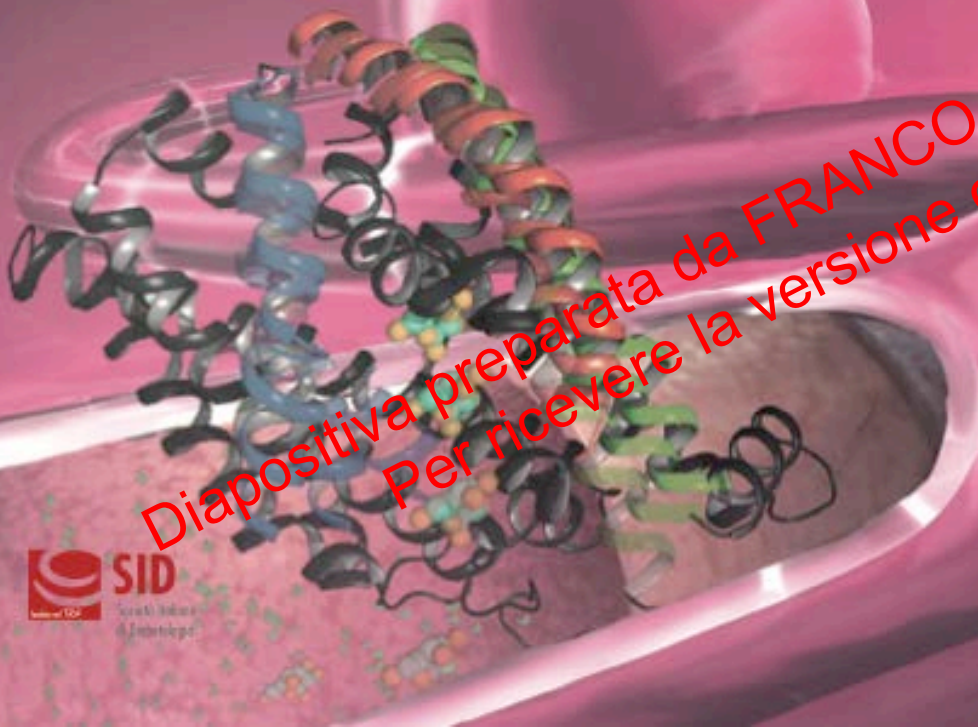


Impatto degli inibitori di **SGLT2** nei pazienti con **DIABETE TIPO 2**

MILANO

26 giugno 2018

HOTEL MICHELANGELO MILAN



LA PROTEZIONE CARDIOVASCOLARE DEGLI INIBITORI DI SGLT2: TRIALS E STUDI OSSERVAZIONALI

DOCT. FRANCO CAVALOT

SSD MALATTIE METABOLICHE E DIABETOLOGIA

AOU SAN LUIGI GONZAGA

Diapositiva preparata da FRANCO CAVALOT e ceduta alla Società Italiana di Diabetologia.
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CONFLITTO D'INTERESSE

- Il dr. Franco Cavalot dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:
- Astra-Zeneca
- Boehringer Ingelheim
- Novo-Nordisk
- Sanofi
- Takeda
- *Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).*

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I PRIMI DATI: - ANN INT MED 2013

Outcome	Comparison†	Studies Contributing Data, <i>n</i>	Participants Analyzed, <i>n</i>		Participants With Outcome, <i>n</i>		Effect Estimate‡ (95% CI)	<i>I</i> ² , %
			SGLT2 Inhibitor	Comparator	SGLT2 Inhibitor	Comparator		
Cardiovascular event	SGLT2 inhibitor vs. placebo or active agent	25	11 372	5808	182	101	0.89 (0.70 to 1.14)	0
	Dapagliflozin vs. placebo or active agent	14	4359	1941	48	30	0.73 (0.46 to 1.16)	0
	Canagliflozin vs. placebo or active agent	16	6769	3705	132	71	0.95 (0.71 to 1.26)	0
Serious adverse event	SGLT2 inhibitor vs. placebo or active agent	24	6324	3051	226	145	0.90 (0.72 to 1.13)	0
	Dapagliflozin vs. placebo or active agent	14	4362	1865	164	98	0.91 (0.70 to 1.20)	0
	Canagliflozin vs. placebo or active agent	5	1094	799	49	39	0.90 (0.58 to 1.39)	0
	Ipragliflozin vs. placebo or active agent	3	597	217	10	5	0.86 (0.29 to 2.51)	0
All-cause mortality	SGLT2 inhibitor vs. placebo or active agent	21	5771	2989	23	8	NE	NE
	Dapagliflozin vs. placebo or active agent	17	4803	2320	19	6	NE	NE
	Canagliflozin vs. placebo or active agent	4	968	669	4	2	1.18 (0.29 to 4.90)	0

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I PRIMI DATI:

- ANN INT MED 2013

- In patients with moderate renal impairment, use of dapagliflozin or high doses of canagliflozin was associated with increased incidence of renal-related adverse events.
- Data on cardiovascular outcomes and death were inconclusive.
- A numerical imbalance in nonfatal stroke events among patients treated with canagliflozin needs clarification and confirmation.
- We also noted a numerical imbalance of bladder and breast cancer cases between patients treated with dapagliflozin and control patients.
- Hence, no robust conclusions can be drawn pending accumulation of longterm data.

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EMPA-REG

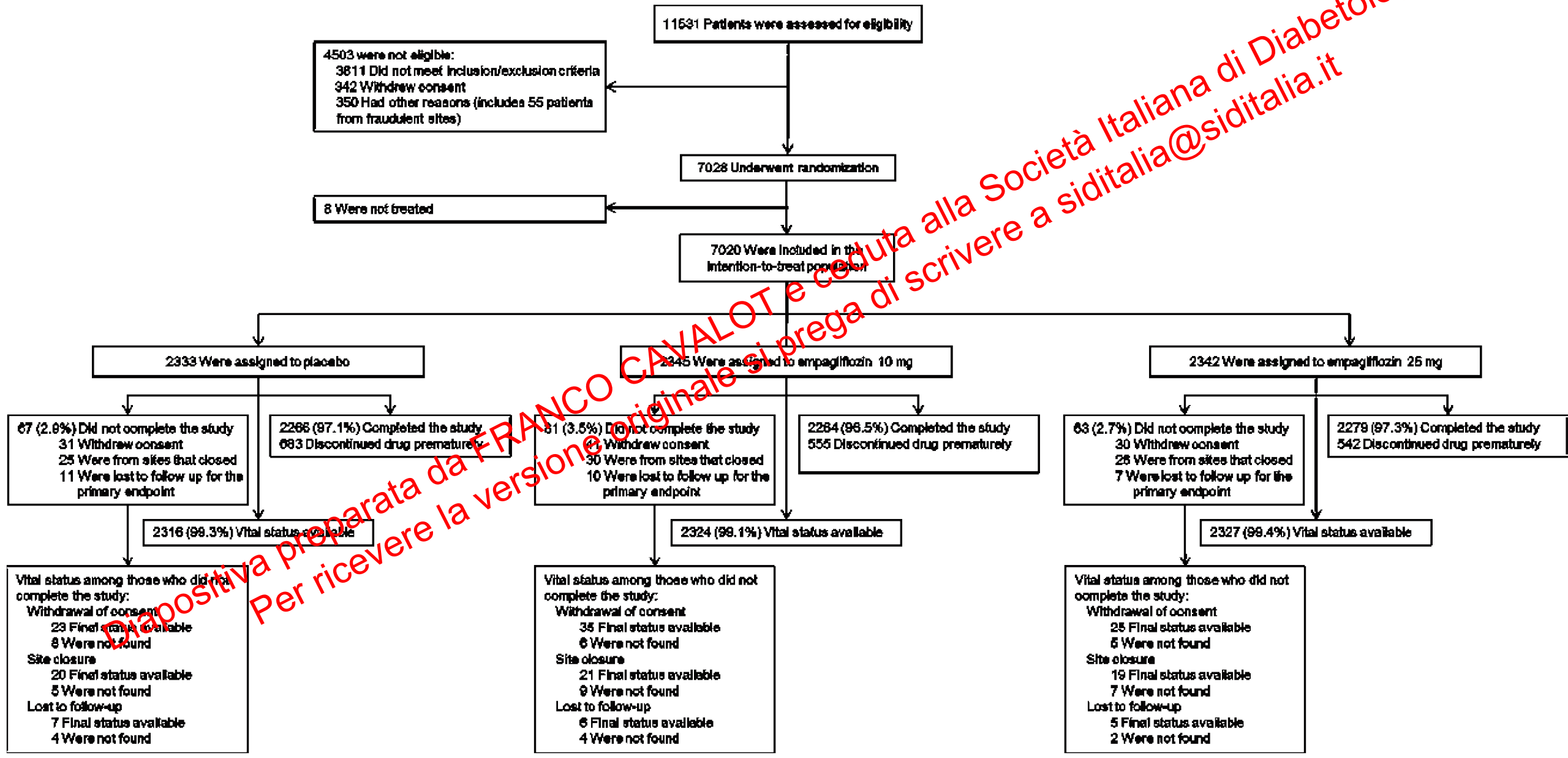
NEJM 2015

- ...**randomized, double-blind, placebo-controlled trial** to assess the effect of once-daily empagliflozin (at a dose of either 10 mg or 25 mg) versus placebo on cardiovascular events in adults with type 2 diabetes at high cardiovascular risk against a background of standard care.
- Eligible patients with type 2 diabetes were adults (≥ 18 years of age) with a **body-mass index (the weight in kilograms divided by the square of the height in meters) of 45 or less** and an **estimated glomerular filtration rate (eGFR) of at least 30 ml per minute per 1.73 m² of body-surface area**, according to the Modification of Diet in Renal Disease criteria. All the patients had **established cardiovascular disease** (as defined in Section C in the Supplementary Appendix) and had received no glucose-lowering agents for at least **12 weeks before randomization** and had a glycated hemoglobin level of at least **7.0%** and no more than **9.0%** or had received stable glucose-lowering therapy for at least **12 weeks before randomization** and had a glycated hemoglobin level of at least **7.0%** and no more than **10.0%**.

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EMPA-REG

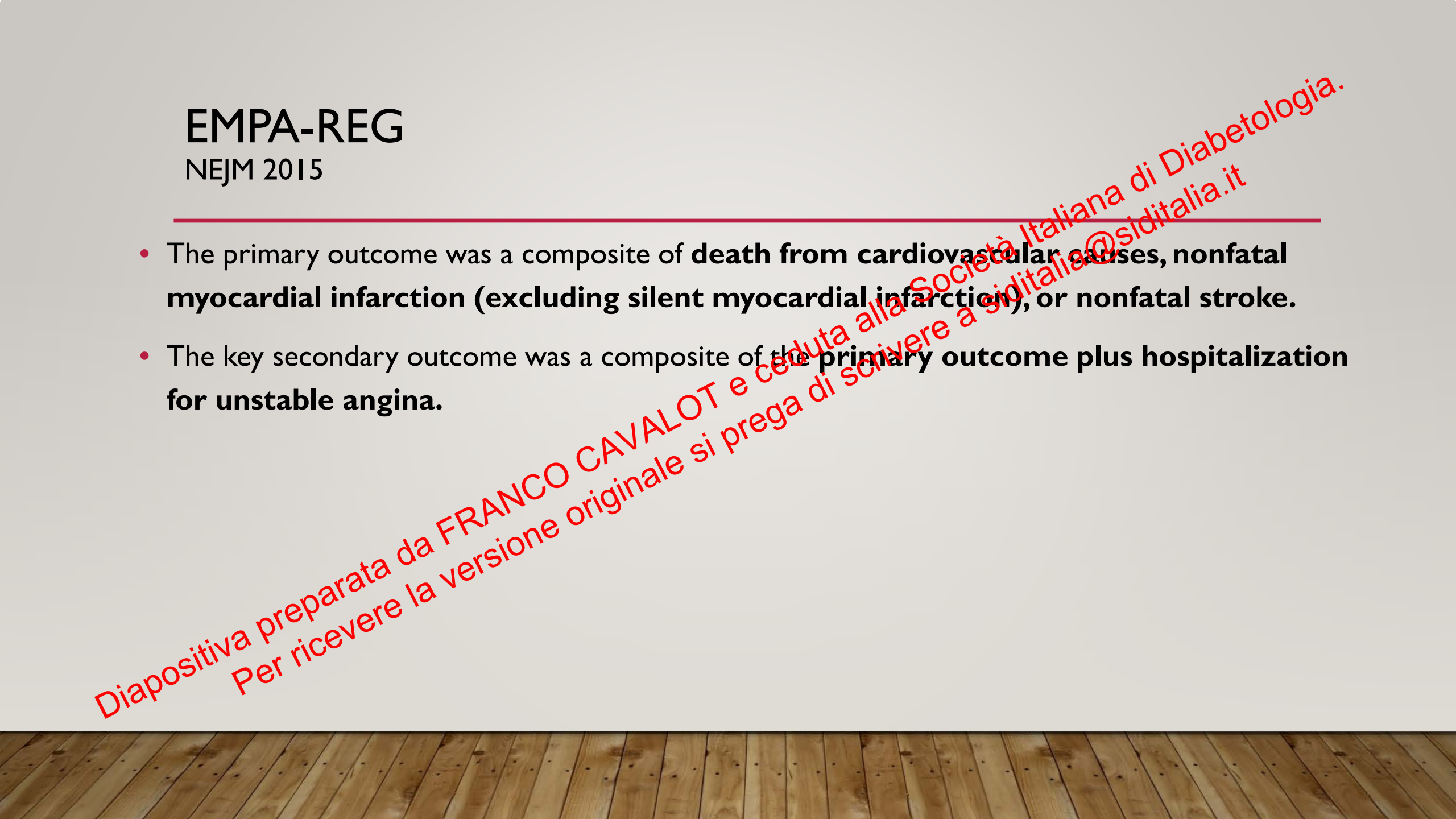
NEJM 2015



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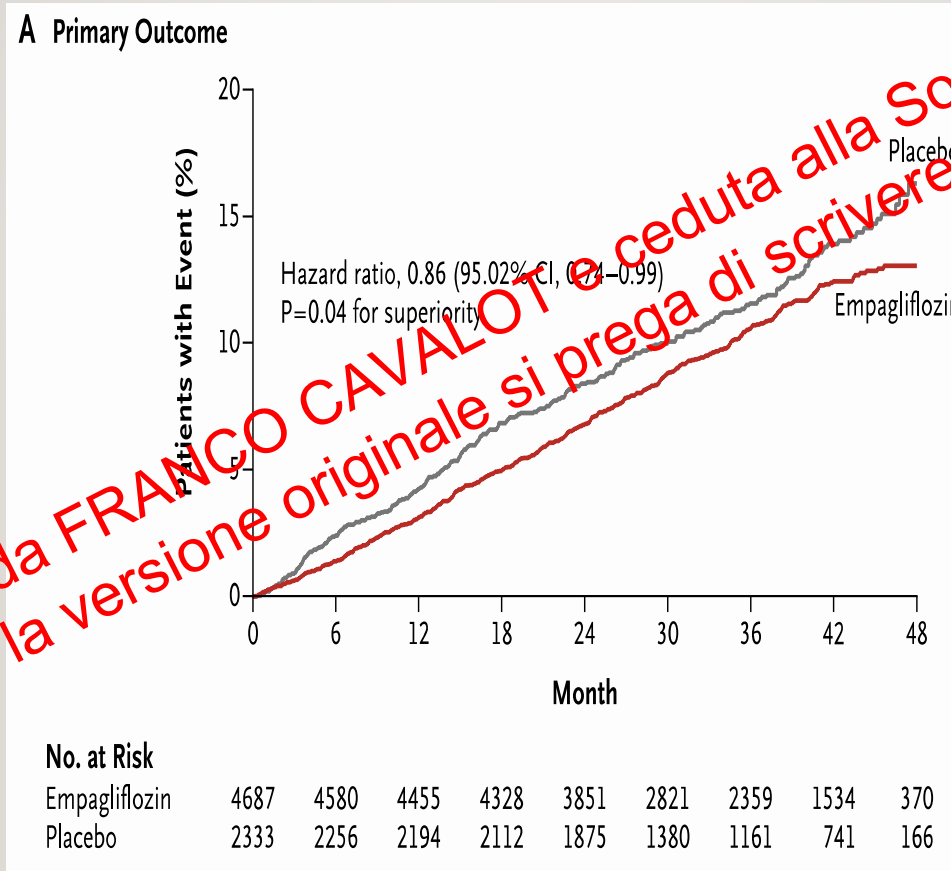
NEJM 2015

- The primary outcome was a composite of **death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke.**
- The key secondary outcome was a composite of the **primary outcome plus hospitalization for unstable angina.**



