Glucose Is the Most Important Target for CV Prevention in Diabetes

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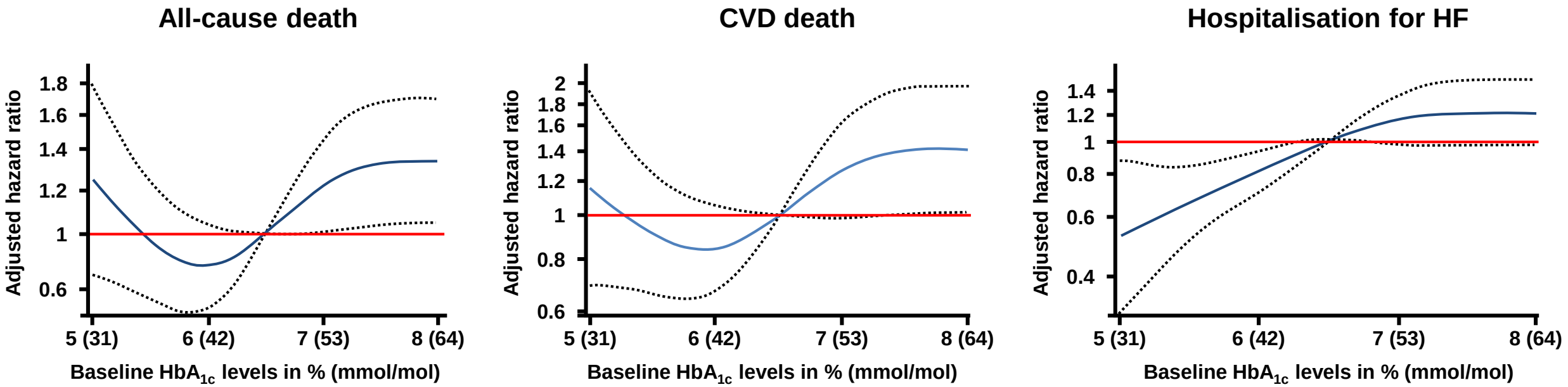
SEZIONE DI MEDICINA INTERNA, ENDOCRINOLOGIA, ANDROLOGIA E MALATTIE METABOLICHE

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

An Increased HbA_{1c} Was Associated with Increased Risk of 1-Year Survival Outcomes



Data are adjusted hazard ratios ± 95% confidence intervals
CVD, cardiovascular disease; HF, heart failure
Dauriz M, et al. *Diabetes Care* 2017; doi: 10.2337/dc16-2016 [Epub ahead of print]

The Three Megatrials on IGC in T2DM

- Action in Diabetes and Vascular Disease–Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)
  n=11,140
  embedded BP trial

- Veterans Affairs Diabetes Trial (VADT)
  n=1,791
  intensive BP and lipid control
  in both arms

- Action to Control Cardiovascular Risk in Diabetes (ACCORD)
  n=10,251
  embedded BP and lipid trials

ACCORD

IGC: individualised therapy at discretion of treating physician; target HbA_{1c} ≤6.0% as early as possible; early and aggressive use of insulin, including multiple injections; monthly visits for the first 6 months, then every 2 months

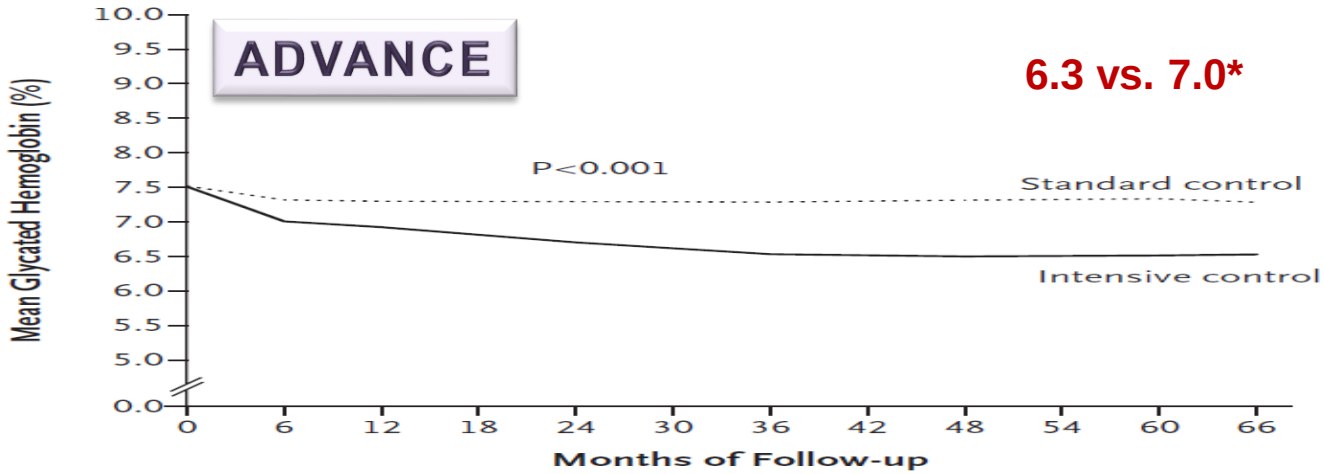
SGC: visits every 4 months

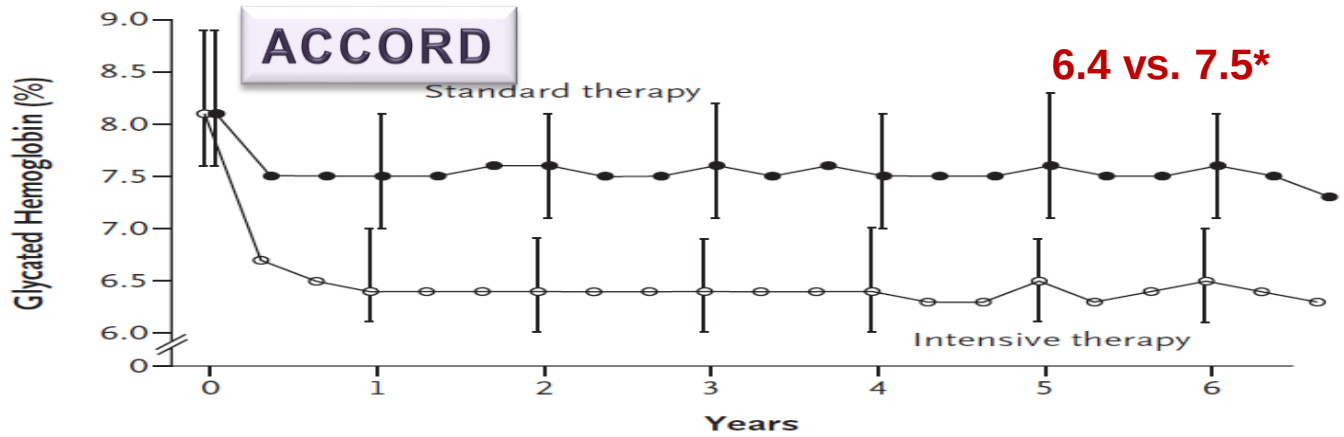
ADVANCE

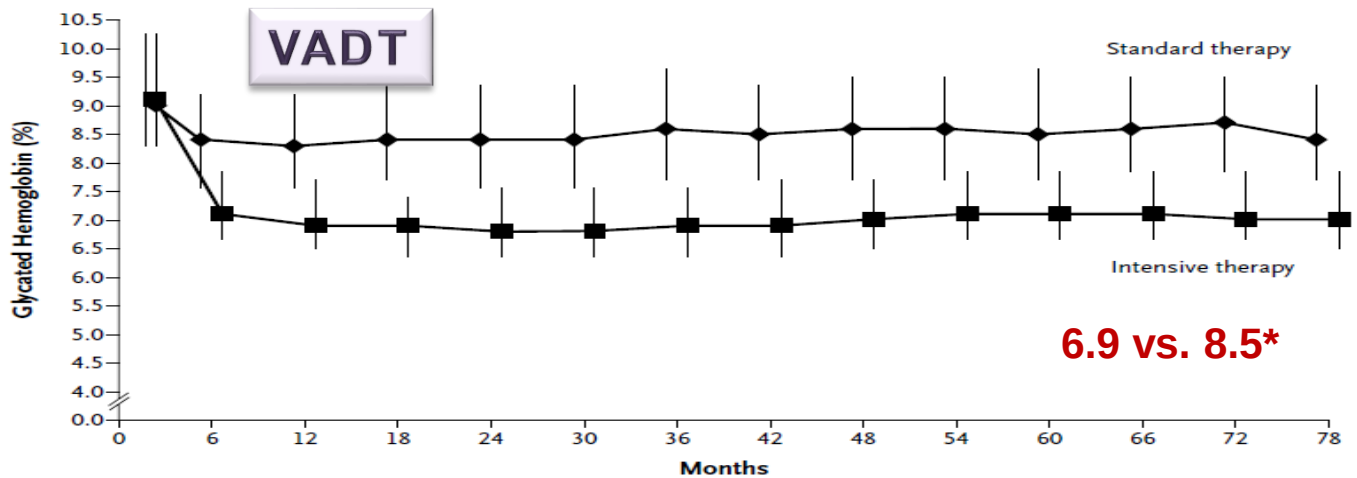
- IGC: Gliclazide MR Unrestricted additional therapy to achieve target HbA1c≤6.5%
  SGC: SU other than Gliclazide MR Unrestricted additional therapy according to standard guidelines
- All other treatment at discretion of treating physician

VADT

- Metformin/Glimepiride
  → Rosiglitazone
  → Insulin
  IGC: max. doses, insulin if HbA_{1c} ≥6%
  SGC: half-max. doses, insulin if HbA_{1c} ≥9%
- Other CV risk factors treated identically
- ASA and statin to all patients (unless contraindicated)


ADVANCE
6.3 vs. 7.0*
Mean Glycated Hemoglobin (%)
P<0.001
Standard control
Intensive control
Months of Follow-up


ACCORD
6.4 vs. 7.5*
Glycated Hemoglobin (%)
Standard therapy
Intensive therapy
Years


VADT
Glycated Hemoglobin (%)
Standard therapy
Intensive therapy
6.9 vs. 8.5*
Months

The Three Megatrials on IGC in T2DM

- Action in Diabetes and Vascular Disease–Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)
  n=11,140
  embedded BP trial

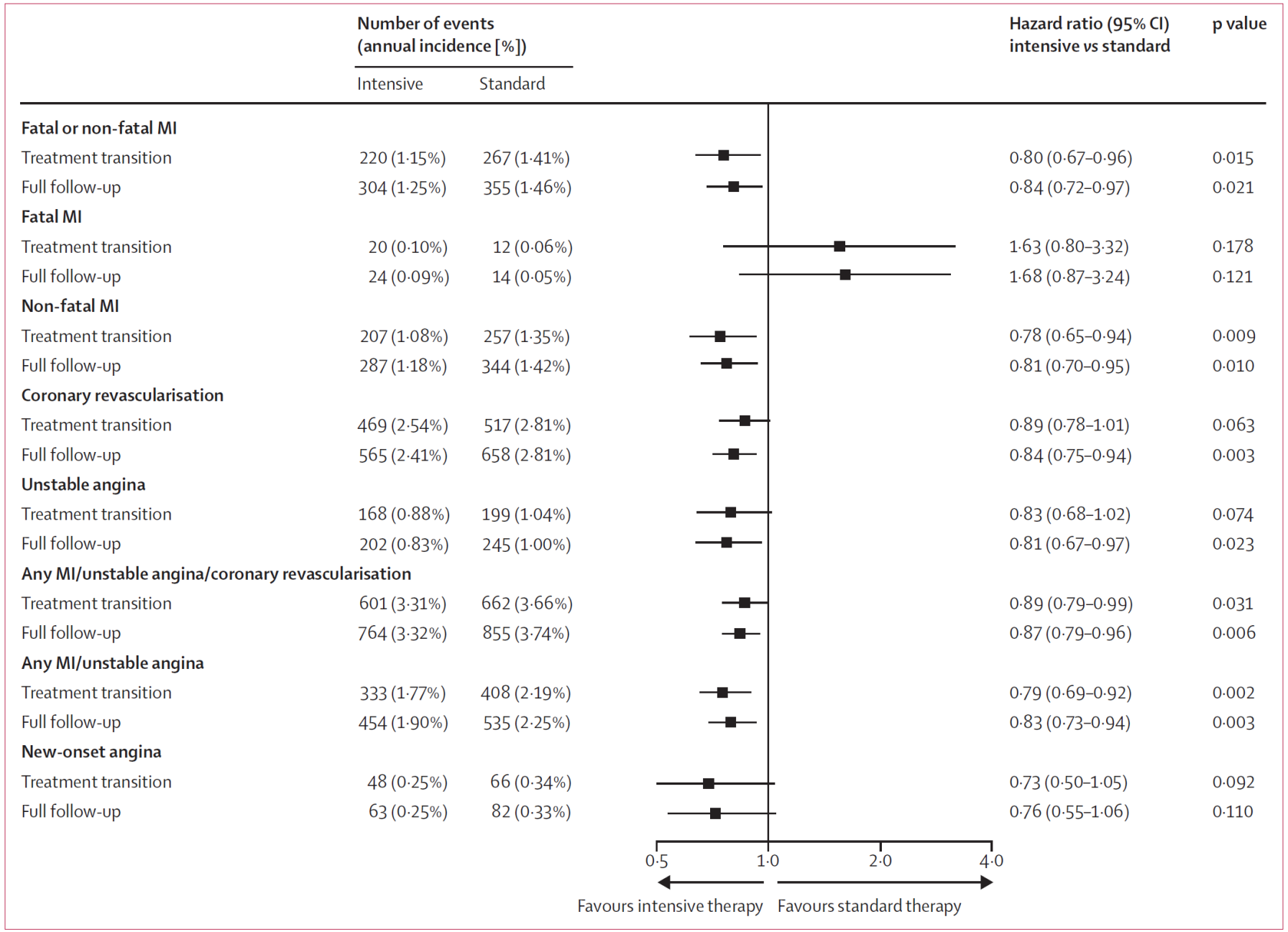
  MI, Stroke, CV death
  RR reduction **6%** (–6% to +16%); **p=0.32**

