CVOTs e GLP1 RA aggiornamenti dalla letteratura

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Dichiarazione di Conflitto di Interessi

Honorarium as a speaker in Scientific Events

Sigma-Tau
AstraZeneca BMS
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Menarini Diag
Novo Nordisk
Lilly/Boheringer Ingelheim
Takeda
Eli-Lilly
Bayer
Roche Diag
Servier
Janssen
Sanofi-Aventis
MSD
Novartis

Grant support

Novo Nordisk (Investigator-Initiated-Study Grant)
Kellogg (Investigator-Initiated-Study Grant)
AstraZeneca, Lilly, Sanofi, Novo Nordisk, Sigma-Tau, Menarini Diag (Travel grants)

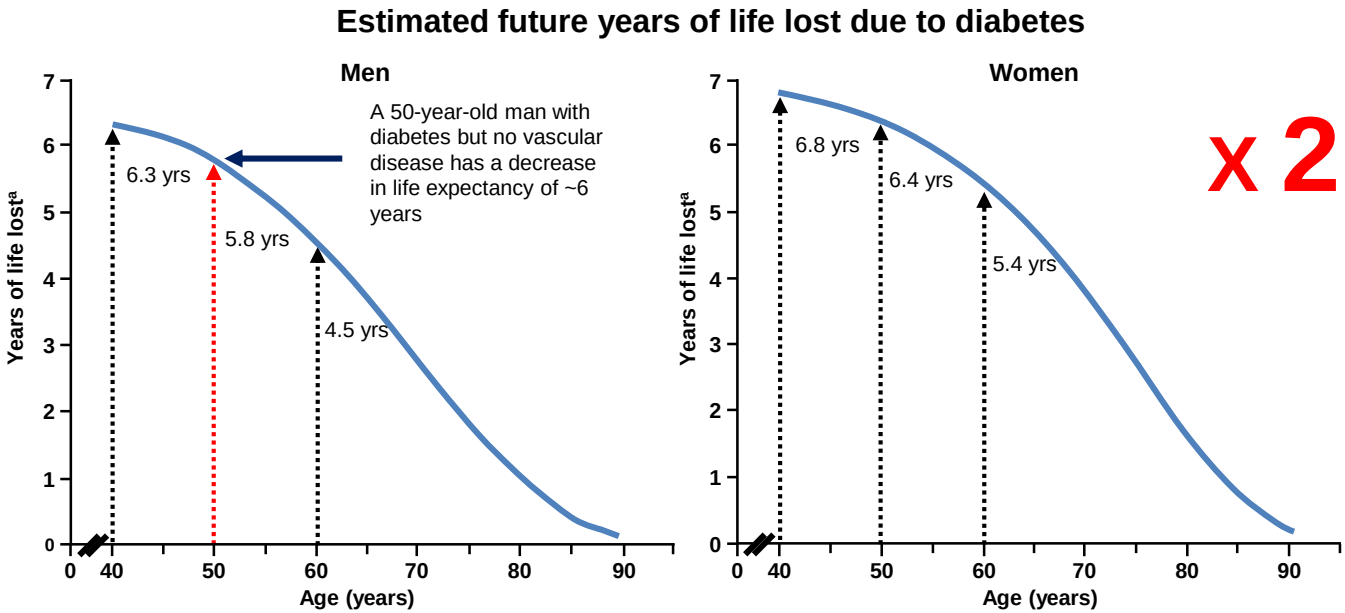
Scientific advisory boards

AstraZeneca, Lilly, Sanofi, Novartis

Today - Topics

- **Diabete e rischio CVD**
- **Effetto della riduzione della glicemia su CVD**
- **I CVOTs: studi di sicurezza**
- **Impatto sulle Linee Guida in paziente con CVD pregressa**
- **Impatto sulle Linee Guida in un paziente senza CVD pregressa**

Type 2 diabetes is associated with a decrease in life expectancy from CV causes



Adapted from The Emerging Risk Factors Collaboration. N Engl J Med 2011

RCTs di trattamento intensivo
UKPDS, ACCORD, VADT, ADVANCE

14% CVD risk reduction

Limitation # 1: takes long time

Limitation # 2: hypoglycemia

Rosiglitazone e
la meta-analisi di Steven Nissen

Diabetes and Cardiovascular Disease: The Perfect Storm

The NEW ENGLAND JOURNAL of MEDICINE

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

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

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

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Source: Nissen SE, Wolski K. N Engl J Med 2007; 356: 2457-2471

Come nascono i CVOTs

2008: Il mandato FDA/CHMP

“Gli sponsor sono tenuti a dimostrare che una nuova terapia antidiabetica non aumenta il rischio CV in misura inaccettabile.”

Confronto di eventi CV tra Prodotto Sperimentale (PS) e controllo – attraverso una meta-analisi di studi di Fase 2/3 o un ampio RCT - per mostrare:

Limite superiore del 95% CI per HR	Conclusione
>1.8	PS non approvabile
>1.3 to <1.8	Necessità di uno studio clinico post marketing che dimostri un HR<1.3
<1.3	Uno studio clinico post marketing può non essere necessario

