Studi Real-Life per la valutazione di effectiveness-safety

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

- Novo Nordisk
- Astra Zeneca
- Eli Lilly
- Sanofi Aventis
- Sigma Tau
- Artsana
- Medtronic
- Dexcom
- Foracare

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Randomized Clinical Trials (RCTs)

- High quality RCTs represent the gold standard for the evaluation of efficacy
- Randomization ensures that groups to be compared have a balanced distribution of all **known and unknown** prognostic factors.
- Biases related to investigator and patient preferences are avoided
- RCTs usually provide evidence on what can be obtained under strictly controlled conditions, in selected groups of patients treated for a defined period of time.

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Strenghts and limitations of RCTs

Strenghts	Limitations
Well defined study population	Exclusion of many patients who could benefit from the treatment
Study design maximizes internal validity	Usually conducted in highly specialized centers
Treatment administered under strictly controlled conditions	Difficulties in generalizing study results
Compliance maximized by rigid protocol guidelines	Limited duration and sample size make difficult the evaluation of long-term effects and rare adverse events
	"Trial effect"

Efficacy trials vs. safety trials

	Efficacy trials
Aim	Demonstrate CV benefit
Aim of treatment	Maximize HbA1c difference
Comparator	Usually active drug
Study population	High proportion of patients without CVD/CKD
Primary endpoint	Heterogeneous
Study duration	Pre-specified
Primary analysis	Superiority

Efficacy trials vs. safety trials

	Efficacy trials	Safety trials
Aim	Demonstrate CV benefit	Demonstrate CV safety
Aim of treatm		bA1c (equipoise)
Comparator		cebo
Study popula		rtion of th CVD/CKD
Primary endp		
Study duration	Pre-specified	Event driven
Primary analysis	Superiority	Non inferiority

HIGH INTERNAL VALIDITY

BUT

LOW GENERALIZABILITY

Real World Evidence

Real-world evidence is most commonly defined as the use of data collected as part of the broader process of care delivery, as opposed to data specifically collected for research purposes, and may be represented by a range of sources, including electronic medical records, administrative (claims and billing) databases, disease and device registries, and potentially data collections derived from social media, consumer-facing applications, and wearable devices.

A. Patel, E. Billot. *Circulation 2017;136:260–262*

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Real World Evidence: aims

- To evaluate the impact of a treatment in broader populations and different healthcare settings
- To evaluate the long-term impact of treatment on a large array of outcomes (even those not considered in RCTs)
- To evaluate the impact of treatment on different patient subgroups, even those usually excluded or underrepresented in RCTs
- To evaluate rare serious adverse events
- To assess the safety profile in different patient subgroups
- To evaluate treatment compliance and persistence
- To assess healthcare resource utilization, costs of treatment and cost-effectiveness
- To evaluate the appropriateness of drug prescription and quality of care

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RWE vs. RCTs: the case of SGLT2-i

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

Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A, Birkeland KI, Jørgensen ME, Thuresson M, Arya N, Bodegård J, Hammar N and Fenici P on behalf of the CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on SGLT-2 inhibitors versus other glucose-lowering drugs: The CVD-REAL Study. *Circulation.* 2017. https://doi.org/10.1161/CIRCULATIONAHA.117.029190

CVDREAL

Study objectives

Primary

- To compare the risk of HHF in patients with T2DM newly initiated on SGLT2 inhibitors versus other glucose-lowering drugs

Secondary

- To compare the risk of all-cause death between the two treatment groups
- To compare the risk of the composite of HHF or all-cause death between the two treatment groups

Data sources

Cohort 1
HHF

US
- Truven Health MarketScan Claims and Encounters and linked Medicare Supplemental and Coordination of Benefits (Medicare Supplemental) databases

Norway
- Linked Prescribed Drug, National Patient and Cause of Death Registries

Sweden
- Linked Prescribed Drug, National Patient and Cause of Death Registries

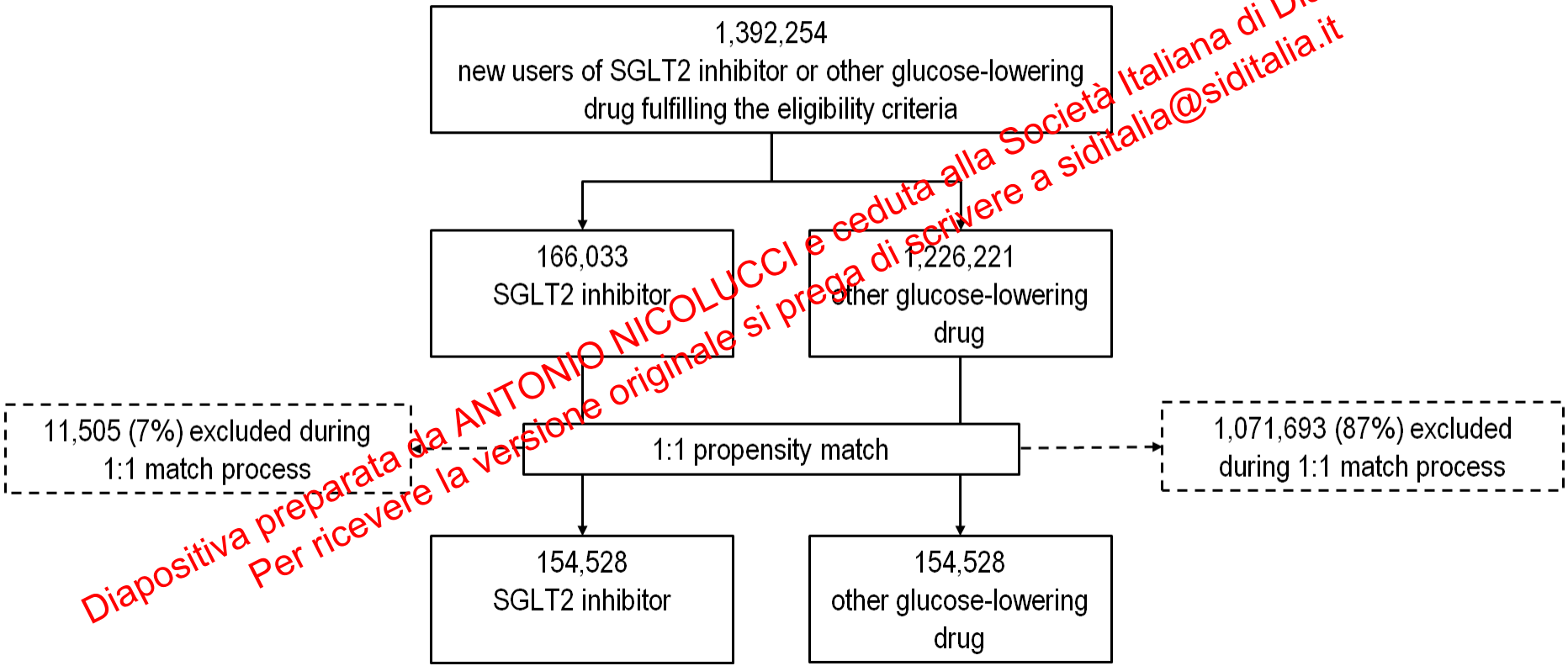
Denmark
- Linked Prescribed Drug, National Patient and Cause of Death Registries

UK
- Clinical Practice Research Datalink (CPRD) dataset
- The Health Improvement Network (THIN) dataset

Germany
- Diabetes-Patienten-Verlaufsdokumentation (Diabetes Prospective Follow-Up; DPV)

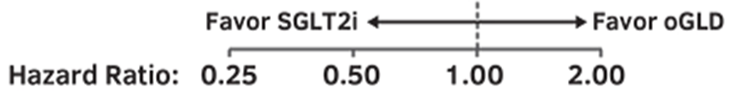
Cohort 2
All-cause death and composite HHF/all-cause death

Patient population for all countries/databases combined



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

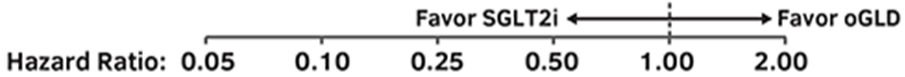
Heterogeneity p-value: 0.089

Data are on treatment, unadjusted.

