Simposio

IL DIABETE NEL PAZIENTE ANZIANO

Controllo Metabolico e Rischio Cardiovascolare

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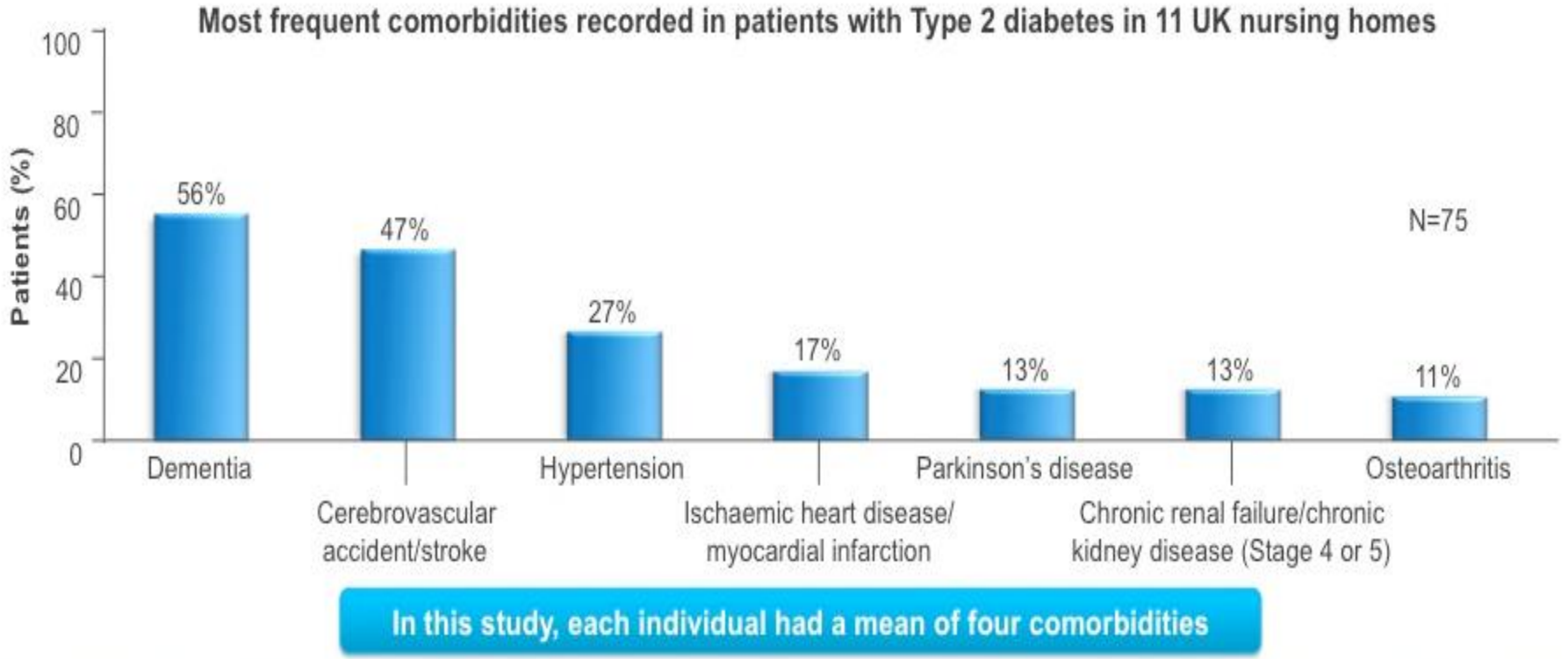
Management of patients with Type 2 diabetes goes beyond control of hyperglycaemia

- Patients with diabetes commonly have additional co-existing disorders
- Comorbidities can affect a patient's ability to manage their self-care and significantly increase the need for medical care[1,2]
- Comorbidities must be treated adequately in order to minimise diabetes-specific risk factors[1]

- Diabetes-related complications
- CVD
- Obesity
- Hypertension
- Dyslipidaemia
- Other CV risk factors

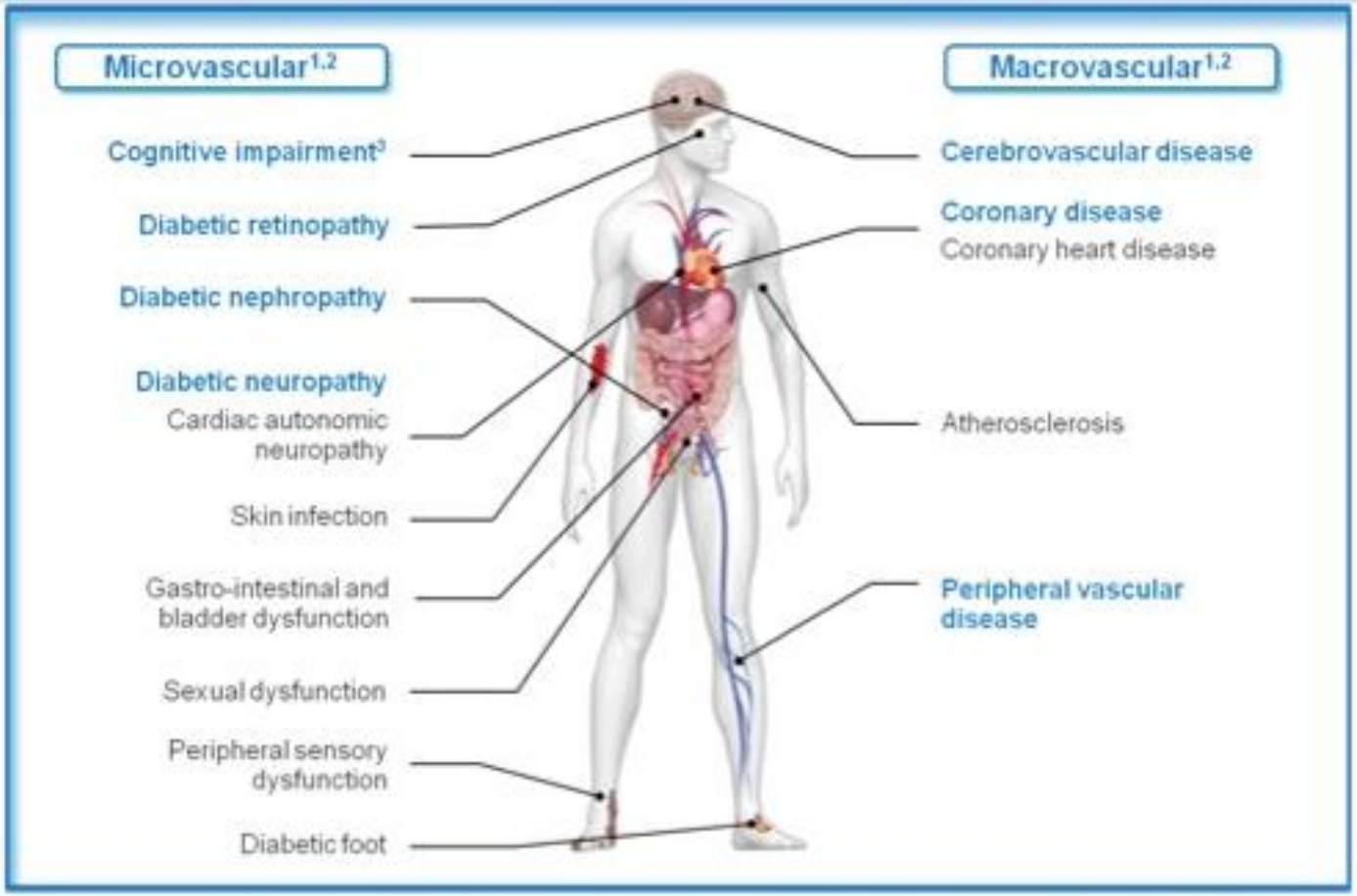
Piette JD et al, Diabetes Care 2006; Struijs JN et al, BMC Health Serv Res 2006

Comorbidities may be particularly common in elderly patients with Type 2 diabetes



A retrospective case notes review of 75 people with diabetes in 11 nursing homes in the UK visited February-April 2010.
Gadsby R et al Diabet Med 2011

Major microvascular and macrovascular complications of diabetes



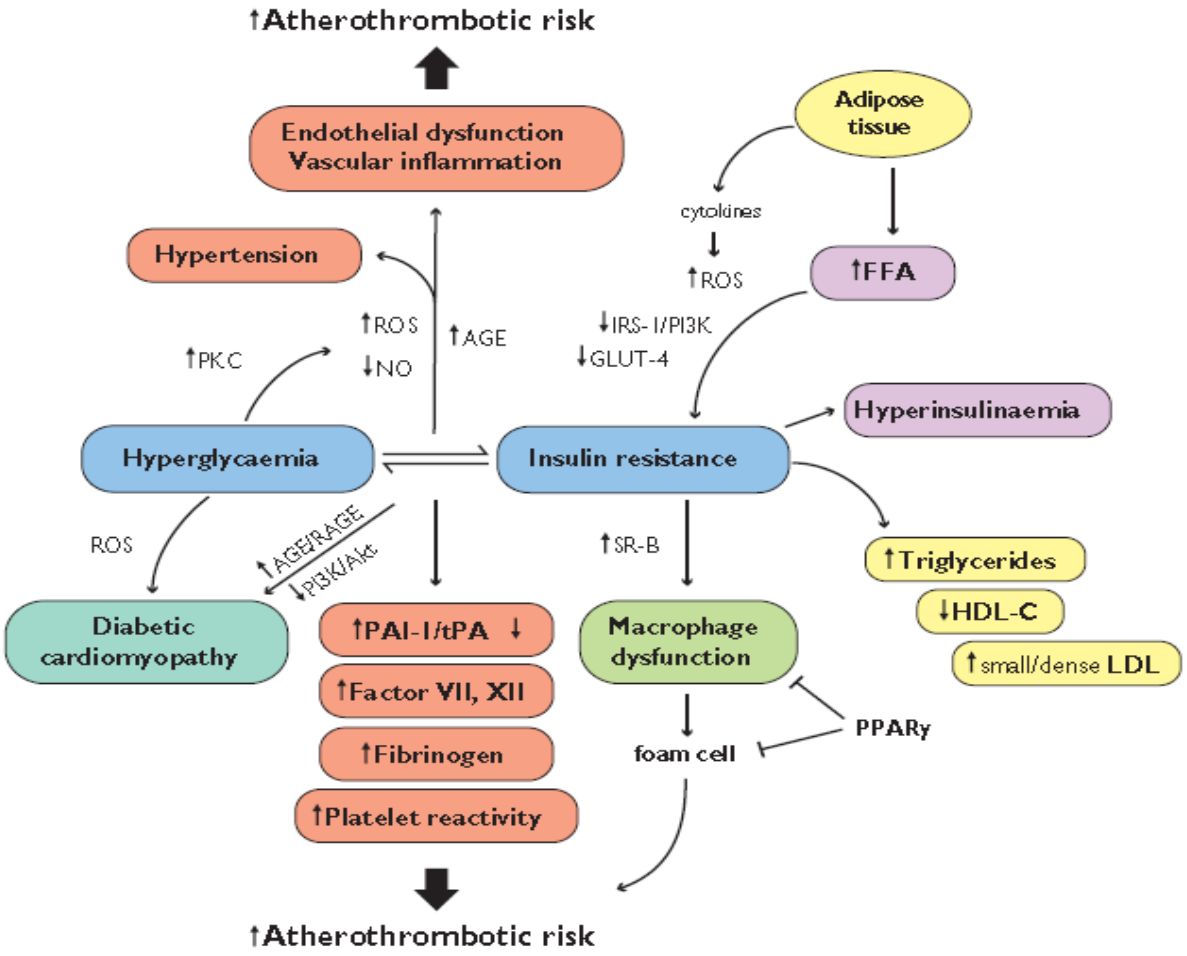
Adapted from IDF. Time to Act: Type 2 diabetes, the metabolic syndrome and cardiovascular disease in Europe, 2006; IDF. Time to Act 2001; Seaguist ER, Diabetes 2010

