

Tra glicemia e complicanze: il loro stretto rapporto e l'importanza del trattamento precoce nel paziente diabetico

Angelo Avogaro. Università di 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 Prof. Angelo Avogaro dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche.

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsiasi modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario

- Novo Nordisk
- Amgen
- Astrazeneca
- Bayer
- Boehringer-Ingelheim
- Servier
- Lilly
- Sanofi
- Takeda
- Mediolanum
- Merck Sharp & Dohme
- Janssen
- Menarini Diagnostici
- Novartis
- Bruno Farmaceutici
- Vifor Pharma

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

Prepregnancy Diabetes and Offspring Risk of Congenital Heart Disease

A Nationwide Cohort Study

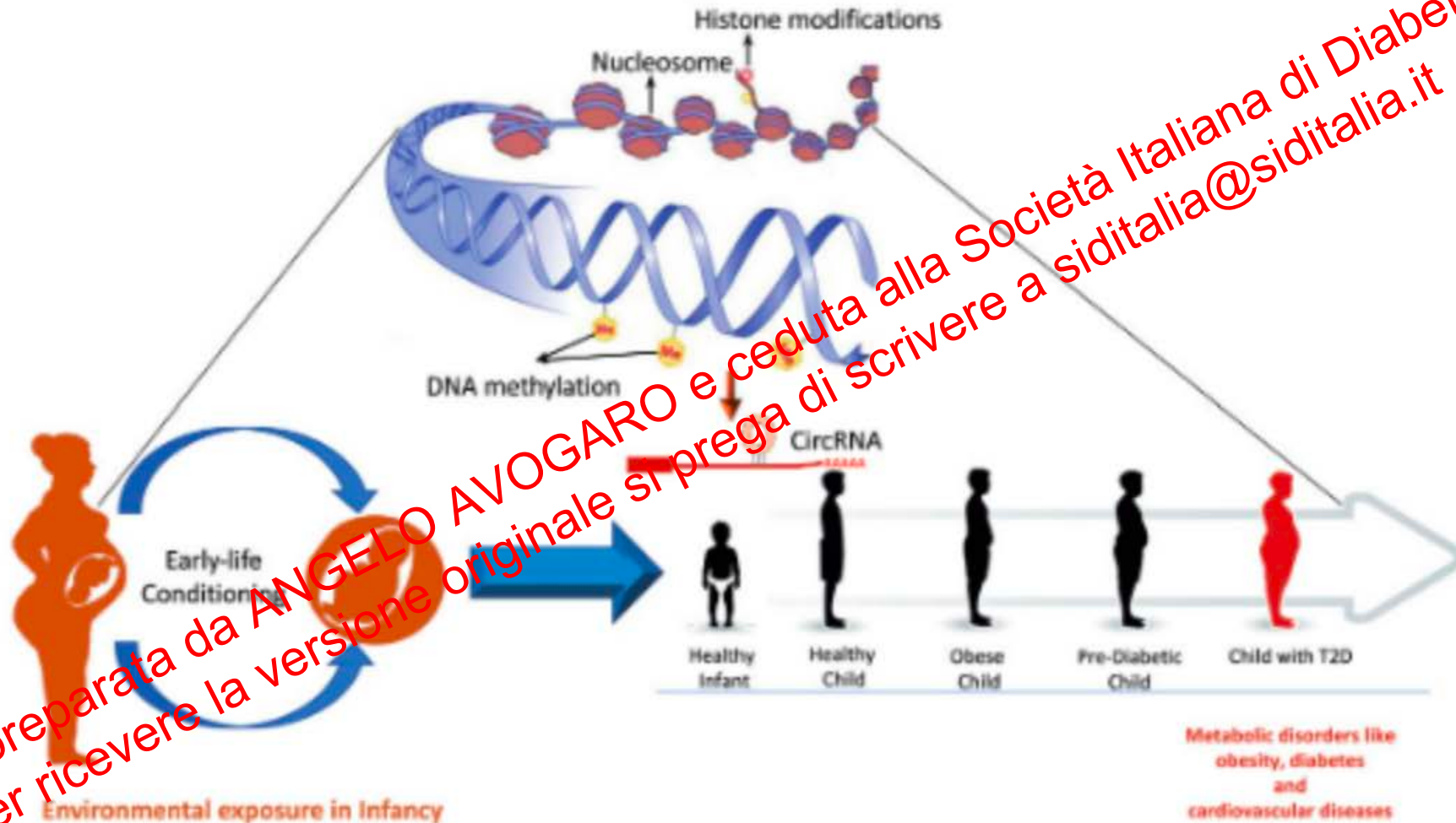
Nina Øyen, MD, MPH, DrMed; Lars J. Diaz, MSc; Elisabeth Leirer, MD;
Heather A. Boyd, PhD; James Priest, MD; Elisabeth R. Mathiesen, MD, PhD;
Thomas Quertermous, MD; Jan Wohlfahrt, MSc, DrMedSc; Mette Melbye, MD, DrMedSc

Table 3. Relative Risk of Any Type of CHD* by Information of Pregestational Diabetes Mellitus,† and Pregestational First-Time Prescription‡ of Insulin or Noninsulin Treatment, in 466 076 Singleton Live Births,§ Denmark, 1996 to 2011

Pregestational Diabetes Mellitus†	First-Time Pregestational Treatment‡	Births N=466 076 n (%)	CHD* n=3625		RR Crude (95% CI)	Adjusted RRI,¶ (95% CI)
			No.	Prevalence per 10 000		
Yes	Total	1905 (0.41)	55	289	3.75 (2.85–4.83)	3.88 (2.95–4.99)
	Insulin	1497 (0.32)	42	281	3.65 (2.66–4.85)	3.73 (2.72–4.96)
	Non-insulin	408 (0.09)	13	319	4.14 (2.29–6.76)	4.47 (2.47–7.28)
No		464 171	3570	77	1 (reference)	1 (reference)

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

Epigenetic modifications



IPERGLICEMIA

- Attivazione della via dei pollioli
- Formazione di AGE
- Attivazione della protein chinasi C
- Attivazione della via delle esosamine

Stress ossidativo

- Ridotta sintesi di nitrossido
- Ridotta sintesi di monossido di carbonio
- Ridotta disponibilità di idrogeno solforato

Vasocostrizione

- Metilazione del DNA
- Modificazioni post-traslazionali degli istoni
- Varianti istoniche
- RNA interferente

Alteredata trascrizione proteica

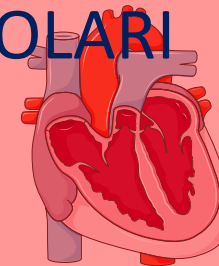
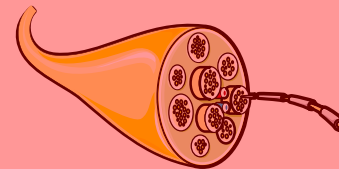
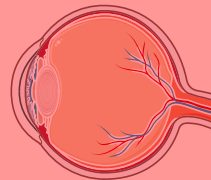
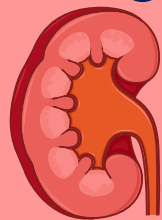
- Attivazione della Neutrophil extracellular traps (NETOSI)

Stress ossidativo
Apoptosi
endoteliale

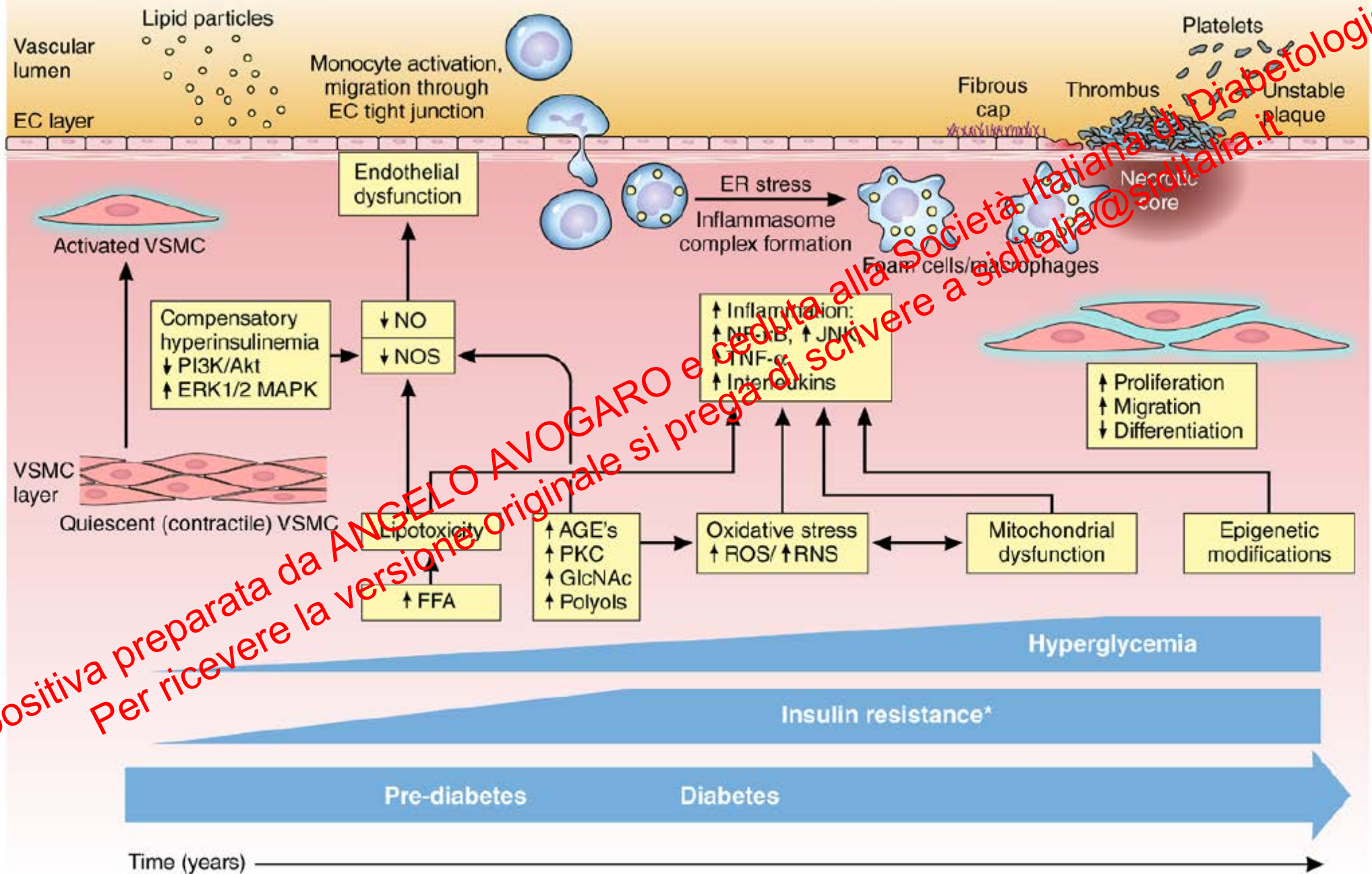
- Mobilopatia midollare
- Ridotte EPC

Ridotta
rigenerazione
vascolare

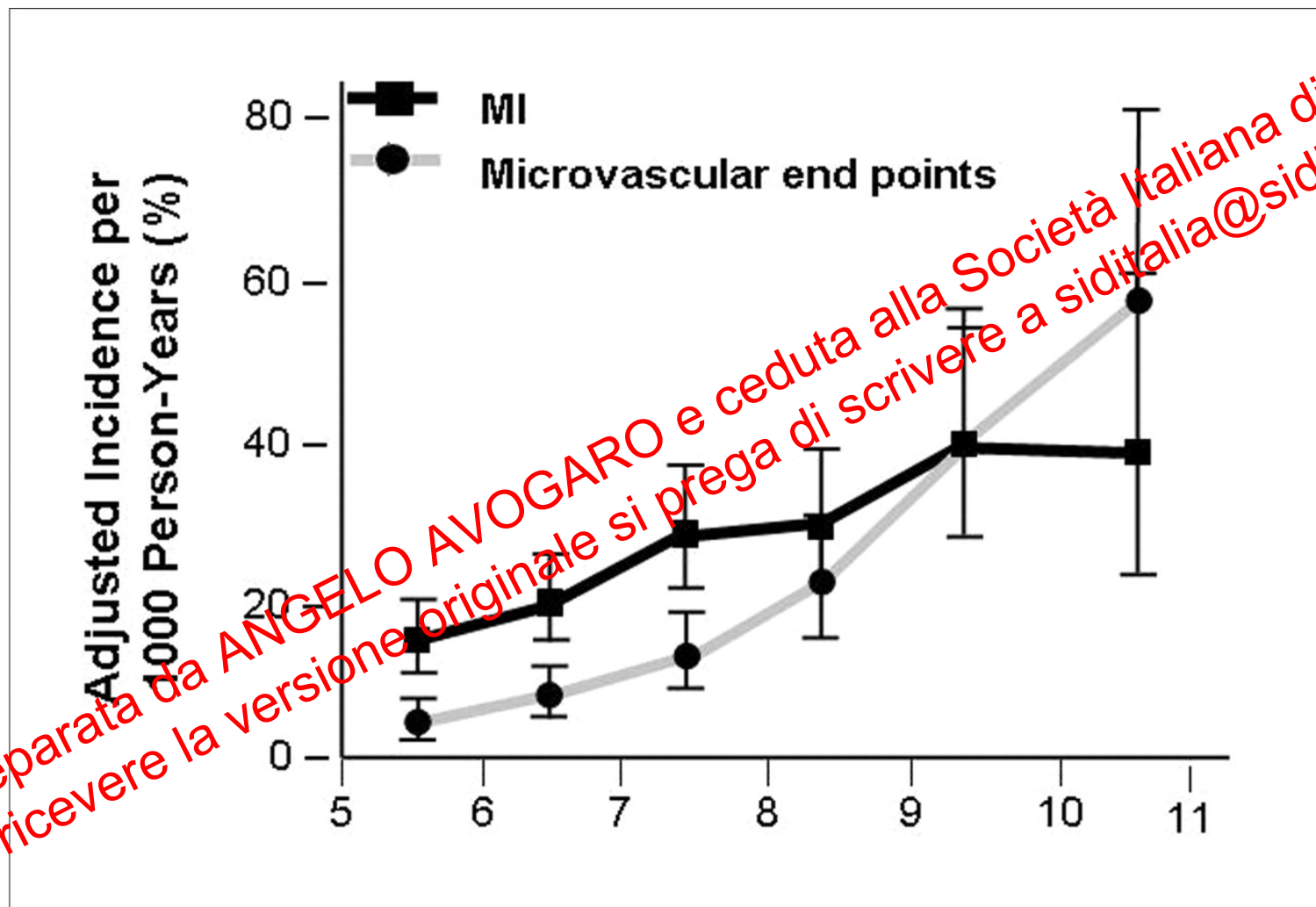
COMPLICANZE MACRO- & MICROVASCOLARI



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



Risk of microvascular and myocardial infarction outcomes based on A1C in the UKPDS.



