



1222 · 2022
800
ANNI



UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Possiamo stringere di nuovo il target glicemico?

Angelo Avogaro, Dip. di Medicina (DIMED)-Università of Padova

Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

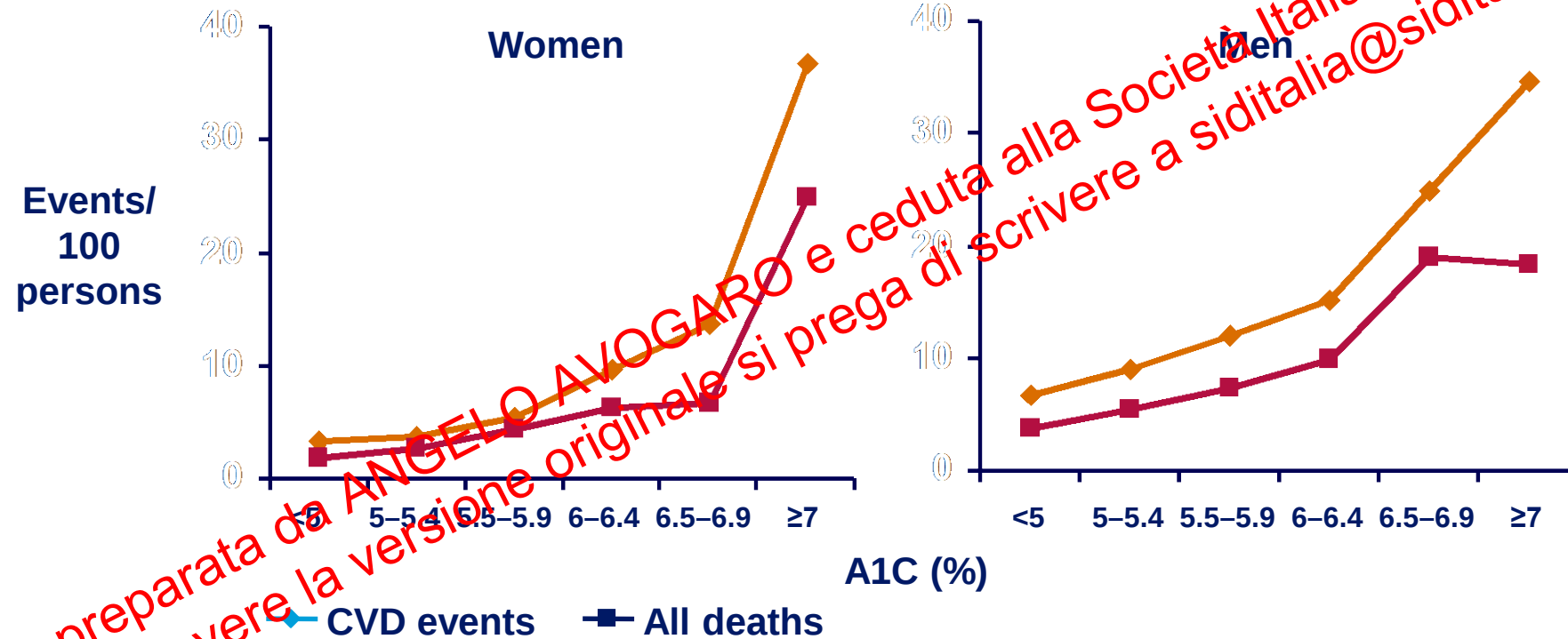
Il dr. **Angelo Avogaro** dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Novo
- Lilly
- Astra Zeneca
- Takeda
- Servier
- Novartis

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

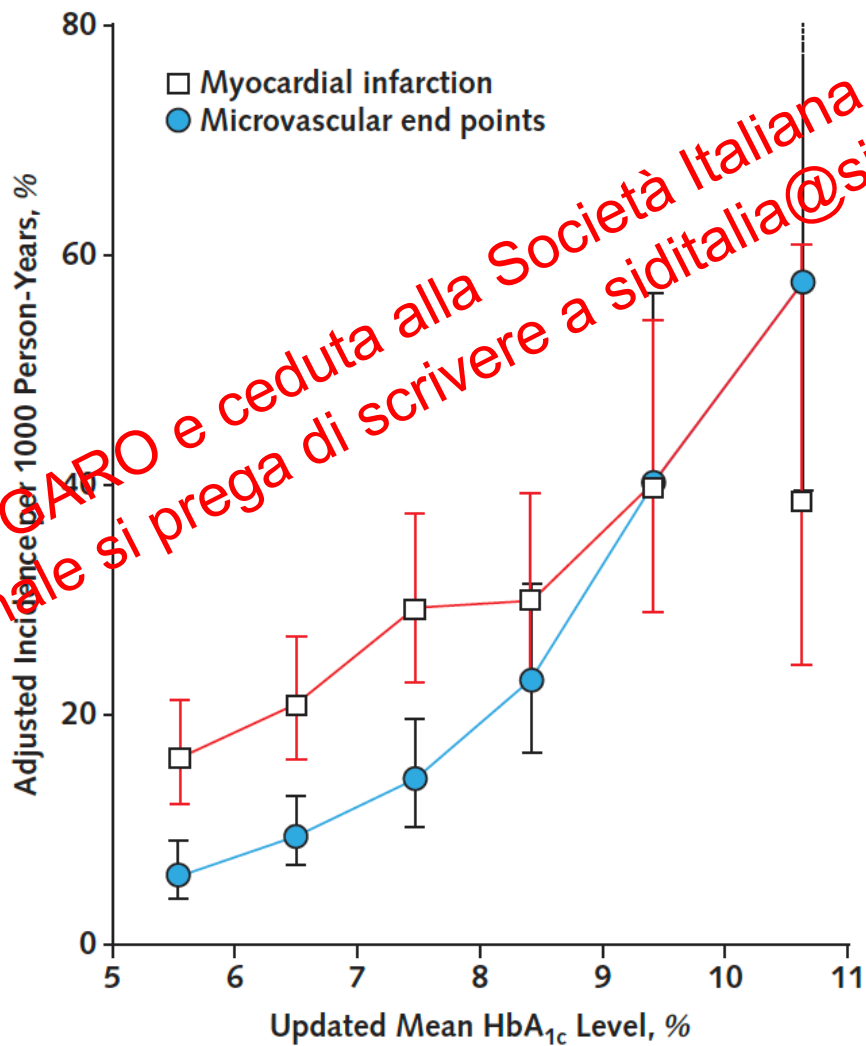
EPIC-Norfolk: CV risk increases with A1C level

N = 10,232



$P_{\text{Trend}} < 0.001$ across A1C categories for all endpoints

**UKPDS:
relationship
between
HbA_{1c} and
Event
Incidence**



UKPDS: Incidence of complications stratified by HbA1c

HbA1c=7%

- AMI: 2.3%/anno
- Micro: 1.5%/anno

HbA1c=6.5%

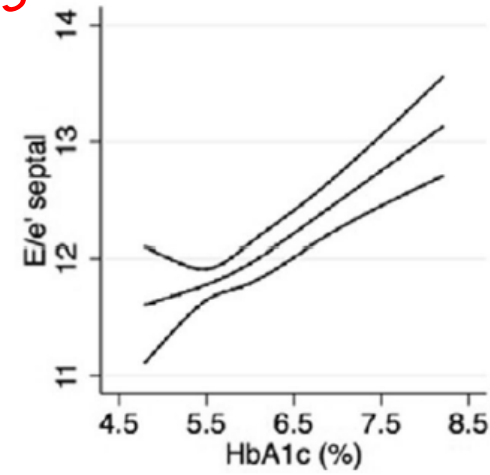
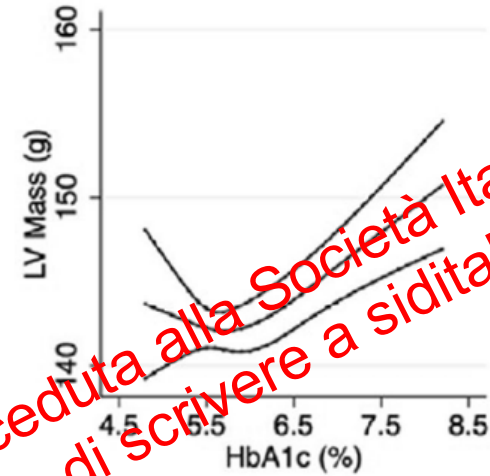
- AMI: 2%/anno
- Micro: 0.8%/anno

HbA1c=5.5%

- AMI: 1.8%/anno
- Micro: 0.5%/anno

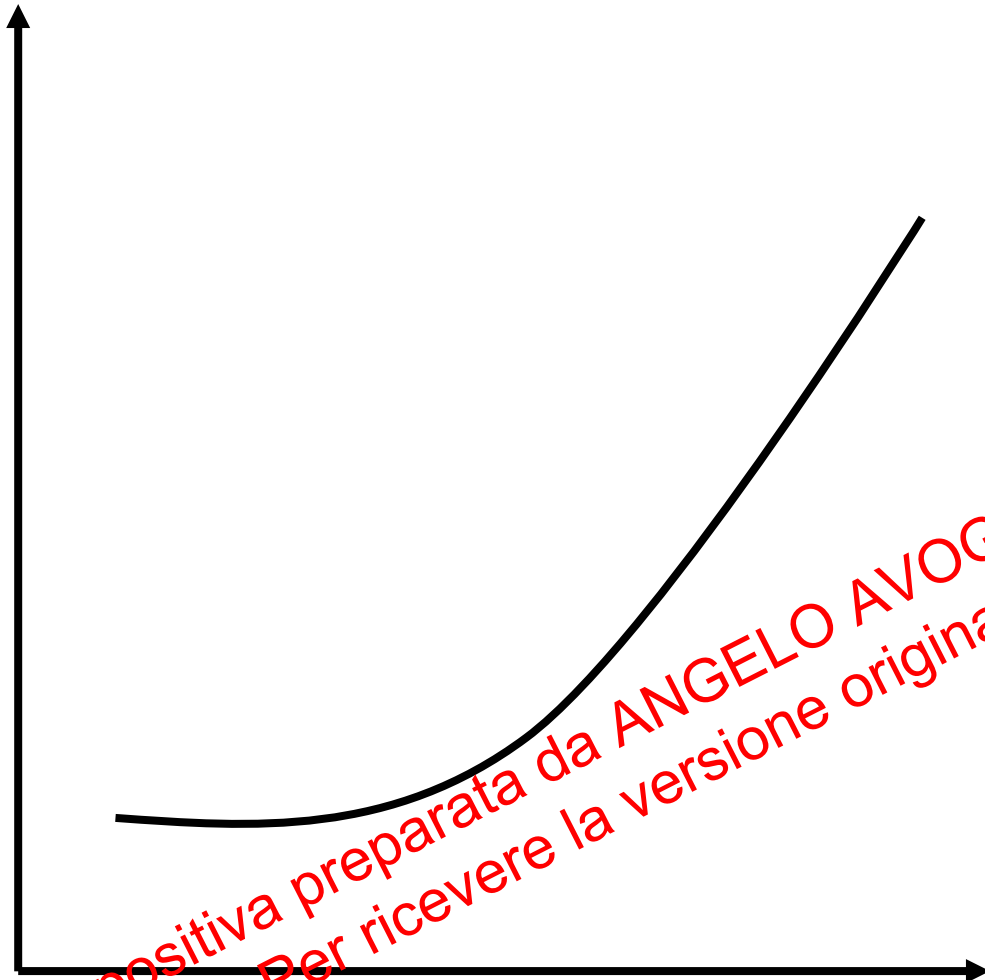
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Association
between HbA1c and
LV mass, AND septal
E/e'
ratio in 4419
participants without
CHD and HF