EMPA-REG

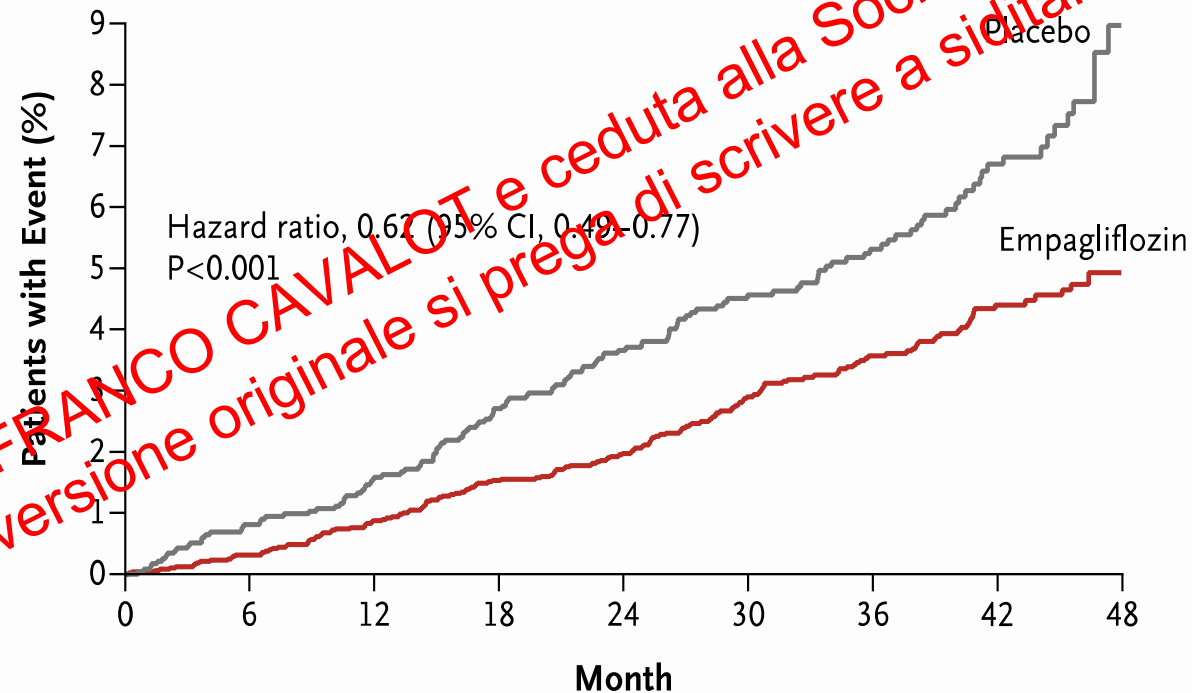
NEJM 2015



EMPA-REG

NEJM 2015

B Death from Cardiovascular Causes



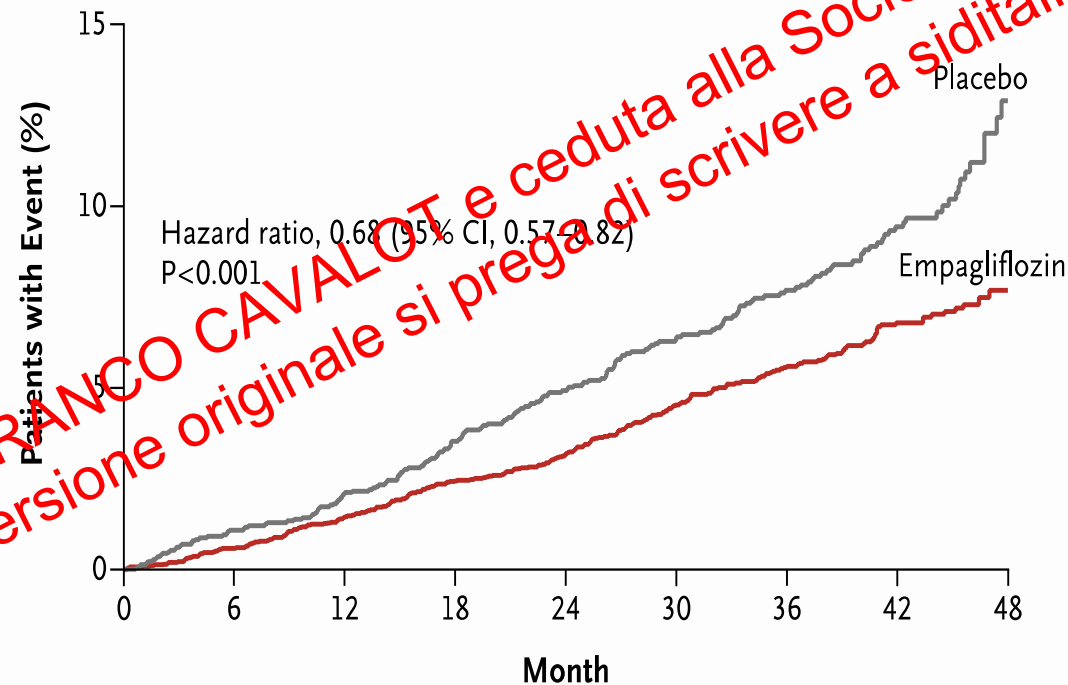
No. at Risk

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

EMPA-REG

NEJM 2015

C Death from Any Cause



No. at Risk

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

EMPA-REG

NEJM 2015

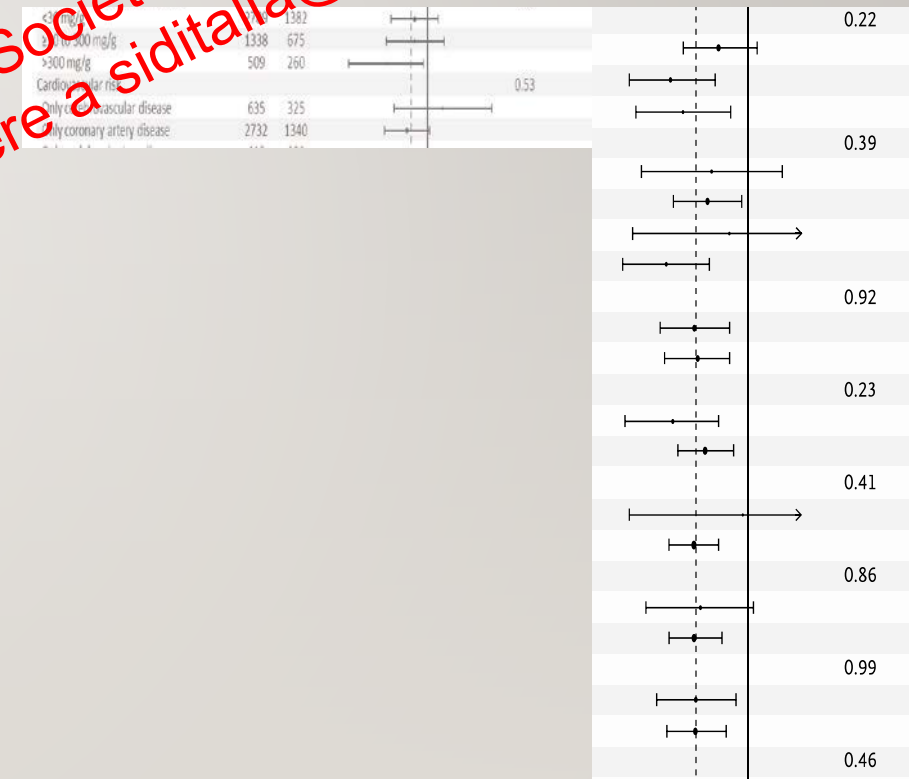
Table 1. Primary and Secondary Cardiovascular Outcomes.

Outcome	Placebo (N = 2333)		Empagliflozin (N = 4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	rate/1000 patient-yr	no. (%)	rate/1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78–1.01)	
Noninferiority						<0.001†
Superiority						0.08†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57–0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

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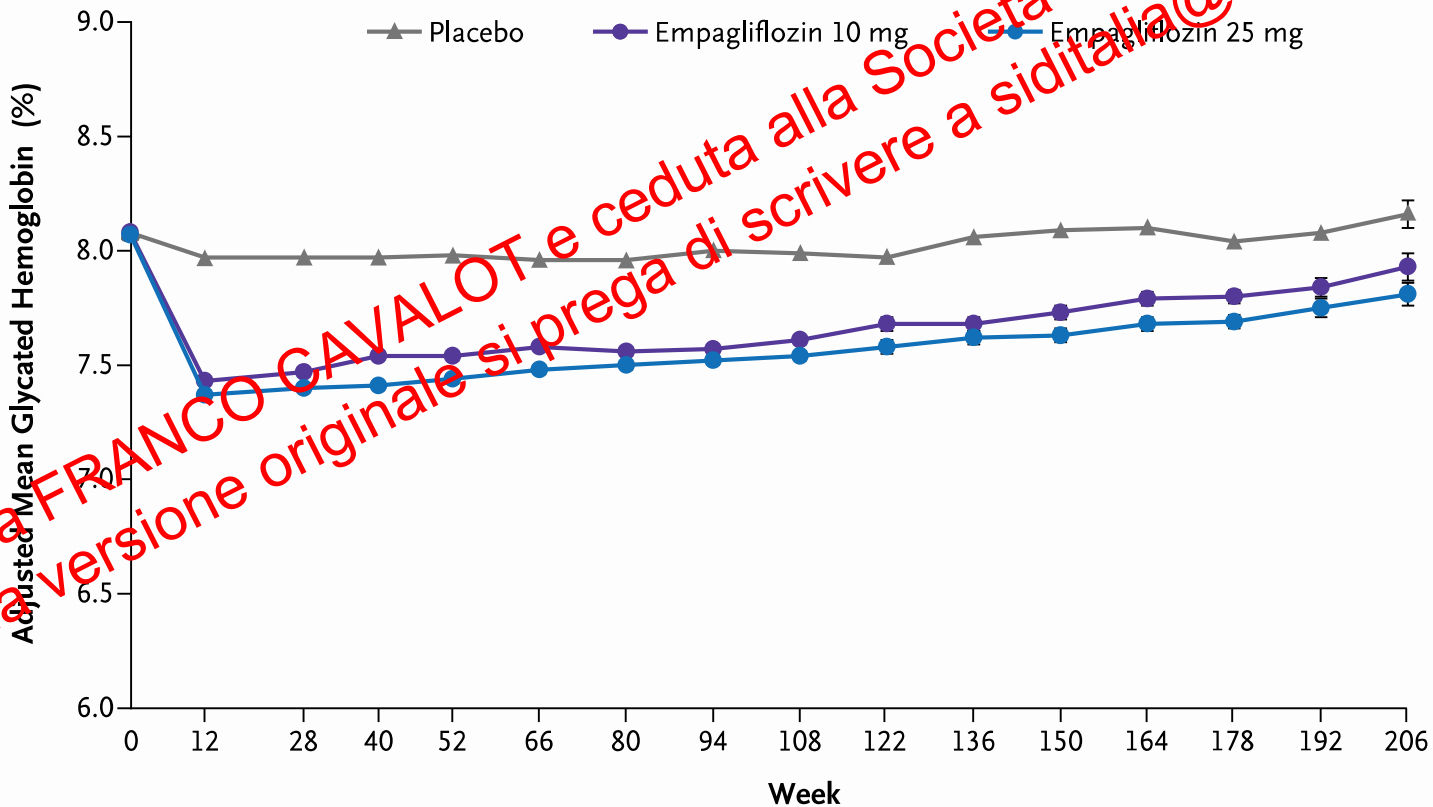
EMPA-REG: ANALISI PER SOTTOGRUPPI

NEJM 2015



EMPA-REG: ANALISI PER SOTTOGRUPPI

NEJM 2015



No. at Risk

Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

EMPA-REG: EVENTI AVVERSI

NEJM 2015

Event	Placebo (N = 2333)	Empagliflozin, 10 mg (N = 2345)	Empagliflozin, 25 mg (N = 2342)	Pooled Empagliflozin (N = 4687)
	number of patients (percent)			
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2) [†]
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5) [‡]
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2) [†]
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8) [§]
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3) [§]
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4) [‡]
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection ^{††}	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4) [†]
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0) [†]
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0) [†]
Event consistent with volume depletion ^{‡‡}	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure ^{§§}	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2) [§]
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0) [‡]
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event ^{§§}	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

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EMPA-REG: CONCLUSIONI

NEJM 2015

- Among patients with type 2 diabetes at high risk for cardiovascular events, those receiving empagliflozin had a **lower rate of the primary composite outcome** of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than did patients receiving placebo.
- The difference between empagliflozin and placebo was driven by a **significant reduction in death from cardiovascular causes, with no significant between-group difference in the risk of myocardial infarction or stroke**. Since the two groups had similar rates of hospitalization for unstable angina, there was no significant difference in the key secondary outcome, which included the risk of hospitalization for unstable angina.
- Patients in the empagliflozin group had significantly **lower risks of death from any cause and for hospitalization for heart failure** than did those in the placebo group.

EMPA-REG: CONCLUSIONI

NEJM 2015

- These benefits were observed in **a population with established cardiovascular disease in whom cardiovascular risk factors**, including blood pressure and dyslipidemia, **were well treated** with the use of renin–angiotensin–aldosterone system inhibitors, statins, and acetylsalicylic acid. The reductions in the risk of cardiovascular death in the empagliflozin group were consistent across subgroups according to baseline characteristics.
- The relative reduction of 32% in the risk of death from any cause in the pooled empagliflozin group means that **39 patients** (41 in the 10-mg group and 38 in the 25-mg group) would need **to be treated during a 3-year period to prevent one death**, but these numbers cannot be extrapolated to patient populations with other clinical characteristics.

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EMPA-REG: CONCLUSIONI

NEJM 2015

- As observed in previous trials, **genital infection** was more common in patients treated with empagliflozin.
- **Urosepsis** was infrequent but reported in more patients treated with empagliflozin, although there was no increase in the overall rate of urinary tract infection, complicated urinary tract infection, or pyelonephritis.
- The proportions of patients with **diabetic ketoacidosis, volume depletion, thromboembolic events, and bone fracture** were low (ranging from <1% for ketoacidosis and thromboembolic events to 5% for volume depletion) and similar in the empagliflozin groups and the placebo group.
- Concern has been expressed about the **renal safety** of inhibitors of sodium–glucose cotransporter 2 over time. However, the percentage of patients with acute renal failure (including acute kidney injury) was lower in the empagliflozin groups than in the placebo group, and renal function was maintained with empagliflozin.

Studio CANVAS

CANVAS Program è costituito da due trials (CANVAS e CANVAS-R) per un totale di 10,142 pazienti con Diabete tipo 2 ad alto rischio CV.

667 centri antidiabete in 30 Paesi

Pazienti randomizzati 1:1 canaglifozin-placebo ed osservati mediamente per 188,2 settimane

End point primario composto:

- Morte per evento CV
- Infarto del miocardio non fatale
- Stroke non fatale

End point secondari:

- Morte per qualsiasi causa
- Progressione microalbuminuria

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

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

ABSTRACT

BACKGROUND

Canagliflozin is a sodium–glucose cotransporter 2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

METHODS

The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

The mean age of the participants was 63.3 years, 35.8% were women, the mean duration of diabetes was 13.5 years, and 65.6% had a history of cardiovascular disease. The rate of the primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; $P < 0.001$ for noninferiority; $P = 0.02$ for superiority). Although on the basis of the prespecified hypothesis testing sequence the renal outcomes are not viewed as statistically significant, the

From the George Institute for Global Health, Faculty of Medicine, UNSW Sydney (B.N., V.P.), the Charles Perkins Centre (B.N.), and the Royal North Shore Hospital (V.P., G.F.), University of Sydney, and the Faculty of Medicine, University of New South Wales (B.N.) — all in Sydney; Imperial College London, London (B.N.), and the Oxford Centre for Diabetes, Endocrinology, and Metabolism and Harris Manchester College, University of Oxford, Oxford (D.R.M.) — both in the United Kingdom; the Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA (K.W.M.); the University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (D.Z.); and Janssen Research and Development, Raritan, NJ (N.E., W.S., G.L., M.D.). Address reprint requests to Dr. Neal at the George Institute for Global Health, UNSW Sydney, Level 5, 1 King St., Newtown, NSW 2042, Australia, or at bneal@georgeinstitute.org.au.

Caratteristiche dei pazienti

- Età media 63,3 anni
- 35,8% donne
- Durata media del diabete 13,5 anni
- 65,6% con storia di malattia CV
- Arruolati pazienti con HbA1c > 7,0% con storia di malattia CV aterosclerotica o ultracinquantenni con almeno due dei seguenti fattori di rischio CV:
 - Diabete da oltre 10 anni
 - Pressione sistolica > 140 mmHg in trattamento con antipertensivi
 - Fumatori
 - Microalbuminuria o macroalbuminuria
 - HDL Colesterolo < 38,7 mg/dl
- Arruolati pazienti con eGFR > 30 ml/min

Table 1. Baseline Characteristics in the Integrated CANVAS Program.*

Characteristic	Canagliflozin (N = 5795)	Placebo (N = 4347)	Total (N = 10,142)†
Age — yr	63.2±8.3	63.4±8.2	63.3±8.3
Female sex — no. (%)	2036 (35.1)	1517 (34.9)	3633 (35.8)
Race — no. (%)‡			
White	4508 (77.8)	3436 (79.0)	7944 (78.3)
Asian	777 (13.4)	507 (11.7)	1284 (12.7)
Black	176 (3.0)	160 (3.7)	336 (3.3)
Other	334 (5.8)	244 (5.6)	578 (5.7)
Current smoker — no. (%)	1347 (23.2)	786 (18.1)	1806 (17.8)
History of hypertension — no. (%)	5188 (89.5)	3937 (90.6)	9125 (90.0)
History of heart failure — no. (%)	803 (13.9)	658 (15.1)	1461 (14.4)
Duration of diabetes — yr	13.5±7.7	13.7±7.8	13.5±7.8
History of microvascular disease — no. (%)			
Retinopathy	1203 (20.8)	926 (21.3)	2129 (21.0)
Nephropathy	994 (17.2)	780 (17.9)	1774 (17.5)
Neuropathy	1787 (30.8)	1323 (30.4)	3110 (30.7)
History of atherosclerotic vascular disease — no. (%)§			
Coronary	3234 (55.8)	2487 (57.2)	5721 (56.4)
Cerebrovascular	1113 (19.2)	845 (19.4)	1958 (19.3)
Peripheral	1176 (20.3)	937 (21.6)	2113 (20.8)
Any	4127 (71.2)	3197 (73.5)	7324 (72.2)
History of cardiovascular disease — no. (%)¶	3756 (64.8)	2900 (66.7)	6656 (65.6)
History of amputation — no. (%)	136 (2.3)	102 (2.3)	238 (2.3)
Body-mass index	31.9±5.9	32.0±6.0	32.0±5.9
Blood pressure — mm Hg			
Systolic	136.4±15.8	136.9±15.8	136.6±15.8
Diastolic	77.6±9.6	77.8±9.7	77.7±9.7
Glycated hemoglobin — %	8.2±0.9	8.2±0.9	8.2±0.9
Cholesterol — mmol/liter			
Total	4.4±1.1	4.4±1.2	4.4±1.2
HDL	1.2±0.3	1.2±0.3	1.2±0.3
LDL	2.3±0.9	2.3±0.9	2.3±0.9
Ratio of LDL to HDL	2.0±0.9	2.0±0.9	2.0±0.9
Triglycerides — mmol/liter	2.0±1.3	2.0±1.5	2.0±1.4
eGFR — ml/min/1.73 m **	76.7±20.3	76.2±20.8	76.5±20.5
Albumin measurements ††			
Median albumin-to-creatinine ratio (interquartile range)	12.4 (6.71–40.9)	12.1 (6.57–43.9)	12.3 (6.65–42.1)
Normoalbuminuria — no./total no. (%)	4012/5740 (69.9)	2995/4293 (69.8)	7007/10,033 (69.8)
Microalbuminuria — no./total no. (%)	1322/5740 (23.0)	944/4293 (22.0)	2266/10,033 (22.6)
Macroalbuminuria — no./total no. (%)	406/5740 (7.1)	354/4293 (8.2)	760/10,033 (7.6)

Studio CANVAS – Materiali e metodi

I pazienti in CANVAS sono stati randomizzati 1:1:1 (Cana 100 mg – Cana 300 mg – placebo)

I pazienti in CANVAS-R 1:1 (Cana 100 mg eventualmente aumentato in corso di terapia a 300 mg – placebo)

CANVAS

2-week placebo run-in

R

Canagliflozin 300 mg

Canagliflozin 100 mg

Placebo

CANVAS-R

2-week placebo run-in

R

Canagliflozin 100 mg with optional up-titration to 300 mg

Placebo

L'uso di altri farmaci per l'ottimizzazione della glicemia era consentito in ottemperanza con le Linee Guida locali

Per il primo anno dopo arruolamento previste 3 visite, poi ogni sei mesi

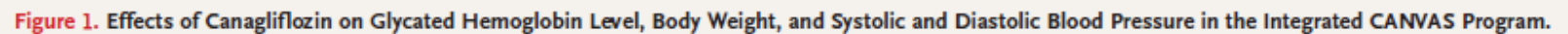
In CANVAS-R il rapporto albumina/creatinina era misurato ogni 26 settimane.

In CANVAS era misurato dopo 12 settimane e poi annualmente

Ogni 26 settimane veniva calcolato eGFR

Vs placebo Cana riduce significativamente:

- pressione diastolica

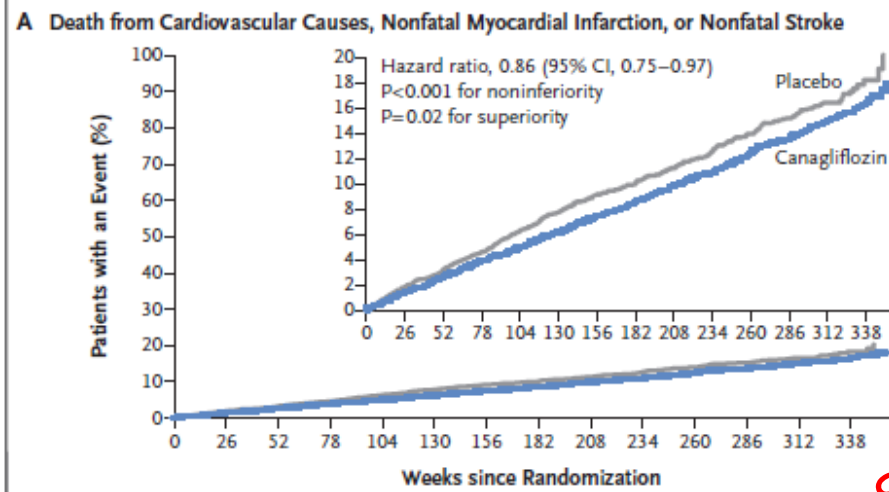


A total of 10,142 participants were included in the CANVAS Program, which comprised two trials: the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS–Renal (CANVAS-R).

