Potential impact of differential drop-in of open-label diabetes medications in EXSCEL

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Background and aims: Greater drop-in of open label diabetes (DM) medications occurred during the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) with placebo (P) than exenatide (E). As some DM medication classes reduced cardiovascular (CV) events in other outcome trials, we evaluated whether imbalanced use of concomitant DM medications during follow up may have impacted time to event analyses for major adverse CV events (MACE3; CV death, nonfatal myocardial infarction, or nonfatal stroke) or all-cause mortality (ACM).
Materials and methods: DM medication use was recorded by drug class at each study visit. Once initiated, new medications were assumed to continue for the study duration. For medication classes where drop-in occurred in >5% of participants and for open label glucagon-like peptide-1 receptor agonists [GLP-1 RA; 3% overall), Cox hazard models were performed by randomized treatment with right censoring at the drop-in visit. Cox hazard models for MACE3 were also recalculated by modelling the impact of drop-in medication by applying effect sizes derived from published trials: HR 1.02 for insulin, 0.99 for dipeptidyl peptidase-4 inhibitors (DPP-4i), 0.88 for GLP-1 RA, and 0.85 for sodium glucose transporter 2 inhibitors (SGLT2i). E vs P HRs for MACE3 and ACM were also recalculated using inverse probability weighting (IPW), preferentially weighting accumulated outcome data for participants who did not experience drop-in of DM medications.
Results: Concomitant DM medication use did not differ between groups at baseline, but during follow-up, drop-in use was more frequent in P for biguanide (6.1 vs 4.8%), sulfonylurea (SU; 8.8 vs 6.9%), DPP-4i (10.6 vs 7.5%), insulin (13.8 vs 9.4%), SGLT2i (5.4 vs 3.7%), and GLP-1 RA (3.6 vs 2.5%). Using censoring analyses, E vs P HRs for MACE3 were minimally altered with drop-in medication (Table) but became nominally statistically significant with SU, SGLT2i or any DM medication. For ACM, neither the HR (95% CI) nor the p-value were altered meaningfully. Modelled E vs P HRs for MACE3 dependent on published effect sizes were 0.92 (0.84, 1.01) for DPP-4i, 0.92 (0.84, 1.01) for GLP-1 RA, 0.92 (0.84, 1.01) for SGLT2i, and 0.92 (0.84, 1.01) for insulin. After IPW, E v. P HRs were 0.89 (0.78, 1.02), p=0.10 for MACE3 and 0.82 (0.64, 1.04), p=0.104 for ACM.
Conclusion: Observed MACE3 and ACM E vs P effect sizes in EXSCEL were robust to several methods of adjusting for the greater drop-in of open-label DM medications in P. Lower p-values ($p< 0.05$) were observed for MACE3 after censoring for SU, SGLT2i, or any medication, suggesting drop-in medications can influence study outcomes. P values were consistently <0.05 for ACM. In summary, greater drop-in of cardioprotective medications with placebo can blunt signal detection and should be considered in the design and analysis of future trials.

		Censored open-label drop-in diabetes medication						
	None	Biguanide	SU	DPP-4i	Insulin	SGLT-2i	GLP-1RA	Any
Median (IQR) follow up (yrs)	3.3 (2.3, 4.4)	2.7 (2.0 4.0)	2.5 (1.7, 3.9)	2.5 (1.6, 3.7)	2.5 (1.9, 3.8)	2.5 (1.6, 3.9)	2.5 (1.6, 3.9)	2.0 (1.3, 3.4)
MACE-3								
HR (95% CI)	0.91 (0.83, 1.00) P=0.061	0.91 (0.83, 1.00) P=0.056	0.89 (0.81, 0.99) P=0.024	0.92 (0.83, 1.02) P=0.103	0.91 (0.82, 1.00) P=0.060	0.90 (0.82, 1.00) P=0.042	0.92 (0.83, 1.01) P=0.080	0.88 (0.79, 0.98) P=0.021
Events (E/P)	839/905	792/852	756/819	763/800	770/803	766/832	766/819	648/659
ACM								
HR (95% CI)	0.86 (0.77, 0.97) P=0.016	0.86 (0.76, 0.97) P=0.017	0.85 (0.75, 0.96) P=0.012	0.87 (0.77, 1.00) P=0.043	0.87 (0.76, 0.98) P=0.029	0.86 (0.76, 0.98) P=0.023	0.87 (0.77, 0.99) P=0.034	0.84 (0.72, 0.97) P=0.016
Events (E/P)	507/584	467/533	445/509	439/482	441/481	444/504	445/498	363/378
	E/P exenatide/placebo; CI confidence interval; DPP-4i dipeptidyl peptidase inhibitor; SGLT-2i sodium-glucose co-transporter 2 inhibitor; GLP-1 RA glucagon-like peptide-1 receptor agonist							

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