



Actotalk In Tabriz

Sept, 2021



Together for a healthy future



Dr Mitra Niafar, MD

Professor of Endocrinology & Metabolism

Department of Internal Medicine, School of Medicine

Endocrine Research Center

Tabriz University of Medical Sciences

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?

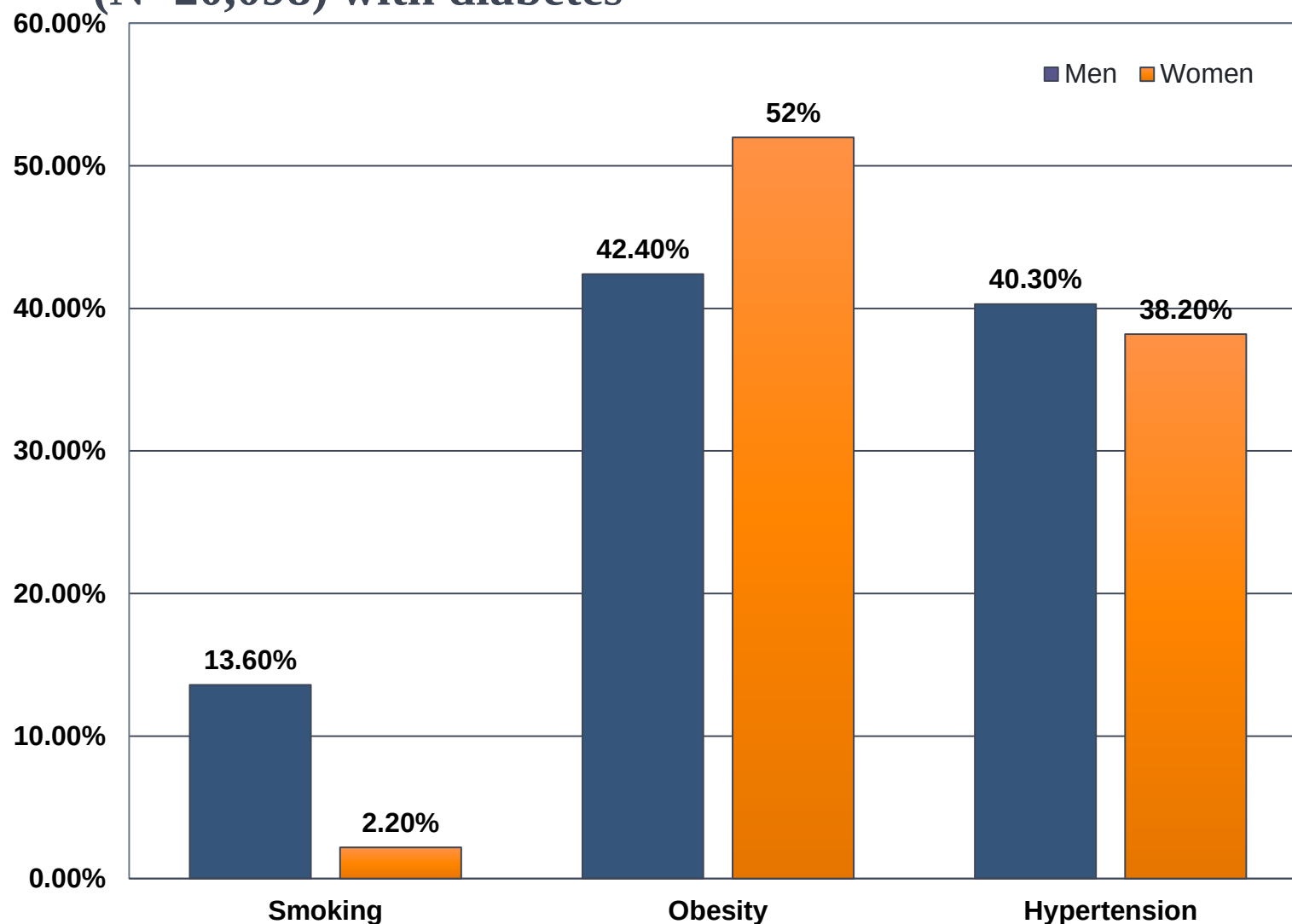
Which one?

