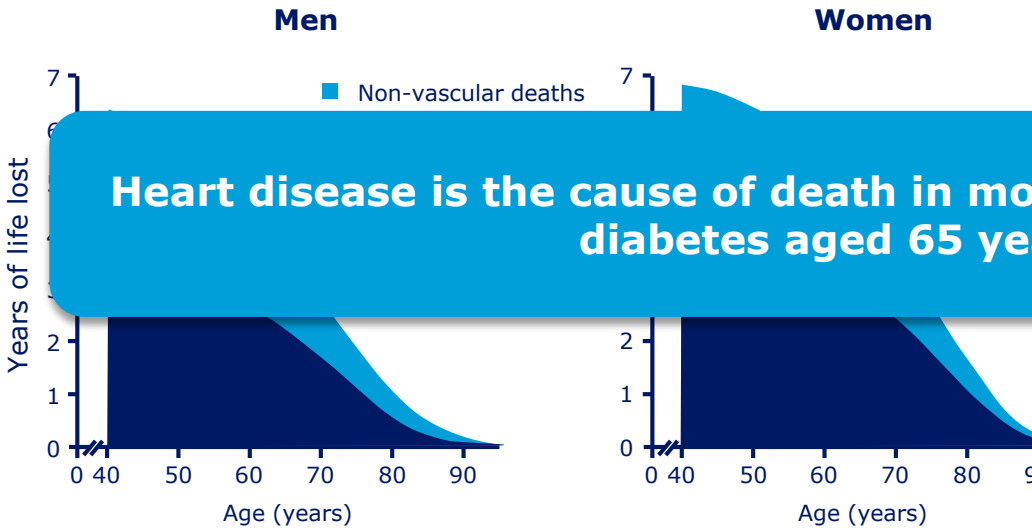
Cardiovascular risk in diabetes: What the Cardiologist Needs to Know

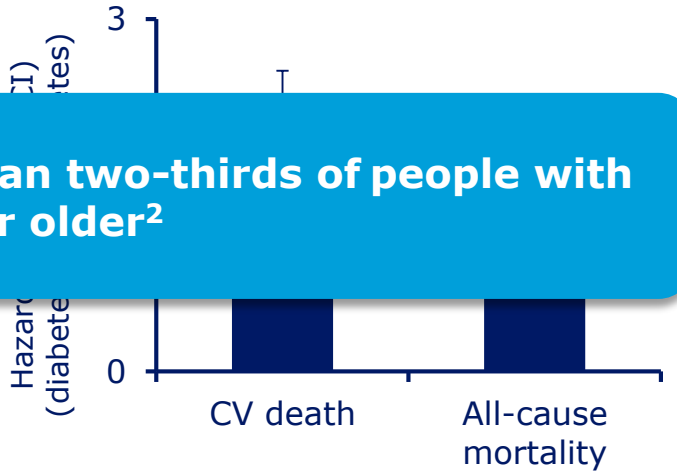
Hani Sabbour MD FACC FHRS

CVD is the leading cause of death among people with diabetes

Years of life lost in people with diabetes* compared with non-diabetes peers[1]



Mortality risk associated with diabetes (n=820,900)[1]



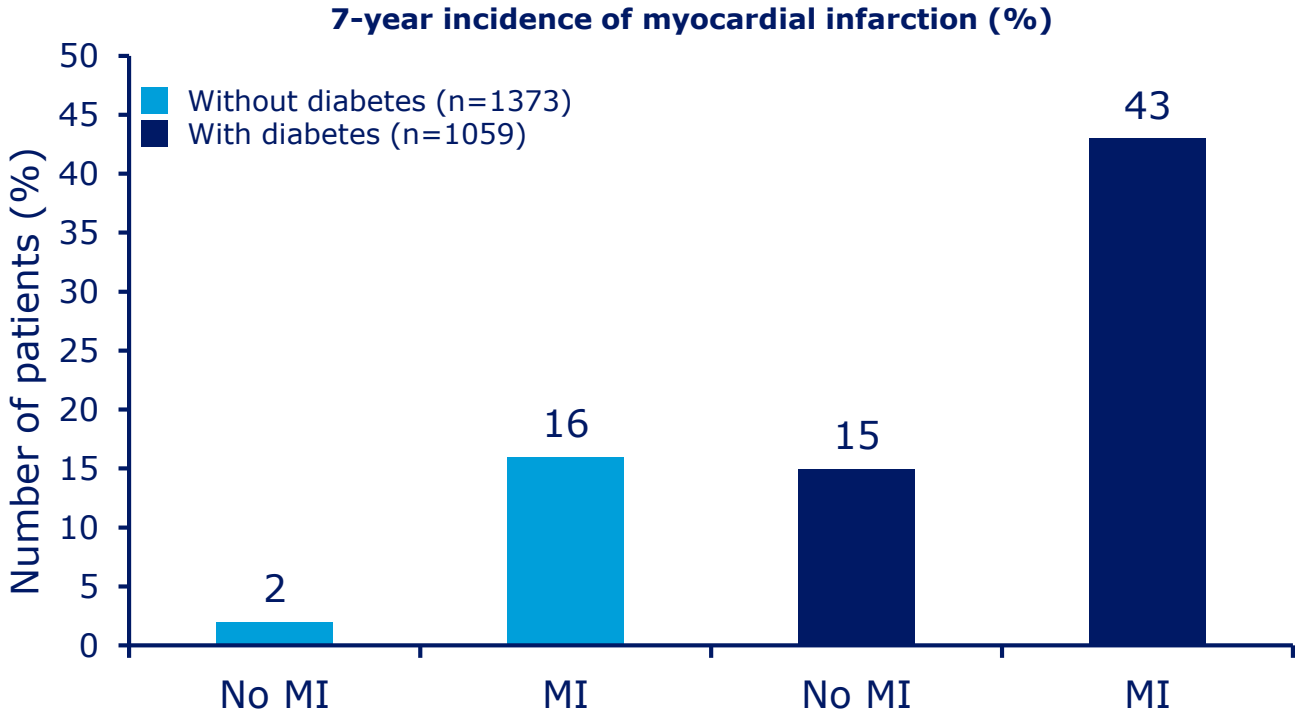
Heart disease is the cause of death in more than two-thirds of people with diabetes aged 65 years or older[2]

In high-income countries, up to 91% of adults with diabetes have type 2 diabetes[3]

*Information on diabetes type (i.e. type 1 or 2) was generally not available; although, the age of the participants suggests that the large majority with diabetes would have type 2
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease.

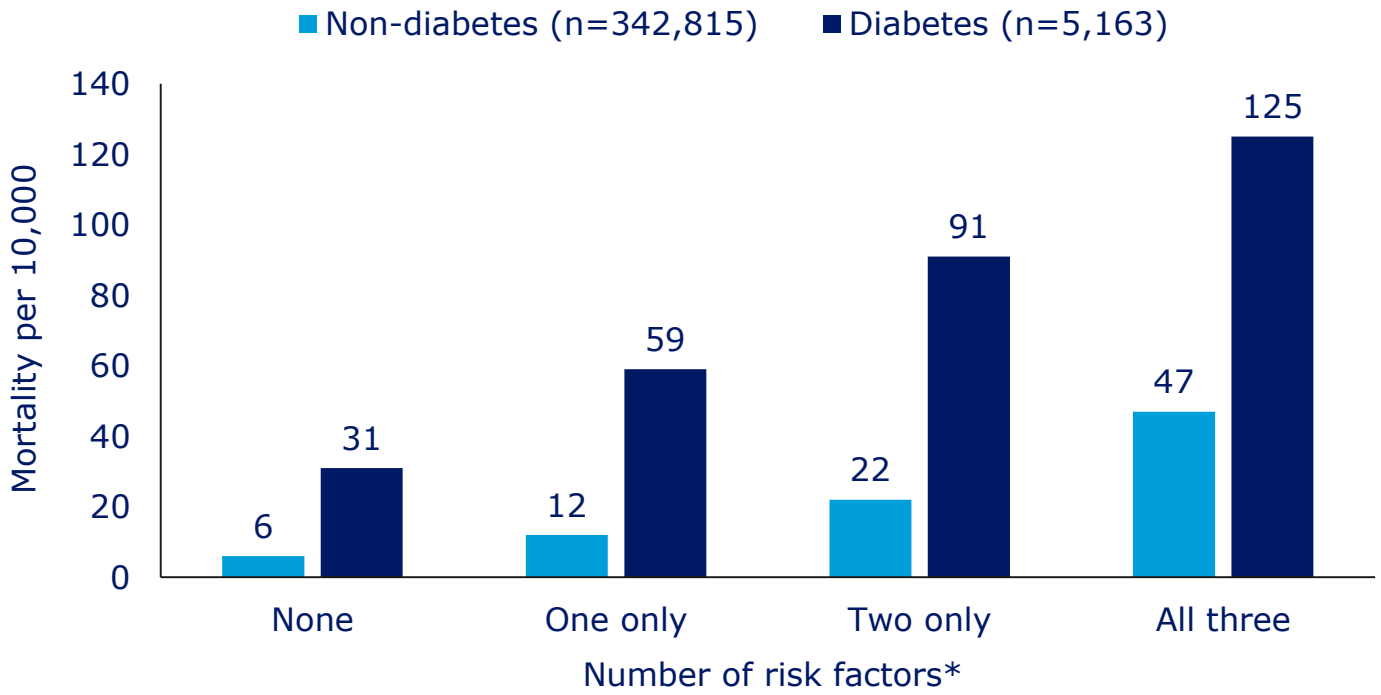
1. Seshasai SR et al. *N Engl J Med* 2011;364:829–841; 2. Centers for Disease Control and Prevention. National Diabetes Fact Sheet 2011. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf; 3. International Diabetes Federation. *IDF Diabetes Atlas, 7th edn.* Brussels, Belgium: International Diabetes Federation, 2015. Available at: http://www.diabetesatlas.org.

Diabetes is associated with an increased risk of CV death whether or not the individual has had a prior MI



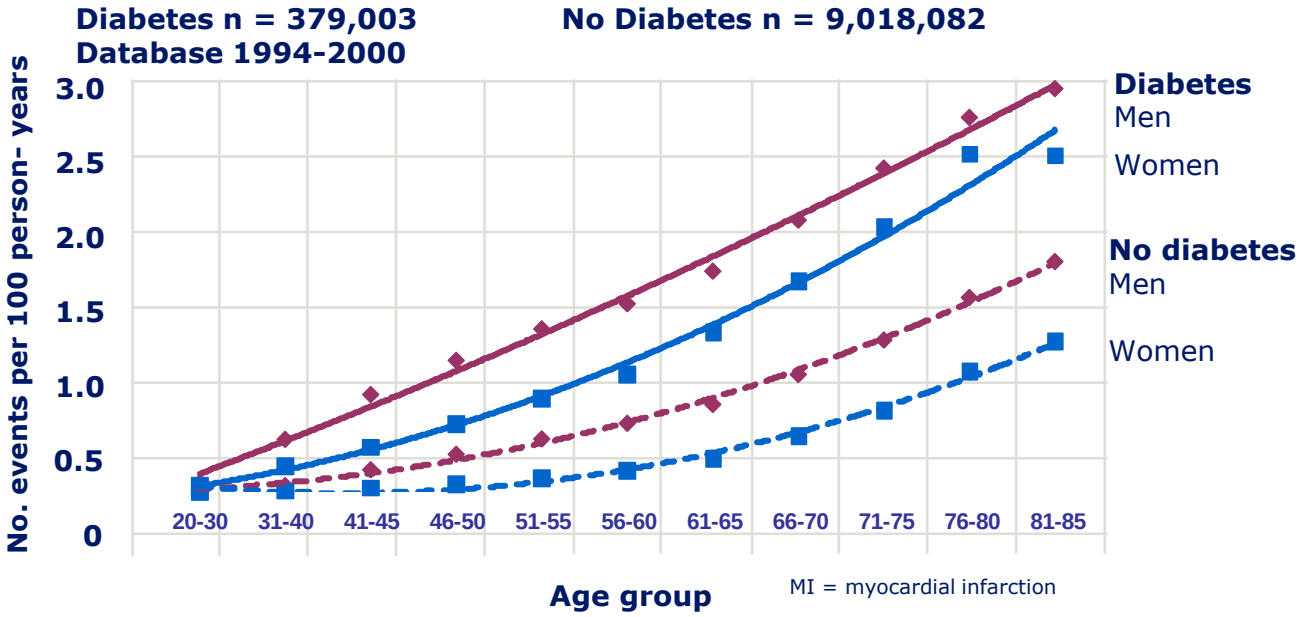
MI, myocardial infarction.
Adapted from: Hafner SM. *N Engl J Med* 1998;339:229–342.

MRFIT: Impact of diabetes on cardiovascular mortality



*Risk factors analysed: smoking, hypercholesterolemia and hypertension.
MRFIT, multiple risk factor intervention trial
Stamler J, et al. *Diabetes Care* 1993; 16(2):434-44

Absolute risk of MI is higher in patients with duration of DM



All lines fitted according to a polynomial equation; R2= 0.99–1.00 for each

Booth GL, et al. *Lancet* 2006;368:29-36.

Risk of myocardial infarction is associated with multiple risk factors: The INTERHEART study

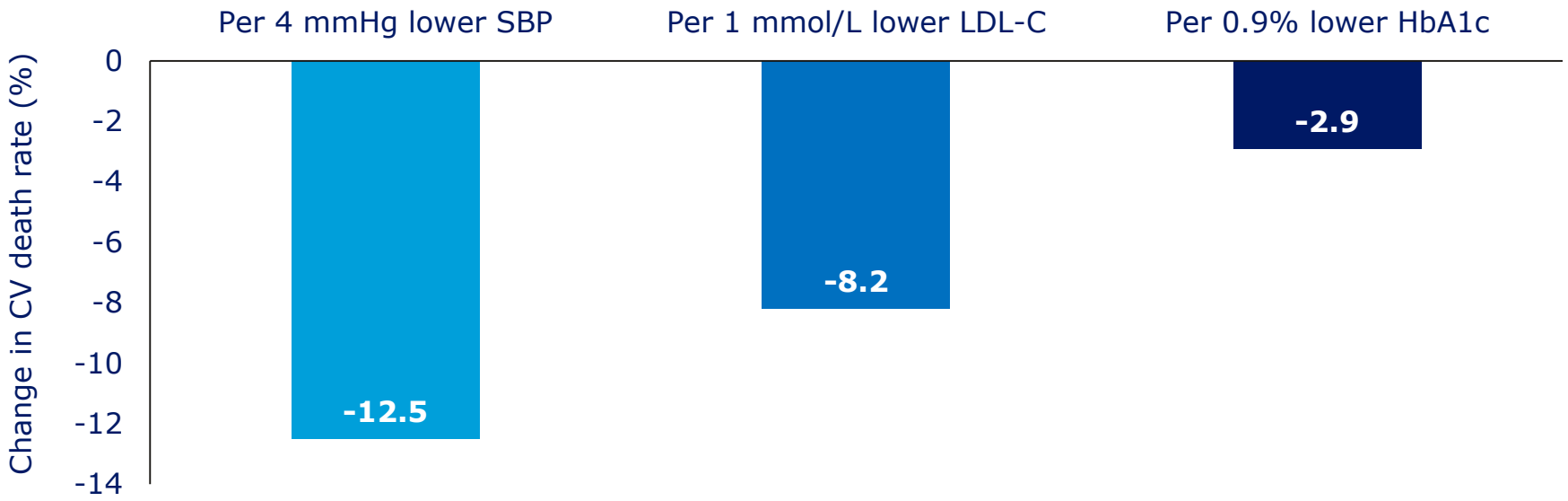
Factor	Odds Ratio	99% CI
Smoking (1)	2.87	2.58 – 3.19
Diabetes mellitus (2)	2.37	2.07 – 2.71
Hypertension (3)	1.91	1.74 – 2.10
Obesity	1.62	1.45 – 1.80
1 + 2 + 3	13.0	10.7 – 15.8
1 + 2 + 3 + Obesity	21.0	—

CI, confidence interval

Yusuf S, et al. *Lancet.* 2004;364:937–952; Yusuf S, et al. *Lancet*. 2005;366:1640-1649.

Benefit of different interventions: $HbA_{1c,}$ SBP and LDL-C

Meta-analysis of different interventions over 5 years

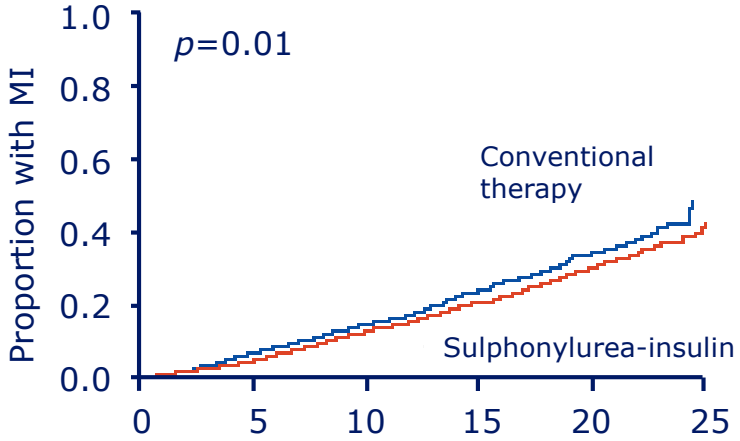


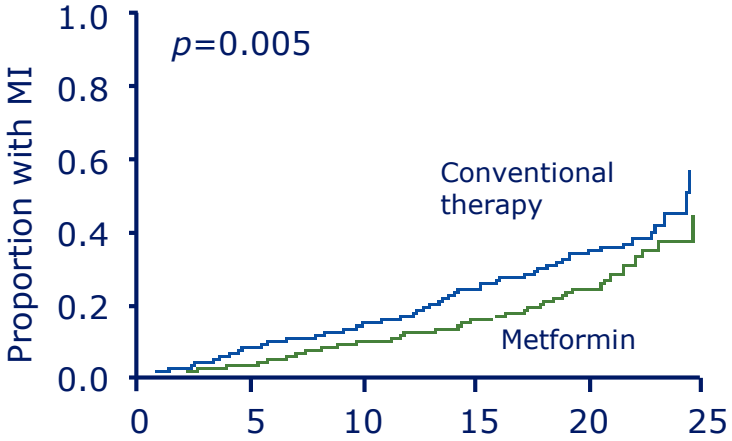
CV, cardiovascular; $HbA_{1c,}$ glycosylated haemoglobin; LDL-C low-density lipoprotein-cholesterol; SBP, systolic blood pressure

Sattar N. *Diabetologia* 2013;56:686–695.

CV benefits of tight glycaemic control – 10 years

UKPDS





No. at risk						
Conventional:	1138	1013	857	578	221	20
SU/insulin:	2729	2488	2097	1459	577	66

No. at risk						
Conventional:	411	360	311	213	95	4
Metformin:	342	317	274	214	106	16

Patients were randomised to conventional glucose control (diet) or intensive glucose control (SU or insulin, or metformin if >120% of ideal body weight)
CV, cardiovascular; MI, myocardial infarction; SU, sulphonylurea; UKPDS, UK Prospective Diabetes Study
Holman et al. *N Engl J Med* 2008;359:1577–1589.

