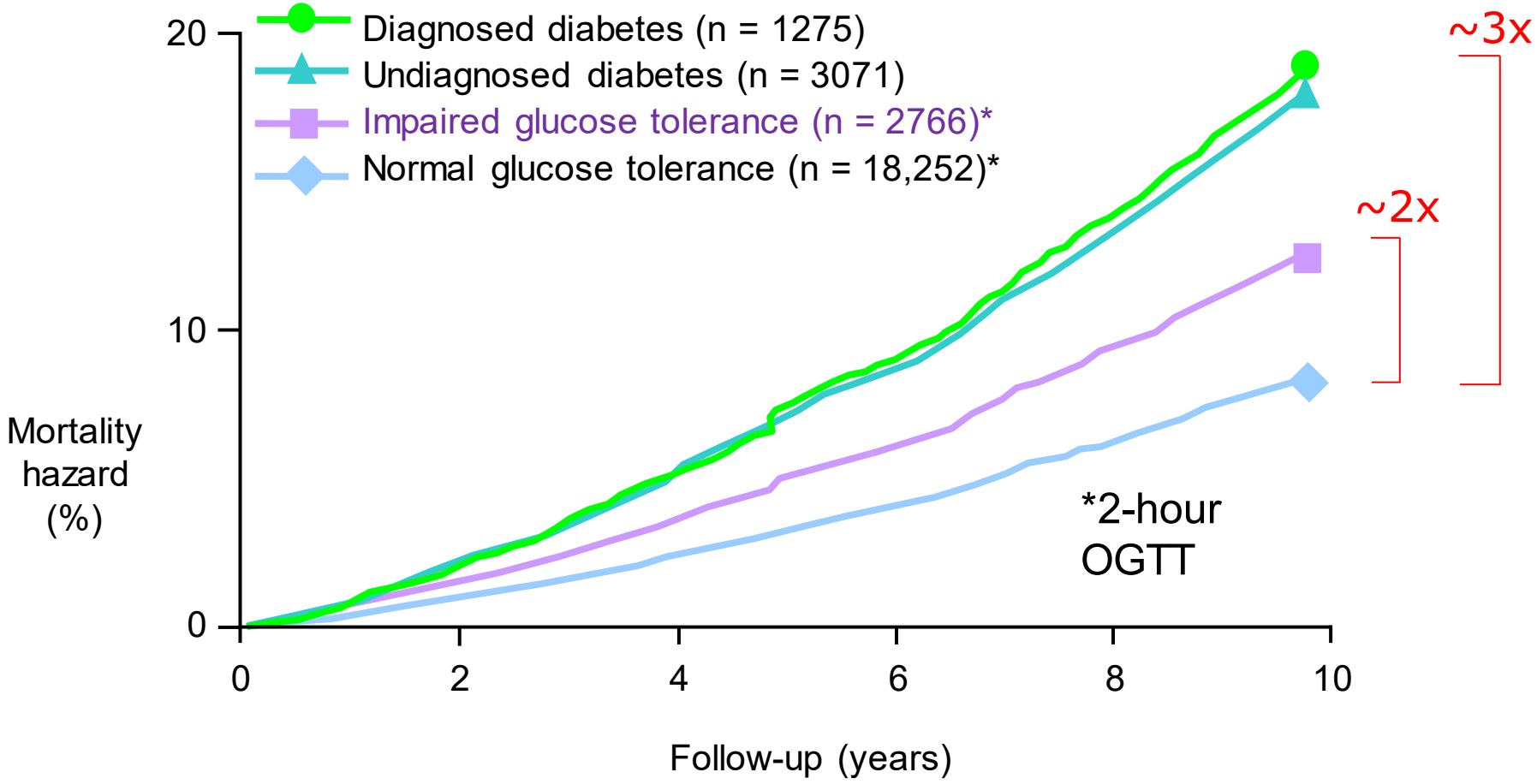
Could we reduce mortality for diabetic patients?

cardiologist's point of view

Dinh Duc Huy, MD, FSCAI

DECODE: even IGT increases mortality risk

Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe
N = 25,364 aged ≥30 years



DECODE Study Group. Lancet. 1999;354:617-21

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 13, 2017 VOL. 376 NO. 15

Mortality & Cardiovascular Disease in Type 1 and Type 2 Diabetes

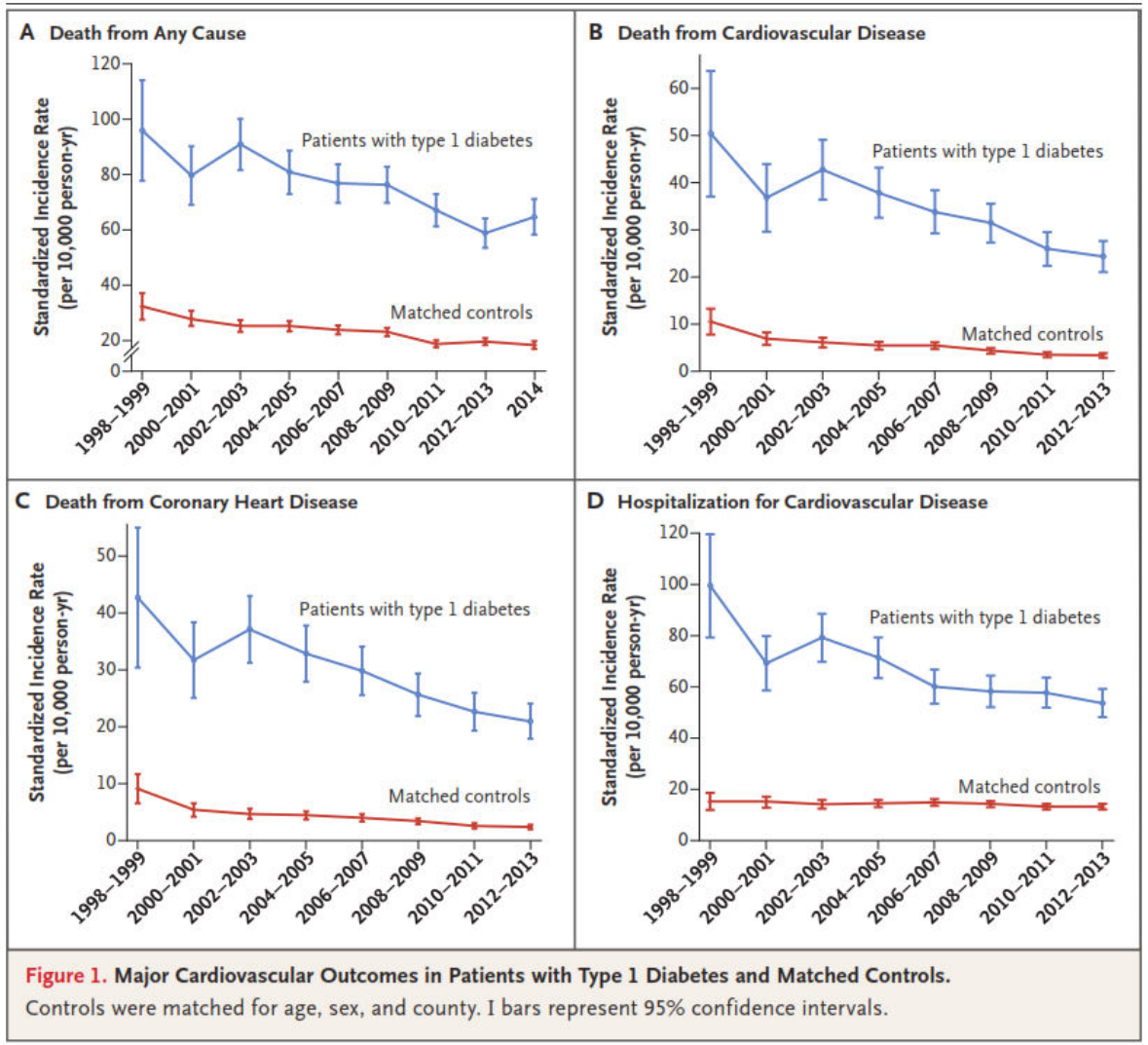


Figure 1. Major Cardiovascular Outcomes in Patients with Type 1 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

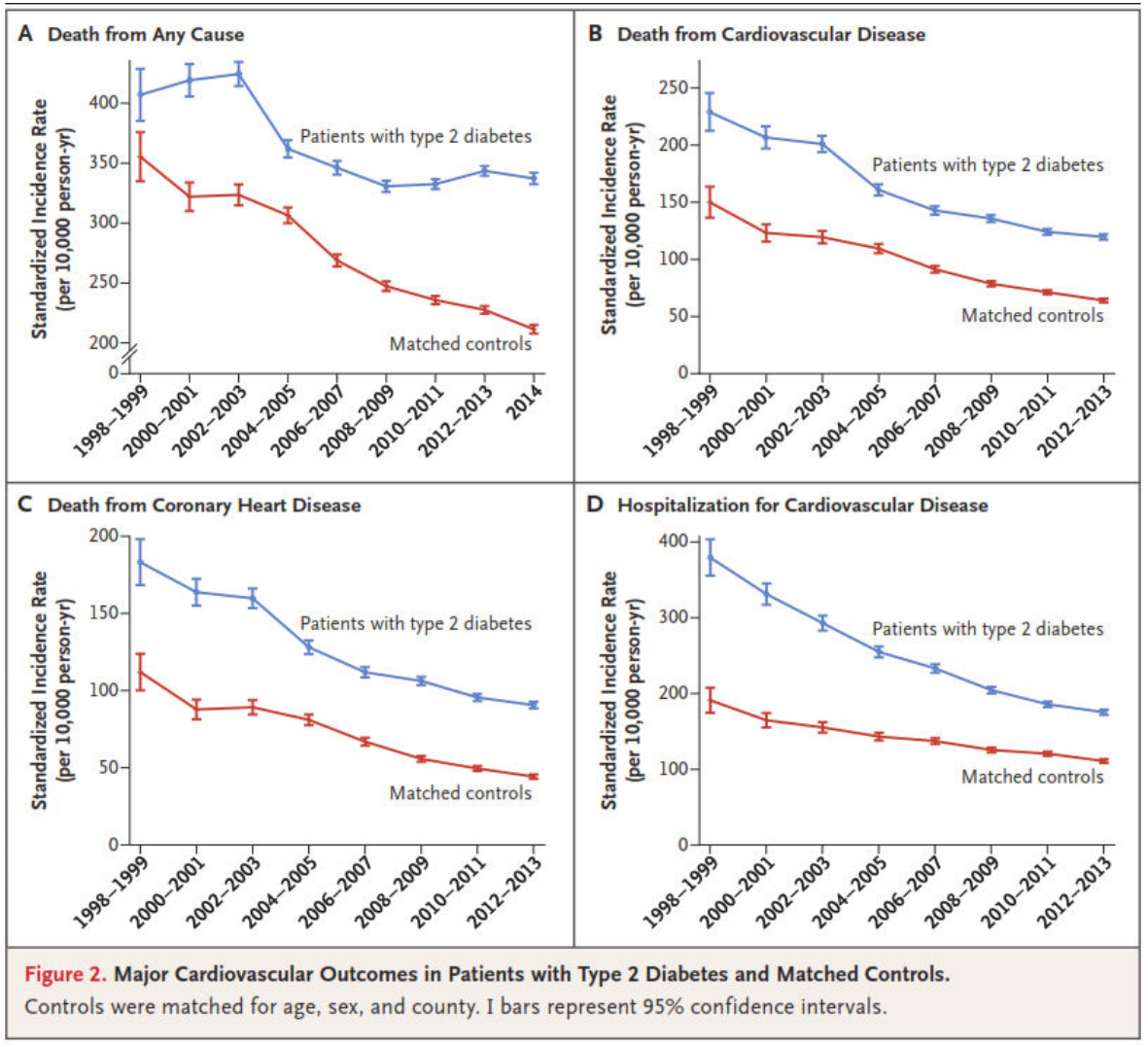


Figure 2. Major Cardiovascular Outcomes in Patients with Type 2 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