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

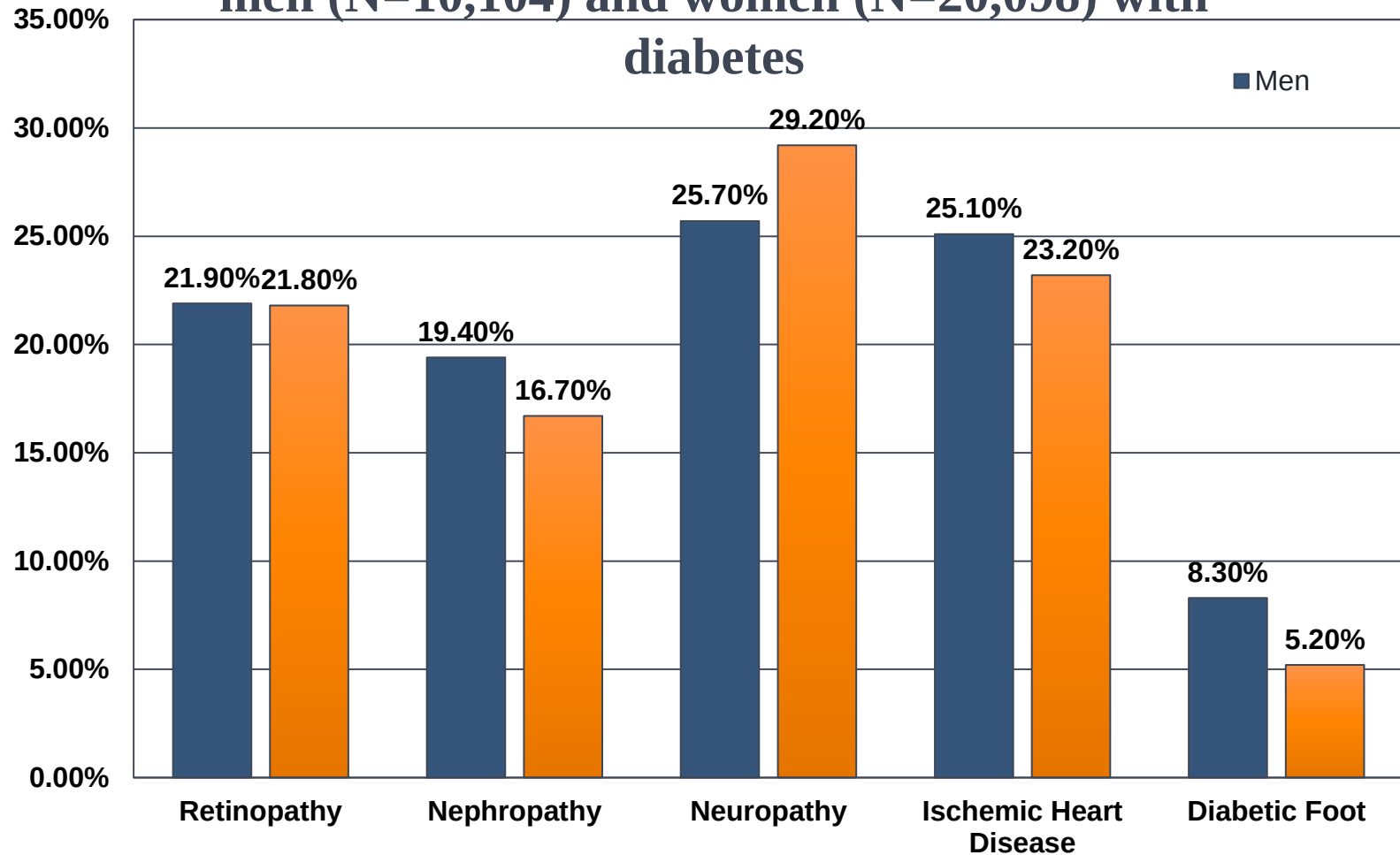
1. Start with Metformin 500 mg BD then add Empagliflozin 10 mg/day or change to Metformin/Empagliflozin (500/5) BD
2. Start with Empagliflozin Plus (500/5) BD then increase to Empagliflozin Plus (1000/5) BD
3. Start with Empagliflozin plus (500/5) BD then add Sitagliptin 50 mg/day
4. Start with Metformin 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***

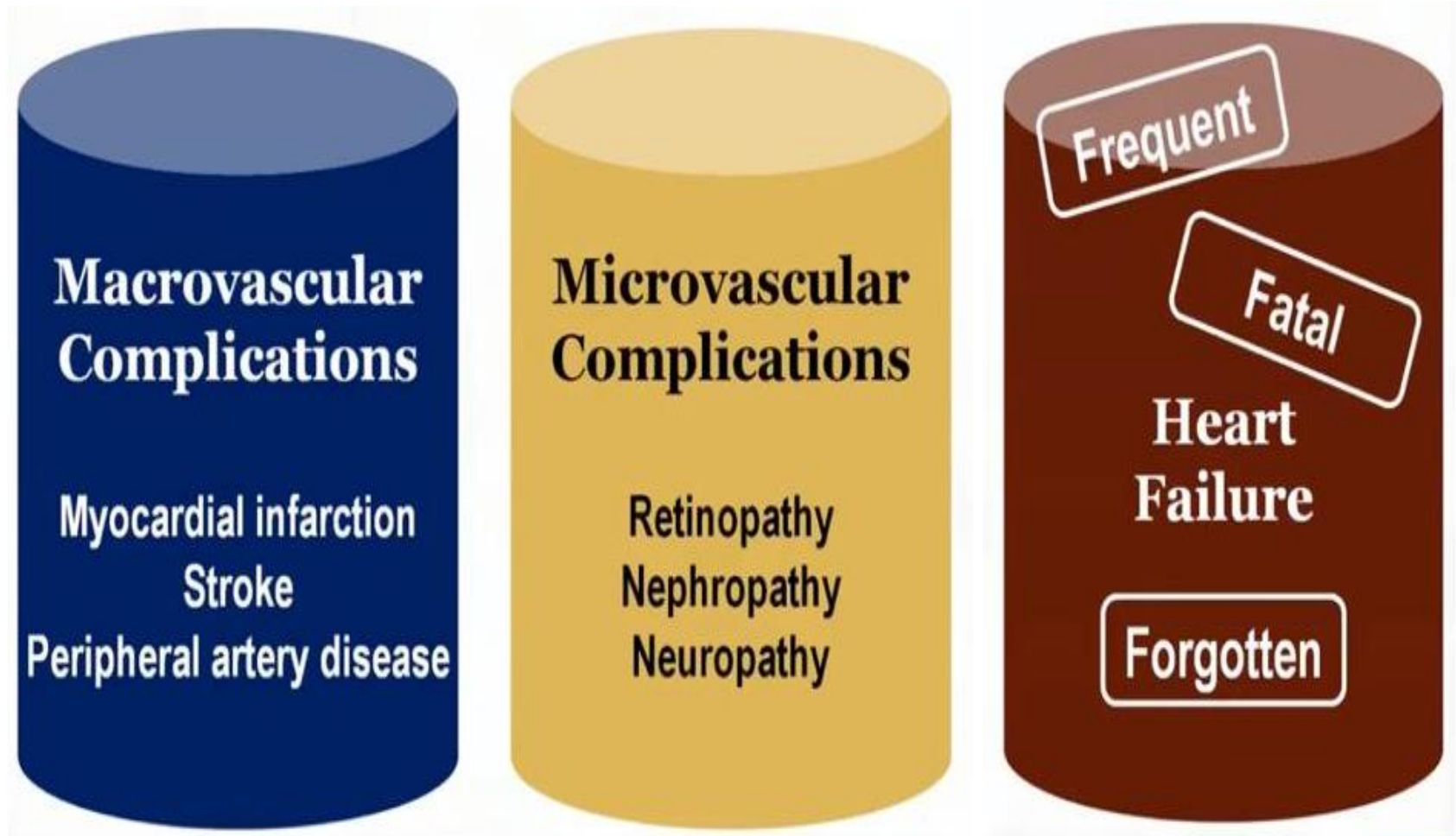
Comorbidities among men (N=10,104) and women (N=20,098) with diabetes