- Veterans Affairs Diabetes Trial (VADT)
  n=1,791
  intensive BP and lipid control in both arms

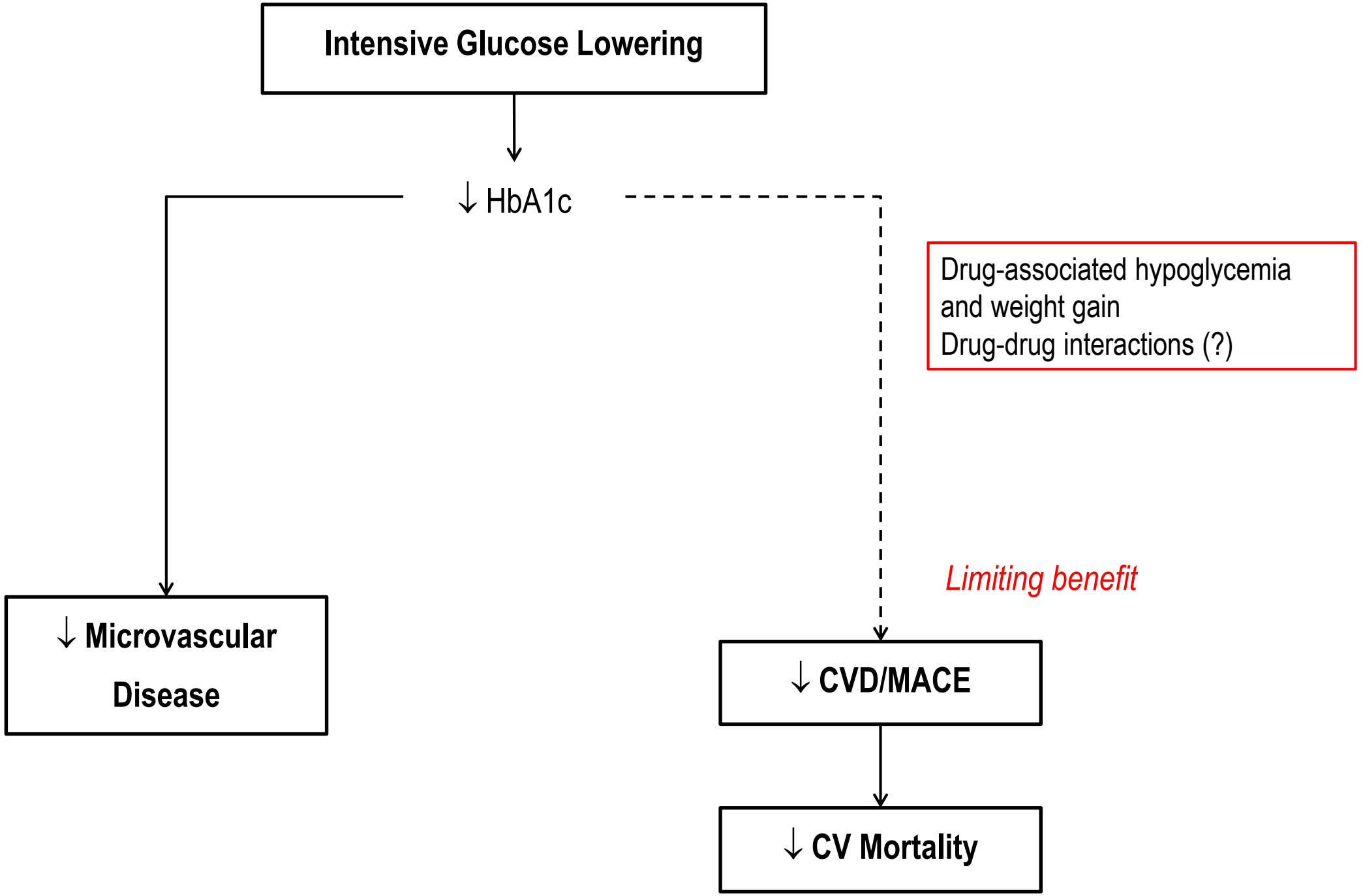
  Composite of CV events (MI, stroke, CV death, CHF, surgery for cardiac, cerebrovascular, or peripheral vascular disease, inoperable CAD, and amputation)
  RR reduction **12%** (–26% to +5%); **p=0.14**

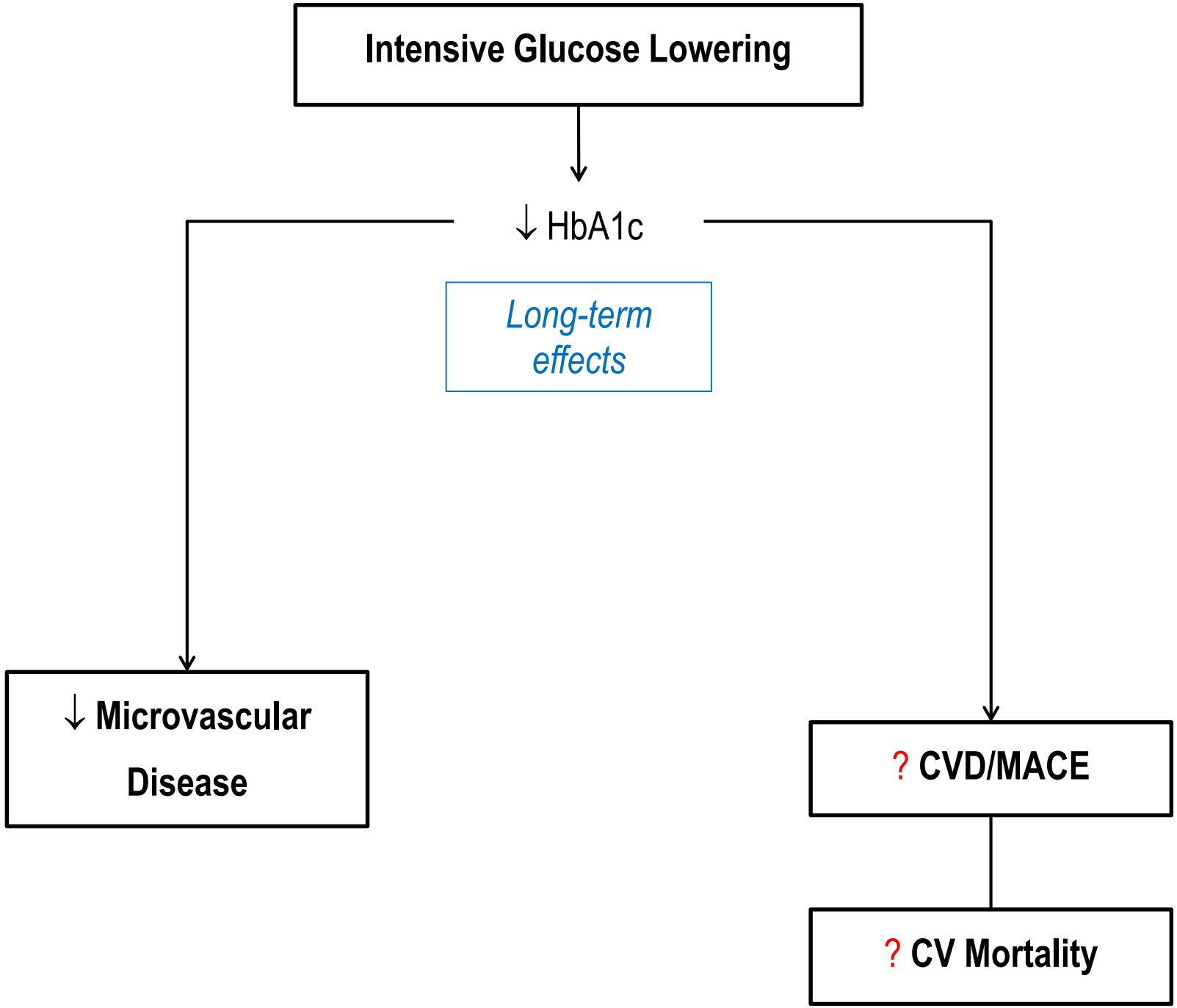
- Action to Control Cardiovascular Risk in Diabetes (ACCORD)
  n=10,251
  embedded BP and lipid trials

  MI, Stroke, CV death
  RR reduction **10%**
  (0.78-1.04) (–22% to +4%); **p=0.16**



Gerstein HC et al, *The Lancet* 2014


Intensive Glucose Lowering
↓ HbA1c
↓ Microvascular Disease
Drug-associated hypoglycemia and weight gain
Drug-drug interactions (?)
Limiting benefit
↓ CVD/MACE
↓ CV Mortality


Intensive Glucose Lowering
↓ HbA1c
Long-term effects
↓ Microvascular Disease
? CVD/MACE
? CV Mortality

UKPDS: Legacy Effect of Earlier Glucose Control

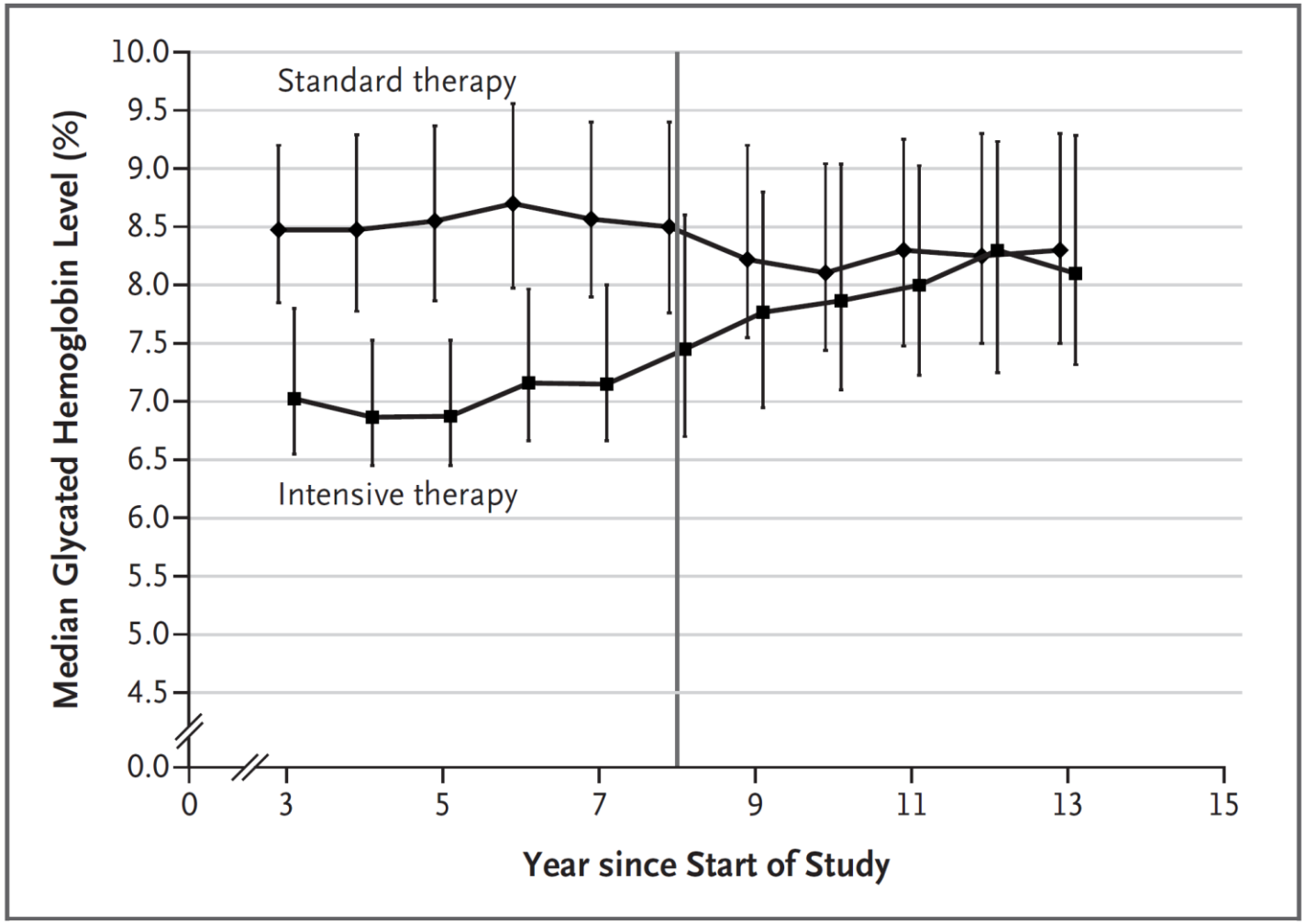
After median 8.5 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	0.052	**0.014**
All-cause mortality	*RRR:*	6%	**13%**
	P:	0.44	**0.007**

