Στεφανιαία νόσος & Σακχαρώδης Διαβήτης

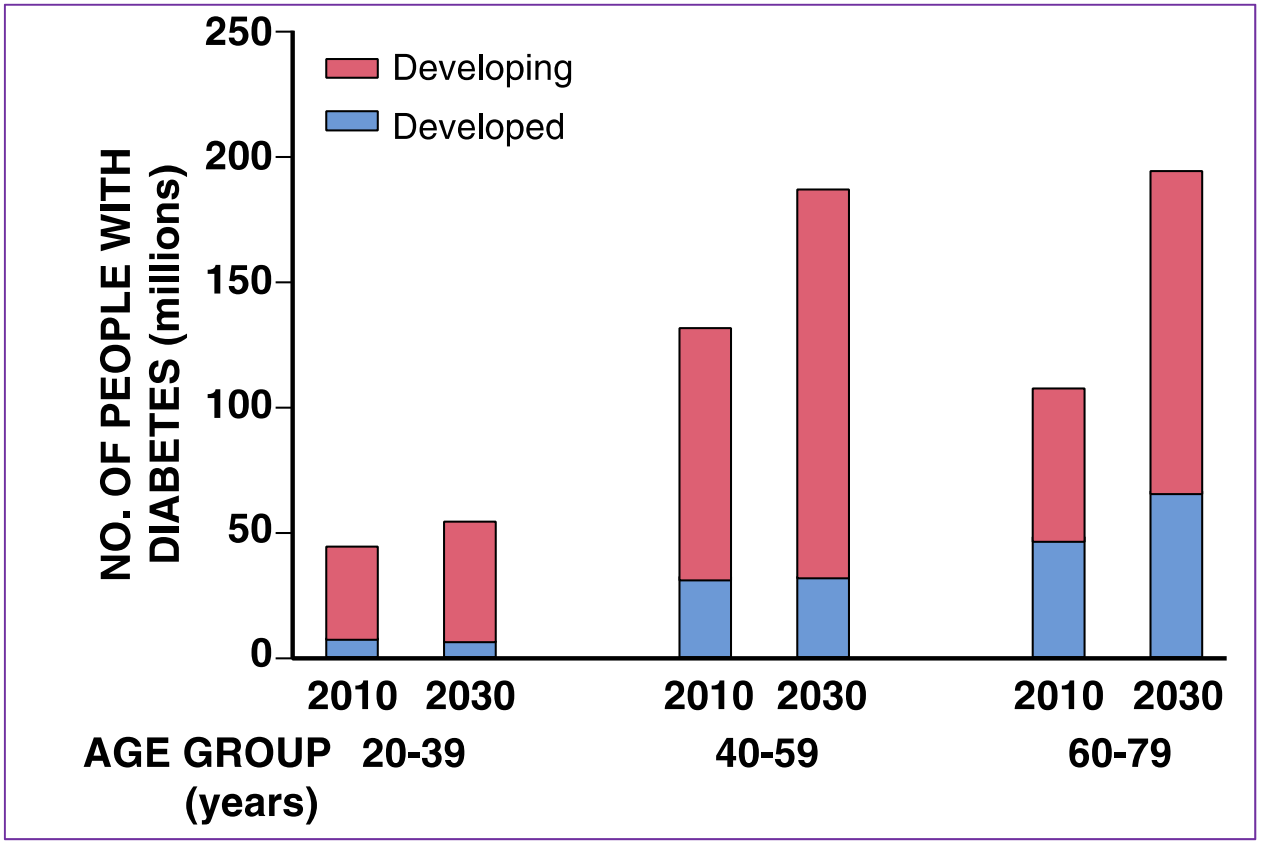
Κωνσταντίνος Τριανταφύλλου,

Επιμελητής Α'

Α' Καρδιολογικό Τμήμα

Γ.Ν.Α. «Ευαγγελισμός»

Global estimates of the prevalence of diabetes for 2010 and 2030.



Shaw JE et al. Diabetes Res Clin Pract 87:4, 2010

Diagnosis of Diabetes Mellitus .

Hb_{A1C} >6.5%*

or

Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L)
(*Fasting* : no caloric intake for at least 8 hours)

or

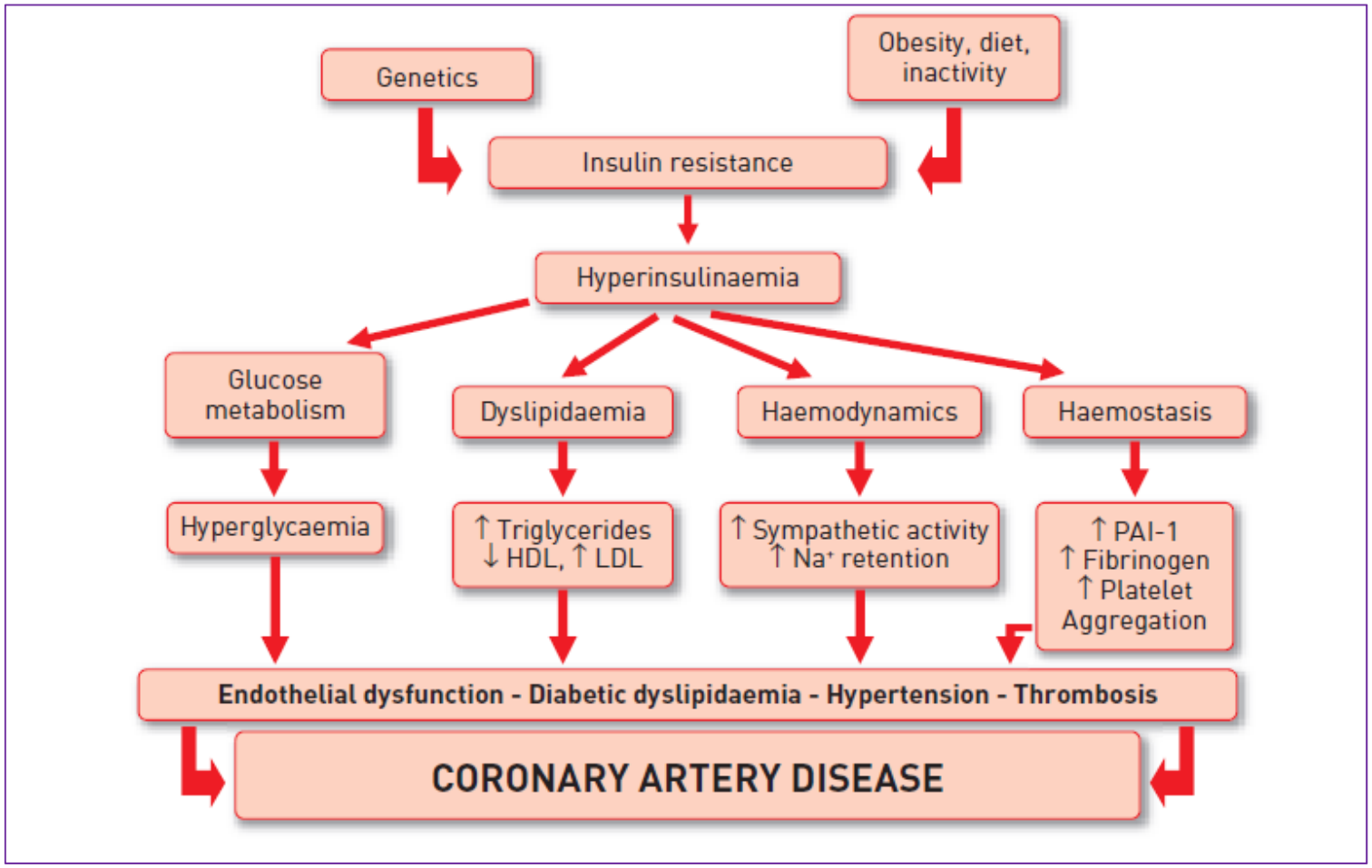
2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L)
(Glucose tolerance test :glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water)

or

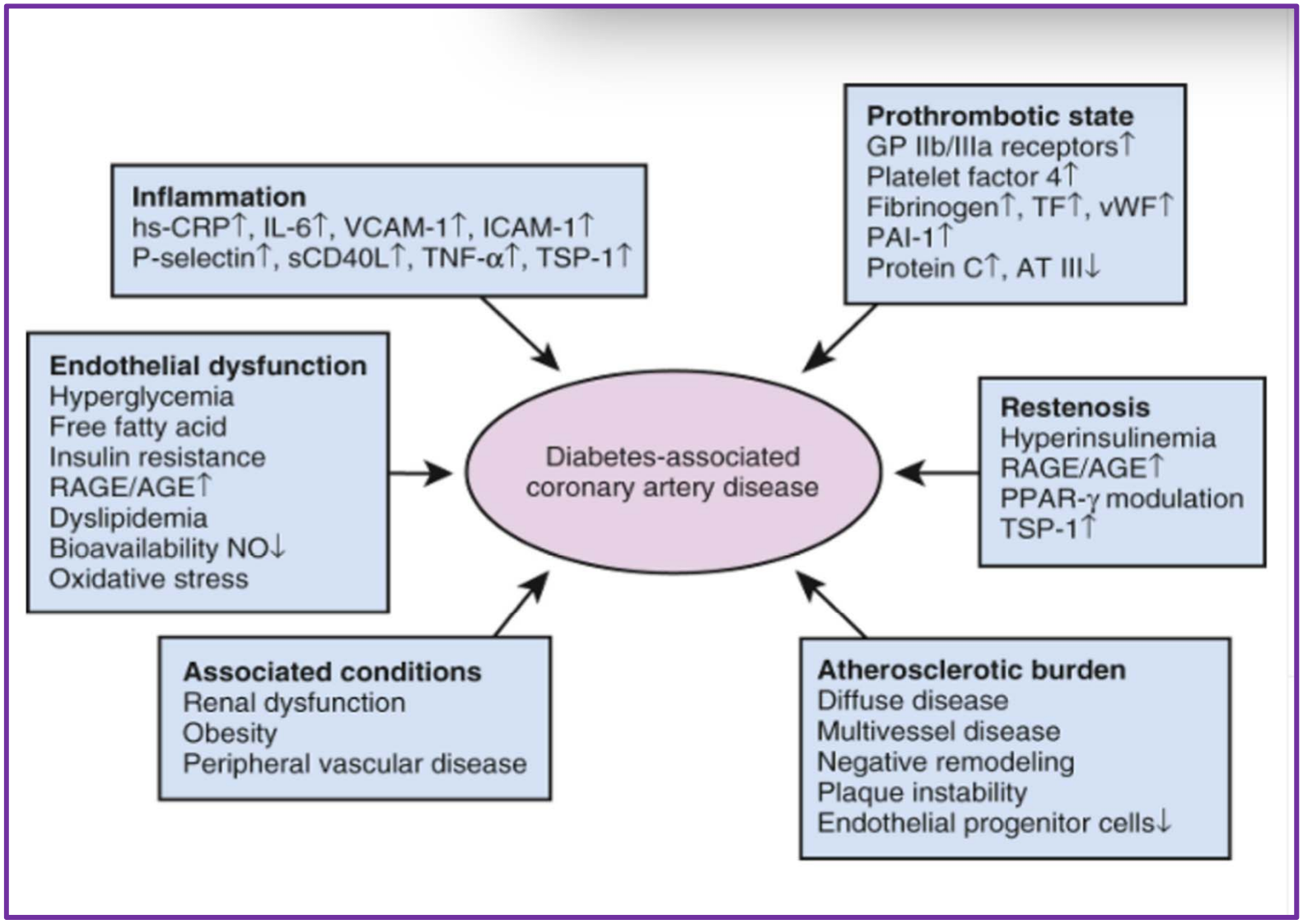
Random plasma glucose ≥200 mg/dL (11.1 mmol/L)
(Classic symptoms of hyperglycemia or hyperglycemic crisis)

***Diabetes Care* 37(Suppl 1):S14-S80, 2014**

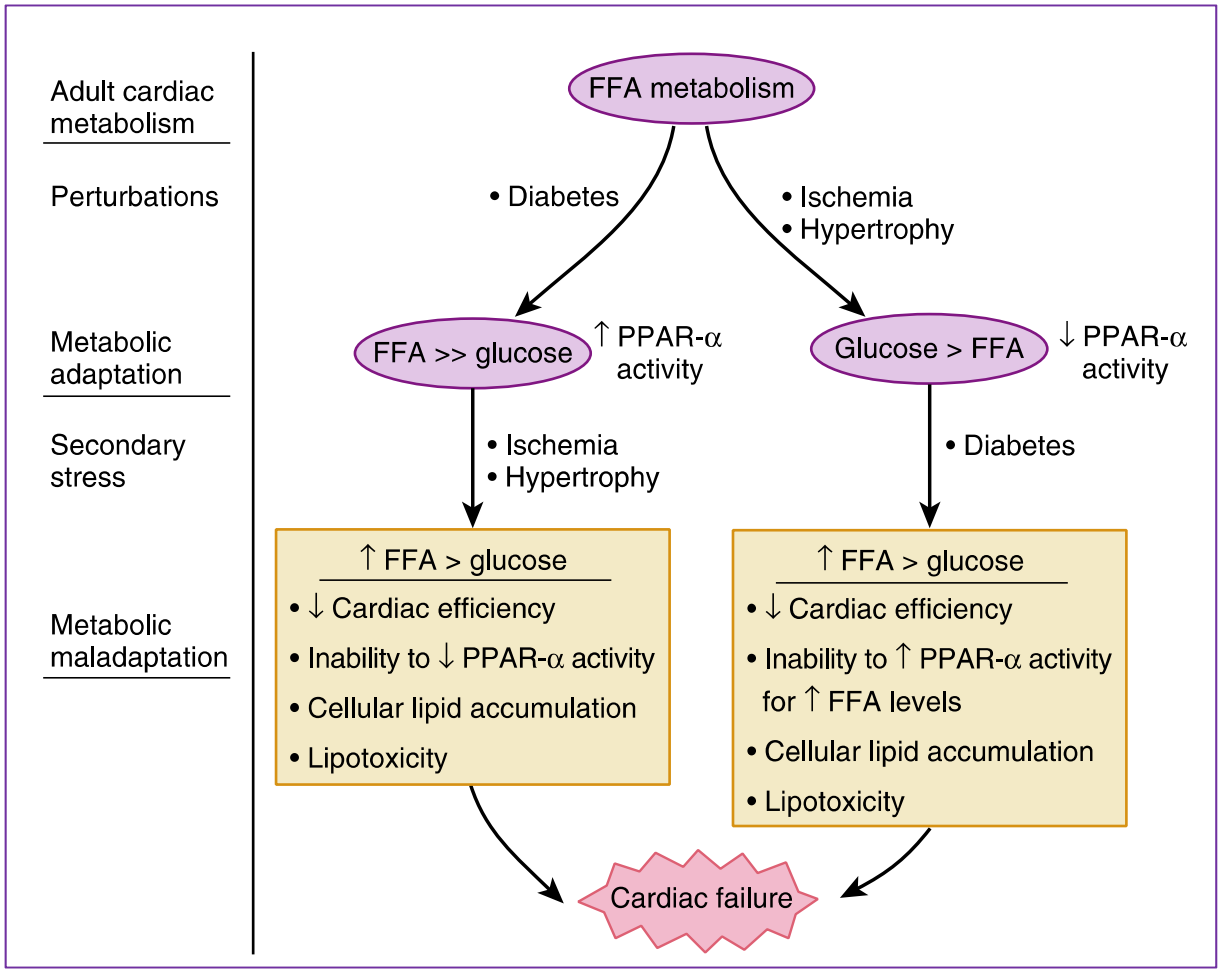
Role of insulin resistance on the features of type 2 DM



Pathophysiology of CAD in DM



Cardiac adaptive and maladaptive metabolic modifications in DM

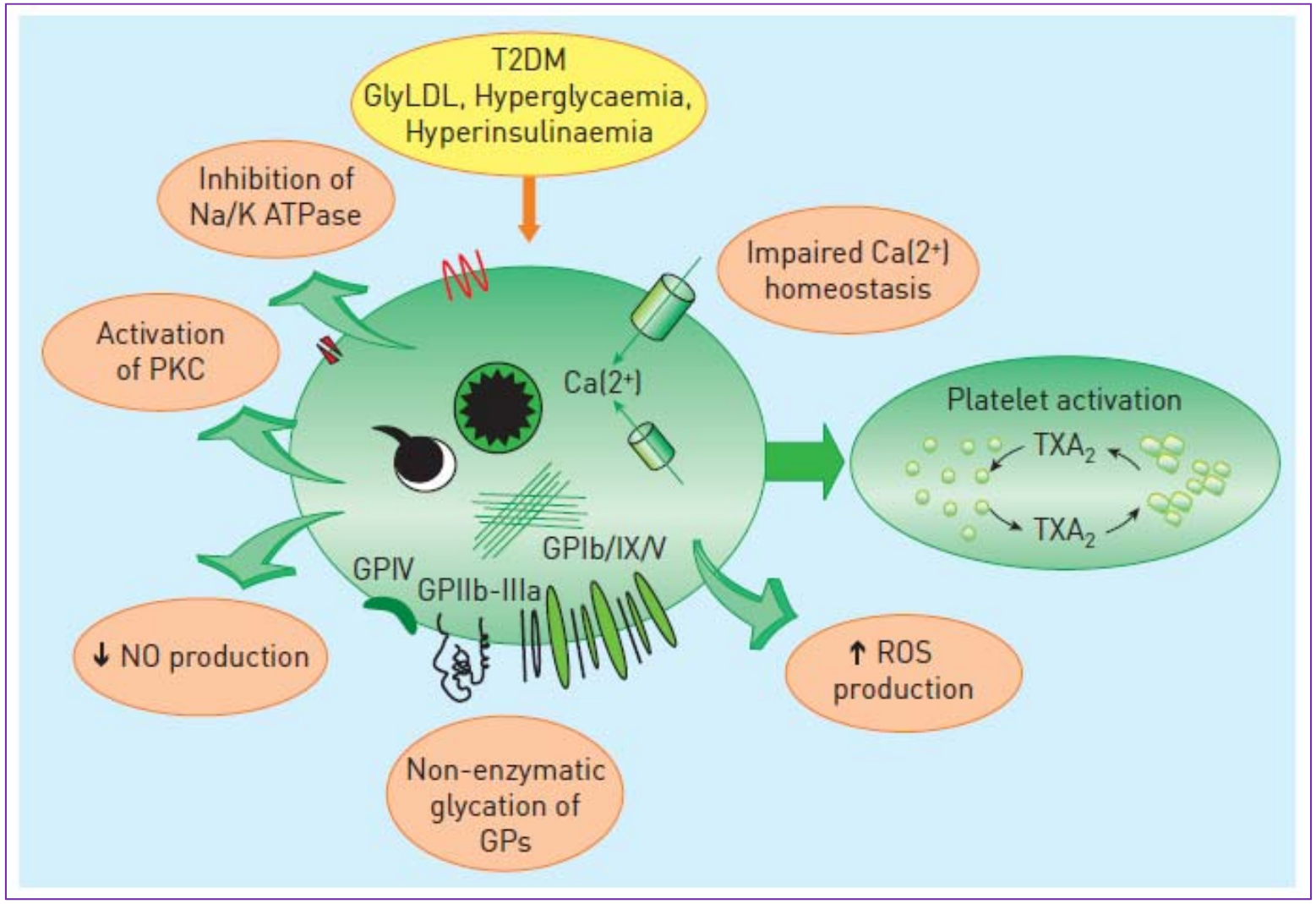


“Diabetic cardiomyopathy”

