Prevention of CVD outcomes among patients with T2DM with or at high CVD risk: to start or not start with metformin

F. Hadaegh
Prevention of Metabolic Disorders Research Center,
Research Institute for Endocrine Sciences,
Shahid Beheshti University of Medical Sciences.

Jan 2023 – Tehran

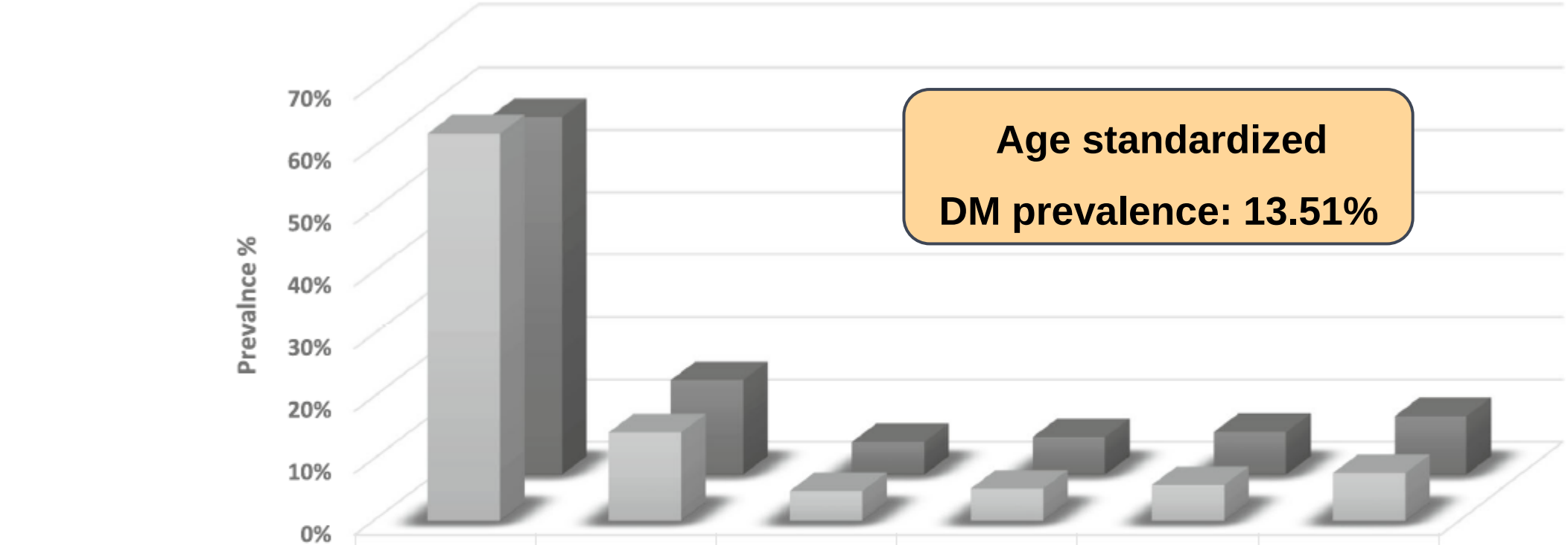
fzhadaegh@endocrine.ac.ir

Agenda

1. Cardiovascular Situation of Type 2 Diabetes Among Iranian Adults
2. Metformin and the UKPDS, What Did It Tell Us?
3. Post-hoc Analysis for Cardiovascular Outcome Trials (CVOTs)
4. Meta-analysis Not Supporting UKPDS Findings
5. RCT of Metformin on Surrogate of CVD and Meta-analysis/Systematic Reviews (Partially or Fully) Supporting UKPDS Findings
6. The European Society of Cardiology (ESC) 2021,ADA 2023 Guidelines on Diabetes, Pre-diabetes and CVD and updated clinical practice guideline
7. Real Data from Population Based Studies
8. Metformin efficacy and combination therapy
9. Take Home Massage

1

Cardiovascular Situation of Type 2 Diabetes Among Iranian Adults

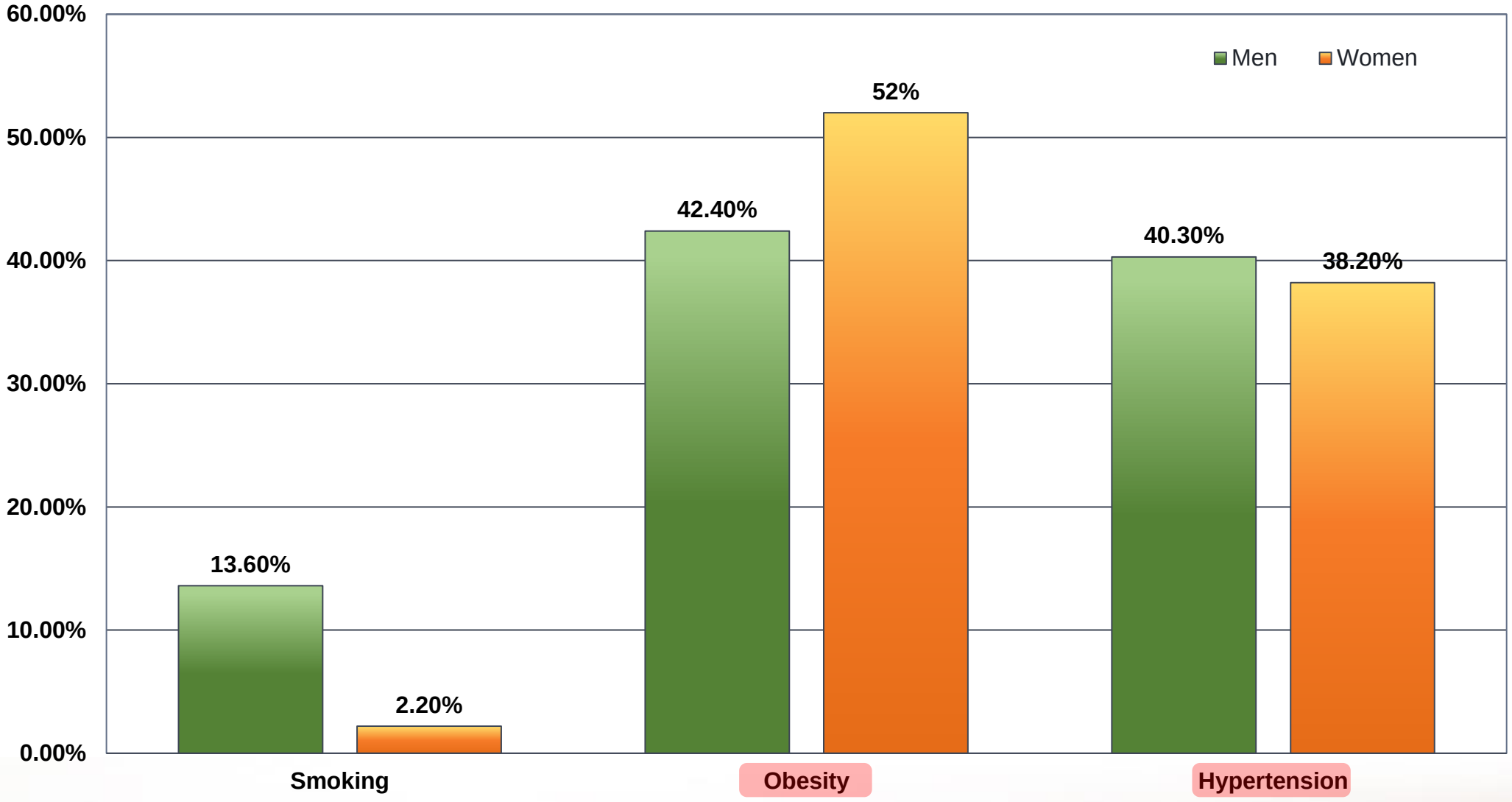


	NFG/NGT	iIFG	iIGT	IFG/IGT	NDM	KDM
Crude prevalence	57.30%	15.17%	5.23%	6.03%	6.85%	9.42%
Age-standardized prevalence*	62.20%	14.30%	4.81%	5.19%	5.79%	7.72%

Fig. 1 Prevalence of different glycemic status: Tehran Lipid and Glucose Study (phase IV: 2008–2011). * Age-standardized prevalence is calculated based on Iranian population distribution data from the National Consensus Bureau for Tehran province (2010). NFG: normal fasting glucose; NGT: normal glucose tolerance; iIFG: isolated impaired fasting glucose; iIGT: isolated impaired glucose tolerance; IFG/IGT: both impaired fasting glucose and impaired glucose tolerance; NDM: newly diagnosed diabetes mellitus; KDM: known diabetes mellitus

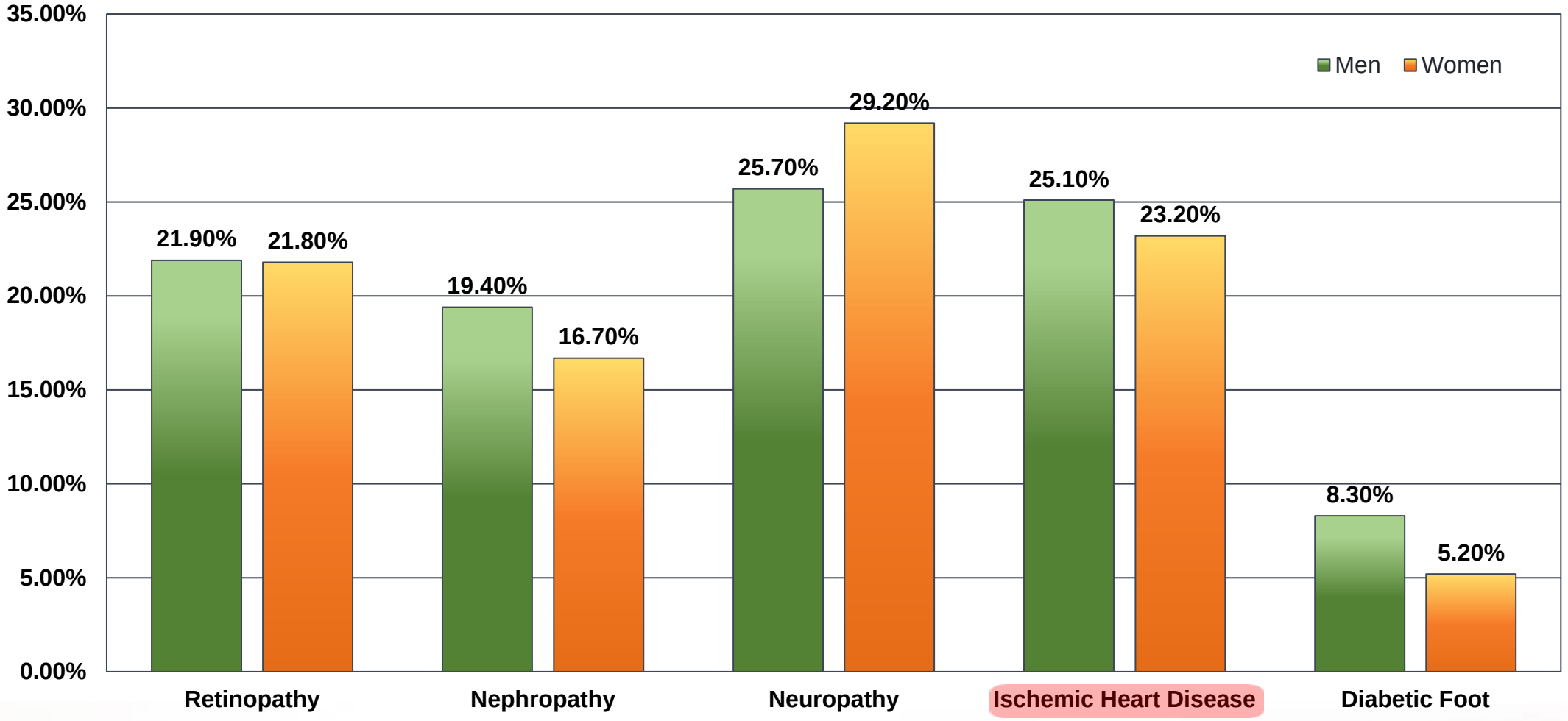
Sex-specific prevalence of coronary heart disease among Tehranian adult population across different glycemic status: Tehran lipid and glucose study, 2008-2011. BMC Public Health . 2020 Oct 6;20(1):1510

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.

Table 2 Prevalence of coronary heart diseases across glycemic categories, by gender: Tehran Lipid and Glucose Study (phase IV: 2008–2011)

	Men			Women		
	Case/Total	Crude prevalence % (95% CI)	Age-standardized prevalence [a] % (95% CI)	Case/Total	Crude prevalence % (95% CI)	Age-standardized prevalence [a] % (95% CI)
NFG/NGT	139/1891	7.35 (6.17–8.53)	7.28 (6.06–8.49)	108/2531	4.27 (3.48–5.05)	5.71 (4.62–6.79)
Prediabetes (IFG or IGT)	126/1000	12.60 (10.54–14.66)	7.95 (6.55–9.36)	88/1040	8.46 (6.77–10.15)	6.62 (5.06–8.19)
DM	133/536	24.81 (21.15–28.47)	13.10 (9.83–16.38)	156/720	21.67 (18.65–24.68)	10.67 (8.90–12.44)
Total	398/3427	11.61 (10.54–12.69)	8.62 (7.81–9.44)	352/4291	8.20 (7.38–9.02)	7.19 (6.46–7.93)

NFG Normal fasting glucose, *NGT* Normal glucose tolerance, *IFG* Impaired fasting glucose, *IGT* Impaired glucose tolerance, *DM* Diabetes mellitus, *CI* Confidence interval

[a]Age-standardized prevalence is calculated based on Iranian population distribution data from the National Consensus Bureau for Tehran province (2010)

Crude CHD prevalence among patients with diabetes in Tehran

Men: 25% , Women: 22%

Crude CHD prevalence among whole population in Tehran

Men: 12% , Women: 8%

Sex-specific prevalence of coronary heart disease among Tehranian adult population across different glycemic status: Tehran lipid and glucose study, 2008-2011. BMC Public Health . 2020 Oct 6;20(1):1510

2

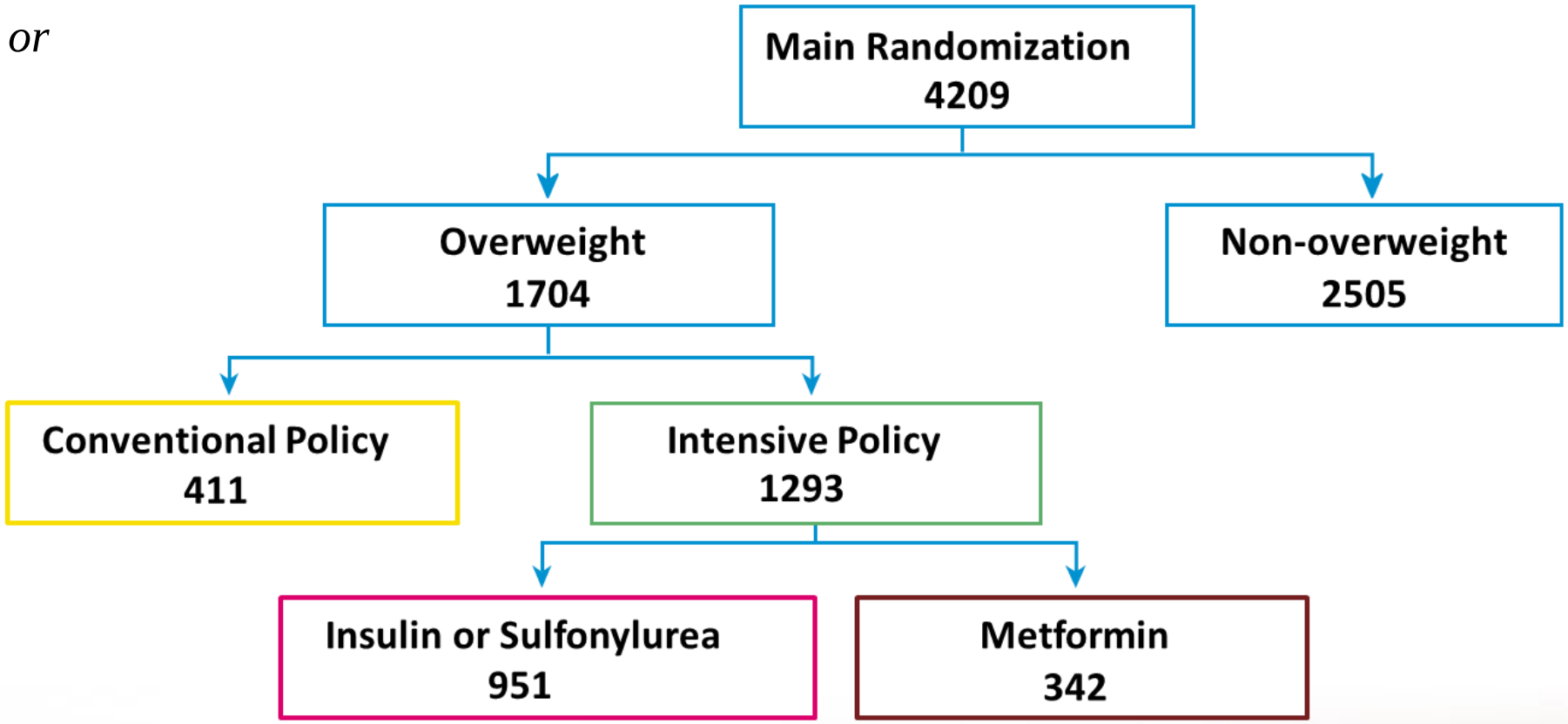
Metformin and the UKPDS, What Did It Tell Us?

This study investigated whether intensive glucose control with metformin has any specific advantage or disadvantage

UKPDS

Metformin Sub study Design

Aim: to determine effect of metformin on outcome in overweight patients with type 2 diabetes



Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). The Lancet. 1998 Sep 12;352(9131):854-65.

AGGREGATE ENDPOINT	p for metformin *vs* other intensive	Patients with aggregate endpoints		Absolute risk (events per 1000 patient-years)		Log-rank 2p	RR (95% CI) *vs* conventional
		Metformin or intensive	Conventional	Metformin or intensive	Conventional		
Any diabetes-related endpoint	p=0·0034						
Metformin		98	160	29·8	43·3	0·0023	0·68 (0·53–0·87)
Intensive		350	160	40·1	43·3	0·46	0·93 (0·77–1·12)
Diabetes-related death	p=0·11						
Metformin		28	55	7·5	12·7	0·017	0·58 (0·37–0·91)
Intensive		103	55	10·3	12·7	0·19	0·80 (0·58–1·11)
All-cause mortality	p=0·021						
Metformin		50	89	13·5	20·6	0·011	0·64 (0·45–0·91)
Intensive		190	89	18·9	20·6	0·49	0·92 (0·71–1·18)
Myocardial infarction	p=0·12						
Metformin		39	73	11·0	18·0	0·01	0·61 (0·41–0·89)
Intensive		139	73	14·4	18·0	0·11	0·79 (0·60–1·05)
Stroke	p=0·032						
Metformin		12	23	3·3	5·5	0·13	0·59 (0·29–1·18)
Intensive		60	23	6·2	5·5	0·60	1·14 (0·70–1·84)
Peripheral vascular disease	p=0·62						
Metformin		6	9	1·6	2·1	0·57	0·74 (0·26–2·09)
Intensive		12	9	1·2	2·1	0·18	0·56 (0·24–1·33)
Microvascular	p=0·39						
Metformin		24	38	6·7	9·2	0·19	0·71 (0·43–1·19)
Intensive		74	38	7·7	9·2	0·38	0·84 (0·57–1·24)

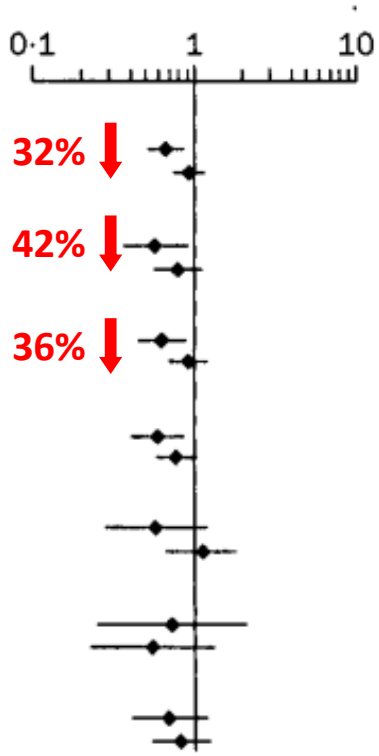


Figure 6: **Incidence of clinical endpoints among patients assigned intensive control with metformin (n=342), intensive control with chlorpropamide, glibenclamide, or insulin (intensive; n=951), or conventional control (n=411)**

Relative risk (RR) is for metformin or intensive group compared with conventional group.

The NEW ENGLAND JOURNAL of MEDICINE
2008 Oct 9;359(15):1577-89

ORIGINAL ARTICLE

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D.,

Background: During the United Kingdom Prospective Diabetes Study (UKPDS), patients with type 2 diabetes mellitus who received intensive glucose therapy had a lower risk of microvascular complications than did those receiving conventional dietary therapy. We conducted post-trial monitoring to determine whether this improved glucose control persisted and whether such therapy had a long-term effect on macrovascular outcomes.

Methods: Of 5102 patients with newly diagnosed type 2 diabetes, 4209 were randomly assigned to receive either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea or insulin or, in overweight patients, Metformin) for glucose control. In post-trial monitoring, 3277 patients were asked to attend annual UKPDS clinics for 5 years, but no attempts were made to maintain their previously assigned therapies.

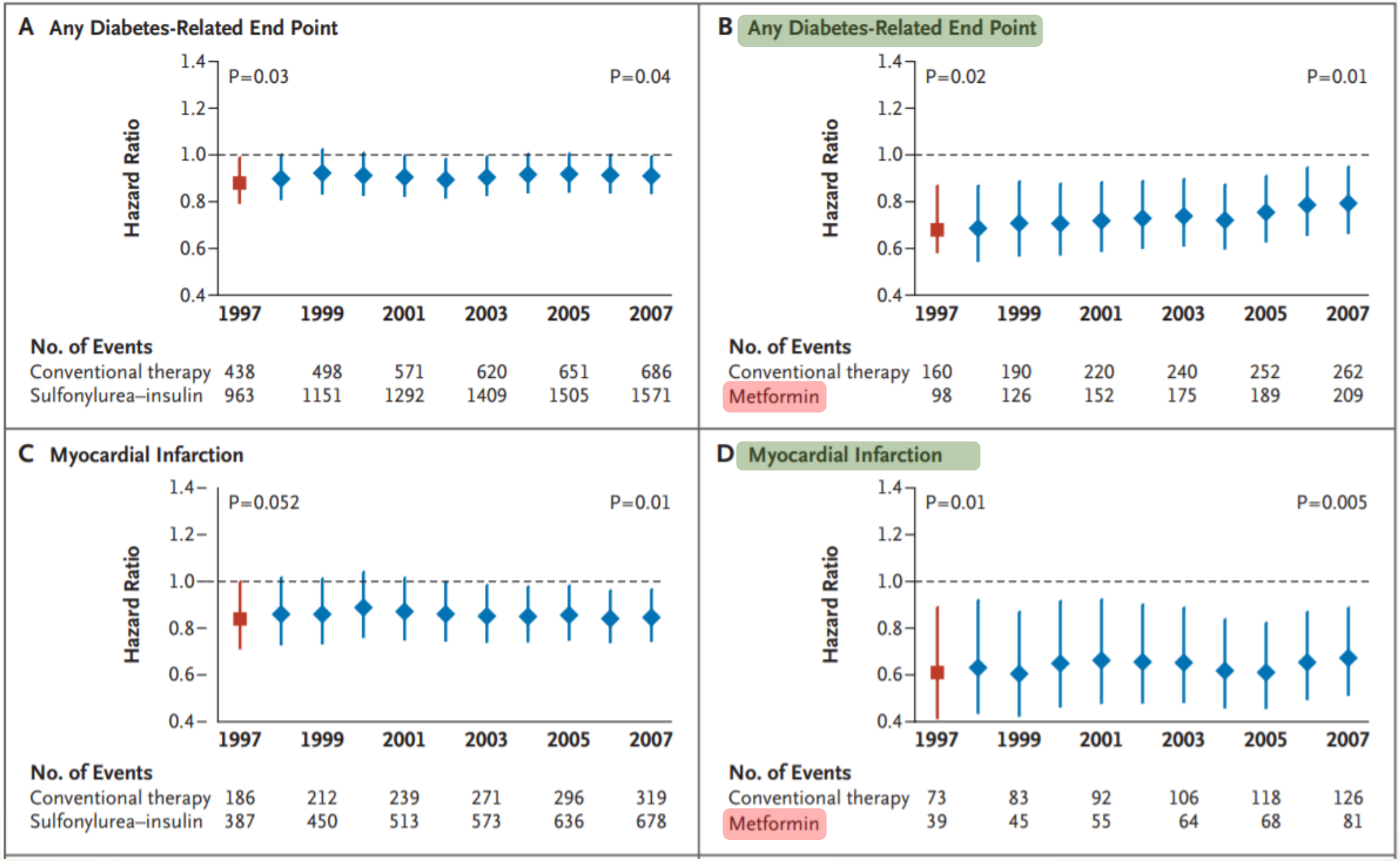


Figure 4 Kaplan–Meier Curves for Four Prespecified Aggregate Clinical Outcomes. Kaplan–Meier plots for cumulative incidence and log-rank P values are shown at 5-year intervals during a 25-year period from the start of the interventional trial.

