Management of PAD in Diabetes: Focus on prevention of Amputation and CV events

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Objectives

- Discuss the association between diabetes, peripheral arterial disease and CVD
- Discuss the evidence behind the ADA guidelines for prevention and management of PAD in diabetes
- Discuss the ABC of diabetes care to prevent and manage PAD in diabetes
- Discuss findings of a recent trial of Semaglutide in subjects with Diabetes and symptomatic PAD
- Discuss the non glycemic effects of GLP-1 agonists from UB endocrine department

Association Between Diabetes,PAD and CVD

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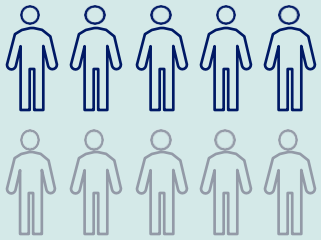
Prevalence of PAD is higher in people with T2D than in those without

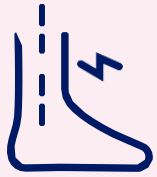
The prevalence of PAD is up to twice as high in people with diabetes as in the general population, and the prevalence of concomitant PAD in people with diabetes is over **50%**[1,2]



Glucose intolerance is associated with a >20% prevalence of an abnormal ankle brachial index* relative to 7% in those with normal glucose tolerance[2]

>20%

Approximately 50–70% of people with chronic limb-threatening ischemia have diabetes[3]

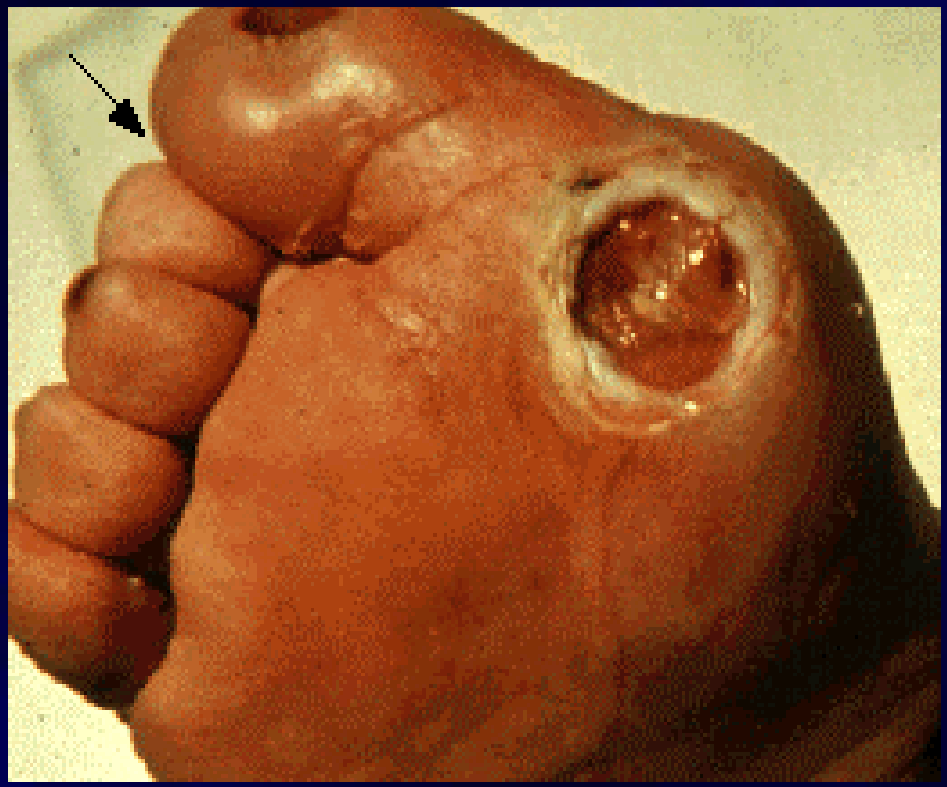


50–70%

**Ankle brachial index is a diagnostic tool for PAD where a lower value indicates a more severe disease state.*
CV, cardiovascular; PAD, peripheral artery disease.
1. Soyoye DO et al. World J Diabetes 2021;12:827–38; 2. Thiruvoipati T et al. World J Diabetes 2015;6:961–69; 3. Marx N et al. Eur Heart J 2023;44:4043–140.

Diabetic Amputations

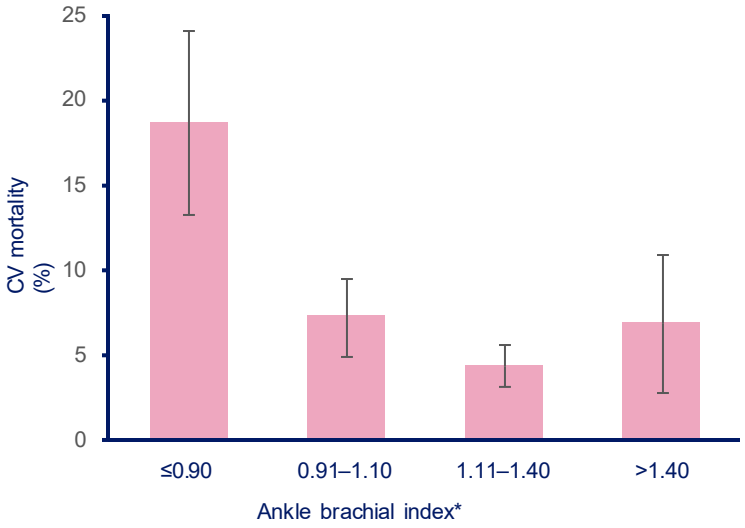
- Diabetes is the # 1 cause of nontraumatic lower extremity amputations in the U.S.
- 15- to 40-fold increase in risk compared with nondiabetic population
- 67,000 limbs lost per year–184 per day
- ADA and CDC: limb loss is preventable



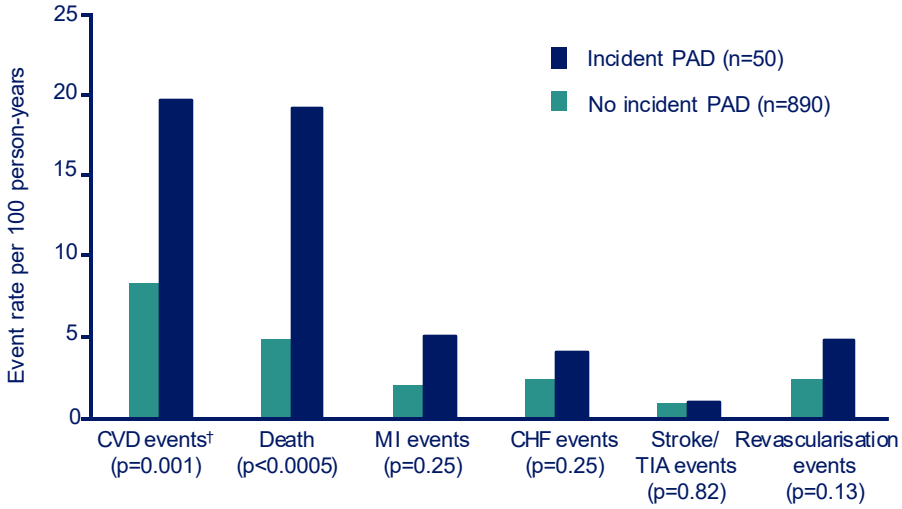
American Diabetes Association. *Diabetes Facts and Figures*. March 2000, Online Edition.
Centers for Disease Control and Prevention. *National Diabetes Fact Sheet*. 1998.

People with PAD have a higher risk of CV events vs those without PAD

Meta-analysis of male participants (N=24,955) from 16 studies showing CV mortality by PAD severity[1]



Prospective cohort study of people with stable CAD ± incident PAD over a 7.2-year follow-up period[2]



*PAD, peripheral artery disease ; CV, Cardiovascular; *Ankle brachial index is a diagnostic tool for PAD where a lower value indicates a more severe disease state. Error bars represent 95% confidence intervals.*
†The primary outcome (CVD events) included a composite of events: death, MI, CHF, stroke, TIA and coronary revascularisation. Secondary outcomes included those events assessed individually.
CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease; TIA, transient ischaemic attack.
1. Ankle Brachial Index Collaboration. JAMA 2008;300:197–208; 2. Grenon SM et al. Vasc Med 2013;18:176–84.

ADA STANDARDS OF MEDICAL CARE IN DIABETES – 2024

Peripheral Artery Disease (PAD)

ADA recommends screening for asymptomatic PAD using ankle brachial index in people with diabetes at high risk for PAD, including any of the following:

age ≥ 50 years

diabetes with duration ≥ 10 years

comorbid microvascular disease

clinical evidence of foot complications

or any end-organ damage from diabetes.

Initial screening for PAD should include:

- Assessment of lower-extremity pulses, capillary refill time
- Rubor on dependency
- Pallor on elevation, and venous filling time
- Individuals with a history of leg fatigue, claudication, and rest pain relieved with dependency or decreased or absent pedal pulses should be referred for ankle-brachial index with toe pressures and for further vascular assessment as appropriate

American Diabetes Association (ADA). Diabetes Care 2024;47(Supplement_1)

Evidence for the ADA guidelines to prevent and manage PAD in diabetes

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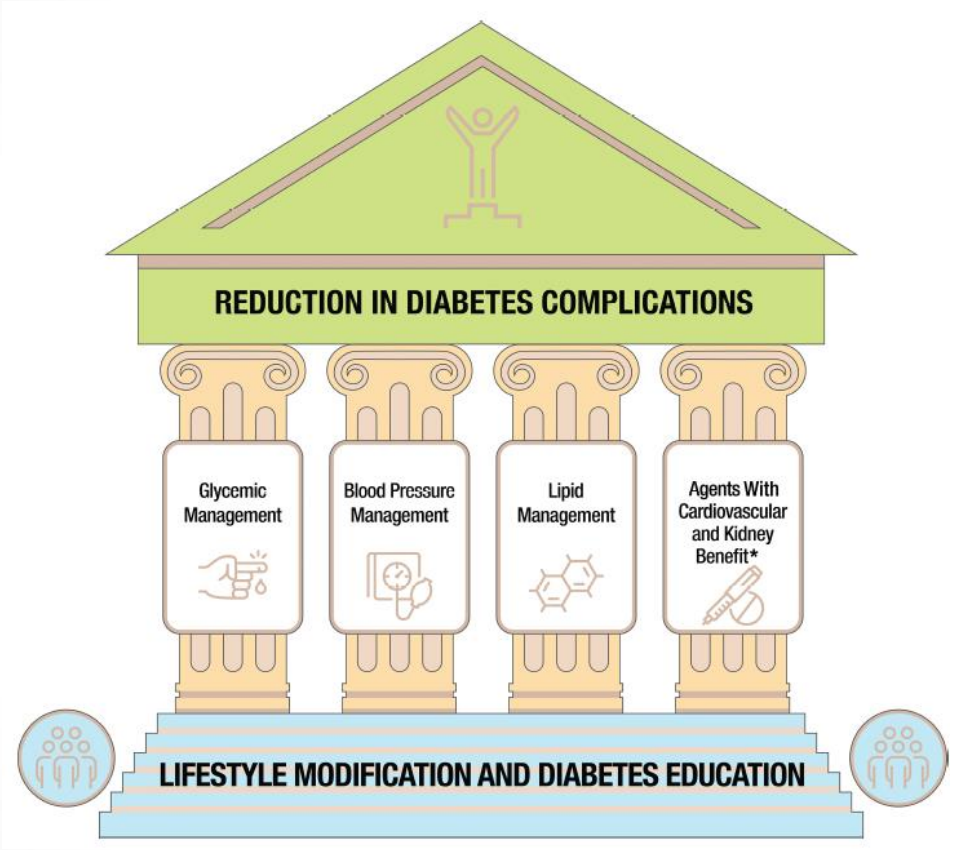
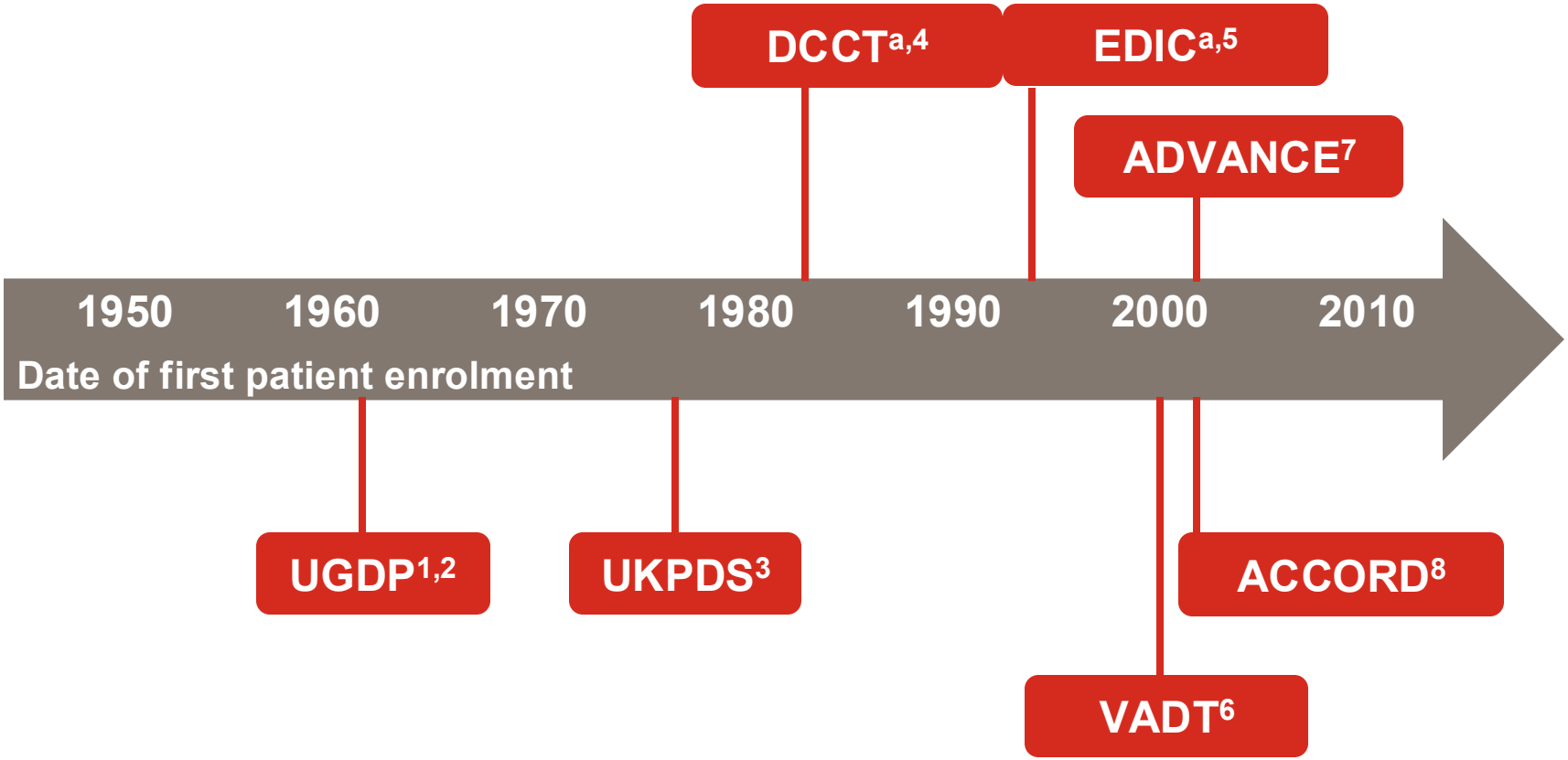
CARDIOVASCULAR DISEASE AND RISK MANAGEMENT



Cardiovascular Disease and Risk Management:
Standards of Care in Diabetes - 2024. Diabetes Care 2024;47(Suppl. 1):S179-S218

American Diabetes Association.
Connected for Life.

