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

# Effect of Dapagliflozin on Risk for Fast Decline in eGFR: Analyses from the DECLARE-TIMI 58 Trial

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האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

# Disclosures

# Background (1)

- SGLT2 inhibitors may lead to short term decrease in eGFR, with later stabilization and long-term reduction in the risk for end stage kidney disease[1-4].

- Fast decline (FD) in eGFR is commonly defined as:
  - a reduction of ≥3 ml/min/1.73m$^2$/year in eGFR

  or
  - a reduction of ≥5 ml/min/1.73m$^2$/year in eGFR

- Fast decline (FD) in eGFR is associated with poor long-term renal prognosis[5].

[1]Wanner C, et al. N Engl J Med 2016; 375: 323–34. [2]Neal B, et al. N Engl J Med 2017; 377: 644–57. [3]Perkovic V, et al. N Engl J Med 2019; [4]Mosenzon O, et al. Lancet Diabetes and Endocrinol. 2019 Aug;7(8):606-617, [5]*Kidney Int Suppl* 3 (2013): 63-72.

# Background (2)

- Reducing the prevalence of fast decline in eGFR in a population of patients with type 2 diabetes can impact the risk for adverse renal outcomes including end stage kidney disease (ESKD).

- We herein report the prevalence of fast decline in eGFR with dapagliflozin vs. placebo in the **DECLARE-TIMI 58 trial**, which included patients with type 2 diabetes and either risk factors for (59.4%) CVD or with eASCVD (40.6%), with mostly preserved renal function at baseline[1].

[1]Wiviott SD et al., NEJM 2019

# DECLARE-TIMI 58 Study Design

17,160 with Type 2 DM
Established CV Disease (6974) or
Multiple Risk Factors (10186)

⟷ Creatinine Clearance >60 ml/min

**RANDOMIZED 1:1 DOUBLE BLINDED**

**DAPAGLIFLOZIN** *10 mg DAILY*

***All other T2D and CVD Rx per treating MD***

**PLACEBO**

**Follow-up visits**
**In Person Q 6 mo/ by telephone Q 3 mo**

**Primary EPs**
**Safety: MACE (CVD/MI/Ischemic Stroke)**
**Dual Efficacy: CVD/HHF, MACE**

**DURATION**
**EVENT DRIVEN**
**≥1390 MACE**

**Median follow up – 4.2 years**

Wiviott SD, et al., *AHJ* 2018; Wiviott SD et al., NEJM 2019

# Definition of Renal Outcomes in the DECLARE-TIMI 58 Trial

## Cardiorenal Composite Outcome:

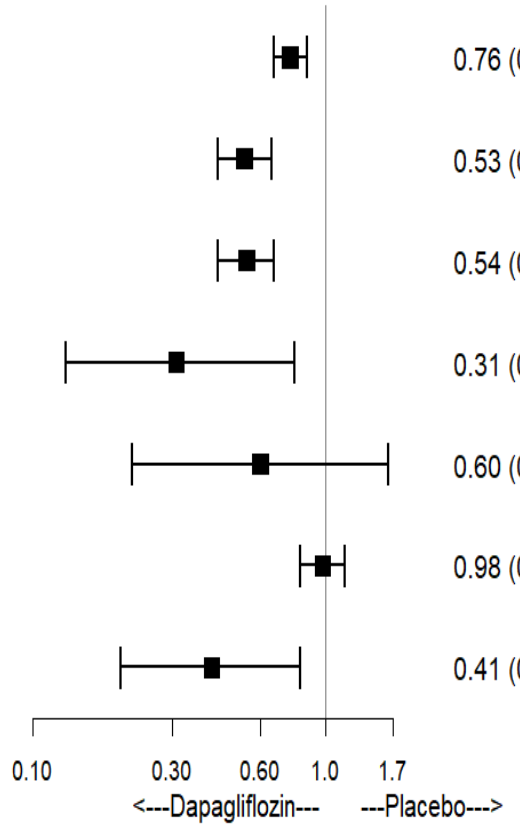
- Sustained confirmed (two tests at the central laboratory at least 4 weeks apart) decline of at least 40% in eGFR to less than 60 mL/min/1.73m²
- End-stage renal disease (defined as dialysis for at least 90 days, kidney transplantation, or confirmed sustained eGFR <15mL/min/1.73 m²)
- Death from renal causes
- Cardiovascular death

## Renal-specific Outcome:

- All of the above without cardiovascular death

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

| | Dapagliflozin | | Placebo | | |
|---|---|---|---|---|---|
| | n/N (%) | Kaplan- Meier event rate (4 years) | n/N (%) | Kaplan- Meier event rate (4 years) | Hazard ratio (95% CI) p-value |
| Cardiorenal composite outcome | 370/8582 (4.3%) | 4.2% | 480/8578 (5.6%) | 5.3% | 0.76 (0.67-0.87) <0.001 |
| Renal-Specific composite outcome | 127/8582 (1.5%) | 1.5% | 238/8578 (2.8%) | 2.6% | 0.53 (0.43-0.66) <0.001 |
| sustained eGFR decrease ≥40% to eGFR <60 | 120/8582 (1.4%) | 1.4% | 221/8578 (2.6%) | 2.5% | 0.54 (0.43-0.67) <0.001 |
| 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) 0.324 |
| CV death | 245/8582 (2.9%) | 2.7% | 249/8578 (2.9%) | 2.7% | 0.98 (0.82-1.17) 0.830 |
| 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 |




Mosenzon O, et al. Lancet Diabetes and Endocrinol. 2019 Aug;7(8):606-617.

# eGFR and eGFR slopes Calculation in the DECLARE-TIMI 58 Trial

- **eGFR:** was calculated according to CKD-EPI[1]
- **eGFR** was analyzed using serum creatinine measurements in a central laboratory at screening, baseline, 6 months, 12 months, and yearly thereafter.
- **eGFR slopes:**
  - calculated as the rate of change in eGFR **per year:**
  - analyzed using repeated measurements model, in ITT population.
  - the model contains terms for randomized treatment groups, baseline eGFR measurement, CV risk category, baseline hematuria, year and year by randomized treatment group interaction.

