Nuovi farmaci antidiabetici e prevenzione cardiovascolare

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Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Astra Zeneca	Takeda
Bayer	Roche
Boehringer	Medtronic
Lifescan	Johnson & Johnson
Lilly	Jannsen
Novo Nordisk	Sanofy

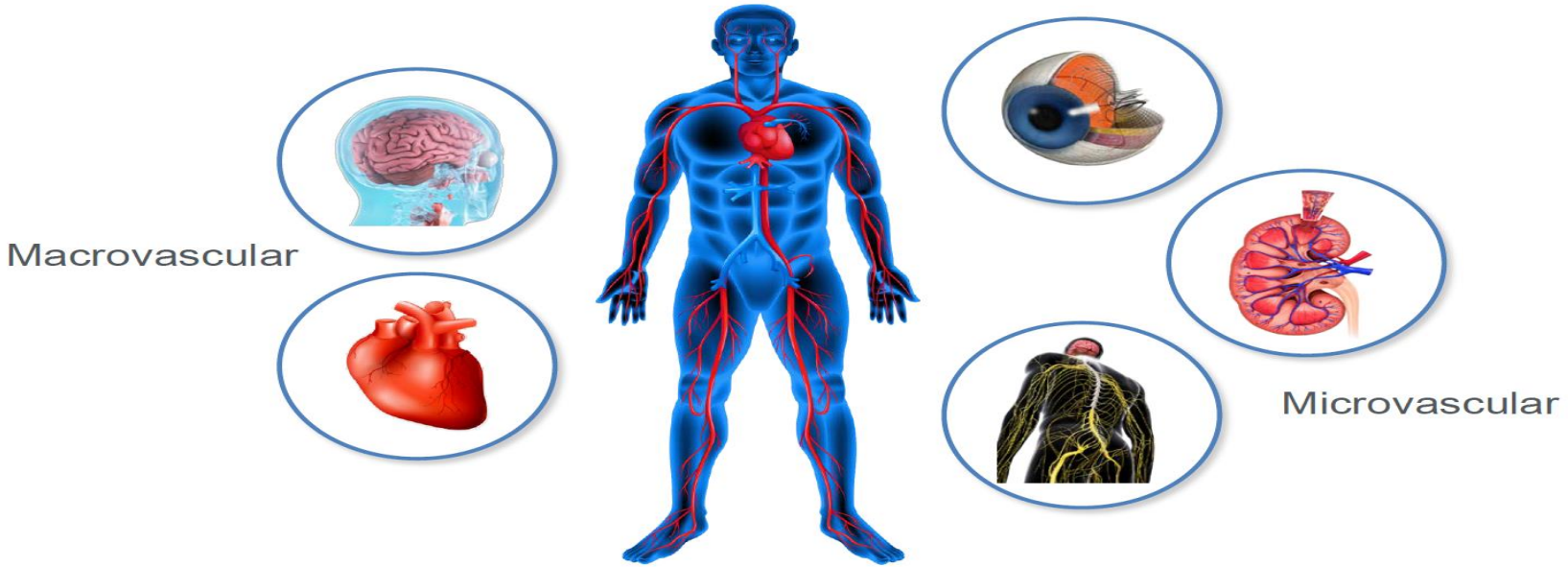
Nuovi farmaci antidiabetici e prevenzione cardiovascolare

GLP-1 RA, DPPIV inibitori, SGLT2 inibitori

Una nuova frontiera terapeutica ?

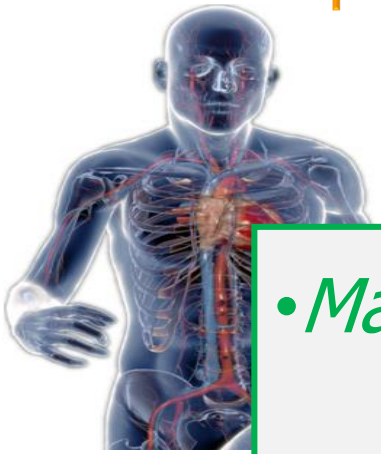
Complicanze croniche del Diabete Mellito

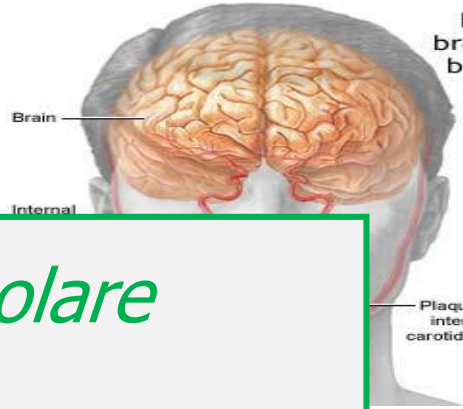
T2D is a major and independent risk factor for both microvascular and macrovascular complications



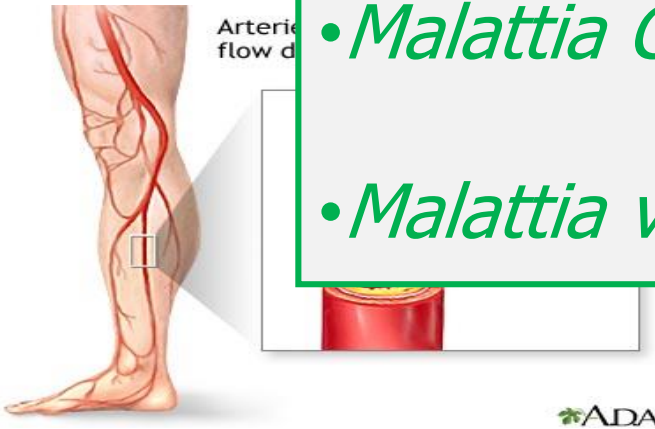
1. World Health Organization. http://www.who.int/diabetes/action_online/basics/en/index3.html

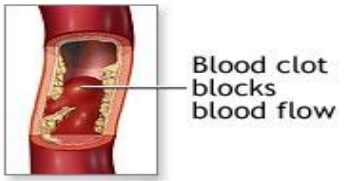
Complicanze croniche del Diabete Mellito





- *Malattia Cerebro-vascolare*
- *Malattia Coronarica*
- *Malattia vascolare periferica*





“ DIABETES IS A CARDIOVASCULAR DISEASE DIAGNOSED BY MEASURING GLYCAEMIA”

Klas Malmberg -2001

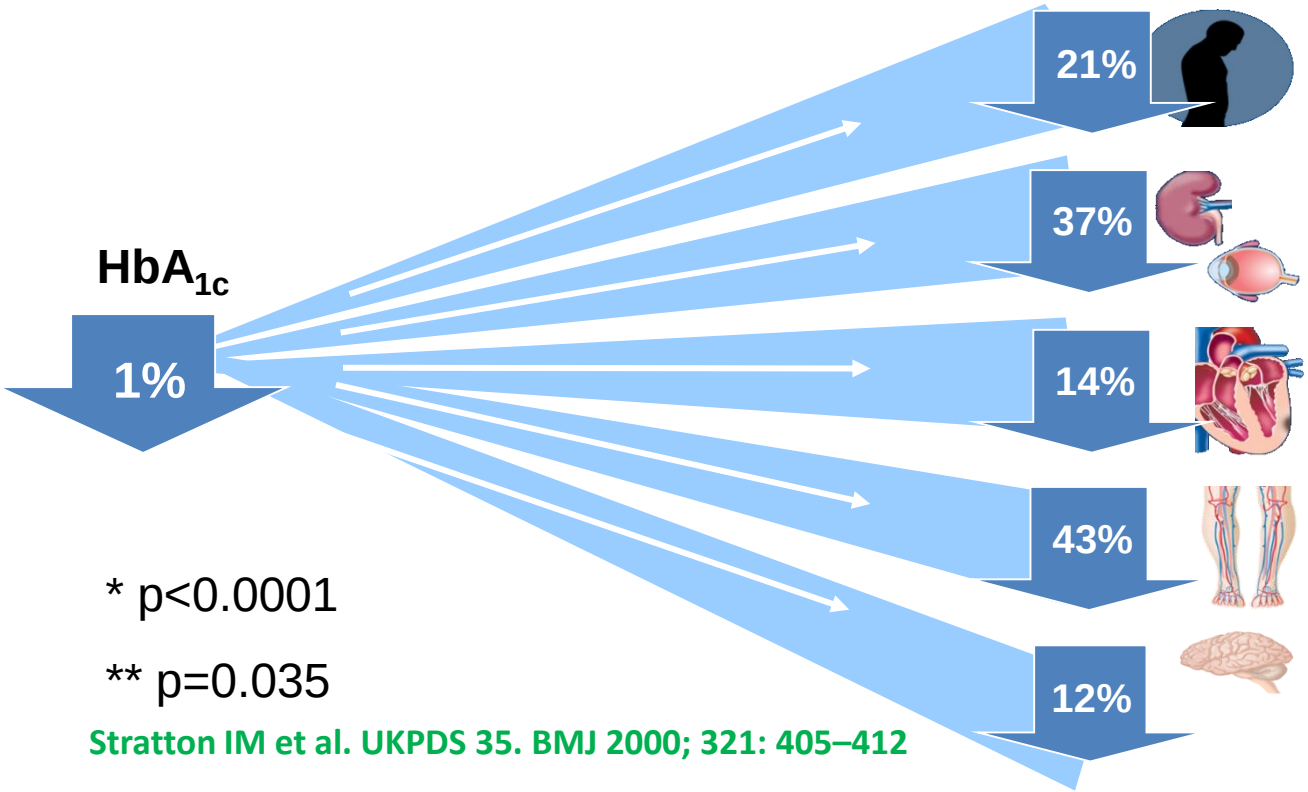
LA MALATTIA CARDIOVASCOLARE NEL DIABETE TIPO 2

- E' la più importante causa di morbidità e mortalità
- Il 50% dei diabetici di tipo 2 ha la malattia coronarica, la metà di essi senza sintomi o segni ECG
- Il rischio di IMA aumenta da 3 a 5 volte
- La sopravvivenza dopo IMA, CABG e PTCA è ridotta
- Il rischio di stroke aumenta da 2 a 3 volte
- Il rischio di amputazioni aumenta di 10-15 volte

Il concetto di Diabete e malattia cardiovascolare si è evoluto da fattore di rischio di patologia cardiovascolare ad equivalente di patologia cardiovascolare

Siete tutti d'accordo con questa affermazione?

UKPDS: Tight Glycaemic Control Reduces Complications



Deaths related to diabetes *

Microvascular complications e.g. kidney disease and blindness *

Heart attack *

Amputation or fatal peripheral blood vessel disease *

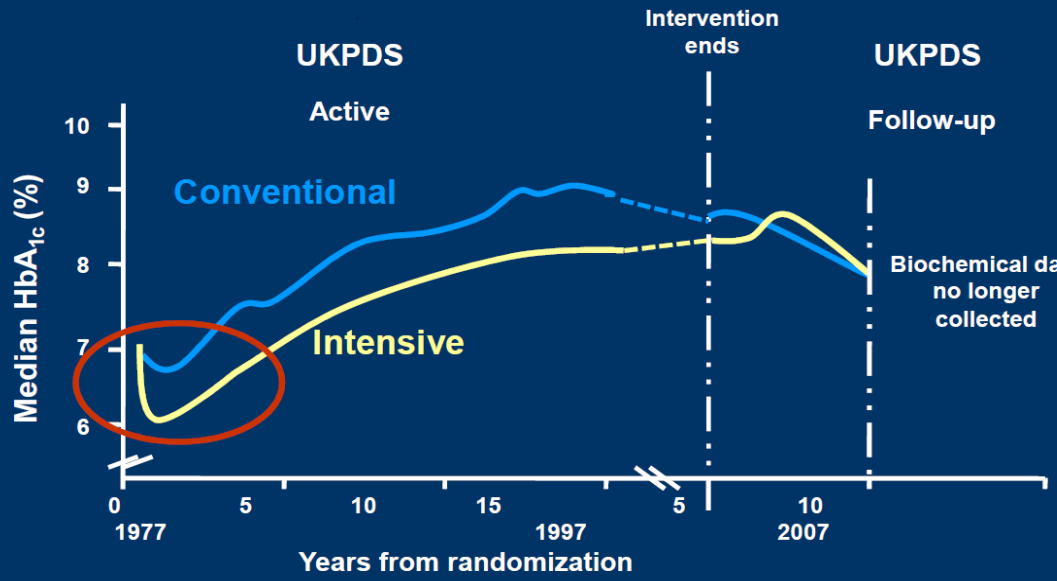
Stroke **

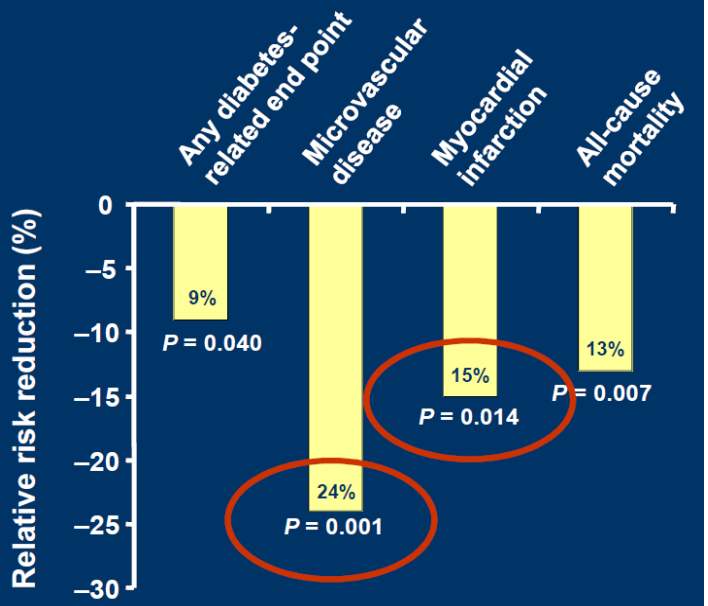
* p<0.0001

** p=0.035

Stratton IM et al. UKPDS 35. BMJ 2000; 321: 405–412

UKPDS: long-term follow-up and legacy effect





Bailey CJ & Day C. *Br J Diabetes Vasc Dis* 2008; **8**:242–247.
Holman RR, *et al*. *N Engl J Med* 2008; **359**:1577–1589.

UKPDS: post-trial follow-up and legacy effect

After median 8.5 years post-trial follow-up

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

RRR = Relative Risk Reduction, P = Log Rank

Translating clinical trials

Into

Clinical Practice

ACCORD

ADVANCE

VADT

?

STENO-2

ADOPT

?

UKPDS

?

Lot's RCTs

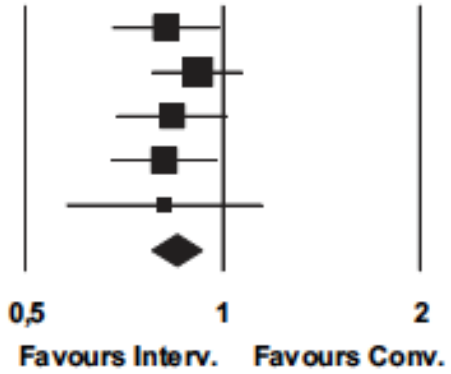
On drugs

Glycemic control and risk of MI in T2DM

Meta-analysis of RCTs on intensification of therapy

B Myocardial infarction

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
ACCORD	0,819	0,677	0,989	-2,074	0,038
ADVANCE	0,915	0,780	1,072	-1,098	0,272
PROACTIVE	0,837	0,690	1,016	-1,800	0,072
UKPDS 33+34	0,814	0,675	0,981	-2,159	0,031
VADT	0,814	0,577	1,148	-1,174	0,240
OVERALL	0,849	0,778	0,926	-3,678	0,000



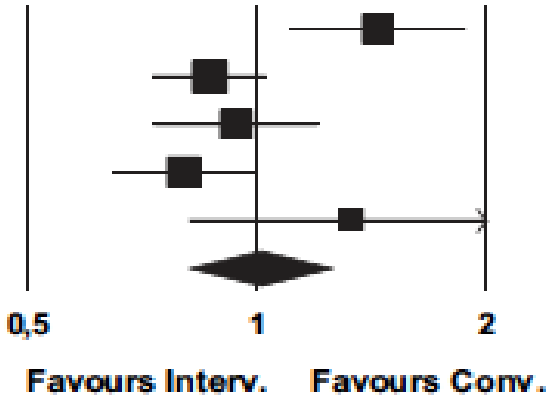
Mannucci E et al. *Nutr Metab Cardiovasc Dis* 19: 604-12, 2009

Glycemic control and cardiovascular mortality in T2DM

Meta-analysis of RCTs on intensification of therapy

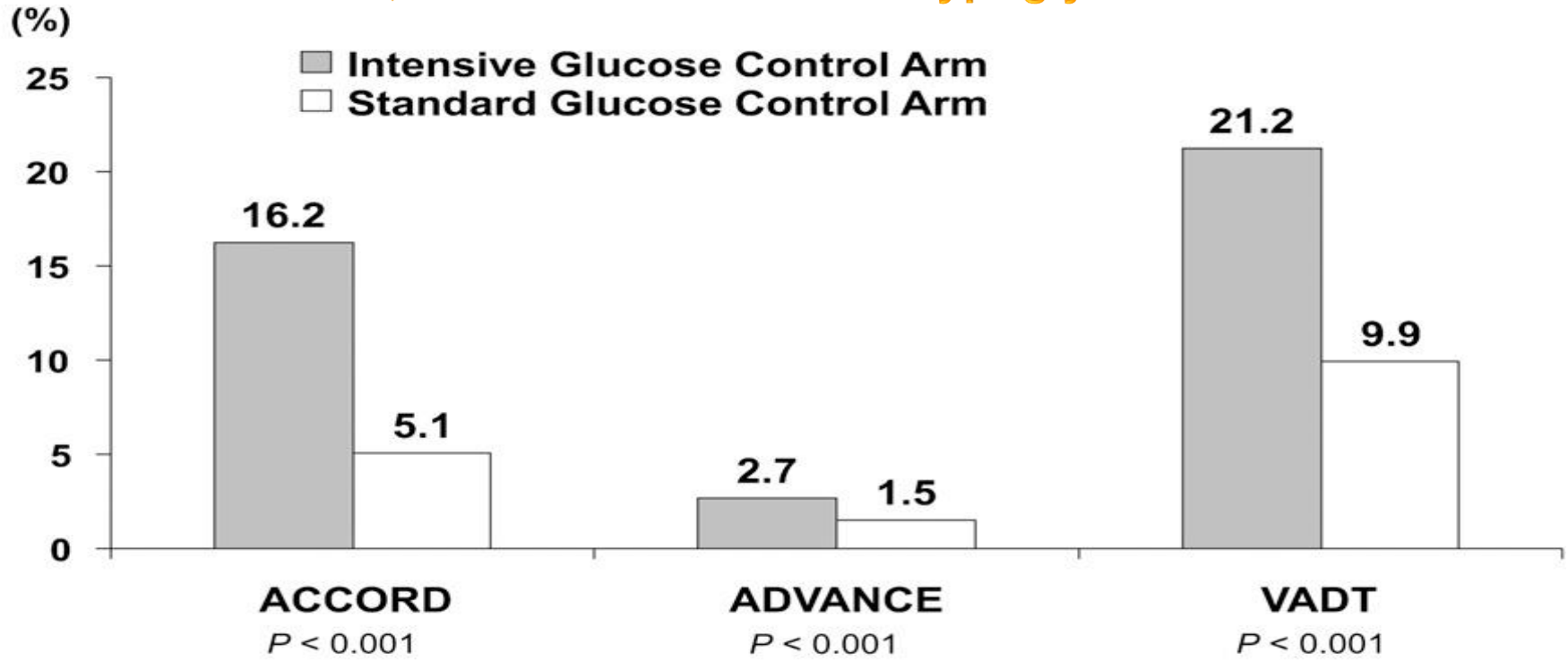
F Cardiovascular mortality

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
ACCORD	1,447	1,108	1,888	2,718	0,007
ADVANCE	0,869	0,731	1,033	-1,589	0,112
PROACTIVE	0,941	0,734	1,206	-0,480	0,631
UKPDS 33+34	0,805	0,647	1,001	-1,950	0,051
VADT	1,335	0,816	2,184	1,150	0,250
OVERALL	1,012	0,815	1,257	0,110	0,912



Mannucci E et al. *Nutr Metab Cardiovasc Dis* 19: 604-12, 2009

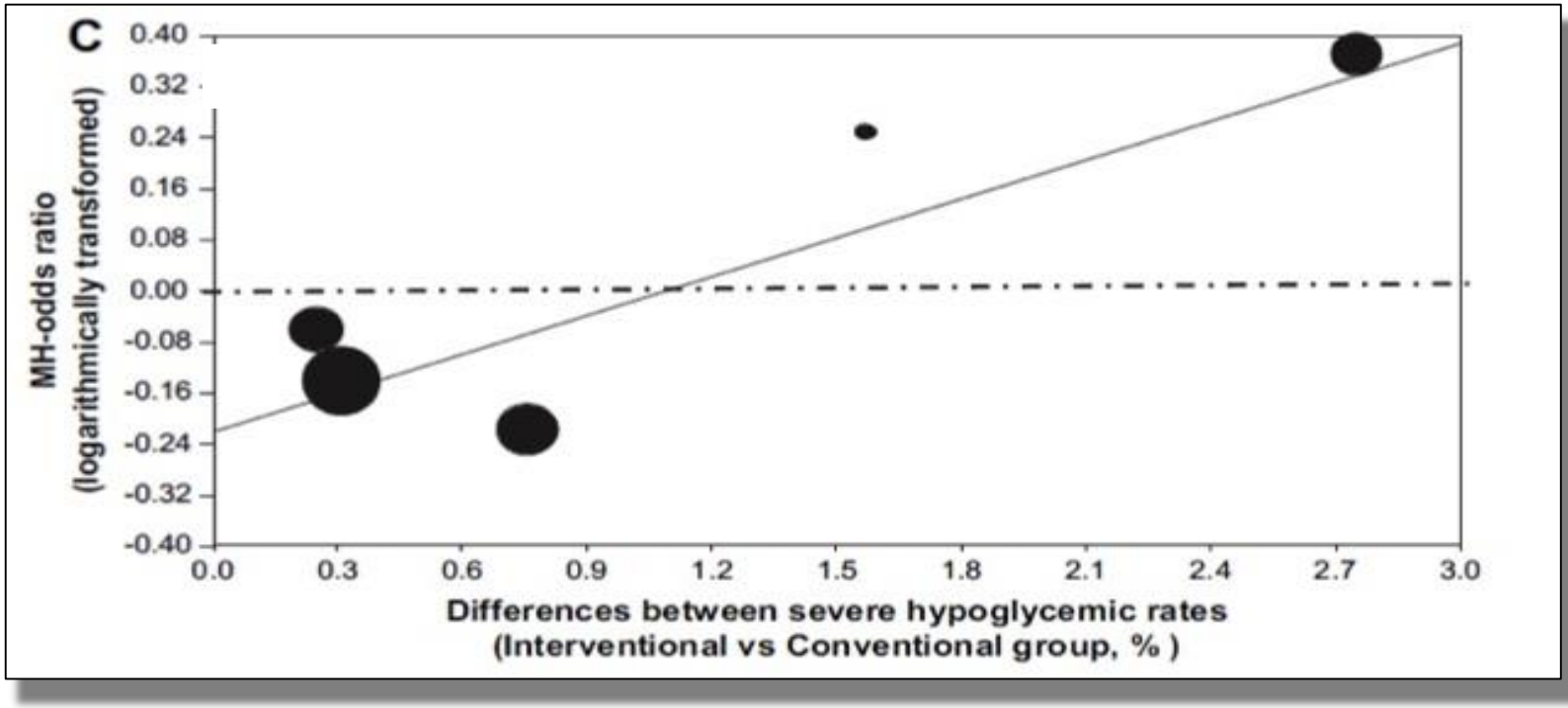
ACCORD, ADVANCE and VADT: Hypoglycemia



Insulin therapy	ACCORD		ADVANCE		VADT	
at entry (%)	35		1.5		52	
final (%)	77	55	40	24	89	74

