

EVIDENCE BASED UPDATE IN THE MANAGEMENT OF DIABETES MELLITUS

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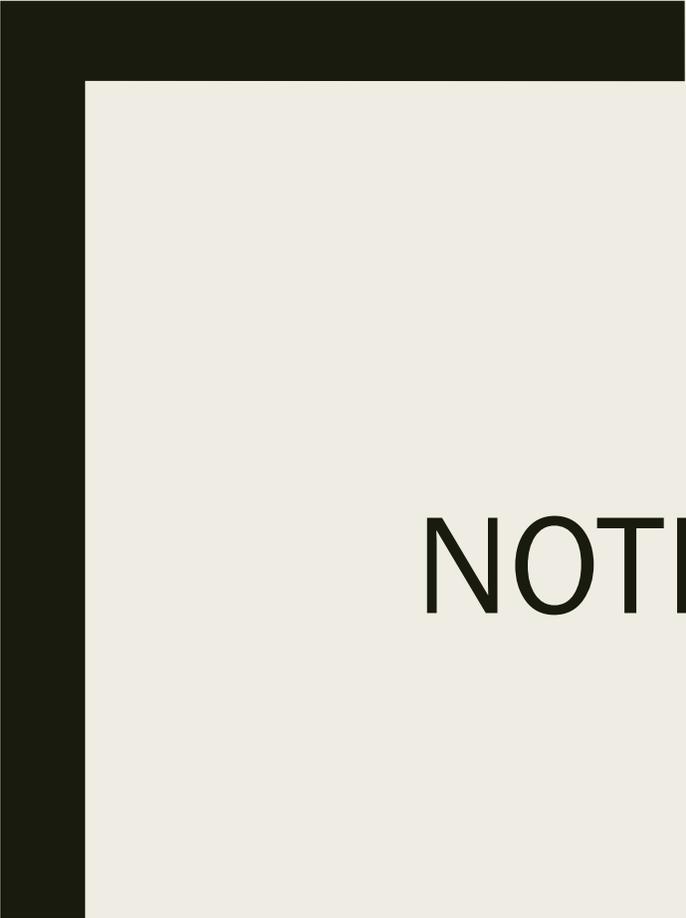
Professor of Medicine UPR School of Medicine

SPED/AACE Endocrine Clinical Update

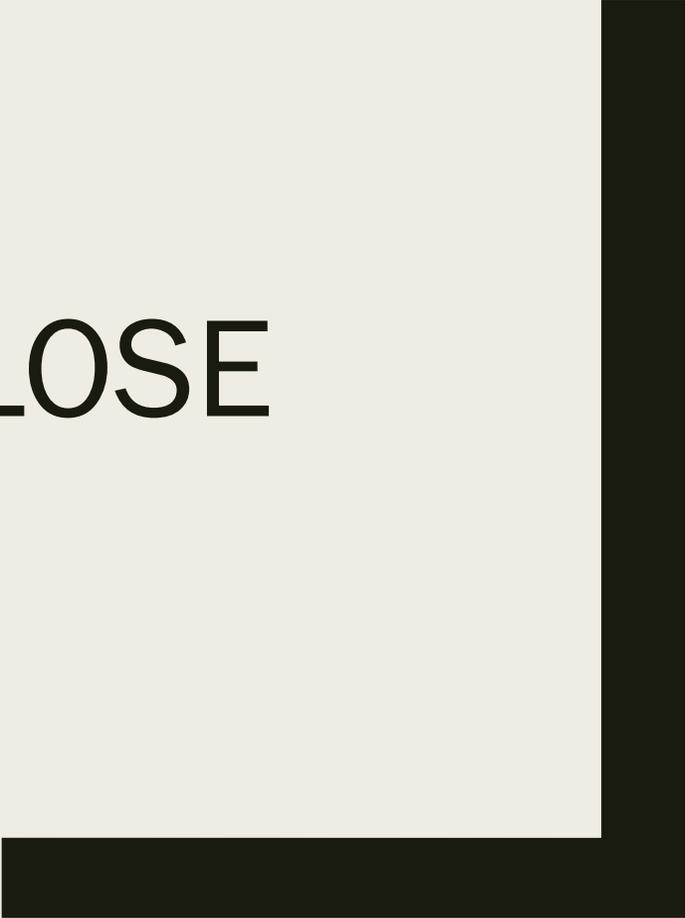
December 15, 2019

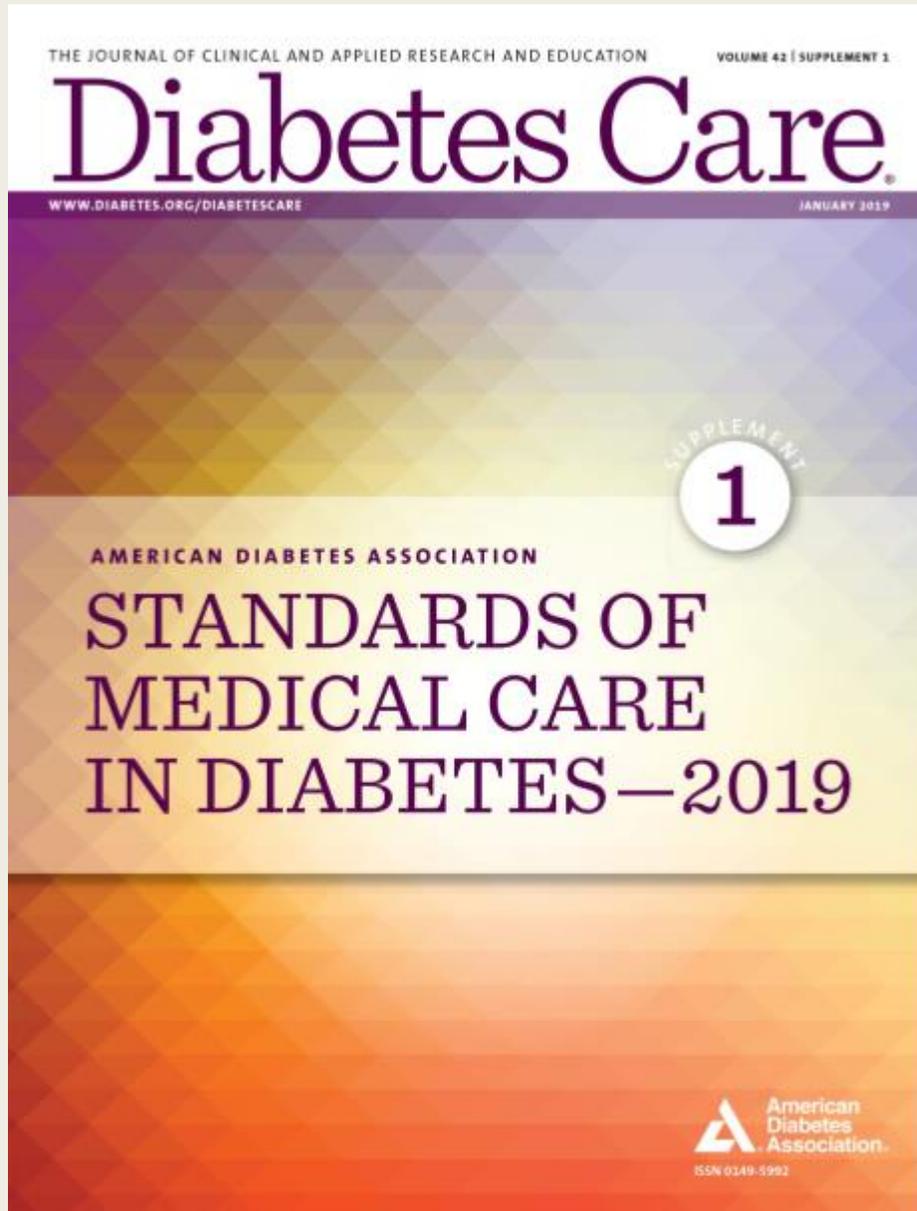
OBJECTIVES

- Recognize complex nature of developing management strategy for Type 2 Diabetes Mellitus
- Be able to set target goals of blood glucose in persons with Type 2 Diabetes Mellitus.
- Identify different properties, mechanism of action and side effects of the newer anti-hyperglycemic drugs impacting their selection as therapy
- Brief mention of non-glycemic properties of the newer anti-hyperglycemic drugs
- Be able to select the appropriate therapy for persons with Diabetes Mellitus according to current guidelines



NOTHING TO DISCLOSE





Standards of Medical Care in Diabetes - 2019



AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AMERICAN COLLEGE OF ENDOCRINOLOGY

AACE/ACE COMPREHENSIVE
TYPE 2 DIABETES
MANAGEMENT ALGORITHM

2

0

1

9



FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity)
 If HbA_{1c} above target proceed as below



ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

HF OR CKD PREDOMINATES

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

COST IS A MAJOR ISSUE⁹⁻¹⁰

EITHER/ OR

GLP-1 RA with proven CVD benefit¹

SGLT2i with proven CVD benefit¹, if eGFR adequate²

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin⁴
- TZD⁵
- SU⁶

PREFERABLY

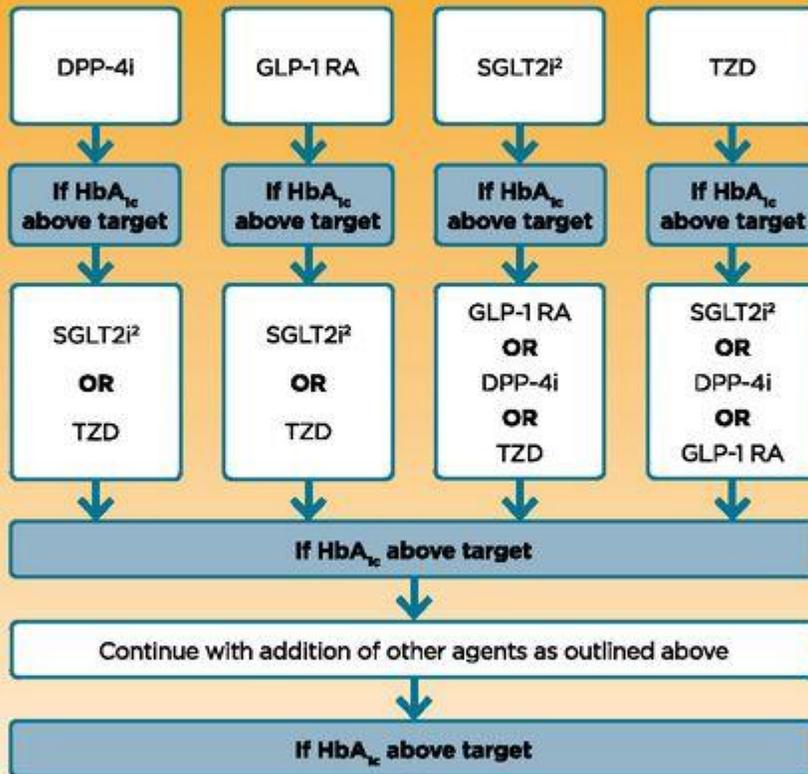
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit¹

If HbA_{1c} above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
- Consider adding the other class with proven CVD benefit¹
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin⁴
- SU⁶



EITHER/ OR

GLP-1 RA with good efficacy for weight loss⁸ OR SGLT2i²

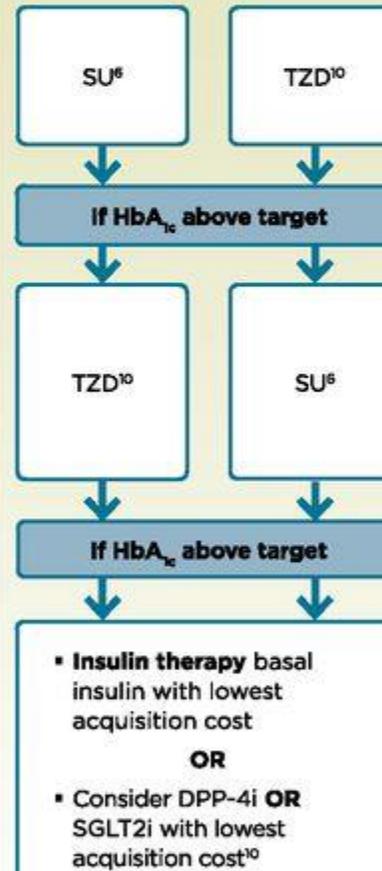
If HbA_{1c} above target

SGLT2i² OR GLP-1 RA with good efficacy for weight loss⁸

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY



Diabetes Education

- Improved self-care behaviors
- Lower A1c
- Improved quality of life
- Lower self-reported weight
- Reduced all cause mortality risk
- Reduced health care costs



Meal Nutrition and Physical Activity



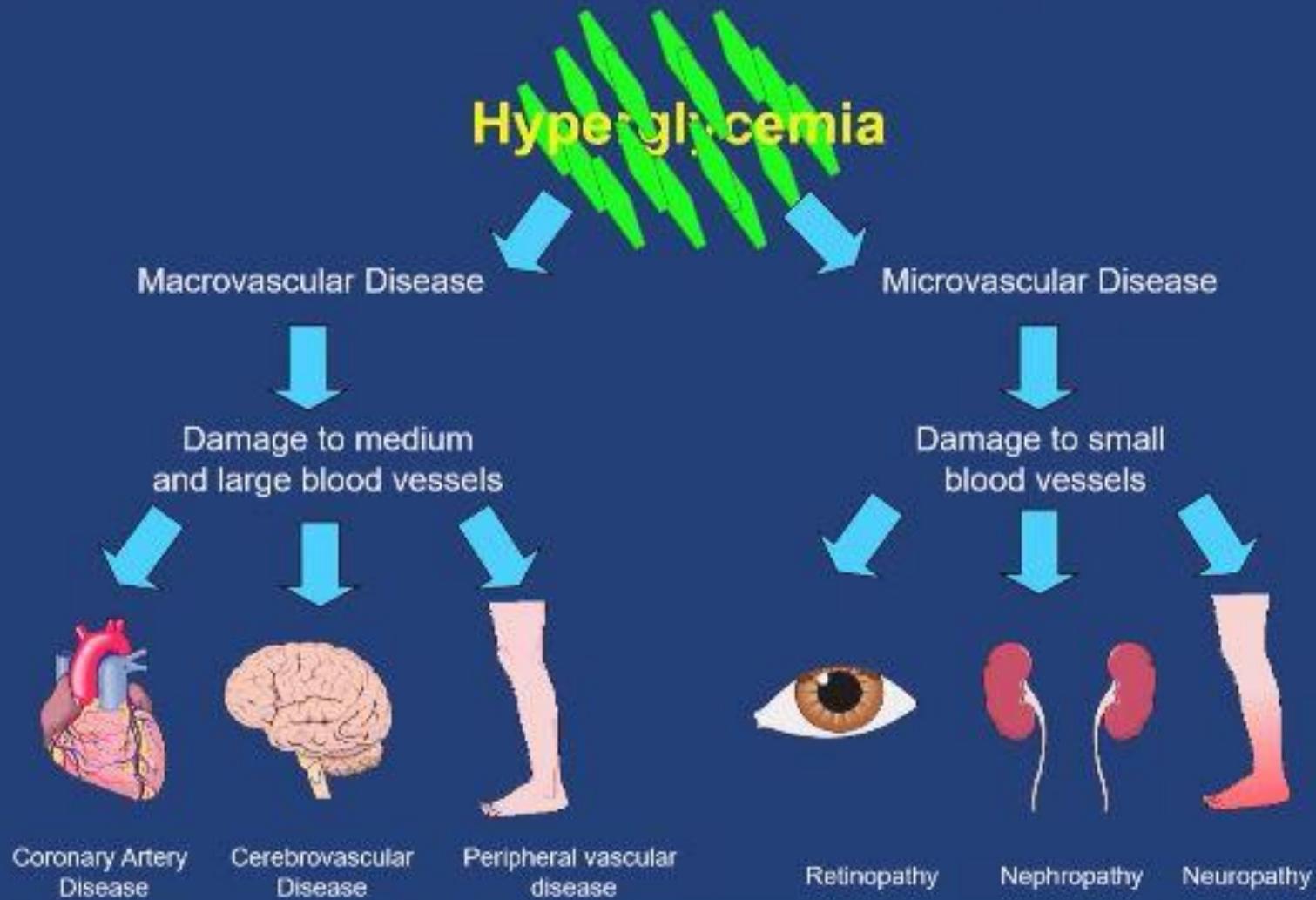
Hemoglobin A1c



Recommendations: Glycemic Goals in Adults

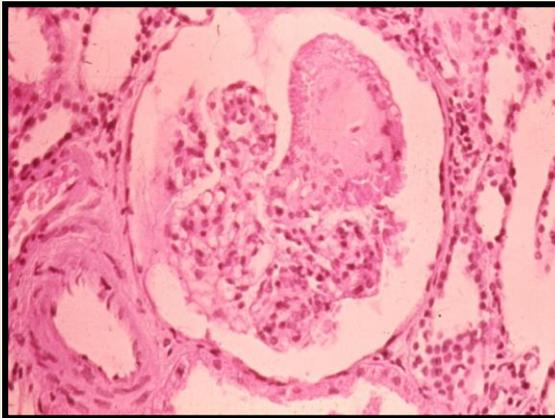
- A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). **A**
- Consider more stringent goals (e.g. <6.5%) for select patients if achievable without significant hypos or other adverse effects. **C**
- Consider less stringent goals (e.g. <8%) for patients with a history of severe hypoglycemia, limited life expectancy, or other conditions that make <7% difficult to attain. **B**