UKPDS 2008 – The “legacy effect”

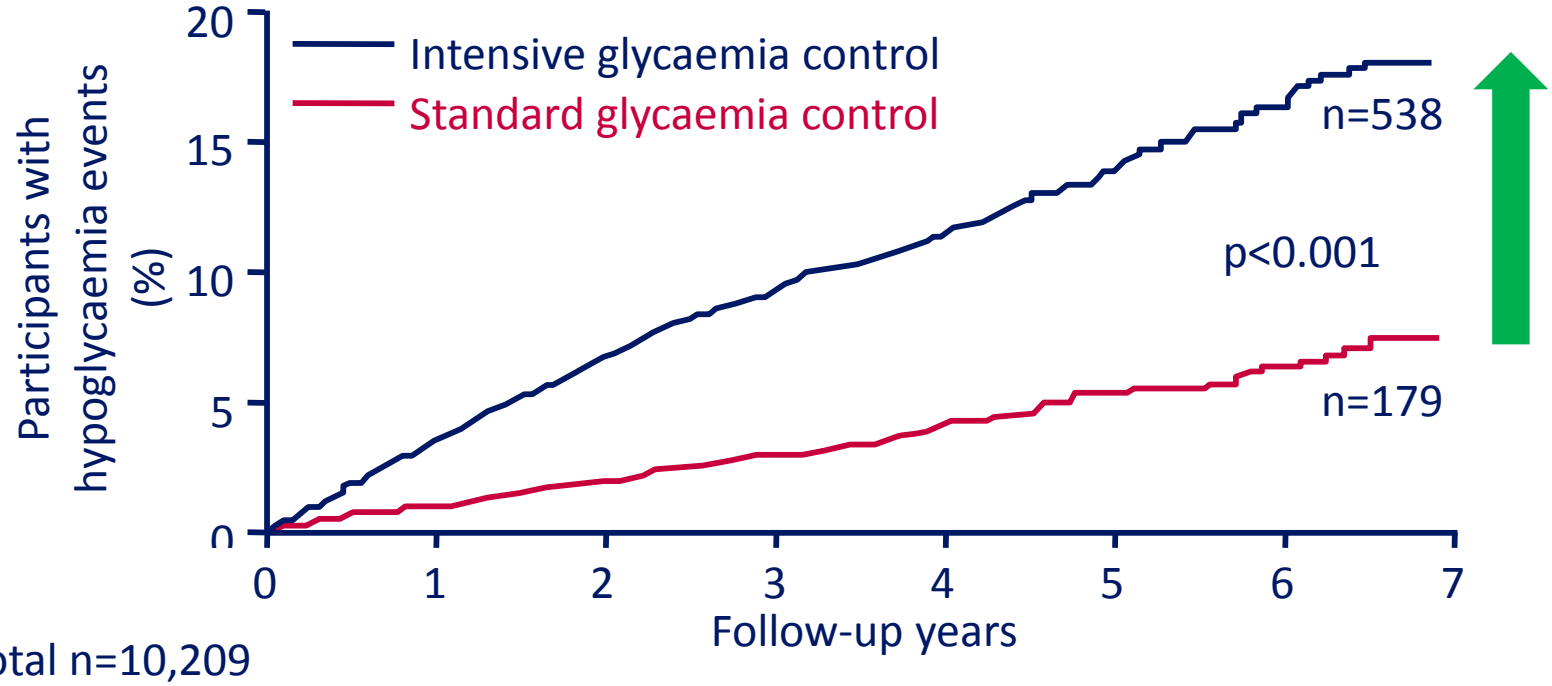
The cardiovascular benefit of intensive glucose control may be greater, if initiated **early** in the development of diabetes!

		End of randomised intervention[1] 1997
Any diabetes-related endpoint	RRR p-value	12% 0.029
Microvascular disease	RRR p-value	25% 0.0099
Myocardial infarction	RRR p-value	16% 0.052, ns
All-cause mortality	RRR p-value	6% 0.44, ns

RRR = relative risk reduction associated with intensive glucose control

[1]UKPDS Group. *Lancet* 1998;352:837–853.
[2]Holman R, *et al. N Engl J Med* 2008;359:1577–1589.

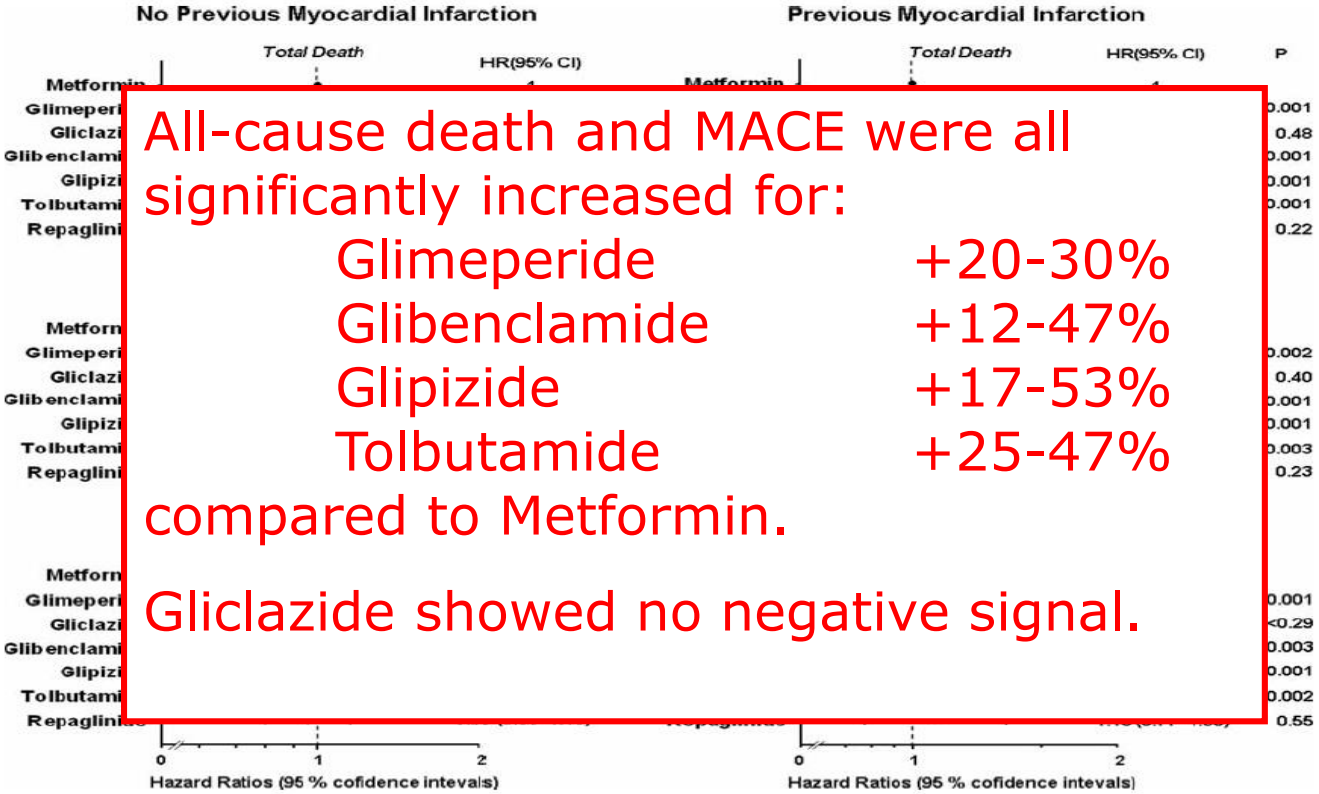
ACCORD study – Effect of glycaemic control on the risk of severe hypoglycaemia



Total n=10,209

Miller et al. *BMJ* 2010;340:b5444 doi: 10.1136/bmj.b5444

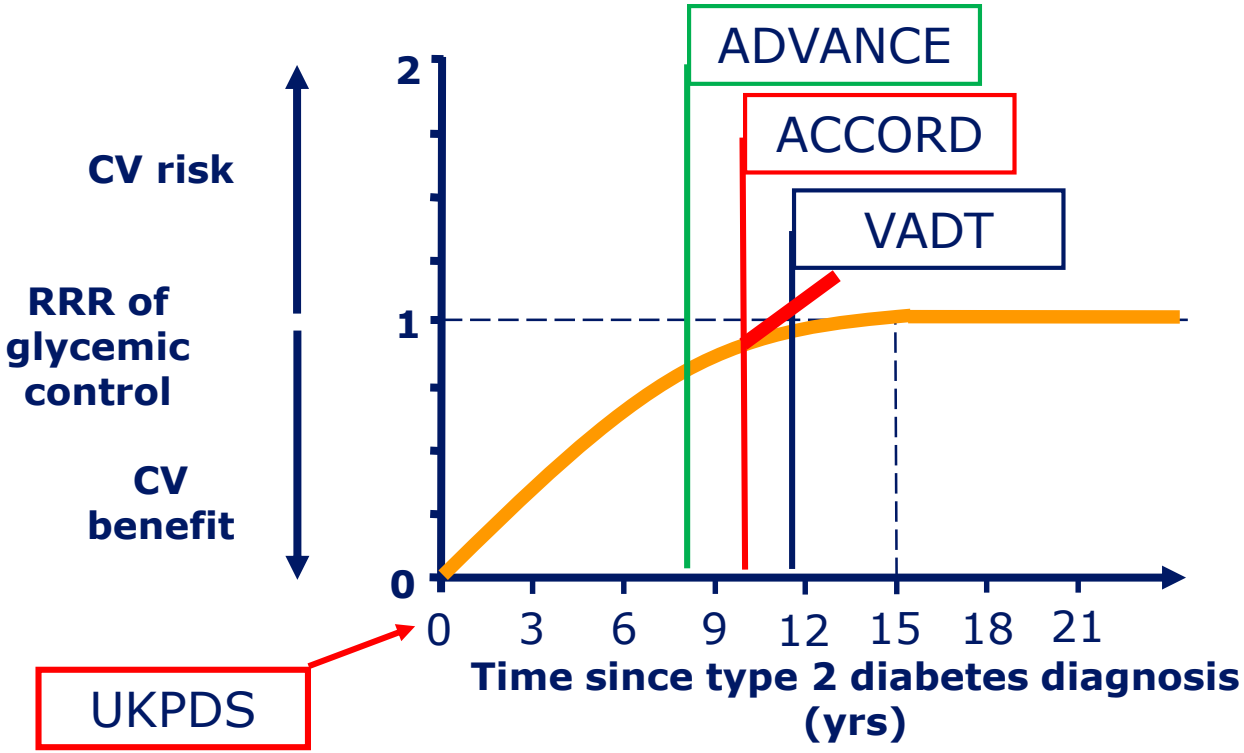
Mortality and CV risk in T2DM treated with Metformin vs. Sulfonylureas: a nationwide Danish study



Schramm TK et al., Eur Heart J 2011: 32(15):1900-8.

Who will benefit from intensive glycaemic control ?

VADT risk model: Benefit of early vs late glycaemic intervention



Adapted from VADT data presented at ADA June 2008.

How to treat Type 2 Diabetes in 2016 ?

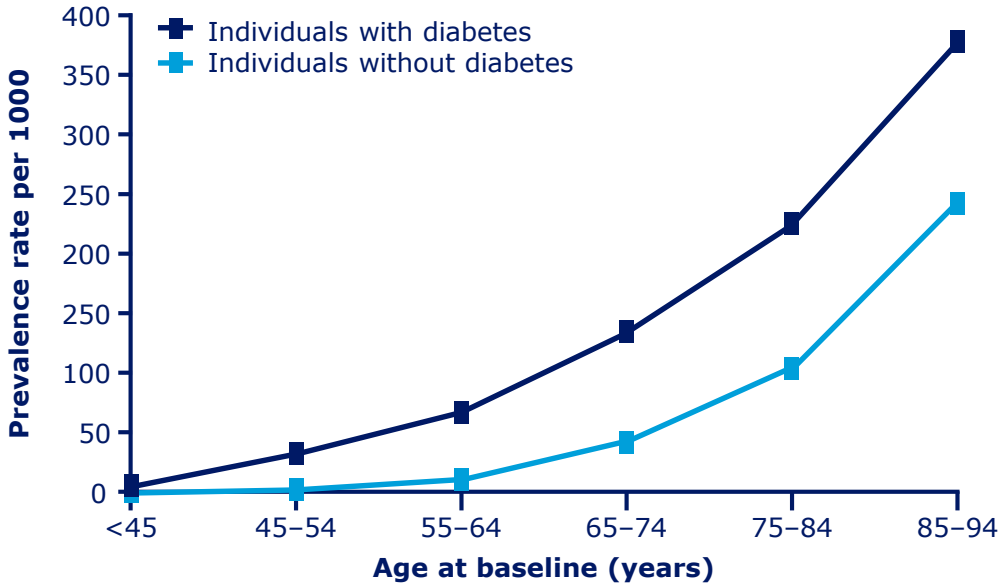
- Avoid Hypoglycaemias
- Avoid Treatment-related Weight Gain
- Reconstitute Beta-cell function and stop Beta cell loss
- Provide stringent and safe glycemic control early after diagnosis

What are the choices?

Heart failure and diabetes

- Data from **The Framingham Study[1]** from 1974 suggest that "diabetes is another discrete cause of congestive heart failure and that some form of cardiomyopathy is associated with diabetes, as a result of either small vessel disease or metabolic disorders."

Age-associated prevalence of heart failure[2]



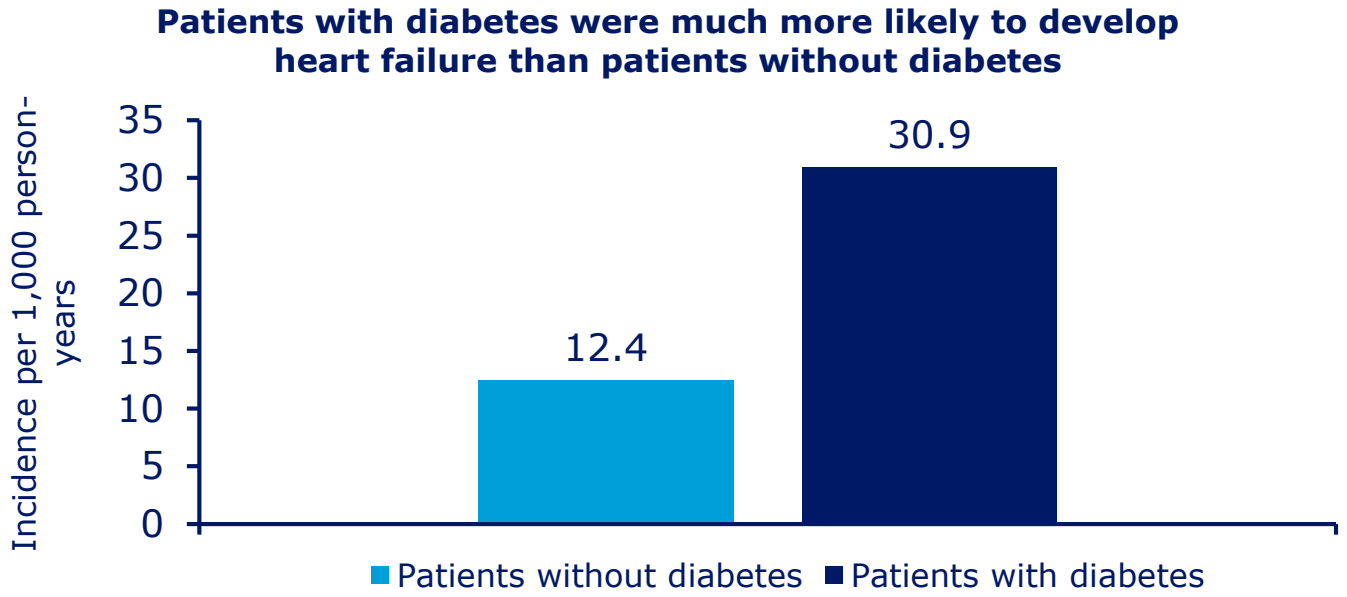
Diabetes is a predictor of poor clinical outcomes in HF patients[3]

HF, heart failure

1. Kannel WB et al. *Am J Cardiol* 1974;34:29–34; 2. Gilbert RE, Krum H. *Lancet* 2015;385:2107–2121; 3. Bauters C et al. *Cardiovasc Diabetol* 2003;2:1.

Incidence of heart failure in diabetes

Retrospective US cohort study



Data from a retrospective cohort study of 8,231 patients with type 2 diabetes and 8,845 nondiabetic patients of similar age and sex, based in the United States of America.

Nichols GA et al. *Diabetes Care* 2004;27:1879–1884.

Diabetic cardiomyopathy

A distinct entity characterized by the presence of abnormal myocardial performance or structure in the absence of epicardial coronary artery disease, hypertension and significant valvular disease.

Rubler S, et al. Am J Cardiol 1972;30:595– 602.

From diabetes to heart failure

Mechanisms of heart failure in diabetes

- Diabetes frequently precedes HTN, CAD and CKD which are major risk factors for HF
- Hypertension: pressure overload
- IHD: diabetes accelerates the appearance and progression of coronary atherosclerosis
- Diabetic nephropathy: fluid retention and eventually volume overload
- Lipotoxicity due to accumulation of FFA in heart muscle

CAD, coronary artery disease; CKD, chronic kidney disease; FFA, free fatty acids; HF, heart failure; HTN, hypertension; IHD, ischaemic heart disease

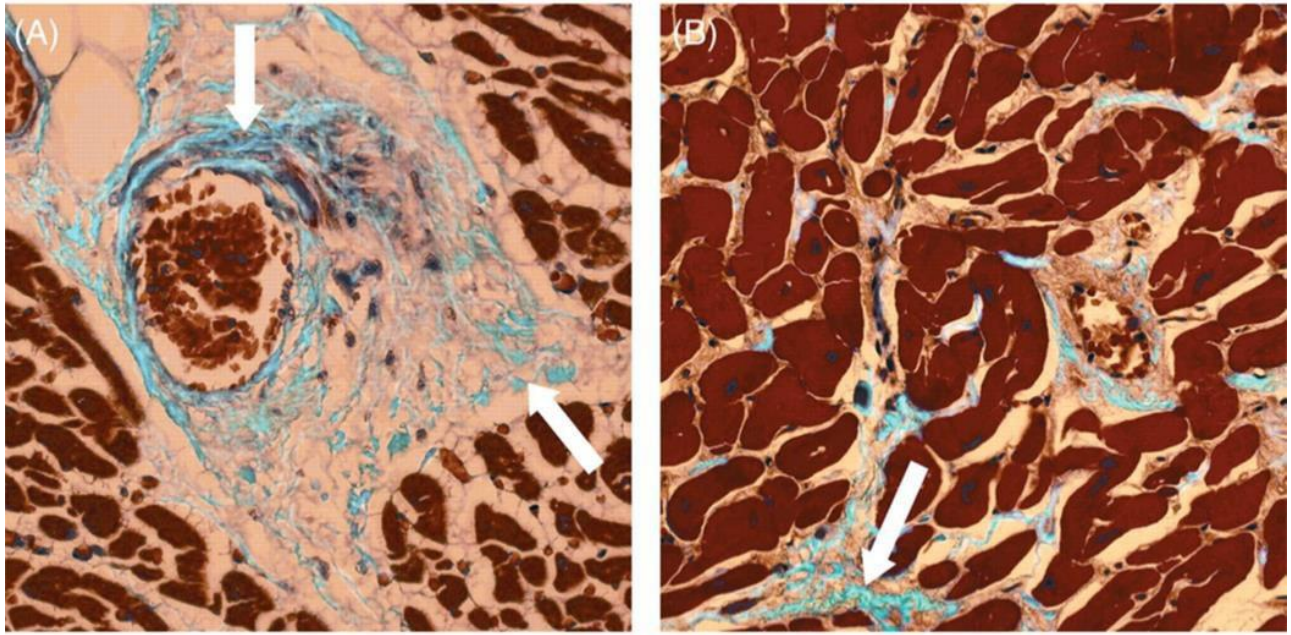
Goyal BR, Mehta AA. *Hum Exp Toxicol* 2013; 32: 571-590. Voulgari C, et al. *Vasc Health Risk Manag* 2010; 6: 883-903.

ECHO HALLMARKS – DIASTOLIC DYSFUNCTION

2D ECHO

- Preserved LV ejection fraction.
- Reduced early diastolic filling.
- Prolongation of isovolumetric relaxation and increased atrial filling.
- Pre – ejection period(PEP) increased.
- LV ejection time(LVET)decreased.
- PEP/LVET increased.

Myocardial fibrosis and myocyte hypertrophy in diabetic cardiomyopathy



Perivascular fibrosis (A) and fibrosis between myocytes (B) in a patient with diabetes mellitus at autopsy

Clinical presentation and diagnostic approach

- In asymptomatic T2DM, TDI revealed LV diastolic dysfunction in 63%, while abnormal transmitral LV filling pattern was detected in 46%
- Overt HF and compromised LV systolic function occurs in advanced stages of HF
- Forward HF
  - Weakness, fatigue, angina, syncope
- Backward HF (very late symptoms)
  - Dyspnoea, raised jugular vein pressure, lower extremity oedema, hepatomegaly

TDI, tissue Doppler imaging

Boyer JK, et al. *Am J Cardiol*. 2004; 93: 870-875.