Pathophysiologic Abnormalities Associated with Cardiac Dysfunction, Congestive Heart Failure, and Adverse Outcomes in Diabetes

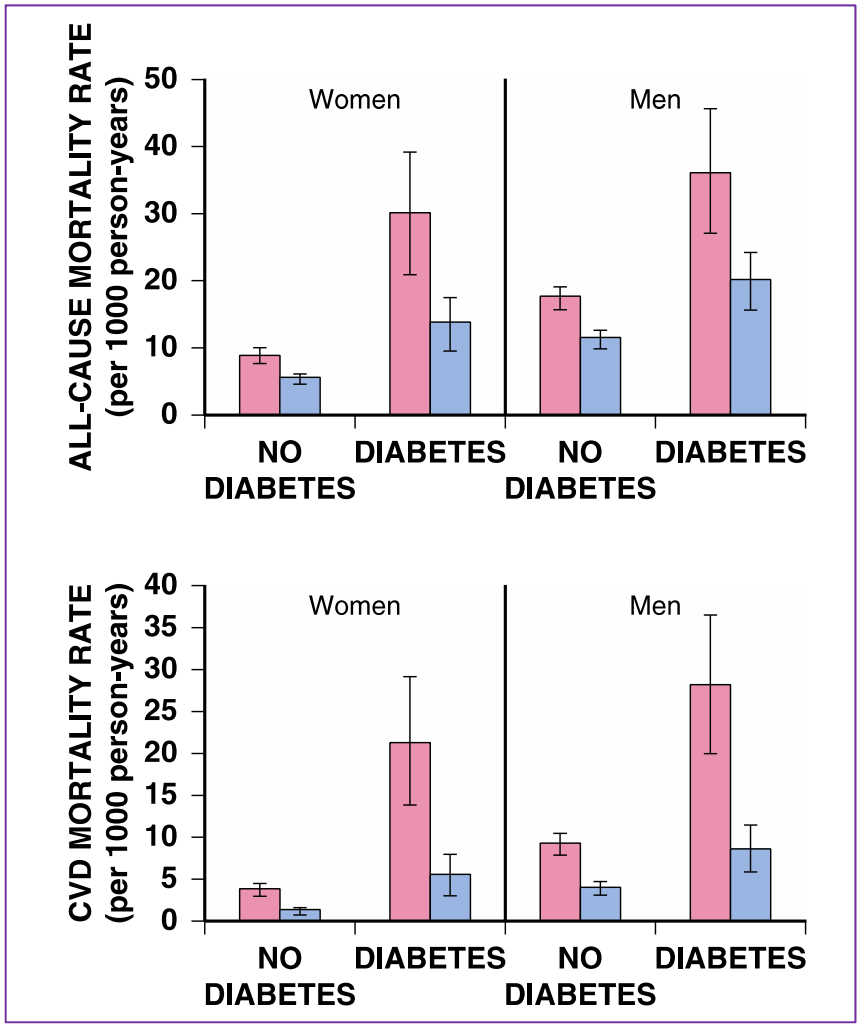
Sympathetic nervous system activation
Renin-angiotensin-aldosterone system activation
Increased sodium and free water retention
Decreased vascular compliance
Elevated endothelin levels (in diabetes)
Loss of “dipping” nocturnal blood pressure pattern
Increased free fatty acid levels
Dysregulated myocardial glucose and fatty acid metabolism
Increased left ventricular hypertrophy or mass via myocyte hypertrophy
Deposition of advanced glycation end products in extracellular matrix
Increased cardiac fibrosis
Increased cardiac steatosis

Effects of type II DM on platelet activation



Ferroni P. et al. J Thromb Haemost. 2004;2:1282-91.

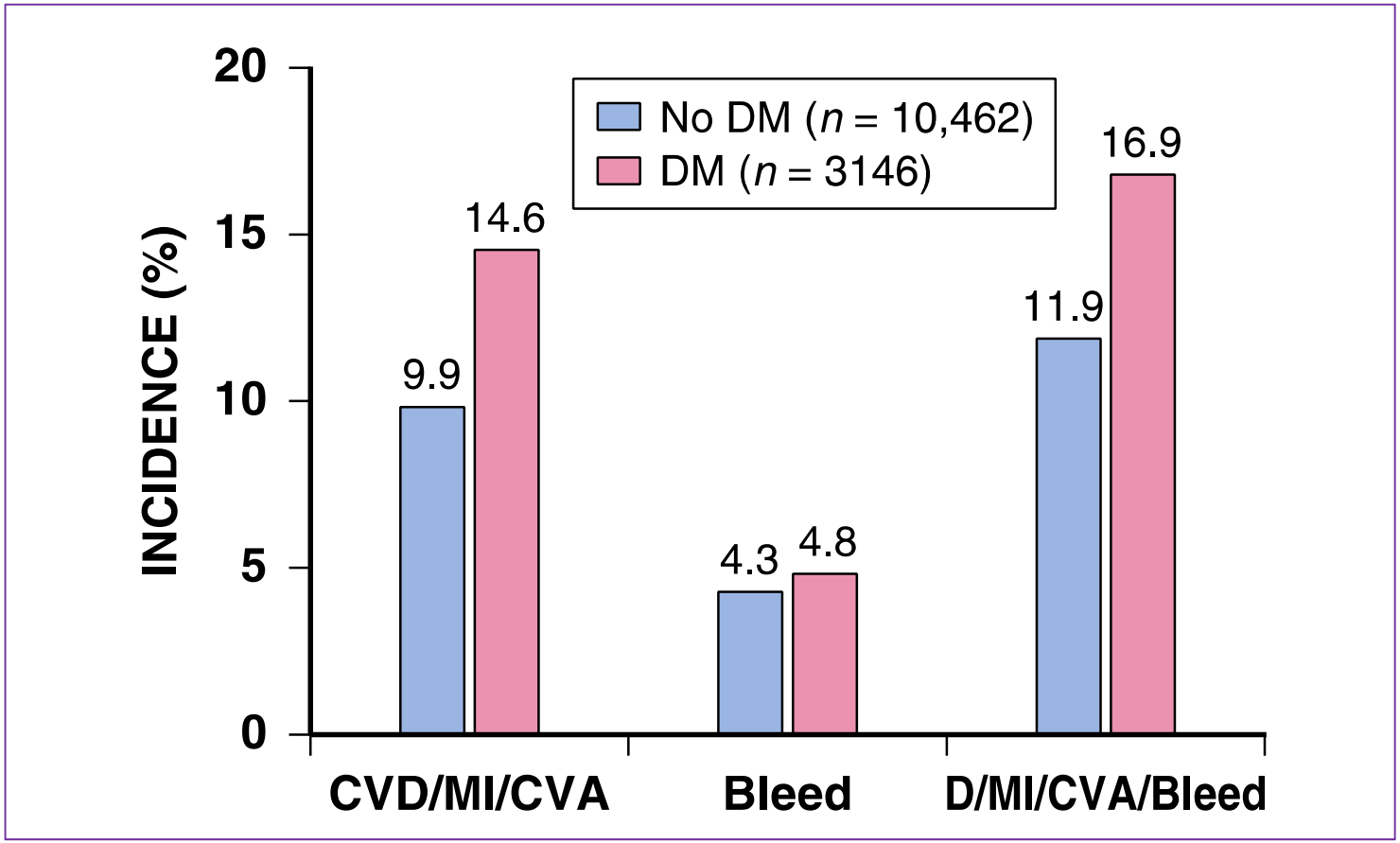
Trends in all-cause and CVD mortality among women and men with and without DM in the Framingham Heart Study.



Preis SR, et al. Circulation 119:1728-1735, 2009.

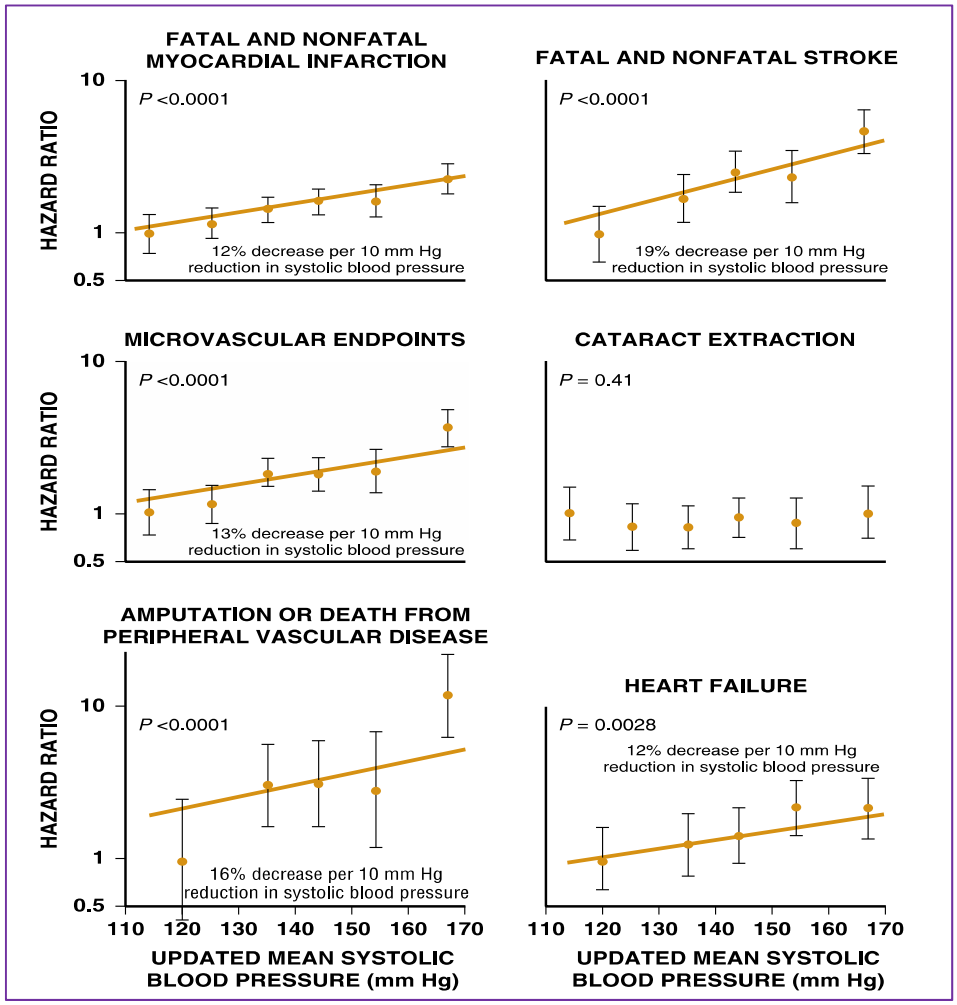
Adverse clinical outcomes after acute coronary syndromes during more than 1 year of follow-up, according to diabetes status

TRITON-TIMI 38 trial



Wiviott SD, et al: Circulation 118:1626, 2008

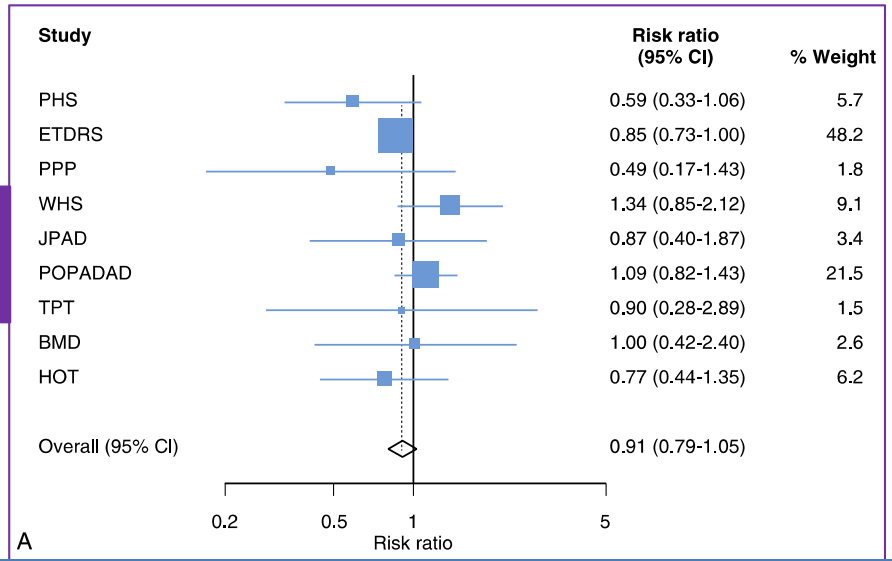
Association of systolic blood pressure with macrovascular and microvascular complications of type 2 DM (UKPDS)



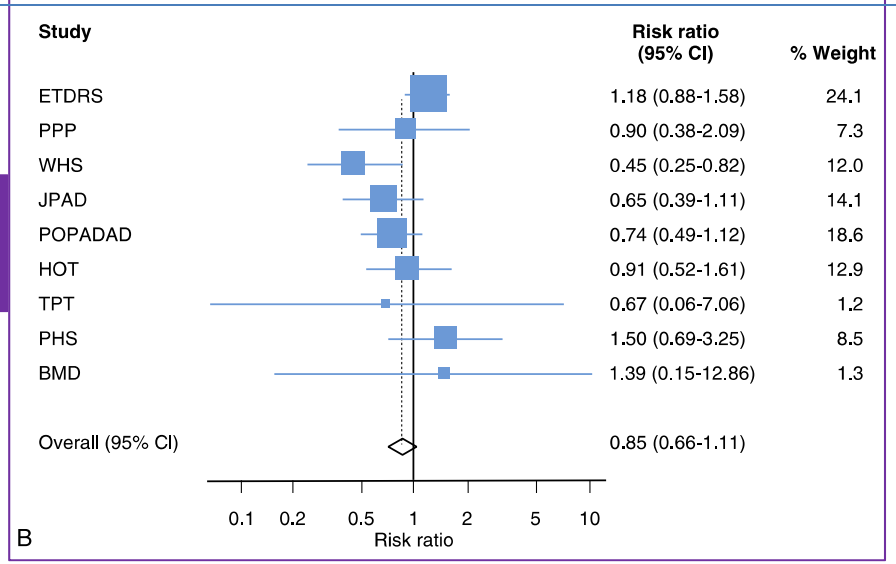
Adler AI, et al. BMJ 321:412, 2000

Aspirin for primary prevention of cardiovascular events in DM (M-A)

CAD events



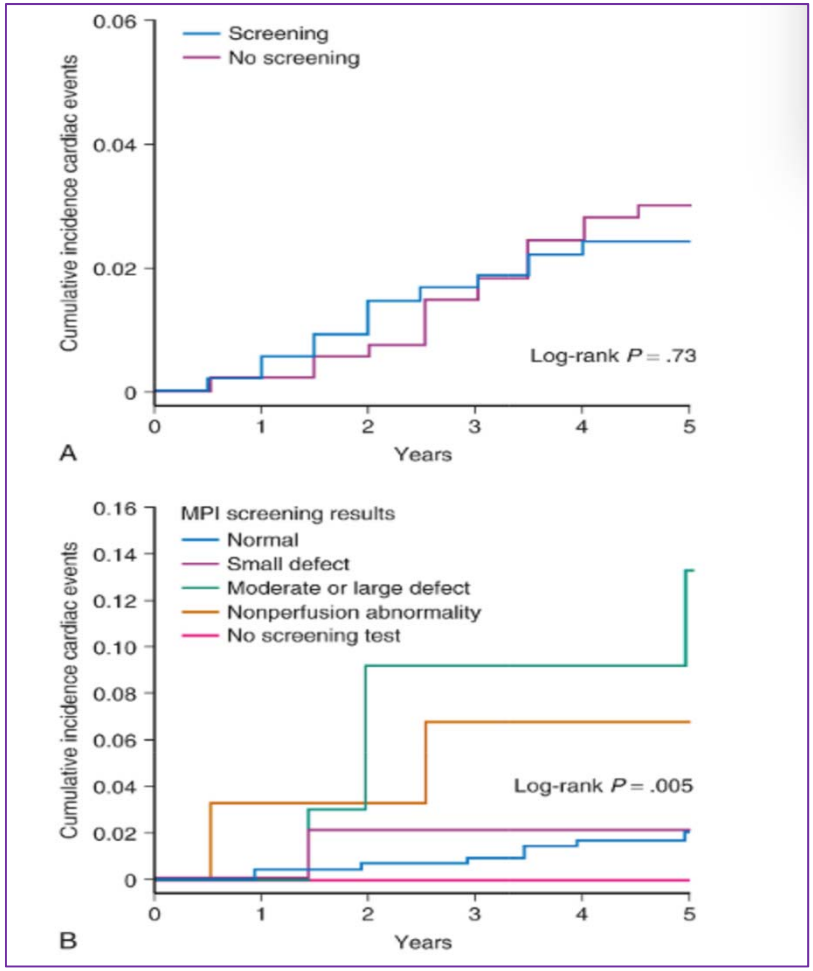
Stroke events



Pignone M, et al: Circulation 121:2694, 2010

Cardiac outcomes after screening for asymptomatic CAD in patients with type 2 DM.