European Heart Journal Advance Access published August 30, 2013

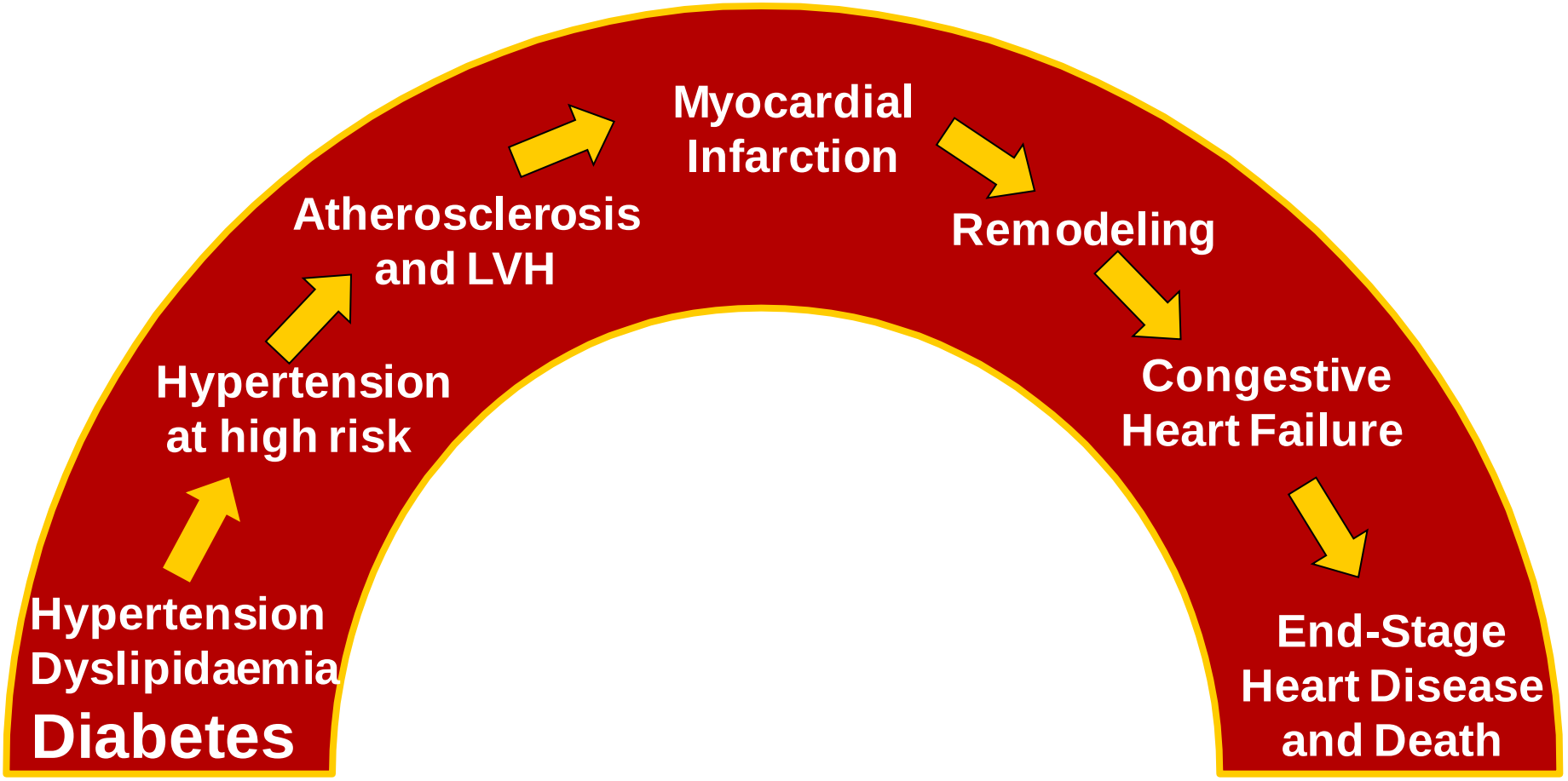
ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

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).

Hyperglycaemia, insulin resistance, and cardiovascular disease

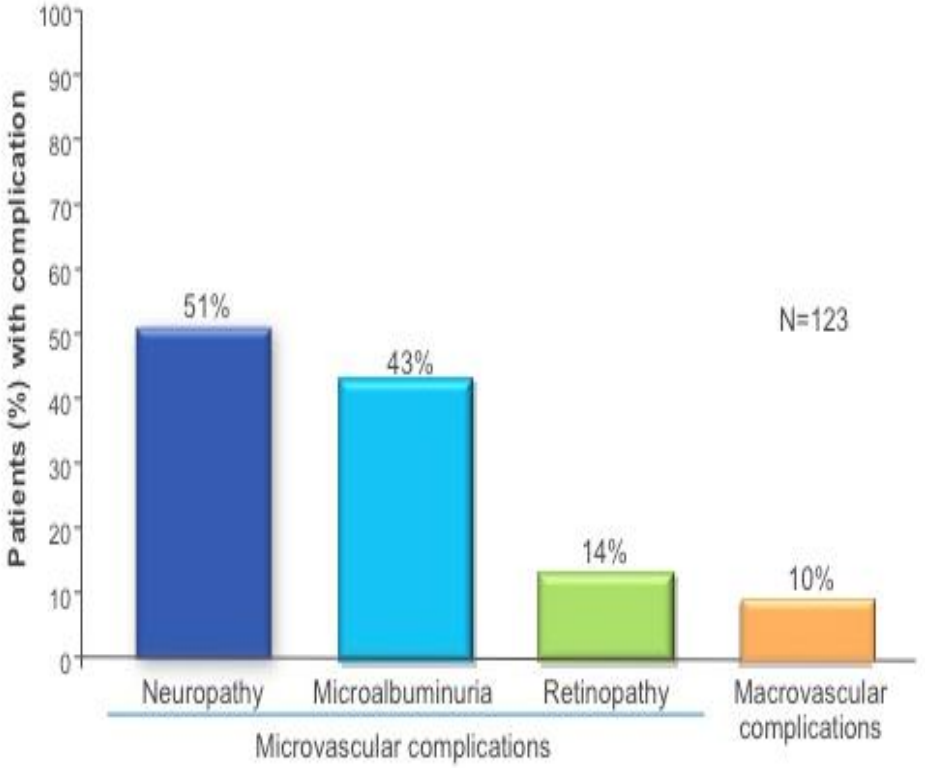


The Risk Factors Continuum



Prevalence of microvascular and macrovascular complications in patients with Type 2 diabetes

- In a cross-sectional study, 68% of people with Type 2 diabetes suffered from at least one complication



An observational cross-sectional study based on review of medical records and interviews of 123 Type 2 Diabetes in Geenland. Mean duration of diabetes 6 years. *Pedersen ML et al, Circum. Health 2010*

Diabetes significantly increases the risk of vascular outcomes: Meta-analysis of 102 prospective studies

Hazard ratios* for vascular outcomes in people with versus without diabetes at baseline (n=530,083)

	Number of cases	Hazard ratio (95% CI)	I^2 (95% CI)
Coronary heart disease*	26,505	2.00 (1.83, 2.19)	64 (54, 71)
Coronary death	11,556	2.31 (2.05, 2.60)	41 (24, 54)
Non-fatal myocardial infarction	14,741	1.82 (1.64, 2.03)	37 (19, 51)
Stroke subtypes†			
Ischaemic stroke	3799	2.27 (1.95, 2.65)	1 (0, 20)
Haemorrhagic stroke	1183	1.56 (1.19, 2.05)	0 (0, 26)
Unclassified stroke	4973	1.84 (1.59, 2.13)	33 (12, 48)
Other vascular deaths	3826	1.73 (1.51, 1.98)	0 (0, 26)

**Adjusted for age, smoking status, BMI, systolic blood pressure, and where appropriate stratified by sex and trial arm†*
Includes both fatal and non-fatal events.

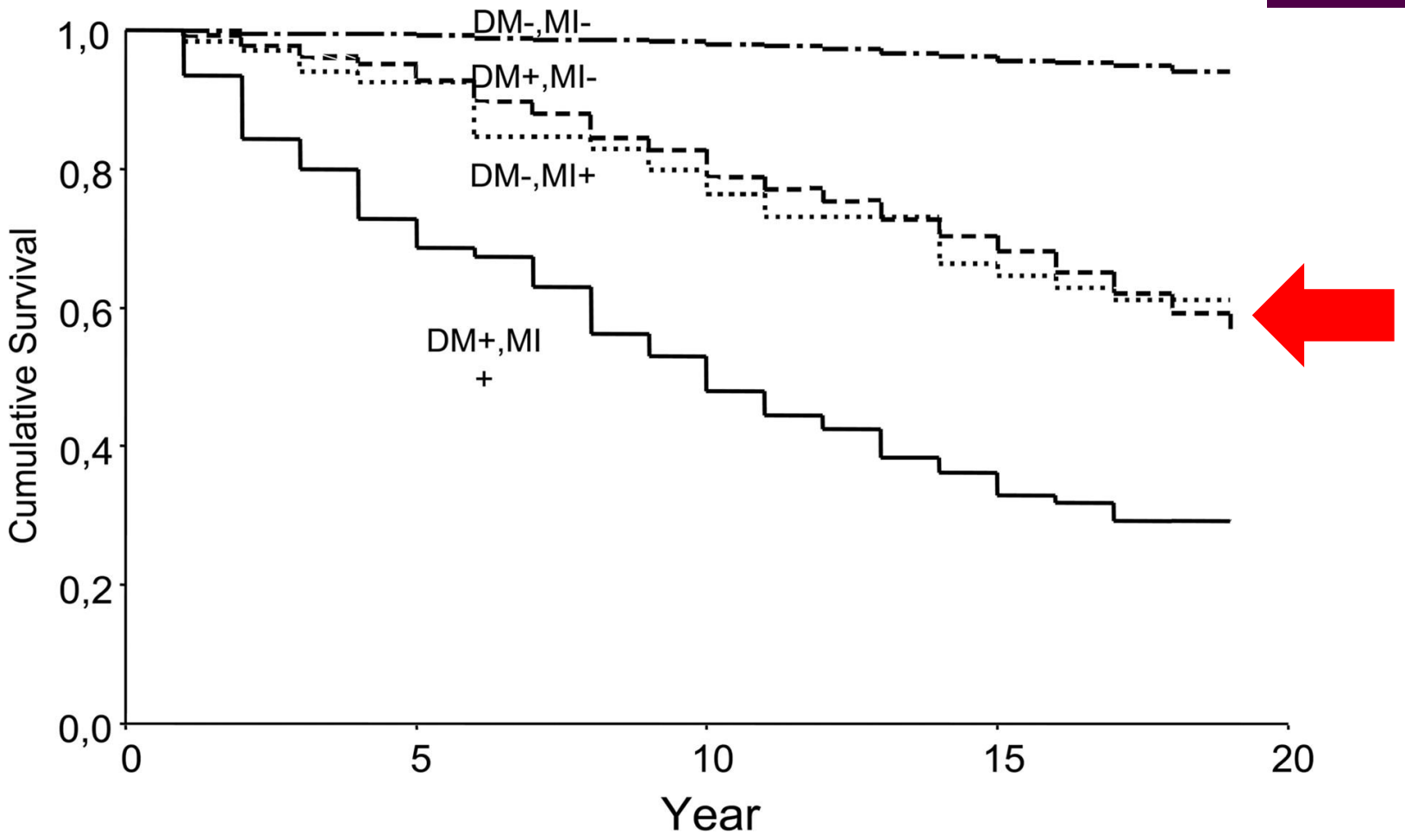
Emerging Risk Factors Collaboration Lancet 2010

Type 2 Diabetes as a "Coronary Heart Disease Equivalent"

