SGLT2 inibitori e rene: prima e dopo lo studio CREDENCE

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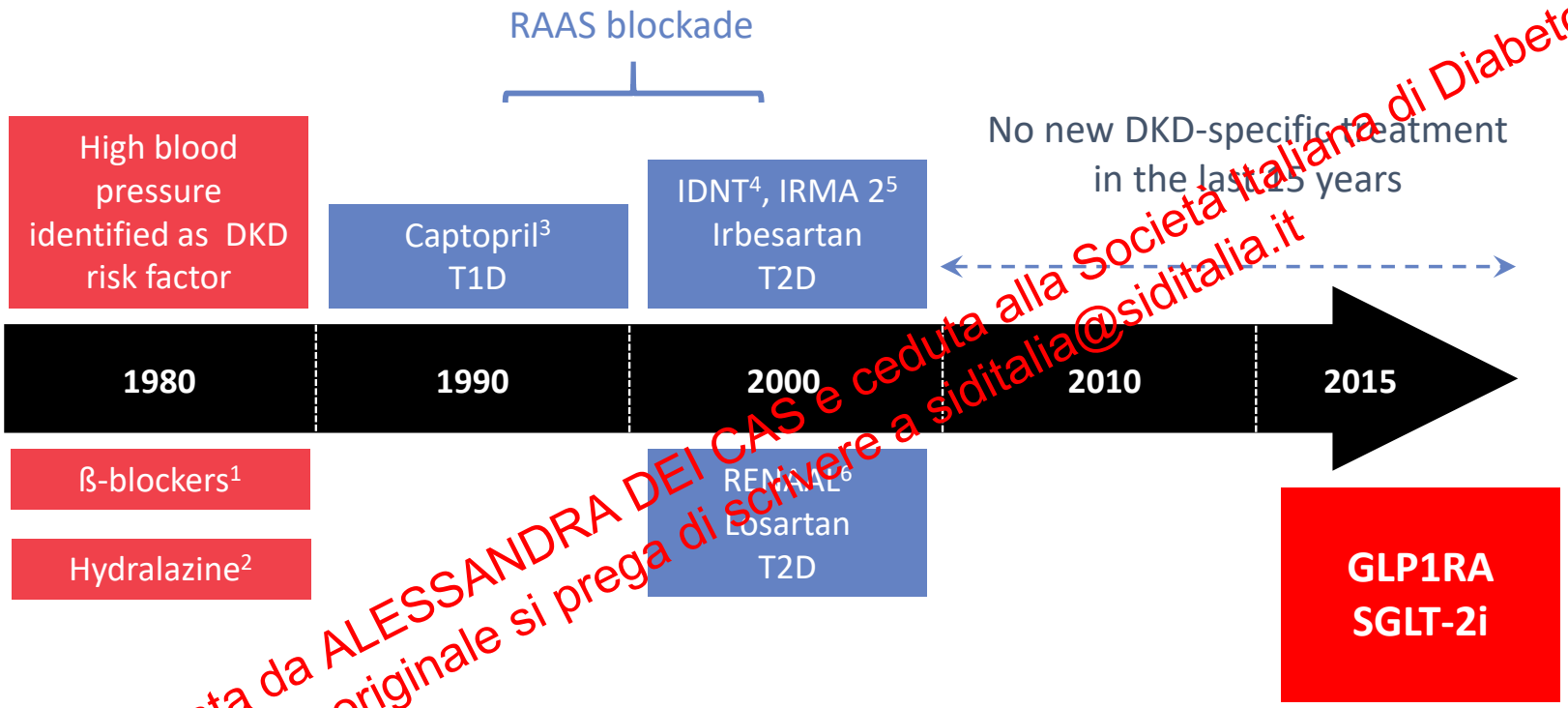
La dr.ssa Alessandra Dei Cas dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Sanofi
- Eli Lilly
- Servier
- Bruno Farmaceutici
- Mundipharma
- MSD

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.).

No new DKD-specific treatment in the last 15 years



DKD, diabetic kidney disease; T1D, type 1 diabetes; T2D, type 2 diabetes; IDNT, Irbesartan Type 2 Diabetic Nephropathy Trial; RAAS, renin–angiotensin-aldosterone system; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.

1. Mogensen CE *et al. Br Med J (Clin Res Ed)*1982;285:685; 2. Parving HH *et al. Lancet* 1983;1:1175; 3. Lewis EJ *et al. N Engl J Med* 1993;329:1456; 4. Lewis EJ *et al. N Engl J Med* 2001;345:851; 6. Brenner BM *et al. N Engl J Med* 2001;345:861