Treatment

- Aggressive glycaemic control
  - Decreases FFA oxidation by myocardial cells and increases glucose utilisation
  - Is intensive glycaemic control associated with better cardiovascular outcomes?
    - May depend on how you achieve it
- ACEi – HOPE (Heart Outcomes Prevention Evaluation) study
  - Decreased cardiovascular morbidity and mortality in diabetic patients
  - 33% reduction in rate of development of new HF
  - Greater benefit in diabetic than non-diabetic patients
- ARBs – additive effects on haemodynamic measurements, neurohormonal activity and LV remodelling with ACE inhibitors

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; FFA, free fatty acid; HF, heart failure; LV, left ventricular

HOPE study investigators. *Lancet* 2000;355(9200):253-9.

Cardiovascular morbidity and mortality in the HOPE study

	All patients	Diabetic patients
Death from cardiovascular causes	26%	37%
MI	20%	22%
Stroke	32%	33%
All-cause mortality	16%	24%
Revascularisation	15%	17%

MI, myocardial infarction

HOPE study investigators. *Lancet* 2000;355(9200):253-9.

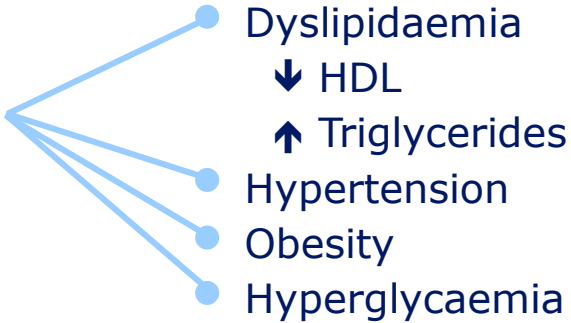
Conclusions

- HF and diabetes frequently co-exist in a bidirectional relationship
- Several pathophysiological connections have been proposed
- Both diabetes and HF are characterised by high morbidity and mortality
- Treatment must target an overall improvement as diabetes treatment can decompensate HF and *vice versa*
- Diabetes drugs should be used with caution in HF

HF, heart failure

Mechanisms of Vascular Injury in Diabetes

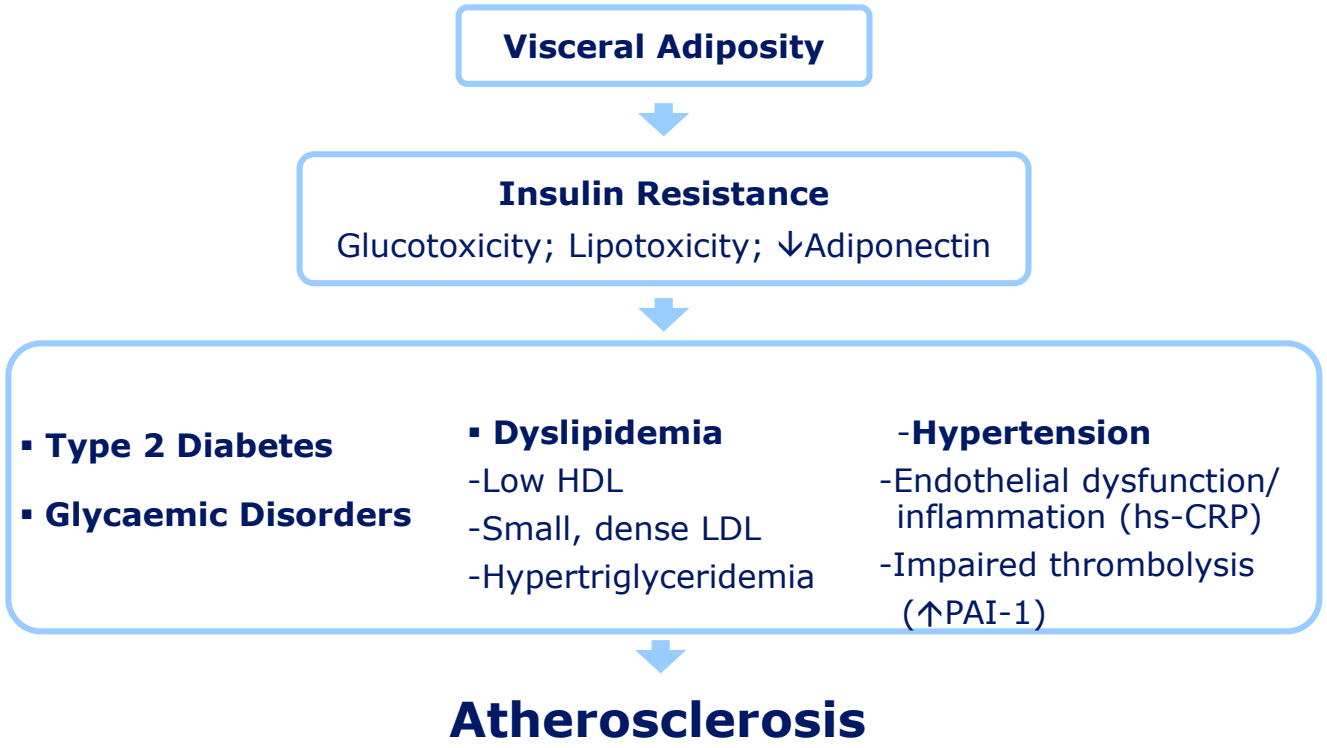
- **Metabolic Syndrome**



- **Increased Free Fatty Acids** cause endothelial dysfunction and are proinflammatory
- **Oxidative Stress** is increased by multiple cardiovascular risk factors

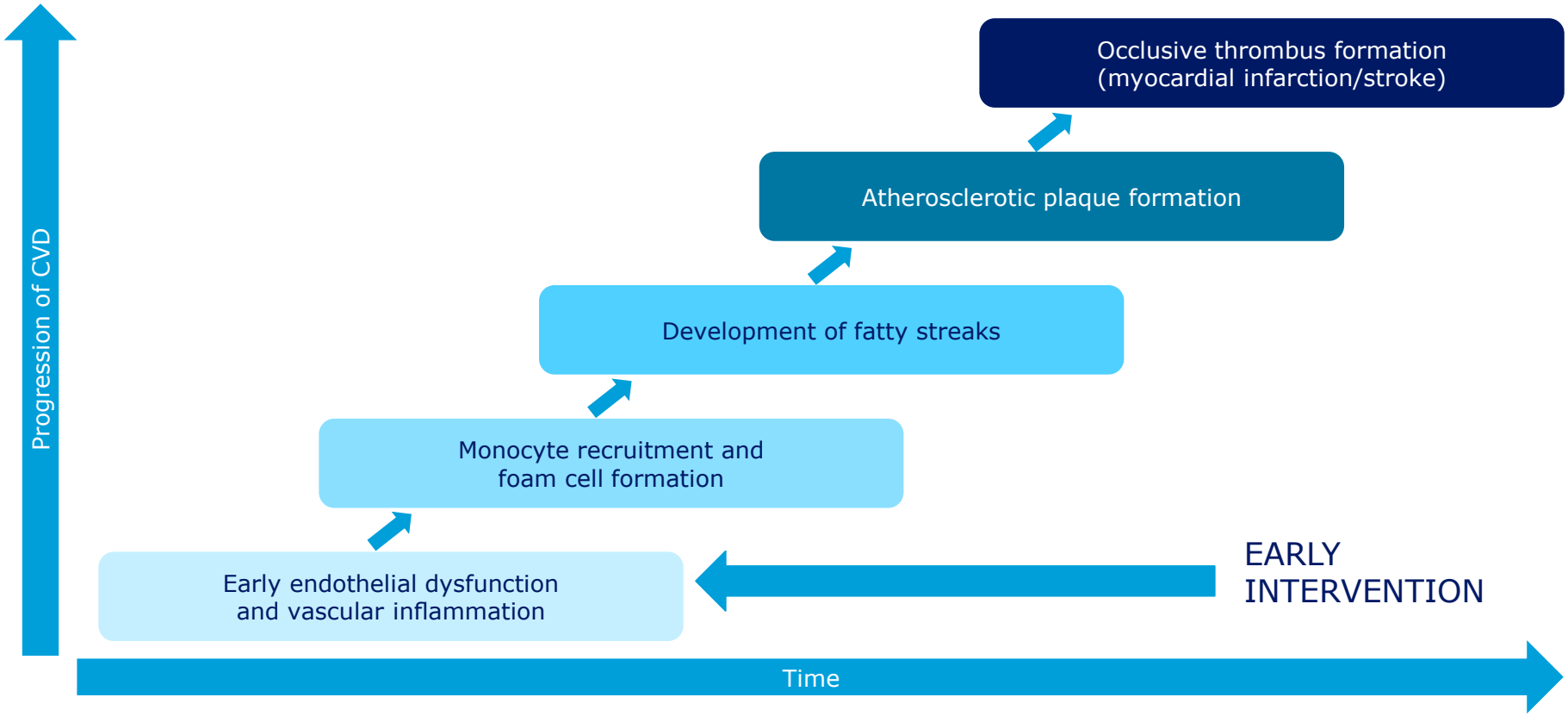
HDL, high-density lipoprotein

Clinical Manifestations of Insulin Resistance



HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1

Development of CVD in people with T2DM

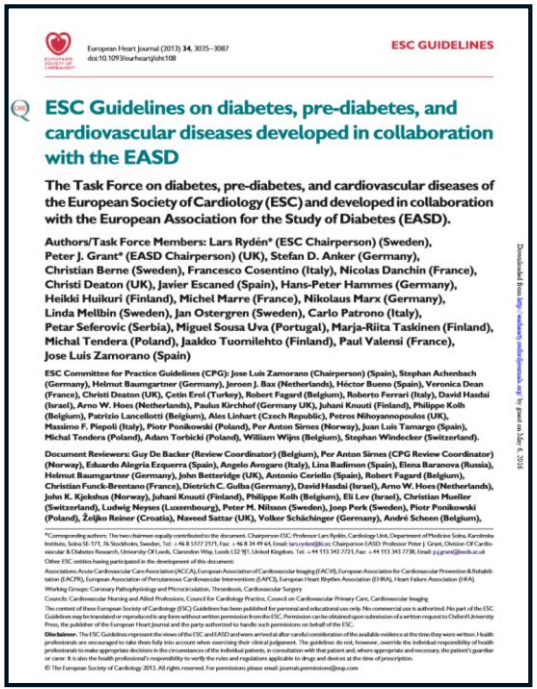


CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.
Ryden L et al. *Eur Heart J* 2013;34:3035–3087.

How is cardiovascular risk managed in type 2 diabetes?

Treatment for T2DM should aim to reduce CV risk

ESC/EASD[1]



European Heart Journal (2013) 34, 3035–3087
doi:10.1093/eurheartj/eht108

ESC GUIDELINES

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

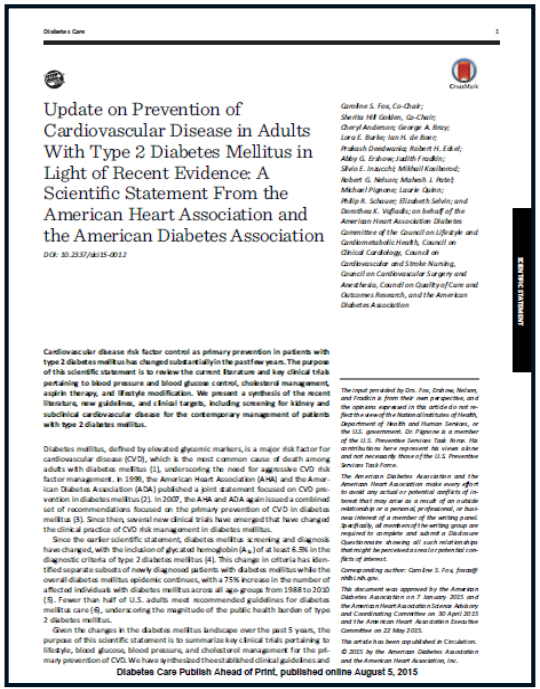
The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD).

Authors/Task Force Members: Lars Rydén* (ESC Chairperson) (Sweden), Peter J. Grant* (EASD Chairperson) (UK), Stefan D. Anker (Germany), Christian Berne (Sweden), Francesco Cosentino (Italy), Nicolas Danchin (France), Christi Deaton (UK), Javier Escaned (Spain), Hans-Peter Hammes (Germany), Heikki Huikuri (Finland), Michel Marre (France), Nikolaus Marx (Germany), Linda Mellbin (Sweden), Jan Ostergren (Sweden), Carlo Patrono (Italy), Petar Seferovic (Serbia), Miguel Sousa Uva (Portugal), Marja-Riita Taskinen (Finland), Michal Tendera (Poland), Jaakko Tuomilehto (Finland), Paul Valensi (France), Jose Luis Zamorano (Spain)

ESC Committee for Practice Guidelines (CPG): Jose Luis Zamorano (Chairperson) (Spain), Stephan Achenbach (Germany), Helmut Baumgartner (Germany), Jeroen J. Bax (Netherlands), Héctor Bueno (Spain), Veronica Dean (France), Christi Deaton (UK), Cetin Erol (Turkey), Robert Fagard (Belgium), Roberto Ferrari (Italy), David Hasdai (Israel), Arno W. Hoes (Netherlands), Paulus Kirchhof (Germany UK), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Patrizio Lancellotti (Belgium), Ales Linhart (Czech Republic), Petros Nihoyannopoulos (UK), Massimo F. Piepoli (Italy), Piotr Ponikowski (Poland), Per Anton Sirnes (Norway), Juan Luis Tamargo (Spain), Michal Tendera (Poland), Adam Torbicki (Poland), William Wijns (Belgium), Stephan Windecker (Switzerland).

Document Reviewers: Guy De Backer (Review Coordinator) (Belgium), Per Anton Sirnes (CPG Review Coordinator) (Norway), Eduardo Alegria Ezquerra (Spain), Angelo Avogaro (Italy), Lina Badimon (Spain), Elena Baranova (Russia), Helmut Baumgartner (Germany), John Betteridge (UK), Antonio Ceriello (Spain), Robert Fagard (Belgium), Christian Funck-Brentano (France), Dietrich C. Gulba (Germany), David Hasdai (Israel), Arno W. Hoes (Netherlands), John K. Kjekshus (Norway), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Eli Lev (Israel), Christian Mueller (Switzerland), Ludwig Neyses (Luxembourg), Peter M. Nilsson (Sweden), Joep Perk (Sweden), Piotr Ponikowski (Poland), Željko Reiner (Croatia), Naveed Sattar (UK), Volker Schächinger (Germany), André Scheen (Belgium),

AHA/ADA[2]



Diabetes Care 1

Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association

DOI: 10.2337/dc15-0012

Caroline S. Fox, Co-Chair; Sheila Hill Golden, Co-Chair; Cheryl Anderson; George A. Bray; Lora E. Burke; Ian K. de Boer; Prakash Deedwania; Robert H. Eckel; Abby G. Ershow; Judith Fradkin; Silvio E. Inzucchi; Mikhail Kosiborod; Robert G. Nelson; Mahesh J. Patel; Michael Pignone; Laurie Quinn; Philip R. Schauer; Elizabeth Selvin; and Dorothea K. Vafiadis; on behalf of the American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Quality of Care and Outcomes Research; and the American Diabetes Association

Cardiovascular disease risk factor control as primary prevention in patients with type 2 diabetes mellitus has changed substantially in the past few years. The purpose of this scientific statement is to review the current literature and key clinical trials pertaining to blood pressure and blood glucose control, cholesterol management, aspirin therapy, and lifestyle modification. We present a synthesis of the recent literature, new guidelines, and clinical targets, including screening for kidney and subclinical cardiovascular disease for the contemporary management of patients with type 2 diabetes mellitus.

Diabetes mellitus, defined by elevated glycemic markers, is a major risk factor for cardiovascular disease (CVD), which is the most common cause of death among adults with diabetes mellitus (1), underscoring the need for aggressive CVD risk factor management. In 1999, the American Heart Association (AHA) and the American Diabetes Association (ADA) published a joint statement focused on CVD prevention in diabetes mellitus (2). In 2007, the AHA and ADA again issued a combined set of recommendations focused on the primary prevention of CVD in diabetes mellitus (3). Since then, several new clinical trials have emerged that have changed the clinical practice of CVD risk management in diabetes mellitus.

Since the earlier scientific statement, diabetes mellitus screening and diagnosis have changed, with the inclusion of glycated hemoglobin (A_{1c}) of at least 6.5% in the diagnostic criteria of type 2 diabetes mellitus (4). This change in criteria has identified separate subsets of newly diagnosed patients with diabetes mellitus while the overall diabetes mellitus epidemic continues, with a 75% increase in the number of affected individuals with diabetes mellitus across all age groups from 1988 to 2010 (5). Fewer than half of U.S. adults meet recommended guidelines for diabetes mellitus care (6), underscoring the magnitude of the public health burden of type 2 diabetes mellitus.

Given the changes in the diabetes mellitus landscape over the past 5 years, the purpose of this scientific statement is to summarize key clinical trials pertaining to lifestyle, blood glucose, blood pressure, and cholesterol management for the primary prevention of CVD. We have synthesized the established clinical guidelines and

Diabetes Care Publish Ahead of Print, published online August 5, 2015

The input provided by Drs. Fox, Erdine, Nelson, and Fradkin is from their own perspective, and the opinions expressed in this article do not reflect the view of the National Institutes of Health, Department of Health and Human Services, or the U.S. government. Dr. Pignone is a member of the U.S. Preventive Services Task Force. His contributions here represent his views alone and not necessarily those of the U.S. Preventive Services Task Force.

The American Diabetes Association and the American Heart Association make every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

Corresponding author: Caroline S. Fox, foxcs@nhlbi.nih.gov.

This document was approved by the American Diabetes Association on 7 January 2015 and the American Heart Association Science Advisory and Coordinating Committee on 30 April 2015 and the American Heart Association Executive Committee on 22 May 2015.

This article has been republished in Circulation.

© 2015 by the American Diabetes Association and the American Heart Association, Inc.

The ESC have also published a 2016 guideline on CVD prevention including a section on diabetes[3]

ADA, American Diabetes Association; AHA, American Heart Association; CV, cardiovascular; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; T2DM, type 2 diabetes mellitus.

1. Rydén L et al. *Eur Heart J* 2013;34:3035–3087; 2. Fox CS et al. *Diabetes Care* 2015;38:1777–1803; 3. Piepoli MF et al. *Eur Heart J* 2016; May 23 [Epub ahead of print]: pii ehw106.

How do we modify CV risk in T2DM?

CV, cardiovascular; T2DM, type 2 diabetes mellitus.

1. Rydén L et al. *Eur Heart J* 2013;34:3035–3087; 2. Fox CS et al. *Diabetes Care* 2015;38:1777–1803; 3. Piepoli MF et al. *Eur Heart J* 2016; [Epub ahead of print]: pii ehw106.

Major clinical trials had shown that intensive glucose control does not decrease CV events. Until recently… Paradigm shift in CV outcome with LEADER and EMPAREG

- Action to Control Cardiovascular Risk in Diabetes (ACCORD)
- Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)
- VA Diabetes Trial (VADT)
- The pathophysiologic effect of glucose on vascular injury remains to be determined
- Effects are long-term, so glucose control should be started early, perhaps in the "prediabetes" stage
- Hypoglycaemia should be avoided

The Action to Control Cardiovascular Risk in Diabetes Study Group. *N Engl J Med.* 2008;358:2545–2559. | ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560–5572. | Duckworth W, et al. *N Engl J Med.* 2008;360:129–139.