An 18-year prospective population-based study in Finnish subjects

Auni Juutilainen, MD[1]
Seppo Lehto, MD[1]
Tapani Rönnemaa, MD[2]
Kalevi Pyörälä, MD[1]
Markku Laakso, MD[1]

Diabetes Care **28:2901–2907, 2005**

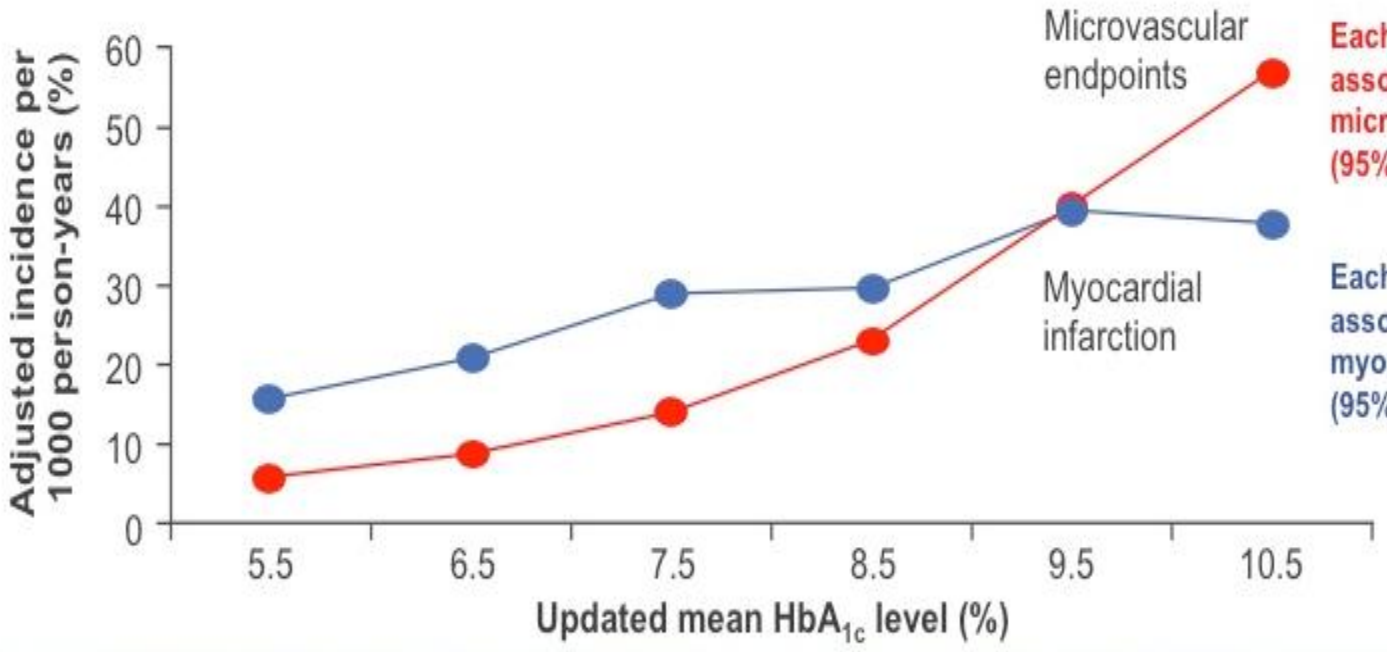


Incidence per 1,000 person-years and Cox model hazard ratio for CHD death (adjusted for age, area of residence, and sex) during the 18-year follow-up according to the presence of diabetes and prior evidence of MI in 1,373 nondiabetic and 1,059 diabetic subjects

There is a strong association between hyperglycaemia and diabetes complications

ACCORD –ADVANCE - VADT

Incidence rates of complications associated with HbA_{1c} level



Each 1% reduction in HbA_{1c} level associated with 37% decrease in microvascular risk (95% CI: 33%, 41%; p<0.0001)

Each 1% reduction in HbA_{1c} level associated with 14% decrease in myocardial infarction risk (95% CI: 8%, 21%; p<0.0001)

Stralton IM et al; BMJ 2000

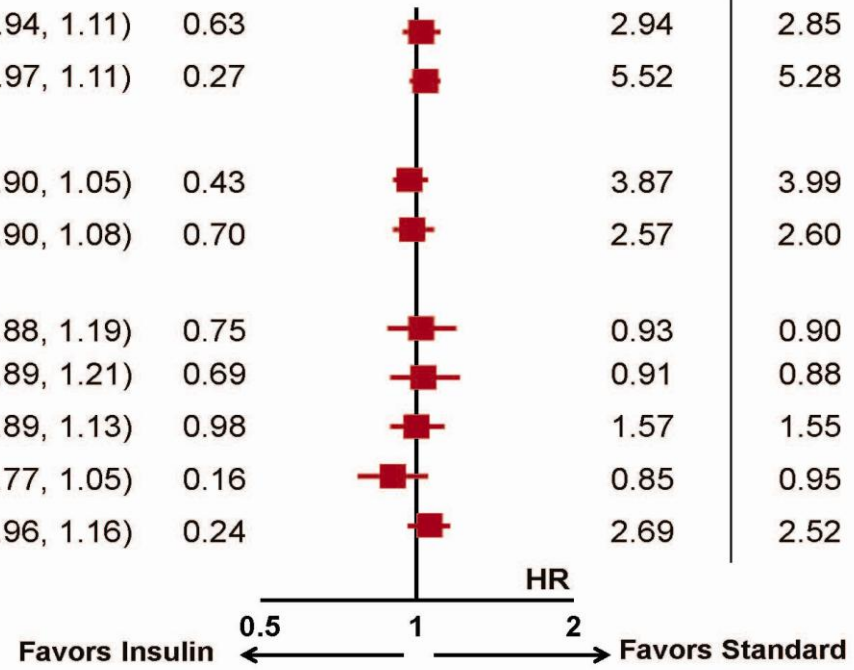
Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

N Eng J Med 2012

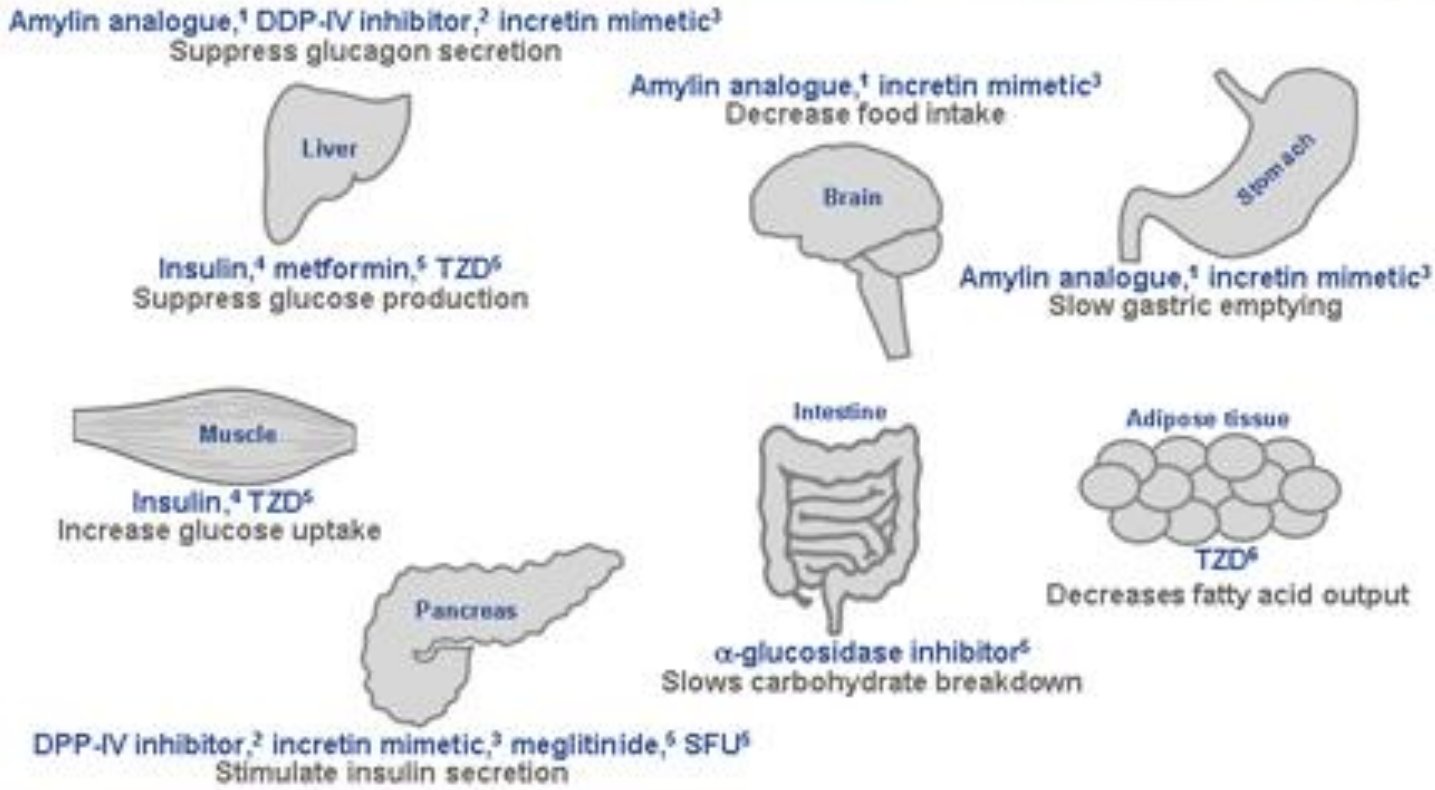
ORIGIN-Outcome Reduction with an Initial Glargine Intervention Trial

	HR (95% CI)	p value	Insulin/ 100 py	Standard/ 100 py
1st Coprimary	1.02 (0.94, 1.11)	0.63	2.94	2.85
2nd Coprimary	1.04 (0.97, 1.11)	0.27	5.52	5.28
Microvascular	0.97 (0.90, 1.05)	0.43	3.87	3.99
Death	0.98 (0.90, 1.08)	0.70	2.57	2.60
MI	1.02 (0.88, 1.19)	0.75	0.93	0.90
Stroke	1.03 (0.89, 1.21)	0.69	0.91	0.88
CV Death	1.00 (0.89, 1.13)	0.98	1.57	1.55
CHF Hospital	0.90 (0.77, 1.05)	0.16	0.85	0.95
Revascularized	1.06 (0.96, 1.16)	0.24	2.69	2.52



This study randomized 12 537 people (mean age, 63.5 years) at high CVD risk plus IFG, IGT or T2DMto receive insulin glargine (with a target fasting blood glucose level of 5.3 mmol/L (≤95 mg/dL) or to standard care.
After a median follow-up of 6.2 years, the rates of incident CV outcomes were similar in the insulin glargine and standard care groups.

Therapies and Primary Mechanisms of Glucose Control in Type 2 Diabetes



DPP-IV, dipeptidyl peptidase-IV; SFU, sulfonylurea; TZD, thiazolidinedione.

1. Symlin [package insert]. San Diego, CA: Amylin Pharmaceuticals Inc; 2007. 2. Januvia [package insert]. Whitehouse Station, NJ: Merck & Co Inc; 2007. 3. Byetta [package insert]. San Diego, CA: Amylin Pharmaceuticals Inc; 2006. 4. NovoLog [package insert]. Princeton, NJ: Novo Nordisk Inc; 2007. 5. American Association of Clinical Endocrinologists. *Endocr Pract.* 2007;13(suppl 1):3-68. 6. Racette SB et al. *Metabolism.* 2002;51(2):169-174.