The NEW ENGLAND JOURNAL of MEDICINE

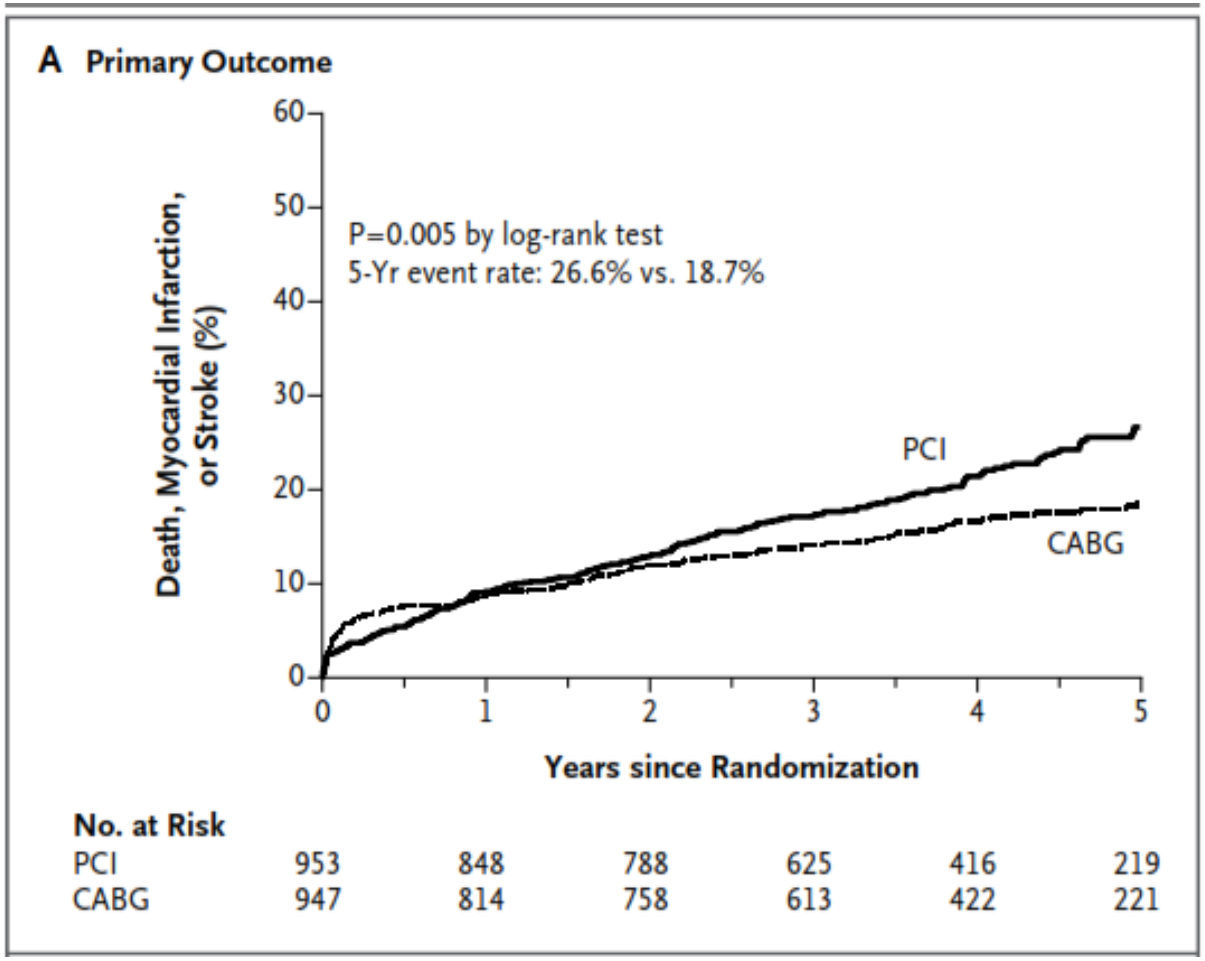
ESTABLISHED IN 1812 DECEMBER 20, 2012 VOL. 367 NO. 25

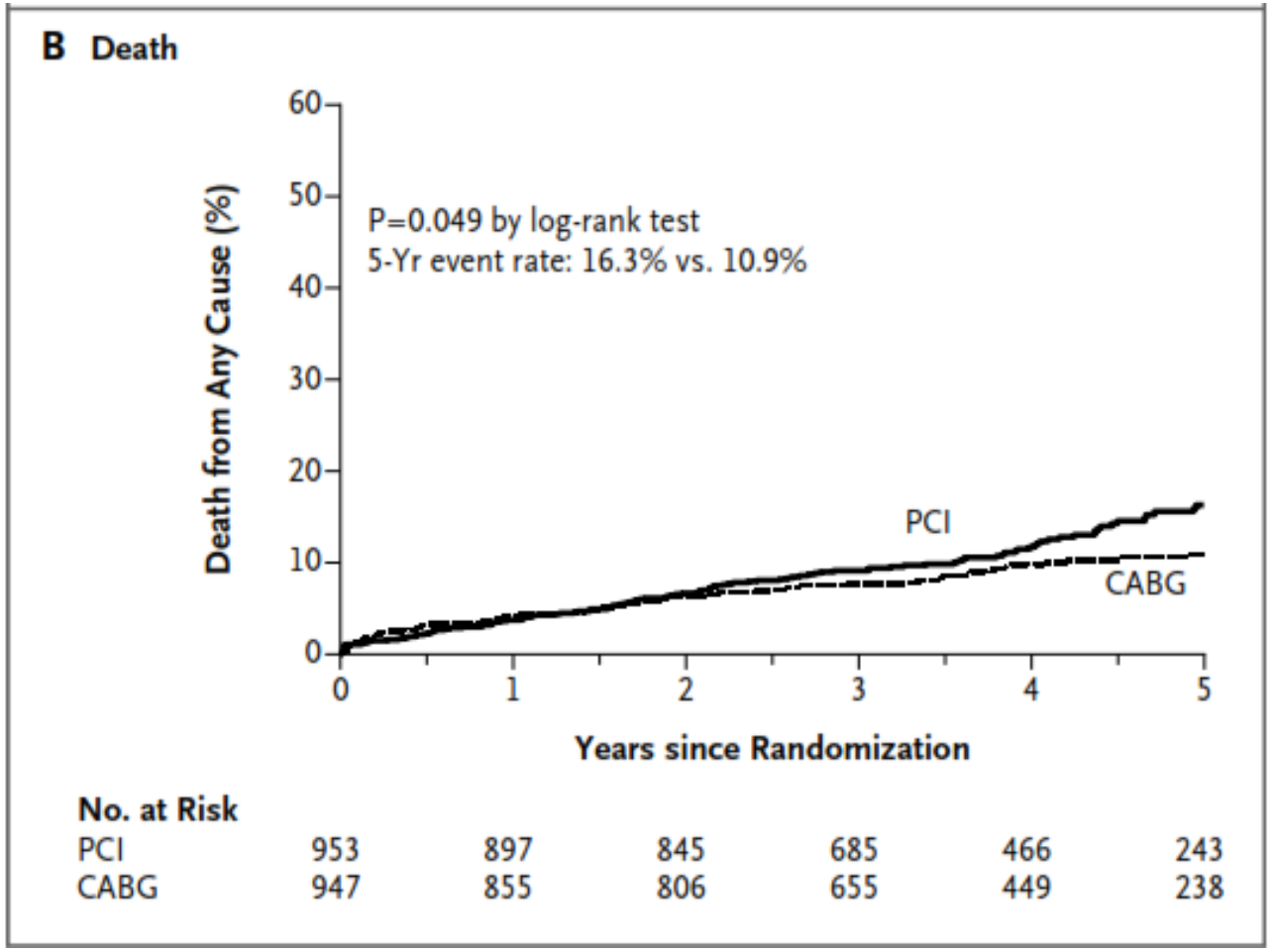
Strategies for Multivessel Revascularization in Patients with Diabetes

- 1900 patients at 140 international centers with diabetes and multivessel CAD
- PCI with DES or CABG.
- Minimum of 2 years f/u (median among survivors, 3.8 years).
- Primary outcome: death from any cause/ nonfatal MI/ nonfatal stroke

Farkouh ME, N Engl J Med 2012

FREEDOM study- Primary outcomes: CABG is better than PCI





Farkouh ME, N Engl J Med 2012

FREEDOM study- Key outcomes & Primary outcomes in subgroups

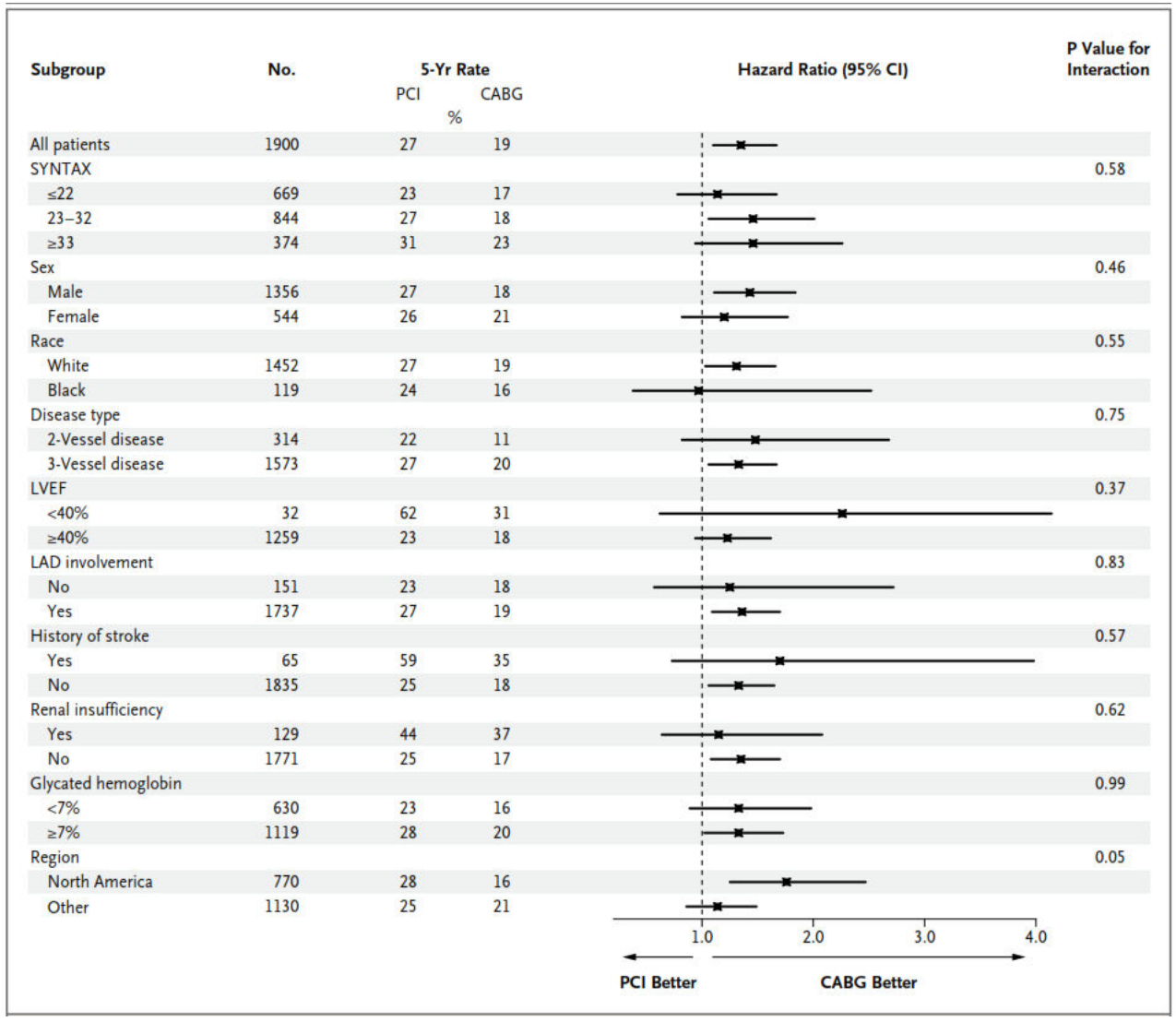


Table 3. Kaplan–Meier Estimates of Major Adverse Cardiovascular and Cerebrovascular Events at 30 Days and 12 Months after the Procedure.

Event	30 Days after Procedure			12 Months after Procedure		
	PCI	CABG	P Value	PCI	CABG	P Value
	number (percent)			*number (percent)*		
Major adverse cardiovascular and cerebrovascular events	45 (4.8)	47 (5.2)	0.68	157 (16.8)	106 (11.8)	0.004
Death	8 (0.8)	15 (1.7)	0.12	32 (3.4)	38 (4.2)	0.35
Myocardial infarction	17 (1.8)	15 (1.7)	0.82	54 (5.8)	30 (3.4)	0.02
Stroke	3 (0.3)	16 (1.8)	0.002	8 (0.9)	17 (1.9)	0.06
Repeat revascularization	31 (3.3)	10 (1.1)	0.002	117 (12.6)	42 (4.8)	<0.001

Table 2. Kaplan–Meier Estimates of Key Outcomes at 2 Years and 5 Years after Randomization.

Outcome	2 Years after Randomization		5 Years after Randomization		Patients with Event		P Value*
	PCI	CABG	PCI	CABG	PCI	CABG	
	number (percent)				*number*		
Primary composite†	121 (13.0)	108 (11.9)	200 (26.6)	146 (18.7)	205	147	0.005‡
Death from any cause	62 (6.7)	57 (6.3)	114 (16.3)	83 (10.9)	118	86	0.049
Myocardial infarction	62 (6.7)	42 (4.7)	98 (13.9)	48 (6.0)	99	48	<0.001
Stroke	14 (1.5)	24 (2.7)	20 (2.4)	37 (5.2)	22	37	0.03§
Cardiovascular death	9 (0.9)	12 (1.3)	73 (10.9)	52 (6.8)	75	55	0.12

Farkouh ME, N Engl J Med 2012

Treatment of complex coronary artery disease in patients with diabetes:

5-year results comparing outcomes of CABG and PCI in the SYNTAX trial

- Subgroups with (*n* = 452) or without (*n* = 1348) diabetes
- Major adverse cardiac or cerebrovascular events (MACCE)
- Composite safety end-point of all-cause death/stroke/MI
- Individual MACCE components death, stroke, MI and repeat revascularization
- Compared with non-diabetic patients (*n* = 1348), those with diabetes (*n* = 452) had a significantly higher risk profile (higher EuroSCORE of 4.0 ± 2.7 vs 3.7 ± 2.6, *P* = 0.027)
- Diabetics also had more coronary lesions (4.6 ± 1.8 vs 4.3 ± 1.8, *P* = 0.003) & more diffuse disease or small vessels (13 vs 10%, *P* = 0.061)
- Mean SYNTAX Score was comparable (29.0 ± 11.2 vs 28.6 ± 11.5, *P* = 0.52).

