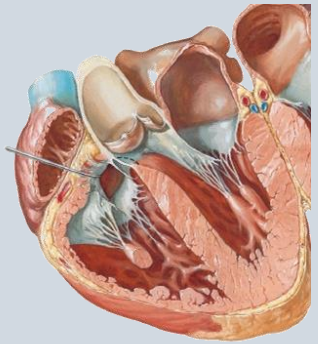
What everyone needs to know about the heart in diabetes – 2024



December 19, 2024 Live Webinar, 12:00 pm – 1:30 pm PST
Directly Provided CME/CE Activity by L.A. Care Health Plan

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Financial Disclosures

The following CME Planner do not have relevant financial relationships with ineligible companies in the past 24 months.

- Leilanie Mercurio, L.A. Care Provider Continuing Education Program Manager, CME Planner.

The following ineligible companies have relevant financial relationships with CME Planner and Presenter Karol Watson, MD, PhD, FACC, Director of the UCLA Barbra Streisand Women's Heart Health Program, Co- Director of the UCLA Program in Preventative Cardiology, and Director of the UCLA Fellowship Program in Cardiovascular Diseases.

- Amgen, Boehringer Ingelheim, Lilly, Novartis.

Dr. Karol Watson is a Consultant of all companies listed here.

All relevant financial relationships of Dr. Karol Watson, CME Planner and Faculty, with ineligible companies have been mitigated.

An ineligible company is any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Commercial support was not received for this CME/CE activity.

Learning Objectives

At the completion of the CME / CE activity, learners can:

a) Identify the link between diabetes and cardiovascular disease (CVD).

b) List two (2) therapies proven to prevent CVD in patients with diabetes.

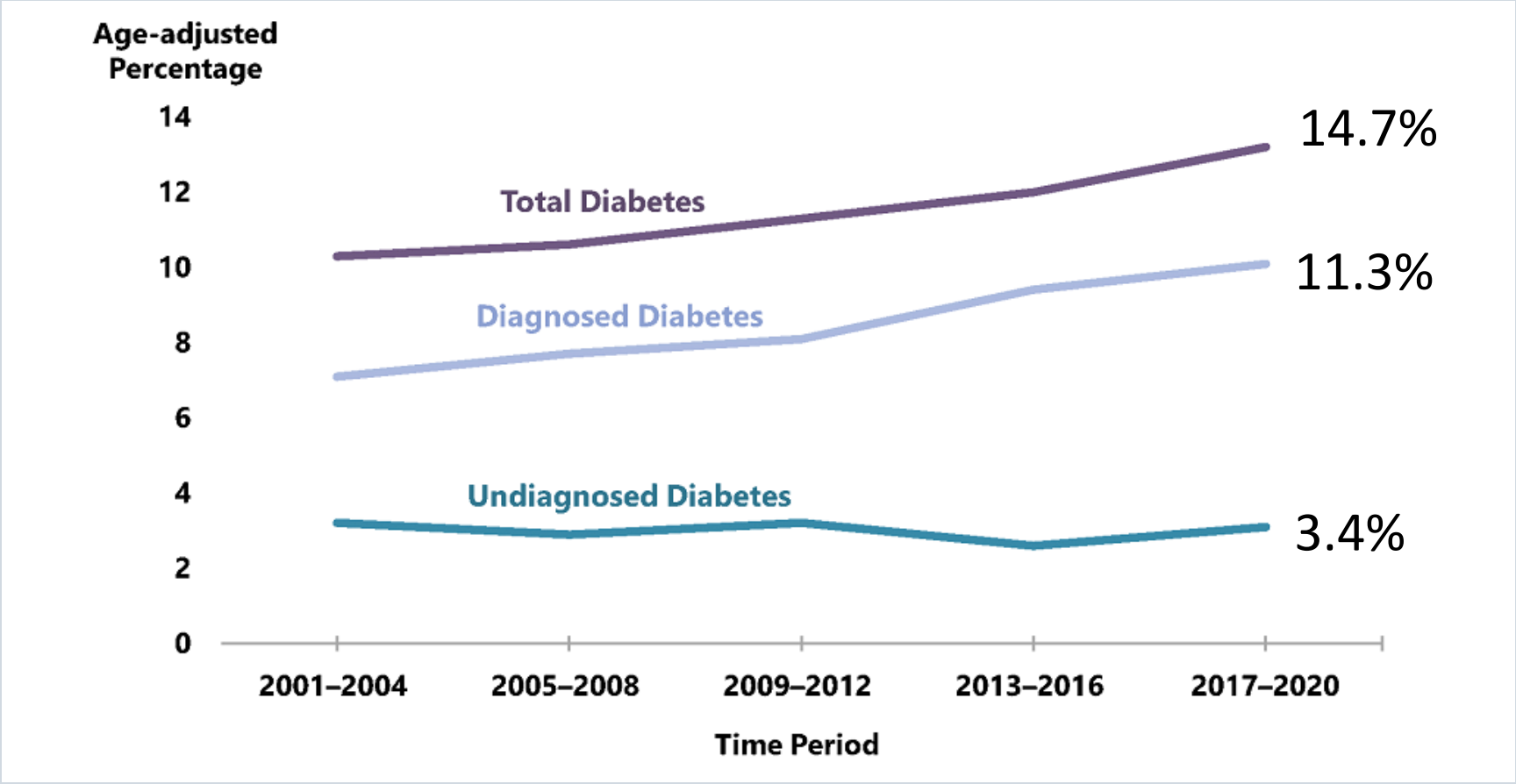
c) Specify two (2) new diabetes drugs that fit in with other therapies for cardiovascular risk reduction.

d) Specify the role of SGLT2 inhibitors and GLP1-RAs in reducing CV events in diabetics.

e) Discuss the role of diabetes therapies in heart failure management.

1. Most cardiac patients have diabetes, pre-diabetes, metabolic syndrome, or insulin resistance

Diabetes Prevalence



https://www.cdc.gov/diabetes/data/statistics-report/diagnosed-undiagnosed-diabetes.html

Many of your patient have diabetes risk

- **Total:** An estimated 34.2 million people have diabetes (10.5 % of the U.S. population). Many of them are undiagnosed
- An estimated 88 million adults ages 18 years or older (34.5 percent of U.S. adults) have **prediabetes**. This includes
  - 24.3 % of all U.S. adults
  - 41.7 % of U.S. adults 45 to 64 years
  - 46.6 % of U.S. adults 65 or older

Diabetes is overrepresented in CVD populations

- Nearly half of patients seen in cardiovascular clinics have
  - Diabetes
  - Pre-diabetes
  - Metabolic syndrome
  - Insulin resistance
- Unrecognized prediabetes and T2D can be identified in 1 in 3 referrals for elective angioplasty, and these patients have more than a 2-fold increased risk for adverse CV events

Mancini et al. Can J Cardiol vol 33, issue 3, Marcy 2017p pg 355-377

Baseline Characteristics of the ISCHEMIA Trial

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Invasive Strategy (N = 2588)	Conservative Strategy (N = 2591)	Total (N = 5179)
Median age (IQR) — yr	64 (58–70)	64 (58–70)	64 (58–70)
Male sex — no. (%)	1982 (76.6)	2029 (78.3)	4011 (77.4)
Race or ethnic group — no./total no. (%)†			
White	1706/2569 (66.4)	1697/2560 (66.3)	3403/5129 (66.3)
Black	96/2569 (3.7)	108/2560 (4.2)	204/5129 (4.0)
Asian	747/2569 (29.1)	738/2560 (28.8)	1485/5129 (29.0)
Hispanic or Latino	372/2402 (15.5)	391/2413 (16.2)	4815 (15.8)
Other or multiple ethnic groups	20/2569 (0.8)	17/2560 (0.7)	37/5129 (0.7)
Hypertension — no./total no. (%)	1894/2579 (73.4)	1895/2582 (73.4)	3789/5161 (73.4)
Diabetes — no. (%)	1071 (41.4)	1093 (42.2)	2164 (41.8)
Use of insulin — no. (%)	239 (9.2)	253 (9.8)	492 (9.5)
Cigarette smoking — no./total no. (%)			
Never smoked	1119/2587 (43.3)	1089/2587 (42.1)	2208/5174 (42.7)
Former smoker	1149/2587 (44.4)	1177/2587 (45.5)	2326/5174 (45.0)
Current sr			
Family histon total n			
Previous myo			
Previous PCI — no./total no. (%)	551/2586 (21.3)	499/2589 (19.3)	1050/5175 (20.3)
Previous CABG — no./total no. (%)	110/2588 (4.3)	93/2591 (3.6)	203/5179 (3.9)
Cardiac catheterization — no./total no. (%)			
Before enrollment	979/2588 (37.8)	925/2591 (35.7)	1904/5179 (36.8)
Before enrollment and ≤12 mo before randomization	338/2504 (13.5)	329/2503 (13.1)	667/5007 (13.3)
CCTA — no./total no. (%)			
Before enrollment	178/2585 (6.9)	175/2588 (6.8)	353/5173 (6.8)
Before enrollment and ≤12 mo before randomization	127/2573 (4.9)	126/2576 (4.9)	253/5149 (4.9)
Heart failure — no. (%)			
History	112 (4.3)	94 (3.6)	206 (4.0)
Previous hospitalization	27 (1.0)	30 (1.2)	57 (1.1)
Median ejection fraction (IQR) — %	60 (55–65)	60 (55–65)	60 (55–65)
History of atrial fibrillation or atrial flutter — no./total no. (%)	128/2587 (4.9)	93/2586 (3.6)	221/5173 (4.3)
Previous stroke — no./total no. (%)	83/2587 (3.2)	68/2591 (2.6)	151/5178 (2.9)
History of cerebrovascular disease — no./total no. (%)‡	201/2582 (7.8)	176/2583 (6.8)	377/5165 (7.3)
History of peripheral-artery disease — no./total no. (%)	116/2585 (4.5)	88/2583 (3.4)	204/5168 (3.9)
Angina			
History — no./total no. (%)	2329/2588 (90.0)	2312/2591 (89.2)	4641/5179 (89.6)
Began or became more frequent within previous 3 mo — no./total no. (%)	680/2584 (26.3)	675/2583 (26.1)	1355/5167 (26.2)
New onset within previous 3 mo — no./total no. (%)	415/2452 (16.9)	440/2466 (17.8)	855/4918 (17.4)
SAQ Angina Frequency score§	80.7±20.0	82.1±19.2	81.4±19.6
Daily or weekly angina — no./total no. (%)§	502/2314 (21.7)	442/2333 (18.9)	944/4647 (20.3)
Angina several times per mo — no./total no. (%)§	1018/2314 (44.0)	1039/2333 (44.5)	2057/4647 (44.3)
No angina in previous 4 wk — no./total no. (%)§	794/2314 (34.3)	852/2333 (36.5)	1646/4647 (35.4)

Diabetes 41.4% 42.2%

Maron DJ et al. N Engl J Med 2020;382:1395-1407

Baseline Characteristics of the SYNTAX Trial

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	PCI (N=903)	CABG (N=897)	P Value
Age — yr	65.2±9.7	65.0±9.8	0.55
Male sex — %	76.4	78.9	0.20
Body-mass index†	28.1±4.8	27.9±4.5	0.37
Medically treated diabetes — %‡			
Any	25.6	24.6	0.64
Requiring insulin	9.9	10.4	0.72
			0.86
			0.06
Previous myocardial infarction — %	31.9	33.8	0.39
			0.33
			0.46
Blood pressure ≥130/85 mm Hg — %	68.9	64.0	0.03
Congestive heart failure — %	4.0	5.3	0.18
Carotid artery disease — %	8.1	8.4	0.83
Hyperlipidemia — %	78.7	77.2	0.44
Triglycerides ≥150 mg/dl (1.7 mmol/liter) — %	32.3	38.7	0.007
HDL cholesterol <40 mg/dl (1.0 mmol/liter) for men or <50 mg/dl (1.3 mmol/liter) for women — %	46.2	52.5	0.01
Angina — %			
Stable	56.9	57.2	0.91
Unstable	28.9	28.0	0.66
Ejection fraction <30% — %	1.3	2.5	0.08
euroSCORE value	3.8±2.6	3.8±2.7	0.78
Parsonnet score	8.5±7.0	8.4±6.8	0.76
SYNTAX score	28.4±11.5	29.1±11.4	0.19
No. of lesions	4.3±1.8	4.4±1.8	0.44
Total occlusion — %	24.2	22.2	0.33
Bifurcation — %	72.4	73.3	0.67
Time to procedure — days	6.9±13.0	17.4±28.0	<0.001
Procedure duration — hr	1.7±0.9	3.4±1.1	<0.001
Postprocedural hospital stay — days	3.4±4.5	9.5±8.0	<0.001
Complete revascularization — %	56.7	63.2	0.005

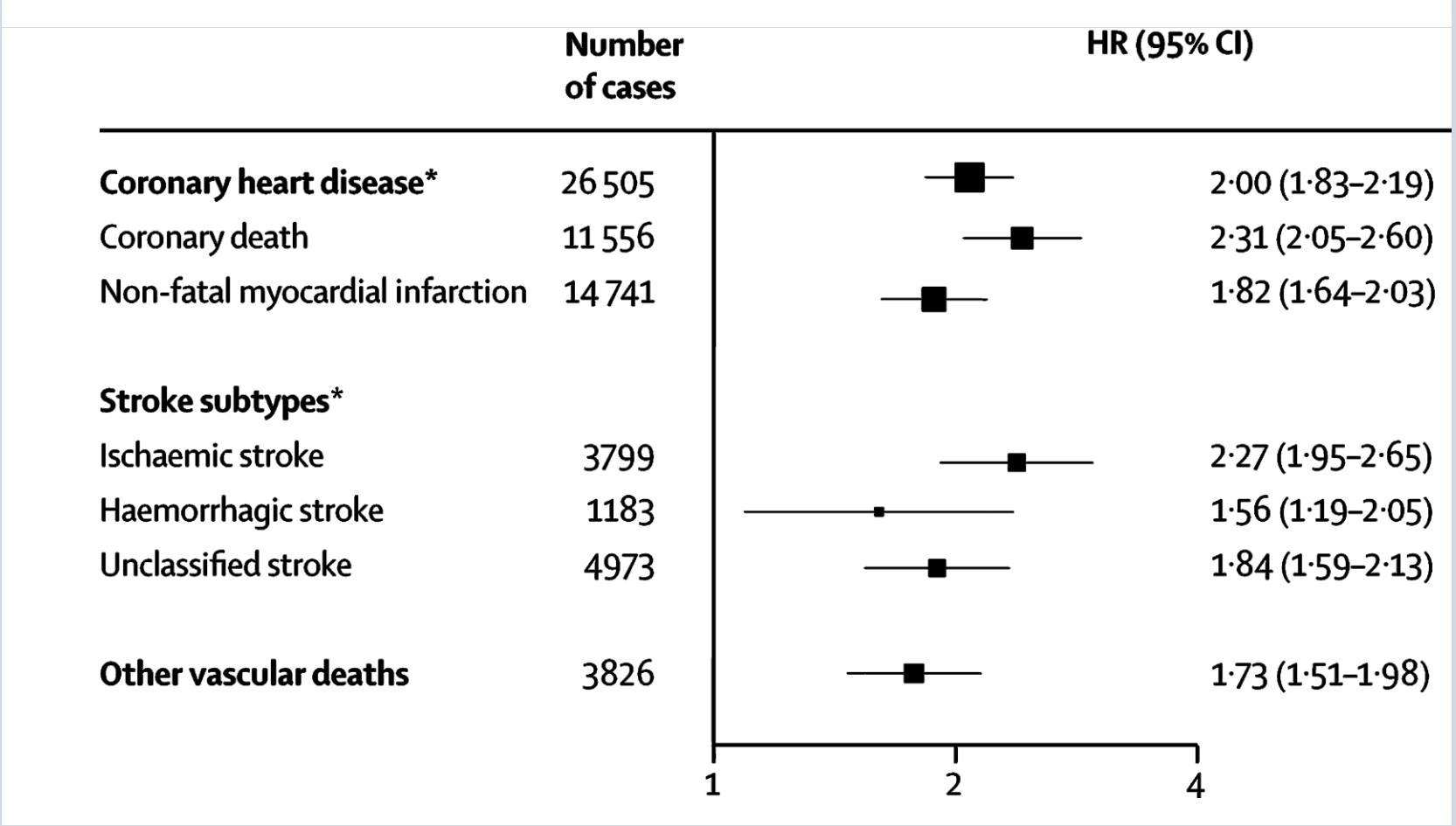
Diabetes 25.6% 24.6%

Metabolic syndrome 46.0% 45.5%

Maron DJ et al. N Engl J Med 2020;382:1395-1407

2. Diabetes is bad for everyone, but especially for women and younger patients

Vascular Outcomes in patients with Diabetes (as compared to those without)



Adjusted for age, smoking, BMI and SBP

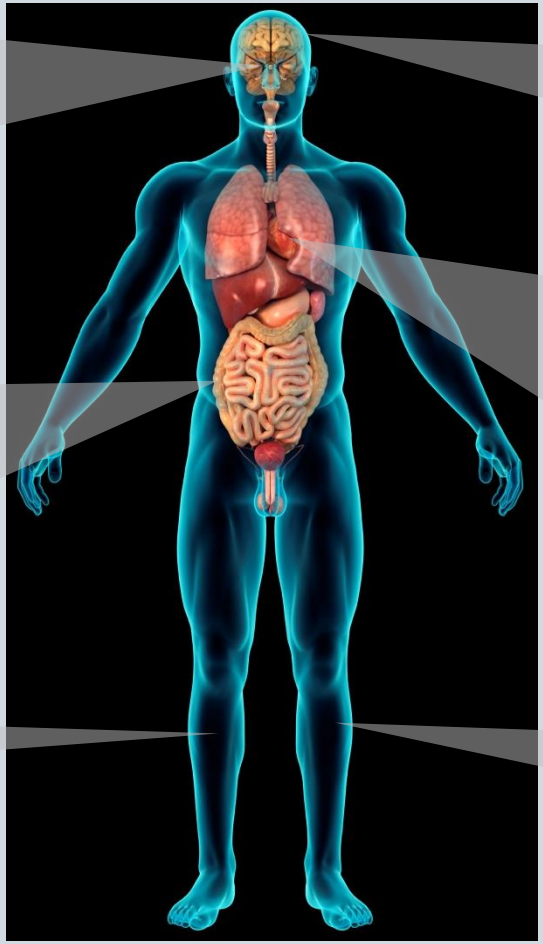
World Health Organisation 2016; Sarwar N. Lancet 2010

Microvascular Complications

Diabetic Retinopathy
Leading cause of blindness in working-age adults[1]

Diabetic Nephropathy
Leading cause of end-stage renal disease[2]

Diabetic Neuropathy
Leading cause of nontraumatic lower extremity amputations[3]



Macrovascular Complications

Stroke
2- to 4-fold increase in cardiovascular mortality and stroke[4,5]

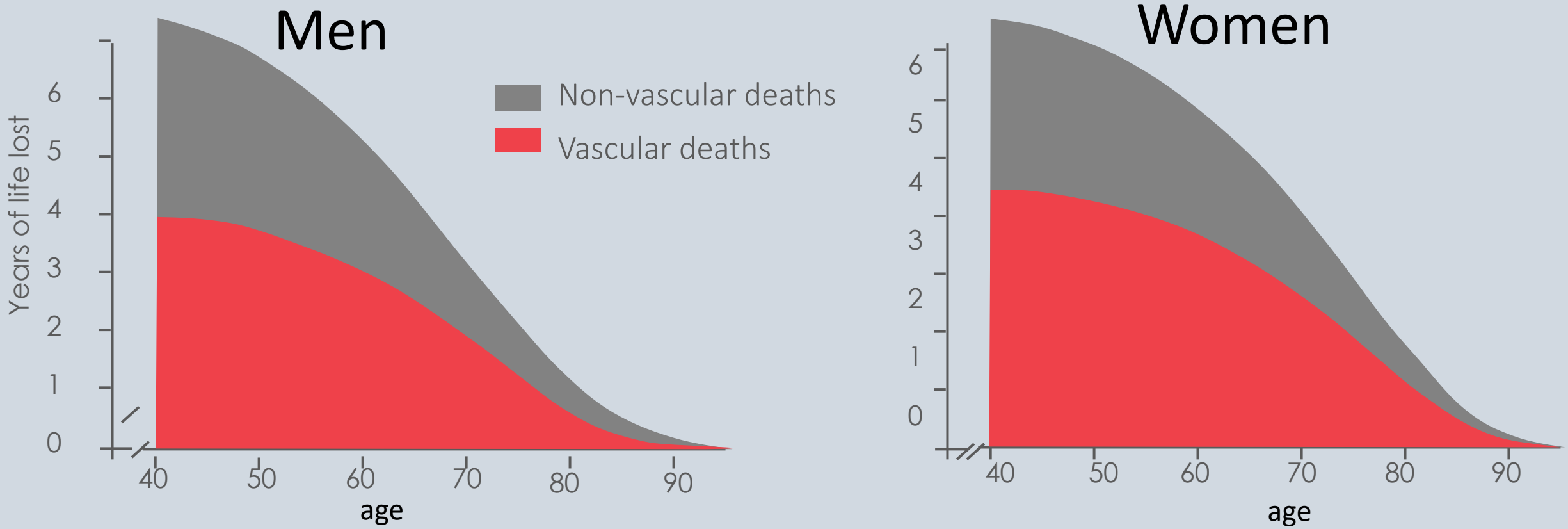
Heart Disease[6]
2-4 fold increase in ASCVD

6-10 fold increase in Heart failure

Peripheral Arterial Disease[6]
4-10 X increased risk

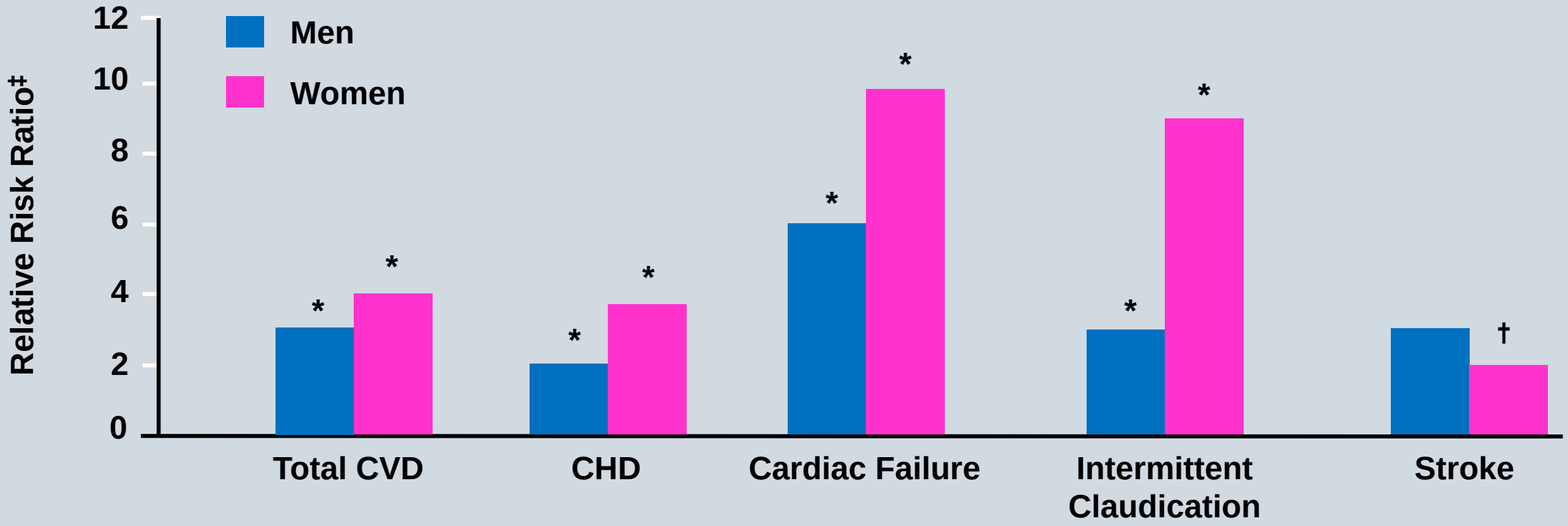
1. IDF. Fact Sheet Diabetes and Eye Disease. 2. The Renal Association. UK Renal Registry. Twelfth Annual Report. December 2009. 3. Dang, CN., Boulton, AJ., International Journal of Lower Extremity Wounds. 2003; 2(1):4-12. 4. Jeerakathil, T., et al. Stroke. 2007;38(6):1739-43. 5. Kaul, S., et al. Circulation. 2010;121:1868-77. 6. IDF. Fact sheet: Diabetes and Cardiovascular Disease (CVD).

Diabetes is associated with substantial mortality



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

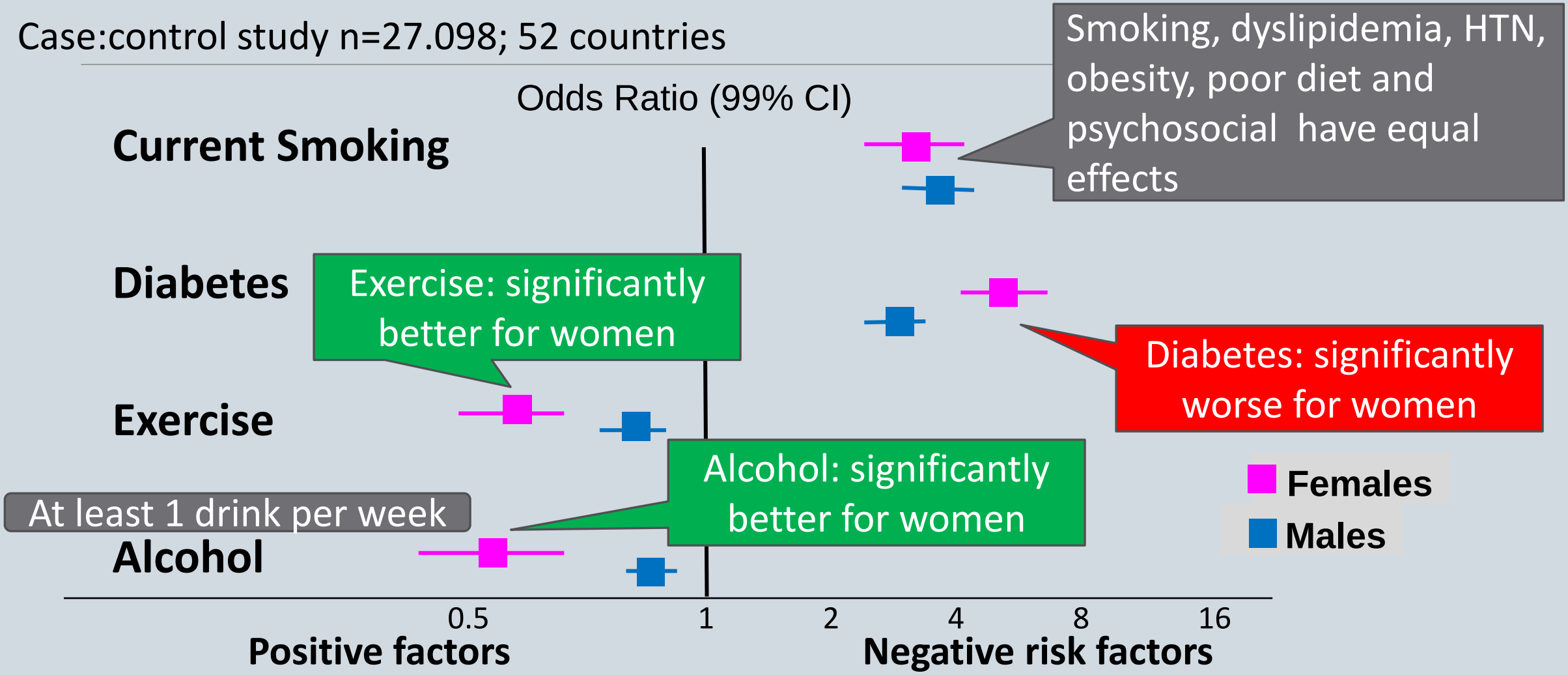
CVD Events in Patients With Diabetes: Framingham 30-Year Follow-Up



Wilson et al. In: Ruderman et al, eds. *Hyperglycemia, Diabetes, and Vascular Disease*. 1992:21-29.

