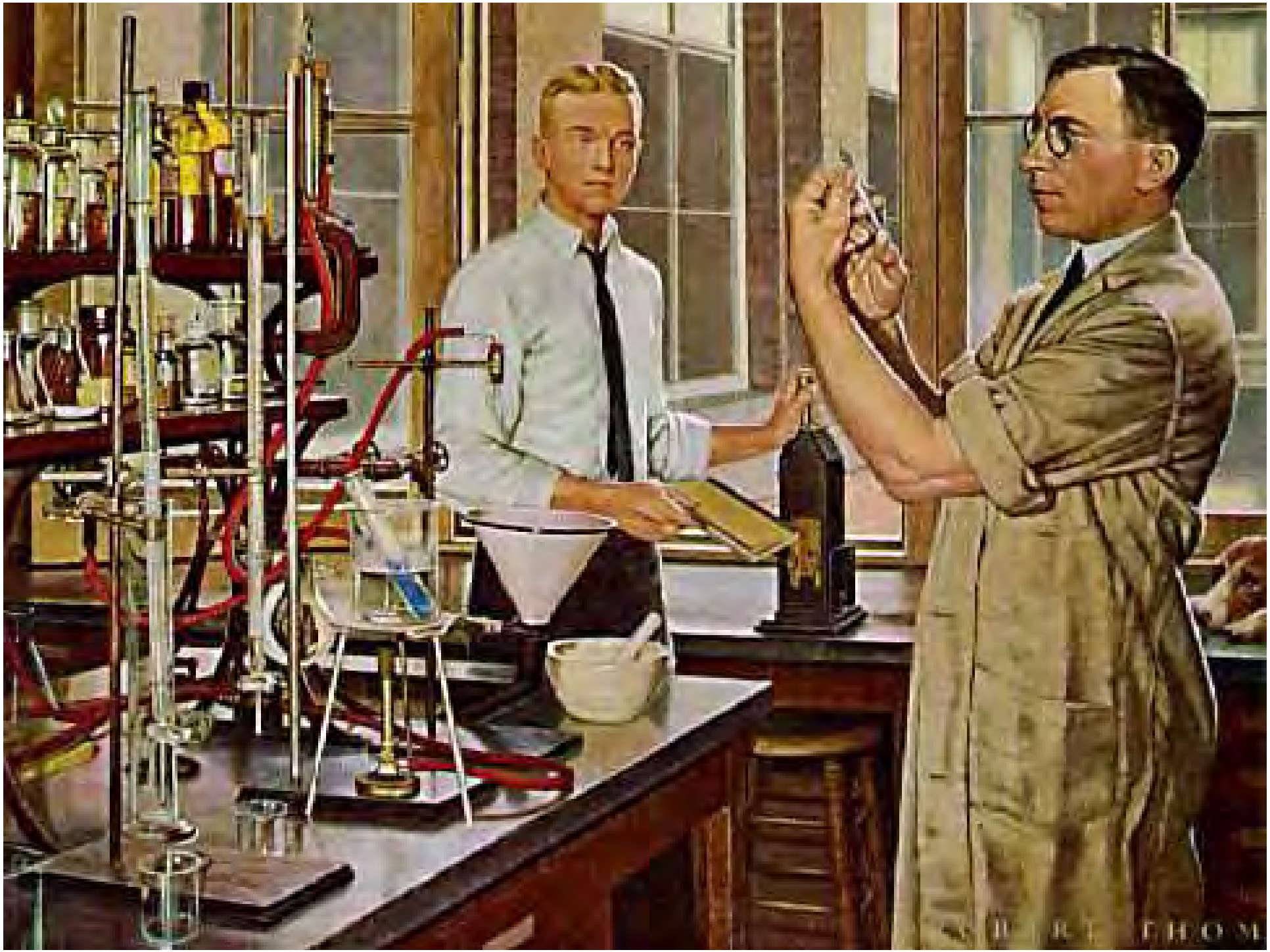
Diabete: dagli ipoglicemizzanti vecchi e nuovi all'insulina

Andrea Corsi

Genova 21/02/14



THE RELATION OF THE ISLETS OF LANGERHANS TO DIABETES WITH SPECIAL REFERENCE TO CASES OF PANCREATIC LITHIASIS

By MOSES BARRON, M.D., Minneapolis, Minnesota
From the Department of Pathology, University of Minnesota, Minneapolis, Minnesota

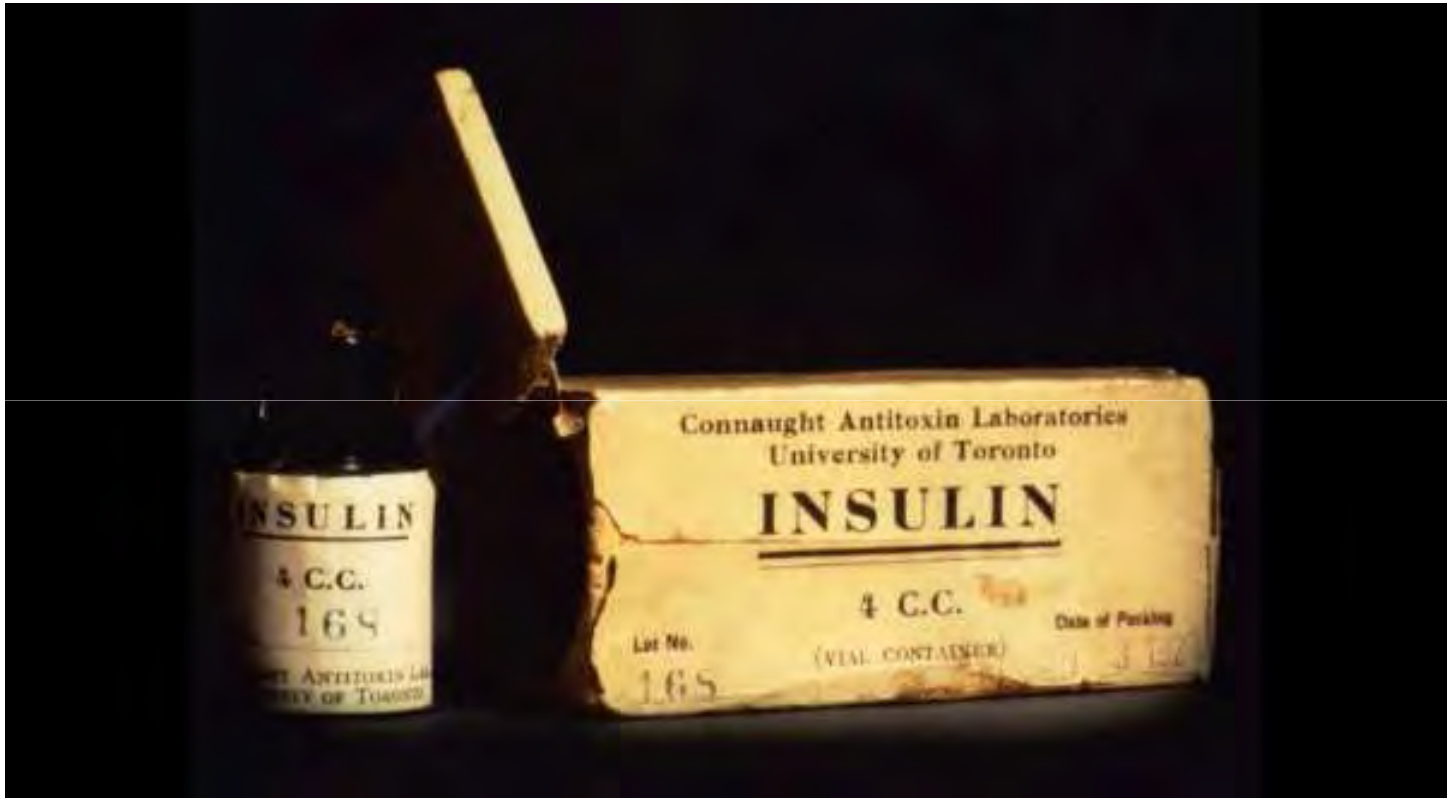
Reprint from
SURGERY, GYNECOLOGY AND OBSTETRICS
November, 1920, pages 437-448

Sir Frederick Banting

J.J.R. Macleod

Charles Best

James Collip


INSULIN
4 C.C.
168
Connaught Antitoxin Laboratories
University of Toronto
INSULIN
4 C.C.
Lot No.
165
(VIAL CONTAINER)
Date of Packing

C O P Y.

THIS INDENTURE made this 30th day of May, A.D.

1922

BETWEEN

The Governors of the University of Toronto,

of the First Part;

-and-

The Eli Lilly Company, Incorporated under the laws of the State of Indiana, of Indianapolis, in Marion County and State of Indiana.

of the Second Part.

WHEREAS the Party of the First Part is the owner of a pancreatic extract or product for the treatment of diabetes mellitus and a process for preparing the same for which application for Letters Patent was filed in the United States Patent Office on or about the 22nd day of May, A. D. 1922 under Serial Number 562, 835.

AND WHEREAS the party of the First Part is not in a position to manufacture the product on a commercial scale and has no financial appropriation to develop the manufacture of the said product.

AND WHEREAS for humanitarian purposes the manufacture of the said product can be more adequately effected by collaboration with one efficient and reliable commercial firm than by collaboration with several firms.

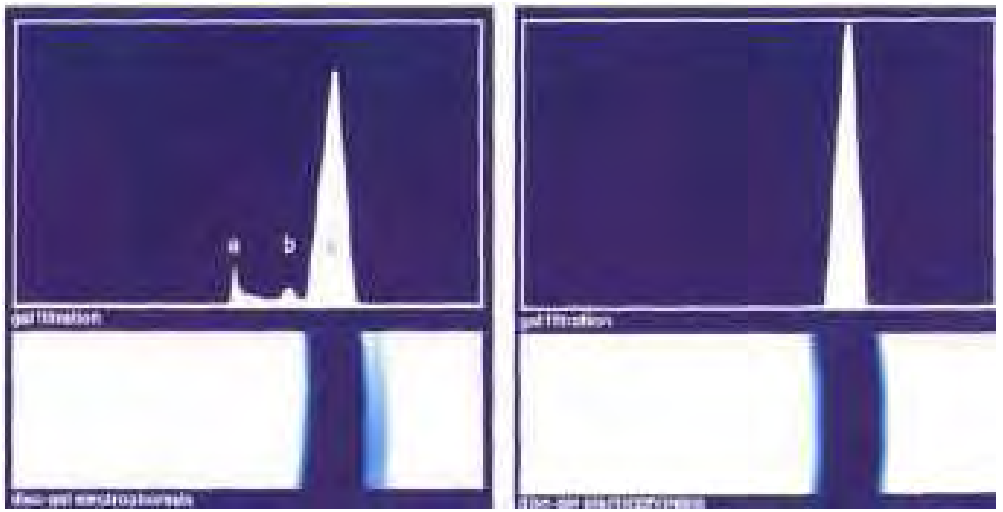
AND WHEREAS the party of the First Part has personal knowledge of the high standing of Dr. Clowes the scientific representative of the said party of the second part and has evidence of the reliability and efficiency of the said party of the second part.

AND WHEREAS the party of the second part is desirous of making and selling the said product and using the said process in the United States of America, Mexico, Cuba, the Central and Southern American Countries.


U 20
INDIANAPOLIS
U 40
AMPOULE
INDIANAPOLIS

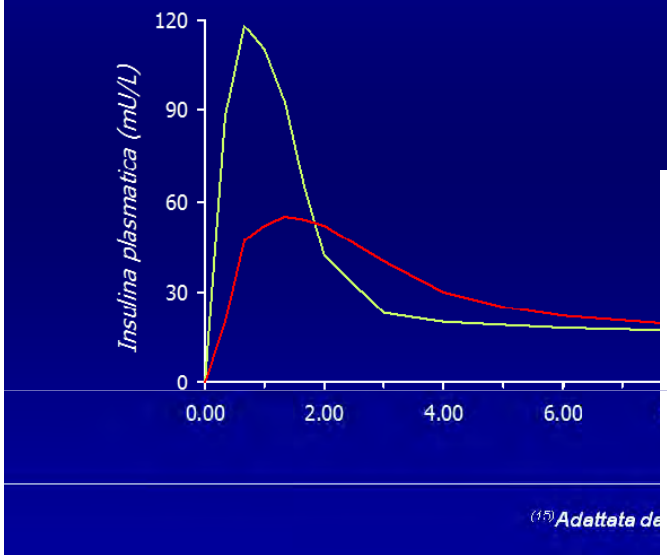
Hagedorn 1935


GI
Insulina humana isófana
Suspensión inyectable
insulina de acción intermedia NPH
(Origen ADN recombinante)
100 UI/ml
PiSA
PiSA
Insulina humana isófa
Suspensión inyectable
100 UI/ml
Frasco ámpula con

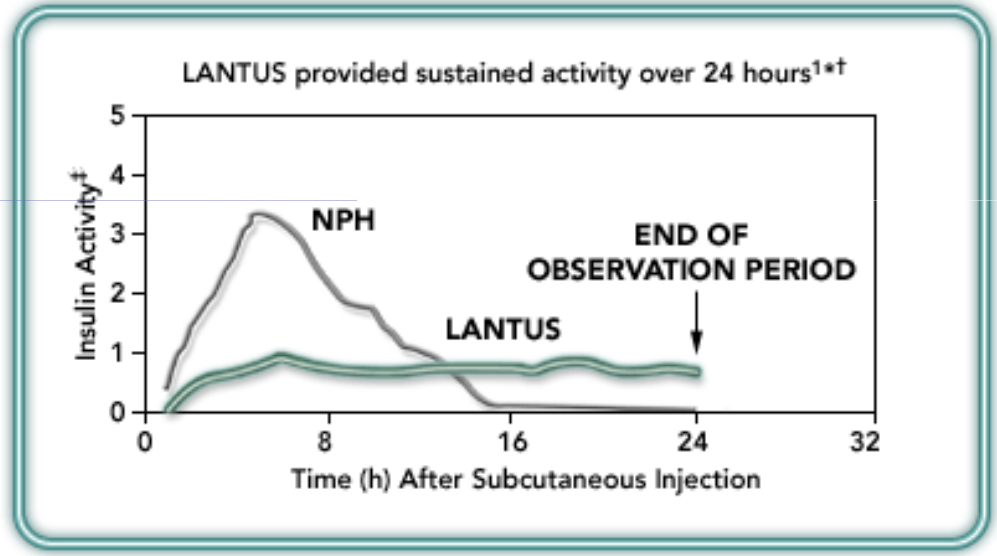


Jörgen Schlichtkrull 1968-70

Profilo insulinemico delle insuline LisPro e Insulina Regolare



(15)Adattata de



*In a double-blind, randomized, crossover euglycemic clamp study involving 20 patients with type 1 diabetes.[2]

†Between patient variability (CV, coefficient of variation); insulin glargine, 84% and NPH, 78%.[1]

‡Glucose utilization rate in mg/kg/min, determined as the amount of glucose infused to maintain constant plasma glucose levels (hourly mean values); indicative of insulin activity.[1]