Glycemic Hypoglycemia and cardiovascular mortality in T2DM

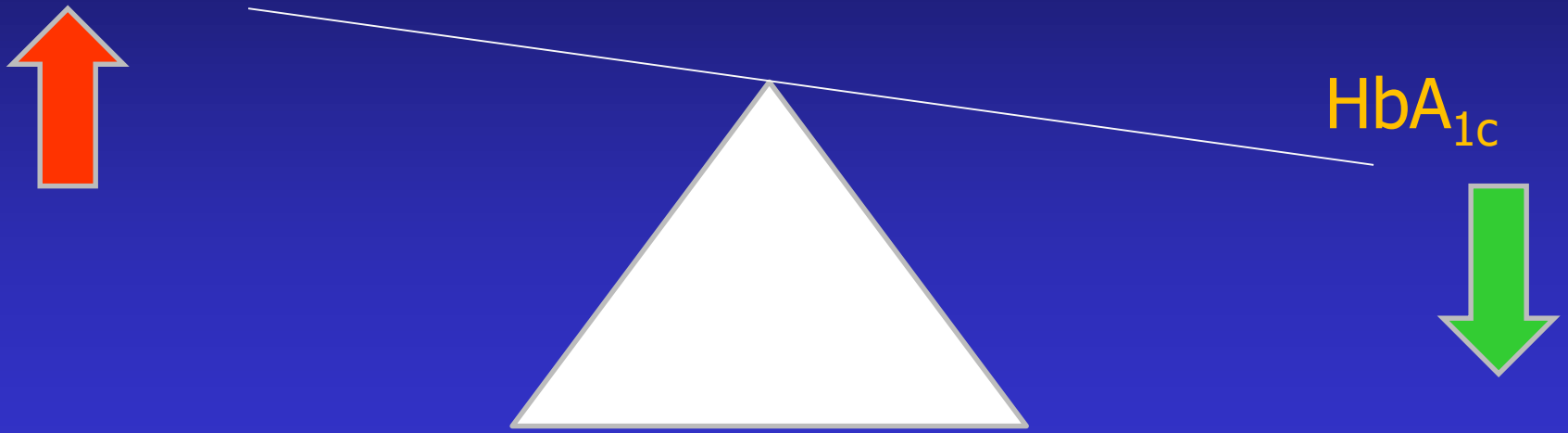
Meta-regression of RCTs on intensification of therapy



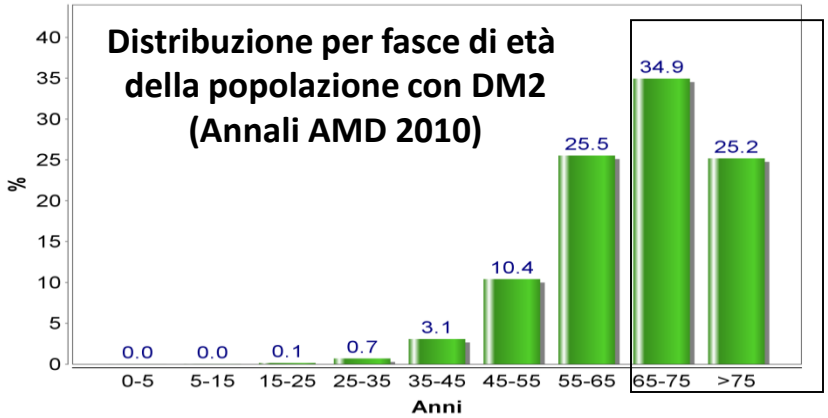
Mannucci E et al. *Nutr Metab Cardiovasc Dis* 19: 604-12, 2009

The challenge of blood glucose control

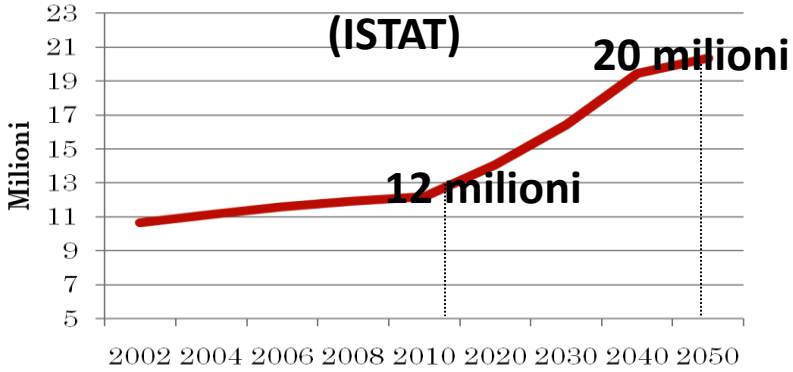
Hypoglycaemia/Weight gain/Quality of life



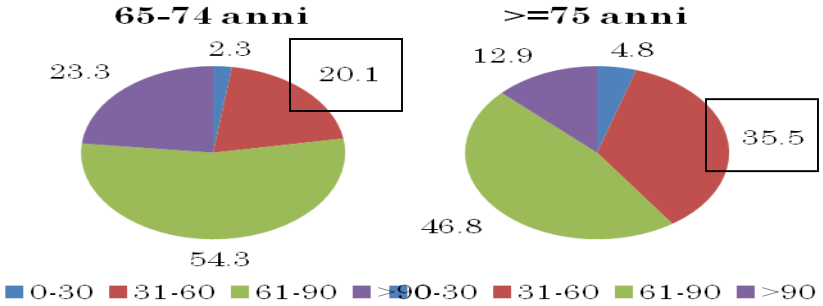
L'età avanzata



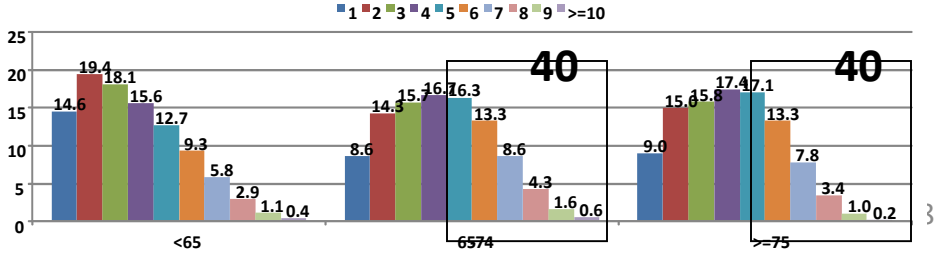
Prevalenza della popolazione di età >=65 anni in Italia e proiezioni (ISTAT)



La ridotta funzionalità renale



Le politerapie e le pluripatologie



Cosa dicono le Linee Guida….

Figura 2. Flow-chart per la terapia del diabete mellito di tipo 2.

Iniziare con solo intervento su stile di vita (se non grave scompenso metabolico [ref. 1])

↓

Aggiungere gradualmente metformina, fino alla dose di almeno 2 g/die

↓

Add on a metformina	Ipoglic.	Peso	Effetti indesid.	CVD	Fattori rischio CV	Scomp. cardiaco	Effetti GI	Costo
Gliptina	1A	1B	Rari	1A	1B	2B (2)	1A	Elevato
A.R. GLP-1	1A	1A	Non indicato in IRC	3B	1A	2B	1C	Elevato
Sulfonilurea o repaglinide	1D	1D	Non indicato in IRC (3)	3C (2)	1B	1B	1A	Basso
Pioglitazione	1A	1D	Fratture	1A	1A	1E	1A	Medio
Acarbosio	1A	1D	Rari	2B	2B	3C	1C	Basso
Gliflozina	1A	1A	Infezioni GU	3C	2B	2B	1A	???
Insulina basale	1D	1A	Rari	1B	1A	1B	1A	Medio

In presenza di un fallimento della terapia iniziale volta a modificare lo stile di vita, prescrivere metformina, che

Colori:

- effetto o parametro negativo o sconsigliato
- effetto o parametro parzialmente negativo o sconsigliato
- effetto o parametro positivo o probabilmente positivo
- il farmaco non ha effetti significativi sul parametro o viene dato un giudizio neutro

Sigle: rappresentano il grado di evidenza (1-6) e di forza (A-E).

Flow chart per la terapia del diabete mellito di tipo 2.

AACE/ACE Consensus Statement

AACE/ACE Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm – *2016 Executive Summary*
ENDOCRINE PRACTICE Vol 22 No. 1 January 2016

PROFILES OF ANTIDIABETIC MEDICATIONS

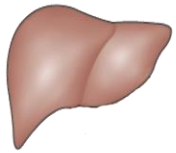
	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/ GU	Contra-indicated CKD Stage 3B,4,5	Exenatide Not Indicated CrCl < 30	Not Effective with eGFR < 45 / Genital Mycotic Infections	Dose Adjustment Necessary (Except Linagliptin)	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GISx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
ASCVD	Benefit		Possible Benefit			Neutral	?		Safe		
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

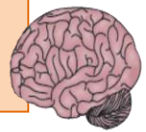
GLP-1: UN AMPIO SPETTRO DI AZIONI BIOLOGICHE

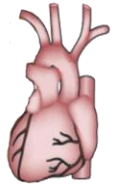
Meier JJ Nat Rev Endocrinol. 2012;8:728-42

Fegato
↑ Immagazzinamento del glicogeno

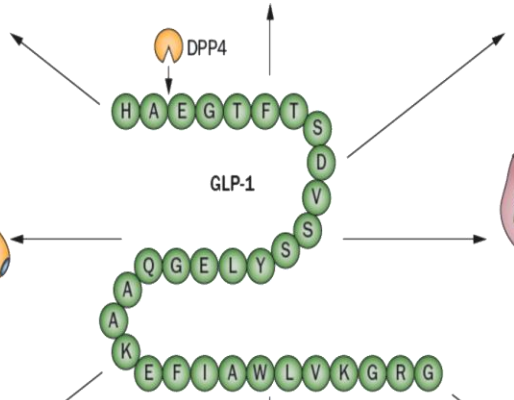


Cervello
↑ Neuroprotezione
↑ Memoria

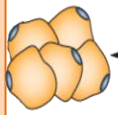


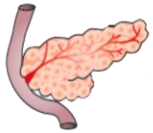


Cuore
↑ Contrattilità miocardica
↑ Frequenza cardiaca
↑ Captazione del glucosio a livello del miocardio
↓ Danno miocardico indotto da ischemia



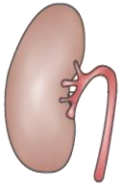
Cellule adipose
↑ Captazione del glucosio
↑ Lipolisi

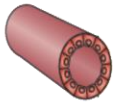




Pancreas
↑ Formazione di nuove cellule β
↓ Apoptosi delle cellule β
↑ Biosintesi dell'insulina

Rene
↑ Natriuresi

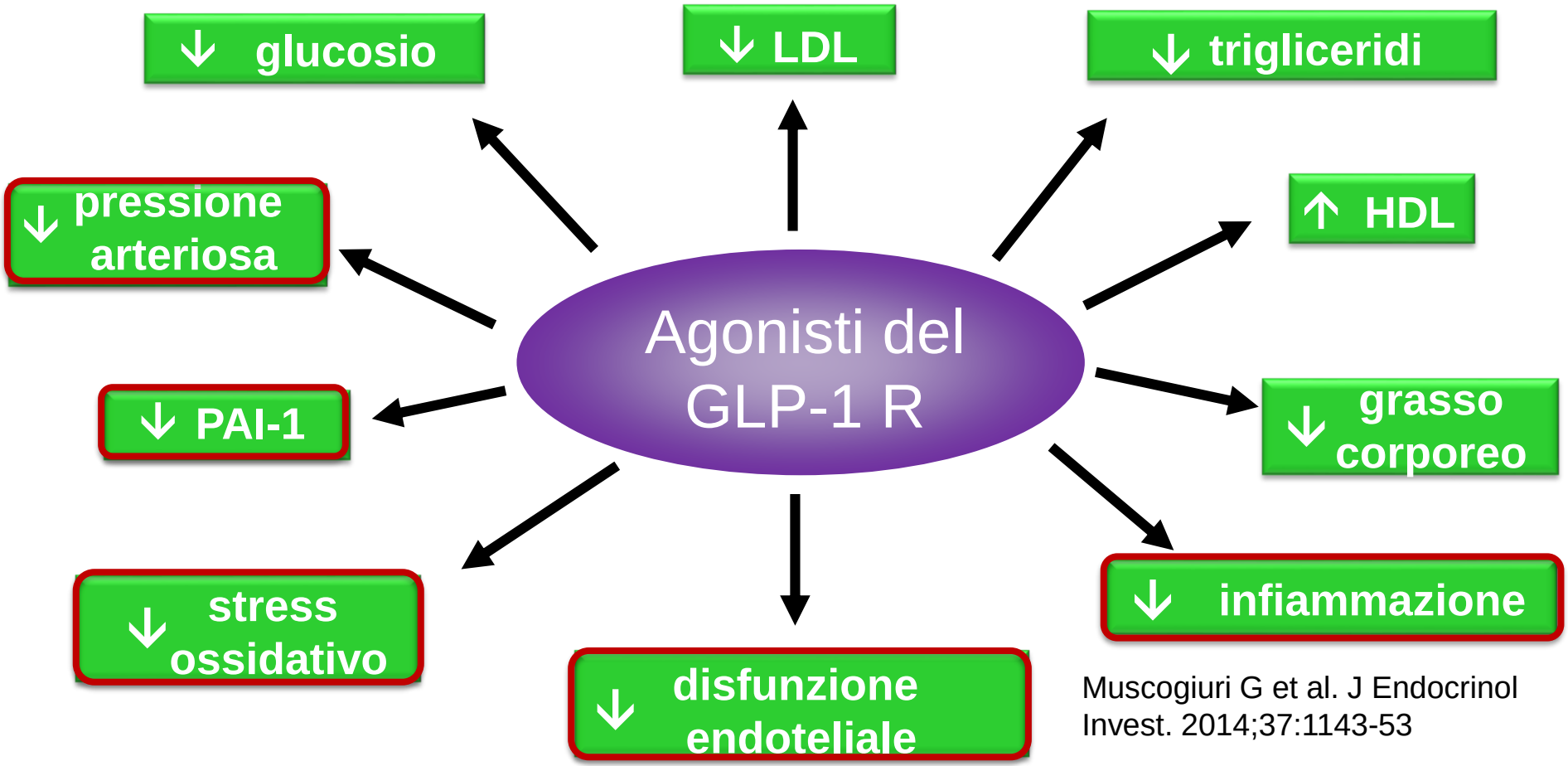




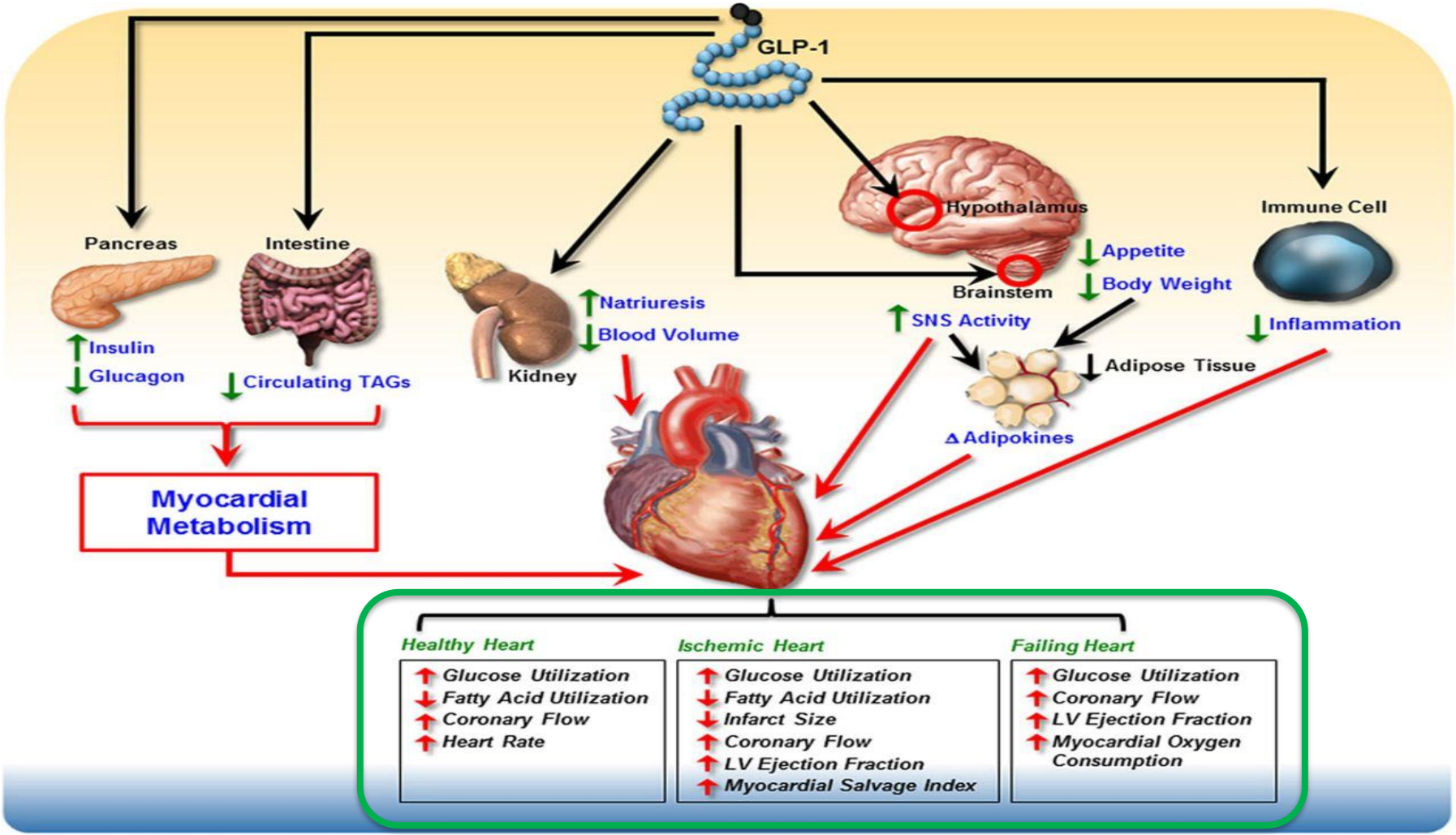
Vaso sanguigno
↑ Vasodilatazione endotelio-dipendente

Muscolo scheletrico
↑ Captazione del glucosio

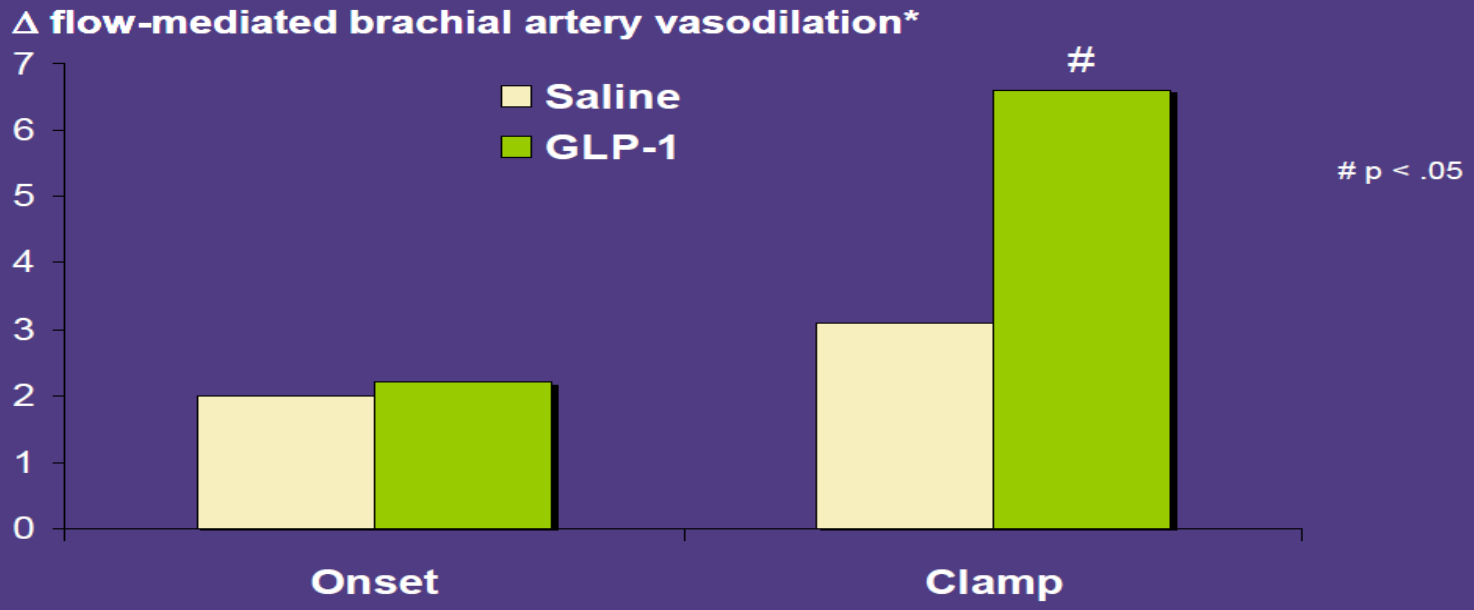
DIVERSI EFFETTI BENEFICI DEI GLP-1 RA



Muscogiuri G et al. J Endocrinol Invest. 2014;37:1143-53


GLP-1
Pancreas
Intestine
Kidney
Hypothalamus
Brainstem
Immune Cell
Insulin
Glucagon
Circulating TAGs
Natriuresis
Blood Volume
Appetite
Body Weight
SNS Activity
Inflammation
Adipose Tissue
Δ Adipokines
Myocardial Metabolism
Healthy Heart
Glucose Utilization
Fatty Acid Utilization
Coronary Flow
Heart Rate
Ischemic Heart
Glucose Utilization
Fatty Acid Utilization
Infarct Size
Coronary Flow
LV Ejection Fraction
Myocardial Salvage Index
Failing Heart
Glucose Utilization
Coronary Flow
LV Ejection Fraction
Myocardial Oxygen Consumption

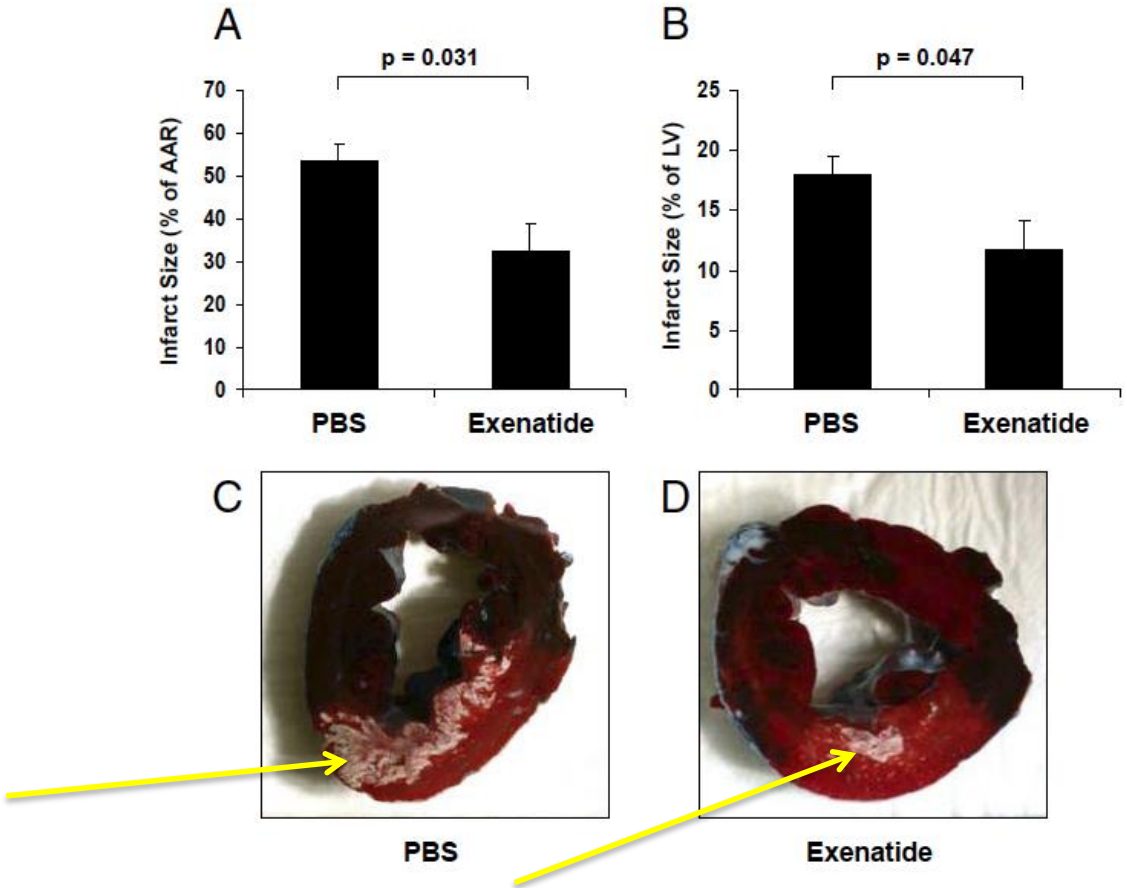
In pazienti diabetici di tipo 2 con coronaropatia stabile la somministrazione acuta di GLP-1 induce un miglioramento della funzione endoteliale



