Effects of Dapagliflozin on Progression of Diabetic Kidney Disease: Analysis from DECLARE-TIMI 58 Trial

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האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

Disclosures

- **Advisory Board:** Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Novartis, AstraZeneca
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Background (1)

- Diabetes is the leading cause of ESRD worldwide[1,2].

- Treatment of diabetic kidney disease includes[1,2]:
  - optimal blood pressure control
  - optimal glucose control
  - RAS blockade
- The residual risk for renal deterioration amongst patients with T2D is large[1-3].

- Early identification and interventions is more effective than later interventions for the prevention of adverse renal outcomes[3].

[1]Molitch ME, et al. Kidney Int 2015; 87: 20–30. [2]Roscioni SS, et al. Nat Rev Nephrol 2014; 10: 77–87. [3]Schievink B, et al. Diabetes Obes Metab 2016; 18: 64–71.

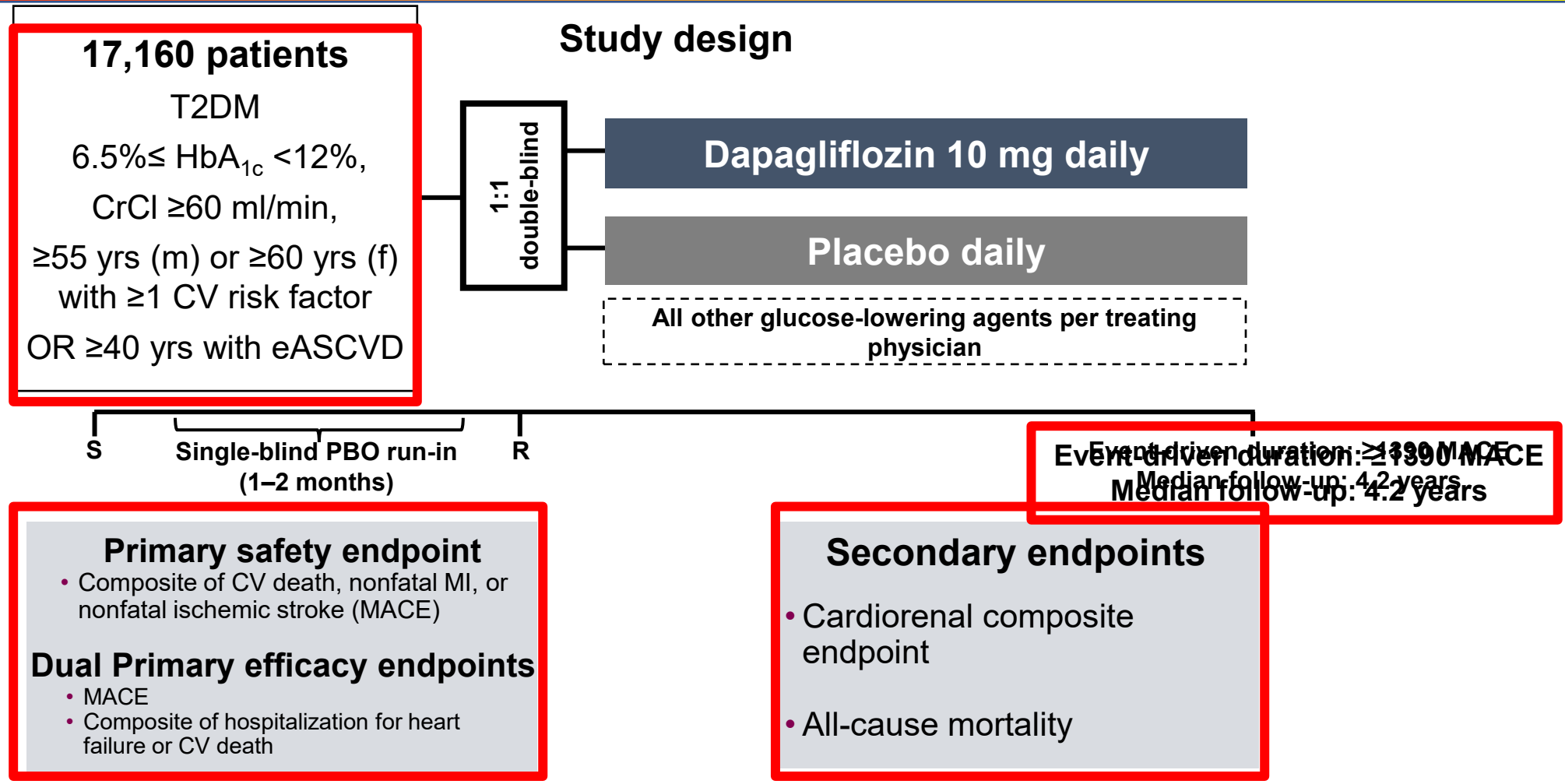
Background (2)

- SGLT2i have demonstrated their ability to reduce adverse renal outcomes and slow the progression of CKD in the:
  - EMPA REG OUTCOME TRIAL
  - CANVAS PROGRAM
  - CREDENCE TRIAL

- However, most patients in these trials had previous ASCVD and/or renal disease (reduced eGFR and/or increased UACR).
- We herein report the renal outcomes with dapagliflozin in the **DECLARE-TIMI 58 trial**, which included either patients with risk factors for (59.4%) or ASCVD (40.6%) and the majority of patients had preserved renal function.

Wanner C, et al. N Engl J Med 2016; 375: 323–34. Neal B, et al. N Engl J Med 2017; 377: 644–57. Perkovic V, et al. N Engl J Med 2019; published online April 14.

DECLARE-TIMI 58 Study Design



Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110;. Wiviott SD, et al. *Am Heart J* 2018;200:83–89; 3. Wiviott SD, et al. *N Engl J Med* 2018 [Epub ahead of print]

DECLARE-TIMI 58 Study Design

17,160 patients

T2DM

6.5%≤ HbA_{1c} <12%,

CrCl ≥60 ml/min,

≥55 yrs (m) or ≥60 yrs (f) with ≥1 CV risk factor

OR ≥40 yrs with eASCVD

Study design

1:1 double-blind

- **Dapagliflozin 10 mg daily**
- **Placebo daily**

All other glucose-lowering agents per treating physician

S — **Single-blind PBO run-in (1–2 months)** — **R**

Event-driven duration: ≥1390 MACE
Median follow-up: 4.2 years

Primary safety endpoint

- Composite of CV death, nonfatal MI, or nonfatal ischemic stroke (MACE)

Dual Primary efficacy endpoints

- MACE
- Composite of hospitalization for heart failure or CV death

Secondary endpoints

- Cardiorenal composite endpoint
- All-cause mortality

The trial met only one of its dual primary outcomes for superiority: all other analyses should be considered hypothesis generating.

Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110;. Wiviott SD, et al. *Am Heart J* 2018;200:83–89; 3. Wiviott SD, et al. *N Engl J Med* 2018 [Epub ahead of print]

Definition of Renal Outcomes in the DECLARE-TIMI 58 Trial(1)

Cardiorenal Composite Outcome:

- Sustained confirmed (two tests at the central laboratory at least 4 weeks apart) decline of at least 40% in eGFR to less than 60 mL/min per 1·73m^2,
- End-stage renal disease (defined as dialysis for at least 90 days, kidney transplantation, or confirmed sustained eGFR <15mL/min per 1·73 m^2),
- Death from renal causes,
- Cardiovascular death;

Renal-specific Outcome:

- All of the above without cardiovascular death;

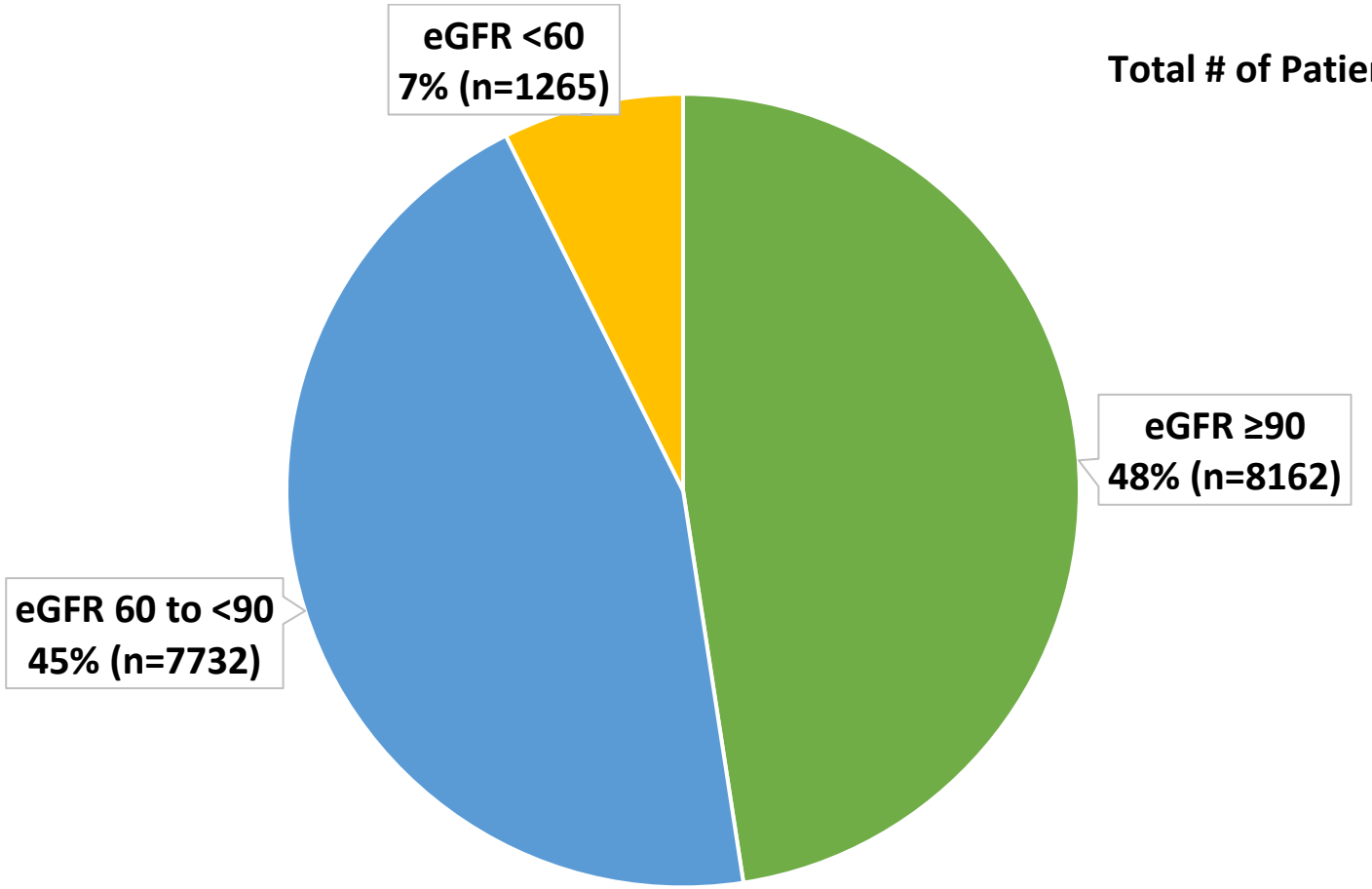
Definition of Renal Outcomes in the DECLARE-TIMI 58 Trial(2)

- The components of the composite outcomes
- Changes in the cardiorenal and renal specific composite outcomes by pre-defined subgroups
- eGFR by treatment group at different time points

- eGFR was calculated according to creatinine measurements at a central laboratory at screening, baseline, 6 months, 12 months, and yearly thereafter.

- UACR based outcomes and other outcomes- will be presented at OR244

Distribution of eGFR Categories Amongst the DECLARE-TIMI 58 Population



Total # of Patients: 17159

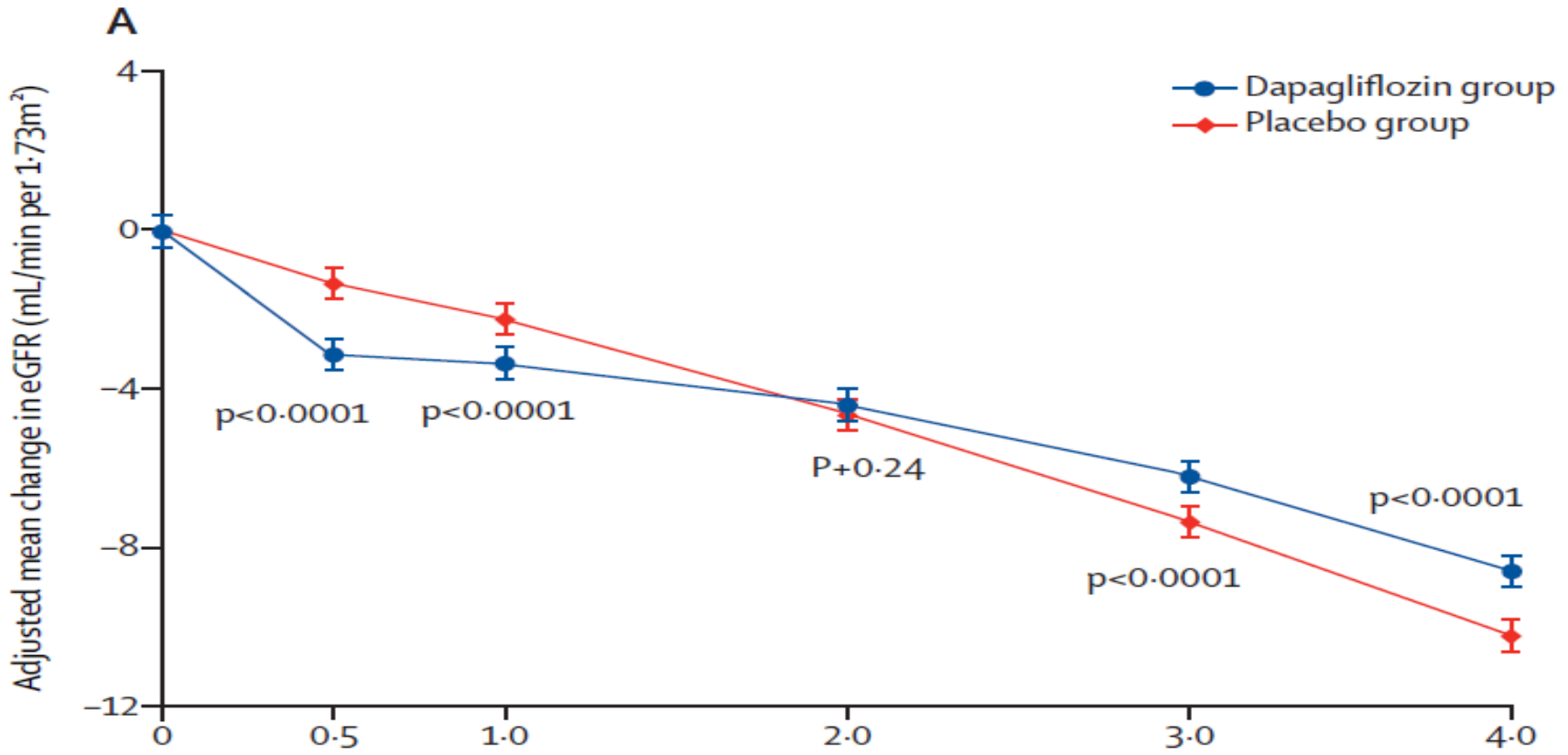
Baseline Characteristics by eGFR Categories at Baseline