10-year follow-up of intensive glucose control in type 2 diabetes. New England journal of medicine. 2008 Oct 9;359(15):1577-89.

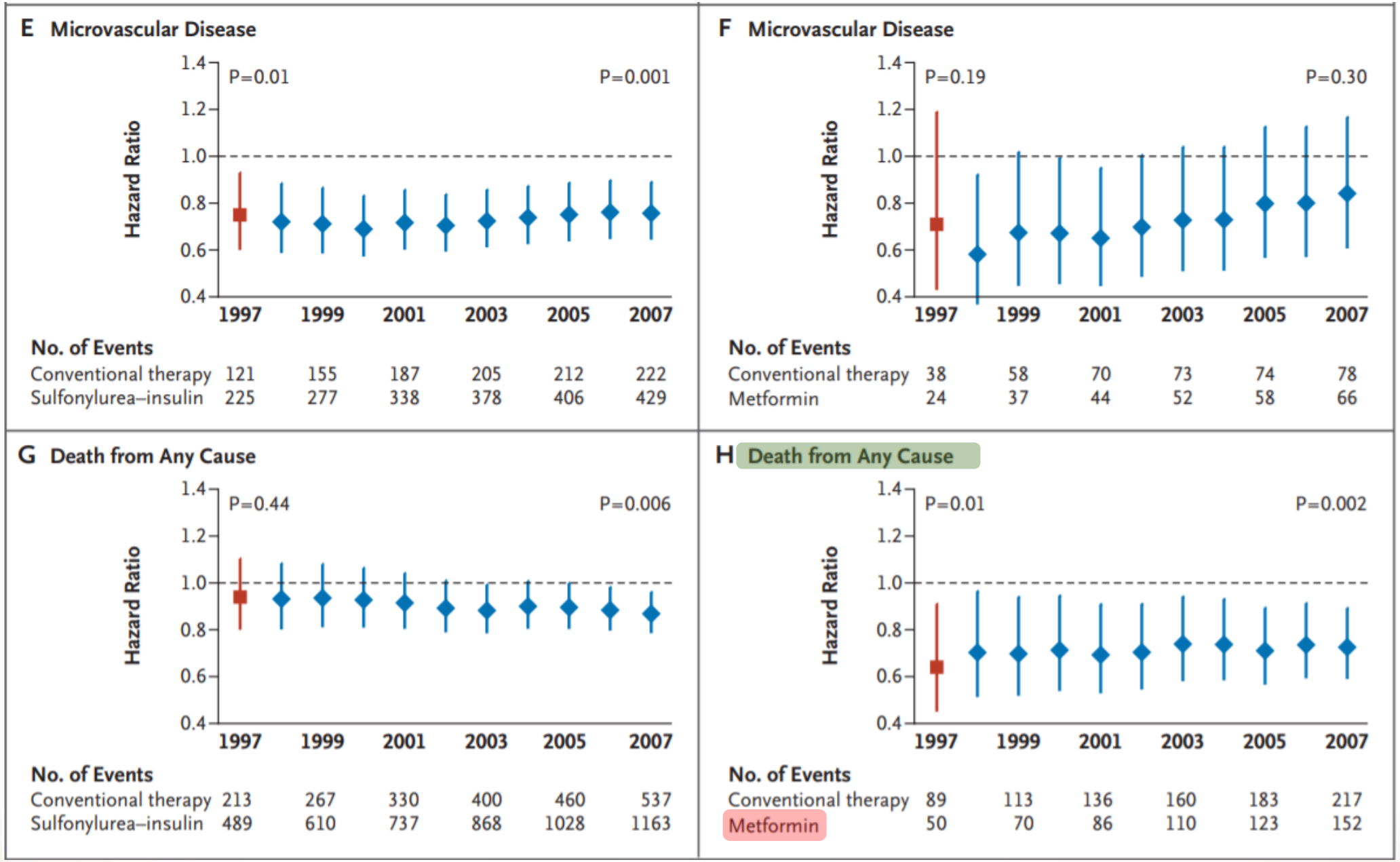


Figure 4 Kaplan–Meier Curves for Four Prespecified Aggregate Clinical Outcomes. Kaplan–Meier plots for cumulative incidence and log-rank P values are shown at 5-year intervals during a 25-year period from the start of the interventional trial.

10-year follow-up of intensive glucose control in type 2 diabetes. New England journal of medicine. 2008 Oct 9;359(15):1577-89.

3

Post-hoc Analysis for Cardiovascular Outcome Trials (CVOTs)

Metformin and CV outcomes

- There is no recent CVOT for metformin. These were introduced in 2008 for new anti-diabetes medications. At that point, metformin was marketed for 49 years.
- The design of the CVOT is derived from UKPDS, in which metformin demonstrated cardiovascular benefit and which pathed metformin 1st line treatment.
- UKPDS was an interventional glucose-lowering program, whereas CVOT aim for glycemic equipoise.
- A CVOT for metformin would not be feasible/ethical in T2DM patients versus placebo, as metformin is standard of care.
- Acute myocardial infarction and unstable angina are contraindications to metformin treatment, as these hypoxic states increase the risk of acidosis.

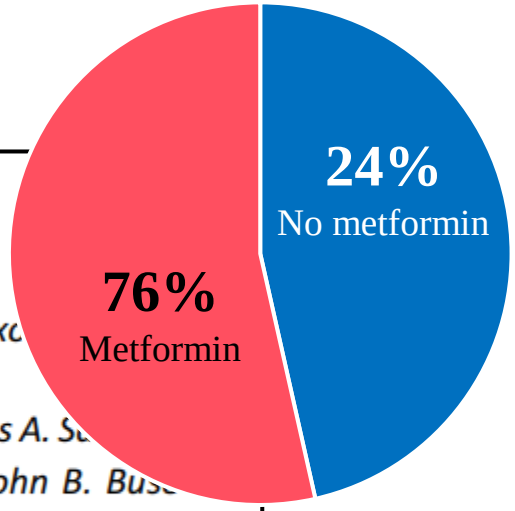
Two major prospective CVOT for metformin in prediabetes are listed on clinicaltrials.gov:

- **VA-IMPACT (USA)**
- **GLINT (UK)**

Effects of Liraglutide on Cardiovascular Outcomes in Type 2 Diabetes Patients With and Without Baseline Metformin Use: Post Hoc Analyses of the LEADER Trial

Matthew J. Crowley,[1,2] Darren K. McGuire,[3] Anastasia-Stefania Alexc Thomas Jon Jensen,[4] Søren Rasmussen,[4] Hans A. Sc Subodh Verma,[5] and John B. Buse

Diabetes Care 2020;43:e108–e110 | https://doi.org/10.2337/dc20-0437



The major inclusion criteria were the following: an age of 50 years or more with at least one cardiovascular coexisting condition (CVD, PVD, CKD of stage 3 or greater, or CHF of New York Heart Association class II or III).

Age of 60 years or more with at least one cardiovascular risk factor, as determined by the investigator (microalbuminuria or proteinuria, hypertension and LVH, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index of less than 0.9).

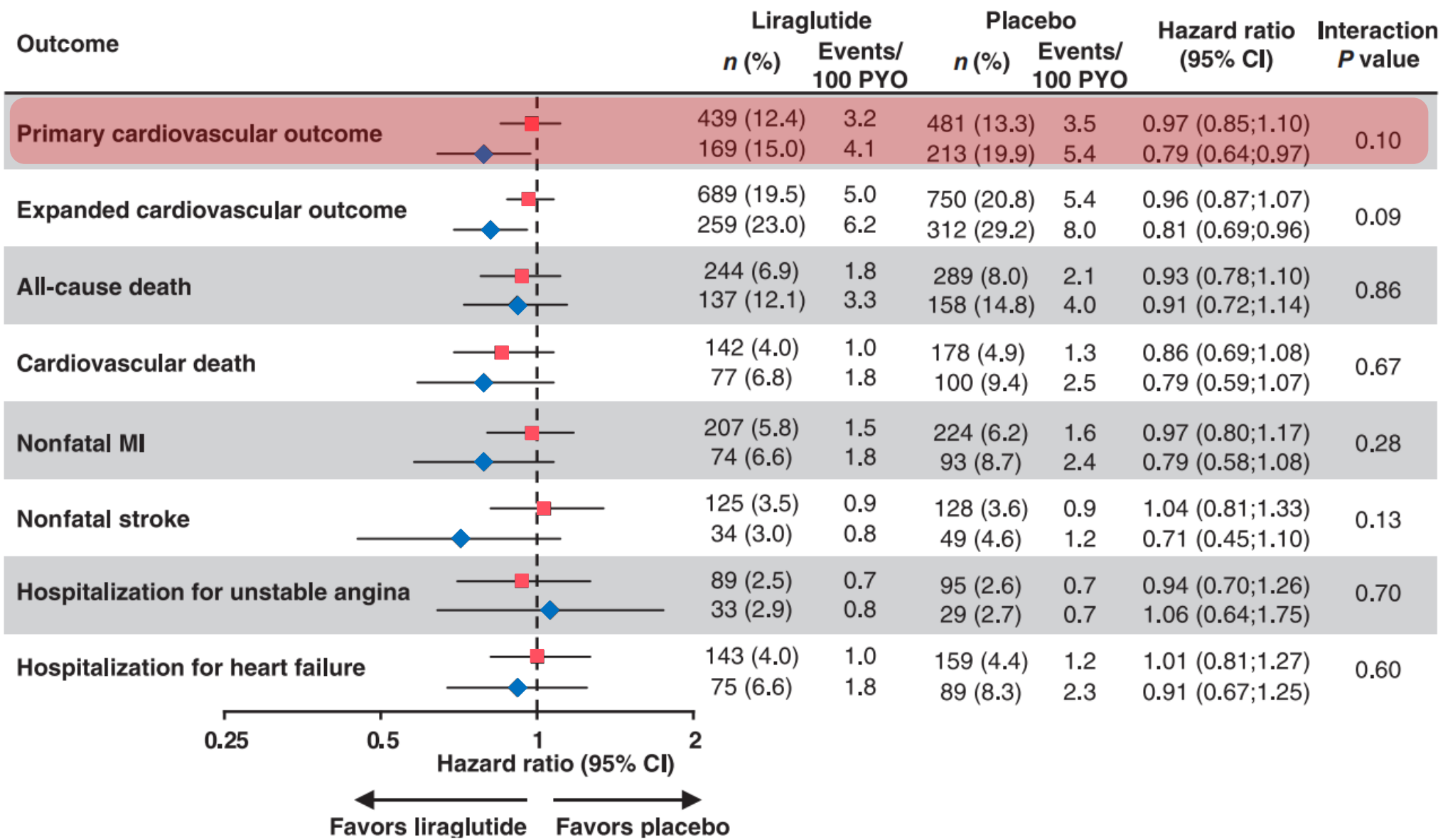


Figure 1—Effects of liraglutide (vs. placebo) on CV outcomes among patients with and without baseline metformin use, adjusted for baseline covariates with inverse probability weighting. HRs derived using a Cox proportional hazards regression model with randomization group, baseline metformin exposure, and the interaction of both as factors, and diabetes duration, eGFR, and age at baseline as additional covariates, adjusted for other baseline covariance including prevalent CVD.

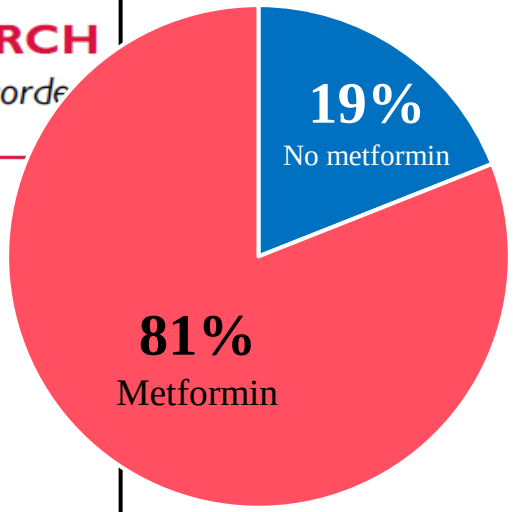
Effects of liraglutide on cardiovascular outcomes in type 2 diabetes patients with and without baseline metformin use: post hoc analyses of the LEADER trial. Diabetes care. 2020 Sep 1;43(9):e108-10.

ESC European Society of Cardiology
European Heart Journal (2020) **00**, 1–9
doi:10.1093/eurheartj/ehaa777

CLINICAL RESEARCH
Diabetes and metabolic disorde

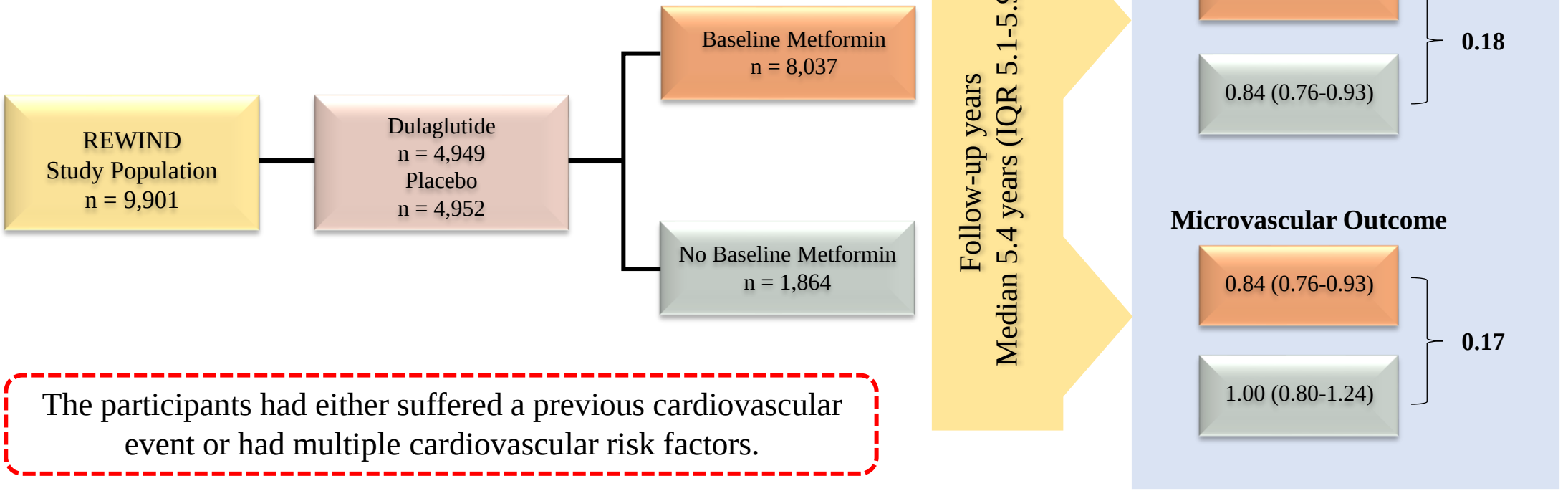
Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin

Giulia Ferrannini [1]*, Hertzel Gerstein [2], Helen Martina Colhoun [3],



In this post hoc analysis, the effect of dulaglutide on CV events was investigated according to the baseline metformin therapy by means of a subgroup analysis of the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial.

Eligible patients were ≥50 years old with type 2 diabetes, HbA1c≤9.5% and BMI ≥ 23 kg/m2 and were on stable treatment for at least 3months with 0–2 glucose-lowering drugs, with or without basal insulin.



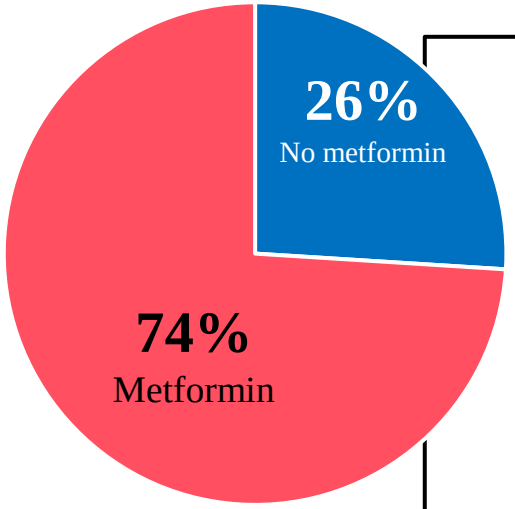
The participants had either suffered a previous cardiovascular event or had multiple cardiovascular risk factors.

Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin. European heart journal. 2021 Jul 7;42(26):2565-73.

Limitation:

- **First**, the study population is a selected trial cohort of people with type 2 diabetes at high cardiovascular risk or with established CVD that may not be fully representative of a wider population of such patients.
- **Second**, REWIND was not specifically designed to assess difference between groups according to baseline therapy; therefore, these results should be considered indicative rather than proof of evidence.

Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin. European heart journal. 2021 Jul 7;42(26):2565-73.



Circulation

Circulation. 2019;140:1004–1014. DOI: 10.1161/CIRCULATIONAHA.119.040144

ORIGINAL RESEARCH ARTICLE

Brian A. Bergmark, MD

Metformin Use and Clinical Outcomes Among Patients With Diabetes Mellitus With or Without Heart Failure or Kidney Dysfunction

Observations From the SAVOR-TIMI 53 Trial

Background: Metformin is first-line therapy for type 2 diabetes mellitus, although its effects on the cardiovascular system are unproved.

Methods: SAVOR-TIMI 53 was a multinational, randomized, controlled, double-blind, event-driven trial among patients with T2DM and moderate to high cardiovascular risk as determined by prior manifest cardiovascular disease or multiple cardiovascular risk factors.

Patients were randomized to receive the dipeptidyl peptidase-4 inhibitor saxagliptin or matching placebo with concurrent glucose-lowering medications and cardiovascular therapies, including diet and lifestyle modification, managed by the treating clinician.

Results: Of the 12 156 patients with baseline biomarker samples, 8971 (74%) had metformin exposure, 1611 (13%) had prior heart failure, and 1332 (11%) had at least moderate chronic kidney disease (estimated glomerular filtration rate ≤45 mL·min−1·1.73 m−2).

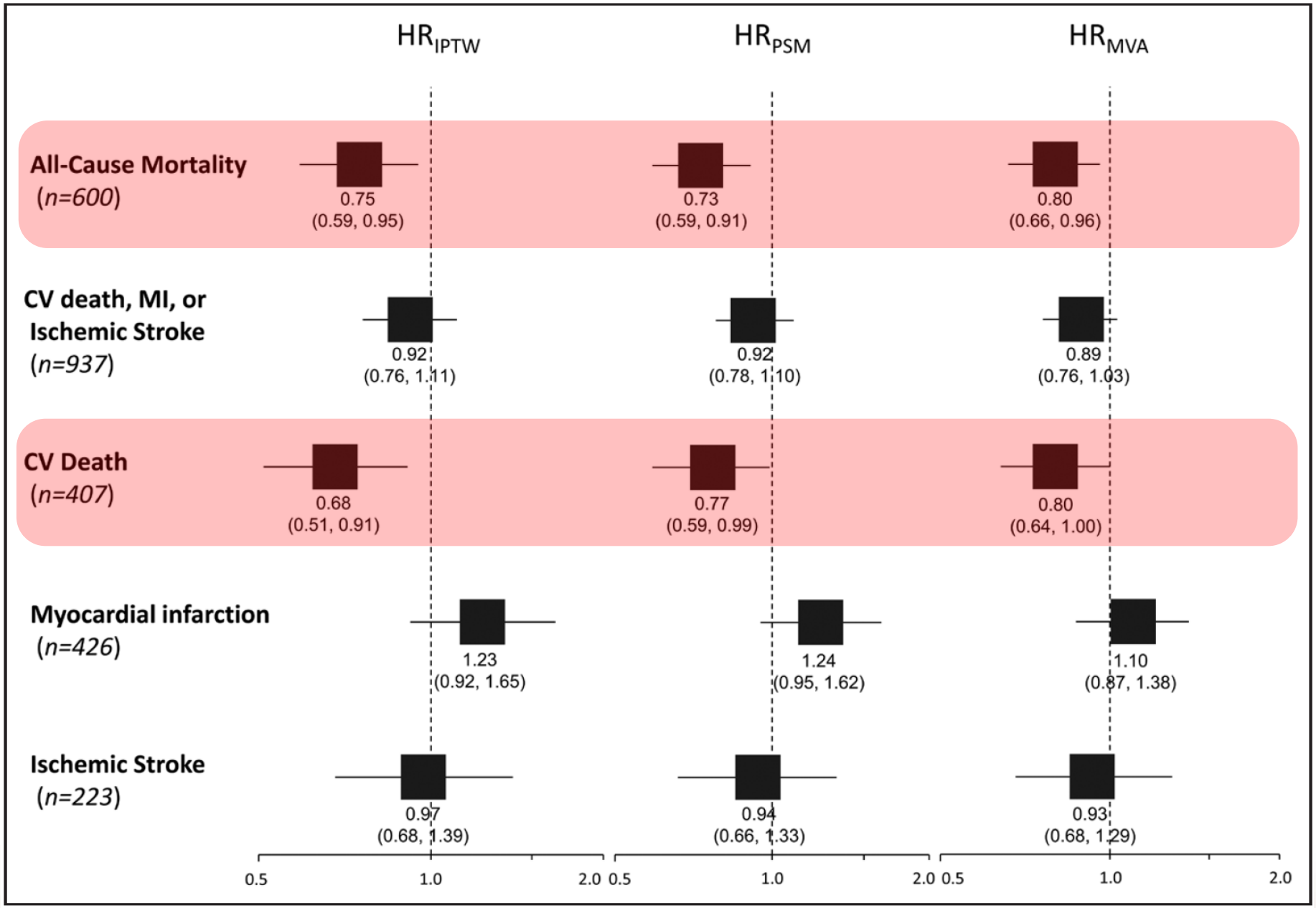


Fig.1
Risk of clinical events by inverse probability of treatment weighting (IPTW), propensity score matching (PSM), and multivariable analysis (MVA).

Metformin use and clinical outcomes among patients with diabetes mellitus with or without heart failure or kidney dysfunction: observations from the SAVOR-TIMI 53 trial. Circulation. 2019 Sep 17;140(12):1004-14.

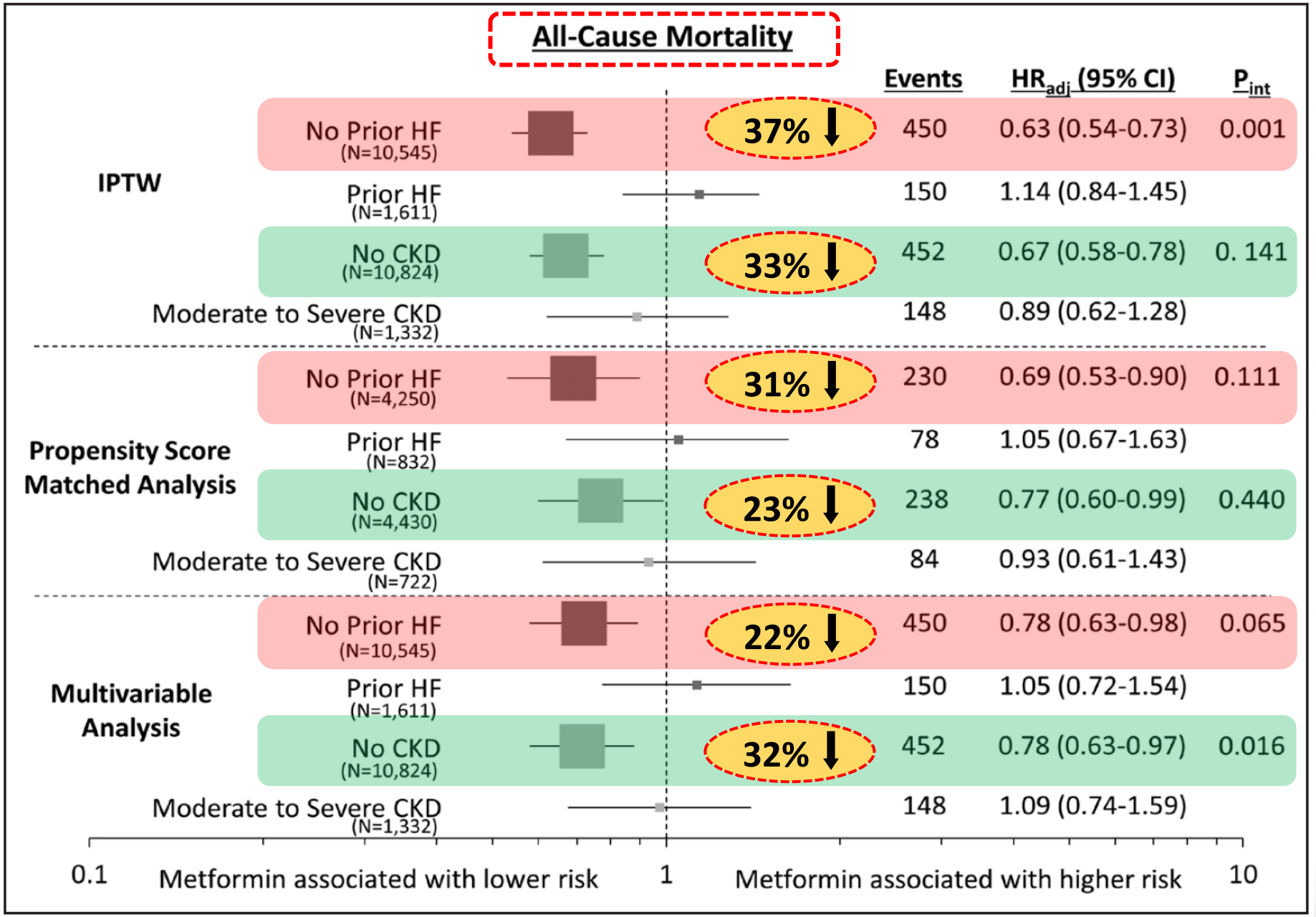


Fig.2
Risk of all-cause mortality by inverse probability of treatment weighting (IPTW), propensity score matching, and multivariable analysis in patients with prior heart failure (HF) or moderate to severe chronic kidney disease (CKD).

