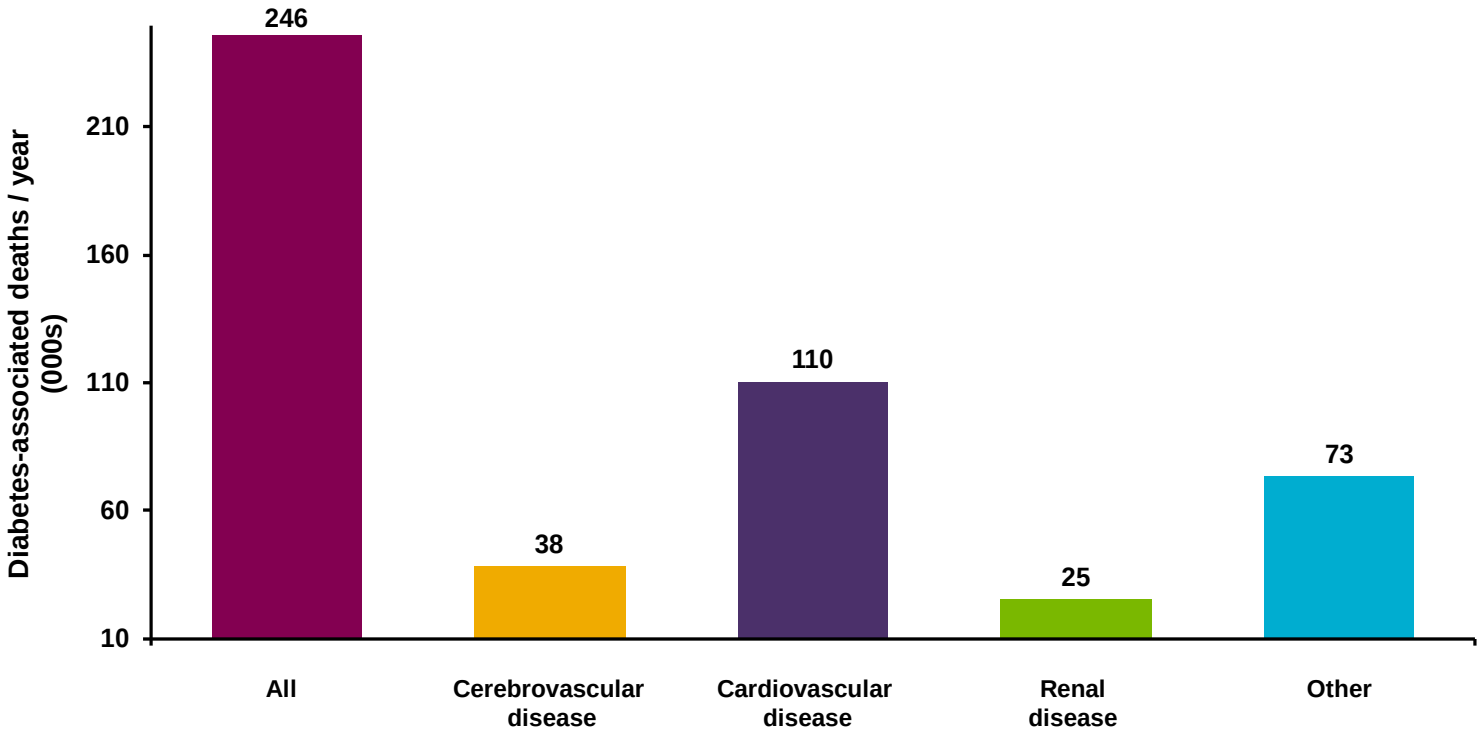
Farmaci antidiabetici ed endpoint cardiovascolari negli studi clinici

Paolo Falasca
UOC di Medicina interna
Ambulatorio di Endocrinologia e Diabetologia
Ospedale Frascati - Marino

Il dr. Paolo FALASCA dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Sanofi
- Lifescan
- NovoNordisk
- Eli Lilly
- Takeda
- Boehringer Ingelheim

Over 50% of Diabetes-associated Deaths Are Attributable to CV Disease

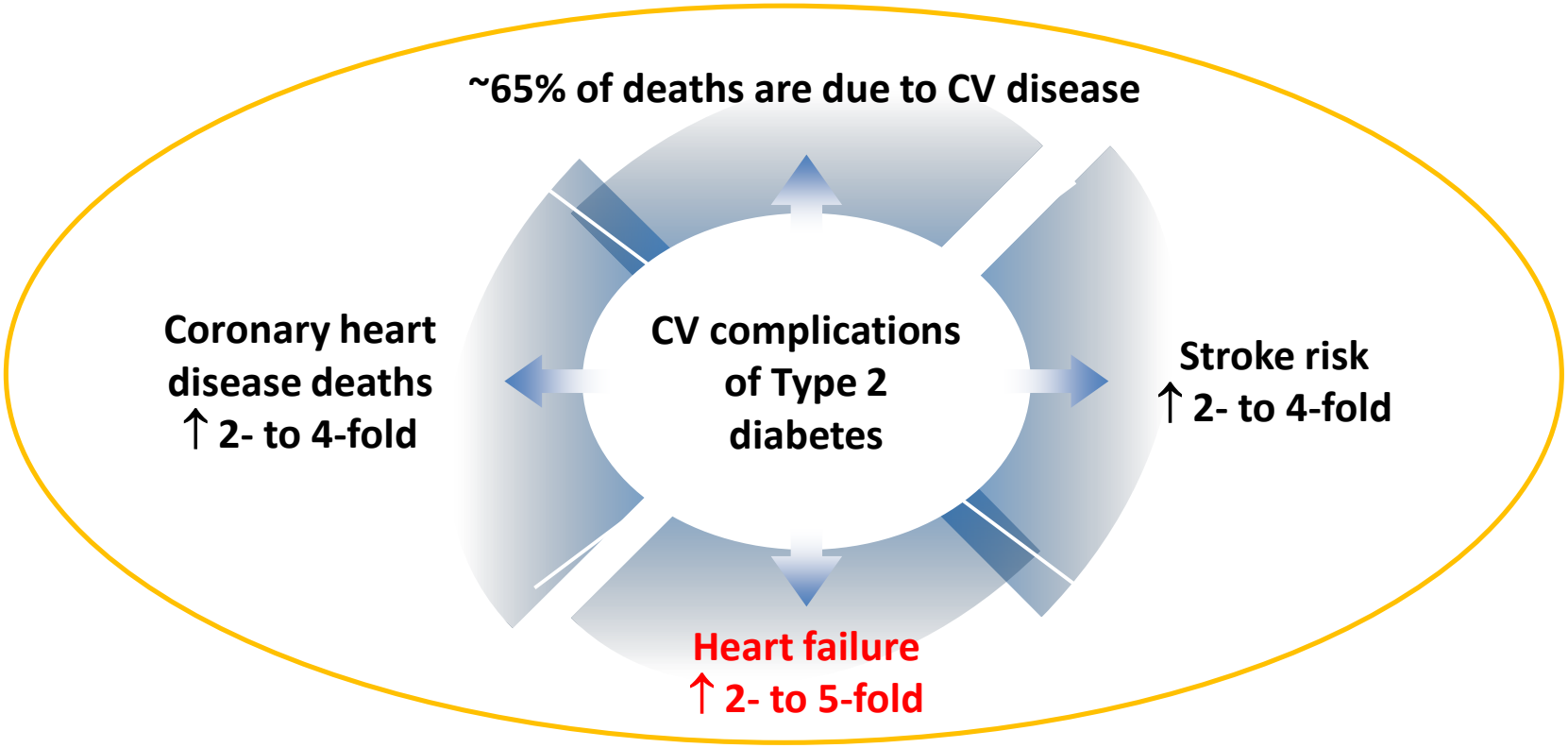


Data source: USA Centers for Disease Control and Prevention National Vital Statistics Reports for total deaths in 2009 by primary cause of death, scaled to 2012 using the annual diabetes population growth rate from
2009 to 2012 for each age, sex, and race/ethnicity group

CV, cardiovascular

ADA. *Diabetes Care* 2013;36:1033–1046

Cardiovascular Disease Complications of Type 2 Diabetes



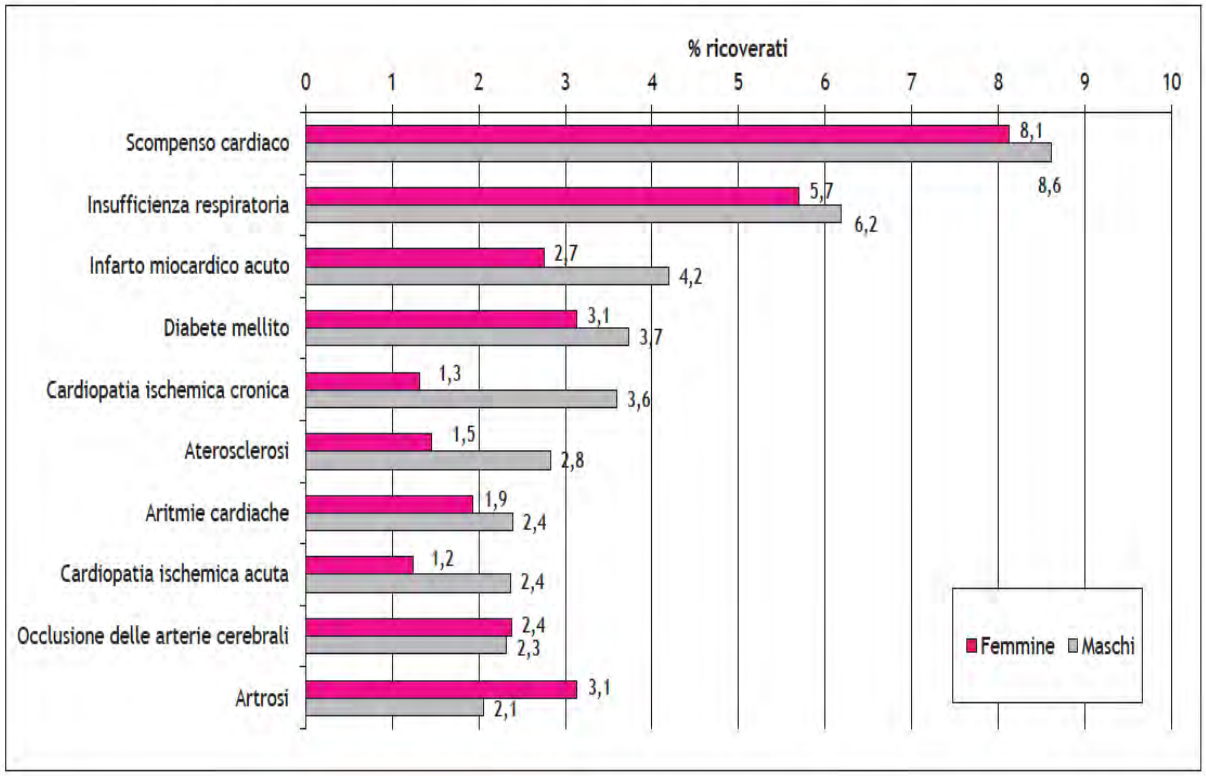
Heart Failure: The frequent, forgotten and often fatal complication of diabetes

Table 1—*Epidemiology of heart failure in diabetic patients*

- HF is two times as common in diabetic men and five times as common in diabetic women as in age-matched nondiabetic subjects.
- About 12% of type 2 diabetic subjects have established HF.
- About 3.3% of type 2 diabetic subjects develop HF each year.
- Elderly diabetic subjects have a 1.3-fold greater risk of developing HF than nondiabetic subjects.
- Prevalence of HF in elderly diabetic subjects is 39%.
- 1% rise in HbA_{1c} is associated with a 15% increased risk of HF in elderly diabetic patients.
- Diabetic patients account for 25% of all patients enrolled in large HF trials.