Characteristics	eGFR ≥90 (n=8162)	eGFR 60 to <90 (n=7732)	eGFR <60 (n=1265)	P-value
Age, years	61·2 (6·1)	66·2 (6·5)	67·3 (6·6)	<0·0001
Sex: Female- n (%)	3105 (38·0%)	2866 (37·1%)	451 (35·7%)	0.1783
BMI- Median (IQR)	31·6 (6·1)	32·1 (5·9)	34·5 (6·0)	<0·0001
HbA1c- Median (IQR)	8·5 (1·2)	8·1 (1·1)	8·2 (1·2)	<0·0001
Medical History:				
ASCVD- n (%)	3193 (39·1%)	3138 (40·6%)	643 (50·8%)	<0·0001
Hypertension- n (%)	7133 (87·4%)	7088 (91·7%)	1205 (95·3%)	<0·0001
Hyperlipidemia- n (%)	6370 (78·0%)	6327 (81·8%)	1098 (86·8%)	<0·0001

Baseline Characteristics by eGFR Categories at Baseline

Characteristics	eGFR ≥90 (n=8162)	eGFR 60 to <90 (n=7732)	eGFR <60 (n=1265)	P-value
ACEI/ARB- n (%)	6434 (78·8%)	6418 (83·0%)	1097 (86·7%)	<0·0001
Diuretic- n (%)	2752 (33·7%)	3442 (44·5%)	773 (61·1%)	<0·0001
Statins or ezetimibe - n (%)	5934 (72·7%)	5903 (76·3%)	1031 (81·5%)	<0·0001
Metformin- n (%)	6961 (85·3%)	6263 (81·0%)	843 (66·6%)	<0·0001
Sulfonylurea- n (%)	3671 (45·0%)	3205 (41·5%)	445 (35·2%)	<0·0001
Insulin- n (%)	3018 (37·0%)	3284 (42·5%)	711 (56·2%)	<0·0001
UACR group (mg/g)				
<30	5691 (70·9%)	5267 (69·5%)	686 (55·6%)	<0·0001
30–300	1887 (23·5%)	1761 (23·2%)	381 (30·9%)	
>300	448 (5·6%)	554 (7·3%)	167 (13·5%)	

Mean eGFR change with Dapagliflozin vs. Placebo in the Total Population



Sample size						
Placebo group	8578	8223	7884	7316	6800	5770
Dapagliflozin group	8581	8273	7978	7513	7098	6050

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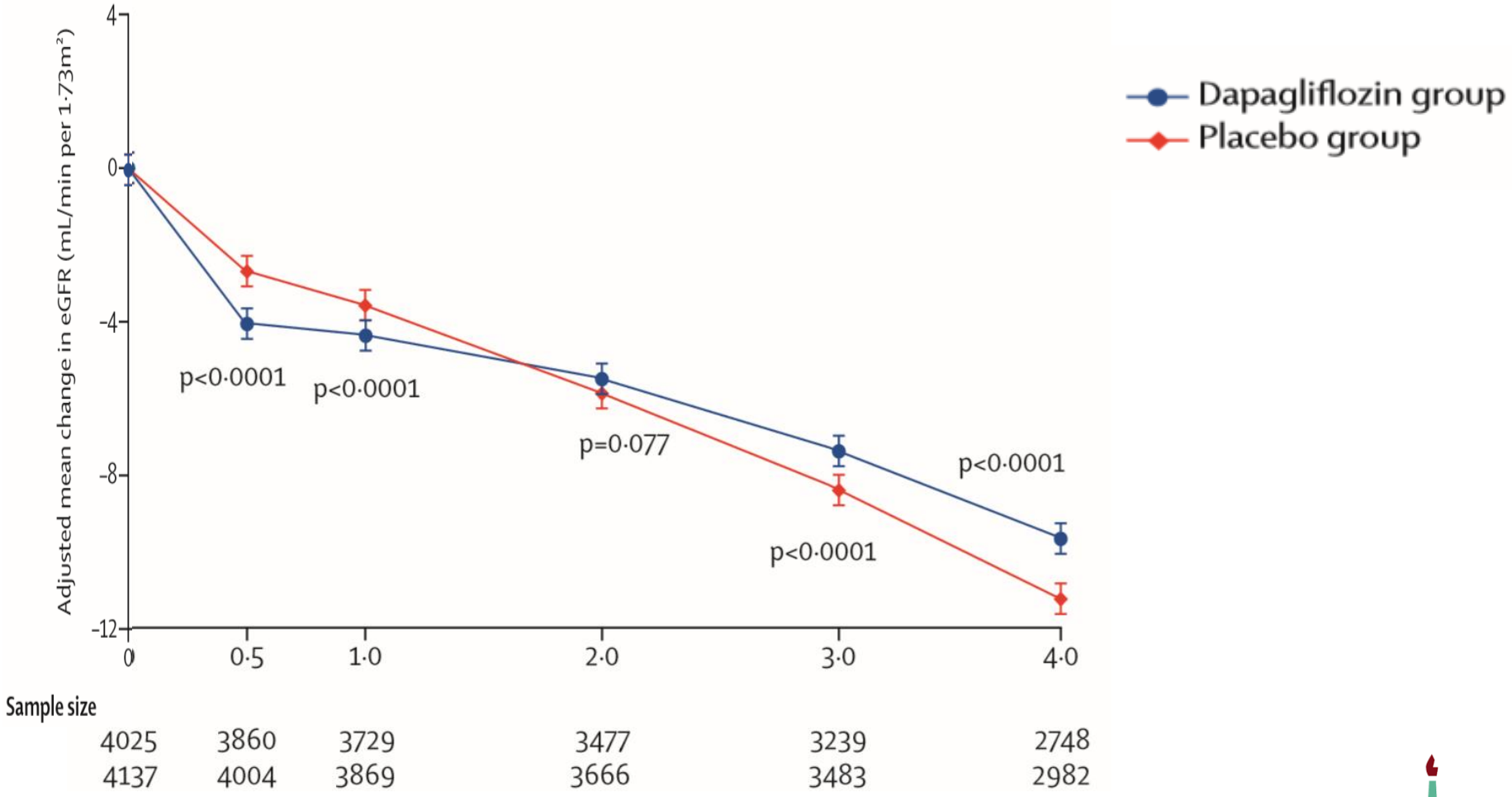
Mean eGFR change with Dapagliflozin vs. Placebo in the baseline eGFR ≥90 ml/min/1.73 m² Population



