Exploring the Possible Impact of Unbalanced Open-Label Drop-In of Glucose-Lowering Medications on EXSCEL Outcomes

BACKGROUND: EXSCEL (Exenatide Study of Cardiovascular Event Lowering) assessed the impact of once-weekly exenatide 2 mg versus placebo in patients with type 2 diabetes mellitus, while aiming for glycemic equipoise. Consequently, greater drop-in of open-label glucose-lowering medications occurred in the placebo group. Accordingly, we explored the potential effects of their unbalanced use on major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction or nonfatal stroke, and all-cause mortality (ACM), given that some of these agents are cardioprotective.

METHODS: Cox hazard models were performed by randomized treatment for drug classes where >5% open-label drop-in glucose-lowering medication occurred, and for glucagon-like peptide-1 receptor agonists (GLP-1 RAs; 3.0%) using three methodologies: drop-in visit right censoring, inverse probability for treatment weighting (IPTW), and applying drug class risk reductions.

RESULTS: Baseline glucose-lowering medications for the 14 752 EXSCEL participants (73.1% with previous cardiovascular disease) did not differ between treatment groups. During median 3.2 years follow-up, open-label drop-in occurred in 33.4% of participants, more frequently with placebo than exenatide (38.1% versus 28.8%), with metformin (6.1% versus 4.9%), sulfonylurea (8.7% versus 6.9%), dipeptidyl peptidase-4 inhibitors (10.6% versus 7.5%), SGLT-2i (10.3% versus 8.1%), GLP-1 RA (3.4% versus 2.4%), and insulin (13.8% versus 9.4%). The MACE effect size was not altered meaningfully by right censoring, but the favorable HR for exenatide became nominally significant in the sulfonylurea and any glucose-lowering medication groups, while the ACM HR and p-values were essentially unchanged. IPTW decreased the MACE HR from 0.91 (P=0.061) to 0.85 (P=0.008) and the ACM HR from 0.86 (P=0.016) to 0.81 (P=0.012). Application of literature-derived risk reductions showed no meaningful changes in MACE or ACM HRs or P values, although simulations of substantially greater use of drop-in cardioprotective glucose-lowering agents demonstrated blunting of signal detection.

CONCLUSIONS: EXSCEL-observed HRs for MACE and ACM remained robust after right censoring or application of literature-derived risk reductions, but the exenatide versus placebo MACE effect size and statistical significance were increased by IPTW. Effects of open-label drop-in cardioprotective medications need to be considered carefully when designing, conducting, and analyzing cardiovascular outcome trials of glucose-lowering agents under the premise of glycemic equipoise.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01144338.

M. Angelyn Bethel, MD
Susanna R. Stevens, MS
John B. Buse, MD, PhD
Jasmine Choi, MS
Stephanie M. Gustavson, PhD
Nayyar Iqbal, MD
Yuliya Lokhnygina, PhD
Robert J. Mentz, MD
Rishi A. Patel, MBChB
Peter Öhman, MD
Guntram Schernthaner, MD
Albert Lecube, MD, PhD
Adrian F. Hernandez, MD
Rury R. Holman, MBChB

Key Words: cardiovascular diseases ■ clinical trial ■ diabetes mellitus, type 2 ■ dipeptidyl-peptidase IV inhibitors ■ glucagon-like peptide-1 receptor ■ mortality

Sources of Funding, see page 1369

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- The design, conduct, and interpretation of placebo-controlled cardiovascular outcome trials in type 2 diabetes mellitus is becoming more complex because of the increasing use of proven cardioprotective glucose-lowering medications in this population.
- Glycemic equipoise clinical trial designs inevitably lead to a greater use of potentially cardioprotective medications in the placebo group, which could mask the true cardiovascular benefits of an intervention being studied.

What Are the Clinical Implications?

- The authors explore methodologies that can be used to estimate the likely impact of drop-in cardioprotective glucose-lowering medications on cardiovascular outcomes and to inform the design of future cardiovascular outcome trials.

Randomized, controlled trials are the cornerstone of modern, evidence-based medicine.[1] Randomization in large-scale clinical outcome studies ensures that measured and unmeasured baseline confounders are balanced between treatment groups. Masking (or blinding) the treatment assignment further minimizes the potential bias of differential post-randomization management of enrolled participants. Many placebo-controlled cardiovascular (CV) outcome trials of glucose-lowering agents have been designed to minimize potential confounding by glycemic differences between treatment groups by applying treat-to-guideline glycemic targets to all participants. This protocol requirement has in turn led to greater use of drop-in, open-label glucose-lowering agents after randomization in the placebo group. Historically, this has not been a major concern, as available glucose-lowering agents had not been proven to reduce or increase CV risk (eg, thiazolidinediones).[2] Previous concerns that sulfonylureas might also increase CV risk have largely been ameliorated by the CAROLINA trial (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes).[3] However, significant CV event reductions have been demonstrated for several newer medications in recent large-scale outcome trials. Liraglutide, semaglutide, albiglutide, and dulaglutide (glucagon-like peptide-1 receptor agonists [GLP-1 RAs]) showed 13%, 26%, 22%, and 12% relative risk reductions (RRR), respectively, for a 3-point major adverse CV events (MACE) composite of CV death, nonfatal myocardial infarction, or nonfatal stroke in populations varying in their degree of CV risk.[4–8] Liraglutide and oral semaglutide also showed 15% and 49% reductions in all-cause mortality (ACM).[4,5] Empagliflozin and canagliflozin (sodium-glucose cotransporter-2 inhibitors [SGLT-2is]) both showed a significant 14% RRR for MACE and reductions in ACM (32%, $P<0.001$ for empagliflozin and 13% [NS] for canagliflozin) in populations either with or at risk of CVD.[9,10] With these cardioprotective glucose-lowering agents being used increasingly in routine clinical practice, there is a greater likelihood that their open-label drop-in in placebo groups could impact clinical trial CV event rates and potentially bias study outcomes.

