14.30-17.00 SESSIONE CONGIUNTA SIMDO - AME

Chair: *V. Toscano*

Co-Chair: *A. Maioli*

Discussant: *M. Rizzo, A. Scorsone*

- La fisiopatologia clinica dell'asse incretinico *S. Settembrini*
- Dobbiamo riclassificare il diabete mellito? *O. Disoteo*
- Terapia del diabete: possiamo ridurre il rischio cardiovascolare? *M. Nizzoli*
- La terapia insulinica tra biosimilari ed innovazione *E. Guastamacchia*
- Quale algoritmo terapeutico? Confronto tra vecchie e nuove terapie *G. Borretta*
- Discussione *Tutti i relatori della sessione*
- Take home messages *V. Toscano*

Terapia del diabete: possiamo ridurre il rischio cardiovascolare ?

Dott. Maurizio Nizzoli

U.O. Medicina Interna

U.O. Endocrinologia e Malattie Metaboliche

o.c. G.B. Morgagni – Forlì

maurizio.nizzoli@auslromagna.it

Il sottoscritto Dott. Maurizio Nizzoli
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni non ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

La malattia aterosclerotica condiziona i 2/3 della mortalità della popolazione diabetica

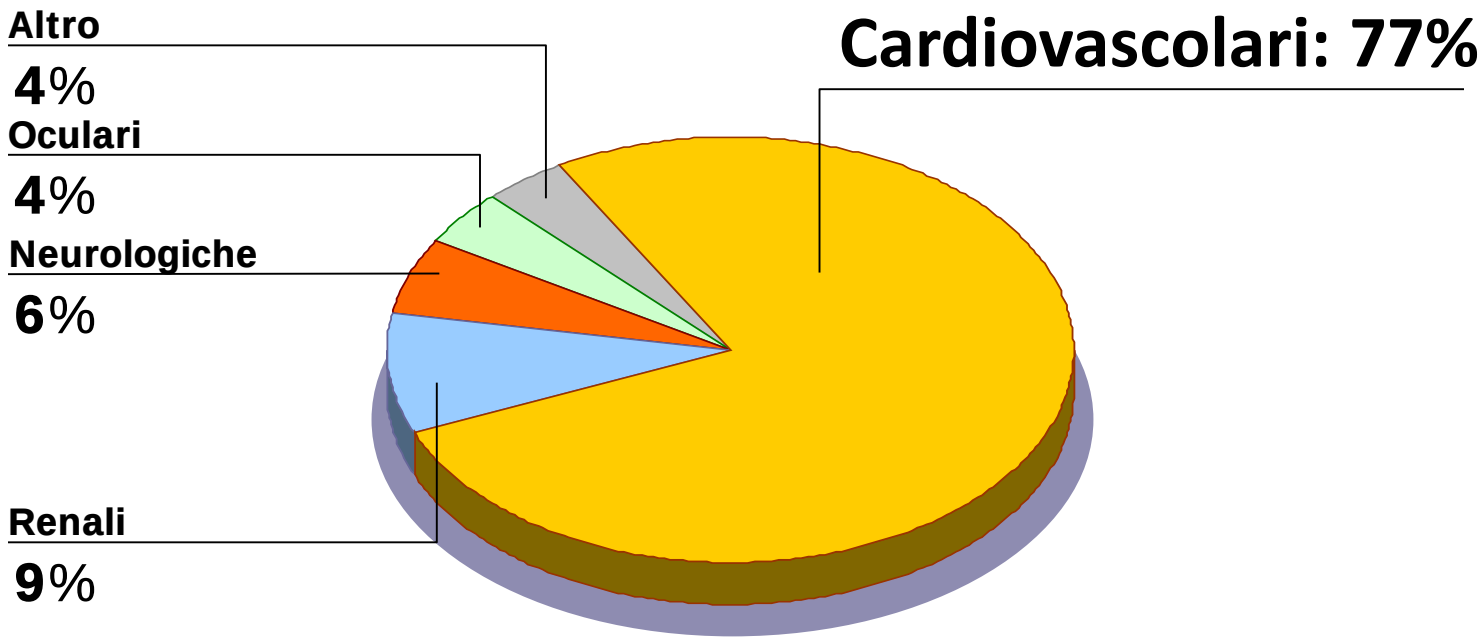
40% cardiopatia ischemica

15% altre cardiopatie in particolare lo scompenso cardiaco

10% Stroke

(Acta Diabetologica ; Aprile ; 2012)

Complicanze croniche del diabete mellito



1° DOGMA (glucocentrico)

THE LOWER, THE BETTER

2° DOGMA (glucocentrico e temporale)

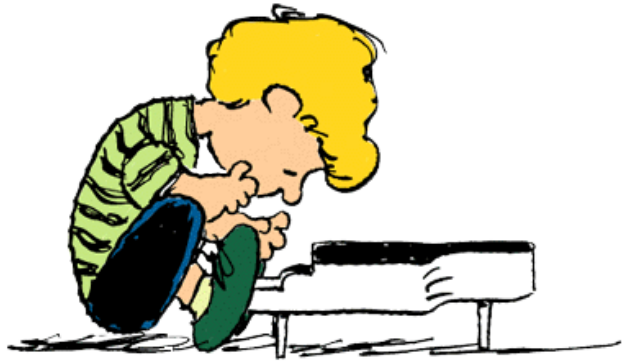
- THE EARLIER, THE BETTER
- Il controllo glicemico è importante per ridurre a medio termine le complicanze microvascolari
- Il controllo glicemico è importante per ridurre le complicanze macrovascolari a lungo termine
- È necessario un lungo follow up per dimostrare il beneficio del controllo glicemico
- Il concetto della memoria metabolica: un controllo glicemico efficace e intensivo nei primi anni di malattia è importantissimo

Effetto del controllo glicemico intensivo VS standard su CVD

End-points	ACCORD	ADVANCE	VADT
Composito CVD	0.90 (0.78-1.04) Morte CVD + IMA e Stroke non fatale **↓ 10% (p=0.16)**	0.94 (0.84-1.06) Morte CVD + IMA e Stroke non fatale **↓ 6% (p=0.37)**	0.87 (0.73-1.04) Morte CVD + IMA e Stroke non fatale + scompenso cardiaco + severa coronaropatoia + amputazione + rivascolarizzazione **↓ 13% (p=0.12)**
Mortalità	**↑ 22% (p=0.04)**	**↓ 7% (p=NS)**	**↓ 6.5 % (p=NS)**
Morte CVD	**↑ 39% (p=0.02)**	**↓ 12% (p=NS)**	**↑ 25% (p=NS)**
Peso	**3.5 vs 0.4**	**0 vs -1**	**7.8 vs 3.4**
Ipoglicemie	**16.2 vs 5.1**	**2.7 vs 1.5**	**21.1 vs 9.9**

Il trattamento intensivo del diabete ci può dare risultati positivi in pazienti:

- *con età < 65 anni*
- *in discreto compenso metabolico HbA1c ≤ 8%*
- *senza precedenti CVD*
- *con storia di malattia < 10 anni*



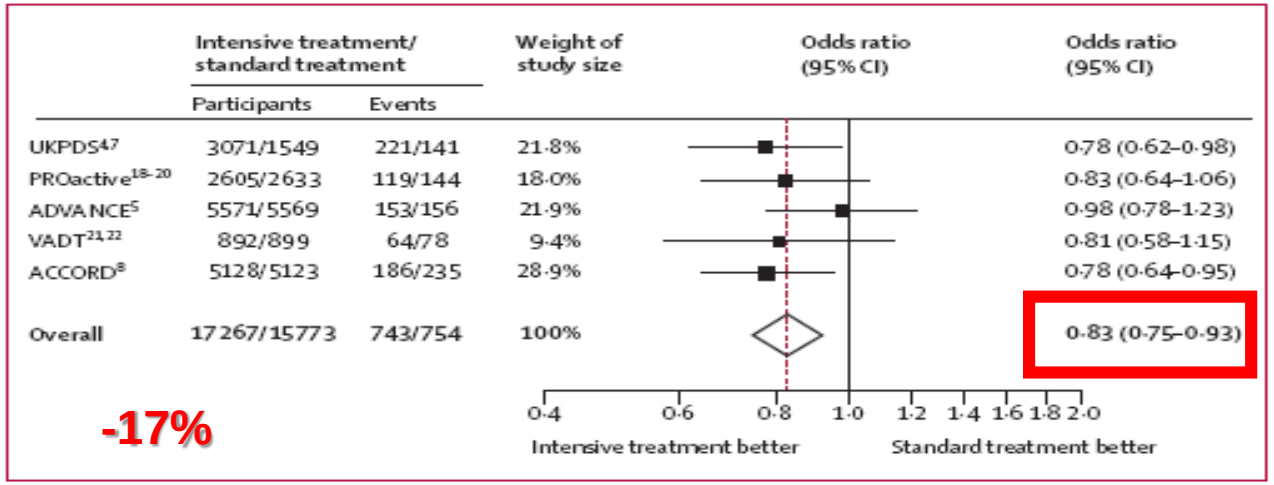


Figure 1: Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment

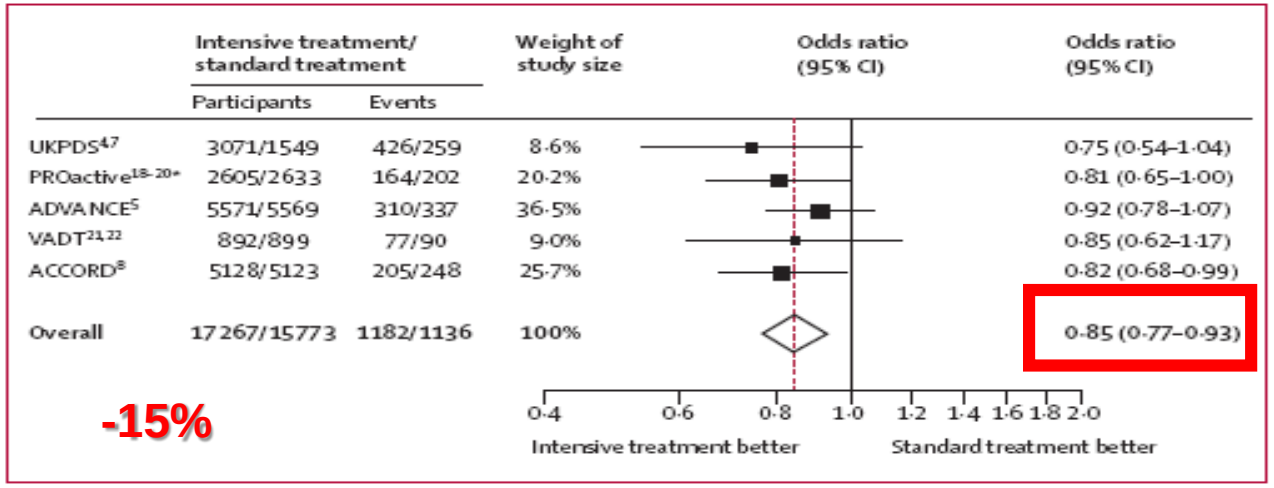


Figure 2: Probability of events of coronary heart disease with intensive glucose-lowering versus standard treatment