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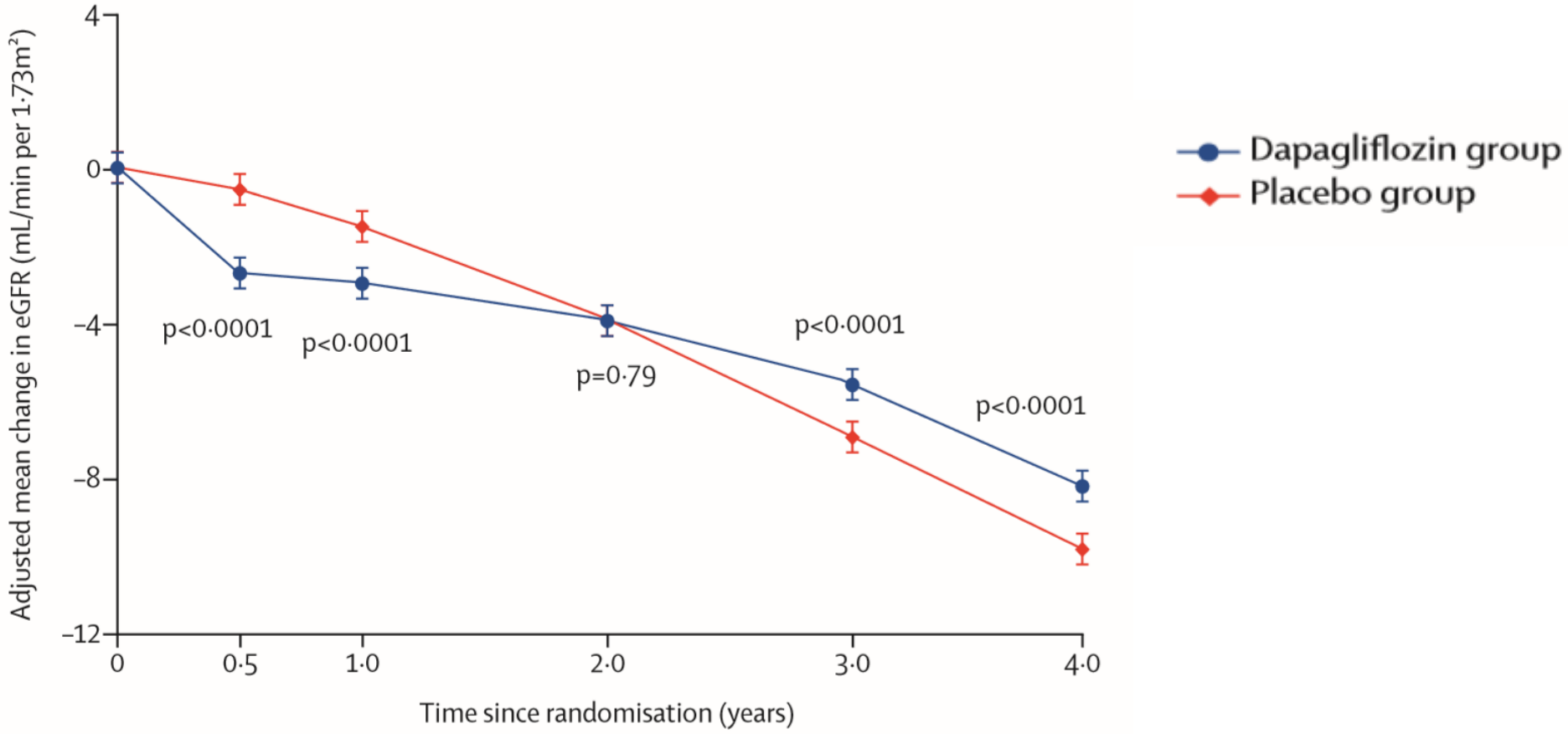
Mean eGFR change with Dapagliflozin vs. Placebo in the baseline 60≤eGFR<90 ml/min/1.73 m² Population



Sample size						
Placebo group	3894	3746	3579	3316	3089	2631
Dapagliflozin group	3838	3693	3565	3354	3161	2686

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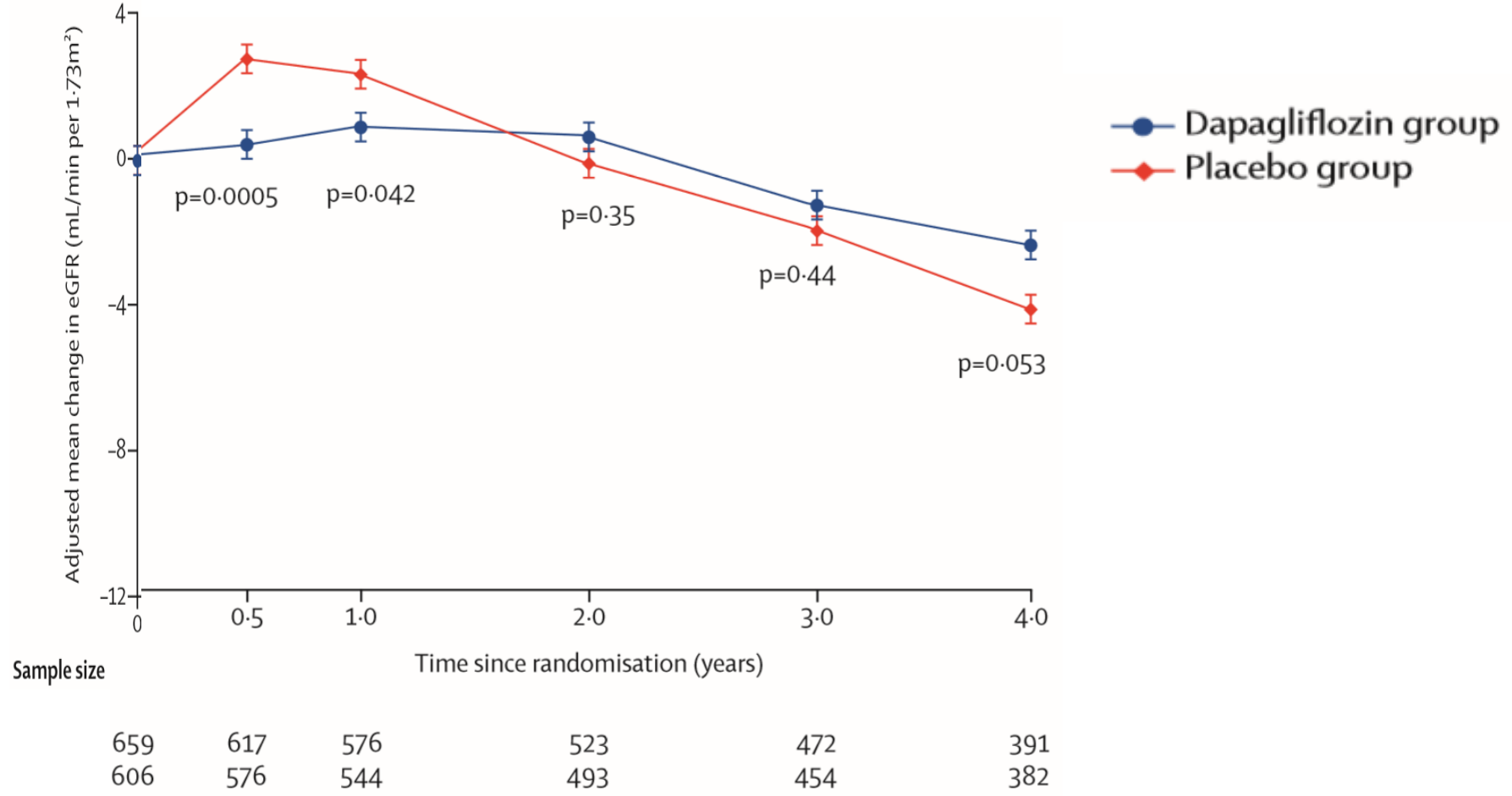
Mean eGFR change with Dapagliflozin vs. Placebo in the baseline eGFR <60 ml/min/1.73 m² Population



