

Diabetes: Beyond the Glycemic Control

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Disclosures

I have received honoraria for lectures and consultancy from

- Diabetes: *AstraZeneca, Bial, Boehringer Ingelheim, MSD, Novo Nordisk, Tecnimede*
- Dyslipidemia: *Abbott, Amgen, Mylan, Tecnimede*
- Antithrombotic therapies: *AstraZeneca, Bayer*

Topics

- High cardiovascular risk
- Treatment objectives that truly matter
- New treatment options in perspective

Diabetes: Beyond the Glycemia Control

HIGH CARDIOVASCULAR RISK



Diabetes

One clinical scenario with new treatment options

Patients who remain at substantial risk of CV morbidity and mortality, for whom **new treatment goals and/or new interventions** can reduce the risk

- **Type 2 diabetes mellitus**
 - HbA1c should be controlled with cardio- and reno-protective agents
 - Lower goals for BP
 - Non-HDL-c is an important target
- **Prior acute coronary syndrome**
 - Strategies to reduce high risk or recurrent ischemic events
 - Aggressive ↓LDL-c, intensive antithrombotic therapy, anti-inflammatory strategies
- **Peripheral arterial disease**
 - Frequently polyvascular disease

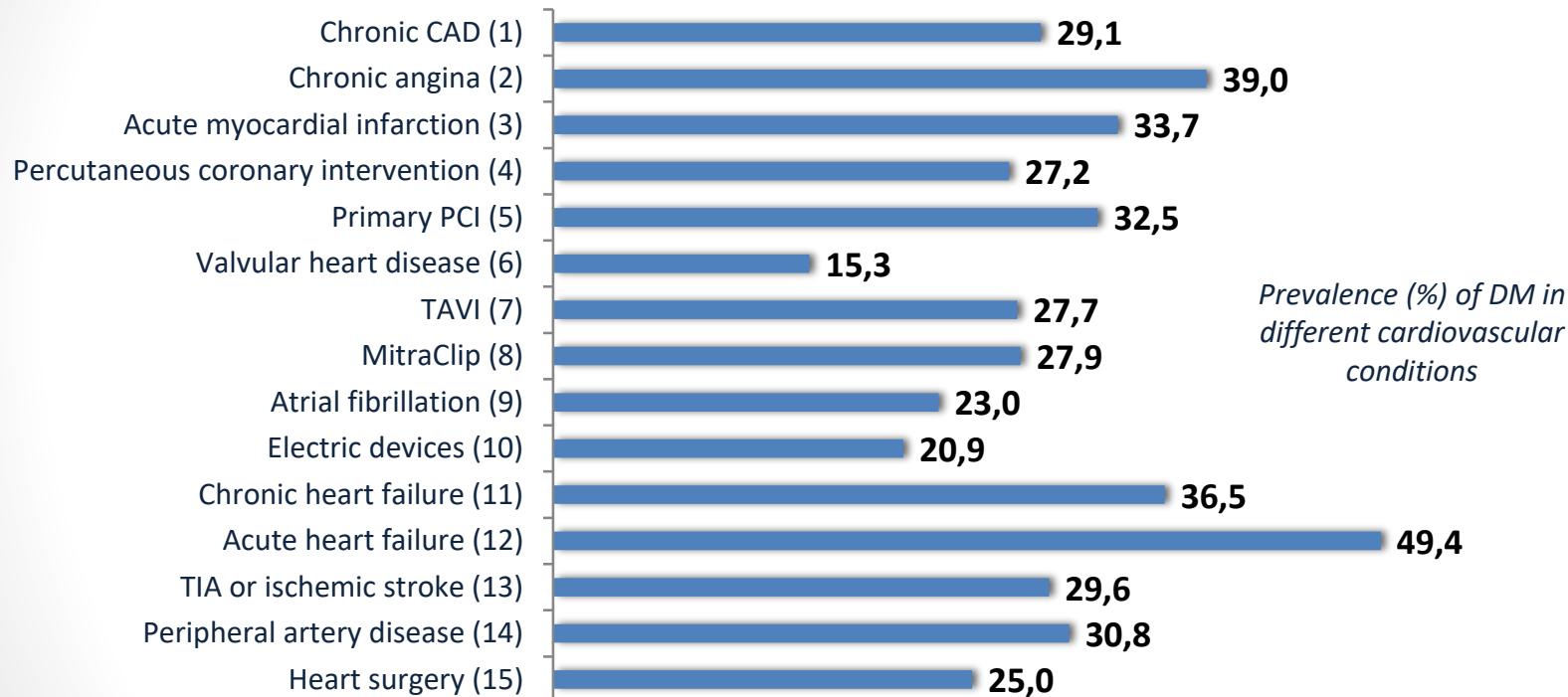
Diabetes

Huge potential to increase life expectancy beyond HbA1c

		Non-smoker								Smoker								Smoker																			
		HbA1c (6%)				HbA1c (8%)				HbA1c (10%)				HbA1c (6%)				HbA1c (8%)				HbA1c (10%)															
Systolic Blood Pressure	Age	4	5	6	7	8	4	5	6	7	8	4	5	6	7	8	4	5	6	7	8	4	5	6	7	8											
		180	8.0	7.6	7.2	6.8	6.7	7.2	6.9	6.5	6.2	6.0	6.5	6.2	5.8	5.6	5.4	6.7	6.4	6.0	5.7	5.4	6.1	5.6	5.3	5.0	4.8										
		160	8.6	8.3	8.0	7.6	7.3	8.0	7.7	7.3	6.9	6.7	7.3	6.8	6.5	6.3	6.1	7.3	6.9	6.5	6.3	6.1	6.8	6.2	6.0	5.7	5.4										
		140	9.1	8.8	8.4	8.1	7.8	8.7	8.2	7.8	7.6	7.4	8.0	7.5	7.2	6.9	6.6	7.8	7.4	7.0	6.9	6.5	7.3	6.8	6.5	6.2	5.9										
		120	9.6	9.2	9.0	8.7	8.4	9.1	8.7	8.5	8.1	7.9	8.4	8.1	7.8	7.5	7.1	8.2	7.8	7.5	7.3	7.1	7.7	7.4	7.0	6.8	6.2										
		180	13.0	12.7	12.2	11.7	11.2	12.3	11.7	11.4	10.7	10.3	11.2	10.8	10.1	9.6	9.5	11.4	10.9	10.4	10.0	9.5	10.5	10.1	9.7	9.1	8.6	8.0									
		160	13.8	13.4	13.1	12.6	11.9	13.3	12.6	12.2	11.7	11.2	12.2	11.6	11.1	10.7	10.4	12.1	11.7	11.2	10.7	10.0	11.9	11.8	11.3	10.9	9.9	9.5	8.7								
		140	14.5	14.0	13.7	13.1	12.9	14.0	13.3	12.8	12.5	12.0	16.0	12.4	11.8	11.6	11.1	12.6	12.2	11.7	11.4	10.9	13.1	12.8	12.5	12.1	11.7	11.3	10.9								
		120	14.9	14.8	14.1	13.8	13.4	14.4	14.0	13.5	13.2	12.7	13.6	13.1	12.8	12.3	11.9	13.1	12.8	12.5	12.1	11.7	12.7	12.1	11.7	11.3	10.9	10.5	10.1								
		180	19.3	18.7	18.5	17.9	17.4	18.4	17.8	17.4	16.8	16.5	17.4	16.9	16.1	15.8	15.3	17.6	16.7	16.4	15.8	15.2	16.5	15.9	15.4	14.8	14.3	15.6	14.7	14.2	13.7	13.2					
		160	20.3	19.8	19.2	18.7	18.4	19.4	18.9	18.3	17.8	17.3	18.4	17.8	17.2	16.8	16.3	18.2	17.7	17.3	16.6	16.3	17.4	17.0	16.2	15.8	15.1	16.5	15.6	15.3	14.6	14.2					
		140	20.8	20.4	19.9	19.5	19.0	20.2	19.7	19.1	18.6	18.4	19.1	18.9	18.3	17.6	17.1	19.1	18.9	18.0	17.4	17.0	18.1	17.6	17.2	16.6	16.1	17.3	16.5	16.0	15.6	15.1					
		120	21.1	20.8	20.4	20.2	19.6	20.6	20.1	19.9	19.3	18.9	19.9	19.6	19.0	18.4	18.0	19.2	18.9	18.4	18.1	17.6	18.8	18.2	17.7	17.2	16.8	16.0	18.0	17.3	16.7	16.4	15.8				
		Cholesterol (Total:HDL)								Cholesterol (Total:HDL)								Cholesterol (Total:HDL)								Cholesterol (Total:HDL)											
WOMEN		HbA1c (6%)				HbA1c (8%)				HbA1c (10%)				HbA1c (6%)				HbA1c (8%)				HbA1c (10%)				HbA1c (6%)											
Systolic Blood Pressure	Age	180	10.1	9.7	9.3	9.0	8.8	9.2	8.9	8.5	8.2	7.9	8.3	7.9	7.7	7.4	7.1	8.7	8.4	8.0	7.7	7.4	8.0	7.6	7.2	6.9	6.7	7.1	6.8	6.4	6.1	5.9					
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		160	15.5	15.3	14.9	14.6	14.3	14.9	14.5	14.2	13.9	13.3	15.6	15.2	15.0	14.6	14.2	14.9	14.5	14.3	13.8	13.4	14.3	14.2	13.7	13.4	13.1	13.3	13.0	12.5	12.0	11.8	12.5	11.9	11.1	10.7	
		140	16.0	15.8	15.4	15.3	15.0	15.6	15.2	15.0	14.6	14.2	15.9	15.7	15.5	15.2	15.0	15.5	15.1	14.7	14.5	14.2	14.8	14.7	14.1	14.0	13.7	13.4	13.2	13.8	13.4	13.0	12.6	12.3	11.7		
		120	16.5	16.2	16.1	15.8	15.4	15.9	15.7	15.5	15.2	15.0	18.7	18.3	17.6	17.3	16.9	19.5	19.2	18.7	18.3	17.9	18.9	18.6	18.1	17.5	17.0	17.7	17.5	17.0	16.2	15.9	15.4	15.0			
		180	20.2	20.0	19.4	19.1	18.9	19.5	19.2	18.8	18.4	18.1	20.3	20.0	19.6	19.6	18.9	19.5	19.0	18.7	18.3	17.9	18.4	18.0	17.6	17.2	16.9	16.6	16.2	16.0	15.8	15.5	15.2	15.0			
		160	21.0	20.7	20.5	20.2	19.8	20.3	20.0	19.6	19.6	18.9	21.0	20.7	20.3	20.0	19.8	20.8	20.5	20.2	19.9	19.5	19.4	18.9	18.6	18.5	18.1	17.8	17.4	17.0	17.7	17.2	16.8	16.4	16.0		
		140	21.3	21.1	20.8	20.5	20.3	21.0	20.7	20.3	20.0	19.8	21.3	21.0	20.7	20.7	20.1	20.8	19.9	19.6	19.2	18.8	19.4	19.1	18.7	18.4	18.3	18.0	17.7	17.4	17.2	16.7	16.4	16.0			
		120	21.8	21.3	21.1	21.1	20.8	21.3	21.0	20.7	20.4	20.1	21.8	21.3	21.1	21.1	20.8	20.8	20.5	20.2	19.9	19.5	19.4	19.1	18.7	18.4	18.3	18.0	17.8	17.5	17.2	16.7	16.4	16.0			