Metformin use and clinical outcomes among patients with diabetes mellitus with or without heart failure or kidney dysfunction: observations from the SAVOR-TIMI 53 trial. Circulation. 2019 Sep 17;140(12):1004-14.

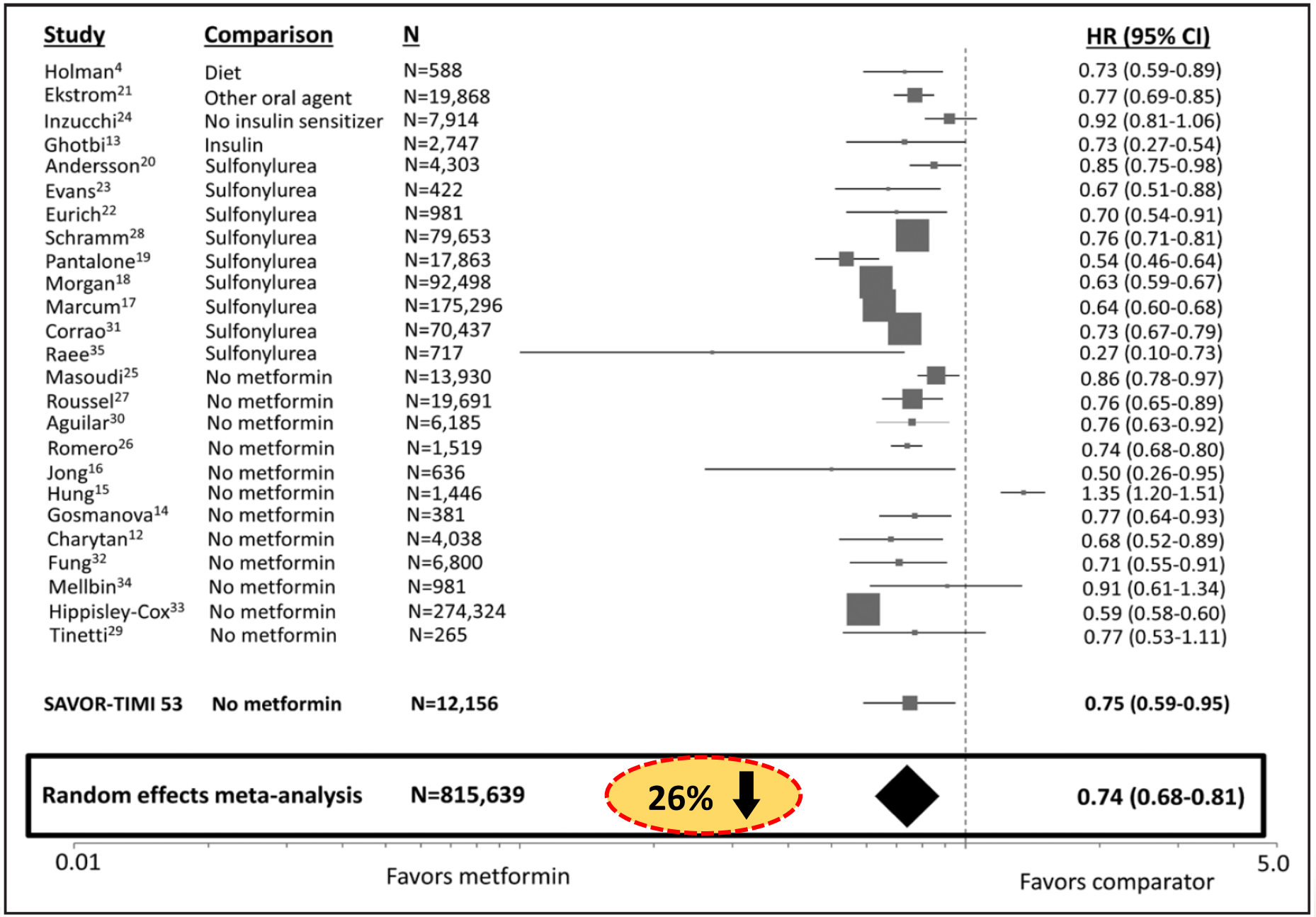


Fig.3
Meta-analysis of studies reporting all-cause mortality based on metformin exposure status and including at least 200 patients with metformin exposure

Metformin use and clinical outcomes among patients with diabetes mellitus with or without heart failure or kidney dysfunction: observations from the SAVOR-TIMI 53 trial. Circulation. 2019 Sep 17;140(12):1004-14.

Conclusion:

In a cohort of 12 156 patients with type 2 diabetes mellitus and high cardiovascular risk, Metformin use was associated with lower rates of all-cause mortality, including after adjustment for clinical variables and biomarkers, but not lower rates of the composite end point of MACE. This association was most apparent in patients without prior heart failure or moderate to severe chronic kidney disease.

Metformin use and clinical outcomes among patients with diabetes mellitus with or without heart failure or kidney dysfunction: observations from the SAVOR-TIMI 53 trial. Circulation. 2019 Sep 17;140(12):1004-14.

The NEW ENGLAND JOURNAL of MEDICINE

2021;385:896-907

ORIGINAL ARTICLE

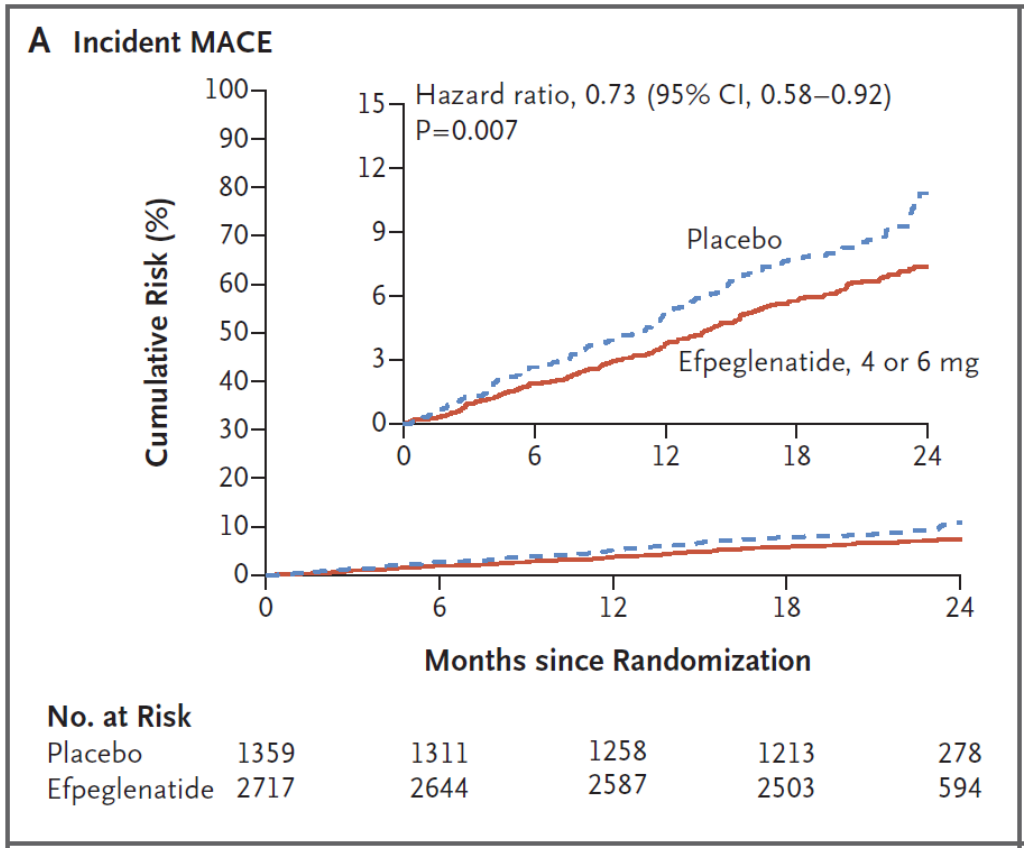
Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes

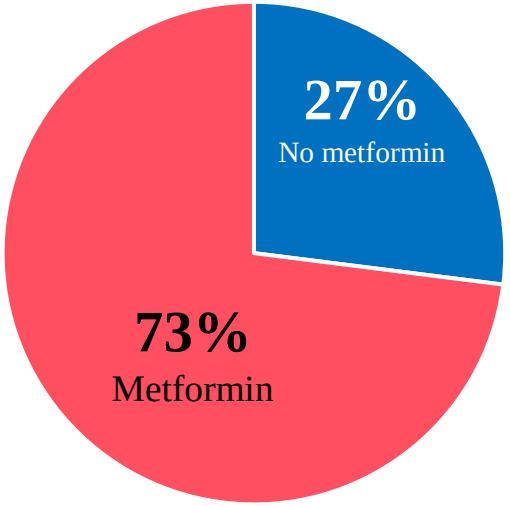
BACKGROUND

The effect of an exendin-based GLP-1 receptor agonist, efpeglenatide, on cardiovascular and renal outcomes in patients with type 2 diabetes who are also at high risk for adverse cardiovascular events is uncertain.

METHODS

In this randomized, placebo-controlled trial conducted at 344 sites across 28 countries, we evaluated efpeglenatide in participants with type 2 diabetes and either a history of cardiovascular disease or current kidney disease (defined as an estimated glomerular filtration rate of 25.0 to 59.9 ml per minute per 1.73 m2 of body-surface area) plus at least one other cardiovascular risk factor.





Subgroup	Efpeglenatide, 4 or 6 mg	Placebo	Efpeglenatide, 4 or 6 mg	Placebo	Hazard Ratio for an Incident MACE (95% CI)
	no. of events/total no. (%)		*no. of events per 100 person-yr*		
Metformin use at baseline					
Yes	127/1993 (6.4)	87/992 (8.8)	3.6	5.0	0.70 (0.53–0.92)
No	62/724 (8.6)	38/367 (10.4)	4.9	6.0	0.80 (0.54–1.20)

0.5 1.0 2.0
Efpeglenatide Better Placebo Better

Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. New England Journal of Medicine. 2021 Sep 2;385(10):896-907.

4

Meta-analysis Not Supporting UKPDS Findings

Diabetologia (2017) 60:1620–1629
DOI 10.1007/s00125-017-4337-9

REVIEW

Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes

Simon J. Griffin [1,2] · James K. Leaver [1] · Greg J. Irving [1]

Aims: We aimed to systematically identify and pool randomized trials reporting cardiovascular outcomes in which the effect of metformin was 'isolated' through comparison to diet, lifestyle or placebo.

Methods: We performed an electronic literature search of MEDLINE, EMBASE and the Cochrane Library. We also manually screened the reference lists of previous meta-analyses of trials of metformin identified through a MEDLINE search. We included RCTs of adults with type 2 diabetes comparing any dose and preparation of oral metformin with no intervention, placebo or a lifestyle intervention and reporting mortality or a cardiovascular outcome.

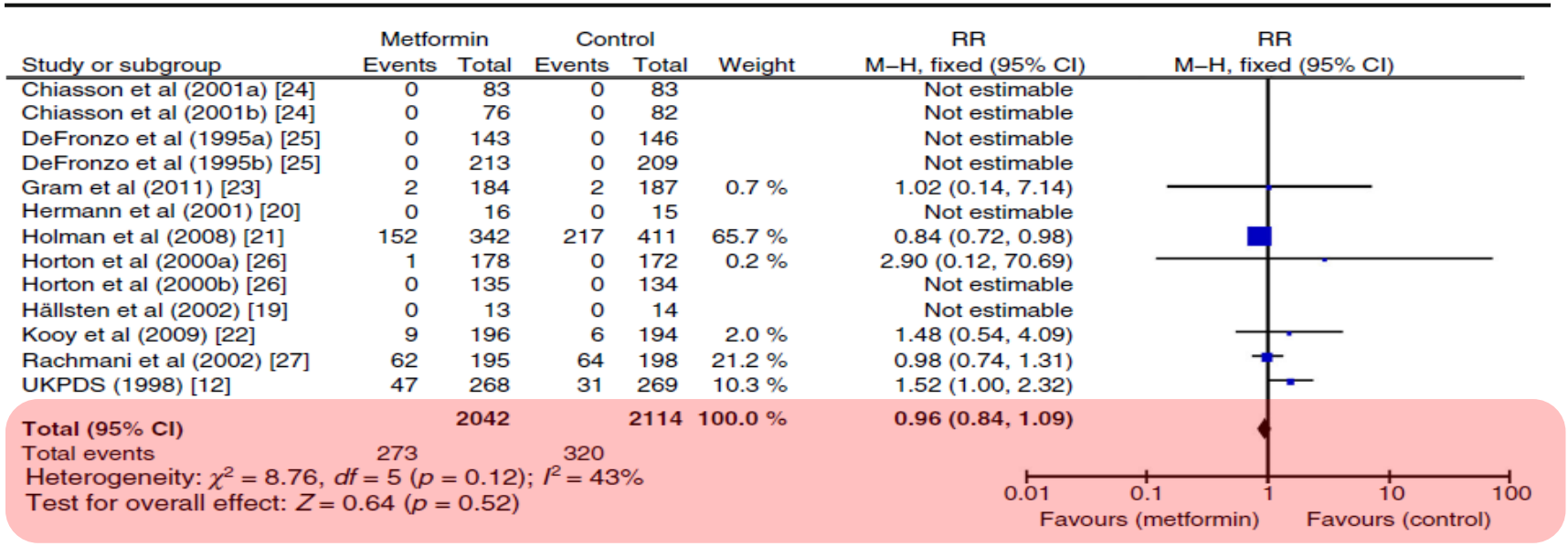


Fig. 3
Forest plot showing the effect of metformin on risk of all-cause mortality

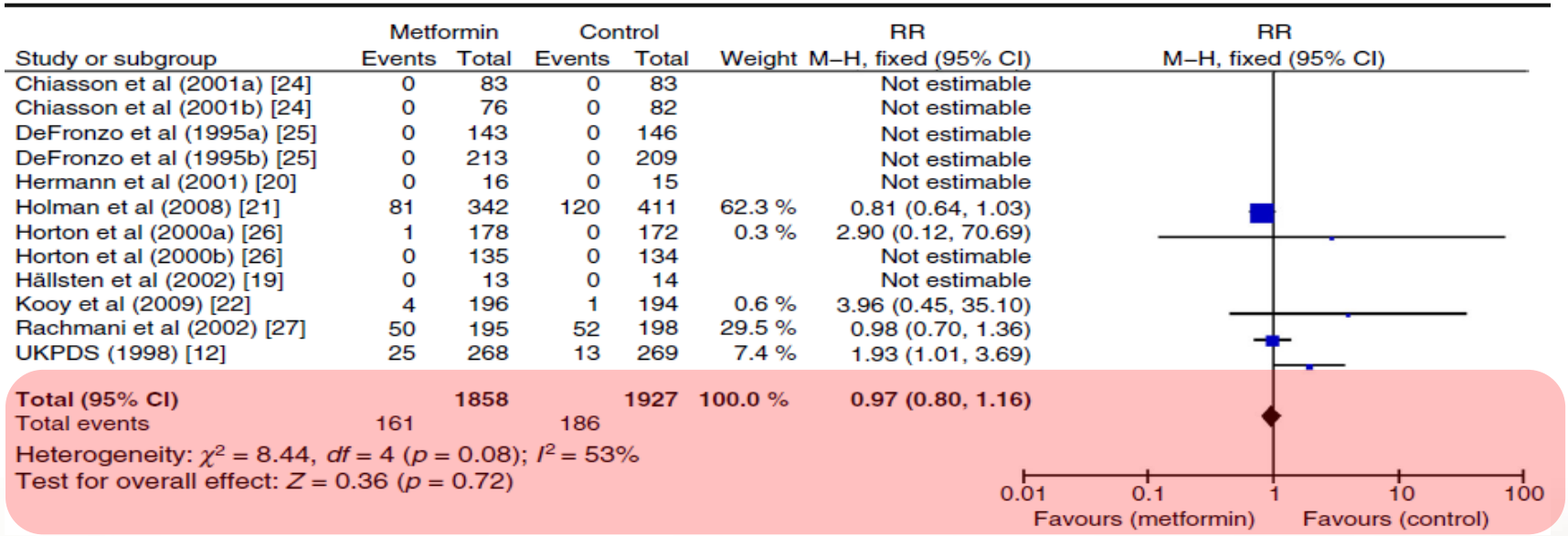


Fig. 4
Forest plot showing the effect of metformin on risk of cardiovascular death

Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. Diabetologia. 2017 Sep;60(9):1620-9.

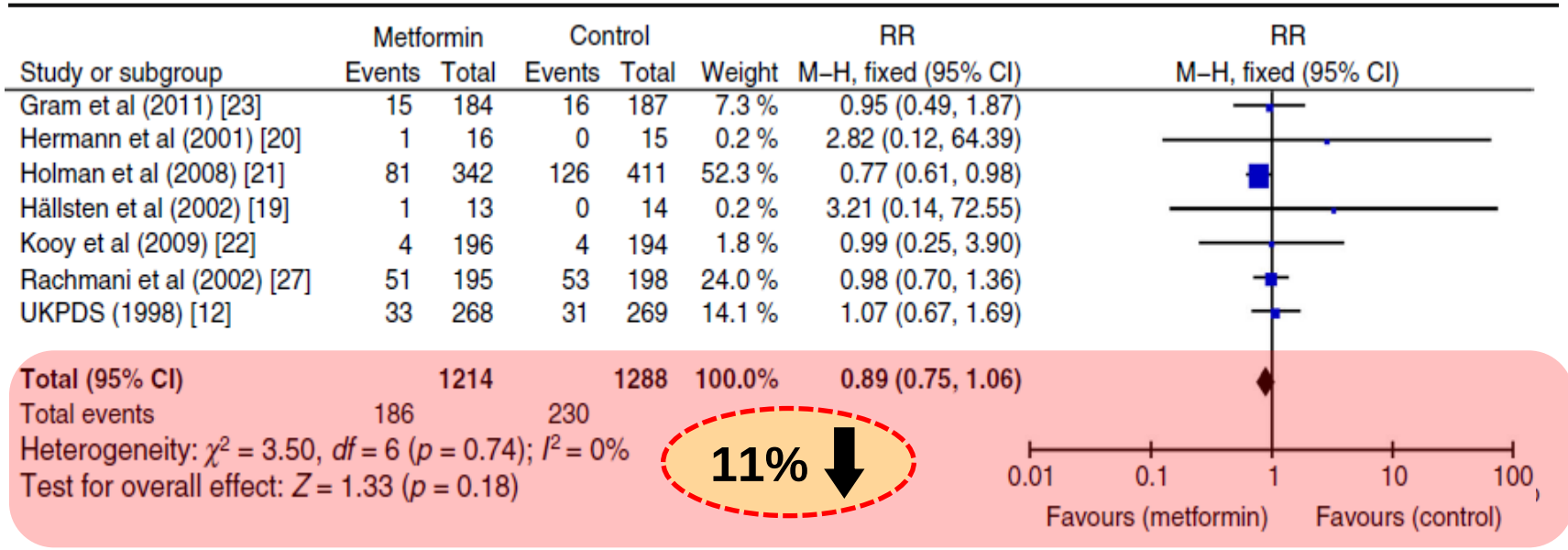


Fig. 5
Forest plot showing the effect of metformin on risk of myocardial infarction

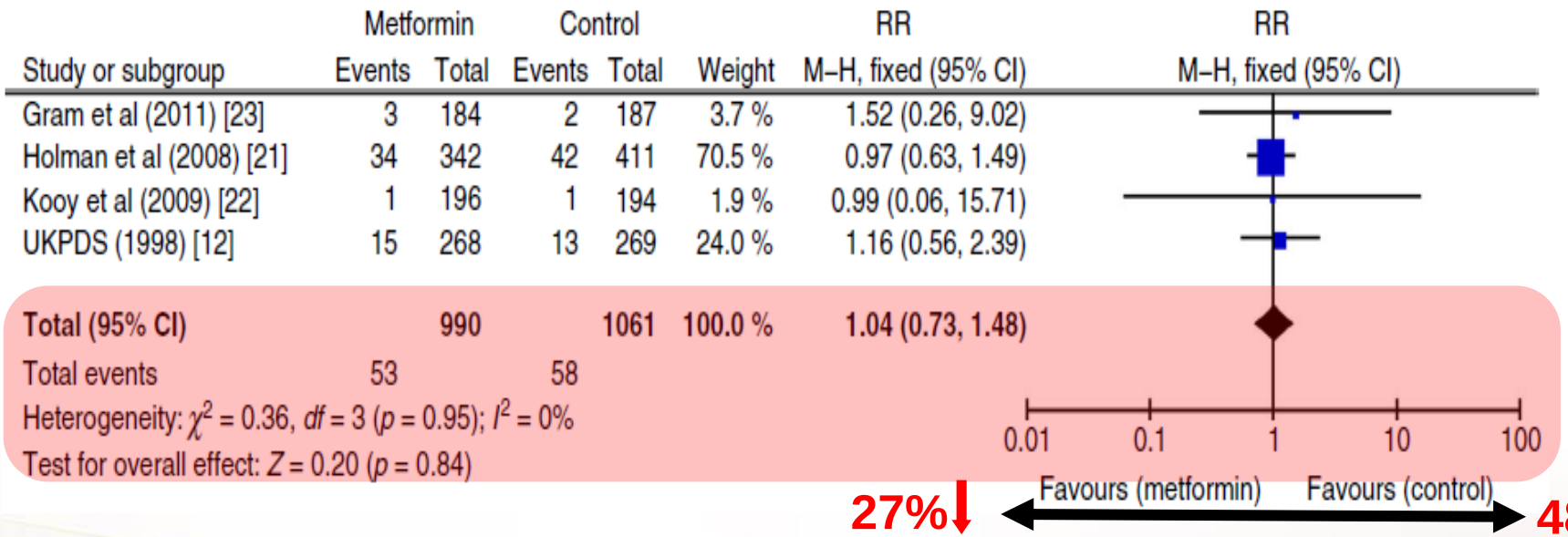


Fig. 6
Forest plot showing the effect of metformin on risk of stroke

Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. Diabetologia. 2017 Sep;60(9):1620-9.

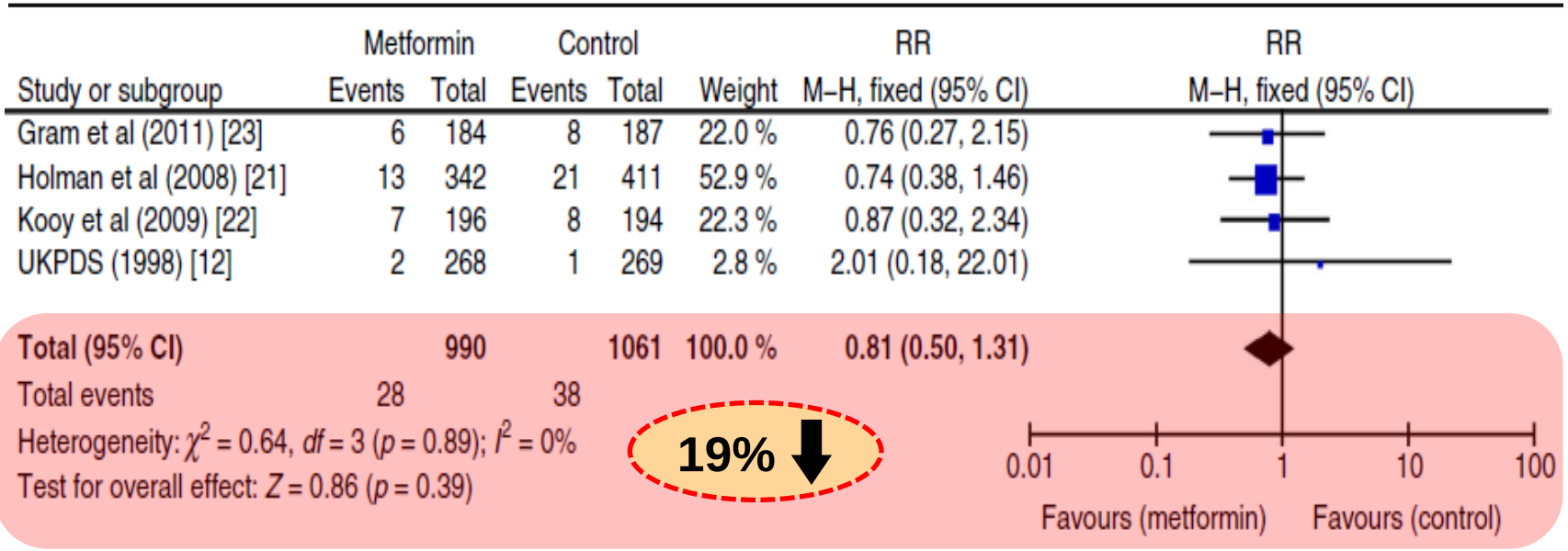


Fig. 7
Forest plot showing the effect of metformin on risk of peripheral vascular disease

All outcomes, with the exception of stroke, favored Metformin, with limited heterogeneity between studies, but none achieved statistical significance.

Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. Diabetologia. 2017 Sep;60(9):1620-9.

