ROMA

14 settembre 2018

CROWNE PLAZA ROME - ST. PETER'S

La protezione cardiovascolare degli inibitori di SGLT2: trial e studi osservazionali

Saula Vigili de Kreutzenberg

Università degli Studi di Padova

SID Società Italiana di Diabetologia

Il /la dr./sa Saula Vigili de Kreutzenberg dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Astra Zeneca
- Bruno Farmaceutici
- Lilly
- MSD
- Servier

SGLT2 inibitori: Studi con outcome cardiovascolari

Trial clinici randomizzati (RCTs) – CVOT

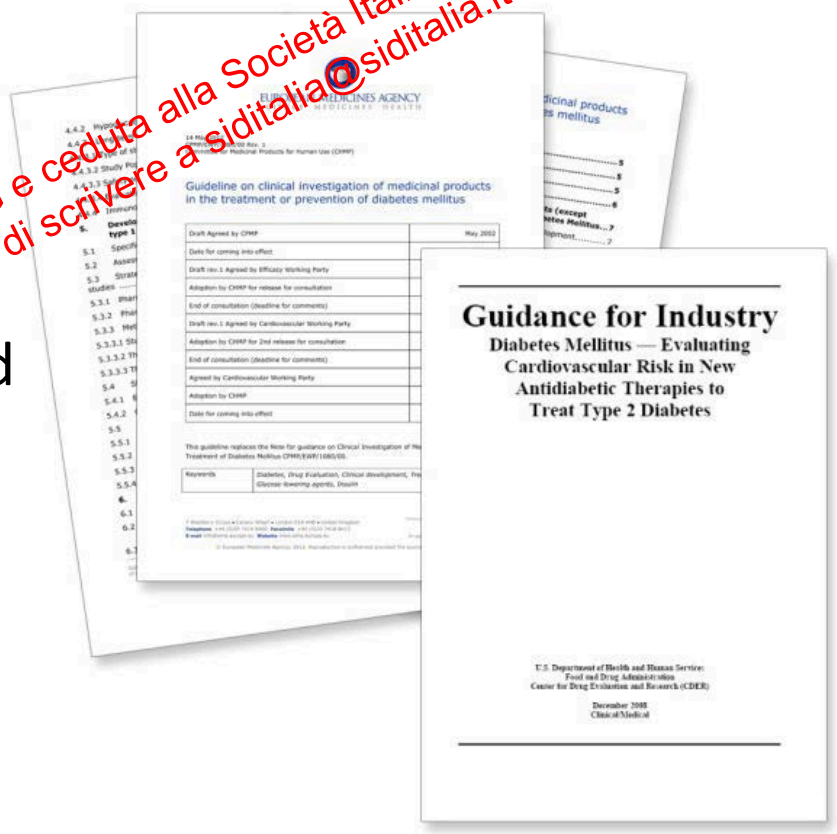
- EMPA-REG OUTCOME (2015)
- CANVAS Program (2017)

Studi osservazionali - Real-world studies:

- SWEDISH REGISTRY (2017)
- CVD-REAL (2017)
- CVD-REAL NORDIC (2017)
- THIN (2017)
- CVD-REAL 2 (2018)
- EASEL (2018)
- OBSERVE-4D (2018)

European Medicines Agency (EMA) and US Food and Drug Administration (FDA): Need for CV Outcomes Studies

"Demonstrate that a new anti-diabetic therapy is not associated with "**unacceptable increase** in cardiovascular risk"



EMA. 2012. http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500129256&mid=WC0b01ac058009a3dc.
FDA. 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

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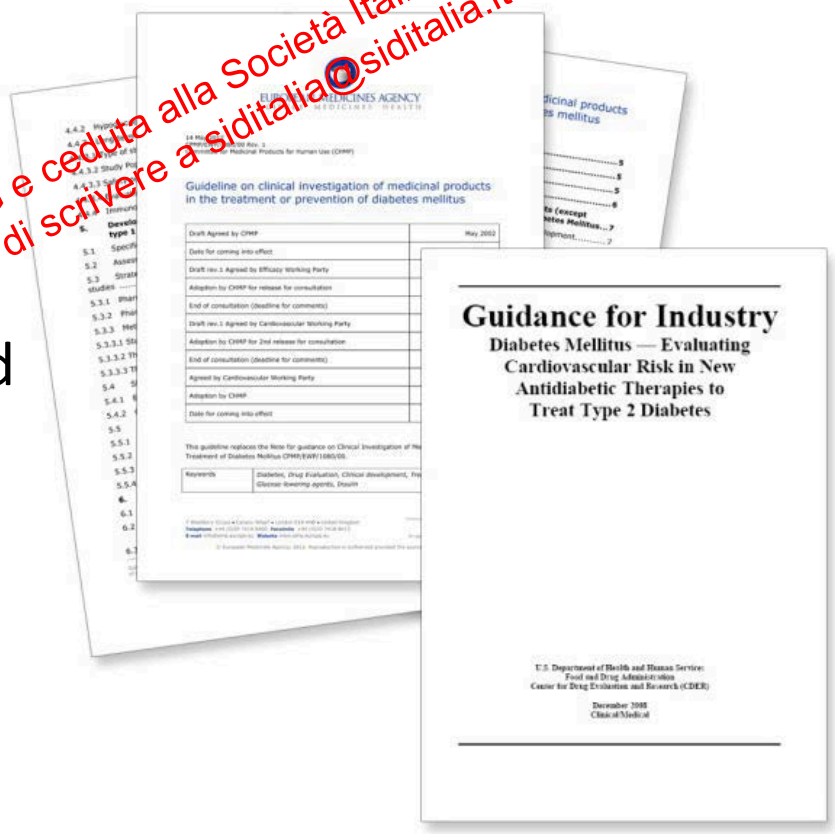


Safety!

EMA. 2012. http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500129256&mid=WC0b01ac058009a3dc.
FDA. 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

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

- Randomised, double-blind, placebo-controlled CV outcomes trial

- **Objective**: The effects of empagliflozin, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk.

Zinman B et al, N Engl I Med 2015;373:2117-28.

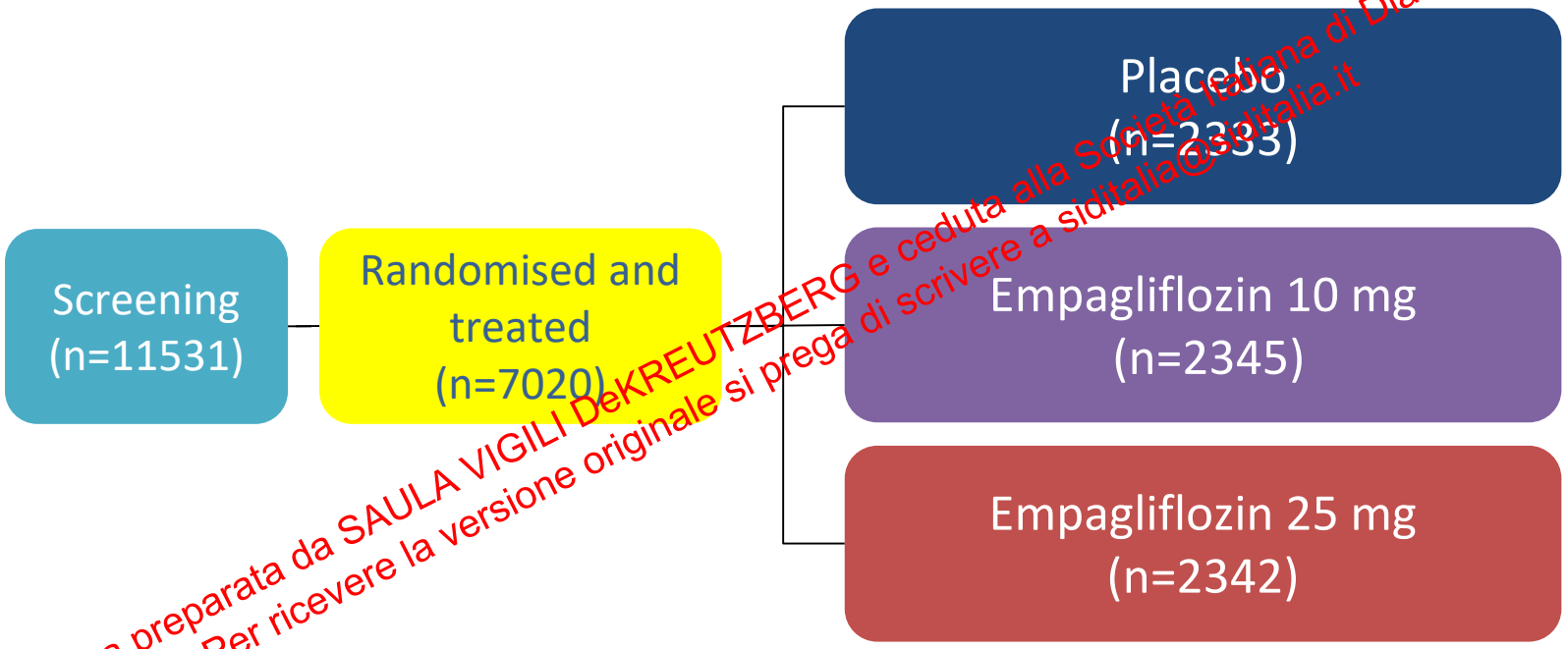
ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

- 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)

Zinman B et al, N Engl I Med 2015;373:2117-28.

EMPA-REG OUTCOME – Trial design

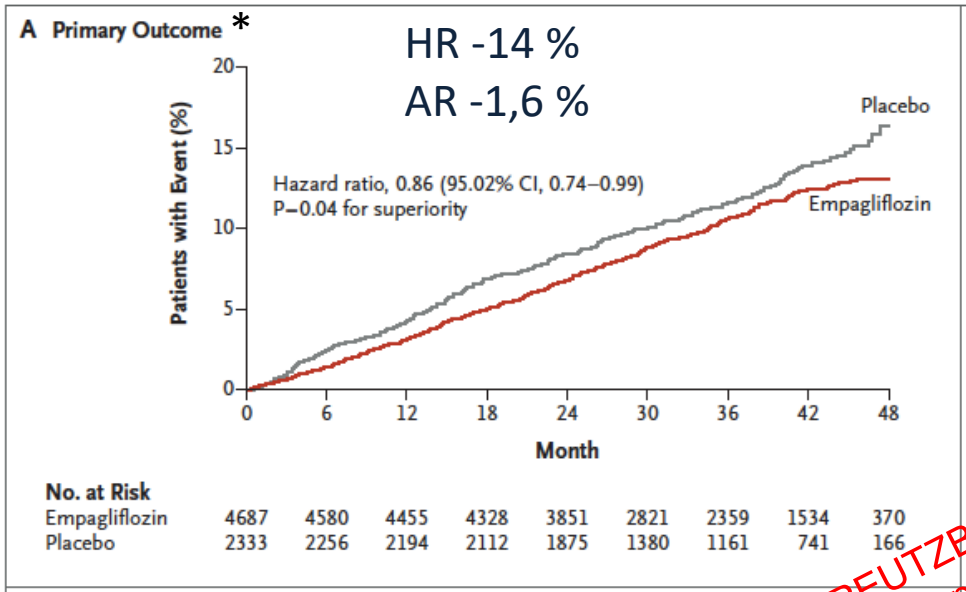


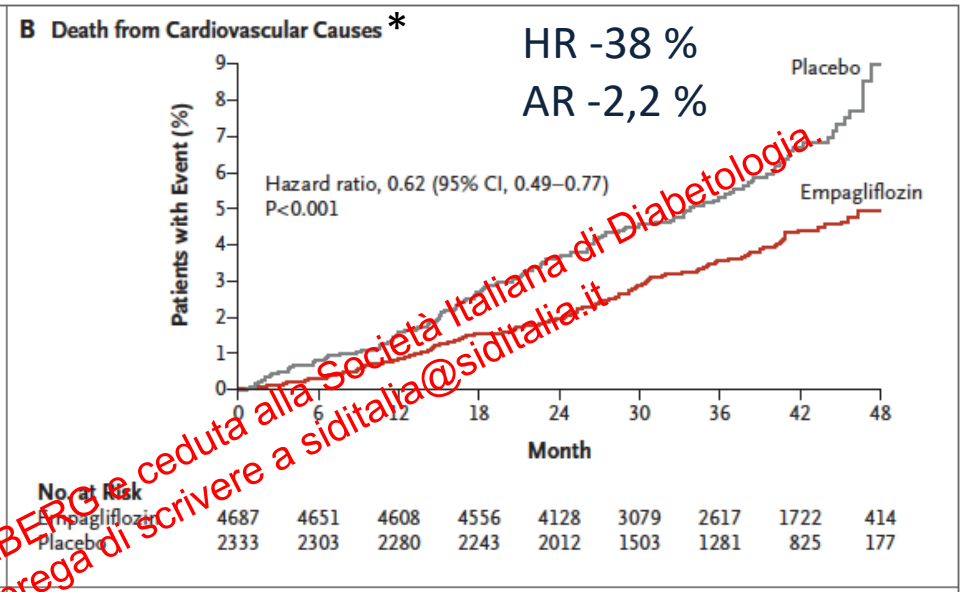
The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event. The median duration of treatment was 2.6 years, and the median observation time was 3.1 years

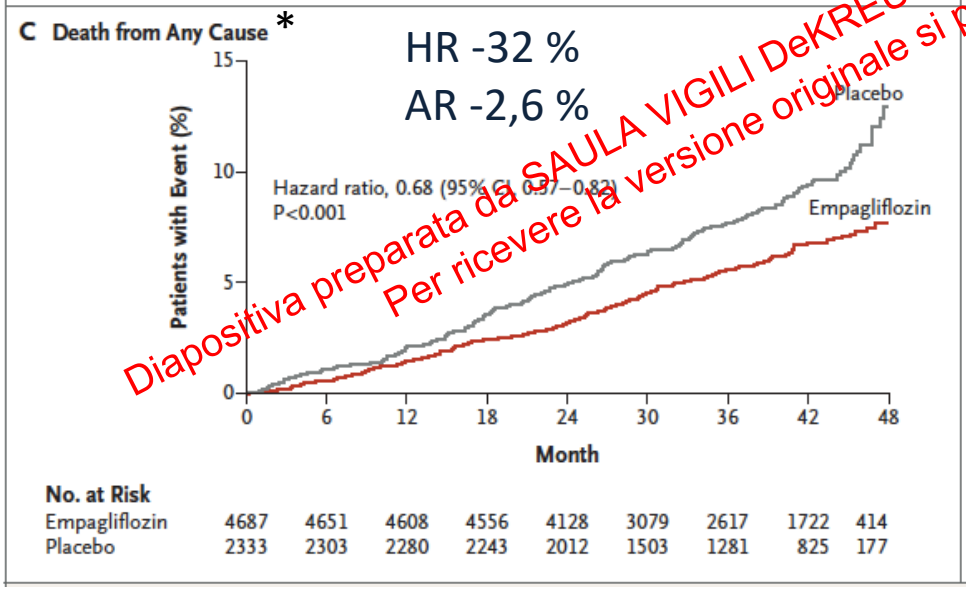
Zinman B et al, N Engl I Med 2015;373:2117-28.