INTERHEART: Risk Factors Significance by Sex

Case:control study n=27.098; 52 countries

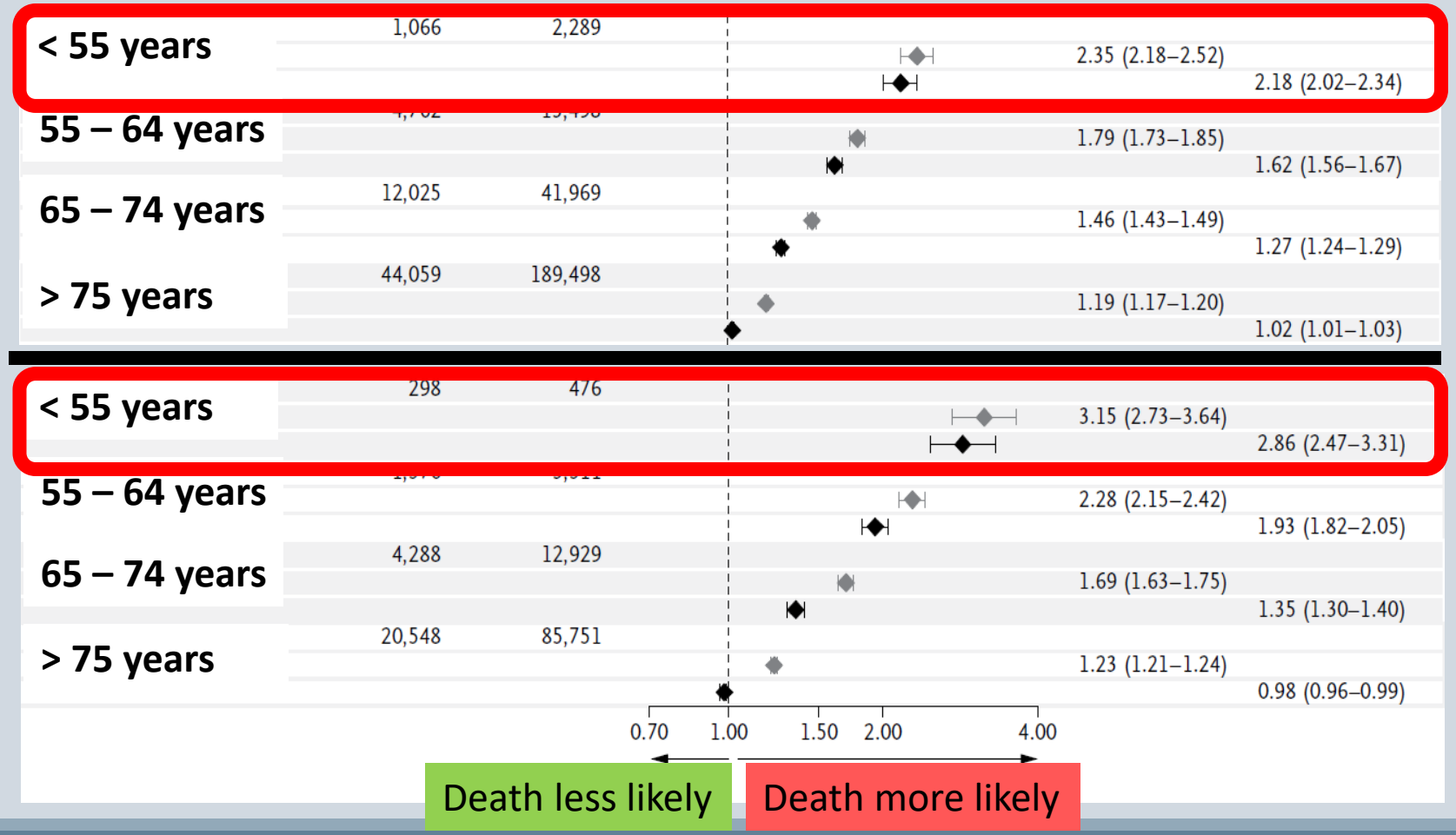


Yusuf S, et al., *Lancet* 2004; 364: 937-52

Adjusted Hazard Ratios for Total and Cardiovascular Mortality in T2DM

Total Mortality

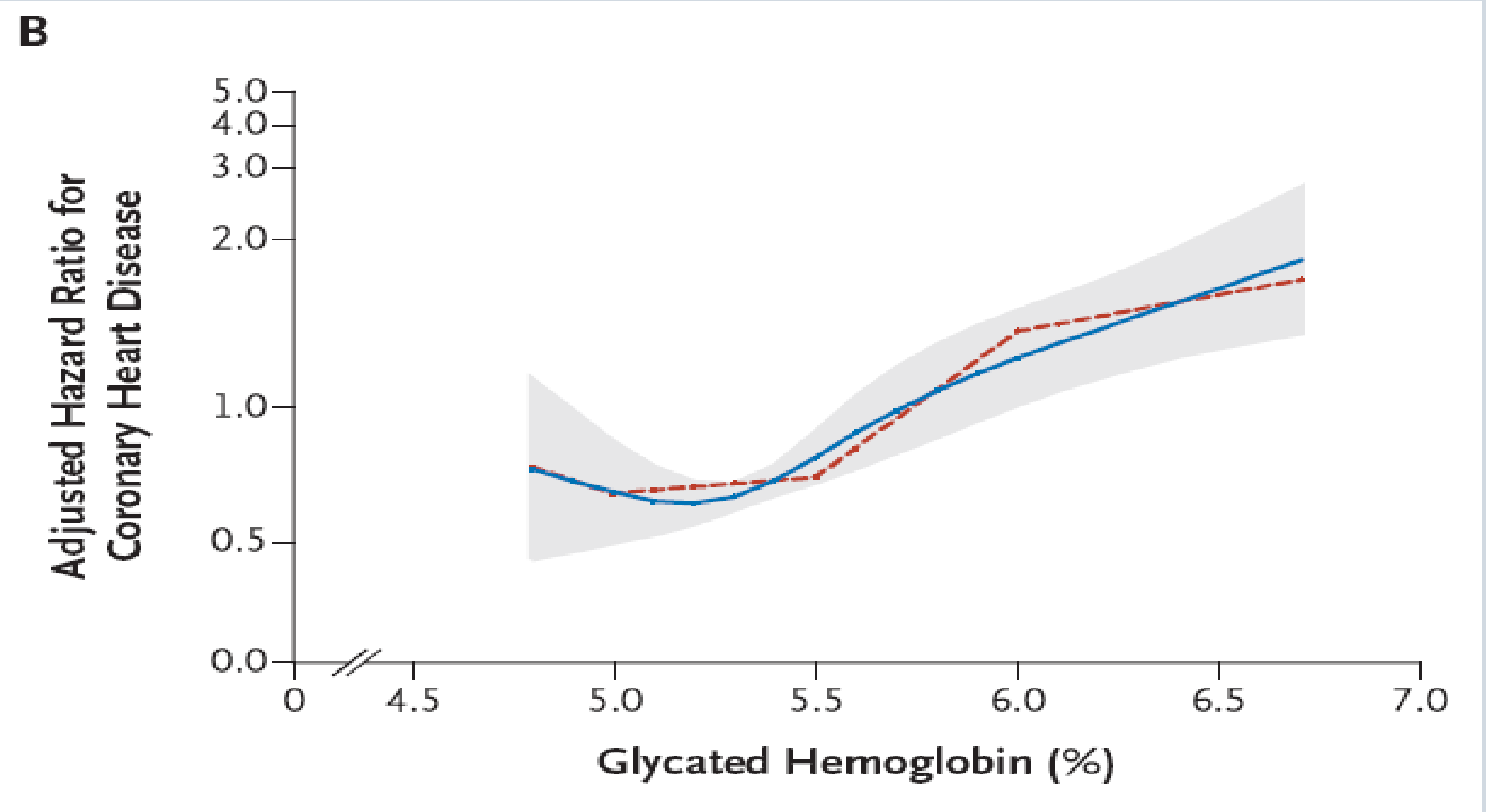
Cardiovascular Mortality



Tancredi M et al. N Engl J Med 2015;373:1720-1732.

3. It’s really not about the glucose

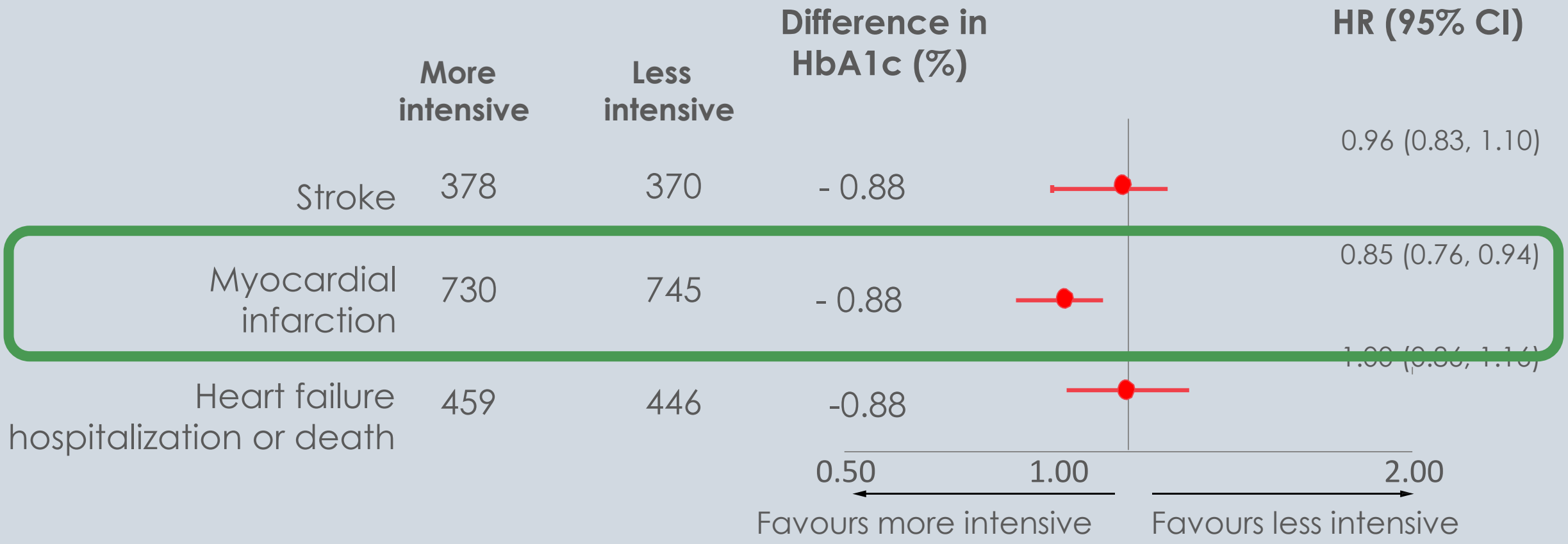
Association between HbA1c and CVD



Sabin et al. NEJM March 2010

Intensive glucose control and CV events

27,049 participants, 2370 major vascular events



Turnbull FM et al. Diabetologia 2009;52:2288–2298

ACCORD Glycemia Trial: 10,251 patients with T2DM randomized to HbA1c goal of <6 or 7-7.9

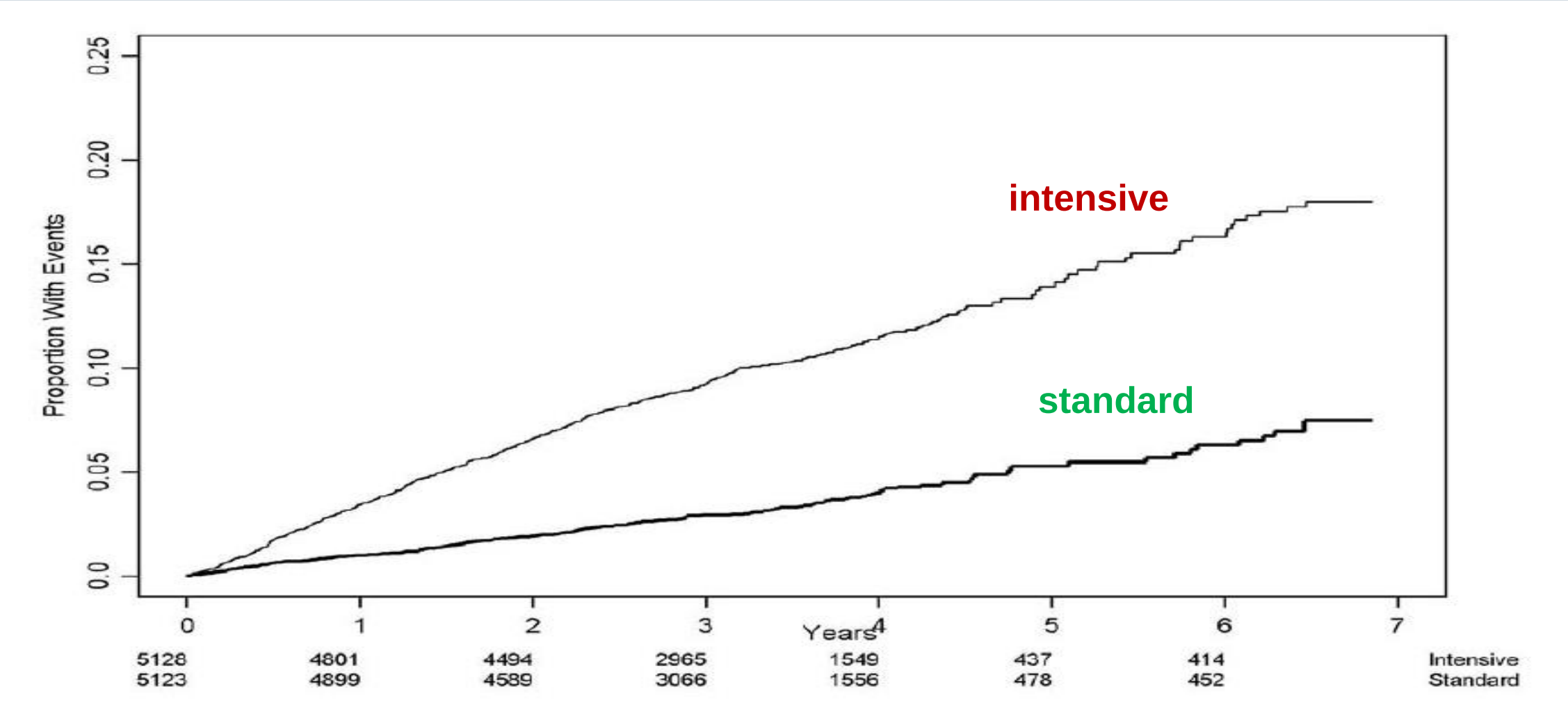
		andard N (%)	HR (95% CI)	P
Primary		1 (7.23)	0.90 (0.78-1.04)	0.16
Secondary				
Mortality	257 (5.01)	203 (3.96)	1.22 (1.01-1.46)	0.04
Nonfatal MI	186 (3.63)	235 (4.59)	0.76 (0.62-0.92)	0.004
Nonfatal Stroke	67 (1.31)	61 (1.19)	1.06 (0.75-1.50)	0.74
CVD Death	135 (2.6			
CHF	152 (2.96)			

22% Increase in mortality with an intensive glucose control strategy

24% decrease in nonfatal myocardial infarctions with an intensive glucose control strategy

ACCORD Study Group, NEJM 2008 358:2545-2549.

Severe Hypoglycemia in ACCORD glycemia Trial



ACCORD Study Group, NEJM 2008 358:2545-2549.

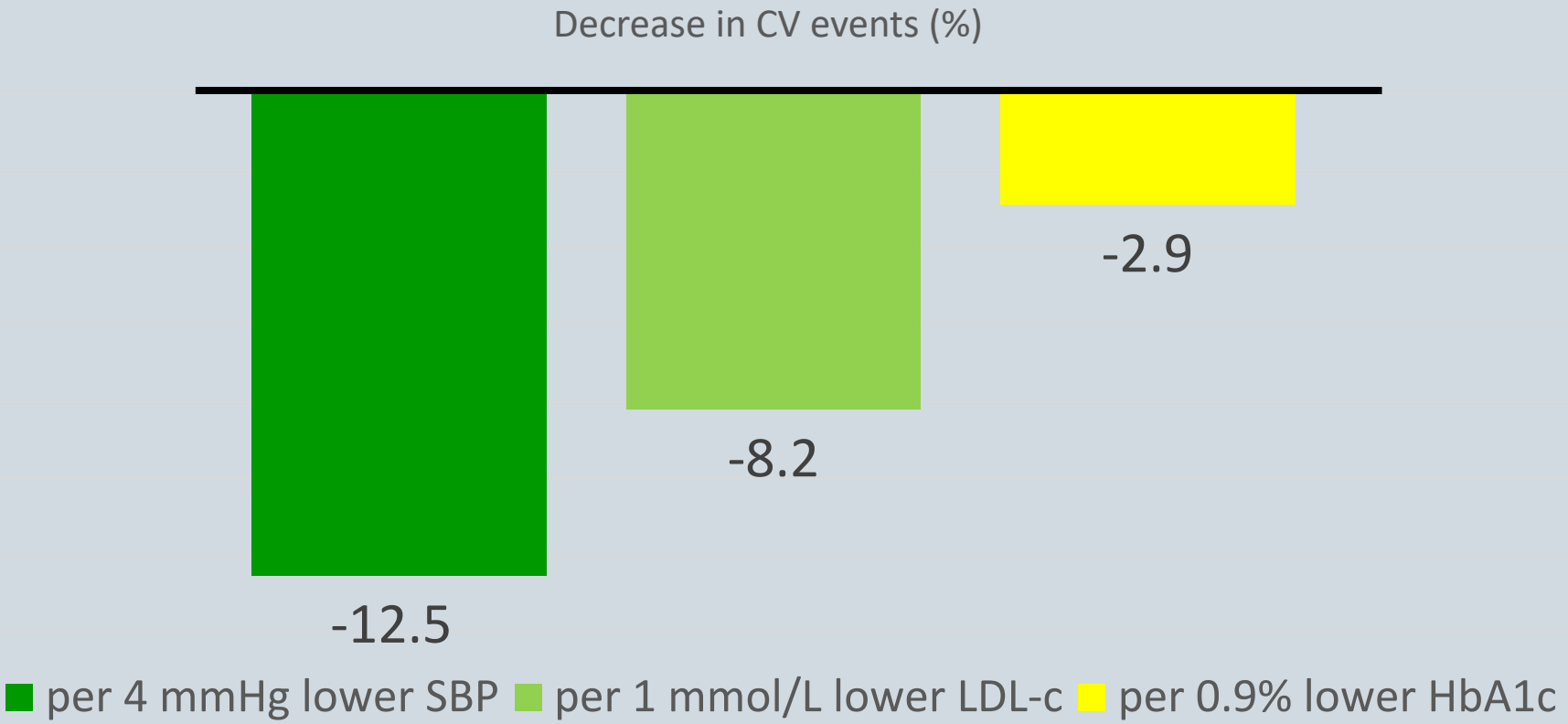
Association between severe hypoglycemia and adverse outcomes

From the Atherosclerosis Risk in Communities (ARIC) Study

	HR	95%CI
Coronary heart disease	2.02	1.27-3.20
All-cause mortality	1.73	1.38-2.17
CV mortality	1.64	1.15-2.34
Cancer mortality	2.49	1.46-4.24

4. It IS about Blood pressure and lipid control

Benefit of different interventions for Type 2 diabetes



CV: cardiovascular; SBP: systolic blood pressure; LDL-c: low density lipoprotein cholesterol; HbA1c: glycated hemoglobin;

Ray et al. Lancet 2009;373(9677):1765-72

Table 10.1—Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	SBP target: <120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 135/70.5 mmHg	• No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death • Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE	1,140 participants with T2D aged ≥55 years with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) SBP/DBP: 136/73 mmHg	Control: placebo Achieved (mean) SBP/DBP: 141.6/75.2 mmHg	• Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) • 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (310)
HOT	8,790 participants, including 1,501 with diabetes	DBP target: ≤80 mmHg Achieved (mean): 81.1 mmHg, ≤80 group; 85.2 mmHg, ≤90 group	DBP target: ≤90 mmHg	• In the overall trial, there was no cardiovascular benefit with more intensive targets • In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events
SPRINT	,361 participants without diabetes	SBP target: <120 mmHg Achieved (mean): 121.4 mmHg	SBP target: <140 mmHg Achieved (mean): 136.2 mmHg	• Intensive SBP target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) • Intensive target reduced risk of death 27% • Intensive therapy increased risks of electrolyte abnormalities and AKI
STEP	,511 participants aged 60–80 years, including 1,627 with diabetes	SBP target: <130 mmHg Achieved (mean): 127.5 mmHg	SBP target: <150 mmHg Achieved (mean): 135.3 mmHg	• Intensive SBP target lowered risk of the primary composite outcome 26% (stroke, ACS [acute MI and hospitalization for unstable angina], acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes) • Intensive target reduced risk of cardiovascular death 28% • Intensive therapy increased risks of hypotension

American Diabetes Association®

Standards of Medical Care

Randomized controlled trials of intensive versus standard hypertension treatment strategies

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Treatment Goals

10.4 The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained. **A**

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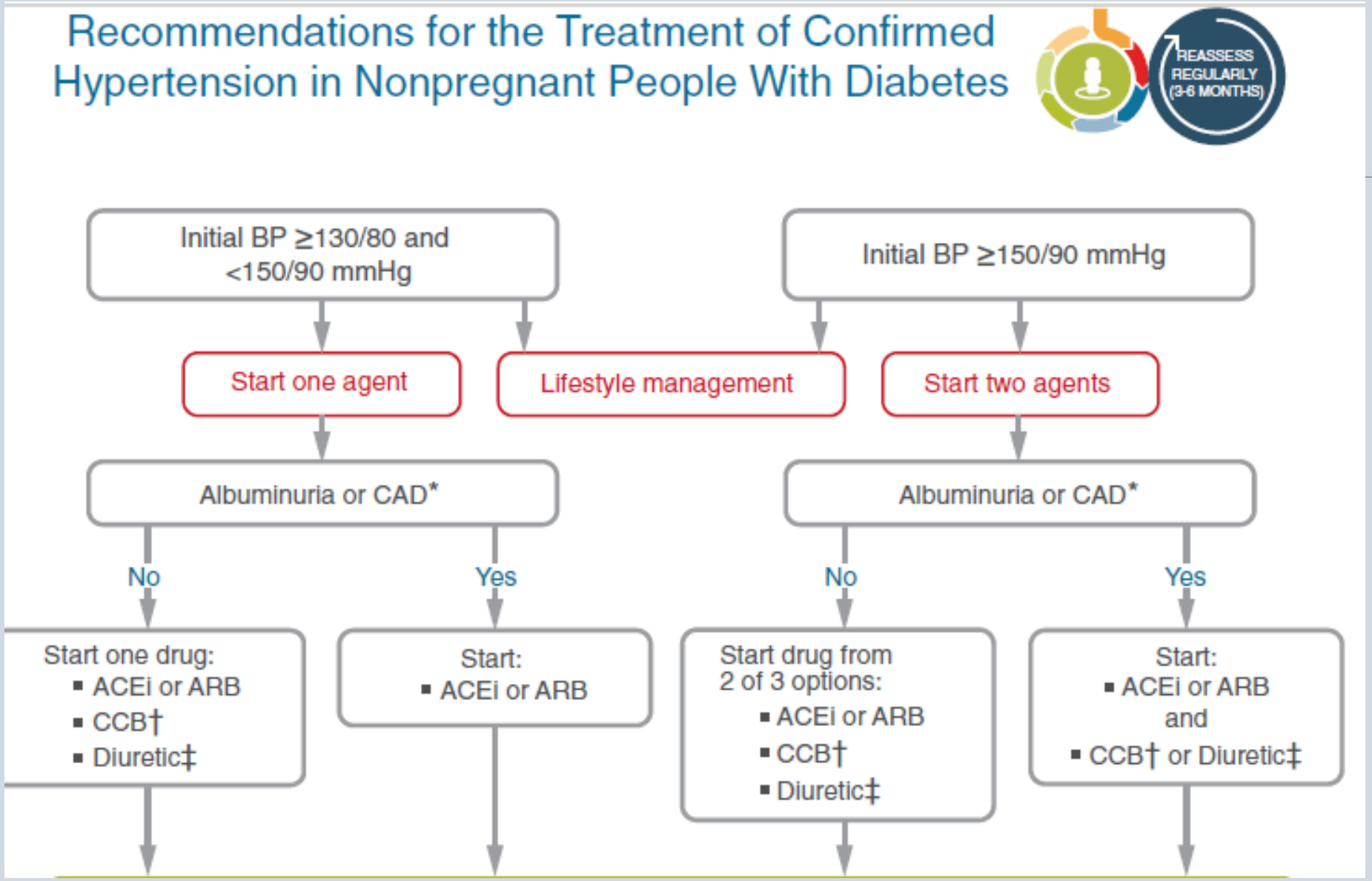
Standards of Medical Care

Treatment Strategies

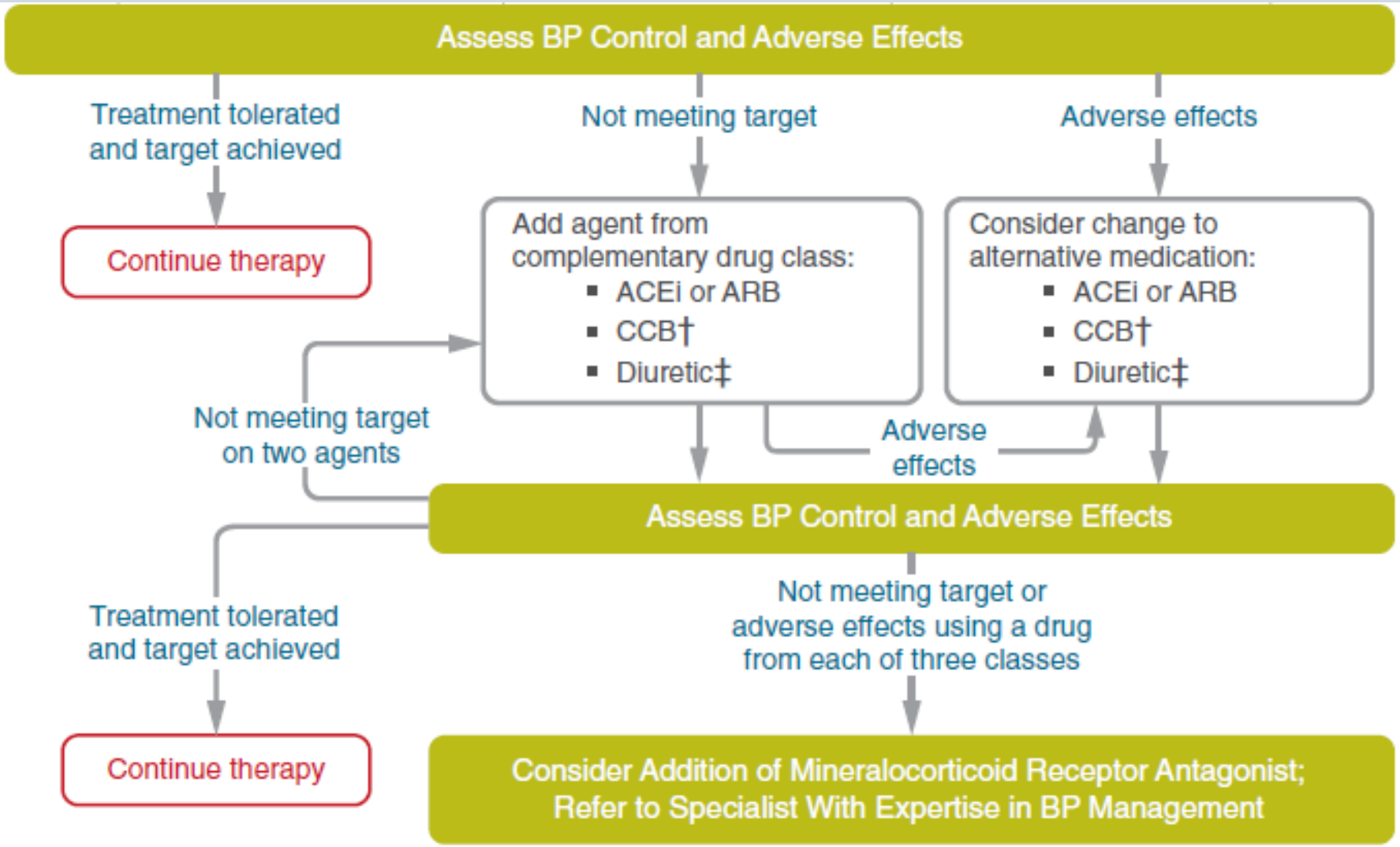
10.10 **Multiple-drug therapy is generally required** to achieve blood pressure targets... **A**

10.11 **An ACE inhibitor or ARB**…is the recommended first-line treatment for hypertension **in people with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g creatinine A**



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

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT



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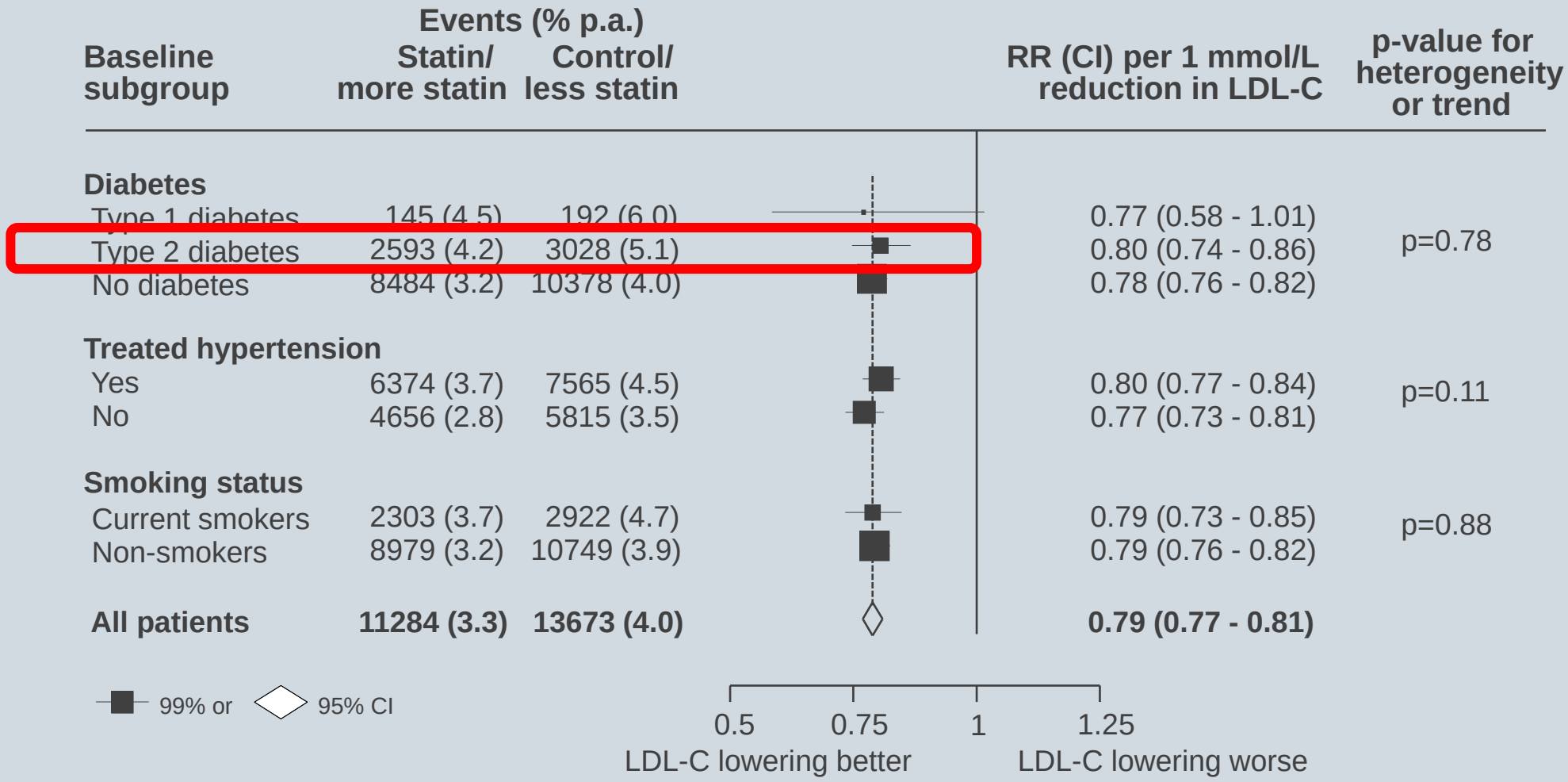
Recommendations for the Treatment of Confirmed Hypertension in People with Diabetes (2 of 2)

Statin Effects on Major Vascular Events



CTT. Lancet 2008 371: 117-125

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Statin Treatment—Primary Prevention

10.18 **For people with diabetes aged 40–75 years without ASCVD, use moderate-intensity statin therapy** in addition to lifestyle therapy. **A**

10.19 **For people with diabetes aged 20–39 years with additional ASCVD risk factors, it may be reasonable** to initiate statin therapy in addition to lifestyle therapy. **C**

10.20 For people with diabetes aged 40–75 years at higher cardiovascular risk…**use high-intensity statin therapy to reduce LDL cholesterol by ≥50%**. **A**

10.21 …**it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy**. **B**

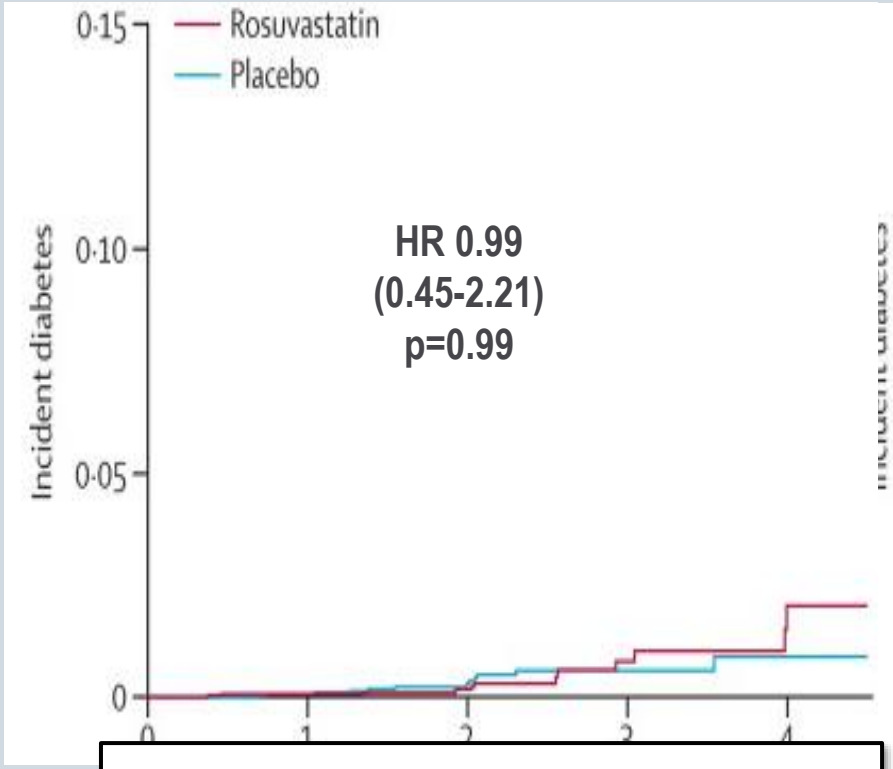
Association between statins and development of diabetes

Statin	Odds ratio (95% CI)
Overall (n=91 140)	**1.09 (1.02–1.17)**
Rosuvastatin only (n=24 714)	1.18 (1.04–1.33)
Atorvastatin only (n=7773)	1.14 (0.89–1.46)
Simvastatin only (n=18 815)	1.11 (0.97–1.26)
Pravastatin (n=33 627)	1.03 (0.90–1.19)
Lovastatin (n=6211)	0.98 (0.70–1.38)

Sattar N et al. *Lancet* 2010;375:735-42.