Analoghi dell’insulina

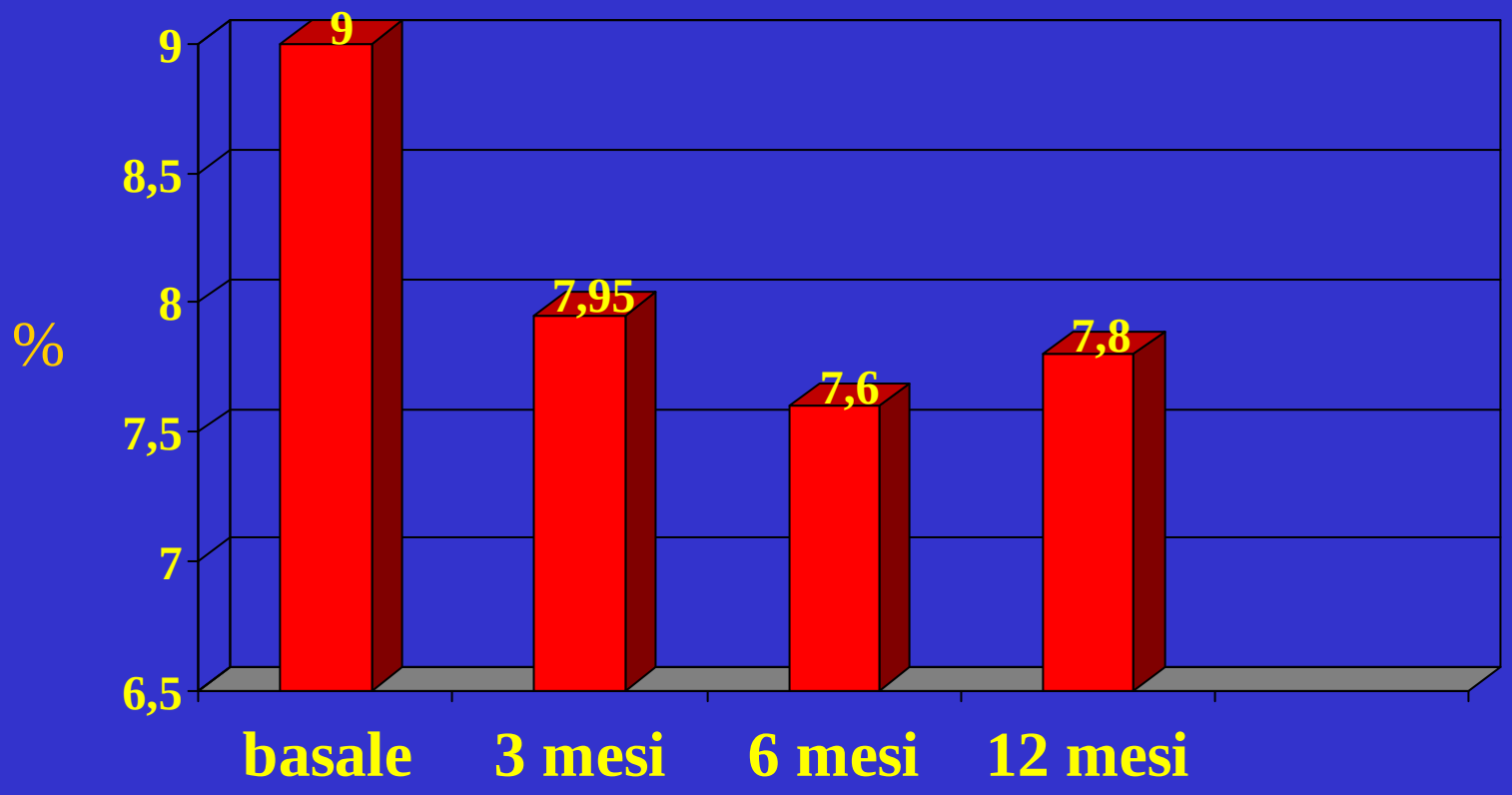
- Compenso glicemico
- Qualità della vita
- Ipoglicemie

Indicazioni riconosciute

	Lyspro	Aspart	Glulisina
Gravidanza	Si	Si	No
Allattamento	No	Si	No
Pediatria	Si >2 anni	Si >2 anni	Si >7 anni

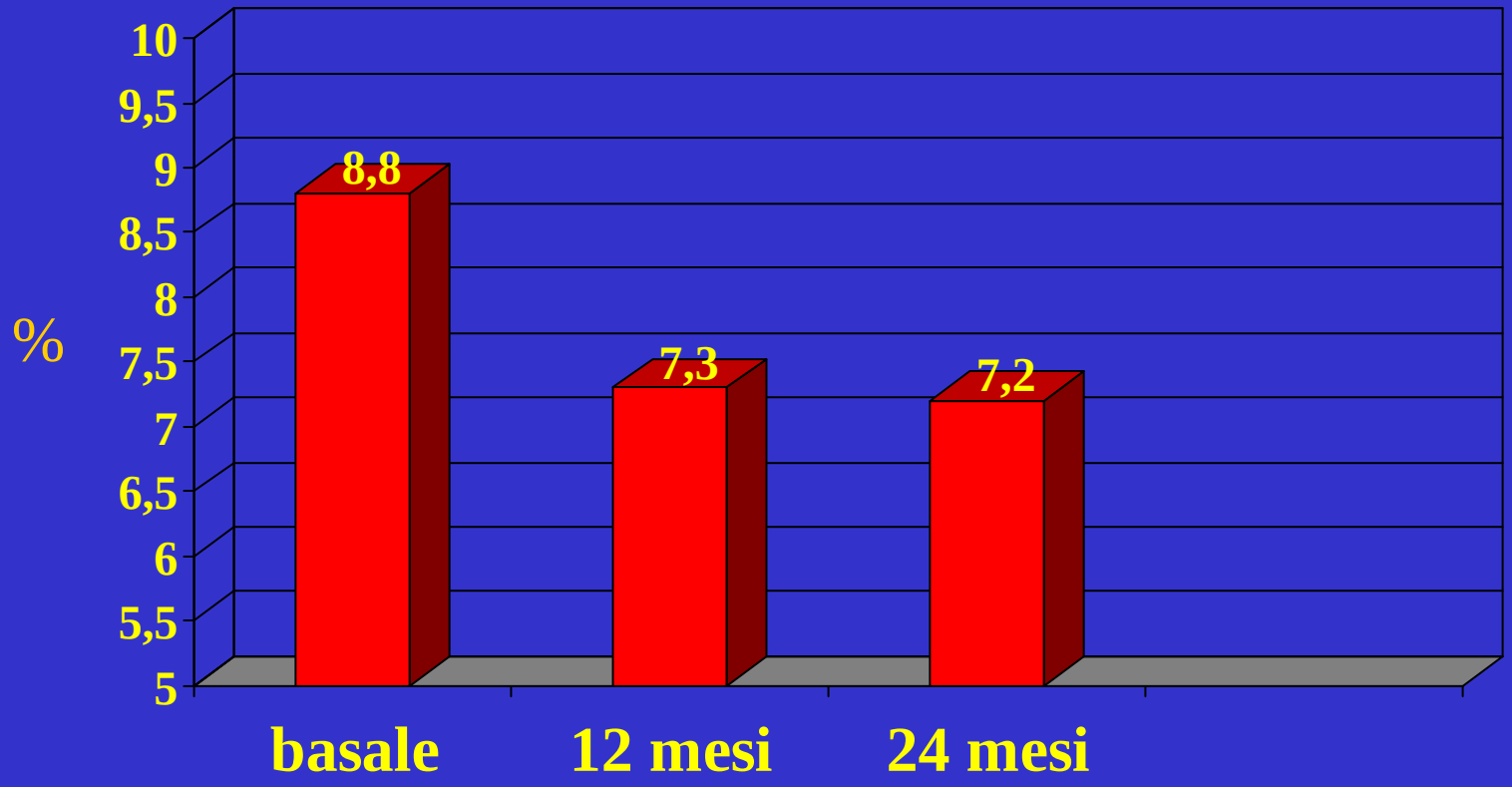

ACCU-CHEK Spirit
1.0u/h

HbA1c dopo 3, 6 e 12 mesi



* p<0,0001

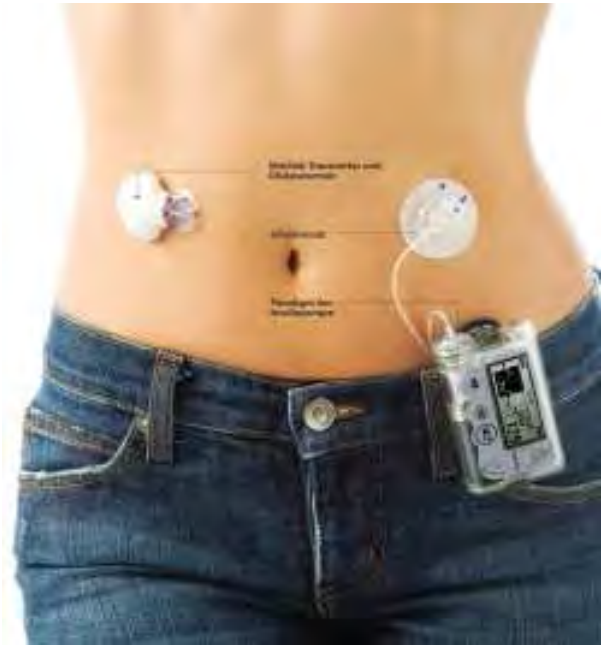
HbA1c dopo 12 e 24 mesi



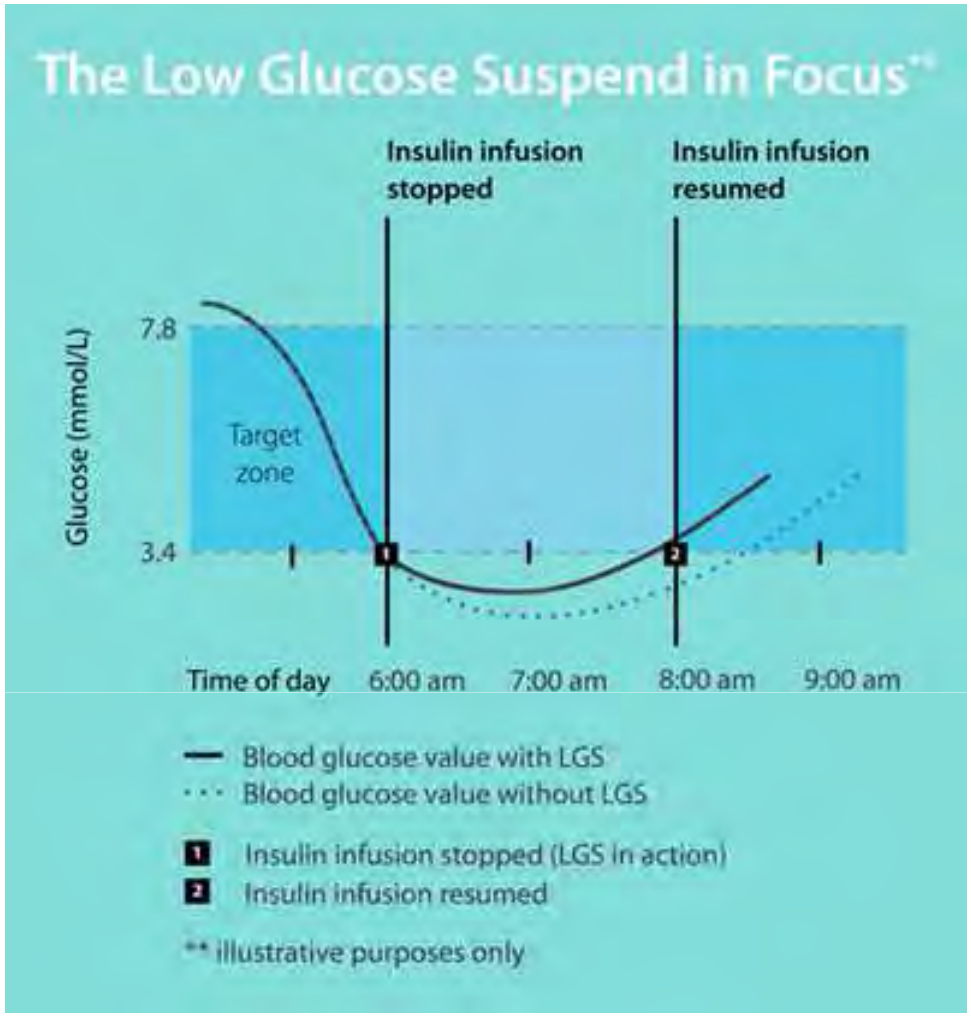
* p<0,05

Microinfusori

- Compenso glicemico
- Variabilità glicemica
- Ipoglicemie
- Qualità della vita



Star 3 trial:
SAP HbA1c da 8,3% a 7,5%
MDI HbA1c da 8,3% a 8,1%



LyT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. **Effect of sensor-augmented insulin pump therapy and automated insuln suspension** vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes. A randomized clinical trial.

JAMA 2013. 25;310(12):1240-7

- Donna di 82 ani si presenta per una visita di controllo routinaria
- APR: dislipidemia, ipertensione, DM T2, artrite reumatoide, toracalgie atipiche, TIA 3 anni prima con “restrizione carotidea”, occasionali perdite di coscienza in corso di ipoglicemia
- EO: PA 128/80, FC 72 bpm r, BMI 31
- Lab: LDL 62 mg/dl, HDL 38 mg/dl, TG 168 mg/dl, glicemia 148 mg/dl, HbA1c 8,6%, eGFR > 60 ml/min/1,73 m2
- Terapia: cardioaspirina, atorvastatina 20 mg, idroclorotiazide 1 c, lisinopril 5 mg, metformina 500 x 3

sulfoniluree

PRO

- Buona efficacia
- Costo contenuto

CONTRO

- Ipoglicemie
- Aumento peso
- Perdita efficacia nel tempo
- IRC > 60 ml/min/1,73m2

repaglinide

PRO

- Ottima efficacia su glic post-prandiale
- Eliminazione epatica

CONTRO

- Ipo
- Peso
- IRC ?

metformina

PRO

- Buona efficacia
- Non ipo
- Non aumento di peso
- Economica

CONTRO

- Acidosi lattica
- IRC (GFR>30?)
- IRAcuta: mezzi di contrasto, chirurgica
- Effetti Gastro Intestinali

acarbosio

PRO

- Buona efficacia
- Non aumento di peso
- Non ipo
- IR (<30 ml/min/1,73 m2

CONTRO

- Disturbi Gastro Intestinali

pioglitazone

PRO

- Buona efficacia
- IRC: eGFR>5
- Durability a 2 anni
- Riduzione IMA Ictus
- No ipoglicemie

CONTRO

- Efficacia max in 4 settimane
- Ritenzione idrica
- Edema
- Scompenso cardiaco
- Aumento peso
- Ematuria/K vescica
- Edema maculare
- Fratture ossee nelle F

gliptine

PRO

- Buona efficacia
- Stimolaz insulina glucosio dipendenete
- Inibizione glucagone
- No aumento di peso
- Non ipoglicemie

CONTRO

- Ricoveri x scompenso cc (saxagliptin)

GLP1

PRO

- ottima efficacia
- Stimolaz insulina glucosio dipendenete
- Inibizione glucagone
- Calo peso
- No ipo

CONTRO

- nausea

SAVOR-TIMI 53: Design

- Double-blind, placebo-controlled trial examining safety, efficacy of DPP-4 inhibitor saxagliptin
- Subjects randomized 1:1 to saxagliptin or matched placebo
  - Other antihyperglycemic, CVD therapies allowed
- Primary endpoint: composite of CV death, nonfatal MI, or nonfatal ischemic stroke
- Secondary endpoint: primary endpoint + hosp for heart failure, coronary revascularization, or unstable angina
- Median follow-up: 2.1 yrs

Subjects (N=16,492)
- **Type 2 diabetes**
- **A1C 6.5% to 12%**
- **Established CVD hx**

