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Sex differences in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

J.B. Green[1], J. Alfredsson[2], S.R. Stevens[1], S.D. Reed[1], D.K. McGuire[3], P.W. Armstrong[4], S.S. Engel[5], M.A. Bethel[6], F. Van de Werf[7], E.D. Peterson[1], R.R. Holman[6];
[1]Duke Clinical Research Institute, Durham, USA, [2]Linköping University, Sweden, [3]University of Texas Southwestern Medical Center, Dallas, USA, [4]Canadian VIGOUR Centre, University of Alberta, Edmonton, Canada, [5]Merck & Co., Inc., Kenilworth, USA, [6]Diabetes Trials Unit, University of Oxford, UK, [7]University of Leuven, Belgium.

Background and aims: TECOS was an international, randomized, double-blind, placebo-controlled trial assessing the impact of sitagliptin added to usual care on cardiovascular (CV) outcomes in patients with type 2 diabetes (T2DM) and atherosclerotic CV disease. Although women without diabetes have lower risk for CV events than men, this advantage is reportedly lost in women with T2DM. We examined sex differences in baseline CV disease burden, risk factor management, and outcomes in the TECOS population.
Materials and methods: Cox proportional hazards models were used to analyze the association between sex and key CV endpoints and secondary outcomes, as well as the interaction between sex and treatment effect, controlling for baseline characteristics.
Results: A total of 4,297 women and 10,374 men in the intention-to-treat population were followed for a median of 3.0 years. At baseline, women were slightly older than men (66 vs 65 years) but had similar median duration of diabetes (10 years). More women had cerebrovascular disease (31.2% vs 21.7%), peripheral arterial disease (20.6% vs 14.9%) and heart failure (21.8% vs 16.4%) while more men had coronary heart disease (79.3% vs 61.3%). Women had higher BMI (30.5 vs 29.2 kg/m^2), systolic BP (135 vs 132 mmHg), and LDL cholesterol levels (2.4 vs 2.1 mmol/L); worse renal function (eGFR 68.0 vs 74.0 mL/min/1.73m^2); but lower rates of smoking (8.5% vs 12.6%) ($p<0.0001$ for all). At baseline women were less likely to use aspirin (72.5% vs 81.0%) or a statin (73.0% vs 82.7%) than men (both $p<0.0001$). During the trial, the primary composite outcome of CV death, myocardial infarction (MI), stroke, or hospitalization for unstable angina (UA) occurred in 418 (9.7%) women and 1,272 (12.3%) men across treatment groups, corresponding to 3.48 vs. 4.38 events/100 patient-years (crude HR 0.79; 95% CI 0.71, 0.89). This association was strengthened after adjustment for baseline characteristics (HR 0.71; 95% CI 0.60, 0.83, $p< 0.0001$). Women also had significantly lower risks of secondary endpoints including a composite of CV death, MI, or stroke as well as the individual endpoints of CV death, all-cause death, MI, or stroke (Table). There were no interactions between sex and the effect of sitagliptin treatment upon CV outcomes ($p>0.10$ for all).
Conclusion: In this large prospective trial of patients with T2DM and CVD, women had worse CV risk factor profiles and less extensive use of indicated medications than men. Despite this, women had significantly lower risk for new major CV events. These data suggest that the cardioprotective effect of female sex extends to populations with T2DM.

Table: Association of Sex and Endpoints

Endpoint	Total events (W)	Events per 100 pt-yrs (W)	Total events (M)	Events per 100 pt-yrs (M)	HR (95% CI) for female v. male	Adjusted HR (95% CI) for female v. male	Adjusted p
CV death, MI, Stroke, or Hospitalization for UA	418	3.48	1272	4.38	0.79 (0.71, 0.89)	0.71 (0.60, 0.83)	<0.0001
CV death, MI, Stroke	371	3.06	1120	3.82	0.80 (0.71, 0.90)	0.69 (0.58, 0.81)	<0.0001
CV death	199	1.55	547	1.76	0.82 (0.70, 0.97)	0.64 (0.50, 0.81)	0.0003
Myocardial infarction	136	1.11	480	1.61	0.73 (0.60, 0.88)	0.70 (0.54, 0.91)	0.0081
Stroke	96	0.78	265	0.88	0.86 (0.68, 1.09)	0.66 (0.47, 0.92)	0.0151
Hospitalization for UA	58	0.47	187	0.62	0.78 (0.58, 1.05)	0.87 (0.56, 1.33)	0.5159
All Cause Death	279	2.17	805	2.58	0.80 (0.69, 0.91)	0.68 (0.56, 0.82)	<0.0001
Hospitalization for HF	115	0.93	342	1.14	0.83 (0.67, 1.03)	0.84 (0.64, 1.12)	0.2414

Cox proportional hazards regression models are used. Data are censored at the last day the patient is known to be free of the event. Models are repeated with adjustment for duration of diabetes and baseline variables determined to differ.
W = women; M = men; MI = myocardial infarction; UA = unstable angina; HF = heart failure

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