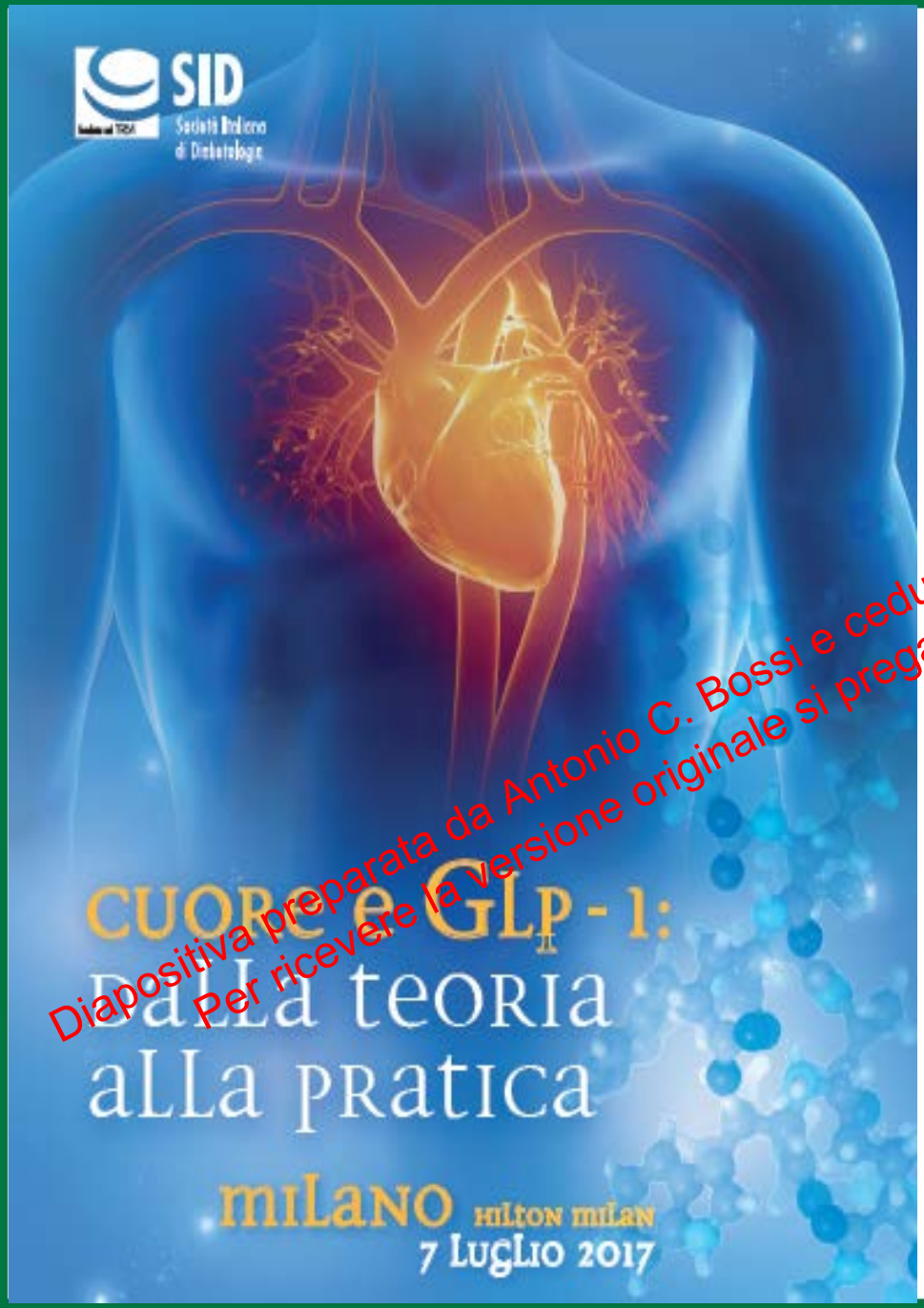

L'evoluzione della terapia del diabete tipo 2

Antonio C. Bossi
UOC Malattie Endocrine –
Centro riferimento regionale Diabete
ASST Bergamo Ovest – Treviglio (Bg)

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

L'evoluzione della terapia del diabete tipo 2

AGENDA

- Introduzione: perché dobbiamo impegnarci a curare bene il diabete
- Milestones dell'evoluzione della terapia del DMT2
  - FDA Guidance for Industry
  - The Ominous Octet
    - Le "incretine"
    - Gli SGLT2 inibitori
  - RCT Outcomes & Real World data
- Considerazioni conclusive
- Q&A

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Centro Regionale Diabete
Centro Studi Aterosclerosi

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L'evoluzione della terapia del diabete tipo 2

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Centro Regionale Diabete
Centro Studi Aterosclerosi

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International Diabetes Federation

UOC Malattie Endocrine
Centro Regionale Diabete
Centro Studi Aterosclerosi

http://www.diabetesatlas.org/

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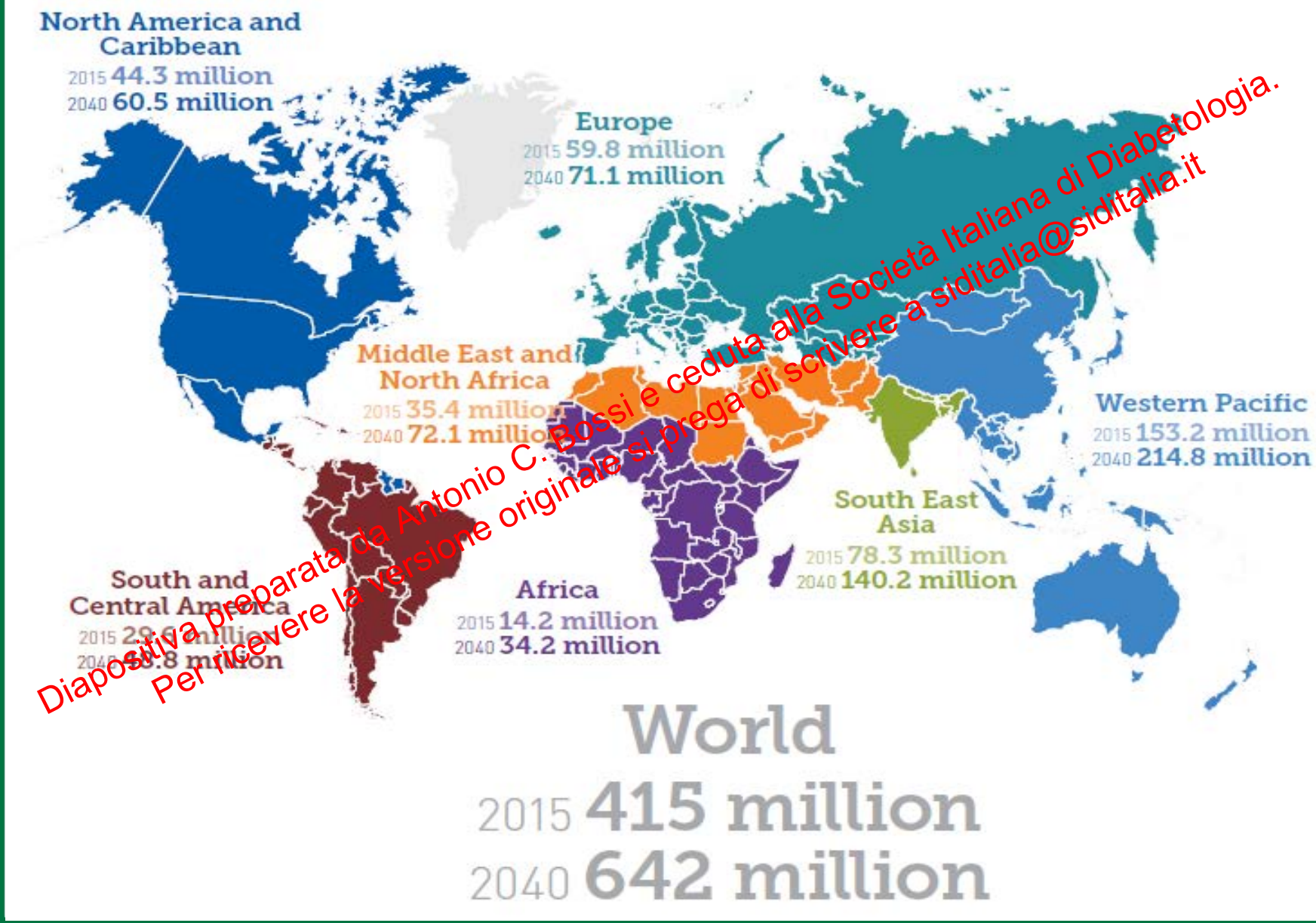
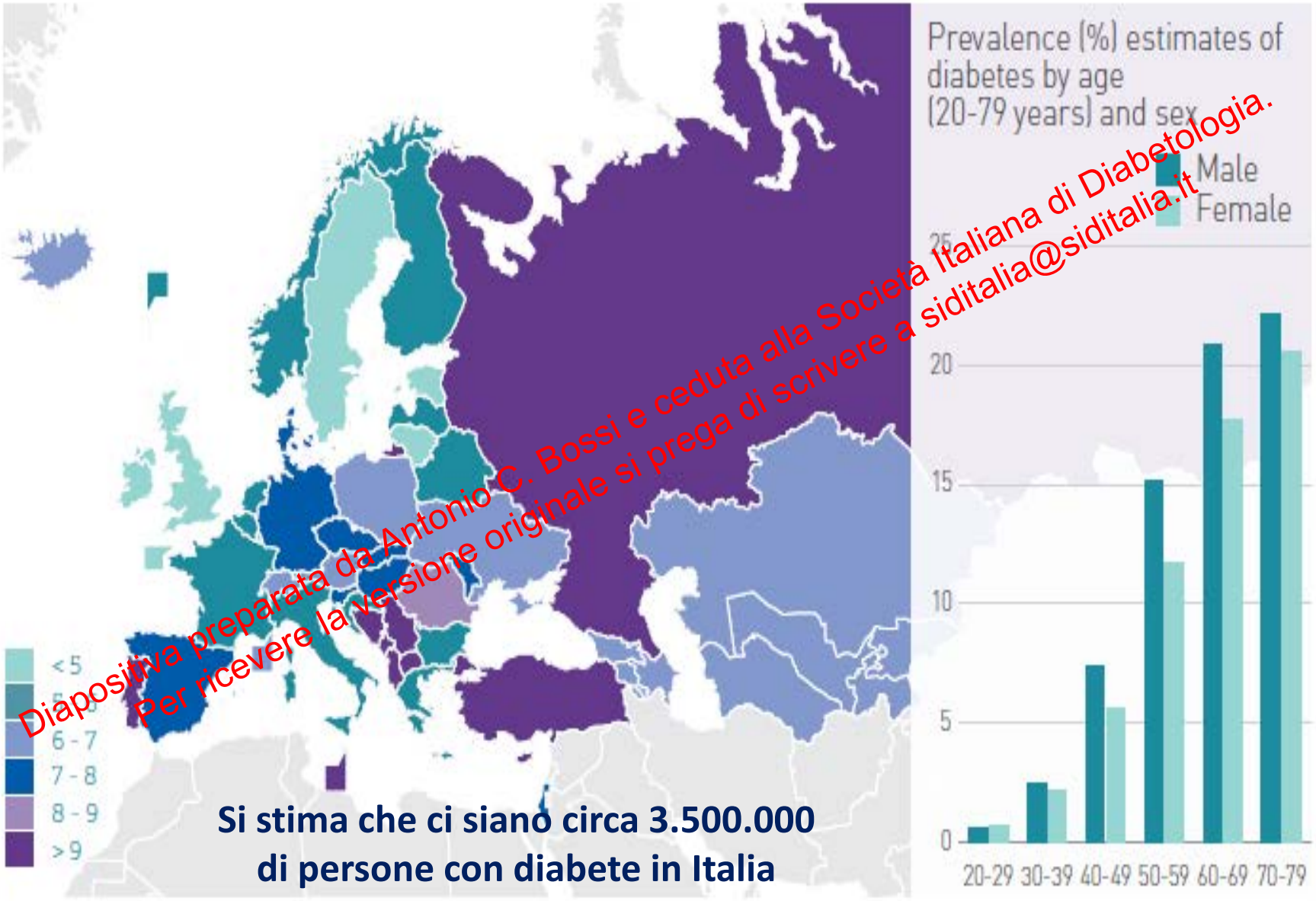
Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



Map 4.2 Prevalence* (%) estimates of diabetes (20-79 years), 2015

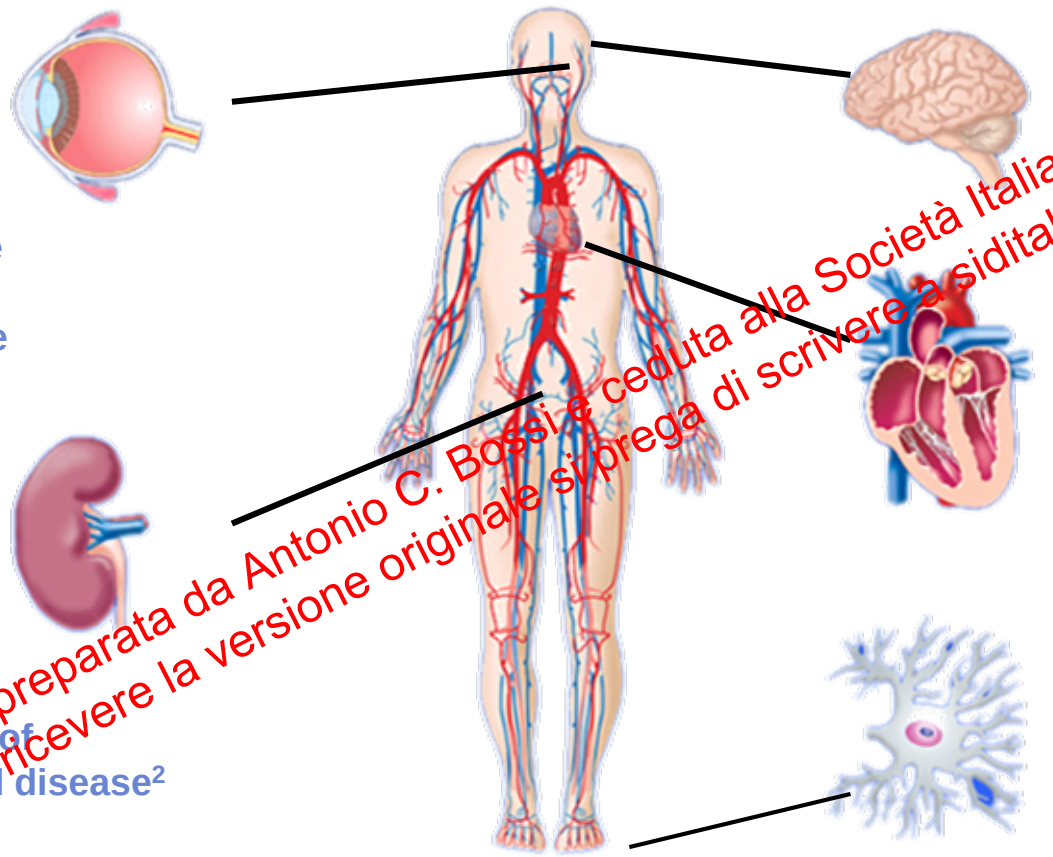


Si stima che ci siano circa 3.500.000 di persone con diabete in Italia

* comparative prevalence

Source: IDF Diabetes Atlas 2015

Il DMT2 è una malattia cronica.
Le sue complicanze micro e macrovascolari sono invalidanti.



Diabetic retinopathy

Leading cause of blindness in working-age adults[1]

Stroke

1.2- to 1.8-fold increase in stroke[3]

Cardiovascular disease

80% diabetic patients die from CV events[4]

Diabetic nephropathy

Leading cause of end-stage renal disease[2]

Diabetic neuropathy and vascular disease

Leading cause of non-traumatic lower extremity amputations[5]

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[1]Fong DS, *et al. Diabetes Care* 2003;26 (Suppl. 1):S99–S102.
[2]Molitch ME, *et al. Diabetes Care* 2003;26 (Suppl. 1):S94–S98.
[3]Kannel WB, *et al. Am Heart J* 1990;120:672–676.
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[5]Mayfield JA, *et al. Diabetes Care* 2003;26 (Suppl. 1):S78–S79.