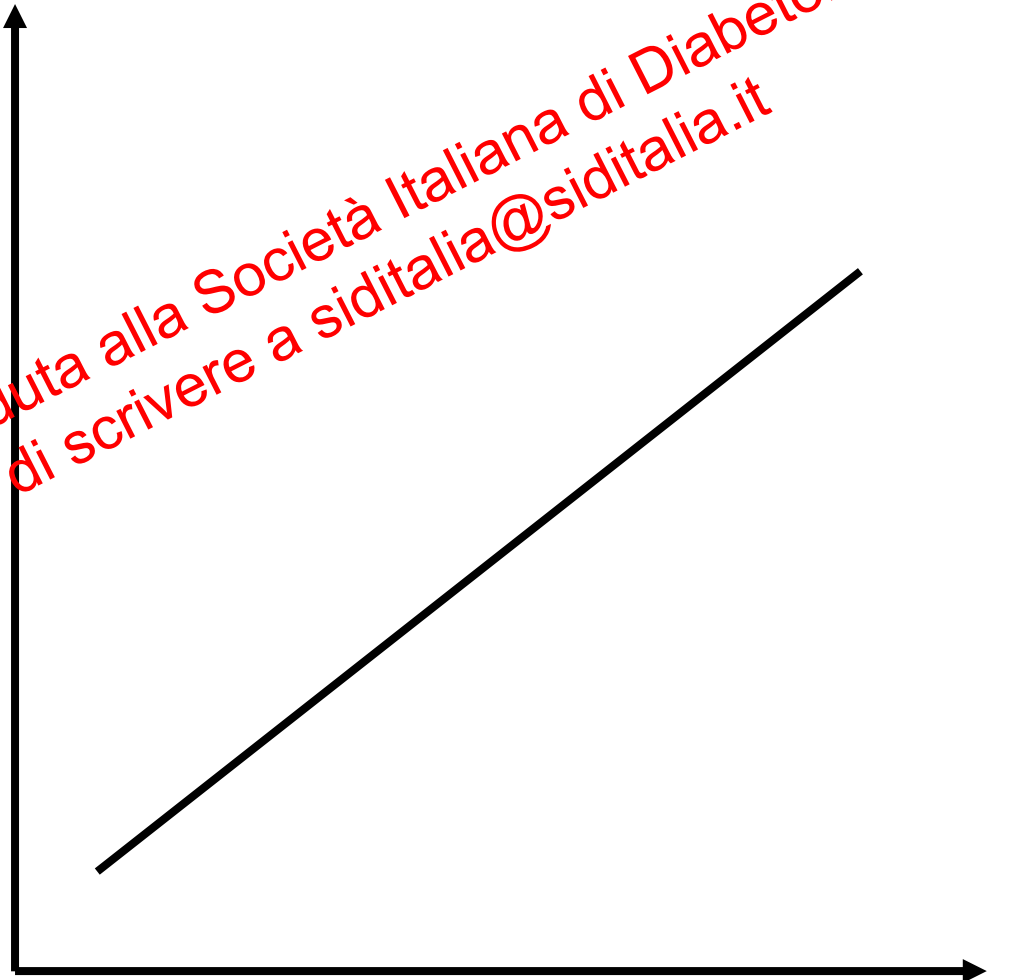
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

CVD risk



HbA1c (%)

CVD risk



HbA1c (%)

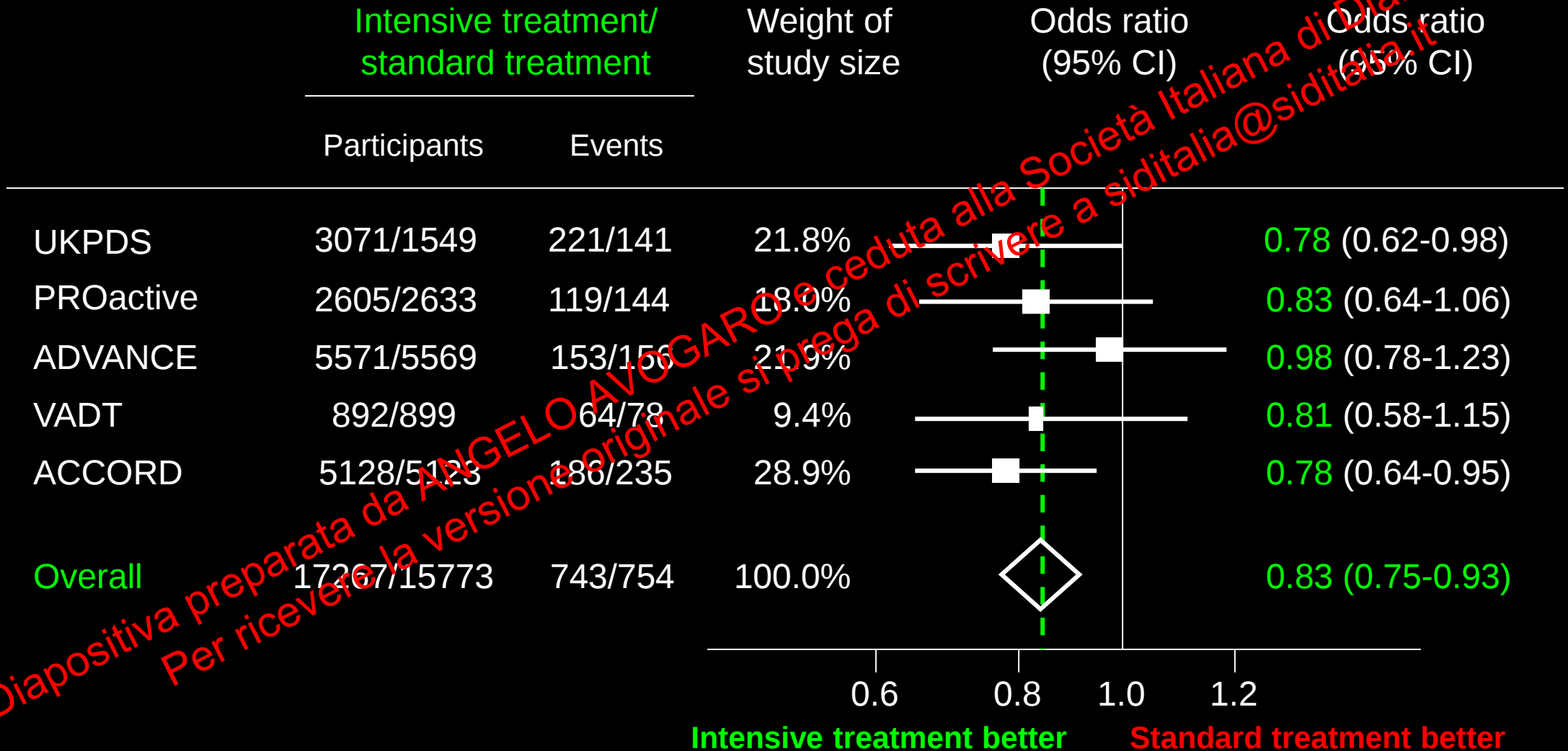
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

HbA1c in Patients with Type 2 Diabetes at Study End of Tretato-Target Trials

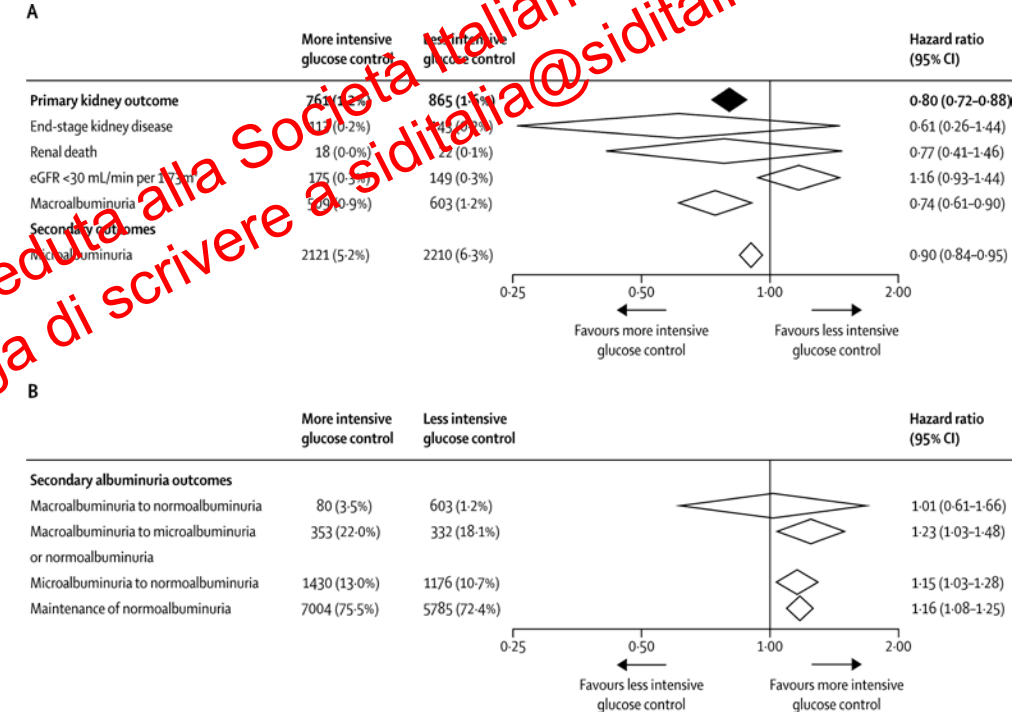
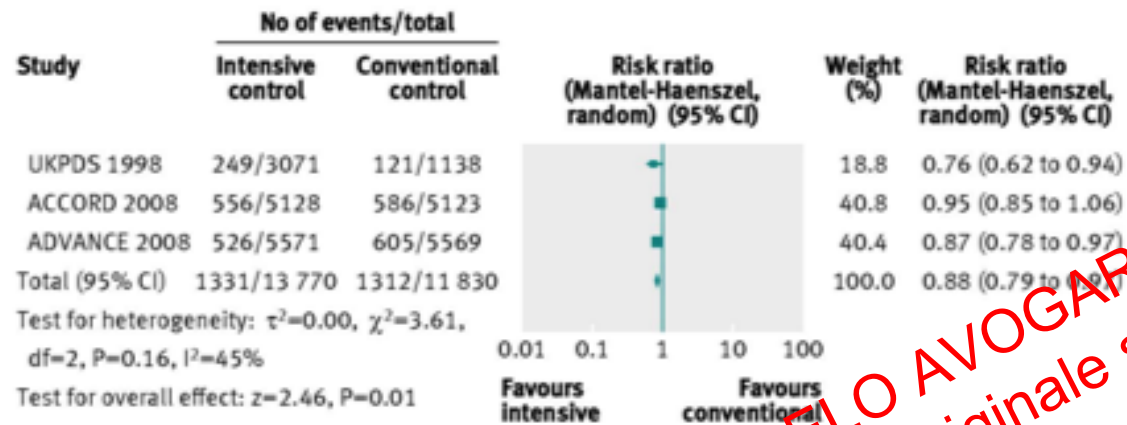
	Initial	Final	Delta
UKPDS	7.9	7.0	0.9
PROactive	7.6	7.0	0.6
ADVANCE	7.5	6.8	0.5
VADT	8.4	6.9	1.5
ACCORD	7.5	6.4	1.1
All	7.5	6.6	0.9

Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

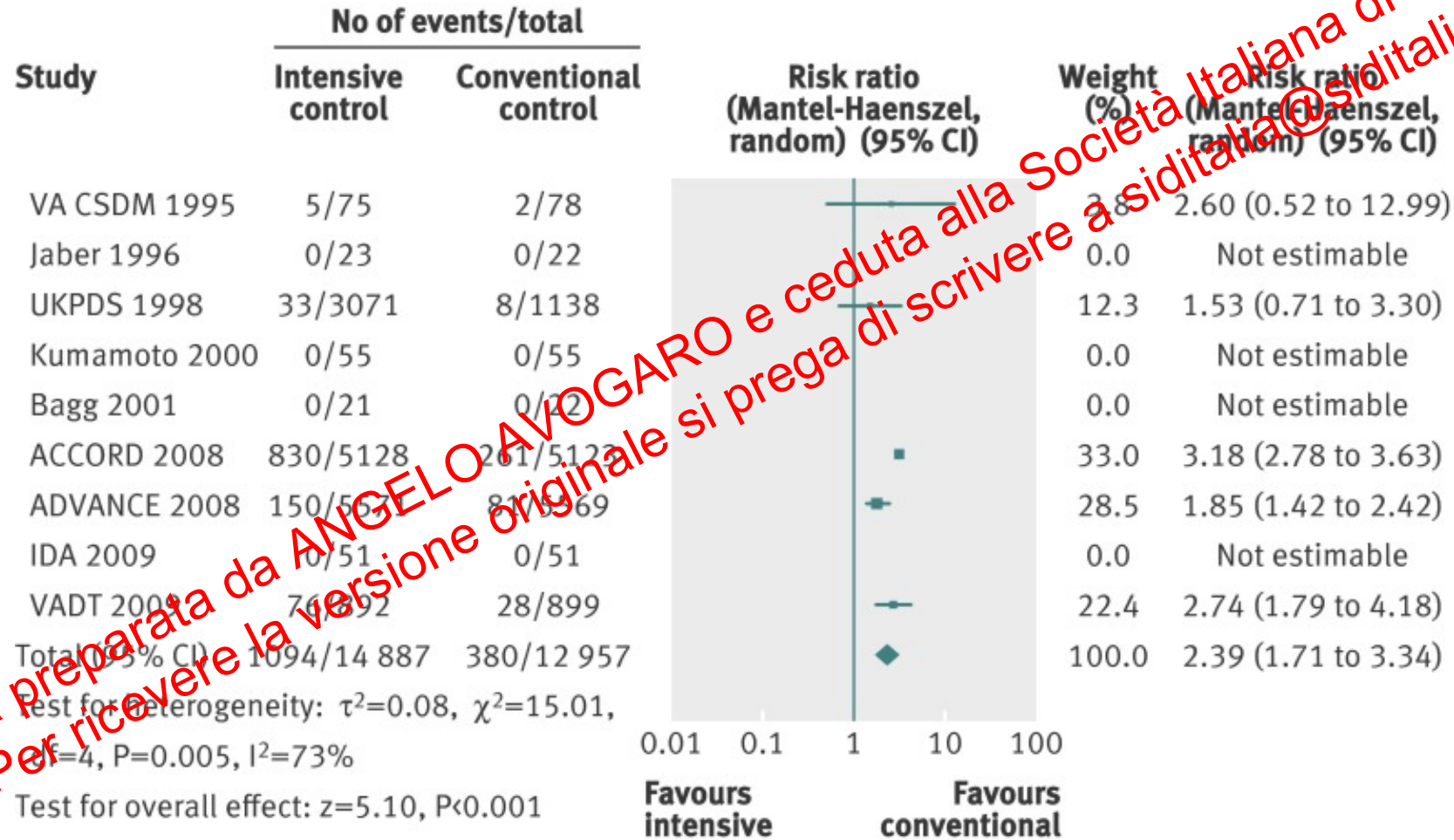
Probability of events of **non-fatal myocardial infarction** with **intensive glucose-lowering** versus **standard treatment**



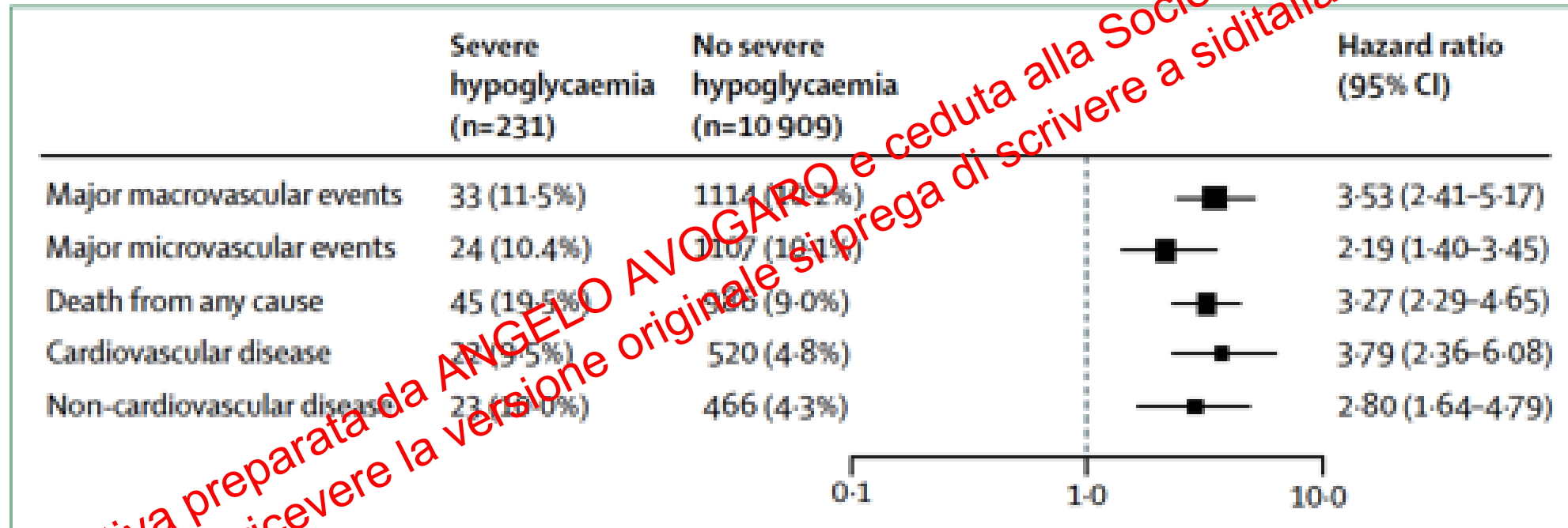
Intensive glucose treatment and microvascular complications



Forest plot for severe hypoglycaemia



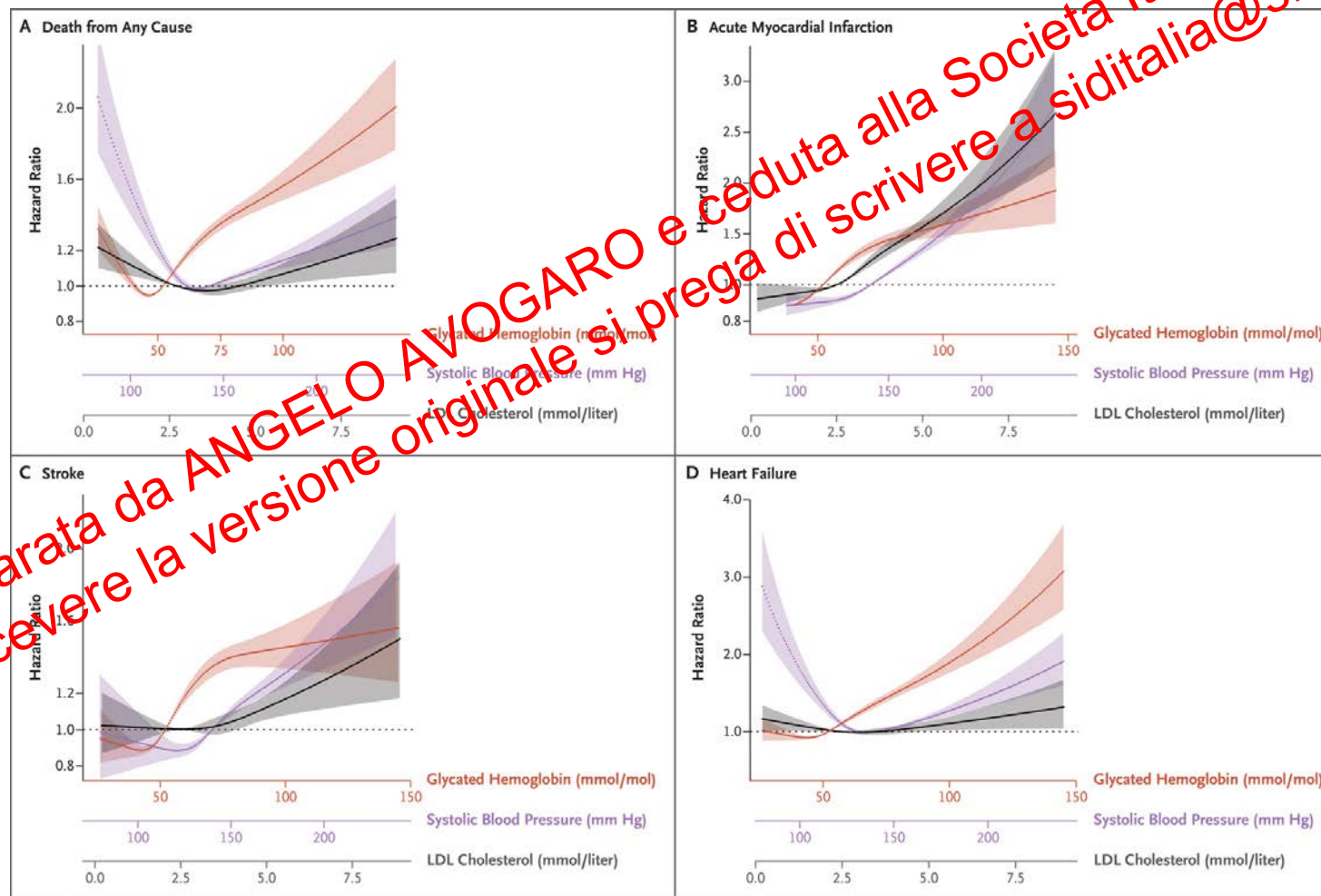
Association of severe hypoglycaemia with the risk of an adverse clinical outcome or death