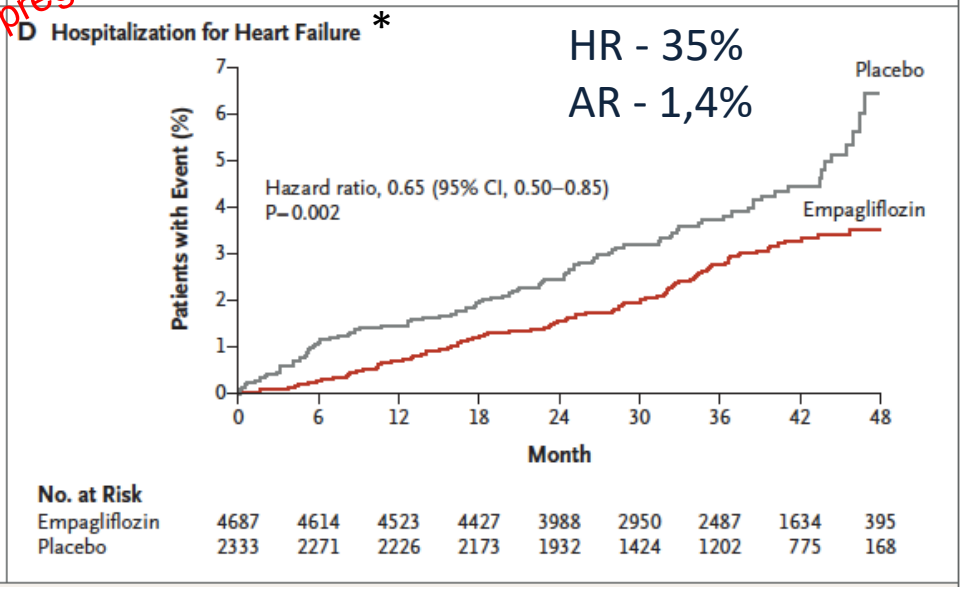
EMPA-REG OUTCOME - Results

Death from cardiovascular causes, nonfatal myocardial infarction/stroke





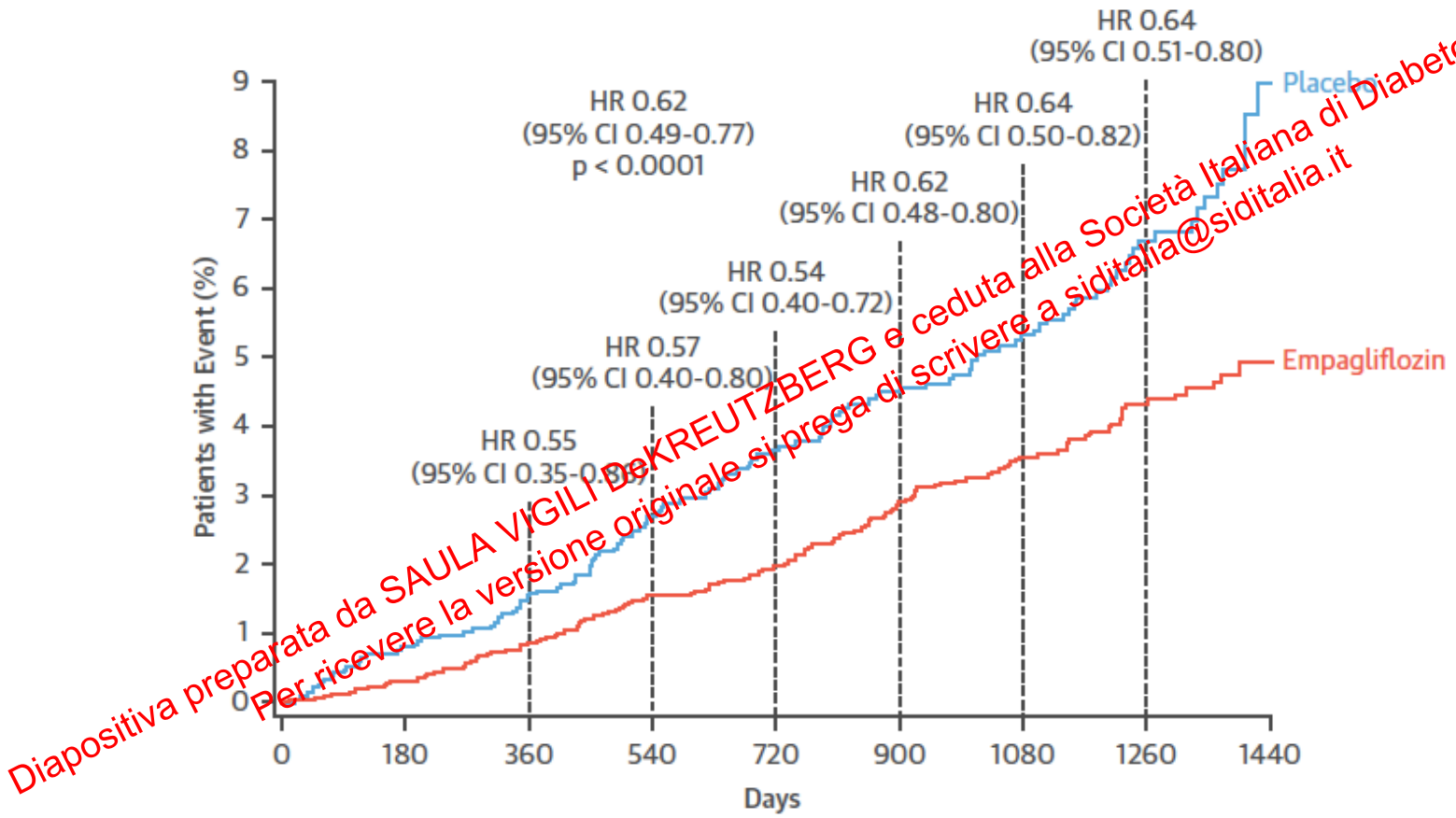




HR = hazard ratio; AR = absolute risk

Zinman B et al, N Engl I Med 2015;373:2117-28.

EMPA-REG OUTCOME Cardiovascular Death Over Time



No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

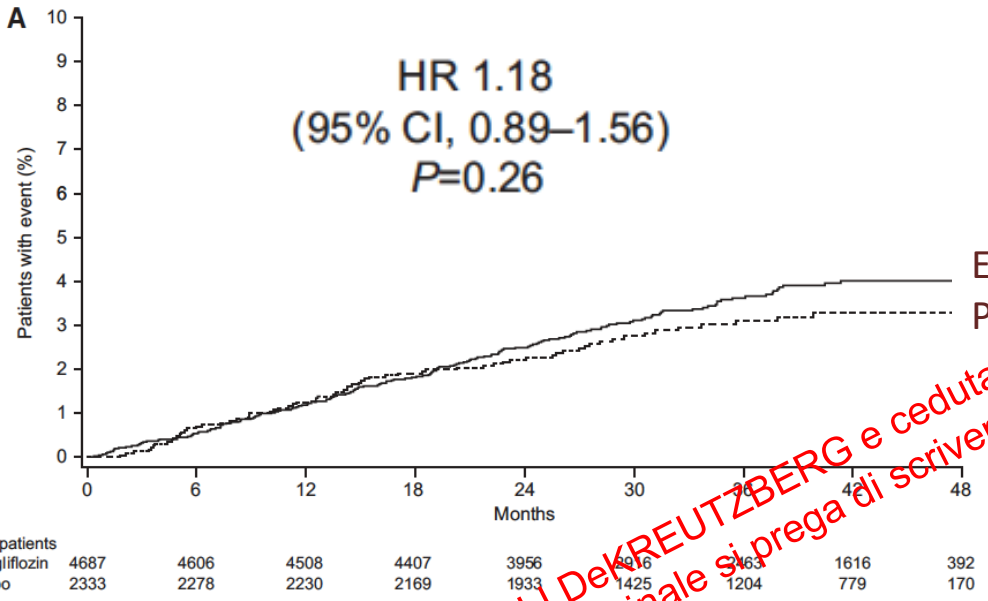
Cox regression analyses in patients treated with ≥1 dose of study drug

Fitchett D et al J Am Coll Cardiol 2018;71

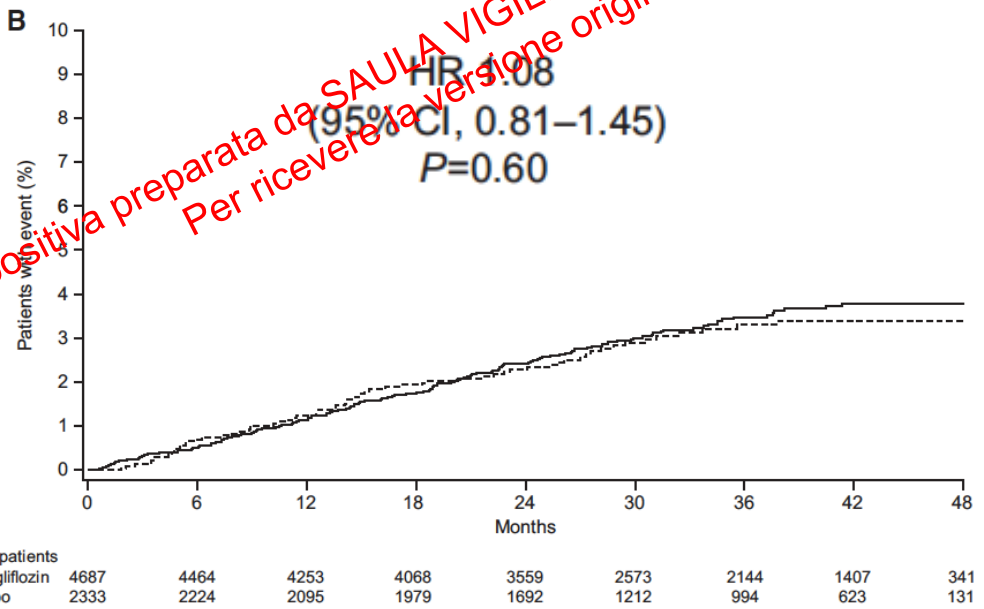
EMPA-REG OUTCOME - Cardiovascular death by cardiovascular disease at baseline and a sensitivity analysis excluding presumed CV death

Fitchett D et al J Am Coll Cardiol 2018;71

Empagliflozin and Cerebrovascular Events in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk



Intent-to-tretat analysis



Sensitivity analysis

Empagliflozin
Placebo

Zinman B et al, Stroke. 2017;48:1218-1225.

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

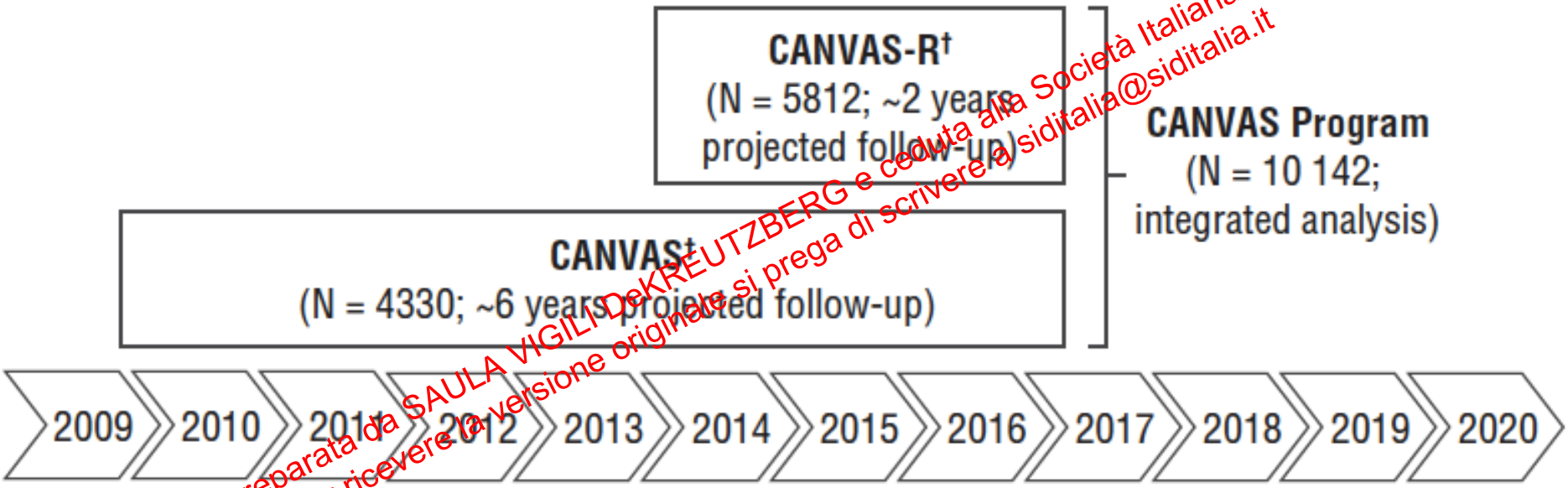
Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D.,
Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D.,
Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D.,
Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch.,
for the CANVAS Program Collaborative Group*

- Randomised, double-blind, placebo-controlled CV outcomes trial

- **Objective**: We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

Neal B et al, N Engl J Med 2017;377:644-57.

Optimizing the analysis strategy for the CANVAS Program: A prespecified plan for the integrated analyses of the CANVAS and CANVAS-R trials



†Populations in CANVAS and CANVAS-R are nearly identical to facilitate an integrated analysis of the data. The trials were scheduled for joint close-out and analysis when at least 688 CV events had been observed.

Neal B et al, Diabetes Obes Metab. 2017;19:926–935.

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

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- Key inclusion criteria
  - Adults with type 2 diabetes
  - HbA1c ≥7 ≤10.5 %*
  - eGFR ≥30 mL/min/1.73m^2 (MDRD)
  - Age ≥30 years and history of prior CV event OR
  - Age ≥50 years with ≥ CV risk factors*

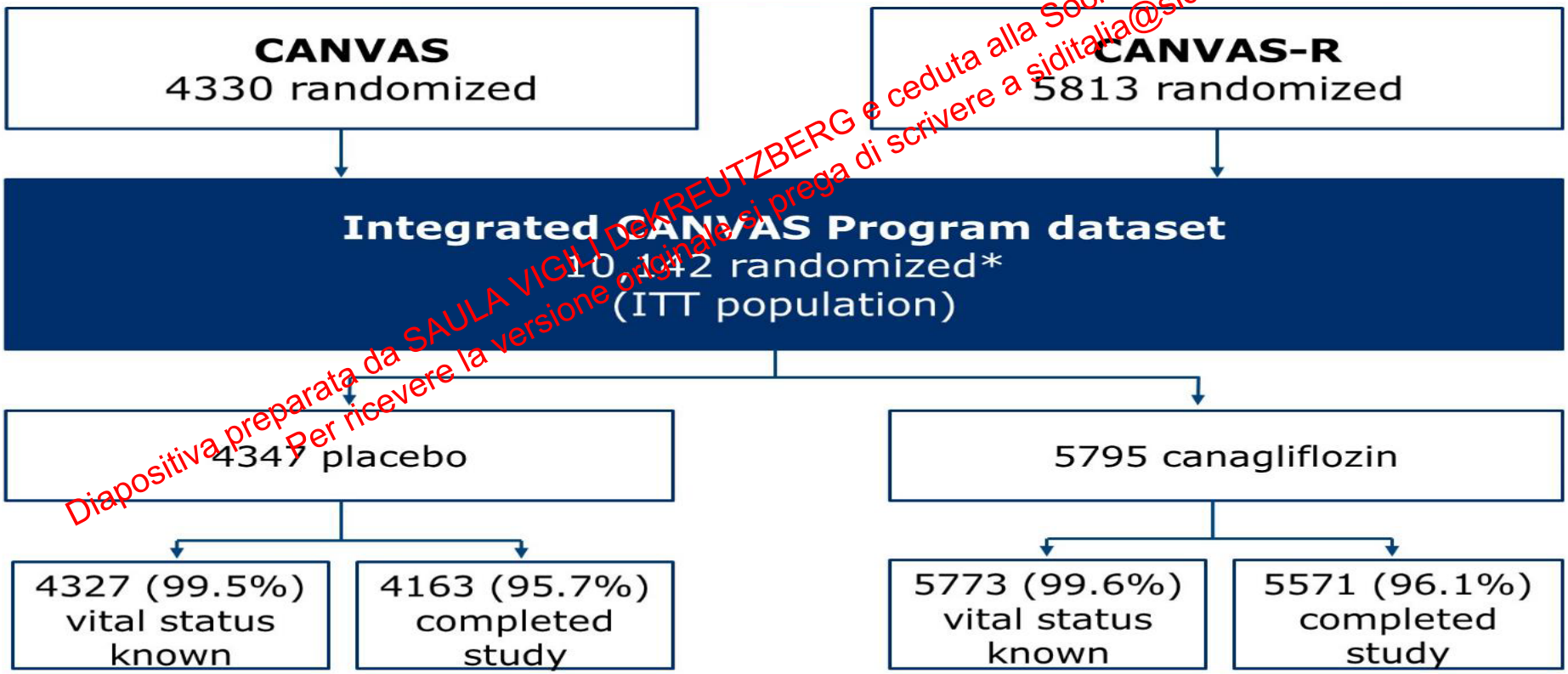
*diabetes duration ≥10 years, SBP >140 mmHg on ≥1 medication, current smoker, micro- or macroalbuminuria, or HDL cholesterol <1 mmol/L

Neal B et al, N Engl J Med 2017;377:644-57.

CANVAS PROGRAM – Randomization

In CANVAS participants were randomly assigned in a 1:1:1 ratio to receive canagliflozin at a dose of 300 mg, canagliflozin at adose of 100 mg, or matching placebo

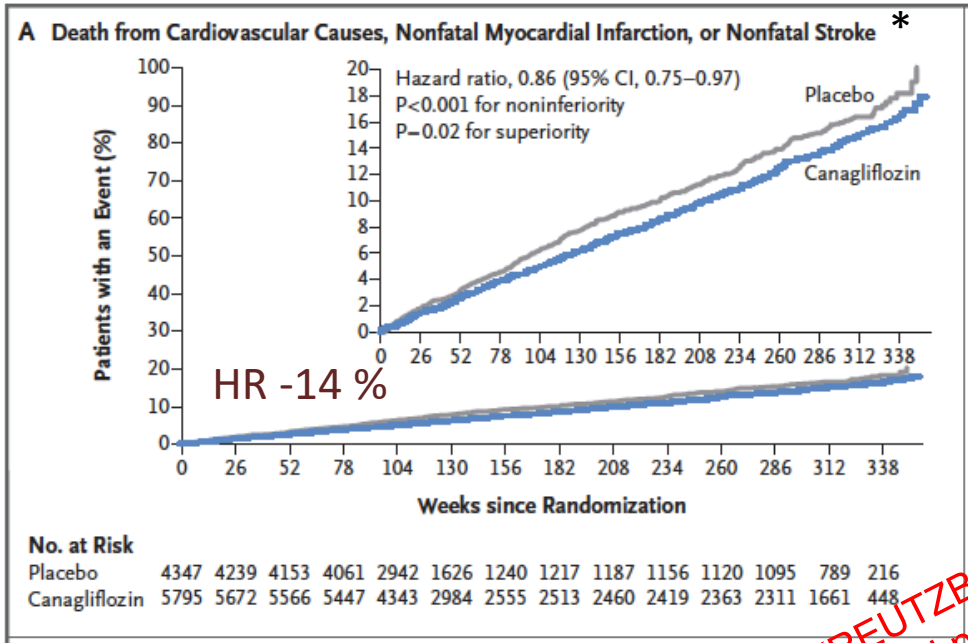
In CANVAS-R participants were randomly assigned in an 1:1 ratio to receive canagliflozin, Administered at an initial dose of 100 mg daily with an optional increase to 300 mg starting from week 13, or matching placebo

