3° CONGRESSO CONGIUNTO
SID - AMD SICILIA

Palermo (PA) 29 novembre – 30 novembre 2018

SGLT2i e outcome cardiovascolare: ultime evidenze dagli RCT al RWE

Gian Paolo Fadini

Professore Associato di Endocrinologia

Dipartimento di Medicina. Università di Padova
Istituto Veneto di Medicina Molecolare

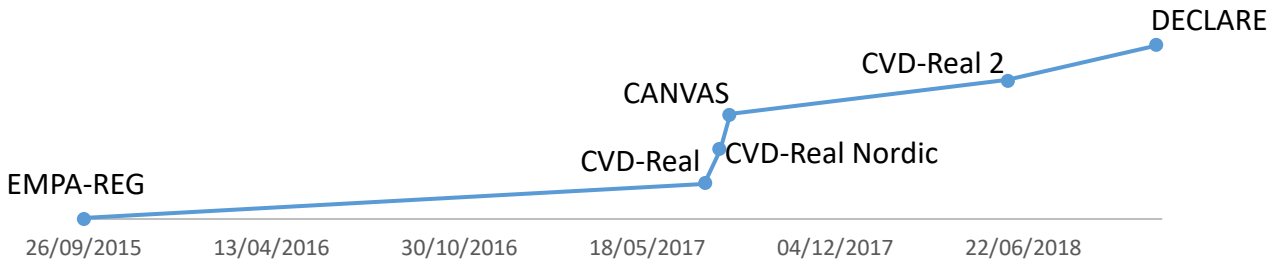
Il prof. Gian Paolo Fadini dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Abbott. AstraZeneca. Boehringer. Eli Lilly. MSD. NovoNordisk. Novartis. Sanofi

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.).

SGLT2i & CVD in T2D

From RCTs to RWE and back



In <3 yrs abundant evidence for the 3 avaialble SGLT2i

SGLT2i & CVD in T2D

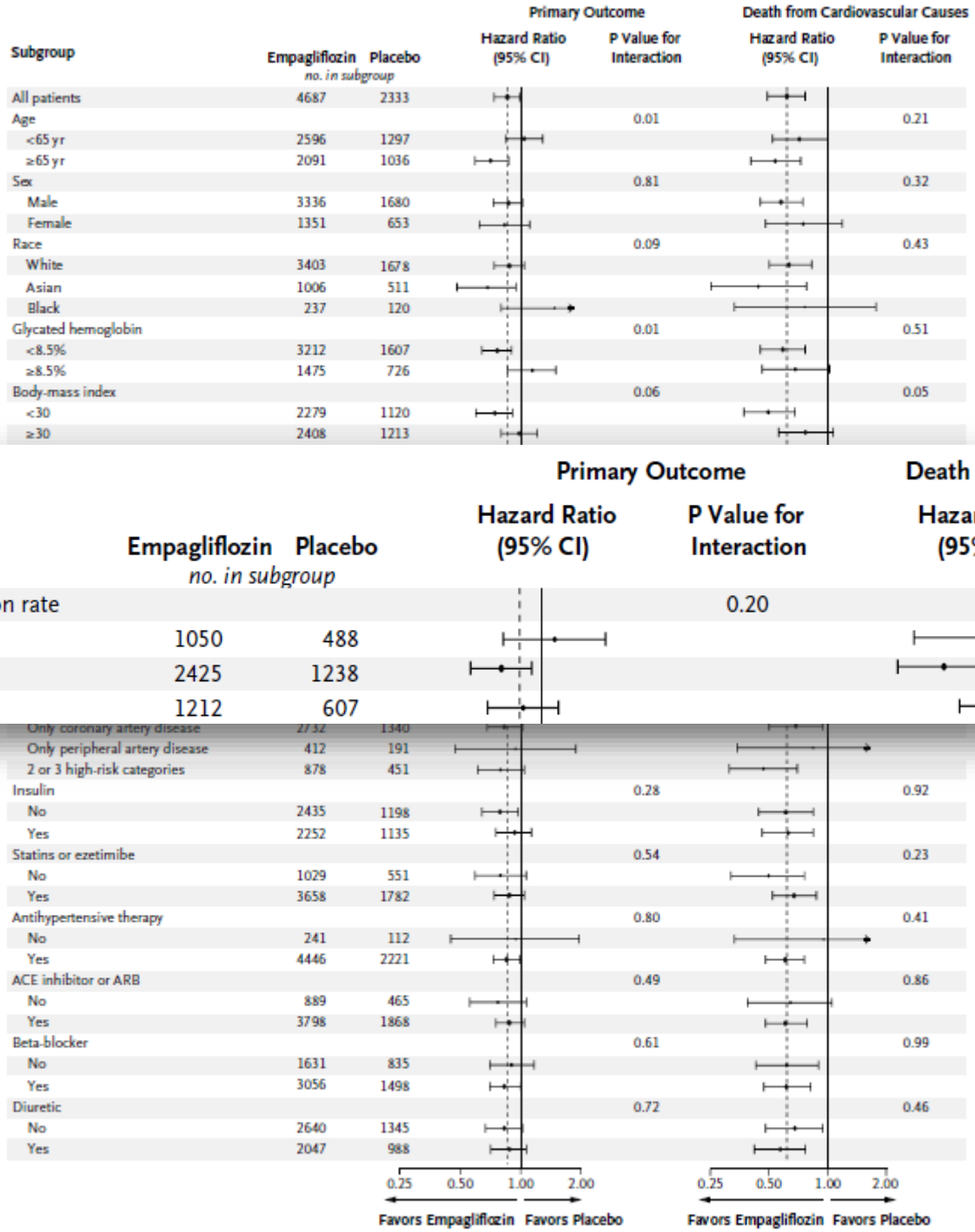
From RCTs to RWE and back

EMPA-REG Outcome

100% in 2nd prevention
n=7072

MACE	HR 0.86 (0.74-0.99)
CV death	HR 0.62 (0.49-0.77)
Death	HR 0.68 (0.57-0.82)
HHF	HR 0.65 (0.50-0.85)

EMPA-REG

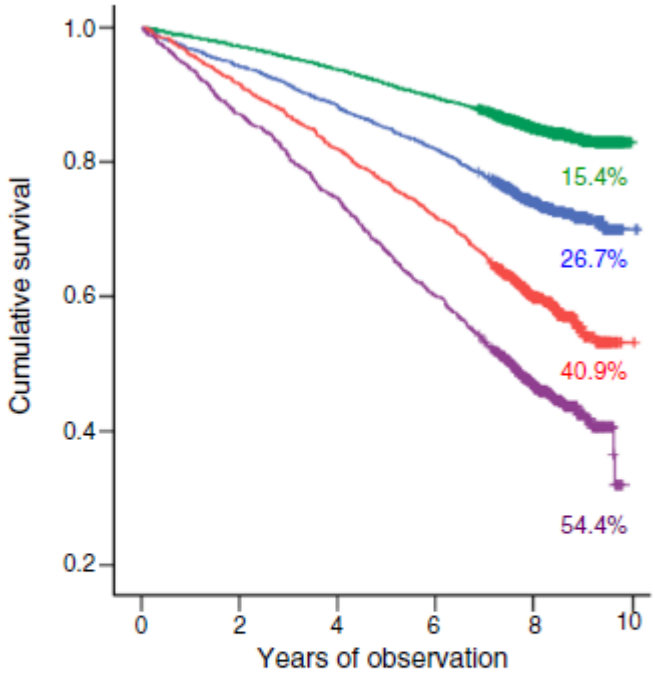

Primary Outcome
Death from Cardiovascular Causes
Subgroup
Empagliflozin
Placebo
no. in subgroup
Hazard Ratio (95% CI)
P Value for Interaction
Hazard Ratio (95% CI)
P Value for Interaction
All patients 4687 2333
Age 0.01 0.21
<65 yr 2596 1297
≥65 yr 2091 1036
Sex 0.81 0.32
Male 3336 1680
Female 1351 653
Race 0.09 0.43
White 3403 1678
Asian 1006 511
Black 237 120
Glycated hemoglobin 0.01 0.51
<8.5% 3212 1607
≥8.5% 1475 726
Body-mass index 0.06 0.05
<30 2279 1120
≥30 2408 1213
Estimated glomerular filtration rate 0.20 0.15
≥90 ml/min/1.73 m² 1050 488
60 to <90 ml/min/1.73 m² 2425 1238
<60 ml/min/1.73 m² 1212 607
Only coronary artery disease 2732 1340
Only peripheral artery disease 412 191
2 or 3 high-risk categories 878 451
Insulin 0.28 0.92
No 2435 1198
Yes 2252 1135
Statins or ezetimibe 0.54 0.23
No 1029 551
Yes 3658 1782
Antihypertensive therapy 0.80 0.41
No 241 112
Yes 4446 2221
ACE inhibitor or ARB 0.49 0.86
No 889 465
Yes 3798 1868
Beta-blocker 0.61 0.99
No 1631 835
Yes 3056 1498
Diuretic 0.72 0.46
No 2640 1345
Yes 2047 988
0.25 0.50 1.00 2.00
Favors Empagliflozin
Favors Placebo
0.25 0.50 1.00 2.00
Favors Empagliflozin
Favors Placebo

Diabetologia (2018) 61:2277–2289
https://doi.org/10.1007/s00125-018-4691-2

ARTICLE

Non-albuminuric renal impairment is a strong predictor of mortality in individuals with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study