Hospitalization for heart failure primary analysis

CVDREAL

Database	N	# of events	HR (95% CI)
US	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)



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

Heterogeneity p-value: 0.169

Data are on treatment, unadjusted.

RWE vs. RCTs

Baseline characteristics	EMPAREG	CVD-REAL	CVD NORDIC
Age (years)	63.1±8.6	66.9±10	61.2±10.9
Male (%)	71.2%	65.7%	59.4%
History of myocardial infarction	46.7%	2.5%	7.6%
Unstable angina		1.6%	3.8%
History of stroke	23.1%	4.1%	6.7%
Peripherhal artery disease	21.0%	3.4%	-
Cardiac failure	9.9%	3.1%	5.0%
CKD	25.9%	2.5%	1.2%

RWE vs. RCTs

Baseline characteristics	EMPAREG	CVD-REAL	CVD NORDIC
Glucose lowering therapy			
Metformin	73.8%	78.6%	74.2%
Sulphonylurea	43.0%	38.4%	26.5%
DPP-4i	11.3%	33.3%	19.3%
TZD	4.2%	8.8%	1.4%
GLP1-ra	2.7%	20.3%	17.0%
Insulin	48.0%	29.5%	29.9%
Antihypertensive therapy	94.9%	80.0%	76.0%
Statin therapy	77.4%	67.3%	67.4%
Aspirin	82.7%	-	36.1%

RWE vs. RCTs

Outcome (SGLT2-I vs. control)	EMPAREG HR (95%CI)	CVD-REAL HR (95%CI)	CVD NORDIC HR (95%CI)
MACE	0.86 (0.74-0.99)	-	0.78 (0.69-0.87)
All-cause mortality	0.68 (0.57-0.82)	0.49 (0.41-0.57)	0.51 (0.45-0.58)
CV mortality	0.62 (0.49-0.77)	-	0.53 (0.40-0.71)
Hospitalization for HF	0.65 (0.50-0.85)	0.61 (0.51-0.73)	0.70 (0.61-0.81)
Myocardial infarction	0.87 (0.70-1.09)	-	0.87 (0.73-1.03)
Stroke	1.24 (0.92-1.67)	-	0.86 (0.72-1.04)

MACE incidence:

Empareg 3.74 per 100 py
CVD Nordic 1.64 per 100 py

WHAT DOES RWE TELL US?

- Results documented in EMPAREG are confirmed in the real world:
  - In larger, less selected populations
  - In low CV risk patients
  - In different settings and countries
  - With different molecules (class effect)
  - In comparison with active drugs

LIMITATIONS

- Given the observational nature of the study, and despite robust propensity-matching and multiple sensitivity analyses, a possibility of residual, unmeasured confounding, cannot be excluded.
- No information on safety
- No information on intermediate outcomes and socio-economic status
- Lack of long-term data

RWE vs. RCTs: the case of Ticagrelor

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European Heart Journal
doi:10.1093/eurheartj/ehw284

CLINICAL RESEARCH
Acute coronary syndromes

Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry

Anders Sahlén[1,2,3]*, Christoph Varenhorst[4], Bo Lagerqvist[4], Henrik Renlund[4], Elmir Omerovic[5], David Erlinge[6], Lars Wallentin[4], Stefan K. James[4], and Tomas Jernberg[1,2]

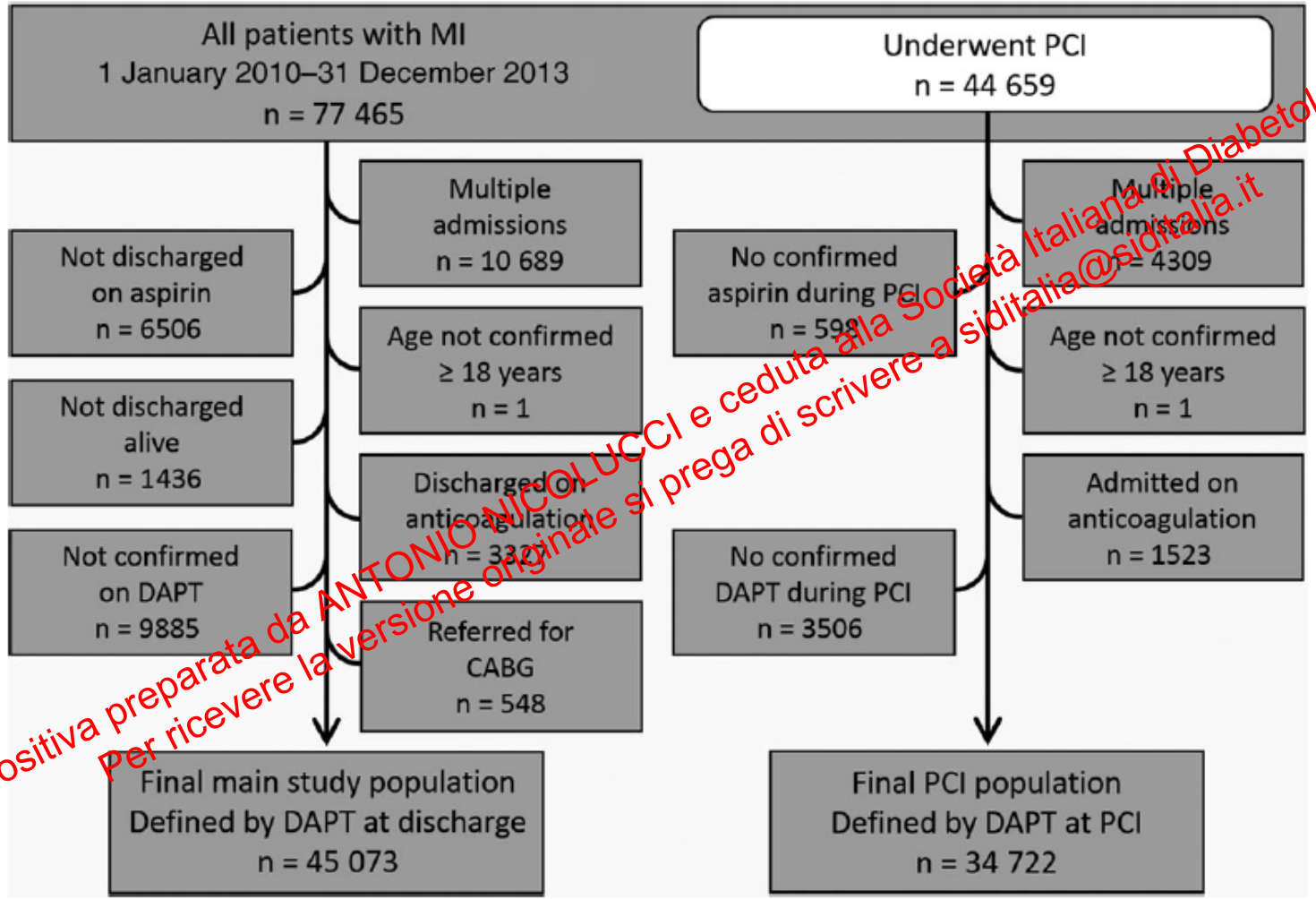

Table 1 **Basic characteristics of the study population**

	All (N = 45 073)	Ticagrelor (N = 11 954)	Clopidogrel (N = 33 119)
Age (years); median (IQR)	70.0 (61.0–79.0)	67.0 (59.0–75.0)	71.0 (62.0–80.0)
Male	66.9% (30 133)	71.5% (8550)	65.2% (21 583)
ST-elevation ACS	35.5% (15 973)	46.7% (5578)	31.4% (10 395)
Diabetes	22.5% (10 144)	20.5% (2446)	23.2% (7698)
Hypertension	54.4% (24 365)	49.8% (5938)	56.1% (18 426)
Current smoker	24.5% (10 417)	27.6% (3202)	23.3% (7215)
Past medical history			
MI	22.2% (9963)	15.1% (1796)	24.8% (8167)
PCI	13.8% (6176)	10.8% (1285)	14.9% (4891)
CABG surgery	6.9% (3098)	4.6% (545)	7.7% (2553)
Congestive heart failure	10.3% (4628)	5.5% (660)	12.0% (3968)
Peripheral vascular disease	4.8% (2154)	3.3% (396)	5.3% (1758)
Ischaemic stroke	8.3% (3750)	5.4% (649)	9.4% (3101)
Bleeding hospitalization	4.9% (2202)	3.7% (437)	5.3% (1765)
COPD	6.6% (2966)	5.2% (616)	7.1% (2350)
Cancer within last 3 years	2.7% (1239)	2.0% (244)	3.0% (995)
Killip class >1 on admission	8.5% (3765)	5.4% (636)	9.7% (3129)