Diabetes and CVD

Common and dangerous liaison



Diabetes and CVD

Common and dangerous liaison

Acute heart failure¹

↑77% hospital mortality
↑16% mortality at 1 year
↑32% HF hospitalization

Chronic heart failure²

↑28% mortality at 1 year
↑37% HF hospitalization

Atrial fibrillation³

↑85% mortality at 1 year

Acute myocardial infarction⁴

↑90% mortality at 5 years
↑130% sudden cardiac deathg at 5 years

TIA or ischemic stroke⁵

↑20% mortality at 1 year
↑15% hospitalization for stroke/TIA at 1 year
↑77% hospitalization for MI at 1 year
↑55% HF hospitalization

Peripheral artery disease⁶

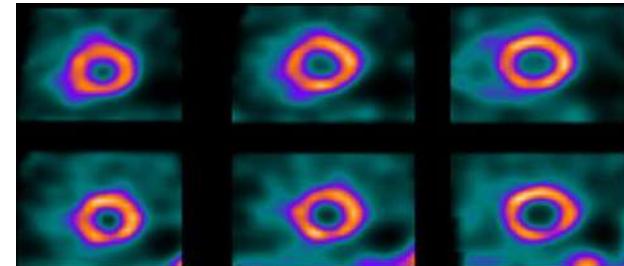
↑89% mortality at 3 years

1. Targher G et al. Eur J Heart Fail 2017;19:54. 2. Dauriz M et al. Diab Care 2017;40:671.
3. Fumagalli S et al. Eur Heart J Cardiovasc Pharmacother 2017 Dec 22. Epub ahead of print. 4. Junntila MJ et al. Heart Rhytym 2010;7:1396.
5. Echouffo-Tcheugui JB et al. Eur Heart J 2018 Feb 9. Epub ahead of print. 6. Vrsalovic M et al. Clin Cardiol 2017;40:287.

Diabetes “without” CVD

The frontier between primary and secondary prevention

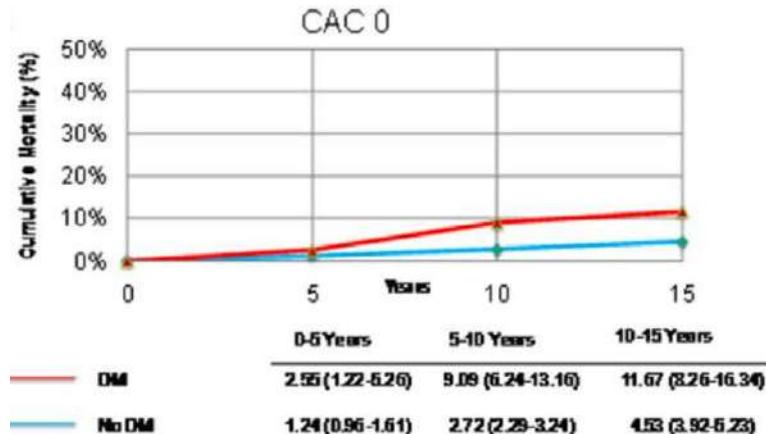
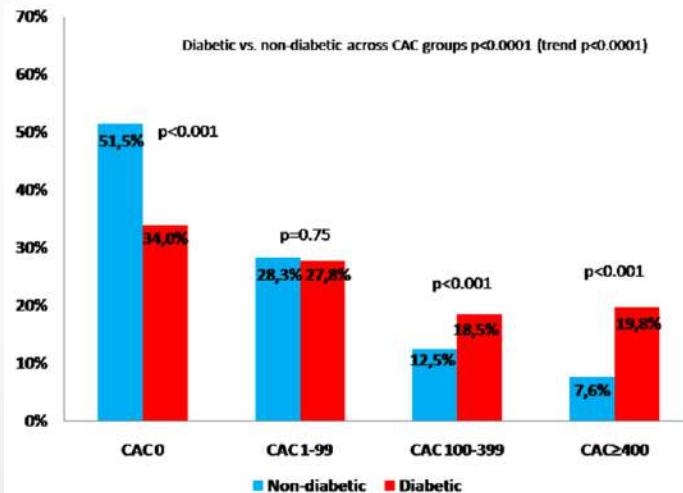
- CVD is frequently subclinical in T2DM
- Angiographic studies in asymptomatic diabetics show atheromatous coronary plaques in >90% patients, >1 plaque in 77% of these, and **significant coronary stenoses** in 33%
- In a study of asymptomatic diabetics with a normal ECG, undergoing SPECT, **silent myocardial ischemia** was present in 27% patients



Diabetes “without” CVD

Poor outcomes even when CAC is zero

- Mortality increases with increasing severity of coronary calcification¹
- In the long-term, all cause mortality is higher in diabetics even when calcium score is zero²



Study of 9715 asymptomatic individuals without known CAD, referred for calcium score evaluation, and followed for a median of 14.7 years

1. Raggi P et al. J Am Coll Cardiol 2004;43:1663. 2. Valenti V et al. Circ Cardiovasc Imaging 2016;9:e003528.

Diabetes “without” CVD

Underdiagnosis of symptomatic left ventricular dysfunction

- Of 581 diabetics >60 years old, followed in primary care in Holland, and without a diagnosis of HF, 161 (28%) were found to have HF

	OR	(95% CI)	AUC	(95% CI)
Model 1: based on patient characteristics and history taking			0.68	(0.64–0.73)
Age >75 years	2.61	1.76–3.88		
Female sex	1.42	0.96–2.12		
History of ischaemic heart disease (prior MI, angina pectoris, CABG, PCI)	2.73	1.71–4.35		
History of hypertension	1.63	1.06–2.51		
History of TIA or stroke	1.80	0.98–3.32		
History of asthma or COPD	1.61	0.93–2.80		
Model 2: model 1 + symptoms			0.80	(0.76–0.83)
+ dyspnoea or fatigue	5.21	3.12–8.71		
+ reported swollen ankles or nocturia	2.38	1.49–3.78		
+ claudicational complaints	3.14	1.46–6.78		
+ palpitations	1.45	0.87–2.41		
Model 3 (clinical model): model 2 + signs			0.82	(0.79–0.86)
+ pulmonary crepitations, elevated jugular pressure, peripheral oedema, hepatomegaly (all signs of water and salt retention)	3.08	1.98–4.80		
Model 4: clinical model + NT-proBNP			0.84	(0.81–0.88)
+ NT-proBNP >15 pmol/L	3.17	1.95–5.16		
Model 5: clinical model + abnormal ECG			0.85	(0.82–0.88)
+ an abnormal ECG	3.86	2.28–6.53		
Model 6: clinical model + NT-pro BNP and ECG			0.86	(0.83–0.89)
+ NT-proBNP >15 pmol/L (~125 pg/mL)	2.70	1.63–4.48		
+ an abnormal ECG	3.39	1.98–5.80		

Diabetes: Beyond the Glycemia Control

TREATMENT OBJECTIVES



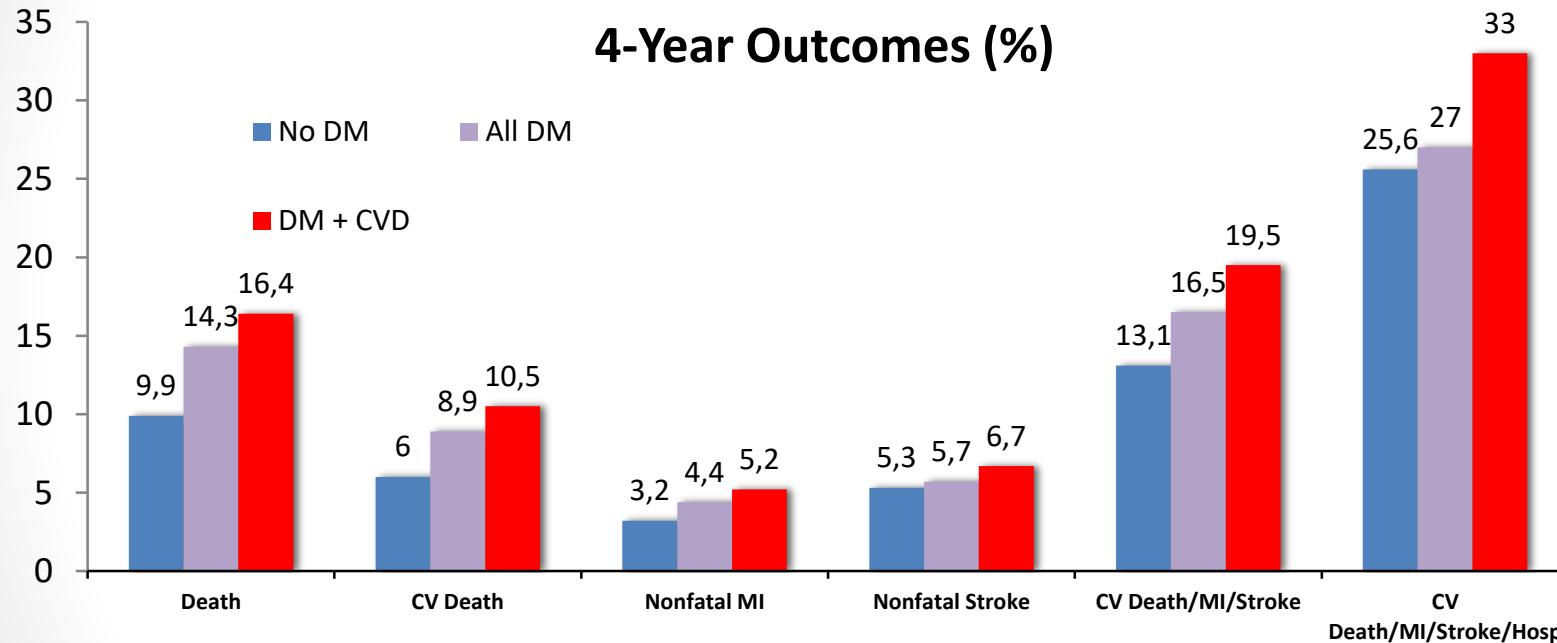
Diabetes

Treatment objectives that truly matter

- Shortened **life expectancy**, high risk of **ischemic events**, increased risk of developing **heart failure**, accelerated decline of **renal function**
 - Stop progression of **atherosclerotic substrate**
 - Reduce **prothrombotic status**
 - Protect **myocardium and LV function**
 - Protect **renal function**
- Risk of other **microvascular complications**
 - **Glycemic control**
- **Quality of life** and functional capacity