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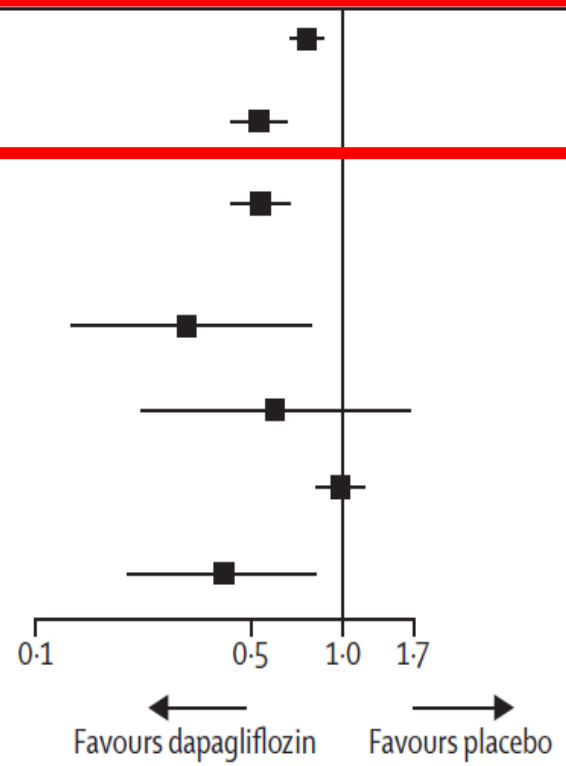
The Renal Composite Outcomes and their Components in the DECLARE-TIMI 58 Trial

	Dapagliflozin group		Placebo group		Hazard ratio (95% CI)	p value
	n/N (%)	Kaplan- Meier event rate (4 years)	n/N (%)	Kaplan- Meier event rate (4 years)		
Composite cardiorenal outcome	370/8582 (4·3%)	4·2%	480/8578 (5·6%)	5·3%	0·76 (0·67–0·87)	<0·0001
Composite renal-specific outcome	127/8582 (1·5%)	1·5%	238/8578 (2·8%)	2·6%	0·53 (0·43–0·66)	<0·0001
Sustained eGFR decrease ≥40% to eGFR <60mL/ min per 1·73m²	120/8582 (1·4%)	1·4%	221/8578 (2·6%)	2·5%	0·54 (0·43–0·67)	<0·0001
End-stage renal disease	6/8582 (0·1%)	0·1%	19/8578 (0·2%)	0·2%	0·31 (0·13–0·79)	0·013
Renal death	6/8582 (0·1%)	0·1%	10/8578 (0·1%)	0·1%	0·60 (0·22–1·65)	0·32
Cardiovascular death	245/8582 (2·9%)	2·7%	249/8578 (2·9%)	2·7%	0·98 (0·82–1·17)	0·83
End-stage renal disease or renal death	11/8582 (0·1%)	0·1%	27/8578 (0·3%)	0·3%	0·41 (0·20–0·82)	0·012



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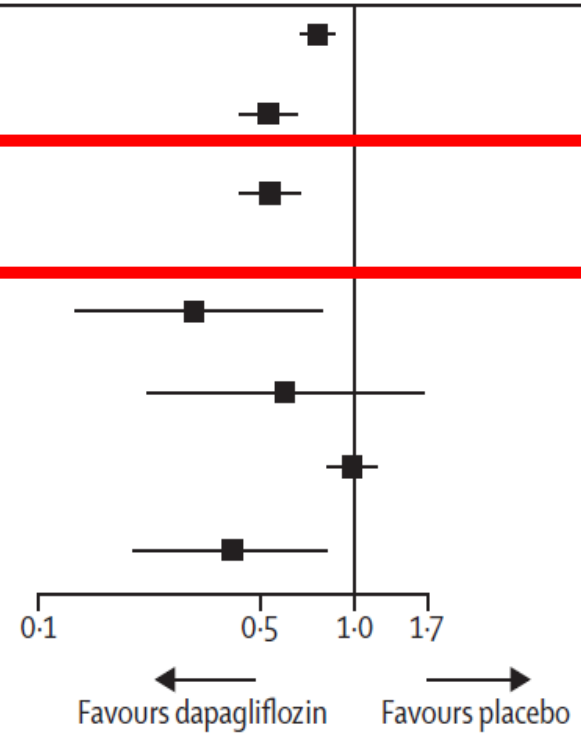

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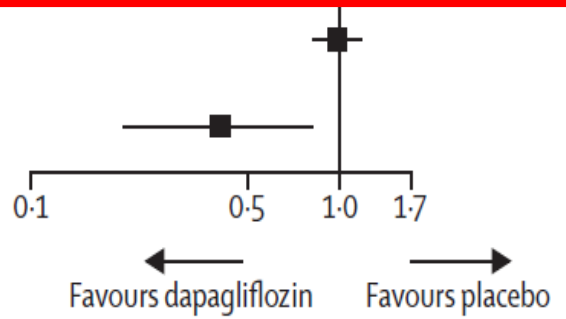

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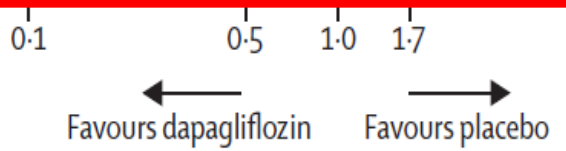