Table I Basic characteristics of the study population

	All (*N* = 45 073)	Ticagrelor (*N* = 11 954)	Clopidogrel (*N* = 33 119)
Medication on admission			
Aspirin	36.1% (16 155)	27.0% (3207)	39.3% (12 948)
Antiplatelet therapy			
Clopidogrel	4.4% (1977)	1.7% (197)	5.4% (1780)
Prasugrel	0.0% (4)	0.0% (1)	0.0% (3)
Ticagrelor	0.3% (114)	0.9% (106)	0.0% (8)
Ticlopidine	0.0% (5)	0.0% (0)	0.0% (5)
Other	0.6% (279)	0.3% (35)	0.7% (244)
β-Blocker	33.4% (14 898)	26.3% (3113)	35.9% (11 785)
Calcium antagonist	18.4% (8240)	17.3% (2044)	18.9% (6196)
Digoxin	0.9% (424)	0.4% (45)	1.2% (379)
ACEi/ARB	17.6% (6260)	16.8% (1651)	18.0% (4609)
Diuretic	19.7% (8816)	13.9% (1649)	21.8% (7167)
Statin	28.0% (12 564)	22.9% (2723)	29.9% (9841)
In-hospital course			
Inotropic support	1.8% (803)	2.0% (239)	1.7% (564)
Diuretic therapy	14.2% (6383)	11.5% (1377)	15.1% (5006)
Coronary angiography	85.8% (38 670)	96.1% (11 486)	82.1% (27 184)
PCI	73.4% (33 072)	88.5% (10 585)	67.9% (22 487)
New-onset AF	2.9% (1294)	2.7% (326)	3.0% (968)

Table I Basic characteristics of the study population

	All (*N* = 45 073)	Ticagrelor (*N* = 11 954)	Clopidogrel (*N* = 33 119)
Medication at discharge			
Aspirin	100% (45 073)	100% (11 954)	100% (33 119)
Intended DAPT duration			
3 months	7.7% (799)	3.3% (233)	17.6% (566)
6 months	4.8% (499)	3.8% (272)	7.0% (227)
12 months	73.6% (7634)	83.8% (9995)	50.9% (1639)
Permanent	5.8% (598)	3.7% (187)	10.3% (331)
Not determined at discharge	5.8% (605)	4.3% (307)	9.2% (298)
β-Blocker	90.5% (40 765)	91.1% (10 889)	90.2% (29 876)
Calcium antagonist	16.2% (7290)	14.0% (1672)	17.0% (5618)
Digoxin	1.1% (508)	0.5% (61)	1.3% (447)
ACEi/ARB inhibitor	80.9% (36 076)	84.4% (10 084)	78.8% (25 992)
Diuretic	24.4% (11 001)	16.8% (2011)	27.1% (8990)
Statin	92.1% (41 508)	96.2% (11 501)	90.6% (30 007)

Table 2 Association between use of ticagrelor vs. clopidogrel and outcomes

Event	Ticagrelor	Clopidogrel	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Primary outcome				
Death, MI, or stroke	11.7	22.3	0.49 (0.46–0.53)	0.85 (0.78–0.93)
Secondary outcomes				
Death	5.8	12.9	0.43 (0.39–0.47)	0.83 (0.75–0.92)
MI	6.1	10.8	0.52 (0.47–0.58)	0.89 (0.78–1.01)
Stroke	1.8	3.8	0.53 (0.44–0.63)	0.81 (0.65–1.01)
Risk of bleeding				
Admission with bleeding	5.5	5.2	1.0 (0.92–1.20)	1.20 (1.04–1.40)

Data shown as cumulative probability of events per 100 patient-years at 24 months.
CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

RWE vs. RCTs

Outcome	PLATO	SWEDEHEART
MACE	0.84 (0.77-0.92)	0.85 (0.78-0.93)
Death from any cause	0.78 (0.69-0.89)	0.83 (0.75-0.92)
Myocardial infarction	0.84 (0.75-0.95)	0.89 (0.79-1.01)
Stroke	1.17 (0.91-1.52)	0.81 (0.65-1.01)
Admission with bleeding		1.20 (1.04-1.40)

RWE vs. RCTs

Baseline characteristics (Ticagrelor group)	PLATO	SWEDEHEART
Age (years)	62	70
Male (%)	71.8%	71.5%
History of myocardial infarction	20.4%	15.1%
PCI	13.6%	10.8%
CABG	5.7%	4.6%
History of stroke	3.8%	5.4%
Peripheral artery disease	6.1%	3.3%
Cardiac failure	5.5%	5.5%
Diabetes	24.9%	20.5%

WHAT DOES RWE TELL US?

- The SWEDHEART study shows that real-world efficacy and safety outcomes in patients with ACS treated with ticagrelor vs. clopidogrel are similar to those documented in the PLATO trial;
- The characteristics of patients treated with ticagrelor in the everyday practice do not substantially differ from those of the trial (trial with good generalizability);
- The characteristics of patients treated with ticagrelor in the everyday practice substantially differ from those of patients treated with clopidogrel. The simple adjustment for such characteristics using traditional multivariate models does not exclude the possibility of residual confounding.

Real World Evidence: aims

- To evaluate the impact of a treatment in broader populations and different healthcare settings
- To evaluate the long-term impact of treatment on a large array of outcomes (even those not considered in RCTs)
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Annals of Internal Medicine | ARTICLE

Comorbidity Affects the Relationship Between Glycemic Control and Cardiovascular Outcomes in Diabetes