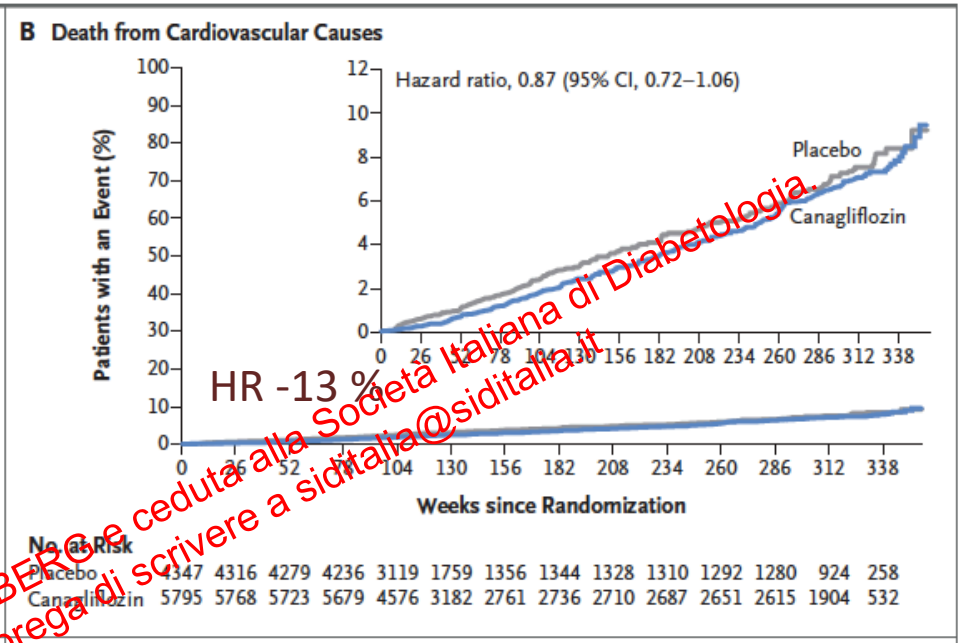


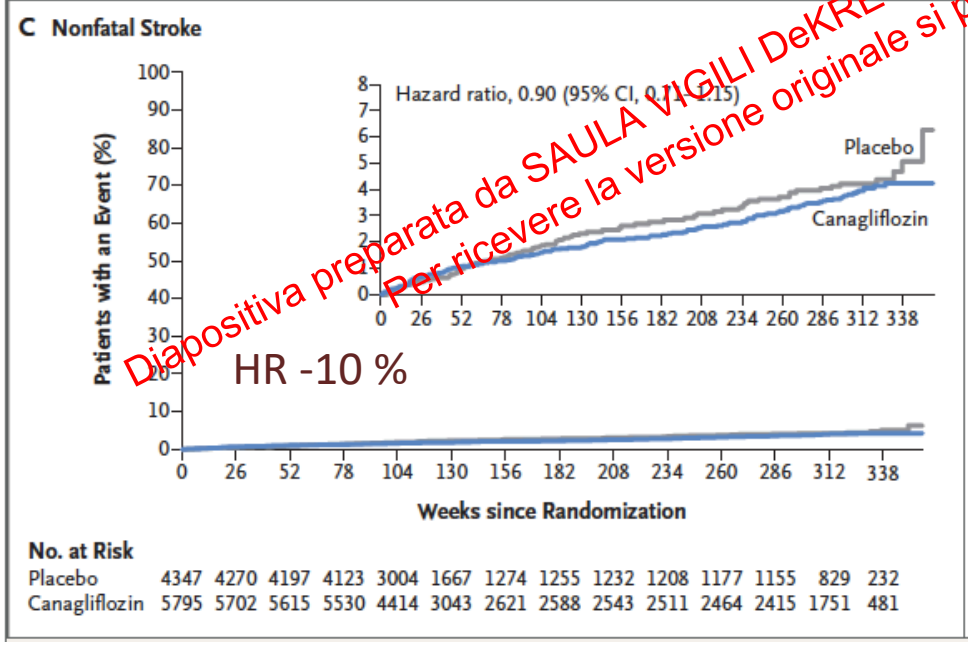
*One participant was randomized at 2 different sites and only the first randomization is included in the ITT analysis set.

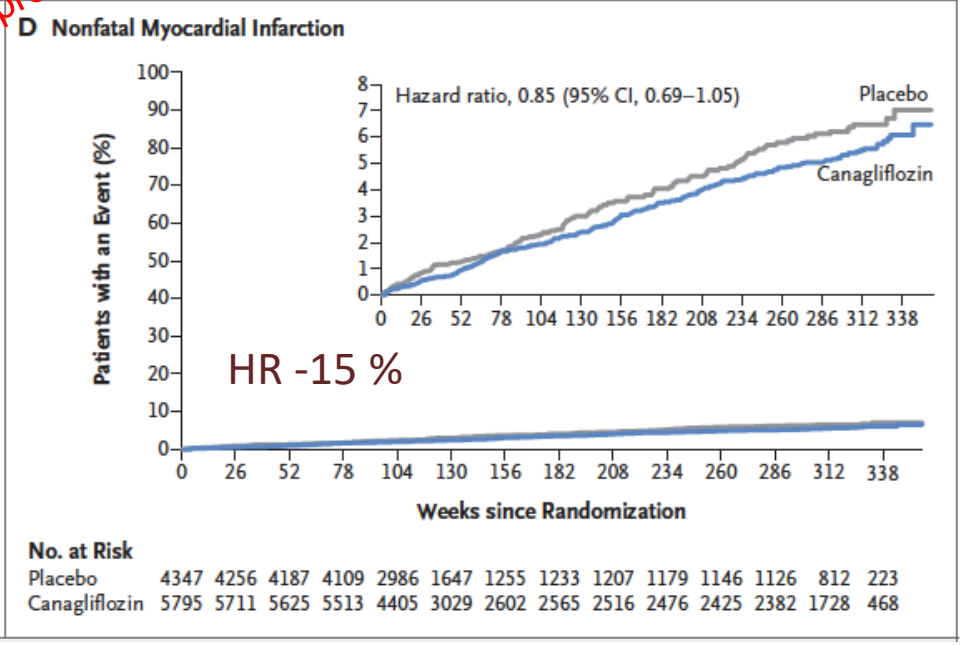
Neal B et al, N Engl J Med 2017;377:644-57.

CANVAS PROGRAM - Results









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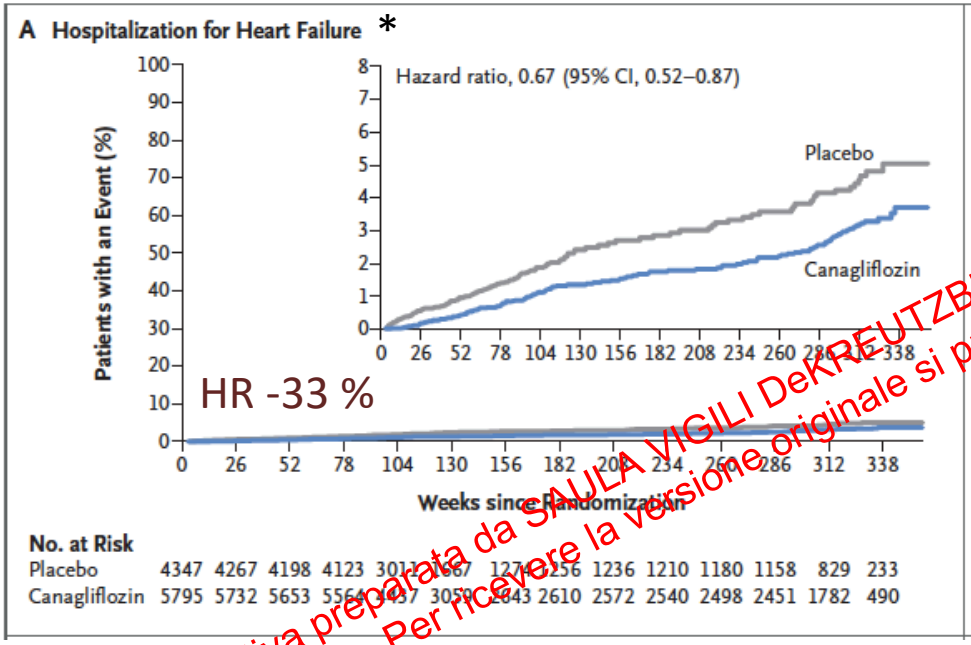

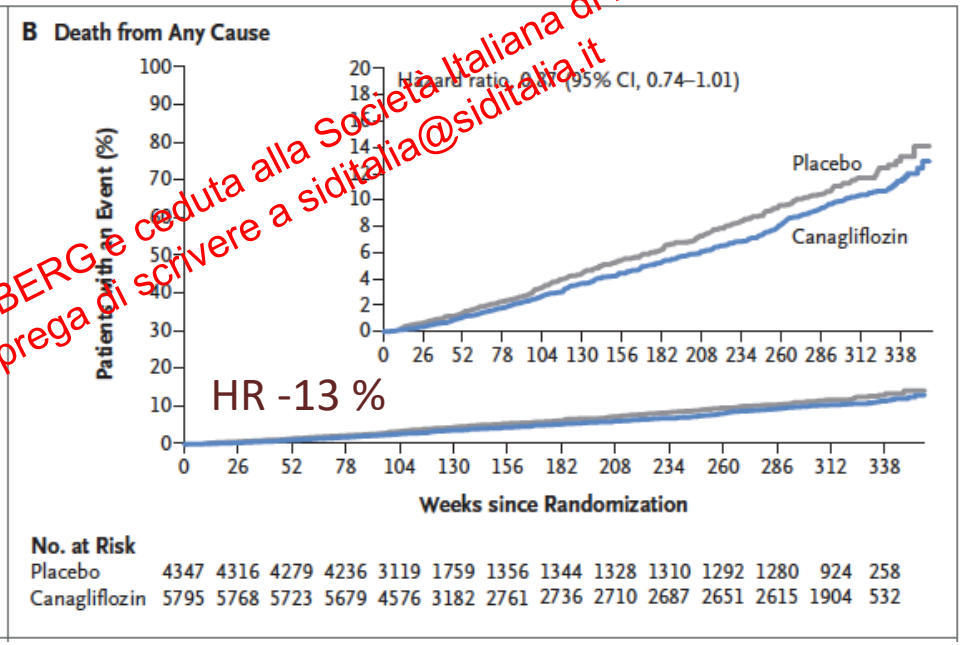

Neal B et al, N Engl J Med 2017;377:644-57.

Risultati negli studi EMPAREG-OUTCOME e CANVAS Program

	Primary Outcome HR (95%CI)	IMA* HR (95%CI)	ICTUS ISCH.* HR (95%CI)	Morte CV HR (95%CI)	Morte Totale HR (95%CI)	HHF HR (95%CI)
EMPA-REG OUTCOME	0.86 (0.74-0.99) P = 0.04	0.87 (0.70-1.09) P = NS	1.18 (0.89-1.56) P = NS	0.62 (0.49-0.77) P < 0.001	0.68 (0.57-0.82) P < 0.001	0.65 (0.50-0.85) P = 0.002
CANVAS PROGRAM	0.86 (075-0.97) P = 0.02	0.85 (0.69-1.05) P = NS	0.90 (0.71-1.15) P = NS	0.87 (0.72-1.06) P = NS	0.87 (0.74-1.01) P = NS	0.67 (0.52-0.87) P < 0.001

Primary outcome=morte CV, IMA non fatale, ictus ischemico non fatale
*fatale e non fatale
HHF=ospedalizzazioni per insufficienza cardiaca

Risultati negli studi EMPAREG-OUTCOME e CANVAS Program

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Primary outcome=morte CV, IMA non fatale, ictus ischemico non fatale
*fatale e non fatale
HHF=ospedalizzazioni per insufficienza cardiaca

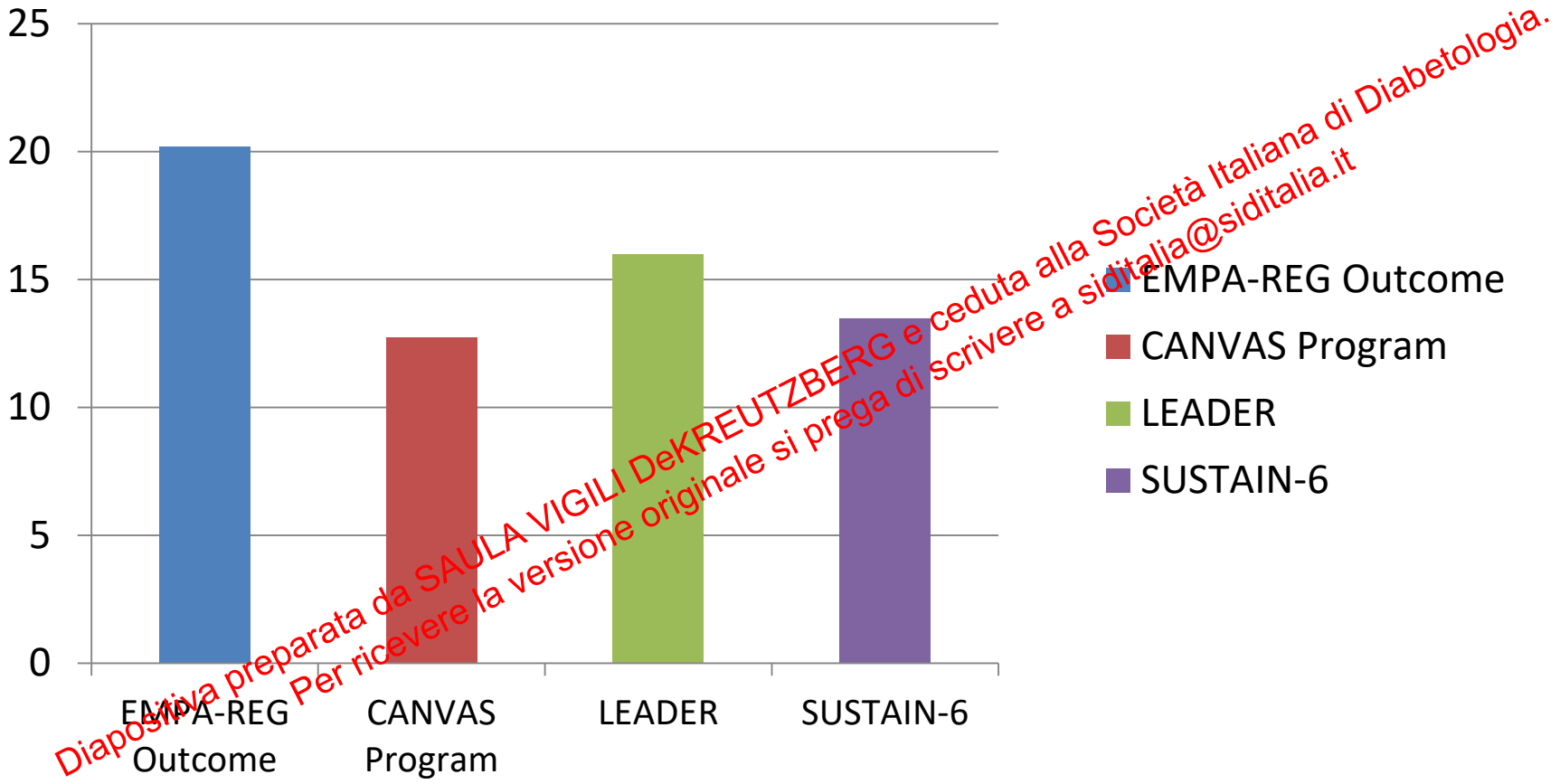
Quale delle seguenti variabili differisce maggiormente tra i soggetti arruolati negli studi EMPA-REG OUTCOME e CANVAS Program, all'arruolamento:

A. L'età media
B. La durata di diabete
C. Il controllo glicemico
D. Il rischio cardiovascolare

Principali caratteristiche dei soggetti arruolati negli studi EMPAREG-OUTCOME e CANVAS

	EMPA-REG OUTCOME	CANVAS
N° farmaco attivo/placebo	4687 / 2333	5795 / 4347
Età (anni)	63.1±8.6	63.3±8.3
Donne (%)	28.8	35.8
Durata diabete (anni)	57% >10	13.5±7.8
Insulina (%)	48.0	50.2
Metformina (%)	73.8	77.2
Sulfoniluree (%)	43.0	43.0
AbA1c basale (%)	8,07±0,85	8,2±0,9
BMI (kg/m2)	30,6±5,3	32,0±5,9
PAS (mmHg)	135,6±16,9	136,6±15,8
eGFR (ML/1.73mq.min)	74,2±21,6	76,5±20,5
Pz con precedente evento CV (%)	99,4	65,6

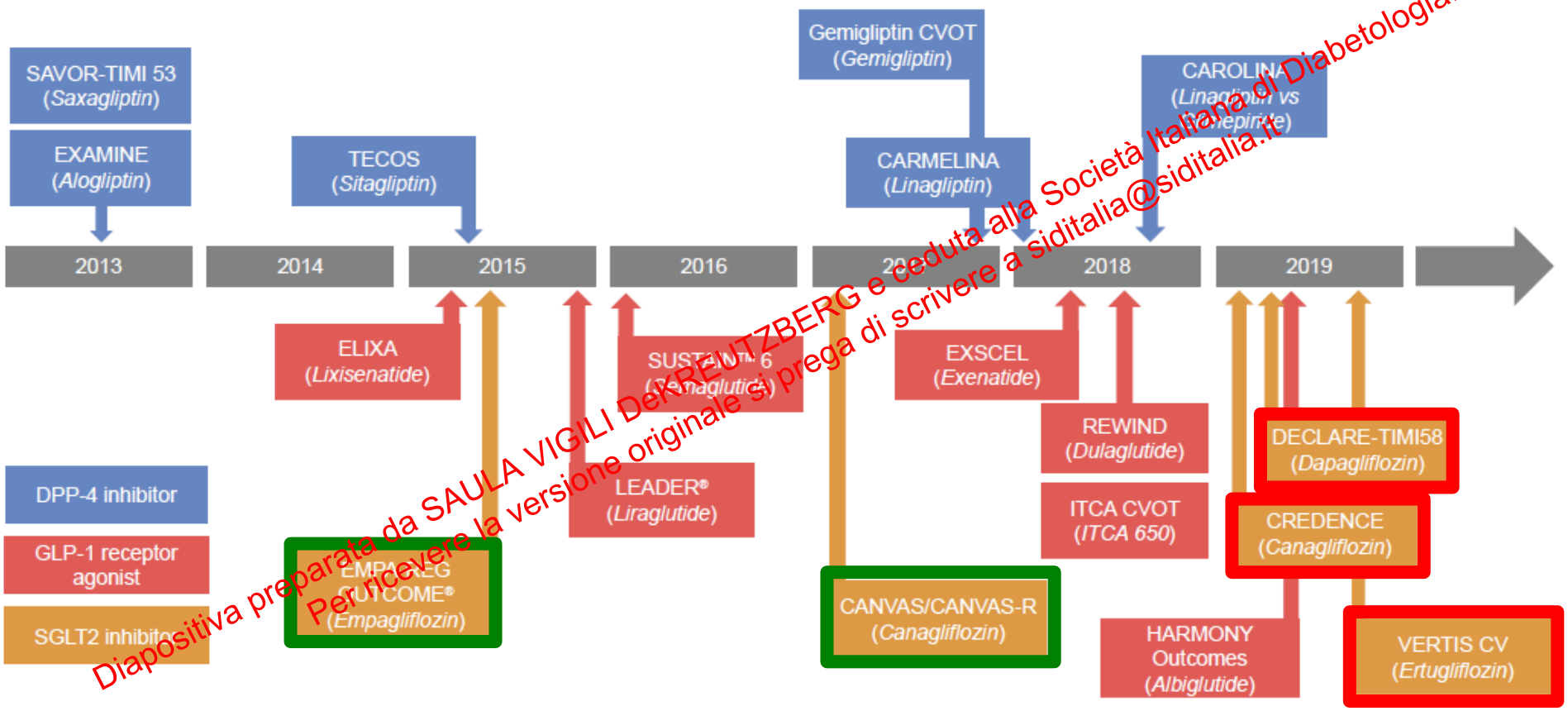
Estimates of Placebo CV Death Rate in CVOT