Giuseppe Penno[1] · Anna Solini[2] · Emanuela Orsi[3] · Enzo Bonora[4] · Cecilia Fondelli[5] · Roberto Trevisan[6] · Monica Vedovato[7] · Franco Cavalot[8] · Olga Lamacchia[9] · Marco Scardapane[10] · Antonio Nicolucci[10] · Giuseppe Pugliese[11] · for the Renal Insufficiency And Cardiovascular Events (RIACE) Study Group



No. at risk						
All	15,656	14,926	14,110	13,179	8243	3
$Alb^-/eGFR^-$	9984	9707	9362	8949	5761	0
$Alb^+/eGFR^-$	2966	2795	2619	2430	1535	1
$Alb^-/eGFR^+$	1476	1352	1210	1060	558	2
$Alb^+/eGFR^+$	1230	1072	919	740	389	0

SGLT2i & CVD in T2D

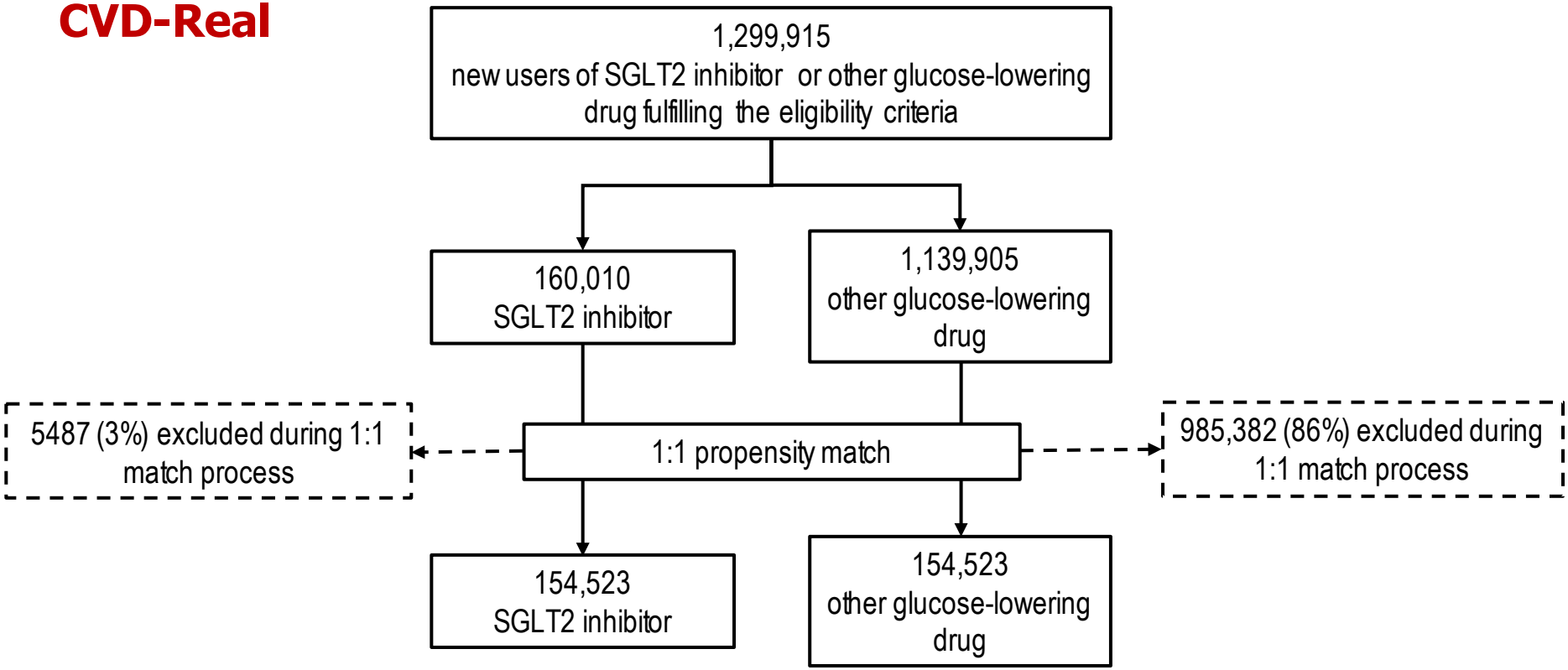
From RCTs to RWE and back

- SGLT2i protect from adverse CV outcomes in T2D patients with estabilished CVD
- Do they work in patients without established CVD?