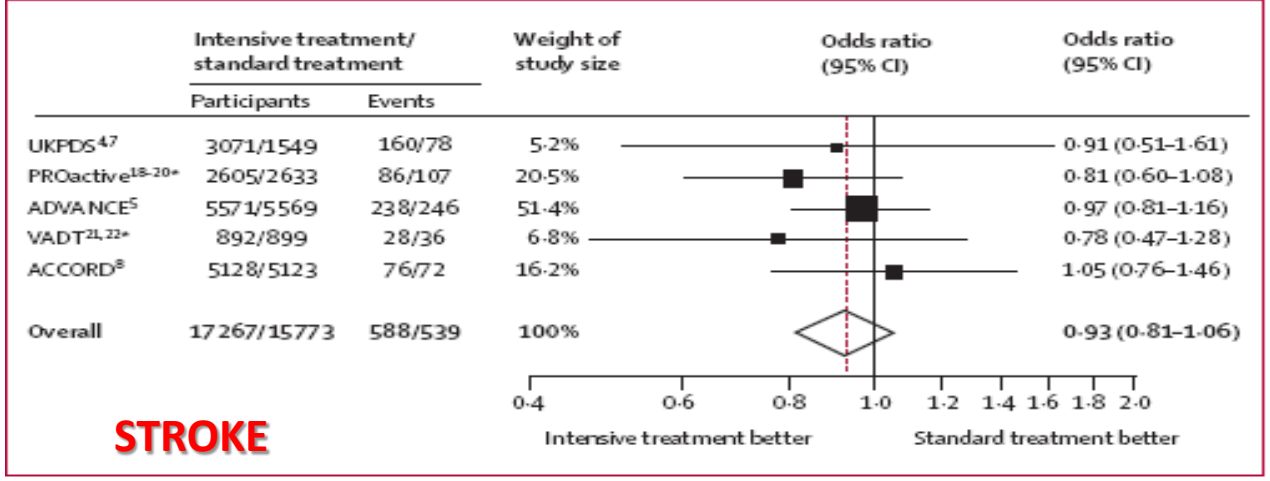


Figure 3: Probability of events of stroke with intensive glucose-lowering versus standard treatment
*Included only non-fatal strokes.

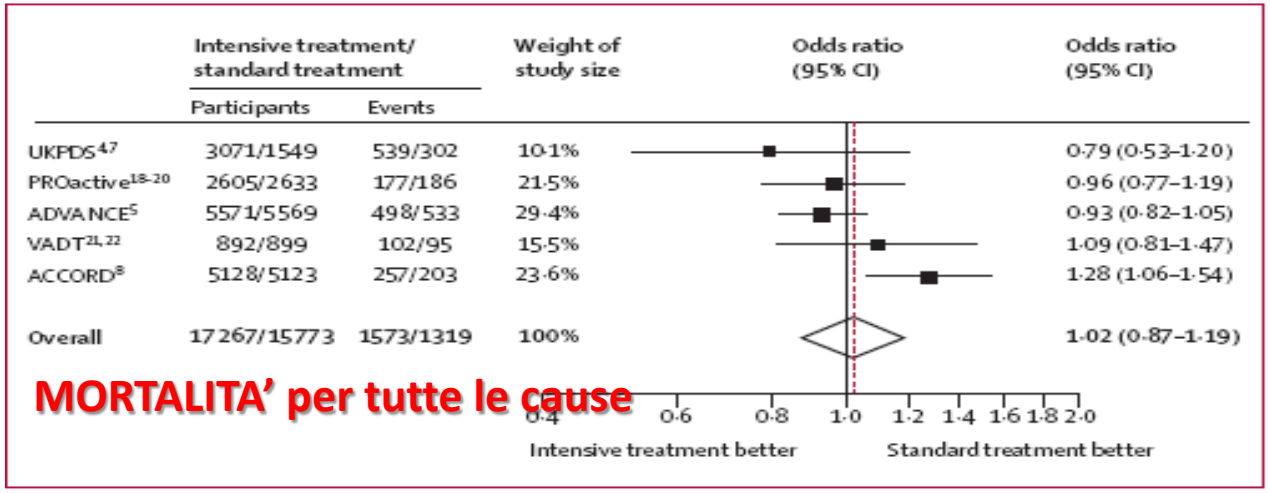


Figure 4: Probability of events of all-cause mortality with intensive glucose-lowering versus standard treatment

Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials

Kausik K Ray, Sreenivasa Rao Kondapally Seshasai, Shanelle Wijesuriya*, Rupa Sivakumaran*, Sarah Nethercott*, David Preiss, Sebhat Erqou, Naveed Sattar*

Lancet 2009; 373: 1765–72

Glycemic Control for Patients With Type 2 Diabetes Mellitus

Our Evolving Faith in the Face of Evidence

(*Circ Cardiovasc Qual Outcomes*. 2016;9:504-512.

René Rodríguez-Gutiérrez, MD, MSc; Victor M. Montori, MD, MSc

MICROANGIOPATIA

Glycemic Control for Patients With Type 2 Diabetes Mellitus

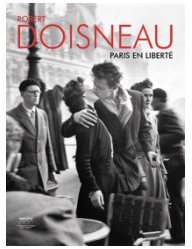
Our Evolving Faith in the Face of Evidence

(*Circ Cardiovasc Qual Outcomes*. 2016;9:504-512.

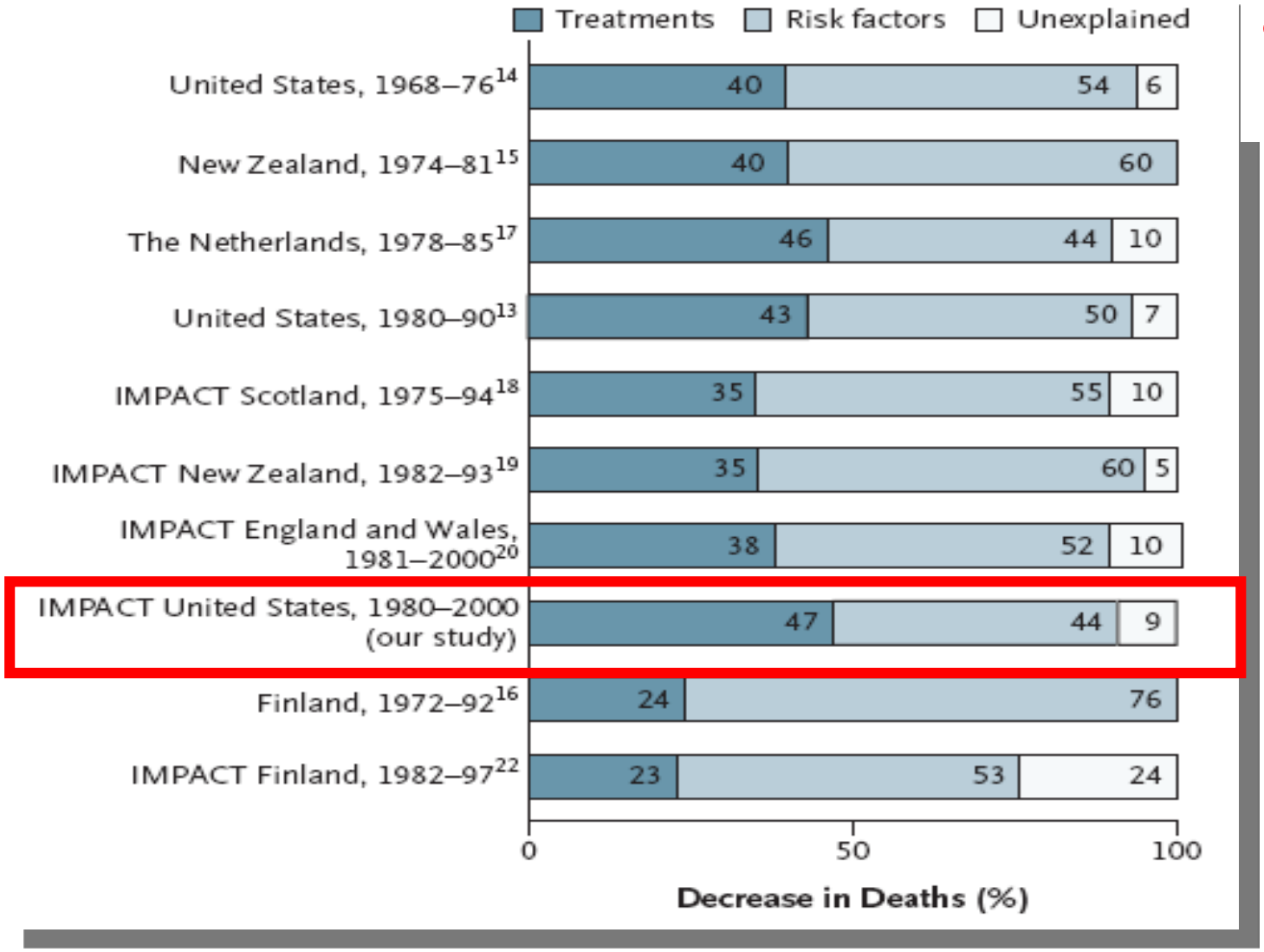
René Rodríguez-Gutiérrez, MD, MSc; Victor M. Montori, MD, MSc