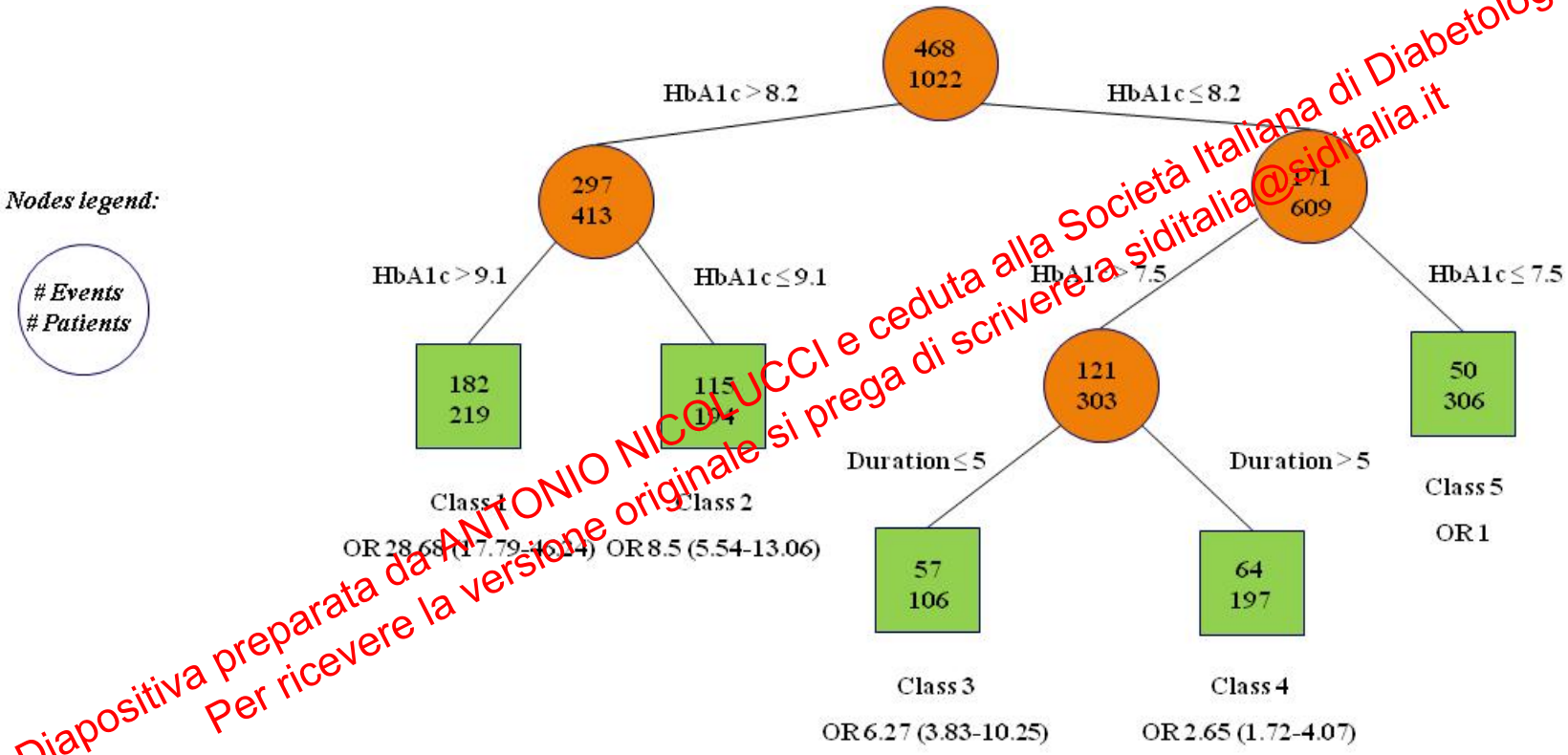
A Cohort Study

Sheldon Greenfield, MD; John Billimek, PhD; Fabio Pellegrini, MS; Monica Franciosi, MSc; Giorgia De Berardis, MSc; Antonio Nicolucci, MD; and Sherrie H. Kaplan, PhD, MPH

Subgroup	HbA$_{1c}$ Target ≤6.5%						
	Cardiovascular Event Rates, *per 100 patient-years*		Unadjusted Model			Adjusted Model*	
	HbA$_{1c}$ ≤6.5%	HbA$_{1c}$ >6.5%	Change	HR (95% CI)	*P* Value†	HR (95% CI)	*P* Value†
TIBI Scores					0.036		0.048
<12	2.2	3.8	1.6	0.58 (0.41–0.82)‡		0.60 (0.42–0.85)‡	
≥12	4.9	5.2	0.3	0.93 (0.68–1.26)		0.92 (0.68–1.25)	
TIBI Score Tertiles					0.32		0.34
1st Tertile	2.3	3.1	0.7	0.76 (0.49–1.20)		0.82 (0.52–1.28)	
2nd Tertile	2.9	4.9	2.0	0.60 (0.39–0.91)‖		0.60 (0.39–0.91)‖	
3rd Tertile	4.8	5.2	0.5	0.88 (0.62–1.24)		0.86 (0.61–1.23)	

HbA$_{1c}$ = hemoglobin A$_{1c}$; HR = Hazard ratio; TIBI = Total Illness Burden Index.
* Adjusted for age and sex.
† Value for interaction between TIBI subgroup and HbA$_{1c}$ level.
‡ $P < 0.010$.
§ $P < 0.001$.
‖ $P < 0.050$.

HbA1c reduction ≥1% after 12 months - RECPAM analysis



HbA1c change	Class 1	Class 2	Class 3	Class 4	Class 5
	-2.2±1.5	-1.0±1.1	-0.9±1.0	-0.5±0.9	-0.1±0.8

Real World Evidence: aims

- To evaluate the impact of a treatment in broader populations and different healthcare settings
- To evaluate the long-term impact of treatment on a large array of outcomes (even those not considered in RCTs)
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- To evaluate rare serious adverse events
- To assess the safety profile in different patient subgroups
- To evaluate treatment compliance and persistence
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- To evaluate the appropriateness of drug prescription and quality of care

RWE on safety

- Sample size of RCTs is usually based on efficacy parameters, not safety;
- Serious, rare adverse events have a very low likelihood to be detected in RCTs;
- The severity of adverse events and the monitoring of laboratory parameters relative to safety are often poorly defined;
- The administration of a drug to individuals with comorbidities and treated with multiple drugs (usually excluded from RCTs) can be responsible for more severe or more frequent drug interactions or side effects;
- The duration, often limited, of RCTs does not allow the evaluation of long-term safety.

Completeness of Safety Reporting in Randomized Trials

An Evaluation of 7 Medical Areas

John P. A. Ioannidis, MD
Joseph Lau, MD

JAMA. 2001;285:437-443

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Adverse Events in Randomized Trials

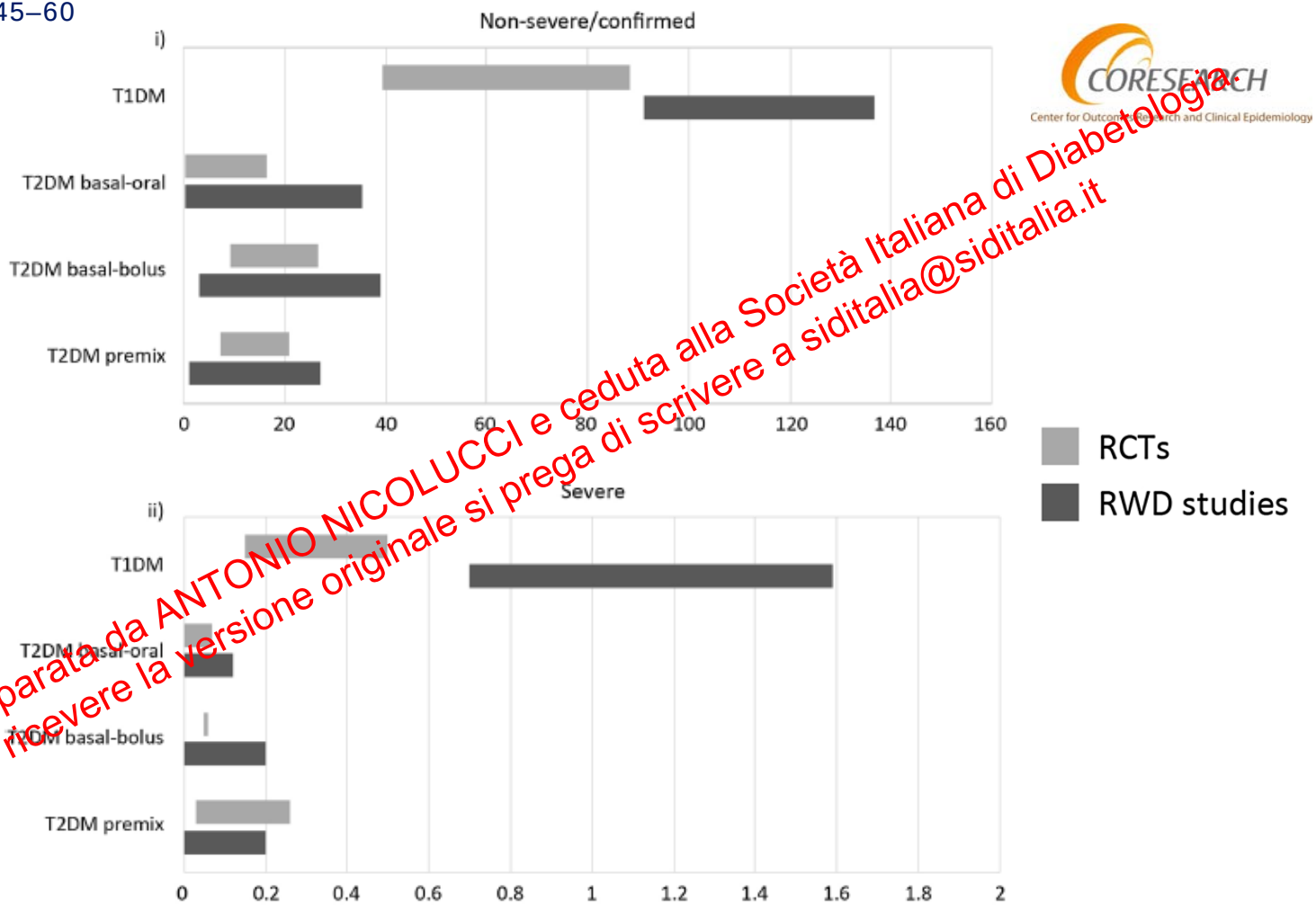
Neglected, Restricted, Distorted, and Silenced

