Effects of Dapagliflozin on the Urinary Albumin-to-Creatinine Ratio in Patients with Type 2 Diabetes: a Predefined Analysis from the DECLARE-TIMI 58 Randomised, Placebo-Controlled Trial

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Disclosures

- **Advisory Board:** AstraZeneca, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk Inc., Sanofi
- **Consultant:** AstraZeneca/Bristol-Myers Squibb, Insuline Medical, Medial EarlySign Ltd, CamerEyes Ltd, Exscopia, Orgenesis Ltd, BOL, Glucome Ltd, DarioHealth, Diabot
- **Speaker's Bureau:** AstraZeneca/Bristol-Myers Squibb, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk Inc., Sanofi
- **Stock/Shareholder:** Glucome Ltd, Orgenesis Ltd, DarioHealth, CamerEyes Ltd, Diabot, BOL
- **Employee:** Diabetes Medical Center

Background (1)

- A high urinary albumin-to creatinine ratio (UACR) is associated with:
  - Increased risk for progression of kidney disease
  - Increased risk for all-cause and cardiovascular mortality

- Reduction in UACR by blockade of the renin– angiotensin system (RAS) is associated with improved renal outcomes.

- Reduction in UACR was previously demonstrated with SGLT2i in phase 2-3 trials.

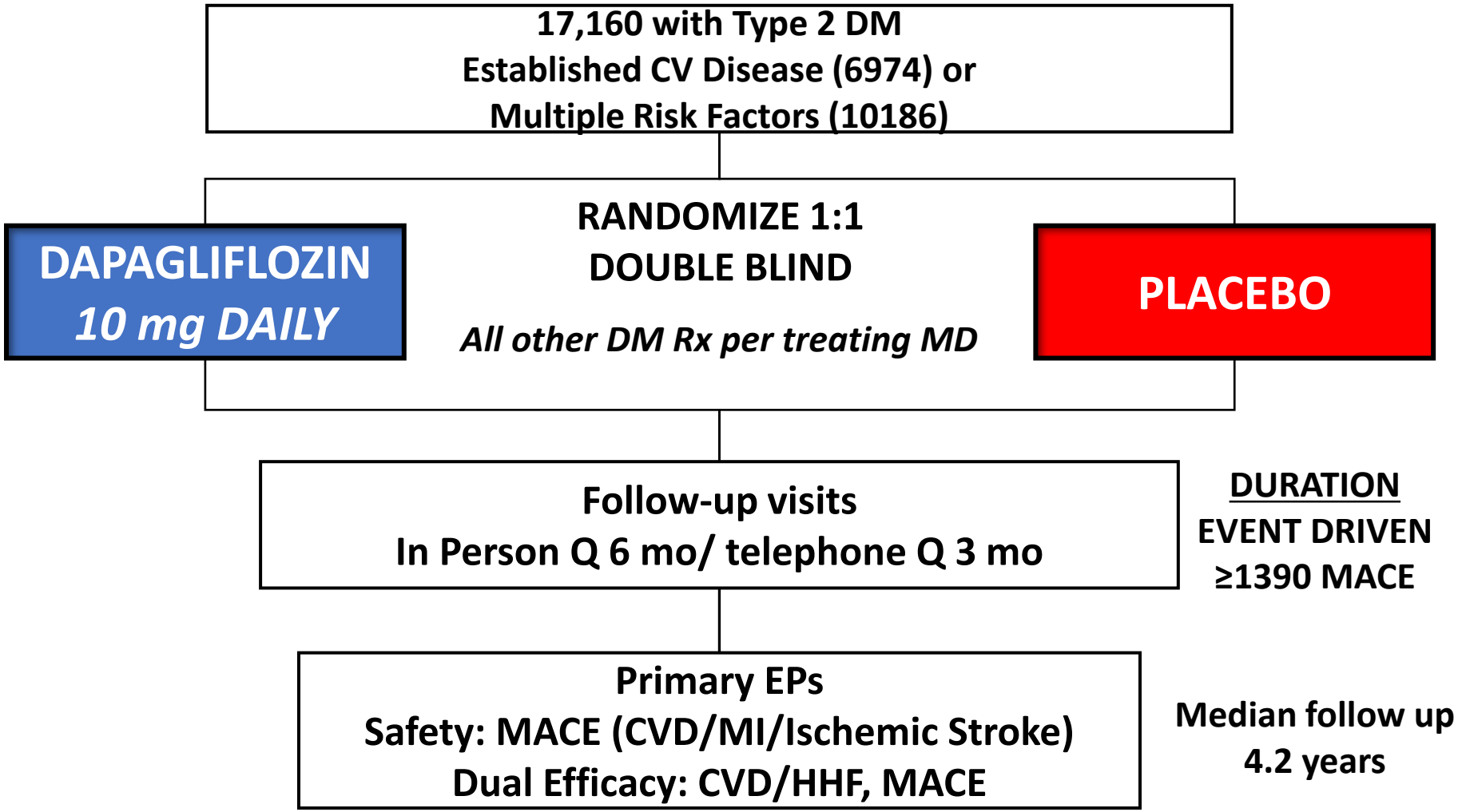
van der Velde et al. Kidney Int 2011; 79: 1341–52. Carrero JJ, et al. Kidney Int 2017; 91: 244–51. Heerspink HJ, et al. J Am Soc Nephrol 2015; 26: 2055–64. Cherney DZ, et al. Diabetologia 2016; 59: 1860–70.

