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Management of Ischaemic Heart Disease in Patients with Diabetes

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Agenda

- Relationship between DM and ASCVD
- Anti-diabetic drugs and beyond
- State-of-the-art management of cholesterol in DM
- BP lowering in diabetics: now what?

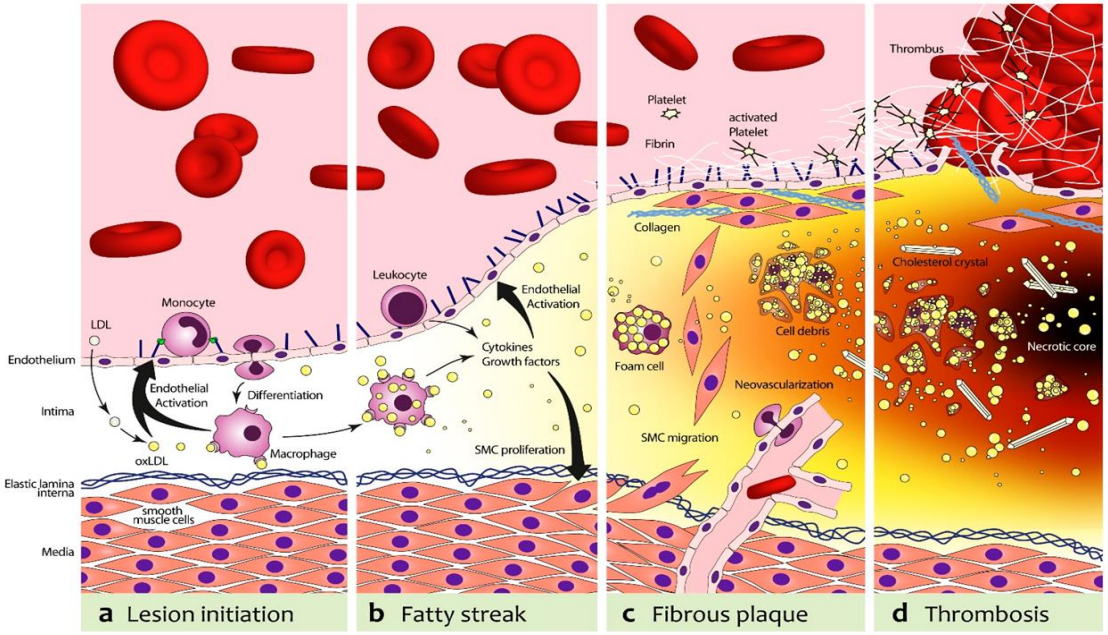
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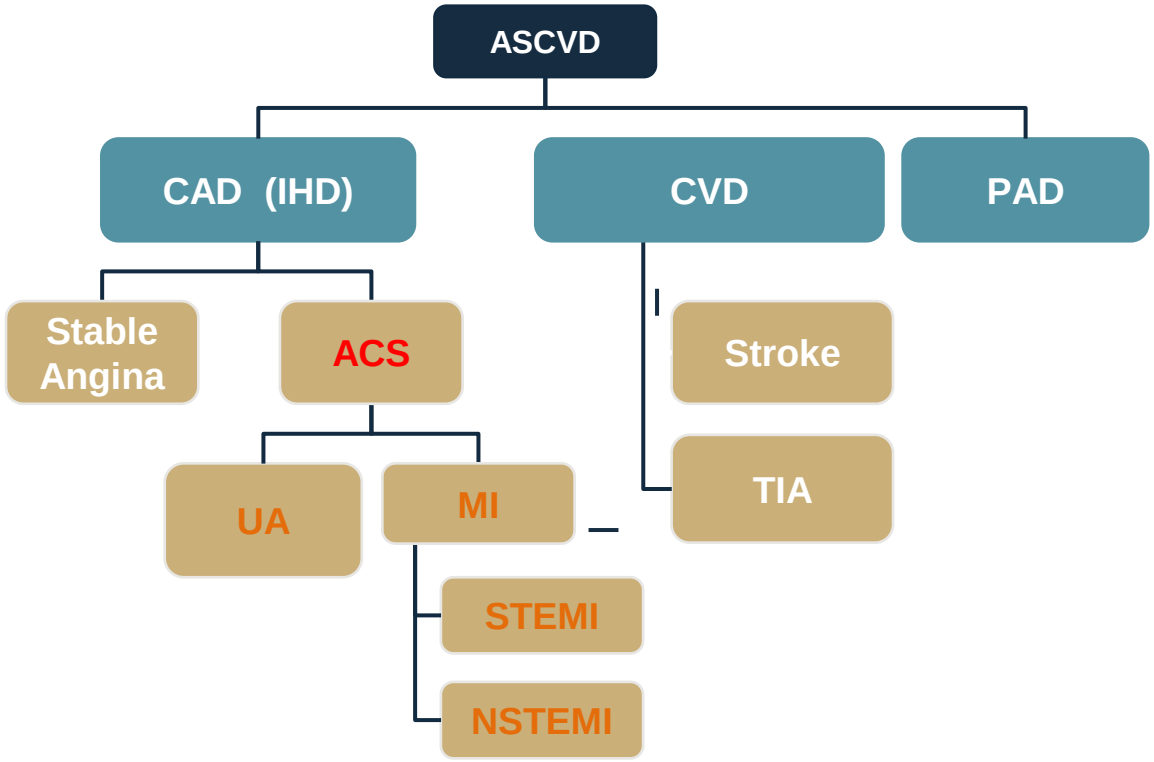
Relationship between DM and ASCVD

DM IS A SIGNIFICANT RISK FACTOR FOR ASCVD

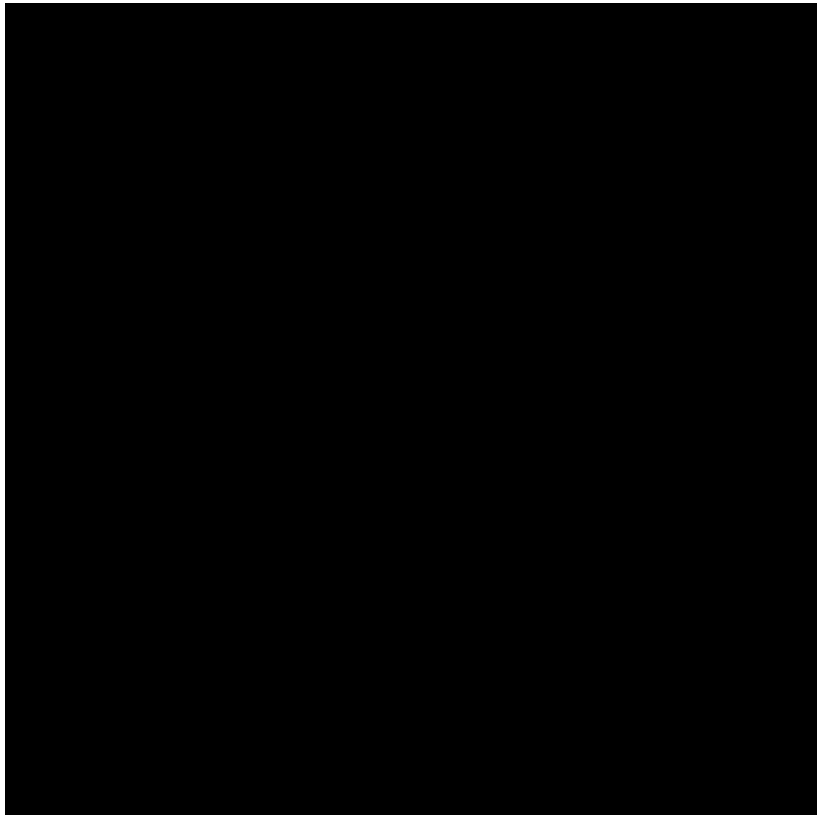
- ASCVD is defined as CAD, cerebrovascular disease, or PAD presumed to be of **atherosclerotic origin**
- The risk of ASCVD has been substantially reduced in recent years due to the introduction of effective **LDL-C-lowering** treatments and effective **disease modifying drugs**

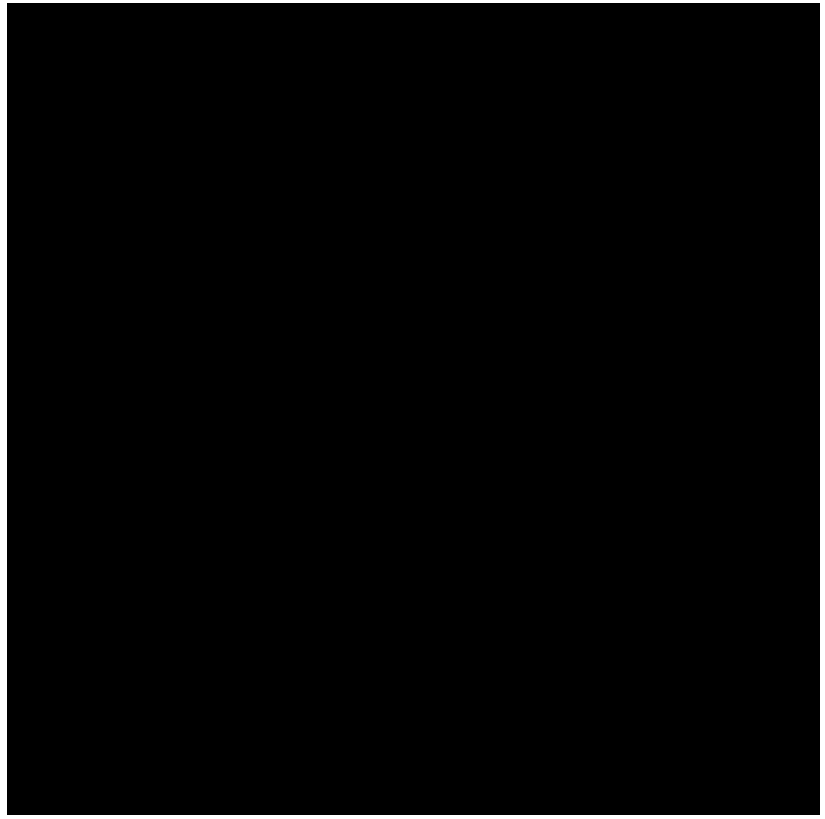


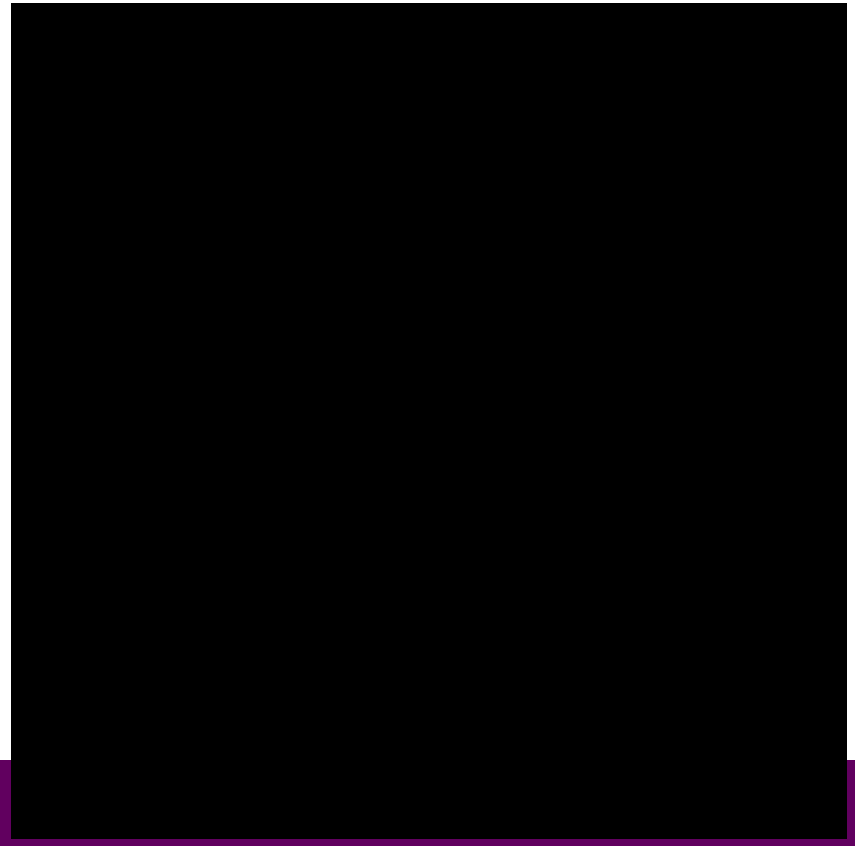
ASCVD is the Leading Cause of Morbidity and Mortality in Patients With DM[1,2]



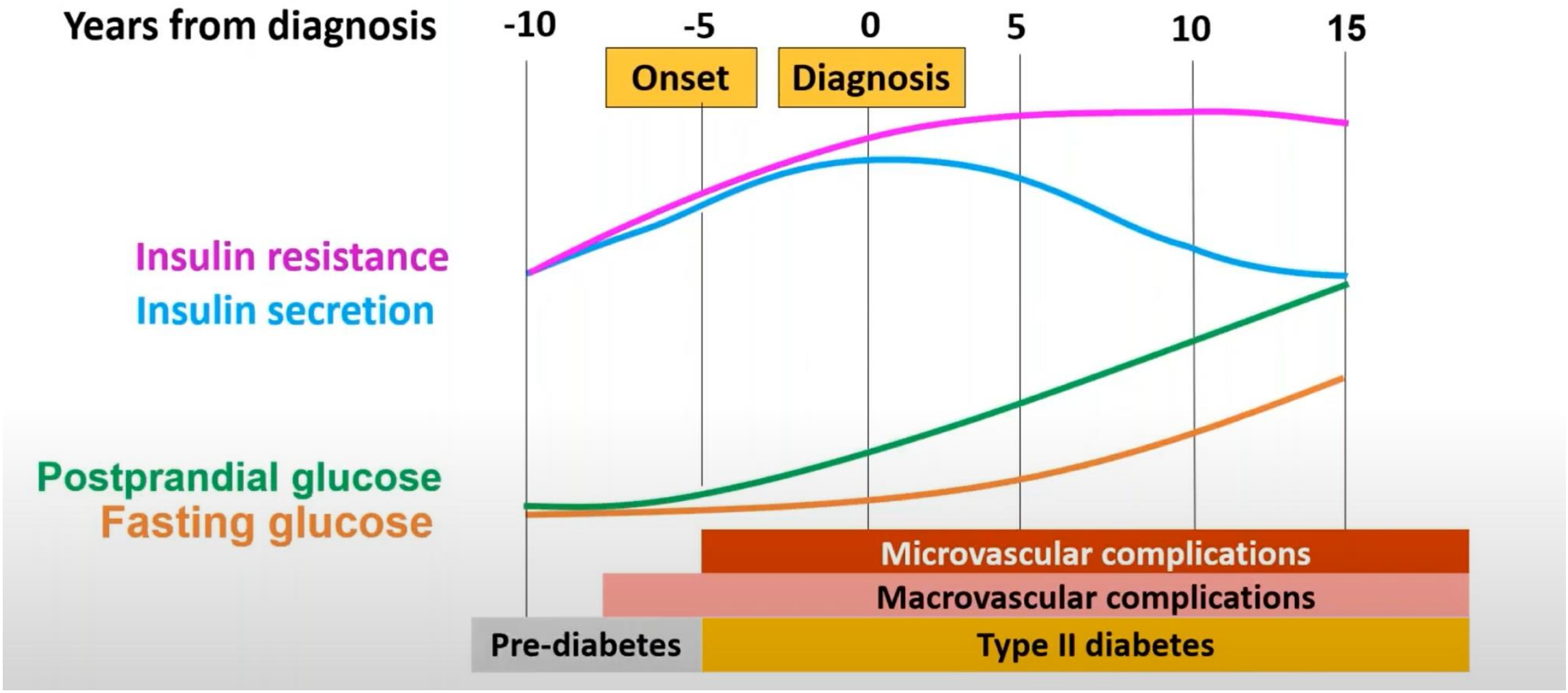
Anterior STEMI – thrombotic occlusion







Natural history of diabetes

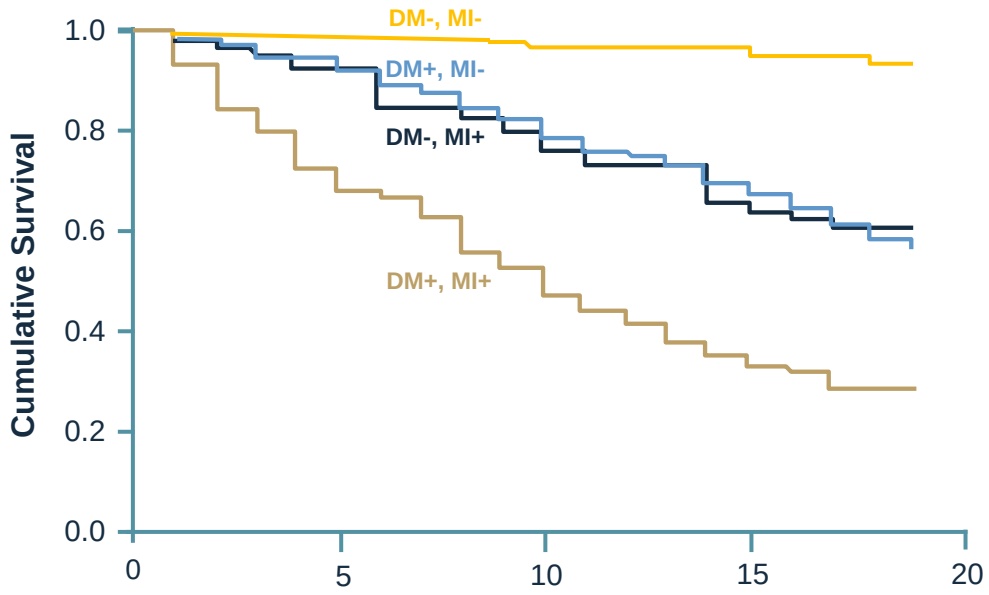


Ramlo-Halsted BA et al. *Prim Care*. 1999;26:771-789

CVD DEVELOPS EARLIER AND ARE MORE FREQUENT

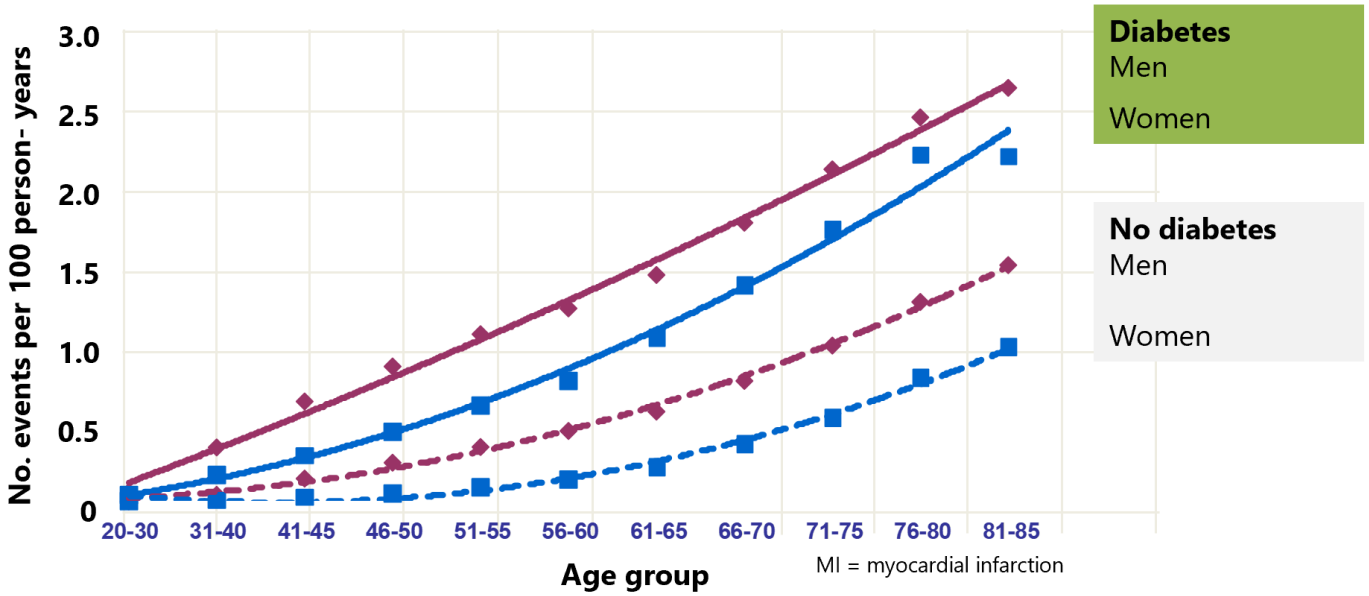
About *two out of every three deaths* in patients with *DM are due to CVD,* of which ~40% are from CHD and 15% from other forms of heart disease[1]

Incidence per 1,000 Person-Years of CHD Death According to the Presence of T2DM and Prior Evidence of MI[2]