Summary of SGLT2i RA CVOTs

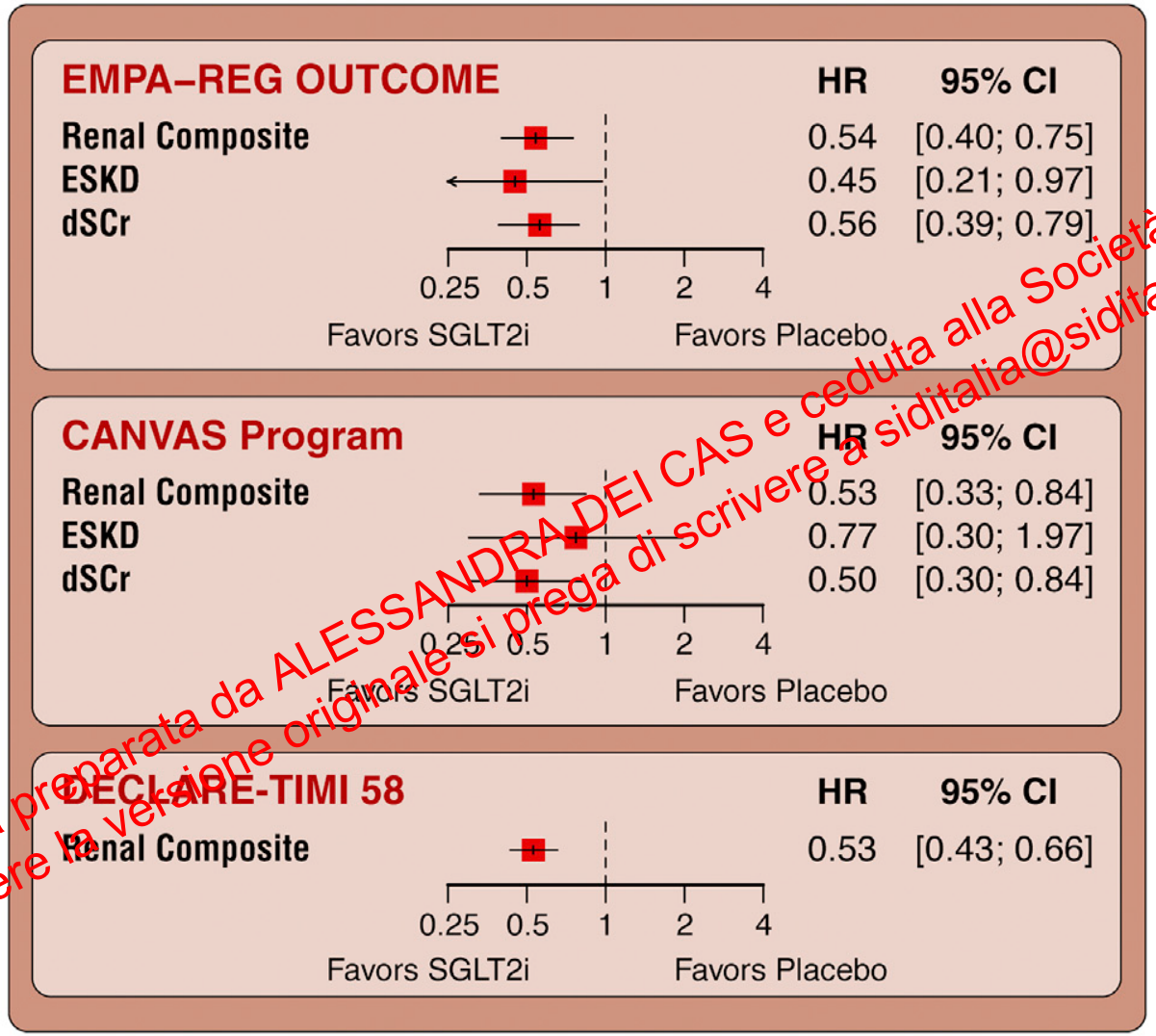
	EMPAREG-OUTCOME	CANVAS program	DECLARE-TIMI
N	7,020	10,142	17,160
Drug Tested	Empagliflozin	Canagliflozin	Dapagliflozin
Prior CVD	99.2%	65,6%	40.6%
Mean Age	63 y	64.3 y	63.9 y
Women	28%	35.7%	36.9%
Median F/U	3.1 y	2.4 y	4,2 y
DM Duration	y	13.5 y	11 y
Baseline A1c	8%	8.2%	8.3%
Baseline eGFR	85.2	76.5	85.2
Secondary Renal Endpoint	Composite*	Composite**	Composite ***

* doubling of serum creatinine with eGFR <45 ml/min, ESRD or renal death

** >40% decrease in eGFR 2 consecutive measures, need for renal replacement therapy.

** >40% decrease in eGFR to a threshold <60, ESRD (dialysis >90 days, GFR<15ml/min, transplantation)

Secondary Renal Outcomes from CVOTs



Cell Metabolism 29, May 7, 2019

Lo studio CREDENCE differisce dagli studi CVOTs con SGLT2i in quanto:

1. La popolazione di pazienti con DMT2 coinvolta nel trial è per il 90% in prevenzione primaria

2. L'endpoint renale comprendeva non solo misure di eGFR ma anche della componente albuminurica della nefropatia diabetica

3. L'endpoint renale rappresenta l'endpoint primario dello studio

4. L'endpoint renale non è composito

Summary of SGLT2i RA CVOTs

	EMPAREG-OUTCOME	CANVAS program	DECLARE-TIMI	CREDENCE
N	7,020	10,142	17,160	4,401
Drug Tested	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
Prior CVD	99.2%	65,6%	40.6%	50.4%
Mean Age	63 y	64.3 y	63.9 y	63 y
Women	28%	35.7%	36.9%	33.9%
Median F/U	3.1 y	2.4 y	4,2 y	2.62 y
DM Duration	y	13.5 y	11 y	15.8y
Baseline A1c	8%	8.2%	8.3%	8.3%
Baseline eGFR	85.2	76.5	85.2	56.2
Secondary Renal Endpoint	Composite*	Composite**	Composite ***	Primary outcome