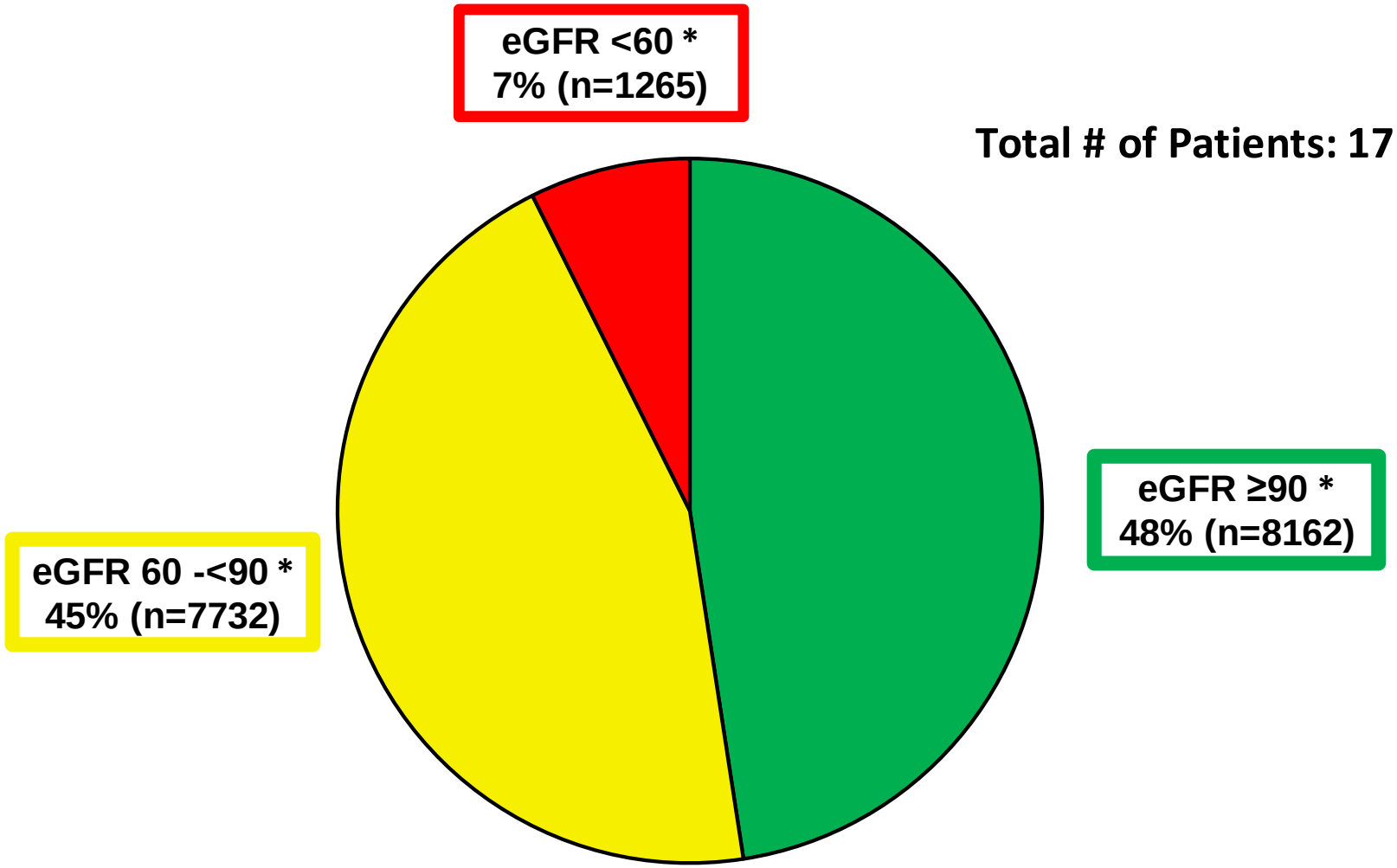


[1] *J Diabetes Complications*. 2017;31:1376–1383.

# eGFR and eGFR slopes Calculation in the DECLARE-TIMI 58 Trial

- **Post-hoc analysis of Change in eGFR per year** was calculated for three different time periods:
  - **Acute eGFR slope:** calculated from baseline to 6 months (presented as rate per year).
  - **Chronic eGFR slope:** calculated from 6 months to year 4.
  - **Total eGFR slope:** calculated from baseline to year 4.
- eGFR slopes comparison at the two treatment arms were done both for the entire trial population and for pre-defined subgroups according to: baseline eGFR, baseline UACR, eCVD vs. MRF for CVD, ACEi/ARB at baseline, diuretics at baseline and History of HTN
- The risk for reduction in eGFR by 30%, 40% and 50% from baseline was analyzed in Cox proportional Hazards models according to treatment arms.