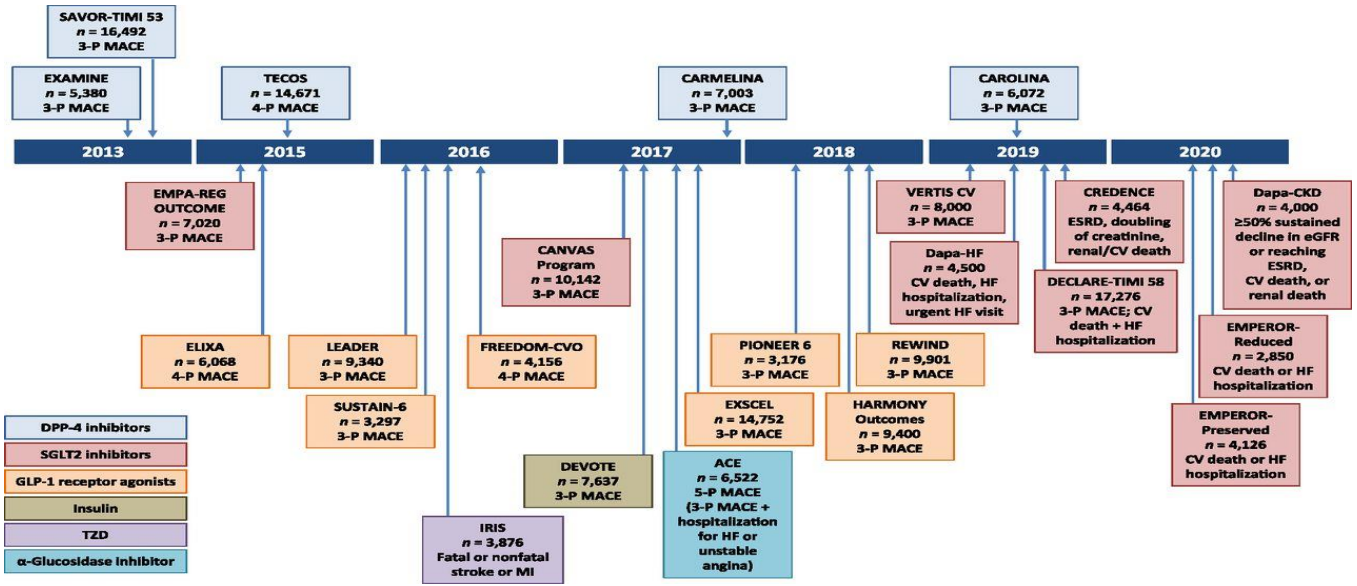
1. Food and Drug Administration. 2008. Guidance for industry. Diabetes mellitus — evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Food and Drug Administration web site. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf. Accessed 17 March 2013

Considerazioni metodologiche

Efficacy trials vs. safety trials

	Efficacy trials	Safety trials
Aim	Demonstrate CV benefit	Demonstrate CV safety
Aim of treatment	Maximize HbA1c difference	Minimize HbA1c difference (equipoise)
Comparator	Usually active drug	Usually placebo
Study population	High proportion of patients without CVD/CKD	High proportion of patients with CVD/CKD
Primary endpoint	Heterogeneous	MACE
Study duration	Pre-specified	Event driven
Primary analysis	Superiority	Non inferiority

CVOTs e dintorni …..

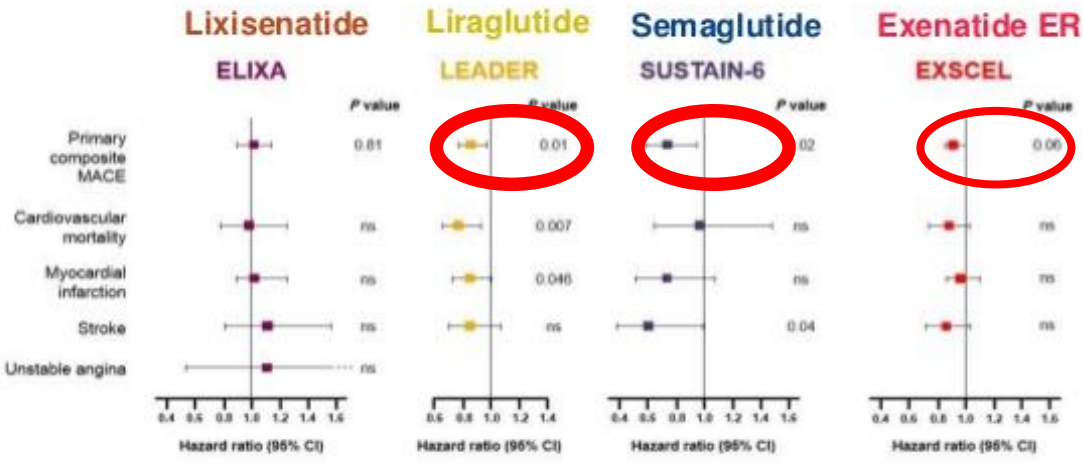


Cefalu WT Diabetes Care 2018

I risultati dei CVOTs

…….

GLP1 Receptor Agonist Trials



CI, confidence interval; MACE, major adverse cardiovascular event; ns, not significant.
Adapted from Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; Marso SP, et al., *N Engl J Med* 2016;375:311-22; Marso SP, et al., *N Engl J Med* 2016;375:1834-1844; Holman RR et al., *N Engl J Med*, in press.