ARCH INTERN MED/VOL 169 (NO. 19), OCT 26, 2009

Reporting of Safety Results in Published Reports of Randomized Controlled Trials

Isabelle Pitrou, MD, MSc; Isabelle Boutron, MD, PhD; Nizar Ahmad, MD, MSc; Philippe Ravaud, MD, PhD

Arch Intern Med. 2009;169(19):1756-1761

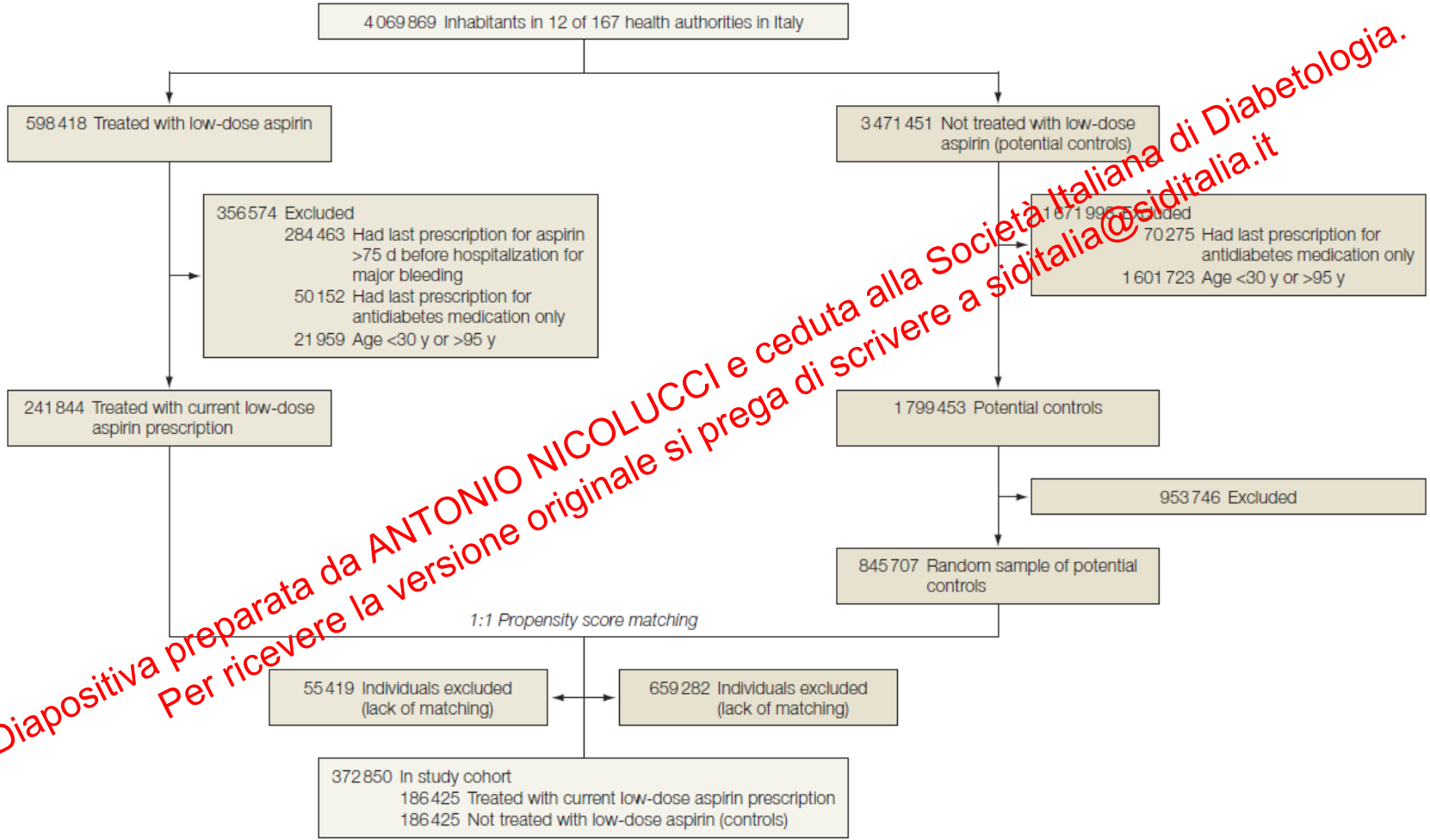


Association of Aspirin Use With Major Bleeding in Patients With and Without Diabetes

Giorgia De Berardis, MSc
Giuseppe Lucisano, MSc
Antonio D'Ettorre, MSc
Fabio Pellegrini, MSc
Vito Lepore, MD
Gianni Tognoni, MD
Antonio Nicolucci, MD