Studio CANVAS

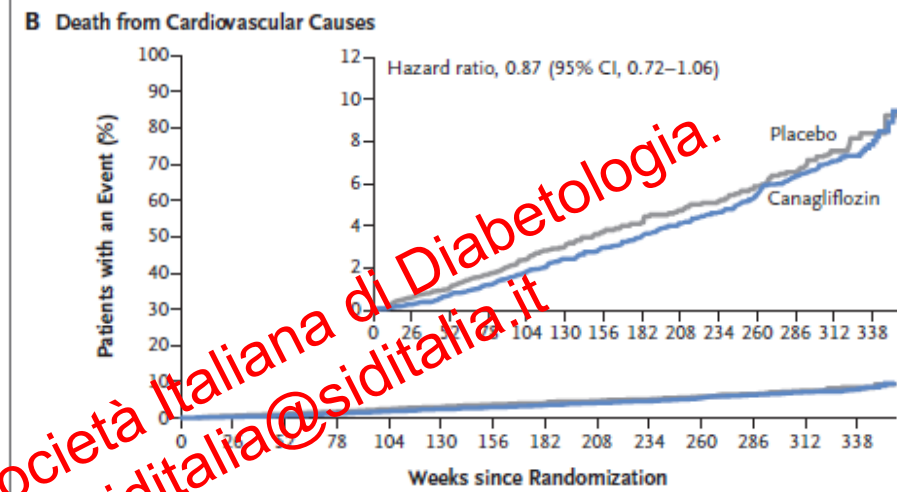
-risultati- 2

Differenza significativa ($p < 0,001$ per non inferiorità; $p = 0,02$ per superiorità) su obiettivo primario composto



No. at Risk

Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	1061	1026	991	956	921	886	851	816	781	746	711	676	641	606	571	536	501	466	431	396	361	326	291	256	221	186	151	116	81	46	11	0																			
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2317	2271	2225	2179	2133	2087	2041	1995	1949	1903	1857	1811	1765	1719	1673	1627	1581	1535	1489	1443	1397	1351	1305	1259	1213	1167	1121	1075	1029	983	937	891	845	799	753	707	661	615	569	523	477	431	385	339	293	247	201	155	109	63	17	0



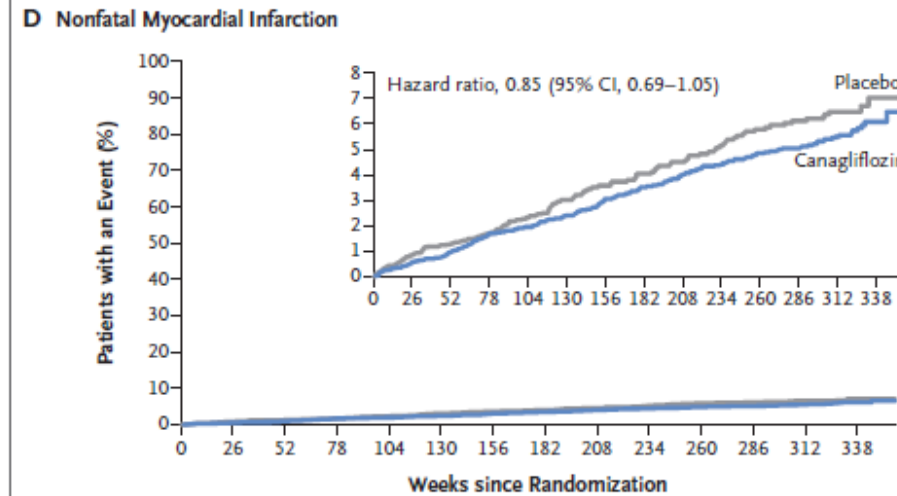
No. at Risk

Placebo	4347	4316	4279	4236	3119	1759	1356	1344	1328	1310	1292	1280	924	258
Canagliflozin	5795	5768	5723	5679	4576	3182	2761	2736	2710	2687	2651	2615	1904	532



No. at Risk

Placebo	4347	4270	4197	4123	3004	1667	1274	1255	1232	1208	1177	1155	829	232
Canagliflozin	5795	5702	5615	5530	4414	3043	2621	2588	2543	2511	2464	2415	1751	481



No. at Risk

Placebo	4347	4256	4187	4109	2986	1647	1255	1233	1207	1179	1146	1126	812	223
Canagliflozin	5795	5711	5625	5513	4405	3029	2602	2565	2516	2476	2425	2382	1728	468

Figure 2. Cardiovascular Outcomes in the Integrated CANVAS Program.

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The hazard ratios and 95% confidence intervals for the primary outcome and the components of the outcome were estimated with the use of Cox regression models with stratification according to trial and history of cardiovascular disease for all canagliflozin groups combined versus placebo. Analyses are based upon the full, integrated data set comprising all participants who underwent randomization. The inset in each panel shows the same data on an enlarged y axis.

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-risultati- 3

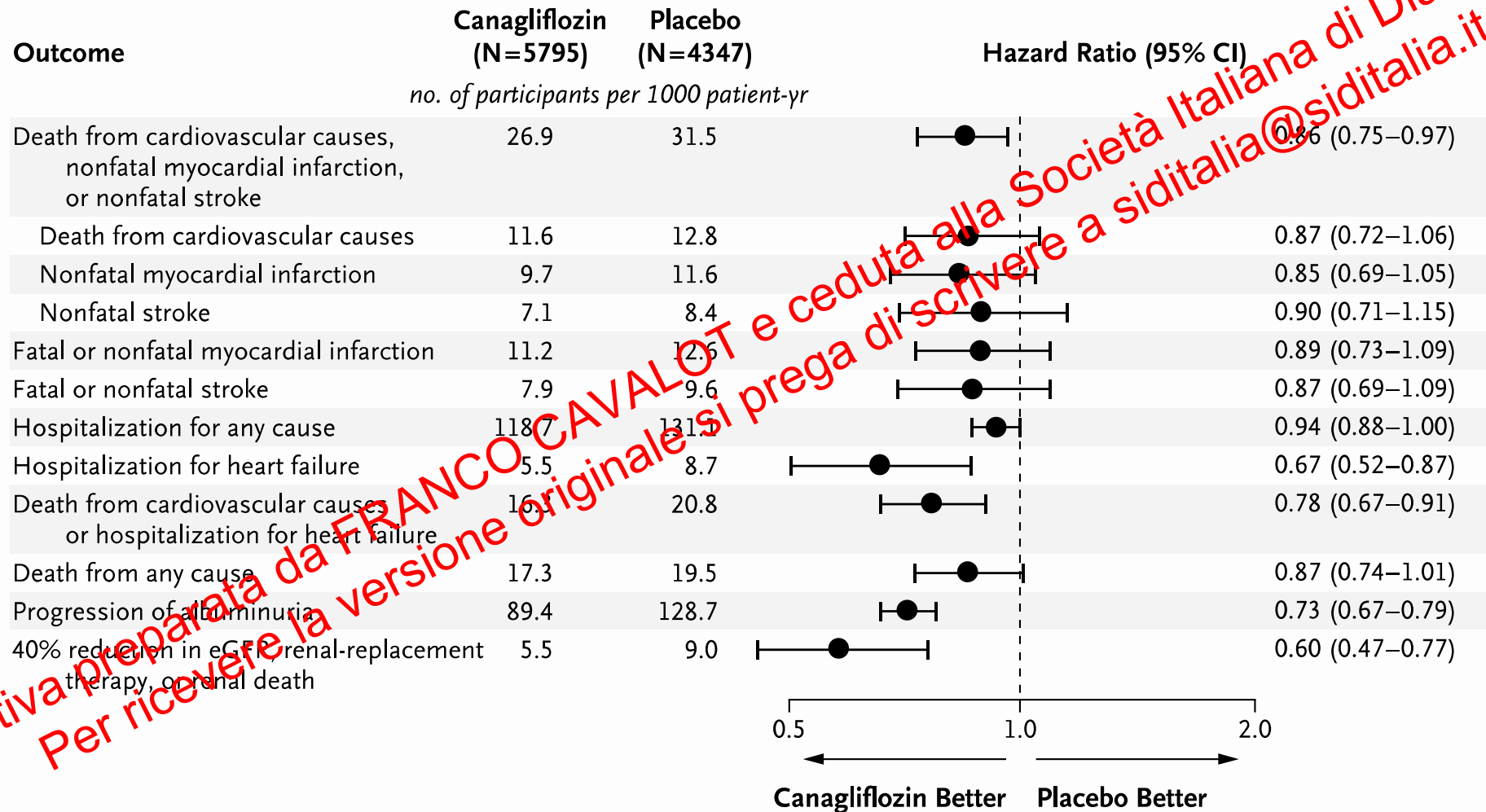


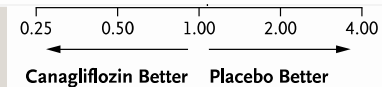
Figure 3. Effects of Canagliflozin on Cardiovascular, Renal, Hospitalization, and Death Events in the Integrated CANVAS Program.

Studio CANVAS

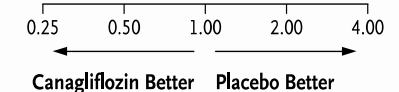
-risultati- 4

Beneficio di Canagliflozin vs placebo in tutte le sottoanalisi

Subgroup	Canagliflozin no. of participants per 1000 patient-yr	Placebo no. of participants per 1000 patient-yr	Hazard Ratio (95% CI)	P Value
All patients	26.9	31.5	0.86 (0.75–0.97)	0.60
Study				
CANVAS	26.9	30.4	0.88 (0.75–1.03)	
CANVAS-R	27.1	33.0	0.82 (0.66–1.01)	0.26
Age				
<65 yr	22.0	23.6	0.91 (0.76–1.10)	
≥65 yr	33.8	42.3	0.80 (0.67–0.95)	0.80
Sex				
Male	29.8	35.1	0.86 (0.74–1.00)	
Female	21.7	25.0	0.84 (0.66–1.06)	0.40
Race				
White	29.1	34.2	0.84 (0.73–0.96)	
Black	18.6	37.0	0.45 (0.19–1.03)	
Asian	18.8	18.4	1.08 (0.72–1.64)	
Other	25.3	24.5	1.01 (0.57–1.80)	0.89
Region				
North America	26.7	30.3	0.84 (0.65–1.09)	
Central America and South America	26.7	33.8	0.84 (0.52–1.34)	
Europe	28.1	35.0	0.89 (0.65–0.99)	0.29
Rest of the world	26.0	28.2	0.94 (0.75–1.18)	
BMI				
<30	25.6	27.8	0.97 (0.79–1.20)	0.64
≥30	27.8	34.0	0.79 (0.67–0.93)	
Blood pressure control				
Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg	28.1	34.0	0.84 (0.70–1.01)	0.64
Systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg	26.1	29.5	0.88 (0.74–1.04)	



Subgroup	Canagliflozin no. of participants per 1000 patient-yr	Placebo no. of participants per 1000 patient-yr	Hazard Ratio (95% CI)	P Value
Duration of diabetes				0.33
≥10 yr	27.0	33.2	0.81 (0.70–0.95)	
<10 yr	26.6	29.7	0.96 (0.76–1.22)	0.29
Glycated hemoglobin				
<8%	24.2	26.8	0.94 (0.77–1.15)	0.20
≥8%	28.8	35.5	0.80 (0.68–0.94)	
eGFR				0.18
30 to <60 ml/min/1.73 m ²	36.4	49.3	0.70 (0.55–0.90)	
60 to <90 ml/min/1.73 m ²	26.8	29.0	0.95 (0.80–1.13)	
≥90 ml/min/1.73 m ²	20.8	23.6	0.84 (0.62–1.12)	0.47
History of cardiovascular disease				
Yes	34.1	41.3	0.82 (0.72–0.95)	0.51
No	15.8	15.5	0.98 (0.74–1.30)	
History of peripheral vascular disease				0.36
Yes	33.9	43.2	0.75 (0.58–0.97)	
No	25.4	28.8	0.89 (0.77–1.03)	0.96
History of heart failure				
Yes	42.2	51.4	0.80 (0.61–1.05)	0.45
No	24.8	28.3	0.87 (0.76–1.01)	
History of amputation				0.86
Yes	44.4	74.3	0.56 (0.28–1.13)	
No	26.5	30.8	0.86 (0.76–0.98)	0.38
Insulin use				
Yes	32.0	37.4	0.85 (0.72–1.00)	0.01
No	21.9	25.6	0.87 (0.71–1.06)	
Statin use				<0.001
Yes	26.3	31.6	0.84 (0.72–0.97)	
No	28.7	31.1	0.91 (0.71–1.16)	0.86
Antithrombotic use				
Yes	30.3	34.8	0.87 (0.75–1.00)	0.38
No	18.5	22.4	0.82 (0.61–1.09)	
RAAS inhibitor use				0.01
Yes	27.6	31.4	0.88 (0.76–1.01)	
No	24.4	31.8	0.77 (0.58–1.03)	0.01
Beta-blocker use				
Yes	29.5	39.0	0.75 (0.64–0.88)	<0.001
No	24.2	23.2	1.04 (0.85–1.28)	
Diuretic use				<0.001
Yes	27.6	41.0	0.66 (0.56–0.79)	
No	26.4	24.0	1.11 (0.93–1.34)	



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Eventi avversi

Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	<i>event rate per 1000 patient-yr</i>		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.7	0.74
Breast	1.2	2.6	0.65
Photosensitivity	1.0	0.3	0.07
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			
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

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STUDIO CANVAS

NEJM, 2017

- Patients with type 2 diabetes and established cardiovascular disease or at high risk for cardiovascular events who were treated with canagliflozin had **significantly lower rates of the primary cardiovascular outcome** than patients assigned to placebo.
- The results also showed that patients treated with canagliflozin had a **lower risk of hospitalization for heart failure, progression of albuminuria, and substantive loss of kidney function** than patients who received placebo, although on the basis of the prespecified hypothesis testing sequence these findings are not considered statistically significant.

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STUDIO CANVAS

NEJM, 2017

- The trial program has certain strengths:
 - It benefits from **the large size** of the combined trials, **the long duration** of the trials, **the randomized design, the breadth of included participants**, and the high standard to which the conduct of the trials was held.
- The trial program has certain limitations:
 - the **moderate number of events** for many important outcomes — in particular, the paucity of events of end-stage kidney disease. The relatively small proportion of participants with established kidney disease also limits generalization to that population.
 - Discontinuation of randomized therapy and greater use of other glucose-lowering agents in the placebo group during the trial program is the likely explanation for the convergence of glycated hemoglobin levels over time and may have resulted in underestimation of any benefits and risks associated with canaglif lozin.

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STUDIO CANVAS

NEJM, 2017

- **The adverse effects** observed in this program of two integrated trials are generally **consistent with the known safety profile of canagliflozin and other SGLT2 inhibitors**.
- The **increased rate of amputation** is a new finding for which the mechanism is unknown, and care is warranted in the use of canagliflozin in patients at risk for amputation.
- **An increase in bone fractures** has been described previously with canagliflozin, but the excess in bone fracture seen in CANVAS was not observed in CANVAS-R.

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STUDI CVD-REAL

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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)

Editorial, see p 1460

BACKGROUND: Clinical trials have shown cardiovascular benefits and potential risks from sodium glucose cotransporter 2 inhibitors (SGLT2i). Trials may have limited ability to address individual end points or safety concerns.

METHODS: We performed a population-based cohort study among patients

Jacob A. Udell, MD, MPH
Zhong Yuan, MD, PhD
Toni Rush, MPH
Nicholas M. Sicignano, MPH
Michael Galitz, MD
Norman Rosenthal, MD

STUDIO EASEL, CIRCULATION 2018

- ...a population-based cohort study among patients with **type 2 diabetes mellitus with established cardiovascular disease** newly initiated on antihyperglycemic agents within the US Department of Defense Military Health System between April 1, 2013, and December 31, 2016.
- Incidence rates, hazard ratios (HRs), and 95% confidence intervals (CIs) for time to first composite end point of **all-cause mortality and hospitalization for heart failure event, major adverse cardiovascular events** (defined as all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke), and individual end points were evaluated using conditional Cox models comparing new SGLT2i users with other antihyperglycemic agents.
- The **exploratory safety end point was below-knee lower extremity amputation**. Intent-to-treat and on-treatment analyses were performed.