* Measured at onset and at steady-state hyperinsulinemic clamp during GLP-1 or saline infusion

Nystrom T et al, Am J Physiol Endocrinol Metab 2004;287:E1209-E1215

Exenatide Reduces Infarct Size in a porcine model of Ischemia and Reperfusion Injury



Timmers L. **JACC** 2009

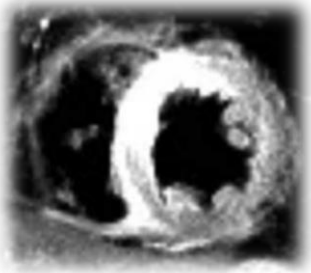
European Heart Journal (2012) 33, 1491–1499
doi:10.1093/eurheartj/ehr309

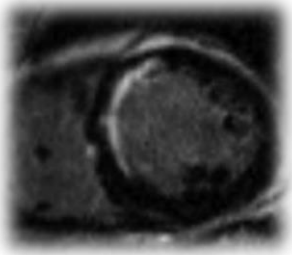
CLINICAL RESEARCH
Acute coronary syndromes

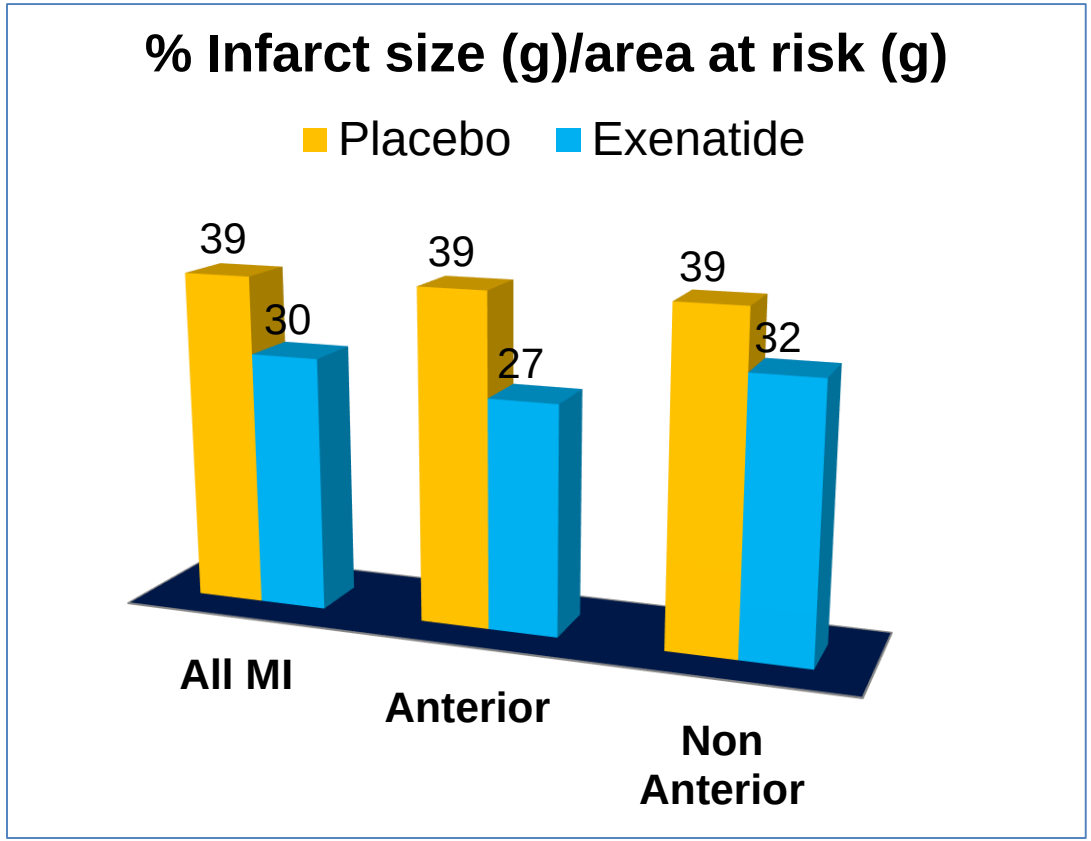
Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction

Jacob Lønborg[1*], Niels Vejlstrup[1], Henning Kelbæk[1], Hans Erik Bøtker[2], Won Yong Kim[2], Anders B. Mathiasen[1], Erik Jørgensen[1], Steffen Helqvist[1], Kari Saunamäki[1], Peter Clemmensen[1], Lene Holmvang[1], Leif Thuesen[2], Lars Romer Krusell[2], Jan S. Jensen[3], Lars Køber[1], Marek Treiman[4], Jens Juul Holst[4], and Thomas Engstrøm[1]

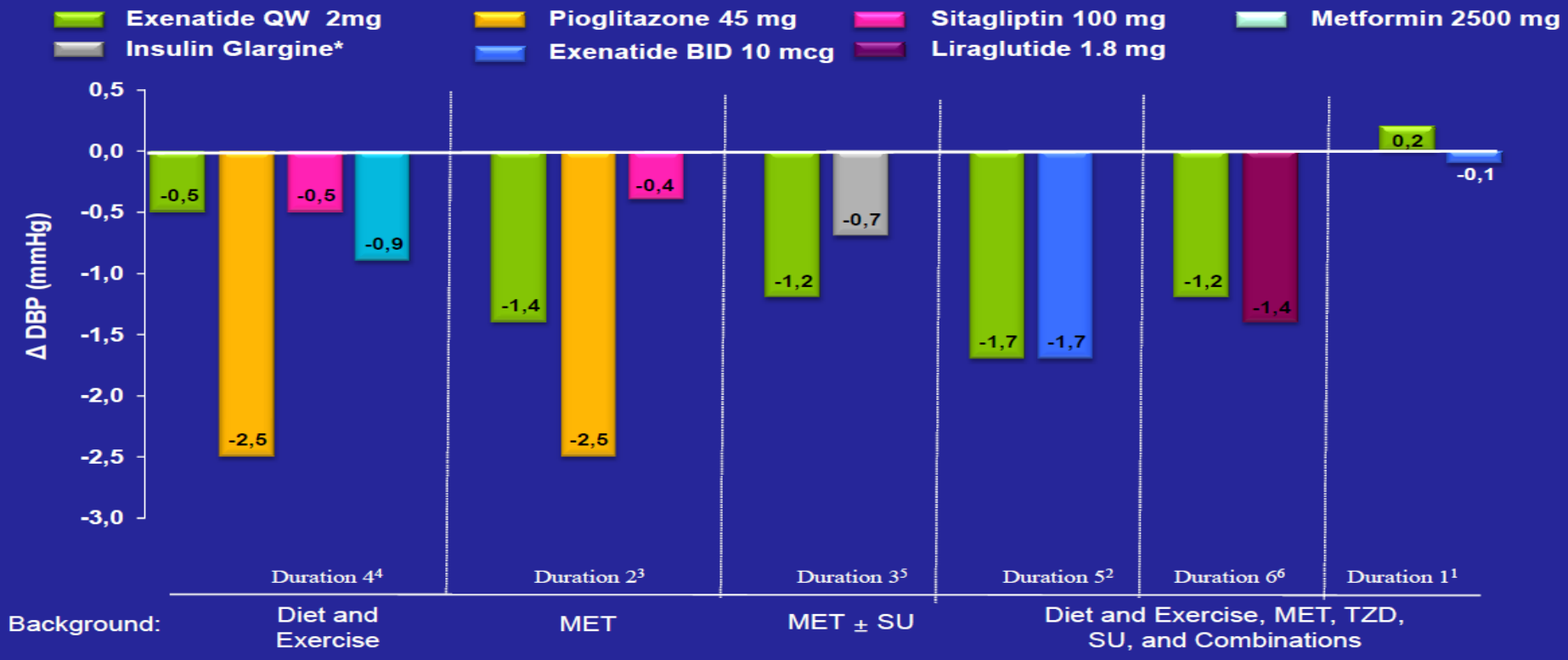
in 172 pazienti con **IMA con STEMI**, in corso di trombolisi **(pPCI)** randomizzati a **placebo** o **Exenatide**







Effect of Exenatide QW on Diastolic Blood Pressure in Phase 3 Clinical Trials



Drucker 2008; Blevins 2011; Bergenstal 2010; Diamant 2011; Diamant 2010; Buse 2011; Buse 2013;

*Insulin Glargine Treat to Target A1c <7.0%

Very low Incidence of Hypoglycemic Events with Vildagliptin in Monotherapy

	Vilda 50 mg daily N=323 n (%)	Vilda 100 mg daily N=1683 n (%)	Met up to 1 g daily N=252 n (%)	Rosi 8 mg daily N=267 n (%)	Pio 30 mg daily N=216 n (%)	PBO N=255 n (%)
No. of patients affected	2 (0.6)	7 (0.4)	1 (0.4)	1 (0.4)	0	0
No. D/C for hypoglycemic events	0	0	0	0	0	0
Severity						
Grade 1	2	7	1	1	0	0
Grade 2	0	0	0	0	0	0
Suspected grade 2	0	0	0	0	0	0

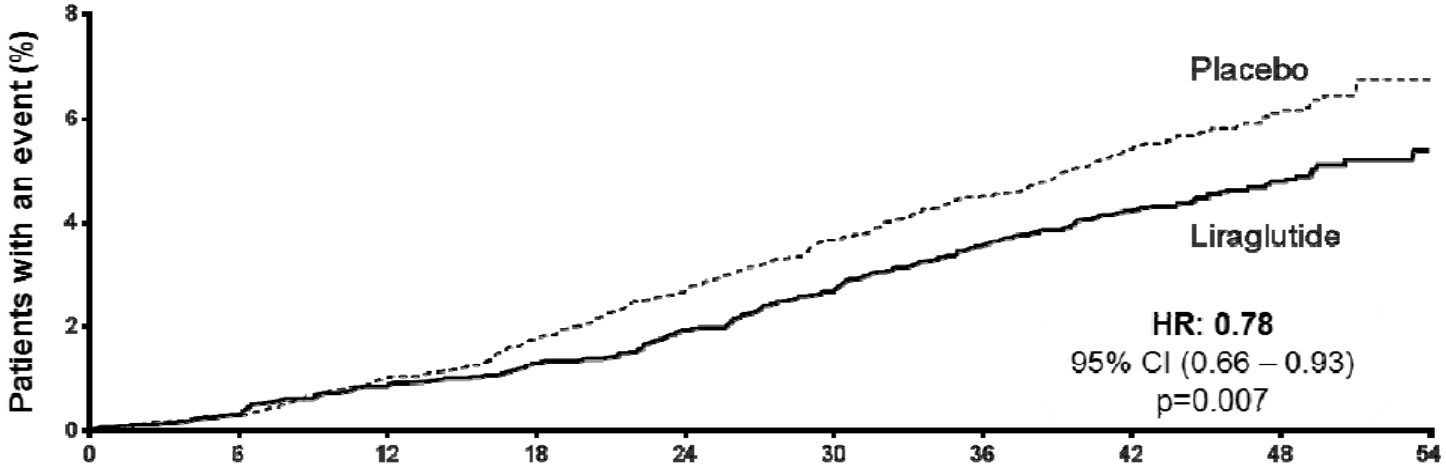
Hypoglycemic events are defined as (a) symptoms, patient is able to self-treat and plasma glucose is <3.1 mmol/L (grade 1), (b) symptoms, patient unable to self-treat, and plasma glucose <3.1 mmol/L (grade 2), (c) symptoms, patient unable to self-treat, and no plasma glucose value available (suspected grade 2).
Vilda 100 mg daily = Vilda 50 mg bid and Vilda 100mg qd combined.
D/C = discontinued; Met = metformin; PBO = placebo; Pio = pioglitazone; Rosi = Rosiglitazone; Vilda = vildagliptin.
Adapted from *Summary of Clinical Safety*,Table 4-27, p. 93.
Data on file, Novartis Pharmaceuticals.

Baseline cardiovascular risk profile

	Liraglutide (N=4668)	Placebo (N=4672)
Established CVD/CKD (age ≥50 years)	**3831 (82.1)**	**3767 (80.6)**
Prior myocardial infarction	1464 (31.4)	1400 (30.0)
Prior stroke or prior TIA	730 (15.6)	777 (16.6)
Prior revascularization	1835 (39.3)	1803 (38.6)
>50% stenosis of coronary, carotid, or lower extremity arteries	1188 (25.4)	1191 (25.5)
Documented symptomatic CHD	412 (8.8)	406 (8.7)
Documented asymptomatic cardiac ischemia	1241 (26.6)	1231 (26.3)
Chronic heart failure NYHA II – III	653 (14.0)	652 (14.0)
Chronic kidney disease (eGFR <60 mL/min/1.73m^2)	1185 (25.4)	1122 (24.0)

	Liraglutide (N=4668)	Placebo (N=4672)
CVD risk factors (age ≥60 years)	**837 (17.9)**	**905 (19.4)**
Microalbuminuria or proteinuria	501 (10.7)	558 (11.9)
Hypertension and left ventricular hypertrophy	248 (5.3)	251 (5.4)
Left ventricular systolic or diastolic dysfunction	203 (4.3)	191 (4.1)
Ankle/brachial index <0.9	110 (2.4)	116 (2.5)

CV death



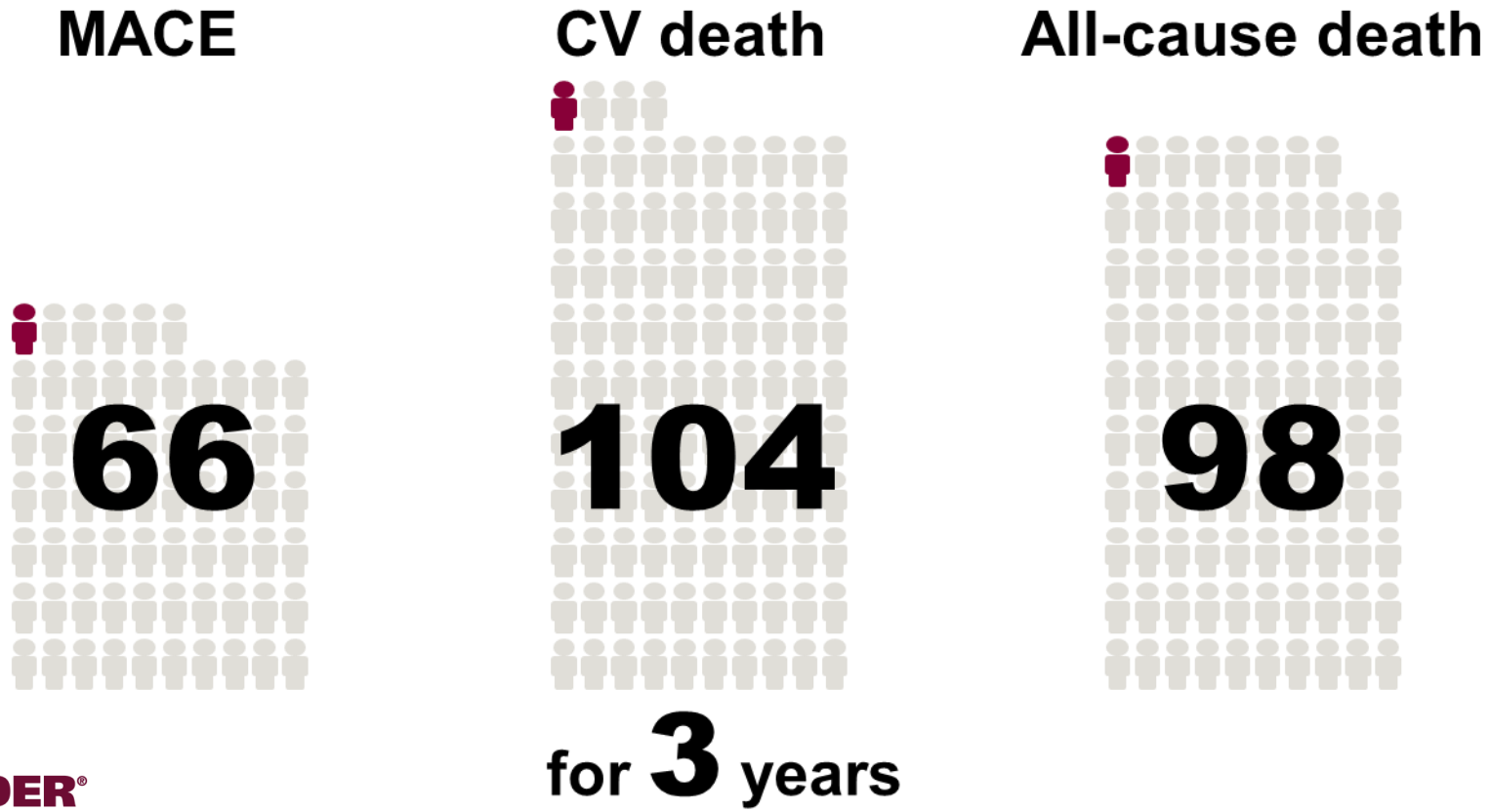
Patients at risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The cumulative incidences 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 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Number needed to treat to prevent one…

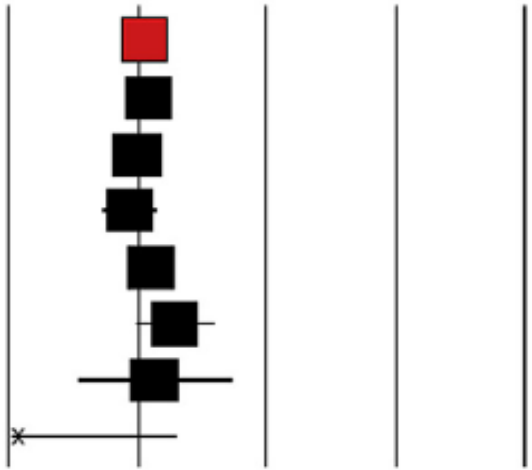


LEADER®
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

CV: cardiovascular; MACE: major adverse cardiovascular event.
Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Impact of SGLT2 inhibitors on SBP

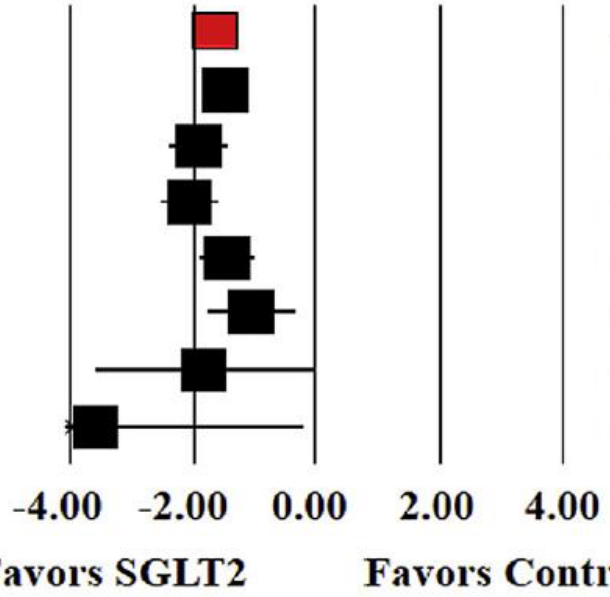
Comparison	n	Point estimate	Lower limit	Upper limit
All Drugs	12960	-3.96	-4.41	-3.51
Placebo-Controlled	7875	-3.82	-4.40	-3.23
Active-Controlled	5085	-4.17	-4.88	-3.46
Canagliflozin	5607	-4.38	-5.08	-3.69
Dapagliflozin	5280	-3.78	-4.49	-3.07
Empagliflozin	1359	-3.02	-4.25	-1.80
Ipragliflozin	679	-3.65	-5.98	-1.31
Remogliflozin	35	-7.83	-12.91	-2.75



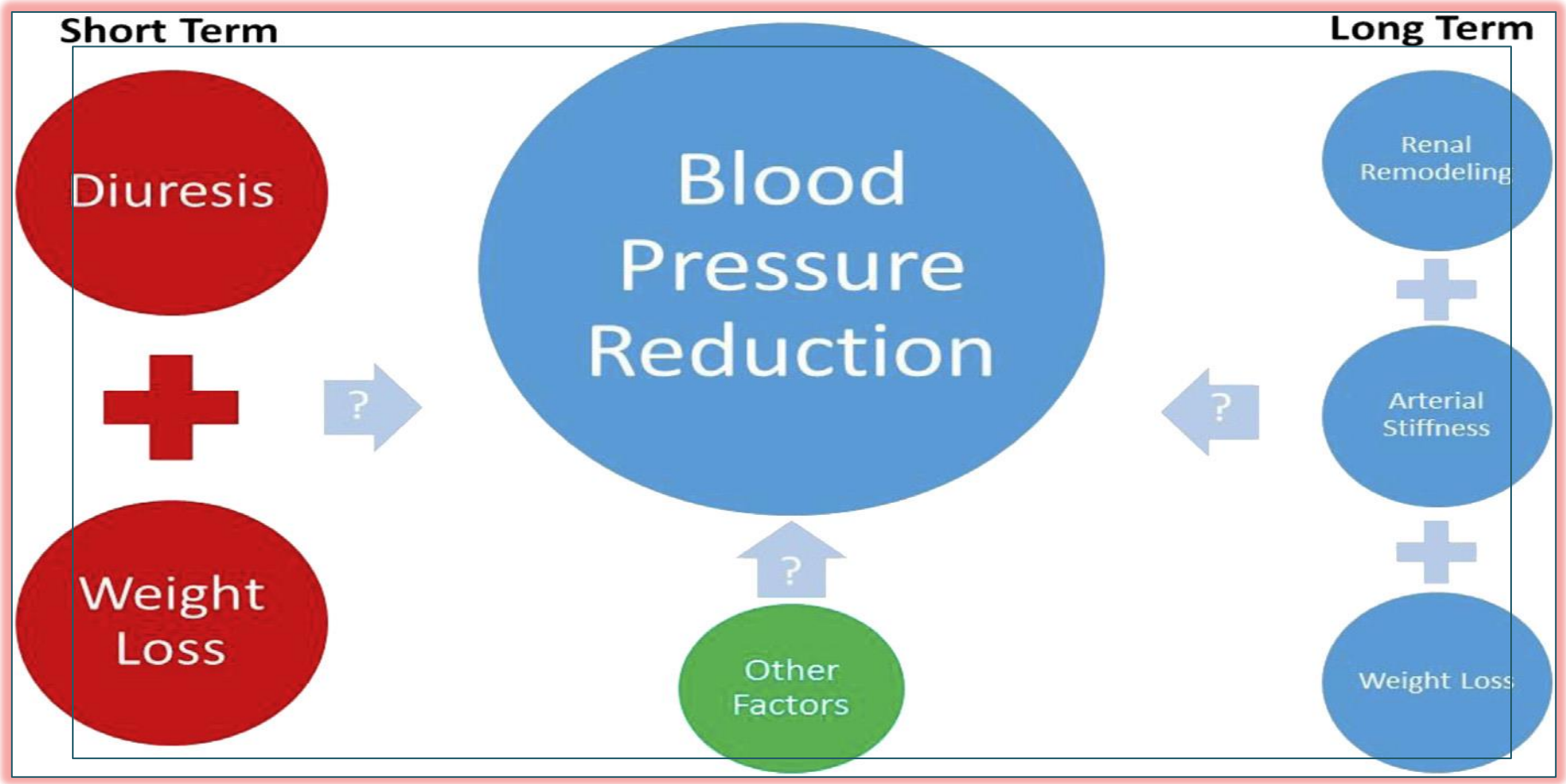
W.L. Baker et al. / Journal of the American Society of Hypertension 8(4) (2014)