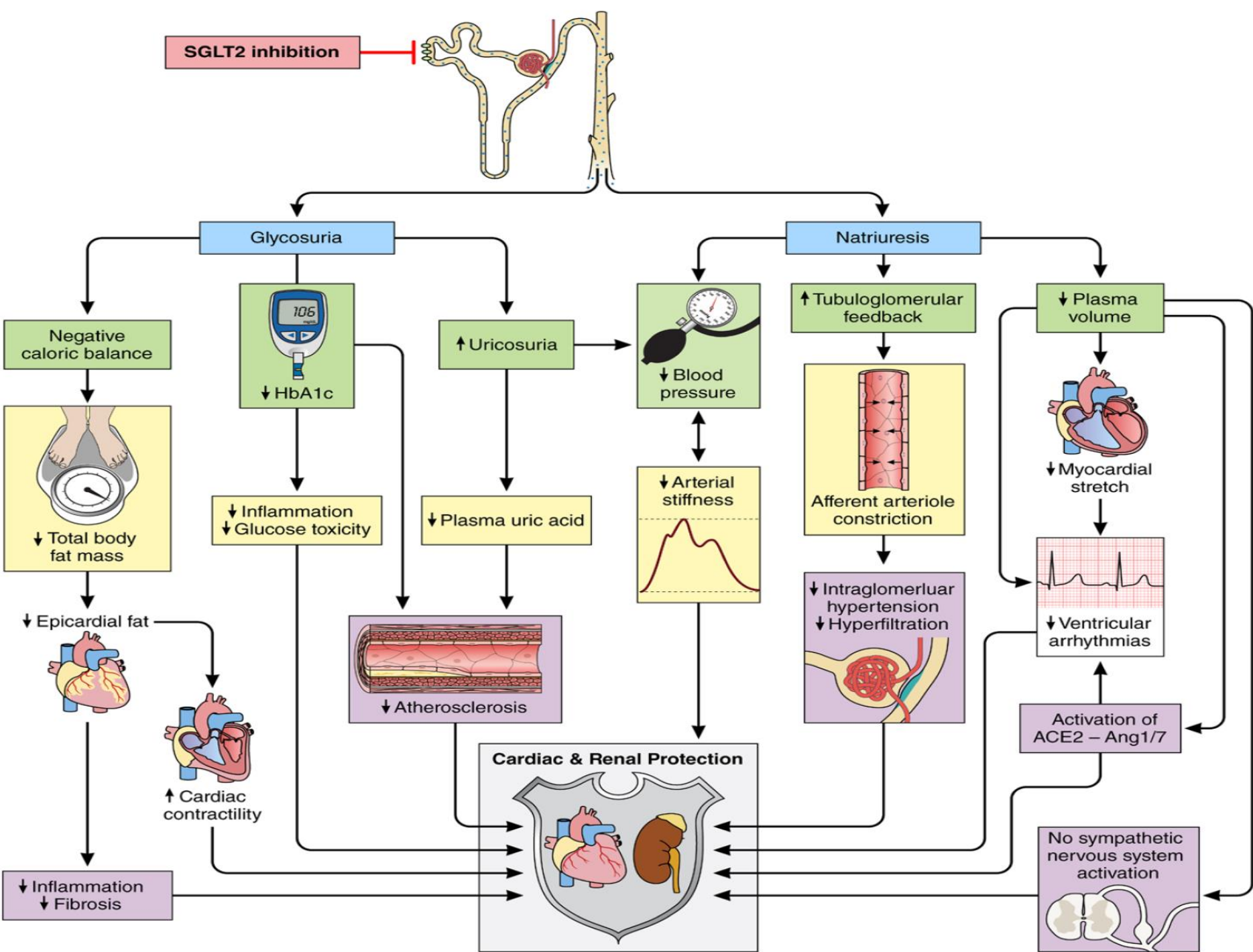
Prevalence of chronic vascular complications among men (N=10,104) and women (N=20,098) with diabetes



Diabetes-associated Complication



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



Cardiovascular Outcomes Trials

ORIGINAL ARTICLE

100%

2° Prevention
(ECVD)

