Share the Experience.

Bologna 16-17 Giugno 2017

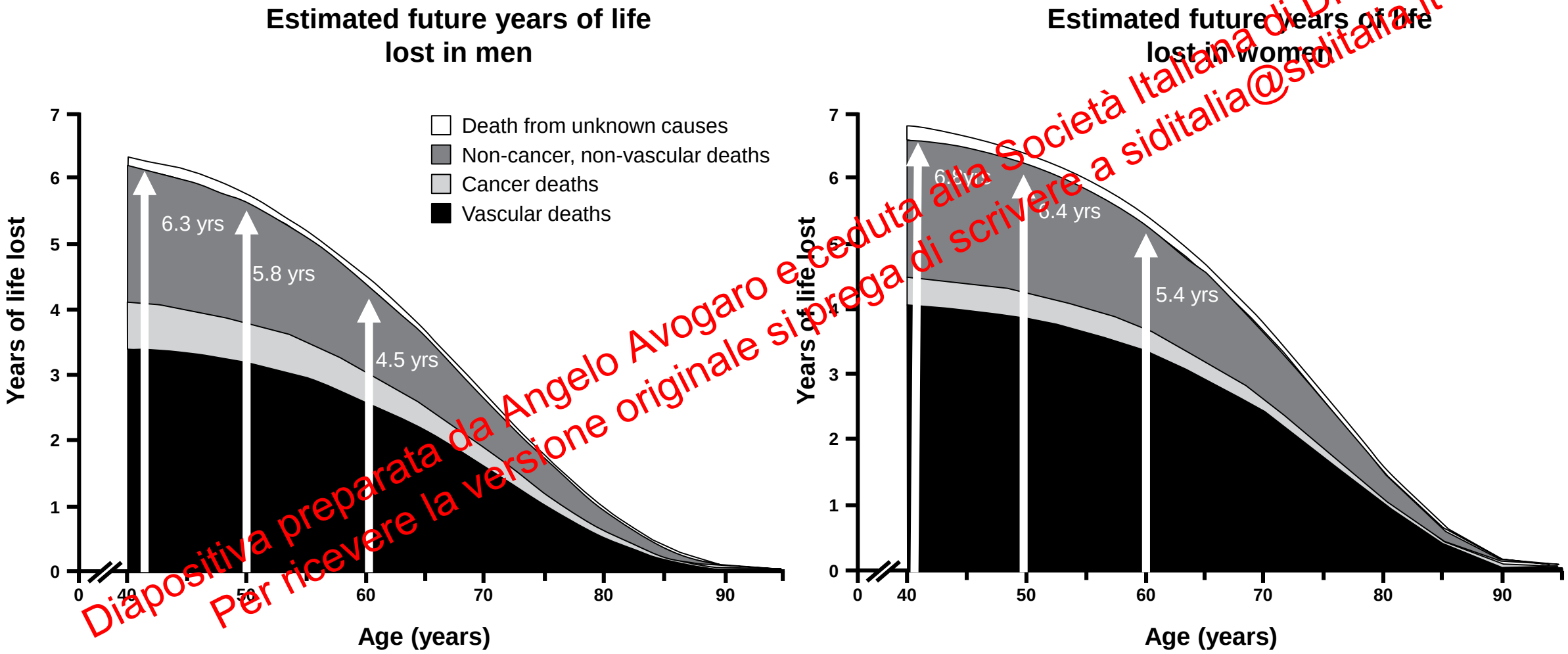
Glicemia e complicanze: lo stretto rapporto tra importanza del trattamento precoce e la prevenzione del rischio nel paziente diabetico

Angelo Avogaro
Università di Padova

Il Prof. Angelo Avogaro dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche:

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

Type 2 diabetes is associated with premature death from CV and non-CV causes



Arrows indicate the number of years of life lost incurred at specific ages by men or women with diabetes but without a history of vascular disease
CV, cardiovascular
Emerging Risk Factors Collaboration. *N Engl J Med* 2011;364:829–841

Association of Type 1 Diabetes vs Type 2 Diabetes Diagnosed During Childhood and Adolescence With Complications During Teenage Years and Young Adulthood

JAMA. 2017;317(8):825-835. doi:10.1001/jama.2017.0686

Complication and Race/Ethnicity Category	Type 1 No.	Type 1 Denominator	Type 1 Age-Adjusted Prevalence, % (95% CI)[a]	Type 2 No.	Type 2 Denominator	Type 2 Age-Adjusted Prevalence, % (95% CI)[a]
Diabetic kidney disease	89	1541	5.8 (4.6 to 7.4)	44	221	15.9 (15.1 to 25.7)
Non-Hispanic white	59	1177	5.2 (3.9 to 7.0)	6	64	9.3 (4.2 to 19.2)
Minority	30	364	8.0 (5.3 to 11.9)	38	157	24.4 (18.2 to 31.9)
Retinopathy	71	1710	5.6 (4.4 to 7.0)	26	267	9.1 (6.3 to 12.9)
Non-Hispanic white	54	1297	5.5 (4.2 to 7.2)	4	72	3.7 (1.4 to 9.9)
Minority	17	413	5.7 (3.5 to 9.0)	32	195	11.2 (7.3 to 16.7)
Peripheral neuropathy	110	1720	8.5 (7.1 to 10.2)	58	265	17.7 (13.6 to 22.7)
Non-Hispanic white	82	1310	8.3 (6.8 to 10.3)	14	71	15.7 (9.1 to 25.6)
Minority	28	410	8.8 (6.1 to 12.7)	44	194	19.6 (14.5 to 26.1)
Cardiovascular autonomic neuropathy	197	1615	14.4 (12.5 to 16.6)	43	252	15.7 (11.7 to 20.6)
Non-Hispanic white	155	1226	15.2 (12.9 to 17.7)	18	66	25.6 (16.6 to 37.4)
Minority	42	389	12.3 (8.9 to 16.7)	25	186	12.7 (8.6 to 18.3)
Arterial stiffness	137	1625	11.6 (9.8 to 13.6)	107	205	47.4 (40.3 to 54.7)
Non-Hispanic white	94	1242	10.2 (8.4 to 12.4)	21	60	30.7 (20.0 to 43.9)
Minority	43	383	15.4 (11.5 to 20.3)	86	145	55.4 (46.8 to 63.7)
Hypertension	141	1743	10.1 (8.6 to 11.9)	66	272	21.6 (17.1 to 26.9)
Non-Hispanic white	100	1325	9.5 (7.8 to 11.5)	16	72	20.0 (12.5 to 30.6)
Minority	41	418	12.2 (8.9 to 16.4)	50	200	22.4 (17.1 to 28.9)

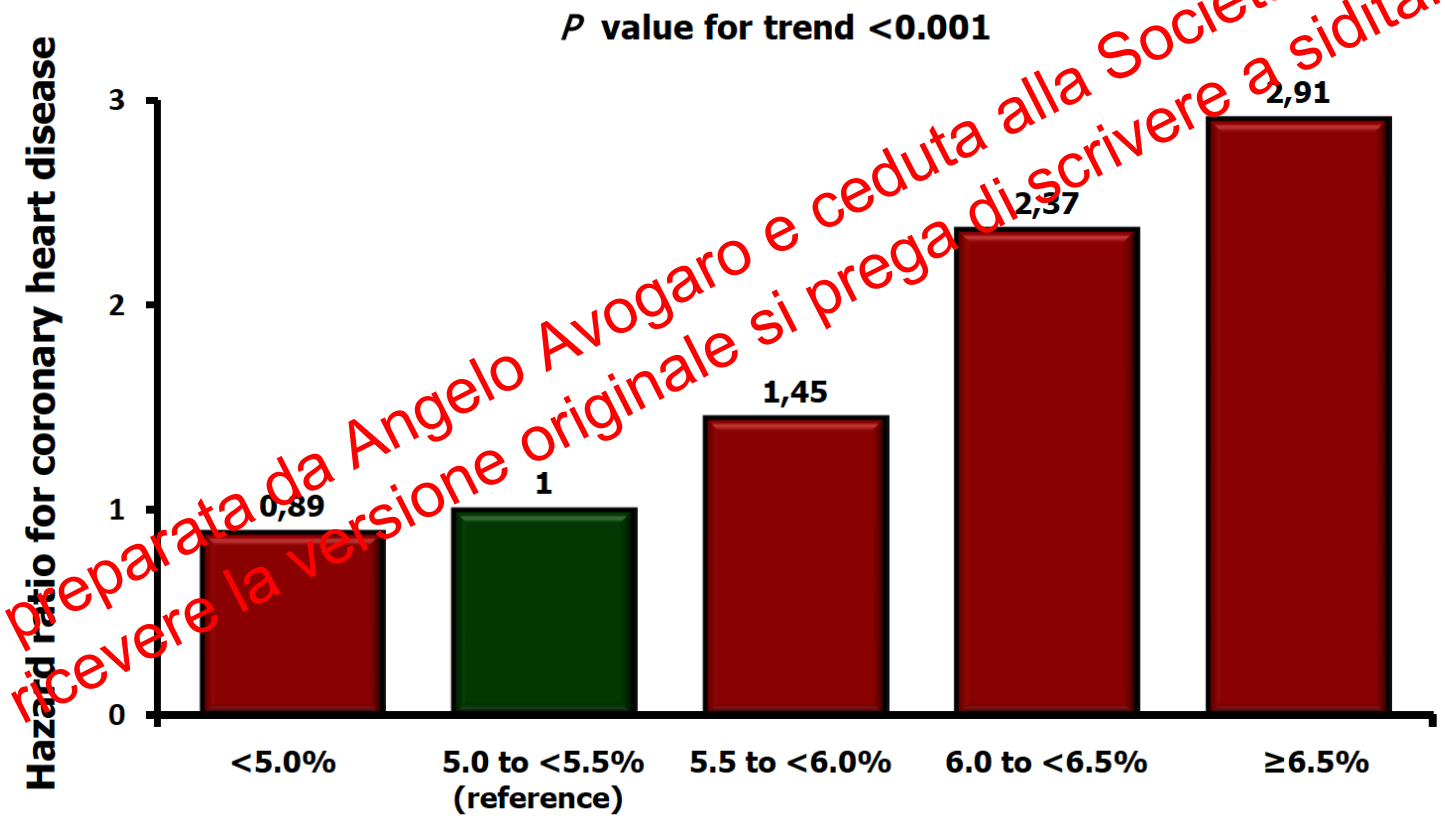
[a] Logistic regression model estimates set age = 21 y for type 1 and type 2 diabetes.

[b] *P* values from age-adjusted logistic regression models.

[c] Hosmer-Lemeshow goodness-of-fit test $P < .05$; indicates poor model fit.

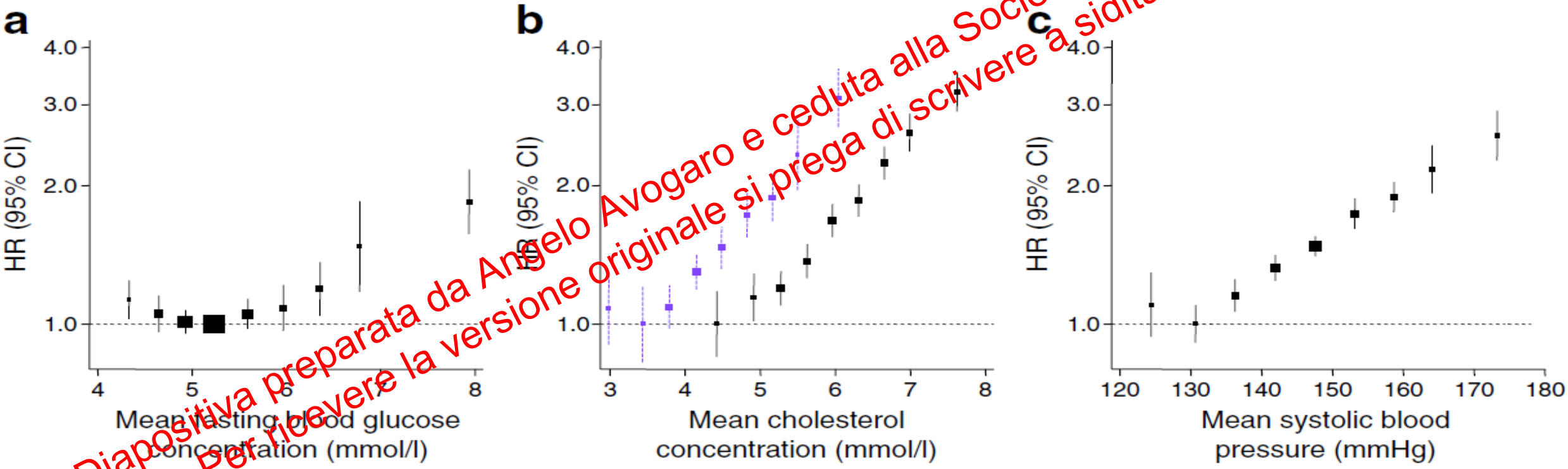
HbA_{1c} levels below the diagnostic threshold for Diabetes associate with an increased risk of cardiovascular disease

Hazard Ratios for coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) population during the 15-Year study period according to HbA1c category at baseline



Selvin E, et al. *N Engl J Med* 2010;362:800–811

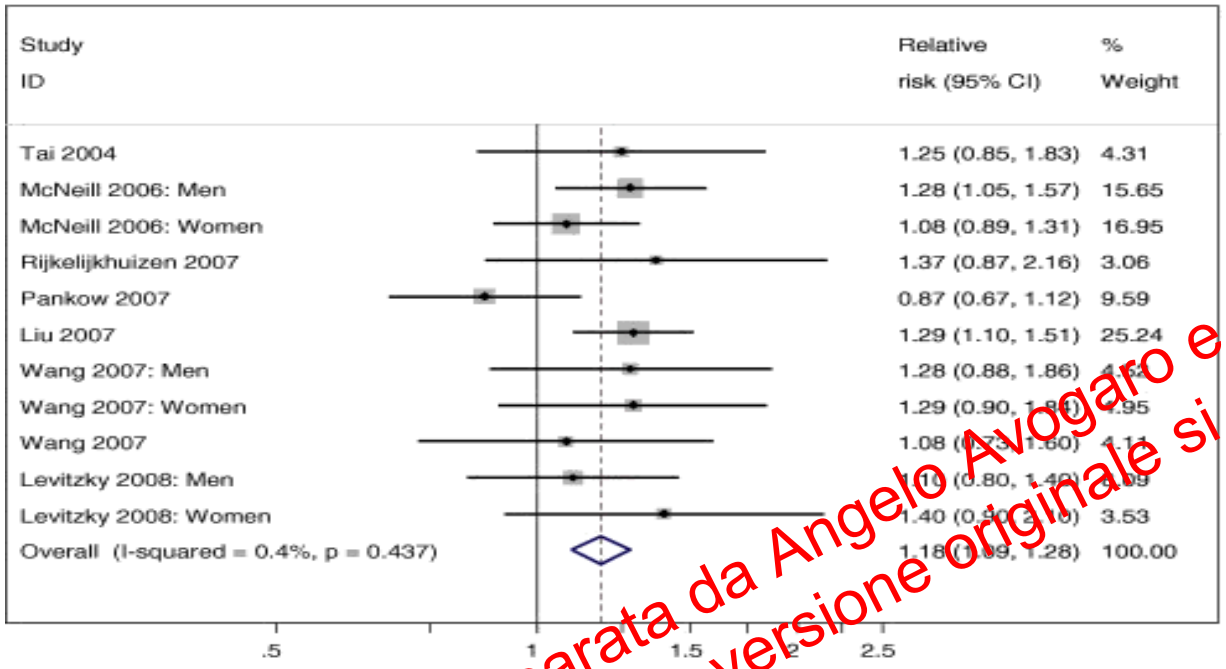
Comparison of HRs for CHD by long-term average concentrations of fasting blood glucose, total (and non-HDL) cholesterol, and systolic blood pressure