These trials were conducted with different designs and evaluated different populations, so direct comparisons of their results cannot be made

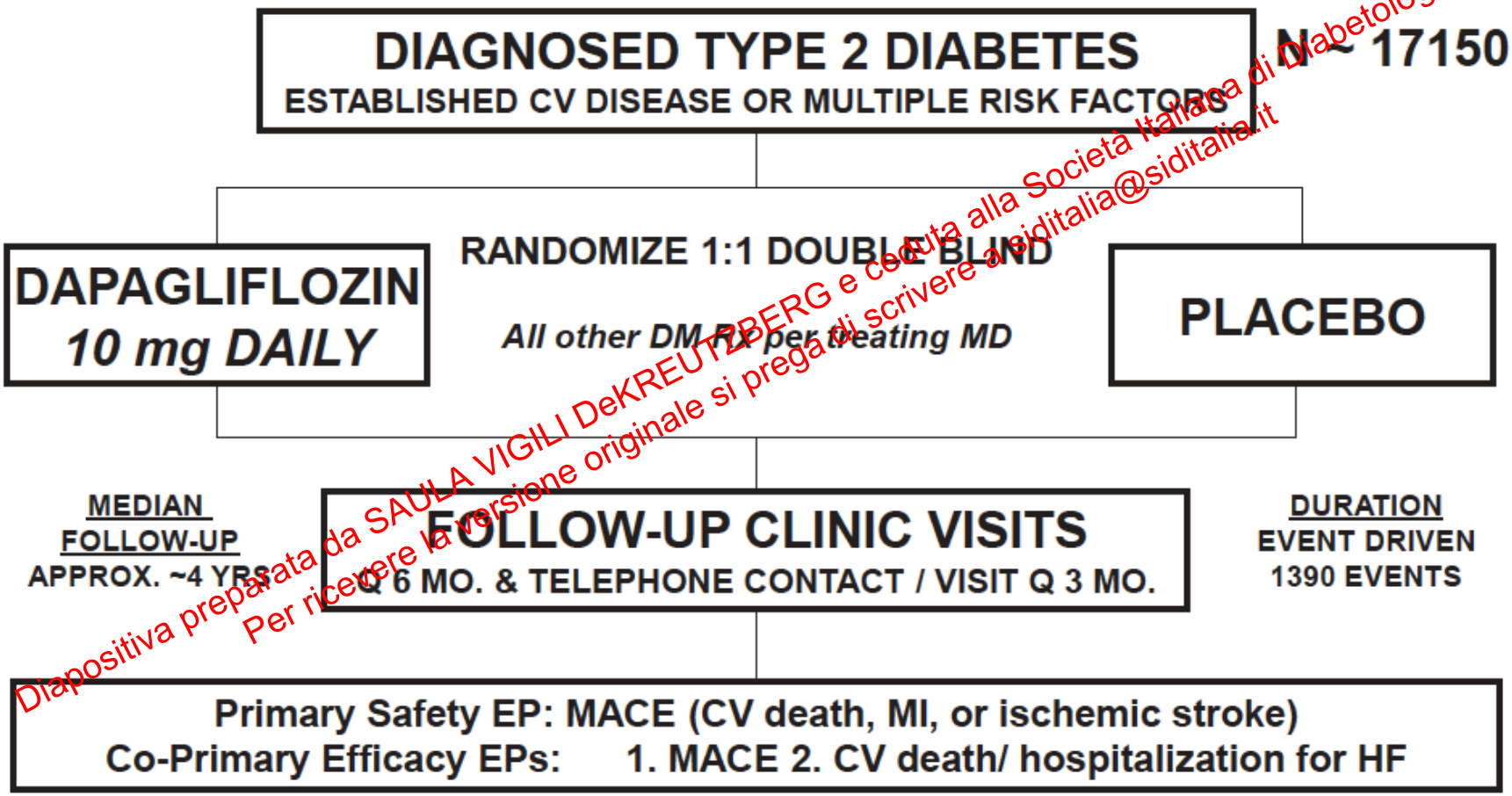
1. Zinman B, et al. *N Engl J Med*. 2015; 373(22):2117-2128.
2. Neal et al. *N Eng J Med,* 2017; DOI:10.1056/NEJMMoa1611925
3. Marso S et al. *N Engl J Med.* 2016;375(4):311-22.
4. Marso S et al. *N Engl J Med. 2016* DOI: 10.1056/NEJMoa1607141

Completed and ongoing cardiovascular outcome trials (CVOT) in type 2 diabetes



Schernthaner G et al, Ther Clin Risk Manag 2017:13 1569–1576

The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)–TIMI 58 Trial



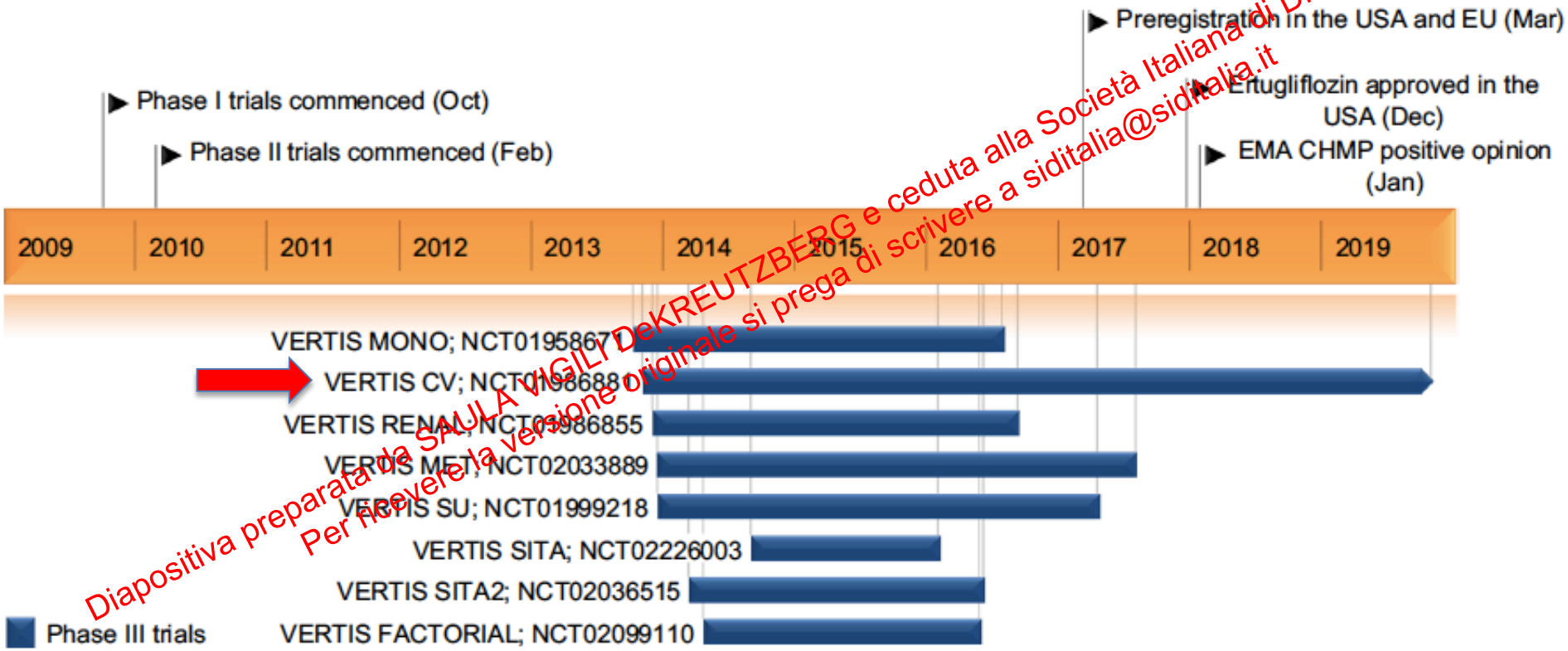
Wiviott SD et al. American Heart Journal 200 (2018) 83–89

Drugs (2018) 78:513–519
https://doi.org/10.1007/s40265-018-0878-6

ADISINSIGHT REPORT

Ertugliflozin: First Global Approval

Anthony Markham[1]



- Enrolled 8,000 patients with evidence or a history of atherosclerosis involving the coronary, cerebral or peripheral vascular systems.
- Randomized to 5 mg or 15 mg of ertugliflozin or placebo
- Primary outcome: time to first occurrence of MACE

SGLT2 inibitori: Studi con outcome cardiovascolari

Trial clinici randomizzati (RCTs) – CVOT

- EMPA-REG OUTCOME (2015)
- CANVAS Program (2017)

Studi osservazionali - Real-world studies:

- SWEDISH REGISTRY (2017)
- CVD-REAL (2017)
- CVD-REAL NORDIC (2017)
- THIN (2017)
- CVD-REAL 2 (2018)
- EASEL (2018)
- OBSERVE-4D (2018)

Quale tra le seguenti definizioni sugli studi real-world è corretta:

A. Gli studi real-world sono simili agli RCT e necessitano sempre del consenso informato

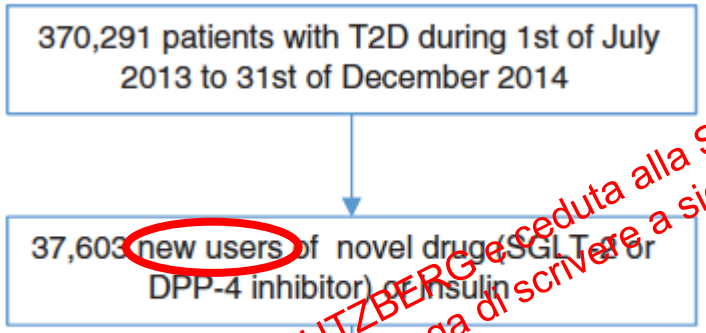
B. Gli studi real-world sono più corretti da un punto di vista statistico in confronto agli RCT

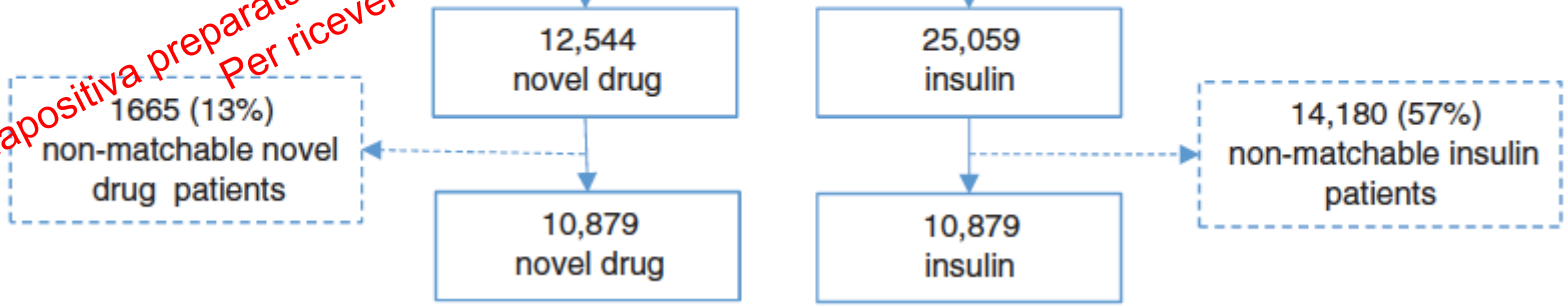
C. Gli studi real-world danno informazioni complementari a quelle degli RCT

D. Gli studi real-world danno le stesse informazioni degli RCT

Novel oral glucose-lowering drugs are associated with lower risk of all-cause mortality, cardiovascular events and severe hypoglycaemia compared with insulin in patients with type 2 diabetes

Data source:
Prescribed Drug Register
National Patient Register



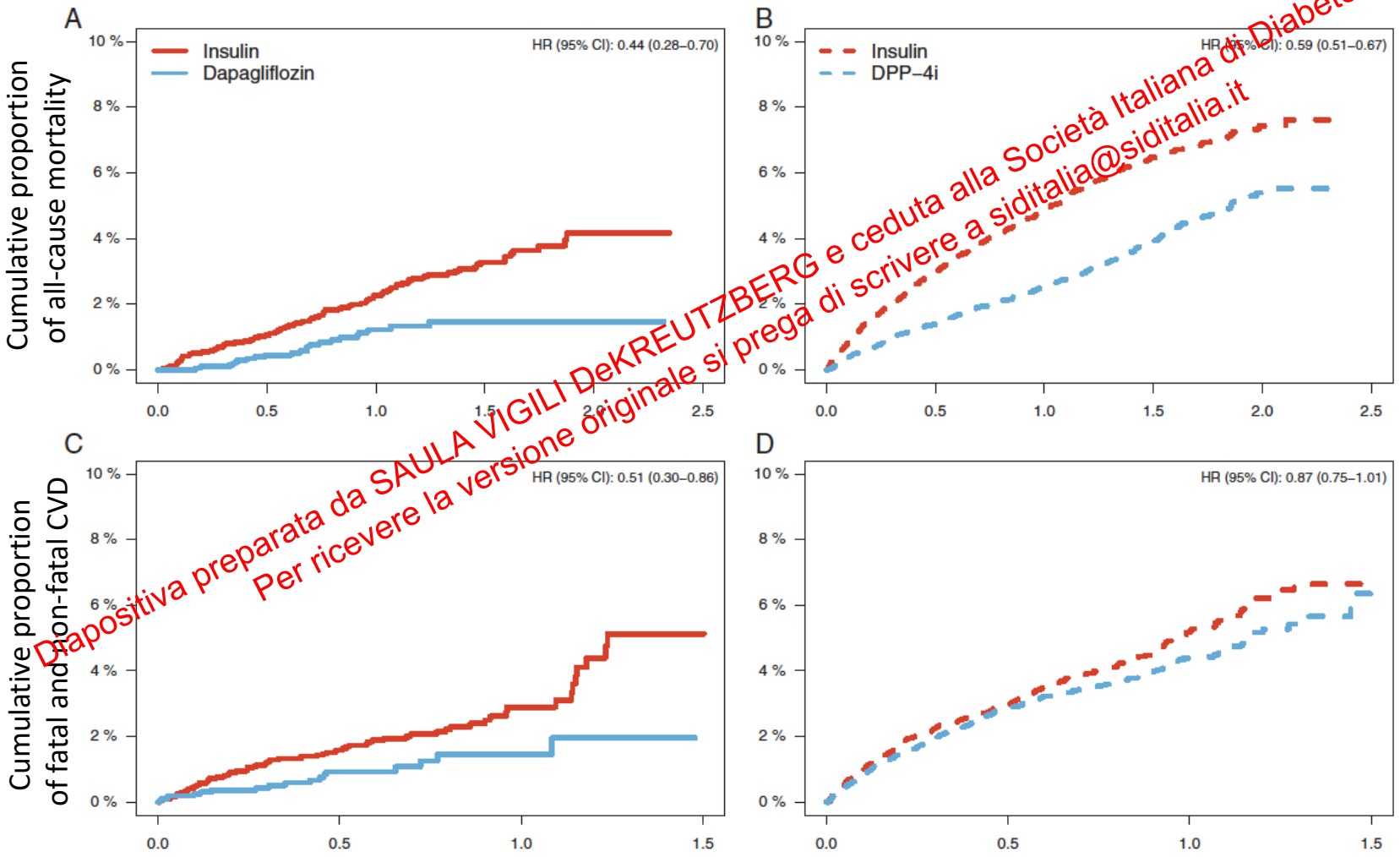


2/3 patients had no previous CVD history

Nyström T et al, Diabetes Obes Metab. 2017;19:831–841.

Novel oral glucose-lowering drugs are associated with lower risk of all-cause mortality, cardiovascular events and severe hypoglycaemia compared with insulin in patients with type 2 diabetes

Nyström T et al, Diabetes Obes Metab. 2017;19:831–841.



Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)

Primary objective

- To compare the risk of hospitalization for heart failure (HHF) in patients with T2DM newly initiated on SGLT2 inhibitors versus other glucose-lowering drugs

Secondary objective

- 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

Kosiborod M et al, Circulation. 2017;136:249-259.

Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

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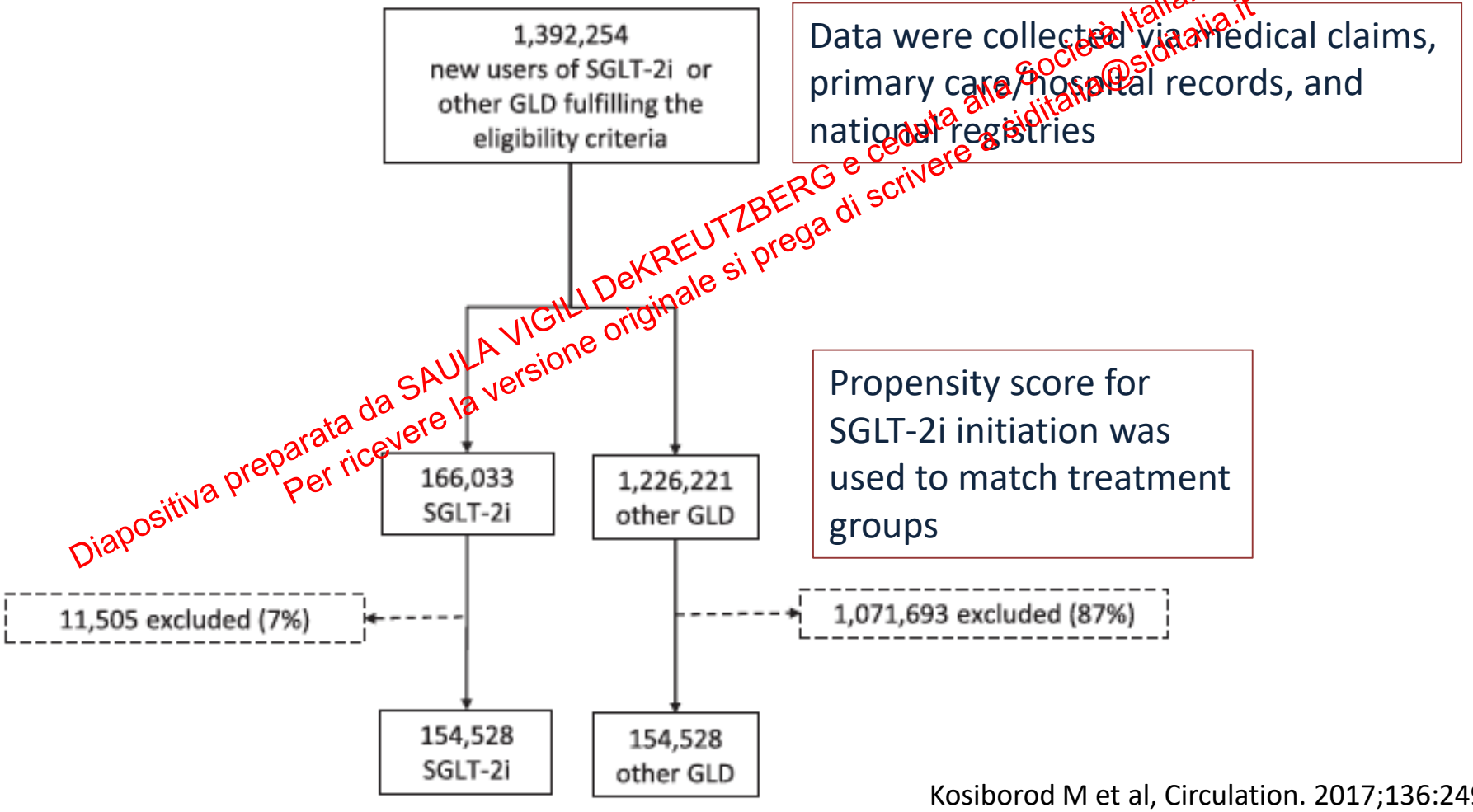
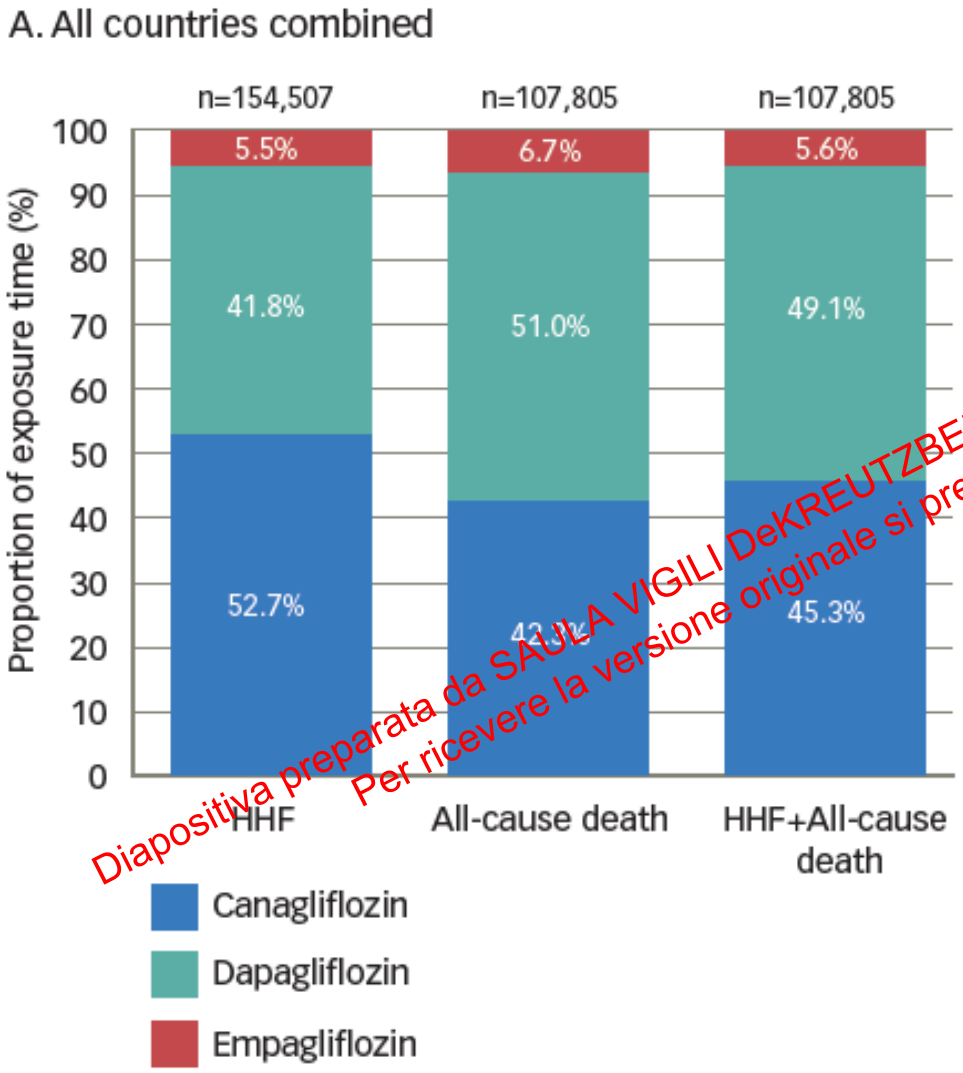
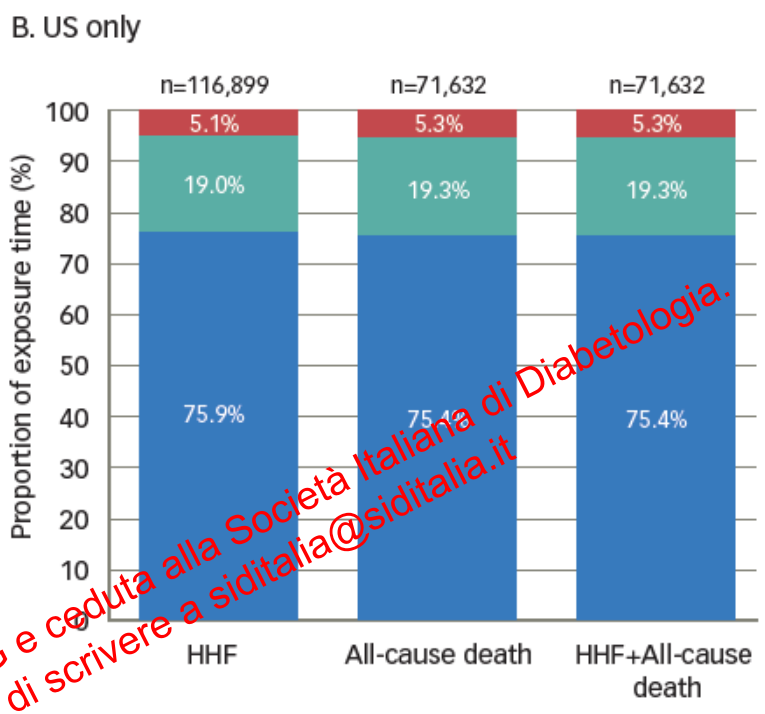
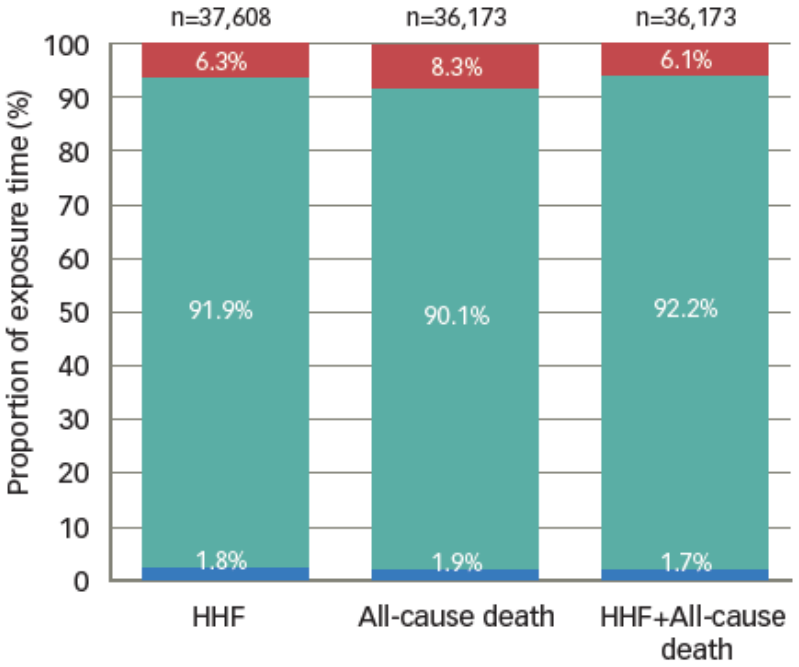


Kosiborod M et al, Circulation. 2017;136:249-259.

The CVD-REAL study





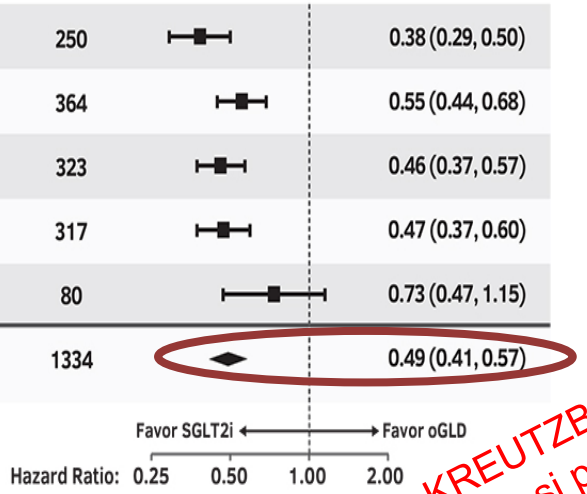


Gallwitz B. European Endocrinology. 2018;14(1):17–23

CVD-REAL primary analysis:

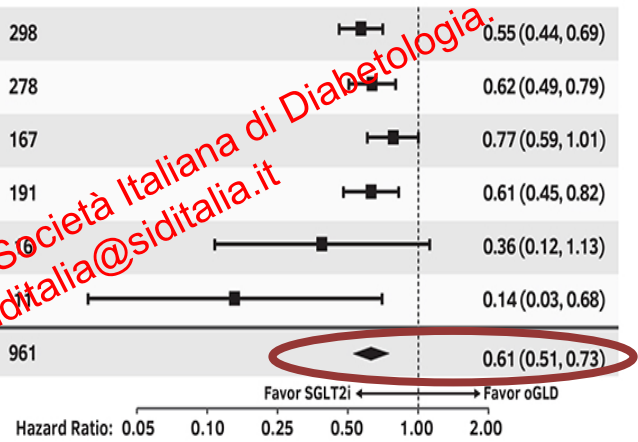
All-cause death

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)



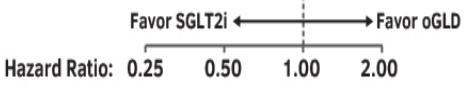
Hospitalization for heart failure

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	6	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)



Hospitalization for heart failure or all-cause death

Database	N	# of events	HR (95% CI)
US	143,264	424	0.44 (0.36, 0.54)
Norway	25,050	622	0.58 (0.50, 0.69)
Denmark	18,468	477	0.57 (0.48, 0.67)
Sweden	18,378	364	0.50 (0.41, 0.63)
UK	10,462	96	0.66 (0.44, 1.00)
Total	215,622	1983	0.54 (0.48, 0.60)



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

Data are on treatment, unadjusted.

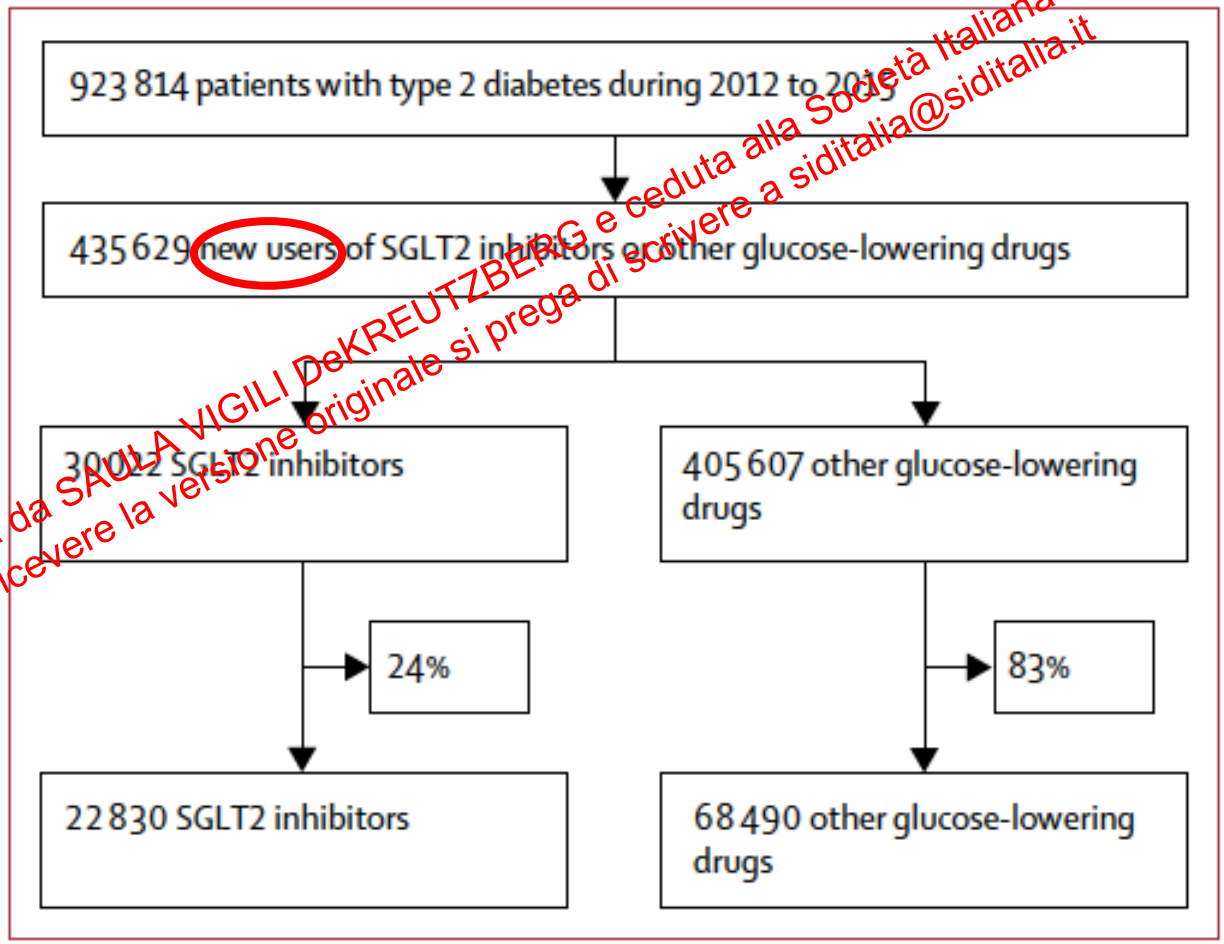
Kosiborod M et al, Circulation. 2017;136:249-259.