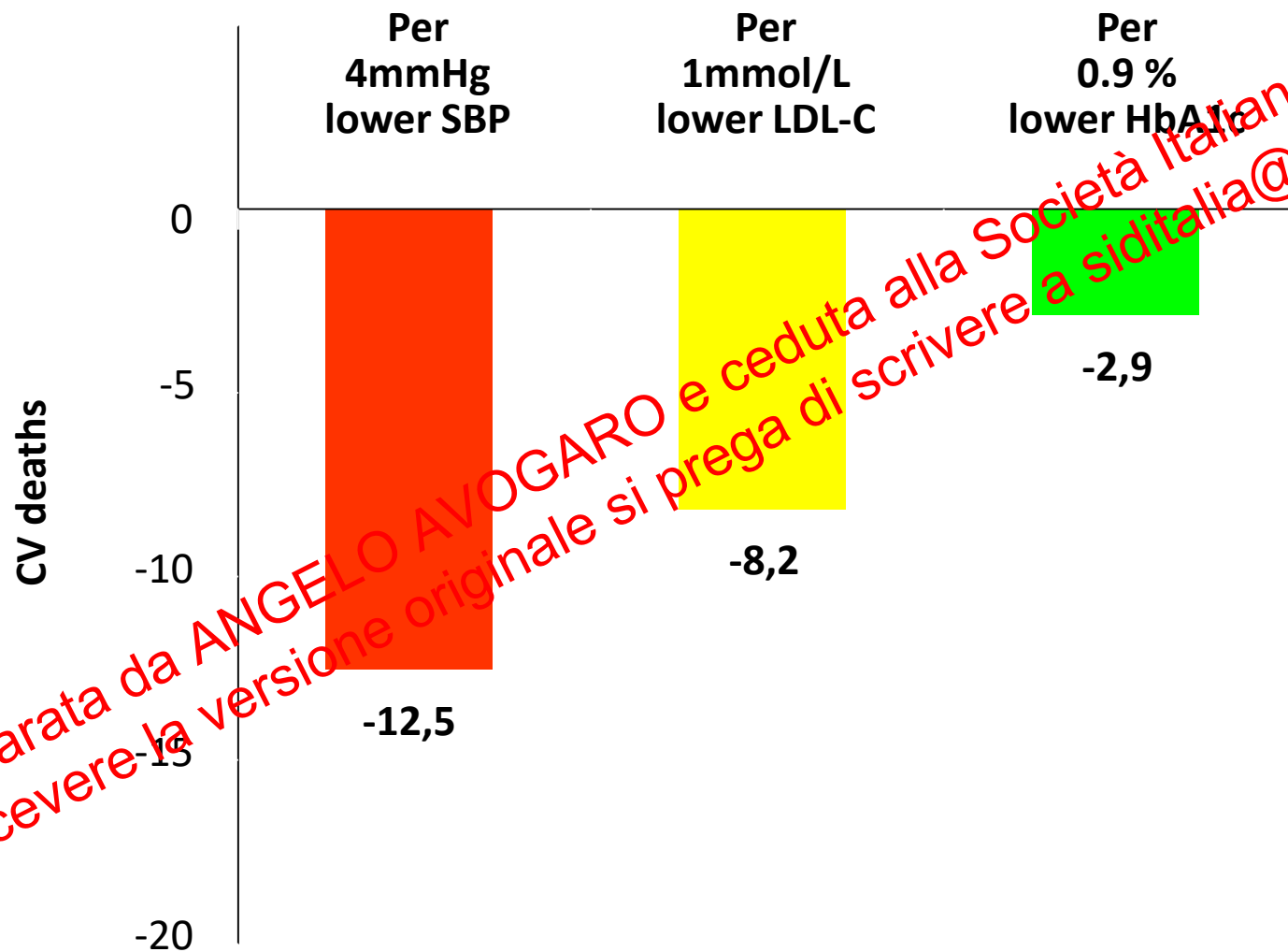
Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Björn Eliasson, M.D., Ph.D.,
Ann-Marie Svensson, Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc.,
Naveed Sattar, M.D., Ph.D., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdóttir, M.D., Ph.D.

Age: 60 yrs
Duration: 4 yrs

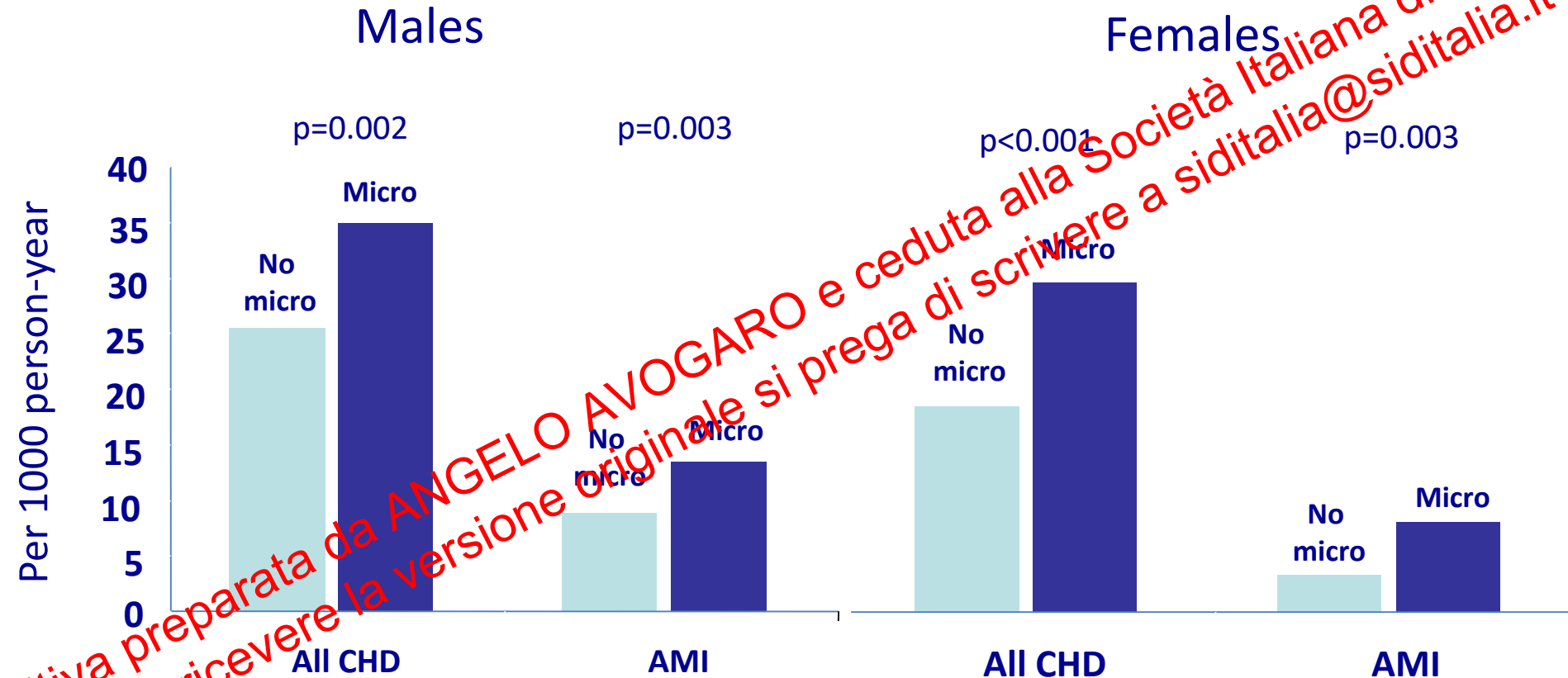


Benefit of different interventions per 1000 diabetic patients treated for 5 years



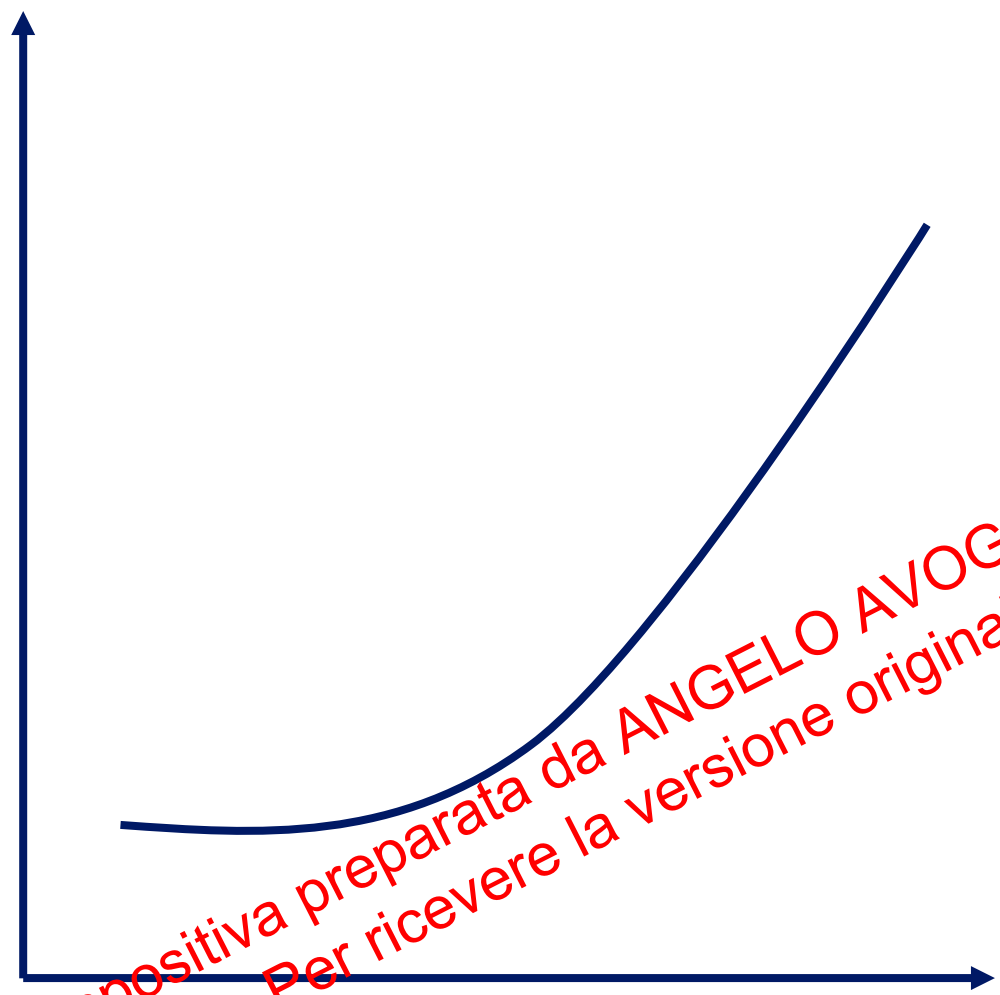
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Incidence Rate of CHD Events: The role of microvascular complications



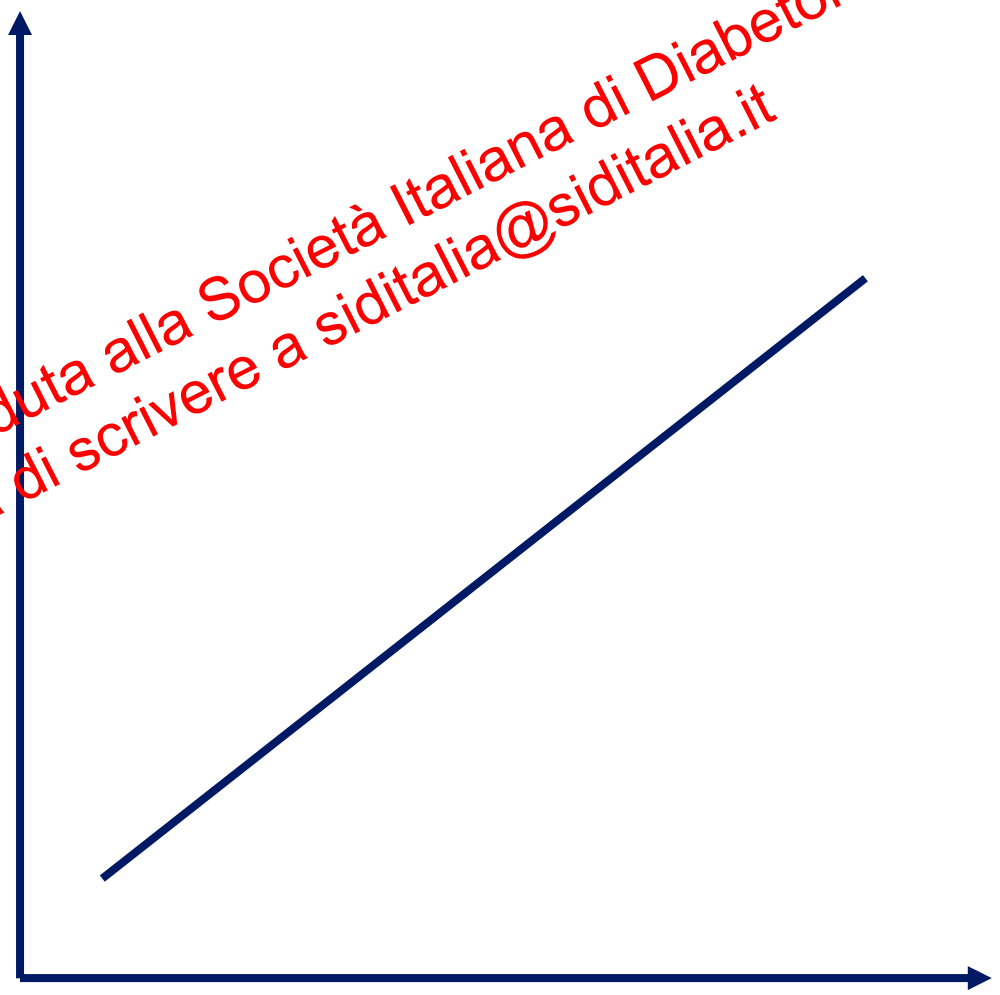
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Microvascular complications risk