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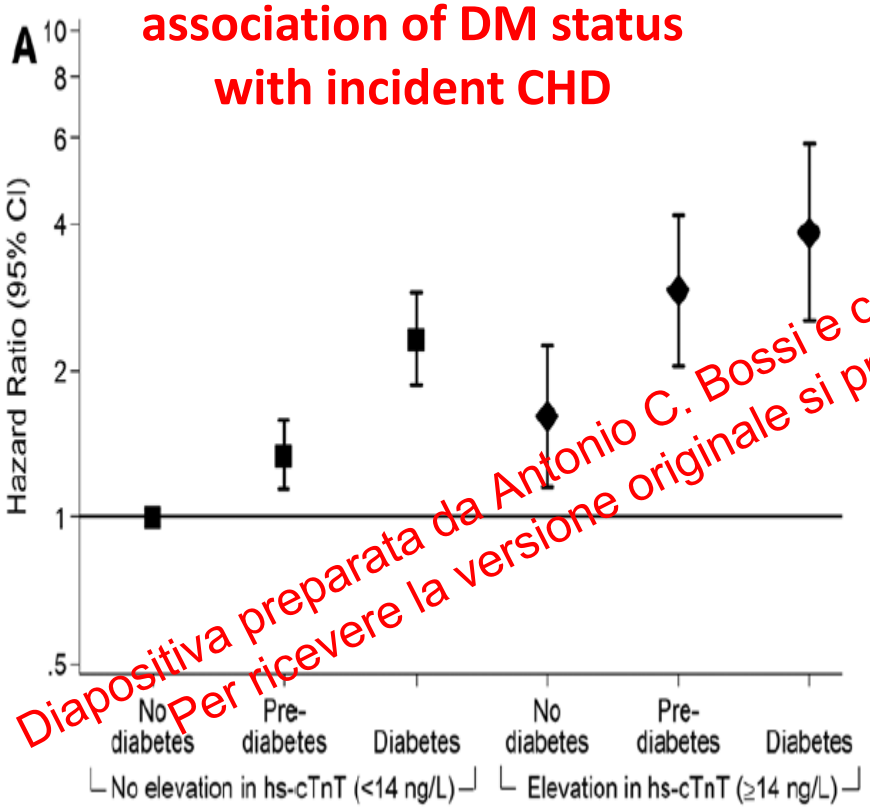
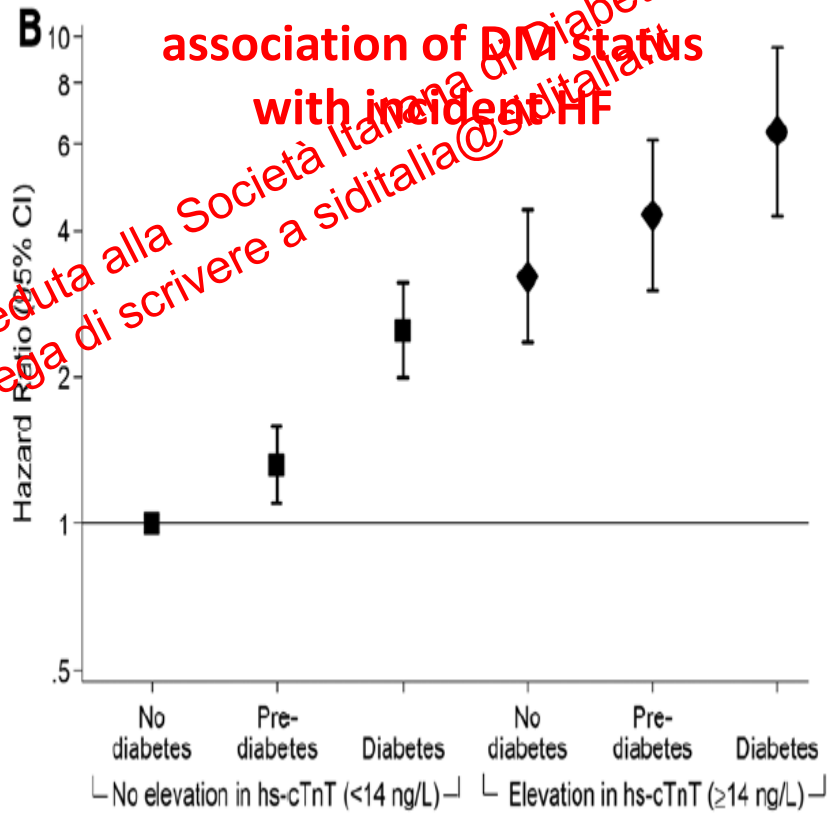
Diabetes Mellitus, Prediabetes, and Incidence of Subclinical Myocardial Damage

Elizabeth Selvin, PhD, MPH; Mariana Lazo, MD, PhD, ScM; Yuan Chen, MS; Lu Shen, BS; Jonathan Rubin, MD, MHS; John W. McEvoy, MB, BCh, BAO, MRCPI; Ron C. Hoogeveen, PhD; A. Richey Sharrett, MD, DrPH; Christie M. Ballantyne, MD; Josef Coresh, MD, PhD, MHS

association of DM status with incident CHD



association of DM status with incident HF



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Circulation. 2014;130:1374-1382

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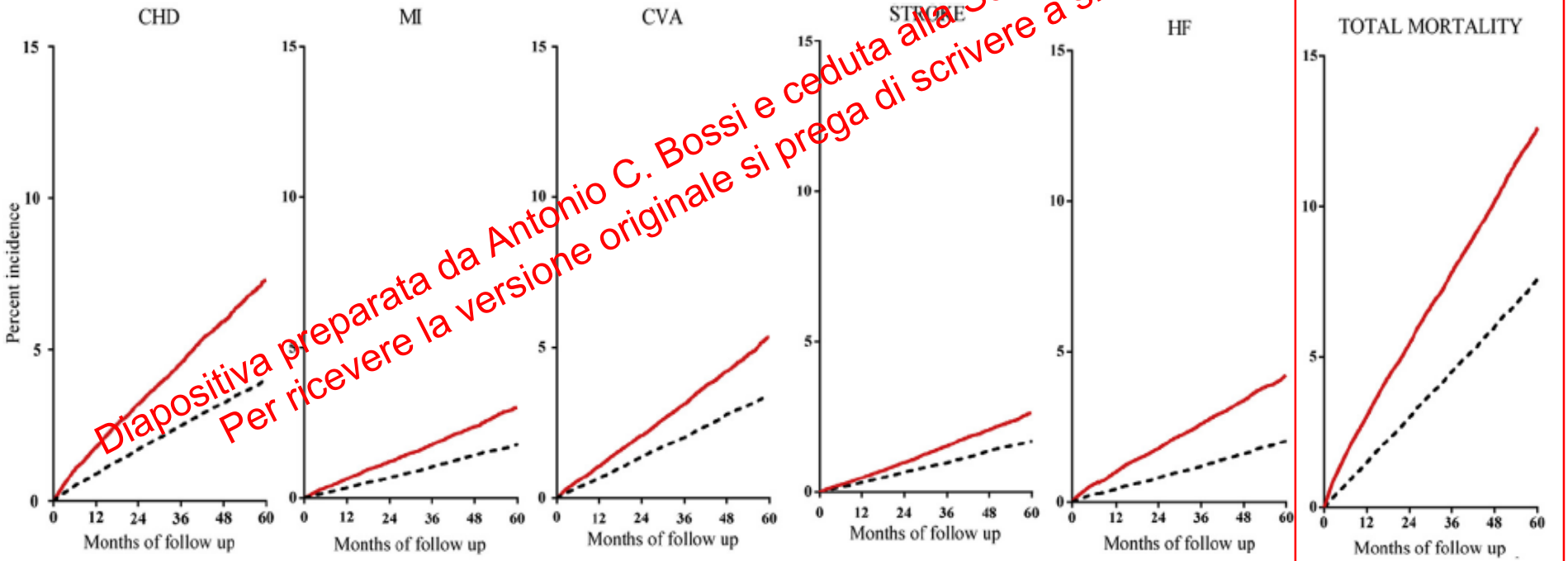
http://dx.doi.org/10.1016/j.numecd.2013.08.005
Nutrition, Metabolism & Cardiovascular Diseases
journal homepage: www.elsevier.com/locate/nmcd

Elevated risk of death and major cardiovascular events in subjects with newly diagnosed diabetes: Findings from an administrative database

L. Monesi [a], M. Tettamanti [b], L. Cortesi [a], M. Baviera [a], I. Marzona [a], F. Avanzini [a], G. Monesi [c], A. Nobili [d], E. Riva [b], I. Fortino [e], A. Bortolotti [e], G. Fontana [e], L. Merlino [e], R. Trevisan [f], M.C. Roncaglioni [a,*]



p (Long-rank test) <0.001 for all comparisons

Incidenza %

Patients with newly diagnosed diabetes — Subjects without diabetes

Diabetes Care Volume 37, February 2014

HbA_{1c} and Coronary Heart Disease Risk Among Diabetic Patients

Wenhui Zhao,[1] Peter T. Katzmarzyk,[1] Ronald Horswell,[1] Yujie Wang,[1] Jolene Johnson,[2] and Gang Hu[1]

Table 3—HR (95% CI) of CHD according to different levels of HbA_{1c} at baseline among various subpopulations

	HbA_{1c} (%) (mmol/mol)							*P* for trend	*P* for interaction
	<6.0 (42)	6.0–6.9 (42–52)	7.0–7.9 (53–63)	8.0–8.9 (64–74)	9.0–9.9 (75–85)	10.0–10.9 (86–96)	≥11.0 (97)		
Sex									<0.05
Male	1.00	1.07 (0.96–1.19)	1.13 (0.99–1.28)	1.25 (1.08–1.44)	1.40 (1.20–1.63)	1.22 (1.03–1.44)	1.33 (1.16–1.52)	<0.001	
Female	1.00	1.05 (0.96–1.14)	1.17 (1.06–1.30)	1.19 (1.06–1.34)	1.27 (1.12–1.45)	1.38 (1.19–1.60)	1.30 (1.16–1.46)	<0.001	
Age-groups, years									<0.001
<50	1.00	1.00 (0.88–1.13)	1.05 (0.90–1.21)	1.02 (0.88–1.19)	1.14 (0.98–1.34)	1.08 (0.92–1.28)	1.11 (0.97–1.28)	0.46	
50–59	1.00	1.06 (0.95–1.19)	1.21 (1.07–1.38)	1.30 (1.12–1.50)	1.27 (1.07–1.50)	1.47 (1.23–1.75)	1.36 (1.18–1.57)	<0.001	
60–94	1.00	1.09 (0.97–1.23)	1.14 (0.98–1.32)	1.25 (1.04–1.51)	1.67 (1.34–2.08)	1.14 (0.84–1.54)	1.19 (0.94–1.52)	0.001	
Smoking status									<0.025
Never	1.00	1.11 (1.02–1.21)	1.21 (1.11–1.33)	1.25 (1.12–1.39)	1.41 (1.25–1.59)	1.39 (1.22–1.59)	1.41 (1.27–1.57)	<0.001	
Ever or current	1.00	0.92 (0.80–1.04)	1.02 (0.88–1.19)	1.14 (0.97–1.35)	1.16 (0.97–1.38)	1.10 (0.91–1.34)	1.10 (0.94–1.29)	0.053	
Using glucose-lowering agents									<0.001
No	1.00	1.09 (0.98–1.23)	1.21 (1.05–1.41)	1.39 (1.17–1.64)	1.40 (1.14–1.72)	1.29 (1.03–1.60)	1.45 (1.22–1.72)	<0.001	
Yes	1.00	1.03 (0.94–1.12)	1.13 (1.02–1.24)	1.15 (1.03–1.28)	1.29 (1.15–1.45)	1.29 (1.14–1.47)	1.26 (1.13–1.39)	<0.001	
Income									<0.001
<Median of income	1.00	1.00 (0.91–1.10)	1.15 (1.02–1.28)	1.20 (1.06–1.36)	1.19 (1.03–1.37)	1.28 (1.09–1.49)	1.26 (1.12–1.43)	<0.001	
≥Median of income	1.00	1.11 (1.01–1.22)	1.17 (1.04–1.30)	1.22 (1.07–1.39)	1.48 (1.29–1.69)	1.32 (1.13–1.54)	1.34 (1.18–1.52)	<0.001	

Adjusted for age, sex, race, type of insurance, income, smoking, BMI, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, glomerular filtration rate, and use of antihypertensive drugs, glucose-lowering agents, and cholesterol-lowering agents at baseline, other than the variable for stratification.

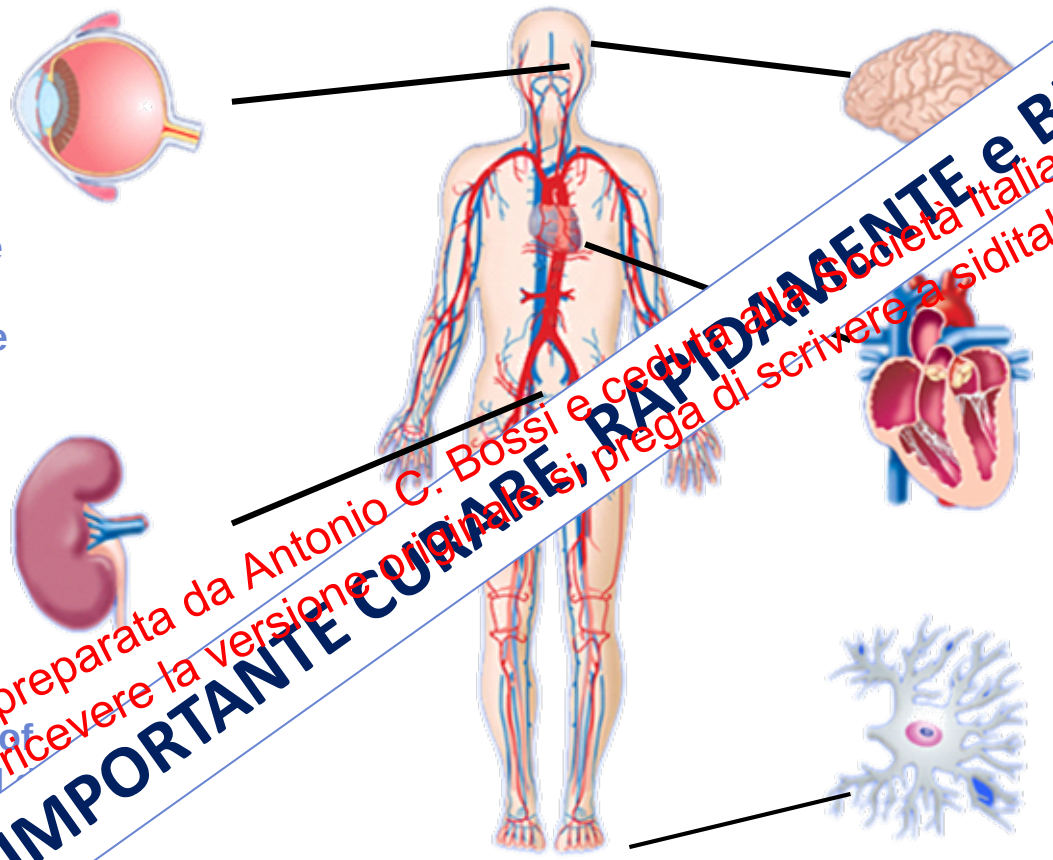
EARLY RELEASE: The Journal of Clinical Endocrinology & Metabolism
J Clin Endocrin Metab. First published ahead of print December 2, 2013 as doi:10.1210/jc.2013-3325

HbA1c and Heart Failure Risk among Diabetic Patients

Wenhui Zhao, Peter T. Katzmarzyk, Ronald Horswell, Yujie Wang, Jolene Johnson, Gang Hu

	HbA1c (%)							
	<6.0	6.0–6.9	7.0–7.9	8.0–8.9	9.0–9.9	≥10.0	P for trend	P for interaction
Baseline								
Age groups, yr								<0.005
<50	1.00	1.05 (0.90–1.23)	1.08 (0.90–1.29)	1.08 (0.90–1.30)	1.34 (1.08–1.57)	1.35 (1.16–1.57)	<0.001	
50–59	1.00	1.05 (0.92–1.21)	1.20 (1.03–1.40)	1.49 (1.25–1.76)	1.34 (1.10–1.64)	1.55 (1.33–1.81)	<0.001	
60–94	1.00	1.05 (0.90–1.21)	1.09 (0.91–1.29)	1.49 (1.21–1.84)	1.55 (1.20–1.99)	1.56 (1.23–1.97)	<0.001	
Gender								>0.1
Male	1.00	1.05 (0.91–1.20)	1.10 (0.94–1.29)	1.40 (1.18–1.67)	1.45 (1.20–1.74)	1.47 (1.27–1.70)	<0.001	
Female	1.00	1.06 (0.95–1.17)	1.17 (1.03–1.32)	1.32 (1.15–1.51)	1.40 (1.20–1.63)	1.59 (1.40–1.80)	<0.001	
Smoking status								>0.1
Never	1.00	1.11 (1.01–1.23)	1.20 (1.08–1.35)	1.44 (1.27–1.63)	1.48 (1.28–1.70)	1.65 (1.48–1.85)	<0.001	
Ever or current	1.00	0.89 (0.75–1.04)	0.94 (0.81–1.10)	1.11 (0.90–1.37)	1.25 (1.01–1.55)	1.26 (1.05–1.50)	0.001	
Using glucose-lowering agents								<0.001
Follow-up								
Age groups, yr								<0.01
<50	1.00	1.06 (0.89–1.27)	1.13 (0.94–1.36)	1.04 (0.86–1.26)	1.16 (0.95–1.41)	1.29 (1.07–1.55)	0.053	
50–59	1.00	0.92 (0.79–1.08)	1.18 (1.00–1.40)	1.44 (1.21–1.72)	1.49 (1.22–1.82)	1.57 (1.28–1.92)	<0.001	
60–94	1.00	0.99 (0.85–1.16)	1.21 (1.02–1.44)	1.42 (1.14–1.77)	1.52 (1.15–2.01)	1.32 (0.85–2.06)	<0.001	
Gender								>0.1
Male	1.00	0.92 (0.79–1.08)	1.13 (0.97–1.33)	1.34 (1.13–1.59)	1.36 (1.12–1.65)	1.53 (1.27–1.85)	<0.001	
Female	1.00	0.99 (0.88–1.11)	1.19 (1.05–1.35)	1.25 (1.09–1.44)	1.37 (1.18–1.60)	1.49 (1.28–1.75)	<0.001	
Smoking status								>0.1
Never	1.00	1.02 (0.92–1.14)	1.24 (1.11–1.40)	1.29 (1.13–1.46)	1.42 (1.23–1.64)	1.61 (1.40–1.86)	<0.001	
Ever or current	1.00	0.84 (0.69–1.01)	1.00 (0.82–1.21)	1.31 (1.07–1.61)	1.29 (1.03–1.61)	1.33 (1.05–1.67)	<0.001	
Using glucose-lowering agents								<0.001
No	1.00	1.04 (0.91–1.19)	1.25 (1.06–1.48)	1.38 (1.14–1.68)	1.36 (1.08–1.71)	1.75 (1.43–2.15)	<0.001	
Yes	1.00	0.91 (0.81–1.04)	1.11 (0.98–1.26)	1.23 (1.07–1.41)	1.34 (1.15–1.56)	1.39 (1.19–1.62)	<0.001	

Il DMT2 è una malattia cronica.
Le sue complicanze micro e macrovascolari sono invalidanti.