CVD-REAL - Strengths

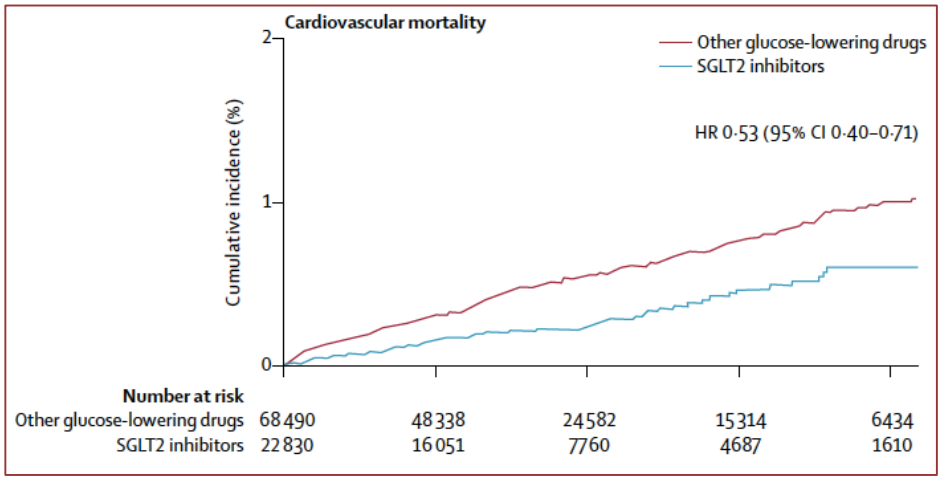
- Large contemporary analysis of real-world clinical practice across six countries, based on a well-matched sample of over 300,000 patients with T2DM and nearly 200,000 patient–years of follow-up
  - This real-world evidence complements that produced in clinical trials
- The majority of patients (87%) did not have a history of established CVD at baseline
- The observed effects were unchanged after additional multivariable adjustment, as well as after multiple sensitivity analyses
- The results were consistent across all countries, regardless of the geographic variability in healthcare systems and SGLT2 inhibitor compound use

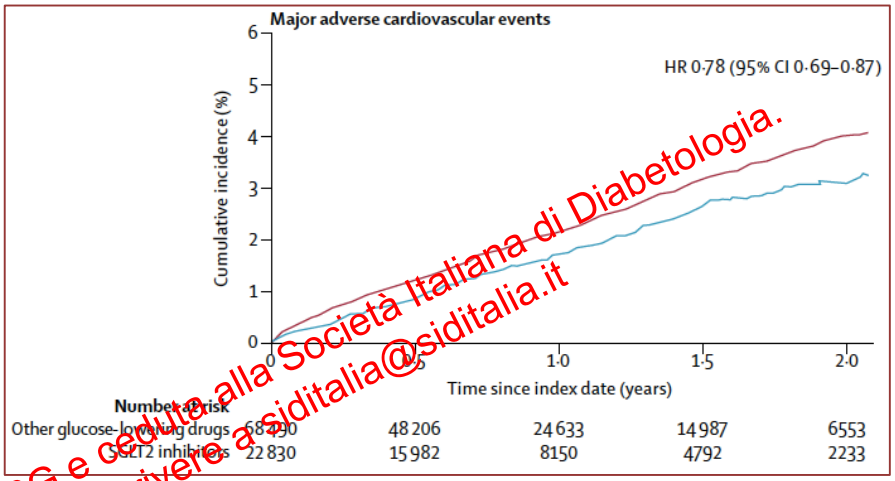
Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis

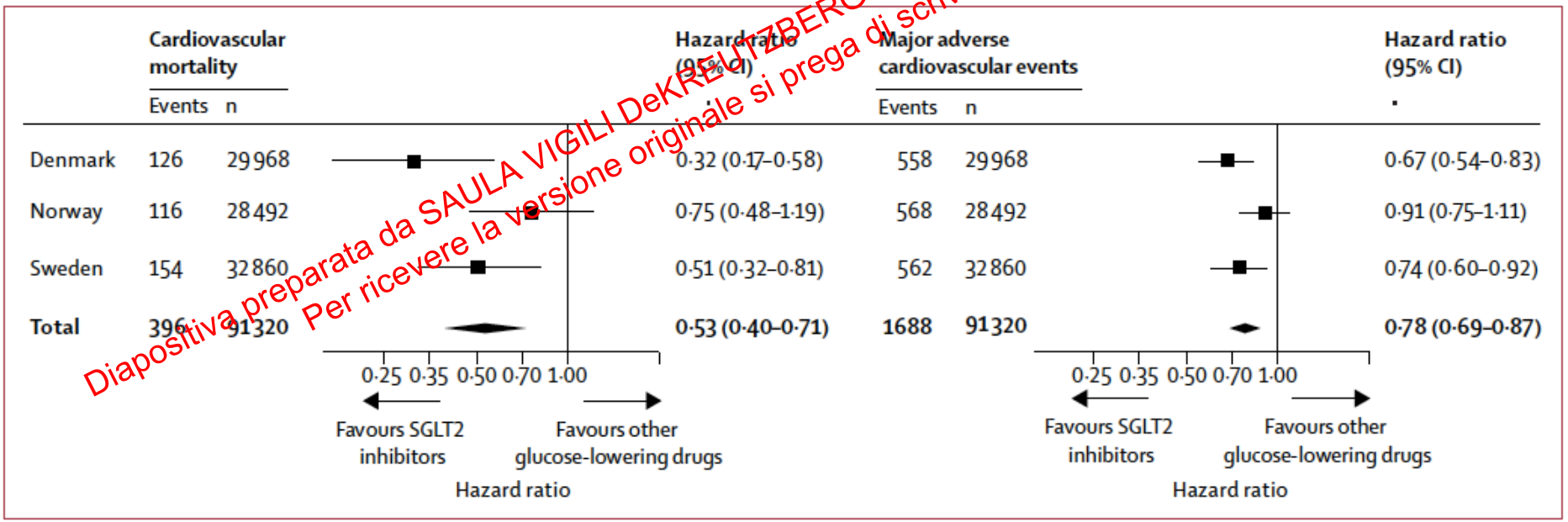
Birkeland KI et al, Lancet Diabetes Endocrinol. 2017;5:709–717



CVD-REAL Nordic





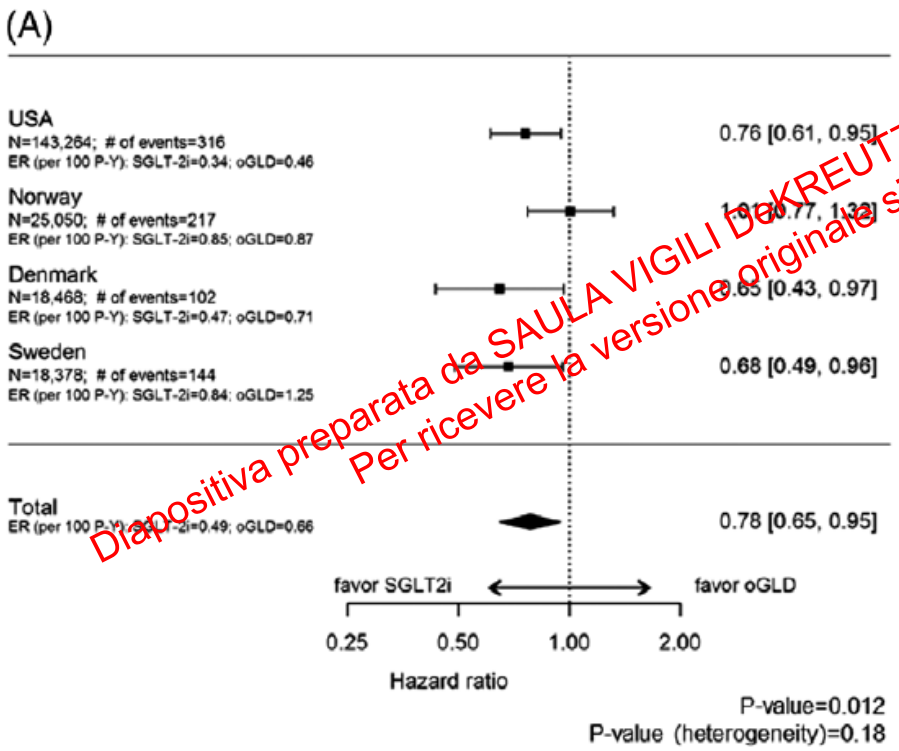


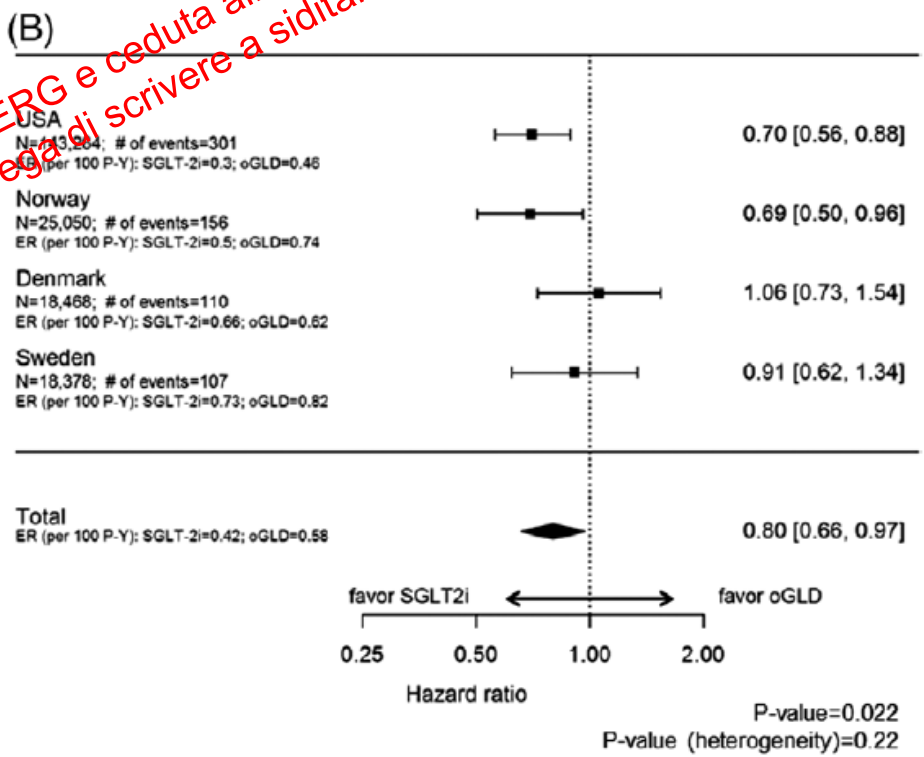
IMA e ictus n.s.

Birkeland KI et al, Lancet Diabetes Endocrinol. 2017;5:709–717

Rates of myocardial infarction and stroke in patients initiating treatment with SGLT2-inhibitors versus other glucose-lowering agents in real-world clinical practice: Results from the CVD-REAL study

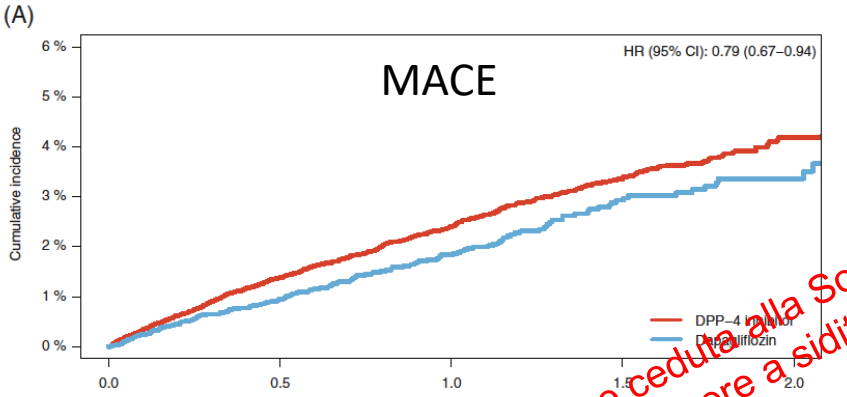
Event rates, unadjusted hazard ratios and 95% CIs for acute myocardial infarction (A) and stroke (B) in the on-treatment population,



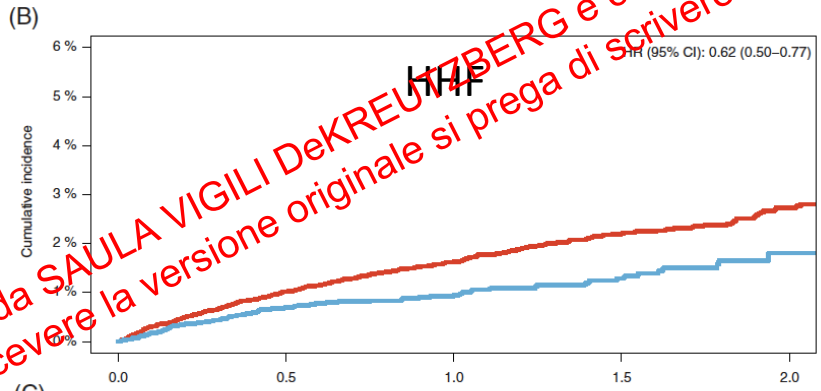


Kosiborod M et al, Diabetes Obes Metab. 2018;20:1983–1987.

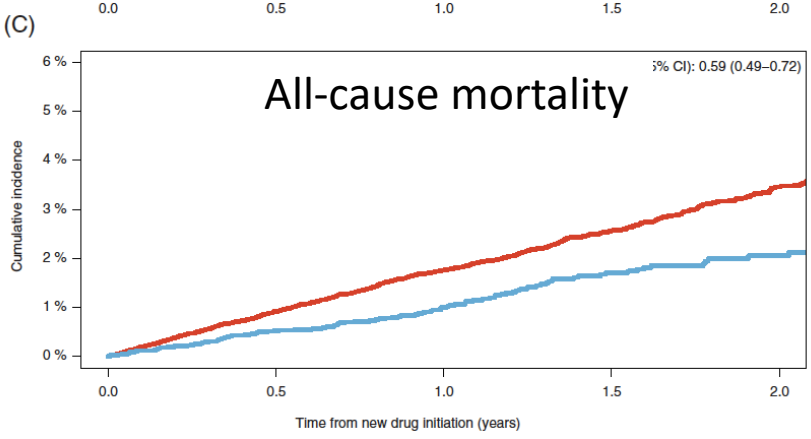
Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: A multinational observational study



HR (95% CI): **0.79** (0.67–0.94)



HR (95% CI): **0.62** (0.50–0.77)



HR (95% CI): **0.59** (0.49–0.72)

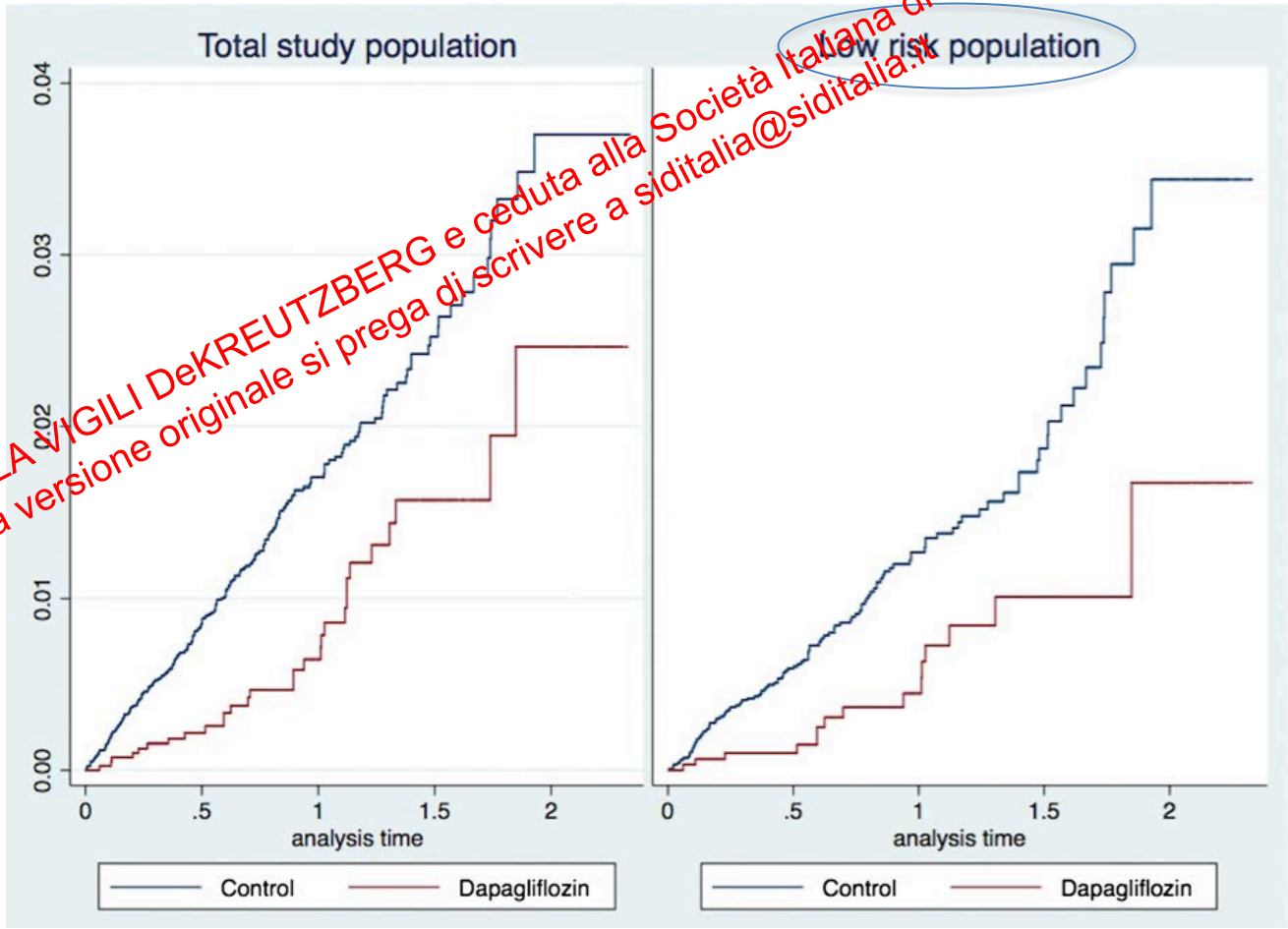
Persson F et al, Diabetes Obes Metab. 2018;20:344–351.

All-Cause Mortality in Patients With Diabetes Under Treatment With Dapagliflozin: A Population-Based, Open-Cohort Study in The Health Improvement Network Database

All-cause mortality (cumulative hazard estimates)

General practice, population-based, retrospective cohort study (Setting: The Health Improvement Network database. January 2013 to September 2015).

22,124 T2DM patients (4444 exposed to **dapagliflozin**; 17,680 unexposed T2DM patients) matched for age, sex, body mass index, T2DM duration, and smoking.