Glycaemic control

ESC/EASD[1], AHA/ADA[2] and ESC[3]

- **HbA_{1c} treatment targets**
  - Generally <7.0% (53 mmol/mol)
  - On an individual basis <6.5–6.9% (48–52 mmol/mol) or above 7%

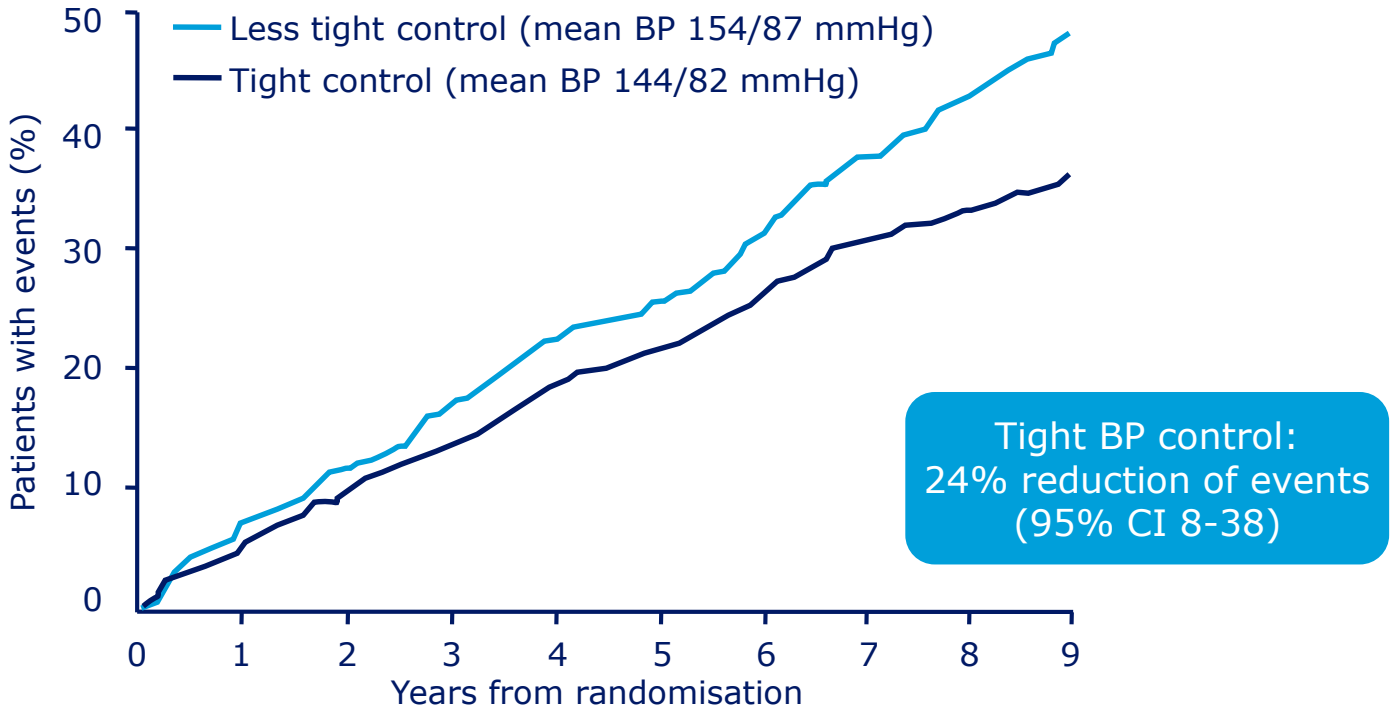
ESC/EASD[1], AHA/ADA[2] and ESC[3]

- **Treatment**
  - Metformin is recommended as first line therapy, if tolerated and not contra-indicated, following evaluation of renal function
  - ***The latest ESC guidelines recommend the use of an SGLT2 inhibitor early in the course of the disease in patients with T2DM and CVD, with a view to reducing cardiovascular and total mortality[3]***

ADA, American Diabetes Association; AHA, American Heart Association; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; HbA_{1c}, glycosylated haemoglobin; SGLT-2i, sodium glucose co-transporter-2 inhibitor; T2DM, type 2 diabetes mellitus

1. Rydén L et al. *Eur Heart J* 2013;34:3035–3087; 2. Fox CS et al. *Diabetes Care* 2015;38:1777–1803; 3. Piepoli MF et al. *Eur Heart J* 2016; [Epub ahead of print]: pii ehw106.

Hypertension in Diabetes UKPDS



BP, blood pressure; CI, confidence interval; UKPDS, United Kingdom Prospective Diabetes Study

UKPDS Study Group. *BMJ 1*998; 317:703-13.

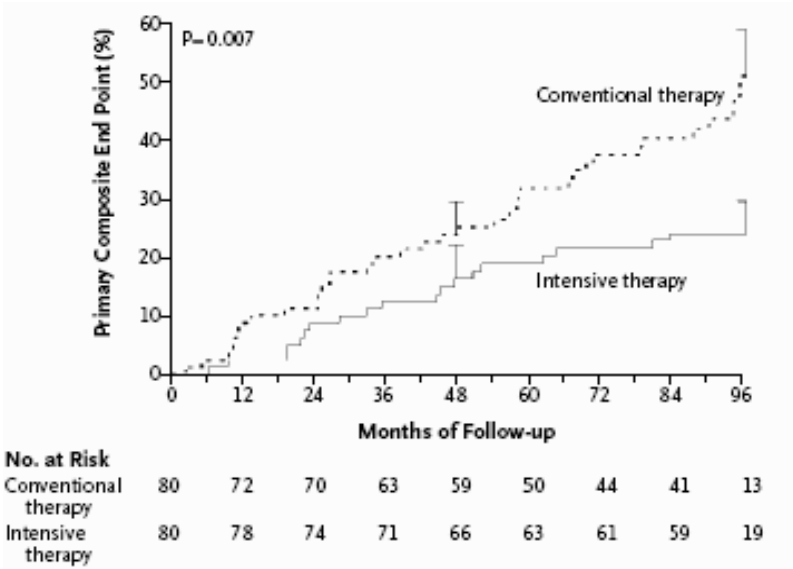
Steno-2 study

The effect of a targeted, intensified, multifactorial intervention vs. conventional therapy on modifiable risk factors for CVD in patients with T2DM and microalbuminuria

Intensive rx arm all received aspirin

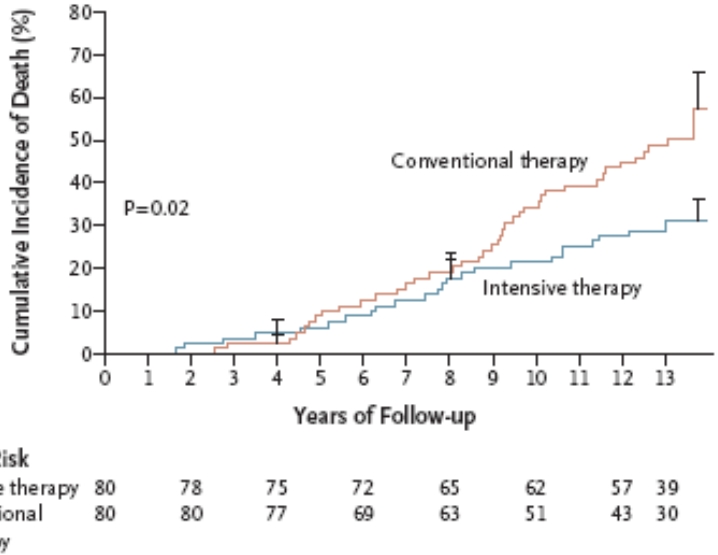
Primary composite endpoint at 8 years' follow up[1]

Death from CV causes, non-fatal MI, non-fatal stroke, revascularisation, and amputation[1]



Death from any cause[2]

Primary endpoint after 13.3 years' mean follow-up



CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; T2DM, type 2 diabetes mellitus

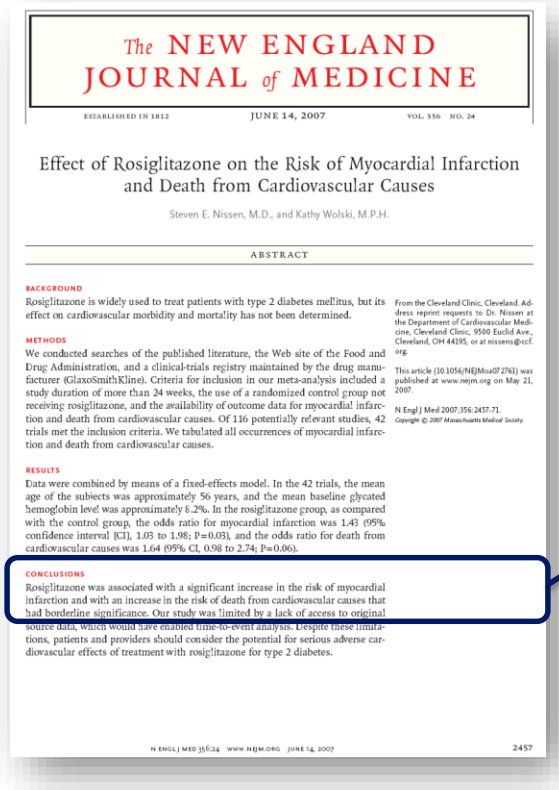
1. Gæde P et al. *N Engl J Med* 2003;348:383–93; 2. Gæde P et al. *N Engl J Med* 2008;358:580–91.

Summary

- Many factors contribute to an increased cardiovascular risk in T2DM
- A multifactorial approach to treating T2DM is recommended to address these risk factors, including:
  - Lifestyle modification
  - Glycaemic control
  - Blood-pressure control
  - Management of dyslipidaemia
  - Platelet inhibition
- Treatment targets and therapy should be individualised depending on individual circumstances and level of CVD risk

CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

Experience with rosiglitazone



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

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

ABSTRACT

BACKGROUND

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

METHODS

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

RESULTS

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

CONCLUSIONS

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

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

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

N Engl J Med 2007;356:2457-71.

Copyright © 2007 Massachusetts Medical Society.

N ENGL J MED 356;24 WWW.NEJM.ORG JUNE 14, 2007 2457

"Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance."

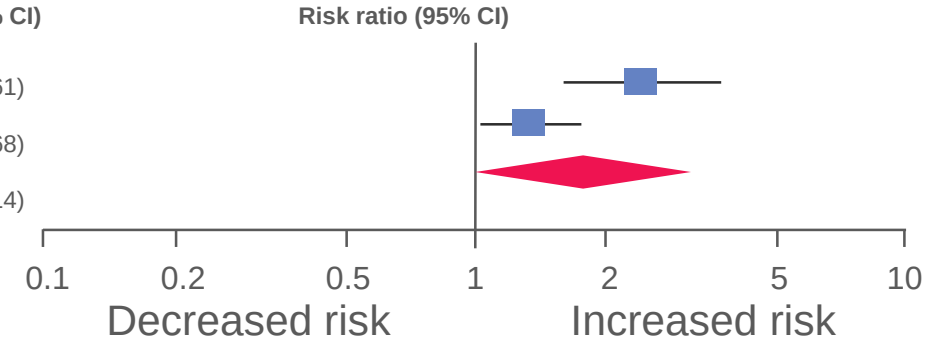
Nissen SE et al. *N Engl J Med* 2007;156:2457–2471.

Meta-analysis showed increased risk for congestive heart failure with both pioglitazone and rosiglitazone

Comparison of risk of congestive heart failure

	Weight	Risk ratio (95% CI)
Rosiglitazone trials	46.2%	2.41 (1.61–3.61)
Pioglitazone trials	53.8%	1.32 (1.04–1.68)
Total	100.0%	1.74 (0.97–3.14)

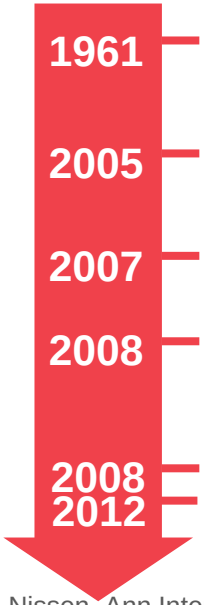
Test for overall effect: *Z* = 1.85 (p = 0.07)



- In a meta-analysis of 20,191 patients with pre-diabetes or T2D, the increased risk for congestive heart failure with TZDs did not differ between rosiglitazone and pioglitazone (p = 0.07)

Lago et al. Lancet 2007;370:1129–36.

Adverse CV events led the FDA to require demonstration of CV safety for new glucose-lowering drugs



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

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

- Sponsor withdrew application[1]

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

- Withdrawn in the EU[1]
- Use restricted in US[1]*

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

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

2008 **New FDA requirements[5]**

2012 **New EMA requirements[6]**

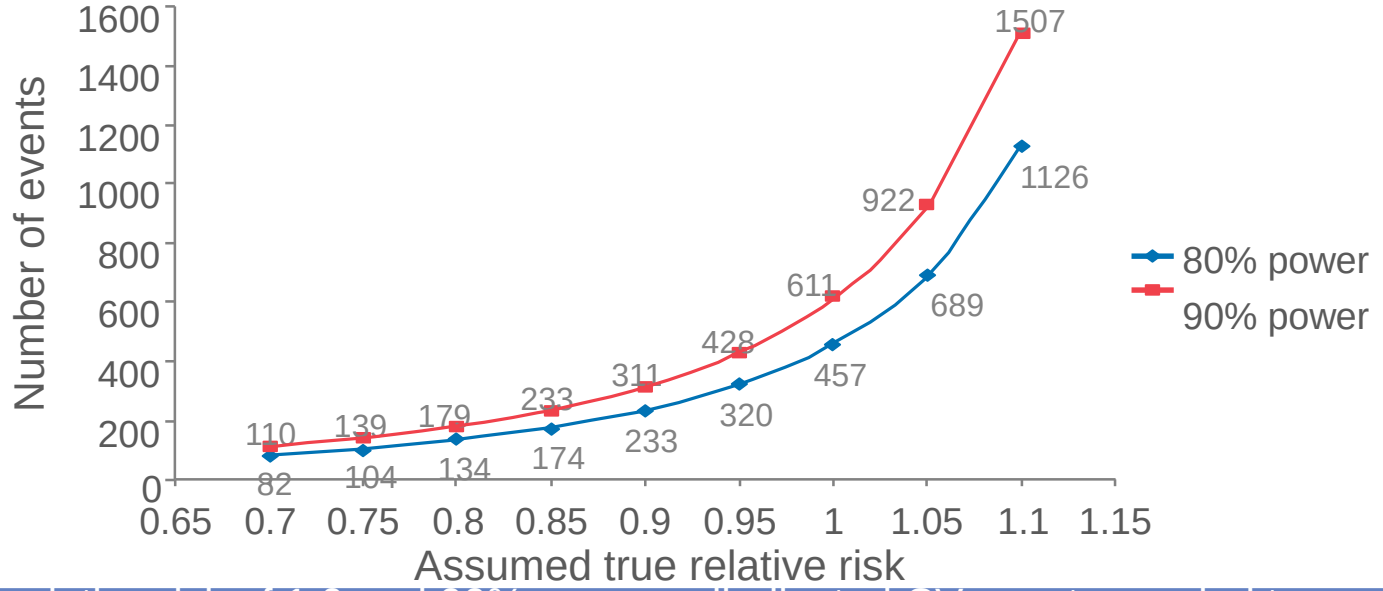
New diabetes drugs should demonstrate CV safety with meta-analysis and a CV outcome trial (CVOT)

1. Nissen. Ann Intern Med 2012;157:671–2. 2. Nissen et al. JAMA 2005;294:2581–6. 3. Nissen et al. N Engl J Med 2007;356:2457–71.
4. ACCORD Study Group. N Engl J Med 2008;358:2545–59.
5. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/%20guidances/ucm071627.pdf
6. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf
7. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm376683.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

ACROSS T2D

Satisfying FDA requirements for CV safety

Number of CV events needed to satisfy 1.3 non-inferiority margin



Assuming relative risk of 1.0 and 90% power, adjudicated CV events needed to satisfy the CI upper limits for non-inferiority:

– 122 events for the 1.8 risk margin

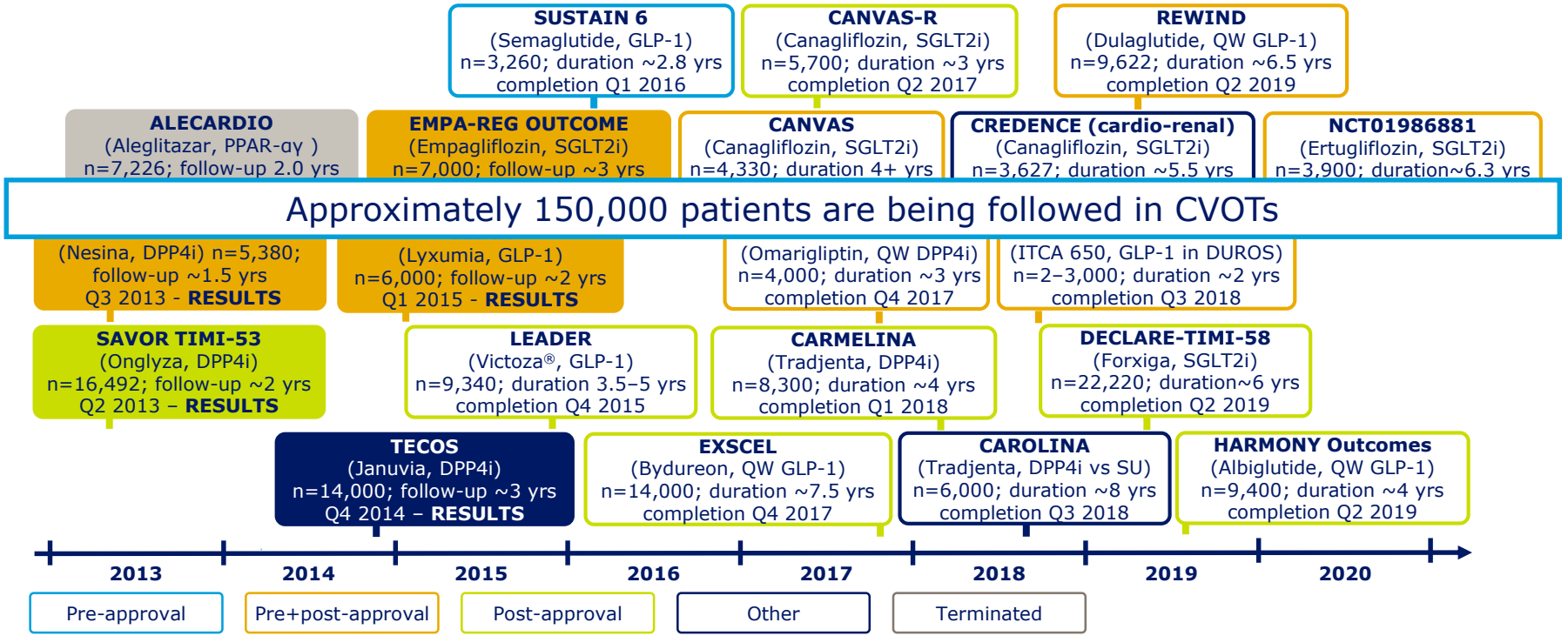
– 611 events for the 1.3 risk margin

Geiger et al. Ther Innovation Reg Science 2014;1–15.

CVOTs designed to assess effects of a specific drug or of a treatment strategy (e.g. glucose lowering)

	Treatment strategy trials (intensive vs standard glucose lowering)	Compound-specific trials
UKPDS[1,2]	FPG < 6 vs < 15 mmol/L	Also assessed metformin vs SU + insulin[2]
VADT[3]	HbA_{1c} ≤ 6% vs 8–9%	
ACCORD[4]	HbA_{1c} < 6% vs 7–7.9%	
ADVANCE[5]	HbA_{1c} < 6.5% vs SOC	Also assessed gliclazide + other drugs in intensive arm vs standard care arm
PROactive[6]		Pioglitazone vs placebo
RECORD[7]		Rosiglitazone + metformin or SU vs metformin + SU
SAVOR-TIMI 53[8]		Saxagliptin vs placebo
EXAMINE[9]		Alogliptin vs placebo
ELIXA[10]		Lixisenatide vs placebo
TECOS[11]		Sitagliptin vs placebo
EMPA-REG OUTCOME®[12]		Empagliflozin vs placebo

Oct. 2016: Ongoing cardiovascular outcomes trials (better: CV safety trials) within the diabetes field



Source: ClinicalTrials.gov (April 2014). 'Completion date' is the estimated completion date for the primary outcomes measure.
CVOT, cardiovascular outcomes trial; DPP4i; dipeptidyl peptidase 4 inhibitor; GLP-1, glucagon-like peptide 1; SU, sulphonylurea.
McMurray JJ et al. *Lancet Diabetes Endocrinol* 2014;2:843–851.