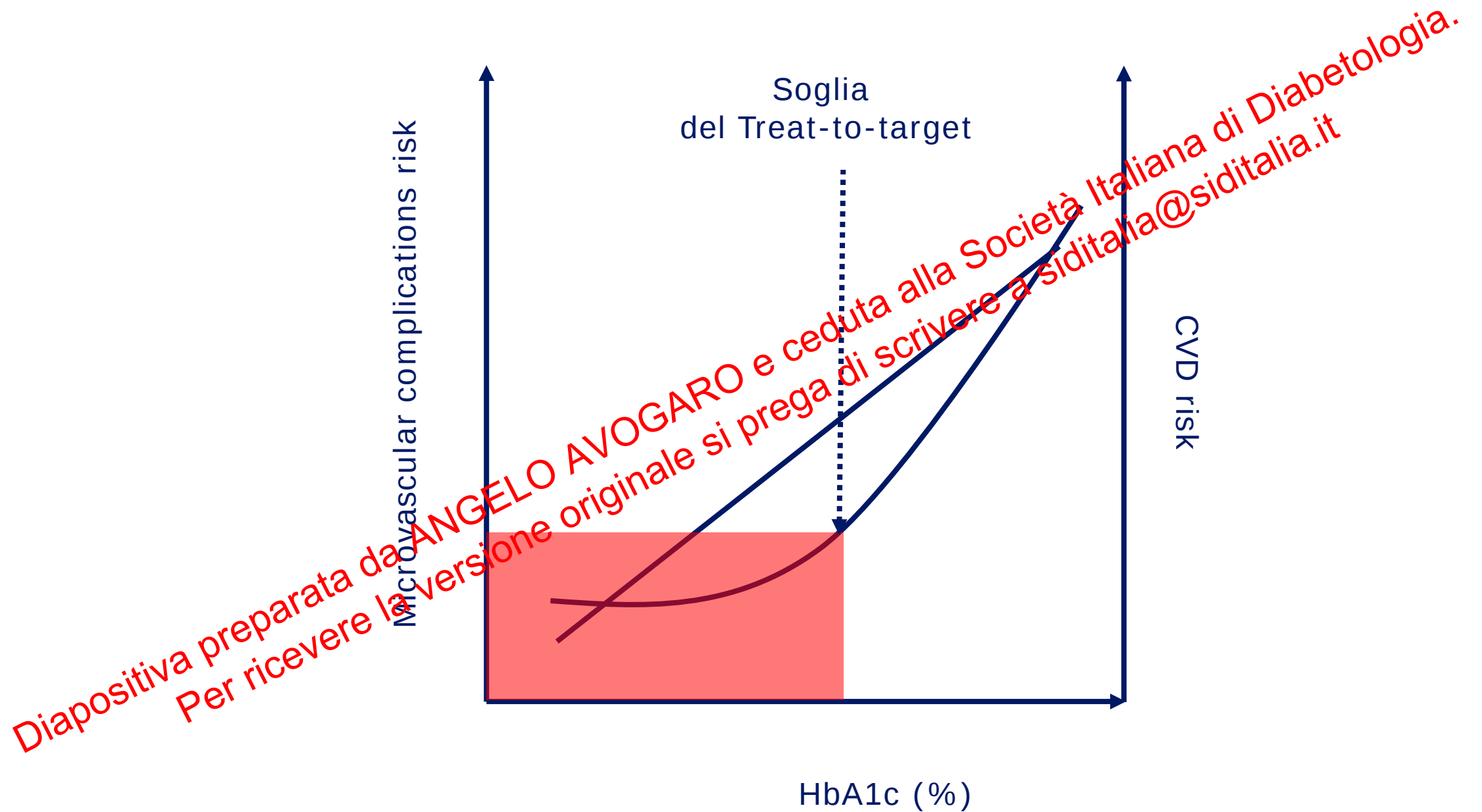
HbA1c (%)

CVB risk



HbA1c (%)

Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it



Treat-to-Target approach

Treatment Intensification to HbA1c
<7%

1. No macrovascular effects
2. No all-cause death results
3. Significant effect on microangiopathy

Hypoglycemia

Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Initial, final, and delta A1c values (%) in the CVOT

Trial	Initial	Final	Delta
LEADER	8.7	7.7	-0.4
SUSTAIN-6	8.7	7.3	-0.9
HARMONY	8.8	7.8	-0.5
REWIND	7.3	7.0	-0.3
EMPAREG	8.1	7.8	-0.3
CANVAS	8.2	7.9	-0.6
DECLARE	8.3	7.9	-0.4
CREDENCE	8.3	7.9	-0.4
All	8.3	7.7	-0.5

Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Change in the risk of MACE, renal, and eye end-points in CVOT

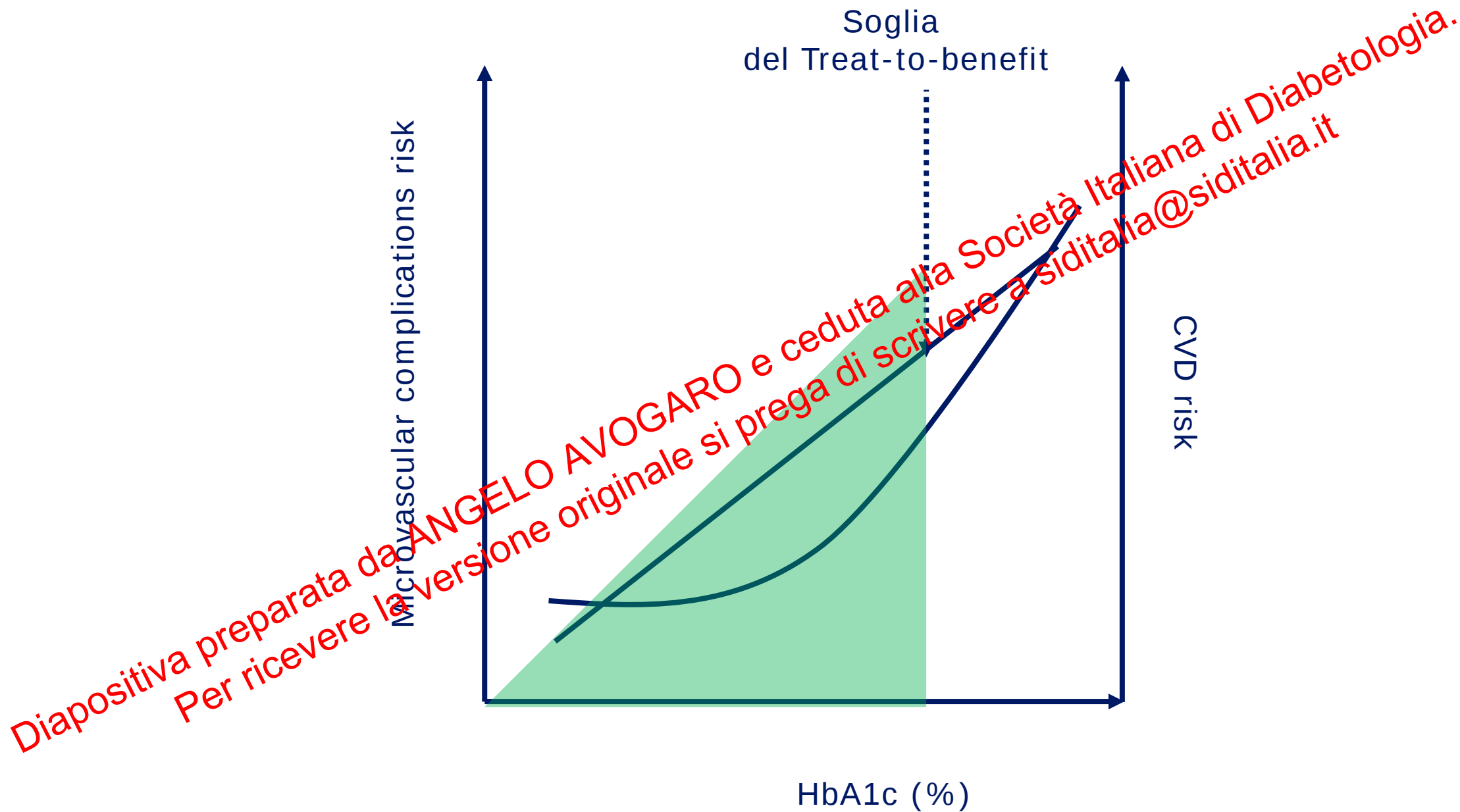
Trial	Change in risk vs. placebo for 3P MACE (%)	Change in renal end-points	Change in eye outcome (%)
LEADER	-13	-22	+15 (p = n.s.)
SUSTAIN-6	-26	-36	+76 (p<0.02)
HARMONY	-22	NA	-12 (p = n.s.)
REWIND	-12	-15	+24 (p = n.s.)
EMPAREG	-14	-39	-22 (p = n.s.)
CANVAS	-14	-40	NA
DECLARE	-17	-47	NA