SGLT2i & CVD in T2D

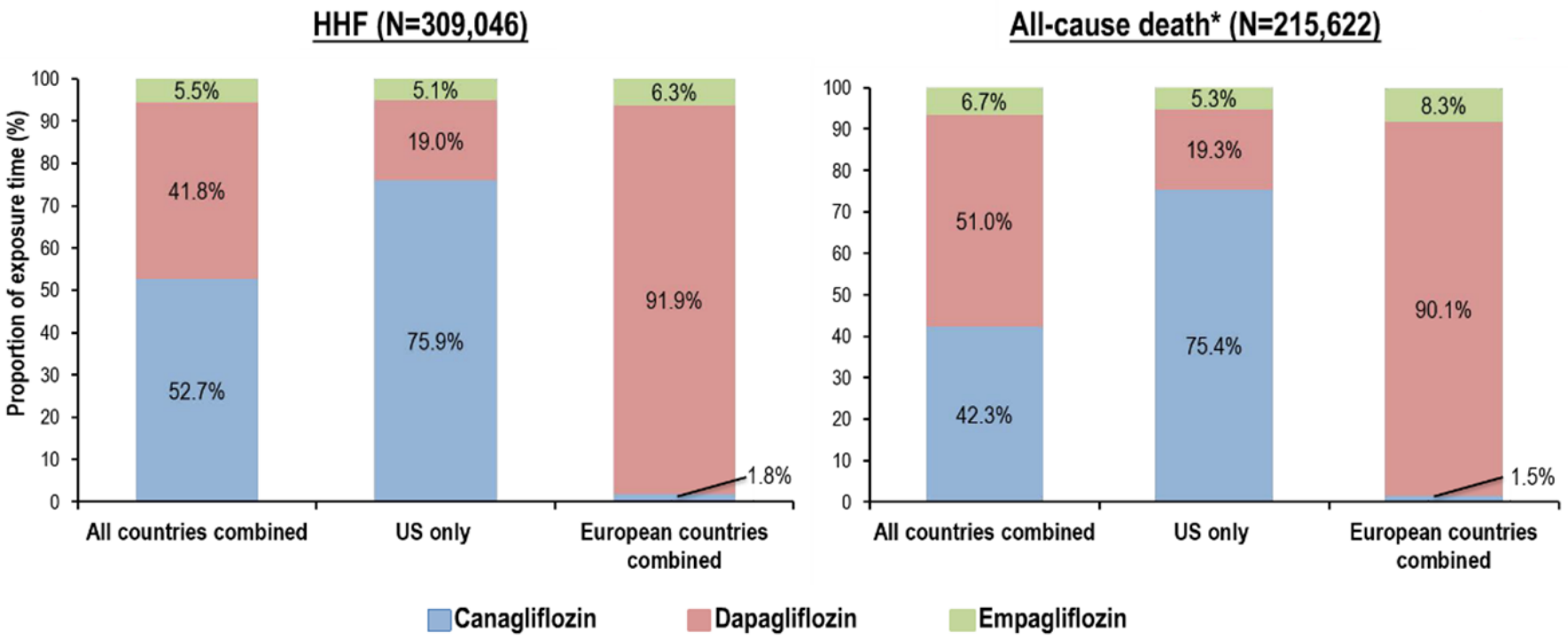
From RCTs to RWE and back

CVD-Real



Established CVD **13%**
Microangiopathy **27%**
CKD **3%**

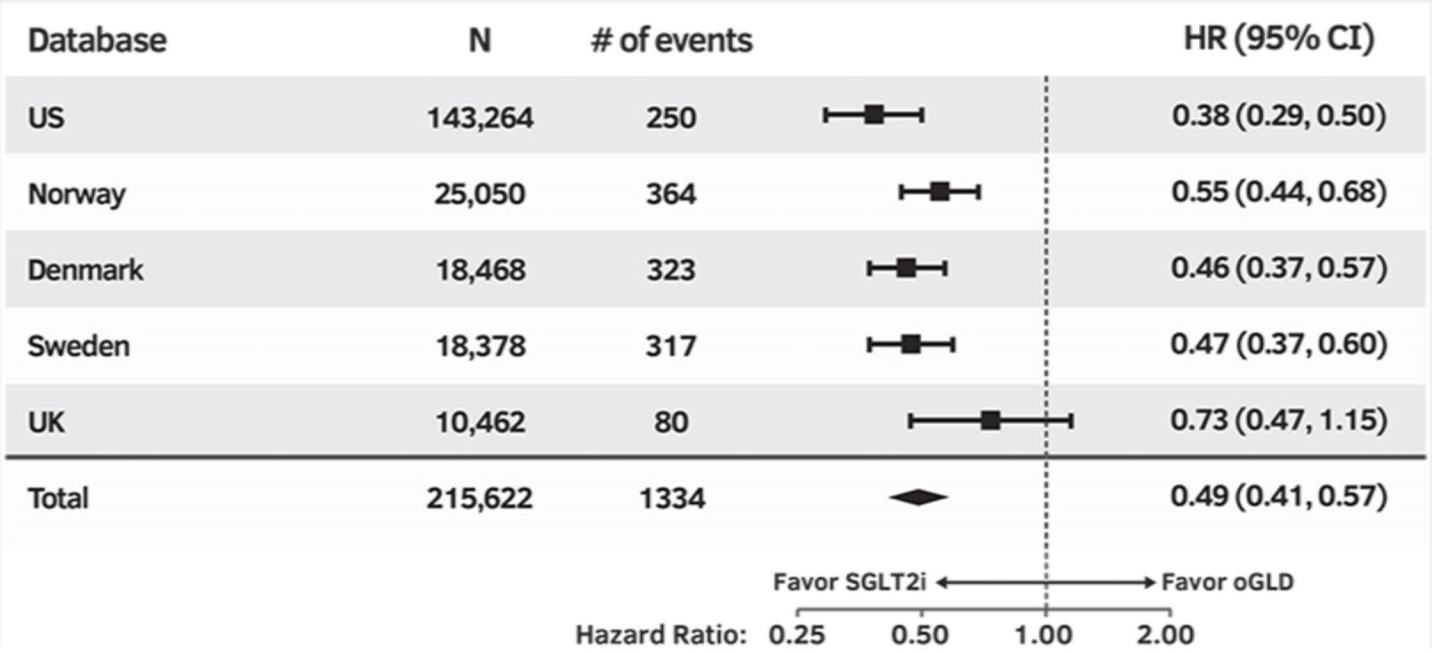
Type of SGLT-2 inhibitor



*Data shown are for all-cause death; data for HHF or all-cause death are similar

CVD-Real

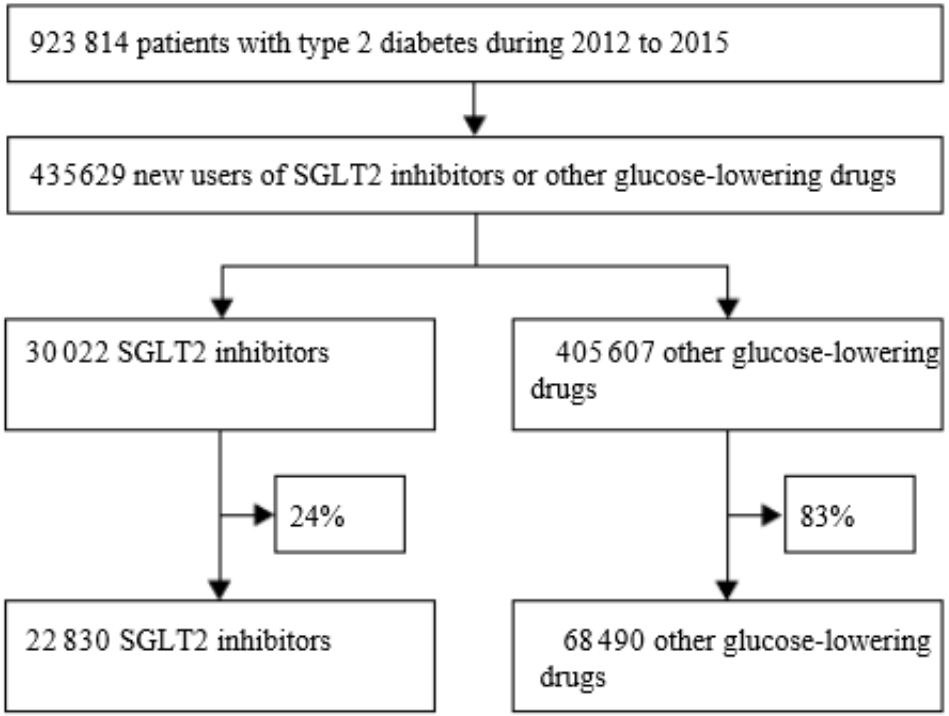
All-cause death



SGLT2i & CVD in T2D

From RCTs to RWE and back

CVD-Real Nordic



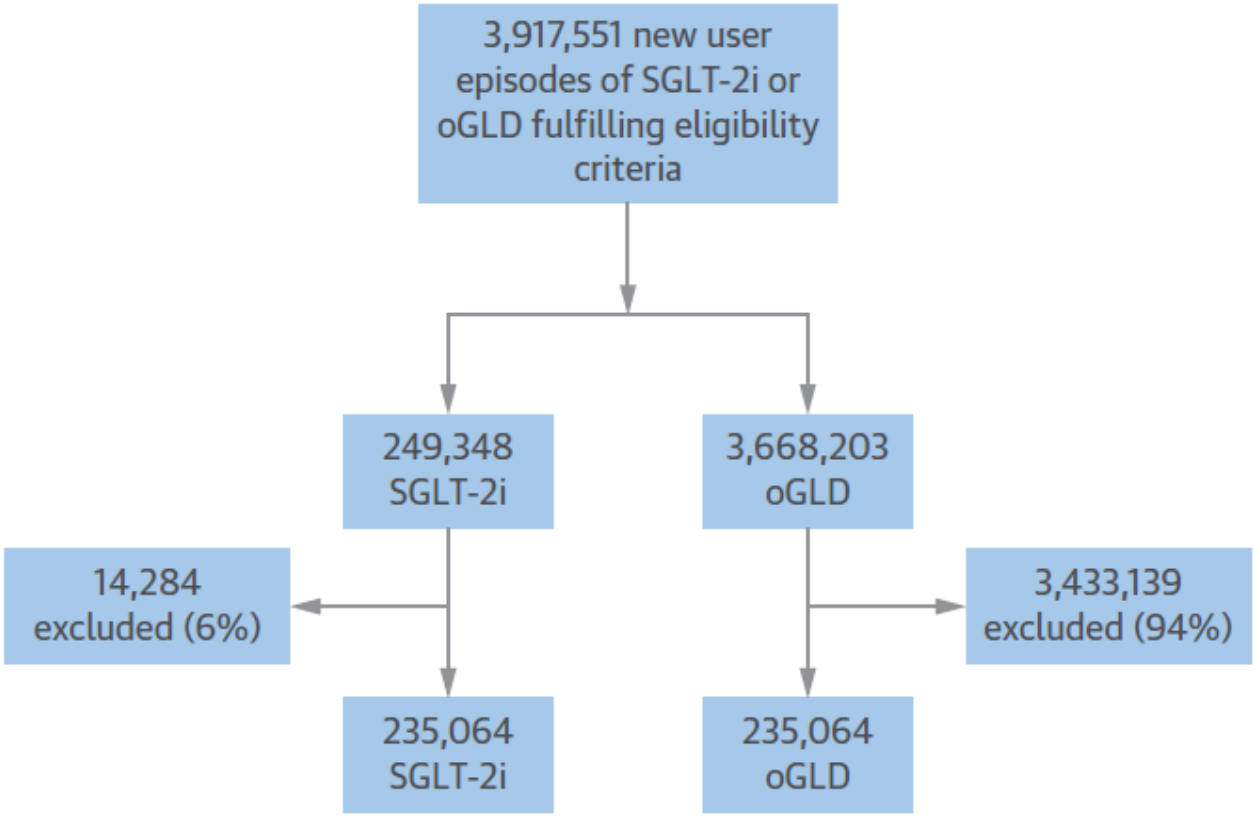
MACE	HR 0.78 (0.69-0.87)
CV death	HR 0.53 (0.40-0.71)
Death	HR 0.51 (0.45-0.58)
HHF	HR 0.70 (0.61-0.81)

