,[6,7,8] Audray St-Jean,[1] Anat Fisher,[9] Eric Tremblay,[10] Shawn C Bugden,[11,12] Silvia Alessi-Severini,[11,13] Paul E Ronksley,[14] Nianping Hu,[15] Colin R Dormuth,[9] Pierre Ernst,[1,2] Samy Suissa,[1,2] on behalf of the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators

Objective: To compare the risk of cardiovascular events between sodium glucose cotransporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors among people with type 2 diabetes in a real world context of clinical practice.

Design: Multi-database retrospective cohort study using a prevalent new user design with subsequent meta-analysis.

Population: 209 867 new users of a SGLT2 inhibitor matched to 209 867 users of a DPP-4 inhibitor on time conditional propensity score and followed for a mean of 0.9 years.

Table 2 | Crude and adjusted hazard ratios for association between sodium glucose cotransporter 2 (SGLT2) inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors and risk of cardiovascular outcomes

Cardiovascular outcomes by drug	No of events	Person years	Crude incidence rate per 1000 person years	Crude hazard ratio (95% CI)*	Adjusted models*†	
					Hazard ratio (95% CI)	I^2 (%)
MACE:						
SGLT2 inhibitors	2146	188 782	11.4	0.72 (0.65 to 0.80)	0.76 (0.69 to 0.84)	47 **28%↓**
DPP-4 inhibitors	3001	181 733	16.5	1.00 (Reference)	1.00 (Reference)	
Myocardial infarction:						
SGLT2 inhibitors	995	196 503	5.1	0.81 (0.72 to 0.92)	0.82 (0.70 to 0.96)	53 **19%↓**
DPP-4 inhibitors	1169	182 398	6.4	1.00 (Reference)	1.00 (Reference)	
Ischaemic stroke:						
SGLT2 inhibitors	501	190 047	2.6	0.78 (0.68 to 0.89)	0.85 (0.72 to 1.01)	28
DPP-4 inhibitors	636	182 731	3.5	1.00 (Reference)	1.00 (Reference)	
Cardiovascular death:						
SGLT2 inhibitors	738	189 276	3.9	0.55 (0.47 to 0.65)	0.60 (0.54 to 0.67)	14 **40%↓**
DPP-4 inhibitors	1399	182 746	7.7	1.00 (Reference)	1.00 (Reference)	
All cause mortality:						
SGLT2 inhibitors	1651	189 278	8.7	0.54 (0.48 to 0.60)	0.60 (0.54 to 0.67)	42 **40%↓**
DPP-4 inhibitors	3156	183 075	17.3	1.00 (Reference)	1.00 (Reference)	
Heart failure:						
SGLT2 inhibitors	587	189 058	3.1	0.40 (0.35 to 0.46)	0.43 (0.37 to 0.51)	43 **57%↓**
DPP-4 inhibitors	1401	181 956	7.7	1.00 (Reference)	1.00 (Reference)	

MACE=major adverse cardiovascular events.

*Users of SGLT2 inhibitors were matched to users of DPP-4 inhibitors from their exposure set (defined on level of antidiabetic therapy, time on DPP-4 inhibitors for prevalent new users only, prior use of glucagon-like peptide-1 receptor agonists, and within 120 days of the SGLT2 prescription) on time-conditional propensity score.

†Adjusted for age (continuous), sex, diabetes duration (continuous), and 10ths of time conditional propensity score.

Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study. BMJ . 2020 Sep 23;370:m3342.

Table 3 | Summary results for stratified analyses of pooled adjusted hazard ratios (95% confidence intervals) for major adverse cardiovascular events (MACE) and heart failure associated with use of sodium glucose cotransporter 2 (SGLT2) inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors

