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


1UNC School of Medicine, Chapel Hill, USA, 2Diabetes Trials Unit, Oxford, UK, 3Duke Clinical Research Institute, Durham, USA, 4AstraZeneca, Gaithersburg, USA.

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 unbalanced 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 vs 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 (<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.

<table>
<thead>
<tr>
<th>Medication</th>
<th>NACE3</th>
<th>CV</th>
<th>DPP-4i</th>
<th>GLP-1 RA</th>
<th>SGLT2i</th>
<th>Other</th>
</tr>
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<tbody>
<tr>
<td>HR (95% CI)</td>
<td>0.92 (0.88, 1.00)</td>
<td>0.92 (0.88, 1.00)</td>
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