ESC European Society of Cardiology

European Journal of Preventive Cardiology (2021) **28**, 69–75
doi:10.1093/eurjpc/zwaa074

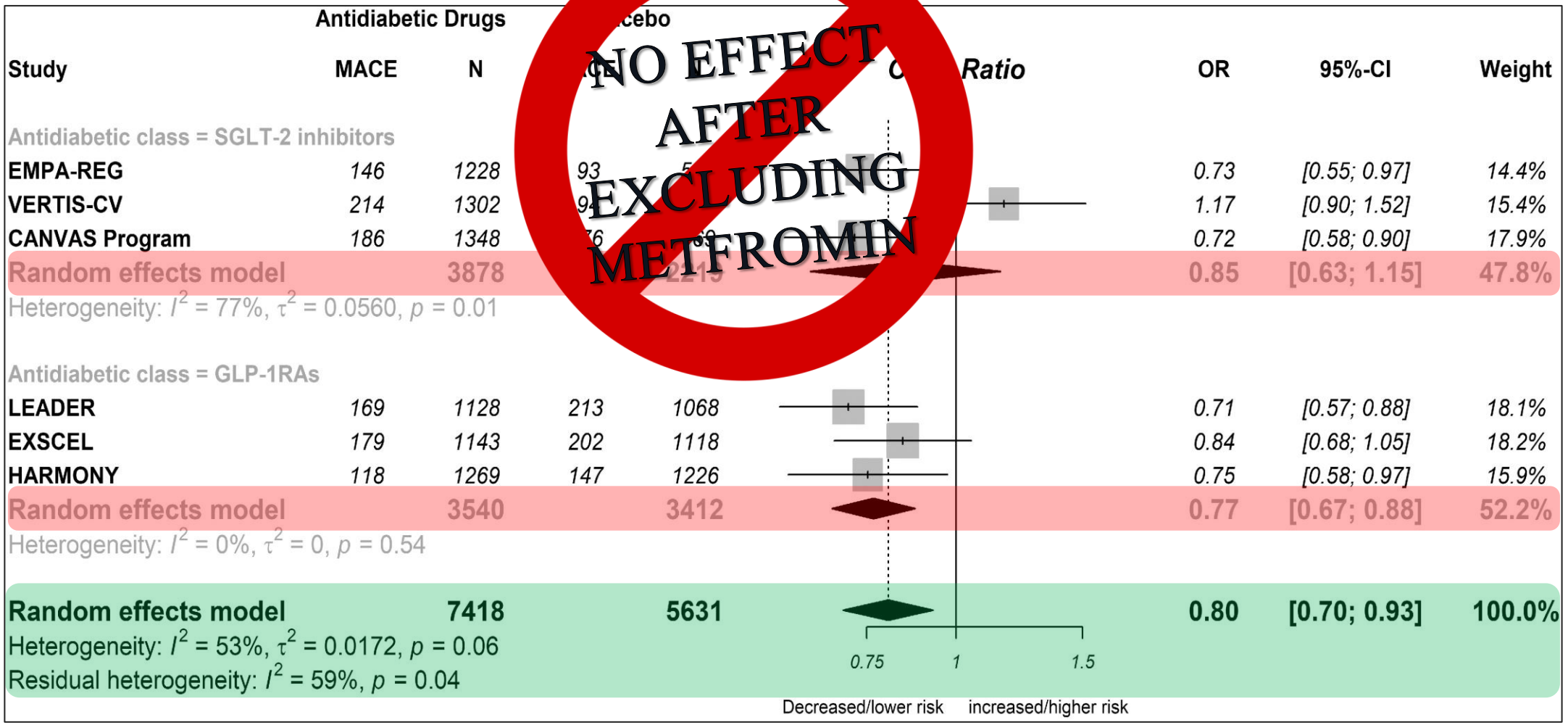
FULL RESEARCH PAPER
Diabetes and Metabolic Syndrome

Novel antidiabetic drugs and risk of cardiovascular events in patients without baseline metformin use: a meta-analysis

Walter Masson[1,2]*, Augusto Lavalle-Cobo[1,3], Martín Lobo[1,4],

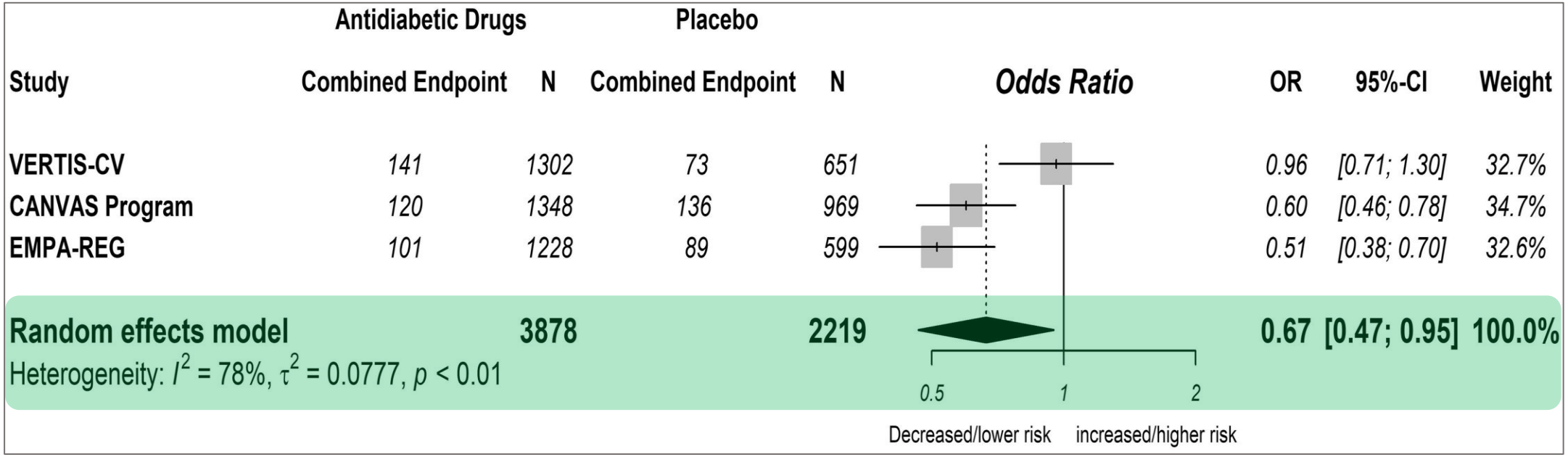
Aims: To evaluate the effect of sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) on major cardiovascular events (MACE) in metformin-naıve patients with type 2 diabetes (T2D).
Methods: A meta-analysis was performed of randomized controlled clinical trials of GLP-1RAs and SGLT-2 inhibitors on T2D populations, after searching the PubMed/MEDLINE, Embase, and Cochrane Controlled Trials databases.
The primary endpoint was MACE.
The secondary endpoint, explored in the subgroup of SGLT-2 inhibitors studies, was cardiovascular death or hospitalization for heart failure. A random-effects meta-analysis model was applied.
Six eligible trials (three studies of SGLT-2 inhibitors and three trials of GLP-1RAs), including 13 049 patients, were identified and considered eligible for the analyses.

Fig 2 Effect of new antidiabetic drugs on MACE. R… effects, odds r… % confidence intervals, and I2 statistics.



Novel antidiabetic drugs and risk of cardiovascular events in patients without baseline metformin use: a meta-analysis. European Journal of Preventive Cardiology. 2021 Jan;28(1):69-75.

Fig 3 Effect of new antidiabetic drugs on cardiovascular mortality and heart failure. Random effects, odds ratio, 95% confidence intervals, and I2 statistics.



Limitation:

- **First**, there were limitations related with clinical heterogeneity (popular characteristics, different schemes of antihyperglycaemic drugs, different follow-up).

- **Second,** the analysis included only **trial-level data** without having the individual data. Consequently, exploratory analyzes of certain subgroups according to baseline characteristics could not be performed.

- **Third,** our study did not assess other cardiovascular endpoints, because we did not have these data in the whole original publications.

- **Fourth,** the characteristics of patients who were not treated with metformin at baseline may not necessarily be similar to those of the total populations of the included studies.

Novel antidiabetic drugs and risk of cardiovascular events in patients without baseline metformin use: a meta-analysis. European Journal of Preventive Cardiology. 2021 Jan;28(1):69-75.

5

RCT of Metformin on Surrogate of CVD and Meta-analysis/Systematic Reviews (Partially or Fully) Supporting UKPDS Findings

ESC European Society of Cardiology

European Heart Journal (2019) **40**, 3409–3417
doi:10.1093/eurheartj/ehz203

CLINICAL RESEARCH
Coronary artery disease

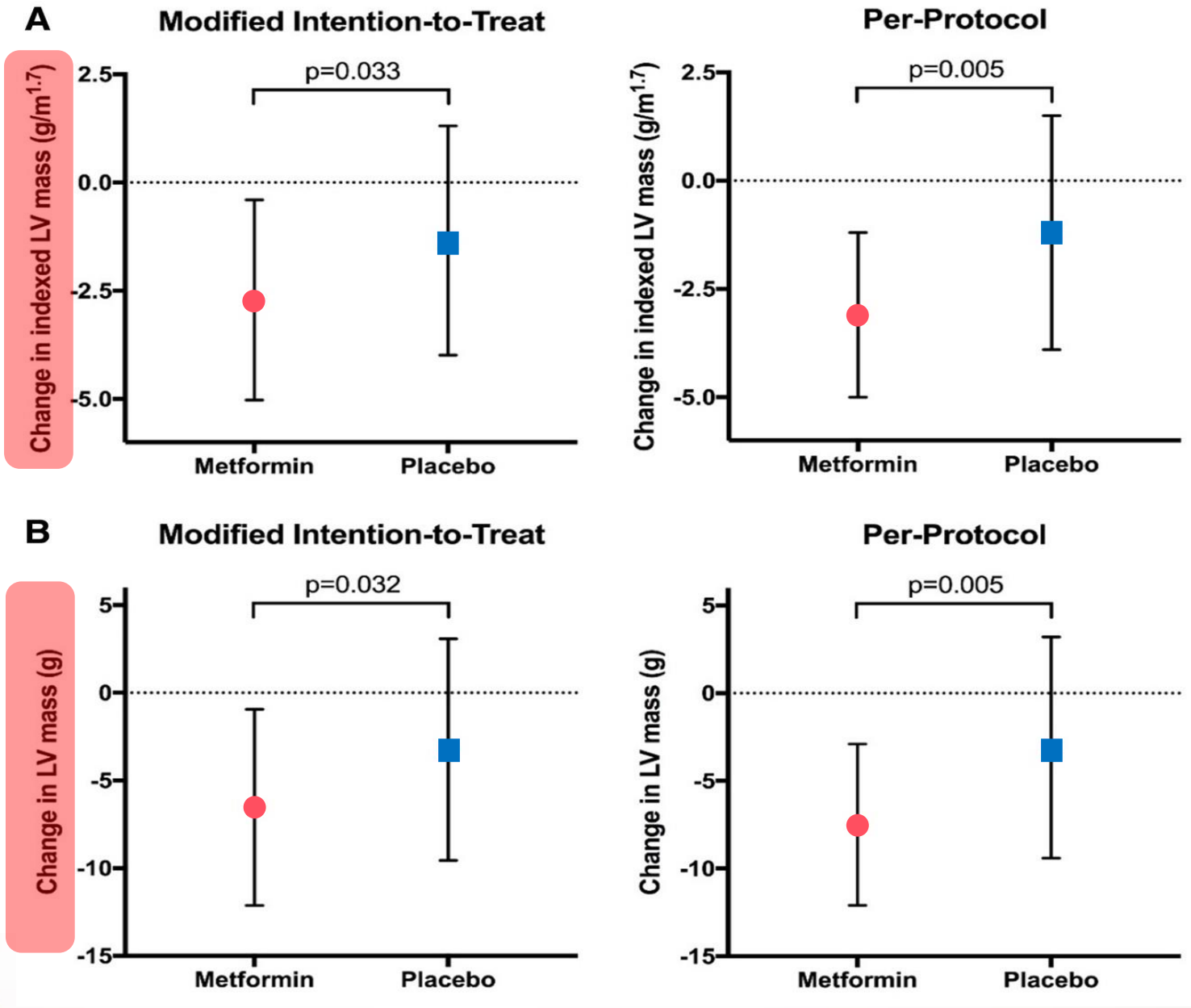
A randomized controlled trial of metformin on left ventricular hypertrophy in patients with coronary artery disease without diabetes: the MET-REMODEL trial

Mohapradeep Mohan[1], Shaween Al-Talabany[1†], Angela McKinnie[2†], Ify R. Mordi[1†],

Aims: We tested the hypothesis that metformin may regress left ventricular hypertrophy (LVH) in patients who have coronary artery disease (CAD), with insulin resistance (IR) and/or pre-diabetes.

Methods: We randomly assigned 68 patients (mean age 65 ± 8 years) without diabetes who have CAD with IR and/or prediabetes (70%) to receive either metformin XL (2000 mg daily dose) or placebo for 12 months. Primary endpoint was change in left ventricular mass indexed to height$^{1.7}$ (LVMI), assessed by magnetic resonance imaging.

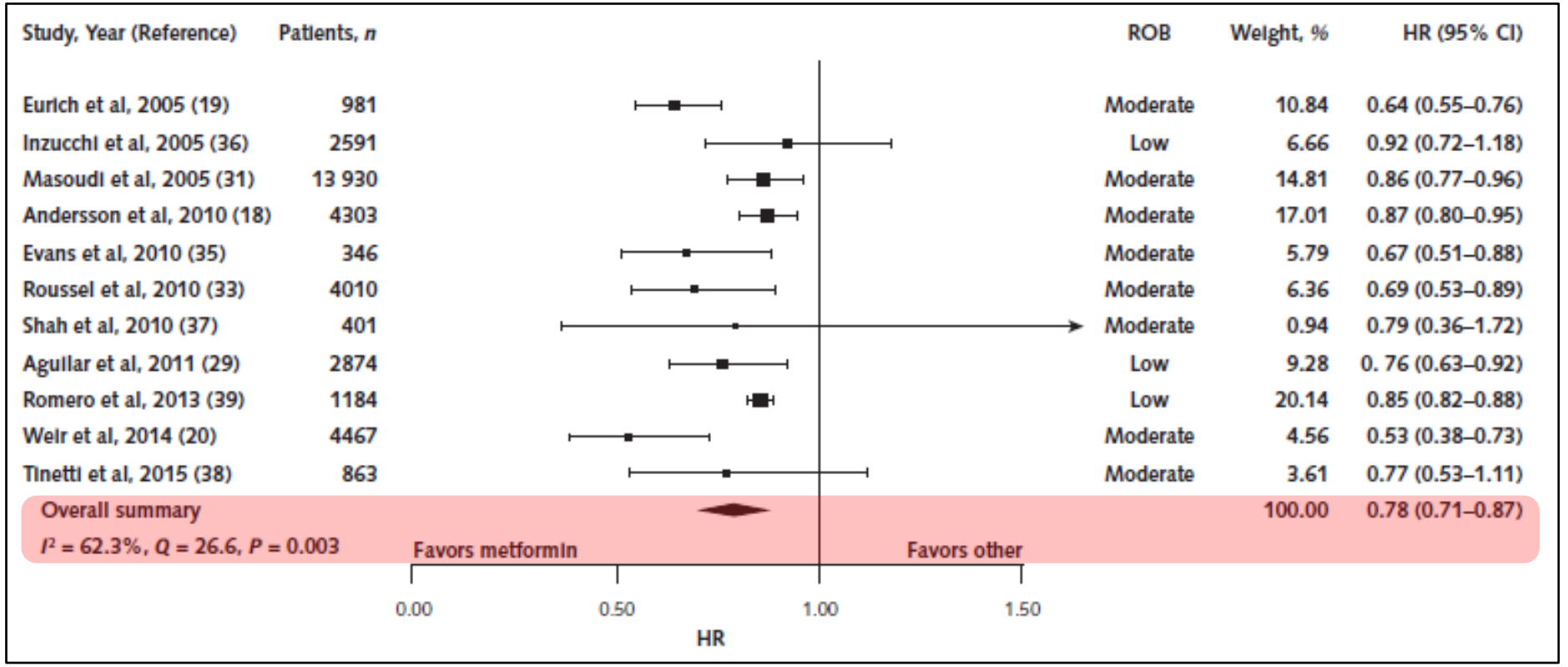
Fig 2
Effect of metformin on left ventricular mass index and left ventricular mass. (A) This graph illustrates the effect of 12 months of metformin or placebo treatment on the left ventricular mass index. (B)



The main finding of our study is that a modified-release 2000mg daily dose of metformin treatment significantly reduced LVMI in patients without T2DM who have CAD, LVH and IR and/or pre-diabetes who were optimally treated with evidence-based therapy.

A randomized controlled trial of metformin on left ventricular hypertrophy in patients with coronary artery disease without diabetes: the MET-REMODEL trial. European heart journal. 2019 Nov 1;40(41):3409-17.

Metformin In CHF



On meta-analysis, the relative chance of dying during follow-up was 22% lower for patients receiving metformin than for those not receiving it.

Metformin In CHF

- Restrictions to use of metformin in patients with medically treated heart failure were removed by the FDA in 2006.

- In fact, observational studies of patients with type 2 diabetes and heart failure suggest that metformin users have better outcomes than patients treated with other anti hyperglycemic agents.

ADA 2023 Guideline

Recommendation:

In patients with type 2 diabetes with stable heart failure, metformin may be continued for glucose lowering if eGFR remains > 30 mL/min but should be avoided in unstable or hospitalized patients with heart failure. B

Effects of liraglutide on cardiovascular outcomes in type 2 diabetes patients with and without baseline metformin use: post hoc analyses of the LEADER trial. Diabetes care. 2023

ORIGINAL INVESTIGATION Open Access

Cardiovasc Diabetol (2019) 18:96

Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis

Yechen Han[1,2], Hongzhi Xie[1,2], Yongtai Liu[1,2], Peng Gao[1,2], Xufei Yang[1,2] and Zhujun Shen[1,2*]

Background: Metformin is the most widely prescribed drug to lower glucose and has a definitive effect on the cardiovascular system. The goal of this systematic review and meta-analysis is to assess the effects of metformin on mortality and cardiac function among patients with coronary artery disease (CAD).

Methods: Relevant studies reported before October 2018 was retrieved from databases including PubMed, EMBASE, Cochrane Library and Web of Science. Hazard ratio (HR) was calculated to evaluate the all-cause mortality, cardiovascular mortality and incidence of cardiovascular events (CV events), to figure out the level of left ventricular ejection fraction (LVEF), creatine kinase MB (CK-MB), type B natriuretic peptide (BNP).

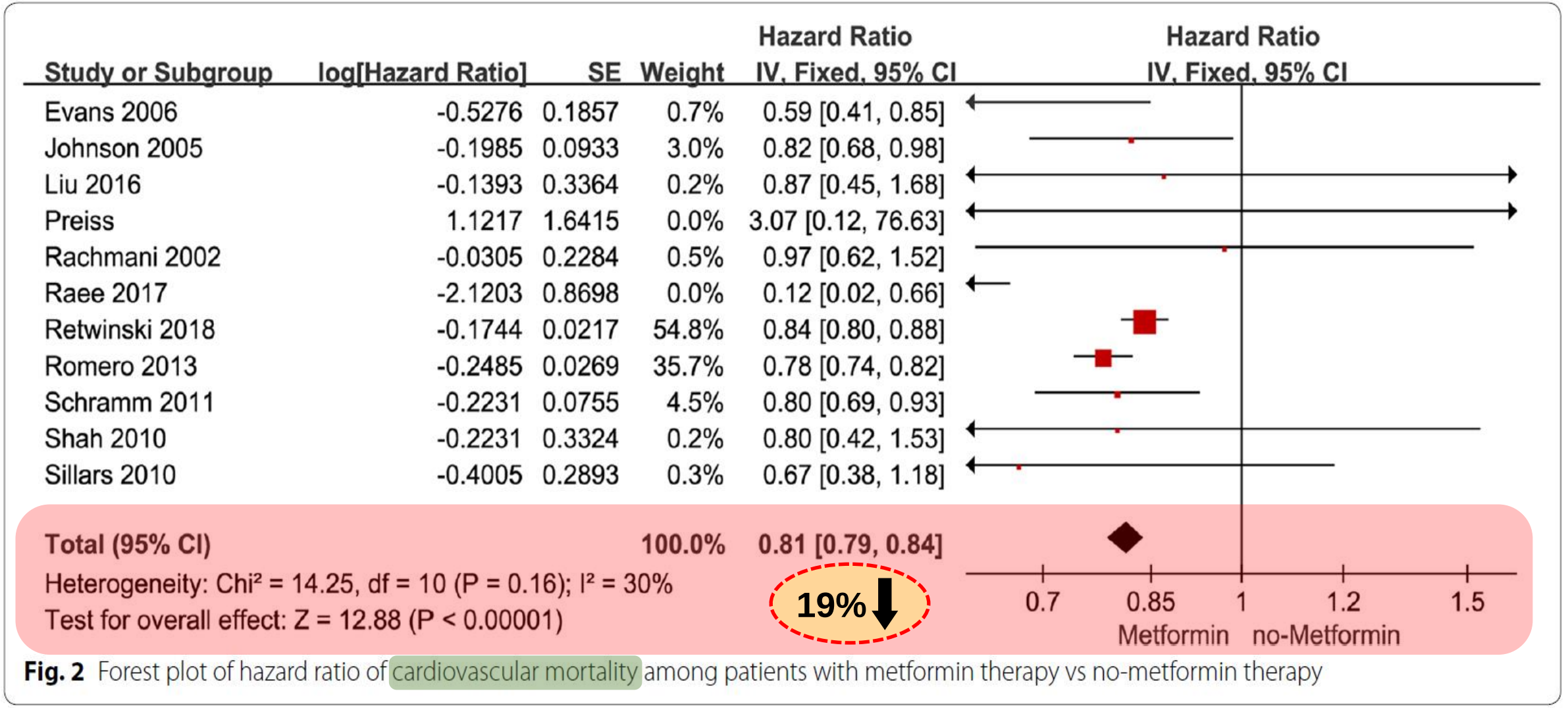


Fig. 2 Forest plot of hazard ratio of cardiovascular mortality among patients with metformin therapy vs no-metformin therapy

Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis. Cardiovascular diabetology. 2019 Dec;18(1):1-6

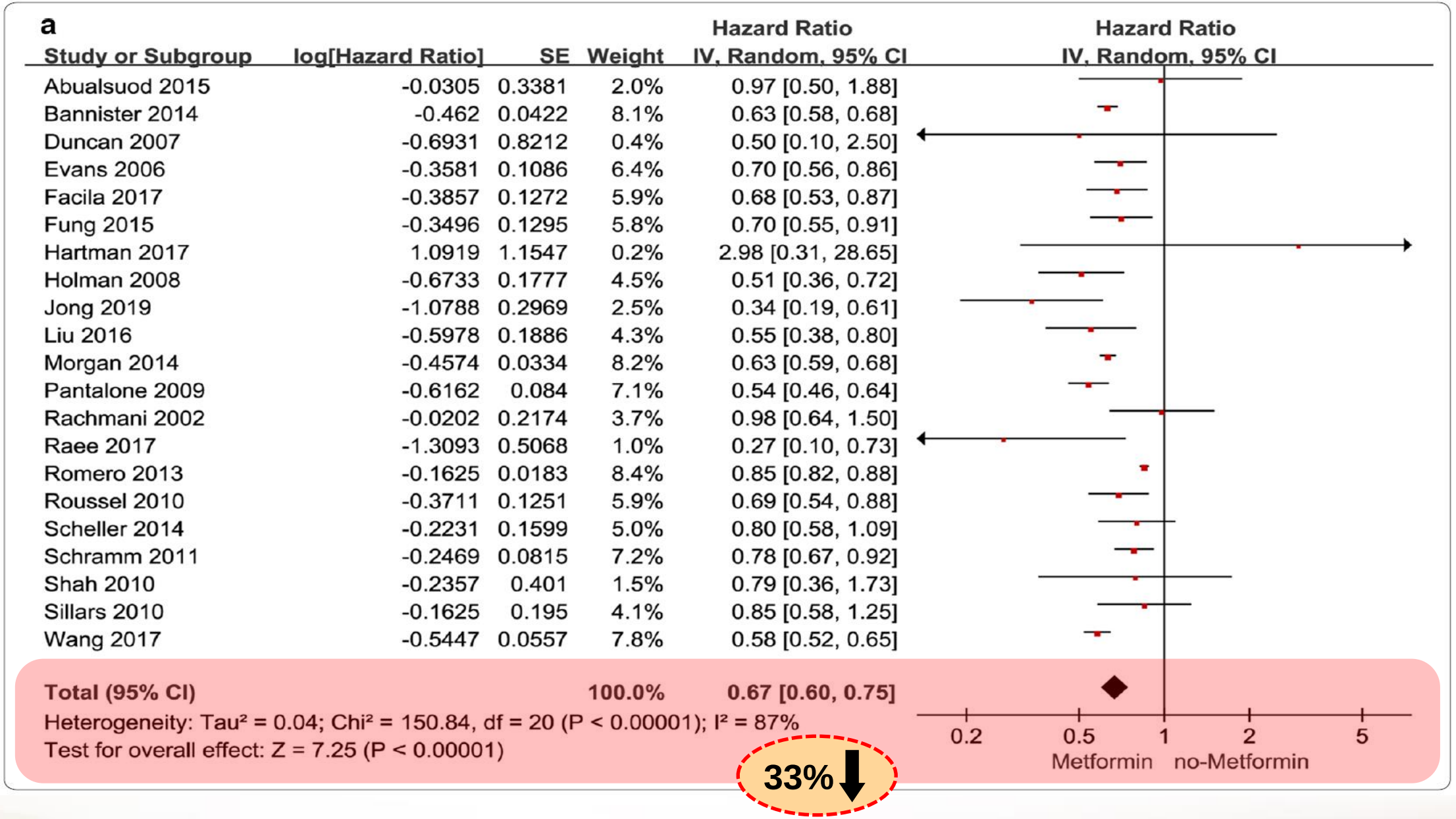


Fig 3
a Forest plot of hazard ratio of all-cause mortality among patients with metformin therapy vs no-metformin therapy.