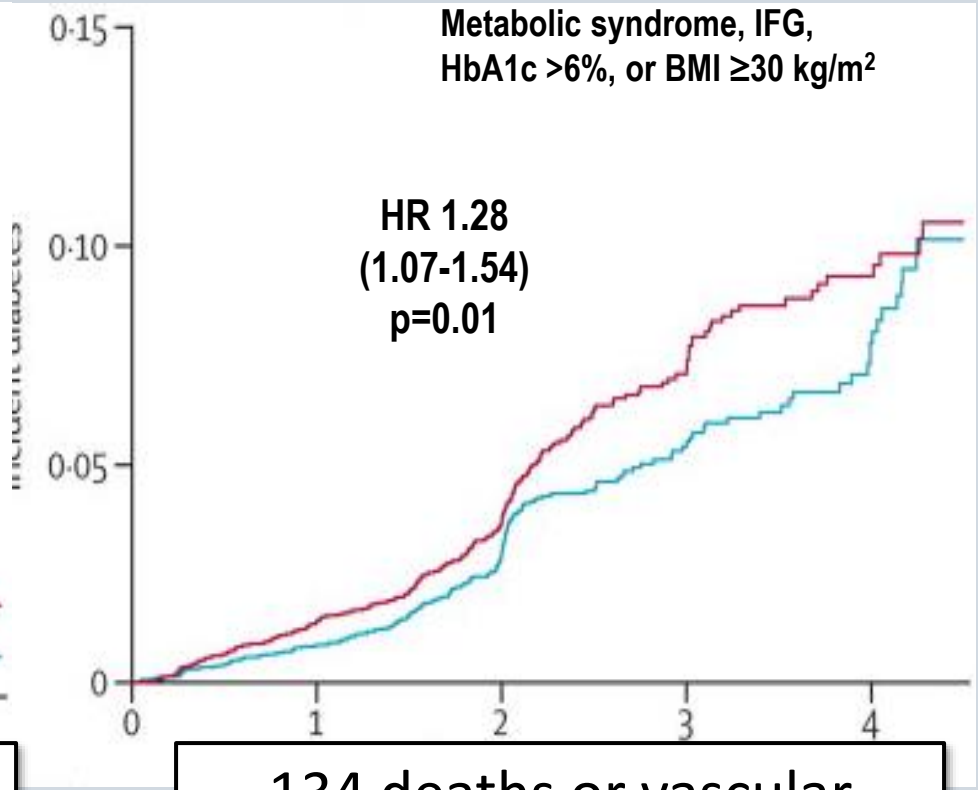
Jupitor Trial: Statins and Diabetes

No major risk factors for diabetes



86 deaths or vascular events prevented
0 excess cases of diabetes

Major risk factors for diabetes

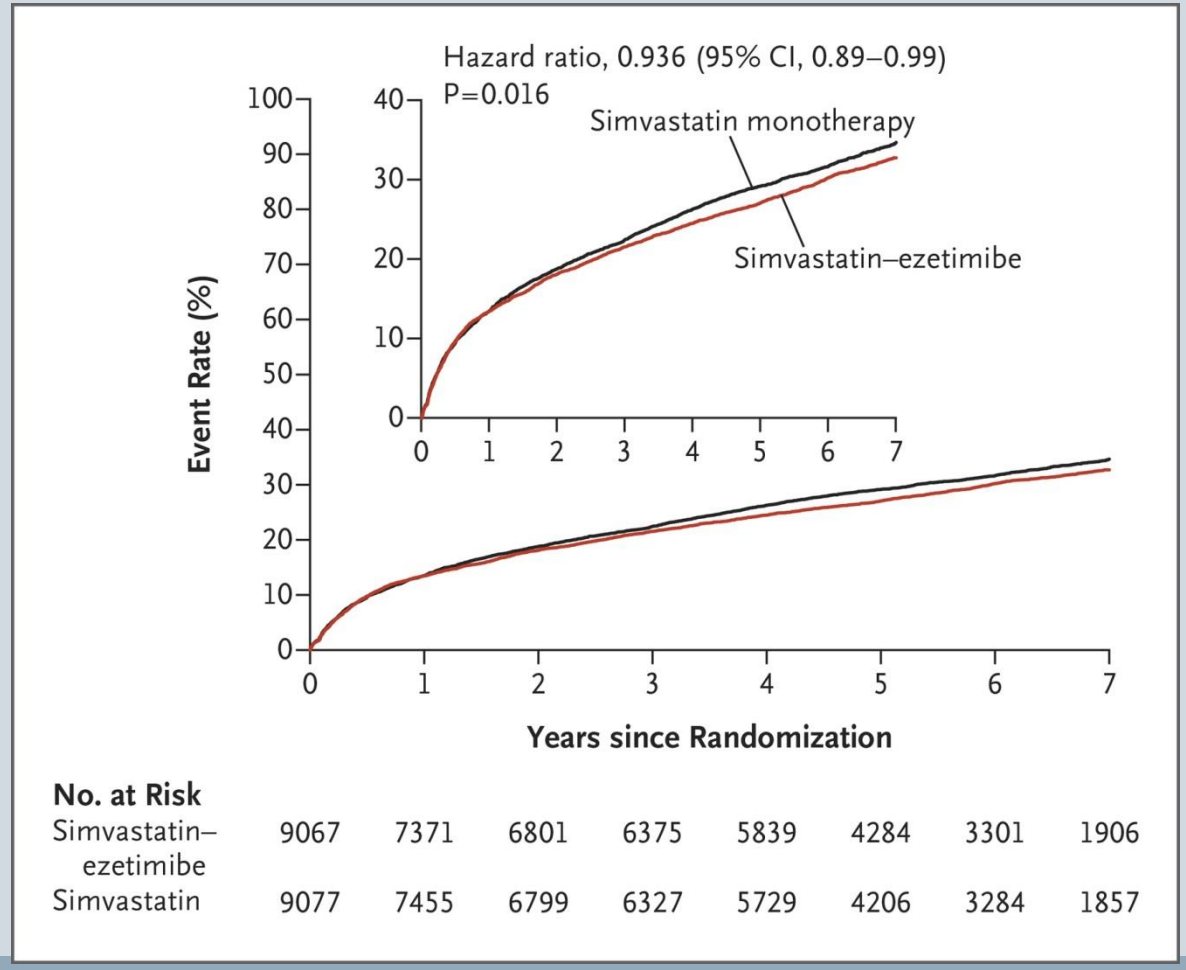


134 deaths or vascular events prevented
54 excess cases of diabetes

Ridker PM et al. *Lancet* 2012;380:565

Improve It Trial — Primary Outcome

Post MI patients on statin therapy randomized to receive addition of ezetimibe or placebo



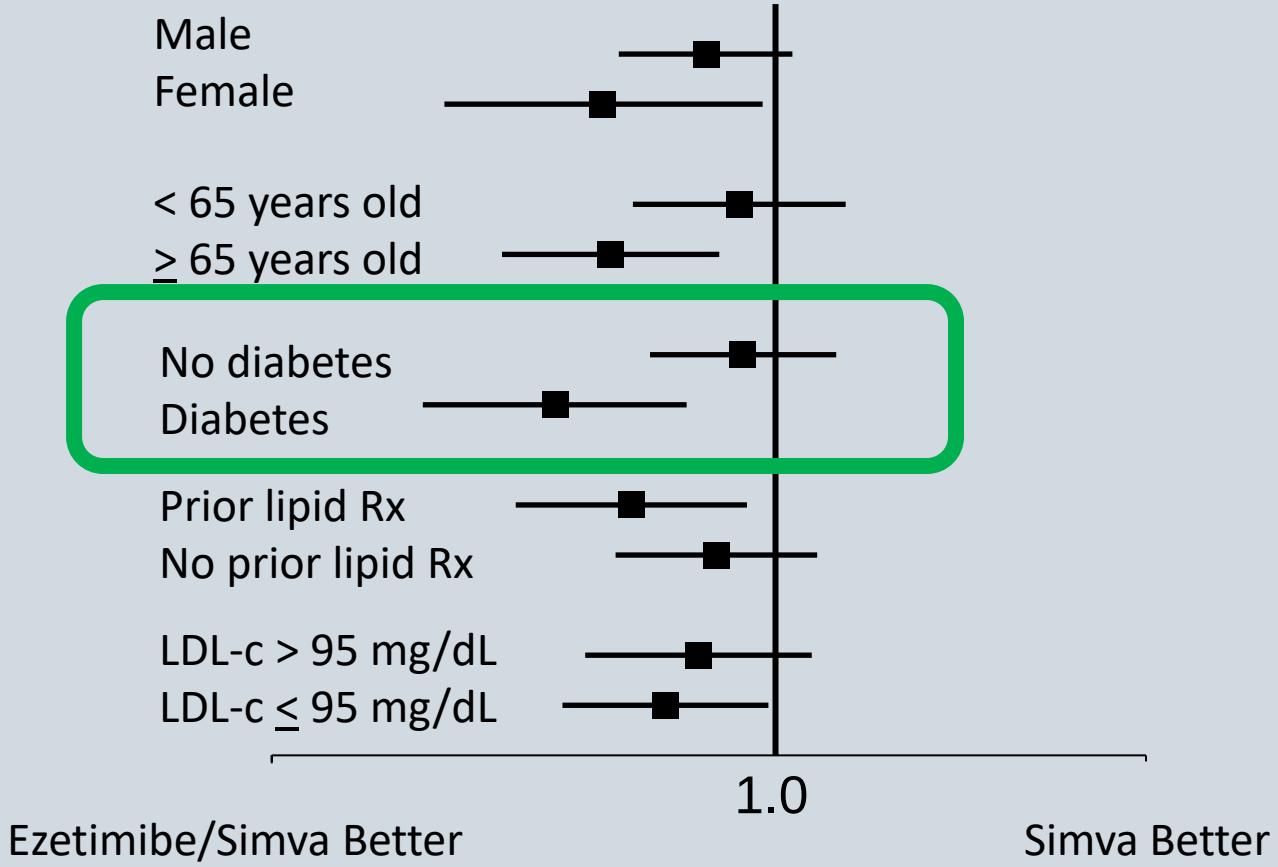
6 % RRR

NNT = 50

Patients with diabetes had particular benefit

Cannon CP et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med June 3, 2015

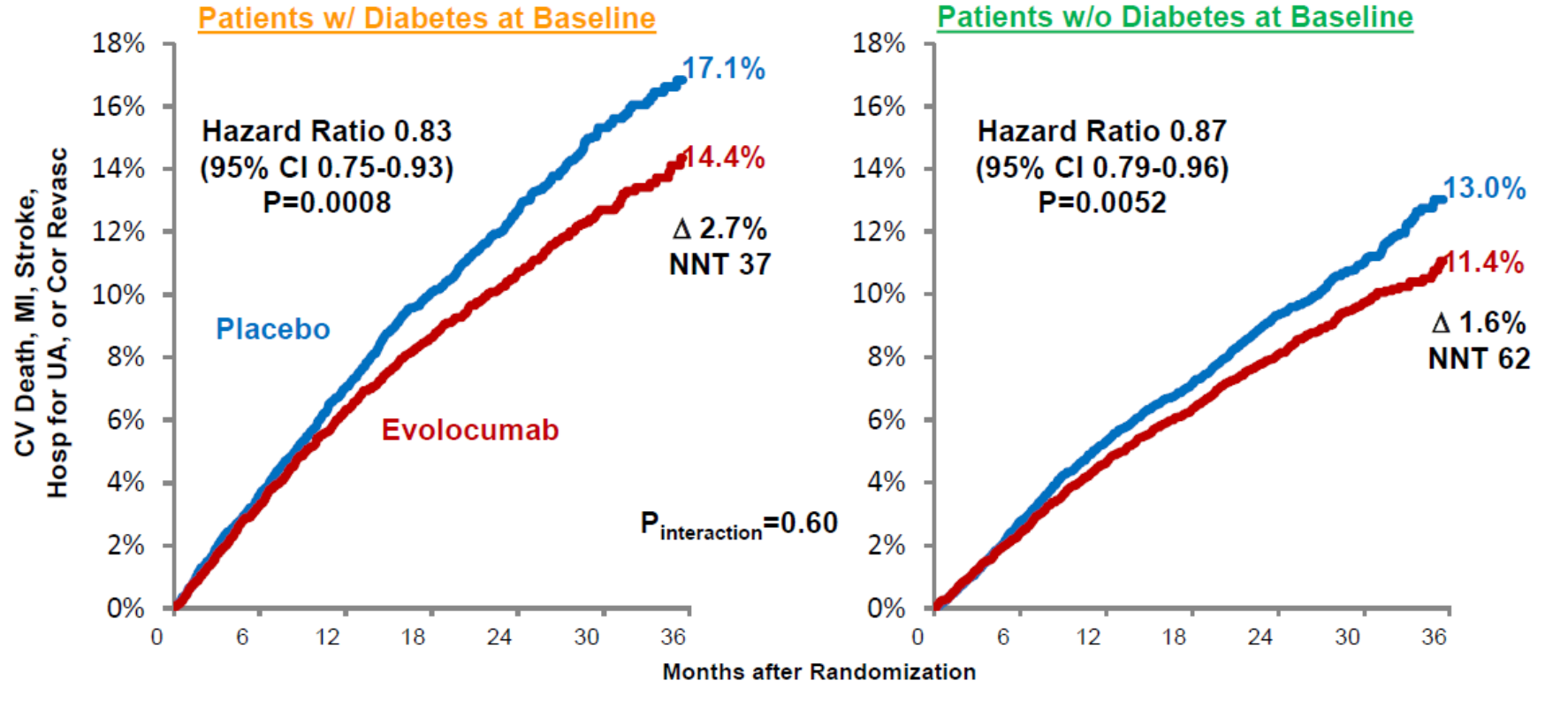
IMPROVE-IT Major Pre-specified Subgroups



Cannon CP et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med June 3, 2015

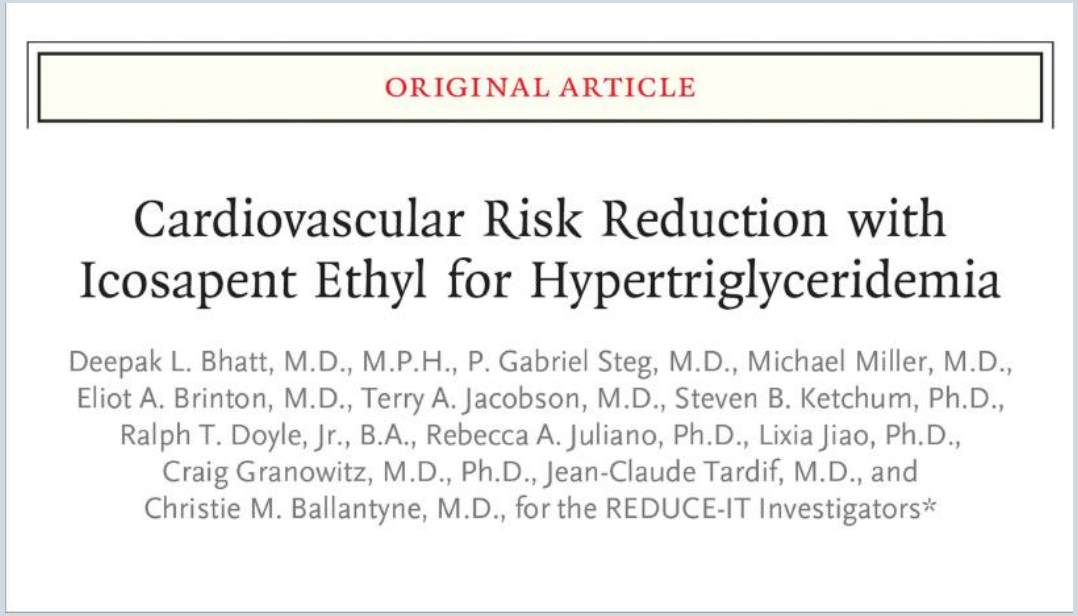
Fourier Trial: Diabetes Subgroup

Post MI patients on statin therapy randomized to receive addition of PCSK9i or placebo



Reduce – It Trial

8,179 patients with elevated triglycerides, on maximum tolerated statin therapy were randomized to EPA only fish oil 4 g daily or mineral oil placebo.



ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Bhatt et. al. January 3, 2019 N Engl J Med 2019; 380:11-22

Reduce – It Baseline Characteristics

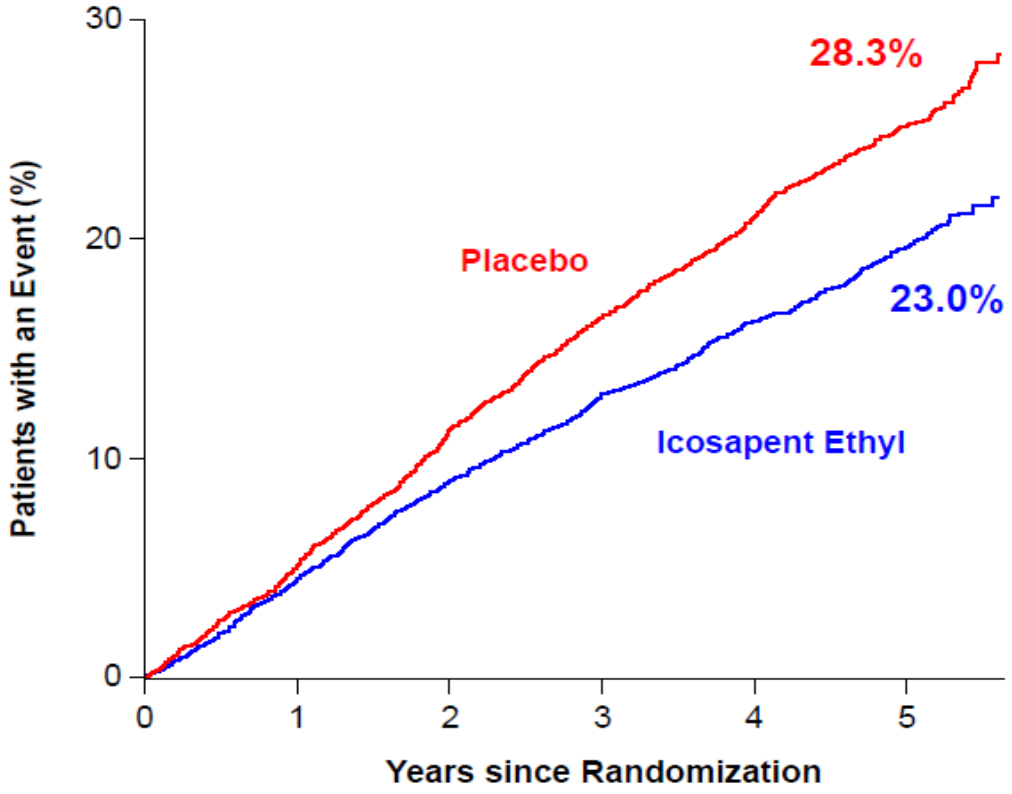
	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, n (%)	1162 (28.4%)	1195 (29.2%)
Non-White, n (%)	398 (9.7%)	401 (9.8%)
Secondary Prevention Cohort	2892 (70.7%)	2893 (70.7%)
Primary Prevention Cohort	1197 (29.3%)	1197 (29.3%)
Low-intensity statin	254 (6.2%)	267 (6.5%)
Moderate-intensity statin	2533 (61.9%)	2575 (63.0%)
High-intensity statin	1290 (31.5%)	1226 (30.0%)
Type 2 Diabetes, n (%)	2367 (57.9%)	2363 (57.8%)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to <200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥200 mg/dL	2481 (60.7%)	2469 (60.4%)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

REDUCE-It Trial

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

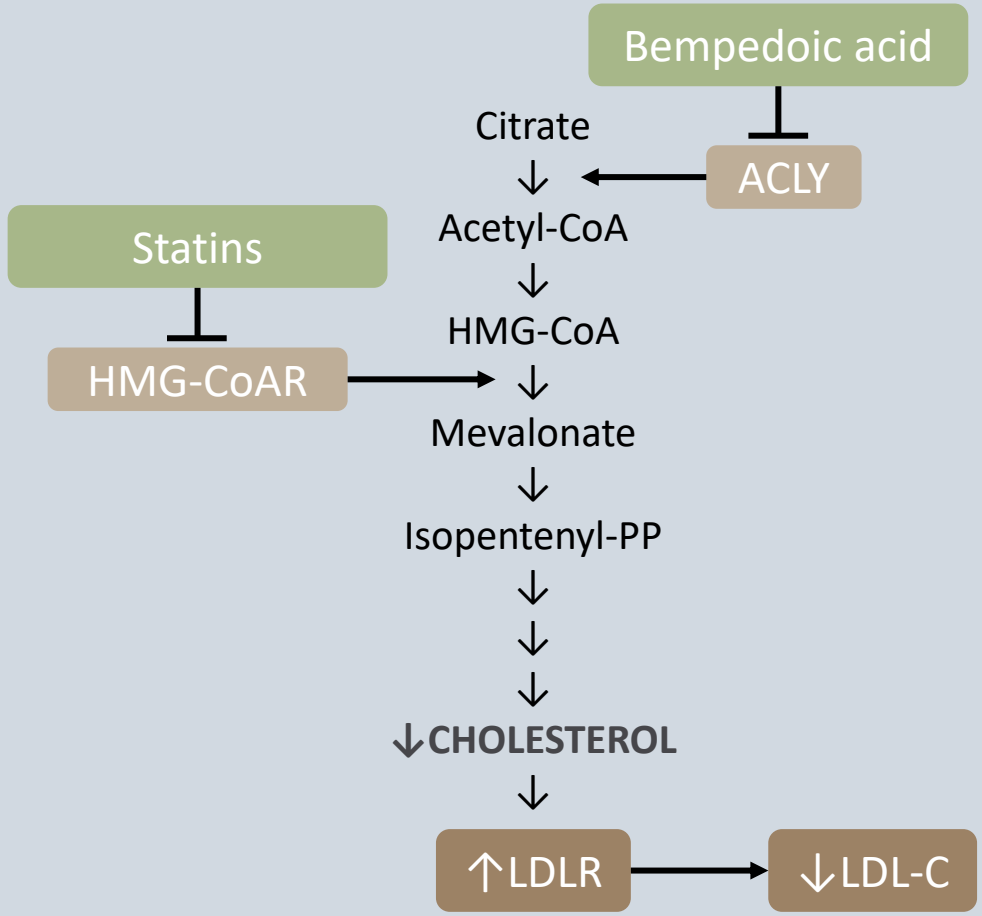
American Diabetes Association®
Standards of Medical Care

Treatment of Other Lipoproteins

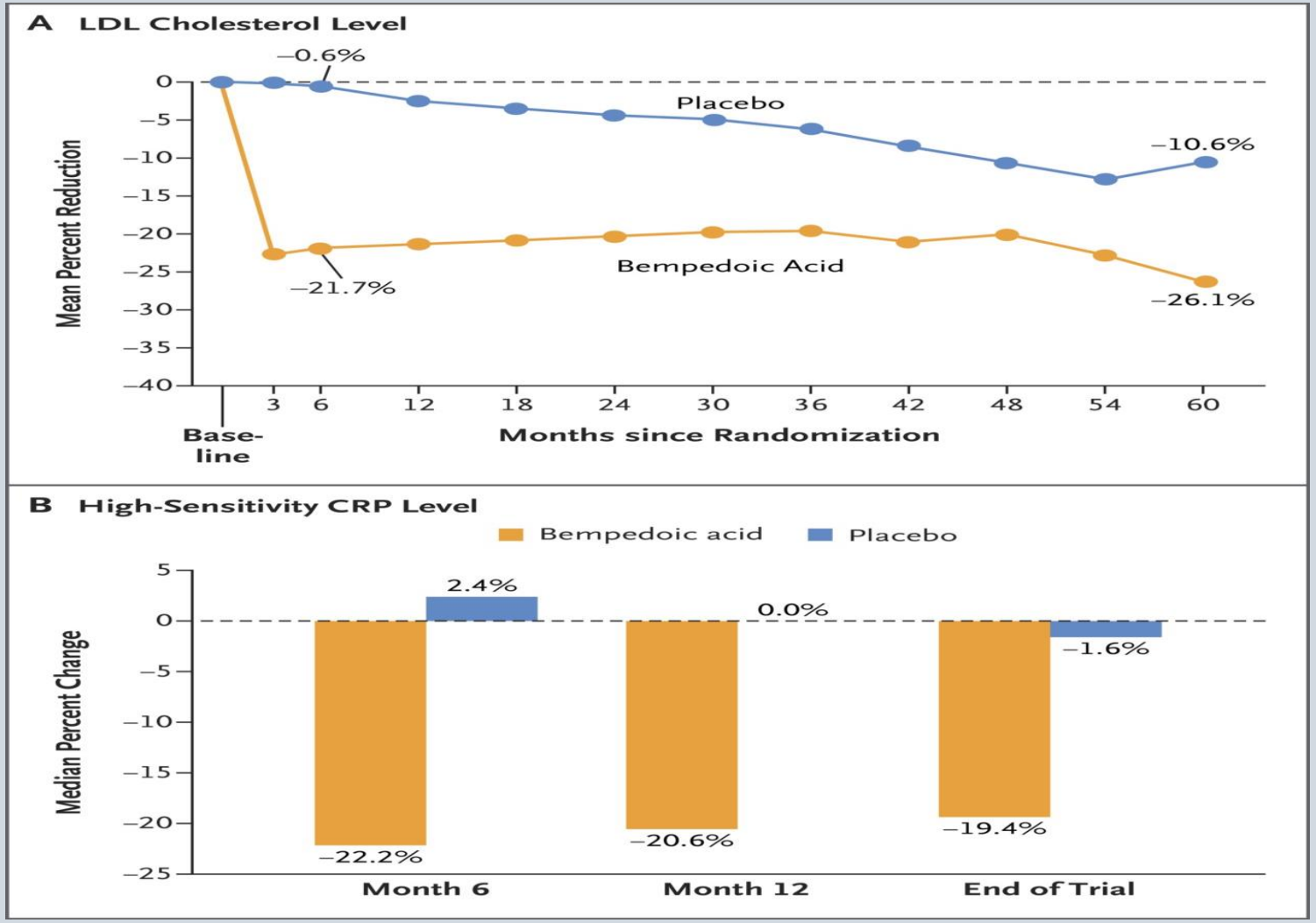
10.31 **In individuals with ASCVD or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL the addition of icosapent ethyl can be considered** to reduce cardiovascular risk. **A**

Bempedoic Acid

Bempedoic acid, a prodrug that is activated by a hepatic enzyme not present in skeletal muscle, inhibits ATP-citrate lyase, an enzyme upstream of HMG-coA reductase in the cholesterol biosynthesis pathway.

