SID
Società Italiana di Diabetologia
fondata nel 1964

Terapia con analoghi del GLP-1: quando e perché - II FASE
Bologna, 19 novembre 2019

II SESSIONE: Analoghi del GLP-1: stato dell'arte e prospettive future

Possiamo stringere di nuovo il target glicemico ?

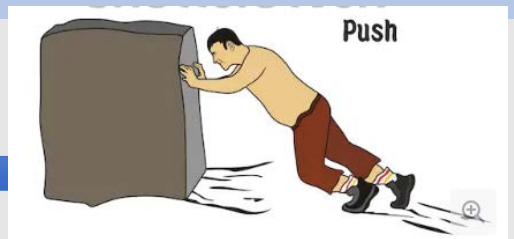
Andrea Natali
Dipartimento di Medicina Clinica e Sperimentale
Università di Pisa

Conflitti di interesse

Supporto alla ricerca:	Boheringer Ingelheim, Eli Lilly, Nestlè
Advisory board:	Astra Zeneca
Inviti a congressi:	Amgen, Boheringer Ingelheim, Astra Zeneca, Nestlè

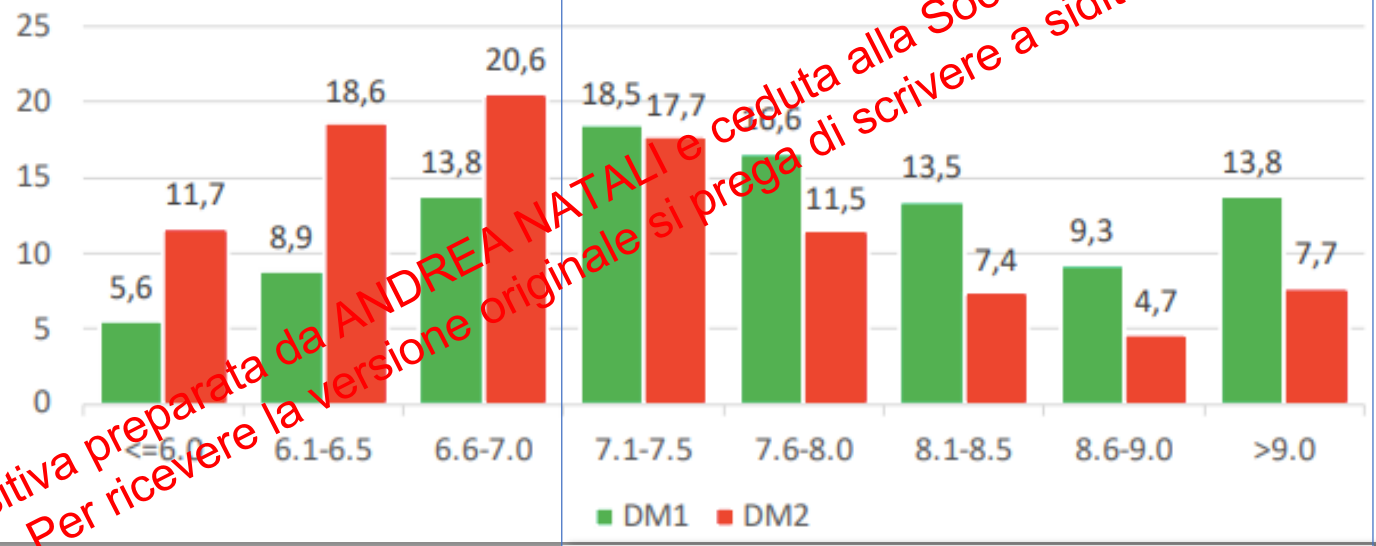
Stringere perché ?

≤7%



Indicatori di esito intermedi

Andamento per 8 classi dell'HbA1c (%)



DM1: 28%
DM2: 50%

DM1: 73%
DM2: 50%

Cosa dicono le linee guida ?

ADA-EASD 2018

A reasonable HbA1c target is around 53 mmol/mol (7%) or less
for most non-pregnant adults with sufficient life expectancy to see microvascular benefits (generally ~10 years) **A**

Providers might reasonably suggest
- more stringent HbA1c goals (<6.5% [48 mmol/mol])
for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment **C**
- less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate
for higher risk individuals **B**

STANDARD DI CURA 2018

<6.5%

Il trattamento dell'iperglicemia deve essere tempestivamente aggiornato quando il controllo è perduto e l'obiettivo di HbA1c dovrebbe essere collocato sotto 48 mmol/mol (6.5%), valori che consentono di prevenire l'incidenza e la progressione delle complicanze microvascolari e macrovascolari. Ciò vale per il diabete mellito di tipo 1 non complicato, essendo plausibile un limite di 53 mmol/mol (7.0%) per i soggetti con complicanze. Nel caso di diabete di tipo 2 è applicabile il limite di 48mmol/mol (6.5%) purché tale livello sia raggiungibile con farmaci che comportano un basso rischio di ipoglicemia. ***I B***

Sono tutti d'accordo ?

Table 5 | Position of different professional organizations regarding glycemic control

Organization	Year	Guideline	Position
ADA	2019	Standards of medical care in diabetes 2019[3]	• HbA_{1c} <7.0% (53 mmol/mol)
			• Preprandial capillary plasma glucose 80-130 mg/dL* (4.4-7.2 mmol/L)
			• Peak postprandial capillary plasma glucose 180 mg/dL† (10.0 mmol/L)
			*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A_{1c} goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1-2 h after the beginning of the meal, generally peak levels in patients with diabetes
ADA/EASD	2018	Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the ADA and the EASD[2]	• A reasonable HbA_{1c} target for most non-pregnant adults with sufficient life expectancy to see microvascular benefits (generally ~10 years) is around 53 mmol/mol (7.0%) or less
			• Glycemic treatment targets should be individualized based on patient preferences and goals, risk of adverse effects of therapy (eg, hypoglycemia and weight gain) and patient characteristics, including frailty and comorbid conditions
AACE/ACE	2019	Diabetes management algorithm[5]	• An HbA_{1c} level of ≤6.5% (48 mmol/mol) is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time
ACP	2018	Hemoglobin A_{1c} targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus[8]	• Clinicians should aim to achieve an HbA_{1c} level between 7.0% and 8.0% (53-64 mmol/mol) in most patients with type 2 diabetes
			• Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels <6.5% (48 mmol/mol)
			• Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care
NICE	2019	Type 2 diabetes in adults: management[7]	• For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycemia, support the person to aim for an HbA_{1c} level of 53 mmol/mol (7.0%)
			• In adults with type 2 diabetes, if HbA_{1c} levels are not adequately controlled by a single drug and are ≥58 mmol/mol (7.5%) or higher, reinforce advice about diet, lifestyle, and adherence to drug treatment and support the person to aim for an HbA_{1c} level of 53 mmol/mol (7.0%) and intensify drug treatment
VA/DoD	2017	Management of type 2 diabetes mellitus in primary care[6]	• We recommend setting an HbA_{1c} target range based on absolute risk reduction of significant microvascular complications, life expectancy, patient preferences, and social determinants of health
			• We suggest a target HbA_{1c} range of 6.0-7.0% (42-53 mmol/mol) for patients with a life expectancy greater than 10-15 years and absent or mild microvascular complications, if it can be safely achieved
			• We recommend that in patients with type 2 diabetes, a range of HbA_{1c} 7.0-8.5% (53-69 mmol/mol) is appropriate for most individuals with established microvascular or macrovascular disease, comorbid conditions, or 5-10 years life expectancy, if it can be safely achieved
			• We suggest a target HbA_{1c} range of 8.0-9.0% (64-75 mmol/mol) for patients with type 2 diabetes with life expectancy <5 years, significant comorbid conditions, advanced complications of diabetes, or difficulties in self management attributable to, for example, mental status, disability, or other factors such as food insecurity and insufficient social support
ACC/AHA	2019	2019 ACC/AHA guideline on the primary prevention of cardiovascular disease[47]	• HbA_{1c} >6.5% (48 mmol/mol): consideration of metformin as first line pharmacologic therapy to improve glycemic control and reduce CVD risk (class IIa); dietary counseling regarding key aspects of a healthy heart diet (class I); ≥150 minutes of moderate to vigorous physical activity (class I); aggressive treatment of other CVD risk factors
			• HbA_{1c} >7.0 (53 mmol/mol) after lifestyle and metformin: if CV risk factors—SGLT-2 inhibitor or GLP-1 receptor agonist to improve glycemic control and CV risk (class IIb); if no CV risk factors—further management of diabetes per primary care provider or endocrinologist

AACE=American Association of Clinical Endocrinologists; ACC=American College of Cardiology; ACE=American College of Endocrinology; ACP=American College of Physicians; ADA=American Diabetes Association; AHA=American Heart Association; CV=cardiovascular; CVD=cardiovascular disease; EASD=European Association for the Study of Diabetes; GLP-1=glucagon-like peptide-1; HbA_{1c}=glycated hemoglobin; NICE=National Institute for Health and Care Excellence; SGLT-2=sodium-glucose transport protein 2; VA/DoD=Veterans Affairs and Department of Defense.