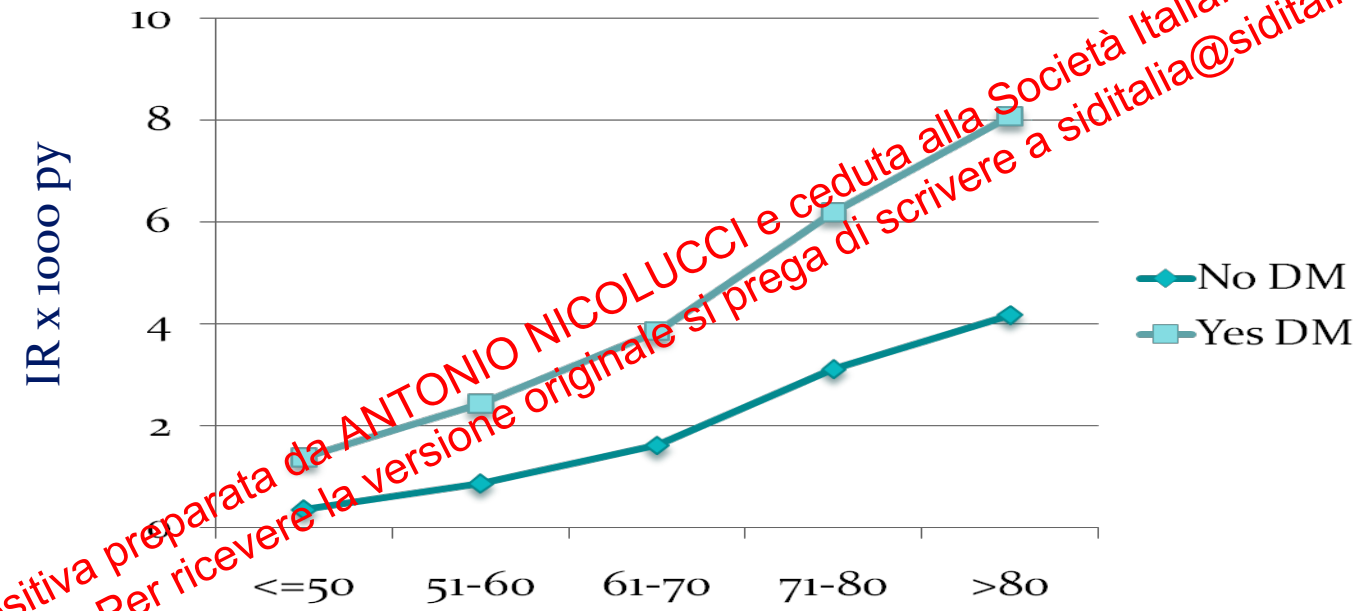
JAMA, June 6, 2012—Vol 307, No. 21

Figure 1. Screening and Enrollment of Participants in the Study



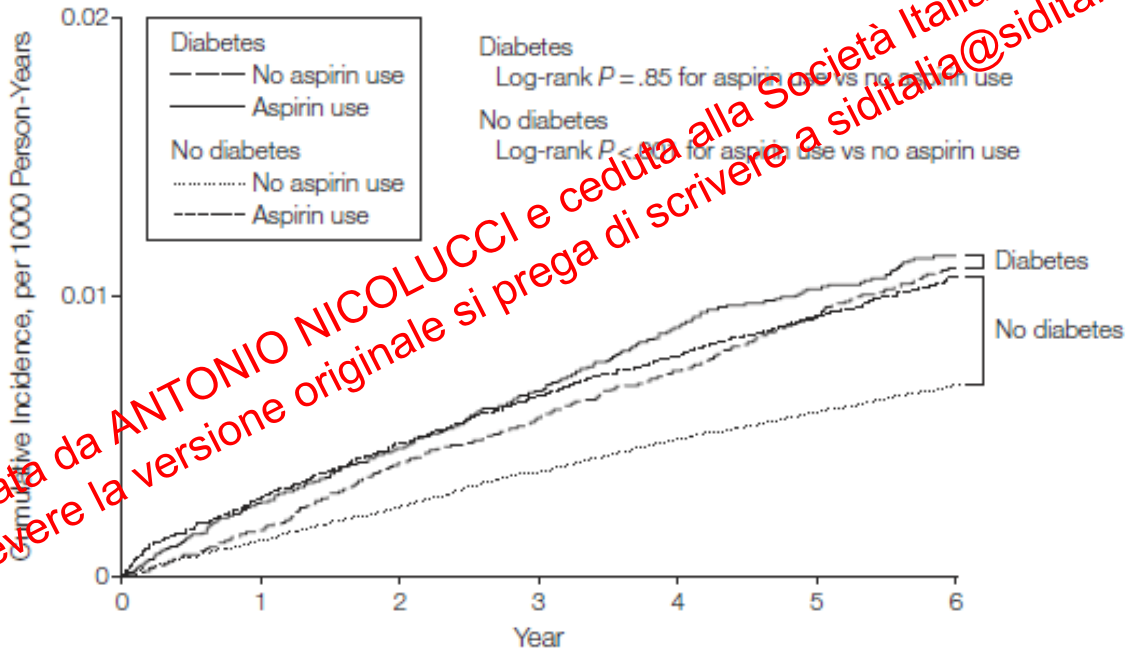
Incidence rate of hemorrhagic events according to age classes

Adjusted analysis



De Berardis G. JAMA 2012; 307:2286-94

Figure 2. Cumulative Proportion of Patients Developing Major Bleeding Events During Follow-up According to Diabetes Status and Aspirin Use



De Berardis G. JAMA 2012; 307:2286-94

Liraglutide and cardiovascular outcomes in T2DM

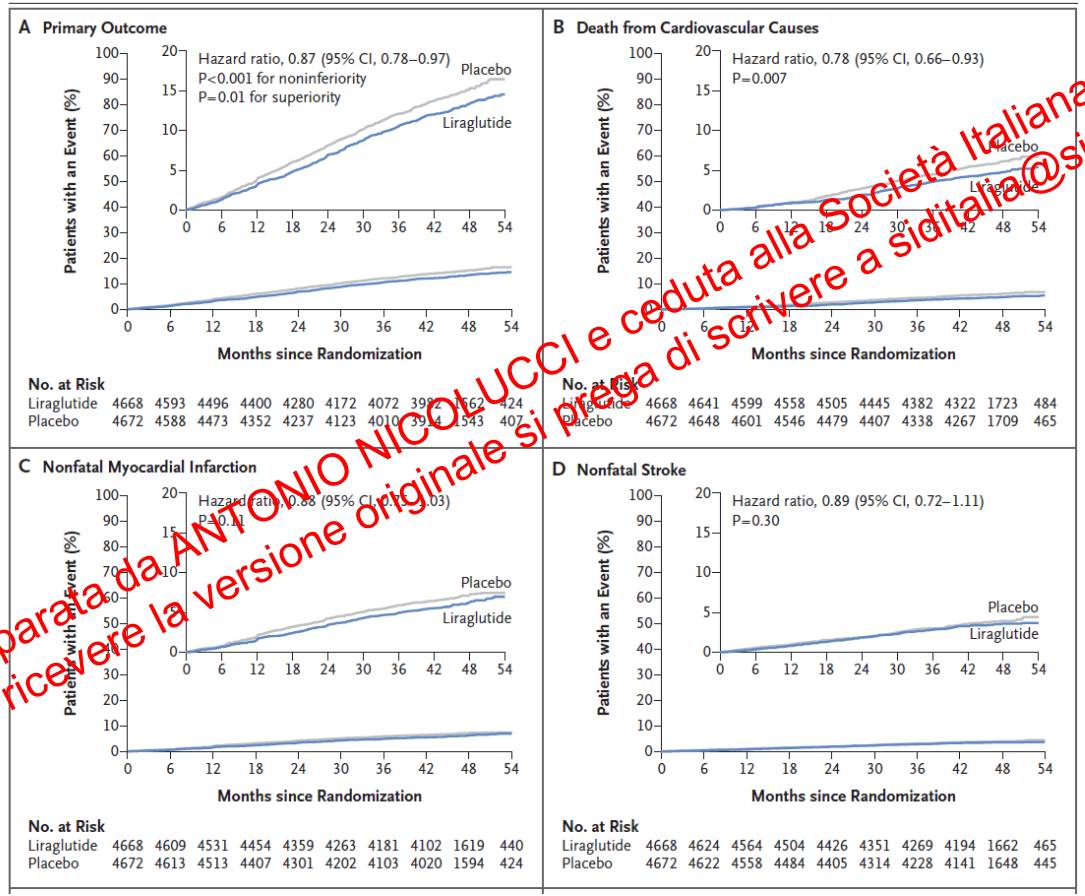


Table S6. Severe hypoglycemia events by randomized treatment.

Treatment group	Number of severe hypoglycemia events	Number of participants experiencing that number of events
Liraglutide	1	90
	2	12
	3	6
	4	3
	5	1
Placebo	1	90
	2	12
	3	6
	4	4
	5	2
	6	1
	47	1
	Total	153

The proportion of participants with one or more severe events (logistic regression adjusted for covariates): odds ratio = 0.75 [95% CI 0.59-0.96].

Death from CV causes: 219 vs. 278

Difference: -59

Severe hypoglycemia: 255 vs. 178

Difference: -77

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logue, liraglutide, and cardiovascular outcomes in type 2 diabetes. N Engl J Med

Mario Negri

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l. Semaglutide and cardio-

e 2 diabetes. N Engl J Med

THE AUTHORS REPLY: Cosmi et al. cite observational studies that associate insulin use with increased cardiovascular risk, and they suggest that the greater new use of insulin in the placebo group than in the semaglutide group may have contributed to the difference in cardiovascular risk observed with semaglutide. However, the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial,[1] a large-scale, randomized, controlled trial evaluating a potential cardiovascular effect of insulin, showed that insulin glargine, as compared with placebo, was not associated with an increased cardiovascular risk. We therefore do not think that the use of insulin contributed to the effect seen in our trial.

Insulin Inhibits Cardiac Contractility by Inducing a G_i-Biased β_2-Adrenergic Signaling in Hearts

Diabetes 2014;63:2676–2689 | DOI: 10.2337/db13-1763

Insulin and β Adrenergic Receptor Signaling: Crosstalk in Heart

Trends in Endocrinology & Metabolism

G_i-Biased β_2AR Signaling Links GRK2 Upregulation to Heart Failure

Circ Res. 2012;110:265-274;

Treatment with Insulin is Associated with Worse Outcome in Patients with Chronic Heart Failure and Diabetes

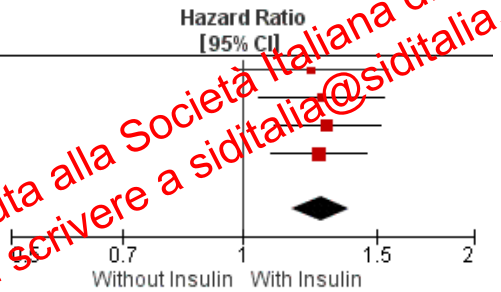
Eur J Heart Fail (in press)

Mortality

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Val-HeFT	0.207	0.117	14.0%	1.23 [0.98, 1.55]
CORONA	0.239	0.096	20.7%	1.27 [1.05, 1.53]
GISSI-HF	0.2546	0.0808	29.3%	1.29 [1.10, 1.51]
ATMOSPHERE	0.2311	0.0728	36.0%	1.26 [1.09, 1.45]
Total (95% CI)			**100.0%**	**1.27 [1.16, 1.38]**