Established CVD	**25%**
Microangiopathy	**25%**
CKD	**1%**

SGLT2i & CVD in T2D

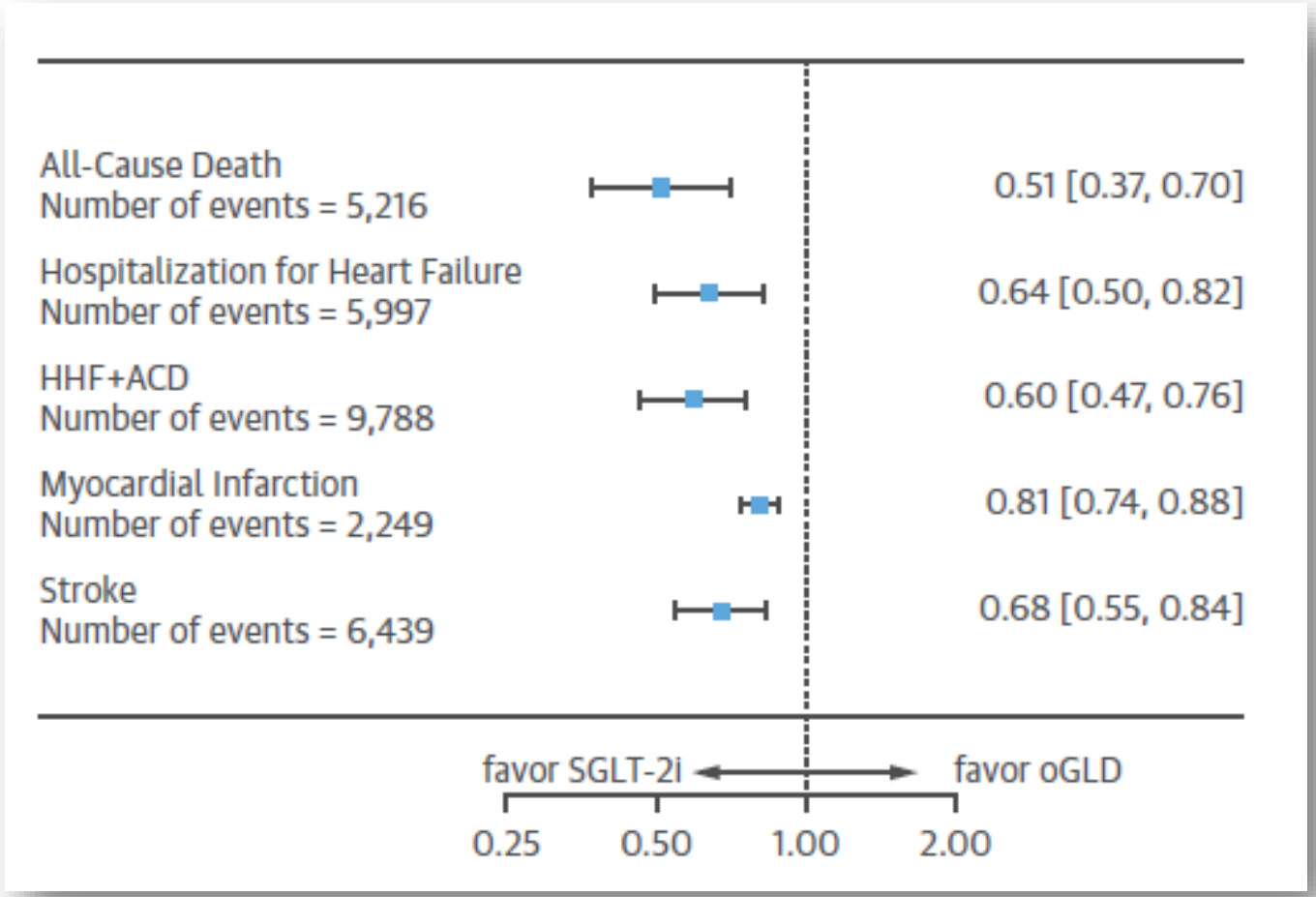
From RCTs to RWE and back

CVD-Real 2
(75% dapa)



CVD 27%
Micro 52%
CKD 2%

CVD-Real 2


All-Cause Death
Number of events = 5,216
0.51 [0.37, 0.70]
Hospitalization for Heart Failure
Number of events = 5,997
0.64 [0.50, 0.82]
HHF+ACD
Number of events = 9,788
0.60 [0.47, 0.76]
Myocardial Infarction
Number of events = 2,249
0.81 [0.74, 0.88]
Stroke
Number of events = 6,439
0.68 [0.55, 0.84]
favor SGLT-2i
favor oGLD
0.25
0.50
1.00
2.00

SGLT2i & CVD in T2D

From RCTs to RWE and back

- SGLT2i protect from adverse CV outcomes in T2D patients with estabilished CVD
- According to RWE. SGLT2i can protect from adverse CV outcomes also T2D patients without established CVD
- Can this be confirmed in RCTs?

SGLT2i & CVD in T2D

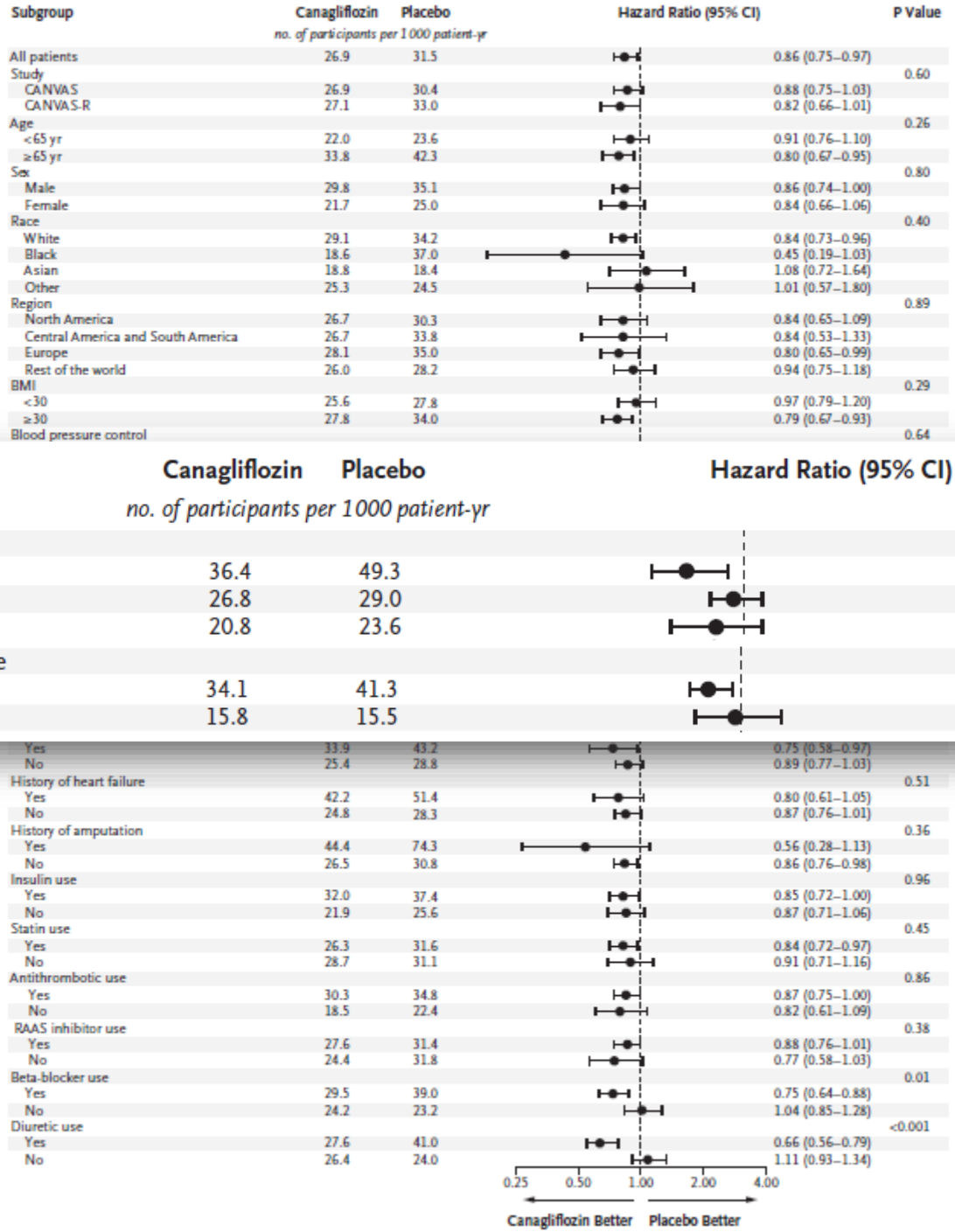
From RCTs to RWE and back

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Death	HR 0.68 (0.57-0.82)
HHF	HR 0.65 (0.50-0.85)

CANVAS



Subgroup	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no. of participants per 1000 patient-yr			
eGFR				0.20
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)	
History of cardiovascular disease				0.18
Yes	34.1	41.3	0.82 (0.72–0.95)	
No	15.8	15.5	0.98 (0.74–1.30)	

SGLT2i & CVD in T2D

From RCTs to RWE and back

DECLARE

Patients

- N=17.160
- N=10.186 (59.4%) without atherosclerotic CVD
- Median f-up 4.2 years

Endpoints

- Safety: 3p MACE
- Efficacy: Coprimary: 3p MACE & <CV Death or HHF>
  Secondary: Renal composite
  All-cause mortality

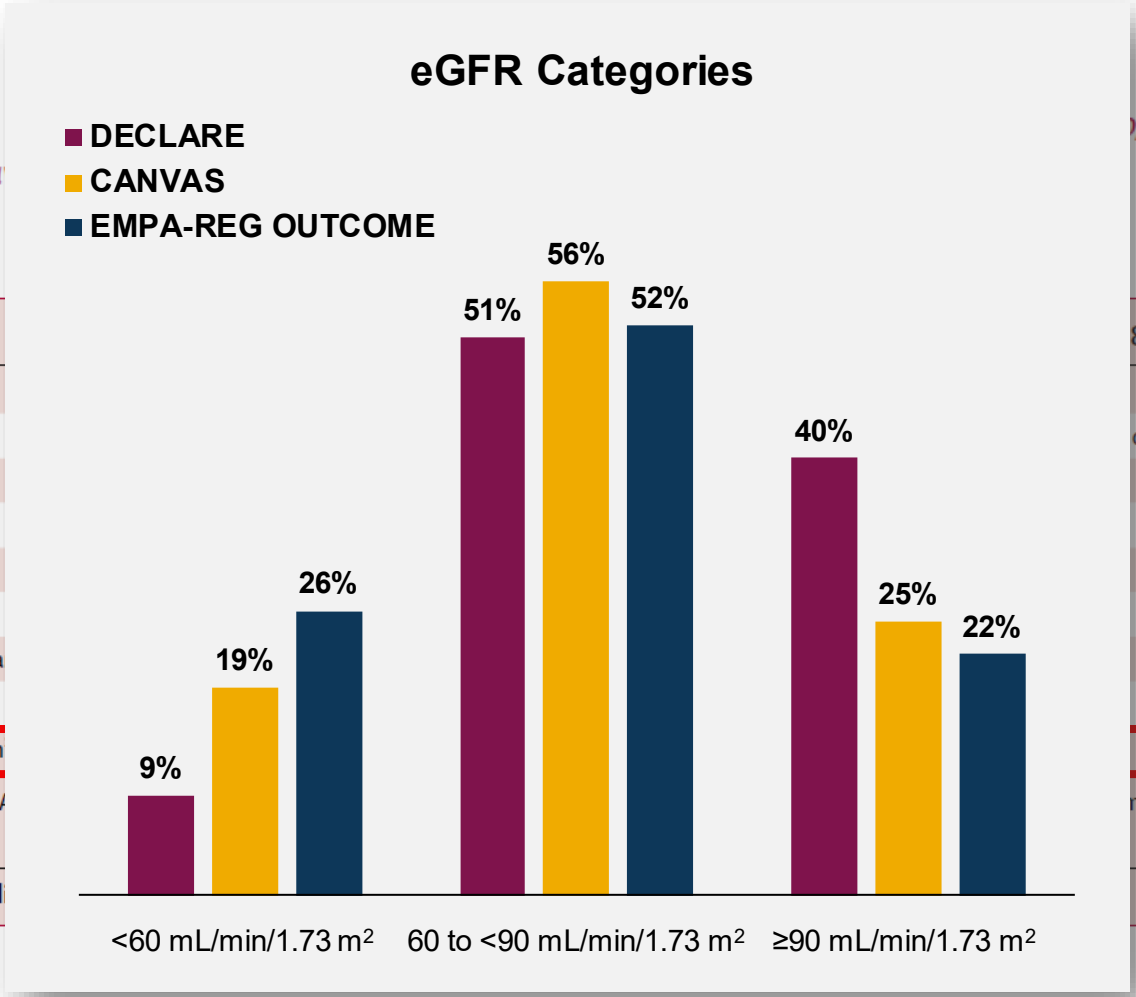
SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, … Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, La…