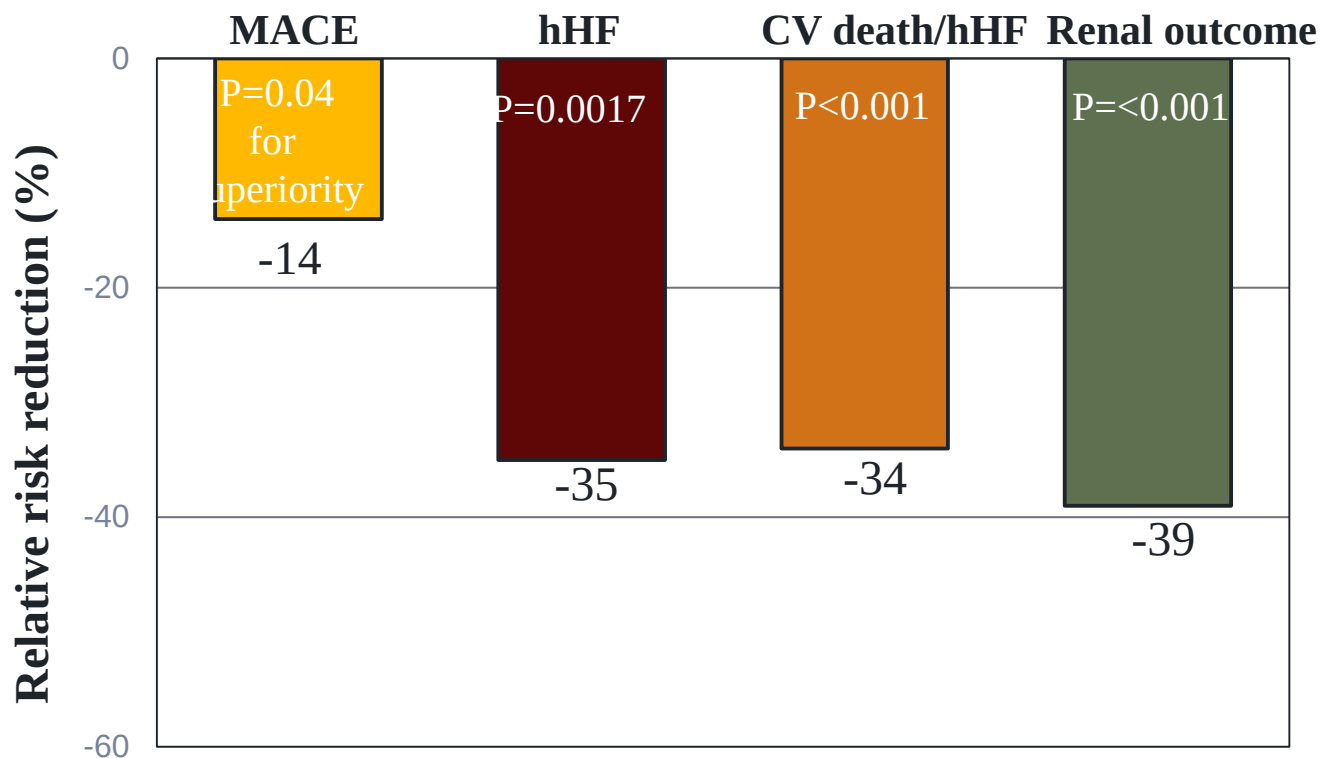
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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

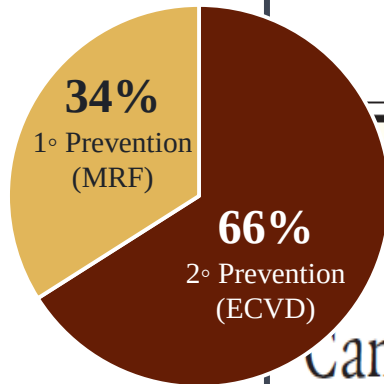
Study Patients: Eligible patients with type 2 diabetes were adults (≥ 18 years of age) with a BMI 45 or less and an eGFR of at least 30 ml per minute per 1.73 m² of body-surface area. All the patients had established cardiovascular disease and had a HbA1c of at least 7.0% and no more than 9.0%.

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 $\leq 45 \text{ mL/min/1.73m}^2$; the initiation of renal-replacement therapy; or death from renal disease.



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.

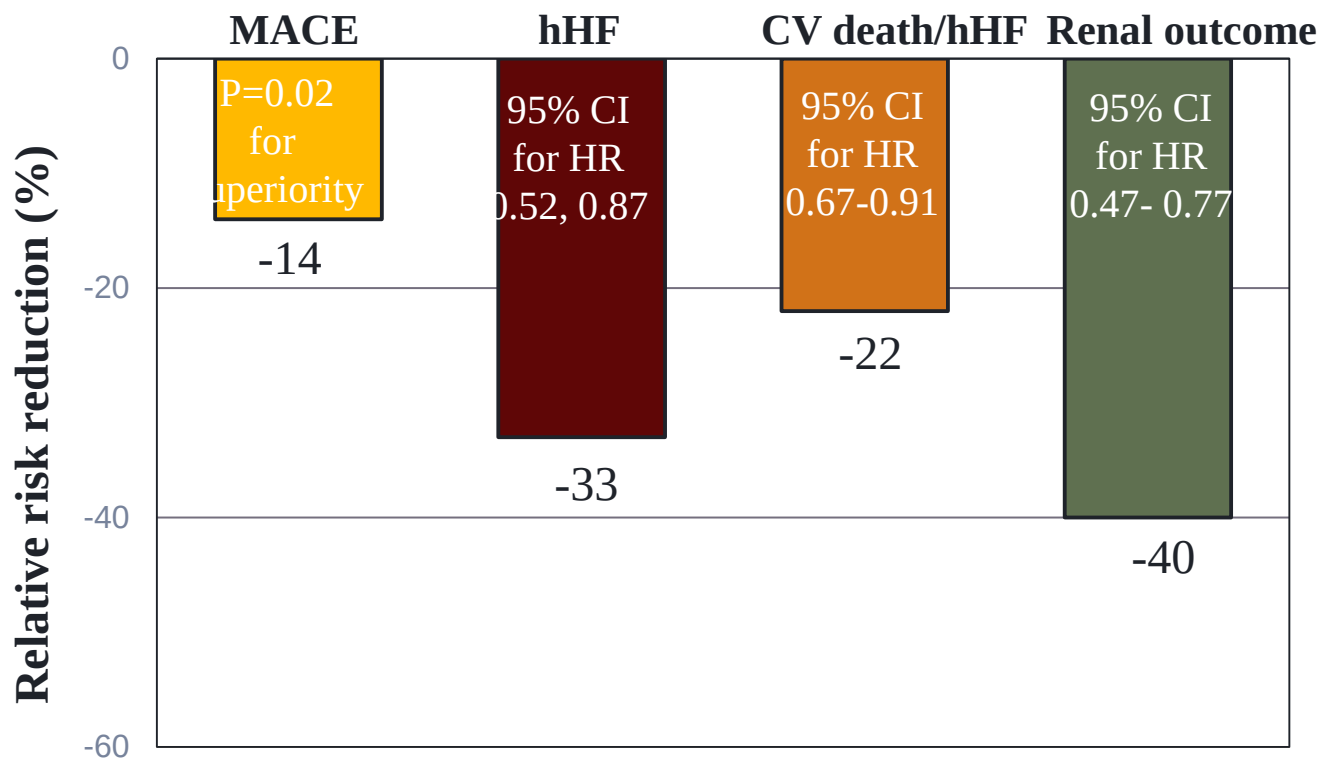
The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Participant