Subgroup	Adjusted hazard ratio (95% CI)*	I^2 (%)	
MACE			
Main analysis	0.76 (0.69 to 0.84)	47	
History of cardiovascular disease†:			
Yes	0.71 (0.59 to 0.86)	67	29%↓
No	0.78 (0.69 to 0.88)	40	22%↓
SGLT2 inhibitor molecule:			
Canagliflozin	0.79 (0.66 to 0.94)	67	
Dapagliflozin	0.73 (0.63 to 0.85)	32	
Empagliflozin	0.77 (0.68 to 0.87)	1	
Heart failure			
Main analysis	0.43 (0.37 to 0.51)	43	
History of heart failure§:			
Yes	0.44 (0.35 to 0.55)	33	56%↓
No	0.47 (0.41 to 0.53)	0	53%↓
SGLT2 inhibitor molecule:			
Canagliflozin	0.41 (0.32 to 0.52)	42	
Dapagliflozin	0.44 (0.36 to 0.54)	0	
Empagliflozin	0.52 (0.43 to 0.65)	4	

Nova Scotia had zero events in one of the treatment groups and thus was not included in the cardiovascular disease (yes) analysis for MACE or in the age (≥70 years), sex, history of heart failure, and SGLT2 inhibitor molecule analyses for heart failure.
*Adjusted for age (continuous), sex, diabetes duration (continuous), and 10ths of time conditional propensity score.