Diabetic retinopathy

Leading cause of blindness in working-age adults[1]

Diabetic nephropathy

Leading cause of end-stage renal

Cardiovascular disease

80% diabetic patients die from CV events[4]

2- to 1[illegible]-fold increase in stroke[3]

Diabetic neuropathy and vascular disease

Leading cause of non-traumatic lower extremity amputations[5]

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L'evoluzione della terapia del diabete tipo 2

AGENDA

- Introduzione: perché dobbiamo impegnarci a curare bene il diabete
- Milestones dell'evoluzione della terapia del DMT2
  - FDA Guidance for Industry

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Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Additional copies are available from:

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Food and Drug Administration
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Silver Spring, MD 20993-0002
E-mail: druginfo@fda.hhs.gov
Fax: 301-847-8714
(Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

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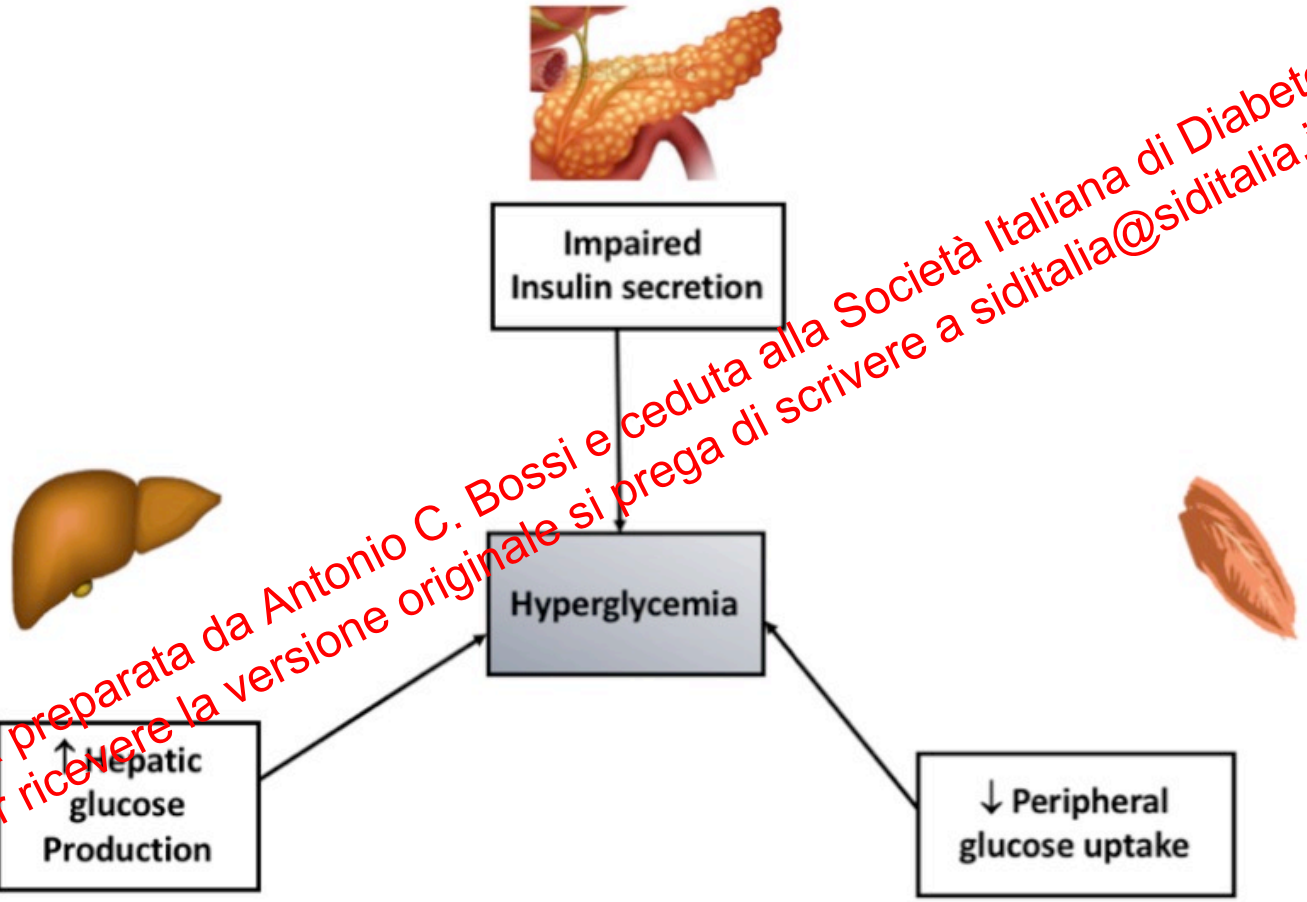
From the Initially Described "Terrible Triumvirate" of Diabetes Pathophysiology…



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Adapted from Ralph A. DeFronzo
Diabetes 2009;58:773-795

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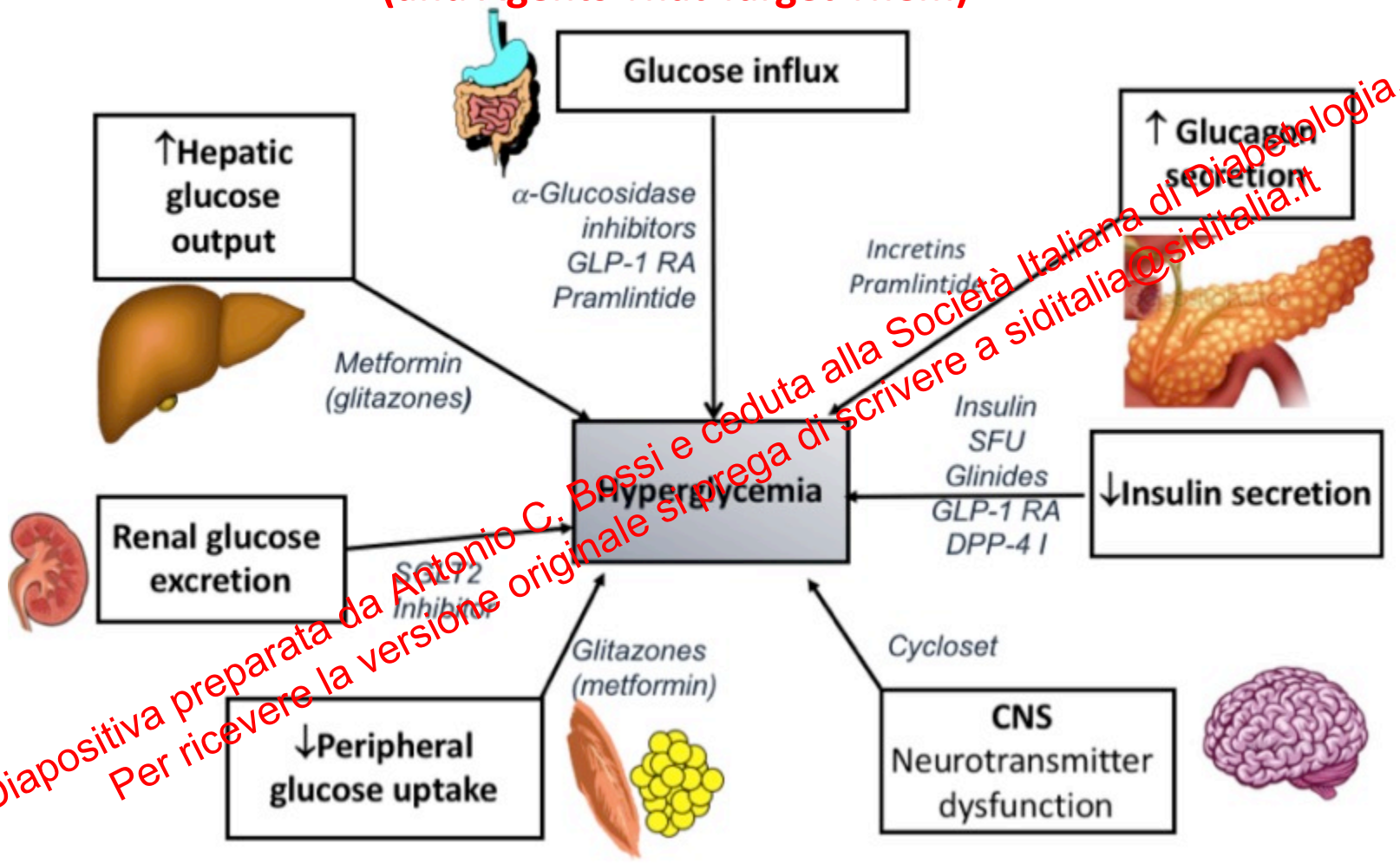
…to the Ominous Octet Pathways
(and Agents That Target Them)



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Mod. from DeFronzo RA.
Diabetes. 2009;58:773-795;
Tahrani AA et al. *Lancet* 2011;378:182–197.

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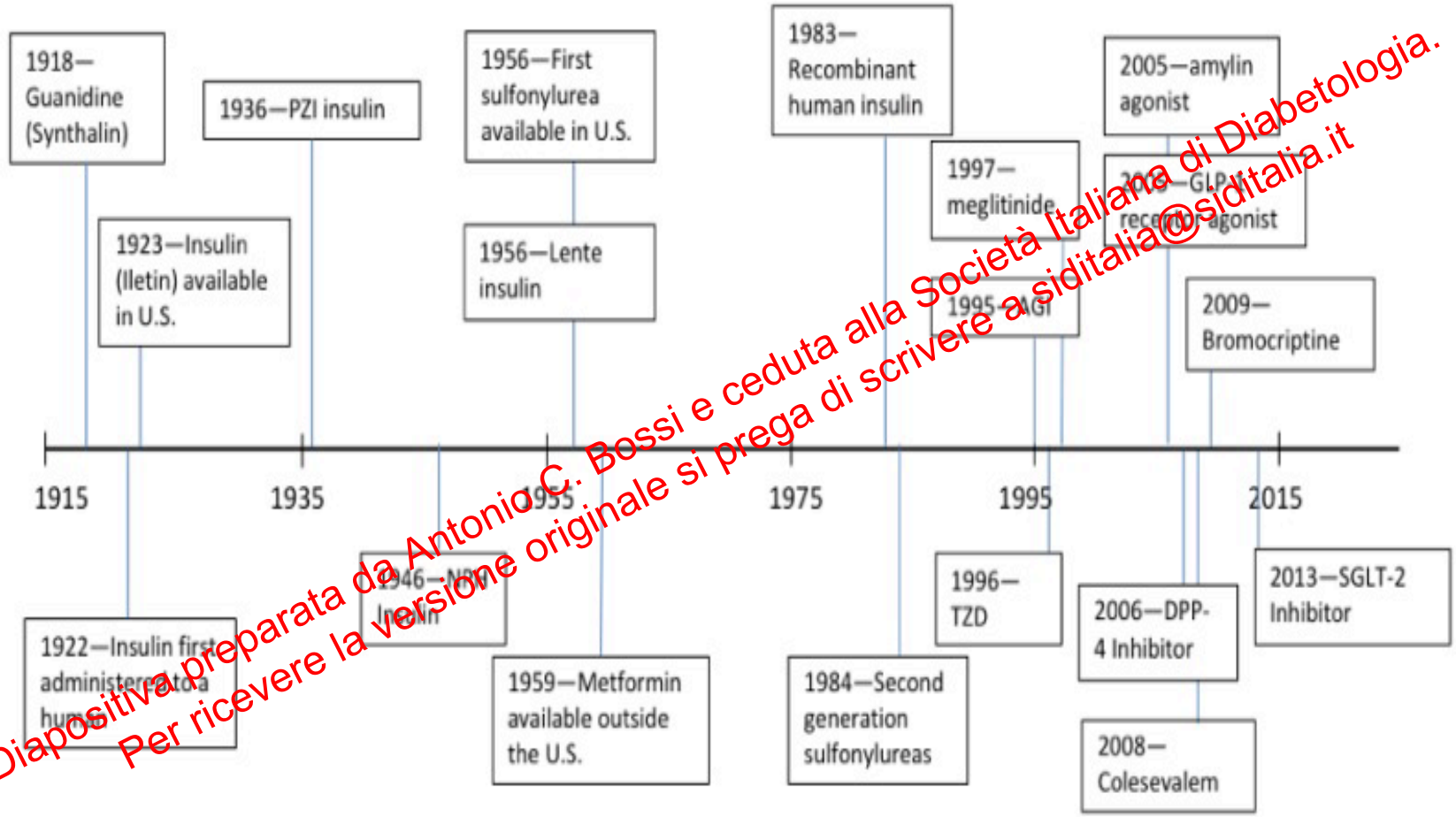
History of Diabetes Medication



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Ruolo dell'inibizione/by-pass dell'enzima DPP-4 nel migliorare il controllo glicemico

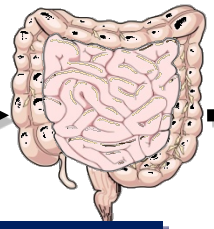
Ingestione del cibo

Rilascio ormoni incretinici:
GLP1→ cellule L tenue distale e colon
GIP→ cellule K duodeno, digiuno,ileo

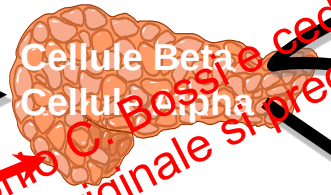
Glucosio dipendente
↑ Insulina
dalle cellule beta
(GLP-1 e GIP)

↑captazione Glucosio nei Muscoli e nel Tessuto Adiposo

Tratto GI



Pancreas



Controllo Glicemico più stabile

GLP-1 e GIP attivi

Agonisti Recettoriali del GLP-1

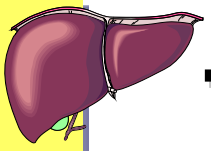
Inibitori DPP-4

Enzima DPP-4

GLP-1 e GIP inattivi

↓ Glucagone
dalle cellule alpha
(GLP-1)
Glucosio dipendente

↓rilascio Glucosio dal Fegato nel circolo ematico



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Brubaker PL, Drucker DJ. *Endocrinology*. 2004;145:2653–2659; Zander M et al. *Lancet*. 2002;359:824–830; Ahrén B. *Curr Diab Rep*. 2003;3:365–372; Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430–441; Holz GG, Chepurny OG. *Curr Med Chem*. 2003;10:2471–2483; Creutzfeldt WOC et al. *Diabetes Care*. 1996;19:580–586; Drucker DJ. *Diabetes Care*. 003;26:2929–2940.