STUDIO EASEL, CIRCULATION 2018

Table. Baseline Characteristics by Treatment Cohort Before and After Propensity Matching*

Characteristic	Before Matching		After Matching	
	Non-SGLT2i (n=97 819)	SGLT2i (n=13 757)	Non-SGLT2i (n=12 629)	SGLT2i (n=12 629)
Age, y†	69.6 (10.6)	65.5 (8.9)	65.9 (9.8)	65.8 (8.9)
Sex, %				
Male	56.2	56.4	55.1	56.7
Female	43.8	43.6	44.9	43.3
Race, %				
White	26.8	36.9	33.6	36.7
Black	6.0	5.6	6.3	5.6
Asian or Pacific Islander	1.7	1.7	1.7	1.7
Other‡	65.4	55.9	58.4	56.1
T2DM duration, y†	5.0 (2.2)	5.7 (1.9)	5.7 (2.0)	5.6 (2.0)
CV disease duration, y†	4.3 (2.2)	4.4 (2.2)	4.4 (2.3)	4.4 (2.2)
Charlson Comorbidity Index score	6.0 (3.1)	5.0 (2.4)	5.0 (2.6)	5.0 (2.4)

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	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		<0.0001
ACM	475	2.26	272	1.29		<0.0001
HHF	188	0.90	108	0.51		<0.0001
MACE	714	3.45	483	2.31		<0.0001
Nonfatal stroke	125	0.60	108	0.51		0.2190
Nonfatal myocardial infarction	148	0.71	121	0.58		0.0888
Composite of MACE and HHF	845	4.11	567	2.72		<0.0001
BAKA*	28	0.09	35	0.17		0.0183

0.25 0.50 1.00 2.00 4.00

← Favors SGLT2i Favors Non-SGLT2i →

ACM indicates all-cause mortality; BKA, below-knee lower extremity amputation; CI, confidence interval; HHF, hospitalization for heart failure;

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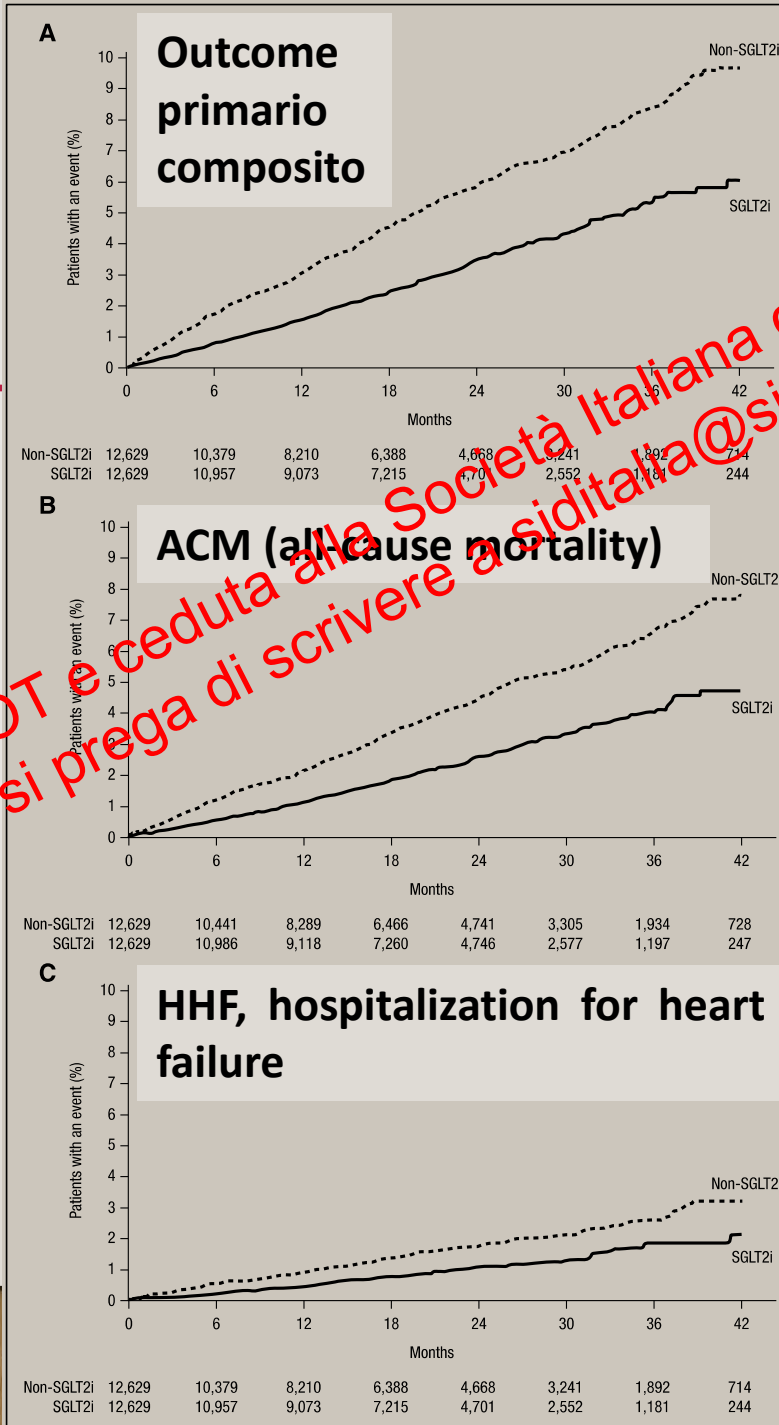


Figure 2. Event curves for the primary composite outcome, ACM, and HHF in the propensity-matched ITT cohort by treatment status.

Event curves for the (A) primary composite outcome, (B) ACM, and (C) HHF in the propensity-matched ITT cohort by treatment status. Propensity-matched using an exposure propensity score. ACM indicates all-cause mortality; HHF, hospitalization for heart failure; ITT, intent to treat; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

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- Our findings in a cohort with T2DM and established CVD support those recently seen in 2 large CV outcome trials—that **initiation of SGLT2i is associated with a lower risk of mortality, HHF, and MACE.**
- However, the use of SGLT2i was also associated with **an $\approx$ 2-fold higher risk of BKA**, a serious adverse event seen in a similar magnitude within the CANVAS Program of canagliflozin.
- Although these observations require replication in other settings, our findings underscore the potential CV benefit and a rare but serious risk that physicians and patients should monitor for when initiating this class of medication.

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LOWER RISK OF CARDIOVASCULAR EVENTS AND DEATH ASSOCIATED WITH INITIATION OF SGLT-2 INHIBITORS VERSUS OTHER GLUCOSE LOWERING DRUGS - REAL WORLD DATA ACROSS THREE MAJOR WORLD REGIONS WITH MORE THAN 400,000 PATIENTS: THE CVD-REAL 2 STUDY

MIKHAIL KOSIBOROD¹, CAROLYN SU PING LAM², SHUN KOHSAKA³, DAE JUNG KIM⁴, AVRAHAM KARASIK⁵, JONATHAN SHAW⁶, NAVDEEP TANGRI⁷, SU-YEN GOH⁸, MARCUS THURESSON⁹, HUNGTA CHEN¹⁰, FILIP SURMONT¹¹, NILAS HAMMAR^{12,13}, PETER FENICI¹⁴ ON BEHALF OF THE CVD-REAL INVESTIGATORS AND STUDY GROUP. PRESENTED AT THE 67TH SCIENTIFIC SESSIONS OF THE AMERICAN COLLEGE OF CARDIOLOGY MEETING; MARCH 10-12, 2018; ORLANDO, FL.

¹SAINT LUKE'S MID AMERICA HEART INSTITUTE AND UNIVERSITY OF MISSOURI-KANSAS CITY, KANSAS CITY, MO, USA; ²NATIONAL HEART CENTRE, SINGAPORE AND SINGHEALTH DUKE-NUS, SINGAPORE; ³KEIO UNIVERSITY SCHOOL OF MEDICINE, TOKYO, JAPAN; ⁴DEPARTMENT OF ENDOCRINOLOGY AND METABOLISM, AJOU UNIVERSITY SCHOOL OF MEDICINE, SUWON, REPUBLIC OF KOREA; ⁵TEL AVIV UNIVERSITY, RAMAT AVIV, AND MACCABI HEALTHCARE ISRAEL; ⁶BAKER IDI HEART AND DIABETES INSTITUTE, MELBOURNE, VICTORIA, AUSTRALIA; ⁷DEPARTMENT OF MEDICINE, UNIVERSITY OF MANITOBA, WINNIPEG MB, CANADA; ⁸SINGAPORE GENERAL HOSPITAL, SINGAPORE; ⁹STATISTICON AB, UPPSALA, SWEDEN; ¹⁰ASTRAZENECA, GAITHERSBURG, MD, USA; ¹¹ASTRAZENECA, LUTON, UK; ¹²KAROLINSKA INSTITUTE, STOCKHOLM, SWEDEN; ¹³ASTRAZENECA, GOTHENBURG, SWEDEN; ¹⁴ASTRAZENECA, CAMBRIDGE, UK

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COUNTRIES AND DATA SOURCES



Australia – National Diabetes Services Scheme (NDSS)*



Canada – Manitoba Population Health Research Data Repository



Israel – The Maccabi Health Management Organization



Japan – Medical Data Vision



Singapore – SingHealth Diabetes Registry



South Korea – National Health Insurance Service (NHIS)

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*Included in the ACD analysis only

INCLUSION/EXCLUSION CRITERIA

- Inclusion

- New users of SGLT-2i or oGLD
 - Established type 2 diabetes on or prior to the index date
 - ≥ 18 years old
 - >1 year historical data available prior to the index date

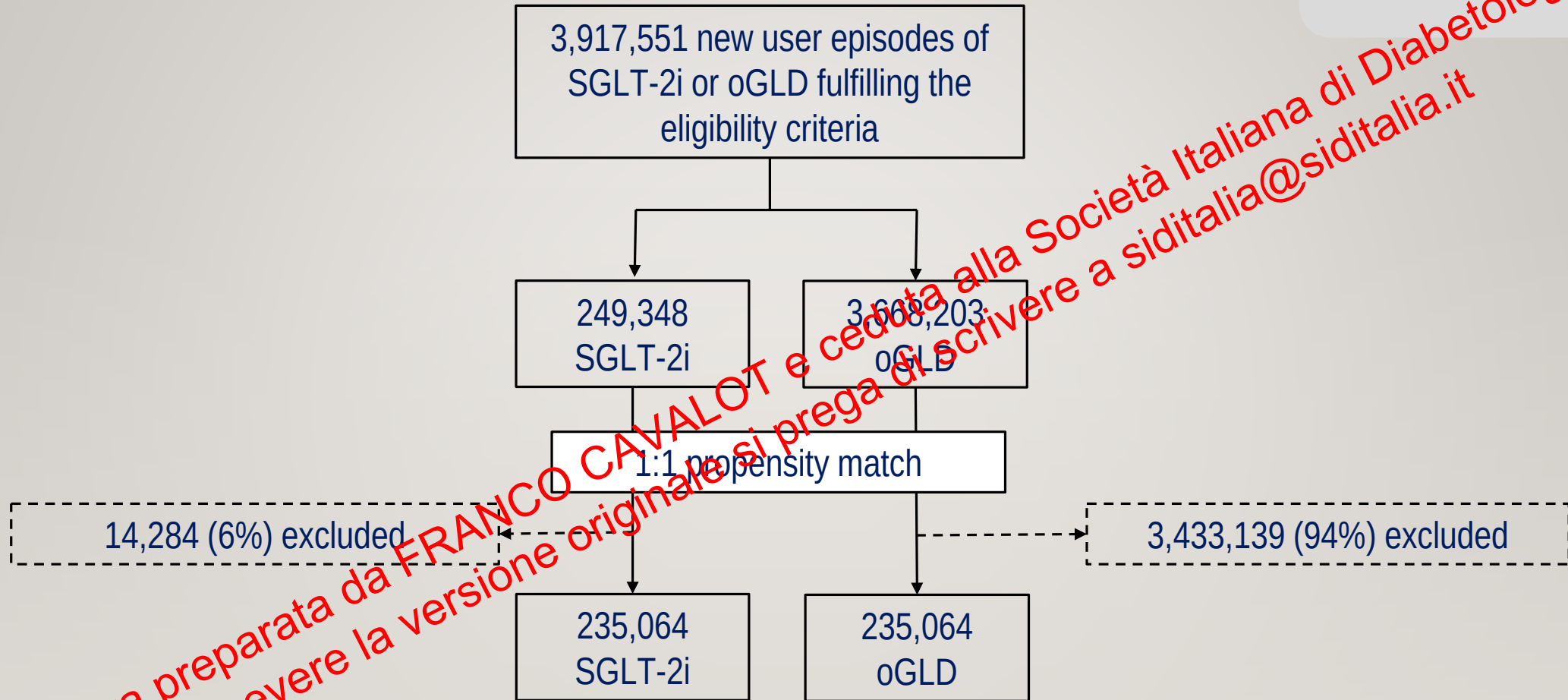
- Exclusion

- Patients with type 1 diabetes or gestational diabetes

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PATIENT POPULATION



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BASELINE CHARACTERISTICS

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Baseline characteristic, n (%)	SGLT-2i (N=235,064)	oGLD (N=235,064)	Standardized Difference
Age, years, mean (SD)	57 (12)	57 (13)	0.4%
Women	105,843 (45)	106,863 (46)	0.9%
Established cardiovascular disease*	59,222 (27)	56,576 (26)	2.7%
Acute myocardial infarction	7,624 (3)	7,479 (3)	0.4%
Unstable angina	12,480 (6)	12,235 (6)	0.5%
Heart failure	15,151 (7)	14,741 (7)	0.7%
Atrial fibrillation	6,021 (3)	5,843 (3)	0.5%
Stroke	20,983 (10)	20,153 (9)	1.3%
Peripheral arterial disease	2,446 (1)	2,384 (1)	0.3%
Microvascular disease†	116,370 (53)	114,630 (52)	1.6%
Chronic kidney disease	4,211 (2)	4,021 (2)	0.6%

*Myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization or occlusive peripheral artery disease; †diabetic mono-/polyneuropathy, diabetic eye complications, diabetic foot/peripheral angiopathy, or diabetic kidney disease

BASELINE THERAPIES

Baseline therapies, n (%)	SGLT-2i (N=235,064)	oGLD (N=235,064)	Standardized Difference
Cardiovascular therapies			
Antihypertensive therapy [†]	147,166 (63)	145,014 (62)	1.9%
Loop diuretics	16,451 (7)	16,100 (9)	0.6%
Thiazides	17,608 (8)	17,173 (7)	0.7%
ACE inhibitors	20,199 (9)	20,062 (9)	0.2%
ARBs	109,620 (47)	109,347 (47)	0.2%
Statins	153,694 (65)	153,466 (65)	0.2%
Beta-blockers	44,086 (19)	43,947 (19)	0.9%
Aldosterone antagonists	6,719 (3)	6,548 (3)	0.4%

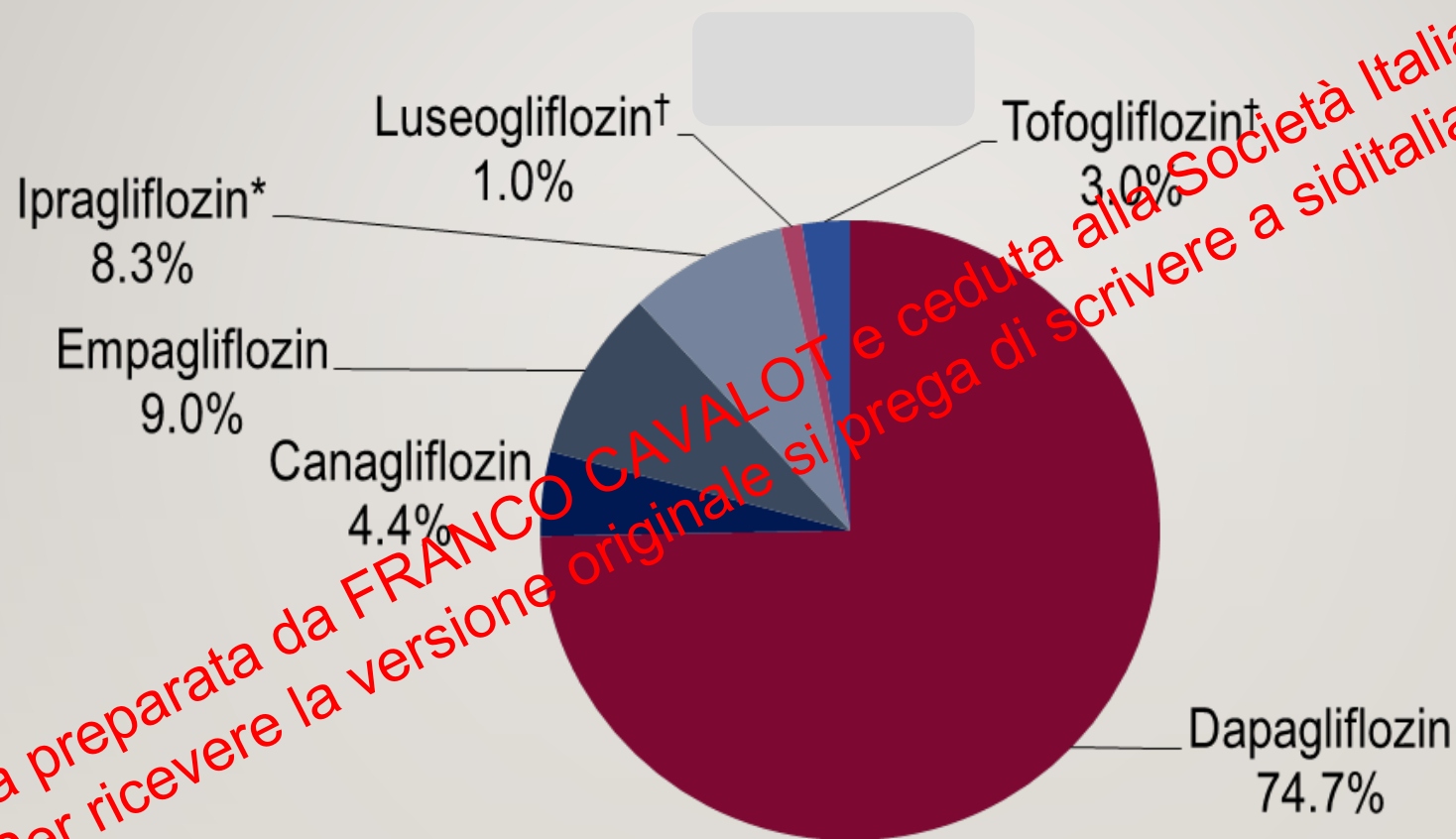
[†]Includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, Ca²⁺ channel blockers, β -blockers, thiazides; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers

Baseline therapies, n (%)	SGLT-2i (N=235,064)	oGLD (N=235,064)	Standardized Difference
Glucose-lowering therapies			
Metformin	173,783 (74)	175,266 (75)	1.4%
Sulfonylurea	121,209 (52)	119,466 (51)	1.5%
DPP-4 inhibitor	130,674 (56)	128,096 (55)	2.2%
Thiazolidinedione	30,503 (13)	29,573 (13)	1.2%
GLP-1 receptor agonist	6,163 (3)	6,022 (3)	0.4%
Insulin	46,486 (20)	44,480 (19)	2.2%

DPP-4, Dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

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USE OF SGLT-2I: PROPORTION OF EXPOSURE TIME