Participants were men and women with type 2 diabetes ($\text{HbA1c} \geq 7.0\%$ and $\leq 10.5\%$) 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.

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.

“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).

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

SGLT-2 Inhibitors and Cardiovascular Risk



An Analysis of CVD-REAL

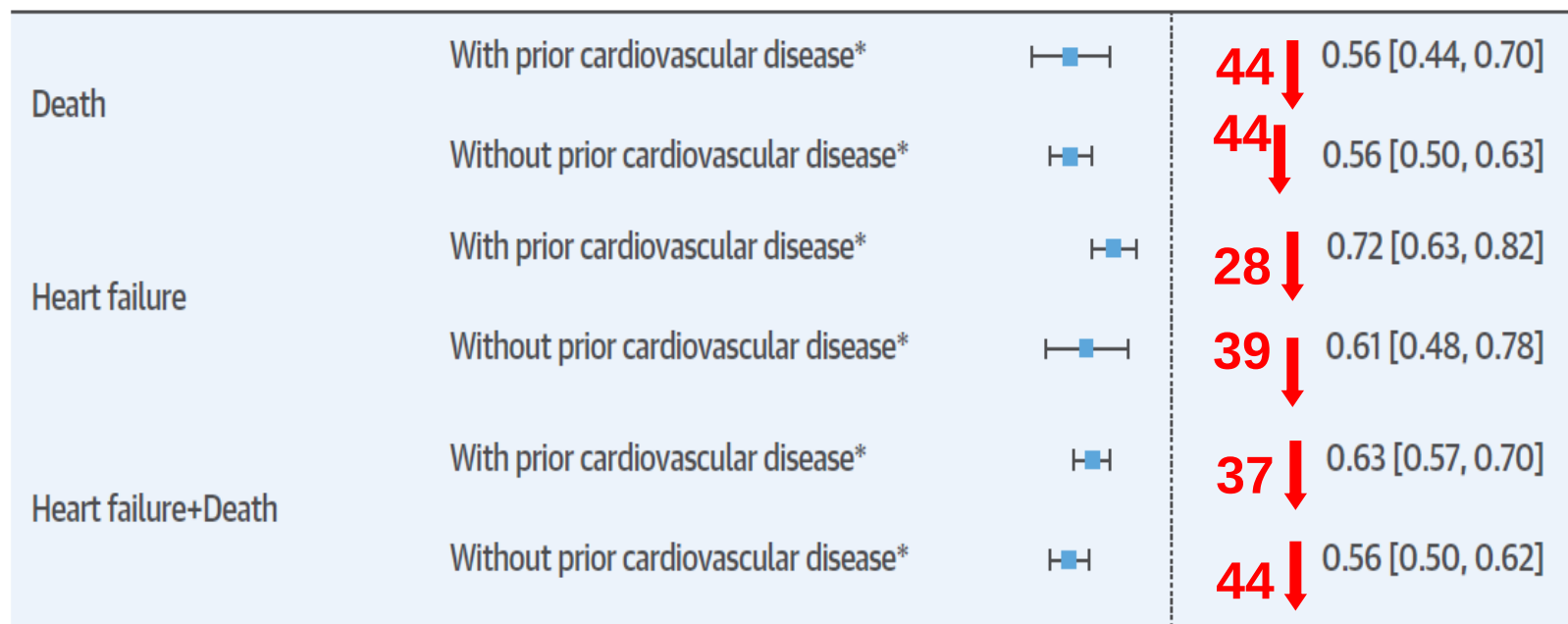
Matthew A. Cavender, MD, MPH,^{a,b} Anna Norhammar, MD,^c Kåre I. Birkeland, MD,^d Marit Eika Jørgensen, MD,^{e,f} John P. Wilding, MD,^g Kamlesh Khunti, MD,^h Alex Z. Fu, PhD,ⁱ Johan Bodegård, MD,^j Betina T. Blak, PhD,^k Eric Wittbrodt, PharmD, MPH,^l Marcus Thuresson, PhD,^m Peter Fenici, MD,ⁿ Niklas 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.