RRR = Relative Risk Reduction, P = Log Rank

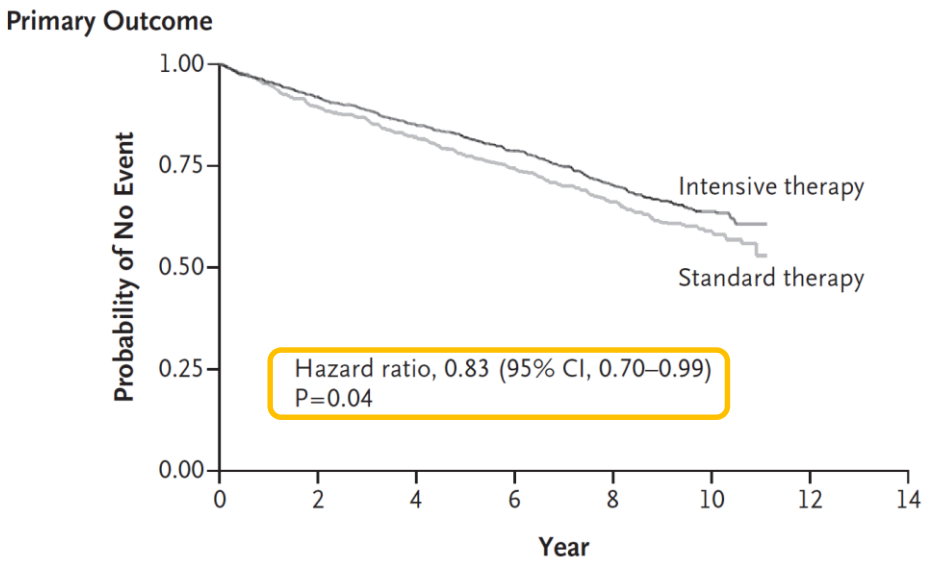
Holman RR et al, *New Engl J Med*, 2008

VADT Follow-up: Changes in Median HbA1c

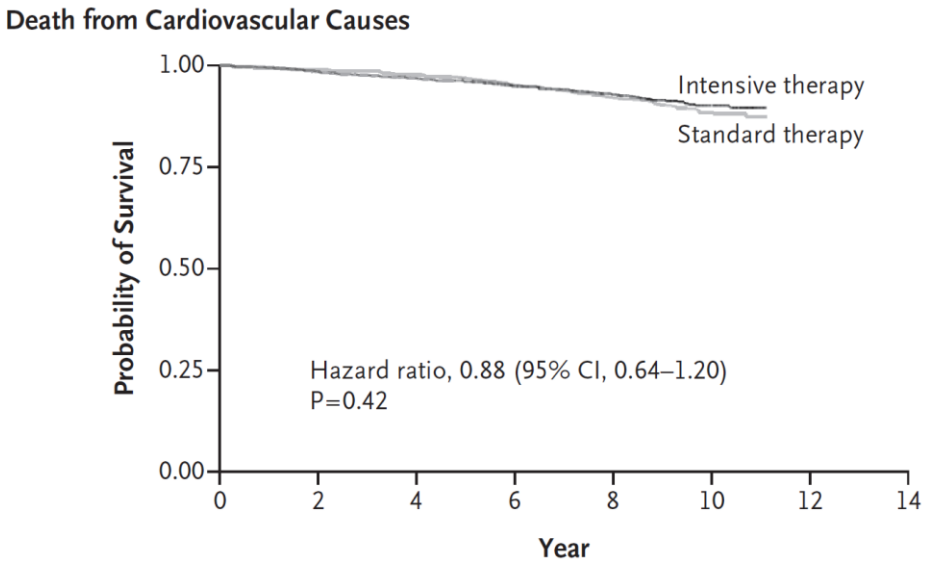


Hayward RA, et al., N Engl J Med. 2015; 372:2197-2206.

VADT Follow-up: Probability Curves for Time to the First Major CV Event and for CV Mortality



No. at Risk						
Standard therapy	899	732	626	475	352	126
Intensive therapy	892	745	650	511	395	154



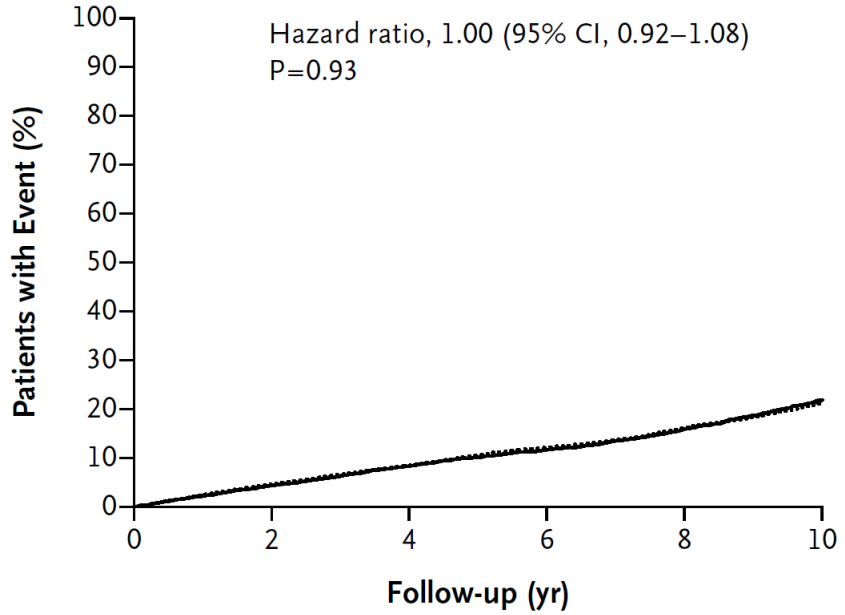
No. at Risk						
Standard therapy	899	830	778	716	649	276
Intensive therapy	892	830	777	731	674	269

In-trial HbA1c Δ: 1.5%
Trial duration: 5.4 yrs
Follow-up duration: 9.8 yrs

Hayward RA, et al., N Engl J Med. 2015; 372:2197-2206.

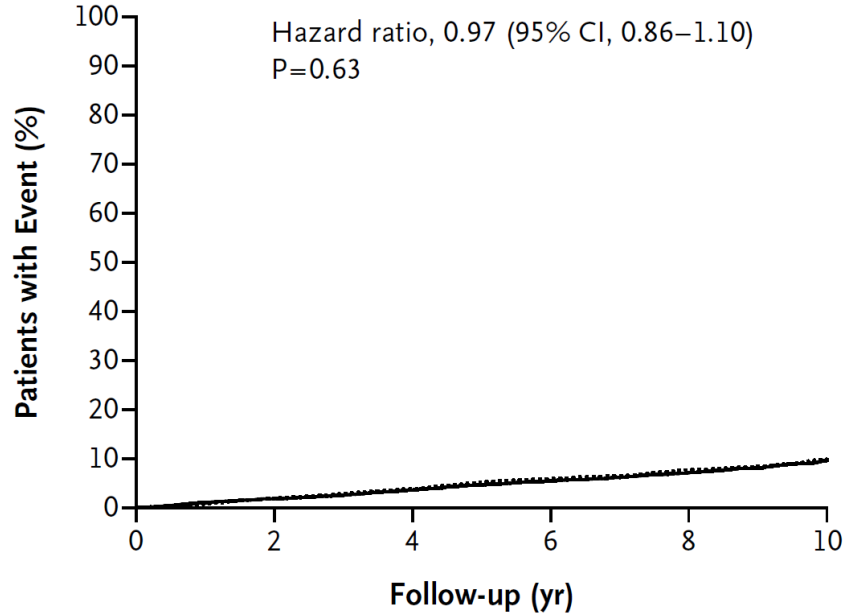
ADVANCE Follow-up: Cumulative Incidence of Events, According to Glucose-Control Study Group

Major Macrovascular Events



No. at Risk						
Intensive	5571	5273	4942	3881	3448	2448
Standard	5569	5253	4940	3774	3359	2363

