

Come si spiega la riduzione di mortalità associata agli inibitori di SGLT2?



Andrea Natali

*Dipartimento di Medicina Clinica e Sperimentale
Università di Pisa*

Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Potenziale conflitto di interesse

Compensi ricevuti negli ultimi due anni

- Eli Lilly Invited speaker, research grant
- Boehringer Ingelheim Invited speaker, research grant

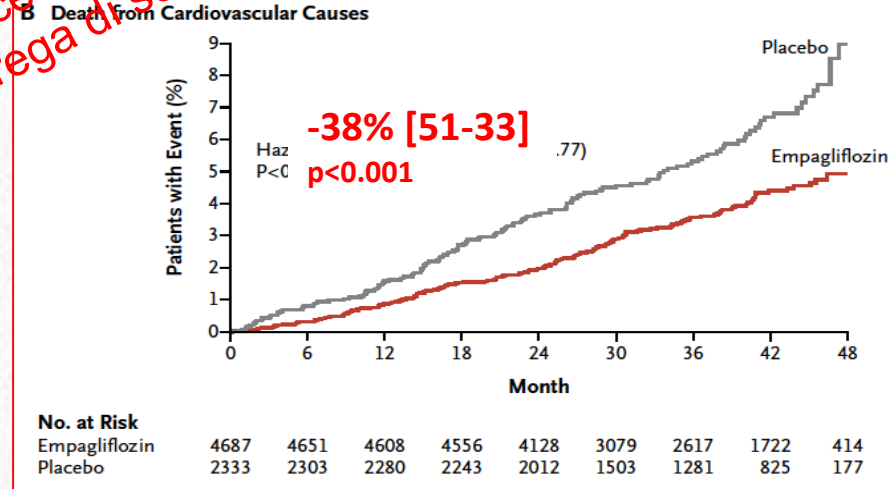
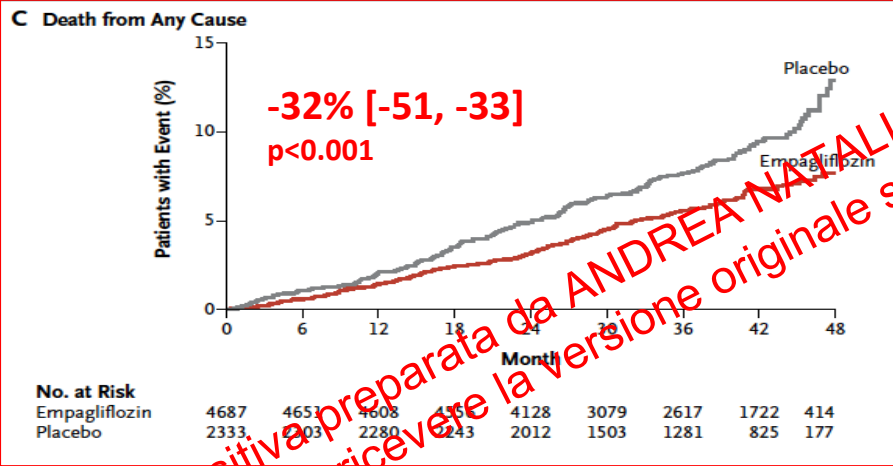
Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

SGLT2i e mortalità

- Quali e quanti eventi letali prevengono gli SGLT2i ?
- Effetto di classe ?
- Tutti gli SGLT2i funzionano in tutti i pazienti con DT2 ?
- Come fanno ?

Diapositiva preparata da ANDREA NATALE e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

EMPA-REG OUTCOMES



Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Cosa è successo ?

EMPA-REG

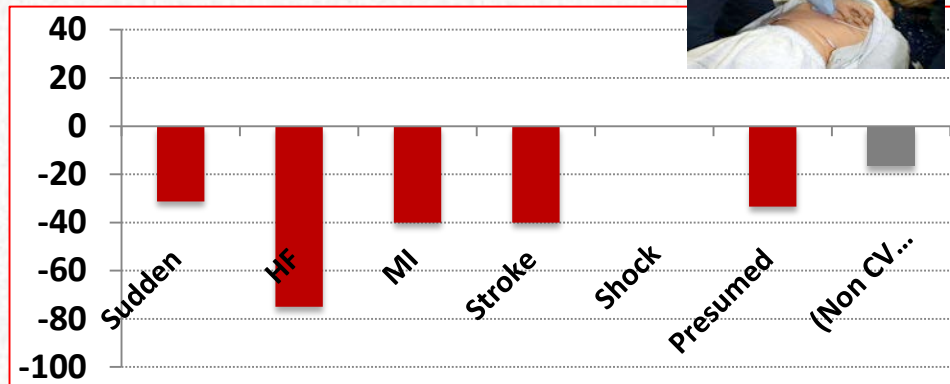
Variazione
%



Nf CHD

Fatal CVD

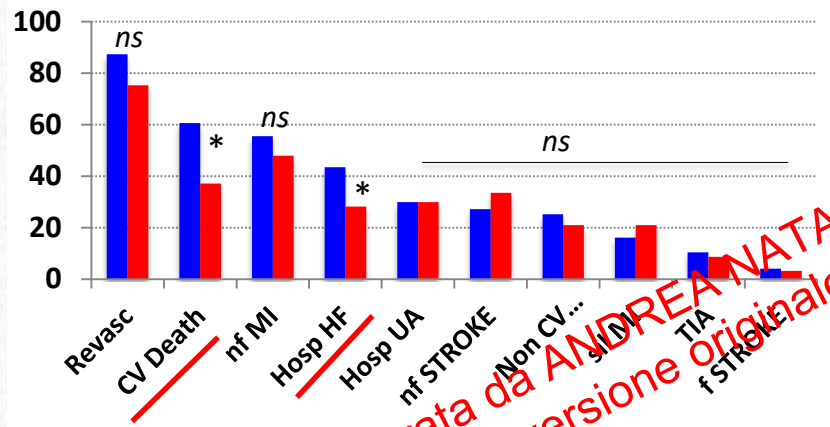
Variazione %



Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Riduzione assoluta degli eventi

Incidenza per 1000 pts per 3 aa



N° eventi "evitati" per 1000 pts per 3 aa

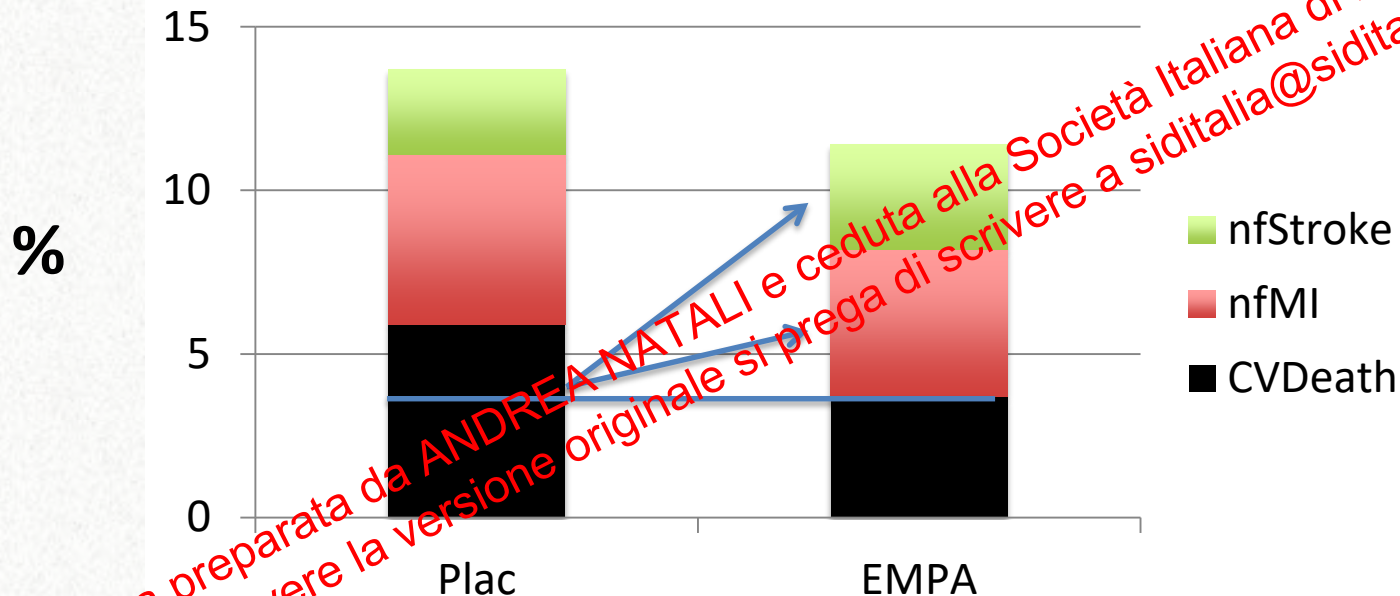


< Morte CV
< Scompenso

24 per 1000 = 2.4 per 100

NNT3y: $100/2.4 = 41$

Cosa è successo ?



Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

SGLT2i e mortalità

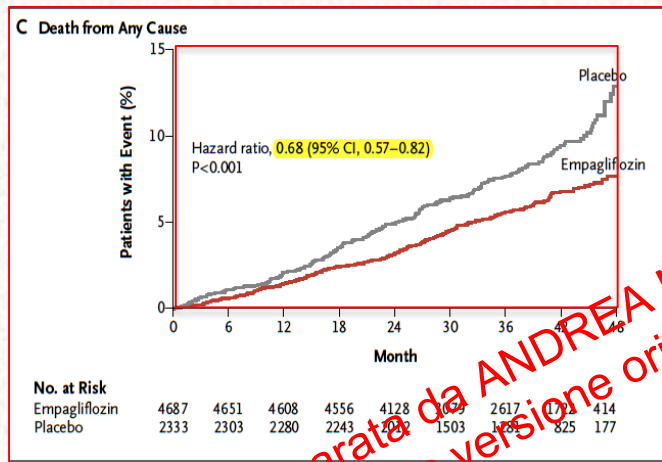
- Quali e quanti eventi letali prevenendo gli SGLT2i ?
- **Effetto di classe ?**
- Tutti gli SGLT2i funzionano in tutti i pazienti con DT2 ?
- Come farlo ?

Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

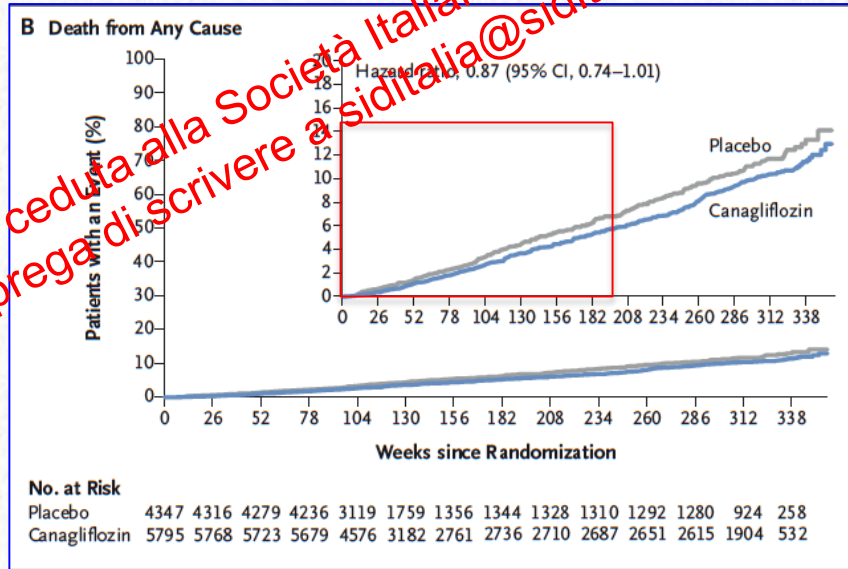
Any cause death: EMPA vs CANA



EMPAREG-OUTCOME



CANVAS



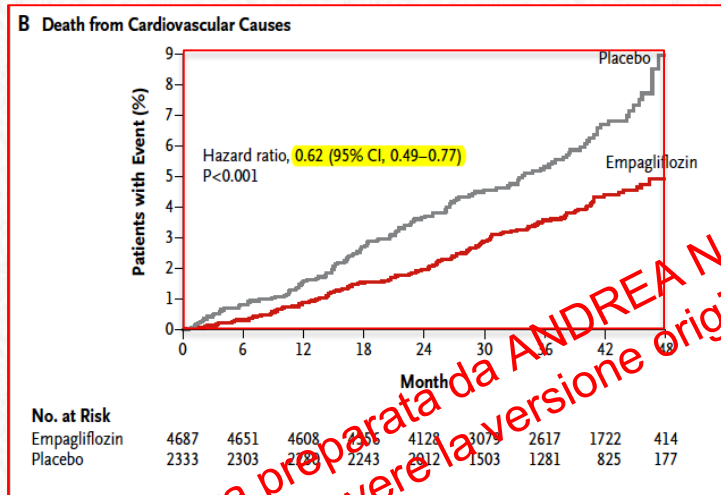
-13% ns

Diapositiva preparata da ANDREA NATALI e ceduta alla Societa Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it



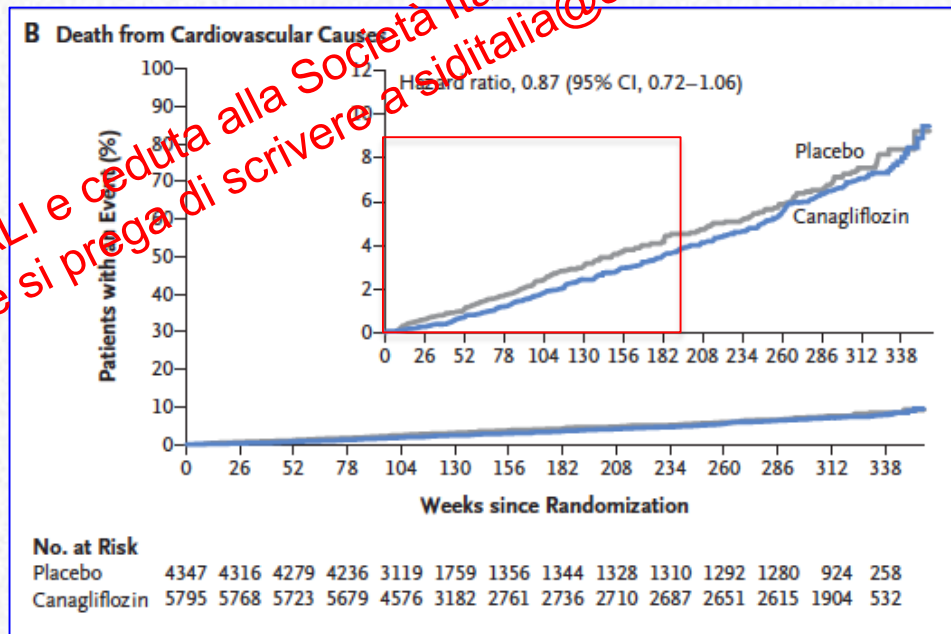
CV Death EMPA vs CANA?

EMPAREG-OUTCOME



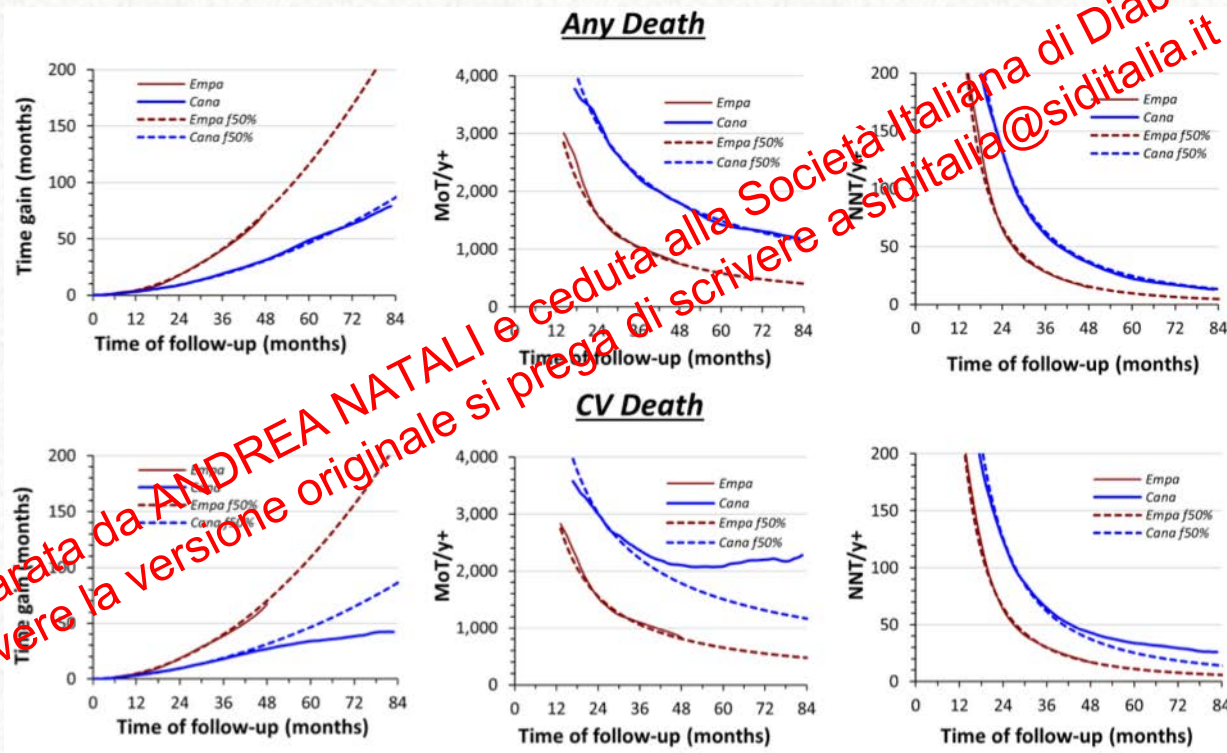
-38% p<0.001

CANVAS



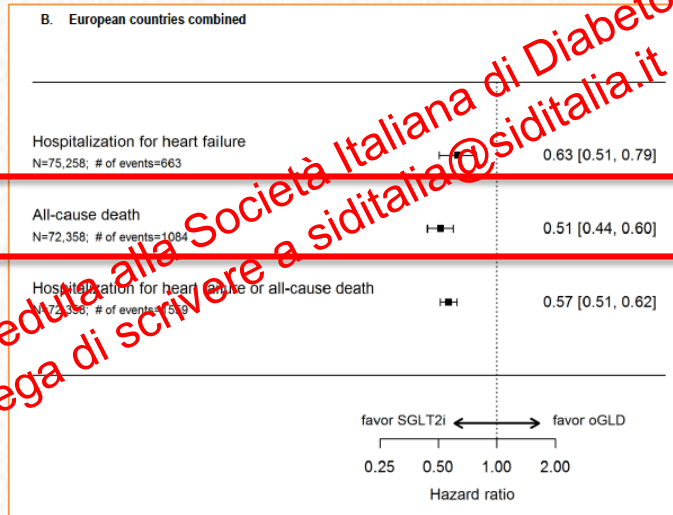
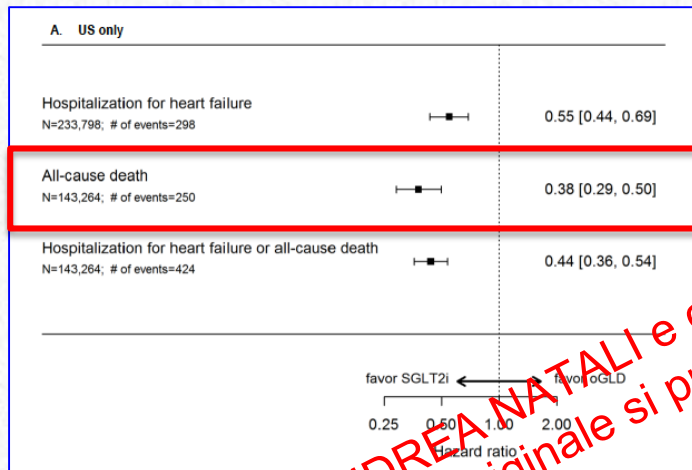
-13% ns

EMPA vs CANA

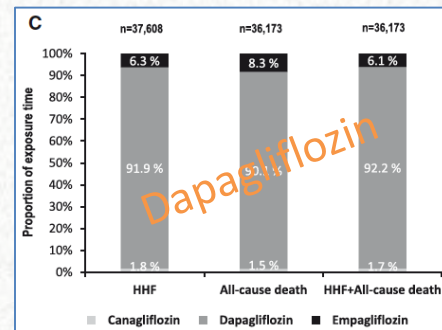
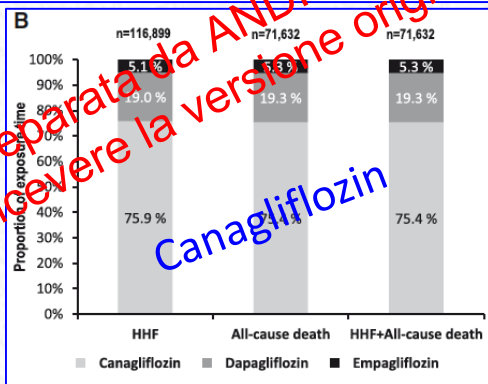


Class effect: real world data

-62% !



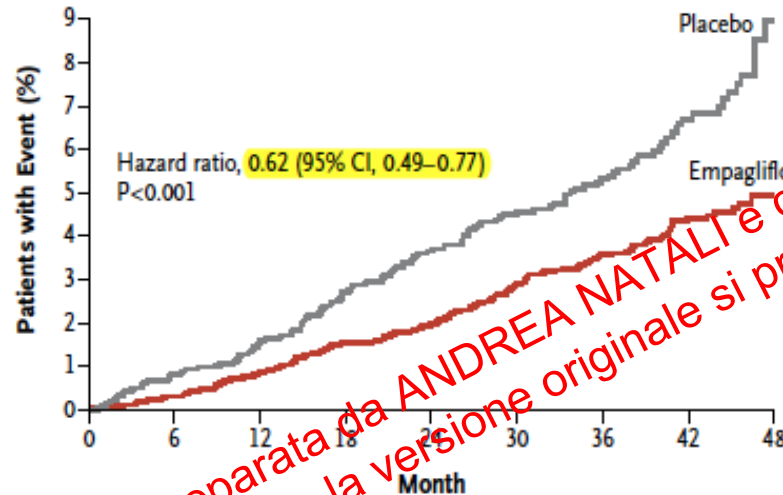
-49%



Class effect ?

