Cardiovascular safety and efficacy of exenatide once-weekly in patients with moderate renal dysfunction in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL)

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Background and aims: EXSCEL, a multinational, randomized, placebo-controlled cardiovascular (CV) outcome trial of 2 mg once-weekly exenatide added to usual care, demonstrated CV safety in patients with type 2 diabetes (T2D) with or without previous CV disease. We report the impact of exenatide on confirmed CV outcomes, all-cause mortality, and key CV safety parameters according to baseline renal function (moderate dysfunction [<60 mL/min/1.73m2] and within Stage 3 [3a: eGFR 45-59 or 3b: 30-44 mL/min/1.73m2] chronic kidney disease).
Materials and methods: For the subgroups by baseline renal function, Cox proportional hazards models were fit to the time to first event of the three-component major adverse CV event (MACE-3) composite outcome (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke). Secondary outcomes were time to all-cause mortality, death from CV cause, nonfatal or fatal myocardial infarction, nonfatal or fatal stroke, hospitalization for heart failure, and hospitalization for acute coronary syndrome.
Results: Of 14,752 patients in the ITT population, 3191 (22%) had eGFR<60, 2288 (16%) had eGFR 45-59 and 889 (6%) had eGFR 30-44 mL/min/1.73m2. Participants with moderate renal dysfunction had a higher mean age (67 vs 61 years) and longer duration of T2D (median [IQR] 14 [9,21] vs 11 [6,17] years). In univariate subgroup analyses, there was no significant interaction between randomized treatment and renal function, either based on eGFR thresholds (± 60 mL/min/1.73m2; p for interaction = 0.12) or on CKD stages (p for interaction = 0.51). In those with eGFR <60 mL/min/1.73m2, first MACE-3 events occurred in 283 (18.1%) participants in the exenatide group and 284 (17.5%) in the placebo group (hazard ratio [HR] 1.01, 95% CI 0.86-1.19). HR and 95% CI for other important CV outcomes are shown in the Table.
Conclusion: In patients with moderate renal dysfunction, 2 mg once-weekly exenatide had a neutral impact on CV outcomes. In univariate analyses unadjusted for multiplicity, modest risk reductions were seen with exenatide in those with baseline eGFR ≥60mL/min/1.73m2 for MACE-3, all-cause mortality, CV death and fatal or non-fatal stroke.

Table. Hazard ratio (HR) and 95% confidence interval (CI) for CV outcomes for allocation to 2mg once-weekly exenatide compared with placebo, according to baseline renal function

eGFR mL/min/1.73m^2	MACE-3 HR (95%CI)	CV Death HR (95%CI)	F/NF MI HR (95%CI)	F/NF stroke HR (95%CI)	ACM HR (95%CI)	HF HR (95%CI)	ACS HR (95%CI)
≥60 (n=11,514)	0.86 (0.77, 0.97)	0.77 (0.64, 0.93)	0.97 (0.83, 1.14)	0.74 (0.58, 0.93)	0.78 (0.67, 0.91)	0.84 (0.66, 1.07)	1.07 (0.93, 1.23)
<60 (n=3191)	1.01 (0.86, 1.19)	1.10 (0.86, 1.40)	0.95 (0.77, 1.18)	1.17 (0.82, 1.67)	1.01 (0.83, 1.23)	1.08 (0.81, 1.44)	1.00 (0.82, 1.22)
Stage 3a: 45-59 (n=2288)	0.97 (0.79, 1.20)	1.05 (0.77, 1.43)	0.95 (0.73, 1.25)	1.23 (0.79, 1.90)	1.01 (0.79, 1.30)	0.80 (0.55, 1.16)	1.02 (0.80, 1.31)
Stage 3b: 30-44 (n=889)	1.11 (0.84, 1.47)	1.18 (0.79, 1.75)	0.99 (0.69, 1.41)	1.07 (0.57, 2.01)	1.01 (0.73, 1.40)	1.80 (1.12, 2.90)	1.00 (0.71, 1.41)

MACE-3: composite of death from cardiovascular causes (CV death), nonfatal myocardial infarction (MI), nonfatal stroke.
F: fatal. NF: nonfatal. ACM: all- cause mortality. HF: hospitalization for heart failure. ACS: hospitalization for acute coronary syndrome

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