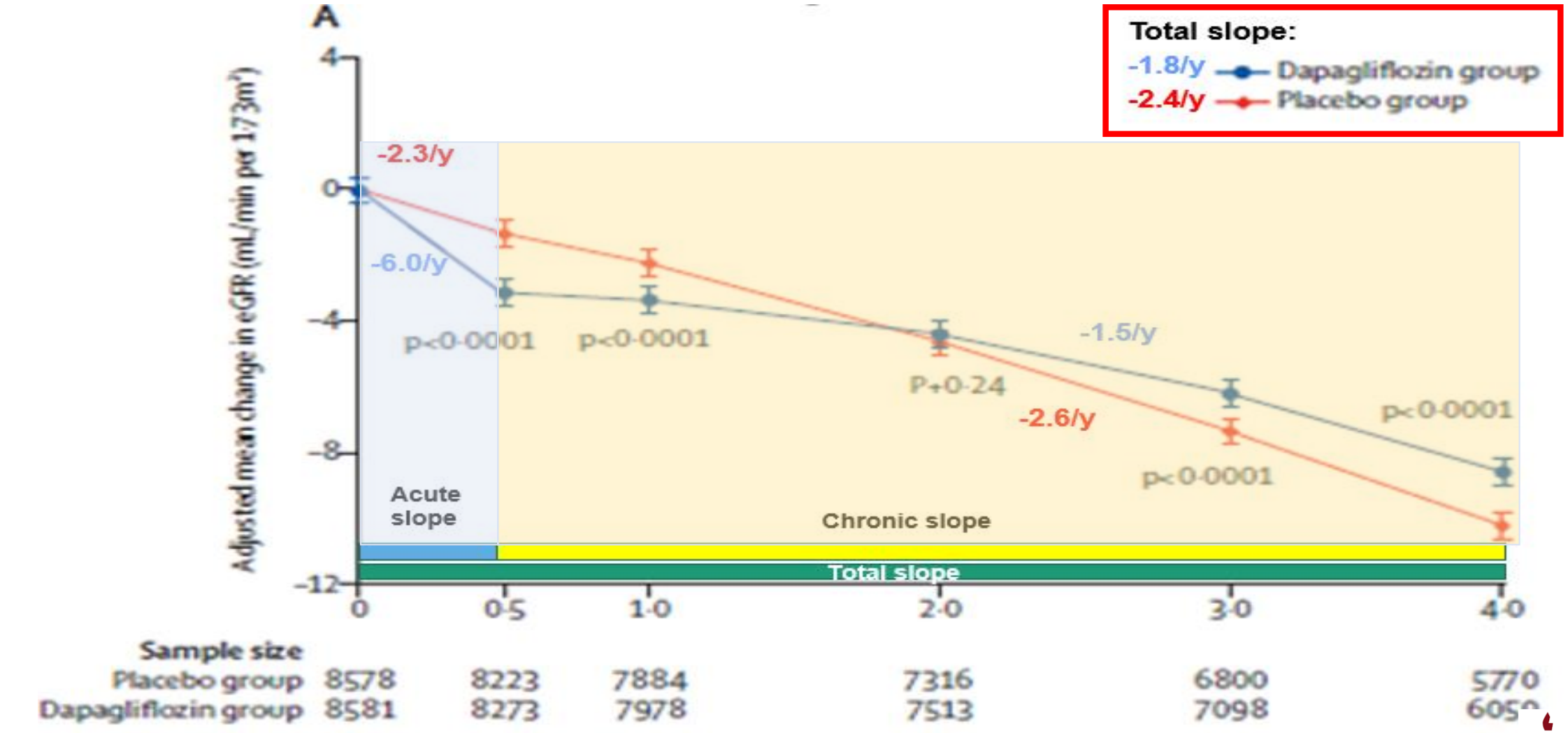
# Distribution of eGFR Categories at Baseline in the DECLARE-TIMI 58 Population




Total # of Patients: 17159

* ml/min/1.73m²

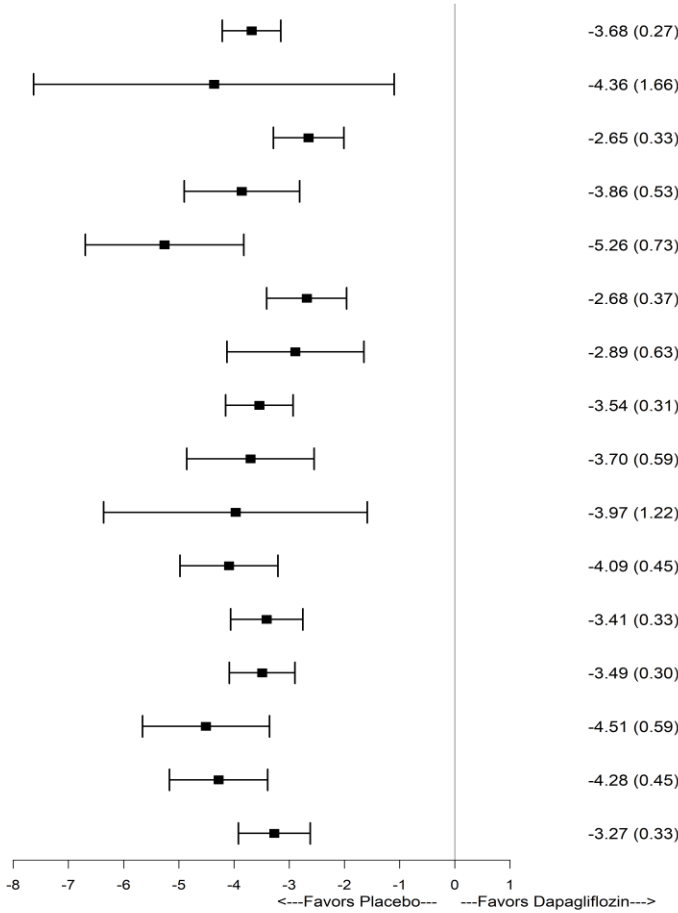
# Mean eGFR change with Dapagliflozin vs. Placebo in the Total Population