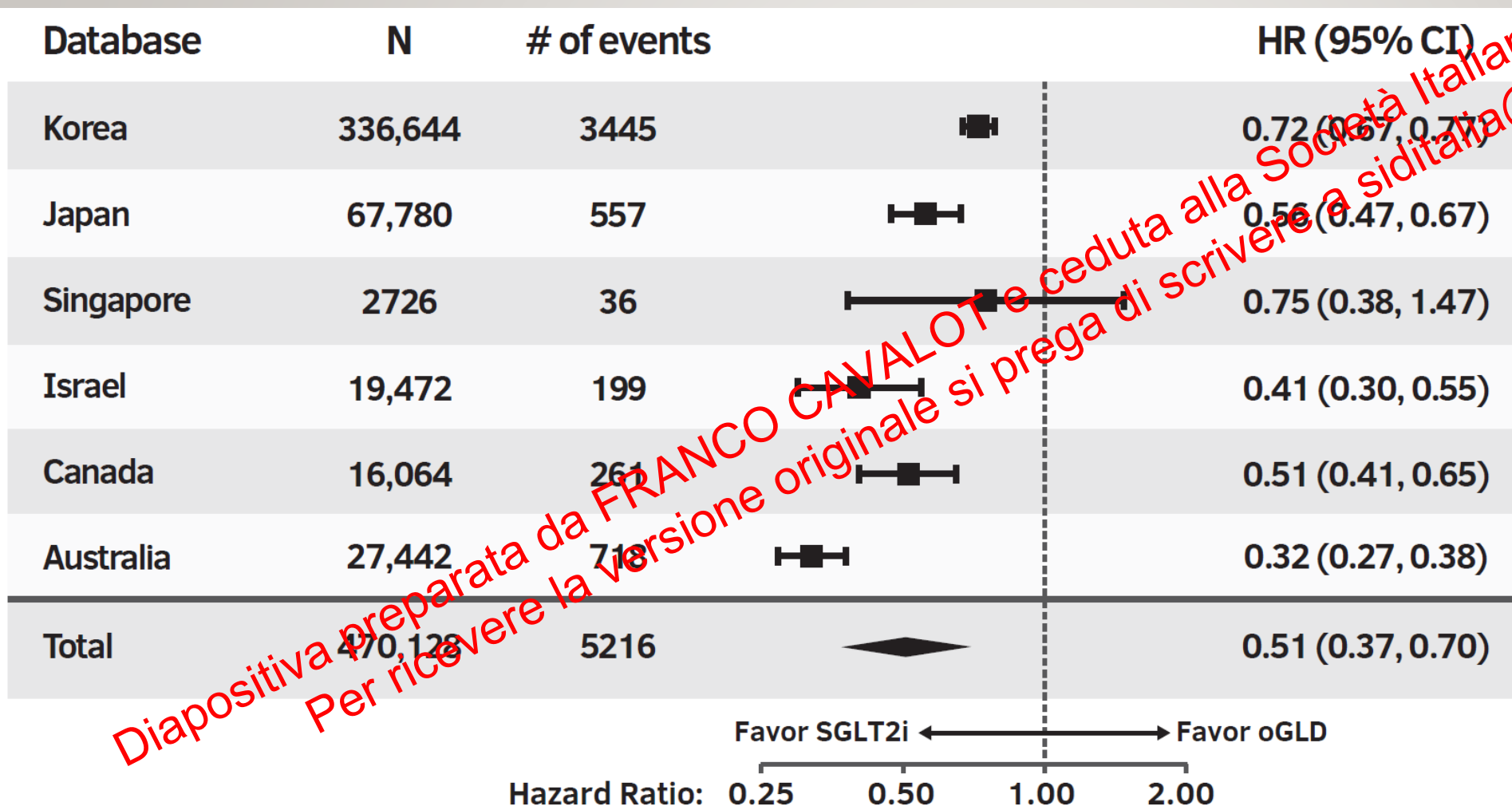


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ALL-CAUSE DEATH

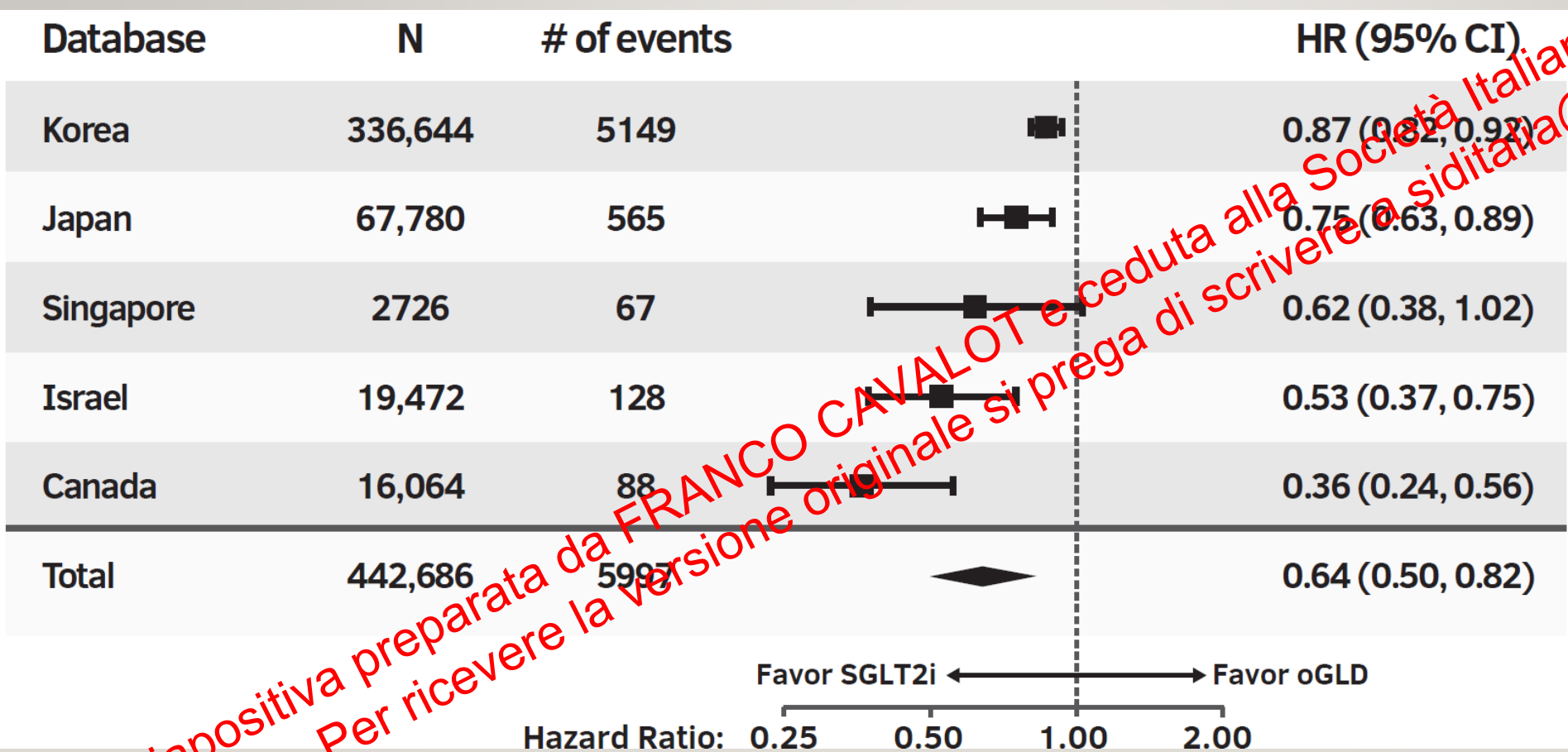
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P-value for
SGLT2i vs. oGLD: $p < 0.001$

Heterogeneity p-value: $p < 0.001$

HOSPITALIZATION FOR HEART FAILURE

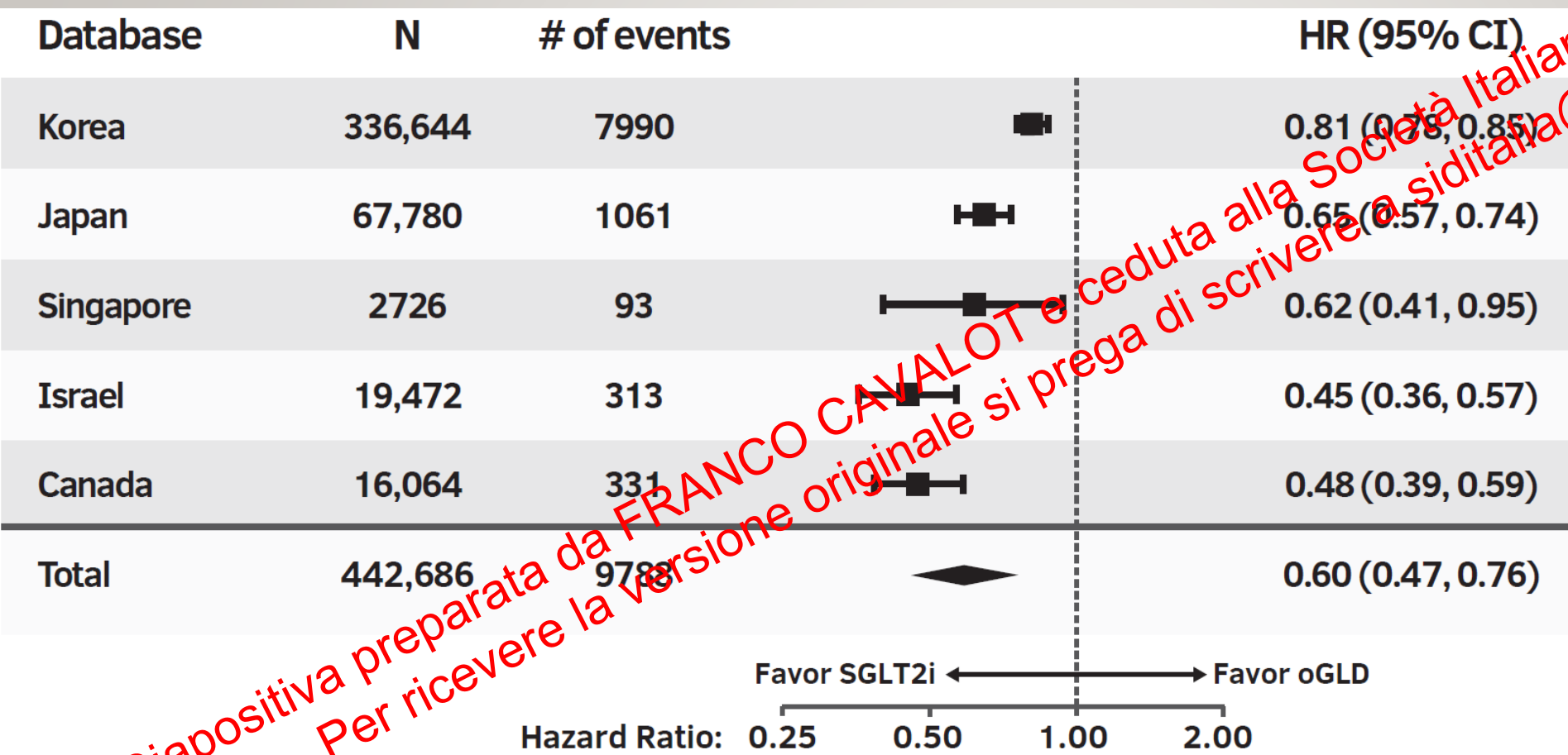


Kosiborod et al, JACC 2018

P-value for
SGLT2i vs. oGLD: p=0.001

Heterogeneity p-value: p<0.001

COMPOSITE OF ALL-CAUSE DEATH OR HHF



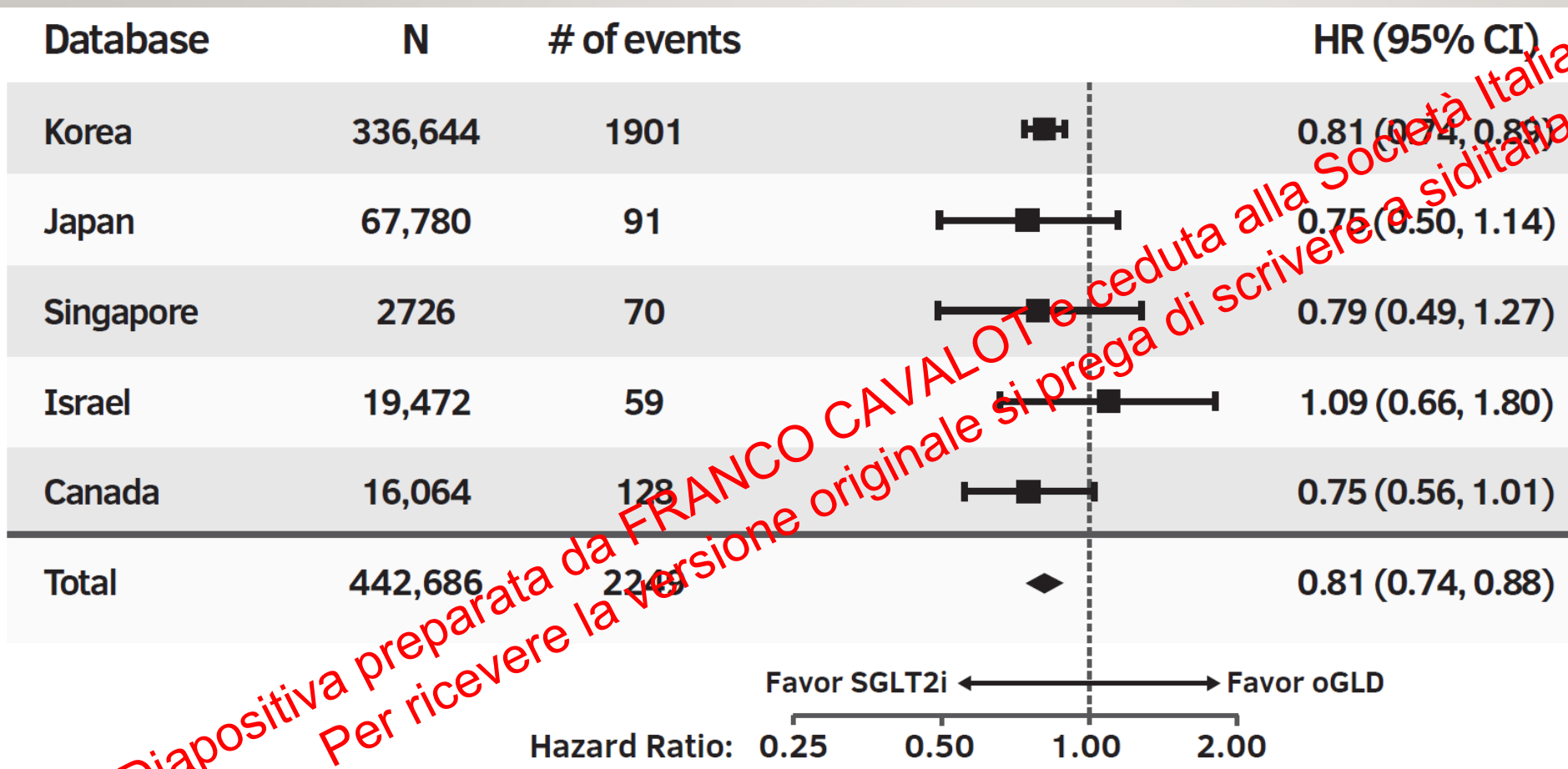
Kosiborod et al, JACC 2018

P-value for
SGLT2i vs. oGLD: $p < 0.001$

Heterogeneity p-value: $p < 0.001$

MYOCARDIAL INFARCTION

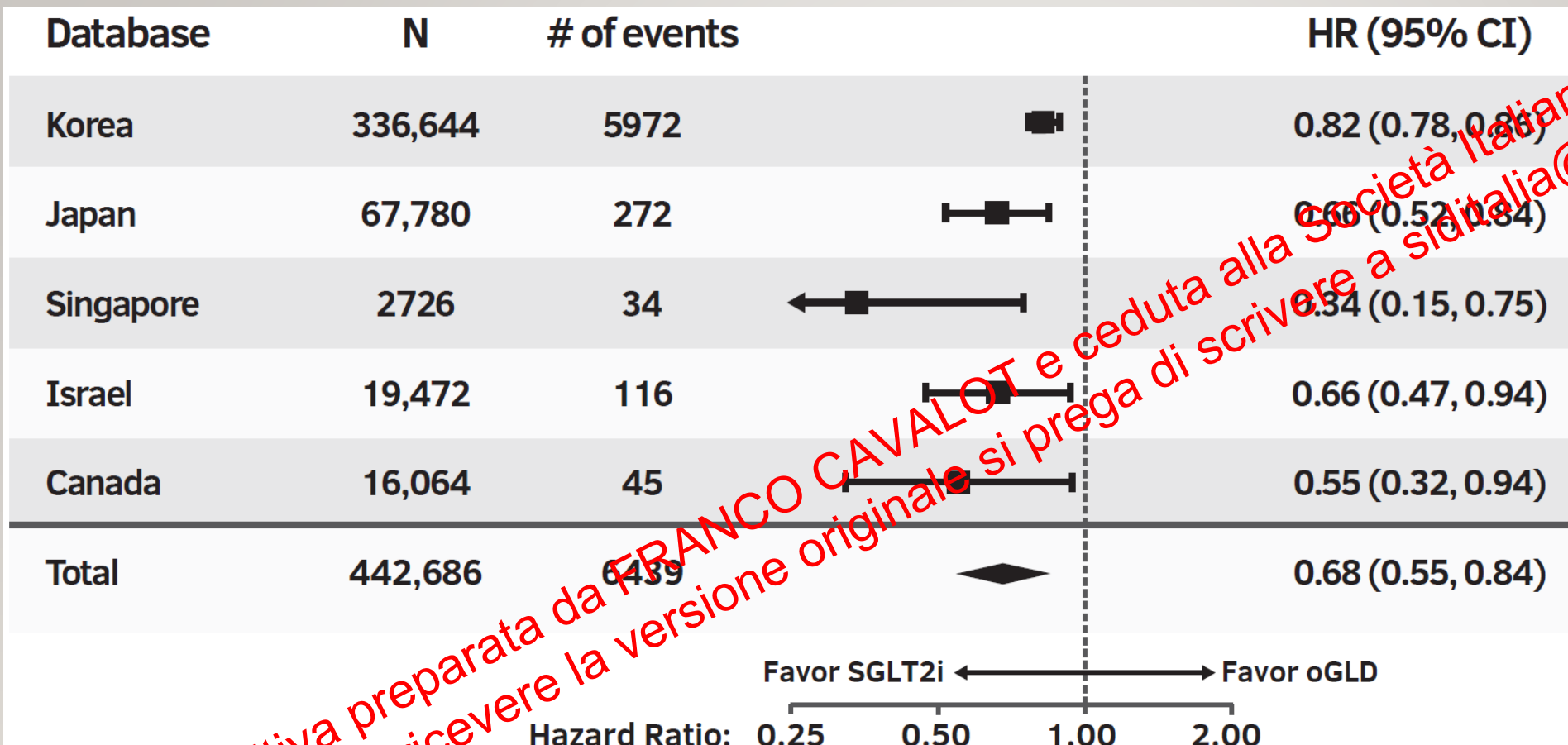
Kosiborod et al, JACC 2018



P-value for
SGLT2i vs. oGLD: $p < 0.001$

Heterogeneity p-value: $p = 0.787$

STROKE

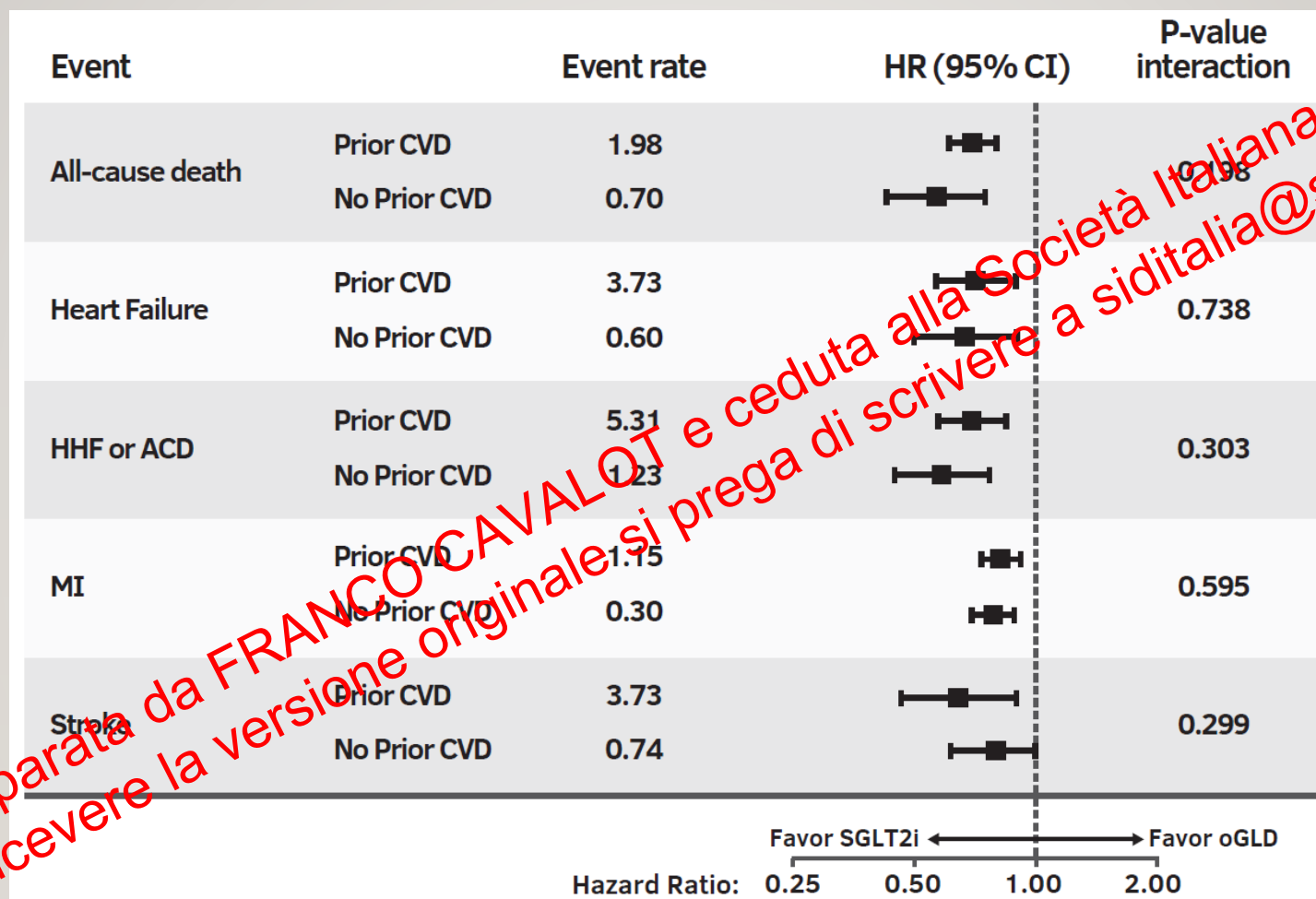


Kosiborod et al, JACC 2018

P-value for
SGLT2i vs. oGLD: $p < 0.001$

Heterogeneity p-value: $p = 0.029$

SUBGROUP ANALYSES – OUTCOMES WITH AND WITHOUT CVD AT BASELINE



Kosiborod et al, JACC 2018

Diapositiva preparata da FRANCO CAVALOT e ceduta alla Società Italiana di Diabetologia.
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CONCLUSIONI