Major Historic CV Outcomes Trials: Intensive vs. Conventional Glycemic Control



[a]DCCT/EDIC study included patients with T1DM; all other studies included patients with T2DM

1. Meinert et al. *Diabetes* 1970;19(Suppl):789-830
2. Schwartz TB and Meinert CL. *Perspect Biol Med* 2004;47(4):564-74
3. UKPDS Group. *Lancet* 1998;352:837-53 (updated 354:602)
4. DCCT Research Group. *N Engl J Med* 1993;329:977-86
5. EDIC. *Diabetes Care* 1999;22:99-111
6. Duckworth et al. *N Engl J Med* 2009;360:129-39
7. ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560-72
8. ACCORD. *N Engl J Med* 2008;358:2545-59

Benefits of Glycemic Control: Preventing Complications

UKPDS: Benefits of 1% HbA_{1c} Reduction on Risk of Complications

	Decrease in Risk per 1% HbA_{1c} Reduction	*P* Value
Stroke	12%	0.035
All-Cause Mortality	14%	<0.0001
MI	14%	<0.0001
Heart Failure	16%	0.021
Cataract Extraction	19%	<0.0001
Any Diabetes-related Endpoint	21%	<0.0001
Diabetes-related Death	21%	<0.0001
Microvascular Endpoints	37%	<0.0001
Amputation or Death From Peripheral Vascular Disease	43%	<0.0001

Stratton IM et al. *BMJ* 2000;321:405-411.

Cholesterol lowering

Statins and Major Adverse Limb Events in Patients with Peripheral Artery Disease: A Systematic Review and Meta-Analysis

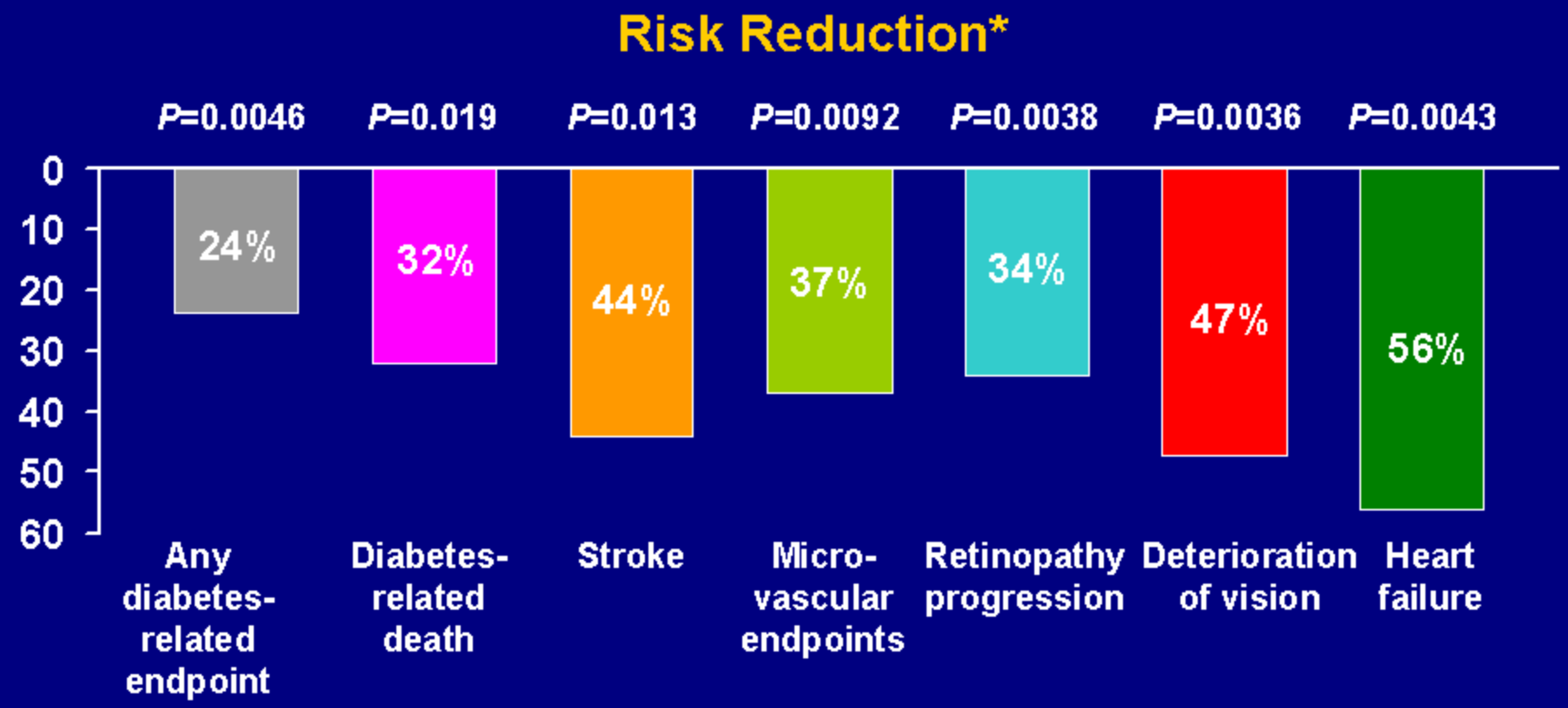
Hazard Ratios Chart

OUTCOME	HAZARD RATIO (HR)	95% CONFIDENCE INTERVAL (CI)
MALE	0.702	0.605–0.815
Amputations	0.654	0.522–0.819
All-cause Mortality	0.608	0.543–0.680
CV Death	0.594	0.455–0.777
Composite CV Endpoints	0.662	0.591–0.741
Ischemic Stroke	0.718	0.620–0.831

Pastori D, Farcomeni A, Milanese A, Del Sole F, Menichelli D, Hiatt WR, Violi F.
Statins and Major Adverse Limb Events in Patients with Peripheral Artery Disease: A Systematic Review and Meta-Analysis.
Thrombosis and Haemostasis. 2020;120(5):866–875.
DOI: 10.1055/s-0040-1709711

BP goals

UKPDS Results: Tight BP Control



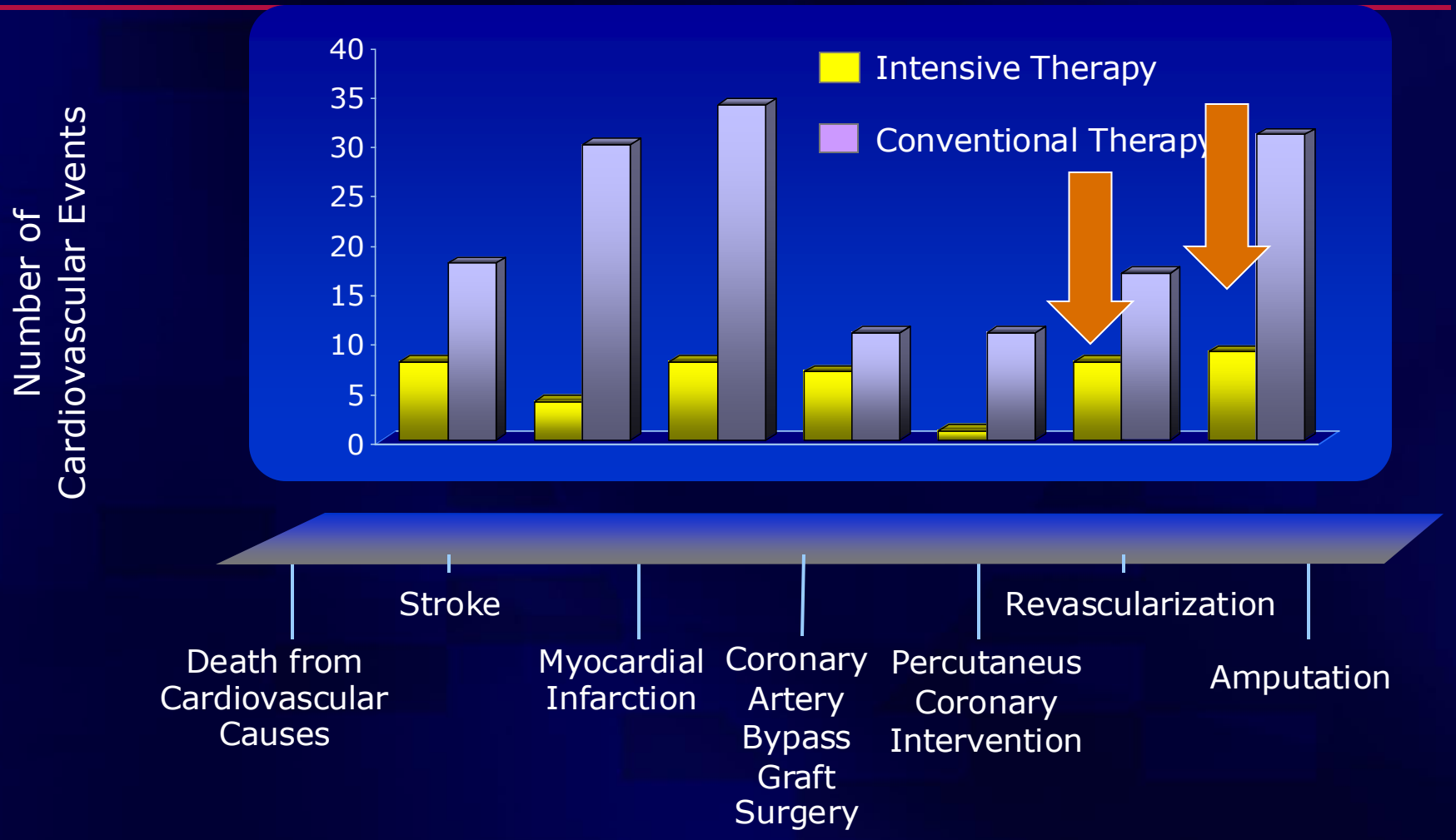
*Compared with less tight control. Captopril and atenolol were equally effective in reducing risk and were equally safe in patients with diabetes.

UKPDS Group. *BMJ.* 1998;317:703-713.

STENO-2: Reduction in Cardiovascular Disease Through a Multifactorial Intervention in Patients Who Have Type 2 Diabetes and Microalbuminuria

Intensive Treatment Goals: hemoglobin A_{1c}, <6.5%; cholesterol, <175 mg/dL; triglycerides, <150 mg/dL; systolic blood pressure, <130 mm Hg; diastolic blood pressure, <80 mm Hg.

STENO-2: No Other Clinical Trial of Patients With Type 2 Diabetes Has Shown Such a Dramatic Reduction in Cardiovascular Events With a Pharmacologic Intervention



ABC of Diabetes Care

A	A1C	<7%
B	Blood pressure	130/80 140/90
C	Cholesterol	statins/ezetimibe icosapent ethyl PCS K9 inhibitor

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, including those with one or more ASCVD risk factors, it is recommended to use high-intensity statin therapy to reduce LDL cholesterol by ≥50% of baseline and to target an LDL cholesterol goal of <70 mg/dL (<1.8 mmol/L). **A**

10.21 For people with diabetes aged 40–75 years at higher cardiovascular risk, especially those with multiple ASCVD risk factors and an LDL cholesterol ≥ 70 mg/dL (≥ 1.8 mmol/L), it may be reasonable to add ezetimibe or a PCSK9 inhibitor to maximum tolerated statin therapy. **B**

Statin Treatment—Secondary Prevention

10.26 For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. **A**

10.27 For people with diabetes and ASCVD, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL (<1.4 mmol/L). Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. **B**

10.28a For individuals who do not tolerate the intended statin intensity, the maximum tolerated statin dose should be used. **E**

10.28b For people with diabetes and ASCVD intolerant to statin therapy, PCSK9 inhibitor therapy with monoclonal antibody treatment, **A** bempedoic acid therapy, **A** or PCSK9 inhibitor therapy with inclisiran siRNA **E** should be considered as an alternative cholesterol-lowering therapy.

Antiplatelet Agents (continued)

10.36 Combination therapy with aspirin plus low-dose rivaroxaban should be considered for individuals with stable coronary and/or peripheral artery disease (PAD) and low bleeding risk to prevent major adverse limb and cardiovascular events. **A**

10.37 Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the individual on the benefits versus the increased risk of bleeding. **A**

Diabetes Endocrinology Center of Western New York Outcomes

Outcomes of patients from Diabetes Endocrinology Center of WNY

- Mean Hba1c: 6.8%
- Mean LDL-C: 75mg/dl
- Mean HDL-C: males: 38mg/dl; females: 45mg/dl
- Mean Systolic BP: 125mm Hg
- Mean Diastolic BP: 78mm Hg
- 85% on statins
- 90% on ACE inhibitors/ARBs
- 85% on aspirin
- 65% on insulin

Clinical Outcomes of patients from Diabetes Endocrinology Center of WNY

- No foot ulcers, gangrene or amputations for 11 years
- No endstage renal failure, dialysis or transplantation for 7 years
- Mean microalbuminuria diminished
- Cessation of laser therapy within two years of attending

Rationale for the 2025 ADA guidelines for using GLP-1 agonists and SGLT2 inhibitors in ASCVD