DIAD study

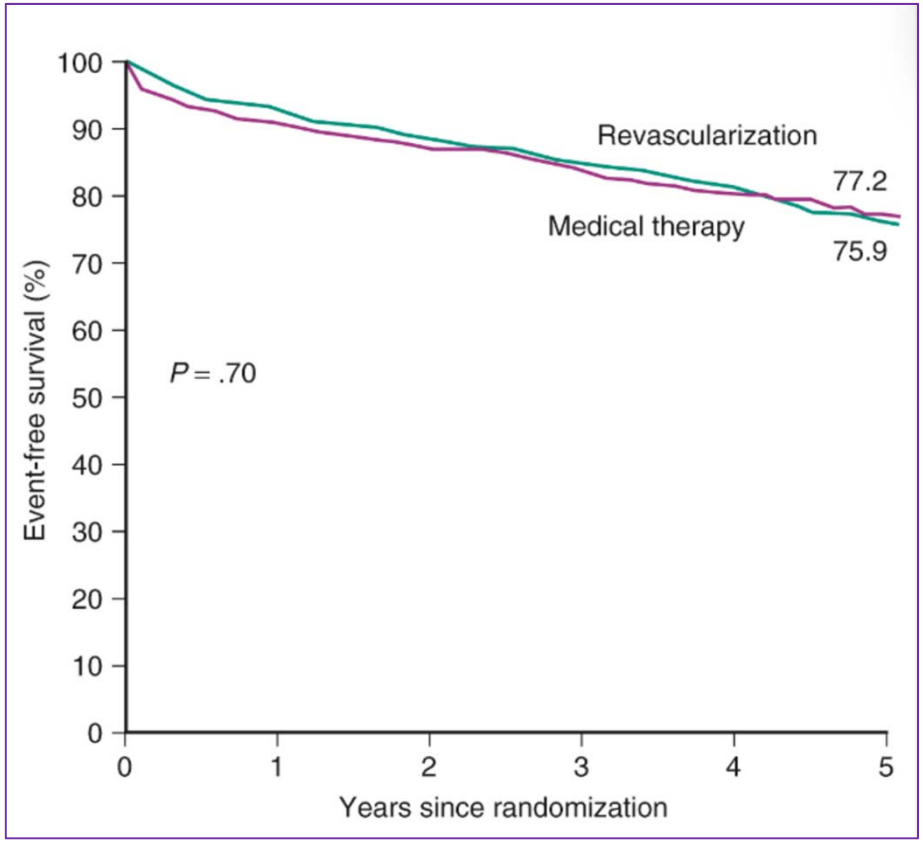


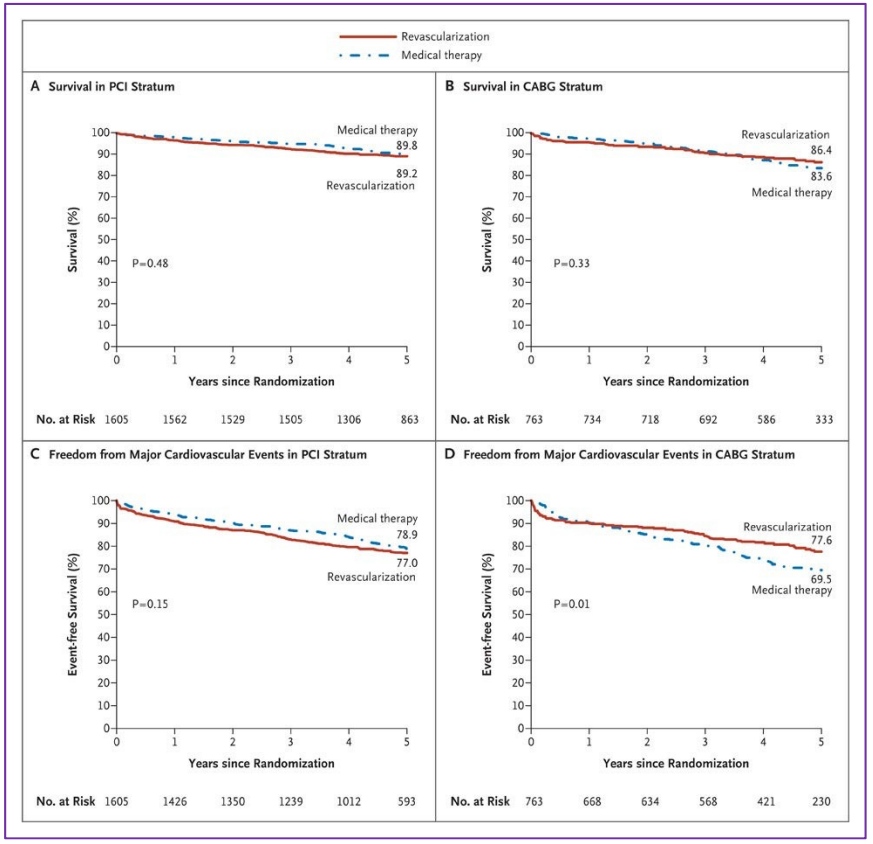
Young LH, et al: JAMA 301:1547-1555, 2009.)

Revascularization versus medical therapy

DM & stable CAD eligible for revascularization

BARI 2D trial – 5 years





Frye RL, et al: N Engl J Med 360:2503-2515, 2009

Specific recommendations for revascularization in patients with diabetes

Recommendations	Class[a]	Level[b]	Ref[c]
In patients presenting with STEMI, primary PCI is recommended over fibrinolysis if it can be performed within recommended time limits.	I	A	363
In patients with NSTE-ACS, an early invasive strategy is recommended over non-invasive management.	I	A	180,338, 364–366
In stable patients with multivessel CAD and/or evidence of ischaemia, revascularization is indicated in order to reduce cardiac adverse events.	I	B	93,367
In patients with stable multivessel CAD and an acceptable surgical risk, CABG is recommended over PCI.	I	A	106,175,349
In patients with stable multivessel CAD and SYNTAX score ≤ 22, PCI should be considered as alternative to CABG.	IIa	B	346,350
New-generation DES are recommended over BMS.	I	A	351,352
Bilateral mammary artery grafting should be considered.	IIa	B	368
In patients on metformin, renal function should be carefully monitored for 2 to 3 days after coronary angiography/PCI.	I	C	

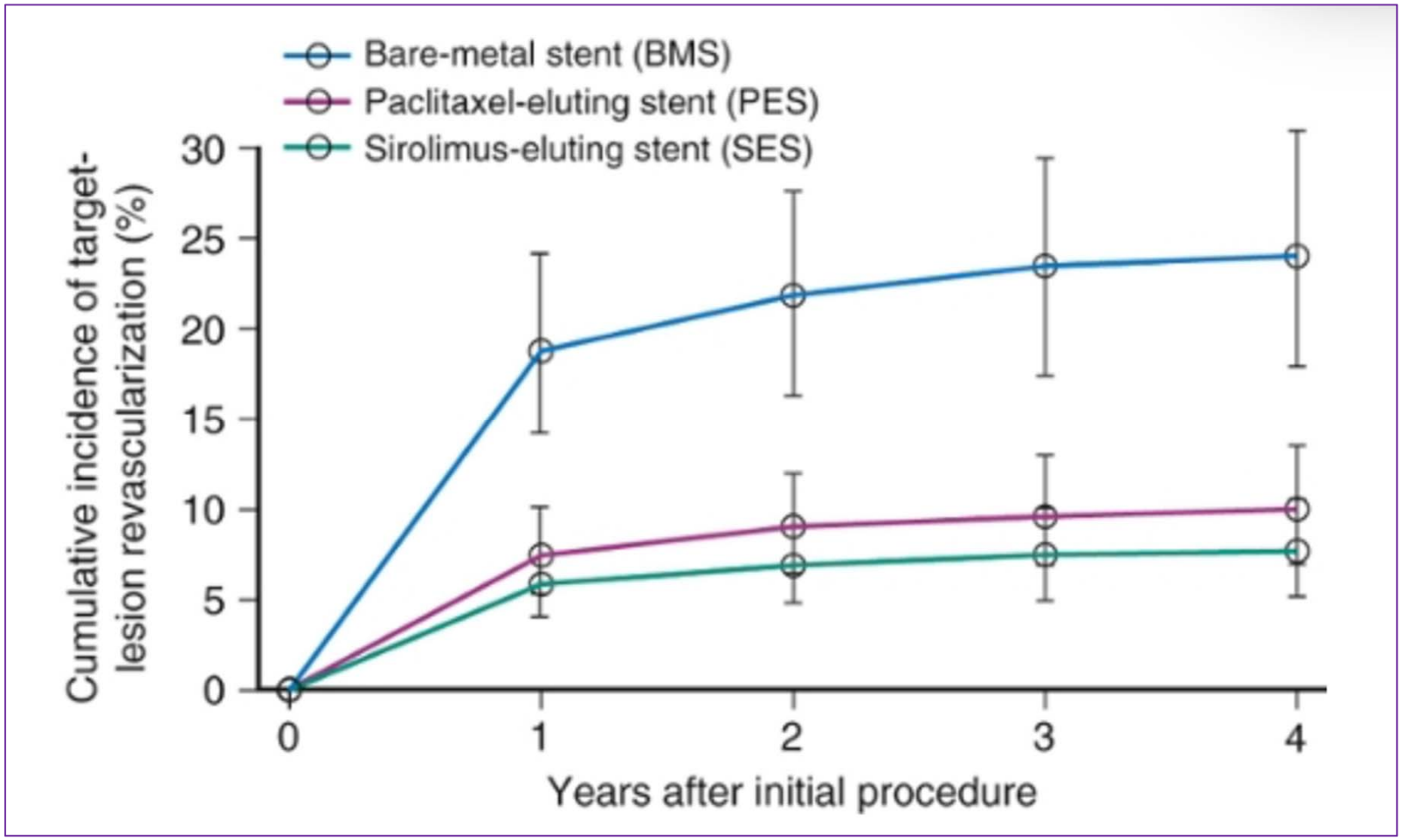
2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2014;35:2541-619.

NSTE ACS :
early invasive management

Primary criteria
1. Relevant rise or fall in troponin
2. Dynamic ST- or T-wave changes (symptomatic or silent)
3. GRACE score >140
Secondary criteria
4. Diabetes mellitus
5. Renal insufficiency (eGFR <60 mL/min/1.73 m²)
6. Reduced LV function (ejection fraction <40%)
7. Early post-infarction angina
8. Recent PCI
9. Prior CABG
10. Intermediate to high GRACE risk score (http://www.gracescore.org)

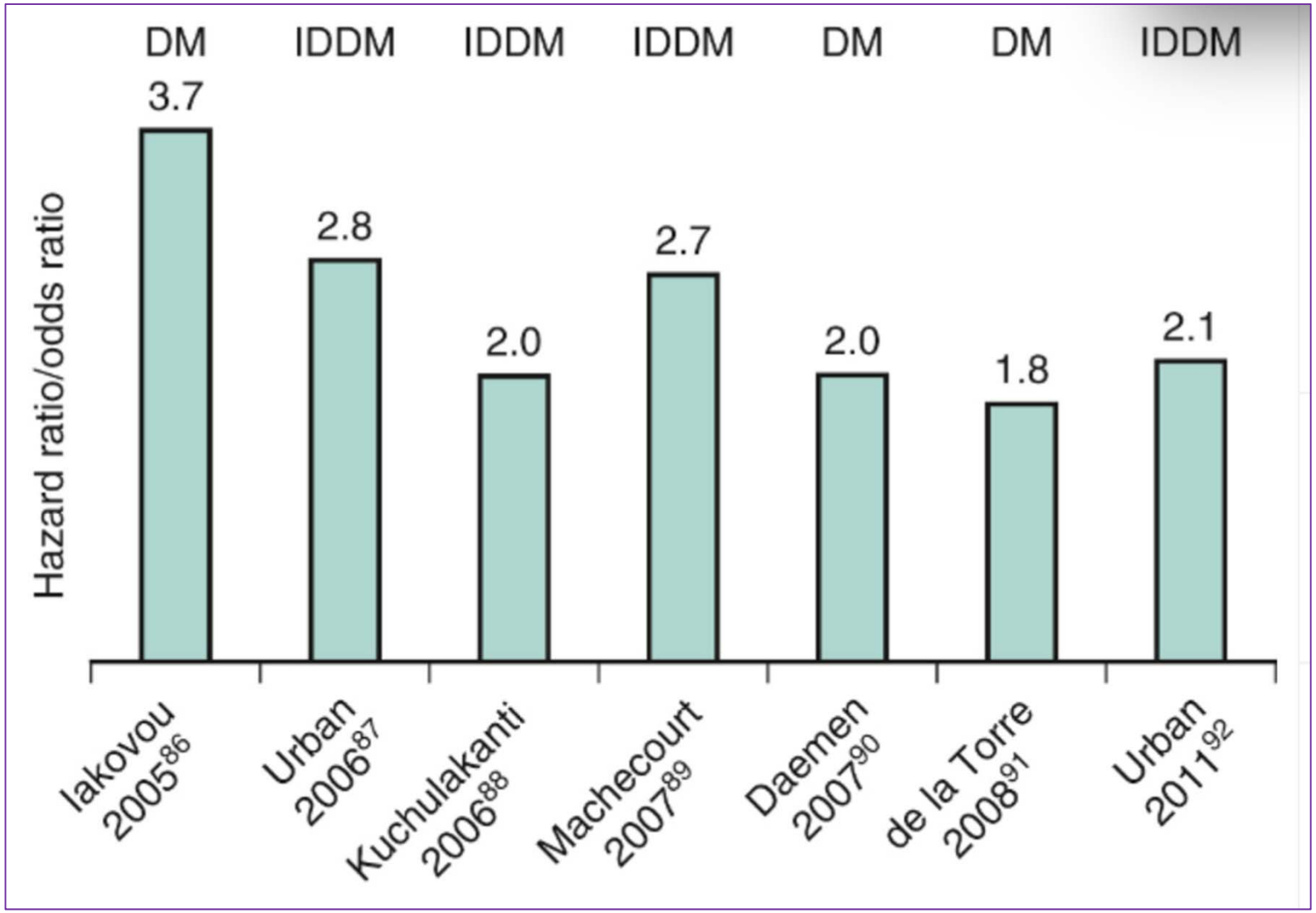
2014 ESC/EACTS Guidelines on myocardial revascularization.
Eur Heart J 2014;35:2541-619.

Drug eluting vs bare metal stents in people with and without diabetes: collaborative network meta-analysis.



Stettler C, et al: BMJ 337:a1331, 2008.