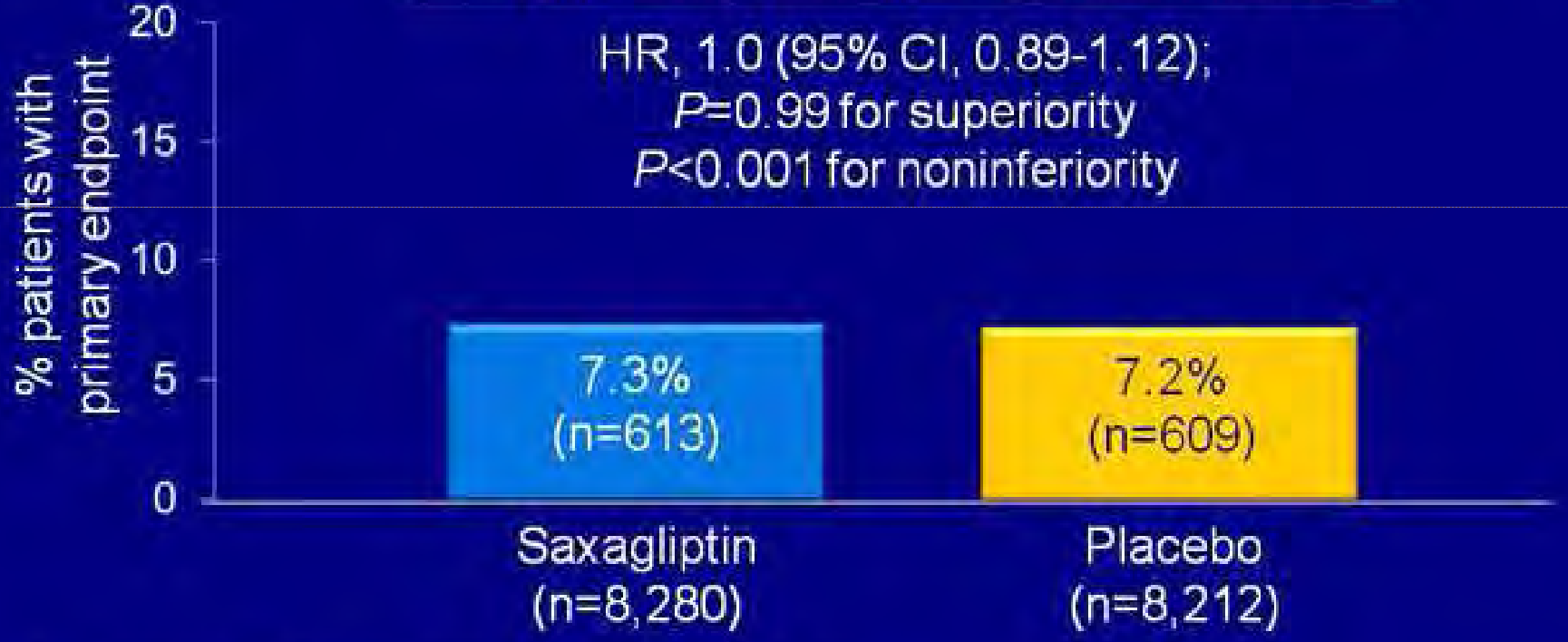
or
- **Multiple CVD risk factors***

*≥1 of the following: dyslipidemia, hypertension, current smoking
Saxagliptin is not FDA approved for cardiovascular risk reduction
SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor; MI=myocardial infarction

Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators
New Engl J Med. 2013. DOI:10.1056/NEJMoa1307684

SAVOR-TIMI 53: No Increase in CV Events with Saxagliptin in Patients With or At Risk for CVD

Primary endpoint: composite of CV death, nonfatal MI, or nonfatal ischemic stroke



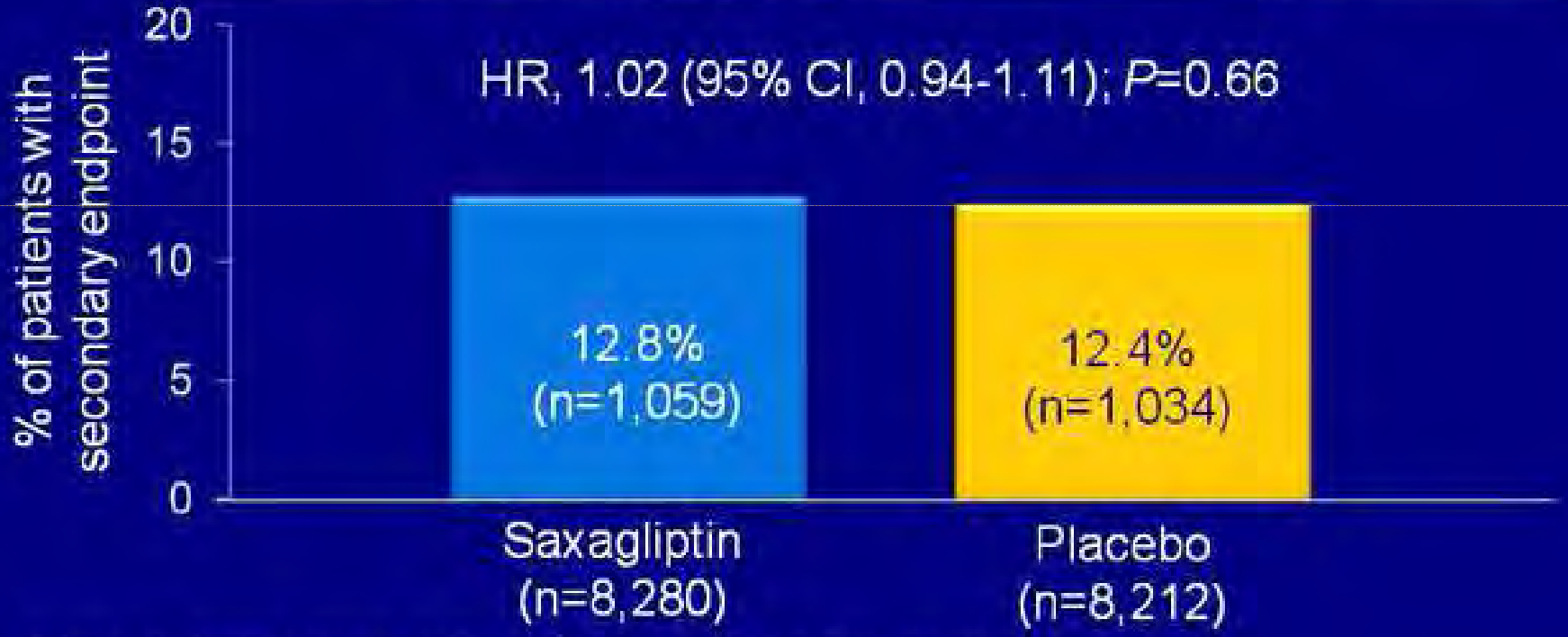
Saxagliptin is not FDA approved for cardiovascular risk reduction

SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; CV=cardiovascular; MI=myocardial infarction

Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. *New Engl J Med*. 2013. DOI:10.1056/NEJMoa1307684.

SAVOR-TIMI 53: No Increase in CV Events with Saxagliptin in Patients With or At Risk for CVD *Secondary Endpoint*

Secondary endpoint: primary endpoint* + hosp for heart failure, coronary revascularization, or unstable angina



*Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke

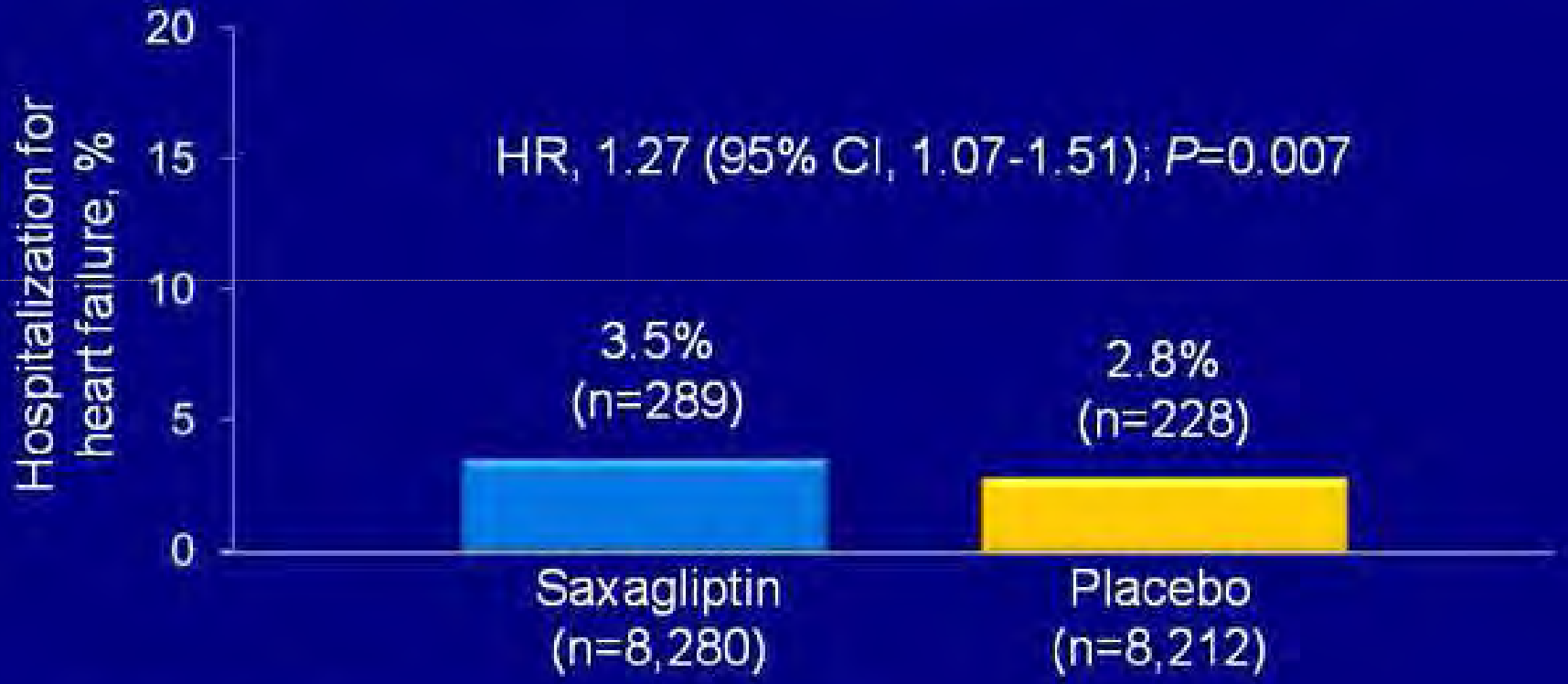
Saxagliptin is not FDA approved for cardiovascular risk reduction

SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53

Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. *New Engl J Med*. 2013. DOI:10.1056/NEJMoa1307684.

Close

SAVOR-TIMI 53: Saxagliptin Increased Hospitalization for Heart Failure



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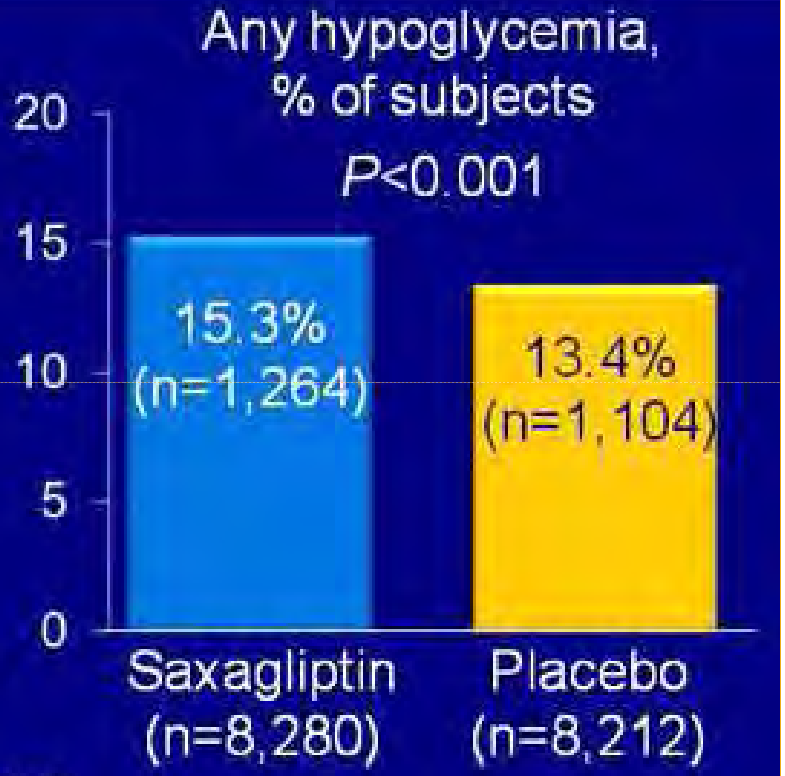
SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53

Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. *New Engl J Med*. 2013. DOI: 10.1056/NEJMoa1307684

SAVOR-TIMI 53: Safety Endpoints

- More hypoglycemia with saxagliptin
- Similar rates in both groups
  - Pancreatitis
  - Thrombocytopenia
  - Lymphocytopenia
  - Infections
  - Hypersensitivity/skin reactions
  - Bone fractures
  - Liver abnormalities
- Cancer rate similar between groups; no excess of pancreatic cancer with saxagliptin
  - 12 cases of pancreatic cancer in placebo group vs 5 cases in saxagliptin group; *P*=0.095



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Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. *New Engl J Med*. 2013. DOI: 10.1056/NEJMoa1307684

stadio IRC	LIEVE	MODERATA	GRAVE	DIALISI
eGFR **(CKD-EPI)**	eGFR > 60	60 > eGFR > 30	30 > eGFR > 15	eGFR < 15
metformina	almeno 2 g	non indicato (utilizzabile)	NO	NO
sitagliptin	100 mg x 1	50 mg x1	25 mg x 1	25 mg x 1
vildagliptin	50 mg x 2	50 mg x 1	50 mg x 1	50 mg x 1
saxagliptin	5 mg x 1	2,5 mg x 1	2,5 mg x 1	NO
linagliptin	5 mg x 1	5 mg x 1	5 mg x 1	5 mg x 1
exenatide	variabile	cautela	NO	NO
liraglutide	variabile	NO	NO	NO
sulfoniluree	variabile	NO	NO	NO
repaglinide	variabile	non indicato (utilizzato)	NO	NO
pioglitazone	variabile	variabile	variabile	NO

HbA_{1c} valori attuali (allineati al DCCT) %	HbA_{1c} valori nuovi (allineati all'IFCC)% mmol/mol
4,0	20
5,0	31
6,0	42
7,0	53
8,0	64
9,0	75
10,0	86

Attività fisica	Movimento corporeo prodotto dalla contrazione di muscoli scheletrici che richiec una spesa energetica in eccesso rispetto alla spesa energetica a riposo
Esercizio fisico	Movimento corporeo programmato, strutturato e ripetuto, eseguito allo scopo di migliorare o mantenere una o più componenti in buona forma fisica
Esercizio aerobico	Movimenti ritmici, ripetuti e continui degli stessi grandi gruppi muscolari per almeno 10 minuti ciascuno. Gli esempi comprendono camminare, andare in bicicletta, corsa lenta, nuoto, esercizi aerobici acquatici e molti sport
Esercizio contro resistenza	Attività che utilizzano la forza muscolare per muovere un peso o lavorare contr un carico che offre resistenza

Met	unità di equivalente metabolico utilizzato per stimare il costo metabolico di un'attività fisica secondo la relazione 1MET=3,5 ml O_2/Kg/min oppure 1MET=1Kcal/Kg/h. il consumo di 1MET/kg/h corrisponde a quello della condizione di assoluto riposo (metabolismo basale).
VO_2max	capacità aerobica massima ; dipende, ovviamente, dal grado di allenamento e dalle capacità respiratoria e cardiovascolare. È una funzione "ALLENABILE". P semplicità corrisponde alla FCMT che si calcola con la formula di Karvonen.
Volume attività fisica	si esprime in METs/h/sett. e si ottiene sommando i mets/h di ciascuna attivita' per la durata in ore delle stesse.