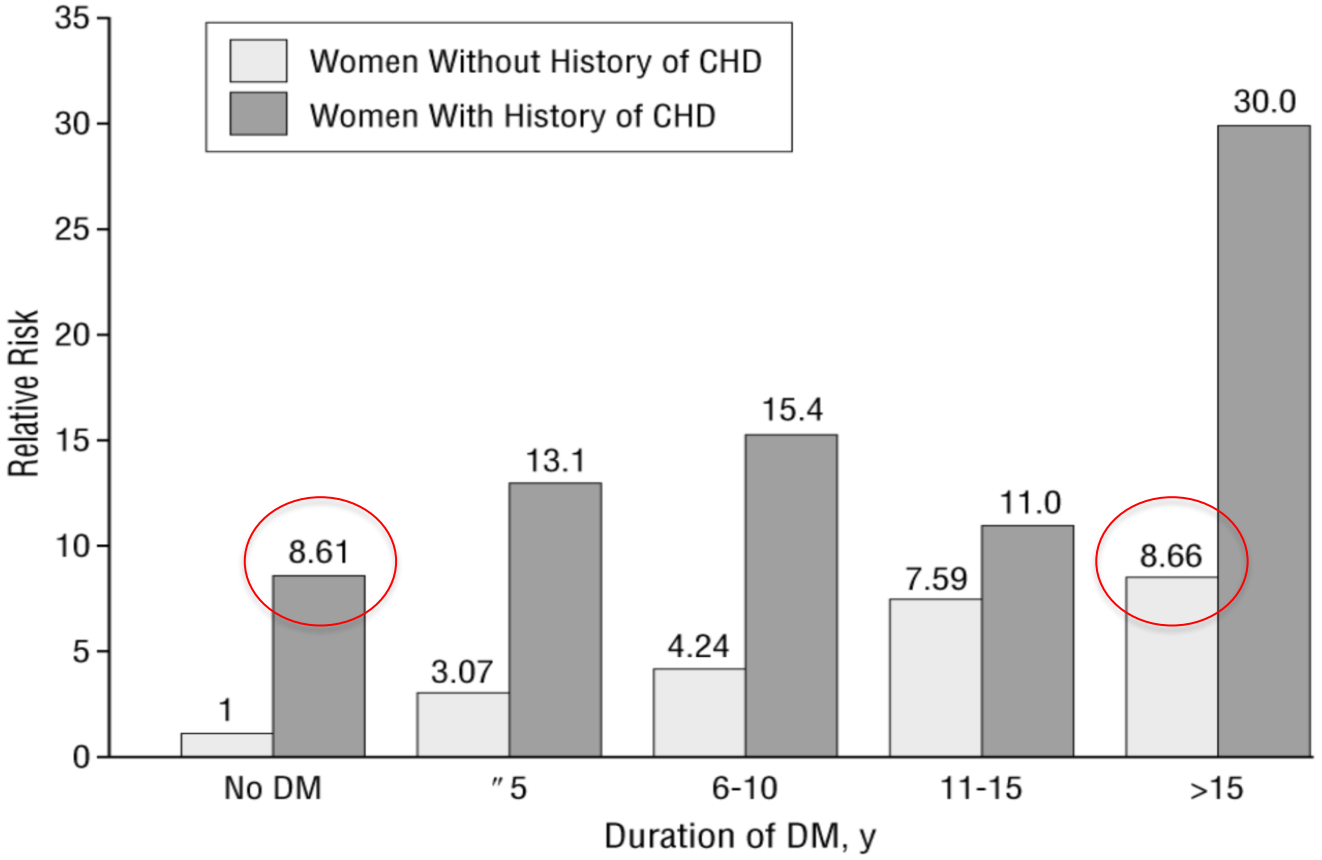
Absolute risks of MI are much higher in diabetics

Diabetes n = 379,003 **No Diabetes n = 9,018,082** **Database 1994-2000**



1. Wang CCL, et al. Circulation. 2016;133:2549–502; 2. Laakso M. *Diabetes Care.* 2010;33:442–9;
2. Booth GL, *et al. Lancet.* 2006;368;29–36; 3. Shah AD, *et al. Lancet Diabetes Endocrinol.* 2015;105–13

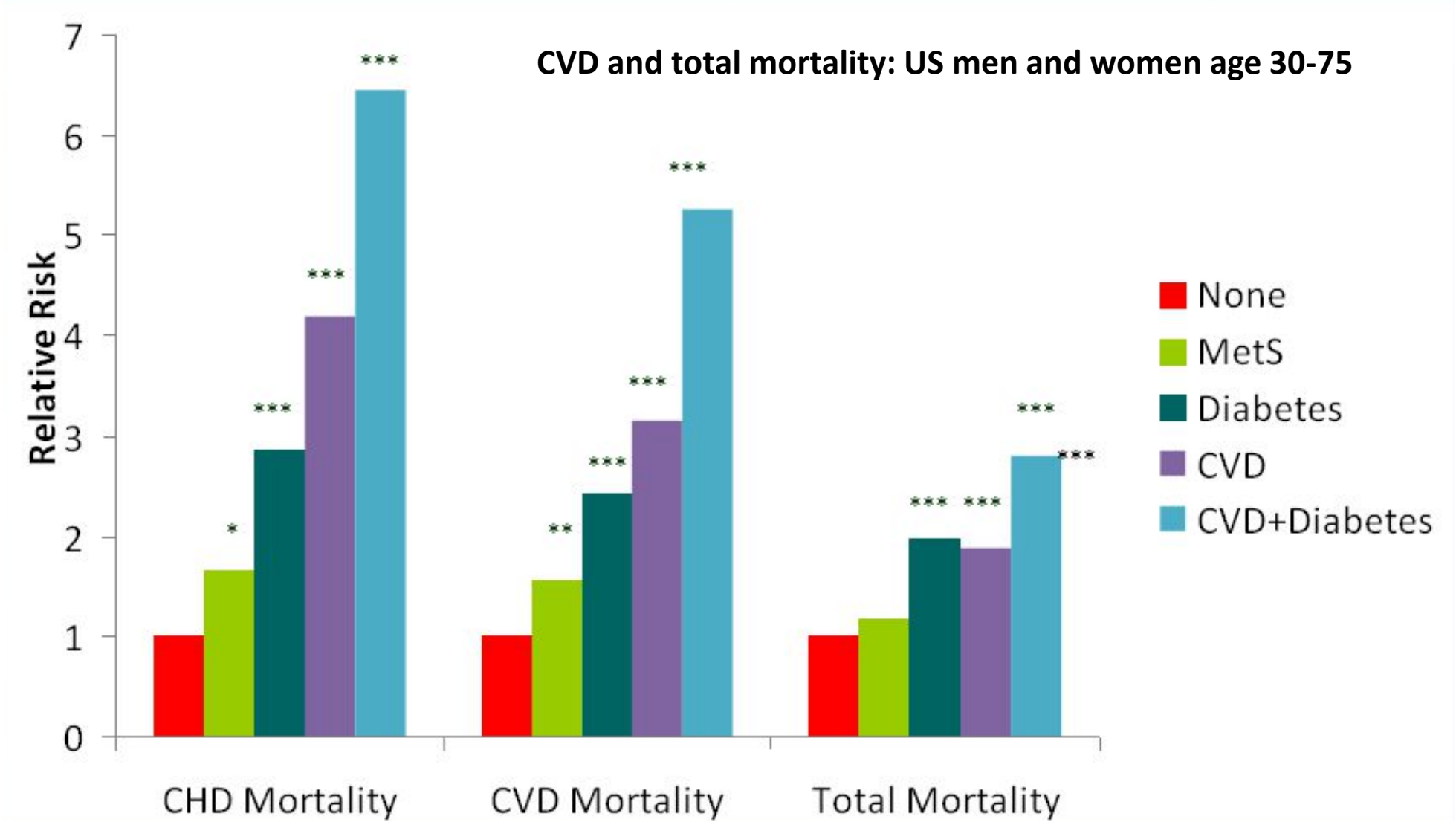
Type 2 DM for >15 Years = Prior CHD and No Diabetes



20 year follow-up of 121,046 women aged 30 to 55 years in Nurses' Health Study

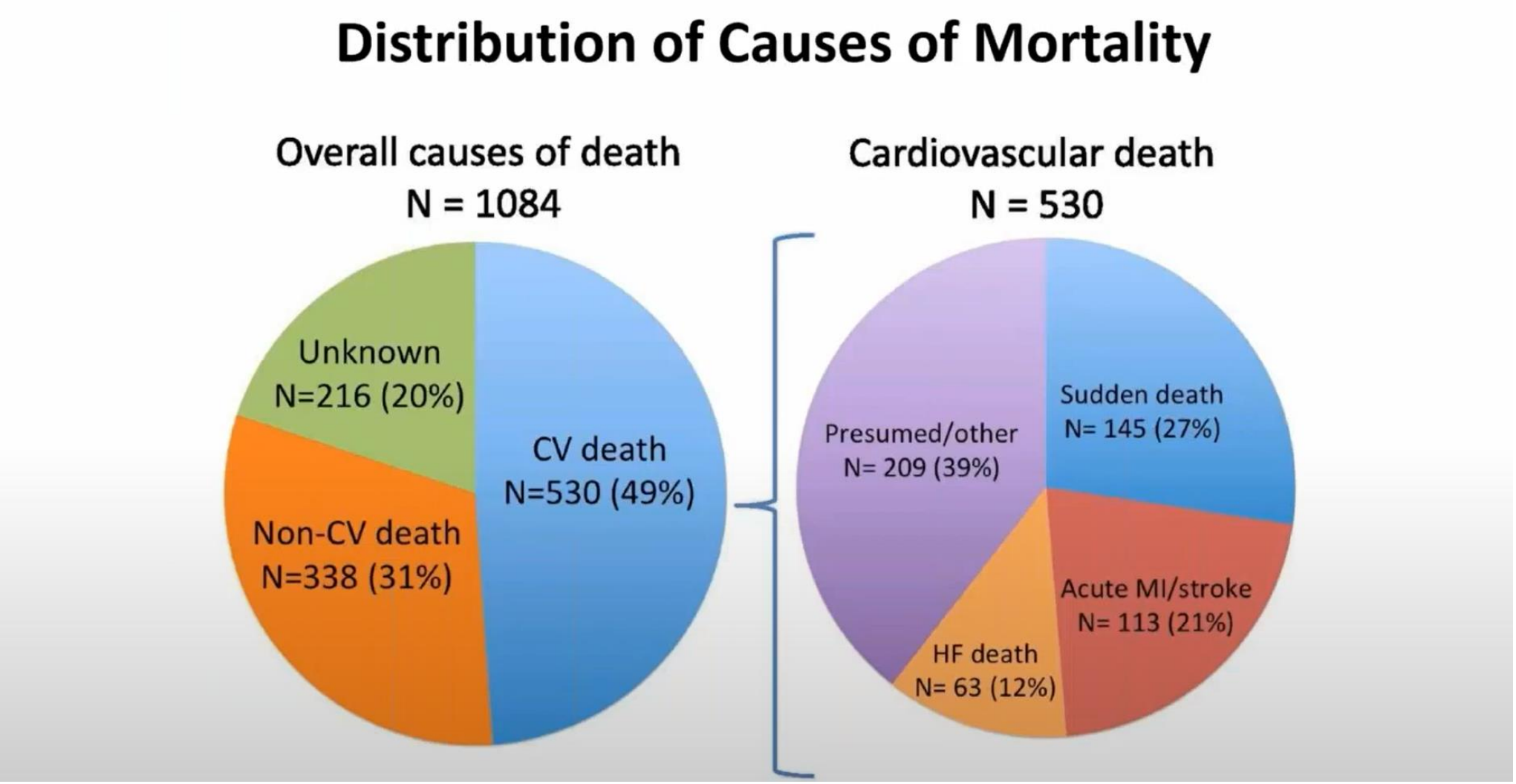
Hu F, et al. Arch Intern Med. 2001;161:1717-1723.

Risk of CV Mortality



Malik and Wong, et al., **Circulation 2004; 110: 1245-1250.**

Causes of death in type II DM

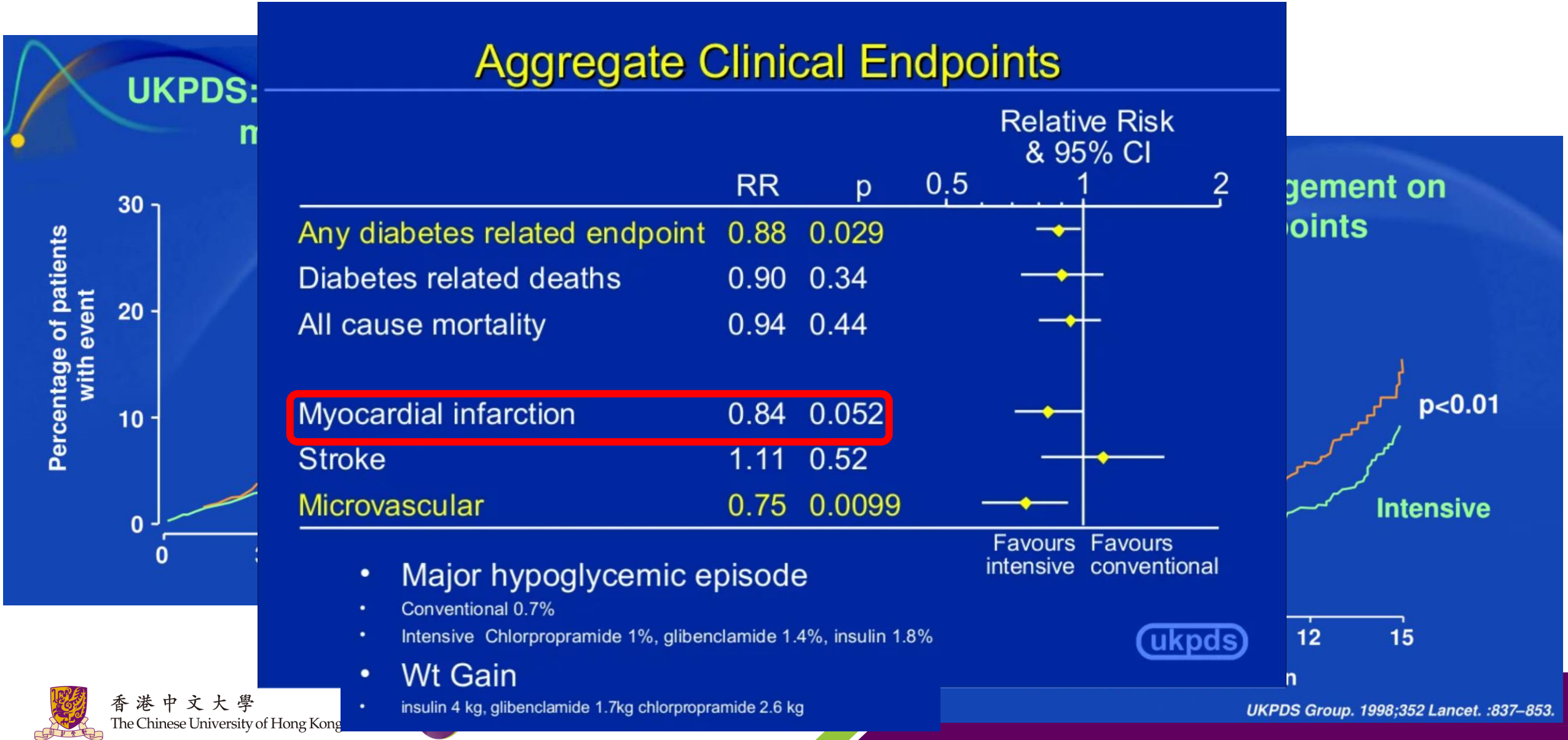


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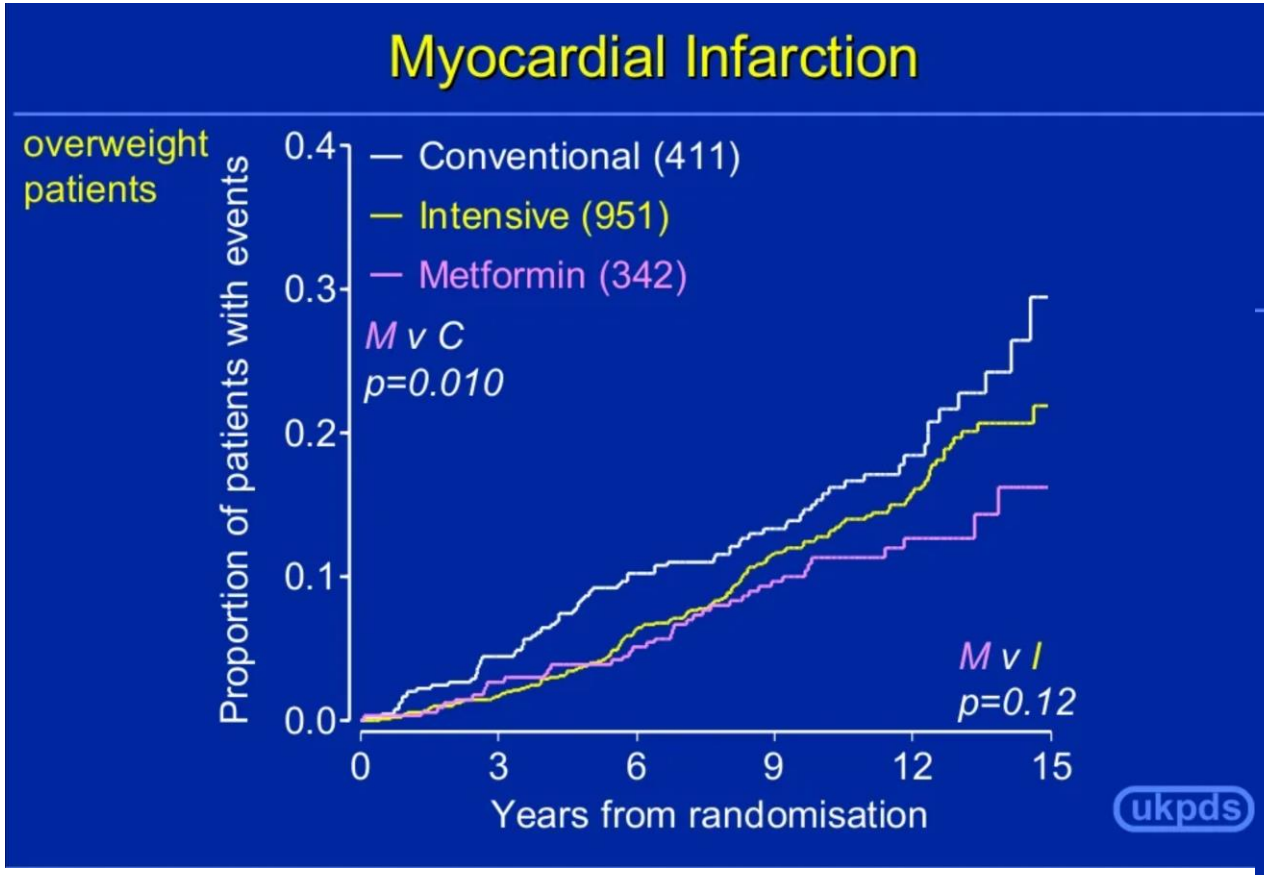
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Anti-diabetic drugs and beyond

Intensive DM management



Metformin is the savior



Metformin in Overweight Patients

- compared with conventional policy

32% risk reduction in any diabetes-related endpoints	p=0.0023
42% risk reduction in diabetes-related deaths	p=0.017
36% risk reduction in all cause mortality	p=0.011
39% risk reduction in myocardial infarction	p=0.01

ukpds

Too low Hba1c may be an issue

ACCORD Trial

Effects of Intensive Glucose Lowering in Type 2 Diabetes
NEJM, 2008

Design

RCT with 10,251 diabetic patients

Key Inclusion Criteria:
- DMII with HbA1c of 7.5% or mo

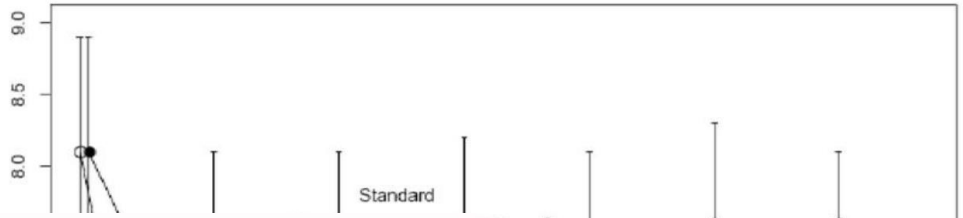
Key Exclusion Criteria:
- Frequent or recent serious hypc
- BMI > 45

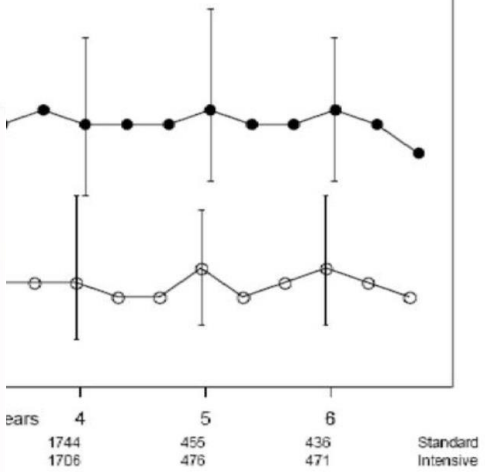
Intervention
- Intensive therapy (HbA1c target

Control
- Standard therapy (HbA1c target

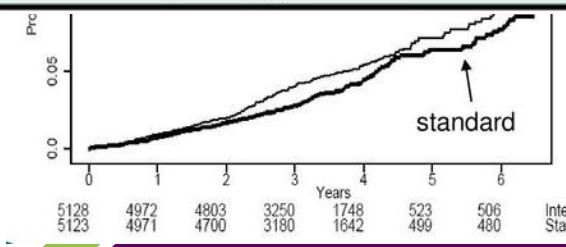
Lower A1C	
Targets (achieved median)	<6% (6.4%) vs 7-7.9% (7.5%)
Greater use of medications:	
More multiple oral meds	70% vs 45% on 3-5 oral classes
More insulin	77% vs 55% on insulin
More combination orals + insulin	62% vs 18% on 3-5 orals + insulin
More consequences of therapy:	
Severe hypoglycemia	10.5% vs 3.5% w/ hypoglycemia event requiring medical assistance
Weight gain	28% vs 14% >10 kg gain
More SAEs	2.2% vs 1.6% w non-hypo SAE

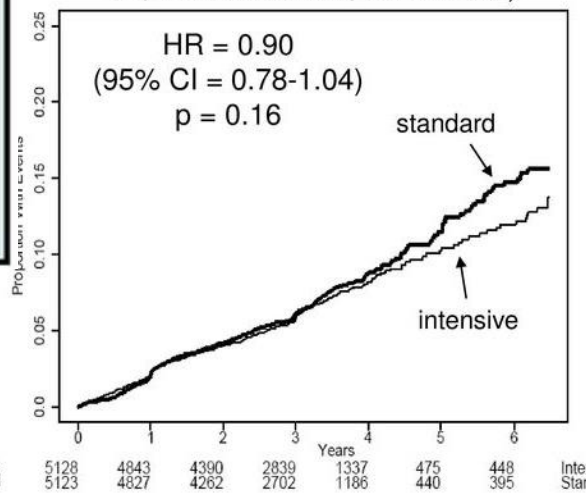
Median A1C and Interquartile Ranges





Primary outcome (composite nonfatal MI, nonfatal stroke, CVD death)





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FDA demands for CV safety

1961 — UGDP trial: tolbutamide discontinued due to increased CV mortality vs other treatment groups[1]

2005 — Muraglitazar found to potentially increase CV risk during FDA assessment[2]

→ • Sponsor withdrew application[1]

2007 — Rosiglitazone associated with increased risk for MI and CV-related death[3]

→ • Withdrawn in the EU[1]
• Use restricted in US[1]*

*In 2013, FDA panel voted to reduce safety restrictions on rosiglitazone[7]

2008 — ACCORD trial: intensive glucose lowering was associated with increased all-cause mortality[4]
HR 1.22 (95% CI 1.01, 1.46); *p*=0.04

2008 — **New FDA requirements[5]**

2012 — **New EMA requirements[6]**
New diabetes drugs should demonstrate CV safety with meta-analysis and a CV outcomes trial (CVOT)



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

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

ABSTRACT

BACKGROUND
Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS
We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS
Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

CONCLUSIONS
Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

This article (10.1056/NEJMoa072761) was published at www.nejm.org on May 21, 2007.