Diabetes

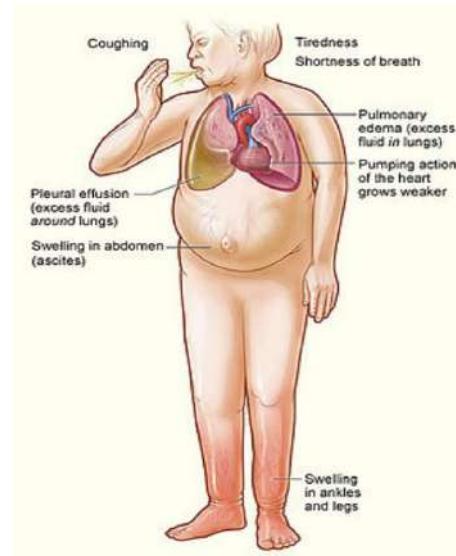
High risk of ischemic events



Diabetes

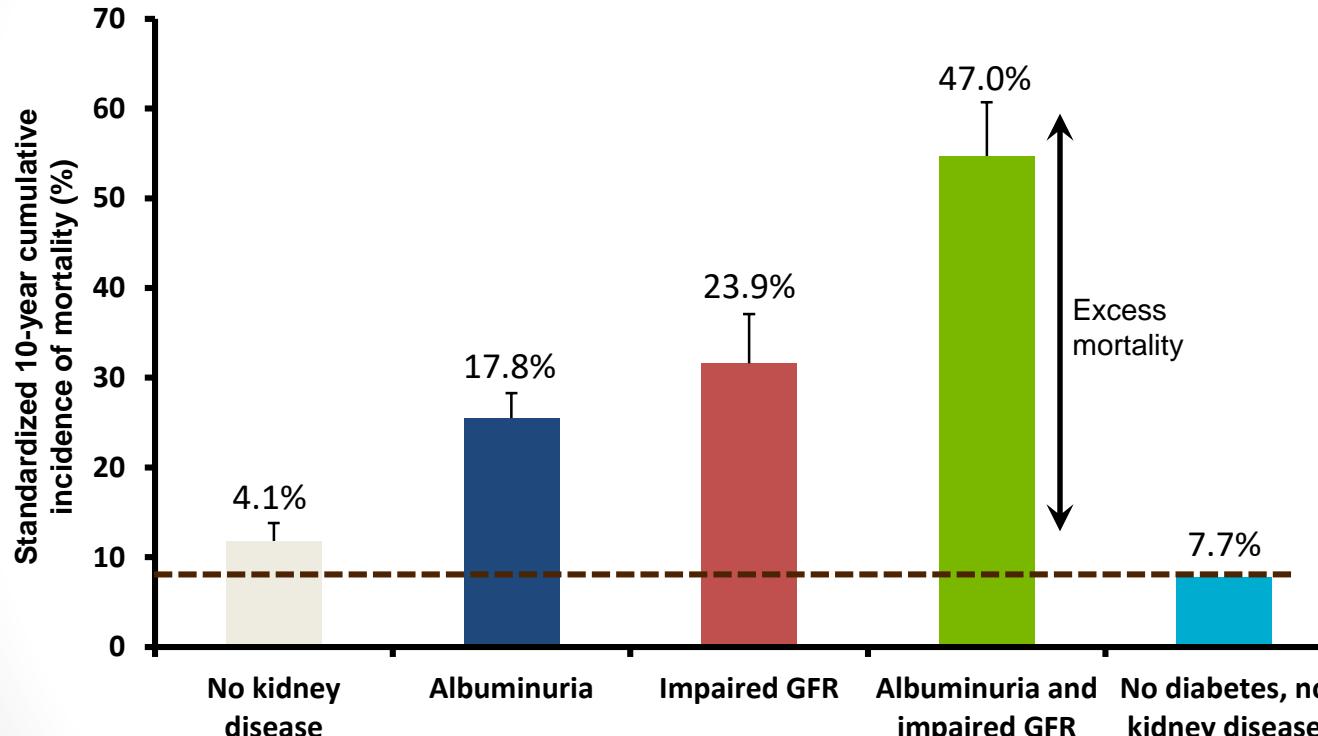
High risk of heart failure

- Framingham: ↑risk of HF in DM
 - 2,4 x for men and 4 x for women
- Pathophysiology^{1,2}: multiple mechanisms
 - Including non-atherosclerotic
- Factors associated with HF in DM
 - Age
 - Diabetes duration
 - Insulin therapy
 - Ischemic heart disease
 - Peripheral artery disease
 - Elevated serum creatinine
 - Poor glycemic control
 - Microalbuminuria



Diabetes

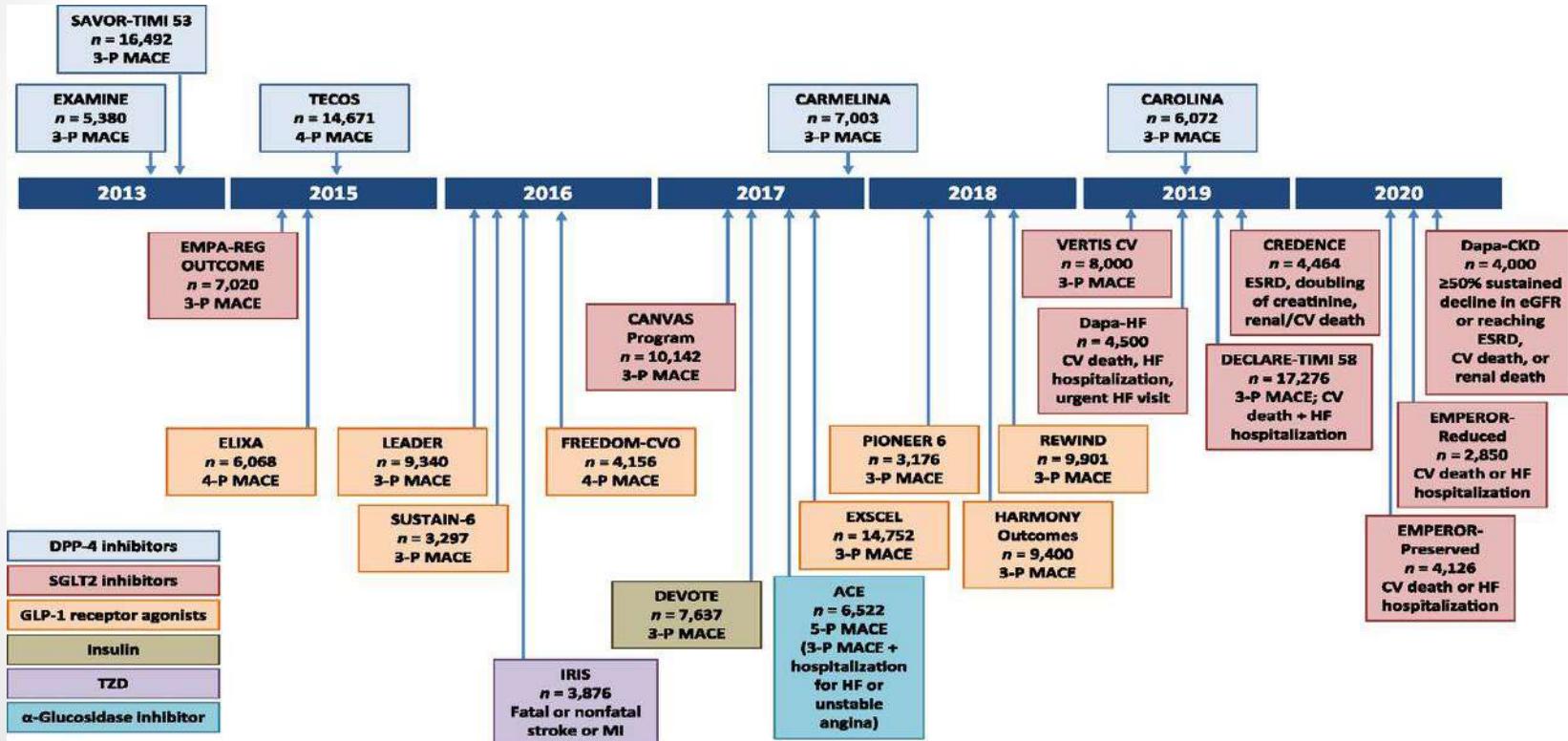
Poor prognosis with kidney disease



The dashed line indicates mortality in persons without diabetes or kidney disease (the reference group).