Impact of SGLT2 inhibitors on DBP

Comparison	n	Point estimate	Lower limit	Upper limit
All Drugs	12960	-1.59	-2.18	-1.01
Placebo-Controlled	7875	-1.45	-1.81	-1.08
Active-Controlled	5085	-1.87	-2.33	-1.40
Canagliflozin	5607	-2.02	-2.48	-1.56
Dapagliflozin	5280	-1.41	-1.86	-0.96
Empagliflozin	1359	-1.01	-1.72	-0.31
Ipragliflozin	679	-1.78	-3.52	-0.04
Remogliflozin	35	-3.50	-6.81	-0.20

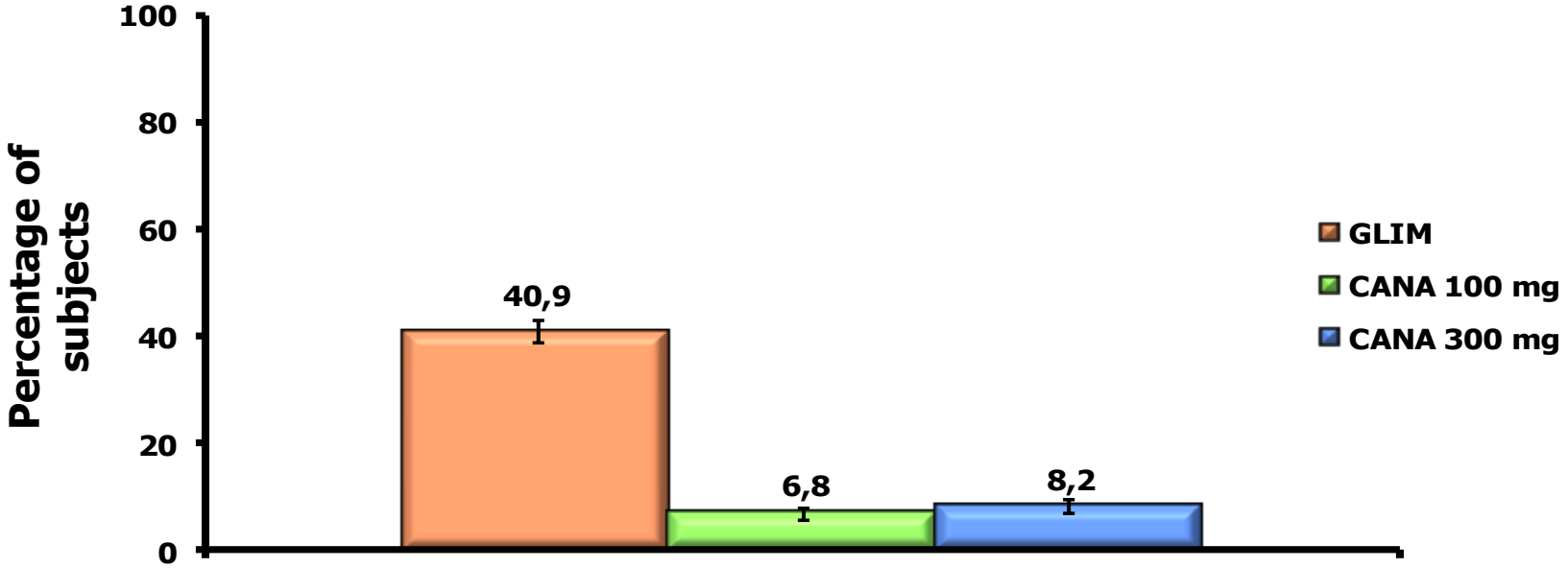


W.L. Baker et al. / Journal of the American Society of Hypertension 8(4) (2014)



G. Maliha et al. Journal of the American Society of Hypertension 9(1) (2015)

Proportion of subjects with documented hypoglycemia episodes through week 104



Rates of severe hypoglycemia were lower with CANA 100 and 300 mg relative to GLIM (0.6%, 0.2%, and 3.3%, respectively).

Cefalu WT et al. Poster presented at the 73rd Scientific sessions of the American Diabetes Association (ADA), 2013; Jun. 21-25; Chicago, Illinois, (65-LB).

Multicentre (590 sites in 42 countries), randomized, double blind, placebo controlled trial

PATIENTS

✓Adults (≥18 ys) diabetic patients (pts) with a BMI ≤45 Kg/m^2 and an eGFR ≥30 ml/min/1.73 m^2

✓**Established CV disease defined as prior myocardial infarction (MI), coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease**

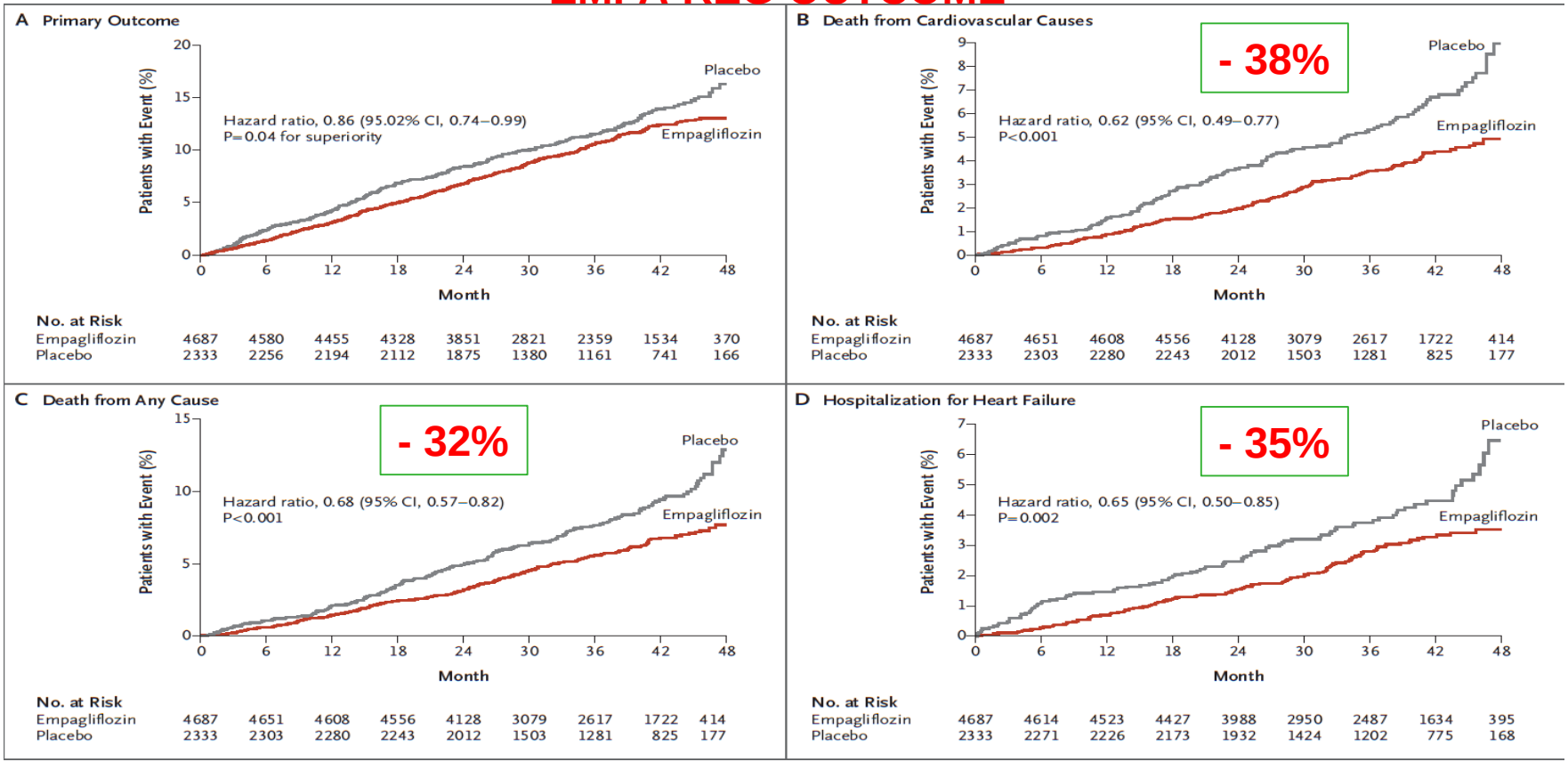
✓Glucose-lowering therapy (GLT)

A. no GLT for at least 12 weeks before randomization and 7.0% ≤HbA1c ≤9.0%
B. stable GLT for at least 12 weeks before randomization and 7.0% ≤HbA1c ≤10.0%

OUTCOMES

- ✓ Primary outcome (3-point MACE): a composite of death from CV causes, nonfatal MI (excluding silent MI) or nonfatal stroke
- ✓ Key secondary outcome: a composite of the primary outcome + hospitalization for unstable angina

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
EMPA-REG OUTCOME



This article was published on September 17, 2015, at NEJM.org.

Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

Simvastatin[1] for 5.4 years

30

High CV risk

5% diabetes, 26% hypertension

Ramipril[2] for 5 years

56

High CV risk

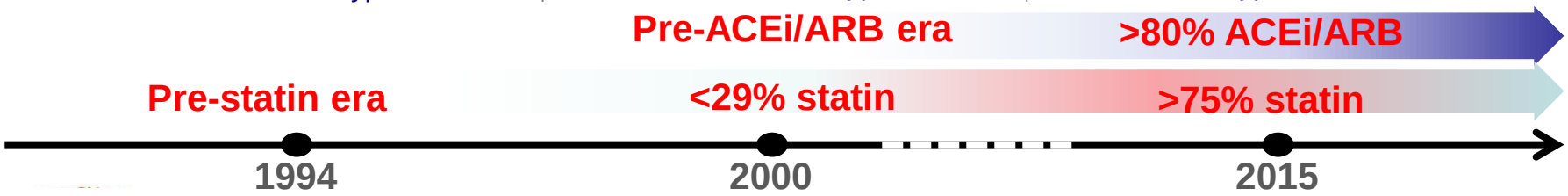
38% diabetes, 46% hypertension

Empagliflozin for 3 years

39

T2DM with high CV risk

92% hypertension



1. 4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm;
2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

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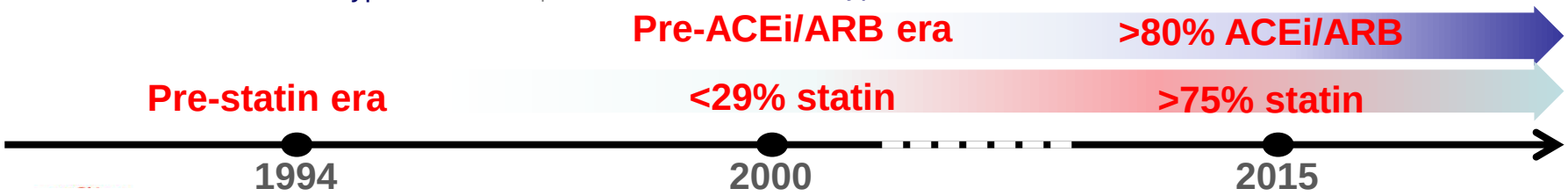


1. 4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm;
2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

Empagliflozin: potential mechanism for CV protection

Table 2 Putative hypothesized mechanisms underlying the reduced cardiovascular mortality observed in the EMPAREG-OUTCOME-study.

Type of mechanism	Mechanism
Systemic, metabolic	↑Ketone bodies
	↑Sodium excretion
	↓Extracellular sodium in myocardium
	↑Hematocrit
	↓**Blood pressure**
	↓**Body weight**
	↑**Diuresis**
	RAS activation
Systemic, endocrine	↑Renal production of erythropoietin
	↑Sympathoadrenergic activity
	↑Glucagon
Direct myocardial effect	Inhibition of cardiomyocyte SGLT1R resulting in:
	↓Depolarization
	↓Sodium/calcium overload
	↓Glucose uptake and glucotoxicity
	↓ROS production

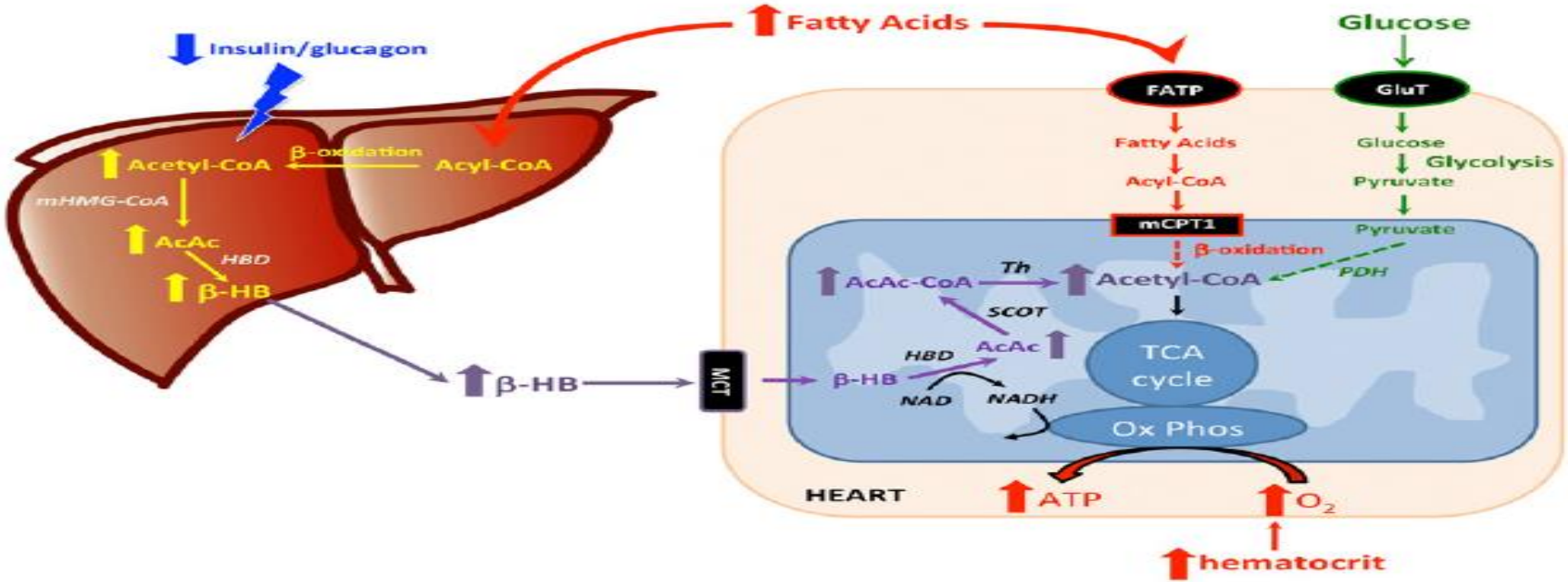
All mechanisms discussed in the present review are listed, according to their nature. The mechanisms assessed in the EMPAREG-OUTCOME study are indicated in bold.

Luconi M, Raimondi L, Di Franco A, Mannucci E
Nutr Metab Cardiovasc Dis 26:1071-8, 2016

CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis

Ele Ferrannini,[1] Michael Mark,[2] and Eric Mayoux[2]

