

# The Efficacy and Safety of Dapagliflozin in Women and Men with Type 2 Diabetes Mellitus: Insights from the DECLARE-TIMI 58 Trial

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## Background

- Women remain underrepresented in clinical trials and at high risk for CV events in type 2 DM (T2DM).
- The SGLT-2 inhibitor dapagliflozin (DAPA) reduces CV death or hospitalization for HF (CVD/HHF) in T2DM (NEJM 2019;380:347), but the relative benefit in women versus men warrants further study.

## Methods

- DECLARE-TIMI 58 randomized 17,160 patients with T2DM with or at risk for atherosclerotic disease to DAPA or placebo (PBO) (median f/u 4.2y)
- The dual efficacy outcomes were the composite of CVD/HHF and CV death, MI or ischemic stroke (MACE).
- Cox models were stratified by sex. The prespecified renal-specific outcome was a  $\geq 40\%$  drop in eGFR to  $<60$  ml/min/1.73m<sup>2</sup>, new ESRD, or renal death.
- Safety events were those leading to drug discontinuation, events of special interest (AEOSI) or serious adverse events (SAEs).

## Results

- At baseline, women (n=6422, 37%) tended to be older, have a higher BMI, higher baseline HbA1c, higher LDL-C and slightly longer duration of T2DM than men. Men were more likely to be white, smokers, North American, report a history of CV disease and have lower LVEF (Table 1).

Table 1: Baseline characteristics by patient sex

Variable	Men (N=10,738)	Women (N=6422)	P value
Age (years)	63 (58-68)	65 (61-69)	<0.01
White	82%	76%	<0.01
BMI (kg/m <sup>2</sup> )	31 (28-35)	33 (28-36)	<0.01
Current tobacco	17%	11%	<0.01
North America	35%	27%	<0.01
Established CV dz	47%	30%	<0.01
Prior MI	26%	13%	<0.01
HbA1c (%)	8.0 (7.3-9.0)	8.1 (7.4-9.1)	<0.01
eGFR (CKD-EPI)	88 (75-97)	89 (75-96)	0.91
UACR (mg/g)	14 (6-53)	12 (7-32)	<0.01
LDL-C (mg/dl)	78 (59-102)	90 (68-117)	<0.01
LVEF (%) (n=4088)	56 (49-62)	60 (55-65)	<0.01
Duration of T2DM, y	10 (6-16)	11 (6-17)	<0.01

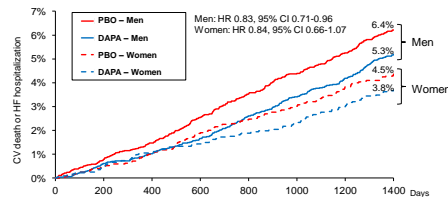
- Despite having a slightly higher HbA1c and longer duration of T2DM, women tended to be on fewer oral antihyperglycemic medications and had similar background insulin use (Table 2).

Table 2: Baseline antihyperglycemic medication use by sex

Variable	Men (N=10,738)	Women (N=6422)	P value
Insulin use	41%	41%	0.71
$\geq 3$ T2DM meds	21%	16%	<0.001
Metformin	83%	81%	<0.001
Sulfonylurea	43%	43%	0.87
DPP4 inhibitor	18%	15%	<0.001
GLP1 agonist	4.8%	3.7%	<0.001

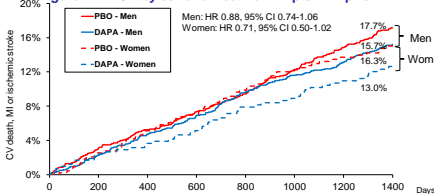
- DAPA reduced CVD/HHF by 16% in women (HR 0.84, 0.66-1.07) and 17% in men (HR 0.83, 0.71-0.96; P int=0.90; Figure 1).

Figure 1: Cumulative incidence of CVD/HHF by sex and treatment



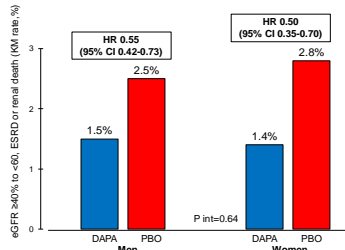
- The HRs for MACE with DAPA were similar in women (HR 0.93, 95% CI 0.77-1.12) and men (HR 0.93, 0.83-1.05; P int=0.99).
- In pts w/ prior MI, DAPA reduced MACE by 29% in women & 12% in men (P int=0.29; Figure 2). DAPA reduced MI by 30% in women (HR 0.70, 0.45-1.10) and 20% in men (HR 0.80, 0.63-1.00; P int= 0.65).

Figure 2: MACE by sex and treatment in pts with prior MI



- Renal-specific events were reduced by 50% in women and 45% in men (P int=0.64; Figure 3).

Figure 3: Renal-specific events by sex and treatment



- Treatment emergent SAEs were less common in DAPA than PBO-treated pts in both women (29.3% vs 31.5%) and men (36.9% vs 39.0%; P int=0.78).
- Urinary tract infections were similar in DAPA vs placebo (women: 2.2% vs 2.1%; men: 1.0% vs 1.2%; P int=0.30), but genital infections were more common with DAPA in both women (1.0% vs 0.1%) and men (0.8% vs 0.1%; P int=0.93).

## Conclusions

- Antihyperglycemic drugs tended to be used less frequently in women than men, despite longer duration of DM and higher HbA1c.
- DAPA offers comparable CV benefit and safety profiles in both women and men, thereby supporting its use for CVD/HF reduction regardless of sex.