Long-term Complications of Type 2 Diabetes

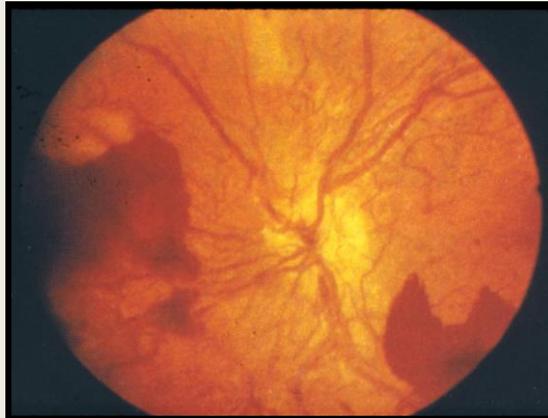


Microvascular Complications of Diabetes

Nephropathy



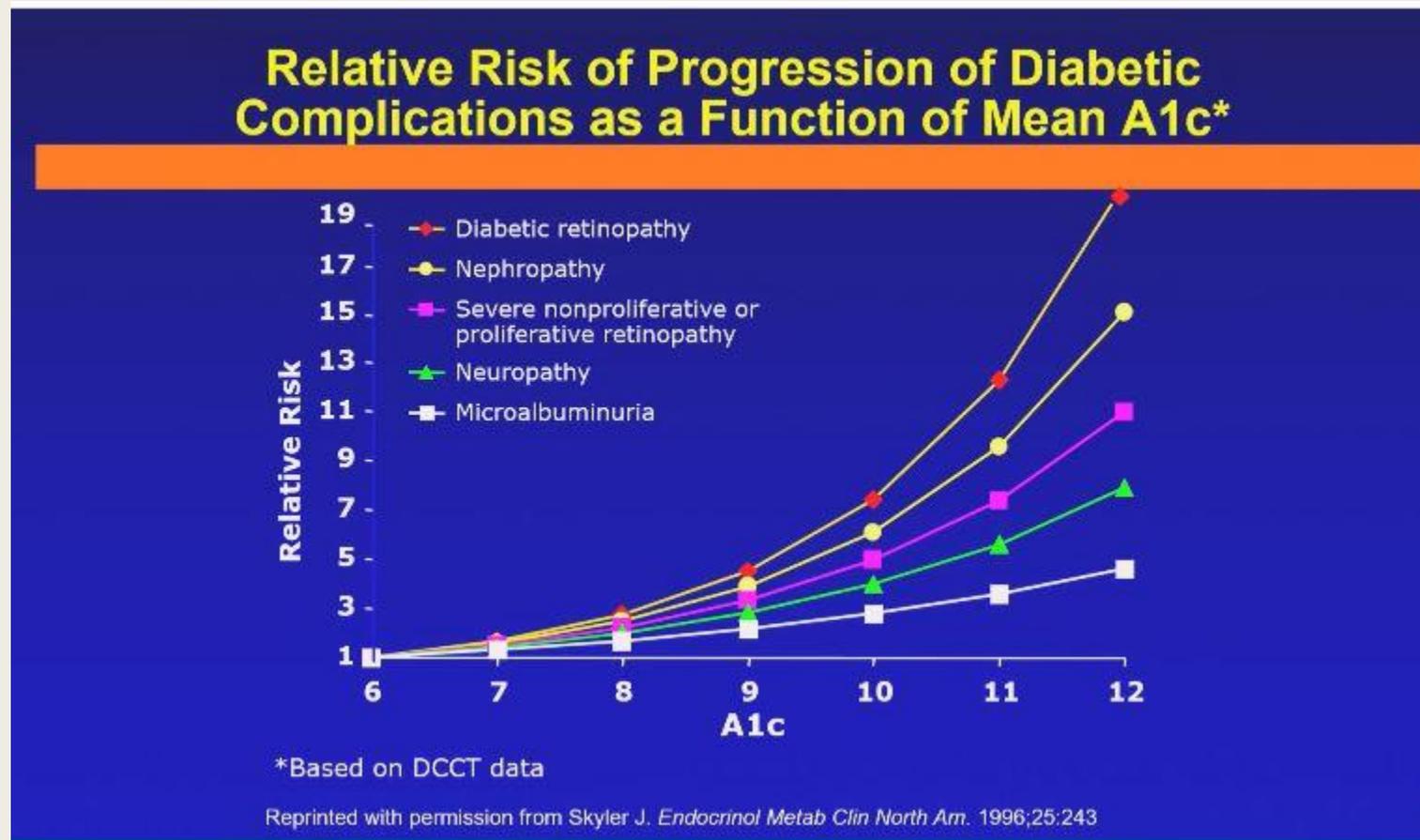
Retinopathy



Neuropathy



Microvascular Complications Increase With Increasing A1C



A1C (%)

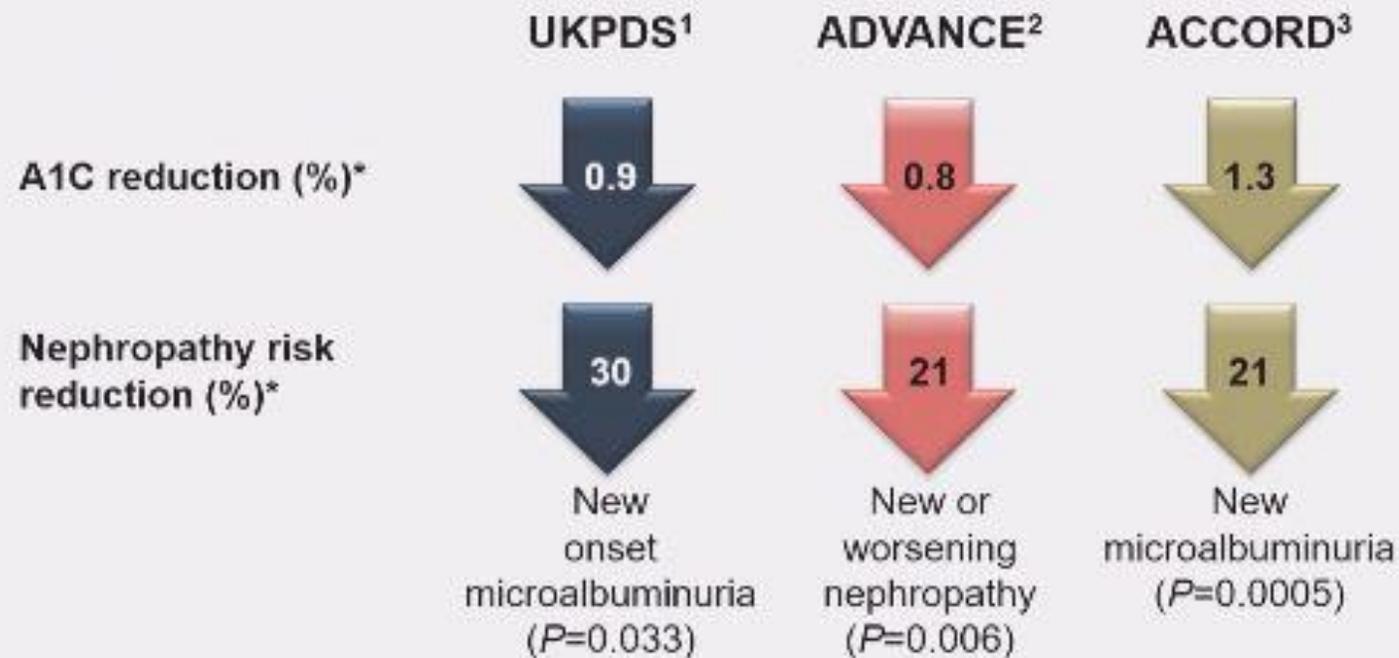
Lowering A1C Reduces Complications in Diabetes

	DCCT	Kumamoto	UKPDS
A1C	9.1% → 7.3%	9.4% → 7.1%	7.9% → 7.0%
Retinopathy	↓ 63%	↓ 69%	↓ 17%–21%
Nephropathy	↓ 54%	↓ 70%	↓ 24%–33%
Neuropathy	↓ 60%	Significantly improved	—
Macrovascular disease	↓ 41%*	—	↓ 16%*

* Not statistically significant

DCCT Research Group. *N Engl J Med.* 1993;329:977-986; Ohkubo Y et al. *Diabetes Res Clin Pract.* 1995;28:103-117; UKPDS Group. *Lancet.* 1998;352:837-853

Reducing A1C Reduces Nephropathy Risk in T2DM



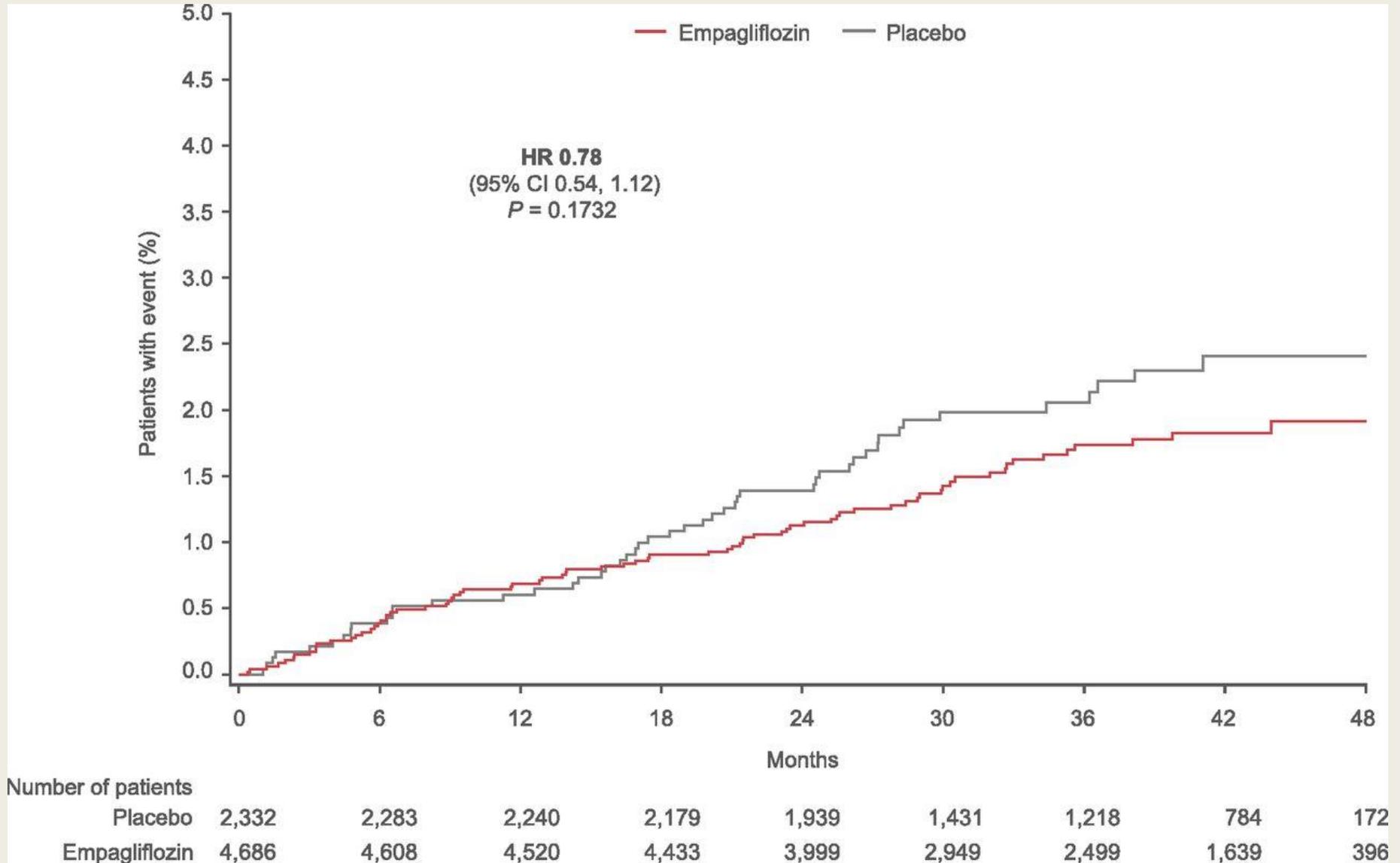
*Intensive vs standard glucose control.

1. UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837-853.

2. ADVANCE Collaborative Group. *N Engl J Med*. 2008;358:2560-2572.

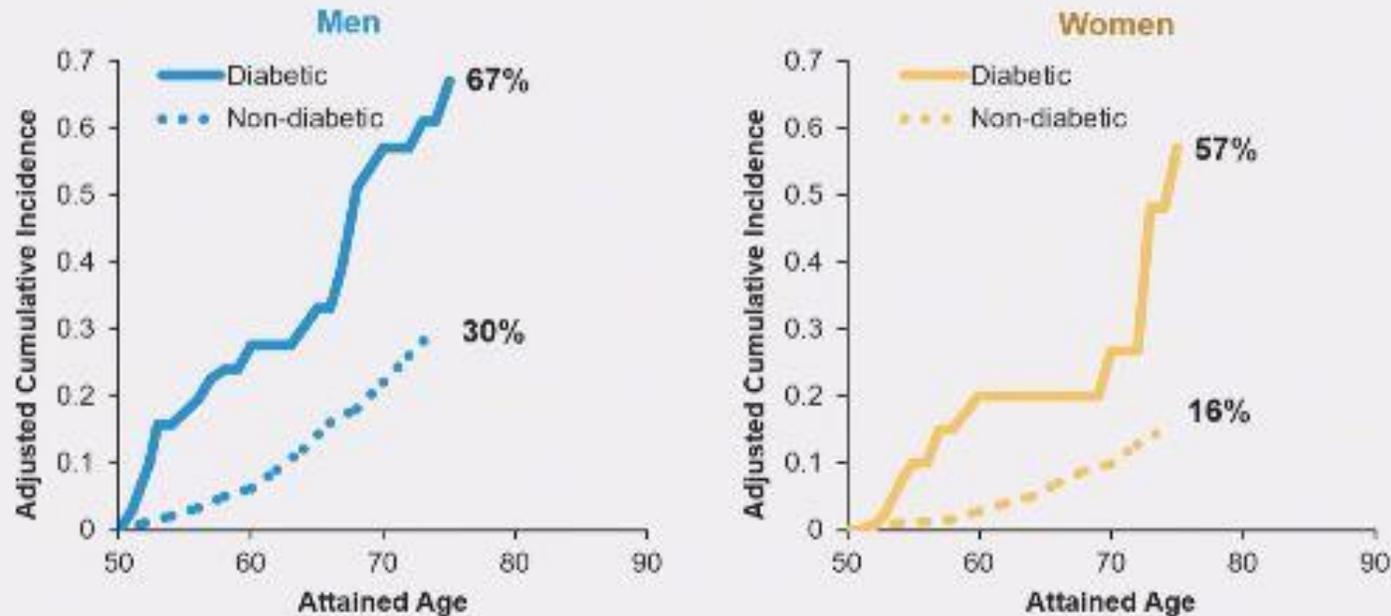
3. Ismail-Beigi F, et al. *Lancet*. 2010;376:419-430.

Retinopathy



Patients With DM Have a Higher Lifetime Risk of CVD Than Patients Without DM

Cumulative Incidence of CVD in Men and Women with DM

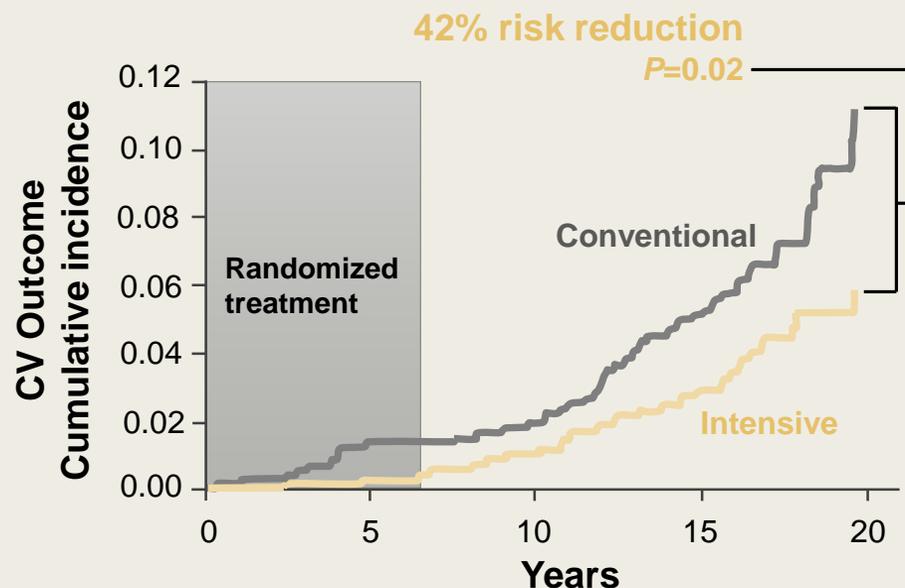


In a 2006 study, Framingham Heart Study participants who were free of CVD at 50 years of age (3,564 men and 4,362 women) were evaluated for a total of 111,777 person-years for lifetime risk of CVD in the presence of DM

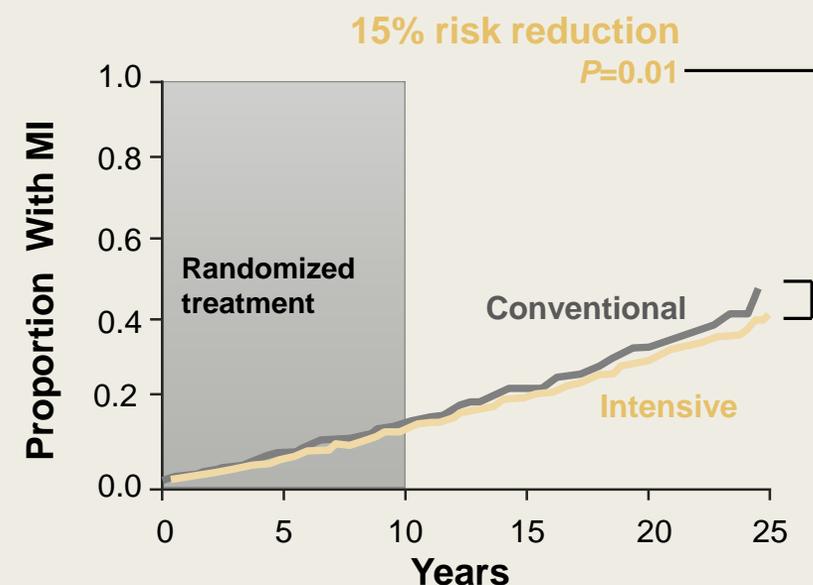
Intensive Glycemic Control Reduces Long-term Macrovascular Risk



DCCT
T1D, 5-6 years duration
(N=1441)



UKPDS
T2D, newly diagnosed
(N=4209)



CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; T1D, type 1 diabetes; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.