EMPAREG-OUTCOMES

B Death from Cardiovascular Causes

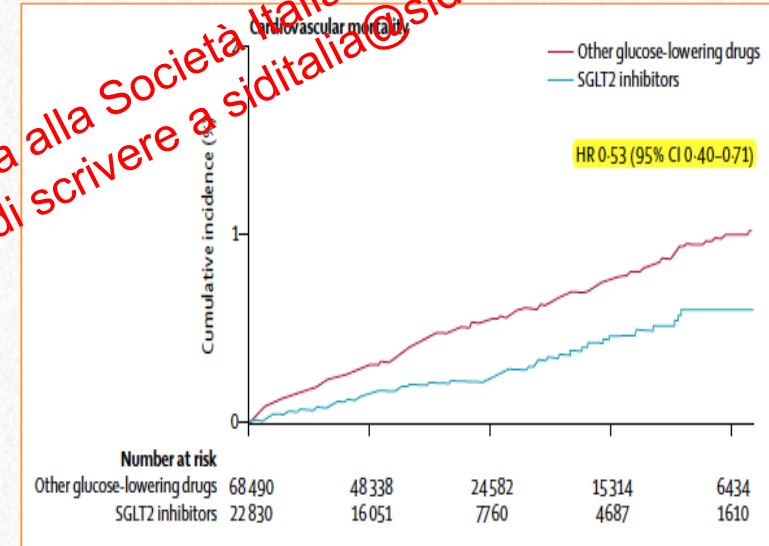


No. at Risk

Month	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2323	2303	2280	2243	2012	1503	1281	825	177

NNT/2yrs = 55

CVD-REAL NORDIC (DAPA 90%)



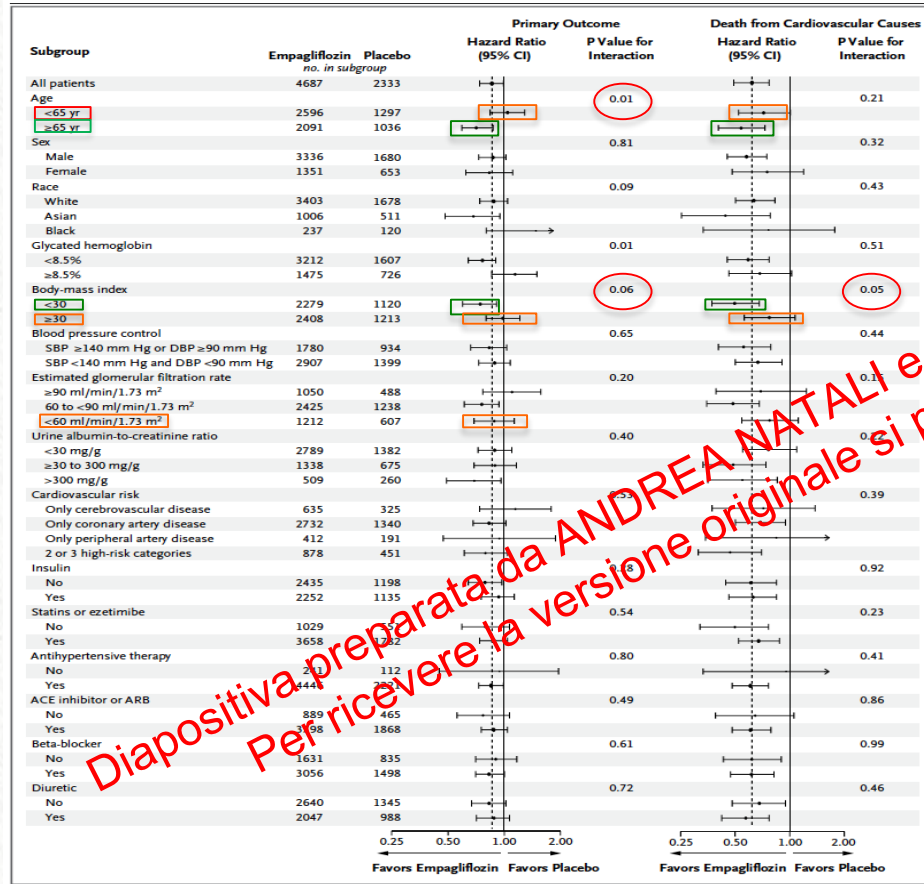
NNT/2yrs = 250

SGLT2i e mortalità

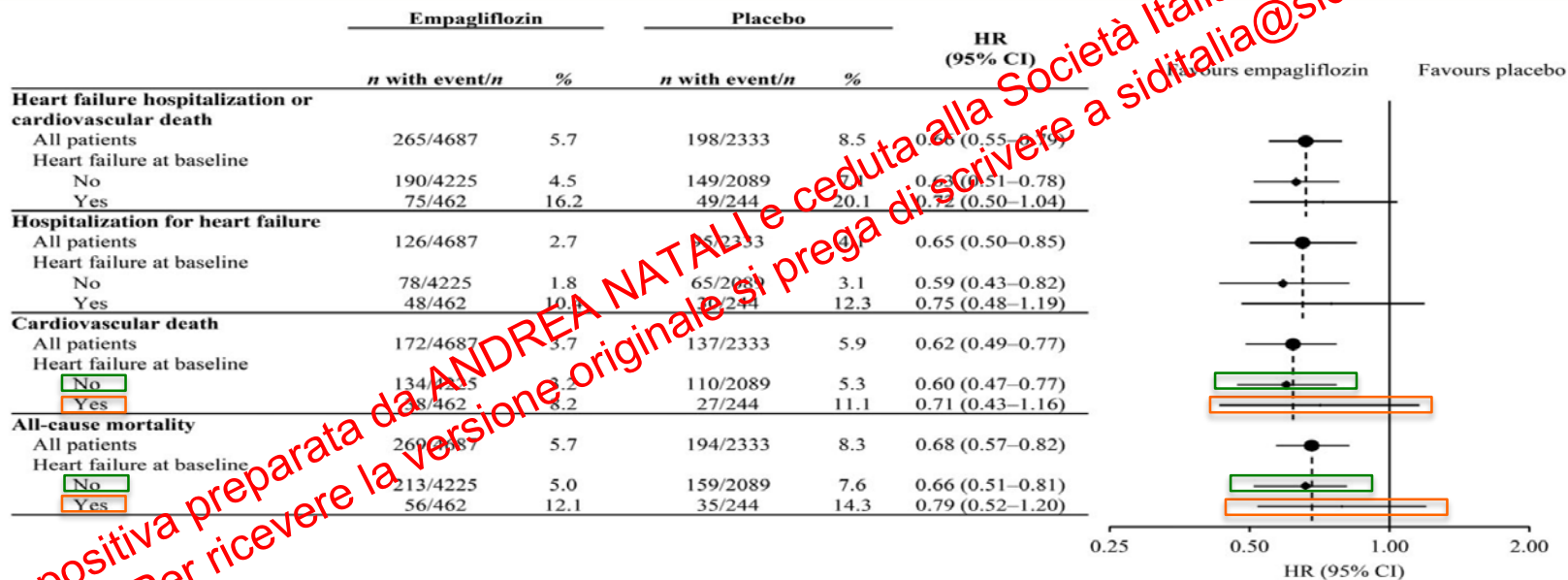
- Quali e quanti eventi letali prevenibili con gli SGLT2i ?
- Effetto di classe ?
- **Tutti gli SGLT2i funzionano in tutti i pazienti con DT2 ?**
- Come farlo ?

Diapositiva preparata da ANDREA NATALE e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

EMPA vs CANA le strane asimmetrie



Is EMPA effect driven by HF patients?



Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Is EMPA effect greater in pts with heart failure ?

Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME[®] trial

David Fitchett^{1*}, Javed Butler², Philippe van de Borne³, Bernard Zinman^{4,5}, John M. Lachin⁶, Christoph Wanner⁷, Hans J. Woerle⁸, Stefan Hantel⁹, Jyothis T. George⁸, Odd Erik Johansen¹⁰, and Silvio E. Inzucchi¹¹, on behalf of the EMPA-REG OUTCOME[®] trial investigators



Table 2 Cardiovascular deaths within various subgroups of patients with baseline and/or incident heart failure

HF subgroup	Placebo	Empagliflozin	HR (95% CI) ^a	Percentage of all CV deaths
HF _{BL} (N = 706)	22/244 (9.1%)	38/462 (8.2%)	0.71 (0.43, 1.16) <i>ns</i>	21.0
HHF (N = 221)	23/95 (24.2%)	18/126 (14.3%)	0.65 (0.35, 1.22) <i>ns</i>	13.3
HF _{AE} ^a (N = 347)	37/143 (26.6%)	36/204 (17.6%)	0.73 (0.46, 1.16) <i>ns</i>	23.9
Patients with HF burden (HF _{BL} , HHF, or HF _{AE}) (N = 958)	54/353 (15.3%)	63/605 (10.4%)	0.67 (0.47, 0.97)	37.9
Patients without HF burden (N = 6062)	83/1980 (4.2%)	109/4082 (2.7%)	0.63 (0.48, 0.84)	62.1

Time to CV death derived from randomization for patients with HF_{BL} and from date of first HF episode for patients with HHF or HF_{AE}.

HR, hazard ratio; CI, confidence interval; HF, heart failure; HF_{BL}, heart failure at baseline; HHF, hospitalization for heart failure; HF_{AE}, heart failure reported as an adverse event by the investigator, according to preferred terms of narrow SMQ 'cardiac failure'.

^aHazard ratio and confidence intervals determined from Cox proportional hazards model.

Is CANA effect greater in pts with heart failure ?



CVD

ACD

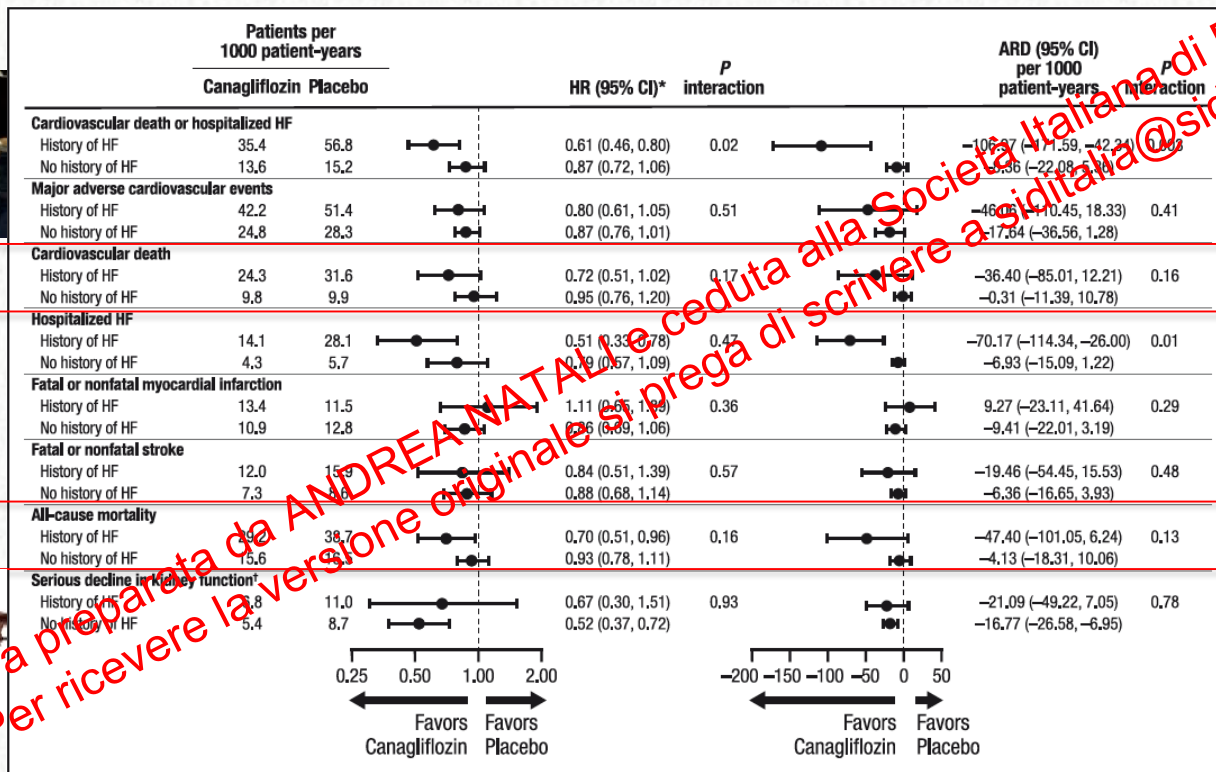


Figure 2. Proportional and absolute effects of canagliflozin compared with placebo on cardiovascular and renal outcomes in patients with and without a history of heart failure at baseline.