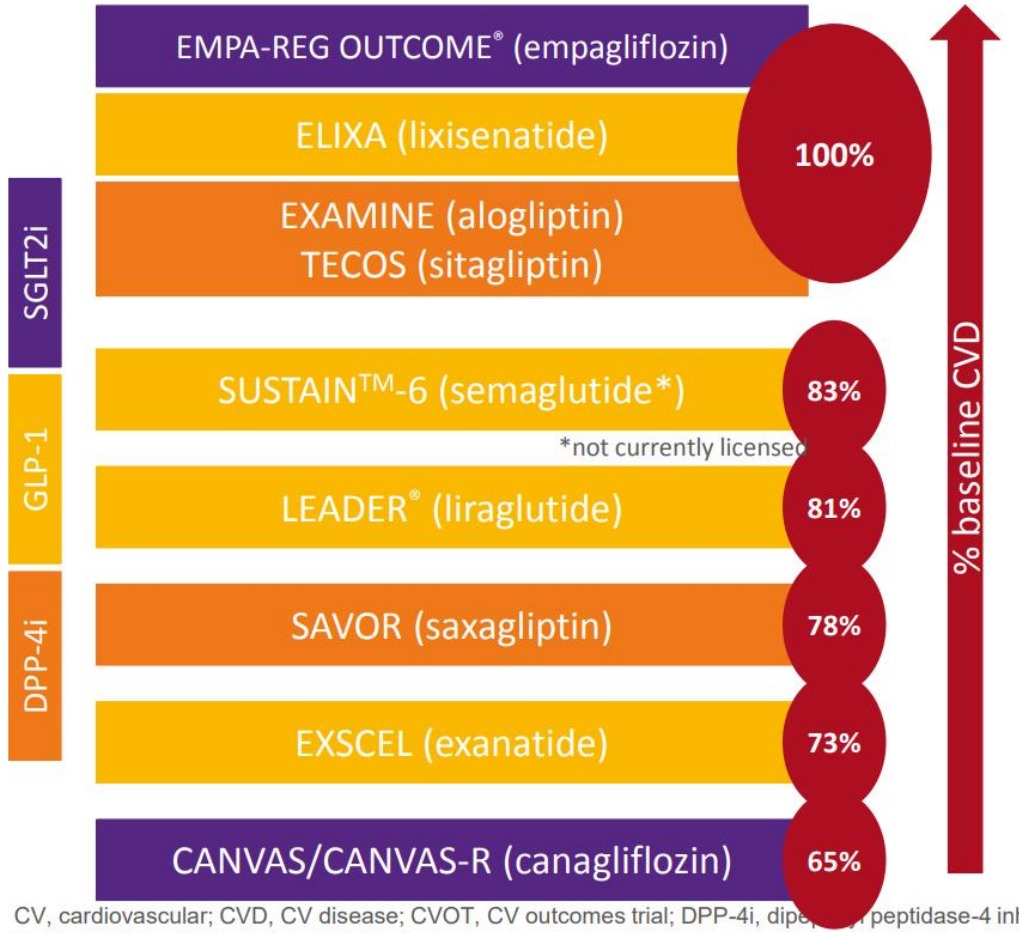
N Engl J Med 2007;356:2457-71.
Copyright © 2007 Massachusetts Medical Society.

ESC Working Group Cardiovascular Pharmacotherapy

Nissen S et al. Ann Intern Med 2012;157:671. Nissen S et al. JAMA 2005;294:2581.
Nissen S et al. N Engl J Med 2007;356:2457. ACCORD Study Group. N Engl J Med 2008;358:2545–59.
FDA guidance 2008; EMA scientific guidelines 2012.

Baseline criteria of recent CVOTs in T2D

Rates of **baseline established CVD varied substantially between CVOTs**, which may have affected outcomes.



Prior CV history used to define CVD also differed between CVOTs, with varying combinations of the following in inclusion criteria:

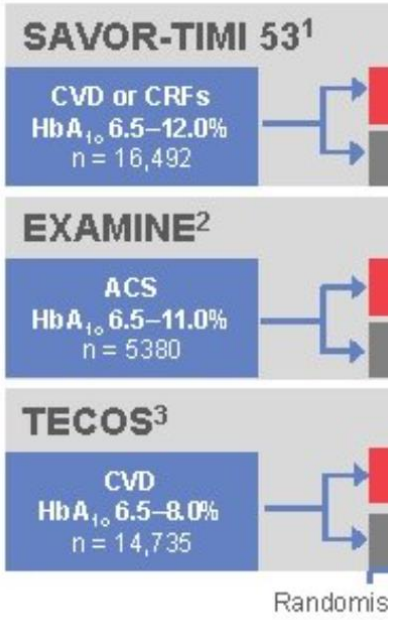
- Cardiovascular disease
- Myocardial infarction
- Acute coronary syndrome
- Coronary heart disease
- Chronic kidney disease
- Peripheral vascular disease
- CV risk factor
- Age
- Time since event
- Number of risk factors

CV, cardiovascular; CVD, CV disease; CVOT, CV outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose transporter 2 inhibitor.

Zinman et al. N Engl J Med 2015;373:2117–28 Neal et al. N Engl J Med 2017;377:644–57 Pfeffer et al. N Engl J Med 2015;373:2247–57 Marso et al. N Engl J Med 2016;375:311–22. Marso et al. N Engl J Med 2016;375:1834–44 Holman et al. N Engl J Med 2017;377:1228–39 Scirica et al. N Engl J Med 2013;369:1317–26 White et al. N Engl J Med 2013;369:1327–35 Green et al. N Engl J Med 2015;373:232–42

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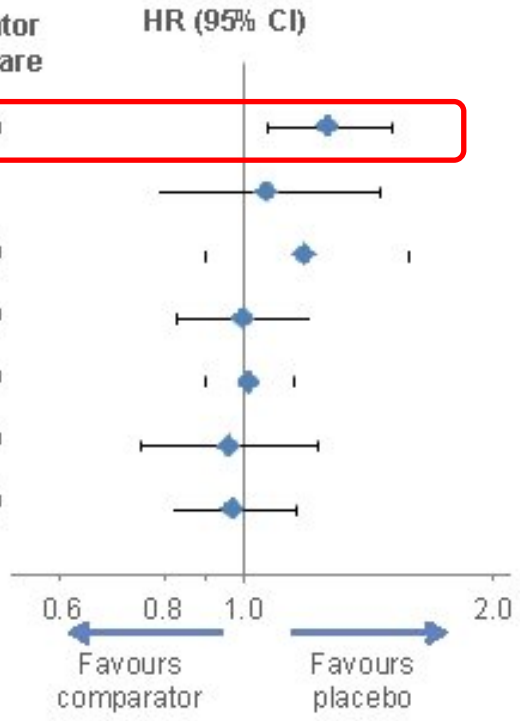
DPP4-inhibitor and CV events



*Upper boundary of 1-sided repeated
1. Scirica et al. N Engl J Med 2013;3
3. Green et al. N Engl J Med 2015; D

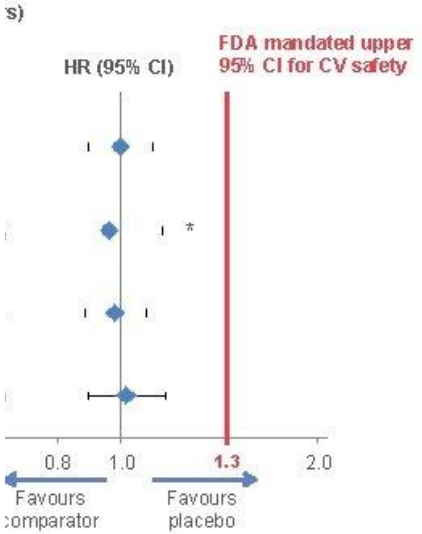
Hospitalisation for heart failure (HHF) data for all completed CVOTs

	Number of events (%)	
	Placebo + usual care	Comparator + usual 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)
ELIXA (HHF)[4]	127 (4.2)	122 (4.0)
ELIXA (HHF + CV death)[4]	253 (8.3)	248 (8.2)



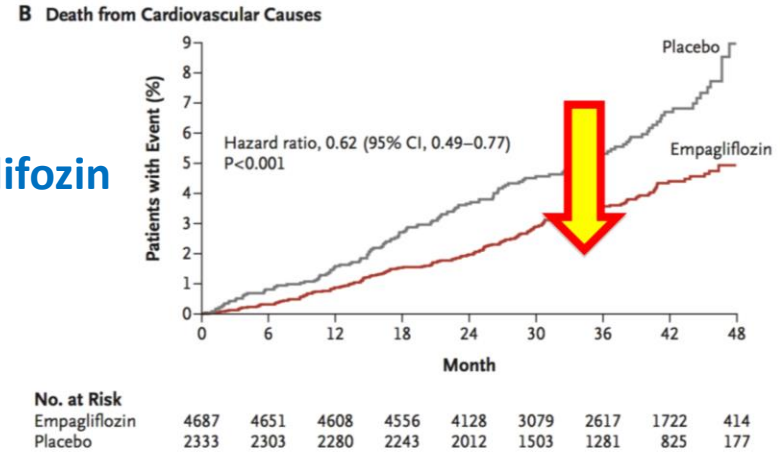
Analysis 1 = as component of expanded MACE

mpleted CVOTs fall
95% CI limit of 1.3



EMPAREG-OUTCOME CV Death

Empaglifozin

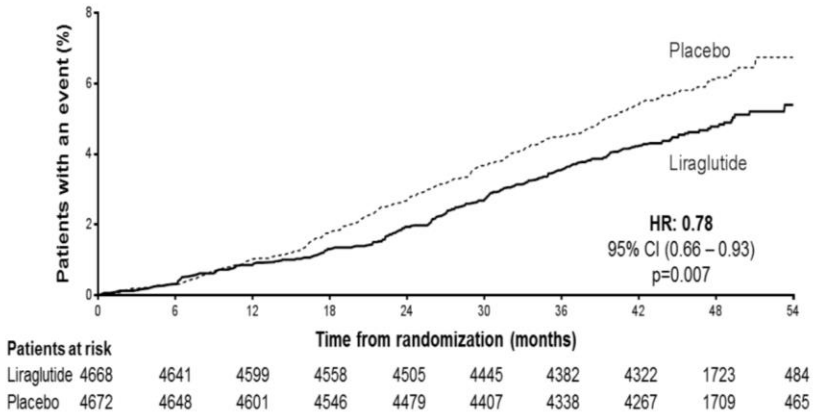


Zinman B et al. N Engl J Med 2015; 373:2117-2128.

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LEADER: Cardiovascular Mortality

Liraglitude



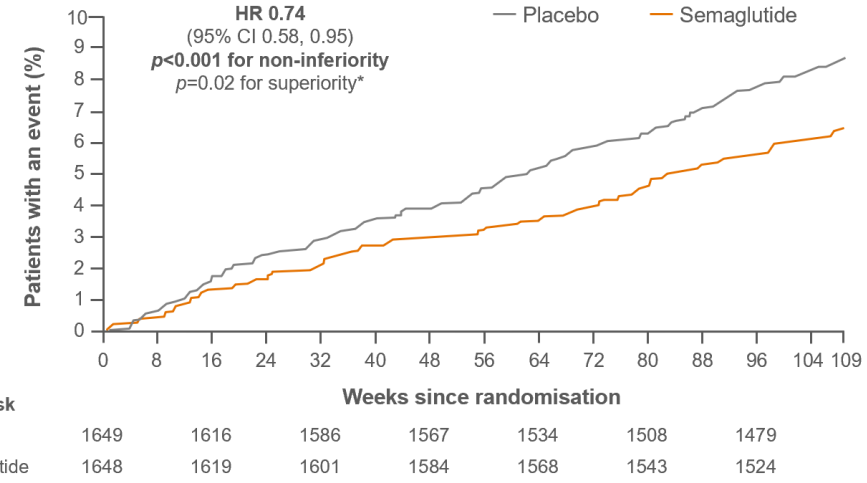
LEADER trial investigators. N Engl J Med 2016; 375: 311-322.

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SUSTAIN-6: primary outcome 3P-MACE

Semaglutide reduced the time to first occurrence of CV death, non-fatal MI or non-fatal stroke

Semaglutide

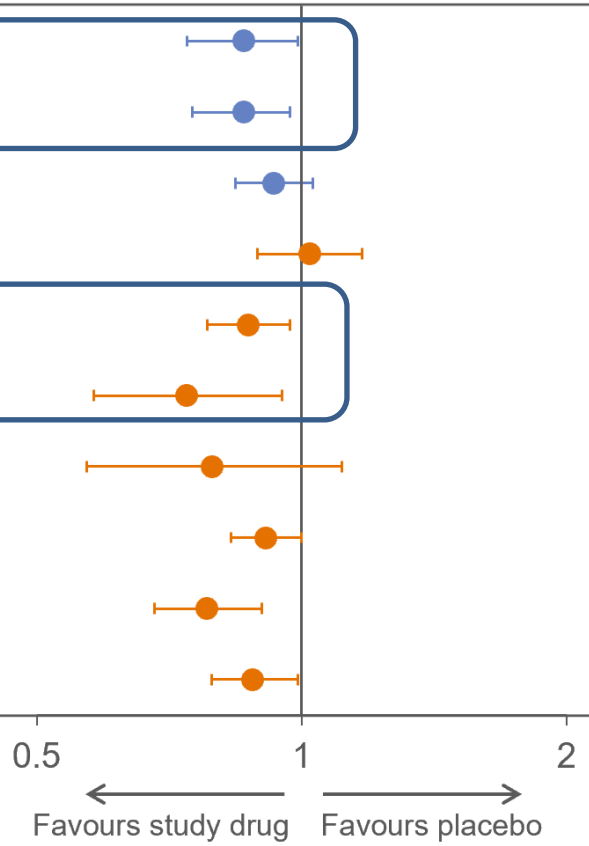


*Testing for superiority was neither pre-specified nor adjusted for multiplicity
3P-MACE, 3-point major adverse cardiovascular events; MI, myocardial infarction
Marso SP *et al. N Engl J Med* 2016;375:1834

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3P-MACE from SGLT2 inhibitor and GLP-1 RA CVOTs

Drug class	Trial (study drug)	HR (95% CI)
SGLT2 inhibitor	EMPA-REG OUTCOME[1] (empagliflozin)	0.86 (0.74, 0.99)
	CANVAS Program[2] (canagliflozin)	0.86 (0.75, 0.97)
	DECLARE-TIMI 58[3] (dapagliflozin)	0.93 (0.84, 1.03)
GLP-1 receptor agonist	ELIXA[4] (lixisenatide)	1.02 (0.89, 1.17)
	LEADER[5] (liraglutide)	0.87 (0.78, 0.97)
	SUSTAIN-6[6] (inj. semaglutide)	0.74 (0.58, 0.95)
	PIONEER 6*[7] (oral semaglutide)	0.79 (0.57, 1.11)
	EXSCEL[8] (exenatide)	0.91 (0.83, 1.00)
	Harmony Outcomes[9] (albiglutide)	0.78 (0.68, 0.90)
	REWIND*[10] (dulaglutide)	0.88 (0.79, 0.99)



Recommendations for glycaemic control in individuals with DM

ESC European Society of Cardiology

Recommendations	Class	Level
It is recommended to apply tight glucose control, targeting a **near-normal HbA1c (<7.0% or <53 mmol/mol)** to decrease **microvascular complications** in DM.	I	A
It is recommended that **HbA1c targets are individualized** according to duration of DM, comorbidities, and age.	I	C
Avoidance of hypoglycaemia is recommended.	I	C
The use of **structured self-monitoring of blood glucose and/or continuous glucose monitoring** should be considered to facilitate optimal glycaemic control.	IIa	A
An **HbA1c target of <7.0%** (or <53 mmol/mol) should be considered for the **prevention of macrovascular complications in individuals with DM.**	IIa	C

www.escardio.org/guidelines

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Cardiovascular risk categories in patients with DM

Very high-risk	Patients with DM **and** established CVD **or** other target organ damage[a] **or** three or more major risk factors[b] **or** early onset T1DM of long duration (>20 years)
High-risk	Patients with DM duration ≥10 years without target organ damage[a] plus any other additional risk factor[b]
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors

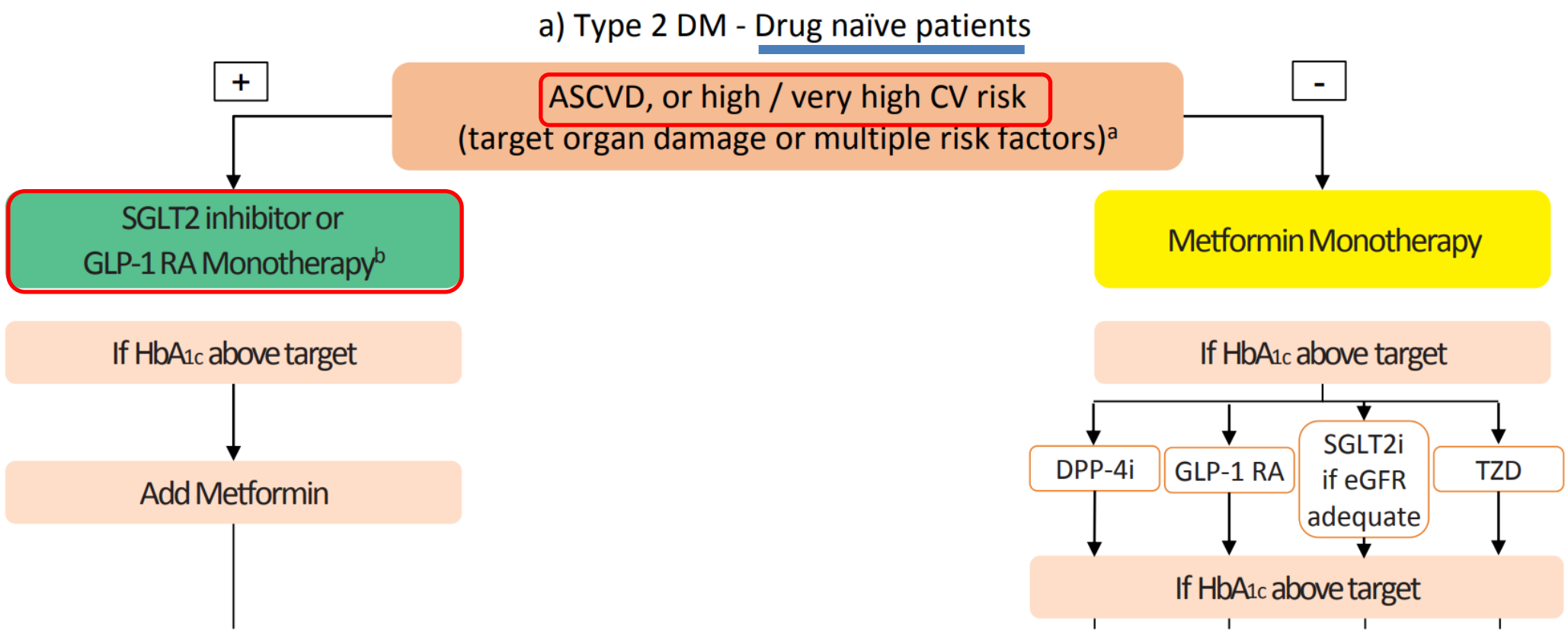
[a] proteinuria, renal impairment defined as eGFR≤30mL/min/1.73m^2.
[b] age, hypertension, dyslipidemia, smoking, obesity.