American Diabetes Association. DiabetesCare

DIABETES AND CARDIOVASCULAR DISEASE

Is There Evidence That Oral Hypoglycemic Agents Reduce Cardiovascular Morbidity/Mortality? Yes

CRISTINA BIANCHI, MD
ROBERTO MICCOLI, MD
GIUSEPPE DANIELE, MD
GIUSEPPE PENNO, MD
STEFANO DEL PRATO, MD

DIABETES AND CARDIOVASCULAR DISEASE

Is There Evidence That Oral Hypoglycemic Agents Reduce Cardiovascular Morbidity or Mortality? No

SAMEER A. KASSEM, MD, PHD
ITAMAR RAZ, MD

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.

N Engl J med 2007

Rates of Myocardial Infarction and Death fromCardiovascular Disease

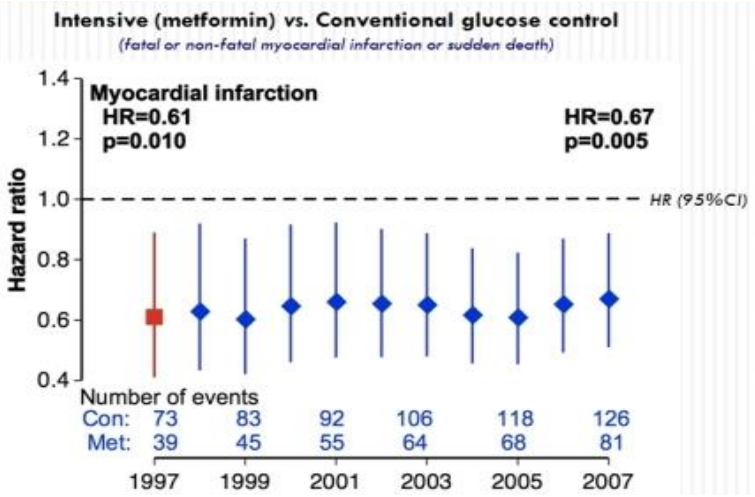
Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,280 (0.43)	22/6105 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.44)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,557 (0.38)	7/3700 (0.19)	2.40 (1.17–4.91)	0.02
DREAM	12/2,365 (0.51)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2854 (0.18)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Cardiovascular safety of glucose-lowering agents

Metformin, Sulfonylureas, Pioglitazone

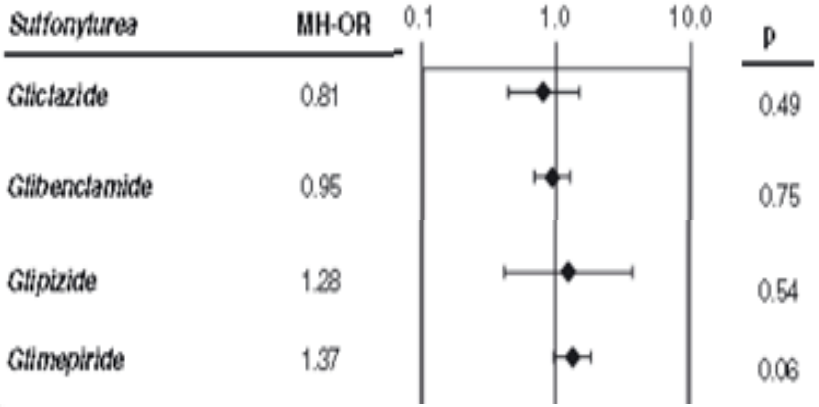
UKPDS follow-up-Myocardial Infarction Hazard Ratio

N Eng J Med 2008



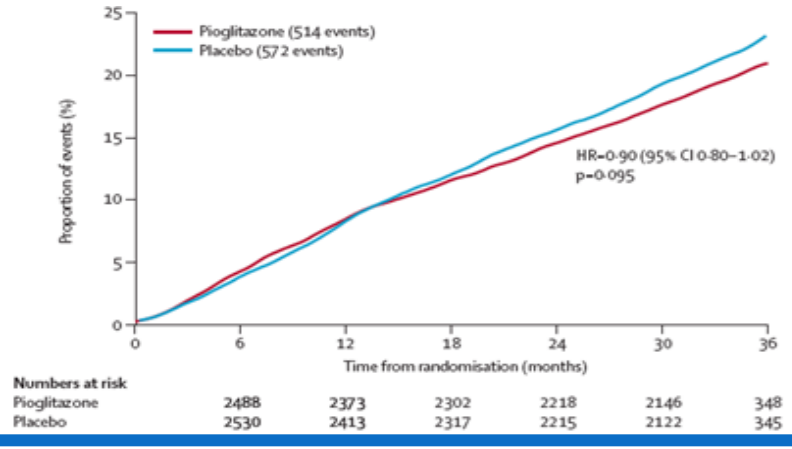
Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials

Diabetes, Obesity and Metabolism 2013



PROACTIVE study-Pioglitazone and macrovascular events

Lancet 2005

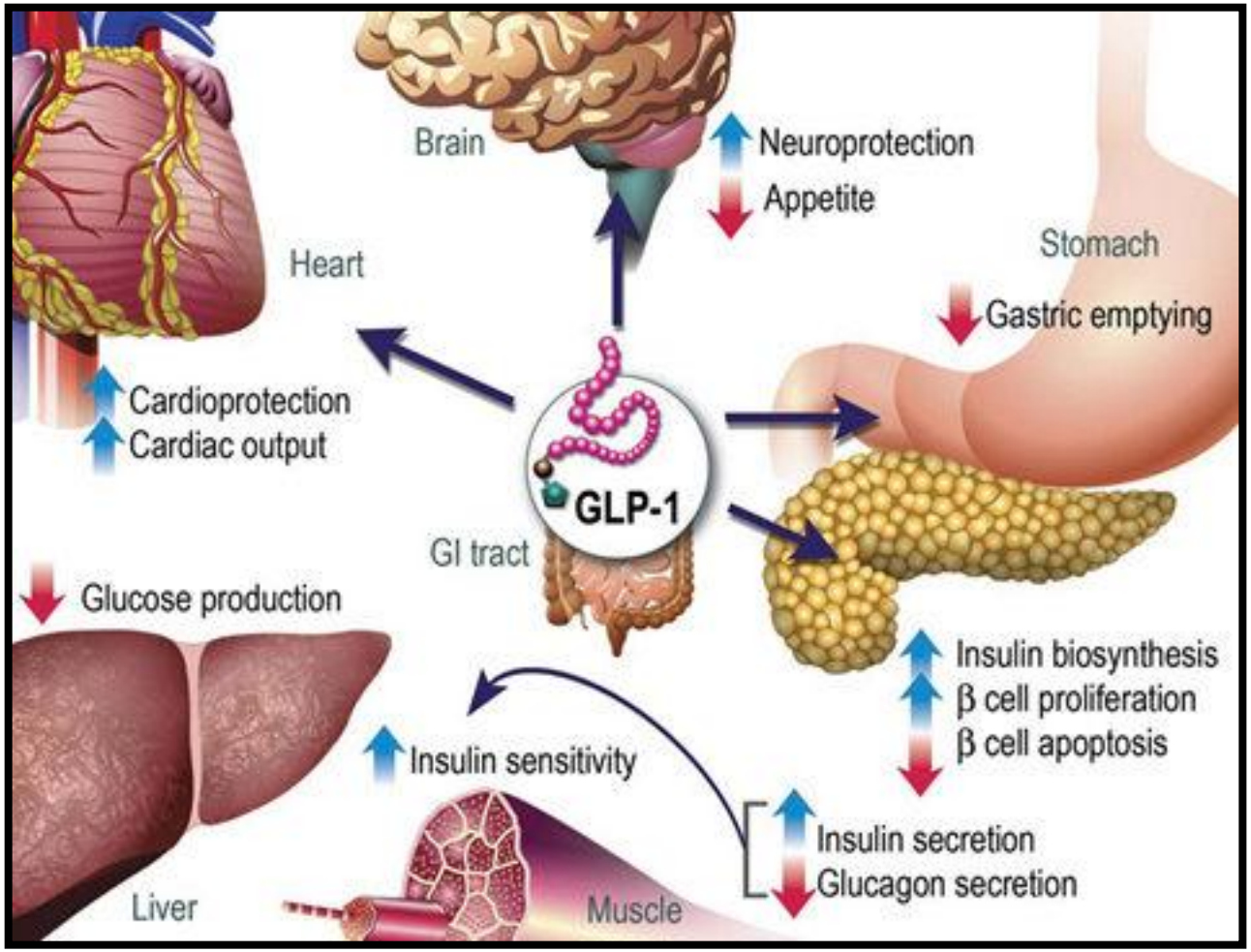


REVIEW

Emerging cardiovascular actions of the incretin hormone glucagon-like peptide-1: potential therapeutic benefits beyond glycaemic control?

David J Grieve[1], Roslyn S Cassidy[1] and Brian D Green[2]

British Journal of Pharmacology (2009), 157, 1340–1351



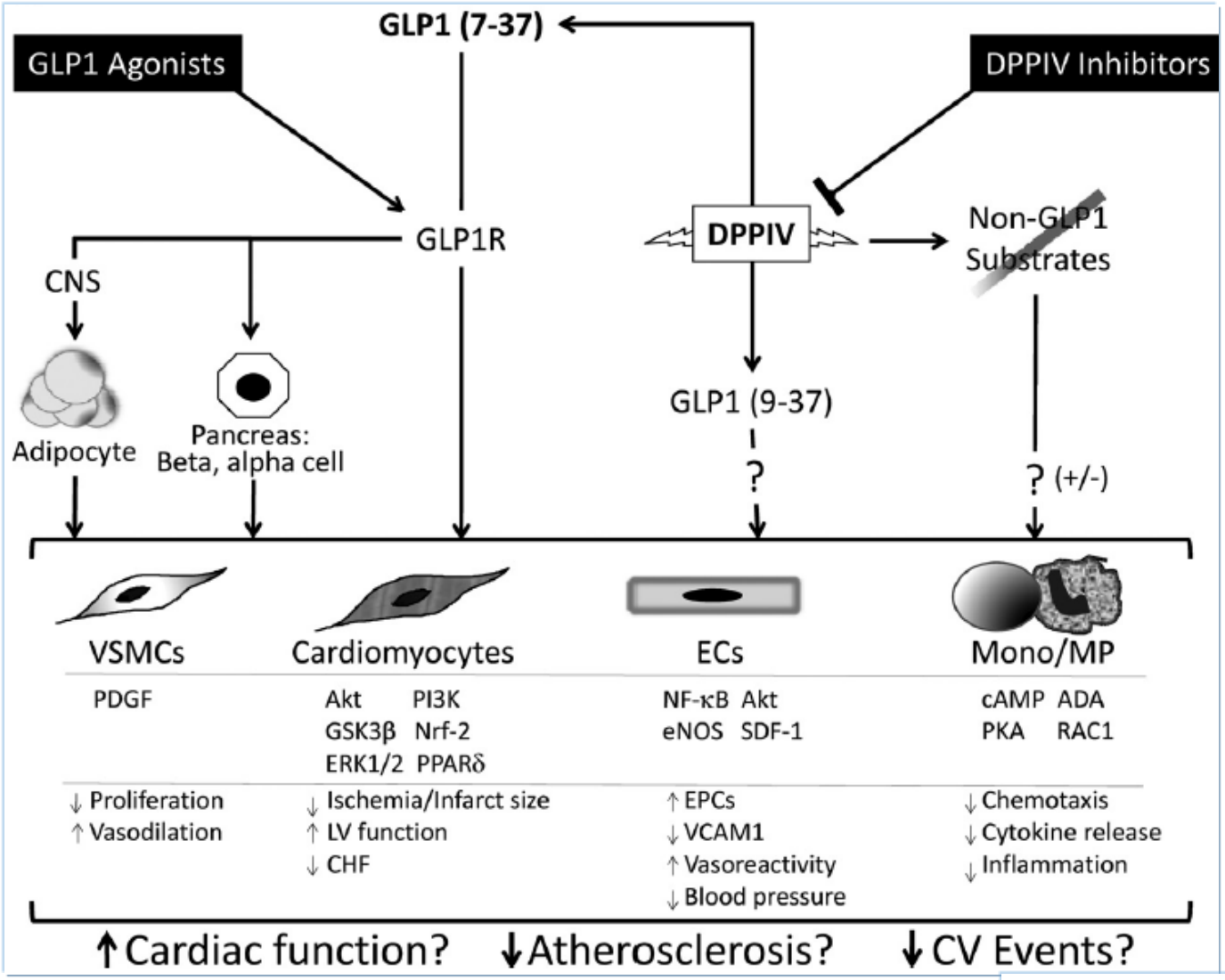
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Editorial