Albiglutide
HARMONY

HR: 0.78
CI95% (0.68-0.90)
P=0.0006

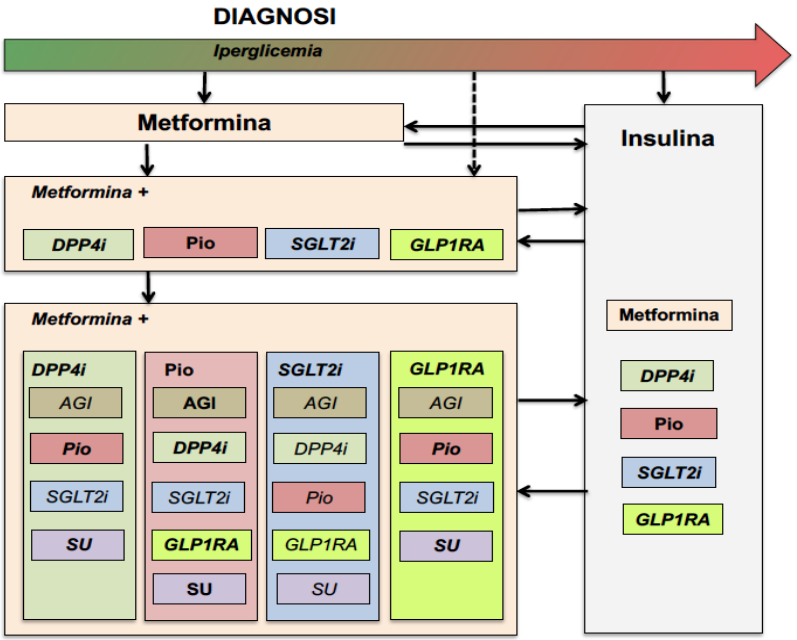
HR: 0.93
CI95% (0.73-1.19)
P=0.578

HR: 0.75
CI95% (0.61-0.90)
P=0.003

HR: 0.86
CI95% (0.66-1.14)
P=0.300

All-cause Mortality	HR 0.94 CI95%: 0.78-1.13 P=0.50	HR 0.85 CI95%: 0.74-0.9 P=	HR 1.05 CI95%: 0.74-1.50 P=0.79	HR: 0.86 CI9 %: 0.77-0.97 P=0.01	HR: 0.95 CI95% 0.79-1.16 P=0.644

I risultati dei CVOTs
……. e le ricadute



Nei pazienti con pregressi eventi cardiovascolari maggiori SGLT-2 inibitori, GLP-1 agonisti a lunga durata d'azione e pioglitazone devono essere considerati farmaci di prima scelta, salvo controindicazioni. *II A*

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies,[1,2] David A. D'Alessio,[3] Judith Fradkin,[4] Walter N. Kernan,[5] Chantal Mathieu,[6] Geltrude Mingrone,[7,8] Peter Rossing,[9,10] Apostolos Tsapas,[11] Deborah J. Wexler,[12,13] and John B. Buse[14]

https://doi.org/10.2337/dci18-0033

Davies MJ et al Diabetes Care, 2018

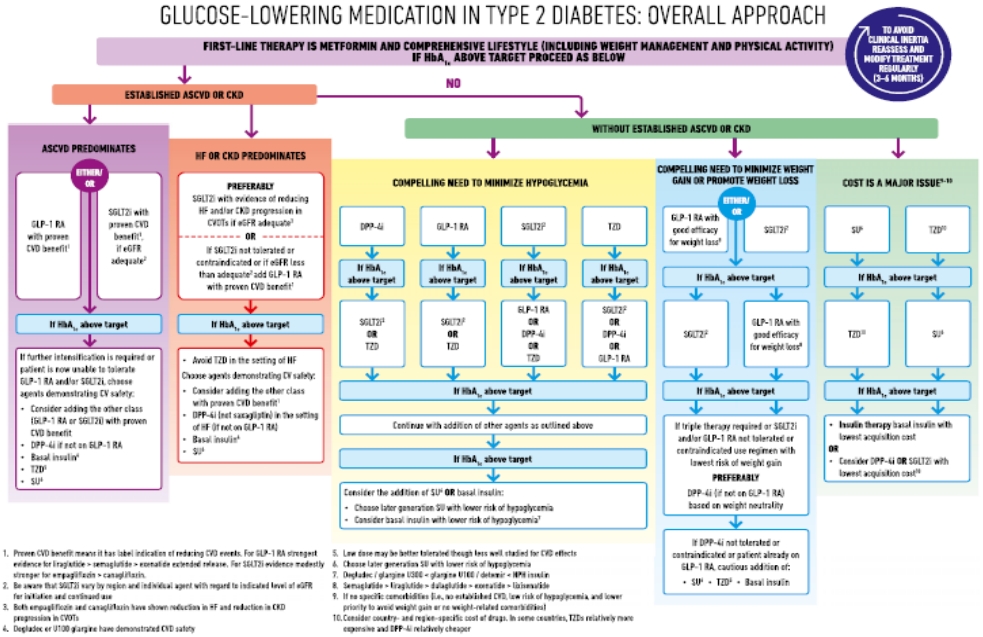
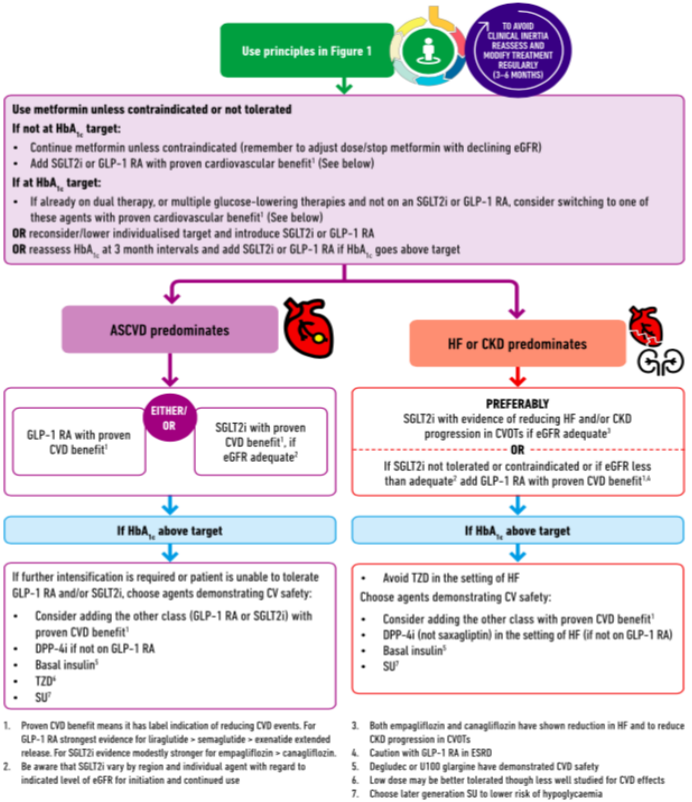


