Terapia farmacologica: I nuovi farmaci, opportunità e criticità. "Dai grandi trial alla real Life"

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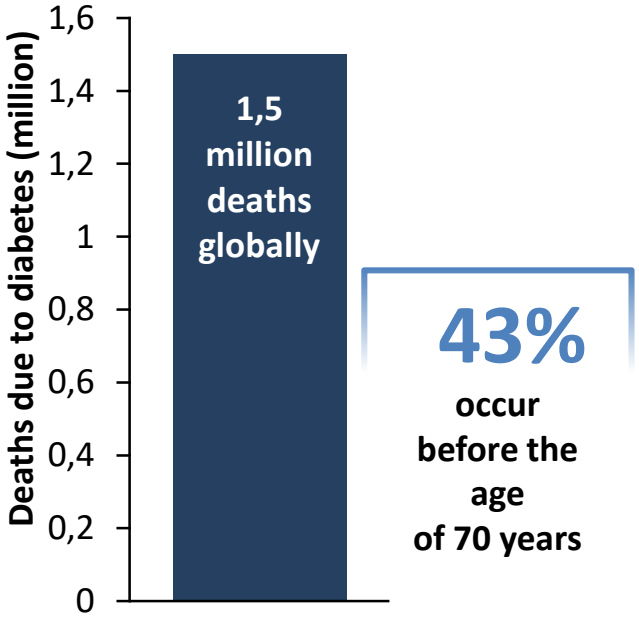
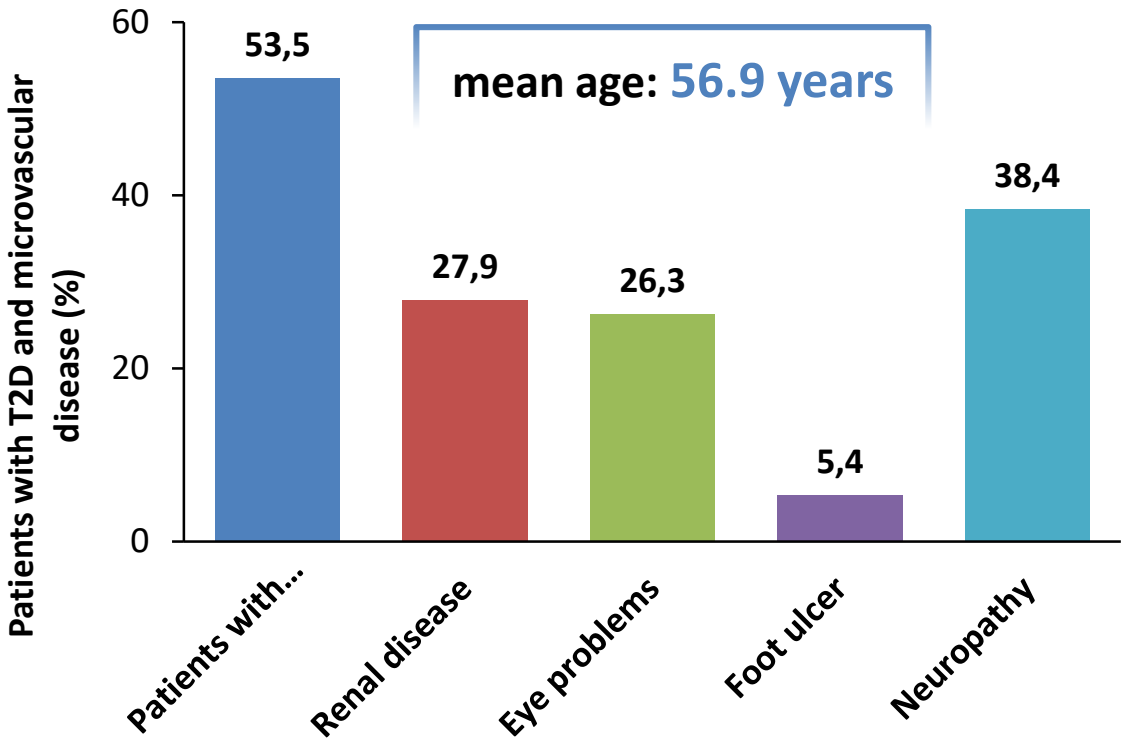
Type 2 diabetes is a major cause of mortality and morbidity

Global deaths due to diabetes[1]



Patients with type 2 diabetes and microvascular complications: A$_1$chieve study (N=66,276)[2,a]

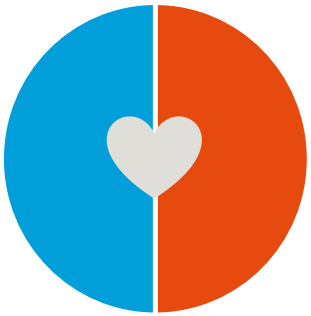


1. World Health Organization. 2016. http://www.who.int/diabetes/global-report/en/ Accessed July 20, 2018; 2. Litwak L, et al. *Diabetol Metab Syndr* 2013;5:57.

Le malattie cardiovascolari (MCV) rappresentano una causa principale di morbilità e mortalità fra le persone con diabete (DM)

OLTRE
2×
AUMENTATO RISCHIO DI MORTE
PER CAUSE CARDIOVASCOLARI[1]

FINO A
4×
AUMENTATO RISCHIO DI INFARTO E ICTUS[2,3]



50-60%
DEI DECESSI
ATTRIBUIBILI ALLE MCV[4,5]

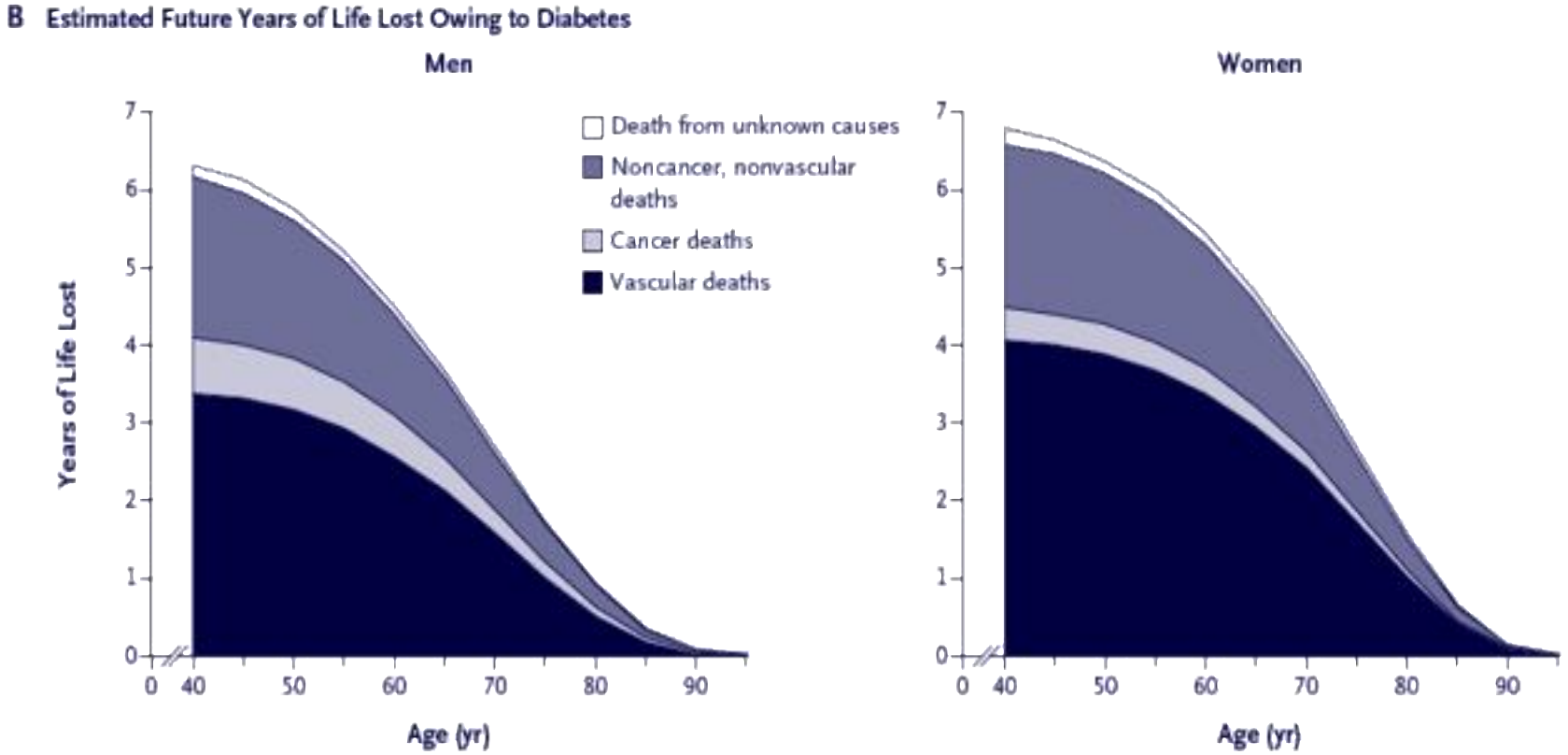
Le persone con diabete vivono fino a

6
anni

di meno rispetto a persone senza diabete nella stessa fascia di rischio[1]

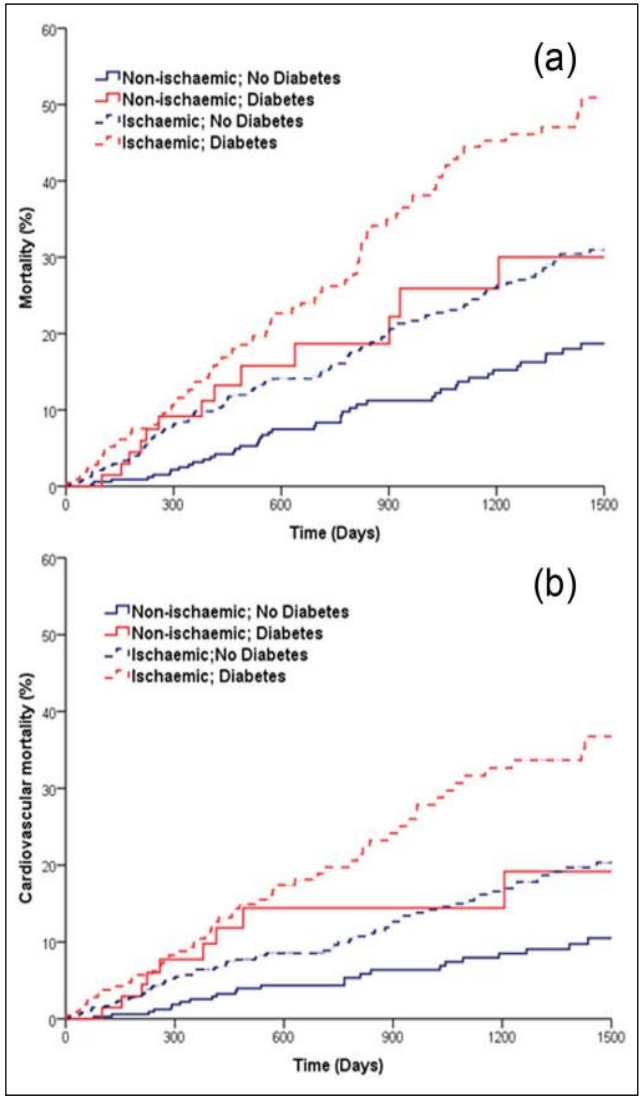
1. Seshasai *et al*. *N Engl J Med* 2011;364:829–841; 2. Folsom *et al*. *Diabetes Care* 1999;22:1077–83; 3. Huxley *et al*. *BMJ* 2006;332:73–8; 4. IDF. Diabetes Atlas. 2015. 5. WHO - Global Atlas on Cardiovascular Diseases Prevention and Control

Il diabete riduce l'aspettativa di vita

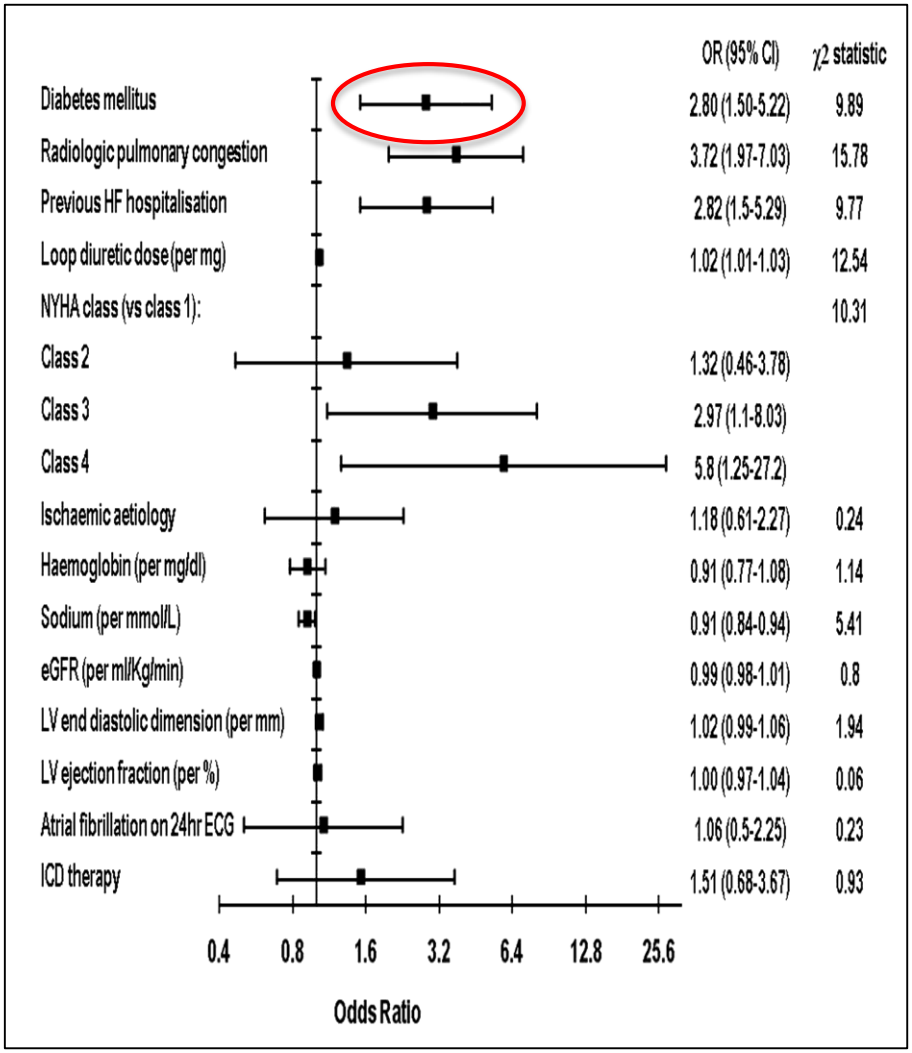


Seshasai *et al*. *N Engl J Med* 2011;364:829–841

Type 2 diabetes is a potent, independent risk factor for heart failure



Cubbon RM et al. *Diab Vasc Dis Res* 2013;**10**:330 – 336.