EXSCEL (Exenatide Study of Cardiovascular Event Lowering) was a multinational, placebo-controlled, pragmatic randomized, controlled CV outcome trial designed to assess the impact of once-weekly exenatide 2 mg versus placebo, when added to usual care in patients with type 2 diabetes mellitus (T2D) at a wide range of CV risk. The primary MACE result for exenatide demonstrated noninferiority, but not superiority, when compared with placebo (hazard ratio [HR], 0.91; 95% CI, 0.83–1.00; $P=0.061$), and a reduced risk for ACM (HR, 0.86; 95% CI, 0.77–0.97; $P=0.016$) that was nominally significant because of the prespecified hierarchical testing paradigm.[11] Initiated in 2010, EXSCEL was designed to target comparable glucose control in both treatment arms.[12] During the trial, management of T2D was performed by participants' usual care providers, in accordance with local and national treatment guidelines, with the choice and adjustment of concomitant glucose-lowering medications also at the discretion of the usual care provider. All glucose-lowering medications were permitted, with the exception of open-label GLP-1 RAs. As a consequence of EXSCEL's glycemic equipoise policy, there was greater drop-in use of open-label glucose-lowering medications in the placebo group. In these exploratory analyses, we have used several statistical and modeling methods to evaluate whether their unbalanced use during the trial might have affected the primary outcome (MACE) or ACM time-to-event analyses.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be submitted at dcri.org/data-sharing.

Study Design

The design, protocol, and primary results of EXSCEL (NCT01144338) have been published previously.[11–13] The study was designed and run independently by the Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit in an academic collaboration with the sponsor, Amylin Pharmaceuticals, a wholly owned subsidiary of AstraZeneca. The protocol was approved by the

ethics committees associated with all participating trial sites, and all participants provided written informed consent for trial participation.

Briefly, 14 752 participants from 35 countries were enrolled between June 2010 and September 2015. Eligible participants were adults (>18 years old) with T2D with HbA_{1c}, 6.5 to 10.0% (48–96 mmol/L) and any degree of previous CV risk, although the trial targeted 70% with a previous coronary, cerebrovascular, or peripheral arterial event. Enrolled patients could be taking up to 3 oral glucose-lowering agents either alone or in combination with insulin. Key exclusion criteria were a history of 2 or more episodes of severe hypoglycemia (defined as hypoglycemia for which a patient received third-party assistance) during the preceding 12 months, end-stage kidney disease or an estimated glomerular filtration rate (eGFR) at entry <30 $mL \cdot min^{-1} \cdot 1.73\ m^2$, a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, a baseline calcitonin level >40 ng/L, or previous treatment with a GLP-1 RA. Study participants were randomized in a double-blind fashion to either once-weekly exenatide 2 mg or matching placebo.

Open-Label Drop-In Glucose-Lowering Medications

During follow-up, treatment for T2D and its comorbidities was provided by usual care providers based on local guidelines, with an intent to achieve comparable glycemic control in the 2 treatment groups. The protocol instructions were: "Concomitant medications will be used at the discretion of the usual care physician (or investigator if also the usual care physician), who will be informed of the participant's enrolment in the trial, the use of blinded trial medication, and that use of GLP-1 receptor agonists is contraindicated during the trial period…Usual care physicians will be encouraged to follow guidelines for care based on local and institutional practice patterns and any relevant published practice guidelines." The addition of any glucose-lowering agent was permitted, with the exception of GLP-1 RAs, which, if started by the usual care provider, prompted discontinuation of study medication. Concomitant medication usage was recorded at all visits by drug class: metformin, sulfonylurea, thiazolidinedione, insulin (including short- and long-acting preparations), pramlintide, nonsulfonylurea secretagogue, α-glucosidase inhibitor, GLP-1 RA (other than the study drug), and dipeptidyl peptidase-4 inhibitor (DPP-4i). Data collection for SGLT-2i use, at baseline and/or during follow-up, commenced in May 2013, before extensive SGLT-2i use in routine clinical practice.[14] For the purposes of these analyses, SGLT-2i use was assumed not to have occurred before this date.

Statistical Analyses

Analyses were limited to glucose-lowering medication classes where open-label drop-in occurred in >5% of participants, and for the GLP-1 RAs that were used by fewer participants but were of special interest given previous studies demonstrating their cardioprotective attributes. Drop-in medications were assumed to continue for the duration of the follow-up period once initiated, as stopping dates were not collected. Baseline characteristics for participants commencing open-label drop-in glucose-lowering medications were summarized by medication class using mean±1 SD or median (25th, 75th percentile) for continuous variables, and by number (percentage) for categorical variables. Three different methodologies were used to explore in the intention-to-treat population the potential impact of within-trial drop-in medications on CV outcomes: (1) right censoring analyses; (2) inverse probability weighting analyses; and (3) applying evidence-based event rate adjustments. The latter methodology was also used to simulate the potential impact of greater drop-in rates than observed in EXSCEL, which may well occur in future CV outcome trials in T2D.

Right Censoring Analyses

To exclude any impact of starting a concomitant diabetes mellitus medication postbaseline on estimation of the randomized treatment effect, time to event outcomes were analyzed using Cox proportional hazards regression models where patients who started drop-in medications were censored at the time of the visit where this occurred. Drop-in medication drug classes were analyzed separately, as well as drop-in of any diabetes mellitus medication. Patients taking the drug class at baseline were not censored for drop-in.

Inverse Probability Weighting Analyses

Inverse probability weighting methods were used to adjust for the potential impact of drop-in medications.[15] Data from participants who initiated a drop-in medication were right censored at the time of drop-in (as mentioned previously), while event rates from those who did not initiate a drop-in medication were weighted by the inverse probability of starting a drop-in medication, as calculated by a proportional hazards regression model. For example, if a 55-year-old male patient had one-third the probability of not starting a drop-in medication, his data would be weighted by a factor of 3 in the analysis, to account for himself and 2 similar patients who did start drop-in medication (and whose data were censored).

To conduct the analysis, a participant day–level dataset was created for each time interval from baseline until medication drop-in, an event of interest occurred, or study end. Probabilities of drop-in were calculated using proportional hazards regression models, separately for exenatide and placebo groups. Models included covariates of baseline age, sex, race, ethnicity, region, smoking, diabetes mellitus duration, New York Heart Association heart failure class, previous CV disease, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, cerebrovascular disease, chronic liver disease, chronic respiratory disease, hyperlipidemia, hypertension, atrial fibrillation, unstable angina, heart rate, body mass index, HbA_{1c}, eGFR, and blood pressure. HbA_{1c} and eGFR measures taken during the study were included as time-varying covariates, as was hospitalization for heart failure. The inverse probabilities from this model were used to weight contributions from patients who did not initiate a drop-in medication in the CV outcomes models, where randomized treatment was the only independent variable. Weights were truncated at the 99th percentile to minimize the impact of a few extreme values.