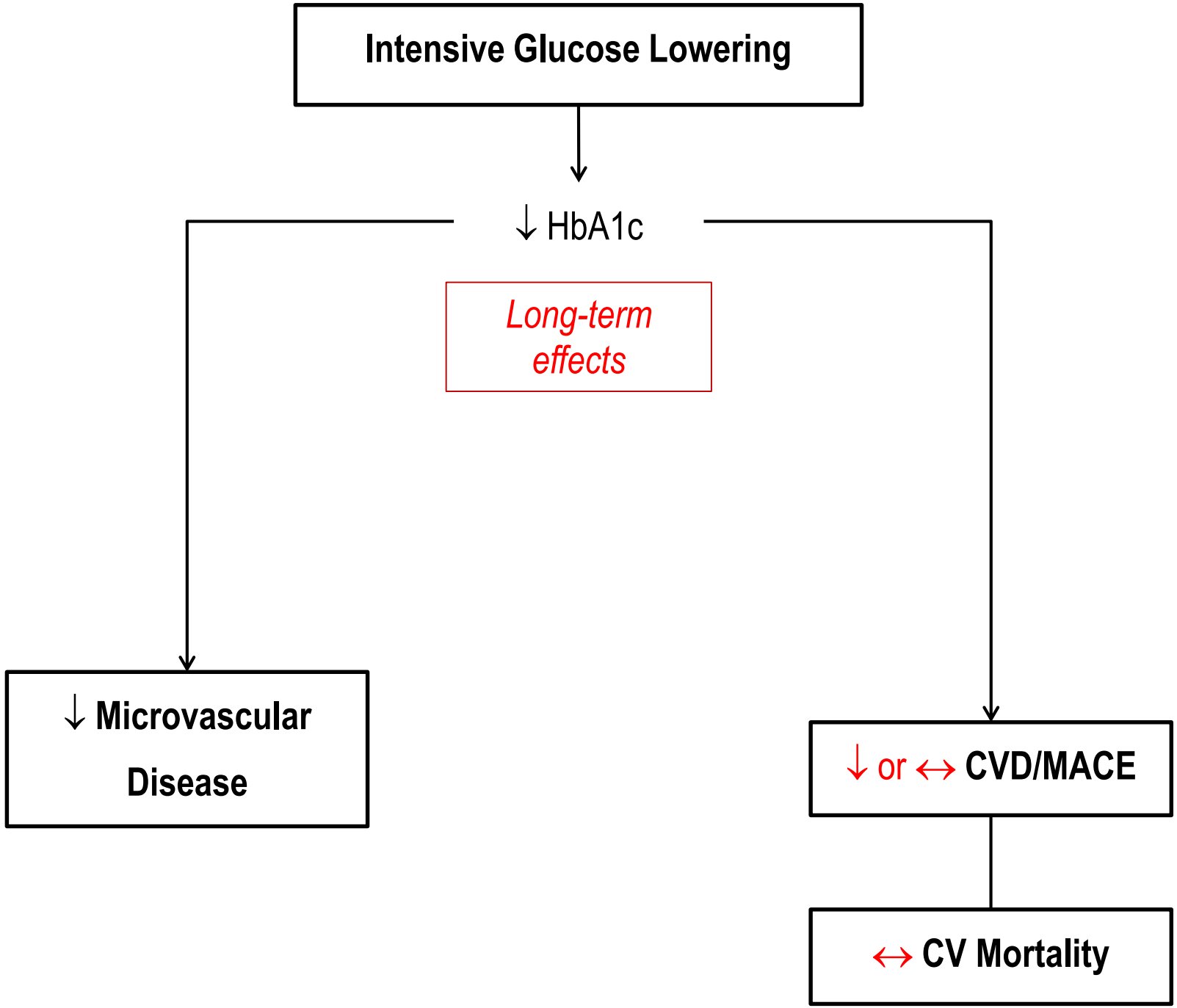
Death from Cardiovascular Causes



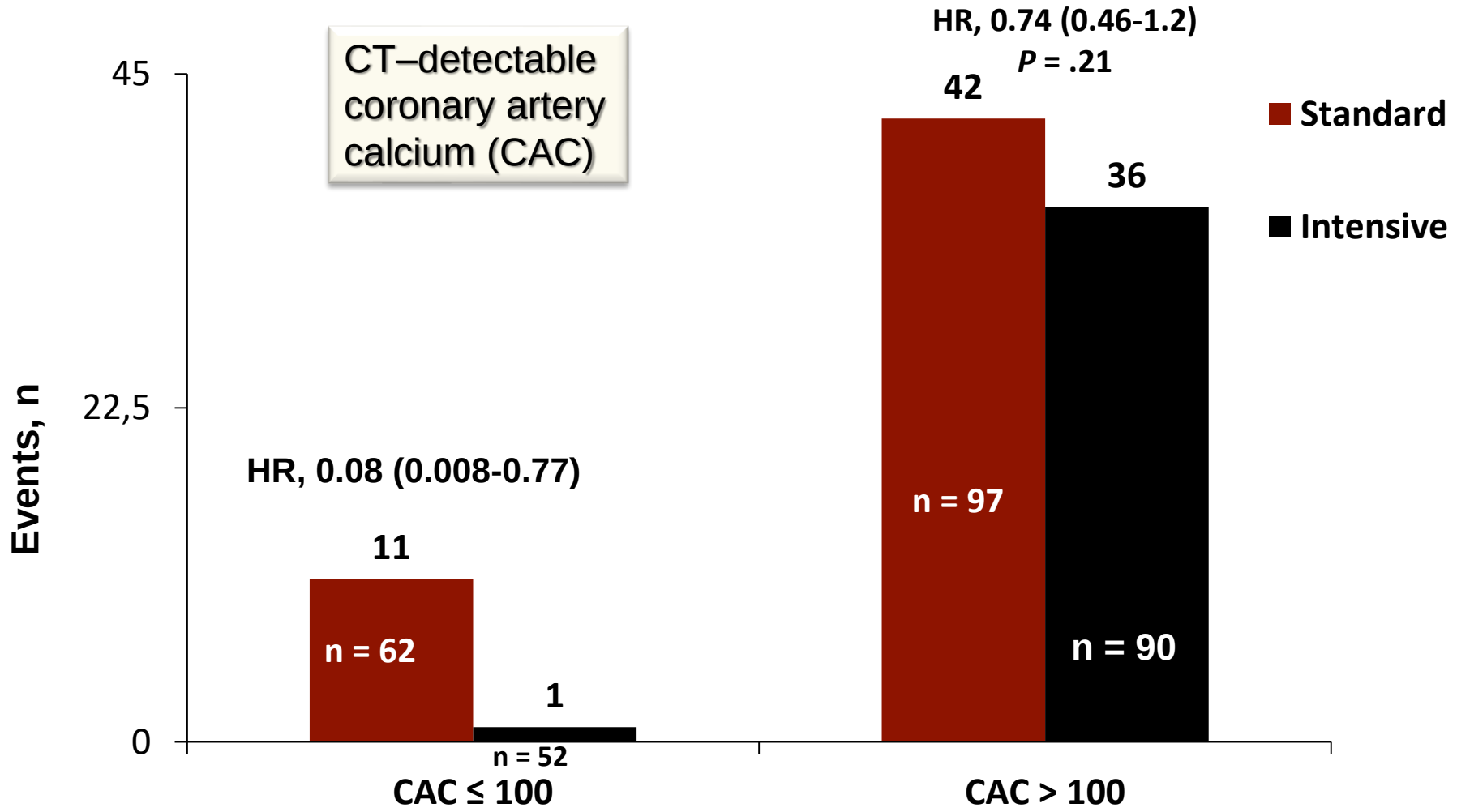
No. at Risk						
Intensive	5571	5414	5197	4125	3772	2822
Standard	5569	5412	5190	4050	3693	2697

In-trial HbA1c Δ: 0.7%
Trial duration: 5.0 yrs
Follow-up duration: 4.9 yrs

Zoungas S, et al., N Engl J Med. 2014; 371:1392-1406.

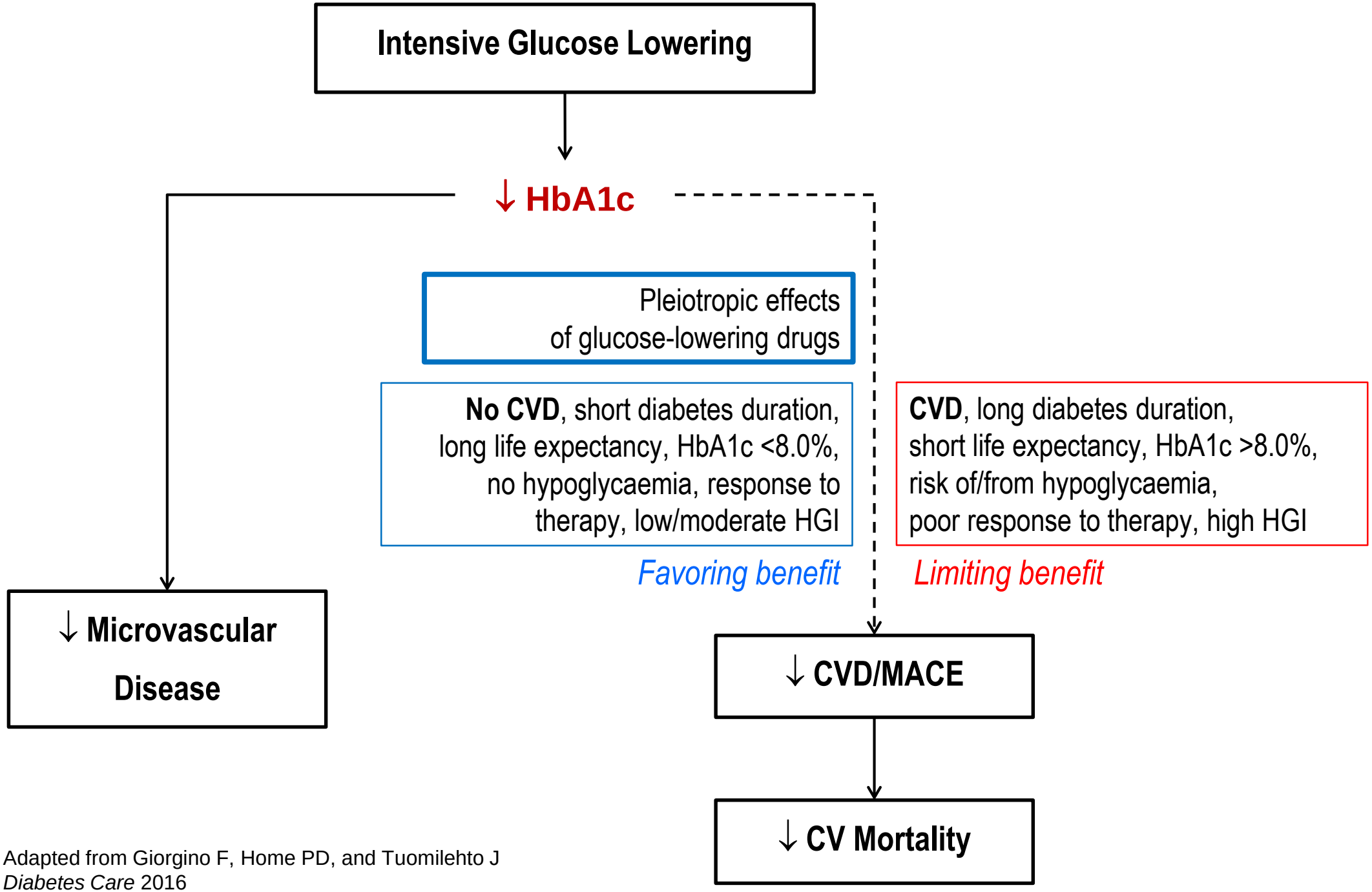

Intensive Glucose Lowering
↓ HbA1c
Long-term effects
↓ Microvascular Disease
↓ or ↔ CVD/MACE
↔ CV Mortality

VADT: Intensive Treatment Reduces CVD Events in Cases With Lower Calcified Coronary Atherosclerosis



*Events: CV death, MI, CHF, revascularization, stroke, inoperable CVD, or amputation.

Reaven PD, et al. *Diabetes*. 2009;58:2642-2648.



Adapted from Giorgino F, Home PD, and Tuomilehto J
Diabetes Care 2016

CVOT with SGLT2i and GLP-1 RA

EMPA-REG[1]

- Established cardiovascular disease (prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease)

Empagliflozin (SGLT2i) vs. usual care

LEADER[2]

- ≥50 years with pre-existing cardiovascular disease, cerebrovascular disease, vascular disease, or renal or heart failure
- ≥60 years with cardiovascular risk factors

Liraglutide (GLP-1 RA) vs. usual care

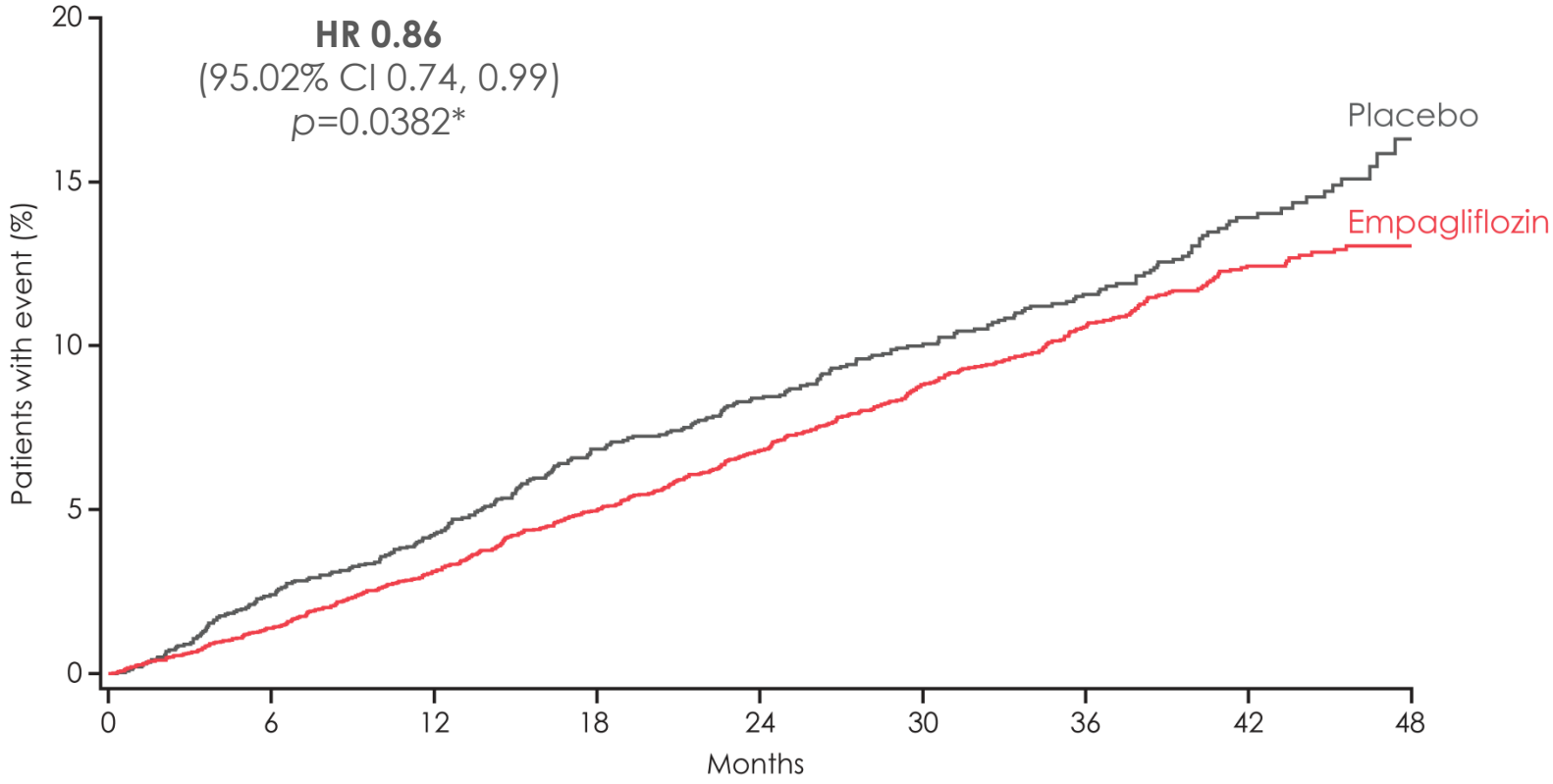
SUSTAIN-6[3]