Kappetein, European Journal of Cardio-Thoracic Surgery, 2013

Five-year clinical outcomes according to diabetes status

Clinical outcome	Non-diabetic (*n* = 1348)			Diabetic (*n* = 452)			Non-diabetic vs diabetic		
	CABG (*n* = 676)	PCI (*n* = 672)	*P*-value	CABG (*n* = 221)	PCI (*n* = 231)	*P*-value	*P*-value (CABG)	*P*-value (PCI)	Interaction *P*-value [a]
MACCE [b]	26.3% (167)	34.1% (226)	0.002	29.0% (59)	46.5% (105)	<0.001	0.37	<0.001	0.17
All-cause death/stroke/myocardial infarction	15.9% (101)	19.8% (131)	0.069	19.1% (39)	23.9% (54)	0.26	0.25	0.18	0.76
All-cause death	10.9% (68)	12.0% (79)	0.48	12.9% (26)	19.5% (44)	0.065	0.34	0.003	0.43
Cardiac death	4.9% (30)	7.7% (50)	0.035	6.5% (13)	12.7% (28)	0.034	0.31	0.018	
Stroke	3.5% (22)	2.2% (14)	0.15	4.7% (9)	3.0% (6)	0.34	0.49	0.55	0.97
Myocardial infarction	3.4% (22)	9.9% (64)	<0.001	5.4% (11)	9.0% (19)	0.20	0.22	0.66	0.18
Repeat revascularization	13.4% (82)	22.8% (145)	<0.001	14.6% (28)	35.3% (75)	<0.001	0.60	<0.001	0.081

Kappetein, European Journal of Cardio-Thoracic Surgery, 2013

Comparison of CABG & PCI in patients with diabetes: a meta-analysis of RCTs

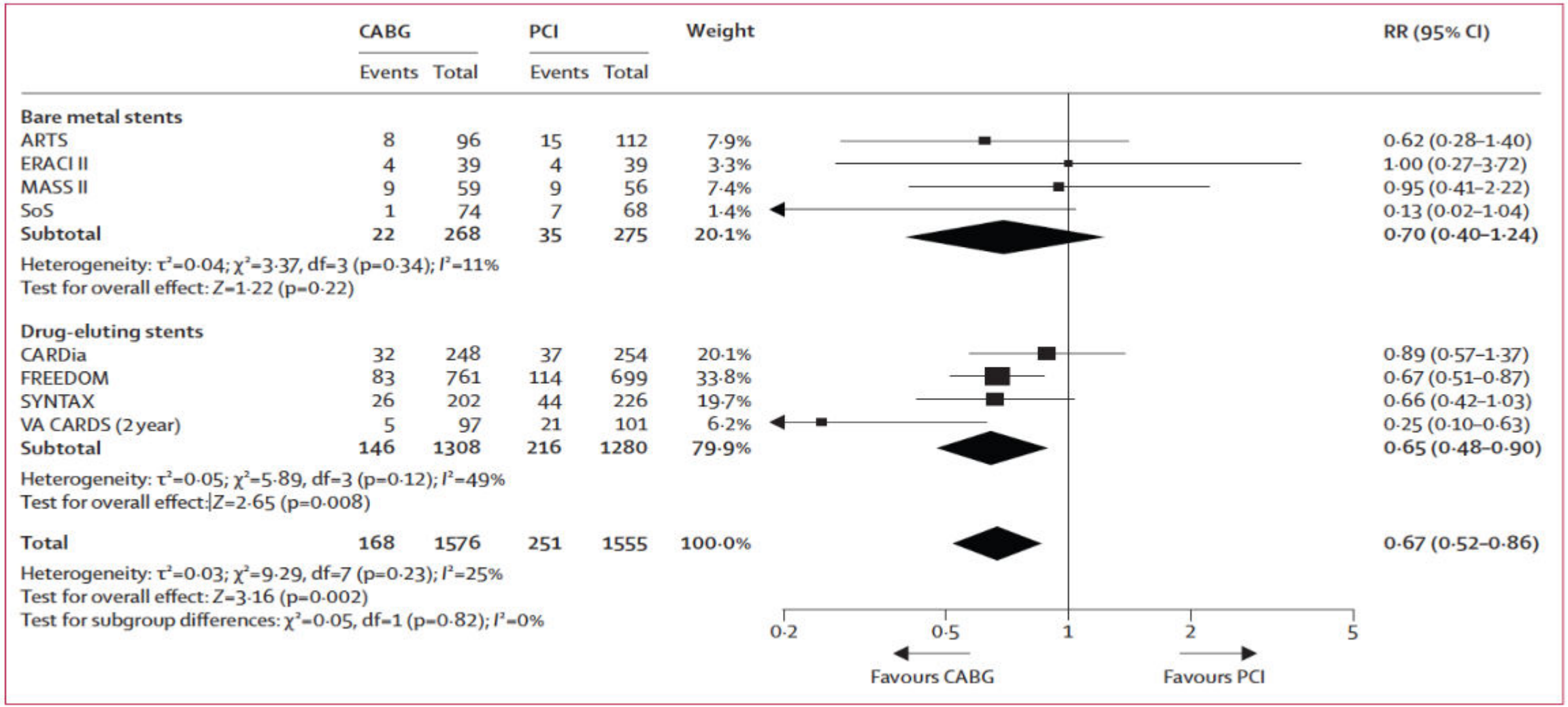
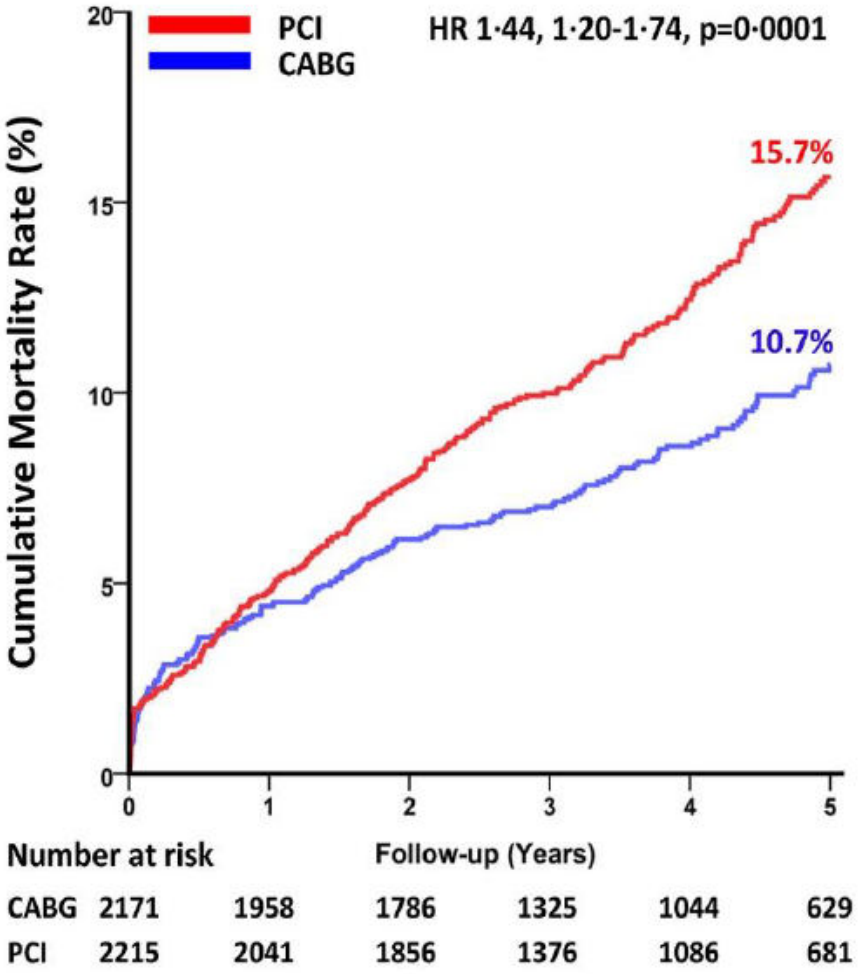


Figure 2: **Forest plot for all-cause mortality at 5-year (or longest) follow-up**

Verma et al. Lancet Diabetes Endocrinol. 2013; 1: 317-28.

Individual-patient-data Analysis from 11 PCI vs. CABG Trials- 11,518 randomized patients

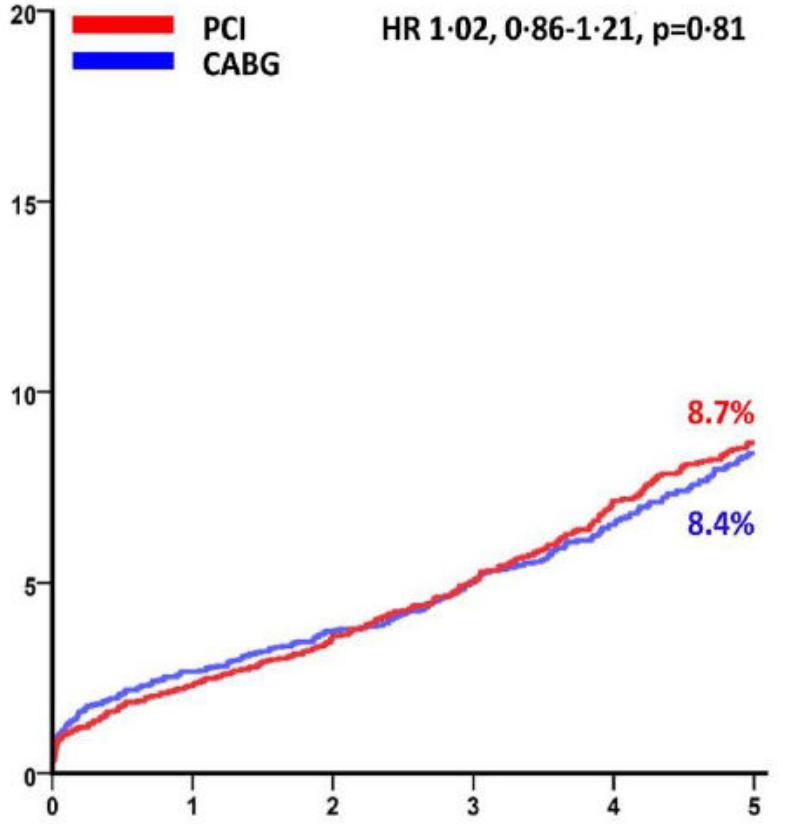
Diabetes



Number at risk

CABG	2171	1958	1786	1325	1044	629
PCI	2215	2041	1856	1376	1086	681

Non Diabetes



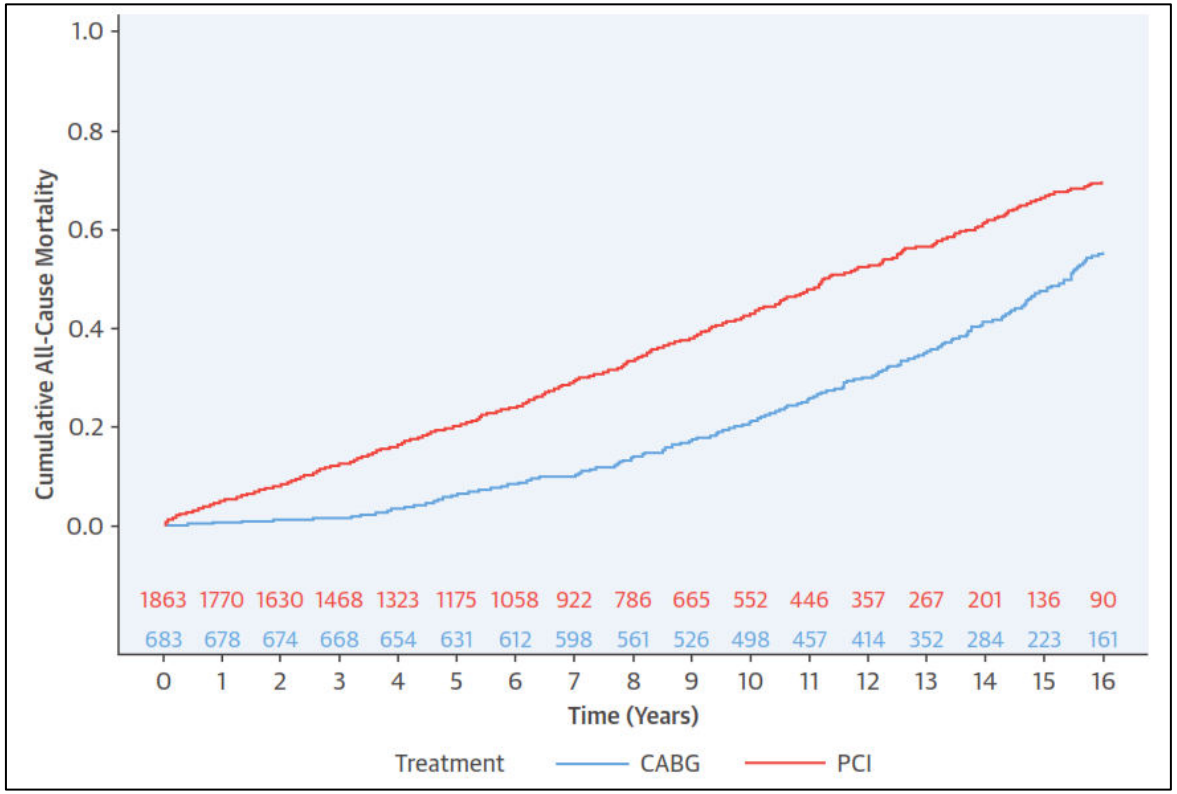
	3594	3402	3208	2436	2255	1633
	3538	3417	3245	2477	2296	1724