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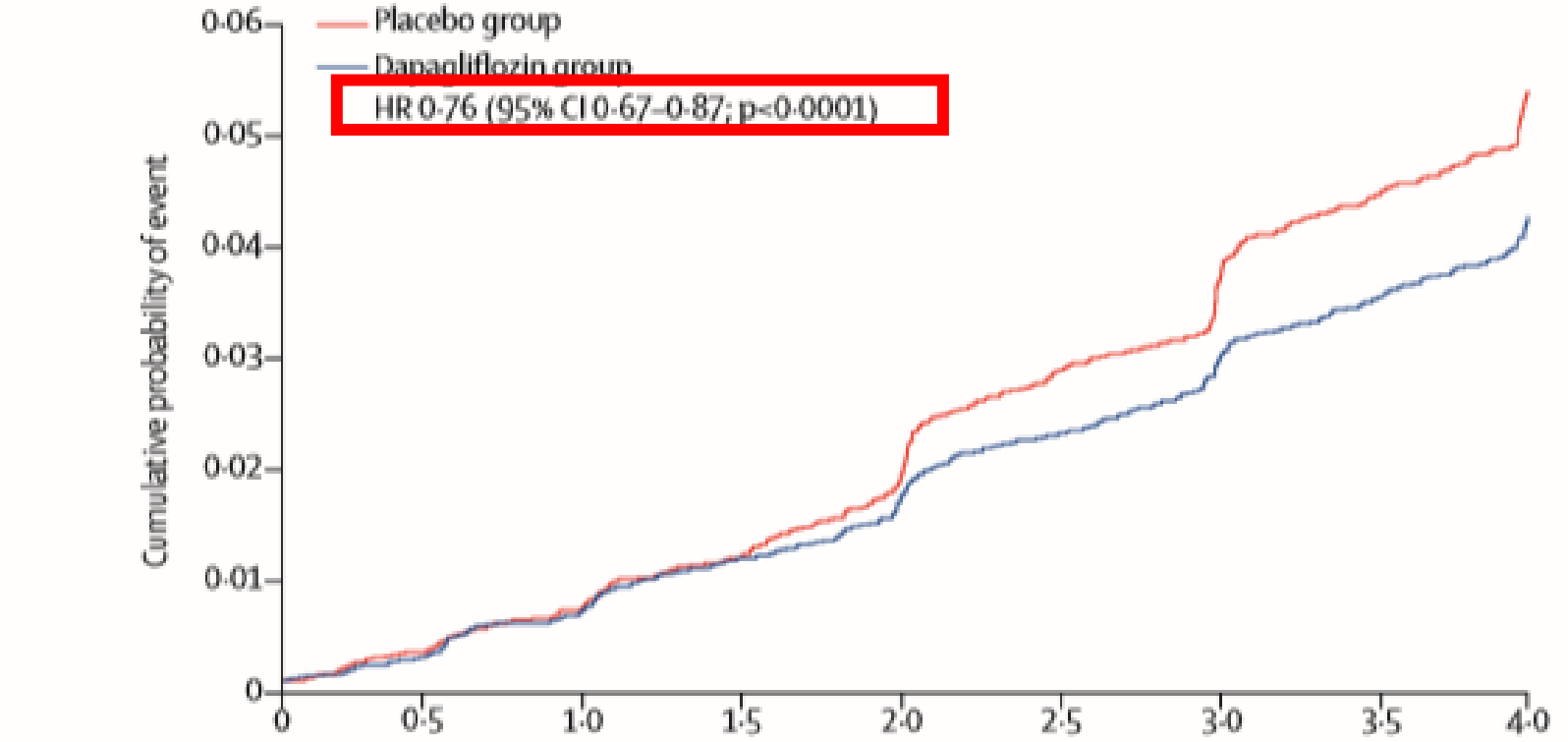
Kaplan-Meier Curves for the Cardiorenal composite outcome



Number at risk									
Placebo group	8578	8508	8422	8326	8200	8056	7932	7409	5389
Dapagliflozin group	8582	8533	8436	8347	8248	8136	8009	7534	5472

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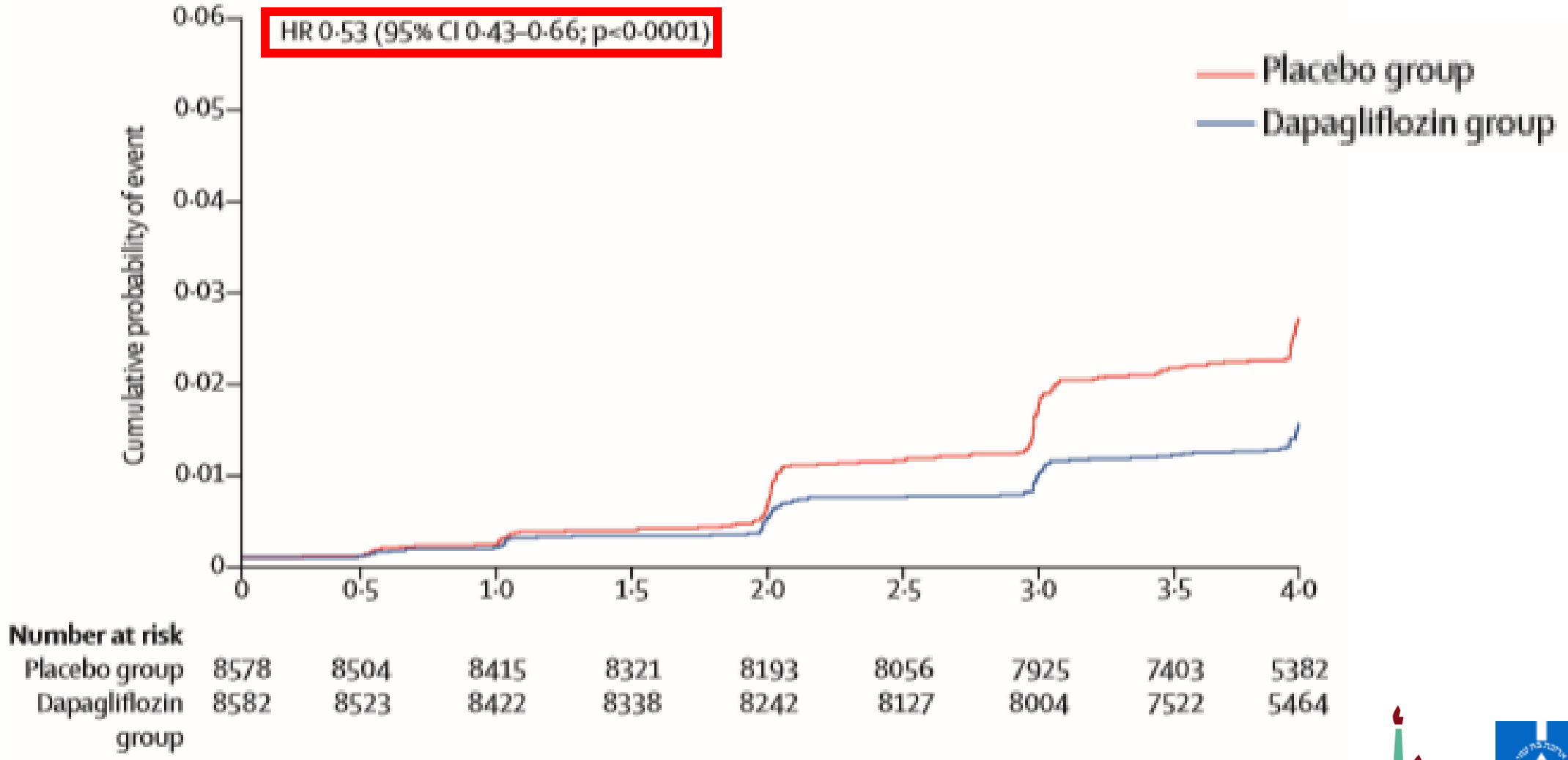
Kaplan-Meier Curves for the Renal-Specific composite outcome