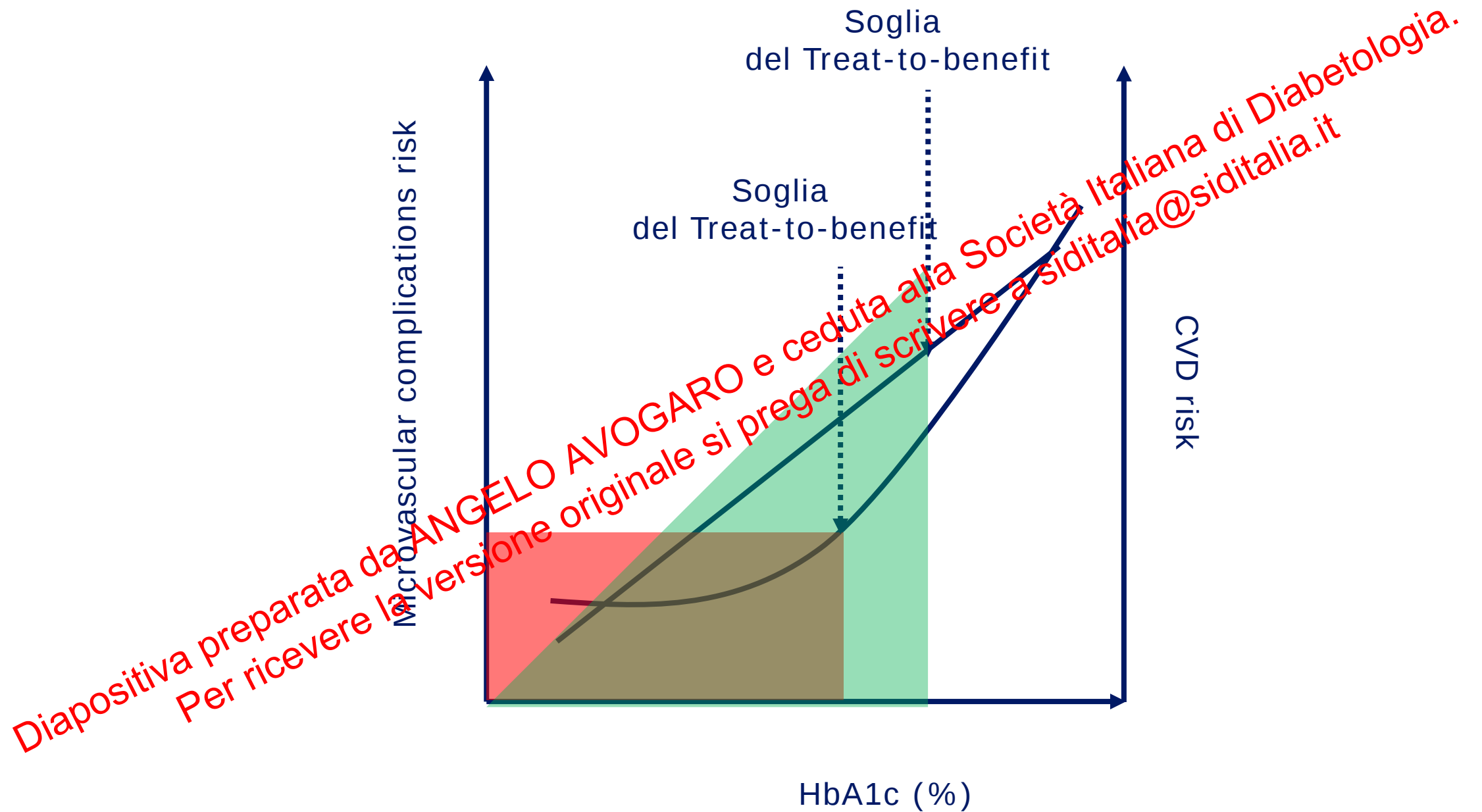
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia. Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Relative Risk Reduction (%) in Kidney outcome in CVOT

Composite Kidney outcome



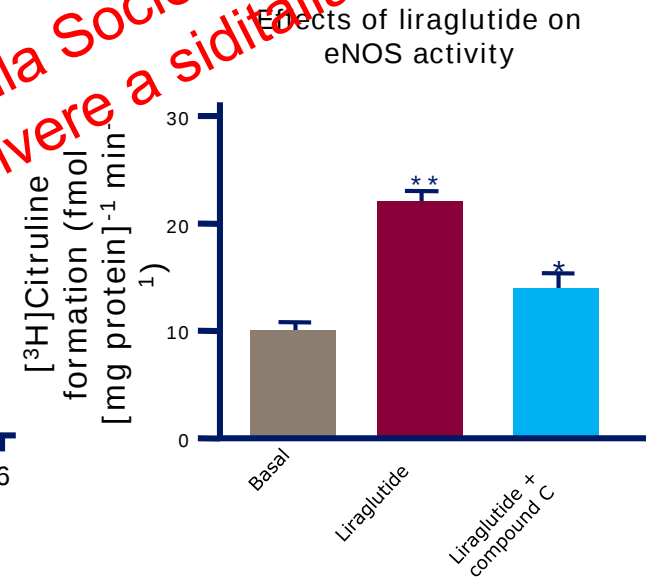
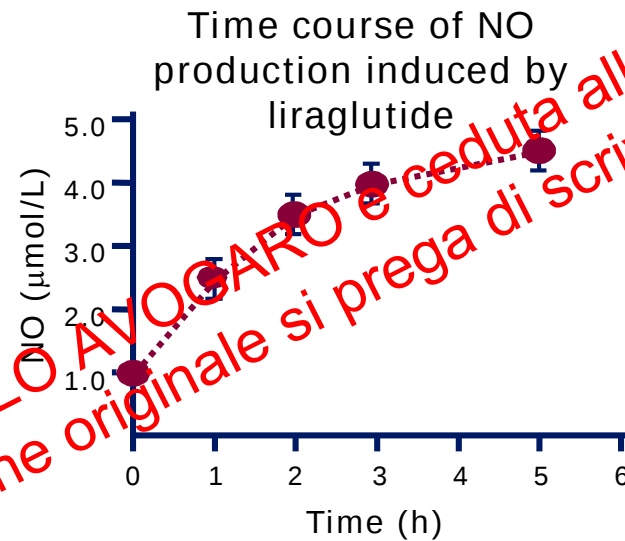
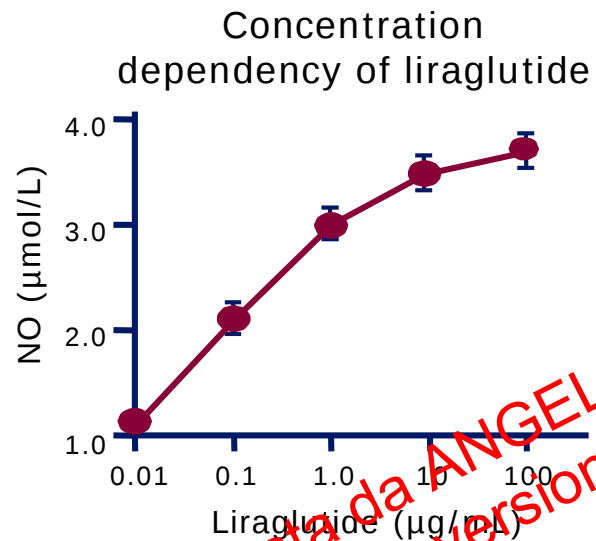




	MET	SUs	PIO	DPP-4i	GLP-1RA	SGLT2i	Insulina
Protezione CV diretta	↑	↓	↑↑	↔	↑↑↑	↑↑↑	↑↑
Riduzione glicemia glucosio-indipendente	↔	↓↓↓	↓	↑↑	↑↑↑↑	↑↑	↓↓↓

Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Liraglutide increases nitric oxide production in human vascular endothelial cells

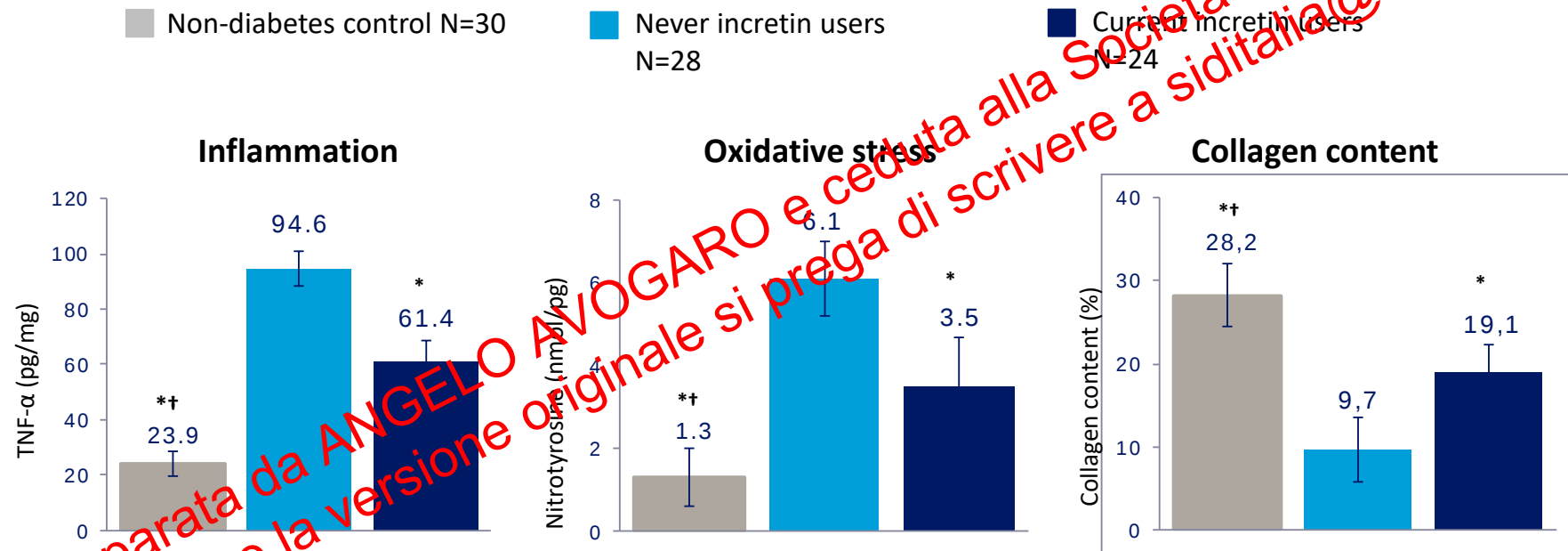


* $p < 0.05$ compared with liraglutide; ** $p < 0.01$ compared with basal
Compound C, AMP-activated protein kinase inhibitor
eNOS, endothelial nitric oxide synthase; NO, nitric oxide

Hattori *et al. Diabetologia* 2010;53:2256–63

human vascular endothelial cells (HUVECs) AMPK inhibitor compound C

Incretin therapy improves indicators of plaque stability in patients with T2DM



* $p < 0.05$ vs. never users group; † $p < 0.05$ vs. current users group.