TCT 2017 Pieter Kappetein

PCI Versus CABG in Patients With Type 1 Diabetes and Multivessel Disease

Thomas Nyström, MD, PhD,[a,b] Ulrik Sartipy, MD, PhD,[c,d] Stefan Franzén, PhD,[e] Björn Eliasson, MD, PhD,[e] Soffia Gudbjörnsdottir, MD, PhD,[e] Mervete Miftaraj, MSc,[e] Bo Lagerqvist, MD, PhD,[f] Ann-Marie Svensson, PhD,[e] Martin J. Holzmann, MD, PhD[g,h]

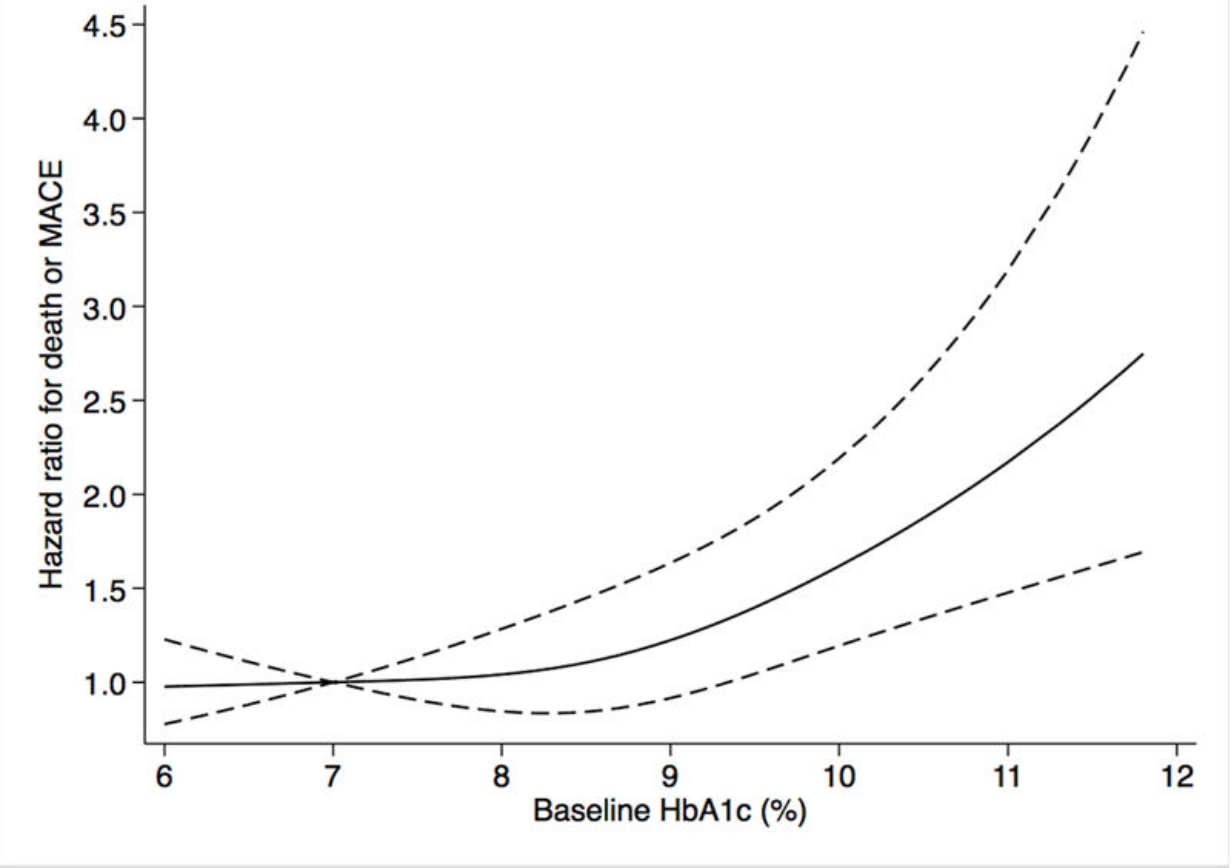
- 683 pts w CABG- 1,863 pts w PCI
- Mean follow-up of 10.6 years
- PCI, compared with CABG, was associated similar risk of all-cause mortality (HR: 1.14; 95% CI: 0.99-1.32); higher risks of death from coronary heart disease (HR: 1.45; 95% CI: 1.21-1.74), MI (HR: 1.47; 95% CI: 1.23-1.78), and repeat revascularization (HR: 5.64; 95% CI: 4.67-6.82)
- No differences in risks of stroke or heart failure were found.



J Am Coll Cardiol. 2017 Sep 19;70(12):1441-1451. doi: 10.1016/j.jacc.2017.07.744. Epub 2017 Aug 26.

Relationship between pre-operative HbA1c & All-cause mortality or MACE

Outcome	No. events/PY	Crude rate [95% CI] per 1000 PY	Adjusted hazard ratio [95% CI]
Death+MACE			
≤7.0 (Ref)	29/358	81 [56 - 116]	1.00
7.1-8.0	76/993	76 [61 - 96]	1.34 [0.82 - 2.21]
8.1-9.0	122/1588	77 [64 - 92]	1.59 [1.00 - 2.54]
9.1-10.0	64/796	80 [63 - 103]	1.73 [1.03 - 2.90]
>10.0	43/355	121 [90 - 163]	2.25 [1.29 - 3.94]



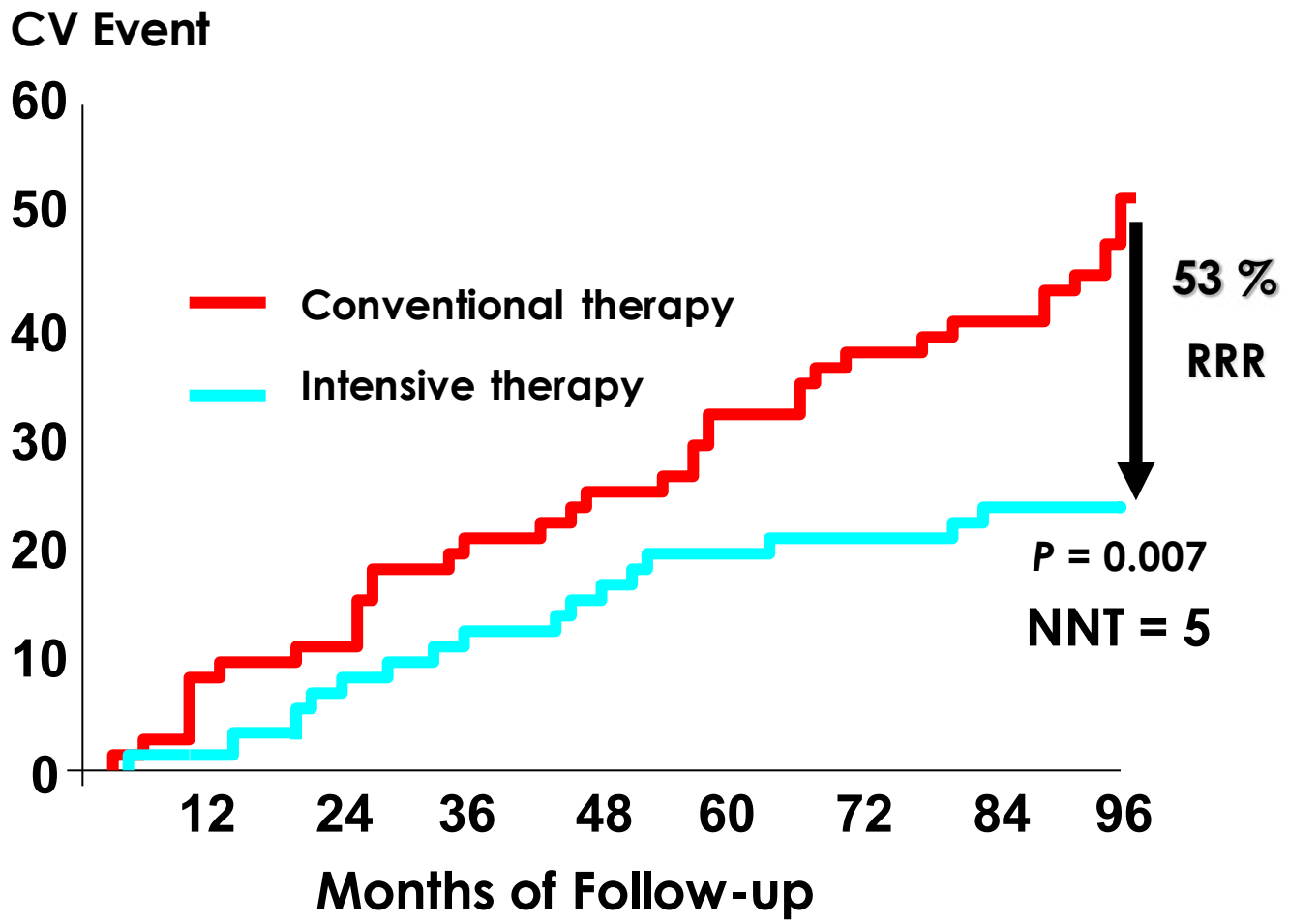
- 2 Swedish nationwide observational cohort studies
- poor glycemic control prior to CABG is associated with an increased risk of death or MACE
- more pronounced in patients with T1DM
- relationship between HbA1c and death or MACE already at HbA1c levels 7.1-8%
- increased by 18% for every 1% absolute increase in HbA1c levels

Kuhl J, Int J Cardiol 2016;202:291-6.
Nyström T, J Am Coll Cardiol 2015;66:535-43.

Impact of Multifaceted Strategy on CV Events in diabetics

Intensive Goals

- Exercise program
- Smoking cessation
- Diet
- Total chol < 4.6
- SBP < 130
- A1C < 6.5
- ACE I / ARB
- ASA

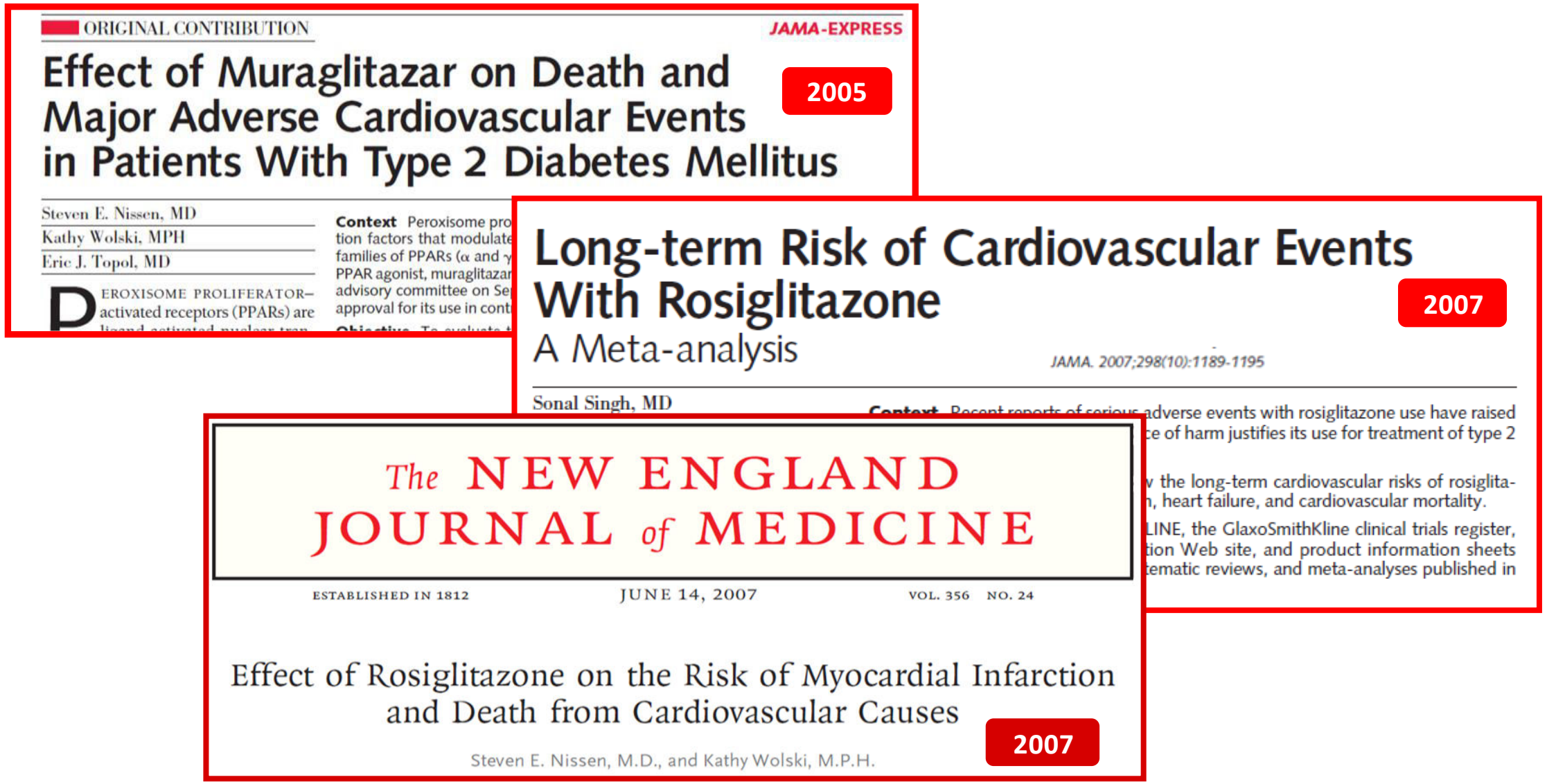


Gaede et al. NEJM. 2003: 348;383-393

Reduction of macrovascular risk with intensive glycemic lowering had not been consistently observed

Randomized Controlled Trials	Follow-up (median)	Microvascular Risk	Macrovascular Risk
DCCT	6.5 years (mean)	↓	↔
UKPDS	10 years	↓	↔
ADVANCE	5 years	↓	↔
ACCORD	3.7 years	↓	↔
VADT	5.6 years	↔	↔
Observational Long-term Follow-up	**Follow-up (median)**	**Microvascular Risk**	**Macrovascular Risk**
DCCT/EDIC	4 (micro) 11 (macro) years post-intervention	↓	↓
UKPDS	10 years post-intervention	↓	↓
ADVANCE-ON	9.9 years	↔	↔
VADT	9.8 years	not reported	↓

Lessons learnt from Rosiglitazone



ORIGINAL CONTRIBUTION

JAMA-EXPRESS

Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

2005

Steven E. Nissen, MD
Kathy Wolski, MPH
Eric J. Topol, MD

PEROXISOME PROLIFERATOR–activated receptors (PPARs) are

Context Peroxisome pro
tion factors that modulate
families of PPARs (α and γ
PPAR agonist, muraglitazar
advisory committee on Se
approval for its use in cont

Long-term Risk of Cardiovascular Events With Rosiglitazone

A Meta-analysis

2007

JAMA. 2007;298(10):1189-1195

Sonal Singh, MD

adverse events with rosiglitazone use have raised
ce of harm justifies its use for treatment of type 2

v the long-term cardiovascular risks of rosiglita-
n, heart failure, and cardiovascular mortality.