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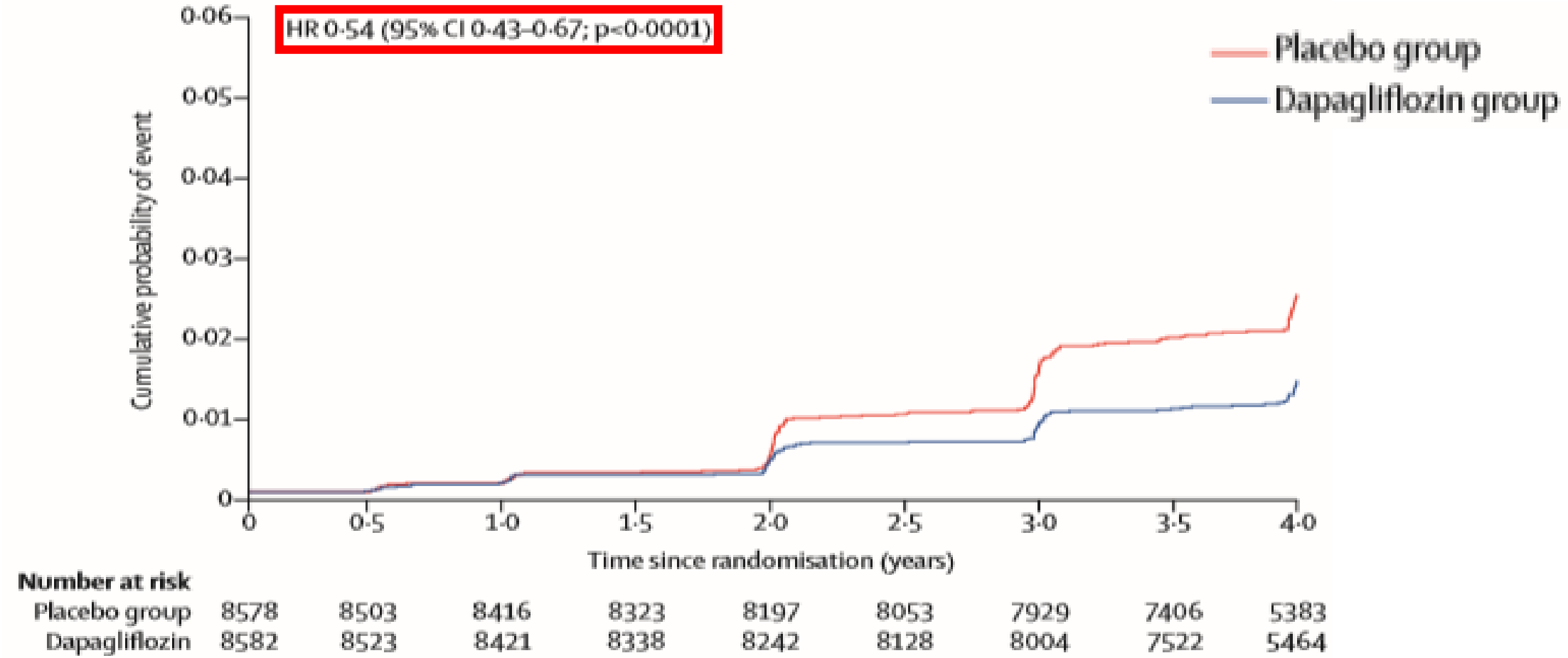
Kaplan-Meier Curves for the Sustained Decrease in eGFR by at least 40% to less than 60 mL/min/1·73 m²



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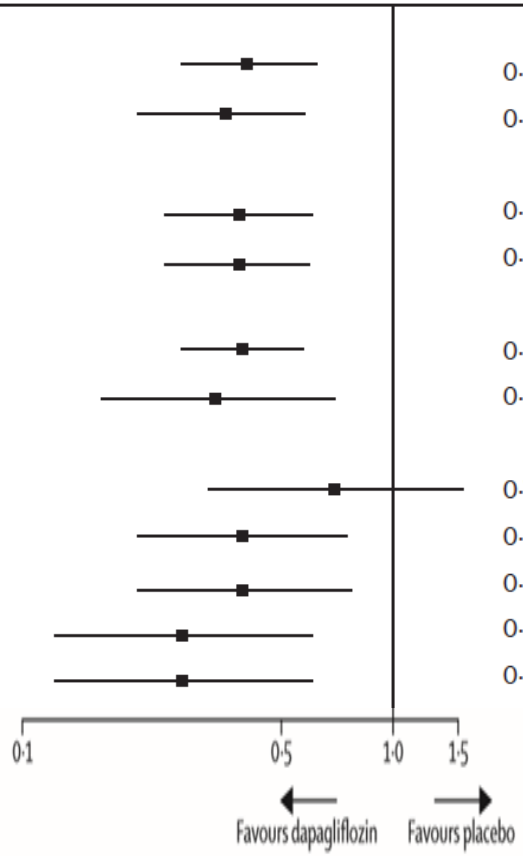
The Renal-Specific Outcome Predefined Sub-Group Analyses (1)

	Dapagliflozin group		Placebo group		Hazard ratio (95% CI)	p value	$p_{interaction}$
	n/N (%)	Kaplan- Meier Event rate (4 years)	n/N (%)	Kaplan- Meier Event rate (4 years)			
Sex							
Male	79/5411 (1·5%)	1·5%	139/5327 (2·6%)	2·5%	0·55 (0·42–0·73)	<0·0001	0·64
Female	48/3171 (1·5%)	1·4%	99/3251 (3·0%)	2·8%	0·50 (0·35–0·70)	<0·0001	
Age (years)							
≥65	62/3951 (1·6%)	1·6%	117/3956 (3·0%)	2·8%	0·53 (0·39–0·72)	<0·0001	0·97
<65	65/4631 (1·4%)	1·4%	121/4622 (2·6%)	2·5%	0·53 (0·39–0·71)	<0·0001	
Race							
White	103/6843 (1·5%)	1·5%	188/6810 (2·8%)	2·5%	0·54 (0·42–0·69)	<0·0001	0·69
Non-white	24/1739 (1·4%)	1·5%	50/1768 (2·8%)	3·2%	0·48 (0·30–0·79)	0·0035	
Diabetes duration (years)							
≤5	25/1887 (1·3%)	1·3%	32/1949 (1·6%)	1·5%	0·79 (0·47–1·34)	0·39	0·44
>5–10	32/2375 (1·3%)	1·3%	59/2356 (2·5%)	2·2%	0·54 (0·35–0·83)	0·0051	
>10–15	31/2015 (1·5%)	1·6%	55/1937 (2·8%)	2·8%	0·54 (0·35–0·84)	0·0061	
>15–20	20/1246 (1·6%)	1·6%	44/1187 (3·7%)	3·7%	0·42 (0·25–0·72)	0·0014	
>20	19/1059 (1·8%)	1·6%	48/1147 (4·2%)	4·0%	0·42 (0·25–0·72)	0·0015	