MACROANGIOPATIA


Une salle de classe, 1957
© Robert Doisneau/Rapho


ROBERT
DOISNEAU
PARIS EN LIBERTÉ

Percentage of decrease in death from CHD attributed to treatments and risk-factor changes in different countries



♂ From 542.9 to 266.8/100.00

♀ From 263.3 to 134.4/100.00

Risk factors 44%

Total cholesterol 24%

Systolic blood pressure 20%

Smoking prevalence 12%

Physical inactivity 5%

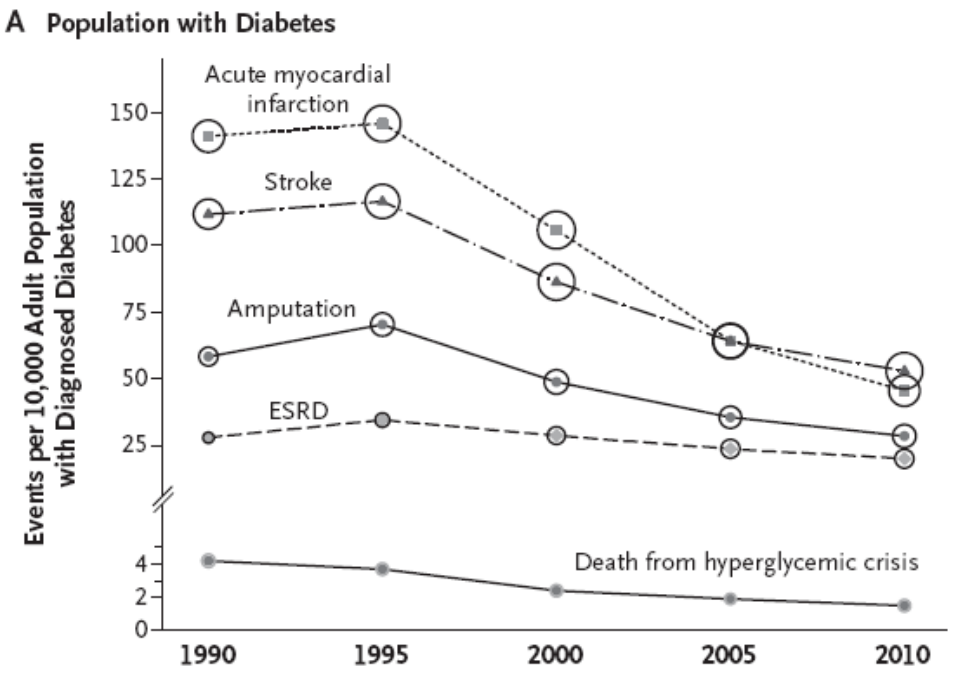
Offset by BMI 8%, diabetes 10%

Ford ES et al, N Engl J Med 2007

Changes in Diabetes-Related Complications in the United States, 1990–2010

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 370;16 NEJM.ORG APRIL 17, 2014

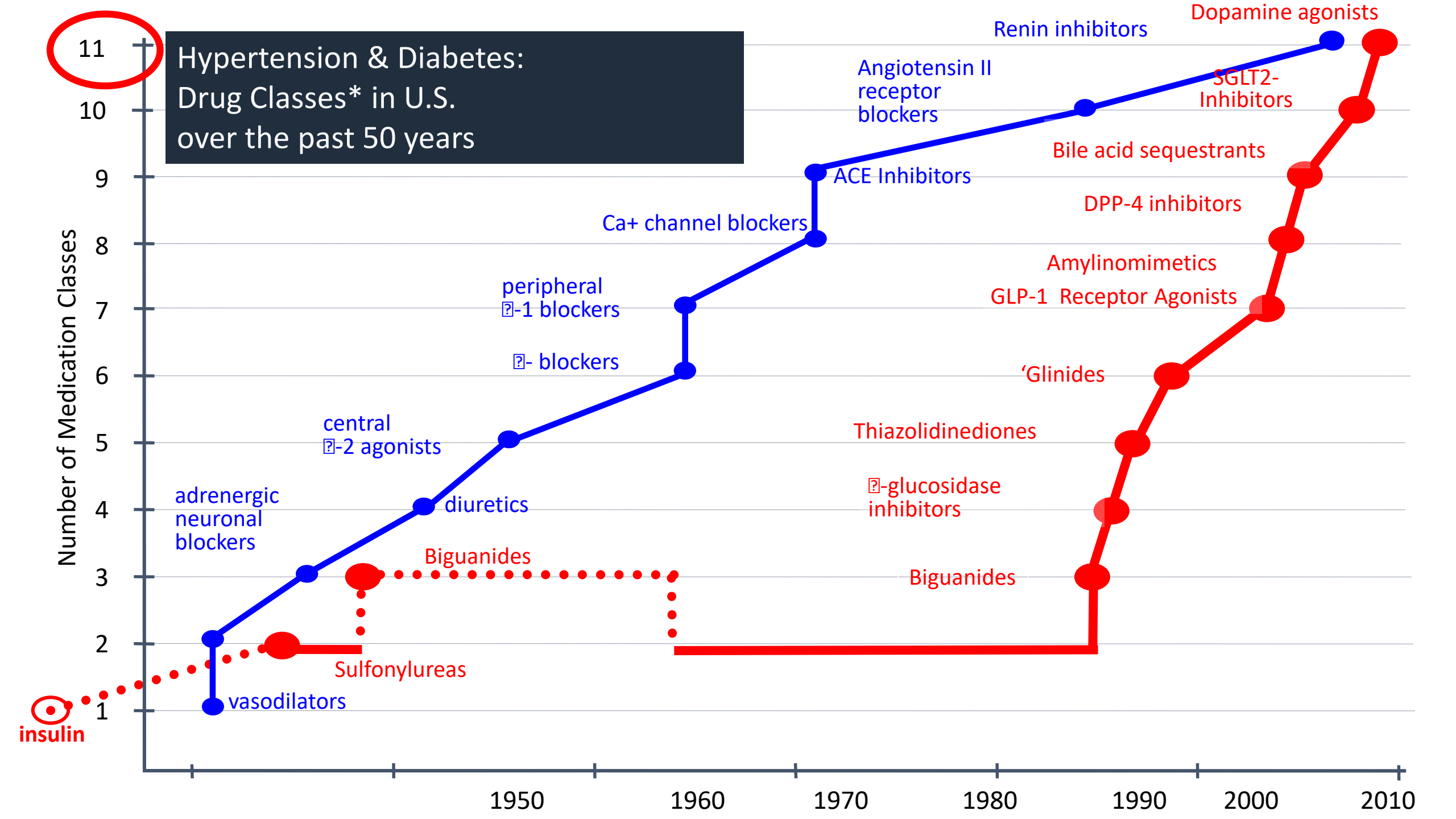


Rischio relativo aggiustato per età			
IMA	STROKE	AMPUTAZIONE	IRC
1.8	1.5	10.5	6.1

	Percent change, 1990 - 2010
IMA con diabete	- 67.8 %
IMA senza diabete	- 31.2 %
Stroke con diabete	- 52.7 %
Stroke senza diabete	- 5.5 %
Amputazione con diabete	- 51.4 %
Amputazione senza diabete	- 12.9 %
IRC con diabete	- 28.3 %
IRC senza diabete	65 %

Obiettivi di una terapia moderna basata sull'evidenza

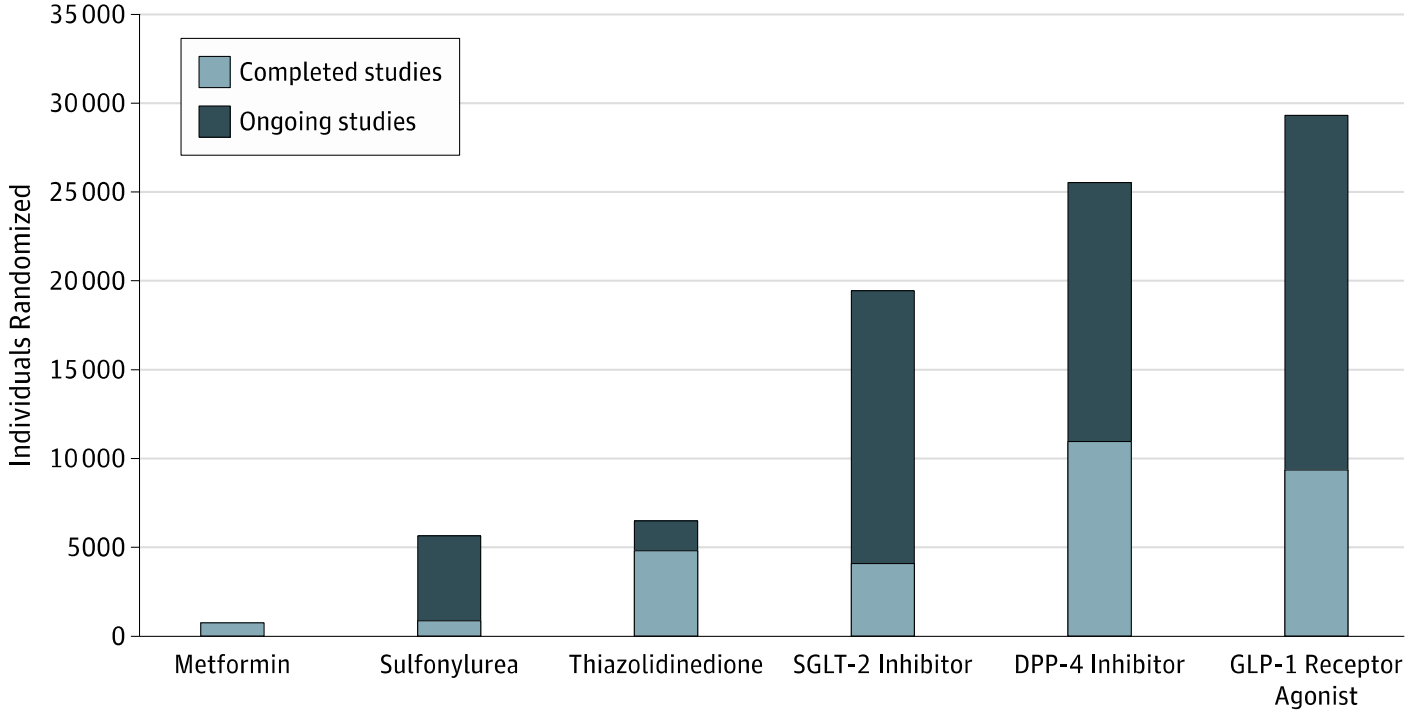
- Portare il pz a target di HbA1c, FPG, PPG e ridurre la variabilità glicemica
- Effettuare una terapia che agisca sui meccanismi fisiopatologici della malattia
- Evitare il rischio di ipoglicemia
- Evitare un aumento di peso corporeo
- Effettuare una terapia personalizzata il più precoce possibile
- Ridurre il rischio cardiovascolare e quindi trattare al meglio tutti i fattori di rischio cardiovascolare