Diabetes Care 26:2433–2441, 2003

Le prime 10 diagnosi in caso di ricovero ordinario in funzione del sesso
(% ricoverati/diabetici con almeno un ricovero nell'anno)[7]



Osservatorio ARNO Diabete

Il profilo assistenziale della popolazione con diabete

Rapporto 2015

Bullet point

- ✓ Il ruolo del trattamento intensivo (vecchi trials)
- ✓ I nuovi trials (SAVOR , TECOS, ELIXA)
- ✓ I «game changer» (EMPA-REG, LEADER, SUSTAIN6)
- ✓ Il futuro (CANVAS, EXCEL, DECLARE, etc)

Complex relationship be… …ia and CV risk

Increased mortality may be related to factors associated with study strategies

Current evidence does not support intensive glycaemic control for reducing CV risk

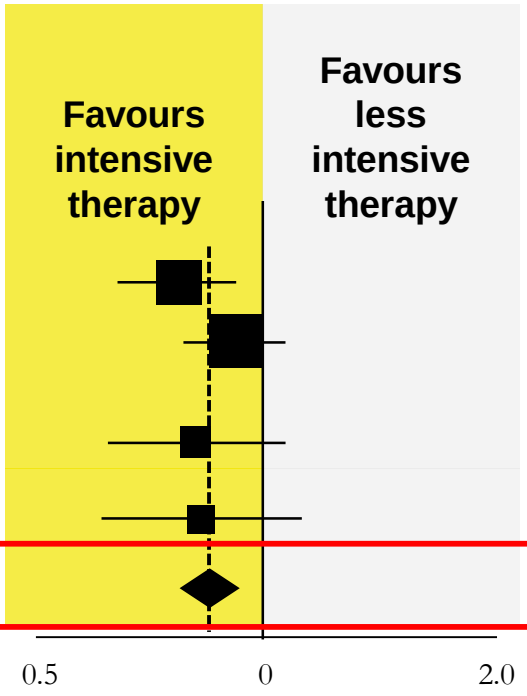
Study	Question	Conclusion
ACCORD	Does a intensive therapy targeting HbA1c < 6.0% versus 7.0–7.9 % reduce CVD risk in middle-aged/older patients with high CV risk?	NO – Intensive glycaemic control had non-significant reduction in CV events (HR 0.9, p = 0.16); may increase mortality (HR 1.22, p = 0.04). Increased risk of hypoglycaemia
ADVANCE	Are micro- and macrovascular events reduced by intensive glucose control ($HbA_{1c} \leq 6.5\%$) compared with standard therapy?	NO – Intensive glycaemic control had no effect on CV events (HR 0.94, p = 0.32), but did reduce microvascular events (HR 0.86, p < 0.01). Increased risk of hypoglycaemia
VADT	Does intensive glycaemic control affect CVD risk compared with standard therapy in older male patients with T2DM?	NO – Intensive control has no impact on CV events (HR 0.88, p = 0.14). Increased risk of hypoglycaemia
UKPDS	Does intensive glucose control with SU or insulin in newly diagnosed patients with T2DM provide any benefit?	YES – Early intensive glycemic control in newly diagnosed patients reduces long-term CV risk (myocardial infarction RR 0.85, p = 0.014)

ACCORD Study Group. N Engl J Med. 2008;358: 2545–2559; ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560–2572; Duckworth W, et al. N Engl J Med. 2009;360:129–139; Holman RR, et al. N Engl J Med. 2008;359:1577–1589.

Intensive glycaemic control may reduce risk of myocardial infarction

Meta-analysis of ACCORD, ADVANCE, VADT and UKPDS suggests intensive glucose control reduces the risk of myocardial infarction by 15%

Study	Number of events (annual event rate, %) More intensive	Less intensive	Difference in HbA_{1c} (%)	Hazard ratio (95% CI)
ACCORD	198 (1.18)	245 (1.51)	–1.01	0.77 (0.64, 0.93)
ADVANCE	310 (1.18)	337 (1.28)	–0.72	0.92 (0.79, 1.07)
UKPDS	150 (1.20)	76 (1.40)	–0.66	0.81 (0.62, 1.07)
VADT	72 (16.5)	87 (1.99)	–1.16	0.83 (0.61, 1.13)
Overall	730	745	–0.88	0.85 (0.76, 0.94)



Turnbull FR, et al. Diabetologia. 2009;52:2288–2298.

History of glucose-lowering therapy and CV scares

1961 – UGDP study, tolbutamide increased CV mortality versus other treatment groups[1]

Regulatory requirements for diabetes drugs:

1. Lower blood glucose levels
2. No obvious safety problems

Pharmaceutical industry did not have to investigate CV outcomes f… …etes treatments/strategies – no outcome studi…

Sponsor withdrew application

Withdrawn in EU
Restricted use in USA

2005 – Muraglitazar fou… …crease CV ri… …ssment[1,2]

2007 – Rosiglitazone …ssociated with increased risk for myocardial infarction (meta-analysis, OR 1.43, p = 0.03)[3]

2008 – ACCORD study, intensive glucose lowering was associated with increased mortality (hazard ratio 1.22, p = 0.04)[4]

2013 – FDA panel vote to reduce safety restrictions on rosiglitazone

Regulatory requirements for outcome data for new diabetes drugs

1. Nissen SE. Ann Intern Med. 2012;157:671–672; 2. Nissen SE, et al. JAMA. 2005;294:2581–2586;
3. Nissen SE, et al. N Engl J Med. 2007;356:245–271; 4. ACCORD Study Group. N Engl J Med. 2008;358:2545–2559.

Regulatory requirements for CV outcome data

FDA: Guidance for industry (Dec 2008)

Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies in Type 2 Diabetes[1]

'To establish the safety of a new antidiabetic drug to treat Type 2 Diabetes, the sponsors should demonstrate that the therapy will not result in an unacceptable increase in CV risk'

- Important CV events should be analysed
- High-risk population to be included
- Long term data required (≥ 2 years)
- Prospective adjudication of CV events by an independent committee

EMA: Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (Sept 2012 – final)[2]

'A fully powered cardiovascular safety assessment, e.g. based on a dedicated CV outcome study, should be submitted before marketing authorization whenever a safety concern is intrinsic in the molecule/mechanism of action or has emerged from preclinical/clinical registration studies; e.g.,

- Increase in LDL
- Increase in triglycerides
- Increase in heart rate
- Increase in body weight
- Increase in incidence of MACE
- Increase in incidence of heart failure'

1. FDA Guidance for Industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf.
2. EMA Guidelines. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf.

Regulatory requirements for CV outcome data

FDA: Guidance for industry (Dec 2008)

Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies in Type 2 Diabetes[1]

Submission with NDA:

- Meta-analysis of important CV events across controlled Phase II and III studies to calculate the risk ratio
- If the upper bound of the two-sided 95% CI for the estimated risk ratio is:
  - **> 1.8**: inadequate data to support approval
  - **1.3–1.8**,*: postmarketing CV trial(s) needed to show definitively < 1.3
  - **< 1.3**,*: postmarketing CV trial(s) generally not necessary

  * With a reassuring point estimate
- Studies included in the meta-analysis must be appropriately designed and include patients at higher CV risk so that sufficient endpoints are obtained to allow a meaningful estimate of risk

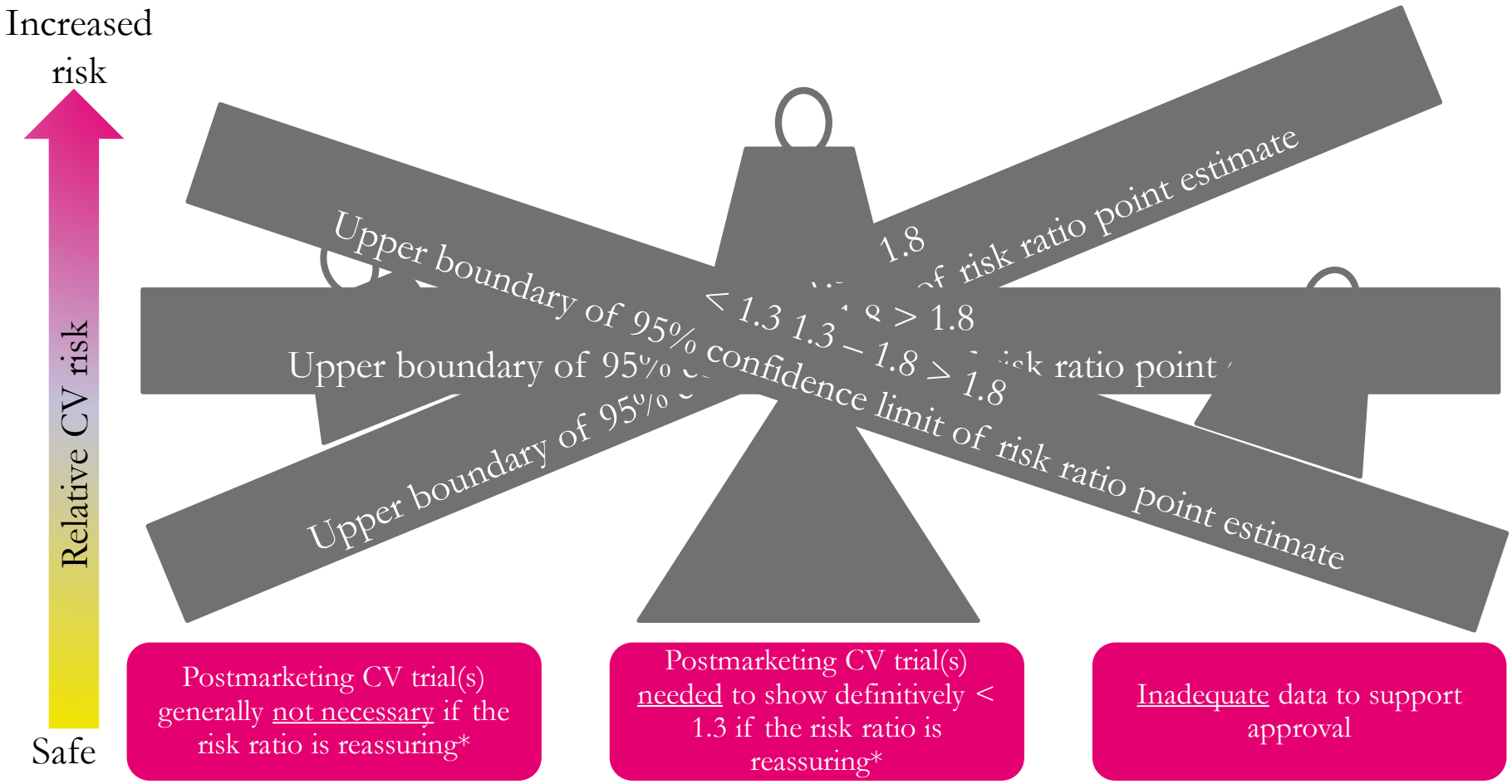
EMA: Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (Sept 2012 – final)[2]

Submission with the MAA:

- Integrated safety analysis (meta-analysis) with specific focus on CV safety
- A fully powered CV safety assessment, submitted before marketing authorization whenever a safety concern is intrinsic in the molecule/mechanism of action or has emerged from preclinical/clinical registration studies
- Long-term CV outcome trials may be requested if there is an indication of increased risk

1. FDA Guidance for Industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf.
2. EMA Guidelines. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf.