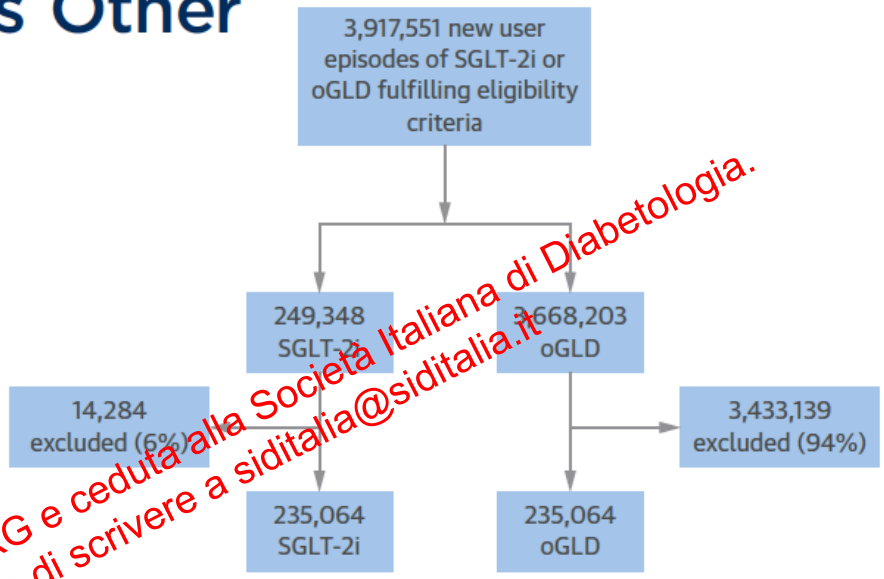


Kostantinos A et al, Clin Endocrinol Metab 102: 1719–1725, 2017

Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL 2 Study

Kosiborod, M. et al. J Am Coll Cardiol. 2018;71(23):2628–39.



- *Claims, medical records, and national registries*

TABLE 2 Composition of SGLT-2i in Terms of Total Exposure Time

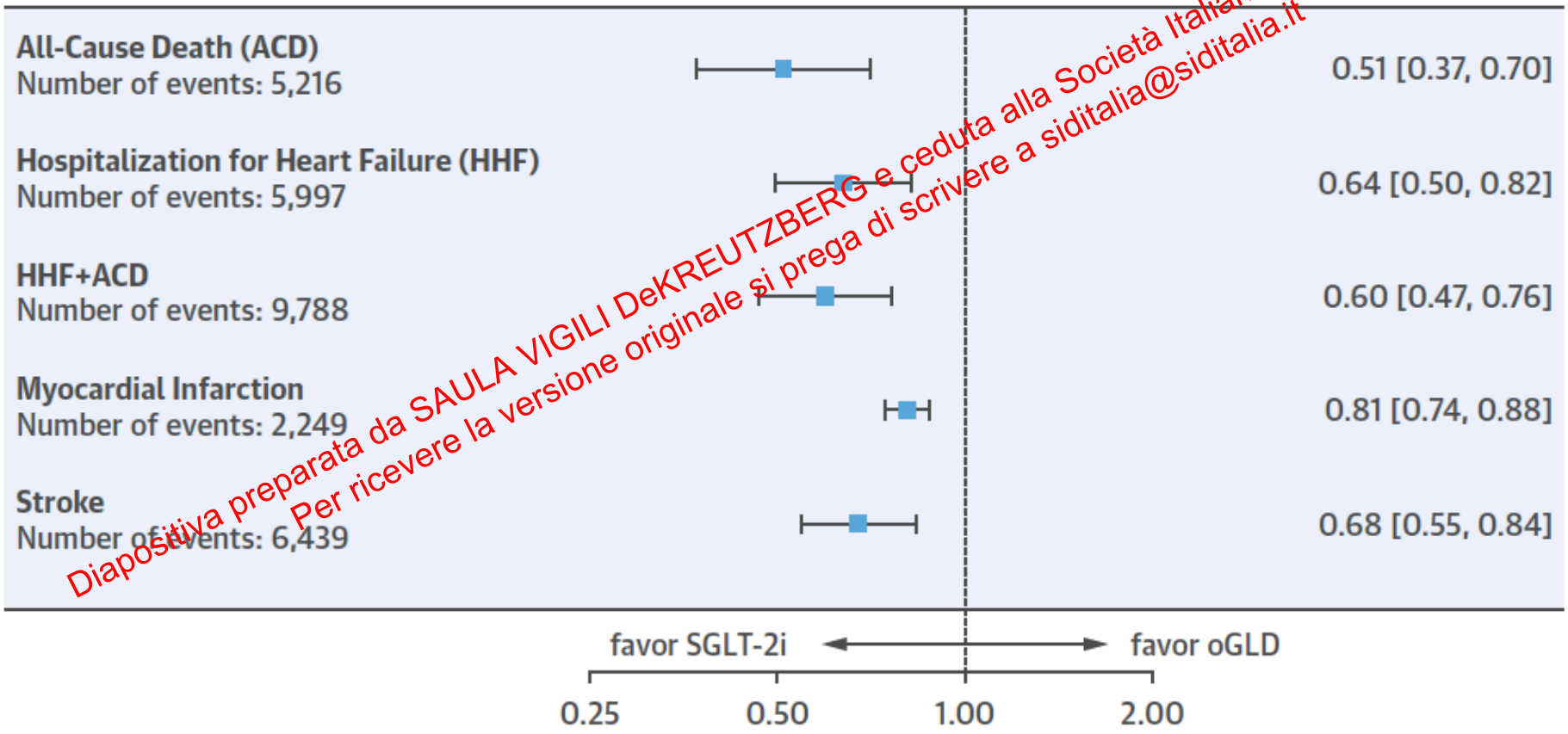
	South Korea	Japan	Singapore	Israel	Canada	Australia	Total
SGLT-2i	168,322	38,890	1,363	9,736	8,032	13,721	235,064
Dapagliflozin	91.3	26.1	68.5	50.9	52.0	80.8	74.7
Empagliflozin	4.3	13.6	17.9	49.1	7.7	0.0	9.0
Canagliflozin	0.0	10.6	13.7	0.0	40.2	19.2	4.4
Ipragliflozin	4.4	29.8	0.0	0.0	0.0	0.0	8.3
Luseogliflozin	0.0	6.3	0.0	0.0	0.0	0.0	1.1
Tofogliflozin	0.0	13.7	0.0	0.0	0.0	0.0	2.5

Values are %.

SGLT-2i = sodium-glucose co-transporter-2 inhibitors.

CVD-REAL 2 Study

Pooled hazard ratios for the outcomes of all-cause death, hospitalization for heart failure, composite of all-cause death or hospitalization for heart failure, myocardial infarction, and stroke

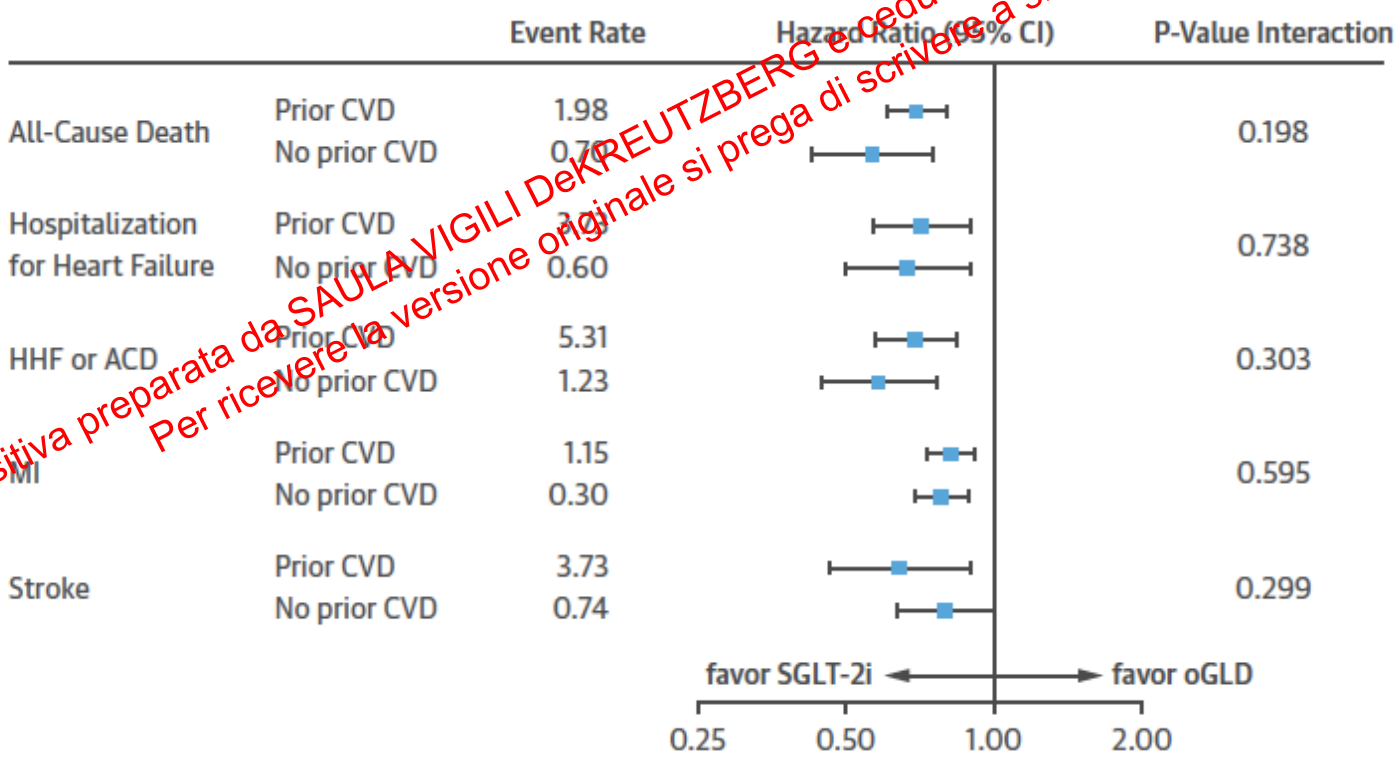


Kosiborod, M. et al. J Am Coll Cardiol. 2018;71(23):2628–39.

Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL 2 Study

Outcomes in subgroups of satients with and without (>70%) established cardiovascular disease at baseline for all 5 outcomes (Intent-to-treat, adjusted analysis)



Kosiborod, M. et al. J Am Coll Cardiol. 2018;71(23):2628–39.

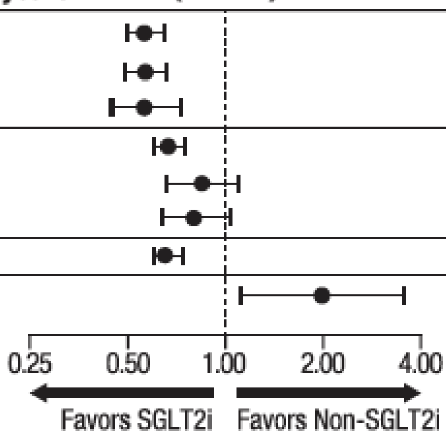
ORIGINAL RESEARCH ARTICLE

Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Cotransporter 2 Inhibitor

Results From the EASEL Population-Based Cohort Study (Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World)

T2DM with established cardiovascular disease newly initiated on antihyperglycemic agents within the US Department of Defensec Military Health System between April 1, 2013, and December 31, 2016.

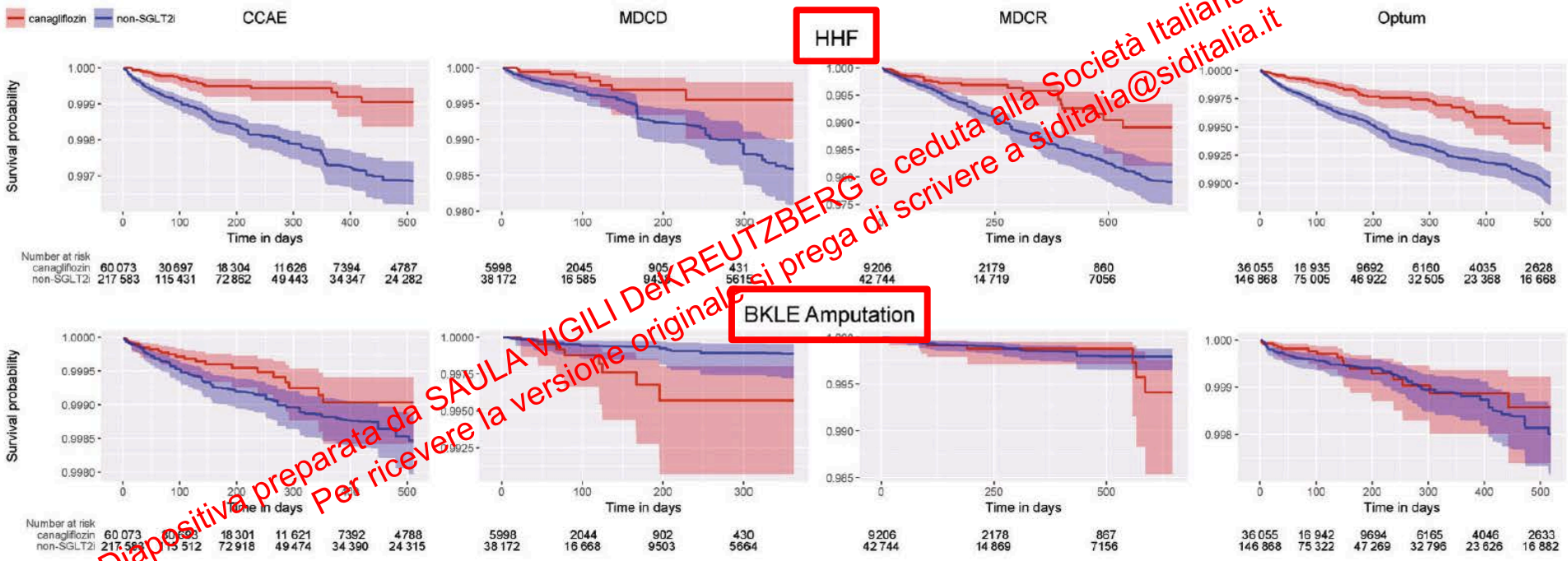
	Non-SGLT2i (N=12,629)		SGLT2i (N=12,629)		Hazard ratio (95% CI)	P value
	Events (n)	Incidence rate per 100 patient-years	Events (n)	Incidence rate per 100 patient-years		
Composite of ACM and HHF	626	3.01	363	1.73	0.57 (0.50–0.65)	<0.0001
ACM	475	2.26	272	1.29	0.57 (0.49–0.66)	<0.0001
HHF	188	0.90	108	0.51	0.57 (0.45–0.73)	<0.0001
MACE	714	3.45	483	2.31	0.67 (0.60–0.75)	<0.0001
Nonfatal stroke	125	0.60	108	0.51	0.85 (0.66–1.10)	0.2190
Nonfatal myocardial infarction	148	0.71	121	0.58	0.81 (0.64–1.03)	0.0888
Composite of MACE and HHF	845	4.11	567	2.72	0.66 (0.60–0.74)	<0.0001
BKA*	18	0.09	35	0.17	1.99 (1.12–3.51)	0.0183



ACM, all-cause mortality
HHF, hospitalization for heart failure
BKA, below-knee lower extremity amputation

Udell JA et al, Circulation. 2018;137:1450–1459.

Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D)



Meta-analytic HR for HHF (HR [95% CI], 0.39 (0.26-0.60) and BKLE amputation (HR [95% CI], 0.75 (0.40-1.41) with canagliflozin vs non-SGLT2i (on-treatment analysis)

Ryan PB et al, Diabetes Obes Metab. 2018;1–13.

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

Dual Therapy

Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 26 July 2018
EMA/CHMP/512327/2018
Committee for Medicinal Products for Human use (CHMP)
EMEA/H/C/002649/II/0034

Opinion of the committee for medicinal products for human use on a type II variation to the terms of the marketing authorisation

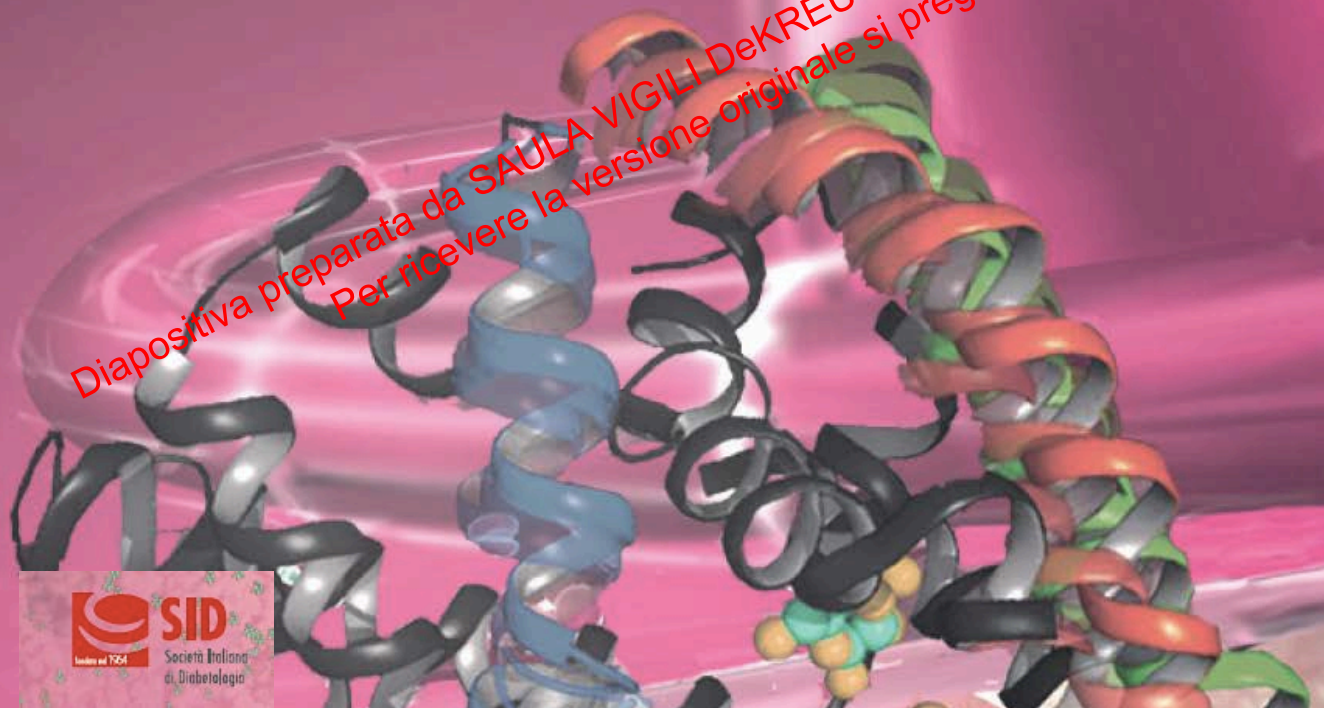
Modification of the indication …. in order **to update the safety and efficacy information on cardiovascular** events following final results from CANVAS Program (DIA3008 and DIA4003); the Package Leaflet is updated accordingly.