Diabetes mellitus as an independent predictor of DES thrombosis

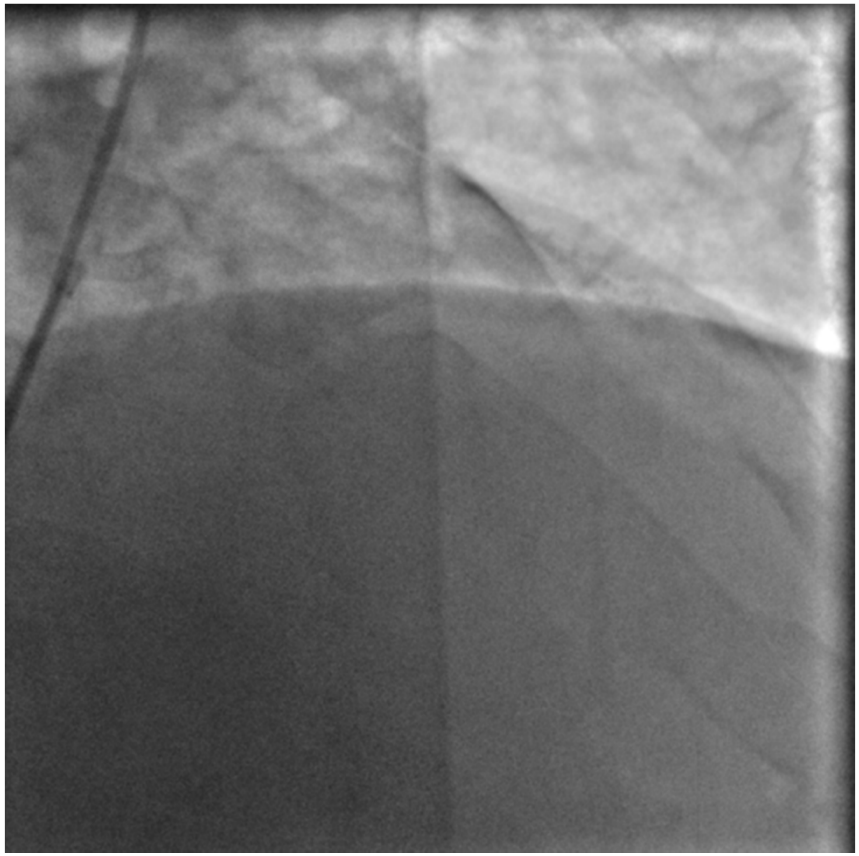


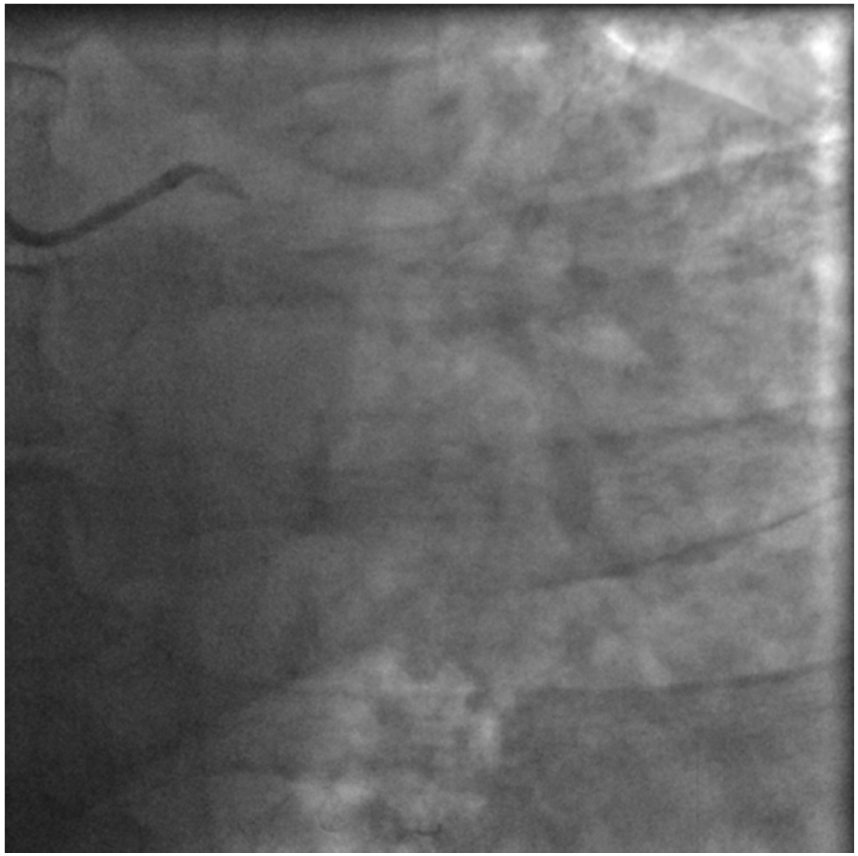
Roffi M, et al. Euro Heart J 32:2748-2757, 2011

NSTEMI, diabetic with MRF, male 52 year-old, smoker.

Hx of GI ulcers & upper GI bleeding

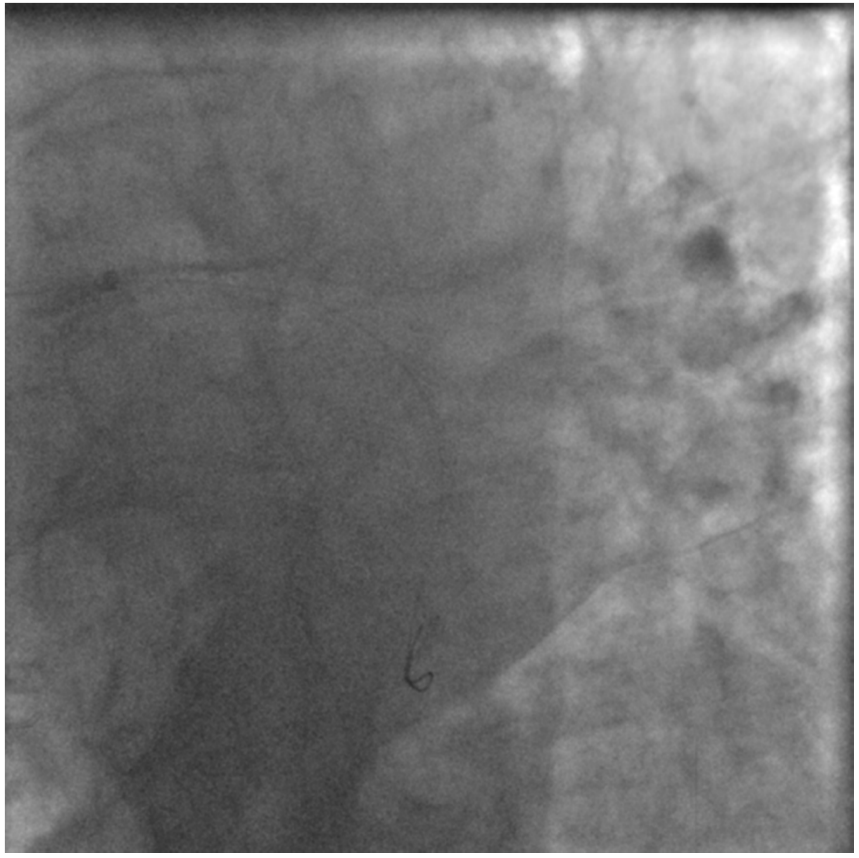
Day 1, PCI 1





Day 1, PCI 1

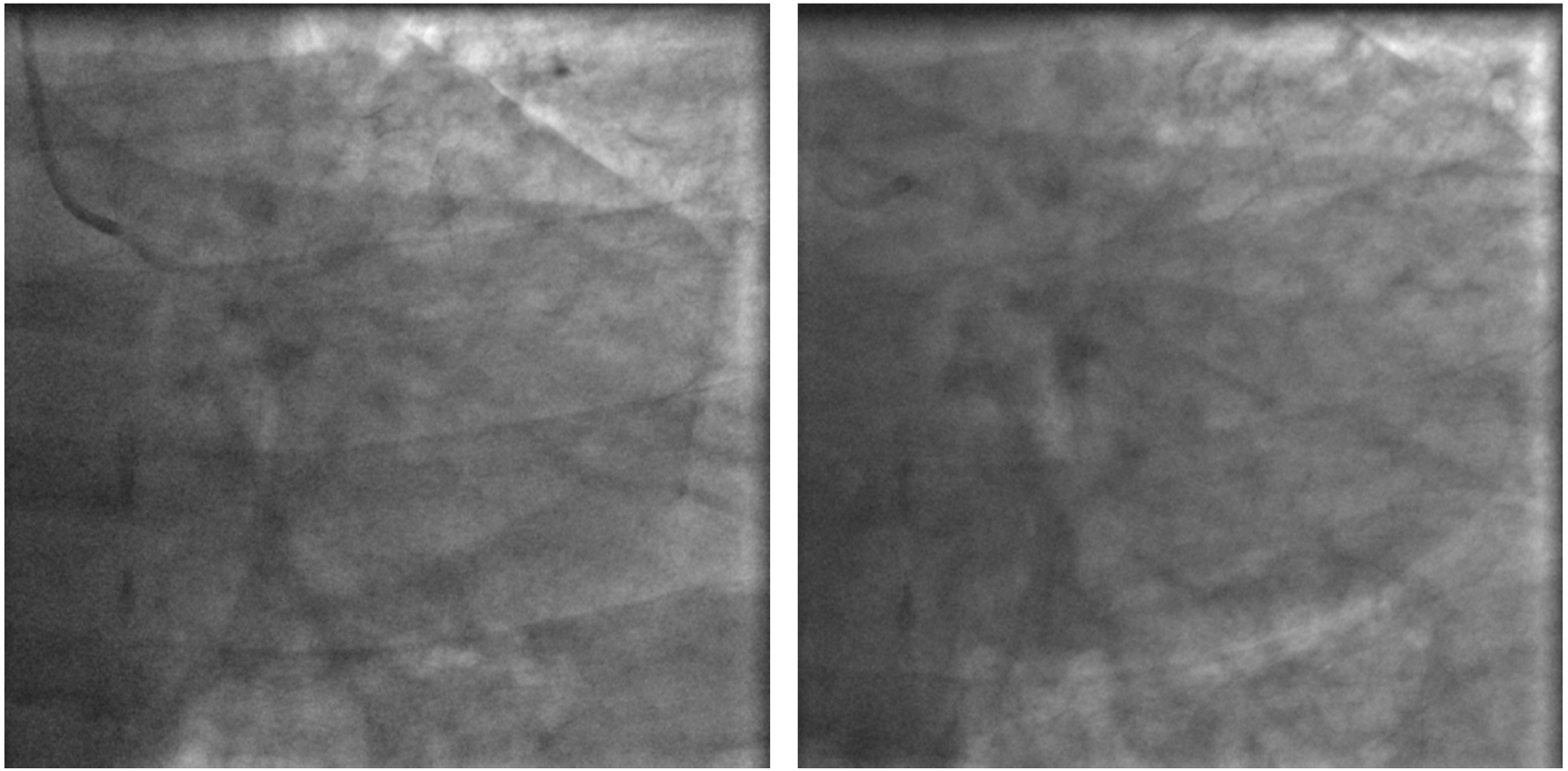
Final result



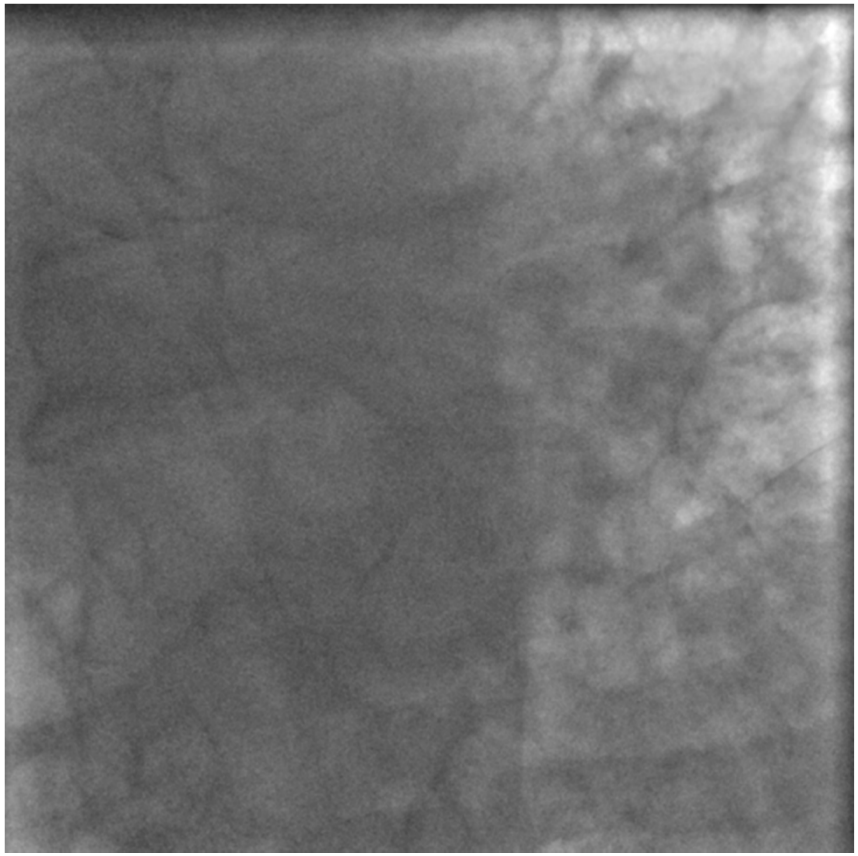
Day 3, PCI 2

Day 5, PCI 3

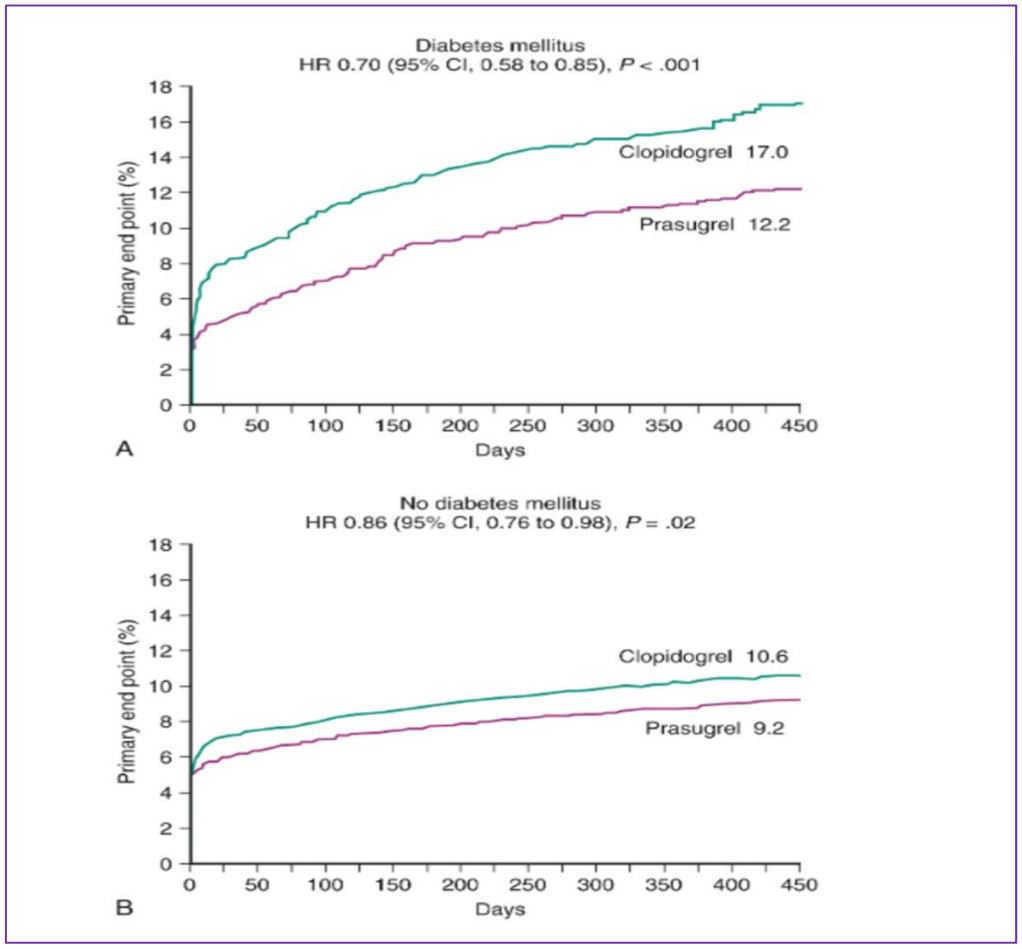
LCx subacute stent thrombosis



Day 12, PCI 4

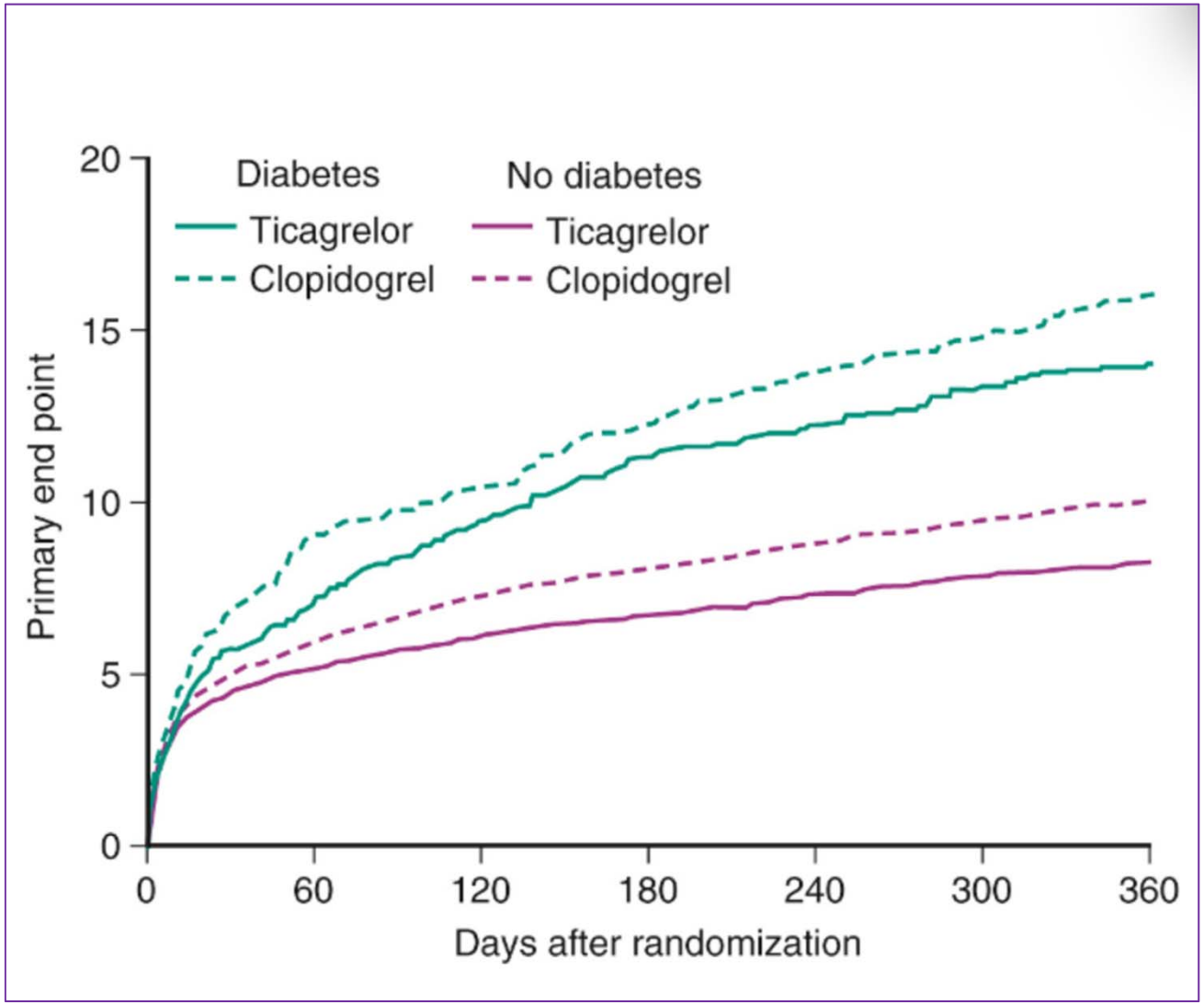


Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with ACS and DM.
TRITON TIMI-38



Wiviott SD, et al: Circulation 118:1626-1636, 2008.