Heterogeneity: $Chi^2 = 0.12$, df = 3 (P = 0.99); $I^2 = 0\%$

Test for overall effect: Z = 5.41 (P < 0.00001)

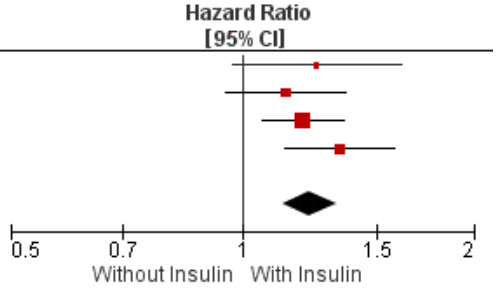


HHF

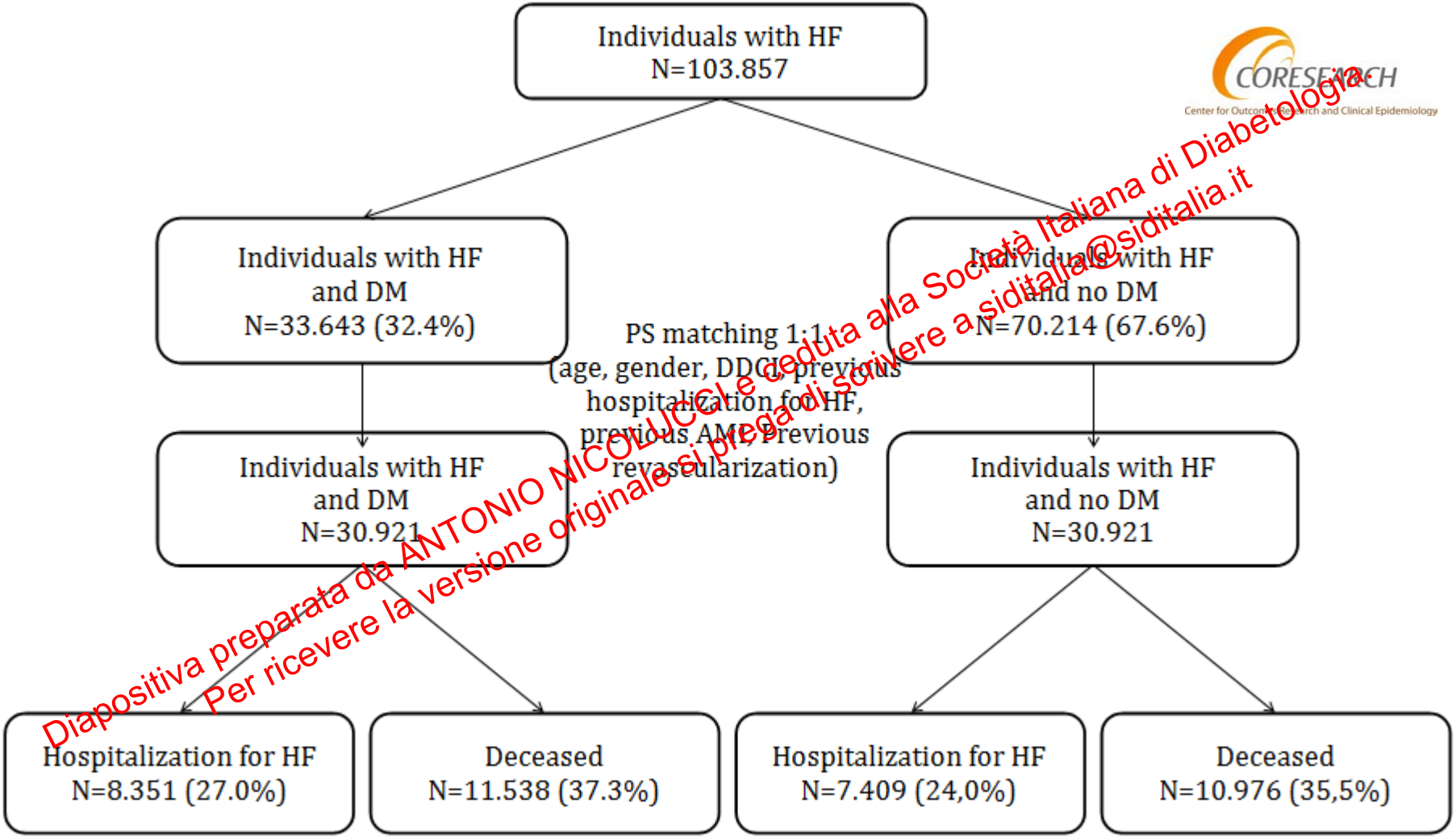
Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Val-HeFT	0.2231	0.1293	10.2%	1.25 [0.97, 1.61]
CORONA	0.131	0.0915	20.4%	1.14 [0.95, 1.36]
GISSI-HF	0.1823	0.0617	44.8%	1.20 [1.06, 1.35]
ATMOSPHERE	0.2927	0.0833	24.6%	1.34 [1.14, 1.58]
Total (95% CI)			**100.0%**	**1.23 [1.13, 1.33]**

Heterogeneity: $Chi^2 = 1.92$, df = 3 (P = 0.59); $I^2 = 0\%$

Test for overall effect: Z = 4.92 (P < 0.00001)



Multivariable Cox model adjusted by propensity score IPTW (Inverse Probability of Treatment Weighted)



Treatment with Insulin is Associated with Worse Outcome in Patients with Chronic Heart Failure and Diabetes

	Hosp. CHF	Mortality
Effect	OR 95%CI	OR 95%CI
Insulin (alone or in combination) vs. Other	1.42 (1.32-1.53)	2.02 (1.87-2.19)

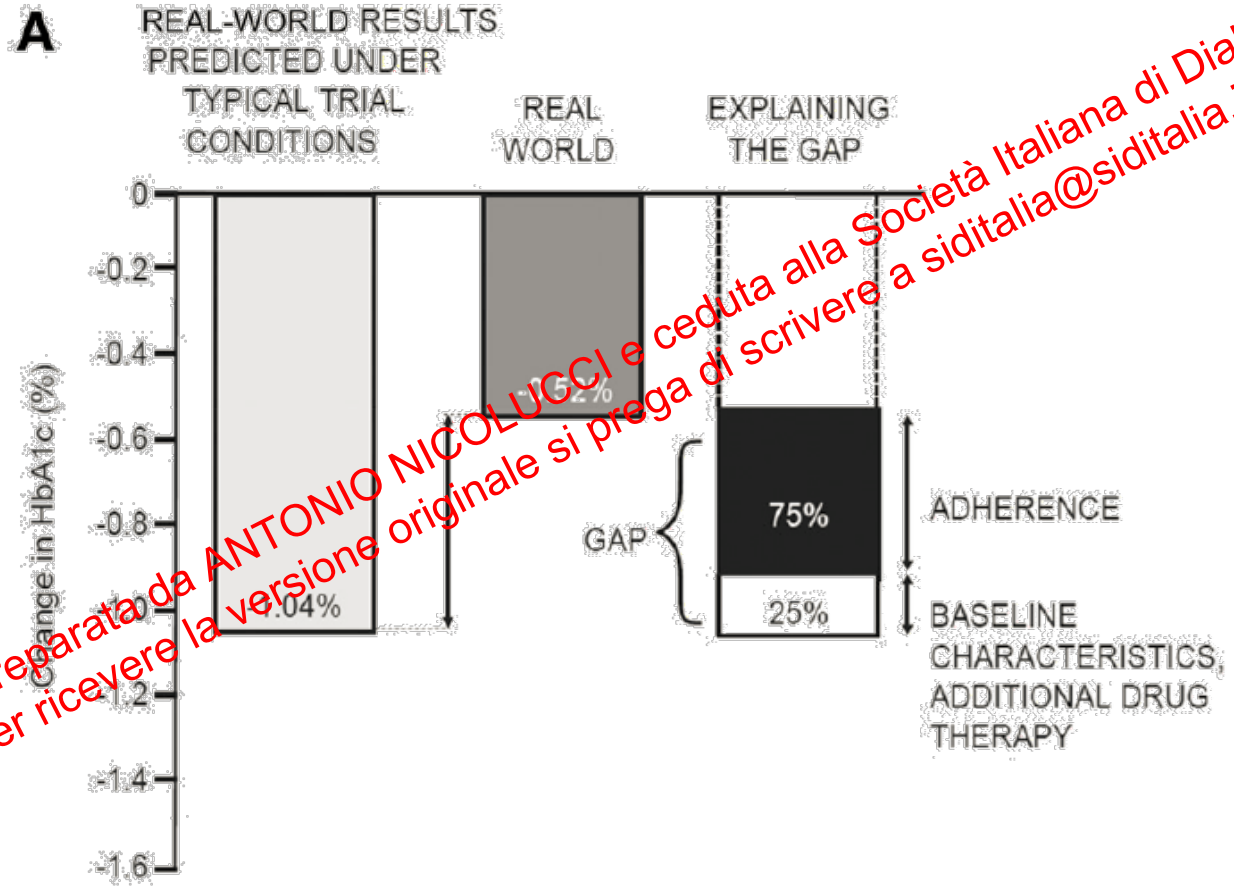
CORESEARCH
Center for Outcomes Research and Clinical Epidemiology