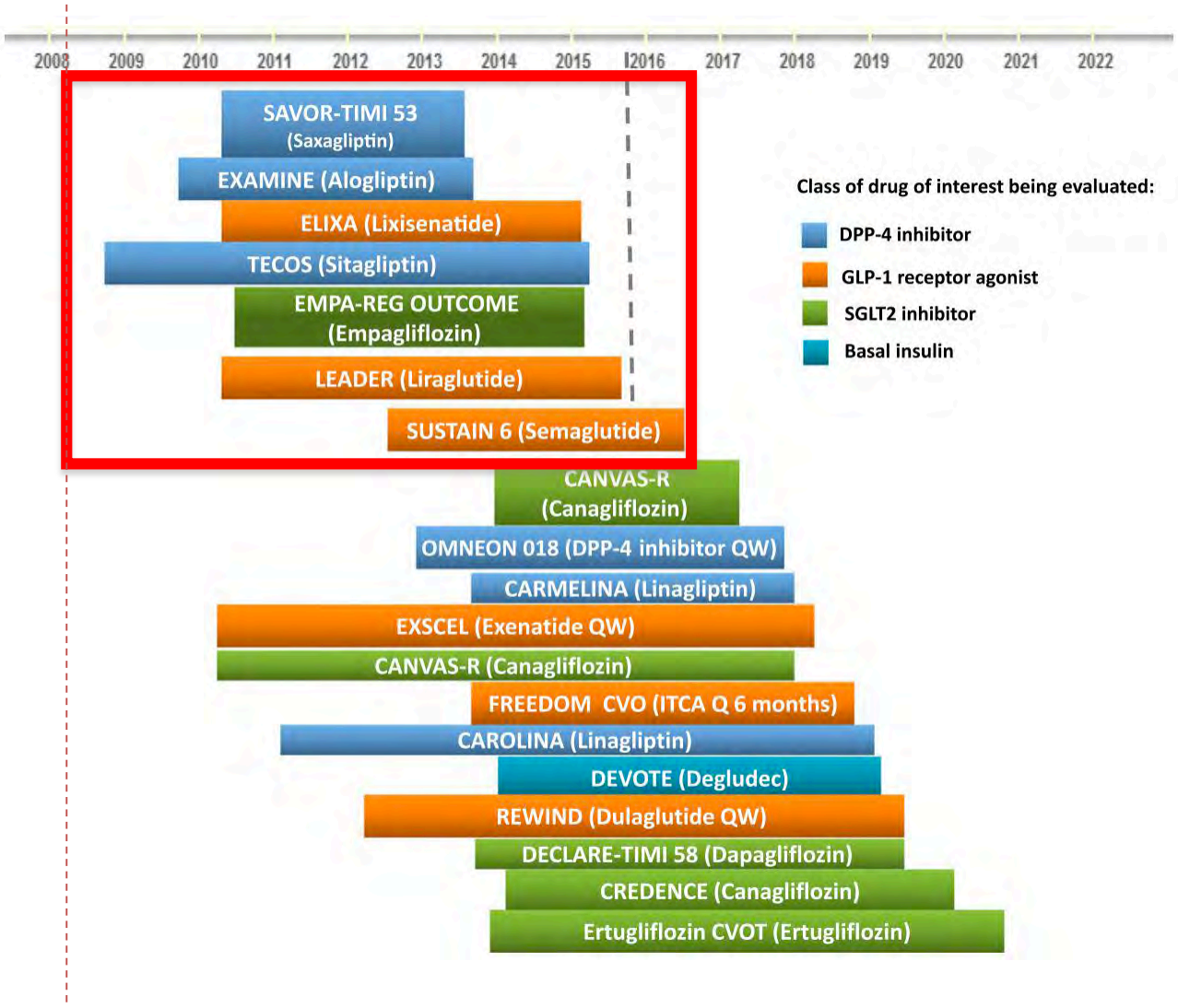
Regulatory requirements for CV outcome data: Meta-analysis* limits and outcome trial requirements



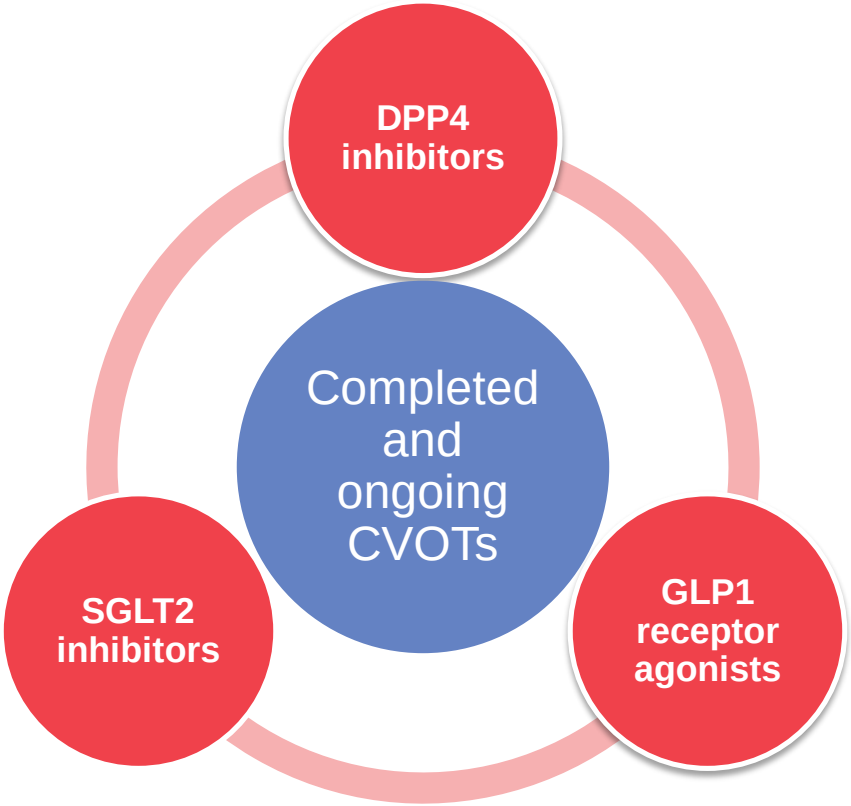
*Studies included in the meta-analysis must be appropriately designed and specifically include patients at higher risk of CV events to obtain sufficient endpoints to allow a meaningful estimate of risk.

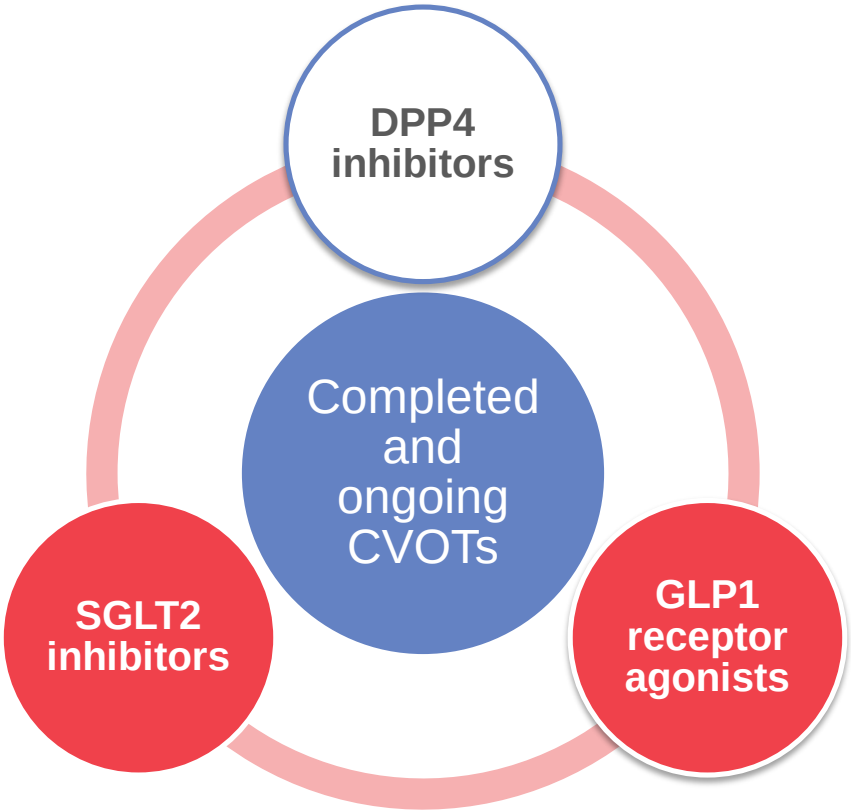
1. FDA Guidance for Industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf.

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



Mannucci and Avogaro Diabetes Care et al. 2016


DPP4 inhibitors
Completed and ongoing CVOTs
SGLT2 inhibitors
GLP1 receptor agonists

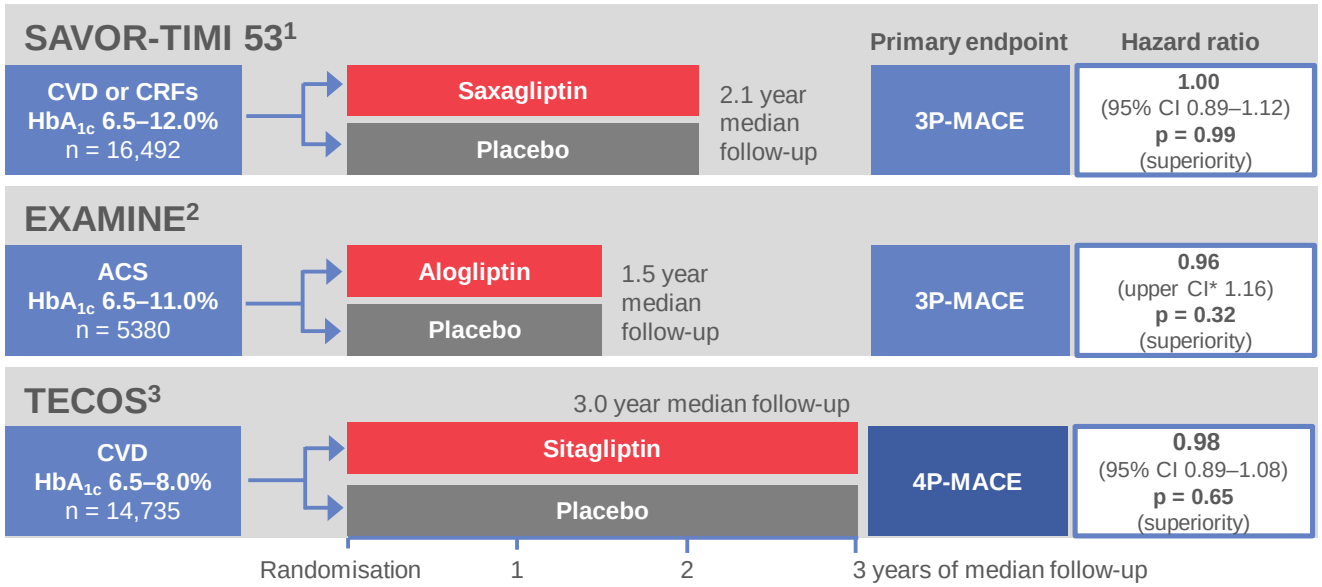

DPP4 inhibitors
Completed and ongoing CVOTs
SGLT2 inhibitors
GLP1 receptor agonists