Greater clinical benefit of more intensive oral antiplatelet therapy with ticagrelor in patients with ACS and DM.
PLATO trial



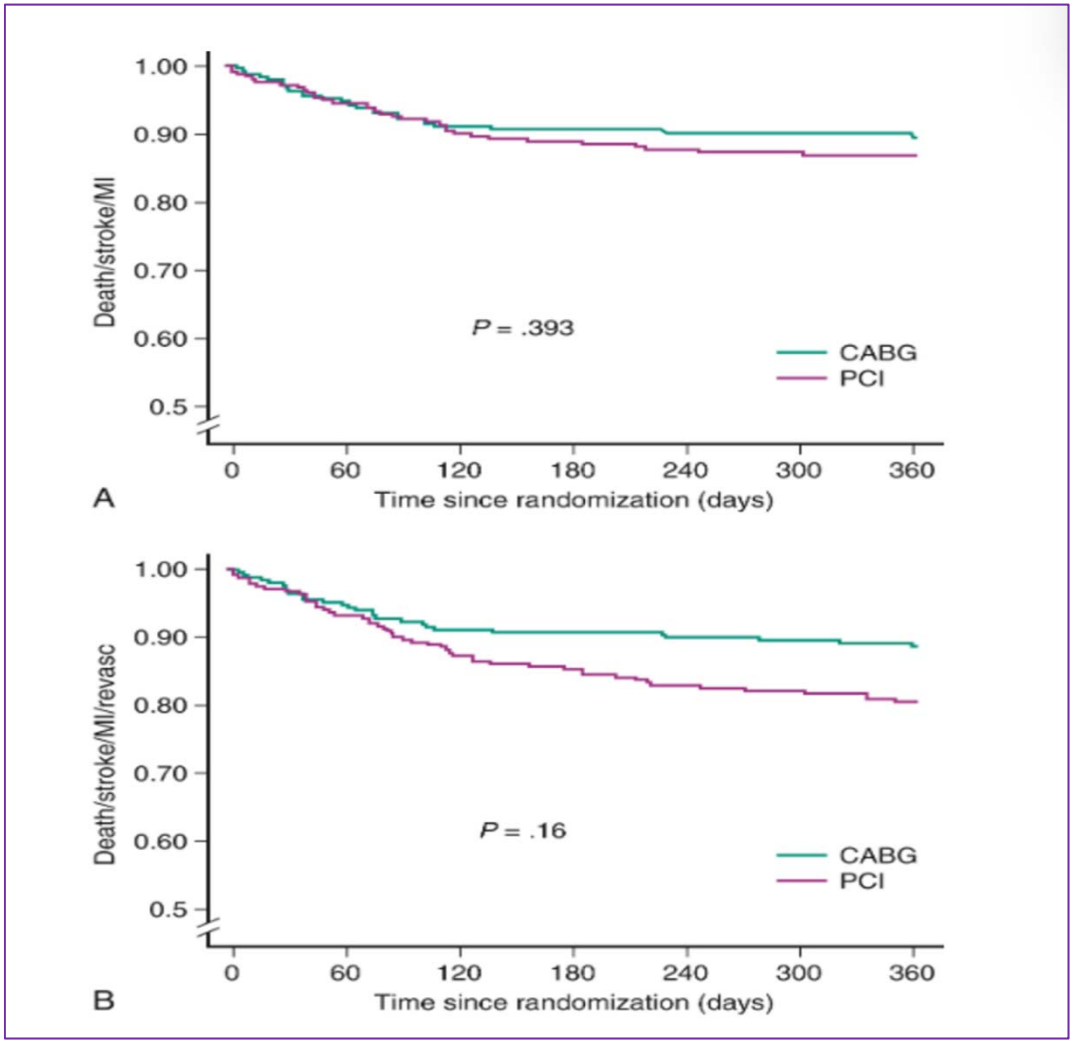
James S, et al. Eur Heart J 31:3006-3016, 2010

RCTs comparing PCI with DES vs CABG in DM with multi-vessel CAD

TRIAL	INCLUSION/EXCLUSION CRITERIA	PRIMARY ENDPOINT	NUMBER RANDOMISED PATIENTS	RESULTS
SYNTAX [115]	MV CAD; Left main disease Amenable for PCI and CABG Diabetes subgroup	MACCE	1,800 452 DM	DM: MACCE at 5 years: PCI: 46.5% vs CABG: 29.0%; P < 0.001
CARDIA [114]	DM, MV CAD, amenable for PCI and CABG	Death, stroke, or non-fatal MI	510 DM	1-year: Death, stroke, MI: 13% PCI vs. 10.5% CABG; p=ns TVR: 11.8% PCI vs. 2% CABG; p<0.001
FREEDOM [113]	DM; MV CAD; amenable to PCI and CABG;	All- cause mortality, MI and stroke	2.400 DM projected; 1,900 finally included	18.7% CABG vs. 26.6% PCI P=0.005 at 5 years

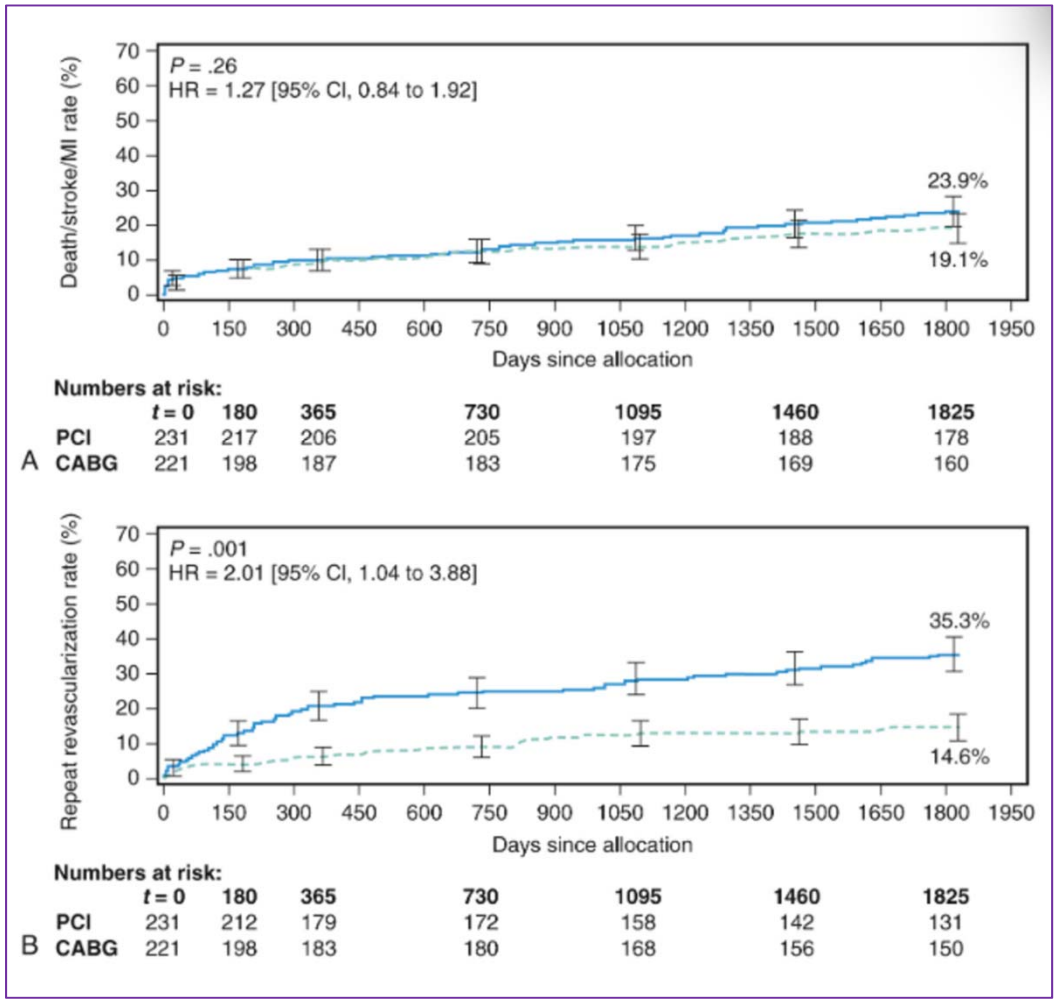
PCI vs CABG in diabetic patients

CARDia trial.



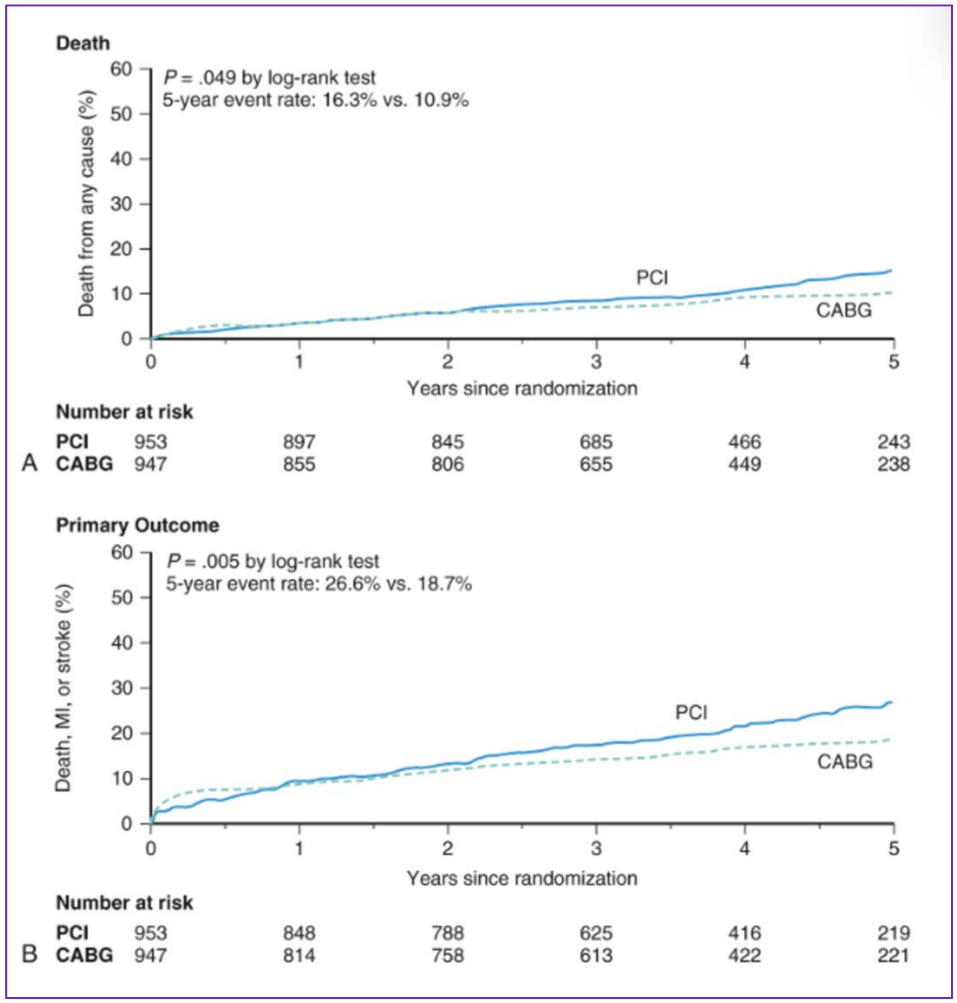
Kapur A, et al. J Am Coll Cardiol 55:432-440, 2010

PCI vs CABG in diabetic patients
SYNTAX trial.



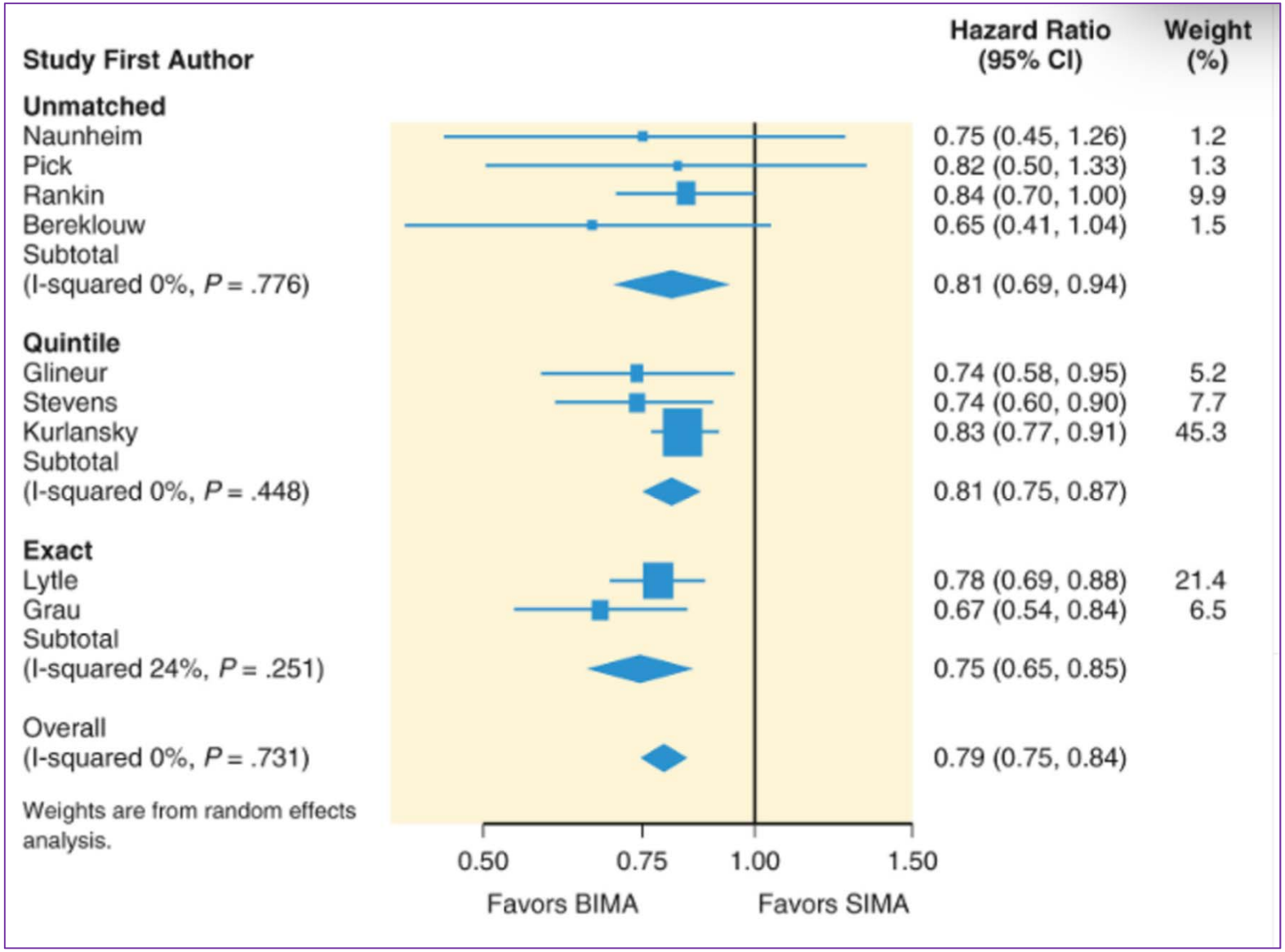
Kappetein AP, et al. Euro J Cardiothorac Surg 43:1006-1013, 2013.

PCI vs CABG in diabetic patients
FREEDOM trial.



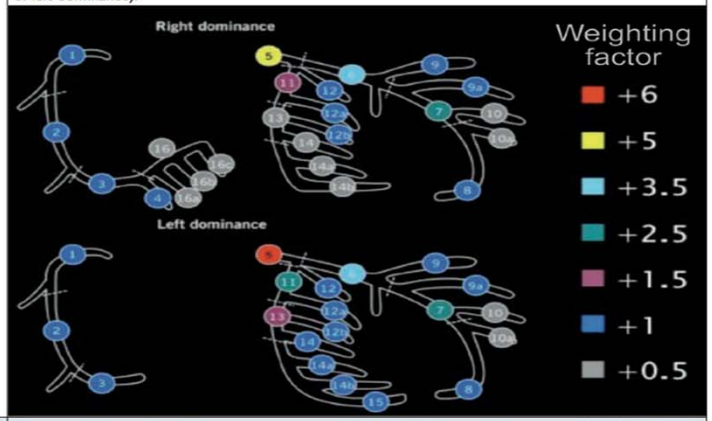
Farkouh ME, et al. New Engl J Med 367:2375-2384, 2012.