Evidence-Based Event Rate Adjustment Analyses

Rates for events observed after drop-in medication during the trial were adjusted using estimates by diabetes mellitus

medication class of their likely impact on the outcomes of interest. To obtain effect size estimates, we performed a literature search to identify published meta-analyses of randomized, placebo-controlled trials listing MACE or ACM as primary or secondary outcomes within each drug class (Table I in the Data Supplement). Events occurring before the use of an open-label drop-in glucose-lowering medication were counted as observed, whereas counts of post–drop-in events were divided by the estimated HR for the medication class concerned. Hazard rates in each treatment group were obtained by dividing a sum of events before drop-in and amended events after drop-in by the total patient-years of follow-up, and HRs were then calculated (Table II in the Data Supplement).

To simulate the potential impact of a much greater rate of open-label drop-in glucose-lowering medication than was observed in EXCSEL, these analyses were repeated assuming that 25% or 50% of placebo group participants, but no exenatide group participants, commenced such medication—a worst-case scenario maximizing the potential for bias. Among placebo patients who were not taking the medication at baseline, additional patients were chosen at random to become drop-ins and were assumed to drop-in immediately at baseline. New follow-up times were simulated from an exponential distribution for patients who died under the assumption that they may not have died had they received drop-in medication. New time to event was simulated for the additional drop-ins. If the simulated time was after the study ended or after the patient was actually censored, patients were assigned to be nonevents; otherwise, they were assigned to be events. Proportional hazards regression analysis was performed using simulated data from additional drop-ins, as described previously, and actual data from all other patients. Estimates from the regression analysis were saved, and the process was repeated 5000 times for each drop-in medication. SAS PROC MIANALYZE was used to combine the estimates from the 5000 repetitions. Results are presented as median number of events across simulations, HR (95% CI), and *P* value.

RESULTS

At baseline, concomitant medication use did not differ between groups (Figure 1A). During follow-up, open-label drop-in of glucose-lowering medication occurred overall in 33.4% of participants, and more frequently in the placebo than the exenatide group (38.1% placebo versus 28.8% exenatide). Drop-in therapies were metformin (6.1% versus 4.9%), sulfonylurea (8.7% versus 6.9%), insulin (13.8% versus 9.4%), DPP-4i (10.6% versus 7.5%), GLP-1 RA (3.4% versus 2.4%), and SGLT-2i (10.3% versus 8.1%; Figure 1B). Baseline characteristics for participants initiating open-label drop-in glucose-lowering medications by drug class show little age difference between medication type (Table). Patients initiating sulfonylurea had the shortest duration of diabetes mellitus, and those starting metformin or an SGLT-2i had the longest. Participants initiating a GLP-1 RA had the highest body mass index followed by patients initiating an SGLT-2i. Median post–drop-in drug exposure times ranged from 1.0 to 2.1 years.

Right Censoring Analyses

The EXSCEL primary outcome (MACE) HR was not altered meaningfully by right censoring for any of the drop-in medications, although the small changes in event numbers did lead to nominally significant *P* values when censoring for sulfonylureas (*P*=0.025) or any drop-in glucose-lowering medication (*P*=0.017; Figure 2A). The ACM HR was not altered meaningfully by right censoring for any of the drop-in medications, with no meaningful change in their associated *P* values (Figure 2B).

Inverse Probability Treatment Weighting Analyses

Using inverse probability weighting to account for the addition of drop-in medications increased the MACE effect size for exenatide, decreasing the HR from 0.91 (95% CI, 0.83–1.00) to 0.85 (95% CI, 0.76–0.96) with a decrease in the *P* value from 0.061 to 0.008. Similarly, the ACM effect size for exenatide was increased, decreasing the HR from 0.86 (0.77–0.97) to 0.81 (0.69–0.96) and decreasing the *P* value from 0.016 to 0.012. The factors most strongly associated with medication drop-in were HbA_{1c} values during follow-up, region, and diabetes mellitus duration (Tables III through VI in the Data Supplement).

Evidence-Based Event Rate Adjustment Analyses

Our literature search identified suitable meta-analyses to estimate the impact on MACE and ACM for insulin,[16] DPP-4i,[17] GLP-1 RA,[18] and SGLT-2i[19] (Table I in the Data Supplement). For metformin and sulfonylurea, suitable meta-analyses were only identified for ACM.[20,21] MACE estimates for metformin and sulfonylurea were provided by the United Kingdom Prospective Diabetes Study Group (Rury Holman, personal communication).

Applying these evidence-based impact estimates to the MACE and ACM event rates observed after open-label glucose-lowering drop-in of medication had occurred did not meaningfully alter the HRs or confidence intervals seen for these outcomes in EXSCEL (Figure 3).

Simulating the Impact of a Substantially Greater Rate of Drop-In Medication

Simulation analyses using evidence-based event rate adjustments and the proportion of placebo-treated patients initiating drop-in medications set to 25% or to