Summary of CV outcomes trials with DPP4 inhibitors

	SAVOR-TIMI 53[1]	EXAMINE[2]	TECOS[3]	CAROLINA®[4]	CARMELINA®[5]
Intervention	Saxagliptin/ placebo	Alogliptin/ placebo	Sitagliptin/ placebo	Linagliptin/ glimepiride	Linagliptin/ placebo
Main inclusion criteria	History of or multiple risk factors for CVD	ACS within 15–90 days before randomisation	CVD	≥ 2 specified traditional CV risk factors or manifest CVD	High risk of CV events (e.g. albuminuria, prior CVD)
No. of patients	16,492	5380	14,671	6041	8300
Primary outcome	3P-MACE	3P-MACE	4P-MACE	4P-MACE	4P-MACE
Key secondary outcome	Expanded MACE	4P-MACE	3P-MACE	3P-MACE	3P-MACE; renal composite
Target no. of events	1040[6]	650	1300	631	625[7]
Median follow-up (y)	2.1	1.5	3.0	6–7*	4*[7]
Estimated completion	Completed	Completed	Completed	2018[8]	2018

ACROSS T2D
The Academy for Cardiovascular Risk, Outcomes and Safety Studies in Type 2 Diabetes

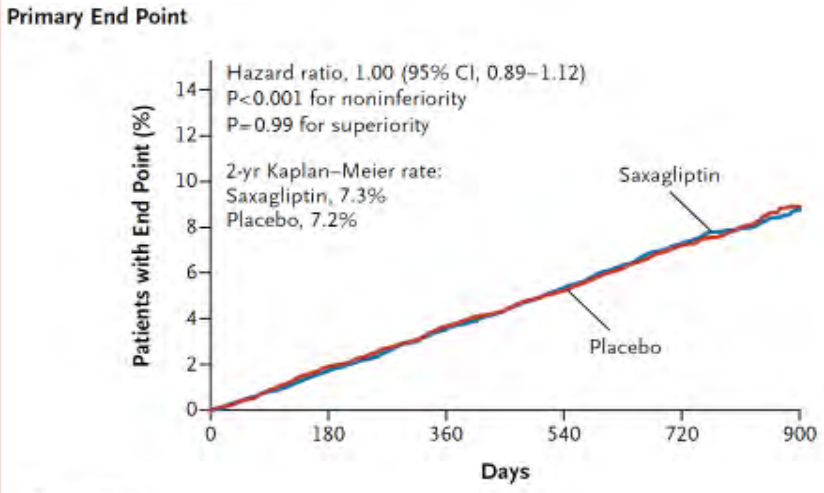
Summary of completed DPP4 inhibitor CVOTS



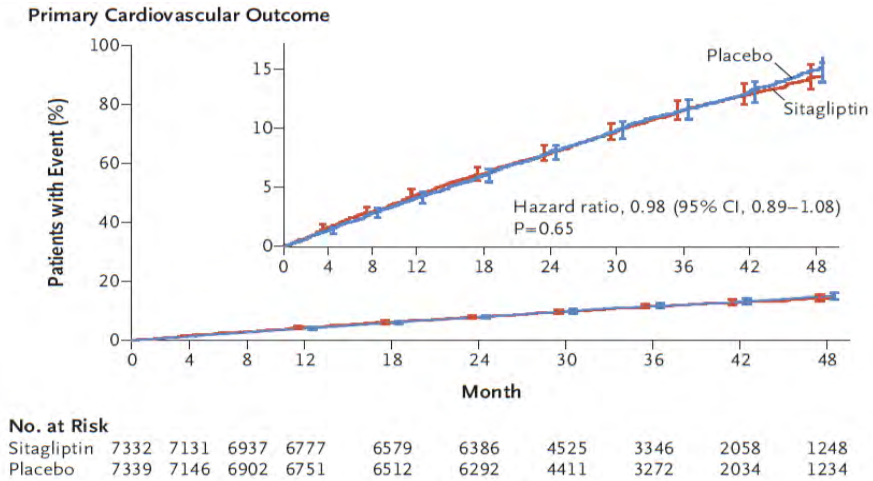
*Upper boundary of 1-sided repeated CI.

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/NEJMoa1501352.

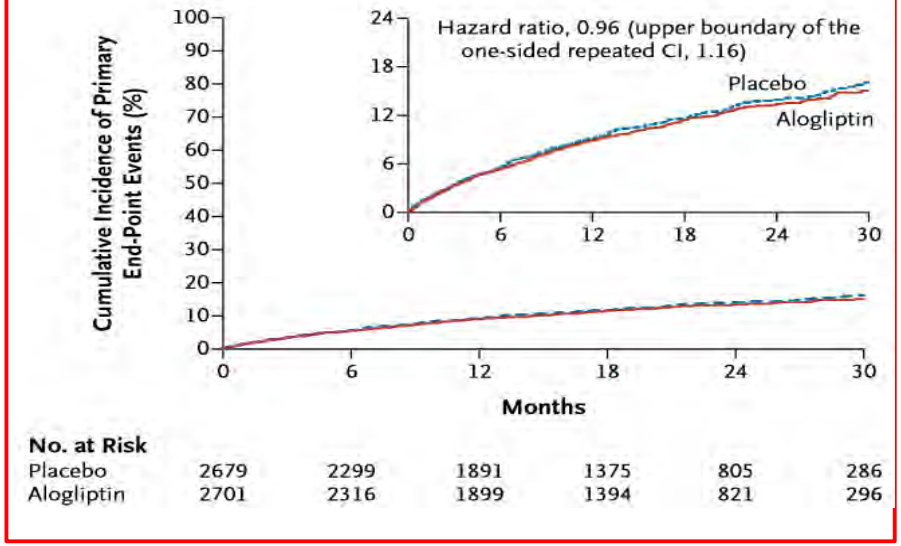
SAVOR study



TECOS study



EXAMINE study



SAVOR-TIMI 53 Saxagliptin and Cardiovascular Outcomes in T2DM Patients

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	**0.007**
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

Scirica BM et al. N Engl J Med (2013)369:1317-26

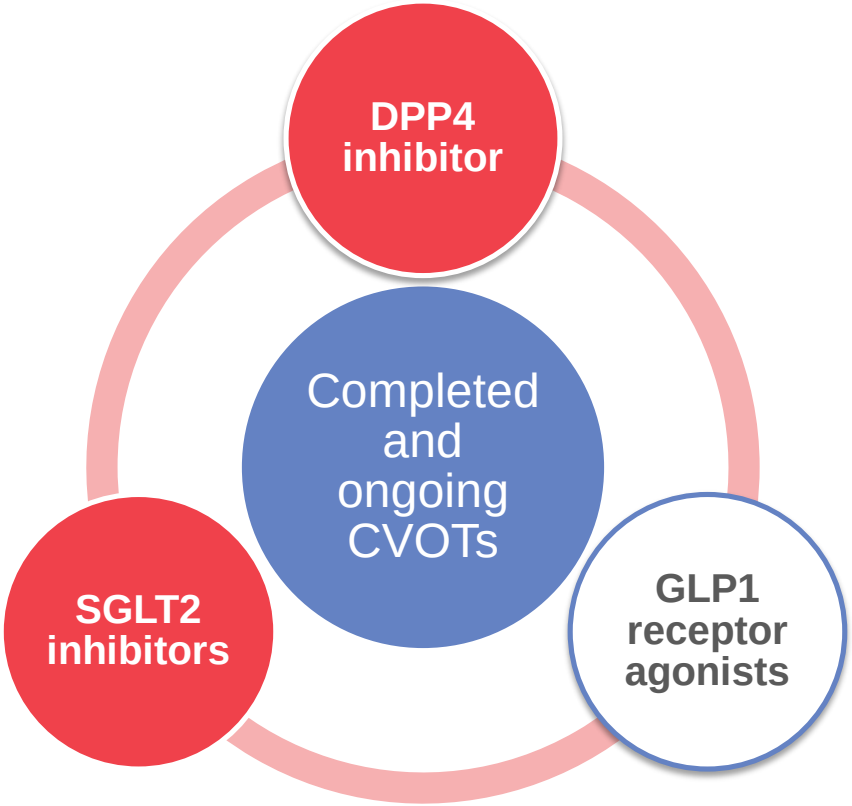
EXAMINE events by history of HF

	All patients		History of heart failure at baseline		No history of heart failure at baseline	
	Alogliptin (n=2701)	Placebo (n=2679)	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Cardiovascular death and hospital admission for heart failure	201 (7·4)	201 (7·5)	107 (13·9)	120 (15·7)	94 (4·9)	81 (4·2)
Hazard ratio (95% CI)	1·00 (0·82–1·21)		0·90 (0·70–1·17)		1·14 (0·85–1·54)	
p value	0·976		0·446		0·337	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·221	..	..	..
Cardiovascular death*	112 (4·1)	130 (4·9)	55 (7·1)	69 (9·1)	57 (3·0)	61 (3·2)
Hazard ratio (95% CI)	0·85 (0·66–1·10)		0·77 (0·54–1·09)		0·92 (0·64–1·32)	
p value	0·212		0·141		0·643	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·508	..	..	..
Hospital admission for heart failure	106 (3·9)	89 (3·3)	63 (8·2)	65 (8·5)	43 (2·2)	24 (1·3)
Hazard ratio (95% CI)	1·19 (0·90–1·58)		1·00 (0·71–1·42)		1·76 (1·07–2·90)	
p value	0·220		0·996		0·026	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·068	..	..	..

*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

Table 4: **Risk of events assessed in the post-hoc analysis, by history of heart failure**

Zannad F et al.: Lancet. 2015 Mar 9.


DPP4 inhibitor
Completed and ongoing CVOTs
SGLT2 inhibitors
GLP1 receptor agonists

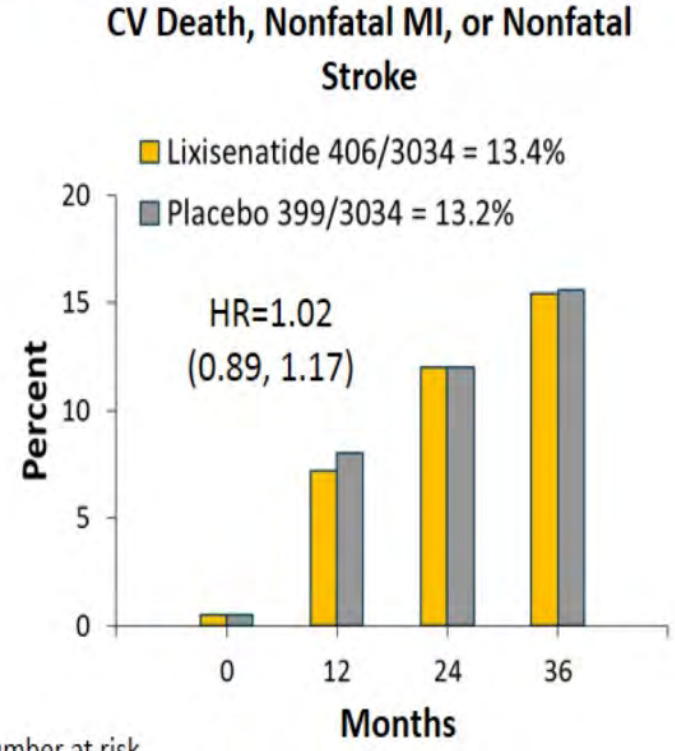
Summary of CV outcomes trials with GLP1 receptor agonists

	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
LEADER®[3]	Liraglutide/ placebo	Vascular disease, or risk factors, or CRF, or CHF	9340	3P-MACE	Expanded MACE	> 611	Up to ~5 years	Completed
SUSTAIN-6™[4]	Semaglutide/ placebo	Evidence of CV disease	3297	3P-MACE	Expanded MACE	Not specified	Up to ~3 years	Completed
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

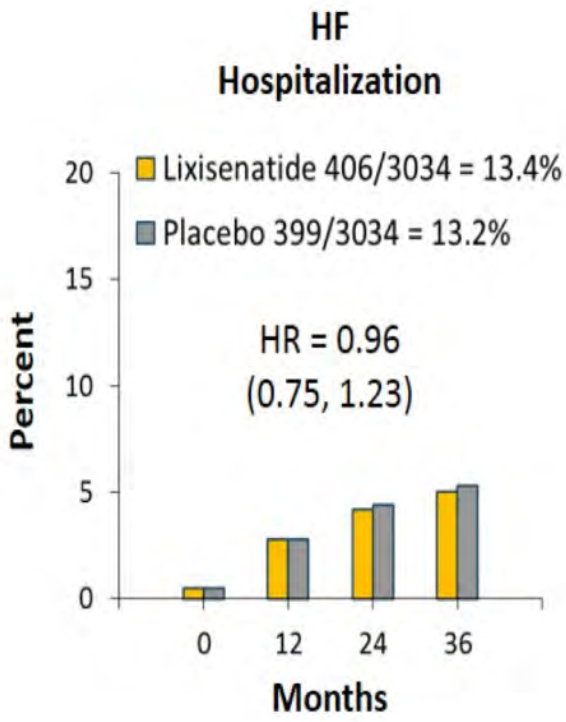
*Once weekly.