Diabetes

Trials of cardiovascular safety



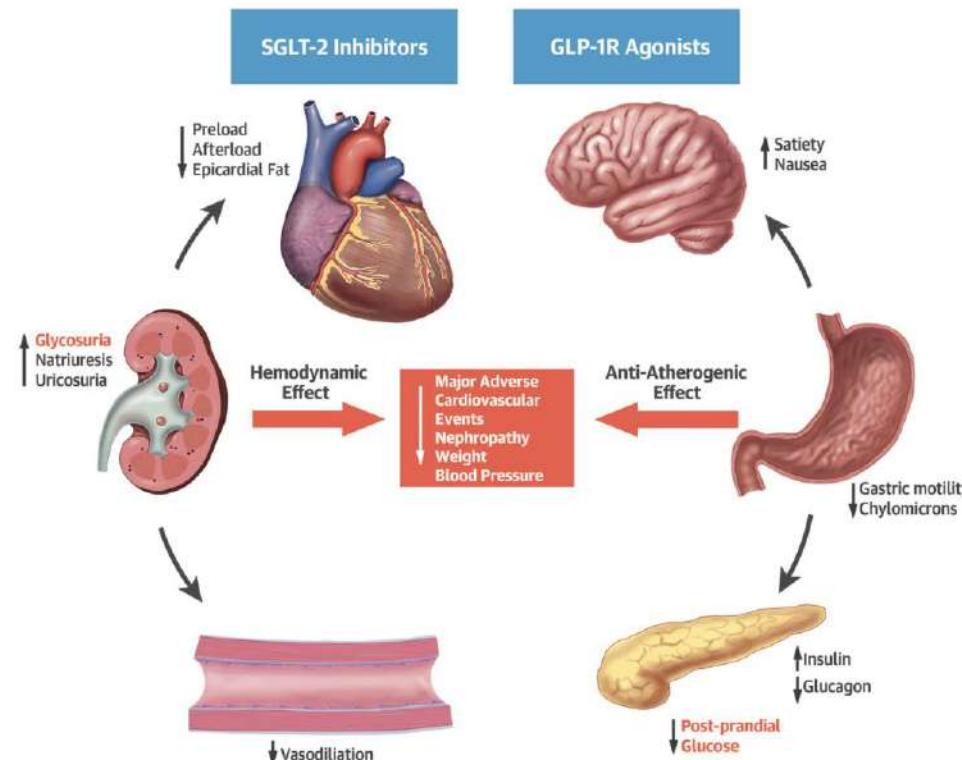
Diabetes: Beyond the Glycemia Control

NEW TREATMENT OPTIONS



Type 2 Diabetes

New treatments for glycemic control and CV protection

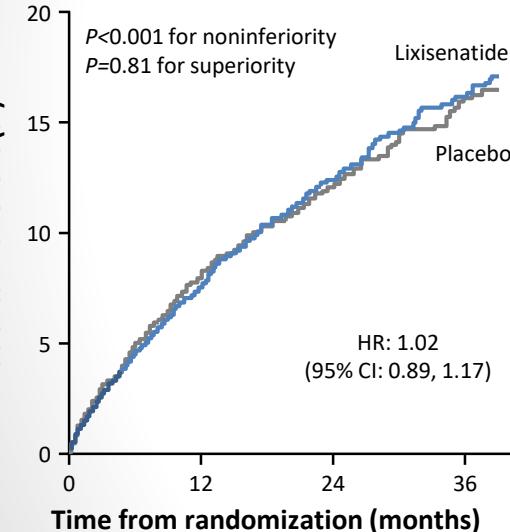


GLP-1 Agonists

Primary endpoint results in the CV safety trials

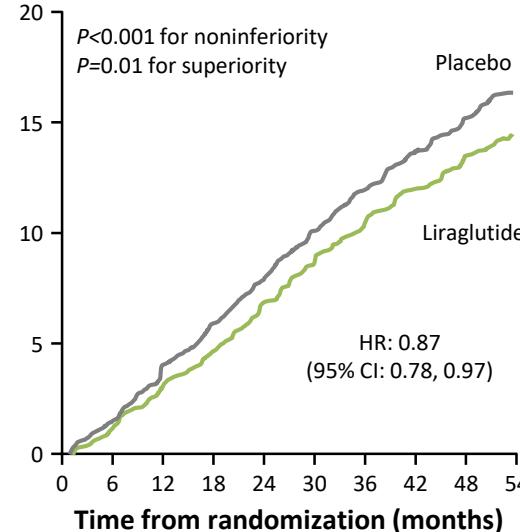
ELIXA¹

CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina



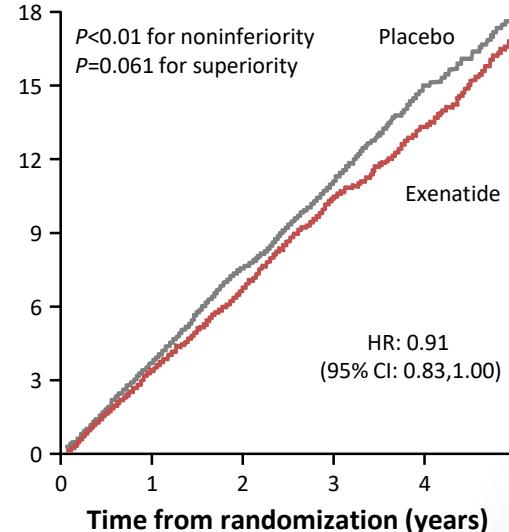
LEADER²

CV death, nonfatal MI, or nonfatal stroke



EXSCEL³

CV death, nonfatal MI, or nonfatal stroke

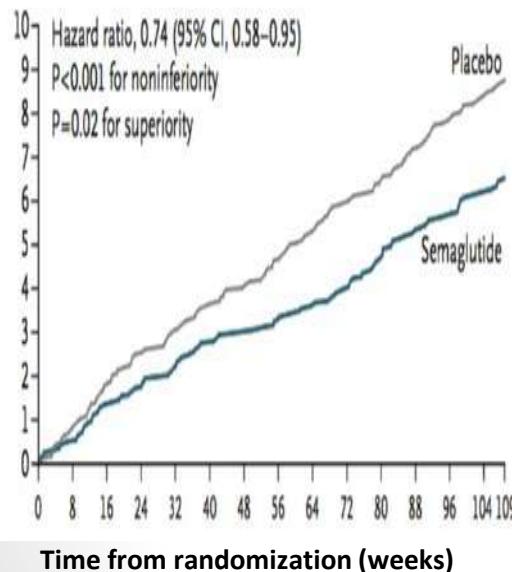


GLP-1 Agonists

Primary endpoint results in the CV safety trials

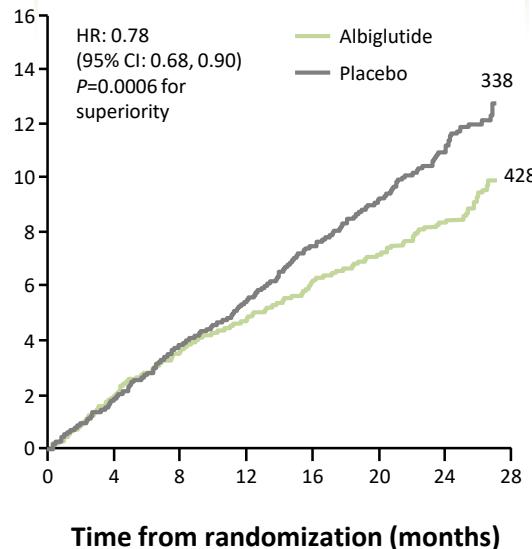
SUSTAIN-6¹

CV death, nonfatal MI, or nonfatal stroke



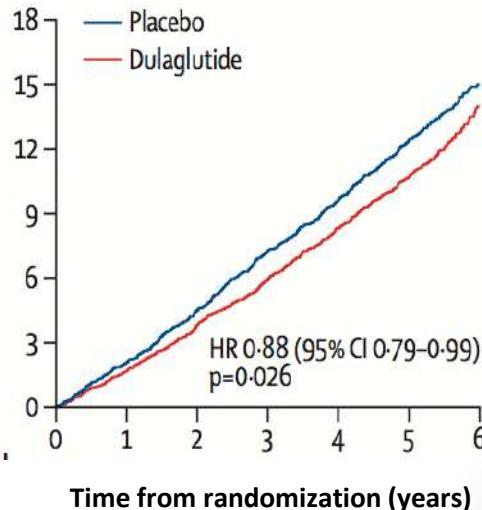
HARMONY²

CV death, nonfatal MI, or nonfatal stroke



REWIND³

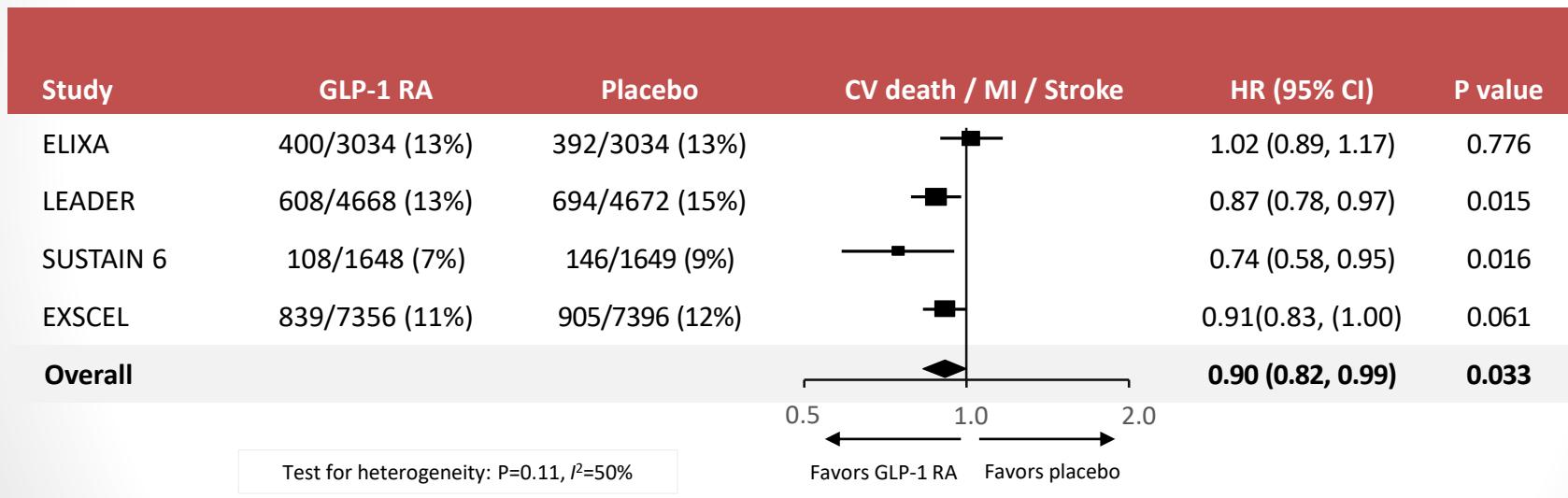
CV/unknown death, nonfatal MI, or nonfatal stroke