†Coronary artery disease, peripheral arterial disease, or cerebrovascular disease in the past three years.
‡Prescription for insulin in past year.
§Two outpatient codes or one inpatient code in the past three years.

Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study. BMJ . 2020 Sep 23;370:m3342.

JAMA Internal Medicine | Original Investigation IF: 21.87

2021 Jun 28;e212488.

Comparative Effectiveness of Sodium-Glucose Cotransporter 2 Inhibitors vs Sulfonylureas in Patients With Type 2 Diabetes

Yan Xie, MPH; Benjamin Bowe, MPH; Andrew K. Gibson, MPH; Janet B. McGill, MD; Geetha Maddukuri, MD; Ziyad Al-Aly, MD

Importance: In the treatment of type 2 diabetes, evidence of the comparative effectiveness of sodium-glucose cotransporter 2 (SGLT2) inhibitors vs sulfonylureas-the second most widely used antihyperglycemic class after metformin-is lacking.

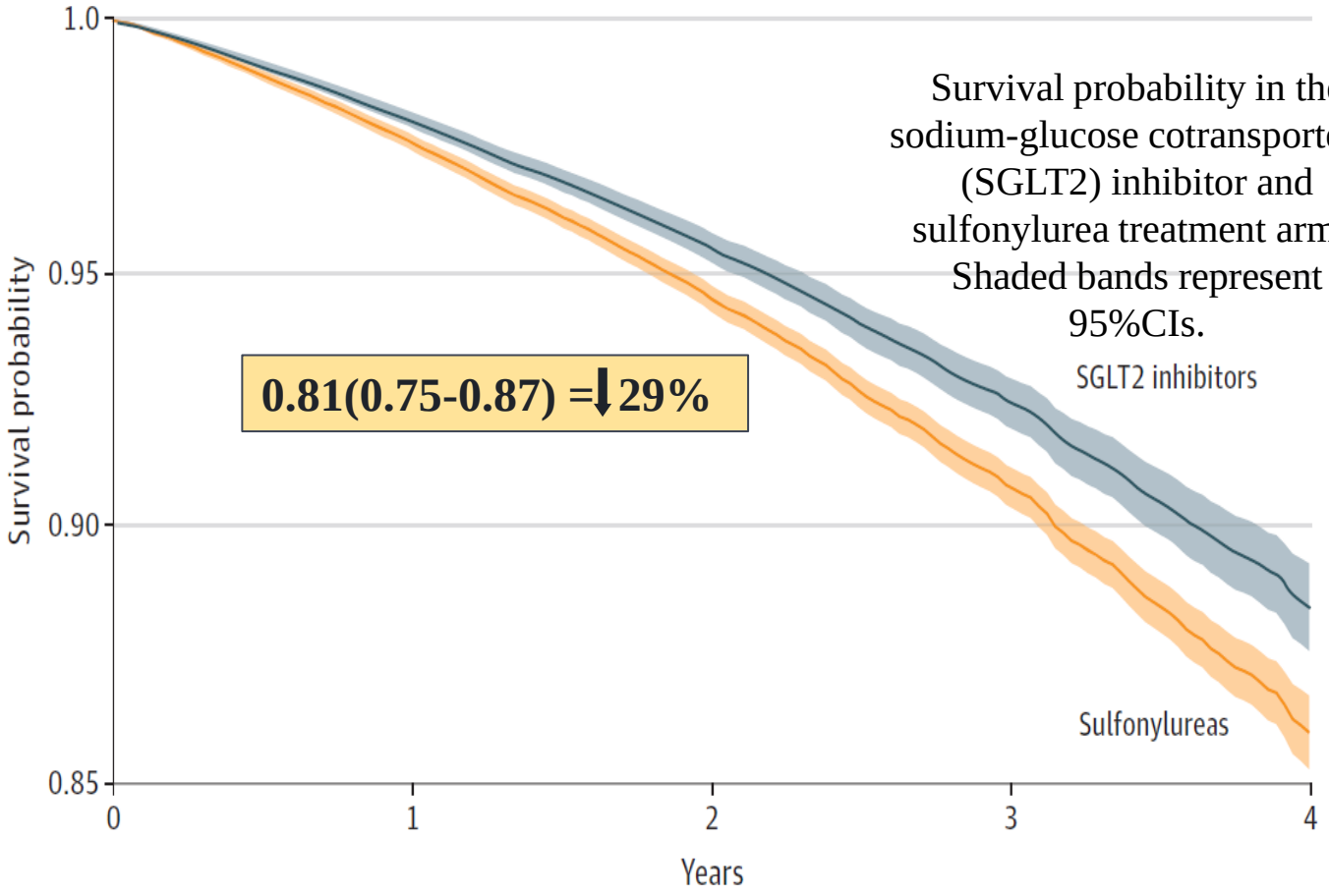
Objective: To evaluate the comparative effectiveness of SGLT2 inhibitors and sulfonylureas associated with the risk of all-cause mortality among patients with type 2 diabetes using metformin.