LINE, the GlaxoSmithKline clinical trials register,
tion Web site, and product information sheets
tematic reviews, and meta-analyses published in

The NEW ENGLAND JOURNAL of MEDICINE

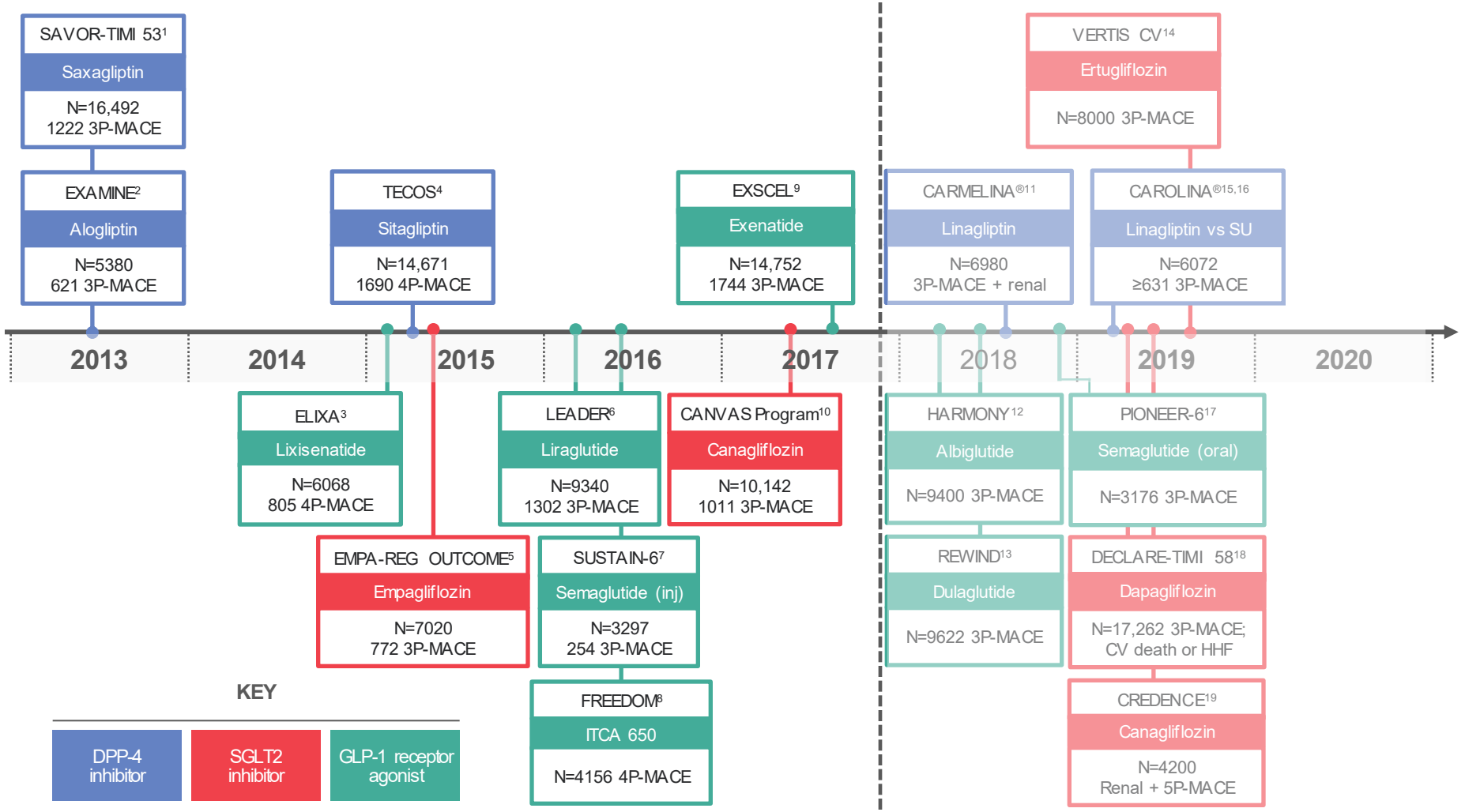
ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

2007

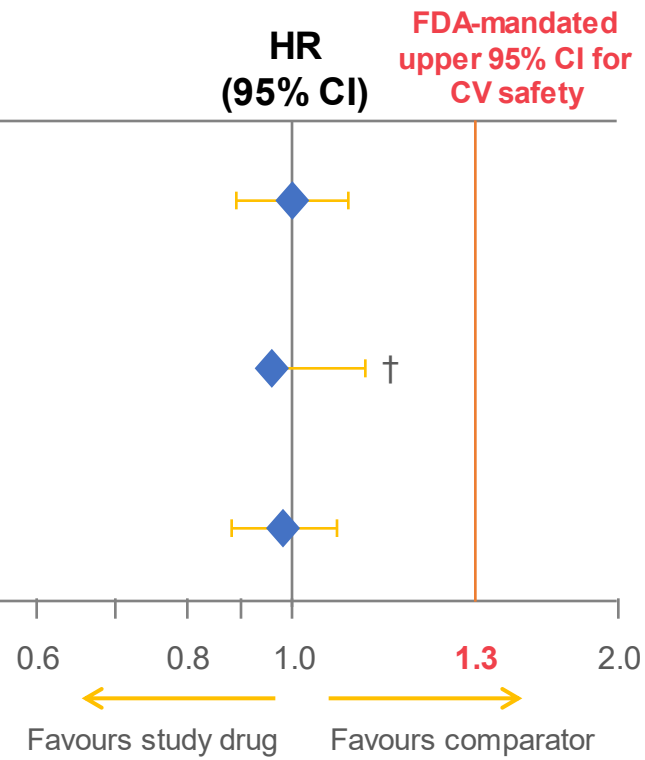
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Timeline of results from CV safety studies of glucose-lowering agents



For the primary outcome, previously completed CVOTs with DPP-4 inhibitors fall within the FDA-mandated upper 95% CI limit of 1.3

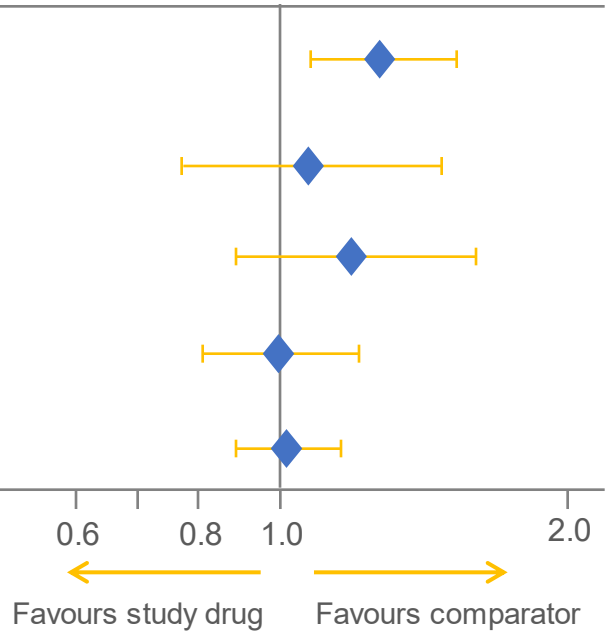
	Number of patients with events (event rate, number of events/ 100 person-years)	
	Placebo + standard of care	Comparator + standard of care
SAVOR-TIMI 53[1]	609 (3.7)	613 (3.7)
EXAMINE[2]	316 (11.8%)*	305 (11.3%)*
TECOS[3]	851 (4.17)	839 (4.06)



1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. White WB *et al. N Engl J Med* 2013;369:1327; 3. Green JB *et al. N Engl J Med* 2015;373;232

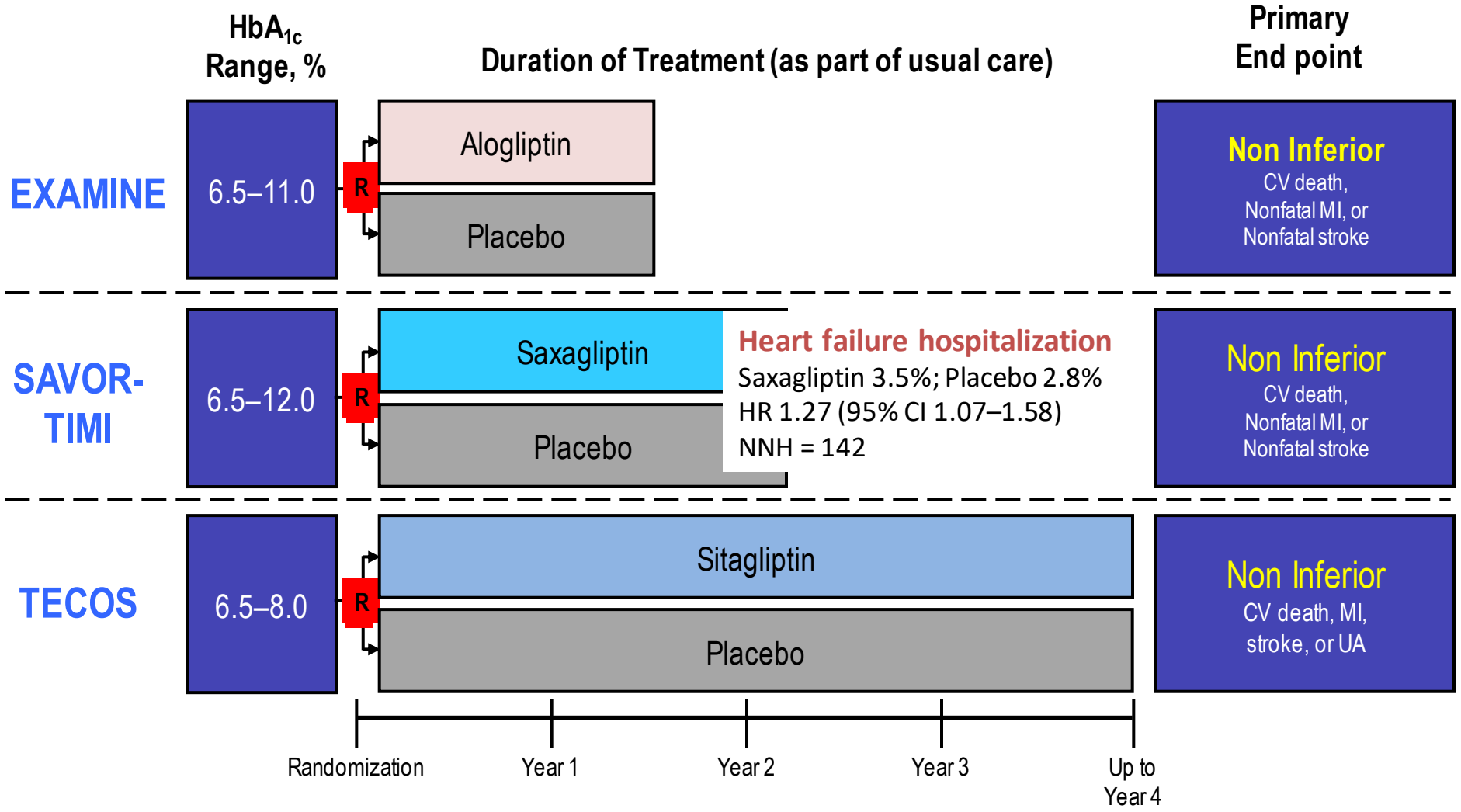
Hospitalisation for heart failure data for previously completed CVOTs with DPP-4i

	Number of events (%)	
	Placebo + standard of care	Comparator + standard of care
SAVOR-TIMI 53 (HHF)[1]	228 (2.8)	289 (3.5)
EXAMINE (HHF analysis 1)[2]	79 (2.9)	85 (3.1)
EXAMINE (HHF analysis 2)[2]	89 (3.3)	106 (3.9)
TECOS (HHF)[3]	229 (3.1)	228 (3.1)
TECOS (HHF + CV death)[3]	525 (7.2)	538 (7.3)



1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. Zannad F *et al. Lancet* 2015;385:2067; 3. Green JB *et al. N Engl J Med* 2015;73:232

DPP4i Trials and CVD Outcomes



Scirica BM *et al. N Engl J Med* 2013;369:1317; White WB *et al. N Engl J Med* 2013;369:1327; Green JB *et al. N Engl J Med* 2015;373;232