Background (2)

- SGLT2i have demonstrated their ability to reduce UACR and adverse renal outcomes and slow the progression of chronic kidney disease (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 baseline and changes in UACR with dapagliflozin in the **DECLARE-TIMI 58 trial**, which included a patient population in which the majority had no previous atherosclerotic cardiovascular disease (ASCVD) and 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: Trial Design



Wiviott SD, Raz I...Sabatine MA, *AHJ* 2018

Definition of Renal Outcomes in the DECLARE-TIMI 58 Trial

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,
- Death from cardiovascular causes;

Renal Specific Composite Outcome:

- All of the above without death from cardiovascular causes

UACR was not part of the two main renal outcomes of the DECLARE-TIMI 58 trial

UACR Outcomes in DECLARE – TIMI 58

Prespecified Exploratory Outcomes:

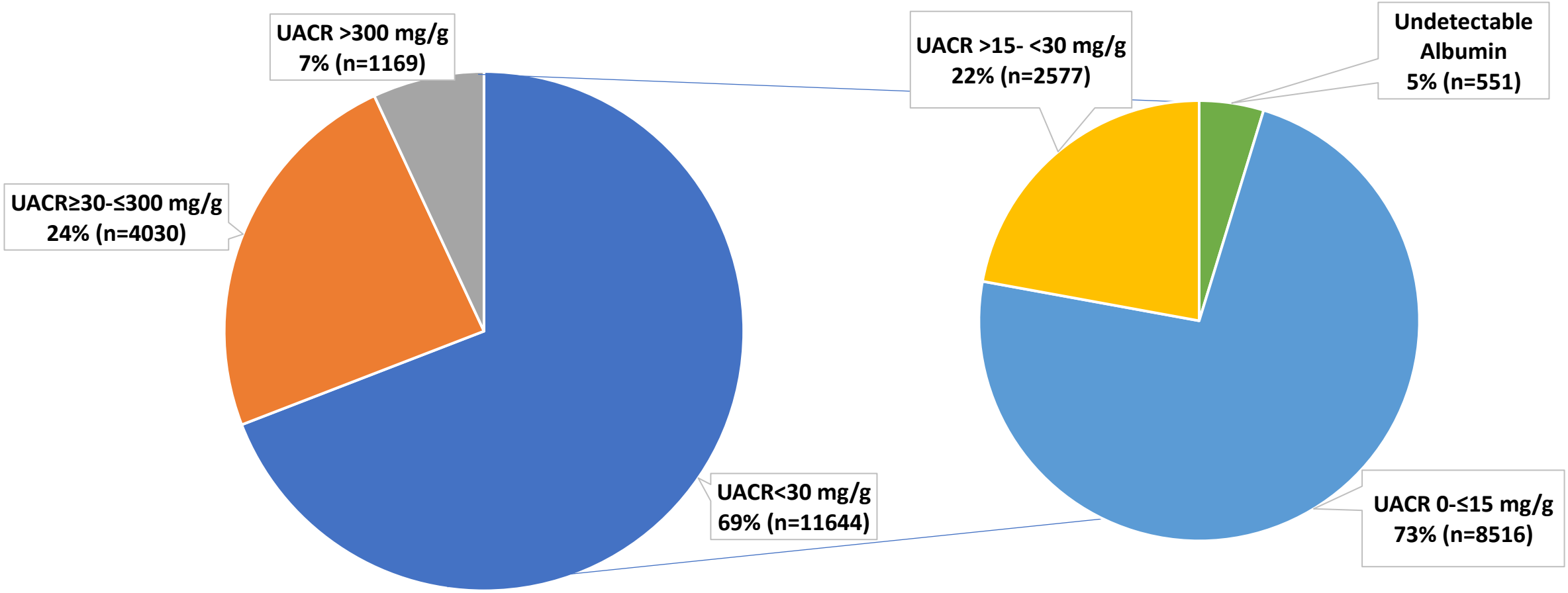
- Development of confirmed sustained* macroalbuminuria (UACR ≥300mg/g) in subjects without macroalbuminuria at baseline (time to first event).