Design, setting, and participants: A cohort study used data from the US Department of Veterans Affairs compared the use of SGLT2 inhibitors vs sulfonylureas in individuals receiving metformin for treatment of type 2 diabetes. A total of 23 870 individuals with new use of SGLT2 inhibitors and 104 423 individuals with new use of sulfonylureas were enrolled between October 1, 2016, and February 29, 2020, and followed up until January 31, 2021.

Exposures: New use of SGLT2 inhibitors or sulfonylureas.

Main outcomes and measures: This study examined the outcome of all-cause mortality.

Figure 1. Adjusted Intention-to-Treat Survival Probability for All-Cause Mortality



Survival probability in the sodium-glucose cotransporter 2 (SGLT2) inhibitor and sulfonylurea treatment arms. Shaded bands represent 95%CIs.

No. at risk									
SGLT2 inhibitors	23870	23686	22446	16029	10264	6717	3956	1948	495
Sulfonylureas	104423	103312	100744	90210	75126	60312	43824	27748	9968

Figure 2. Intention-to-Treat Hazard Ratios (HRs) and Event Rate Reduction for All-Cause Mortality in the Overall Cohort and Prespecified Subgroups

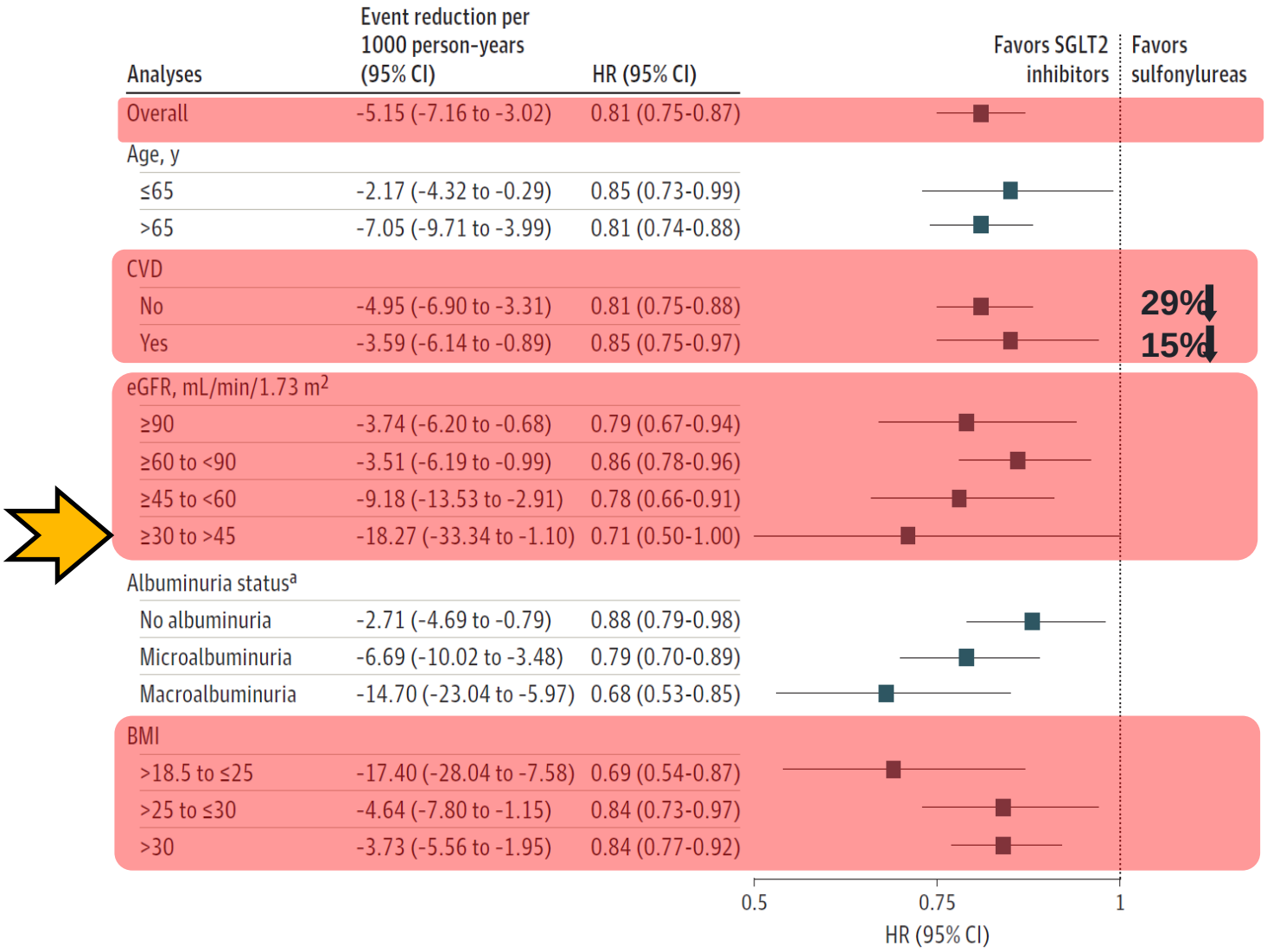
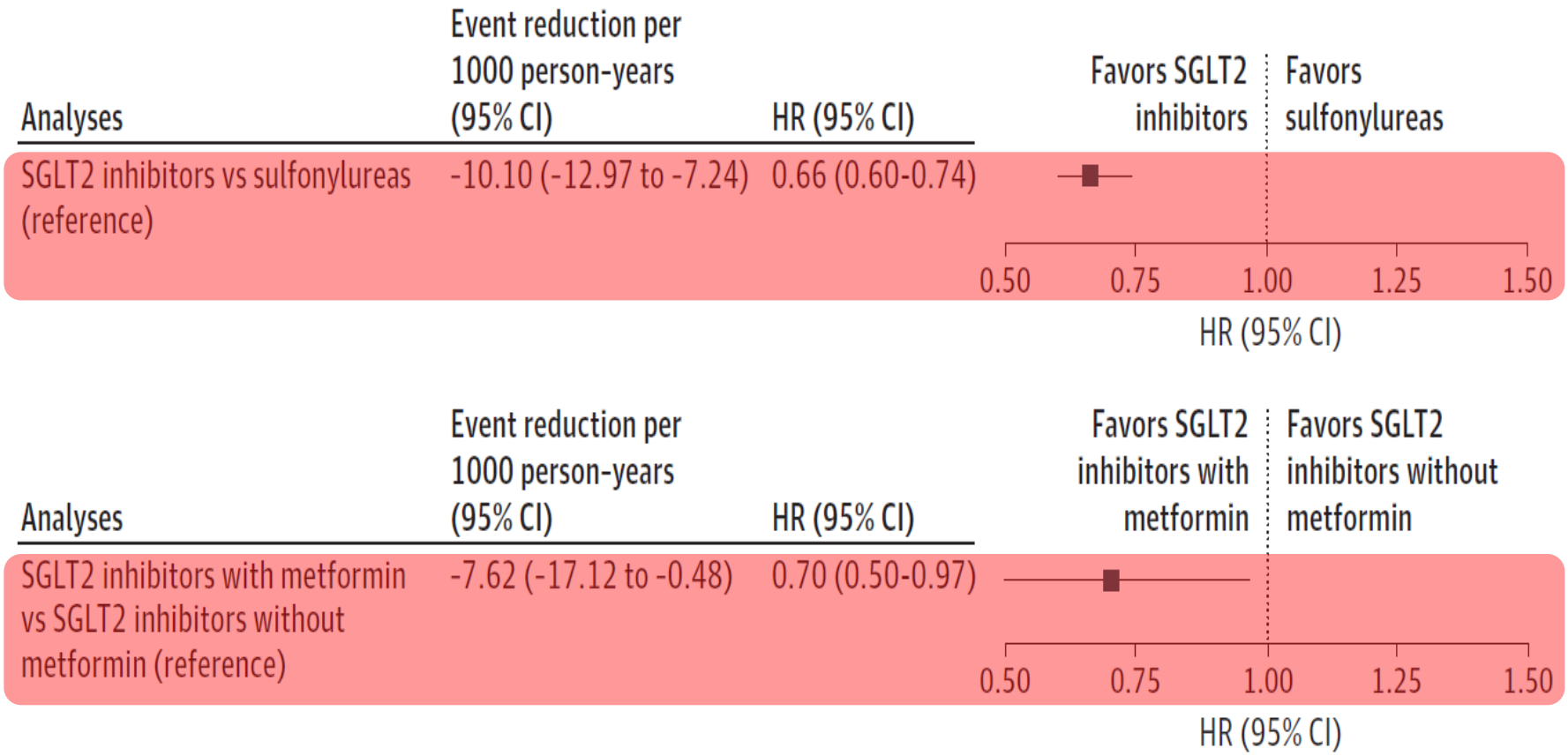