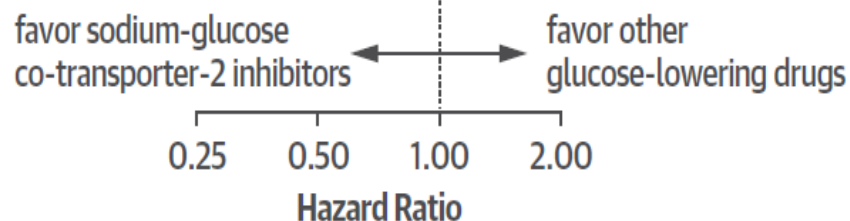
Objectives: This study sought to determine the association between initiation of SGLT-2i therapy and HF or death in patients with and without CVD.

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

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



*Diagnosis of AMI, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization (CABG or PCI) or occlusive peripheral artery disease prior to index drug initiation



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.

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.

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.

Comparative Effectiveness of Sodium-Glucose Cotransporter 2 Inhibitors vs Sulfonyleureas 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 sulfonyleureas-the second most widely used antihyperglycemic class after metformin-is lacking.

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

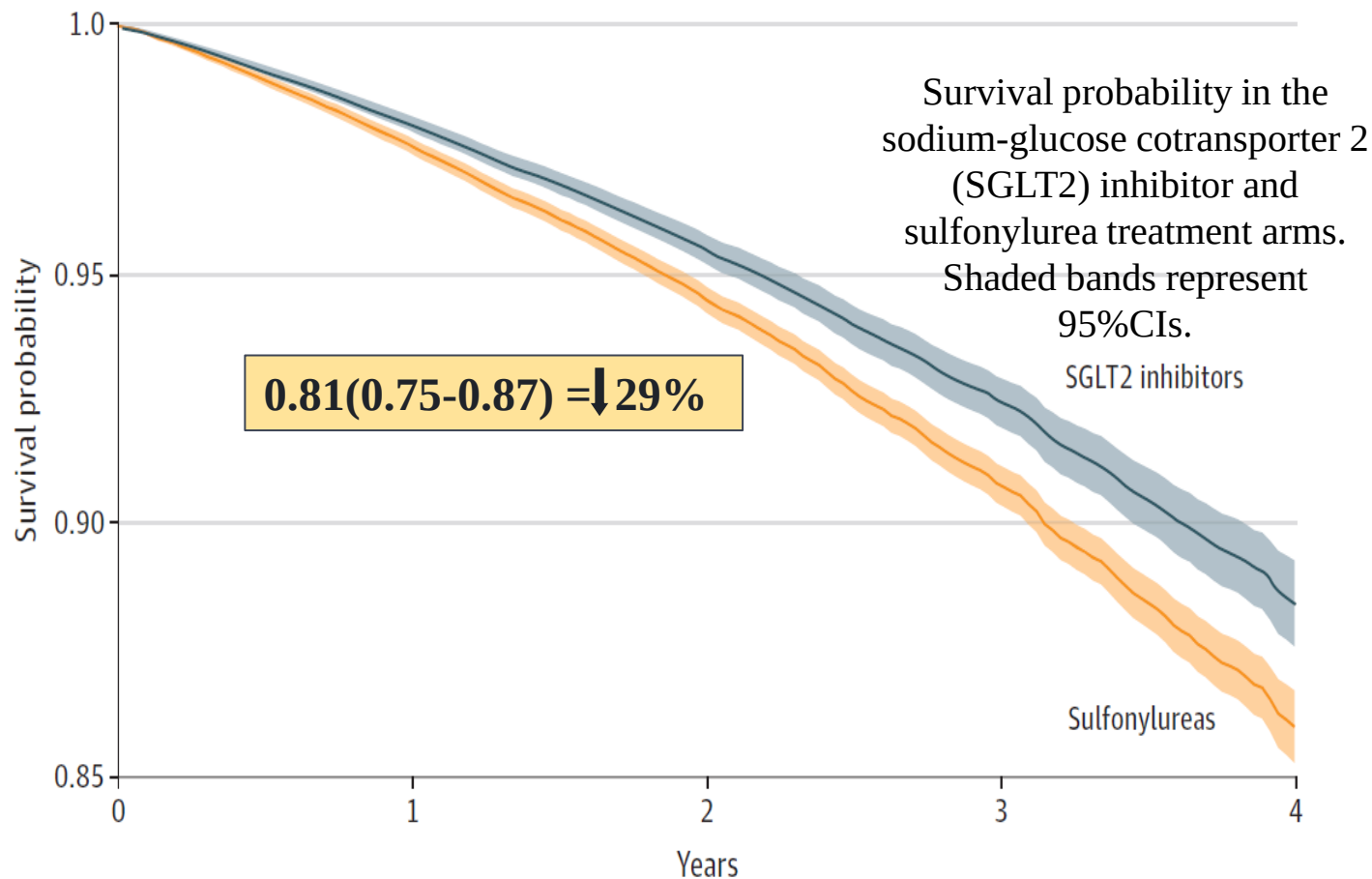
Design, setting, and participants: A cohort study used data from the US Department of Veterans Affairs compared the use of SGLT2 inhibitors vs sulfonyleureas in individuals receiving metformin for treatment of type 2 diabetes. A total of 23 870 individuals with new use of SGLT2 inhibitors and 104 423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

Exposures: New use of SGLT2 inhibitors or sulfonyleureas.