Mosenzon O et al. J Am Soc Nephrol 30: 2019 TH-PO1205

# Post- hoc Analysis: Comparison of eGFR slopes between treatment arms during the acute phase

| | Dapagliflozin | | Placebo | | Diffrence Dapagliflozin-Placebo | | |
|---|---|---|---|---|---|---|---|
| **Population** | **N** | **Mean (SE)** | **N** | **Mean (SE)** | **Mean (SE)** | **95% CI** | **P-Value** |
| Overall | 8581 | -5.98 (0.19) | 8578 | -2.30 (0.19) | -3.68 (0.27) | (-4.21, -3.15) | <.0001 |
| eGFR > 110 mL/min per 1·73m² | 205 | -11.74 (1.19) | 214 | -7.38 (1.16) | -4.36 (1.66) | (-7.63, -1.10) | 0.0089 |
| eGFR 90-110 mL/min per 1·73m² | 3932 | -7.68 (0.23) | 3811 | -5.03 (0.23) | -2.65 (0.33) | (-3.28, -2.01) | <.0001 |
| eGFR 75-<90 mL/min per 1·73m² | 2392 | -6.64 (0.38) | 2416 | -2.78 (0.38) | -3.86 (0.53) | (-4.90, -2.81) | <.0001 |
| eGFR 60-<75 mL/min per 1·73m² | 1446 | -2.91 (0.52) | 1478 | 2.34 (0.51) | -5.26 (0.73) | (-6.69, -3.82) | <.0001 |
| eGFR >=90 mL/min per 1·73m², ACEi/ARB at BL | 3238 | -8.08 (0.26) | 3196 | -5.40 (0.26) | -2.68 (0.37) | (-3.41, -1.96) | <.0001 |
| eGFR >=90 mL/min per 1·73m², no ACEi/ARB at BL | 899 | -7.12 (0.44) | 829 | -4.24 (0.46) | -2.89 (0.63) | (-4.13, -1.65) | <.0001 |
| UACR <30 mg/g | 5819 | -5.04 (0.22) | 5825 | -1.50 (0.22) | -3.54 (0.31) | (-4.15, -2.93) | <.0001 |
| UACR >=30-<=300 mg/g | 2016 | -7.18 (0.42) | 2013 | -3.48 (0.42) | -3.70 (0.59) | (-4.86, -2.55) | <.0001 |
| UACR >300 mg/g | 594 | -10.96 (0.86) | 575 | -6.99 (0.87) | -3.97 (1.22) | (-6.36, -1.59) | 0.0011 |
| eASCVD | 3474 | -6.26 (0.32) | 3500 | -2.17 (0.32) | -4.09 (0.45) | (-4.98, -3.20) | <.0001 |
| MRF | 5107 | -5.79 (0.24) | 5078 | -2.39 (0.24) | -3.41 (0.33) | (-4.06, -2.75) | <.0001 |
| ACEi/ARB at Baseline | 6976 | -6.06 (0.21) | 6973 | -2.57 (0.21) | -3.49 (0.30) | (-4.08, -2.90) | <.0001 |
| No ACEi/ARB at Baseline | 1605 | -5.63 (0.41) | 1605 | -1.13 (0.41) | -4.51 (0.59) | (-5.66, -3.36) | <.0001 |
| Diuretics at Baseline | 3488 | -6.89 (0.32) | 3479 | -2.61 (0.32) | -4.28 (0.45) | (-5.17, -3.39) | <.0001 |
| No Diuretics at Baseline | 5093 | -5.36 (0.23) | 5099 | -2.09 (0.23) | -3.27 (0.33) | (-3.92, -2.62) | <.0001 |




N=Number at baseline

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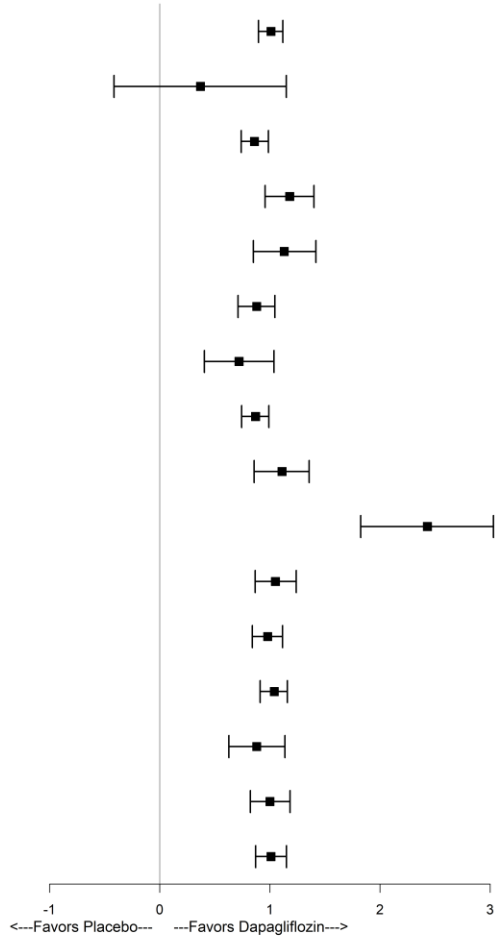
# Post- hoc Analysis: Comparison of eGFR slopes between treatment arms during the chronic phase