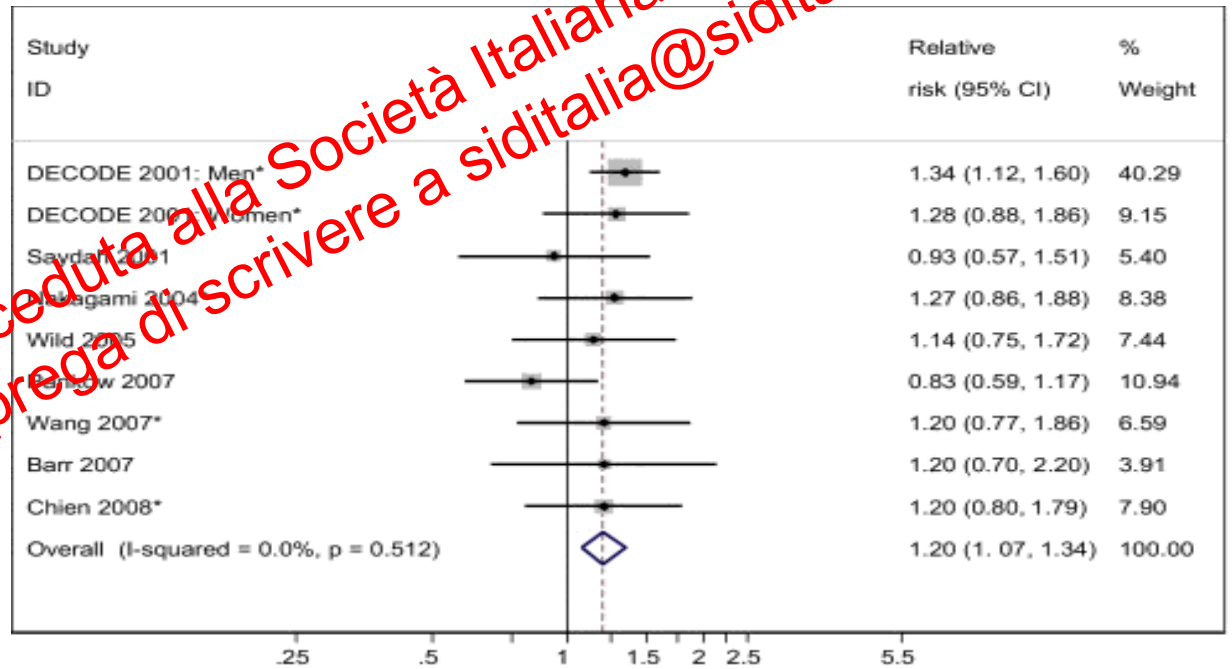
The Emerging Risk Factors Collaboration. Lancet 375:2215–2222, 2010

Pre-Diabetic Conditions: Risk of Cardiovascular Disease

Meta-analysis of 18 clinical trials evaluating the risk of CV disease among patients with impaired fasting glucose and/or impaired glucose tolerance



Impaired fasting glucose



Impaired glucose tolerance

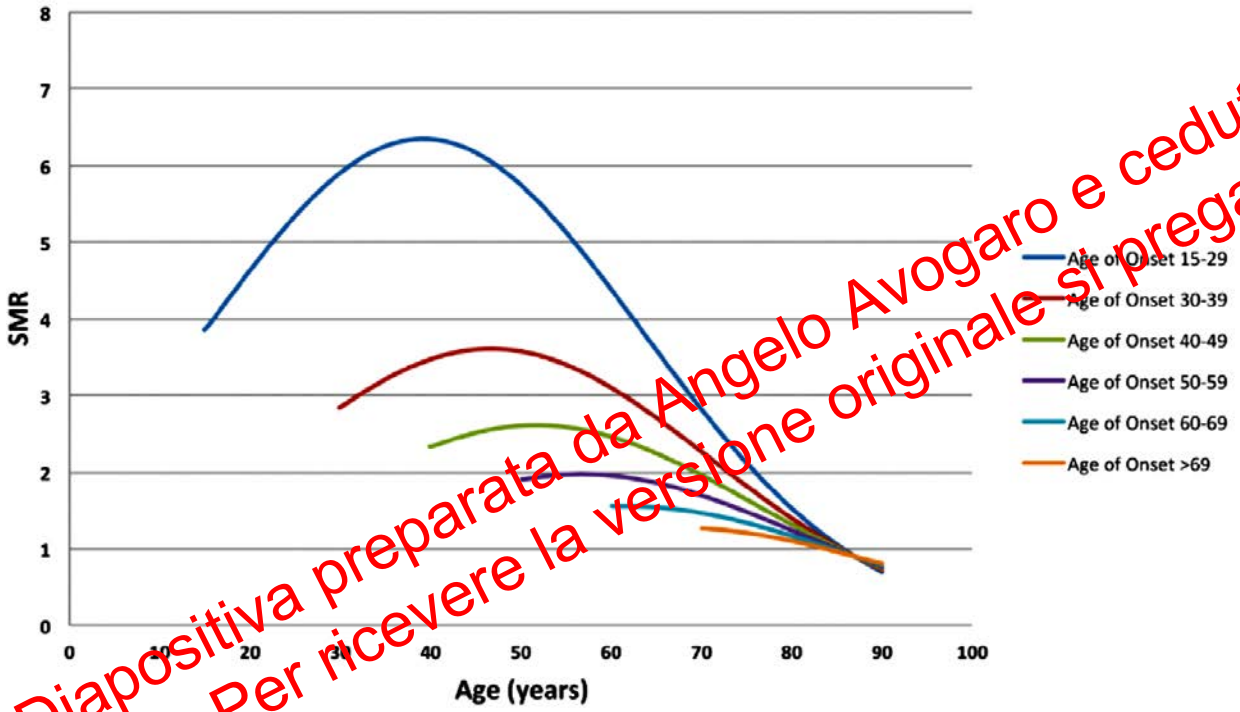
Both types of pre-diabetic conditions increase the risk of CV disease

CV=Cardiovascular

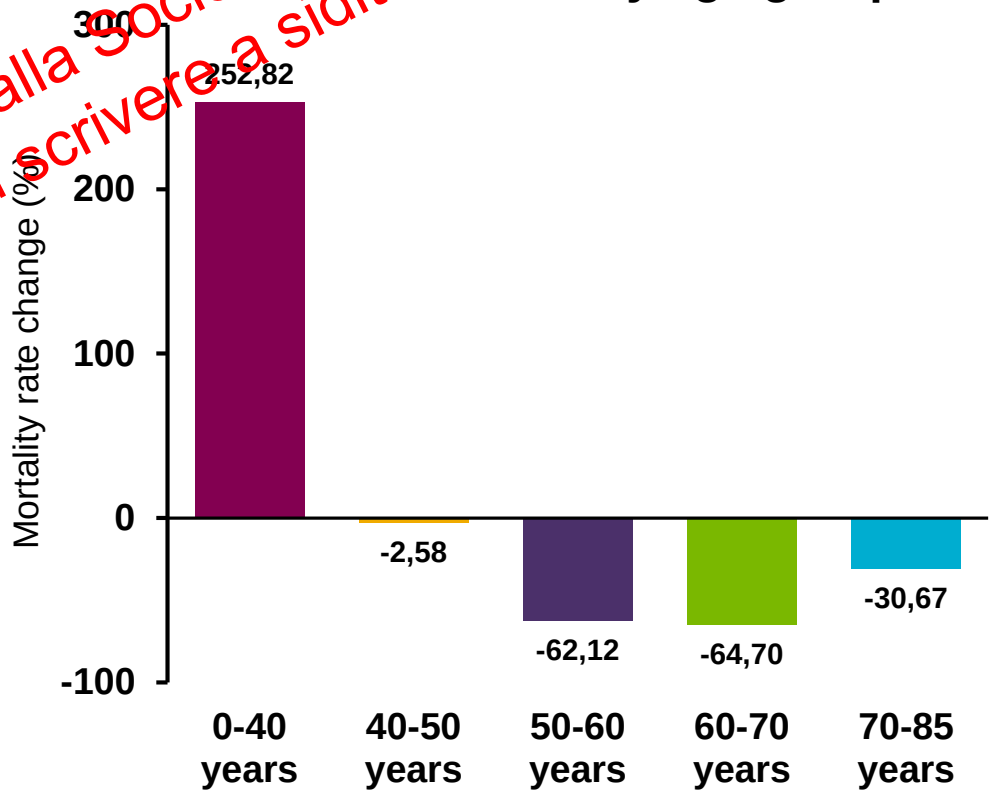
Source: Ford ES et al. *JACC* 2010;55:1310-1317

Early onset Type 2 diabetes is associated with higher rates of diabetes-related mortality compared with standard onset

Standardised mortality ratios for attained age for each age-of-onset cohort (n=15,238)[1]



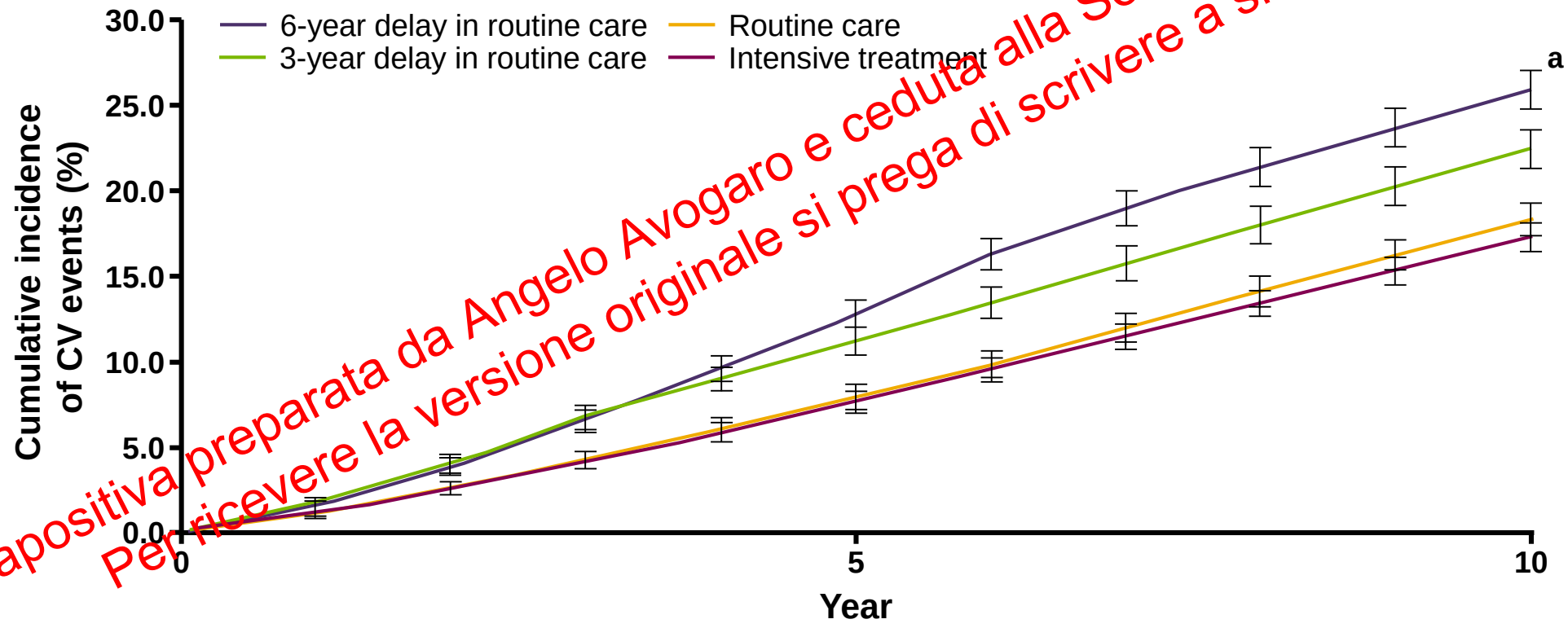
Change in Type 2 diabetes-related mortality between 2000–2011 by age group[2]



- SMR, standardised mortality ratio
- 1. Al-Saeed AH, et al. *Diabetes Care* 2016;39:823–829; 2. Harding JL, et al. *Diabetes Care* 2016;39:1018–1026

Future mortality: Early detection and treatment of Type 2 diabetes is predicted to reduce the rate of CV events, including mortality

- Simulation of data from the ADDITION-Europe trial demonstrated the time of initiation of treatment is more important than the intensity of glucose-lowering therapy for reducing CV events, including mortality



[a]Outcome defined as stroke, MI, revascularisation, amputation or CV death; the error bars indicate SDs calculated from 100 simulations
CV, cardiovascular; MI, myocardial infarction
Herman WH, et al. *Diabetes Care* 2015;38:1449–1455

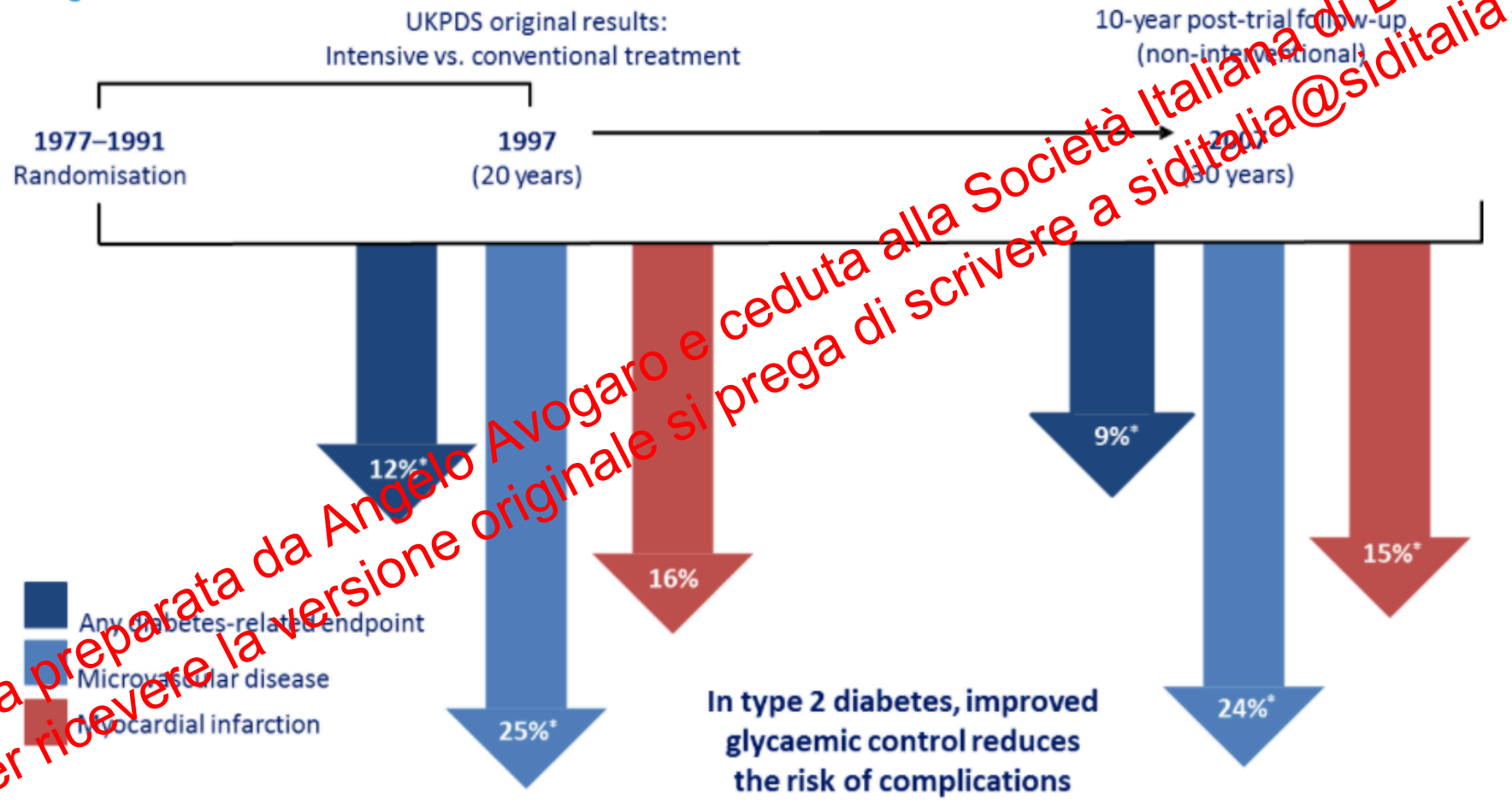
Serious complications of T2D are present at diagnosis