* doubling of serum creatinine with eGFR <45 ml/min, ESRD or renal death

** >40% decrease in eGFR 2 consecutive measures, need for renal replacement therapy.

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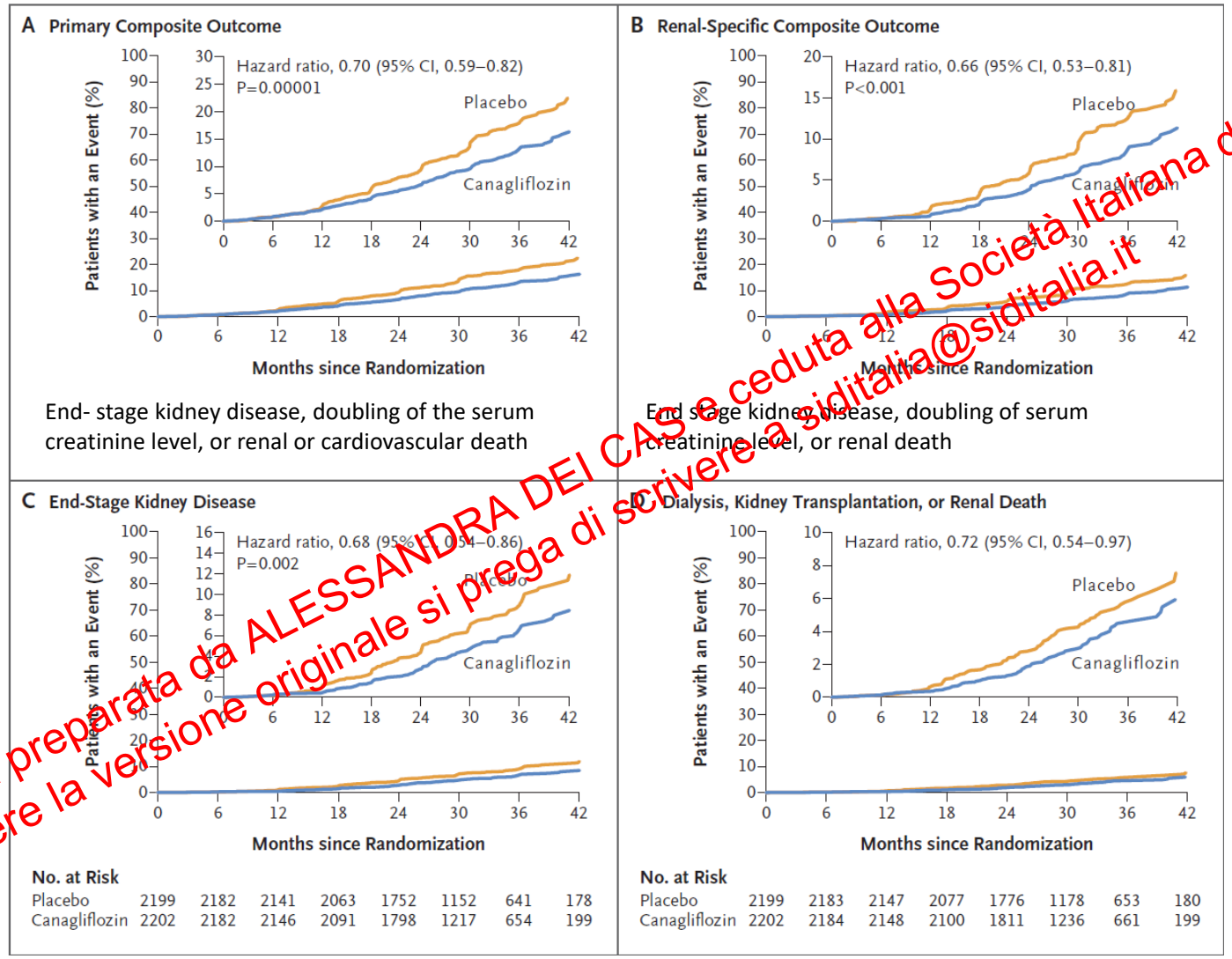
Primary Composite and Renal Outcomes in the CREDENCE trial



N Engl J Med 2019;380:2295-306.

L’effetto di canagliflozin nello studio CREDENCE è coerente per tutti i livelli di eGRF?

1. SI
2. NO
3. NON LO SO

New information from CREDENCE

- ✓ SGLT2 inhibition across different levels of eGFR

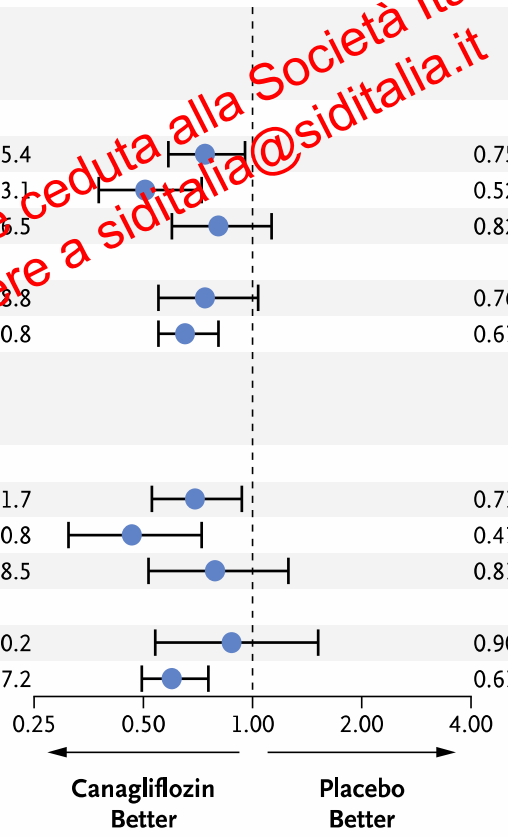
Renal characteristics of studies

	EMPA-REG OUTCOME	CANVAS Program	DECLARE–TIMI 58	CREDENCE
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
Dose (mg)	10 and 25	100 and 300	10	100
Number of participants	7020	10 142	17 160	4401
Mean age (years)	63·1	63·3	63·9	63·0
Sex				
Men	5016 (71·5%)	6509 (64·2%)	10 738 (62·6%)	2907 (66·1%)
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)	1494 (33·9%)
Median follow-up (years)	3·1	2·4	4·2	2·6*
eGFR inclusion criteria	≥30 (MDRD)	≥30 (MDRD)	CrCl ≥60 mL/min (Cockcroft-Gault)	30 to <90 (CKD-EPI)
Baseline eGFR subgroup (mL/min per 1·73 m²)‡				
≥90	2568 (21·9%)	2476 (24·4%)	8162 (47·6%)	0
60 to <90	3661 (52·2%)	5625 (55·5%)	7732 (45·1%)	1809 (41·1%)
45 to <60	1249 (17·8%)	1485 (14·6%)	1265 (7·4%)§	1279 (29·1%)
<45	570 (8·1%)	554 (5·5%)	NA	1313 (29·8%)
Missing baseline eGFR	2 (<0·1%)	2 (<0·1%)	1 (<0·1%)	0
UACR criteria (mg/g)	None	None	None	>300 to 5000
Baseline UACR subgroup (mg/g)‡				
<30	4171 (59·4%)	7007 (69·1%)	11 644 (67·9%)	0
30–300	2013 (28·7%)	2266 (22·3%)	4030 (23·5%)	0
>300	769 (11·0%)	760 (7·5%)	1169 (6·8%)	4401 (100·0%)
Missing baseline UACR	67 (1·0%)	109 (1·1%)	317 (1·8%)	0
Baseline use of RAS blockade	5666 (80·7%)	8116 (80·0%)	13 950 (81·3%)	4395 (99·9%)