Cubbon RM et al. *Heart* 2014;**100**:923–929

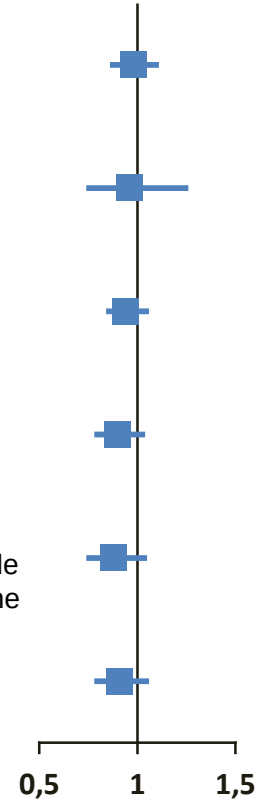
‘Classic’ studies in patients with type 2 diabetes have demonstrated that tight glycemic control improves microvascular outcomes

Outcome	Trials							
	UKPDS[1,2] (n=3867)		ADVANCE[3,4] (n=11,140)		VADT[5] (n=1791)		ACCORD[6–9] (n=10,251)	
	In-trial 10 years	Including extension 20 years	In-trial 5 years	Including extension 10 years	In-trial 5.6 years	Including extension 9.8 years	In-trial 4–5 years	Including extension 8 years
All microvascular	↓	↓	↓	–	–	–	↔	–
Nephropathy	↓	–	↓	↓ (ESRD)	↓	–	↓	–
Neuropathy	↔	–	↑	–	↔	–	↓	–
Retinopathy	↓	–	↓	–	↓	–	↓	↓

1. UKPDS 33. *Lancet* 1998;352:837–853; 2. Holman RR, et al. *N Engl J Med* 2008;359:1577–1589; 3. ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572; 4. Wong MG, et al. *Diabetes Care* 2016;pii:dc152322; 5. Duckworth W, et al. *N Engl J Med* 2009;360:129–139; 6. ACCORD Study Group. *N Engl J Med* 2008;358:
2545–2559; 7. Ismail-Beigi F, et al. *Lancet* 2010;376:419–430; 8. ACCORD Study Group and ACCORD Eye Study Group. *N Engl J Med* 2010;363:233–244;
9. ACCORDION Eye Study Group and ACCORDION Study Group. *Diabetes Care* 2016; doi:10.2337/dc16-0024

‘Older’ glucose-lowering agents have not definitively shown positive effects on major CV events …

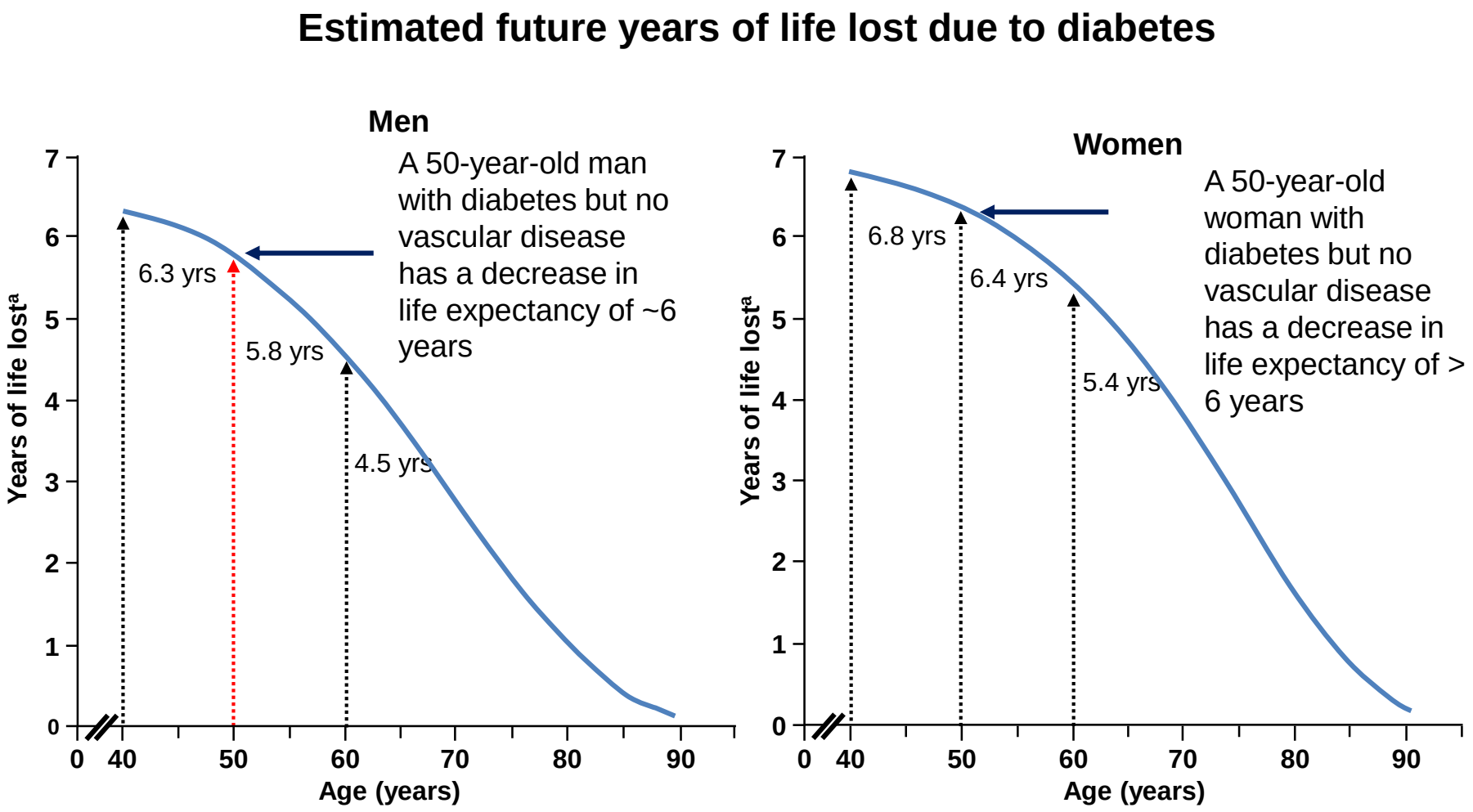
Trial	Outcome	HR (95% CI)
ACE (N=6522)[1] **Acarbose versus placebo + CV prevention therapy**	5P-MACE: CV death, NF-MI, NF-stroke, hUA, hHF	0.98 (0.86, 1.11)
TOSCA.IT (N=3,028)[2] **PIO versus SU as add-on to MET**	All-cause death, NF-MI, silent MI, NF-stroke, urgent coronary revascularization	0.96 (0.74, 1.26)
ADVANCE (N=11,140)[3] **HbA_{1c} ≤6.5% versus HbA_{1c} >6.5% (gliclazide + any other agent)**	3P-MACE: CV death, NF-MI, NF-stroke	0.94 (0.84, 1.06)
ACCORD (N=10,251)[4] **HbA_{1c} <6.0% versus HbA_{1c} 7.0–7.9% (MET, SU, TZD, insulin)**	3P-MACE: CV death, NF-MI, NF-stroke	0.90 (0.78, 1.04)
VADT (N=1791)[5] **HbA_{1c} –1.5% versus the standard group (MET or GLIM, ROSI, insulin)**	7P-MACE: CV death, MI, stroke, HF, surgery for vascular disease, inoperable CHD, amputation for ischemic gangrene	0.88 (0.74, 1.05)
DEVOTE (N=7367)[6] **IGlar versus IDeg**	3P-MACE: CV death, NF-MI, NF-stroke	0.91 (0.78, 1.06)



CI, confidence interval; CV, cardiovascular; GLIM, glimepiride; HR, hazard ratio; MACE, major adverse cardiovascular event; hHF, hospitalization for heart failure;
HF, heart failure; hUA, hospitalization for unstable angina; MET, metformin; NF, non-fatal; PIO, pioglitazone; ROSI, rosiglitazone; SU, sulfonylurea; TZD, thiazolidinedione

1. Holman RR, et al. *Lancet Diabetes Endocrinol* 2017; doi: 10.1016/S2213-8587(17)30318-2; 2. Vaccaro O, et al. *Lancet Diabetes Endocrinol* 2017;5:887–897;
3. ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560–2572; 4. The ACCORD Study Group. *N Engl J Med* 2008;358:2545–2559;
5. Duckworth W, et al. *N Engl J Med* 2009;360:129–139; 6. Marso SP, et al. *N Engl J Med* 2017;377:723–732

However, type 2 diabetes continues to be associated with a decrease in life expectancy from CV causes

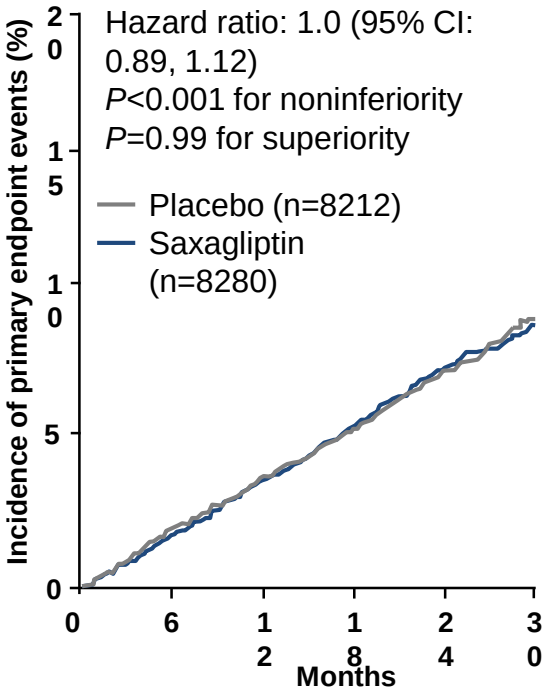


Seshasai et al. N Engl J Med 2011;364:829-41

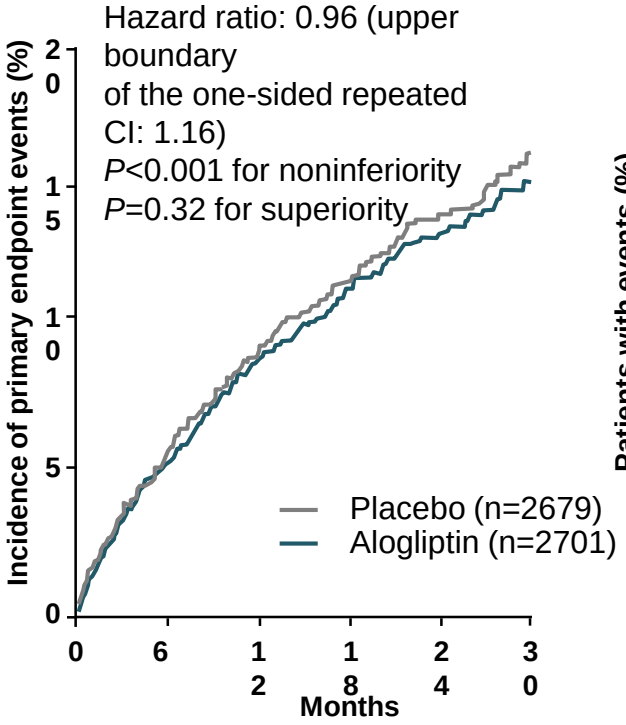
DPP-4 inhibitors were largely CV neutral

Saxagliptin (SAVOR trial)[1] Alogliptin (EXAMINE trial)[2] Sitagliptin (TECOS trial)[3]

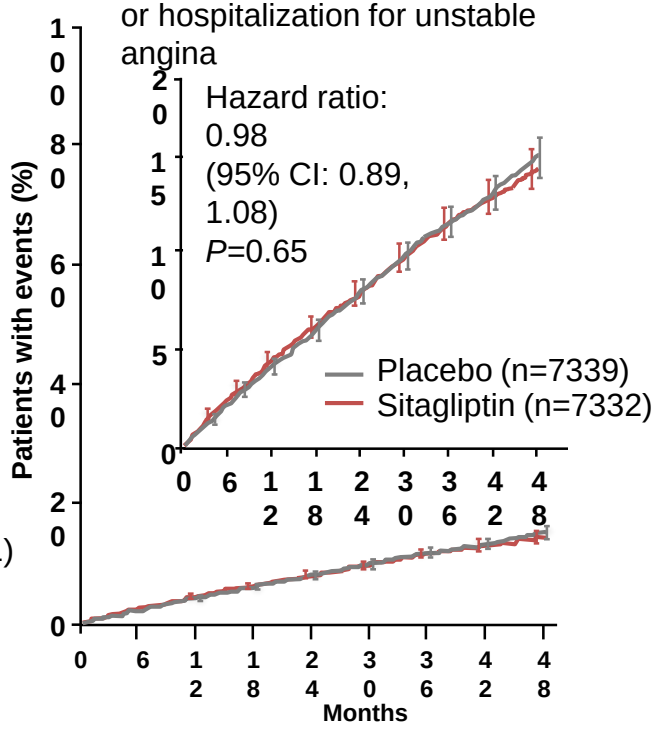
Primary endpoint: Composite of CV death, myocardial infarction, or ischemic stroke



Primary endpoint: Composite of CV death, nonfatal myocardial infarction, or nonfatal stroke



Primary endpoint: Composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina



CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

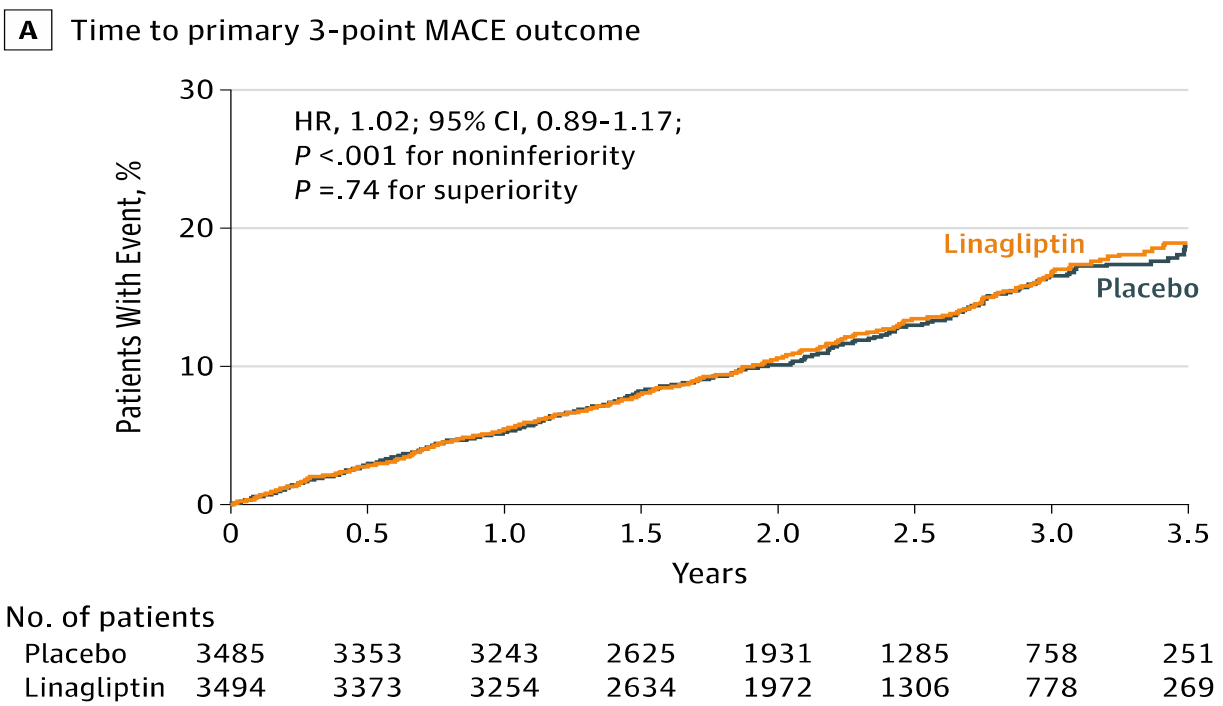
1. Adapted from Scirica B, et al. *N Engl J Med* 2013;369:1317–1326; 2. Adapted from White W, et al. *N Engl J Med* 2013;369:1327−1335;
3. Adapted from Green JB, et al. *N Engl J Med* 2015;373:232–242

Rosenstock J et al. JAMA. 2018 Nov 9. doi: 10.1001/jama.2018.18269

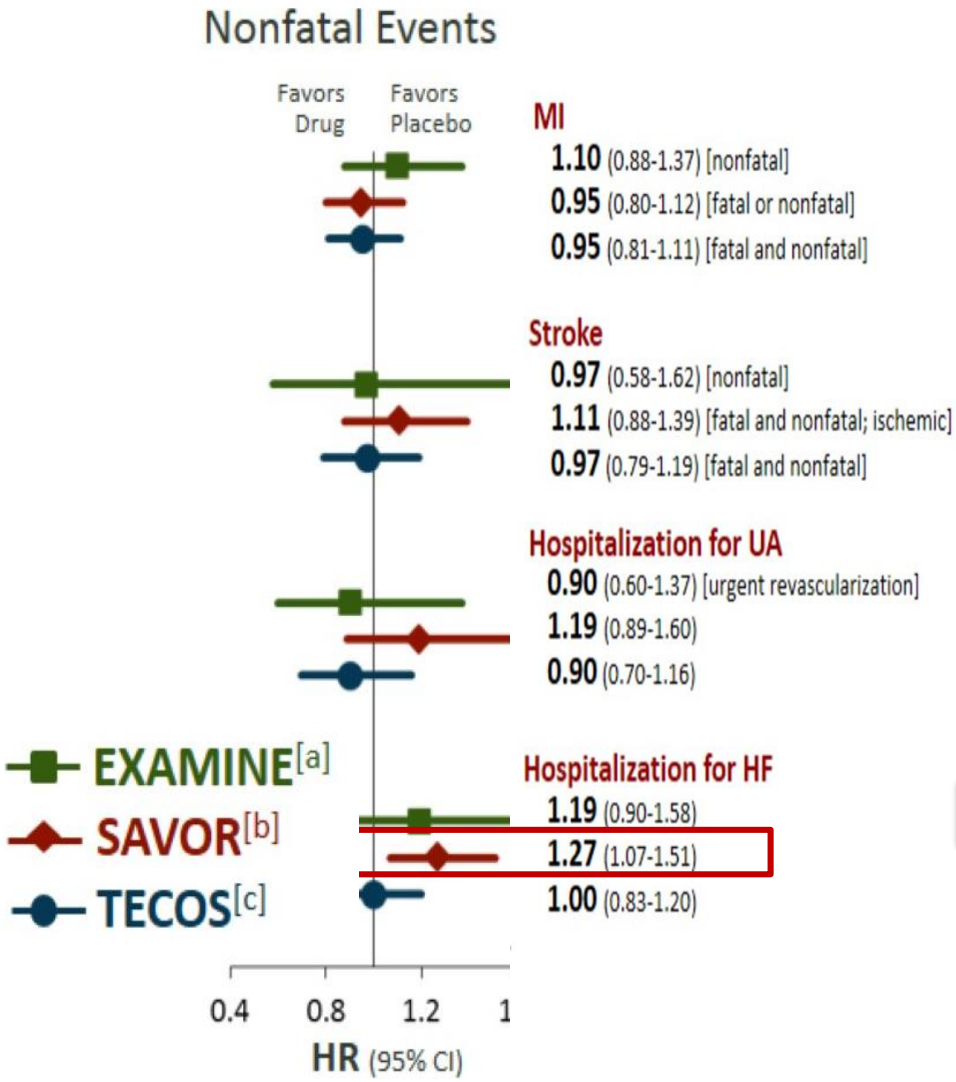
Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk

The CARMELINA Randomized Clinical Trial

Figure 2. Time to Primary and Secondary Outcomes



DPP-4 inibitori e Scompenso Cardiaco



CARMELINA

Exploratory Cardiovascular and Death Outcomes							
All-cause death	367 (10.5)	4.69	373 (10.7)	4.80	−0.11 (−0.79 to 0.58)	0.98 (0.84-1.13)	.74
Cardiovascular death	255 (7.3)	3.26	264 (7.6)	3.40	−0.14 (−0.71 to 0.44).	0.96 (0.81-1.14)	.63
Noncardiovascular death	112 (3.2)	1.43	109 (3.1)	1.40	0.03 (−0.34 to 0.40)	1.02 (0.78-1.33)	.89
Fatal myocardial infarction	11 (0.3)	0.14	14 (0.4)	0.18	−0.04 (−0.17 to 0.09)	0.78 (0.36-1.72)	.54
Nonfatal myocardial infarction	156 (4.5)	2.06	135 (3.9)	1.80	0.27 (−0.18 to 0.71)	1.15 (0.91-1.45)	.23
Fatal or nonfatal myocardial infarction	165 (4.7)	2.18	146 (4.2)	1.94	0.24 (−0.22 to 0.70)	1.12 (0.90-1.40)	.30
Fatal stroke	17 (0.5)	0.22	16 (0.5)	0.21	0.01 (−0.13 to 0.16)	1.05 (0.53-2.09)	.88
Nonfatal stroke	65 (1.9)	0.85	73 (2.1)	0.96	−0.12 (−0.42 to 0.19)	0.88 (0.63-1.23)	.45
Fatal or nonfatal stroke	81 (2.3)	1.06	88 (2.5)	1.16	−0.11 (−0.44 to 0.23)	0.91 (0.67-1.23)	.53
4-point MACE (3-point MACE plus hospitalization for unstable angina)	463 (13.3)	6.20	459 (13.2)	6.21	−0.02 (−0.82 to 0.79)	1.00 (0.88-1.13)	.96
Hospitalization for unstable angina	42 (1.2)	0.55	48 (1.4)	0.63	−0.09 (−0.33 to 0.16)	0.87 (0.57-1.31)	.50
Coronary revascularization procedure	160 (4.6)	2.12	149 (4.3)	1.99	0.13 (−0.33 to 0.59)	1.07 (0.85-1.33)	.57
Hospitalization for heart failure	209 (6.0)	2.77	226 (6.5)	3.04	−0.27 (−0.82 to 0.28)	0.90 (0.74-1.08)	.26

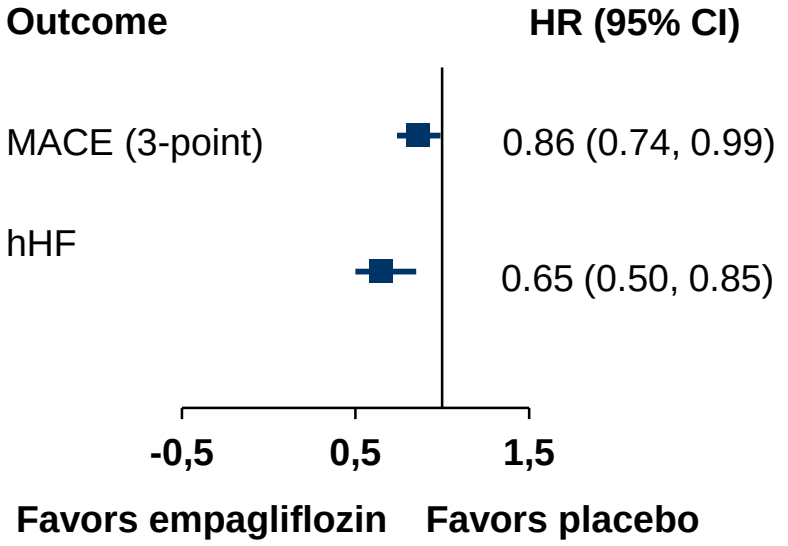
Rosenstock J et al. JAMA. 2018 Nov 9. doi: 10.1001/jama.2018.18269

Bando YK and Murohara T. J Atheroscler Thromb, 2016; 23: 147-154

CV outcomes data for SGLT2 inhibitors are building

Two SGLT2 studies demonstrate a reduction in both MACE and heart failure endpoints

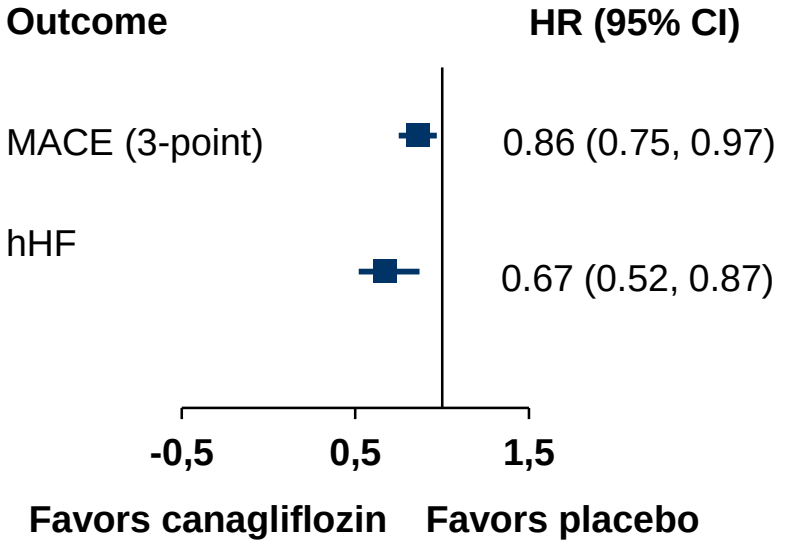
EMPA-REG OUTCOME



Demonstrated a significant reduction in CV events in patients receiving empagliflozin

Established CVD: 99%

CANVAS



Demonstrated a significant reduction in CV events in patients receiving canagliflozin

Established CVD: 66%

MACE, major adverse cardiovascular event (CV death, nonfatal MI and nonfatal stroke); MI, myocardial infarction; hHF hospitalization for heart failure.

Zinman B, et al. *N Engl J Med* 2015;373:2117–2128;
Neal B, et al. *N Engl J Med* 2017 377:644-57

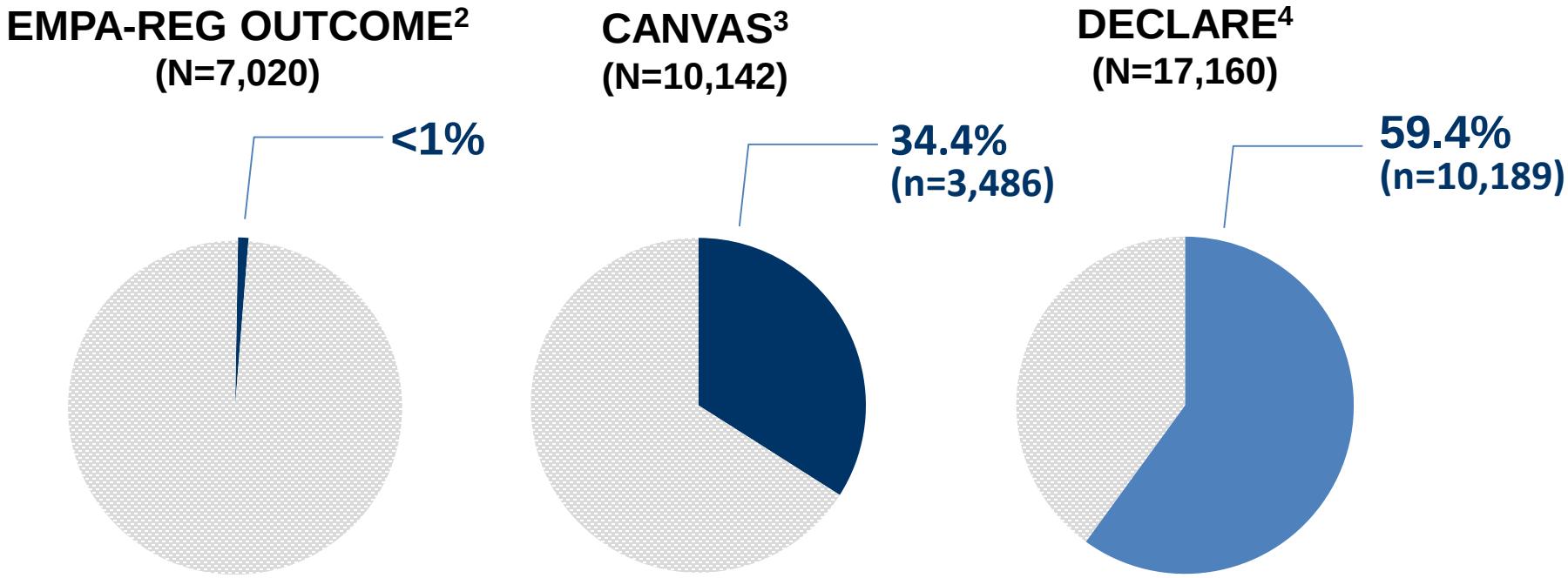
EMPA-REG OUTCOME - CANVAS

Endpoint	EMPA REG (n =7,020)	CANVAS (n=10,142)
MACE 3 punti	0.86 (0.74 -0.99)	0.86 (0.75 -0.97)
Mortalità CV	0.62 (0.49 -0.77)	0.87 (0.72-1.06)
MI non fatale	0.87 (0.70 -1.09)	0.85 (0.69 -1.05)
Stroke non fatale	1.24 (0.92 -1.67)	0.90 (0.71-1.15)
Mortalità per tutte le cause	0.68 (0.57 -0.82)	0.87 (0.74 -1.01)
Ospedalizzazione per HF	0.65 (0.50 -0.85)	0.67 (0.52-0.87)

Zinman B, et al. *N Engl J Med* 2015;373:2117–2128;
Neal B, et al. *N Engl J Med* 2017 377:644-57

DECLARE had the largest number of T2D patients without eCVD among the SGLT2i CV outcomes studies to date

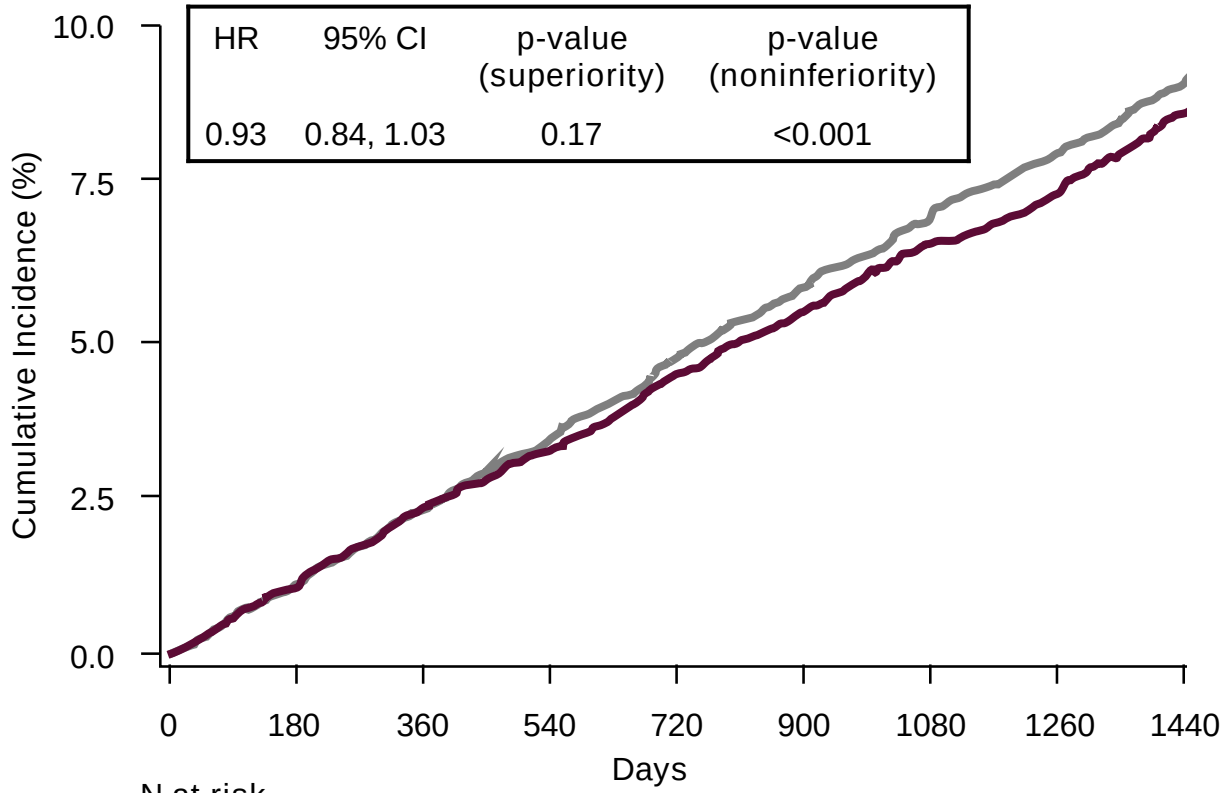
In the T2D patient population, most patients do not have established CV disease[1]



CV, cardiovascular; eCVD, established CV disease; SGLT2i, sodium glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

1.Einarson TR, et al. *Cardiovasc Diabetol* 2018;17:83; 2. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 3. Neal B, et al. *N Engl J Med* 2017;377:644–657;
4. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110

Primary Endpoint: MACE



N at risk

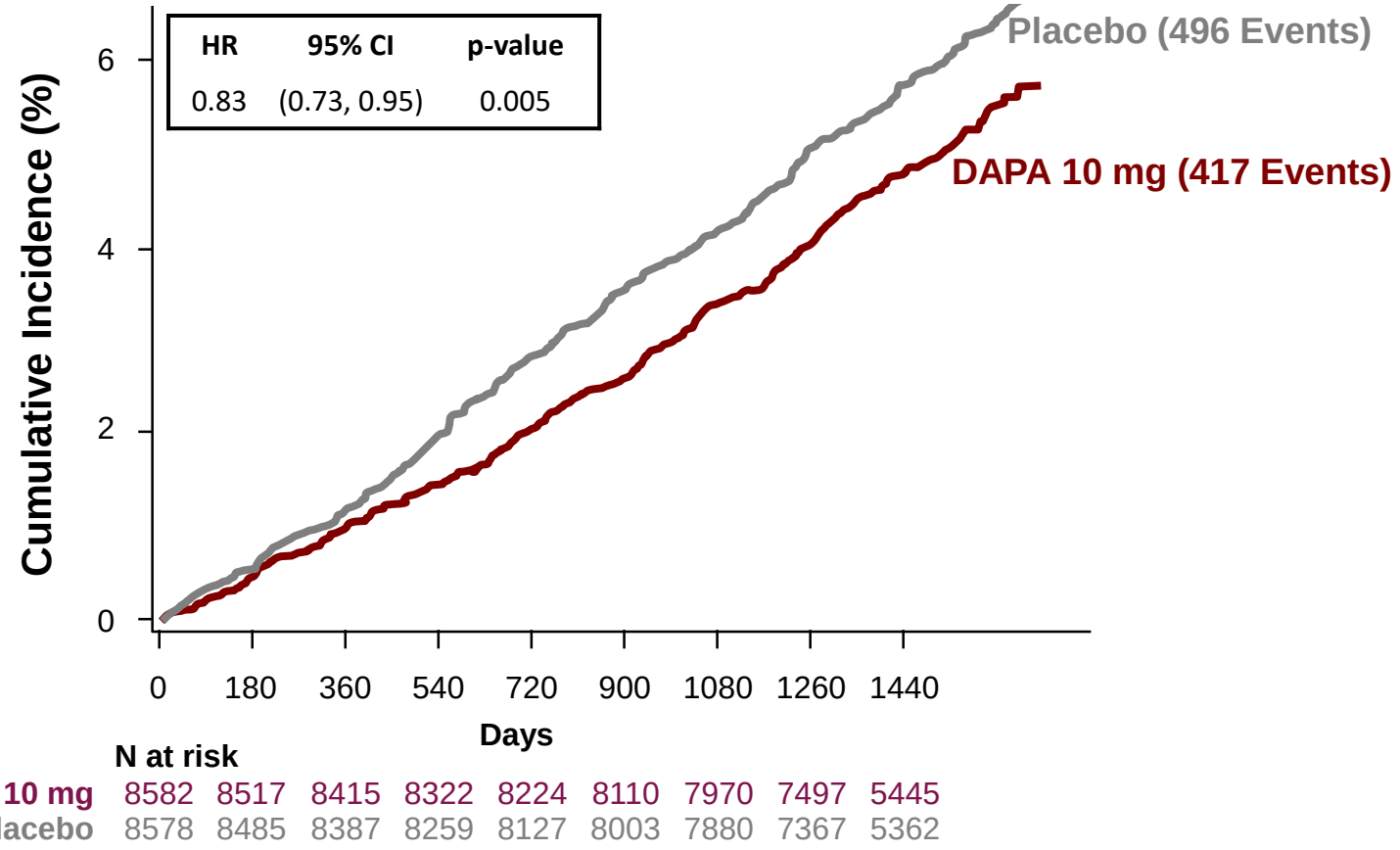
DAPA 10 mg	8582	8466	8303	8166	8017	7873	7708	7237	5225
Placebo	8578	8433	8281	8129	7969	7805	7649	7137	5158

N at risk is the number of patients at risk at the beginning of the period.