GLP-1 Agonists

Metanalysis

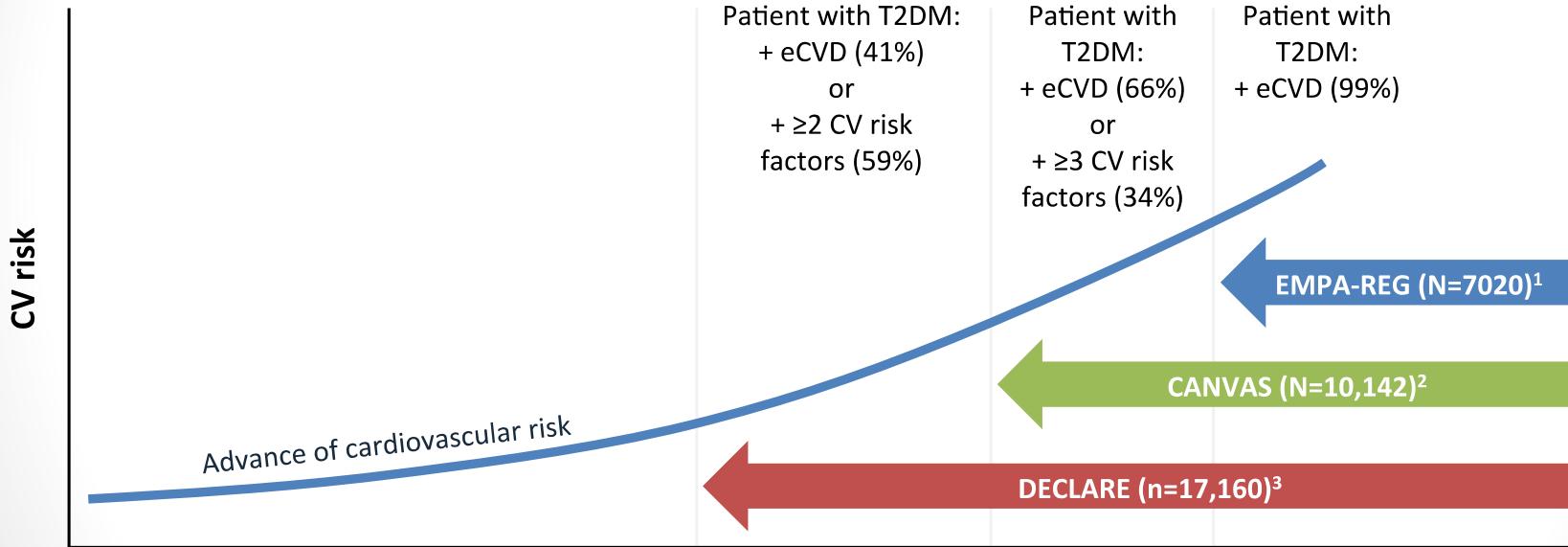
10% RRR CV death, nonfatal MI or nonfatal stroke
13% RRR CV mortality, 12% RRR total mortality



SGLT-2 Inhibitors

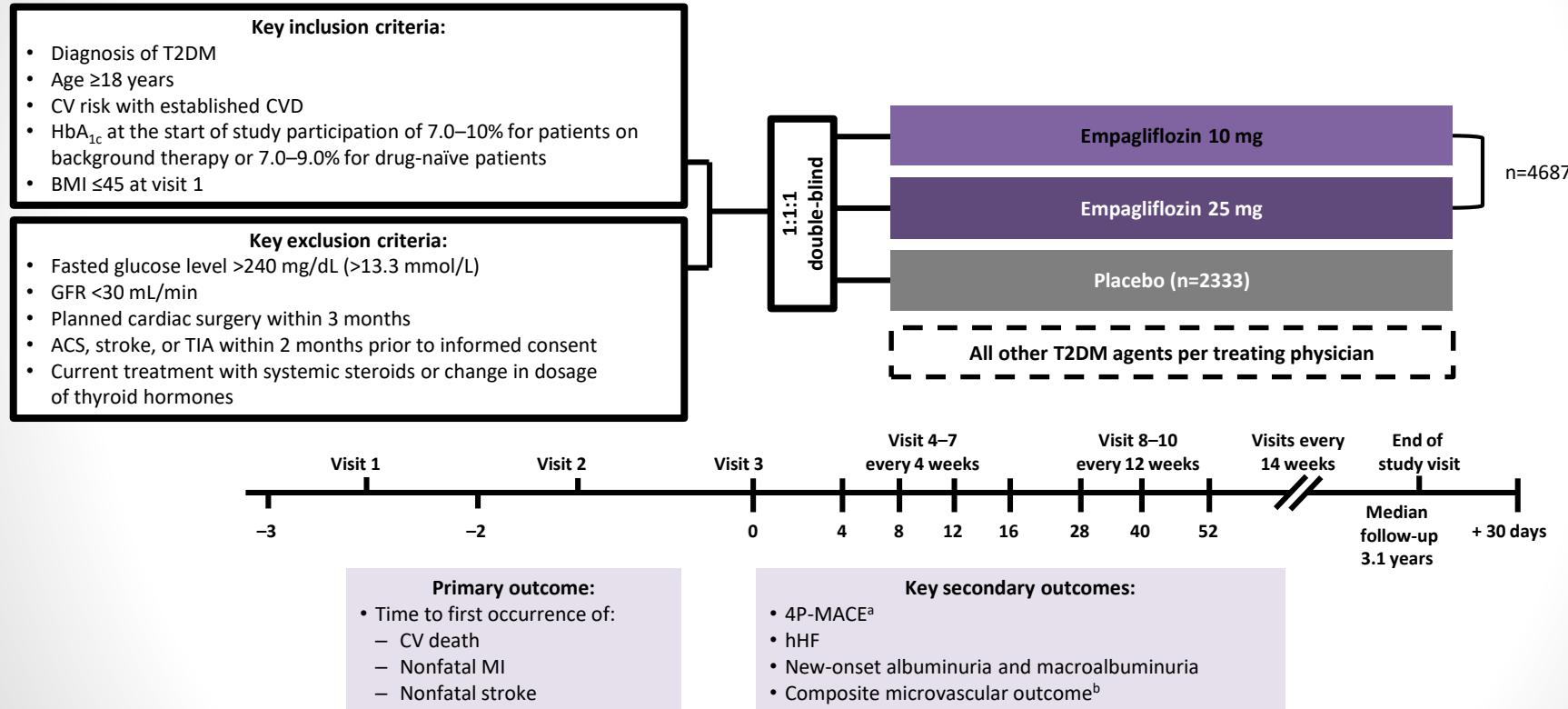
3 main CV outcome trials concluded

Patient risk factor criteria in each SGLT2i CVOT



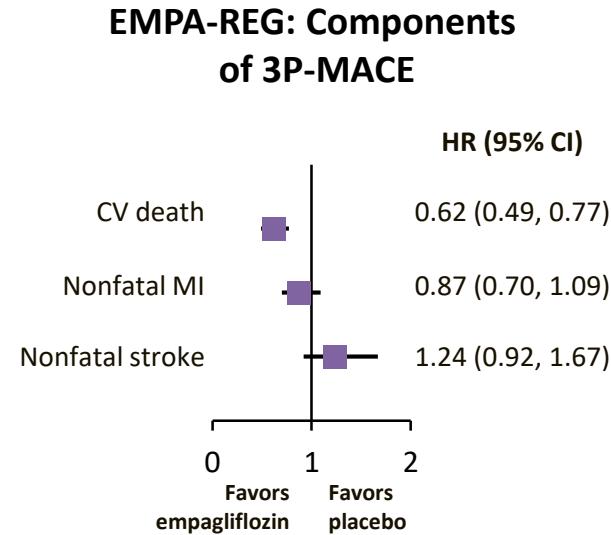
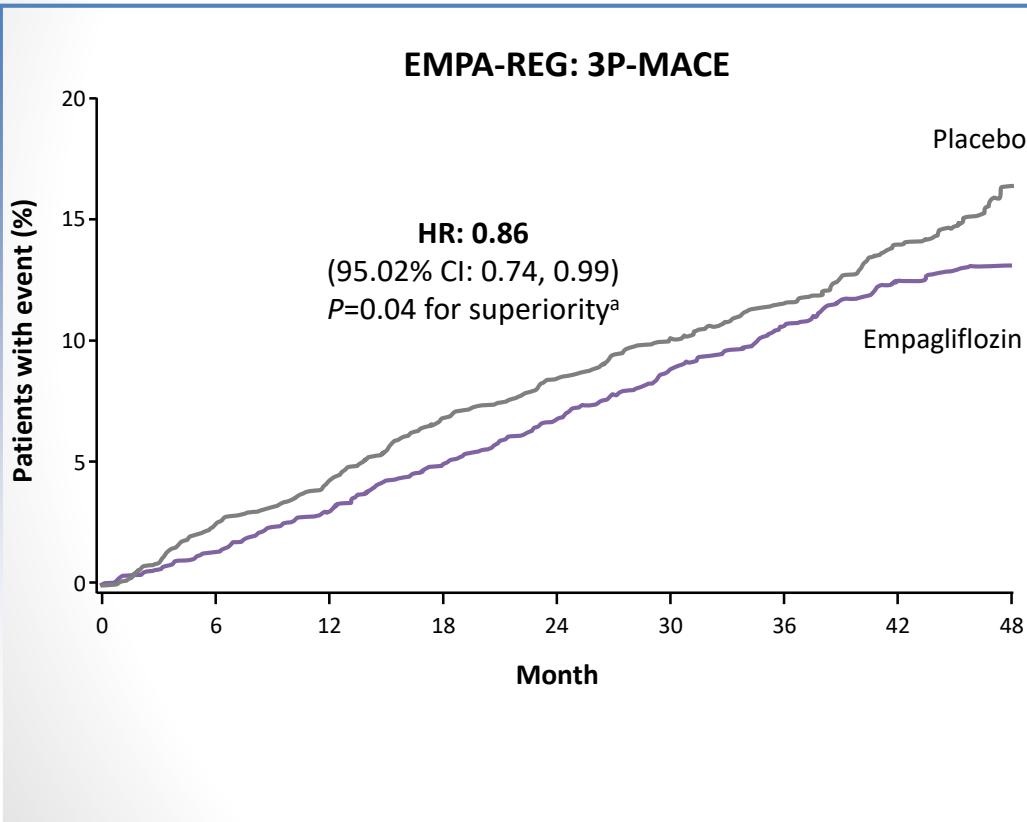
EMPAREG-Outcome