Figure 2—Glucose-lowering medication in type 2 diabetes: overall approach. CV, cardiovascular; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

Consensus ADA EASD 2018



Davies M et al Management of hyperglycaemia in type 2 diabetes, 2018.
A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

2019 ESC/EASD Guidelines on diabetes and CVD

Target 1

Target 2

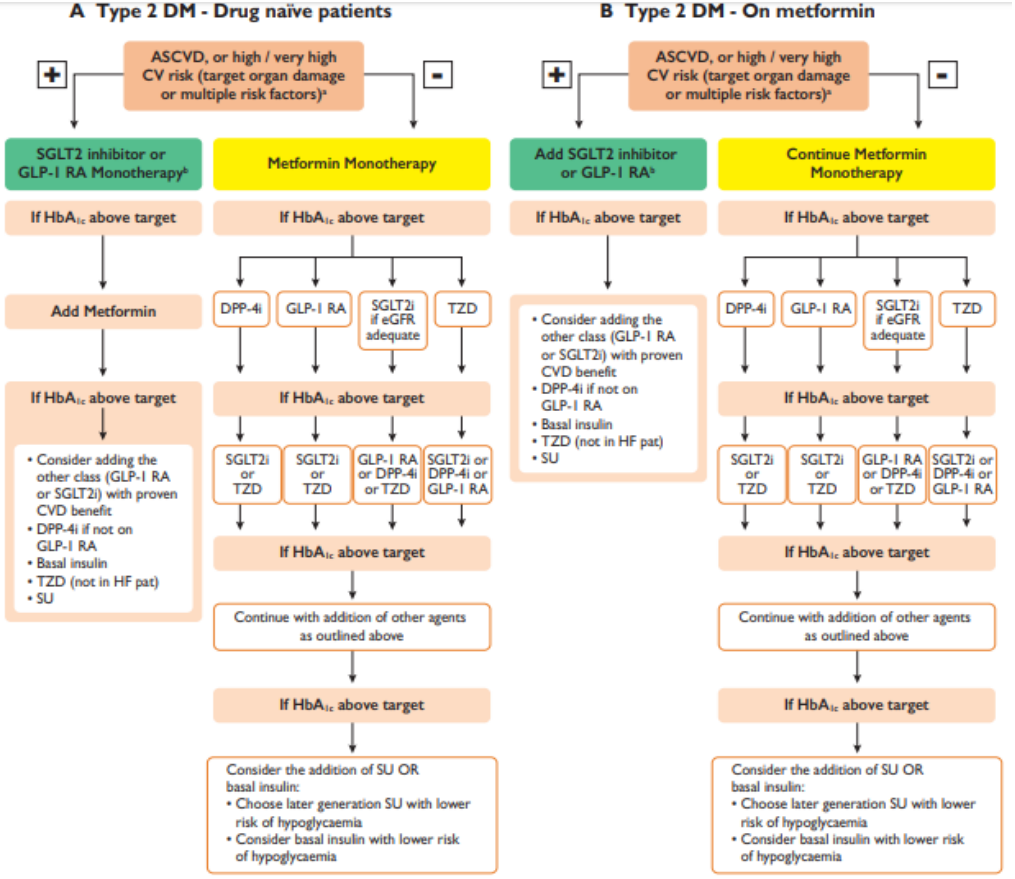


Table 7 **Cardiovascular risk categories in patients with diabetes[a]**

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

[c]Age, hypertension, dyslipidemia, smoking, obesity.