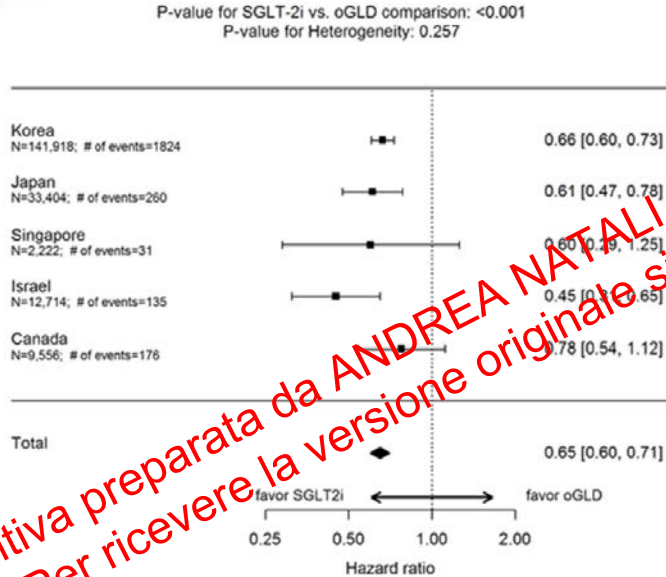
Probably

In real world, if any, it is less effective in HF

New SGLT-2i vs oGLD (n=235,064 x 2)



D/E/C
80/11/0
24/19/11
74/17/8
36/64/0
51/11/39



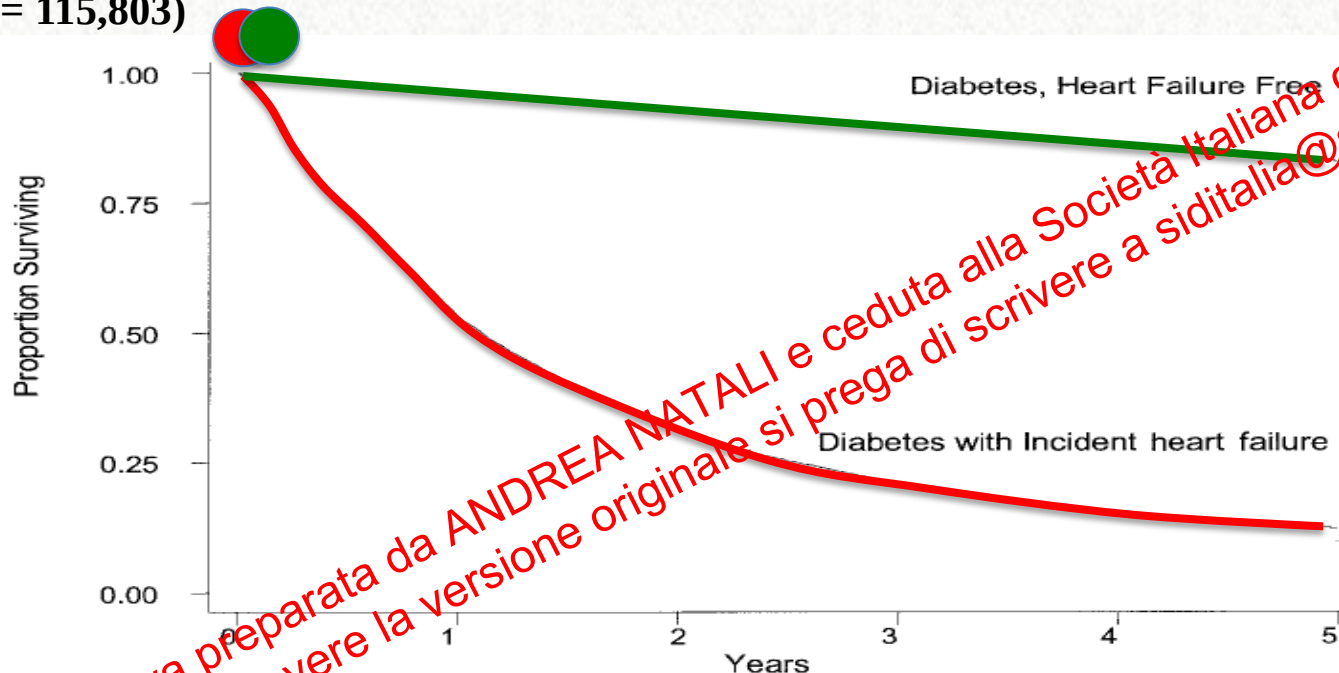
Online Figure 7. Subgroup analyses for all-cause death including age, gender, chronic kidney disease, cardiovascular and diabetes medications at baseline (intent-to-treat; adjusted)



Kosiborod M, JACC 2018

T2D&HF in the real world

(n = 115,803)

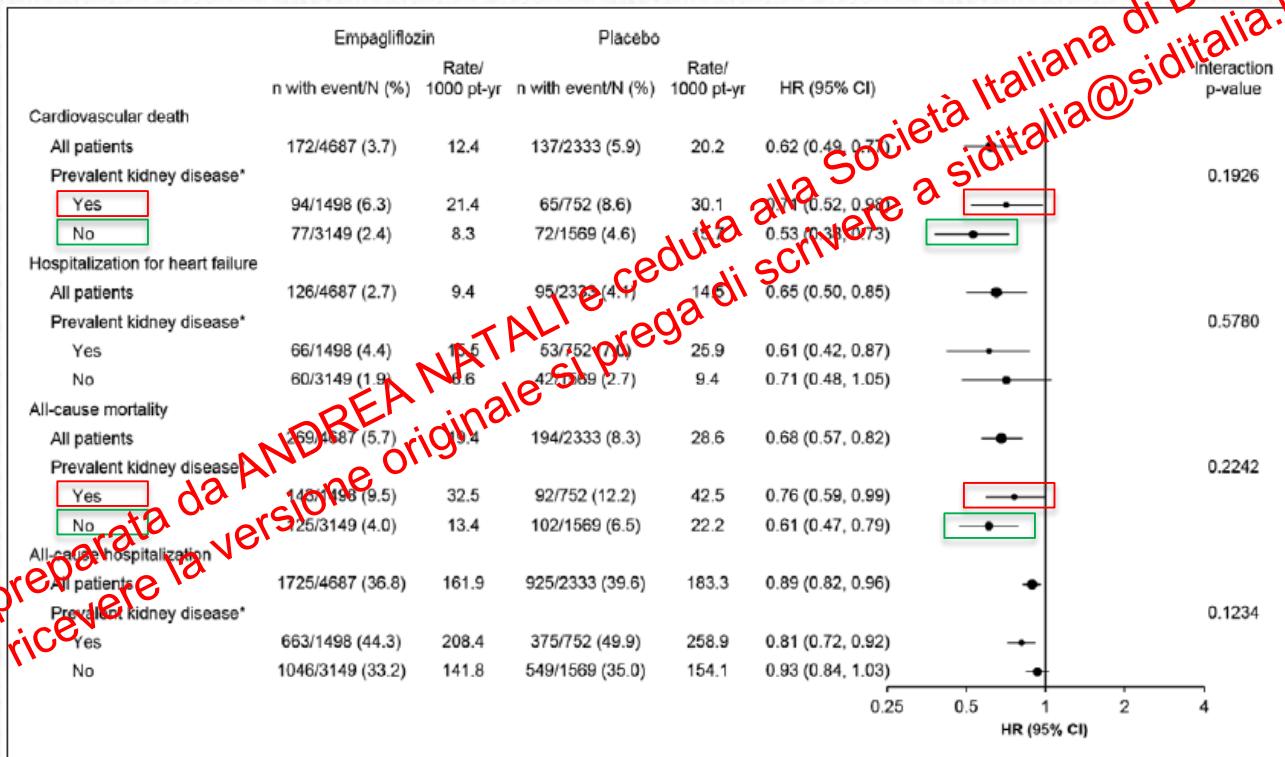


n = 45,542 (39%)

Figure 1—Five-year Kaplan-Meier survival estimates for 115,803 adults age ≥ 65 years in fee-for-service Medicare with diabetes by incident heart failure status.

EMPA&death: no better in pt. with CKD

2,250 (32%) eGFR≤60 and/or MA



SGLT2i e mortalità

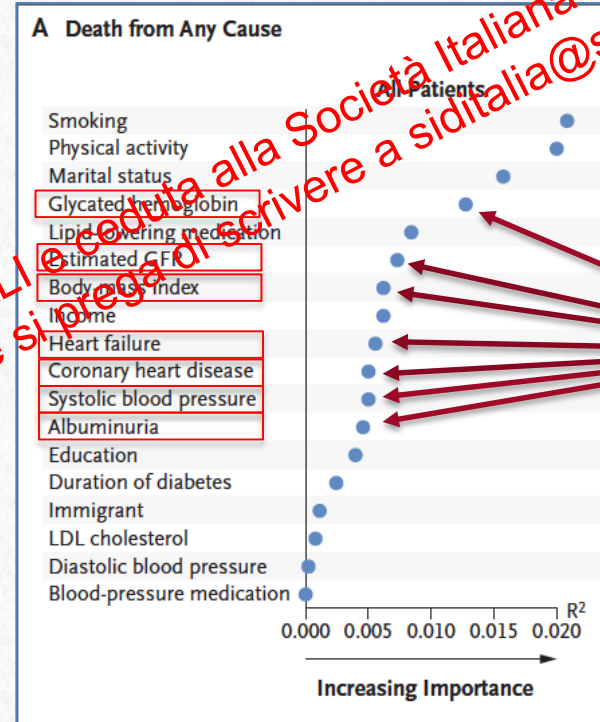
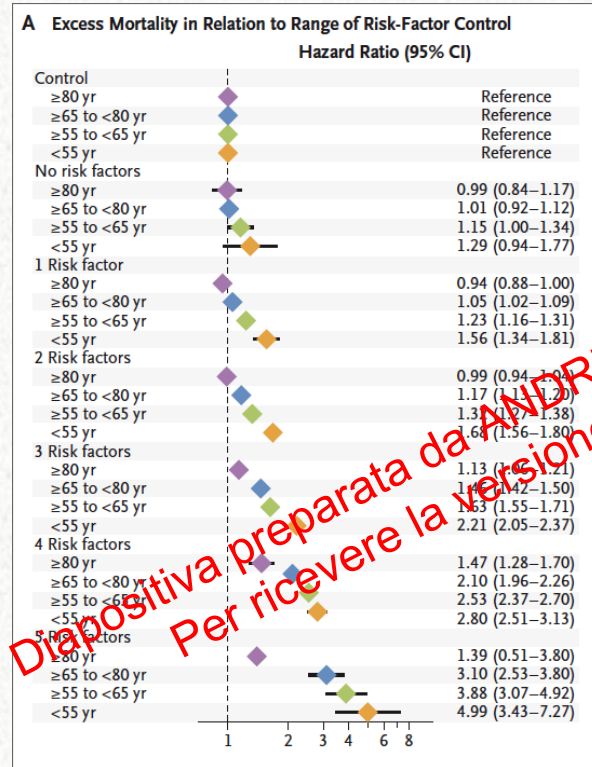
- Quali e quanti eventi letali prevenendo gli SGLT2i ?
- Effetto di classe ?
- Tutti gli SGLT2i funzionano in tutti i pazienti con DT2 ?
- **Come fanno ?**

Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

N Engl J Med 2018;379:633-44.