- ...initiation of SGLT-2i as compared with oGLD was associated with significantly **lower risk of cardiovascular outcomes, including death, heart failure and atherothrombotic events.**
- Collectively, our results suggest that the cardiovascular benefits of SGLT-2i may be applicable to a **considerably broader patient population than previously considered.**

Kosiborod et al, JACC 2018

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METANALISI JAMA 2018

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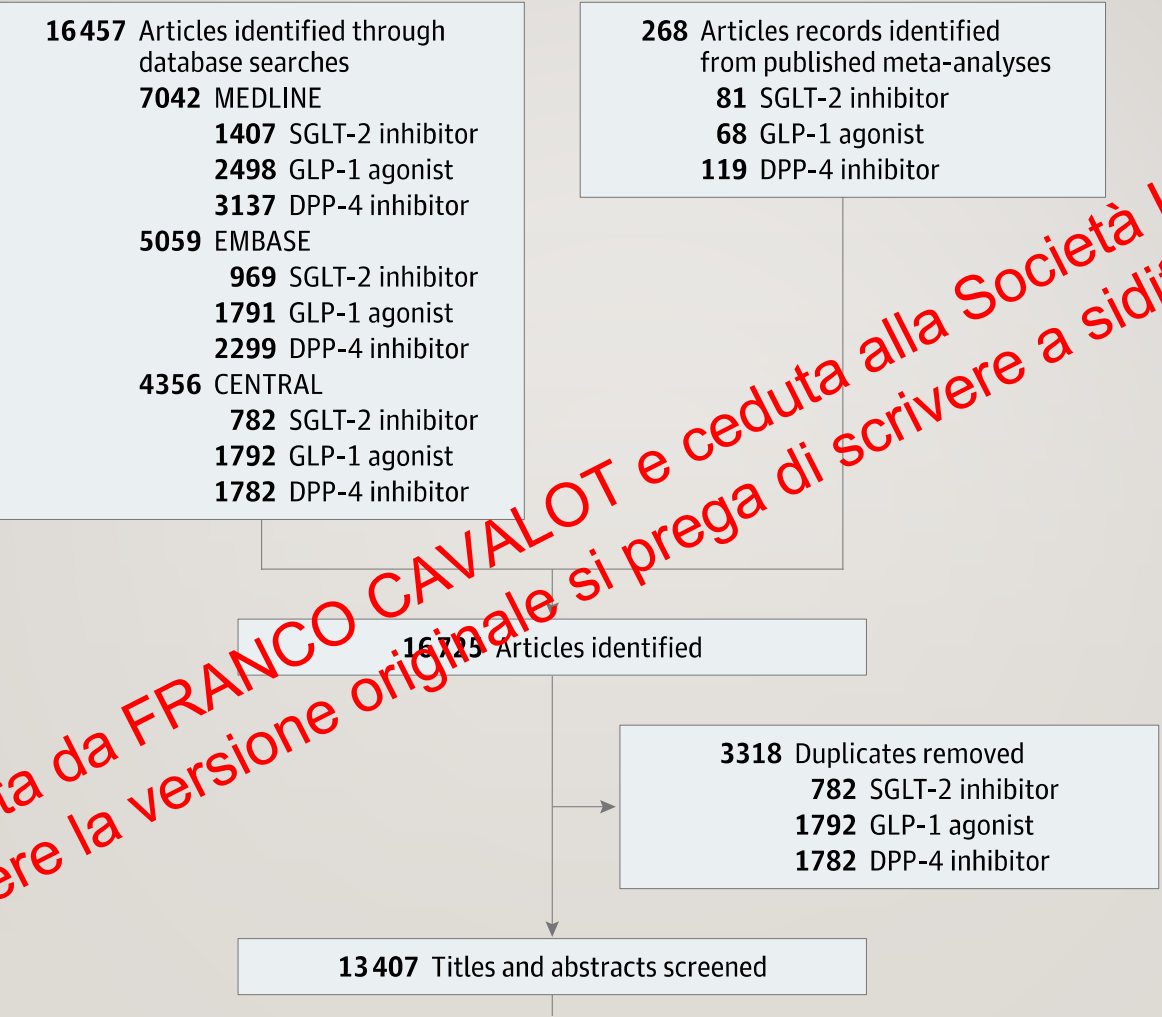


Figure Legend:

Summary of Study Retrieval and Identification for Network Meta-analysis DPP-4 indicates dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; and SGLT-2, sodium-glucose cotransporter 2.

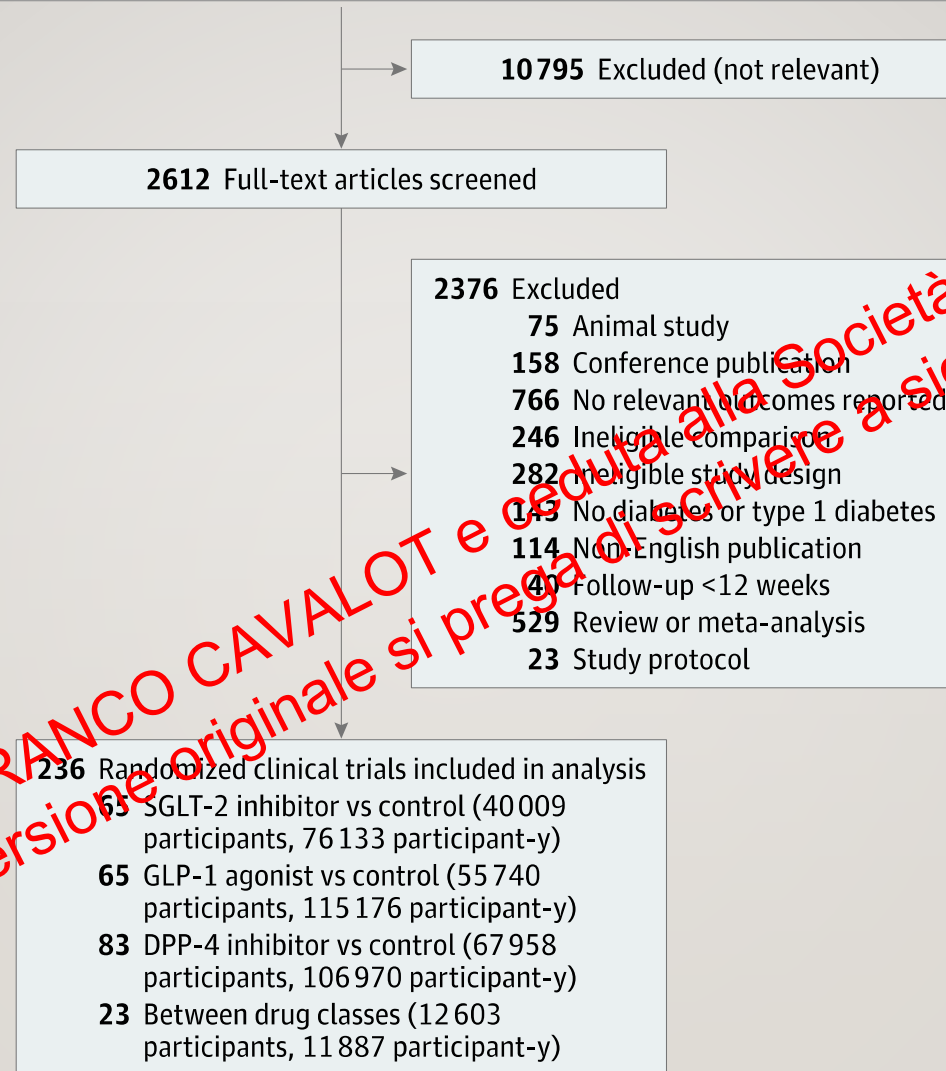
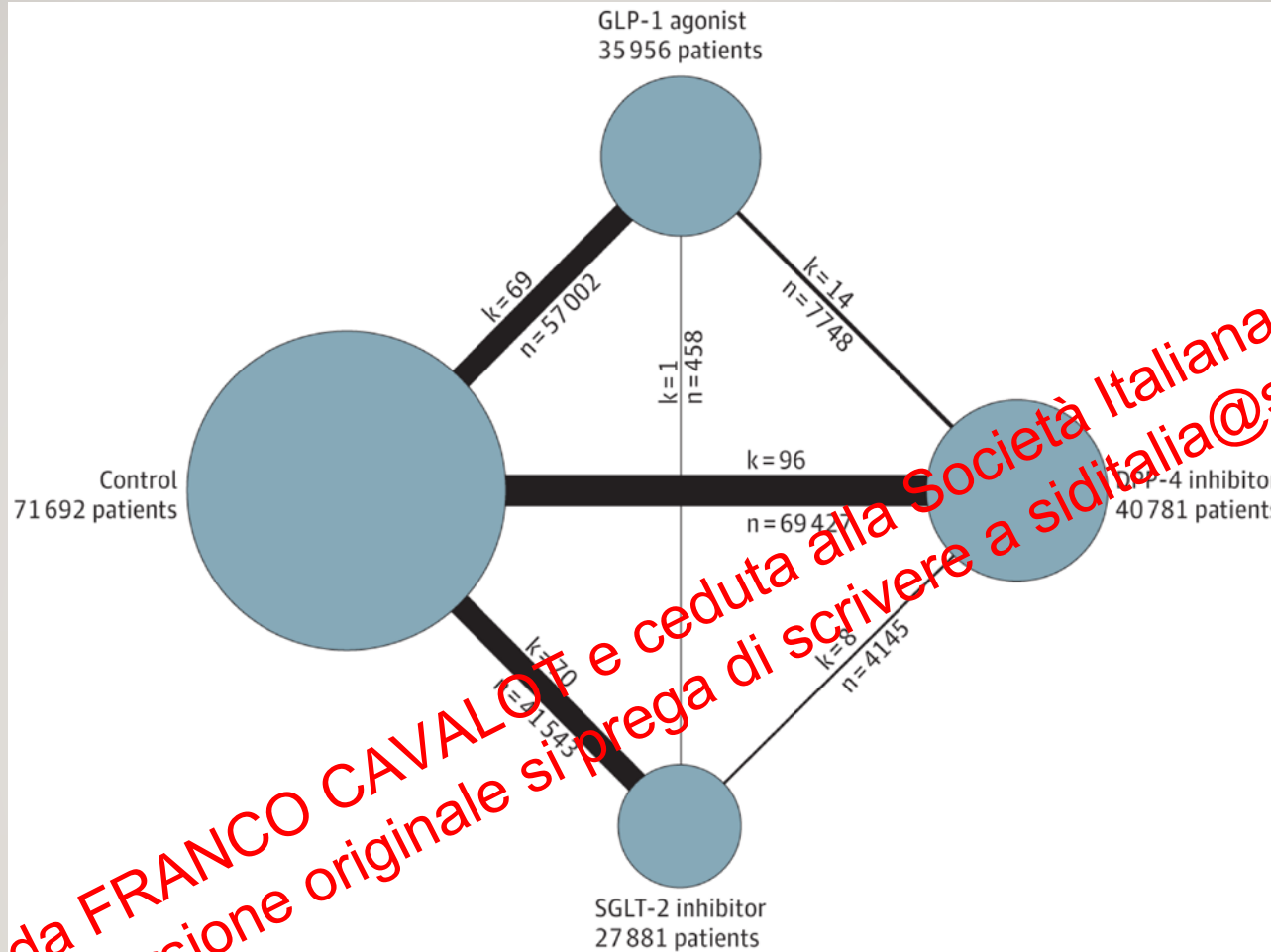


Figure Legend:

Summary of Study Retrieval and Identification for Network Meta-analysis DPP-4 indicates dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; and SGLT-2, sodium-glucose cotransporter 2.



Network Plot for All Studies. Graphical representation of network for all included trials. Connecting lines represent head-to-head comparisons between drugs, indicated by nodes. Multigroup trials contribute multiple comparisons, resulting in 258 comparisons from 236 trials. The thickness of lines between nodes is proportional to the number of trials comparing the treatments. The sizes of the nodes are proportional to the number of patients in each treatment. Patients may be included in multiple comparisons: for example, in a study of 3 groups consisting of control and 2 different drug classes, the control group is compared with each drug class. This is accounted for within the network model and does not constitute duplication of participants.

DPP-4 indicates dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; k, the number of comparisons; n, the number of patients per comparison; and SGLT-2, sodium-glucose cotransporter 2.

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Table. Study Participant Characteristics^a

Drug Type	No. of Trials	Total No. Randomized	Mean (SD)			
			Men, %	Age, y	BMI	HbA _{1c} , %
DPP-4 inhibitor vs control	83	67 958	54.7 (9.4)	57.9 (5.3)	29.3 (2.9)	8.16 (0.61)
GLP-1 agonist vs control	65	55 740	55.1 (11.4)	57.1 (3.8)	31.5 (3.5)	8.11 (0.36)
SGLT-2 inhibitor vs control	65	40 009	57.9 (10.4)	58.0 (3.7)	29.3 (5.0)	8.05 (0.32)
DPP-4 inhibitor vs GLP-1 agonist	14	8024	50.9 (7.5)	52.9 (4.4)	32.6 (2.3)	8.2 (0.20)
DPP-4 inhibitor vs SGLT-2 inhibitor	8	4011	56.0 (5.5)	55.5 (2.1)	30.9 (1.2)	8.0 (0.39)
GLP-1 agonist vs SGLT-2 inhibitor	1	458				

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HbA_{1c}, hemoglobin A_{1c}; SGLT2, sodium-glucose cotransporter 2.

^a The Table represents data from studies stratified by the intervention and comparator. Control refers to placebo or no treatment. There was 1 study assessing GLP-1 agonist compared with a SGLT-2 inhibitor.

A Primary outcome: all-cause mortality, 97 trials; I² = 12%

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.1 (-0.3 to 0.6)	1.02 (0.94 to 1.11)
GLP-1 agonist		-0.6 (-1.0 to -0.3)	0.88 (0.81 to 0.94)
SGLT-2 inhibitor		-1.0 (-1.5 to -0.6)	0.80 (0.71 to 0.89)
Control	vs DPP-4 inhibitor	-0.1 (-0.4 to 0.2)	0.98 (0.90 to 1.06)
GLP-1 agonist		-0.5 (-0.9 to -0.2)	0.86 (0.77 to 0.96)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.4)	0.78 (0.68 to 0.90)
Control	vs GLP-1 agonist	0.6 (0.3 to 1.0)	1.14 (1.06 to 1.23)
DPP-4 inhibitor		0.7 (0.2 to 1.3)	1.17 (1.04 to 1.30)
SGLT-2 inhibitor		-0.4 (-0.9 to 0.2)	0.91 (0.79 to 1.04)
Control	vs SGLT-2 inhibitor	0.9 (0.4 to 1.5)	1.25 (1.12 to 1.40)
DPP-4 inhibitor		1.0 (0.4 to 1.7)	1.28 (1.11 to 1.47)
GLP-1 agonist		0.4 (-0.1 to 0.9)	1.10 (0.96 to 1.26)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	88	2955 (5.2)	57 022
DPP-4 inhibitor	49	1171 (3.9)	30 178
GLP-1 agonist	32	1195 (4.4)	27 373
SGLT-2 inhibitor	29	714 (3.6)	19 587

B Cardiovascular mortality, 56 trials; I² = 19%

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.0 (-0.3 to 0.4)	1.00 (0.90 to 1.11)
GLP-1 agonist		-0.5 (-0.8 to -0.1)	0.85 (0.77 to 0.94)
SGLT-2 inhibitor		-0.8 (-1.1 to -0.3)	0.79 (0.69 to 0.91)
Control	vs DPP-4 inhibitor	0.0 (-0.3 to 0.3)	1.00 (0.90 to 1.10)
GLP-1 agonist		-0.5 (-0.8 to -0.1)	0.84 (0.74 to 0.98)
SGLT-2 inhibitor		-0.7 (-1.1 to -0.2)	0.79 (0.66 to 0.94)
Control	vs GLP-1 agonist	0.5 (0.2 to 0.9)	1.17 (1.06 to 1.30)
DPP-4 inhibitor		0.5 (-0.1 to 1.1)	1.18 (1.02 to 1.36)
SGLT-2 inhibitor		-0.2 (-0.7 to 0.3)	0.93 (0.78 to 1.10)
Control	vs SGLT-2 inhibitor	0.8 (0.3 to 1.3)	1.27 (1.10 to 1.46)
DPP-4 inhibitor		0.8 (0.2 to 1.5)	1.27 (1.07 to 1.51)
GLP-1 agonist		0.2 (-0.3 to 0.8)	1.08 (0.91 to 1.29)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	50	1833 (3.6)	50 869
DPP-4 inhibitor	27	763 (3.1)	24 519
GLP-1 agonist	19	704 (3.0)	23 554
SGLT-2 inhibitor	19	468 (2.5)	18 407

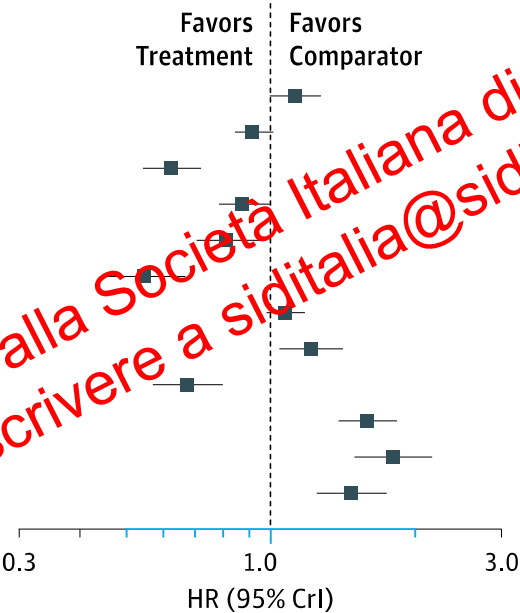
Forest Plots for All-Cause Mortality, Cardiovascular Mortality, and Heart FailureAll outcomes are reported in hazard ratios (HRs) for treatment vs the comparator and 95% credible intervals (CrIs). Absolute risk differences (RDs) were calculated by multiplying the RD by the event rate in the comparator group. The 95% CrIs for absolute RDs are calculated by multiplying the 95% CrIs by the event rate in the comparator group. Heterogeneity was assessed using the I² statistic; low heterogeneity was determined by an I² of 25% or less. The x-axis scale shown in blue indicates the range of the HR from 0.5 to 2.0. Tables below the forest plots show, for each drug class, the number of trials, number of participants with events, and the total number of randomized participants. For example, for all-cause mortality, 88 trials randomized 57 022 participants to the control treatment with 2955 participants having events, and 49 trials randomized 30 178 participants to DPP-4 inhibitors with 1171 participants having events. Control represents either placebo or no treatment; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; and SGLT-2, sodium-glucose cotransporter 2.