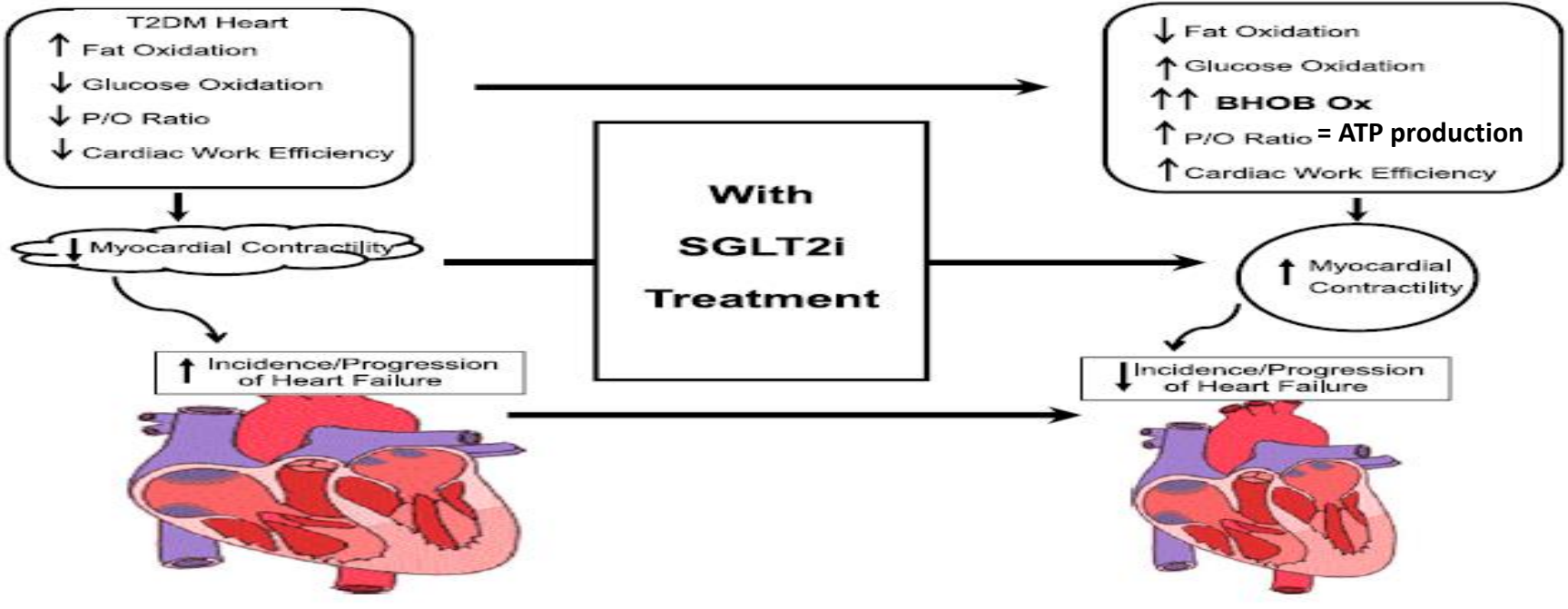
DOI: 10.2337/dc16-0330



Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis

Sunder Mudaliar, Sindura Alloju, and Robert R. Henry

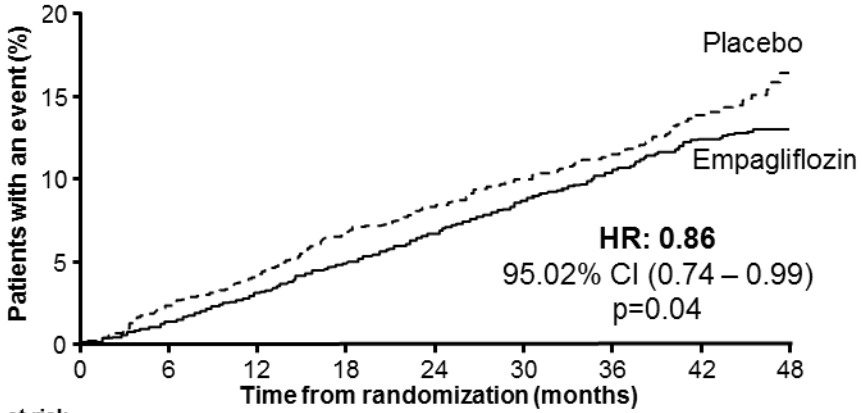
DOI: 10.2337/dc16-0542



Empagliflozin and Liraglutide

EMPA-REG OUTCOME

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

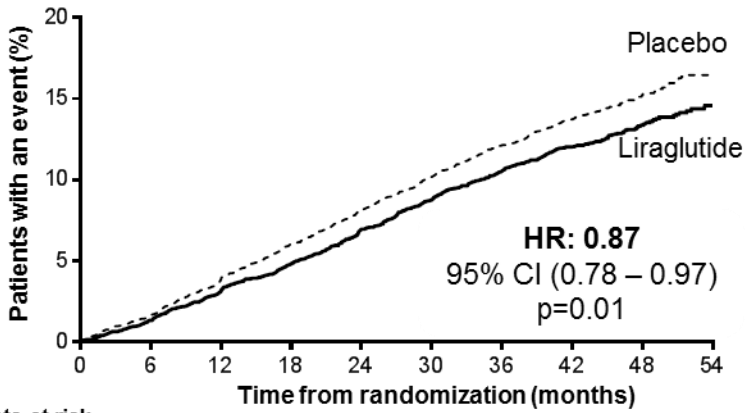


Patients at risk

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

LEADER

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

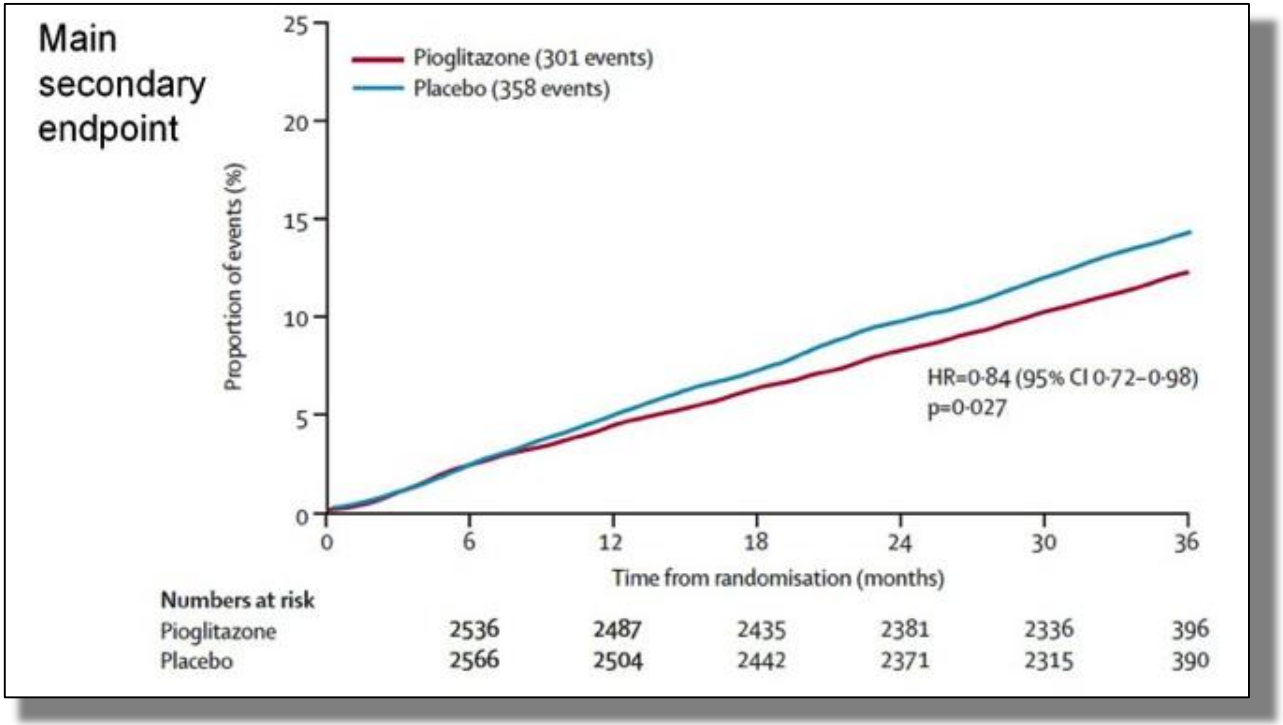


Patients at risk

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

Pioglitazone: effect on major cardiovascular events

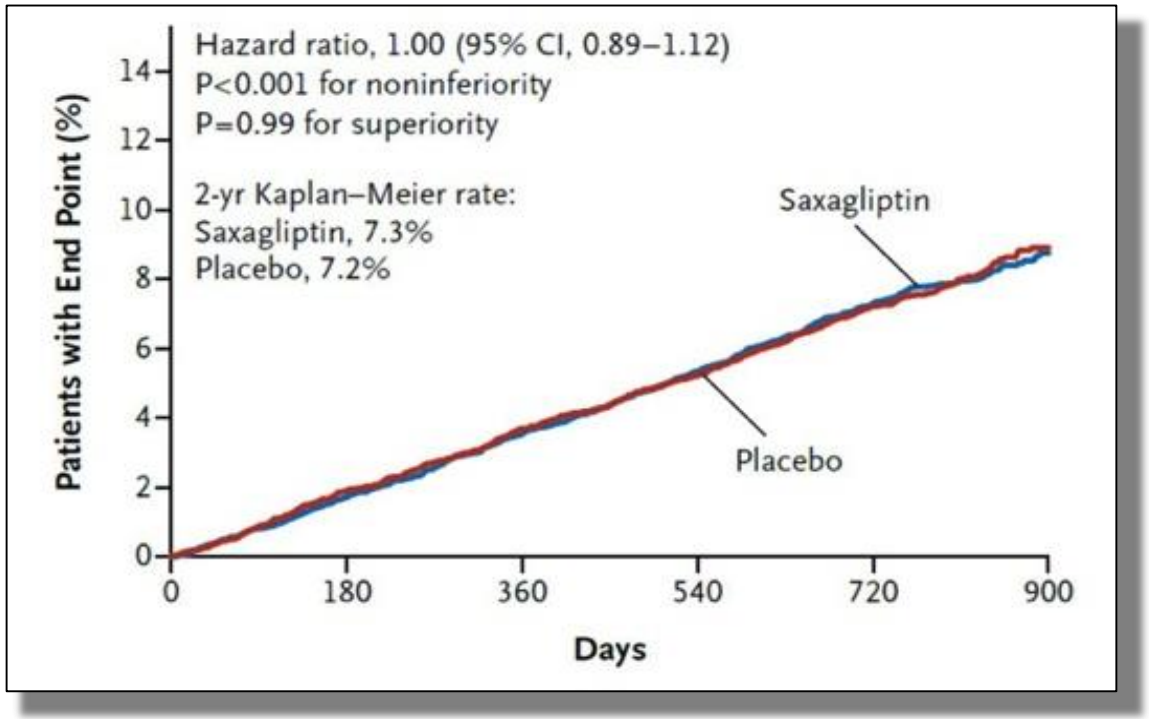
Results of the PROACTIVE trial



Dormandy J et al. *Lancet* 366: 1279-89, 2005

Saxagliptin: effect on major cardiovascular events

Results of the SAVOR-TIMI trial



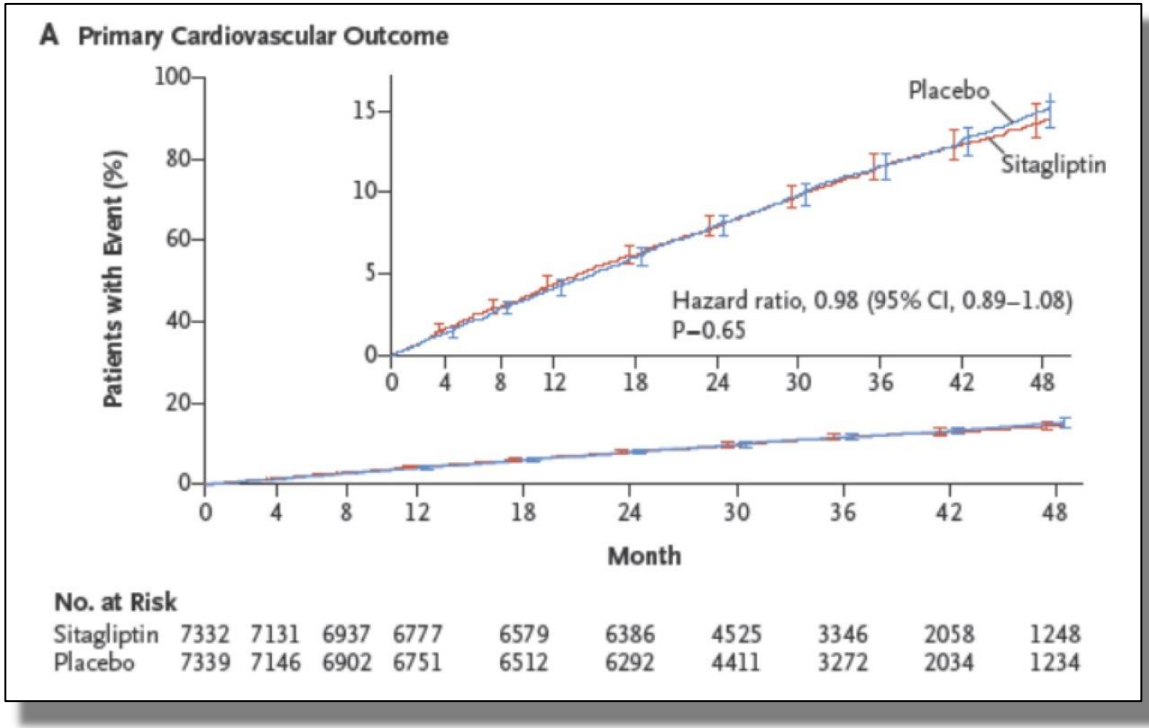
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

16,492 T2DM patients with prior CVD/high CV risk, saxagliptin vs placebo 1:1.
Follow-up: 2.1 y

Scirica BM et al. *N Engl J Med* 369:1317-26, 2013

Sitagliptin: effect on major cardiovascular events

Results of the TECOS trial



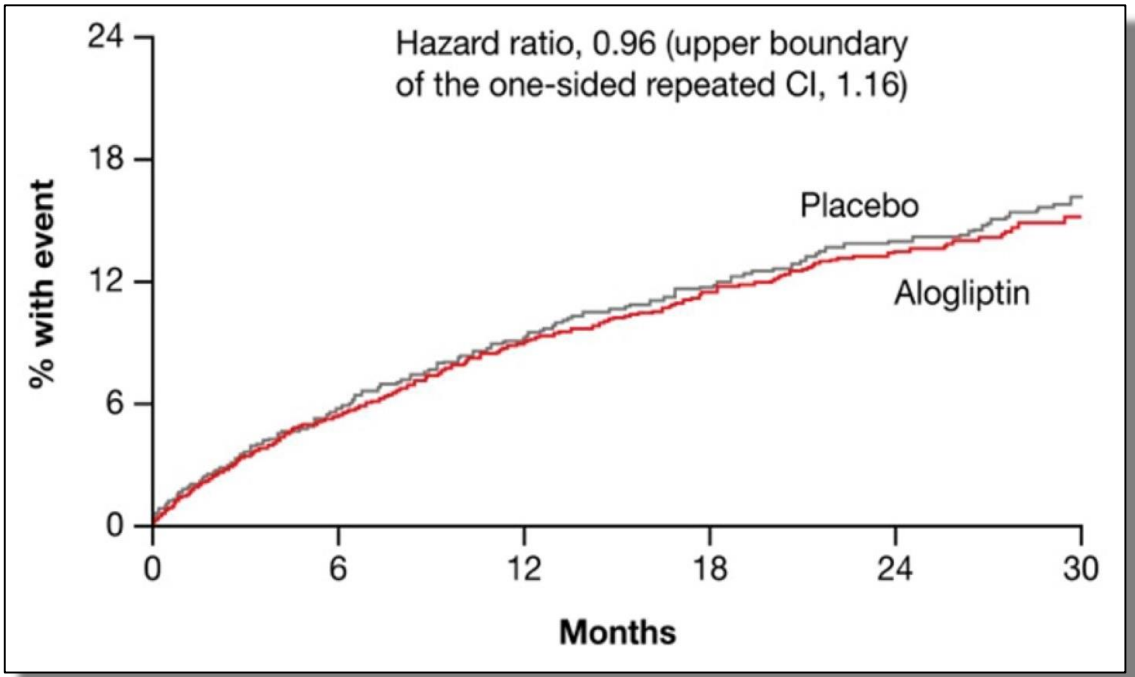
Principal endpoint:
4-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death, hospitalization for unstable angina)

14,671 T2DM patients with prior CVD,
sitagliptin vs placebo 1:1.
Follow-up: 3 y

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

Alogliptin: effect on major cardiovascular events

Results of the EXAMINE trial



Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

5380 T2DM patients with recent acute coronary syndrome, alogliptin vs placebo 1:1.
Follow-up: 1.5 y

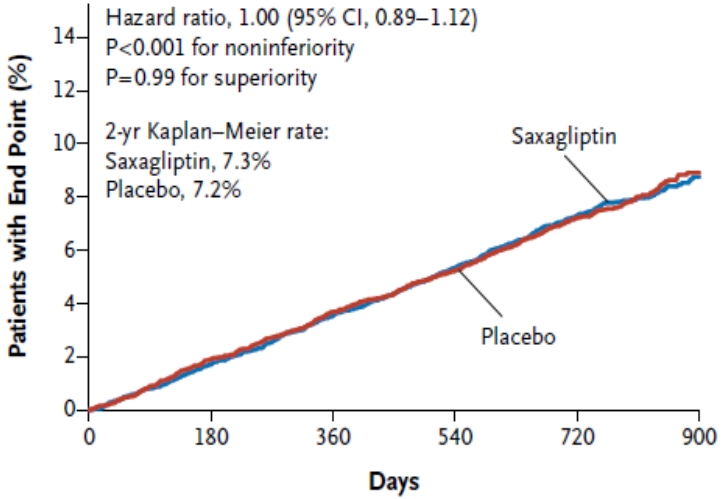
White et al. *N Engl J Med* 369:1327-35, 2013

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

BM Scirica et Al for the **SAVOR-TIMI 53** Steering Committee and Investigators.
N Engl J Med 2013;369:1317-26. DOI: 10.1056/NEJMoa1307684

a composite of death from CV causes, MI, or ischemic stroke

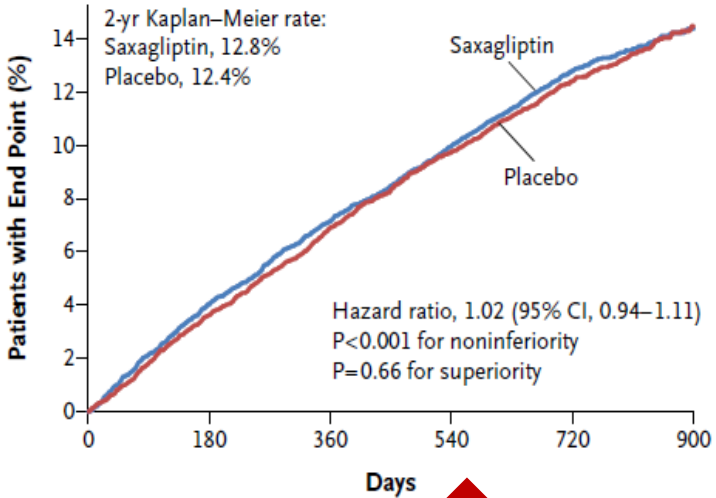
A Primary End Point



No. at Risk						
Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

As A, + hospitalization for unstable angina, coronary revasc., or HF*

B Secondary End Point

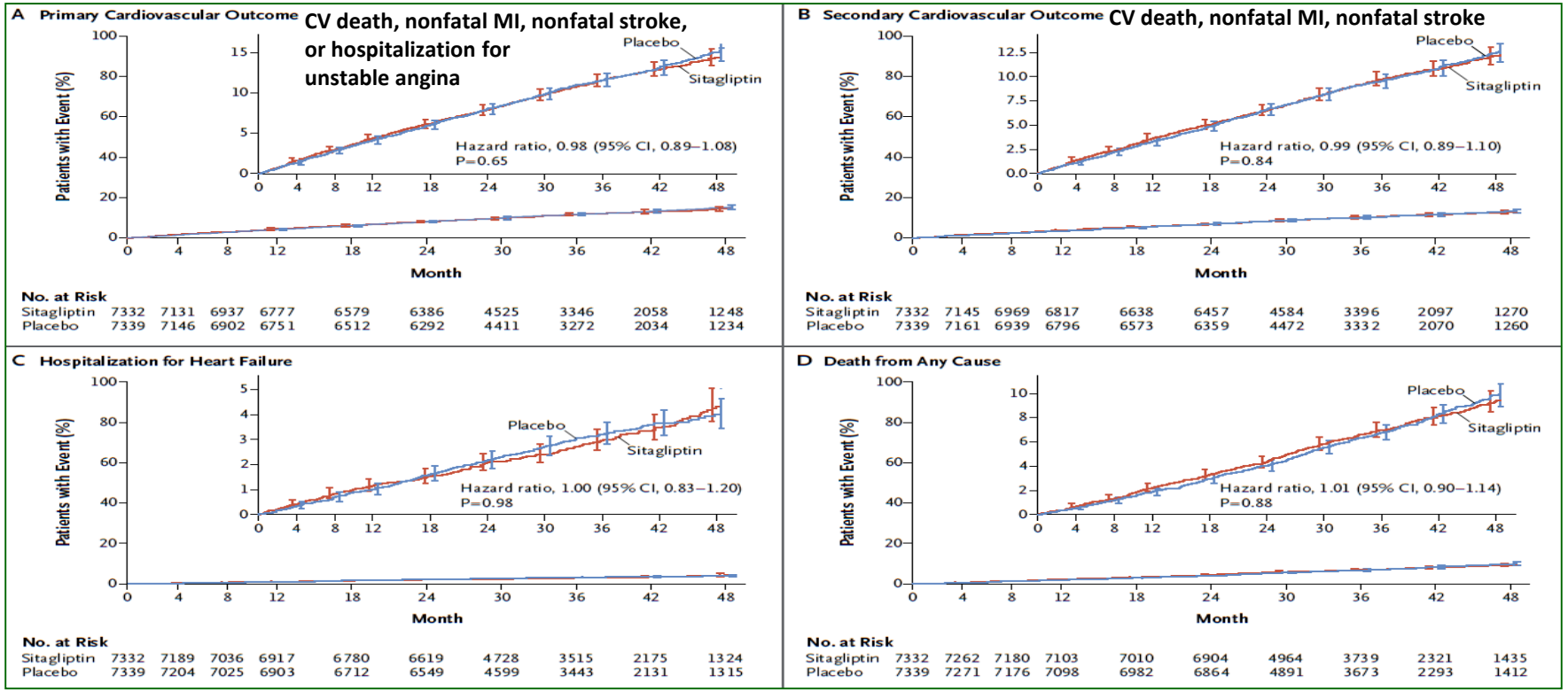


No. at Risk						
Placebo	8212	7843	7502	6926	4602	813
Saxagliptin	8280	7880	7539	6963	4660	817

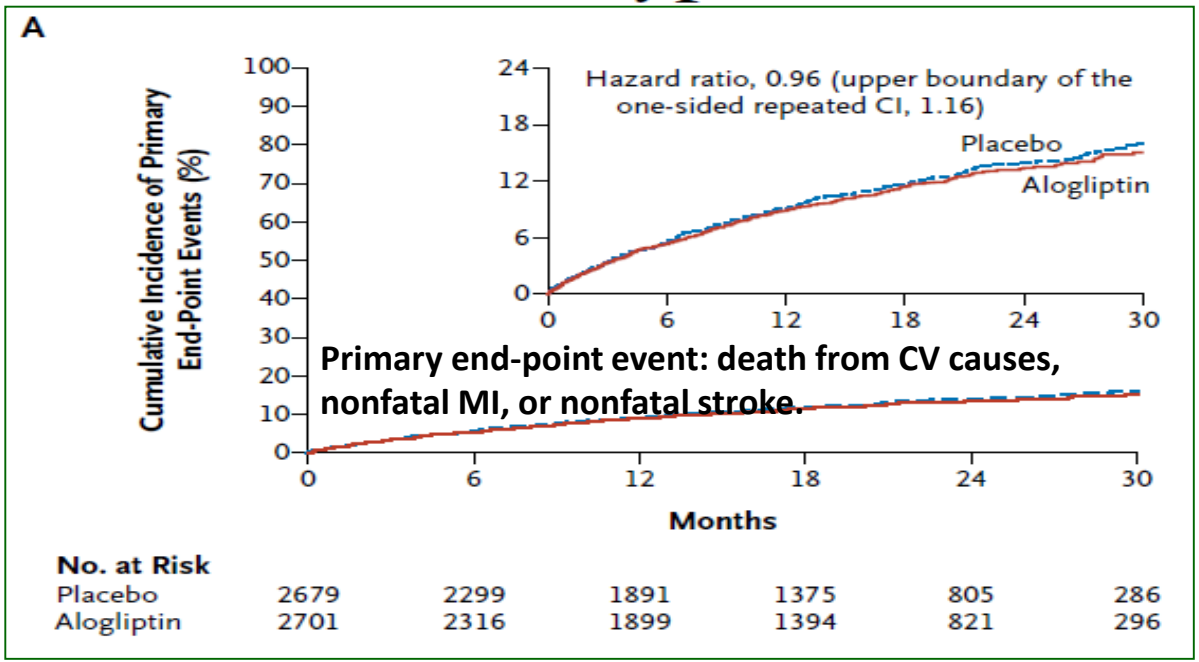
* **HF p=0.007**

Green JB, et al. for the **TECOS Study Group** – NEJM, 2015. DOI: 10.1056/NEJMoa1501352

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes



Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes



WB White for the **EXAMINE** Investigators. N Engl J Med 2013;369:1327-35. DOI: 10.1056/NEJMoa1305889

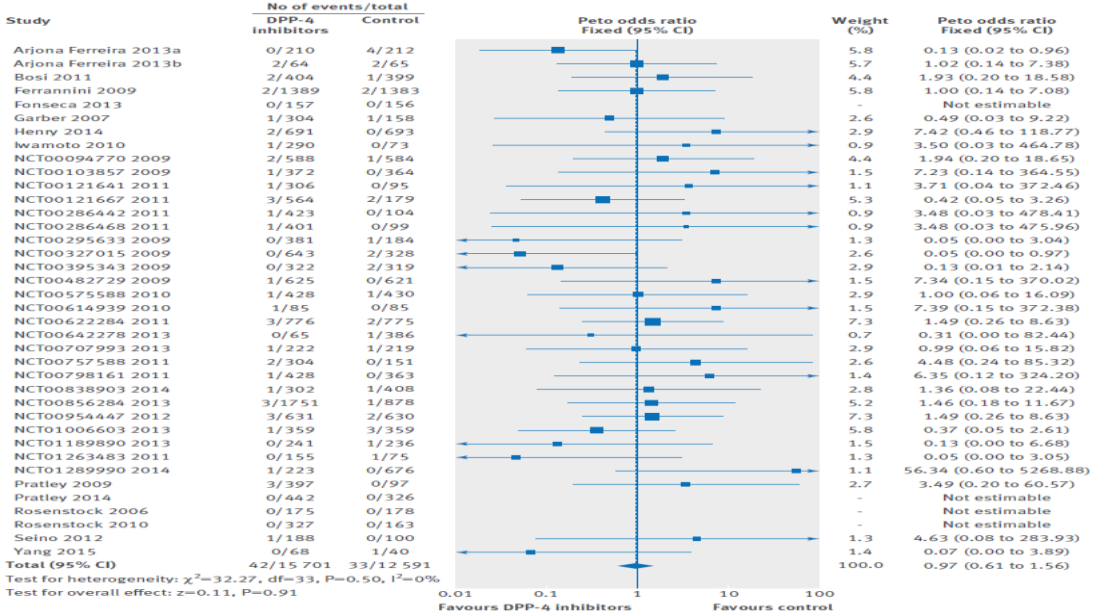
Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies

Ling Li,[1] Sheyu Li,[2] Ke Deng,[3] Jiali Liu,[1] Per Olav Vandvik,[4, 5] Pujing Zhao,[1] Longhao Zhang,[1] Jiantong Shen,[1] Malgorzata M Bala,[6] Zahra N Sohani,[7, 8] Evelyn Wong,[9] Jason W Busse,[7, 10, 11] Shanil Ebrahim,[7, 10, 12, 13] German Malaga,[14] Lorena P Rios,[15] Yingqiang Wang,[16] Qunfei Chen,[17] Gordon H Guyatt,[7, 18] Xin Sun[1]

Risk of HF in patients with T2DM who received DPP-4i vs control from RCT
Total (% CI)

DPP4i 42/15.701
Control 33/12.591

OR = 0.97 (0.61 to 1.56)
P = n.s.