HbA1c, LDL-C, UALB, smoking, BP



SGLT-2i

Ipoglicemia ?

CV death

Placebo	-	-	0.94 (0.75 to 1.20) 1 study; 5238 patients	1.00 (0.90 to 1.10) $i^2=21.3\%$ 5 studies; 37076 patients	0.63 (0.51 to 0.78) $i^2=0.0\%$ 4 studies; 8609 patients
0.75 (0.33 to 1.70)	Metformin	1.62 (0.72 to 3.68) $i^2=0.0\%$ 2 studies; 3199 patients	1.81 (0.39 to 8.47) $i^2=0.0\%$ 2 studies; 5135 patients	2.84 (0.12 to 69.08) 1 study; 286 patients	
1.20 (0.72 to 1.90)	1.60 (0.77 to 3.30)	Sulfonylurea	1.12 (0.58 to 2.16) $i^2=0.0\%$ 8 studies; 8273 patients	0.94 (0.90 to 1.10) $i^2=0.0\%$ 6 studies; 7021 patients	0.03 (0.03 to 2.21) $i^2=0.0\%$ 2 studies; 2264 patients
0.92 (0.73 to 1.20)	1.20 (0.55 to 2.80)	1.28 (0.24 to 1.30) TZD	1.20 (0.55 to 2.80) TZD	-	1.02 (0.09 to 11.18) 1 study; 598 patients
1.00 (0.91 to 1.10)	1.30 (0.60 to 2.56)	0.85 (0.46 to 1.38)	1.10 (0.85 to 1.40)	DPP4 inhibitor	-
0.74 (0.50 to 0.76)	0.81 (0.36 to 1.90)	0.52 (0.31 to 0.88)	0.66 (0.49 to 0.91)	0.61 (0.48 to 0.77)	SGLT2 inhibitor

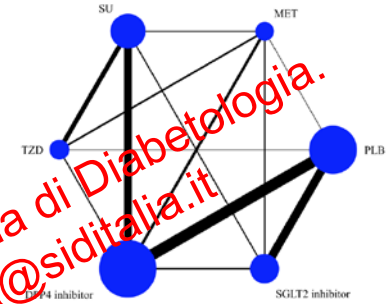


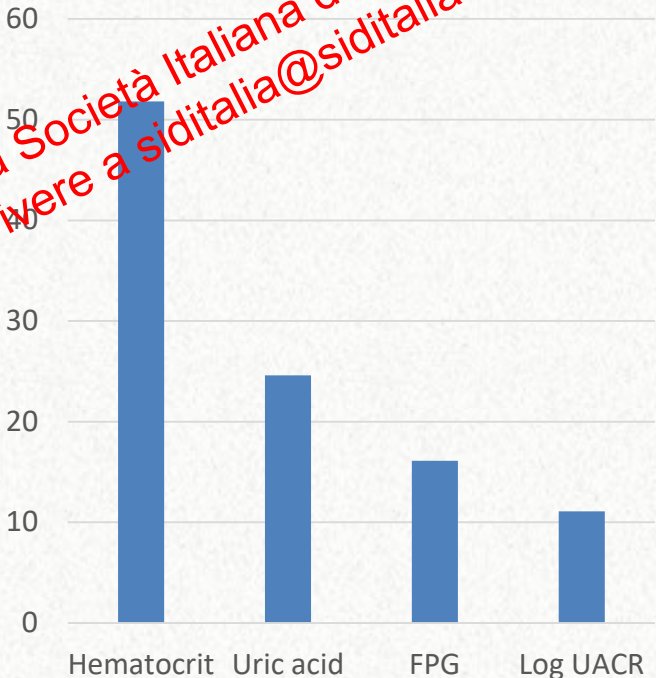
Fig 2. Network of oral antidiabetic drugs comparison of all-cause mortality for the network meta-analysis. Each circle node represents a drug included in the analysis and the size of circle is proportional to the number of patients randomly assigned to the drug. Each line corresponds to direct comparisons between drugs and the width of line is proportional to the number of trials comparing each pair of treatments. TZD: thiazolidinedione. DPP4: dipeptidyl peptidase-4. SGLT2: sodium glucose cotransporter-2.

CVDeath: Mediation analysis

Table 2—Univariable mediation analysis of risk of CV death with empagliflozin versus placebo: time-dependent covariate analysis adjusting for the change from baseline in each variable

	HR for CV death with empagliflozin vs. placebo (95% CI)	Percentage mediation
Unadjusted	0.615 (0.491, 0.770)	
Adjusted for		
HbA _{1c}	0.624 (0.496, 0.785)	3.0
FPG	0.665 (0.529, 0.837)	16.1
SBP	0.593 (0.473, 0.743)	−7.5
DBP	0.614 (0.490, 0.769)	−0.3
Heart rate	0.621 (0.495, 0.780)	−3.0
LDL-C	0.596 (0.475, 0.748)	−6.5
HDL-C	0.636 (0.506, 0.799)	6.9
logTG	0.604 (0.482, 0.758)	−5.7
FFAs	0.586 (0.463, 0.741)	−9.9
logUACR	0.649 (0.518, 0.815)	11.1
eGFR (MDRD)	0.631 (0.504, 0.790)	5.3
eGFR (CKD-EPI)	0.632 (0.505, 0.791)	5.6
Weight	0.570 (0.461, 0.727)	−12.4
BMI	0.578 (0.460, 0.726)	−12.8
WC	0.598 (0.477, 0.750)	−5.8
Hematocrit	0.791 (0.626, 1.000)	51.8
Hemoglobin	0.780 (0.619, 0.983)	48.9
Albumin	0.696 (0.555, 0.873)	25.5
Uric acid	0.693 (0.553, 0.869)	24.6

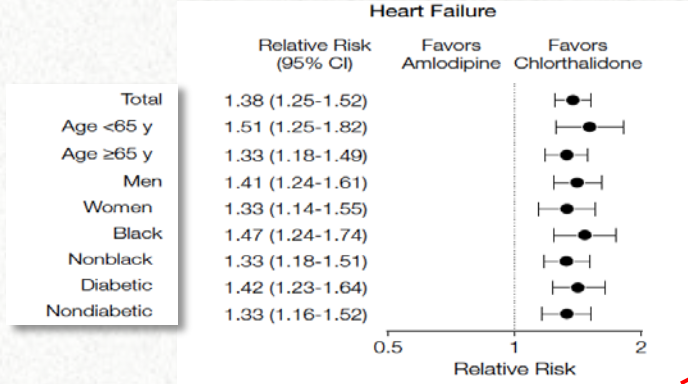
Cox proportional hazards regression analysis in patients treated with one or more doses of study drug. FFA, free fatty acid; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; WC, waist circumference.



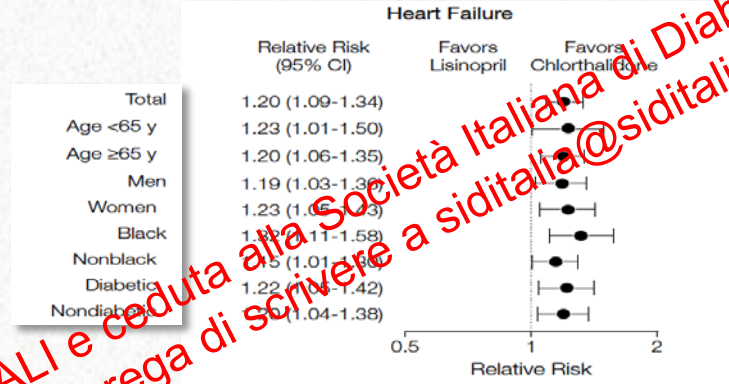
85.2% mediation

I diuretici funzionano ? (ALLHAT)

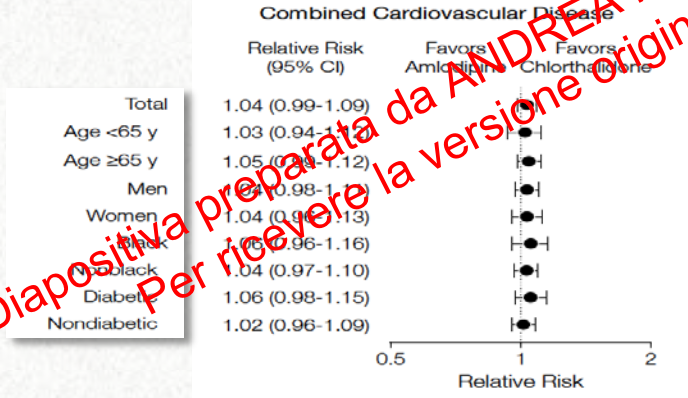
Heart Failure



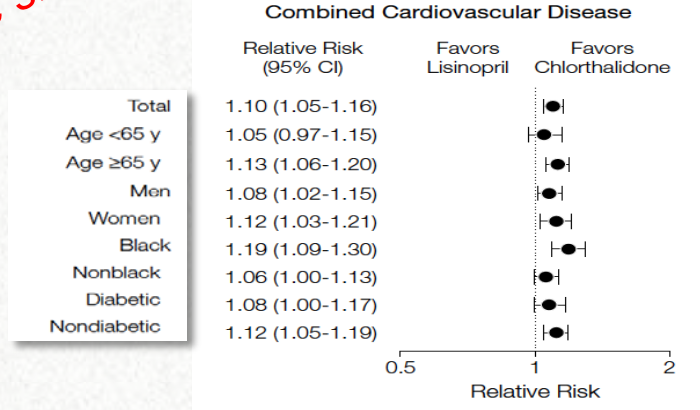
Heart Failure



Combined Cardiovascular Disease



Combined Cardiovascular Disease



SI

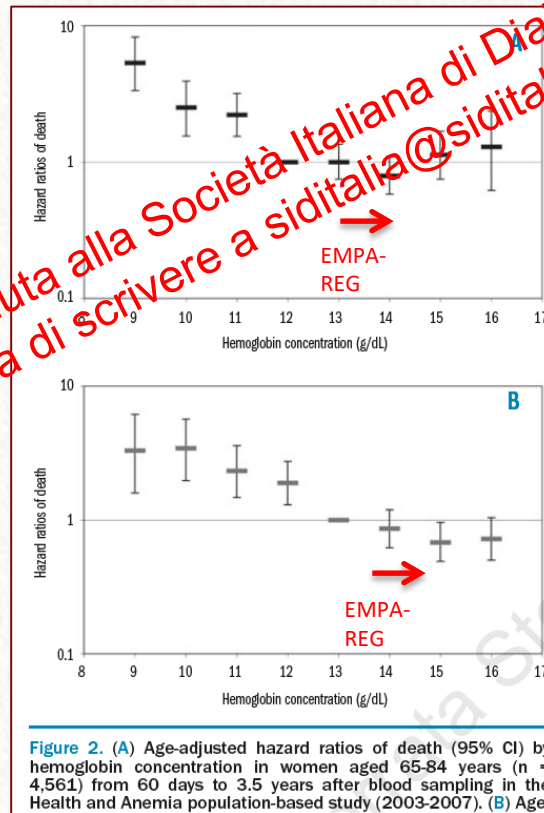
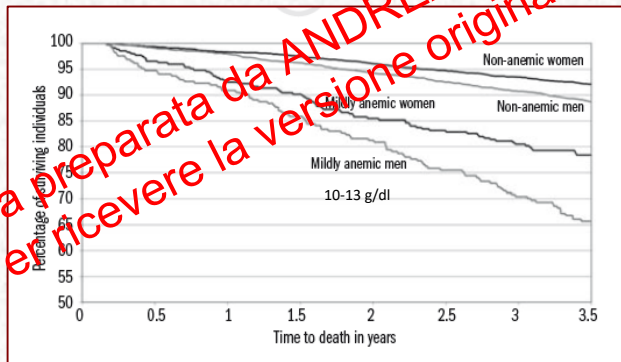
?

Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Haemoglobin and ACD in the elderly (65-80)

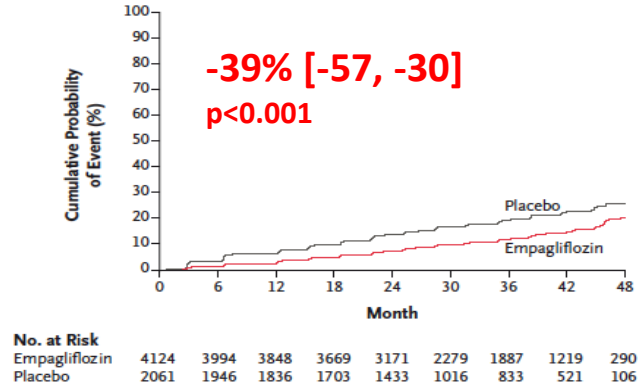
Characteristic	Non-anemic (n=4,157)	Mildly anemic (n=313)	p value
Mean age (SD) (years)	73.4 (5.2)	75.1 (5.5)	<0.0001
Women (%)	61.0	54	0.0213
Mean education (SD) (years)	7.8 (3.8)	7.1 (3.9)	0.0029
Current smoker (%)	14.6	9.9	0.0221
Mean body mass index (SD) (kg/m ²)	25.0 (4.1)	24.6 (4.2)	0.0693
Mean hemoglobin (SD) (g/dL)	14.3 (1.2)	11.6 (0.7)	
Hypertension (%)	53.2	55.0	0.5480
Myocardial infarction (%)	4.9	7.0	0.0959
Heart failure (%)	5.6	9.0	0.0147
Diabetes (%)	8.8	16.9	< 0.0001
Respiratory failure (%)	5.8	10.5	0.0008
Renal failure (%)	1.5	8.7	< 0.0001
Neurological diseases (%)	7.3	13.4	< 0.0001
Cancer (%)	11.2	12.5	0.4907

F: 10-12
M: 10-13

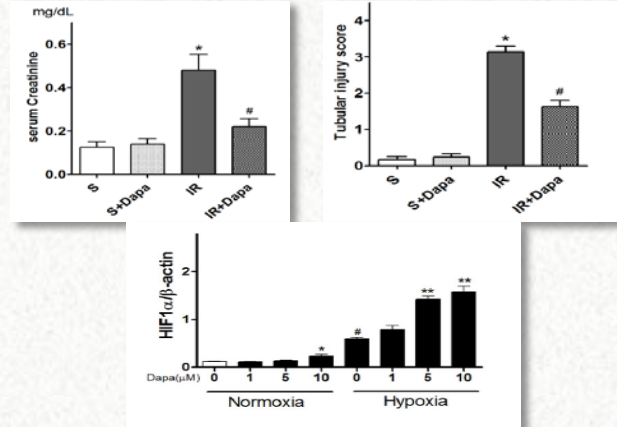
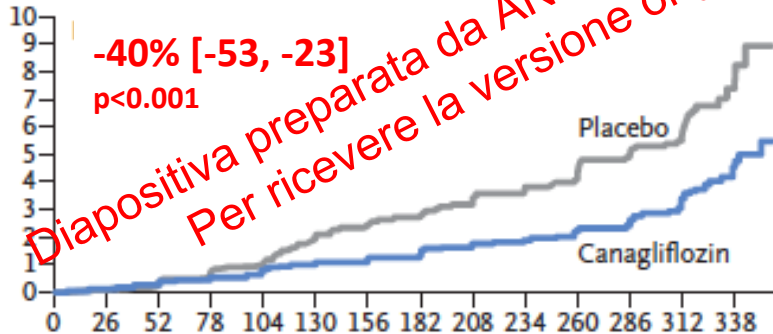


Attraverso il rene ?

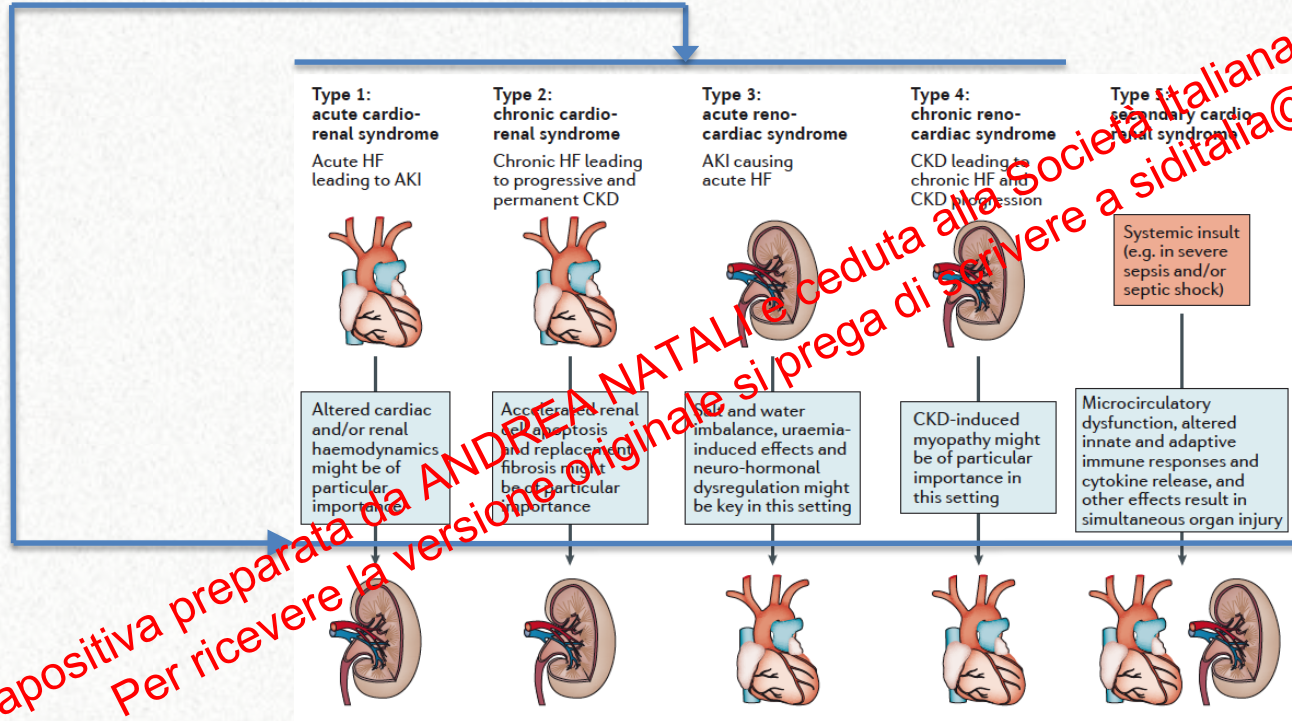
A Incident or Worsening Nephropathy



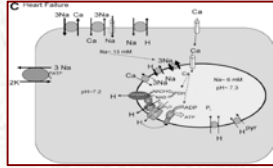
D Composite of 40% Reduction in eGFR, Requirement for Renal-Replacement Therapy or Death from Renal Causes



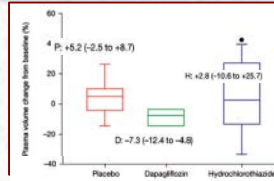
Sindromi cardio renali



Meccanismi

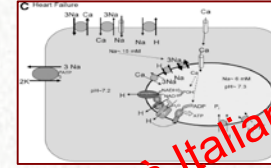


↓ Cardio myoc.
Sodium overload



↓ Volume
= SNS
↑ Ang 1-7 ?

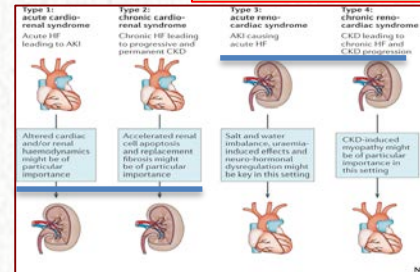
Heart failure ↓



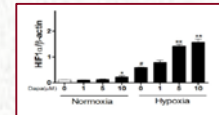
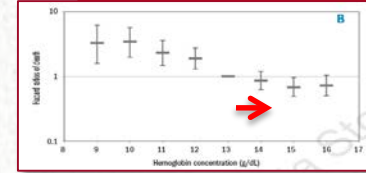
↓ Cardio myoc.
Na overload

CV Death ↓

Kidney
protection



↑ Haematocrit ?



Diapositiva preparata da ANDREA SIDITALIA e ceduta alla Societa Italiana di Diabetologia. Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

A pragmatic and personal point of view



Infections

GI blood loss

Pulmonary embolism

Acute Kidney Injury

Heart failure

Resp. insufficiency

UA/MI

SGLT-2



Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

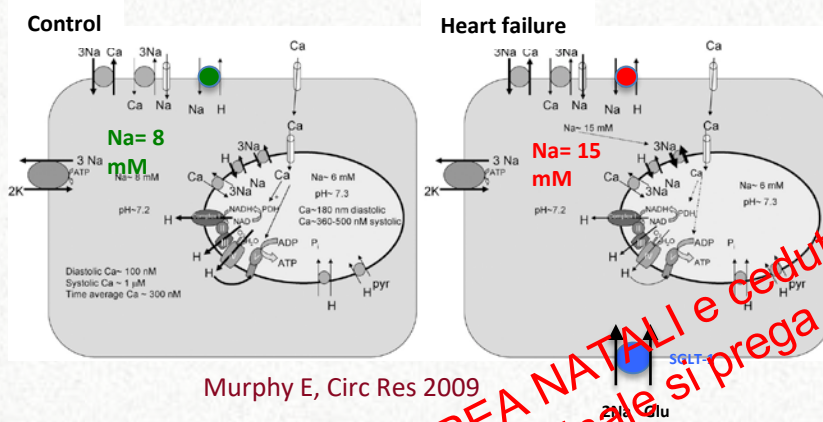
Domande aperte

- Effetto di classe ?
- BMI/età ?
- Persistenza nel tempo ?
- Altri meccanismi ?
- Non diabetici?