C Heart failure events, 58 trials; I² = 19%

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.4 (0.0 to 0.8)	1.13 (1.00 to 1.28)
GLP-1 agonist		-0.2 (-0.5 to 0.1)	0.93 (0.84 to 1.02)
SGLT-2 inhibitor		-1.1 (-1.3 to -0.8)	0.62 (0.54 to 0.72)
Control	vs DPP-4 inhibitor	-0.3 (-0.5 to 0.0)	0.88 (0.78 to 1.00)
GLP-1 agonist		-0.4 (-0.7 to -0.1)	0.82 (0.70 to 0.95)
SGLT-2 inhibitor		-1.1 (-1.3 to -0.8)	0.55 (0.46 to 0.67)
Control	vs GLP-1 agonist	0.2 (-0.1 to 0.5)	1.08 (0.98 to 1.18)
DPP-4 inhibitor		0.6 (0.1 to 1.1)	1.22 (1.05 to 1.42)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.5)	0.67 (0.57 to 0.78)
Control	vs SGLT-2 inhibitor	1.0 (0.6 to 1.4)	1.60 (1.30 to 1.84)
DPP-4 inhibitor		1.3 (0.8 to 2.0)	1.81 (1.50 to 2.18)
GLP-1 agonist		0.8 (0.4 to 1.3)	1.48 (1.25 to 1.76)

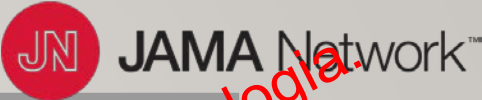
Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	55	1370 (2.8)	48 363
DPP-4 inhibitor	24	644 (2.4)	26 527
GLP-1 agonist	21	638 (2.7)	23 363
SGLT-2 inhibitor	19	466 (1.7)	15 989



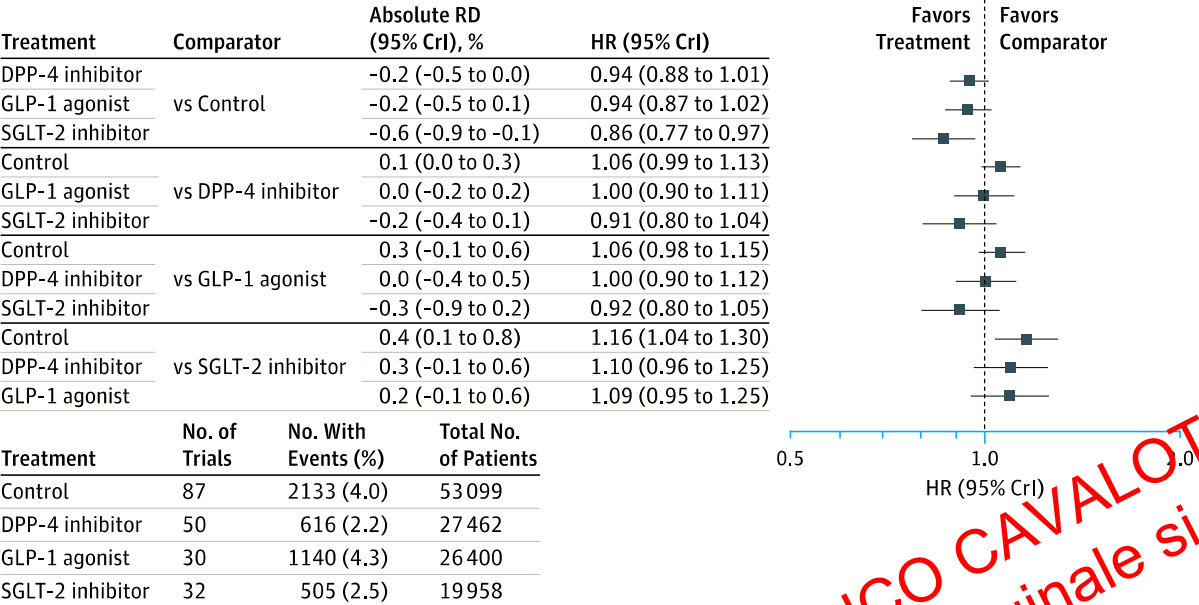
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From: Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 DiabetesA Systematic Review and Meta-analysis

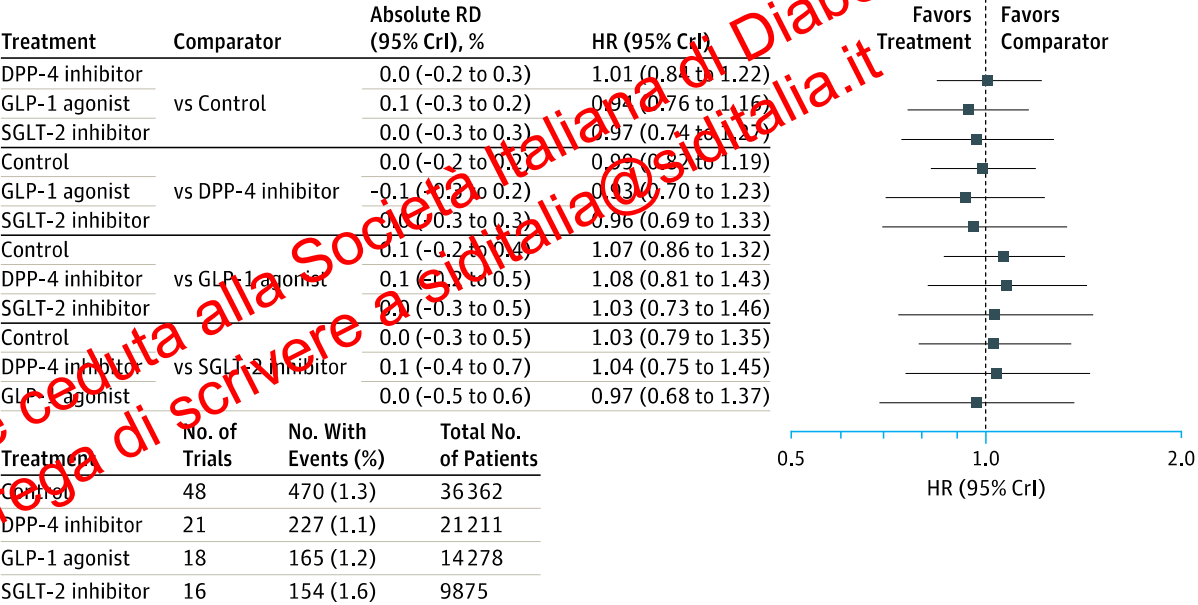
JAMA. 2018;319(15):1580-1591. doi:10.1001/jama.2018.3024



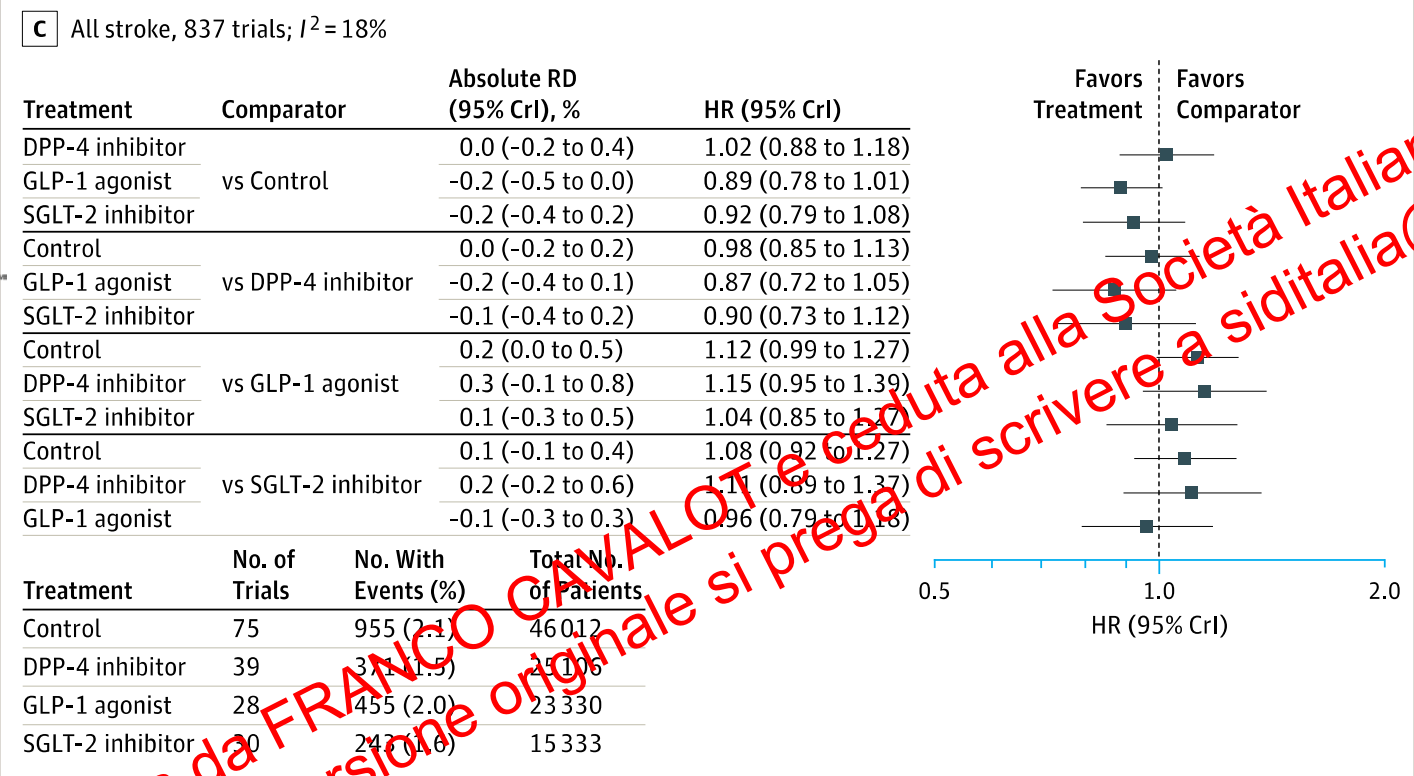
A All myocardial infarction, 97 trials; I² = 15%



B Unstable angina, 50 trials; I² = 20%



Forest Plots for Myocardial Infarction, Unstable Angina, and StrokeAll outcomes are reported in hazard ratios (HRs) for treatment vs the comparator and 95% credible intervals (CrIs). Absolute risk differences (RDs) were calculated by multiplying the RD by the event rate in the comparator group. The 95% CrIs for absolute RDs are calculated by multiplying the 95% CrIs by the event rate in the comparator group. Heterogeneity was assessed using the I² statistic; low heterogeneity was determined by an I² of 25% or less. The x-axis scale shown in blue indicates the range of the HR from 0.5 to 2.0. Tables below the forest plots show for each drug class, the number of trials, number of participants with events, and the total number of randomized participants. For example, for all myocardial infarction, 87 trials randomized 53 099 participants to the control treatment with 2133 participants having events, and 50 trials randomized 27 462 participants to DPP-4 inhibitors with 616 participants having events. Control represents either placebo or no treatment; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; and SGLT-2, sodium-glucose cotransporter 2.



Forest Plots for Myocardial Infarction, Unstable Angina, and StrokeAll outcomes are reported in hazard ratios (HRs) for treatment vs the comparator and 95% credible intervals (CrIs). Absolute risk differences (RDs) were calculated by multiplying the RD by the event rate in the comparator group. The 95% CrIs for absolute RDs are calculated by multiplying the 95% CrIs by the event rate in the comparator group. Heterogeneity was assessed using the I^2 statistic; low heterogeneity was determined by an I^2 of 25% or less. The x-axis scale shown in blue indicates the range of the HR from 0.5 to 2.0. Tables below the forest plots show for each drug class, the number of trials, number of participants with events, and the total number of randomized participants. For example, for all myocardial infarction, 87 trials randomized 53 099 participants to the control treatment with 2133 participants having events, and 50 trials randomized 27 462 participants to DPP-4 inhibitors with 616 participants having events. Control represents either placebo or no treatment; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; and SGLT-2, sodium-glucose cotransporter 2.



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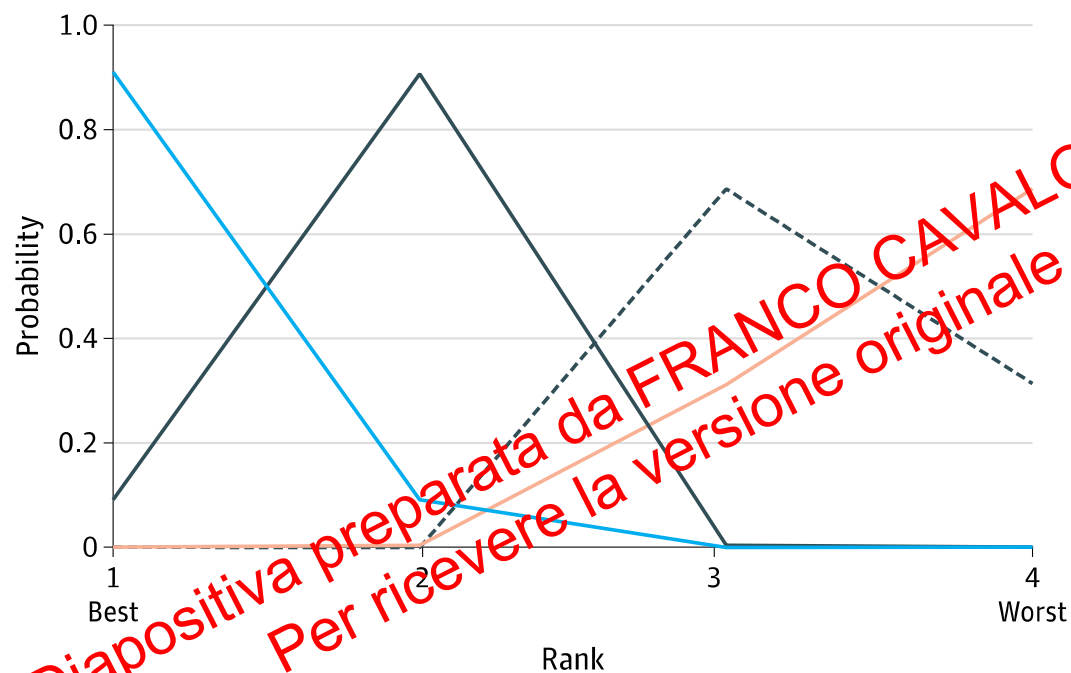
A Primary outcome: all-cause mortality