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ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

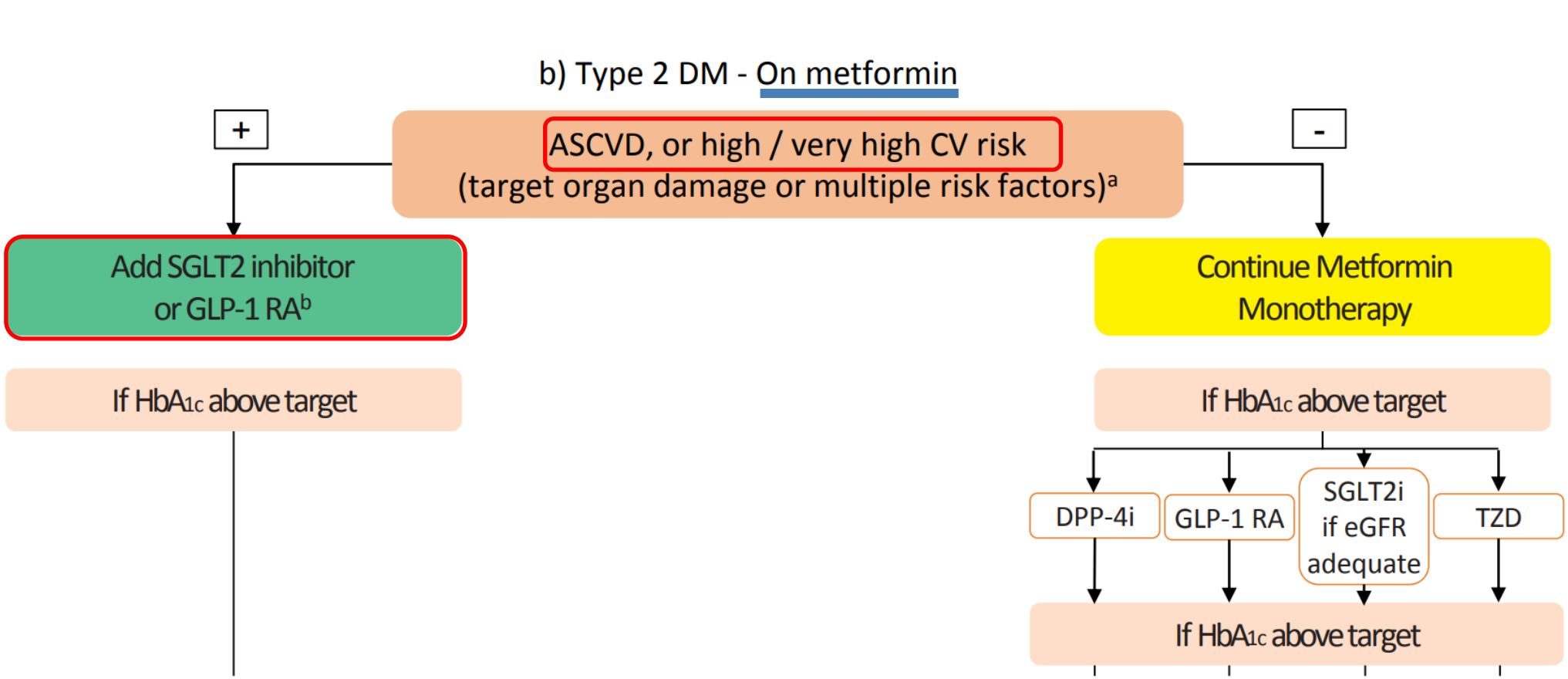
Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk - drug naïve (1)



www.escardio.org/guidelines

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk - metformin treated (1)



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ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

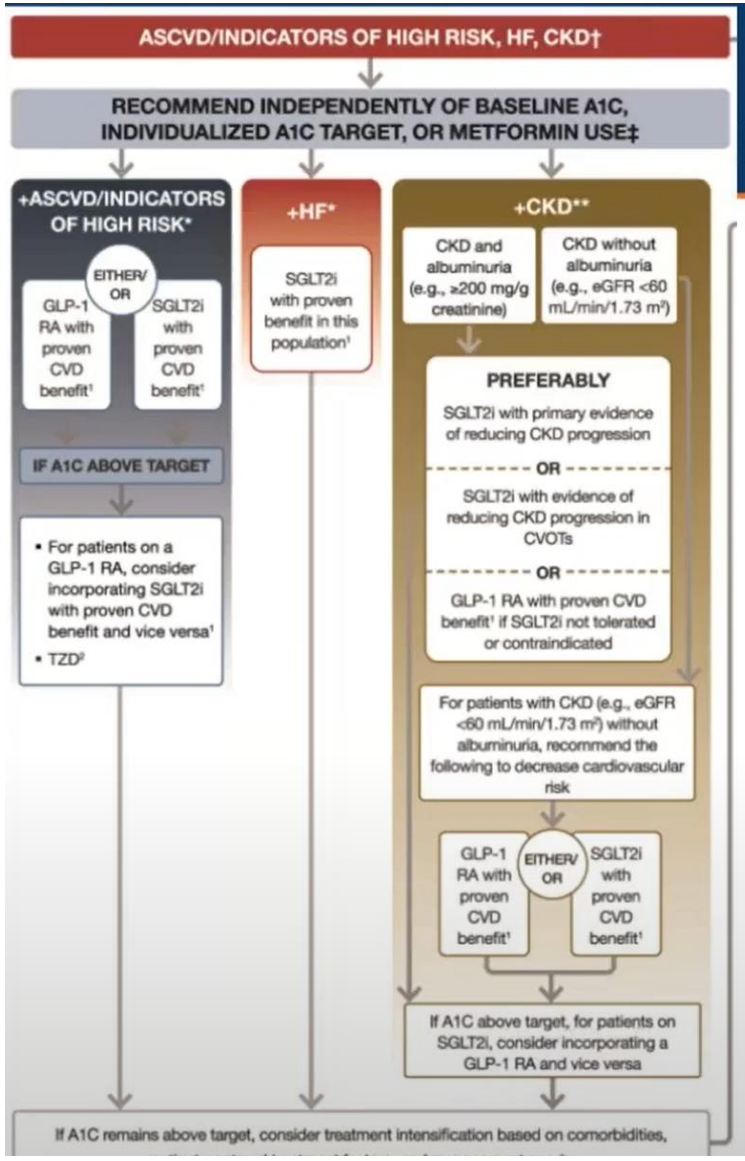
Recommendations for glucose-lowering treatment in DM (1)

ESC European Society of Cardiology

Recommendations	Class	Level
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD or at very high/high CV risk to reduce CV events.	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.	I	B
GLP1-RAs		
Liraglutide, semaglutide or dulaglutide are recommended in patients with T2DM and CVD or at very high/high CV risk to reduce CV events.	I	A
Liraglutide is recommended in patients with T2DM and CVD or at very high/high CV risk to reduce the risk of death.	I	B

Recommendations	Class	Level
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.	IIa	C
Insulin		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities.	IIa	C
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF.	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and a high-risk of HF.	III	B

Cardiologist's choice of DM meds



Which class for which patients?

The reality is: many cardiologists are going to think about <u>SGLT2 inhibitors</u> first in patients with ASCVD

- 14-36% of MI patients develop HF
- Half of ASCVD patients have CKD

- Oral dosing
- Once daily dosing
- No need for dose titration
- No need for routine laboratory monitoring after initiation

Diabetes Care 2022;45(Supplement_1):S125–S143; Pharmacologic treatment of hyperglycemia in adults with type 2

SGLT2-I concern

- BP: ↓3-5mmHg
- A1c: ↓~0.5-0.8%
- Weight: ↓ 1-3kg
- Genital mycotic infections:
  RR 3-4x (~5% vs. 1%)
- Orthostatic symptoms:
  OR 2.68 (95%CI 1.14-6.29)
- Euglycemic DKA:
  0.5/1000 patient years

<u>Things to tell patients when starting:</u>

- Good genital hygiene
- Monitor for orthostatic hypotension
- DKA warning signs

<u>Things cardiologists need to know:</u>

- Caution in eGFR <45 and prior DKA
- May need to adjust SU/insulin dose when starting if A1c < 8.5%
- If decreased PO intake, hospitalized, and/or about to undergo surgery – hold SGLT2i
- How to diagnose/manage euglycemic DKA

Summary of non-insulin DM meds

	A1c Reduction	Weight Change	CV Benefit	Renal Benefit	Cost	Value
Metformin	1.0–2.0%	Neutral	Potential benefit	Neutral	Low	High
SGLT2 inhibitors	0.5–1.0%	Loss	Benefit	Benefit	High	High
GLP-1 agonists	0.8–2.0%	Loss	Benefit*	Neutral	High	High
DPP-4 inhibitors	0.5–0.8%	Neutral	Neutral–potential harm in CHF	Neutral	Moderate-High	Low
Pioglitazone	0.5–1.4%	Gain	Neutral–potential harm in CHF	Neutral	Low	Medium
Sulfonylureas	0.4–1.2%	Gain	Neutral	Neutral	Low	Medium

Case 1

- M/56, ex-smoker, PMH of IHD, DM, HT, obesity BMI 35kg/m2 and OSA on good compliance of CPAP. No HF symptoms, denied of any chest pain. He is currently on amlodipine 10mg daily, losartan 100mg daily, metoprolol CR 200mg daily, indapamide SR 1.5mg daily, aspirin EC 100mg daily, Janumet 50/1000mg 1tab BD, rosuvastatin 20mg daily. His office BP was 134/76mmHg. CBC normal, LFT normal, Cr 105umol/L, K 4.8mmol/L, Hba1c 7.5%, and LDL-C 1.4mmol/L. How are you going to optimize his DM medication?

1. Add on oral Gliclazide
2. Add on oral Acarbose
3. Add on oral Long acting Insulin
4. Add on oral Empagliflozin
5. Add on s.c. Exenatide

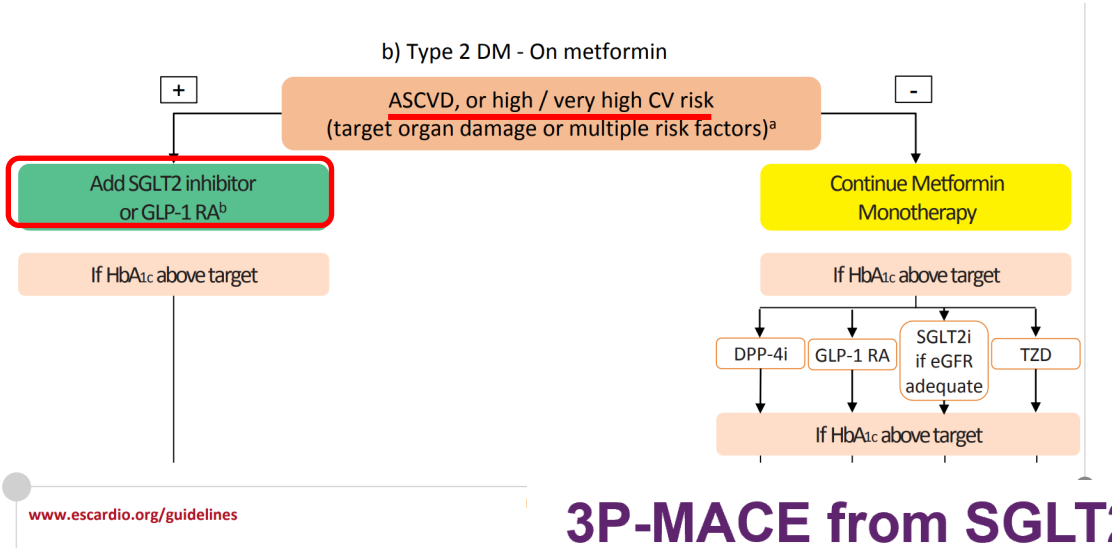
Case 1

- M/56, ex-smoker, PMH of IHD, DM, HT, obesity BMI 35kg/m2 and OSA on good compliance of CPAP. No HF symptoms, denied of any chest pain. He is currently on amlodipine 10mg daily, losartan 100mg daily, metoprolol CR 200mg daily, indapamide SR 1.5mg daily, aspirin EC 100mg daily, Janumet 50/1000mg 1tab BD, rosuvastatin 20mg daily. His office BP was 134/76mmHg. CBC normal, LFT normal, Cr 105umol/L, K 4.8mmol/L, Hba1c 7.5%, and LDL-C 1.4mmol/L. How are you going to optimize his DM medication?

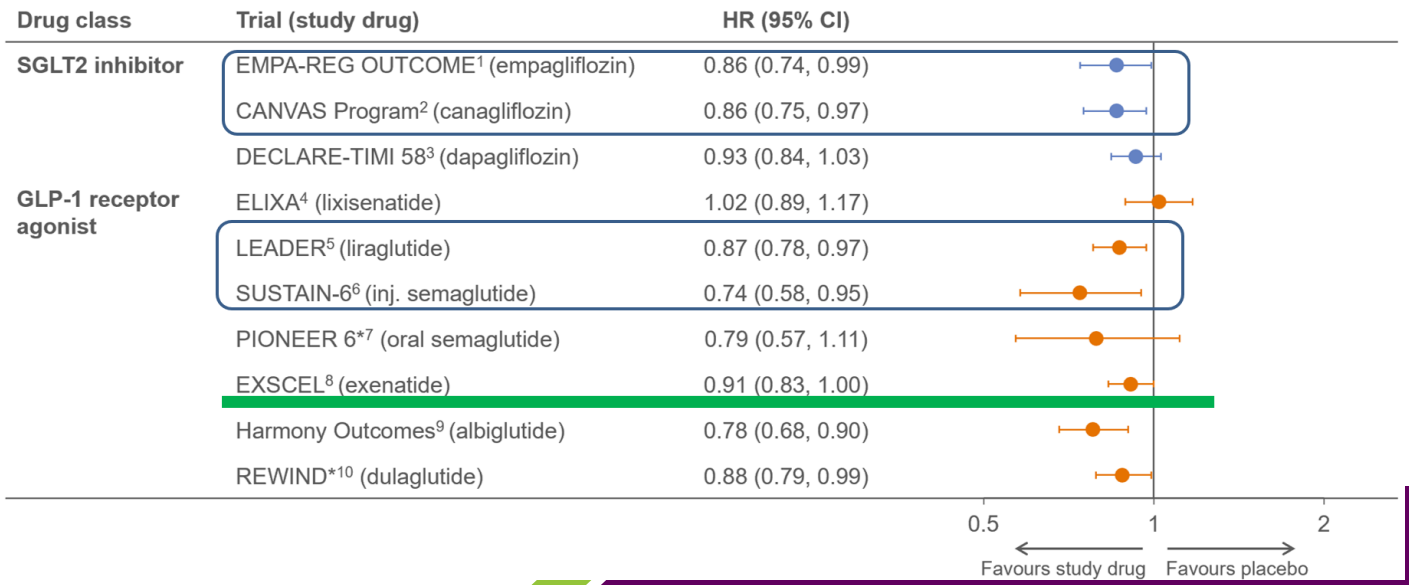
1. Add on oral Gliclazide
2. Add on oral Acarbose
3. Add on oral Long acting Insulin
4. Add on oral Empagliflozin
5. Add on s.c. Exenatide

Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk - metformin treated (1)

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3P-MACE from SGLT2 inhibitor and GLP-1 RA CVOTs



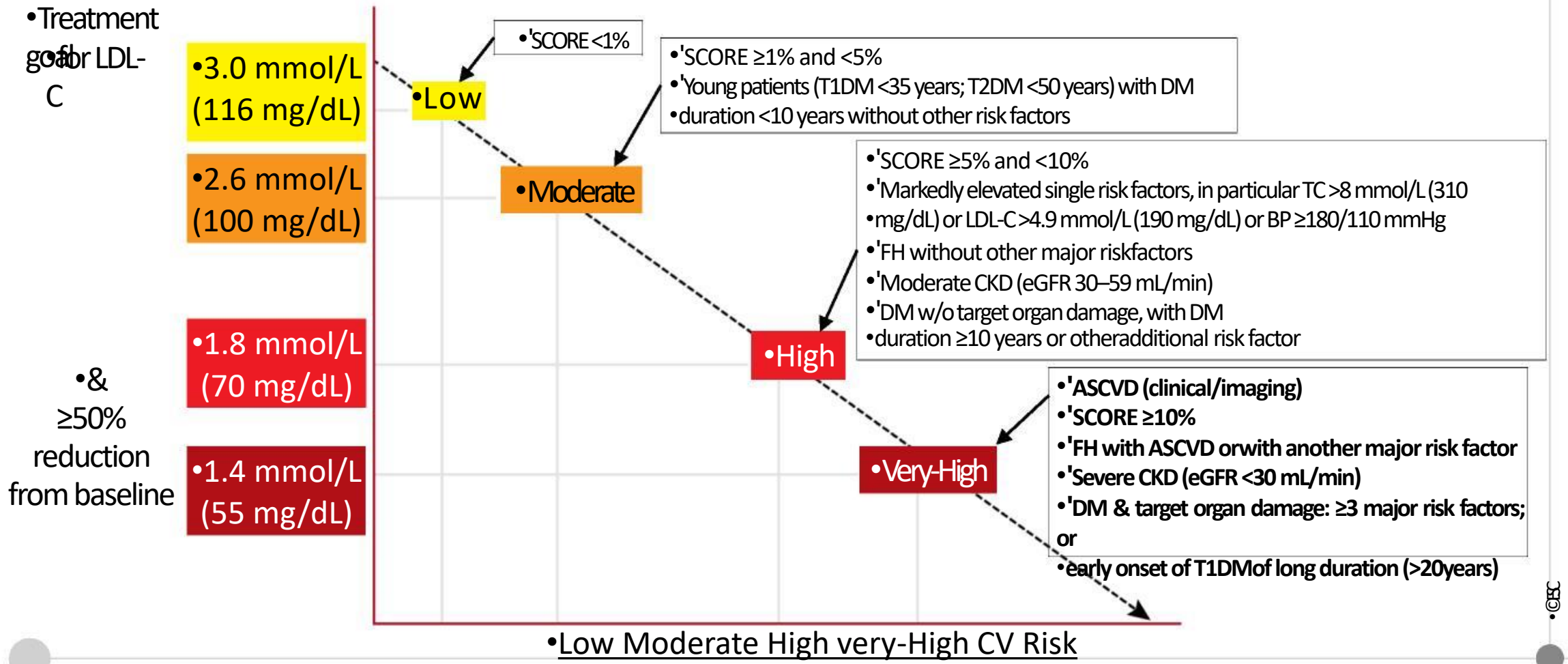
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State-of-the-art management of cholesterol in DM

•Treatment goals for low-density lipoprotein •cholesterol (LDL-C) across categories of total cardiovascular •disease risk