BMJ 2016;352:i610
http://dx.doi.org/10.1136/bmj.i610

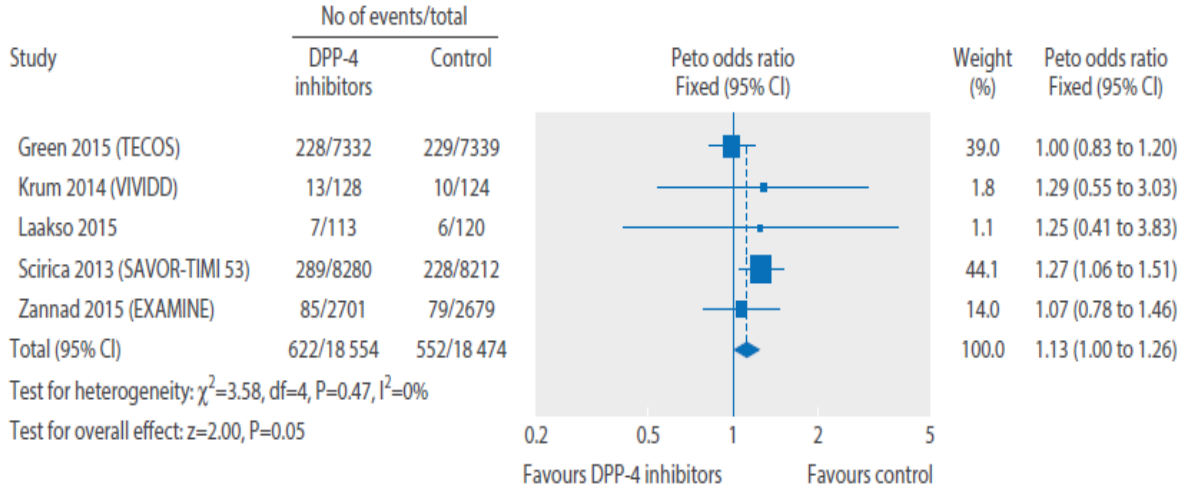
Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies

Ling Li,[1] Sheyu Li,[2] Ke Deng,[3] Jiali Liu,[1] Per Olav Vandvik,[4, 5] Pujing Zhao,[1] Longhao Zhang,[1] Jiantong Shen,[1] Malgorzata M Bala,[6] Zahra N Sohani,[7, 8] Evelyn Wong,[9] Jason W Busse,[7, 10, 11] Shanil Ebrahim,[7, 10, 12, 13] German Malaga,[14] Lorena P Rios,[15] Yingqiang Wang,[16] Qunfei Chen,[17] Gordon H Guyatt,[7, 18] Xin Sun[1]

Risk of hospital admission for HF in patients with T2DM who received DPP-4i vs control from RCT
Total (% CI)

DPP4i 622/18.554
Control 552/18.474

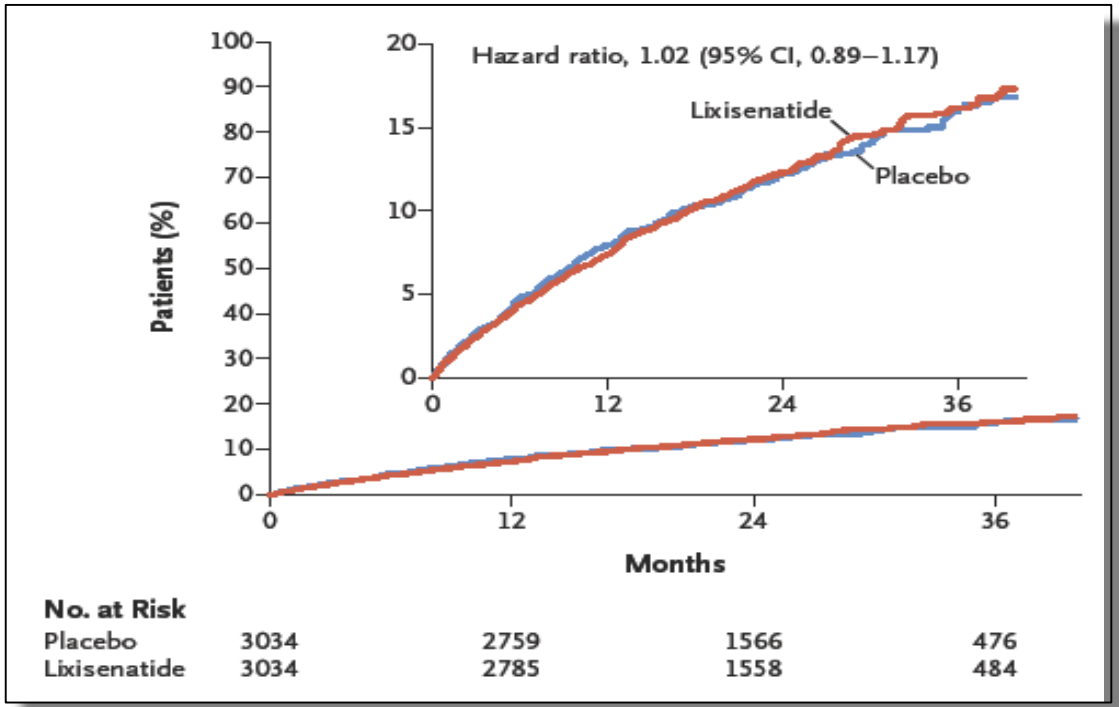
OR = 1.13 (1.00 to 1.26)
P = 0.05



BMJ 2016;352:i610
http://dx.doi.org/10.1136/bmj.i610

Lixisenatide: effect on major cardiovascular events

Results of the ELIXA trial



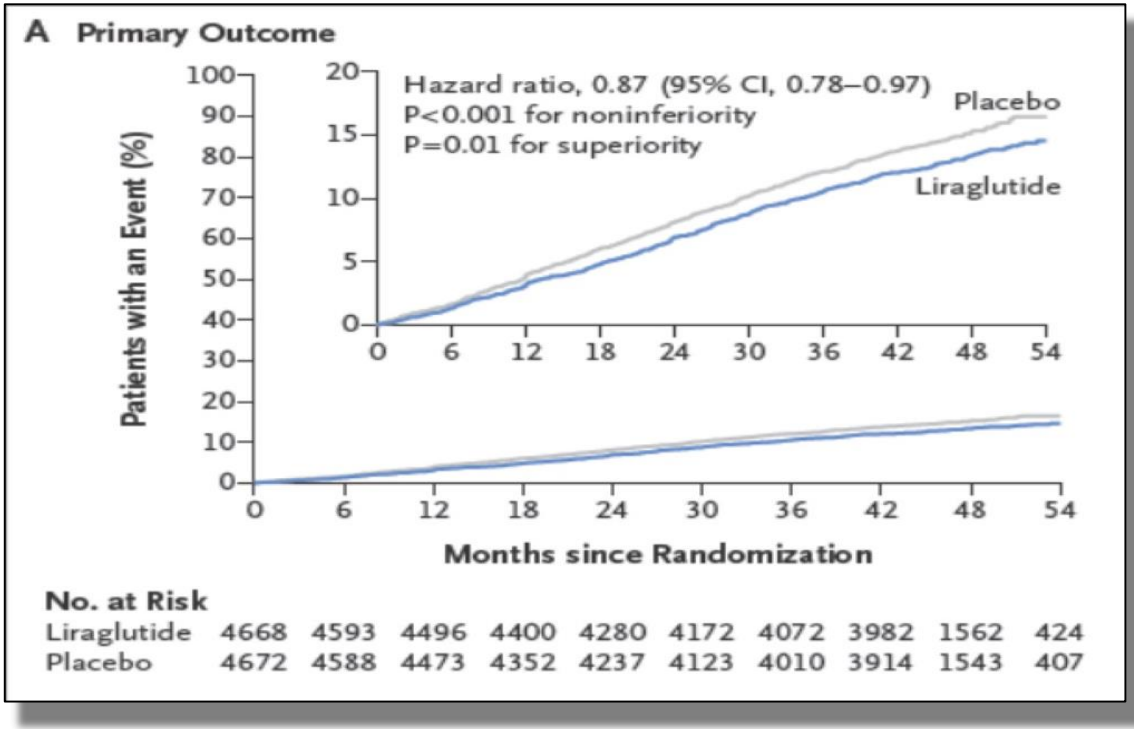
Principal endpoint:
4-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death, hospitalization for unstable angina)

6068 T2DM patients with recent acute coronary syndrome, lixisenatide vs placebo 1:1.
Follow-up: 2.1 y

Pfeffer MA et al. *N Engl J Med* 373: 2247-57, 2015

Liraglutide: effect on major cardiovascular events

Results of the LEADER trial



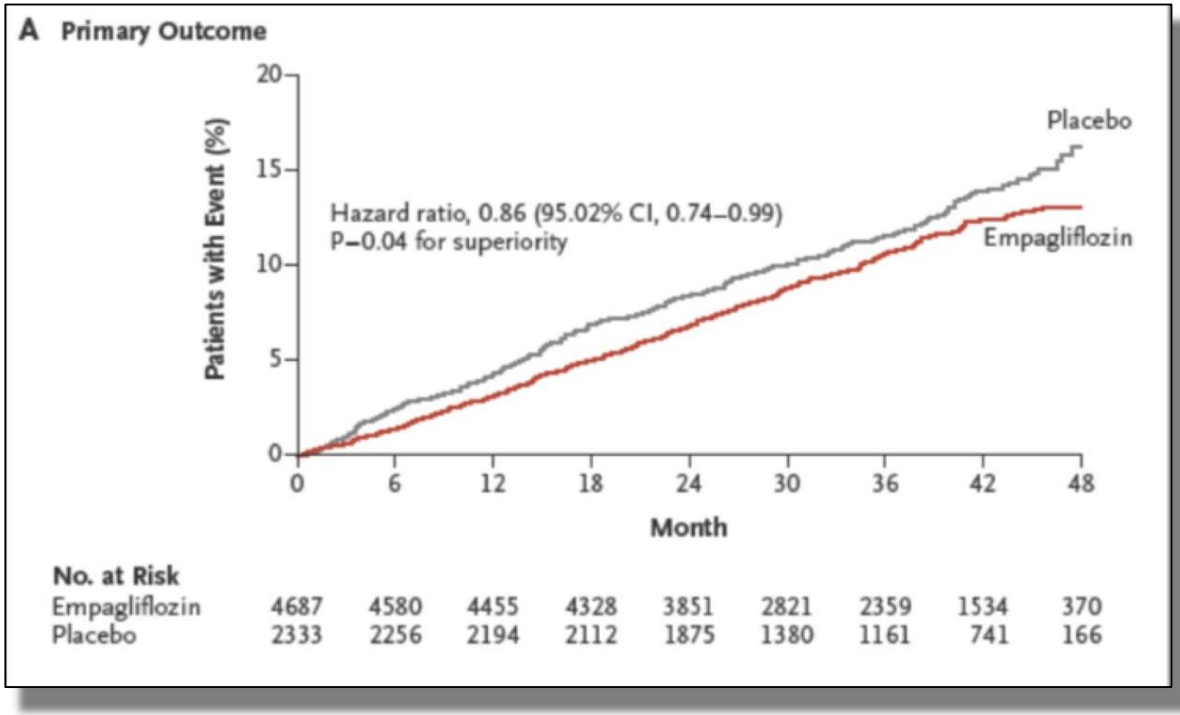
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

9,340 T2DM patients with prior cardiovascular disease and/or high CV risk, Liraglutide vs placebo 1:1.
Follow-up: 4 y

Marso SP et al. *N Engl J Med* 375: 311-22, 2016

Empagliflozin: effect on major cardiovascular events

Results of the EMPAREG-OUTCOME trial



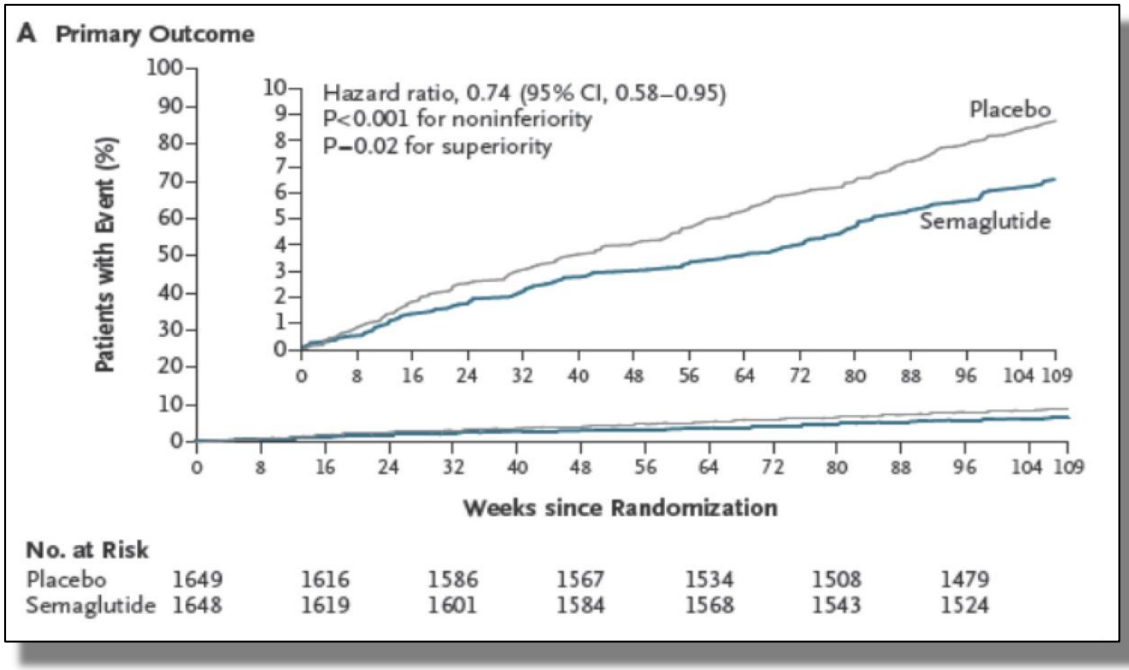
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

9,340 T2DM patients with prior CVD, Empagliflozin vs placebo
Follow-up: 3 y

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

Semaglutide: effect on major cardiovascular events

Results of the SUSTAIN-6 trial



Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

3,297 T2DM patients with prior cardiovascular disease and/or high CV risk, Semaglutide vs placebo 1:1.
Follow-up: 2 y

Marso SP et al. *N Engl J Med* 375: 1834-44, 2016

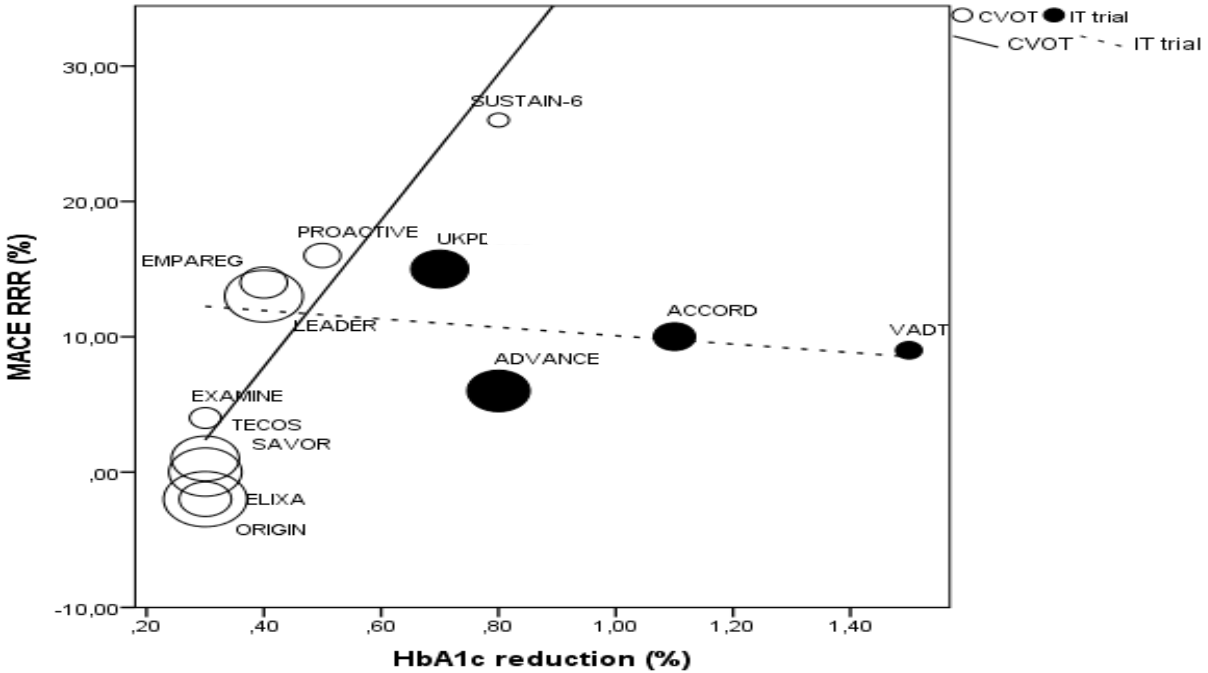
CV risk factors in CV safety trials in dabetes

Mean differences between active treatment and placebo

Study	Drug	A1c (%)	BW (kg)	sBP (mmHg)	MACE (%)
TECOS	Sitagliptin	-0.3	0	0	-2
EXAMINE	Alogliptin	-0.3	0	0	-4
SAVOR	Saxagliptin	-0.2	0	0	0
ELIXA	Lixisenatide	-0.2	-0.6	-0.8	+2
LEADER	Liraglutide	-0.4	-2.3	-1.2	-13
SUSTAIN-6	Semaglutide	-0.9	-3.9	-1.9	-26
EMPAREG	Empagliflozin	-0.4	-1.0	-2.8	-14

Glycemic control and cardiovascular risk in T2DM

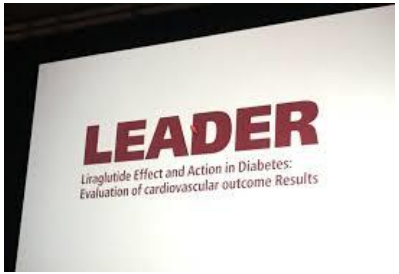
Summary of CVOTs and RCTs on intensification of therapy



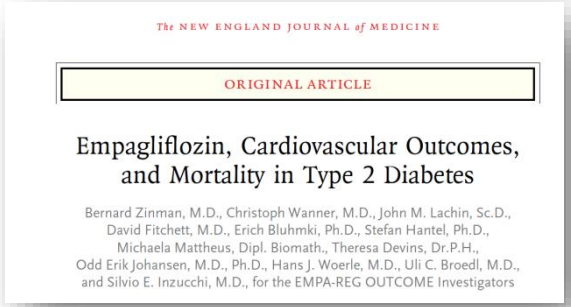
Mannucci E, Monami M, Ceriello A, Rotella CM. *Nutr Metab Cardiovasc Dis*, 2017

Oltre il compenso glicemico

EMPA-REG OUTCOME®



SUSTAIN™ 6


The NEW ENGLAND JOURNAL of MEDICINE

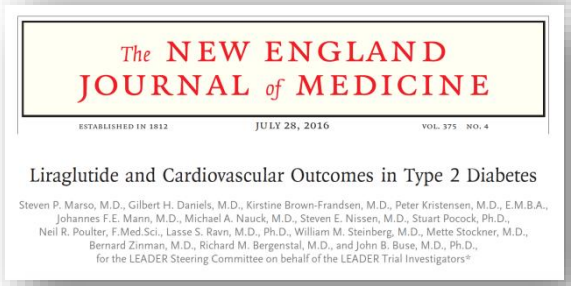
ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

EASD 2015

NEJM 373; 22 2015


The NEW ENGLAND JOURNAL of MEDICINE

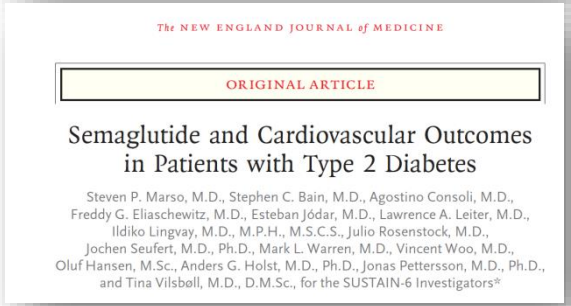
ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

ADA 2016

NEJM 375; 4 2016


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

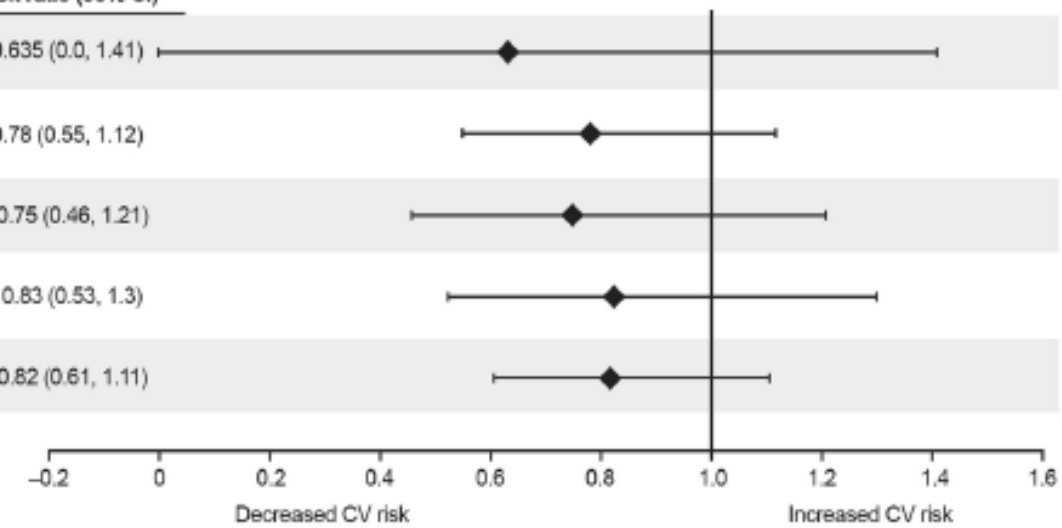
EASD 2016

NEJM 375; 19 2016

DPP4 inhibitors: effect on major cardiovascular events

Pooled analyses of phase 2-3 trials

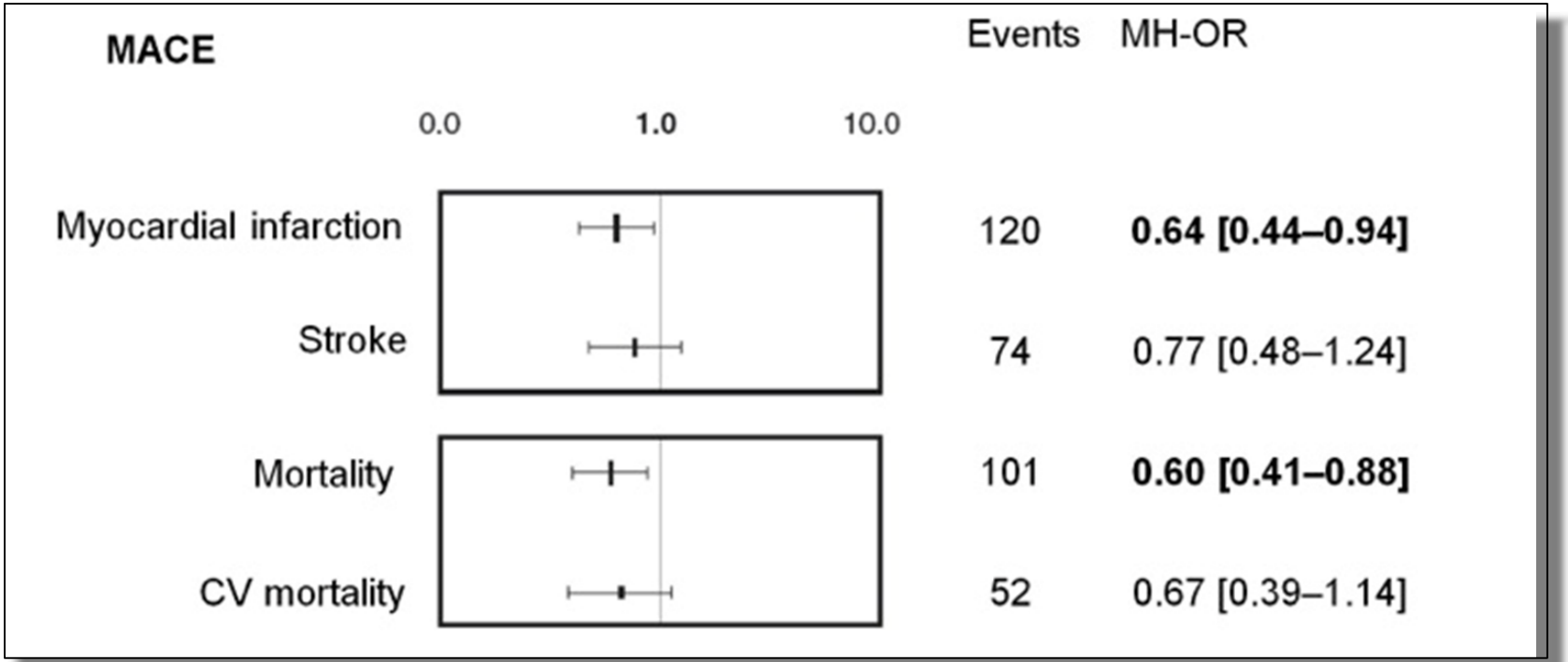
Drug [reference]	Primary statistical method	Number of patients	Risk ratio (95% CI)
Alogliptin [26]	Cox proportional hazards	6028	0.635 (0.0, 1.41)
Linagliptin [21]	Cox HR estimate	9459	0.78 (0.55, 1.12)
Saxagliptin [24]	Cox HR estimate	9156	0.75 (0.46, 1.21)
Sitagliptin [23]	Adjusted incidence rate ratio using Exact method for Poisson processes	14611	0.83 (0.53, 1.3)
Vildagliptin[a] [25]	Mantel–Haenszel RR	17446	0.82 (0.61, 1.11)