Hypertension & Diabetes:
Drug Classes* in U.S.
over the past 50 years
Number of Medication Classes
11
10
9
8
7
6
5
4
3
2
1
1950
1960
1970
1980
1990
2000
2010
insulin
vasodilators
adrenergic neuronal blockers
central -2 agonists
diuretics
peripheral -1 blockers
- blockers
Ca+ channel blockers
ACE Inhibitors
Angiotensin II receptor blockers
Renin inhibitors
Dopamine agonists
Biguanides
Sulfonylureas
Biguanides
-glucosidase inhibitors
Thiazolidinediones
'Glinides
GLP-1 Receptor Agonists
Amylinomimetics
DPP-4 inhibitors
Bile acid sequestrants
SGLT2-Inhibitors

Will Cardiovascular Outcomes Data on Newer Diabetes Drugs Bury the Older Agents?

JAMA Internal Medicine March 2017 Volume 177, Number 3

Figure. Randomized Clinical Trials of Drugs for Type 2 Diabetes With a Primary Cardiovascular Outcome



2014

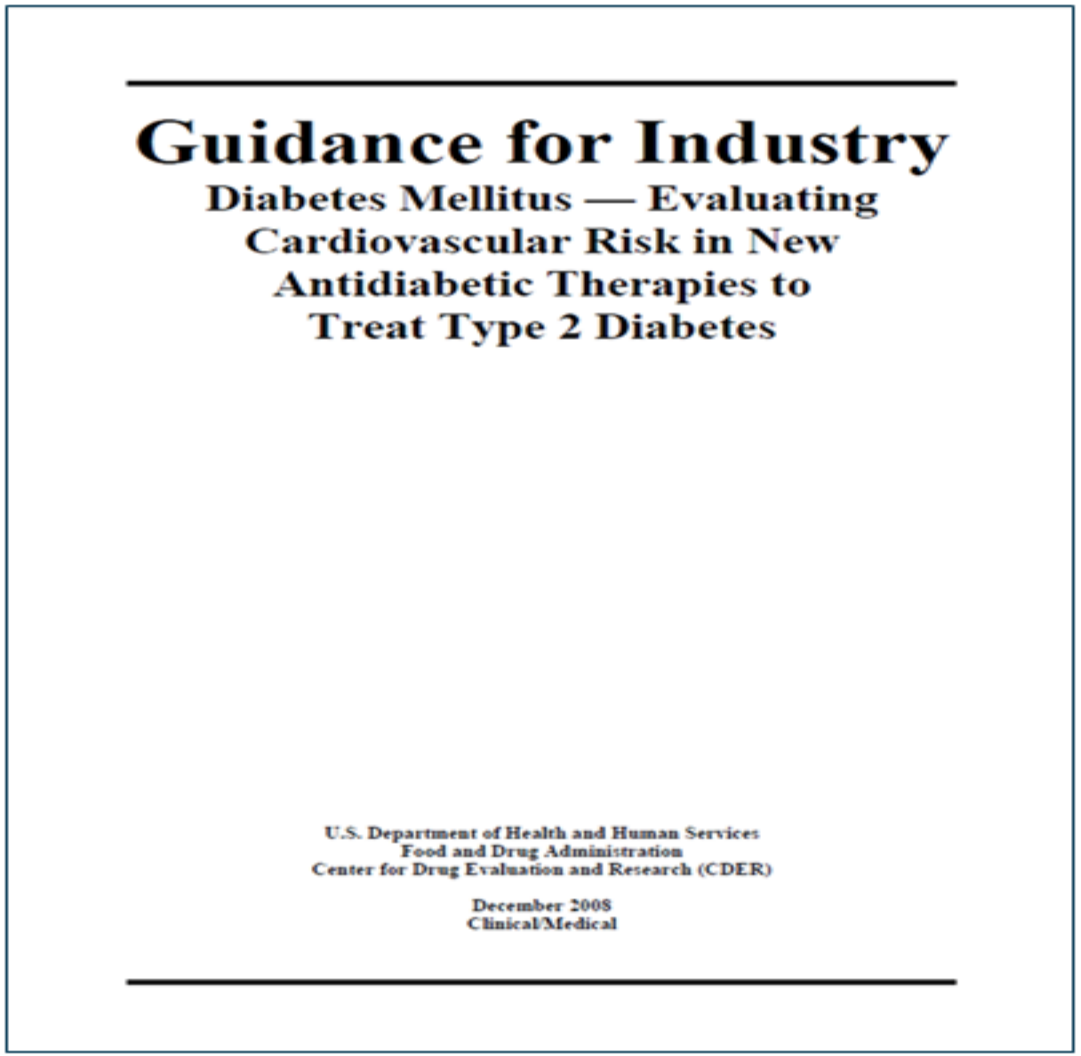
- **Metformina 53%**
- **Sulfonilurea 30%**
- **Glitazoni 5%**
- **DDP-IV inhibitors 13%**
- **GLP-1 agonists 2%**
- **SGLT-2 inhibitors 1%**

Meta-analysis of Rosiglitazone Studies: Risk for MI

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)
	No. of Events/Total No. (%)		
MI			
Small trials combined	44/10285 (0.43)	22/6106 (0.36)	1.45 (0.88-2.39)
DREAM	15/2635 (0.57)	9/2634 (0.34)	1.65 (0.74-3.68)
ADOPT	27/1456 (1.85)	41/2895 (1.42)	1.33 (0.80-2.21)
Overall			1.43 (1.03-1.98)

Nissen SE, et al. *N Engl J Med*. 2007;356:2457-2471.

December 2008 FDA Guidance on Evaluating CV Risk in New Antidiabetic Therapies for T2DM



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

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

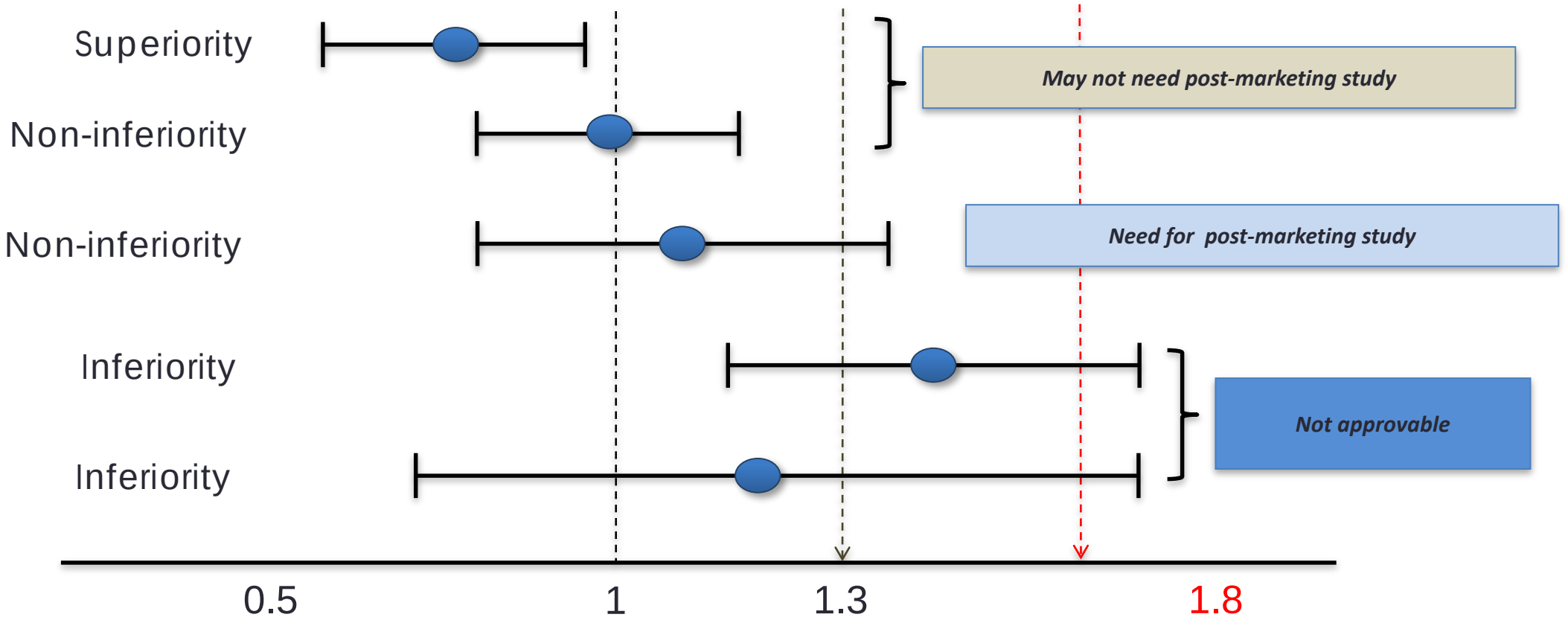
- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