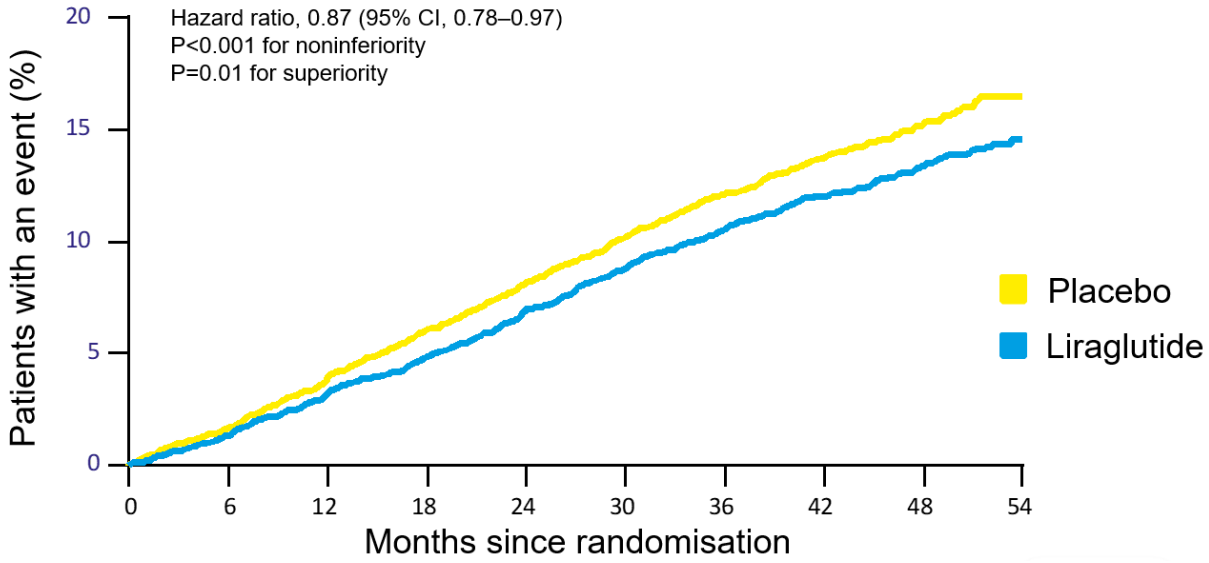
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

GLP-1 receptor agonist CVOT

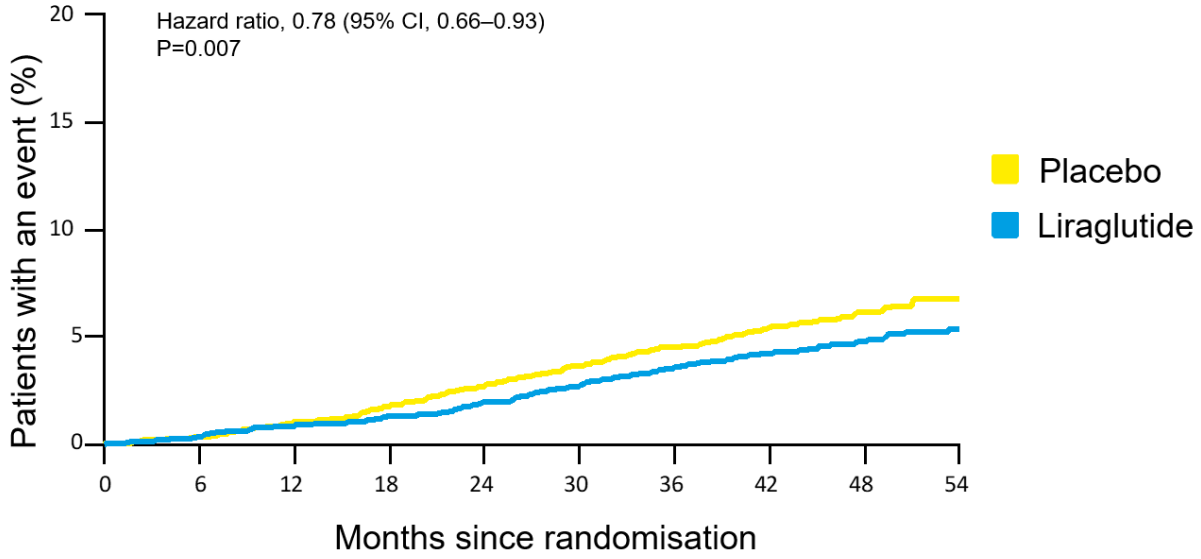
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

LEADER trial: Primary Outcome

First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis in patients with type 2 diabetes and high CV risk.

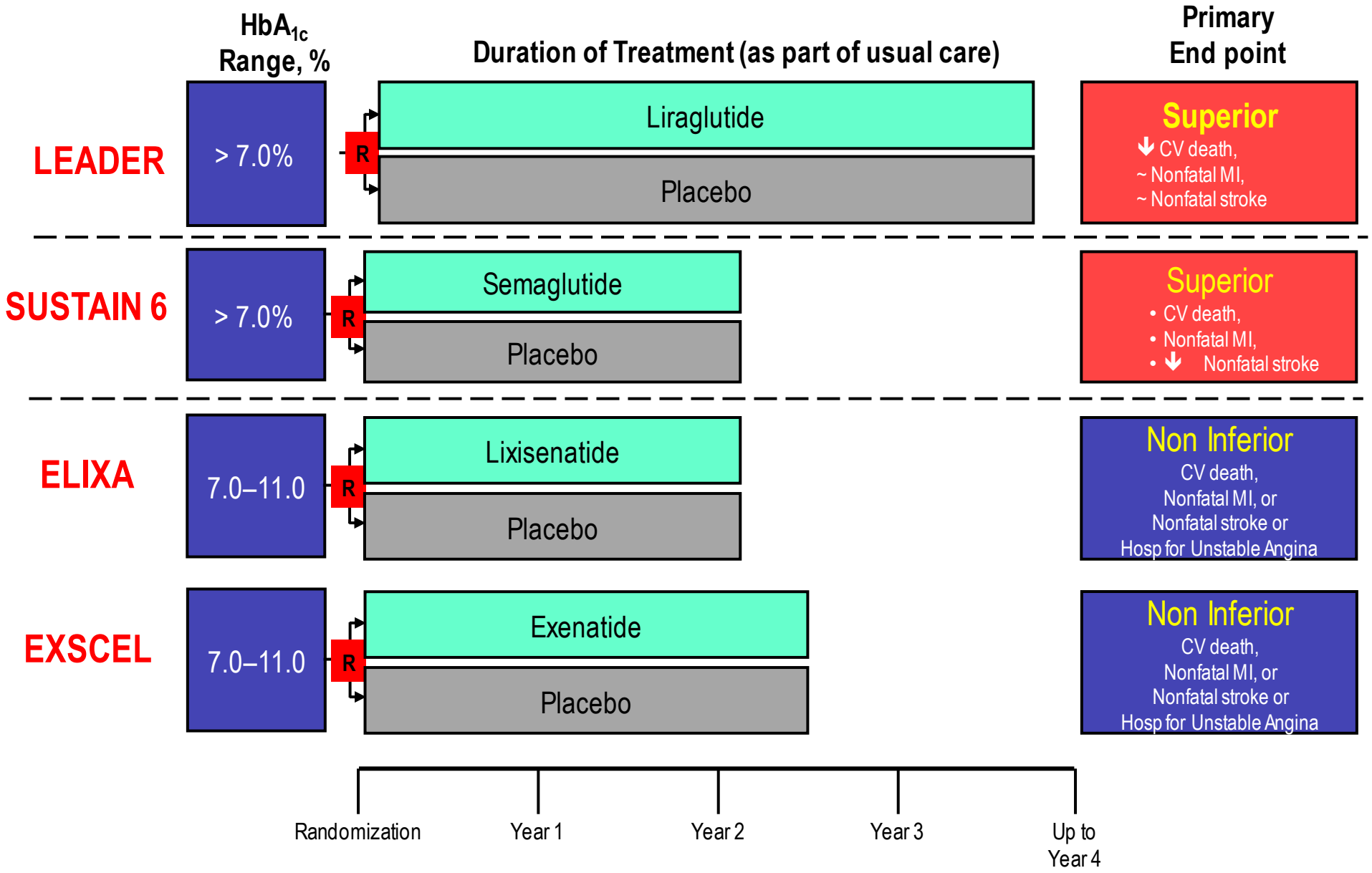


LEADER trial: Death from Cardiovascular Causes

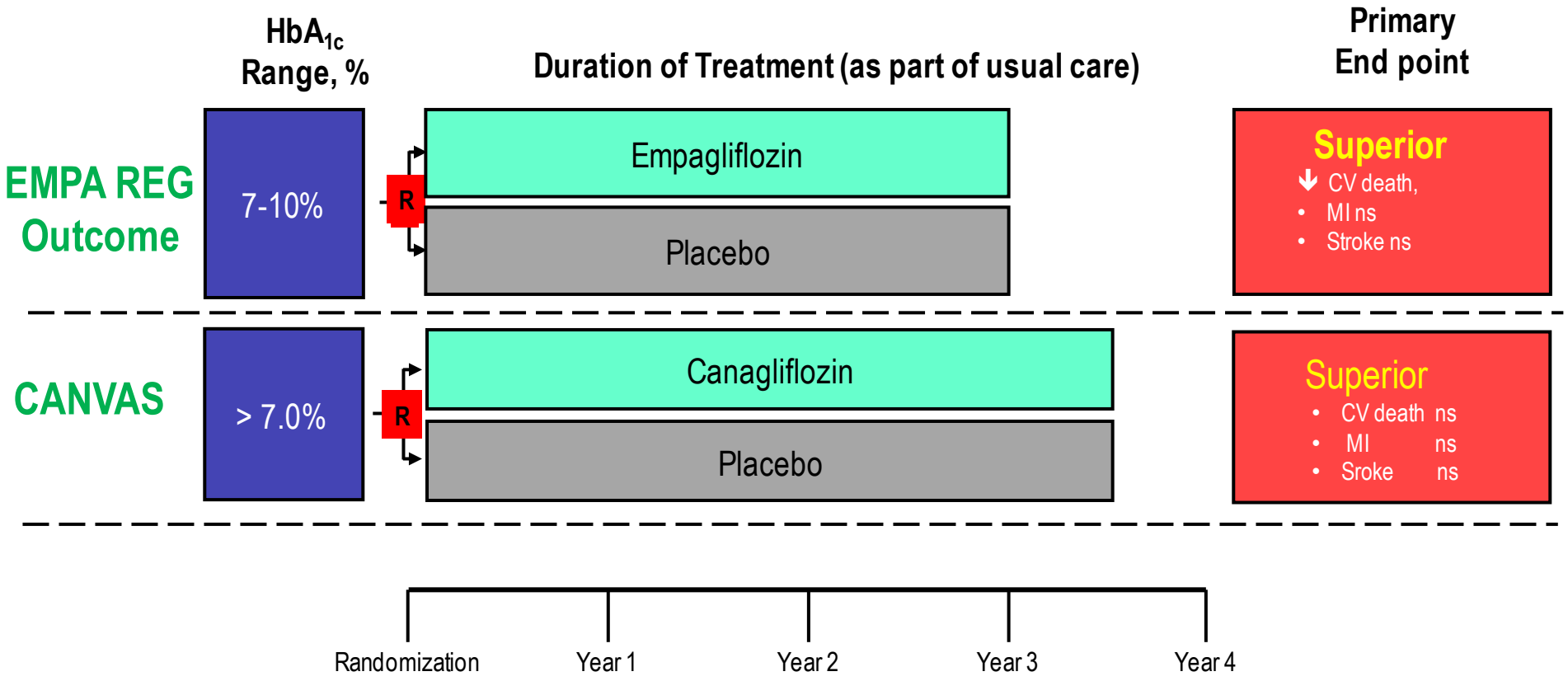


Marso SP, NEJM 2016

GLP1 Agonist Trials and CVD Outcomes



SGLT2i and CVD Outcomes



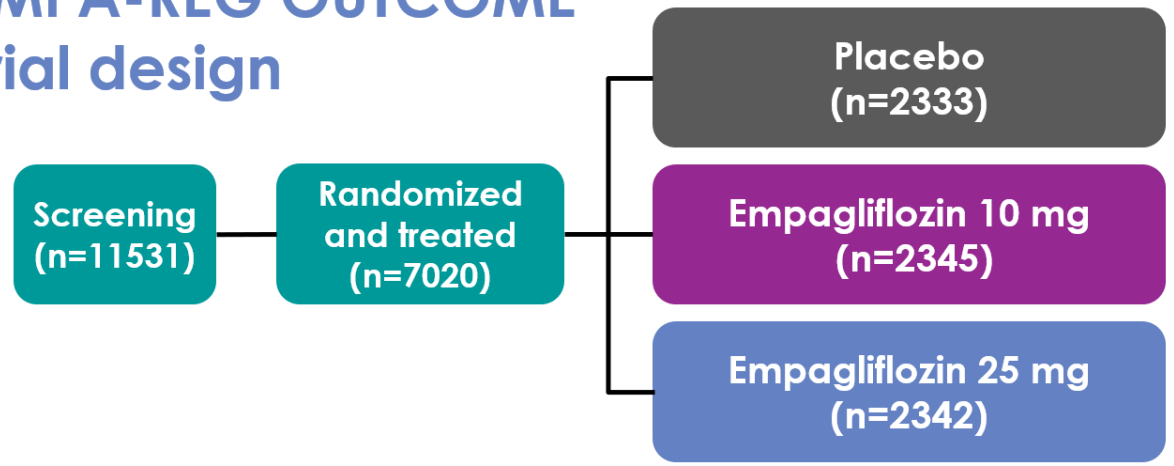
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Established CV disease – History of MI or stroke >2 months before study – Coronary artery disease – Peripheral occlusive arterial disease
Adults (≥18 years of age) with T2D
BMI ≤45 kg/m^2
HbA1c ≥7% and ≤10%*
eGFR <30 ml/min/1.73 m^2 (MDRD)
Acute coronary syndrome, stroke or transient ischaemic attack within 2 months before informed consent