<7%

+/-

~7% or <

≤6.5%

7-8%

=6.5% if on 1 drug no hypo

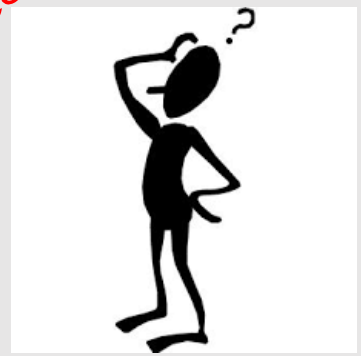
=7% all others

6-7% LE 10-15yrs, MicV-

7-8.5% MicC&MacVC or LE 5-10 yrs

8-9% LE<5 yrs

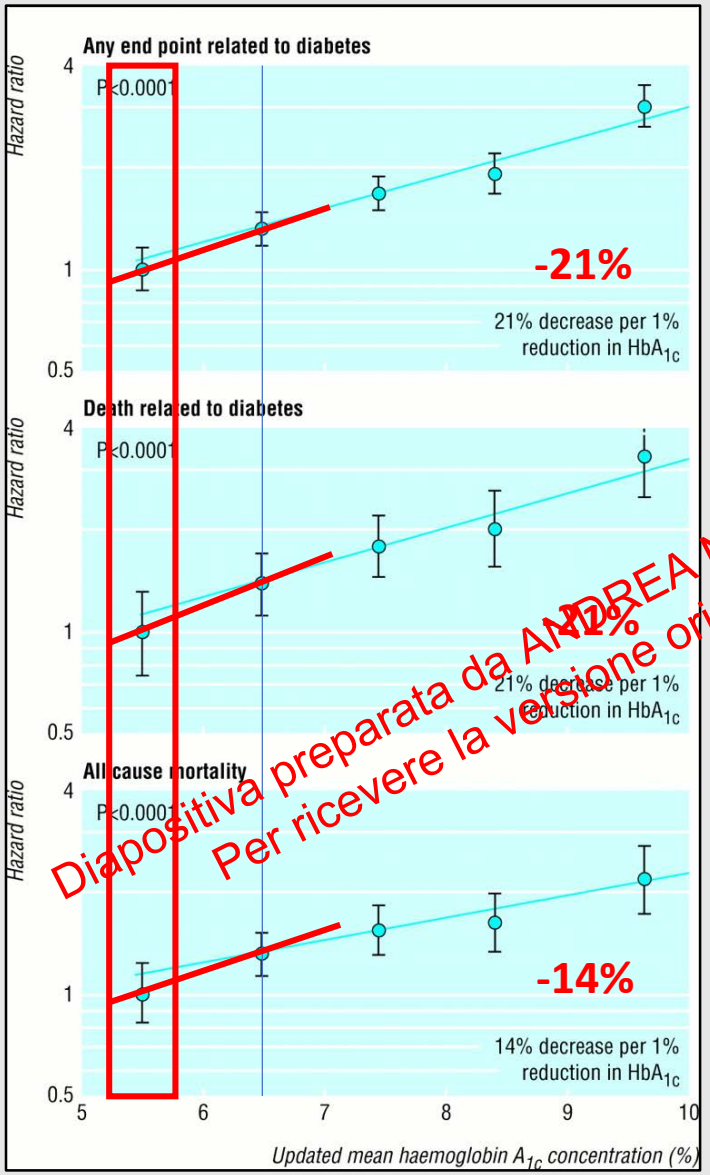
≤7%

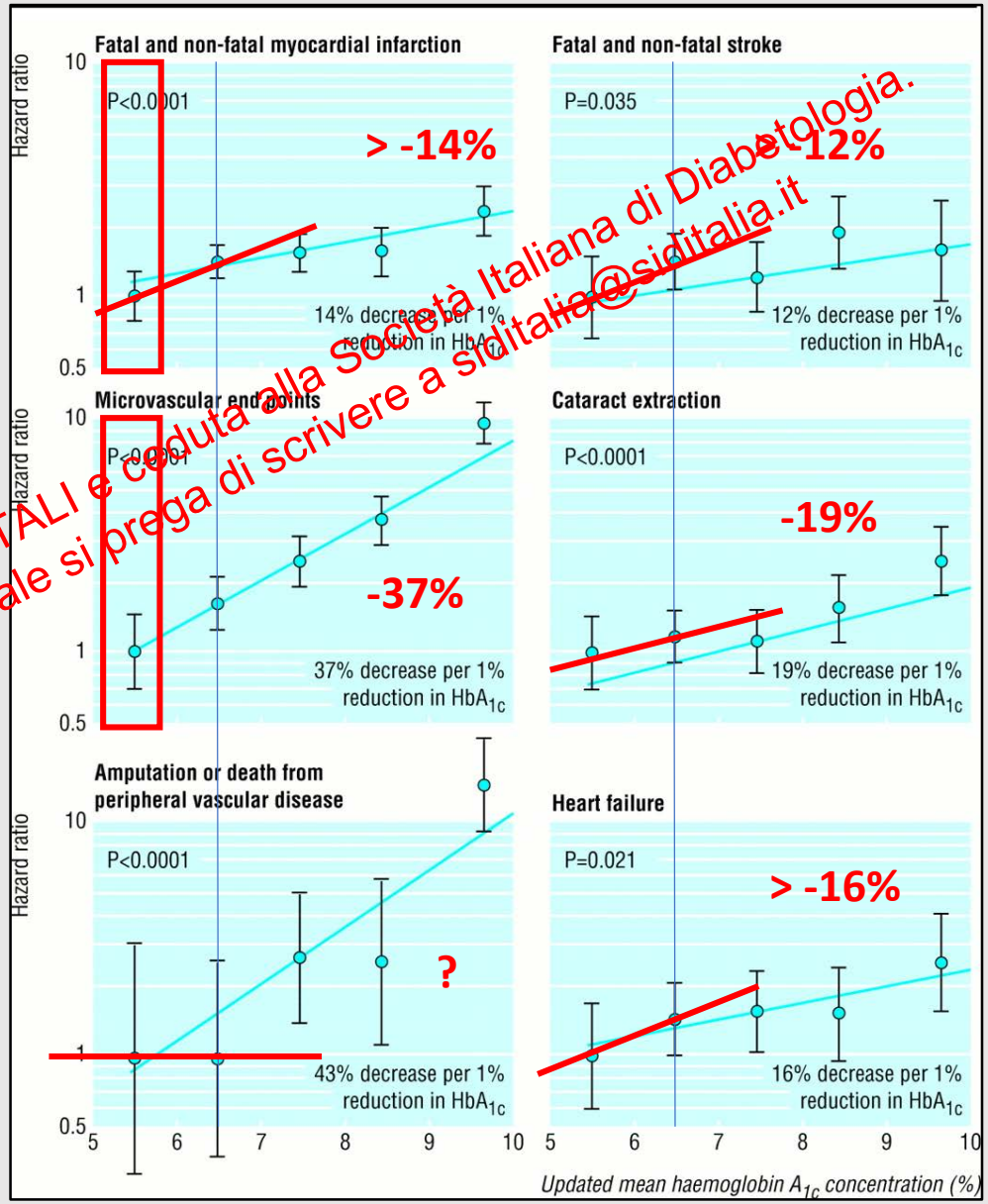


Quale è il messaggio ?

1) **Le complicanze MicroV e MacroV non si osservano se HbA1c ≤ 7-6.5%**
2) **Il beneficio di un più stretto controllo si osserva solo se**
   - **il p. non ha complicanze MicroV o MacroV**
   - **Il p. ha una aspettativa di vita >10 aa**
   - **non ci sono ipoglicemie**

5.5 vs 6.5% ?



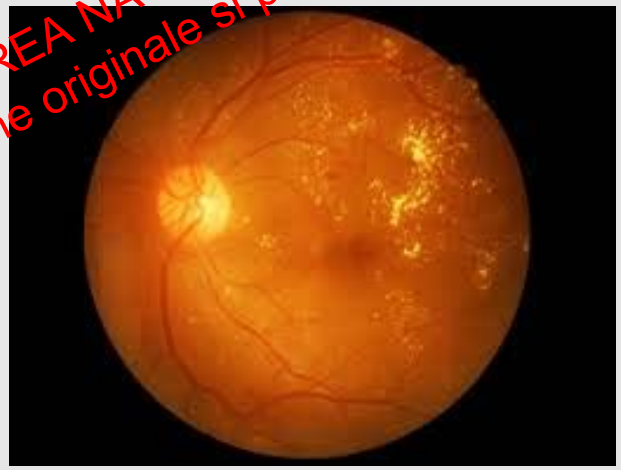


Commento degli autori

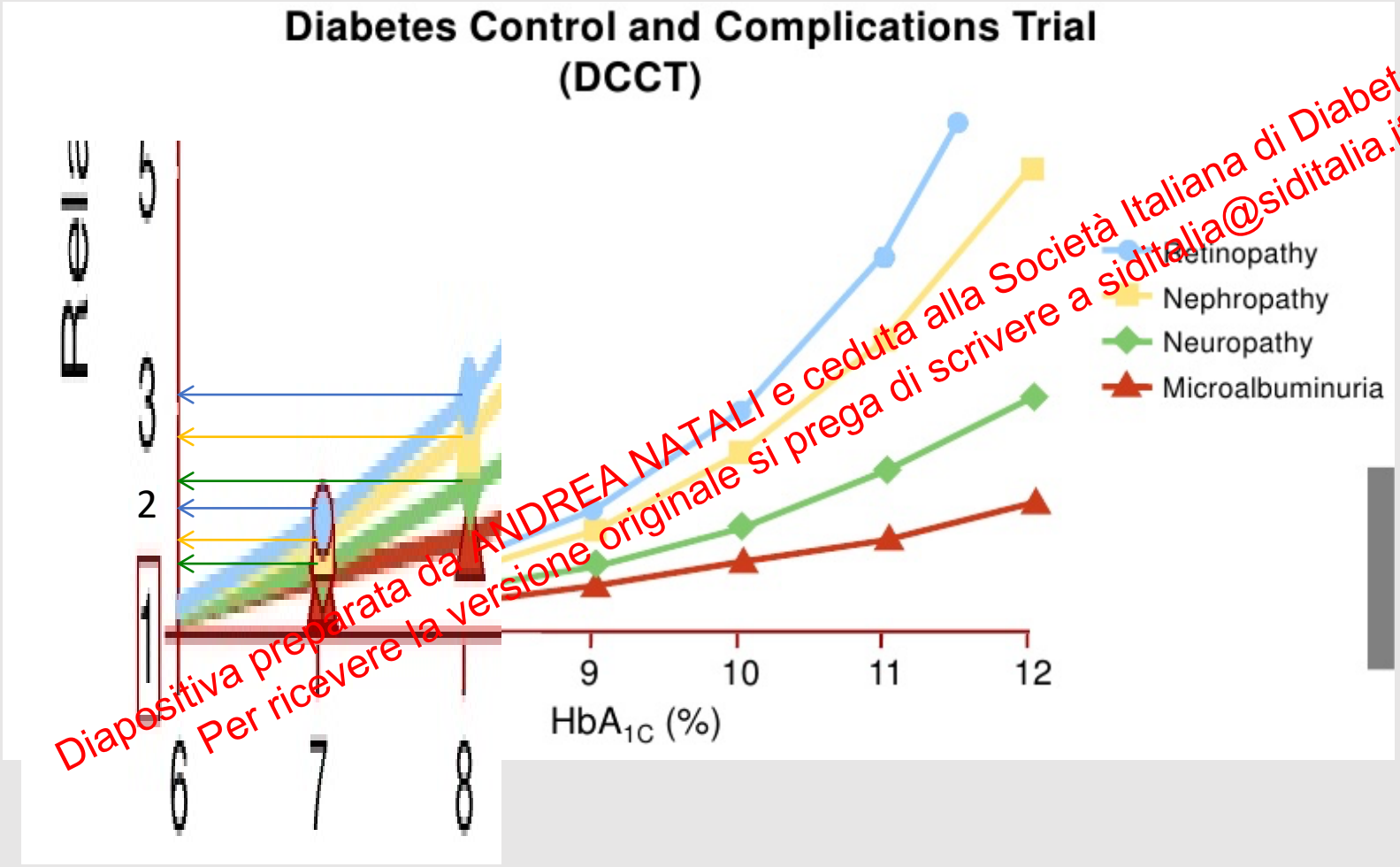
UKPDS 35

«We observed no thresholds of glycaemia for any type of complication of diabetes. This suggests that there is no specific target value of haemoglobin A_{1c} for which one should aim but that the nearer to normal the haemoglobin A_{1c} concentration the better.»