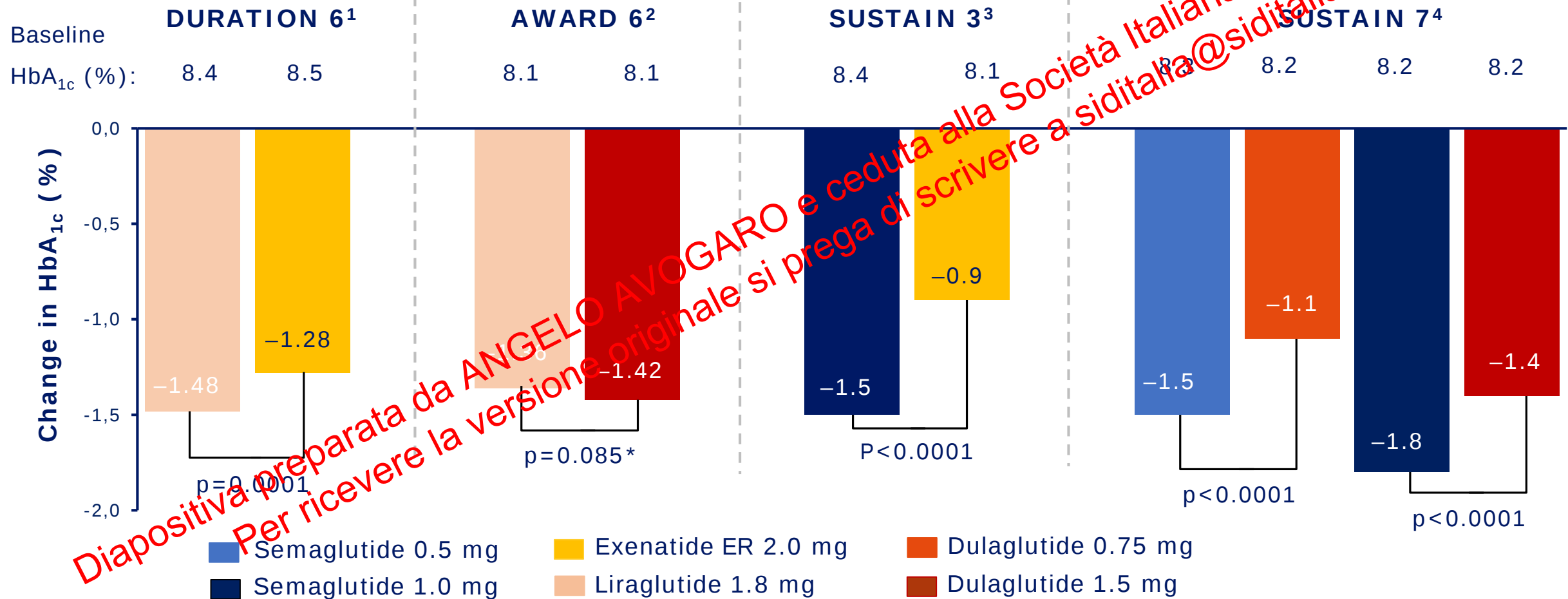
Atherosclerotic plaques from patients undergoing carotid endarterectomy; patients included patients without diabetes and patients with T2DM ± incretin therapy.

TNF-α, tumour necrosis factor-α; T2DM, type 2 diabetes mellitus.

Balestrieri ML et al. *Diabetes* 2015;64:1395–1406.

GLP-1RAs Reduce HbA_{1c}

RESULTS FROM COMPARATIVE TRIALS

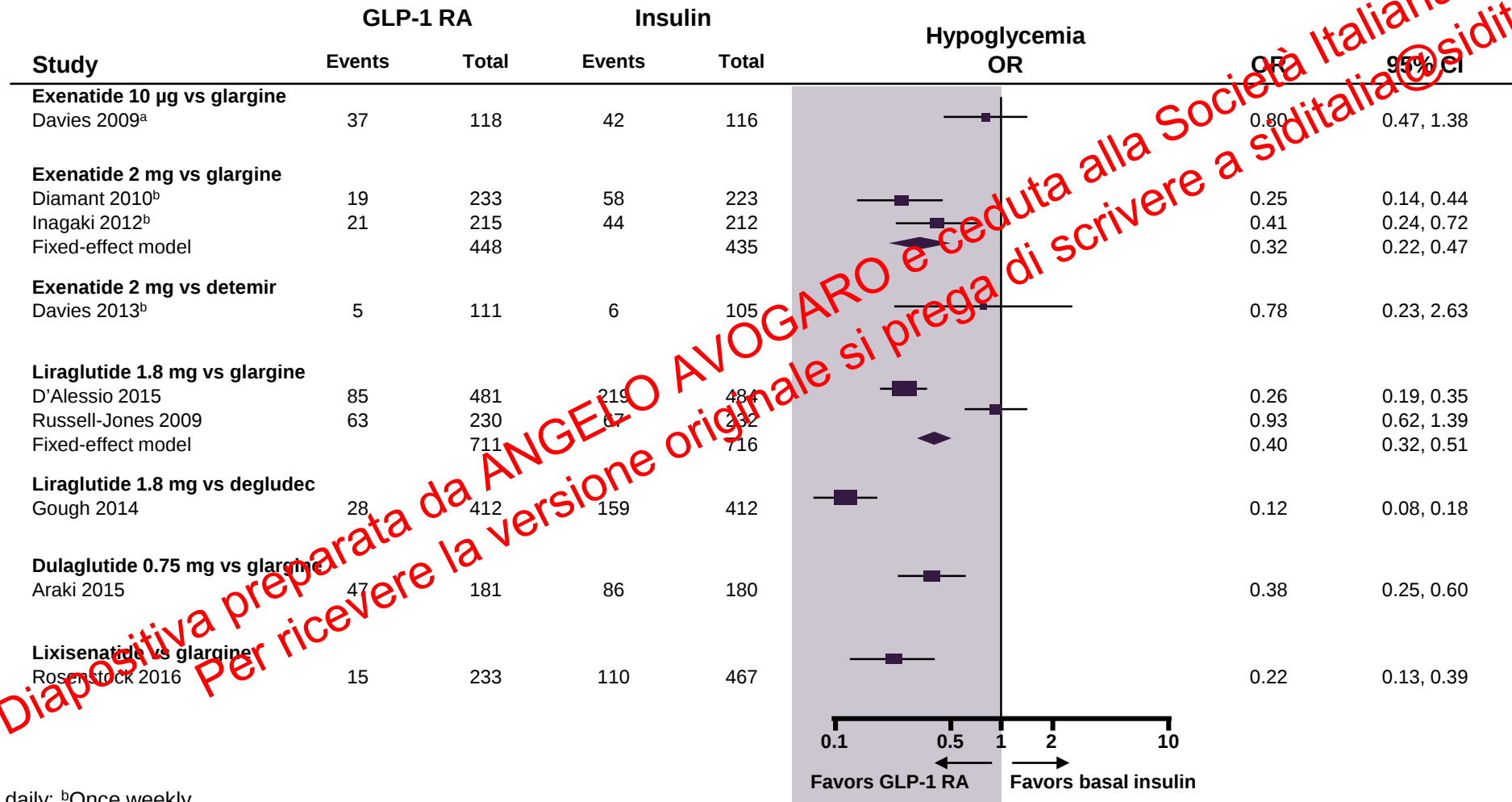


*Treatment difference (nominal 95% CI) = -0.06 (-0.19;0.07), p<0.0001 for non inferiority vs liraglutide. Direct comparisons should not be made between trials. CI, confidence interval; exenatide ER, exenatide extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist.

1. Buse JB et al. *Lancet* 2013;381:117-24; 2. Dungan KM et al. *Lancet* 2014;384:1349-57; 3. Ahmann AJ et al. *Diabetes Care* 2018;41:258-66; 4. Pratley RE et al. *Lancet Diabetes Endocrinol* 2018;6:275-86.

In Addition to Greater Efficacy, GLP-1 RAs are also Associated with a Reduced Risk of Hypoglycemia Versus Insulin

- A meta-analysis of 11 RCTs comparing GLP-1 RAs versus basal insulins in T2DM

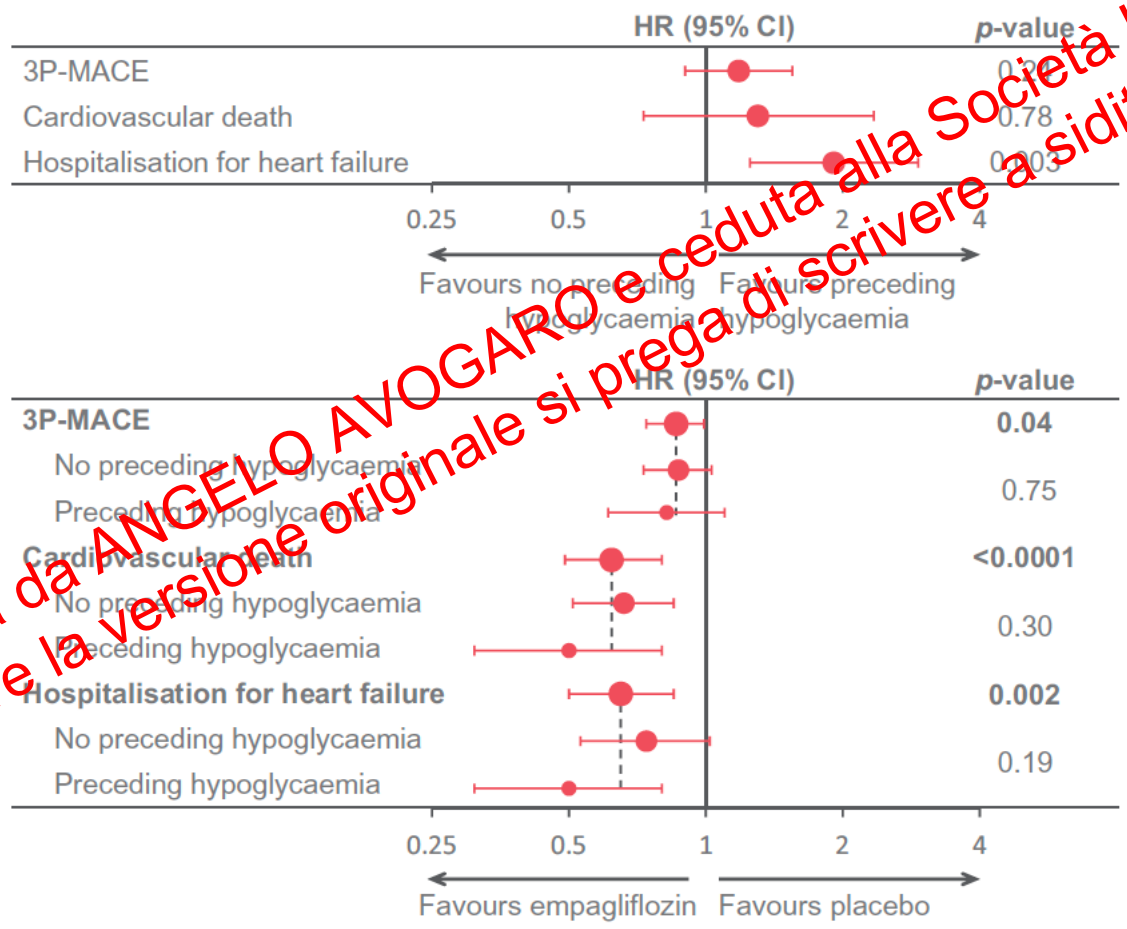


^aTwice daily; ^bOnce weekly

CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OR, odds ratio; RCT, randomized controlled trial