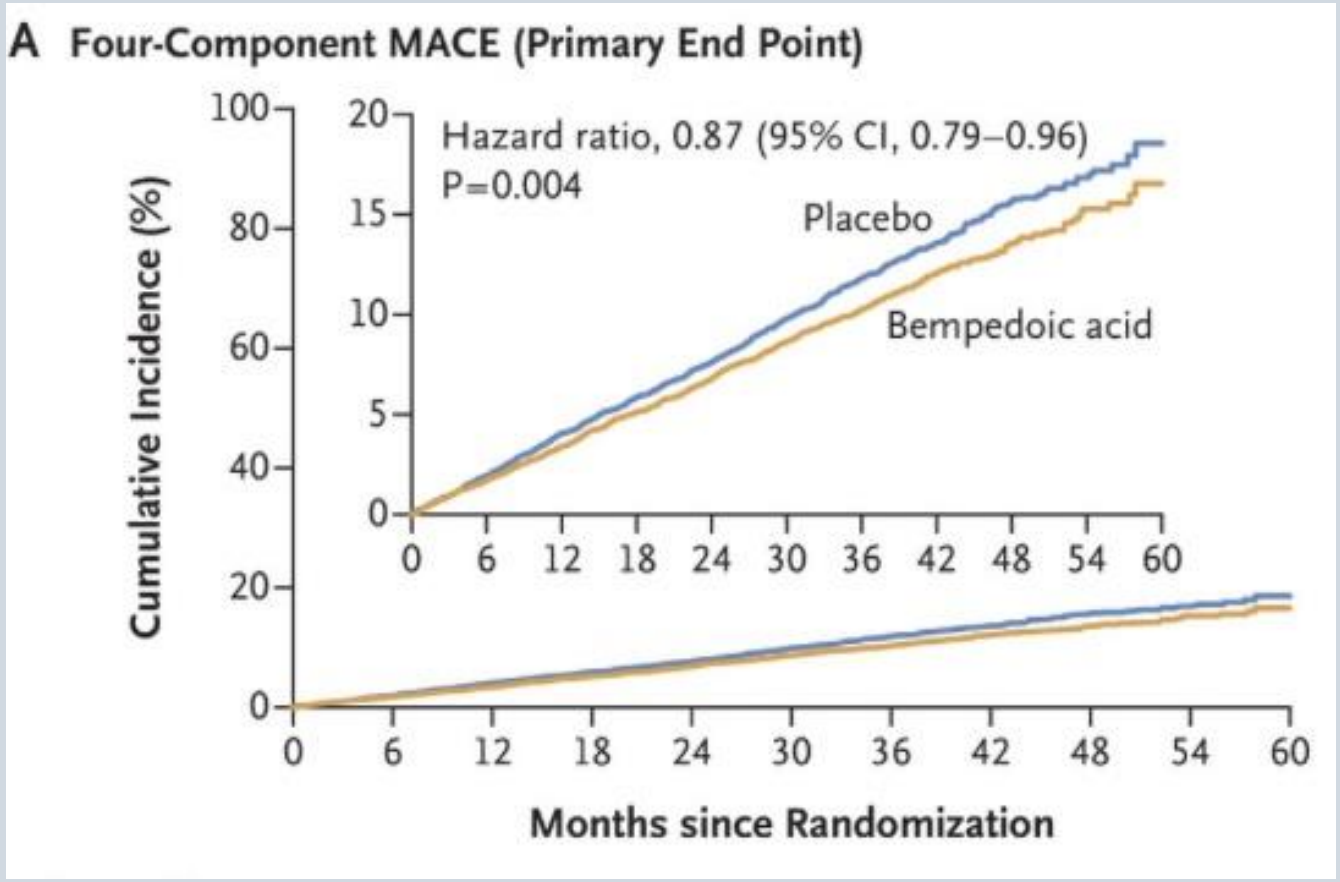


Changes in LDL Cholesterol and CRP



Nissen SE et al. N Engl J Med2023;388:1353-1364

Primary Outcome: 4 point MACE



13% RRR

NNT = 63

American Diabetes Association®
Standards of Medical Care

Statin Treatment—Primary Prevention (continued)

10.24 In people with diabetes **intolerant to statin therapy, treatment with bempedoic acid is recommended to reduce cardiovascular event rates as an alternative cholesterol-lowering plan. A**

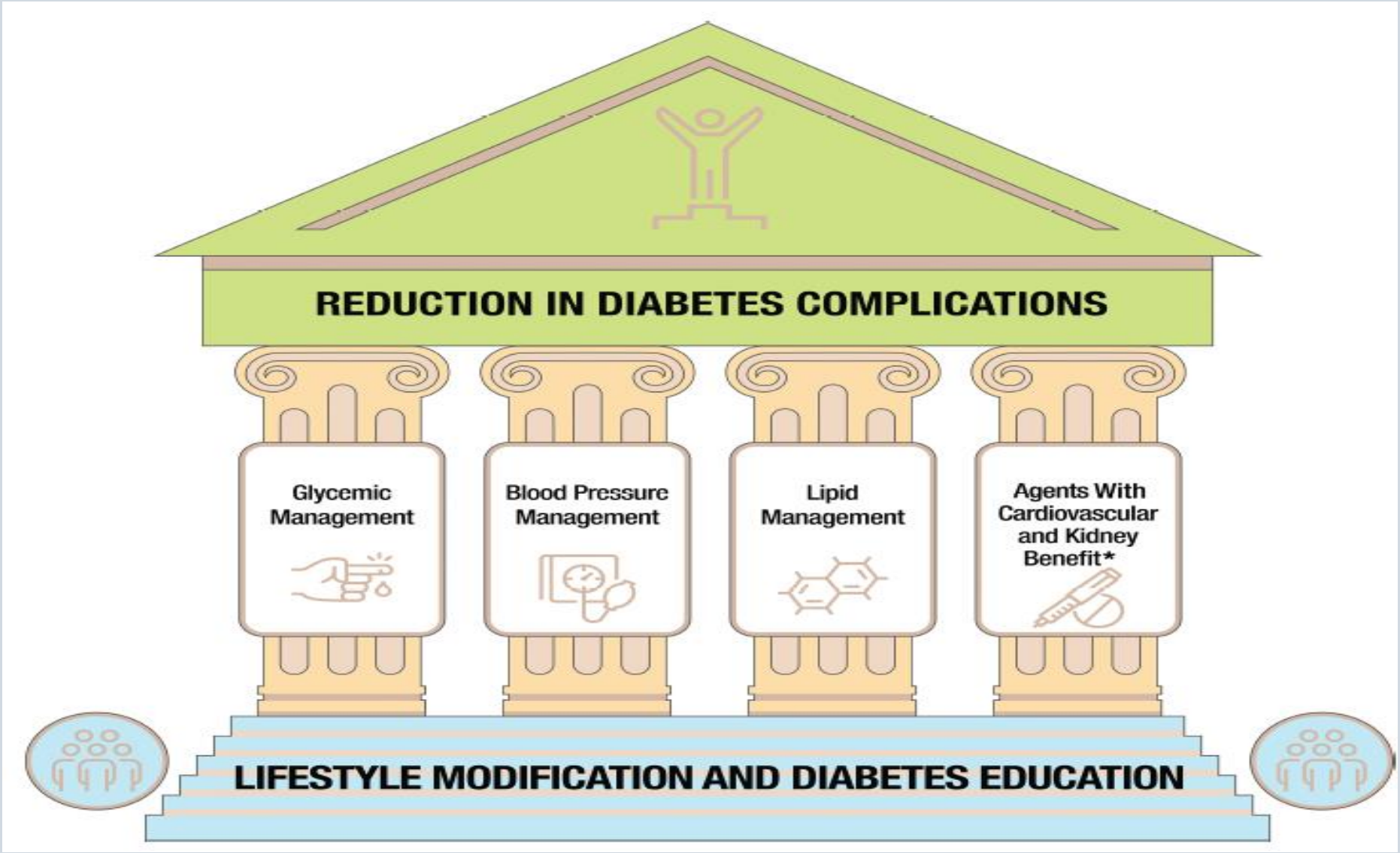
American Diabetes Association®
Standards of Medical Care

Other Combination Therapy

10.32 **Statin plus fibrate combination therapy…is generally not recommended.** **A**

10.33 **Statin plus niacin…is generally not recommended.** **A**

Cardiovascular Disease and Risk Management

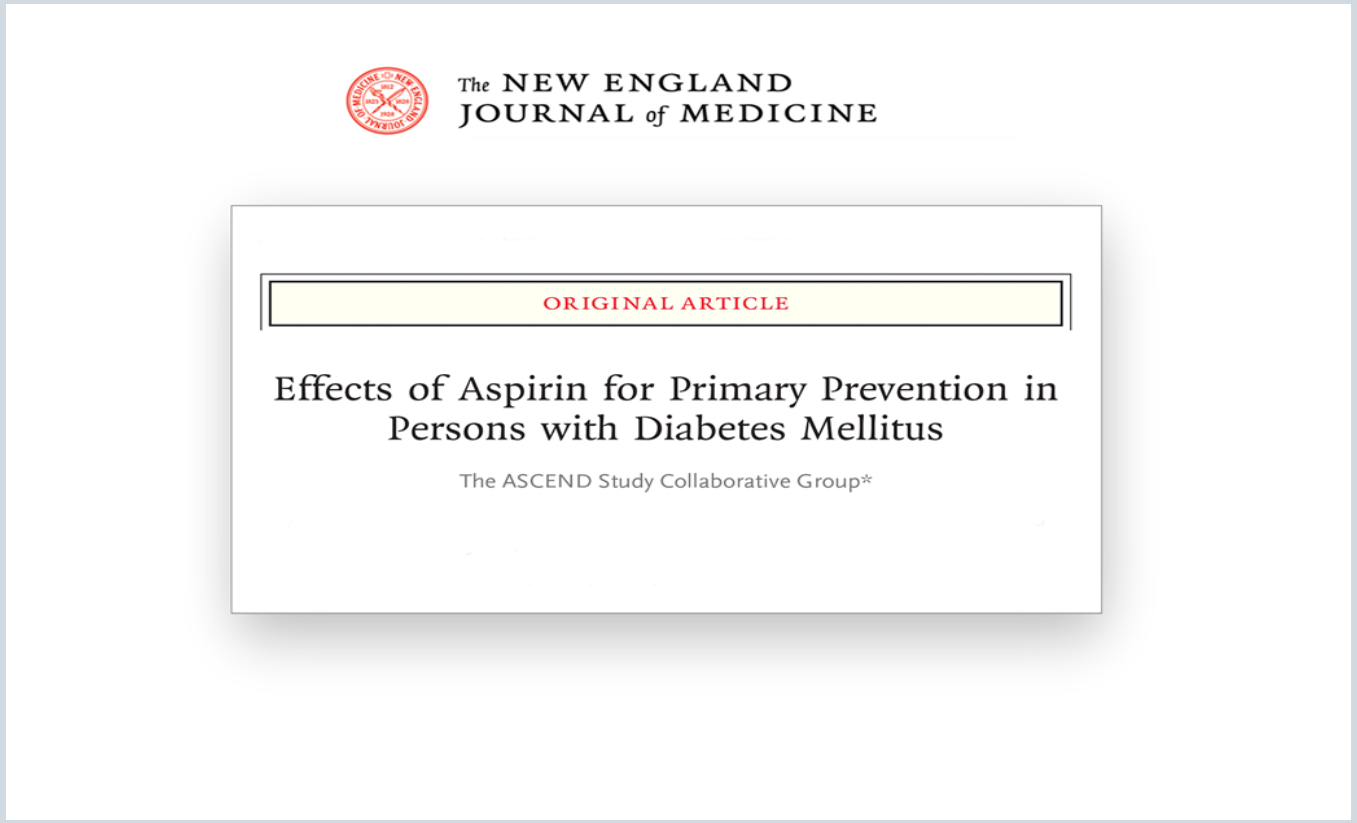


American Diabetes Association®

Standards of Medical Care

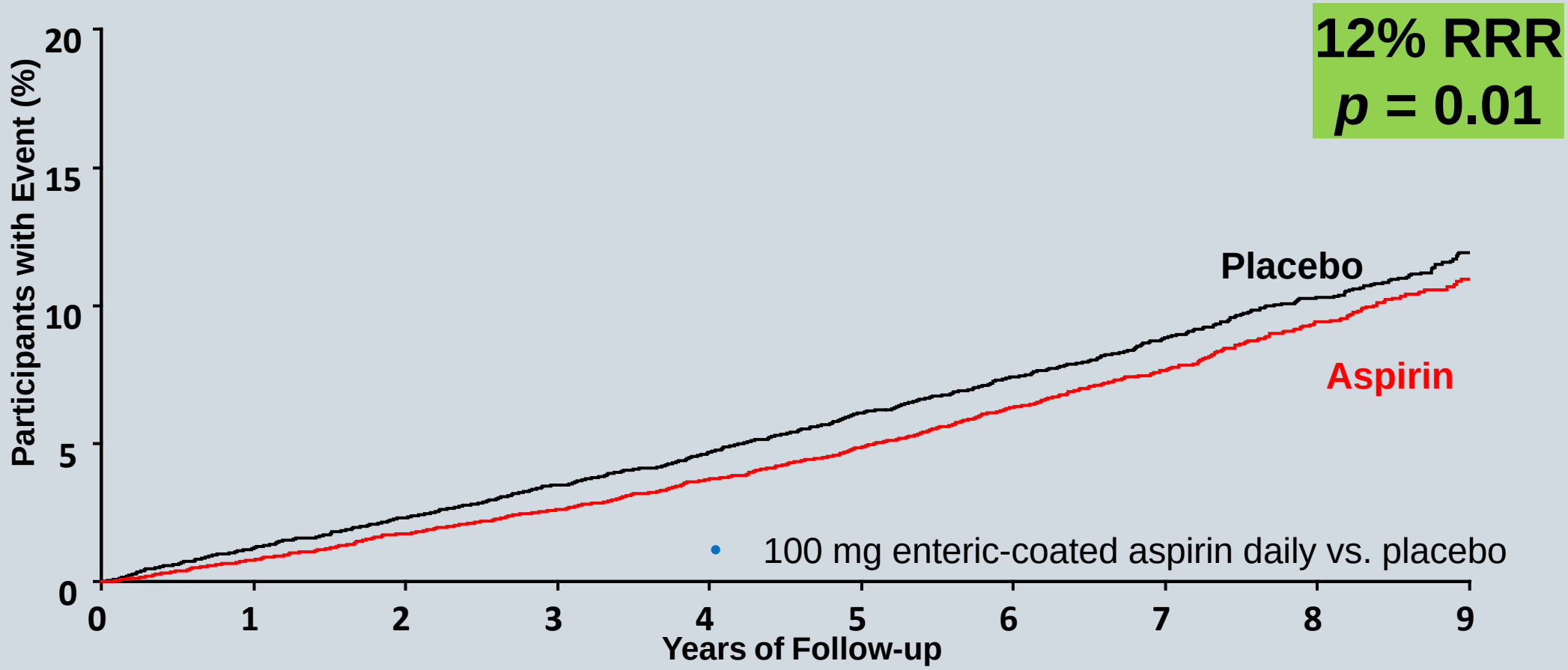
Pharmacologic Approaches to Glycemic Treatment:
Standards of Care in Diabetes - 2024. *Diabetes Care* 2024;47(Suppl. 1):S158-S178

5. Aspirin has not shown net benefit for primary prevention in patients with diabetes



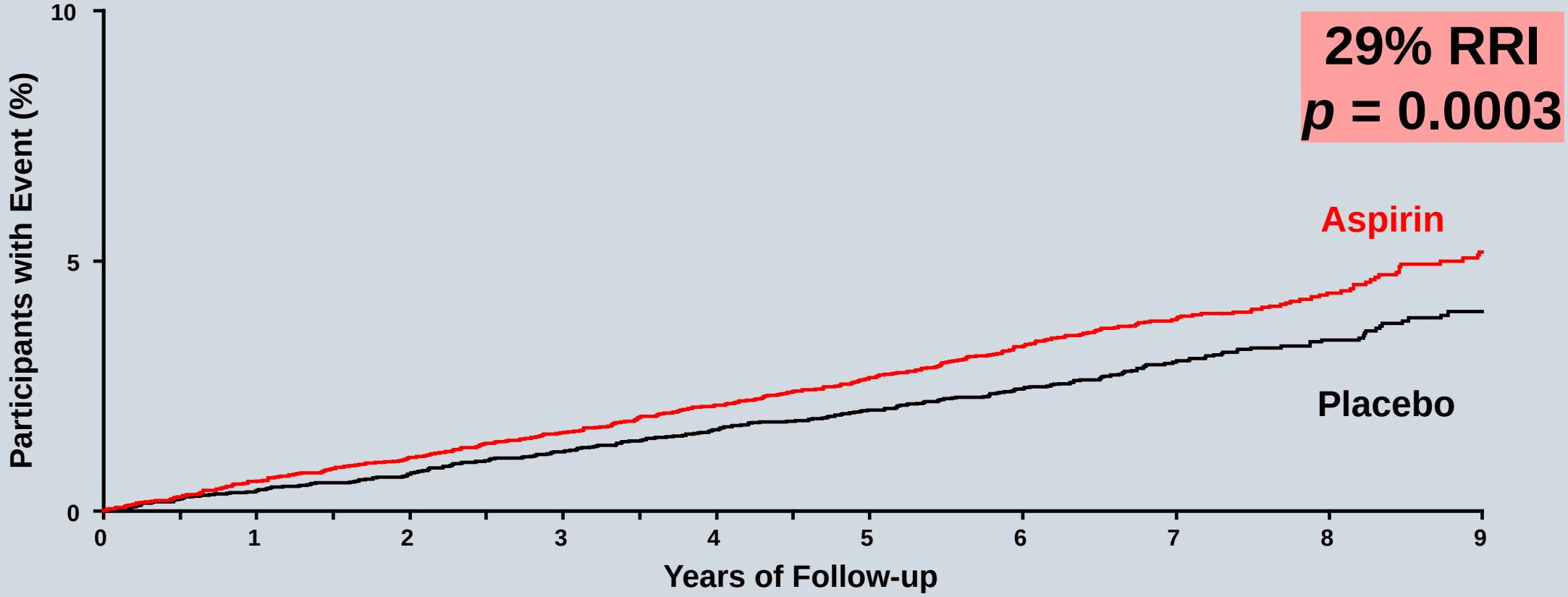
ASCEND: **15,480 patients** Age ≥ 40 years, + DIABETES and no baseline cardiovascular disease; **Randomized to Aspirin 100 mg daily vs. placebo**

ASCEND: Primary Outcome CVD death, MI, UA, Stroke or TIA



ASCEND Study Collaborative Group. Am Heart J 2018;198:135-144

ASCEND: major bleeding



American Diabetes Association®
Standards of Medical Care

Antiplatelet Agents

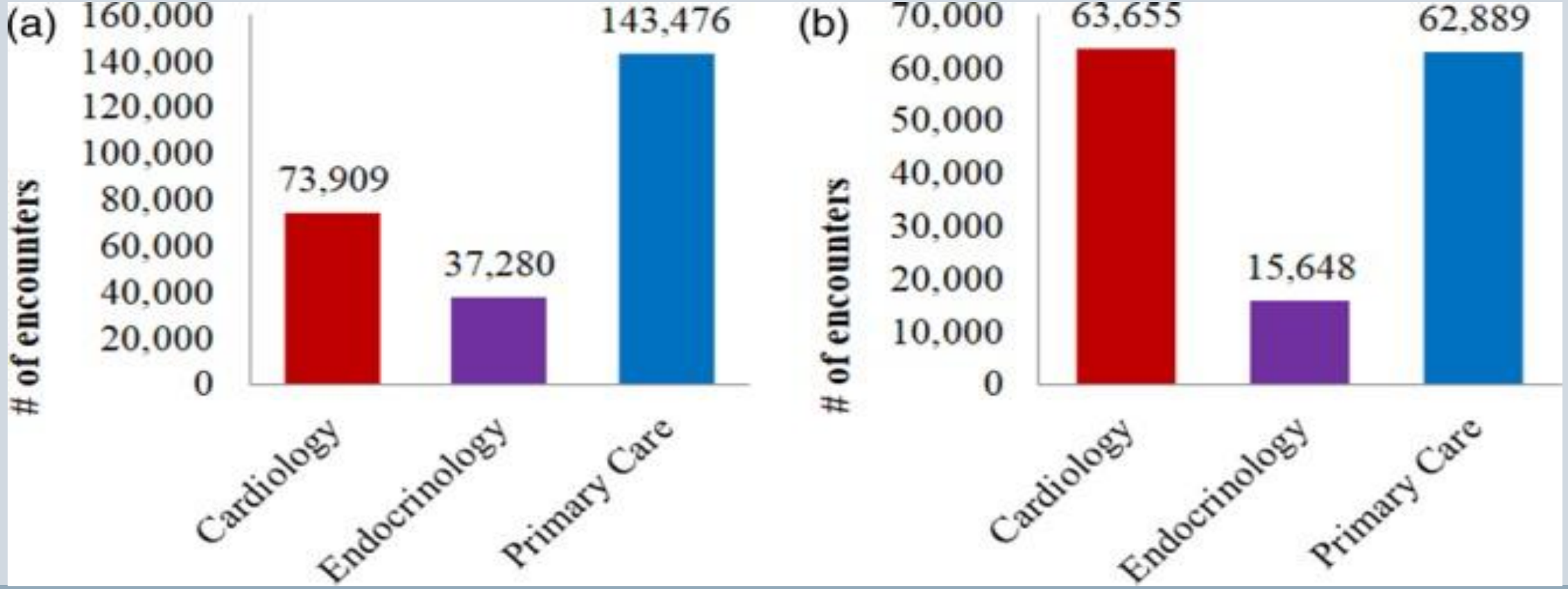
10.34 Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD. **A**

6. Patients with diabetes see their cardiologist more than their endocrinologist

Physician visits by patients with diabetes

Patients with diabetes

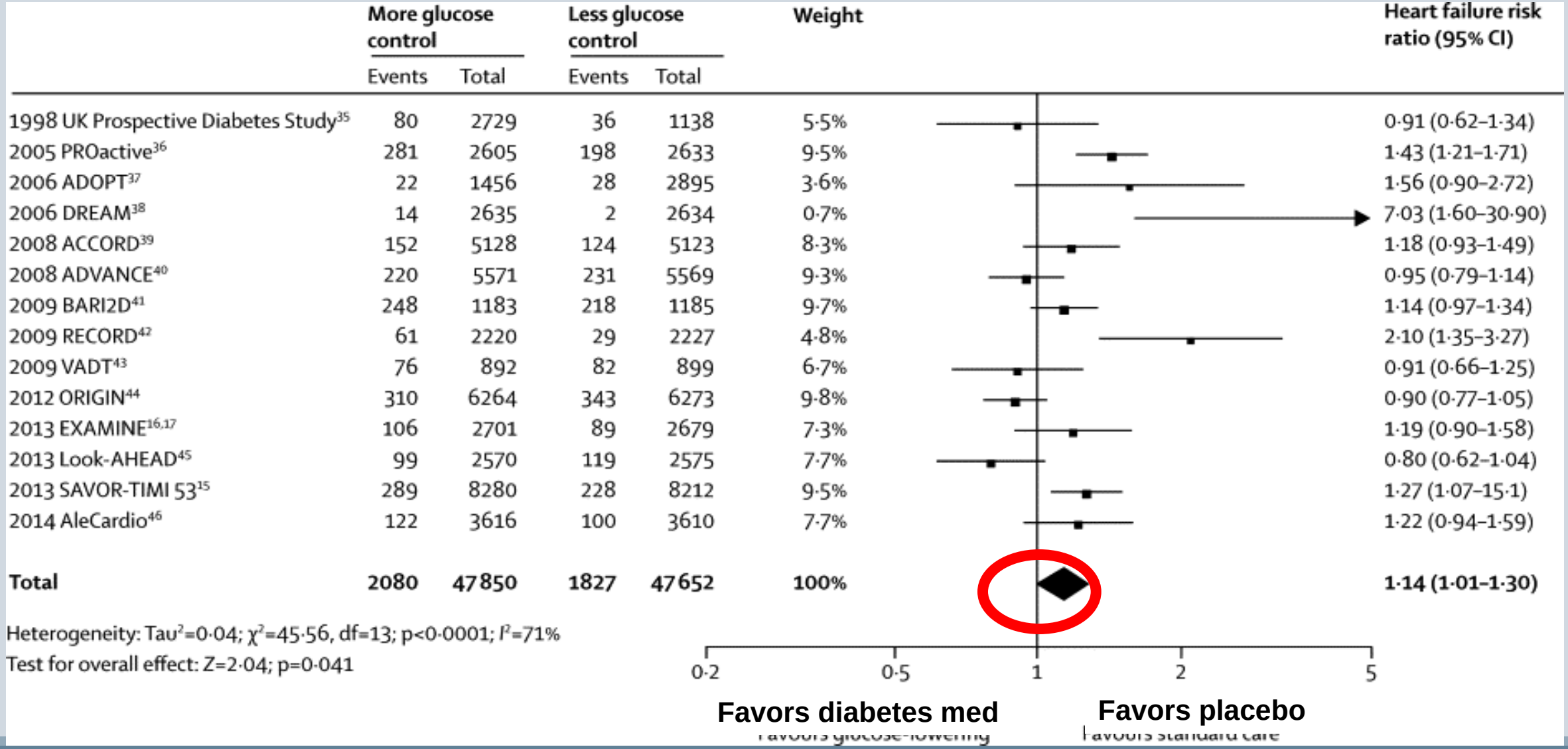
Patients with diabetes and CVD



Cardiovasc Endocrinol Metab. 2020 Jun; 9(2): 56–59. Published online 2020 May 15.

7. Most diabetes drugs are not good for the heart.

Diabetes medications and cardiovascular events



	More glucose control		Less glucose control		Weight	Heart failure risk ratio (95% CI)
	Events	Total	Events	Total		
1998 UK Prospective Diabetes Study[35]	80	2729	36	1138	5·5%	0·91 (0·62–1·34)
2005 PROactive[36]	281	2605	198	2633	9·5%	1·43 (1·21–1·71)
2006 ADOPT[37]	22	1456	28	2895	3·6%	1·56 (0·90–2·72)
2006 DREAM[38]	14	2635	2	2634	0·7%	7·03 (1·60–30·90)
2008 ACCORD[39]	152	5128	124	5123	8·3%	1·18 (0·93–1·49)
2008 ADVANCE[40]	220	5571	231	5569	9·3%	0·95 (0·79–1·14)
2009 BARI2D[41]	248	1183	218	1185	9·7%	1·14 (0·97–1·34)
2009 RECORD[42]	61	2220	29	2227	4·8%	2·10 (1·35–3·27)
2009 VADT[43]	76	892	82	899	6·7%	0·91 (0·66–1·25)
2012 ORIGIN[44]	310	6264	343	6273	9·8%	0·90 (0·77–1·05)
2013 EXAMINE[16,17]	106	2701	89	2679	7·3%	1·19 (0·90–1·58)
2013 Look-AHEAD[45]	99	2570	119	2575	7·7%	0·80 (0·62–1·04)
2013 SAVOR-TIMI 53[15]	289	8280	228	8212	9·5%	1·27 (1·07–15·1)
2014 AleCardio[46]	122	3616	100	3610	7·7%	1·22 (0·94–1·59)
Total	**2080**	**47850**	**1827**	**47652**	**100%**	**1·14 (1·01–1·30)**

Heterogeneity: Tau²=0·04; χ^2=45·56, df=13; p<0·0001; I^2=71%
Test for overall effect: Z=2·04; p=0·041

Jacob A Udell, et al., *Lancet Diabetes Endocrinol.*, published online 16 March 2015,

Mortality Risk With Sulfonylurea Therapy

Meta-analysis of 18 studies reporting mortality or MI risk in patients receiving sulfonylureas (N = 167,327)

RR of Death (95% CI)	SU vs Metformin
Tolbutamide	3.76 (2.97-4.76)
Glibenclamide	3.52 (3.16-3.91)
Glipizide	3.50 (3.10-3.94)
Glimepiride	2.89 (2.56-3.25)
Gliclazide	1.93 (1.56-2.39)

Simpson SH, et al. Lancet Diabetes Endocrinol. 2015;3:43-51.

Diabetes medications through the years

INSULIN

METFORMIN

ALPHA GLUCOSIDASE INHIBITORS

THIAZOLIDINEDIONES (TZDs)

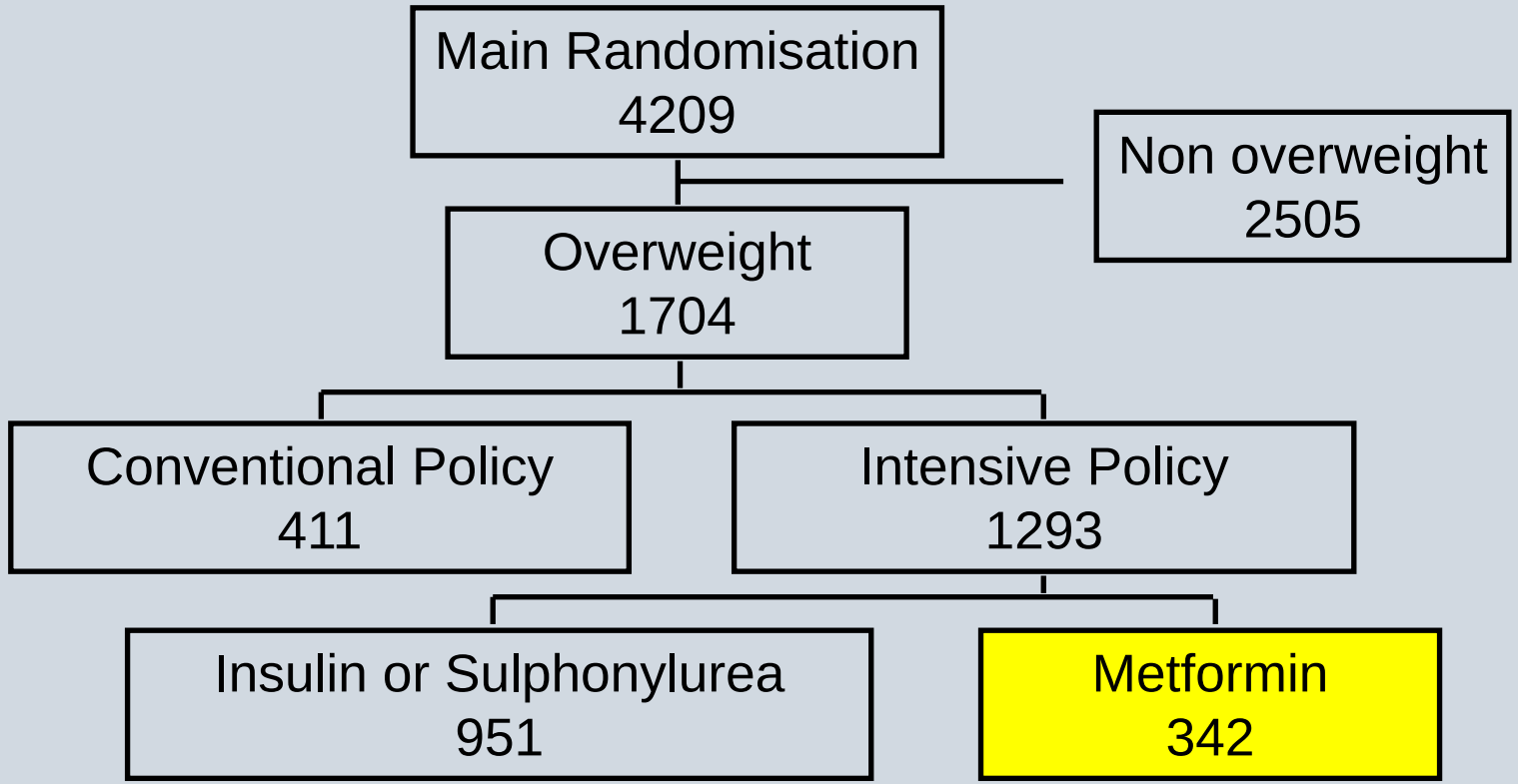
MEGLITINIDES

1921 | 1930’s | 1950’s | 1980’S | 1990’S

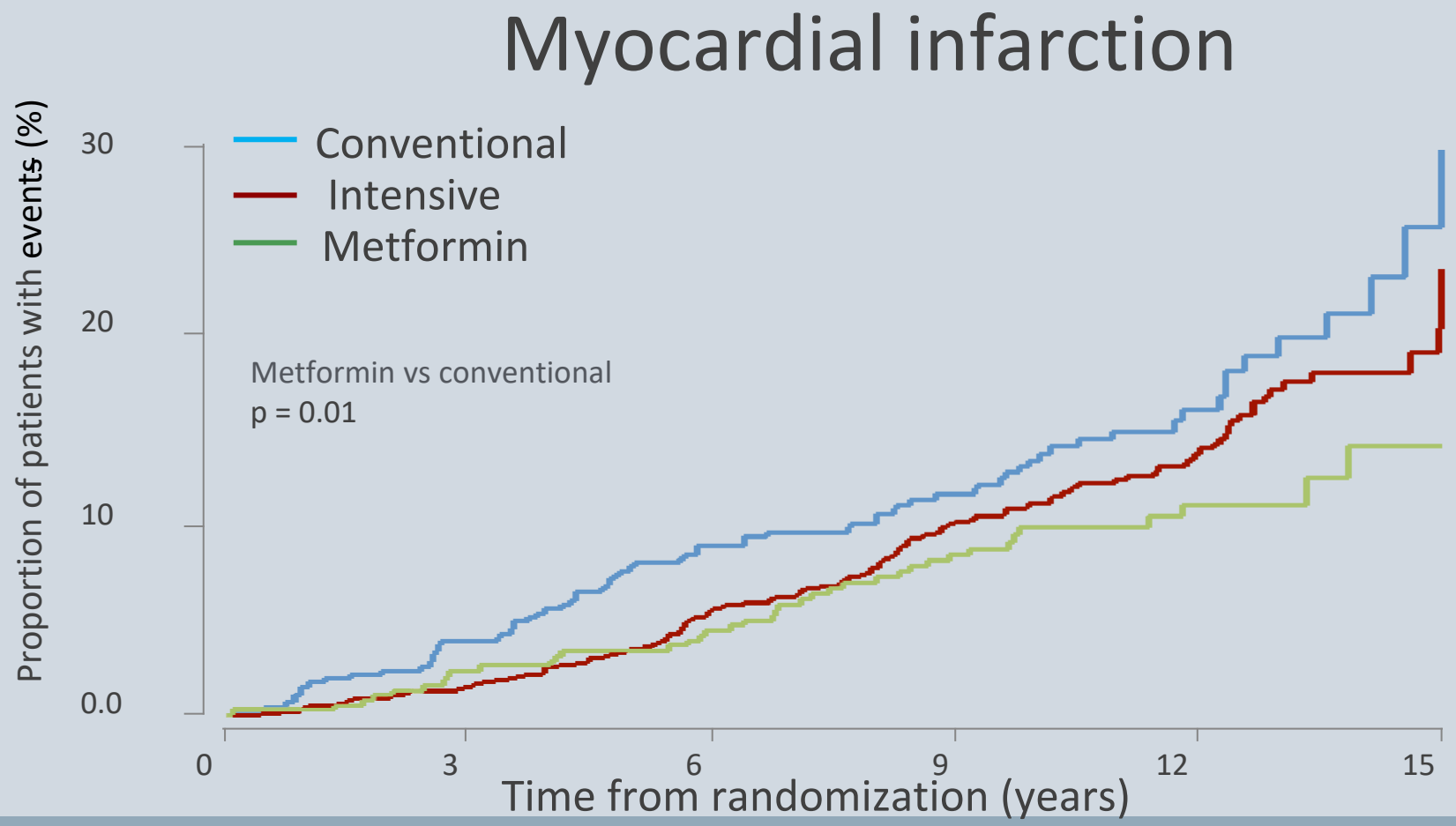
INSULIN

SULPHONYLUREAS

UKPDS: Newly-diagnosed obese, type 2 diabetes patients randomized to metformin, intensive glucose control (with SU or insulin), or conventional glucose control (SU or insulin)



UKPDS



UKPDS 34. Lancet 1998;352:854–65.