Microvascular Complications



Non sono tutte uguali



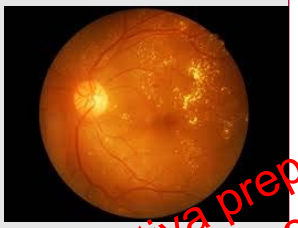
MicroV complications trials

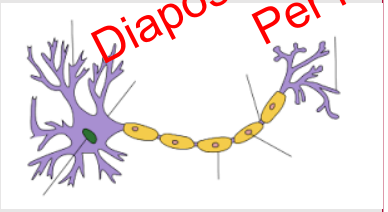
Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials

Sophia Zoungas, Hisatomi Arima, Hertzel C Gerstein, Rury R Holman, Mark Woodward, Peter Reaven, Rodney A Hayward, Timothy Craven, Ruth L Coleman, John Chalmers, the Collaborators on Trials of Lowering Glucose (CONTROL) group

Lancet Diabetes Endocrinol 2017

∂HbA1c=-0.9%





	More intensive glucose control	Less intensive glucose control	Hazard ratio (95% CI)
Primary kidney outcome			
ACCORD[9]	383/21641 (1·8%)	484/21554 (2·2%)	0·79 (0·69–0·90)
ADVANCE[10]	233/25728 (0·9%)	301/25675 (1·2%)	0·77 (0·65–0·91)
UKPDS[8]	127/10852 (1·2%)	54/4515 (1·2%)	0·98 (0·71–1·35)
VADT[11]	18/3818 (0·5%)	26/3878 (0·7%)	0·70 (0·39–1·28)
Overall	**761/62039 (1·2%)**	**865/55622 (1·6%)**	**0·80 (0·72–0·88)**
I^2=0·0%; p=0·58			
Primary eye outcome			
ACCORD[9]	131/6135 (2·1%)	167/6104 (2·7%)	0·79 (0·64–0·98)
ADVANCE[10]	35/2982 (1·2%)	49/2901 (1·7%)	0·83 (0·56–1·22)
UKPDS[8]	210/5300 (3·8%)	88/2251 (3·9%)	0·95 (0·74–1·23)
VADT[11]	62/450 (13·8%)	63/453 (13·9%)	0·94 (0·66–1·34)
Overall	**428/14877 (2·9%)**	**367/11709 (3·1%)**	**0·87 (0·76–1·00)**
I^2=0·0%; p=0·69			
Primary nerve outcome			
ACCORD	2055/14979 (13·7%)	2210/14923 (14·8%)	0·92 (0·87–0·98)
ADVANCE	1373/23752 (5·8%)	1299/23876 (5·4%)	1·07 (0·99–1·15)
UKPDS	453/12247 (3·7%)	208/5087 (4·1%)	0·93 (0·78–1·10)
Overall	**3881/50978 (7·6%)**	**3717/43887 (8·5%)**	**0·98 (0·87–1·09)**
I^2=78·1%; p=0·011			

0·25 0·50 1·00 2·00

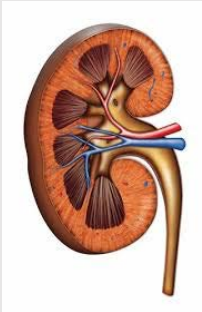
Favours more intensive glucose control — Favours less intensive glucose control

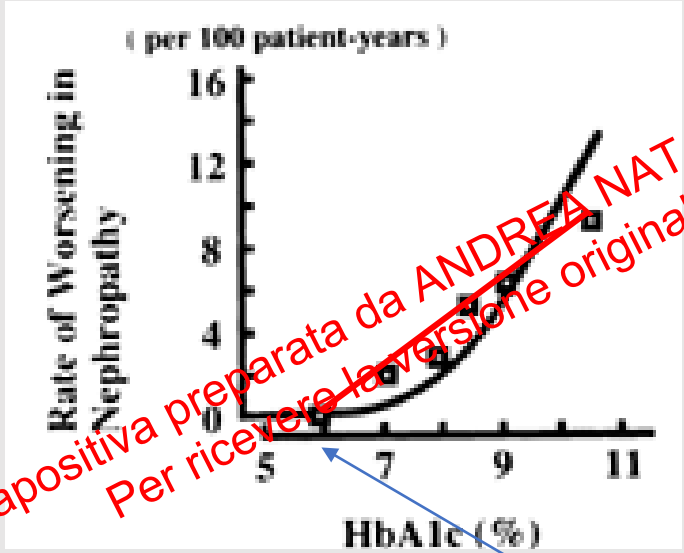
-20%

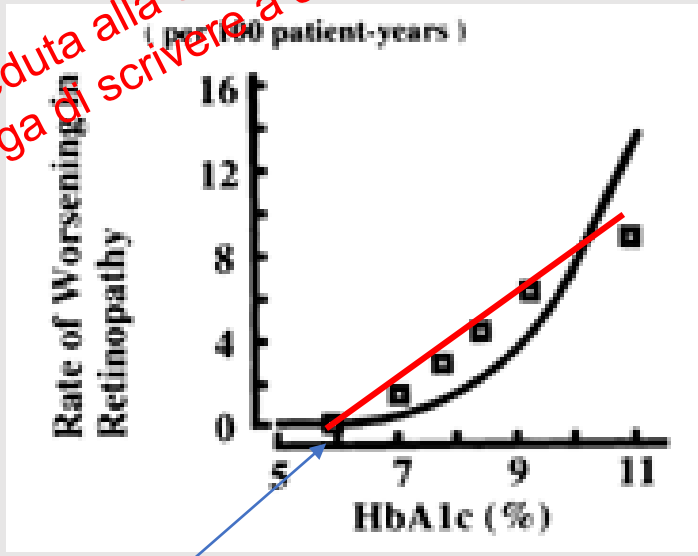
-13%

-2%

Kumamoto HbA1v & MicroV compl







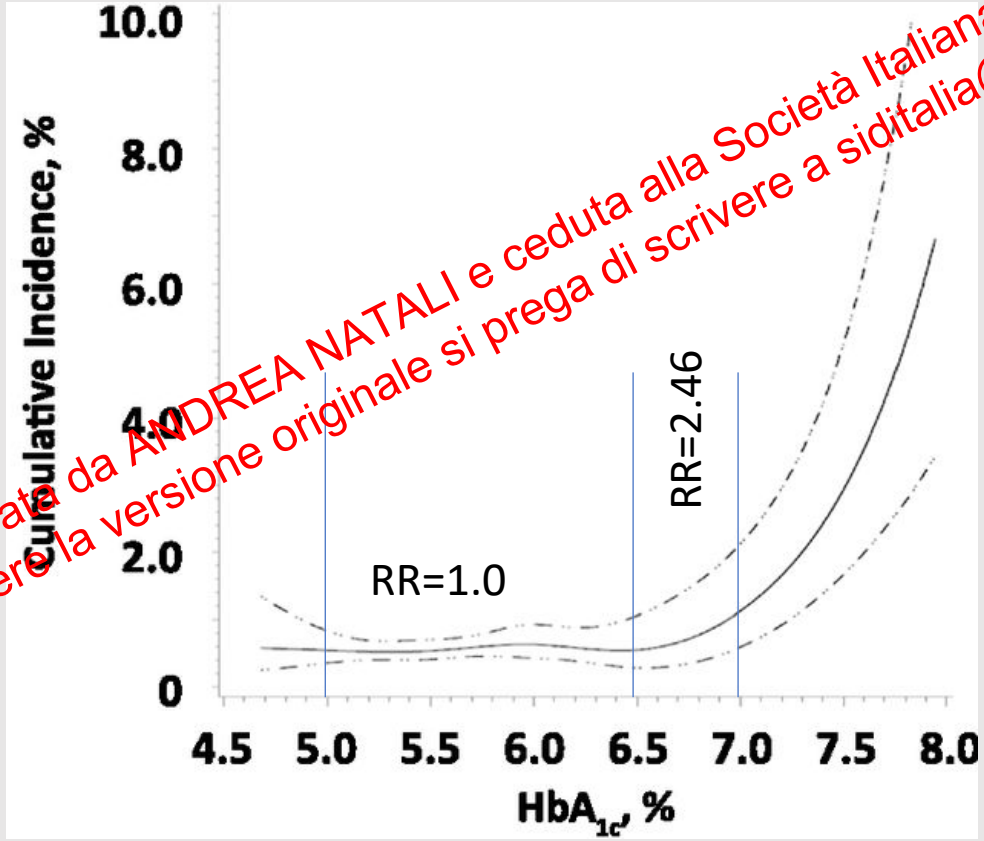
HbA1c 6% = 0 progression

Shichiri M, *Diab Care* 2000

LE >10 aa? Quanto bisogna aspettare ?