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

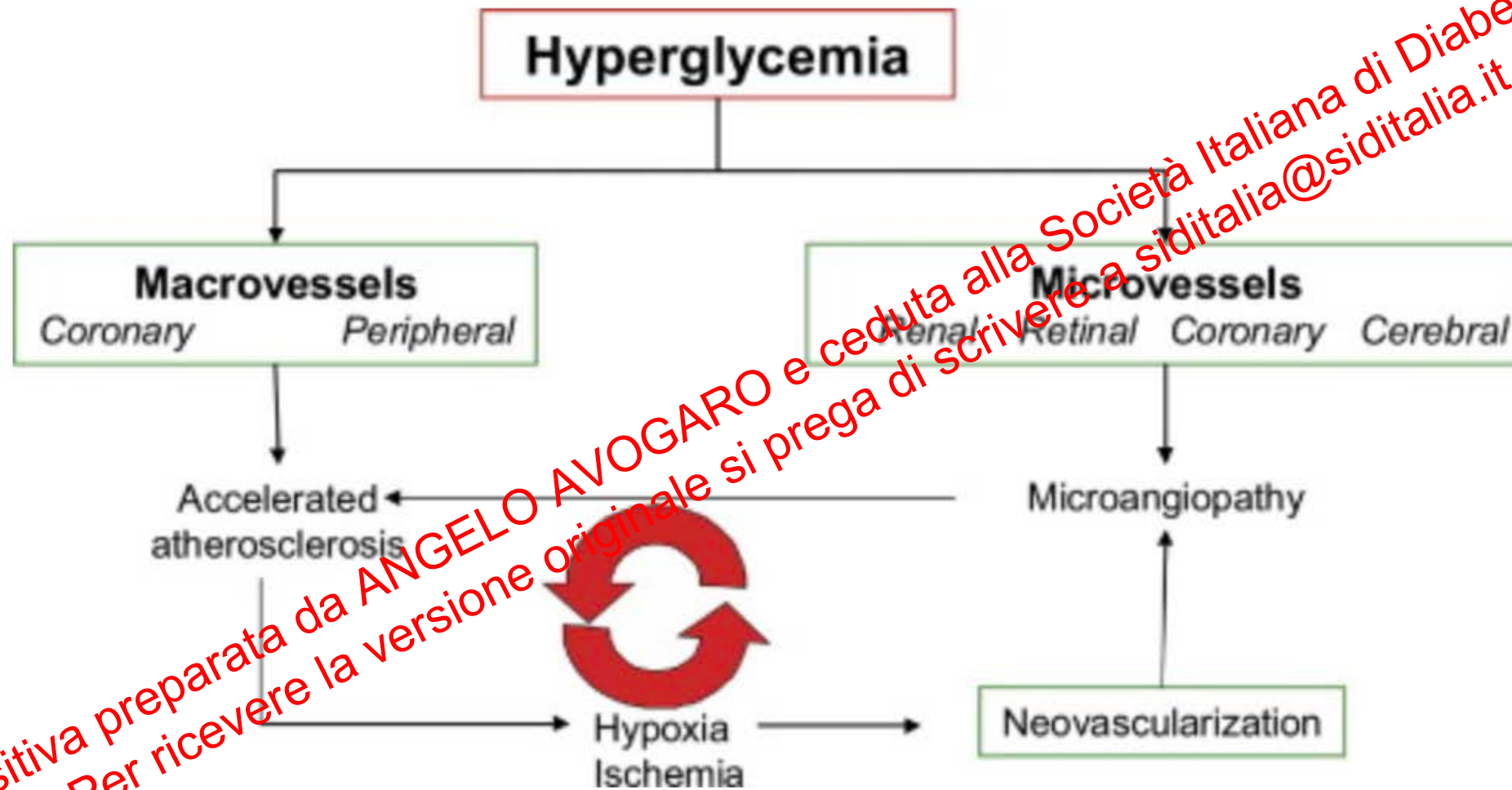
Dysglycemia and the consequences of diabetes

Association between retinal disease and risk of diabetes-related complications

	Risk with retinal disease versus no retinal disease (type of diabetes)
Ischaemic cardiovascular disease	4·1-fold higher incidence (type 1) ⁶³ 2·3-fold higher incidence (type 2) ⁶³
Heart failure	2·7-fold higher incidence (type 2) ⁶⁴
Macroalbuminuria	3·2-fold higher incidence (type 1) ⁶⁵
Renal insufficiency*	2·8-fold higher incidence (type 1) ⁶⁵
Renal insufficiency or albuminuria	1·4-fold higher incidence (type 2) ⁶⁶
Neuropathy	1·8-fold higher prevalence (type 2) ⁶⁷
Erectile dysfunction	2·8-fold higher prevalence (type 2) ⁶⁸
Lower limb amputations	25·0-fold higher incidence (ie, proliferative vs none in type 1) ⁶⁹ 5·0-fold higher incidence (ie, proliferative vs none in type 2) ⁶⁹
Skeletal fractures	5·4-fold higher incidence (type 1 or type 2) ⁷⁰
Non-alcoholic fatty liver disease	3·3-fold higher prevalence (type 1) ⁷¹ 1·8-fold higher prevalence (type 2) ⁷²
Sleep apnoea	Higher prevalence (type 2) ⁷³
Depression	2·2-fold higher prevalence (type 2) ⁷⁴
*With pre-existing microalbuminuria.	

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

Linking macro to microangiopathy



Cardiovascular Events (%/yr)

7
6
5
4
3
2
1

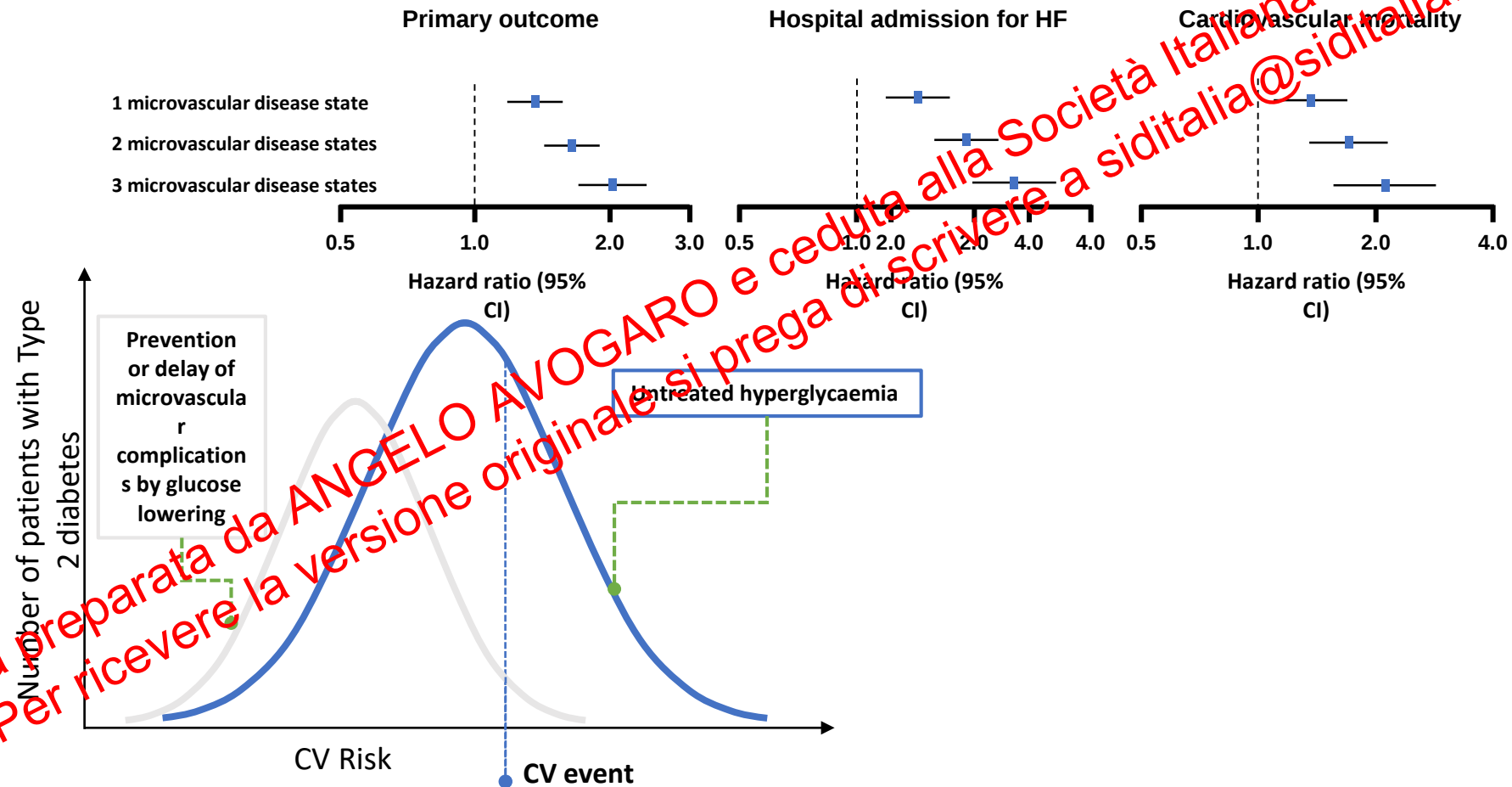
Microvascular complications



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

Prevention or delay of progression of microvascular complications may help reduce CV risks

The burden of microvascular disease is a determinant of **future CV risk**

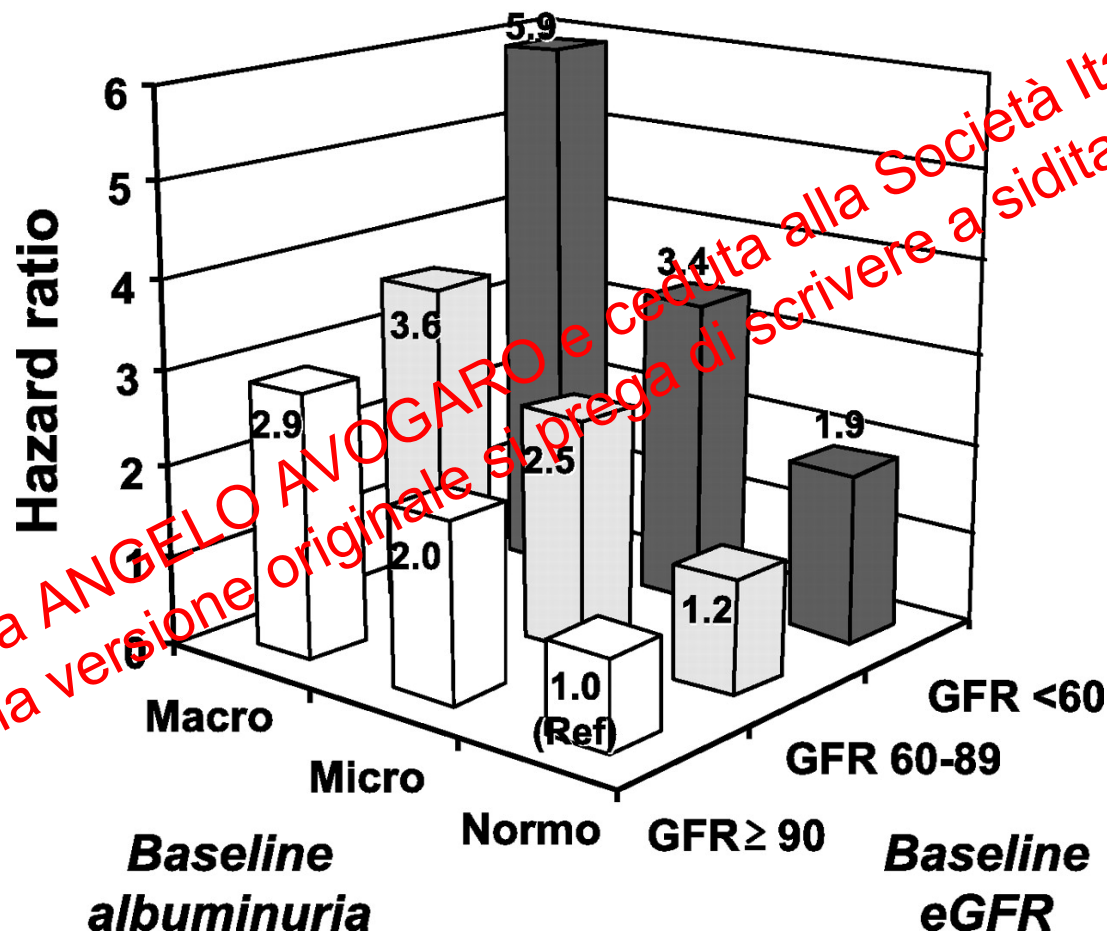


CV, cardiovascular; RCT, randomized control trial

1. Adapted from Brownrigg JR et al., Lancet Diabetes Endocrinol 2016;4:588–597

Combined effects of albuminuria and eGFR levels at baseline on the risk for adverse outcomes.

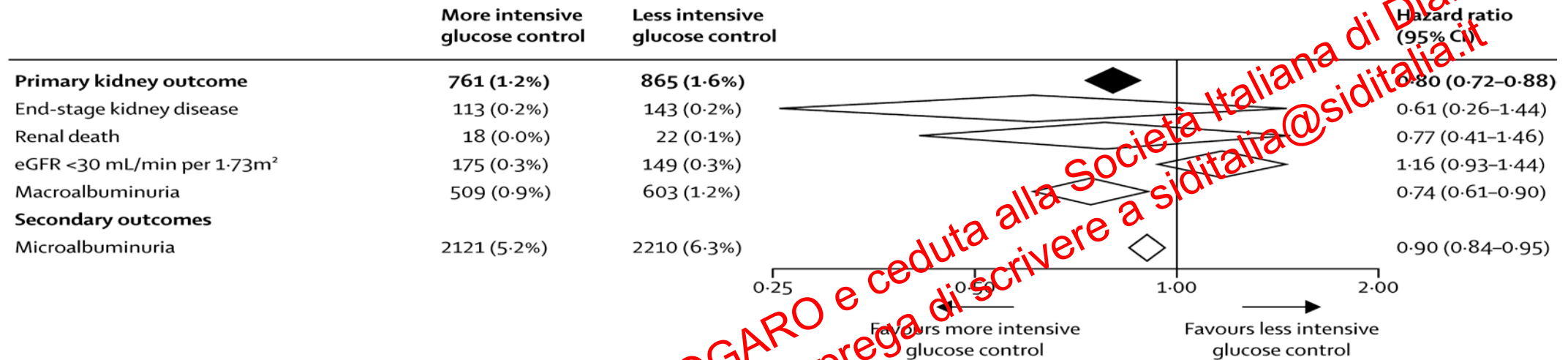
Cardiovascular death



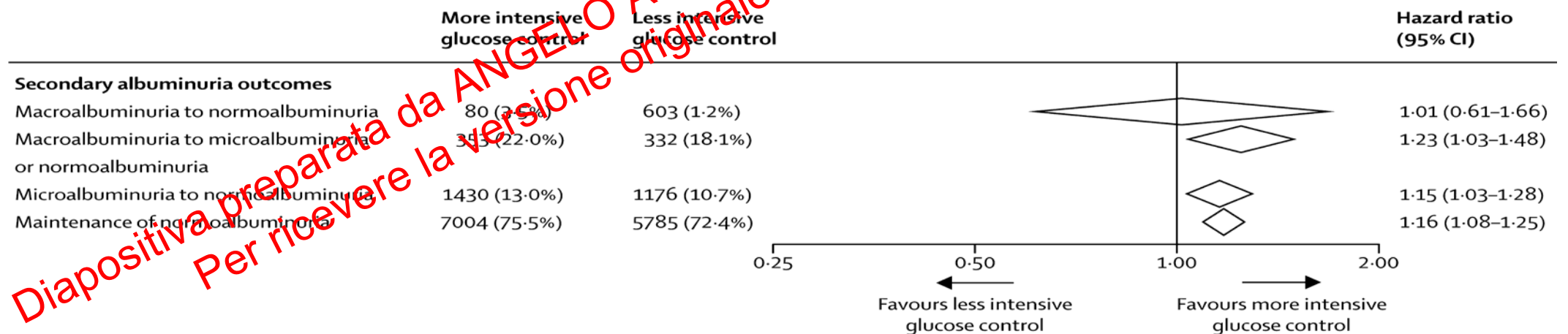
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Effect of intensive glucose control on (A) Primary kidney outcome, its components, and microalbuminuria. (B) Regression of albuminuria