Lancet Diabetes Endocrinol 2019; 7: 845–54

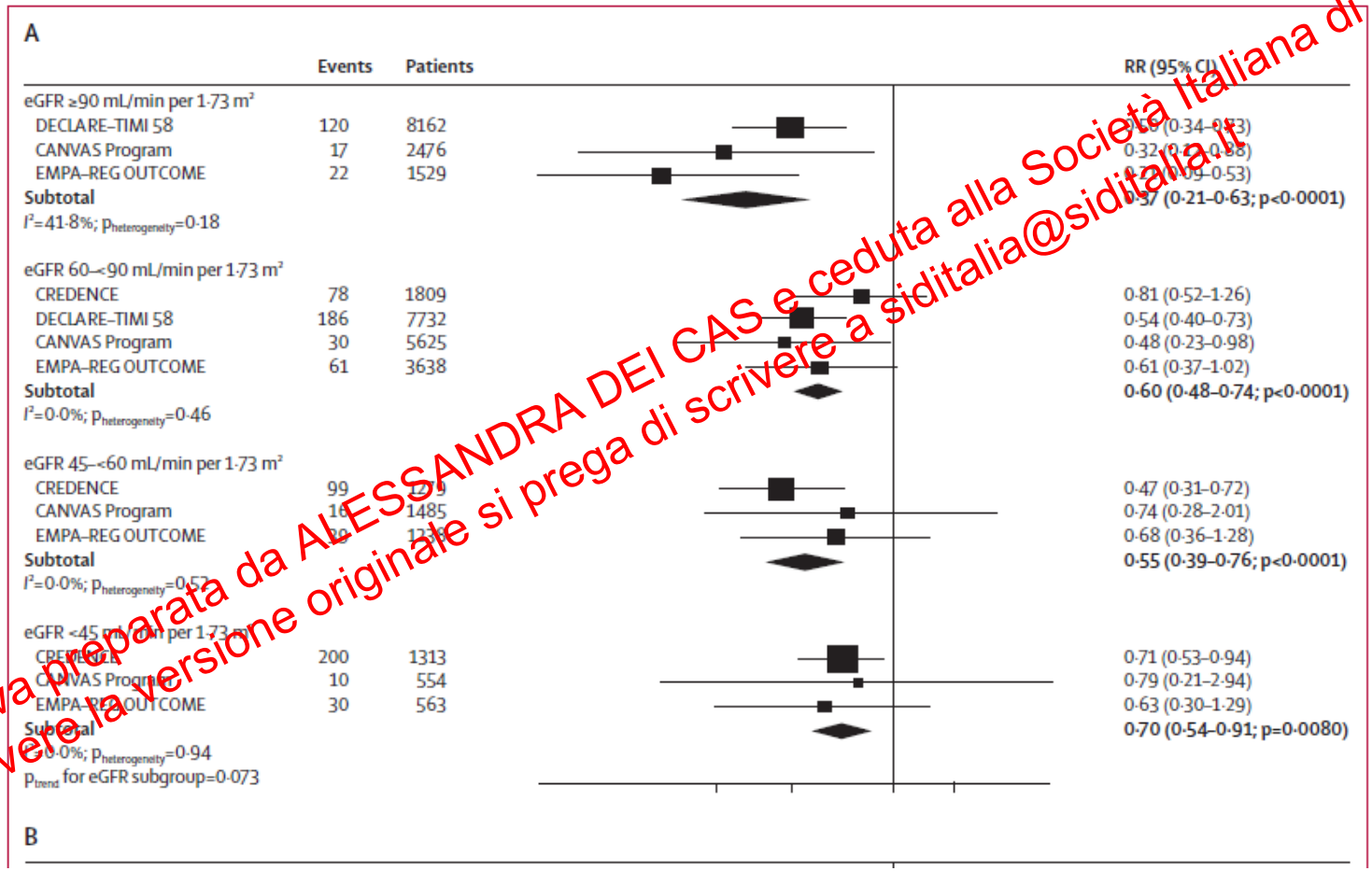
The CREDENCE Study: subgroup analysis by eGFR shows beneficial effects of canagliflozin even in the 30-45 ml/min/1.73 m^2 range of eGFR

Subgroup	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.		*events/1000 patient-yr*			
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m^2	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m^2	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m^2	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m^2	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m^2	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m^2	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)	