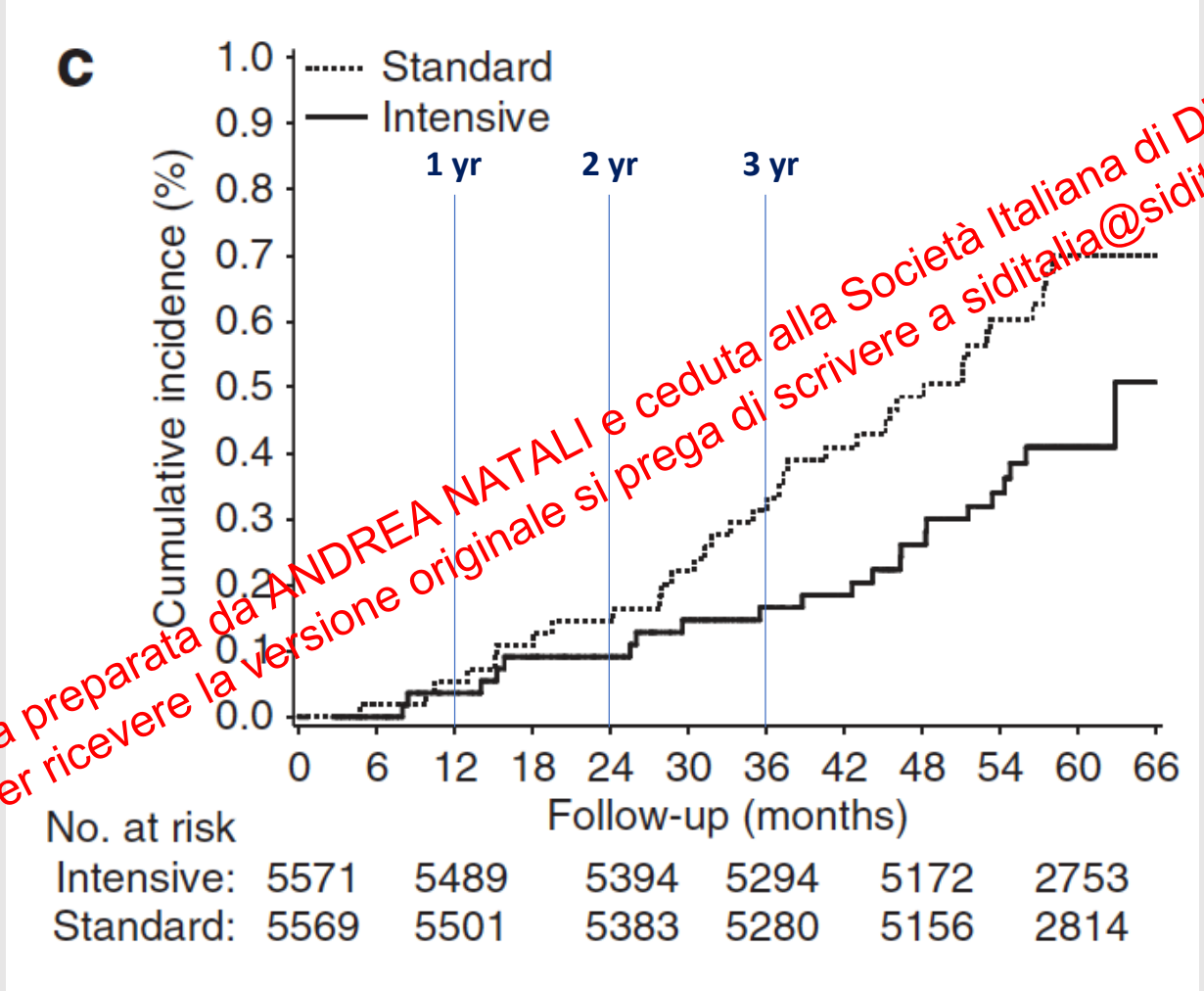
3-yrs incidence of retinopathy

19,897 Japanese adults



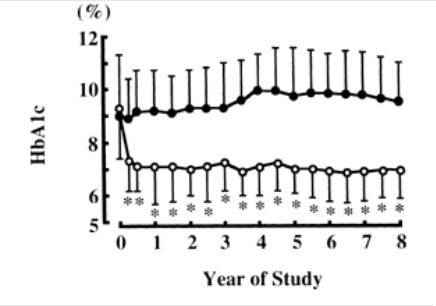
Tsugawa Y, Diabetes Care 2012

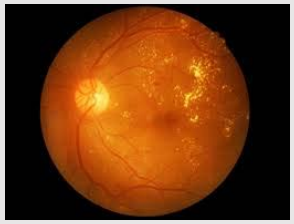
LE 10 yrs? ESRD or Renal death (ADVANCE)

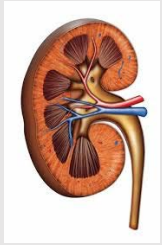


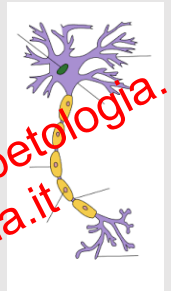
Perkovic W *Kidney Int* 2013

MicroV compl: Time course & 1 vs 2 prev

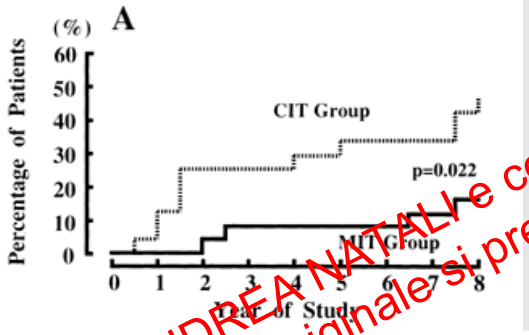


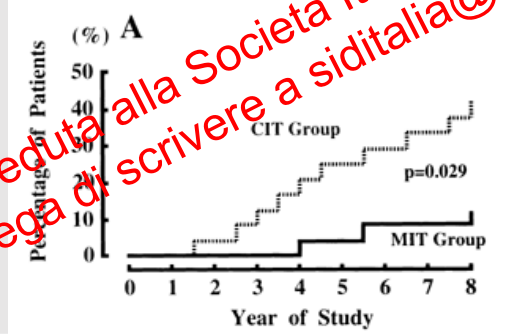


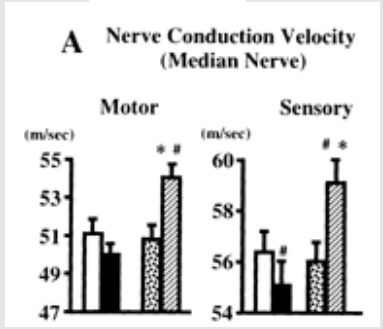




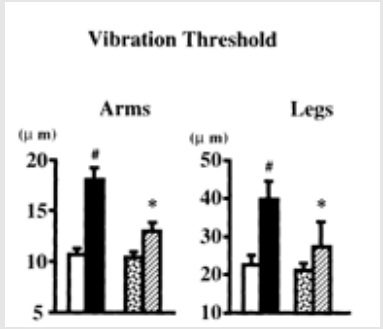
Primary prev.





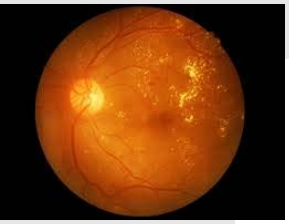


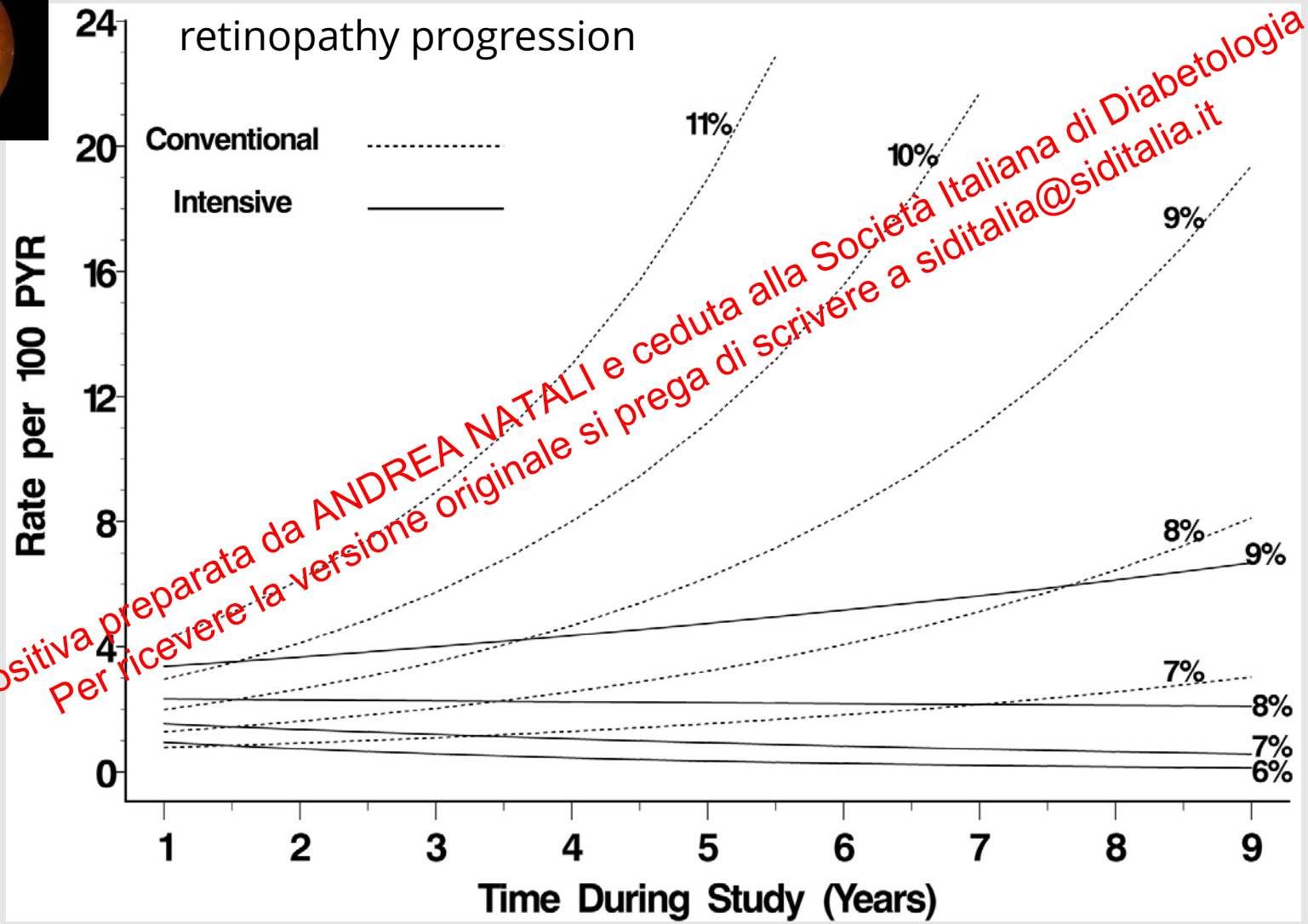
Secondary prev.



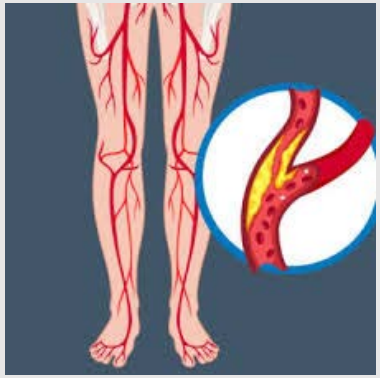
Kumamoto Study Diab care 2000

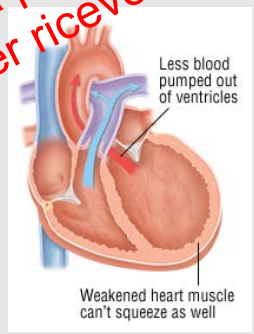
DCTT: The magic of intensive therapy





Macrovascular complications





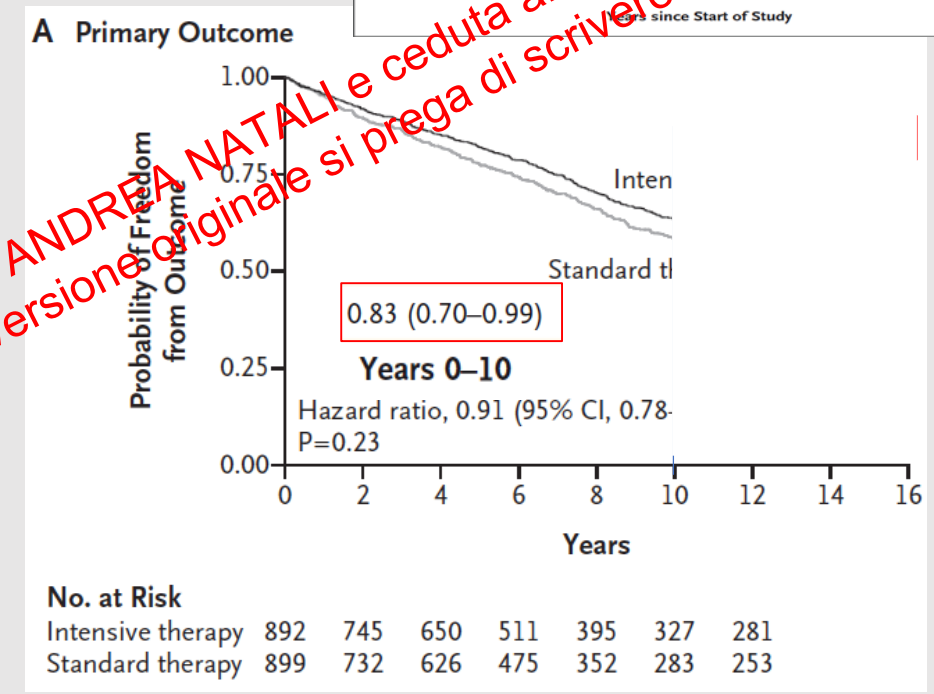
VADT – Short legacy for CVD

Intensive Glucose Control in Patients with Type 2 Diabetes — 15-Year Follow-up

Peter D. Reaven, M.D., Nicholas V. Emanuele, M.D., Wyndy L. Wiitala, Ph.D., Gideon D. Bahn, Ph.D., Domenic J. Reda, Ph.D., Madeline McCarren, Ph.D., William C. Duckworth, M.D., and Rodney A. Hayward, M.D., for the VADT Investigators*