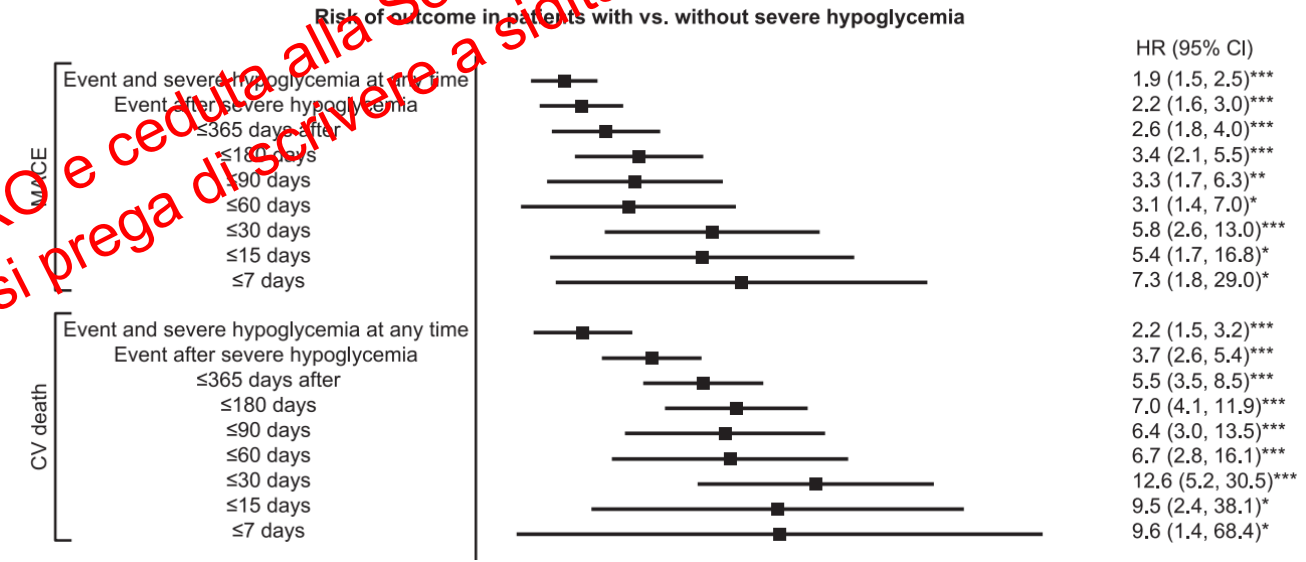
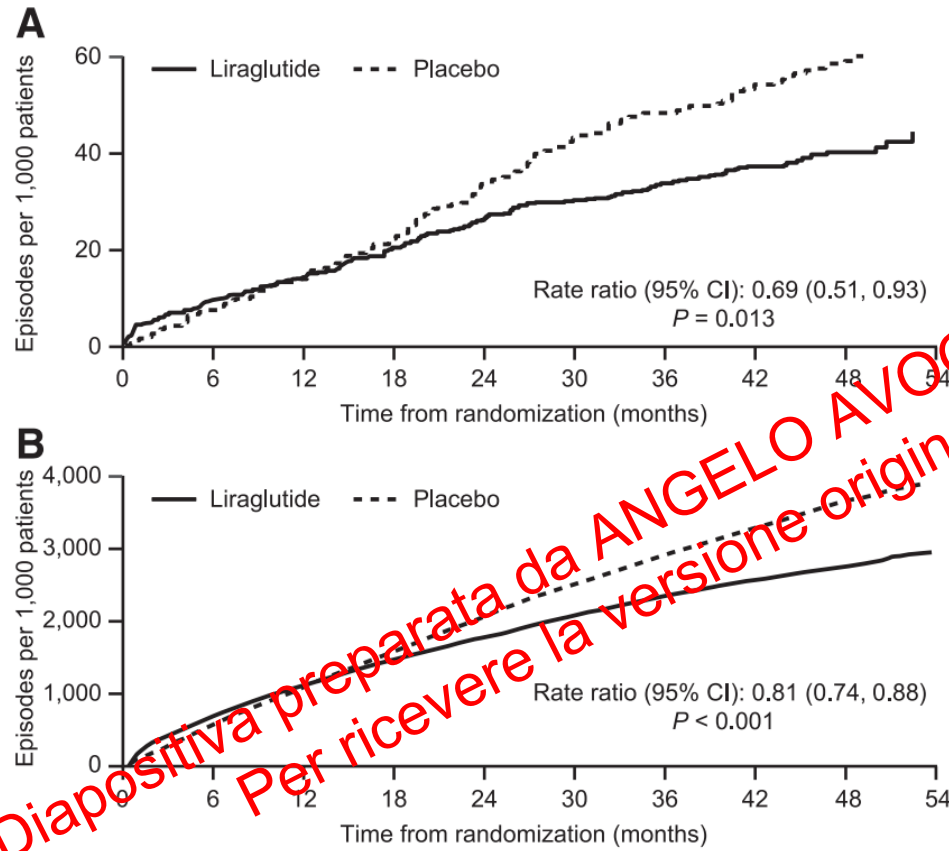
Adapted from Singh S, et al. *Diabetes Obes Metab* 2017;19:228–238

Relationship between occurrence vs. non-occurrence of hypoglycaemia and select outcomes in the placebo group of EMPA-REG OUTCOME

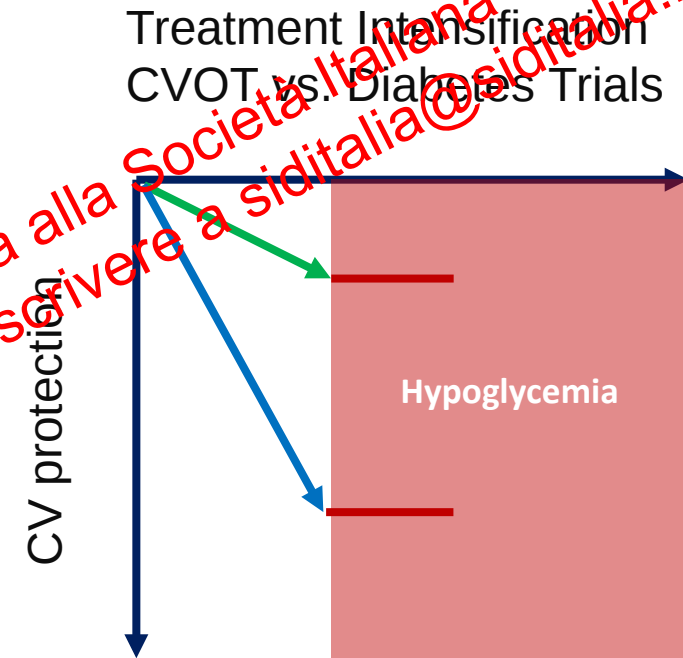


Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Hypoglycemia, Cardiovascular Outcomes, and Death: The LEADER Experience

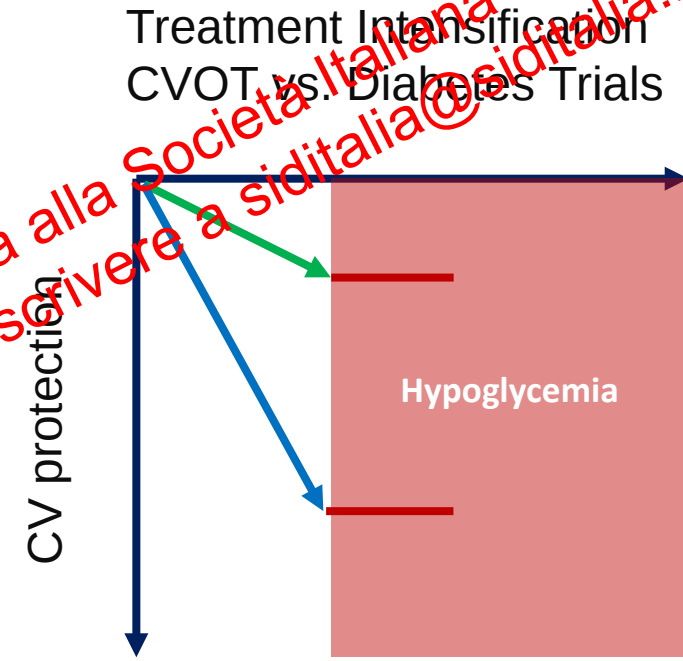
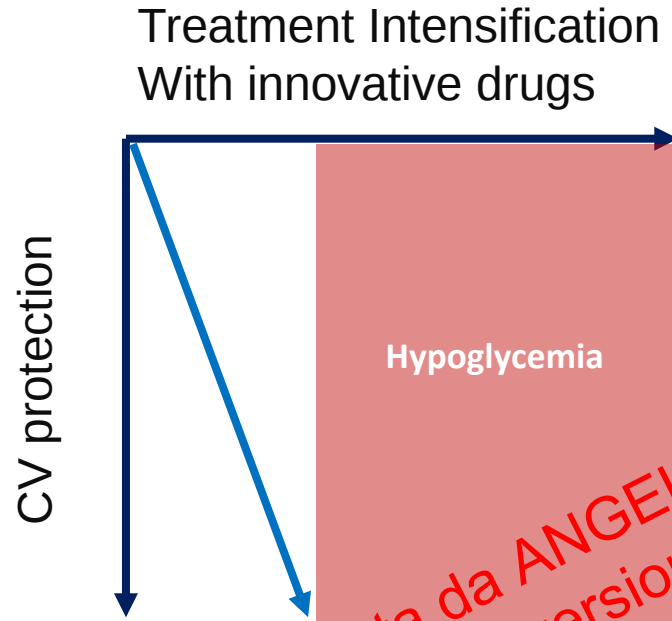


Treatment of Diabetes with new drugs: A new paradigm

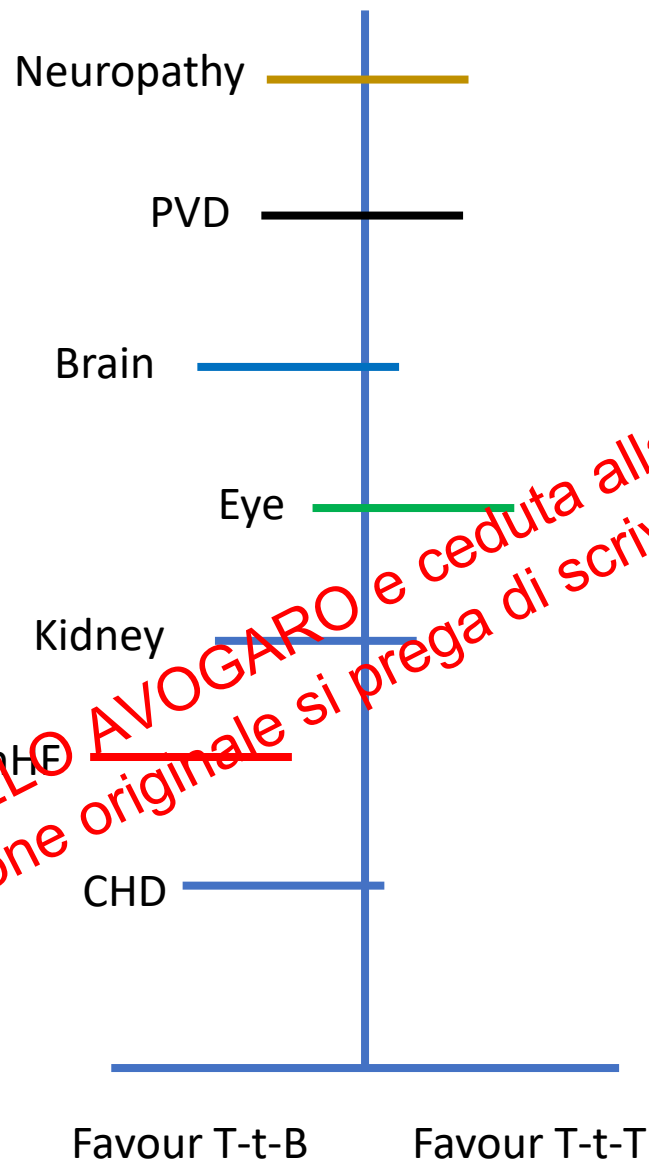


Diapositiva preparata da ANGELO AVOGARO e ceduta alla Societa Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Treatment of Diabetes with new drugs: A new paradigm



Diapositiva preparata da ANGELO AVOGARO e ceduta alla Societa Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it



Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Take Home Messages

- L'approccio treat-to-target con i vecchi farmaci antidiabetici, pur garantendo la normalizzazione dell'A1c, espone il paziente ad eccessive ipoglicemie garantendo solamente una modesta protezione microvascolare .
- L'approccio treat-to-benefit garantisce un'ottima protezione macrovascolare e una parziale protezione microvascolare
- E' auspicabile un approccio treat-to-target con i farmaci innovativi per garantire una protezione sia macro- sia microvascolare

Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it