Figure 3. Per-Protocol Hazard Ratios (HRs) and Event Rate Reduction for All-Cause Mortality

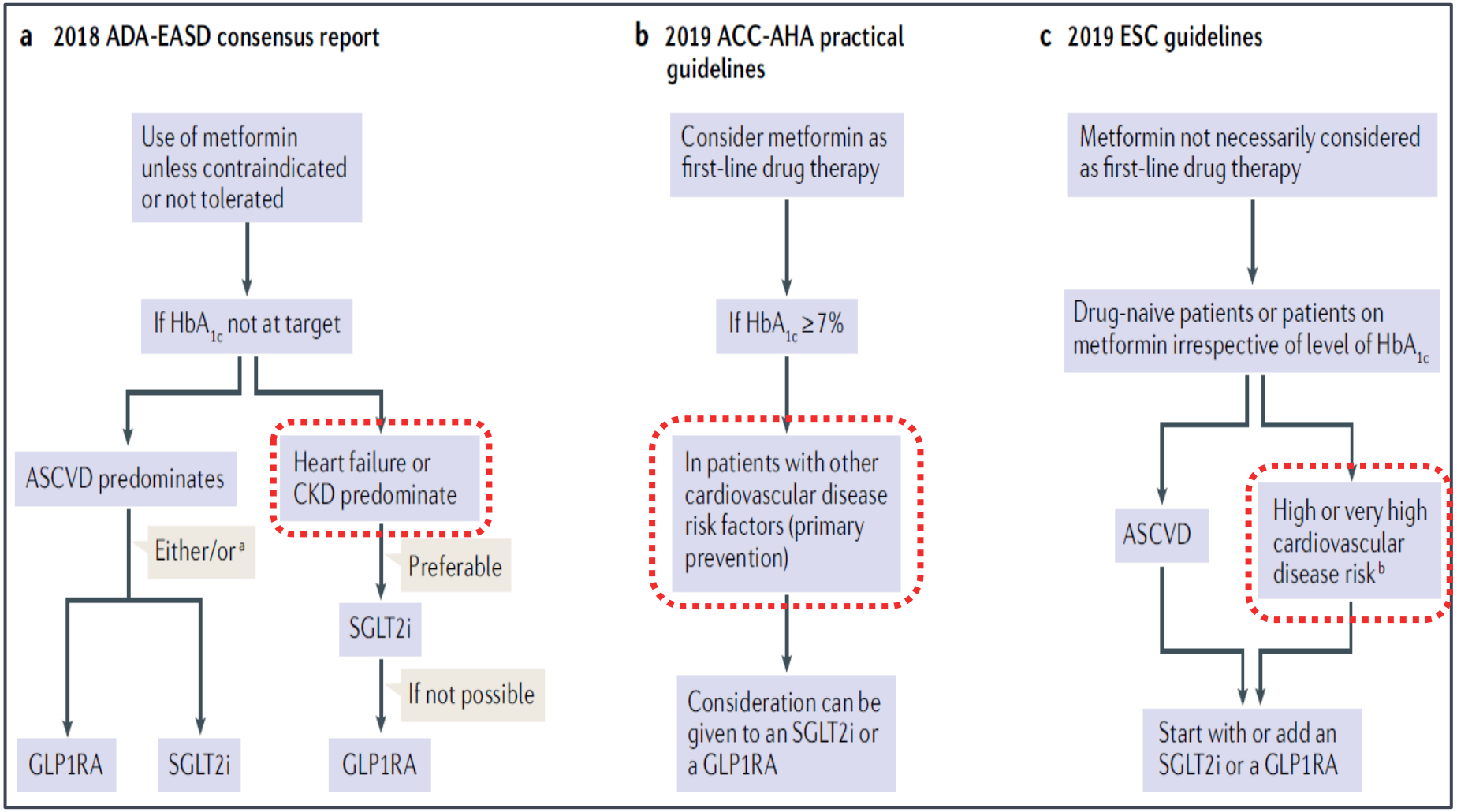


Hazard ratios of all-cause mortality in continued use of sodium-glucose cotransporter 2 (SGLT2) inhibitors or sulfonylureas (reference group) throughout follow-up (top graph) and continued use of SGLT2 inhibitors with metformin or SGLT2 inhibitors without metformin (reference group) throughout follow up (bottom graph)

Conclusion

In this comparative effectiveness study analyzing data from the US Department of Veterans Affairs, among patients with type 2 diabetes receiving metformin therapy, SGLT2 inhibitor treatment was associated with a reduced risk of all-cause mortality compared with sulfonylureas. The results provide data from a real-world setting that might help guide the choice of antihyperglycemic therapy.

Fig. 3 Position of SglT2is in international guidelines



Sodium–glucose cotransporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. Nature Reviews Endocrinology . 2020

Which one?

Along side of life style modification (calorie restriction and increasing physical activity):

1. **Start with Metformin 500 mg BD then add Empagliflozin 10 mg/day or change to Metformin/Empagliflozin (500/5) BD**
2. **Start with Empagliflozin Plus (500/5) BD then increase to Empagliflozin Plus (1000/5) BD**
3. **Start with Empagliflozin plus (500/5) BD then add Sitagliptin 50 mg/day**
4. **Start with Metformin 500 mg BD and Liraglutide**
5. **Start with Metformin 500 mg BD and Liraglutide then add Empagliflozin 10 mg/day**
6. **Start with Glibenclamide 5 mg/day**
7. **Start with Gliclazide MR 30 mg/day then increase the dose or add Metformin**
8. **Other options?**

{special}

THANKS

to

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Together for a healthy future

team

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