- ≥50 years with pre-existing cardiovascular disease
- ≥60 years with pre-cardiovascular disease

Semaglutide (GLP-1 RA) vs. usual care

1. Zinman B, et al. *N Engl J Med* 2015;373:2217–2128; 2. Marso SP, et al. *N Engl J Med* 2016;375:311–322; 3. Marso SP, et al. *N Engl J Med* 2016;375:1834–1844

Primary Outcome: 3-Point MACE



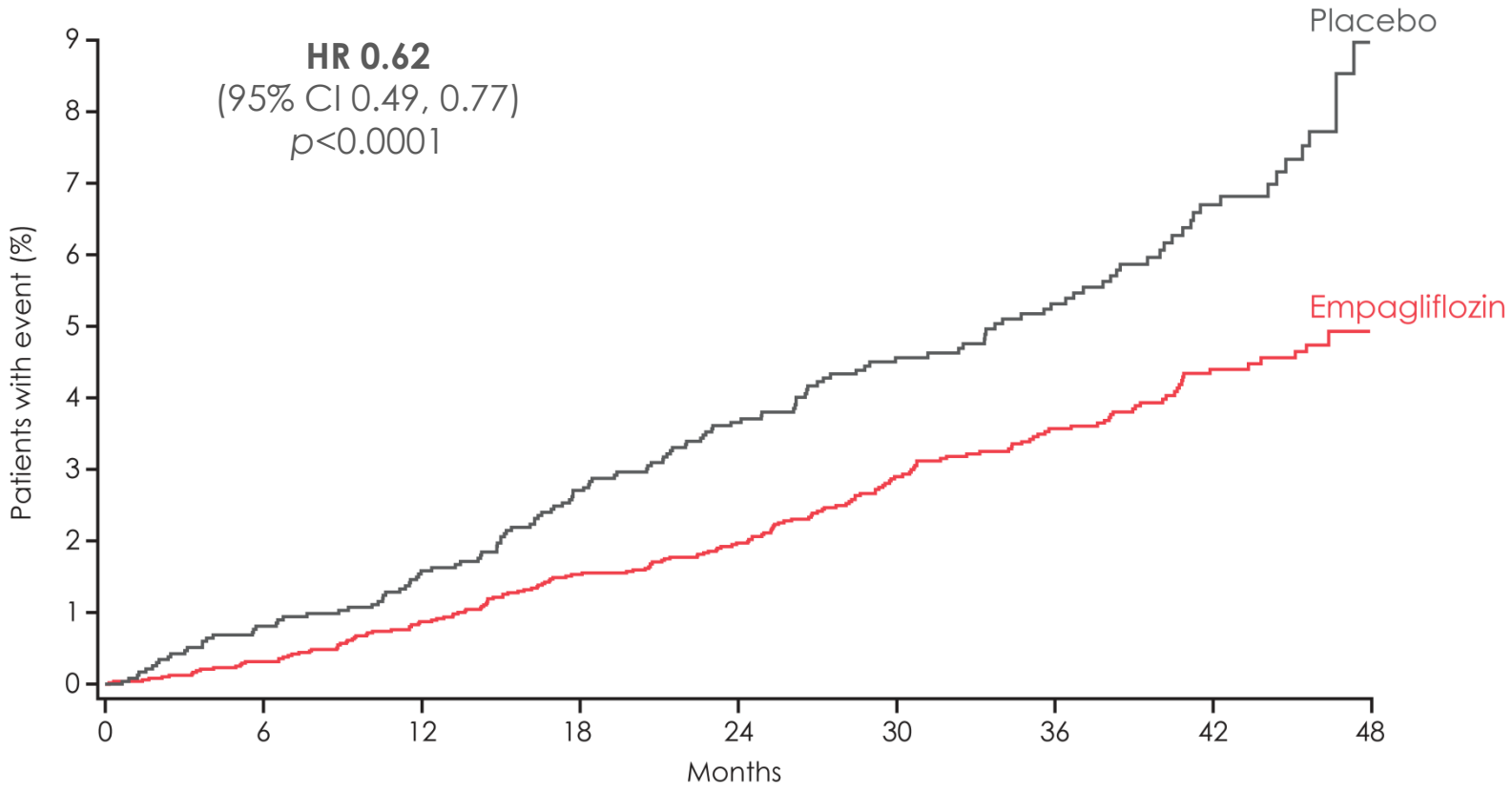
No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

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

EMPA-REG OUTCOME®

CV Death



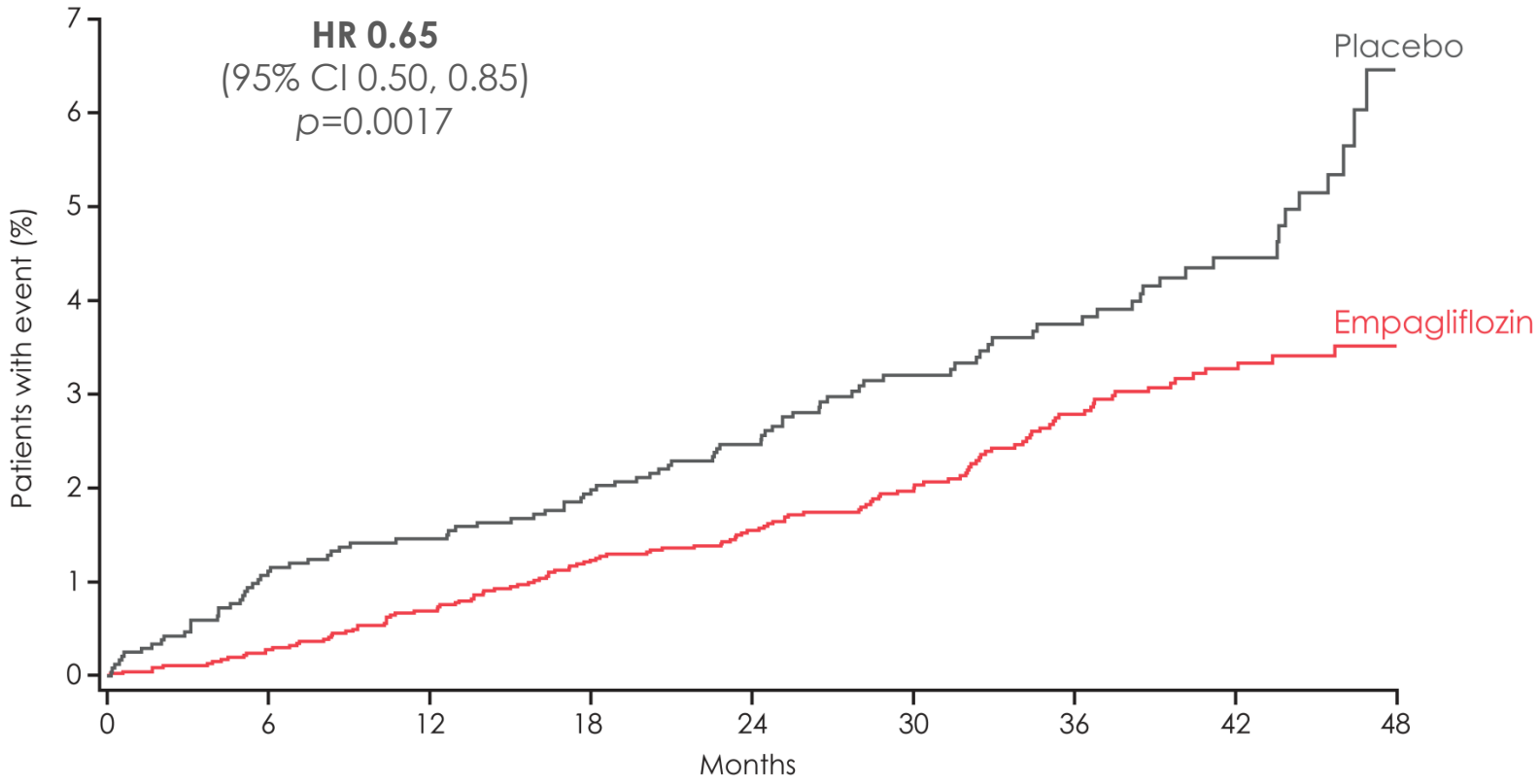
No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function. HR, hazard ratio

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

EMPA-REG OUTCOME®

Hospitalisation for Heart Failure

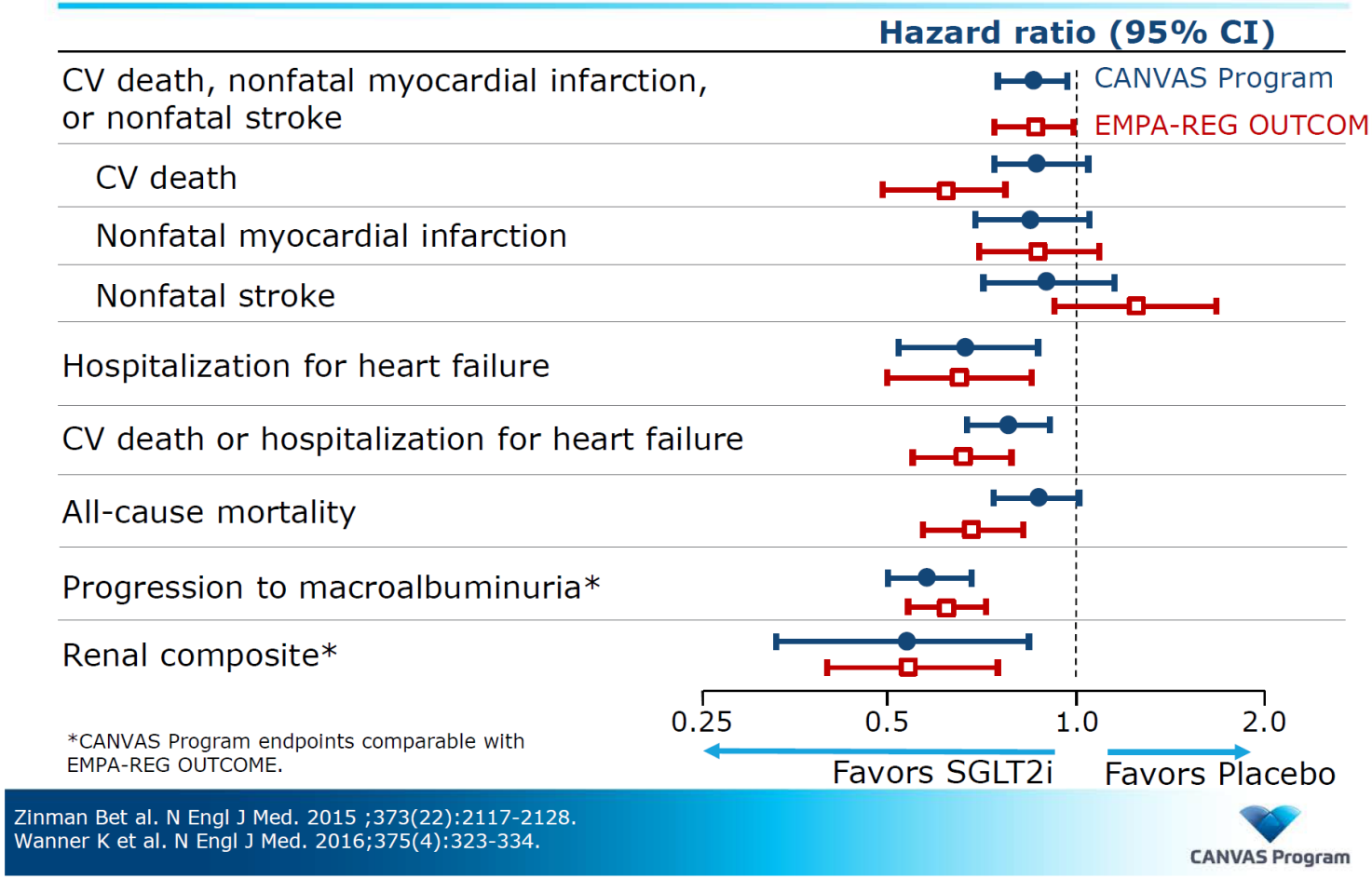


Cumulative incidence function. HR, hazard ratio

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

EMPA-REG OUTCOME®

Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME

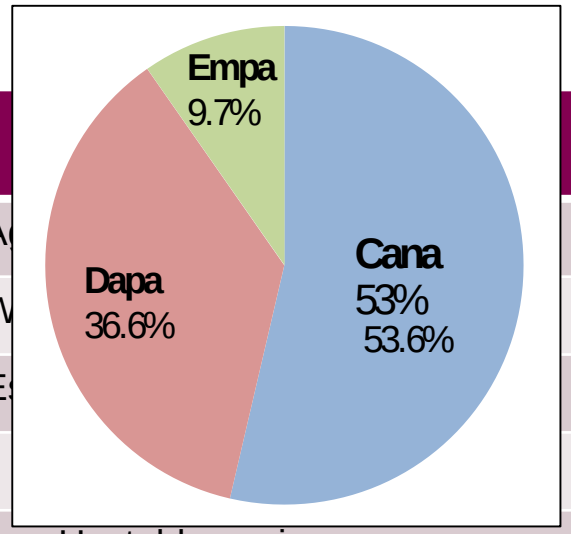


Canagliflozin (SGLT2i) vs. usual care

Empagliflozin (SGLT2i) vs. usual care

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

CVD-REAL: Baseline Characteristics



	SGLT2 inhibitors N=154,523	Other glucose-lowering drugs N=154,523
A(	57.0 (9.9)	57.0 (10.1)
W	68,419 (44.3)	68,770 (44.5)
E	20,043 (13.0)	20,302 (13.1)
	3,792 (2.5)	3,882 (2.5)
Unstable angina	2,529 (1.6)	2,568 (1.7)
Heart failure	4,714 (3.1)	4,759 (3.1)
Atrial fibrillation	5,632 (3.6)	5,698 (3.7)
Stroke	6,347 (4.1)	6,394 (4.1)
Peripheral arterial disease	5,239 (3.4)	5,229 (3.4)
Microvascular disease	42,214 (27.3)	42,221 (27.3)
CKD	3,920 (2.5)	4,170 (2.7)