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

I risultati dei CVOTs
……. le news dal 2019

Semaglutide - Orale

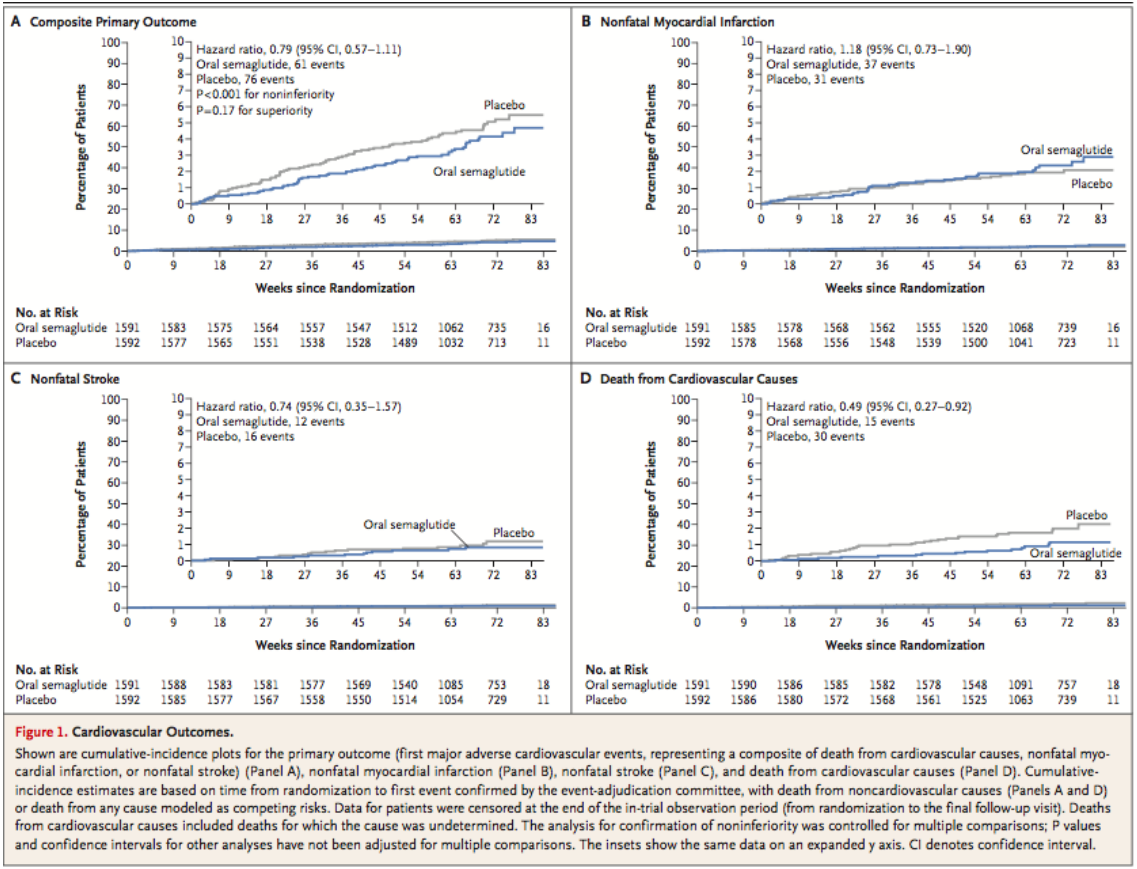


Figure 1. Cardiovascular Outcomes.

Shown are cumulative-incidence plots for the primary outcome (first major adverse cardiovascular events, representing a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). Cumulative-incidence estimates are based on time from randomization to first event confirmed by the event-adjudication committee, with death from noncardiovascular causes (Panels A and D) or death from any cause modeled as competing risks. Data for patients were censored at the end of the in-trial observation period (from randomization to the final follow-up visit). Deaths from cardiovascular causes included deaths for which the cause was undetermined. The analysis for confirmation of noninferiority was controlled for multiple comparisons; P values and confidence intervals for other analyses have not been adjusted for multiple comparisons. The insets show the same data on an expanded y axis. CI denotes confidence interval.

Husain M et al N Engl J Med, 2019

Dulaglutide – Once weekly

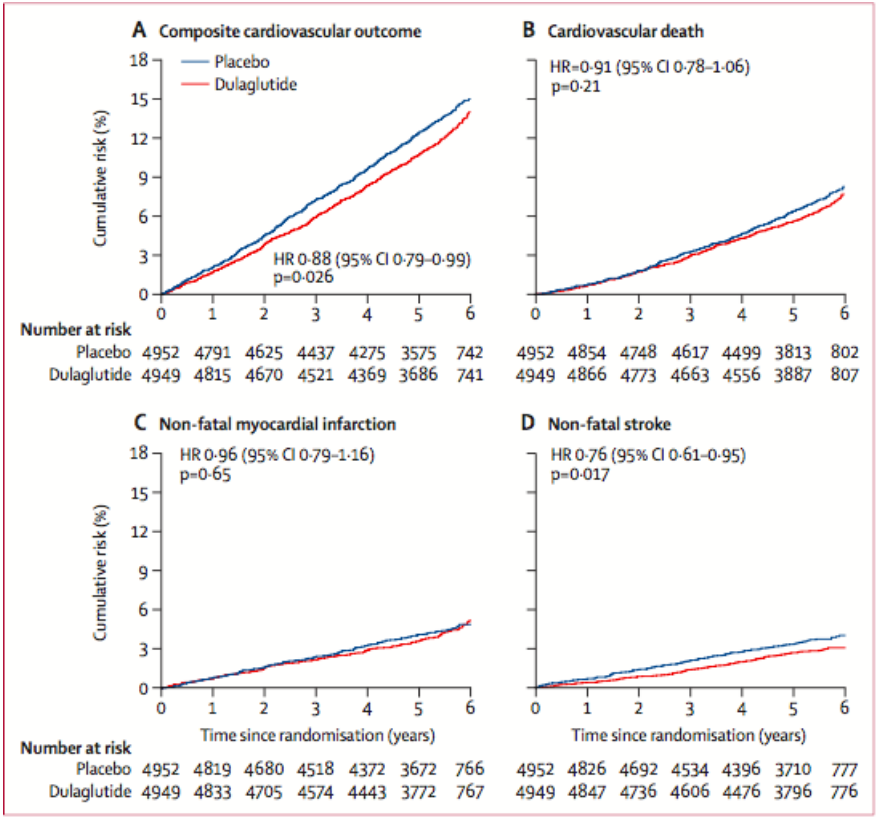


Figure 2: **Cumulative incidence of cardiovascular outcomes**
HR=hazard ratio. HbA_{1c}=glycated haemoglobin A_{1c}.

Gerstein HC et al Lancet, 2019

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

Published Online
June 10, 2019
http://dx.doi.org/10.1016/
S0140-6736(19)31149-3

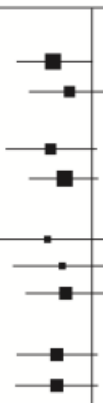
*Hertzel C Gerstein, Helen M Colhoun, Gilles R Dagenais, Rafael Diaz, Mark Lakshmanan, Prem Pais, Jeffrey Probstfield, Jeffrey S Riesmeyer, Matthew C Riddle, Lars Rydén, Denis Xavier, Charles Messan Atisso, Leanne Dyal, Stephanie Hall, Purnima Rao-Melacini, Gloria Wong, Alvaro Avezum, Jan Basile, Namsik Chung, Ignacio Conget, William C Cushman, Edward Franek, Nicolae Hancu, Markolf Hanefeld, Shaun Holt, Petr Jansky, Matyas Keltai, Fernando Lanas, Lawrence A Leiter, Patricio Lopez-Jaramillo, Ernesto German Cardona Munoz, Valdis Pirags, Nana Pogosova, Peter J Raubenheimer, Jonathan E Shaw, Wayne H-H Sheu, Theodora Temelkova-Kurktschiev, for the REWIND Investigators**

Added value of this study

The REWIND trial of 9901 people had a long median follow-up period of 5·4 years, recruited a low proportion of people (31·5%) with previous cardiovascular disease, a high proportion of women (46·3%), and followed people with a mean HbA_{1c} of 7·3%.