FDA criteria for assessing CV safety



Alcune considerazioni

- Sono studi dimensionati per la sicurezza, ma sottodimensionati rispetto a un obiettivo di efficacia
- Vengono scelti pazienti in prevenzione secondaria o ad altissimo rischio per cui non possiamo sapere, ma solo immaginare, cosa succede se trattassimo paziente a più basso rischio
- Trattandosi di pazienti in prevenzione secondaria sono tutti ipertrattati con aspirina, statina, ecc.
- La riduzione della glicemia comunque può avere un effetto (samaglutide, liraglutide)
- Non è corretto scomporre l'endpoint primario perché il campione sarebbe ulteriormente sottodimensionato

	EXAMINE 18 m (5300 pz)	SAVOR-TIMI 2.5 a (16492)	TECOS 3 a (14600 pz)
Età	61.0	65.1	65.4
Durata D.	7.1	10.3	11.6
BMI	29.7	31.1	30.2
HbA1c	9.0 (- 0.3%)	8.0 (- 0.2%)	7.2 (-0.3%)

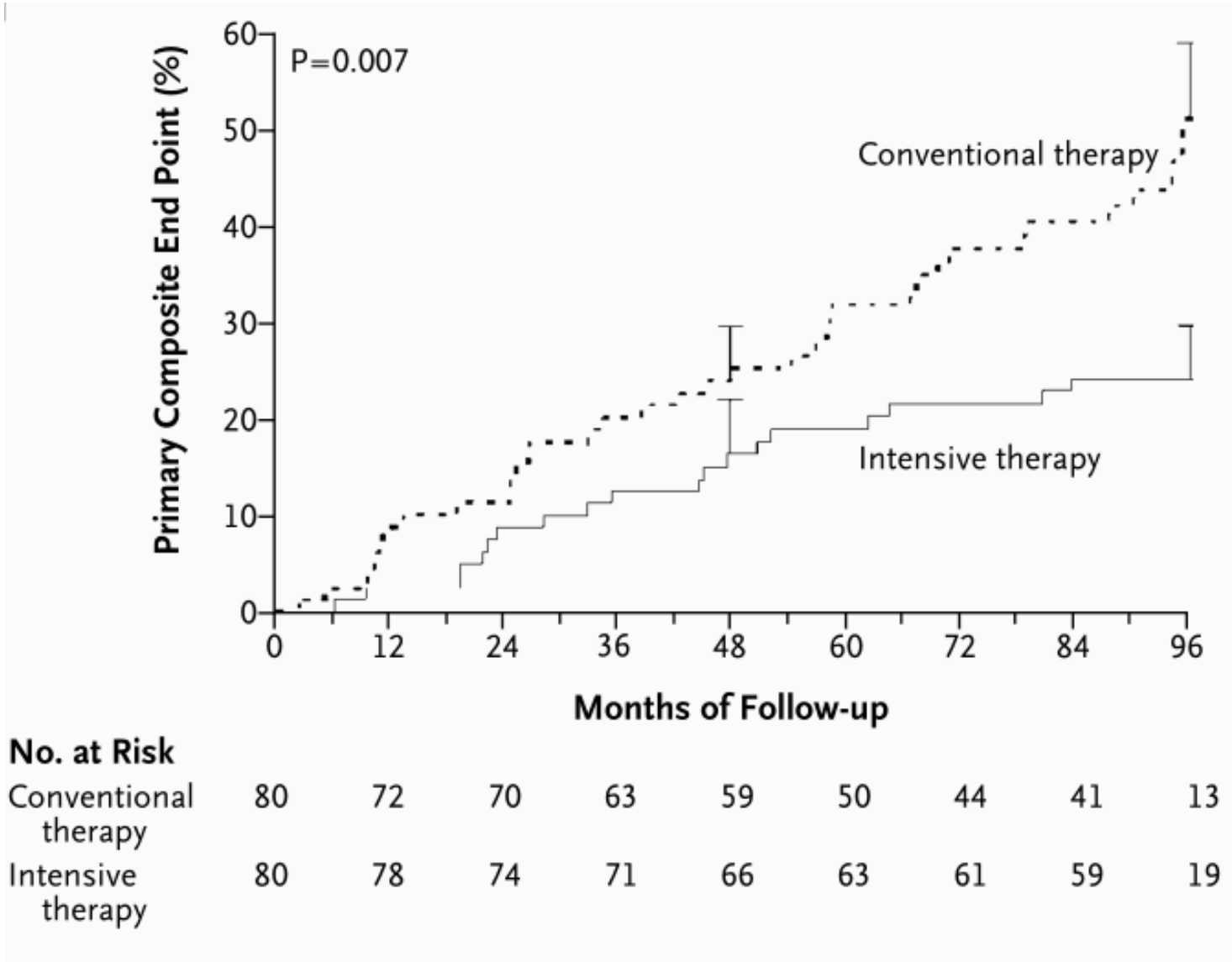
Studio	% MACE	HR	IC 95%	p
TECOS[a]	Sitagliptin: 11.4%, placebo: 11.6%	0.98	0.88-1.00	<0.001
SAVOR-TIMI 53[b]	Saxagliptin: 7.3%, placebo: 7.2%	1.00	0.89-1.12	<0.001
EXAMINE[b]	Alogliptin: 11.3%, placebo: 11.8%	0.96	1.16[c]	<0.001

PAD	9.7	11.9	16.6
Dislipidemia	27.1	71.2	77

CONFRONTO

	LEADER[65]	SUSTAIN-6[66]	EMPA-REG OUTCOME[64]
Farmaco	Liraglutide	Semaglutide	Empagliflozin
Meccanismo d'azione	GLP-1RA giornaliero	GLP-1RA settimanale	Inibitori di SGLT2
Fenotipo pazienti	Nota MCV o alto rischio	Nota MCV o alto rischio	Nota MCV
Durata dello studio	3.8 anni	2.1 anni	3 anni
Endpoint primario (3 punti MACE)	↓13%	↓26%	↓14%
Morte CV	↓22%	Neutro (rispetto al placebo)	↓38%
Infarto non fatale	Neutro (rispetto al placebo)	↓26%	Neutro (rispetto al placebo)
Ictus non fatale	Neutro (rispetto al placebo)	↓39%	Neutro (rispetto al placebo)
Scompenso cardiaco	Neutro (rispetto al placebo)	Neutro (rispetto al placebo)	↓35%
Nuova nefropatia/progressione	↓22%	↓14%	↓39%
Neoplasie	Neutro (rispetto al placebo)	Neutro (rispetto al placebo)	Neutro (rispetto al placebo)

CV, cardiovascolare; GLP-1RA, agonista del recettore del *glucagon-like receptor 1*; MACE, eventi cardiaci avversi maggiori; MCV, malattia cardiovascolare; SGLT2, cotrasportatore renale di sodio-glucosio di tipo 2.



No. at Risk

Conventional therapy	80	72	70	63	59	50	44	41	13
Intensive therapy	80	78	74	71	66	63	61	59	19

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 30, 2003 VOL. 348 NO. 5

Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

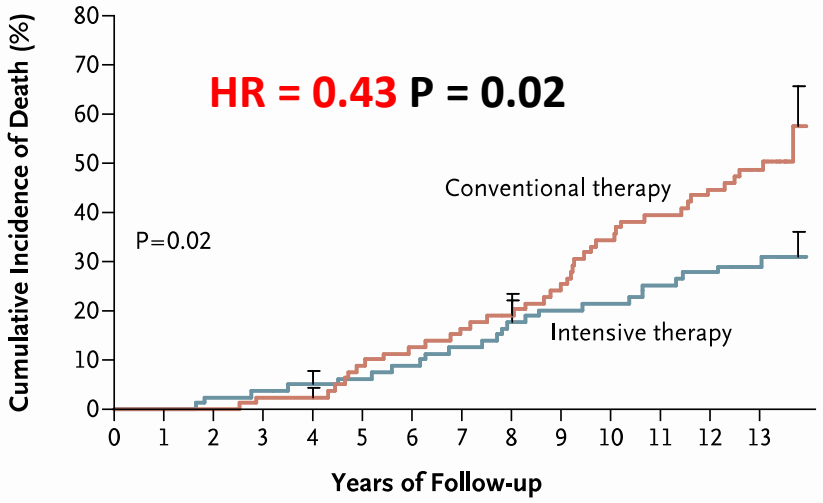
Peter Gæde, M.D., Pernille Vedel, M.D., Ph.D., Nicolai Larsen, M.D., Ph.D., Gunnar V.H. Jensen, M.D., Ph.D., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

End Point: Morte cardiovascolare, IMA non fatale, CABG, PTCA, Stroke non fatale, amputazione, chirurgia periferica vascolare

The NEW ENGLAND JOURNAL of MEDICINE

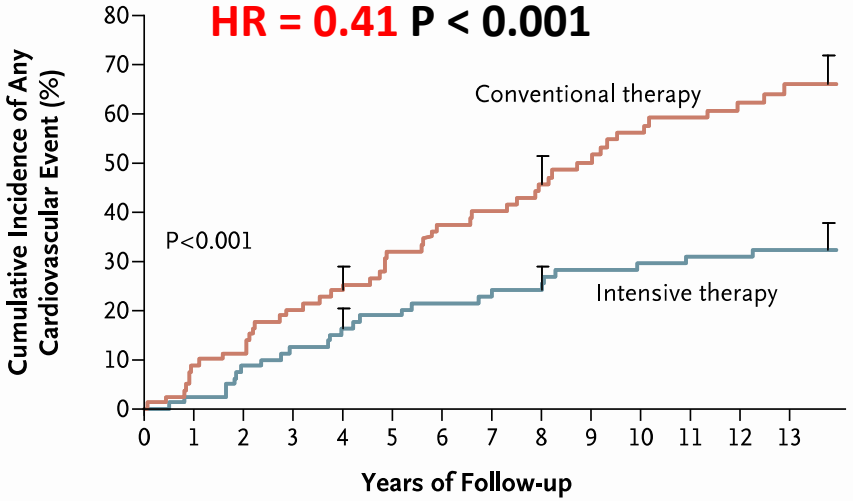
Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