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

ELIXA: Primary and Secondary Outcomes



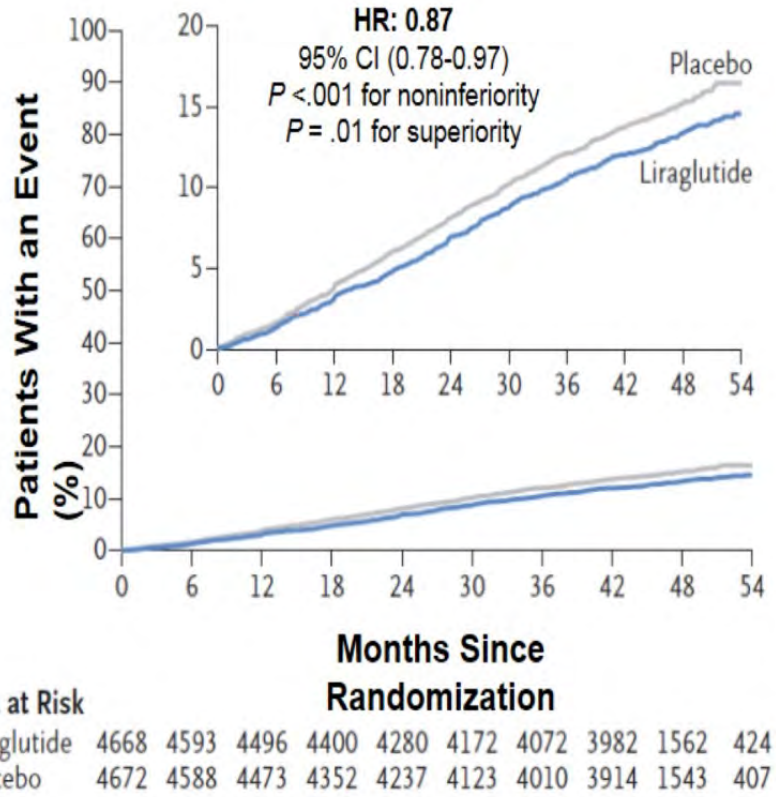
Number at risk				
Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484



- Subgroup interactions were analysed, but none were significant

Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257.

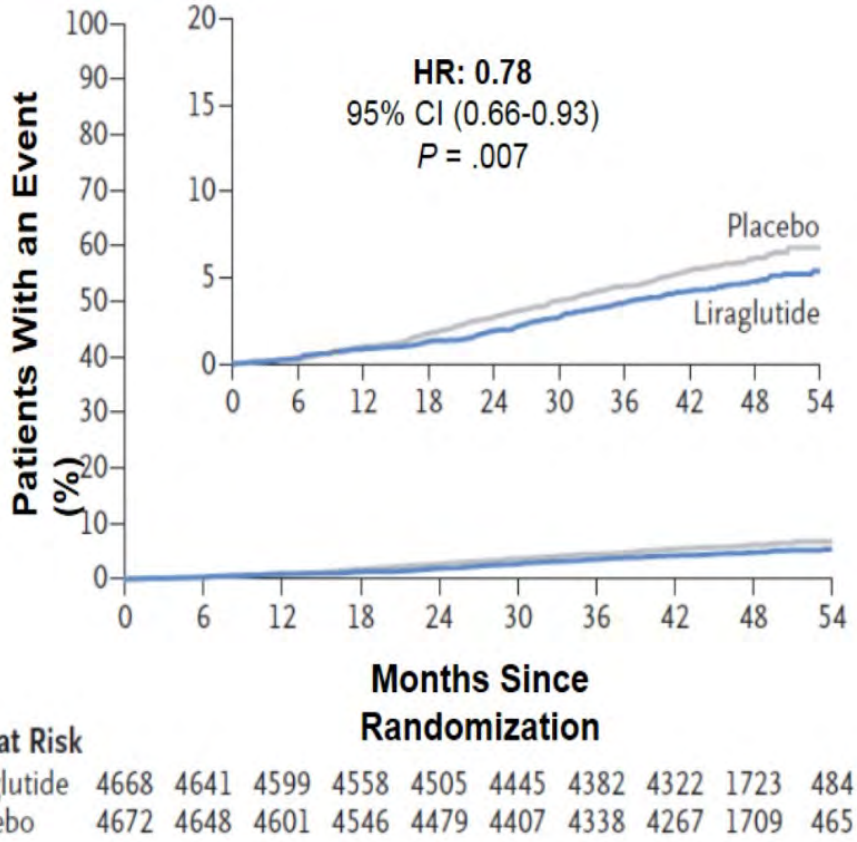
LEADER: Primary Outcome*



*3-point MACE consisting of CV death, nonfatal MI, or nonfatal stroke

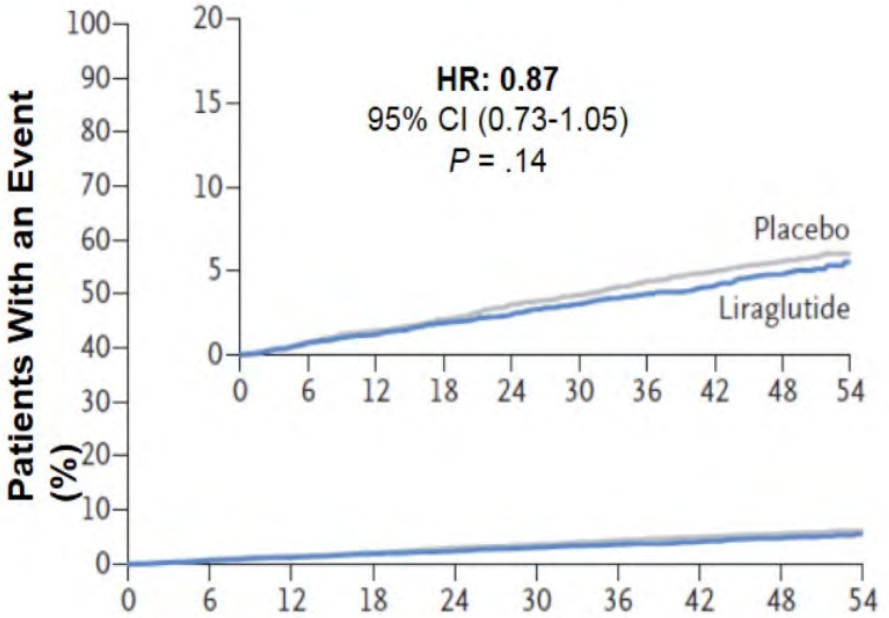
Marso SP, et al. *N Engl J Med*. 2016;375:311-322. Reprinted with permission from Massachusetts Medical Society.

LEADER: CV Death



Marso SP, et al. *N Engl J Med*. 2016;375:311-322. Reprinted with permission from Massachusetts Medical Society.

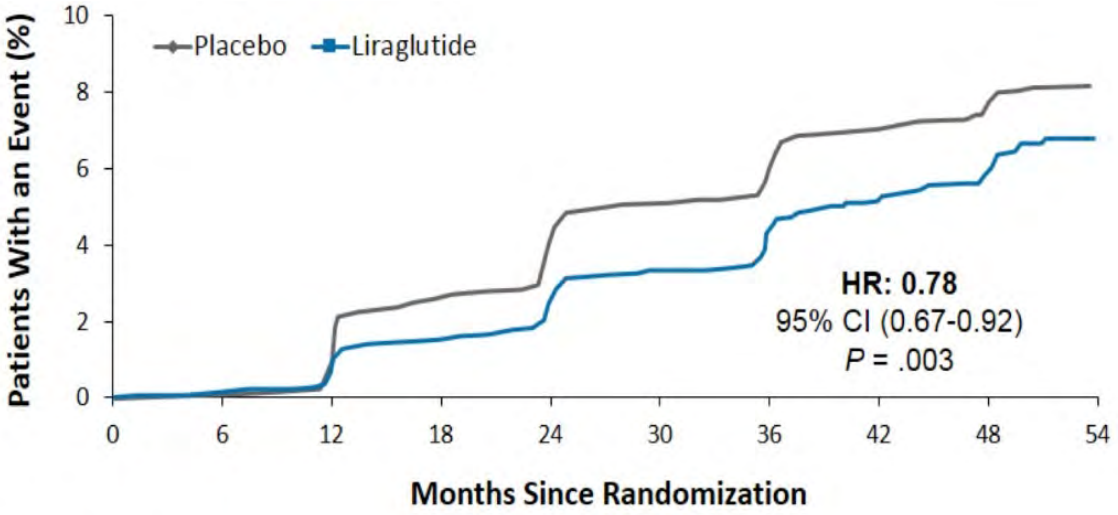
LEADER: Hospitalization for HF



No. at Risk										
Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

Marso SP, et al. *N Engl J Med*. 2016;375:311-322. Reprinted with permission from Massachusetts Medical Society.

LEADER: Time to First Renal Event*



Patients at risk

Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

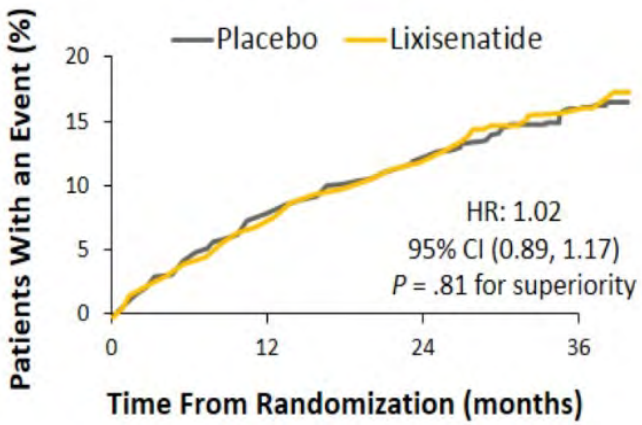
*Macroalbuminuria, doubling of serum creatinine, ESRD, or renal death

Mann JF. ADA 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA.