In cosa si differenzia ?

	Dulaglutide		Placebo		Hazard ratio (95% CI)	$p_{interaction}$
	Events/patients (%)	Incidence (per 100 person-years)	Events/patients (%)	Incidence (per 100 person-years)		
Age (years)						0·57
≥66	331/2314 (14·3%)	2·9	384/2350 (16·3%)	3·3	0·86 (0·74–1·00)	
<66	263/2635 (10·0%)	1·9	279/2602 (10·7%)	2·1	0·92 (0·78–1·09)	
Sex						0·60
Female	218/2306 (9·5%)	1·8	249/2283 (10·9%)	2·1	0·85 (0·71–1·02)	
Male	376/2643 (14·2%)	2·8	414/2669 (15·5%)	3·1	0·90 (0·79–1·04)	
Duration of diabetes (years)						0·88
<5	128/1227 (10·4%)	2·0	146/1192 (12·2%)	2·4	0·84 (0·66–1·06)	
5–10	174/1446 (12·0%)	2·3	196/1476 (13·3%)	2·6	0·89 (0·73–1·09)	
≥10	292/2276 (12·8%)	2·5	321/2284 (14·1%)	2·8	0·90 (0·77–1·06)	
History of cardiovascular disease*						0·97
Yes	280/1560 (17·9%)	3·7	315/1554 (20·3%)	4·2	0·87 (0·74–1·02)	
No	277/3093 (8·9%)	1·7	317/3128 (10·1%)	2·0	0·87 (0·74–1·02)	



Treatment DM2 in primary prevention of CVD

Recommendations for Adults With Type 2 Diabetes Mellitus

Referenced studies that support recommendations are summarized in Online Data Supplement 10.

COR	LOE	Recommendations
I	A	1. For all adults with T2DM, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-1, S4.2-2).
I	A	2. Adults with T2DM should perform at least 150 minutes per week of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity to improve glycemic control, achieve weight loss if needed, and improve other ASCVD risk factors (S4.2-3, S4.2-4).
IIa	B-R	3. For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk (S4.2-5–S4.2-8).
IIb	B-R	4. For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce CVD risk (S4.2-9–S4.2-14).

Arnett et al. 2019 ACC/AHA Guideline

on the Primary Prevention of Cardiovascular Disease

GLP1 – RA
segnali robusti e consistenti

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Søren L Kristensen, Rasmus Rørth, Pardeep S Jhund, Kieran F Docherty, Naveed Sattar, David Preiss, Lars Køber, Mark C Petrie, John J V McMurray

CVD prognosis

6 large safety RCTs
1 large efficacy RCT

MACE
CVD death
MI
Stroke

Lancet Diabetes Endocrinol 2019
Published Online
August 14, 2019
http://dx.doi.org/10.1016/S2213-8587(19)30249-9

SGLT2-i
NNT = 97

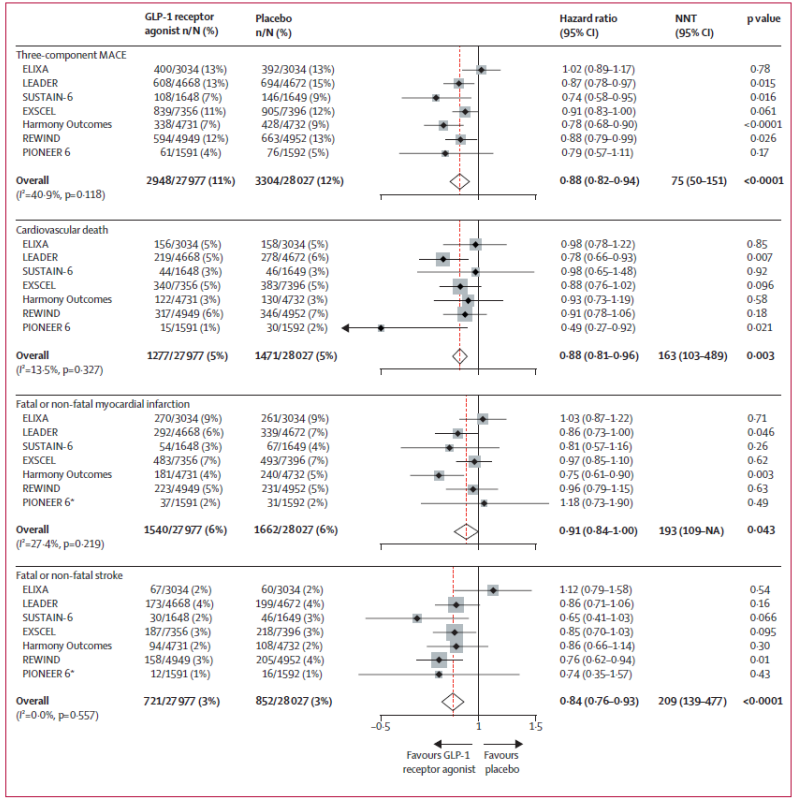


Figure 2: **Risk of MACE and each of its components**
Three-component MACE consisted of cardiovascular death, myocardial infarction, and stroke. NNTs are calculated over an estimated median follow-up of 3·2 years. MACE=major adverse cardiovascular events. GLP-1=glucagon-like peptide-1. NNT=number needed to treat. *For PIONEER 6, data for fatal and non-fatal myocardial infarction and stroke were not available, so numbers and estimates refer to non-fatal myocardial infarction and non-fatal stroke exclusively.