Perkovic V. et al.; NEJM 2019

Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by baseline eGFR



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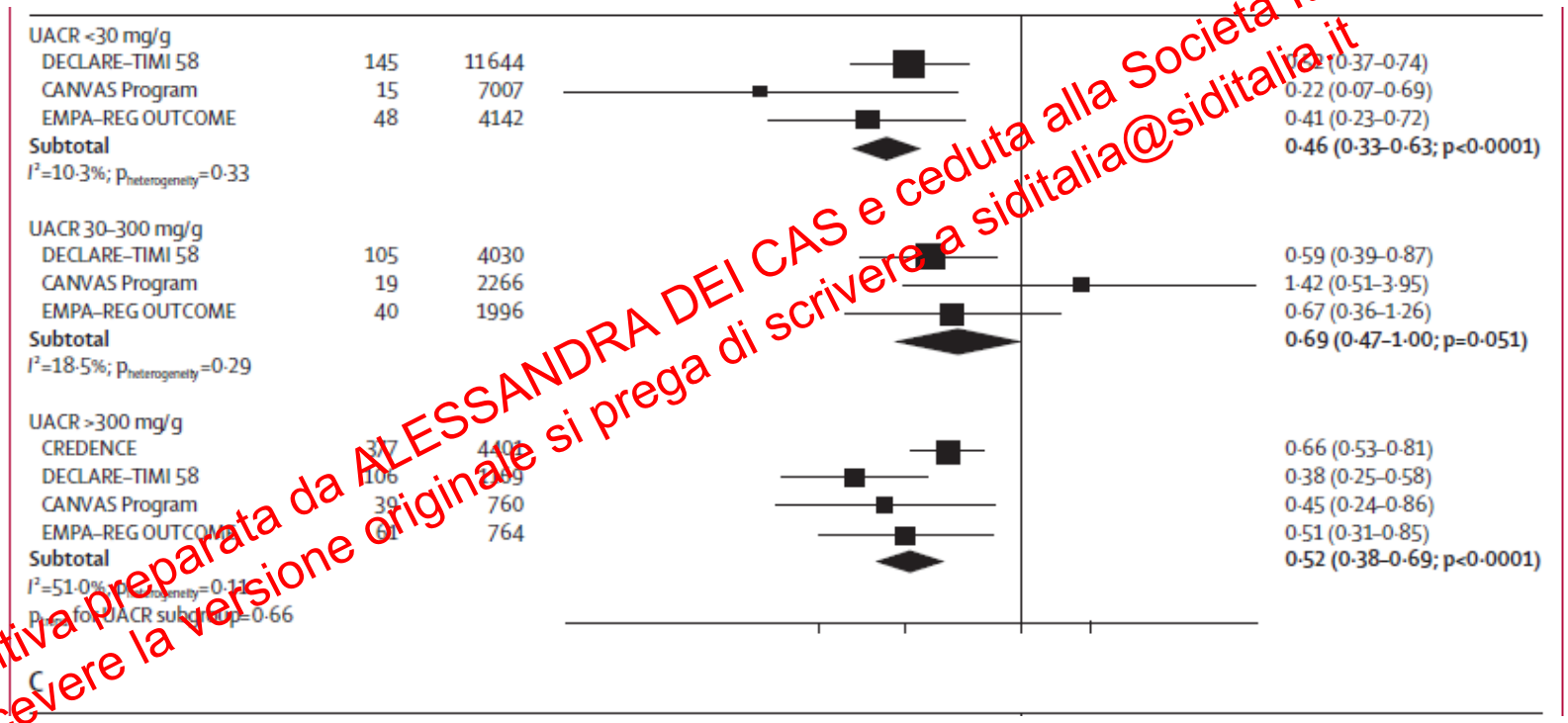
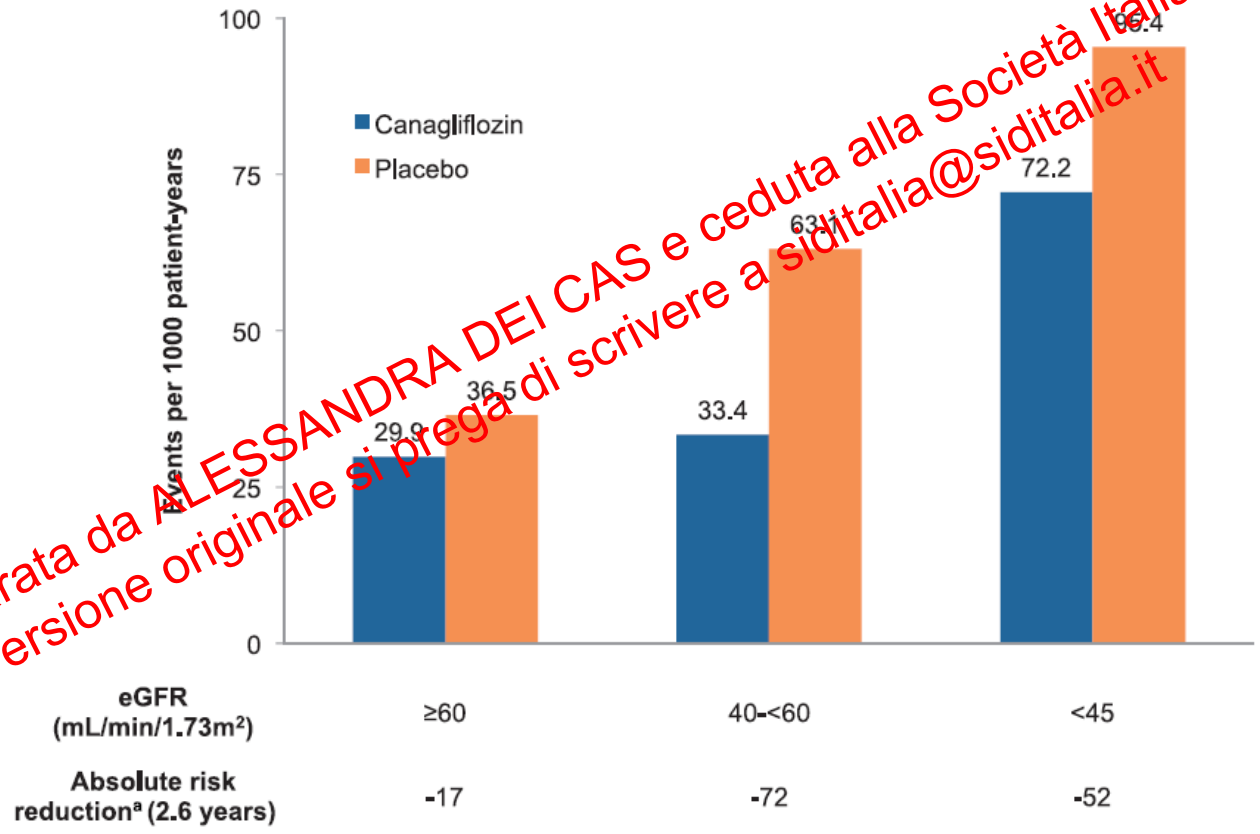


Lancet Diabetes Endocrinol 2019; 7: 845–54

Estimated number of primary events (doubling of serum creatinine, ESKD or cardiovascular or kidney-related death) prevented per 1000 patients treated over 2.6 years in the CREDENCE trial by baseline eGFR. Absolute risk reductions estimated as the number of events prevented per 1000 patients treated over 2.6 years.