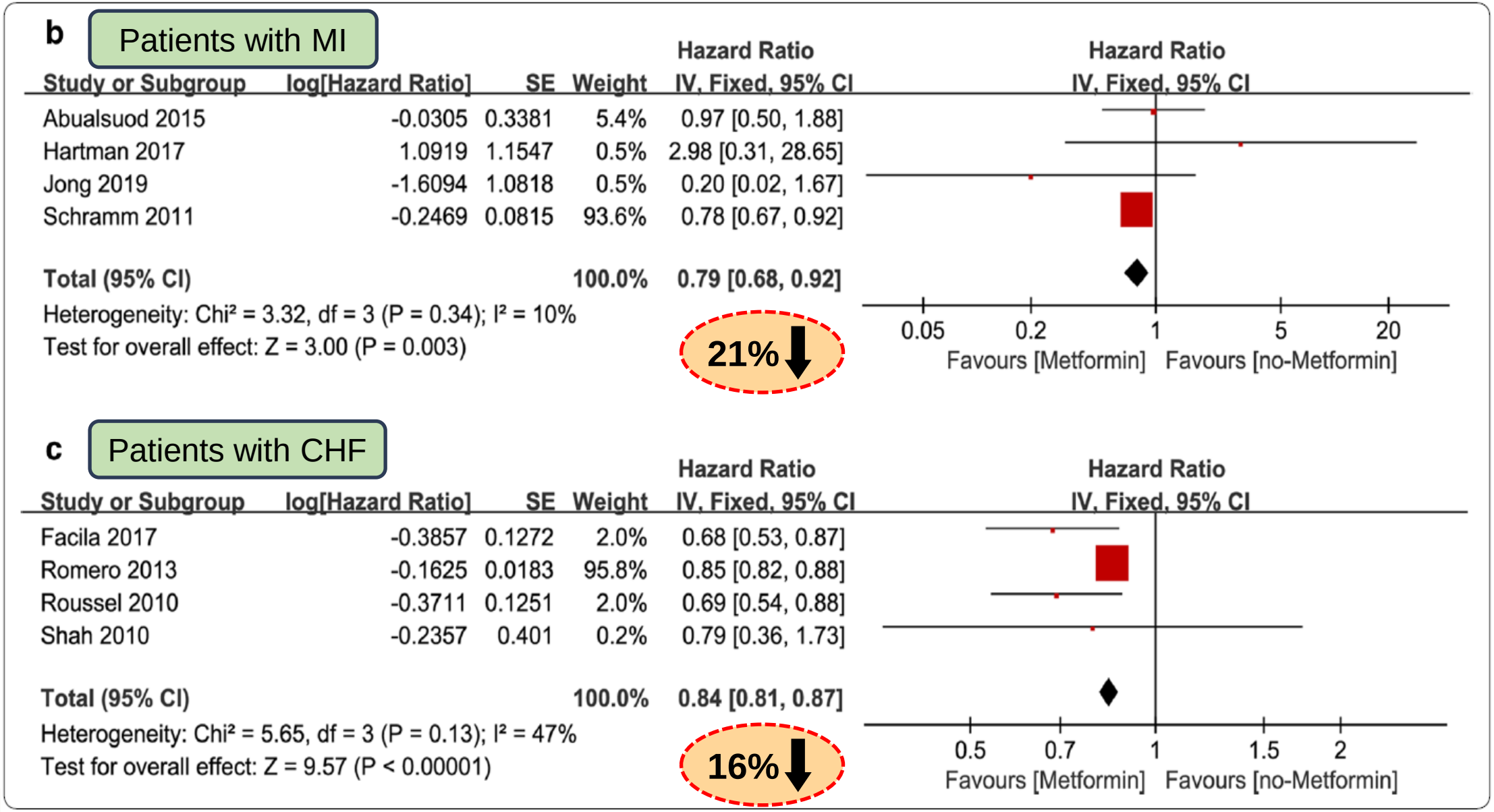


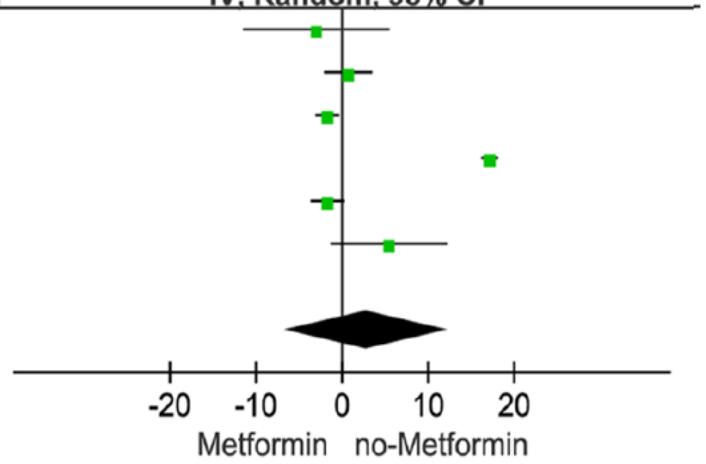
Fig 3
b Forest plot of hazard ratio of all-cause mortality among patients with MI at baseline

c Forest plot of hazard ratio of all-cause mortality among patients with HF at baseline.

a LVEF%

Study or Subgroup	Metformin Mean	SD	Total	no-Metformin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Al 2016	55	38.3951	118	58	27.5435	119	15.2%	-3.00 [-11.51, 5.51]
Basnet 2015	43.5	11.1	127	42.8	11.6	127	17.1%	0.70 [-2.09, 3.49]
Eppinga 2016	53	3.447	185	54.7	8.9867	186	17.3%	-1.70 [-3.08, -0.32]
Lexis 2012	66.108	3.649	175	48.9632	5.4608	175	17.3%	17.14 [16.17, 18.12]
Lexis 2014	53.1	10.5096	191	54.8	9.0355	188	17.2%	-1.70 [-3.67, 0.27]
Wong 2012	34.35	13.5	36	28.9	12.2	22	15.9%	5.45 [-1.29, 12.19]
Total (95% CI)			**832**			**817**	**100.0%**	**2.91 [-6.51, 12.34]**

Heterogeneity: Tau² = 133.37; Chi² = 652.44, df = 5 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.61 (P = 0.54)



b CK-MB

Study or Subgroup	Metformin Mean	SD	Total	no-Metformin Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Basnet 2015	149.4	136	136	167.6	180.7	136	19.6%	-0.11 [-0.35, 0.12]
Duncan 2007	662.8	640.8	439	693.8	779.7	440	30.9%	-0.04 [-0.18, 0.09]
Lexis 2014	159.4	281.9	185	193.2	310.3	475	26.4%	-0.11 [-0.28, 0.06]
Li 2014	2.7	4.3	76	6.3	8	76	13.5%	-0.56 [-0.88, -0.23]
Zeller 2016	1,567.3	2,433.6	31	1,907.7	3,612.6	89	9.6%	-0.10 [-0.51, 0.31]
Total (95% CI)			**867**			**1216**	**100.0%**	**-0.15 [-0.29, -0.01]**

Heterogeneity: Tau² = 0.01; Chi² = 8.30, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 2.03 (P = 0.04)

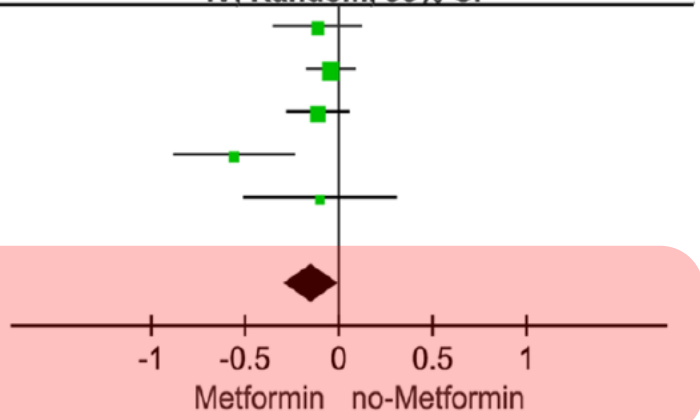


Fig 6

a Forest plot of mean difference of LVEF% among patients with metformin therapy vs no-metformin therapy.

b Forest plot of mean difference of CK-MB among patients with metformin therapy vs no-metformin therapy.

40 clinical trials were included in this study involving 1,066,408 subjects:

1. **Metformin** could remarkably reduce cardiovascular mortality;
2. **Metformin** could significantly reduce all-cause mortality, including in patients with MI and HF;
3. **Metformin** could reduce the incidence of CVD.
4. **Metformin** could significantly reduce the incidence of cardiovascular events in HF patients, but wasn't effective in MI patients.
5. **Metformin** was effective in reducing the incidence of CVD compared to those who take sulfonylureas or those who didn't take anything;
6. **Metformin** could reduce CK-MB level, but couldn't improve LEVF and BNP.

Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis. Cardiovascular diabetology. 2019 Dec;18(1):1-6

6

The European Society of Cardiology (ESC) 2021 Guidelines on Diabetes, Pre-diabetes and CVD, ADA 2023

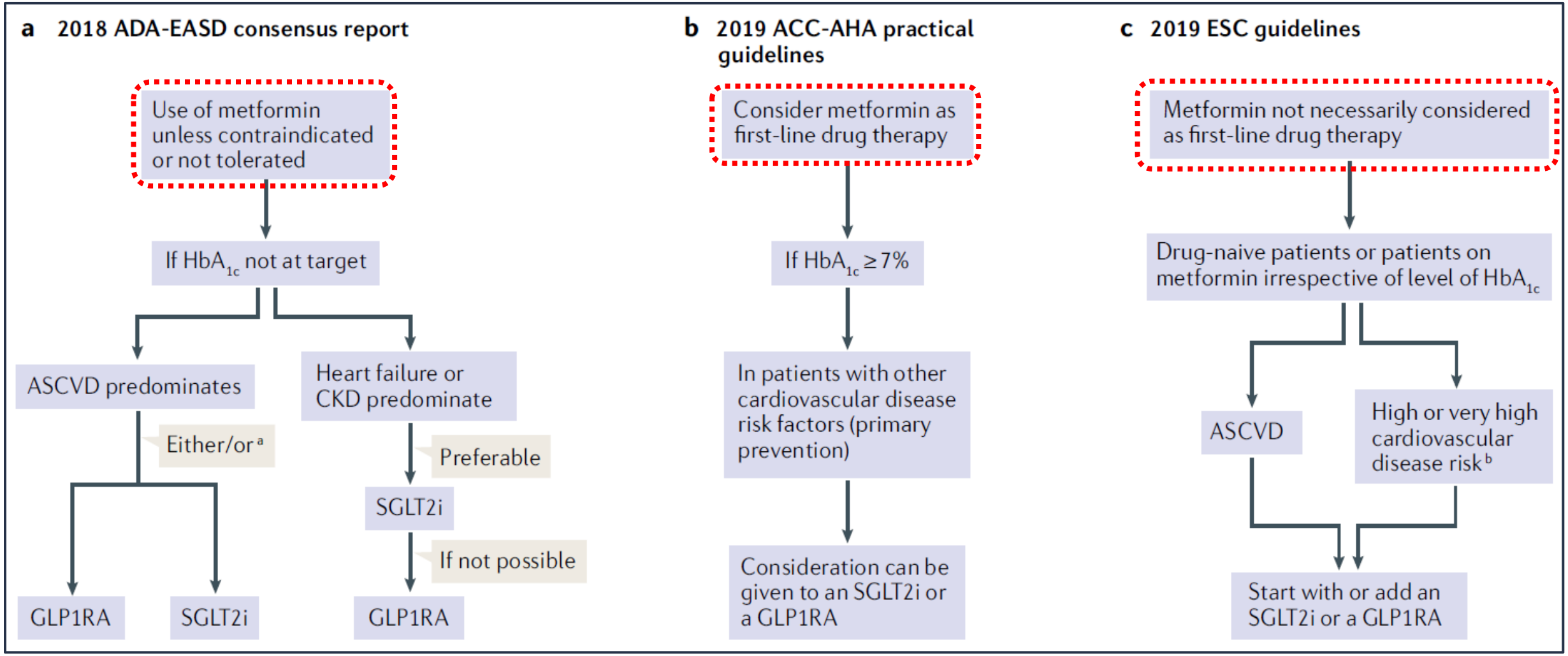
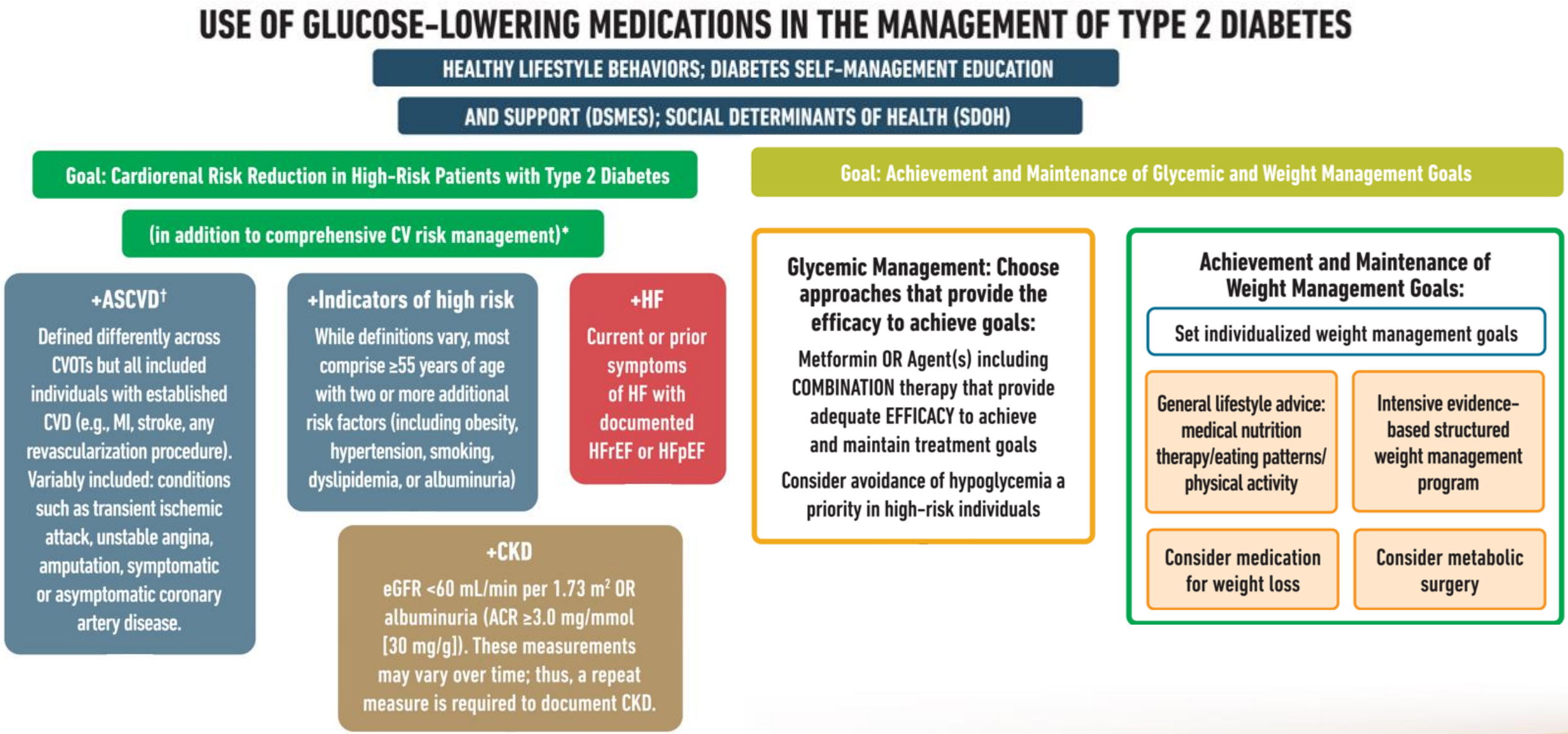


Fig. 3 Position of SglT2is in international guidelines.

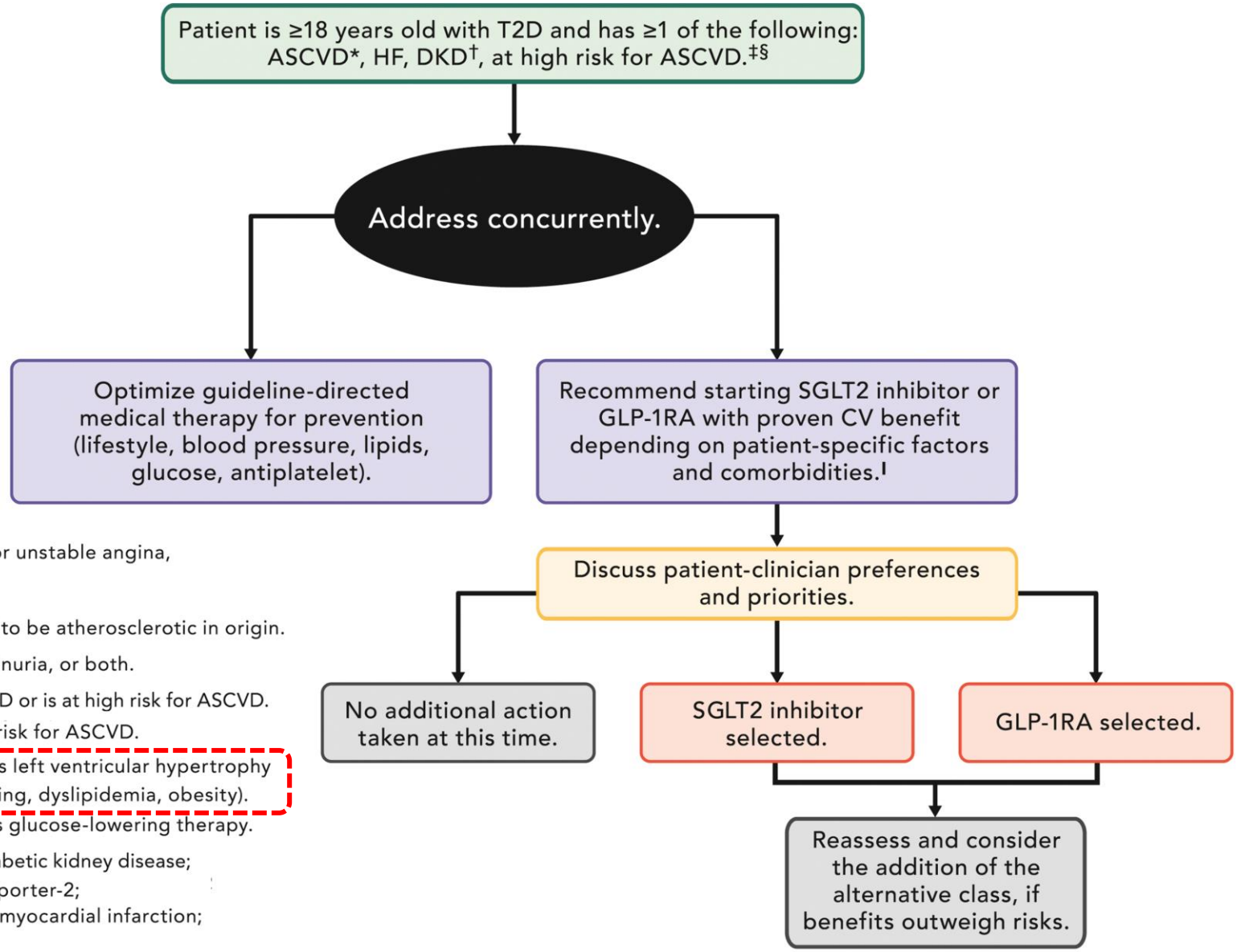
Sodium–glucose cotransporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. Nature Reviews Endocrinology . 2020

Figure 9.3 Use of glucose-lowering medications in the management of type 2 diabetes



ADA 2023

Figure 10.3
Approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy.



*ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization,

other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

†DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡ Consider an SGLT2 inhibitor when your patient has established ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD.

§ Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

¶ Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; SGLT2 = sodium-glucose cotransporter-2; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; T2D = type 2 diabetes

RAPID RECOMMENDATIONS

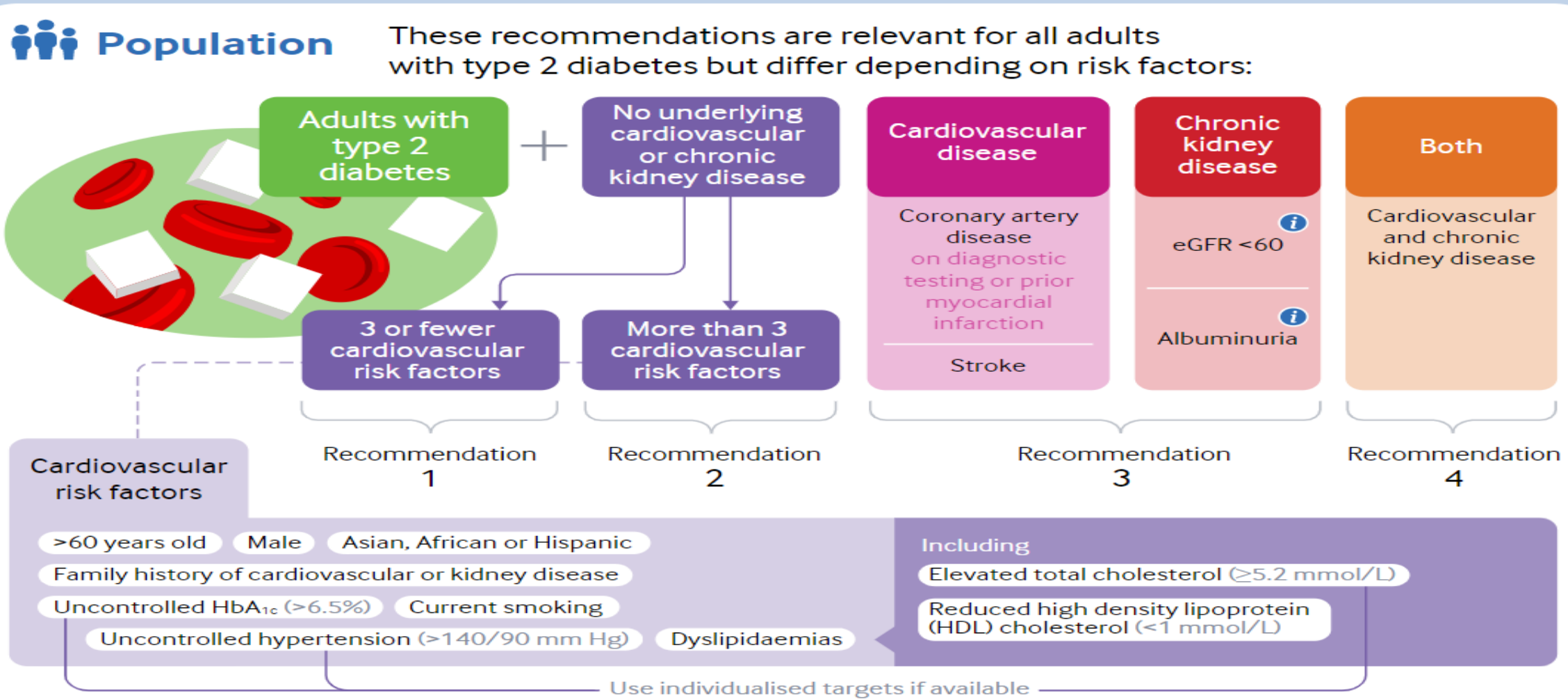
BMJ 2021;373:n1091

SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline

Sheyu Li, [1,2] Per Olav Vandvik, [3,4] Lyubov Lytvyn, [5] Gordon H Guyatt, [5,6] Suetonia C Palmer, [7]

Clinical question: What are the benefits and harms of sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists when added to usual care (lifestyle interventions and/or other diabetes drugs) in adults with type 2 diabetes at different risk for cardiovascular and kidney outcomes?