EAS ESC European Society of Cardiology



•©ESC

•www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Cop

ACC/AHA guideline 2019

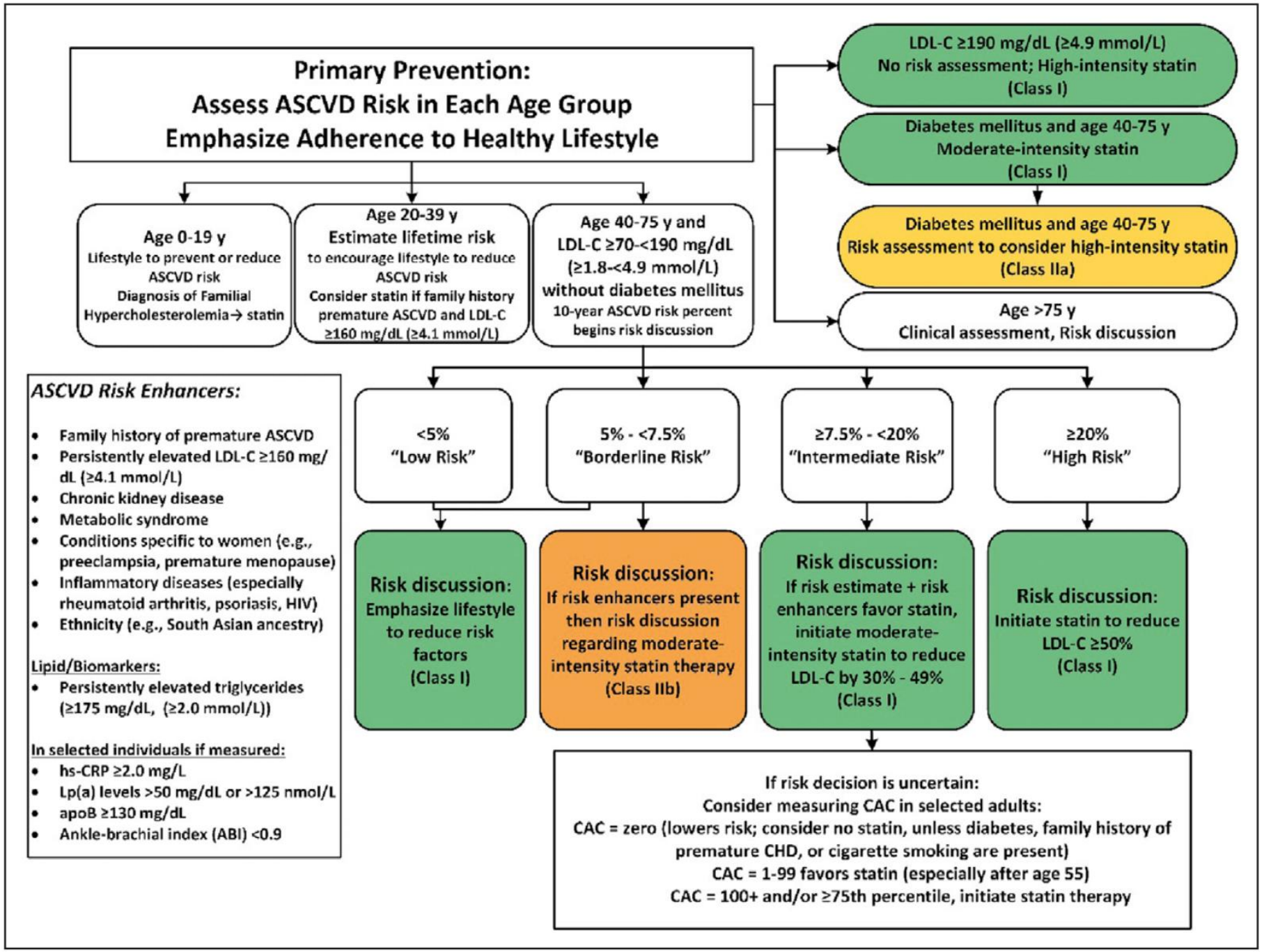
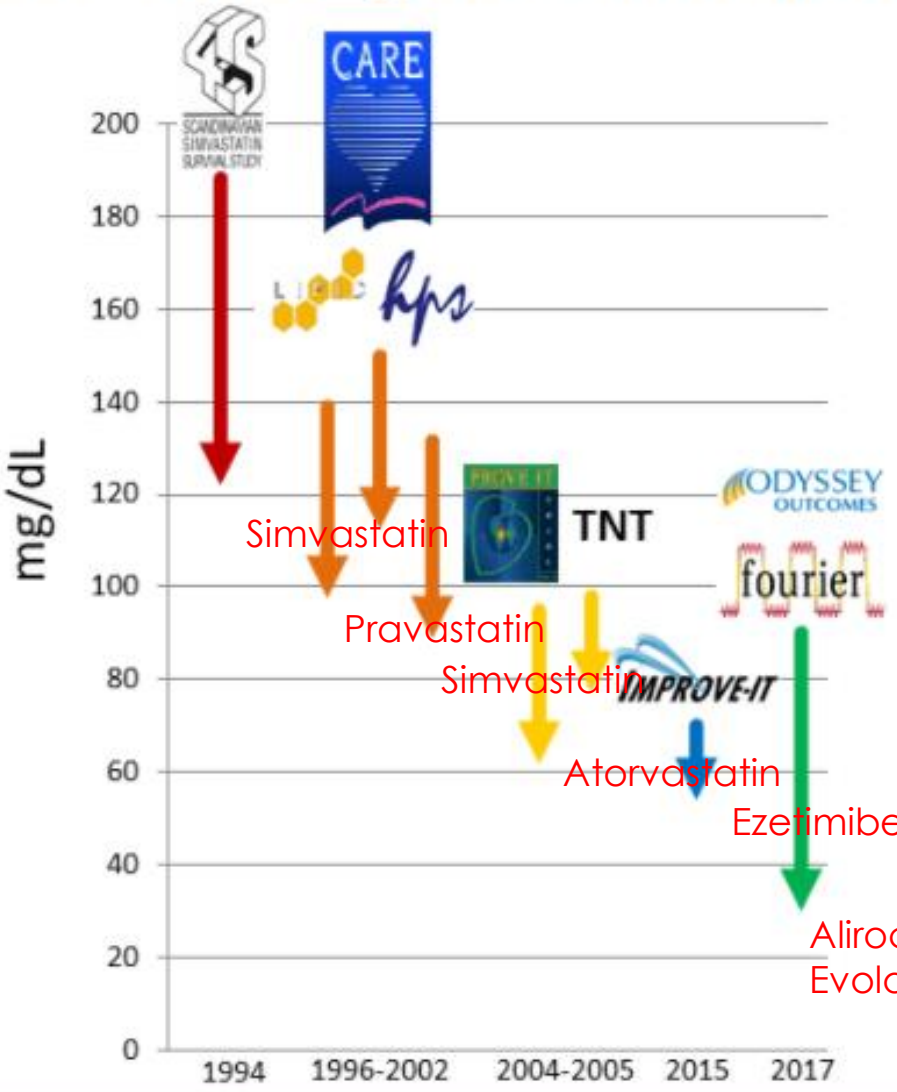


Figure 3 Primary prevention

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Even below LDL-c target further LDL-c reduction gives additional CV benefit



A quarter of a century of treating LDL-C

High is bad

Average is not good

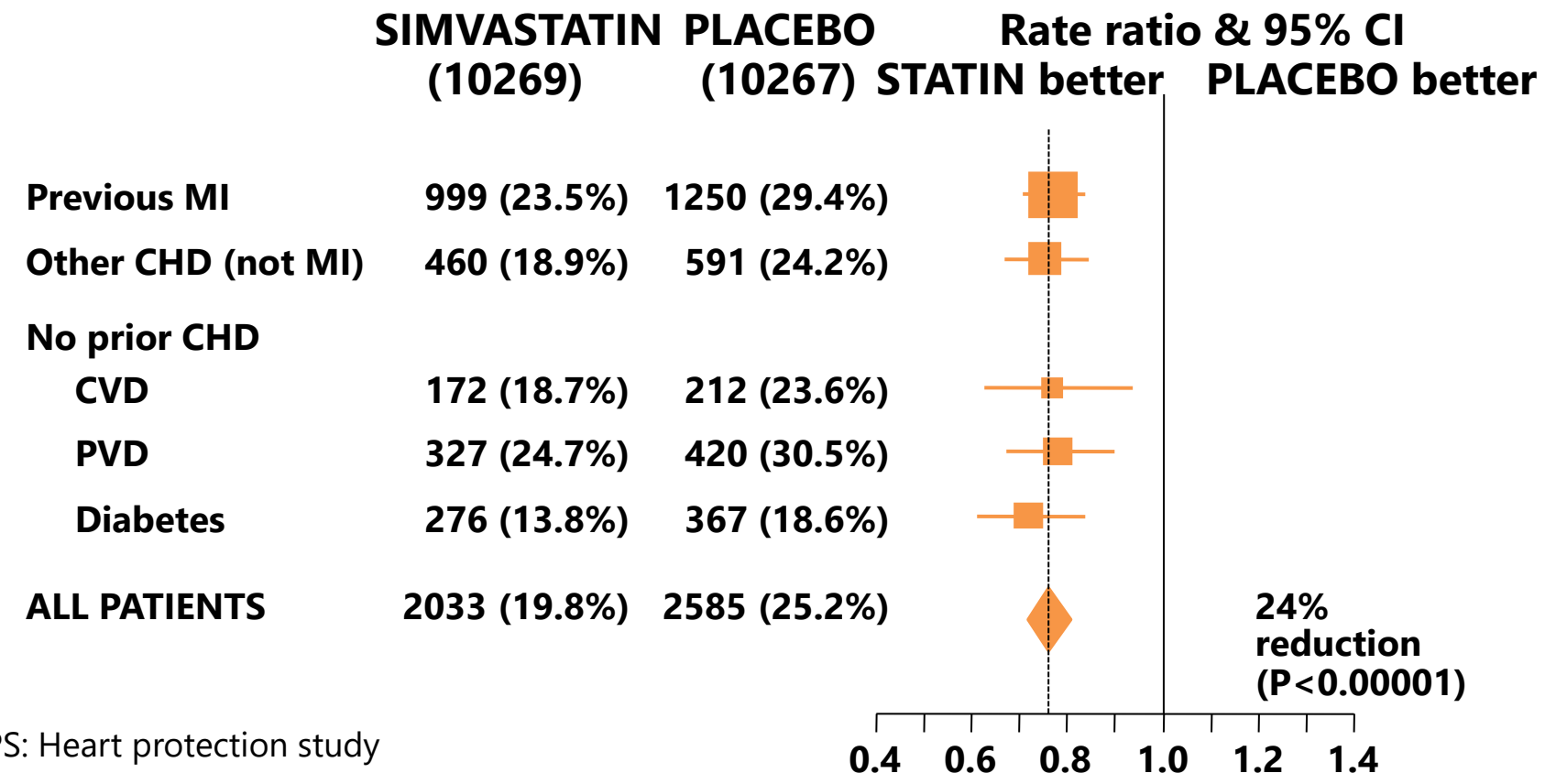
Lower is better

Even lower is even better

Lowest is best

Copyrigh

Statin Therapy Beneficial Among Patients with Diabetes

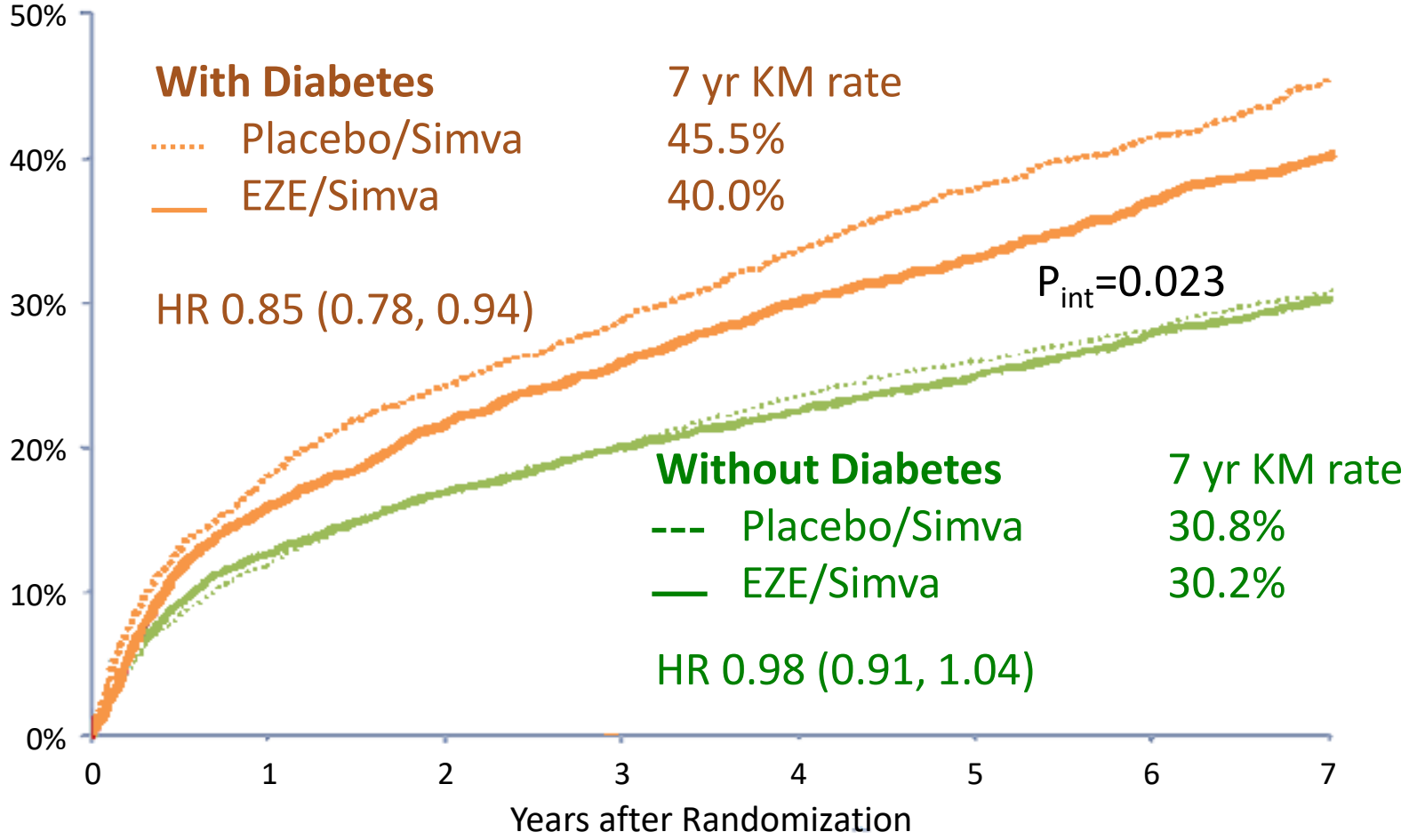


HPS: Heart protection study

HPS *Lancet* 2002;360:7-22

IMPROVE-IT: Ezetimibe add-on to statin reduced CV events in people with ACS and diabetes

CV death, MI, UA requiring re-hospitalization, coronary revascularization (≥30 days), or stroke



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CV, cardiovascular; *MI*, myocardial infarction; *UA*, unstable angina.
Giguliano RP et al. Circulation. 2017 Dec

PCKS9i plays an important role in atherosclerosis progression

Reverse endothelial dysfunction (EVOLVE)

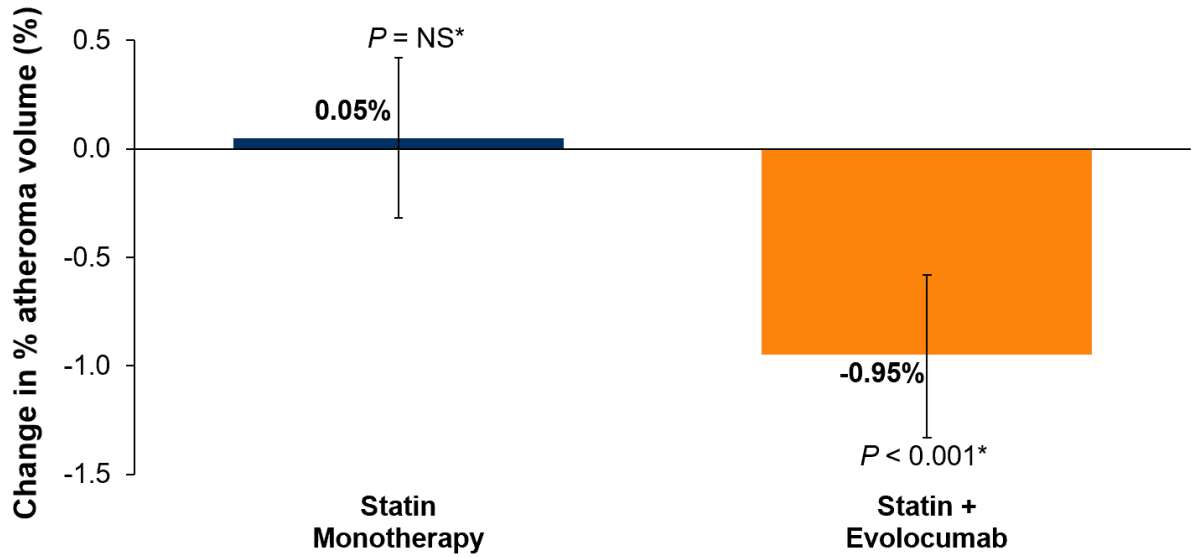
In d

(@12 weeks) Plaque stabilization

(PAV) in 60% patients

Primary endpoint: Nominal change in PAV at week 78

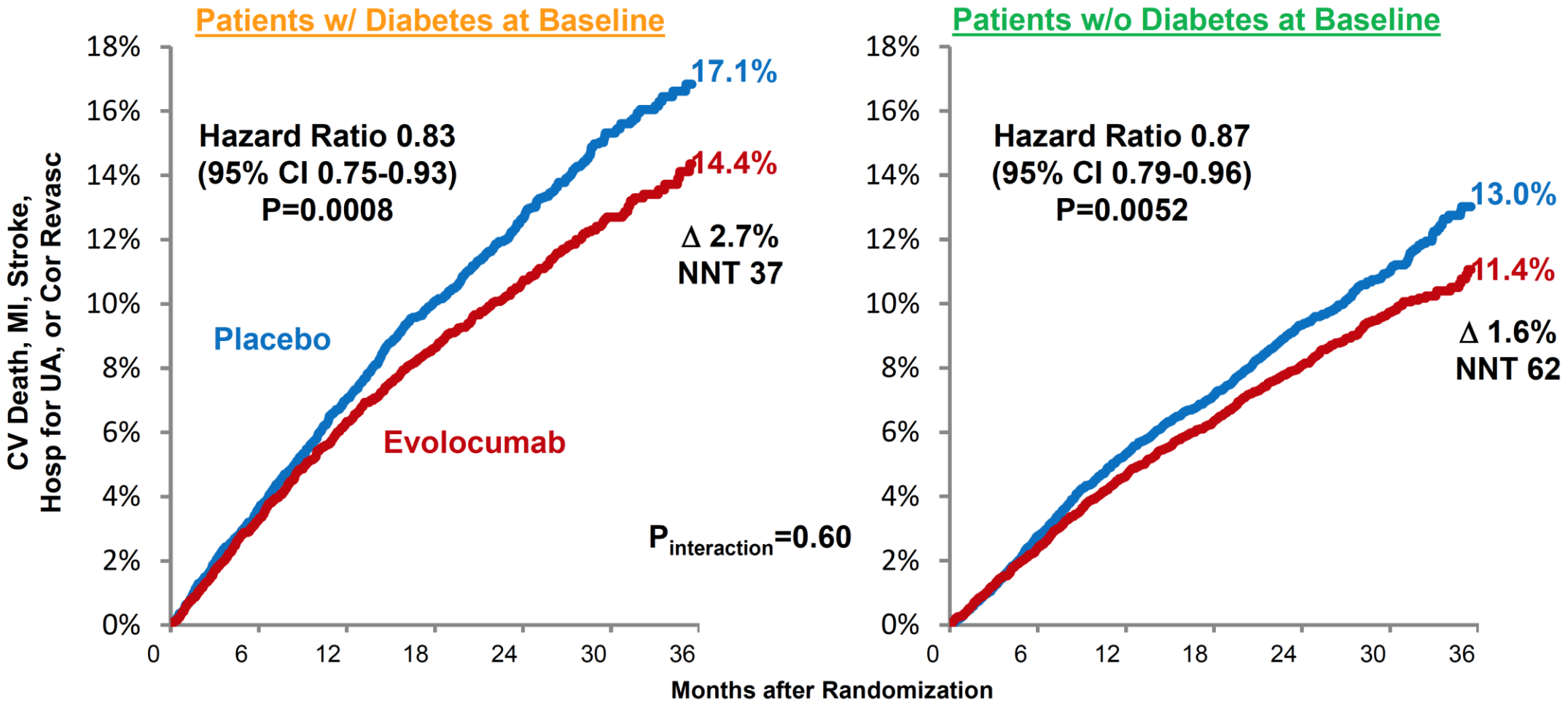
Difference between groups: -1.0% (-1.8 to -0.64); *P* < 0.001



Kaufmann B.A. and Stenil D.C, Int. J. Mol. Sci. 2015, 16 (5); 9749-9769, Nicholls SJ, et al. JAMA. [published online ahead of print November 15, 2016]. doi: 10.1001/jama.2016.16951.

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FOURIER: Evolocumab add-on to statin reduced CV events



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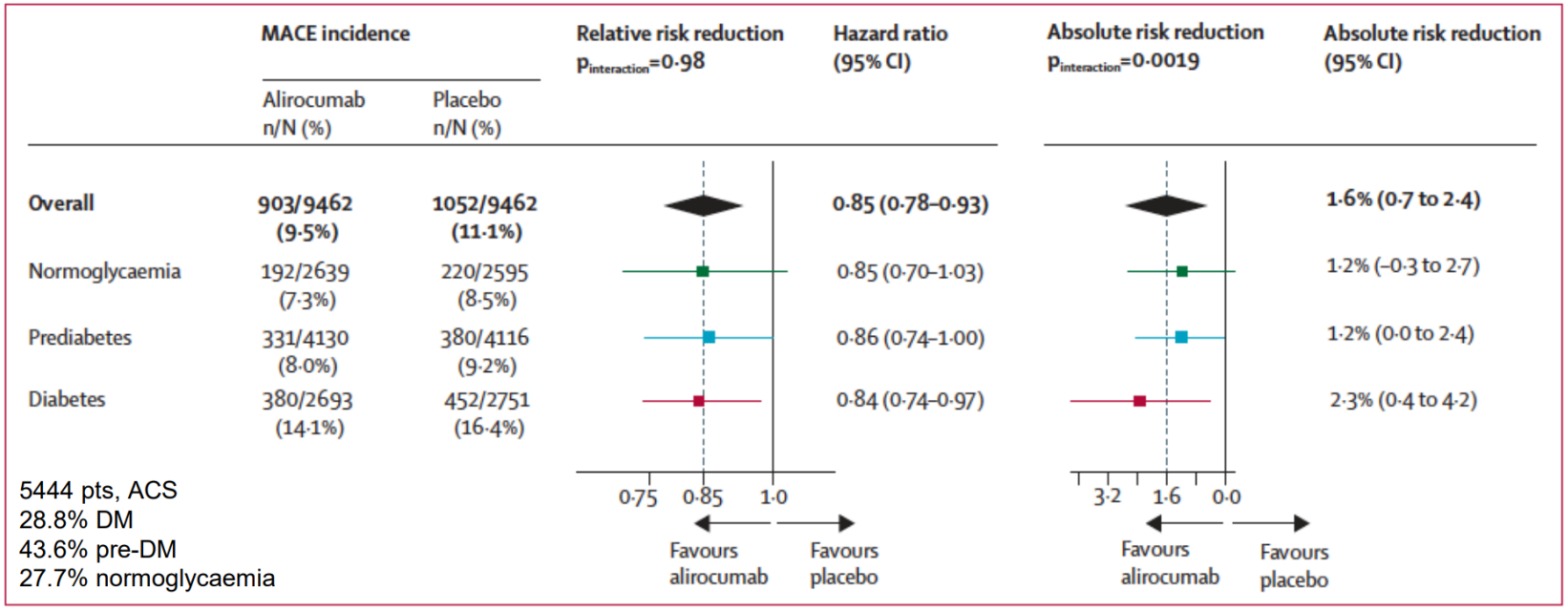
Sabatine MS, et al. Lancet Diab Endocrinol 2017; 5(12):941-950

ODYSSEY OUTCOMES

Alirocumab in patients with/without diabetes after ACS

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prespecified analysis: *effect by glycaemic status*



5444 pts, ACS
28.8% DM
43.6% pre-DM
27.7% normoglycaemia

Ray KK et al. Lancet Diabetes Endocrinol 2019

www.escardio.org/guidelines

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

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New lipid targets

ESC European Society of Cardiology

Change in recommendations

2013	2019
Lipid targets	
In patients with T2DM at • high CV risk, an LDL-C target of <2.5 mmol/L (<100 mg/dL) • very high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL)	In patients with T2DM at • moderate CV risk, an LDL-C target of <2.6 mmol/L (<100 mg/dL) • high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% • very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50%

www.escardio.org/guidelines

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Case 2

- M/39, teacher, admitted for Anterior STEMI, with PPCI to pLAD. Newly diagnosed DM with HbA1c 7.9%. Given aspirin, ticagrelor, pantoprazole, atorvastatin 40 mg daily, bisoprolol, lisinopril and metformin. LDL-C was 4.1 mmol/L on admission before statin initiation. The patient complained of muscle pain while on statin. CK >5x ULN. RLFT and TFT all normal. What is the next appropriate step?