The data for Metformin is…thin

But all other therapies are tested on a background of metformin

Diabetes medications through the years

INSULIN

METFORMIN
ALPHA GLUCOSIDASE INHIBITORS
THIAZOLIDINEDIONES
MEGLITINIDES

DPP4 inhibitors

SGLT2 inhibitors

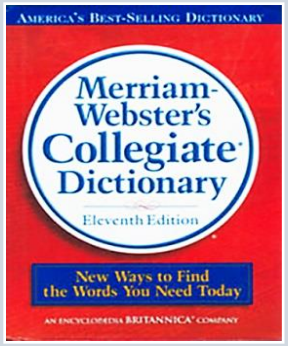
1921 | 1930's | 1950's | 1980'S | 1990'S | 2000 | 2001-10 | 2010-15

GLP1 receptor agonists

INSULIN

SULPHONYLUREAS

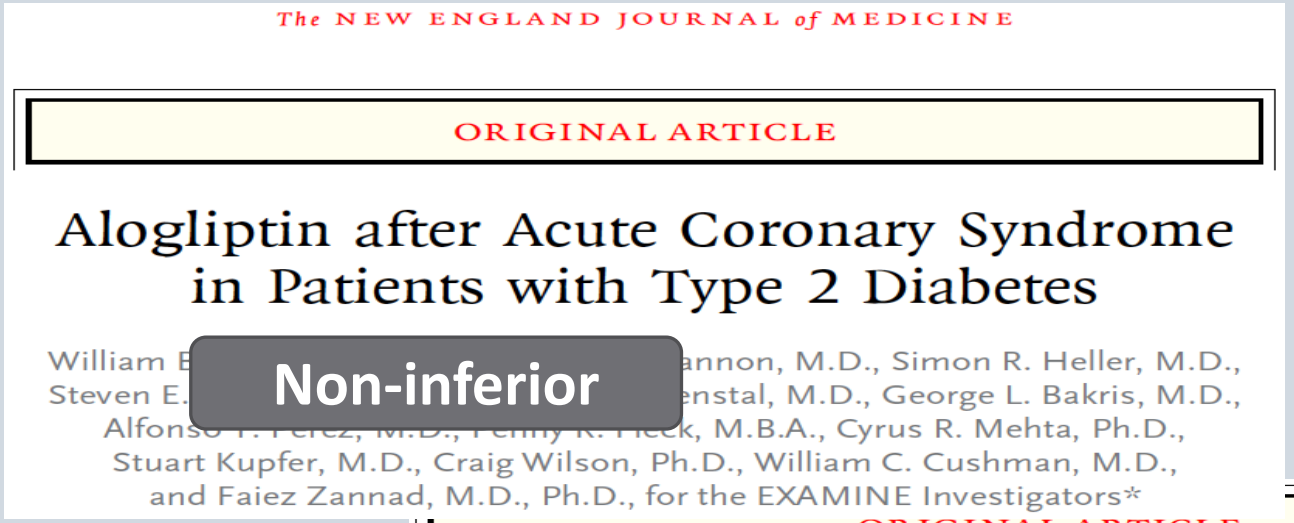
“Although cardiovascular disease is the cause of death in 75% of diabetics, there exist no well-designed, adequately-powered comparative effectiveness trials evaluating macrovascular outcomes for diabetes drugs”



glu-co-cen-tricity |ˈgloōkō senˈtrisitē
noun

The irrational belief that lowering blood sugar using virtually any pharmacological means will produce a reliable reduction in adverse outcomes

The DPP-4 inhibitor Studies


The NEW ENGLAND JOURNAL of MEDICINE

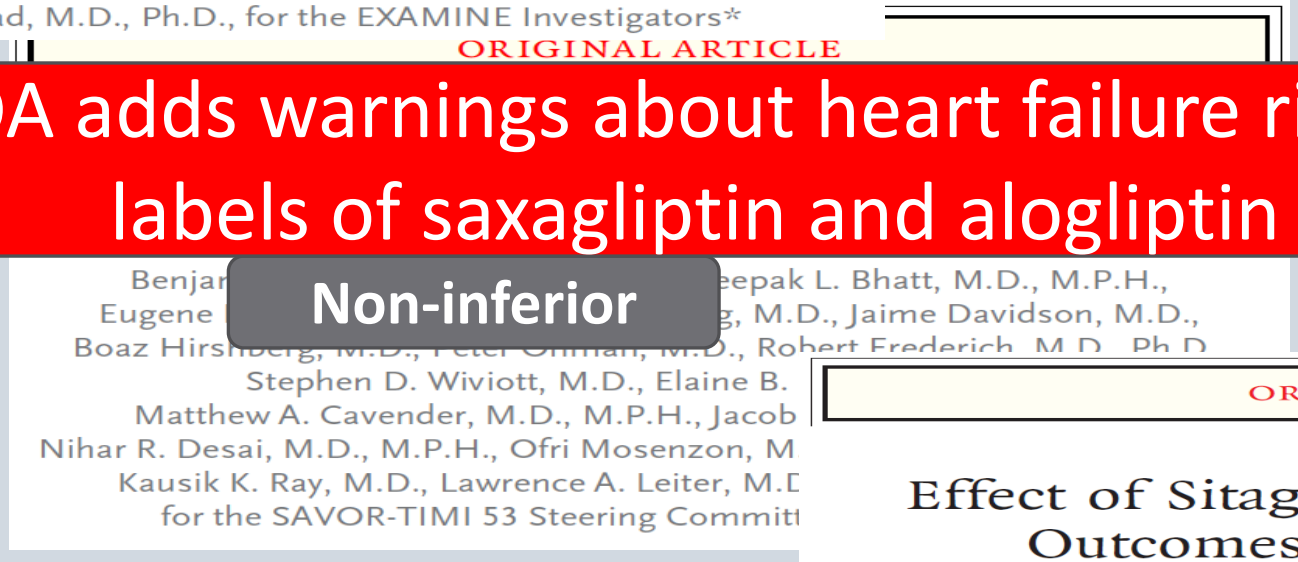
ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William E[illegible]annon, M.D., Simon R. Heller, M.D., Steven E.[illegible]enstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Heck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

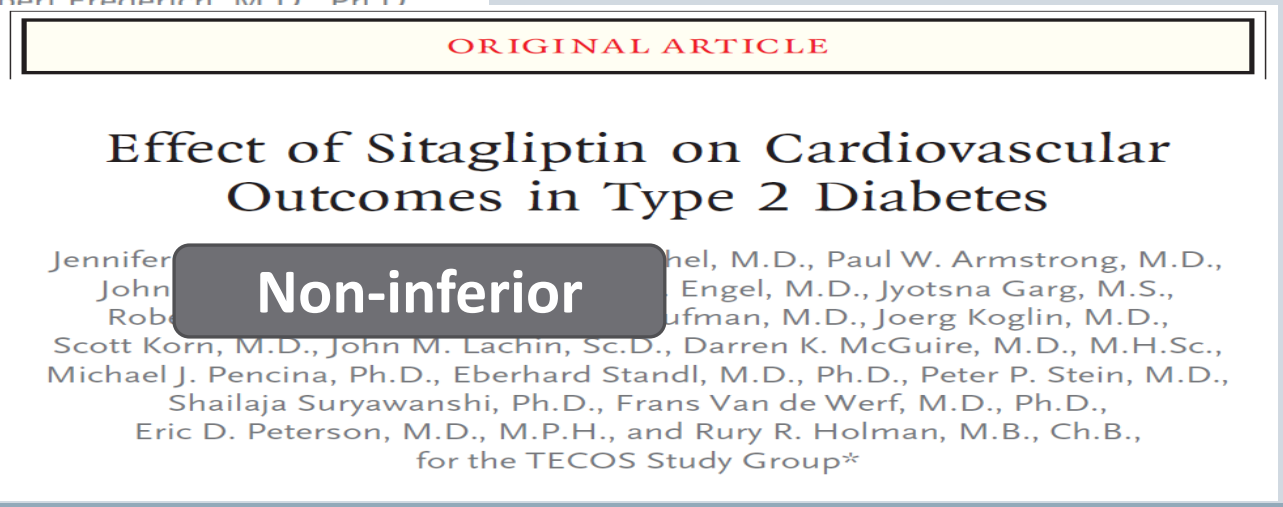
Non-inferior

FDA adds warnings about heart failure risk to labels of saxagliptin and alogliptin


ORIGINAL ARTICLE

Benjar[illegible]eepak L. Bhatt, M.D., M.P.H., Eugene [illegible]g, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Matthew A. Cavender, M.D., M.P.H., Jacob Nihar R. Desai, M.D., M.P.H., Ofri Mosenzon, M Kausik K. Ray, M.D., Lawrence A. Leiter, M.D for the SAVOR-TIMI 53 Steering Committ

Non-inferior


ORIGINAL ARTICLE

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Jennifer[illegible]hel, M.D., Paul W. Armstrong, M.D., John[illegible]Engel, M.D., Jyotsna Garg, M.S., Robe[illegible]ufman, M.D., Joerg Koglin, M.D., Scott Korn, M.D., John M. Lachin, Sc.D., Darren K. McGuire, M.D., M.H.Sc., Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.D., Peter P. Stein, M.D., Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D., Eric D. Peterson, M.D., M.P.H., and Rury R. Holman, M.B., Ch.B., for the TECOS Study Group*

Non-inferior

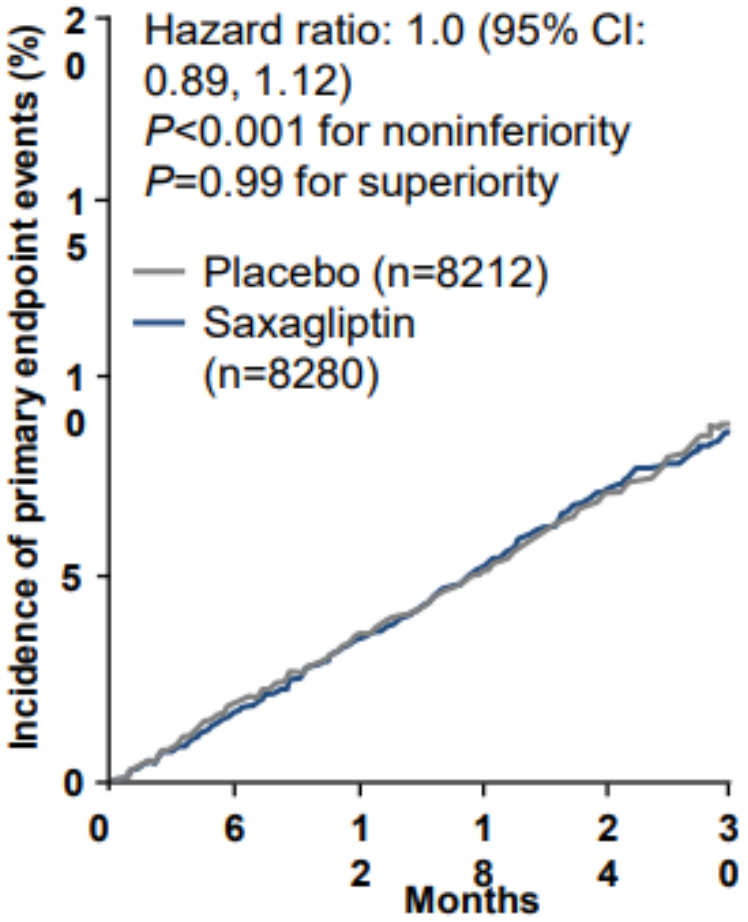
White WB et. al. N Engl J Med 2013; 369:1327-1335

Scirica BM et. al. N Engl J Med 2013; 369:1317-1326

Green JB et. al. N Engl J Med 2015; 373:232-242

Saxagliptin (SAVOR trial)

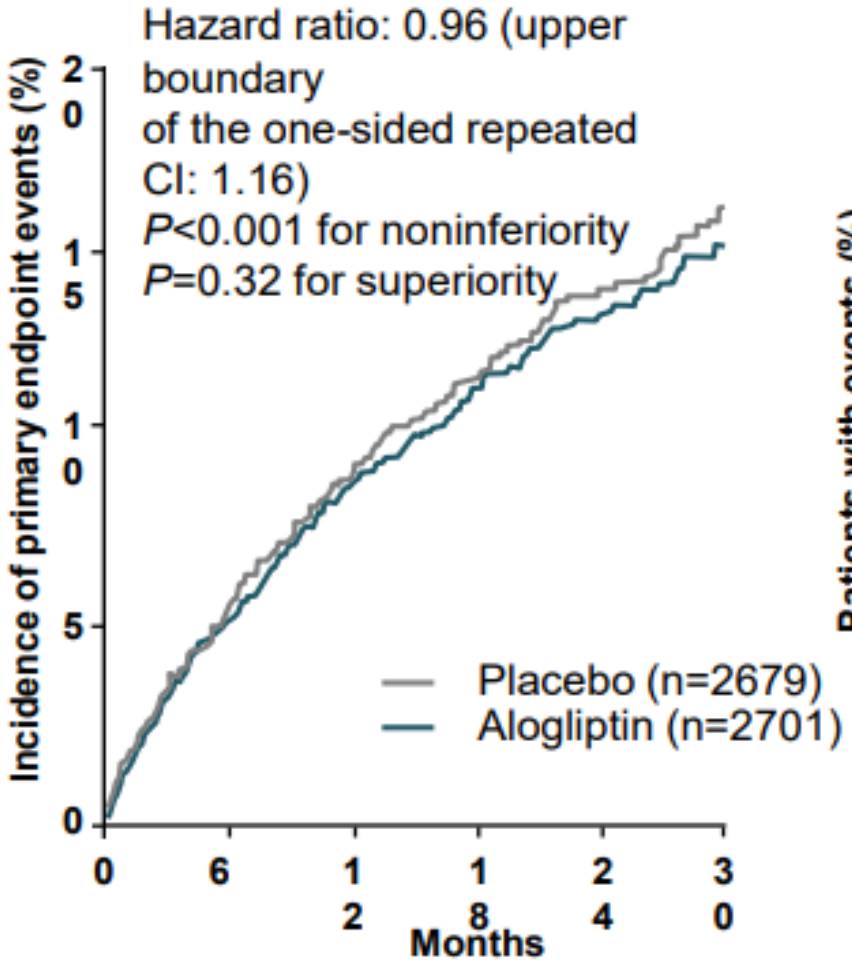
Primary endpoint: Composite of CV death, myocardial infarction, or ischemic stroke



Scirica BM et. al. N Engl J Med 2013; 369:1317-1326

Alogliptin (EXAMINE trial)

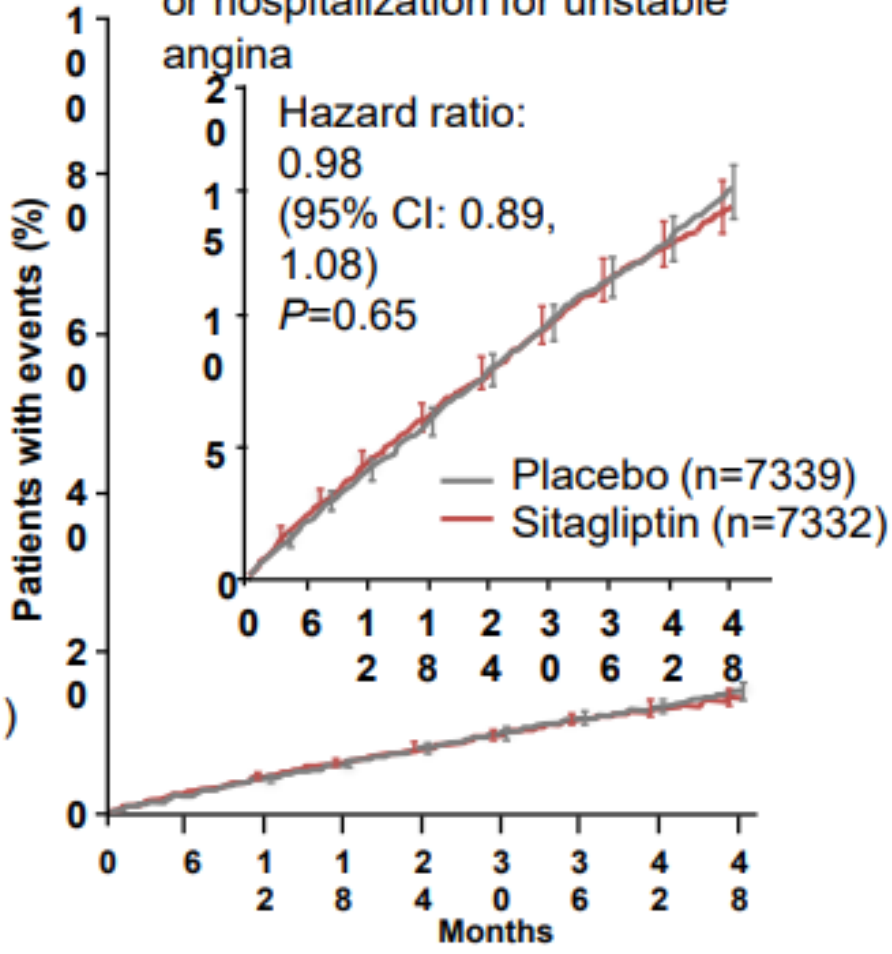
Primary endpoint: Composite of CV death, nonfatal myocardial infarction, or nonfatal stroke



White WB et. al. N Engl J Med 2013; 369:1327-1335

Sitagliptin (TECOS trial)

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



Green JB et. al. N Engl J Med 2015; 373:232-242

The GLP1-RA Studies

ORIGINAL ARTICLE

Lixisenatide in Patients with Type 2 Diabetes ...te Coronary Syndrome

Non-inferior

Marc A. Pfeffer, M.D., Ph.D., Brian Claggett, Ph.D., Rafael Diaz, M.D.,
Kenneth Dickstein, M...
Francesca C. ...
Eldrin F. ...
John J.V. Mc...
Matthew C. Riddle, M...

ORIGINAL ARTICLE

Liraglutide and Cardiovascular Outcomes ...e 2 Diabetes

SUPERIOR

Steven ... aniels, M.D., Kirstine Brown-Frandsen, M.D.,
Peter Kristensen, M...
Michael A. Nauck, M.D.
Neil R. Poulter, ...
William M. Steinberg, M.D...
Richard M. Bergenstal, M.D...
Steering Committee ...

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes ...ts with Type 2 Diabetes

SUPERIOR

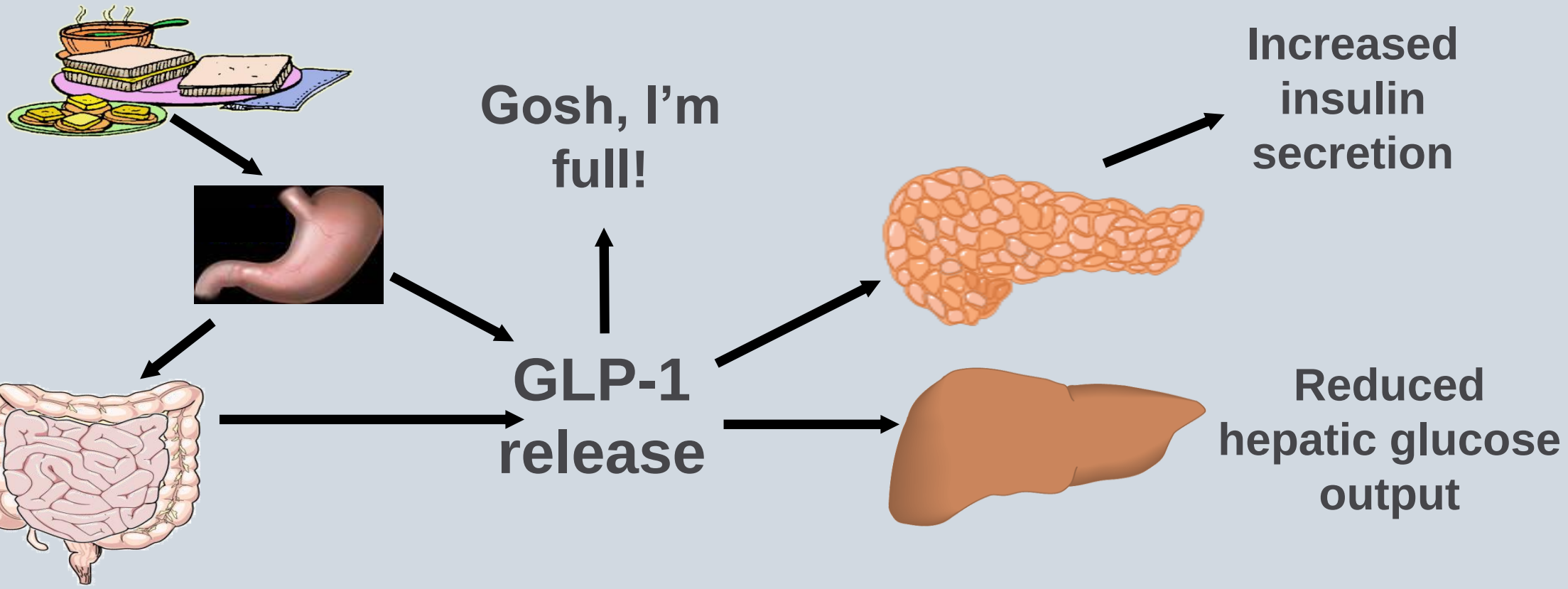
Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D.,
Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D.,
Ildik...
Jochen S...
Oluf Hansen, ...
and Ti...

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

SUPERIOR

Pfeffer MA et. al. NEJM 2015; 373:2247-2257 Marso SP et.al. NEJM 2016; 375:311-322 Marso SP et. al. NEJM 2016; 375:1834-1844 Hernandez AF et. al. Lancet 2018; 392:1519-1529

GLP-1 : Mechanisms of Action

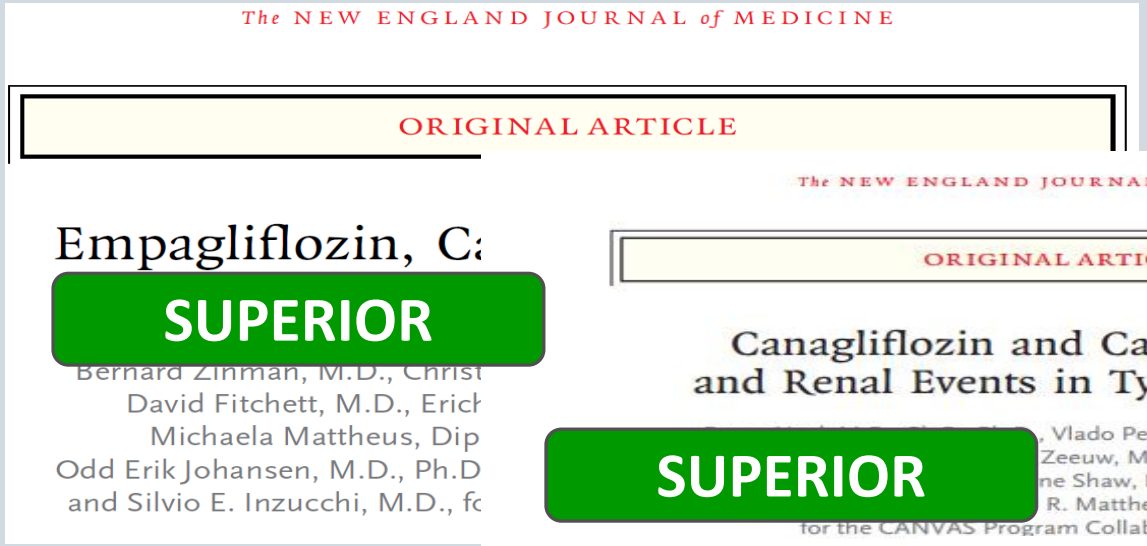


Select side effects with GLP-1 Receptor Agonists

Risks

- Common side effects of nausea, vomiting and diarrhea
- Increase hypoglycemic effect of insulin and sulfonylureas
- Increased risk gallbladder events
- Increased retinopathy complications in patients with baseline retinopathy and rapid improvement in glycemic control (semaglutide)

The SGLT-2i Studies

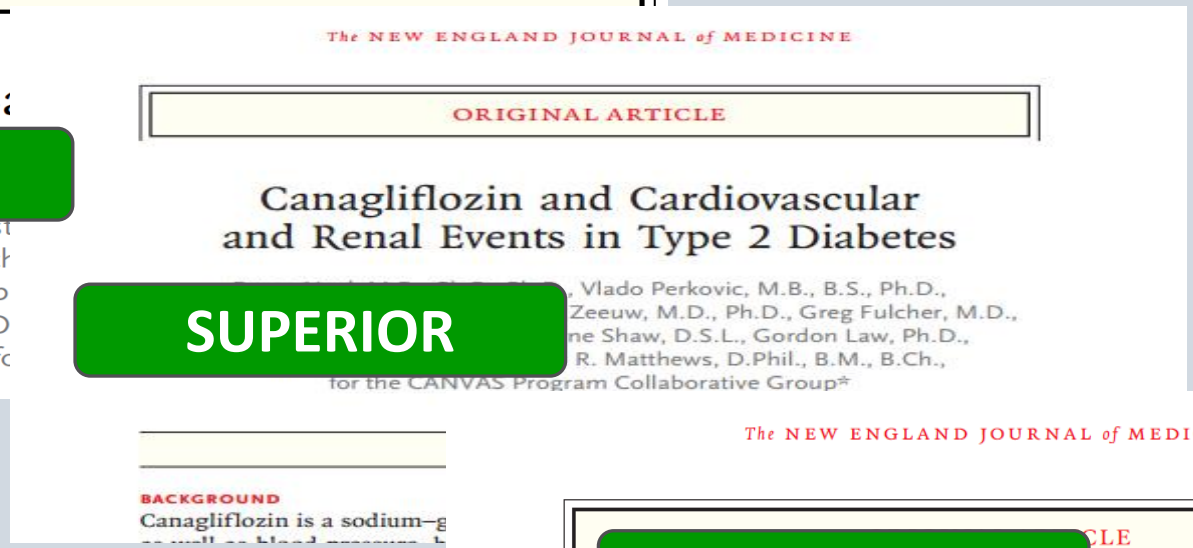

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, C

SUPERIOR

Bernard Zinman, M.D., Christ
David Fitchett, M.D., Erick
Michaela Mattheus, Dip
Odd Erik Johansen, M.D., Ph.D
and Silvio E. Inzucchi, M.D., fc


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

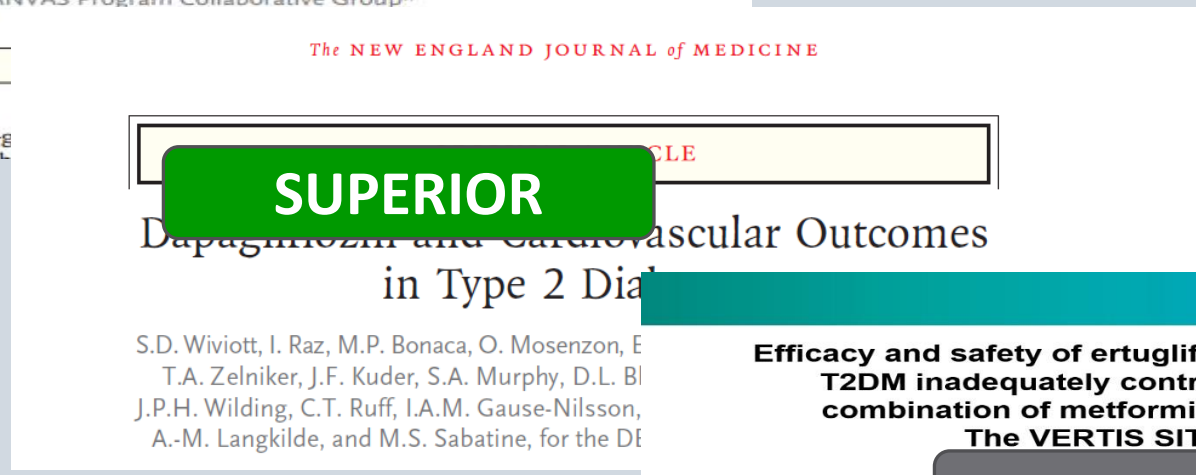
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