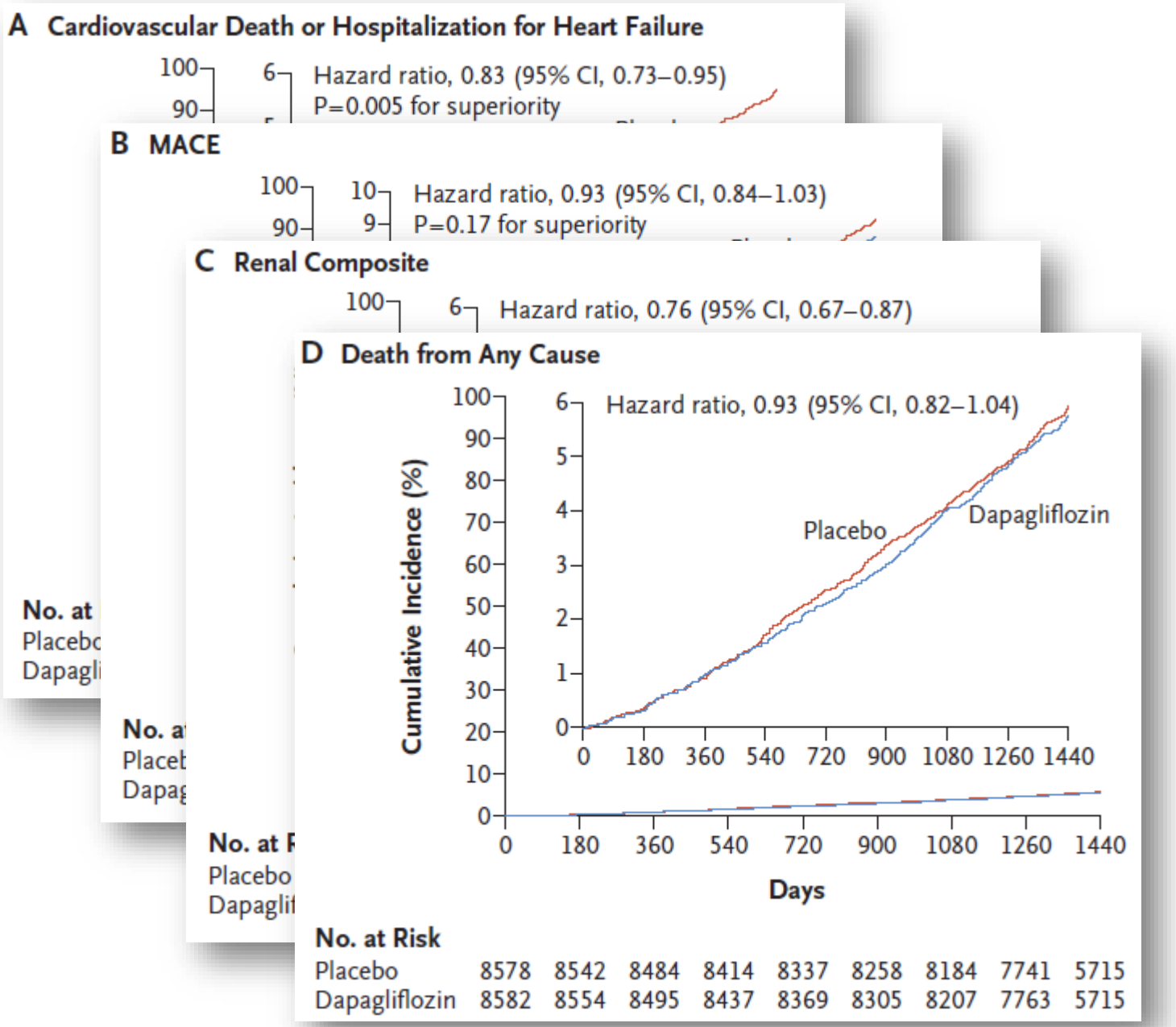
Drug
Doses analysed
Median follow-up time, years
Trial participants
Age, mean
Women
Patients with established atherosclerotic ca
Patients with a history of heart failure
Patients with eGFR <60 mL/min per 1·73 m

Data are n (%) unless otherwise specified. The CA… filtration rate.

Table: Randomised controlled phase 3/4 cl…

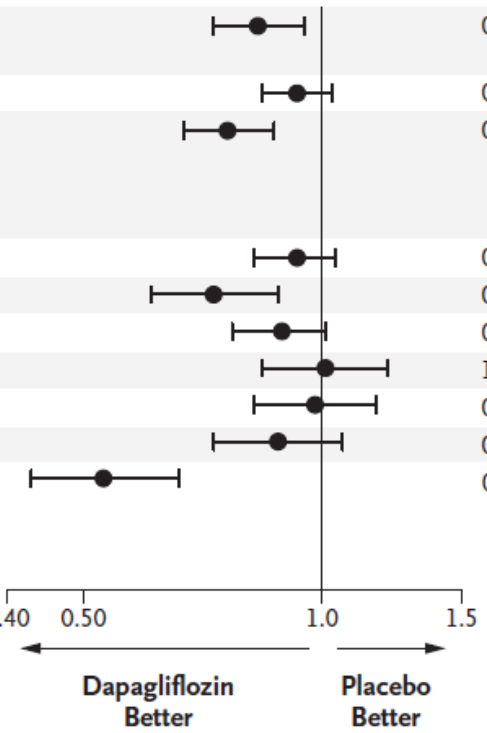


DECLARE


A Cardiovascular Death or Hospitalization for Heart Failure
Hazard ratio, 0.83 (95% CI, 0.73–0.95)
P=0.005 for superiority
B MACE
Hazard ratio, 0.93 (95% CI, 0.84–1.03)
P=0.17 for superiority
C Renal Composite
Hazard ratio, 0.76 (95% CI, 0.67–0.87)
D Death from Any Cause
Hazard ratio, 0.93 (95% CI, 0.82–1.04)
Placebo
Dapagliflozin
Cumulative Incidence (%)
Days
No. at Risk
Placebo 8578 8542 8484 8414 8337 8258 8184 7741 5715
Dapagliflozin 8582 8554 8495 8437 8369 8305 8207 7763 5715

DECLARE

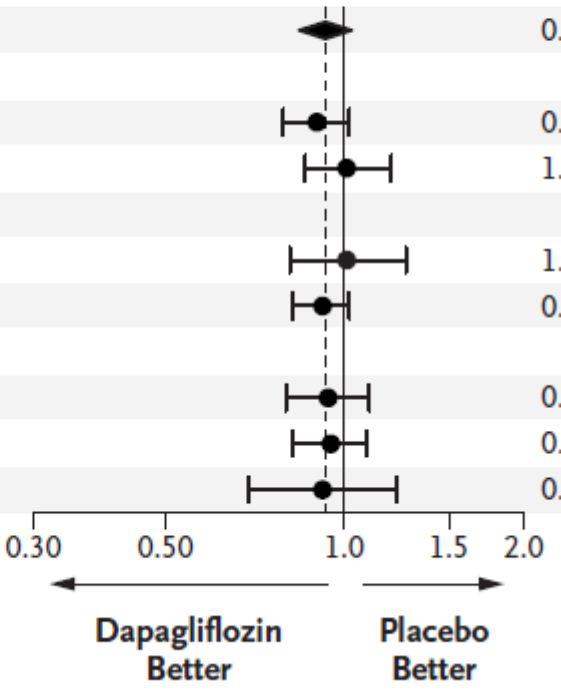
Outcome	Dapagliflozin (N=8582)		Placebo (N=8578)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	