GLP-1 RA CVOTs: A Comparison[a]

ELIXA[b]

CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

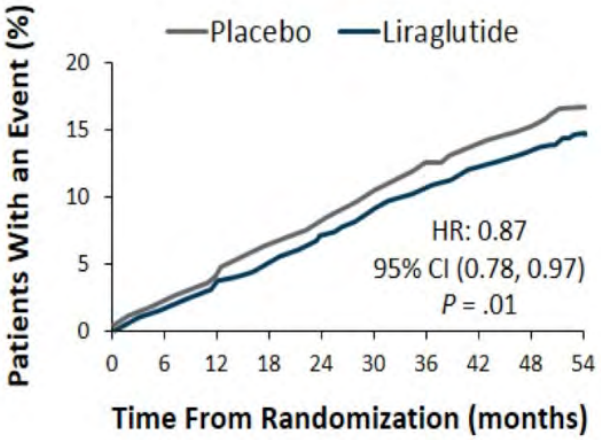


Number at risk

Lixisenatide	3034	2759	1566	476
Placebo	3034	2785	1558	484

LEADER[c]

CV death, nonfatal MI, or nonfatal stroke

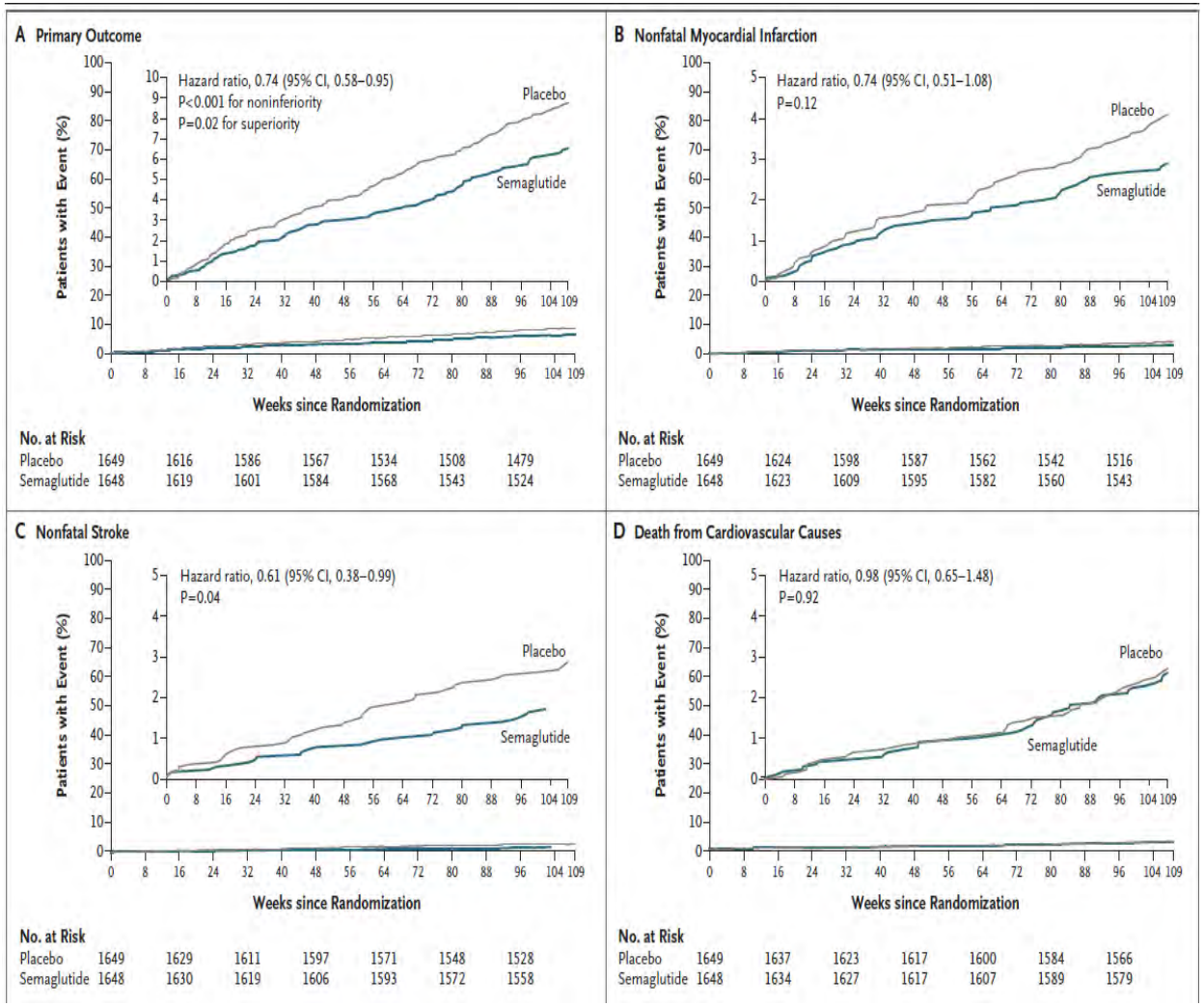


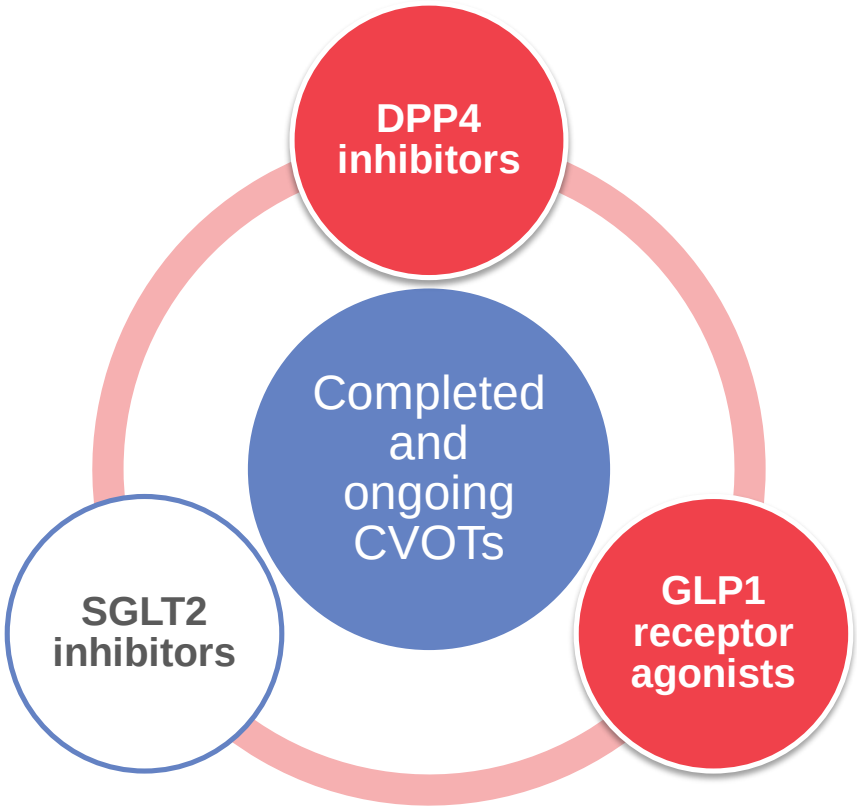
Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

a. Buse JB. ADA 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA.
b. Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257
c. Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes




DPP4 inhibitors
Completed and ongoing CVOTs
SGLT2 inhibitors
GLP1 receptor agonists

Summary of CV outcome trials with SGLT2 inhibitors

	EMPA-REG OUTCOME®[1]	CANVAS[2]	CANVAS-R[3]	CREDENCE[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	Completed	Apr 2017	2017	2019	2019	2021

ACROSS T2D
The Academy for Cardiovascular Risk, Outcomes and Safety Studies in Type 2 Diabetes

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

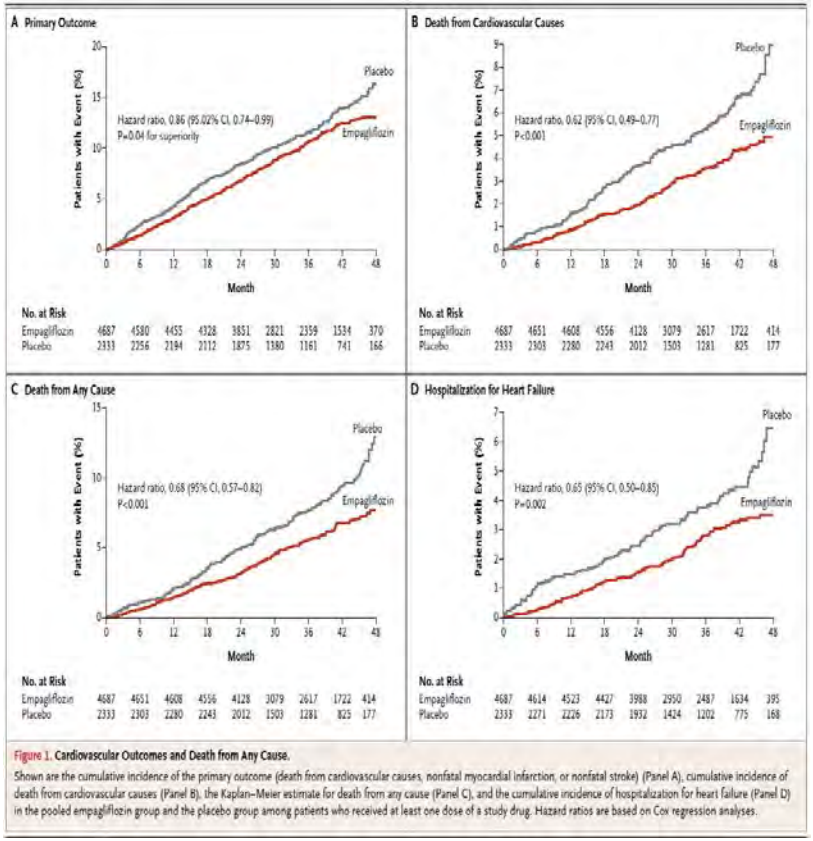


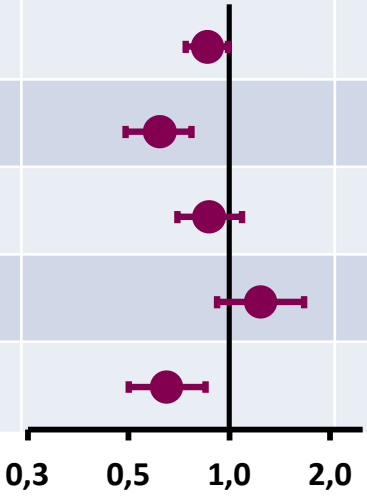
Figure 1. **Cardiovascular Outcomes and Death from Any Cause.**

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

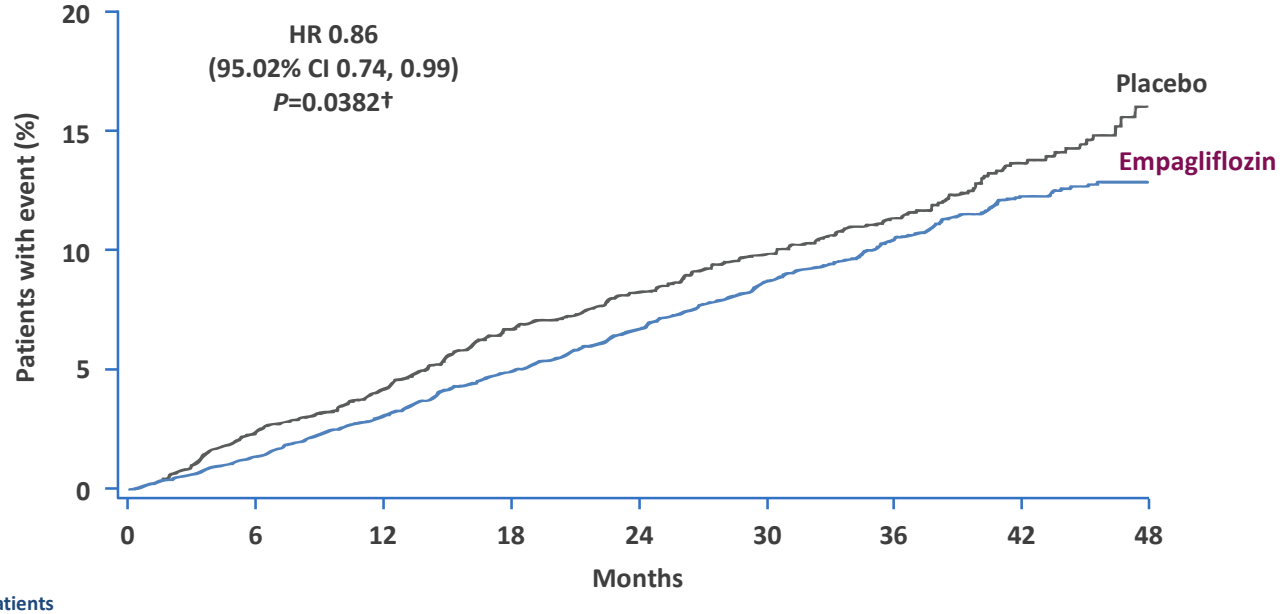
N Engl J Med 2015;373:2117-28.