Mannucci E, Monami M. *Adv Ther* 34:1-40, 2017

DPP4 inhibitors: effect on major cardovascular events

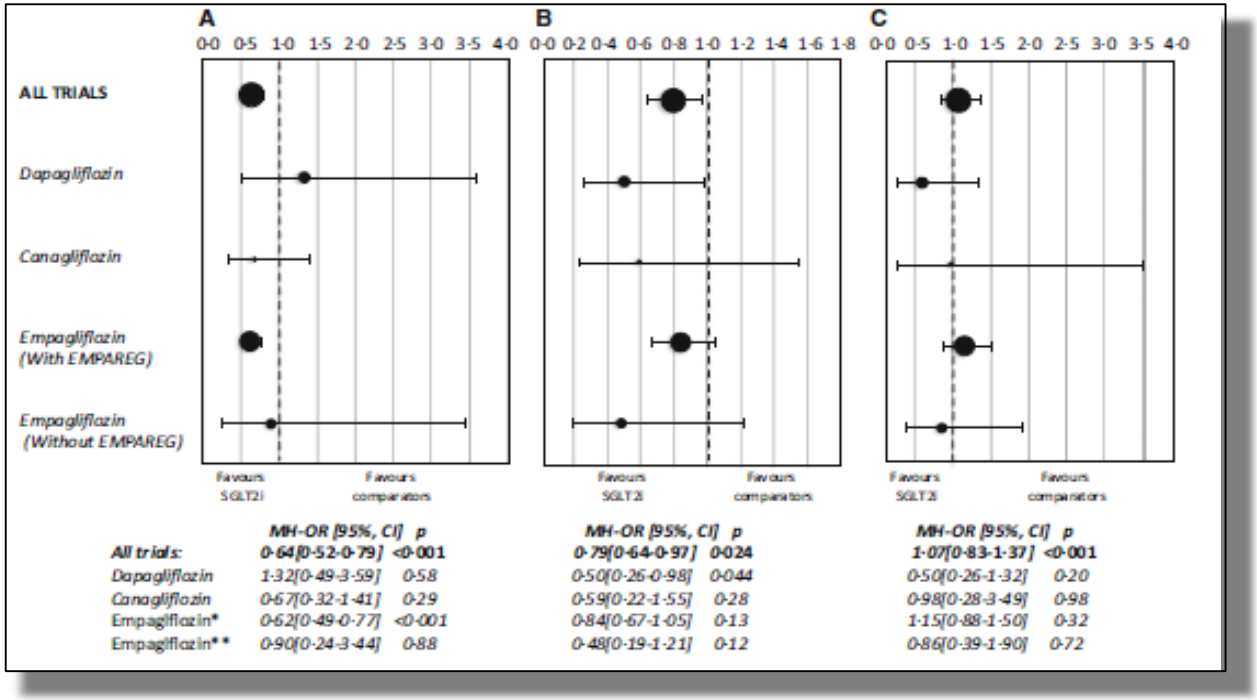
Results of a meta-analysis of phase 3 and early phase 4 trials



Monami M, Ahrén B, Dicembrini I, Mannucci E. *Diabetes Obes Metab* 15:112-20, 2013

SGLTi and CV risk

Meta-analysis of available RCTs



	A: MH-OR [95% CI]	A: p	B: MH-OR [95% CI]	B: p	C: MH-OR [95% CI]	C: p
All trials:	*0·64 [0·52–0·79]*	*<0·001*	*0·79 [0·64–0·97]*	*0·024*	*1·07 [0·83–1·37]*	*<0·001*
Dapagliflozin	*1·32 [0·49–3·59]*	*0·58*	*0·50 [0·26–0·98]*	*0·044*	*0·50 [0·26–1·32]*	*0·20*
Canagliflozin	*0·67 [0·32–1·41]*	*0·29*	*0·59 [0·22–1·55]*	*0·28*	*0·98 [0·28–3·49]*	*0·98*
Empagliflozin*	*0·62 [0·49–0·77]*	*<0·001*	*0·84 [0·67–1·05]*	*0·13*	*1·15 [0·88–1·50]*	*0·32*
Empagliflozin**	*0·90 [0·24–3·44]*	*0·88*	*0·48 [0·19–1·21]*	*0·12*	*0·86 [0·39–1·90]*	*0·72*

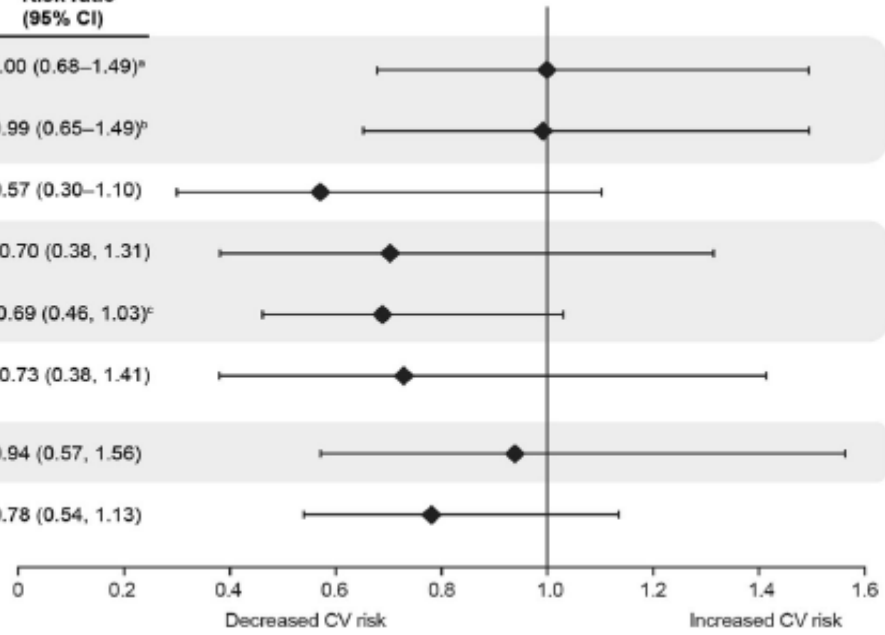
A: CV mortality
B: Myocardial infarction
C: Stroke

Monami M, Dicembrini I, Mannucci E. *Acta Diabetol* 2017; 54: 19-36

GLP1RA: effect on major cardiovascular events

Pooled analyses of phase 2-3 trials

Drug [Reference]	Type of analysis	Primary statistical analysis	Number of patients	Risk ratio (95% CI)
Albiglutide [53]	Pooled analysis	Cox proportional hazards	5107	1.00 (0.68–1.49)[a] 0.99 (0.65–1.49)[b]
Dulaglutide [54]	Pooled analysis	Cox proportional hazards	6010	0.57 (0.30–1.10)
Exenatide twice daily [51]	Pooled analysis	Mantel–Haenszel RR	3945	0.70 (0.38, 1.31) 0.69 (0.46, 1.03)[c]
Liraglutide [50]	Pooled analysis	Incidence ratios estimated by Cochran–Mantel–Haenszel	6638	0.73 (0.38, 1.41)
Taspoglutide [52]	Pooled analysis	Peto fixed-effects OR	7056	0.94 (0.57, 1.56)
GLP-1 receptor agonists [12]	Meta-analysis	Mantel–Haenszel OR	12475	0.78 (0.54, 1.13)



Mannucci E, Monami M. *Adv Ther* 34:1-40, 2017

Continued efforts to translate diabetes cardiovascular outcome trials into clinical practice

	Normal or subclinical **ENDOTHELIAL DYSFUNCTION**	**ESTABLISHED ATHERO-SCLEROSIS**	**ACUTE CORONARY SYNDROME**	**HEART FAILURE**
Stage I-II CKD **eGFR 90-60 ml/min/1.73 m²**	Metformin[a], Pioglitazone[b] DPP4-I[c-e], GLP-1 RA[f], SGLT2-I[g], Insulin[1h] SUs[1]	Metformin, SGLT2-I[g], GLP-1RA[f], Pioglitazone[b], DPP4-I[c-e], Insulin[h], Gliclazide[k]	Insulin[m] DPP4-I[e], GLP-1RA[j],	SLGT2-I[g] DPP4-I[d,e], GLP-1RA[f], Insulin[h]
Stage III CKD **eGFR 59-30 ml/min/1.73 m²**	Metformin[2], Pioglitazone[3b], SLGT2-I[4g], GLP-1RA[f], DPP4-I[2c-e], Gliclazide[2k], Insulin[h]	Metformin[2], GLP-1RA[f], SGLT2-I[4g], Pioglitazone[3b], DPP4-I[2c-e], Insulin[h], Gliclazide[2k]	Insulin[m] DPP4-I[e], GLP-1RA[j],	SLGT2-I[g] DPP4-I[d,e], GLP-1RA[f], Insulin[h]
Stage IV CKD **eGFR 29-15 ml/min/1.73 m²**	Pioglitazone[3], DPP4-I[2], Insulin[2]	Pioglitazone[3], DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]
Stage V CKD **eGFR <15 ml/min/1.73 m²**	Pioglitazone[3], DPP4-I[2], Insulin[2]	Pioglitazone[3], DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]

Evidence of efficacy **Evidence of safety** **Author consensus**

Fig. 1 A treatment algorithm based on cardiac and renal co-morbidities and CVOTs. [1]To be used with caution because of the risk of hypoglycemia; [2]consider dose reduction (except for linagliptin) and monitor eGFR frequently; [3]preferred in the presence of marked insulin resistance; [4]initiation of therapy currently not recommended. [a]UKPDS; [b]PROACTIVE trial; [c]SAVOR; [d]TECOS, [e]EXAMINE; [f]LEADER trial; [g]EMPA-REG Outcome trial; [h]ORIGIN trial; [k]ADVANCE; [j]ELIXA; [m]DIGAMI 1

Avogaro et al. Cardiovasc Diabetol (2016) 15:111

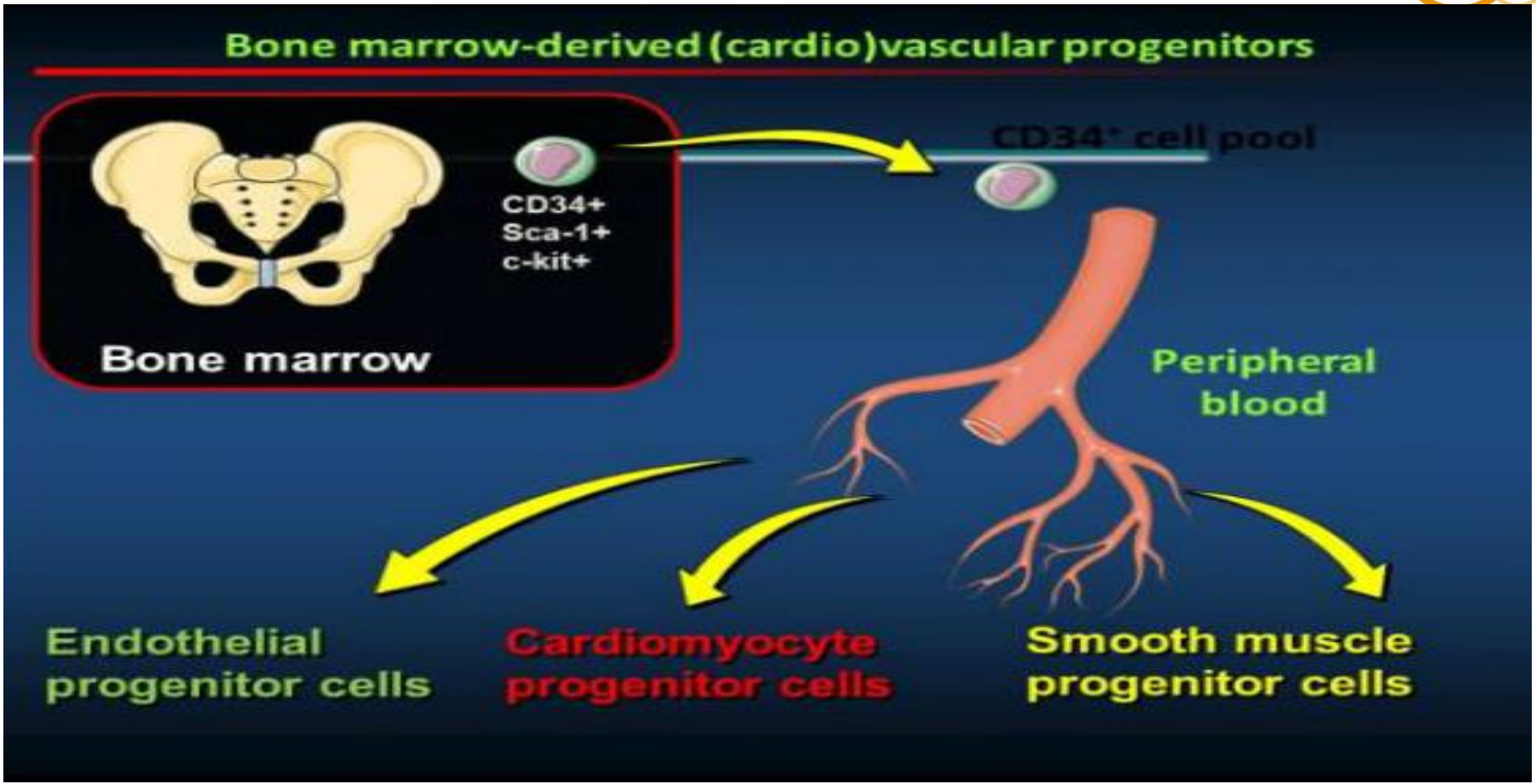
Nuovi farmaci antidiabetici e prevenzione cardiovascolare

GLP-1 RA, DPPIV inibitori, SGLT2 inibitori

APPENDICE

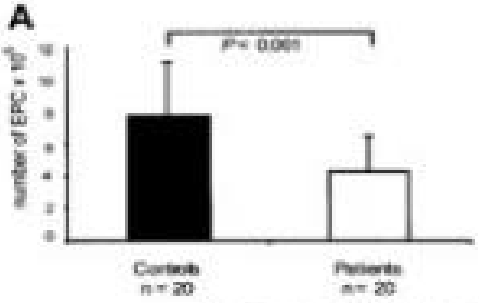
Cellule progenitrici endoteliali

Cardiomiopatia diabetica


Bone marrow-derived (cardio)vascular progenitors
CD34+
Sca-1+
c-kit+
Bone marrow
CD34+ cell pool
Peripheral blood
Endothelial progenitor cells
Cardiomyocyte progenitor cells
Smooth muscle progenitor cells

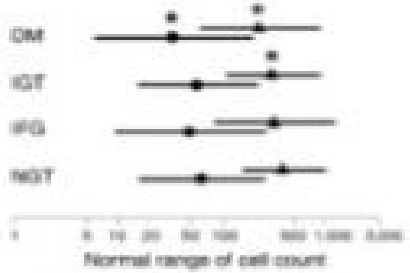
Diabetic patients had reduced level of circulating endothelial progenitors

Type 1 Diabetes



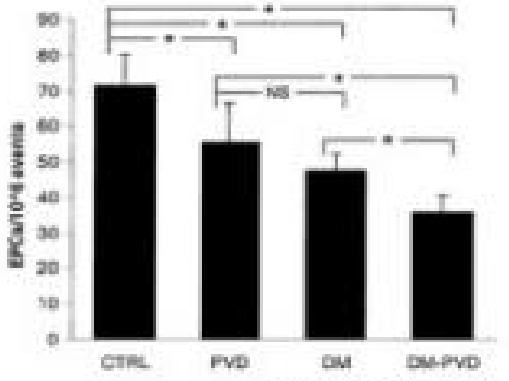
Loomans et al. *Diabetes* 2004

Type 2 Diabetes



Fadini et al., *Diabetologia*, 2008

Type 2 Diabetes + PVD

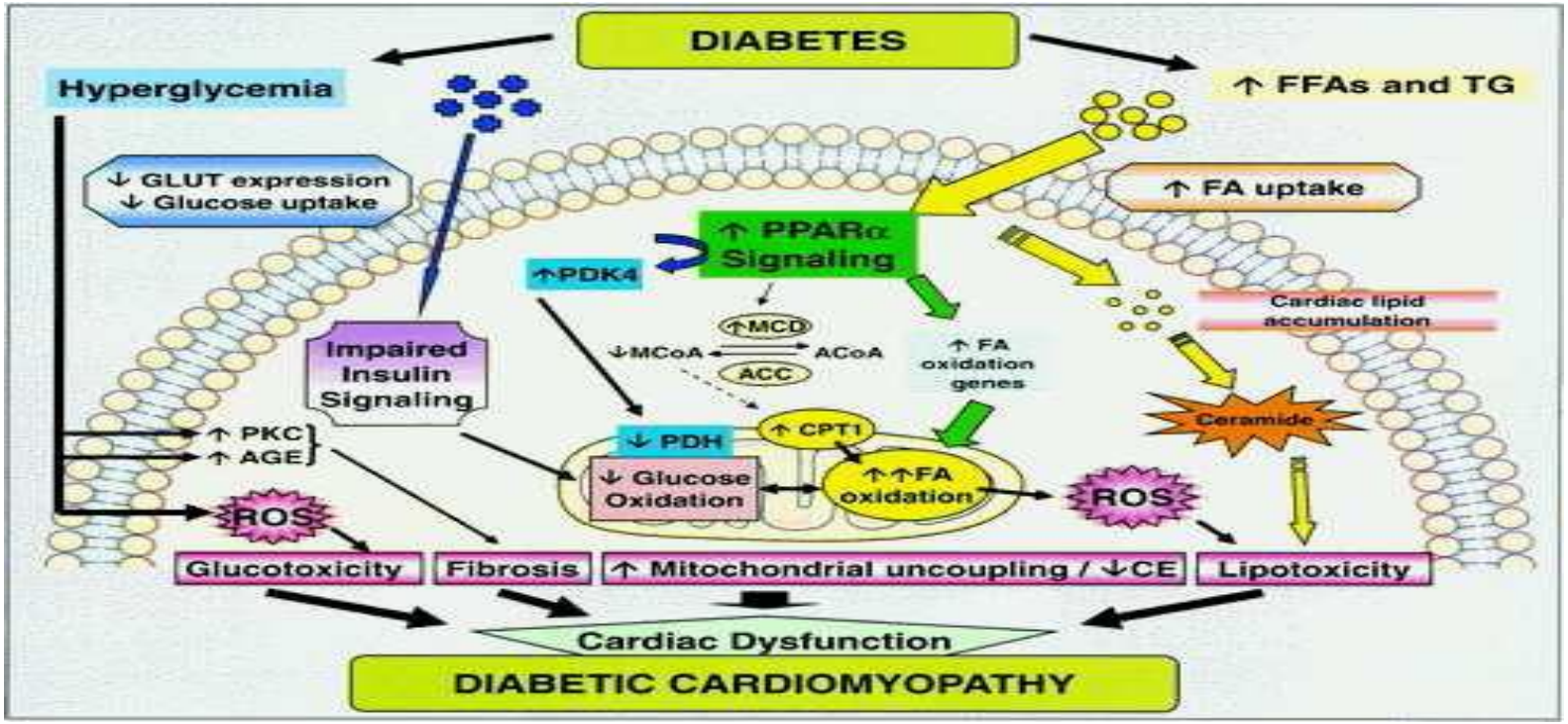


Fadini et al. JACC 2005

EPC defect may contribute to vascular complication in diabetes

E’ un’entità nosologica distinta, caratterizzata da disfunzione ventricolare indipendente da cause riconosciute (coronaropatia o ipertensione arteriosa)

Cardiomiopatia Diabetica



Scompenso cardiaco

- Il diabete mellito è la più frequente patologia a carattere sistemico coinvolta nella patogenesi dello scompenso cardiaco
- La probabilità di scompenso è doppia nei maschi diabetici e cinque volte maggiore nelle femmine diabetiche *(Kannel WB et al. Am J Cardiol 1974; 34: 29-34 – Framingham Study)*
- La cardiomiopatia diabetica può causare insufficienza cardiaca indipendentemente dalla CHD *(Bell DS Diabetes care 2003; 26:2433-2411)*
- Il 12% dei pazienti con DMT2 è affetto da scompenso cardiaco ed il 30% dei ricoverati per scompenso cardiaco è diabetico *(Tarantini L. et al. Ital Heart J Suppl 2004; 5: 605-615)*.

Framingham Heart Study
Follow-up a 30 anni

Eventi cardiovascolari in pazienti con diabete (Età 35-64)

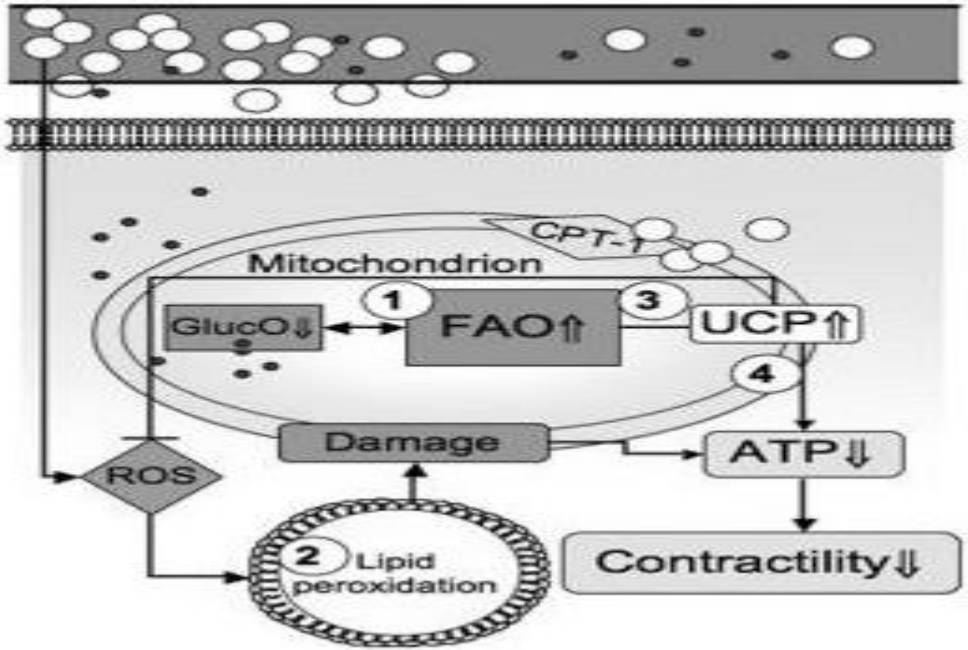
Incidenza annuale/1.000 aggiustata per l'età

P<0.001 tranne **P*<0.05

Wilson PWF, Kannel WB. In: *Hyperglycemia, Diabetes and Vascular Disease*. Ruderman N et al, eds. Oxford; 1992

Pathophysiology of diabetic cardiomyopathy

Mechanisms involved in decreasing cardiac energetics.



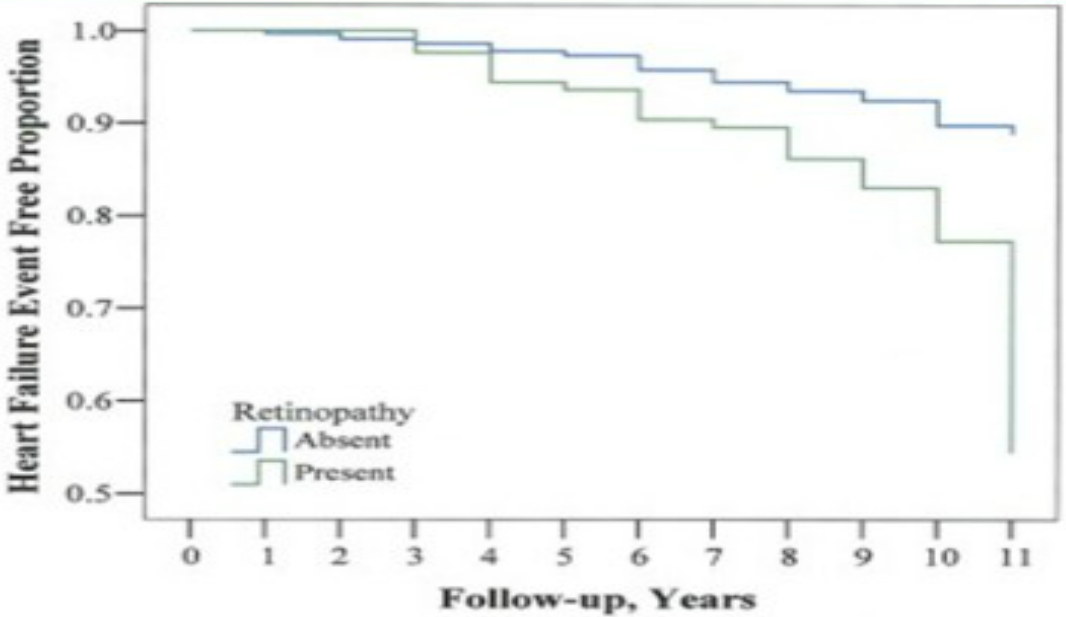
van de Weijer T et al. Cardiovasc Res 2011;92:10-18

Testing for a specific diabetic cardiomyopathy

- ✓ Careful medical history
- ✓ Physical examination
- ✓ Microalbuminuria
- ✓ Diabetic Neuropathy testing
- ✓ Retinopathy (independent predictor of HF even in persons without pre-existing CHD, diabetes, or hypertension)
- ✓ Echocardiography

Heart Failure Free Survival in Participants With and Without Diabetic Retinopathy.