Evidence for the guidelines

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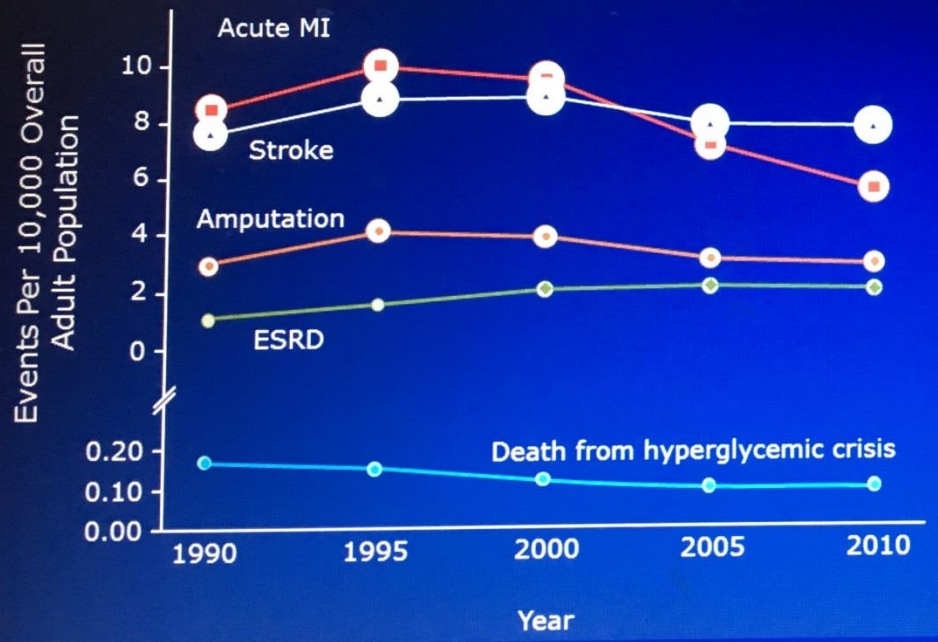
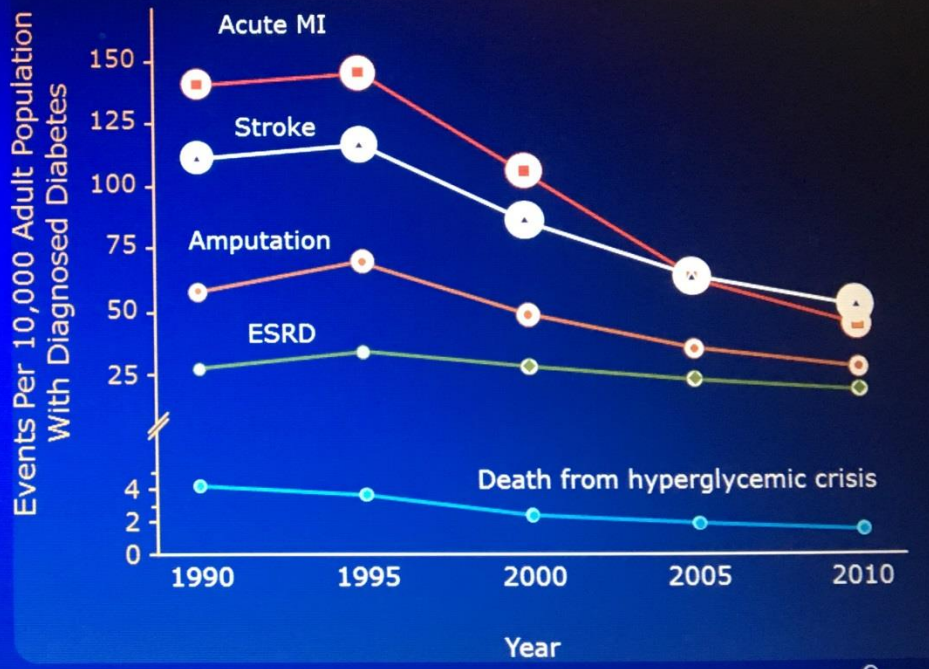
Diabetes-Related Complications Have Declined, but Considerable Residual Risk Remains

Population with or without diabetes



Population with diabetes



ESRD=end-stage renal disease; MI=myocardial infarction.

Gregg EW et al. *N Engl J Med.* 2014;370(16):1514–1523.

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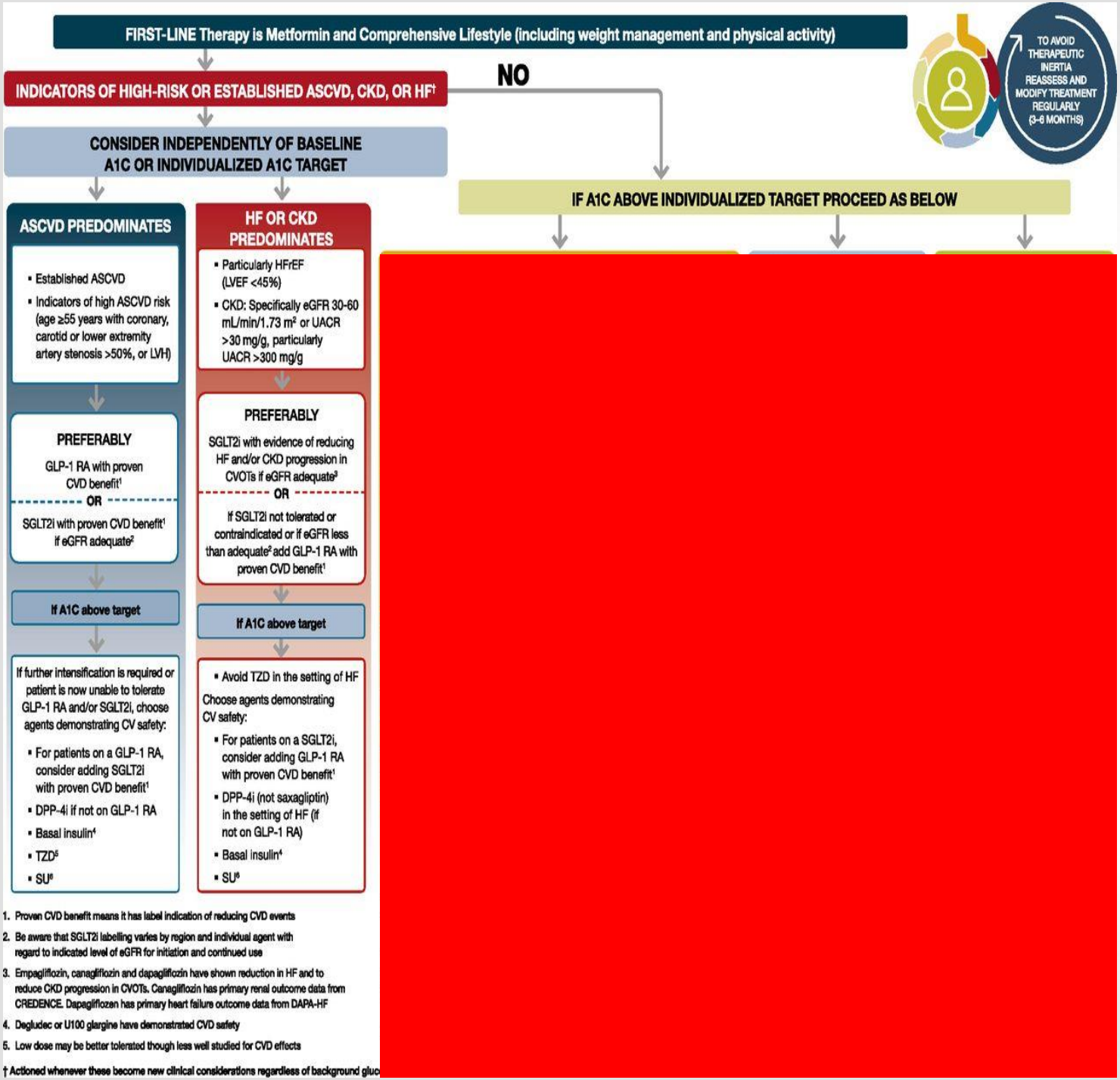
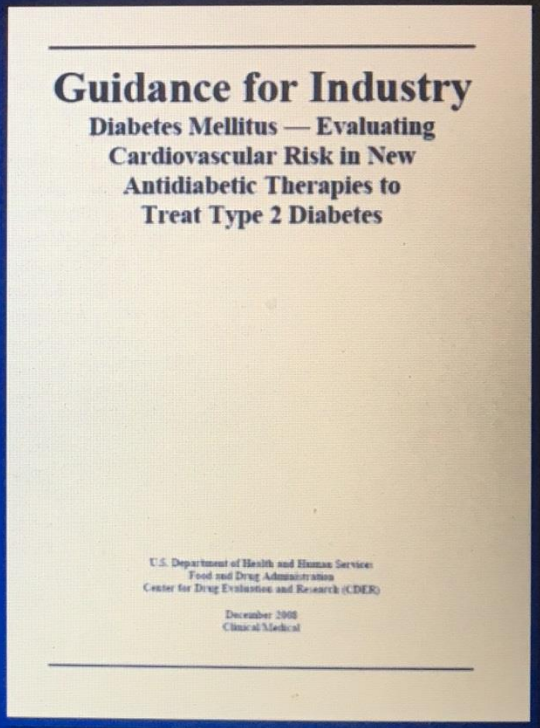


Glucose-lowering Medication in Type 2 Diabetes: Overall Approach

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2020. Diabetes Care* 2020;43(Suppl. 1):S98-S110

In 2008, the FDA Released Guidelines for the Development of Therapies to Treat Type 2 Diabetes

- Nissen and Wolski 2007 meta-analysis on adverse CV effects of rosiglitazone[1]
- Alarm over approval and near approval of antidiabetic drugs associated with CV events[2,3]
- Lack of clear-cut evidence of macrovascular risk reduction with any antidiabetic drug or regimen[4]
- Industry should demonstrate that **new therapies will not result in an unacceptable increase in CV risk**



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

V=cardiovascular; FDA=US Food and Drug Administration.

Nissen SE, Wolski K. *New Engl J Med.* 2007;356(24):2457–2471. 2. Menon V, Lincoff AM. *Circulation.* 2014;129(25):2705–2713. 3. Hirshberg B, Raz I. *Diabetes Care.* 2011;34(suppl 2):S101–106. 4. Parks MH. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM209087.pdf. Accessed October 31, 2016.

Study Design for Diabetes Efficacy Trials vs Diabetes CVOTs

Aim: Diabetes Efficacy	Aim: Demonstrate CV Safety and/or Benefit
Initiation of treatment vs comparator (eg, experimental agent vs active comparator)	Initiation of treatment vs comparator (eg, experimental agent vs placebo, both with standard-of-care)
Treatment administered per random assignment	**Treatment adjustment to achieve similar A1C**
Differentiation in biomarkers between treatment arms	**Common glycemic target** between treatment arms
Observe differences in **glycemia and other parameters**[a] between experimental agent and comparator	Observe differences in **CV outcomes (such as composite MACE)** between experimental agent and comparator

A1C=glycated hemoglobin; FPG=fasting plasma glucose.

[a]Other parameters include hypoglycemic risk, weight gain, blood pressure, lipid profile, β-cell function, and insulin sensitivity.

John M et al. *Indian Heart J*. 2016;68(4):564–571.

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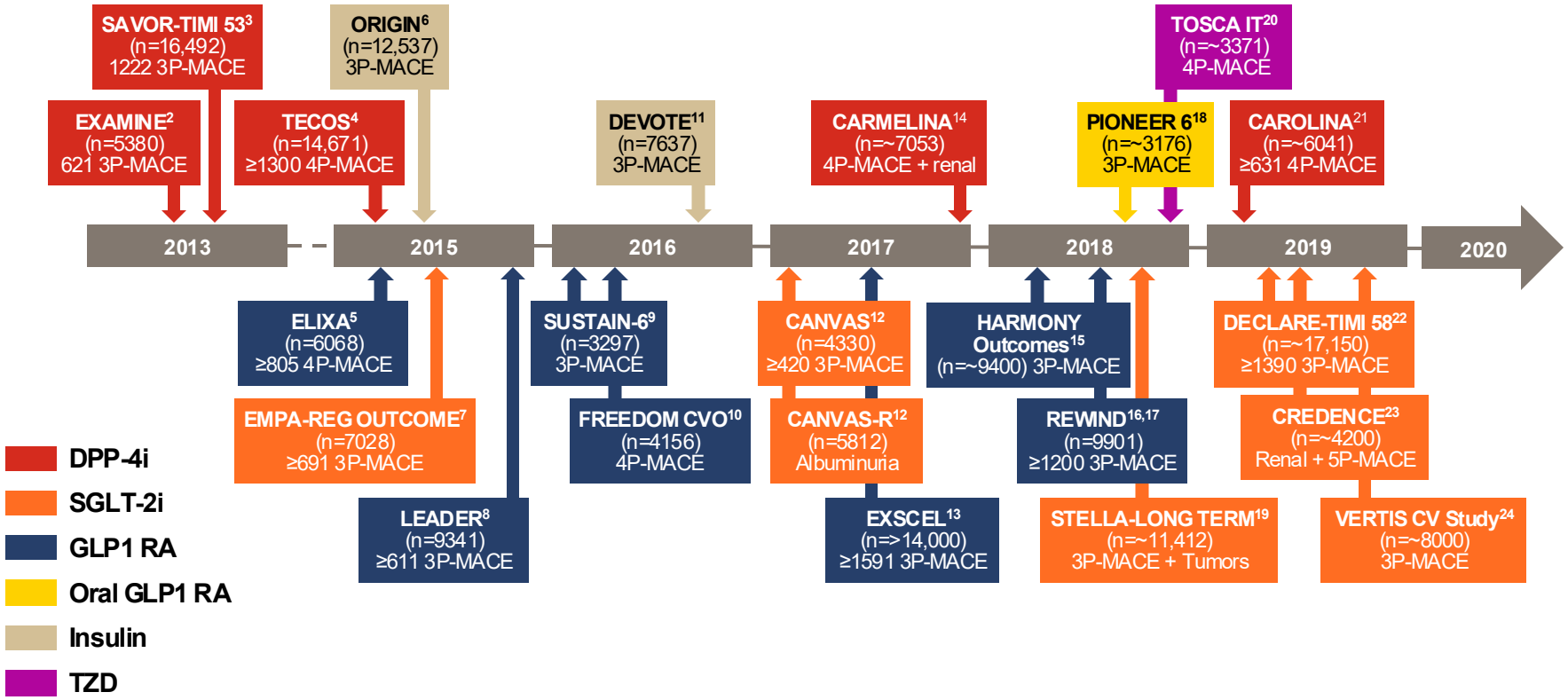
Overview of CVOTs of Glucose-lowering Drugs[1] (1 of 2)



Timings represent estimated completion dates as per ClinicalTrials.gov

1. Johansen OE. 2015
2. White WB et al. 2013
3. Scirica BM et al. 2013
4. Green JB et al. 2015
5. Pfeffer MA et al. 2015
6. ORIGIN. 2012
7. Zinman B et al. 2015
8. Marso SP et al. 2016
9. Marso SP et al. 2016
10. NCT01455896
11. Marso SP et al. 2017
12. Neal B et al. 2017
13. NCT01144338
14. NCT01897532
15. NCT02465515
16. NCT02065791
17. Gerstein HC et al. 2017
18. NCT02692716
19. NCT02479399
20. NCT00700856
21. NCT01243424
22. NCT01730534
23. NCT01394952
24. NCT01986881