Eur J Heart Fail (in press)

Real World Evidence: aims

- To evaluate the impact of a treatment in broader populations and different healthcare settings
- To evaluate the long-term impact of treatment on a large array of outcomes (even those not considered in RCTs)
- To evaluate the impact of treatment on different patient subgroups, even those usually excluded or underrepresented in RCTs
- To evaluate rare serious adverse events
- To assess the safety profile in different patient subgroups
- To evaluate treatment compliance and persistence
- To assess healthcare resource utilization, costs of treatment and cost-effectiveness
- To evaluate the appropriateness of drug prescription and quality of care

Diabetes Care 2017;40:1425–1432



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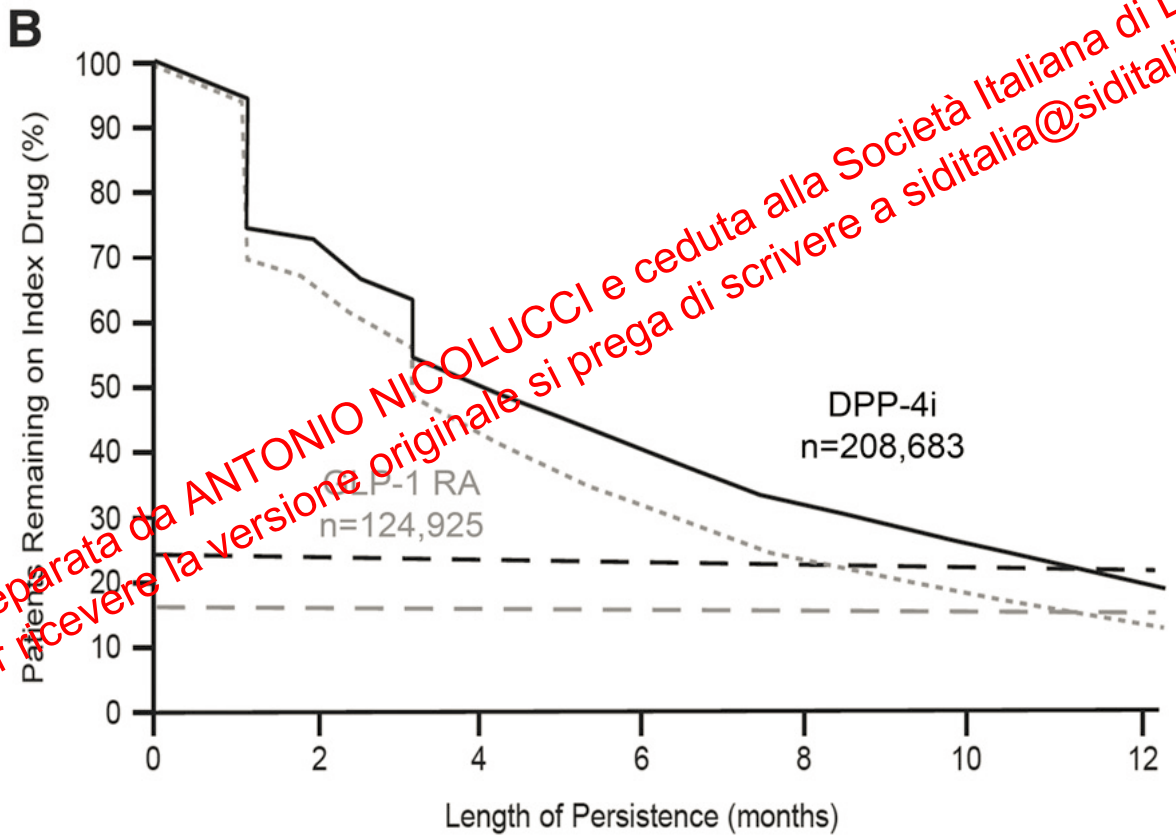
Real World Evidence: USA

Diabetes Care 2017;40:1425–1432



CORESEARCH
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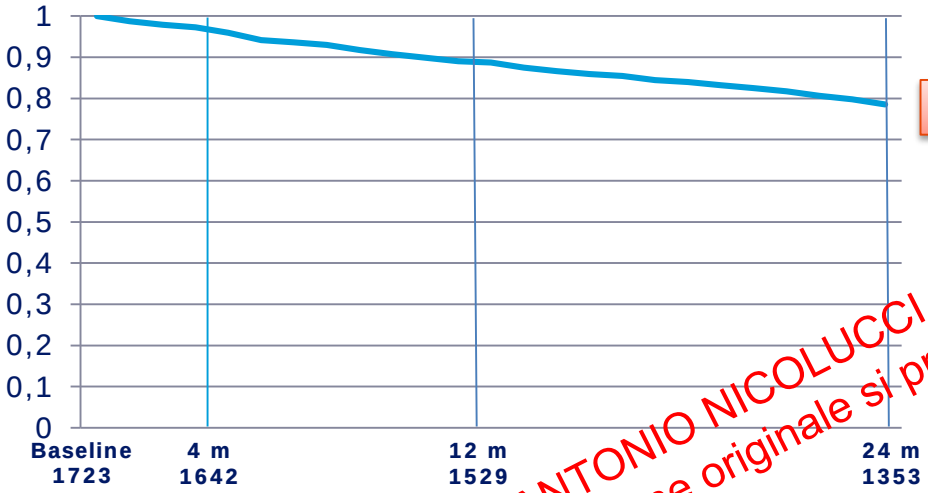
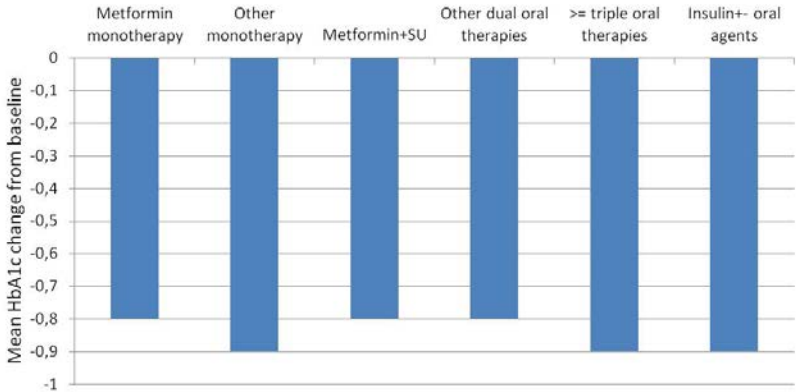
Real World Evidence: Italy



-21.5%

Mean HbA1c changes from baseline, adjusted for baseline values, according to concomitant treatment



CONCLUSIONS

- RWE represents an important complement to RCTs, allowing a deeper understanding of the risk-benefit profile of a treatement when administered under routine clinical practice conditions, in unselected populations;
- In the era of personalized medicine, it is important that clinical practice guidelines target relevant patient risk subgroups. Large, well designed observational studies will help to provide evidence to support “segmented” guidelines;
- The identification of patient subgroups more likely to benefit from the treatment can inform payers and decision makers in the definition of reimbursement policies.