Iniziare con solo intervento su stile di vita (se non grave scompenso metabolico)

↓

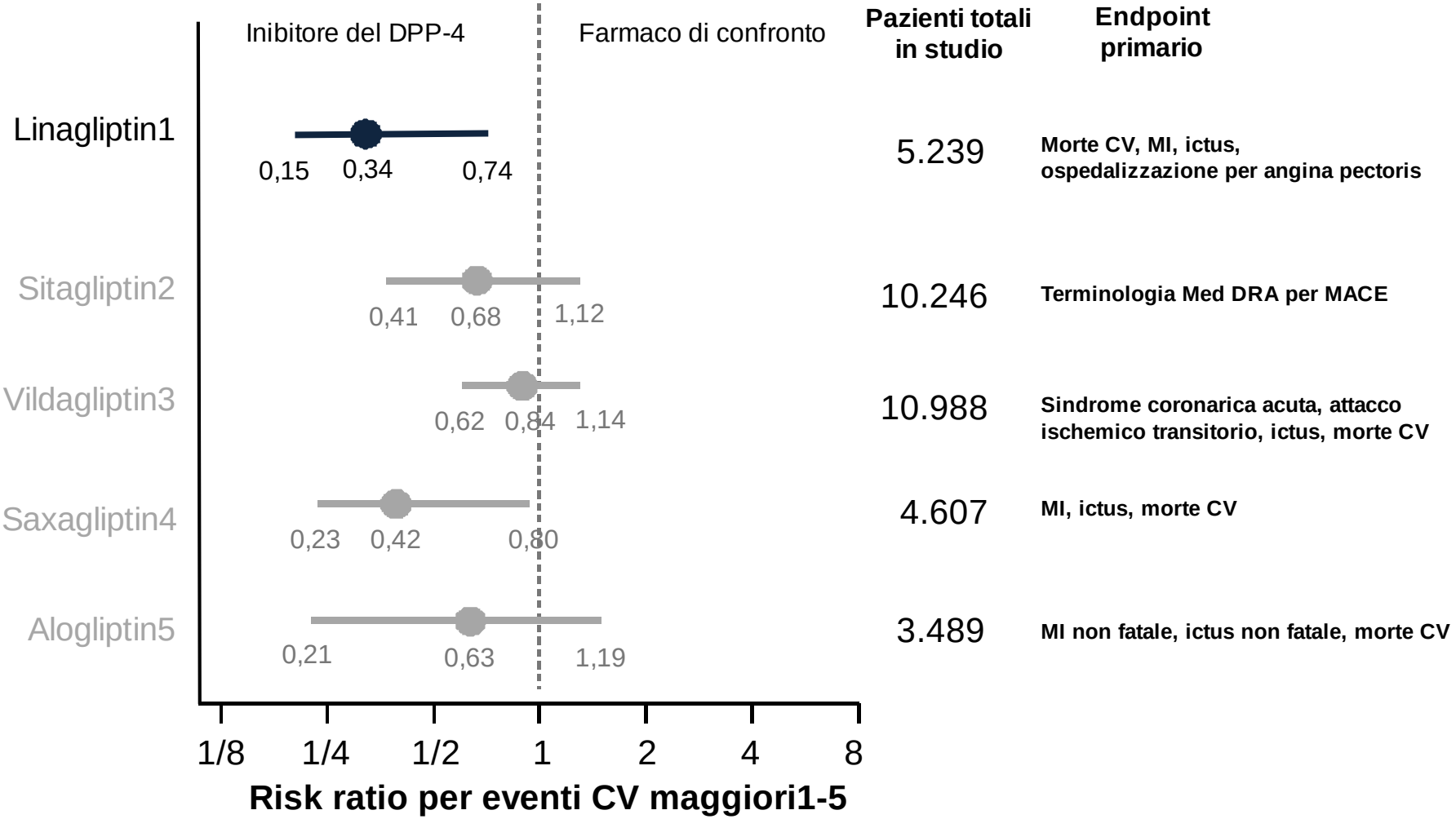
Aggiungere gradualmente metformina, fino alla dose di almeno 2 g die

↓

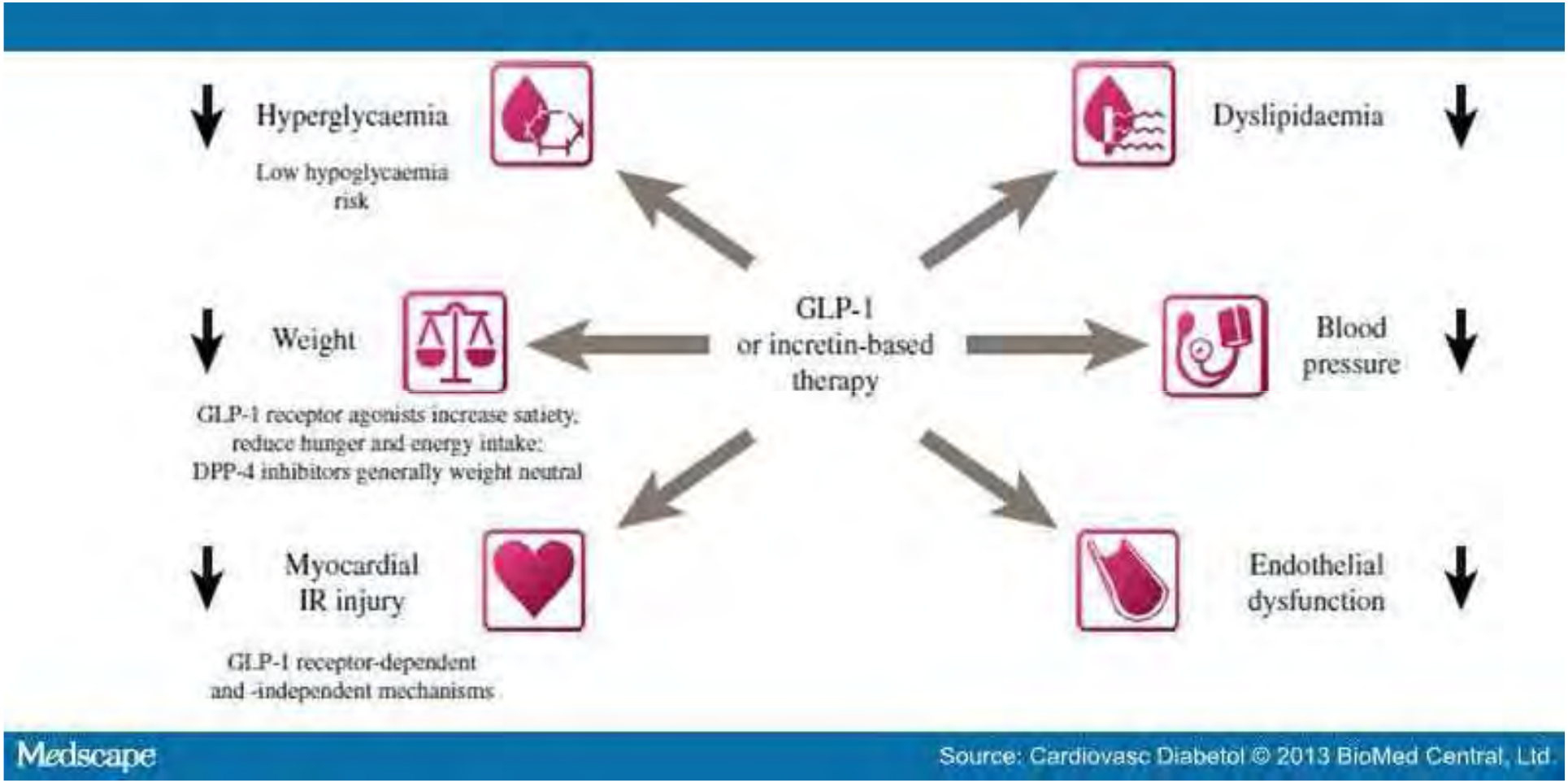
Add on a metformina	Ipoglic.	Peso	Effetti indesid.	CVD	Fattori rischio CV	Scomp. cardiaco	Effetti G.I.	Costo
Gliptina	1A	1B	Rari	1A	1B	2B[1]	1A	elevato
A. R. GLP-1	1A	1A	Non indicato in IRC	3B	1A	2B	1C	elevato
Sulfonilurea o Repaglinide	1D	1D	Non indicato in IRC[2]	3C[3]	1B	1B	1A	basso
Pioglitazone	1A	1D	Fratture	1A	1A	1E	1A	medio
Acarbosio	1A	1C	Rari	2B	2B	3C	1C	basso
Gliflozina	1A	1A	Infezioni G.U.	3C	2B	2B	1A	???
Insulina Basale	1D	1D	Rari	1B	1A	1B	1A	medio

Promettenti dati di sicurezza CV: tutti gli inibitori del DPP-4 sono attualmente oggetto di studi sugli esiti a lungo termine

Non è stato riscontrato un aumentato rischio di eventi CV nei pazienti randomizzati a ricevere inibitori del DPP-4

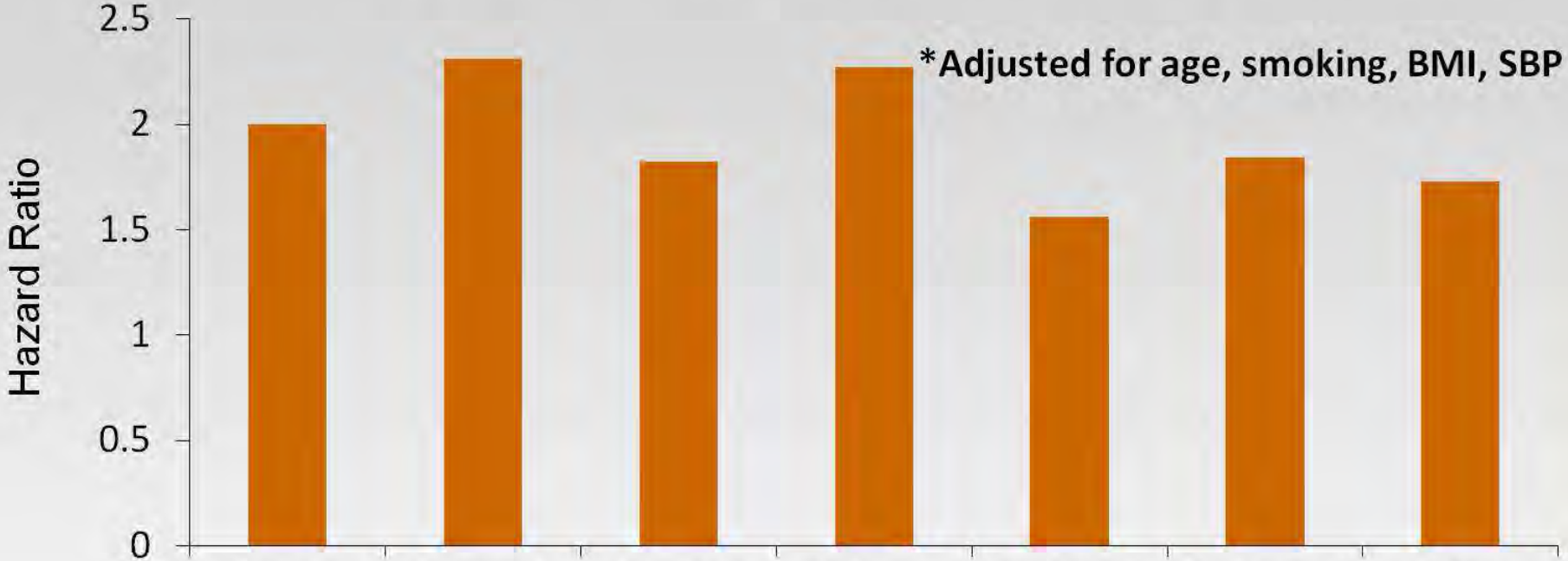


1. Johansen O-E., et al. ADA 2011 Late breaker 30-LB; 2. Williams-Herman D, et al. *BMC Endocr Disord*. 2010;10:7.
3. Schweizer A, et al. *Diabetes Obes Metab* . 2010;12(6):485–494; 4. Frederich R, et al. *Postgrad Med*. 2010;122(3):16–27;
5. White et al. 2010, ADA Scientific Sessions. Abstract 391-PP



Diabetes and Risk of CV Outcomes

102 prospective studies; 700K people; 8.5M patient-years follow-up



	Coronary Heart Disease*	Coronary Death	Nonfatal Myocardial Infarction	Ischemic Stroke	Hemorrhagic Stroke	Unclassified Stroke	Other Vascular Deaths
Number of Cases	26,505	11,556	14,741	3799	1183	4973	3826
95% CI	1.83-2.19	2.05-2.60	1.64-2.03	1.95-2.65	1.19-2.05	1.59-2.13	1.73-1.98

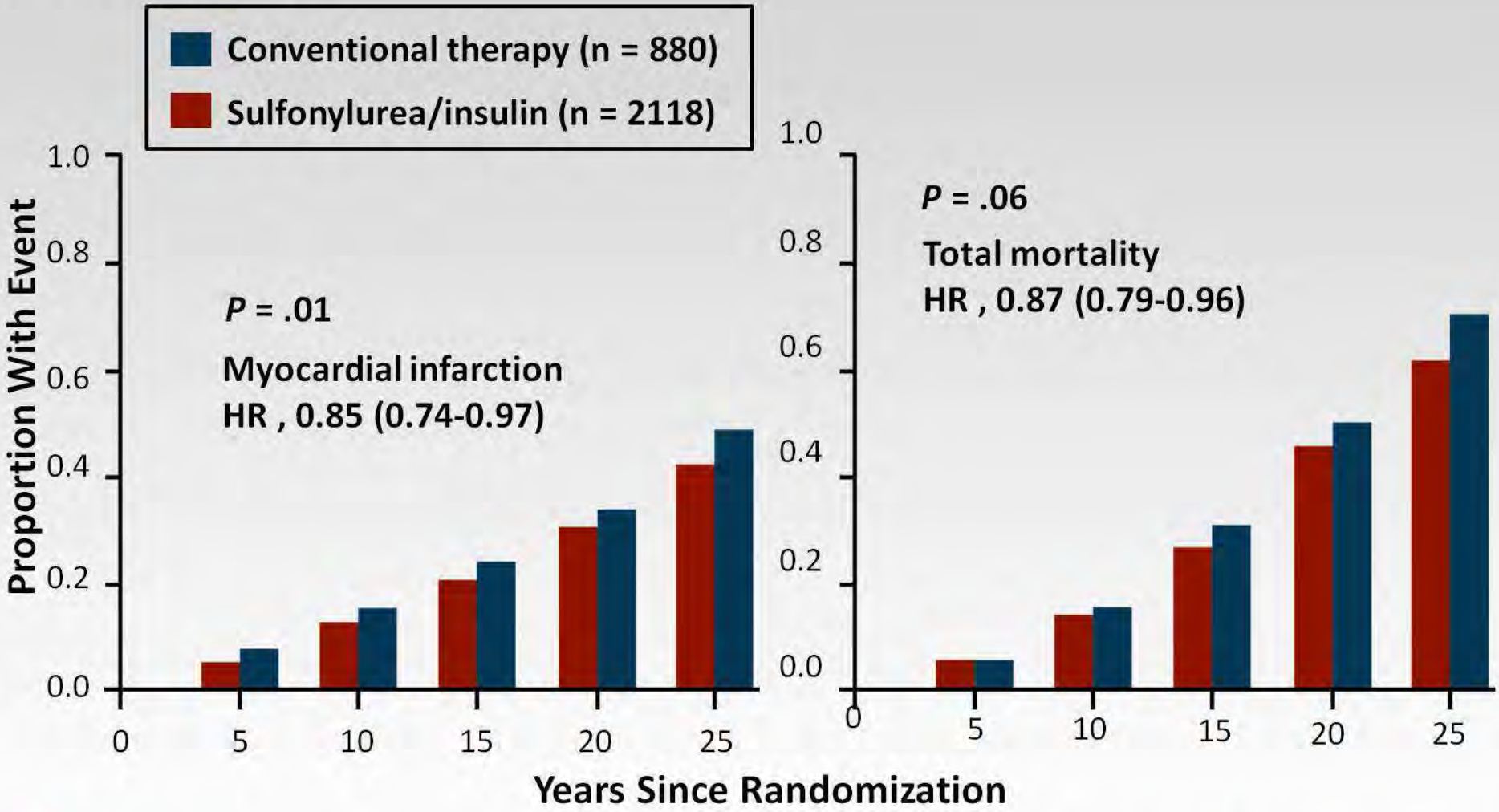
LIPID & METABOLIC

The Emerging Risk Factors Collaboration, et al. *Lancet*. 2010;375:2215-2222.[1]

theheart.org from WebMD

Medscape EDUCATION

UKPDS: Insulin/Sulfonylurea and Outcomes in New T2D



LIPID & METABOLIC

Holman RR, et al. *N Engl J Med.* 2008;359:1577-1589.[2]

the heart.org from WebMD

Medscape EDUCATION

Trials	Number of Events, Annual Event Rate, % More Intensive	Less Intensive	ΔHBA$_{1c}$, %	Favors more Intensive	Favors less Intensive	HR, 95% CI
Myocardial Infarction						
ACCORD	198 (1.18)	245 (1.51)	-1.01			0.77 (0.64-0.93)
ADVANCE	310 (1.18)	337 (1.28)	-0.72			0.92 (0.79-1.07)
UKPDS	150 (1.20)	76 (1.40)	-0.66			0.81 (0.62-1.07)
VADT	72 (1.65)	87 (1.99)	-1.16			0.83 (0.61-1.13)
Overall	730	745	-0.88			0.85 (0.76-0.94) (Q = 2.25; *P* = .52; I^2 = 0.0%)
Major Cardiovascular Events						
Overall	1194	1176	-0.88			0.91 (0.84-0.99) (Q = 1.32; *P* = .72; I^2 = 0.0%)
Stroke						
Overall	378	370	-0.88			0.96 (0.83-1.10) (Q = 0.40; *P* = .94; I^2 = 0.0%)
Hospitalized/Fatal Heart Failure						
Overall	459	446	-0.88			1.00 (0.86-1.16) (Q = 3.59; *P* = .31; I^2 = 16.4%)