The Incretin Axis in Cardiovascular Disease

Jorge Plutzky, MD

American Heart Association
Learn and Live



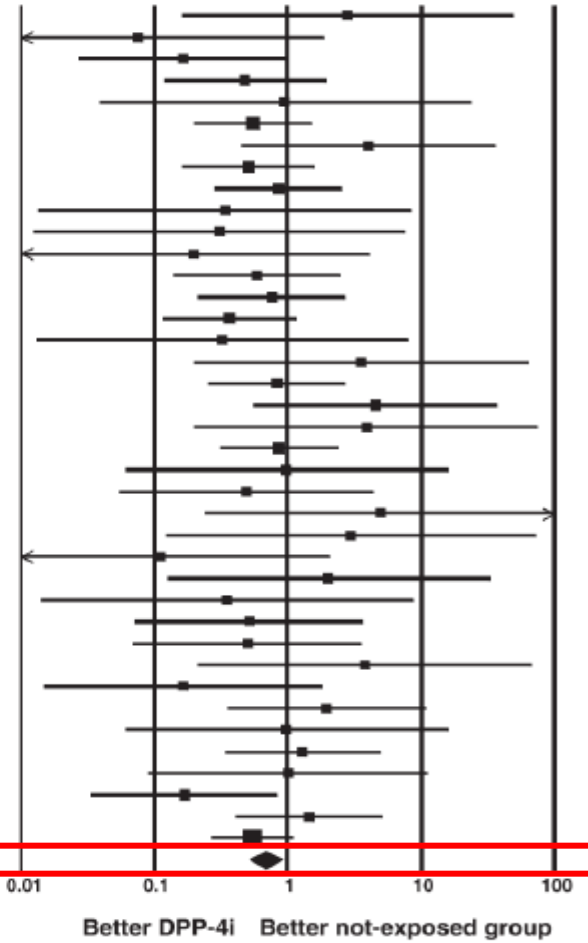
Original article

Monami M et al Curr Med Res 2011

Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials

Major Cardiovascular Events (MACE)

Study name	MH odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Pratley 2009 (a) (1)	2,822	0,161	49,496	0,710	0,478
Nauck 2009 (4)	0,076	0,003	1,879	−1,575	0,115
CV181–038 (8)	0,164	0,027	0,999	−1,961	0,050
Hollander 2010 (10)	0,477	0,118	1,931	−1,037	0,300
DeFronzo 2009 (11)	0,956	0,039	23,562	−0,028	0,978
Jadzinsky 2009 (12)	0,549	0,198	1,523	−1,151	0,250
NCT00698932 (13)	4,043	0,449	36,406	1,246	0,213
Chacra 2009 (14)	0,508	0,162	1,590	−1,164	0,245
Goke 2010 (15)	0,859	0,286	2,578	−0,271	0,787
NCT00305604 (13)	0,337	0,014	8,359	−0,664	0,506
NCT01028391 (13)	0,309	0,012	7,643	−0,717	0,473
Yoon 2011 (18)	0,197	0,009	4,122	−1,047	0,295
Visboll 2010 (19)	0,591	0,140	2,492	−0,717	0,473
Charbonnel 2006 (20)	0,763	0,213	2,731	−0,416	0,678
Aschner 2006 (21)	0,364	0,114	1,158	−1,712	0,087
Raz 2008 (22)	0,323	0,013	8,029	−0,689	0,491
Raz 2006 (23)	3,543	0,198	63,368	0,860	0,390
NCT00482729 (13)	0,827	0,251	2,723	−0,313	0,754
Chan 2008 (24)	4,545	0,551	37,465	1,407	0,159
NCT00350779 (13)	3,866	0,198	75,655	0,891	0,373
Williams 2010 (25)	0,856	0,308	2,376	−0,299	0,765
NCT00449930 (13)	0,989	0,062	15,847	−0,008	0,994
Bergenstal 2010 (27)	0,486	0,054	4,387	−0,642	0,521
NCT00532935 (13)	4,942	0,236	103,448	1,030	0,303
Seck 2010 (28)	2,985	0,121	73,416	0,669	0,503
Arechavaleta 2011 (29)	0,111	0,006	2,065	−1,474	0,140
Pratley 2011 (30)	2,041	0,127	32,790	0,504	0,614
Fonseca 2007 (31)	0,349	0,014	8,649	−0,642	0,521
Garber 2008 (34)	0,515	0,072	3,690	−0,661	0,509
Bosi 2007 (35)	0,500	0,070	3,579	−0,690	0,490
Dejager 2007 (37)	3,776	0,208	68,676	0,898	0,369
Bosi 2009 (38)	0,165	0,015	1,828	−1,468	0,142
Scherbaum 2008 (39)	1,947	0,351	10,793	0,763	0,446
Schweizer 2009 (40)	0,982	0,061	15,833	−0,013	0,990
Schweizer 2007 (41)	1,292	0,340	4,912	0,376	0,707
Pan 2008 (42)	1,000	0,090	11,089	0,000	1,000
Rosenstock 2007 (a) (44)	0,168	0,034	0,840	−2,173	0,030
Filozof 2010 (45)	1,450	0,407	5,169	0,573	0,567
Ferrannini 2009 (46)	0,540	0,266	1,096	−1,706	0,088
Overall	0,689	0,528	0,899	−2,747	0,006



……..The present meta-analysis suggest a possible direct effect protective from cardiovascular events……..

Monami M et al Curr Med Res 2011

Original article

Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials

53 trials
trial duration was 24-104 wks

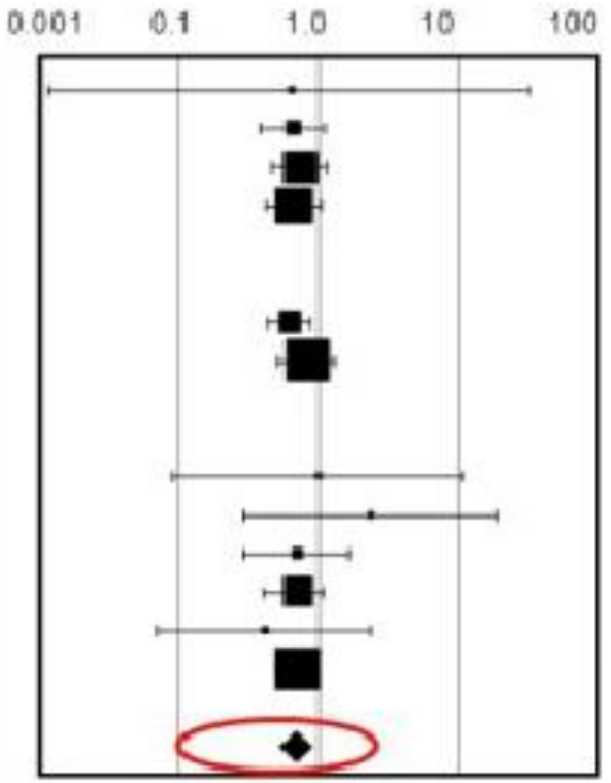
(MACE)
Major Cardiovascular Events

Drugs	MH-OR (95%,CI)	p	# Trials
Alogliptin	0.630 [0.012;33.048]	0.819	2
Saxagliptin	0.655 [0.382; 1.123]	0.124	8
Sitagliptin	0.740 [0.479; 1.147]	0.173	18
Vildagliptin	0.666 [0.428; 1.036]	0.072	12
Trial duration			
< 52 weeks	0.626 [0.444; 0.884]	0.008	30
≥ 52 weeks	0.831 [0.523; 1.321]	0.157	10
Comparator			
Acarbose	1.000 [0.090; 11.090]	1.000	1
Liraglutide	2.376 [0.291; 19.390]	0.419	2
Metformin	0.697[0.291; 1.666]	0.417	5
Sulfonylureas	0.718[0.410; 1.100]	0.098	5
Thiazolidinediones	0.411[0.070; 2.428]	0.327	3
Placebo	0.705[0.500; 0.993]	**0.045**	26
OVERALL	**0.689 [0.528; 0.899]**	**0.006**	**43**

20.312 patients →

13.569 patients →

Mantel Haenzel Odd Ratio, 95% Confidential Intervals



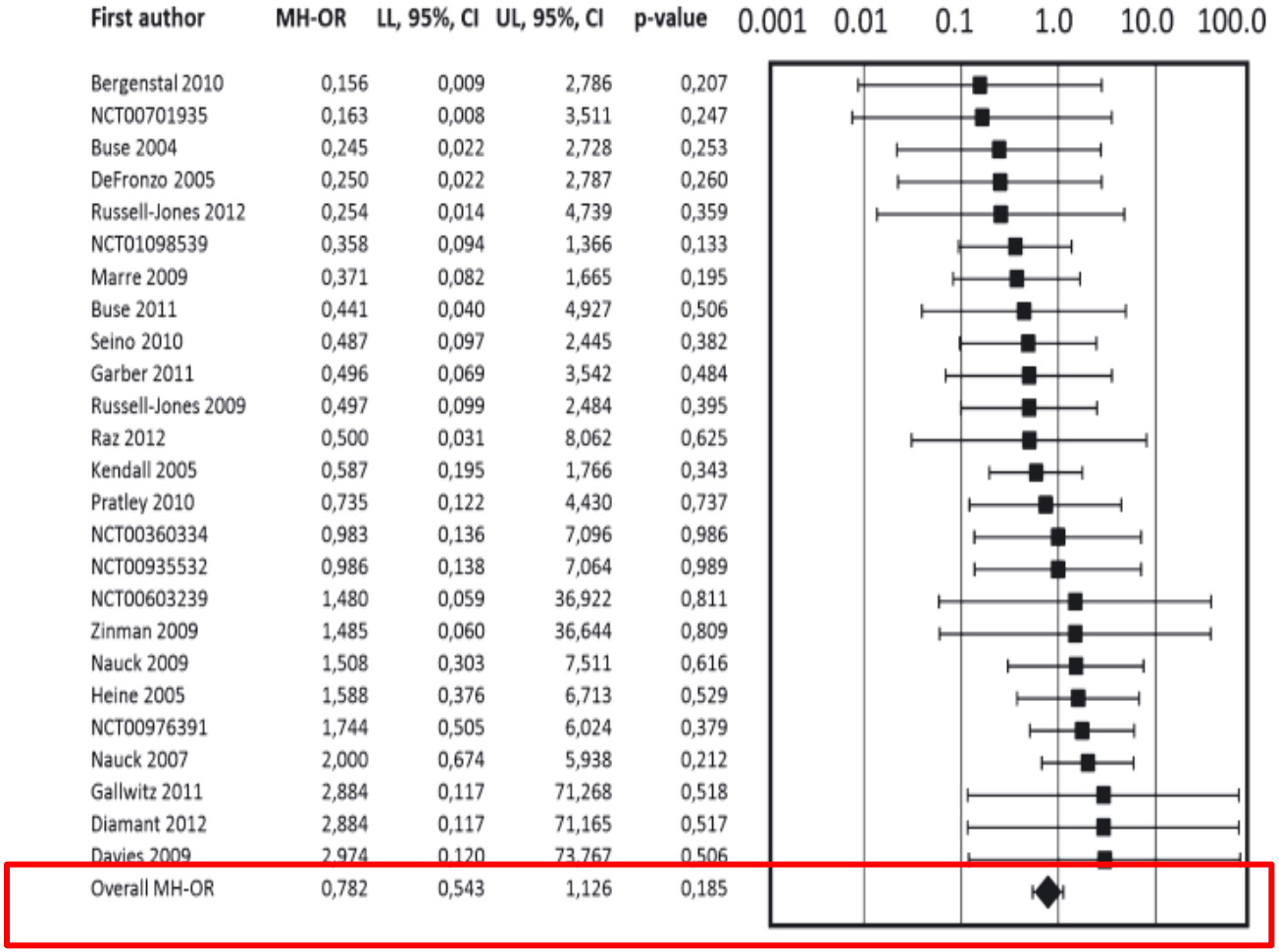
….This result should be interpreted with caution, as those events were not the principal endpoint, the trial duration was short and the characteristics of patients included could be different from routine clinical practice. DPP4 I were associated with a significantly lower risk of MACE irrespective of trial duraion, type of DPP4I or comparator…….

Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: a meta-analysis of randomized clinical trials

Diabetes, Obesity and Metabolism 2013.

The difference in the incidence of MACE between GLP-1 RA and comparators did not reach statistical significance

A total of 37 trials fulfilling the inclusion criteria were identified.
Retrieved trials included 8619 and 6779 patients in GLP-1 RA and comparator groups, respectively; mean trial duration was 42 weeks.
Of those, 33, 29, 29, 33 and 31 reported information on MACE,MI, stroke, all-cause and cardiovascular mortality, respectively.
The mean age, duration of diabetes, baseline HbA1c and body mass index (BMI) of enrolled patients were 56.0 years, 6.7 years, 8.4% and 31.6 kg/m2, respectively.

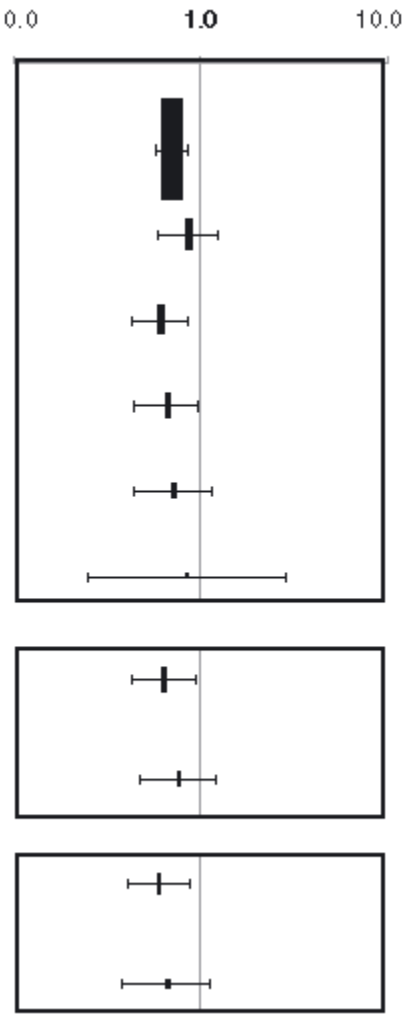


Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials

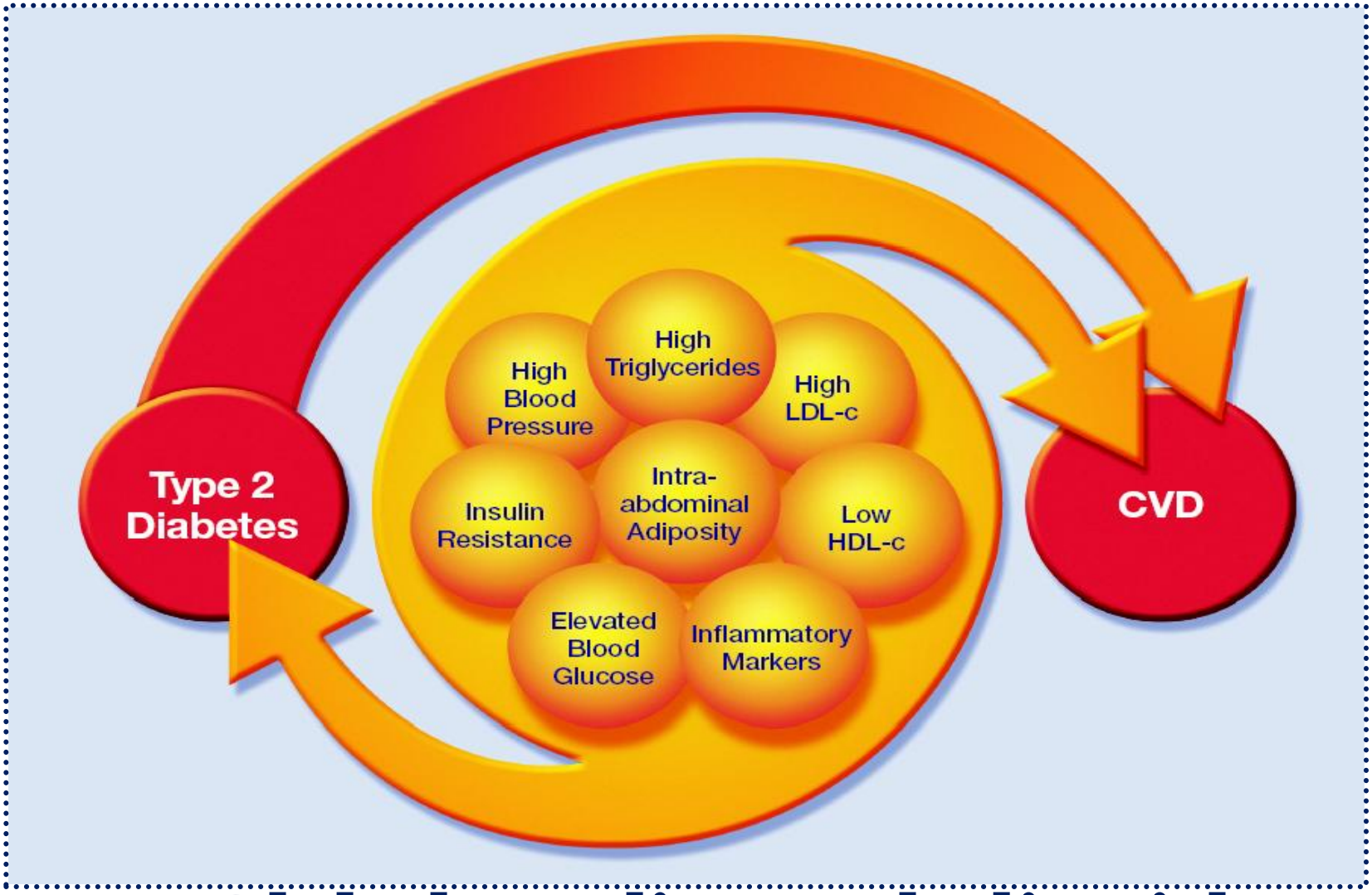
Diabetes, Obesity and Metabolism 15: 112 – 120, 2013.

42.959 patients
trial duration was 24-104 wks

	70 # trials	# trials with events	# events (DPP4i)	# events (Comparator)	MH-OR [95%, CI]	p
MACE	70	63	263	232	**0.71[0.59;0.86]**	**<0.001**
Sitagliptin	27	24	77	67	0.86[0.60;1.24]	0.430
Vildagliptin	16	15	75	74	0.61[0.43;0.86]	0.005
Saxagliptin	13	12	62	46	0.67[0.45;0.99]	0.047
Linagliptin	9	8	37	41	0.72[0.45;1.16]	0.18
Alogliptin	5	4	12	4	0.86[0.25;2.93]	0.81
AMI	**62**	**41**	**61**	**59**	**0.64[0.44;0.94]**	**0.023**
Stroke	**63**	**29**	**41**	**33**	**0.77[0.48;1.24]**	**0.290**
Mortality	**53**	**30**	**50**	**51**	**0.60[0.41;0.88]**	**0.008**
CV Mortality		**20**	**26**	**26**	**0.67[0.39;1.14]**	**0.140**



Global cardiovascular risk



Global cardiometabolic risk

Gelfand EV *et al*, 2006; Vasudevan AR *et al*, 2005

Brief review

Incretin-based therapies and cardiovascular risk

Current Medical Research & Opinion Vol. 28, No. 5, 2012, 715–721

Effects of GLP-1 receptor agonists and DPP4 inhibitors on cardiovascular risk factors

Effect	GLP-1 RA	DPP4 inh.
Reduction of HbA_{1c} and blood glucose	++	+
Reduction of blood pressure	+	+/–
Reduction of LDL cholesterol	+/–	+/–
Reduction of triglyceride	+	+/–
Increase of HDL cholesterol	+/–	+/–
Reduction of body weight	+	–

GLP-1 RA: GLP-1 receptor agonists; DPP4 inh: DPP4 inhibitors.

Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials

Diabetes, Obesity and Metabolism 15: 112–120, 2013.

HbA1c, Lipid Profile and Blood Pressure

Mean baseline HbA1c was 8.2% and this was reduced by DPP4i by −0.4(−0.5; −0.3)%, ($p < 0.01$). Furthermore, the effect of DPP4i on total and HDL cholesterol, and systolic blood pressure, was −0.28(−0.46; −0.10) mmol/l, $p = 0.02$; −0.02(−0.04; +0.01) mmol/l, $p = 0.21$; and −0.1(−1.2; +0.8) mmHg, $p = 0.76$, respectively. Expect for HbA1c, these data were available only for a small fraction of trials ($N = 10$ for total and HDL cholesterol, $N = 6$ for blood pressure). On the basis of those variations, considering that the mean endpoint total and HDL cholesterol in comparator groups were 5.15 and 1.22 mmol/l, respectively, the expected reduction in the incidence of MI, based on the UKPDS engine [18], was 7.5% of control. Considering that the observed yearly incidence of MI in comparator groups was 0.45%, the expected (UKPDS-estimated) incidence with DPP4i was 0.42%, corresponding to 79 incident cases (vs. 61 actually observed; $p = 0.12$).

Limitations of previous trials: CVD and glucose-lowering therapy

- Safety database had patient exposures of 3000–5000 patients, mostly uncontrolled long-term data[1]
- Variation in study design
  - Inclusion criteria (duration of diabetes, lack of CVD risk)
  - Length of follow-up
- CV risk assessment based on reported adverse events[1]
  - No central, blinded adjudication process
  - No planned analyses
  - Recent retrospective meta-analyses based on these data

***Parks M. Clinical perspectives on FDA guidance for industry: Diabetes mellitus –evaluating CV risk in new anti-diabetic therapies to treat T2DM. Available at*: http//www.fda.gov/downloads/Drugs/NewsEvents/UCM209087.pdf**

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

- Evaluate CV end points in Phase II and III studies.
- Establish independent CV end point adjudication committees for each Phase II or III study.
- Perform a meta-analysis of CV end points across all Phase II and III trials.
- Demonstrate that the upper bound of the two-sided 95 percent confidence interval for the estimated increase in CV risk across all Phase II and III studies has a hazard ratio (HR) less than 1.8. If the HR upper bound is less than 1.3, a post-marketing trial of CV risk may not be necessary.