| Population | Dapagliflozin N | Dapagliflozin Mean (SE) | Placebo N | Placebo Mean (SE) | Diffrence Dapagliflozin-Placebo Mean (SE) | 95% CI | P-Value |
|---|---|---|---|---|---|---|---|
| Overall | 8581 | -1.54 (0.04) | 8578 | -2.55 (0.04) | 1.01 (0.06) | (0.90, 1.12) | <.0001 |
| eGFR > 110 mL/min per 1·73m² | 205 | -1.88 (0.29) | 214 | -2.25 (0.28) | 0.37 (0.40) | (-0.41, 1.15) | 0.3556 |
| eGFR 90-110 mL/min per 1·73m² | 3932 | -1.58 (0.04) | 3811 | -2.45 (0.05) | 0.86 (0.06) | (0.74, 0.99) | <.0001 |
| eGFR 75-<90 mL/min per 1·73m² | 2392 | -1.67 (0.08) | 2416 | -2.85 (0.08) | 1.18 (0.11) | (0.96, 1.40) | <.0001 |
| eGFR 60-<75 mL/min per 1·73m² | 1446 | -1.36 (0.1) | 1478 | -2.50 (0.10) | 1.13 (0.14) | (0.85, 1.42) | <.0001 |
| eGFR >=90 mL/min per 1·73m², ACEi/ARB at BL | 3238 | -1.65 (0.06) | 3196 | -2.53 (0.06) | 0.88 (0.09) | (0.71, 1.05) | <.0001 |
| eGFR >=90 mL/min per 1·73m², no ACEi/ARB at BL | 899 | -1.43 (0.11) | 829 | -2.16 (0.12) | 0.72 (0.16) | (0.41, 1.04) | <.0001 |
| UACR <30 mg/g | 5819 | -1.37 (0.04) | 5825 | -2.23 (0.04) | 0.87 (0.06) | (0.74, 0.99) | <.0001 |
| UACR >=30-<=300 mg/g | 2016 | -1.78 (0.09) | 2013 | -2.89 (0.09) | 1.11 (0.13) | (0.86, 1.36) | <.0001 |
| UACR >300 mg/g | 594 | -2.51 (0.21) | 575 | -4.94 (0.22) | 2.43 (0.31) | (1.83, 3.03) | <.0001 |
| eASCVD | 3474 | -1.66 (0.07) | 3500 | -2.71 (0.07) | 1.05 (0.10) | (0.87, 1.24) | <.0001 |
| MRF | 5107 | -1.47 (0.05) | 5078 | -2.44 (0.05) | 0.98 (0.07) | (0.84, 1.11) | <.0001 |
| ACEi/ARB at Baseline | 6976 | -1.55 (0.04) | 6973 | -2.59 (0.04) | 1.04 (0.06) | (0.91, 1.16) | <.0001 |
| No ACEi/ARB at Baseline | 1605 | -1.48 (0.09) | 1605 | -2.37 (0.09) | 0.88 (0.13) | (0.63, 1.14) | <.0001 |
| Diuretics at Baseline | 3488 | -1.63 (0.06) | 3479 | -2.64 (0.07) | 1.00 (0.09) | (0.82, 1.18) | <.0001 |
| No Diuretics at Baseline | 5093 | -1.48 (0.05) | 5099 | -2.49 (0.05) | 1.01 (0.07) | (0.87, 1.15) | <.0001 |




N=Number at baseline

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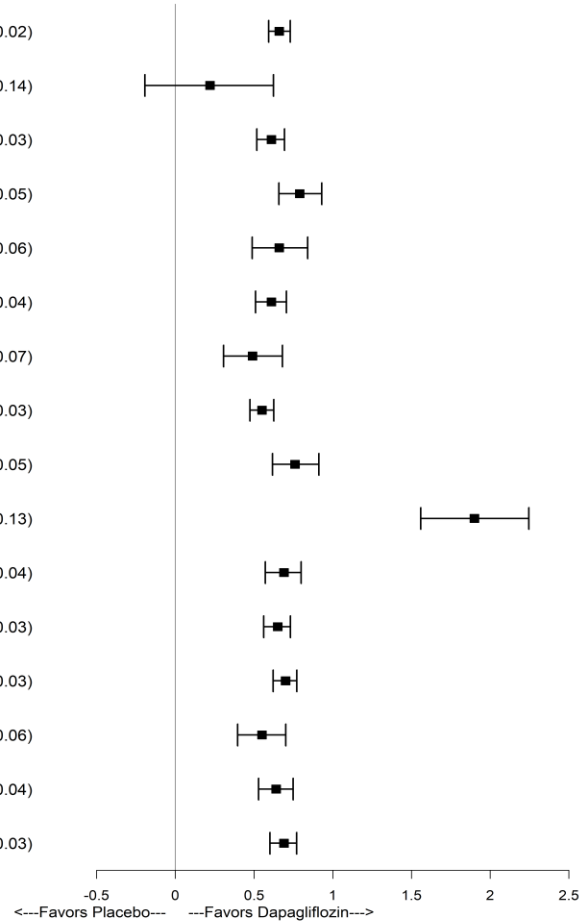
# Post- hoc Analysis: Comparison of eGFR slopes between treatment arms during the entire trial

| | | Dapagliflozin | | Placebo | | Diffrence Dapagliflozin-Placebo | | |
|---|---|---|---|---|---|---|---|---|
| **Population** | **N** | **Mean (SE)** | **N** | **Mean (SE)** | | **Mean (SE)** | **95% CI** | **P-Value** |
| Overall | 8581 | -1.78 (0.02) | 8578 | -2.44 (0.02) | | 0.66 (0.03) | (0.59, 0.73) | <.0001 |
| eGFR > 110 mL/min per 1·73m² | 205 | -2.40 (0.15) | 214 | -2.62 (0.14) | | 0.22 (0.21) | (-0.19, 0.62) | 0.3016 |
| eGFR 90-110 mL/min per 1·73m² | 3932 | -1.97 (0.03) | 3811 | -2.58 (0.03) | | 0.61 (0.04) | (0.52, 0.69) | <.0001 |
| eGFR 75-<90 mL/min per 1·73m² | 2392 | -1.97 (0.05) | 2416 | -2.76 (0.05) | | 0.79 (0.07) | (0.66, 0.93) | <.0001 |
| eGFR 60-<75 mL/min per 1·73m² | 1446 | -1.39 (0.06) | 1478 | -2.05 (0.06) | | 0.66 (0.09) | (0.49, 0.84) | <.0001 |
| eGFR >=90 mL/min per 1·73m², ACEi/ARB at BL | 3238 | -2.04 (0.03) | 3196 | -2.65 (0.04) | | 0.61 (0.05) | (0.51, 0.71) | <.0001 |
| eGFR >=90 mL/min per 1·73m², no ACEi/ARB at BL | 899 | -1.79 (0.07) | 829 | -2.28 (0.07) | | 0.49 (0.10) | (0.31, 0.68) | <.0001 |
| UACR <30 mg/g | 5819 | -1.57 (0.03) | 5825 | -2.12 (0.03) | | 0.55 (0.04) | (0.47, 0.63) | <.0001 |
| UACR >=30-<=300 mg/g | 2016 | -2.08 (0.05) | 2013 | -2.85 (0.05) | | 0.76 (0.08) | (0.62, 0.91) | <.0001 |
| UACR >300 mg/g | 594 | -3.02 (0.12) | 575 | -4.93 (0.13) | | 1.90 (0.18) | (1.56, 2.25) | <.0001 |
| eASCVD | 3474 | -1.88 (0.04) | 3500 | -2.57 (0.04) | | 0.69 (0.06) | (0.57, 0.80) | <.0001 |
| MRF | 5107 | -1.72 (0.03) | 5078 | -2.36 (0.03) | | 0.65 (0.04) | (0.56, 0.73) | <.0001 |
| ACEi/ARB at Baseline | 6976 | -1.81 (0.03) | 6973 | -2.51 (0.03) | | 0.70 (0.04) | (0.62, 0.77) | <.0001 |
| No ACEi/ARB at Baseline | 1605 | -1.67 (0.05) | 1605 | -2.22 (0.06) | | 0.55 (0.08) | (0.40, 0.70) | <.0001 |
| Diuretics at Baseline | 3488 | -1.91 (0.04) | 3479 | -2.55 (0.04) | | 0.64 (0.06) | (0.53, 0.75) | <.0001 |
| No Diuretics at Baseline | 5093 | -1.71 (0.03) | 5099 | -2.40 (0.03) | | 0.69 (0.04) | (0.60, 0.77) | <.0001 |