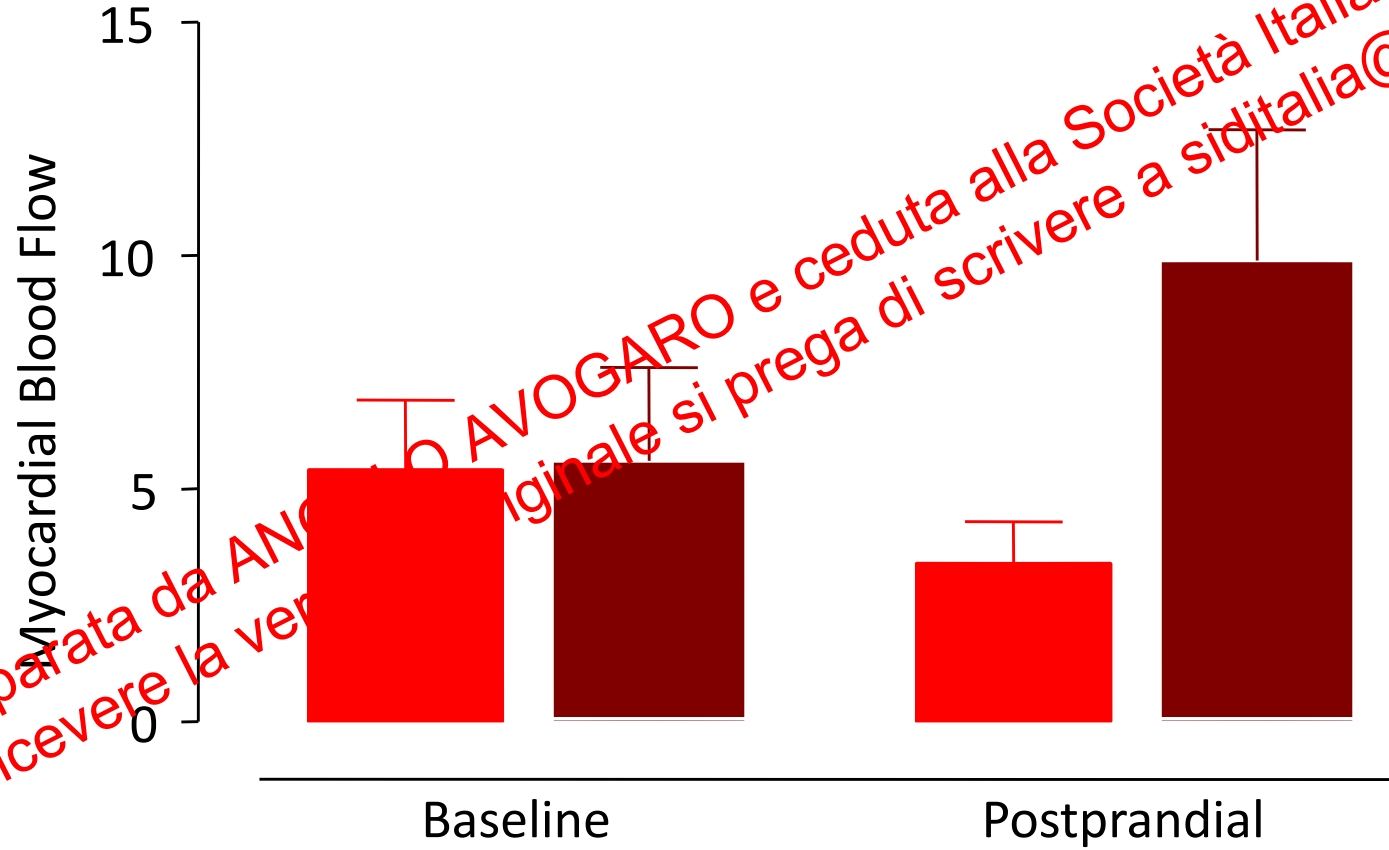
A



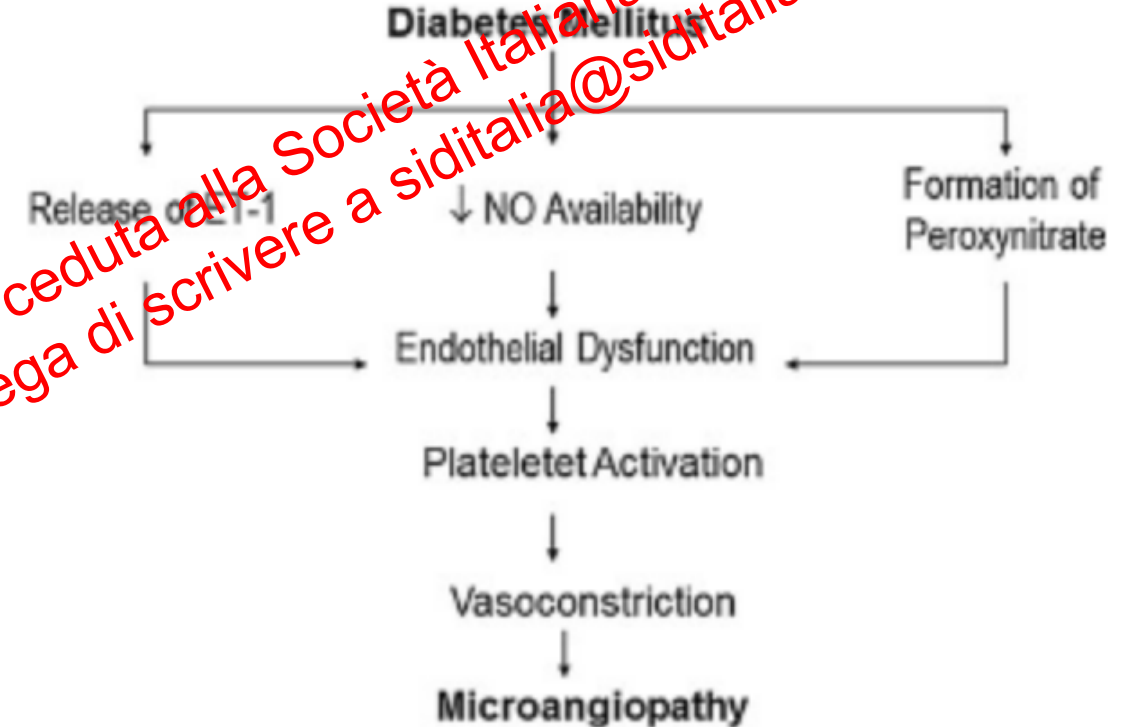
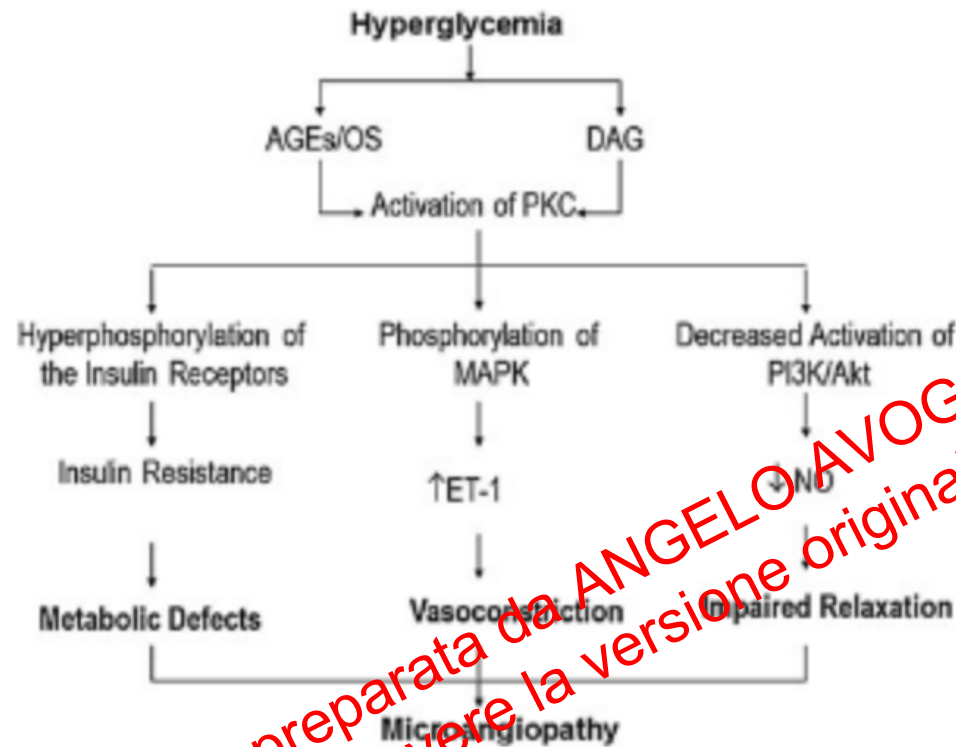
B



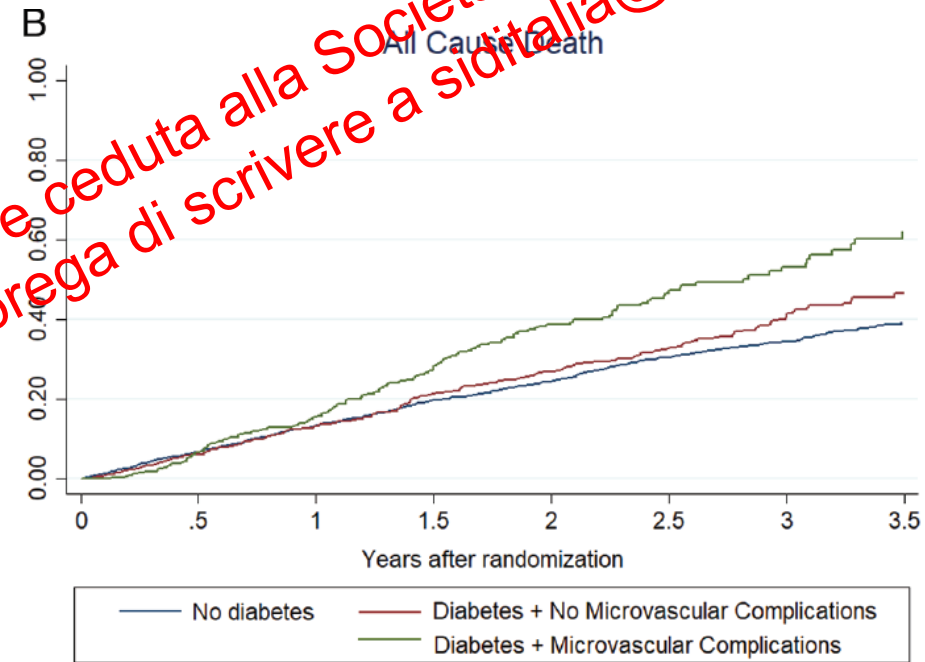
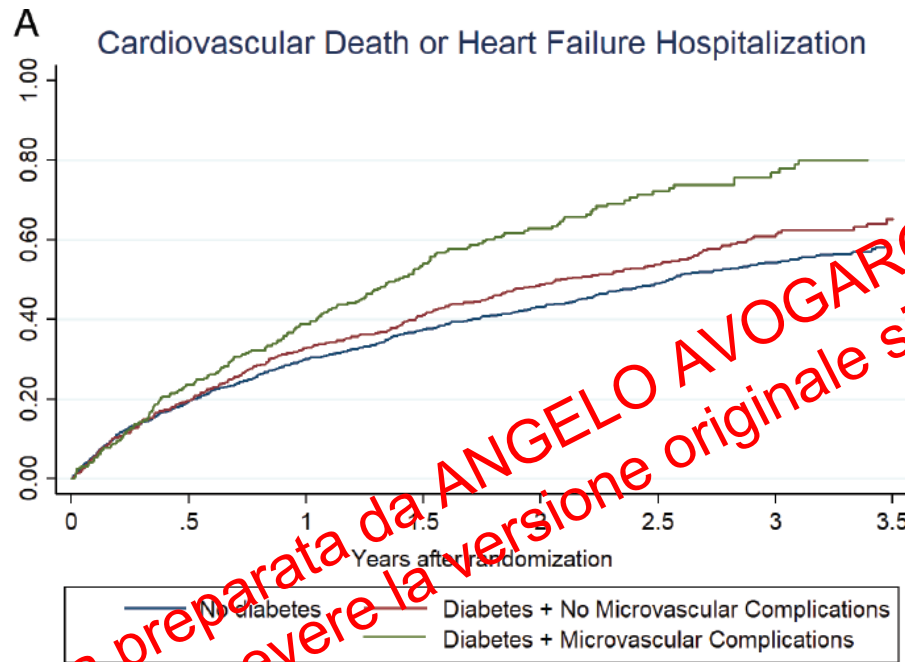
Postprandial Myocardial Perfusion is impaired in T2D patients without coronary heart disease



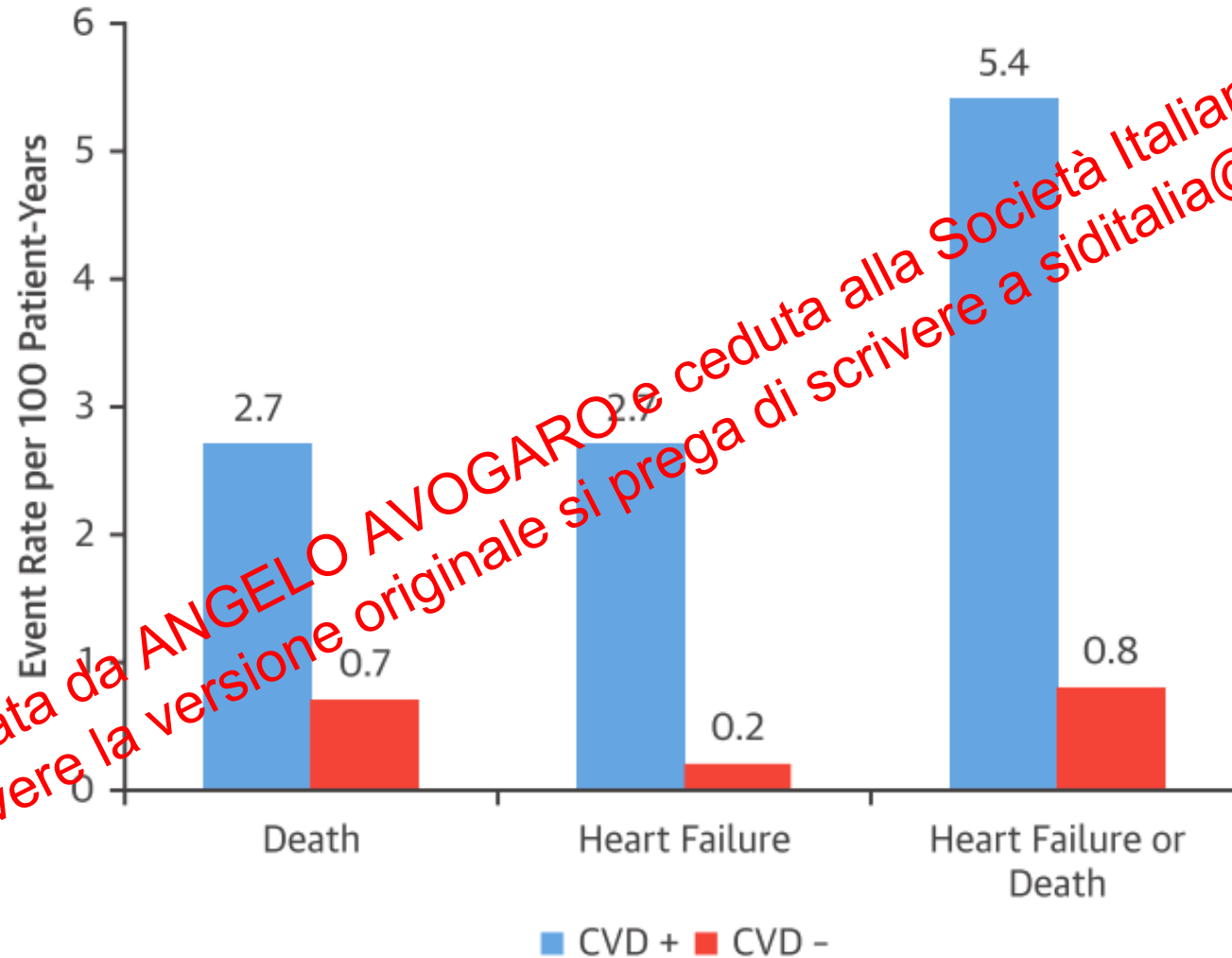
Linking endothelial dysfunction and microangiopathy



Cumulative incidence of cardiovascular death or heart failure hospitalization, and of all-cause death.