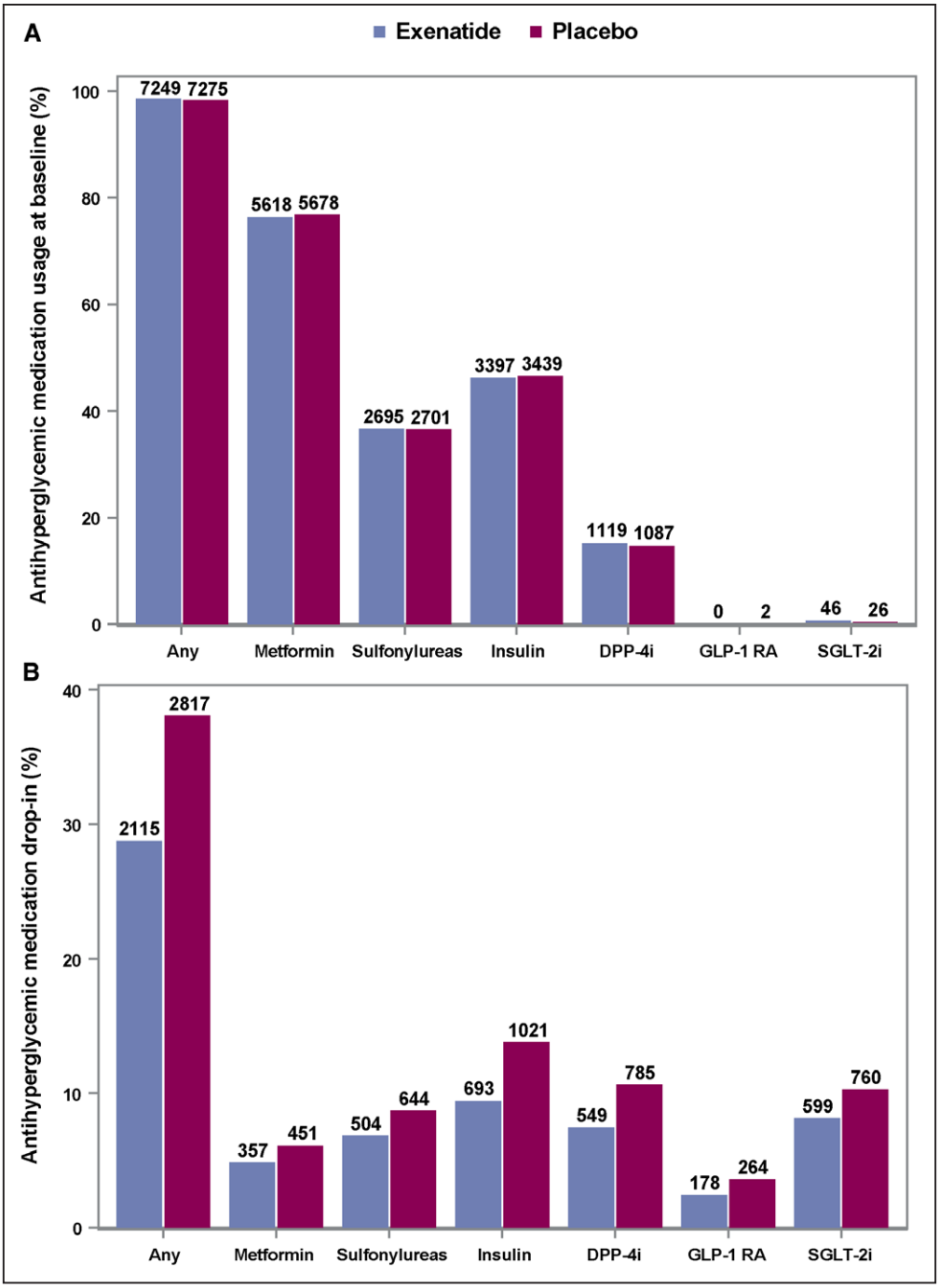

Figure 1. Glucose-lowering medication use by treatment group in EXSCEL (Exenatide Study of Cardiovascular Event Lowering).
Pictured is medication use at baseline (**A**) and during follow-up (**B**). Data presented are only for those drop-in medication classes used in >5% of EXSCEL participants and for the glucagon-like peptide-1 receptor agonist (GLP-1 RA) class that was used by fewer participants but is of special interest given previous studies demonstrating their cardioprotective attributes. Percentages are for available data from the intention-to-treat population. Information regarding sodium-glucose cotransporter-2 inhibitor (SGLT-2i) use was added to the electronic case report form on May 9, 2013. DPP-4i indicates dipeptidyl peptidase-4 inhibitor.

50% showed that MACE HRs remain largely unchanged from the main trial for most medications, ranging from 0.91 to 0.93 for sulfonylurea, insulin, and DPP-4i, regardless of the proportion with drop-in.

HRs were higher (>0.93) for metformin at 50% drop-in and for both GLP-1 RA and SGLT-2i at both 25% and 50% drop-in, suggesting that upwards of 25% of placebo-treated patients in EXSCEL would have needed to commence an SGLT-2i or GLP-1 RA to have made a substantive change to the MACE trial results. HRs for ACM were most markedly altered by GLP-1 RA and SGLT-2i drop-in, with reductions in effect size seen for both 25% and 50% drop-in, with loss of statistical significance in all cases.

Table. **Baseline Patient Characteristics and Exposure Time According to Type of Diabetes Mellitus Medication Initiated Postrandomization**

	Metformin (N=808)	Sulfonylurea (N=1148)	Insulin (N=1714)	DPP-4i (N=1334)	GLP-1 RA (N=442)	SGLT-2i (N=1359)
Exposure time, y	2.0 (0.9–3.2)	2.1 (1.0–3.5)	2.0 (0.9–3.3)	1.8 (0.8–3.0)	1.5 (0.6–3.0)	1.0 (0.4–1.6)
Age at randomization, y	62 (56–69)	60 (54–67)	61 (54–67)	62 (56–68)	60 (53–66)	60 (53–66)
Female sex	307 (38.0%)	472 (41.1%)	663 (38.7%)	469 (35.2%)	184 (41.6%)	437 (32.2%)
Race						
White	615 (76.1%)	870 (75.9%)	1360 (79.3%)	974 (73.0%)	379 (85.9%)	1161 (85.6%)
Black	61 (7.5%)	82 (7.1%)	98 (5.7%)	69 (5.2%)	21 (4.8%)	43 (3.2%)
Asian	70 (8.7%)	103 (9.0%)	108 (6.3%)	187 (14.0%)	17 (3.9%)	112 (8.3%)
Hispanic	61 (7.5%)	86 (7.5%)	133 (7.8%)	96 (7.2%)	20 (4.5%)	37 (2.7%)
Other	1 (0.1%)	6 (0.5%)	15 (0.9%)	8 (0.6%)	4 (0.9%)	4 (0.3%)
Duration of type 2 diabetes mellitus, y	12 (6–18)	9 (5–14)	10 (6–15)	11 (7–17)	11 (7–17)	12 (7–17)
History of cardiovascular disease						
Coronary artery disease	451 (55.8%)	571 (49.7%)	745 (43.5%)	731 (54.8%)	217 (49.1%)	687 (50.6%)
Cerebrovascular disease	144 (17.8%)	183 (15.9%)	240 (14.0%)	213 (16.0%)	61 (13.8%)	168 (12.4%)
Peripheral artery disease	168 (20.8%)	178 (15.5%)	242 (14.1%)	170 (12.7%)	44 (10.0%)	156 (11.5%)
Heart failure	156 (19.3%)	145 (12.6%)	207 (12.1%)	174 (13.0%)	40 (9.0%)	152 (11.2%)
Systolic blood pressure, mm Hg	135 (124–148)	133 (124–145)	134 (123–145)	134 (123–144)	134 (123–143)	133 (123–144)
Diastolic blood pressure, mm Hg	80 (70–85)	80 (72–86)	80 (72–85)	80 (71–85)	78 (70–85)	80 (71–85)
Heart rate, bpm	72 (65–78)	72 (65–80)	72 (66–80)	72 (66–80)	73 (68–80)	73 (67–80)
Body mass index, kg/m^2	32.4 (28.4–37.0)	32.0 (28.0–36.9)	32.0 (28.3–36.8)	31.8 (28.4–36.6)	35.0 (31.4–39.8)	33.6 (29.8–38.2)
HbA1c, %	8.1 (7.4–9.0)	8.0 (7.3–8.8)	8.3 (7.6–9.0)	8.2 (7.5–9.0)	8.1 (7.4–8.9)	8.1 (7.5–9.0)
LDL, mg/dL	88 (67–121)	87 (68–114)	86 (66–114)	86 (66–111)	82 (66–106)	81 (63–106)
eGFR, mL·min^{-1}·1.73m^2	73 (58–90)	80 (63–95)	78 (62–93)	77 (61–94)	79 (63–97)	83 (69–97)
≥90	212 (26.3%)	373 (32.6%)	524 (30.7%)	421 (31.7%)	156 (35.4%)	507 (37.4%)
60–89	374 (46.3%)	547 (47.9%)	829 (48.6%)	606 (45.6%)	205 (46.5%)	687 (50.6%)
30–59	221 (27.4%)	223 (19.5%)	353 (20.7%)	301 (22.6%)	80 (18.1%)	163 (12.0%)
<30	0	0	0	1 (0.1%)	0	0
Cardiovascular medications						
Aspirin	521 (64.5%)	712 (62.0%)	1010 (58.9%)	848 (63.6%)	300 (67.9%)	865 (63.6%)
Thienopyridines	160 (19.8%)	185 (16.1%)	231 (13.5%)	218 (16.3%)	57 (12.9%)	197 (14.5%)
Any antiplatelets	598 (74.1%)	804 (70.2%)	1156 (67.4%)	983 (73.7%)	333 (75.3%)	990 (72.9%)
ACEI or ARB	603 (74.6%)	869 (75.7%)	1283 (74.9%)	1043 (78.2%)	336 (76.0%)	1092 (80.4%)
Beta blockers	464 (57.4%)	592 (51.6%)	865 (50.5%)	738 (55.3%)	236 (53.4%)	746 (54.9%)
Calcium channel blockers	250 (30.9%)	338 (29.4%)	472 (27.5%)	404 (30.3%)	123 (27.8%)	428 (31.5%)
Any antihypertensive	721 (89.2%)	1006 (87.6%)	1507 (87.9%)	1209 (90.6%)	393 (88.9%)	1242 (91.4%)
Statin	582 (72.0%)	832 (72.5%)	1219 (71.1%)	1003 (75.2%)	336 (76.0%)	1063 (78.2%)
Any lipid lowering medication	610 (75.5%)	864 (75.3%)	1302 (76.0%)	1045 (78.3%)	355 (80.3%)	1110 (81.7%)