N Engl J Med 2019;380:2215-24.

nonfatal MI
nonfatal stroke
new or worsening HF
Amputation
CV death



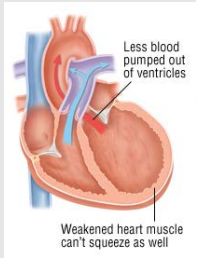
AGE (yrs) : 60+/-8 70+/-8

<15%IMA, <10%CVE = Stroke, =HF

1.04 for all-cause mortality (95% CI 0.90–1.20)

Turnbull FM
Diabetologia 2009

MACE



Trials	Number of events (annual event rate, %) More intensive	Number of events (annual event rate, %) Less intensive	ΔHbA$_{1c}$ (%)	Hazard ratio (95% CI)
Major cardiovascular events				
ACCORD	352 (2.11)	371 (2.29)	−1.01	0.90 (0.78–1.04)
ADVANCE	557 (2.15)	590 (2.28)	−0.72	0.94 (0.84–1.06)
UKPDS	169 (1.30)	87 (1.60)	−0.66	0.80 (0.62–1.04)
VADT	116 (2.68)	128 (2.98)	−1.16	0.90 (0.70–1.16)
Overall	1,194	1,176	−0.88	0.91 (0.84–0.99) (Q=1.32, p=0.72, I^2=0.0%)
Stroke				
ACCORD	73 (0.43)	70 (0.42)	−1.01	1.00 (0.72–1.39)
ADVANCE	238 (0.91)	246 (0.94)	−0.72	0.97 (0.81–1.16)
UKPDS	35 (0.26)	17 (0.31)	−0.66	0.85 (0.48–1.52)
VADT	32 (0.71)	37 (0.82)	−1.16	0.87 (0.54–1.39)
Overall	378	370	−0.88	0.96 (0.83–1.10) (Q=0.40, p=0.94, I^2=0.0%)
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=0.52, I^2=0.0%)
Hospitalised/fatal heart failure				
ACCORD	152 (0.90)	124 (0.75)	−1.01	1.18 (0.93–1.49)
ADVANCE	220 (0.83)	231 (0.88)	−0.72	0.95 (0.79–1.14)
UKPDS	8 (0.06)	6 (0.11)	−0.66	0.55 (0.19–1.60)
VADT	79 (1.80)	85 (1.94)	−1.16	0.92 (0.68–1.25)
Overall	459	446	−0.88	1.00 (0.86–1.16) (Q=3.59, p=0.31, I^2=16.4%)

Favours more intensive | Favours less intensive

0.5 | 1.0 | 2.0

Hazard ratio (95% CI)

-9%

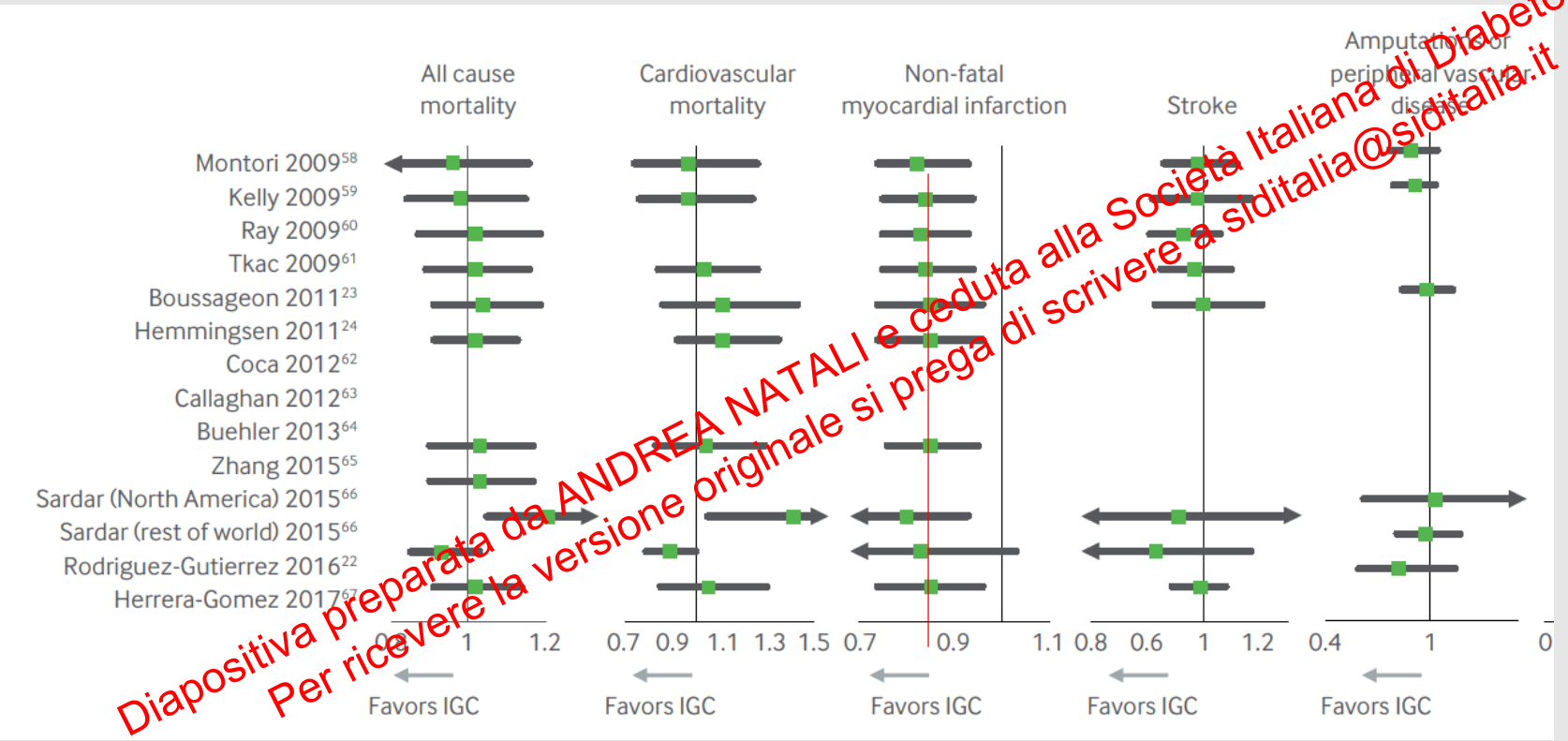
-4% (ns)

-15%

0%

Metanalyses collection

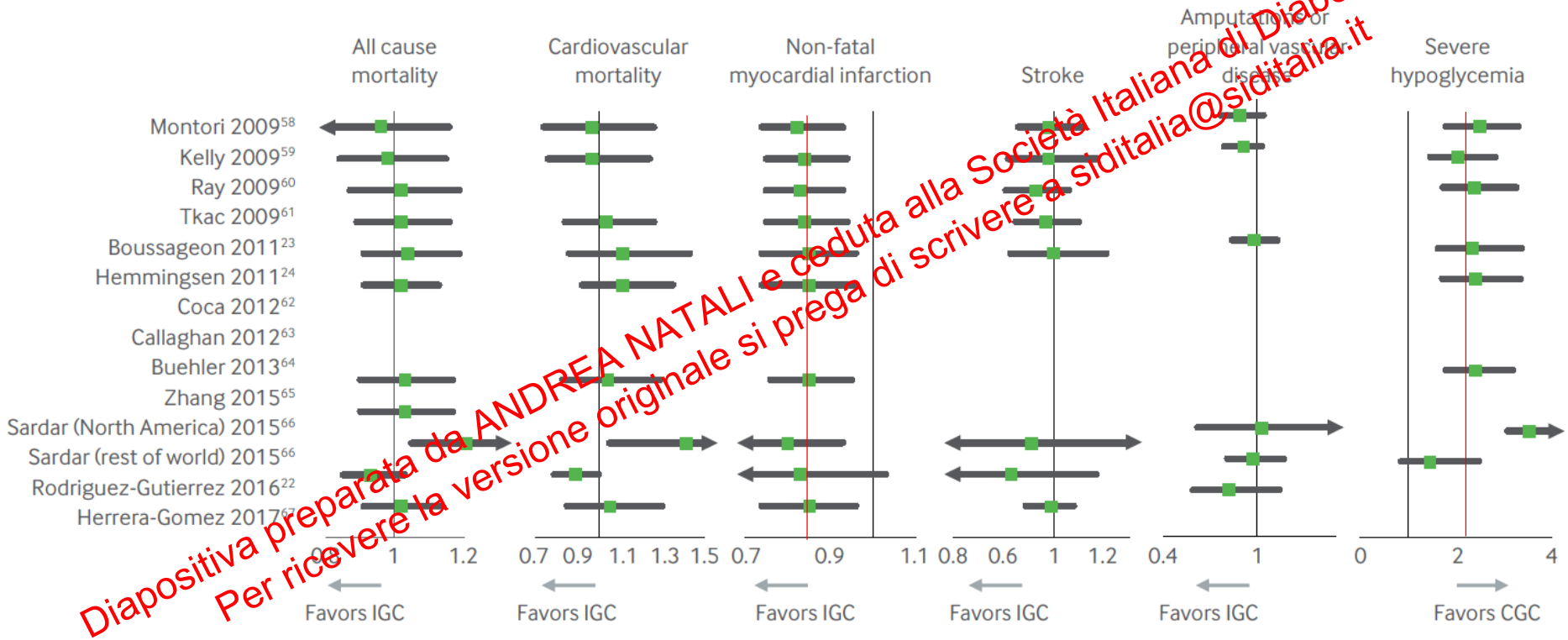
Intensive (<7%) vs conventional (7-8.5%)