Event rates following initiation of GL therapies in patients with and without CVD



ITT cohort; $p < 0.001$ for all comparisons

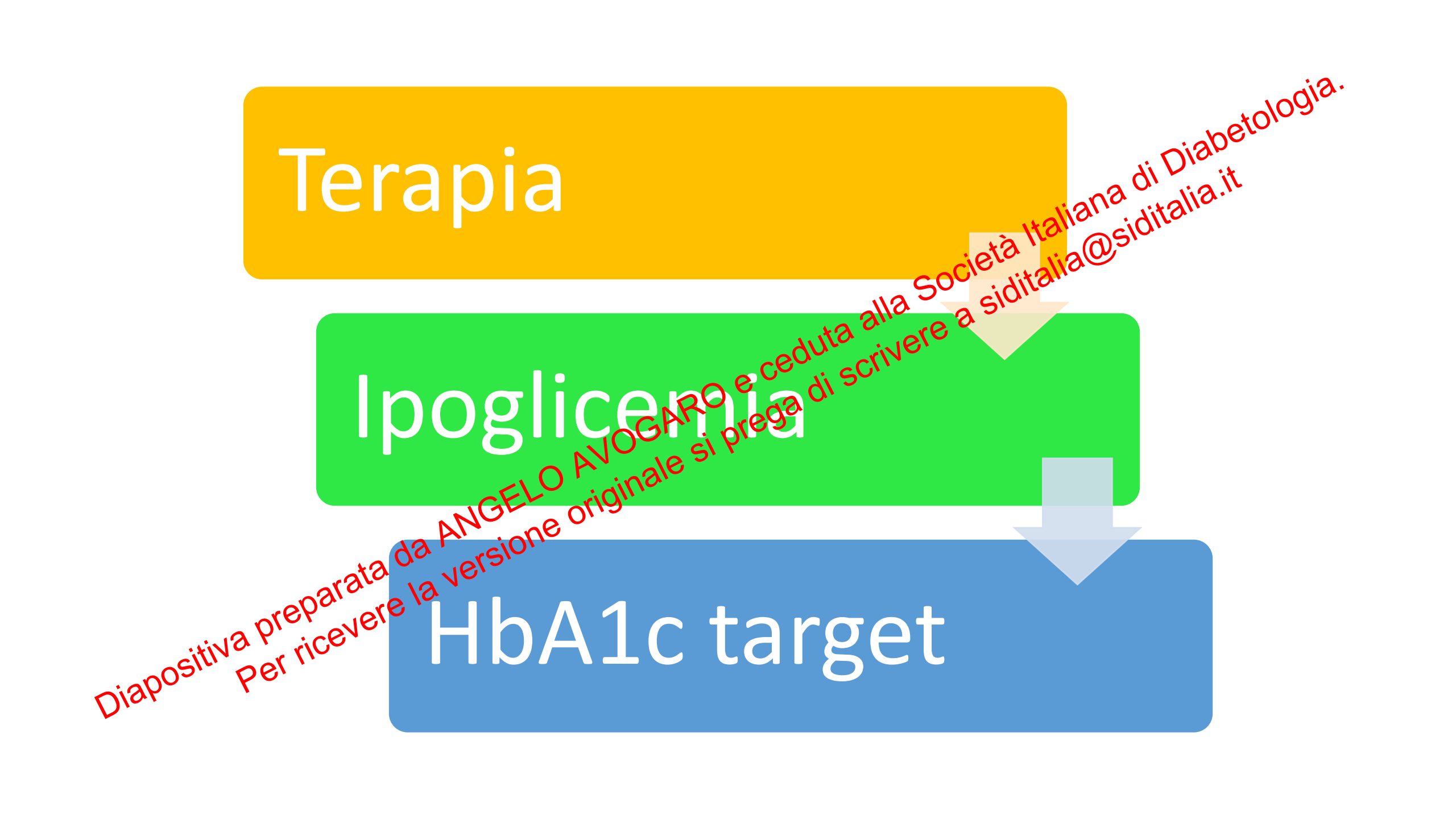
Cavender et al. JACC 2018

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

Terapia

Ipoglicemia

HbA1c target



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

Morbidity of Hypoglycaemia in Diabetes



Cardiovascular

Myocardial
ischaemia,
cardiac arrhythmias



Brain

Coma, seizures,
stroke,
cognitive impairment



Musculoskeletal

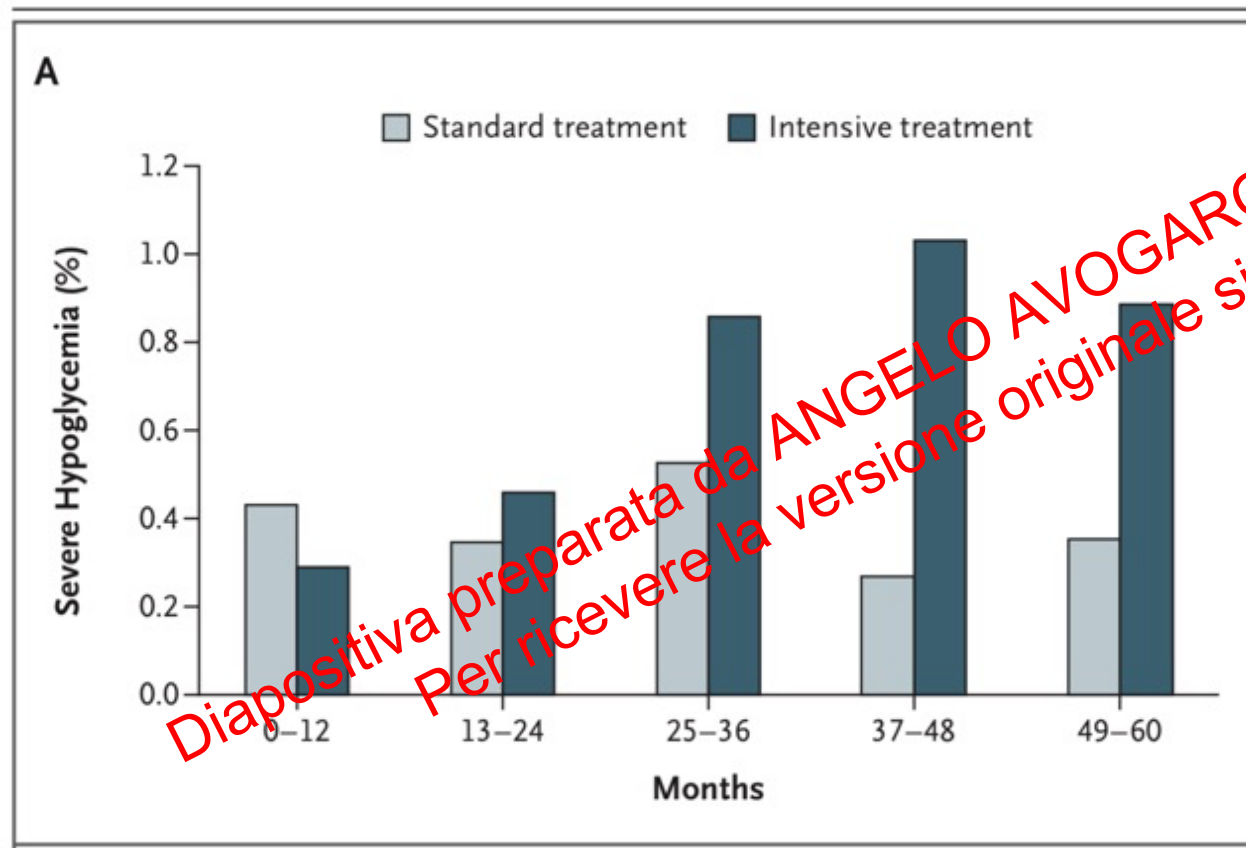
Falls, accidents,
fractures, dislocations,
driving mishaps

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

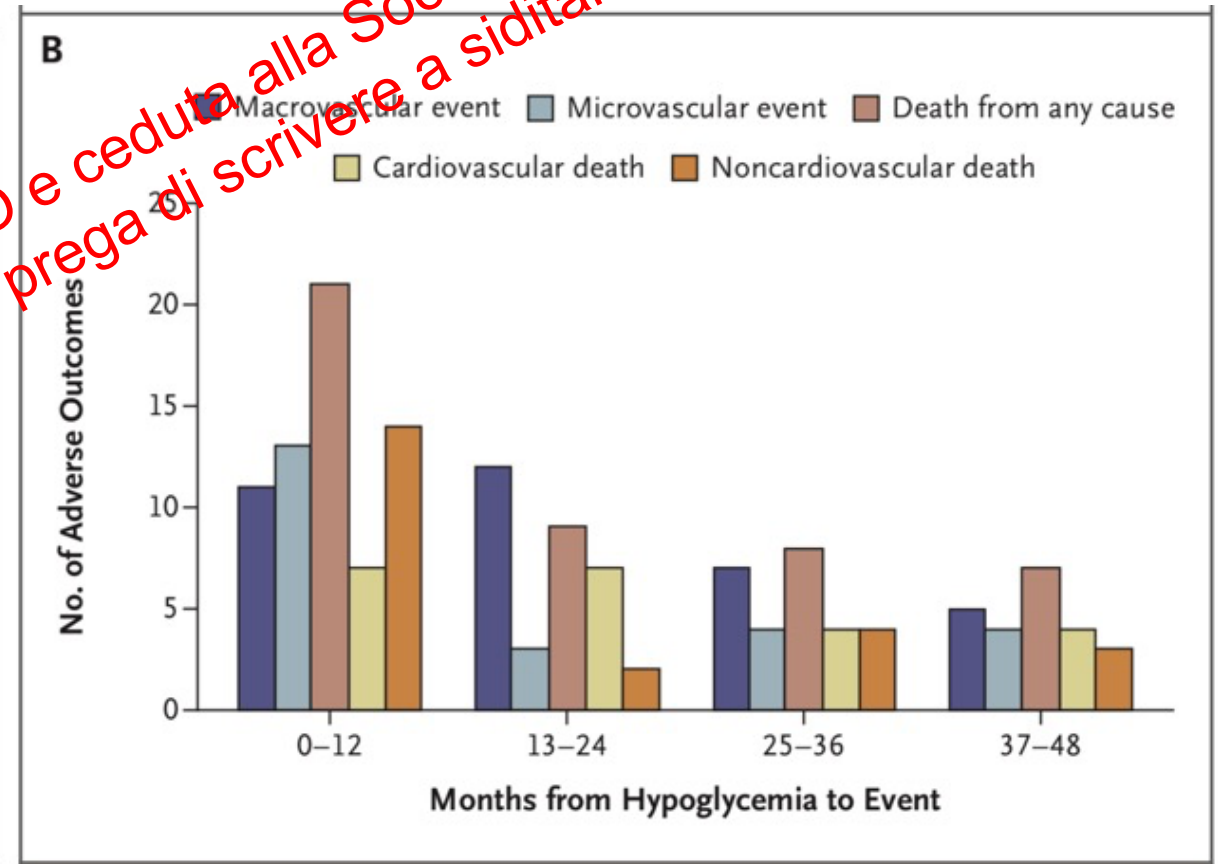
Severe Hypoglycemia and Risks of Vascular Events and Death