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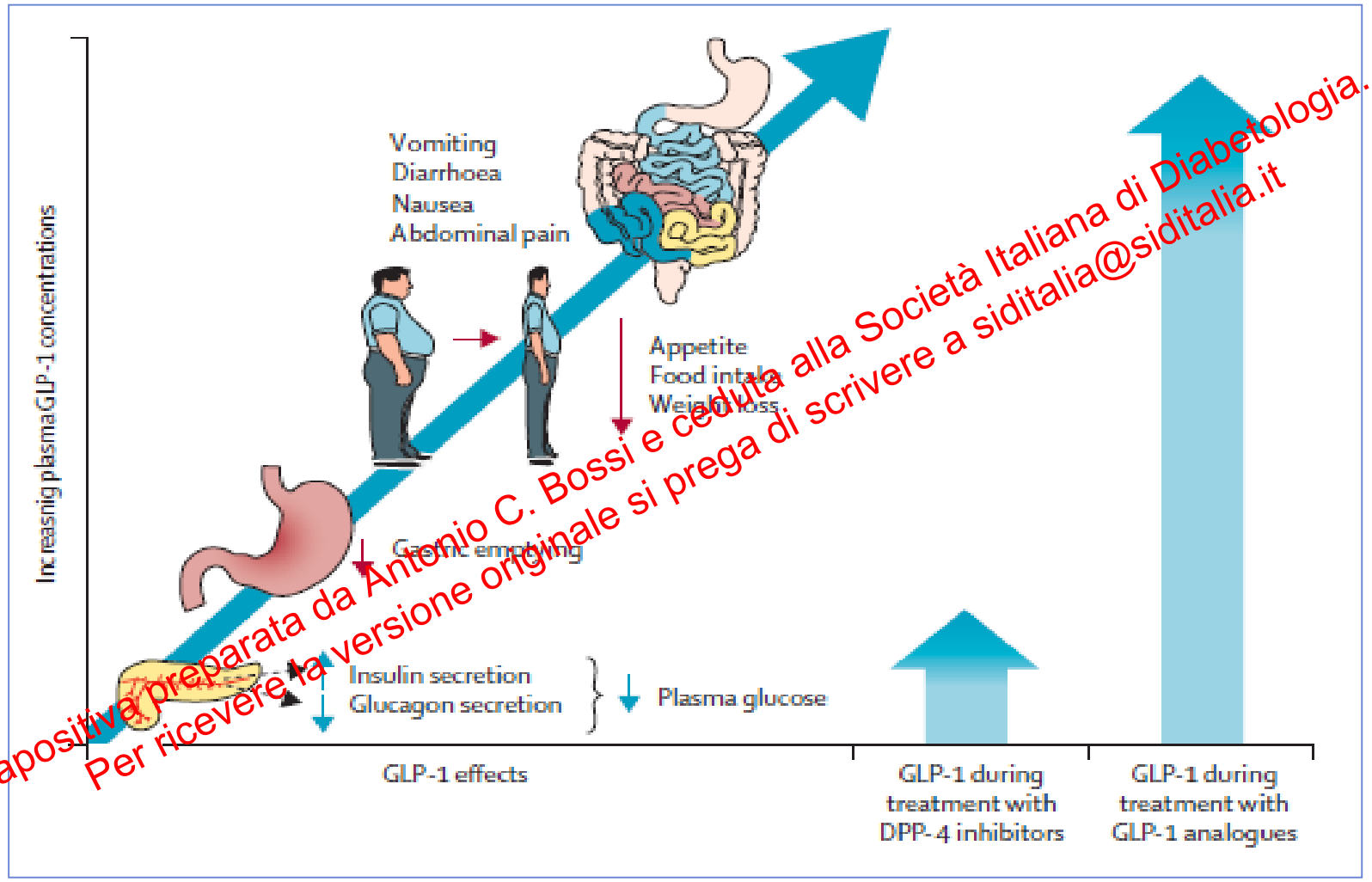
Terapia basata sulle incretine nel diabete mellito



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Sten Madsbad. The Lancet Published **Online** September 25, 2008
DOI:10.1016/S0140-6736(08)61247-7

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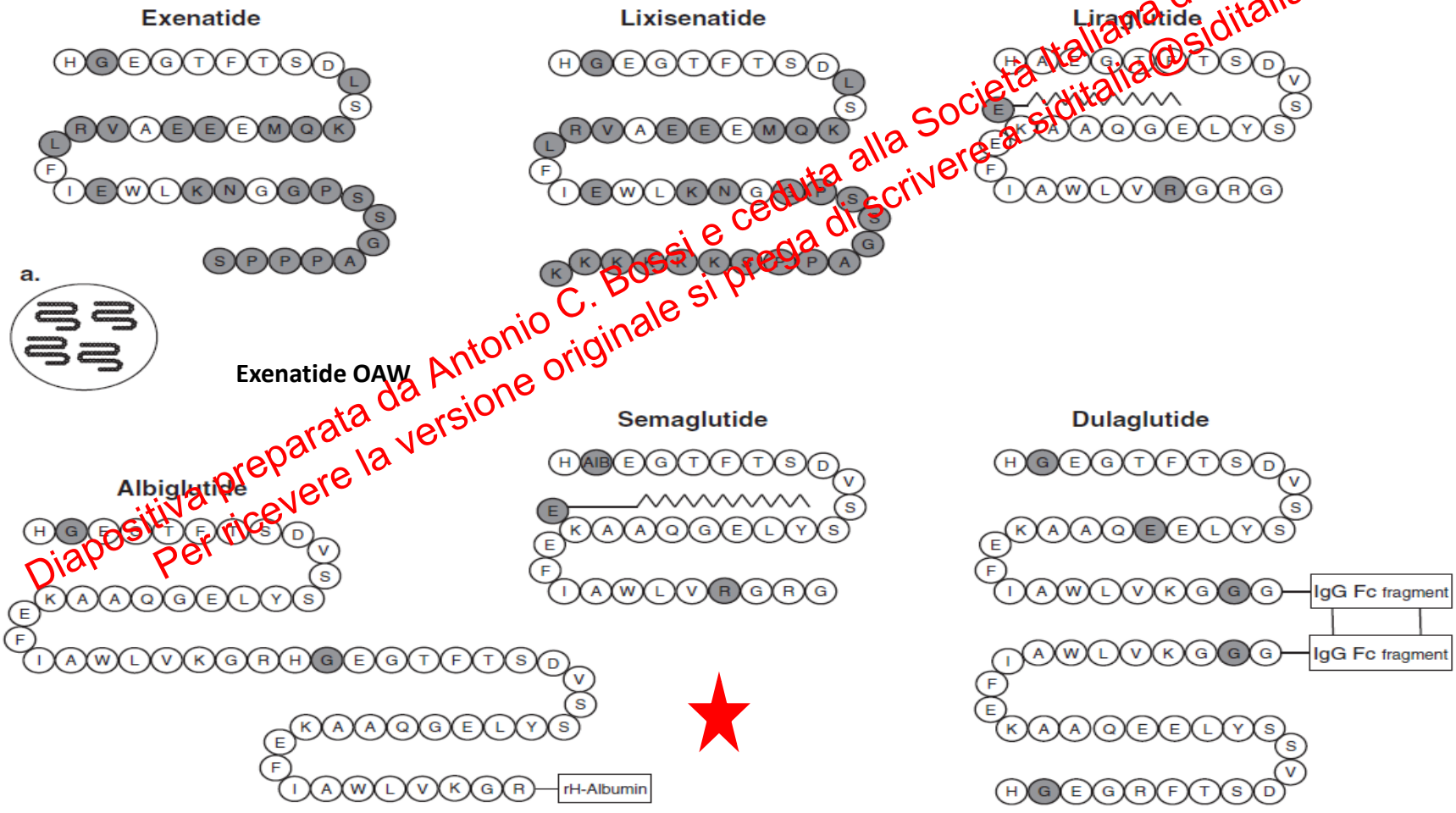
Eur J Intern Med (2014), http://dx.doi.org/10.1016/j.ejim.2014.03.005

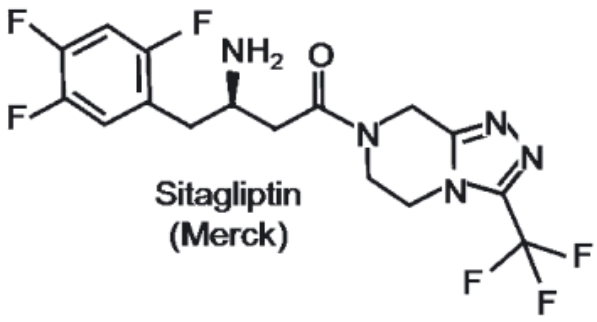
Review Article

Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes: Differences and similarities

Asger Lund [a,b], Filip K. Knop [a,b], Tina Vilsbøll [a,*]

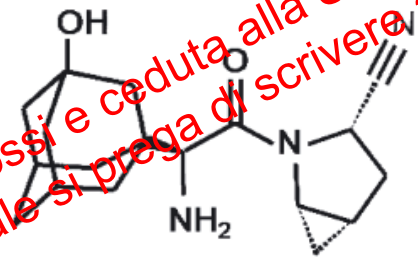


Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review

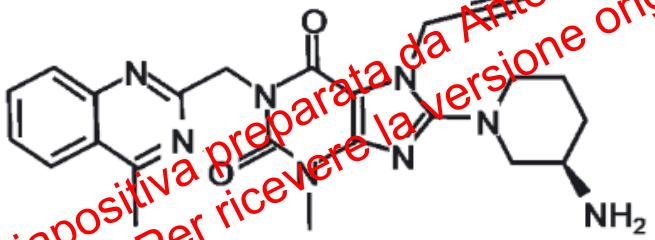


Sitagliptin
(Merck)

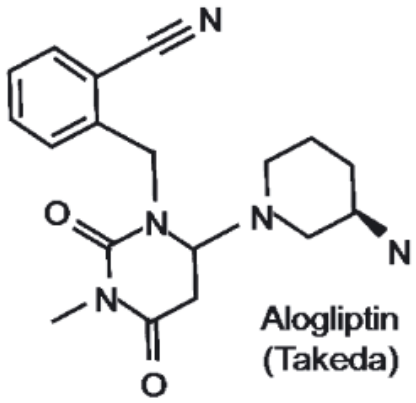
Vildagliptin
(Novartis)



Saxagliptin
(BMS/Astra Zeneca)



Linagliptin
(Boehringer Ingelheim)



Alogliptin
(Takeda)

UOC Malattie Endocrine
Centro Regionale Diabete
Centro Studi Aterosclerosi

CF Deacon. Diabetes, Obesity and Metabolism
13: 7–18, 2011.

Sistema Socio Sanitario
Regione Lombardia
ASST Bergamo Ovest

Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review

CF Deacon.
Diabetes, Obesity and Metabolism 2011,13,7

Differences
Chemical structures
In vitro selectivity
Metabolism (changed/unchanged, active/inactive metabolite)
Elimination (renal/hepatic)
Preclinical toxicities
Potency (therapeutic dose)
Dosing frequency (once/twice daily)
Use in patient subpopulations (e.g. impaired renal/hepatic function)

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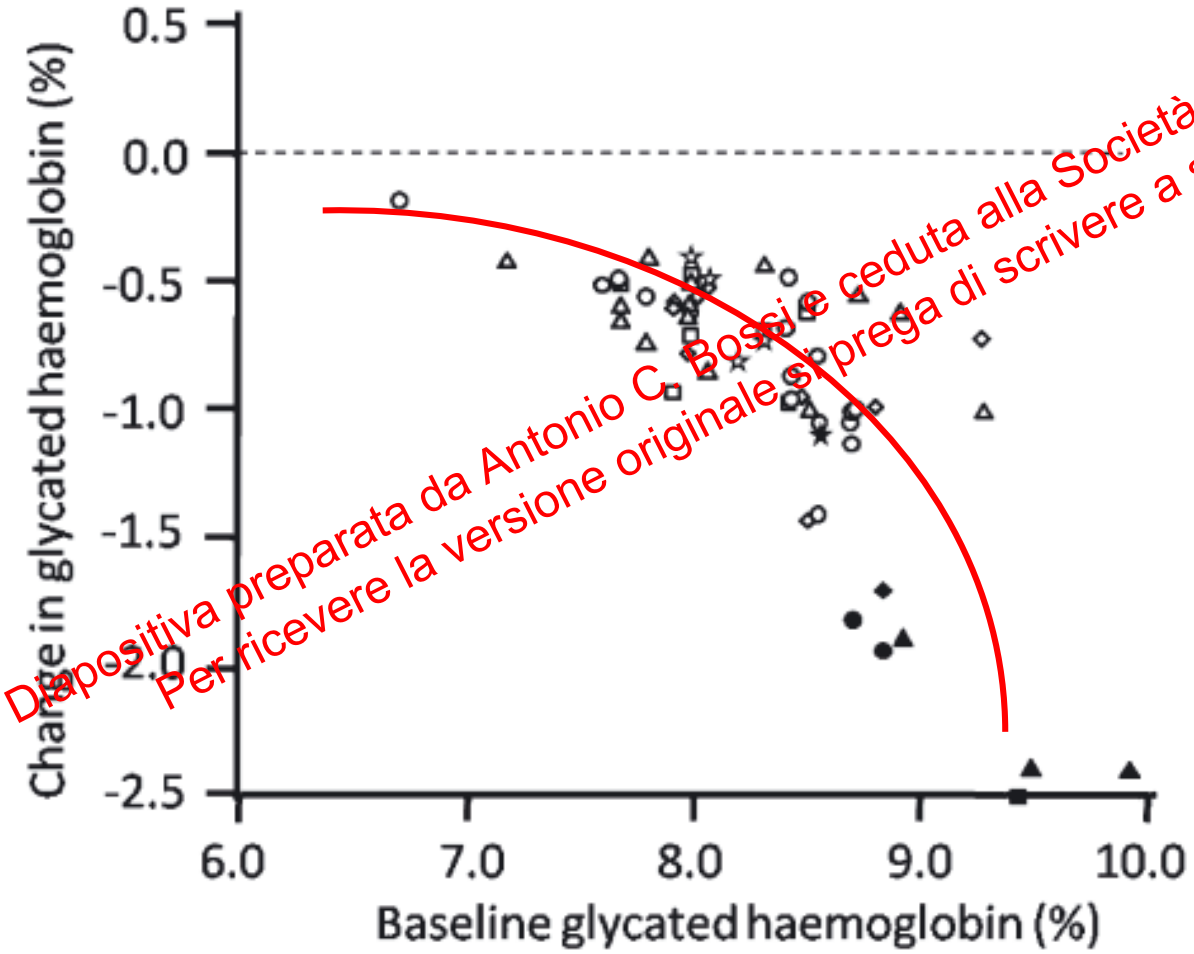
Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review

CF Deacon.
Diabetes, Obesity and Metabolism 2011,13,7



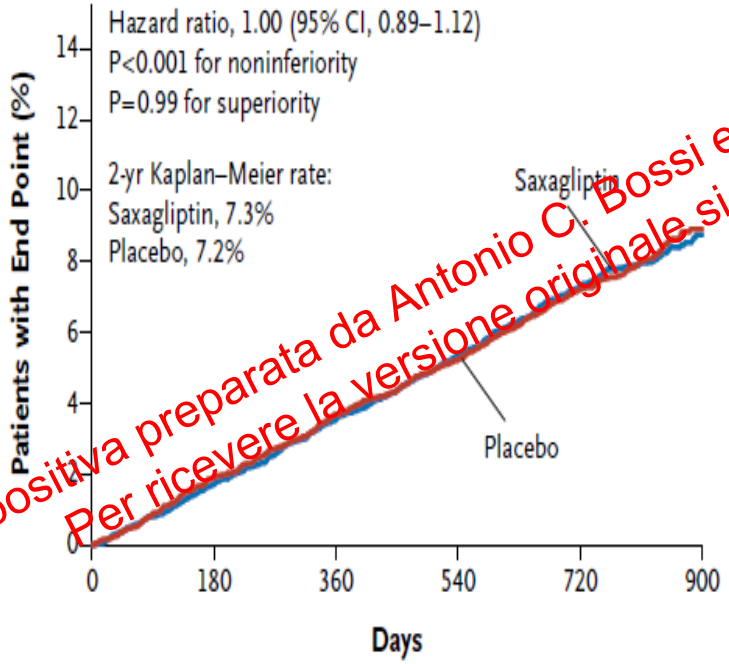
Sitagliptin
Vildagliptin
Saxagliptin
Linagliptin
Alogliptin