ROMA

14 settembre 2018

CROWNE PLAZA ROME - ST. PETER'S

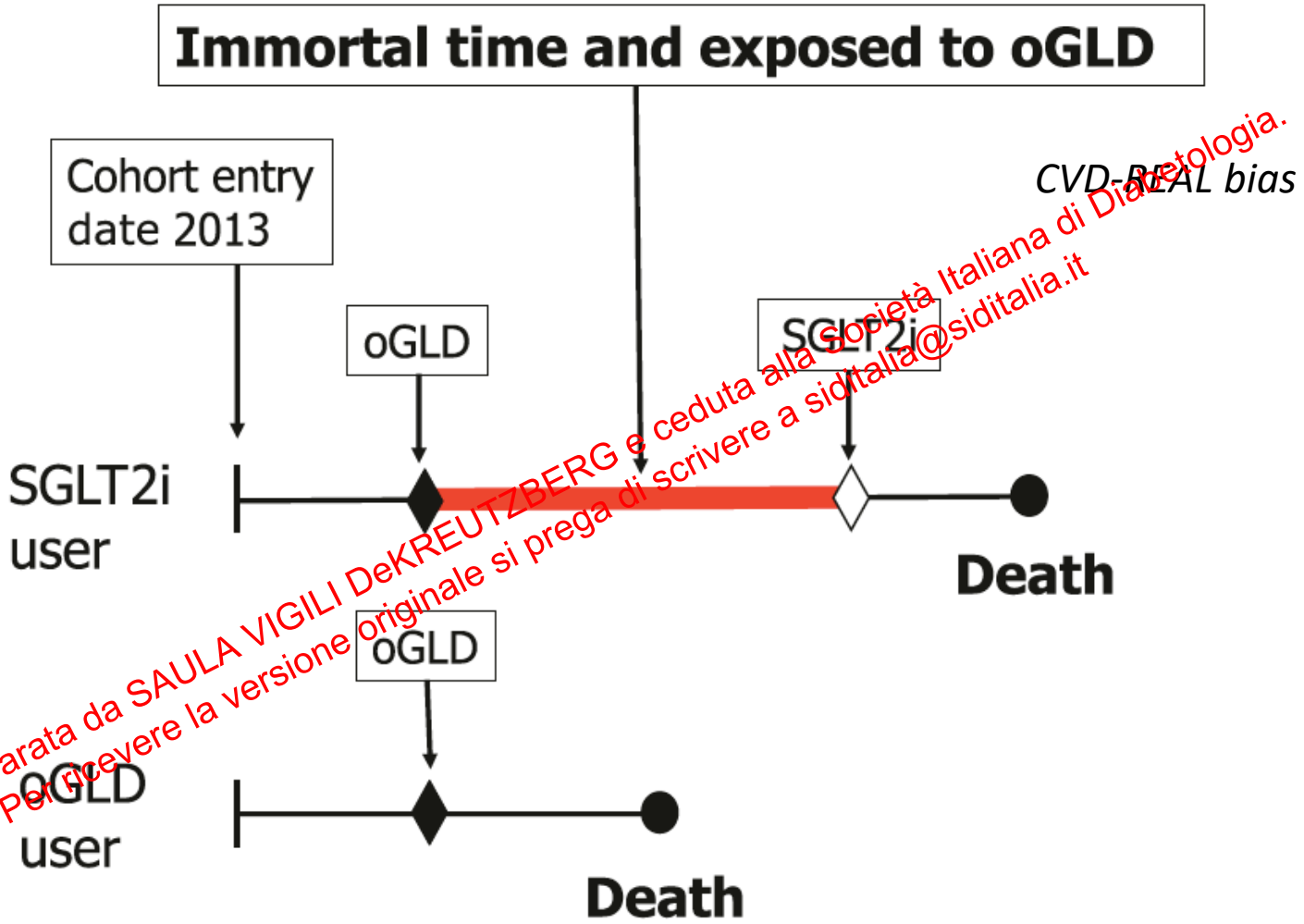
Grazie per l'attenzione



SID Società Italiana di Diabetologia

Lower Risk of Death With SGLT2 Inhibitors in Observational Studies: Real or Bias?

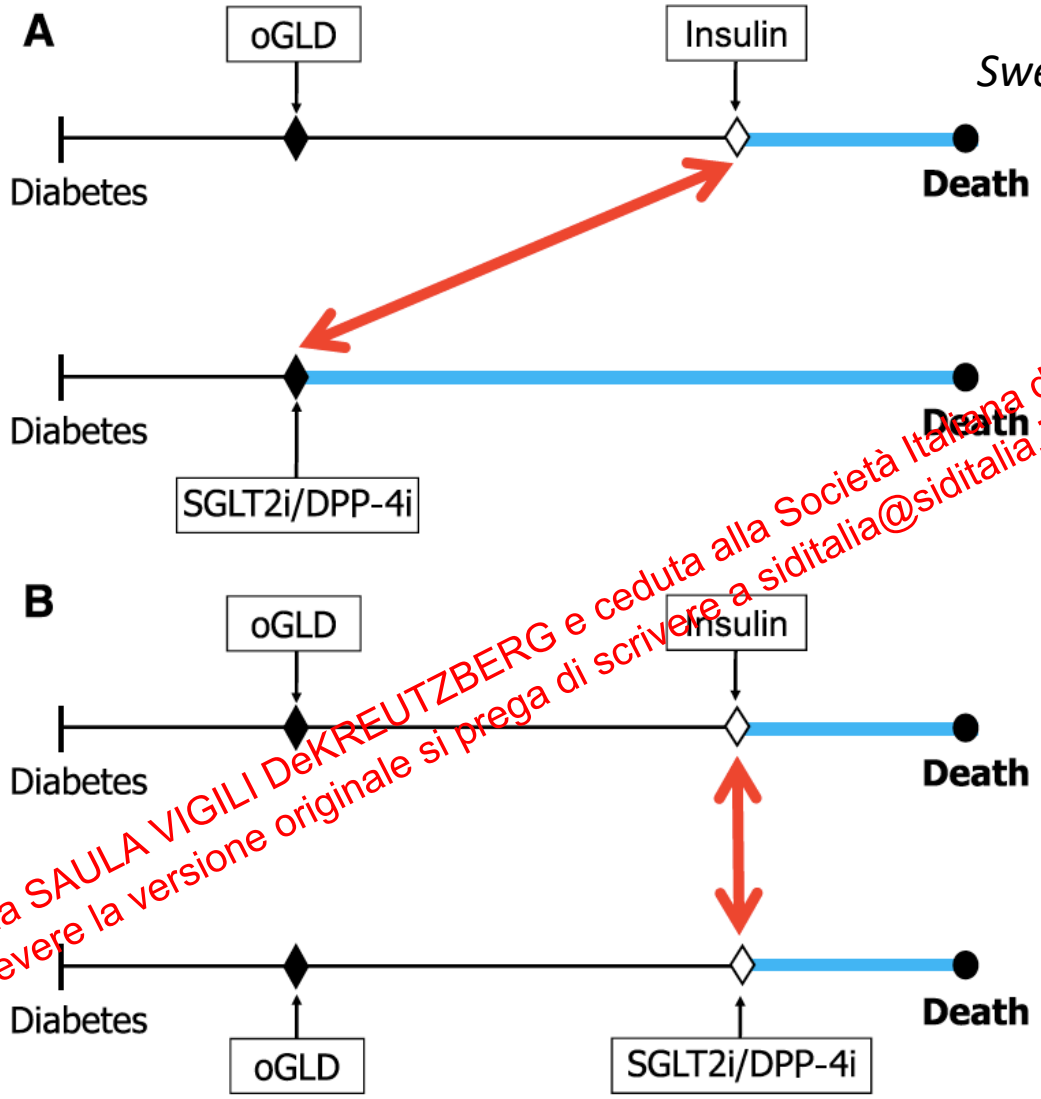
Suissa S, Diabetes Care 2018;41:6–10



Depiction of immortal time bias: description of SGLT2i-exposed and oGLD-exposed patient swho die of any cause according to the definition used in the CVD-REAL observational study (2). The top patient initiated treatment with an oGLD and subsequently switched to or added an SGLT2i, but the patient was classified as an SGLT2i user. The time between the first oGLD prescription and the first SGLT2i prescription is thus immortal (thick red line), since the subjectmust survive to receive this first SGLT2i prescription, but is not included as exposed to oGLD, leading to immortal time bias.

time-lag bias

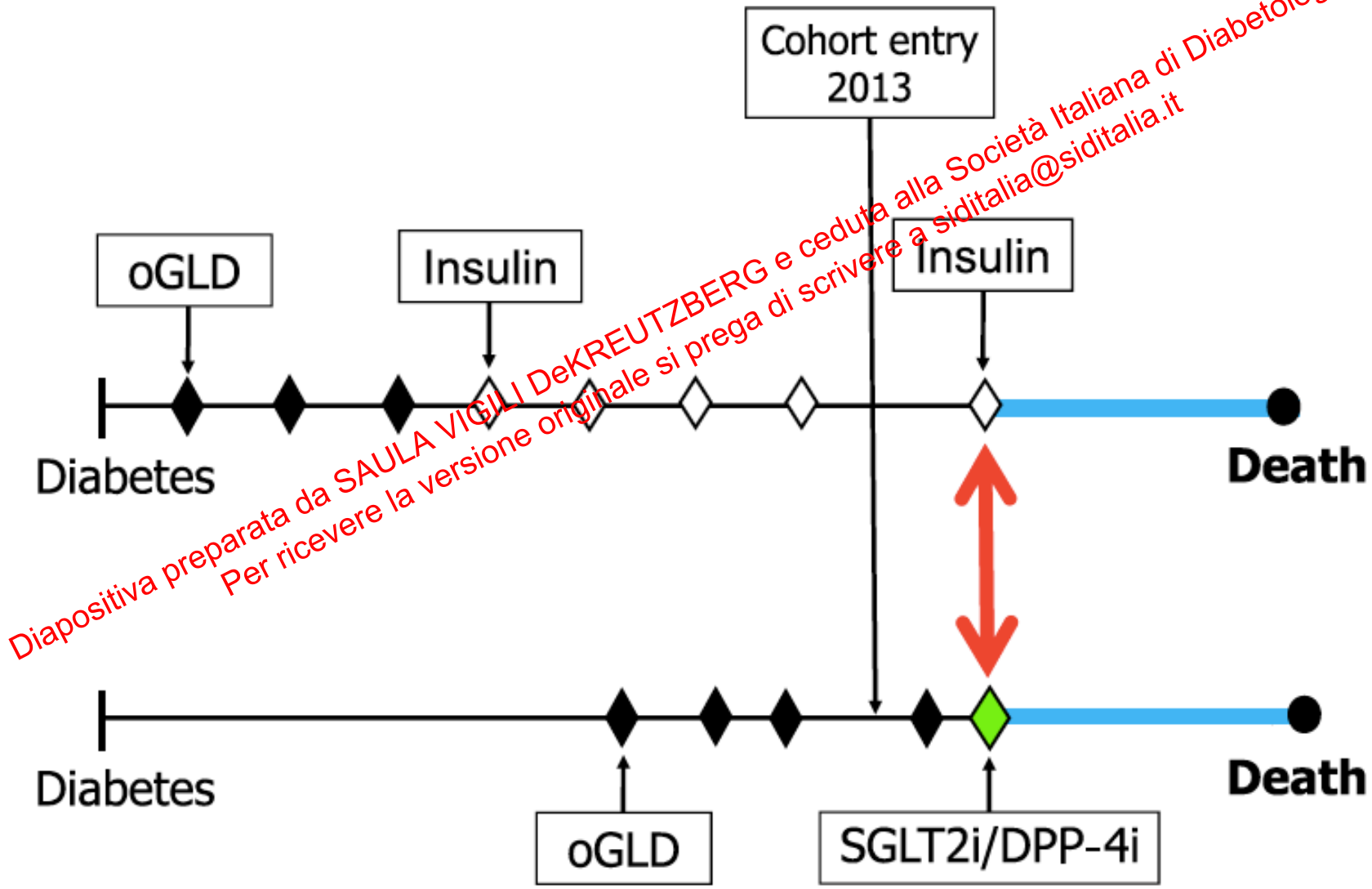
Swedish Study bias



Depiction of A) time-lag bias in comparing a second-line drug (SGLT2i/DPP-4i) used at an earlier stage of diabetes with third-line insulin and B) cohort design that controls for time-lag bias by comparing two patients at the same stage of diabetes and with similar previous medication use (oGLD).

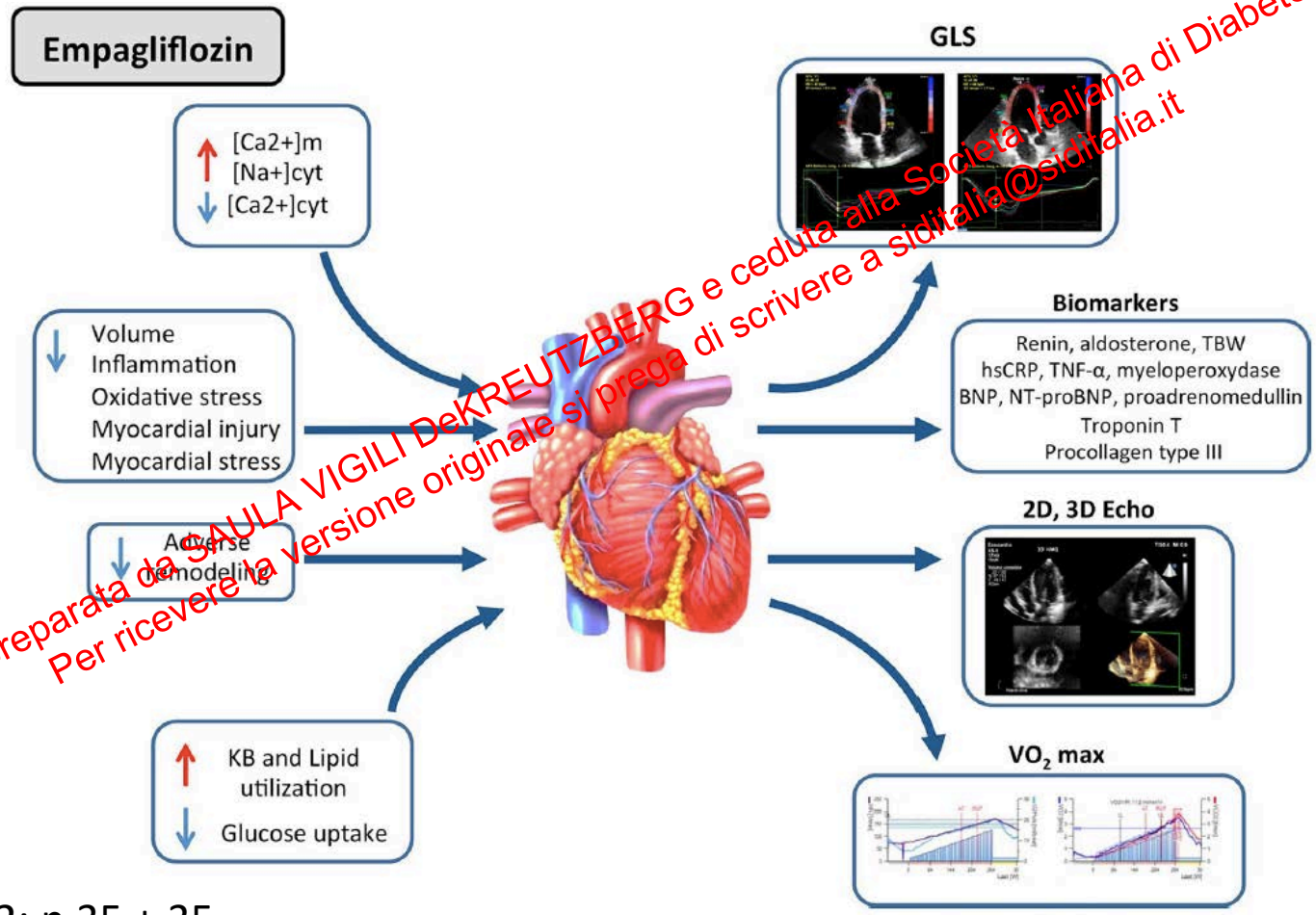
Suissa S, Diabetes Care 2018;41:6–10

Depiction of prevalent/incident bias from comparing patients at their first-ever SGLT2i prescription (incident users) to patients at their **first insulin prescription after 2013**, who could also have used insulin previously (prevalent users), leading to potential confounding bias by disease severity.



- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors (**Table 8.1**). A*
- In patients with type 2 diabetes and established atherosderotic cardiovascular disease, after lifestyle management and metformin, the antihyperglycemic agent canagliflozin may be considered to reduce major adverse cardiovascular events, based on drug-specific and patient factors (**Table 8.1**). C*

Impact of empagliflozin on subclinical left ventricular dysfunctions and on the mechanisms involved in myocardial disease progression in type 2 diabetes: rationale and design of the EMPA-HEART trial



Subjects: DM2; n 35 + 35
Empagliflozin 10 mg vs Sitagliptin 100 mg

Natali A. et al. Cardiovasc Diabetol (2017) 16:130