Data are shown as n (%) for categorical variables and median (interquartile range) for continuous variables.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; bpm, beats per minute; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; and SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

DISCUSSION

The once-weekly exenatide effect sizes observed in EXSCEL for the MACE primary outcome and ACM were effectively unchanged when exploratory analyses were performed using right censoring to preclude any impact of open-label drop-in glucose-lowering medications. Similarly, no meaningful changes were observed after applying literature-derived effect sizes to post open-label drop-in medication event rates. Once-weekly exenatide effect sizes, however, were increased when inverse probability weighting was applied, with the MACE HR decreasing from 0.91 to 0.85 and achieving statistical significance. The already nominally significant

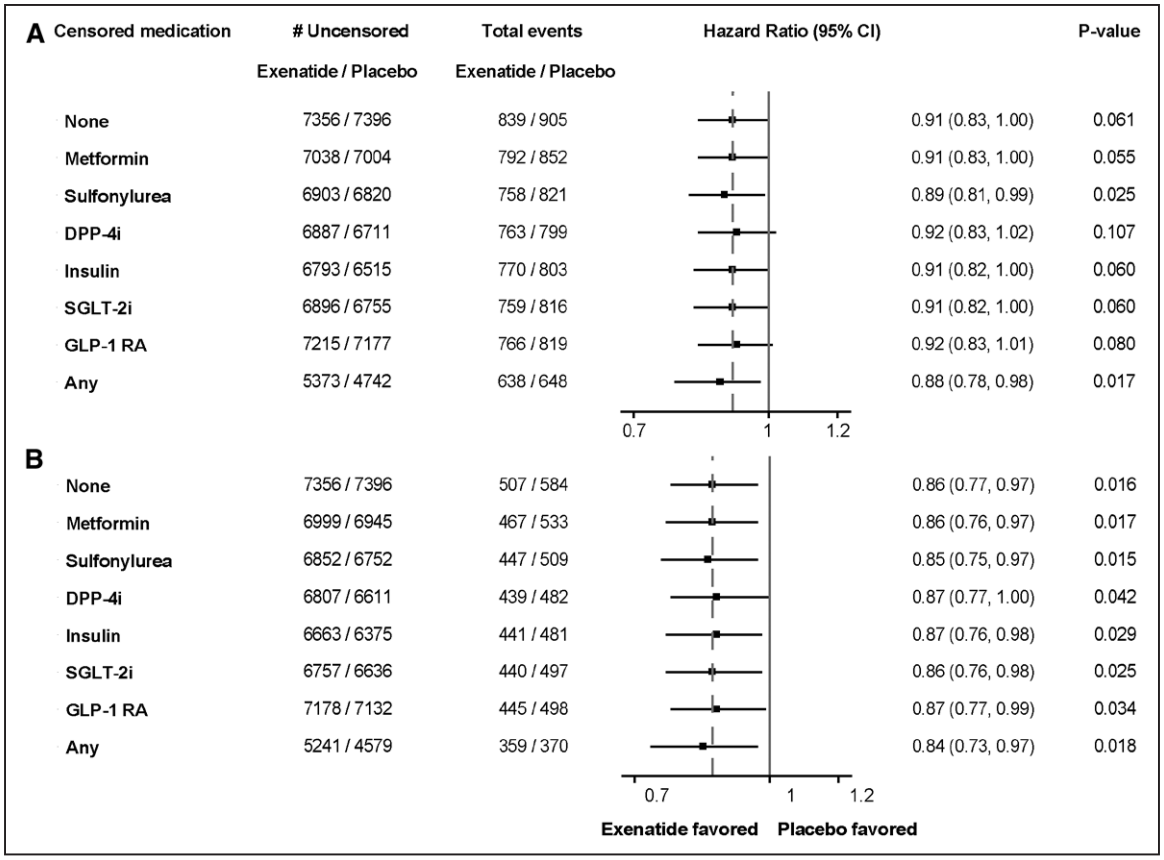

Figure 2. Right censored analyses.
Shown are analyses for (**A**) major adverse cardiovascular event and (**B**) all-cause mortality. "# Uncensored" indicates the number who were not censored because they had drop-in of the given medication before the event or end of follow-up for event. The number uncensored includes patients who were censored before event or end of follow-up because they had shorter follow-up for drop-in than for event. DPP-4i indicates dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; and SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

ACM HR decreased from 0.86 to 0.81. *P* values for the MACE HR were also reduced after right censoring for sulfonylurea or the use of any drop-in medication. The unbalanced use of open-label drop-in glucose-lowering medications during EXCSEL was an inevitable consequence of the protocol requirement to aim for glycemic equipoise between treatment groups. These analyses suggest that the CV effects of some agents might have had a discernible impact on the MACE and ACM findings in EXSCEL.