N=Number at baseline

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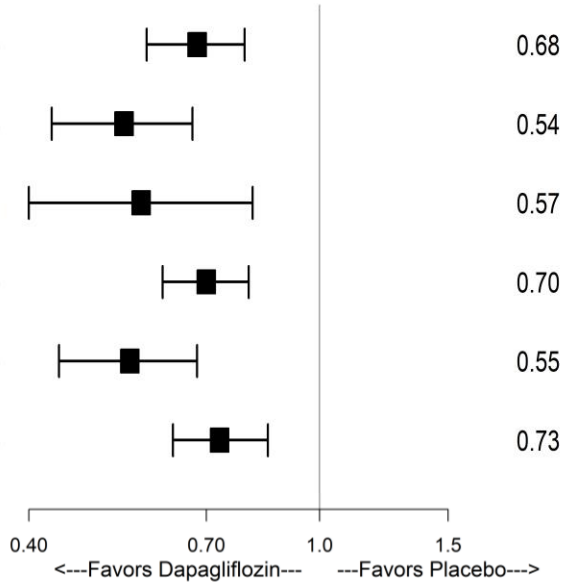
# Comparison of 30%, 40% and 50% reduction in eGFR between treatment arms

| Endpoint | Dapagliflozin n/N(%) | Placebo n/N(%) | Hazard ratio (95% CI) | Cox p-value |
|---|---|---|---|---|
| **Confirmed sustained eGFR change** | | | | |
| Decrease of at least 30% in eGFR to eGFR<60 | 293/8582 (3.4%) | 427/8578 (5.0%) | 0.68 (0.58-0.79) | <.0001 |
| Decrease of at least 40% in eGFR to eGFR<60 | 120/8582 (1.4%) | 221/8578 (2.6%) | 0.54 (0.43-0.67) | <.0001 |
| Decrease of at least 50% in eGFR to eGFR<60 | 49/8582 (0.6%) | 85/8578 (1.0%) | 0.57 (0.40-0.81) | 0.0019 |
| Decrease of at least 30% in eGFR | 366/8582 (4.3%) | 515/8578 (6.0%) | 0.70 (0.61-0.80) | <.0001 |
| Decrease of at least 40% in eGFR | 125/8582 (1.5%) | 225/8578 (2.6%) | 0.55 (0.44-0.68) | <.0001 |
| eGFR<60 in subjects with eGFR>70 at BL | 313/6982 (4.5%) | 419/6907 (6.1%) | 0.73 (0.63-0.85) | <.0001 |



# Definition of Fast Decline in eGFR in the DECLARE-TIMI 58 Trial

- **Fast decline in eGFR was defined as a reduction of ≥3 ml/min/1.73m$^2$/year**

- Fast decline was defined in a post-hoc analysis for three periods:
  - **Acute Fast Decline:** baseline to 6 months.
  - **Chronic Fast Decline:** 6 months to year 4.
  - **Total fast Decline:** baseline to year 4.

- The prevalence of fast decline was calculated according to treatment arms for prespecified subgroups: : baseline eGFR, baseline UACR, eCVD vs. MRF for CVD, ACEi/ARB at baseline, diuretics at baseline and history of HTN

# Change in eGFR in Fast Decliners vs. Non-Fast Decliners from 6 months to 4 years

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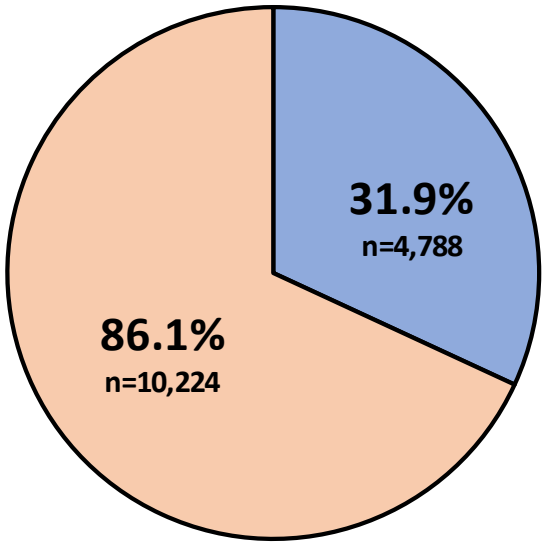
TIMI