- 11,140 type 2 pts
- Follow up : 5 yrs
- ADVANCE Collaborative Group

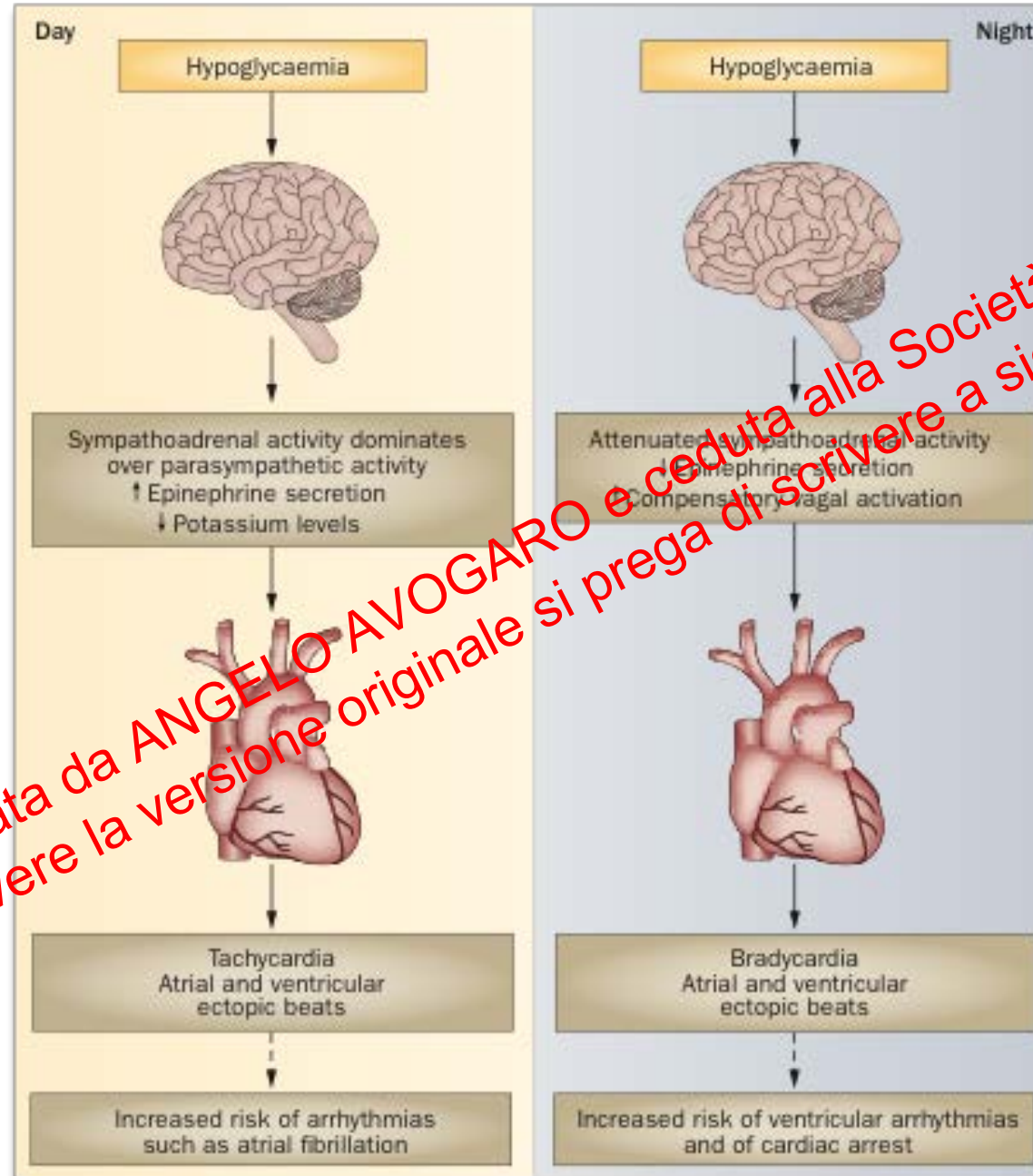
Annual rates of SH



Adverse Clinical Outcomes

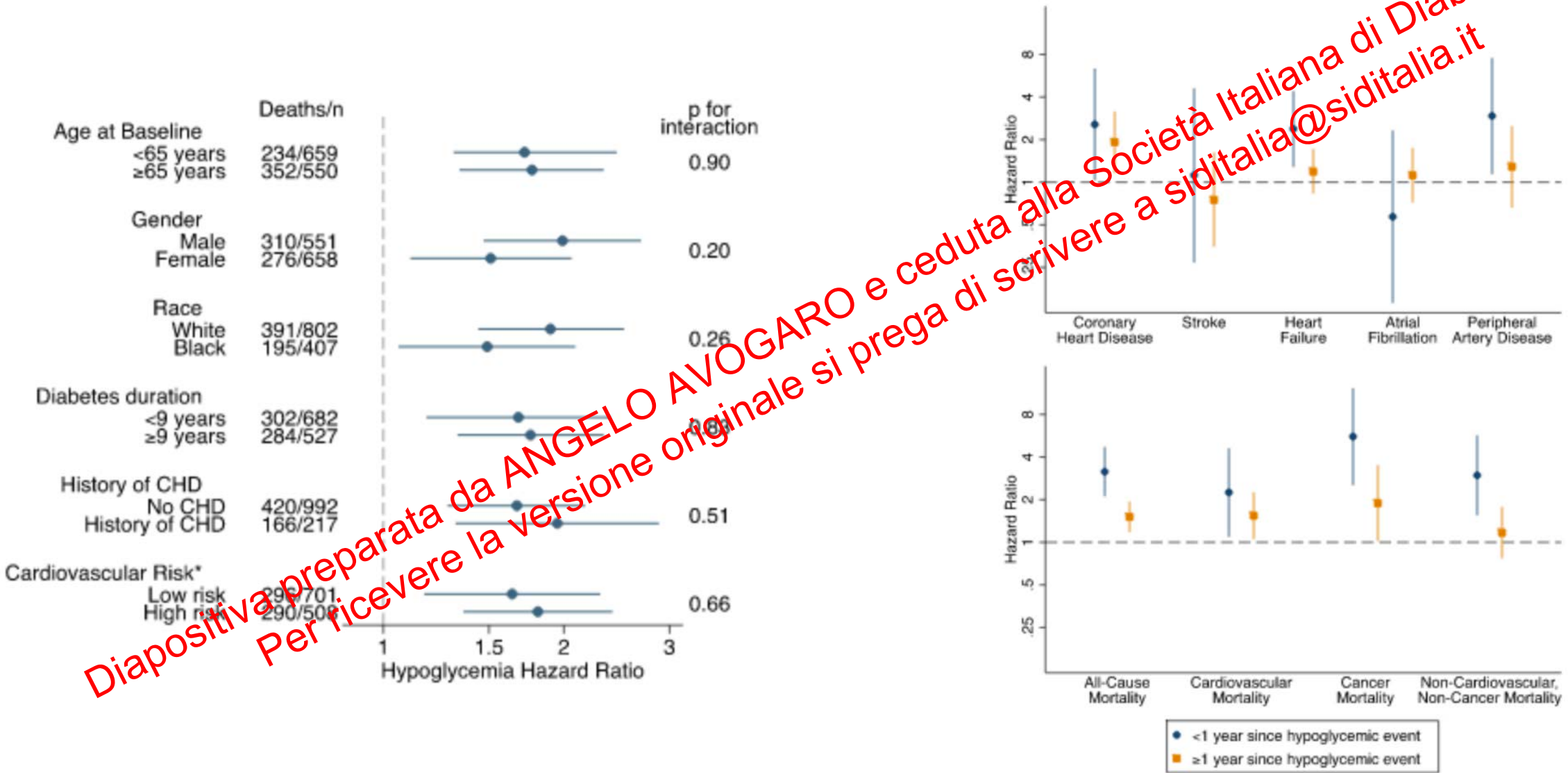


Hypoglycaemia: effects on cardiac activity



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

Severe hypoglycemia and incident CV mortality inpatients with Type 2 diabetes



Complications

CKD

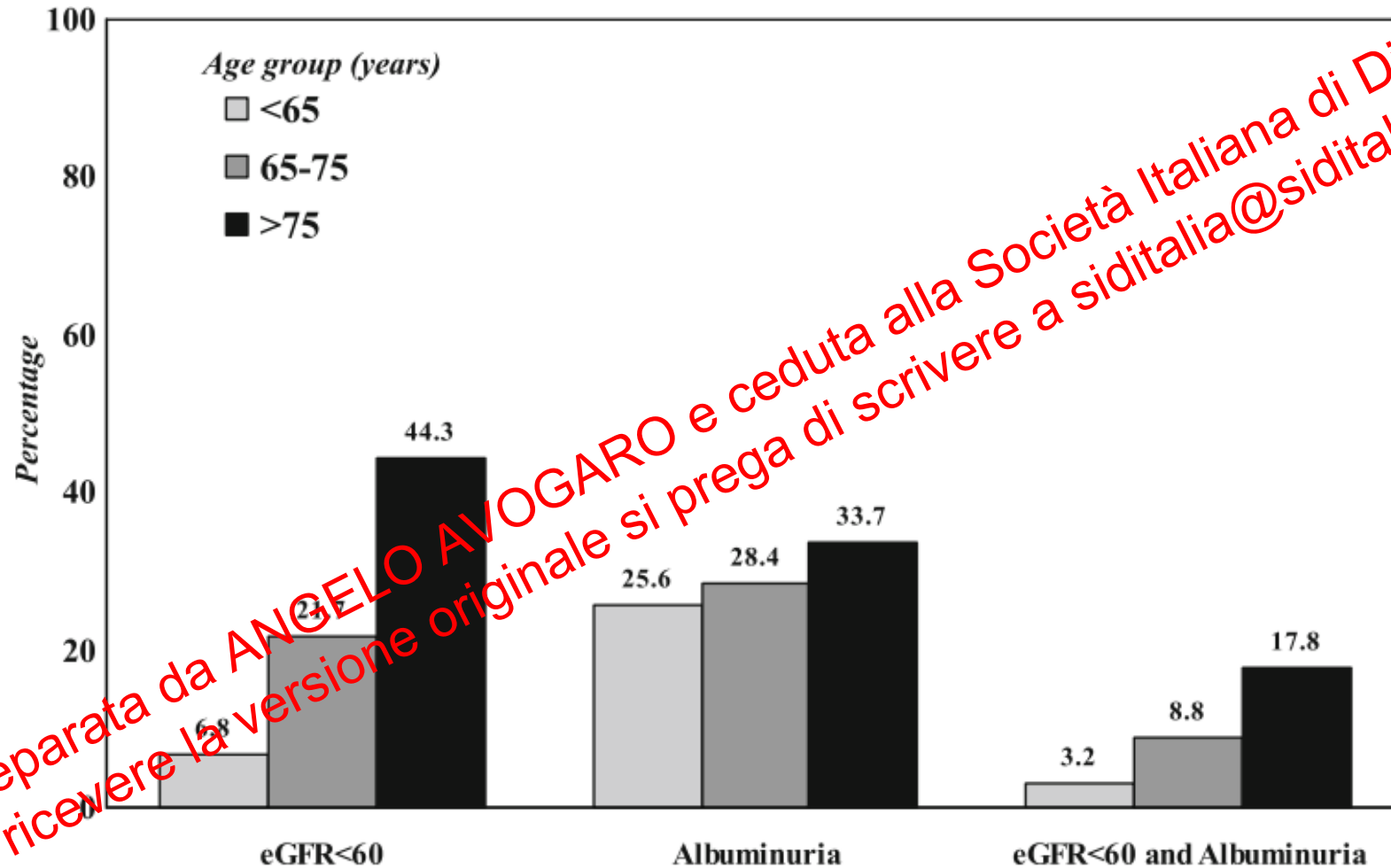
Ageing

Hypoglycemia

Comorbidities

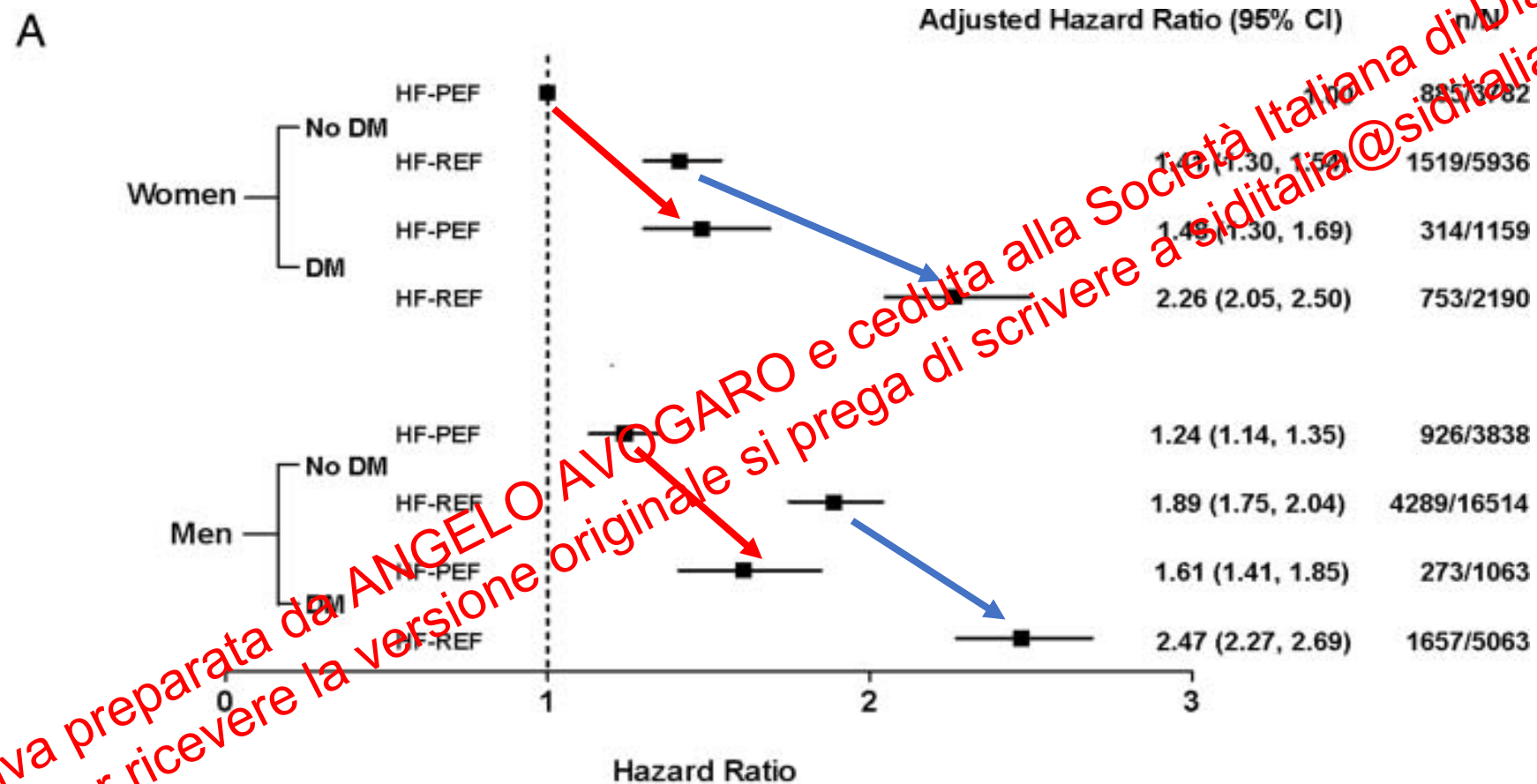
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Proportion of patients with eGFR < 60 mL/min/1.73 m² or albuminuria, by age groups



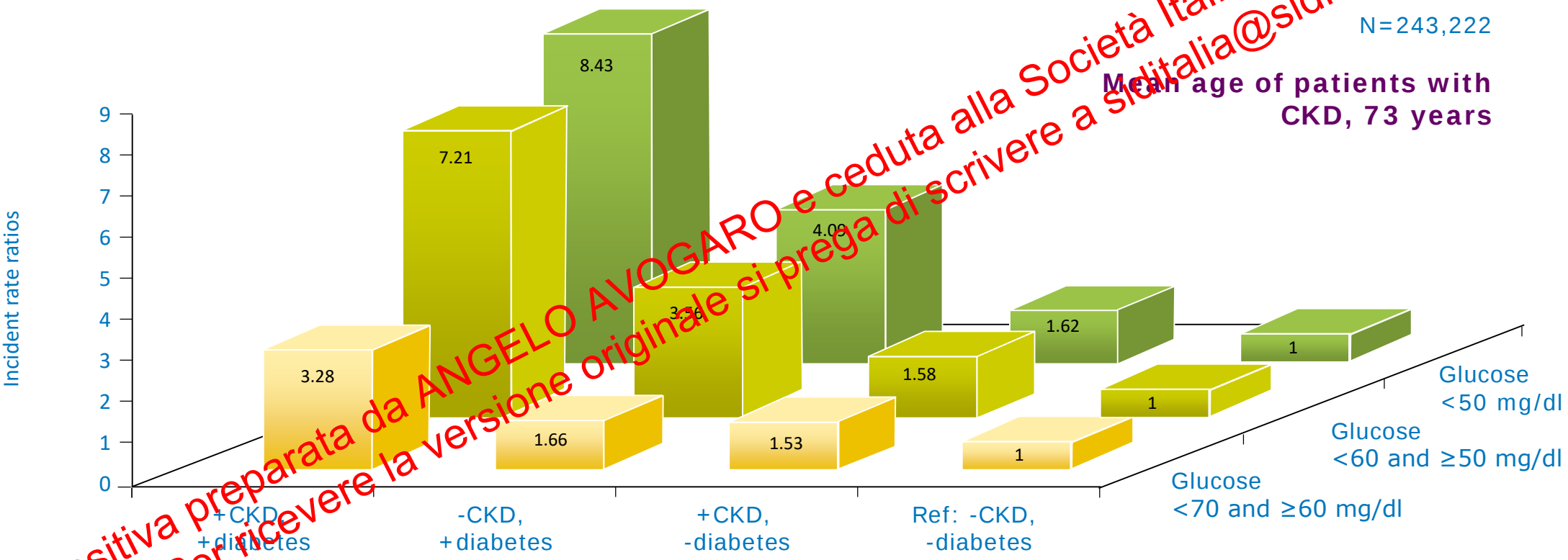
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Risk of death of heart failure patients by sex, diabetes mellitus, and ejection fraction group



Diabetes increases the risk of hypoglycaemia in patients with chronic kidney disease

Risk for hypoglycaemia of varying severity and adjusted incidence rate ratio classified by presence or absence of CKD and diabetes