Effect of bilateral internal mammary artery on long-term survival (M-A)



Yi G, et al:. Circulation 130:539-545, 2014

SYNTAX score calculation

Steps	Variable assessed	Description
Step 1	Dominance	The weight of individual coronary segments varies according to coronary artery dominance (right or left). Co-dominance does not exist as an option in the SYNTAX score.
Step 2	Coronary segment	The diseased coronary segment directly affects the score as each coronary segment is assigned a weight, depending on its location, ranging from 0.5 (i.e. posterolateral branch) to 6 (i.e. left main in case of left dominance). 
Step 3	Diameter stenosis	The score of each diseased coronary segment is multiplied by 2 in case of a stenosis 50–99% and by 5 in case of total occlusion. In case of total occlusion, additional points will be added as follows: - Age >3 months or unknown +1 - Blunt stump +1 - Bridging +1 - First segment visible distally +1 per non visible segment - Side branch at the occlusion +1 if <1.5mm diameter +1 if both <1.5 and ≥1.5mm diameter +0 if ≥1.5mm diameter (i.e. bifurcation lesion)
Step 4	Trifurcation lesion	The presence of a trifurcation lesion adds additional points based on the number of diseased segments: - 1 segment +3 - 2 segments +4 - 3 segments +5 - 4 segments +6
Step 5	Bifurcation lesion	The presence of a bifurcation lesion adds additional points based on the type of bifurcation according to the Medina classification:[29] - Medina 1,0,0 or 0,1,0 or 1,1,0: add 1 additional point - Medina 1,1,1 or 0,0,1 or 1,0,1 or 0,1,1: add 2 additional point Additionally, the presence of a bifurcation angle <70° adds 1 additional point.
Step 6	Aorto-ostial lesion	The presence of aorto-ostial lesion segments adds 1 additional point
Step 7	Severe tortuosity	The presence of severe tortuosity proximal of the diseased segment adds 2 additional points
Step 8	Lesion length	Lesion length >20 mm adds 1 additional point
Step 9	Calcification	The presence of heavy calcification adds 2 additional points
Step 10	Thrombus	The presence of thrombus adds 1 additional point
Step 11	Diffuse disease/small vessels	The presence of diffusely diseased and narrowed segments distal to the lesion (i.e. when at least 75% of the length of the segment distal to the lesion has a vessel diameter of <2mm) adds 1 point per segment number

2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2014;35:2541-619.

Risk models to assess medium to long term (≥ 1 year) outcome

Score	Development cohort	Patient inclusion	Coronary procedures	Number of variables		Outcome	Recommendation		Validation studies	Calculation	Ref[a]
				Clinical	Anatomical		CABG	PCI			
SYNTAX	none, expert opinion	none	-	0	11 (3 general, 8 per lesion)	MACCE	I B	I B	>50	www.syntaxscore.com	30
SYNTAX II	1 800 Multicentre	03/2005 – 04/2007	50% CABG, 50% PCI	6	12	4-year mortality	IIa B	IIa B	<5	-	25
ASCERT CABG	174 506 Multicentre	01/2002 – 12/2007	100% (i)CABG	23	2	Mortality >2 years	IIa B		<5	-	27
ASCERT PCI	206 081 Multicentre	2004 – 2007	100% PCI	17	2	Mortality >1 year		IIa B	<5	-	28
Logistic Clinical SYNTAX	6 508 Multicentre	03/2005 – 04-2007	100% PCI	3	11	1-year MACE and mortality		IIa B	<5	-	24

2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2014;35:2541-619.

Risk models to assess short term (in-hospital or 30-day) outcome

Score	Development cohort (patients, design)	Patient inclusion	Coronary procedures	Number of variables		Outcome	Recommendation		Validation studies	Calculation	Ref[a]
				Clinical	Anatomical		CABG	PCI			
STS Score	*n* = 774 881 Multicentre	01/2006 – 12/2006	100% (i)CABG	40	2	In-hospital or 30-day[b] mortality, and in-hospital morbidity[c]	I B		5–10	http://riskcalc.sts.org	15, 16
EuroSCORE II	*n* =16 828 Multicentre	05/2010 – 07/2010	47% (i)CABG	18	0	In-hospital mortality	IIa B	IIb C	>10	www.euroscore.org/calc.html	11
ACEF	*n* = 4 557 Single-centre	2001 – 2003	-	3	0	In-hospital or 30-day[b] mortality	IIb C	IIb C	5–10	[Age/ejection fraction (%)] + 1[d]	22
NCDR CathPCI	181 775 Multicentre	01/2004 – 03/2006	100% PCI	8	0	In-hospital mortality		IIb B	<5	-	21
EuroSCORE	*n* =19 030 Multicentre	09/1995 – 11/1995	64% (i)CABG	17	0	Operative mortality	III B	III C	>50	www.euroscore.org/calcold.html	7,8

ACEF = age, creatinine, ejection fraction; (i)CABG = (isolated) coronary artery bypass grafting; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

[a]References.

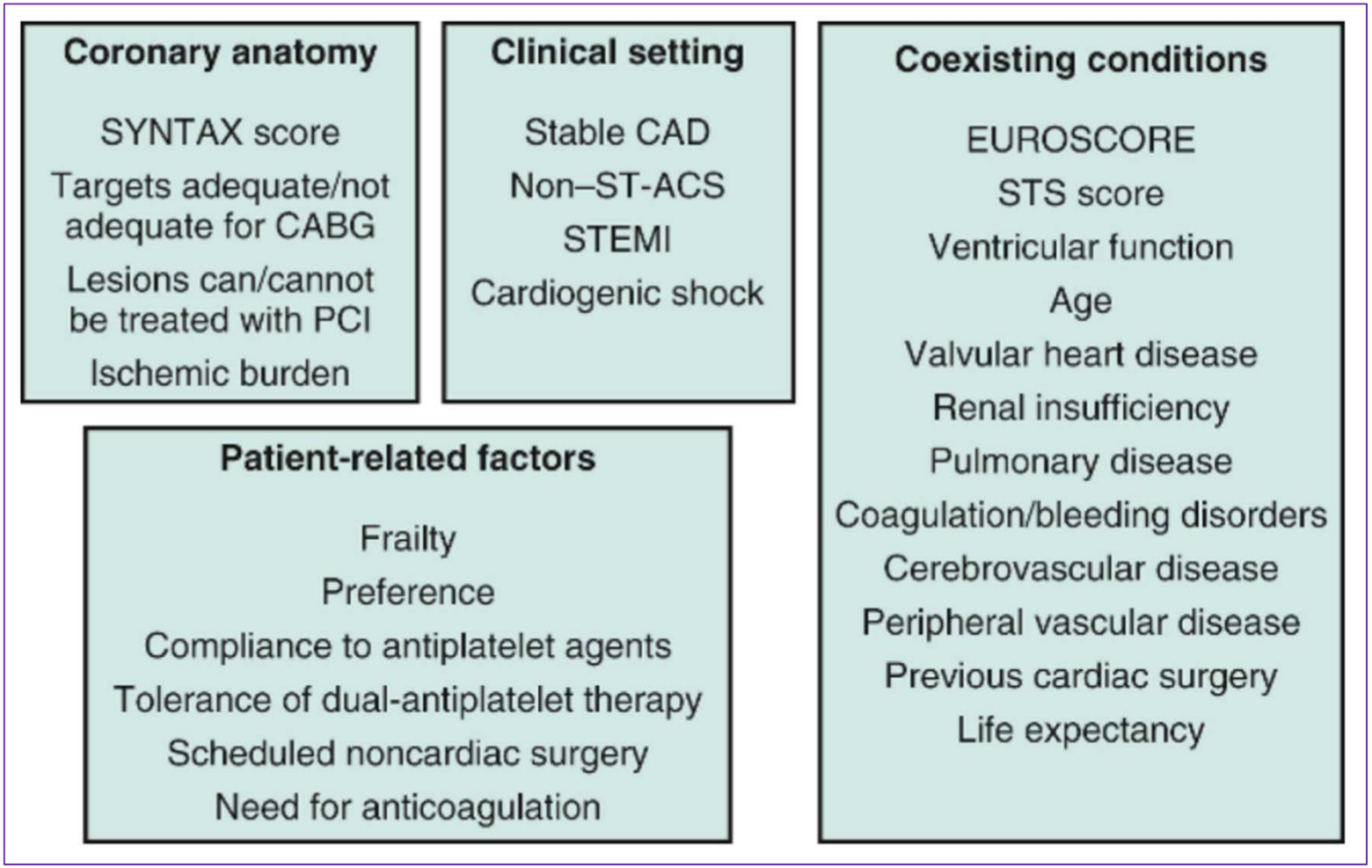
[b]Whichever occurs last.

[c]Permanent stroke, renal failure, prolonged ventilation, deep sternal wound infection, re-operation, length of stay <6 or >14 days.

[d]If creatinine is >2 mg/dL.

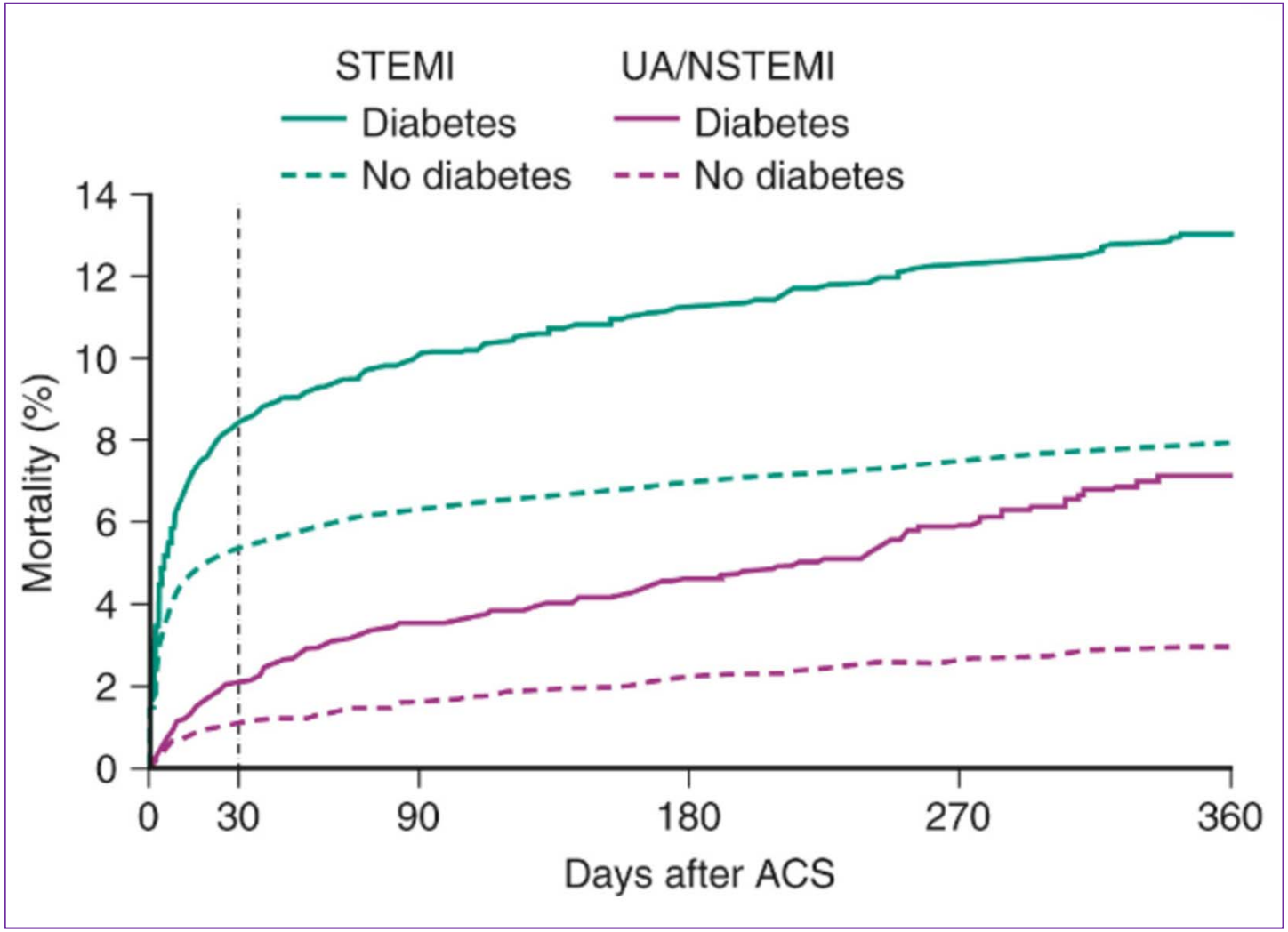
2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2014;35:2541-619.

Parameters guiding the choice of revascularization strategy in diabetic patients



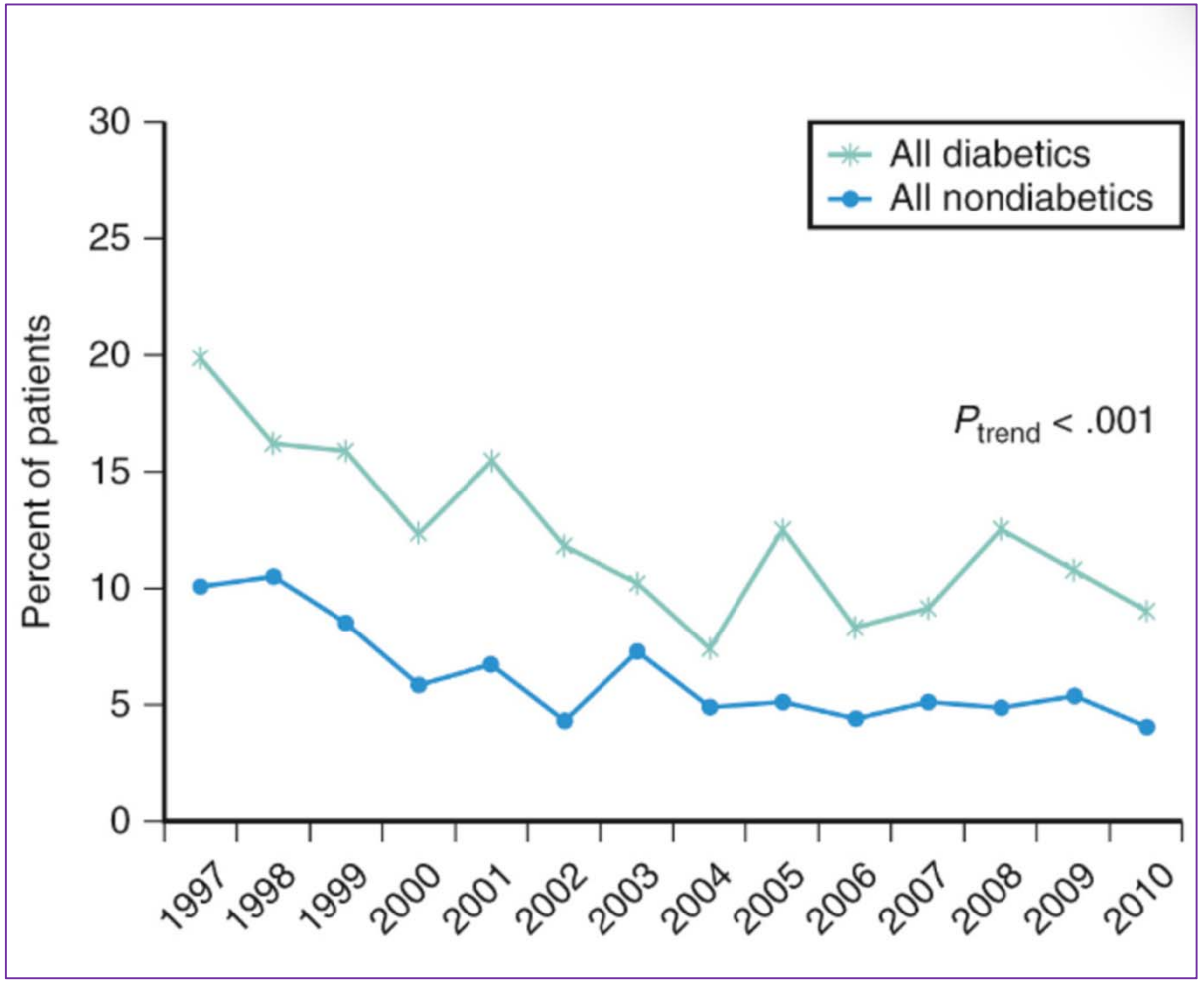
Roffi M, et al. Euro Heart J 32:2748-2757, 2011

Diabetes and mortality following acute coronary syndromes



Donahoe SM, et al. JAMA 298:765-775, 2007

Trends in STEMI in-hospital mortality stratified by diabetes status



Roffi M, et al: Eur Heart J Acute Cardiovasc Care2:342-349, 2013

Main Results from 3 Large Cardiovascular RTs in Patients with Type 2 DM at High CVD risk