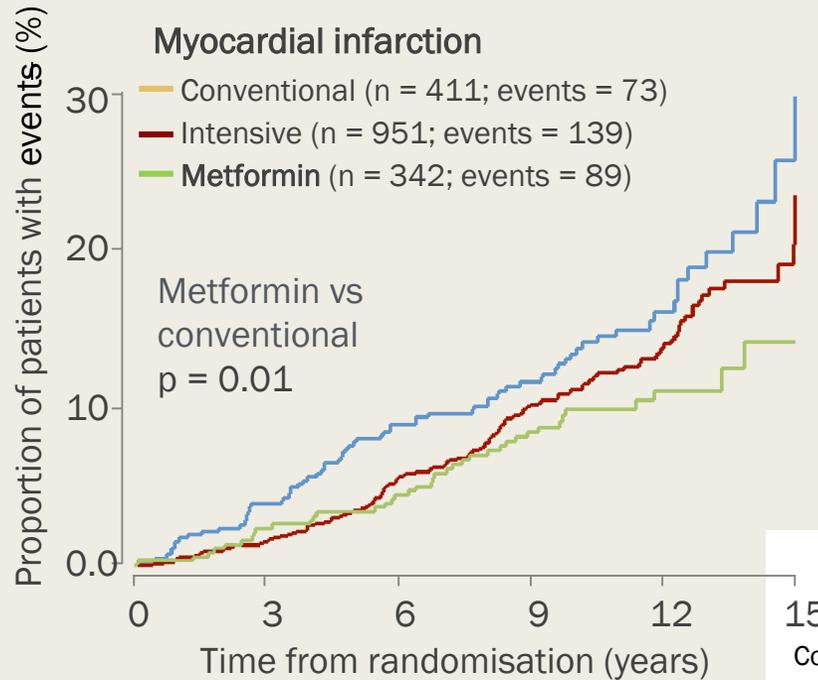
Nathan DM, et al. *N Engl J Med.* 2005;353:2643-2653. Holman RR, et al. *N Engl J Med.* 2008;359:1577-1589.

UKPDS 34 provides some evidence for beneficial CV effects of metformin in overweight patients

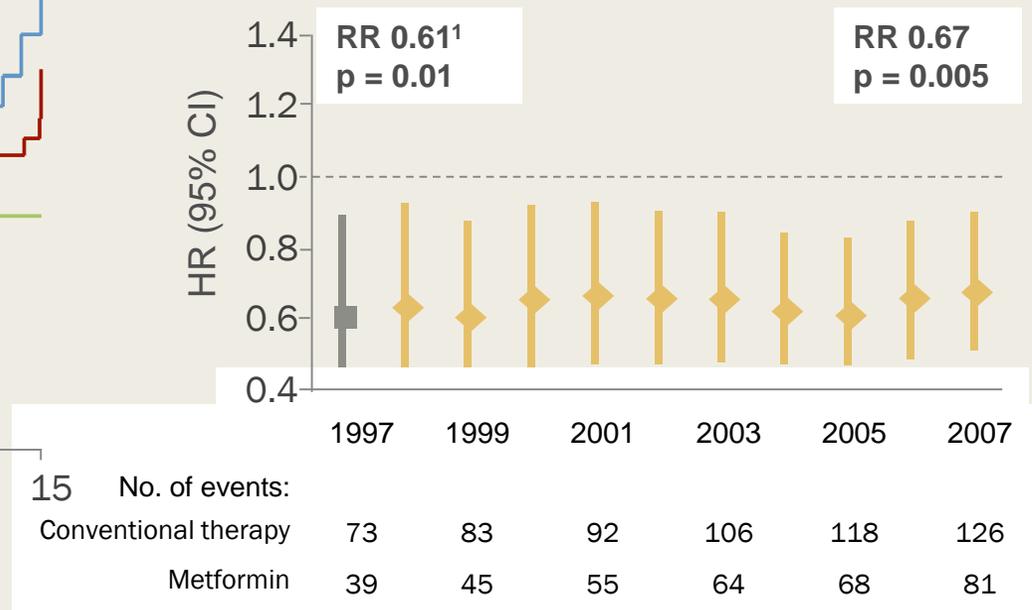
EVIDENCE

Risk of MI is 39% lower with metformin vs conventional therapy in obese patients^{1,2}

Significant reduction in MI maintained over 10 years' follow-up³



■ Overall values at study end in 1997
◆ Annual values during 10-year post-trial monitoring period

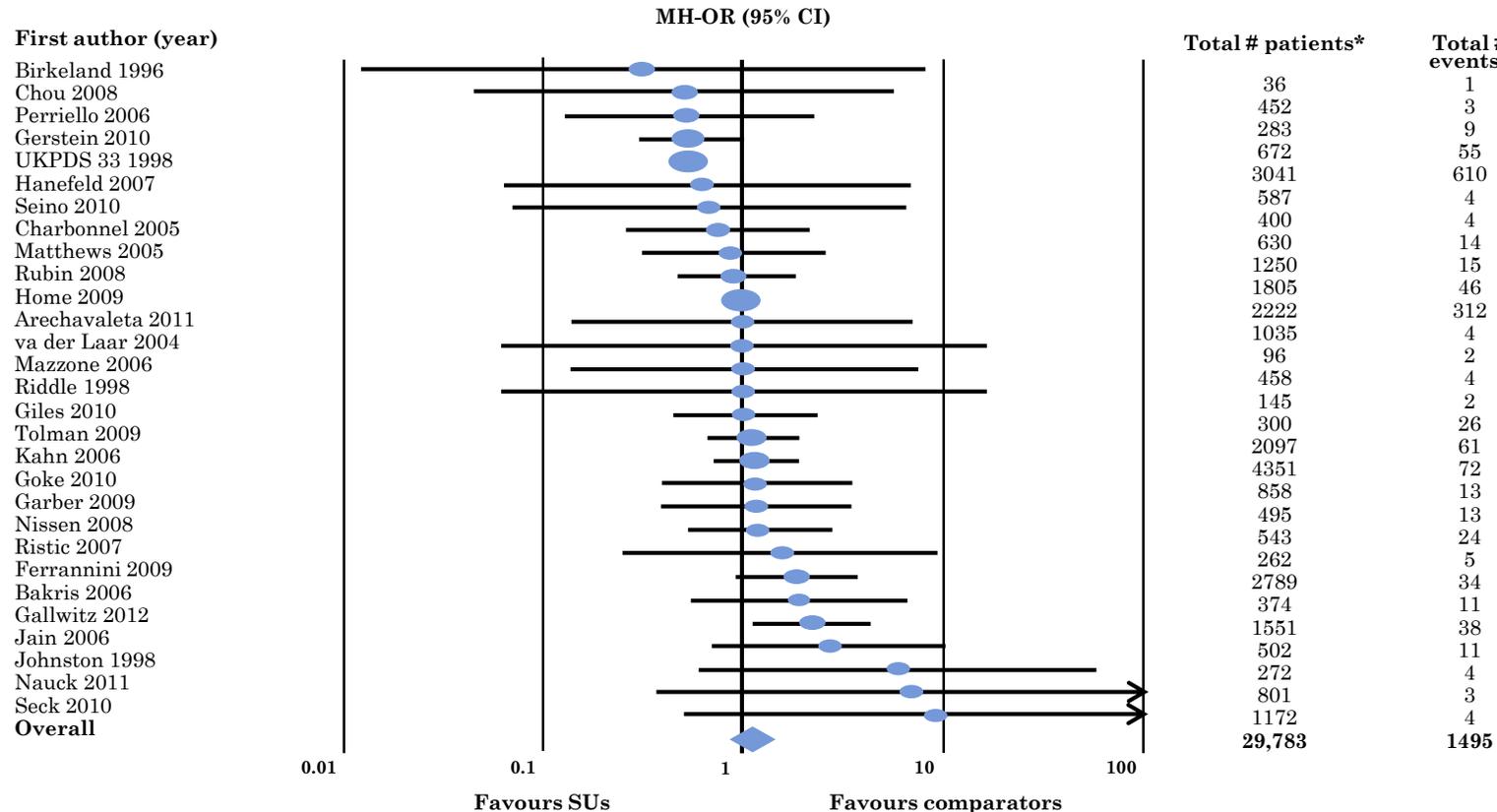


1. UKPDS 34. Lancet 1998;352:854-65. 2. <http://www.medicines.org.uk/emc/medicine/23244/SPC>.
3. Holman et al. N Engl J Med 2008;359:1577-89.

SULFONYLUREAS

EVIDENCE

META-ANALYSIS OF SU CV SAFETY TRIALS (≥ 6 MONTHS) FOUND NO CONSISTENT ASSOCIATION WITH MACE RISK

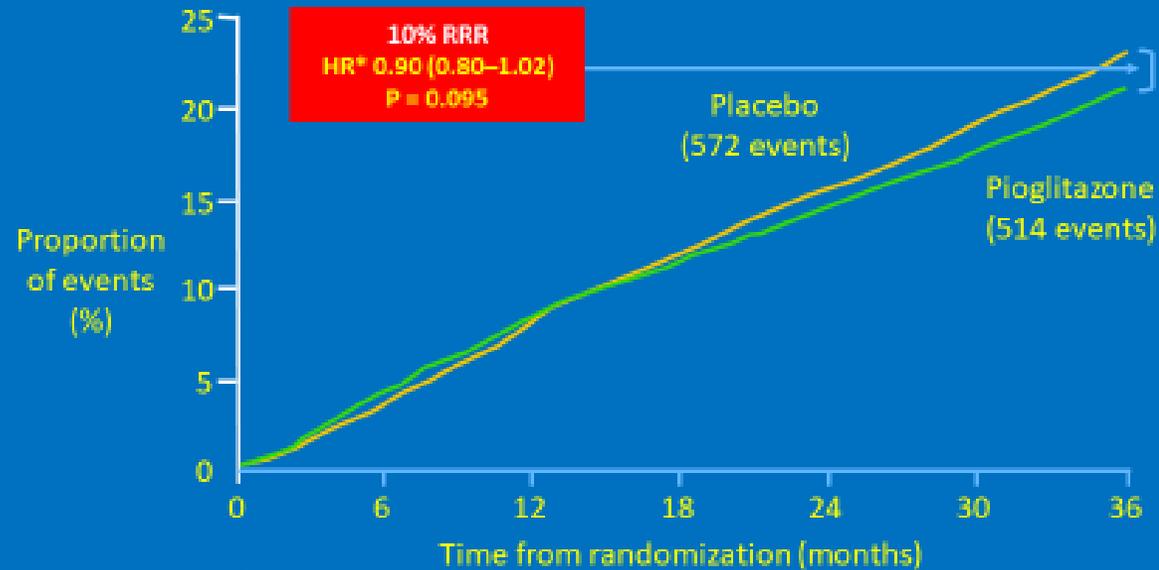


Overall MACE risk estimate for SU vs comparators was not increased: MH-OR 1.08 (95% CI: 0.86–1.36); p = 0.52

- *SU + comparator groups combined.
- Monami et al. Diabetes Obes Metab 2013;15:938–53.

PROactive: Reduction in primary outcome

All-cause mortality, nonfatal MI (including silent MI), ACS, revascularization, leg amputation, stroke



Number at risk

Pioglitazone	2488	2373	2302	2218	2146	348
Placebo	2530	2413	2317	2215	2122	345

*Unadjusted

Ian Gallen

Dormandy JA et al. *Lancet*. 2005;366:1279-89.

EVIDENCE

EVIDENCE

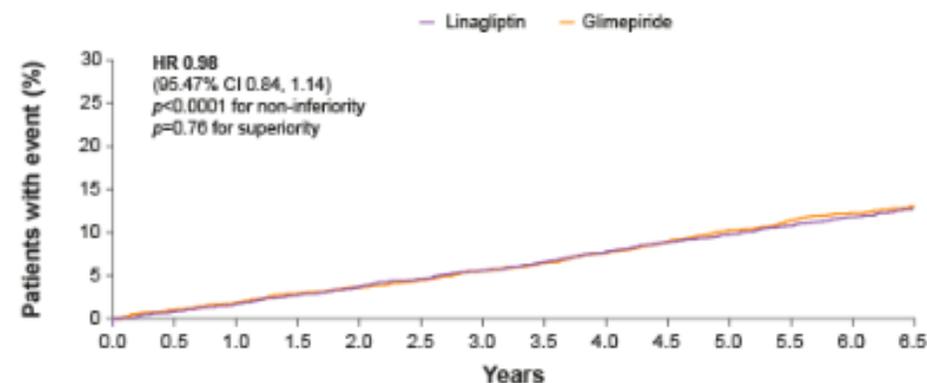
CAROLINA demonstrated the long-term CV and overall safety profile of linagliptin versus glimepiride^{6,7}

Cardiovascular

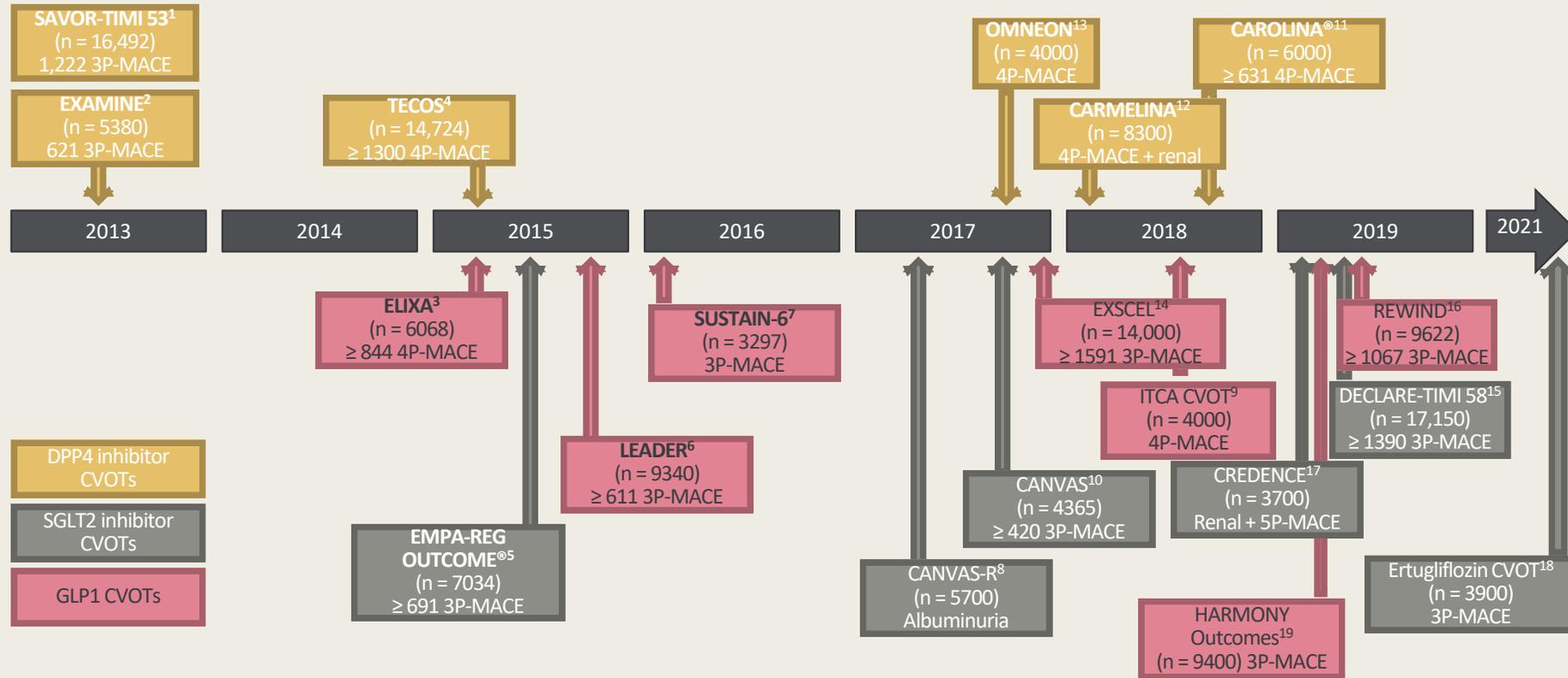


The long-term CV safety profile of linagliptin versus glimepiride was confirmed⁸

The 3P-MACE primary outcome occurred in 356/3023 (11.8%) and 362/3010 (12.0%) patients in the linagliptin and glimepiride groups, respectively