**Non-fast decliners**

**Mean (SD) = 0.0 (2.5)**
**Median (IQR) = -0.6 (-1.6–0.9)**

**(ml/min/1.73m²/year)**

**Overall**

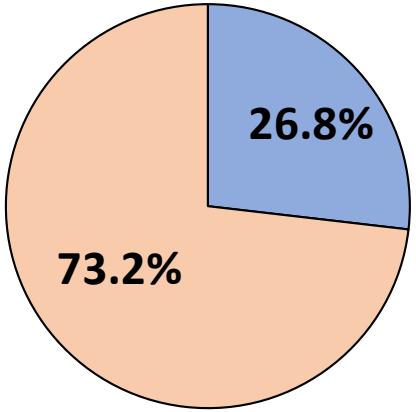



***Fast decliners**

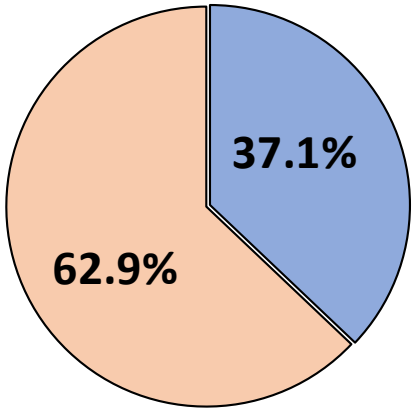
**Mean (SD) = -6.3 (3.7)**
**Median (IQR) = -5.1 (-7.3– -4.0)**

**(ml/min/1.73m²/year)**

**Dapagliflozin**




**Placebo**

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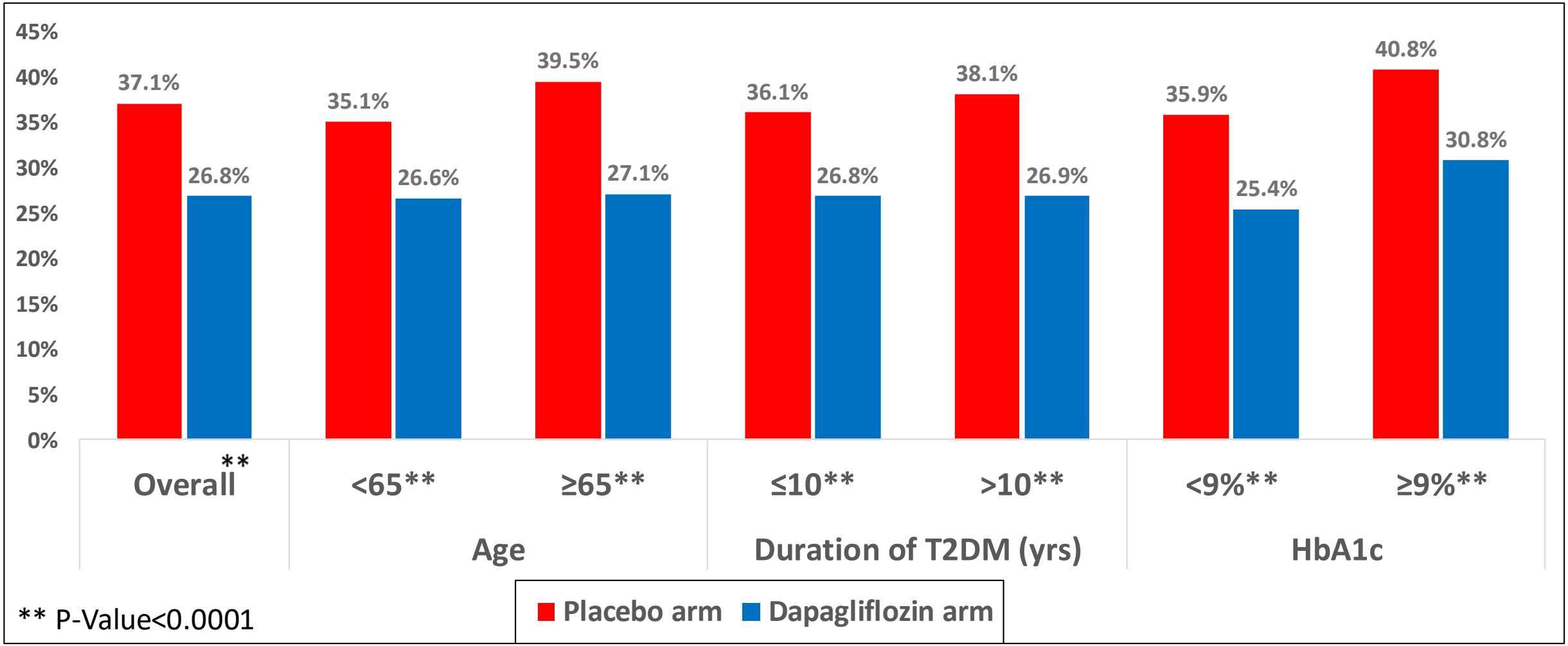
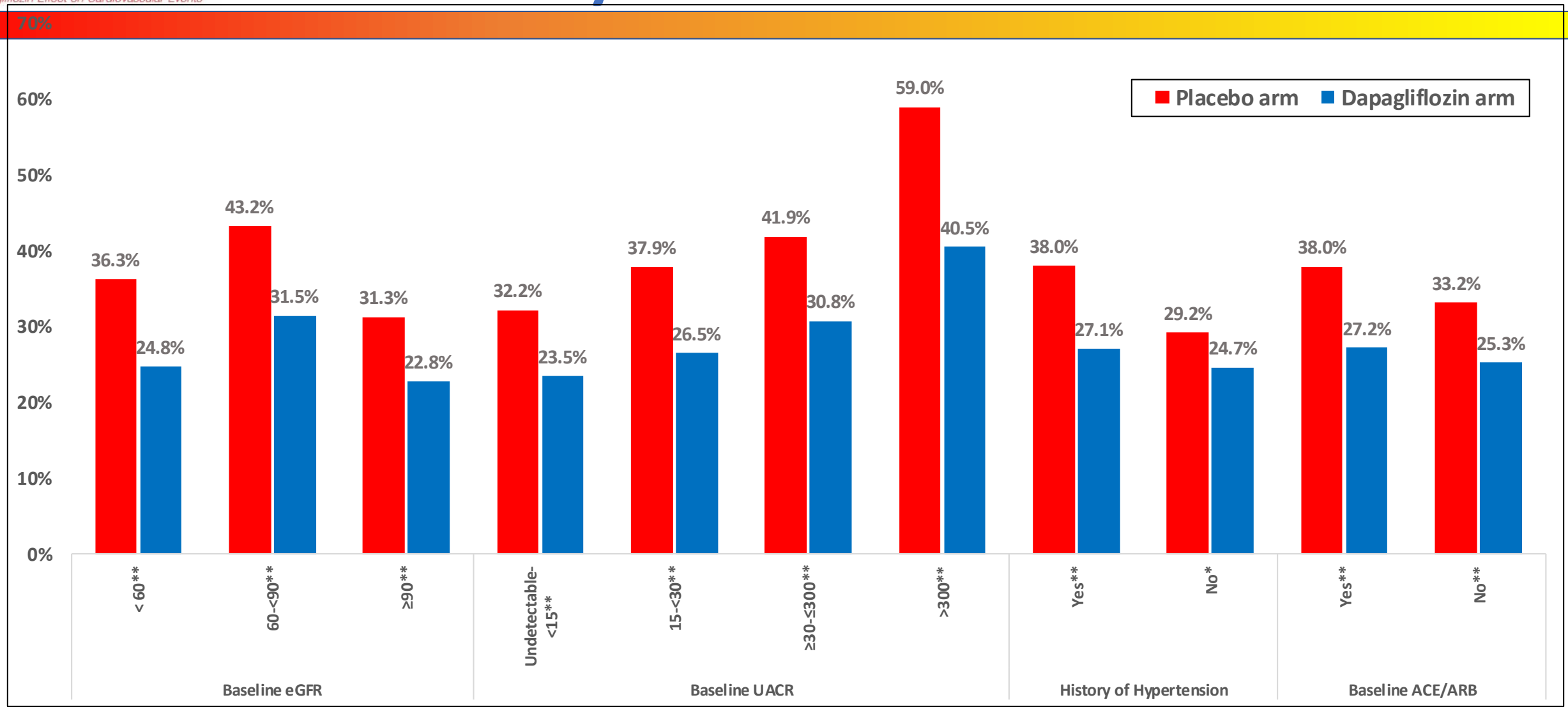
*** Fast decline is defined as an eGFR reduction of ≥3 ml/min/1.73m²/year**