Complication	Prevalence (%)*
Any complication	50
Retinopathy	21
Abnormal ECG	18
Absent foot pulses (≥2) and/or ischaemic feet	14
Impaired reflexes and/or decreased vibration sense	7
Myocardial infarction/angina/claudication	~2–3
Stroke/transient ischaemic attack	~1

*Some patients had more than 1 complication at time of diagnosis

Adapted from UKPDS VIII. *Diabetologia* 1991;34:877–890

Early and sustained proactive glycaemic control is important: 20- and 30-year follow-up results

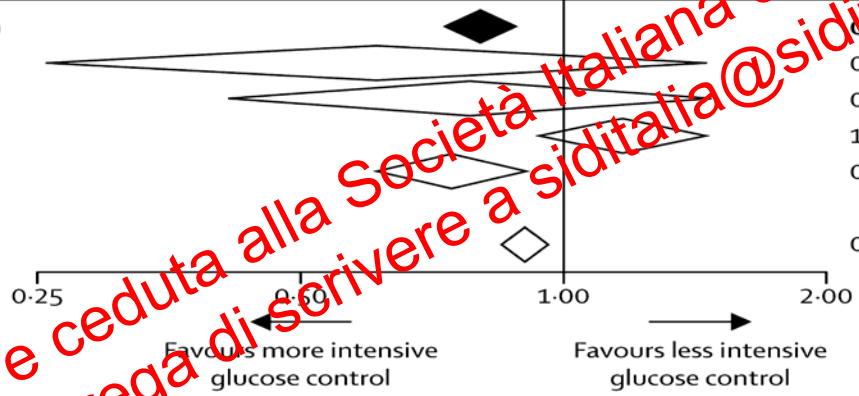


*P<0.05; intensive vs. conventional treatment.
UKPDS, United Kingdom Prospective Diabetes Study.
Adapted from Holman RR et al. *N Engl J Med* 2008; 359: 1577–1589; UKPDS 33 Study Group. *Lancet* 1998; 352: 837–853.

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

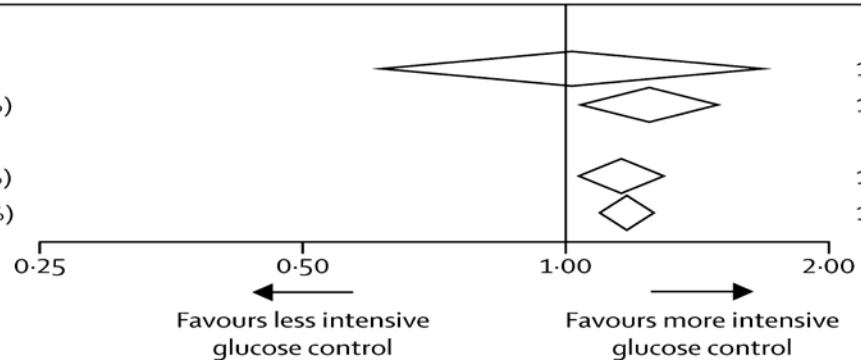
A

	More intensive glucose control	Less intensive glucose control	Hazard ratio (95% CI)
Primary kidney outcome	**761 (1·2%)**	**865 (1·6%)**	**0·80 (0·72–0·88)**
End-stage kidney disease	113 (0·2%)	143 (0·2%)	0·61 (0·26–1·44)
Renal death	18 (0·0%)	22 (0·1%)	0·77 (0·41–1·46)
eGFR <30 mL/min per 1·73m²	175 (0·3%)	149 (0·3%)	1·16 (0·93–1·44)
Macroalbuminuria	509 (0·9%)	603 (1·2%)	0·74 (0·61–0·90)
Secondary outcomes			
Microalbuminuria	2121 (5·2%)	2210 (6·3%)	0·90 (0·84–0·95)



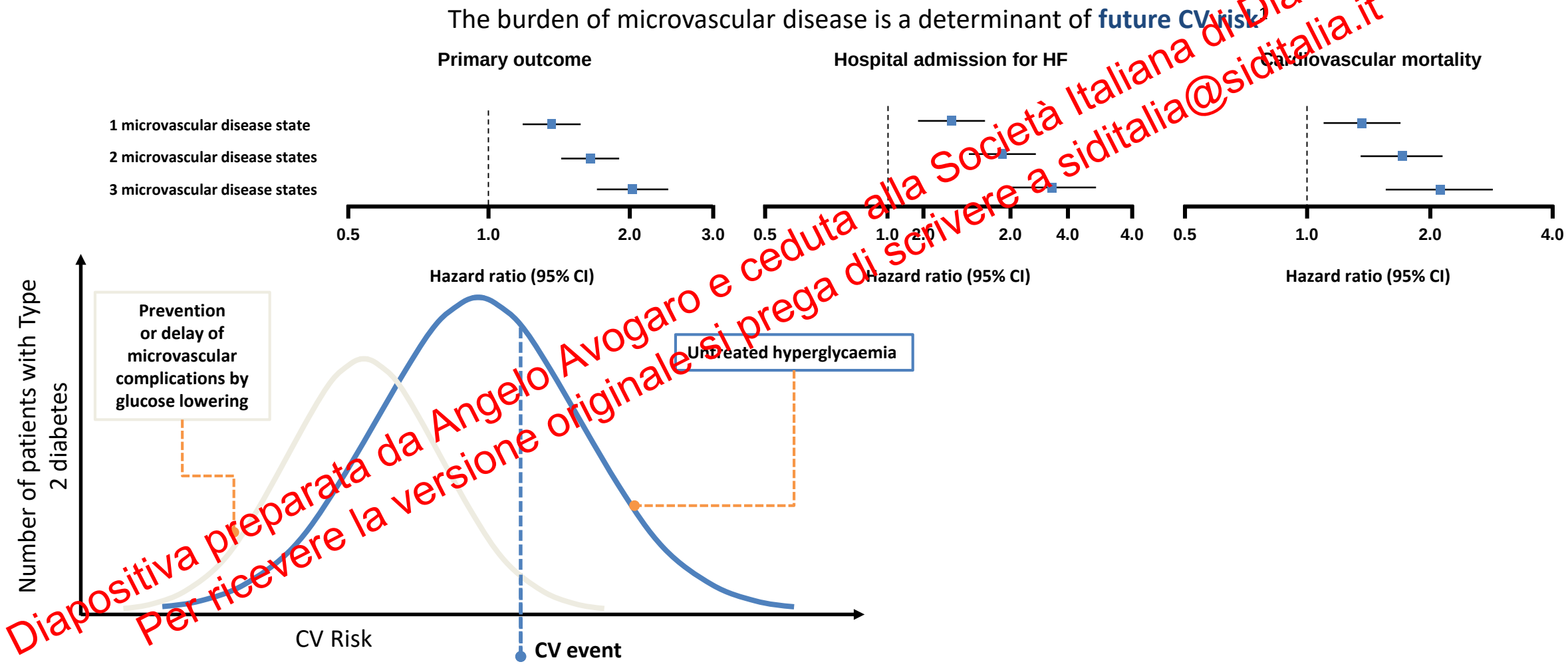
B

	More intensive glucose control	Less intensive glucose control	Hazard ratio (95% CI)
Secondary albuminuria outcomes			
Macroalbuminuria to normoalbuminuria	80 (3·5%)	603 (1·2%)	1·01 (0·61–1·66)
Macroalbuminuria to microalbuminuria or normoalbuminuria	358 (22·0%)	332 (18·1%)	1·23 (1·03–1·48)
Microalbuminuria to normoalbuminuria	1430 (13·0%)	1176 (10·7%)	1·15 (1·03–1·28)
Maintenance of normoalbuminuria	7004 (75·5%)	5785 (72·4%)	1·16 (1·08–1·25)



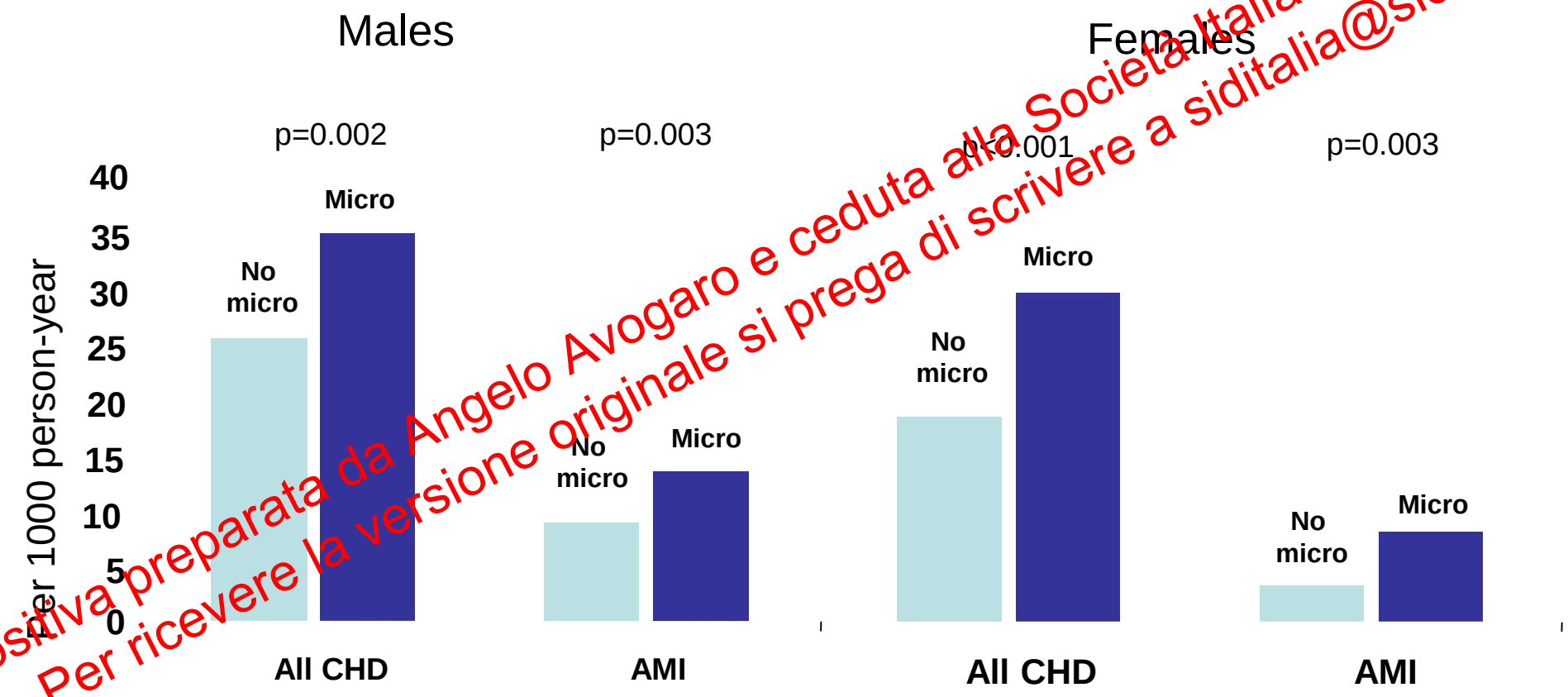
The Lancet Diabetes & Endocrinology DOI: (10.1016/S2213-8587(17)30104-3)

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



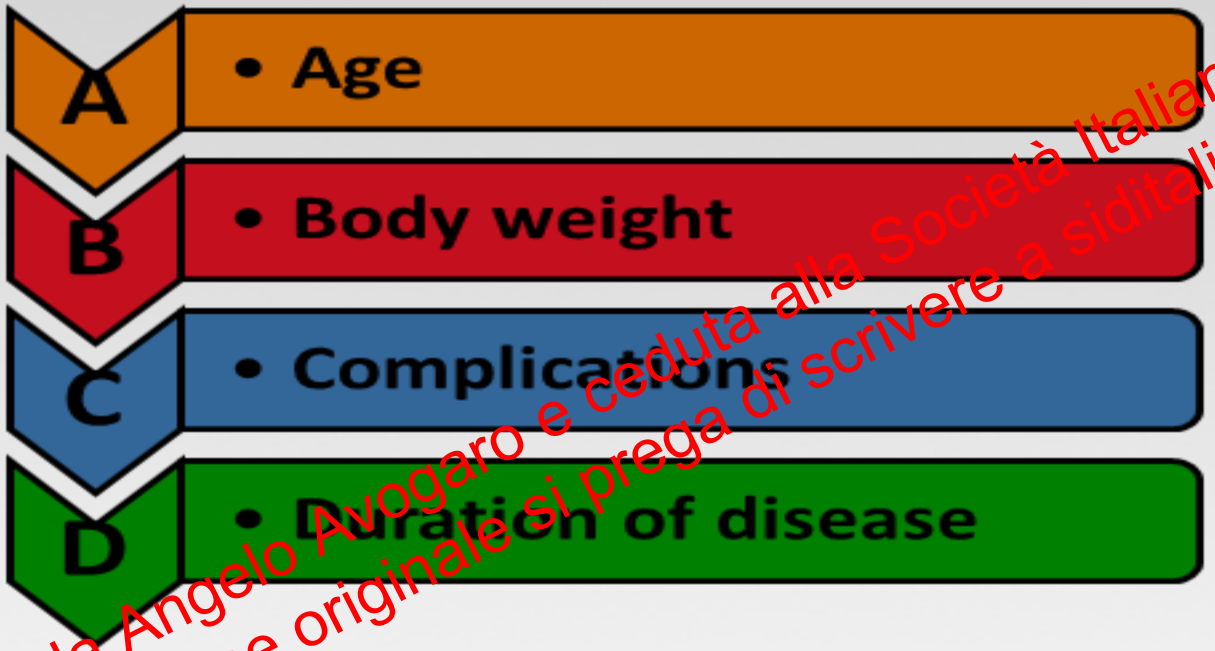
CV, cardiovascular; RCT, randomized control trial
1. Adapted from Brownrigg JR et al., *Lancet Diabetes Endocrinol* 2016;4:588–597

Incidence Rate of CHD Events: The role of microvascular complications



Avogaro et al Diabetes Care. 2007

ABCs of Individualization in Patients With T2DM: Factors to Consider When Selecting a Glycemic Target



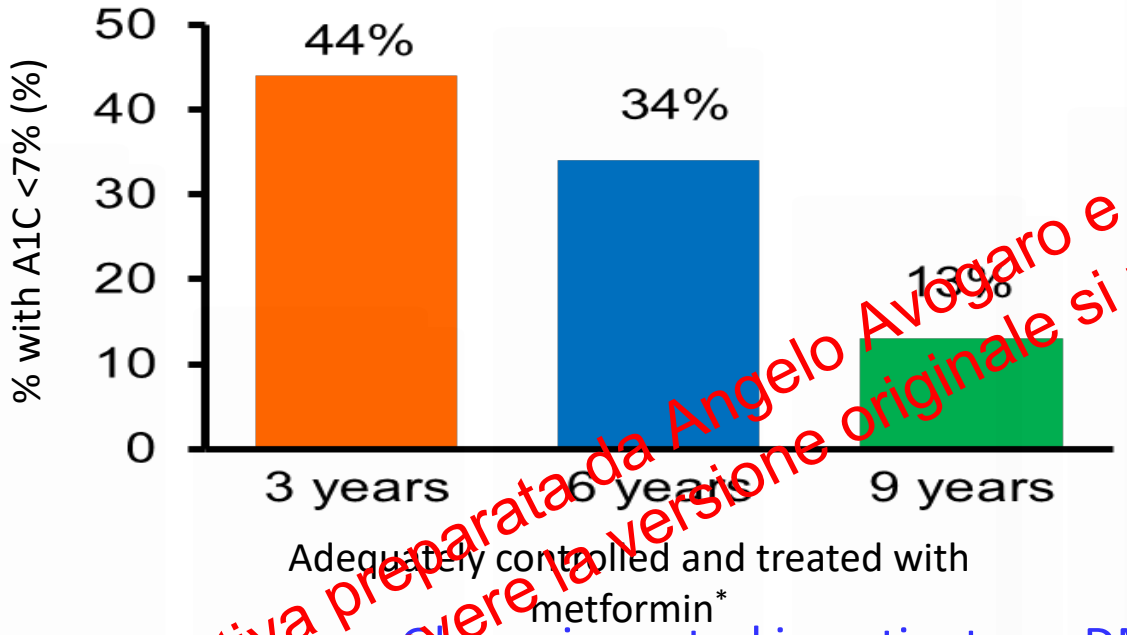
- HbA1c < 7.0% for most; individualization is key
  - Tighter targets (6.0%-6.5%) for younger, healthier patients
  - Looser targets (7.5%-8.0%) for older patients, those with comorbidities, and those prone to hypoglycemia

Inzucchi SE, et al. *Diabetologia*. 2012;55(6):1577-1596.