CV safety trials are being conducted for each compound within the newer classes

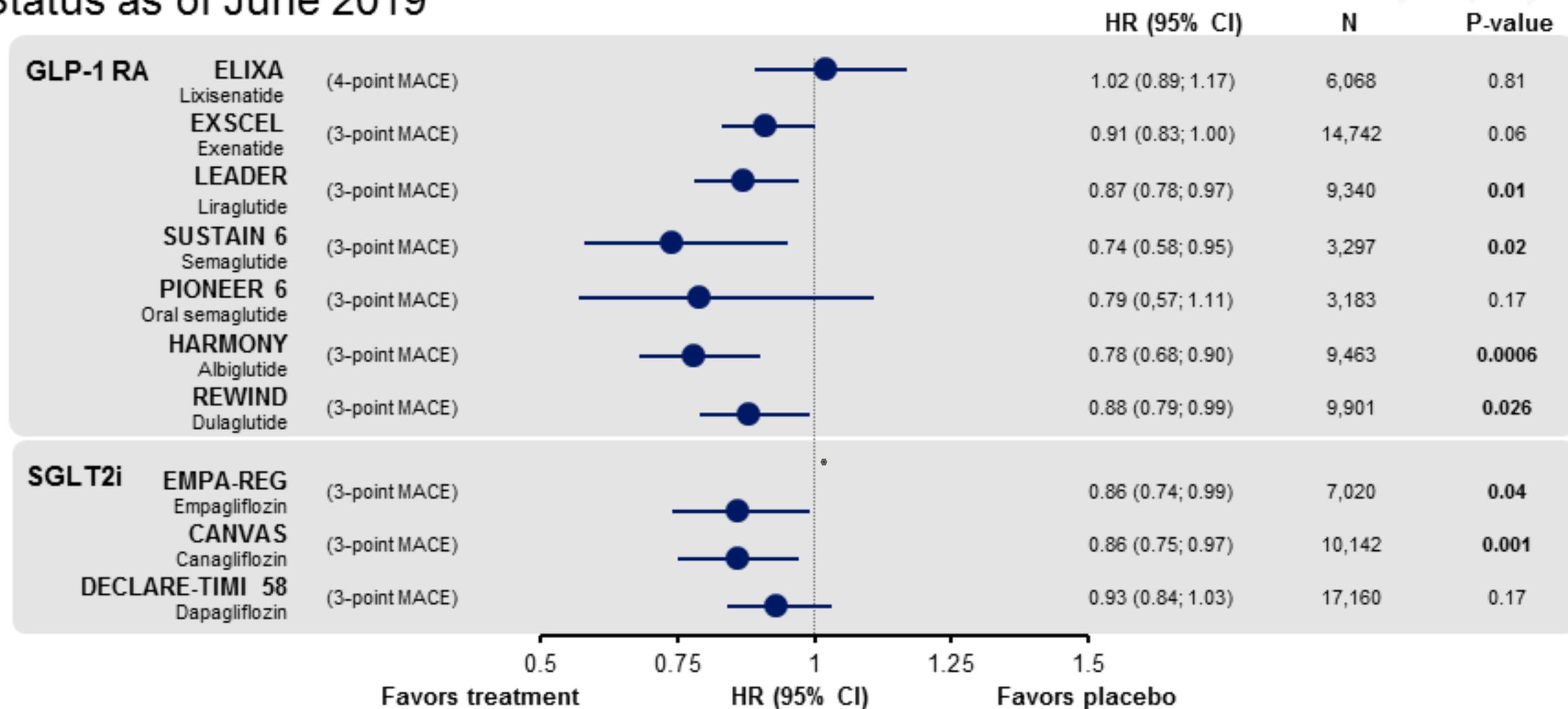


Timings represent estimated completion dates as per ClinicalTrials.gov.

Adapted from Johansen. World J Diabetes 2015;6:1092-96. (references 1-19 expanded in slide notes)

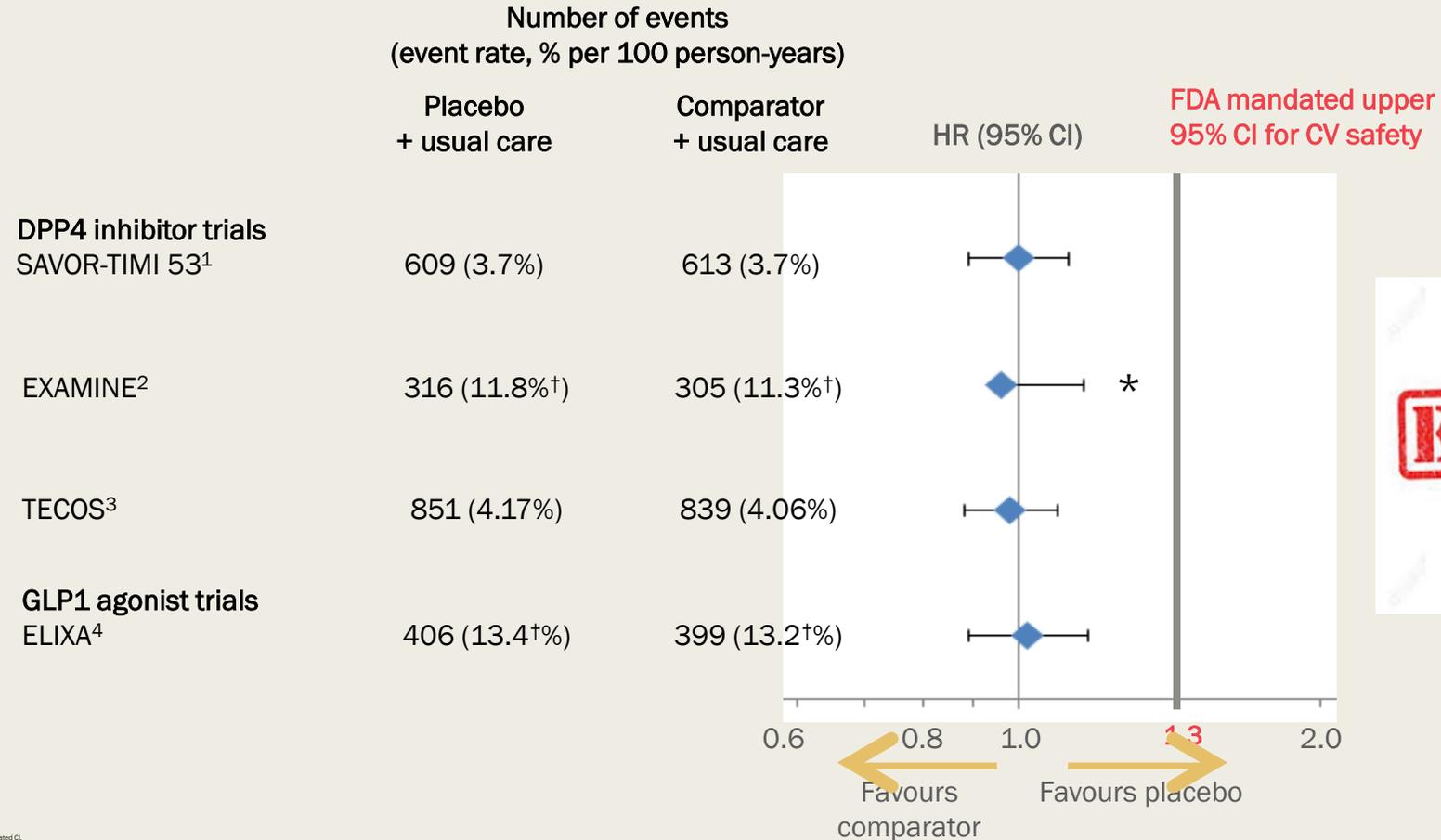
Overview of results from CVOT in T2D

Status as of June 2019



CI, confidence interval; CVOT, cardiovascular outcomes trial; GLP-1RA, GLP-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event; SGLT2i, SGLT2 inhibitor. Adapted from Singh et al. *Indian J Endocrinol Metab* 2017;21:4–10; Holman et al. *N Engl J Med* 2017;377:1228–39; Neal et al. *N Engl J Med* 2017;377:644–57; Hernandez et al. *Lancet*; Epub ahead of print; Wiviott et al. *N Engl J Med* 2018; Epub ahead of print.

For the primary outcome, all completed CVOTs fall within the FDA mandated upper 95% CI limit of 1.3



*Upper boundary of 1-sided repeated CI.

†Total event rate, %.

¹ Scirica et al. N Engl J Med 2013;369:1117-26. ² White et al. N Engl J Med 2013;369:1127-35. ³ Green et al. N Engl J Med 2015; DOI: 10.1056/NEJoa1501362. ⁴ Preferential. ADA, 8 Jun 2015, Boston, USA (oral presentation).

Summary of CV outcomes trials with GLP1 receptor agonists



	Intervention	Main inclusion criteria	No. of patients	Primary outcome	Key 2° outcome	Target no. of events	Estimated follow-up	Estimated completion
ELIXA ^{1,2}	Lixisenatide/ placebo	History of ACS	6068	4P-MACE	Expanded MACE	844	2.1 years median	Completed
Link to study design + data								
LEADER ^{®3}	Liraglutide/ placebo	Vascular disease, or risk factors, or CRF, or CHF	9340	3P-MACE	Expanded MACE	> 611	Up to ~5 years	Nov-15
Link to study + baseline data								
SUSTAIN-6 ^{™4}	Semaglutide/ placebo	Evidence of CV disease	3297	3P-MACE	Expanded MACE	Not specified	Up to ~3 years	Jan-16
EXSCEL ⁵	Exenatide ER*/ placebo	No CV criteria specified	14,000	3P-MACE	All-cause mortality; HHF	Not specified	Up to ~7.5 years	Apr-18
REWIND ⁶	Dulaglutide/ placebo	Pre-existing vascular disease or ≥2 CV risk factors	9622	3P-MACE	Microvascular composite	Not specified	Up to ~6.5 years	Apr-19
HARMONY OUTCOMES ⁷	Albiglutide/ placebo	Established CVD	9400	3P-MACE	Expanded MACE	Not specified	3–5 years	May-19

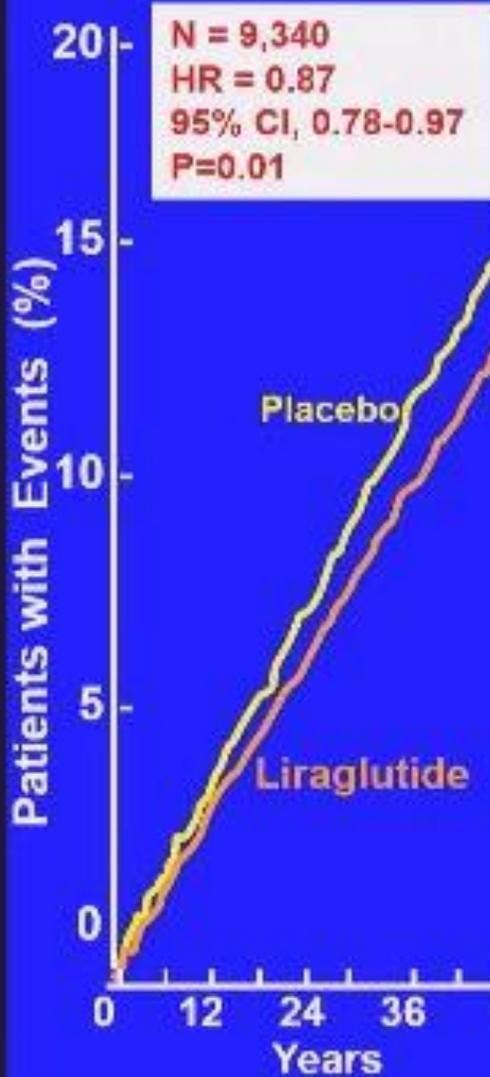
*Once weekly.

1. NCT01147250. 2. Bentley-Lewis et al. Am Heart J 2015;0:1-8.e7. 3. Marso et al. Am Heart J 2013;166:823–30.e5. 4. NCT01720446.

5. NCT01144338. 6. NCT01394952. 7. NCT02465515

EFFECT OF LIRAGLUTIDE ON MACE IN LEADER

N = 9,340
 HR = 0.87
 95% CI, 0.78-0.97
 P=0.01



Marso et al, NEJM June 13, 2016

EFFECT OF SEMAGLUTIDE ON MACE IN SUSTAIN-6

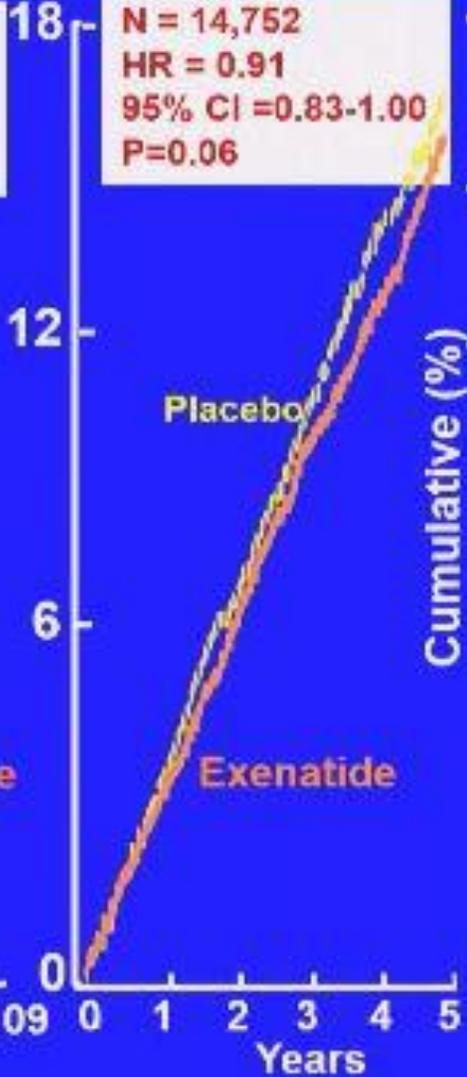
N = 3297
 HR = 0.74
 95% CI, 0.58-0.95
 P = 0.02



Marso et al, NEJM, Sept 16, 2016

EFFECT OF ONCE WEEKLY EXENATIDE ON MACE IN EXSCEL

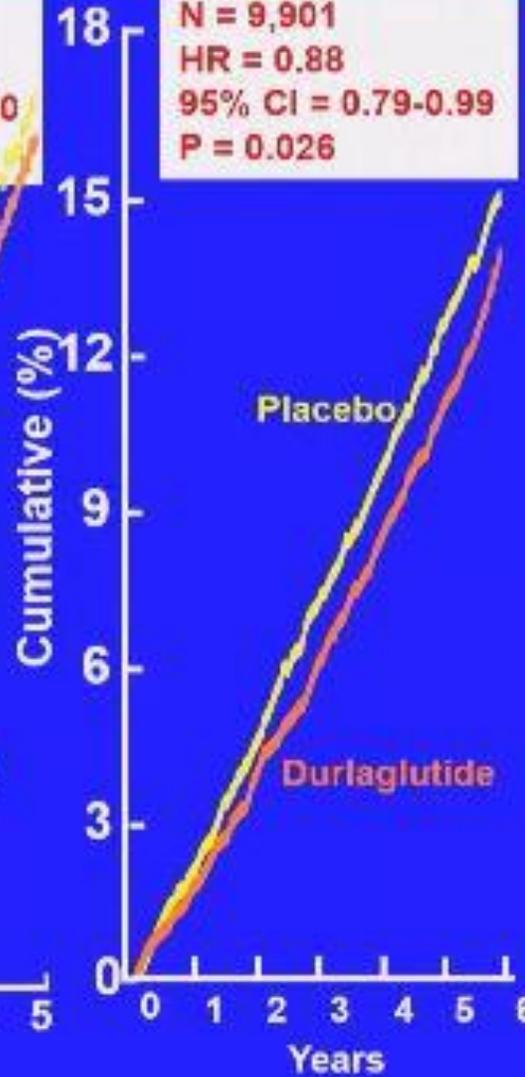
N = 14,752
 HR = 0.91
 95% CI =0.83-1.00
 P=0.06