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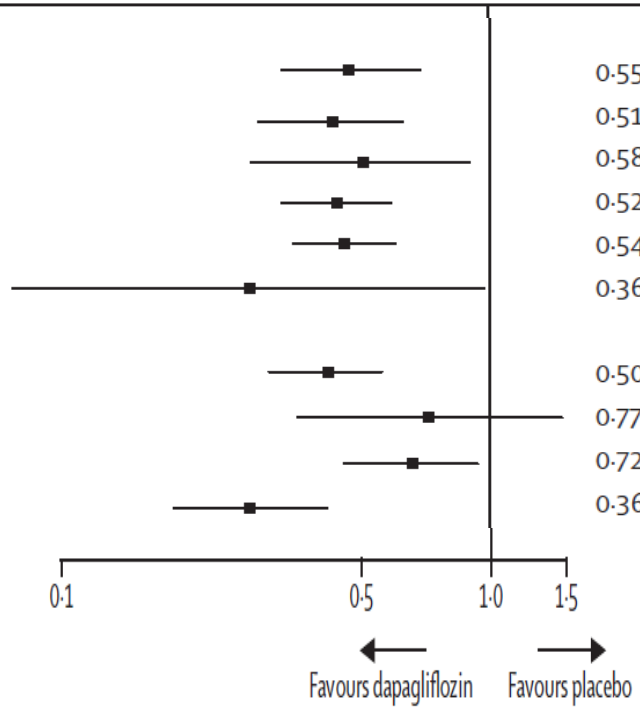
The Renal-Specific Outcome Predefined Sub-Group Analyses (2)

	Dapagliflozin group		Placebo group		Hazard ratio (95% CI)	p value	$p_{interaction}$
	n/N (%)	Kaplan- Meier Event rate (4 years)	n/N (%)	Kaplan- Meier Event rate (4 years)			
Medical history							
Established cardiovascular disease	65/3474 (1·9%)	1·9%	118/3500 (3·4%)	3·2%	0·55 (0·41–0·75)	0·0001	0·72
Multiple cardiovascular risk factors	62/5108 (1·2%)	1·2%	120/5078 (2·4%)	2·3%	0·51 (0·37–0·69)	<0·0001	
History of heart failure	27/852 (3·2%)	3·3%	48/872 (5·5%)	5·4%	0·58 (0·36–0·92)	0·022	0·78
No history of heart failure	100/7730 (1·3%)	1·3%	190/7706 (2·5%)	2·3%	0·52 (0·41–0·66)	<0·0001	
History of hypertension	122/7769 (1·6%)	1·6%	222/7658 (2·9%)	2·7%	0·54 (0·43–0·67)	<0·0001	0·41
No history of hypertension	5/813 (0·6%)	0·5%	16/920 (1·7%)	1·8%	0·36 (0·13–0·98)	0·046	
Background medication							
ACE inhibitor or ARB use at baseline	106/6977 (1·5%)	1·5%	211/6973 (3·0%)	2·9%	0·50 (0·39–0·63)	<0·0001	0·16
No ACE inhibitor or ARB use at baseline	21/1605 (1·3%)	1·3%	27/1605 (1·7%)	1·4%	0·77 (0·44–1·37)	0·37	
Diuretic use at baseline	81/3488 (2·3%)	2·3%	111/3479 (3·2%)	2·9%	0·72 (0·54–0·95)	0·023	0·0021
No diuretic use at baseline	46/5094 (0·9%)	0·9%	127/5099 (2·5%)	2·4%	0·36 (0·26–0·50)	<0·0001	



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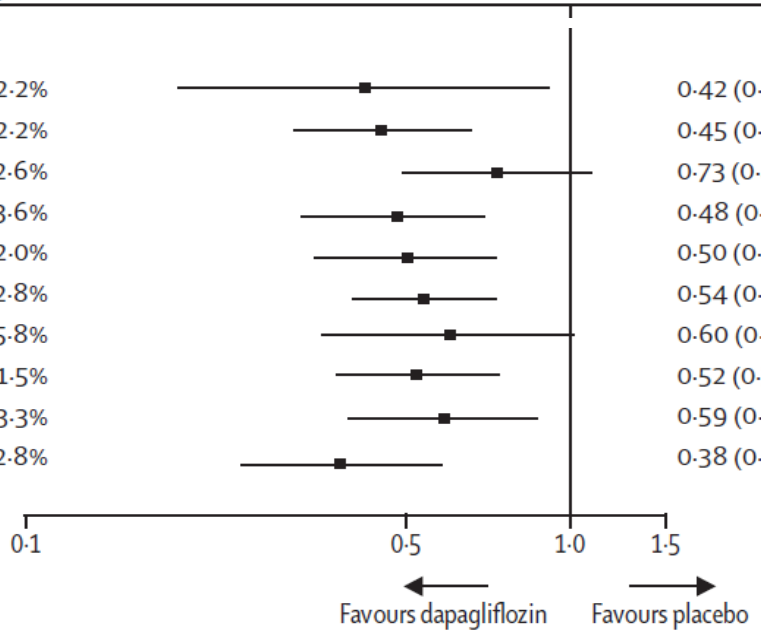
The Renal-Specific Outcome Predefined Sub-Group Analyses (3)

	Dapagliflozin group		Placebo group		Hazard ratio (95% CI)	p value	$p_{interaction}$
	n/N (%)	Kaplan- Meier Event rate (4 years)	n/N (%)	Kaplan- Meier Event rate (4 years)			
Laboratory measurements							
Hba_{1c} <7%	9/773 (1·2%)	1·0%	21/774 (2·7%)	2·2%	0·42 (0·19–0·91)	0·028	0·26
Hba_{1c} 7 to <8%	38/3317 (1·1%)	1·2%	83/3309 (2·5%)	2·2%	0·45 (0·31–0·66)	<0·0001	
Hba_{1c} 8 to <9%	41/2193 (1·9%)	1·9%	59/2327 (2·5%)	2·6%	0·73 (0·49–1·09)	0·12	
Hba_{1c} ≥9%	39/2297 (1·7%)	1·7%	75/2164 (3·5%)	3·6%	0·48 (0·32–0·70)	0·0002	
eGFR ≥90 mL/min per 1·73m²	41/4137 (1·0%)	1·0%	79/4025 (2·0%)	2·0%	0·50 (0·34–0·73)	0·0003	0·87
eGFR 60 to <90 mL/min per 1·73m²	65/3838 (1·7%)	1·6%	121/3894 (3·1%)	2·8%	0·54 (0·40–0·73)	<0·0001	
eGFR <60 mL/min per 1·73m²	21/606 (3·5%)	3·8%	38/659 (5·8%)	5·8%	0·60 (0·35–1·02)	0·059	
UACR <30 mg/g	50/5819 (0·9%)	0·9%	95/5825 (1·6%)	1·5%	0·52 (0·37–0·74)	0·0002	0·30
UACR 30–300 mg/g	39/2017 (1·9%)	2·0%	66/2013 (3·3%)	3·3%	0·59 (0·39–0·87)	0·0082	
UACR >300 mg/g	31/594 (5·2%)	4·8%	75/575 (13·0%)	12·8%	0·38 (0·25–0·58)	<0·0001	



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Summary

- In the DECLARE–TIMI 58 trial, patients treated with dapagliflozin had a significantly reduced frequency of the composite cardiorenal and renal-specific outcomes compared with those in the placebo group, demonstrating the benefits of dapagliflozin on reduction of both new or worsening nephropathy.

- Components of the composite outcomes were also significantly reduced with dapagliflozin.

- These benefits occurred in a large and broad population of patients with type 2 diabetes, irrespective of the presence of ASCVD and baseline renal function.

Conclusion

- These results emphasize the value of SGLT2 inhibitors as an important component of both **prevention** and **treatment** of chronic kidney disease among patients with type 2 diabetes.

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Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE–TIMI 58 randomised trial

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