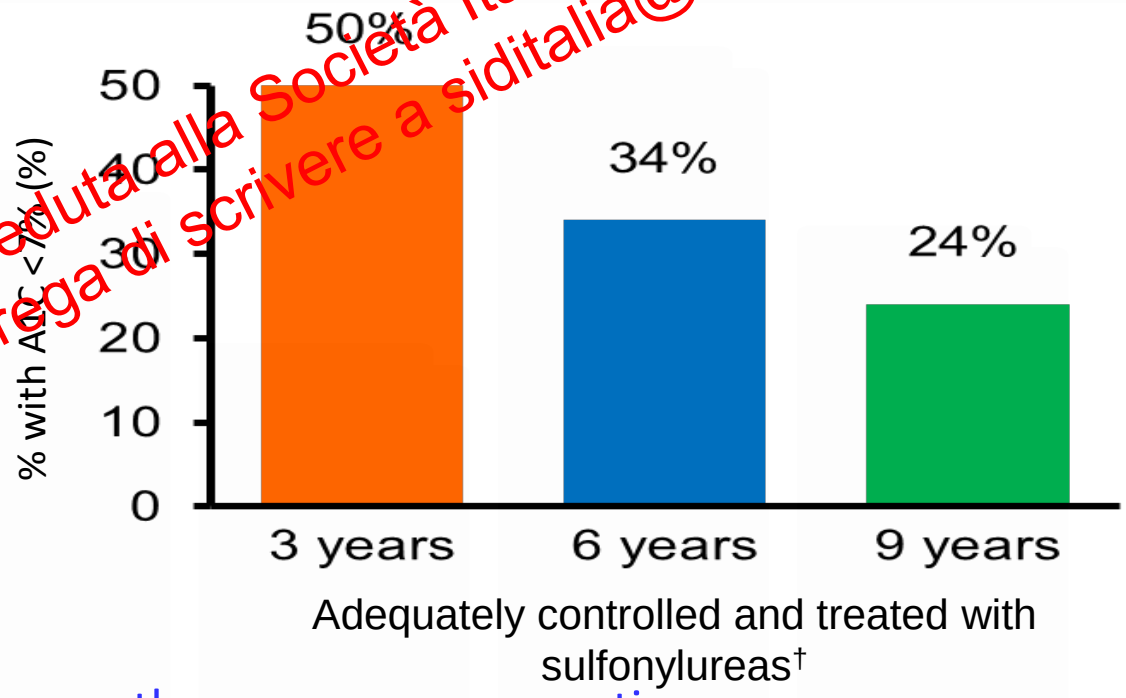
Diabetes Mellitus: Change in Glycemic Control Over Time

United Kingdom Prospective Diabetes Study (UKPDS) 49

4,075 patients with DM randomized to diet alone, insulin, sulfonylurea, or metformin for 9 years



Adequately controlled and treated with metformin*



Adequately controlled and treated with sulfonylureas†

Glycemic control in patients on DM monotherapy worsens over time

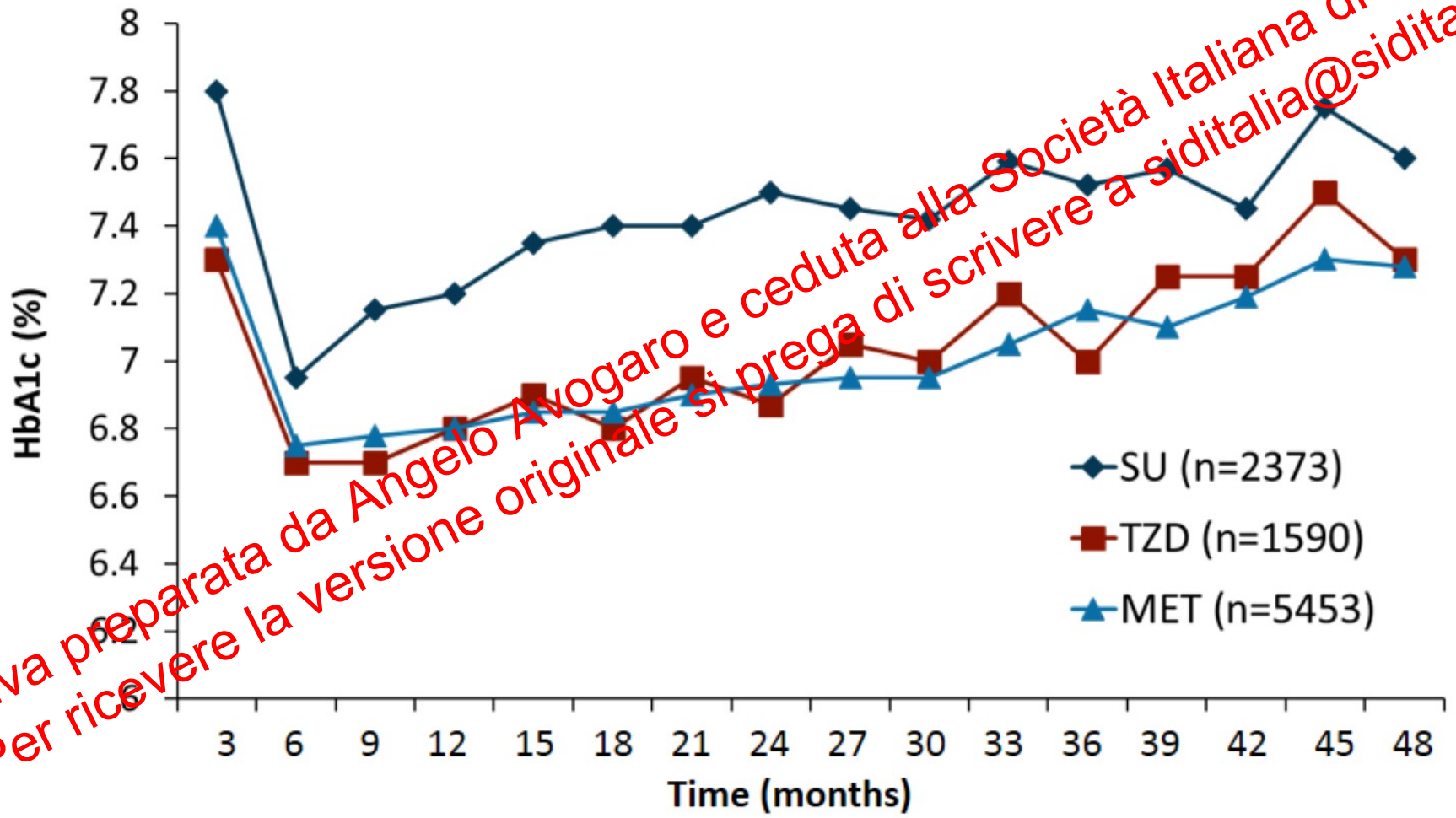
*Overweight drug-naïve patients

†Normal weight and overweight drug-naïve patients

DM=Diabetes mellitus, HbA_{1C}=Glycosylated hemoglobin

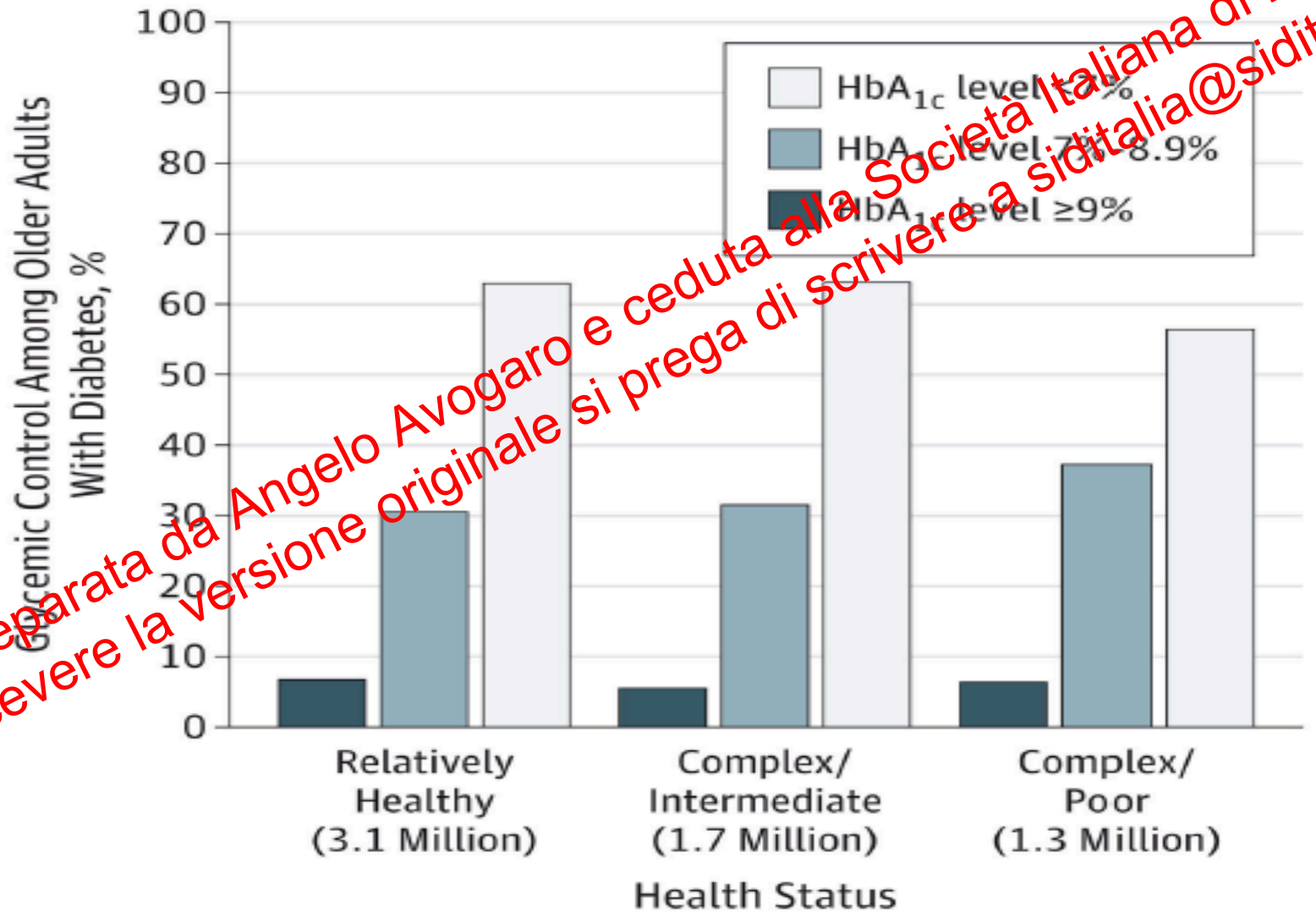
Source: Turner RC et al. *JAMA* 1999;281:2005-2012

T2DM Control Is Not Durable



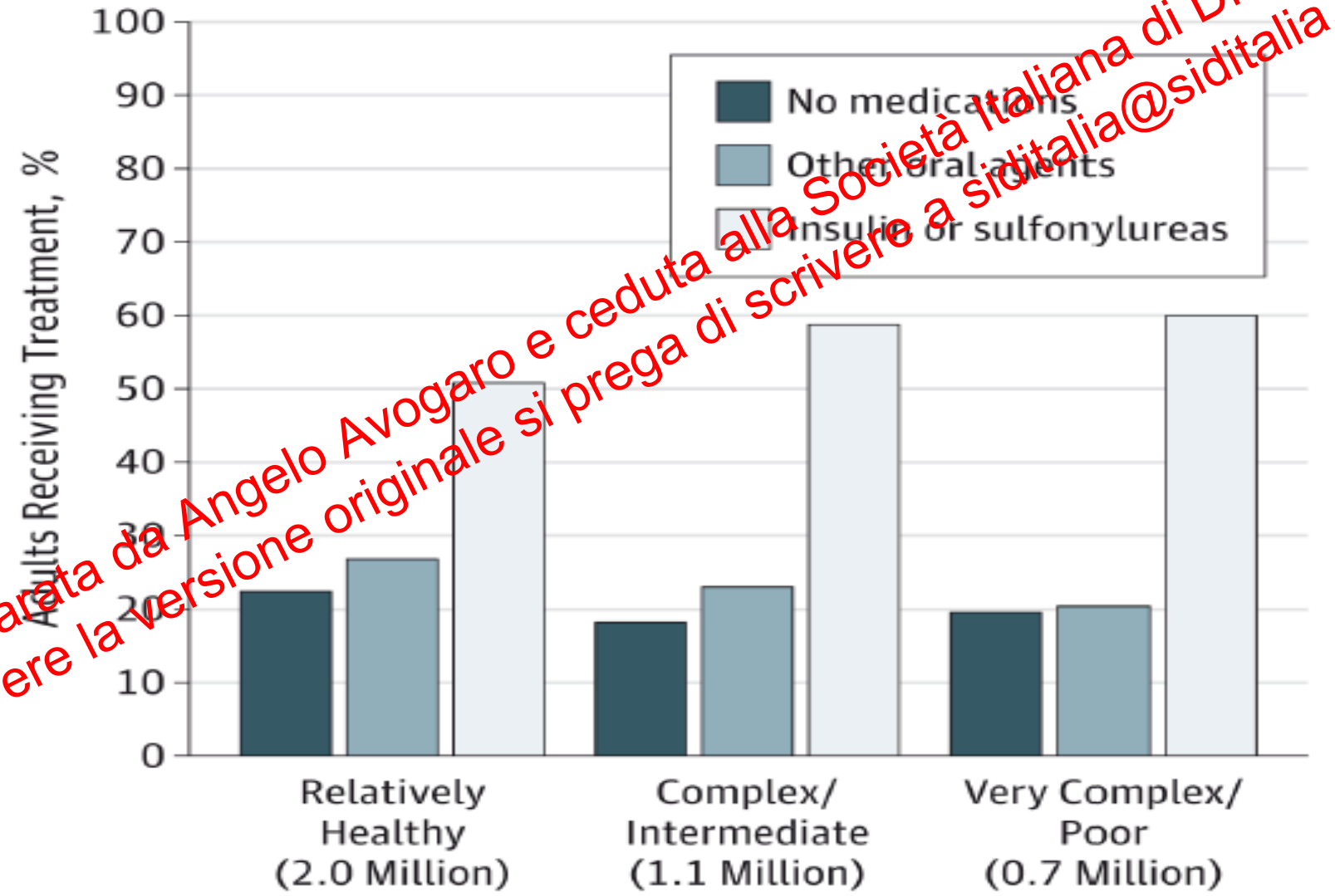
Bloomgarden ZT. *Diabetes Care*. 2007;30:174-180.