9/14/2021

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



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

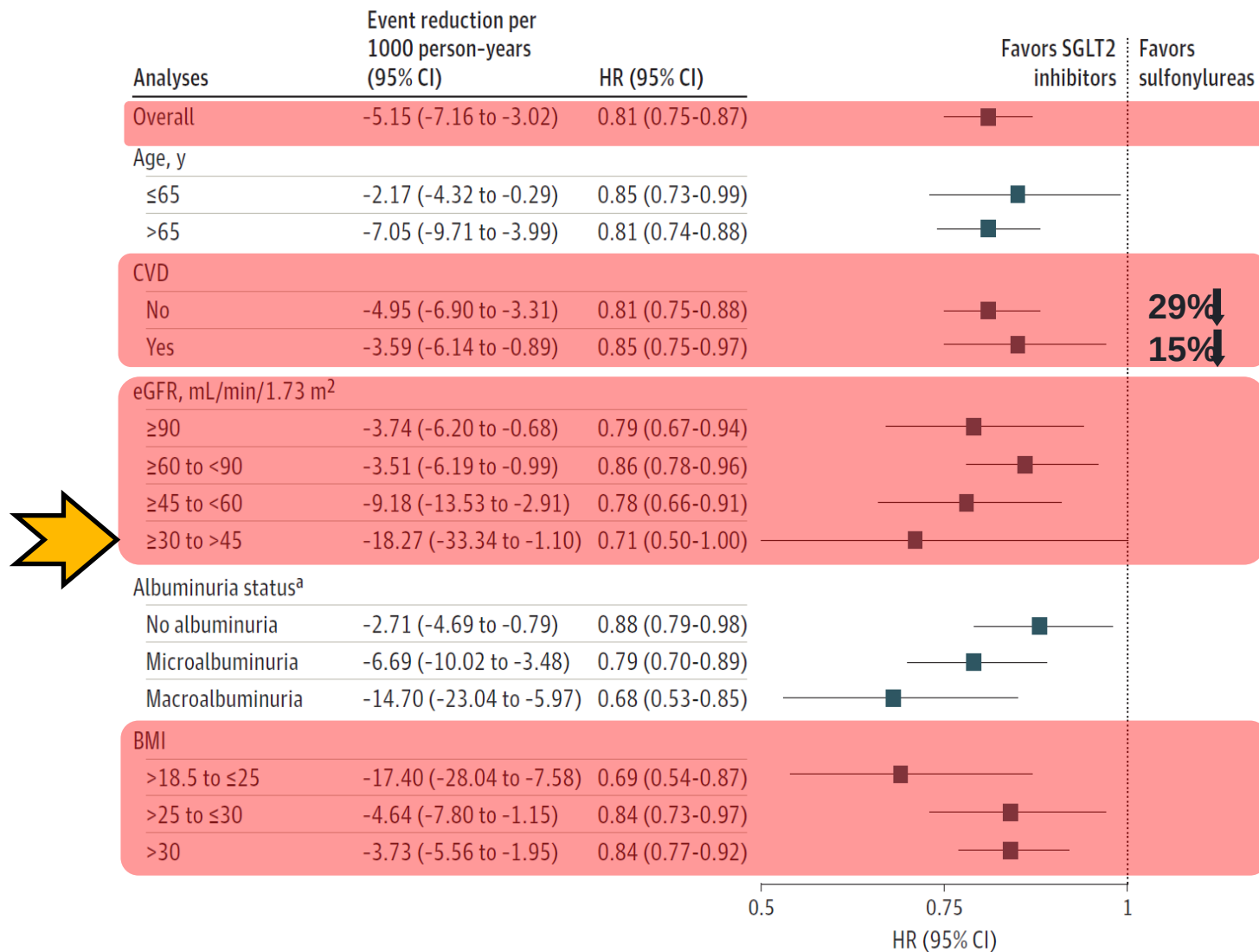
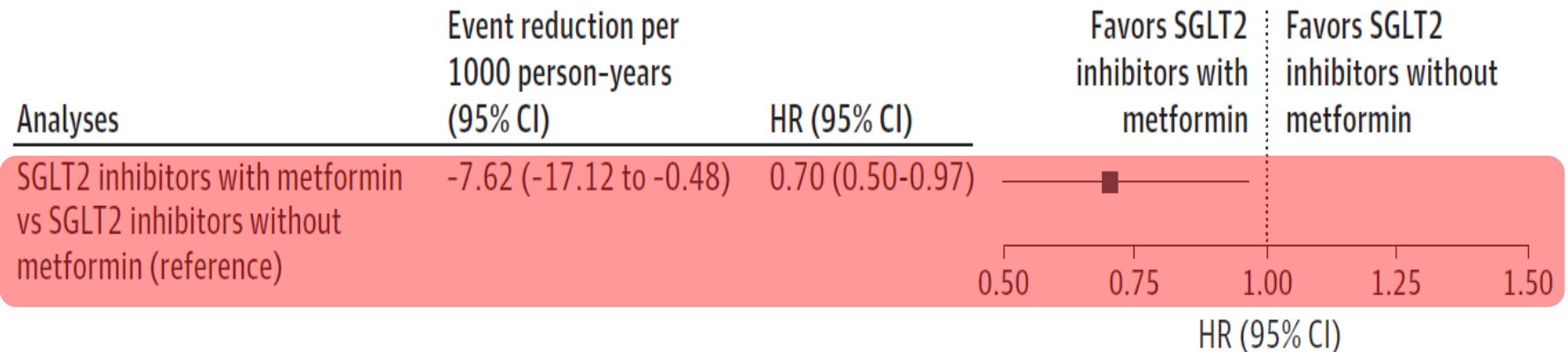
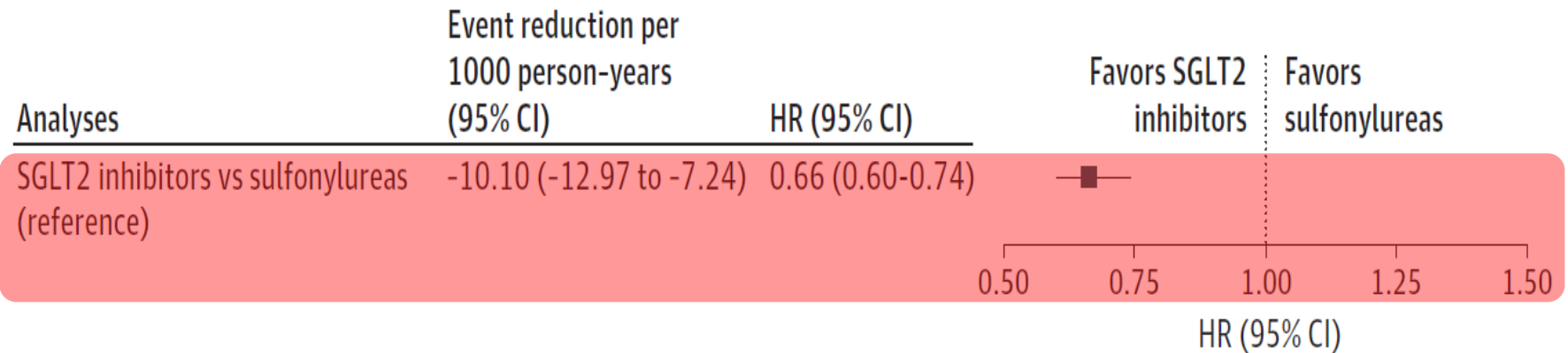