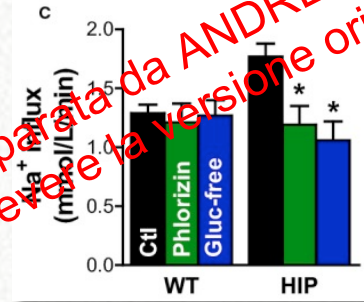
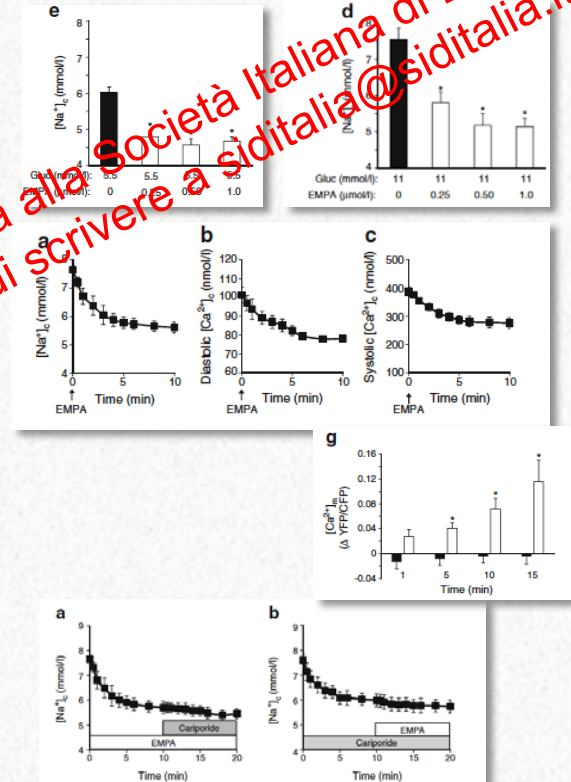
Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Sodio e Calcio intracellulare

Na⁺/H⁺ exchanger (NHE)



Isolated ventricular myocytes (rabbits and rats)

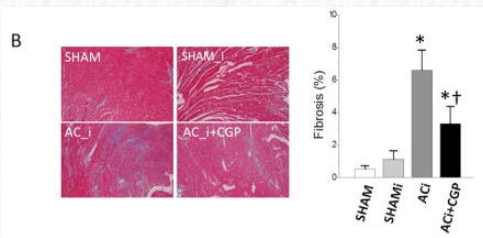
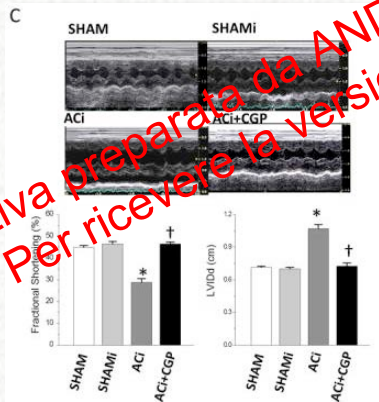
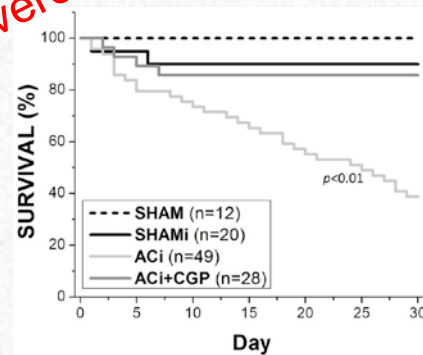
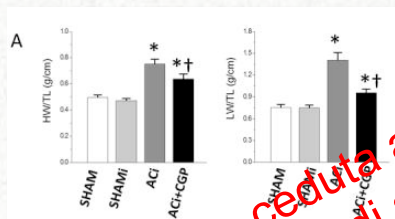
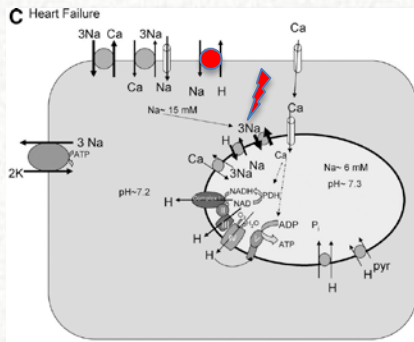


Lambert R, J Am Heart Assoc 2015

Baartscheer A, Diabetologia 2016

Sodio e Calcio intra mitocondriale

guinea pig HF model: aortic constriction (AC) + daily β -adr receptor stimulation isoproterenol (I)
CGP-37157 (CGP): inhibitor of the mitochondrial $\text{Na}^+/\text{Ca}^{2+}$ exchanger



Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Chi sono i pazienti EMPA-REG ?

≥18 years

BMI<45

eGFR>30

Established CVD*

Untreated HbA1c: 7 - 9%

Treated HbA1c: 7 - 10%

*

CAD	Previous MI or PTCA (>2 months) ≥2 vessels or LDA, ≥50% at AngioTC 1 vessel no PTCA + stress test OR UA (<12 months)
CVD	Previous stroke (>2 months)
PAD	Limb revascularization Limb or foot amputation >50% on angiography Ankle brachial index <0.9

	PLACEBO	EMPA
Age (yrs)	63±9	63±9
Male (%)	72	71
White (%)	72	72
BMI (kg/m ²)	31±5	31±5
Diab. dur>5y (%)	81	82
Insulin (%/U)	49/52	48/54
eGFR	74±21	74±21
HbA1c (%)	8.1±0.8	8.1±0.8
LDL-C (mg/dl)	85	86
BP (mmHg)	136/77	135/77
Statins (%)	76	77
ACE (%)	80	81
ASA/CPG (%)	93	93
CAD (%)	76	76
MI (%)	46	47
STROKE (%)	24	23
PAD (%)	21	21
HF (%)	11	10

*Tipici
T2D+CVD*

*Discretamente
controllati*

*Intensivamente
trattati*

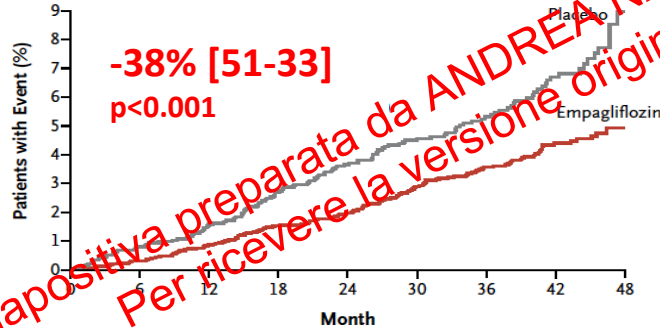
*Molto
vascolari*

Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

EMPA-REG specific outcomes

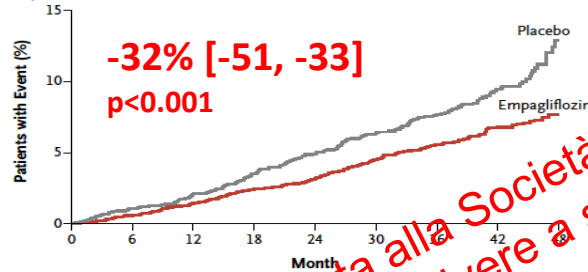


B Death from Cardiovascular Causes



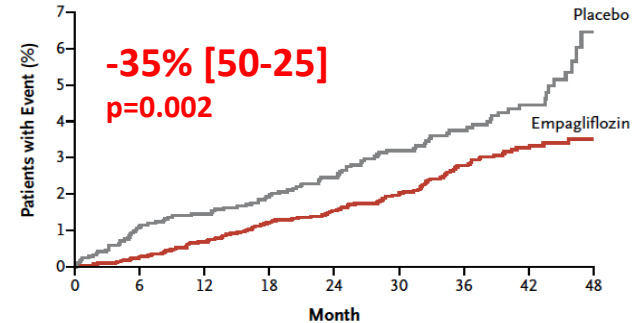
No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

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

D Hospitalization for Heart Failure



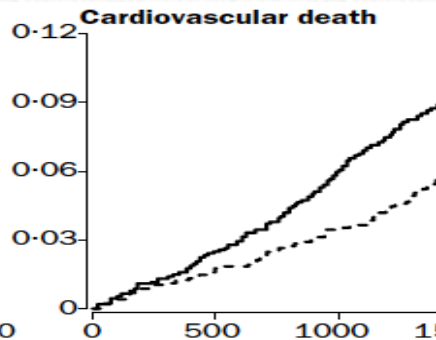
No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168



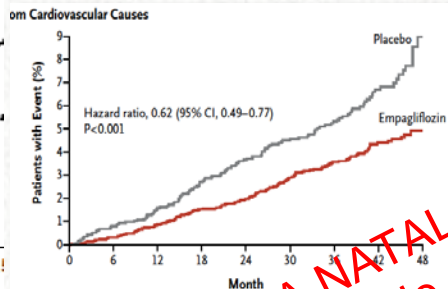
Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

SGLT-2 ≥ ACEi

HOPE



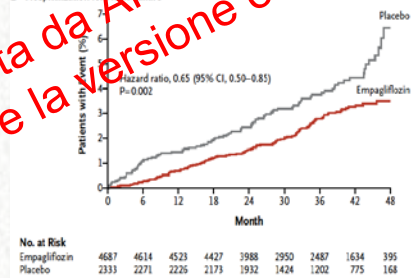
EMPA-REG



CVD death

	Pl	AT	RR	p
Ram	9.7	6.2	-37% [-51, -21]	<0.001
Empa	5.9	3.7	-38% [-51, -23]	<0.001

D Hospitalization for heart failure

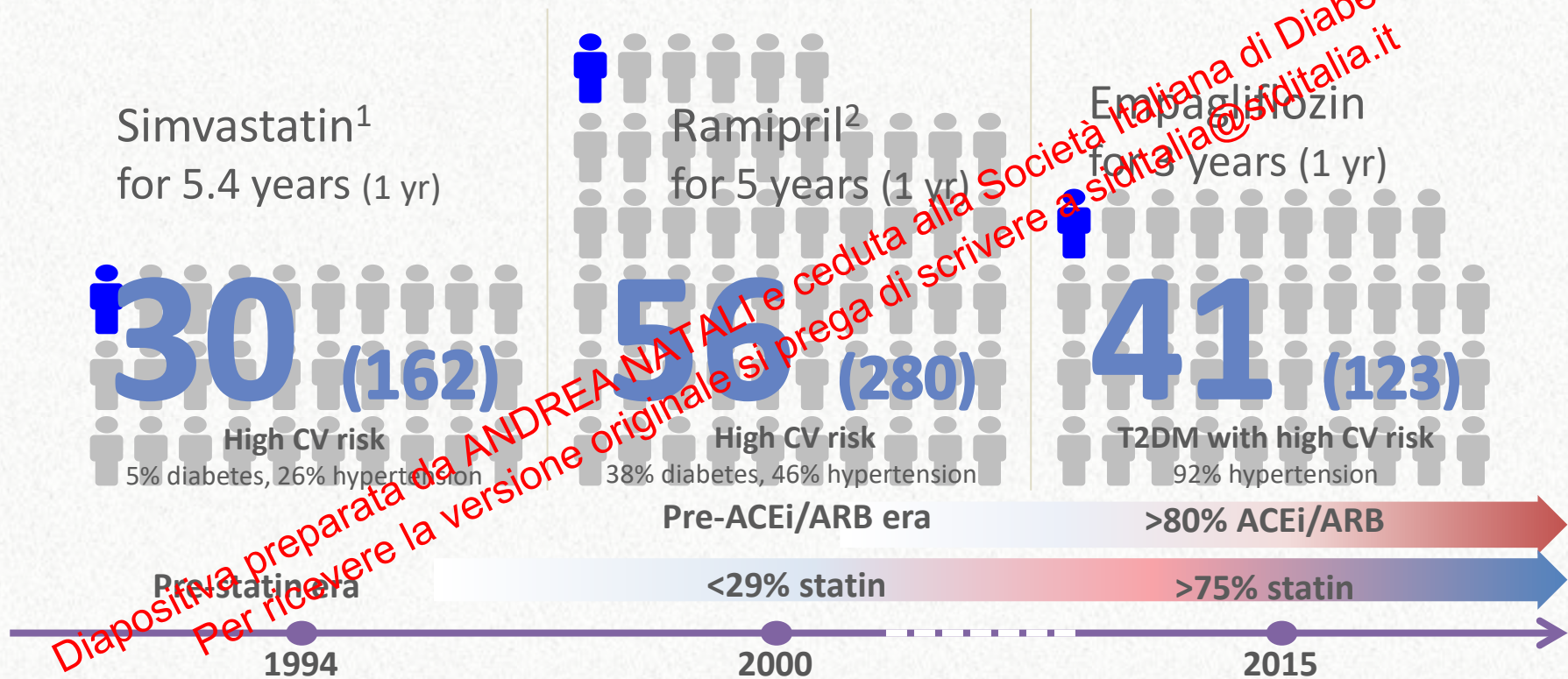


Hospitalization for heart failure (%)