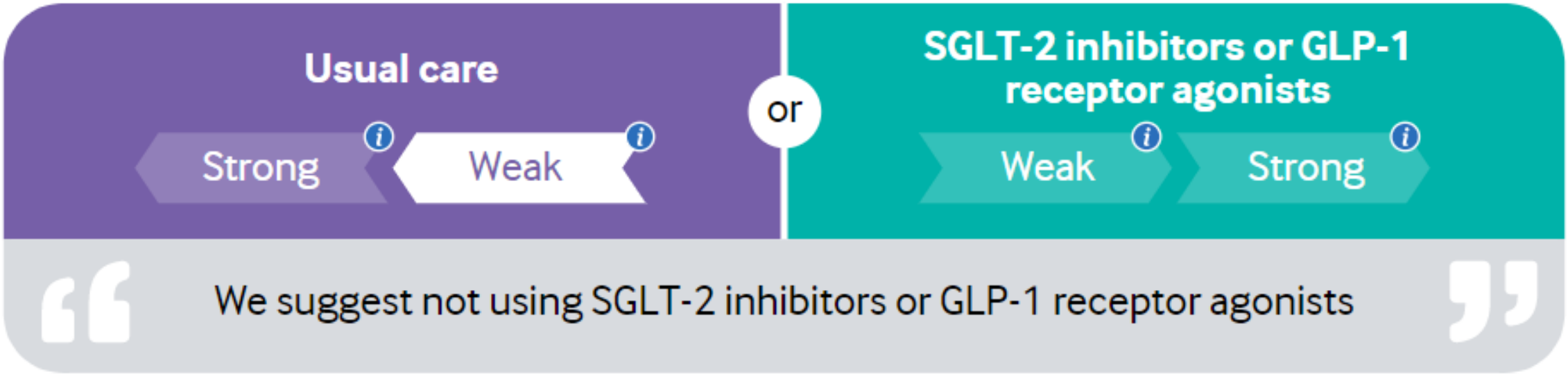
Visual summary of recommendation



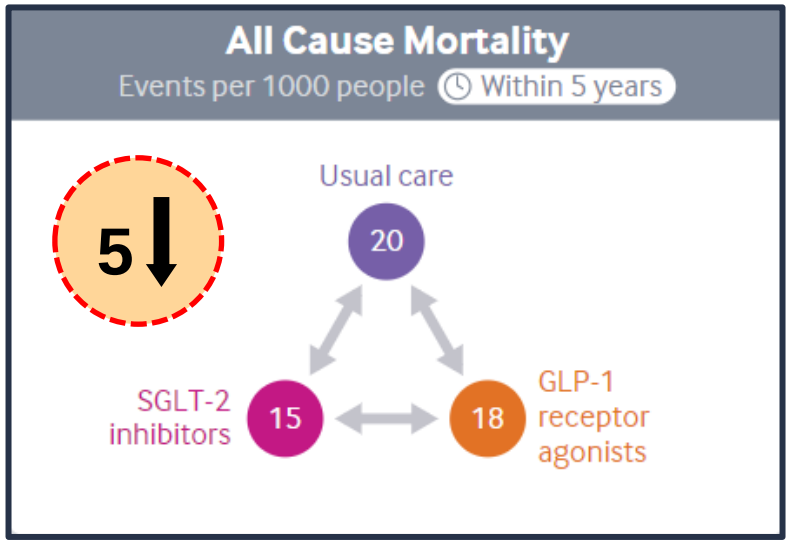
SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. bmj. 2021 May 11;373.

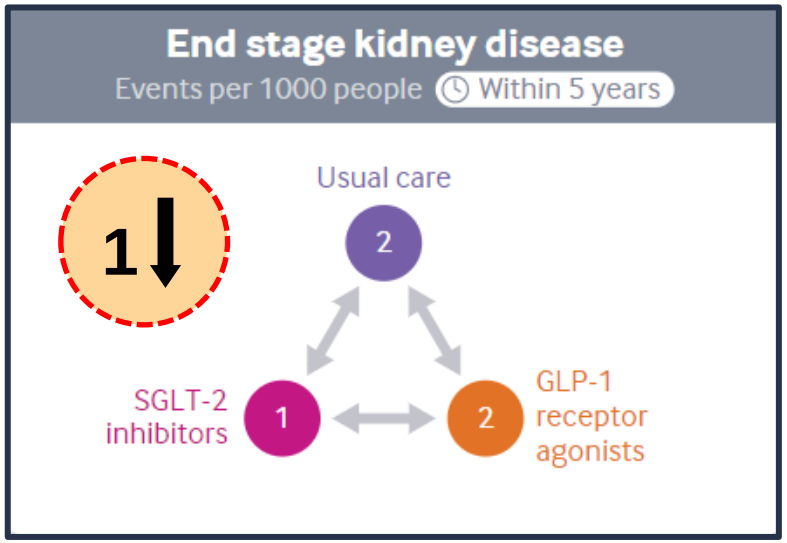
Recommendation 1

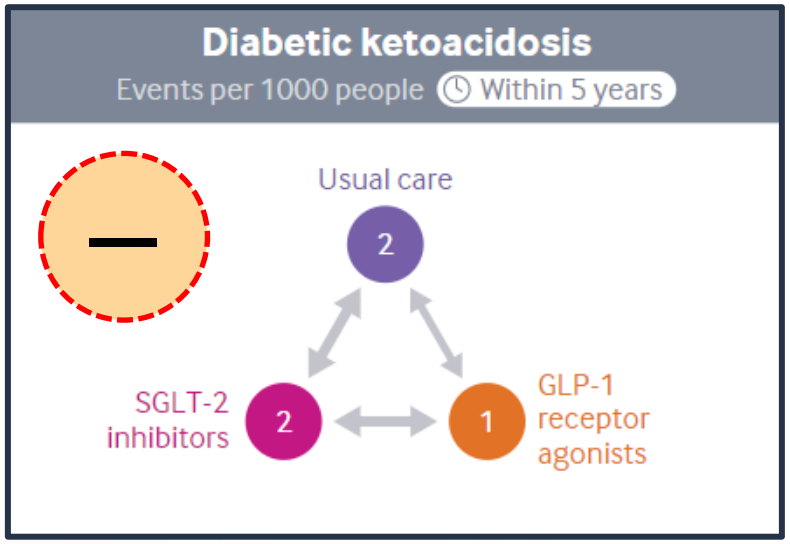
Patients with 3 or fewer cardiovascular risk factors

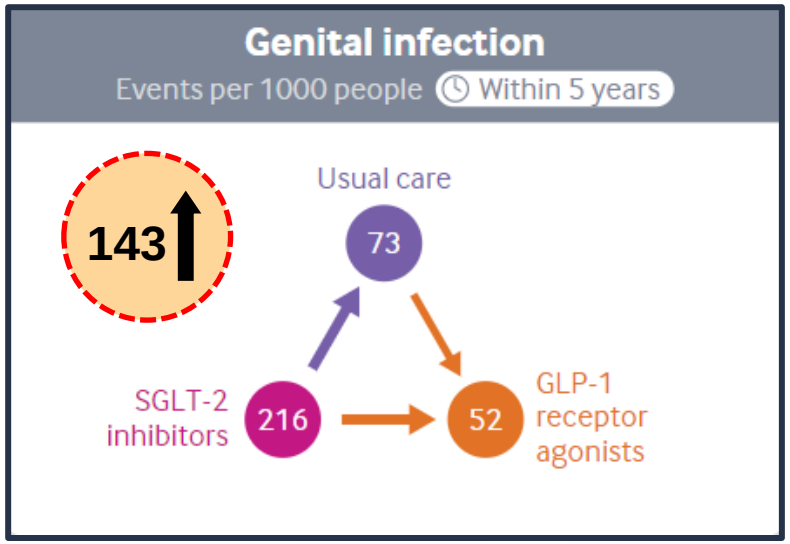


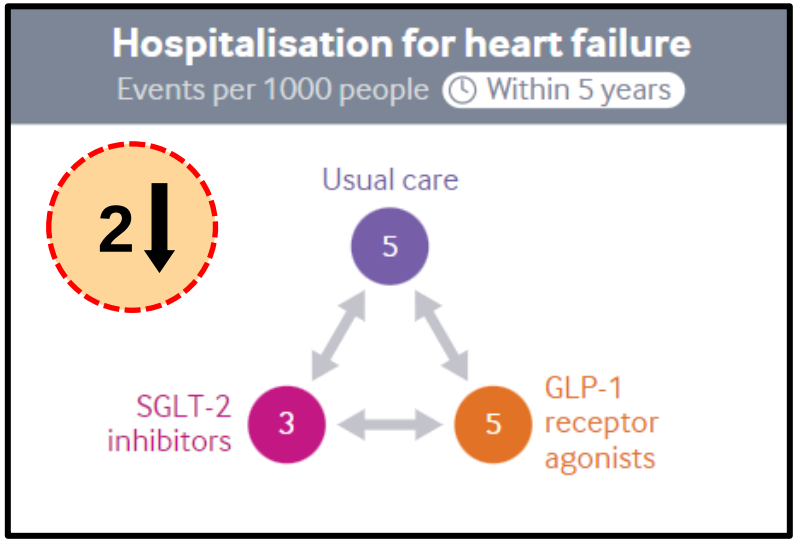
SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. bmj. 2021 May 11;373.







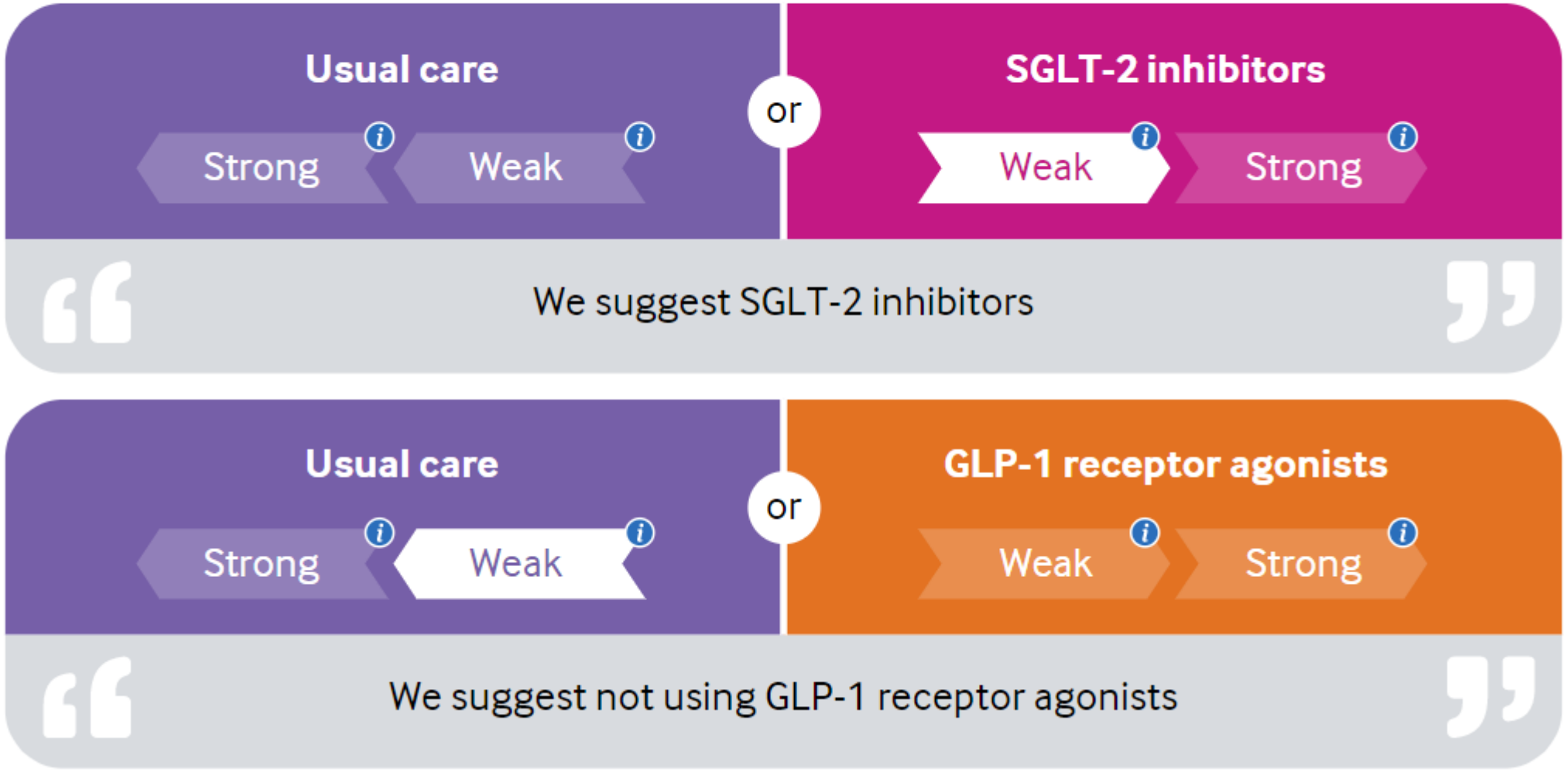




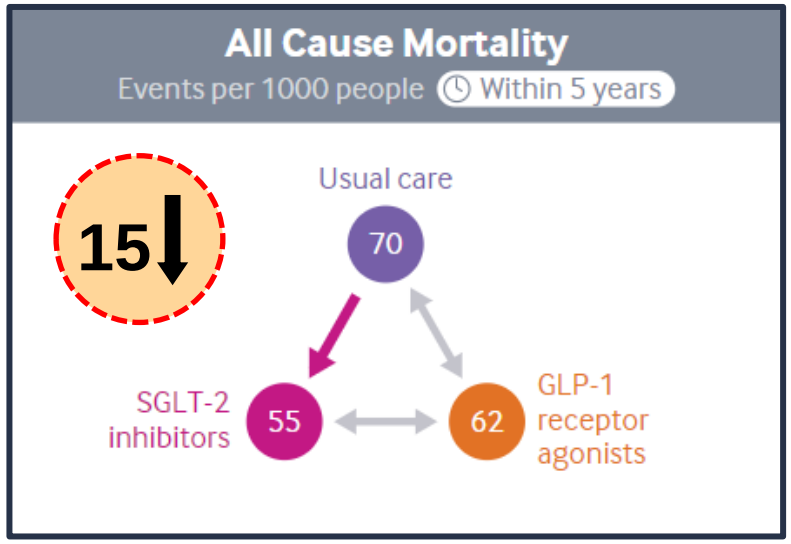
SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. bmj. 2021 May 11;373.

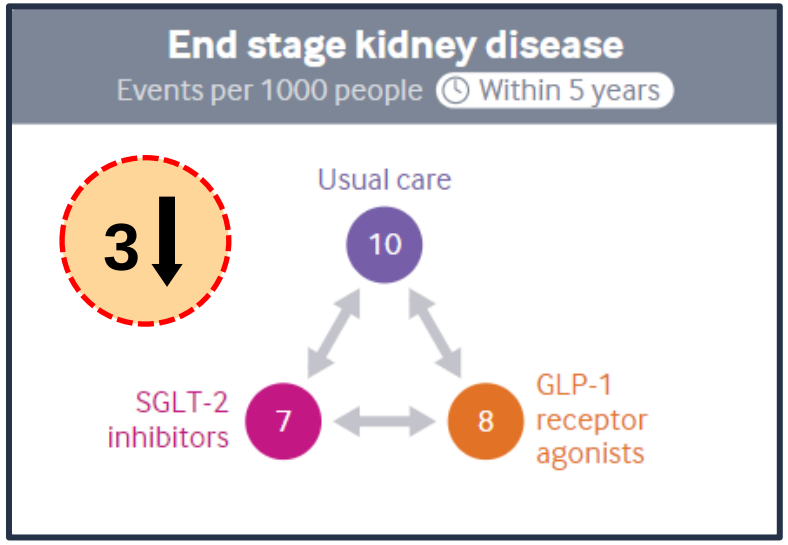
Recommendation 2

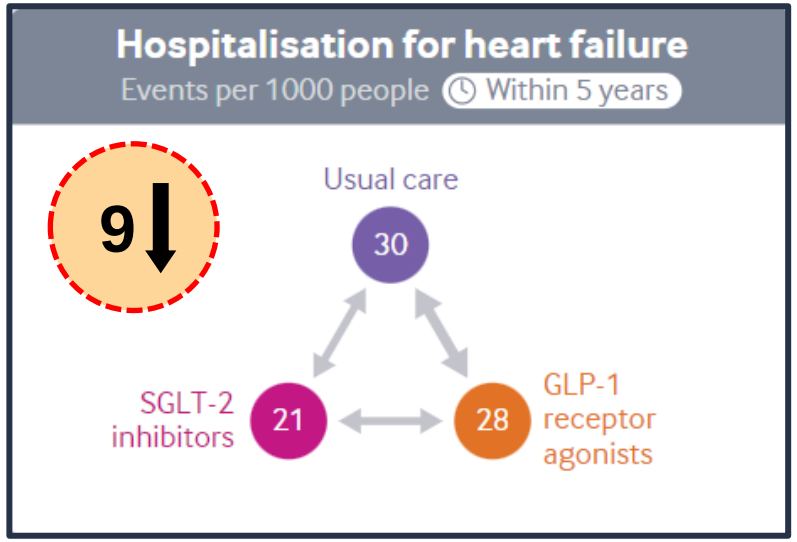
Patients with more than 3 cardiovascular risk factors

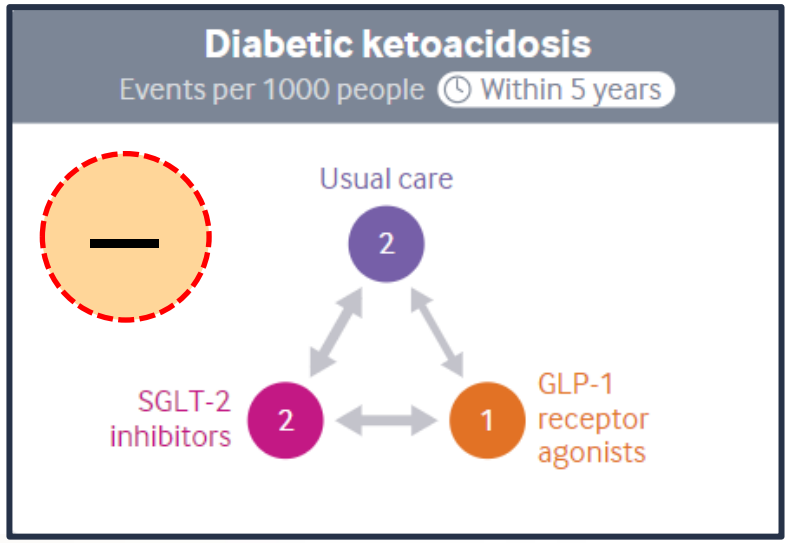


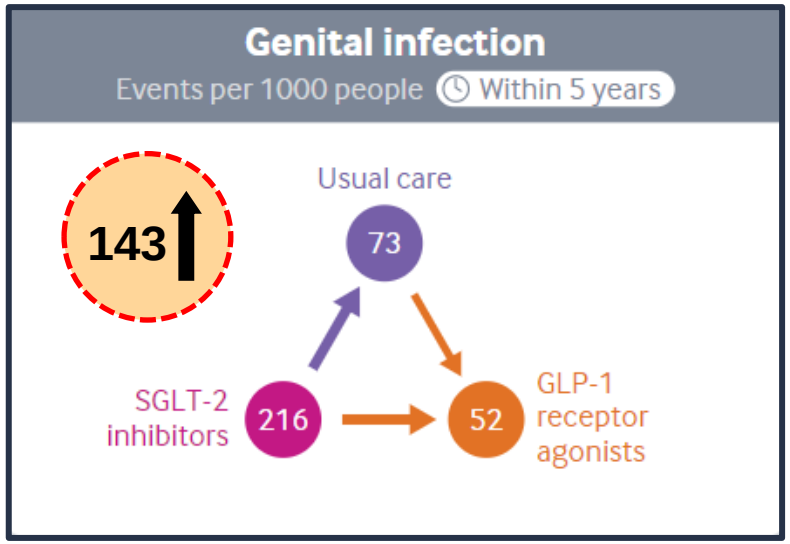
SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. bmj. 2021 May 11;373.







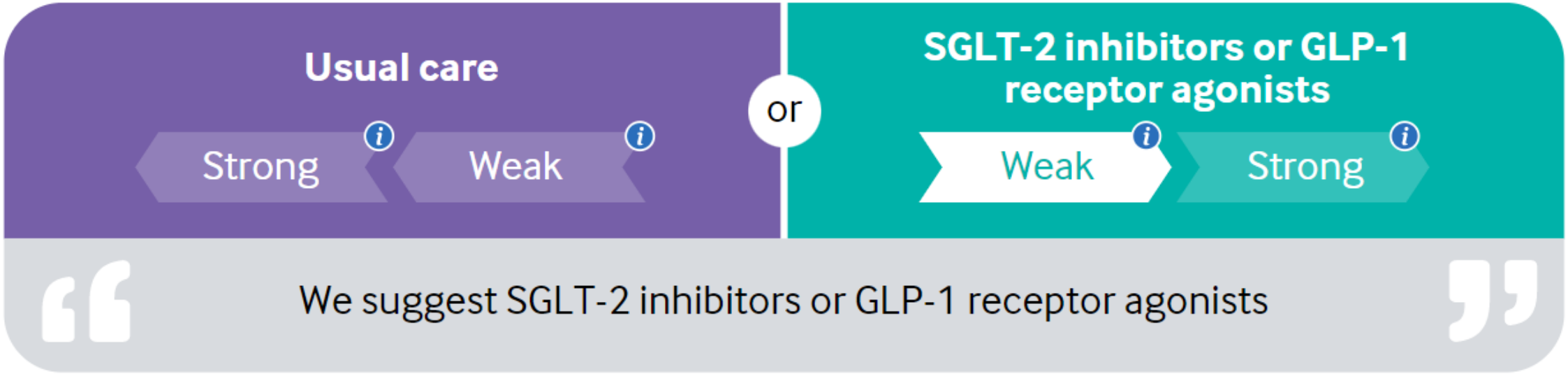




SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. bmj. 2021 May 11;373.

Recommendation 3

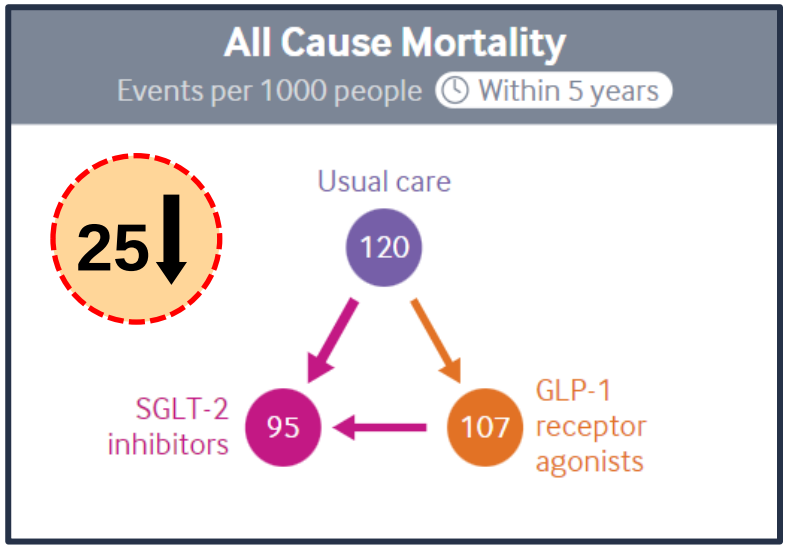
Patients with established cardiovascular or renal disease

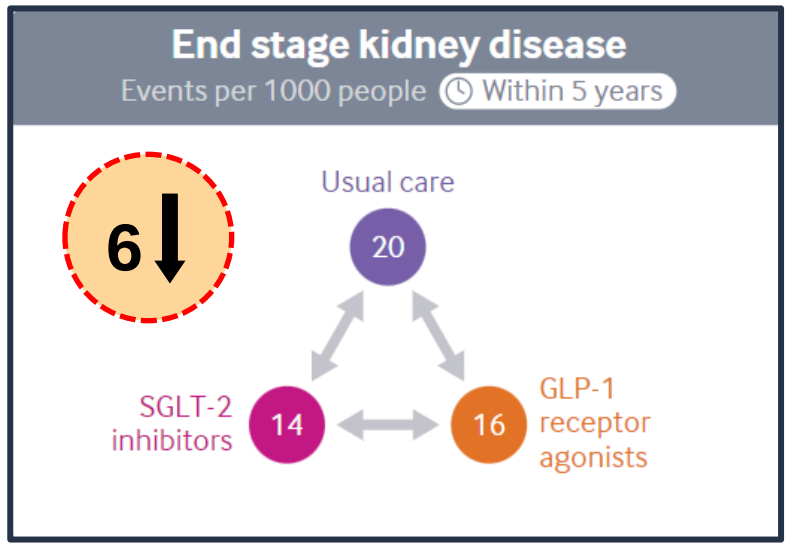


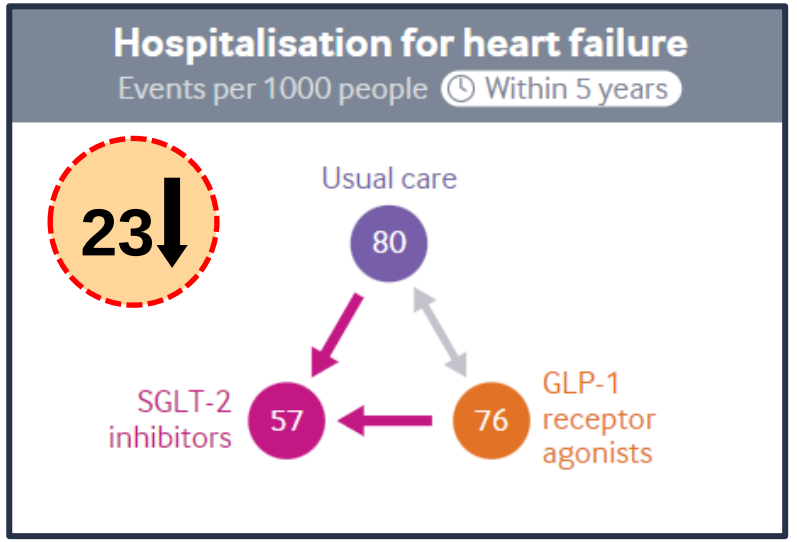
We suggest SGLT-2 inhibitors or GLP-1 receptor agonists

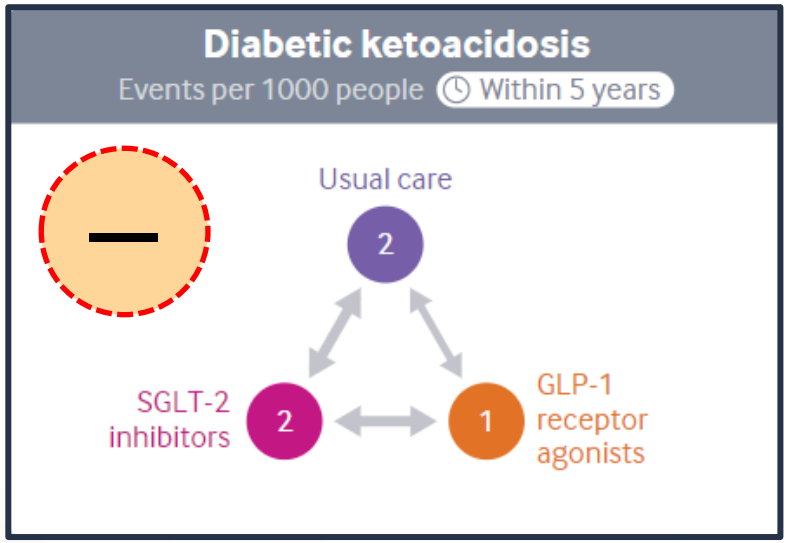
SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. bmj. 2021 May 11;373.