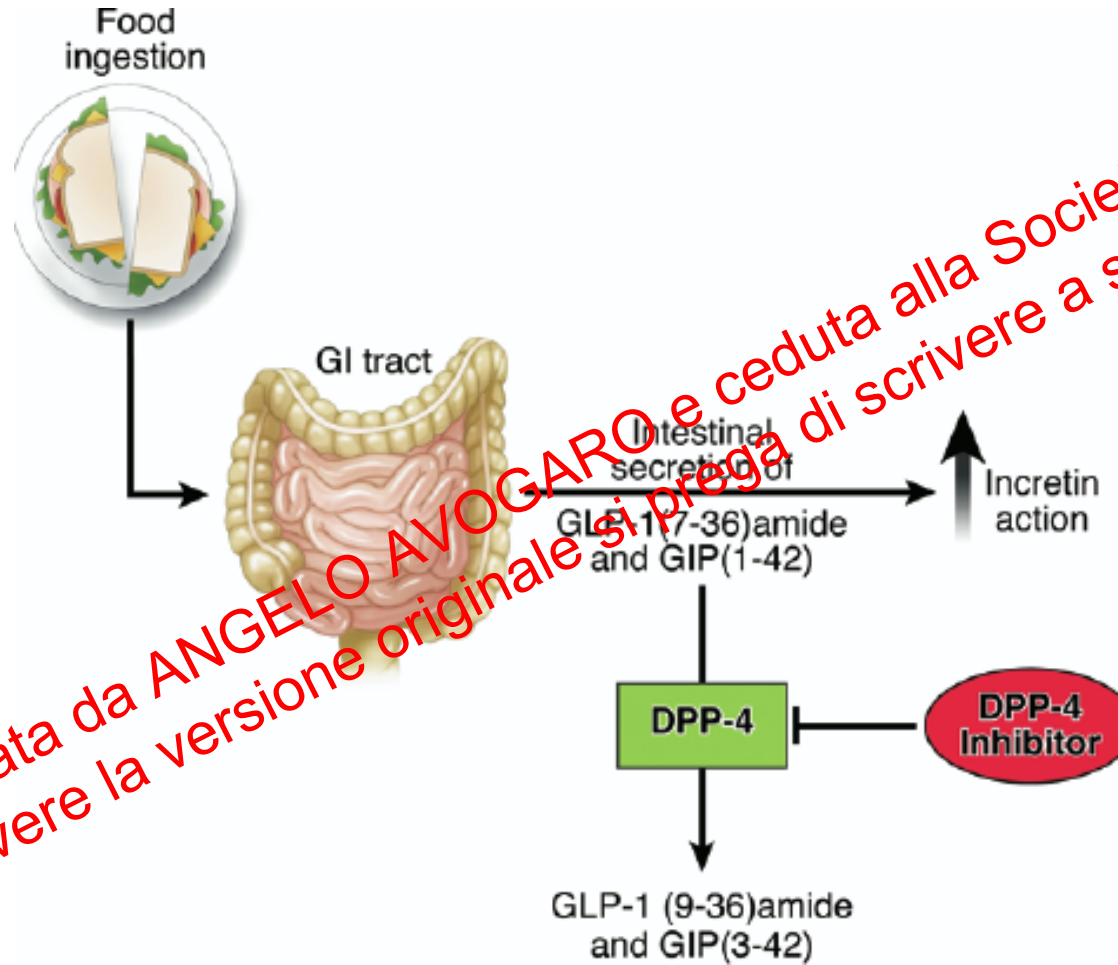
N=243,222

Mean age of patients with CKD, 73 years

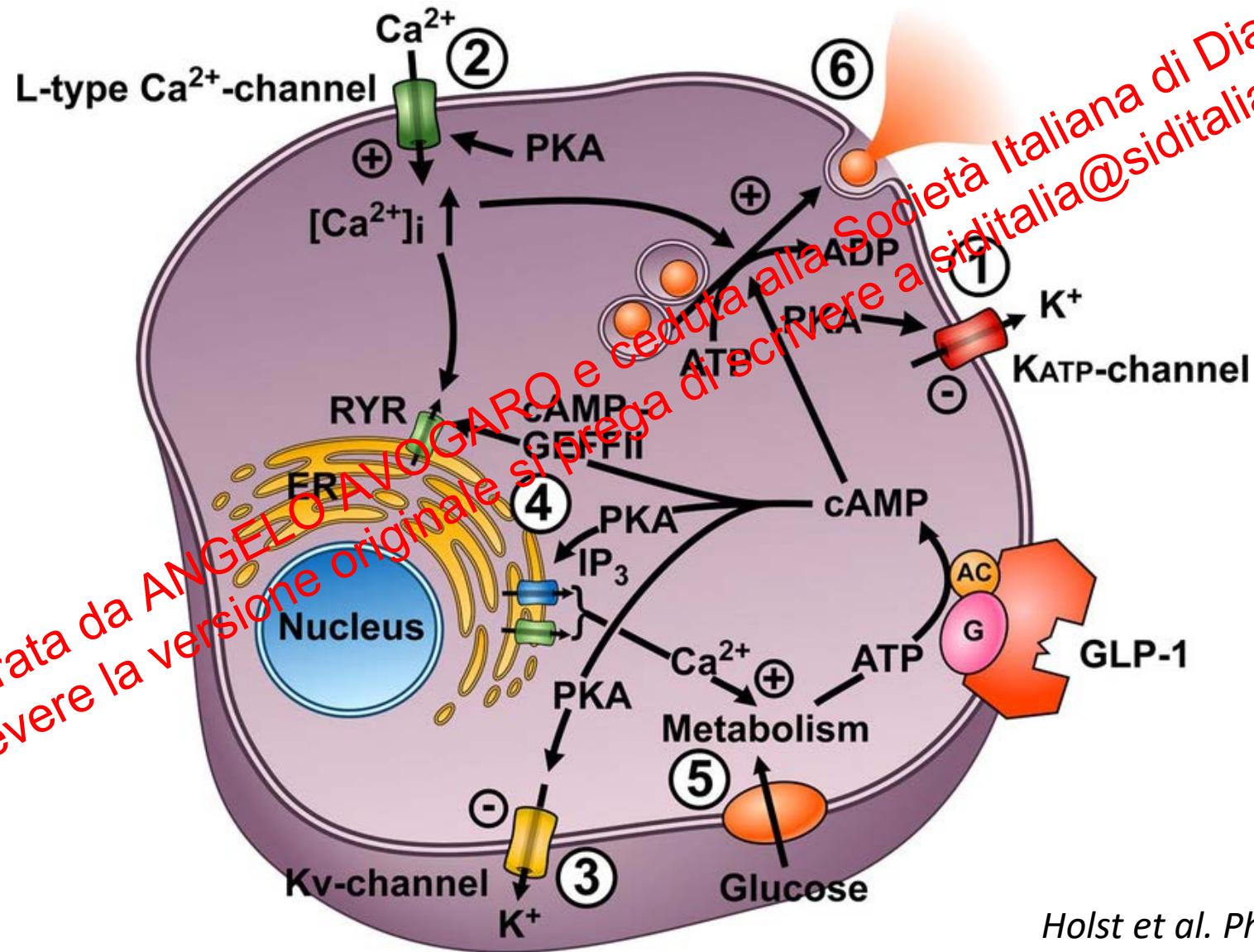
- Nei diabetici anziani gli obiettivi glicemici devono essere individualizzati in funzione del farmaco utilizzato ed il potenziale rischio di ipoglicemia.
- In caso di utilizzo di farmaci a basso rischio di ipoglicemia (metformina, DPP4 inibitori, pioglitazone, SGLT-2 inibitori, agonisti del recettore del GLP-1 ed acarbosio o loro combinazioni) l'obiettivo di HbA1c è $< 7,0\%$ (< 53 mmol/mol).

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

The Biology of Incretins



GLP-1 & Insulin secretion



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

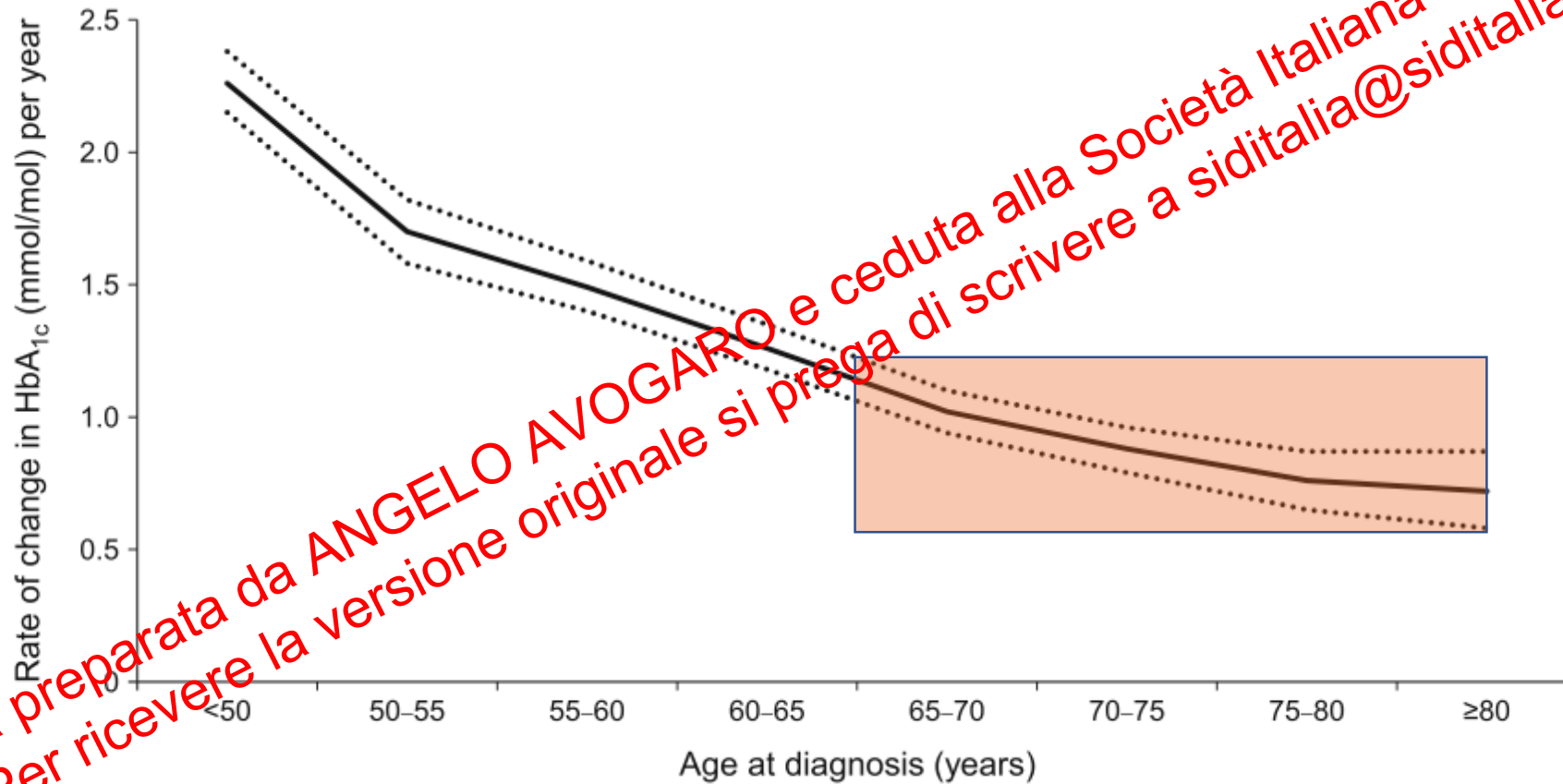
Long-term DPP-4 inhibitor efficacy in renal impairment: A systematic review



Included moderate, severe and ESRD patients
DPP-4, dipeptidyl peptidase-4; ESRD, end stage renal disease; HbA1c, glycosylated haemoglobin; LINA, linagliptin; PBO, placebo, SAXA, saxagliptin, SITA, sitagliptin; VILDA, vildagliptin

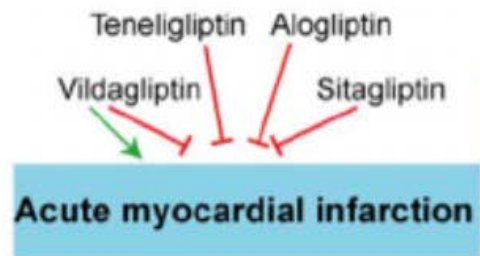
Adapted from: Thomas MC et al. Systematic literature review of clinical trials of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes and renal impairment. Diabetes Therapy 2016

Mean rate of glycaemic deterioration (increase in adjusted HbA_{1c} per year characterised in mmol/mol units), by age at diagnosis.



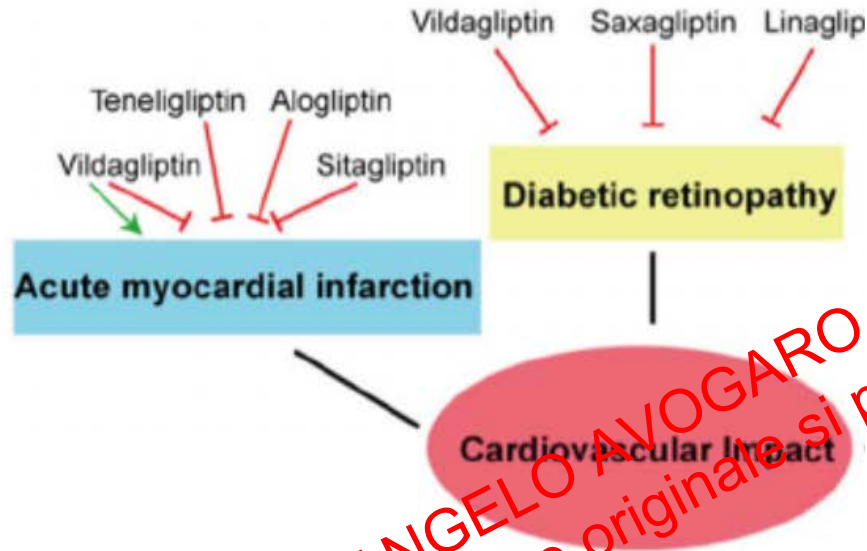
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

The proposed cardiovascular impact of DPP-4 inhibitors beyond glucose control



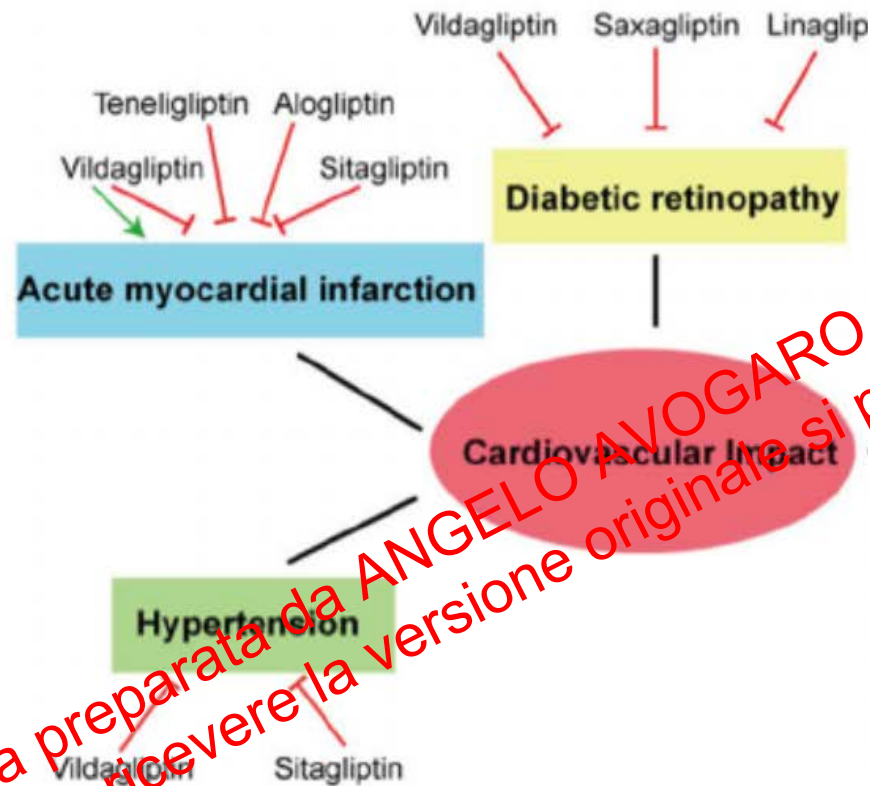
Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