Meta-analysis of GLP-1 agonist trials

Lancet Diabetes Endocrinol
2019; 7:776–85

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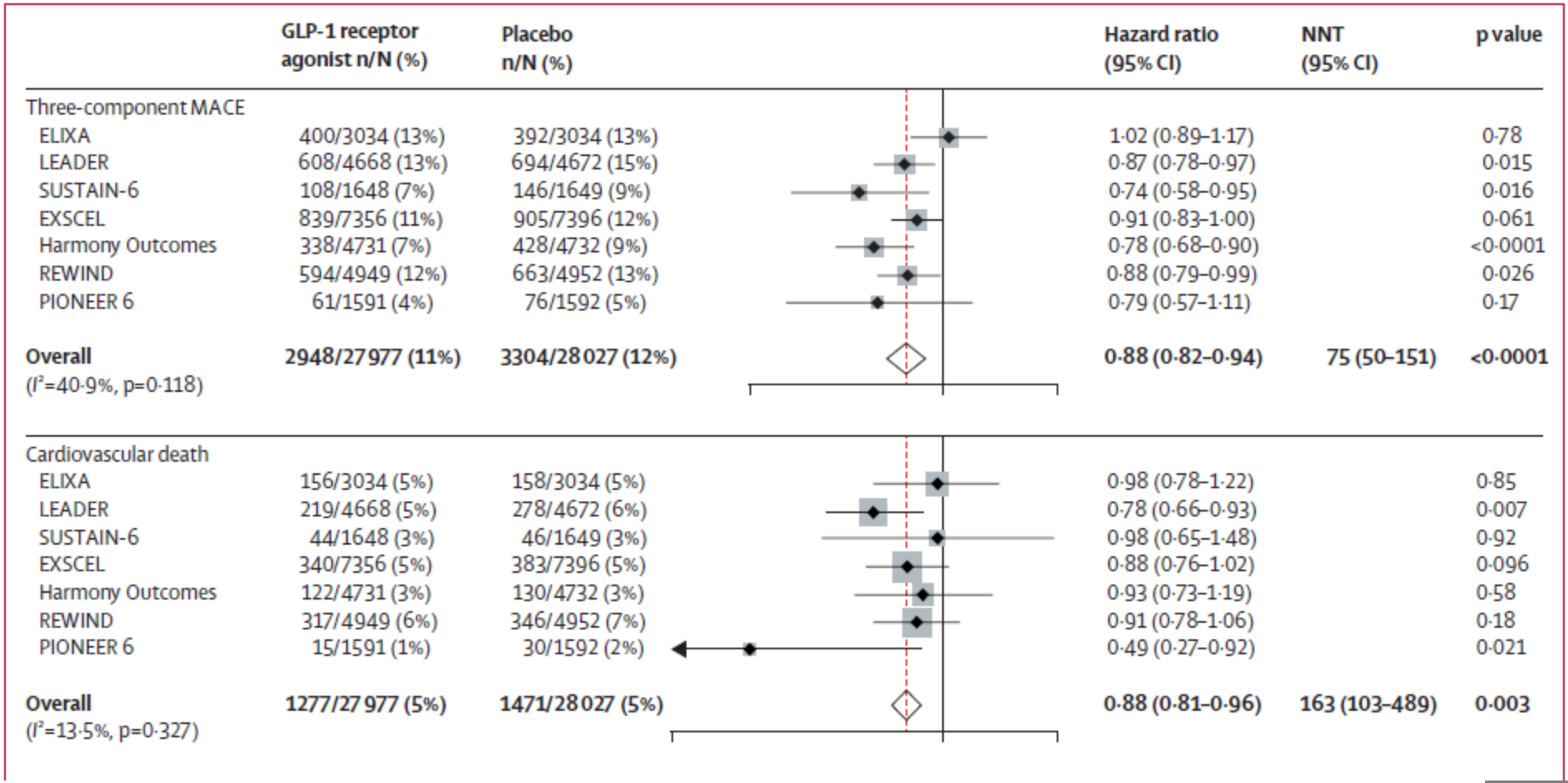
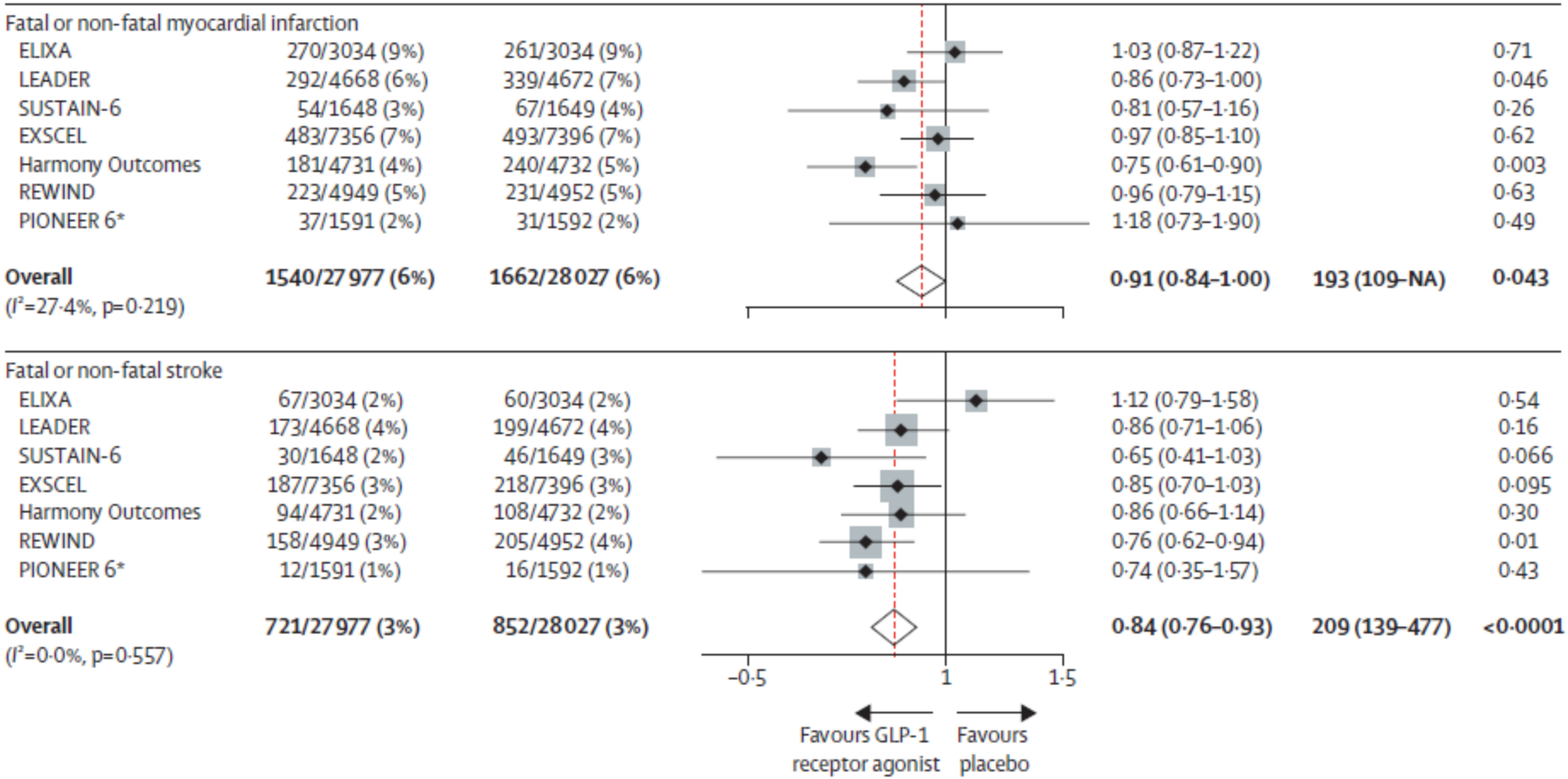
MACE AND CV DEATH: REDUCTION BY 12%



	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-component MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·015
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		<0·0001
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
Overall (I^2=40·9%, p=0·118)	**2948/27 977 (11%)**	**3304/28 027 (12%)**	**0·88 (0·82–0·94)**	**75 (50–151)**	**<0·0001**
Cardiovascular death					
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)		0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)		0·007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)		0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·18
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
Overall (I^2=13·5%, p=0·327)	**1277/27 977 (5%)**	**1471/28 027 (5%)**	**0·88 (0·81–0·96)**	**163 (103–489)**	**0·003**

MI : 9% REDUCTION
STROKE: 16% REDUCTION



All Cause mortality: 12% reduction
Hospitalization for HF: 9% Reduction

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78–1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74–0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74–1·50)		0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77–0·97)		0·016*
Harmony Outcomes	196/4731 (4%)	295/4732 (4%)	0·95 (0·79–1·16)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80–1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31–0·84)		0·008
Overall (I^2=16·5%, p=0·304)	**1916/27977 (7%)**	**2246/28027 (8%)**	**0·88 (0·83–0·95)**	**108 (77 to 260)**	**0·001**
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75–1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73–1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77–1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78–1·13)		0·51
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53–0·94)		<0·0001
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77–1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48–1·44)		0·59
Overall (I^2=0·0%, p=0·595)	**936/27977 (3%)**	**1016/28027 (4%)**	**0·91 (0·83–0·99)**	**312 (165 to 2810)**	**0·028**

GLP-1 Agonists with CV benefits

- Liraglutide and Semaglutide for established CVD

- Dulaglutide for established CVD and those with CV risk factors

SGLT2 inhibitors with CV benefits

- Empagliflozin for reduction of CV death in established CVD
- Canagliflozin for reduction of CV events in established CVD
- Dapagliflozin for reduction of hospitalization for heart failure in established CVD or multiple risk factors

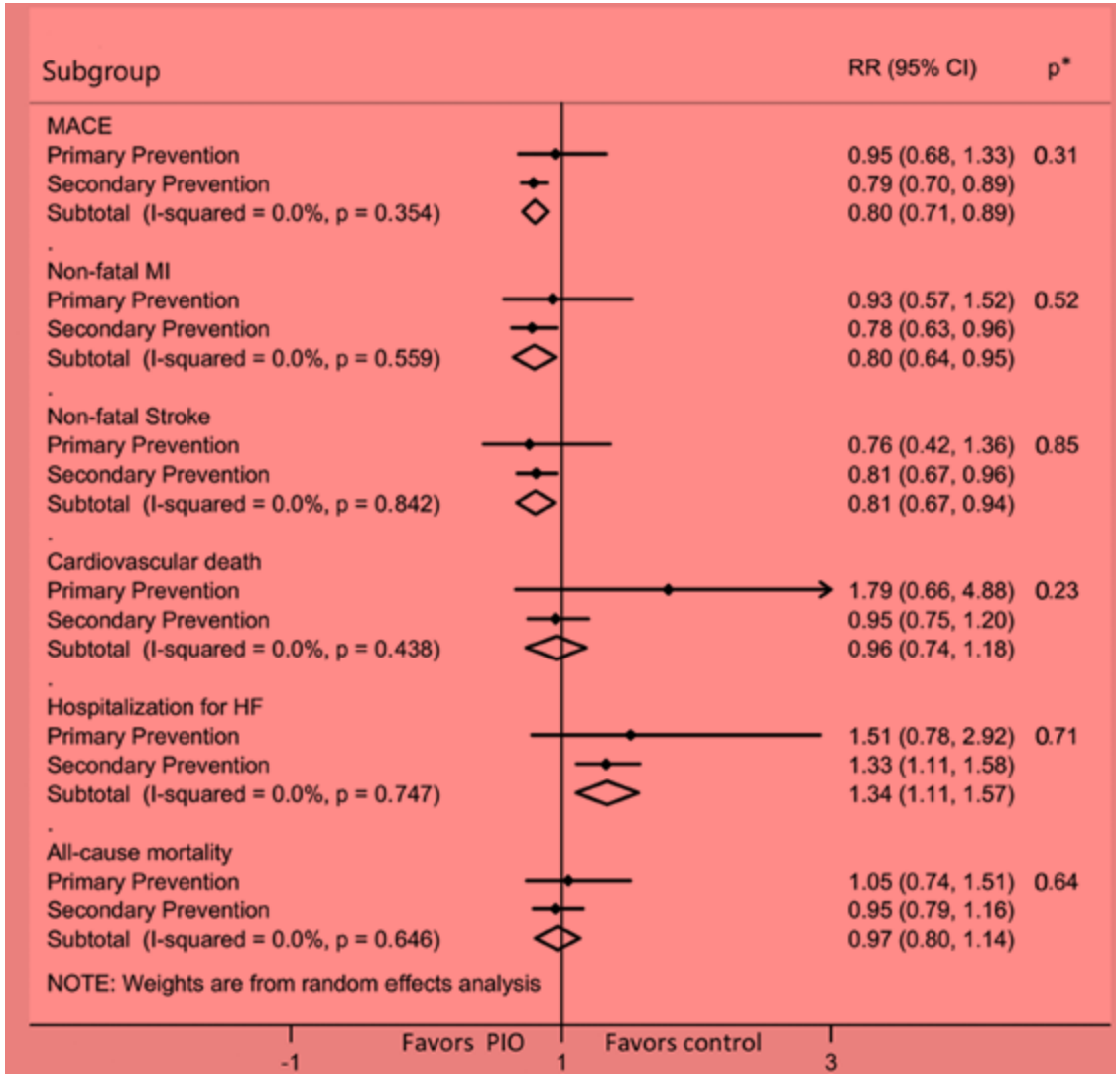
Cardiovascular Outcome Trials for Thiazolidinediones

Study Identifier	No. of Patients	Study Design	Primary Endpoint	Results HR (95% CI)
PROactive[1] HbA1c >6.5%	5238	Pioglitazone Placebo	6P-MACE[a]	**0.90 (0.80-1.02)** p=.095
RECORD[2] HbA1c >7.0-9.0%; on Met or SU monotherapy	4447	Met/SU + Rosiglitazone Met + SU	CV hospitalization or CV death	**0.99 (0.85-1.16)** p=.93
IRIS[3] IR and TIA or stroke	3876	Pioglitazone Placebo	Stroke or MI	**0.76 (0.62-0.93)** p=.007
TOSCA IT[4,5] HbA1c ≥7.0-9.0%	3371	Pioglitazone SU	4P-MACE[b]	2018[c]

[a]Composite of all-cause mortality, nonfatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle
[b]Composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, and unplanned coronary revascularization
[c]Estimated study completion per clinicaltrials.gov
Click on the study title to view additional details regarding each study