Study design



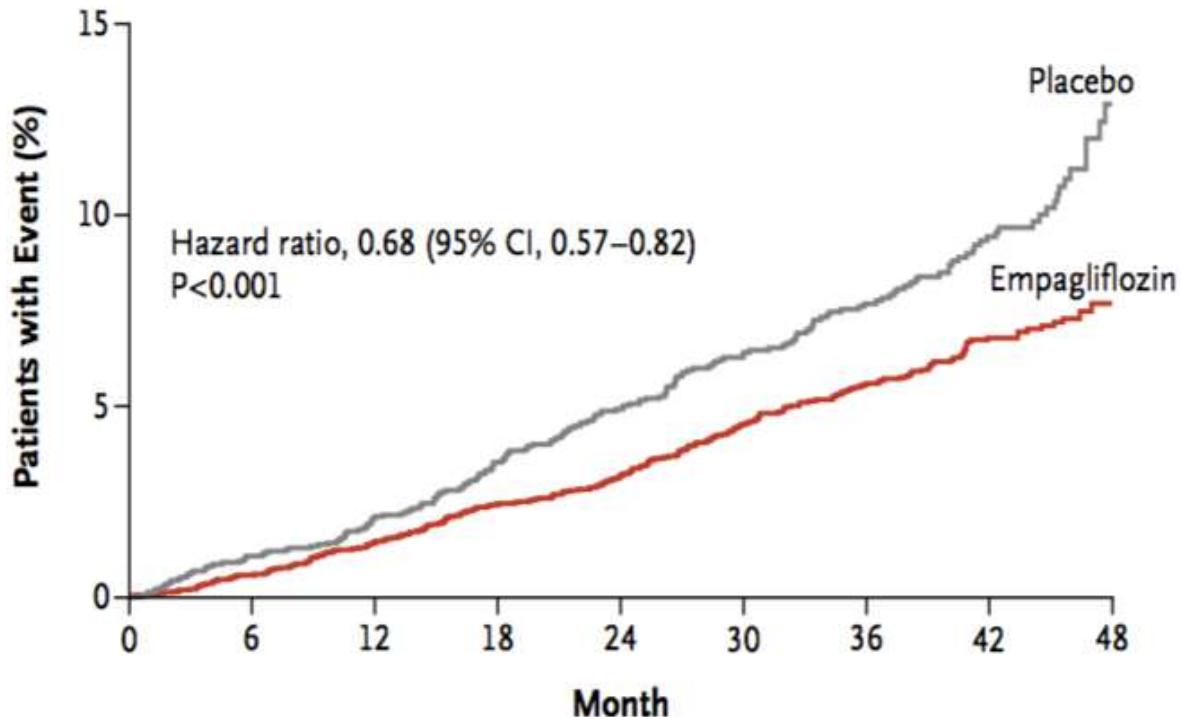
EMPAREG-Outcome

Primary endpoint results



EMPAREG-Outcome

All cause mortality

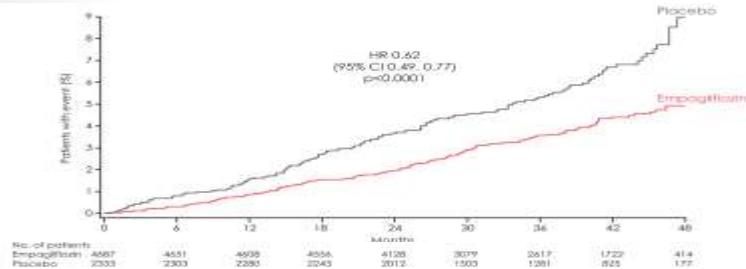


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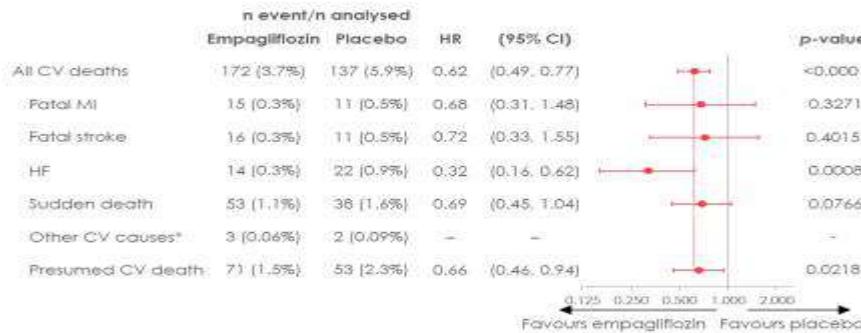
EMPAREG-Outcome

Other endpoint results

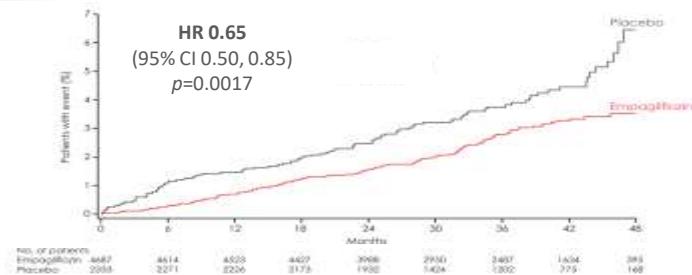
CV Death



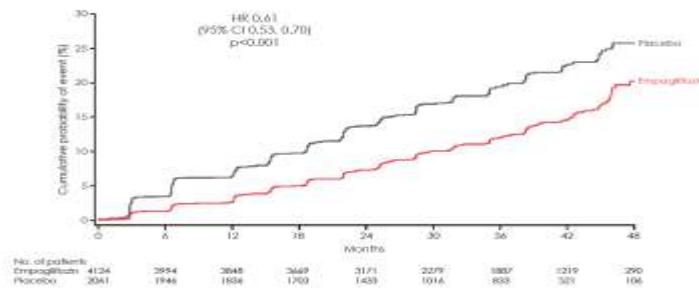
CV death categories



HF Hospitalization

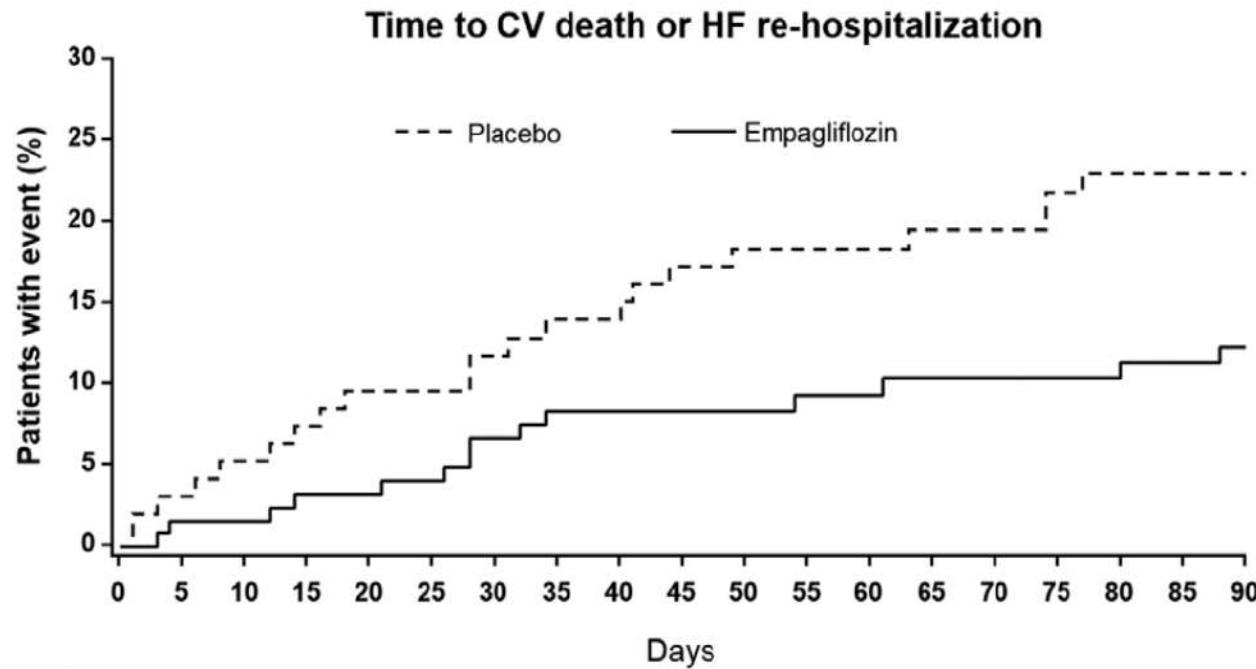


Incident or worsening kidney disease



EMPEREG-Outcome

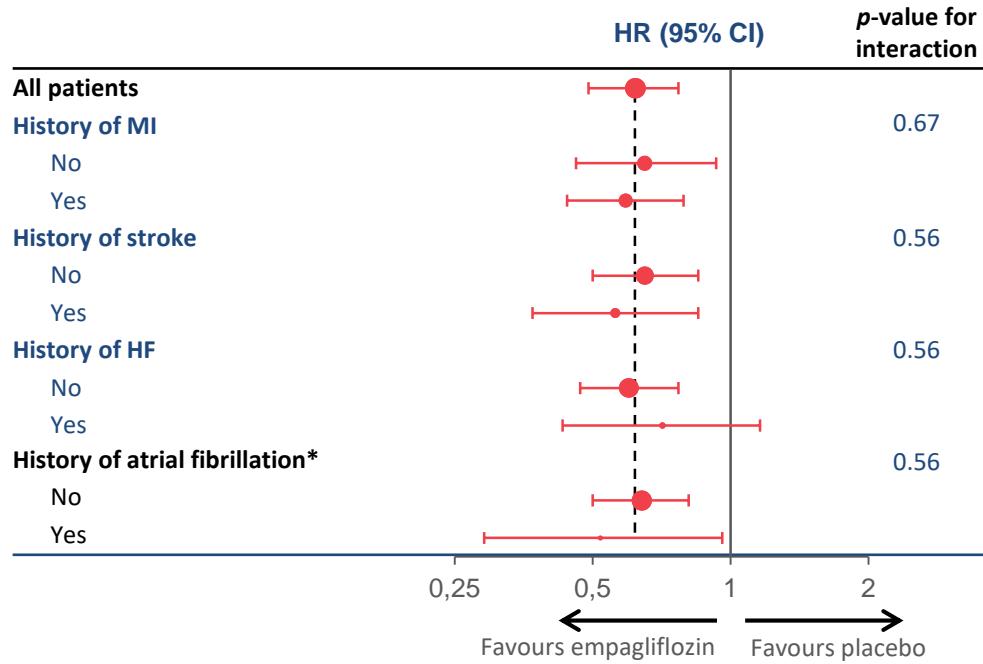
Outcomes after HF hospitalization



Frequency of HF re-hospitalization (second events) or CV death following admission date of first HHF (221 patients)