The paradigm for Type 2 Diabetes therapy in 2016:

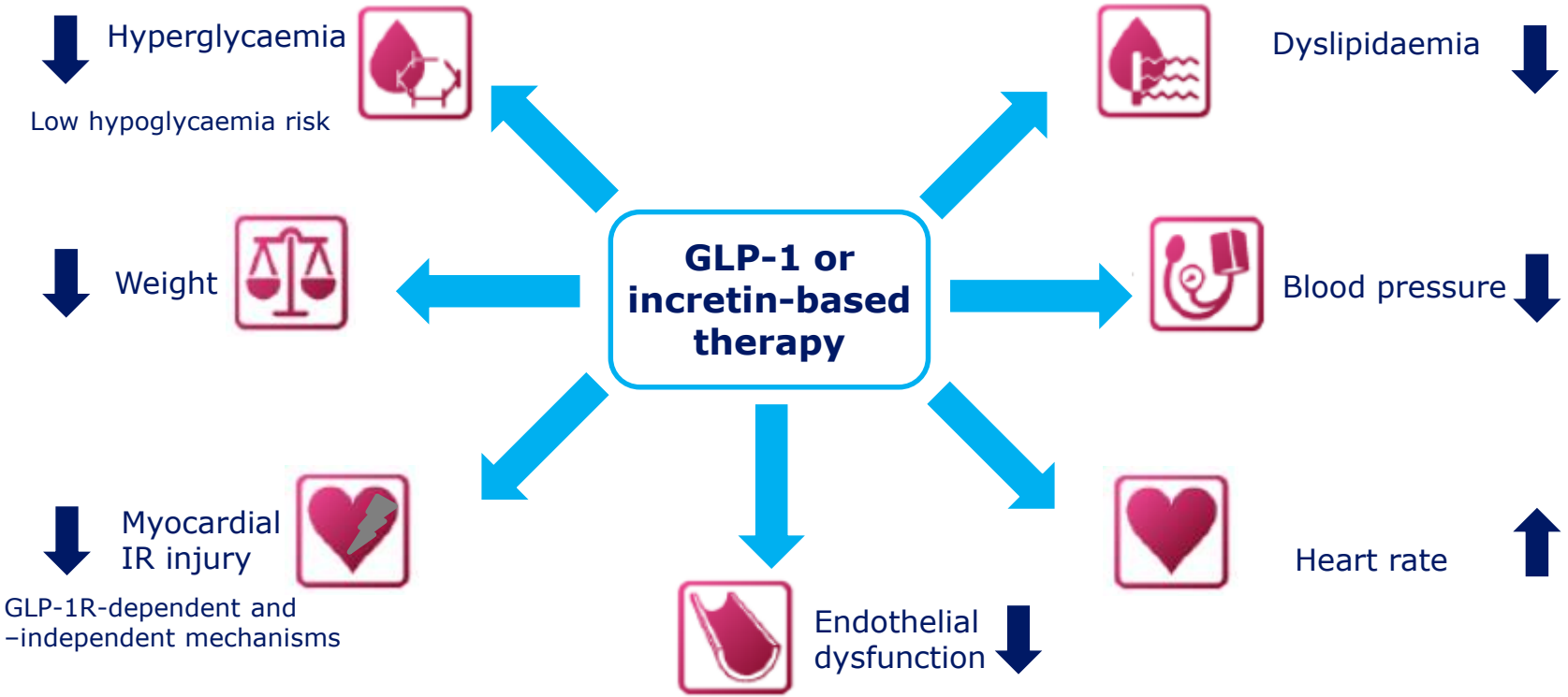
Individualize treatment and targets according to the patient´s need !
Get to target early after diagnosis !

Avoid hypoglycaemia and weight gain !

Provide CV safety, reduce CV risk!

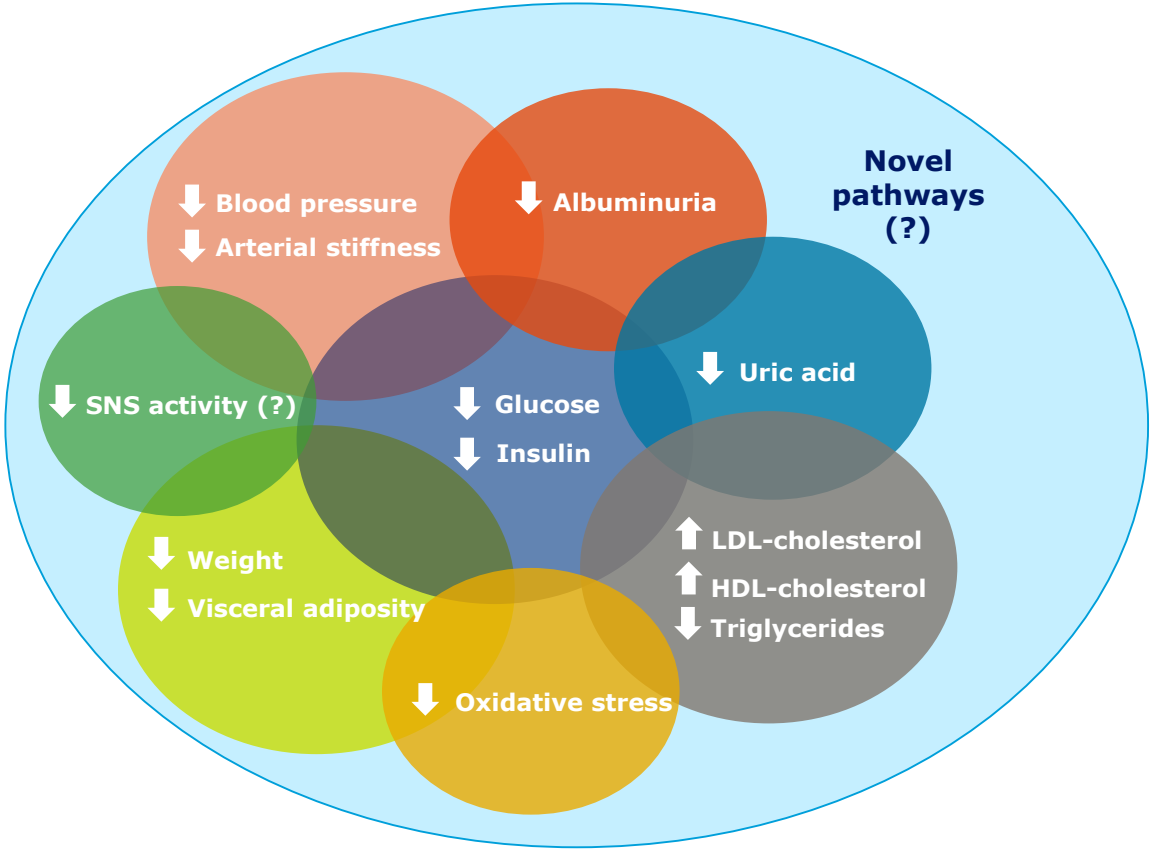
GLP-1- RA-based therapy and SGLT-2-Is show great promise !

Incretin-based therapies affect multiple CV risk factors



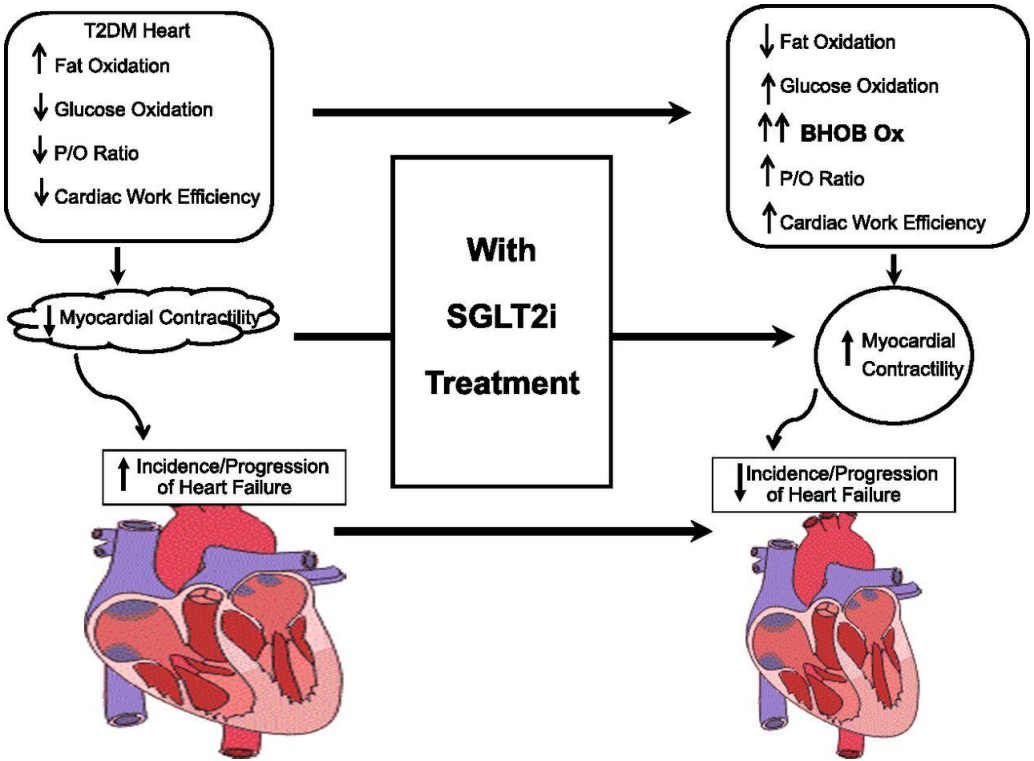
CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; GLP-1R, glucagon-like peptide-1 receptor; IR, ischaemia reperfusion.
Petrie JR. *Cardiovasc Diabetol* 2013;12:130; Monami M et al. *Diabetes Obes Metab* 2014;16:38–47.

Identified potential and novel pathways associated with CV effects of SGLT-2 inhibitors based on clinical and mechanistic studies



Copyright © by SAGE Publications
Adapted from Inzucchi SE et al. Diabetes Vascr Dis Res 2015;12:90-100

Postulated changes in myocardium fuel metabolism before and after SGLT-2 inhibitor therapy

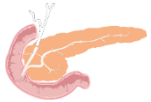


Mudaliar S, Alloju S, Henry RR. *Diabetes Care* 2016 Jul;39(7):1115-22

Cardiovascular actions of GLP-1 in T2D

GLP-1

METABOLIC BENEFITS



↑ B-cell function

↑ Insulin secretion

↓ Glucose output

↓ Appetite

↓ Gastric emptying

↑ Insulin sensitivity

CARDIOVASCULAR RISK FACTORS

↓ Hypertension

↓ Dyslipidaemia

↓ Obesity

DIRECT CARDIOVASCULAR BENEFITS

INDIRECT CARDIOVASCULAR BENEFITS

↓ Inflammation

↓ Cell apoptosis

↑ Cardiac/vascular function

↓ Endothelial dysfunction

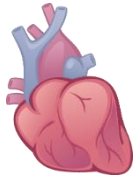
↓ ECM remodelling

↑ Angiogenesis

↓ Hypertension

↓ Atherosclerosis

CARDIOVASCULAR DISEASE



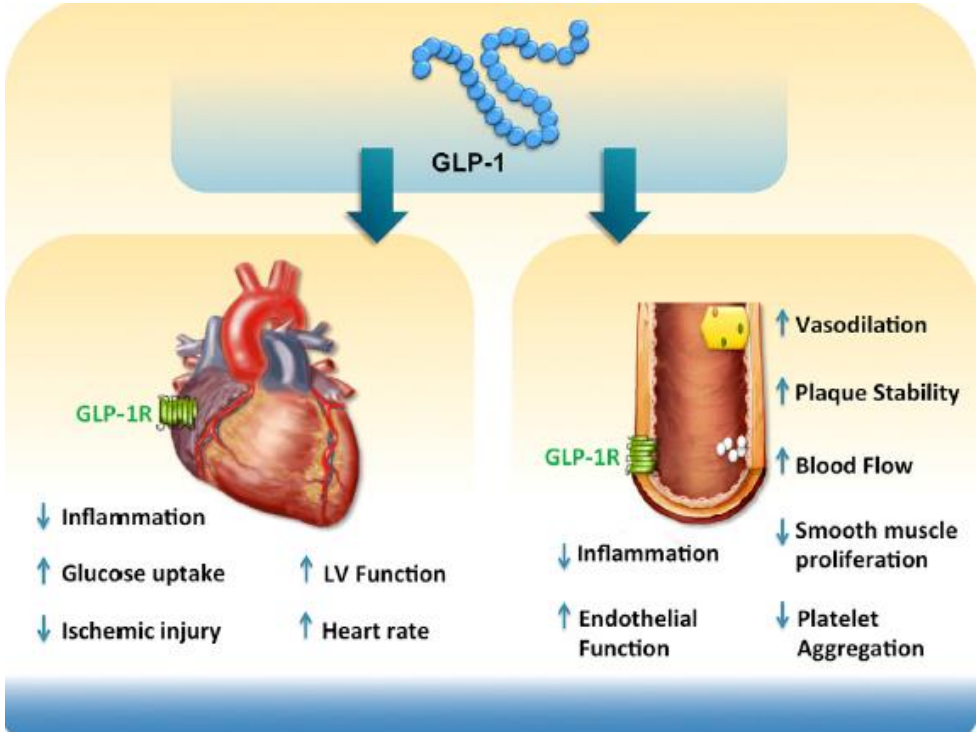
↓ Myocardial infarction

↓ Cardiac remodelling

HEART FAILURE

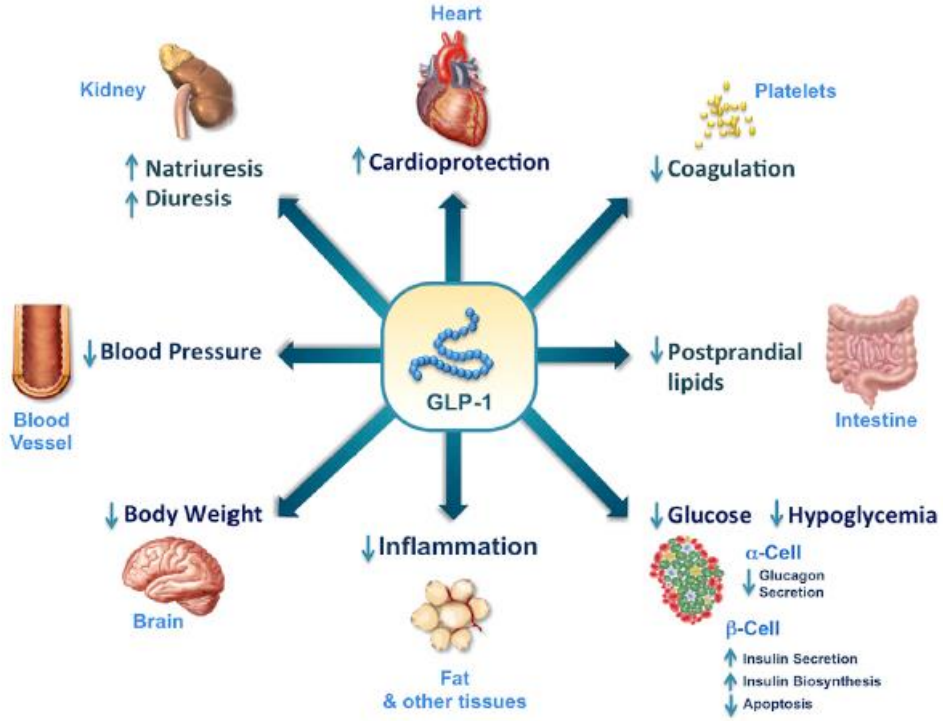
Tate M et al. *Br J Pharmacol*. 2015; 172(3): 721–736.

Direct and Indirect Actions of GLP-1 in the Heart and Blood Vessels



Drucker DJ. *Cell Metab* 2016;24(1):15-30.

GLP-1 Modifies CV Risk through Direct and Indirect Actions in Multiple Organs

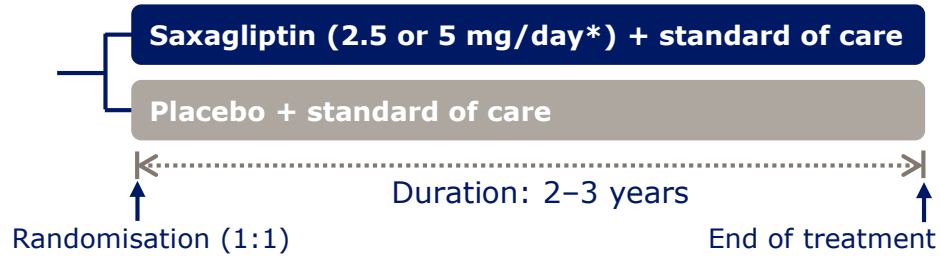


Drucker DJ. *Cell Metab* 2016;24(1):15-30.

SAVOR TIMI 53: Study design

16,492 patients

- T2DM
- HbA_{1c} >6.5% and <12%
- Antidiabetic drug-naïve; ≥1 OADs; or insulin (± OADs), excluding GLP-1RA and DPP-4i
- High-risk CV profile



Primary endpoint

- Composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal ischaemic stroke

Key secondary endpoint

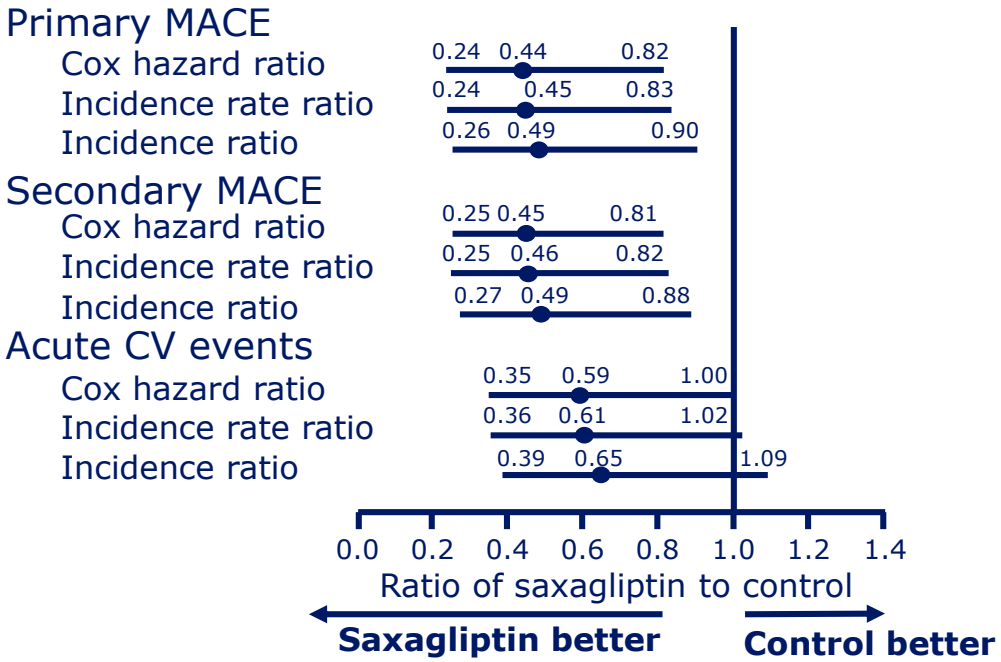
- Primary composite endpoint plus hospitalisation for heart failure, coronary revascularisation or unstable angina

Similar trial population to LEADER

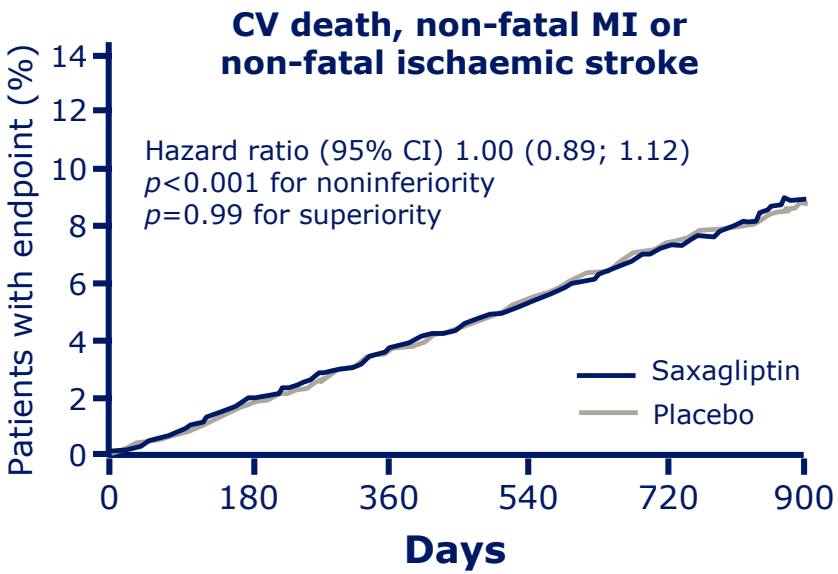
*Determined by eGFR (5 mg/day for eGFR >50 mL/min and 2.5 mg/day for eGFR ≤50 mL/min).
CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; OADs, oral antidiabetic drugs; T2DM, type 2 diabetes mellitus.
Scirica BM, et al. *N Engl J Med* 2013;369:1317-1326.