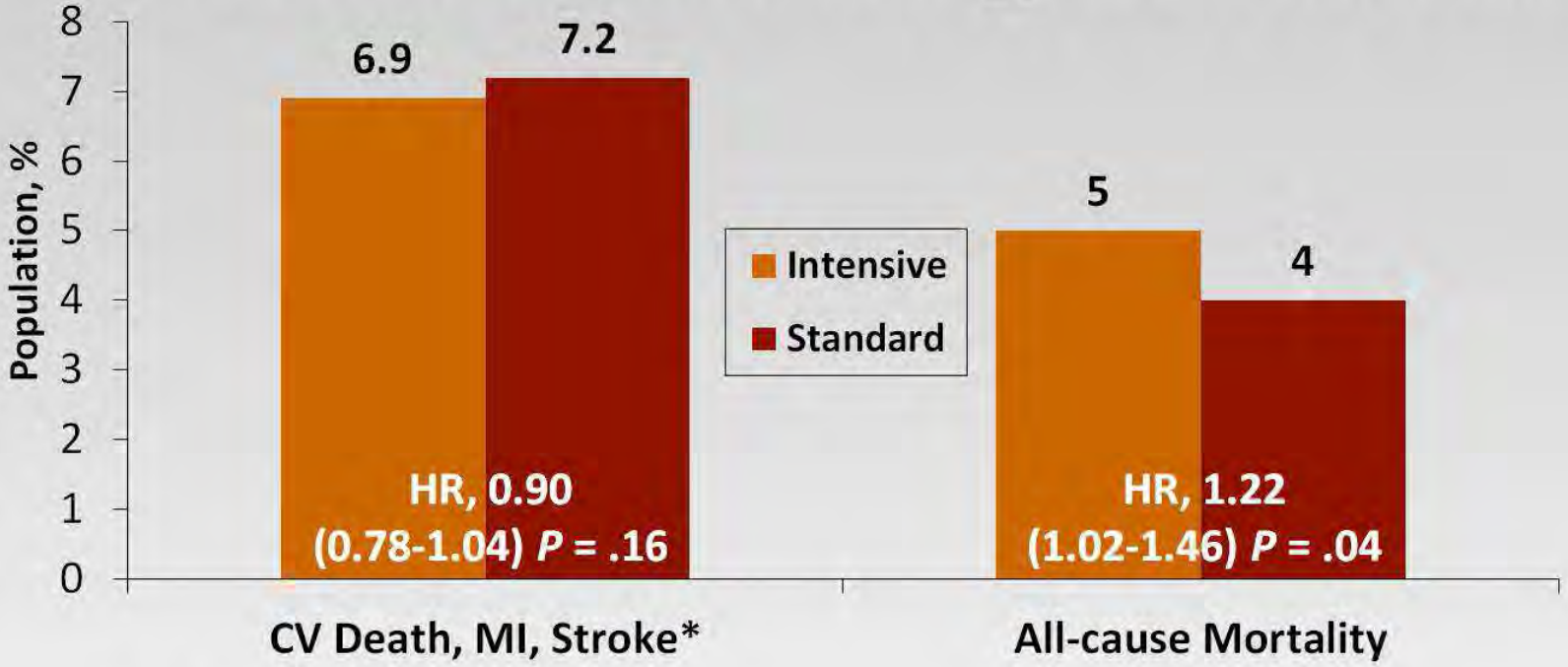
LIPID & METABOLIC

Turnbull FM, et al. *Diabetologia*. 2009;52:2288-2298.[3]

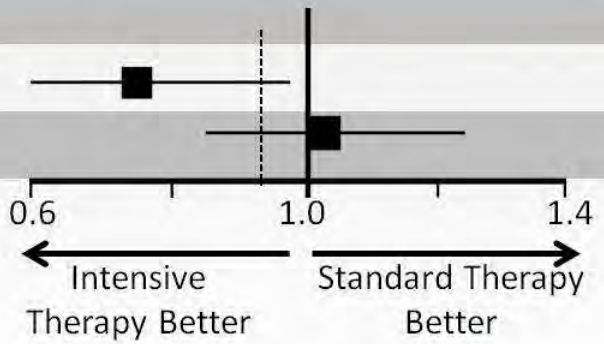
theheart.org from WebMD

Medscape EDUCATION

ACCORD: Baseline HbA_{1c} and Outcomes



CV Death, MI, Stroke			HR	*P* Value
HbA_{1c} at baseline	Patients, n	Events, n		.03
≤ 8.0%	4868	284		
> 8.0%	5360	438		



Vertical dashed line = overall HR

LIPID & METABOLIC

The ACCORD Study Group, et al. *N Engl J Med.* 2008;358:2545-2559.[4]

theheart.org from WebMD

Medscape EDUCATION

ORIGIN: Severe Hypoglycemia and Outcome

Risks of Events With Severe Hypoglycemia*	HR (95% CI)
CV death, MI, stroke	1.58 (1.24-2.02)
Mortality	1.74 (1.39-2.19)
Arrhythmic death	1.77 (1.17-2.67)
CV death	1.71 (1.27-2.30)

N = 12,537 participants with dysglycemia and high CV risk
Severe hypoglycemia: 5.7% glargine, 1.5% standard group

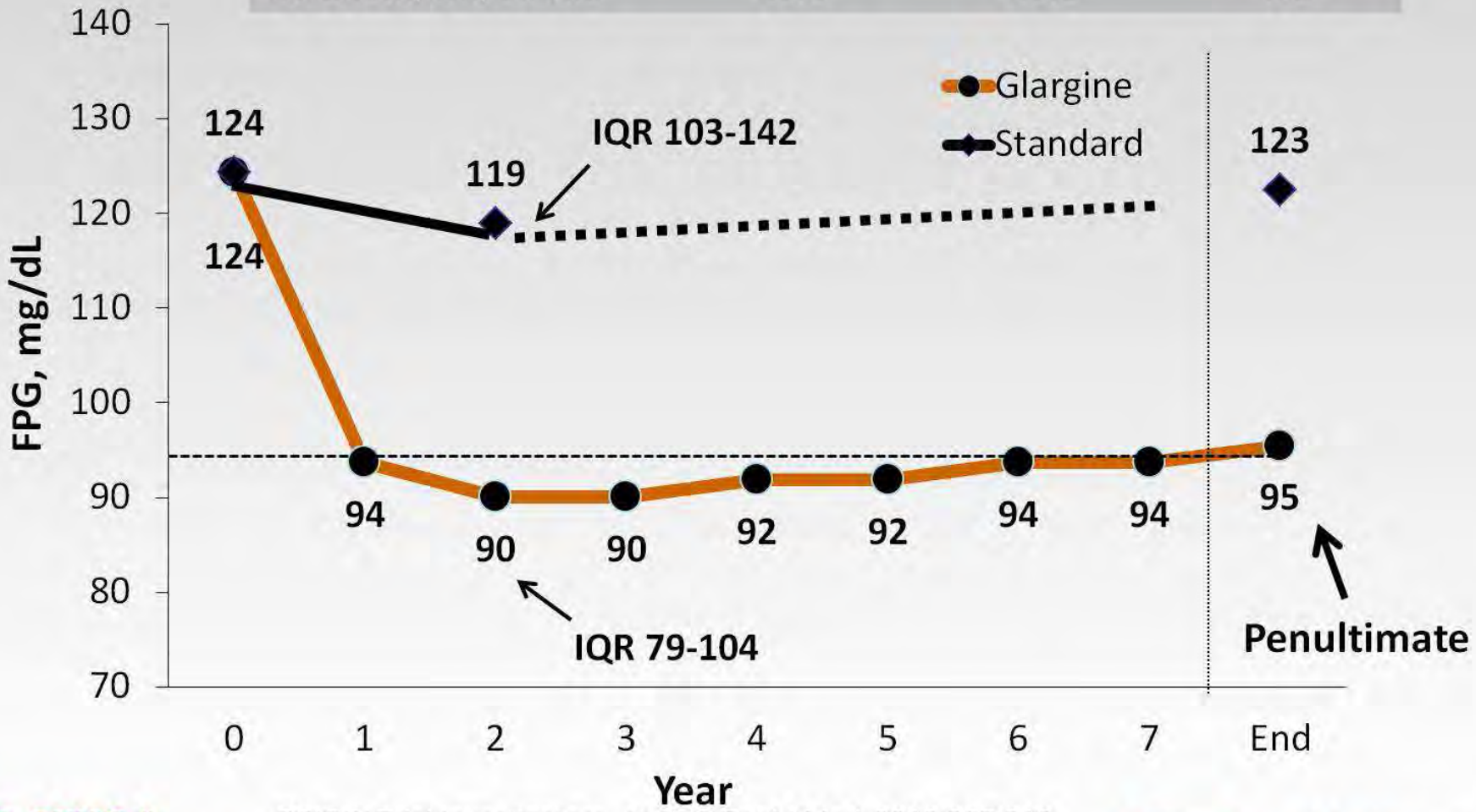
***Meets all 3 criteria:**

a) Signs and/or symptoms of hypoglycemia
b) Required assistance to help self
c) Spontaneous recovery with carbohydrate/glucagon OR any measured glucose ≤ 36 mg/dL (2 mmol/L)

The ORIGIN Trial Investigators. *Eur Heart J.* 2013 Sep 2 [Epub ahead of print].[5]

ORIGIN: Median Fasting Plasma Glucose

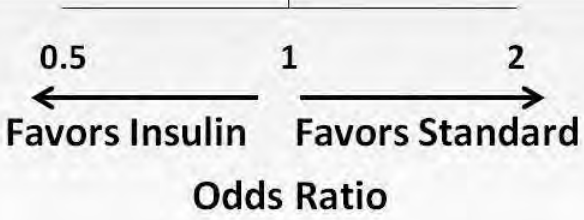
Primary End Point	Glargine (n = 6264)	Standard (n = 6273)	*P* Value
CV death, MI, stroke	16.6	16.1	.63



ORIGIN Trial Investigators, et al. *N Engl J Med.* 2012;367:319-328.[6]

ORIGIN: Intervening Early More Beneficial

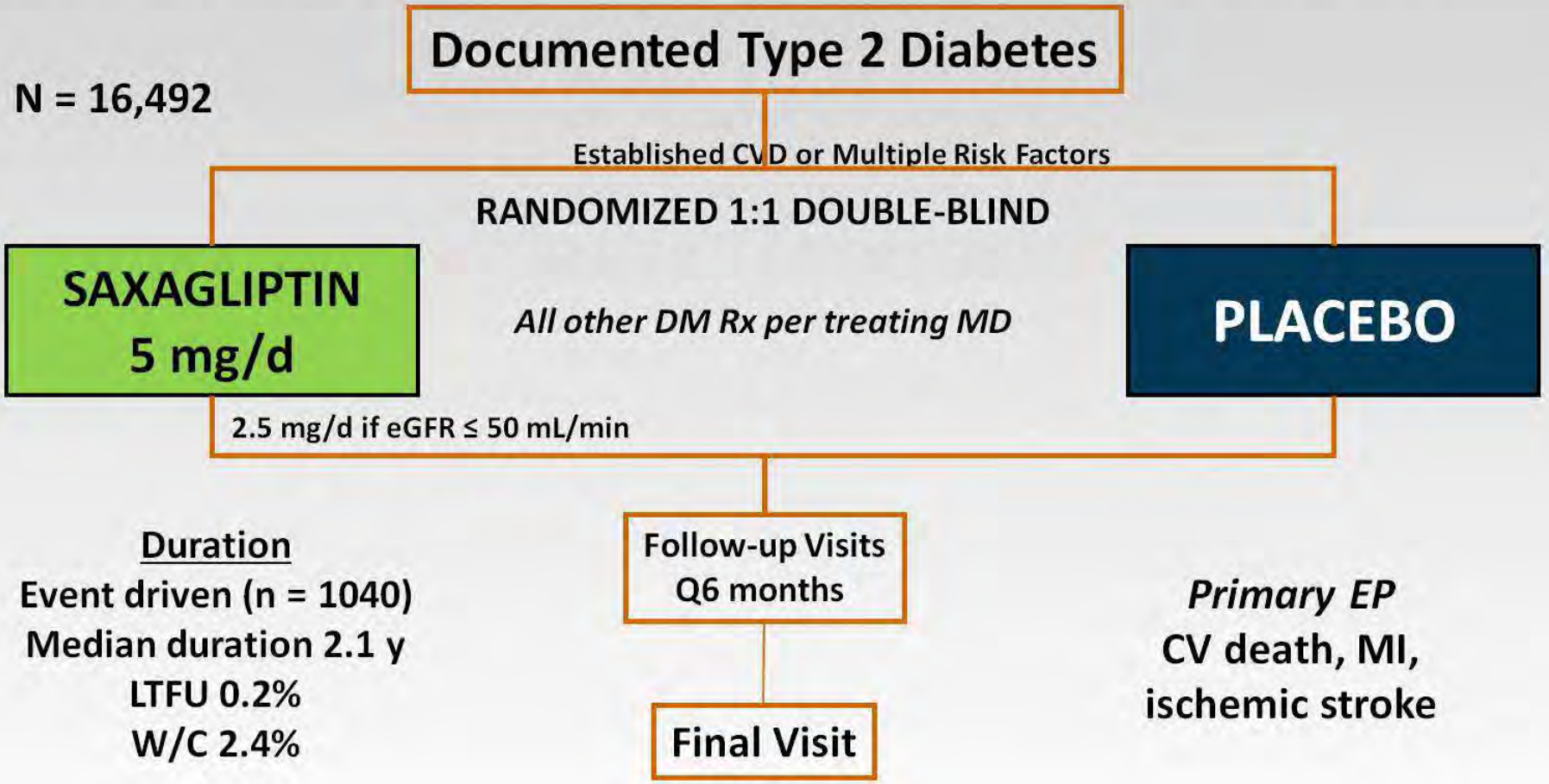
	OR (95% CI)	*P*	Glargine (N = 737)	Standard (N = 719)
New diabetes*	0.72 (0.58-0.91)	.006	182 (24.7)	225 (31.2)
After second OGTT	0.80 (0.64-1.00)	.050	219 (29.7)	248 (34.5)
Adjudicated + uncertain cases	0.69 (0.56-0.86)	.001	254 (34.5)	310 (43.1)



***Predefined new diabetes outcome: results up to and including first OGTT.**

ORIGIN Trial Investigators, et al. *N Engl J Med.* 2012;367:319-328.[6]

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with DM: SAVOR-TIMI 53



Major Secondary EP: CV death, MI, ischemic stroke, or hospitalization for heart failure, unstable angina, or coronary revascularization