EMPA-REG OUTCOME® Trial design

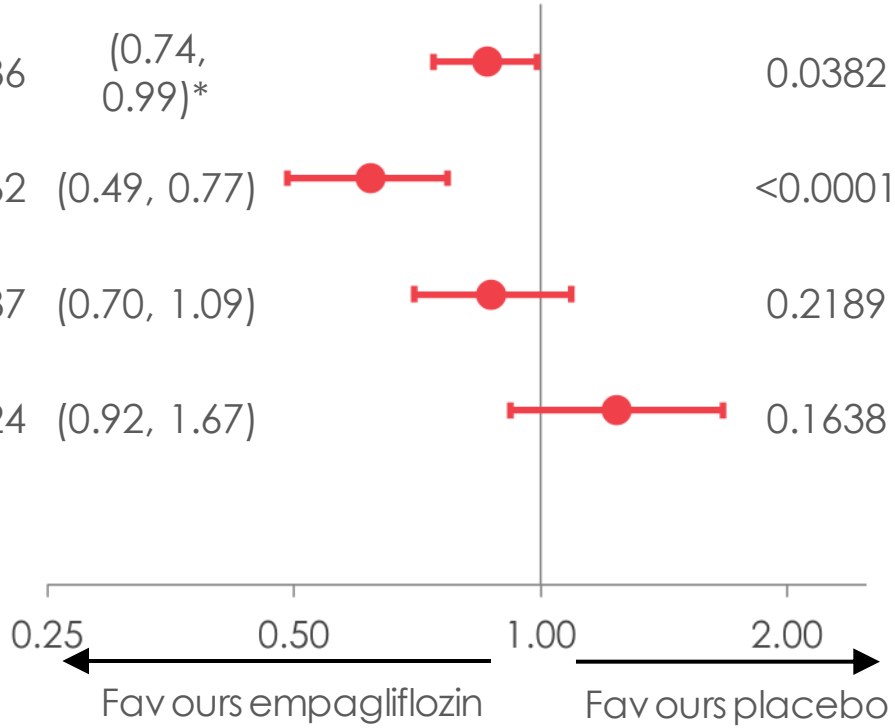


- Study medication was given in addition to standard of care.
- The trial was to continue until ≥ 691 patients experienced an adjudicated primary outcome event.

Zinman B et al. N Engl J Med 2015

EMPA- REG OUTCOME: CV death, MI and stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	p-value
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

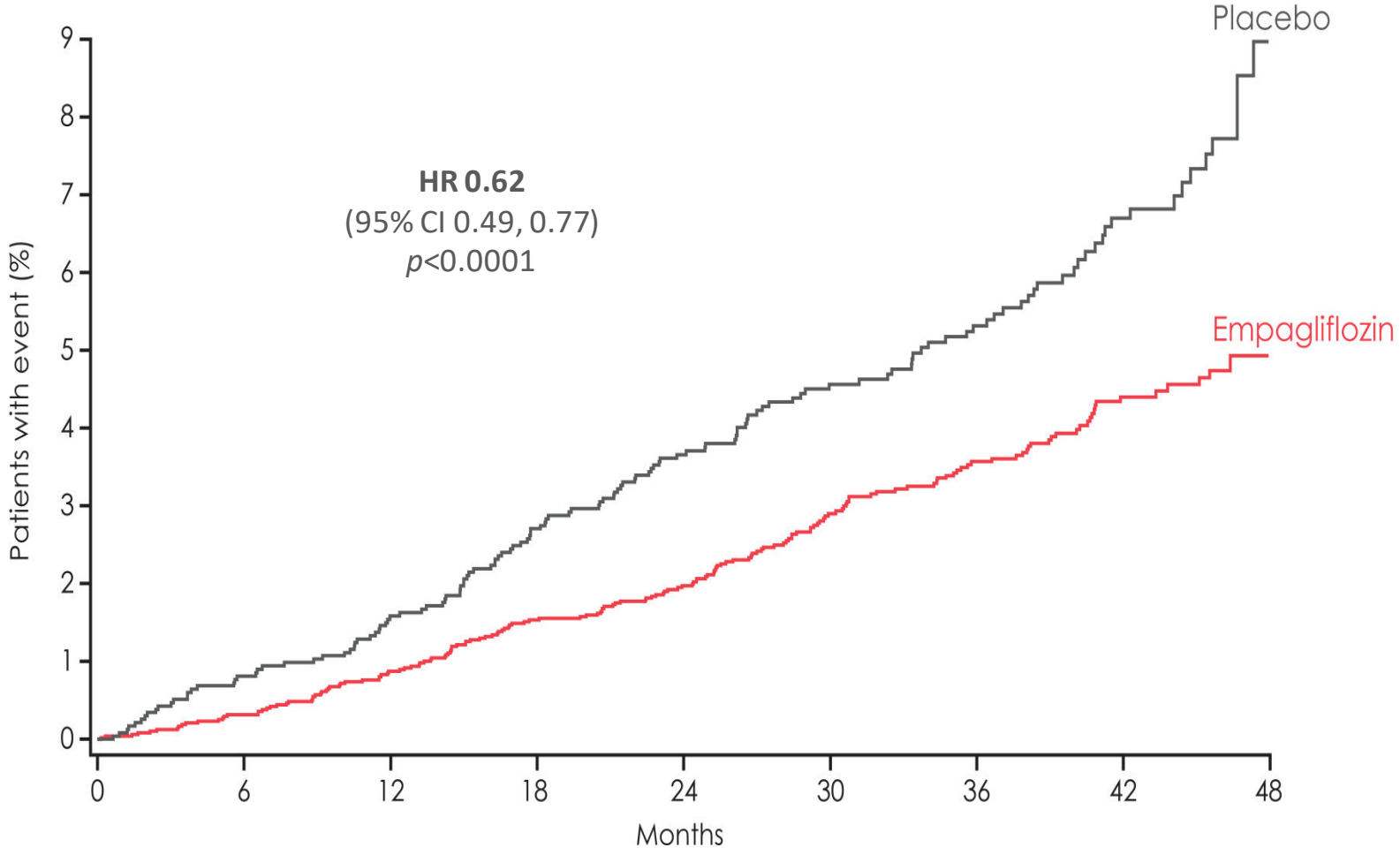


Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

Zinman B et al. N Engl J Med 2015

EMPA-REG OUTCOME®

EMPA- REG OUTCOME: CV death

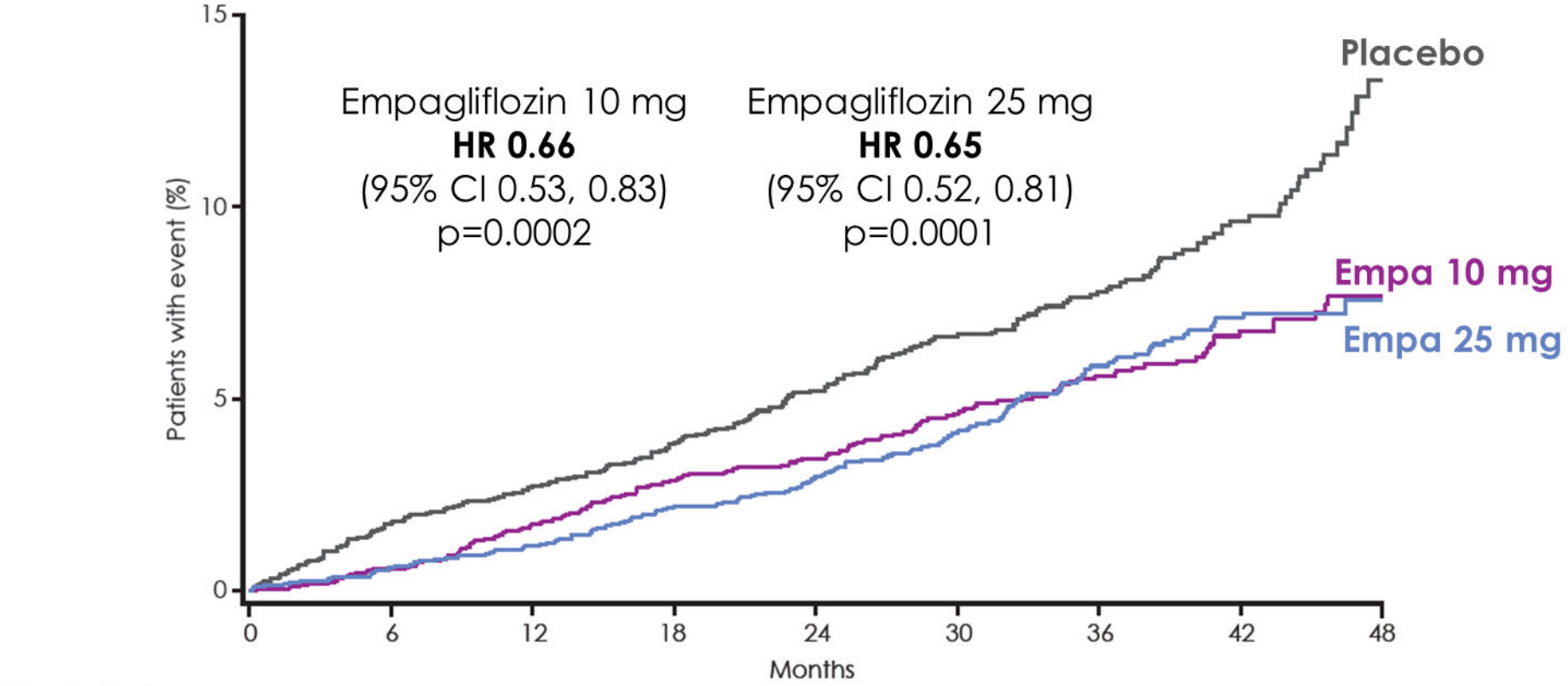


No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Zinman B et al. N Engl J Med 2015

EMPA-REG OUTCOME®

Heart failure hospitalization or CV death



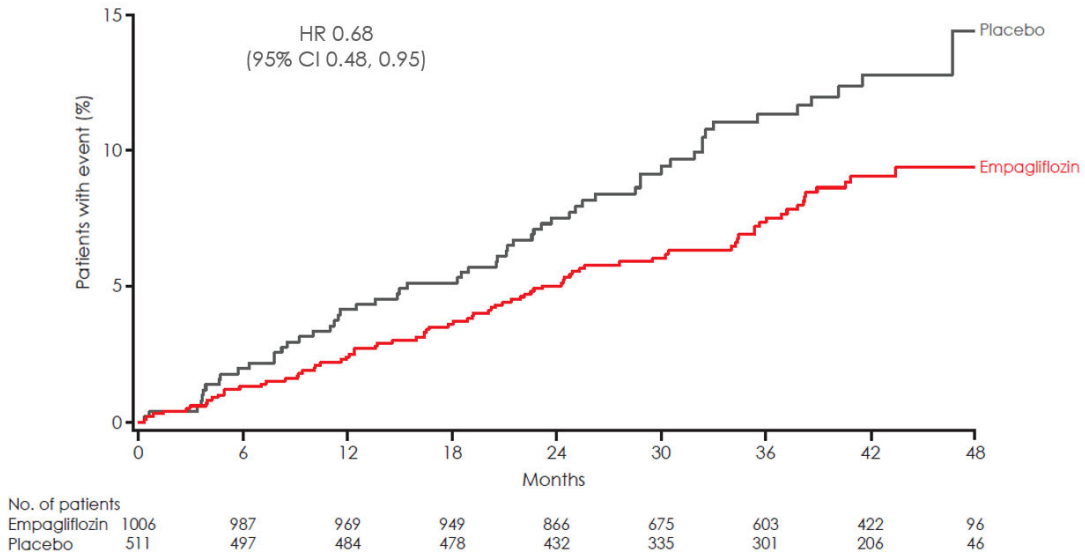
No. of patients									
Empagliflozin 10 mg	2345	2306	2256	2204	1981	1473	1240	804	188
Empagliflozin 25 mg	2342	2308	2267	2223	2007	1477	1247	830	207
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Zinman B et al. N Engl J Med 2015