EMPA-REG OUTCOME: Empagliflozin Improved CV Outcomes in Patients with T2DM

Outcome	Patients with event / analyzed		Hazard ratio	95% CI		*P* value
	Empagliflozin	Placebo				
3-point MACE	490/4687	282/2333	0.86	0.74, 0.99*		0.0382
CV death	172/4687	137/2333	0.62	0.49, 0.77		<0.0001
Nonfatal MI	213/4687	121/2333	0.87	0.70, 1.09		0.2189
Nonfatal stroke	150/4687	60/2333	1.24	0.92, 1.67		0.1638
Hospitalization for heart failure	126/4687	95/2333	0.65	0.50, 0.85		0.0017



Primary End Point: 3P-MACE*



No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

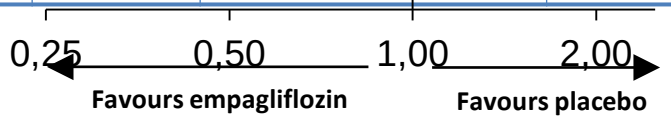
Cumulative incidence function. MACE=Major Adverse Cardiovascular Event; HR=hazard ratio.

* *CV death, nonfatal MI, nonfatal stroke*

† Two sided tests for superiority were conducted (statistics of significance was indicated if *P*=0.0498)

3P-MACE* and 4-P MACE

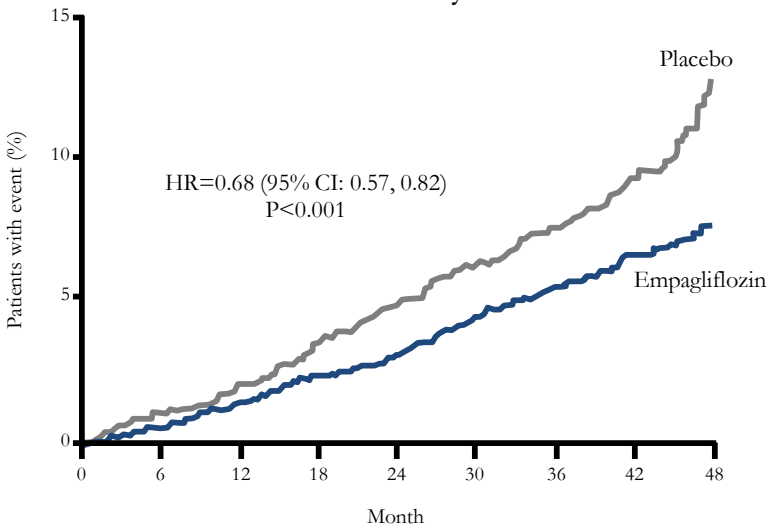
	Patients with event/analysed					*P*-value
	Empagliflozin	Placebo	HR	(95% CI)		
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*		0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)		<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)		0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)		0.1638
4-point MACE	599/4687	333/2333	0.89	(0.78, 1.01)*		0.0795



Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

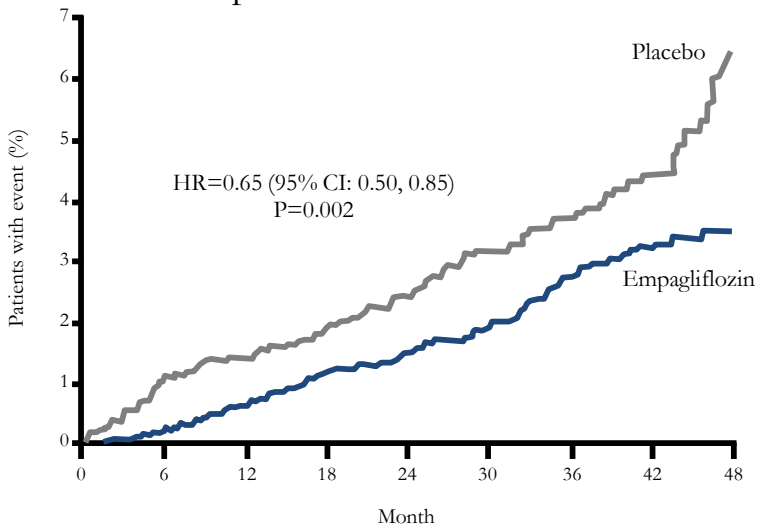
EMPA-REG OUTCOME: Empagliflozin and CV Outcomes

Death from any cause



No. at risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

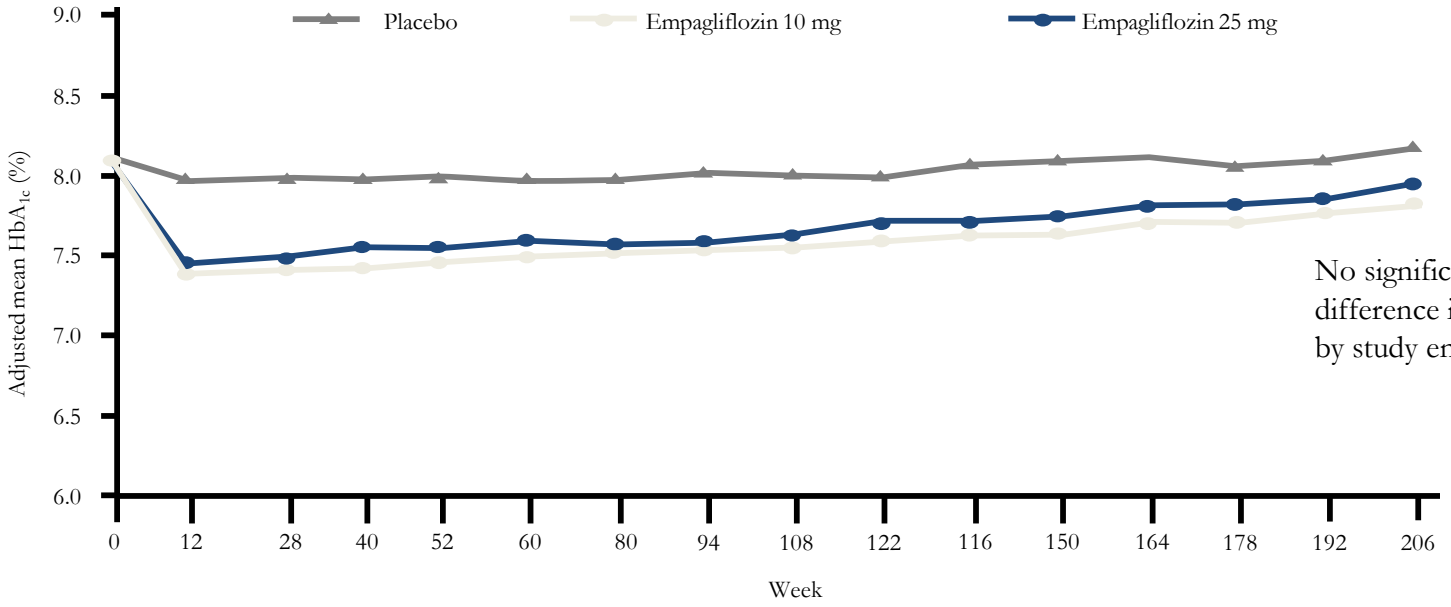
Hospitalization for heart failure



No. at risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Zinman B, et al. *N Engl J Med* 2015;373:2217–2128

Cardioprotective Results From EMPA-REG are Likely to be Unrelated to Glycemic Control

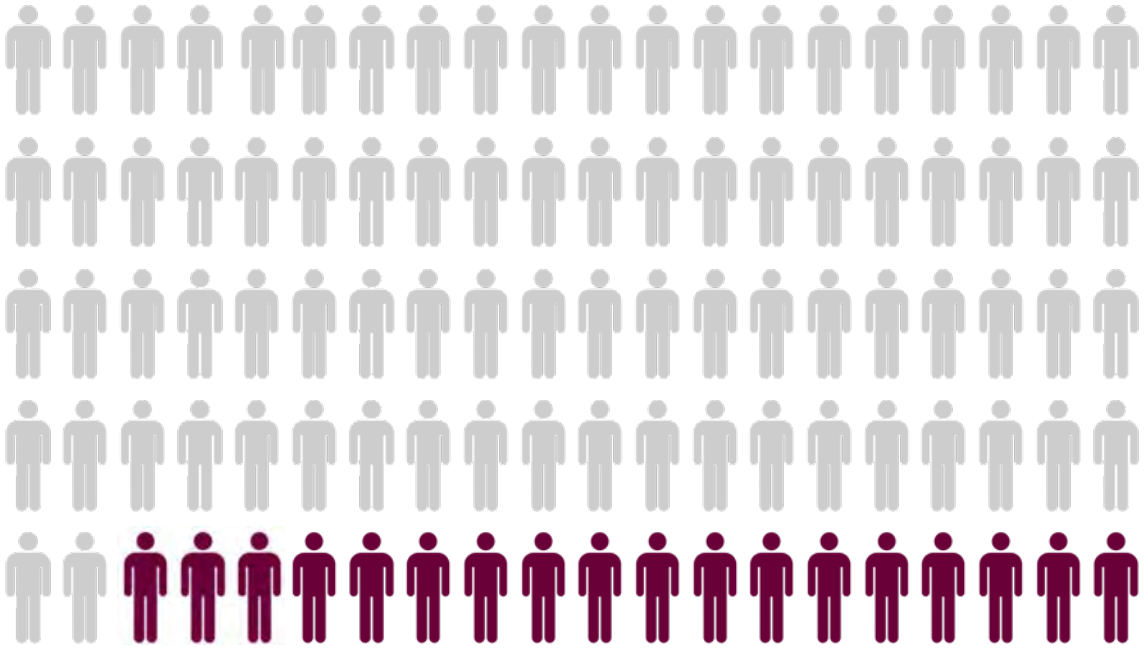


No significant difference in HbA_{1c} by study end

No. at risk																
Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

Zinman B, et al. *N Engl J Med* 2015;373:2217–2128

How Applicable Might the EMPA-REG Results Be To The General Population of Patients with T2DM?