SUPERIOR

, Vlado Perkovic, M.B., B.S., Ph.D.,
Zeeuw, M.D., Ph.D., Greg Fulcher, M.D.,
ne Shaw, D.S.L., Gordon Law, Ph.D.,
R. Matthews, D.Phil., B.M., B.Ch.,
for the CANVAS Program Collaborative Group*

BACKGROUND

Canagliflozin is a sodium–g

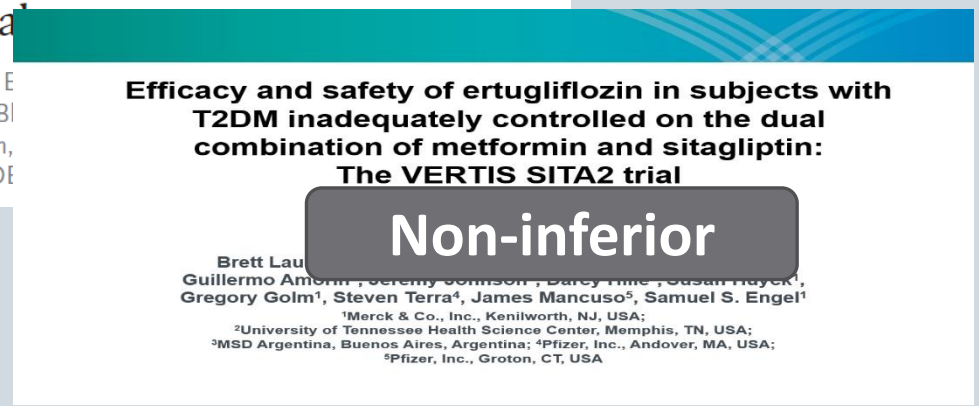

The NEW ENGLAND JOURNAL of MEDICINE

CLE

SUPERIOR

ascular Outcomes
in Type 2 Dia

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E
T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bl
J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson,
A.-M. Langkilde, and M.S. Sabatine, for the DE


Efficacy and safety of ertugliflozin in subjects with T2DM inadequately controlled on the dual combination of metformin and sitagliptin: The VERTIS SITA2 trial

Non-inferior

Brett Lau
Guillermo Amorin, Jeremy Johnson, Darcy Hille, Susan Hayek,
Gregory Golm[1], Steven Terra[4], James Mancuso[5], Samuel S. Engel[1]
[1]Merck & Co., Inc., Kenilworth, NJ, USA;
[2]University of Tennessee Health Science Center, Memphis, TN, USA;
[3]MSD Argentina, Buenos Aires, Argentina; [4]Pfizer, Inc., Andover, MA, USA;
[5]Pfizer, Inc., Groton, CT, USA

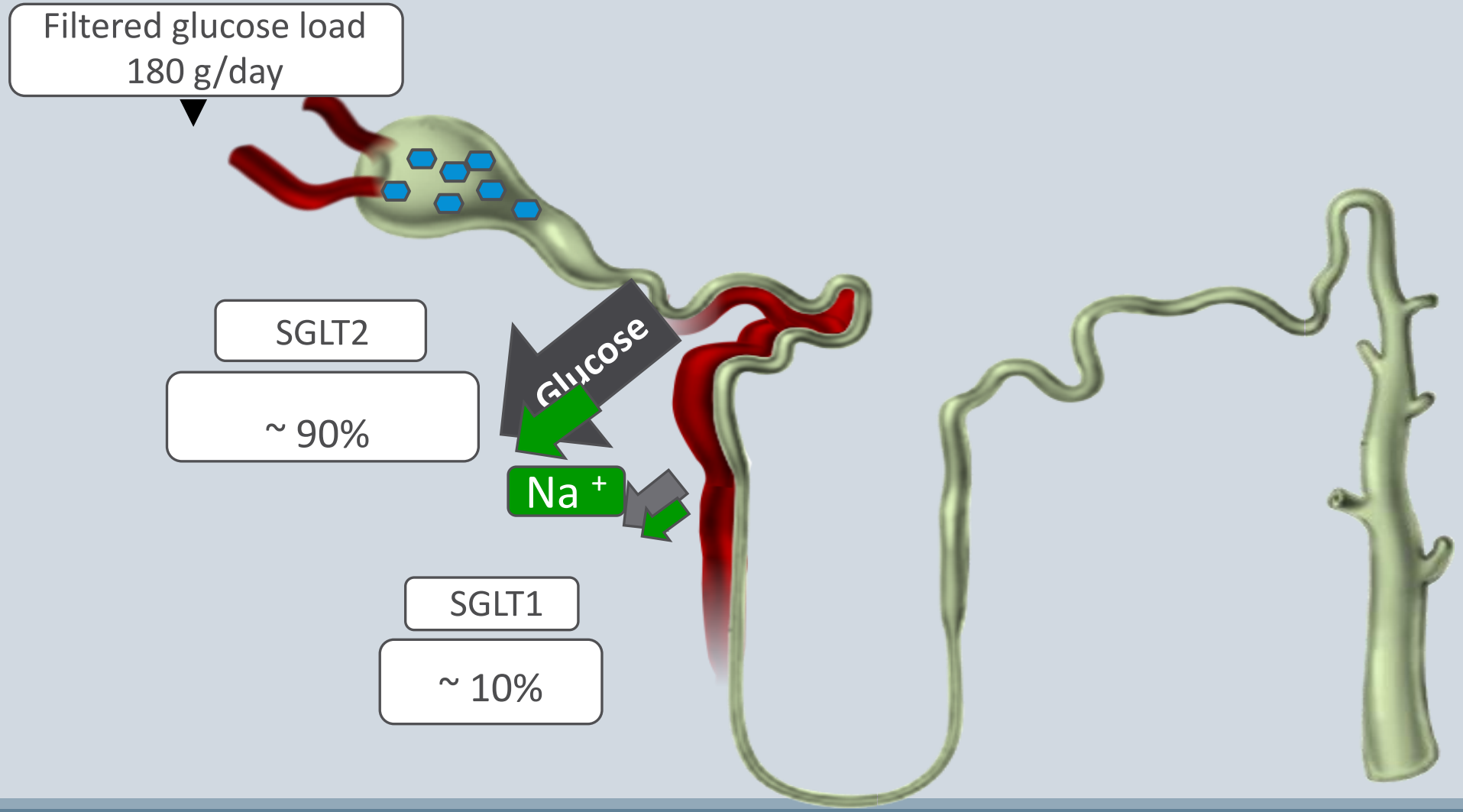
Zinman B et al. N Engl J Med 2015; 373: 2117-28

Neal B et al. N ngl J Med 2017. DOI: 10.1056/NEJMoa1611925

Wiviott SB et al. N ngl J Med 2018.

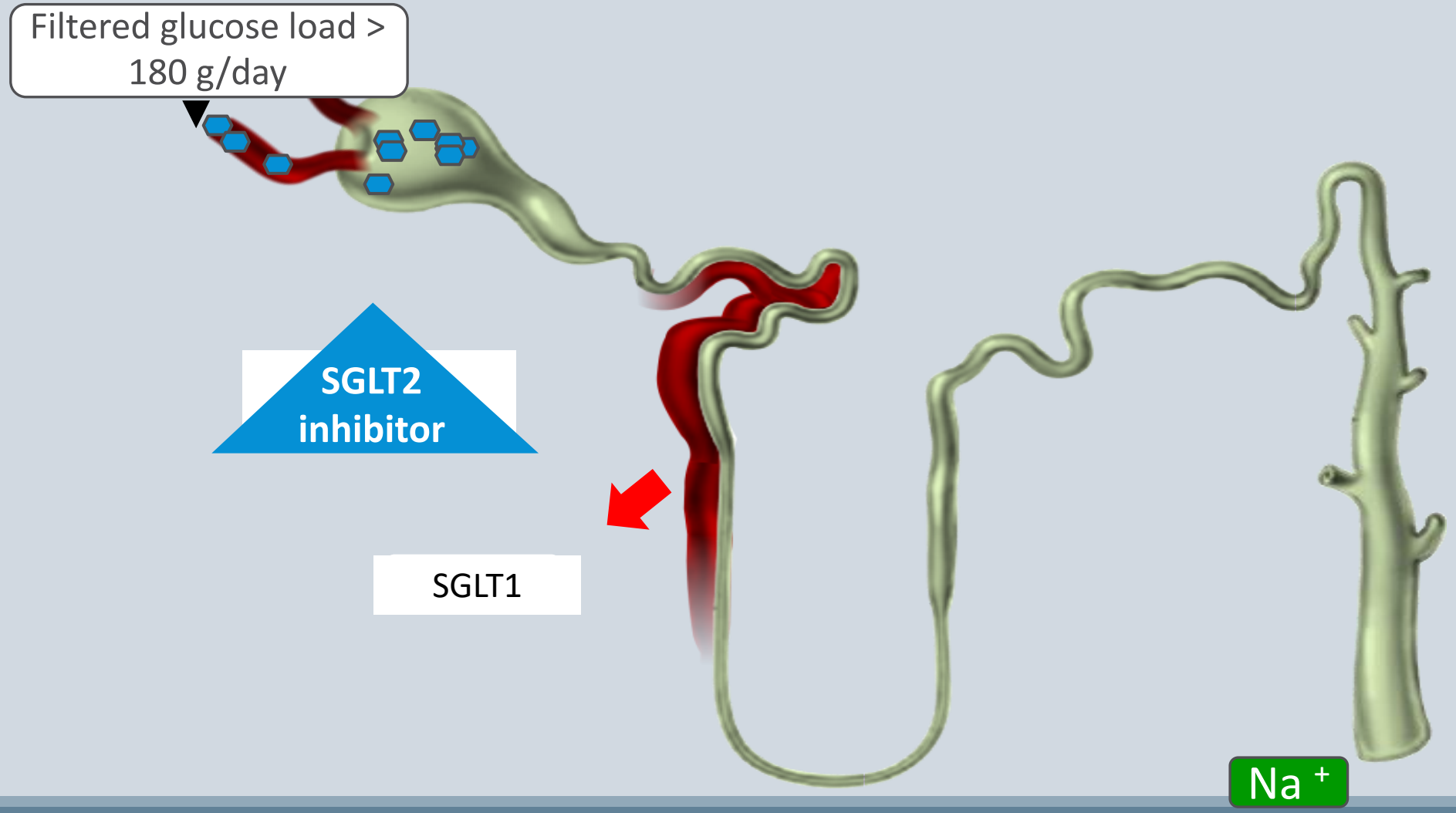
Presented at EASD 2016

Renal handling of glucose



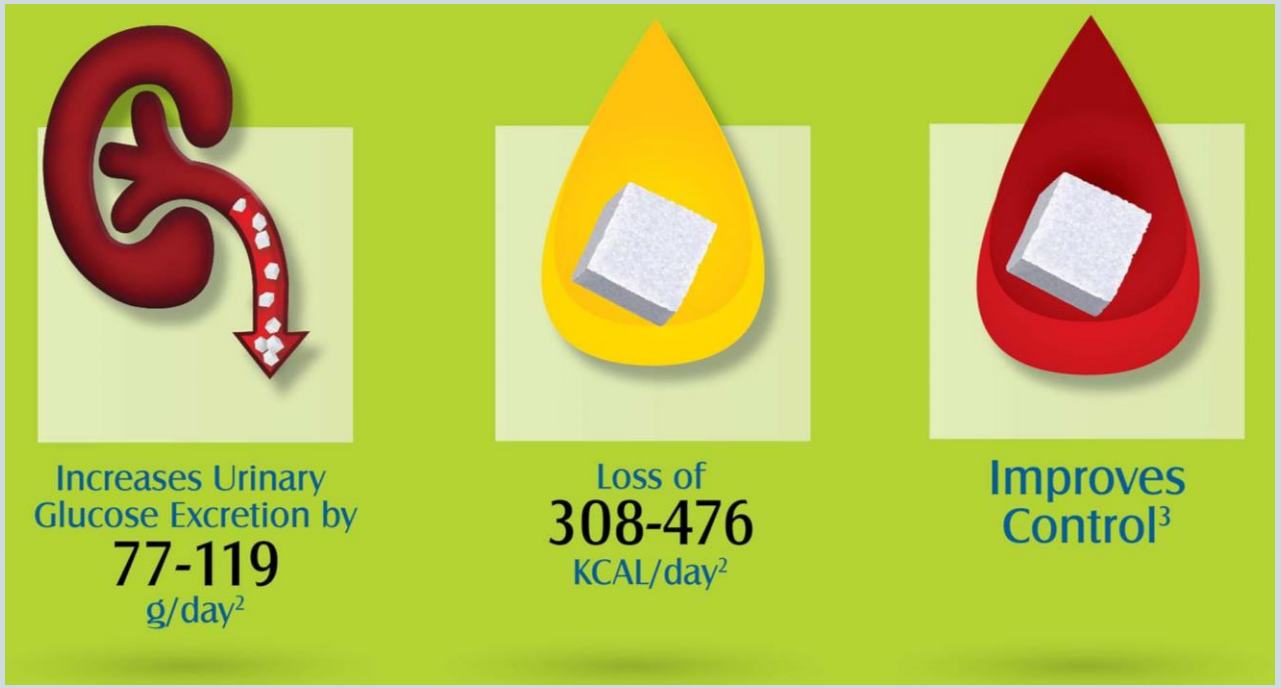
Gerich JE. *Diabet Med*. 2010;27:136–142.

SGLT2 inhibitor mechanism



1Bakris et al. Kidney Int 2009;75;1272–7.

SGLT2 inhibitors: Glucose loss



1 g glucose = 4 kcal

1. Nomura S, et al. J Med Chem. 2010; 53(17):6355-6360. 2. Sha S, et al.; Diabetes Obes Metab. 2011;13(7):669-672. 3. Liang Y, et al. PLoS One. 2012; 7(2):e30555. 4. Devineni D, et al. Diabetes Obes Metab. 2012. 5. Rosenstock J, et al. Diabetes Care. 2012 Abdul-Ghani MA, DeFronzo RA. Endocr Pract. 2008; Nair S, Wilding JP. J Clin Endocrinol Metab. 2010.

Select side effects with SGLT2 inhibitors

Risks

- Small increase in hemoglobin/hematocrit[1]
- Urinary tract infections[2]
- Polyuria / dehydration[2]
- Small increase in LDL-C[2]
- Diabetic ketoacidosis[3]
- Genital mycotic infections[3]
- Acute kidney injury[3]
- Dehydration[3]
- Orthostatic hypotension[3]
- Lower limb amputation (canagliflozin)[3]
- Fractures (canagliflozin)[3]

Fournier’s gangrene warning

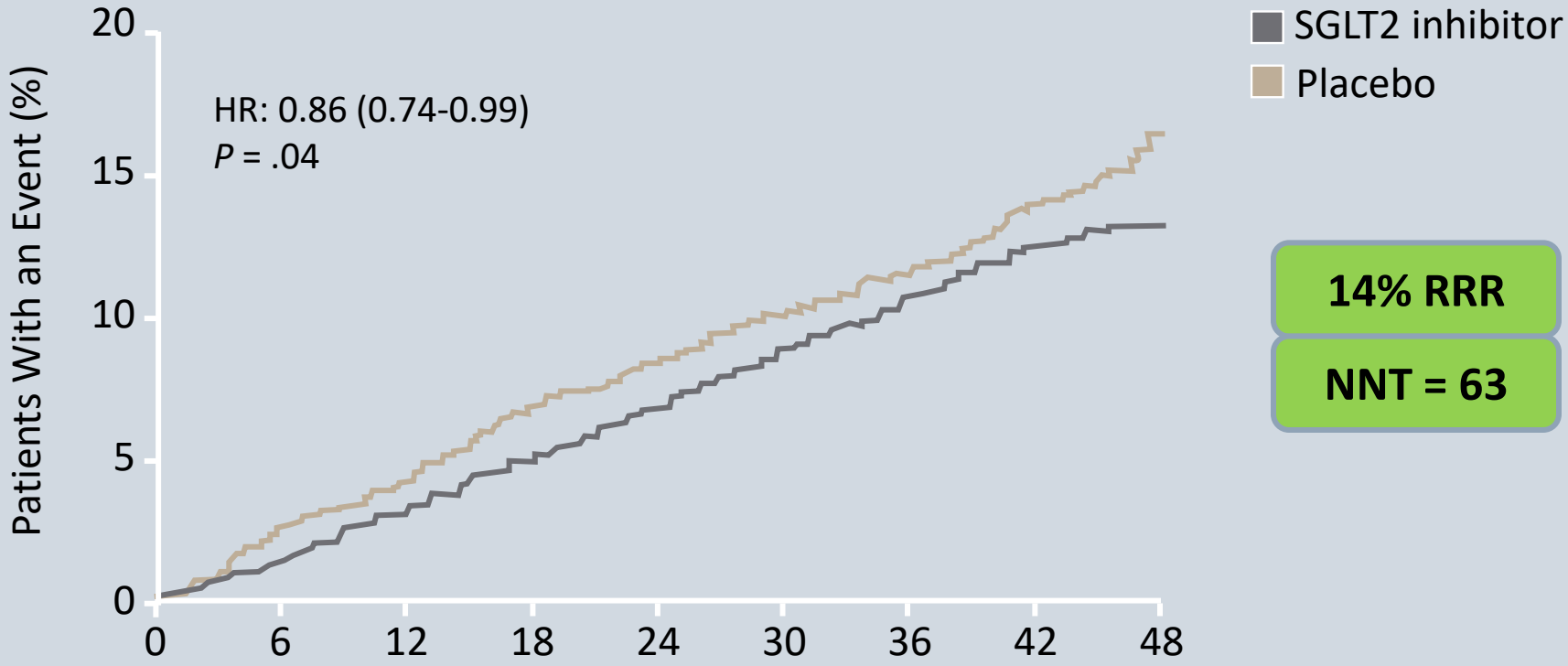
FDA issues warning on SGLT2 inhibitors for diabetes

Cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of T2D medicines called SGLT2 inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier’s gangrene.

August 29, 2018

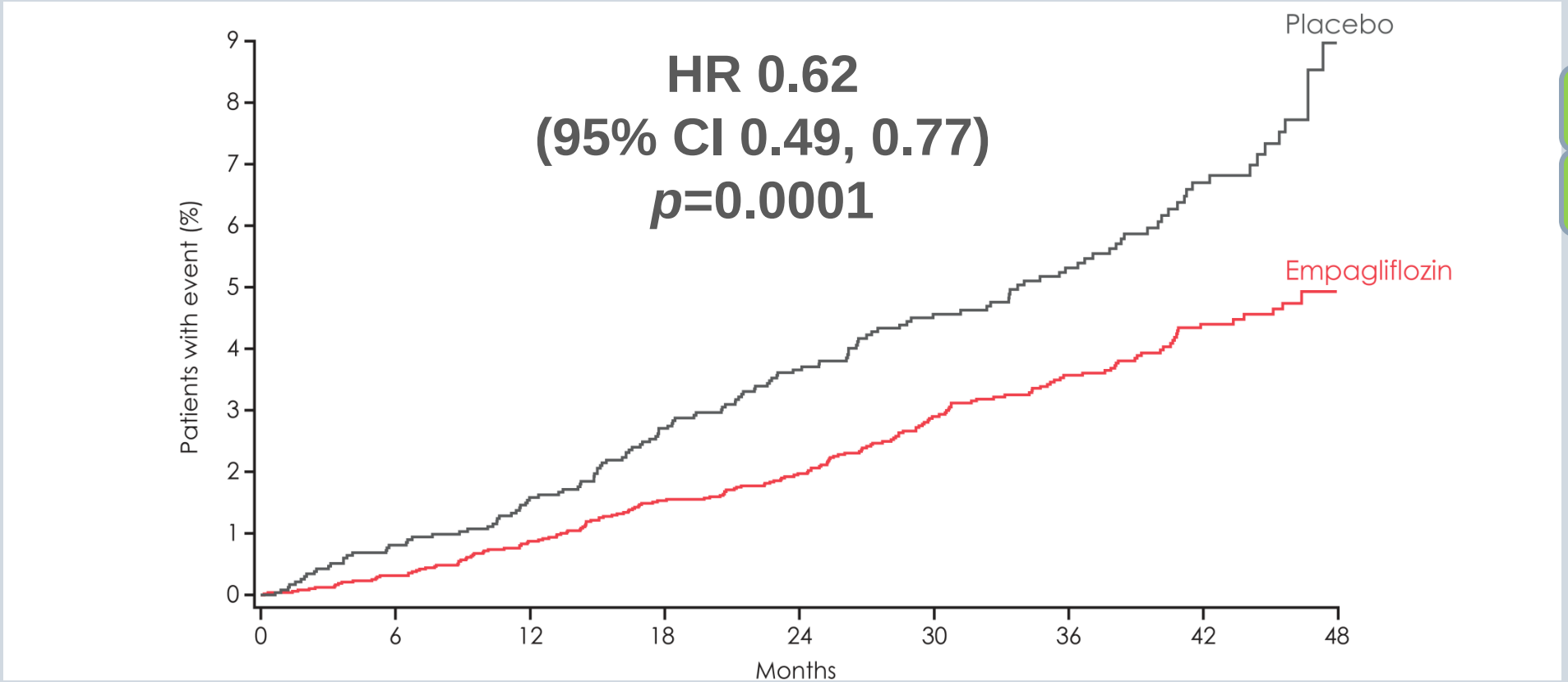
EMPA-REG OUTCOME: Primary Composite Outcome (MI, stroke, CV death)

7,020 patients with T2DM and CVD (N = 7020)



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

EMPA-REG OUTCOME: Cardiovascular death



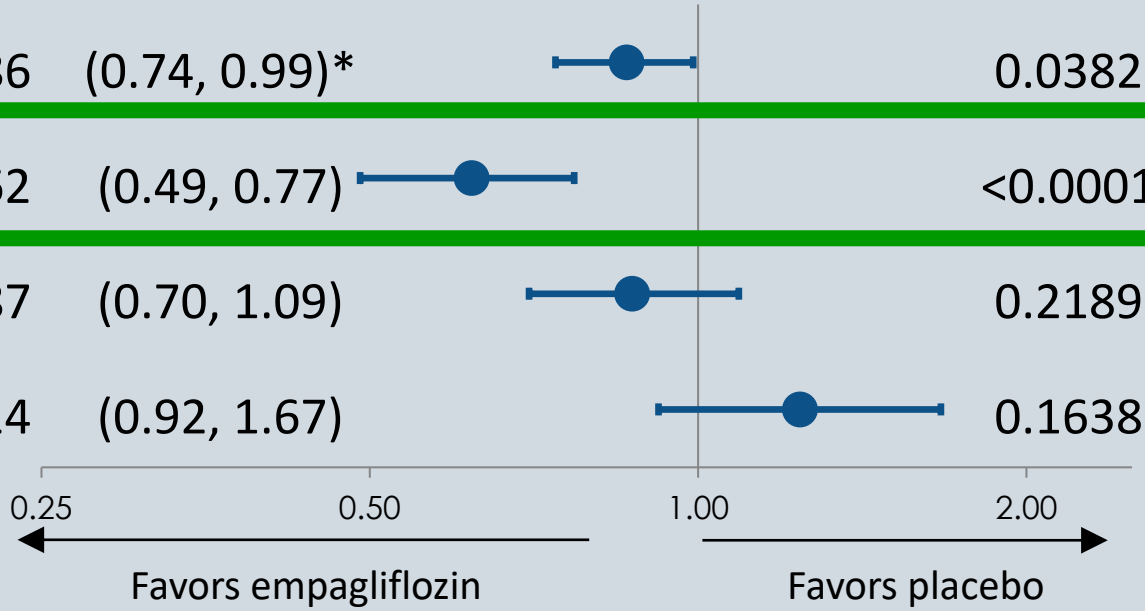
38% RRR

NNT = 45

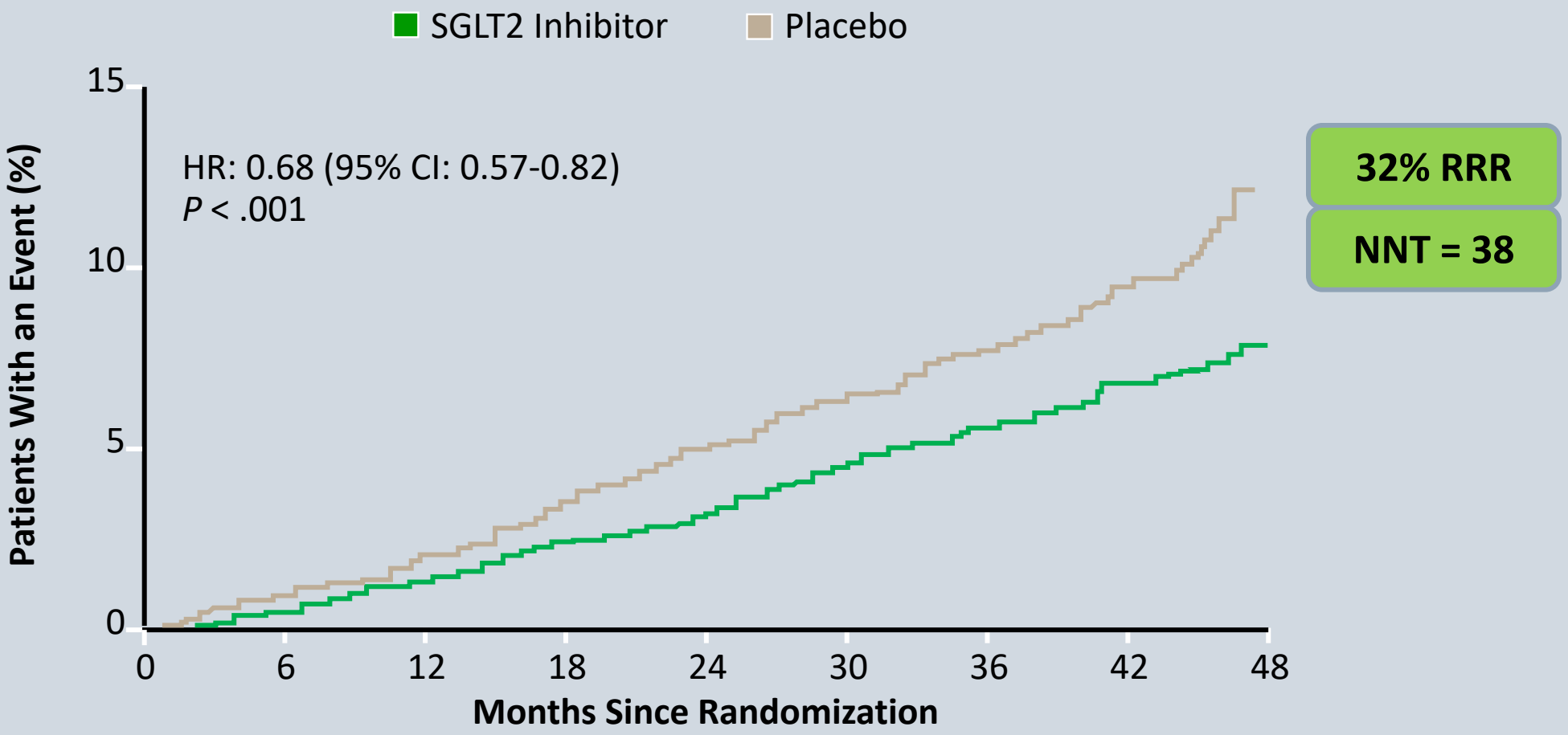
Zinman B *et al. N Engl J Med* 2015, published on-line, 9-1-15, DOI:10.1056/NEJMoa1504720

EMPA-REG OUTCOME: 3-point MACE

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
Primary outcome:					
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638

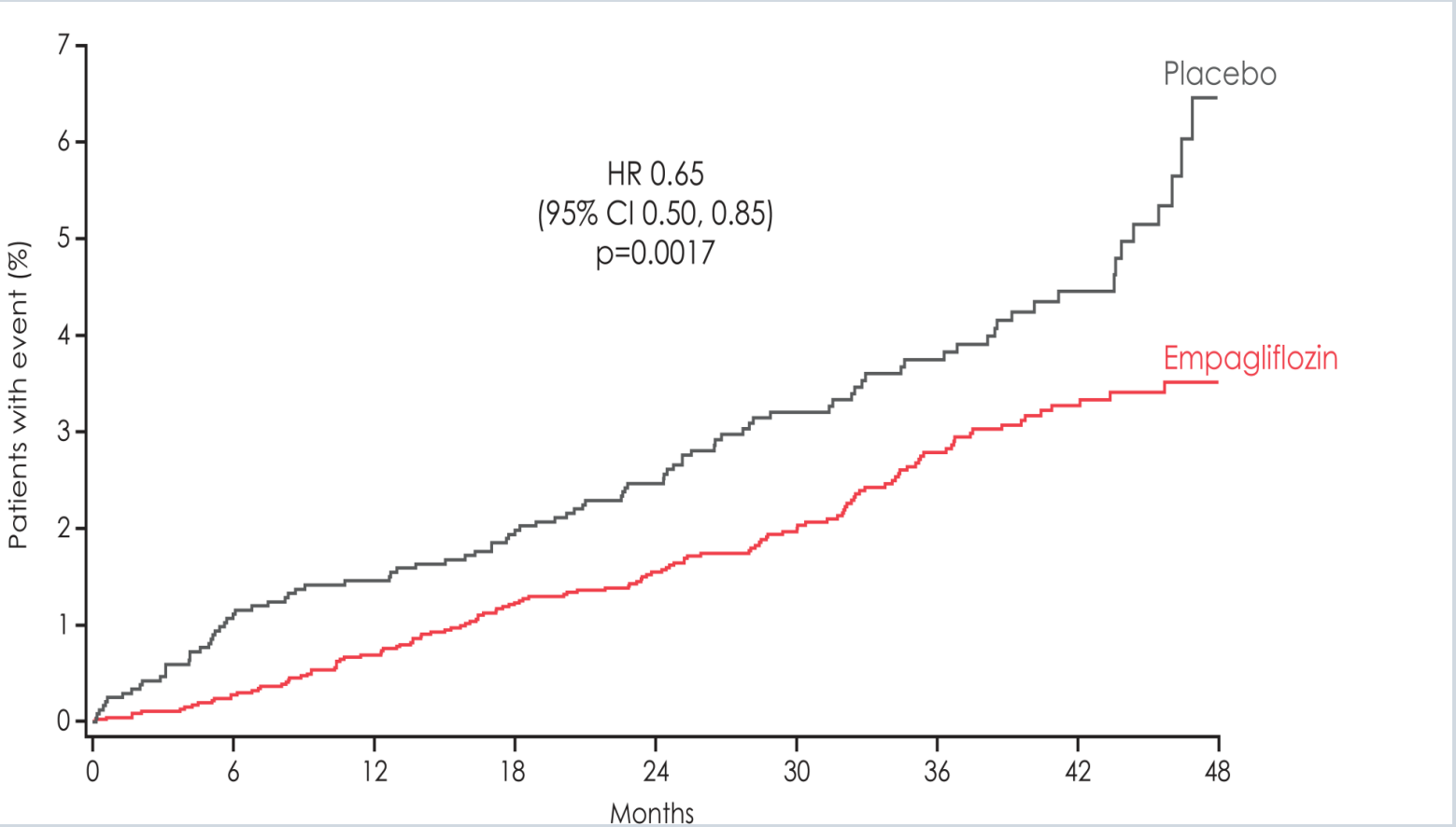


EMPA-REG OUTCOME: Total Mortality



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

EMPA-REG OUTCOME: Hospitalization for heart failure



35% RRR

NNT = 71

Zinman B et al. N Engl J Med 2015; 373: 2117-28

8. SGLT2 Inhibitors and GLP1-RA are cardiac drugs

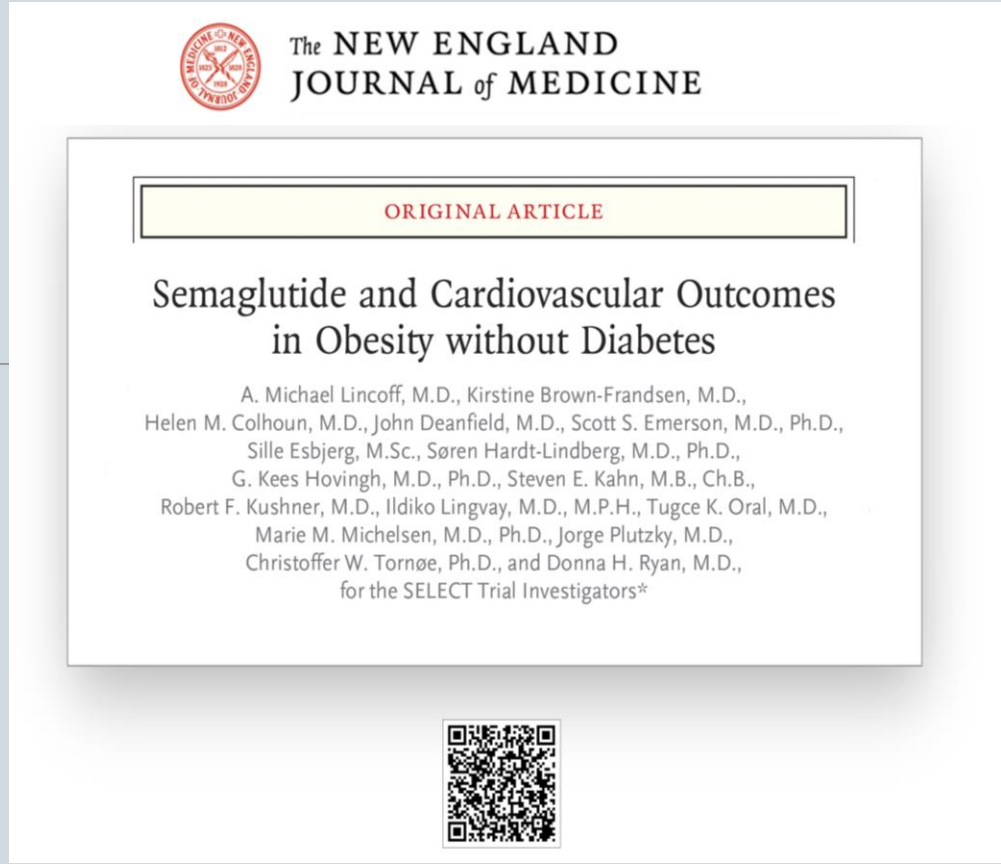
SELECT Trial

randomized, double-blind, placebo-controlled

event driven

superiority

804 clinical sites in 41 countries



Addition of semaglutide 2.4 mg SC once weekly to standard of care will reduce the incidence of major CV events among patients with overweight or obesity and pre-existing CV disease, who do not have diabetes.