Figure 3. Per-Protocol Hazard Ratios (HRs) and Event Rate Reduction for All-Cause Mortality

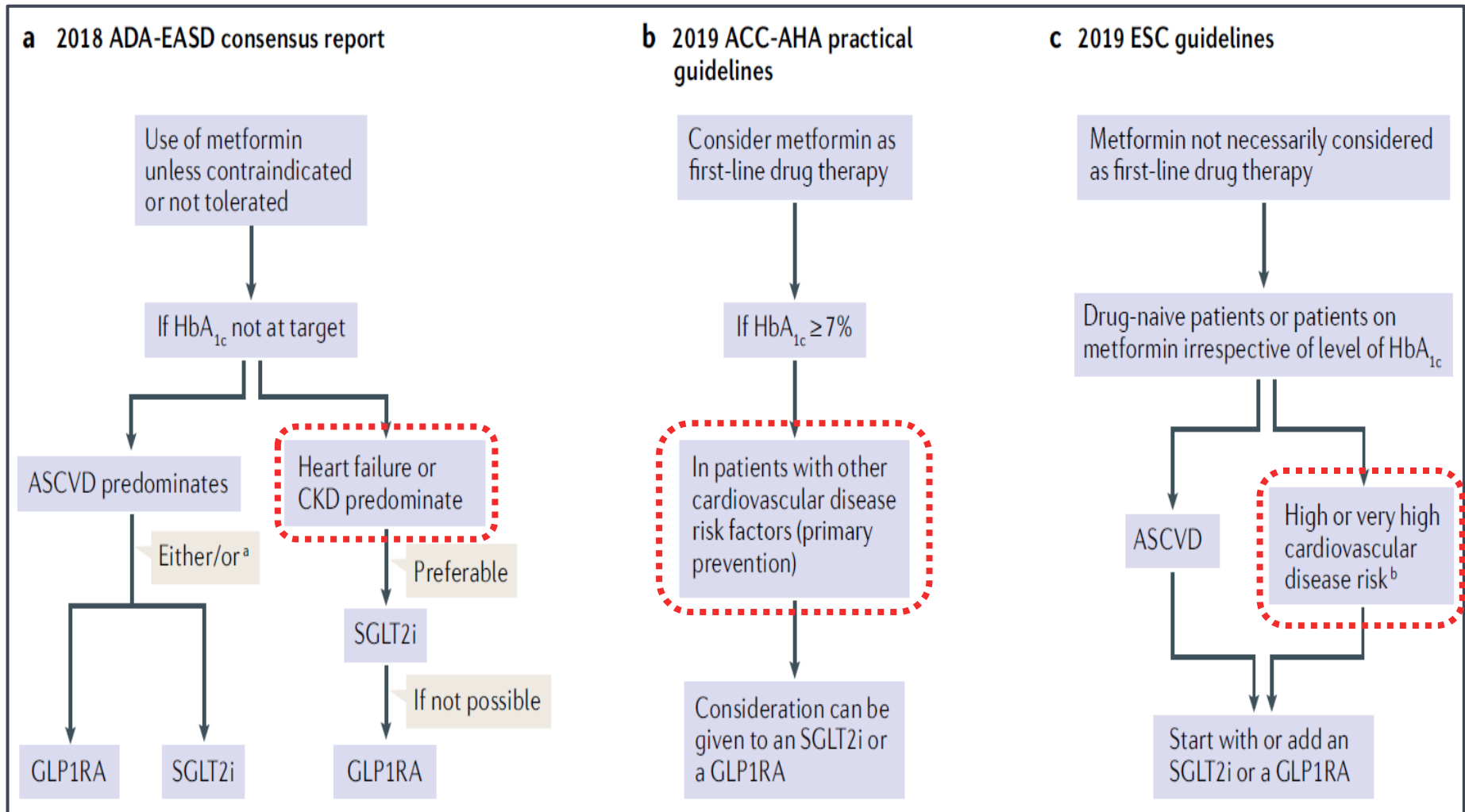


Hazard ratios of all-cause mortality in continued use of sodium-glucose cotransporter 2 (SGLT2) inhibitors or sulfonylureas (reference group) throughout follow-up (top graph) and continued use of SGLT2 inhibitors with metformin or SGLT2 inhibitors without metformin (reference group) throughout follow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



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



Together for a healthy future

team



No. 58, 8th St., Kooye Nasr (Gisha St.),
Tehran, IR Iran, Postal Code: 1446863914
Telefax: +98 (21) 41637000

www.actoverco.com



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