A



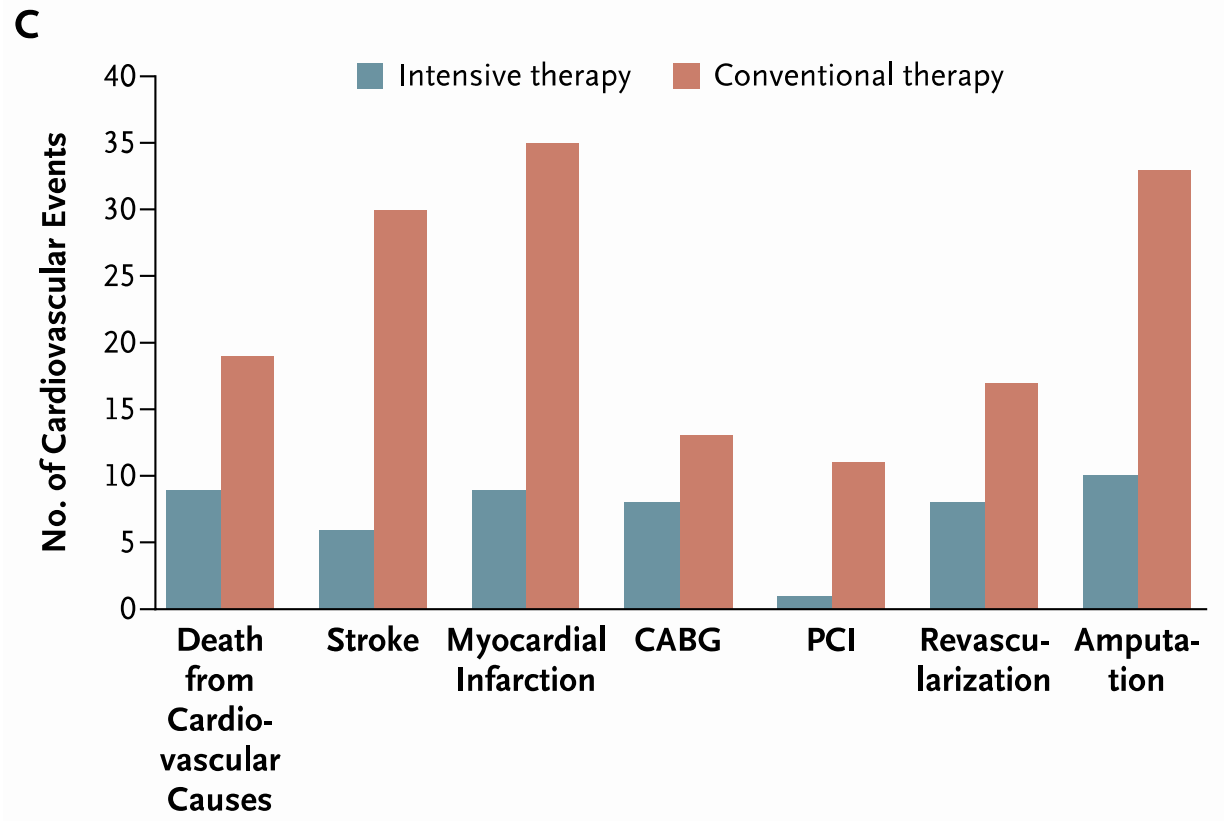
No. at Risk								
Intensive therapy	80	78	75	72	65	62	57	39
Conventional therapy	80	80	77	69	63	51	43	30

B



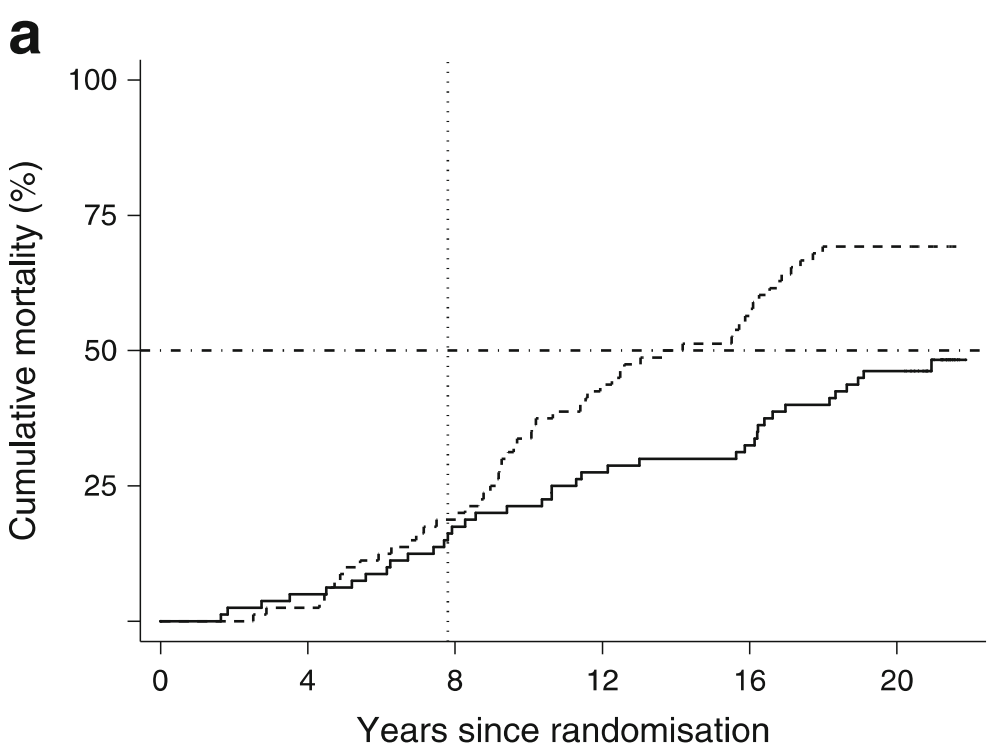
No. at Risk								
Intensive therapy	80	72	65	61	56	50	47	31
Conventional therapy	80	70	60	46	38	29	25	14

C

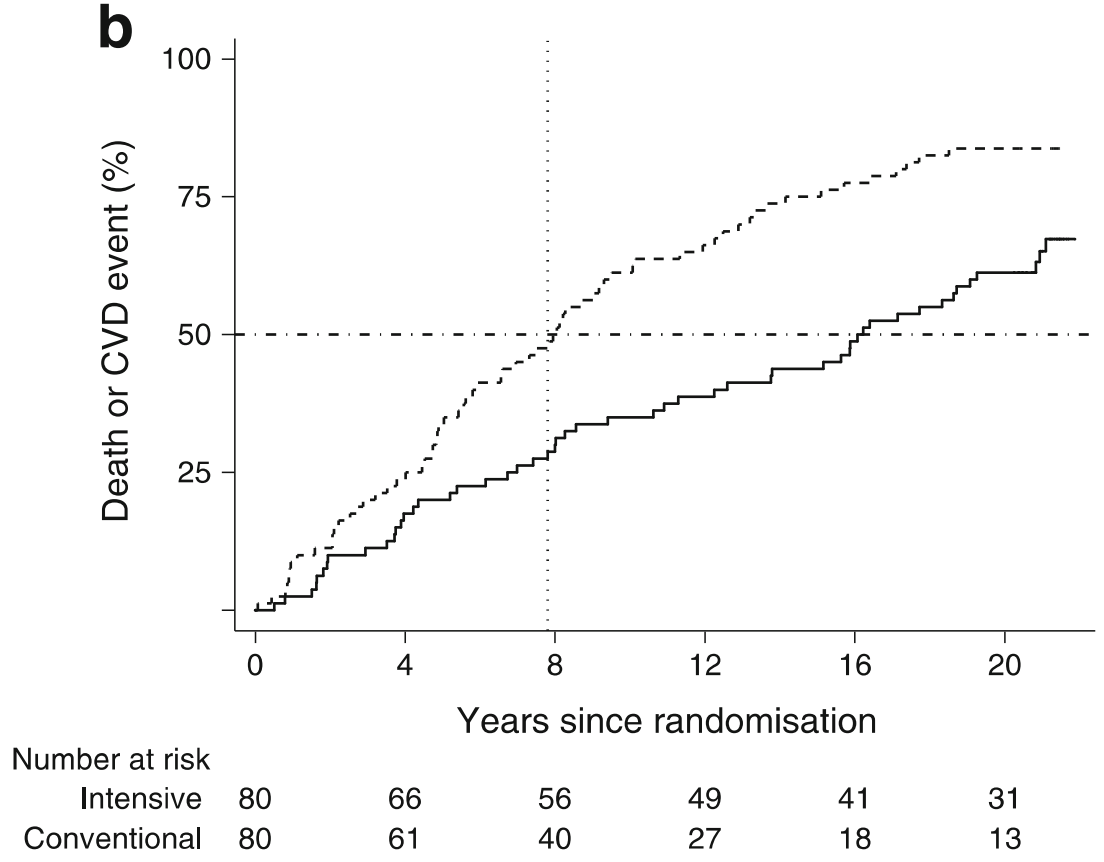


Diabetologia (2016) 59:2298–2307

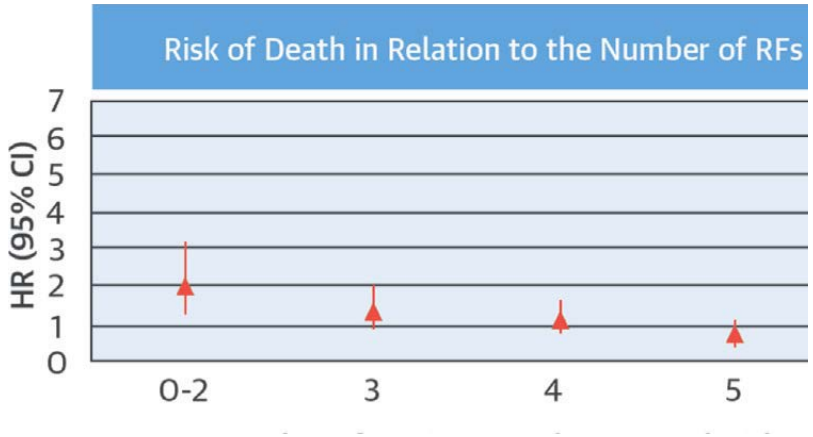
Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial



7.9 anni guadagnati



8.1 anni liberi da eventi

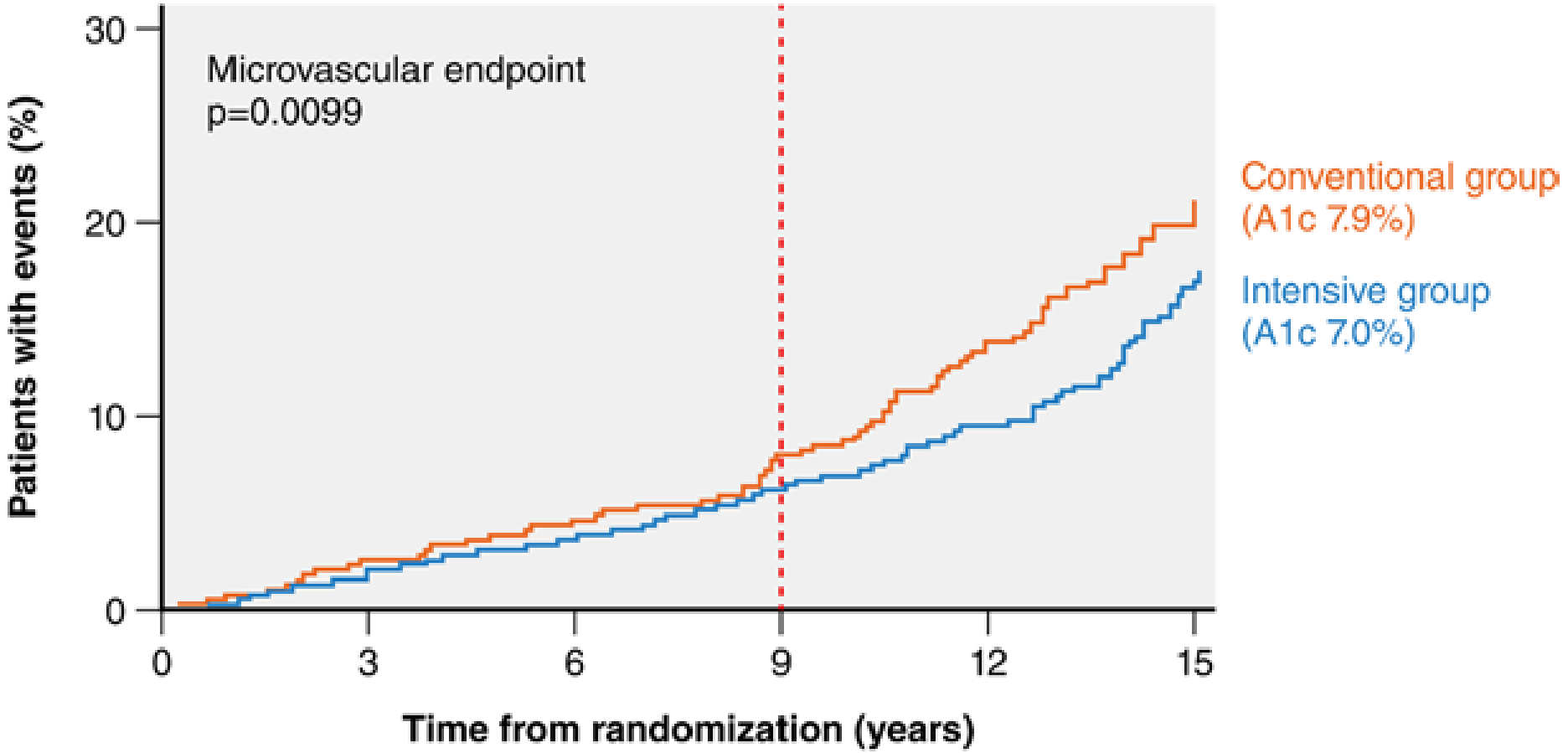


Il controllo dei fattori di rischio migliora la sopravvivenza e riduce gli eventi cardiovascolari

An Evidence-Based Medicine Approach to Antihyperglycemic Therapy in Diabetes Mellitus to Overcome Overtreatment

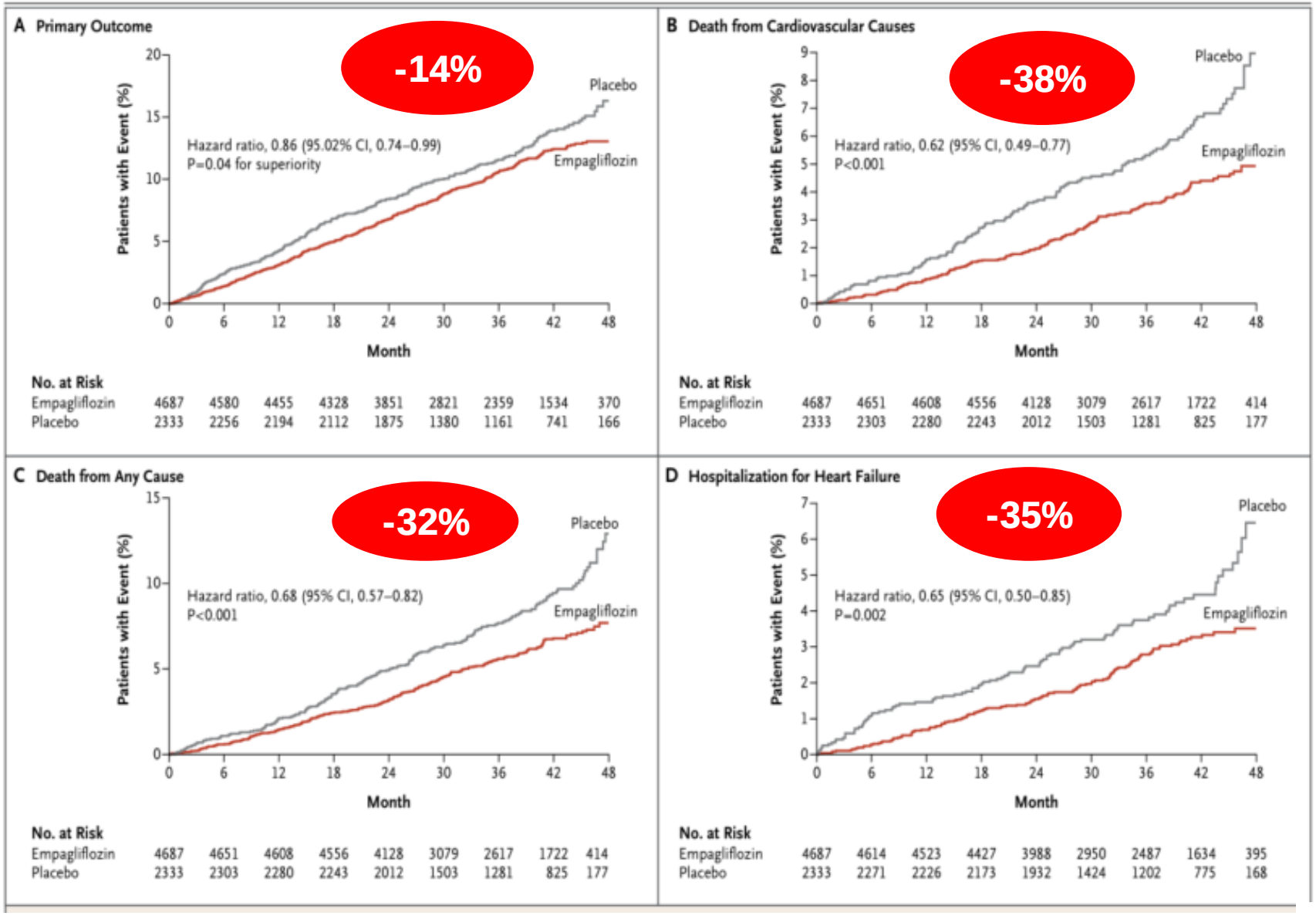
Circulation. 2017;135:180–195.

UKPDS



Time Horizon to benefit for intensive glycemic control for intermediate microvascular outcomes

EMPA-REG OUTCOME



Early and unusual divarication of mortality curves:
Suggests little effect on atherosclerosis progression also supported by the lack of any significant effect on nonfatal MI and stroke

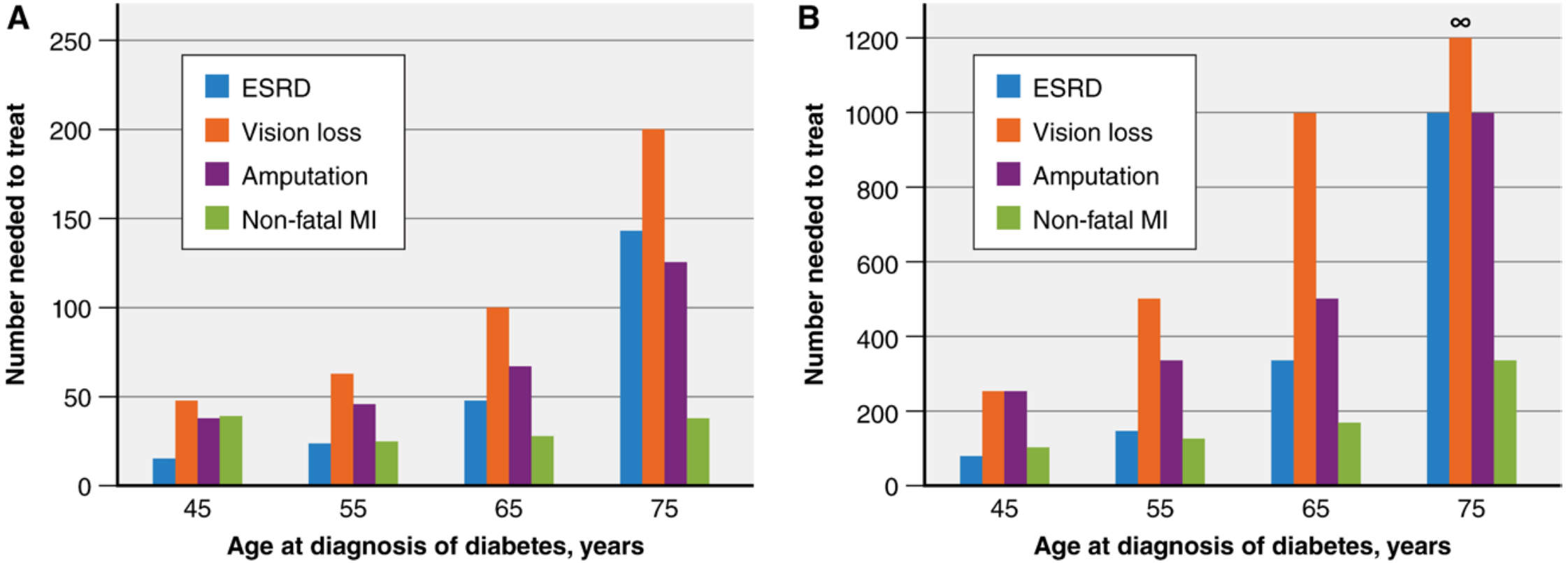
These results suggest that the use of empagliflozin does not necessary protect from the CV event, rather with the mortality linked to the event itself