Differential use of background diabetes mellitus medication, influenced by age, duration and control of diabetes mellitus, renal function, and other demographic and clinical factors, is a common characteristic of clinical trials. One of the key values of randomization in large-scale trials is that these baseline characteristics will be distributed evenly between treatment groups, thereby avoiding bias for measured outcomes. However, unequal drop-in of new medications during a trial is a nonrandomized event that requires careful consideration. The reasons for drop-in are difficult to discern and are likely multifactorial, ranging from the clinical need to intensify treatment in a progressive disease to issues of cost, concomitant illness, tolerability, or patient-led and physician-led preferences. Unequal drop-in of cardioprotective medications during follow-up has the potential to reduce the number of CV events overall, and to a greater extent in the group(s) using them most frequently. Disproportionate reduction of events could reduce the effect size attributable to study medication in a clinical trial or, in a worst-case scenario, nullify a real difference. For the relatively few EXSCEL participants experiencing drop-in of glucose-lowering medications known to be cardioprotective, the likely effects would appear to be too small to have impacted on the trial findings, but for future CV outcome trials, significant background use of both medication classes is likely.

The 3 statistical and modelling approaches used here each provide different approaches to estimating the potential impact of unequal between-group use of potentially cardioprotective medications during the follow-up period of a randomized, controlled trial. The censoring analysis, arguably the most conservative approach, simply discards data from patients after the time of drop-in. While this undeniably removes any influence attributable to the drop-in medication itself, it also reduces the number of participants contributing events,

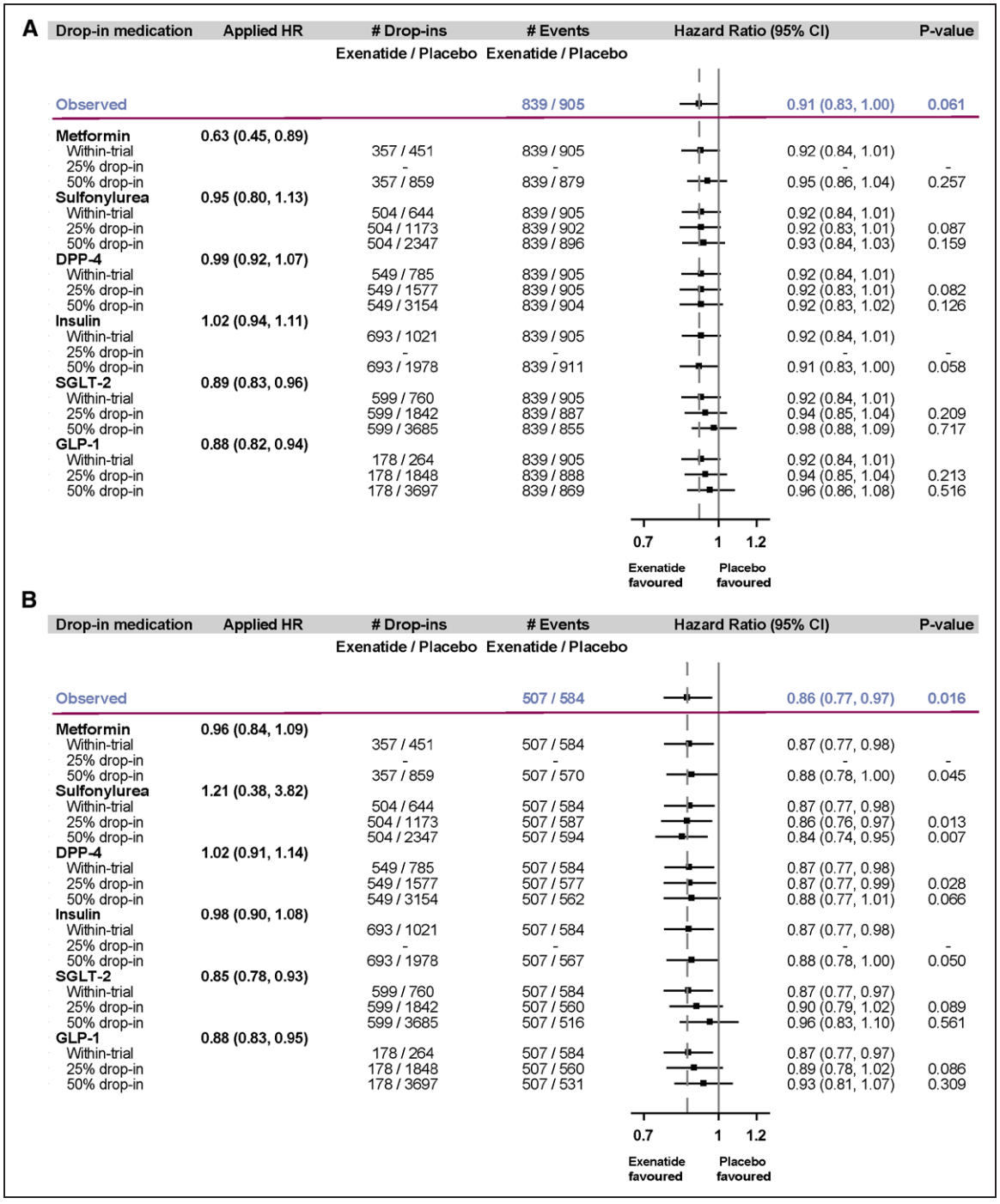

Figure 3. Evidence-based effect size adjustment analyses.

Shown are analyses for (**A**) major adverse cardiovascular event and (**B**) all-cause mortality. These outcomes were adjusted for risk reductions attributable to drop-in medication, as derived from published placebo-controlled studies. The first row for each medication shows the number of patients in each treatment group who began the medication during the trial and the number experiencing events, thereby estimating the within-trial impact of drop-in medications. The second and third rows for each medication class show the simulated effect if drop-ins had been more pervasive (25% or 50% of placebo-treated patients) than was seen in EXSCEL (Exenatide Study of Cardiovascular Event Lowering). For both metformin and insulin, drop-in within EXSCEL was seen in 25% of participants and these results have not been re-estimated in the sensitivity analysis. DPP-4 indicates dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; and SGLT-2, sodium-glucose cotransporter-2 inhibitor.

reducing the power to detect treatment-related differences. Right-censoring may also introduce bias because it is a nonrandom event that may result from multiple or multifactorial causes that likely differ in the exenatide group (eg, inability to tolerate exenatide or inadequate durability of glycemic impact of exenatide) compared with the placebo group (routine intensification of therapy). It is reassuring, however, that no meaningful impact is seen on the EXSCEL findings when using this robust methodology.