DAPA, dapgliflozin; MACE, major adverse cardiovascular events..

Wiviott SD et al. N Engl J Med. 2018 Nov 10. doi: 10.1056/NEJMoa1812389. [Epub ahead of print]

Primary Endpoint: Composite of hHF or CV Death

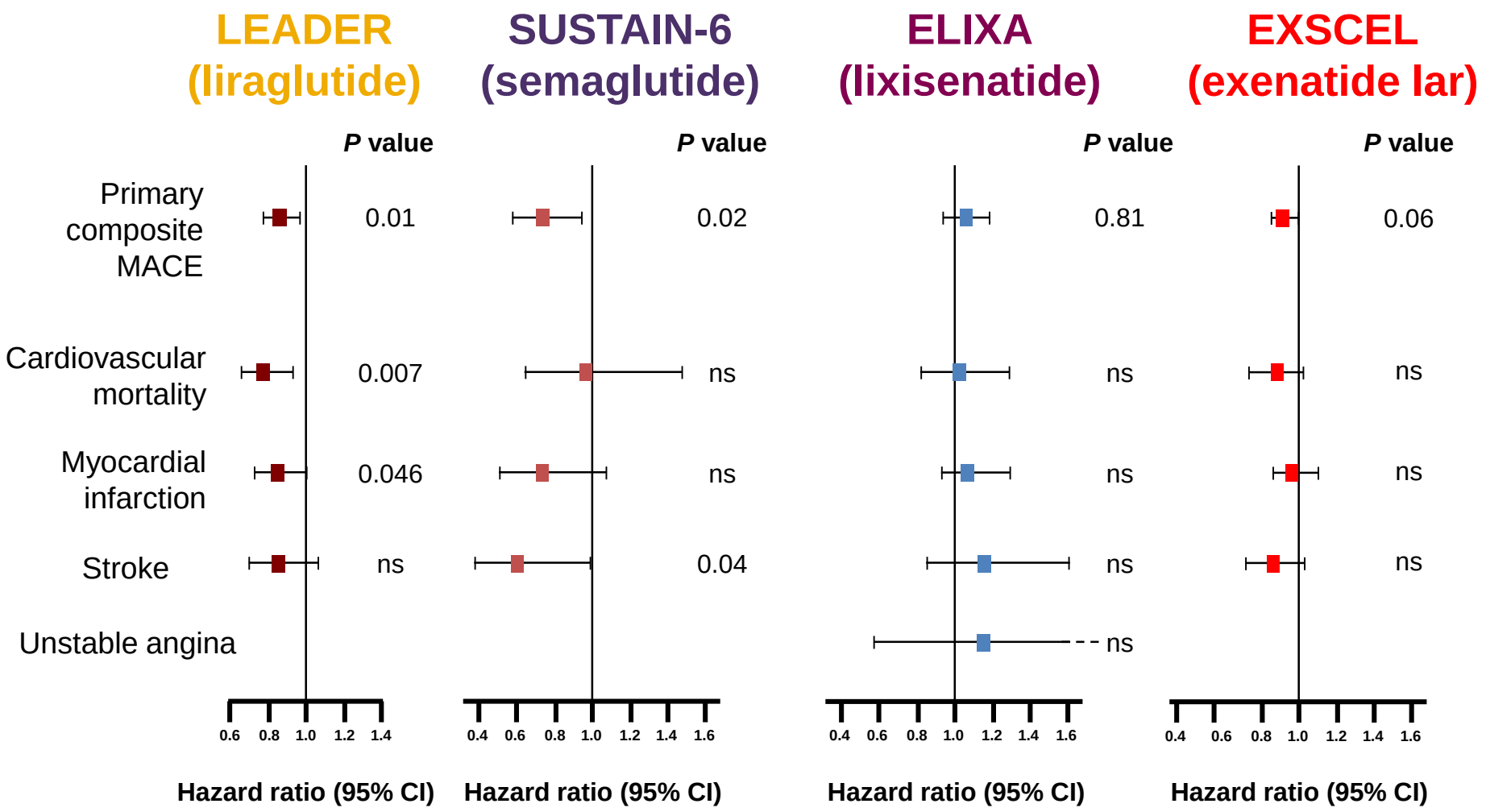


N at risk is the number of patients at risk at the beginning of the period.

CV, cardiovascular; DAPA, dapagliflozin; hHF, hospitalization for heart failure.

Wiviott SD et al. N Engl J Med. 2018 Nov 10. doi: 10.1056/NEJMoa1812389. [Epub ahead of print]

Primary Endpoint and Its Individual Components in LEADER, SUSTAIN-6, ELIXA and EXSCEL



CI, confidence interval; MACE, major adverse cardiovascular event; ns, not significant.
Adapted from Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; Marso SP, et al., *N Engl J Med* 2016;375:311-22; Marso SP, et al., *N Engl J Med* 2016 375:1834-1844; Holman RR et al., *N Engl J Med, 2017*.

ELIXA, LEADER, SUSTAIN-6 and EXSCEL: Results

	ELIXA[1] N=6.068	LEADER[2] N=9.340	SUSTAIN-6[3] N=3.297	EXSCEL[4] N=14.752
Outcomes	Lixisenatide vs Placebo Hazard Ratio (95% CI)	Liragludite vs Placebo Hazard Ratio (95% CI)	Semaglutide vs Placebo Hazard Ratio (95% CI)	Extended-release exenatide vs Placebo Hazard Ratio (95% CI)
3-point MACE	1.02 (0.89 - 1.17)	0.87 (0.78 - 0.97)	0.74 (0.58 - 0.95)	0.91 (0.83-1.00)
CV death	0.98 (0.78 - 1.22)	0.78 (0.66 - 0.93)	0.98 (0.65 - 1.48)	0.88 (0.76-1.02)
Non-fatal MI	1.03 (0.87 - 1.22)	0.88 (0.75 - 1.03)	0.74 (0.51 - 1.08)	0.95 (0.84 -1.09)
Non-fatal stroke	1.12 (0.79 - 1.58)	0.89 (0.72 - 1.11)	0.61 (0.38 - 0.99)	0.86 (0.70-1.07)
Death from any cause	0.94 (0.78 - 1.13)	0.85 (0.74 – 0.97)	1.05 (0.74 - 1.50)	0.86* (0.77 – 0.97)

* This difference was not considered to be statistically significant on the basis of the hierarchical testing plan

1 Pfeffer MA et al. N Engl J Med 373:2247-57, 2015; 2 Marso SP et al. N Engl J Med 375(4):311-22, 2016; 3 Marso SP et al. N Engl J Med 375:1834-44, 2016; 4 Holman R et al. N Engl J Med 2017

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial

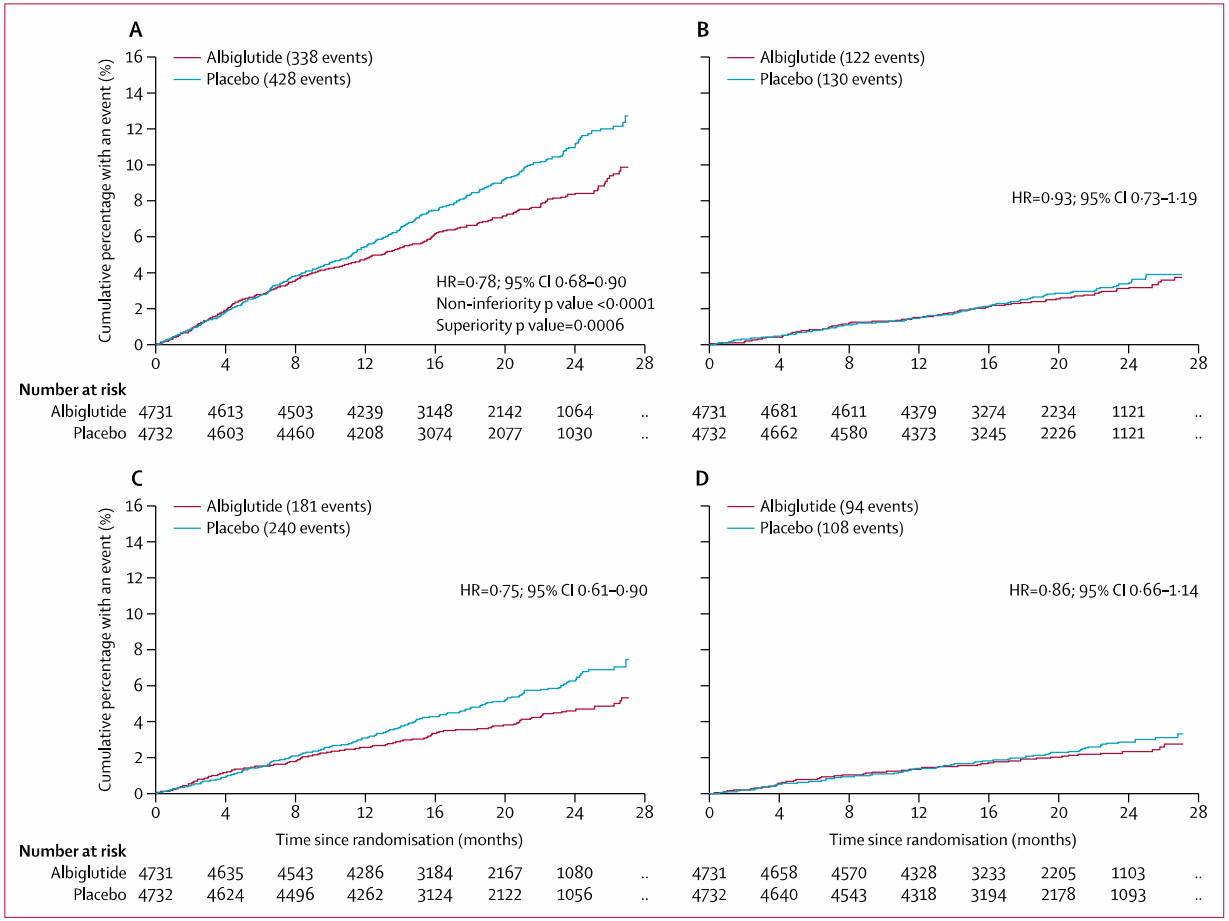
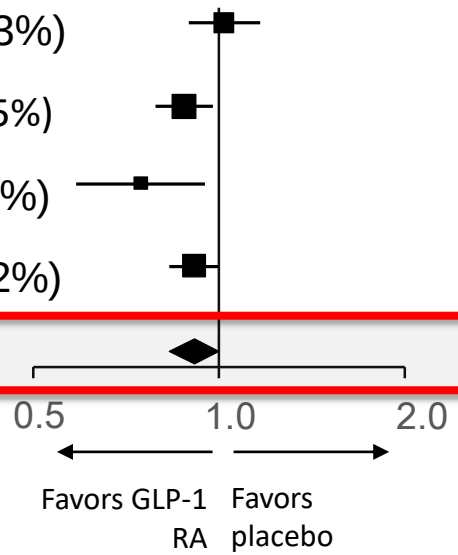


***Figure 2*: Kaplan-Meier plot of time to first occurrence of major adverse cardiovascular events**
Data are (A) the primary outcome, which was a composite of death from cardiovascular causes, myocardial infarction, or stroke; and each of these components individually: (B) cardiovascular death, (C) myocardial infarction, and (D) stroke. Analyses are of all participants who were randomly assigned to groups. The graphs are truncated at the point at which less than 10% of patients remain at risk. HR=hazard ratio.

Hernandez AF et al. *Lancet* 2018; 392: 1519–29

Primary Efficacy Outcome: Three-Point MACE

Study	GLP-1 RA	Placebo	HR (95% CI)	P value
ELIXA	400/3034 (13%)	392/3034 (13%)	1.02 (0.89, 1.17)	0.776
LEADER	608/4668 (13%)	694/4672 (15%)	0.87 (0.78, 0.97)	0.015
SUSTAIN 6	108/1648 (7%)	146/1649 (9%)	0.74 (0.58, 0.95)	0.016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0.91(0.83, (1.00)	0.061
Overall			**0.90 (0.82, 0.99)**	**0.033**



Test for heterogeneity: P=0.11, I^2=50%

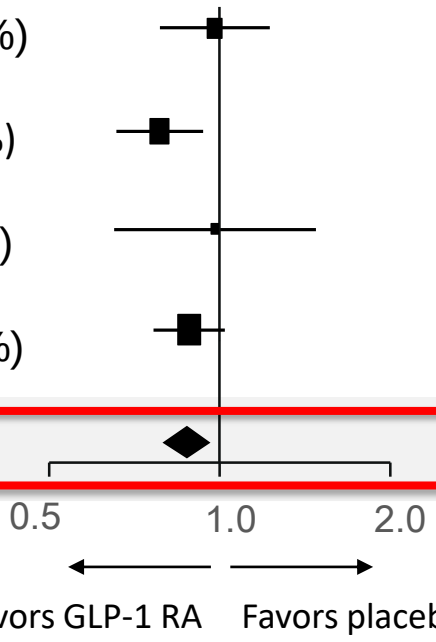
Three-point MACE is a composite of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke.

CI = confidence interval; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HR = hazard ratio; MACE = major adverse cardiovascular event.

Bethel MA et al. *Lancet Diabetes Endocrinol.* 2018;6:105-113.

Cardiovascular Mortality

Study	GLP-1 RA	Placebo	HR (95% CI)	P value
ELIXA	156/3034 (5%)	158/3034 (5%)	0.98 (0.78, 1.22)	0.85
LEADER	219/4668 (5%)	278/4672 (6%)	0.78 (0.66, 0.93)	0.007
SUSTAIN 6	44/1648 (3%)	46/1649 (3%)	0.98 (0.65, 1.48)	0.92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0.88 (0.76, 1.02)	0.096
Overall			**0.87 (0.79, 0.96)**	**0.007**



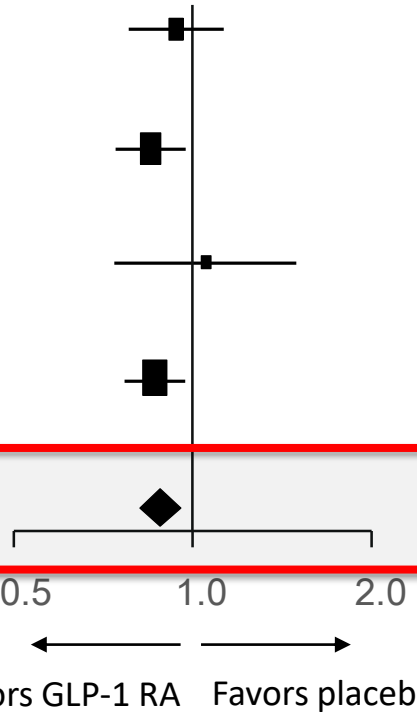
Test for heterogeneity:
P=0.43, I^2=0%

CI = confidence interval; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HR = hazard ratio.

Bethel MA et al. *Lancet Diabetes Endocrinol.* 2018;6:105-113.

All-cause Mortality

Study	GLP-1 RA	Placebo	HR (95% CI)	P value
ELIXA	211/3034 (7%)	223/3034 (7%)	0.94 (0.78, 1.13)	0.50
LEADER	381/4668 (8%)	447/4672 (10%)	0.85 (0.74, 0.97)	0.020
SUSTAIN 6	62/1648 (4%)	60/1649 (4%)	1.05 (0.74, 1.50)	0.79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0.86 (0.77, 0.97)	0.016*
Overall			**0.88 (0.81, 0.95)**	**0.002**



Test for heterogeneity: P=0.63, I^2=0%

*The within-trial difference in all-cause mortality in EXSCEL was not regarded as significant on the basis of the hierarchical testing plan.