- Development of confirmed sustained albuminuria in patients without albuminuria at baseline (UACR ≥30 mg/g; time to first event).

- Regression in sustained confirmed albuminuria, defined in three ways:
  - Baseline microalbuminuria and/or macroalbuminuria to normoalbuminuria,
  - Baseline macroalbuminuria to microalbuminuria,
  - The previous two combined

* Confirmation is required, meaning that albuminuria should be present at two visits. Time to onset would be the first of the two subsequent laboratory assessments with albuminuria.

Distribution of UACR Categories Amongst the DECLARE-TIMI 58 Population



Baseline Characteristics by UACR Categories at Baseline

Characteristics	Undetectable Albumin (N=551)	UACR 0-≤15 mg/g (N=8516)	UACR >15- <30 mg/g (N=2577)	UACR ≥30-≤300 mg/g (N=4030)	UACR >300 mg/g (N=1169)	P-value
Age- Median (IQR)	63.0 (59.0-68.0)	64.0 (60.0-68.0)	64.0 (60.0-69.0)	64.0 (60.0-69.0)	64.0 (59.0-68.0)	<.0001
Sex: Female- n (%)	221 (40.1)	3362 (39.5)	1083 (42.0)	1292 (32.1)	339 (29.0)	<.0001
BMI- Median (IQR)	30.5 (26.5-34.5)	31.2 (27.8-35.3)	31.2 (27.7-35.4)	31.5 (28.0-35.5)	32.0 (28.1-36.3)	<.0001
HbA1c- Median (IQR)	7.7 (7.2-8.6)	7.9 (7.3-8.8)	8.1 (7.5-9.1)	8.3 (7.5-9.3)	8.4 (7.6-9.6)	<.0001
ASCVD- n (%)	212 (38.5)	3203 (37.6)	1037 (40.2)	1786 (44.3)	578 (49.4)	
MRF- n (%)	339 (61.5)	5313 (62.4)	1540 (59.8)	2244 (55.7)	591 (50.6)	<.0001
Hypertension- n (%)*	476 (86.4)	7549 (88.6)	2333 (90.5)	3690 (91.6)	1096 (93.8)	<.0001
Hyperlipidemia- n (%)*	469 (85.1)	6850 (80.4)	2071 (80.4)	3217 (79.8)	930 (79.6)	0.0576
Smoker- n (%)*	71 (12.9)	1183 (13.9)	348 (13.5)	626 (15.5)	208 (17.8)	0.0006