Patients with Comorbidities are Frequently Overtreated



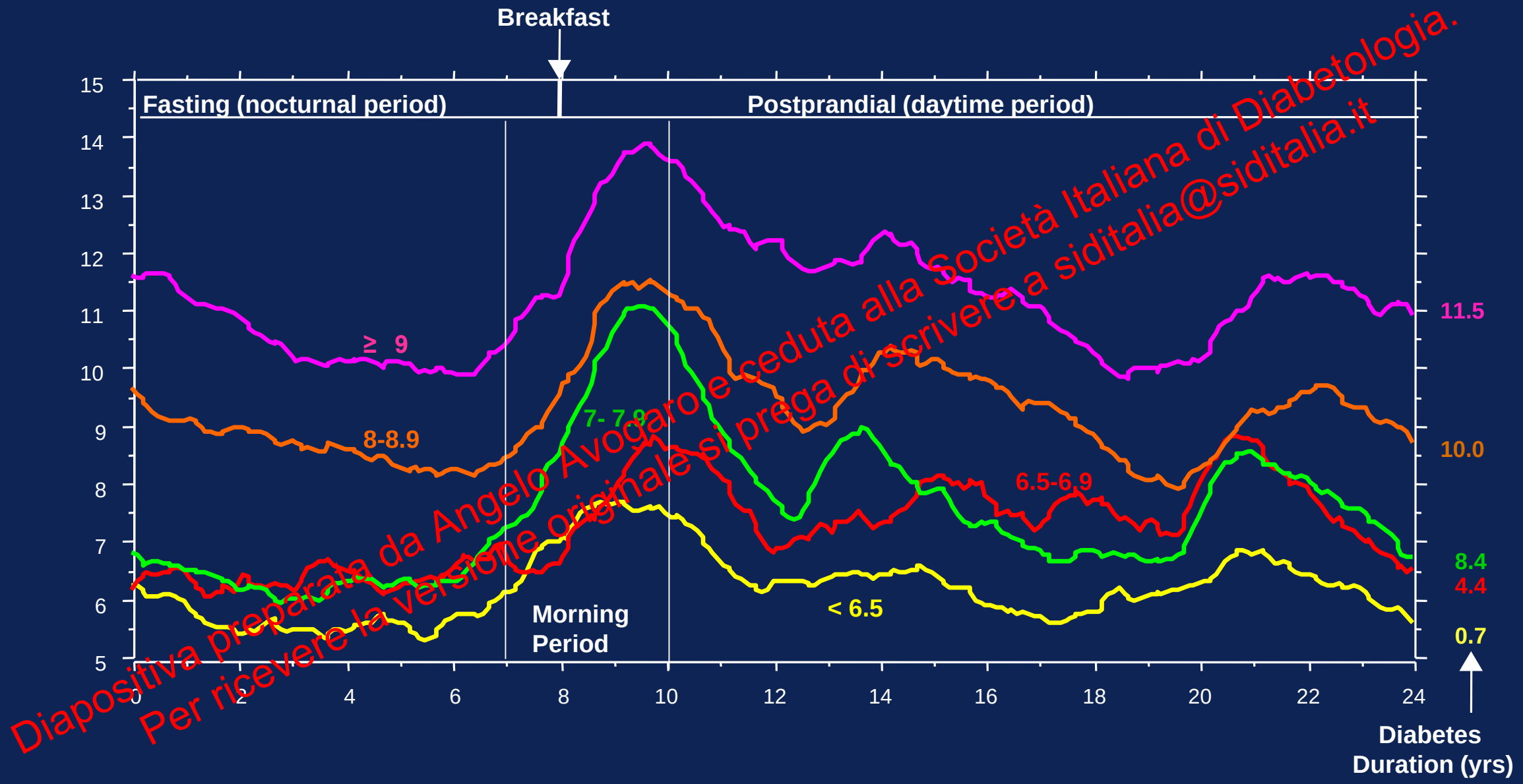
Lipska et al. 2015

Comorbid Patients frequently receive inappropriate therapies



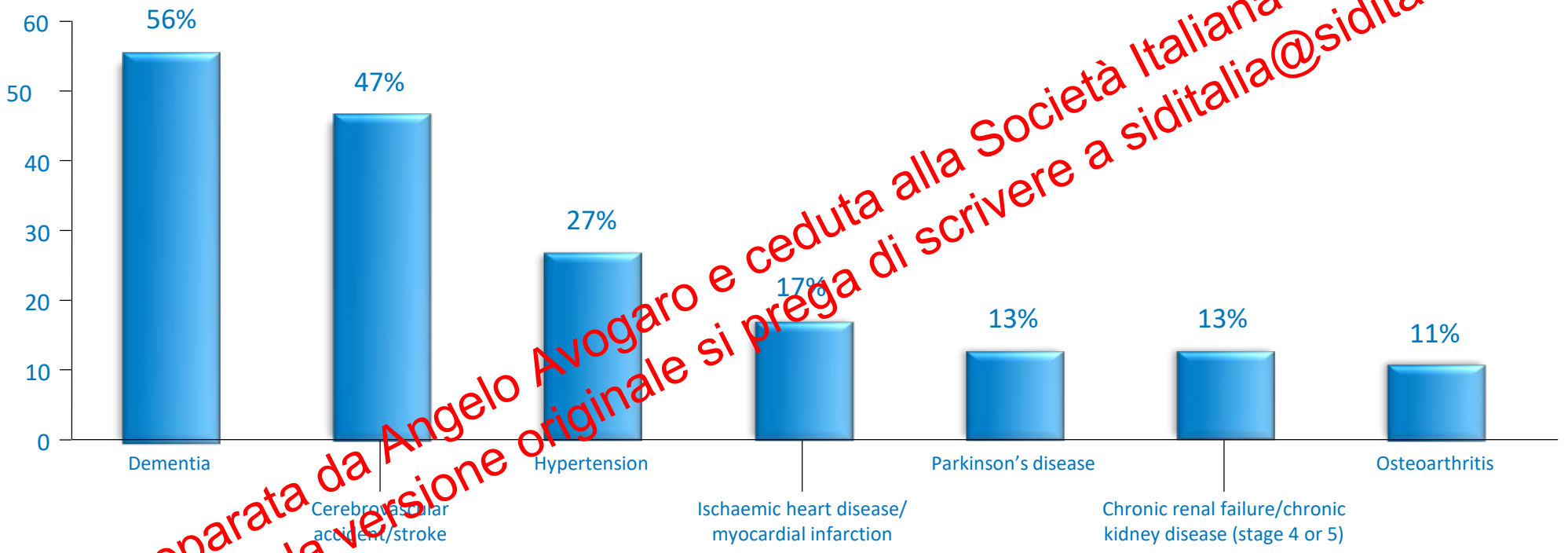
Lipska et al. 2015

Daily glycemic variation (mmol/L) with worsening type 2 diabetes



L Monnier ,C Colette, G Dunseath and D Owens . Diabetes Care. 2007;30:263-269

Patients with type 2 diabetes in nursing homes frequently have many comorbidities



In this study, each individual had a mean of four comorbidities

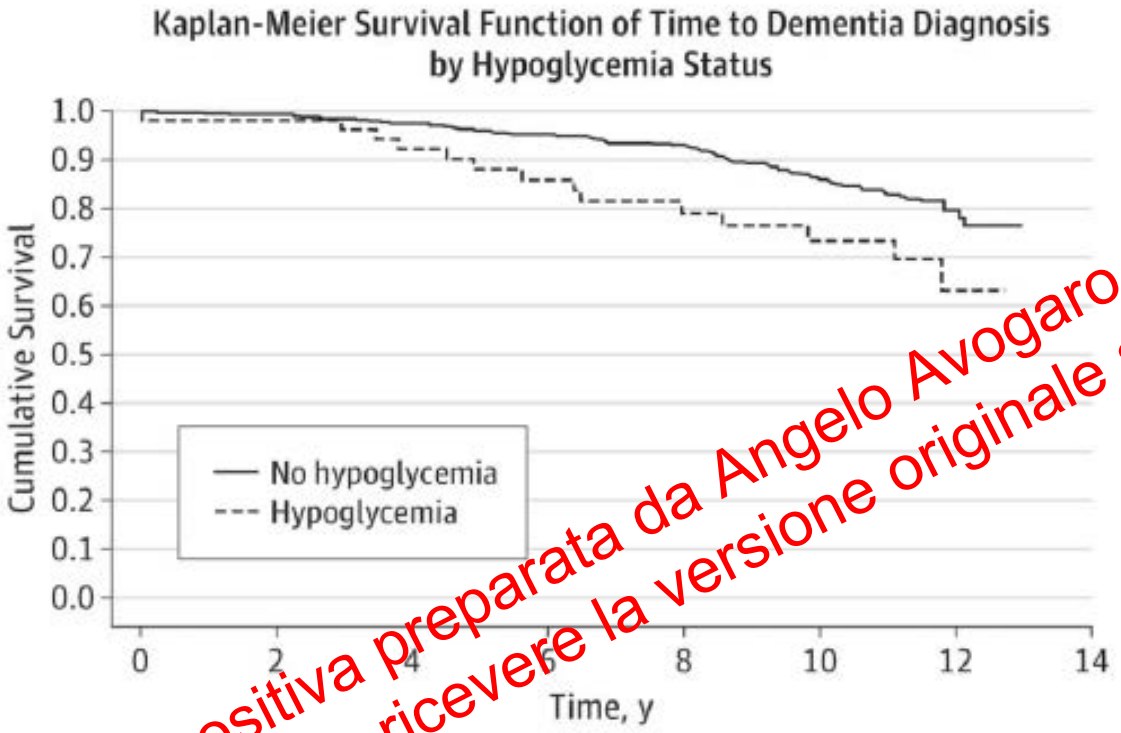
Gadsby R, et al. Diabet. Med. 2011;28:778-80.

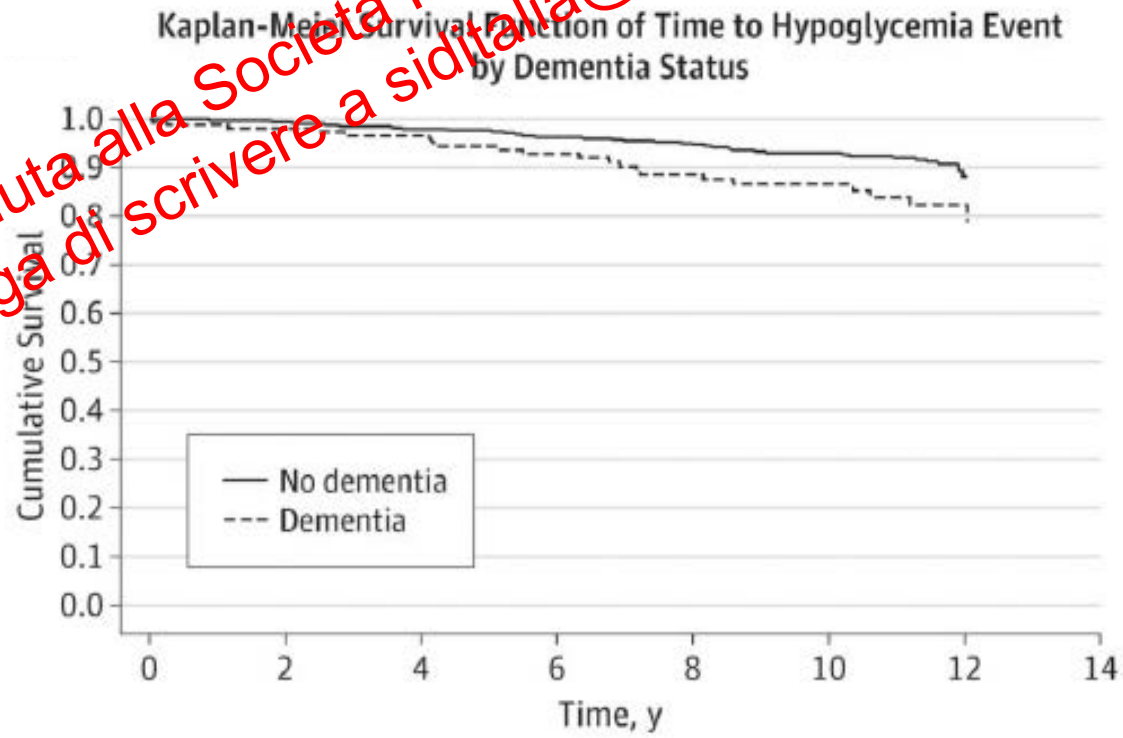
Treatment in Comorbid Diabetic Patients can be Problematic

Al momento la terapia è la seguente:

- Rocefin 1 g	1 somministrazione ore 14
- Zaroxolin 10 mg	1 cp ore 8
- Renagel 800 mg	1 cp x 3 (ore 8-14-18)
- Dilatrend 6.25 mg	1 cp x 3 (ore 8-14-18)
- Mimpara 60 mg	1 cp ore 8
- Eskim 1000 mg	1 cp ore 8
- Lasix 500 mg	½ cp x 2 (ore 8-18)
- Aprovel 150 mg	1 cp x 2 (ore 8 e 18)
- Metocal 1250 mg	1 cp ore 14
- Foznol 1000 mg	1 cp x 2 (ore 8 e 18)
- Calcitriolo 0.25 mcg	1 cp ore 14
- Adalat crono 30 mg	1 cp ore 22
- Pantoprazolo 20 mg	1 cp x 2 (ore 8 e 18)
- Cardioaspirin 100 mg	1 cp ore 14
- Selectin 40 mg	1 cp ore 22
- Motilex 0.5 mg	1 cp a pranzo
- Zyloric 300 mg	½ cp a giorni alterni
- Lormetazepam gtt	XV gtt la sera al bisogno
- Peptalgan 1 g	1 somministrazione e.v. a.b.
- Kayexalate	a giorni alterni (somministrato ieri)
- Catapresan TTS 2 cerotto	1 applicazione/settimana (sostituito 16/09/2010)
- Neorecormon 10.000 U	1 somministrazione ogni 5 die (somministrato il 20/09)
- Cardura 4 mg	1 cp al bisogno
- Catapresan 300 mg	1 cp al bisogno
- Insulina Humalog	6 U a colazione (secondo stick pre prandiale)
- Insulina Humalog	11 U a pranzo (secondo stick pre prandiale)
- Insulina Humalog	12 U a cena (secondo stick pre prandiale)
- Insulina Lantus	14 U ore 22

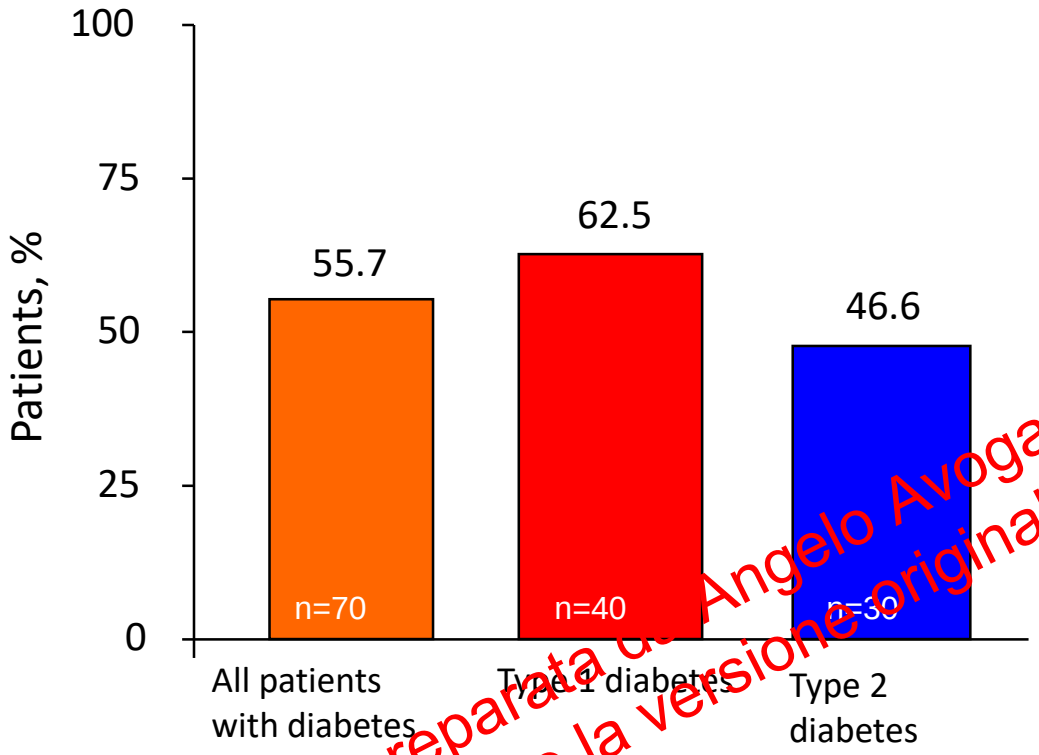
Biderectional association between hypoglycemia and dementia