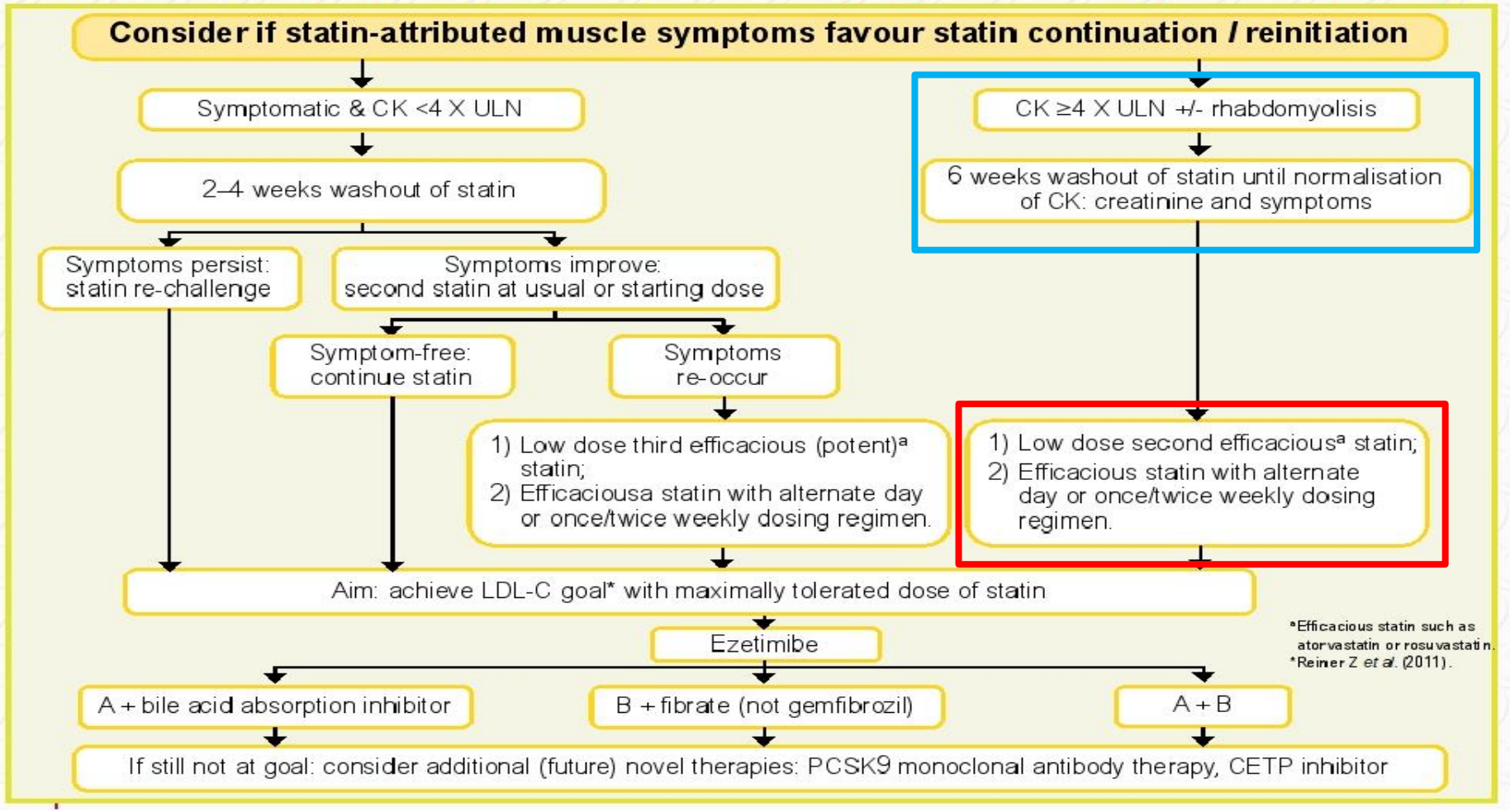
1. Stop atorvastatin permanently, change to ezetimibe 10mg daily
2. Stop atorvastatin permanently, change to alirocumab 150mg Q2weeks s.c.
3. Stop atorvastatin permanently, change to gemfibrozil 600mg BD
4. Withhold statin for 6 weeks until normalization of CK and resolution of myalgia, start rosuvastatin 5mg daily
5. Withhold statin for 2-4 weeks until normalization of CK and resolution of myalgia, restart atorvastatin 10mg daily

Case 22

- M/39, teacher, admitted for Anterior STEMI, with PPCI to pLAD. Newly diagnosed DM with HbA1c 7.9%. Given aspirin, ticagrelor, pantoprazole, atorvastatin 40 mg daily, bisoprolol, lisinopril and metformin. LDL-C was 4.1 mmol/L on admission before statin initiation. The patient complained of muscle pain while on statin. CK >5x ULN. RLFT and TFT all normal. What is the next appropriate step?

1. Stop atorvastatin permanently, change to ezetimibe 10mg daily
2. Stop atorvastatin permanently, change to alirocumab 150mg Q2weeks s.c.
3. Stop atorvastatin permanently, change to gemfibrozil 600mg BD
4. Withhold statin for 6 weeks until normalization of CK and resolution of myalgia, start rosuvastatin 5mg daily
5. Withhold statin for 2-4 weeks until normalization of CK and resolution of myalgia, restart atorvastatin 10mg daily

Algorithm for treatment of muscular symptoms during statin treatment

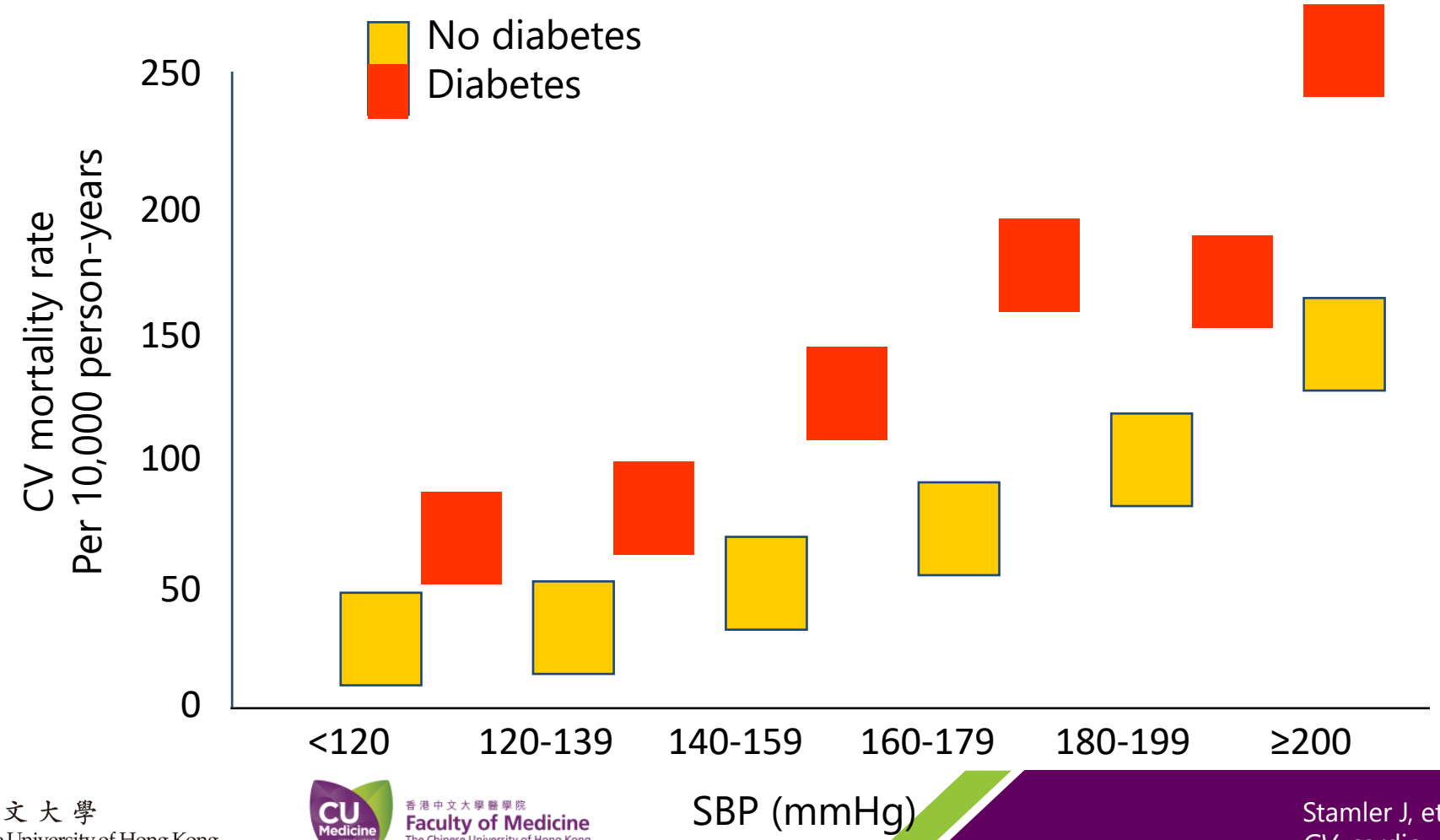


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BP lowering in diabetics: now what?

Association of SBP and CV Mortality in Men With Type 2 Diabetes

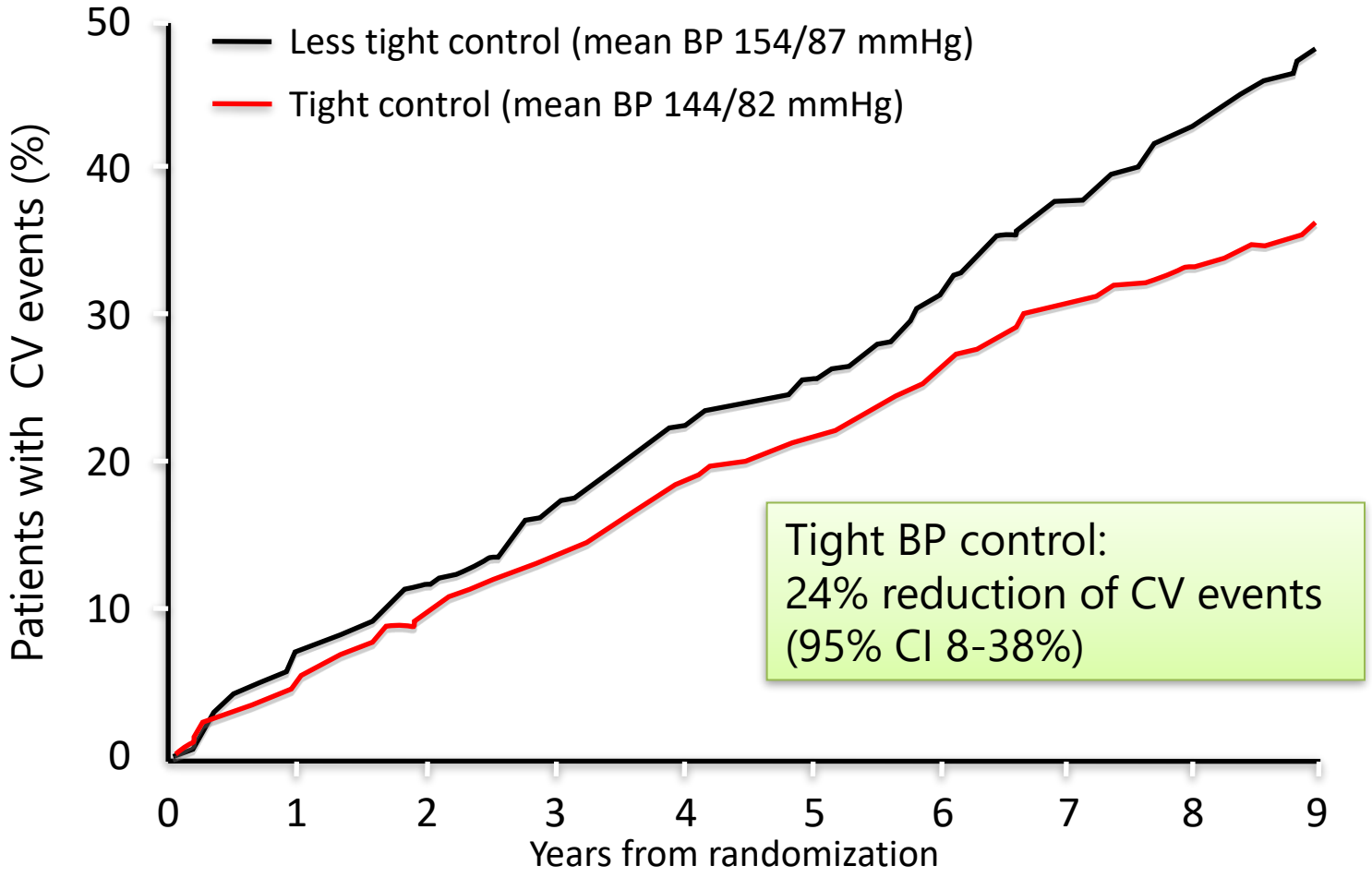


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Stamler J, et al. *Diabetes Care*. 1993;16:434-444.
CV, cardiovascular; *SBP*, systolic blood pressure

UKPDS: BP control in Diabetes



UKPDS Study Group. *BMJ 1*998; 317:703-13.
BP, blood pressure; *CV,* cardiovascular

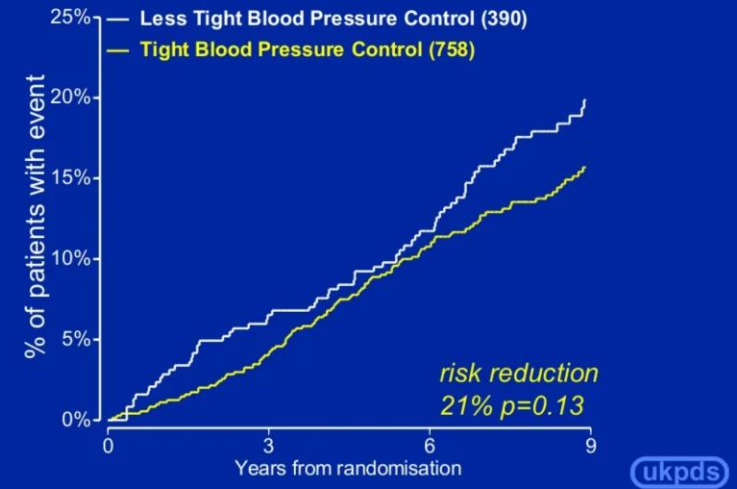
Blood Pressure Control Study

in 1148 Type 2 diabetic patients
a tight blood pressure control policy which achieved blood pressure of 144 / 82 mmHg gave reduced risk for

any diabetes-related endpoint	24%	p=0.0046
diabetes-related deaths	32%	p=0.019
stroke	44%	p=0.013
microvascular disease	37%	p=0.0092
heart failure	56%	p=0.0043
retinopathy progression	34%	p=0.0038
deterioration of vision	47%	p=0.0036

ukpds

Myocardial Infarction



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

- 4733 T2D pts randomised to target SBP **120** mmHg (*intensive* Rx) *vs* **140** mmHg (*standard* Rx)
- Setting: 7 health networks in USA and Canada

N Engl J Med 2010;362:1575-85.

ACCORD BP

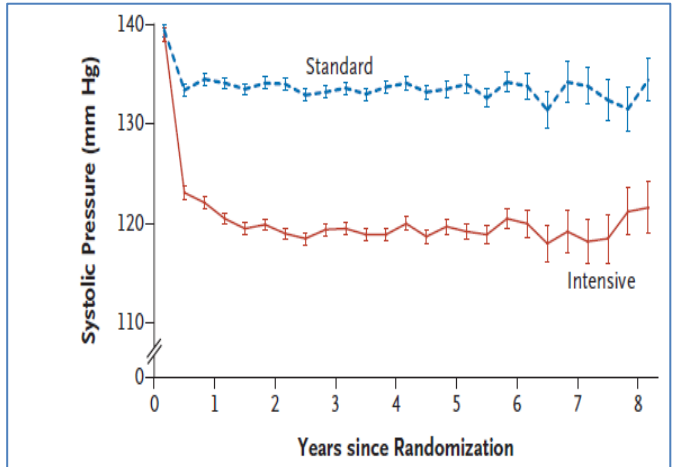
- Primary outcome: composite of non-fatal MI, non-fatal stroke, or CV death
- Mean follow-up: 4.7 y
- Intensive BP lowering in DM →

  ↓macroalbuminuria (6.6% *vs* 8.7%, *P* = 0.009),

  ↓eGFR (74.8% *vs* 80.6%, *P* <0.001),

  ↑no. of events attributable to BP Rx

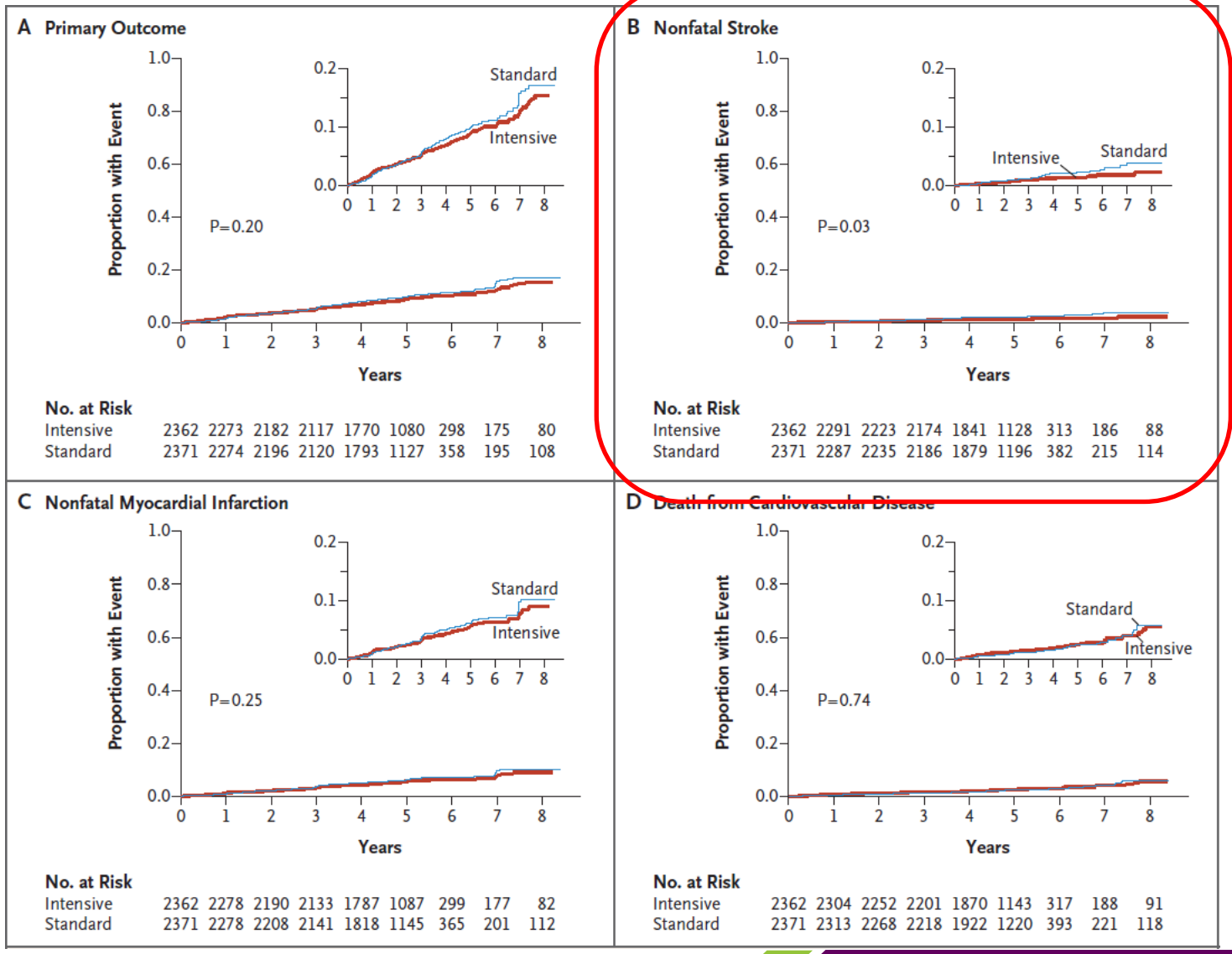
  (overall, 77 *vs* 30; **hypotension**, 17 *vs* 1; *P* <0.001)