Holman et al, NEJM, Sept 13, 2017

EFFECT OF DULAGLUTIDE ON MACE IN REWIND

N = 9,901
 HR = 0.88
 95% CI = 0.79-0.99
 P = 0.026



Gerstein et al, Lancet, June 2019

EVIDENCE

Cardiovascular Outcomes Studies of GLP 1's

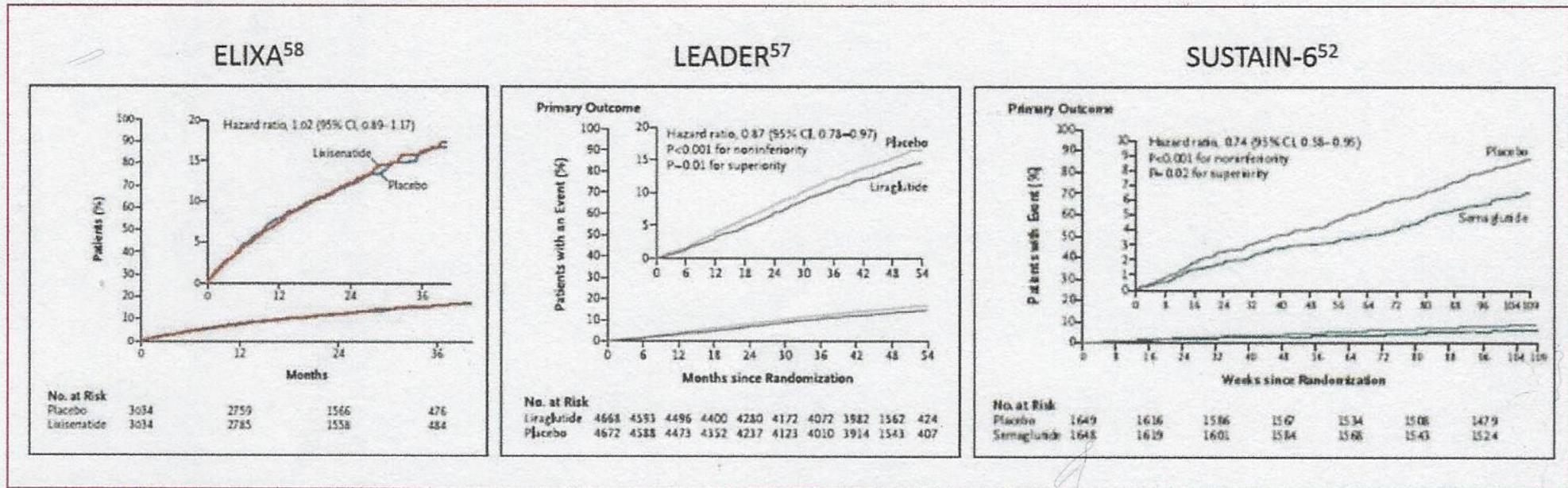


Fig. 3. Comparison of glucagon-like peptide 1 (GLP-1) receptor agonist cardiovascular (CV) outcomes trials: time to primary composite endpoint (52,57,58). All of the reported CV outcomes trials with GLP-1 receptor agonists demonstrated noninferiority to placebo for their primary CV composite endpoint, thus meeting the primary endpoint of CV safety (Table 1) (52,57-62). Liraglutide and semaglutide not only met the noninferiority safety endpoints but also demonstrated improvement in CV outcomes compared with placebo (52,57,58). *CI* = confidence interval. Left: **Pfeffer MA, Claggett B, Diaz R, et al.** Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med.* 2015;373:2247-2257. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Center: **Marso SP, Daniels GH, Brown-Frandsen K, et al.** Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375:311-322. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Right: **Marso SP, Bain SC, Consoli A, et al.** Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375:1834-1844. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

SGLT-2i CVOT EFFICACY OUTCOMES

Zeiniker TA et al. *Lancet*. 2018 Nov 9. pii: S0140-6736(18)32590-X. doi: 10.1016/S0140-6736(18)32590-X

Endpoint

Hazard Ratio

DECLARE
CANVAS
EMPA-REG

MACE Composite

0.93

0.86

0.86

CV death

0.98

0.87

0.62

Nonfatal MI

0.89

0.85

0.87

Nonfatal stroke

1.01

0.90

1.24

HHF/CVD

0.83

0.78

0.66

HHF

0.73

0.67

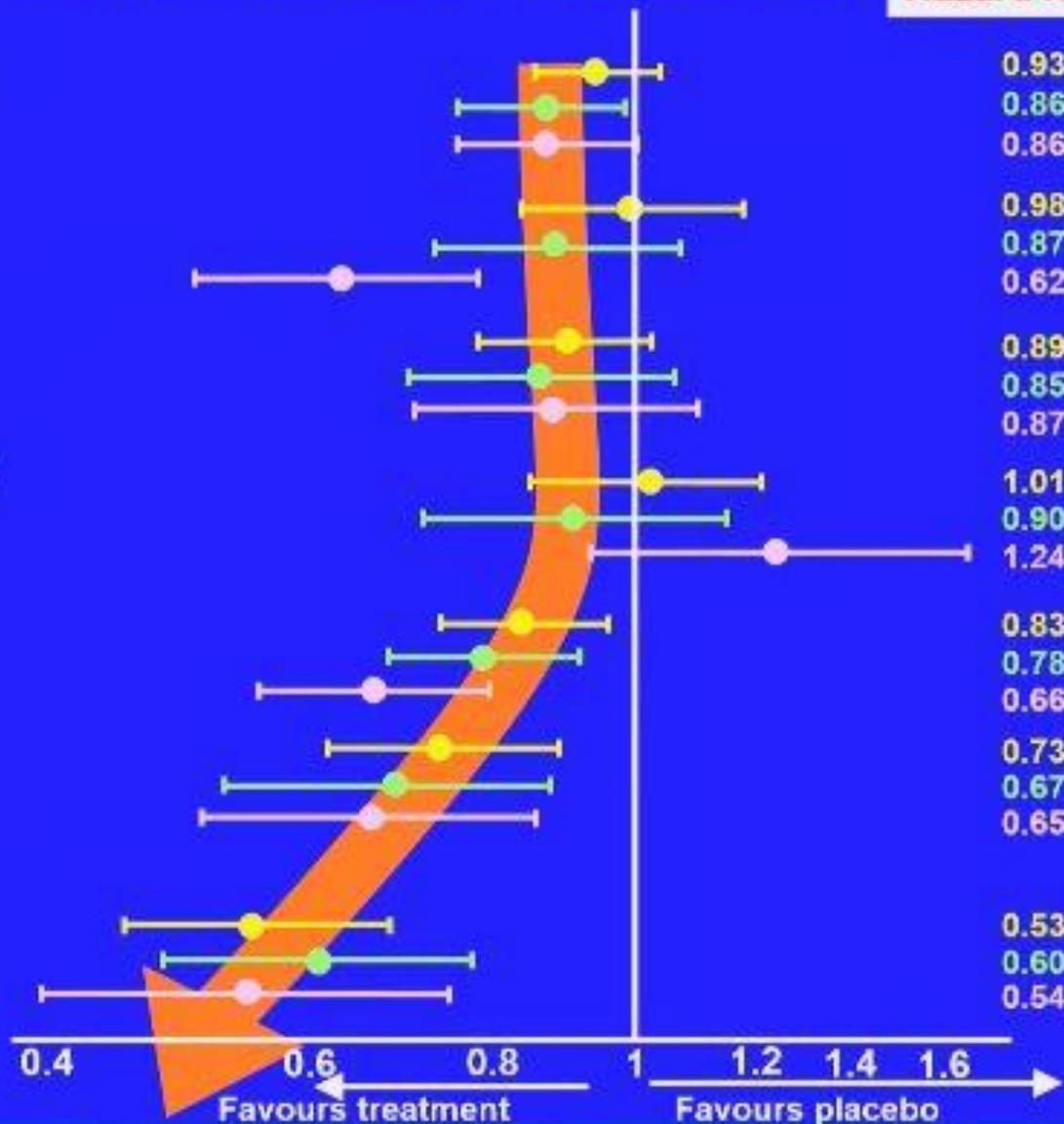
0.65

Renal Composite

0.53

0.60

0.54



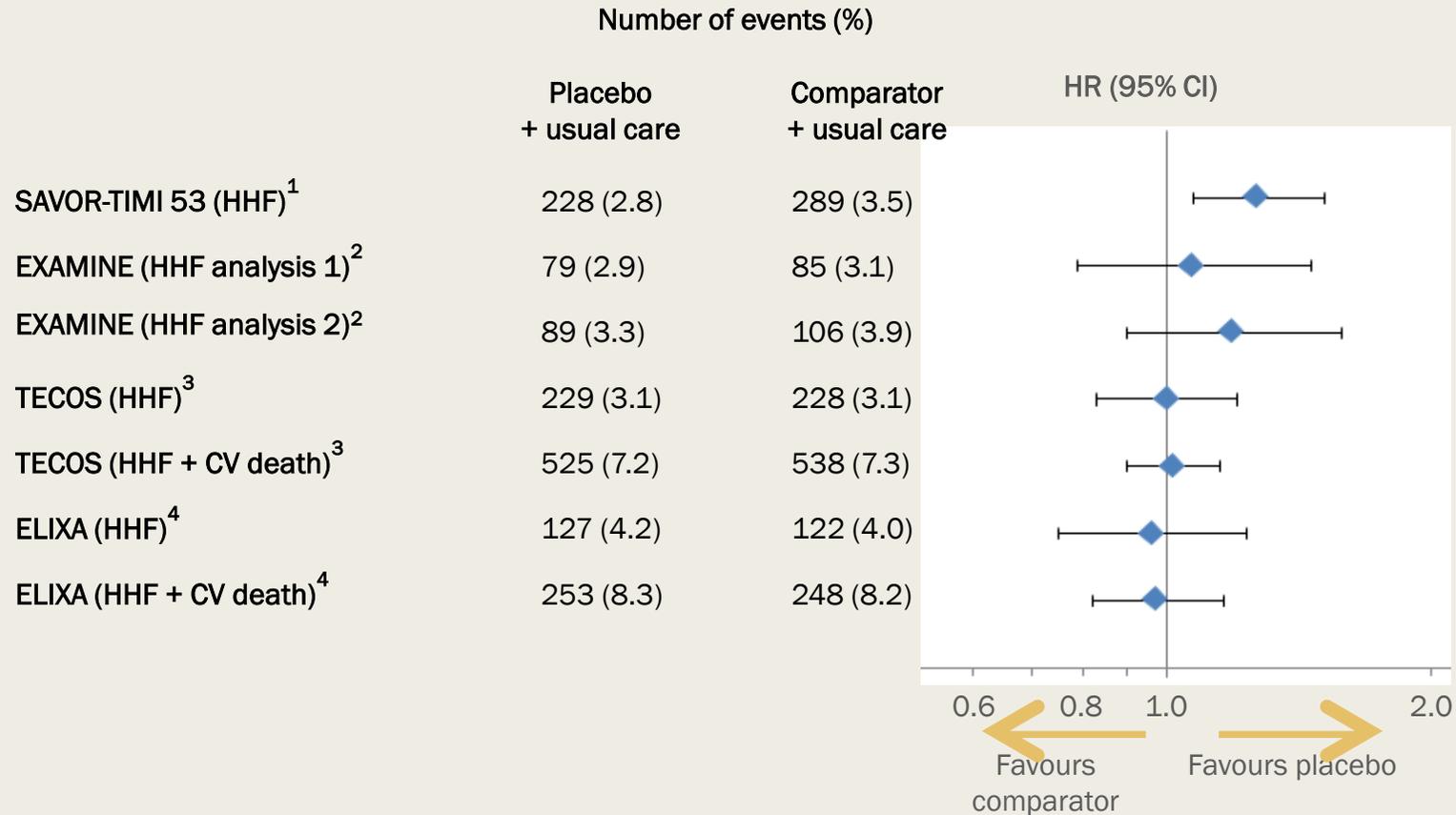
EVIDENCE

CV outcome trials with SGLT2 inhibitors

	EMPA-REG OUTCOME™ ¹	CANVAS ²	CANVAS-R ³	CREDESCENCE ⁴	DECLARE-TIMI 58 ⁵	Ertugliflozin CVOT ⁶
Interventions	Empagliflozin/ placebo	Canagliflozin/ placebo	Canagliflozin/ placebo	Canagliflozin/ placebo	Dapagliflozin/ placebo	Ertugliflozin/ placebo
Main inclusion criteria	Est. vascular complications	Est. vascular complications or ≥ 2 CV risk factors	Est. vascular complications or ≥ 2 CV risk factors	Stage 2 or 3 CKD + macroalbuminuria	High risk for CV events	Est. vascular complications
No. of patients	7034	4339	5700	3627	17,150	3900
Primary outcome	3P-MACE	3P-MACE	Progression of albuminuria	ESKD, S-creatinine doubling, renal/CV death	3P-MACE	3P-MACE
Key secondary outcome	4P-MACE	Fasting insulin secretion, progression of albuminuria	Regression of albuminuria, change in eGFR	4P-MACE + HHF	4P-MACE + HHF + revascularisation	4P-MACE
Target no. of events	691	≥ 420	TBD	TBD	1390	TBD
Estimated median FU	~3 years	6–7 years	3 years	~4 years	4–5 years	5–7 years
Estimated completion	2015	Apr 2017	2017	2019	2019	2021

EVIDENCE

Hospitalisation for heart failure (HHF) data for all completed CVOTs



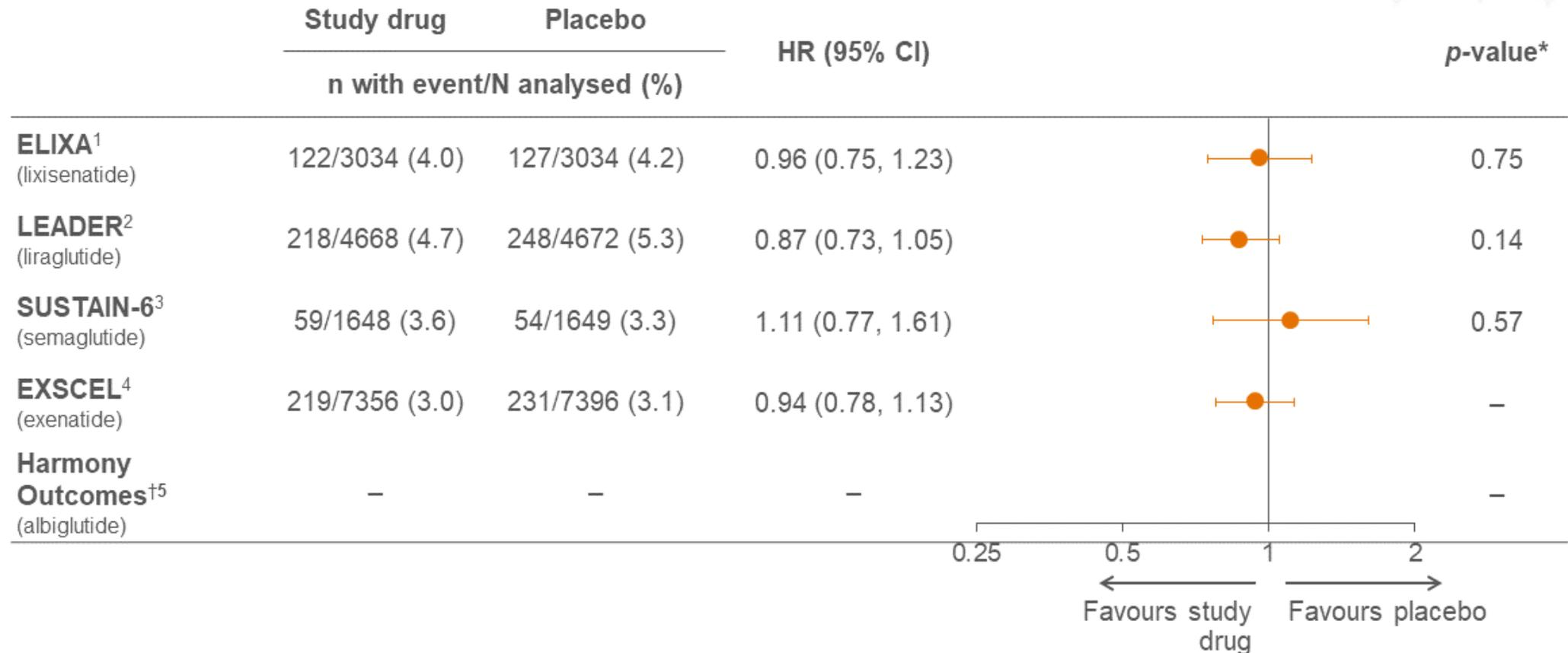
Analysis 1 = as component of expanded MACE.

Analysis 2 = as component of post-hoc composite of CV death and HHF.

¹ Scirica et al. N Engl J Med 2013;369:1117-26. ² White et al. N Engl J Med 2013;369:1127-36. ³ Green et al. N Engl J Med 2015; DOI: 10.1056/NEJoa1501362. ⁴ Pfeffer et al. JAMA. 8 Jun 2015; Boston, USA (oral presentation).