Nephrol Dial Transplant (2020) 35: i48–i55

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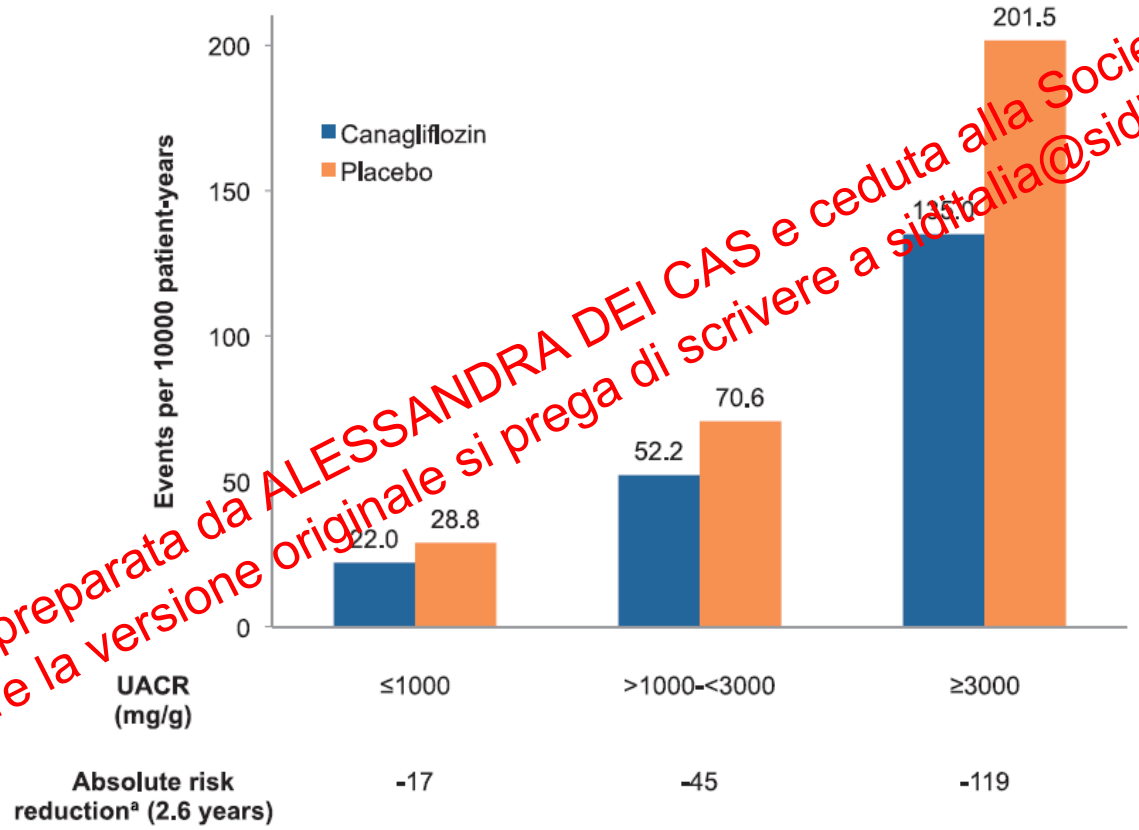


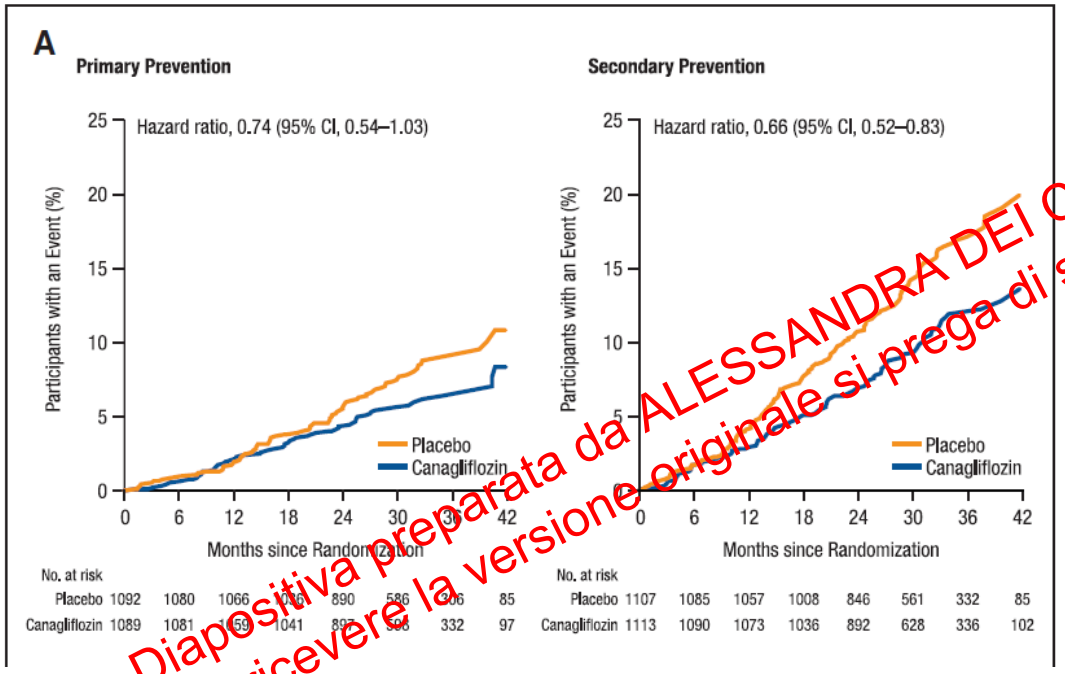
Nephrol Dial Transplant (2020) 35: i48–i55