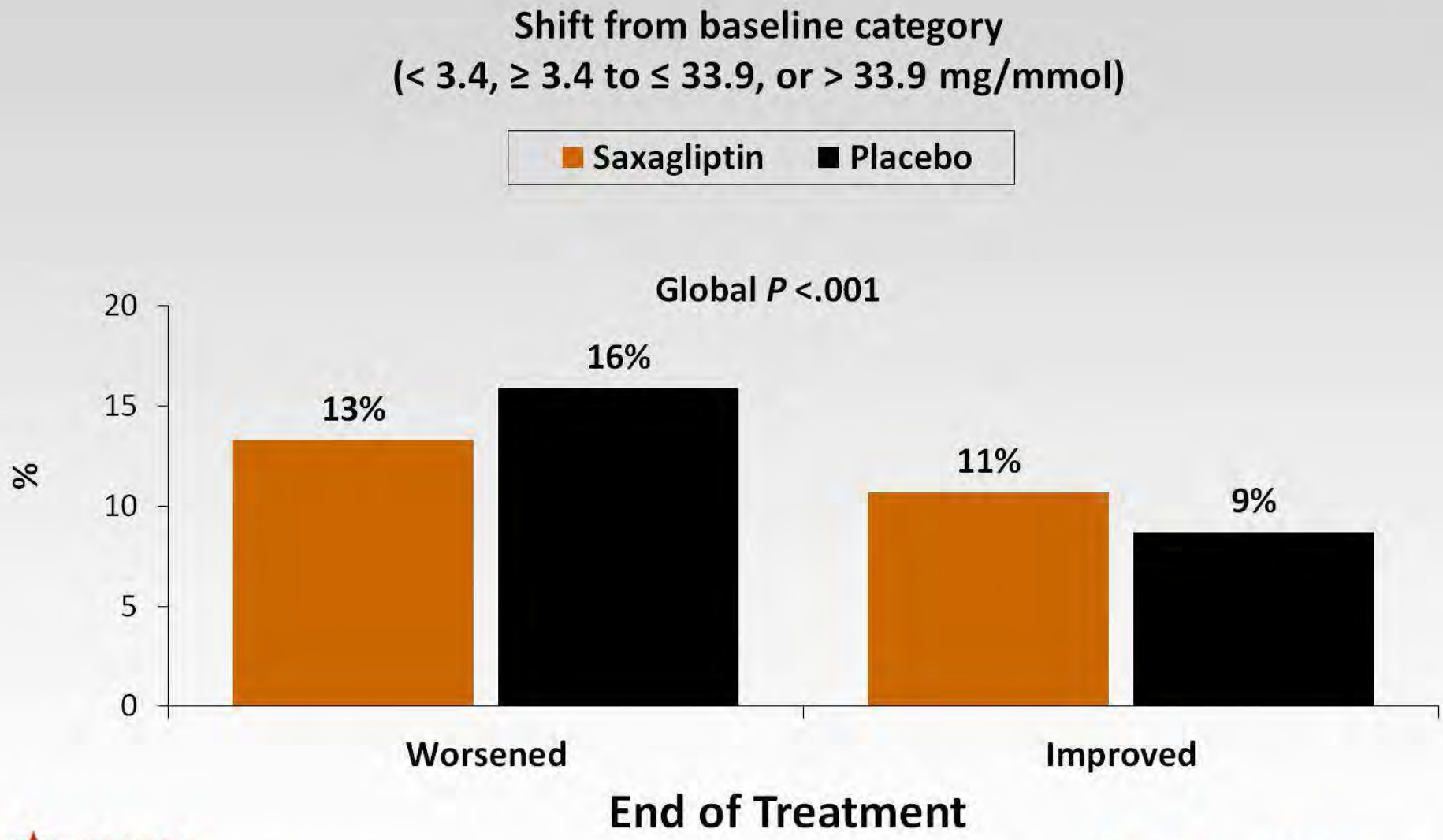
Scirica BM, et al. *N Engl J Med.* 2013; 369:1317-1326.[7]

SAVOR-TIMI 53: Primary Objective

- To determine whether when added to background therapy, **saxagliptin** would be noninferior to placebo for the composite end point of CV death, nonfatal MI, or nonfatal ischemic stroke (Upper 95% CI of HR < 1.3)
- And if noninferiority were met, to determine if **saxagliptin** would be superior to placebo

Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]

SAVOR-TIMI 53: Changes in Microalbuminuria



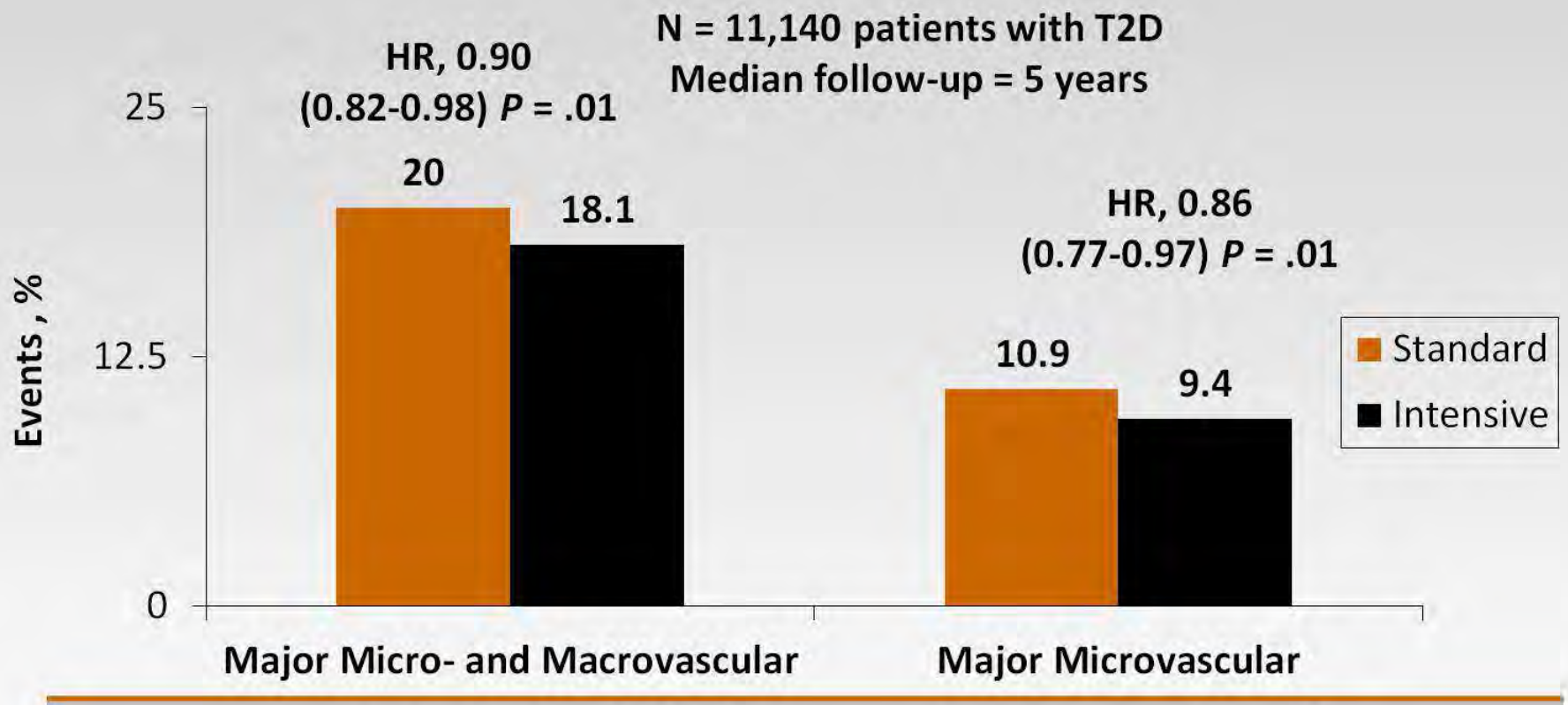
LIPID & METABOLIC

Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]

theheart.org from WebMD

Medscape EDUCATION

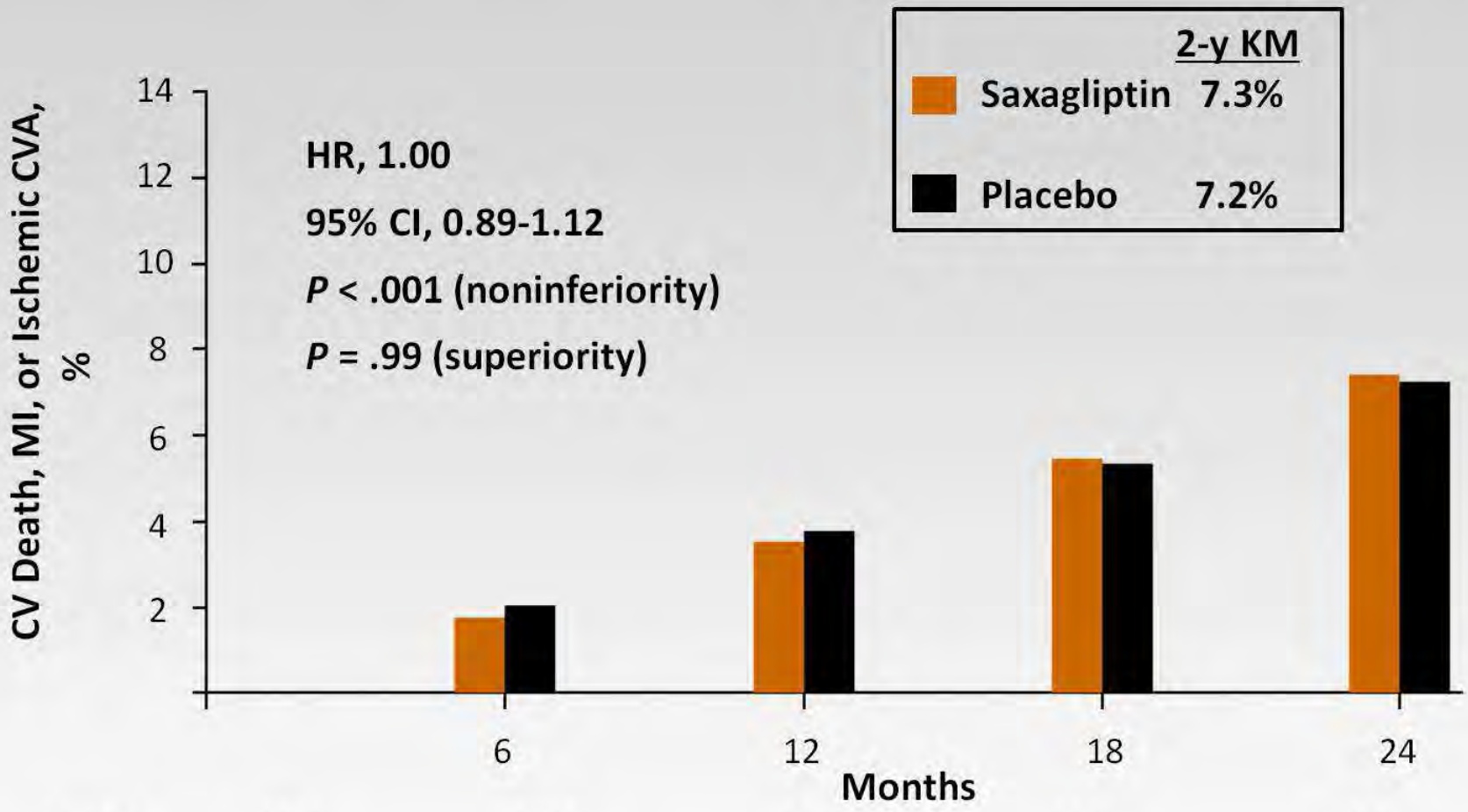
ADVANCE: Reducing HbA_{1c} Lowers Microvascular Events



	Standard	Intensive
Mean HbA1c, %	7.3	6.5

The ADVANCE Collaborative Group, et al. *N Engl J Med.* 2008;358:2560-2572.[8]

SAVOR-TIMI 53: Primary End Point



Placebo	8212	7983	7761	7267	4855
Saxagliptin	8280	8071	7836	7313	4920

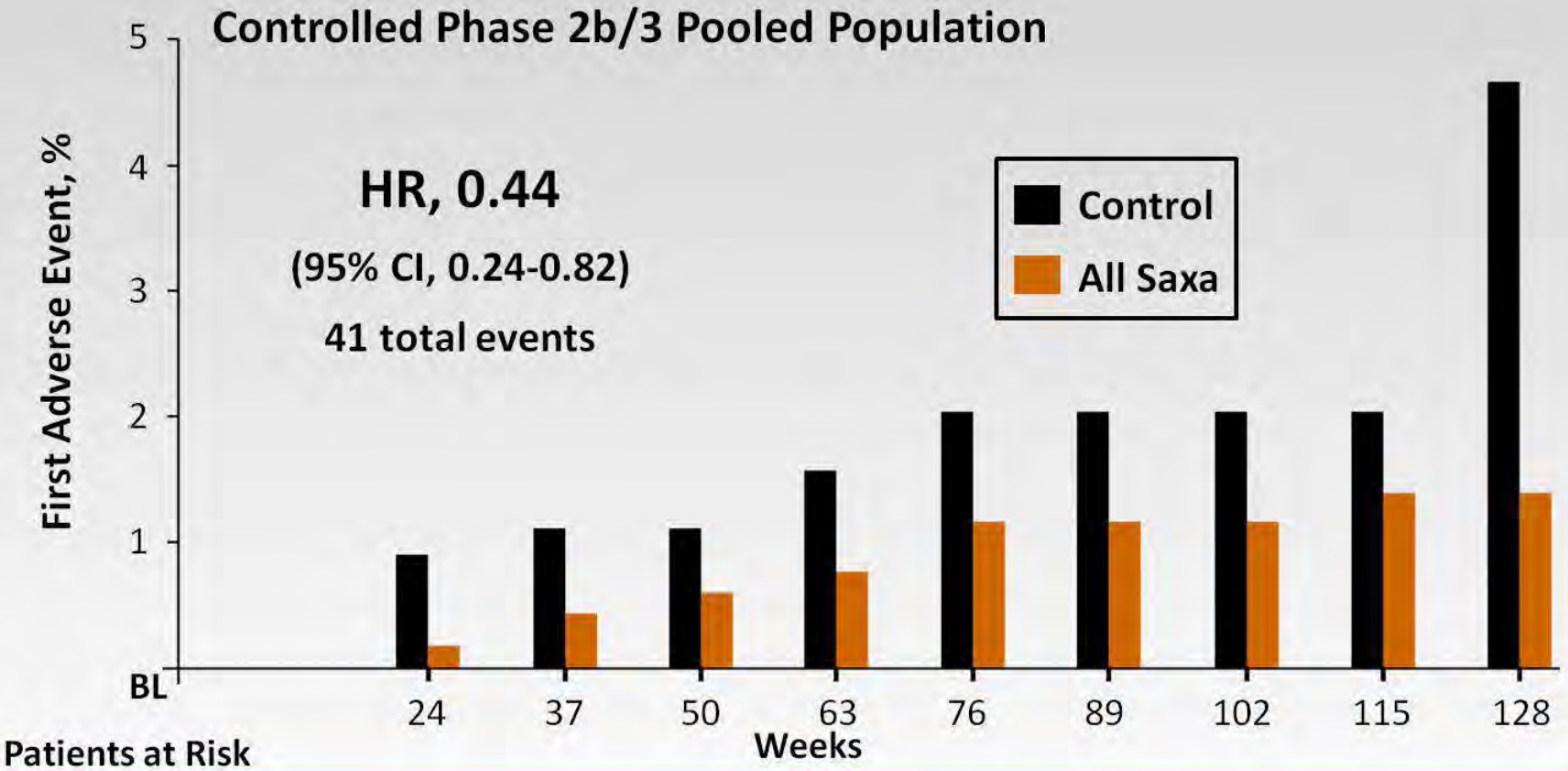
LIPID & METABOLIC

Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]

theheart.org from WebMD

Medscape EDUCATION

Time to Onset of First Primary MACE in Prior Pooled Analysis



Patients at Risk										
Control	1251	935	860	774	545	288	144	123	102	57
All saxa	3356	2615	2419	2209	1638	994	498	436	373	197