	pl	AT	RR	p
Ram	3.4	3.0	-12% (-30, +10)	0.25
Empa	4.1	2.7	-35% (-50, -15)	0.002

Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

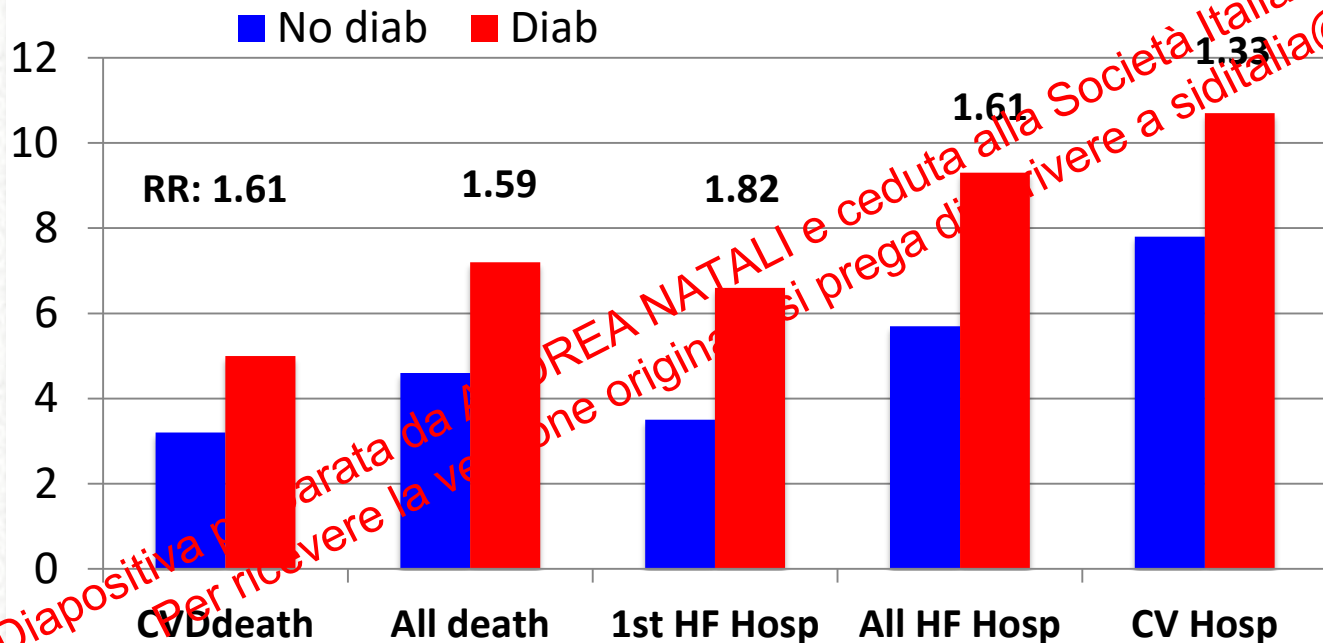
Number needed to treat (NNT) to “prevent” one CVD death across landmark trials in patients with high CV risk



HFpEF in a large trial (I-Preserve)

4,128 pts (27% Diab), Age: 71+/-7 yrs, EF: 60+/-9%, NT-proBNP: 154-1023 pg/ml NYHA: II-III

Event rate (n/100pyr)



More signs of congestion:

- Rx
- Jug. vein dist.
- Edema
- NT-pro BNP (400 vs 320)
- (Hb -0.3 g/dl)

EMPA vs CANA le strane asimmetrie

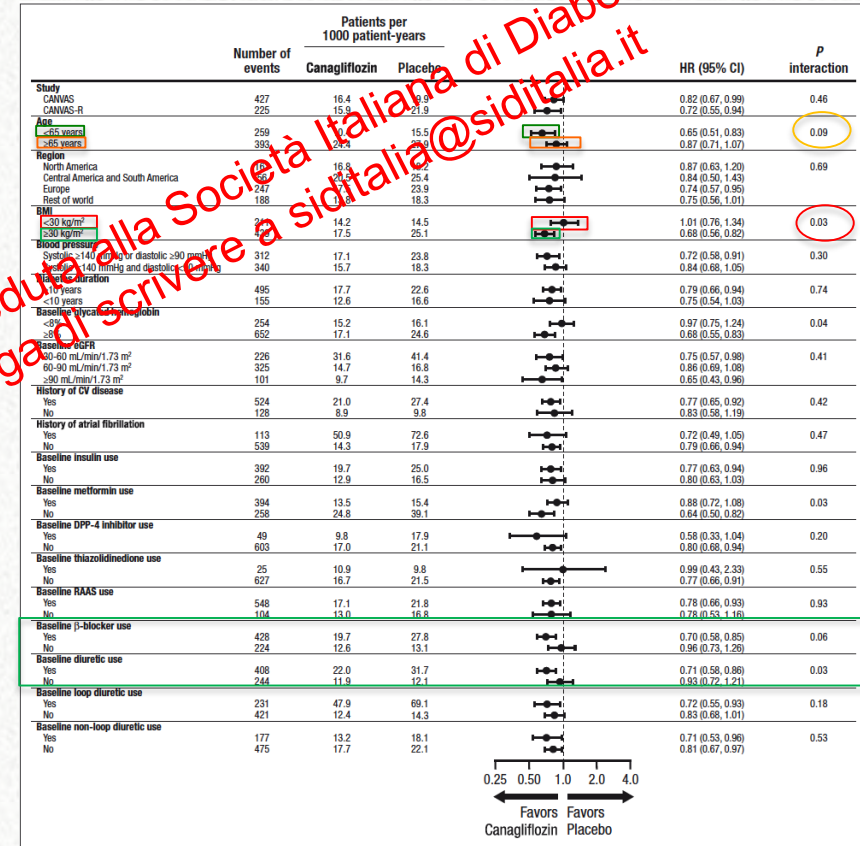
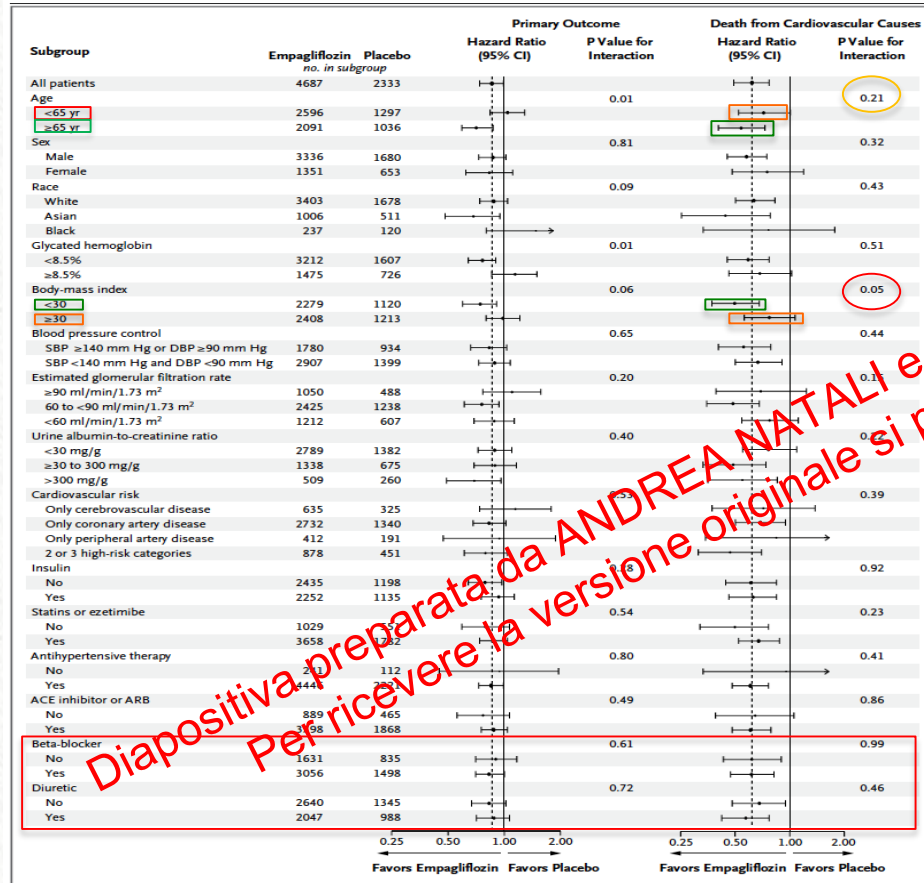
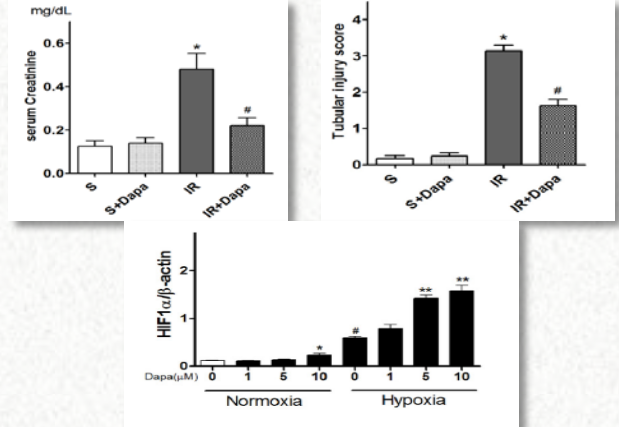
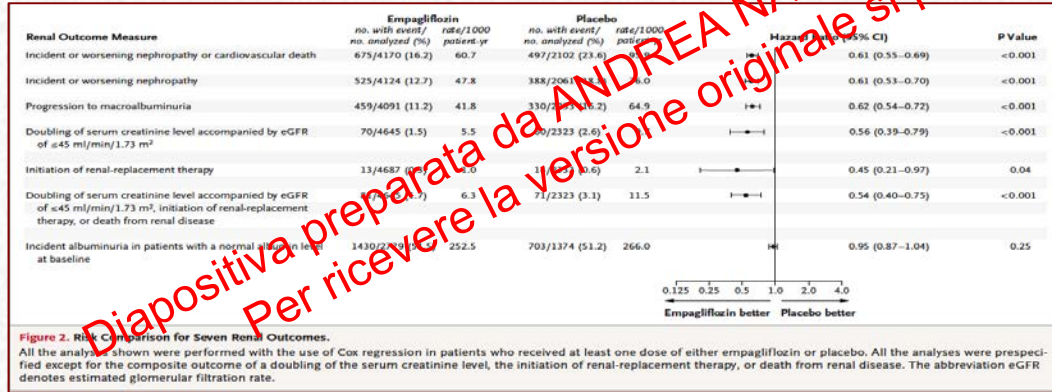
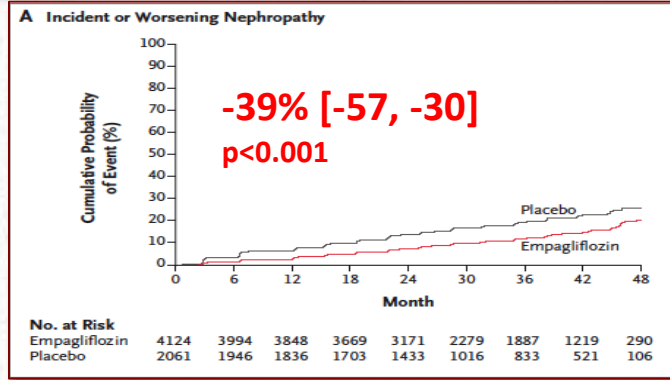


Figure 3. Effects on cardiovascular death or hospitalized heart failure in subgroups defined by demographic and disease characteristics.

Attraverso il rene ?



Effetto di classe?

Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Tutti gli SGLT2i funzionano in tutti i pazienti con DT2 ?

Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it

Come fanno?

Diapositiva preparata da ANDREA NATALI e ceduta alla Società Italiana di Diabetologia.
Per ricevere la versione originale si prega di scrivere a siditalia@siditalia.it