HHF in completed GLP-1 receptor agonist CVOTs

EVIDENCE

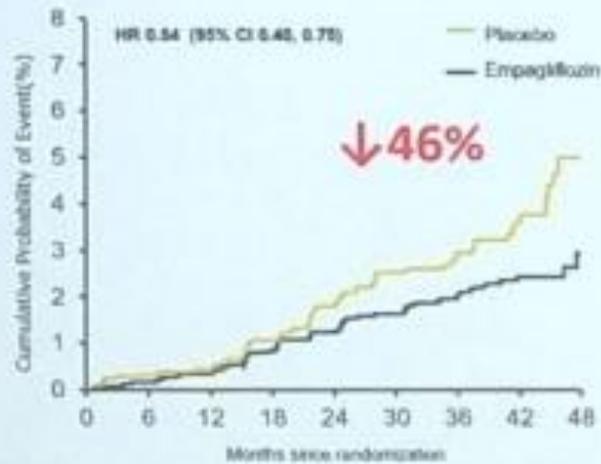


Comparison of trials should be interpreted with caution due to differences in study design, populations and methodology

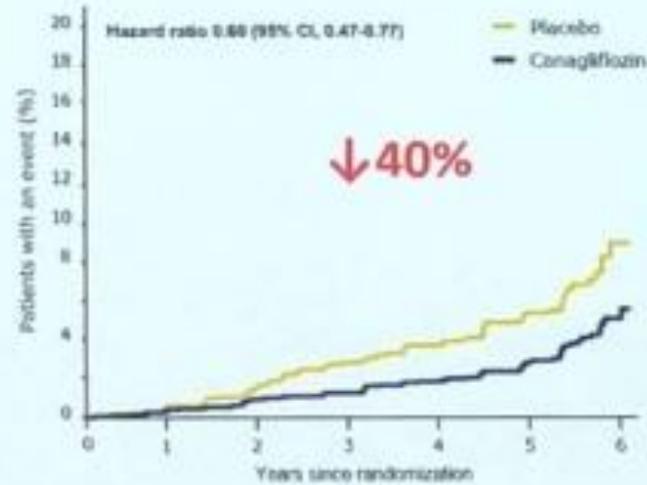
*p-values for superiority; †The composite of HHF or CV death was a prespecified secondary outcome CVOT, cardiovascular outcomes trial; GLP-1, glucagon-like peptide-1; HHF, hospitalisation for heart failure. 1. Pfeffer MA *et al. N Engl J Med* 2015;373:2247; 2. Marso SP *et al. N Engl J Med* 2016;375:311; 3. Marso SP *et al. N Engl J Med* 2016;375:1834; 4. Holman RR *et al. N Engl J Med* 2017;377:1228; 5. Hernandez AF *et al. Lancet* 2018;392:1519

SGLT2 y ERD

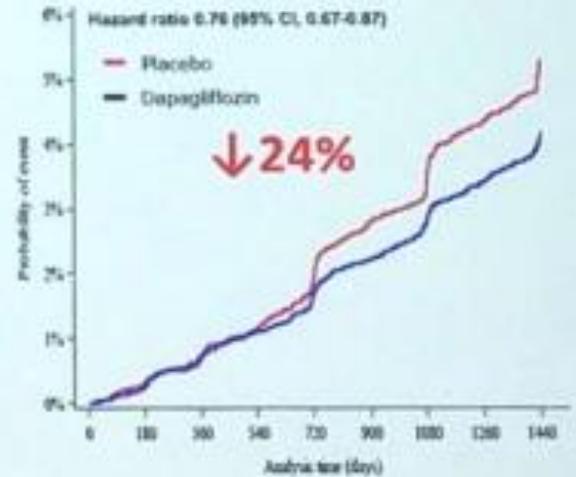
Composite Renal Outcome



Doubling of serum creatinine, ESKD, or death from renal causes



Doubling of serum creatinine and /or reduction of 40% eGFR, ESKD, or death from renal causes



Reduction of 40% eGFR, ESKD, or death from renal causes

Wanner C et al. NEJM 2016; Neal B. et al. NEJM 2017; Wiviott S et al. NEJM 2018



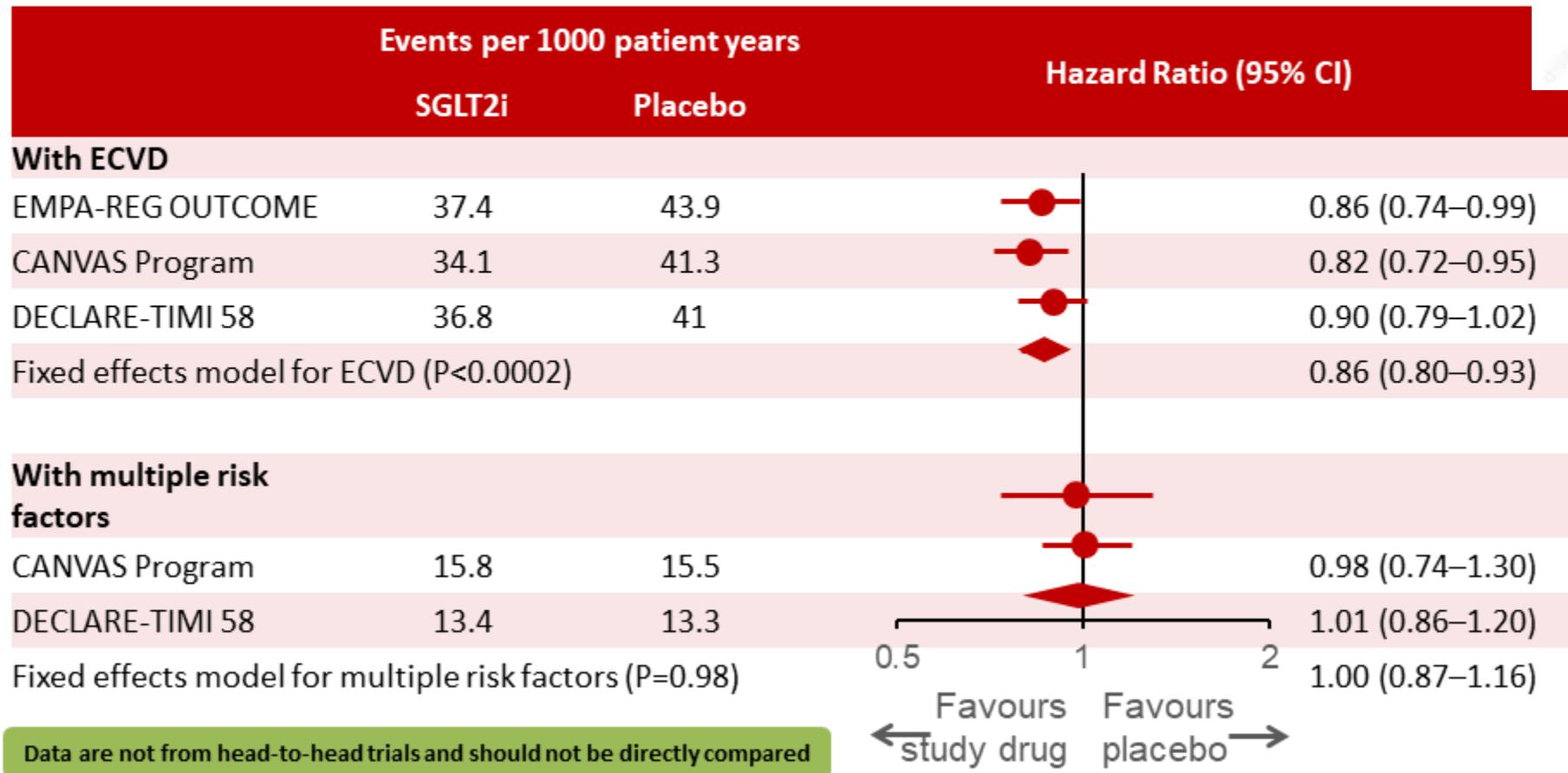
XLIX CONGRESO NACIONAL DE NEFROLOGÍA S.E.N. 2019
Vall d'Hebron Hospital
14-17 de octubre 2019

5 de octubre
CURSOS PRECONGRESO



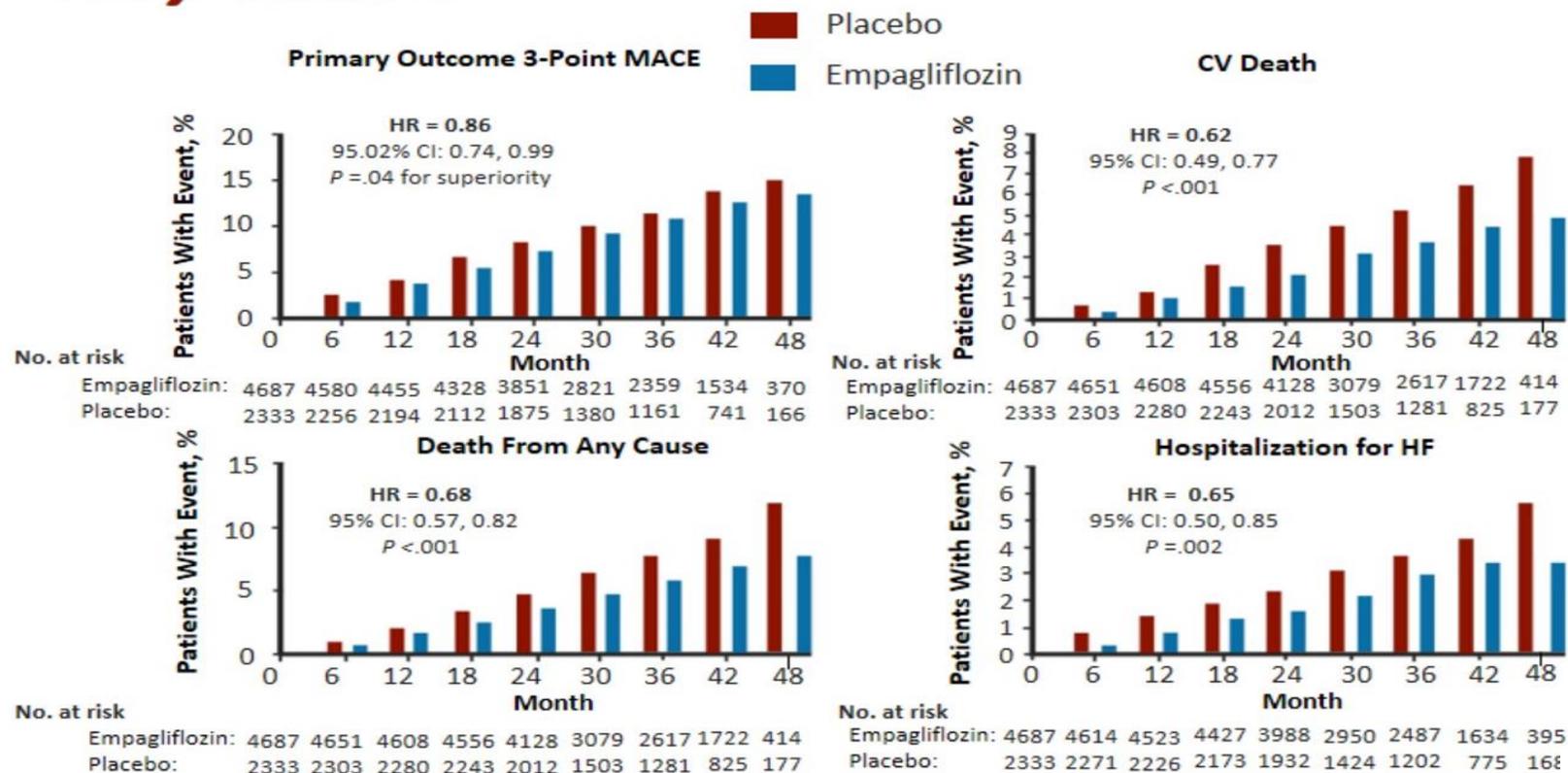
MACE by the Presence of Established CVD

EVIDENCE



EMPA-REG OUTCOME Trial

Cardiovascular Outcomes and Death From Any Cause

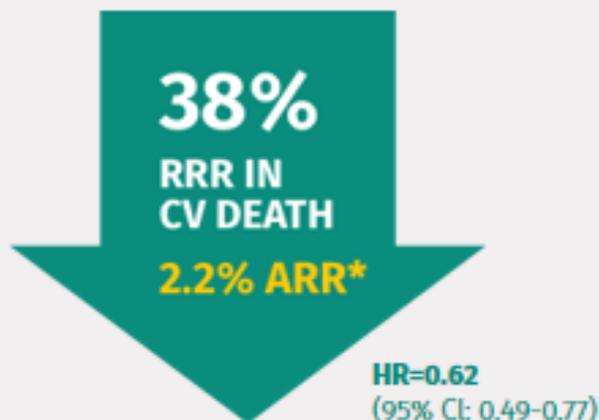


Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.

EVIDENCE

FOR ADULTS WITH ESTABLISHED CV DISEASE AND TYPE 2 DIABETES

Do more to fight CV death: Add JARDIANCE as part of your standard of care



PATIENTS WERE ACTIVELY MANAGED WITH
STANDARD OF CARE MEDICATIONS[†]

CARDIOVASCULAR MEDICATIONS

including ACEIs/ARBs, aspirin, statins,
and beta blockers.

TYPE 2 DIABETES MEDICATIONS

including metformin, insulin, DPP-4
inhibitors, GLP-1 agonists, SUs, and TZDs.

EVIDENCE

Trial Design 

PRIMARY COMPOSITE ENDPOINT

JARDIANCE demonstrated a **14% RRR** (HR=0.86 [95% CI: 0.74-0.99]; p=0.04).

The absolute risk reduction for the composite endpoint was **1.6%**.

There was no change in risk of nonfatal MI (HR=0.87 [95% CI: 0.70-1.09]) or nonfatal stroke (HR=1.24 [95% CI: 0.92-1.67]); the 14% RRR in CV events was due to a reduction in the risk of CV death (HR=0.62 [95% CI: 0.49-0.77]).

46 

Number needed to treat (NNT) to prevent one CV death (median 3.1 years)

NNT is the number of patients that need to be treated to prevent one death.

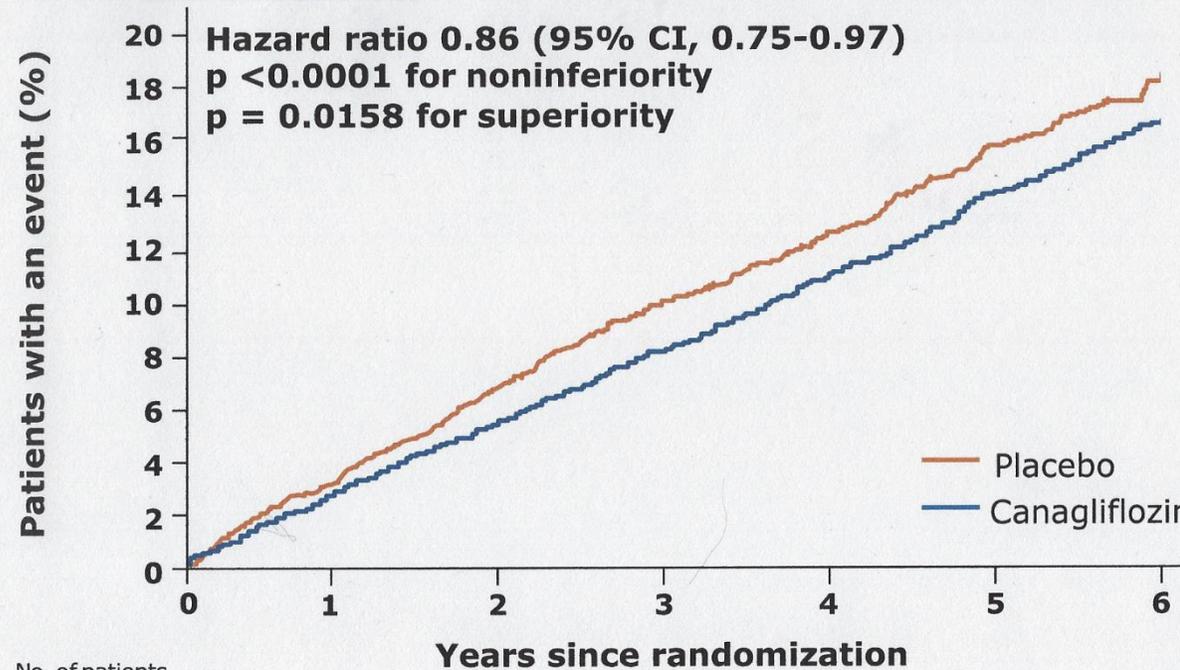


JARDIANCE is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes, and also to reduce the risk of cardiovascular death in adults with type 2 diabetes who have known cardiovascular disease.