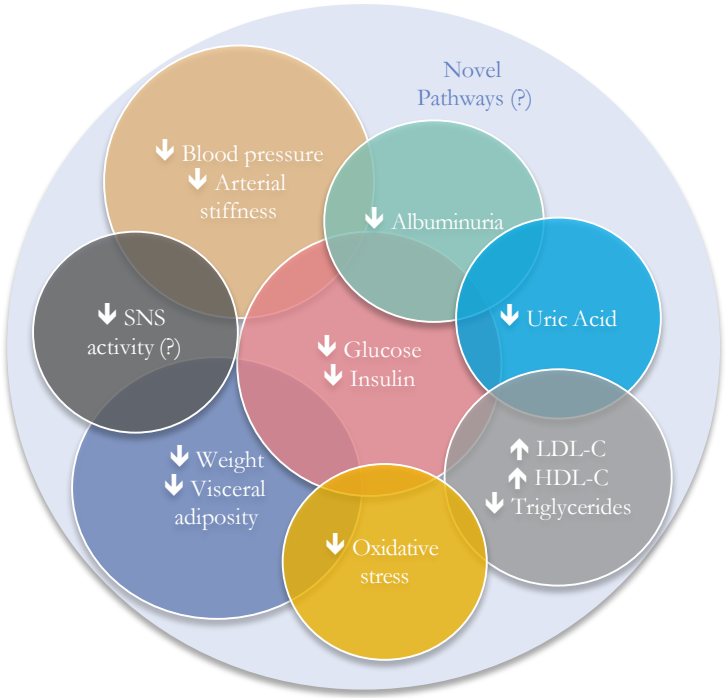
17.9% of patients with T2DM had a first CV presentation

CV, cardiovascular; EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus; T2DM, Type 2 diabetes mellitus

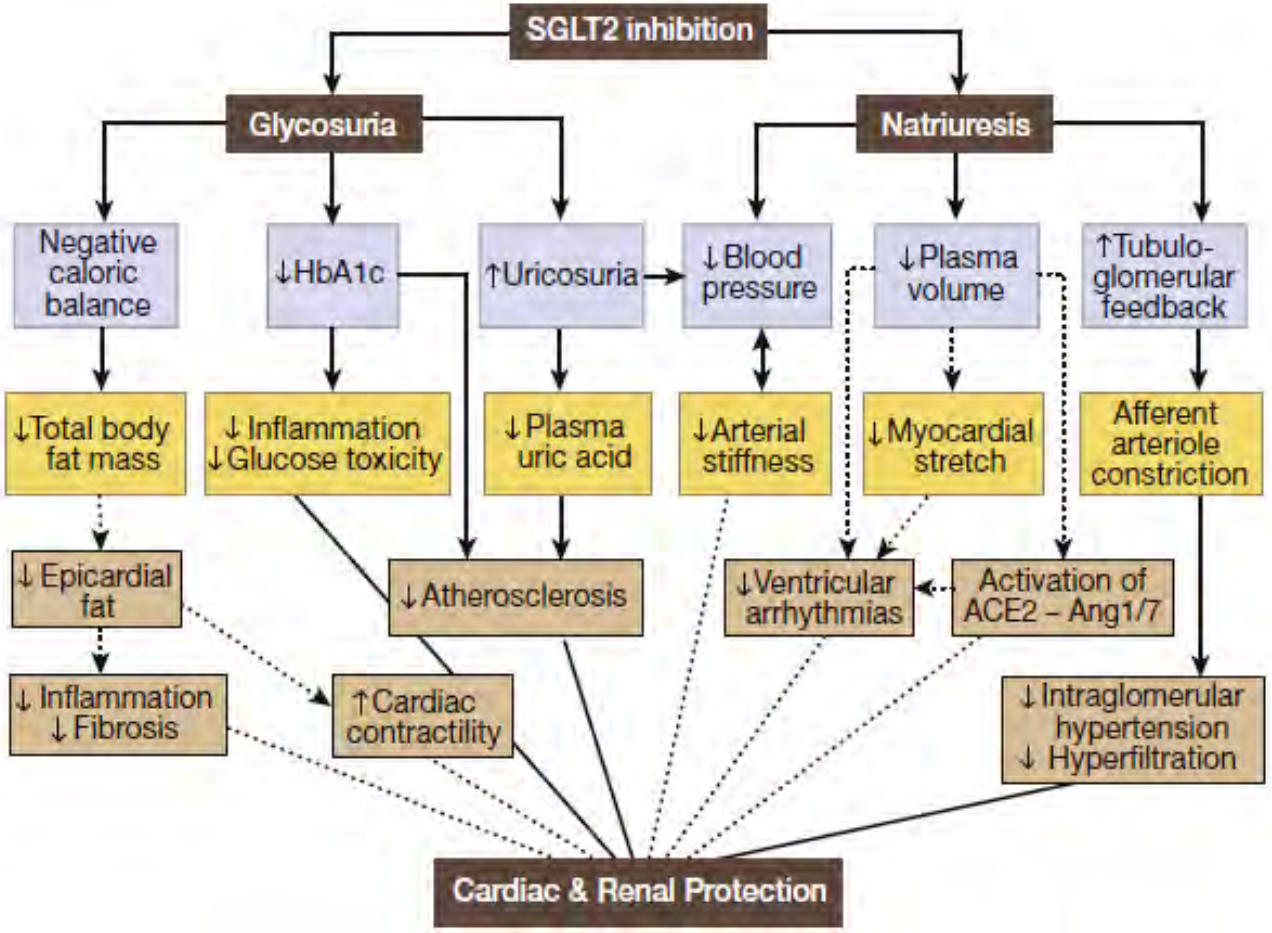
Shah AD, et al. *Lancet Diabetes Endcrinol* 2015;3:105–113

SGLT2 inhibitors modulate a range of factors related to CV risk

Based on clinical and mechanistic studies

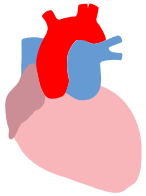


Inzucchi et al. Diab Vasc Dis Res 2015;12:90–100.



Rajasekeran, Harindra et al. Kidney International , Volume 89 , Issue 3 , 524 - 526

Super-fuel Hypothesis: Shift in Fuel Metabolism with SGLT2i



Improvements in …

- Myocardial energy substrate metabolism
- Myocardial contractility
- Cardiac efficiency

→ … by shifting to a more energy-efficient fuel: ketone bodies instead of fatty acids / glucose

Mudaliar S, et al. Diabetes Care 2016;39:1115–1122

The lesson of the cardiovascular outcome trials

- All trials on DPP4 inhibitors (SAVOR, EXAMINE, TECOS) have achieved the primary endpoint of safety. In the SAVOR study was observed an increase in hospitalizations for heart failure in patients treated with saxagliptin, despite not being observed an increase in death from CV causes. This has led to further analysis in observational studies and meta-analyzes that have finally concluded the effect neutrality of DPP4 inhibitors in risk of HF.
- The ELIXA study with lixisenatide showed neutrality on CV outcomes, no increase in the risk of hospitalizations for heart failure.
- The LEADER study with liraglutide showed superiority on CV outcomes, no increase in the risk of hospitalizations for heart failure.
- The EMPA-REG and LEADER trials support the use of empagliflozin or liraglutide in patients who have previous CV or MACE diseases
- So far between the two GLP1 RA evaluated in CV outcomes trial, only liraglutide and not lixisenatide showed a cardioprotective effect but before concluding that it is a specific drug effect is to assess differences in the population of patients between the two studies and design of these, waiting to have the results of ongoing trials of other GLP1 RA.
- Patients with renal impairment are those who have benefited most of the treatments with empagliflozin and liraglutide.

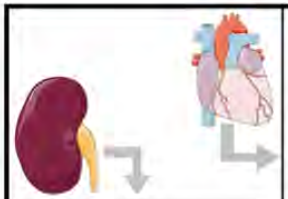
Novel antidiabetic drugs and cardiovascular risk: Primum non nocere. Bonadonna RC, Borghi C, Consoli A, Volpe M. Nutr Metab Cardiovasc Dis. 2016 Sep;26(9):759-66.

Conclusions

- FDA guidance from 2008 requests CV outcome trials (CVOTs) to demonstrate CV safety of all new glucose-lowering compounds[1]
- CVOTs designed to assess impact of drugs on CV outcomes (MACE) vs placebo on top of usual care for glucose and CV risk factor management
  - Not designed to assess impact of differences between treatment arms in, for example, HbA_{1c} on CV outcomes
- Completed CVOTs in DPP4 inhibitor and GLP1 class report neutral or superior effects on CV outcomes confirming CV safety as defined by FDA[2-6]
- Ongoing CVOTs will provide further clarity on the CV safety of individual glucose-lowering agents

1. FDA Guidance for Industry. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf.
2. Scirica et al. N Engl J Med 2013;369:1317–26. 3. White et al. N Engl J Med 2013;369:1327–35.
4. Zannad et al. Lancet 2015;385:2067–76. 5. Green et al. N Engl J Med 2015; DOI: 10.1056/NEJMoa1501352.
6. Pfeffer et al. ADA, 8 Jun 2015, Boston, USA (oral presentation).

Comorbidities-driven treatment



	Normal or subclinical **ENDOTHELIAL DYSFUNCTION**	**ESTABLISHED ATHERO-SCLEROSIS**	**ACUTE CORONARY SYNDROME**	**HEART FAILURE**
Stage I-II CKD **eGFR 90-60 ml/min/1.73 m²**	Metformin[a], Pioglitazone[b] DPP4-I[c-e], GLP-1 RA[f], SGLT2-I[g], Insulin[1h] SUs[1]	Metformin, SGLT2-I[g], GLP-1RA[f], Pioglitazone[b], DPP4-I[c-e], Insulin[h], Gliclazide[k]	Insulin[m] DPP4-I[e], GLP-1RA[j],	SLGT2-I[g] DPP4-I[d,e], GLP-1RA[f], Insulin[h]
Stage III CKD **eGFR 59-30 ml/min/1.73 m²**	Metformin[2], Pioglitazone[3b], SLGT2-I[4g], GLP-1RA[f], DPP4-I[2c-e], Gliclazide[2k], Insulin[h]	Metformin[2], GLP-1RA[f], SGLT2-I[4g], Pioglitazone[3b], DPP4-I[2c-e], Insulin[h], Gliclazide[2k]	Insulin[m] DPP4-I[e], GLP-1RA[j],	SLGT2-I[g] DPP4-I[d,e], GLP-1RA[f], Insulin[h]
Stage IV CKD **eGFR 29-15 ml/min/1.73 m²**	Pioglitazone[3], DPP4-I[2], Insulin[2]	Pioglitazone[3], DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]
Stage V CKD **eGFR <15 ml/min/1.73 m²**	Pioglitazone[3], DPP4-I[2], Insulin[2]	Pioglitazone[3], DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]

Evidence of efficacy **Evidence of safety** **Author consensus**

Fig. 1 A treatment algorithm based on cardiac and renal co-morbidities and CVOTs. [1]To be used with caution because of the risk of hypoglycemia; [2]consider dose reduction (except for linagliptin) and monitor eGFR frequently; [3]preferred in the presence of marked insulin resistance; [4]initiation of therapy currently not recommended. [a]UKPDS; [b]PROACTIVE trial; [c]SAVOR; [d]TECOS, [e]EXAMINE; [f]LEADER trial; [g]EMPA-REG Outcome trial; [h]ORIGIN trial; [k]ADVANCE; [j]ELIXA; [m]DIGAMI 1

Grazie per l’attenzione!