Inverse probability weighting analysis gives a complementary view in which event data for patients are not calculated according to medication class, but according to the overall likelihood of starting any new medication. Data from those starting new medications are still lost after censoring, but observations remaining in the analysis are not treated equally. Participants with a higher probability of starting a new medication—in this case, patients with longer duration of diabetes mellitus and higher HbA1c—contribute less toward the assessment of outcomes than those less likely to experience drop-in. Inverse probability weighting is used to reduce bias by indication introduced in postrandomization medication selection, but it should be noted that some factors predicting medication drop-in may have more to do with regional differences in health care systems and availability of medications than with individual patient characteristics.

The application of externally derived effect sizes for each medication class takes an alternative approach to quantifying the impact of concomitant medication drop-in. Here, the number of within-trial events accrued for EXSCEL patients before the commencement of medication drop-in was added to the number of events accrued after drop-in, with the latter adjusted both by an HR derived from the literature to approximate the impact of the medication and by a maximum estimate of potential exposure time to the drop-in medication. These amended event numbers were then used to calculate revised HRs and confidence intervals to account for the likely evidence-based changes in risk attributable to drop-in medication for the duration that they were taken. While this approach was relatively straightforward for newer diabetes mellitus medications which all have had multiple well-conducted CV outcome trials informing robust meta-analyses, the exercise was more difficult for older medications for which little CV outcomes data exist to derive a credible attributable "class effect." The meta-analysis driven adjustment factors available likely overestimate the population impact on MACE for medication classes studied, a well-described phenomenon in clinical research,[22] and particularly for trials using composite outcomes.[23] However, estimates for ACM tend to be more robust at the population level because there are fewer confounders related to the use of surrogate outcomes, event definitions, or event acquisition. Finally, this approach attributed the value of a medication class effect, potentially ignoring situations in which one drug in a class has a markedly different degree of benefit. The analyses performed here again provide reassurance that, for EXSCEL, the within-trial impact of drop-in medications, particularly for GLP-1 RAs and SGLT-2is, was small.

Simulating substantially greater imbalances of open-label drop-in glucose-lowering medications that are cardioprotective shows that these agents could have the ability to blunt signal detection for some endpoints. Such impacts need to be carefully considered when designing and conducting future CV outcome trials in T2D, possibly informed by the methodologies used in this study. Given the proven CV benefit for some glucose-lowering agents, their use will become widespread, and it would be unethical to prohibit their use during clinical trials, particularly those enrolling patients at high CV risk.

There are other limitations to consider in interpreting these data. EXSCEL was neither designed nor powered to look for treatment differences according to concomitant medication use. Power was further limited by the small sample sizes within each medication subgroup. Likewise, medication exposure times, although comparable between medication classes (ranging from 1.0–2.1 years), are short when compared with potential lifetime exposures more typical of routine clinical practice for patients with T2D, making predictions for longer term outcomes difficult. It is possible that exposure times for new medications have been overestimated if the assumption that newly initiated medications continued throughout follow-up is untrue, a limitation that would primarily affect the evidence-based modeling. In clinical practice, switching and stopping new medications is common as a result of adverse events, inadequate response, nonadherence, and other changes in circumstances. We are also unable to comment on the potential impact of combination therapies because these analyses have considered each medication class independently.

The advent of drugs providing simultaneous glucose lowering and cardioprotection is a major therapeutic advance in diabetes mellitus treatment. Future CV outcome trials will require some mechanism to account for the impact of nonrandomized drop-in of these medications during trial follow-up. Although we have demonstrated that observed MACE and ACM effect sizes for EXSCEL were robust to multiple methods of adjusting for the greater drop-in of diabetes mellitus medications in the placebo arm, drop-in for some medications induced small changes in event numbers that altered the assessment of statistical significance for MACE. In EXSCEL, the proportion of patients experiencing drop-in of potentially cardioprotective medications (eg, SGLT-2is and GLP-1 RAs) was small; however, on a larger scale as is simulated here, the influence of these medications could blunt signal detection and alter future study conclusions. Because we believe it to be unethical to withhold proven CV risk-lowering treatments in trials enrolling participants with T2D with clinical atherosclerotic CV disease or heart failure, prohibiting the use of these medications in future CV outcome trials is not the answer. Careful consideration in future trials should factor in the unbalanced drop-in of these agents for the

placebo group, their growing use in routine clinical practice, a likely steady increase in numbers of participants experiencing drop-in during trial follow-up, and the potential cardioprotective impact attributable to each medication class.

ARTICLE INFORMATION

Received August 19, 2019; accepted January 31, 2020.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.119.043353.

Correspondence

Rury R. Holman, MBChB, Diabetes Trials Unit, OCDEM, Churchill Hospital, Oxford OX3 7LJ, United Kingdom. Email rury.holman@dtu.ox.ac.uk

Affiliations

Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, UK (M.A.B., R.A.P., R.R.H.). Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (S.R.S., Y.L., R.J.M., A.F.H.). Department of Medicine, University of North Carolina School of Medicine, Chapel Hill (J.B.B.). AstraZeneca Research and Development, Gaithersburg, MD (J.C., S.M.G., N.I., P.Ö.). Department of Medicine, Rudolfstiftung Hospital-Vienna, Austria (G.S.). University Hospital Arnau de Vilanova, Obesity, Diabetes and Metabolism Research Group (IRBLleida), Lleida, Spain (A.L.). Dr Bethel is now at Eli Lilly and Co., Indianapolis, IN. Dr Patel is now with the National Health Service, UK.

Sources of Funding

EXSCEL was sponsored and funded by Amylin Pharmaceuticals Inc. (San Diego, CA), a wholly owned subsidiary of AstraZeneca (Gaithersburg, MD).