Intensive versus standard glucose control

STUDY FEATURE/RESULT	ACCORD		ADVANCE		VADT	
No. of patients	10,251		11,140		1791	
Age (mean, years)	62		66		60	
BMI (mean, kg/m^2)	32		28		31	
Follow-up (mean, years)	3.5		5		5.6	
HbA1c target	<6.0% versus 7.0%-7.9%		≤6.5% versus "standard"		<6% versus 8%-9%	
Baseline HbA1c (mean)	8.3%		7.5%		9.4%	
Endpoint HbA1c (mean)	Intensive 6.4%	Standard 7.5%	Intensive 6.4%	Standard 7.0%	Intensive 6.9%	Standard 8.4%
Severe hypoglycemic events	Intensive 10.5%	Standard 3.5%	Intensive 2.7%	Standard 1.5%	Intensive 8.5%	Standard 2.1%
Weight change	Intensive +3.5 kg	Standard +0.4 kg	Intensive –0.1 kg	Standard –1.0 kg	Intensive +8.1%	Standard +4.1%
Major macrovascular or microvascular event	Not reported		HR 0.9 (0.82-0.98); $P = 0.01$		HR 0.88 (0.74-1.05), $P = 0.14$	
Nonfatal MI/stroke, CV death	HR 0.9 (0.78-1.04); $P = 0.16$		HR 0.94 (0.84-1.06); $P = 0.32$		Not reported	
All-cause mortality	HR 1.22 (1.01-1.46); $P = 0.04$		HR 0.93 (0.83-1.06); $P = 0.28$		HR 1.07 (0.81-1.42); $P = 0.62$	
Nonfatal MI	HR 0.76 (0.62-0.92); $P = 0.004$		HR 0.98 (0.77-1.22); P = NS		HR 0.82 (059-1.14); $P = 0.24$	

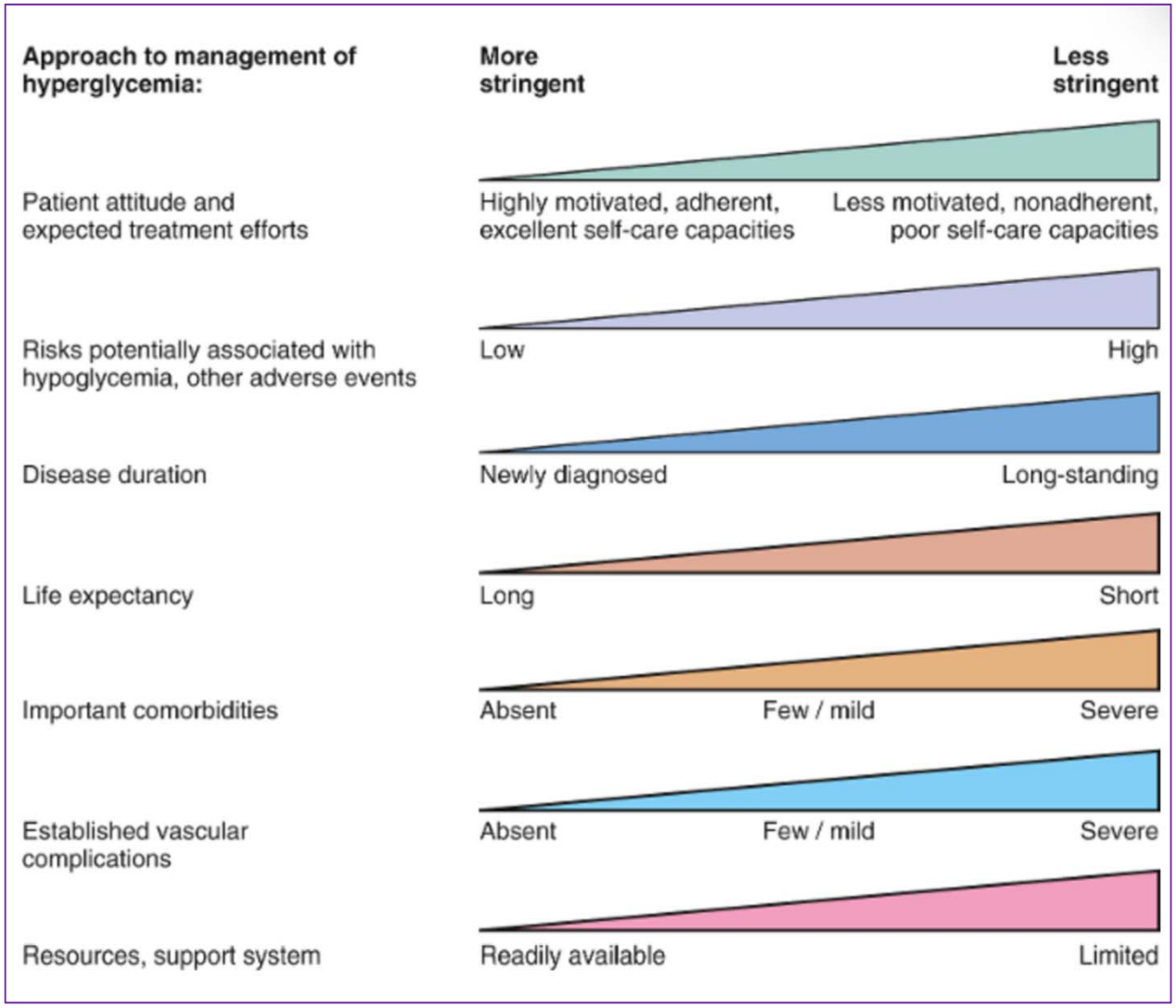
Summary of Selected Randomized Trials Assessing the Effect of Insulin Infusion on Major Adverse Cardiovascular Outcomes Among Patients with Acute Coronary Syndrome Events

STUDY FEATURE	DIGAMI	ECLA	GIPS	CREATE	HI-5	POL-GIK
No. of Patients	620	407	940	20,000+	240	954
Dose (units/hour)	5	1.4/5.2	5	5	2.0	1.3→0.8
Infusion period (hours)	24-72	24	8-12	24	24	24
Glucose target (mg/dL)	126-180	126-198	126-198	126-198	72-180	(<300)
Results	↓ Mortality	↓ Mortality	↓ Mortality*	Neutral	↑ Mortality*	↑ Mortality

Summary of Randomized Trials Comparing Normalization of Blood Glucose Concentration with Insulin Infusion, Against Standard of Care, in a Variety of Intensive Care Unit Settings

STUDY	POPULATION	GLUCOSE TARGET (mg/dL)	PRIMARY ENDPOINT	RESULT	FREQUENCY OF HYPOGLYCEMIA
Van den Berghe-1	SICU (*n* = 1548)	80-110 versus 180-200	ICU death	42% RRR	7.2% (<40 mg/dL)
Van den Berghe-2	MICU (*n* = 1200)	80-110 versus 180-215	Hospital death	No difference	18.7% (mean, 32 mg/dL)
VISEP*	MICU, sepsis (*n* = 488)	80-110 versus 180-200	28-day death	↑ Mortality trend	17.0% (<40 mg/dL)
GIST-UK*	Stroke ICU (*n* = 933)	72-126 versus usual care	90-day death	No difference	15.7% (<70 mg/dL)
European Glucontrol*	MICU (*n* = 1101)	80-110 versus 140-180	Hospital death	↑ Mortality trend	8.6% (<40 mg/dL)
NICE-SUGAR	MICU (*n* = 6104)	81-108 versus <180	90-day death	14% ↑ Mortality	6.8% (<40 mg/dL)

Elements of decision making to determine glycemic targets



Inzucchi SE, et al. Diabetes Care 35:1364-1379, 2012.

FDA regulatory guidance for type 2 DM drugs
12 drug class options (2018)

FDA News Release
December 17, 2008

FDA Announces New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

"We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs' cardiovascular risks during the product's development stage," said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. "FDA's guidance outlines the agency's recommendations for doing such an assessment."

"...sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk."

Requires ~15,000 patient-years of exposure.

www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116994.htm.

- Options for T2DM
  - Metformin
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - Alpha-glucosidase inhibitors
  - TZD
  - Sulfonylureas
  - Glinides
  - Colesevelam
  - Bromocriptine QR
  - Insulin
  - Pramlintide

Garber AJ, et al. *Endocr Pract*. 2016.

Metformin vs other treatments

All-cause mortality

Pooled, adjusted Risk Ratios

Study or subgroup	log [risk ratio]	SE	Weight	Risk ratio IV, random, 95% CI	Year
Evans	−0.5108	0.25	2.6%	0.60 (0.37, 0.98)	2005
Eurich	−0.4156	0.2	4.1%	0.66 (0.45, 0.98)	2005
Masoudi	−0.1393	0.06	29.0%	0.87 (0.77, 0.98)	2005
Inzucchi	−0.0834	0.13	8.9%	0.92 (0.71, 1.19)	2005
Shah	−0.2357	0.4	1.1%	0.79 (0.36, 1.73)	2010
MacDonald	−0.4308	0.15	6.9%	0.65 (0.48, 0.87)	2010
Roussel	−0.3711	0.13	8.9%	0.69 (0.53, 0.89)	2010
Andersson	−0.1625	0.0682	24.6%	0.85 (0.74, 0.97)	2010
Aguilar	−0.2744	0.1	13.9%	0.76 (0.62, 0.92)	2011
Total (95% CI)			100.0%	0.80 (0.74, 0.87)	

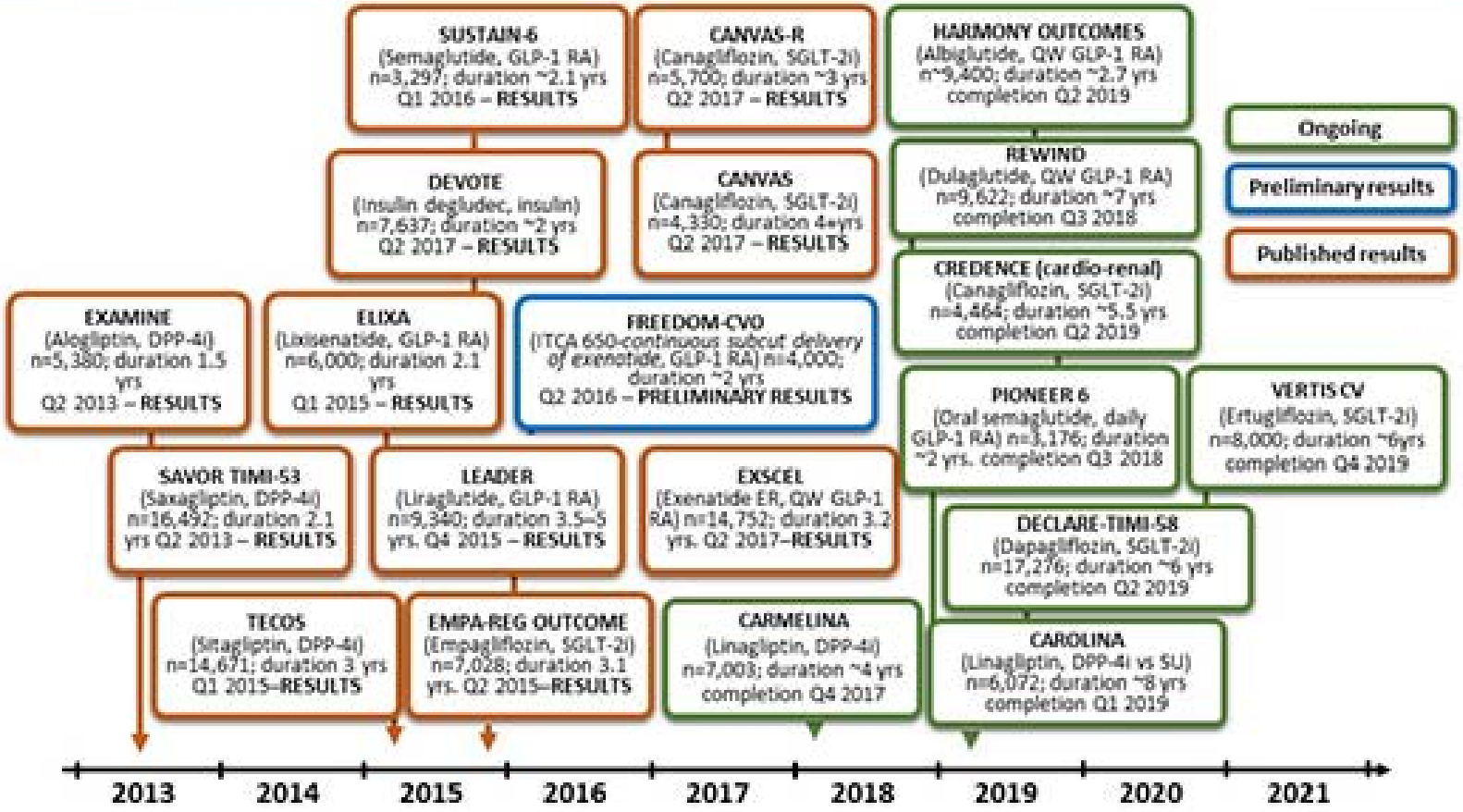
Heterogeneity: Tau^2=0.00; Chi^2=9.45, df=8 (P=0.31); I^2=15%
Test for overall effect: Z=5.35 (P<0.00001)

Observational data!

Eurich DT, et al. *Circ Heart Fail.* 2013.

Cardiovascular outcome trials (CVOTs)

Recent & ongoing



www.clinicaltrials.gov. As of November 13, 2017.

DPP-4i CVOTs

	A1C, %	Duration of Treatment (as part of usual care)	Median FU, y	Primary End Point	HR (95% CI)
SAVOR-TIMI 53 Established CVD and/or multiple risk factors	6.5–12.0	Saxagliptin / Placebo	2.1	CV death, Nonfatal MI, or Nonfatal stroke	1.00 (0.89, 1.12)
EXAMINE ACS within 15 to 90 days	6.5–11.0	Alogliptin / Placebo	1.5	CV death, Nonfatal MI, or Nonfatal stroke	0.96 (≤1.16)
TECOS Preexisting CVD	6.5–8.0	Sitagliptin / Placebo	3.0	CV death, Nonfatal MI, Nonfatal stroke, or UA requiring hospitalizatio	0.98 (0.89, 1.08)
CARMELINA High vascular risk	6.5–10.0	Linagliptin / Placebo	Ongoing	CV death, Nonfatal MI, Nonfatal stroke, or UA requiring hospitalization	Ongoing
CAROLINA High CV risk	6.5–8.5	Linagliptin / Glimepiride	Ongoing	CV death, Nonfatal MI, or Nonfatal stroke	Ongoing

Randomization — Year 1 — Year 2 — Year 3

Median Duration of Follow-up

Green JB, et al. *N Engl J Med*. 2015; Scirica BM, et al. *N Engl J Med*. 2013; White WB, et al. *N Engl J Med*. 2013; www.clinicaltrials.gov.

Hospitalization for Heart Failure
SAVOR-TIMI 53, EXAMINE & TECOS

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	*P*-value
SAVOR-TIMI 53 (saxagliptin vs placebo)	289/8,280 (3.5%)	228/8,212 (2.8%)	1.27	1.07, 1.51	0.007
EXAMINE (alogliptin vs placebo)	106/2,701 (3.9%)	89/2,679 (3.3%)	1.19	0.89, 1.59	0.235
TECOS (sitagliptin vs placebo)	228/7,332 (3.1%)	229/7,339 (3.1%)	1.00	0.84, 1.20	1.000
SAVOR-TIMI 53 + EXAMINE + TECOS	623/18,313 (3.4%)	546/18,230 (3.0%)	1.14	0.97, 1.34	0.102

Adapted from Armstrong PW, Van de Werf: TECOS. European Society of Cardiology. 2015; Scirica BM, et al. *N Engl J Med*. 2013; Zannad F, et al. *Lancet*. 2015; Green JB, et al. *N Engl J Med*. 2015.

Summary of CVOTs with GLP-1 RAs

REPORTED

	Intervention	Main Inclusion Criteria	N	Primary Outcome	Secondary Outcome	Follow-up Period
ELIXA[1]	Lixisenatide Placebo	ACS event ≤180 days prior to screening	6,068	4P-MACE	Expanded MACE	2.1 years median
LEADER[2]	Liraglutide Placebo	Established CVD (≥50 years), or ≥60 years + ≥1 CV risk factor	9,340	3P-MACE	Expanded MACE	3.8 years median
SUSTAIN-6[3]	Semaglutide* Placebo	Established CVD, HF or CKD stage ≥3 (≥50 years), or ≥60 years + ≥1 CV risk factor	3,297	3P-MACE	Expanded MACE	2.1 years median
EXSCEL[4]	Exenatide ER* Placebo	Any level of CV risk, including prior CV event	14,752	3P-MACE	All-cause mortality, HHF, hospitalization for ACS	3.2 years median

*once weekly; †via DUROS device

[1]Pfeffer MA, et al. *N Engl J Med*. 2015; [2]Marso SP, et al; LEADER Investigators. *N Engl J Med*. 2016; [3]Marso SP, et al; SUSTAIN-6 Investigators. *N Engl J Med*. 2016; [4]Holman RR, et al. *N Engl J Med*. 2017; [5]www.clinicaltrials.gov.