97 Trials

6035 Patients with events

134160 Patients

291245 Patient-years



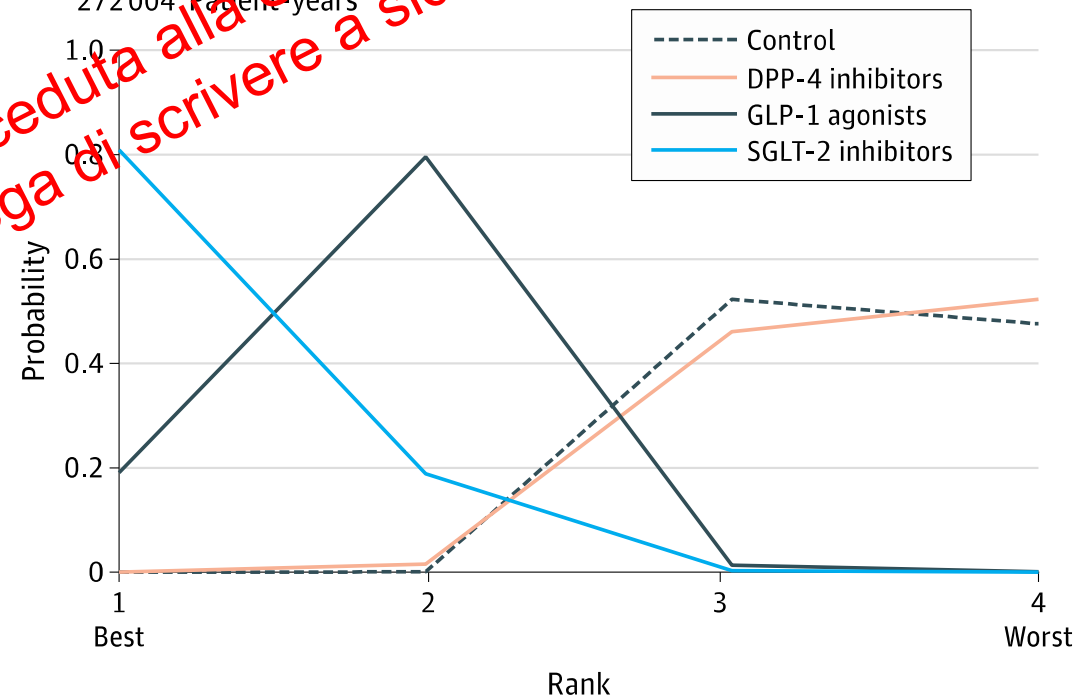
B Cardiovascular mortality

56 Trials

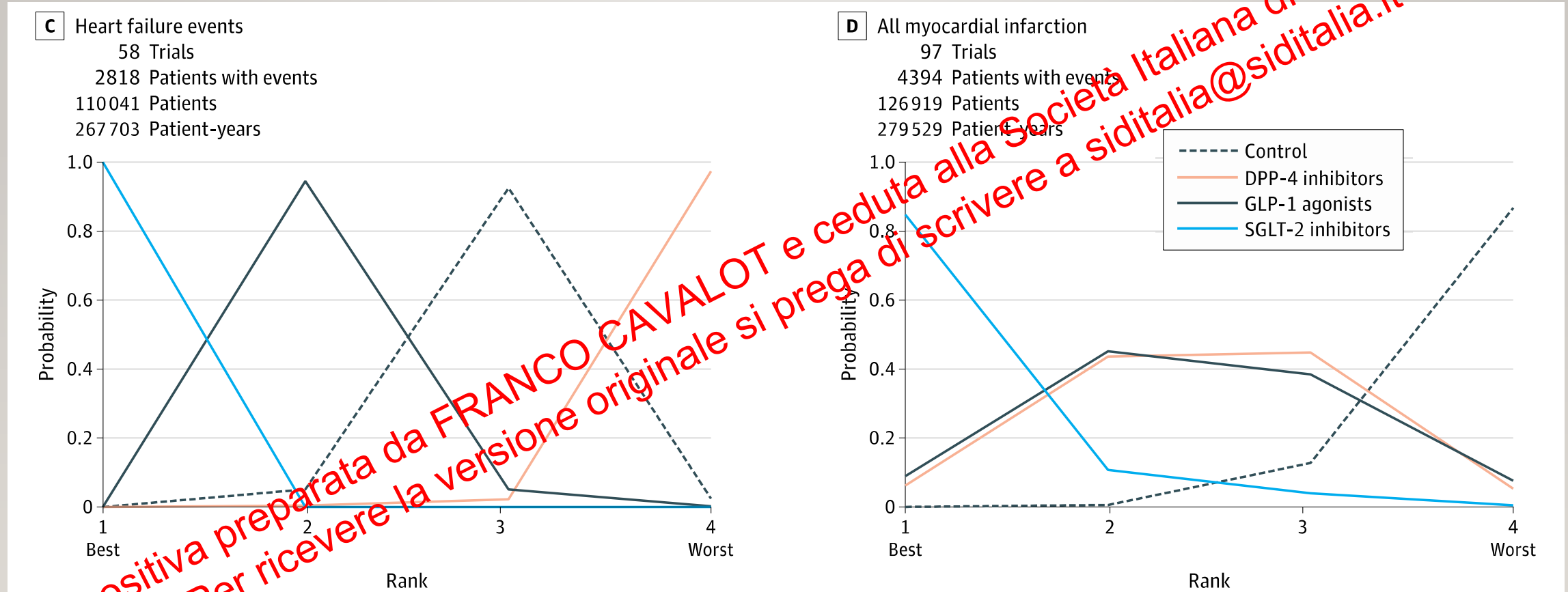
3818 Patients with events

115349 Patients

272004 Patient-years



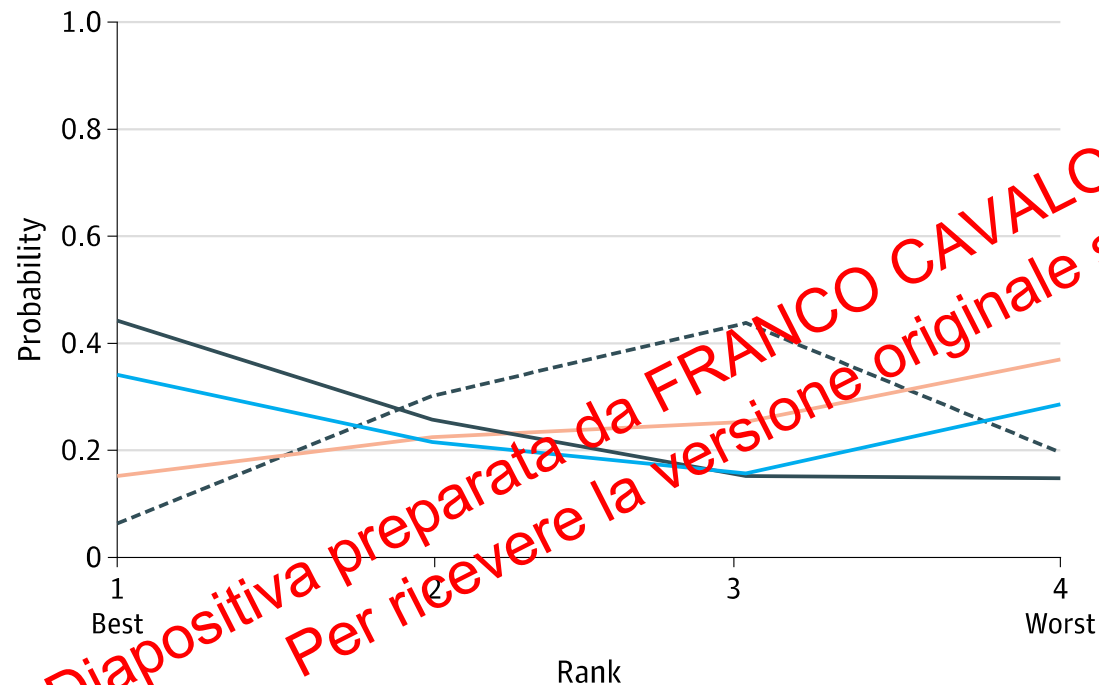
Ranking Plots Drug ranking plots for primary and secondary outcomes are stratified by treatment. Each line represents 1 drug class and shows the probability of its ranking from best to worst. The peak of the line represents the rank that the drug is most likely to be for each given outcome. For example, for all-cause mortality, sodium-glucose cotransporter 2 (SGLT-2) inhibitors are most likely to rank best; glucagon-like peptide 1 (GLP-1) agonists, second best; control, third best; and dipeptidyl peptidase 4 (DPP-4) inhibitors, worst. Control includes placebo and no treatment.



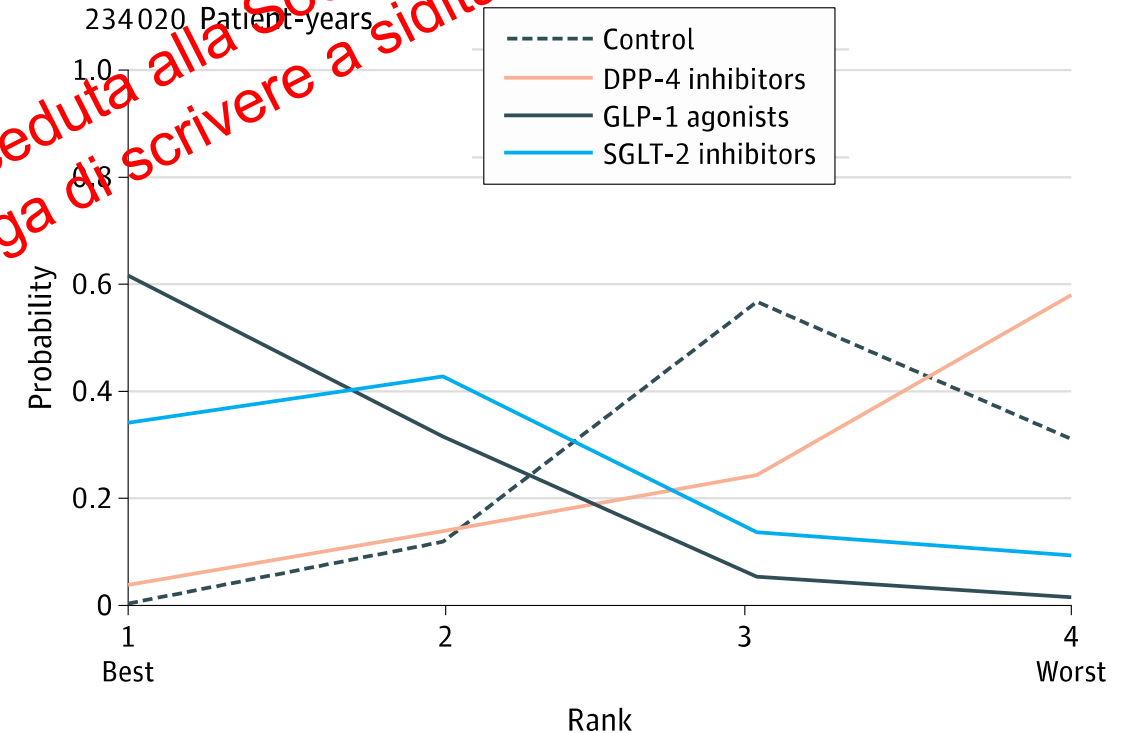
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E Unstable angina
50 Trials
1016 Patients with events
81726 Patients
179666 Patient-years



F All stroke
83 Trials
2024 Patients with events
109781 Patients
234020 Patient-years



Ranking Plots Drug ranking plots for primary and secondary outcomes are stratified by treatment. Each line represents 1 drug class and shows the probability of its ranking from best to worst. The peak of the line represents the rank that the drug is most likely to be for each given outcome. For example, for all-cause mortality, sodium-glucose cotransporter 2 (SGLT-2) inhibitors are most likely to rank best; glucagon-like peptide 1 (GLP-1) agonists, second best; control, third best; and dipeptidyl peptidase 4 (DPP-4) inhibitors, worst. Control includes placebo and no treatment.

CONCLUSIONI METANALISI

- In this network meta-analysis of 236 trials enrolling 176 310 participants with type 2 diabetes, **SGLT-2 inhibitors and GLP-1 agonists were associated with reductions in all-cause and cardiovascular mortality** compared with DPP-4 inhibitors and the control groups.
- The **SGLT-2 inhibitors were associated with additional cardiovascular** benefits for **heart failure events** compared with incretin-based therapies and control groups and for MI events compared with control groups.
- Of the 3 classes tested, SGLT-2 inhibition may be preferred over the incretin-based therapies based on their association with lower mortality and their favorable adverse event profile.

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CONCLUSIONI METANALISI

- Compared with control groups, the use of **SGLT-2 inhibitors** was associated with **absolute risk reductions (RRs) in all-cause and cardiovascular mortality of 1% and 0.8%**, respectively. For the same outcomes, **GLP-1 agonists** had more modest absolute RRs of **0.6% and 0.5%**, respectively.
- Given **that absolute RR depends on the baseline risk**, it is probable that these estimates are greater in higher-risk populations with a corresponding lower number needed to treat and better cost-effectiveness.
- The magnitudes of these absolute RRs using SGLT-2 inhibitors and GLP-1 agonists are important in the context of established standards of care in diabetes. For example, the associated absolute RR in mortality has been shown to be 0.5% for lowering blood pressure and 0.9% for lowering low-density lipoprotein cholesterol (per mmol/L reduction).

Metanalisi

Xin-Lin et al, J Am Heart Assoc. 2018

Cardiovascular Safety, Long-Term Noncardiovascular Safety, and Efficacy of Sodium–Glucose Cotransporter 2 Inhibitors in Patients With Type 2 Diabetes Mellitus: A Systemic Review and Meta-Analysis With Trial Sequential Analysis

Xin-Lin Zhang, MD;* Qing-Qing Zhu, MD;* Yu-Han Chen, MD; Xue-Ling Li, MD; Fu Chen, MD; Jian-An Huang, MD; Biao Xu, MD, PhD

J AM HEART ASSOC. 2018;7:E007165. DOI: 10.1161/JAHA.117.007165.

Diapositiva preparata da FRANCO CHESALOT
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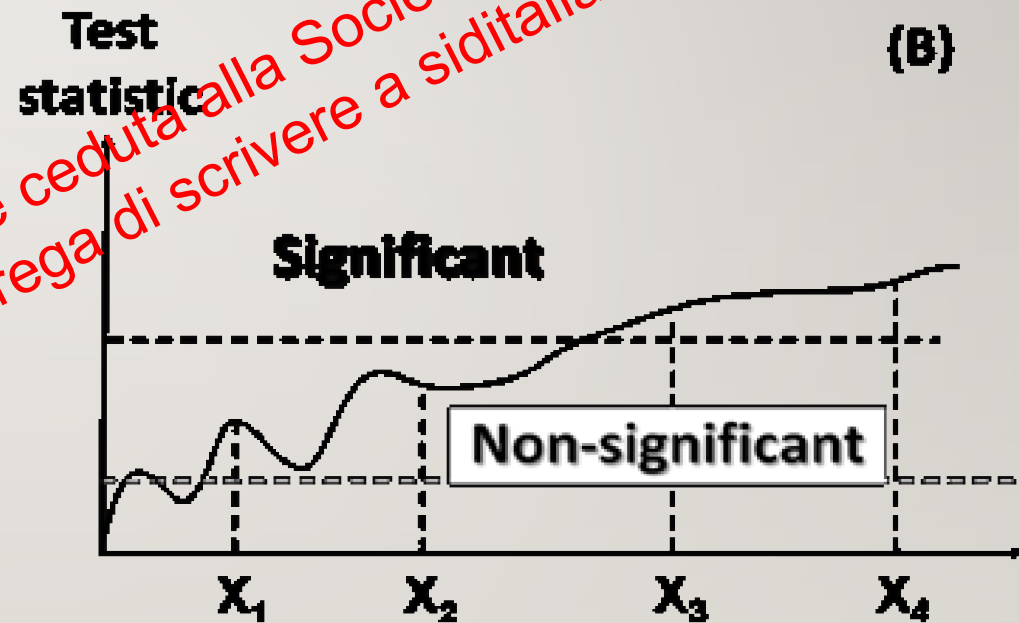
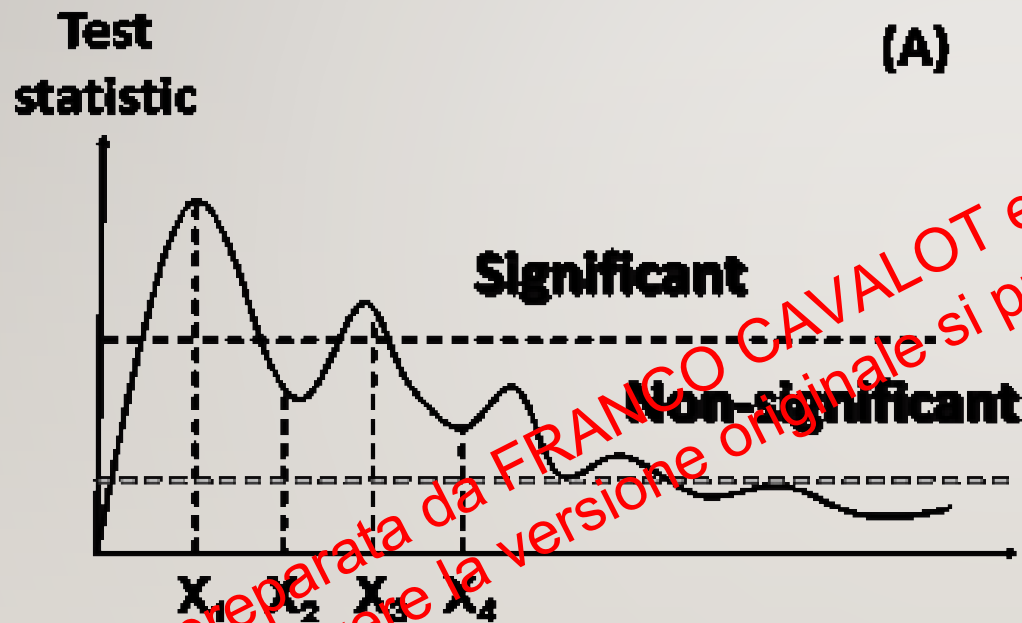
Metanalisi

Xin-Lin et al, J Am Heart Assoc. 2018

-
- In this context, ... a meta-analysis of RCTs and observational studies to determine the cardiovascular and long-term noncardiovascular safety of SGLT2 inhibitors and performed **trial sequential analysis (TSA)** to reduce type I error in meta-analysis to confirm and determine whether conclusions from meta-analyses were conclusive.
 - also evaluated all long-term efficacy of SGLT2 inhibitors.

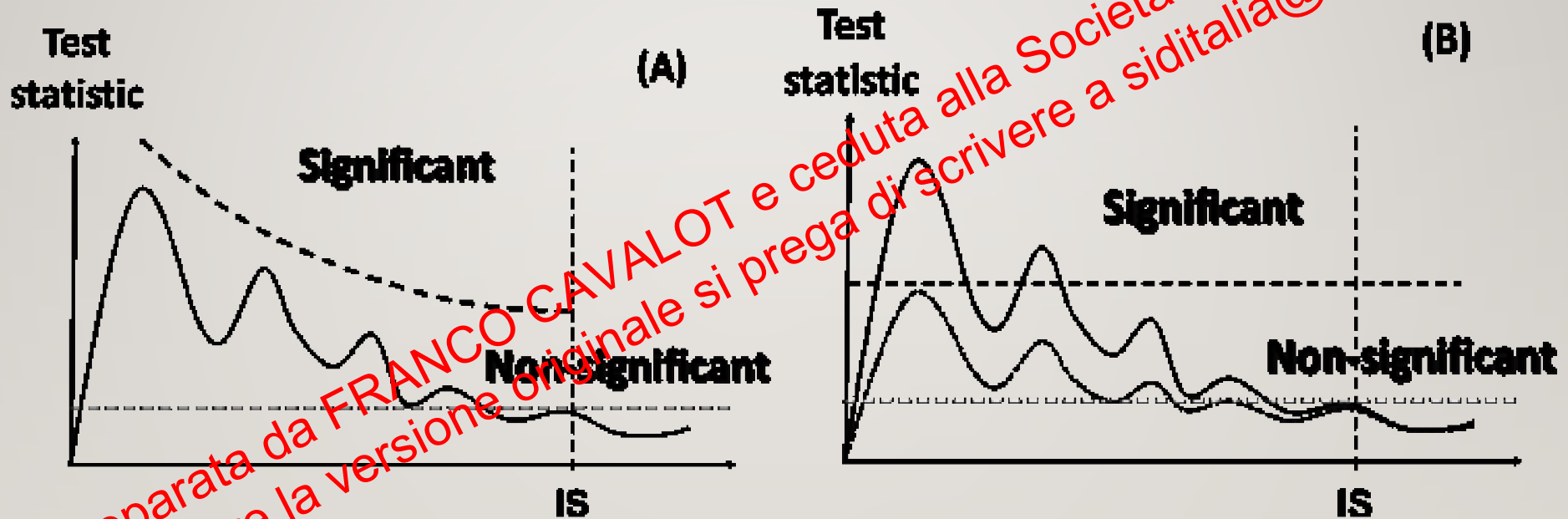
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TRIAL SPECIFIC ANALYSIS (TSA)



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TRIAL SPECIFIC ANALYSIS (TSA)

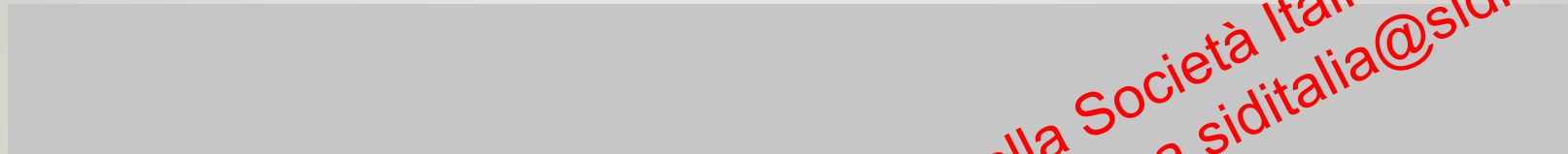


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Xin-Lin et al, J Am Heart Assoc. 2018



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XIN-LIN ET AL, J AM HEART ASSOC. 2018

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- First, meta-analyses for cardiovascular outcomes analysis with 351,476 patients showed that SGLT2 inhibitors were associated with a statistically **significant reduction in risk of MACE, all-cause mortality, cardiovascular mortality, nonfatal MI, and hospitalization for heart failure.**
 - Second, TSA provided firm evidence of a 20% reduction in MACE, all-cause mortality, and hospitalization for heart failure with SGLT2 inhibitors compared with control treatments, but **evidence remain inconclusive for cardiovascular mortality.**
 - Third, SGLT2 inhibitors were also associated with a **significant reduction in progression of albuminuria.**

Diapositiva preparata da FRANCO CAVALLIOT e ceduta alla Società Italiana di Diabetologia.
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METANALISI

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- Fourth, there was **no significant difference in risk of nonfatal stroke**.
- Fifth, SGLT2 inhibitors significantly **reduced incidence of hypoglycemia and acute kidney injury** but were associated with higher incidence of urinary tract infection and higher risk of genital infection in both female and male patients.
- Sixth, SGLT2 inhibitors showed **sustained reduction in HbA1c levels and a number of other metabolic risk factors**.

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METANALISI

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- **SGLT2 inhibitors showed remarkable cardiovascular- and renal-protective effects and good long-term noncardiovascular safety with sustained efficacy and should be strongly considered in type 2 diabetes mellitus patients with established or high risk of cardiovascular disease.**

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LOONEY TUNES



"That's all Folks!"

Frank Tashler

1954



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