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

BM Scirica et Al for the **SAVOR-TIMI 53** Steering Committee and Investigators

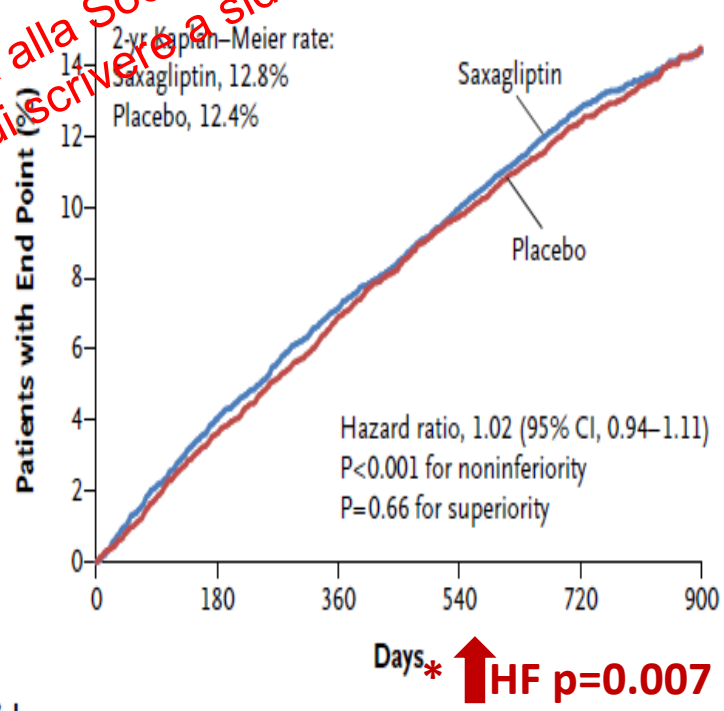
N Engl J Med 2013;369:1317-26. DOI: 10.1056/NEJMoa1307684

A Primary End Point — **a composite of death from CV causes, MI, or ischemic stroke**



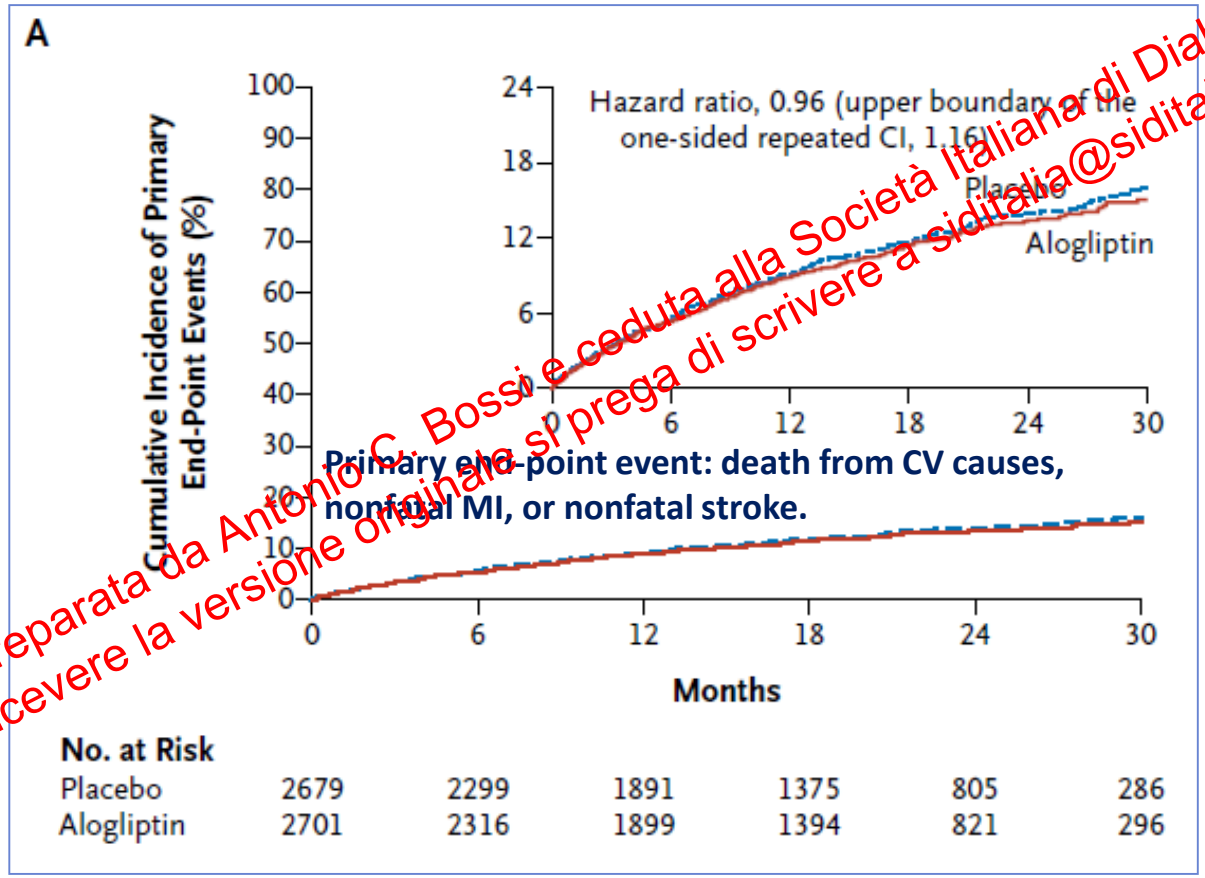
No. at Risk						
Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

B Secondary End Point — **As A, + hospitalization for unstable angina, coronary revasc., or HF***



No. at Risk						
Placebo	8212	7843	7502	6926	4602	813
Saxagliptin	8280	7880	7539	6963	4660	817

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes



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WB White for the **EXAMINE** Investigators.
N Engl J Med 2013;369:1327-35. DOI: 10.1056/NEJMoa1305889

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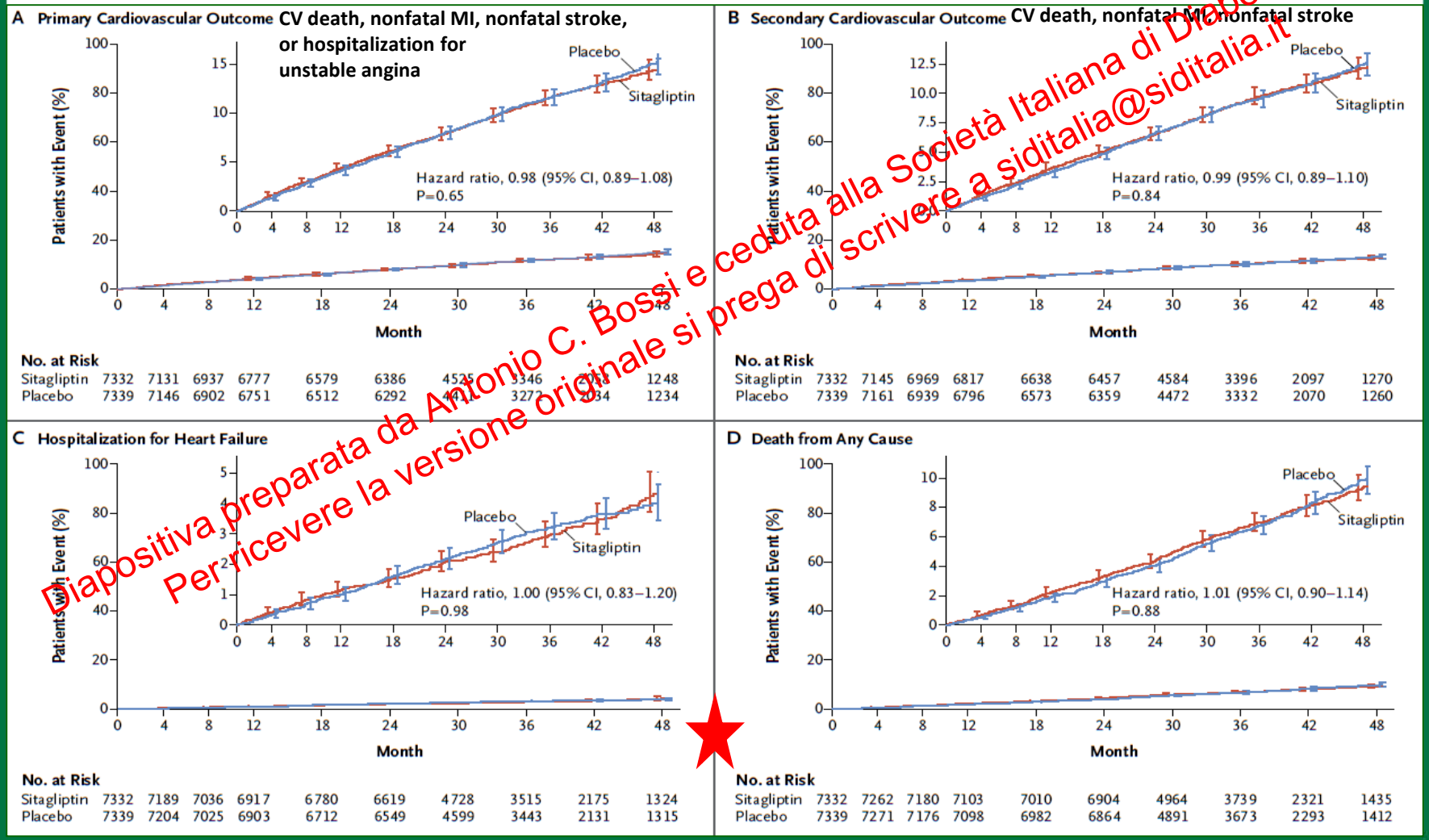
Green JB, et al. for the **TECOS Study Group** – NEJM, 2015. DOI: 10.1056/NEJMoa1501352

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes



Problema dello scompenso cardiaco: RCTs vs. RWD

Are DPP4-in associated with HF ?

Studio Italiano

European Heart Journal (2015) 36, 2454–2462
doi:10.1093/eurheartj/ehv301

FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

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†

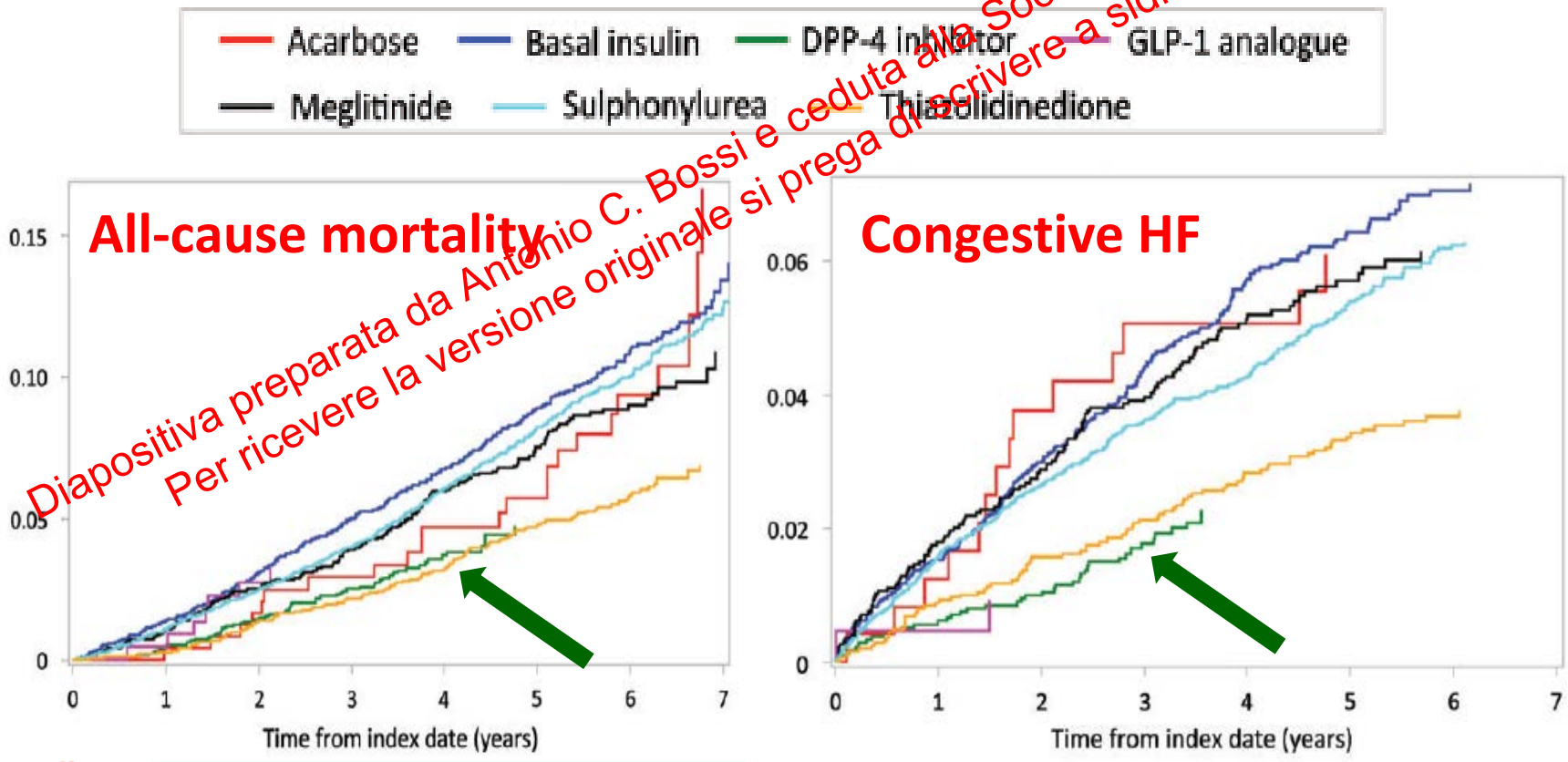
Table 4 Results of the Cox proportional hazard multiple regression analysis in the whole study population including hospitalization episodes with a primary or secondary HF diagnosis

Variable	Before propensity matching		After propensity matching	
	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

Cardiovascular safety of glucose-lowering agents as add-on medication to metformin treatment in type 2 diabetes: report from the Swedish National Diabetes Register

Nils Ekström MD, PhD[1,2] | Ann-Marie Svensson RN, PhD[3] | Mervete Miftaraj MSC[3] | Stefan Franzén PhD[3] | Björn Zethelius MD, PhD[4,5] | Björn Eliasson MD, PhD[1] | Soffia Gudbjörnsdottir MD, PhD[1,3]

Diabetes Obes Metab. 2016 Oct;18(10):990-8. doi: 10.1111/dom.12704.



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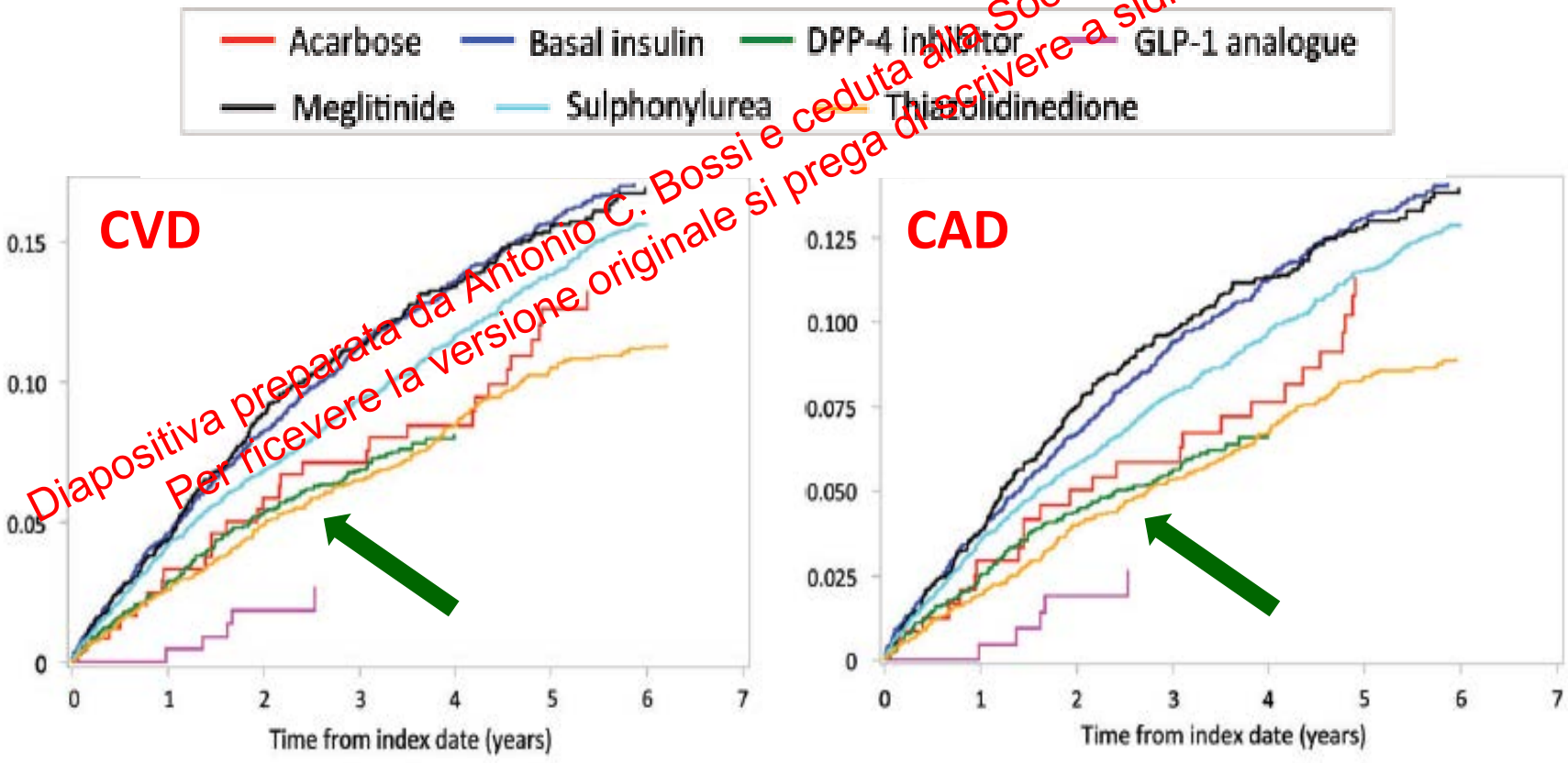
Nils Ekström MD, PhD[1,2] | Ann-Marie Svensson RN, PhD[3] | Mervete Miftaraj MSC[3] | Stefan Franzén PhD[3] | Björn Zethelius MD, PhD[4,5] | Björn Eliasson MD, PhD[1] | Soffia Gudbjörnsdottir MD, PhD[1,3]

Diabetes Obes Metab. 2016 Oct;18(10):990-8. doi: 10.1111/dom.12704.