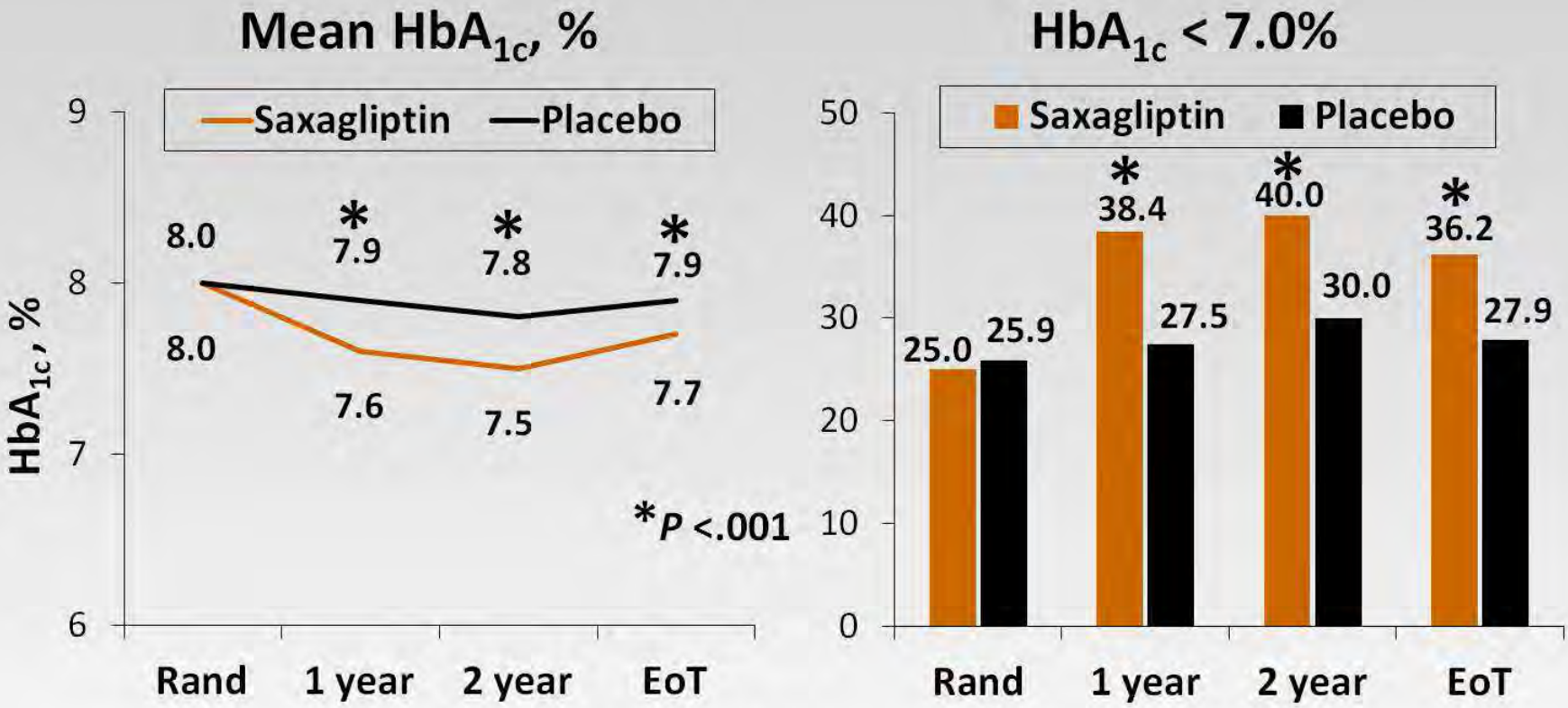
LIPID & METABOLIC

Frederich R, et al. *Postgrad Med.* 2010;122:16-27.[9]

theheart.org from WebMD

Medscape EDUCATION

SAVOR-TIMI 53: Glycemic Indices Over Time



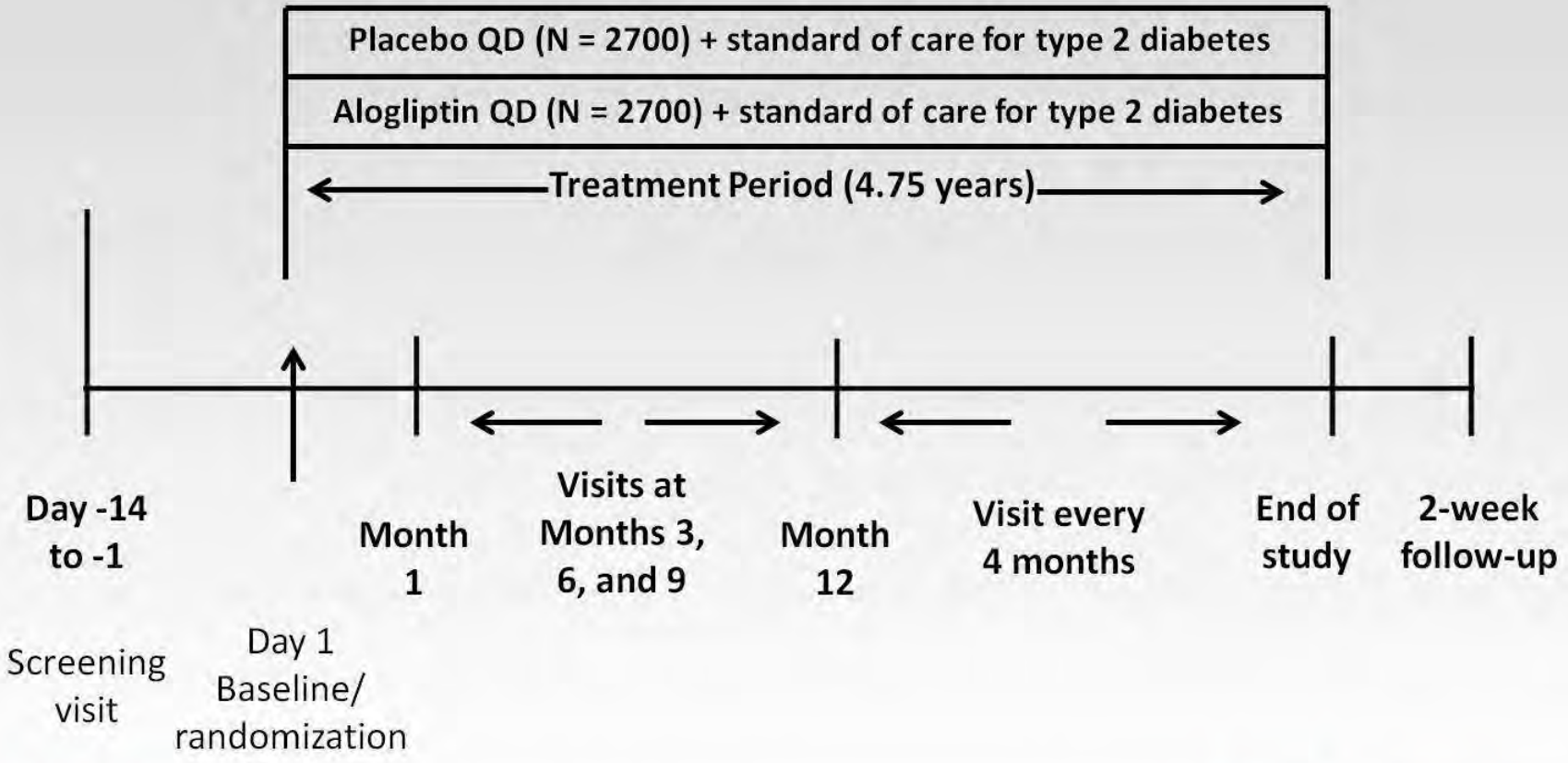
These changes were in the context of:

- 23% ↓ in the intensification of antihyperglycemic medications with saxagliptin vs control ($P < .001$), and
- 30% ↓ in the initiation of insulin therapy for more than 3 months with saxagliptin vs control ($P < .001$).

Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]

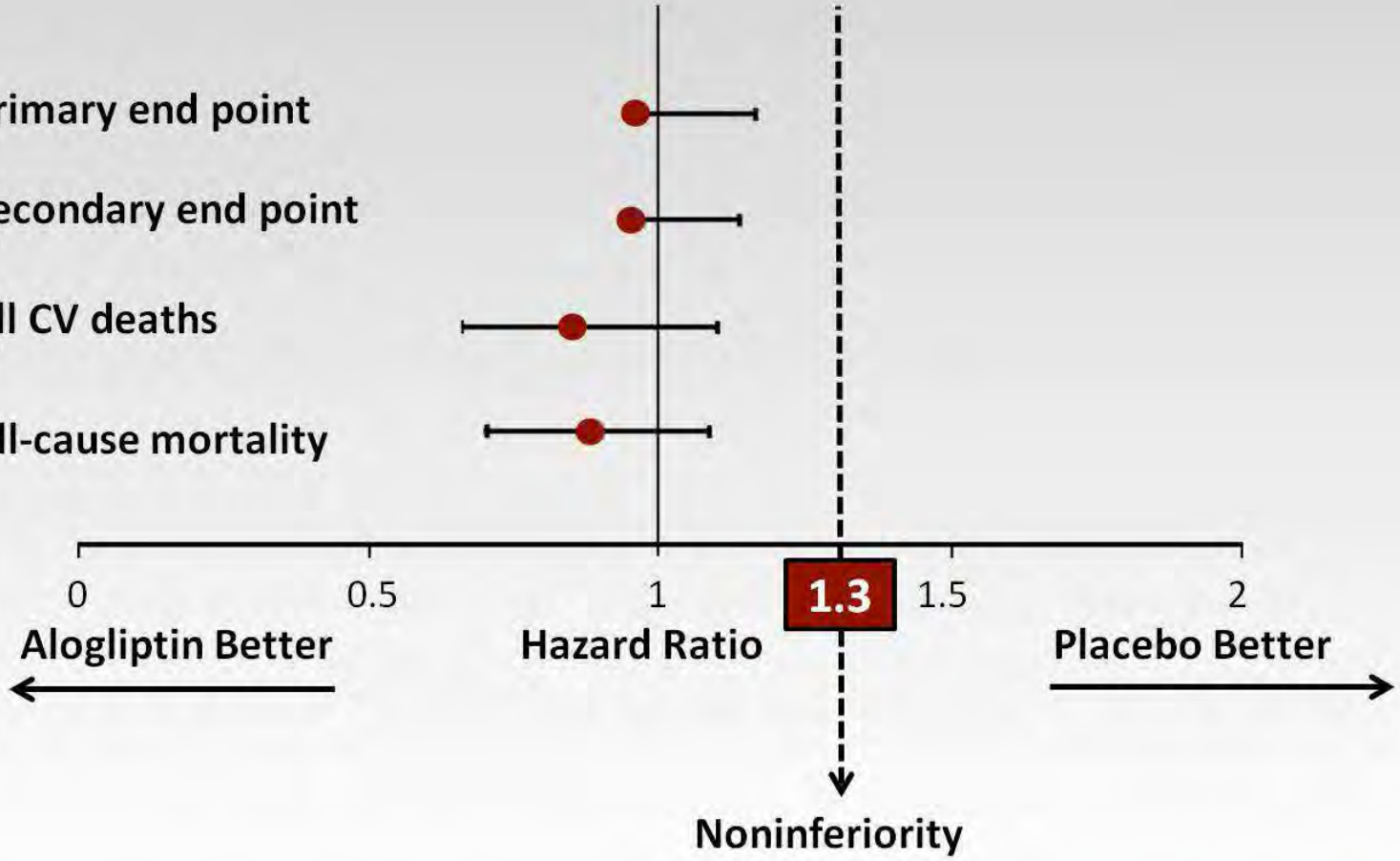
EXAMINE: Trial Design

N = 5380 patients with T2D within 15-90 days of AMI/UA



White WB, et al. *Am Heart J.* 2011;162:620-626.[10]

EXAMINE: Noninferiority Met



White WB, et al. *N Engl J Med*. 2013;369:1327-1335.[11]

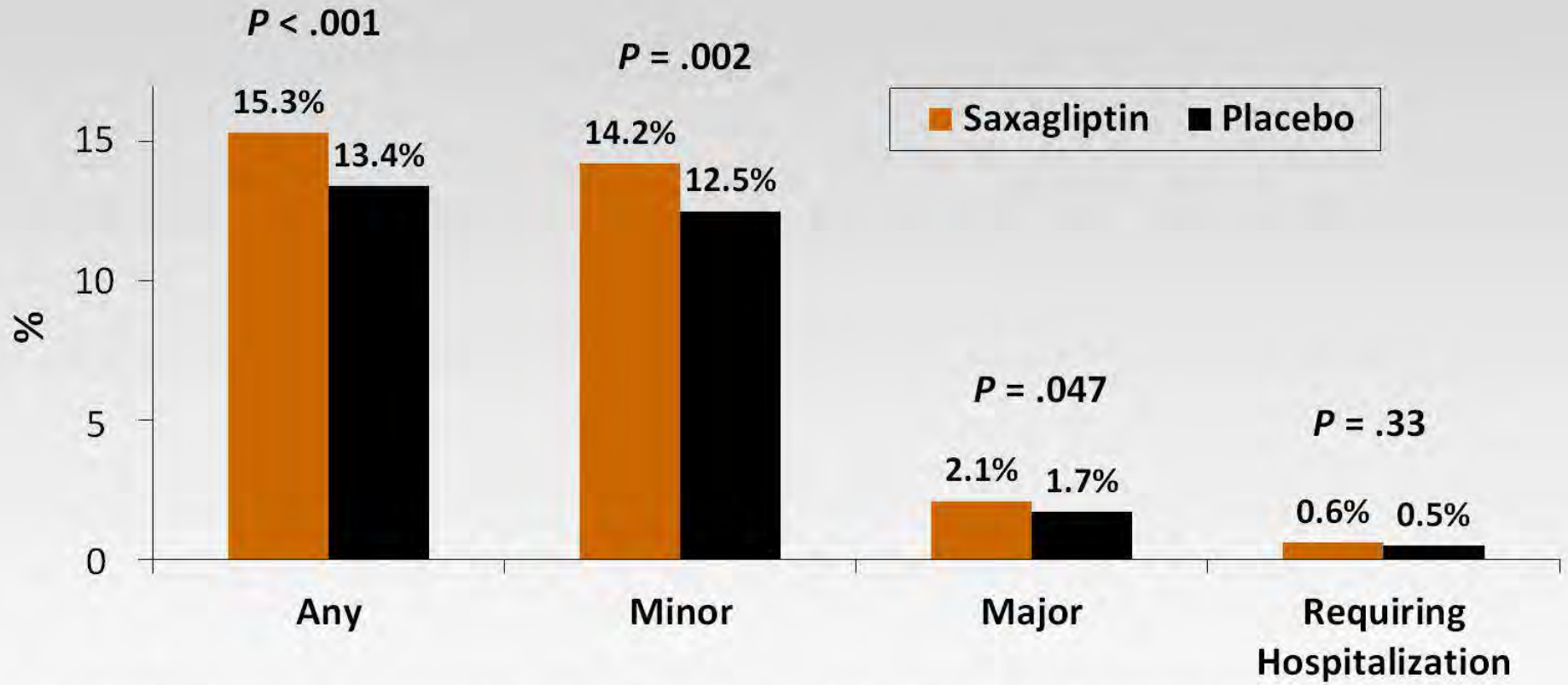
SAVOR-TIMI 53 and EXAMINE: Effect on CV Risk Factors

	Saxagliptin	Alogliptin E
Lipids	Not yet analyzed	No change
HR	No change	Not yet analyzed
SBP/DBP	No change	Not yet analyzed
Weight	No change	No change

Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]
White WB, et al. *N Engl J Med.* 2013;369:1327-1335.[11]

SAVOR-TIMI 53: Hypoglycemia

No increase in hypoglycemia seen in EXAMINE

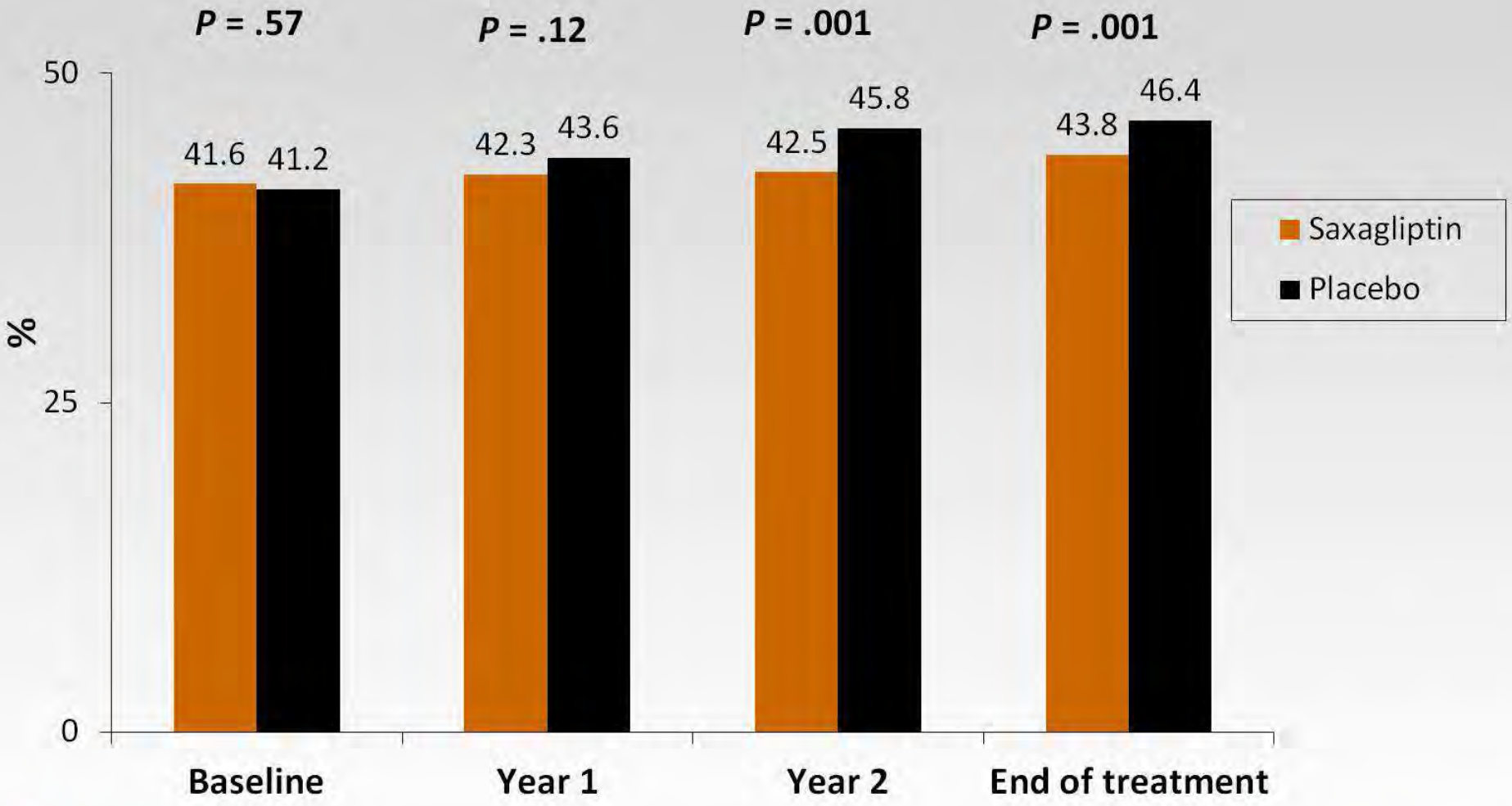


Minor: Symptoms but recovered by themselves within 30 minutes or glucose level < 54 mg/dL, regardless of symptoms