New information from CREDENCE

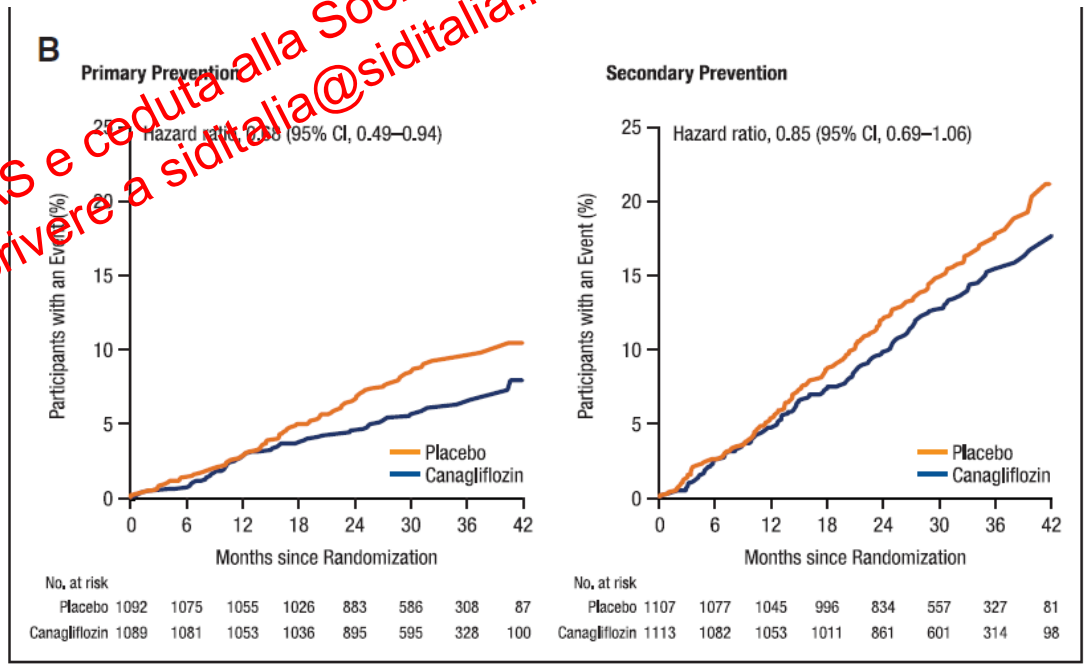
- ✓ SGLT2 inhibition across different levels of eGFR
- ✓ The effects of canagliflozin on MACE are not modified by baseline kidney function and is confirmed in subgroups in primary and secondary preventions

Effects of canagliflozin on cardiovascular outcomes in the primary and secondary prevention cohorts.

Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke



Cardiovascular death and hospitalization for heart failure

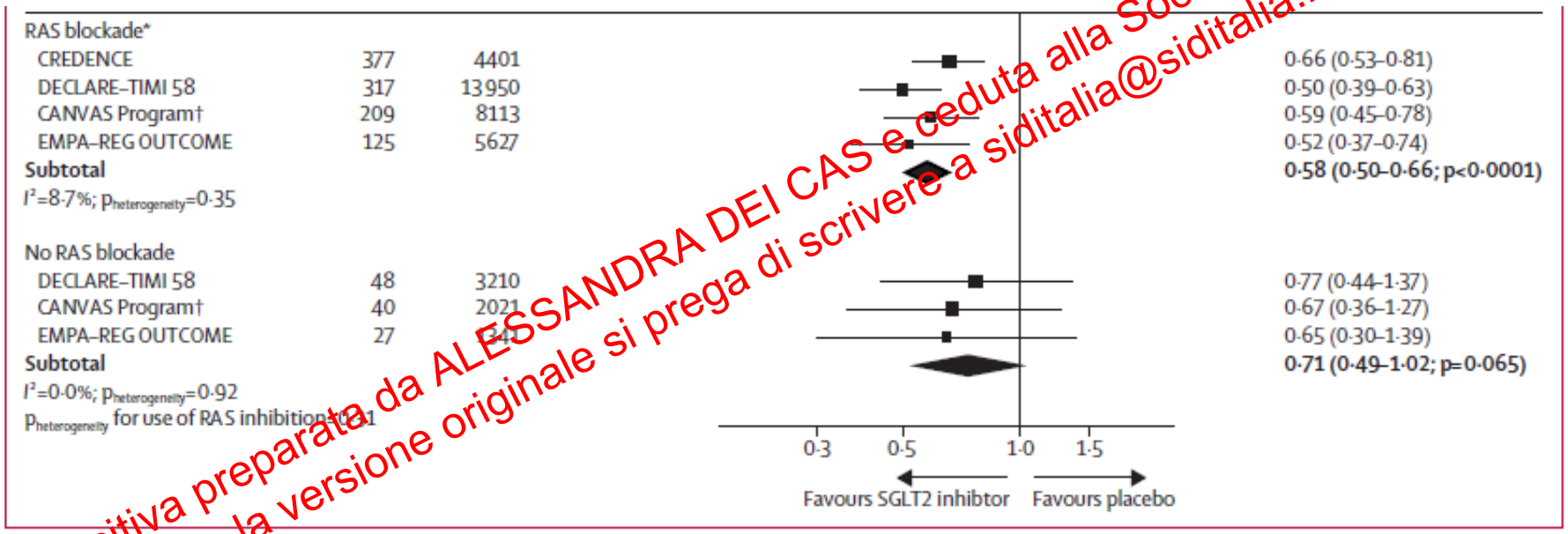


Circulation. 2019;140:739–750

New information from CREDENCE

- ✓ SGLT2 inhibition across different levels of eGFR
- ✓ The effects of canagliflozin on MACE are not modified by baseline kidney function and is confirmed in subgroups in primary and secondary preventions
- ✓ SGLT2 inhibition with or without RAS inhibition

Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by baseline use of RAS blockade



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- ✓ SGLT2 inhibition across different levels of eGFR
- ✓ The effects of canagliflozin on MACE are not modified by baseline kidney function and is confirmed in subgroups in primary and secondary preventions
- ✓ SGLT2 inhibition with or without RAS inhibition
- ✓ Safety issues