Yaffe K et al. JAMA 2013; 173(14): 1300–1306

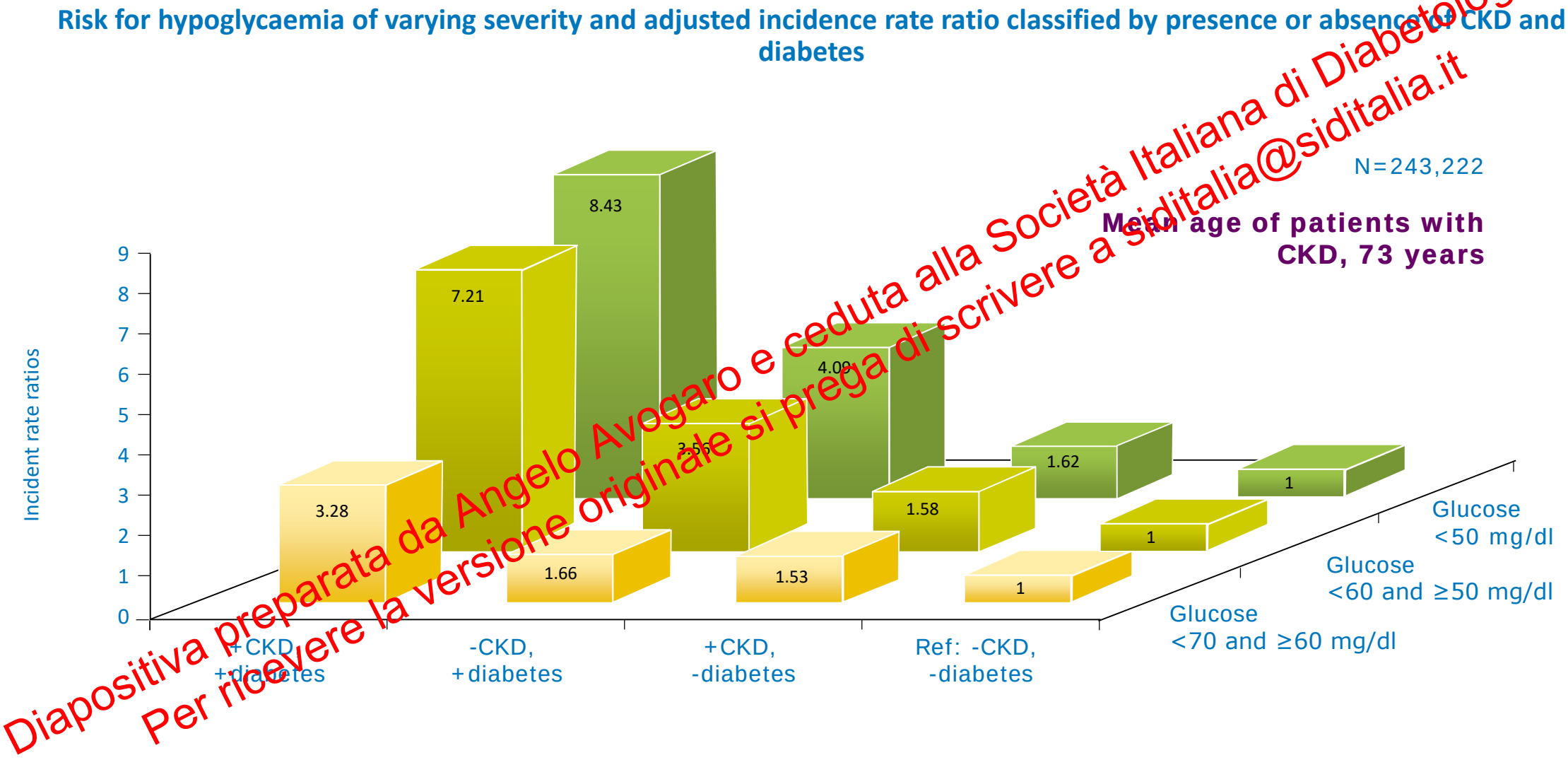
Asymptomatic episodes of hypoglycemia may go unreported



- In a cohort of patients with diabetes, more than **50% had asymptomatic (unrecognized) hypoglycemia**, as identified by continuous glucose monitorin[1]

Chico A, *et al. Diabetes Care* 2003;26(4):1153-1157.

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



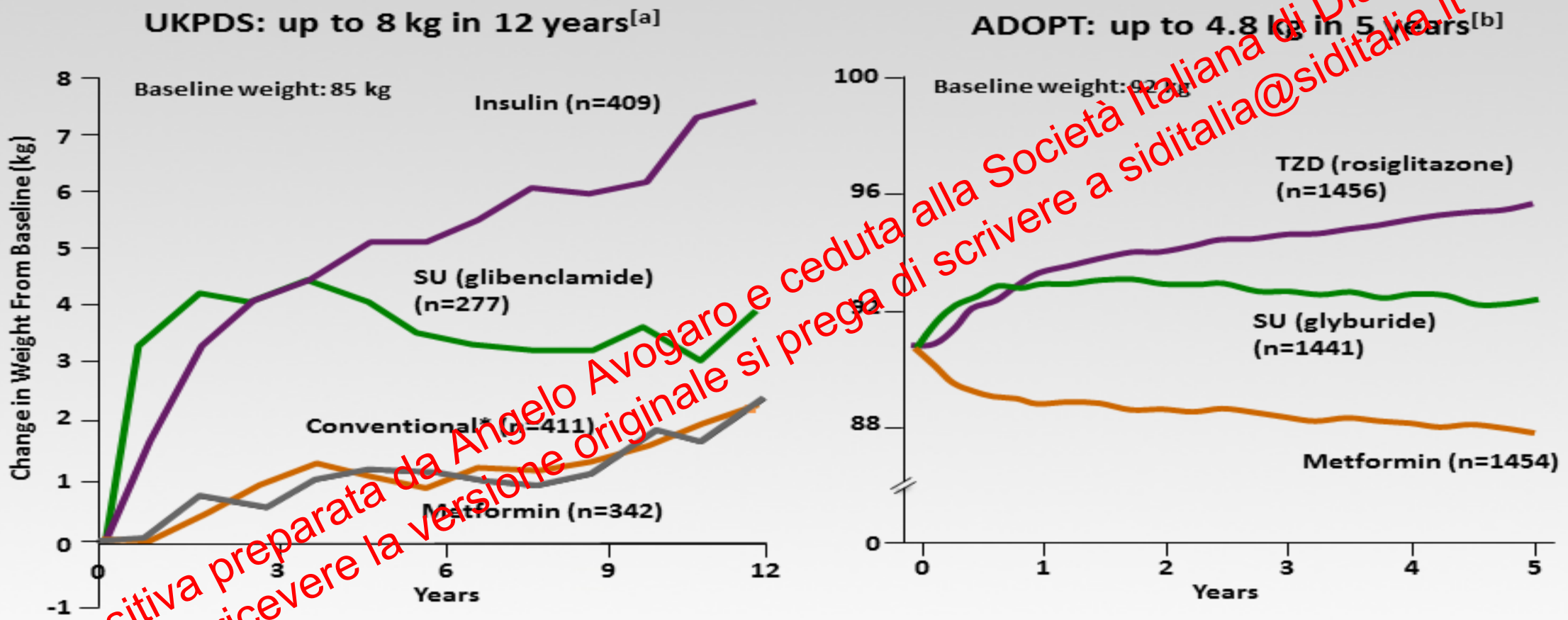
Moef MF, et al. Clin J Am Soc Nephrol. 2009;4:1121-7.

Association of hypoglycemia and cardiac ischemia. A study based upon continuous glucose monitoring and ECG monitoring

(Desouza et al; Diabetes Care 26: 1485, 2003)

	Total episodes	Episodes with cardiac pain	Episodes with ECG abnormalities
Hypoglycemia	54	10	6
Asymptomatic	28	-	2
Symptomatic	26	10	4
Normoglycemia	-	0	0
Hyperglycemia	59	1	0
Glucose increase >100 mg in 1 h	50	9	2

Many Current Antihyperglycemic Agents Result in Weight Gain Over Time



ADOPT = A Diabetes Outcome Progression Trial; TZD = thiazolidinedione

*Conventional treatment = diet initially, then SUs, insulin, and/or metformin if fasting plasm

a. UKPDS Group. *Lancet.* 1998;352(9131):854-865.
b. Kahn SE, et al. *N Engl J Med.* 2006;355(23):2427-2443.

Università degli Studi di Padova

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/ GU	Contra-Indicated CKD Stage 3B,4,5	Exenatide Contra-Indicated CrCl < 30	Genital Mycotic Infections	Dose Adjustment May be Necessary (Except Linagliptin)	Neutral	May Worsen Fluid Retention	More Hypo Risk	Neutral	Neutral	More Hypo Risk & Fluid Retention	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit		Increased LDL			Neutral	?		Safe		
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects

The Patient who needs Combination Therapy: Data from 15 RCT (Phung et al. DOM 2014)

Mean age: 48-63 years

HbA1c: 7.2-9.9%

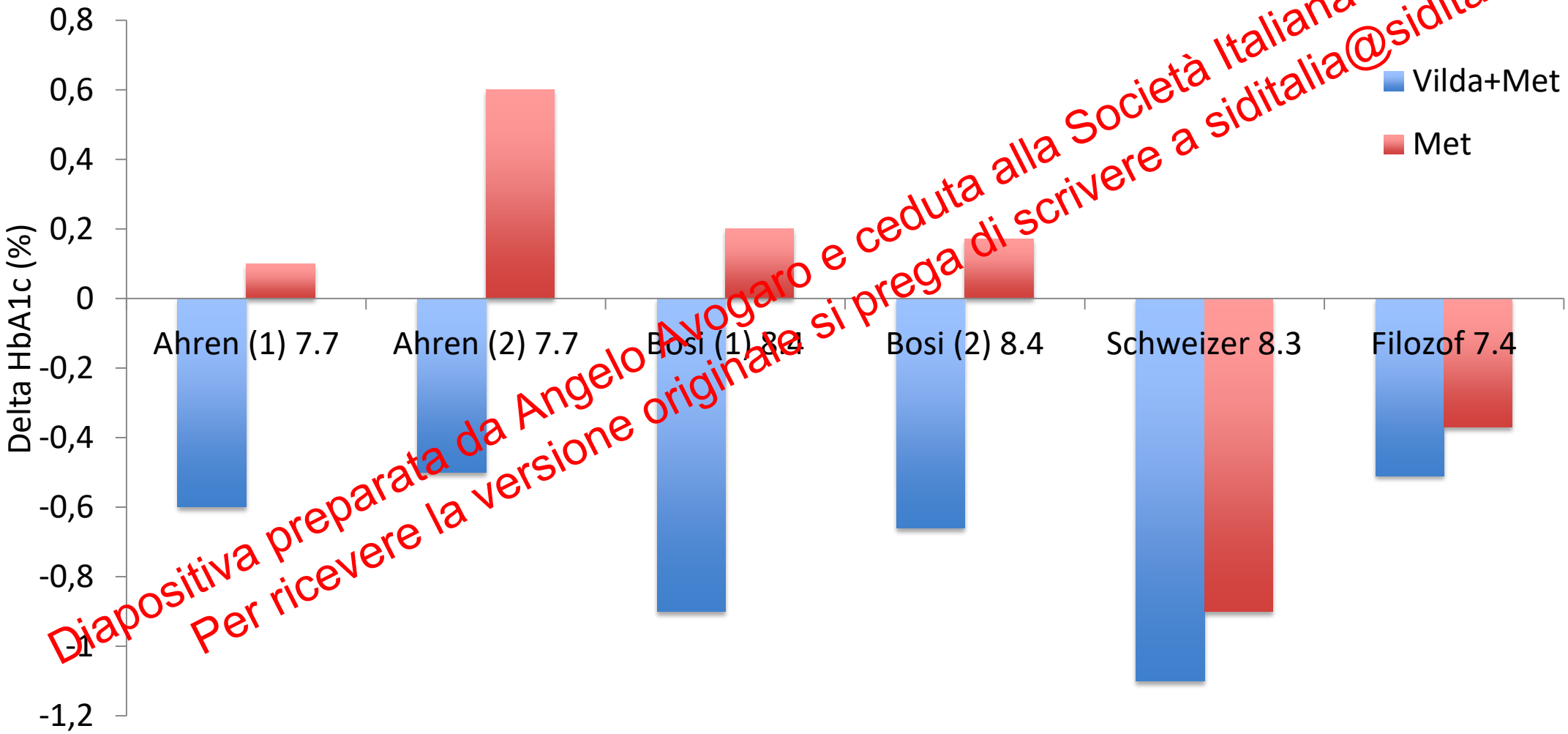
Mean duration of Diabetes: 1.6-4.1 years

Rationale for Combination Therapy

1. Complementary Action between DPP-4 Inhibitors and Metformin
2. Evidence for the Direct Effects of Metformin on GLP-1 Level and Bioactivity
3. The Inhibitory Effect of Metformin on DPP-4 Activity.
4. Upregulation of GLP-1 Receptor Expression by Metformin in Pancreatic Islet β-Cells.

Clinical trials demonstrating the additive effect on glycemic control of combination therapy with vildagliptin and metformin.