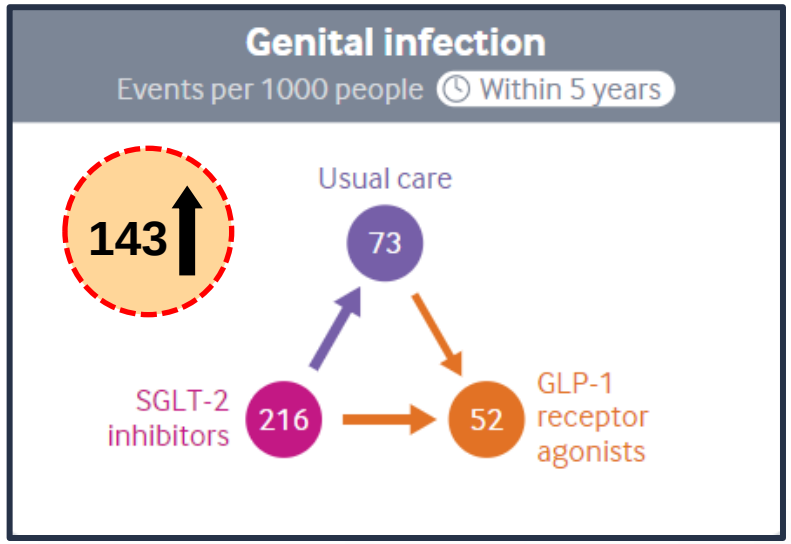
Evidence profile - patients with cardiovascular disease







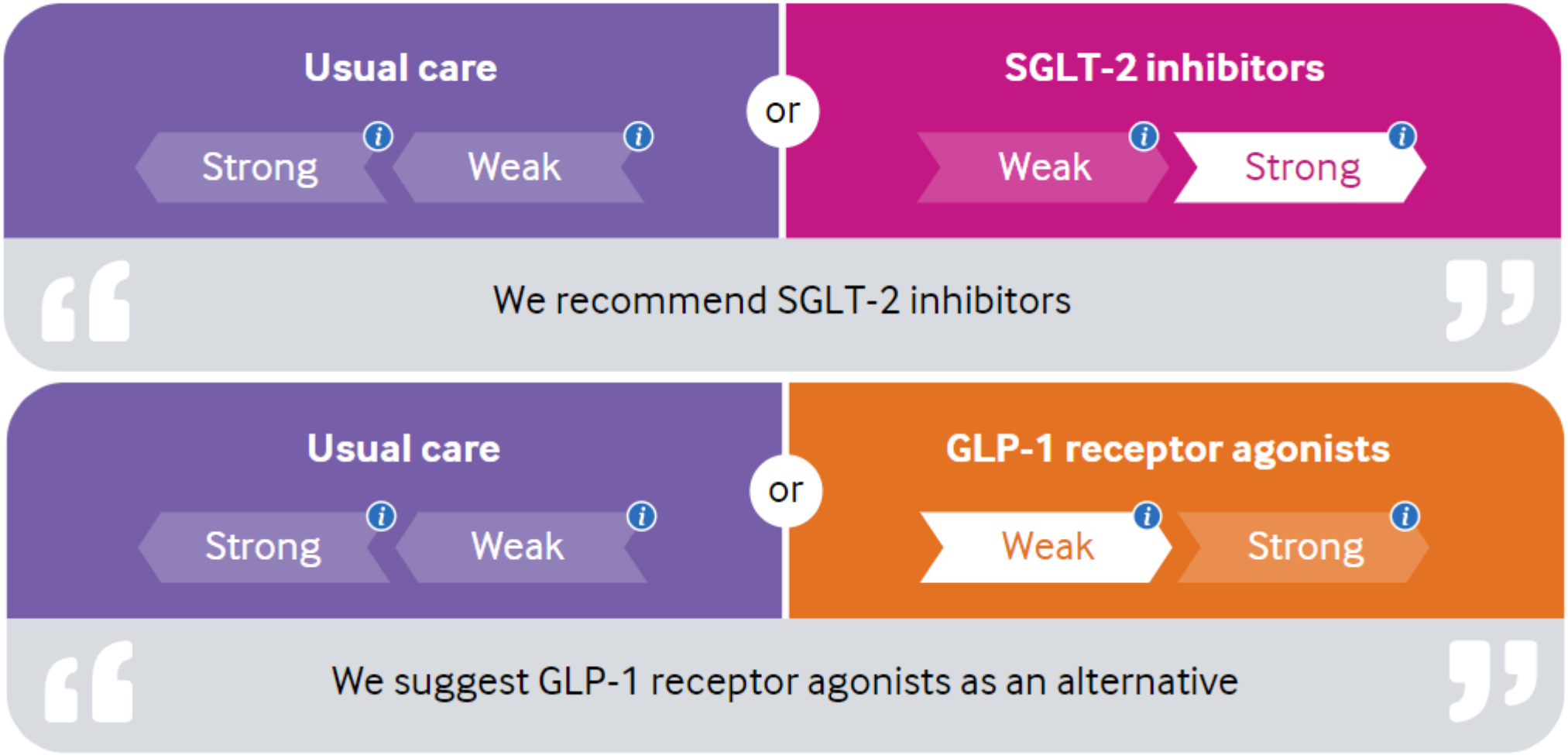




SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. bmj. 2021 May 11;373.

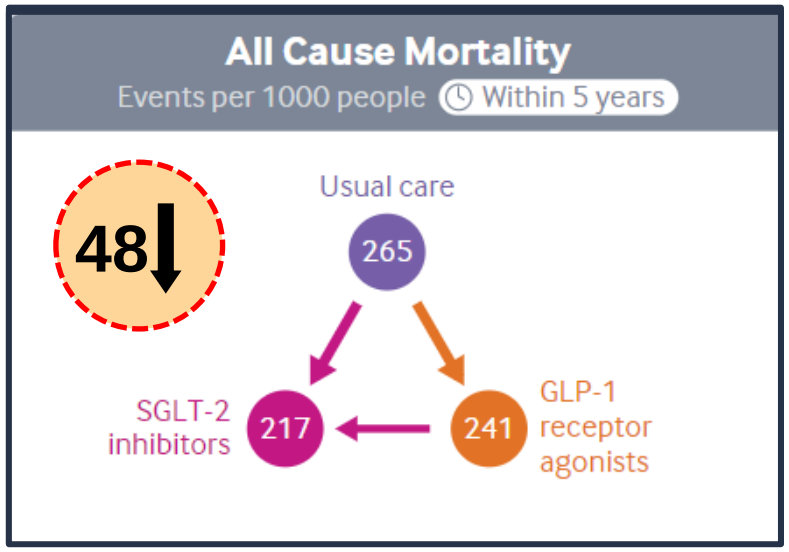
Recommendation 4

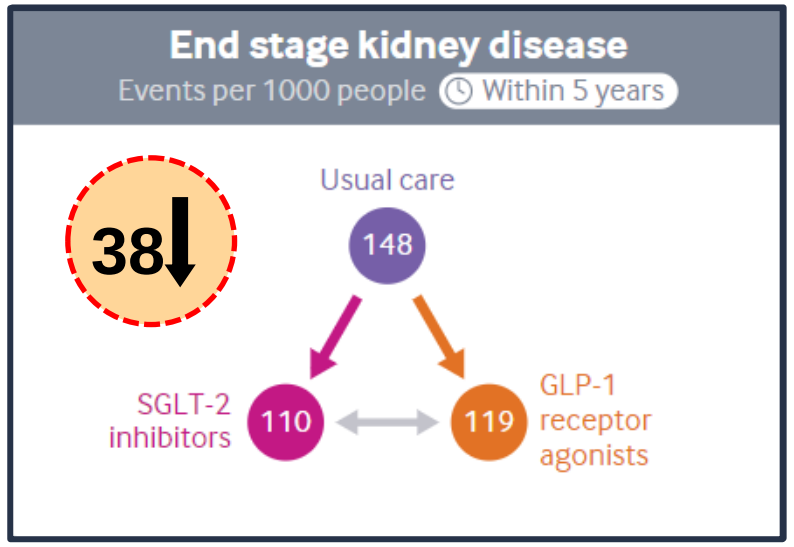
Patients with established cardiovascular and renal disease

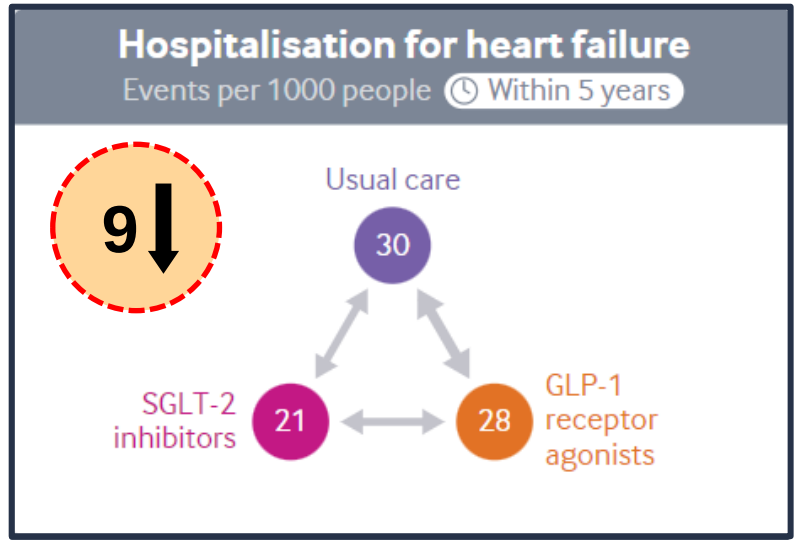


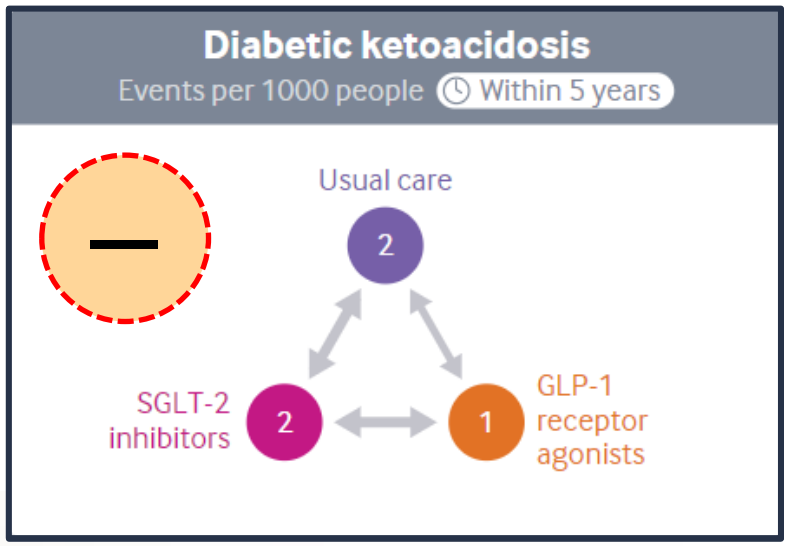
SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. bmj. 2021 May 11;373.

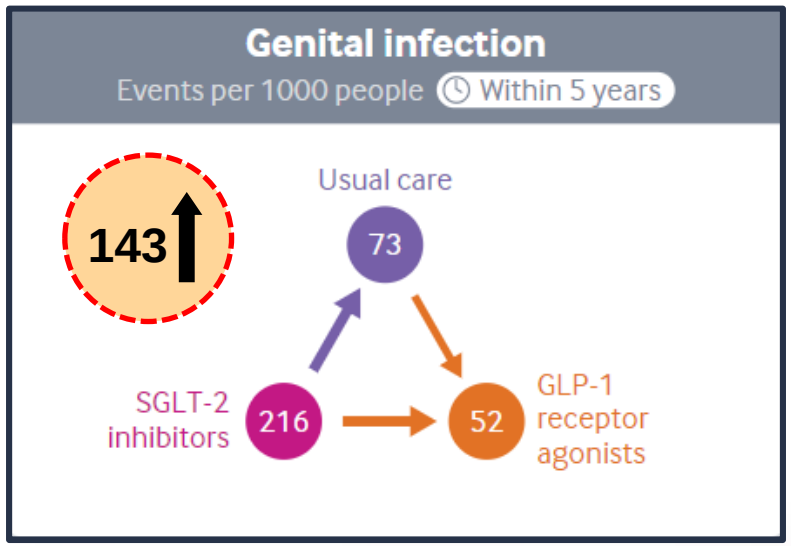
Evidence profile - patients with renal disease











SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. bmj. 2021 May 11;373.

Recommendations:

- 3 ≤ CVD risk factors without established CVD or CKD: Weak recommendation against starting SGLT-2 inhibitors or GLP-1 receptor agonists.
- 3 > CVD risk factors without established CVD or CKD: Weak recommendation for starting SGLT-2 inhibitors and weak against starting GLP-1 receptor agonists.
- Established CVD or CKD: Weak recommendation for starting SGLT-2 inhibitors and GLP-1 receptor agonists.
- Established CVD and CKD: Strong recommendation for starting SGLT-2 inhibitors and weak recommendation for starting GLP-1 receptor agonists.

SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. bmj. 2021 May 11;373.

Recommendations	Class[a]	Level[b]
Treatment of hyperglycaemia and ASCVD/cardiorenal risks		
Metformin is recommended as first-line therapy, following evaluation of renal function, in the majority of patients without previous ASCVD, CKD, or HF.[589]	I	B
In persons with type 2 DM with ASCVD, metformin should be considered, unless contraindications are present.[5,590–592]	IIa	B
Avoidance of hypoglycaemia and excessive weight gain should be considered.[559,588,593]	IIa	B
In persons with type 2 DM and ASCVD, the use of a GLP-1RA or SGLT2 inhibitor with proven outcome benefits is recommended to reduce CV and/or cardiorenal outcomes.[590–592]	I	A

Severe TOD:

1. eGFR <45 irrespective of albuminuria
2. eGFR 45-59 and microalbuminuria (ACR 30 -300 mg/g)
3. Proteinuria (ACR >300 mg/g)
4. Presence of microvascular disease in at least 3 different sites

Recommendations	Class[a]	Level[b]
Treatment of hyperglycaemia and ASCVD/cardiorenal risks		
In patients with type 2 DM and TOD,[c] the use of an SGLT2 inhibitor or GLP-1RA with proven outcome benefits may be considered to reduce future CV and total mortality.[594–597]	IIb	B
In patients with type 2 DM and CKD, the use of an SGLT2 inhibitor is recommended to improve ASCVD and/or cardiorenal outcomes.[598,599]	I	A
In patients with type 2 DM and HFrEF, use of an SGLT2 inhibitor with proven outcome benefits is recommended to lessen HF hospitalizations and CV death.[600,601]	I	A
In patients with type 2 DM but without ASCVD, HF, or CKD, use of an SGLT2 inhibitor or GLP-1RA should be considered based on estimated future risks (e.g. with the ADVANCE risk score or DIAL model) for adverse CVD or cardiorenal outcomes from risk factor profiles.[602]	IIa	B

Recommendations:

The view of the ESC is that metformin should be considered, but is not mandatory first-line treatment in patients with ASCVD or evidence of TOD. Certainly, the initiation of metformin in such patients should not forego or delay the initiation of evidence-based SGLT2 inhibitors or GLP-1RAs. A risk score plus cost-effective analyses would be useful to determine which patients free from ASCVD or evidence of TOD may be recommended for these newer drugs.

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). European Heart Journal. 2021 Sep 7;42(34):3227-337.

7

Real Data from Population Based Studies

Received: 25 March 2021 | Revised: 3 June 2021 | Accepted: 18 June 2021
DOI: 10.1111/dom.14474

ORIGINAL ARTICLE

WILEY

Comparative effectiveness and safety of sodium-glucose cotransporter-2 inhibitors versus metformin in patients with type 2 diabetes: An observational study using data from routine care

Michael Fralick MD[1,2,3] | Sebastian Schneeweiss MD[1] |

Aim: To assess the effectiveness and safety of sodium-glucose cotransporter-2 (SGLT2) inhibitors in treatment-naïve patients compared with metformin.

Participants and Methods: We conducted a cohort study of US adults with type 2 diabetes mellitus who had not filled a prescription for a diabetes medication in the preceding year.

We then identified patients who newly filled a prescription for an SGLT2 inhibitor or metformin between 2013 and 2018. The primary outcome was a **composite of heart failure, myocardial infarction or stroke**. Safety outcomes included hypoglycaemia, diabetic ketoacidosis, genital infection, lactic acidosis and acute kidney injury.

After 1:1 propensity-score (PS) matching, proportional hazards models were fit to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).

TABLE 2 Propensity score-matched rate of cardiovascular composite outcome and its components

	Entire cohort		Patients with HTN and HLD		Patients with HTN or HLD and cardiovascular disease	
	Metformin	SGLT2 inhibitors	Metformin	SGLT2 inhibitors	Metformin	SGLT2 inhibitors
Composite outcome						
Number of patients	9964	9964	5299	5299	5137	5137
Number of events	84	54	45	28	51	33
Rate per 1000 PY	8.52	7.19	8.10	6.75	9.66	8.18
HR (95% CI)	Ref.	0.82 (0.58, 1.15)	Ref.	0.81 (0.50, 1.30)	Ref.	0.83 (0.54, 1.30)
Unadjusted HR (95% CI)	Ref.	0.88 (0.67, 1.14)	Ref.	0.73 (0.51, 1.05)	Ref.	0.73 (0.53, 1.02)

Note: Unadjusted refers to results in the unmatched population (ie, propensity score matching was not performed).

Abbreviations: CI, confidence interval; HLD, hyperlipidaemia; HR, hazard ratio; HTN, hypertension; PY, person-years; Ref., referent group; SGLT2, sodium glucose cotransporter 2.

Comparative effectiveness and safety of sodium-glucose cotransporter-2 inhibitors versus metformin in patients with type 2 diabetes: An observational study using data from routine care. Diabetes, Obesity and Metabolism. 2021 Jul 13.

TABLE 3 Propensity score-matched rate of adverse events

	Metformin	SGLT2 inhibitors
Hypoglycaemia		
Number of patients	9964	9964
Number of events	33	22
Rate per 1000 PY	3.33	2.92
HR (95% CI)	Ref.	0.83 (0.48, 1.42)
Unadjusted HR (95% CI)	Ref.	0.95 (0.62, 1.44)
Acute kidney injury		
Number of patients	9964	9964
Number of events	46	34
Rate per 1000 PY	4.65	4.51
HR (95% CI)	Ref.	0.94 (0.60, 1.47)
Unadjusted HR (95% CI)	Ref.	0.73 (0.53, 1.02)

	Metformin	SGLT2 inhibitors
Diabetic ketoacidosis		
Number of patients	9964	9964
Number of events	23	32
Rate per 1000 PY	2.32	4.25
HR (95% CI)	Ref.	1.58 (0.92, 2.70)
Unadjusted HR (95% CI)	Ref.	1.57 (1.11, 2.23)
Genital infections		
Number of patients	9964	9964
Number of events	153	282
Rate per 1000 PY	15.64	38.31
HR (95% CI)	Ref.	2.28 (1.87, 2.78)
Unadjusted HR (95% CI)	Ref.	2.80 (2.49, 3.15)

We observed a numerically lower rate of short-/mid-term cardiovascular events for patients newly prescribed an SGLT2 inhibitor compared to metformin, albeit with wide CIs that include the possibility of a null effect. SGLT2 inhibitors were associated with a higher rate of genital infection and diabetic ketoacidosis.

Comparative effectiveness and safety of sodium-glucose cotransporter-2 inhibitors versus metformin in patients with type 2 diabetes: An observational study using data from routine care. Diabetes, Obesity and Metabolism. 2021 Jul 13.

JAMA Internal Medicine | Original Investigation 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.

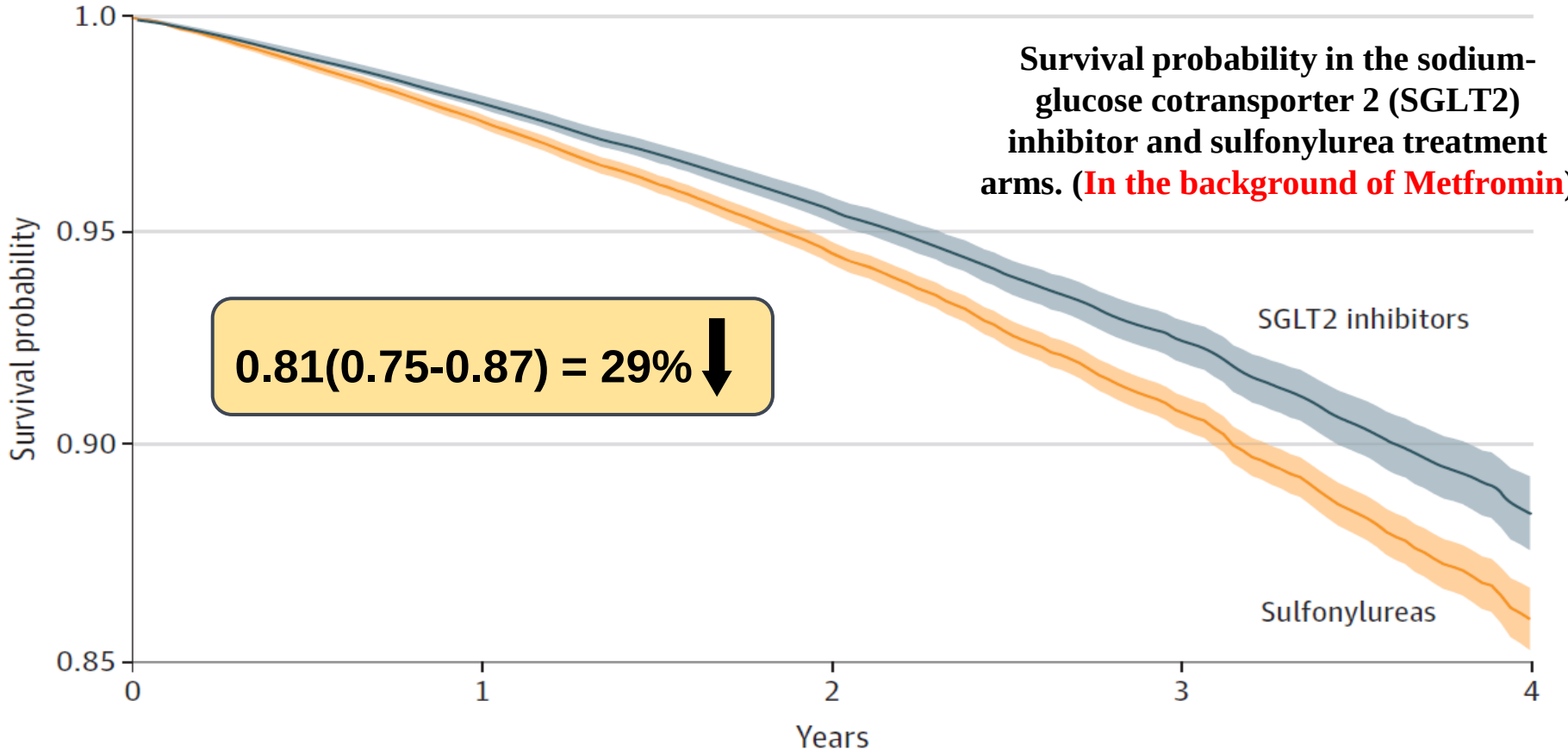
Objective: To evaluate the comparative effectiveness of SGLT2 inhibitors and sulfonylureas associated with the risk of all-cause mortality among patients with type 2 diabetes using metformin.