Lincoff AM et al. for the SELECT Trial Investigators. N Engl J Med. 2023 Dec 14;389(24):2221-2232. doi: 10.1056/NEJMoa2307563. Epub 2023 Nov 11. PMID: 37952131.

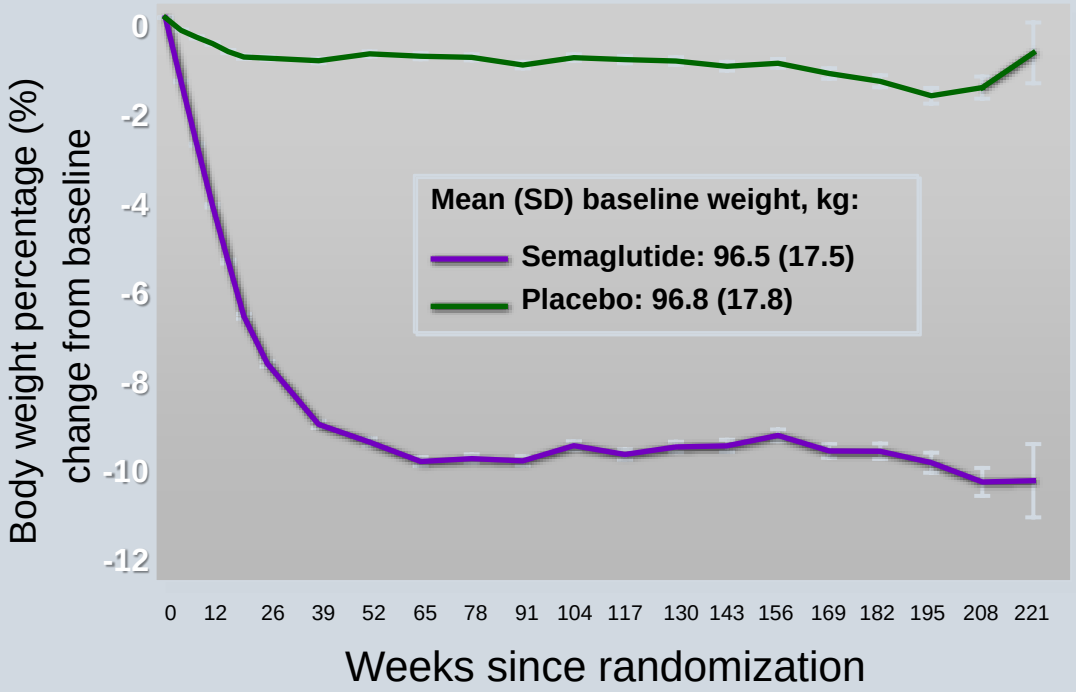
Baseline Characteristics

(Percent of patients unless otherwise noted)	Semaglutide (N = 8803)	Placebo (N = 8801)
Age (yrs) – mean ± SD	61.6 ± 8.9	61.6 ± 8.8
Female sex	27.8	27.5
Body Mass Index (BMI, kg/m^2) – mean ± SD	33.3 ± 5.0	33.4 ± 5.0
HbA_{1c} (%) – mean ± SD	5.78 ± 0.34	5.78 ± 0.33
Prior MI	76.4	76.2
Systolic BP (mm Hg) – mean ± SD	131.0 ± 15.6	130.9 ± 15.3
Statin therapy	87.7	87.6
LDL Cholesterol (mg/dL) – median (IQR)	78 (61 -102)	78 (61 -102)
Triglycerides (mg/dL) – median (IQR)	134 (99 - 188)	135 (100 - 190)

Lincoff AM et al. for the SELECT Trial Investigators. N Engl J Med. 2023 Dec 14;389(24):2221-2232. doi: 10.1056/NEJMoa2307563. Epub 2023 Nov 11. PMID: 37952131.

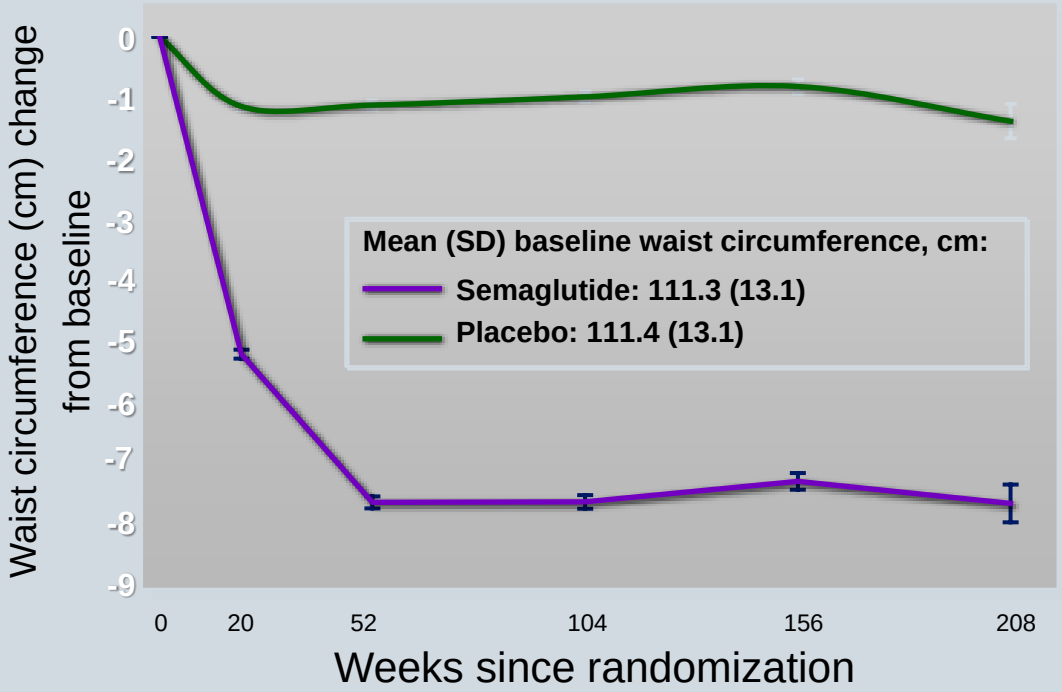
SELECT Trial – Metabolic Outcomes

Body Weight



Change in Body Weight by 104 Weeks
Semaglutide: -9.4%
Placebo: -0.9%

Waist Circumference



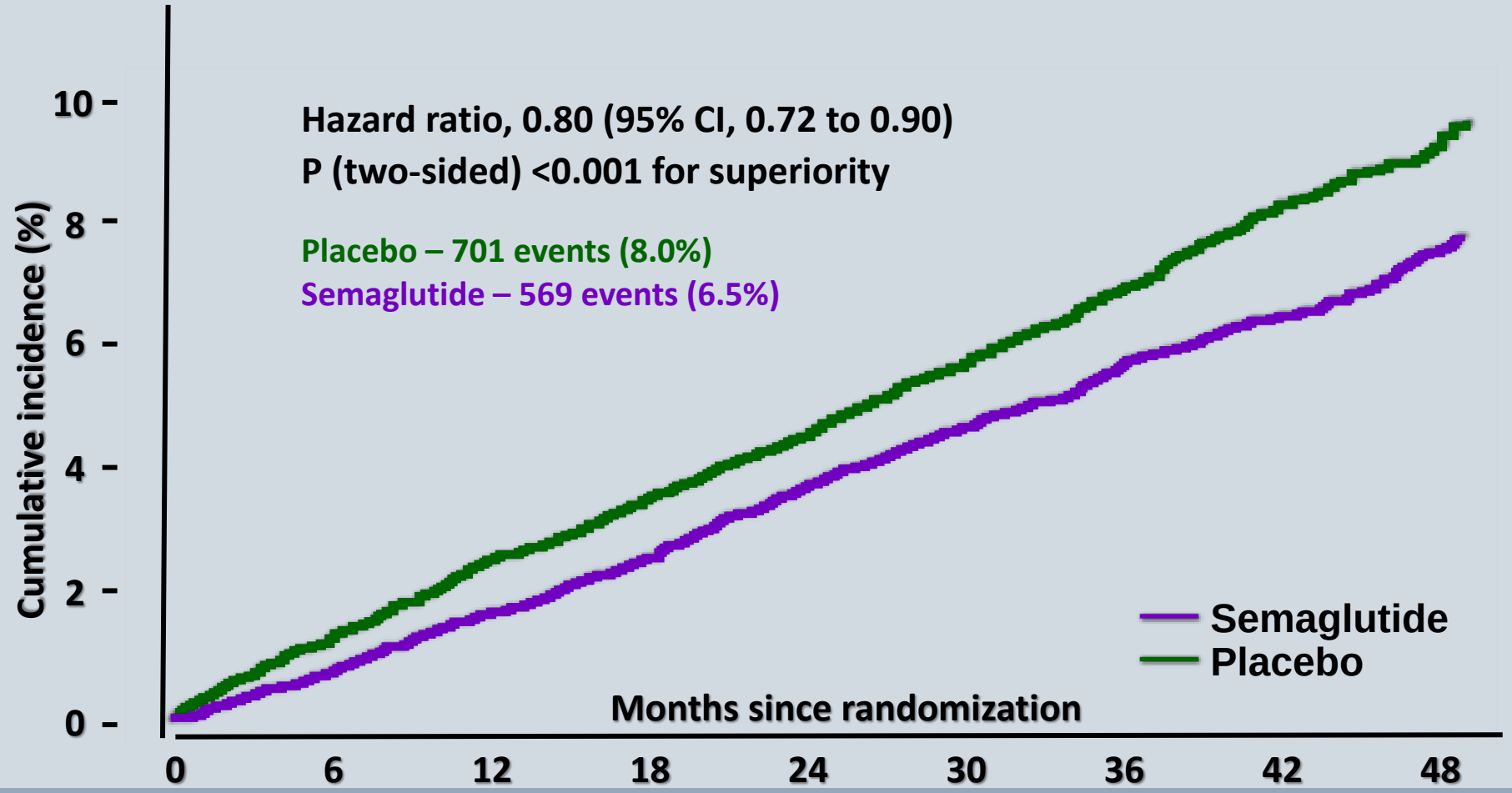
Change in Waist Circumference by 104 Weeks
Semaglutide: -7.6 cm
Placebo: -1.0 cm

Lincoff AM et al. for the SELECT Trial Investigators. N Engl J Med. 2023 Dec 14;389(24):2221-2232. doi: 10.1056/NEJMoa2307563. Epub 2023 Nov 11. PMID: 37952131.

SELECT Trial – Cardiovascular Efficacy

CV Death, Nonfatal MI, or Nonfatal Stroke

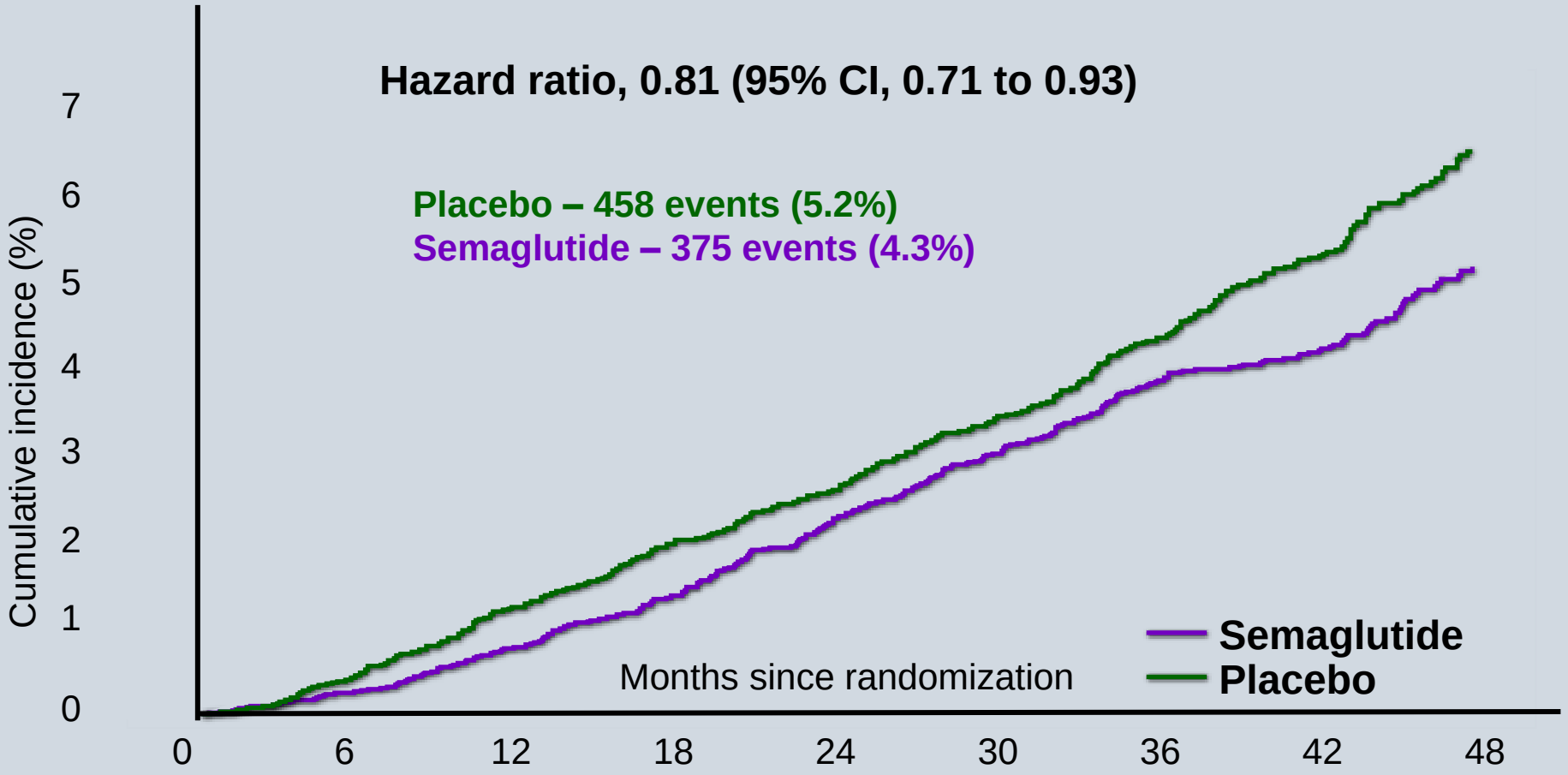
Primary Cardiovascular Composite Endpoint



Lincoff AM et al. for the SELECT Trial Investigators. N Engl J Med. 2023 Dec 14;389(24):2221-2232. doi: 10.1056/NEJMoa2307563. Epub 2023 Nov 11. PMID: 37952131.

SELECT Trial – Cardiovascular Efficacy

Death from Any Cause: 3rd Confirmatory Secondary Endpoint



Lincoff AM et al. for the SELECT Trial Investigators. N Engl J Med. 2023 Dec 14;389(24):2221-2232. doi: 10.1056/NEJMoa2307563. Epub 2023 Nov 11. PMID: 37952131.

Pharmacologic Therapy for Adults With Type 2 Diabetes

American Diabetes Association®
Standards of Medical Care

9.18 **In adults with type 2 diabetes and established or high risk of ASCVD, heart failure, and/or chronic kidney disease (CKD), the treatment plan should include agent(s) that reduce cardiovascular and kidney disease risk (e.g., sodium-glucose cotransporter 2 inhibitor [SGLT2] and/or glucagon-like peptide 1 receptor agonist [GLP-1 RA])** A

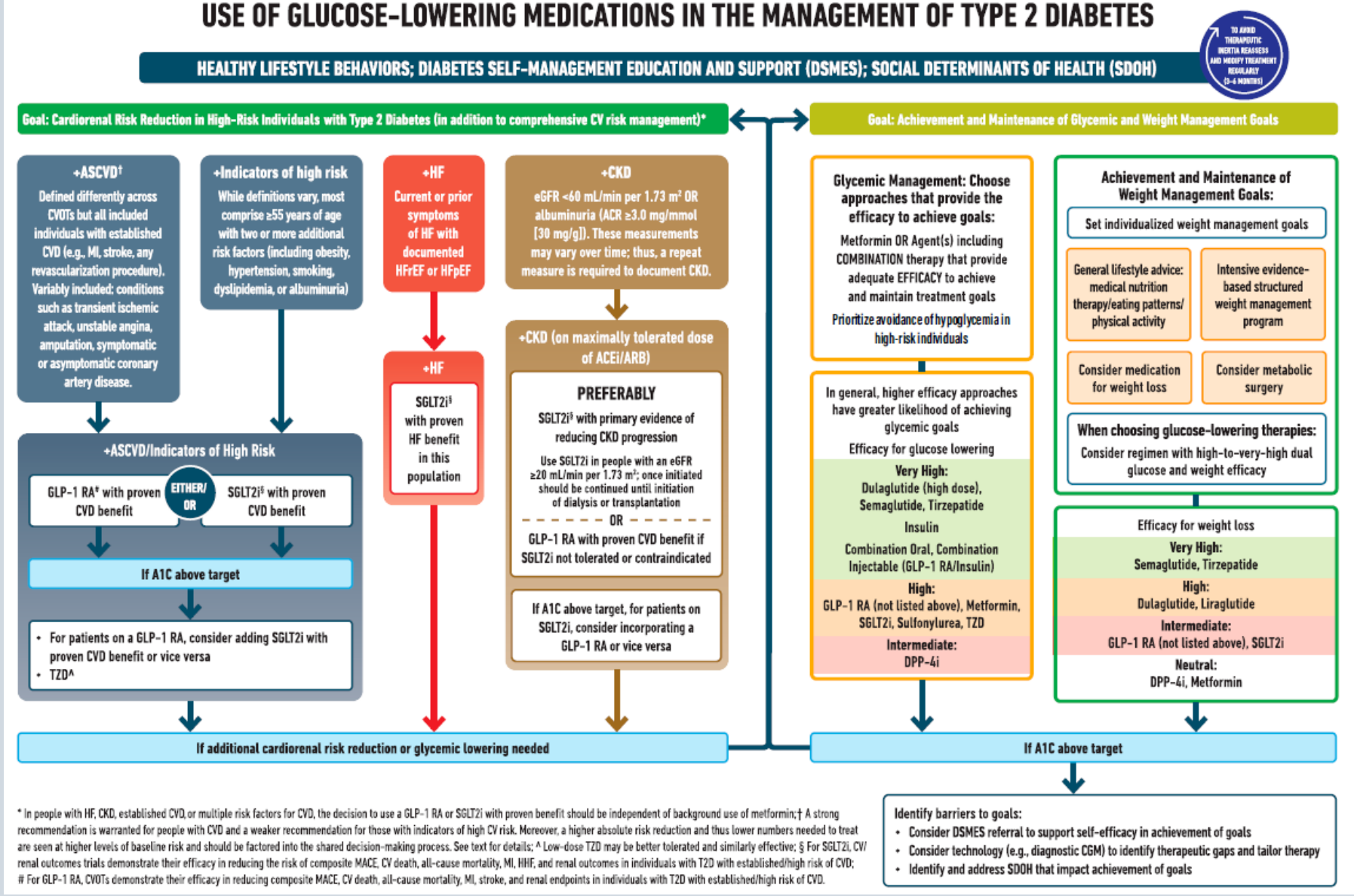
American Diabetes Association®
Standards of Medical Care

Cardiovascular Disease—Treatment

10.41 Among **people with type 2 diabetes who have established ASCVD or established kidney disease, an SGLT2 inhibitor or GLP-1 receptor agonist** with demonstrated cardiovascular disease benefit…**is recommended**. A

10.41c **In people with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, combined therapy with an SGLT2** inhibitor with demonstrated cardiovascular benefit **and a GLP-1** receptor agonist with demonstrated cardiovascular benefit **may be considered**... **A**

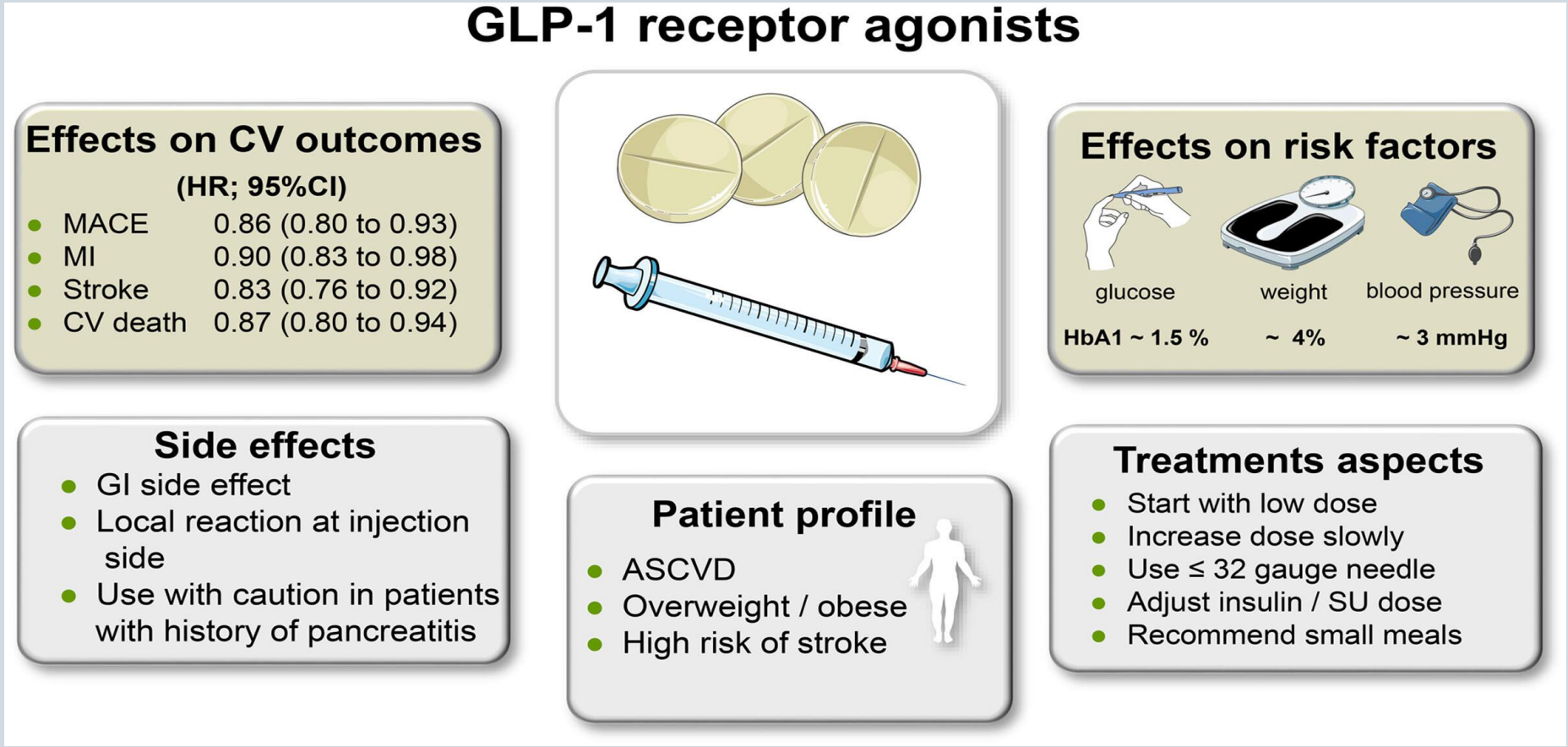
USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

Pharmacologic Approaches to Glycemic Treatment:
Standards of Care in Diabetes - 2024. *Diabetes Care* 2024;47(Suppl. 1):S158-S178

Tips for Initiating GLP-1 Receptor Agonists



Nikolaus Marx. Circulation. GLP-1 Receptor Agonists for the Reduction of Atherosclerotic Cardiovascular Risk in Patients With Type 2 Diabetes, Volume: 146, Issue: 24, Pages: 1882-1894, DOI: (10.1161/CIRCULATIONAHA.122.059595)

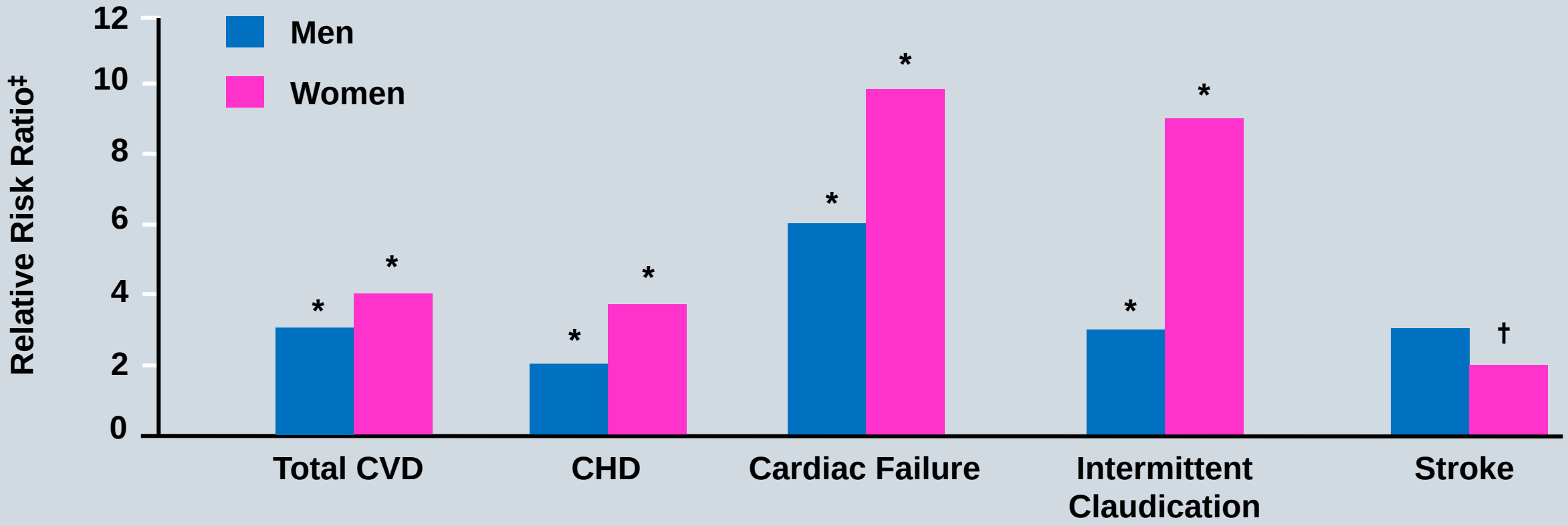
GLP-1 RA and surgery

…for patients on weekly dosing consider holding GLP-1 agonists a week prior to the procedure/surgery.