Saxagliptin CV outcomes

MACE analysis

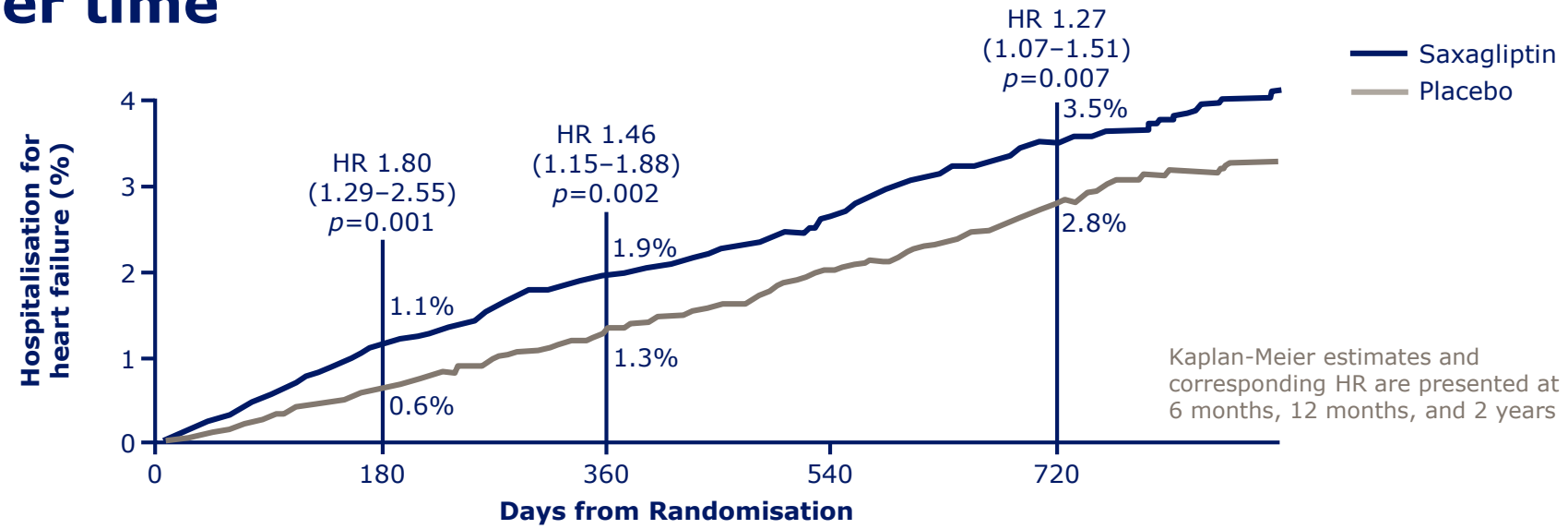


SAVOR TIMI 53



CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiac event; MI, myocardial infarction.
FDA. Briefing document. Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM148109.pdf; Frederich R et al. *Postgrad Med* 2010;122:16–27.

SAVOR TIMI 53: Hospitalisation for heart failure over time



Kaplan-Meier estimates and corresponding HR are presented at 6 months, 12 months, and 2 years

Placebo	8212	8036	7856	7389	4959
Saxagliptin	8280	8064	7867	7375	4978

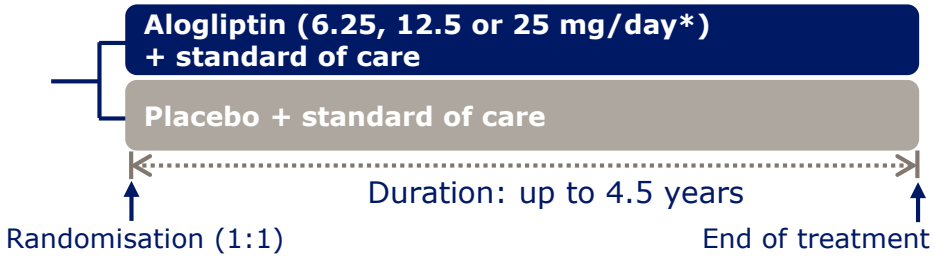
Over 2 years of follow-up, more patients in the saxagliptin group (3.5%) were hospitalised for heart failure vs placebo (2.8%)

CI, confidence interval; HR, hazard ratio.

Scirica BM et al. *Circulation* 2014;130:1579–1588.

EXAMINE: Study design

5380 patients
- T2DM
- ACS within 15 to 90 days
- HbA_{1c} >6.5% and <11% (HbA_{1c} >7% and <11% if on an antidiabetic regimen that includes insulin)



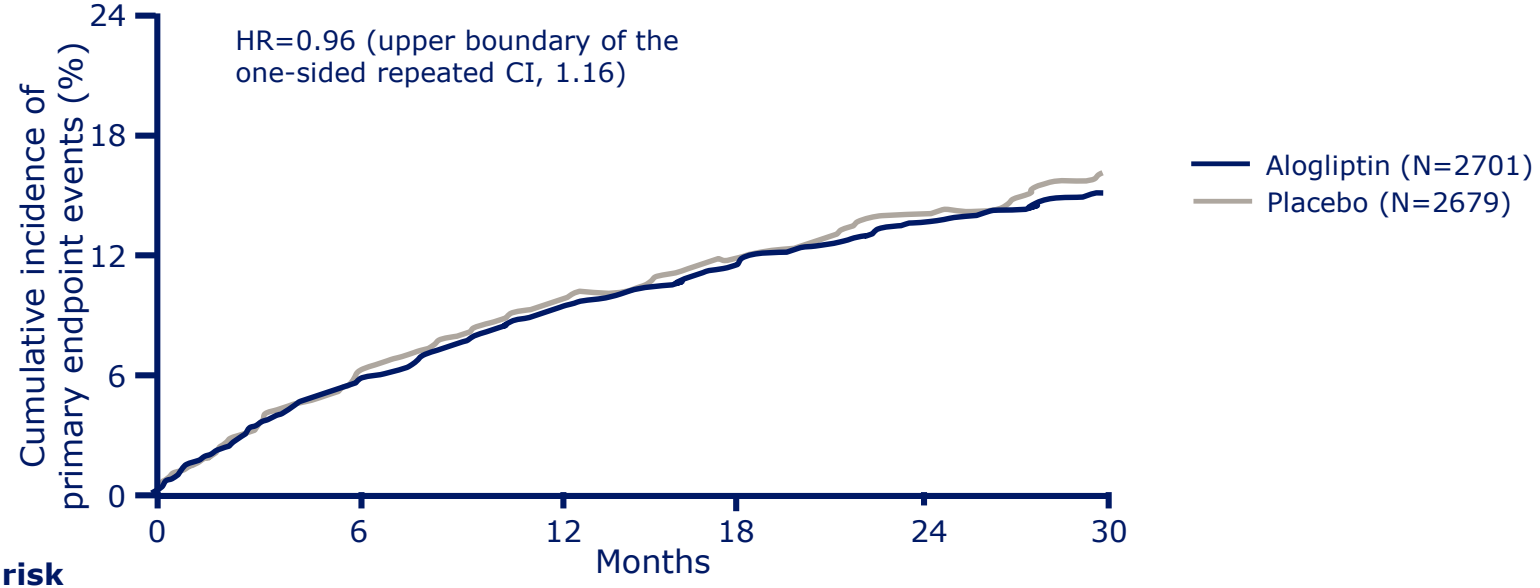
Primary endpoint
- Composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke

Key secondary endpoint
- Primary composite endpoint plus urgent revascularisation due to unstable angina within 24 hours after hospital admission

*Determined by eGFR (6.25 mg/day for eGFR <30 mL/min/1.73m^2, 12.5 mg/day for eGFR of 30 to <60 mL/min/1.73 m^2, and 25 mg/day for eGFR ≥60 mL/min/1.73 m^2).
ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated haemoglobin; T2DM, type 2 diabetes mellitus.
White WB et al. *Am Heart J* 2011;162(4):620–626; White WB et al. *N Engl J Med* 2013;3;369(14):1327–1335.

EXAMINE: CV death, non-fatal MI or non-fatal ischaemic stroke

- After a median exposure of 18 months, the rates of primary composite endpoints were similar in the alogliptin and placebo groups (11.3% and 11.8%, respectively)

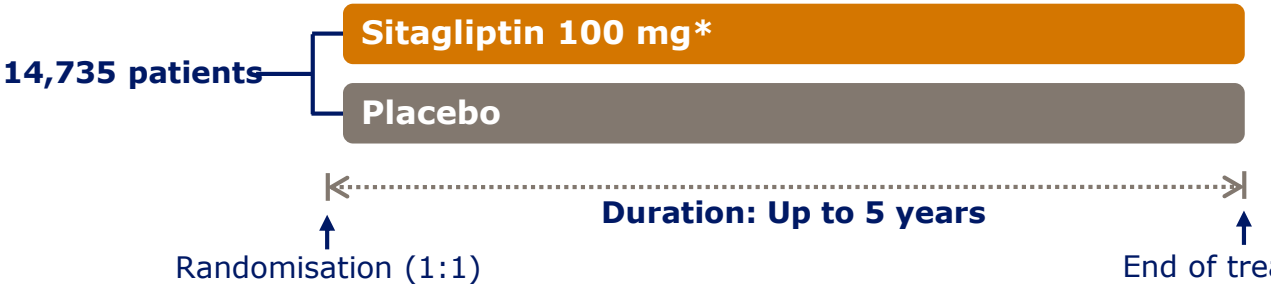


No. at risk

Placebo	2679	2299	1891	1375	805	286
Alogliptin	2701	2316	1899	1394	821	296

CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Adapted from White WB et al. *N Engl J Med* 2013;3;369:1327–1335.

TECOS: Study design



Trial information

- Multicentre
- Double-blind
- Parallel-group
- Randomised
- Dec 2008 – Mar 2015

Key inclusion criteria

- Age ≥50 years with T2DM
- HbA_{1c} 6.5–8.0% (48–64 mmol/mol)
- Stable doses of one or two oral antihyperglycaemic agents (metformin, pioglitazone, or sulfonylurea) or of insulin with or without metformin
- Pre-existing CV disease

Key exclusion criteria

- History of ≥2 episodes of severe hypoglycaemia during the 12 months prior to enrolment
- eGFR<30 mL/min/1.73 m^2
- Use of another DPP-4 inhibitor, GLP-1RA, or TZD other than pioglitazone in previous 3 months

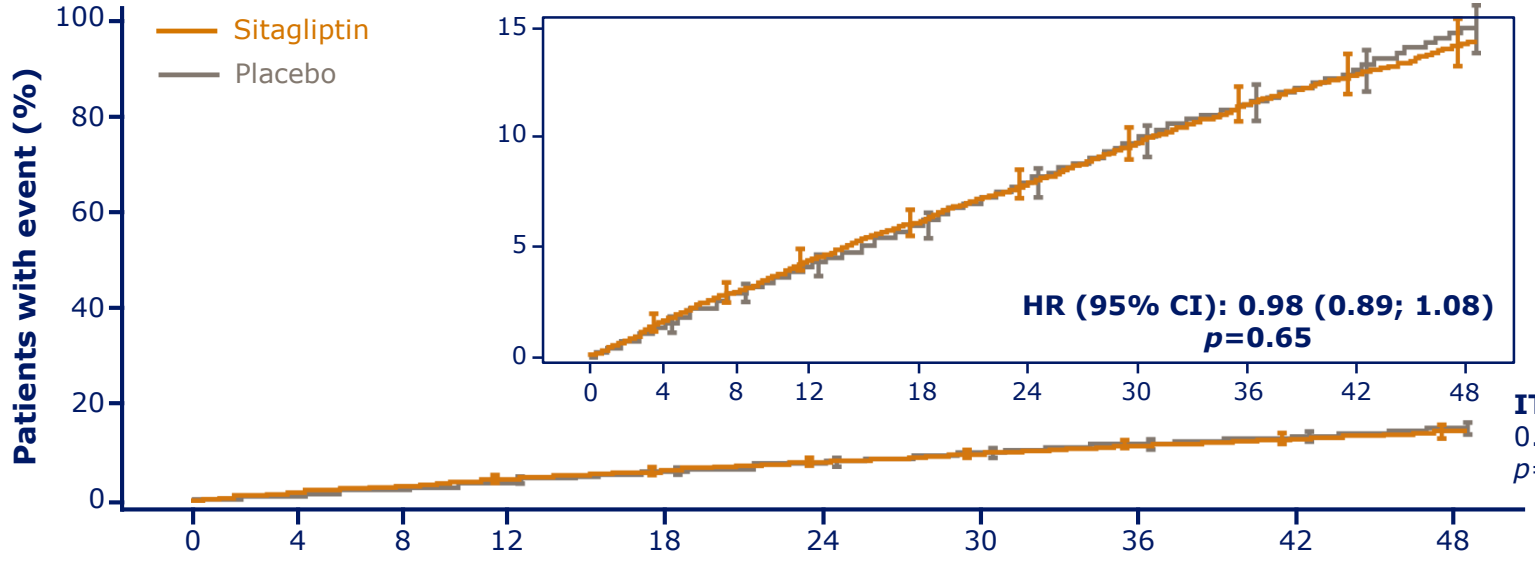
*50 mg daily if the baseline eGFR ≥30 and <50 mL/min/1.73 m^2.

CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

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

TECOS: Primary composite endpoint

ITT analysis for superiority



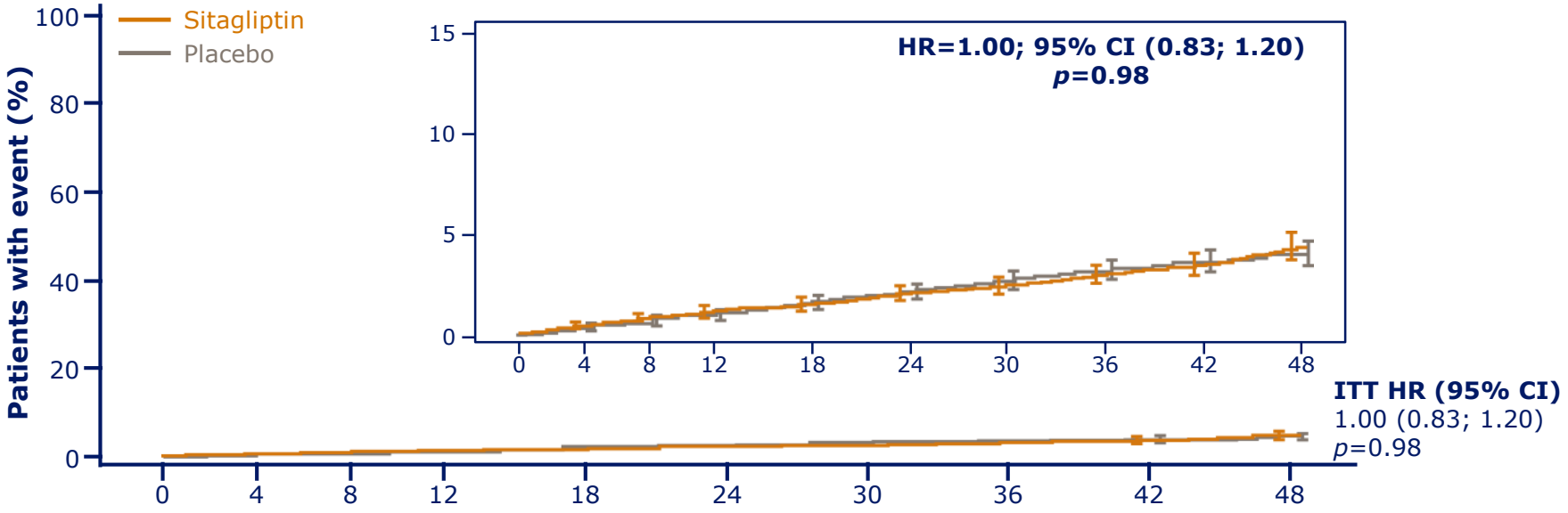
ITT HR (95% CI)
0.98 (0.89; 1.08)
p=0.65

No. at risk:										
Sitagliptin	7332	7131	6937	6777	6579	6386	4525	3346	2058	1248
Placebo	7339	7146	6902	6751	6512	6292	4411	3272	2034	1234

The primary composite endpoint was a composite of CV death, nonfatal MI, nonfatal stroke, and hospitalisation for unstable angina.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intention-to-treat; MI, myocardial infarction.
Green JB et al. *N Engl J Med* 2015;373:232–242.

TECOS: Hospitalisation for heart failure*

ITT analysis

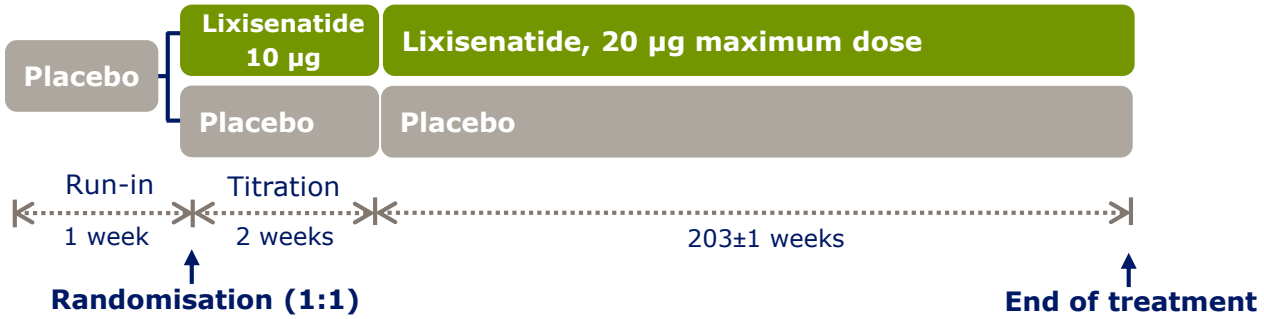


No. at risk:

Sitagliptin	7332	7189	7036	6917	6780	6619	4728	3515	2175	1324
Placebo	7339	7204	7025	6903	6712	6549	4599	3443	2131	1315

*Adjusted for history of heart failure at baseline.
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat.
Green JB et al. *N Engl J Med* 2015;373:232–242.

ELIXA: Study design



Trial information

- Multi-centre
- Double-blind
- Parallel-group
- Event-driven
- Randomised

Run-in period

- Patients were trained in self-administration of daily subcutaneous volume-matched placebo

Titration

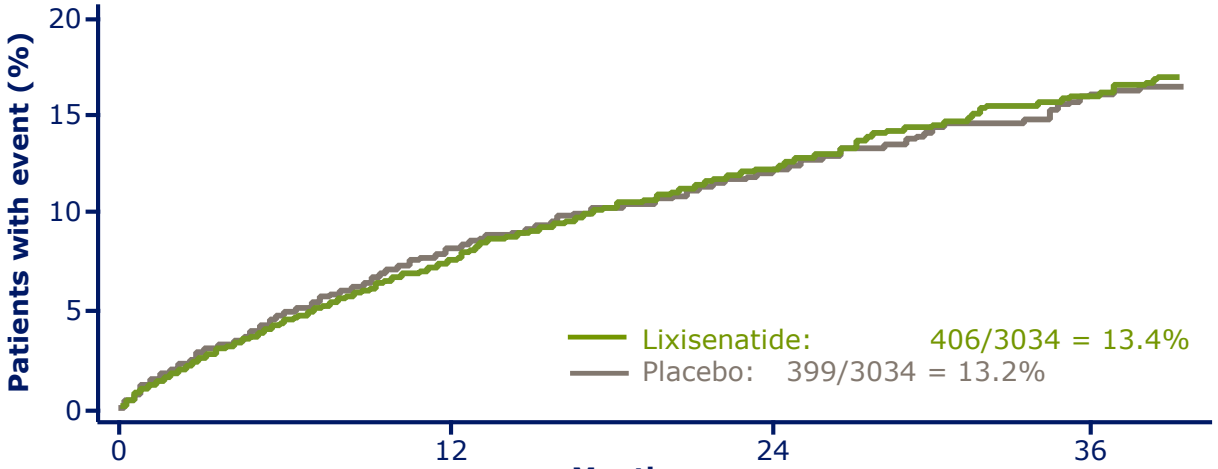
- Lixisenatide or matching placebo (1:1)
  - Initial dose 10 µg/day
  - Down- or up-titration permitted to maximum of 20 µg/day

- Glucose control was managed by site investigators' judgement

Bentley-Lewis R et al. *AHJ* 2015;169:631–638.e7; Oral presentation 3-CT-SY28. Presented at the American Diabetes Association 75th Annual Scientific Sessions, Boston, MA, 8 June 2015.