Open Access Research

BMJ Open Diabetes Research & Care

PERS&O (PERsistent Sitagliptin treatment & Outcomes): observational retrospective study on cardiovascular risk evolution in patients with type 2 diabetes on persistent sitagliptin treatment

[1]Endocrine Unit, Diabetes Regional Center, Treviglio, Italy
[2]Pharmacy Unit, ASST Bergamo Ovest (Bg), Treviglio, Italy
[3]Emmonos, IT HealthCare Senior Consultant, Como, Italy

Correspondence to:
Dr Antonio C Bossi;
antonio.bossi@asst-bgovest.it

Giulia Buonaiuto,[1] Valentina De Mori,[1] Alessandra Braus,[2] Annalisa Balini,[1] Denise Berzi,[1] Rita Carpinteri,[1] Franco Forloni,[1] Giancarla Meregalli,[1] Gian Luca Ronco,[3] Antonio C Bossi[1]

UOC Malattie Endocrine
Centro Regionale Diabete
Centro Studi Aterosclerosi

BMJ Open Diabetes Research and Care 2016; 4:e000216. doi:10.1136/bmjdrc-2016-000216

Sistema Socio Sanitario
Regione Lombardia
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PERS&O (PERsistent Sitagliptin treatment & Outcomes):

observational retrospective study on cardiovascular risk evolution in Type 2 diabetic patients on persistent sitagliptin treatment.

Key messages

- The UK Prospective Diabetes Study (UKPDS) Risk Engine (RE) validation in Italian patients with type 2 diabetes (T2D) confirms the broader use of the algorithm.
- UKPDS RE appears reliable in newly diagnosed patients with T2D, as well as in participants with non-prespecified diabetes duration, in the presence (or not) of previous cardiovascular (CV) disease.
- UKPDS RE confirmed the expected CV risk gender difference in this single-center Italian cohort of participants with T2D.
- 'Real-world' data obtained applying UKPDS RE may reflect patients' and clinician's interest in realizing individual CV risk, and its evolution.

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Centro Regionale Diabete
Centro Studi Aterosclerosi

BMJ Open Diabetes Research and Care 2016;
4:e000216. doi:10.1136/bmjdrc-2016-000216

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L'evoluzione della terapia del diabete tipo 2

AGENDA

- Introduzione: perché dobbiamo impegnarci a curare bene il diabete
- Milestones dell'evoluzione della terapia del DMT2
  - FDA Guidance for Industry
  - The Ominous Octet
    - Le "incretine"
    - Gli SGLT2 inibitori
  - RCT Outcomes & Real World

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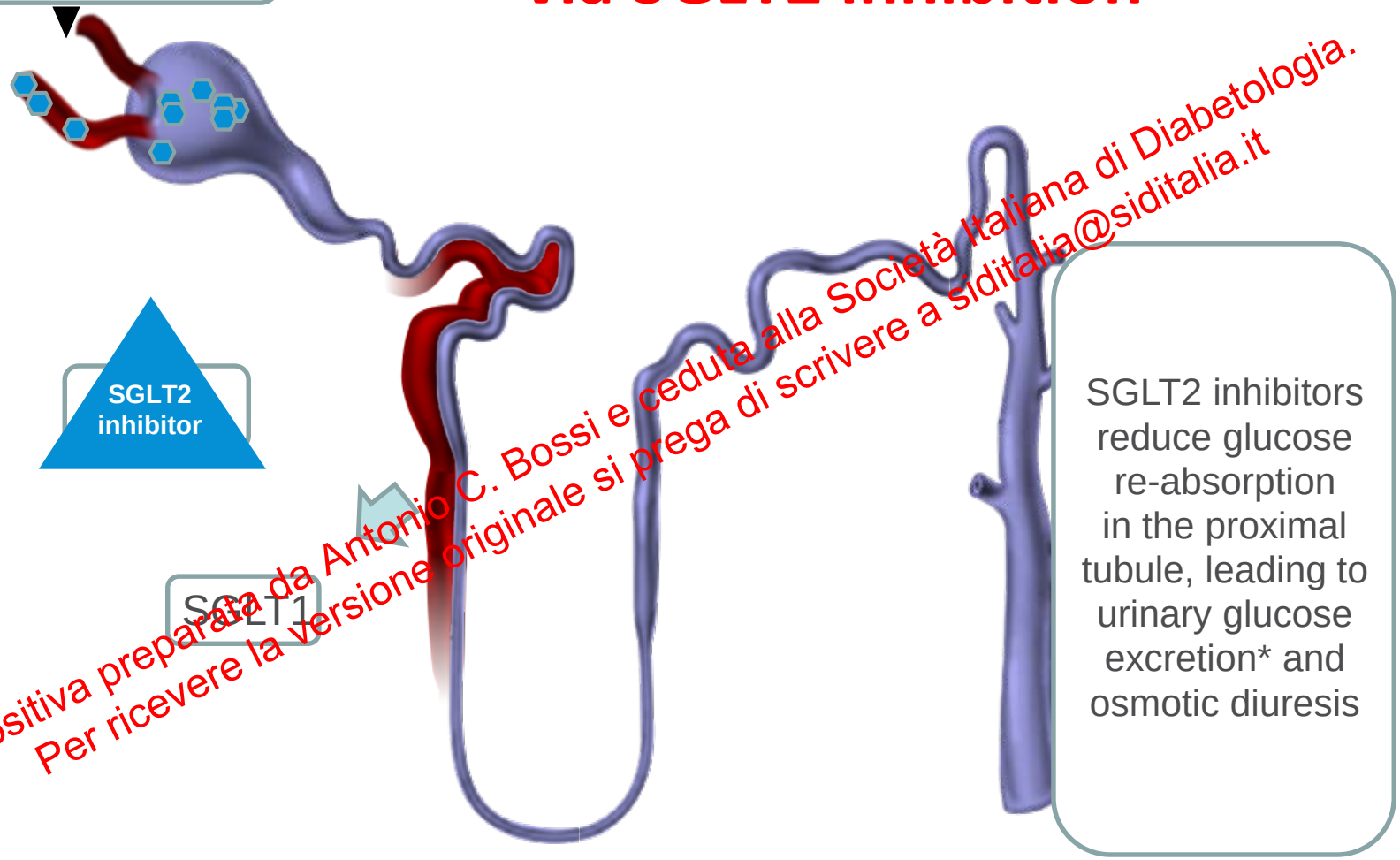
Urinary glucose excretion via SGLT2 inhibition[1]

Filtered glucose load > 180 g/day



SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

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Centro Studi Aterosclerosi

SGLT, sodium glucose cotransporter.
*Loss of ~ 80 g of glucose per day = 240 cal/day.

1. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

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Caratteristiche degli Inibitori degli SGLT2 disponibili in Italia

	Canagliflozin	Dapagliflozin	Empagliflozin
Selettività verso SGLT-2 (Rapporto verso SGLT1)	1:414	1:1200	1:2500
Dose (Cp)	100 mg, 300 mg	5 mg, 10 mg	10mg, 25 mg
Vita media (h)	12-15	17	10-19
Picco ematico (h dopo la somministrazione)	2.8 - 4	1.5	1.5
24-hr EUG (Escrezione urinaria di glucosio)	300 mg : 51.4 g	10 mg : circa 50 g	25 mg: 56.5 g

Elaborazione personale

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

This article was published on September 17, 2015, at NEJM.org.
DOI: 10.1056/NEJMoa1504720

Key inclusion and exclusion criteria

- **Key inclusion criteria**
  - Adults with type 2 diabetes
  - BMI ≤45 kg/m^2
  - HbA1c 7–10%*
  - **Established cardiovascular disease**
    - **Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease**
- **Key exclusion criteria**
  - eGFR <30 mL/min/1.73m^2 (MDRD)

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease. *No glucose-lowering therapy for ≥12 weeks prior to randomisation or no change in dose for ≥12 weeks prior to randomisation or, in the case of insulin, unchanged by >10% compared to the dose at randomisation.

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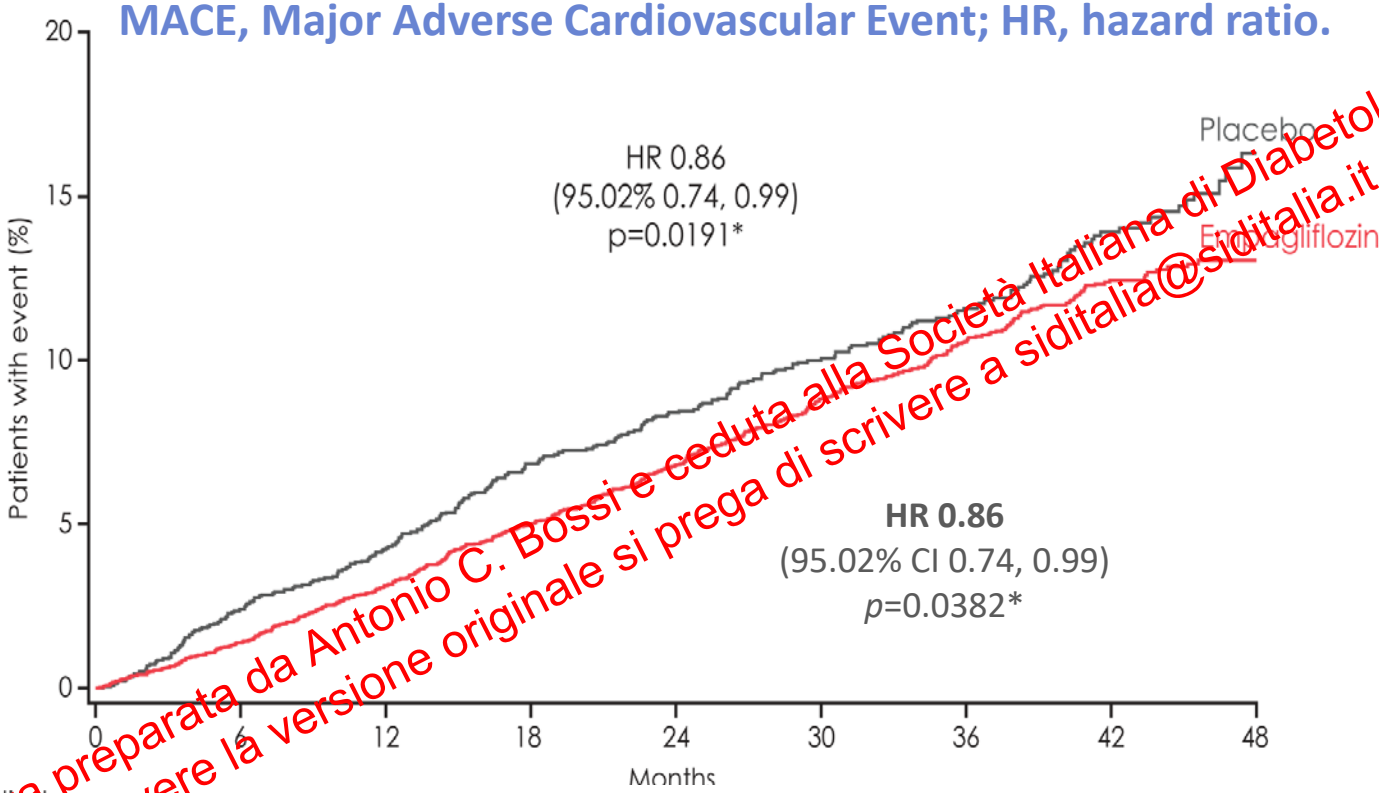
Primary outcome: 3-point MACE

Cumulative incidence function.

MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.



*Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

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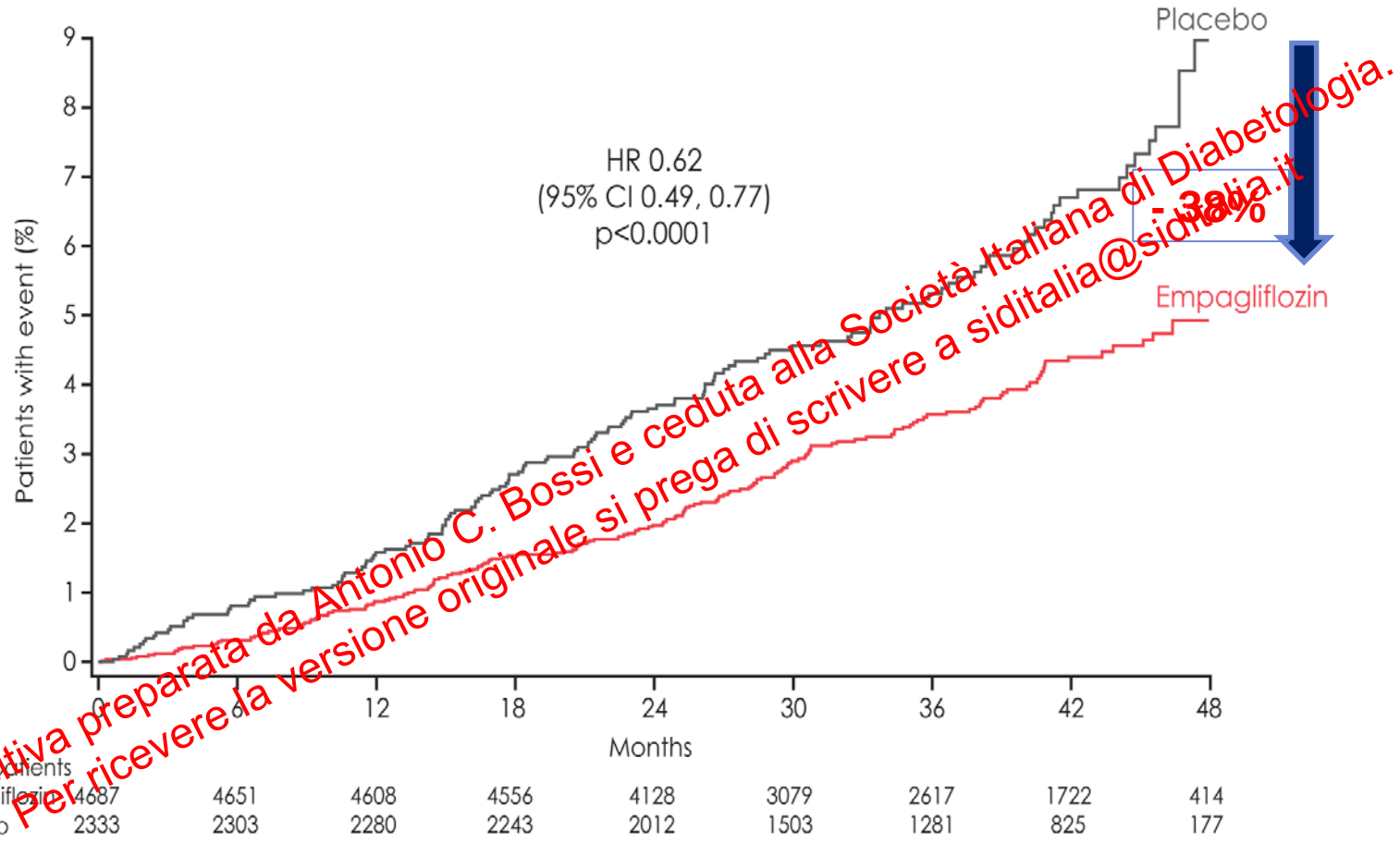
CV death