-15%

Metanalyses collection

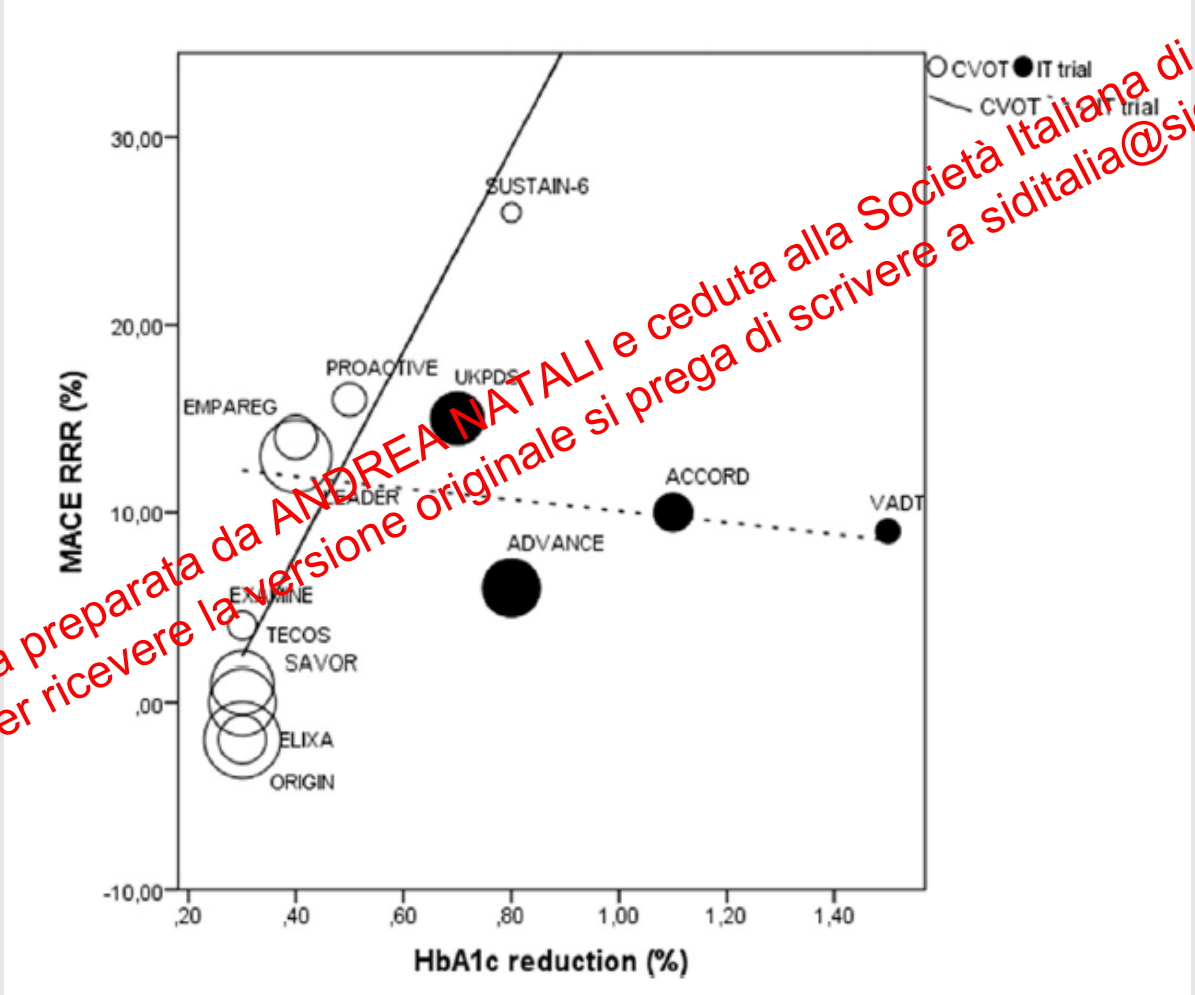
Intensive (<7%) vs conventional (7-8.5%)



*Nonostante il raddoppio del rischio di ipoglicemia cercare di **portare HbA1c sotto 7%** è **sicuro** dal punto di vista **cardiovascolare** anche in soggetti ad alto rischio, anzi si ha una **riduzione del 15%** del rischio di **infarto non fatale***

HypoG vs non hypoG drugs

Back to glycemic control: An alternative look at the results of cardiovascular outcome trials in type 2 diabetes



Mannucci, Monami, Ceriello *NMCD* 2017

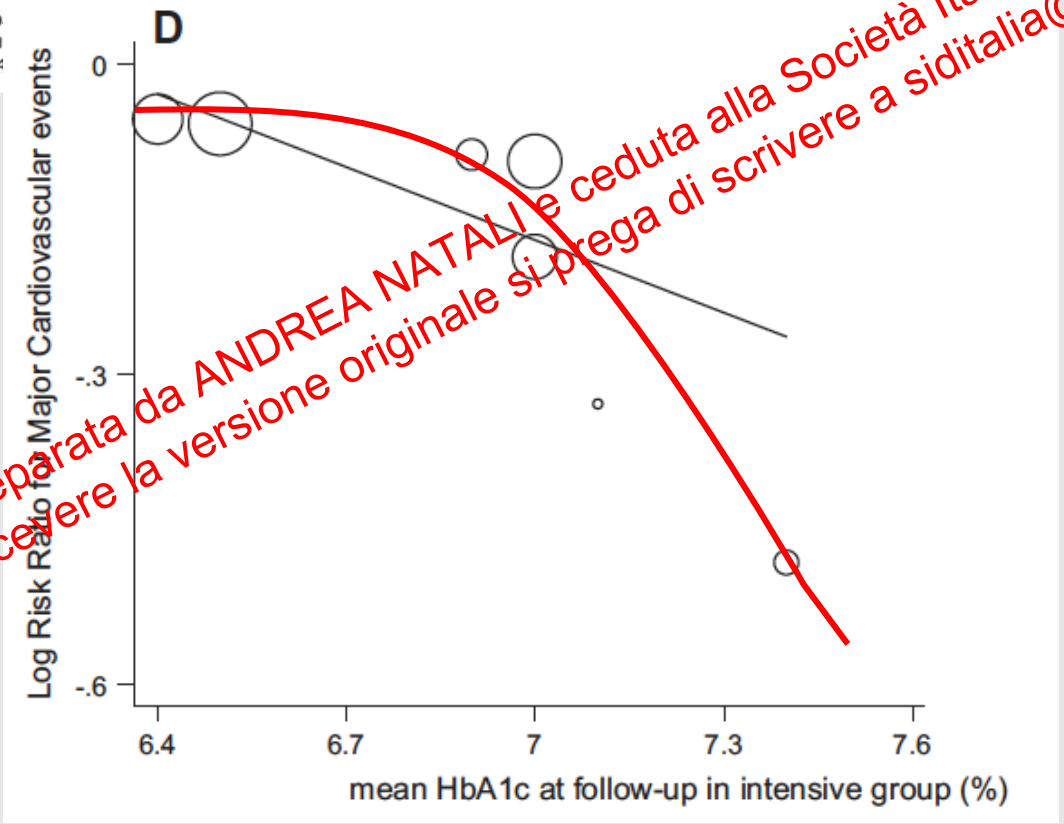
Effects of intensive glucose control on incidence of cardiovascular events in patients with type 2 diabetes: A meta-analysis

A Major cardiovascular events.

Study or Subgroup	intensive Events	intensive Total	conventional Events	conventional Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ACCORD	352	5128	371	5123	19.5%	0.95 [0.82, 1.09]
ADVANCE	557	5571	590	5569	31.0%	0.94 [0.85, 1.05]
PROactive	257	2605	313	2633	16.4%	0.83 [0.71, 0.97]
UKPDS33	585	2729	268	1138	19.9%	0.91 [0.80, 1.03]
UKPDS34 a	55	342	107	411	5.1%	0.62 [0.46, 0.83]
VADT	130	892	143	899	7.5%	0.92 [0.74, 1.14]
Veterans Affairs	9	75	13	78	0.7%	0.72 [0.33, 1.58]
Total (95% CI)						
Total events	19					

Heterogeneity: Chi² = 9.03, d

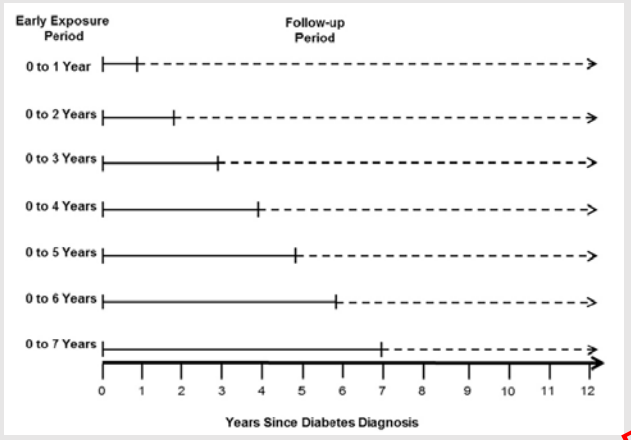
Test for overall effect: Z = 3.4



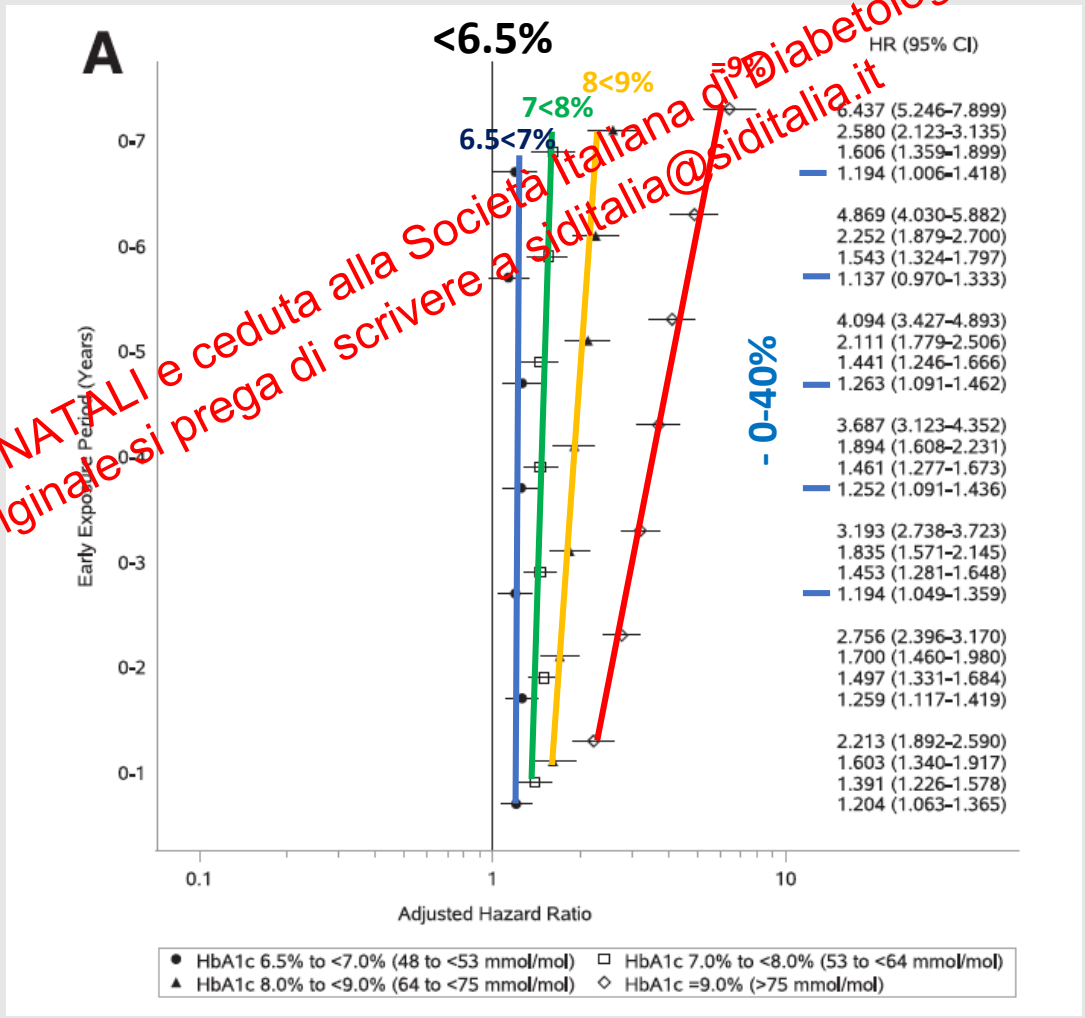
Zang C, Annals of Medicine 2010

Real world: HbA1c and MicroV compl.