EMPAR EG-Outcome

CV death reduction even in patients without prior CV event

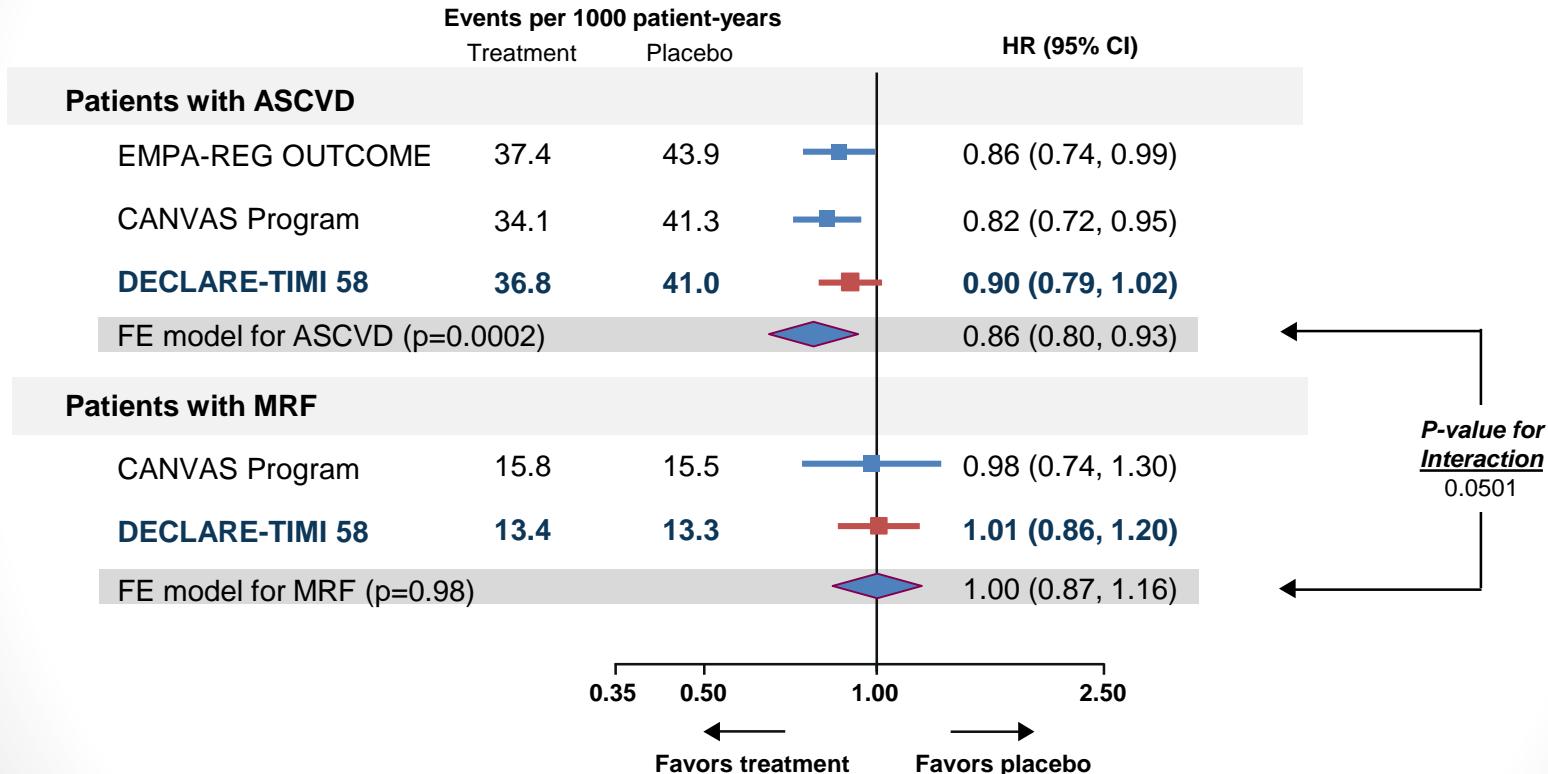


35% of patients with CV disease did not have a prior atherothrombotic event

1. Zinman B et al. AHA 2016; poster S2044.
2. Inzucchi S et al. ACC 2017; oral presentation 911-12.
3. Fitchett D et al. J Am Coll Cardiol 2018;71:364.