Canvas Program

Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



No. of patients

Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

Intent-to-treat analysis

EVIDENCE

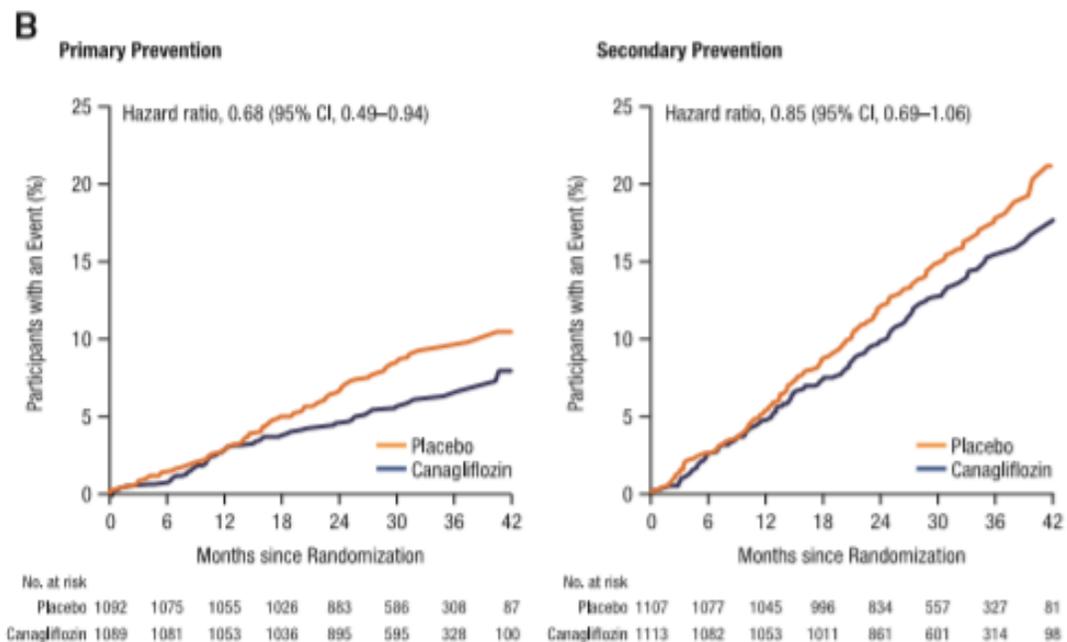
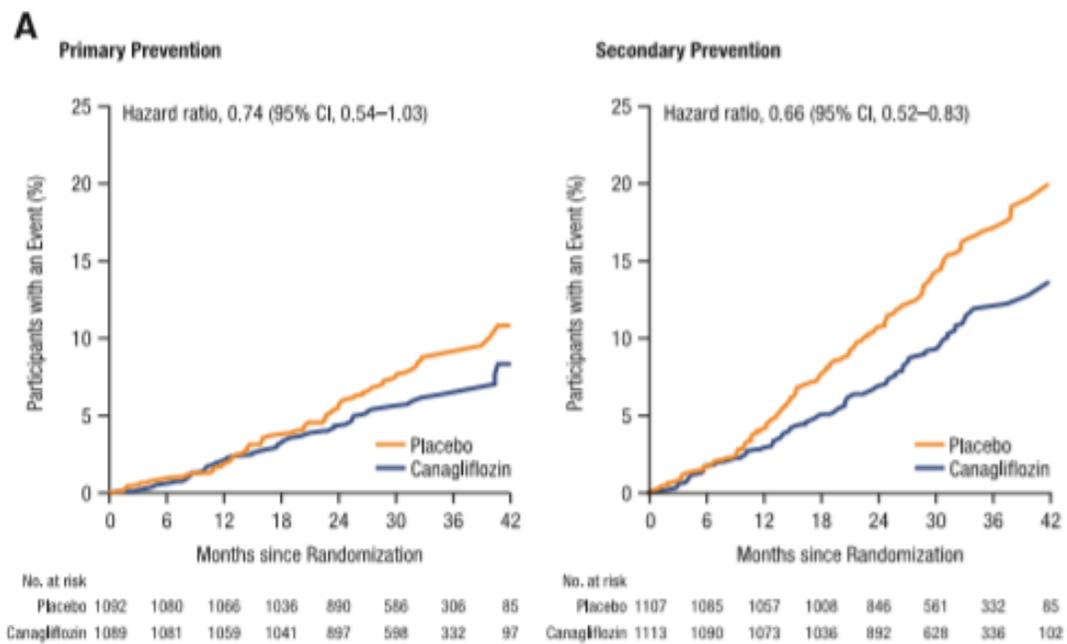


Figure 2. Effects of canagliflozin on cardiovascular outcomes in the primary and secondary prevention cohorts.
A, Cardiovascular death and hospitalization for heart failure. **B,** Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

EVIDENCE

CREDENCE STUDY

Inclusion Criteria

T2DM with A1c = 6.5-12.0%
eGFR = 30-90 ml/min•1.73m²
60% had eGFR = 30-60 ml/min•1.73m²
Urine ACR: > 300 to < 5000 mg/gram
On ACE/ARB for ≥ 4 weeks
Median follow up = 2.6 years
60% had eGFR = 30-60 ml/min.1.73m₂

Primary Composite Endpoint

End stage kidney disease (dialysis,
transplantation, sustained eGFR <
15 ml/min•1.72m²)
Doubling of serum creatinine
Renal or CV death

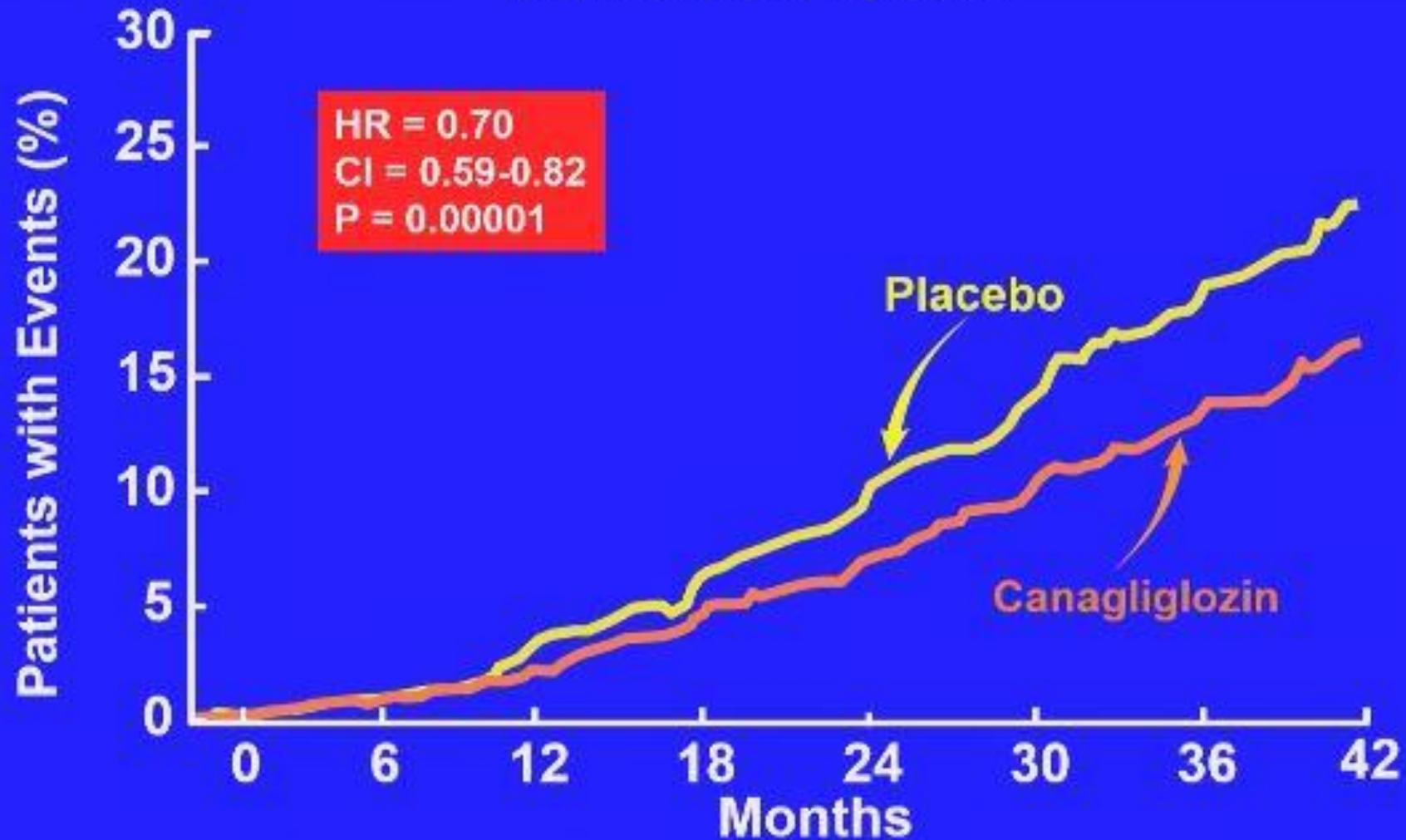
Secondary Endpoints

Individual components of primary endpoint
MACE
Hospitalization for heart failure
CV death
All cause mortality

EVIDENCE

EFFECT OF CANAGLIGLOZIN VERSUS PLACEBO ON THE PRIMARY COMPOSITE OUTCOME IN CREDENCE

Perkovic et al, NEJM, May 1, 2019



Placebo:	2199	2141	1752	641	178
CANA:	2202	2146	1798	654	199

EVIDENCE



[About INVOKANA®](#)

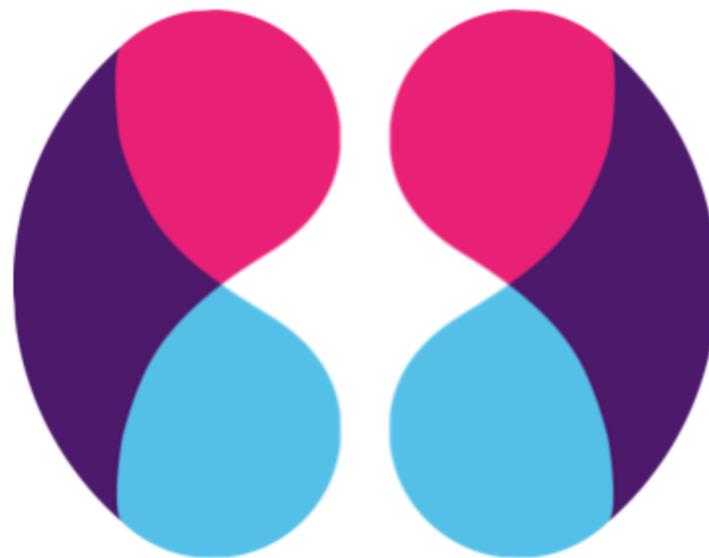
[Savings Program](#)

Now Approved—The only type 2 diabetes medicine proven to lower the risks of:

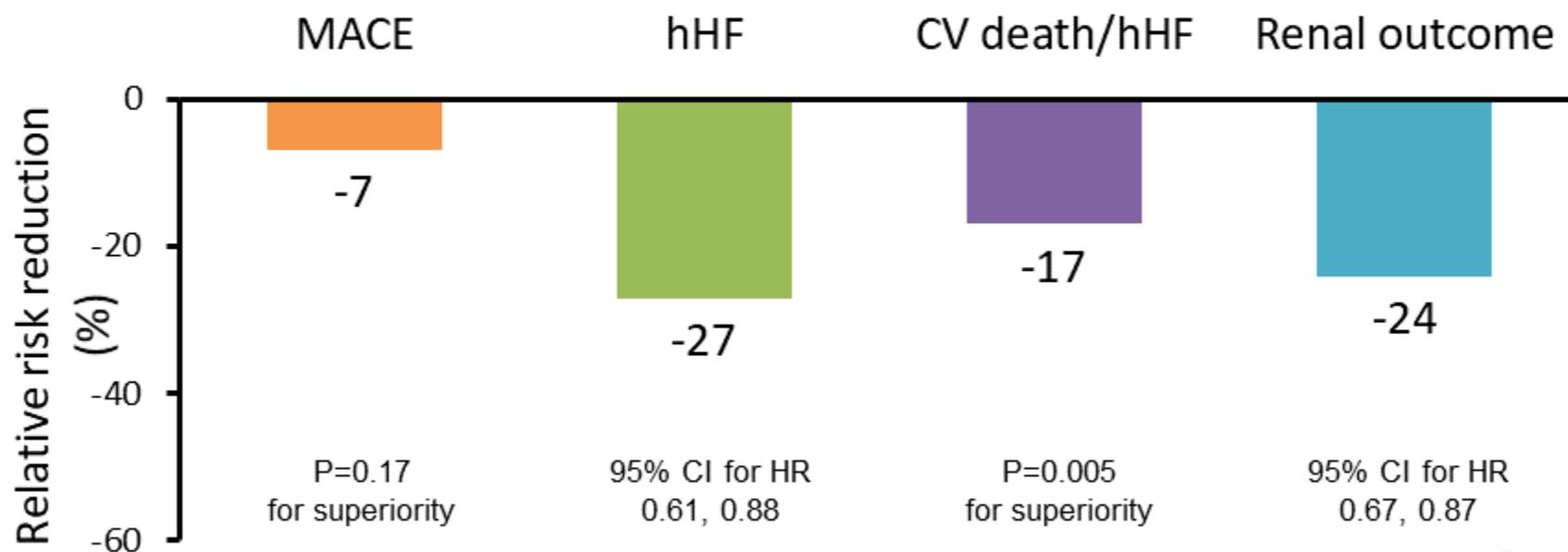
- end-stage kidney disease (ESKD)
- worsening of kidney function
- cardiovascular death
- hospitalization for heart failure

in adults with type 2 diabetes and diabetic kidney disease (nephropathy) with a certain amount of protein in the urine

[Learn More](#)



Key CV Outcomes from DECLARE-TIMI 58



Indication of Dapagliflozin/SGLT2i is not for heart failure or death.

EVIDENCE

FARXIGA is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors

FARXIGA is not recommended for patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

NOW APPROVED



FARXIGA, the SGLT2i with the **broadest***
indication to reduce the risk of hospitalization
for heart failure¹⁻⁴

*Hospitalization for heart failure indication is not limited by diabetic nephropathy or presence of macroalbuminuria.

2018 ADA/EASD ALGORITHM FOR GLYCEMIC CONTROL

FIRST LINE = METFORMIN

**ASCVD
Predominates**

**HEART FAILURE
Predominates**

**RENAL DISEASE
Predominates**



Metformin

Recommended for All Patients, Unless Contraindicated or Not Tolerated

Hypoglycemia	Neutral
Weight	Slight loss
Renal / Genitourinary	Contraindicated if eGFR <30 mL/min/1.73 m ²
Gastrointestinal adverse effects	Moderate
Cardiac	Neutral
Bone	Neutral
Ketoacidosis	Neutral

Few adverse events or possible benefits Use with caution Likelihood of adverse effects Uncertain effect

eGFR = estimated glomerular filtration rate.
Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

**FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity)
If HbA_{1c} above target proceed as below**

LIMITATIONS OF METFORMIN

- **Not an insulin sensitizer (inhibits hepatic gluconeogenesis)**
- **Does not improve beta cell function**
- **A1c reduction is not durable**
- **Corrects only one pathophysiologic disturbance of the Ominous Octet**
- **Does not have proven antiatherogenic benefit**
 - UKPDS (n = 342)
 - UKPDS (39% increase in CV mortality when added to SU; p<0.01)



Patient has T2D* and established clinical ASCVD

Address Concurrently

Guideline-directed medical therapy (lifestyle, antiplatelet, BP, lipids) and glucose-lowering therapy (metformin)

Consider addition of an SGLT2i or GLP-1RA with demonstrated CV outcome benefit

Initiate clinician-patient discussion

* most trials of SGLT2i & GLP-1RA required baseline A1C $\geq 7\%$, and most patients were already on metformin as the first-line therapy if tolerated and not contraindicated.

No additional action taken: patient declines SGLT2i/GLP-1 RA

SGLT2i selected: Empagliflozin preferred

GLP-1RA selected: Liraglutide preferred

HF or CKD predominate and MACE

MACE predominates

Das, Sandeep R et al, JACC 2018



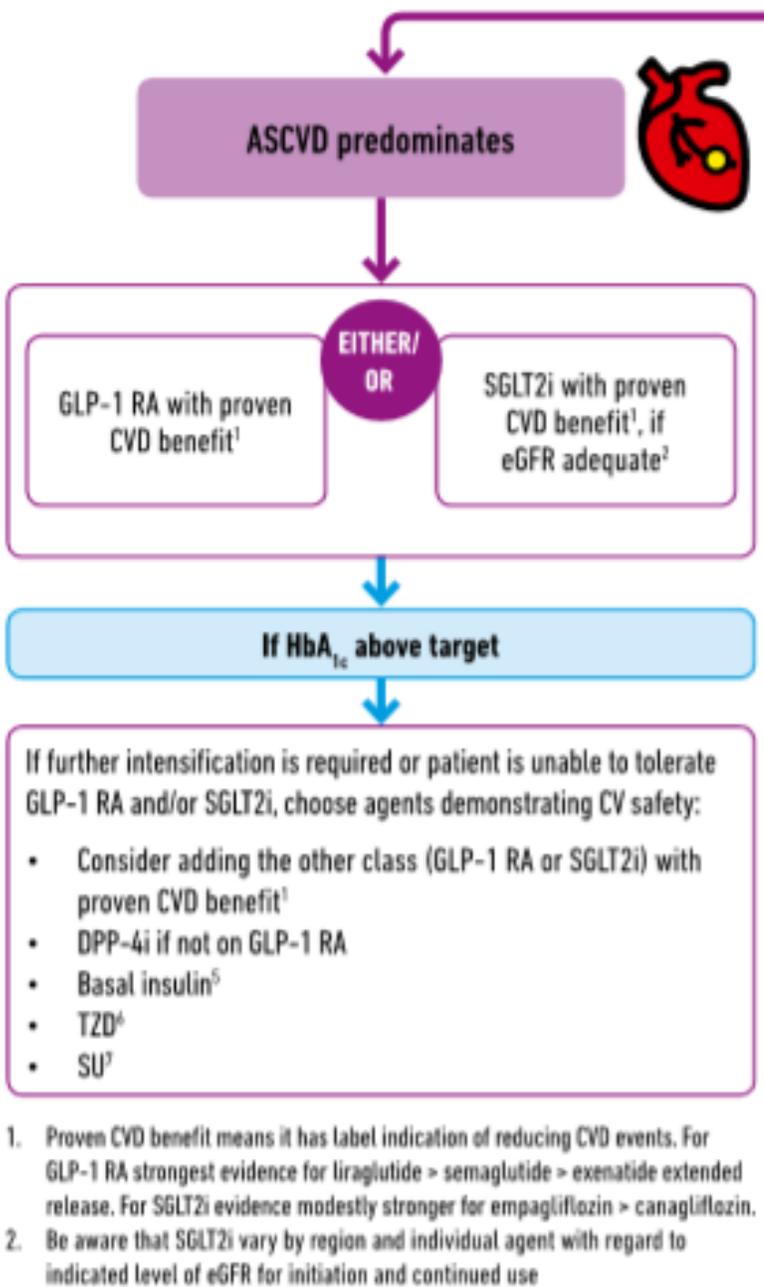
Sodium Glucose Cotransporter 2 Inhibitors (SGLT2is)