(Cheung et al.)



	No. at Risk by Follow-up Years										
	0	1	2	3	4	5	6	7	8	9	10
Retinopathy	125	125	125	122	118	116	109	106	83	44	14
No Retinopathy	854	851	846	842	833	821	798	778	763	490	192

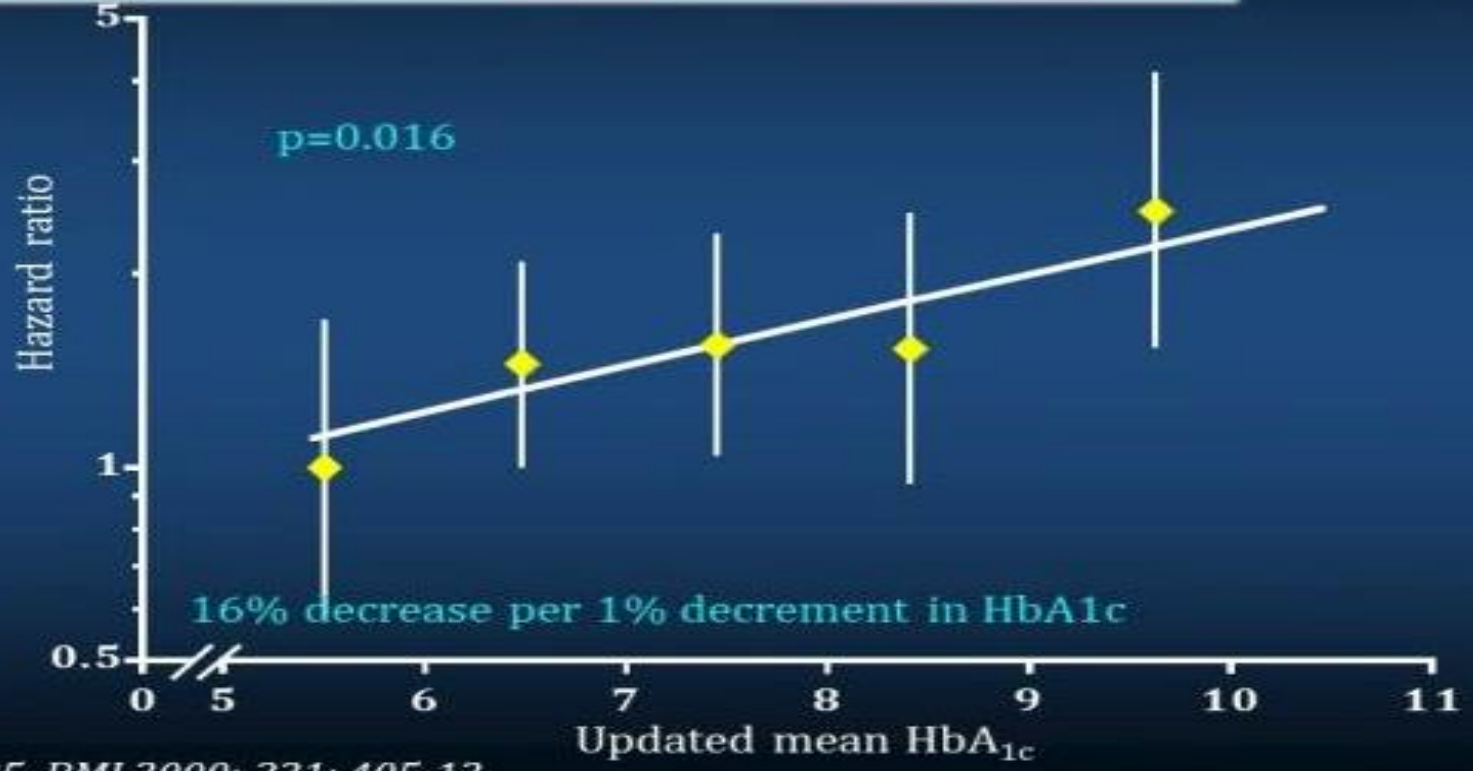
Relative Risk of CVD and Mortality in 3498 DM by Quartile of Albuminuria

ACR (mg/mmol) quartiles RR (95% CI)

	1st	2nd	3rd	4th	
Variable	**<0.22**	**0.22 - 0.57**	**0.58 - 1.62**	**>1.62**	**P for trend**
MI, Stroke & CV death	1	0.85 (0.63 – 1.14)	1.11 (0.86 – 1.43)	1.89 (1.52 – 2.63)	<0.001
All cause mortality	1	0.86 (0.58 – 1.28)	1.41 (1.01 – 1.95)	2.38 (1.80 – 3.20)	<0.001
CHF	1	0.72 (0.32 – 1.63)	1.83 (0.98 – 3.43)	3.65 (2.06 – 6.46)	<0.001

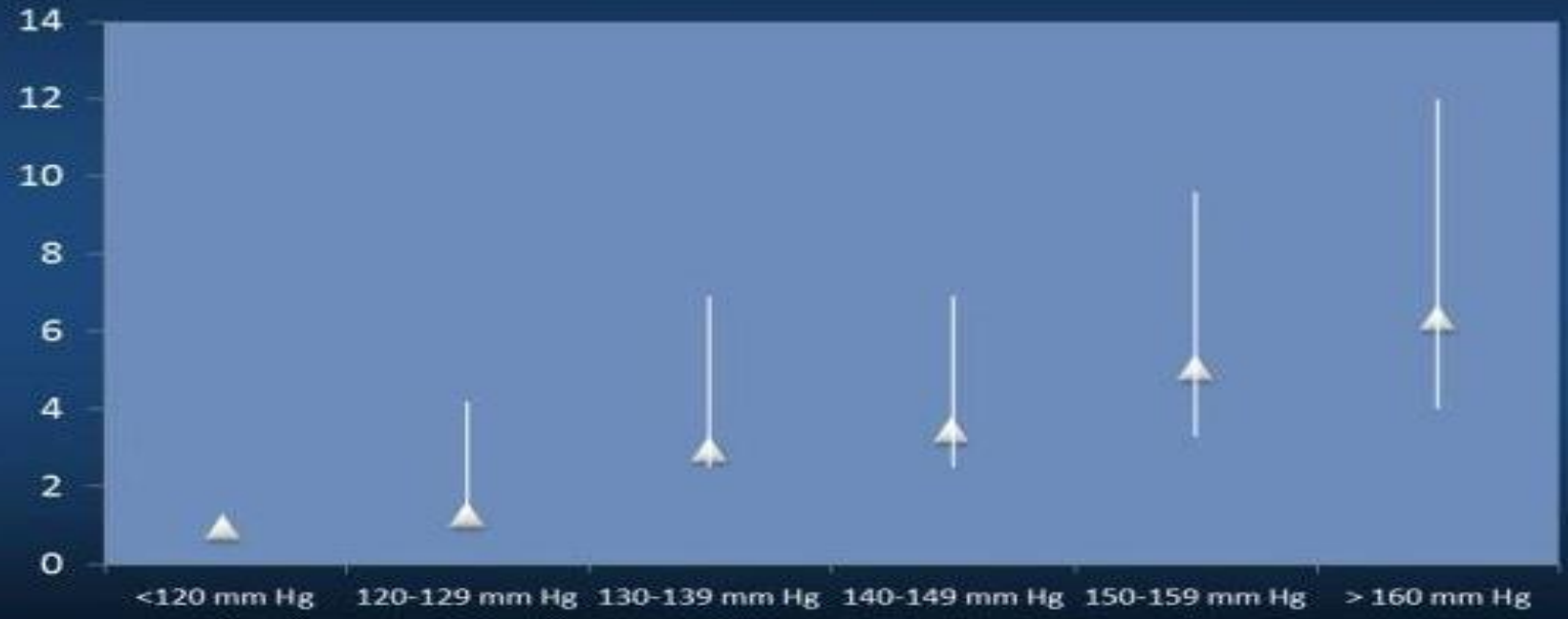
Gerstein et al. *JAMA* 2001

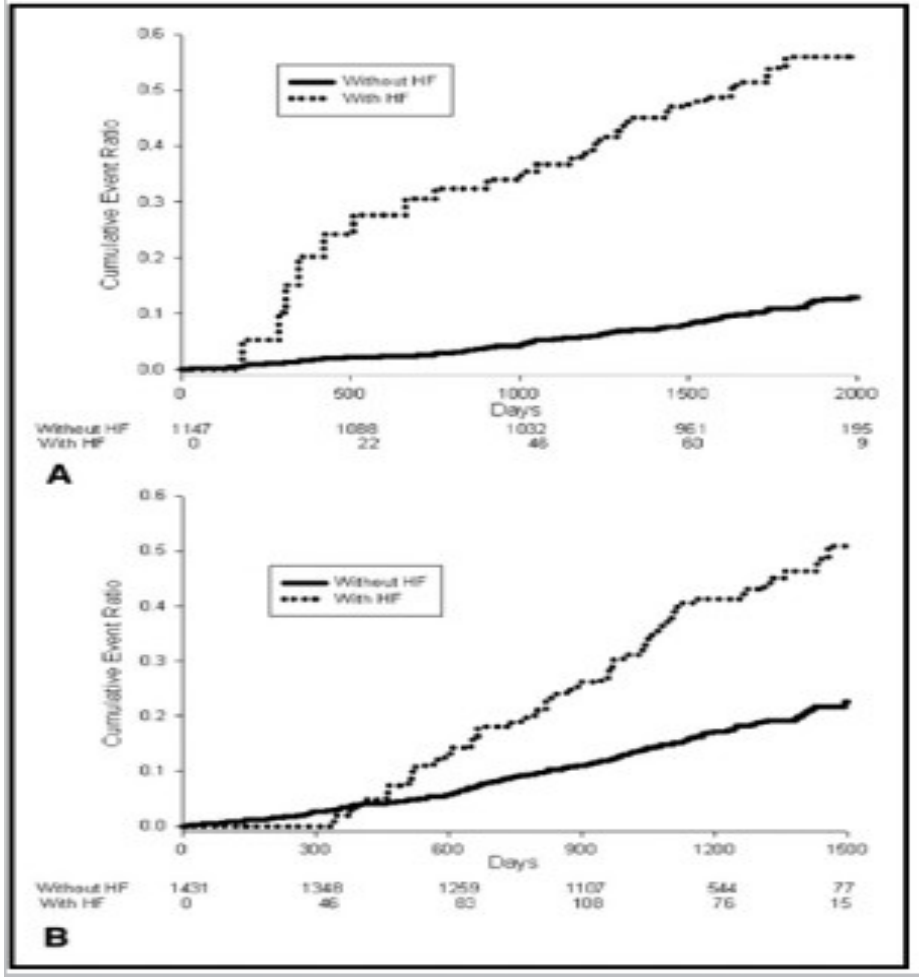
Heart Failure



UKPDS 35. BMJ 2000; 321: 405-12

Incidence of Heart Failure in patients with type 2 diabetes by category of updated mean systolic blood pressure. Rates per 1000 person years' (Adler et al.)





Risk of death after development of HF. (A) Mortality stratified by development of HF in LIFE diabetics

(B) Mortality stratified by development of HF in RENAAL

(Carr et al.)

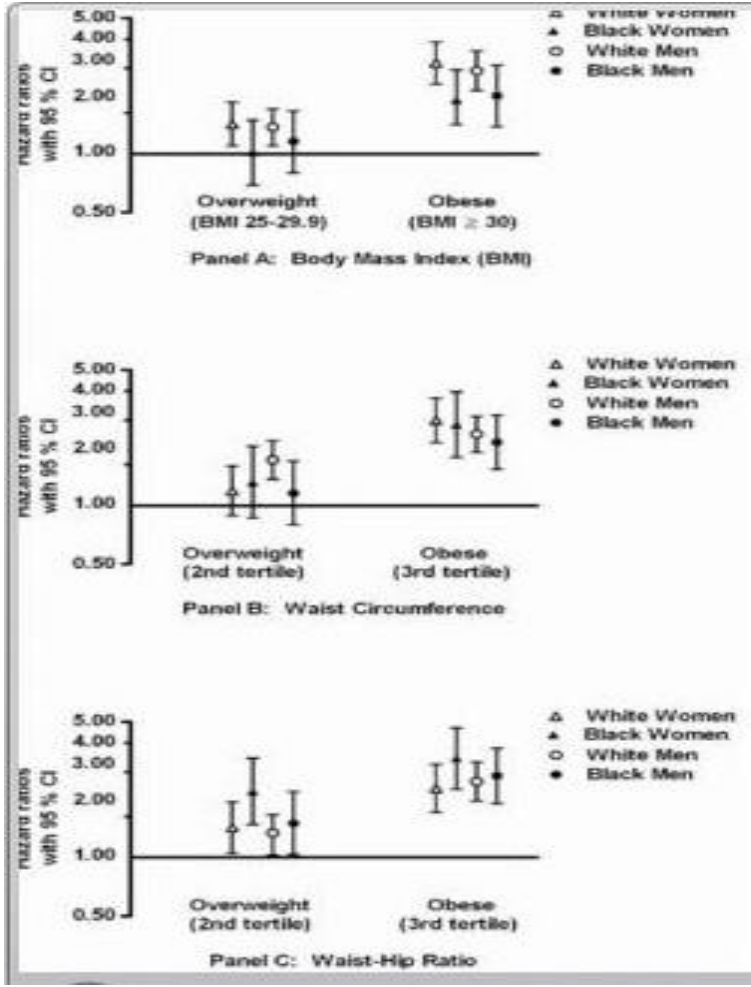
Congestive Heart Failure in Type 2 Diabetes

Prevalence, incidence, and risk factors

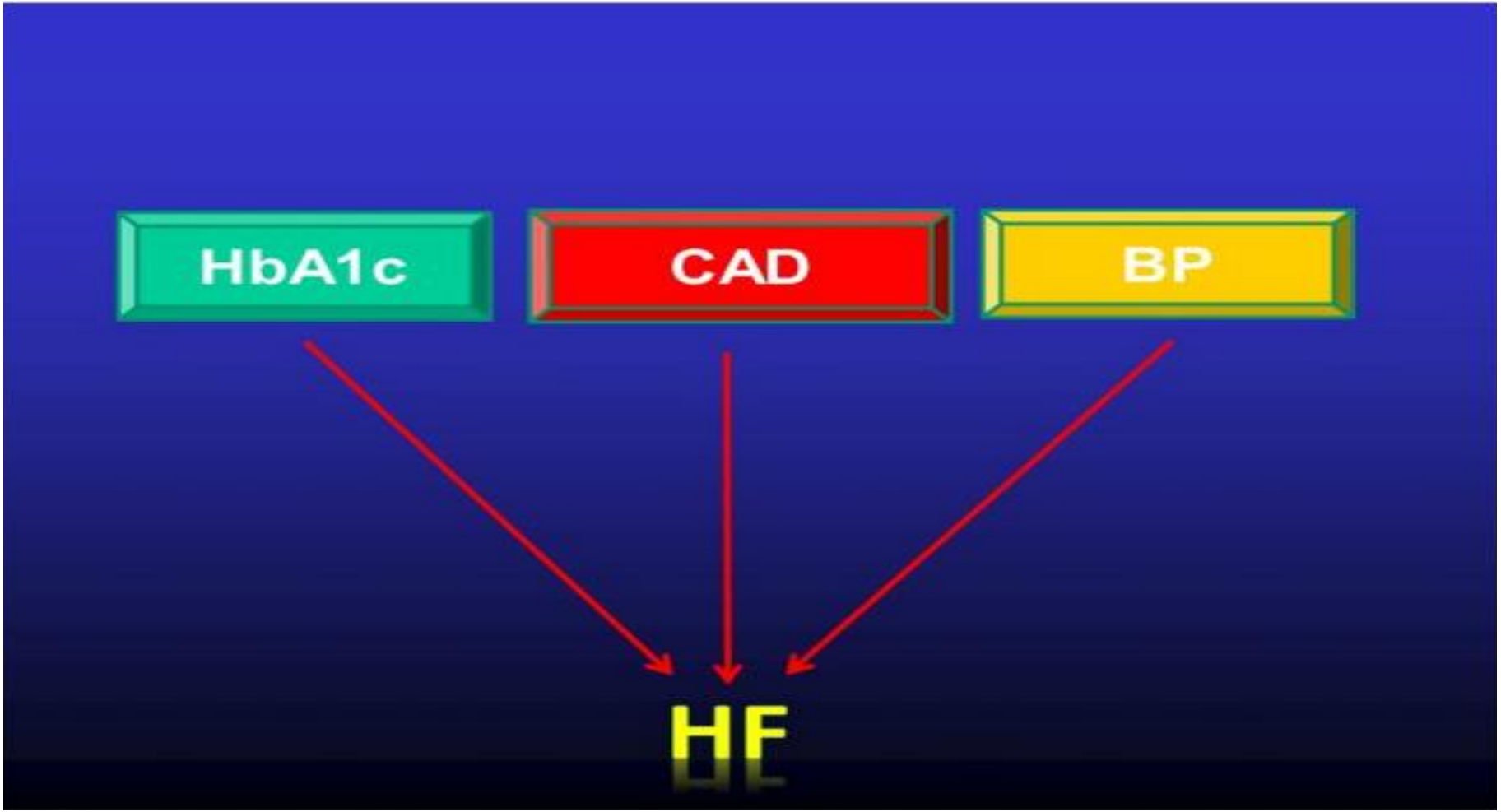
GREGORY A. NICHOLS, PHD[1]
TERESA A. HILLIER, MD, MS[1]
JOHN R. ERBEY, PHD[2]
JONATHAN B. BROWN, PHD, MPP[1]

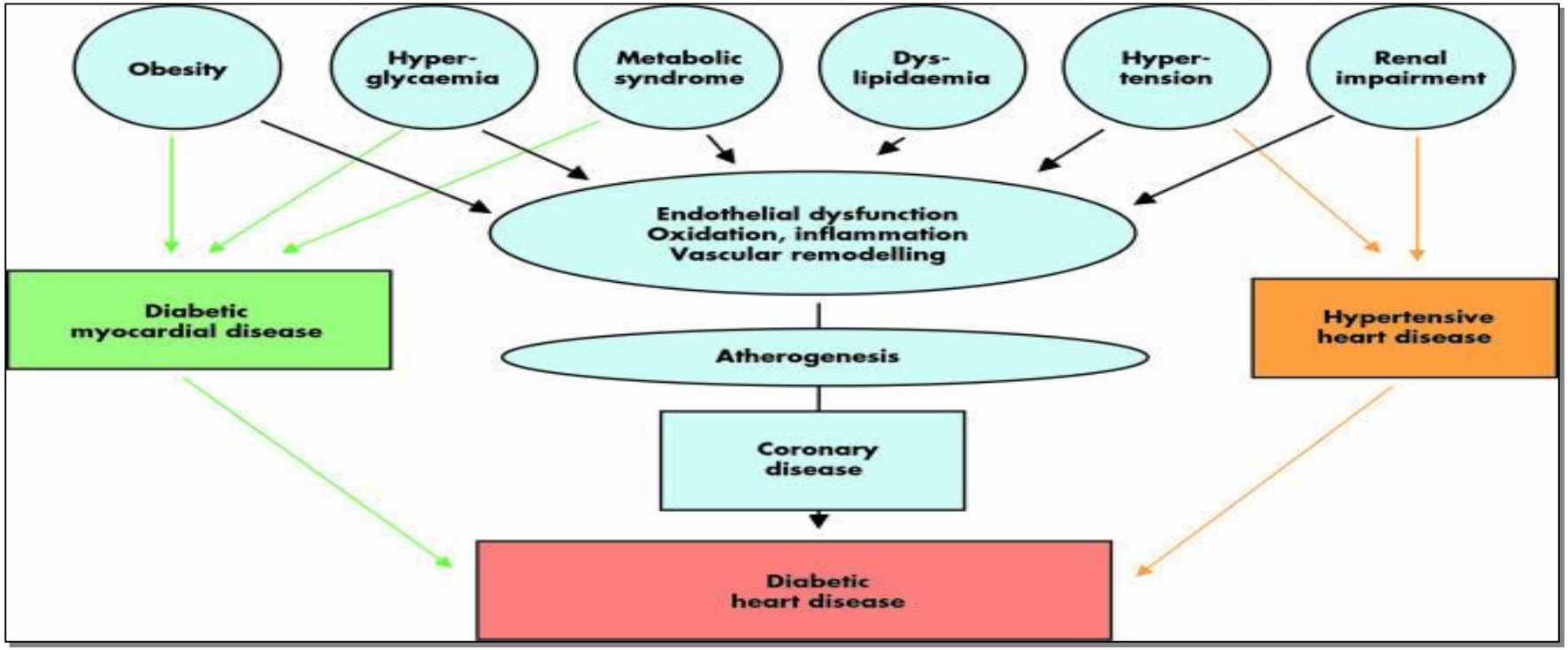
Table 2—*Risk factors for prevalent CHF in multivariate modeling using logistic regression*

Variable	β	SE	*P*	OR	95% CI
Age	0.318	0.005	0.001	1.05	1.04–1.06
Female sex	0.082	0.090	0.001	1.35	1.13–1.61
Duration of diabetes	0.077	0.014	0.005	1.04	1.01–1.07
Use of oral agent	−0.055	0.096	0.032	0.82	0.68–0.98
Use of insulin	0.088	0.117	0.001	1.47	1.17–1.85
HbA_{1c}	−0.006	0.029	0.799	0.99	0.94–1.05
Serum creatinine	0.154	0.076	0.001	1.73	1.49–2.01
Systolic blood pressure	−0.090	0.002	0.001	0.99	0.99–1.00
Diastolic blood pressure	−0.107	0.004	0.001	0.98	0.97–0.99
Weight	−0.004	0.001	0.879	1.00	1.00–1.00
Ischemic heart disease	0.365	0.087	0.001	4.44	3.74–5.26
Hypertension	0.143	0.098	0.001	1.69	1.40–2.05



Graphical representation of race- and gender-stratified adjusted hazard ratios, for overweight and obese as compared to referent as measured by BMI (Panel A), waist circumference (Panel B), and waist-hip ratio (Panel C) (Loher et al.)


HbA1c
CAD
BP
HF



Il Diabete mellito è responsabile di uno spettro di malattie cardiovascolari. Le complicazioni più note derivano da disfunzione endoteliale, ossidazione, infiammazione e rimodellamento vascolare e contribuiscono a aterogenesi.

Diabete e Scompenso: possibili meccanismi causali

Possono esserne presi in esame tre:

- ✓ La comorbilità (condivisione di fattori di rischio)
- ✓ La malattia coronarica
- ✓ La cardiomiopatia diabetica

Bauters et al. Cardiovascular Diabetology 2003, 2