Data are presented as n (%) unless otherwise stated

[a] Myocardial infarction, unstable angina, stroke, heart failure, transient ischaemic attack, coronary revascularisation or occlusive peripheral artery disease

CKD, chronic kidney disease; CV, cardiovascular; hHF, hospitalisation for heart failure; SD, standard deviation; SGLT2. sodium–glucose co-transporter 2

Kosiborod M, et al. Circulation, 2017

CVD-REAL: Treatment with SGLT2 Inhibitors was Associated with Reductions in hHF vs Other GLDs

Database	N	No of events	HR (95% CI)
US	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2,900	11	0.14 (0.03, 0.68)
Total	**309,056**	**961**	**0.61 (0.51, 0.73)**

***P* value for SGLT2 inhibitor vs other GLD: <0.001**

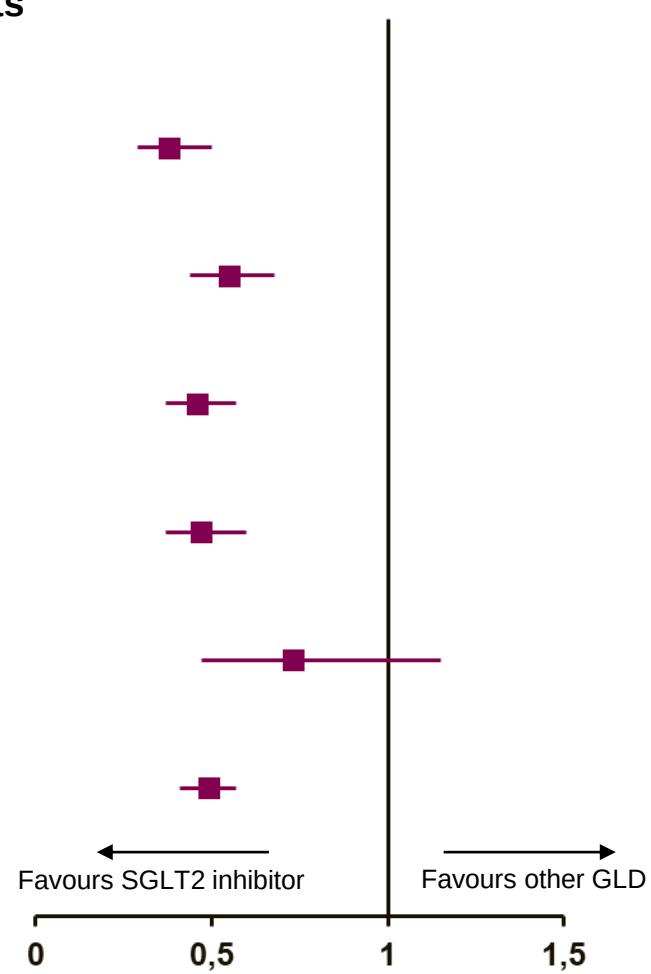
Heterogeneity
P value: 0.17

CI, confidence interval; GLD, glucose-lowering drug; hHF, hospitalisation for heart failure; HR, hazard ratio; SGLT2, sodium–glucose co-transporter 2

Kosiborod M, et al. Circulation, 2017

CVD-REAL: Treatment with SGLT2 Inhibitors was Associated with Reductions in All-cause Death vs Other GLDs

Database	N	No of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	**215,622**	**1334**	**0.49 (0.41, 0.57)**



***P* value for SGLT2 inhibitor vs other GLD: <0.001**

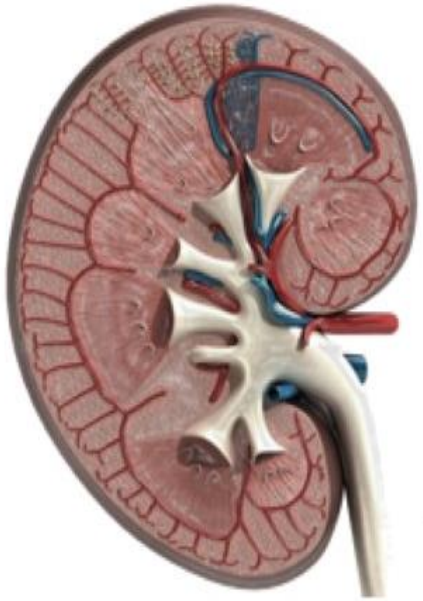
Heterogeneity
P value: 0.09

CI, confidence interval; GLD, glucose-lowering drug; HR, hazard ratio; SGLT2, sodium–glucose co-transporter 2

Kosiborod M, et al. Circulation, 2017

Some Expected Clinical Effects of SGLT2 Inhibition Based on the Mode of Action

SGLT2 Inhibition

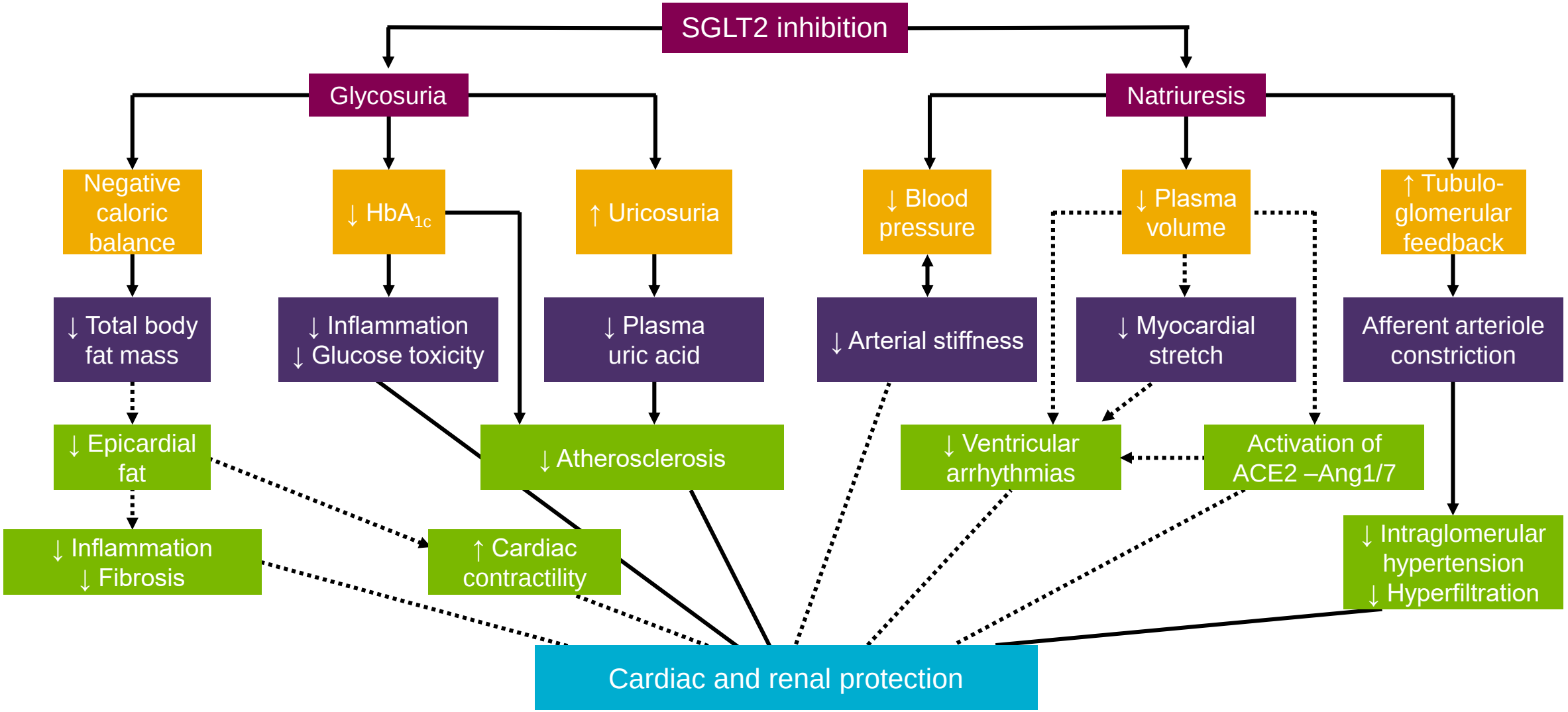


- **Increased glucose excretion**
  - → **Reduced FPG and PPG** → **HbA_{1c} reduction**
  - → **Loss of energy (calories)** → **Weight loss**
- **Increased sodium excretion** → **Reduced sodium load** → **BP reduction**

BP, blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; PPG, post-prandial glucose; SGLT2, sodium–glucose co-transporter 2

Abdul-Ghani MA, et al. *Encocr Rev* 2011;32:515–531

SGLT2 Inhibitors Reduce CVD Risk in a Multifaceted Manner

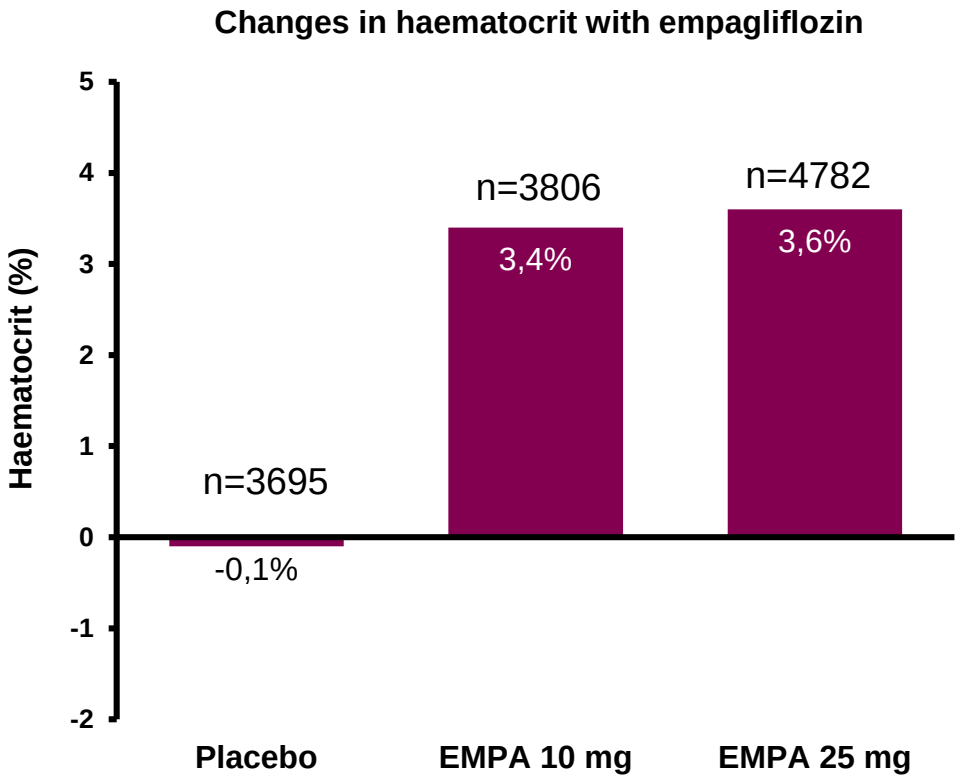


ACE2, angiotensin-converting enzyme-2; Ang 1/7, angiotensin 1/7; CVD, cardiovascular disease; HbA_{1c}, glycated haemoglobin; SGLT2, sodium–glucose co-transporter 2