CI = confidence interval; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HR = hazard ratio.

Bethel MA et al. *Lancet Diabetes Endocrinol.* 2018;6:105-113.

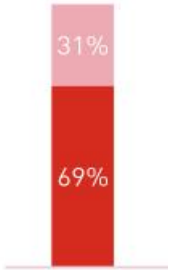
REWIND trial: Trial Design and Other GLP-1 RA CVOTs

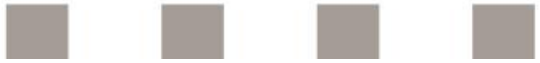
REWIND trial design is different from other GLP-1 RA CVOTs

Majority of participants did not have stablished CV disease*

CV Disease History

Prior CV Disease
No Prior CV Disease

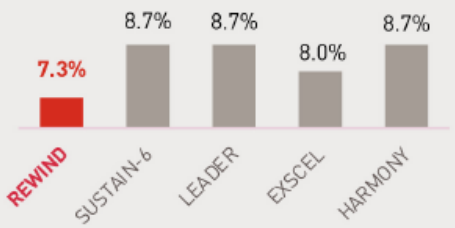




*REWIND defined established CV disease as including at least one of the following

Study population had a lower mean baseline A1C

Mean Baseline A1C



Longest follow-up period of any CV outcome trial in the GLP-1 RA class

Median Follow-up Time (Years)

REWIND trial

Trulicity® (dulaglutide) demonstrates superiority in reduction of cardiovascular events for broad range of people with type 2 diabetes

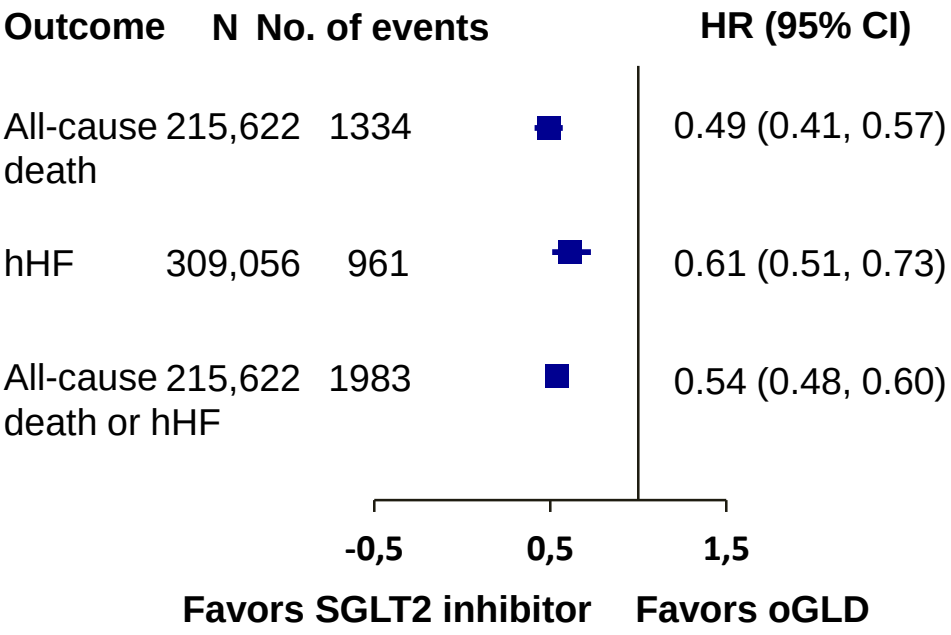
November 5, 2018

Only 31 percent of REWIND trial participants had established CV disease

INDIANAPOLIS, Nov. 5, 2018 /PRNewswire/ -- Trulicity® (dulaglutide) significantly reduced major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (heart attack) or non-fatal stroke, meeting the primary efficacy objective in the precedent-setting REWIND trial. Eli Lilly and Company's (NYSE: LLY) once-weekly Trulicity is the first type 2 diabetes medicine to demonstrate superiority in the reduction of MACE events in a clinical trial that included a majority of participants who did not have established CV disease.

In CVD-REAL, SGLT2 inhibitors were associated with reductions in CV endpoints in a population earlier in their CV risk continuum

All-cause death and hHF for SGLT2 inhibitors vs oGLDs[1]



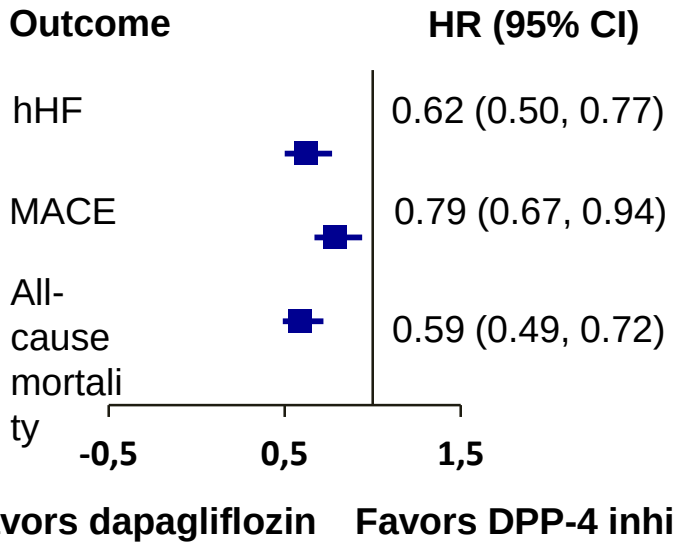
13% of patients in both cohorts had established CVD suggesting they were earlier in the CV risk continuum compared to EMPA-REG and CANVAS

[a]Previous event of myocardial infarction, stroke, unstable angina, heart failure or atrial fibrillation
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease;; hHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiac event; SGLT2, sodium–glucose co-transporter 2; oGLD, other glucose-lowering drug

1. Kosiborod M., et al. *Circulation* 2017;136:249–259
2. Persson F, et al. *Diabetes Obes Metab* 2018;20:344-351

In CVD-REAL, dapagliflozin was associated with reductions in CV endpoints and death in a population with a broad cardiovascular risk profile versus DPP-4 inhibitors

MACE and all-cause mortality for dapagliflozin vs DPP-4 inhibitors[2]

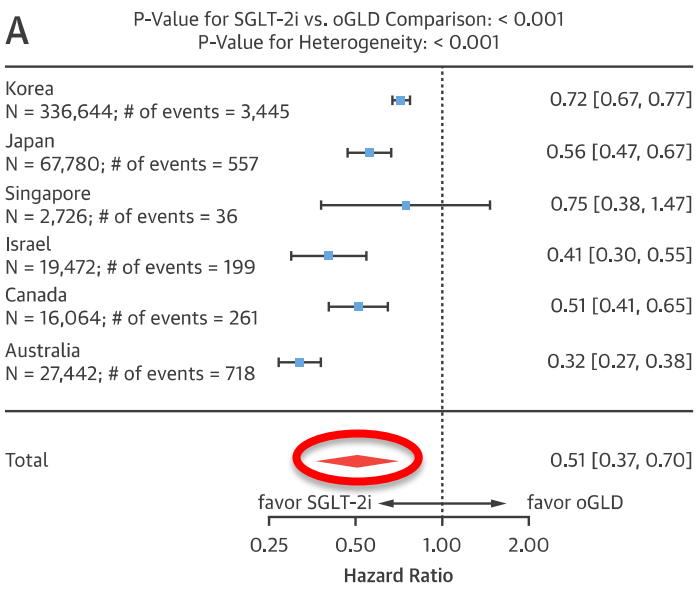


23% of patients had established CVD, suggesting this was a population **earlier in the CV risk continuum compared to EMPA-REG and CANVAS**

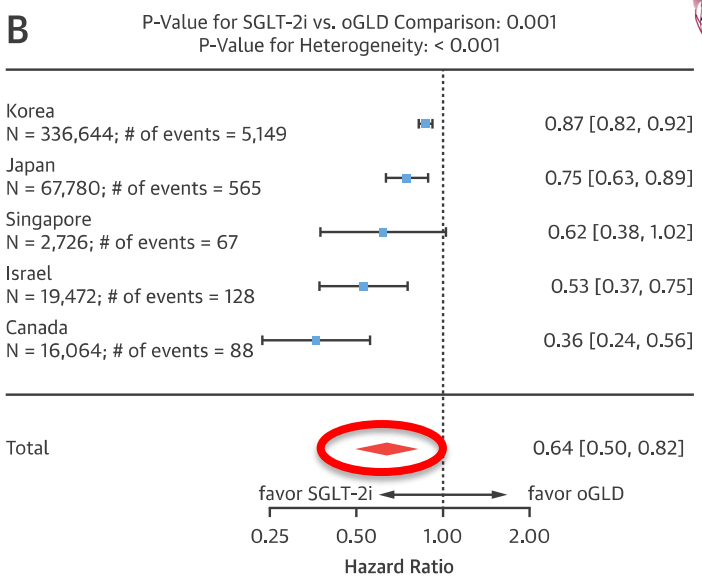
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; hHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiac event; SGLT2, sodium–glucose co-transporter 2; oGLD, other glucose-lowering drug.

Persson F, et al. *Diabetes Obes Metab* 2018;20:344-351

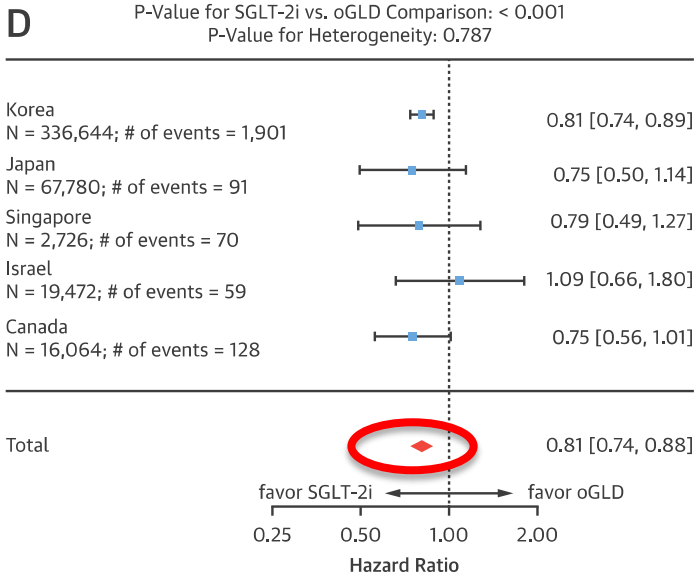
All-cause death



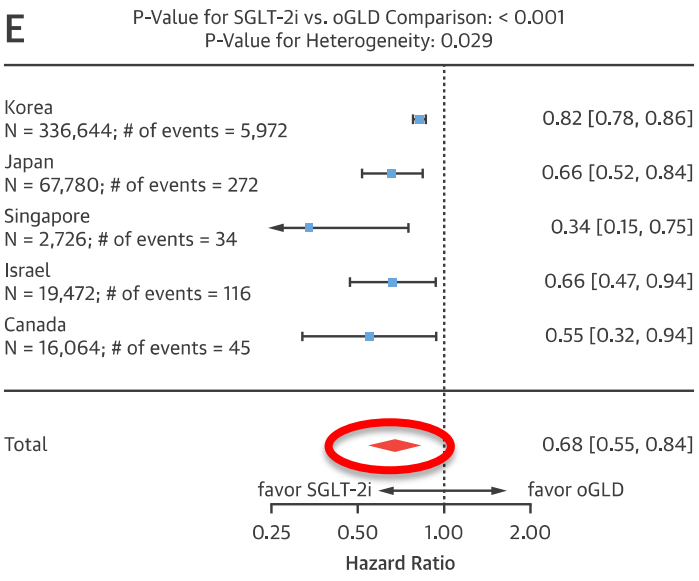
HF hospitalization



Myocardial infarction



Stroke



CVDREAL 2

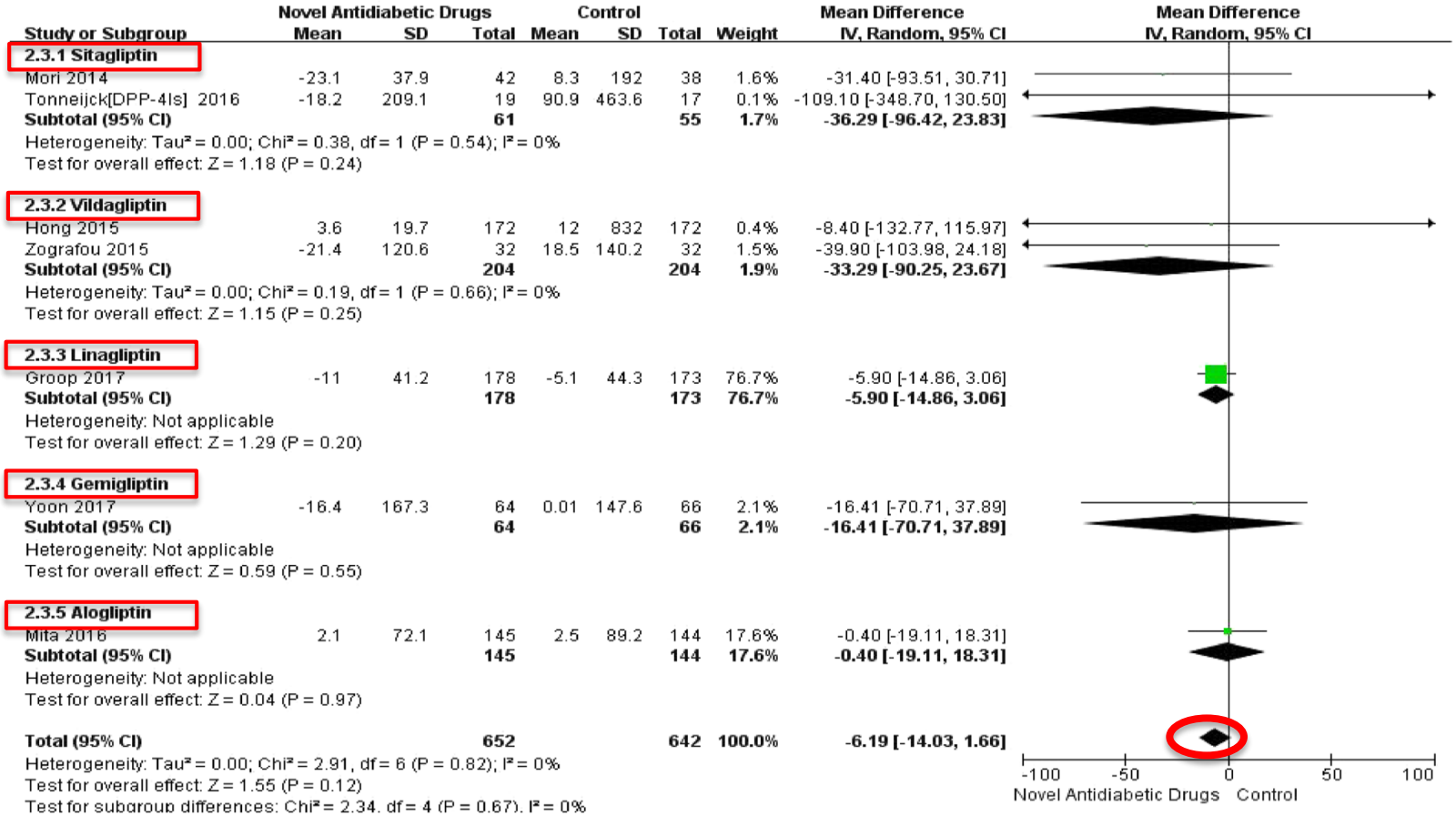
Kosiborod M et al. J Am Coll Cardiol. 2018 Jun 12;71(23):2628-2639