The proposed cardiovascular impact of DPP-4 inhibitors beyond glucose control

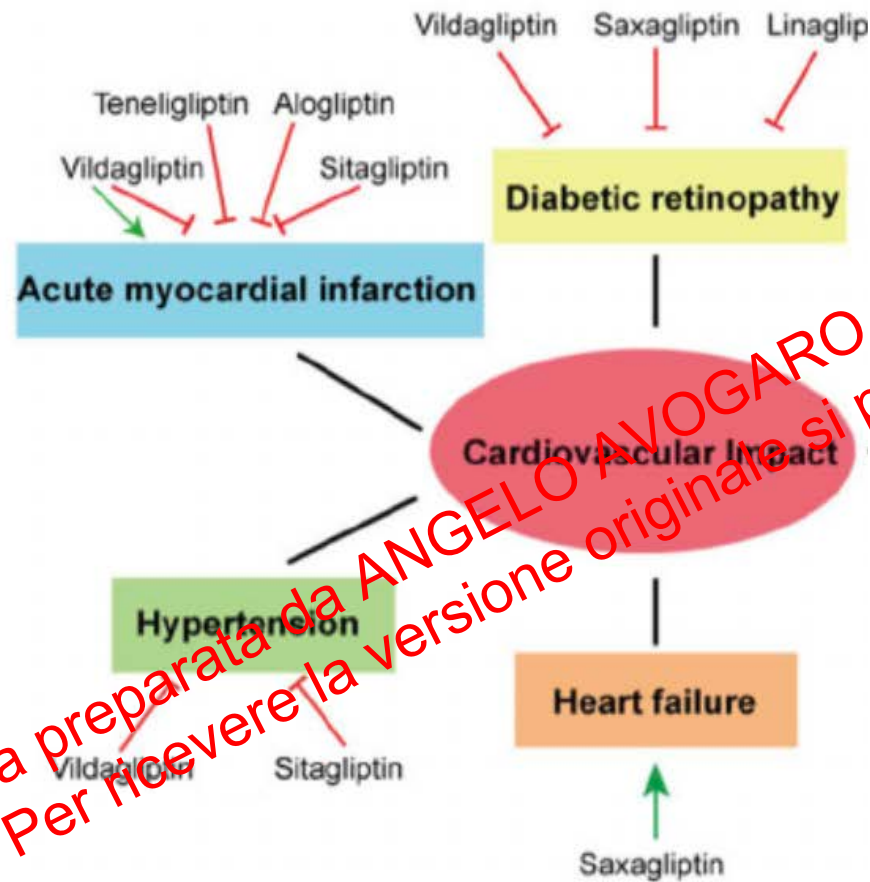


Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

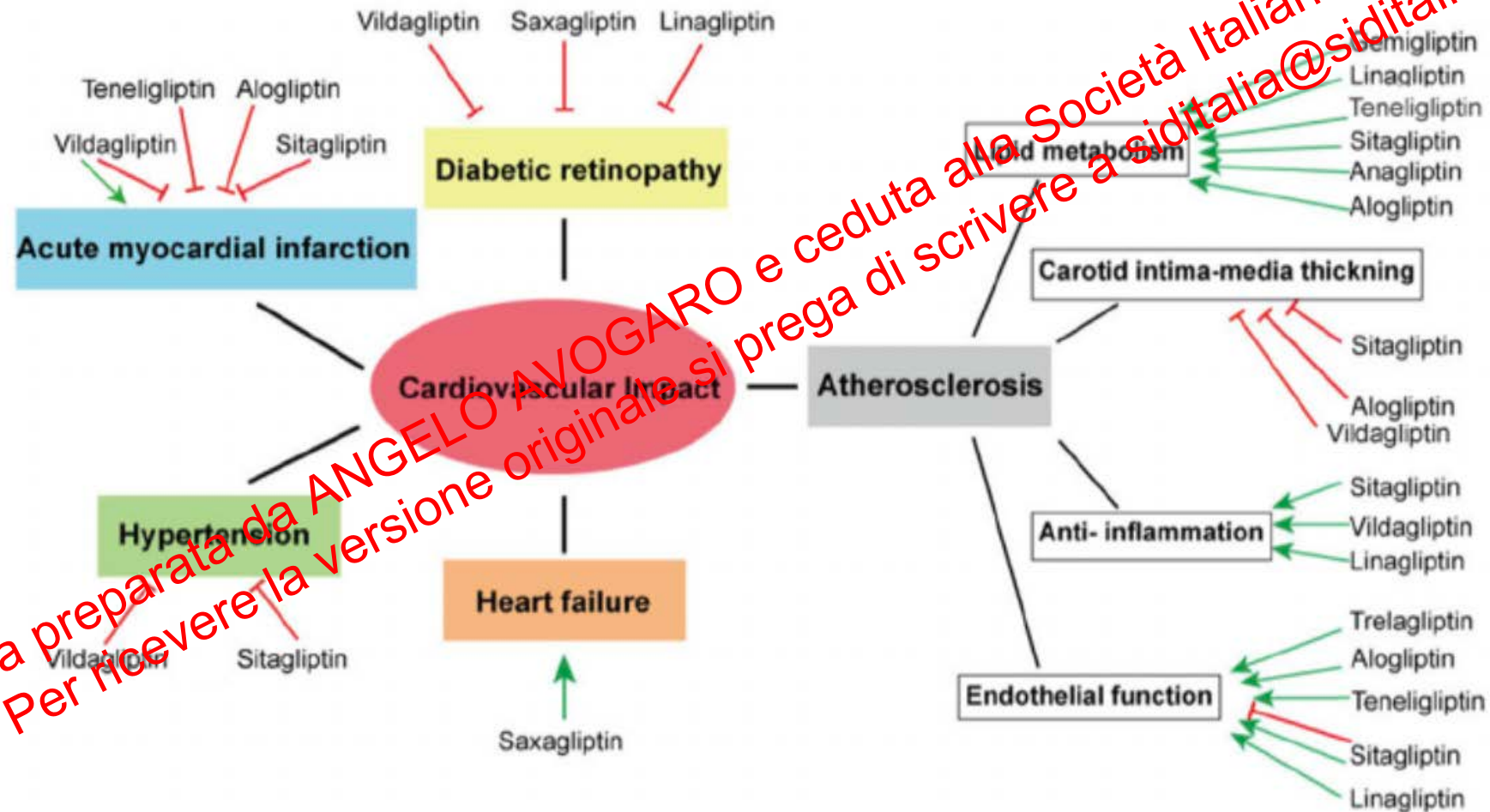
The proposed cardiovascular impact of DPP-4 inhibitors beyond glucose control



The proposed cardiovascular impact of DPP-4 inhibitors beyond glucose control



The proposed cardiovascular impact of DPP-4 inhibitors beyond glucose control



Cardiovascular outcome trials for DPP4 Inhibitors

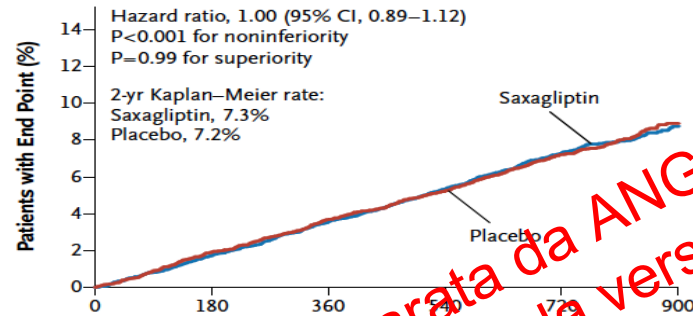
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederick, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. Udell, M.D., M.P.H., Nihar R. Desai, M.D., M.P.H., Ofri Mosenzon, M.D., Darren K. McGuire, M.D., Kausik K. Ray, M.D., Lawrence A. Leiter, M.D., and Itamar Raz, M.D., for the SAVOR-TIMI 53 Steering Committee and Investigators*

A Primary End Point

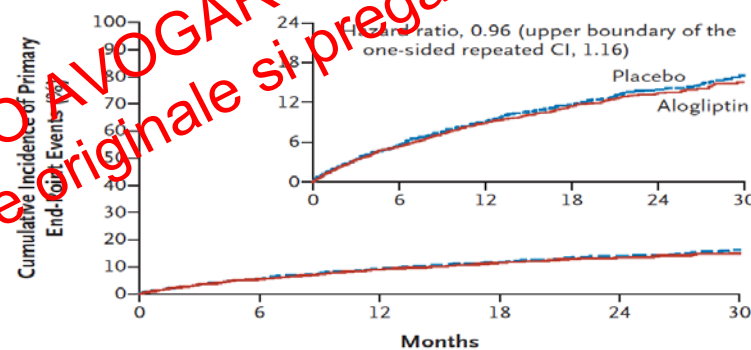


No. at Risk	0	180	360	540	720	900
Placebo	8212	7983	7761	7557	4855	851
Saxagliptin	8280	8011	7836	7613	4920	847

ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*



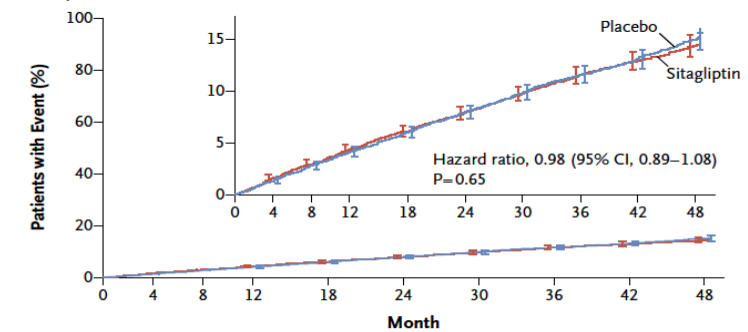
No. at Risk	0	6	12	18	24	30
Placebo	2679	2299	1891	1375	805	286
Alogliptin	2701	2316	1899	1394	821	296

ORIGINAL ARTICLE

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Amir B. Cosentino, M.D., M. Angelyn Bethel, M.D., Paul W. Armstrong, M.D., John A. Ezekowitz, M.D., Ph.D., Samuel S. Engel, M.D., Jyotsna Garg, M.S., Robert A. Josse, M.B., B.S., Keith D. Kaufman, M.D., Joerg Koglin, M.D., Peter Korn, M.D., John M. Lachin, Sc.D., Darren K. McGuire, M.D., M.H.Sc., Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.D., Peter P. Stein, M.D., Shailaja Suryawanshi, Ph.D., Frans Van de Werf, M.D., Ph.D., Eric D. Peterson, M.D., M.P.H., and Rury R. Holman, M.B., Ch.B., for the TECOS Study Group*

A Primary Cardiovascular Outcome



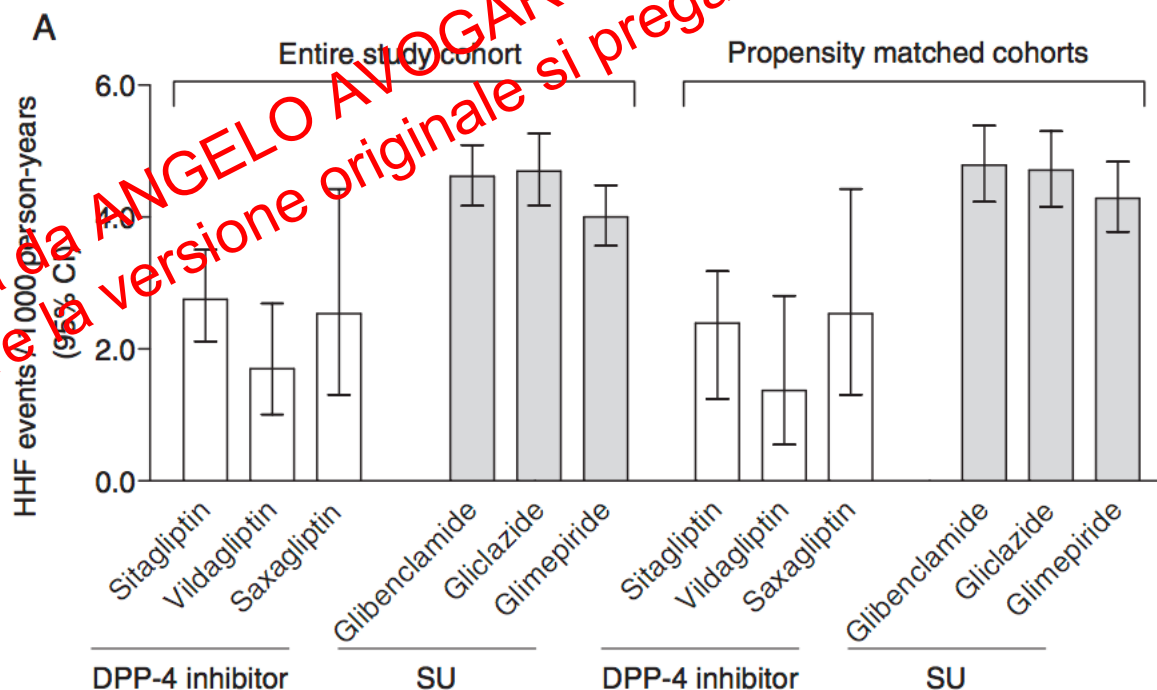
No. at Risk	0	4	8	12	16	20	24	28	32	36	40	44	48
Sitagliptin	7332	7131	6937	6777	6579	6386	4525	3346	2058	1248			
Placebo	7339	7146	6902	6751	6512	6292	4411	3272	2034	1234			

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

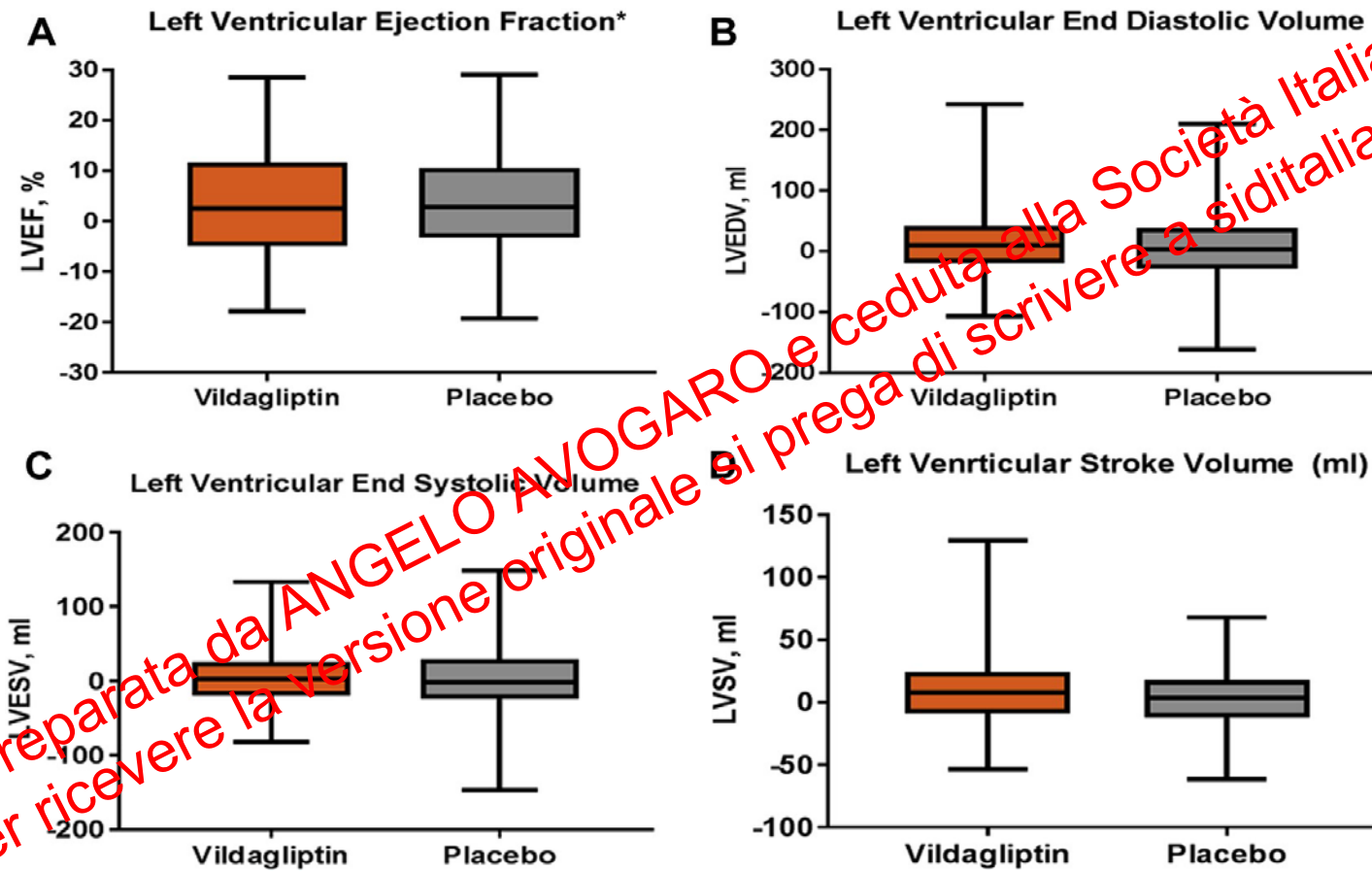
ORIGINAL ARTICLE

Intraclass differences in the risk of hospitalization for heart failure among patients with type 2 diabetes initiating a dipeptidyl peptidase-4 inhibitor or a sulphonylurea: Results from the OsMed Health-DB registry

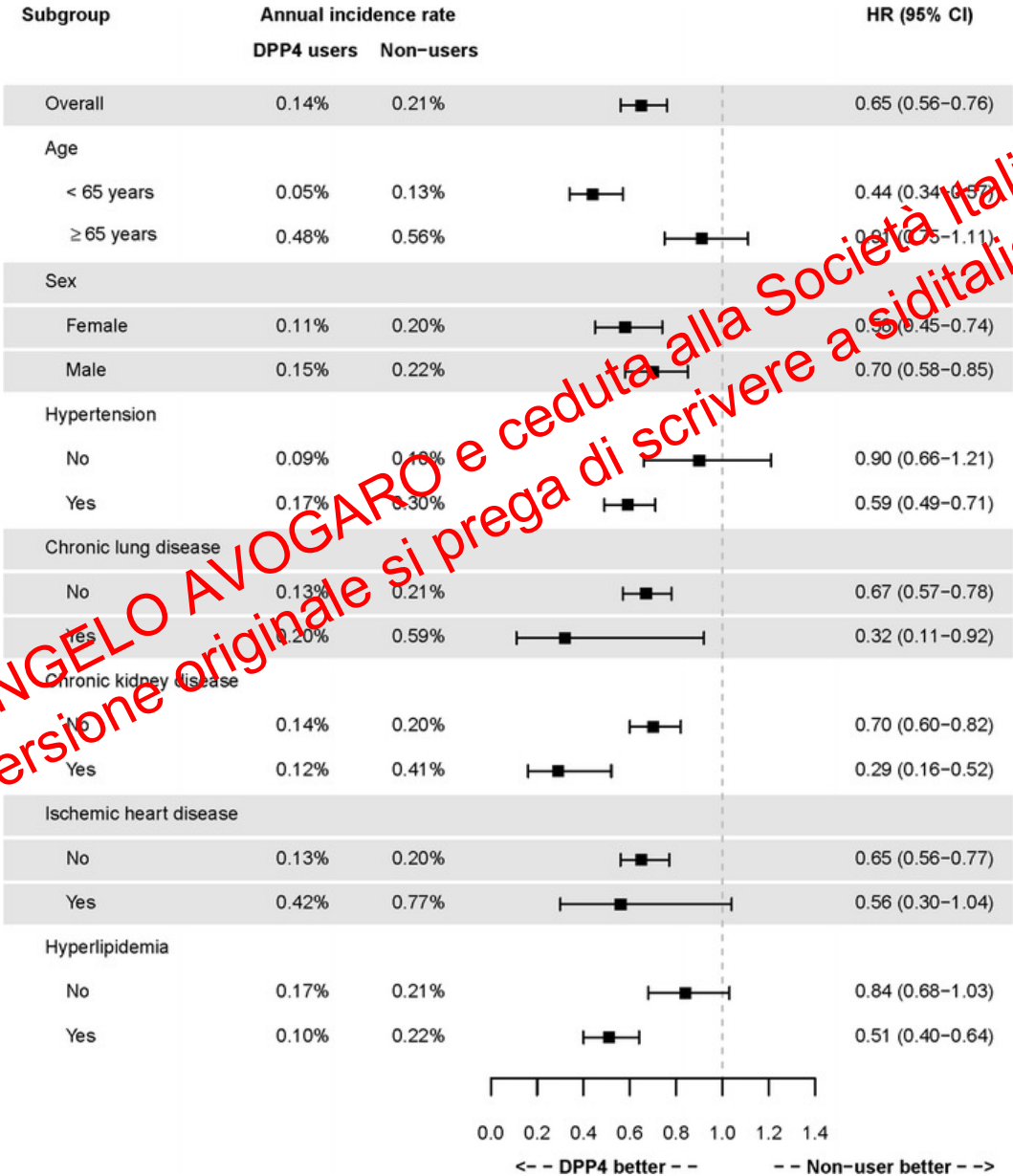
Gian Paolo Fadini MD, PhD^{1†} | Stefania Saragoni PhD^{3†} | Pierluigi Russo MD² | Luca Degli Esposti PhD³ | Saula Vigili de Kreutzenberg MD, PhD⁴ | Mario Melazzini MD² | Angelo Avogaro MD, PhD¹ | on behalf of the OsMed Health DB Network[‡]