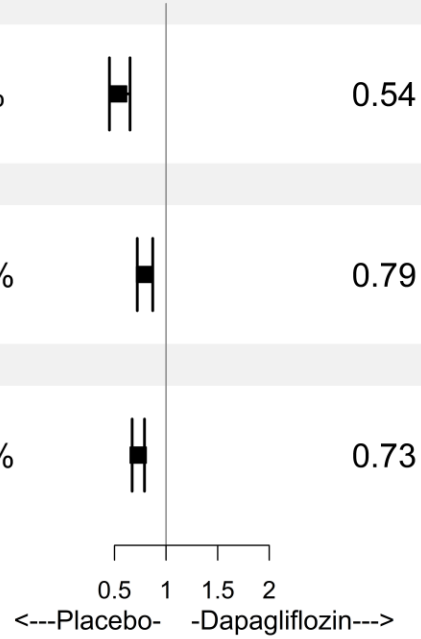
* from total population

Baseline Characteristics by UACR Categories at Baseline

Characteristics	Undetectable Albumin (N=551)	UACR 0-≤15 mg/g (N=8516)	UACR >15- <30 mg/g (N=2577)	UACR ≥30-≤300 mg/g (N=4030)	UACR >300 mg/g (N=1169)	P-value
ACEI/ARB- n (%)	433 (78.6)	6824 (80.1)	2115 (82.1)	3316 (82.3)	1000 (85.5)	<.0001
Diuretic- n (%)	176 (31.9)	3385 (39.7)	1051 (40.8)	1708 (42.4)	517 (44.2)	<.0001
Statin- n (%)	430 (78.0)	6269 (73.6)	1936 (75.1)	3017 (74.9)	872 (74.6)	0.1008
Metformin- n (%)	457 (82.9)	7025 (82.5)	2119 (82.2)	3308 (82.1)	919 (78.6)	0.0283
Sulfonylurea- n (%)	246 (44.6)	3650 (42.9)	1137 (44.1)	1680 (41.7)	489 (41.8)	0.2778
Insulin- n (%)	201 (36.5)	3047 (35.8)	1073 (41.6)	1897 (47.1)	656 (56.1)	<.0001
eGFR (CKD-EPI) - n (%)						
< 60 mL/min 1.73m²	35 (6.4)	473 (5.6)	178 (6.9)	381 (9.5)	167 (14.3)	<.0001
60-<90 mL/min 1.73m²	262 (47.5)	3894 (45.7)	1111 (43.1)	1761 (43.7)	554 (47.4)	
>=90 mL/min 1.73m²	254 (46.1)	4149 (48.7)	1288 (50.0)	1887 (46.8)	448 (38.3)	

Deterioration in Confirmed Sustained Categorical UACR

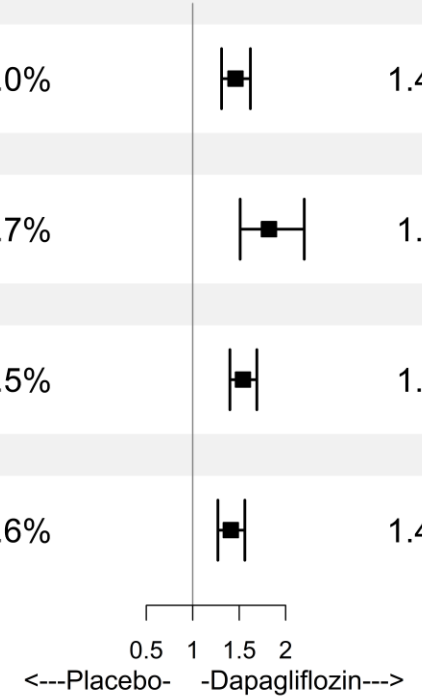
Endpoint	Dapagliflozin n/N (%)	Dapagliflozin KM event rate	Placebo n/N (%)	Placebo KM event rate	Hazard ratio (95% CI)	Cox p value
Deterioration from baseline						
normo/micro to macro	181/7836 (2.3%)	2.30%	330/7838 (4.2%)	4.2%	0.54 (0.45, 0.65)	<.0001
normo to micro/macro	772/5819 (13.3%)	13.30%	959/5825 (16.5%)	16.3%	0.79 (0.72, 0.87)	<.0001
normo to micro/macro or micro to macro	928/7836 (11.8%)	11.90%	1243/7838 (15.9%)	15.8%	0.73 (0.67, 0.79)	<.0001



Normo= Normo-albuminuria; Micro= Microalbuminuria; Macro= Macro albuminuria;