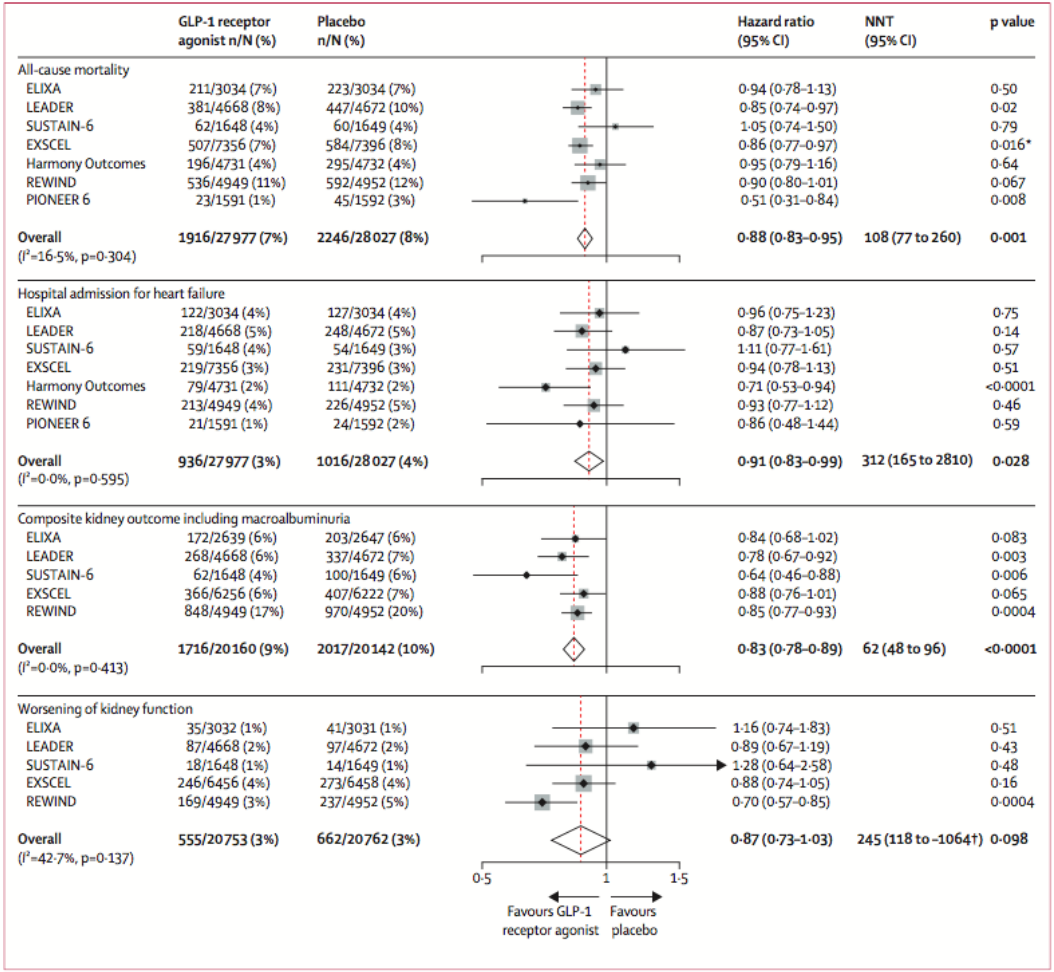


Figure 4: **All-cause mortality, hospital admission for heart failure, and kidney outcomes**

All-cause Mortality

NNT SGLT2-i 101

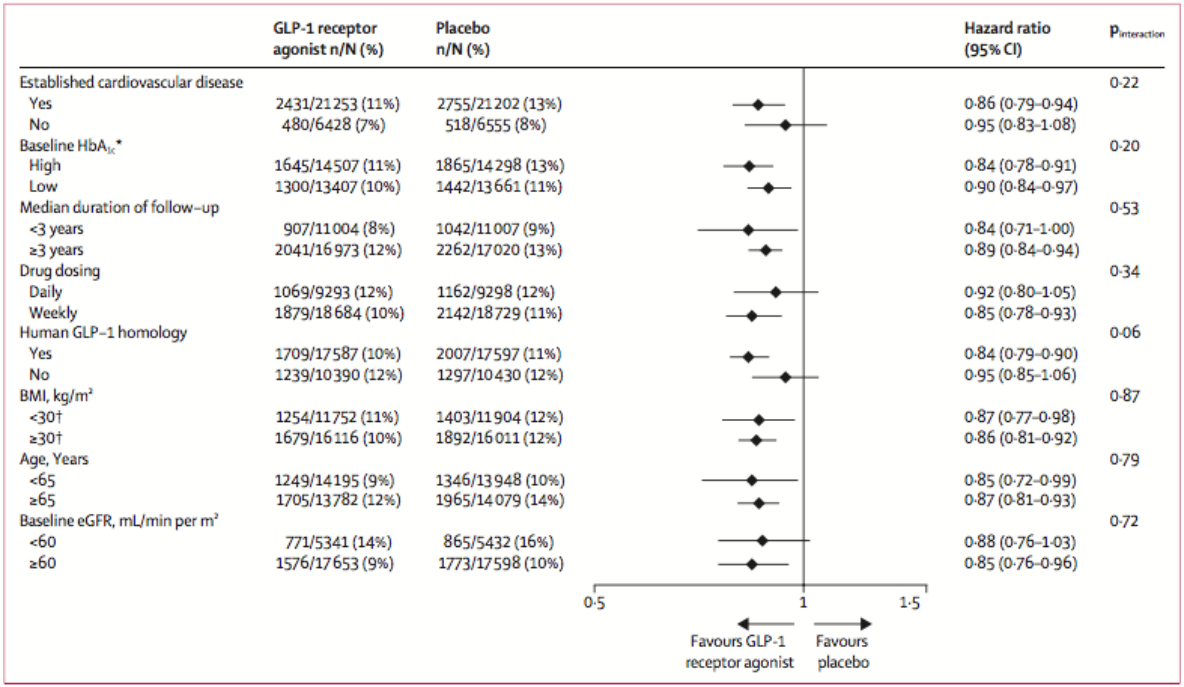
HHF

Composito renale

Peggioramento eGFR

Lancet Diabetes Endocrinol 2019
Published Online August 14, 2019
http://dx.doi.org/10.1016/S2213-8587(19)30249-9

Omologia con GLP1 umano ?