For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA):

…….a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This can be achieved by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed postmarketing safety trial. This clinical trial will be a required postmarketing safety trial

The NEW ENGLAND JOURNAL of MEDICINE

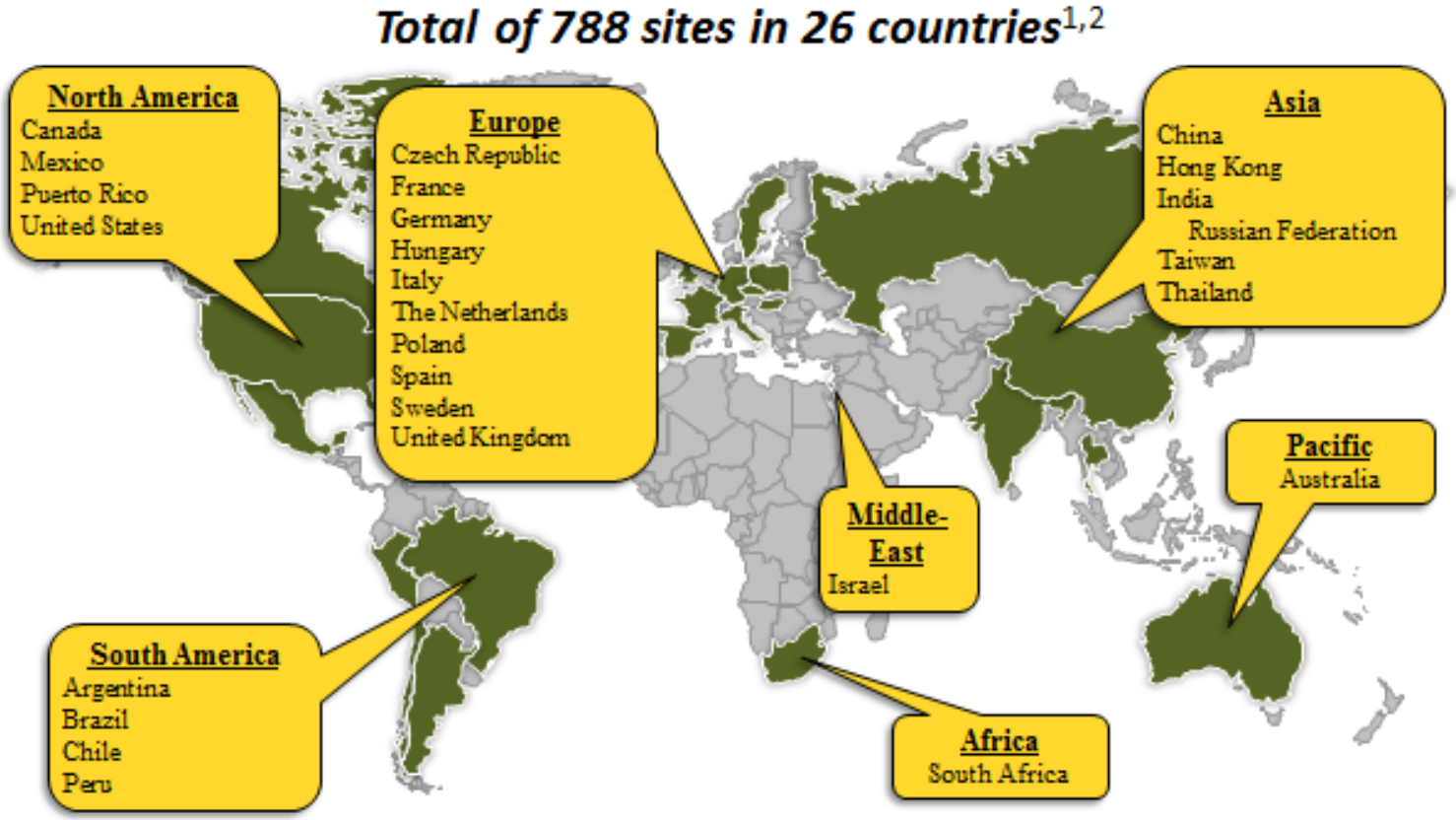
Scirica BM, et al. *N Engl J Med.* 2013; White WB, et al. *N Engl J Med.* 2013 .

	SAVOR (Saxagliptin) N = 16,492	EXAMINE (Alogliptin) N = 5400
Timing	Began 2010 Complete	Began 2009 Complete
Planned Duration	Event-driven until the occurrence of 1040 primary events	Event driven with multiple interim analyses after 80, 100, 125, 150, 550, 600, and 650 events (~5 years)
Statistical Analysis	Superiority	Non-inferiority
1° or 2° Prevention	Both	Secondary

SAVOR

Saxagliptin Assessment of Vascular Outcomes recorded in Patients with diabetes mellitus

International, Multi-Center, Phase 4 Study, Randomized, Double blind



1. Scirica BM, et al. *N Engl J Med.* 2013.10.1056/NEJMoa1307684; 2. Mosenzon O, et al. *Diabetes Metab Res Rev*. 2013;29:417-426.

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

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N Engl J Med 2013

Study Design

Superiority

N≈16,500 patients

Documented T2DM and established CVD (secondary prevention) or multiple CV risk factors (primary prevention)

RANDOMIZE 1:1 DOUBLE BLIND

Dosing based on eGFR

All other diabetes therapy per treating doctors

SAXAGLIPTIN 5 mg/d

(2.5 mg for eGFR ≤50 ml/min)

PLACEBO

Follow-up visits Q6 months

Final Visit

All other therapy for the management of the patient's diabetes and cardiovascular disease — including adding, discontinuing, or changing the dose of concomitant antihyperglycemic drugs — was at the discretion of the responsible physician.

CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate

Scirica BM, et al. *Am Heart J*. 2011;162:818-825. (Permission requested)

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Key Inclusion and Exclusion Criteria

Inclusion Criteria[1]

Documented T2DM and HbA1c ≥6.5% and <12.0%; AND

History of Established CVD
- ≥40 yrs
- Documented atherosclerosis (coronary, cerebrovascular, PV)

Multiple risk factors:
- ≥55 yrs (male) or ≥60 yrs (female)
- ≥1 additional risk factor (dyslipidemia, HTN, smoking)

Exclusion Criteria[1,2]

- Current or previous (within 6 months) incretin-based therapy†
- Acute vascular (cardiac or stroke) event <2 months before randomization

†Includes other DPP-4 inhibitors and GLP-1 agonists

GLP-1: glucagon-like peptide 1; PV: peripheral vascular ; HTN = hypertension

1. Scirica BM, et al. *N Engl J Med.* 2013.10.1056/NEJMoa1307684; 2. Scirica BM, et al. *Am Heart J*. 2011;162:818-825.

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N≈16,500 patients

RANDOMIZE 1:1 DOUBLE BLIND

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(2.5 mg for eGFR ≤50 ml/min)

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Final Visit

Primary endpoint

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

Secondar endpoint

Primary composite + Hospidalization for HF and coronary revascularization or unstable angina

CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate

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N Engl J Med 2013

Prespecified Clinical End Points

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

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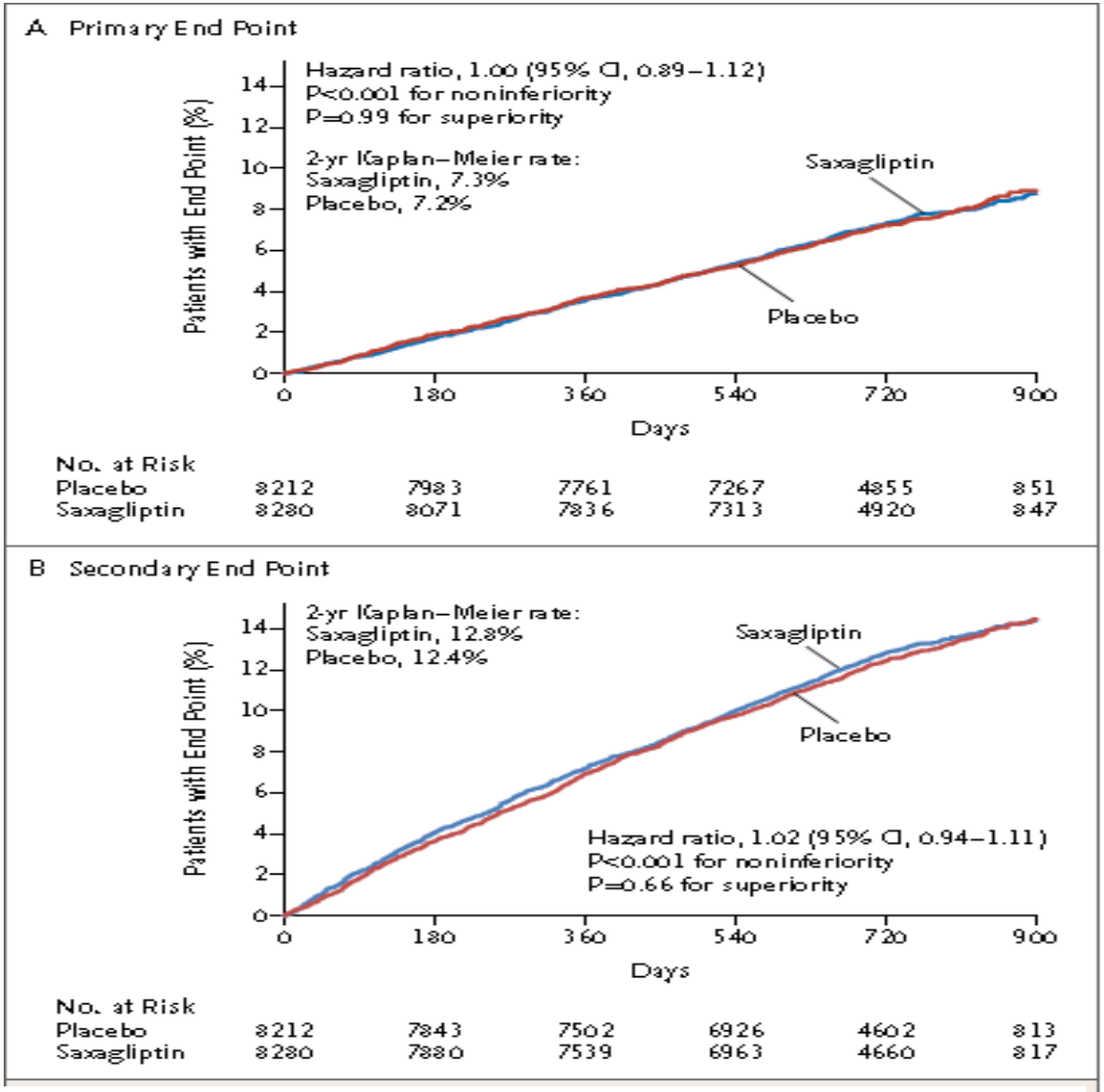
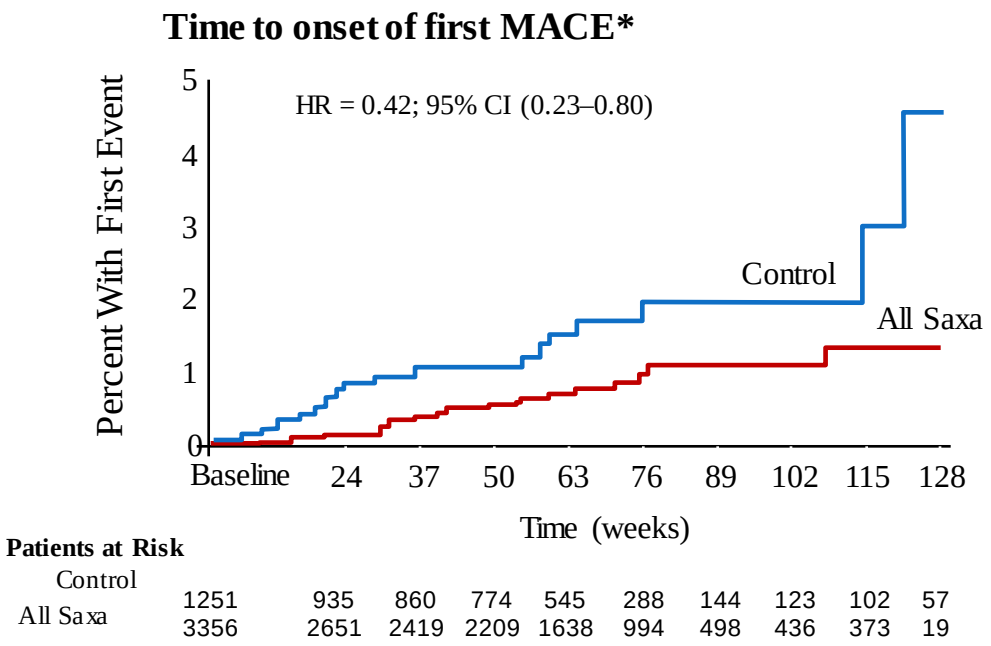


In this randomized, placebo-controlled trial, the DPP-4 inhibitor saxagliptin neither reduced nor increased the risk of the primary composite end point of cardiovascular death, myocardial infarction, or ischemic stroke, when added to the standard of care in patients at high risk for cardiovascular events, thus meeting the criterion for non inferiority to placebo but not providing any cardioprotective benefit.