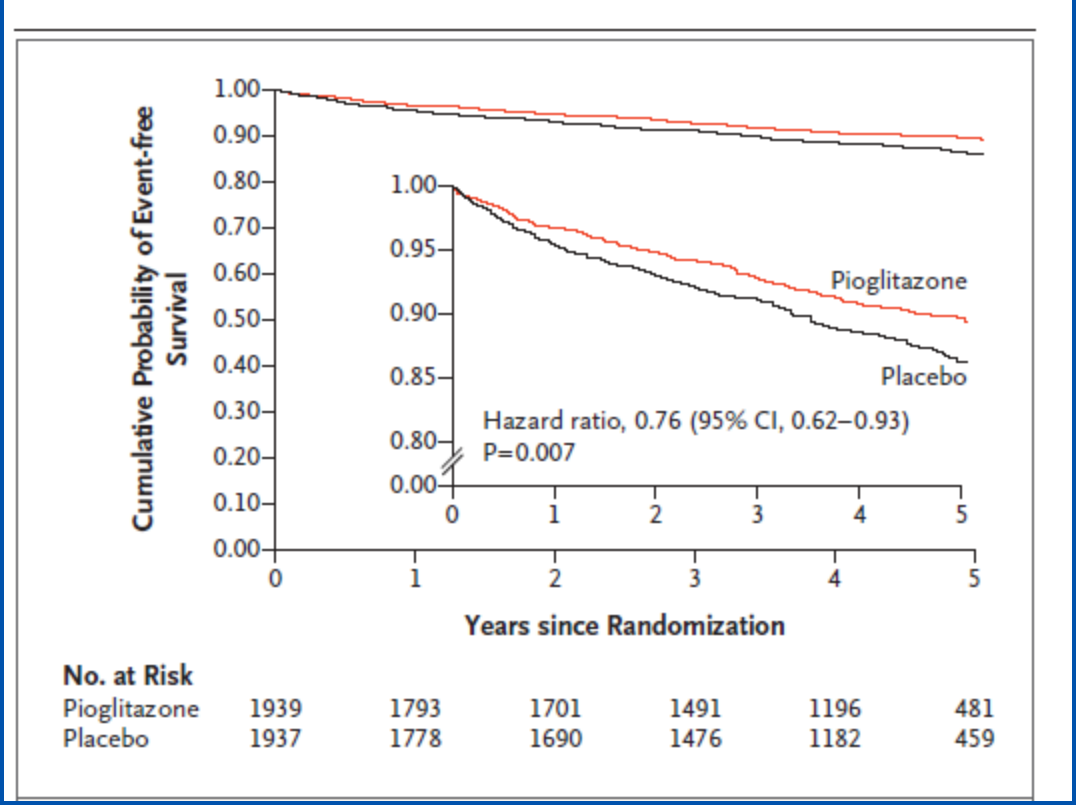
1. Dormandy JA et al. *Lancet* 2005;366:1279-89
2. Home PD et al. *Lancet* 2009;373:2125-35
3. Kernan WN et al. *N Engl J Med* 2016;374:1321-31
4. Vaccaro O et al. *Nutr Metab Cardiovasc Dis* 2012;22:997-1006
5. https://clinicaltrials.gov/ct2/show/NCT00700856

Pioglitazone – CV benefits in established CVD- 20% reduction in MACE; increase in heart failure



Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

N ENGL J MED 374;14 NEJM.ORG APRIL 7, 2016



Three antihyperglycemic therapies with CV Benefits: GLP-1 agonists, SGLT2 inhibitors, TZDs

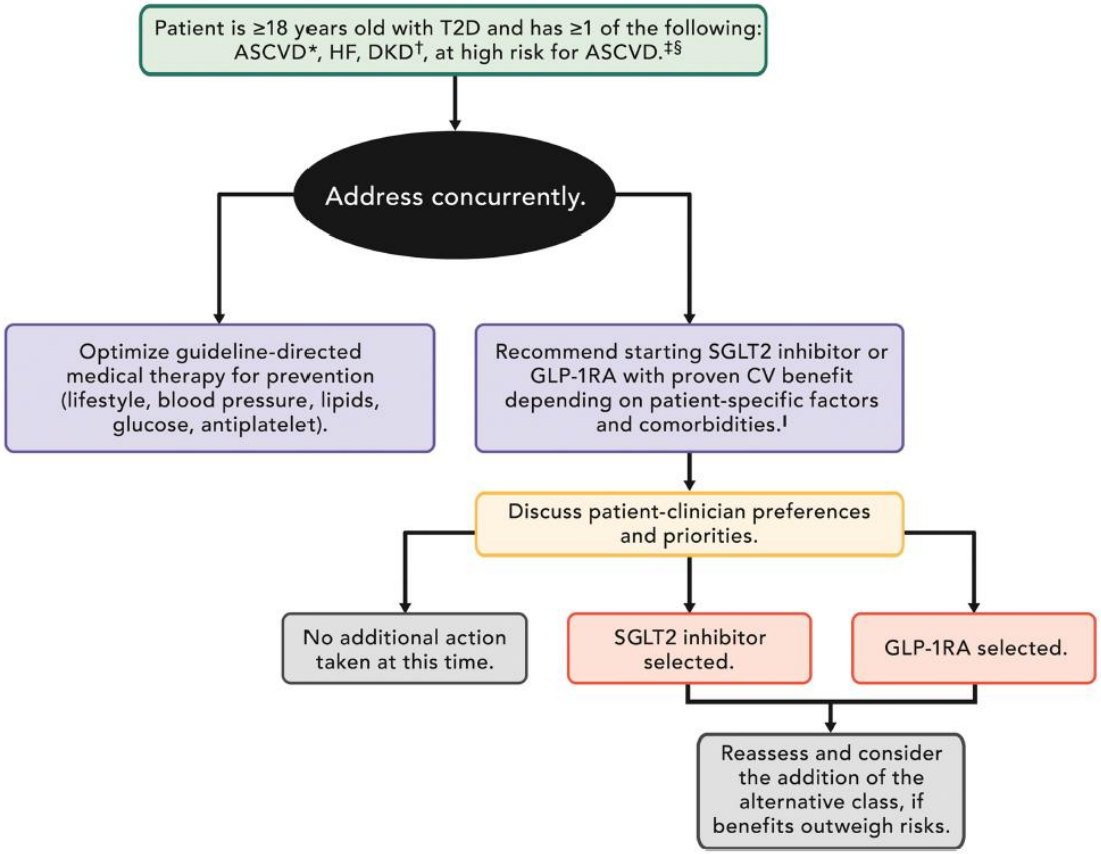


Figure 10.3—Approach to risk reduction with SGLT2 inhibitor or GLP-1 receptor agonist therapy in conjunction with other traditional, guideline-based preventive medical therapies for blood pressure, lipids, and glycemia and antiplatelet therapy

Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2024*. *Diabetes Care* 2024;47(Suppl. 1):S179-S218

Effect of Semaglutide in symptomatic PAD

Full Results Online Now

THE LANCET

Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes (STRIDE): a phase 3b, double-blind, randomised, placebo-controlled trial

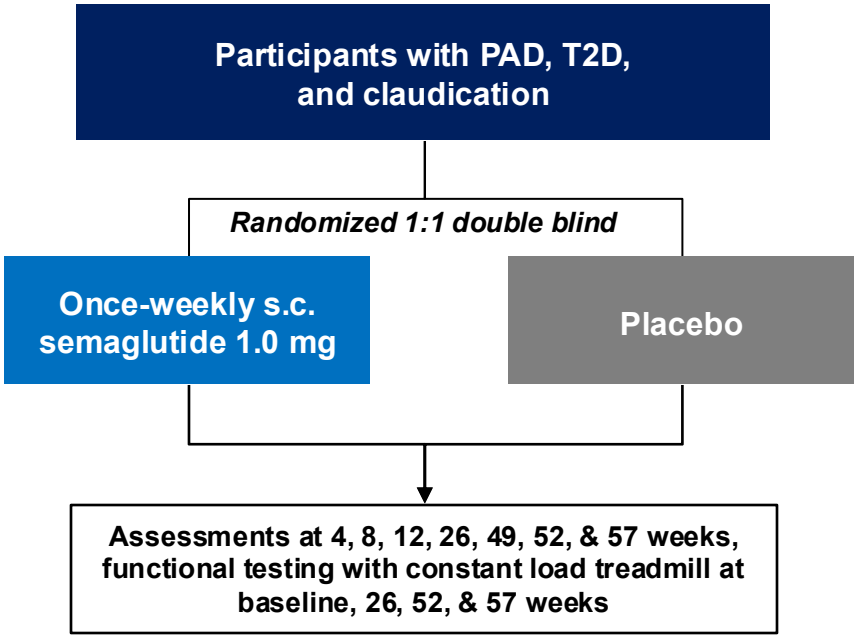
Marc P Bonaca, Andrei-Mircea Catarig, Kim Houlind, Bernhard Ludvik, Joakim Nordanstig, Chethana Kalmady Ramesh, Neda Rasouli, Harald Sourij, Alex Videmark, Subodh Verma, for the STRIDE Trial Investigators

SCAN ME
FOR THE MANUSCRIPT

An Affiliate of
CPC Clinical Research
University of Colorado Anschutz Medical Campus

Objectives and Trial Design

Objective: To demonstrate the effect of once weekly semaglutide 1.0 mg vs. placebo on functional capacity in people with T2D and symptomatic PAD



Inclusion criteria

- Age ≥18 years old
- T2D diagnosis ≥180 days prior to screening
- HbA_{1c} ≤10%
- Early-stage symptomatic PAD (Fontaine stage IIa)
- PFWD ≥200 m (flat treadmill test)
- MWD ≤600 m (constant load treadmill test)
- ABI ≤0.9 or TBI ≤0.7

Exclusion criteria

- Conditions other than PAD that limit walking
- Vascular revascularization ≤180 days prior to screening or planned arterial revascularization
- Heart failure (NYHA Class III–IV)
- MI, stroke, hospitalization for unstable angina, or TIA within 180 days prior to screening

ABI, ankle-brachial index; HbA_{1c}, glycated hemoglobin; MI, myocardial infarction; MWD, maximum walking distance; NYHA, New York Heart Association; PAD, peripheral artery disease; PFWD, pain-free walking distance; s.c., subcutaneous; T2D, type 2 diabetes; TBI, toe-brachial index; TIA, transient ischemic attack.

Bonaca MP et al. *Eur Heart J Cardiovasc Pharmacother* 2025;10:728–737.

OUTCOMES

Primary	Change in maximal walking distance (MWD) from baseline to week 52	Function
Confirmatory secondary	Change in MWD from baseline to week 57	Function
	Change in VascuQoL-6 from baseline to week 52	Quality of Life
	Change in pain free walking distance (PFWD) from baseline to week 52	Symptoms
Supportive secondary	Change in PFWD from baseline to week 57	Symptoms
	Change in HbA_{1c}, body weight*, SBP, blood lipids† from baseline to week 52	Mechanism
	Change from screening (week –2) to week 52 in ABI	Mechanism
	Change from baseline to week 52 in SF-36 physical functioning domain	Quality of Life
Exploratory	Anchor measure to assess clinical meaningfulness of observed change in MWD	Clinical Impact
	Clinical outcomes (rescue treatment, major adverse limb events, mortality‡)	Clinical Impact

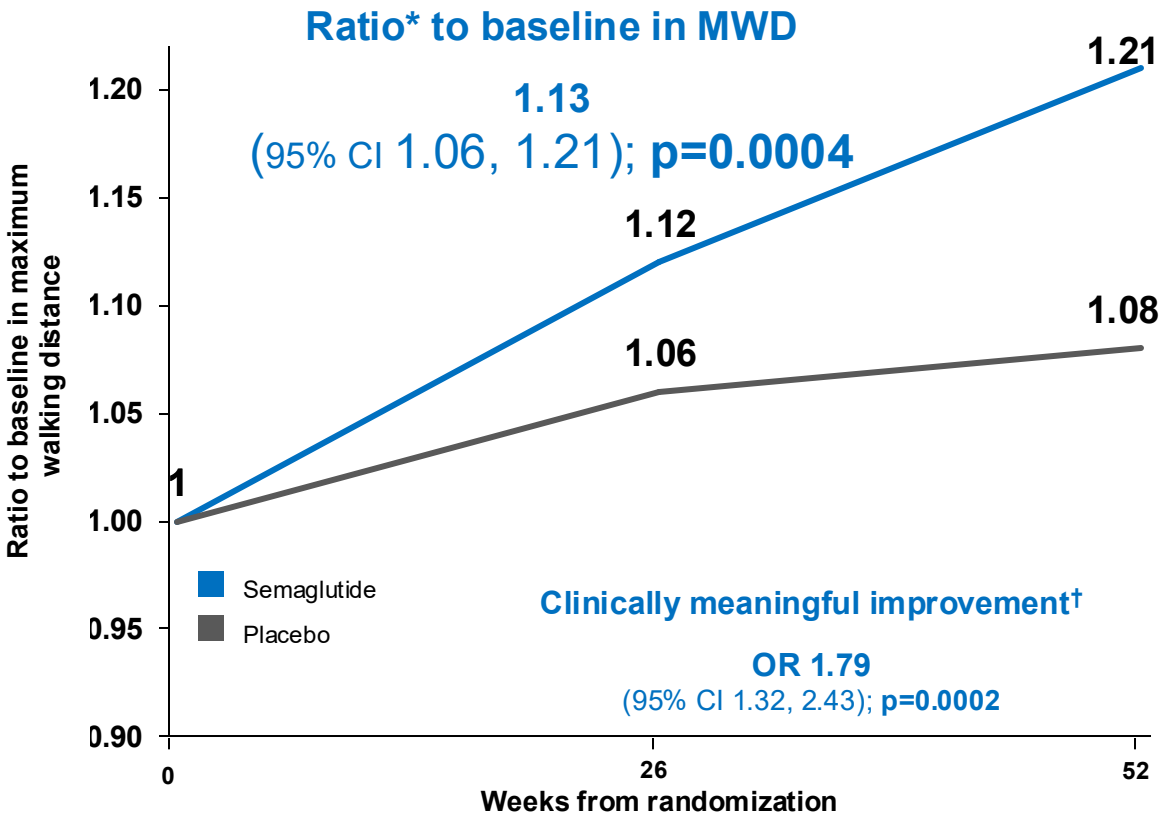
*A *post hoc* exploratory analyses evaluated correlations between MWD and BMI. †Total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides. ‡Pre-specified data collection with *post hoc* composite for analysis.
ABI, ankle-brachial index; BMI, body mass index; HbA_{1c}, glycated hemoglobin; MWD, maximum walking distance; PFWD, pain-free walking distance; QoL, quality of life; SBP, systolic blood pressure; SF-36, 36-Item Short Form Survey; VascuQoL-6, Vascular QoL Questionnaire-6.

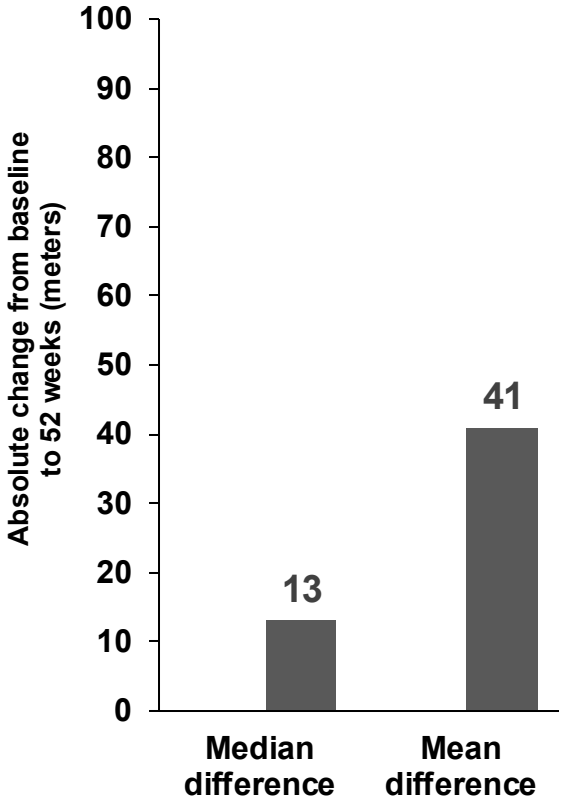
BASELINE CHARACTERISTICS

		Semaglutide 1.0 mg (n=396) %	Placebo (n=396) %
	Age – yr – median	68	68
	Female	27	22
	White	65	70
	Asian	33	28
Weight	BMI – kg/m^2 – median	29	28
	<27	37	35
Smoking	Current smoker	24	27
	Previous smoker	45	48
	Hypertension	86	90
	Prior myocardial infarction	15	22
	NYHA Class I–II	14	14
	HbA_{1c} – % – median (IQR)	7.0 (6.5–7.8)	7.2 (6.5–8.1)*
	eGFR – mL/min/1.73 m^2 – median (IQR)	89.0 (70.0–99.0)	87.0 (67.0–98.5)
Medical Therapy	LDL – mg/dL – geometric mean (CV)†	69.2 (0.5)	68.7 (0.5)
	Metformin	80	81
	SGLT2i	37	33
	Insulin	30	34
	Statins	83	82
	Ezetimibe and/or PCSK9i	16	15
	Aspirin or $P2Y_{12}$ inhibitor	73	74
	Direct oral anticoagulants or VKA	13	12
	Cilostazol	11	11

*N=395; †n=381 and n=376 for semaglutide and placebo, respectively. Data shown are percentages unless stated otherwise.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; NYHA, New York Heart Association; $P2Y_{12}$, purinergic receptor $P2Y_{12}$; PCSK9i, proprotein convertase subtilisin/kexin type 9; SGLT2i, sodium–glucose cotransporter-2 inhibitor; VKA, vitamin K antagonist.