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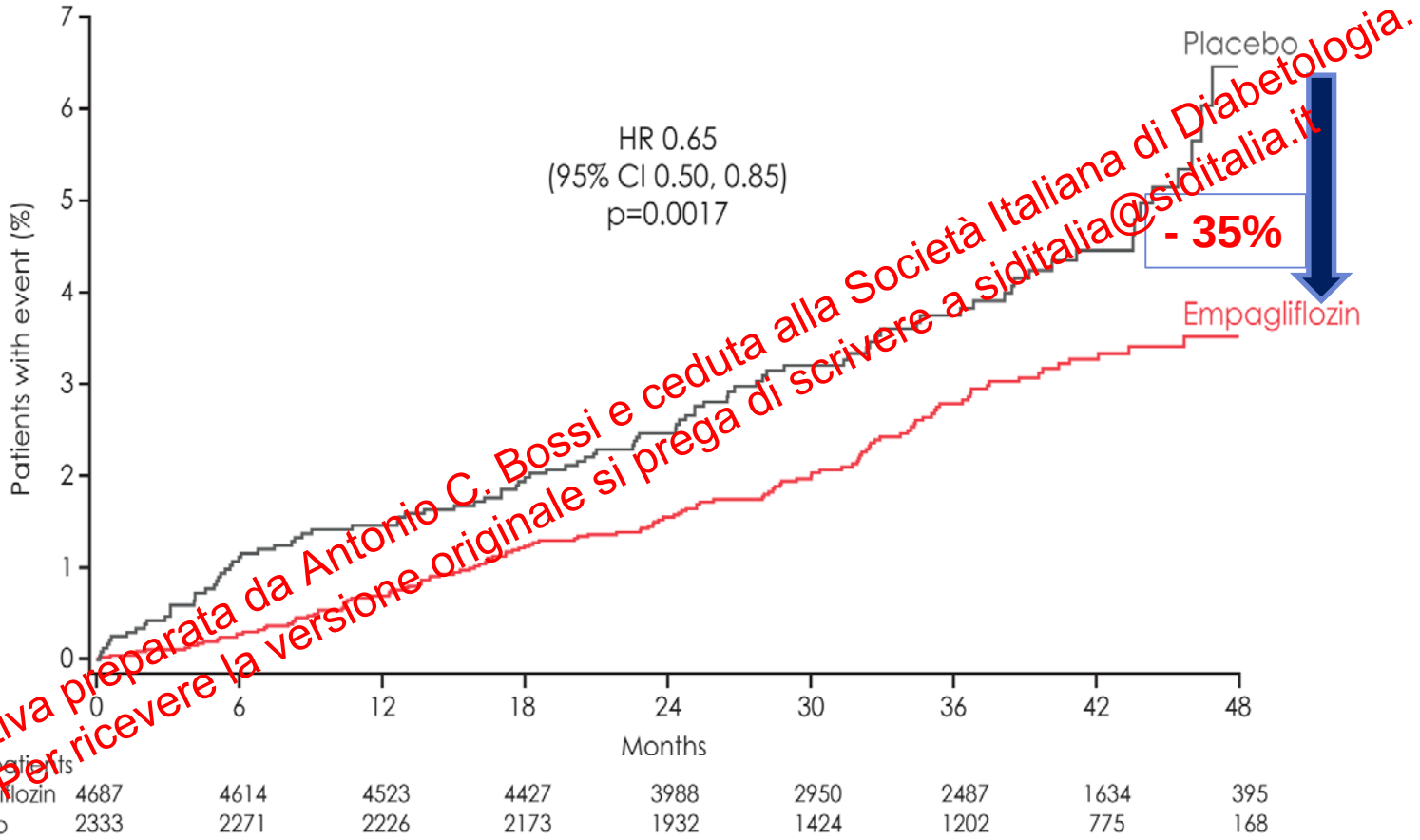
Hospitalisation for heart failure



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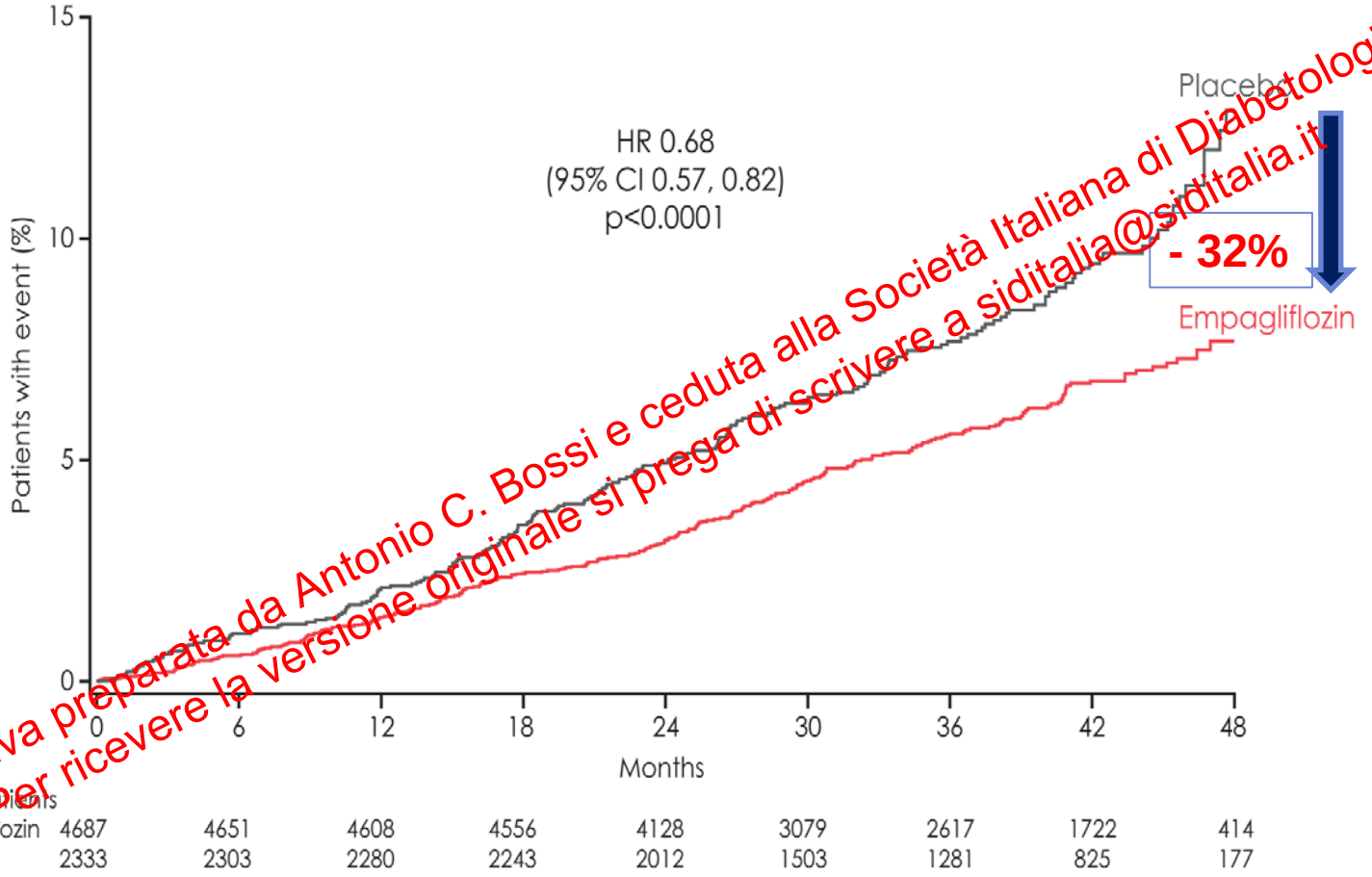
All-cause mortality



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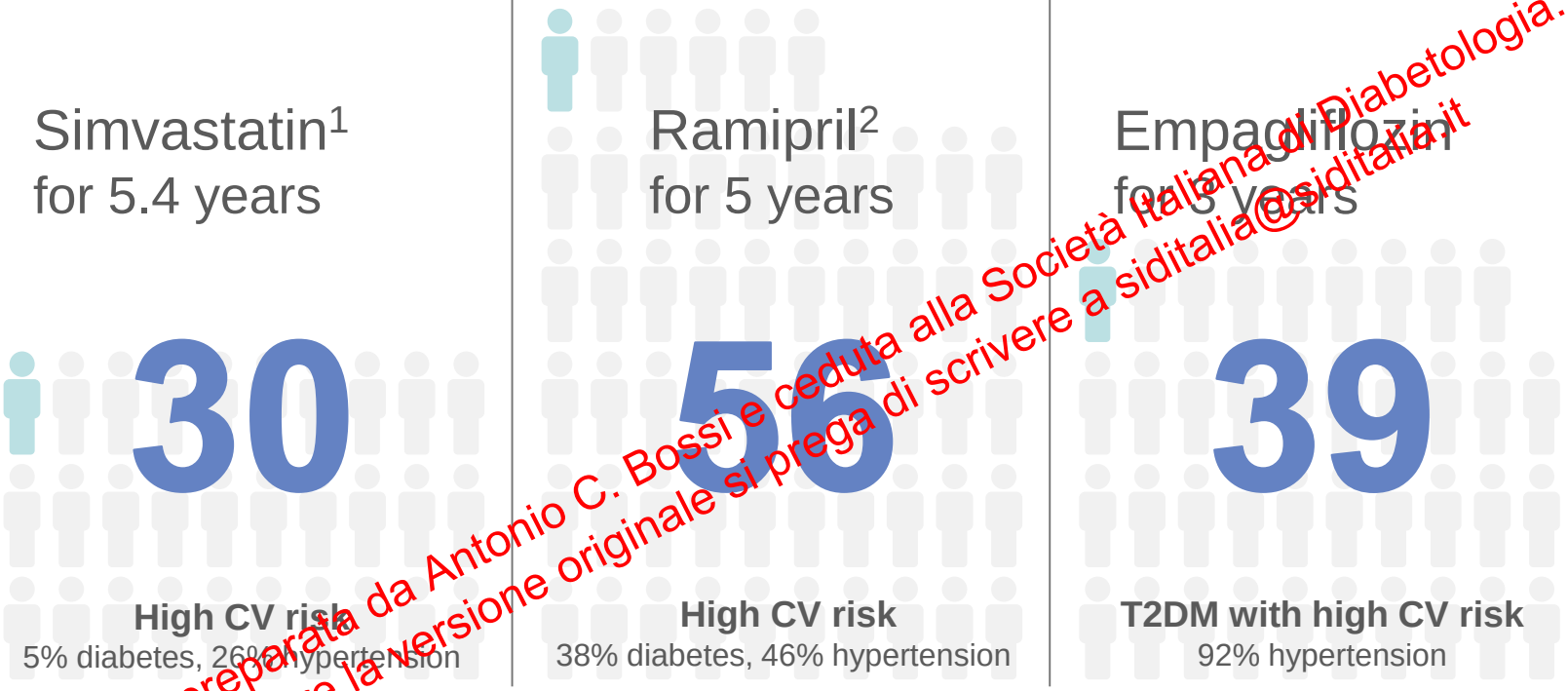
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk



1. 4S investigator. Lancet 1994; 344: 1383, http://www.trialresultscenter.org/study2590-4S.htm;
2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

Simvastatin[1]
for 5.4 years

30

High CV risk
5% diabetes, 26% hypertension

Ramipril[2]
for 5 years

56

High CV risk
38% diabetes, 46% hypertension

Empagliflozin
for 5 years

25

T2DM with high CV risk
92% hypertension

Pre-statin era → **Pre-ACEi/ARB era** → **>80% ACEi/ARB**

<29% statin → **>75% statin**

1994 — **2000** — **2015**

1. 4S investigator. Lancet 1994; 344: 1383, http://www.trialresultscenter.org/study2590-4S.htm;
2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

Circulation

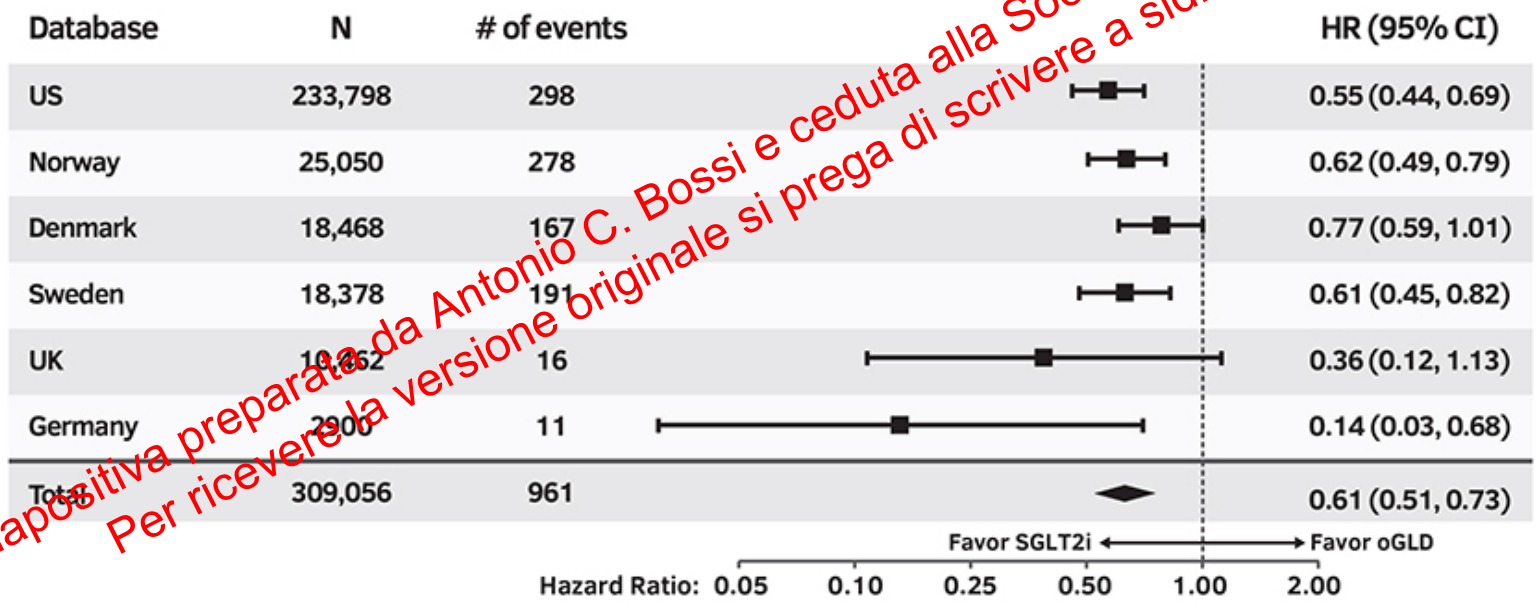
American Heart Association

Lower Risk of Heart Failure and Death in Patients Initiated on SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study

Mikhail Kosiborod, Matthew A. Cavender, Alex Z. Fu, John P. Wilding, Kamlesh Khunti, Bernhard W. Holl, Anna Norhammar, Kåre I. Birkeland, Marit Jørgensen, Marcus Thuresson, Niki Arya, Johan Bodegård, Niklas Hammar, Peter Fenici and on behalf of the CVD-REAL Investigators and Study Group

on behalf of the CVD-REAL Investigators and Study Group

Hospitalization for heart failure primary analysis



P-value for SGLT2 inhibitor vs other glucose-lowering drug: <0.001

Heterogeneity p-value: 0.17

UOC Malattie Endocrine
Centro Regionale Diabete
Centro Studi Aterosclerosi

Circulation. published online May 18, 2017;
http://circ.ahajournals.org/content/early/2017/05/16/CIRCULATIONAHA.117.029190

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Circulation

American Heart Association

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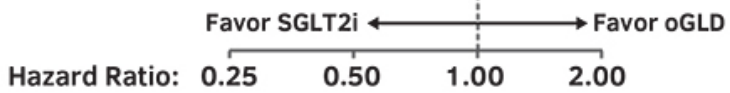
Mikhail Kosiborod, Matthew A. Cavender, Alex Z. Fu, John P. Wilding, Kamlesh Khunti, Bernhard W. Holl, Anna Norhammar, Kåre I. Birkeland, Marit Jørgensen, Marcus Thuresson, Niki Arya, Johan Bodegård, Niklas Hammar, Peter Fenici and on behalf of the CVD-REAL Investigators and Study Group

on behalf of the CVD-REAL Investigators and Study Group

All-cause death primary analysis

Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)



P-value for SGLT2i vs other glucose-lowering drug: <0.001

Heterogeneity p-value: 0.09

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Centro Regionale Diabete
Centro Studi Aterosclerosi

Circulation. published online May 18, 2017;
http://circ.ahajournals.org/content/early/2017/05/16/CIRCULATIONAHA.117.029190