At least part of the beneficial effect of empagliflozin to be exerted through:
- volume depletion
- switch to fatty acid utilization, concurrent with better oxygen delivery to the tissues, cooperates with small changes in body weight and blood pressure to achieve cardioprotection by SGLT2 inhibition

N ENGL J MED 373;22 NEJM.ORG NOVEMBER 26, 2015

An Evidence-Based Medicine Approach to Antihyperglycemic Therapy in Diabetes Mellitus to Overcome Overtreatment

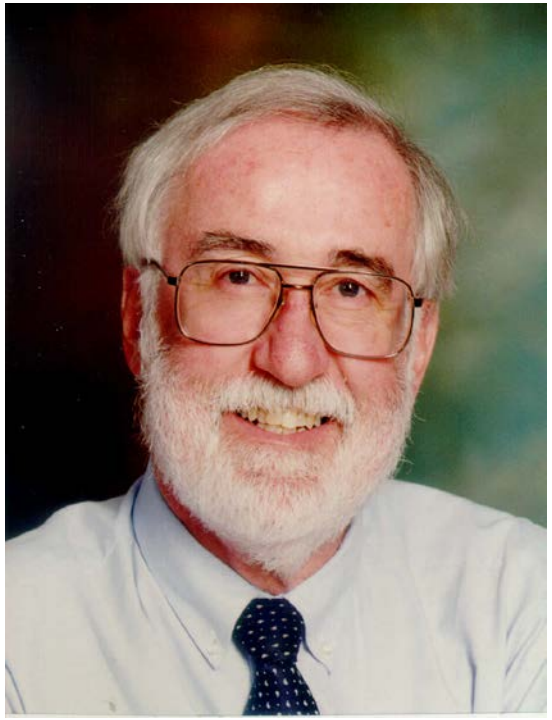
Circulation. 2017;135:180–195.



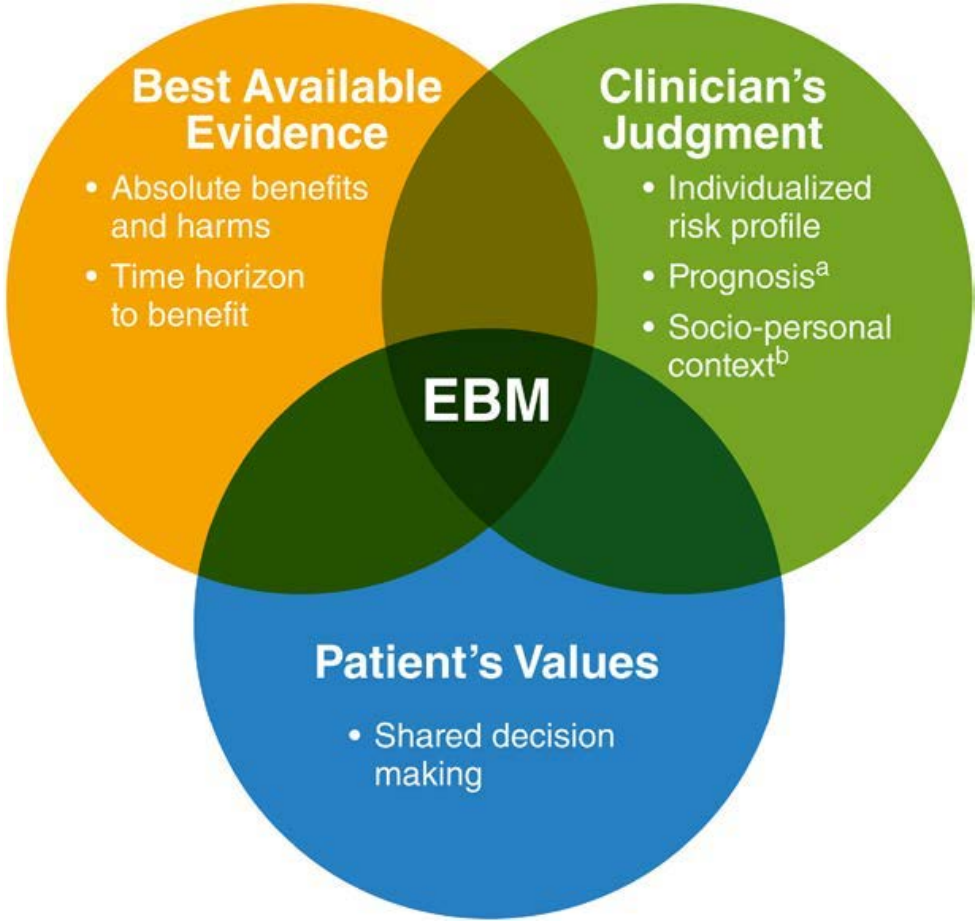
Estimated lifetime absolute benefits of intensive glycemic control for preventing microvascular oucomes and Non-fatal MI

What is evidence-based medicine?

Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values



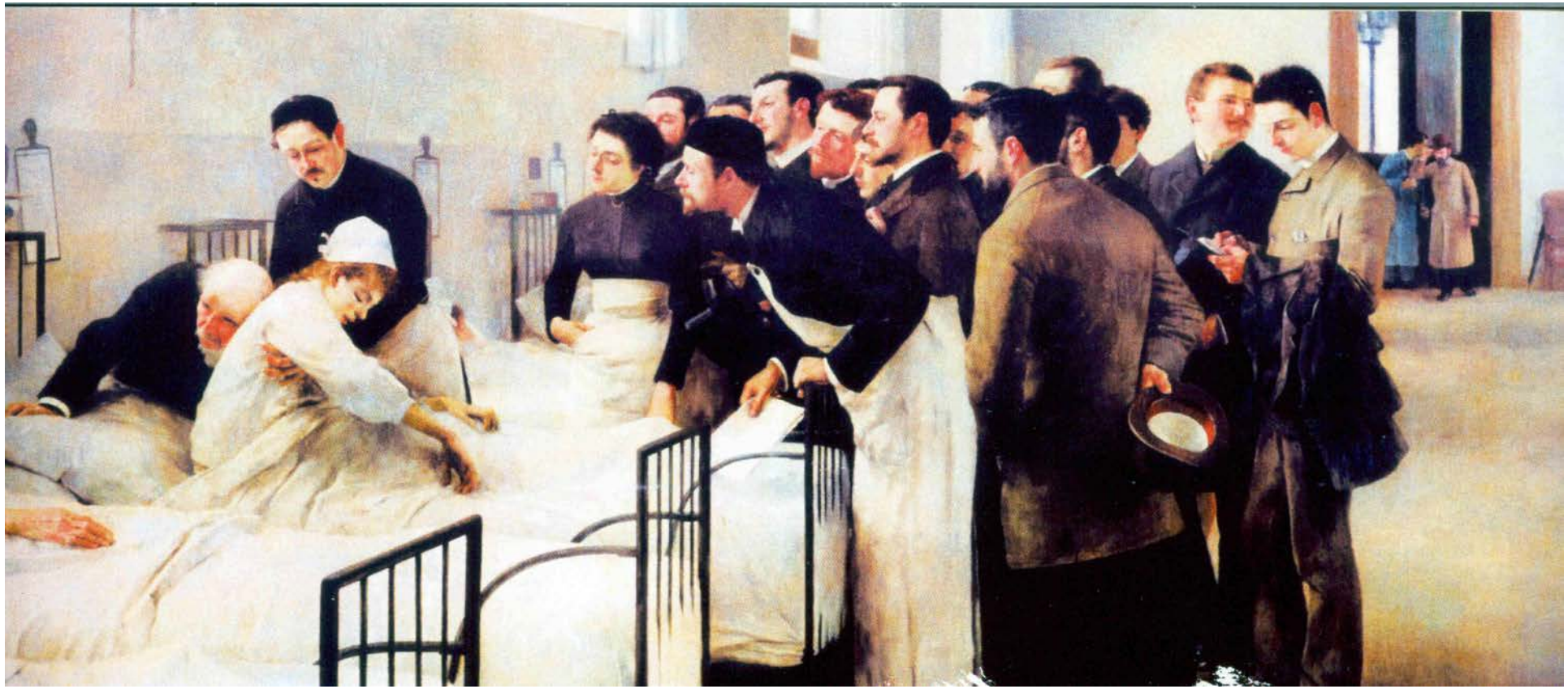
David Sackett



Sackett DL et al.: BMJ 1996;312:71-2.

CONCLUSIONI

- Stiamo vivendo un momento straordinario, una nuova era, per la cura del diabete mellito
- Per la prima volta abbiamo farmaci che forse ci consentono di andare oltre la glicemia
- Abbiamo la conferma indiretta che la progressione della malattia aterosclerotica nella popolazione diabetica sia un processo molto più complicato e collegato non solo alla iperglicemia
- Dobbiamo però essere cauti nel trasferire i risultati degli studi di sicurezza cardiovascolare alla pratica clinica, in particolare ai pazienti in prevenzione primaria
- Molto probabilmente dobbiamo utilizzare parametri di evidenza diversi rispetto a quelli che sino ad ora ci hanno consentito di scrivere le linea guida



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