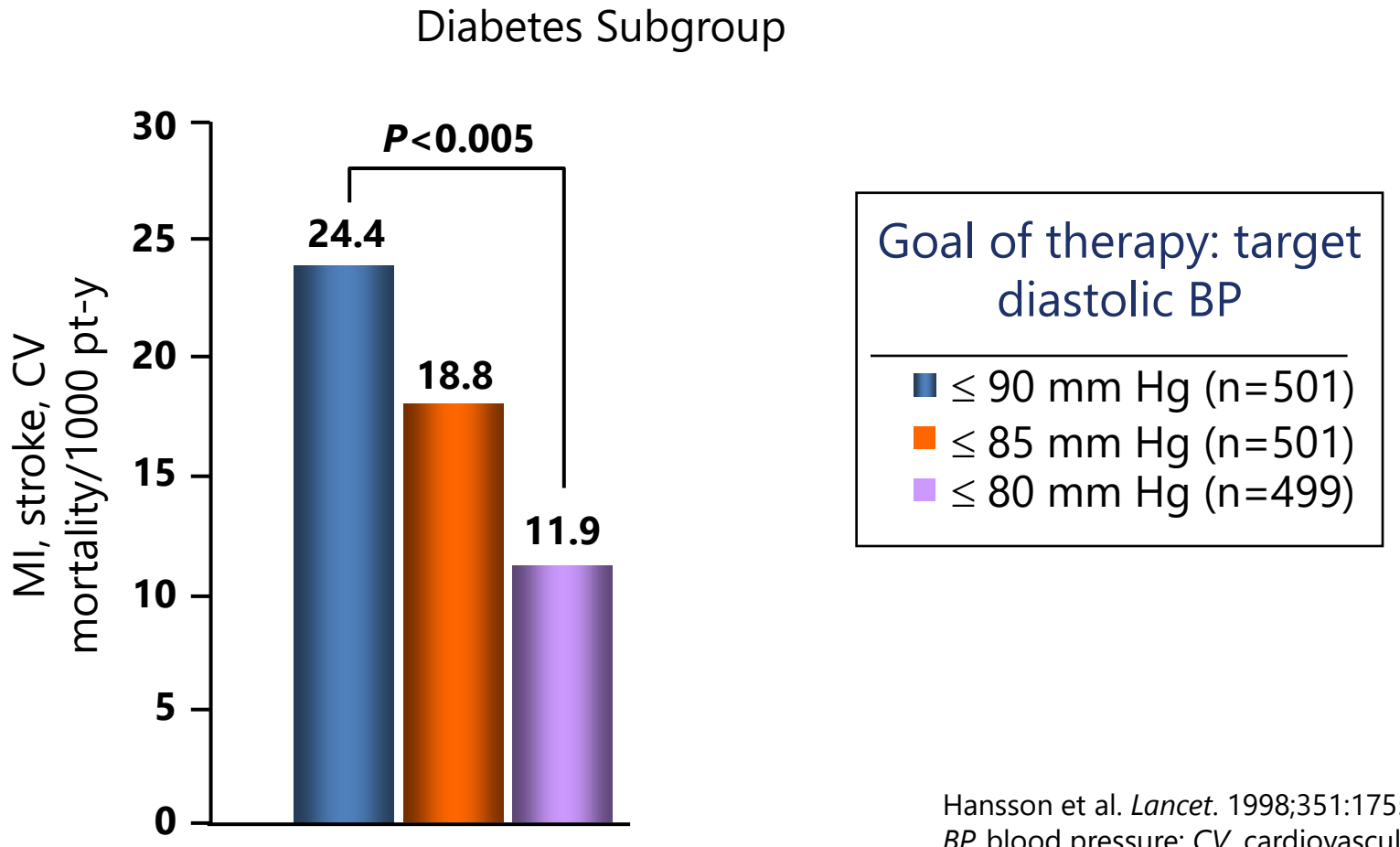
Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

N Engl J Med 2010;362:1575-85.

ACCORD BP

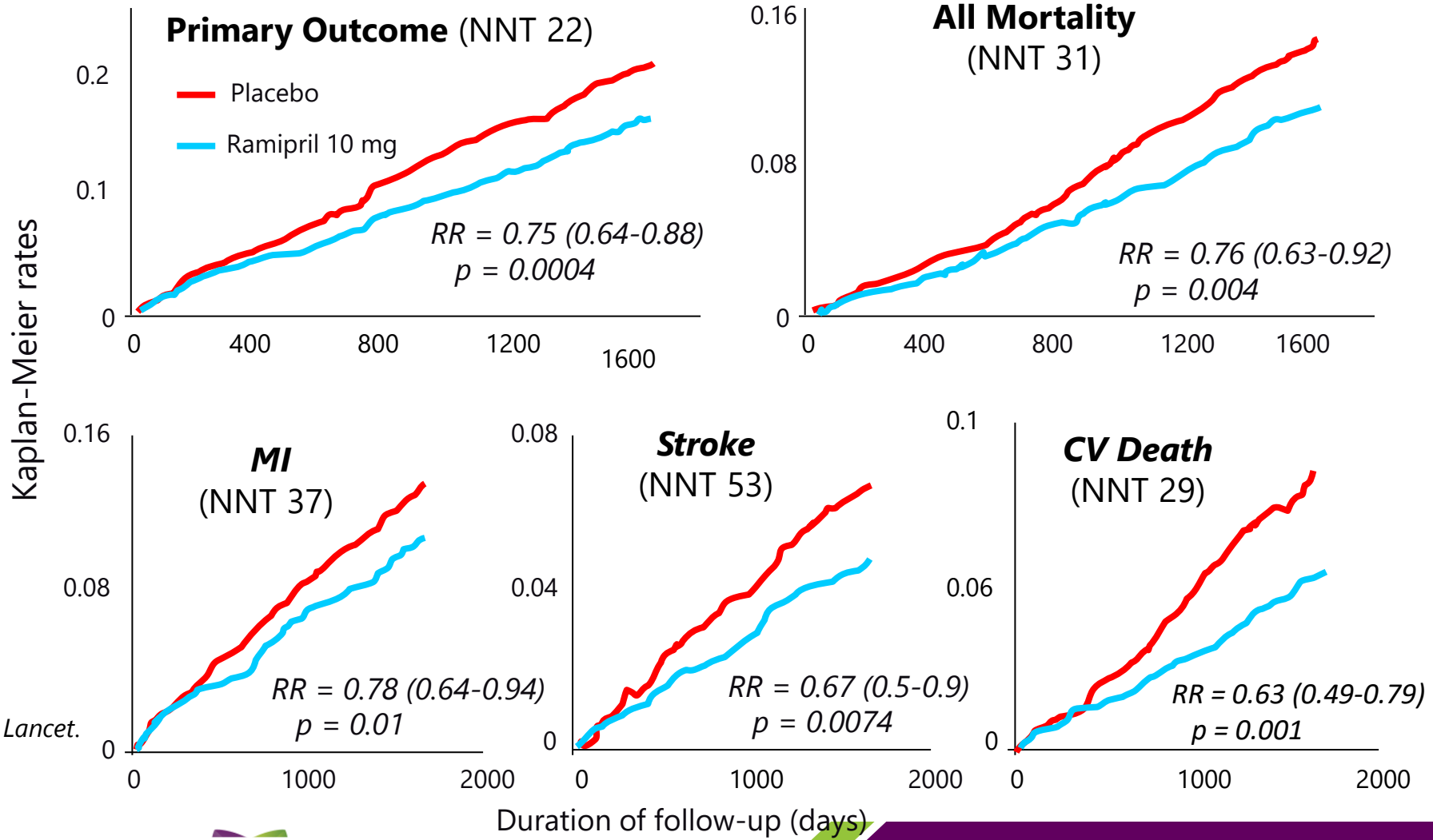

A Primary Outcome
Proportion with Event
Standard
Intensive
P=0.20
Years
No. at Risk
Intensive 2362 2273 2182 2117 1770 1080 298 175 80
Standard 2371 2274 2196 2120 1793 1127 358 195 108
B Nonfatal Stroke
Proportion with Event
Intensive
Standard
P=0.03
Years
No. at Risk
Intensive 2362 2291 2223 2174 1841 1128 313 186 88
Standard 2371 2287 2235 2186 1879 1196 382 215 114
C Nonfatal Myocardial Infarction
Proportion with Event
Standard
Intensive
P=0.25
Years
No. at Risk
Intensive 2362 2278 2190 2133 1787 1087 299 177 82
Standard 2371 2278 2208 2141 1818 1145 365 201 112
D Death from Cardiovascular Disease
Proportion with Event
Standard
Intensive
P=0.74
Years
No. at Risk
Intensive 2362 2304 2252 2201 1870 1143 317 188 91
Standard 2371 2313 2268 2218 1922 1220 393 221 118

HOT: DBP Control Reduces CV Events



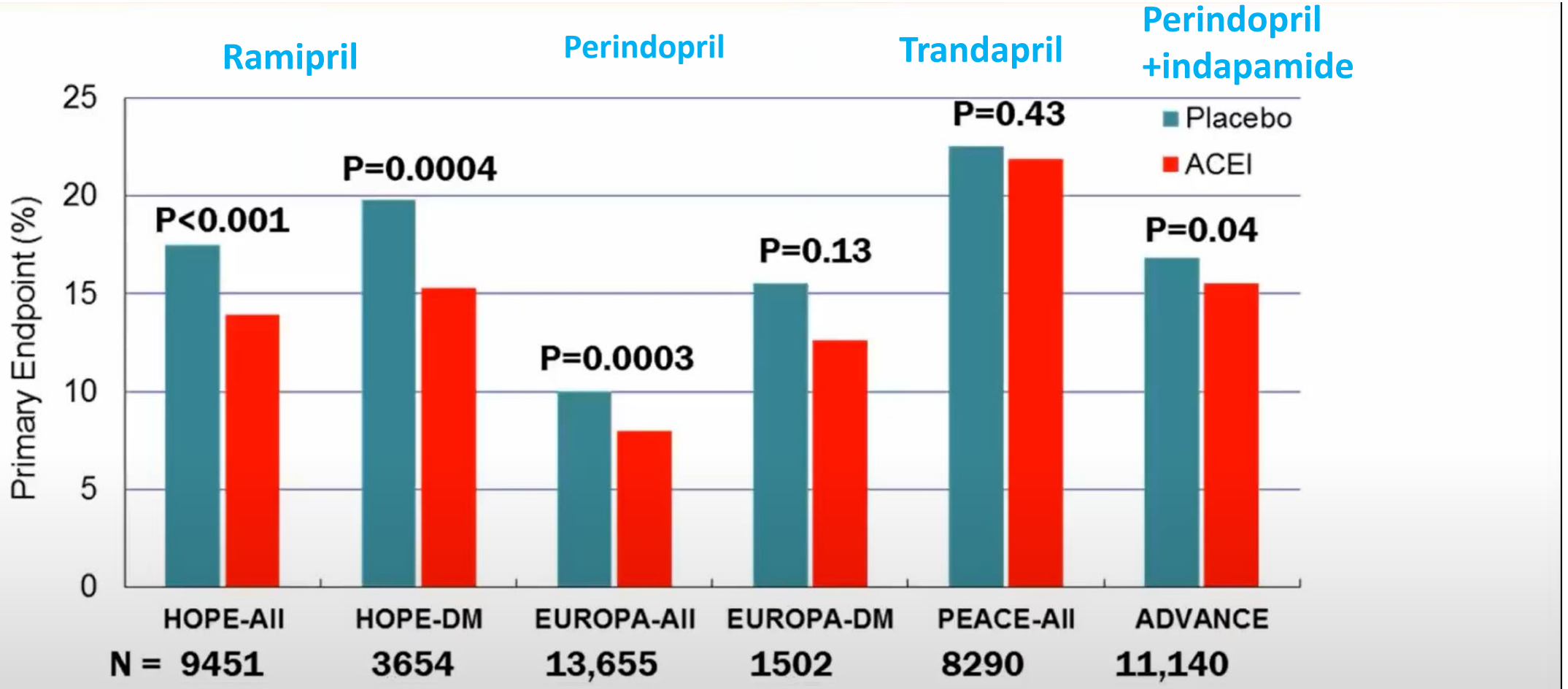
Hansson et al. *Lancet*. 1998;351:1755.
BP, blood pressure; *CV*, cardiovascular; *MI*, myocardial infarct

HOPE Study on ACEi (Ramipril): CV Benefits



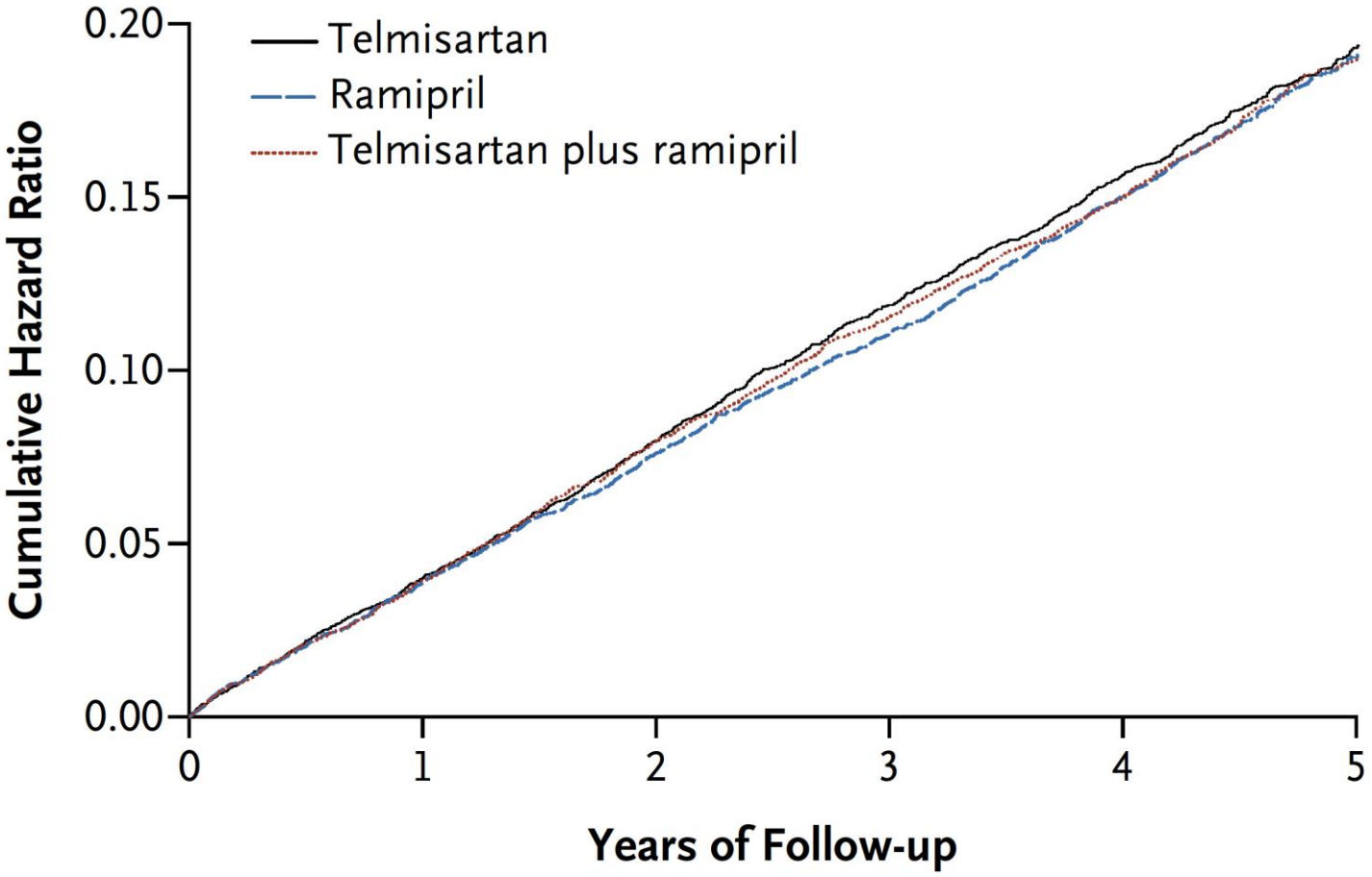
HOPE study investigators. *Lancet*. 2000;355:253-59.

ACEi in patients with diabetes



Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000; 355: 253-259; Fox KM et al. *Lancet* 2003; 362: 782-788; Patel A et al. *Lancet* 2007; 370: 829-840; Daly CA et al. *Eur Heart J* 2005;14:1347-349 ; The PEACE Trial Investigators. *NEJM* 2004;351:2058-2068; ADVANCE Collaborative Group. *NEJM* 2008;358:2560-2572

ONTARGET: ARB Therapy (i.e. Telmisartan) is as Effective as ACEi for CVD Prevention

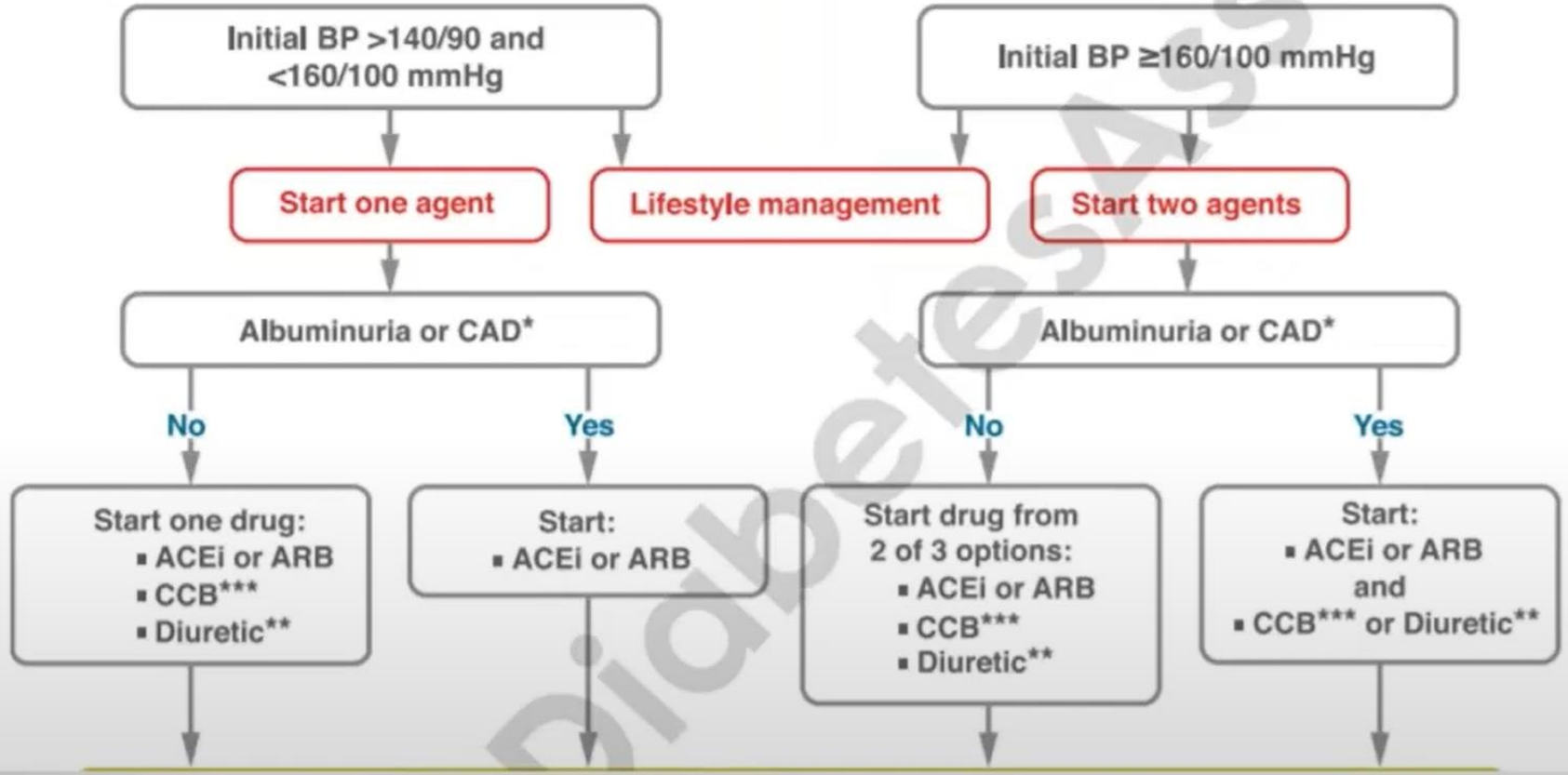


ONTARGET study investigators. *NEJM*. 2008:358:1547-59.

CVD, cardiovascular disease

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes





Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes - 2022. Diabetes Care 2021;45(Suppl. 1):S144-S174

Recommendations for the Treatment of Confirmed Hypertension in People with Diabetes (1 of 2)

American Diabetes Association.