Safety in the CREDENCE trial

Table 2. Efficacy and Safety.*

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		events/1000 patient-yr			
Safety‡						NA
Any adverse event	1784/2200	1860/2197	351.4	379.3	0.87 (0.82–0.93)	NA
Any serious adverse event	737/2200	806/2197	145.2	164.4	0.87 (0.79–0.97)	NA
Serious adverse event related to trial drug	62/2200	42/2197	12.2	8.6	1.45 (0.98–2.14)	NA
Amputation	70/2200	63/2197	12.3	11.2	1.11 (0.79–1.56)	NA
Fracture	67/2200	68/2197	11.8	12.1	0.98 (0.70–1.37)	NA
Cancer						
Renal-cell carcinoma	1/2200	5/2197	0.2	0.9	NA	NA
Breast cancer§	8/761	3/731	4.1	1.6	2.59 (0.69–9.76)	NA
Bladder cancer	10/2200	9/2197	1.7	1.6	1.10 (0.45–2.72)	NA
Acute pancreatitis	5/2200	2/2197	1.0	0.4	NA	NA
Hyperkalemia¶	151/2200	181/2197	29.7	36.9	0.80 (0.65–1.00)	NA
Acute kidney injury	86/2200	98/2197	16.9	20.0	0.85 (0.64–1.13)	NA
Diabetic ketoacidosis‖	11/2200	1/2197	2.2	0.2	10.80 (1.39–83.65)	NA

N Engl J Med 2019;380:2295-306.

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- ✓ SGLT2 inhibition with or without RAS inhibition
- ✓ Safety issues
- ✓ Implementation ef evidence into clinical practice

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- ✓ SGLT2 inhibition across different levels of eGFR
- ✓ The effects of canagliflozin on MACE are not modified by baseline kidney function and is confirmed in subgroups in primary and secondary preventions
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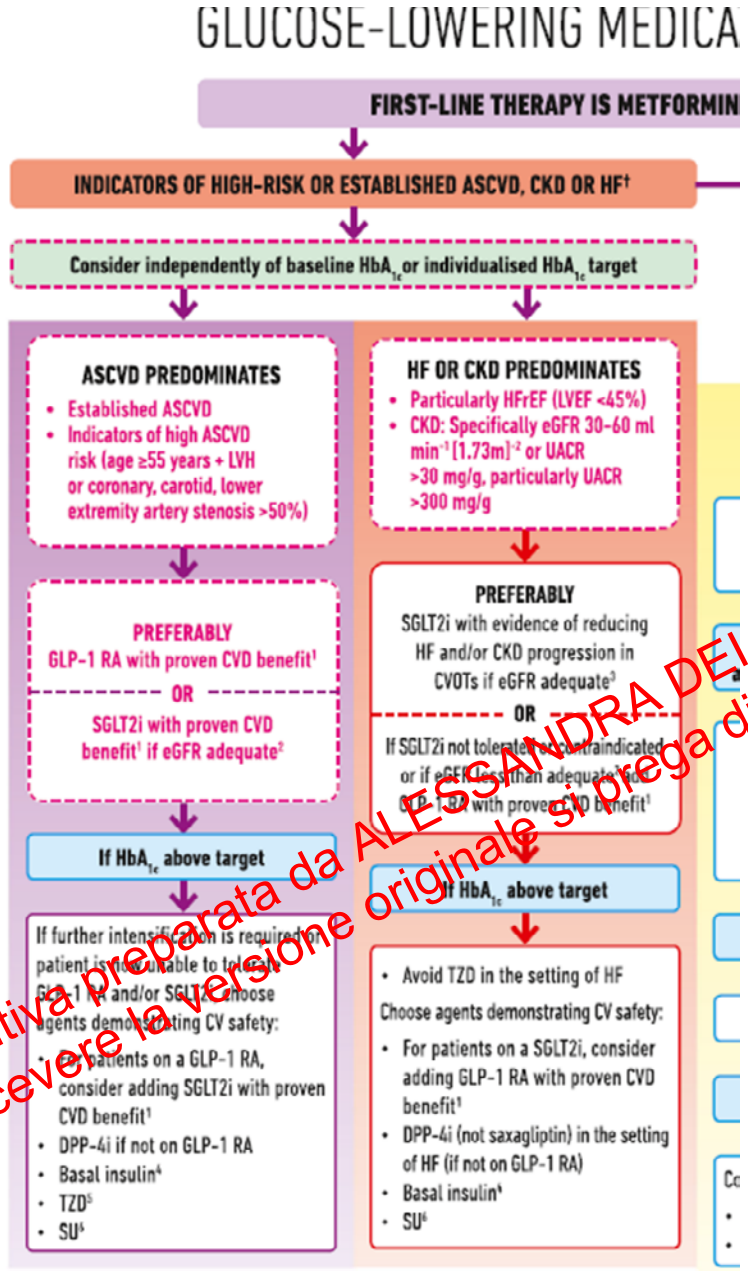
- ✓ ould this evidence be applied in routine practice to maximize benefits and ensure potential harms are minimized?
- ✓ Are there other patient groups, aside from those with T2DM, who may benefit from SGLT2 inhibitors? Finally, how should these agents be used in combination with other currently available
- ✓ and future treatments?



Diabetologia. 2020 Feb;63(2):221-228.

Conclusions

- ✓ SGLT2i are **disease-modyfing treatments** also for kidney disease . We should shift from the rationale for their use from glucose-lowering agents to strategies to reduce disease risk
- ✓ The CREDENCE trial ha s answered to some critical questions
- ✓ Future work will need to answer to open questions….

Open questions

- ✓ How should this evidence be applied in routine practice to maximize benefits and ensure potential harms are minimized?
- ✓ Are there other patient groups, aside from those with T2DM, who may benefit from SGLT2 inhibitors (i.e. type 1 diabetes, nephropathy without DM)?
- ✓ Finally, how should these agents be used in combination with other currently available and future treatments?