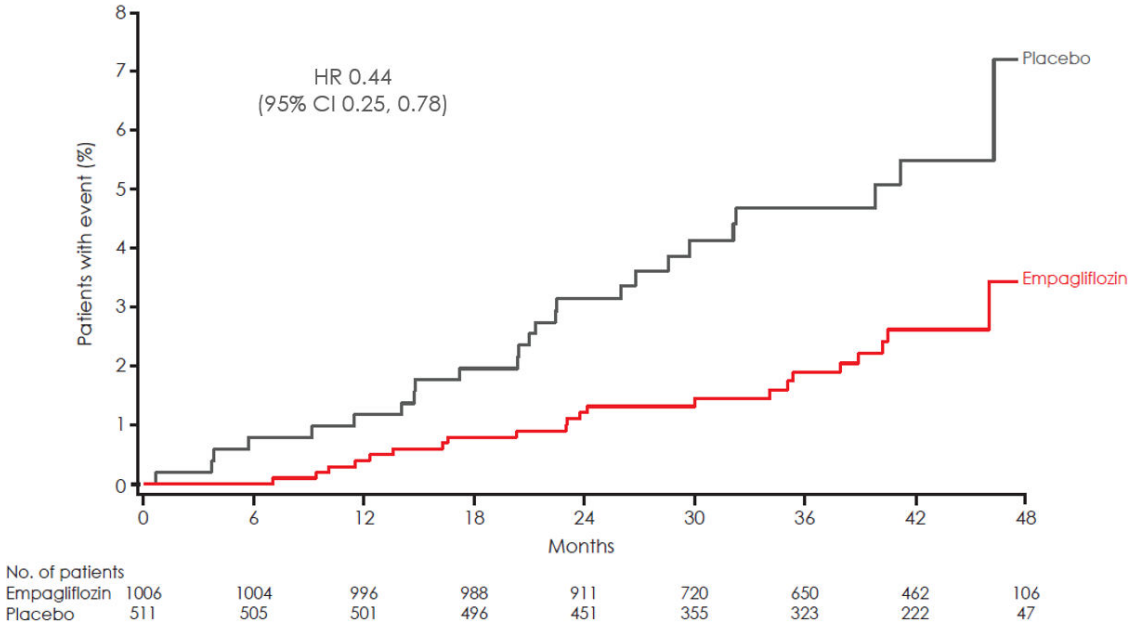
EMPA-REG OUTCOME®

EMPA- REG OUTCOME: Asian patients

3-point MACE in Asian patients



CV death in Asian patients

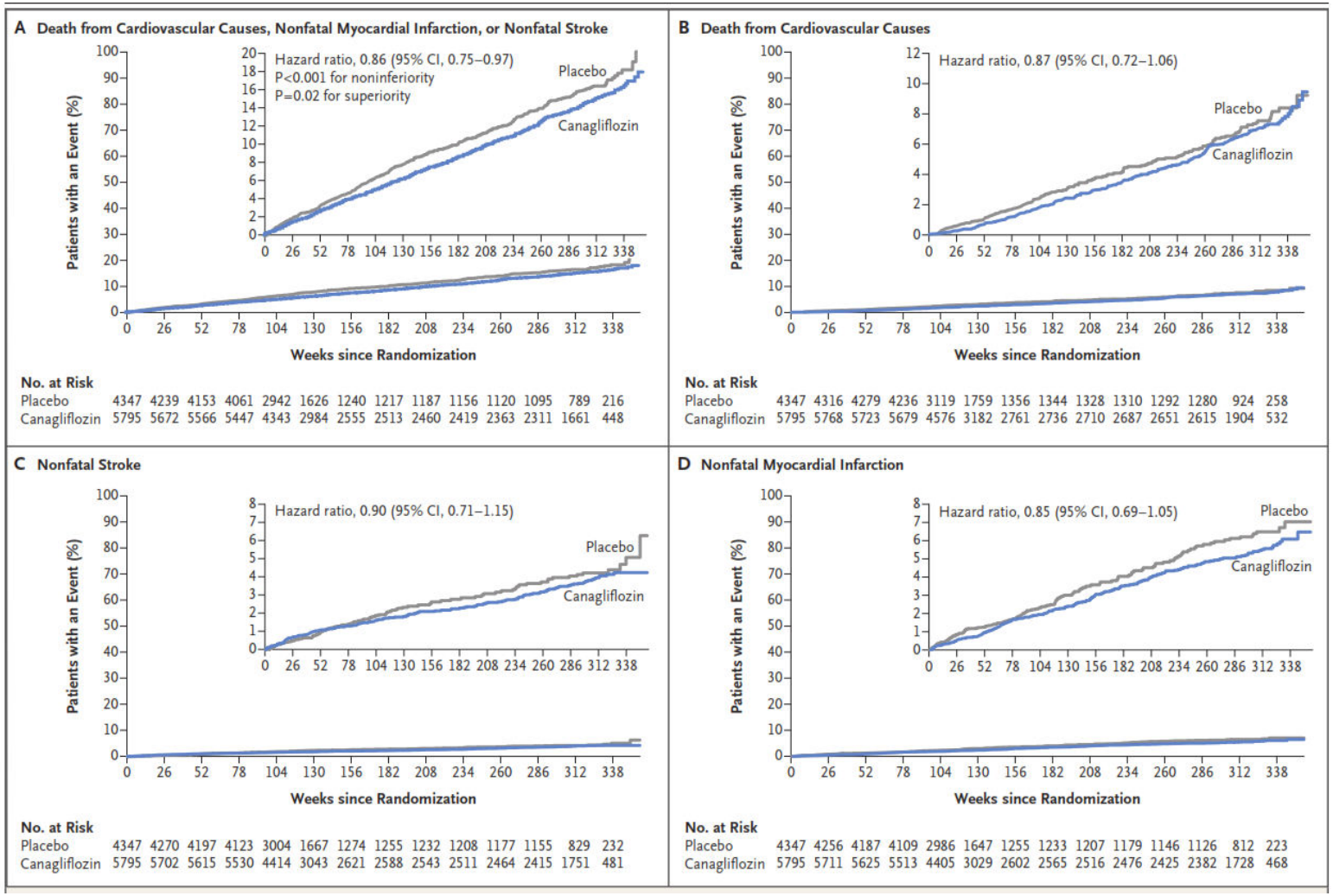


EMPA-REG OUTCOME®

The NEW ENGLAND JOURNAL of MEDICINE

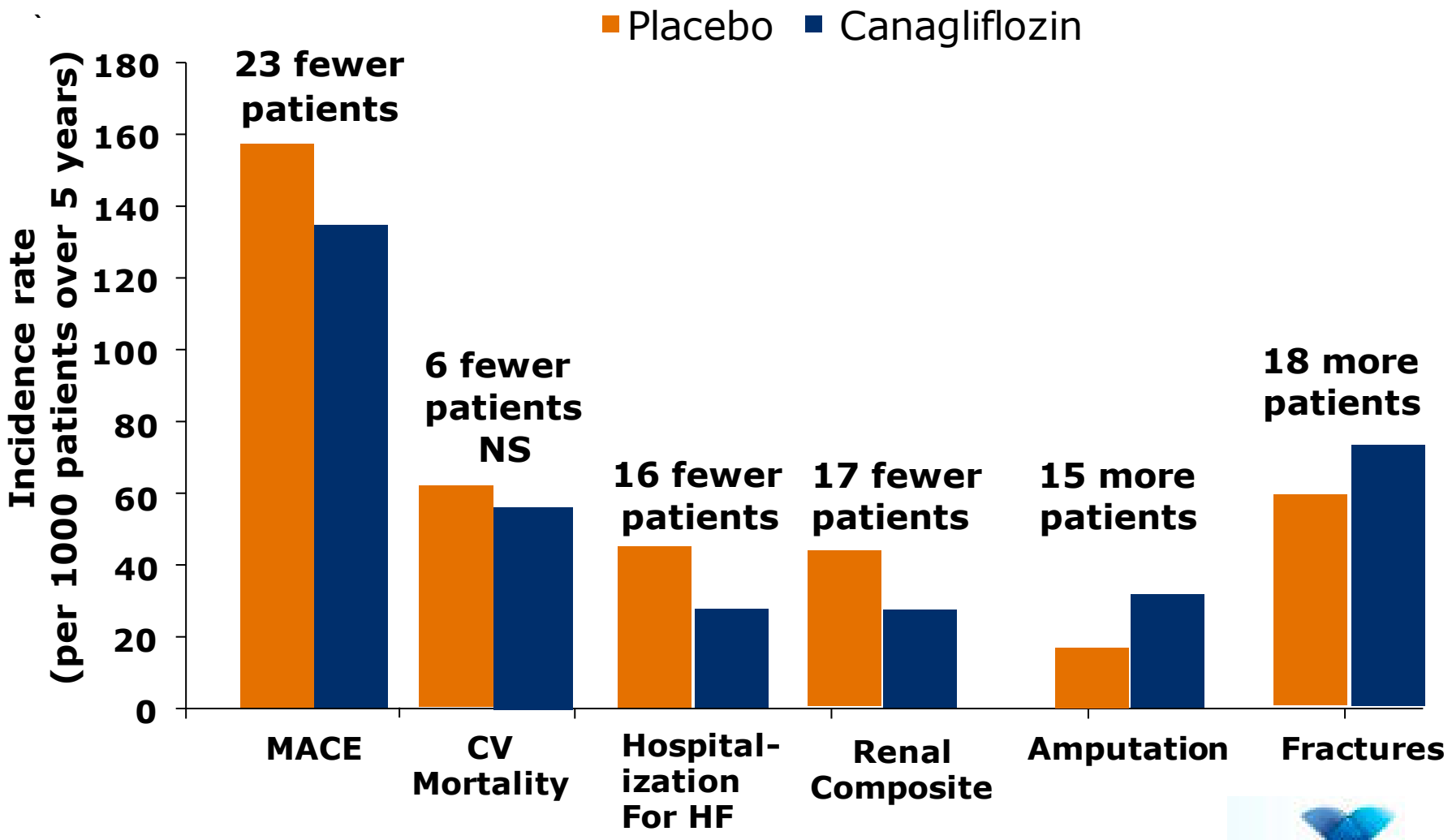
ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes



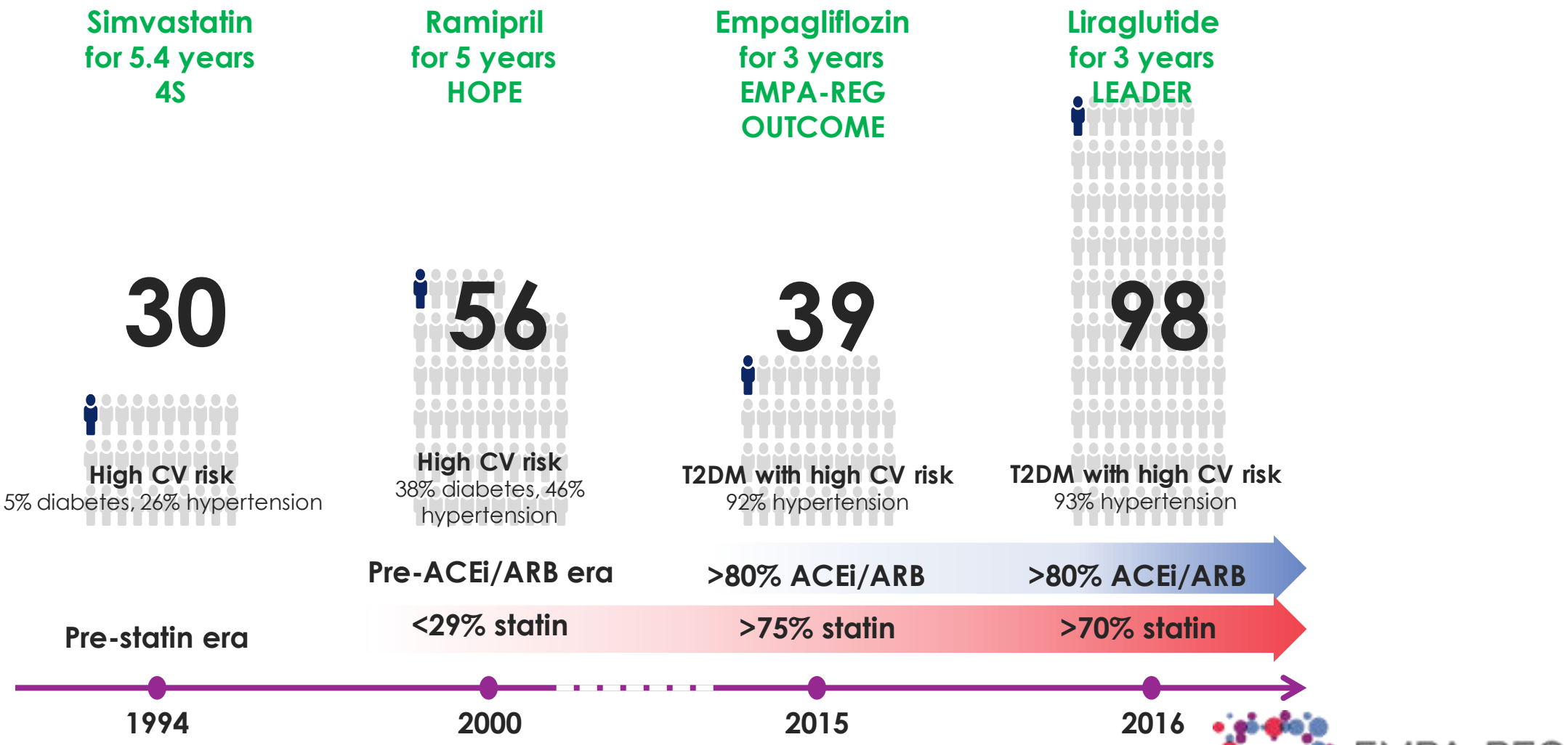
- The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk.
- Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks.
- The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

CANVAS- Benefits and Risk in 1000 patients in 5 years



CANVAS Program

NNT to prevent one death across landmark trials in patients with high CV risk



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My take-home messages

1. People with diabetes have an increased risk for CAD compared with people without diabetes.
2. Complex multivessel CAD in patients with diabetes addresses an important challenge for the best revascularization options, in which strong evidence supports the use of CABG over PCI.
3. Choice of Glucose Lowering Drug in Patients with Cardiovascular Disease to Reduce CV Events

Liraglutide:	Reduced MACE and CV mortality
	Can be used over wide range of renal function
	Injectable- Cost
Empagliflozin:	Reduced MACE, CV mortality and HF
	Good adverse outcome (genital infection…)
Canagliflozin:	Reduced MACE and HF
	Important adverse outcome (amputation…)