	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	$p_{interaction}$
Established cardiovascular disease				0·22
Yes	2431/21253 (11%)	2755/21202 (13%)	0·86 (0·79–0·94)	
No	480/6428 (7%)	518/6555 (8%)	0·95 (0·83–1·08)	
Baseline HbA_{1c}*				0·20
High	1645/14507 (11%)	1865/14298 (13%)	0·84 (0·78–0·91)	
Low	1300/13407 (10%)	1442/13661 (11%)	0·90 (0·84–0·97)	
Median duration of follow-up				0·53
<3 years	907/11004 (8%)	1042/11007 (9%)	0·84 (0·71–1·00)	
≥3 years	2041/16973 (12%)	2262/17020 (13%)	0·89 (0·84–0·94)	
Drug dosing				0·34
Daily	1069/9293 (12%)	1162/9298 (12%)	0·92 (0·80–1·05)	
Weekly	1879/18684 (10%)	2142/18729 (11%)	0·85 (0·78–0·93)	
Human GLP-1 homology				0·06
Yes	1709/17587 (10%)	2007/17597 (11%)	0·84 (0·79–0·90)	
No	1239/10390 (12%)	1297/10430 (12%)	0·95 (0·85–1·06)	
BMI, kg/m^2				0·87
<30†	1254/11752 (11%)	1403/11904 (12%)	0·87 (0·77–0·98)	
≥30†	1679/16116 (10%)	1892/16011 (12%)	0·86 (0·81–0·92)	
Age, Years				0·79
<65	1249/14195 (9%)	1346/13948 (10%)	0·85 (0·72–0·99)	
≥65	1705/13782 (12%)	1965/14079 (14%)	0·87 (0·81–0·93)	
Baseline eGFR, mL/min per m^2				0·72
<60	771/5341 (14%)	865/5432 (16%)	0·88 (0·76–1·03)	
≥60	1576/17653 (9%)	1773/17598 (10%)	0·85 (0·76–0·96)	

***Figure 3*: Subgroup analyses for risk of three-component MACE**

Three-component MACE consisted of cardiovascular death, myocardial infarction, and stroke. Subgroup denominators are participants with available data. MACE=major adverse cardiovascular events. GLP-1=glucagon-like peptide-1. eGFR=estimated glomerular filtration rate. *High baseline HbA_{1c} was defined as >7·5% in ELIXA, >8·3% in LEADER, >8·5% in SUSTAIN-6, >8·0% in EXSCEL, >8·0% in Harmony Outcomes, >7·2% in REWIND, and >8·5% in PIONEER 6. †In REWIND, the BMI categories used were ≤32 kg/m^2 and >32 kg/m^2. ‡In REWIND, the age group categories used were <66 and ≥66 years; in LEADER, the age group categories used were <60 and ≥60 years.

AMPLITUDE-O CVOT (NCT03496298) with efpeglenatide

«Task» del diabetologo

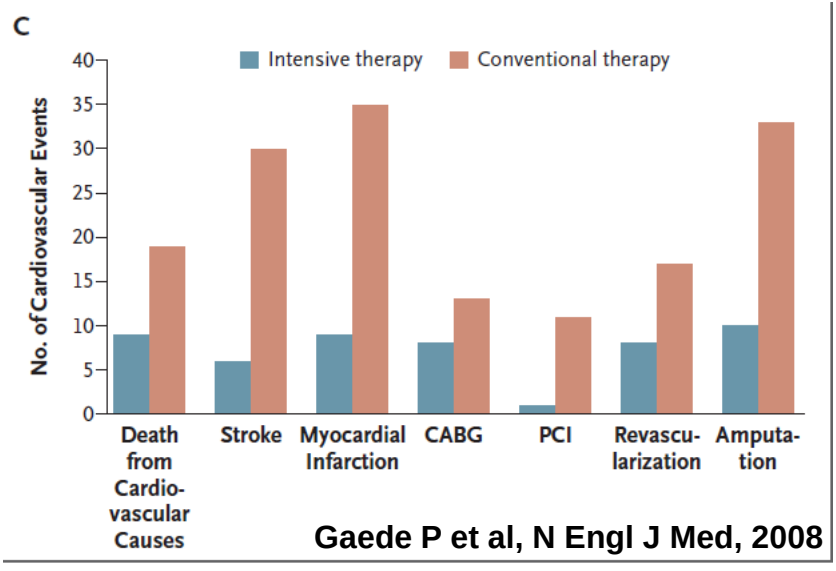
A. MALATTIA CARDIOVASCOLARE

RACCOMANDAZIONE GENERALE

Un intervento intensivo e multifattoriale teso all'ottimizzazione di tutti i fattori di rischio cardiovascolare mediante modificazioni dello stile di vita e idonea terapia farmacologica deve essere implementato in tutti i pazienti con diabete tipo 2.

(Livello della prova I, Forza della raccomandazione A)

Standard italiani
per la cura del diabete mellito
2016



Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

Peter Gæde, M.D., D.M.Sc., Henrik Lund-Andersen, M.D., D.M.Sc., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

Gaede P et al, N Engl J Med, 2008

Conclusioni

- **Visione glucocentrica *vs.* visione complicanze-centrica**
  - **dalla treat to target (HbA1c)**
  - **alla treat to prevent (CVD e CKD ... HHF)**

- **Personalizzazione della terapia *o* massificazione della terapia**

- **Sartorializzazione della terapia**
  - **dalla ricerca dell'indicazione**
  - **alla ricerca della contro-indicazione**