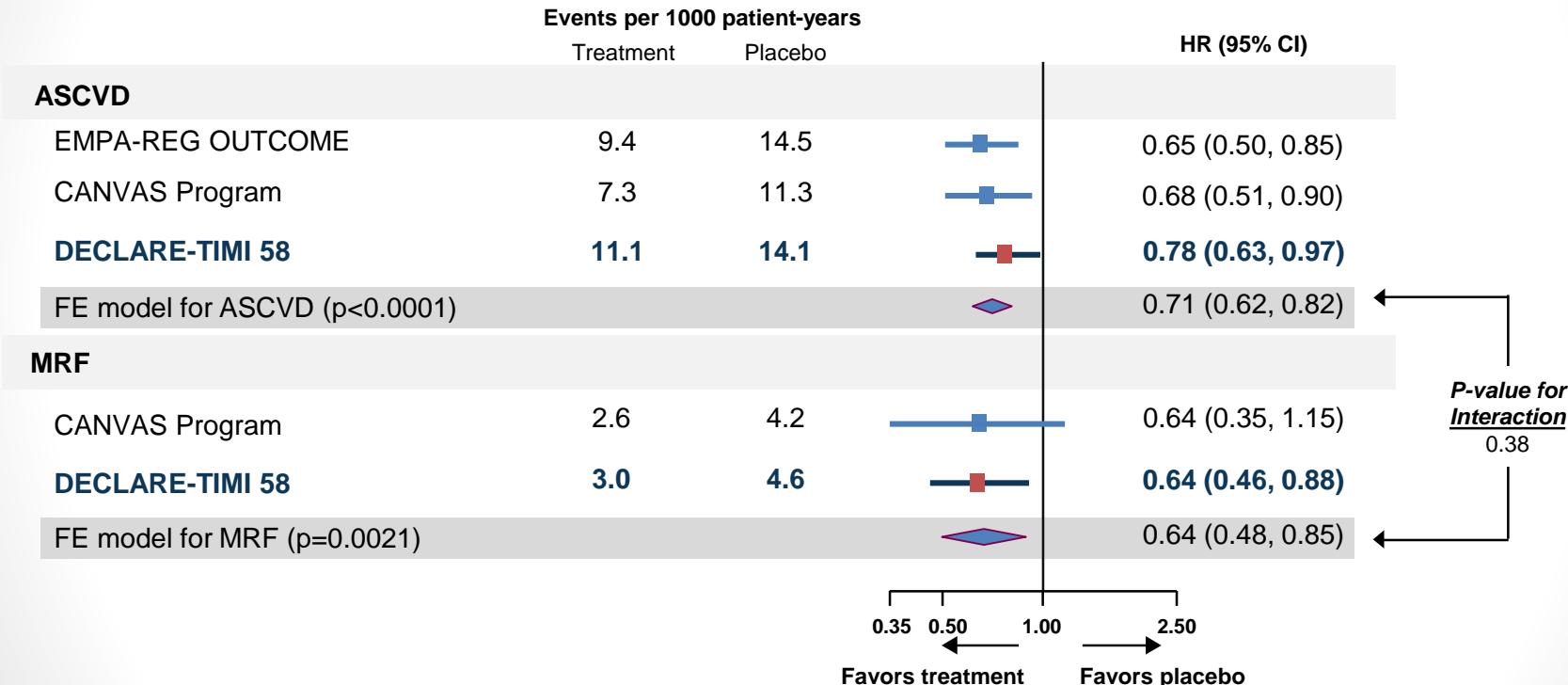
SGLT-2 Inhibitors

Metanalysis: MACE in patients with or without CVD



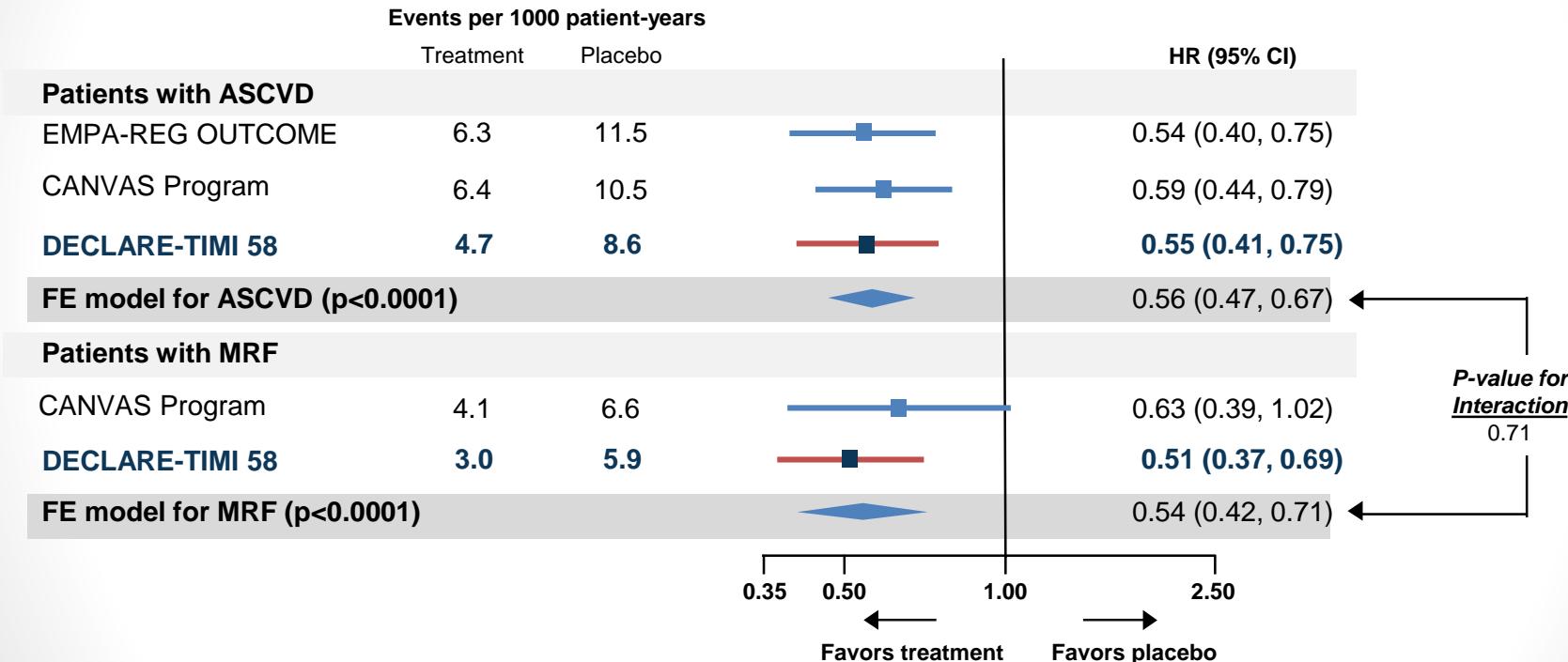
SGLT-2 Inhibitors

Metanalysis: HF admission in patients with or without CVD



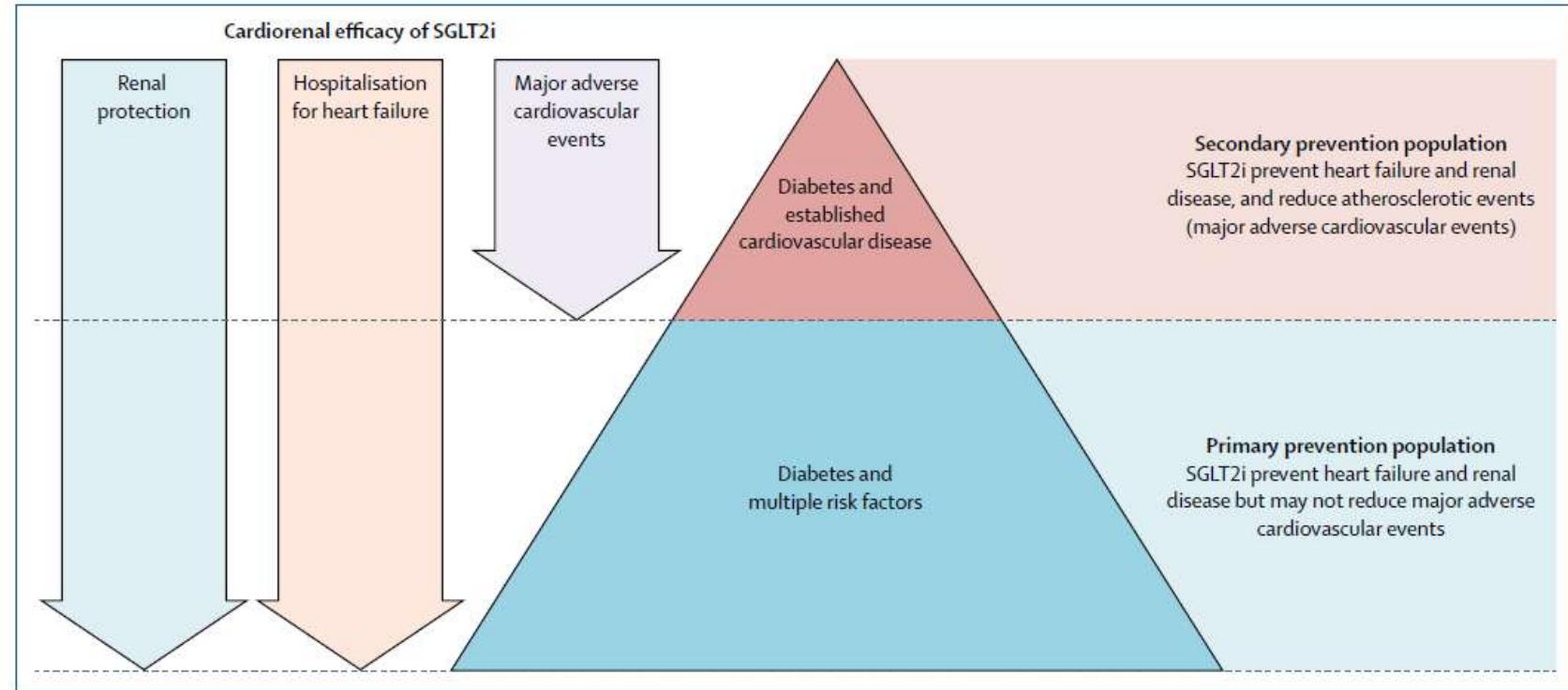
SGLT-2 Inhibitors

Metanalysis: Renal outcomes in patients with or without CVD



SGLT-2 Inhibitors

Cardiorenal protection



Empagliflozin

Ongoing studies

EMPEROR
REDUCED

EMPEROR
PRESERVED

EMPEROR-Reduced and
EMPEROR-Preserved are
dedicated outcomes trials
of empagliflozin for the
treatment of chronic HF

EMPERIAL
REDUCED

EMPERIAL
PRESERVED

EMPERIAL-Reduced and
EMPERIAL-Preserved will
investigate the effects of
empagliflozin on exercise
capacity and **quality of life**
in patients with chronic HF

EMPA-VISION

EMPA-VISION is a
mechanistic study to help
explain how empagliflozin
may **improve HF-related**
outcomes

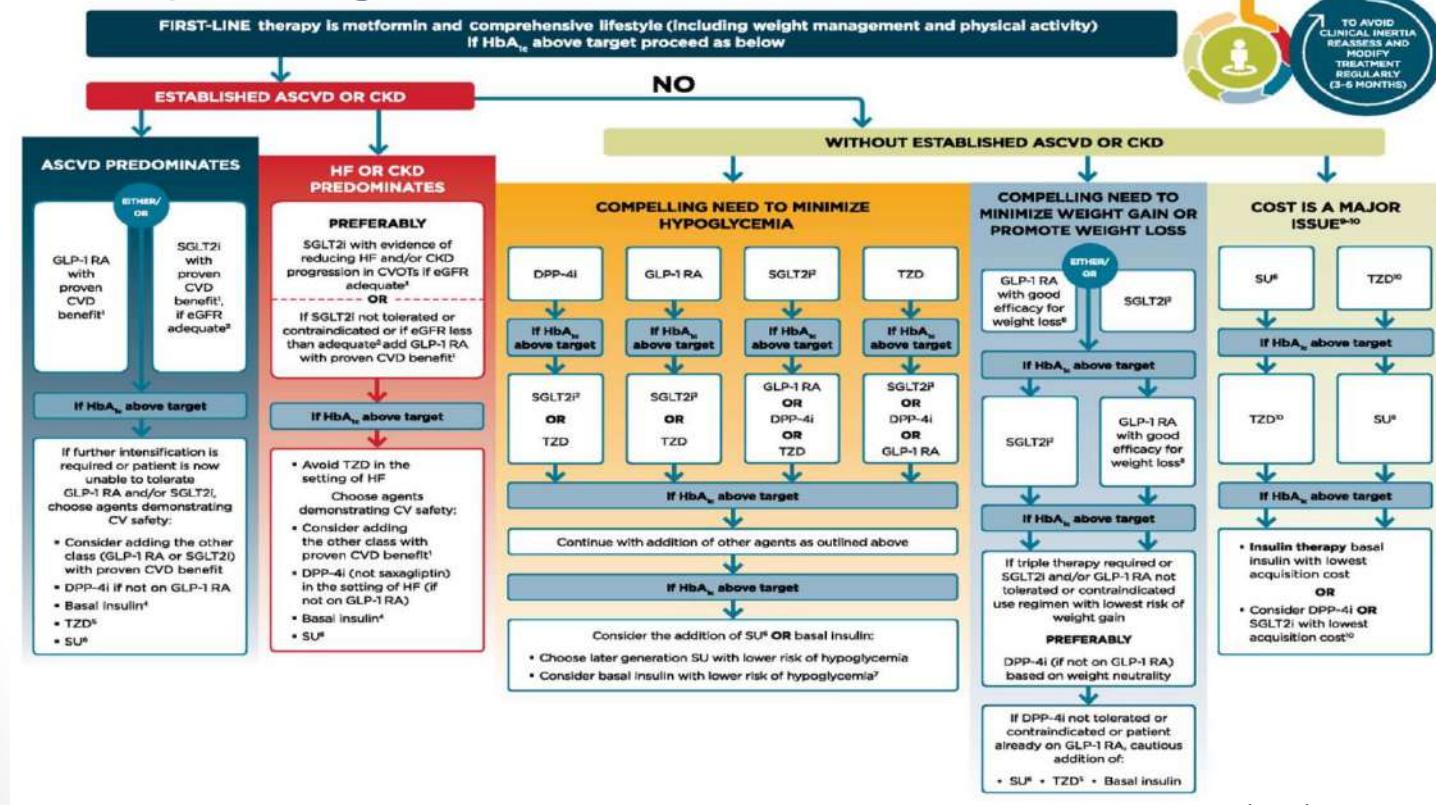
Diabetes: Beyond the Glycemia Control

TAKE-HOME MESSAGES



Type 2 Diabetes

New ADA/EASD guidelines



Type 2 Diabetes

Treatment objectives that truly matter

Drug	Life expectancy	Ischemic events	HF prevention	Renal protection
Beta-blocker	↑ if prior MI + LVSD (↓total/CV deaths) ¹	↓nonfatal MI if prior MI + LVSD ¹ ; no ↓stroke ²	Prevents LV remodeling if prior MI + LVSD ³	Inferior to RASI; carvedilol superior to metoprolol ⁴
RAS inhibitor	↑ if prior MI (↓total/CV/sudden cardiac deaths) ⁵	↓nonfatal MI if prior MI + LVSD ⁶ ; ↓stroke if HTN + high CV risk ⁷	Prevents LV remodeling if prior MI + LVSD ⁸	ARB superior to CCB for diabetic nephropathy ⁹
Statin	Prolongs (↓total/CV deaths) ¹⁰	↓nonfatal/fatal MI ¹⁰ ; ↓nonfatal stroke ¹⁰	↓HF hospitalization but not HF death ¹¹	No effect on proteinuria nor on renal function ^{12,13}
ASA (2 ^o prevention)	Prolongs (↓total deaths) ¹⁴	↓MI and ↓stroke ¹⁴	No HF prevention ¹⁵ ; may ↑HF hosp. if prior HF ¹⁶	No effect on albuminuria nor on renal function ¹⁷
SGLT-2 inhibitor	Prolongs (↓total/CV deaths) ¹⁸	↓MI if prior MI ¹⁹ ; no stroke prevention ¹⁸	↓HF hospitalization; ↓HF deaths ¹⁸ ; HFrEF: ↓total/CV death ²⁰	Slows ↓GFR & albuminuria progress ²¹ ↓ESRD and renal deaths ²²
GLP-1 agonist	Prolongs (↓total/CV deaths) ²³	No MI prevention and no stroke prevention ²³	No effect on HF hospitalizations ²³	Slows ↓GFR and albuminuria progression ²²

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Conclusions

- Treatment of T2DM must go much beyond glycemic control
- Treatment must be individualized but **treatment objectives must be universal**
 - Reduce atherothrombotic risk
 - Protect cardiac and renal functions
- **SGLT2 inhibitors offer a unique opportunity for enhanced cardio-renal protection** in patients eligible for treatment
- Ongoing studies will clarify mechanisms of protection and determine whether some of the benefits may be applicable to patients without T2DM