DECLARE

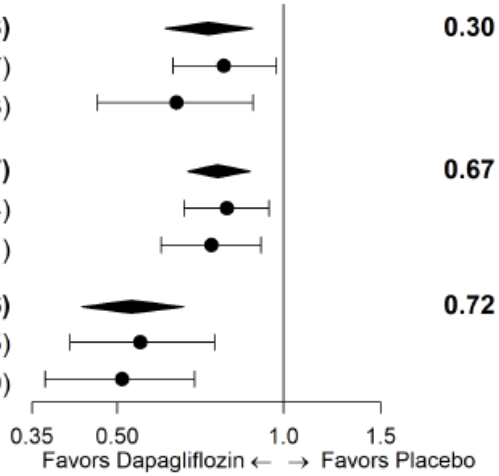
MACE

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/no. of patients			
Total cohort	756/8582	803/8578	0.93 (0.84–1.03)	
Risk group				0.25
ASCVD	483/3474	537/3500	0.90 (0.79–1.02)	
MRF	273/5108	266/5078	1.01 (0.86–1.20)	
History of heart failure				0.46
Yes	153/852	151/872	1.01 (0.81–1.27)	
No	603/7730	652/7706	0.92 (0.82–1.02)	
eGFR				0.99
≥90 ml/min/1.73 m^2	304/4137	309/4025	0.94 (0.80–1.10)	
60 to <90 ml/min/1.73 m^2	367/3838	390/3894	0.95 (0.82–1.09)	
<60 ml/min/1.73 m^2	85/606	104/659	0.92 (0.69–1.23)	

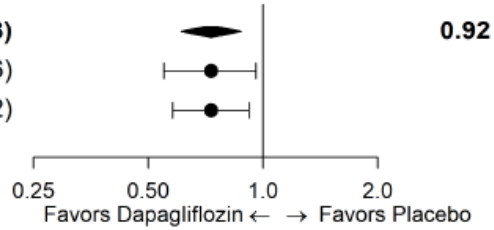


DECLARE

Outcomes	Dapagliflozin n/N	Placebo n/N	Hazard Ratio (95% CI)	P value for interaction
HHF	**212/8582**	**286/8578**	**0.73 (0.61-0.88)**	**0.30**
ASCVD	151/3474	192/3500	0.78 (0.63-0.97)	
MRF	61/5108	94/5078	0.64 (0.46-0.88)	
40% decrease in eGFR, ESRD, or renal or CV death	**370/8582**	**480/8578**	**0.76 (0.67-0.87)**	**0.67**
ASCVD	216/3474	275/3500	0.79 (0.66-0.94)	
MRF	154/5108	205/5078	0.74 (0.60-0.91)	
40% decrease in eGFR, ESRD, or renal death	**127/8582**	**238/8578**	**0.53 (0.43-0.66)**	**0.72**
ASCVD	65/3474	118/3500	0.55 (0.41-0.75)	
MRF	62/5108	120/5078	0.51 (0.37-0.69)	



Outcomes	Dapagliflozin n/N	Placebo n/N	Hazard Ratio (95% CI)	P value for interaction
HHF	**212/8582**	**286/8578**	**0.73 (0.61-0.88)**	**0.92**
Prior HF	87/852	115/872	0.73 (0.55-0.96)	
No HF	125/7730	171/7706	0.73 (0.58-0.92)	



SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

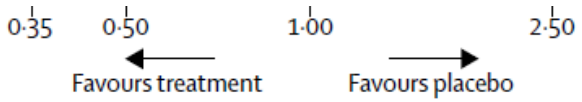
Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

Lancet. 10 Nov 2018

How DECLARE enriches state of the art

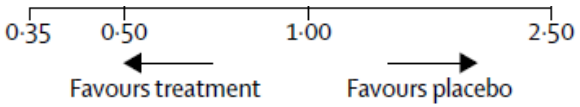
3p MACE

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756/6656	2900/6656	796	34·1	41·3	32·4		0·82 (0·72–0·95)
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	215	15·8	15·5	25·9		0·98 (0·74–1·30)



CVD & HHF

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19·7	30·1	30·9		0·66 (0·55–0·79)
CANVAS Program	3756/6656	2900/6656	524	21·0	27·4	32·8		0·77 (0·65–0·92)
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	128	8·9	9·8	30·2		0·83 (0·58–1·19)

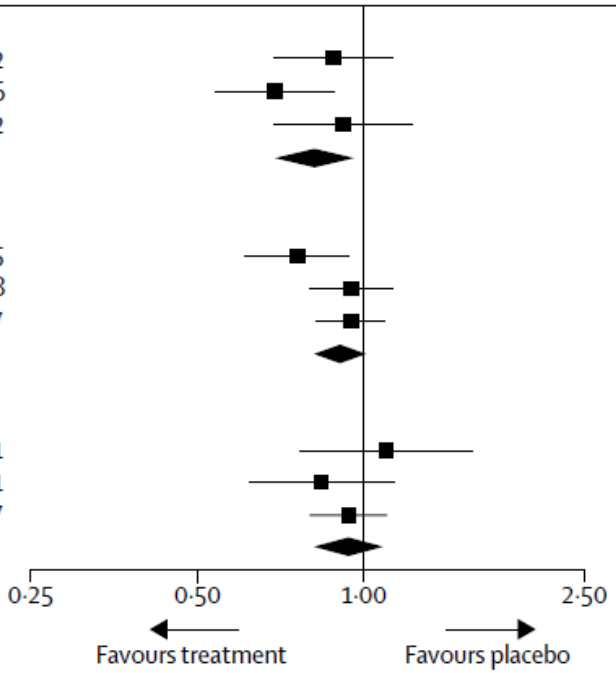


How DECLARE enriches state of the art

Sensitivity analysis by renal function

3p MACE

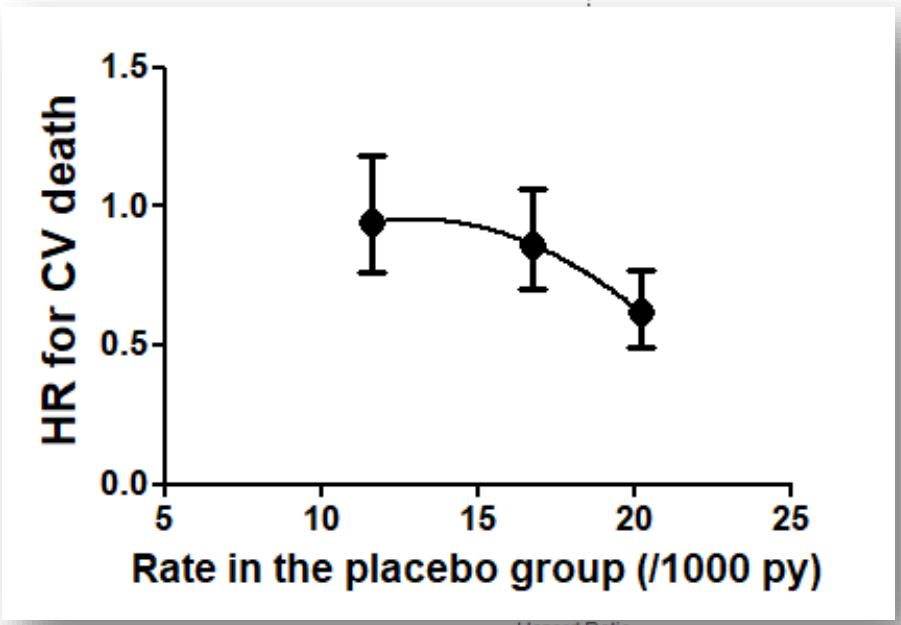
	Patients		Events	Events per 1000		Weight	HR (95% CI)
eGFR <60 mL/min per m²							
EMPA-REG OUTCOME	1212/1819	607/1819	275	52·7	60·5	36·2	0·88 (0·69–1·13)
CANVAS Program	NA/2039	NA/2039	261	36·3	49·5	36·6	0·69 (0·54–0·89)
DECLARE-TIMI 58	606/1265	659/1265	189	37·3	43·1	27·2	0·92 (0·69–1·23)
Fixed effects model for eGFR <60 (p=0·0077)							**0·82 (0·70–0·95)**
eGFR 60 to <90 mL/min per m²							
EMPA-REG OUTCOME	2423/3661	1238/3661	351	30·8	40·6	22·5	0·76 (0·61–0·94)
CANVAS Program	NA/5625	NA/5625	563	26·8	29·0	32·8	0·95 (0·80–1·13)
DECLARE-TIMI 58	3838/7732	3894/7732	757	24·5	25·8	44·7	0·95 (0·82–1·09)
Fixed effects model for eGFR 60 to <90 (p=0·0520)							**0·91 (0·82–1·00)**
eGFR ≥90 mL/min per m²							
EMPA-REG OUTCOME	1050/1538	488/1538	146	35·4	32·2	15·1	1·10 (0·77–1·57)
CANVAS Program	NA/2476	NA/2476	187	20·8	23·6	21·1	0·84 (0·62–1·13)
DECLARE-TIMI 58	4137/8162	4025/8162	613	18·8	19·7	63·7	0·94 (0·80–1·10)
Fixed effects model for eGFR ≥90 (p=0·35)							**0·94 (0·82–1·07)**