Invidualized blood pressure targets

ESC European Society of Cardiology

Change in recommendations

2013	2019
BP targets	
BP target <140/85 mmHg for all	SBP to 130 mmHg and, if well tolerated, <130 mmHg, but not <120 mmHg In older people (>65 years) target SBP to a range of 130–139 mmHg DBP to <80 mmHg but not <70 mmHg
	On-treatment SBP to <1 cerebrovascular events

I	SBP:B-R[SR]	5. In adults with T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher, with a treatment goal of less than 130/80 mm Hg.[S4.4-33,S4.4-47,S4.4-49–S4.4-54] Adapted from recommendations in the 2017 Hypertension Clinical Practice Guidelines.[S4.4-1]
	DBP:C-EO	

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with EA

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ACC/AHA guideline 2019

2019 new recommendations (3)

ESC
European Society of Cardiology

BP management
Lifestyle changes encouraged in hypertension
RAAS blockers rather than beta-blockers/diuretics for BP control in pre-DM
Initiate pharmacological treatment with the combination of a RAAS blocker with a calcium-channel blocker or thiazide/thiazide-like diuretic
Home BP self-monitoring encouraged in patients with DM
24-h ABPM for BP assessment, and adjustment of antihypertensive treatment

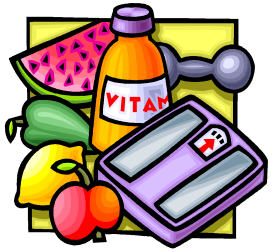
Vascular Protection Checklist: more than ABC

- ✓ A • A1C – optimal glycemic control (usually ≤7%)
- ✓ B • BP – optimal blood pressure control (<130/80mmHg)
- ✓ C • Cholesterol – LDL-C < 2.0 mmol/L or >50% reduction
- ✓ D • Drugs to protect the heart

  A – ACEi or ARB | S – Statin | A – ASA if indicated | SGLT2i / GLP-1RA with demonstrated CV benefit if type 2 DM with CVD and A1C not at target
- ✓ E • Exercise / Healthy Eating
- ✓ S • Smoking cessation

ACEi, angiotensin converting enzyme inhibitor; *ARB*, angiotension receptor blocker; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DM*, diabetes mellitus

Use a Multifaceted Vascular Protection Strategy



Healthy Behaviours/weight management

BP <130/80 mmHg



Smoking Cessation



A1C ≤7%



Physical Activity



Rx:
Statins
ACEi/ARB
Certain Antihyperglycemic Agents

Case 3

- F/63, ex-smoker, sedentary lifestyle, presenting to clinic following recent diagnosis of T2DM. Asymptomatic, no history of chest pain. BP 145/77, 152/72; HR 72; BMI 32. HbA1c 6.7%, recently started on metformin. ECG showed no LVH. What is your next step in managing this patient's BP?

1. Lifestyle management and review in clinic in 3 months
2. Check urine for albumin:Cr ratio and decide on treatment
3. Start lisinopril
4. Start atenolol
5. Start amlodipine

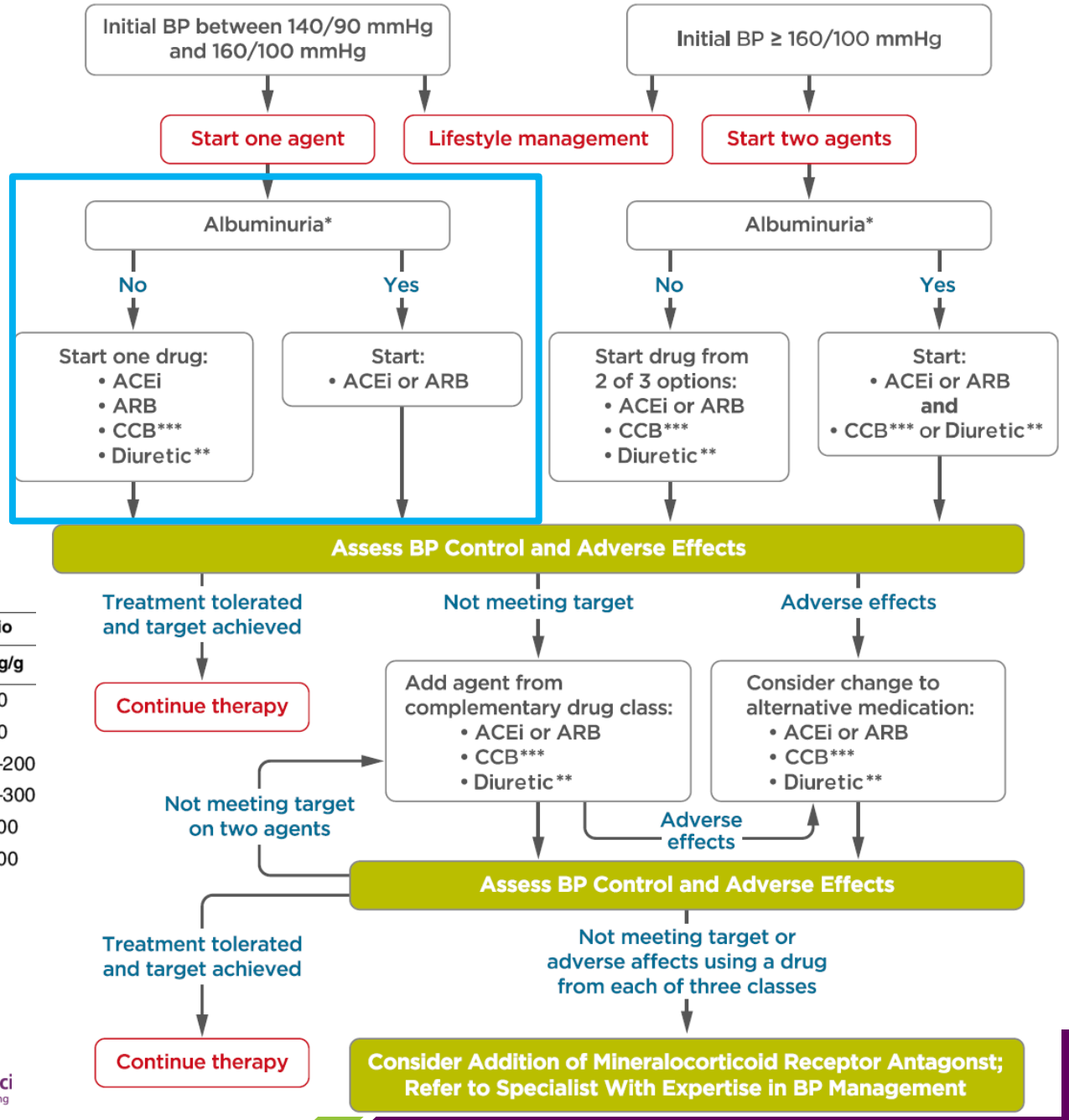
Case 2

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4. Start atenolol
5. Start amlodipine

ADA algorithm (2018)

for DM pts with confirmed HT:



	24-Hour Urine: Urinary Albumin Excretion, mg/24 hours	First Morning Void			
		Urinary Albumin Concentration, mg/L	Albumin:Creatinine Ratio		
			Sex	mg/mmol	mg/g
Normoalbuminuria	<30	<20	Male	<2.5	<20
			Female	<3.5	<30
Microalbuminuria	30–300	20–200	Male	2.5–25	20–200
			Female	3.5–35	30–300
Macroalbuminuria	>300	>200	Male	>25	>200
			Female	>35	>300

**Thiazide-like diuretic

ADA. *Diabetes Care* 2018 Jan; 41(Suppl 1): S86-S104.

Pharmacological management of hypertension in DM individual

Important points to note:

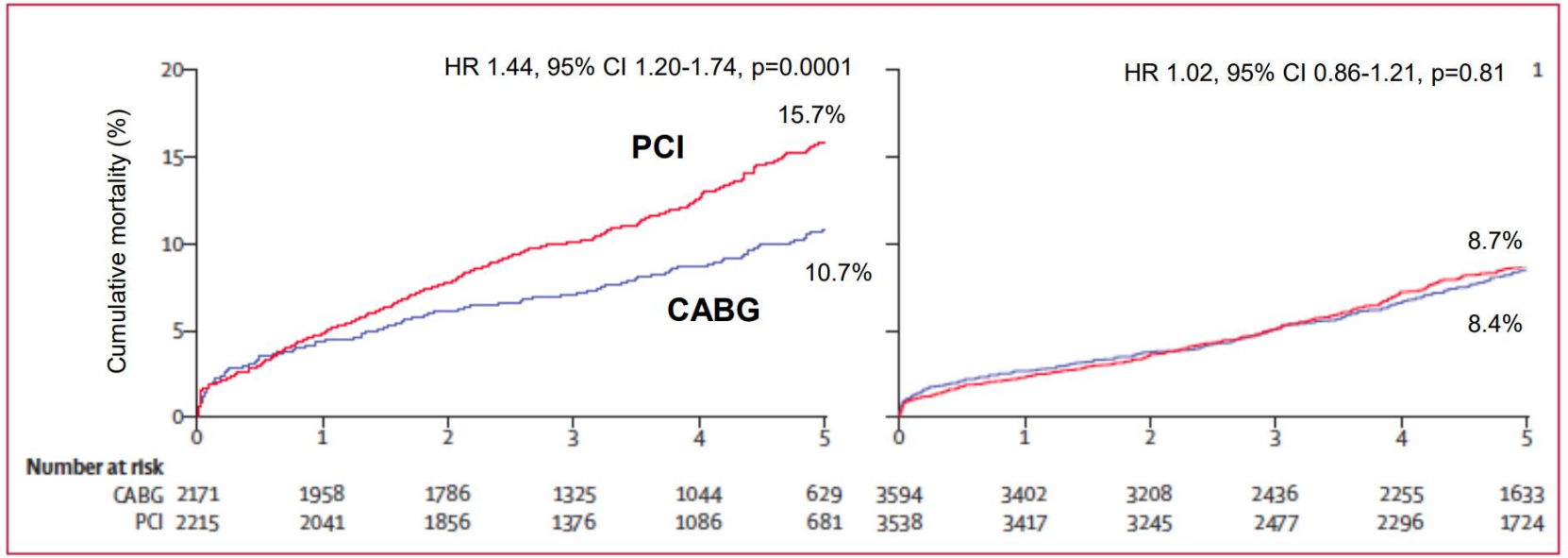
- Maximally tolerated dose of ACEi/ARB as first-line for HT in DM pts with U alb:Cr (UACR) ≥300 mg/g creatinine (LOE A), or 30-299 mg/g creatinine (LOE B)
- When UACR ≥30 mg/g, should include an ACEi/ARB
- Never co-administer ACEi and ARB, or ACEi/ARB with renin inhibitors

ADA. *Diabetes Care* 2018 Jan; 41(Suppl 1): S86-S104.

Courtesy of Prof. Erik Fung

Impact of diabetes on mortality after CABG vs PCI

Pooled analysis of individual patient data from 11 trials



Head SJ et al. Lancet 2018

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

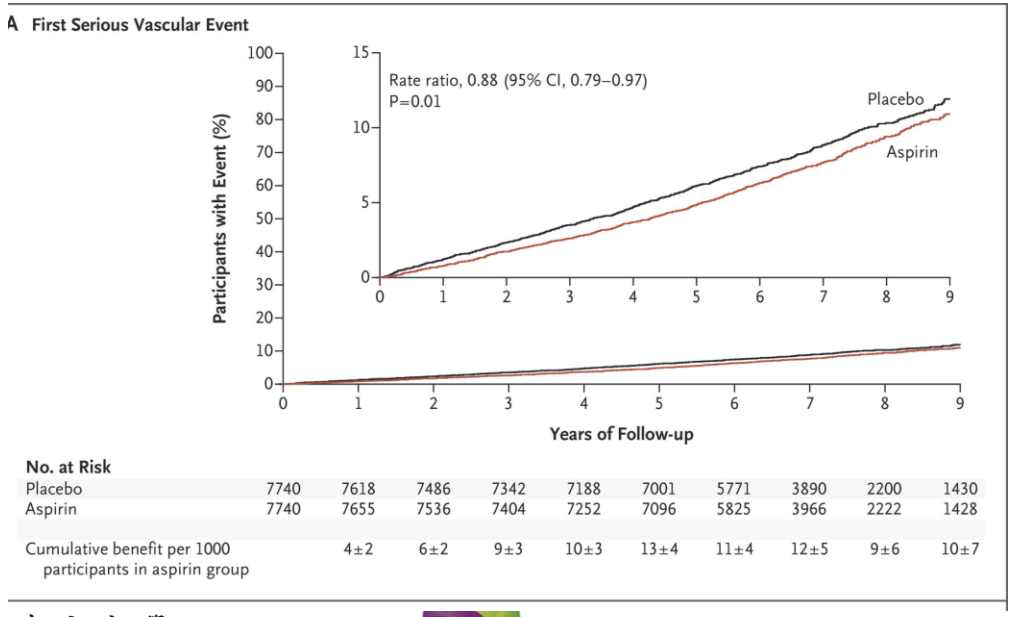
Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

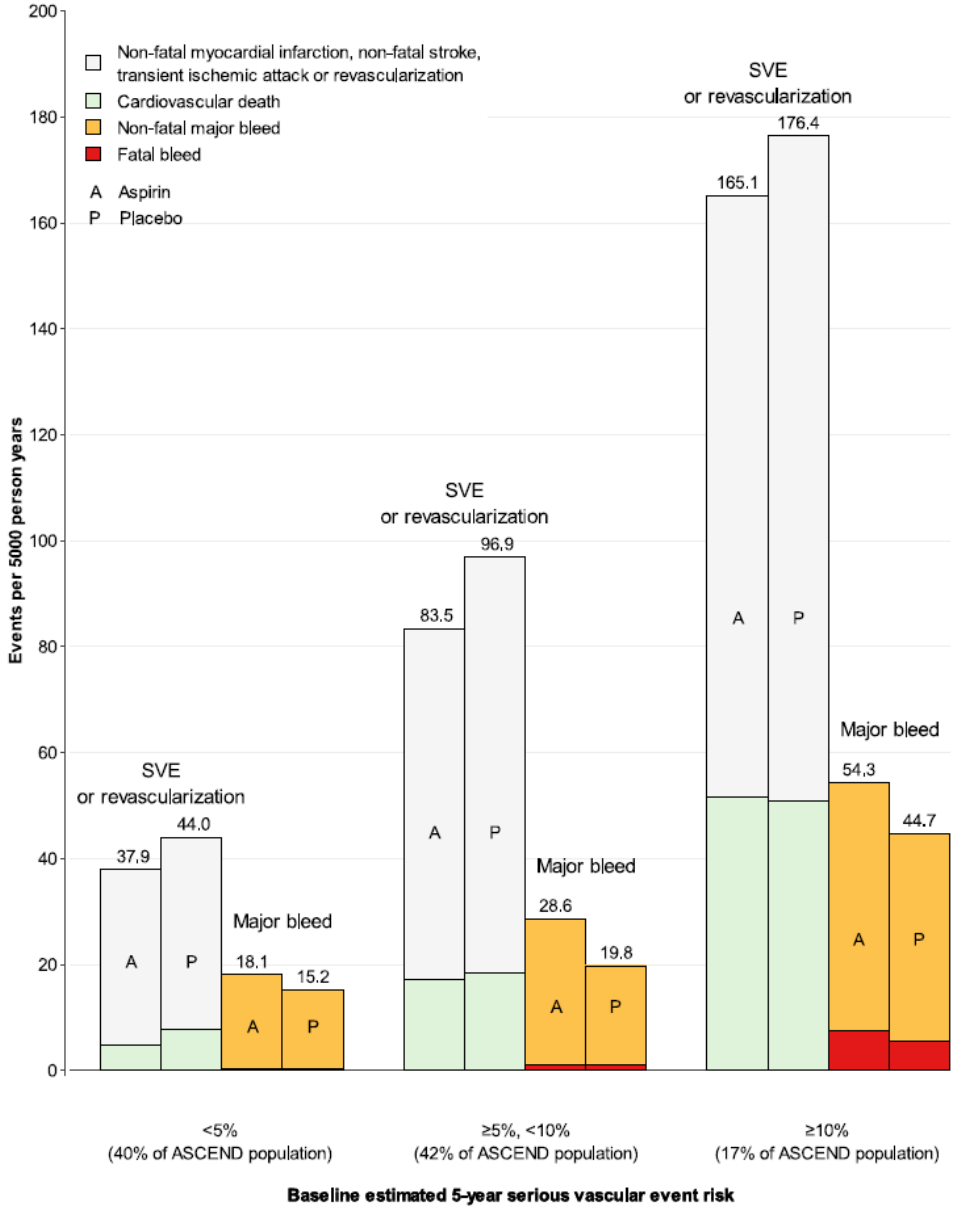
The ASCEND Study Collaborative Group*

ABSTRACT

BACKGROUND

Diabetes mellitus is associated with an increased risk of cardiovascular events. Aspirin use reduces the risk of occlusive vascular events but increases the risk of bleeding; the balance of benefits and hazards for the prevention of first cardiovascular events in patients with diabetes is unclear.





Observed numbers of events per 5000 person years (SE)

Serious vascular events (SVE) avoided	5.7 (3.7)	11.2 (5.4)	4.9 (12.9)
SVE or revascularizations avoided	6.1 (4.2)	13.4 (6.3)	11.3 (14.3)
Major bleeds caused	2.8 (2.6)	8.9 (3.2)	9.6 (7.5)

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Antiplatelet therapy in primary prevention in DM

ESC European Society of Cardiology

Change in recommendations

2013	2019
Antiplatelet therapy	
Aspirin for primary prevention is not recommended in DM at low CVD risk	**Aspirin (75–100 mg/day) for primary prevention may be considered in patients with DM at very high/high risk in the absence of clear contraindications**
	Aspirin for primary prevention is not recommended in patients with DM at moderate CV risk

Key Messages for People with Diabetes

Ask your doctor about the ABCDEs to reduce your risk of heart attack and stroke:

- **A** = A1C – Blood glucose control. The target is usually 7% or less
- **B** = BP – Blood pressure control (less than 130/80 mm Hg)
- **C** = Cholesterol – LDL-cholesterol less than 1.4 mmol/L in ASCVD. Your physician or nurse practitioner may advise you to start cholesterol lowering medication
- **D** = Drugs to protect your heart: These include DM meds (SGLT2i, GLP1A), blood pressure pills ("ACE inhibitors or ARBs), cholesterol lowering medication ("statins and PCSK9i"), and in people with existing cardiovascular disease, certain blood glucose lowering medications. These blood glucose lowering medications can protect your heart even if your blood pressure and/or LDL-cholesterol are already at target
- E = Exercise /Eating – Regular physical activity which includes healthy eating, and achievement and maintenance of a healthy body weight
- **S** = **Stop smoking** and manage stress

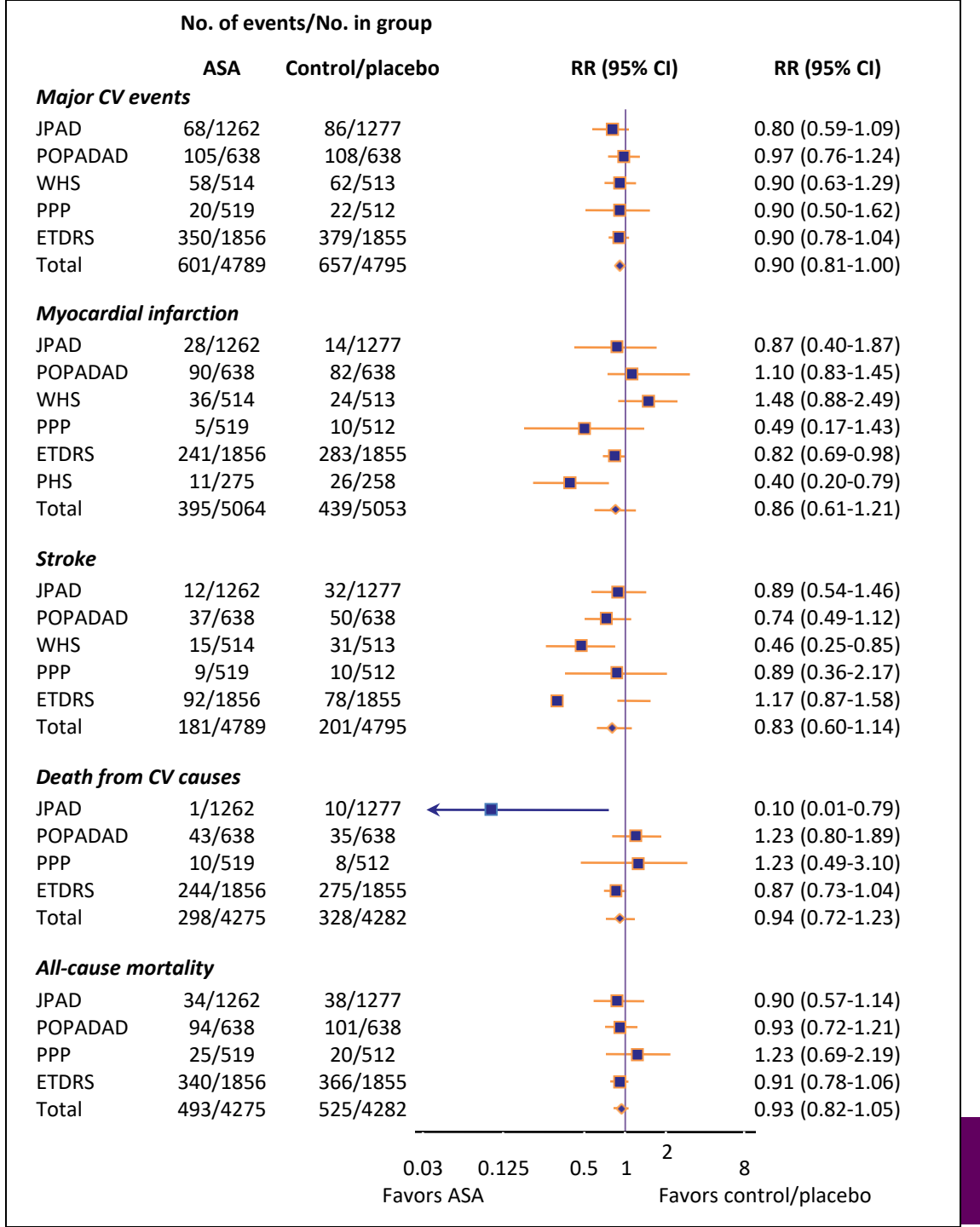
ASA for 1º Prevention in Diabetes

Meta analysis of 6 studies
(n = 10,117)

No overall benefit for:

- Major CV events
- MI
- Stroke
- CV mortality
- All-cause mortality

JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes
POPADAD = Prevention of Progression of Arterial Disease and Diabetes
PPP = Primary Prevention Project
ETDRS = Early Treatment Diabetic Retinopathy Study
PHS = Physicians' Health Study
WHS = Women's Health Study



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De Berardis G, et al. BMJ 2009; 339:b4531.