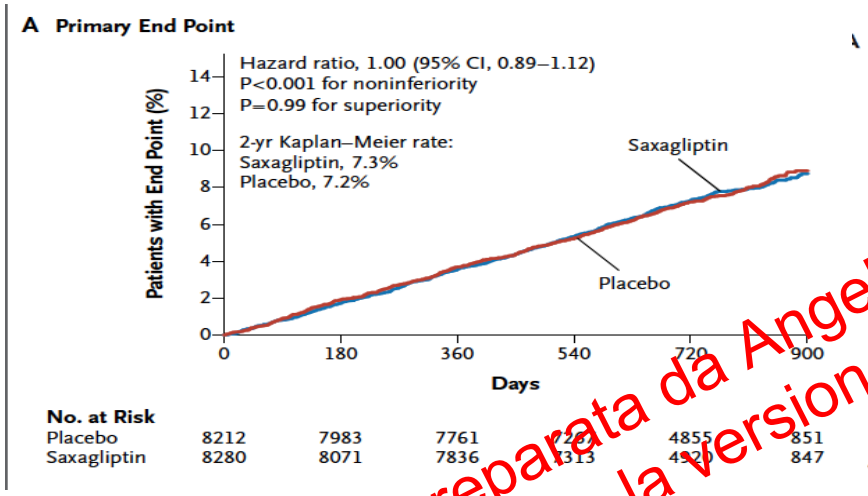
(redrawn from Dotta et al. 2012)



ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

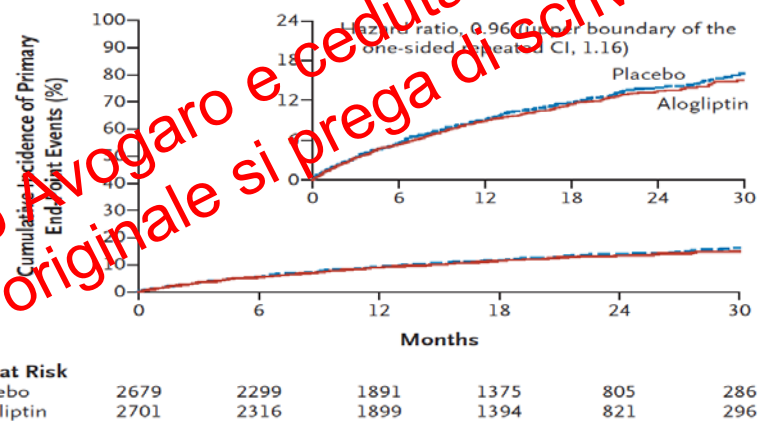
Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. 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*



ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

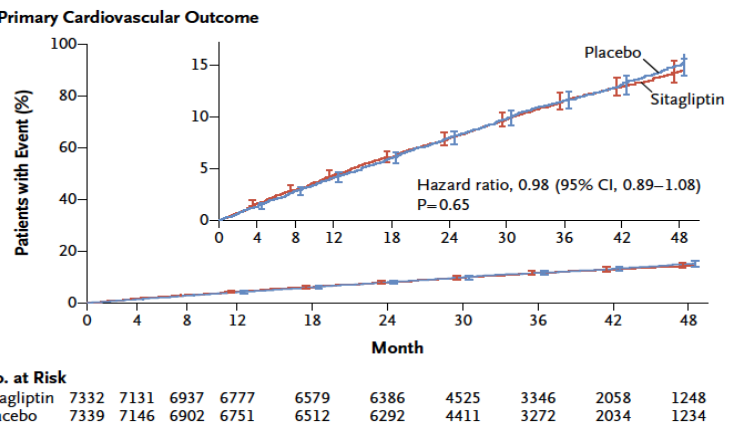
William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez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



ORIGINAL ARTICLE

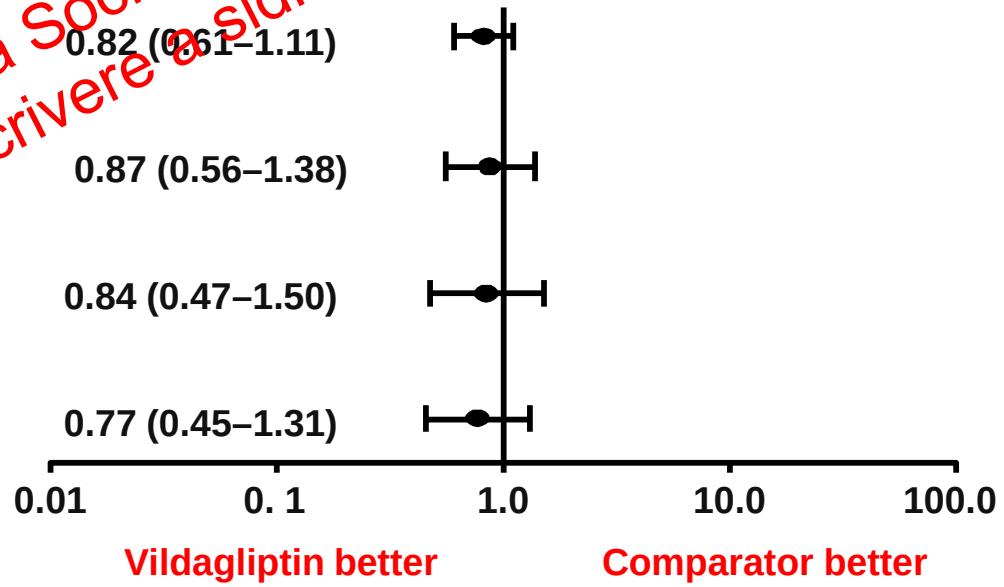
Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Jennifer B. Green, M.D., M. Angelyn Bethel, M.D., Paul W. Armstrong, M.D., John B. Buse, M.D., Ph.D., Samuel S. Engel, M.D., Jyotsna Garg, M.S., Rhonda Josse, M.B., Ch.B., Keith D. Kaufman, M.D., Joerg Koglin, M.D., Joel Mahn, M.D., Richard 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., Shaista 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*



Incidences and risk ratios for adjudicated MACE* and its individual components

	Vildagliptin n/N (%)	Comparators n/N (%)	M-H RR (95% CI)
MACE composite endpoint	83/9599 (0.86)	85/7102 (1.20)	0.82 (0.61–1.11)
Myocardial infarction	38/9599 (0.40)	35/7102 (0.49)	0.87 (0.56–1.38)
Stroke	24/9599 (0.25)	25/7102 (0.35)	0.84 (0.47–1.50)
CV death	25/9599 (0.26)	28/7102 (0.39)	0.77 (0.45–1.31)



*MACE, major adverse cardiovascular (CV) events–non-fatal myocardial infarction, non-fatal stroke or CV death
Vildagliptin = 50 mg qd/bid; M-H RR, Mantel-Haenszel risk ratio
Adapted from McInnes G et al. Poster no 891 presented at the 50th EASD Annual Meeting, Sep 15–19, 2014, Vienna, Austria.

Hospitalisations for heart failure, DPP-4i class effect?

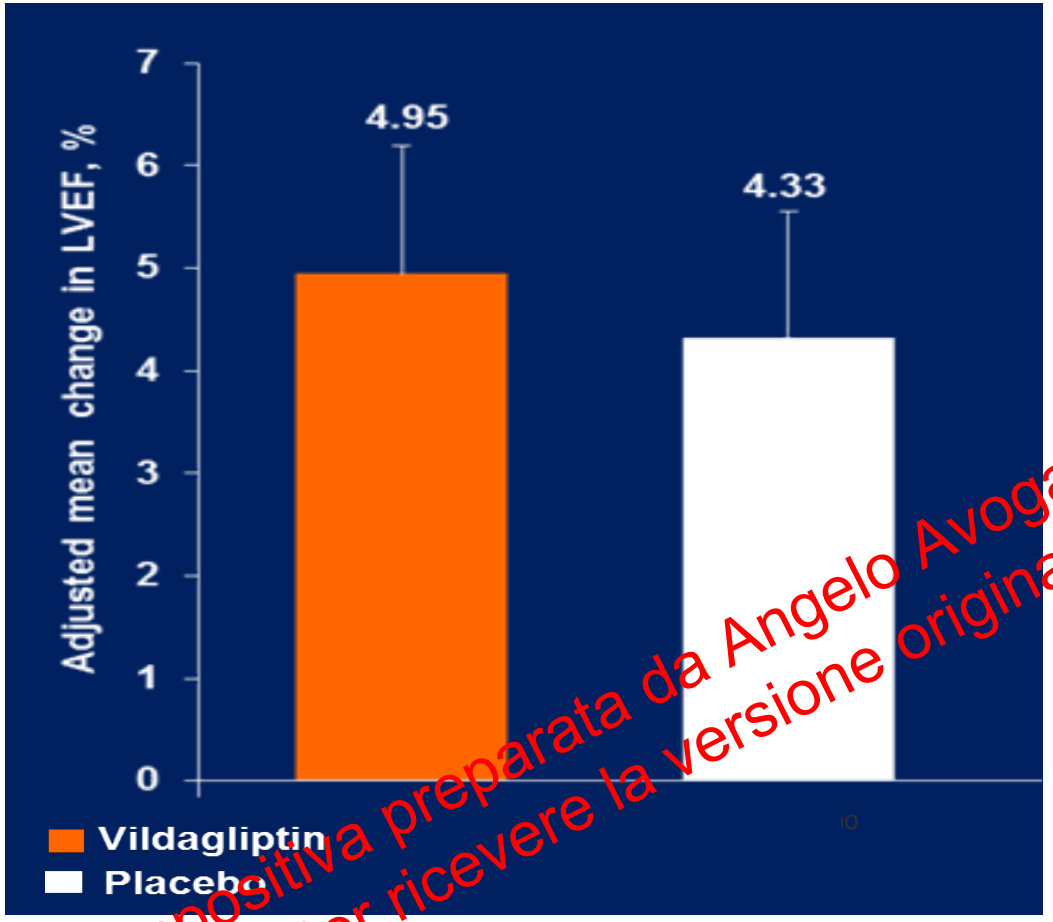
Combined analysis

Analysis	DPP-4i's	Placebo	HR (95%CI)	P value
SAVOR TIMI *(n=16,492)*	289 (3.5%)	228 (2.8%)	1.27 (1.07,1.51)	0.009
EXAMINE *(n=5380)*	106 (3.9%)	89 (3.3%)	1.19 (0.89, 1.58)	0.238
TECOS *(n=14,671)*	228 (3.1%)	229 (3.1%)	1.00 (0.83, 1.20)	0.983
COMBINED ANALYSIS	623 (3.4%)	546 (3.0%)	*1.14 (0.97, 1.34)*	

Test for heterogeneity for 3 trials:
$p=0.178$, $I^2= 42\%$

Presented at ADA2015 on June 8th, unpublished data

VIVIDD met it's primary efficacy endpoint (non-inferiority for LVEF change) - *all CV events were adjudicated for VIVIDD*



Patients with event, n(%)	Vildagliptin n=128	Placebo n=125	P value*
Any adjudicated event	35 (27.3)	31 (24.8)	0.646
CV death	7 (5.5)	4 (3.2)	0.377
HF	23 (18.0)	22 (17.6)	0.939
hHF	13 (10.2)	10 (8.0)	0.552

*P values were based on CMH test (or Fisher exact test if 25% of the expected frequency is <5)

Krum H et al. No significant difference in risk of heart failure hospitalization with vildagliptin in diabetic patients with systolic chronic heart failure: VIVIDD study. Poster presented at the 74th Scientific Sessions of the American Diabetes Association (ADA), June 13–17, 2014, San Francisco, CA, USA

European Heart Journal
doi:10.1093/eurheartj/ehv301

Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database

Gian Paolo Fadini[1], Angelo Avogaro[1]*, Luca Degli Esposti[2], Pierluigi Russo[3], Stefania Saragoni[2], Stefano Buda[2], Giuseppe Rosano[3,4,5], Sergio Pecorelli[3,6], and Luca Pani[3], on behalf of the OsMed Health-DB Network[†]

	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Glucose-lowering medications				
Sulphonylureas (reference)	1.000		1.000	
Glitazones	0.926 (0.807–1.063)	0.277	0.777 (0.635–0.950)	0.014
DPP-4 inhibitors	0.751 (0.630–0.895)	0.001	0.642 (0.510–0.808)	<0.001

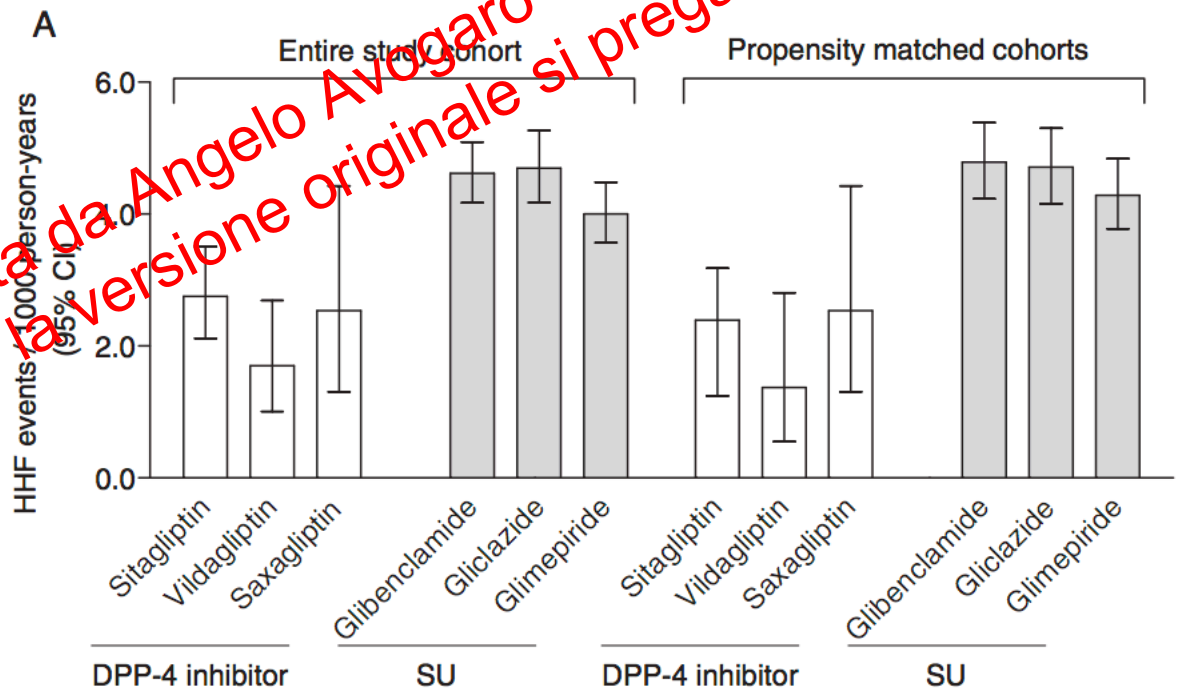
Received: 31 January 2017 | Revised: 5 April 2017 | Accepted: 18 April 2017
DOI: 10.1111/dom.12979

WILEY

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

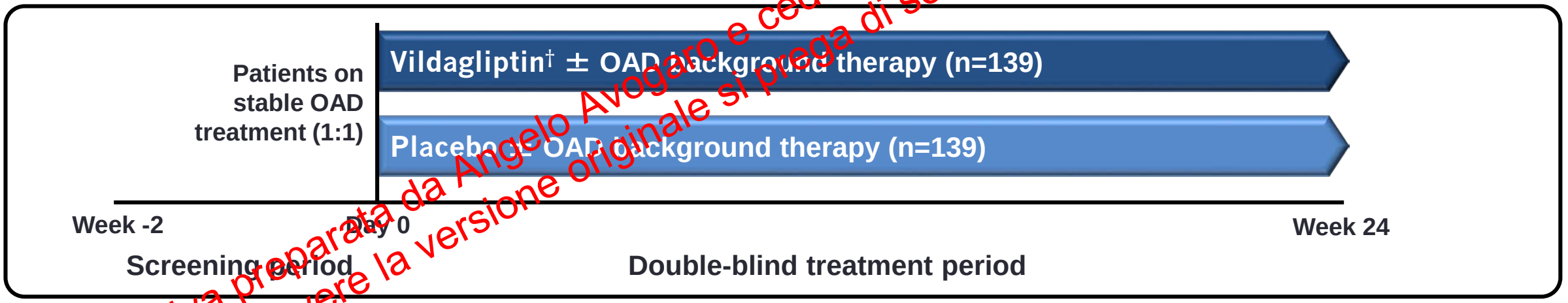
Gian Paolo Fadini MD, PhD[1†] | Stefania Saragoni PhD[3†] | Pierluigi Russo MD[2] | Luca Degli Esposti PhD[3] | Saula Vigili de Kreutzenberg MD, PhD[2] | Mario Melazzini MD[2] | Angelo Avogaro MD, PhD[1] | on behalf of the OsMed Health DB Network[‡]



INTERVAL: randomised study with individualised treatment targets

- **INTERVAL**: **IN**dividualised **T**reatment targets for **E**lde**R**ly patients with type 2 diabetes using **V**ildagliptin **A**dd-on or **L**one therapy

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



*Patients with T2DM, ≥70 years old; †Patients who were drug-naive 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 intolerance[2]
OAD = oral antidiabetic agent

Strain WD et al. Lancet. 2013;382:409–16

INTERVAL Study: Baseline Data

	Vildagliptin (n=139)	Placebo (n=139)
Age (years)	75·1 (4·3)	74·4 (4·0)
Range	70·0–97·0	70·0–89·0
Men	73 (52·5%)	53 (38·1%)
Race		
White	135 (97·1%)	134 (96·4%)
Other	4 (2·9%)	5 (3·6%)
Systolic blood pressure (mm Hg)	137·0 (13·3)	137·5 (15·8)
Diastolic blood pressure (mm Hg)	76·8 (8·3)	76·9 (7·9)
Body-mass index (kg/m²)	29·1 (3·8)	30·5 (4·8)
HbA_{1c} (%)	7·9 (0·8)	7·9 (0·7)
Fasting plasma glucose (mmol/L)	9·6 (2·3)	9·9 (2·1)
Duration of type 2 diabetes (years)	12·2 (7·9)	10·9 (6·9)
Range	1·3–35·0	0·3–35·8
GFR (MDRD) (mL/min/1·73 m²)		
Normal (>80)	34 (24·5%)	31 (22·3%)
Mild (≥50 to ≤80)	86 (61·9%)	87 (62·6%)
Moderate (≥30 to <50)	19 (13·7%)	21 (15·1%)
Frailty status		
Yes	12 (8·6%)	14 (10·1%)
No	126 (90·6%)	123 (88·5%)
Missing	1 (0·7%)	2 (1·4%)

Data are mean (SD) or number (%). HbA_{1c}=glycosylated haemoglobin A_{1c}. GFR (MDRD)=glomerular filtration rate estimated using the modification of diet in renal disease formula.