How DECLARE enriches state of the art

Background risk in the placebo group

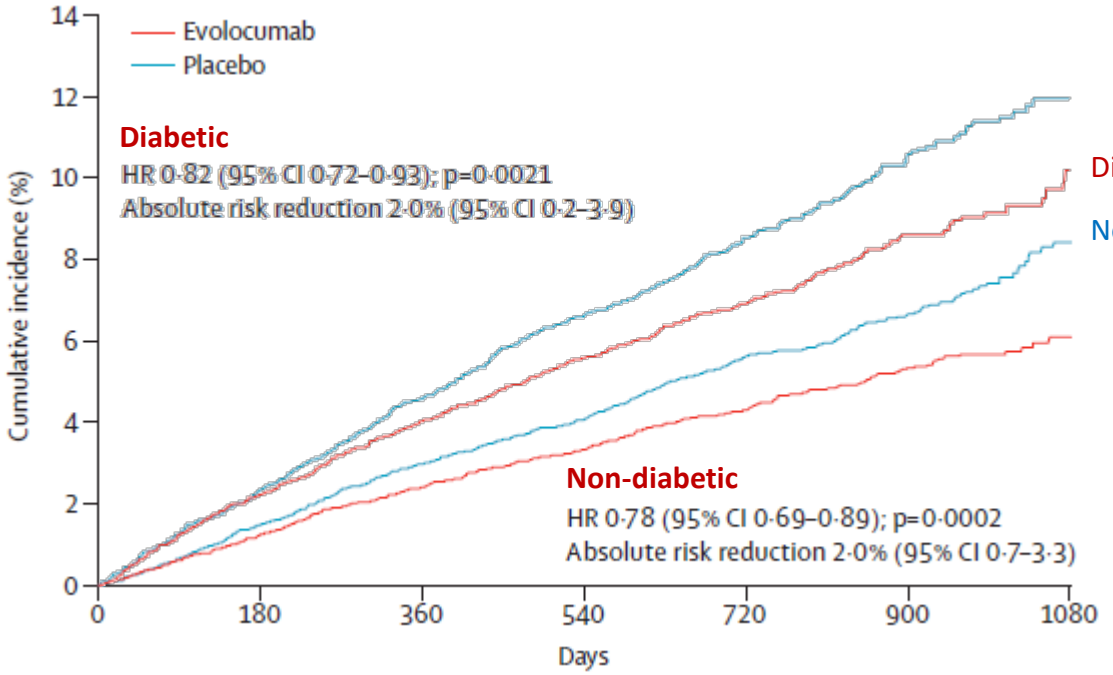
CVD	Patients	Events	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	Weights (%)	HR [95% CI]
Atherosclerotic Cardiovascular Disease:						
EMPA-REG OUTCOME	7020	309				
CANVAS Program	6656	362				
DECLARE-TIMI 58	6974	316				
FE Model for ASCVD (P-value = 0.0005)						
Multiple Risk Factor:						
CANVAS Program	3486	91				
DECLARE-TIMI 58	10186	178				
FE Model for MRF (P-value = 0.89)						



Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial

Marc S Sabatine, Lawrence A Leiter, Stephen D Wiviott, Robert P Giugliano, Prakash Deedwania, Gaetano M De Ferrari, Sabina A Murphy, Julia F Kuder, Ioanna Gouni-Berthold, Basil S Lewis, Yehuda Handelsman, Armando Lira Pineda, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen

Key secondary endpoint (MACE)



Diabetic + Evo: LDL 31 mg/dl

Non-diabetic + Plb: LDL 94 mg/dl

SGLT2i & CVD in T2D

From RCTs to RWE and back

Other important take-home messages after intergrating DECLARE into state of the art:

- CV protection by SGLT2i mainly refers to HHF
- eGFR drives the risk
- Residual risk remains high
- Renal protection even more important

SGLT2i & CVD in T2D

From RCTs to RWE and back

- SGLT2i protect from adverse CV outcomes in T2D patients with estabilished CVD
- According to RWE. SGLT2i can protect from adverse CV outcomes also T2D patients without established CVD
- DECLARE confirms that SGLT2i protect from adverse CV outcomes also in T2D patients without established CVD
- What about safety?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

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

increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; hazard ratio, 1.97; 95% CI, 1.41 to 2.75); amputations were primarily at the level of the toe or metatarsal.

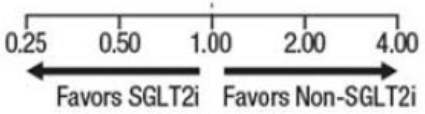
Circulation

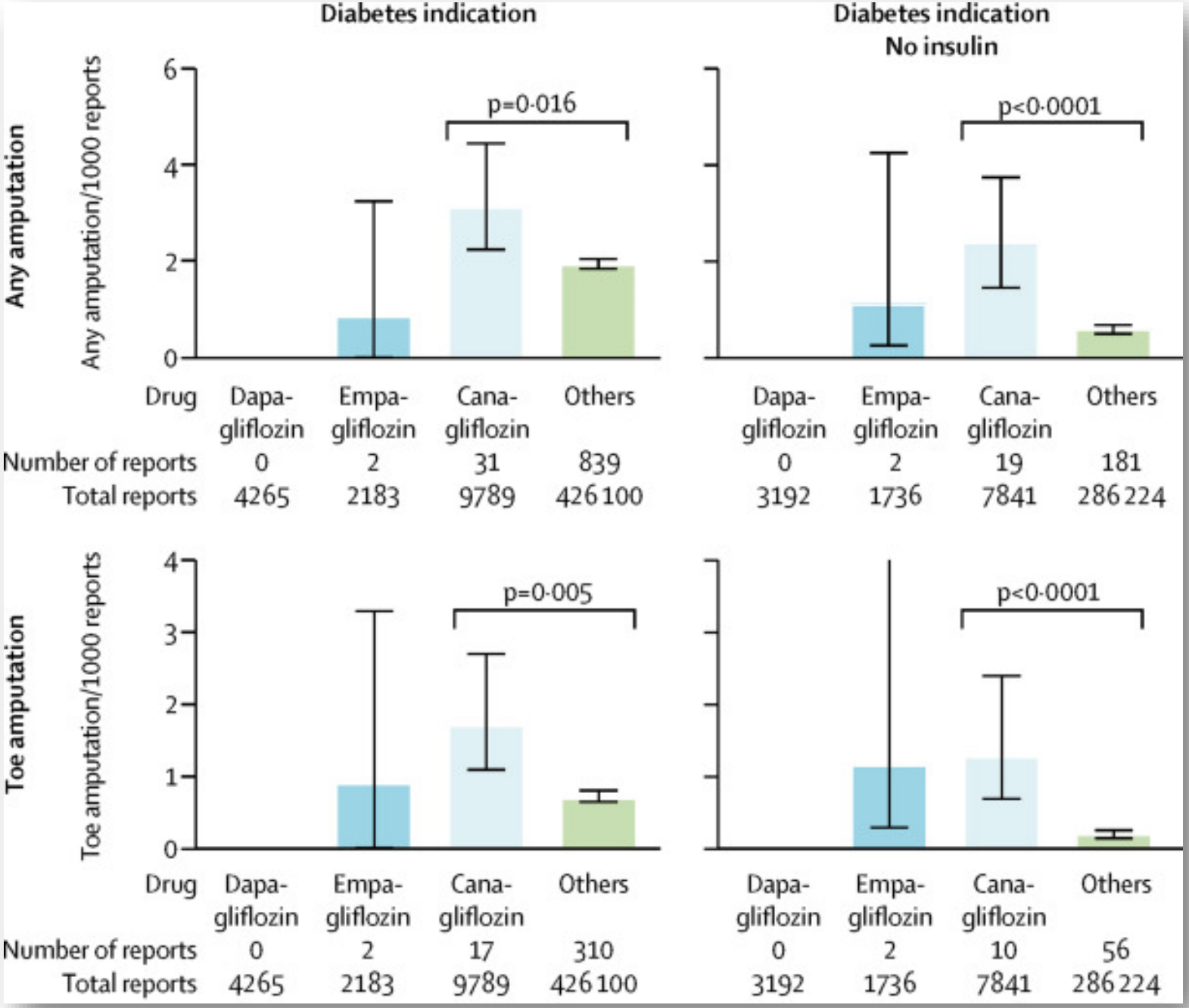
ORIGINAL RESEARCH ARTICLE

Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Co-Transporter 2 Inhibitor: Results From the EASEL Population-Based Cohort Study

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

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




Diabetes indication
Diabetes indication
No insulin
Any amputation
Any amputation/1000 reports
6
4
2
0
p=0·016
p<0·0001
Drug
Dapa-gliflozin
Empa-gliflozin
Cana-gliflozin
Others
Number of reports
0
2
31
839
19
181
Total reports
4265
2183
9789
426 100
3192
1736
7841
286 224
Toe amputation
Toe amputation/1000 reports
4
3
2
1
0
p=0·005
p<0·0001
Drug
Dapa-gliflozin
Empa-gliflozin
Cana-gliflozin
Others
Number of reports
0
2
17
310
10
56
Total reports
4265
2183
9789
426 100
3192
1736
7841
286 224