Major: Required assistance to actively intervene

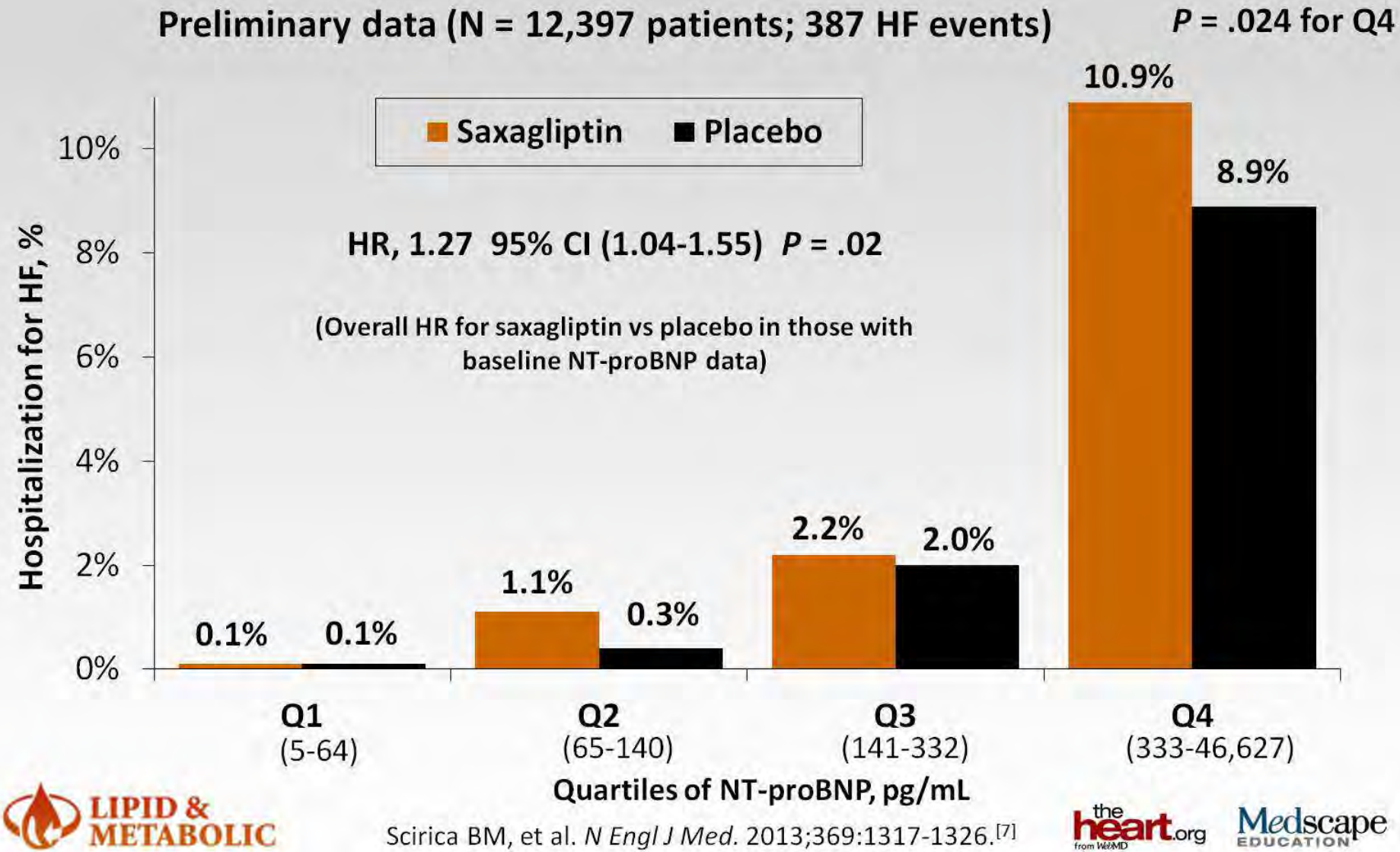
Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]

SAVOR-TIMI 53: Insulin Use



Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]

SAVOR-TIMI 53: Baseline NT-proBNP and Hospitalization for Heart Failure



Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]

SAVOR-TIMI 53 and EXAMINE: Conclusions

	Saxagliptin	Alogliptin
CV events	No increase/decrease	No increase/decrease
Glycemic control	Improved	Improved
Hypoglycemia	Increased (when combined with sulfonylurea)	No increase
Need for insulin	Decreased	Decreased
Pancreatitis/ pancreatic cancer	No increase	No increase

Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]
White WB, et al. *N Engl J Med.* 2013;369:1327-1335.[11]

Abbreviations

ACC = American College of Cardiology

ACCORD = Action to Control Cardiovascular Risk in Diabetes

ACS = acute coronary syndrome

ADVANCE = The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled EvaluationAHA = American Heart Association

AMI = acute myocardial infarction

BL = baseline

BMI = body mass index

BNP = B-type natriuretic protein

CHMP = Committee for Medicinal Products for Human Use

CI = confidence interval

CV = cardiovascular

CVA = cerebral vascular accident

CVD = cardiovascular disease

DBP = diastolic blood pressure

DPP-4 = dipeptidyl peptidase-4

eGFR = estimated glomerular filtration rate

Abbreviations (cont)

EMA = European Medicines Agency

EoT = end of trial

EP = end point

ESC = European Society of Cardiology

EXAMINE = Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome

FDA = US Food and Drug Administration

FPG = fasting plasma glucose

HbA1c = glycated hemoglobin

HF = heart failure

HR = hazard ratio

IQR = interquartile range

KM = Kaplan Meier

LTFU = long-term follow-up

MACE = major adverse cardiac event

MI = myocardial infarction

NT-proBNP = N-terminal pro-brain natriuretic peptide

Abbreviations (cont)

OGTT = oral glucose tolerance test

OR = odds ratio

ORIGIN = Outcome Reduction With Initial Glargine Intervention

QD = every day

SAVOR-TIMI 53 = Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications

SBP = systolic blood pressure

T2D = type 2 diabetes

UA = unstable angina

UKPDS = United Kingdom Prospective Diabetes Study

VADT = Veterans Affairs Diabetes Trial

W/C = Withdrawal of consent

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9. Frederich R, Alexander JH, Fiedorek FT, et al. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. *Postgrad Med*. 2010;122:16-27.

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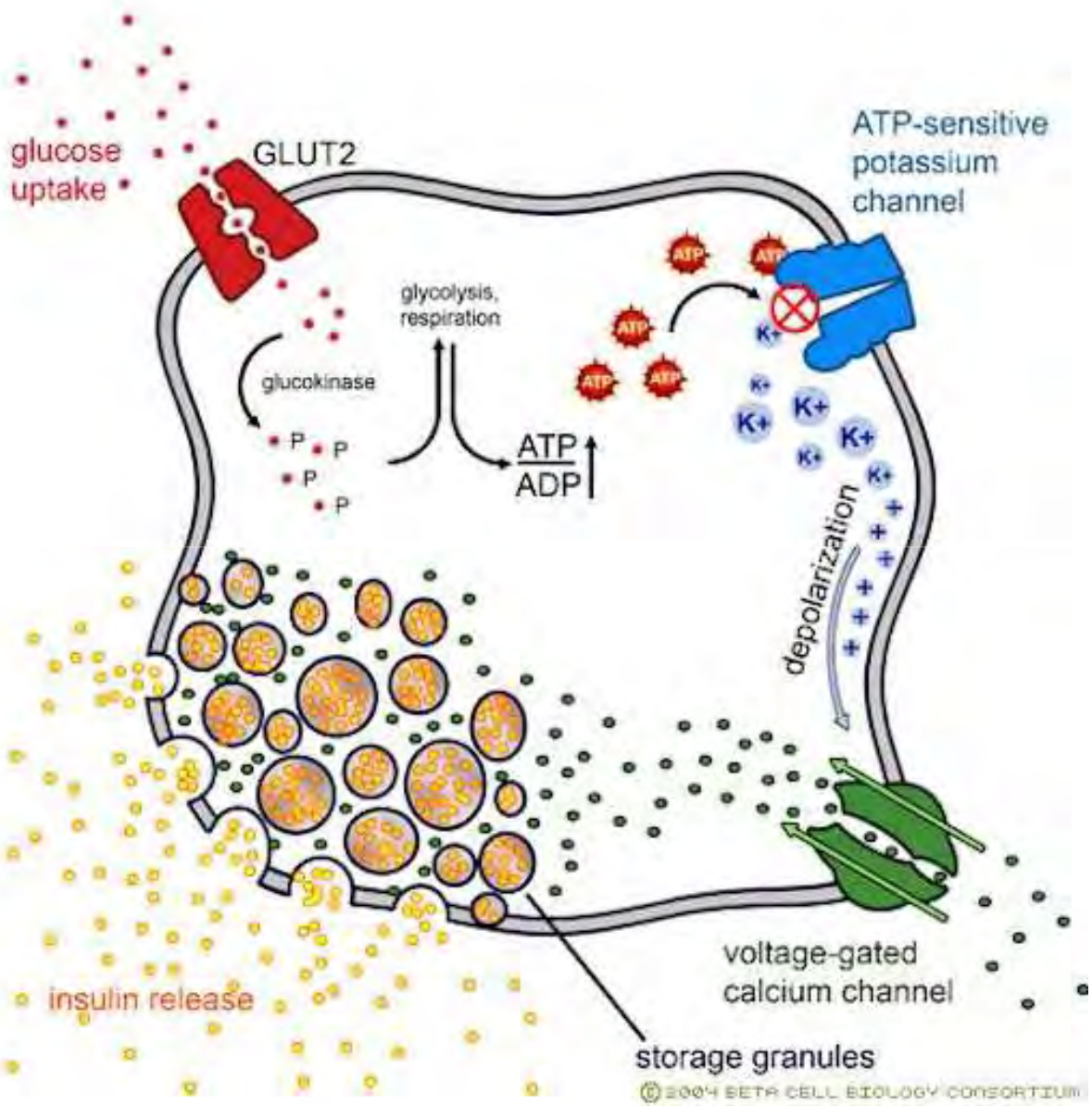
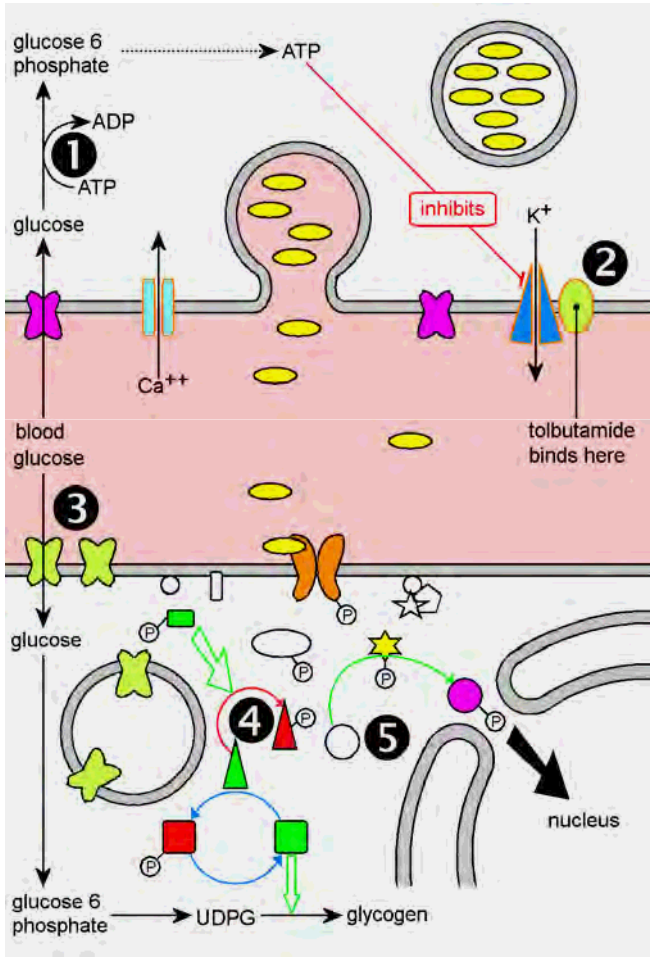
11. White WB, Cannon CP, Heller SR, et al; the EXAMINE Investigators. Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. *N Engl J Med*. 2013; 369:1327-1335.


glucose uptake
GLUT2
ATP-sensitive potassium channel
glycolysis, respiration
glucokinase
ATP
ADP
depolarization
voltage-gated calcium channel
insulin release
storage granules
© 2004 BETA CELL BIOLOGY CONSORTIUM


glucose 6
phosphate
ATP
ADP
1
ATP
glucose
inhibits
K+
2
Ca++
blood
glucose
tolbutamide
binds here
3
glucose
4
5
nucleus
glucose 6
phosphate
UDPG
glycogen

Tab.1: Caratteristiche degli interventi oggi utilizzati nella terapia del diabete tipo 2..

Interventi	↓HbA1c	Vantaggi	Svantaggi
Stile di vita	1-2%	Basso costo, molti benefici	Spesso fallimentare, specie a lungo termine
Insulino-secretagoghi			
-Sulfoniluree	1,5%	Basso costo	Ipoglicemia, ↑peso
-Glinidi	1-1,5%	Breve durata d'azione	Ipoglicemia, ↑peso, 3 somminis
Insulino-sensibilizzanti			
-Metformina	1-1,5	Basso costo, neutrale sul peso, ↓trigliceridi, no ipoglicemia	Disturbi gastroenterici, sapore metallico in bocca, ac. lattica
-Glitazoni	0,7-1%	Azioni sui lipidi, effetti anti-infiammatorio e antiproliferativo	Costose, ritenzione idrica, ↑peso, scompenso cardiaco
Inibitori α-glucosidasi			
- Acarbose	0,5-0,8%	Neutrale sul peso	3 dosi/die, disturbi intestinali
- Miglitolo	0,5-0,7%	Neutrale sul peso	Non commercializzato
Insulina	1,5-2,0%	↓glicotossicità e lipotossicità	Ipoglicemia, ↑peso, parenterale

anni quello di apidra) si rimanda ai capitoli specifici. Relativamente all'utilizzo degli analoghi rapidi in pazienti con insufficienza epatica, si sottolinea come la risposta glucodinamica all'insulino lispro non risulti influenzata, ed anzi mostri un assorbimento ed un'eliminazione più rapidi dell'insulina umana solubile (19). Le proprietà farmacocinetiche dell'insulina glulisina non sono state studiate, mentre la velocità di assorbimento dell'insulina aspart risulta diminuita e più variabile nei pazienti con insufficienza epatica moderata e grave (19).