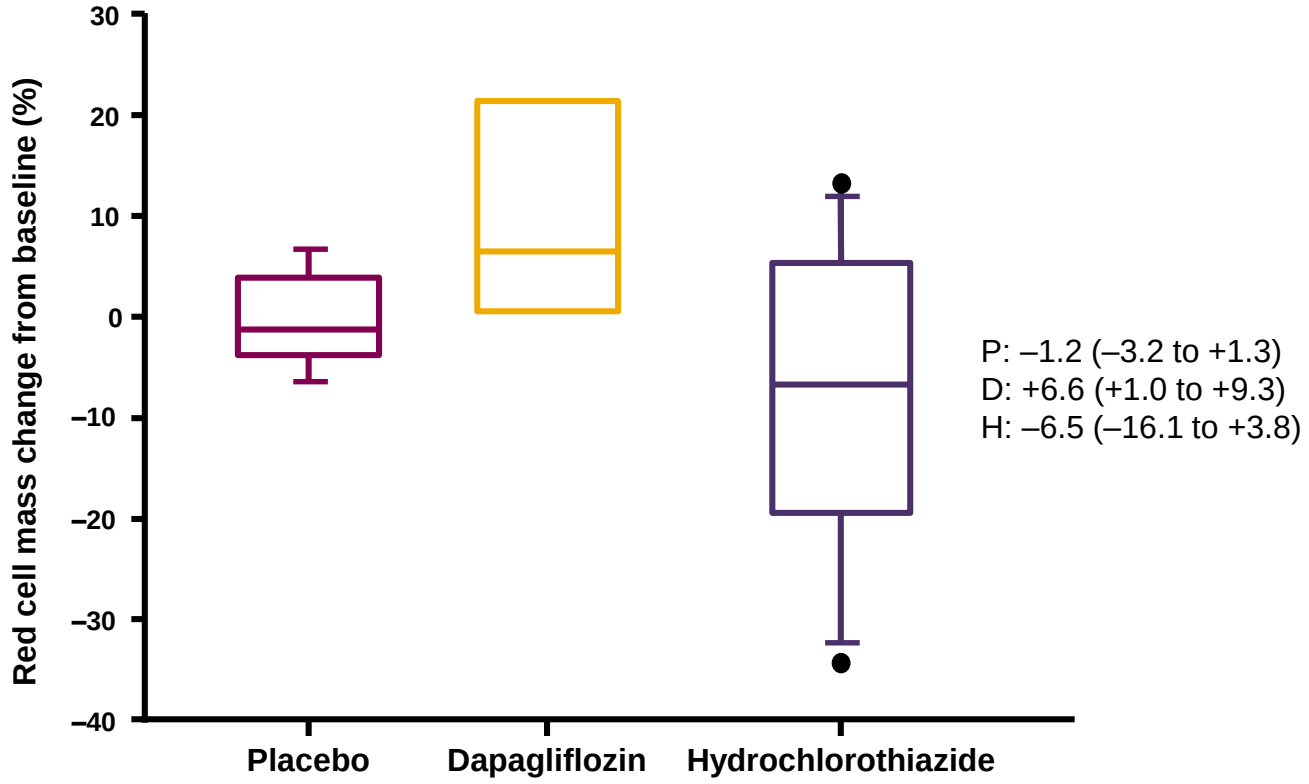
Rajasekeran H, et al. *Kidney Int* 2016;89:524–526

SGLT2 Inhibition is Associated with Increased Haematocrit and RBC Mass Which May Increase Tissue Oxygen Delivery

Pooled data from 17 randomised trials in patients with Type 2 diabetes[1]



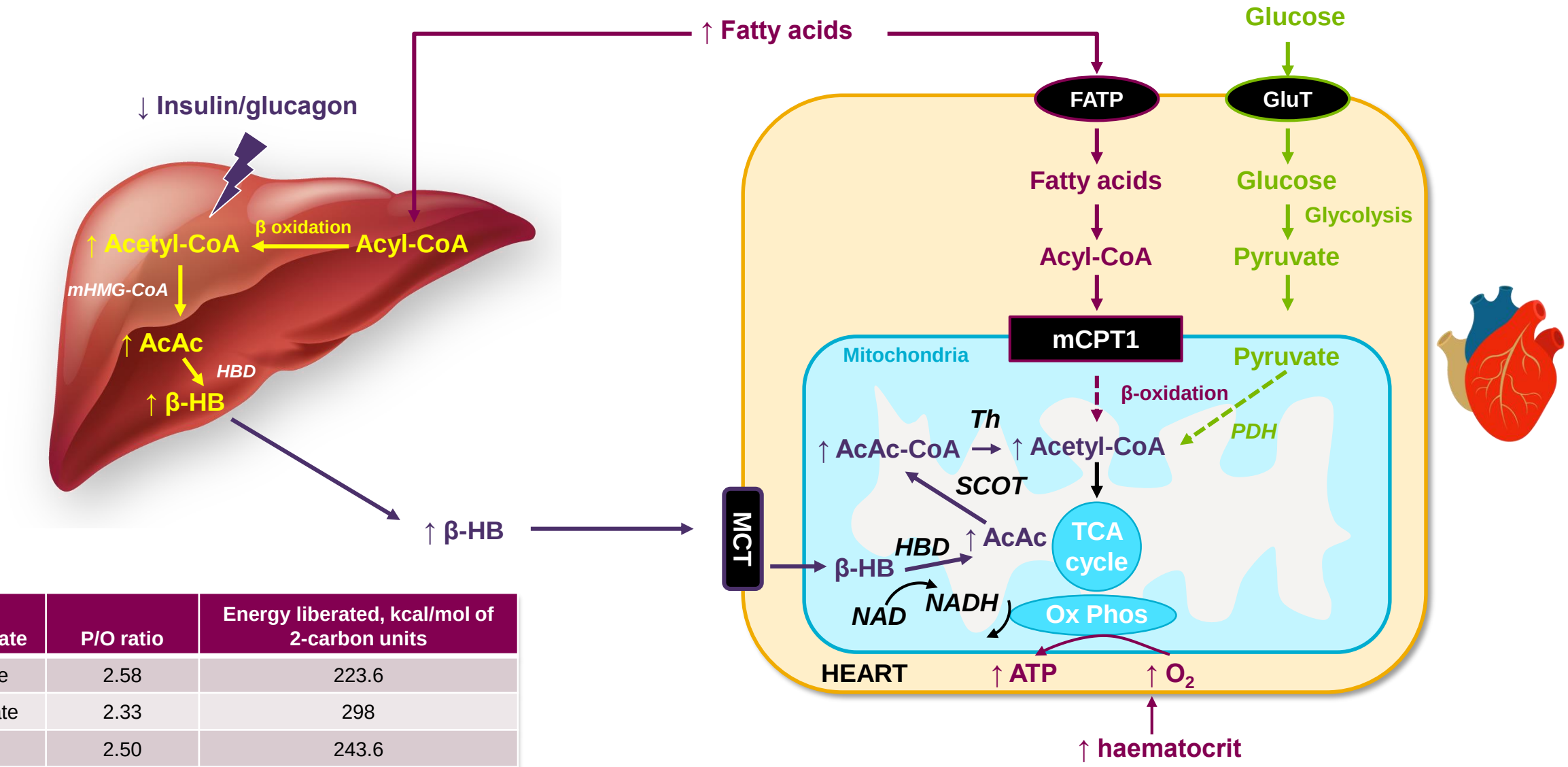
Increased red blood cell mass (~6%) was observed following treatment with dapagliflozin, which may indicate stimulation of erythropoiesis[2]



CV, cardiovascular; EMPA, empagliflozin; SGLT2, sodium–glucose co-transporter 2

1. Kohler S. *Clin Ther* 2016;38:1299–1313; 2. Lambers Heerspink HJ, et al. *Diabetes Obes Metab* 2013;15:853–862

Possible Metabolic Changes with SGLT2 Inhibition



Substrate	P/O ratio	Energy liberated, kcal/mol of 2-carbon units
Glucose	2.58	223.6
Palmitate	2.33	298
β-HB	2.50	243.6

AcAc, acetoacetate; CoA,co-enzyme A; mHMG, mitochondrial 3-hydroxy-3-methylglutaryl synthase; FATP, fatty acid transport protein; β-HB, β-hydroxybutyrate; HBD, β-hydroxybutyrate dehydrogenase; MCT, monocarboxylate transporter; PDH, pyruvate dehydrogenase; SCOT, succinyl-CoA:3-oxoacid CoA transferase; TCA, tricarboxylic acid cycle; Th, thiolase

Adapted from Ferrannini E, et al. *Diabetes Care* 2016;39:1108–1114

CVOT with SGLT2i and GLP-1 RA

EMPA-REG[1]

- Established cardiovascular disease (prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease)

Empagliflozin (SGLT2i) vs. usual care

LEADER[2]

- ≥50 years with pre-existing cardiovascular disease, cerebrovascular disease, vascular disease, or renal or heart failure
- ≥60 years with cardiovascular risk factors

Liraglutide (GLP-1 RA) vs. usual care

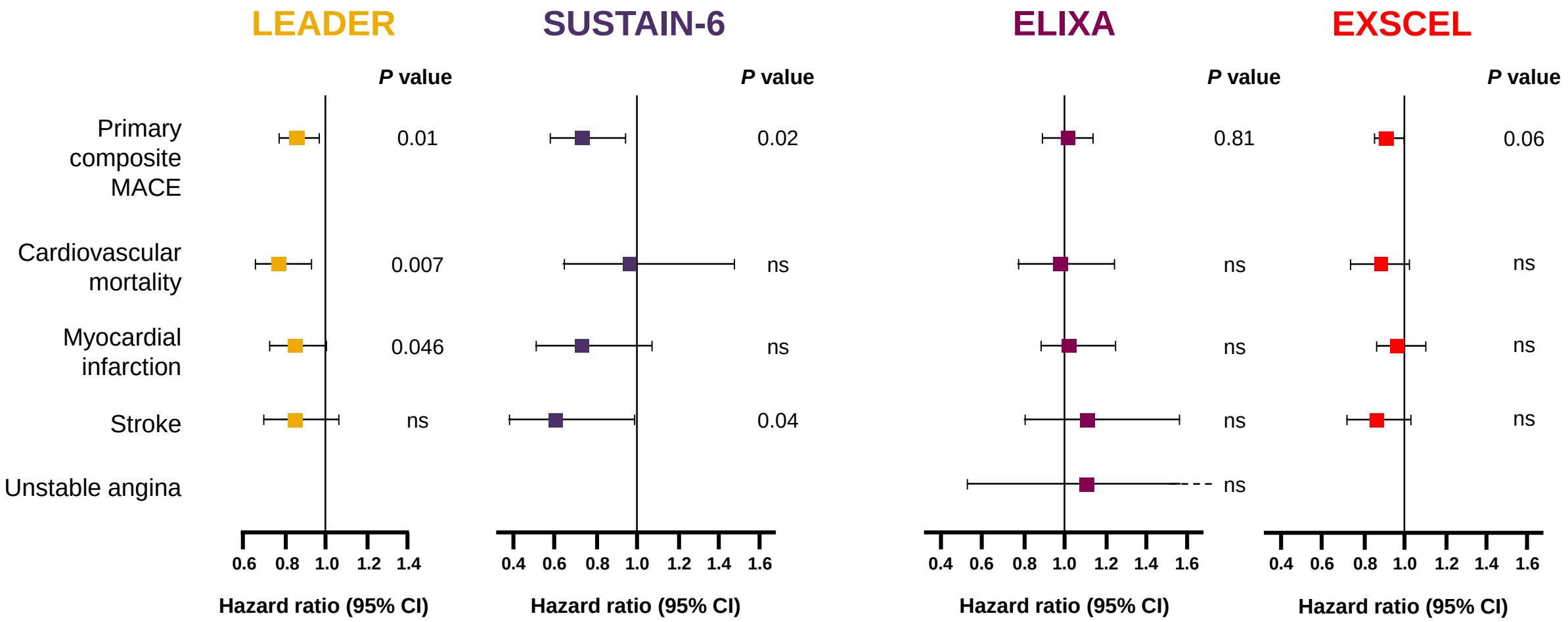
SUSTAIN-6[3]

- ≥50 years with pre-existing cardiovascular disease
- ≥60 years with pre-cardiovascular disease

Semaglutide (GLP-1 RA) vs. usual care

1. Zinman B, et al. *N Engl J Med* 2015;373:2217–2128; 2. Marso SP, et al. *N Engl J Med* 2016;375:311–322; 3. Marso SP, et al. *N Engl J Med* 2016;375:1834–1844