Canagliflozin and amputations



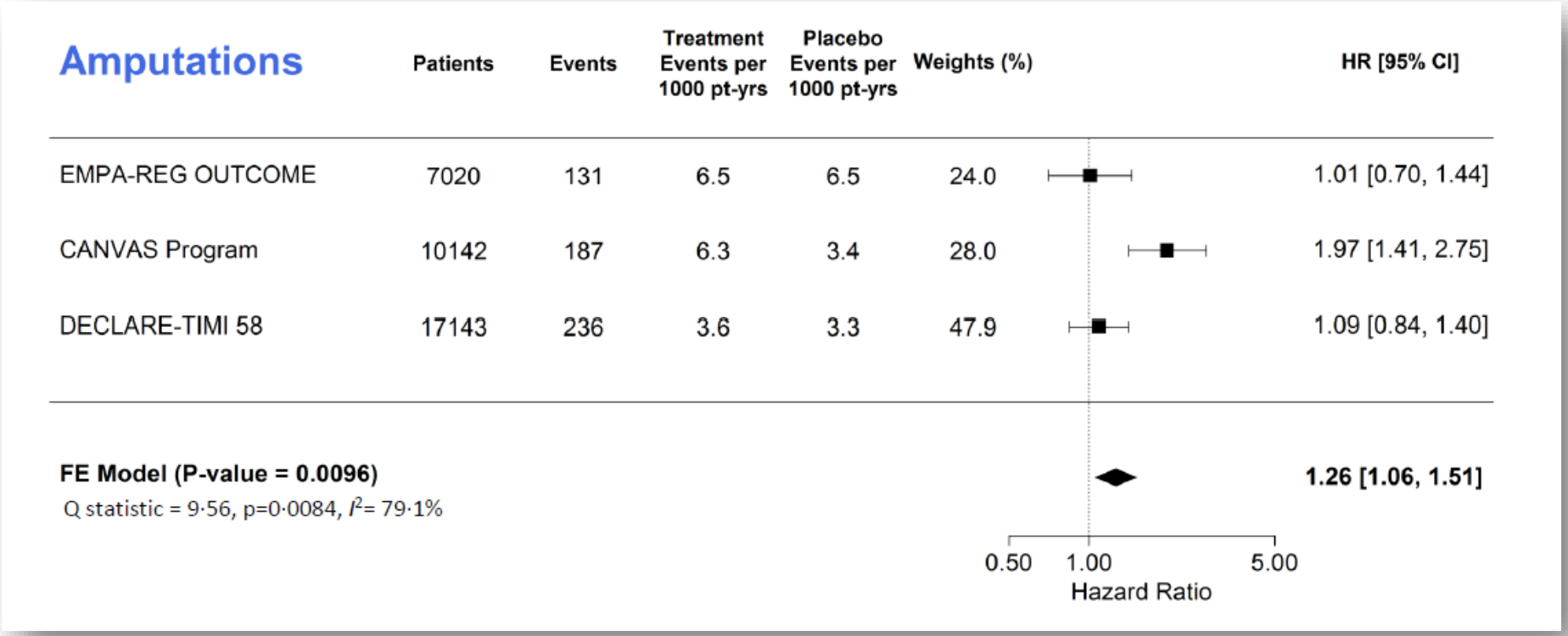
Source	Point estimate	95% C.I.
CANVAS	1.97	(1.41-2.75)
FAERS	2.40	(1.50-3.80)
EASEL	1.99	(1.12-3.51)

DECLARE

Table 2. Safety Events.*

Event	Dapagliflozin (N=8574)	Placebo (N=8569)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Serious adverse event	2925 (34.1)	3100 (36.2)	0.91 (0.87–0.96)	<0.001
Adverse event leading to discontinuation of trial regimen	693 (8.1)	592 (6.9)	1.15 (1.03–1.28)	0.01
Major hypoglycemic event	58 (0.7)	83 (1.0)	0.68 (0.49–0.95)	0.02
Diabetic ketoacidosis	27 (0.3)	12 (0.1)	2.18 (1.10–4.30)	0.02
Amputation	123 (1.4)	113 (1.3)	1.09 (0.84–1.40)	0.53
Fracture	457 (5.3)	440 (5.1)	1.04 (0.91–1.18)	0.59
Symptoms of volume depletion	213 (2.5)	207 (2.4)	1.00 (0.83–1.21)	0.99
Acute kidney injury	125 (1.5)	175 (2.0)	0.69 (0.55–0.87)	0.002
Genital infection	76 (0.9)	9 (0.1)	8.36 (4.19–16.68)	<0.001
Urinary tract infection	127 (1.5)	133 (1.6)	0.93 (0.73–1.18)	0.54
Cancer	481 (5.6)	486 (5.7)	0.99 (0.87–1.12)	0.83
Bladder cancer	26 (0.3)	45 (0.5)	0.57 (0.35–0.93)	0.02
Breast cancer	36 (0.4)	35 (0.4)	1.02 (0.64–1.63)	0.92
Hypersensitivity	32 (0.4)	36 (0.4)	0.87 (0.54–1.40)	0.57
Hepatic event	82 (1.0)	87 (1.0)	0.92 (0.68–1.25)	0.60

META-ANALYSIS



SGLT2i & CVD in T2D

From RCTs to RWE and back

- SGLT2i protect from adverse CV outcomes in T2D patients with estabilished CVD
- According to RWE. SGLT2i can protect from adverse CV outcomes also T2D patients without established CVD
- DECLARE confirms that SGLT2i protect from adverse CV outcomes also in T2D patients without established CVD
- Data on GTI and DKA are highly consisent. while only canagliflozin showed excess risk of amputations
- Back to the real world…

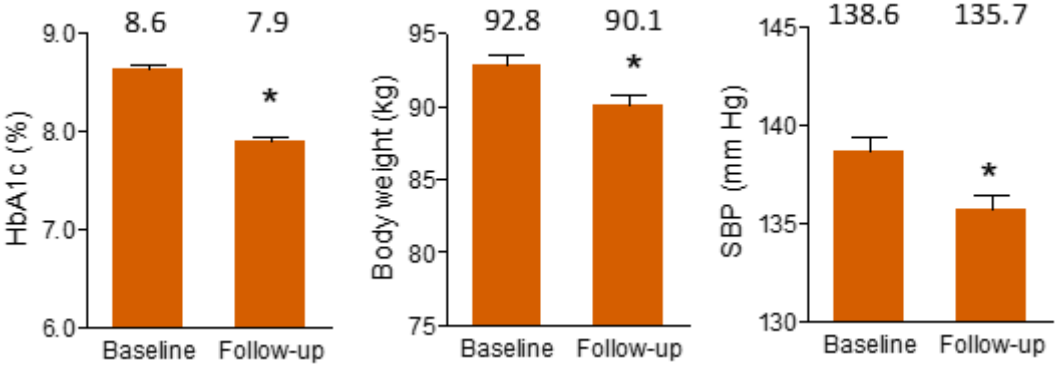
SID DARWIN-T2D

DApagliflozin Real World evIdeNce in Type 2 Diabetes

Characteristic	DECLARE	DARWIN-T2D
Age, yrs	64	60
Sex male, %	73	58
BMI, kg/M^2	32	33
Duration, yrs	11	12
HbA1c, %	8.3	8,6
eGFR, ml/min/1.73 mq	85.4	107
Insulin, %	41.6	55
CVD, %	40.5	31.4

SID DARWIN-T2D

DApagliflozin Real World evIdeNce in Type 2 Diabetes

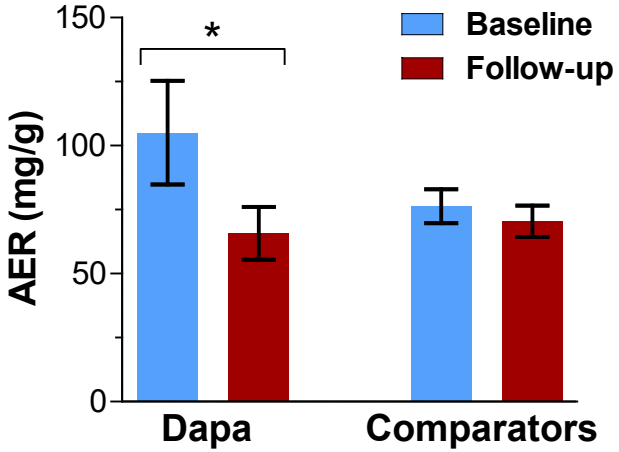


Estimated CV risk

	Baseline	Follow-up	p
CHD	37.7±25.6%	32.9±24.4%	<0.001
Fatal CHD	32.3±25.8%	27.8±24.5%	<0.001
Stroke	29.8±30.0%	28.7±29.6%	<0.001
Fatal stroke	5.0±6.2%	4.5±5.5%	0.015

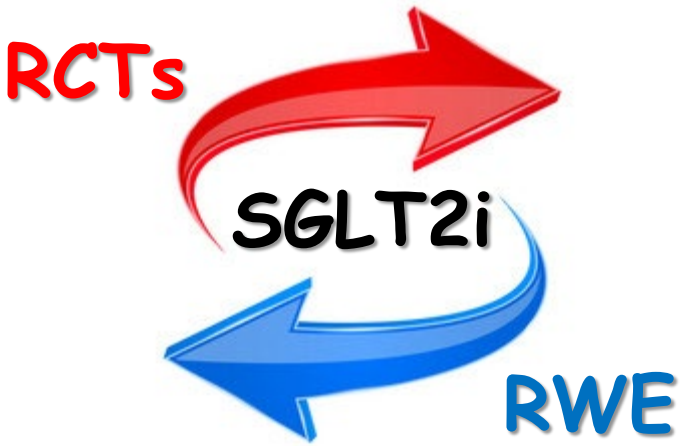
Effective reduction of A1c. body weight. blood pressure

(Fadini et al. DOM 2018)



Effective reduction in AER without eGFR worsening

(Fadini et al. DOM 2018b)


RCTs
SGLT2i
RWE