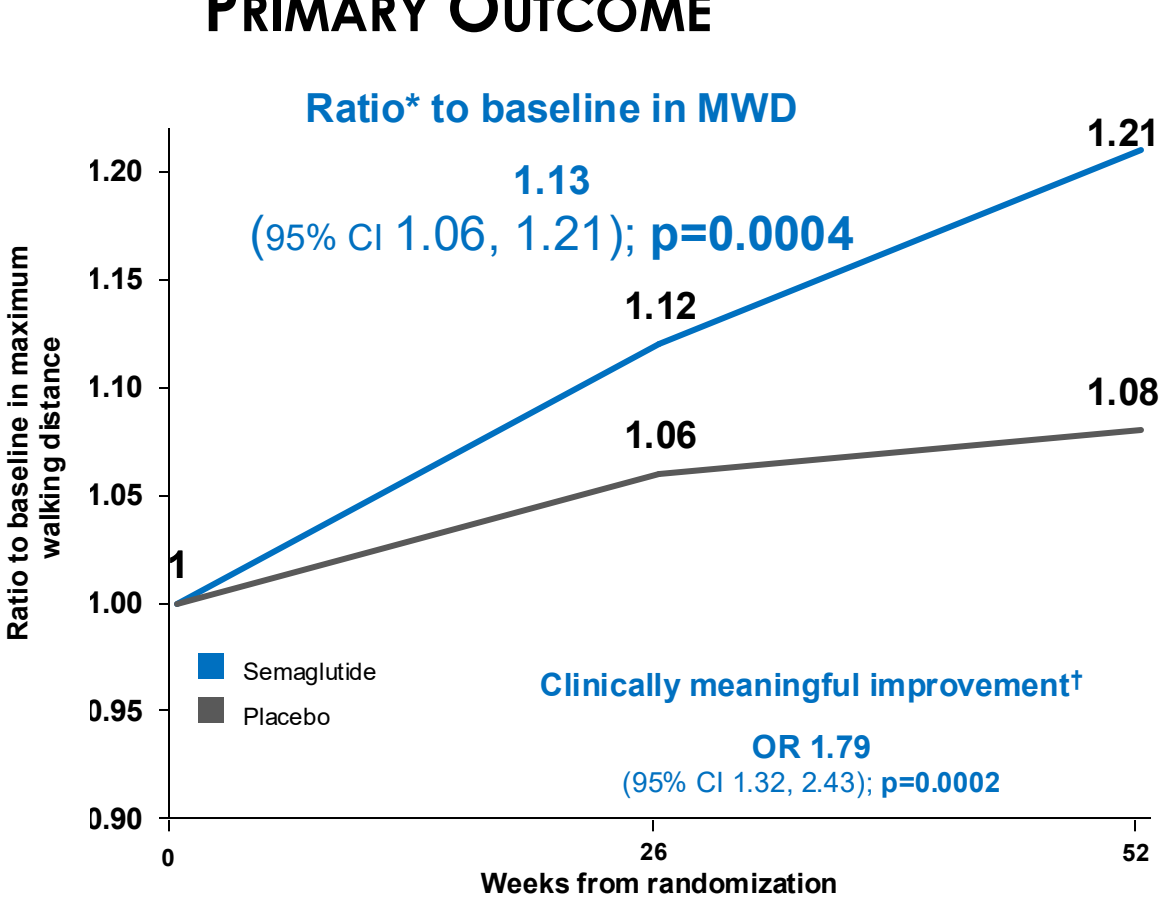
PRIMARY OUTCOME

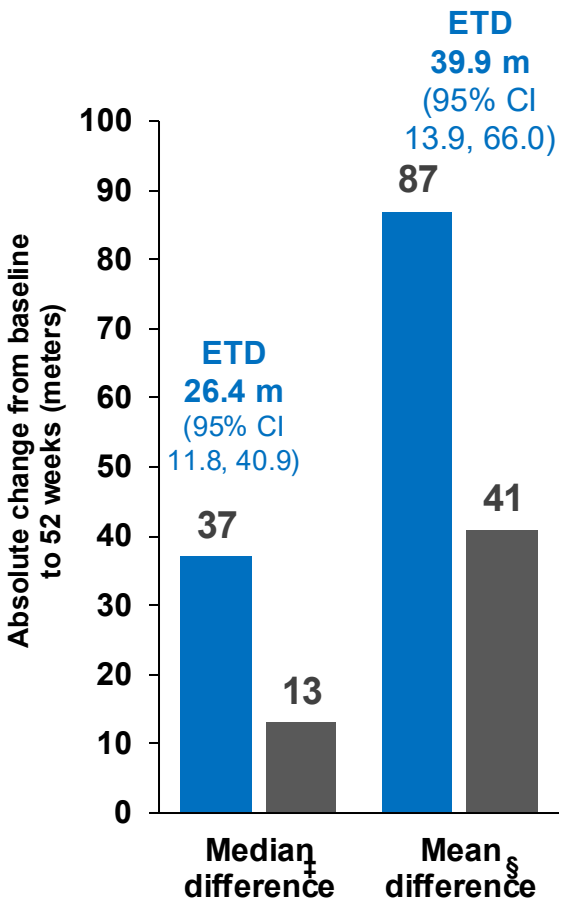




*Estimated treatment ratio; †Using a prespecified anchor measure to assess clinical meaningfulness of change with semaglutide versus placebo.
Absolute change from baseline to 52 weeks was an exploratory outcome, based on the in-trial observation period for the median difference estimate, and the on-treatment without rescue (revascularization or medication) observation period for the mean difference.
CI, confidence interval; MWD, maximum walking distance; OR, odds ratio.

PRIMARY OUTCOME



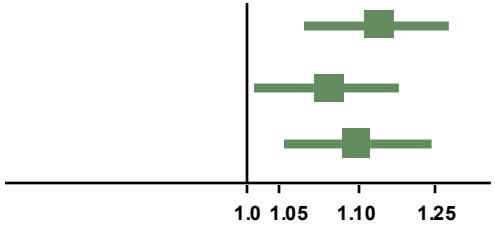


*Estimated treatment ratio; †Using a prespecified anchor measure to assess clinical meaningfulness of change with semaglutide versus placebo; ‡Treatment policy estimand; §Trial product (hypothetical) estimand. Absolute change from baseline to 52 weeks was an exploratory outcome, based on the in-trial observation period for the median difference estimate, and the on-treatment without rescue (revascularization or medication) observation period for the mean difference.
CI, confidence interval; ETD, estimated treatment difference; MWD, maximum walking distance; OR, odds ratio.

Primary and Secondary Outcomes

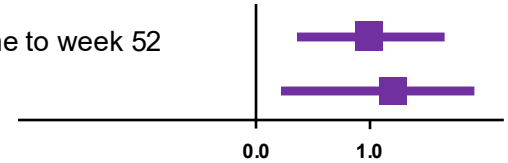
Function

1	Ratio to baseline in MWD at week 52	1.13 (95% CI 1.06, 1.21)	p=0.0004
2	Ratio to baseline in MWD at week 57	1.08 (95% CI 1.00, 1.16)	p=0.0380
2	Ratio to baseline in PFWD at week 52	1.11 (95% CI 1.03, 1.20)	p=0.0046



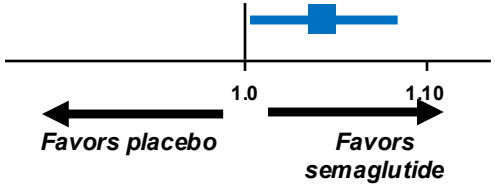
Quality of life

2	Change in VascuQoL-6 total score from baseline to week 52	1.00 (95% CI 0.48, 1.52)	p=0.011
3	Change in SF-36 Physical Functioning Domain	1.25 (95% CI 0.26, 2.24)	p=0.013



Hemodynamics (ABI)

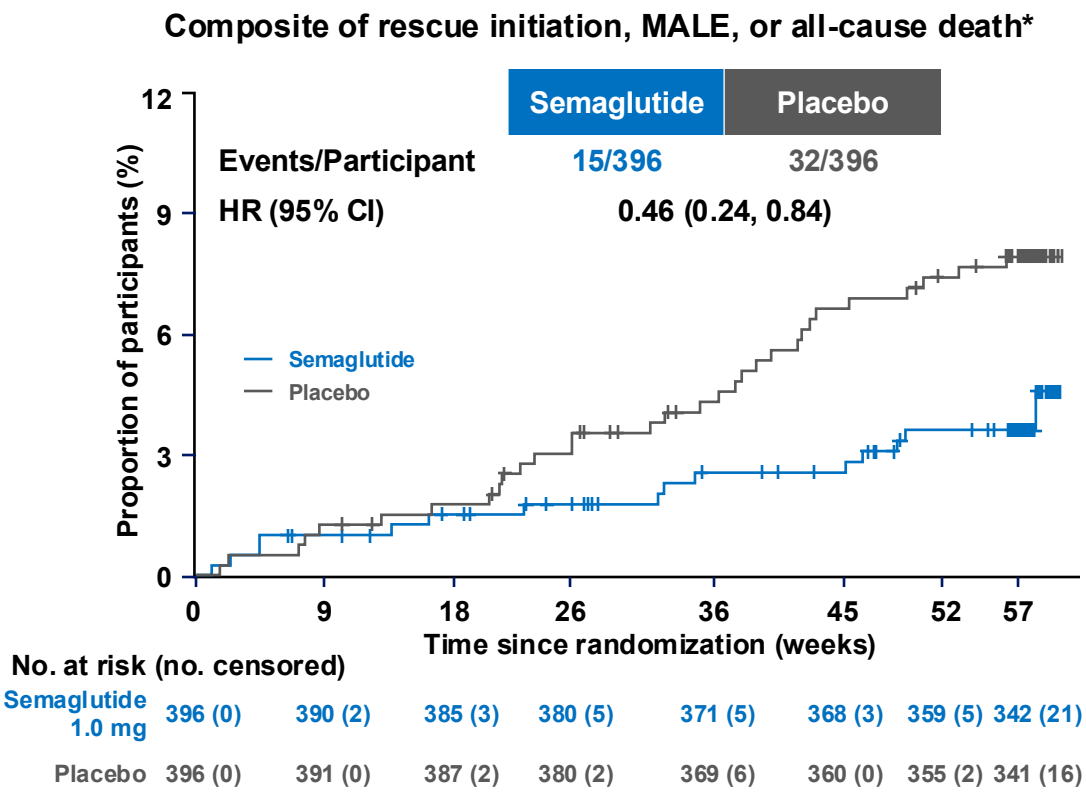
3	Geometric mean ABI ratio to baseline	1.05 (95% CI 1.02, 1.09)	p=0.0037

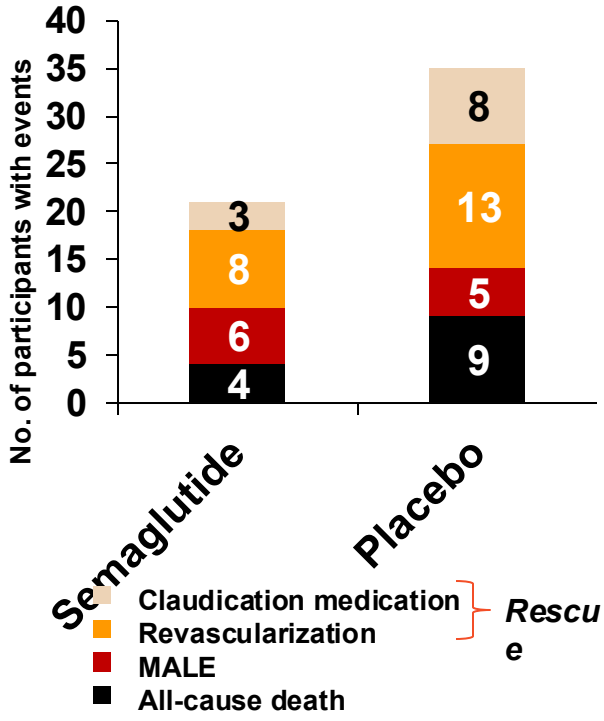


1 Primary endpoint
2 Confirmatory secondary endpoint
3 Supportive secondary endpoint

ABI, ankle-brachial index; CI, confidence interval; MWD, maximum walking distance; PFWD, pain-free walking distance; QoL quality of life; SF-36, 36-Item Short Form Survey; VascuQoL-6, Vascular Quality of Life Questionnaire-6.

EXPLORATORY ANALYSIS OF PROGRESSION OUTCOMES





*Pre-specified data collection with a *post hoc* exploratory analysis evaluating the composite of rescue initiation, MALE, or all-cause death, and the individual components.
CI, confidence interval; HR, hazard ratio; MALE, major adverse limb events.

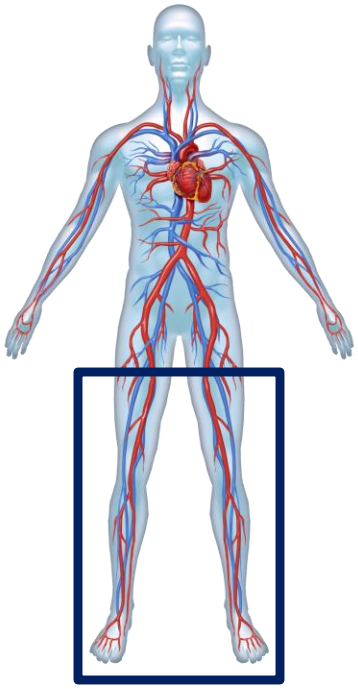
SUMMARY

Known benefits of semaglutide[1–5]

- ↓ Weight
- ↓ HbA_{1c}
- ↓ Inflammation
- ↓ Blood pressure
- ↓ Cardiometabolic risk
- ↑ Function & ↓ symptoms in HF
- ↓ MACE in ASCVD
- ↓ Kidney complications

PAD-specific benefits of semaglutide

- ✓ Improves function
- ✓ Improves symptoms
- ✓ Improves hemodynamics (ABI)
- ✓ Lower rates of rescue therapy (treatment or revascularization)



Significantly improved function and met criteria for a clinically meaningful change

Significantly improved symptoms and quality of life

Reduced disease progression

Improved ABI

Safety consistent with previous trials with no unexpected safety findings

ABI, ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; HbA_{1c}, glycated hemoglobin; HF, heart failure; MACE, major adverse cardiovascular events; PAD, peripheral artery disease; T2D, type 2 diabetes.