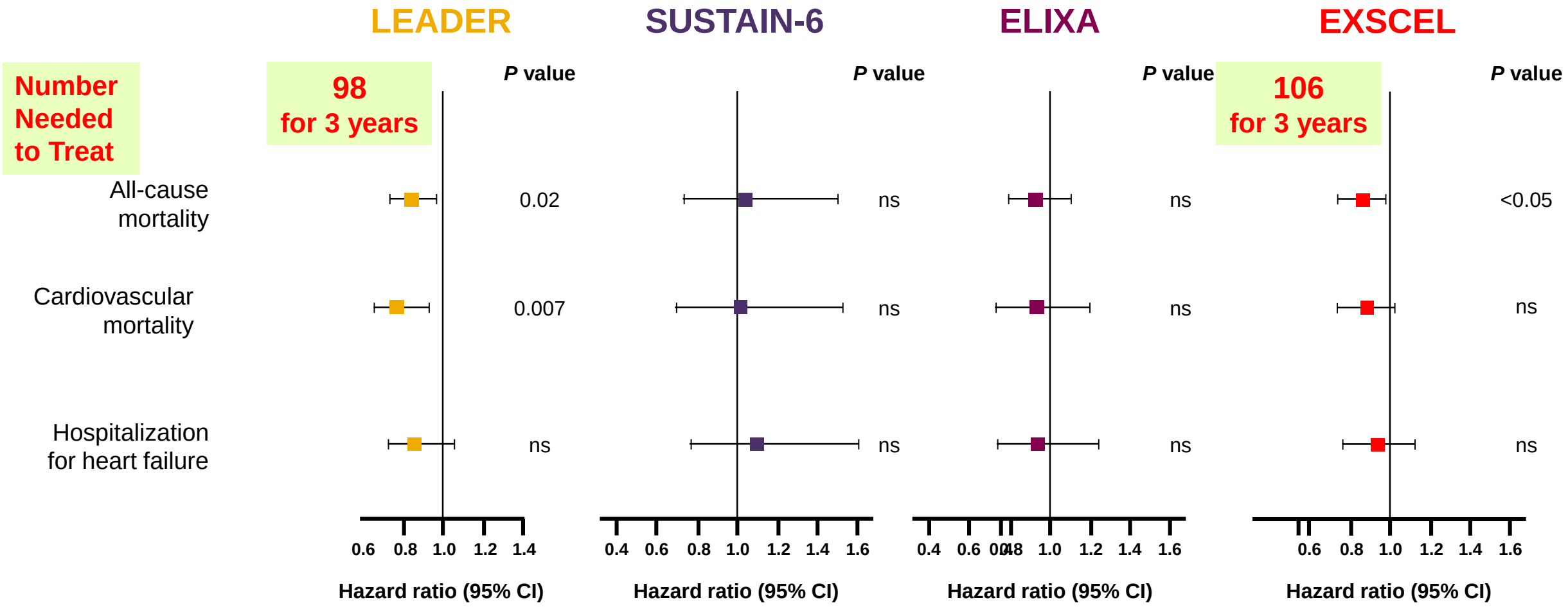
Primary Endpoint and Its Individual Components in LEADER, SUSTAIN-6, ELIXA and EXSCEL



CI, confidence interval; MACE, major adverse cardiovascular event; ns, not significant.

Adapted from Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; Marso SP, et al., *N Engl J Med* 2016;375:311-22; Marso SP, et al., *N Engl J Med* 2016 375:1834-1844; Holman RR et al., *N Engl J Med,* in press.

All-Cause Mortality and Hospitalization for Heart Failure in LEADER, SUSTAIN-6, ELIXA and EXSCEL



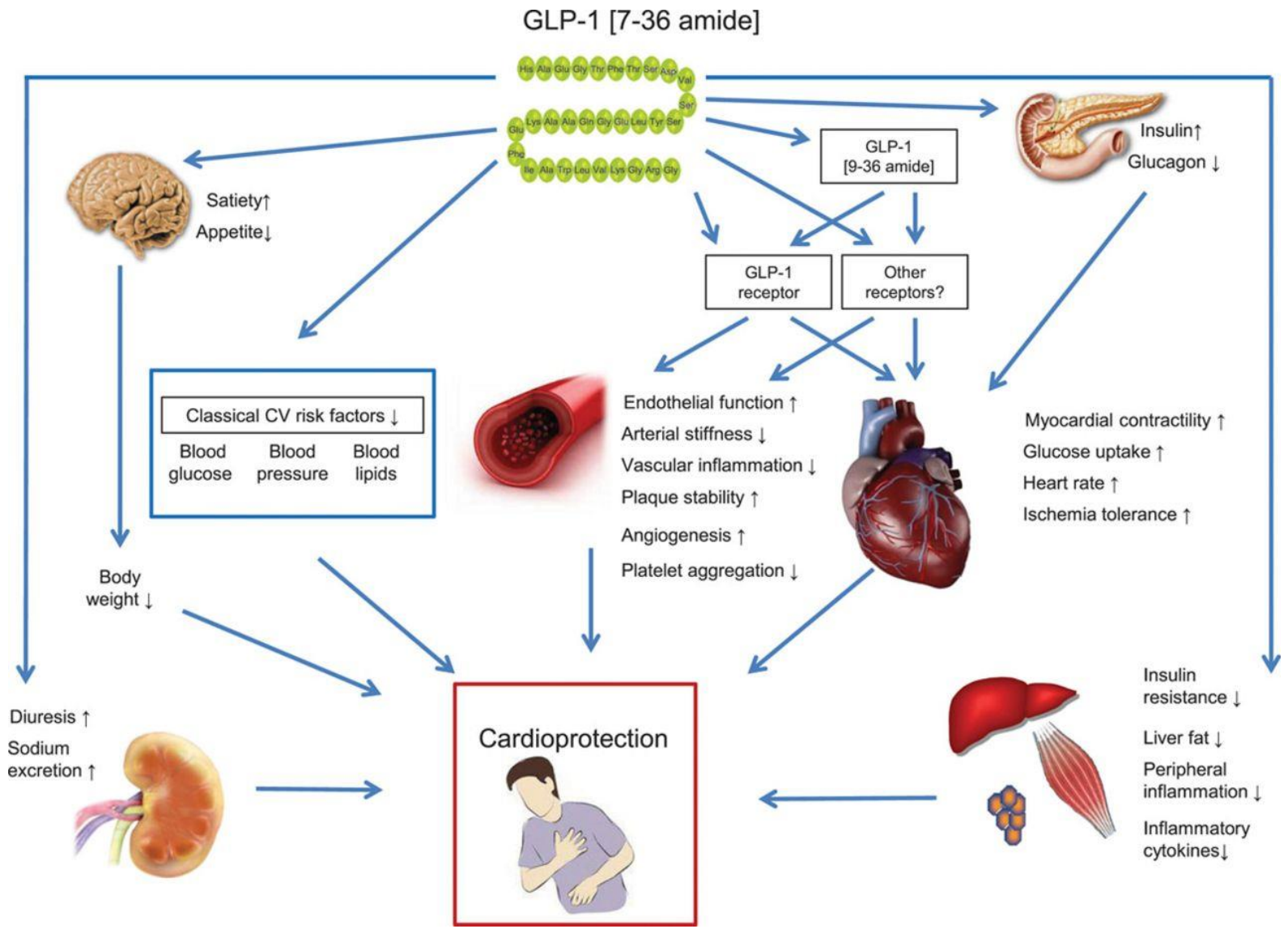
CI, confidence interval; MACE, major adverse cardiovascular event; NNT, number needed to treat; ns, not significant.
Adapted from Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; Marso SP, et al., *N Engl J Med* 2016;375:311-22; Marso SP, et al., *N Engl J Med* 2016 375:1834-1844; Holman RR et al.,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

Characteristics and Outcomes of CV Outcome Studies of More Intensive Glucose Lowering

Study	N	Follow-up (yr)	Age (yr)	Diabetes duration (yr)	CVD history (%)	HbA_{1c} (%) difference between arms	Primary endpoint	Primary endpoint HR (95% CI)	All-cause mortality HR (95% CI)
ACCORD	10,251	3.5	62	10	35	1.1	MACE	0.90 (0.78-1.04)	1.22 (1.01-1.46)
ADVANCE	11,140	5.0	66	8	32	0.8	MACE	0.94 (0.84-1.06)	0.93 (0.83-1.06)
VADT	1,791	5.6	60	12	40	1.5	MACE + HF, vascular surgery, new, ischemic amputation	0.88 (0.74-1.05)	1.07 (0.81-1.42)
UKPDS	3,867	10	54	0	2	0.9	MI	0.84 (0.71-1.00)	0.94 (0.80-1.10)
LEADER	9,340	3.8	64	13	81	0.4	MACE	0.87 (0.78–0.97)	0.85 (0.74–0.97)
EXSCEL	14,752	3.2	63	12	73.1	0.53	MACE	0.91 (0.83-1.00)	0.86 (0.77-0.97)

CVD, cardiovascular disease; HR, hazard ratio, CI, confidence intervals; MACE, CV-death + non-fatal MI or stroke; MI, myocardial infarction; HF, heart failure.
Adapted from Giorgino F. et al., *Diabetes Care* 39 Suppl 2:S187-95, 2016.

Mechanisms Mediating a Beneficial Effect of GLP-1R Activation on Cardioprotection



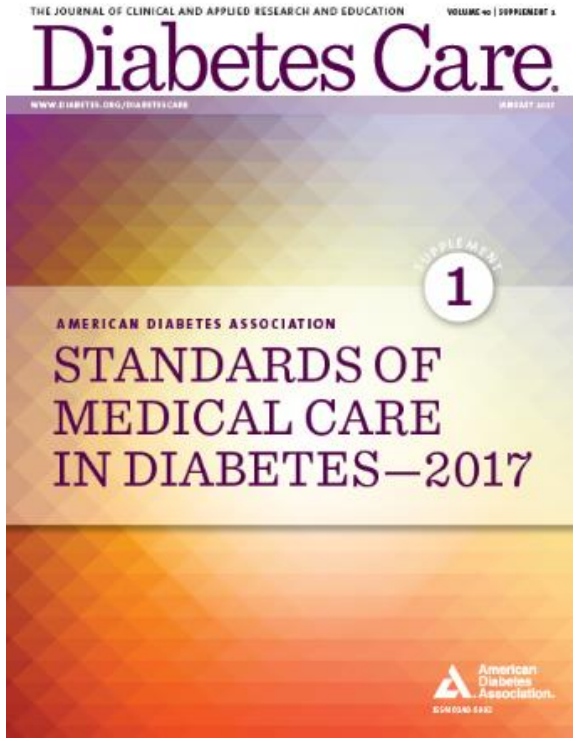
Adapted from Nauck MA, et al., *Circulation* 2017;136:849-870

Effects of GLP-1 or GLP-1 Receptor Agonists in Human Studies, with Potential Impact on Cardiovascular Function

Effect	GLP-1 [7-36 amide or 7-37]	Liraglutide	Exenatide
Cardioprotection against ischemia	↑ LVEF; ↑ regional wall motility	preserved LVEF after PCI/NSTEMI	↑ salvage index after STEMI; ↓ infarct size
Angiogenesis, ECs Proliferation CPCs survival	New vessel formation from ECs; ↓ CPCs apoptosis by oxidative stress	Not reported	Proliferation of coronary artery ECs; ↓ CPCs apoptosis by saturated fatty acids
Endothelium-dependent vasodilation (NO production)	↑ eNOS in HUVECs; ↑ ACh–induced vasodilation (healthy subjects and T2D with stable CAD)	↓ TNFα-induced oxidative stress in HUVECs; ↑ eNOS; ↑ ACh–induced forearm blood flow (ns)	↑ eNOS in HUVECs; ↑ postprandial endothelial function
Inflammatory cytokines in mononuclear cells	↓ IL-6	↓ TNFα, ↓ IL-1s, ↓ IL-6	↓ TNFα, ↓ IL-1s, etc.
C-reactive protein	Not reported	↓ by 23%	↓ by 61%

ACh, acethylcholine; CPC, cardiac progenitor cell; EC, endothelial cell; HUVEC, human umbilical vein endothelial cell; IL, interleukin; LVEF, left ventricular ejection fraction; NOS, nitric oxide synthase; NSTEMI, non ST-elevated myocardial infarction; PCI, primary coronary intervention; T2D, type 2 diabetics; TNF, tumour necrosis factor..
Adapted from Nauck MA, et al., *Circulation* 2017;136:849-870

ADA Standards of Medical Care in Diabetes 2017



In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, **empagliflozin or liraglutide** should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes. **B**

Why Glucose Is the Most Important Target for CV Prevention in Diabetes

- **Correction of hyperglycemia results in reduced CV outcomes if it is early/timely, sustained, and «safe» (e.g., w/o hypoglycemia)**
- **New drugs that target glucose metabolism (i.e., SGLT2i) greatly benefit the CV system**
- **Pleiotropic properties of specific anti-diabetes medications (e.g., GLP-1 RA) could mediate the observed reduction in CV outcomes and all-cause death**