ELIXA: Primary composite endpoint

- Time to first occurrence of the primary CV event: CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina[1]



Number at risk				
Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

CV, cardiovascular; MI, myocardial infarction.

1. Clinicaltrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT01147250. Accessed October 2015;
Oral presentation 3-CT-SY28. Presented at the American Diabetes Association 75th Annual Scientific Sessions, Boston, MA, 8 June 2015.

FREEDOM trials: The ITCA 650 device provides continuous sc delivery of exenatide

- Matchstick-sized (4 mm x 44 mm) osmotic pump
- Once- or twice-yearly subdermal placement in the abdomen with a simple in-office procedure
- Provides continuous sc delivery of exenatide
- Expected to improve patient adherence and avoid fluctuations in therapeutic drug concentration

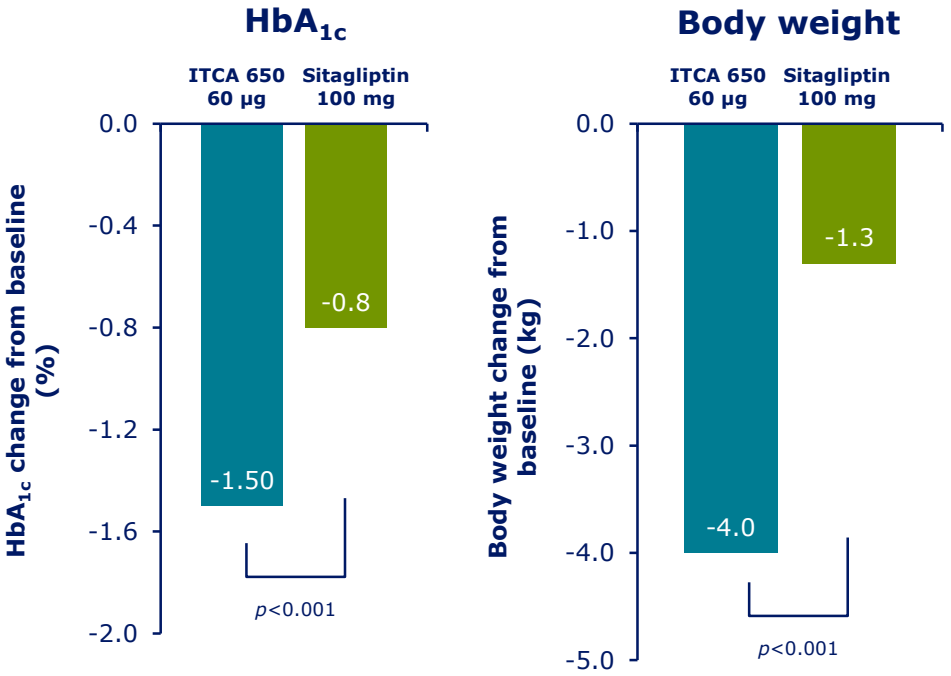
SC, subcutaneous

Intarcia Therapeutics Inc. Company pipeline. Available at: http://intarcia.com/pipeline-technology/. Accessed August 2015; Henry RR et al. *J Diabetes Complications* 2014;28:393–398; Henry RR et al. American Diabetes Association 2015, Boston MA, USA. Poster 1107-P

ITCA 650 is an investigational product and not currently approved

ITCA 650 device: FREEDOM-2

Change in HbA_{1c} and body weight at Week 52



Adverse-event profile

- The most common AEs were gastrointestinal events consistent with the GLP-1 class
- Low rate of AEs leading to discontinuation

AE, adverse event; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycosylated haemoglobin

Intarcia Therapeutics Inc. Press release 18 August 2015. Available at: http://intarcia.com/media/press-releases/2015-aug-18-freedom2.html. Accessed September 2016. Rosenstock J et al. American Diabetes Association 2015, Boston, MA, USA. Oral presentation 276-OR

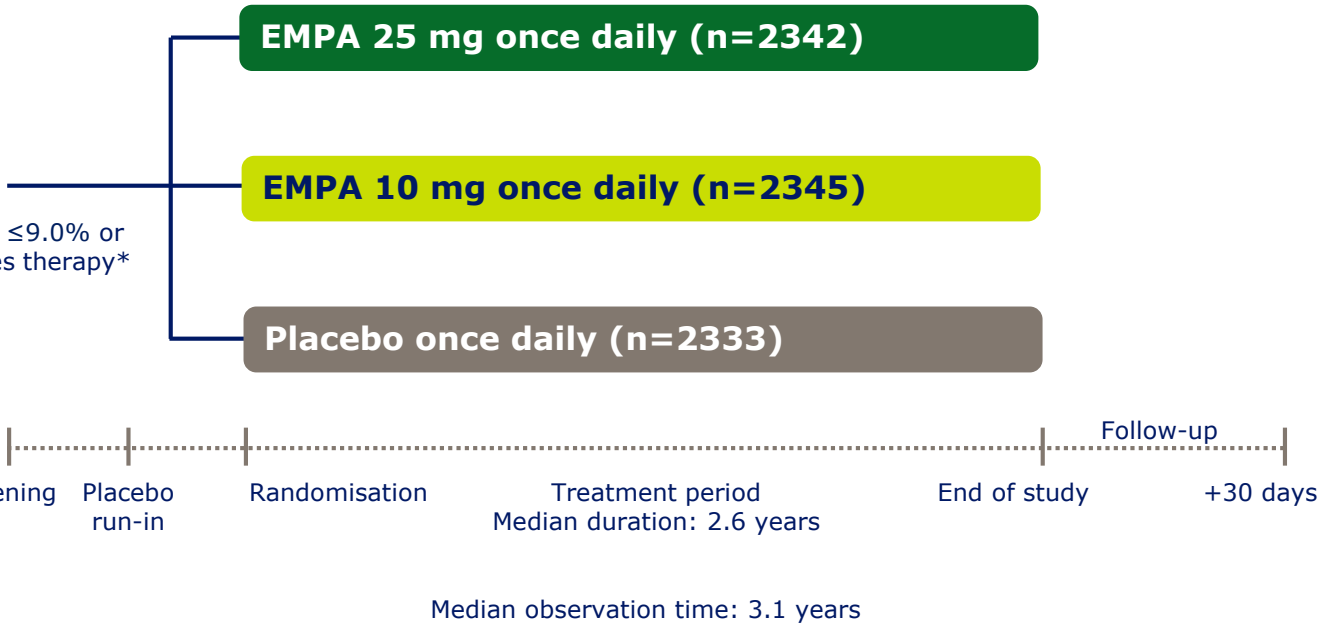
EMPA-REG OUTCOME: Empagliflozin (SGLT-2i) CVOT

Randomised, double-blind, placebo-controlled CVOT

N=7028

Key inclusion criteria

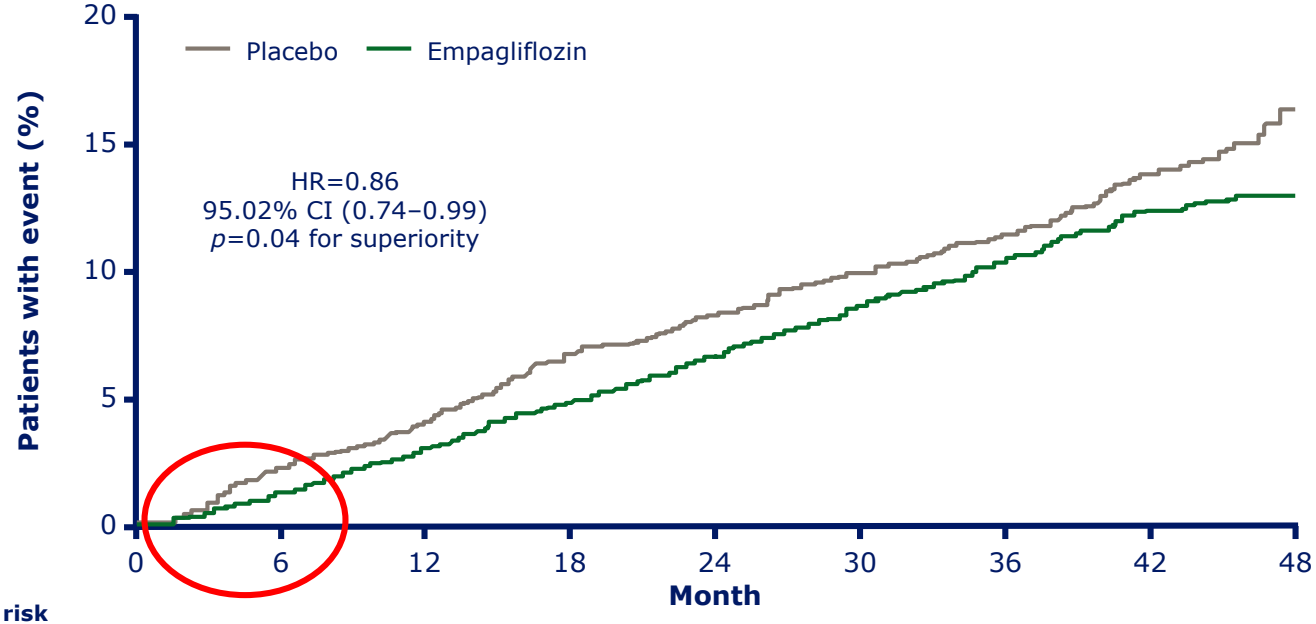
- Type 2 diabetes
- Age ≥18 years
  ≥20 years in Japan
  ≤65 years in India
- Established CV disease
- Drug naïve and HbA_{1c} ≥7.0 to ≤9.0% or stable background antidiabetes therapy* and HbA_{1c} ≥7.0 to ≤10.0%
- BMI ≤45.0 kg/m^2
- eGFR ≥30 mL/min/1.73m^2



*Except pioglitazone in Japan.
Background glucose-lowering therapy unchanged in first 12 weeks, then adjusted at the investigator's discretion to achieve desired glycaemic control.
BMI, body mass index; CV, cardiovascular; CVOT, cardiovascular outcome trial; eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; HbA_{1c}, glycosylated haemoglobin.
Zinman B et al. *Cardiovasc Diabetol* 2014;13:102; Zinman B et al. *N Engl J Med* 2015;doi: 10.1056/NEJMoa1504720. [Epub ahead of print].

EMPA-REG OUTCOME: Primary endpoint

- Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke



Number at risk

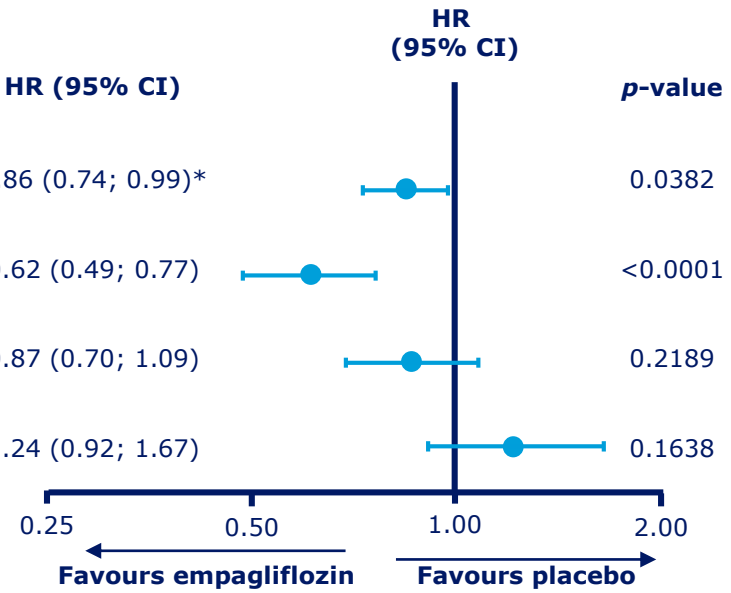
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

CI, confidence interval; HR, hazard ratio.

Zinman B et al. *N Engl J Med* 2015; doi: 10.1056/NEJMoa1504720. [Epub ahead of print].

EMPA-REG OUTCOME: Primary endpoint and individual components

	Patients with event/analysed			
	Empagliflozin	Placebo	HR (95% CI)	*p*-value
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

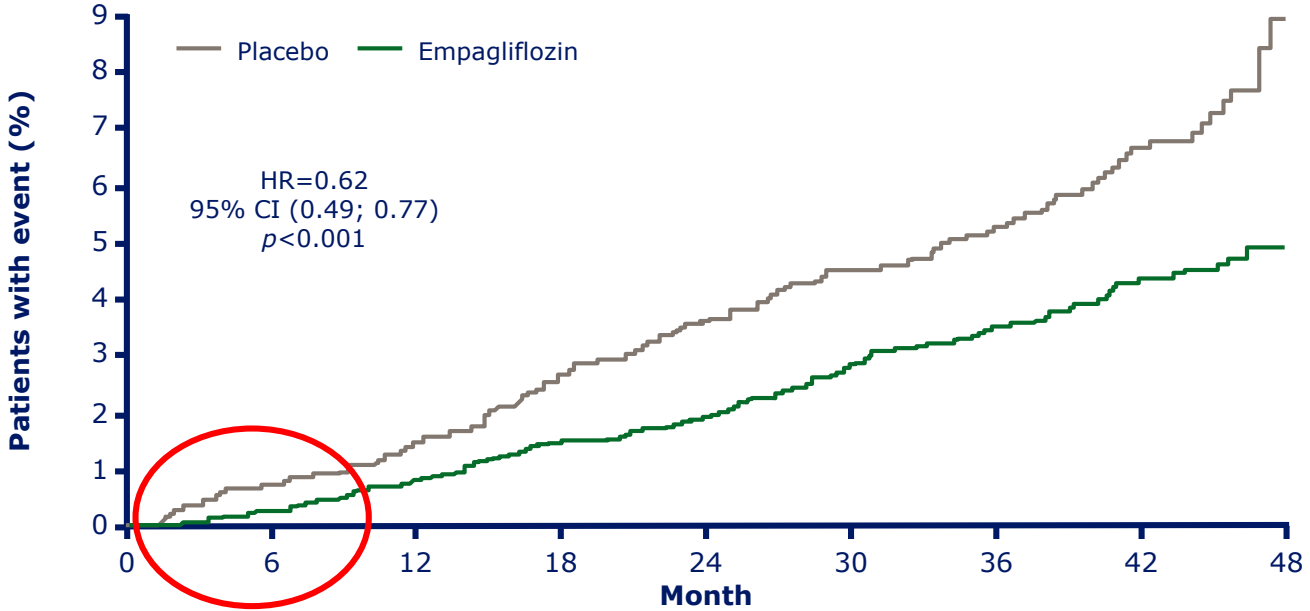


*95.02% CI.

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event.

Zinman B et al. Presented at European Association for the Study of Diabetes 2015, Stockholm, Sweden.

EMPA-REG OUTCOME: Death from cardiovascular causes



Number at risk

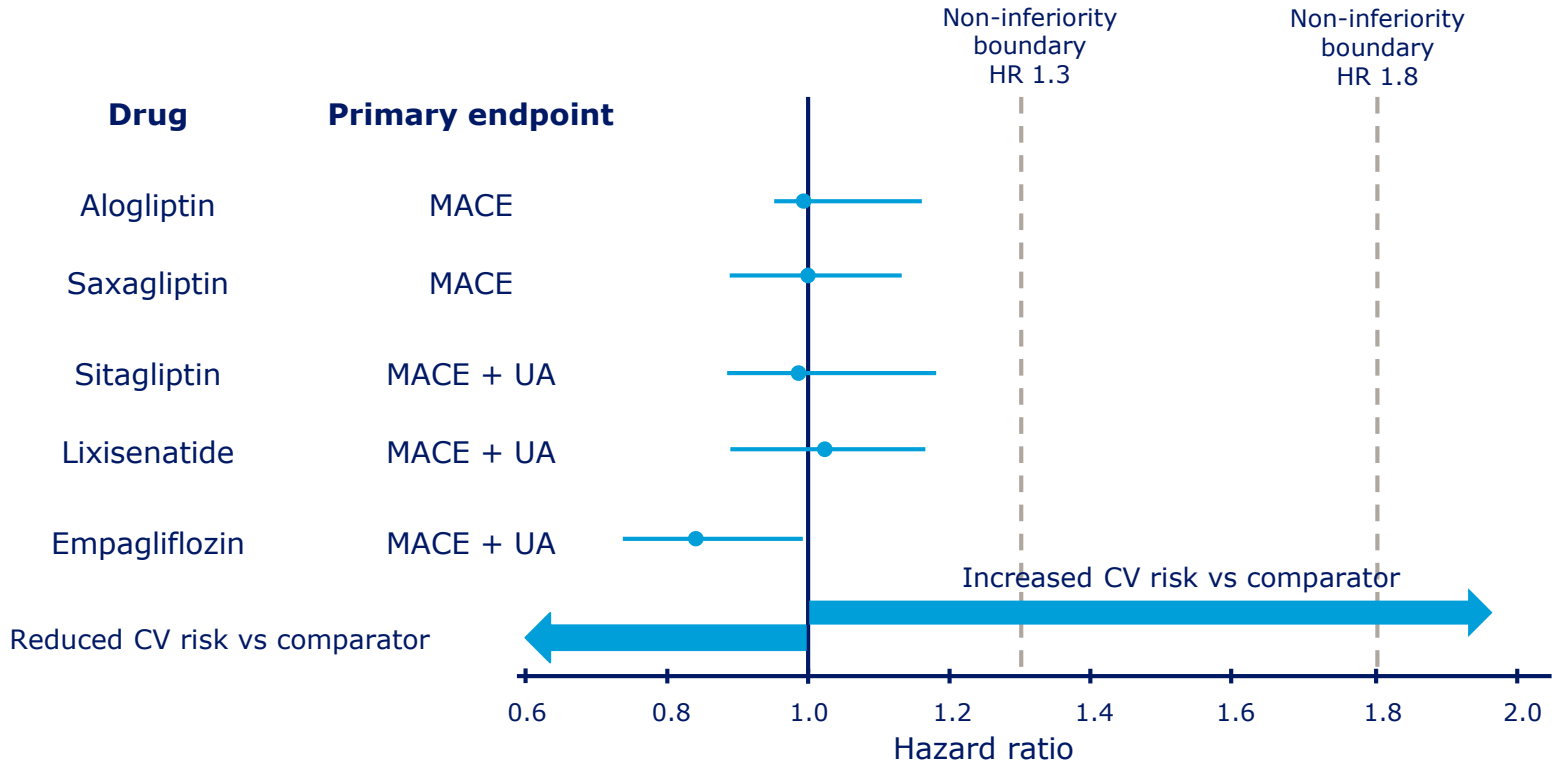
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

CI, confidence interval; HR, hazard ratio.

Zinman B et al. *N Engl J Med* 2015;doi: 10.1056/NEJMoa1504720. [Epub ahead of print].