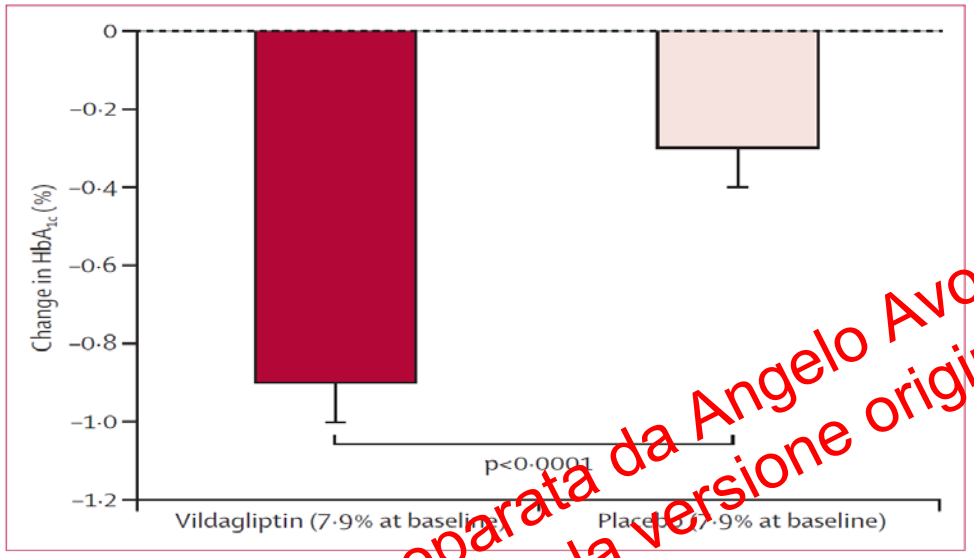
Table 1: **Baseline demographics and clinical characteristics**

Metformin and sulphonylureas were the most frequently used OADs; of the randomly assigned patients, nearly half were taking metformin, whereas a third were using sulphonylureas.

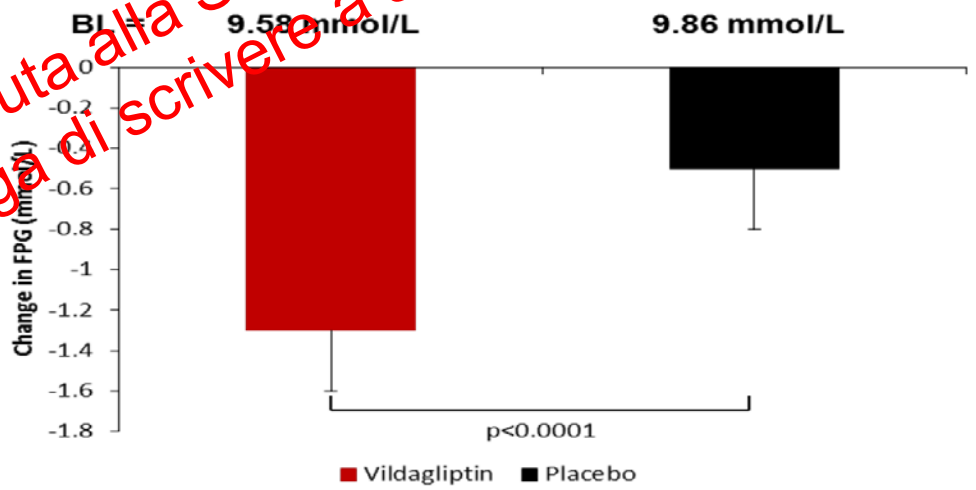
Strain et al, Lancet online May 23, 2013

INTERVAL Study: Vildagliptin reduces HbA_{1c} and FPG at 24° week in elderly patients

HbA_{1c}



FPG



Full analysis set was used for analysis.

BL, baseline; HbA_{1c}, glycosylated hemoglobin $A_{1c;}$ SEM, standard error of mean

FPG; fasting plasma glucose.

Strain et al, Lancet 2013

Studio INTERVAL: safety of treatments

	Vildagliptin (n=139)	Placebo (n=139)
Overall*	66 (47·5%)	63 (45·3%)
SAEs†	8 (5·8%)	5 (3·6%)
Discontinuations due to AEs	6 (4·3%)	3 (2·2%)
Deaths	1 (0·7%)	1 (0·7%)
AEs (of any severity) in ≥5% of participants in any treatment group		
Dizziness	11 (7·9%)	3 (2·2%)
Headache	8 (5·8%)	4 (2·9%)
Nasopharyngitis	7 (5·0%)	7 (5·0%)
Any predefined risk‡	21 (15·1%)	24 (17·3%)
Hepatic-related AEs	0	0
Infection-related AEs	18 (12·9%)	24 (17·3%)
Pancreatitis-related AEs	0	0
Muscle-related AEs	1 (0·7%)	0
Neuropsychiatric-related AEs	1 (0·7%)	0
Lactic-acidosis-related AEs	0	0
Skin or vascular-related AEs	1 (0·7%)	0
Cardiovascular or cerebrovascular AEs	5 (3·6%)	3 (2·2%)

Most AEs were mild to moderate, occurred at a far lower frequency than expected, and seemed to be less frequent than reported in other studies with DPP4 inhibitors, although such a comparison does have its limitations. Our study further corroborates the safe profile of vildagliptin reported in two separate pooled analyses of vildagliptin studies in elderly patients with type 2 diabetes.

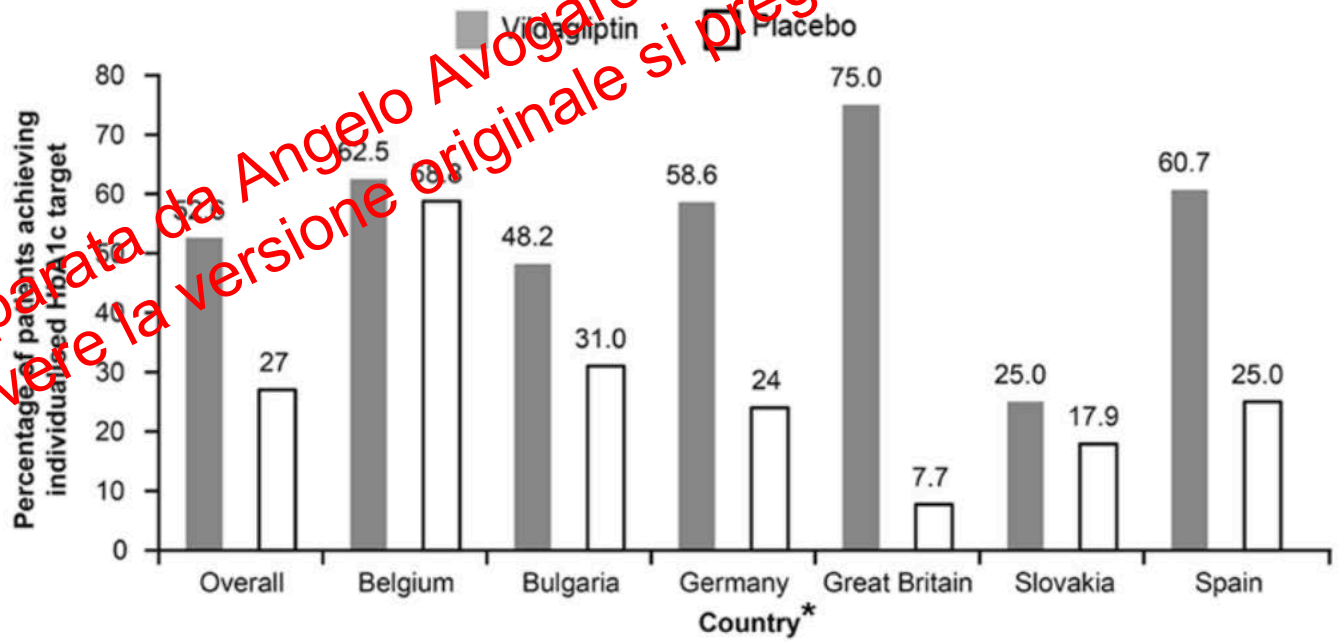
Strain et al, Lancet online May 23, 2013

www.aging-us.com AGING 2017, Vol. 9, No. 3

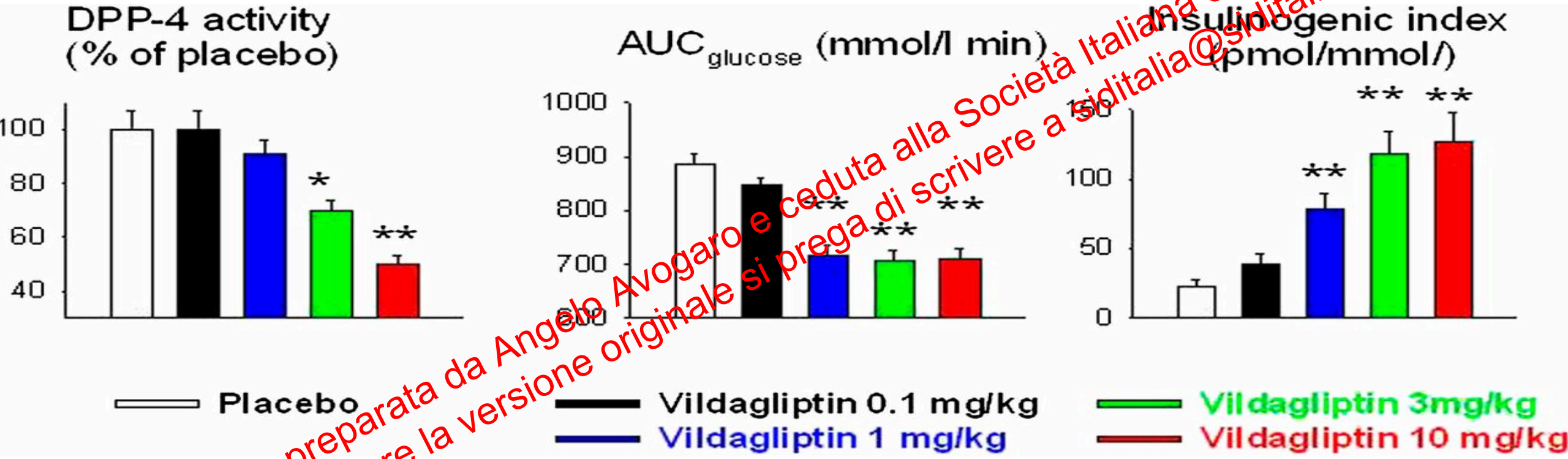
Research Paper

Individualizing treatment targets for elderly patients with type 2 diabetes: factors influencing clinical decision making in the 24-week, randomized INTERVAL study

W. David Strain[1], Abhijit S. Agarwal[2], Päivi M. Paldánius[3]

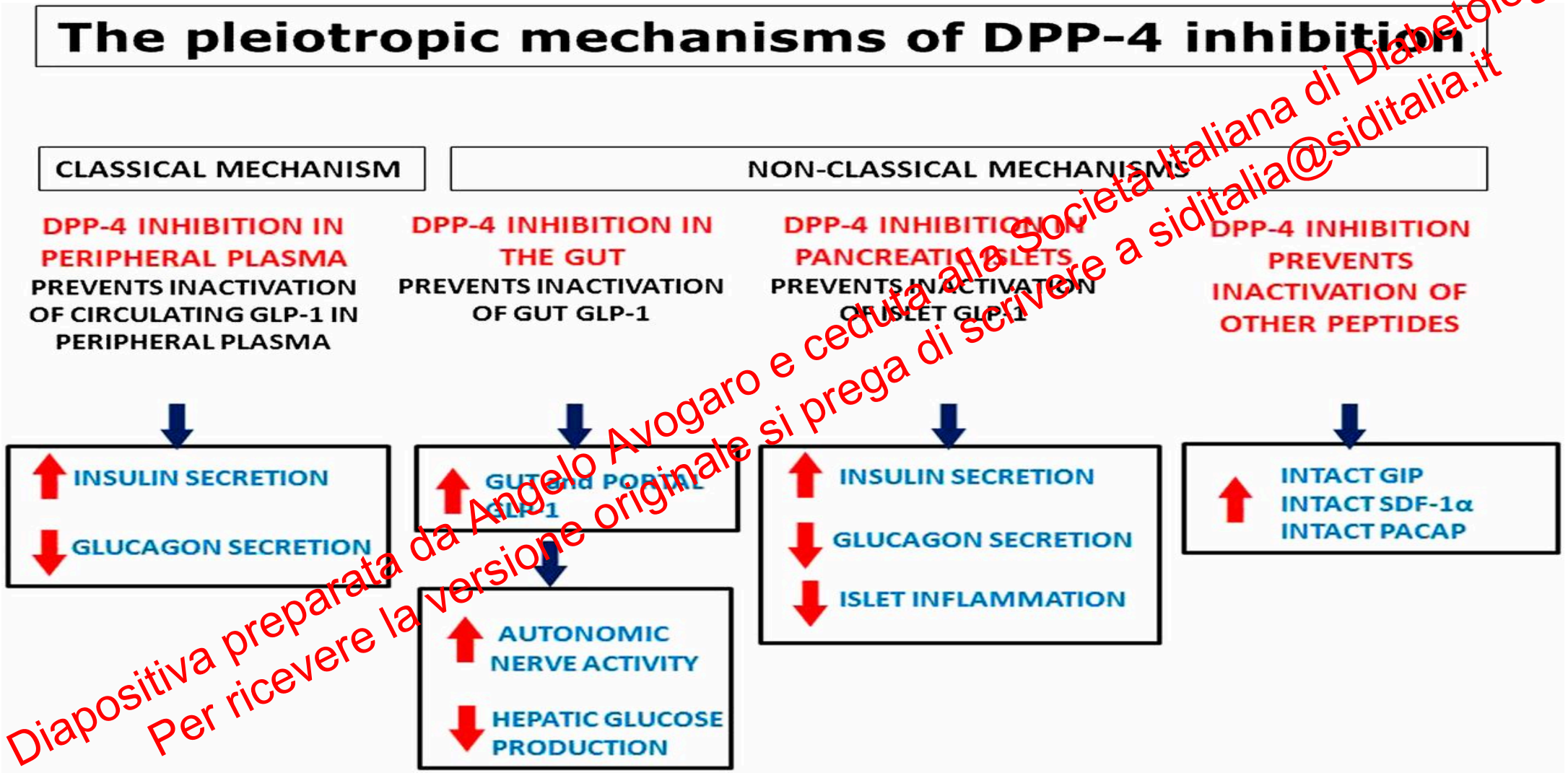


DPP-4 activity in peripheral plasma at 120 min after oral administration of the DPP-4 inhibitor vildagliptin at different doses or placebo



Bilal Omar, and Bo Ahrén Diabetes 2014;63:2196-2202

The classical and nonclassical mechanisms for the glucose-lowering effect of DPP-4 inhibition.



Bilal Omar, and Bo Ahrén Diabetes 2014;63:2196-2202