# Fast Decline in eGFR from 6 Months to 4 Years by Treatment Arms




P-values were calculated using Wald test

# Fast Decline in eGFR from 6 Months to 4 Years by Treatment Arms




*. P-Value<0.05 **. P-Value<0.001 P-values were calculated using Wald test

# Fast Decline in eGFR from Baseline to 4 Years by Treatment Arms

| Subgroup | | Placebo | | Dapagliflozin | | P- value |
|---|---|---|---|---|---|---|
| | | N | Percent of FD | N | Percent of FD | |
| | Overall | 8012 | 36.96% | 8096 | 33.65% | <.0001 |
| Age | <65 | 4355 | 35.82% | 4380 | 32.79% | 0.003 |
| | >=65 | 3657 | 38.31% | 3716 | 34.66% | 0.001 |
| Duration of T2DM (years) | <=10 | 4053 | 35.55% | 4030 | 32.21% | 0.001 |
| | >10 | 3958 | 38.40% | 4066 | 35.07% | 0.002 |
| Baseline HbA1c | <9% | 5994 | 35.50% | 5940 | 31.60% | <.0001 |
| | >=9% | 2014 | 41.36% | 2154 | 39.32% | 0.180 |
| Baseline eGFR | < 60 | 592 | 27.36% | 555 | 25.95% | 0.587 |
| | 60-<90 | 3636 | 40.48% | 3614 | 37.22% | 0.004 |
| | >=90 | 3784 | 35.07% | 3927 | 31.45% | 0.001 |
| Baseline UACR | Undetectable-<15 | 4261 | 30.88% | 4298 | 28.08% | 0.004 |
| | 15-<30 | 1209 | 36.89% | 1212 | 34.32% | 0.187 |
| | >=30-<=300 | 1864 | 42.92% | 1898 | 39.88% | 0.059 |
| | >300 | 528 | 65.34% | 548 | 53.65% | <.0001 |
| History of Hypertension | Yes | 7150 | 37.66% | 7327 | 34.24% | <.0001 |
| | No | 862 | 31.09% | 769 | 27.96% | 0.166 |
| Baseline ACE/ARB | Yes | 6529 | 37.91% | 6579 | 34.11% | <.0001 |
| | No | 1483 | 32.77% | 1517 | 31.64% | 0.508 |

P-values were calculated using Wald test

# Summary (1)

- In the DECLARE-TIMI 58 trial there were:
  - **4,788** patients that had **fast decline in eGFR** (defined as ≥3 ml/min/1.73m$^2$/year), their mean (SD) eGFR decline from 6 months to 4 years was: **6.3 (3.7)** ml/min/1.73m$^2$/year.
  - **10,224** patients that **did not have fast decline in eGFR** (defined as <3 ml/min/1.73m$^2$/year), their mean (SD) eGFR decline from 6 months to 4 years was: **0.0 (2.5)** ml/min/1.73m$^2$/year.

# Summary (2)

- In the DECLARE–TIMI 58 trial, patients treated with dapagliflozin had a significantly reduced frequency of fast decline in eGFR both:
  - During the 6 months-4 years
  - During the entire trial.

- The prevalence of fast decline was reduced by dapagliflozin in the whole treatment group and for prespecified subgroups: baseline eGFR, baseline UACR, eCVD vs. MRF for CVD, ACEi/ARB at baseline, diuretics at baseline and history of HTN

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