Clinical Drug Investigation
https://doi.org/10.1007/s40261-018-0707-4

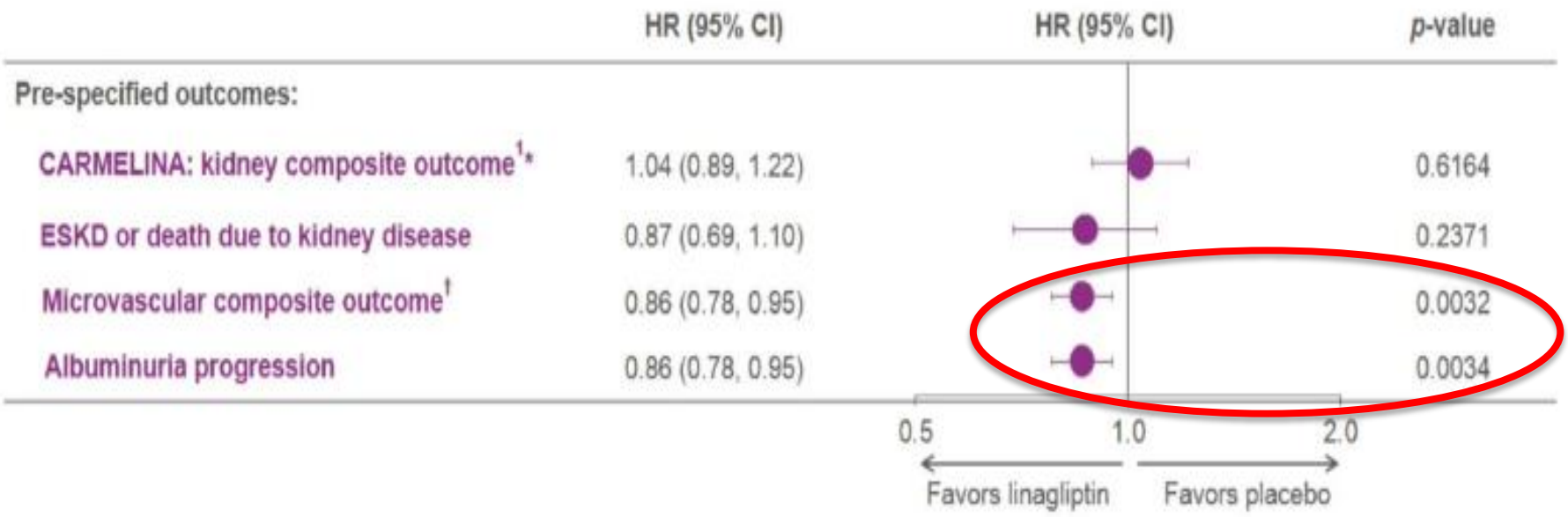
Ya Luo[1] · Kai Lu[1] · Gang Liu[1] · Jing Wang[1] · Irakoze Laurent[2] · Xiaoli Zhou[1]

SYSTEMATIC REVIEW

The Effects of Novel Antidiabetic Drugs on Albuminuria in Type 2 Diabetes Mellitus: A Systematic Review and Meta-analysis of Randomized Controlled Trials



CARMELINA: kidney and microvascular outcomes



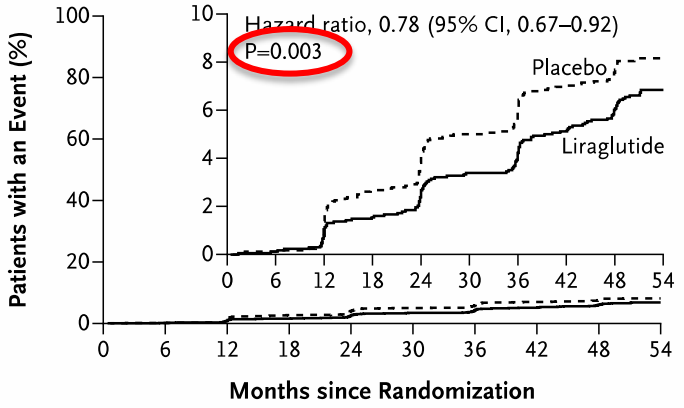
The key secondary kidney outcome was pre-specified, adequately powered, and adjudicated in CARMELINA

*Sustained end-stage kidney disease (ESKD), sustained decrease of ≥40% in eGFR from baseline or death due to kidney disease
†Sustained ESKD, sustained decrease of ≥50% in eGFR, death due to kidney disease, albuminuria progression, retinal photocoagulation or intravitreal injection of an anti-VEGF therapy for diabetic retinopathy, vitreous haemorrhage or diabetes-related blindness
eGFR, estimated glomerular filtration, VEGF, vascular endothelial growth factor 1. Rosenstock J *et al. EASD. October 4th, 2018*

CARMELINA

Liraglutide and Renal Outcome in Type 2 Diabetes

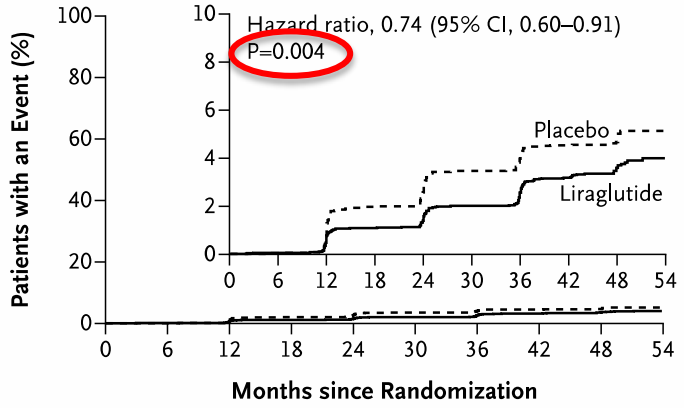
A Composite Renal Outcome



No. at Risk

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

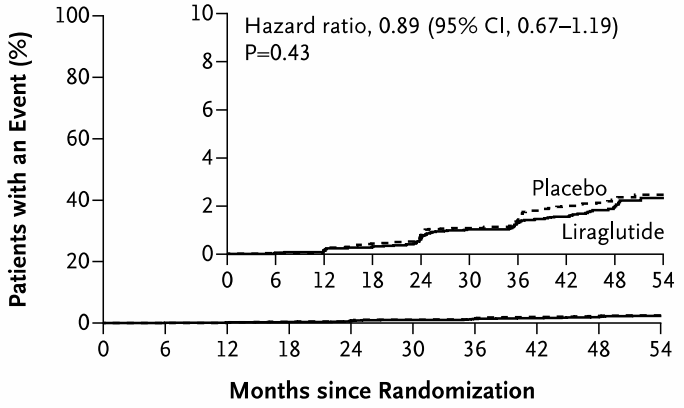
B New Onset of Persistent Macroalbuminuria



No. at Risk

Placebo	4672	4646	4551	4455	4359	4252	4162	4073	1642	442
Liraglutide	4668	4638	4570	4508	4437	4353	4268	4182	1662	461

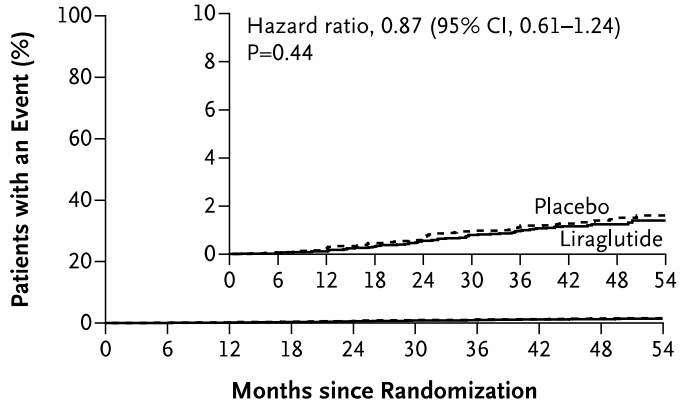
C Persistent Doubling of Serum Creatinine Level



No. at Risk

Placebo	4672	4647	4596	4529	4447	4367	4282	4196	1682	456
Liraglutide	4668	4639	4591	4544	4476	4403	4332	4264	1692	475

D Continuous Renal-Replacement Therapy



No. at Risk

Placebo	4672	4645	4590	4527	4454	4370	4299	4227	1699	461
Liraglutide	4668	4640	4596	4547	4484	4416	4349	4282	1710	483

The composite renal outcome consisted of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level and an estimated glomerular filtration rate of 45 ml or less per minute per 1.73 m2 of body-surface area, the need for continuous renal-replacement therapy (end-stage renal disease), or death due to renal disease.

Mann JFE et al. N Engl J Med 2017;377:839-48

ORIGINAL ARTICLE

Marso SP et al. N Engl J Med. 2016 Sep 15. [Epub ahead of print]

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

New or worsening nephropathy includes **persistent macroalbuminuria, persistent doubling of the serum creatinine level** and a **creatinine clearance of less than 45 ml** per minute per 1.73 m^2 of body-surface area (according to the Modification of Diet in Renal Disease criteria), or the **need for continuous renal-replacement therapy**.

Diabetes Complications of Interest

- Investigators evaluated **EQW's impact on the following renal outcomes** based on a prespecified analysis plan:

eGFR

New-onset macroalbuminuria

Renal Composite 1:
- 40% eGFR decline
- Renal replacement
- Renal death

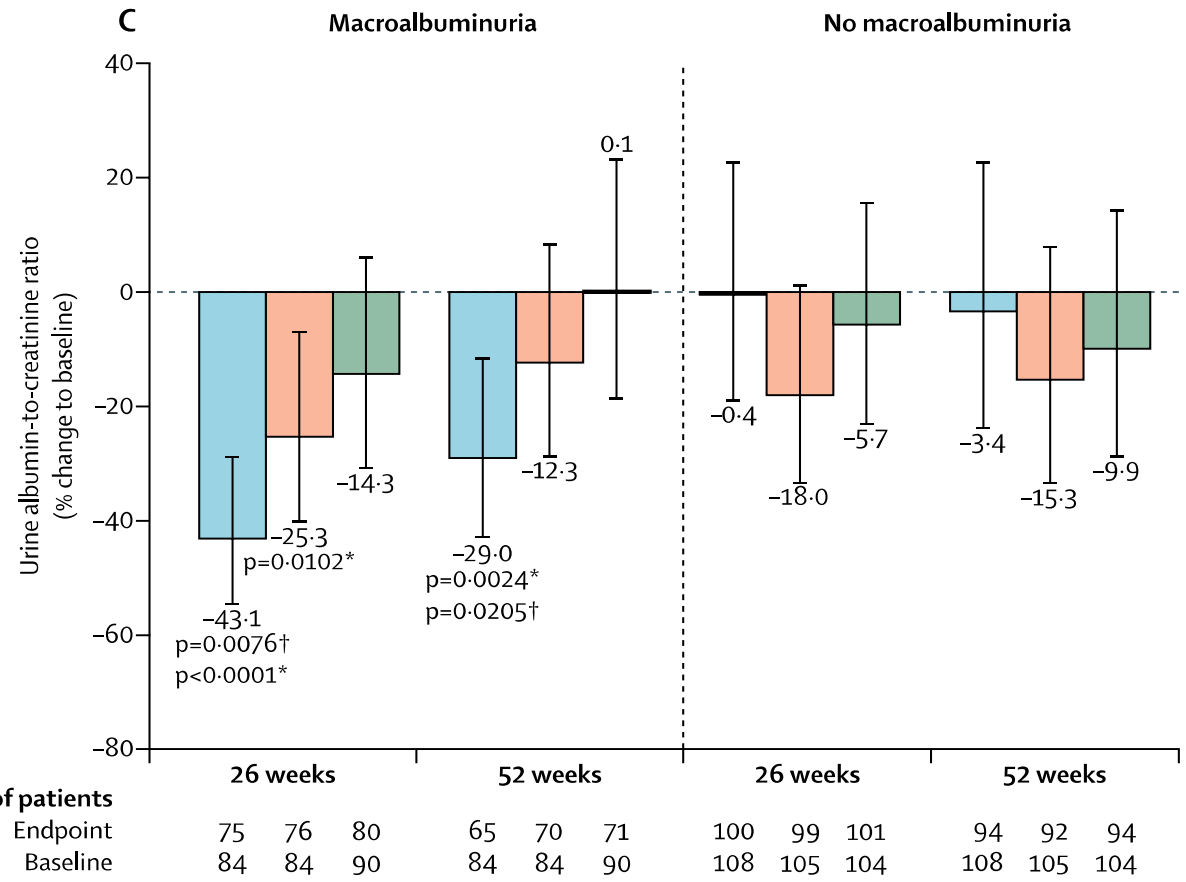
Renal Composite 2:
- 40% eGFR decline
- Renal replacement
- Renal death
- New-onset macroalbuminuria

- There was a **15% lower adjusted risk for Renal Composite 2** in an adjusted analysis[a] for the EQW-treated patients (adjusted HR 0.85; 95% CI, 0.74-0.98; p=0.03).
- Other renal outcomes numerically improved but were not statistically significant.

[a]Adjusted for age, sex, ethnicity, race, region, duration of diabetes, prior history of CV event, insulin use, baseline HbA1c, eGFR, and BMI.
BMI = body mass index; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; EQW = exenatide once-weekly; HbA1c = glycated haemoglobin; HR = hazard ratio.
Bethel MA et al. Presented at: ADA 78th Scientific Sessions; June 22-26, 2018; Orlando, FL. Poster 522-P.

Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

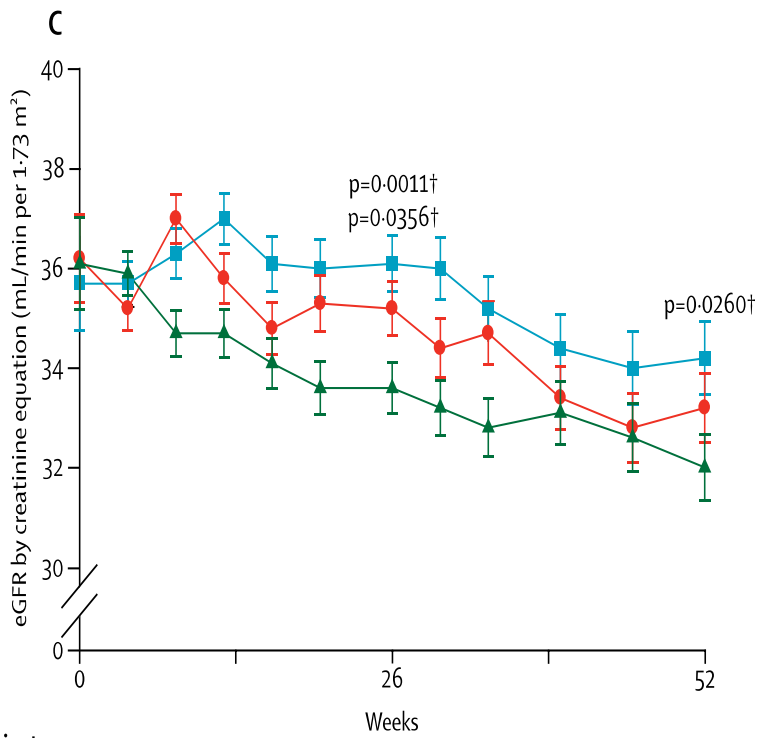
Katherine R Tuttle, Mark C Lakshmanan, Brian Rayner, Robert S Busch, Alan G Zimmermann, D Bradley Woodward, Fady T Botros



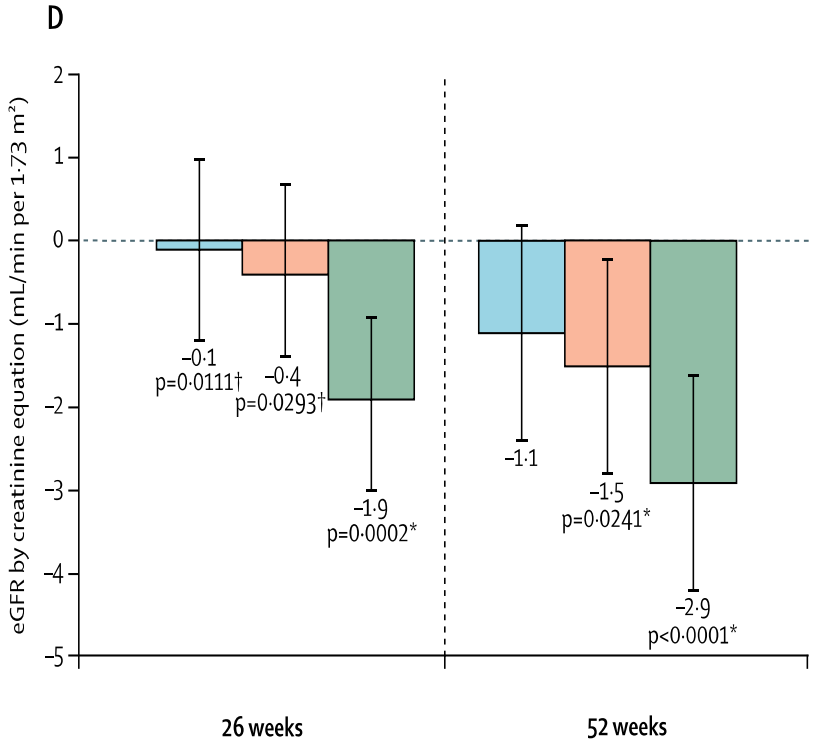
Lancet Diabetes Endocrinol 2018; 6: 605–17

Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

Katherine R Tuttle, Mark C Lakshmanan, Brian Rayner, Robert S Busch, Alan G Zimmermann, D Bradley Woodward, Fady T Botros



Number of patients			
Dulaglutide 1·5 mg	192	163	157
Dulaglutide 0·75 mg	190	169	160
Insulin glargine	194	176	164



Number of patients						
Endpoint	163	169	176	157	160	164
Baseline	192	190	194	192	190	194

Lancet Diabetes Endocrinol 2018; 6: 605–17

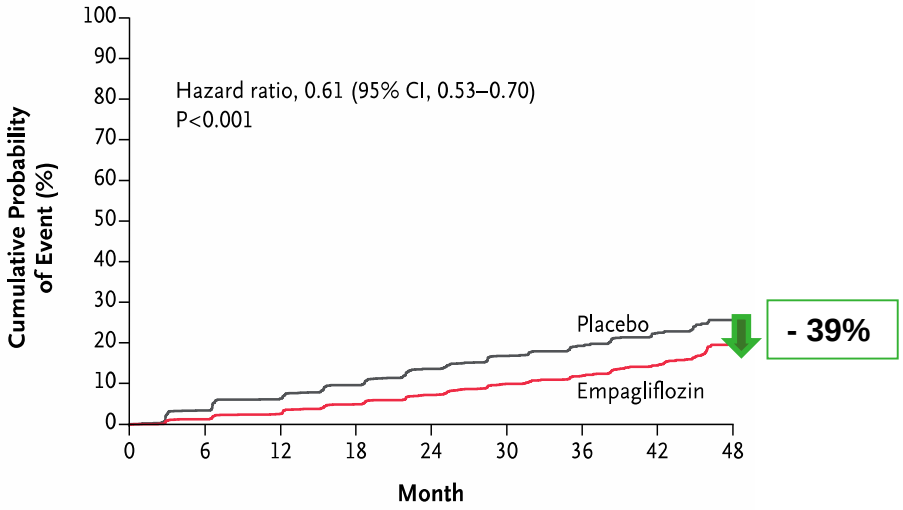
The NEW ENGLAND JOURNAL of MEDICINE

Christoph Wanner et al. 2016 Jul 28;375(4):323-34.