CVOTs of type 2 diabetes therapies

Trial	Drug	Primary endpoint
EXAMINE[1]	Alogliptin	MACE
SAVOR-TIMI-53[2]	Saxagliptin	MACE
TECOS[3]	Sitagliptin	MACE + UA
ELIXA[4]	Lixisenatide	MACE + UA
EMPA-REG[5]	Empagliflozin	MACE + UA

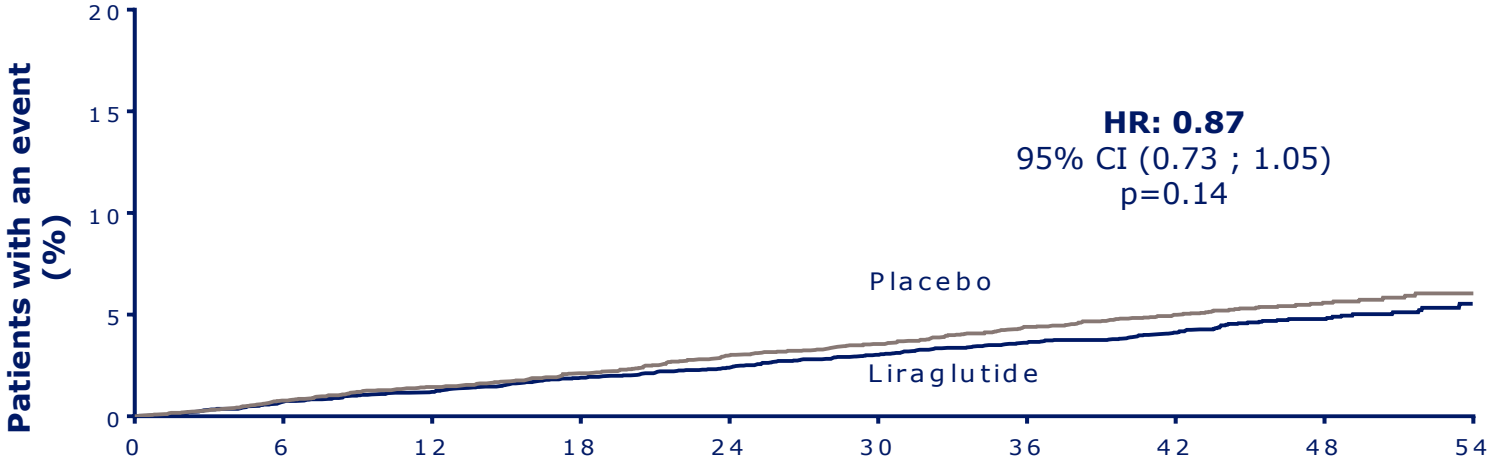


CVOT, cardiovascular outcomes trial; HR, hazard ratio; MACE, major cardiovascular endpoint; T2DM, type 2 diabetes; UA, unstable angina.

1. White et al. *N Engl J Med* 2013;369(14):1327–1335; 2. Scirica et al. *N Engl J Med* 2013;369(14):1317–1326; 3. Green et al. *N Engl J Med* 2015;16;373(3):232–242; 4. https://dxlink.ca/ADAReport/; 5. Zinman et al. *N Engl J Med* 2015 [Epub ahead of print].

Hospitalisation for heart failure

- >12 hour or overnight stay
- Clinical symptoms
- Additional/increased therapy



Patients at risk

Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months

CI: confidence interval; HR: hazard ratio

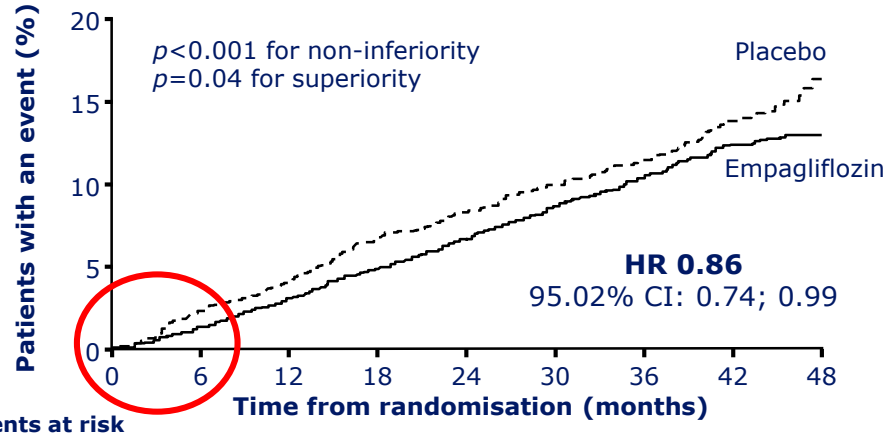
Marso SP et al. *N Engl J Med* 2016; 375(4):311-22.

CVOTs and their implications on treatment decision-making in diabetes

Empagliflozin and liraglutide

EMPA-REG OUTCOME[1]

CV death, non-fatal MI, or non-fatal stroke

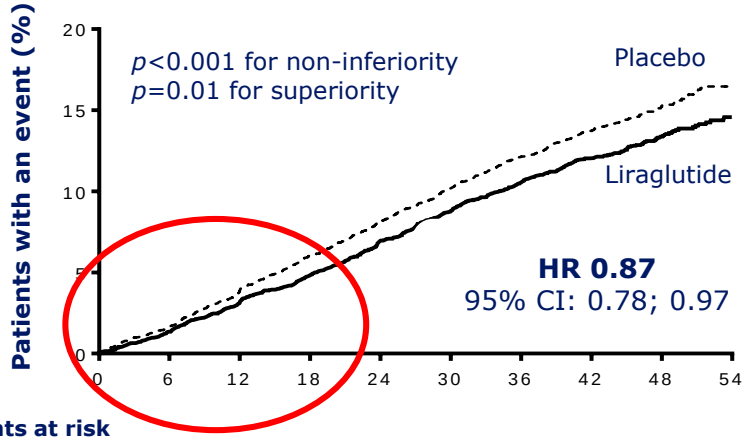


Patients at risk

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

LEADER[2]

CV death, non-fatal MI, or non-fatal stroke



Patients at risk

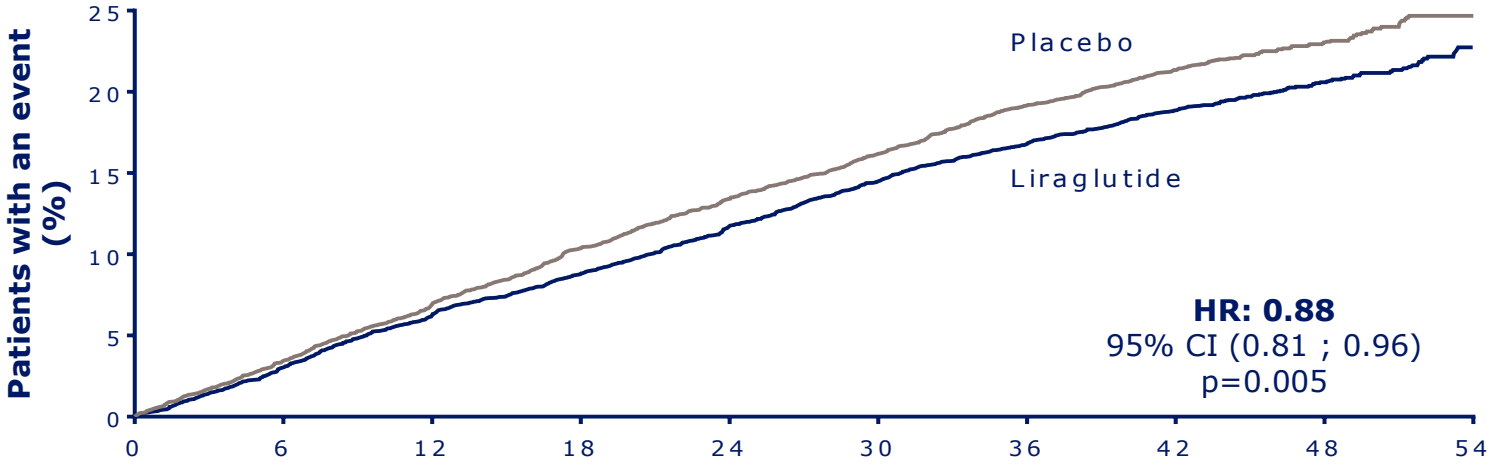
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

1. Zinman B et al. *N Engl J Med* 2015;373:2117–2128; 2. Marso SP et al. *N Eng J Med* 2016; DOI: 10.1056/NEJMoa1603827

Expanded MACE

CV death, non-fatal MI, non-fatal stroke, coronary revascularisation, or hospitalisation for unstable angina pectoris or heart failure



Patients at risk

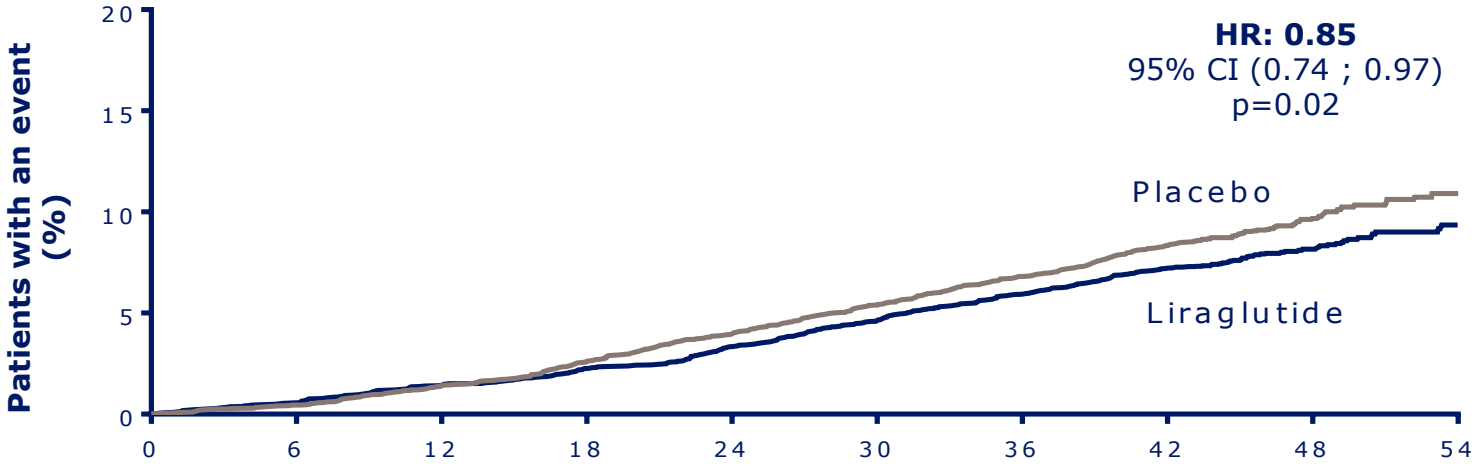
Liraglutide	4668	4515	4356	4221	4063	3914	3793	3682	1452	395
Placebo	4672	4506	4336	4157	4002	3857	3697	3581	1410	366

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MACE: major adverse cardiovascular event; MI: myocardial infarction

Marso SP et al. *N Engl J Med* 2016; 375(4):311-22.

All-cause death



Patients at risk

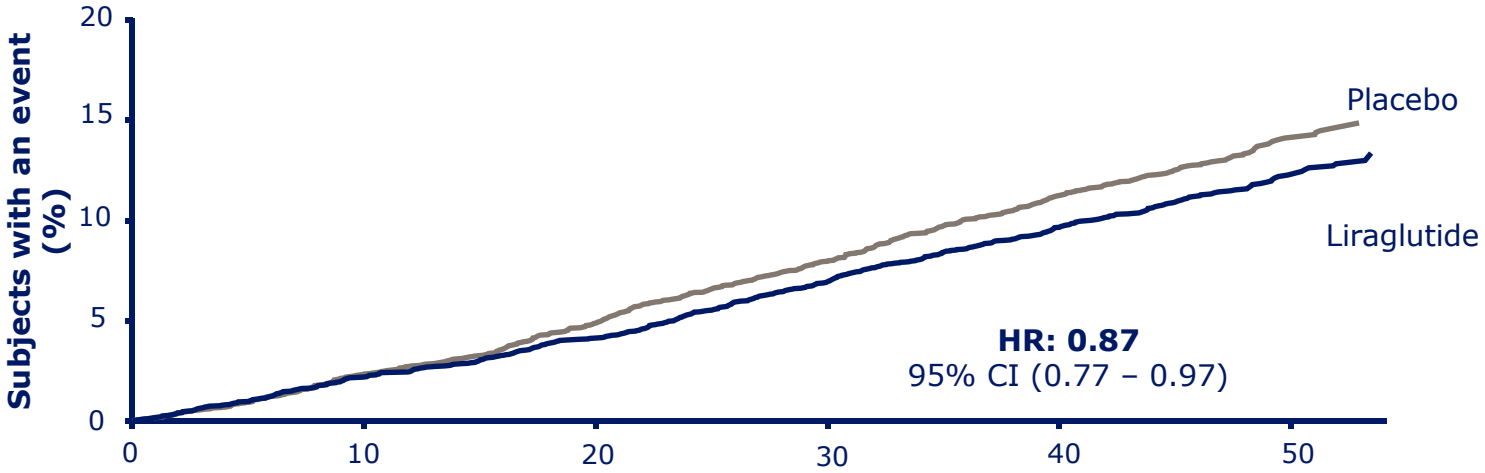
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months

CI: confidence interval; HR: hazard ratio

Marso SP et al. *N Engl J Med* 2016; 375(4):311-22.

Hospitalisation for heart failure or all-cause death



Patients at risk						
Liraglutide	4668	4563	4470	4337	4209	1016
Placebo	4672	4560	4470	4288	4132	976

Full analysis set. The cumulative incidences of time to EAC-confirmed first hospitalisation for heart failure or all-cause death were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 48 months, because less than 10% of the patients had an observation time beyond 48 months

CI: confidence interval; EAC: event adjudication committee; HR: hazard ratio

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

Number needed to treat to prevent one...

MACE

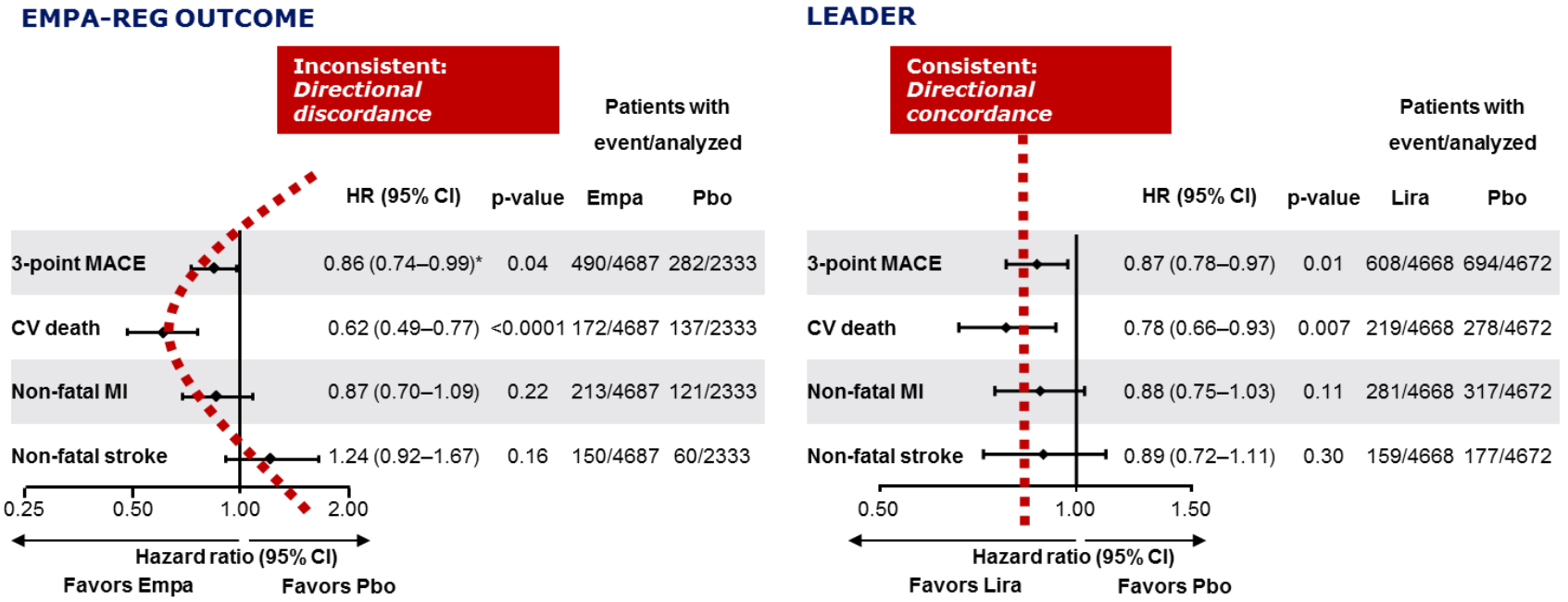
All-cause death

for 3 years

MACE, major adverse cardiovascular event.

Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

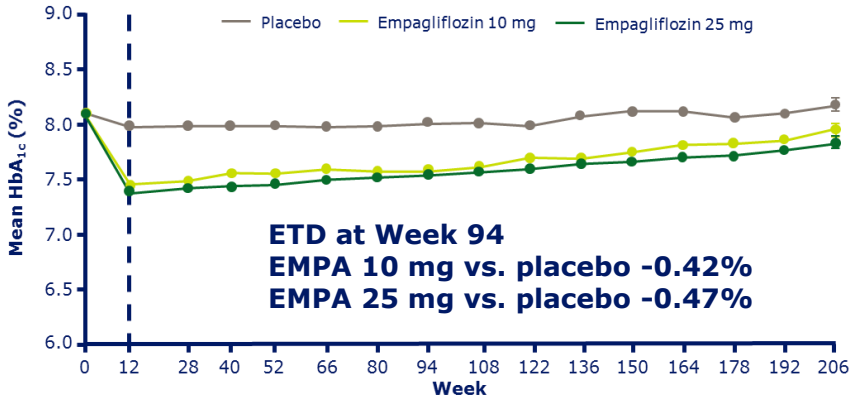
Individual components of the primary endpoint

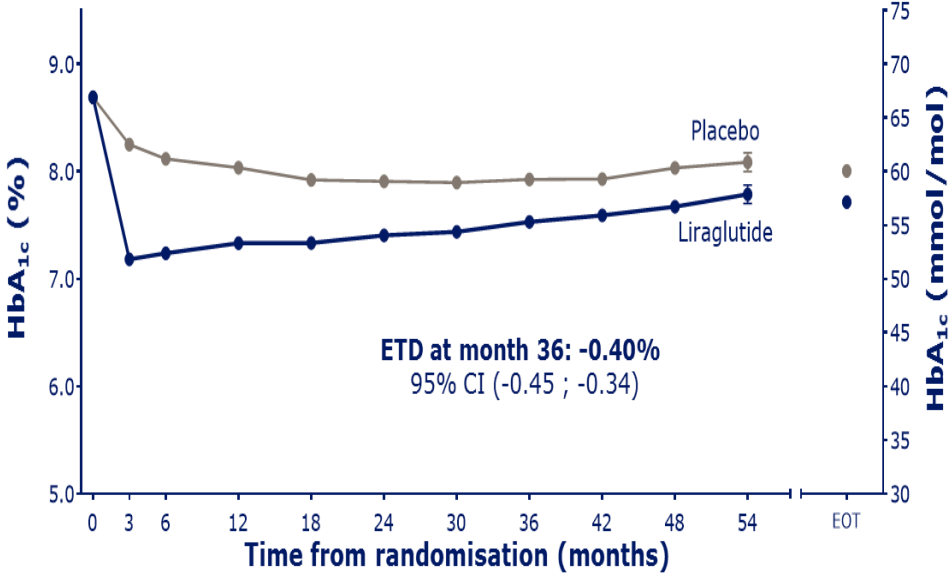


CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

1. Zinman B et al. *N Engl J Med* 2015;373:2117–2128; 2. Marso SP et al. *N Eng J Med* 2016; DOI: 10.1056/NEJMoa1603827

EMPA-REG OUTCOME and LEADER: effects on HbA_{1c}





CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin.

1. Zinman B et al. *N Engl J Med* 2015;373:2117–2128; 2. Marso SP et al. *N Eng J Med* 2016; DOI: 10.1056/NEJMoa1603827

LEADER and EMPA-REG OUTCOME comparison:

- These trials do not provide knowledge on the mode of action
- From the observed effects, different mechanisms for empagliflozin and liraglutide are possible
- The observed benefit in EMPA-REG OUTCOME may be more closely linked to haemodynamic changes; whereas in the LEADER trial, the observed benefits appear later and are perhaps more compatible with a more “generalised” effect on the pathogenesis of atherosclerotic vascular disease

LEADER and EMPA-REG OUTCOME comparison:

- Effects cannot be extrapolated beyond the drugs used
  - In the only other GLP-1 receptor agonist CVOT to report to date (ELIXA), lixisenatide did not demonstrate superiority to placebo and standard of care
  - ITCA 650 (exenatide implant) also reported non-inferiority versus placebo in FREEDOM
  - No other SGLT-2 inhibitor CVOTs have reported yet
  - There were differences in CV outcomes among the DPP-4 inhibitors in the CVOTs that have reported, particularly with respect to heart failure

- Undiagnosed heart failure is common in patients with T2DM
  - This may affect the CV impact of treating with various antidiabetic agents

CVOT, cardiovascular outcome trial