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



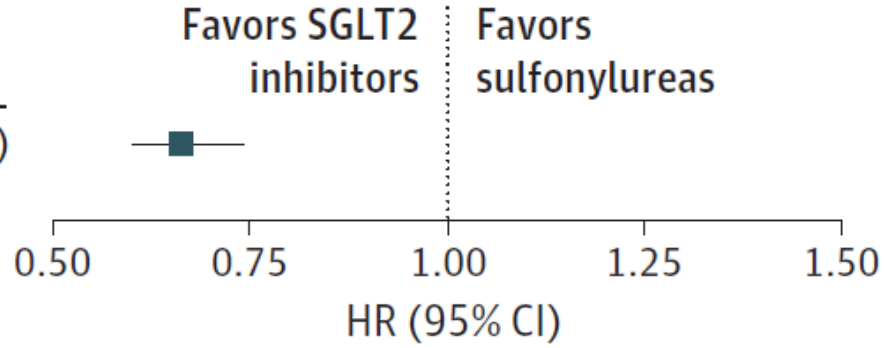
Survival probability in the sodium-glucose cotransporter 2 (SGLT2) inhibitor and sulfonylurea treatment arms. (In the background of Metfromin)

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

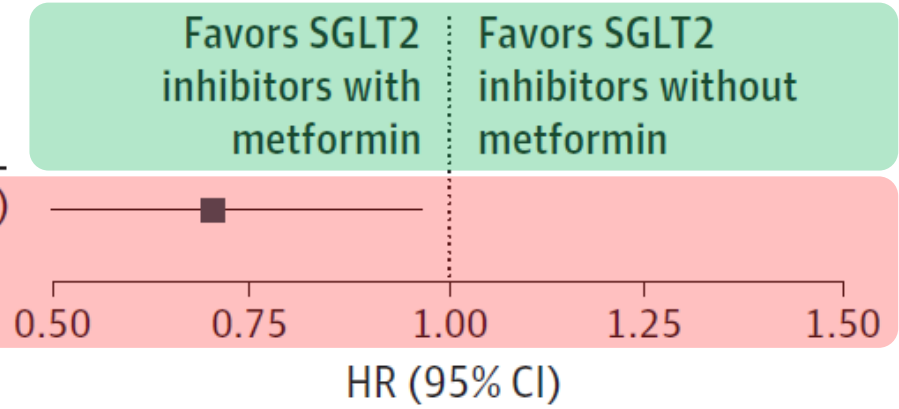
Comparative Effectiveness of Sodium-Glucose Cotransporter 2 Inhibitors vs Sulfonylureas in Patients With Type 2 Diabetes. JAMA Intern Med . 2021 Jun 28;e212488.

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

Analyses	Event reduction per 1000 person-years (95% CI)	HR (95% CI)
SGLT2 inhibitors vs sulfonylureas (reference)	-10.10 (-12.97 to -7.24)	0.66 (0.60-0.74)



Analyses	Event reduction per 1000 person-years (95% CI)	HR (95% CI)
SGLT2 inhibitors with metformin vs SGLT2 inhibitors without metformin (reference)	-7.62 (-17.12 to -0.48)	0.70 (0.50-0.97)



30%⬇ Mortality

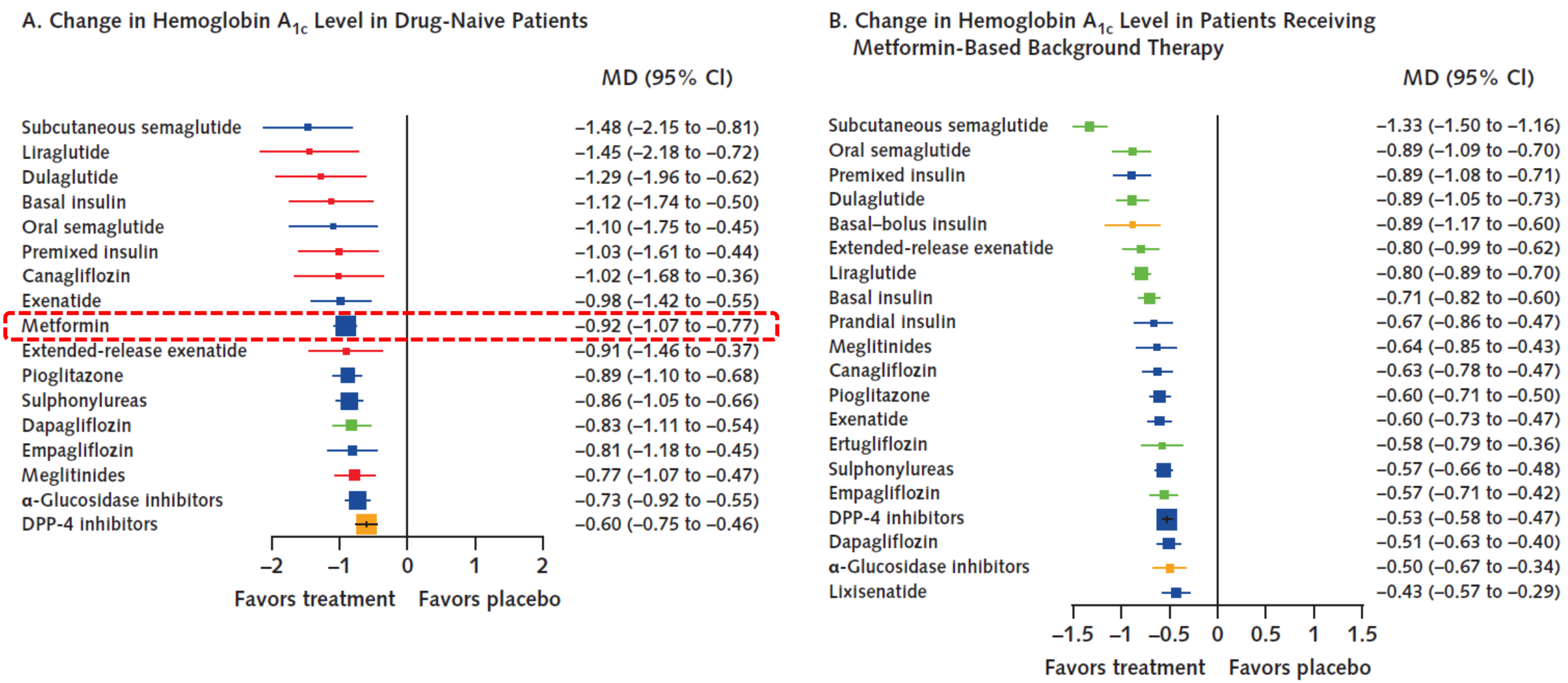
Hazard ratios of all-cause mortality in continued use of sodium-glucose cotransporter 2 (SGLT2) inhibitors or sulfonylureas (reference group) throughout follow-up (top graph) and continued use of SGLT2 inhibitors with metformin or SGLT2 inhibitors without metformin (reference group) throughout follow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

Comparative Effectiveness of Sodium-Glucose Cotransporter 2 Inhibitors vs Sulfonylureas in Patients With Type 2 Diabetes. JAMA Intern Med . 2021 Jun 28;e212488.

8

Metformin efficacy and combination therapy

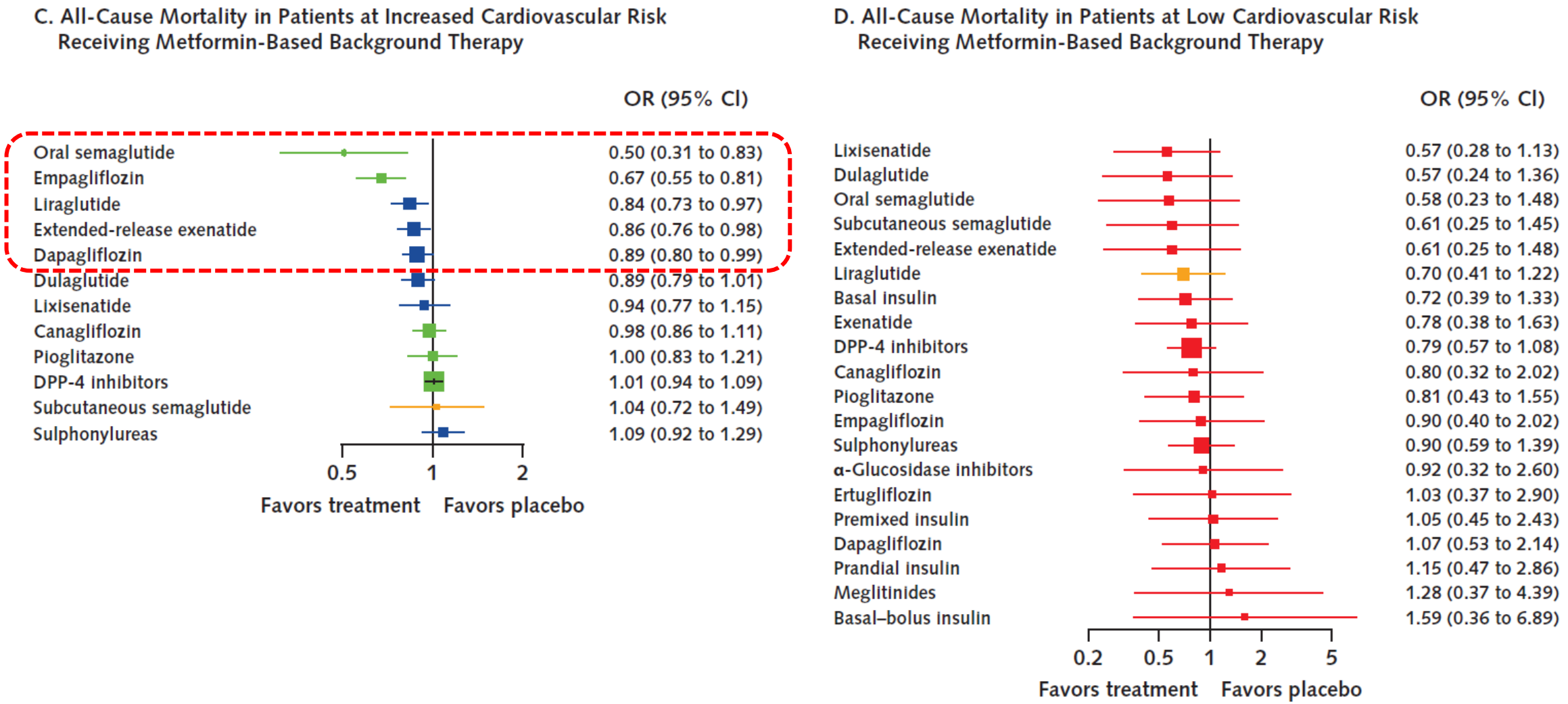
Figure 2. Network meta-analysis results for the primary outcomes compared with placebo.



Treatments are presented according to their effect estimate compared with placebo. Effect sizes are presented as MDs or ORs with 95% CIs. Colors indicate the confidence in the effect estimates according to the CINeMA (Confidence In Network Meta-Analysis) framework: green = high, blue = moderate, orange = low, red = very low. DPP-4 = dipeptidyl peptidase-4; MD = mean difference; OR = odds ratio.

Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. Annals of internal medicine. 2020 Aug 18;173(4):278-86.

Figure 2. Network meta-analysis results for the primary outcomes compared with placebo.

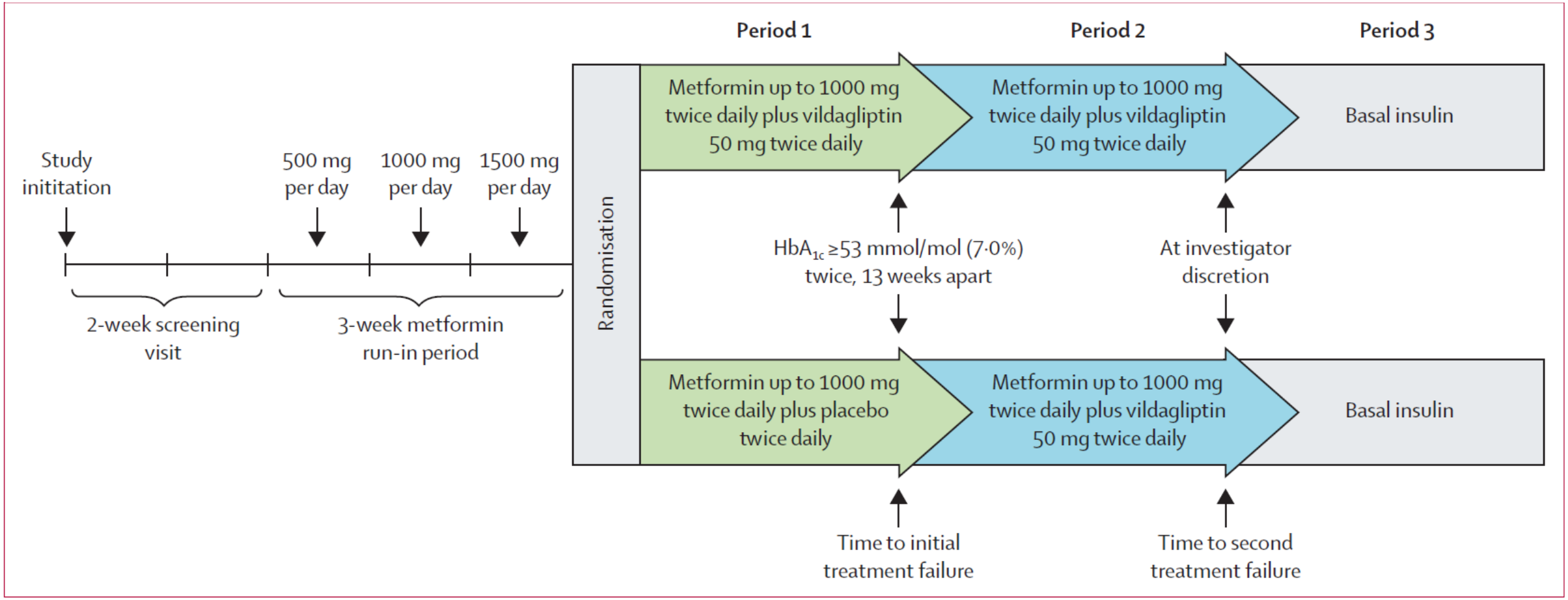


Treatments are presented according to their effect estimate compared with placebo. Effect sizes are presented as MDs or ORs with 95% CIs. Colors indicate the confidence in the effect estimates according to the CINeMA (Confidence In Network Meta-Analysis) framework: green = high, blue = moderate, orange = low, red = very low. DPP-4 = dipeptidyl peptidase-4; MD = mean difference; OR = odds ratio.

Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. Annals of internal medicine. 2020 Aug 18;173(4):278-86.

Figure 1: **Study design**

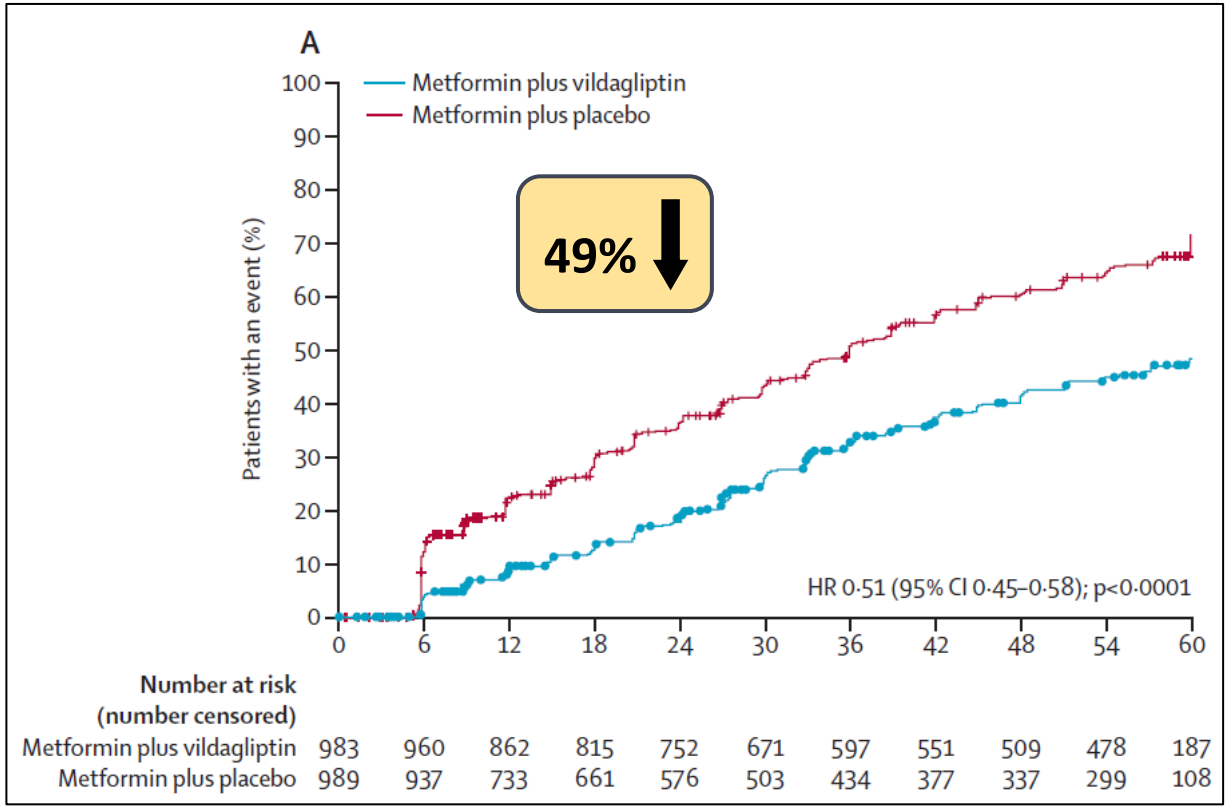
Adapted from Del Prato and colleagues.[12] The duration of period 1 can differ between the two treatments. HbA_{1c}=glycated haemoglobin A_{1c}.

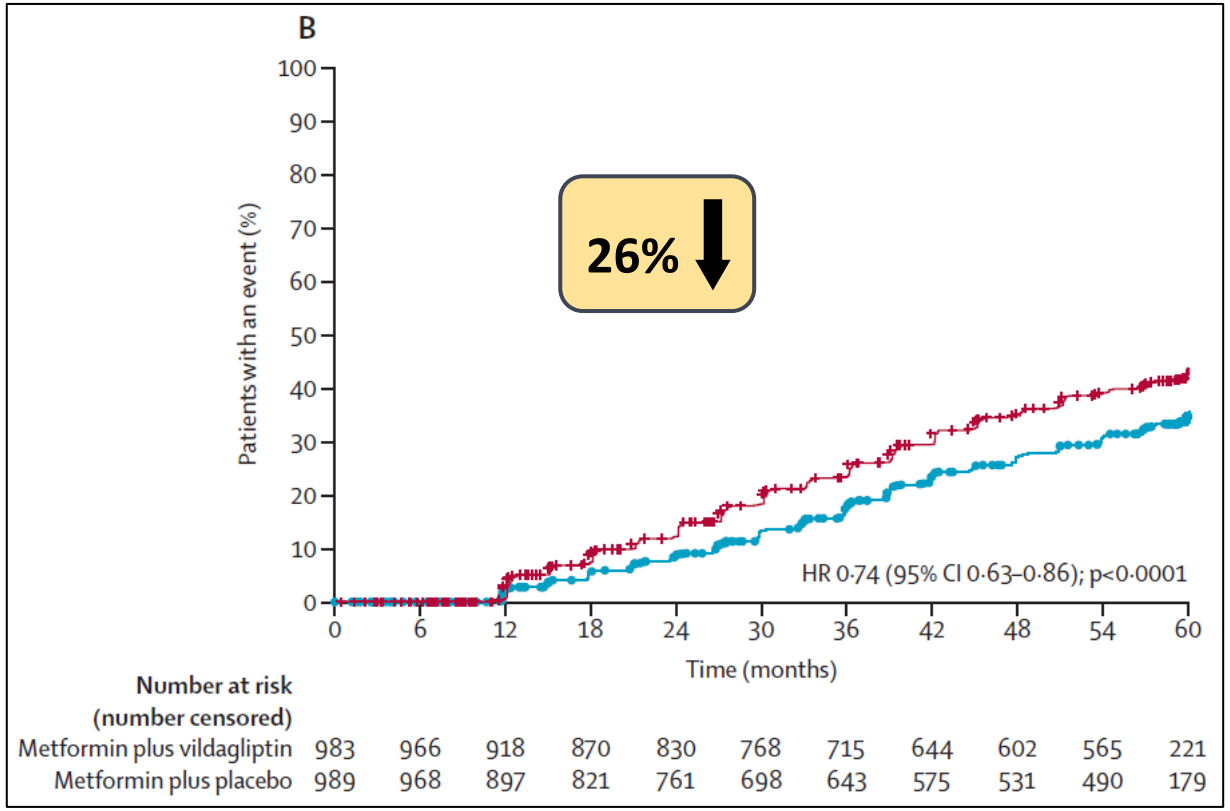


Methods: Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes (VERIFY) was a randomised, double-blind, parallel-group study of newly diagnosed patients with type 2 diabetes. The study consisted of a 2-week screening visit, a 3-week metformin-alone run-in period, and a 5-year treatment period, which was further split into study periods 1, 2, and 3. Patients aged 18–70 years were included if they had type 2 diabetes diagnosed within 2 years prior to enrolment, and centrally confirmed glycated haemoglobin A1c (HbA1c) of 6·5–7·5% and a body-mass index of 22–40 kg/m².

Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. The Lancet. 2019 Oct 26;394(10208):1519-29.

Figure 3: Time to treatment failure (HbA1c measurement of at
least 7.0% at two consecutive scheduled visits, 13 weeks apart from randomisation through period 1.)
(A) Cumulative probability of initial treatment failure.
(B) (B) Cumulative probability of second treatment failure.





Early intervention with a combination therapy of vildagliptin plus metformin provides greater and durable long-term benefits compared with the current standard-of-care initial metformin monotherapy for patients with newly diagnosed type 2 diabetes.

Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. The Lancet. 2019 Oct 26;394(10208):1519-29.

9

Take Home Massage

First-line metformin treatment for type 2 diabetes

Begin treatment	Optional approach
Start with initial dose of 500 mg daily	• Consider extended-release form to minimize risk of gastrointestinal (GI) adverse effects

Adjust dose	Approach for GI side effects
Increase dose gradually to 2000 mg daily if tolerated	• Try extended-release form and consider using highest dose tolerable rather than stopping medication

Common obstacles to using metformin

Condition	Suggested approach
GI intolerance	• Reduce dose until adverse effects resolve • Consider use of extended-release form
Impaired kidney function	• Use freely if eGFR ≥45 mL/min • Use with caution if eGFR 30-45 mL/min • Do not use if eGFR <30 mL/min
Heart failure	• Acceptable to use with stable, chronic heart failure • Do not use with acute heart failure and evidence of end-organ hypoperfusion
Liver disease	• Acceptable to use with chronic liver disease (including mildly elevated liver enzymes, but intact liver function) • Do not use with functional hepatic failure or acute liver injury

Figure

Suggested Starting Regimen for Metformin, Common Obstacles to Use, and Alternatives

Noninsulin alternatives to metformin

Medication	Pros	Cons	Potential risks
Sodium-glucose cotransporter 2 (SGLT-2) inhibitors	• Cardiovascular (CV) benefit • Weight loss	• High cost • Genitourinary infections	• Amputations • Fractures • Euglycemic diabetic ketoacidosis
Glucagon-like peptide 1 (GLP-1) receptor agonists	• CV benefit • Weight loss	• High cost • Requires injections • GI adverse effects	• Pancreatitis
Dipeptidyl peptidase 4 (DDP-4) inhibitors	• Few side effects	• High cost • Modest effect on glucose levels • No CV benefit	• Pancreatitis • Heart failure (alogliptin, saxagliptin)
Sulfonylureas	• Low cost	• Weight gain • Hypoglycemia • No CV benefit	
Thiazolidinediones	• Low cost • Possible CV benefit after stroke	• Weight gain • Edema • Heart failure • Fractures	• Bladder cancer

Flory J, Lipska K. Metformin in 2019. Jama. 2019 May 21;321(19):1926-7.

Effective

60 year safety profile

Cheap

Suitable for use at all stages of diabetes

We Still considered Metformin as the first line medication in the management of the type 2 diabetes

Simple to administer

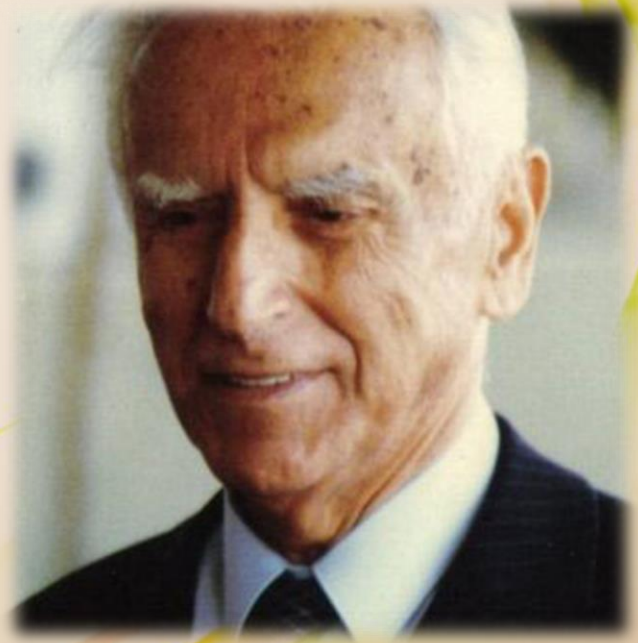
Potential for CVD risk reduction

Across a range of co-morbidities

Suitable for use in combination therapies

Durable

Good adherence



در هر حرفه ای که هستید نه اجازه دهید که به بدبینی‌های بی‌حاصل آلوده شوید و نه بگذارید که بعضی لحظات تاسف بار که برای هر ملتی پیش می‌آید شما را به یاس و ناامیدی بکشاند.

در آرامش حاکم بر آزمایشگاه‌ها و کتابخانه‌هایتان زندگی کنید و نخست از خود بپرسید برای یادگیری و خودآموزی چه کرده‌ام؟

سپس همچنانکه پیشتر می‌روید، بپرسید من برای کشورم چه کرده‌ام؟ و این پرسش را آنقدر ادامه دهید تا به این احساس هیجان انگیز برسید که شاید سهم کوچکی در اعتلای بشریت داشته‌اید.

اما هر پاداشی که زندگی به تلاشهایمان بدهد یا ندهد، هنگامیکه به پایان راه نزدیک می‌شویم هر کدام از ما باید حق آن را داشته باشیم که با صدای بلند بگوییم:

من هر آنچه که در توان داشته‌ام انجام داده‌ام