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

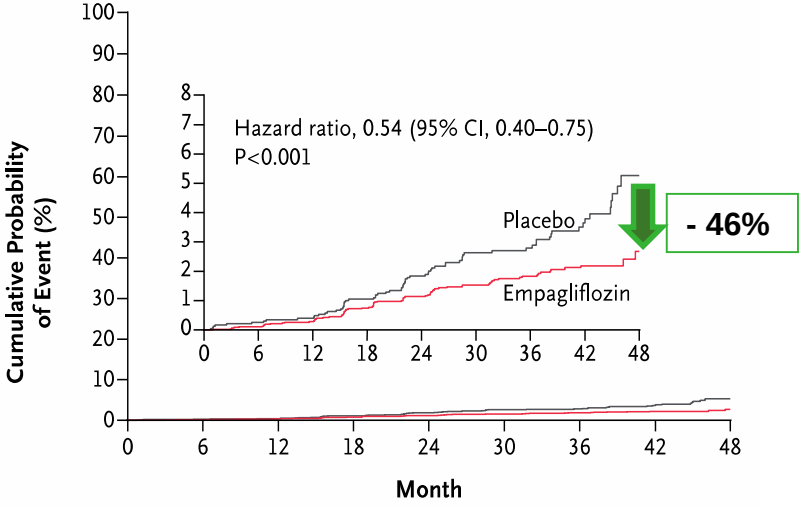
A Incident or Worsening Nephropathy



No. at Risk									
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Incident or worsening nephropathy

B Post Hoc Renal Composite Outcome



No. at Risk									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease

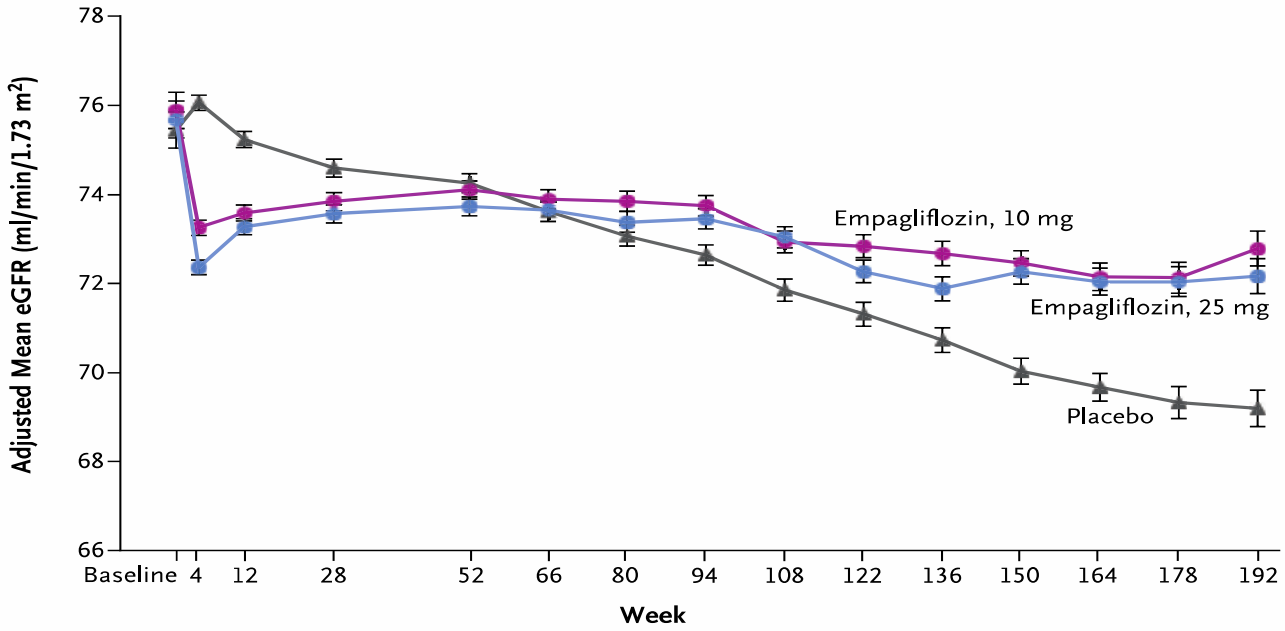
The NEW ENGLAND JOURNAL of MEDICINE

Christoph Wanner et al. 2016 Jul 28;375(4):323-34.

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

A **Change in eGFR over 192 Wk**

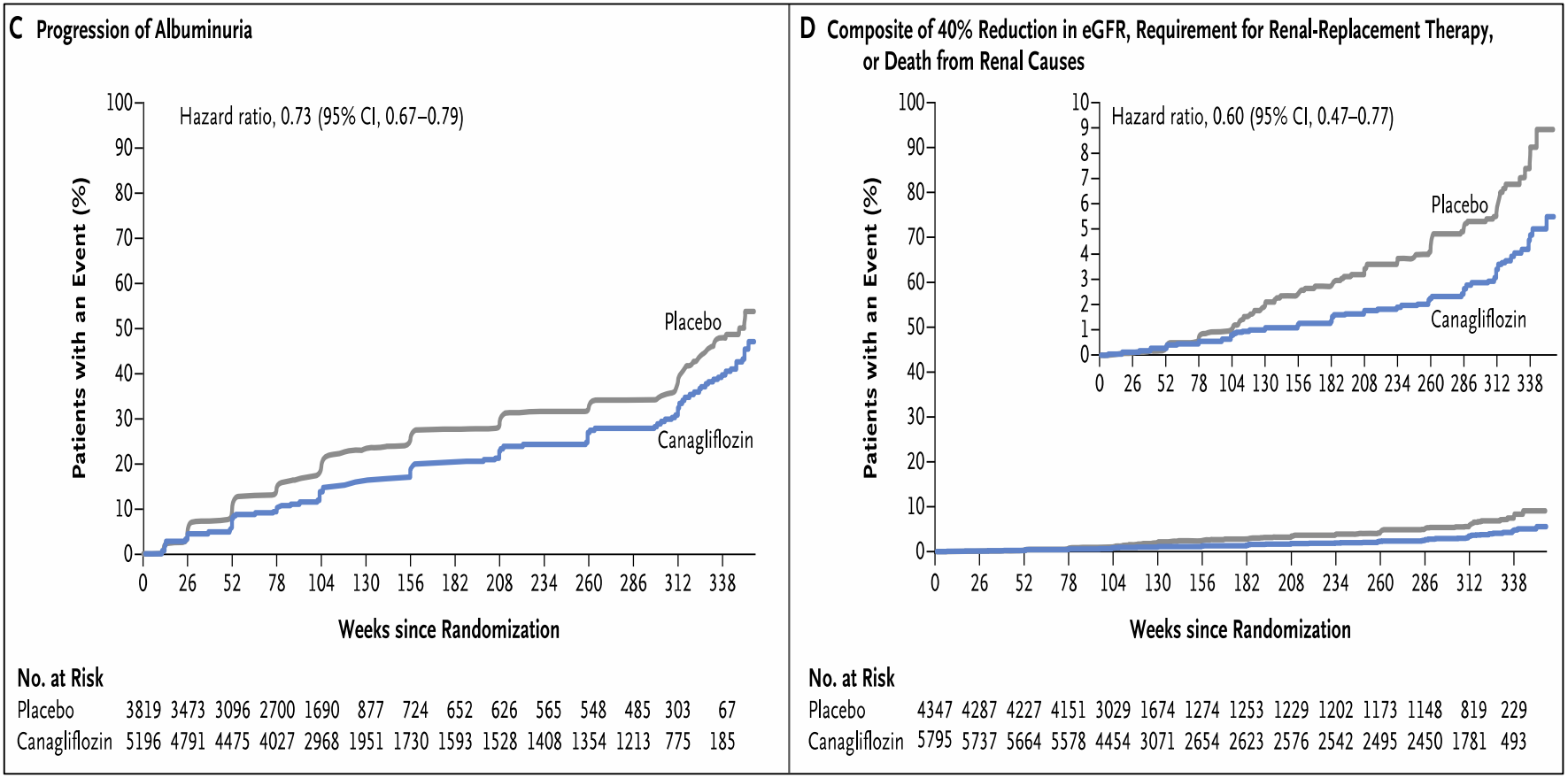


No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

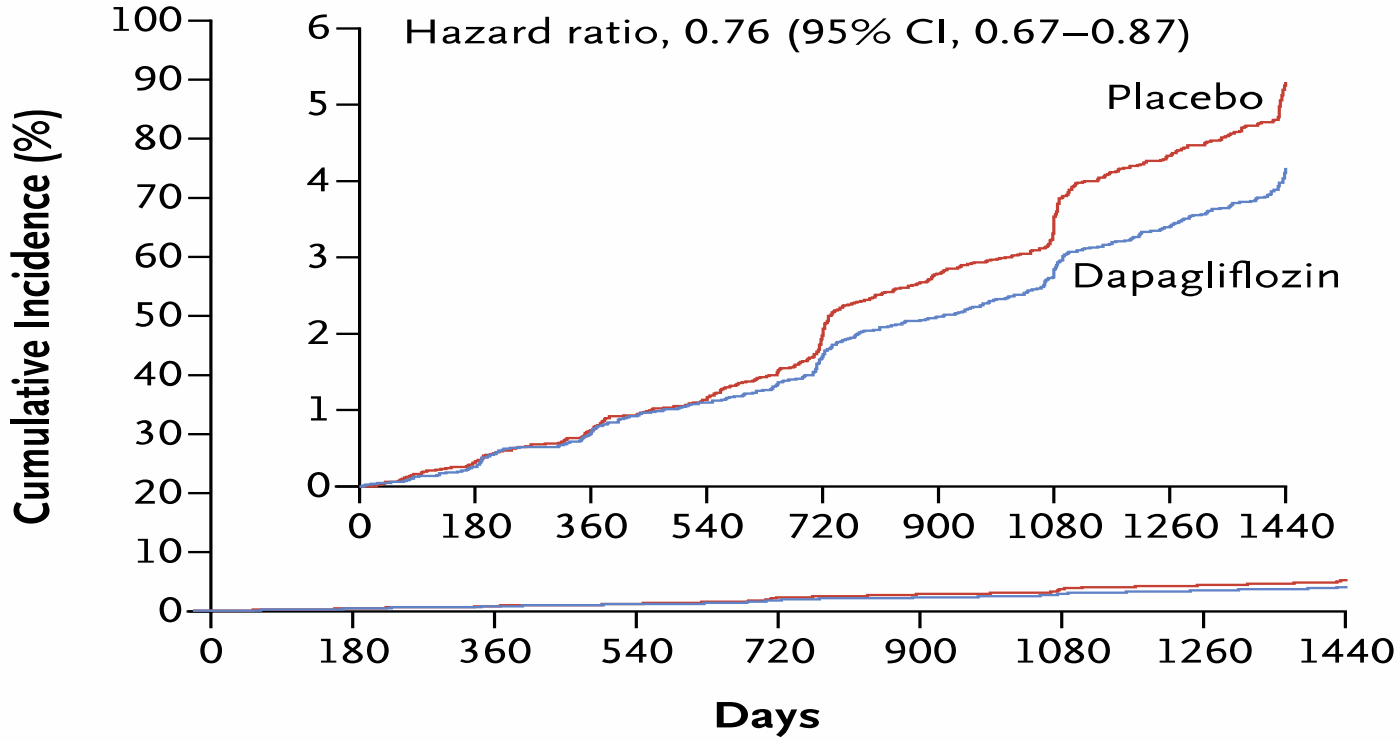
The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2017;377:644-57

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes



DECLARE-TIMI 58 Trial: Renal Outcomes



Renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes)

Wiviott SD et al. N Engl J Med. 2018 Nov 10. doi: 10.1056/NEJMoa1812389. [Epub ahead of print]

Original Report: Patient-Oriented, Translational Research

American Journal of Nephrology

Am J Nephrol 2017;46:462–472
DOI: 10.1159/000484633

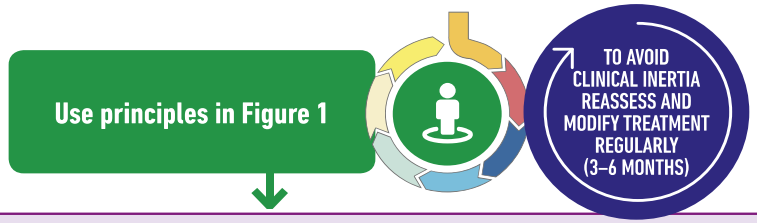
Received: September 22, 2017
Accepted: October 27, 2017
Published online: December 1, 2017

The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics

- **CREDENCE assessed canaglilfozin for renal protection** by evaluating the risk reduction of the composite endpoint of time to dialysis or kidney transplantation, doubling of serum creatinine, and renal or cardiovascular death, when used in addition to standard of care.
- The trial enrolled approximately 4,400 patients with T2D, estimated glomerular filtration rate ≥30 to <90 mL/min/1.73m^2, and albuminuria.

Phase 3 CREDENCE Renal Outcomes Trial of INVOKANA® (canagliflozin) is Being Stopped Early for Positive Efficacy Findings

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)



Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (see below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (see below)

OR reconsider/lower individualized target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3-month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target

ASCVD predominates

GLP-1 RA with proven CVD benefit[1]

EITHER/ OR

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

HF or CKD predominates

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

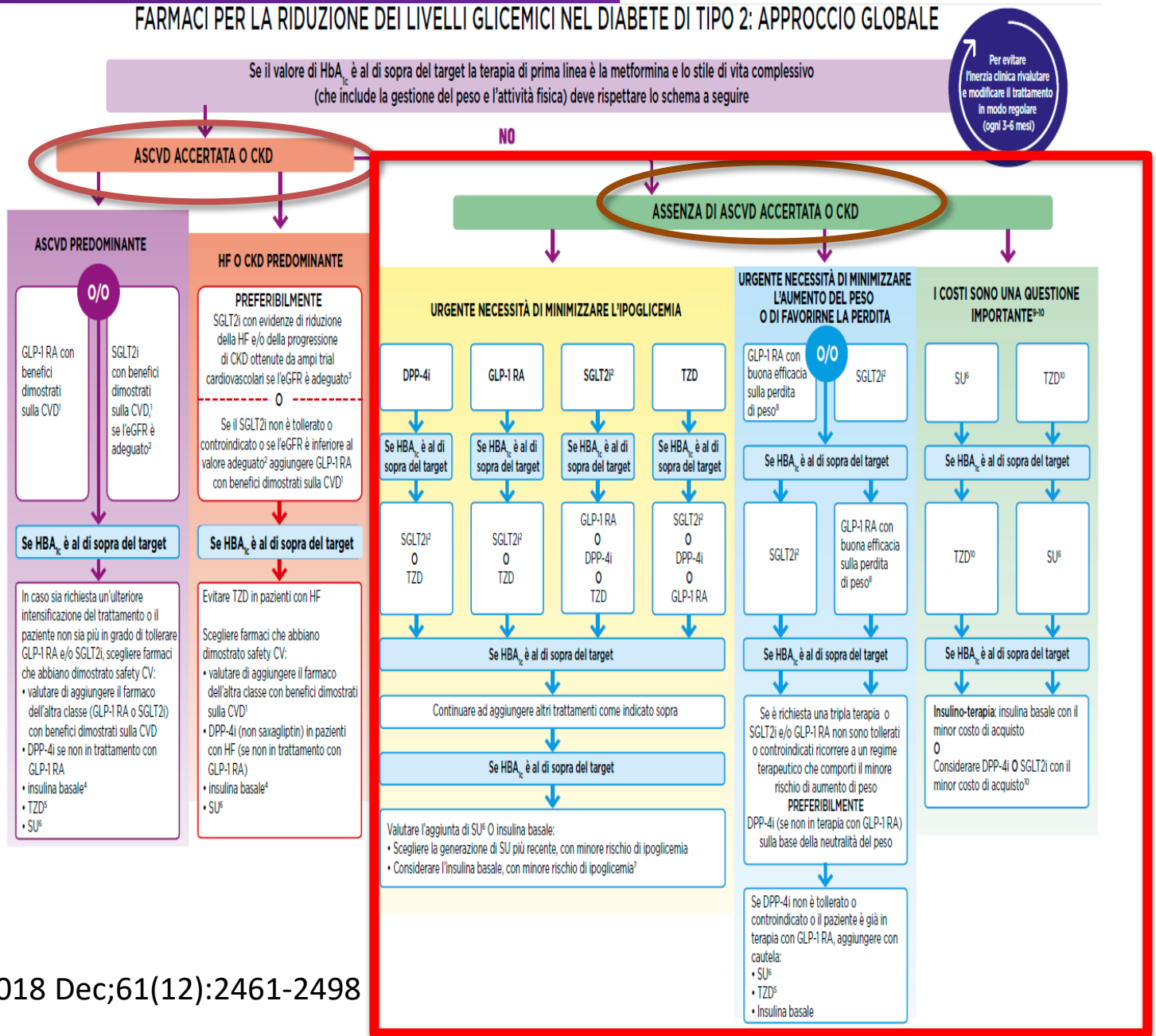
OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1,4]