Saxagliptin CV Safety

Pooled Analysis *(8 trials)* From Phase 2/3 Development Program (N = 4607)

- Saxagliptin-treated patients vs control patients had a lower rate of CEC-adjudicated MACE



Conclusion: No increased risk of CV death/MI/stroke

*Includes CV death, MI, and stroke ; CEC, clinical events committee; MACE, major adverse CV event

Frederich R, et al. *Postgrad Med*. 2010;122:16-27.

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N≈16,500 patients

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Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

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EXAMINE

Examination Outcomes with Alogliptin versus Standard of Care

Multi-Center, Phase 4 Study, Randomized, Double blind

	EXAMINE (Alogliptin) N = 5400
Timing	Began 2009 Complete
Planned Duration	Event driven with multiple interim analyses after 80, 100, 125, 150, 550, 600, and 650 events (~5 years)
Statistical Analysis	Non-inferiority
1° or 2° Prevention	Secondary

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N Engl J Med 2013

Study Design

Non inferiority

N≈5,380 patients

Documented T2DM and acute coronary syndrome within 15-90 days before randomization (secondary prevention)

RANDOMIZE 1:1 DOUBLE BLIND

Dosing based on eGFR

ALOGLIPTIN 25 mg/d

12.5 mg for eGFR 60 -30 ml/min

6.5 mg for eGFR < 30 ml/min

PLACEBO

Follow-up visits 1, 3, 6, 9, 12 months after randomization

Final Visit

Primary endpoint
CV death, non-fatal MI, non-fatal ischemic stroke

Secondar endpoint
Primary composite + urgent revascularization due to unstable angina within 24 hours after hospital admission

Patients were randomly assigned to receive alo-
gli… double-
b… of-care
t… ough-
c… eceive
s… abetes
a… to re-
g… leared

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MAJOR SAFETY END POIN

End Point	Placebo (N=2679)	Alogliptin (N=2701)	Hazard Ratio for Alogliptin Group (95% CI)	P Value*
	no. (%)			
Primary end point†	316 (11.8)	305 (11.3)	0.96 (≤1.16)‡	0.32
Components of primary end point				
Death from cardiovascular causes	111 (4.1)	89 (3.3)	0.79 (0.60–1.04)	0.10
Nonfatal myocardial infarction	173 (6.5)	187 (6.9)	1.08 (0.88–1.33)	0.47
Nonfatal stroke	32 (1.2)	29 (1.1)	0.91 (0.55–1.50)	0.71
Principal secondary end point§	359 (13.4)	344 (12.7)	0.95 (≤1.14)‡	0.26
Other end points				
Death from any cause	173 (6.5)	153 (5.7)	0.88 (0.71–1.09)	0.23
Death from cardiovascular causes¶	130 (4.9)	112 (4.1)	0.85 (0.66–1.10)	0.21

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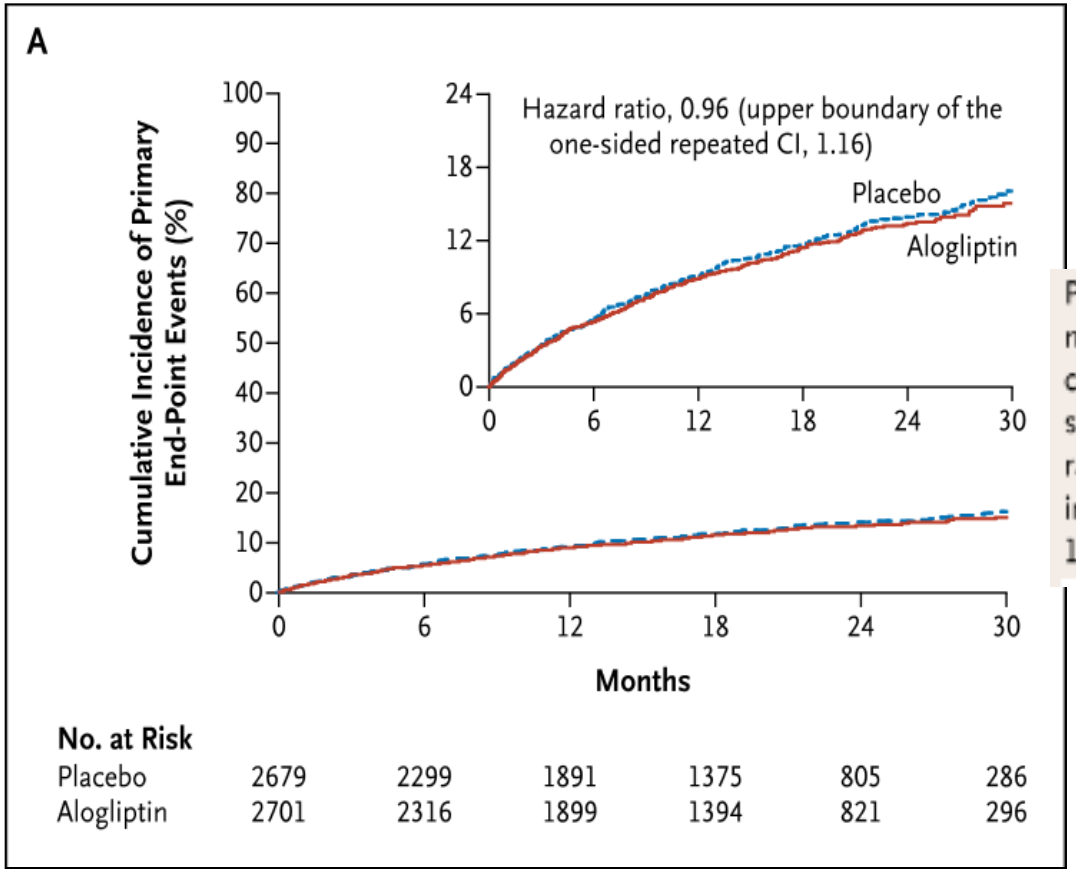

Panel A shows the time to the first occurrence of a primary end-point event — death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. After a median exposure of 18 months, the rates of the primary composite end point were similar in the alogliptin and placebo groups (11.3% and 11.8%, respectively).

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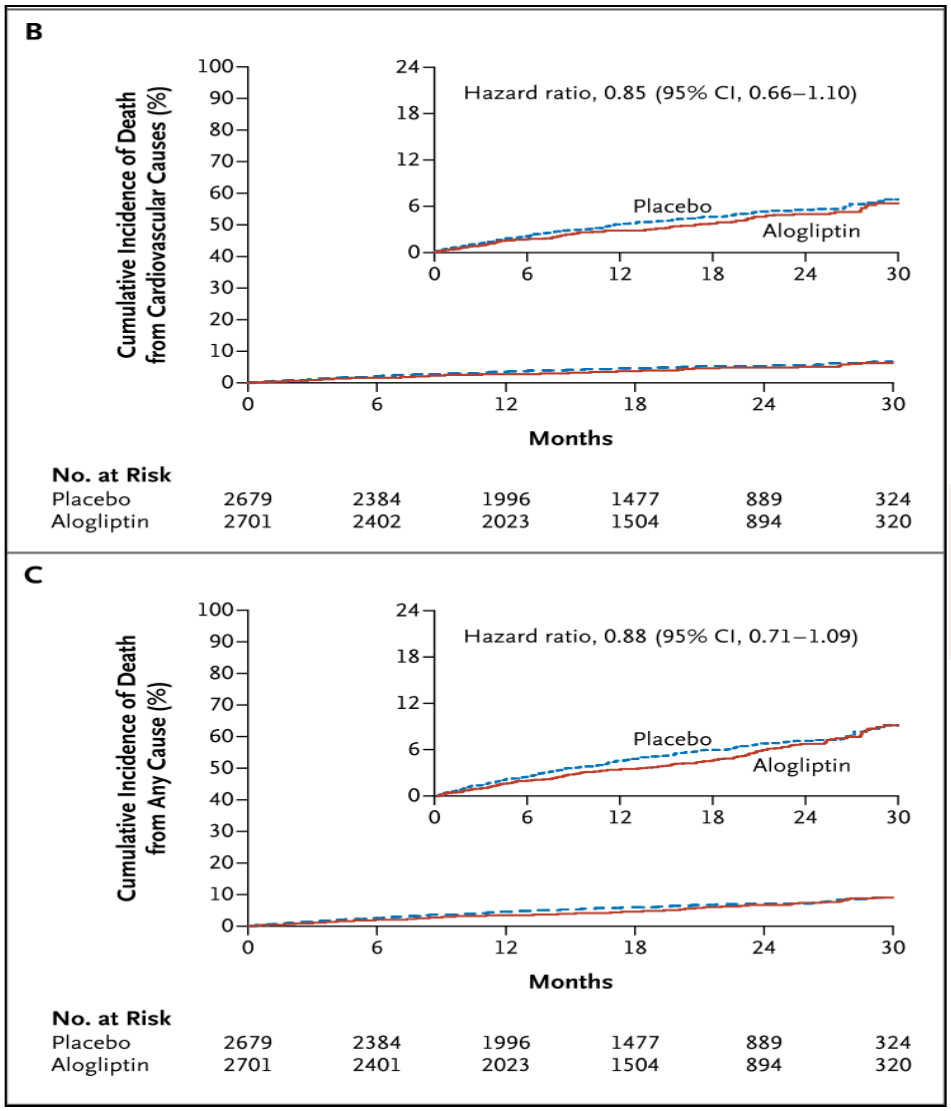

Panel B shows the time to death from cardiovascular causes, and Panel C, the time to death from any cause. In each panel, the inset shows the same data on an enlarged y axis.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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Conclusion:

In patients with type 2 diabetes and recent acute coronary syndrome, major adverse cardiovascular event rates for the DPP-4 inhibitor alogliptin were not increased compared with placebo

Numerous Studies Assessing CV Outcomes in T2DM Drugs Are Either Recently Completed or Ongoing

Trial Name	Drug	Target Enrollment	Timing*
DPP-4 Inhibitors			
SAVOR	Saxagliptin	N=16,492	Began 2010; Complete
EXAMINE	Alogliptin	N=5384	Began 2009; Complete
TECOS	Sitagliptin	N=14,000	Began 2008; Ending 2014
CAROLINA	Linagliptin	N=6000	Began 2010; Ending 2018
CARMELINA	Linagliptin	N=8300	Began 2013; Ending 2018
GLP-1 Agonists			
ELIXA	Lixisenatide	N=6000	Began 2010; Ending 2014
EXSCEL	Exenatide	N=9500	Began 2010; Ending 2017
LEADER	Liraglutide	N=9340	Began 2010; Ending 2016
REWIND	Dulaglutide	N=9622	Began 2011; Ending 2019
SUSTAIN 6	Semaglutide	N=3260	Began 2013; Ending 2016
SGLT-2 Inhibitors			
CANVAS	Canagliflozin	N=4410	Began 2009; Ending 2018
C-SCADE 8	Empagliflozin	N=7000	Began 2010; Ending 2018
DECLARE	Dapagliflozin	N=17,150	Began 2013; Ending 2019

*Trial ending dates are anticipated based on publicly available information.

Clinicaltrials.gov; Accessed on Aug 12, 2013.