Hypoglycemia	Neutral
Weight	Loss
Renal / Genitourinary	Not indicated for eGFR <45 mL/min/1.73 m ² Genital mycotic infections
	Benefit of empagliflozin; canagliflozin
Gastrointestinal adverse effects	Neutral
Cardiac—CHF	Benefit of empagliflozin, canagliflozin, dapagliflozin
Cardiac--ASCVD	Cardiovascular benefit of empagliflozin, canagliflozin
Bone	Canagliflozin warning
Ketoacidosis	DKA occurring in T2D in various stress settings

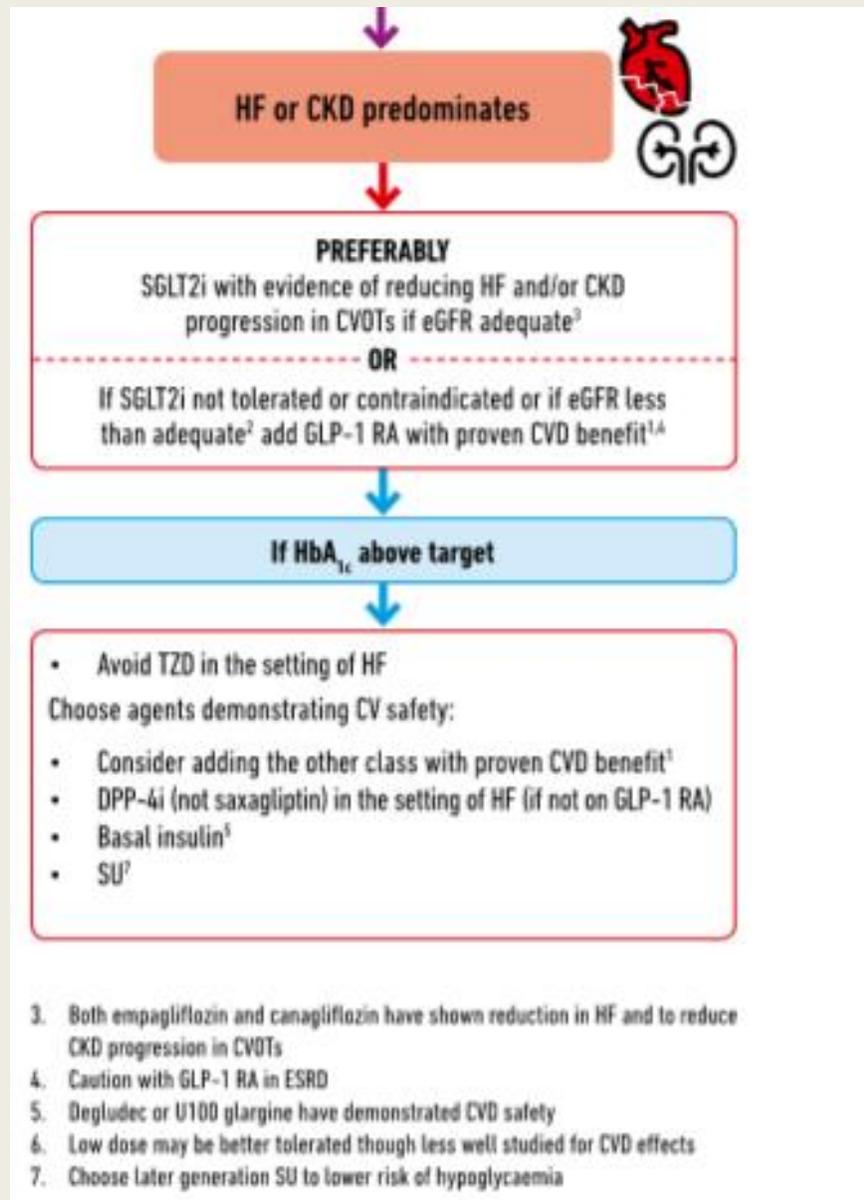
■ Few adverse events or possible benefits
 ■ Use with caution
 ■ Likelihood of adverse effects
 ■ ? Uncertain effect

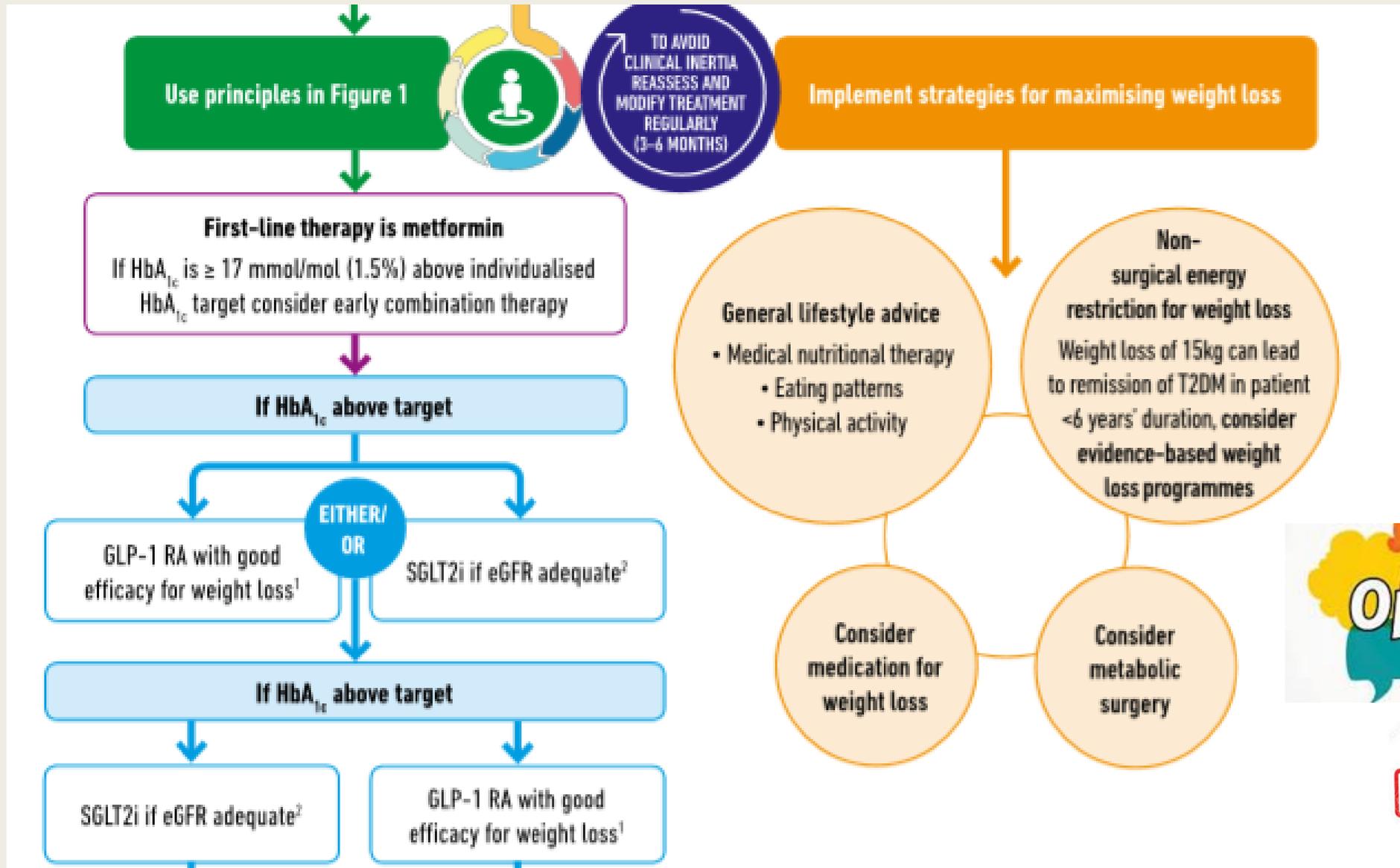
ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes.

Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

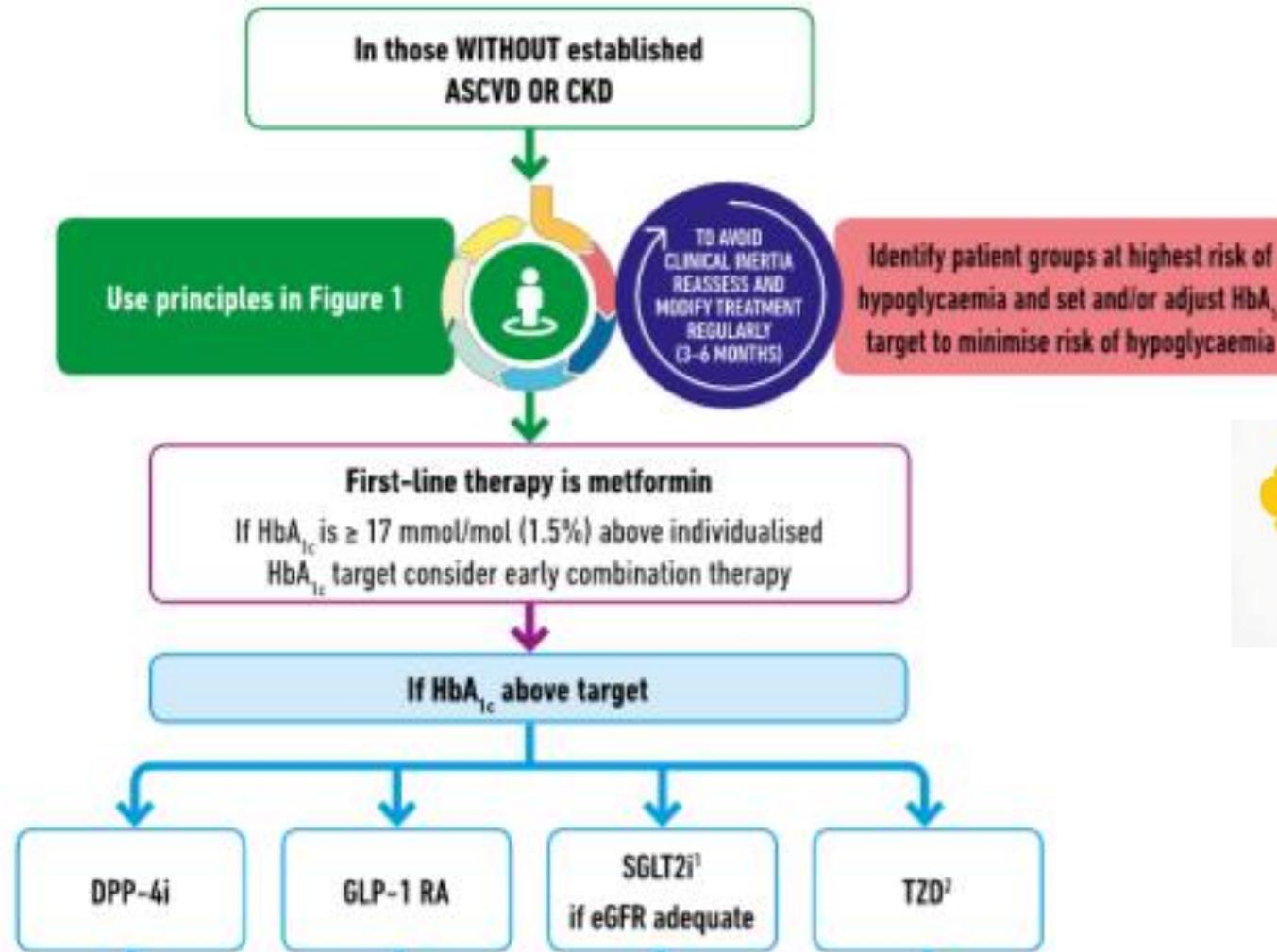


EVIDENCE





CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA



Opinion

EVIDENCE

DPP4 inhibitor CVOTs: baseline characteristics

	SAVOR-TIMI 53 ¹		EXAMINE ²		TECOS ³		CAROLINA ^{®4}		CARMELINA ^{®5}	
Mean age, years	65.1		61.0*		65.4		64.0		66.1	
% with prior MI	38.0		87.5		42.7		13.8		58.1	
% with prior HF	12.8		27.8		17.8		-		27	
% with prior CVD	78.4		-		73.6		34.5			
Diabetes duration, y	10.3*		7.3*		11.6		6.2*		15	
HbA _{1c} , %	8.0		8.0		7.2		7.2		7.9	
Statin use, %	78.3		90.6		79.8		64.1		71.4	
T2D therapy, %	Naive	4.1	Naive	1.1	Naive	-	Naive	9.2		
	Metformin	69.9	Metformin	65.0	Mono	47.7	Mono	66.0	Metformin 54.8	
	SU	40.5	SU	46.9	Dual	51.4	Dual	23.8	Sulfonylureas 34.9	
	TZD	6.2	TZD	2.5	TZD	-	TZD	-	Insulin 54.9	
	Insulin	41.6	Insulin	29.4	Insulin	23.5	Insulin	Ex.		

Data are provided for the DPP4 inhibitor treatment arm. Mean values show unless otherwise indicated.

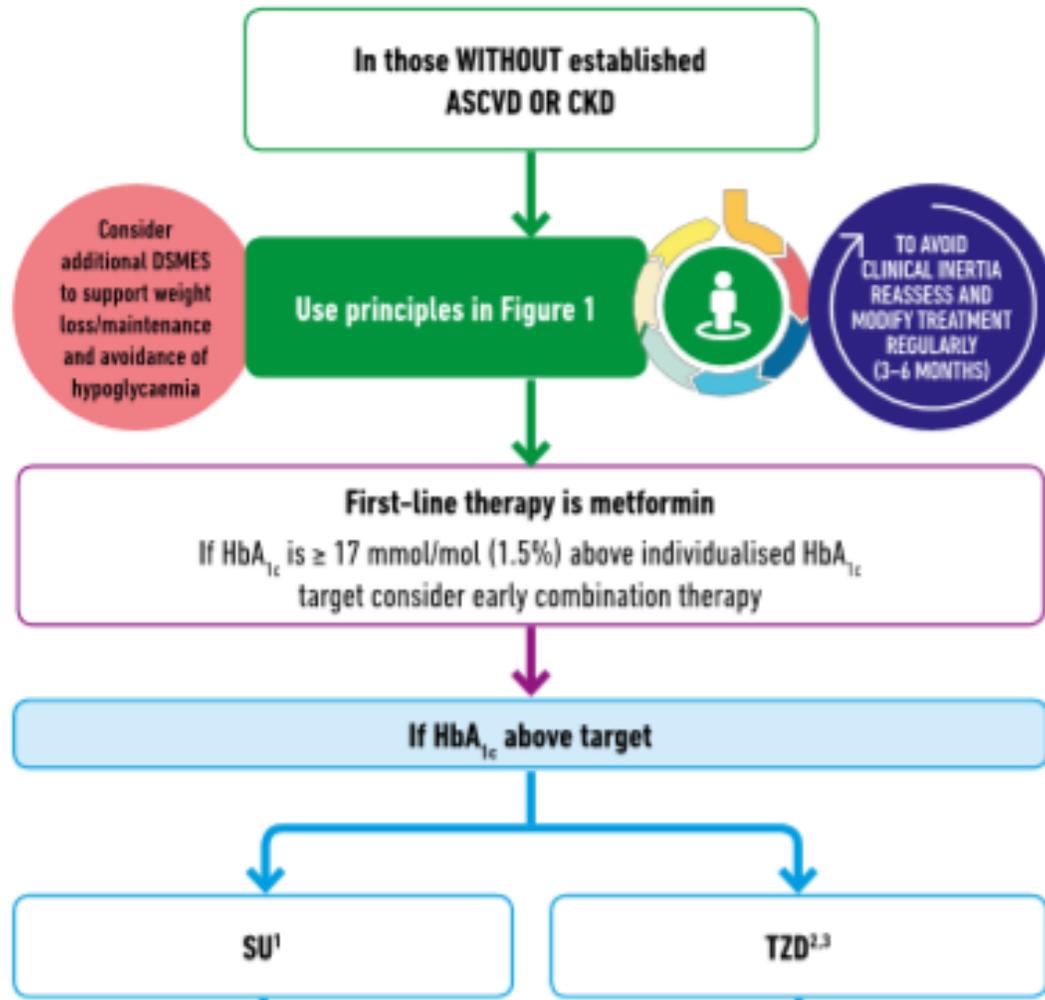
- indicates that the data are not reported.

*Median.

1. Scirica et al. N Engl J Med 2013;369:1317-26. 2. White et al. N Engl J Med 2013;369:1327-35. 3. Green et al. N Engl J Med 2015; DOI: 10.1056/NEJMoa1501852. 4. Heav et al. Diabetes Vasc Dis Res 2015;12:164-74. 5. NCT01897132.



CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE



Secretagogues

	SU	GLN
Hypoglycemia	Moderate / severe	Mild
Weight	Gain	
Renal / Genitourinary	More hypoglycemia risk	
Gastrointestinal adverse effects	Neutral	
Cardiac—CHF	More CHF risk	
Cardiac--ASCVD	No increased risk	
Bone	Neutral	
Ketoacidosis	Neutral	

■ Few adverse events or possible benefits
 ■ Use with caution
 ■ Likelihood of adverse effects
 ■ ? Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; GLN = glinide; SU = sulfonylurea.

Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

The image features two thick black L-shaped brackets. One is positioned in the top-left corner, and the other is in the bottom-right corner. They are oriented towards each other, framing the central text.

UPDATE IN MANAGEMENT DIABETES MELLITUS

SUMMARY

SUMMARY

- Target goals of blood glucose in persons with Type 2 Diabetes Mellitus should be individualized.
- Different properties, mechanism of action and side effects of the anti-hyperglycemic drugs impact their selection as therapy
- Selecting the appropriate therapy for persons with Diabetes Mellitus varies according to changing guidelines based on scientific evidence.