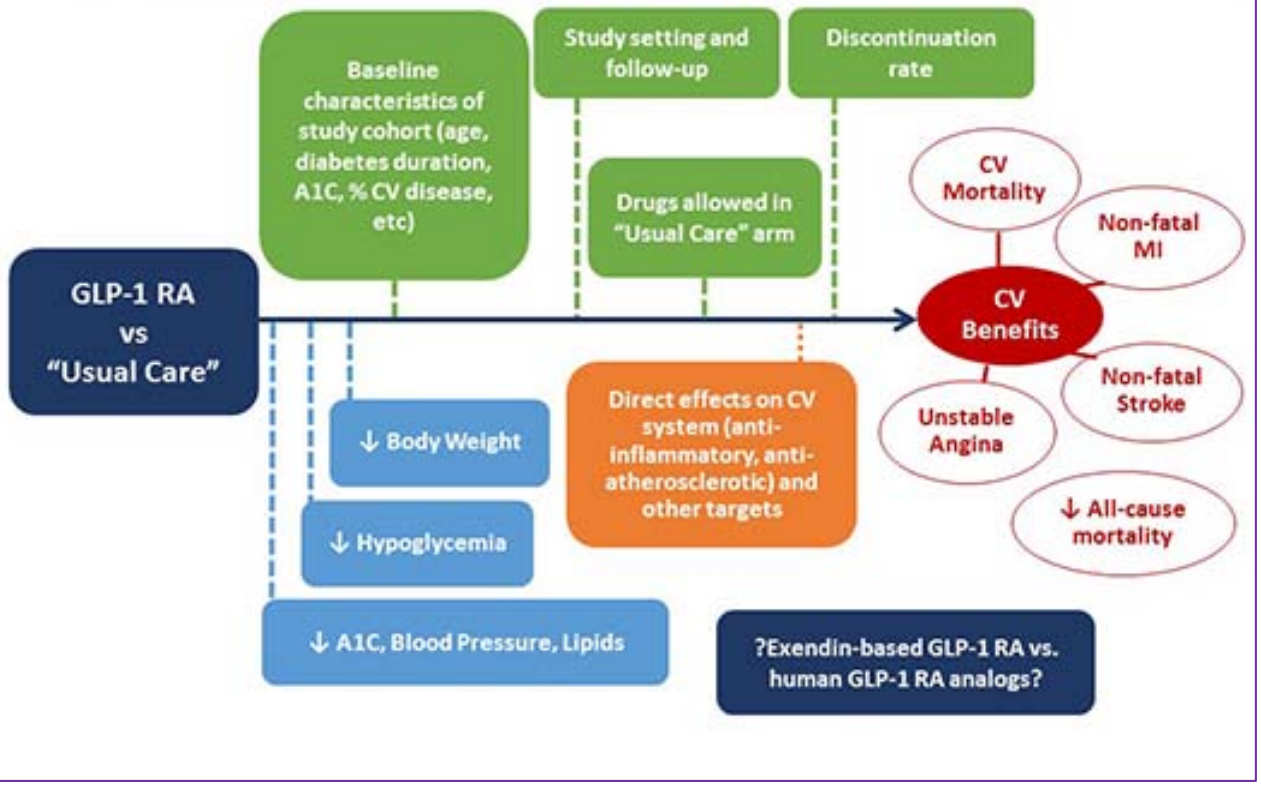
ELIXA, LEADER, SUSTAIN-6 and EXSCEL

Primary Endpoint and the Individual Components

	ELIXA		LEADER		SUSTAIN-6		EXSCEL	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
1^{O} composite MACE	1.02 (0.89–1.17)	**0.81**	0.87 (0.78–0.97)	**0.01**	0.74 (0.58–0.95)	**0.02**	0.91 (0.83–1.00)	**0.06**
CV mortality	0.98 (0.78–1.22)	**NS**	0.78 (0.66–0.93)	**0.007**	0.98 (0.65–1.48)	**NS**	0.88 (0.76–1.02)	**NS**
Myocardial infarction	1.03 (0.87–1.22)	**NS**	0.86 (0.73–1.00)	**0.046**	0.74 (0.51–1.08)	**NS**	0.97 (0.85–1.10)	**NS**
Stroke	1.12 (0.79–1.58)	**NS**	0.86 (0.71–1.06)	**NS**	0.61 (0.38–0.99)	**0.04**	0.85 (0.70–1.03)	**NS**
Unstable angina	1.11 (0.47–2.62)	**NS**						

Adapted from Pfeffer MA, et al. *N Engl J Med*. 2015; Marso SP, et al; LEADER Trial Investigators. *N Engl J Med*. 2016; Marso SP, et al; SUSTAIN-6 Trial Investigators. *N Engl J Med*. 2016; Holman RR, et al. *N Engl J Med*. 2017.

CV Outcomes Trials with GLP-1 RAs



SGLT-2 inhibitors RCTs

	EMPA-REG OUTCOME	CANVAS PROGRAM
Study drug	Empagliflozin	Canagliflozin
CV risk	Established CVD (99%)	Established CVD (65%) / MRF (35%)
Sample size, N	7,020	10,142
Mean duration of diabetes, years	57% >10 years	13.5
Mean A1C, %	8.1	8.2
Mean age, years	63	63
History of heart failure, %	10	14.4
ACE-inhibitors / ARBs, %	81	80
Statins, %	77	75
Acetylsalicylic acid, %	83	74

Zinman B, et al. *N Engl J Med*. 2015; Neal B, et al. *N Engl J Med*. 2017.

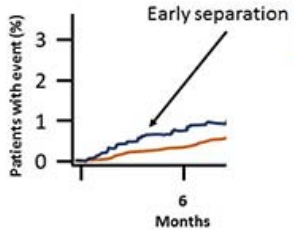
EMPA-REG outcomes

	Patients with event/analysed				
	Empagliflozin	Placebo	HR	(95% CI)	*P*-value
Primary outcome:					
3-point MACE	490/4,687	282/2,333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4,687	137/2,333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4,687	121/2,333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4,687	60/2,333	1.24	(0.92, 1.67)	0.1638

Cox regression analysis. 3-point MACE: Time to first occurrence of CV death, non-fatal MI or non-fatal stroke.
*95.02% CI

Zinman B, et al. *N Engl J Med*. 2015.

CV death

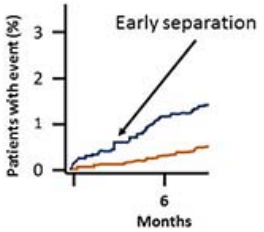


	HR (95% CI)	*P*-value
Empagliflozin (pooled)	0.62 (0.49, 0.77)	*P*<0.0001
Empagliflozin 10 mg	0.65 (0.50, 0.85)	*P*=0.0016
Empagliflozin 25 mg	0.59 (0.45, 0.77)	*P*=0.0001

Placebo
Empagliflozin

Zinman B, et al. *N Engl J Med*. 2015.

HF hospitalization



	HR (95% CI)	*P*-value
Empagliflozin (pooled)	0.65 (0.50, 0.85)	*P*=0.0017
Empagliflozin 10 mg	0.62 (0.45, 0.86)	*P*=0.0044
Empagliflozin 25 mg	0.68 (0.50, 0.93)	*P*=0.0166

Placebo
Empagliflozin

Zinman B, et al. *N Engl J Med*. 2015.

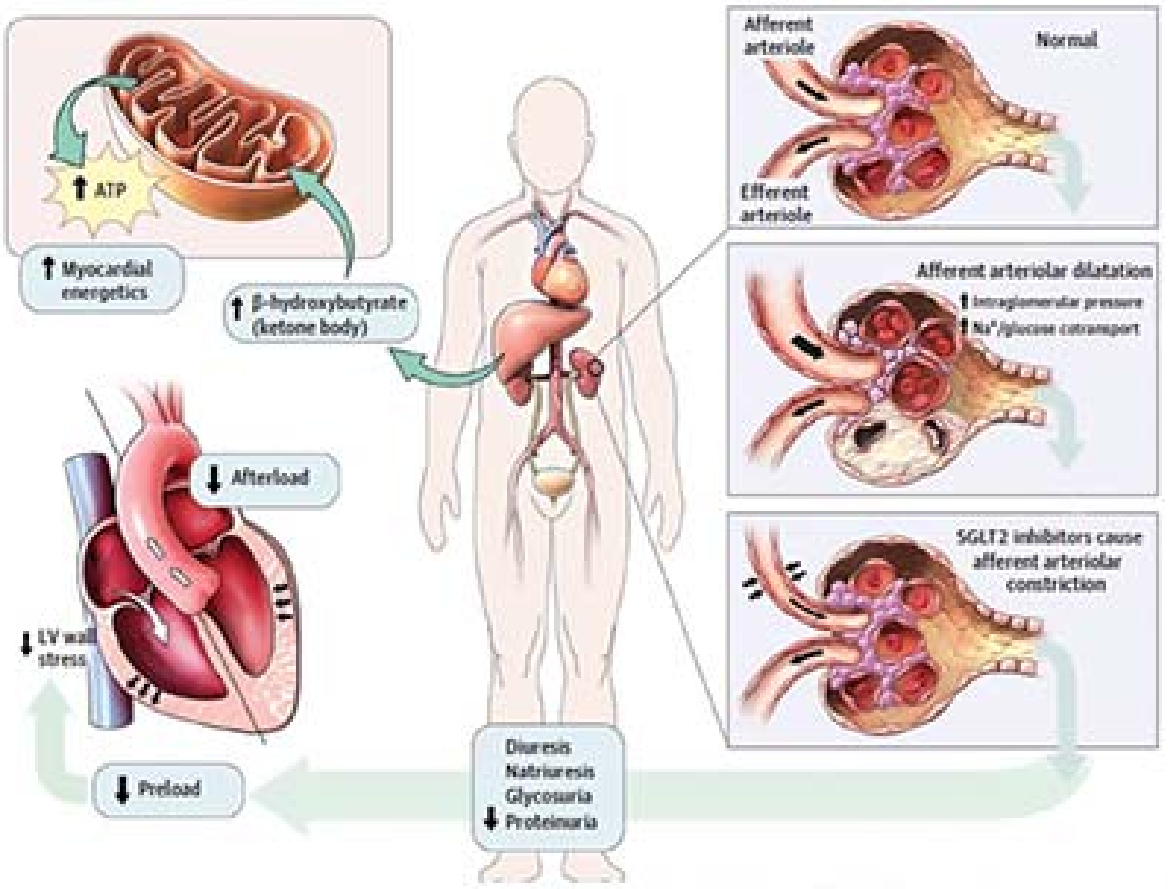
CANVAS outcomes

	Canagliflozin (N=5,795) No. of participants per 1000 patient yr	Placebo (N=4,347) No. of participants per 1000 patient yr	HR	(95% CI)	P
3-point MACE	26.9	31.5	0.86	(0.75, 0.97)	0.02†
CV death	11.6	12.8	0.87	(0.72, 1.06)	NR
Non-fatal MI	9.7	11.6	0.85	0.69, 1.05)	NR
Non-fatal stroke	7.1	8.4	0.90	(0.71, 1.15)	NR
Hospitalization for heart failure	5.5	8.7	0.67	(0.52, 0,87)	NR

Participants treated with ≥1 dose of study drug
Rate=per 100 patient-years
†=*P*-value for superiority

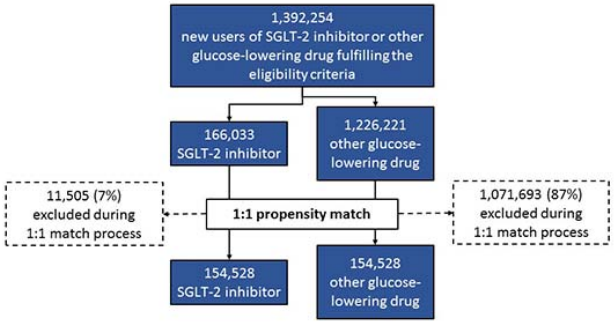
Neal B, et al. *N Engl J Med*. 2017.

Proposed Mechanism of Cardiorenal Protection with SGLT-2 Inhibitors



CVD – REAL study

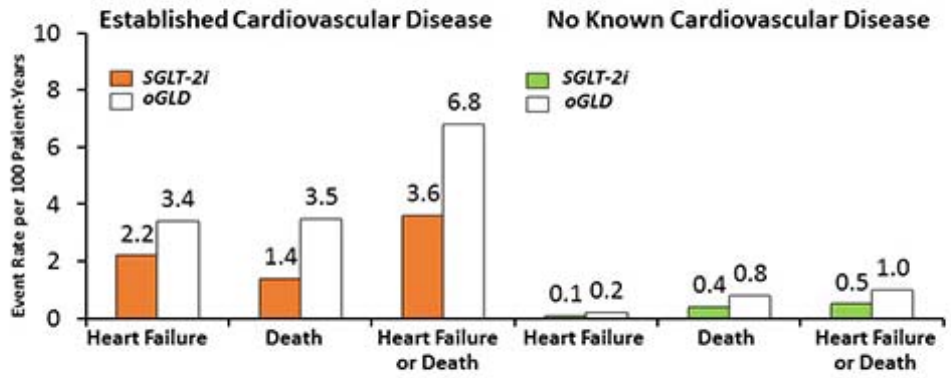
Patient Population – All Countries/Databases Combined



Kosiborod M, et al. *Circulation*. 2017.

Absolute Rates of CV Events in Patients Treated with SGLT-2i and oGLD

P<0.001 for all comparisons

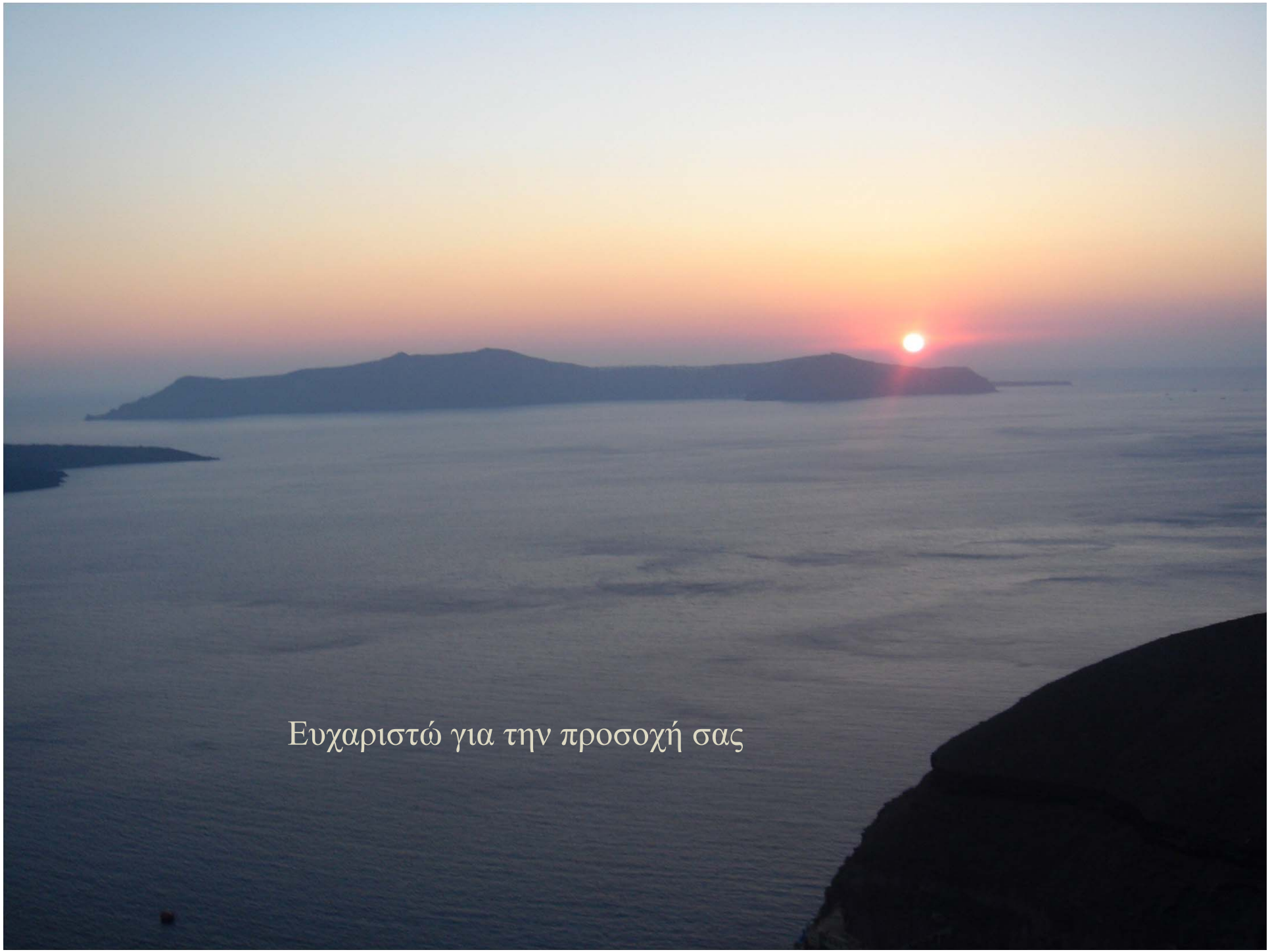


SGLT-2i=sodium-glucose cotransporter-2 inhibitors
oGLD=other glucose-lowering drug

Cavender M, at al. Presented at ADA Scientific Sessions. 2017.

CAD & DM: 10 key points

- **Diabetic > 40 year-old : + 15 year-old equivalent**
- **Diabetic vs non-diabetic CAD mortality: x2 (persistent over time)**
- **CAD is more prevalent, more severe and appears earlier in diabetics.**
- **Accelerated atherosclerosis in diabetes: chronic hyperglycemia, dyslipidemia, oxidative stress & insulin resistance lead to enhanced inflammation, pro-thrombotic state & endothelial dysfunction.**
- **Screening for CAD in diabetics: for symptomatic and asymptomatic with high risk features.**
- **In diabetics with stable CAD not requiring immediate revascularization OMT is a valuable alternative.**
- **Diabetics with ACS: more aggressive management : early invasive strategy and potent platelet inhibition.**
- **Choice of revascularization strategy: based on anatomic complexity / surgical risk, threshold for CABG low.**
- **Optimal glycemic control: beneficial for microvascular, new agents collaterally benefit macrovascular complications.**
- **With advanced age, disease duration, CVD , comorbidities less stringent glycemic control is needed.**


Ευχαριστώ για την προσοχή σας