Diabetologia. 2018 Dec;61(12):2461-2498

La **metformina** continua ad essere il **primo farmaco da usare** nel DMT2 (nei pazienti in cui è ben tollerata o non controindicata) insieme a dieta ed esercizio fisico

La scelta di un add-on a metformina è basata sulle **caratteristiche cliniche del paziente** e in particolare sulla presenza o meno di malattia CV, scompenso cardiaco (HF) e malattia renale (CKD)



Diabetologia. 2018 Dec;61(12):2461-2498

PIANO TERAPEUTICO

La rimborsabilità a carico del S.S.N., in regime di dispensazione RRL-PT/PHT, è limitata ai pazienti adulti con diabete tipo 2 qualora siano soddisfatte le seguenti condizioni alla prima prescrizione:

1. Fallimento terapeutico, definito da livelli di HbA_{1c} ≥7.5% (58 mmol/mol)[6], alla dose massima tollerata della terapia ipoglicemizzante corrente e **dopo adeguata e documentata modifica dello stile di vita (dieta e attività fisica)**;
2. HbA_{1c} ≤8.5% (69 mmol/mol), cioè un livello dal quale sia ragionevole raggiungere il *target* desiderato con l'aggiunta del nuovo farmaco, considerata la riduzione media di HbA_{1c} con i farmaci attivi sul sistema delle incretine di circa ≤1%
3. Rischio di ipoglicemie severe o comunque condizionanti le attività quotidiane che sconsigli l'utilizzo di altre classi di ipoglicemizzanti. Conseguentemente la rimborsabilità dell'associazione con sulfoniluree è limitata esclusivamente ai casi di controindicazione o intolleranza alla metformina.

PIANO TERAPEUTICO AIFA PER LA PRESCRIZIONE DEGLI AGONISTI DEL GLP-1R NEL DIABETE DI TIPO 2

Da redigere ai fini della rimborsabilità a cura delle strutture diabetologiche individuate dalle Regioni, ed inviare al Servizio Farmaceutico della ASL e al Medico di Medicina Generale che ha in carico l'assistito. La validità temporale del Piano Terapeutico è di dodici mesi; durante tale periodo la continuità di prescrizione può quindi essere affidata al Medico di Medicina Generale. Qualora il valore di Hb_{A1c} dopo sei mesi di terapia non rientrasse nei limiti inizialmente indicati dallo specialista redattore del Piano Terapeutico, oppure siano sopraggiunte controindicazioni o intolleranza alla terapia prescritta, la rivalutazione della stessa da parte dello specialista dovrà essere anticipata rispetto al limite dei dodici mesi.

Centro Diabetologico prescrittore_____

Medico specialista prescrittore_____

Tel. _____ e-mail _____

Medico di Medicina Generale_____

Paziente (cognome, nome) _____

Data di nascita _____ sesso M ☐ F ☐

Comune di nascita _____ Estero ☐

Codice fiscale |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

Residente a _____ Tel. _____

Regione _____ ASL di residenza_____ Prov._____

Dati clinici

Pregresso evento cardiovascolare Si ☐ No ☐ _____

Alto* rischio cardiovascolare Si ☐ No ☐ _____

Peso (kg) ____ Altezza (cm) ___ BMI ___ Durata di malattia (anni) ____

Ultimo Valore di Hb_{A1c} (% *oppure* mmol/mol) _____

Target o intervallo appropriato di Hb_{A1c} a giudizio dello specialista (% *oppure* mmol/mol) _____

Ipoglicemie severe o comunque condizionanti le attività quotidiane negli ultimi tre mesi? Si ☐ No ☐

Reazioni avverse (soltanto al follow-up)

Si ☐ (compilare la scheda di segnalazione ADR Ministeriale come da Normativa vigente); No ☐

*Si definiscono soggetti ad alto rischio cardiovascolare coloro che presentano una probabilità, calcolata mediante le carte italiane del rischio cardiovascolare, ≥ 20% di presentare un evento CV fatale o non fatale nei successivi 10 anni (http://www.cuore.iss.it/valutazione/carte.asp). Vedi carte del rischio allegate.

LIMITAZIONI PRESCRIVIBILITÀ

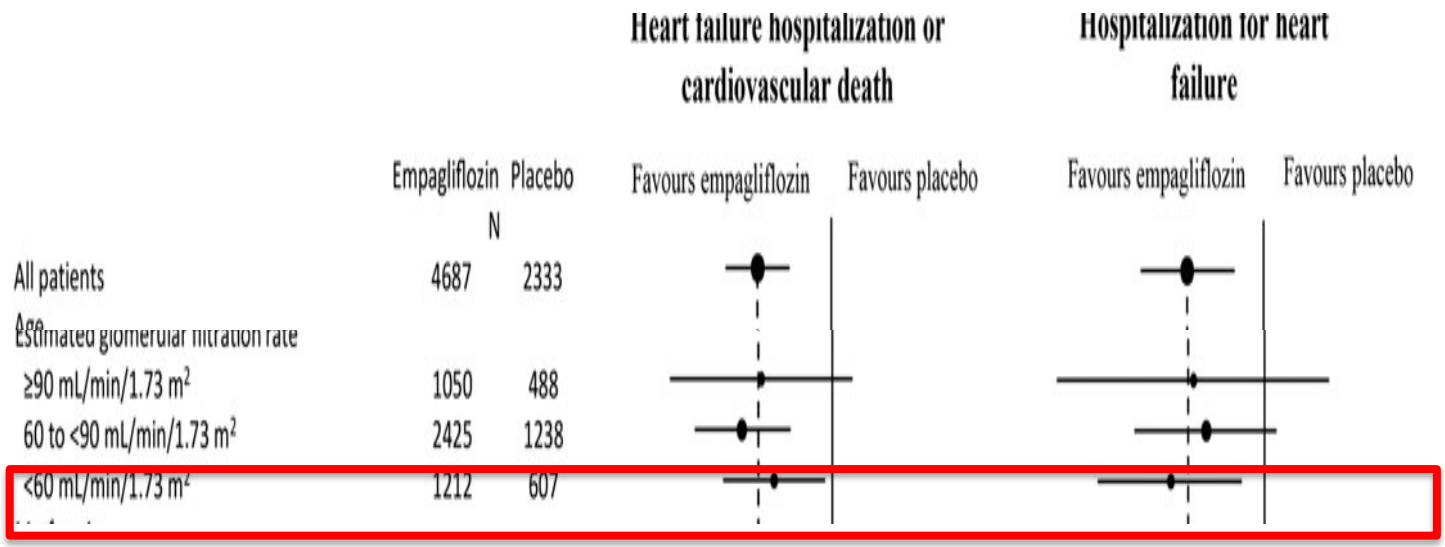
	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Glucose-lowering medication*			
Metformin	1734 (74.3)	1729 (73.7)	1730 (73.9)
Sulphonylurea	992 (42.5)	985 (42.0)	1029 (43.9)
Thiazolidinedione	101 (4.3)	96 (4.1)	102 (4.4)
Insulin	1135 (48.6)	1132 (48.3)	1120 (47.8)

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

	DAPA 10 mg (N=8582)	Placebo[a] (N=8578)
Glucose-lowering therapies		
Metformin	7020 (81.8)	7048 (82.2)
Insulin	3567 (41.6)	3446 (40.2)
Sulfonylurea	3615 (42.1)	3707 (43.2)
DPP-4 inhibitor	1418 (16.5)	1470 (17.1)
GLP-1 RA	397 (4.6)	353 (4.1)

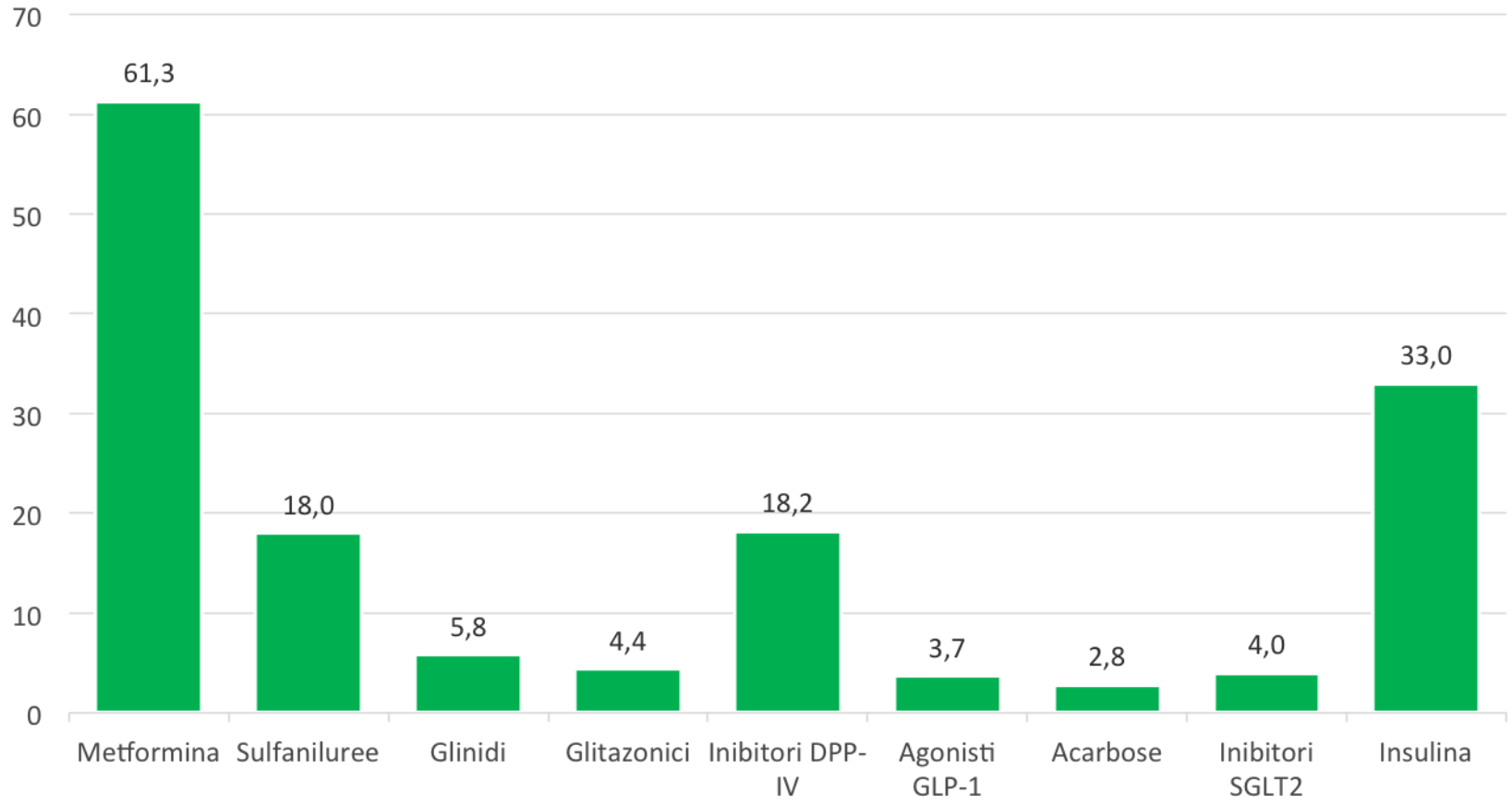
Wiviott SD et al. Online ahead of print. *New Engl J Med.* 2018.

LIMITAZIONI SCHEDA TECNICA



eGFR fino a (ml/min*1.73 m²)	90	80	70	60	50	40	30	20	15	Dialisi
Gliflozine										
Dapagliflozin										
Empagliflozin[c]										
Canagliflozin[c]										

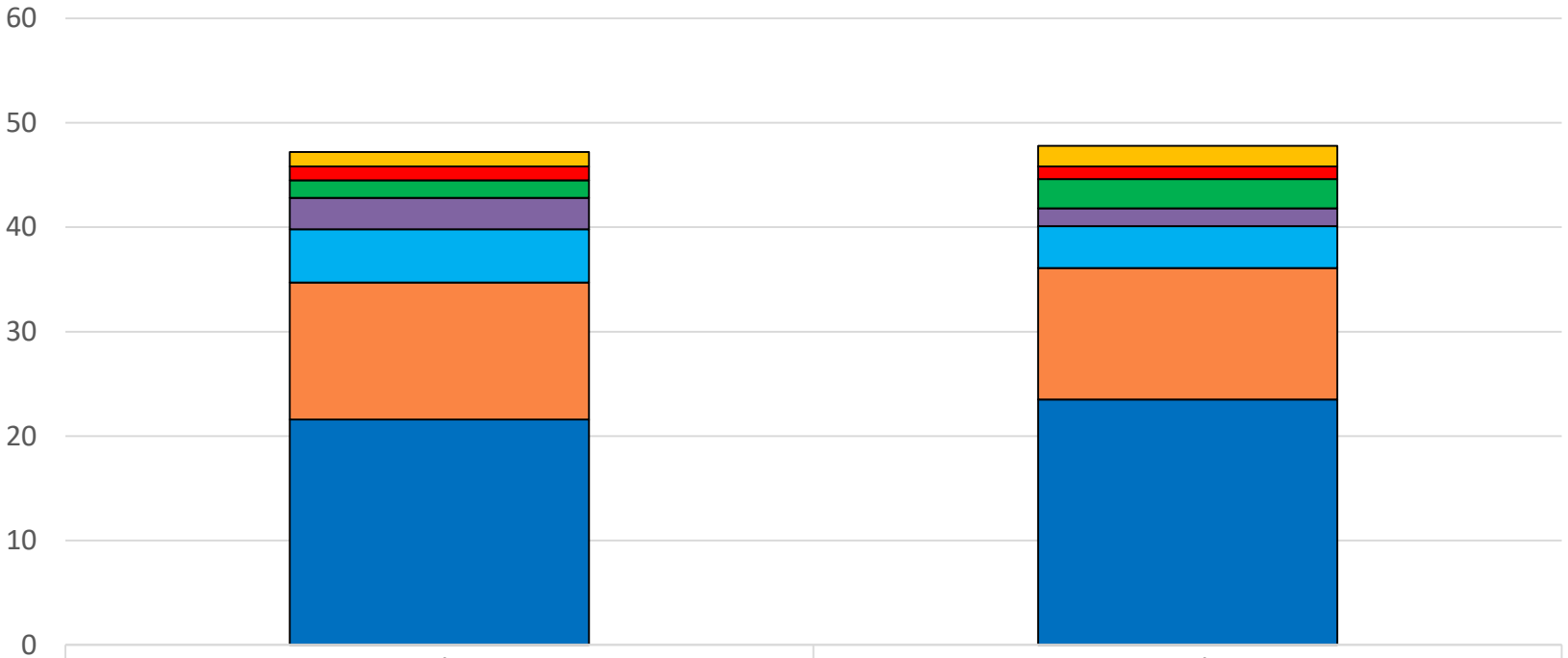
Distribuzione dei pazienti per classe di farmaco ipoglicemizzante (%)



Italia vs FVG

AIFA OSMED 2017 – Direzione Centrale Salute fvg

DDD/1000 ab/die



	Italia	Friuli
SGLT2	1,4	2
GLP1-RA	1,3	1,2
Pioglitazione	1,7	2,8
Glinidi	3	1,7
Gliptine	5,1	4
Altri (SU)	13,1	12,6
Biguanidi	21,6	23,5

Da Porto A. Progetto RADAR