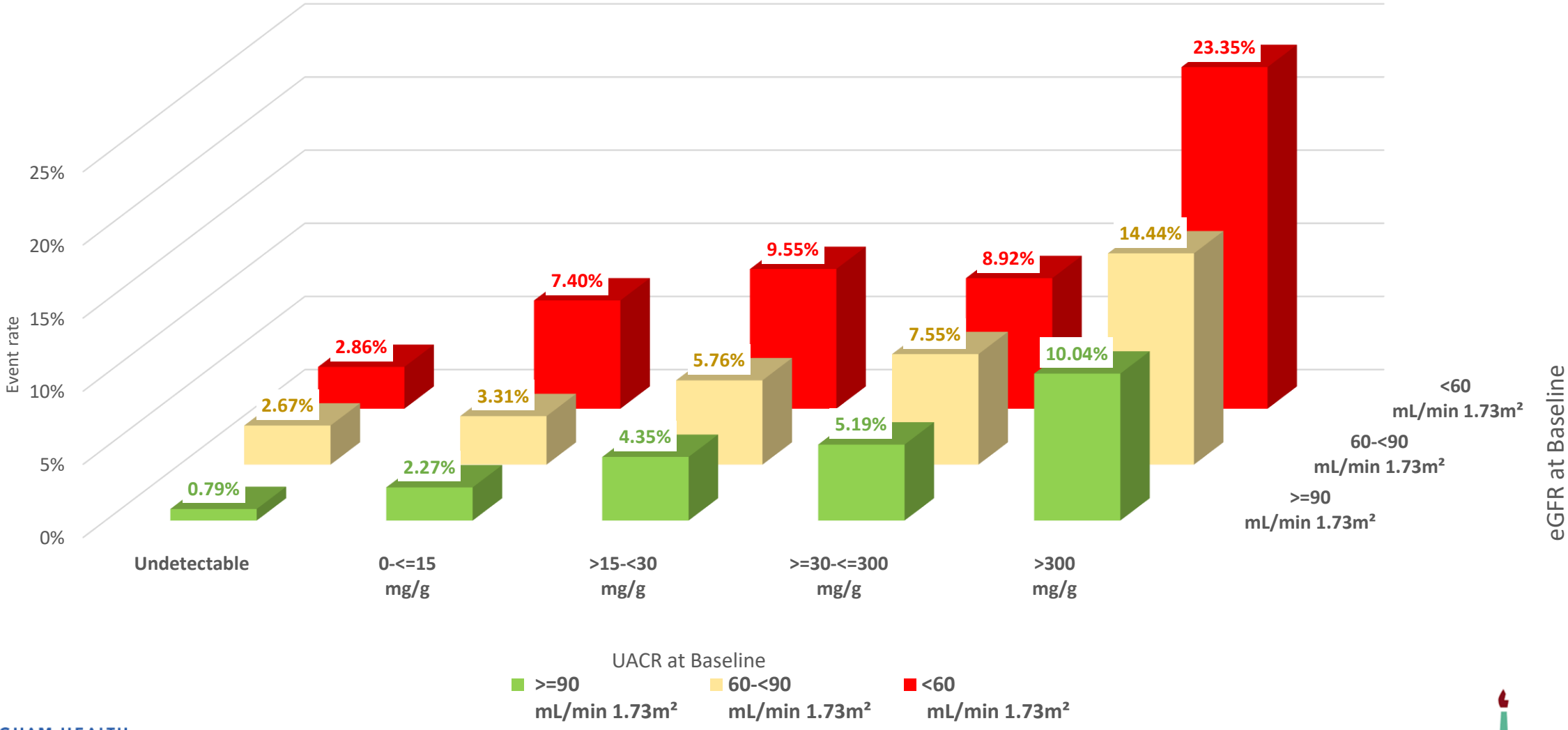
Improvement in Confirmed Sustained Categorical UACR

Endpoint	Dapagliflozin n/N (%)	Dapagliflozin KM event rate	Placebo n/N (%)	Placebo KM event rate	Hazard ratio (95% CI)	Cox p value
Improvement from baseline						
micro to normo	774/2017 (38.4%)	38.90%	576/2013 (28.6%)	29.0%	1.46 (1.31, 1.62)	<.0001
macro to normo/micro	282/594 (47.5%)	48.10%	175/575 (30.4%)	31.7%	1.82 (1.51, 2.2)	<.0001
macro to normo/micro or micro to normo	1056/2611 (40.4%)	41.00%	751/2588 (29.0%)	29.5%	1.54 (1.4, 1.69)	<.0001
micro/macro to normo	809/2611 (31.0%)	31.50%	604/2588 (23.3%)	23.6%	1.41 (1.27, 1.56)	<.0001



Normo= Normo-albuminuria; Micro= Microalbuminuria; Macro= Macro albuminuria;