34,737 newly diagnosed T2D with 10 years of survival (1997-2013)



Microvascular events

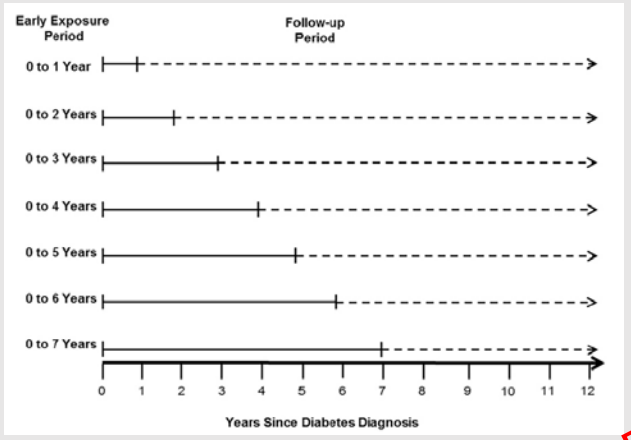


HRs adjusted for:
age at diagnosis,
sex, race/ethnicity, BMI,
SBP, DBP, T-Chol, HDL-C
smoking status
HbA1c after each exposure period
comorbidity

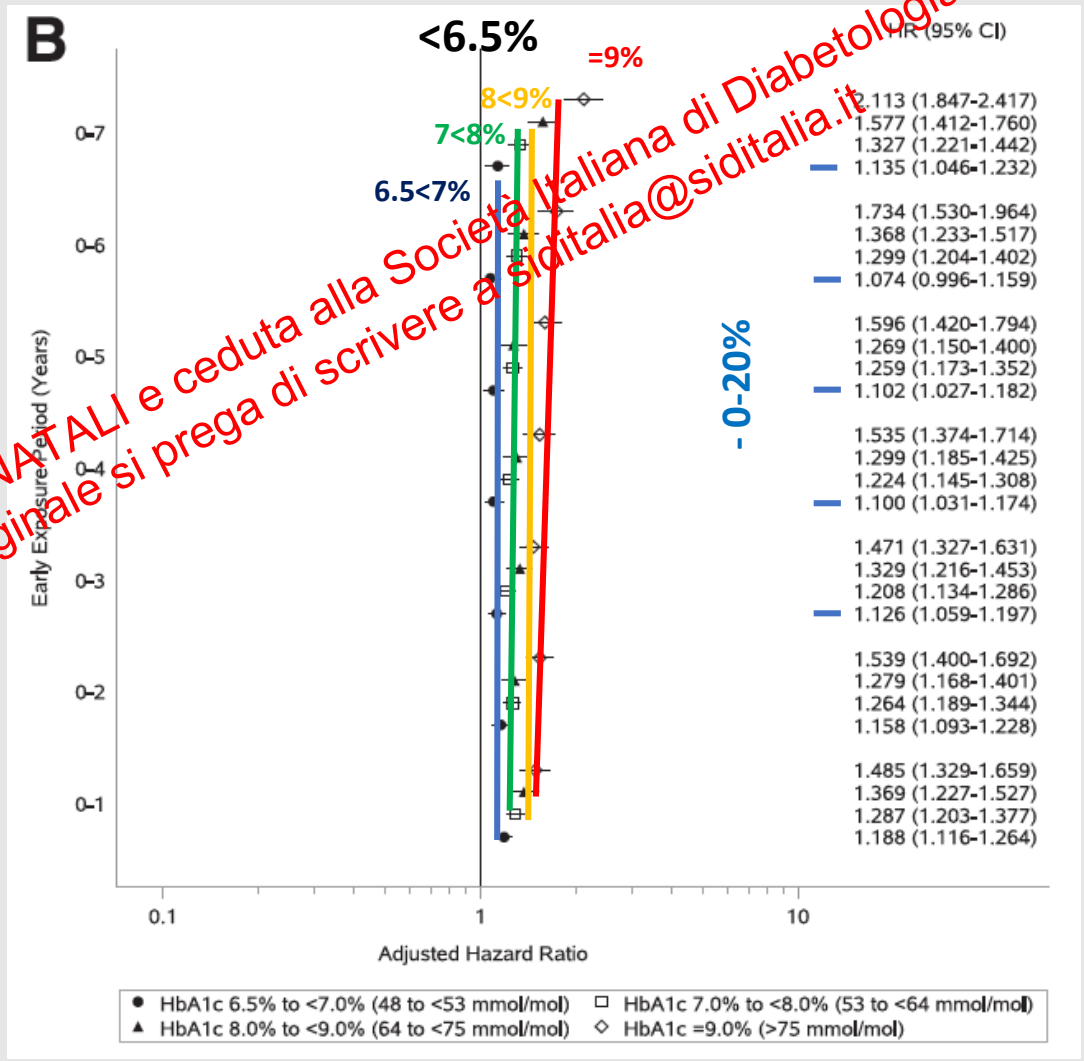
Laiteerapong N, *Diab Care* 2019

Real world: HbA1c and MacroV compl.

34,737 newly diagnosed T2D with 10 years of survival (1997-2013)



Macrovascular events



HRs adjusted for:
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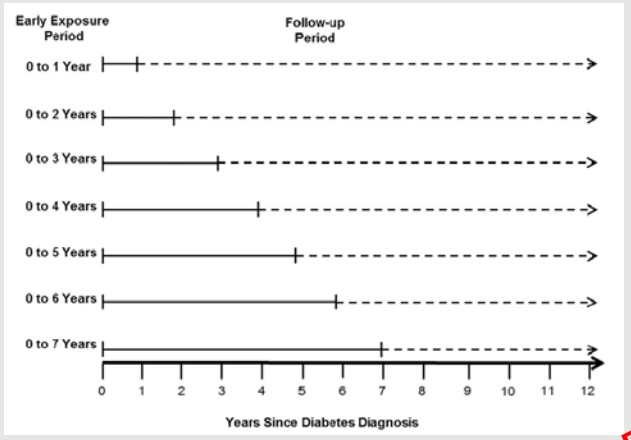
SBP, DBP, T-Chol, HDL-C
smoking status
HbA1c after each exposure period
comorbidity

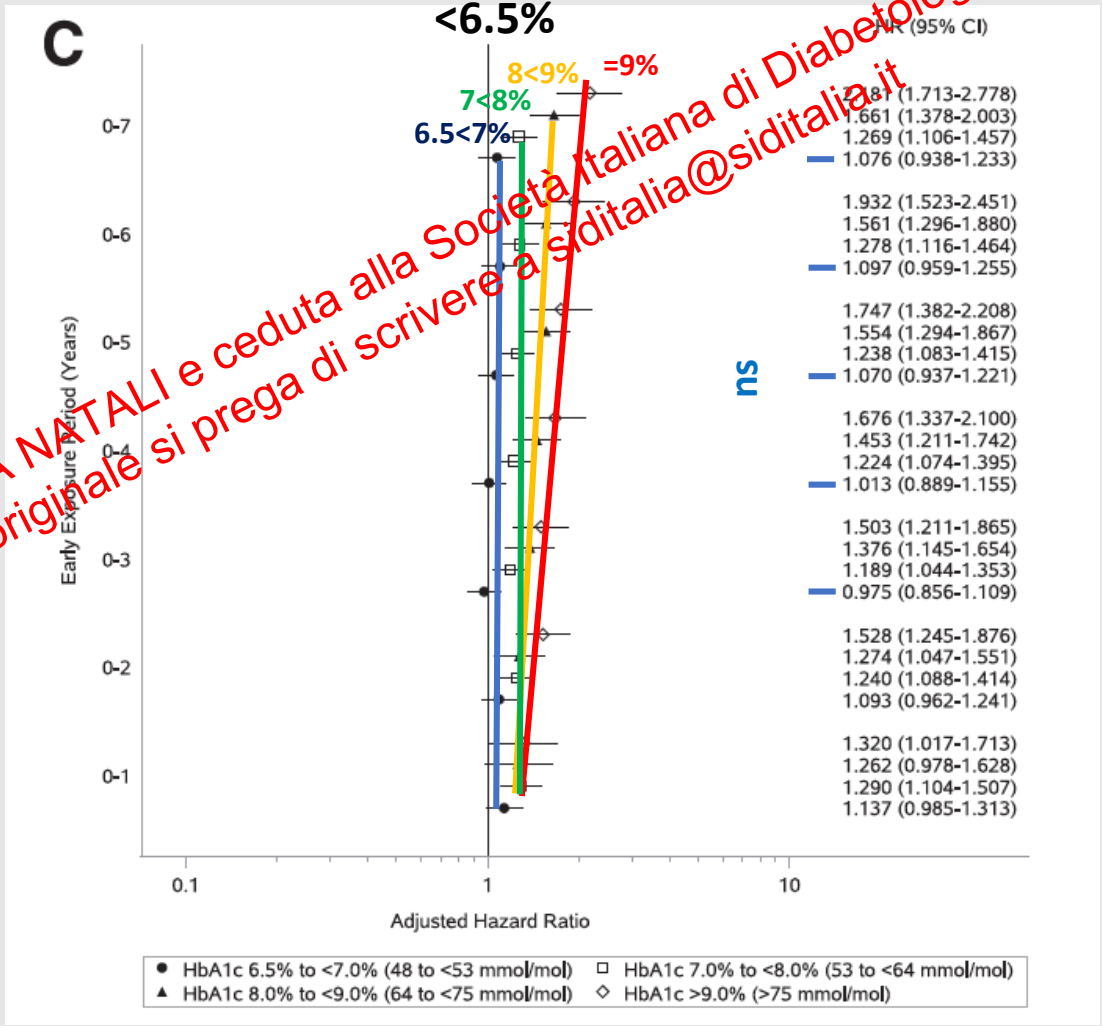
Laiteerapong N, *Diab Care* 2019

Early metabolic control and Death

34,737 newly diagnosed T2D with 10 years of survival (1997-2013)