Change From Baseline in LVEF (Primary Endpoint) and Other Echocardiographic Measurements



New onset AF and DPP-4 Inhibitors

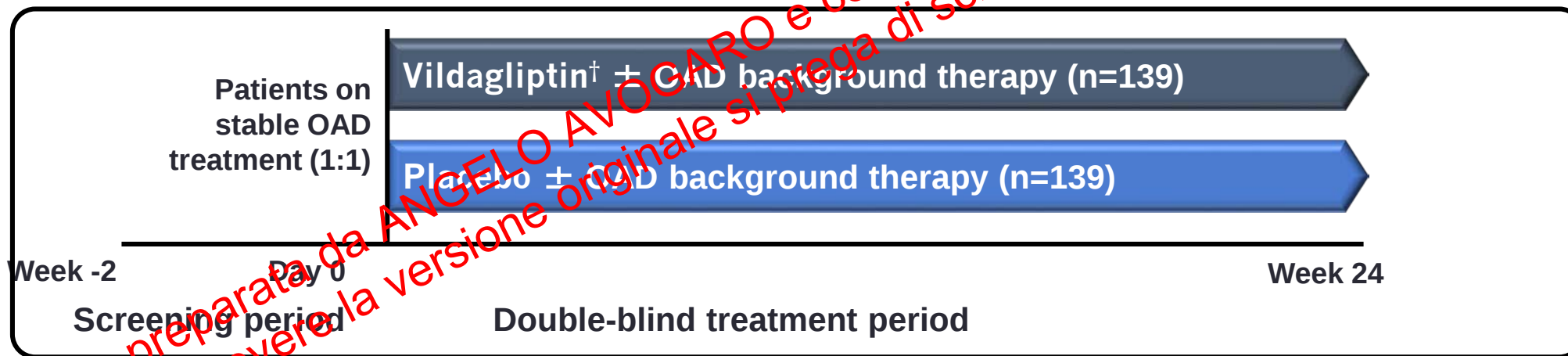


Diapositiva preparata da ANGELO AVOGARO e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

INTERVAL: randomised study with individualised treatment targets

- **INTERVAL:** Individualised Treatment targets for Elderly patients with type 2 diabetes using Vildagliptin Add-on or Lone therapy

- With unique per-patient, investigator-defined HbA_{1c} targets, based on clinical judgement



Strain et al. Lancet 2013

*Patients with T2DM, ≥70 years old; [†]Patients who were drug-naïve or on other background OAD therapy received vildagliptin (50 mg) twice daily; patients on sulphonylurea monotherapy received vildagliptin (50 mg) once daily; [‡]Vildagliptin is indicated as monotherapy in patients inadequately controlled by diet and exercise alone, and for whom metformin is inappropriate due to contraindications or intolerance²
OAD = oral antidiabetic agent

The Elderly Patient

Individualised treatment targets for elderly patients with type 2 diabetes using Vildagliptin add-on or lone therapy (INTERVAL)

A 24 week, randomised, double-blind, placebo-controlled study

278 pts >70 aa HbA1c 7-10%

Individualized HbA1c end-point:

- Placebo 27%
- Vildagliptin 53%

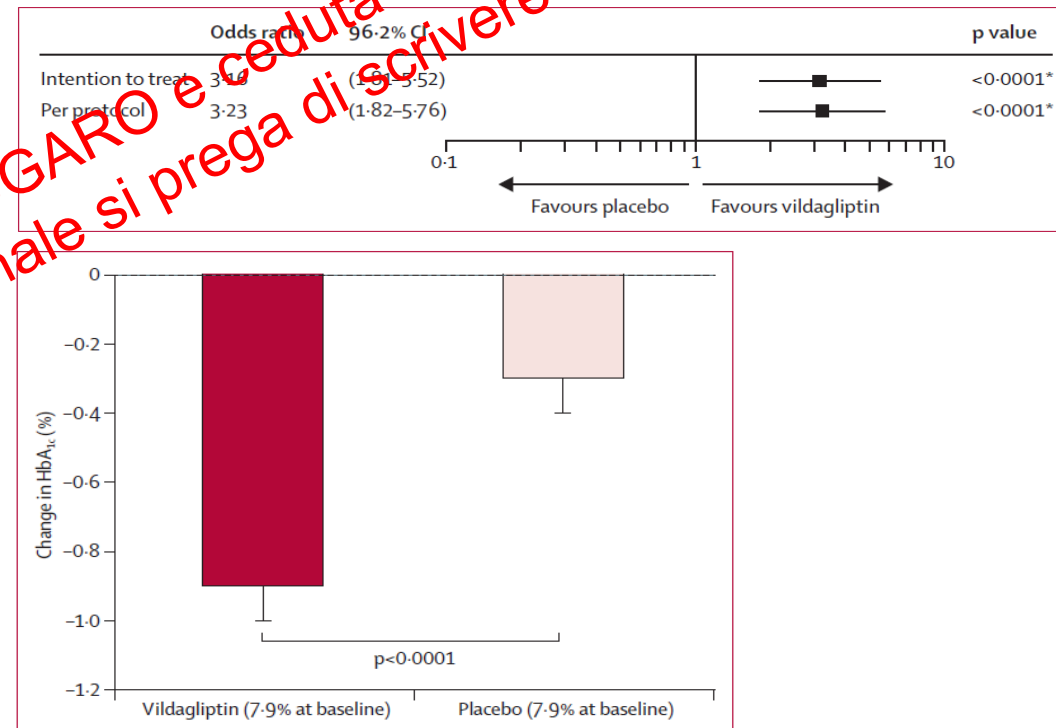
$p < 0.0001$

HbA1c reduction

- Placebo -0.3%
- Vildagliptin -0.9%

Delta 0.6% ($p < 0.0001$)

Strain et al. Lancet 2013



Cardiovascular outcome trials with DPP4 inhibitors, GLP1 receptor agonists, and SGLT2 inhibitors: primary endpoints

Saxagliptin (SAVOR TIMI 53)

HR = 1.00
(95% CI: 0.89-1.12)

Alogliptin (EXAMINE)

HR = 0.96
(one-side CI: 1.16)

Sitagliptin (TECOS)

HR = 0.98
(95% CI: 0.88-1.09)

Lixisenatide (ELIXA)

HR = 1.02
(95% CI: 0.89-1.17)

Liraglutide (LEADER)

HR = 0.87
(95% CI: 0.78-0.97)

Semaglutide (SUSTAIN-6)

HR = 0.74
(95% CI: 0.58-0.95)

Exenatide (EXSCEL)

HR = 0.91
(95% CI: 0.83-1.00)

Empagliflozin

(EMPA-REG Outcome)

HR = 0.86
(95% CI: 0.74-0.99)

Canagliflozin

(CANVAS-program)

HR = 0.86
(95% CI: 0.75-0.97)

0.10 0.40 0.70 1.00 1.30

HR (95% CI)

0.10 0.40 0.70 1.00 1.30

HR (95% CI)

0.10 0.40 0.70 1.00 1.30

HR (95% CI)

DIABETES TYPE 2

HEART FAILURE

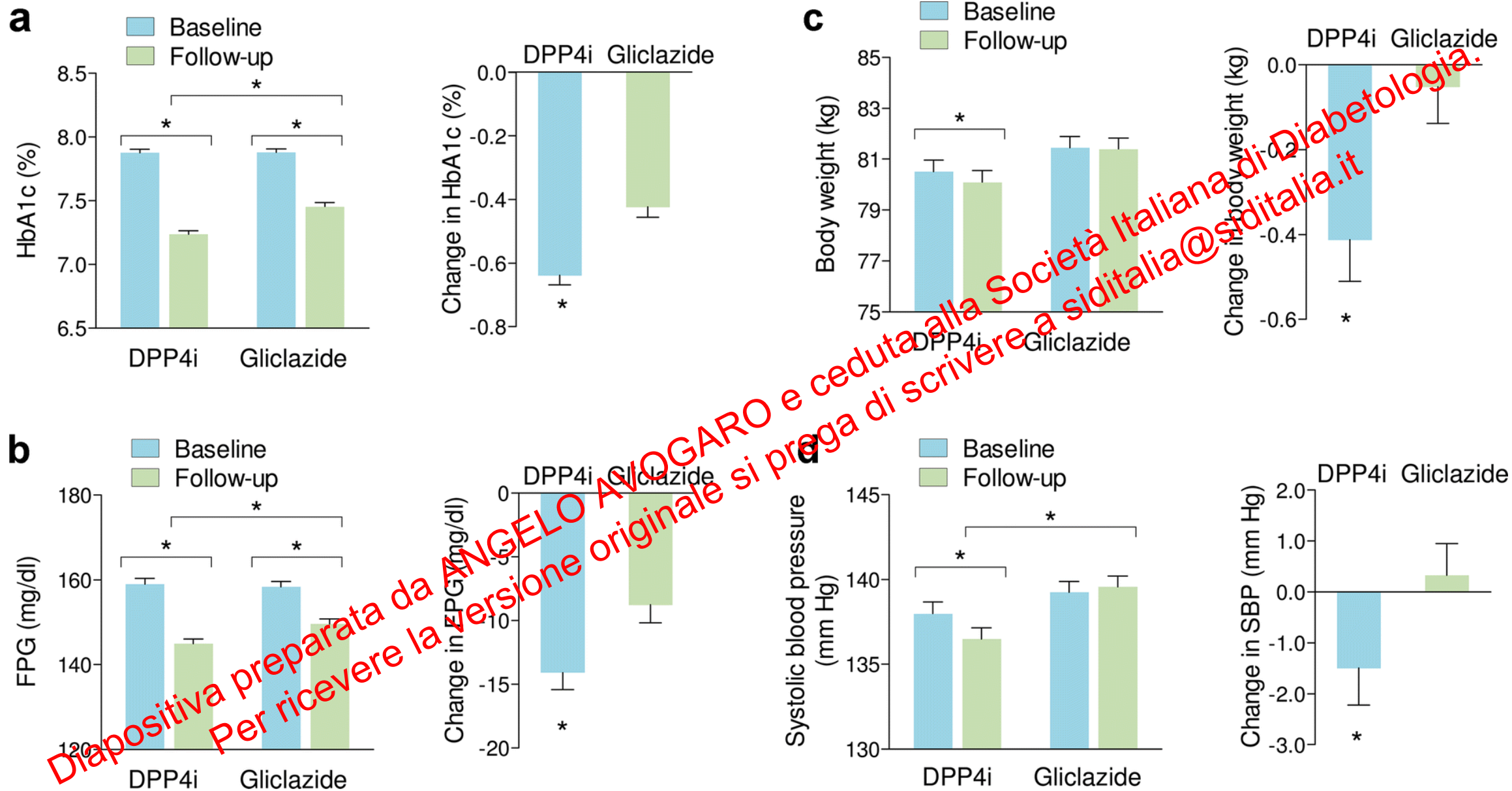
PRIMARY PREVENTION

GFR < 60
ml/min

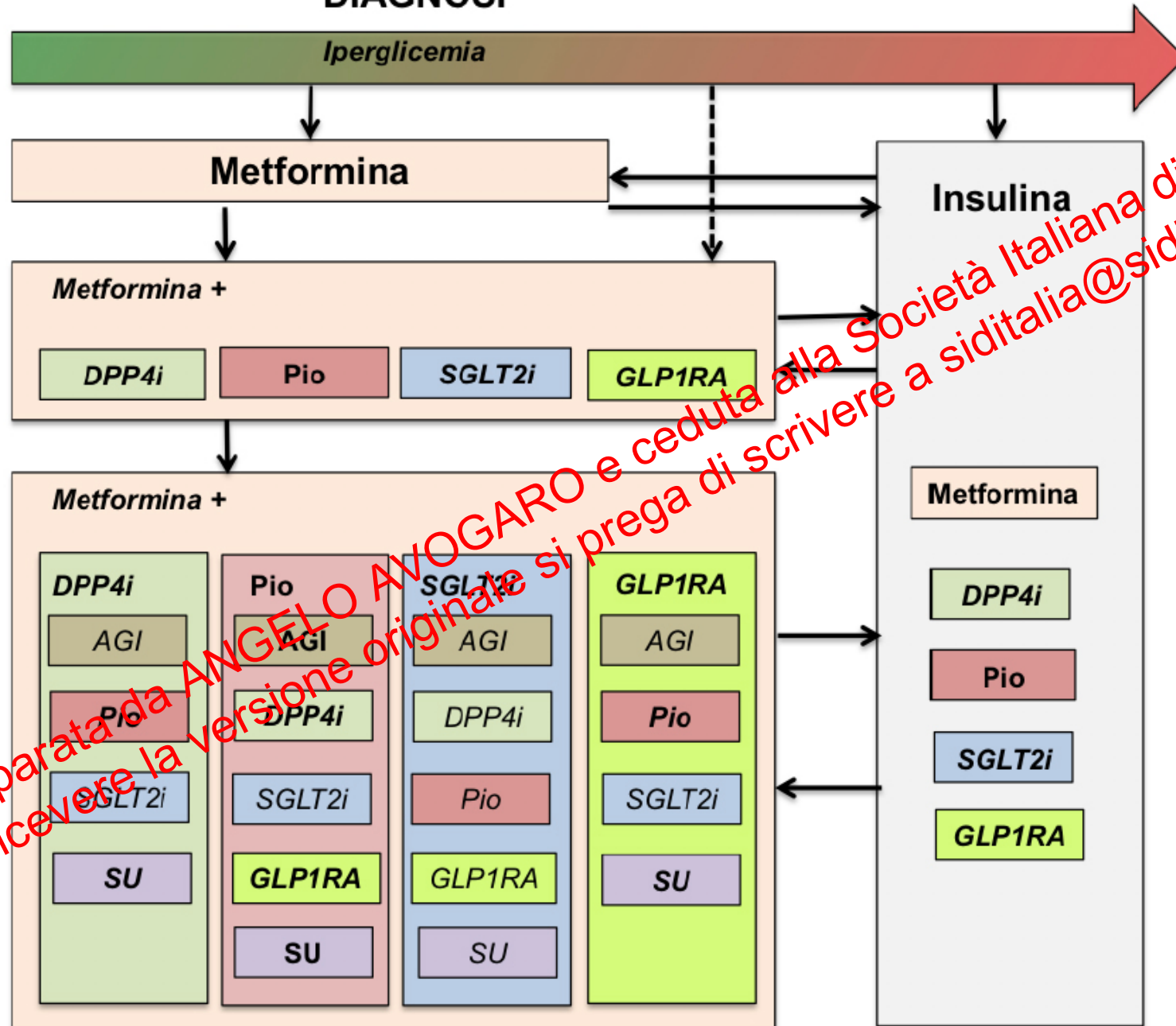
SECONDARY
PREVENTION

RENAL
IMPAIRMENT
(30-50)

Diapositiva preparata da ANCD
Per ricevere la versione
OGARO e ceduta alla
nale si prega di
Italiana di Diabetologia.
siditalia.it



DIAGNOSI



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