American Society of Anesthesiology

9. Diabetes is a powerful risk factor for heart failure

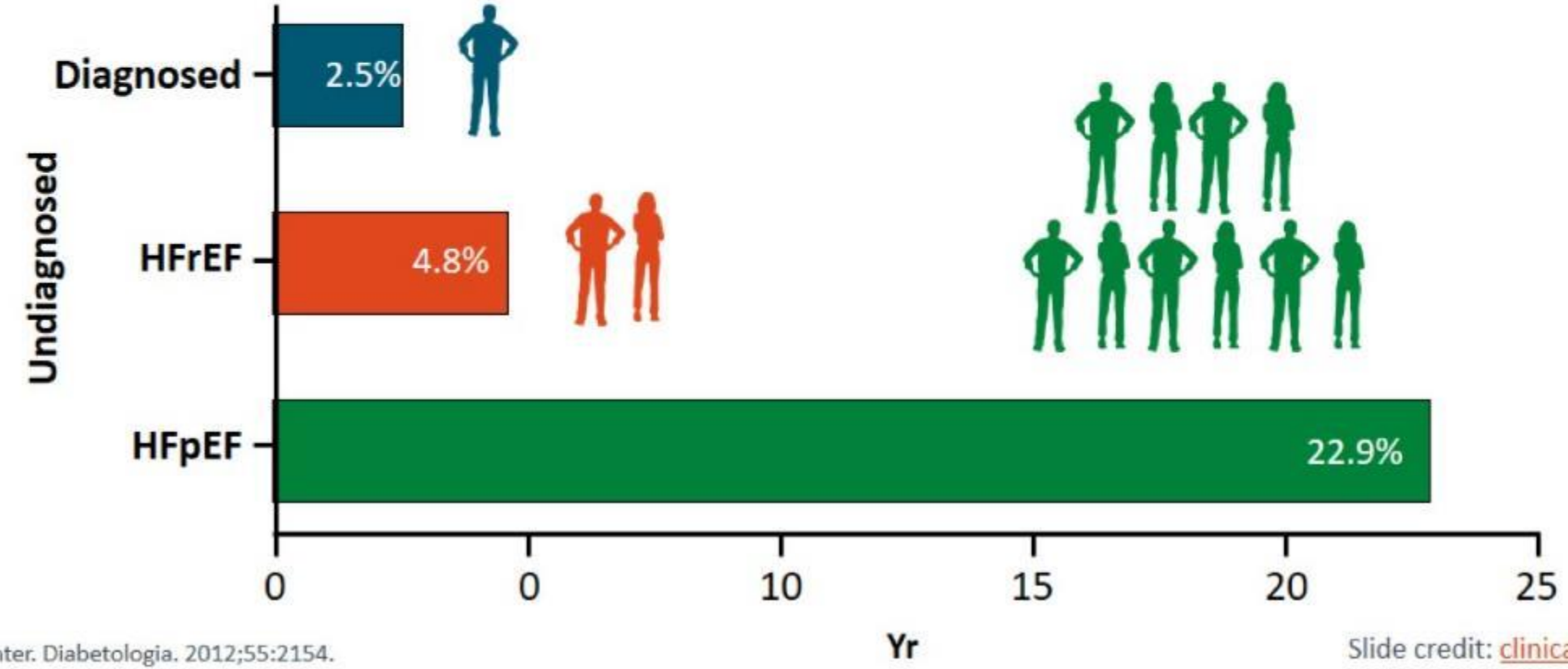
CVD Events in Patients With Diabetes: Framingham 30-Year Follow-Up



Wilson et al. In: Ruderman et al, eds. *Hyperglycemia, Diabetes, and Vascular Disease*. 1992:21-29.

Prevalence of HF in T2D

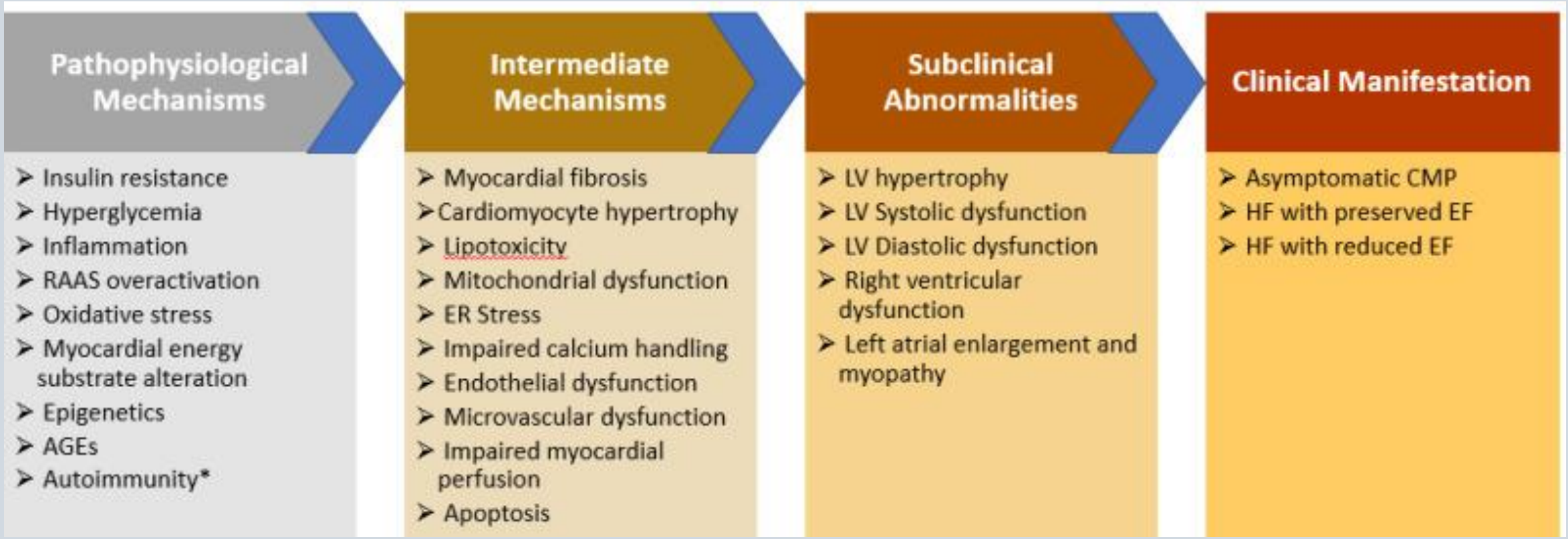
- Patients older than 60 yr of age with T2D evaluated for unknown HF in primary care setting, Zeeland, the Netherlands (N = 605)
  - Symptoms, signs, echocardiography, adjudication using ESC criteria for diagnosis of HF



Boonman-de Winter. Diabetologia. 2012;55:2154.

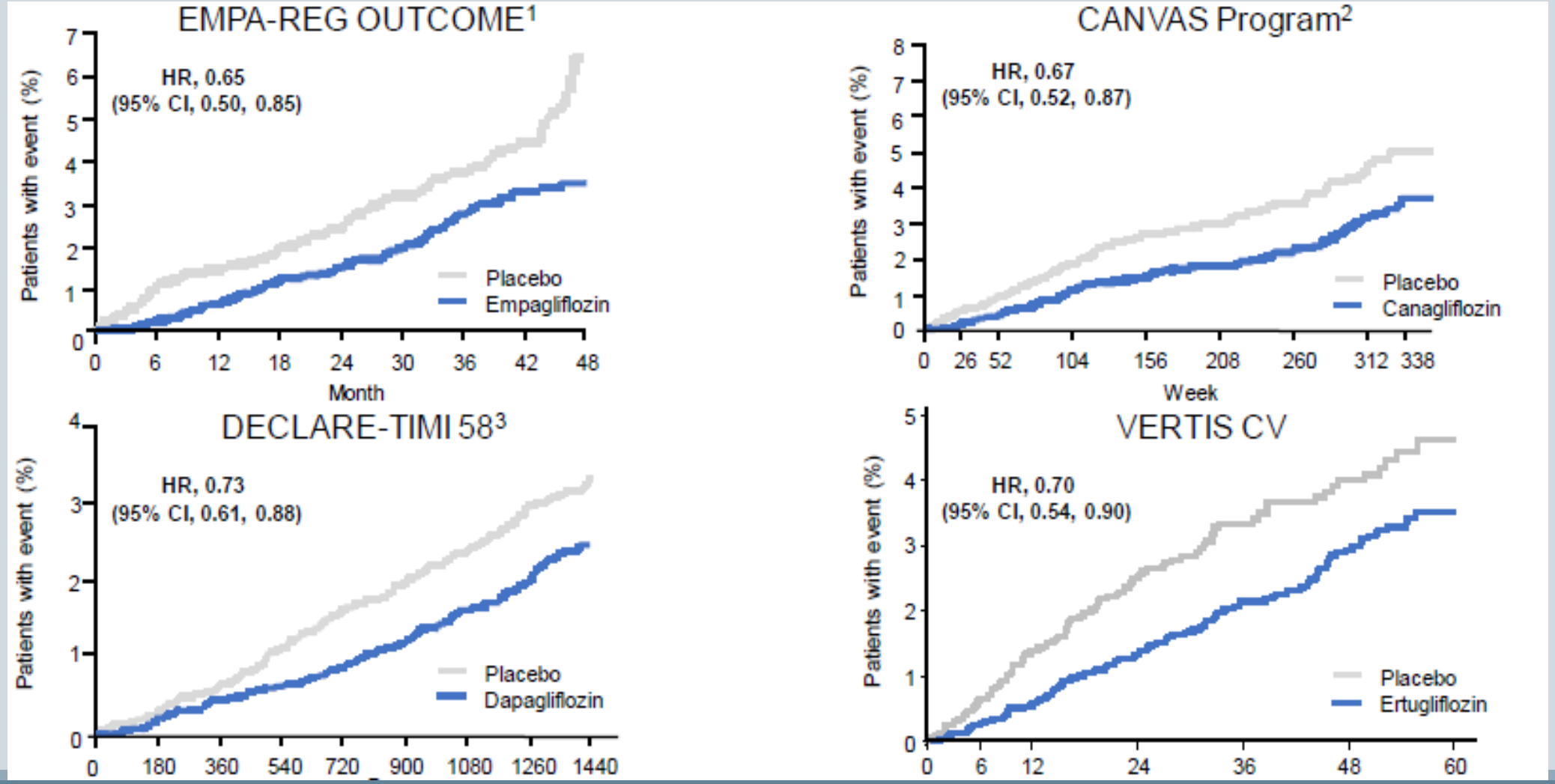
Slide credit: clinicaloptions.com

Pathogenesis of Heart Failure (HF) in Diabetes

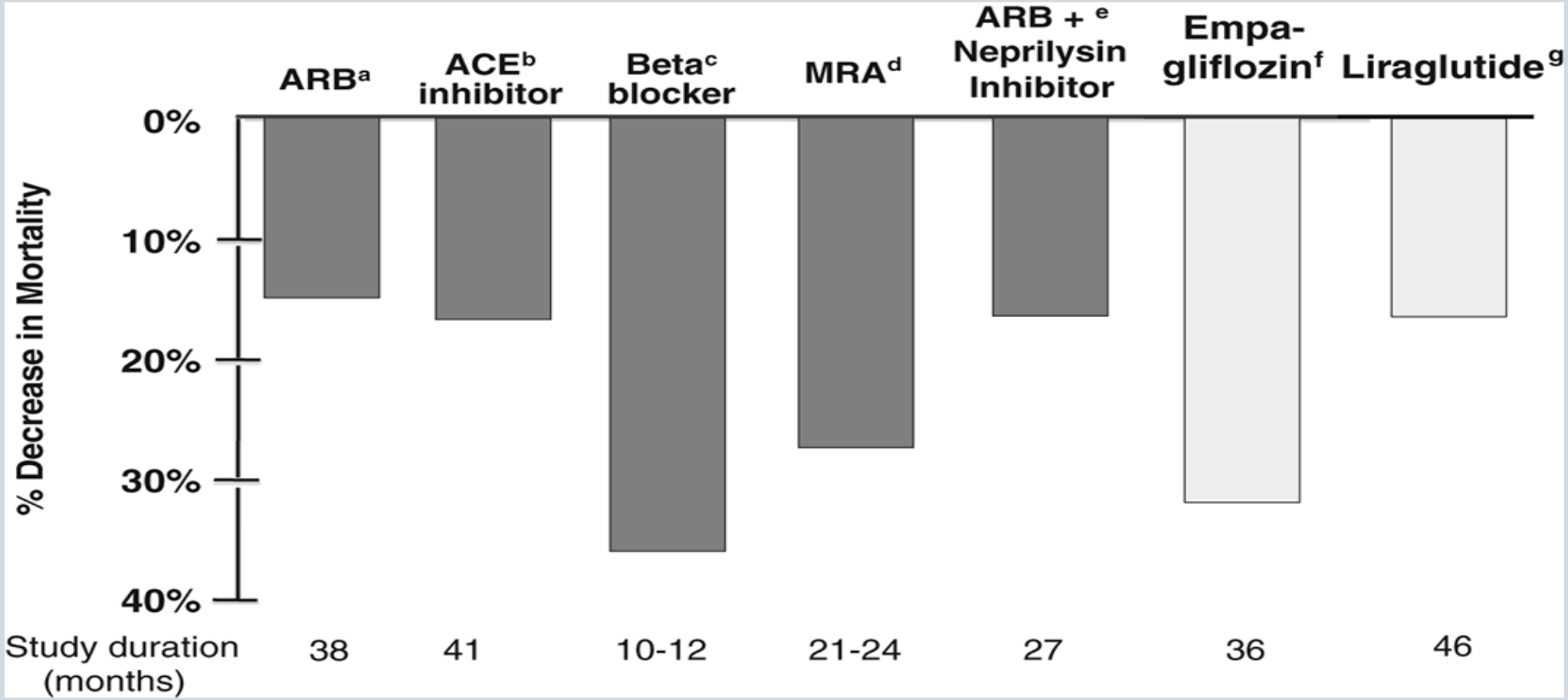


Oktay et al. Diabetes, Cardiomyopathy, and Heart Failure. [Updated 2023 Sep 26]. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560257/

SGLT2i: Consistent benefit on HF Hospitalization



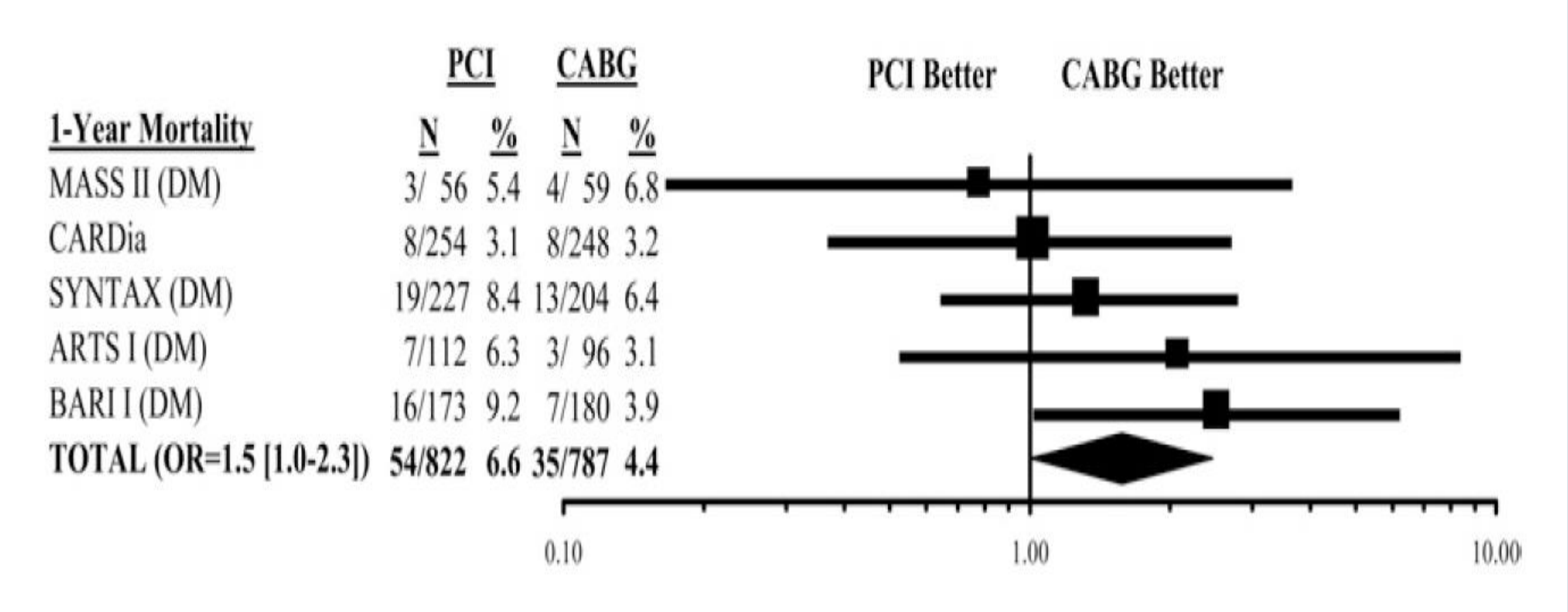
Heart failure outcomes in clinical trials



European Journal of Heart Failure. Volume 19, Issue 1, pages 43-53, 21 SEP 2016 DOI: 10.1002/ejhf.633

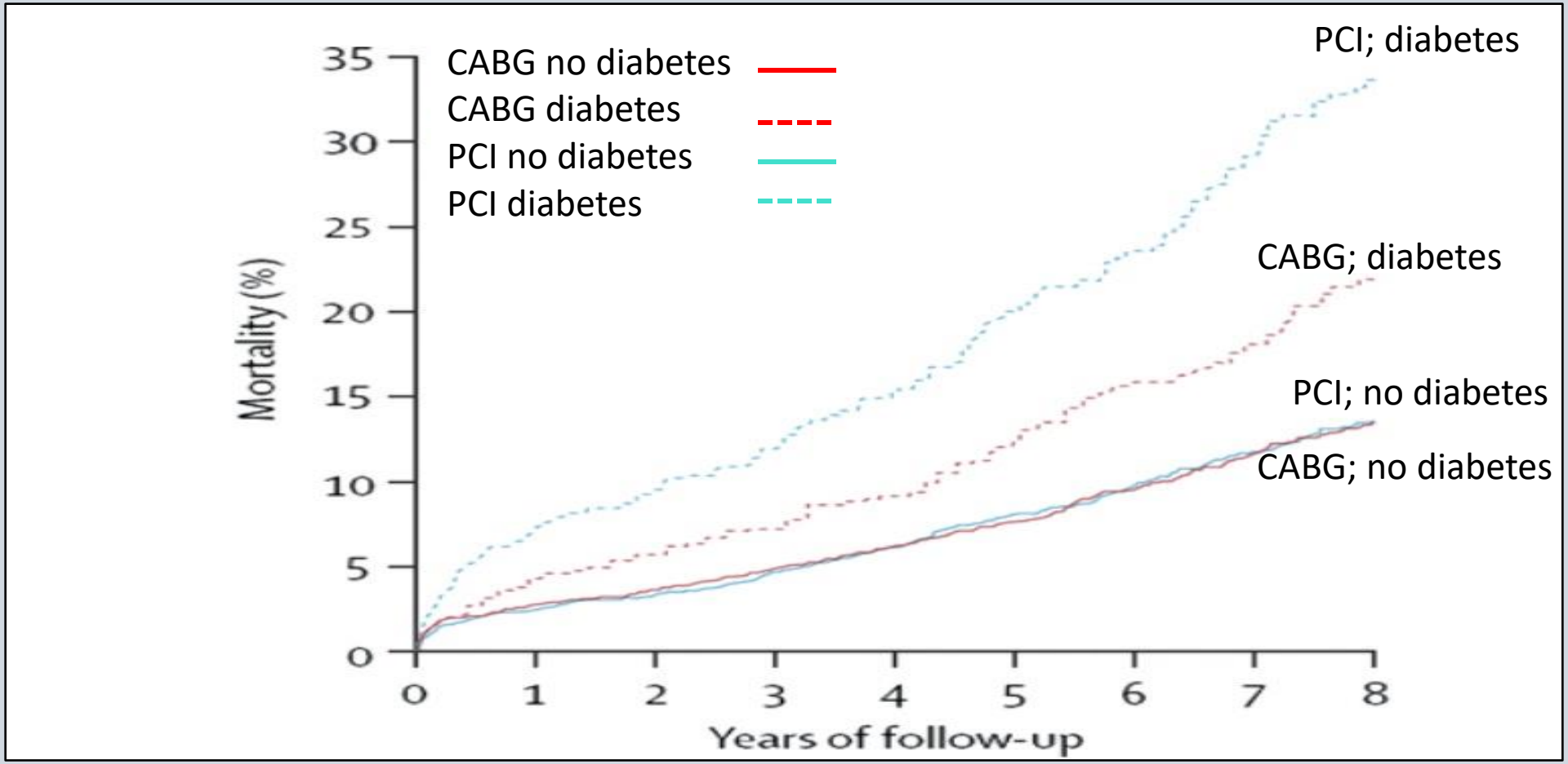
10. CABG is the preferred revascularization strategy for most patient with diabetes

Trials of Patients With Diabetes and Multivessel CAD, Comparing PCI With CABG



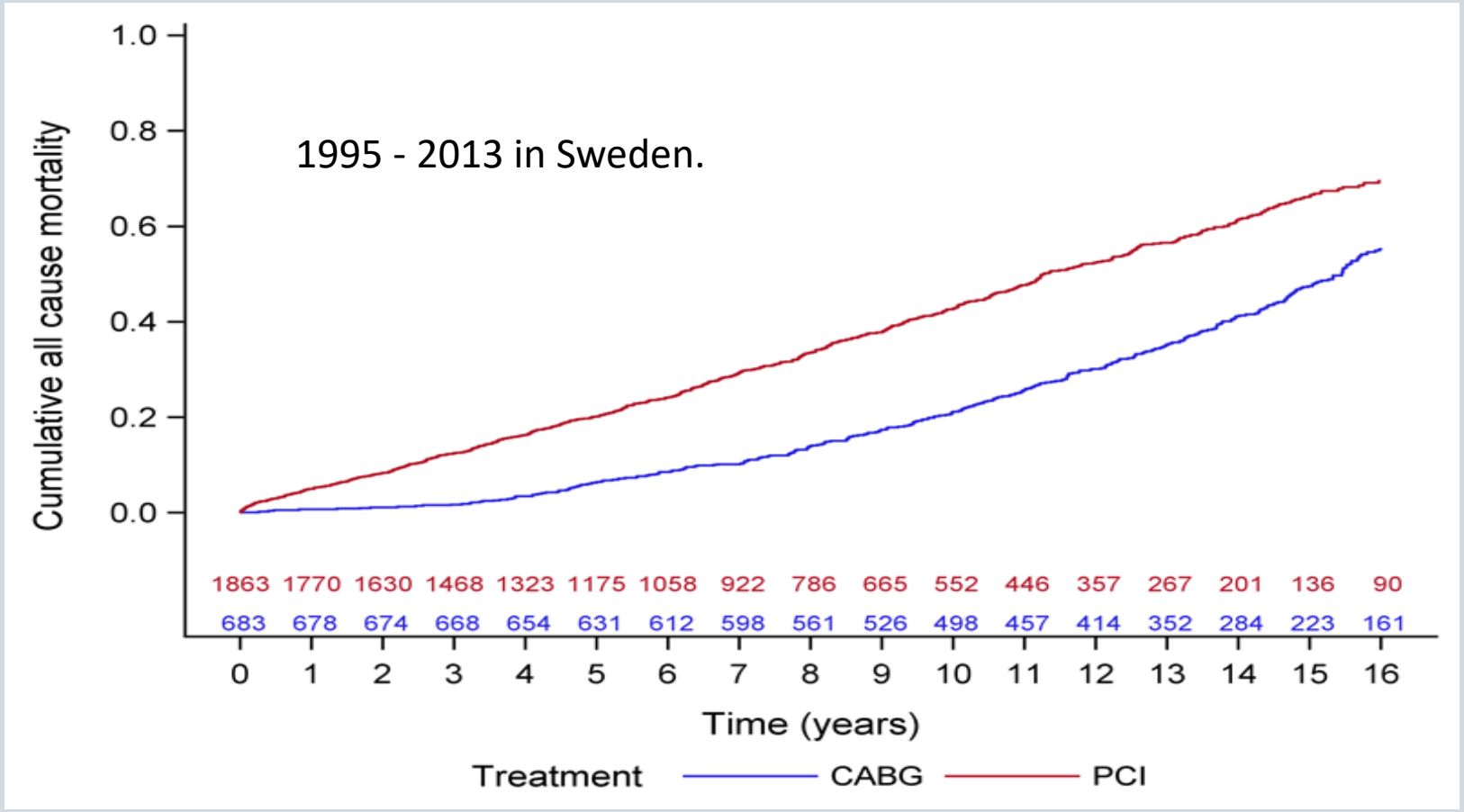
Lima et al. Am Heart J 2013 Aug;166(2):250-7 Kapur et al. Am Heart J 2005 Jan;149(1):13-9 Mack et al. Ann Thorac Surg 2011 Dec;92(6):2140-6 Serruys et al. JACC Vol. 46, No. 4, 200
BARI Investigators. JACC 2007 Apr 17;49(15):1600-1606

Mortality in patients assigned to CABG or PCI by diabetes status - analysis of 10 randomized trials



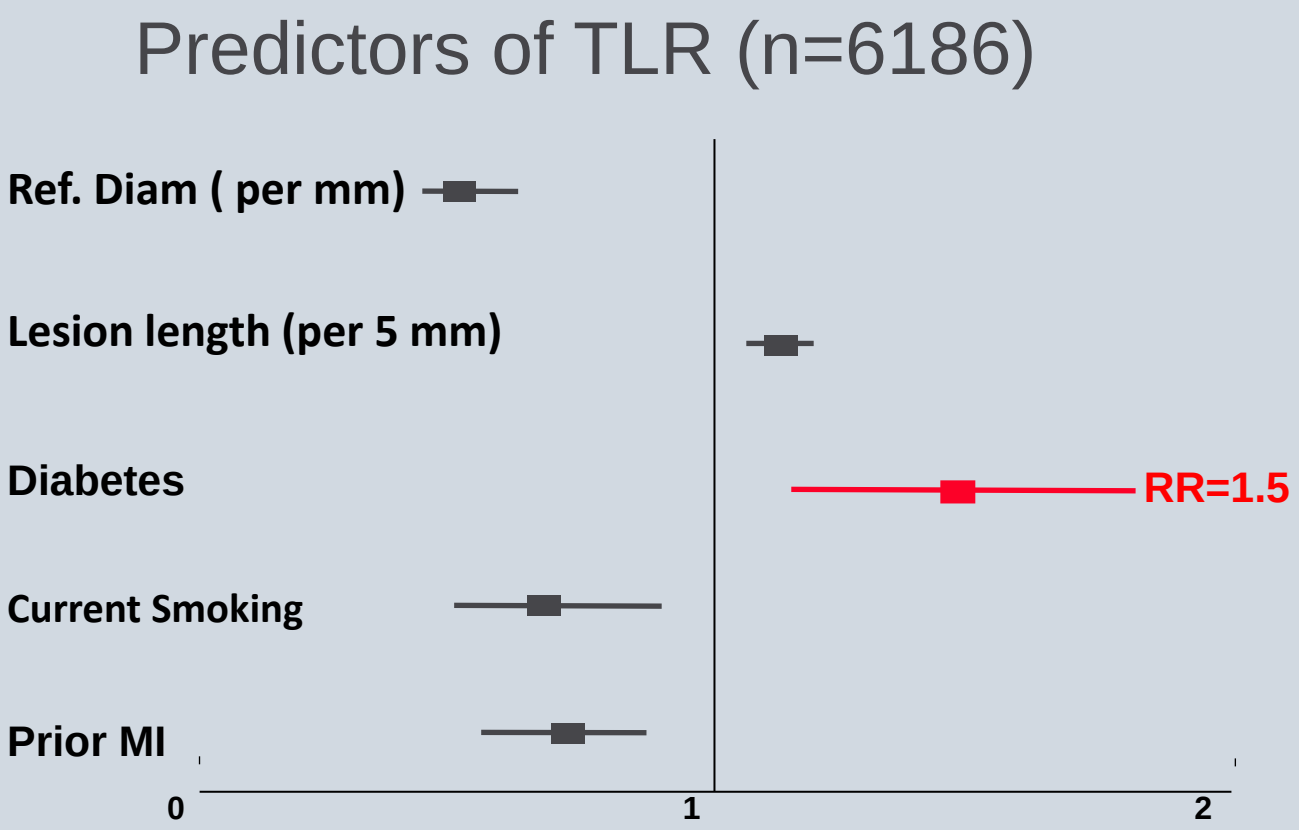
Hlatkey MA, et al. Lancet, 2009, vol. 373 (pg. 1190-1197)

T1DM patients with multivessel CAD who underwent CABG (n = 683) or PCI (n = 1,863)



Nyström T, et. al. *J Am Coll Cardiol* 2017;70:1441-51.

Impact of Diabetes on Outcomes of PCI



Conclusion

1. Most cardiac patients have diabetes, pre-diabetes, or MetSyn
2. Be very afraid of diabetes (especially in women & young patients)
3. It's not about the glucose
4. It's all about blood pressure and lipid control
5. Aspirin has no net benefit for primary prevention in diabetes patients
6. Most diabetes drugs are not good for the heart.
7. SGLT2 inhibitors are cardiac drugs.
8. Diabetes is a powerful risk factor for heart failure
9. CABG is the preferred revascularization strategy for most with diabetes

FAQs

1. Can we prevent diabetes?

Yes. Diabetes can be prevented with lifestyle measures such as diet and exercise.

2. Does tight glycemic control reduce CVD?

Tight glycemic control has been shown to consistently decrease microvascular events such as neuropathy, nephrophathy, and blindness. But tight glycemic control has NOT been consistently shown to decrease MACROvascular events such as CVD events of myocardial infarction and stroke.

3. How do the new diabetes drugs fit in with other therapies for cardiovascular prevention?

New diabetes therapies with documented cardiovascular benefit should be used in conjunction with other preventive therapies in diabetes such as statins.

4. Are the new diabetes drugs useful for preventing CVD in metabolic syndrome patients?

This has never been studied.

Q & A Session

L.A. Care PCE Program Friendly Reminders

Friendly Reminder, a survey will pop up on your web browser after the webinar ends. Please do not close your web browser and wait a few seconds, and please complete the online survey.

Please note: ***the online survey may appear in another window or tab after the webinar ends.***

Upon completion of the online survey, you will receive the PDF CME or CE certificate based on your credential, verification of name and attendance duration time of at least 75 minutes, ***within two (2) weeks after today's webinar.***

Webinar participants will only have up to two weeks after webinar date to email Leilanie Mercurio at lmercurio@lacare.org to request the evaluation form if the online survey is not completed yet. No name, no survey or completed evaluation and less than 75 minutes attendance duration time via log in means No CME or CE credit, No CME or CE certificate.

Thank you!