Death

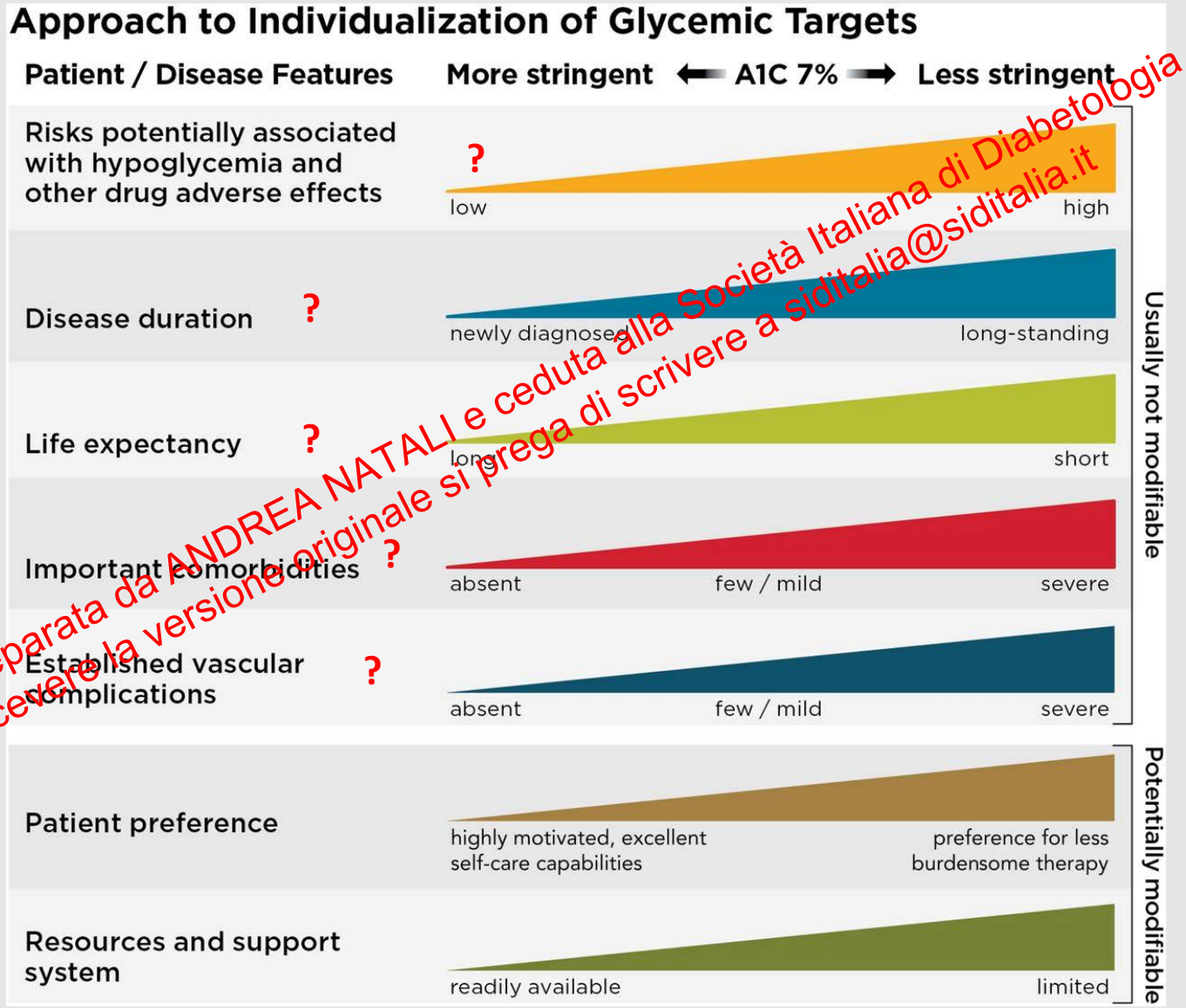


HRs adjusted for:
age at diagnosis,
sex, race/ethnicity, BMI,
SBP, DBP, T-Chol, HDL-C
smoking status
HbA1c after each exposure period
comorbidity

Laiteerapong N, *Diab Care* 2019

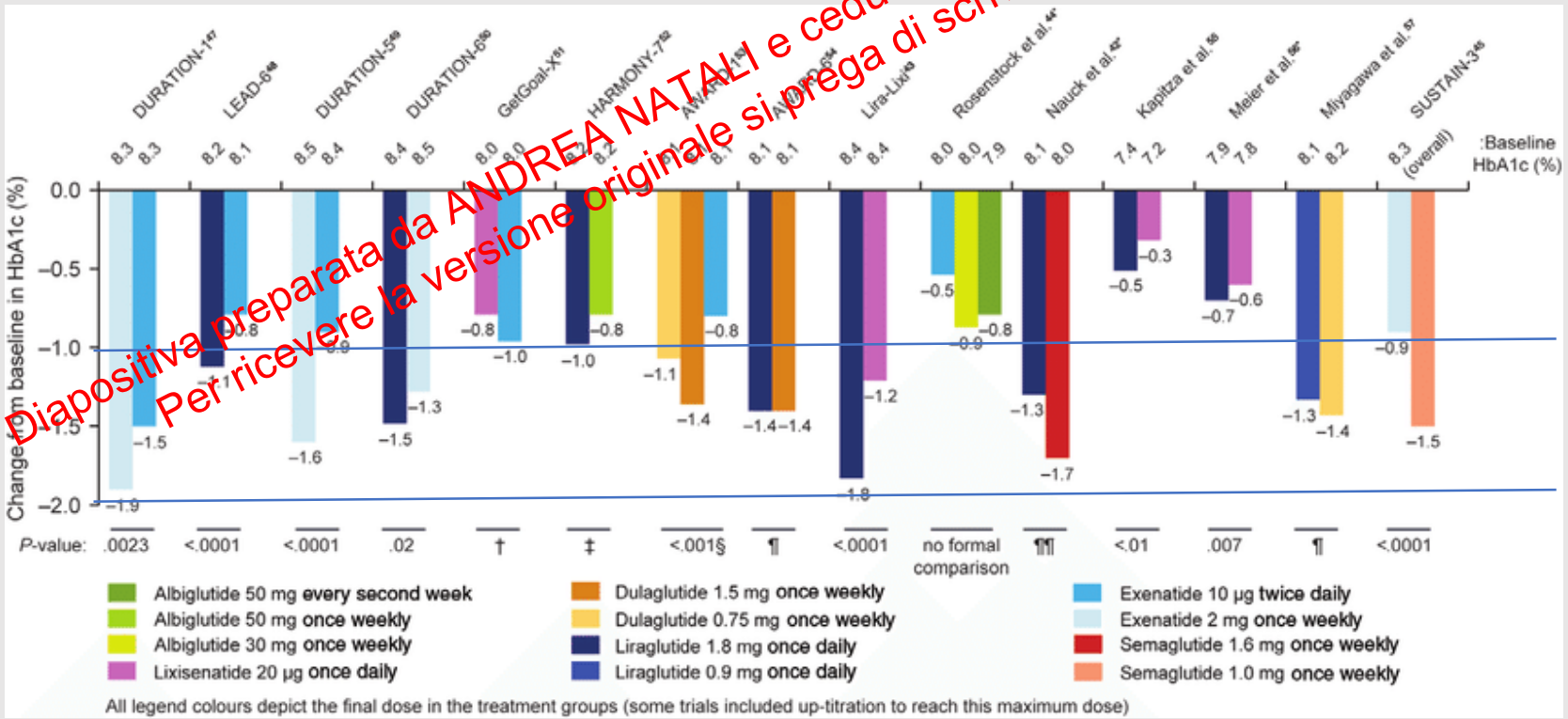
In sintesi

Glycemic Targets: ***Standards of Medical Care in Diabetes—2019***



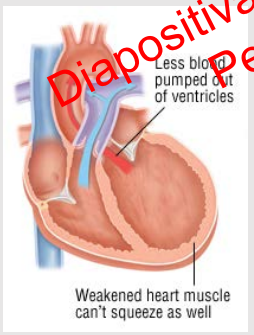
Conclusioni

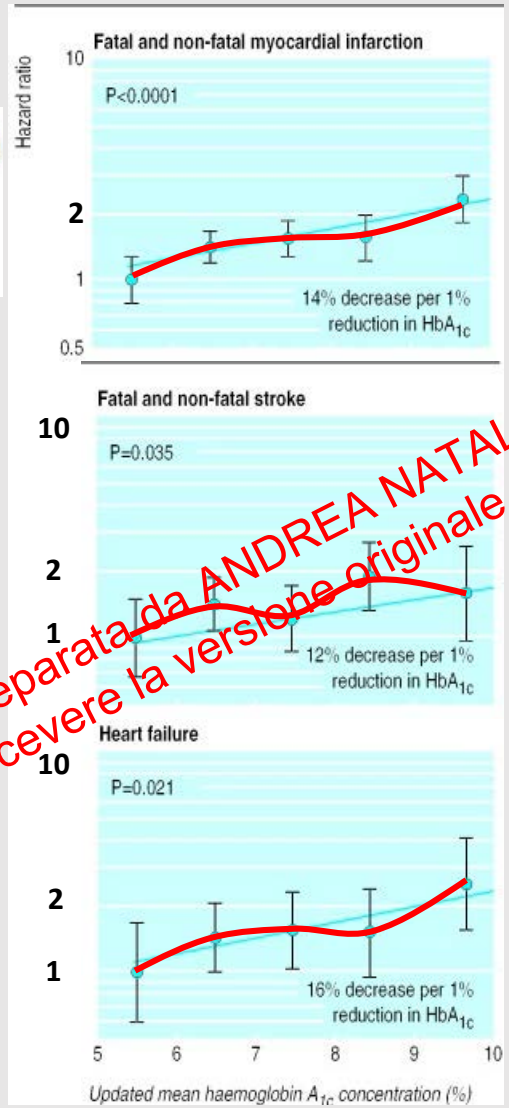
Se il paziente ha più di 3 anni di aspettativa di vita, portare HbA1c < di 6.5% previene lo sviluppo e la progressione della complicanze microvascolari (Retina e Rene e probabilmente Neuro) senza incrementare né il rischio di complicanze macrovascolari neppure nei pazienti ad alto rischio (anzi riduce IMA non fatale) né il rischio di mortalità per tutte le cause.



Macro e Micro diversa curva DR

Target <6% ?





Target: the lower the better