1. Wilding JPH et al. *N Engl J Med* 2021;384:989–1002; **2.** Kosiborod MN et al. *N Engl J Med* 2023;389:1069–1084; **3.** Kosiborod MN et al. *Lancet* 2024;404:949–961; **4.** Lincoff AM et al. *N Engl J Med* 2023;389:2221–2232; **5.** Perkovic V et al. *N Engl J Med* 2024;391:109–121.

Putative Mechanisms for the CV benefits of GLP-1 agonists

TABLE 9 Hypothesized Mechanisms of GLP-1RA to Lower CV Events

Effect	Consequence
■ Blood pressure reduction	■ Reduced myocardial work, reduced filling pressures, pre-/afterload reduction
■ Weight loss	■ Improved CV disease risk profile, lower blood pressure
■ Low-density lipoprotein cholesterol reduction	■ Reduced atherogenesis
■ Anti-inflammatory action	■ Upregulated nitric oxide and suppressed NF-κB activation

CV = cardiovascular; GLP-RA = glucagon-like peptide-1 receptor agonists; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells.

J Am Coll Cardiol 2018;72:3200-23.

UB Endocrine Department studies

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Anti-inflammatory effect of GLP-1 agonists

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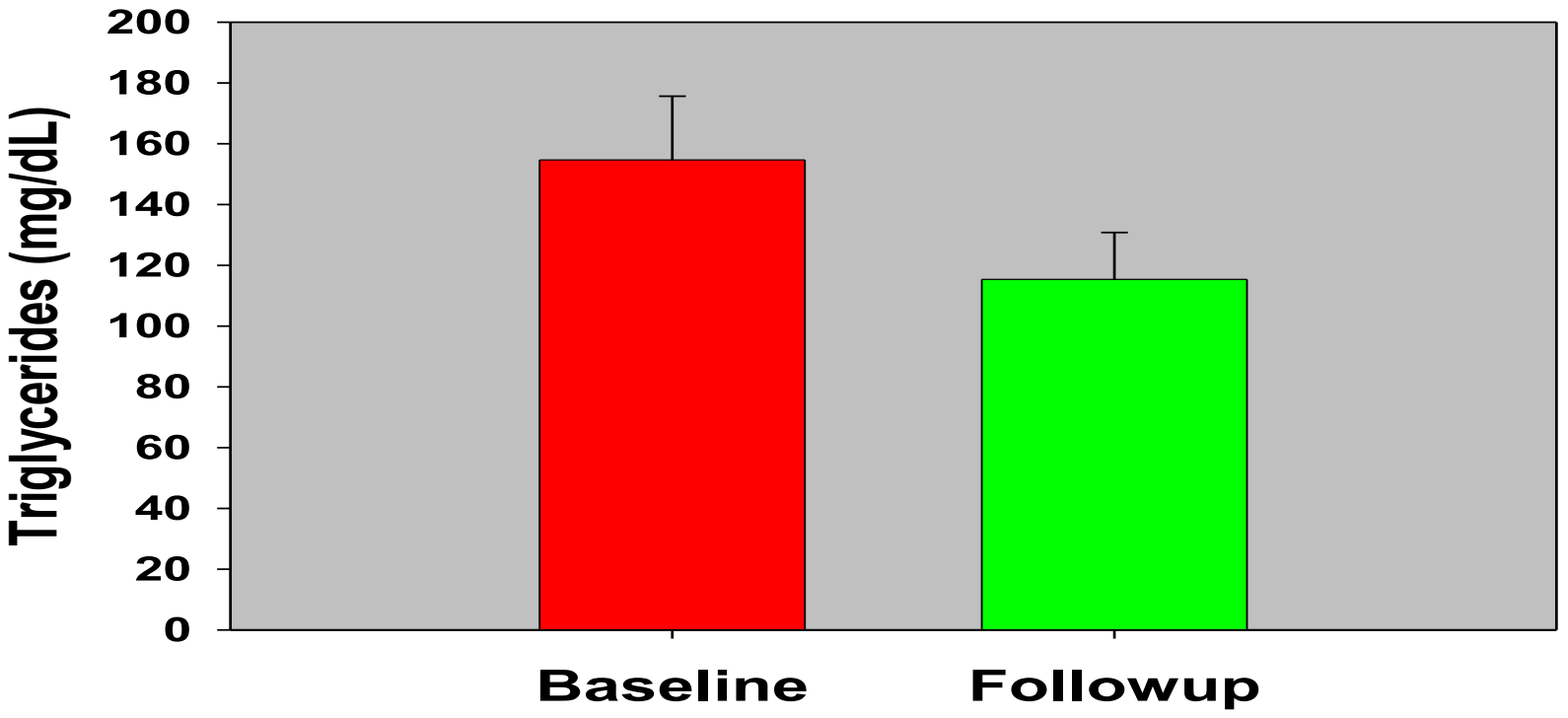
Exenatide Causes Weight Loss And a Reduction in the Insulin Dose Along With an Improvement in HbA1c in Obese Type 2 Diabetics on Insulin

Ruchi Bhatia[1], Prabhakar Viswanathan, PhD[1], Ajay Chaudhuri, MD[1], Priya Mohanty, MD[1], Vishal Bhatia, MD[1] and Paresh Dandona, MD[1].

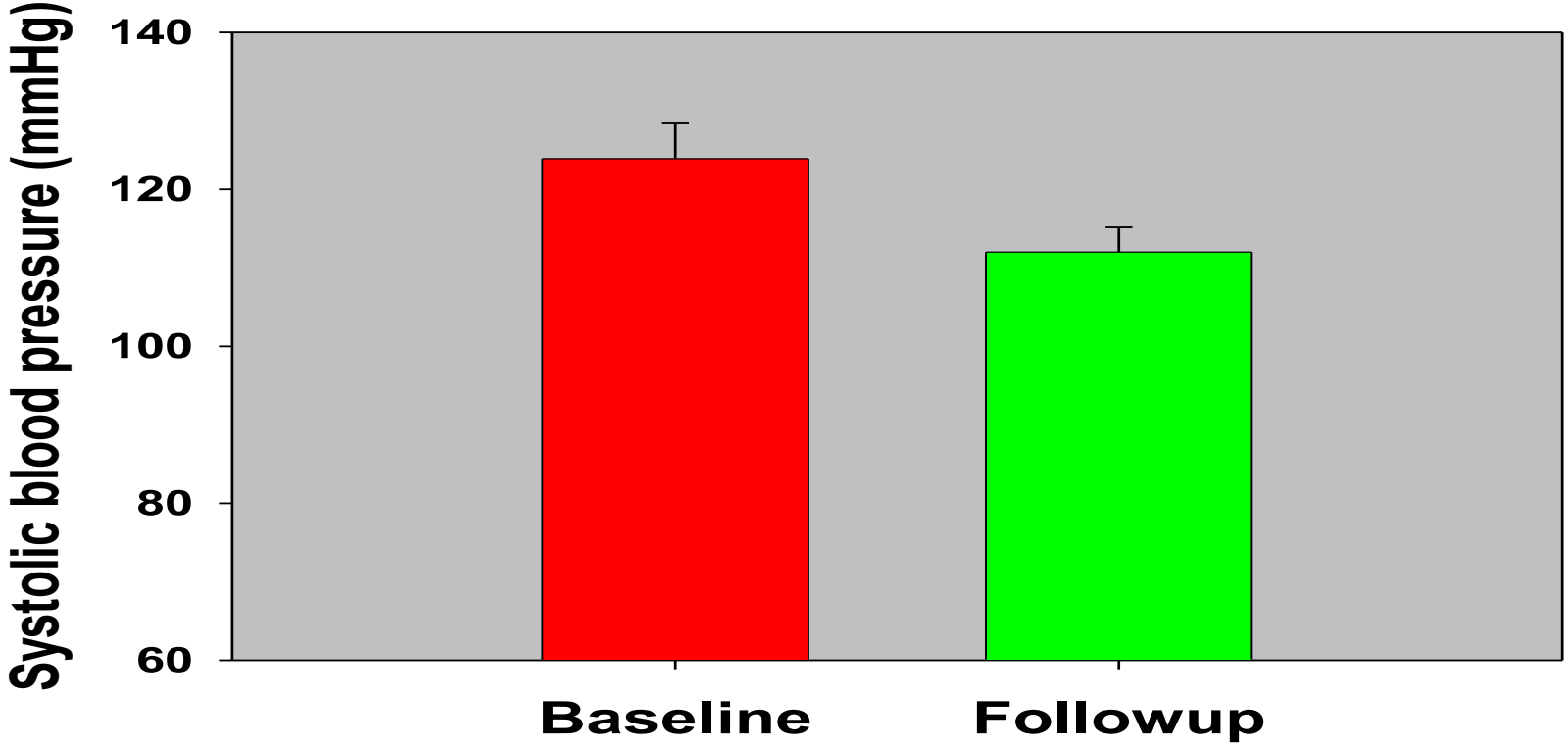
SUNY at Buffalo, Endocrinology Division, Kaleida Health, Buffalo, NY, United States.

Exenatide: Change in triglycerides



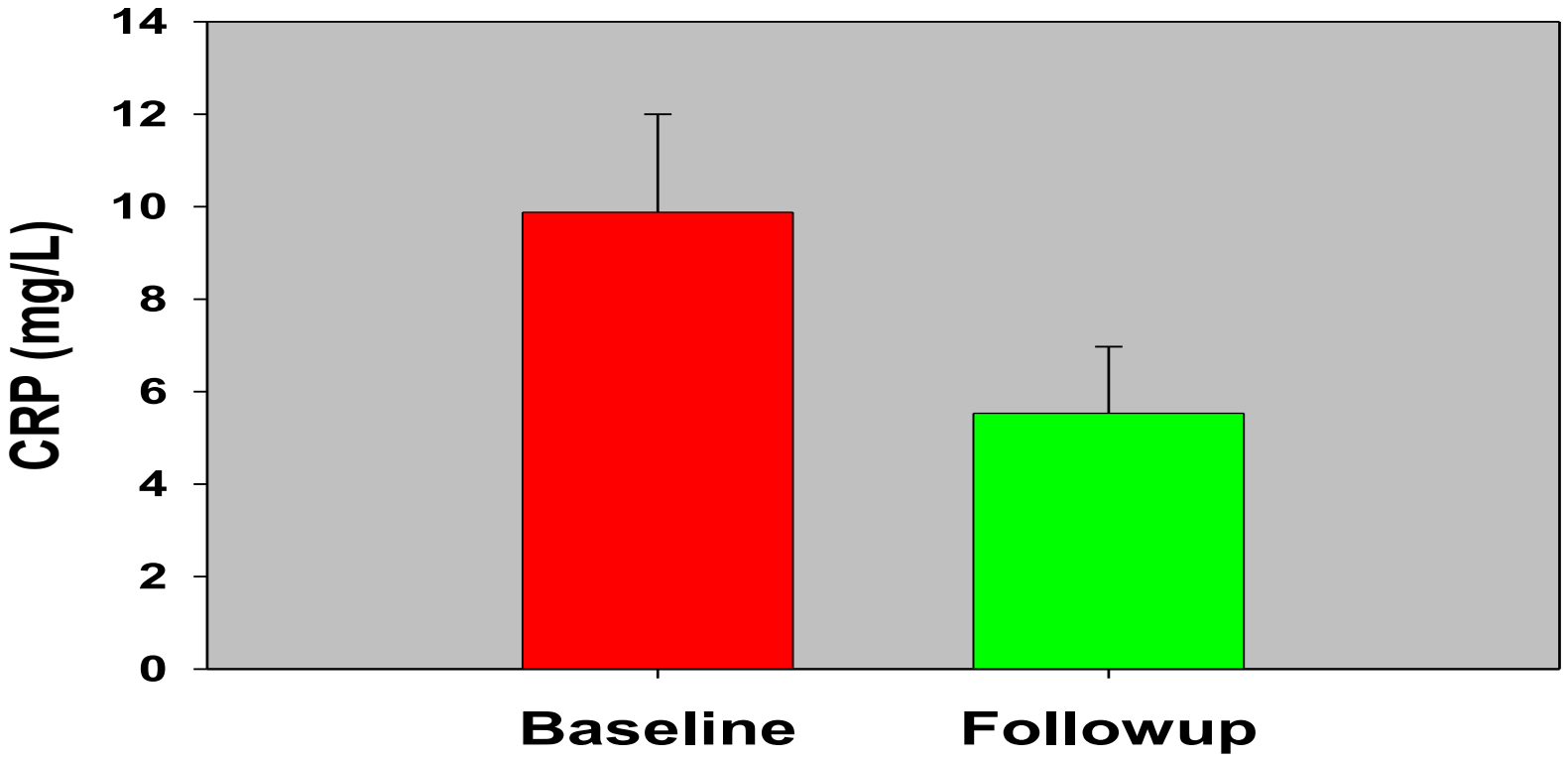
VISIT	WEEKS (MEAN)	N	MEAN (mg/dL)	STD DEV	SEM	P VALUE
Baseline		42	154.68	139.09	20.97	
Follow-up	26 ± 2	42	115.33	100.02	15.43	0.02

Exenatide: Change in systolic blood pressure



VISIT	WEEKS (MEAN)	N	MEAN (mm Hg)	STD DEV	SEM	P VALUE
Baseline		39	123.89	28.19	4.63	
Follow-up	18.16	39	112.00	19.07	3.14	P = 0.003

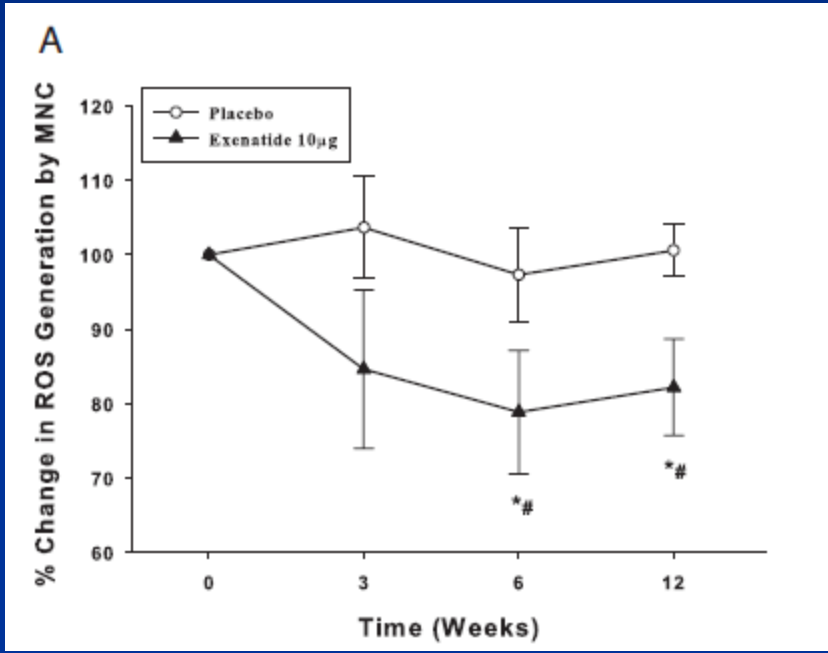
Exenatide: Change in C-Reactive Protein (CRP)