Cardiorenal Composite Outcome according to eGFR and UACR subgroups



DECLARE TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events

TIMI

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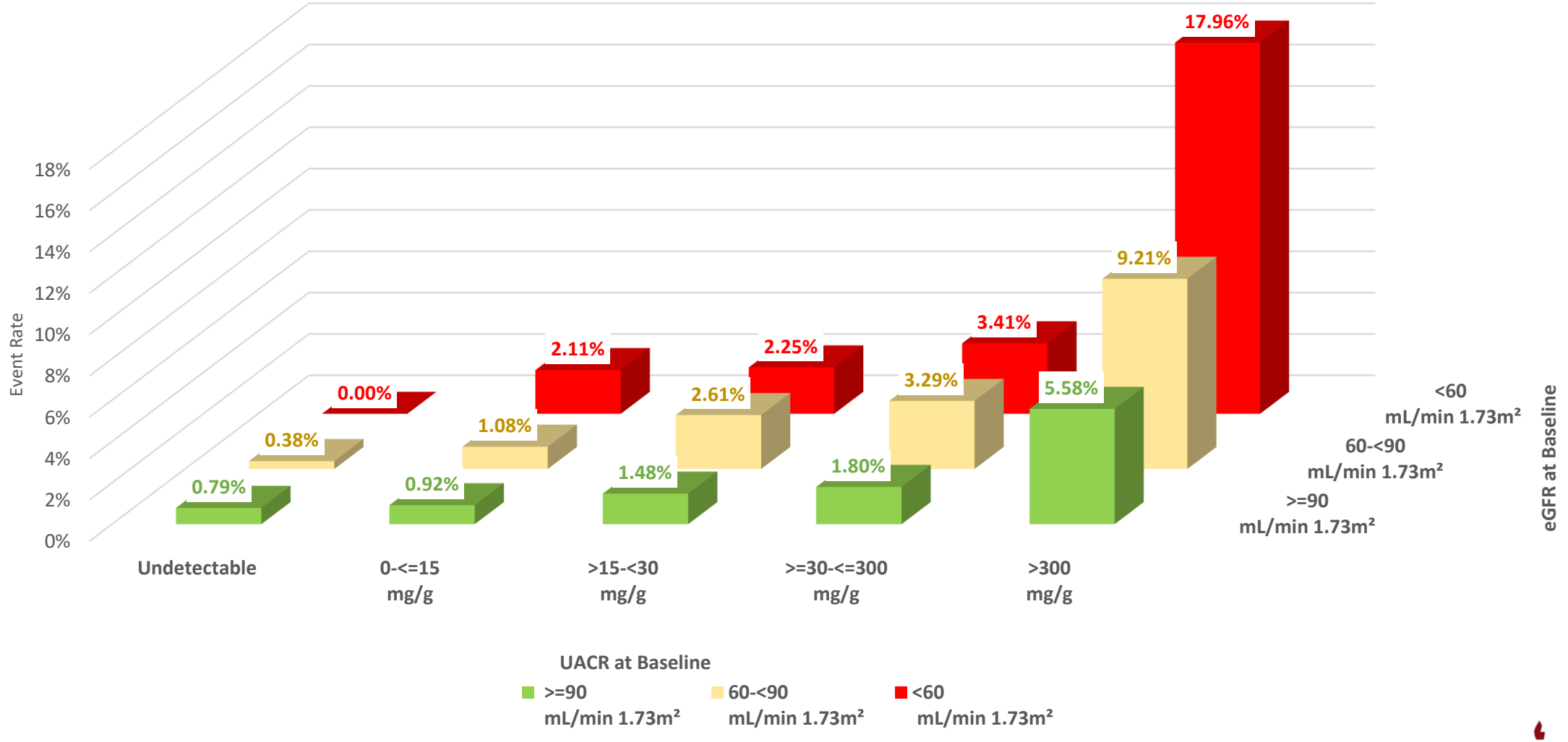
Renal-Specific Composite Outcome according to eGFR and UACR subgroups



BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Summary

- In the DECLARE–TIMI 58 trial, patients treated with dapagliflozin compared to placebo, had higher rates of improvement in confirmed sustain categorical UACR and lower rates of confirmed sustain deterioration in categorical UACR.

- These benefits occurred in a large and broad population of patients with type 2 diabetes, in which the majority had no previous ASCVD and preserved renal function.

- In the DECLARE-TIMI 58 trial the rate of both cardiorenal and renal specific composite outcomes were associated with both baseline eGFR and UACR baseline categories.

Conclusion

- These results shows the beneficial effect of SGLT2 inhibitor on both, **reduction of albuminuria as well as protection from development of albuminuria.**