Sistema Socio Sanitario
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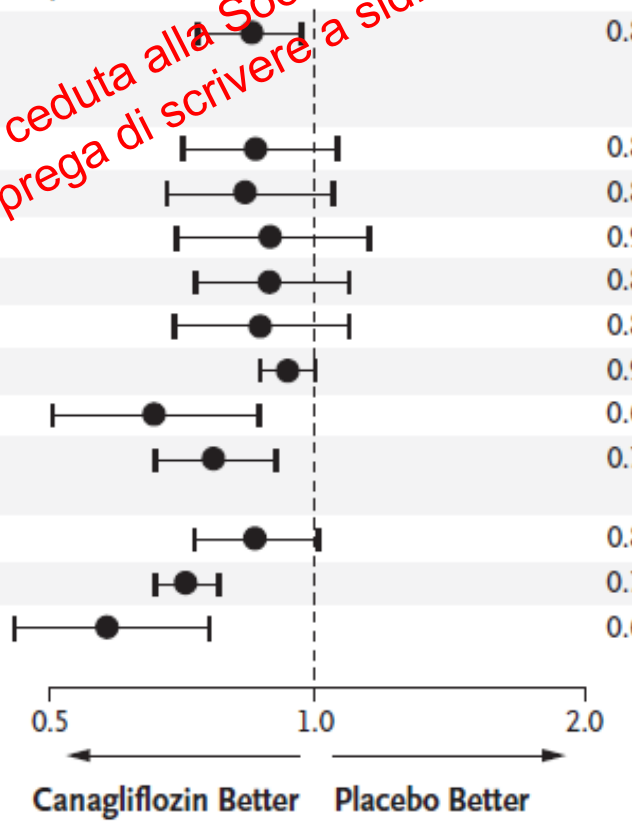
ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Neal B. et Al., for the CANVAS Program Collaborative Group.
This article was published on June 12, 2017, at NEJM.org. DOI: 10.1056/NEJMoa1611925

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Neal B. et Al., for the CANVAS Program Collaborative Group.
This article was published on June 12, 2017, at NEJM.org. DOI: 10.1056/NEJMoa1611925

Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001

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Centro Studi Aterosclerosi

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L'evoluzione della terapia del diabete tipo 2

AGENDA

- Introduzione: perché dobbiamo impegnarci a curare bene il diabete
- Milestones dell'evoluzione della terapia del DMT2
  - FDA Guidance for Industry
  - The Ominous Octet
    - Le "incretine"
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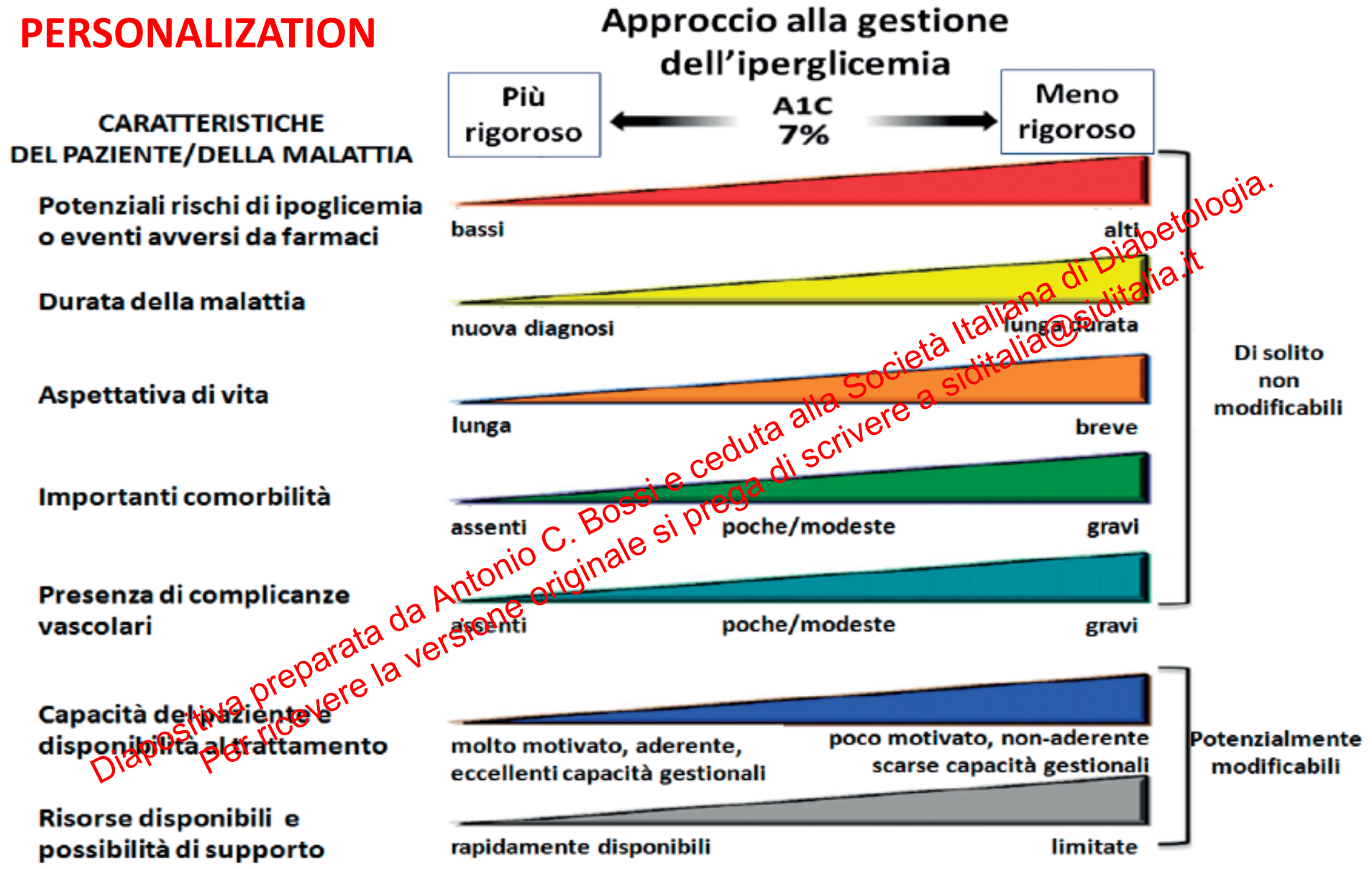
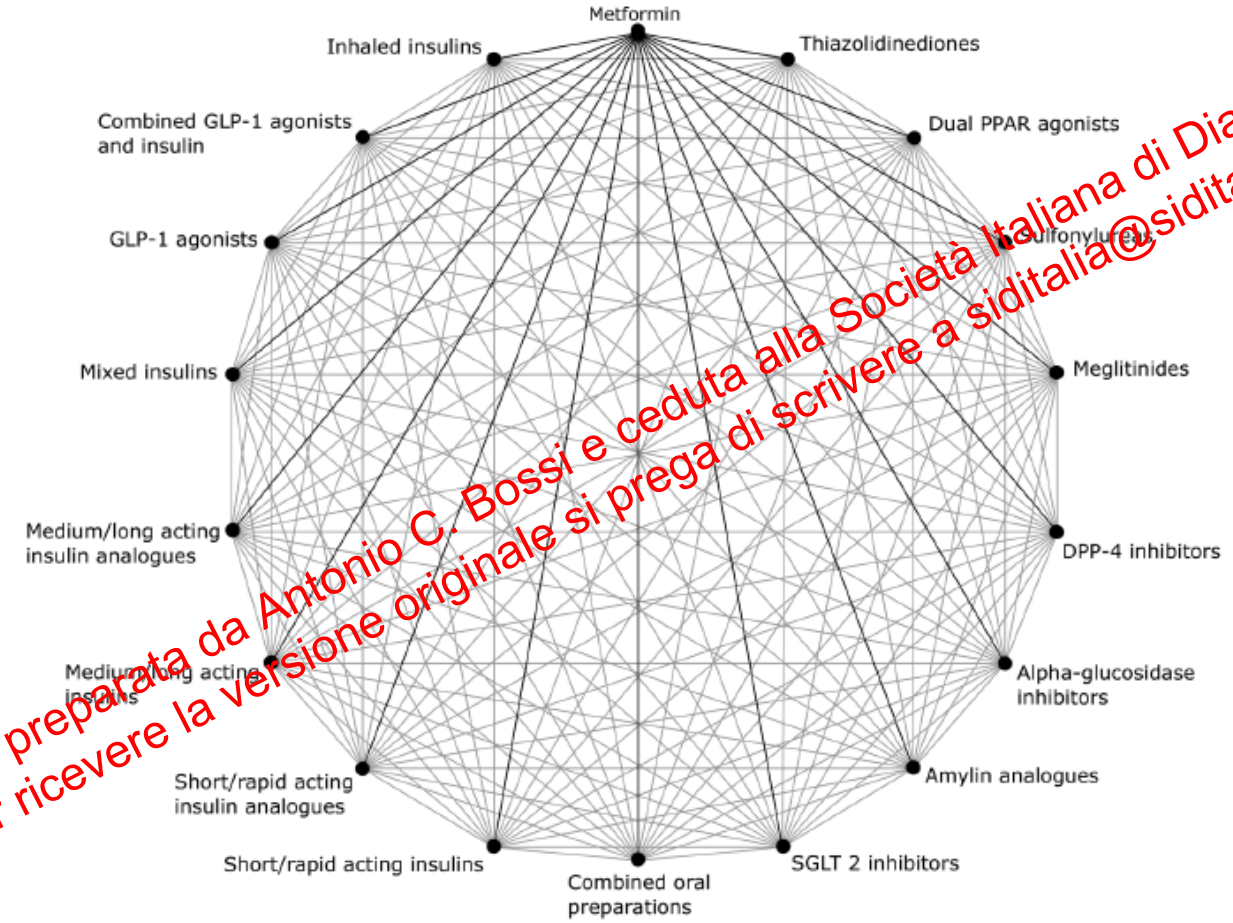
PERSONALIZATION



Modificata da Inzucchi et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149.

BMJ Open Systematic review of adherence rates by medication class in type 2 diabetes: a study protocol

ADHERENCE



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McGovern A, Tippu Z, Hinton W, et al.
BMJ Open 2016;6:e010469.
doi:10.1136/bmjopen-2015-010469

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Cost per month of various diabetes medication

COSTS

CLASS	DRUG	$$$/Month
GLP-1 RA	Liraglutide 1.8mg	720.00$
SGLT-1i	Canagliflozin 300mg	400.00$
DPP4-i	Sitagliptin 100g	380.00$
Basal Insulin	Glargine vial 30units/day	365.00$
NPH Insulin	NPH vial 30 units/day	145.00$
TZD	Pioglitazone 30mg	14.00$
Biguanide	Metformin 2000mg	10.00$
Sulfonylurea	Glimepiride 4mg	4.00$

From: Cavaiola TS and Pettus JH.
Management of Type 2 Diabetes: Selecting Amongst Available Pharmacological Agents
www.endotext.org (Last update 2017 March 31)

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Circulation

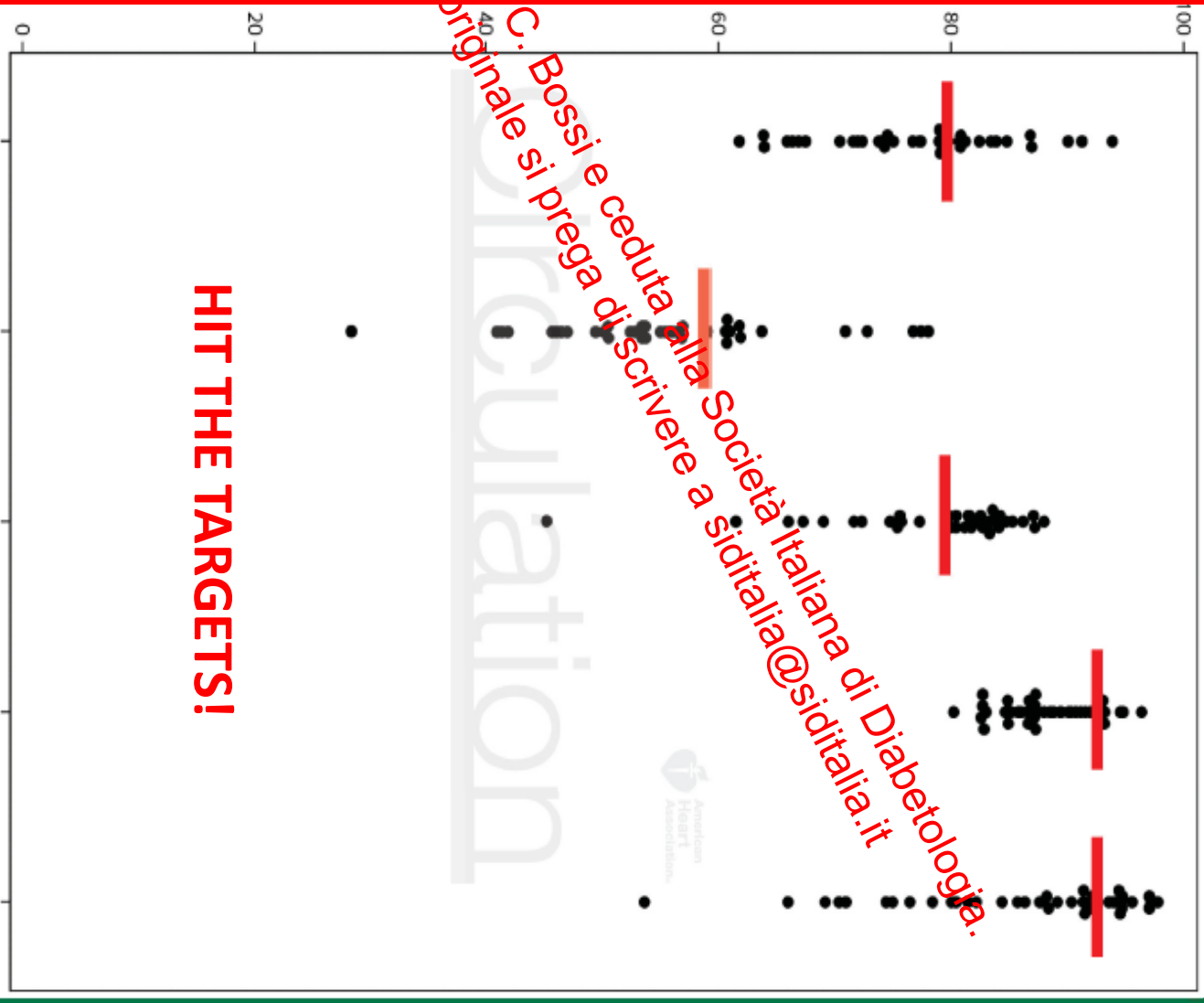
American Heart Association

Secondary Prevention of Cardiovascular Disease in Patients with Type 2 Diabetes: International Insights from the TECOS Trial

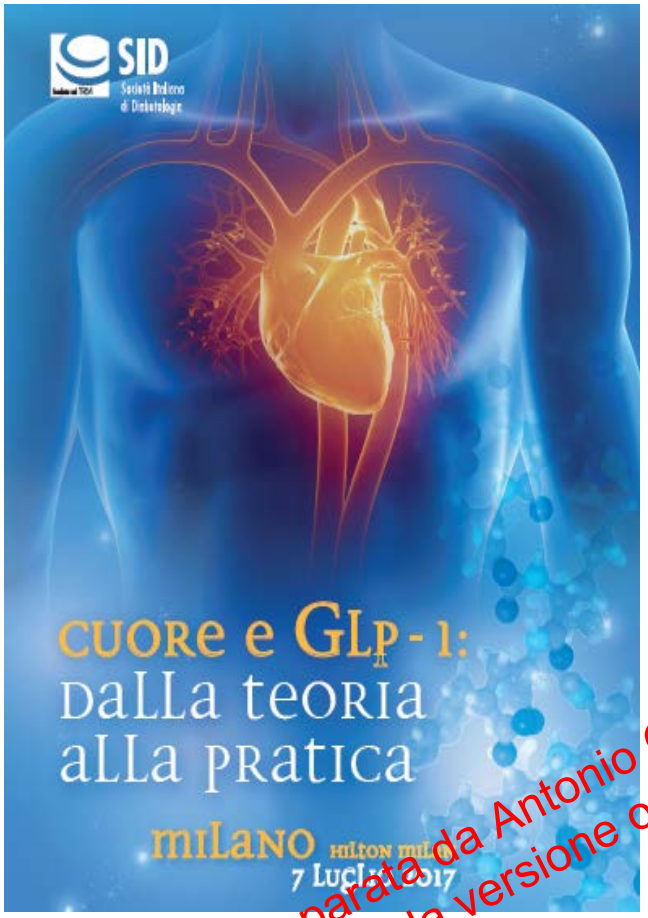
Neha J. Pagidipati, Ann Marie Navar, Karen S. Pieper, Jennifer B. Green, M. Angelyn Bethel, Paul W. Armstrong, Robert M. Califf, Darren K. McGuire, Yuliya Lokhnygina, Jan H. Cornel, Sigrun Halvorsen, Timo E. Strandberg, Tuncay Delibasi, Rury R. Holman and Eric D. Peterson
On behalf of the TECOS Study Group

Circulation: published online June 16, 2017;
http://circ.ahajournals.org/content/early/2017/06/16/CIRCULATIONAHA.117.027252

% with secondary prevention control



HIT THE TARGETS!



L'evoluzione della terapia del diabete tipo 2

Antonio C. Bossi
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GRAZIE per la Vostra Attenzione!

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