VISIT	WEEKS (MEAN)	N	MEAN (mg/L)	STD DEV	SEM	P VALUE
Baseline		29	9.88	11.42	2.12	
Follow-up	26 ± 2	29	5.53	7.77	1.44	P = 0.002

Exenatide Exerts a Potent Antiinflammatory Effect

Ajay Chaudhuri, Husam Ghanim, Mehul Vora, Chang Ling Sia,
Kelly Korzeniewski, Sandeep Dhindsa, Antoine Makdissi, and Paresh Dandona



J Clin Endocrinol Metab, January 2012, 97(1):198–207

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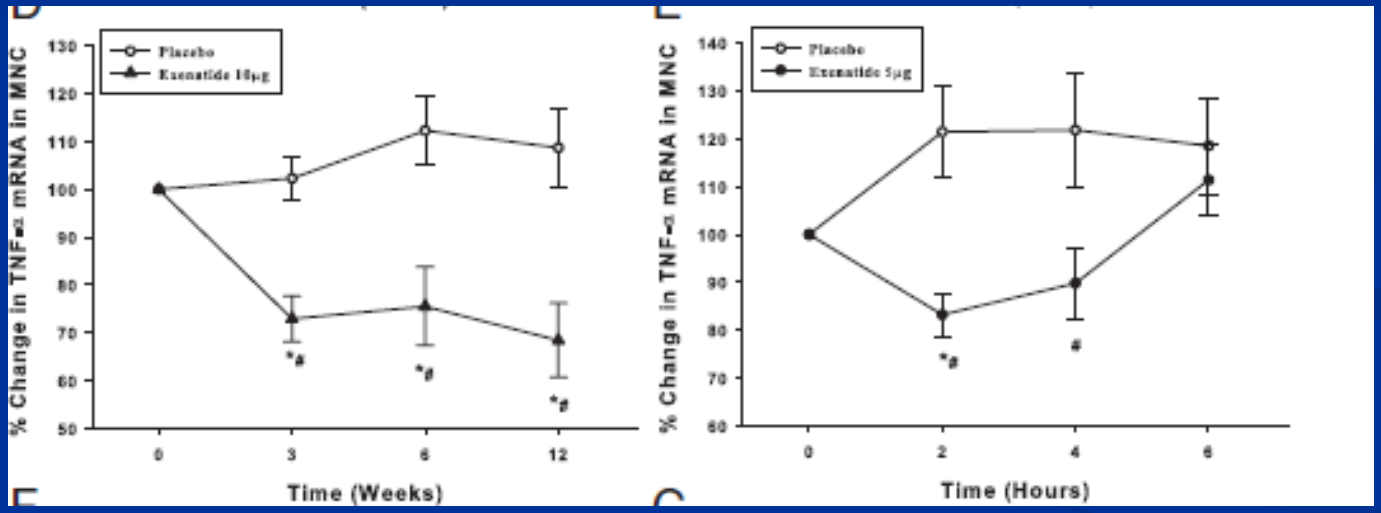

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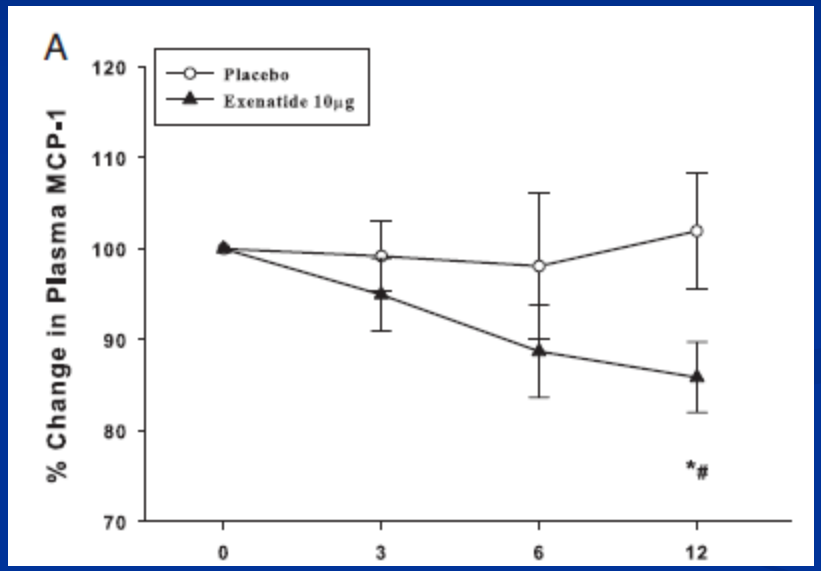

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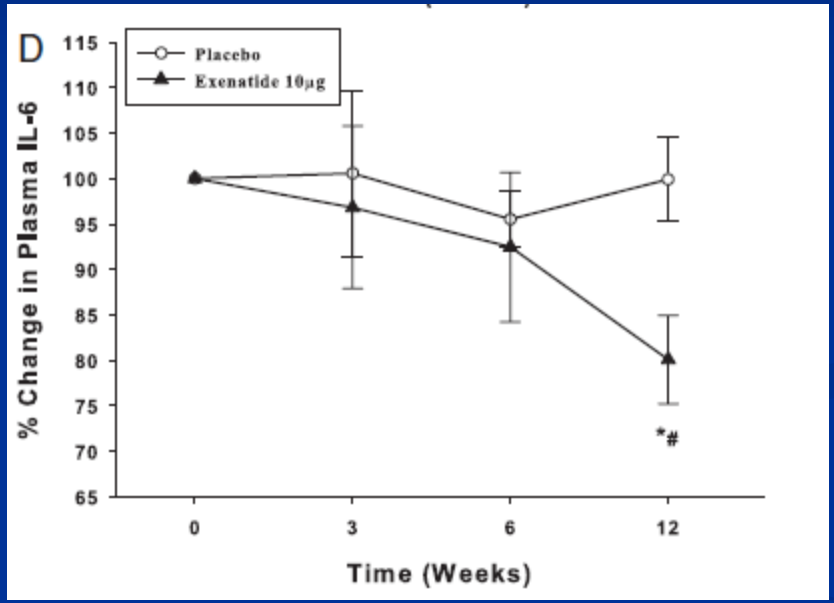
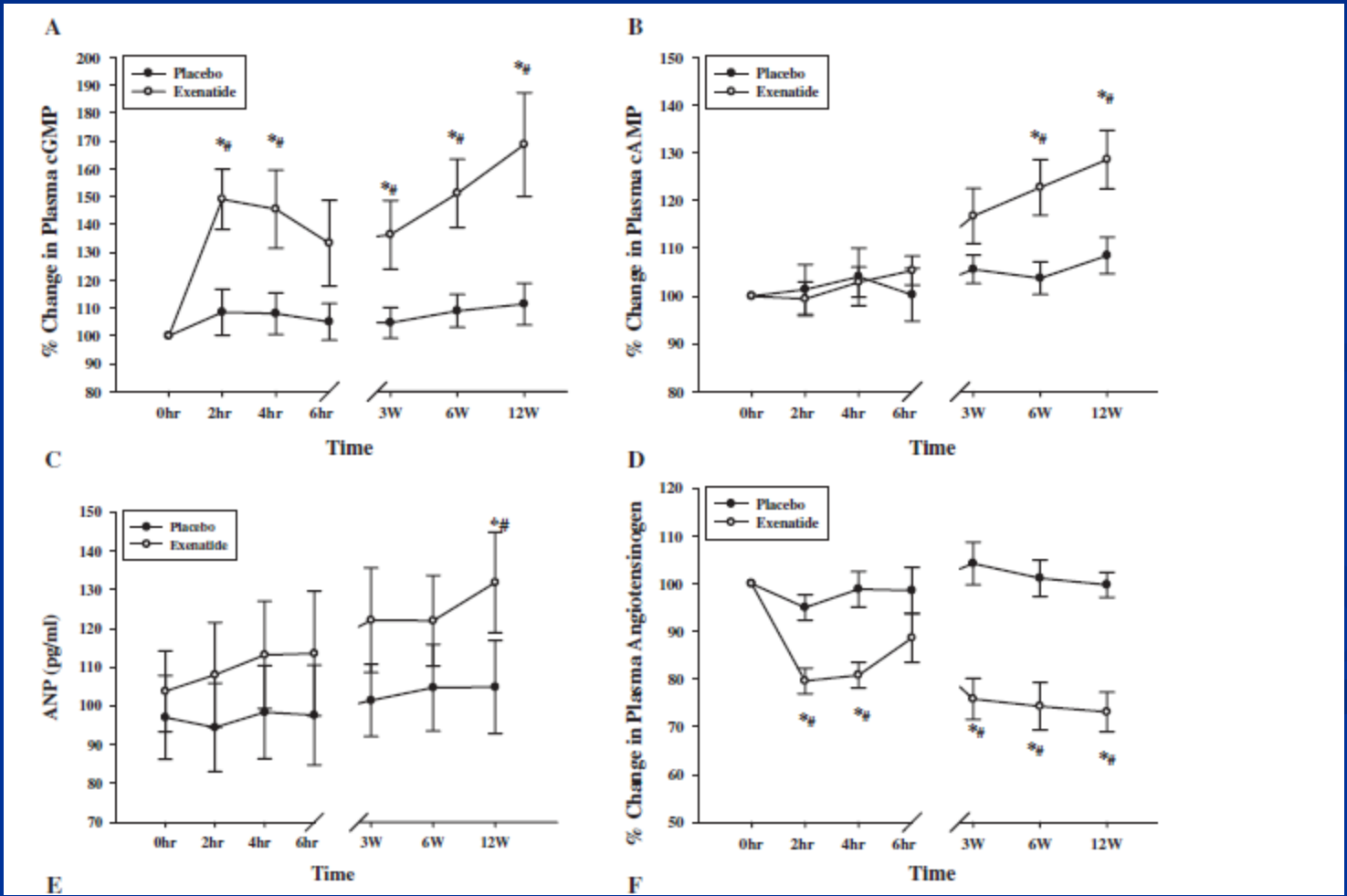


J Clin Endocrinol Metab, January 2012, 97(1):198–207

Exenatide induces an increase in vasodilatory and a decrease in vasoconstrictive mediators

Ajay Chaudhuri MD† | Husam Ghanim PhD† | Antoine Makdissi MD | Kelly Green BS | Sanaa Abuaysheh BS | Manav Batra MD | Nitesh D. Kuhadiya MD | Paresh Dandona MD, PhD

Diabetes Obes Metab. 2017;**19**:729–733.



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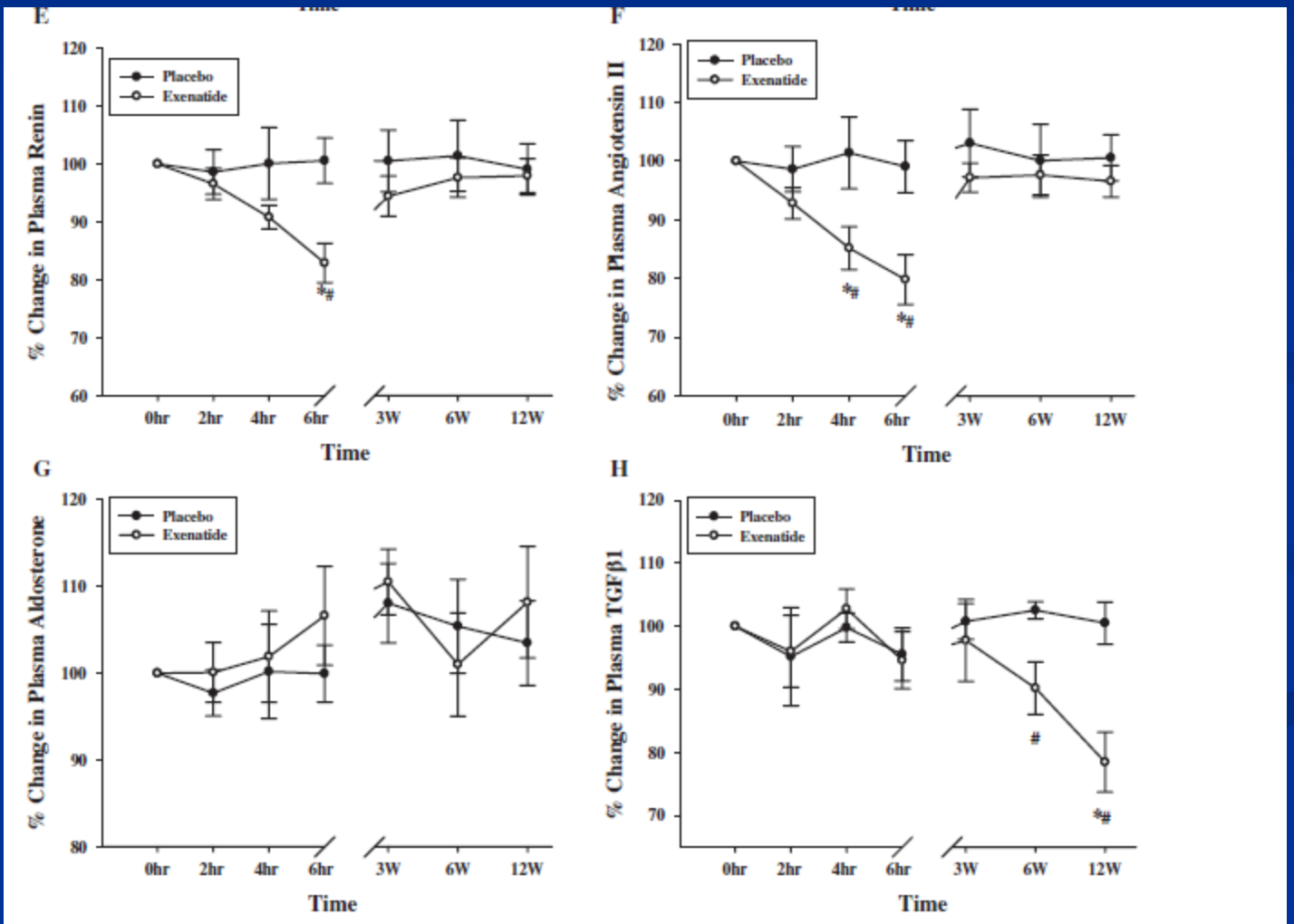

CONCLUSION

- PAD is preventable in subjects with diabetes mellitus
- ABC of diabetes care is beneficial in the primary and secondary prevention of PAD in diabetes
- GLP-1 agonists, SGLT2 inhibitors and TZDs provide CV benefits independent of glycemic control in subjects with Diabetes and ASCVD
- Guideline based therapy can prevent and reduce the risk of MALE in subkects with diabetes and PAD