Disclosures

Dr Bethel reports research support from Merck and Astra Zeneca; participating in advisory boards for Boehringer Ingelheim and NovoNordisk; receiving honoraria, personal fees, and other support from Merck, Novo Nordisk, Astra Zeneca, and Sanofi; receiving nonfinancial research support from Bayer and Merck Serono, and has been an employee of Eli Lilly from May 2018. Dr Buse reports contracted consulting fees and associated travel support paid to the University of North Carolina by Adocia, AstraZeneca, Dance Biopharm, Dexcom, Eli Lilly, Fractyl, GI Dynamics, Intarcia Therapeutics, Lexicon, MannKind, Metavention, NovaTarg, Novo Nordisk, Orexigen, PhaseBio, Sanofi, Senseonics, vTv Therapeutics, and Zafgen; he reports grant support from AstraZeneca, Eli Lilly, Intarcia Therapeutics, Johnson & Johnson, Lexicon, Medtronic, Novo Nordisk, Sanofi, Theracos, Tolerion, and vTv Therapeutics; he is a consultant to Cirius Therapeutics Inc, CSL Behring, Mellitus Health, Neurimmune AG, Pendulum Therapeutics, and Stability Health; he holds stock/options in Mellitus Health, Pendulum Therapeutics, PhaseBio, and Stability Health; and he is supported by grants from the National Institutes of Health (UL1TR002489, U01DK098246, UC4DK108612, U54DK118612), PCORI, and ADA. Drs Gustavson, Iqbal, and Öhman and Jasmine Choi are employees of AstraZeneca. Dr Lokhnygina reports grants from Merck, Janssen Research & Development, AstraZeneca, GlaxoSmithKline, and Bayer HealthCare AG. Dr Mentz reports grants from AstraZeneca and GlaxoSmithKline and personal fees from Boehringer-Ingelheim. Dr Schernthaner reports honoraria from Boehringer Ingelheim, Eli Lilly, Mundipharma, Servier and Takeda for adboard meetings and from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Mundipharma, and Takeda for lectures. Dr Lecube reports research funding from AstraZeneca, Gen inCode, Menarini SA and NovoNordisk, and consulting fees from AstraZeneca and NovoNordisk. Dr Hernandez reports research funding from AstraZeneca, GlaxoSmithKline, Merck, Novartis, and consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Merck, Novartis, and Pfizer. Dr Holman reports research support from AstraZeneca, grants and personal fees from Bayer, Boehringer Ingelheim and Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc., personal fees from Novartis, Amgen, and Servier, and financial support from Elcelyx, GlaxoSmithKline, Janssen, and Takeda. The other authors report no conflicts.

Supplemental Materials

Data Supplement Tables I–VI

REFERENCES

1. Gerstein HC, McMurray J, Holman RR. Real-world studies no substitute for RCTs in establishing efficacy. *Lancet.* 2019;393:210–211. doi: 10.1016/S0140-6736(18)32840-X
2. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007;356:2457–2471. doi: 10.1056/NEJMoa072761
3. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, Pfarr E, Keller A, Mattheus M, Baanstra D, et al; CAROLINA Investigators. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *JAMA*. 2019 Sep 19. doi: 10.1001/jama.2019.13772. [Epub ahead of print]
4. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375:311–322. doi: 10.1056/NEJMoa1603827
5. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, et al; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2019;381:841–851. doi: 10.1056/NEJMoa1901118
6. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375:1834–1844. doi: 10.1056/NEJMoa1607141
7. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC, et al; Harmony Outcomes committees and investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet.* 2018;392:1519–1529. doi: 10.1016/S0140-6736(18)32261-X
8. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Rydén L, et al; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet.* 2019;394:121–130. doi: 10.1016/S0140-6736(19)31149-3
9. Zinman B, Inzucchi SE, Lachin JM, Wanner C, Fitchett D, Kohler S, Mattheus M, Woerle HJ, Broedl UC, Johansen OE, et al; EMPA-REG OUTCOME Investigators (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients). Empagliflozin and cerebrovascular events in patients with type 2 diabetes mellitus at high cardiovascular risk. *Stroke.* 2017;48:1218–1225. doi: 10.1161/STROKEAHA.116.015756
10. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377:644–657. doi: 10.1056/NEJMoa1611925
11. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, et al; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2017;377:1228–1239. doi: 10.1056/NEJMoa1612917
12. Mentz RJ, Bethel MA, Gustavson S, Thompson VP, Pagidipati NJ, Buse JB, Chan JC, Iqbal N, Maggioni AP, Marso SP, et al. Baseline characteristics of patients enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL). *Am Heart J.* 2017;187:1–9. doi: 10.1016/j.ahj.2017.02.005
13. Holman RR, Bethel MA, George J, Sourij H, Doran Z, Keenan J, Khurmi NS, Mentz RJ, Oulhaj A, Buse JB, et al. Rationale and design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial. *Am Heart J.* 2016;174:103–110. doi: 10.1016/j.ahj.2015.12.009
14. Poyner L. *Type 2 Diabetes, 2018-2027. CVrg Market Strategies Report*. Palo Alto, CA: CardioVascular Resource Group, 2018.
15. Zhang M, Tsiatis AA, Davidian M, Pieper KS, Mahaffey KW. Inference on treatment effects from a randomized clinical trial in the presence of premature treatment discontinuation: the SYNERGY trial. *Biostatistics.* 2011;12:258–269. doi: 10.1093/biostatistics/kxq054
16. Bosch J, Gerstein HC, Dagenais GR, Díaz R, Dyal L, Jung H, Maggiono AP, Probstfield J, Ramachandran A, Riddle MC, et al; ORIGIN Trial Investigators.

n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med.* 2012;367:309–318. doi: 10.1056/NEJMoa1203859
17. Liu J, Li L, Deng K, Xu C, Busse JW, Vandvik PO, Li S, Guyatt GH, Sun X. Incretin based treatments and mortality in patients with type 2 diabetes: systematic review and meta-analysis. *BMJ.* 2017;357:j2499. doi: 10.1136/bmj.j2499
18. Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, Pagidipati NJ, Chan JC, Gustavson SM, Iqbal N, et al; EXSCEL Study Group. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol.* 2018;6:105–113. doi: 10.1016/S2213-8587(17)30412-6
19. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet.* 2019;393:31–39. doi: 10.1016/S0140-6736(18)32590-X
20. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia.* 2017;60:1620–1629. doi: 10.1007/s00125-017-4337-9
21. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab.* 2013;15:938–953. doi: 10.1111/dom.12116
22. Chanfreau-Coffinier C, Teutsch SM, Fielding JE. *Assessing the Population Impact of Published Intervention Studies*. Discussion Paper, Institute of Medicine, Washington, DC, 2015. Available at https://nam.edu/perspectives-2015-assessing-the-population-impact-of-published-intervention-studies/.
23. Heneghan C, Goldacre B, Mahtani KR. Why clinical trial outcomes fail to translate into benefits for patients. *Trials.* 2017;18:122. doi: 10.1186/s13063-017-1870-2