Comment on Generalizability of GLP-1 RA CVOTs in US T2D Population

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I read with great interest the article published in an April 2018 supplement titled "Generalizability of Glucagon-Like Peptide-1 Receptor Agonist Cardiovascular Outcome Trials Enrollment Criteria to the US Type 2 Diabetes Population" by Wittbrodt et al.[1] Although the authors made an important contribution to the literature by examining the generalizability of cardiovascular (CV) outcome trials to the population of US adults with type 2 diabetes (T2D), I believe that their analysis contains an important omission. Specifically, the authors state that the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial contains no eligibility criteria regarding CV events.[1] However, although patients with any level of CV risk may be enrolled, the original protocol clearly states that "recruitment will be constrained such that 40% will not have had a prior CV event and 60% will have had a prior CV event..."[2] This requirement was subsequently made more restrictive in the protocol amendment, which modified the inclusion and exclusion criteria such that "...approximately 30% will not have had a prior CV event and 70% will have had a prior event."[2] An examination of the characteristics of patients who actually enrolled in the trial revealed that this more restrictive requirement was used, with 73% of patients enrolled in EXSCEL having a prior CV event.[3] Although the EXSCEL trial did include patients both with and without prior CV events, it is not true that the study had no eligibility requirement regarding CV events.

An examination of the 2013-2014 National Health and Nutrition Examination Survey (NHANES) data[4] revealed that this omission has a significant impact on the findings presented in the authors' research. Specifically, a replication of the Wittbrodt et al[1] examination of the EXSCEL trial revealed that, ignoring the CV enrollment criteria, 50.5% of patients with T2D would be eligible for inclusion in the EXSCEL study (**Table**[1,5,6]). This number is similar to the finding of the authors, using NHANES data from 2009-2010 and 2011-2012, which found that 47.2% of adults with T2D would be eligible for EXSCEL. However, within this 50.5% sample of individuals who fit the eligibility requirements examined by Wittbrodt et al, just 10.7% had a prior CV event (Table[1,5,6]). When also incorporating the recruitment criteria that 60% of patients should have had a prior

TAKEAWAY POINTS

Cardiovascular outcome trials (CVOTs) that examine glucagon-like peptide-1 receptor agonists (GLP-1 RAs) often include patients at high risk of cardiovascular disease. Subsequently, the results of these trials may not be generalizable to the overall type 2 diabetes (T2D) population. Recent research has compared the generalizability of several CVOTs of GLP-1 RAs.

- Previous research has overstated the generalizability of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial results to the US T2D population by ignoring the inclusion and exclusion criteria regarding the percentage of patients with prior cardiovascular events permitted into the study.
- The analysis herein that corrects for this bias will provide clinicians with more accurate information regarding the generalizability of the EXSCEL trial to their patient population.

TABLE. NHANES-Weighted Variables Analyzed for Adults With T2D Identified From NHANES Data (for 2013-2014)[1,5,6]

Descriptive Statistics (weighted variables)	
Age in years, mean (SD)	59.3 (13.6)
Sex (%)	
Male	52.2
Female	47.8
Race/ethnicity (%)	
Non-Hispanic white	62.2
Non-Hispanic black	14.2
Mexican American	10.0
Other Hispanic	5.0
Other race (including multiracial)	8.6
CKD[a] (%)	
Evidence of CKD	7.5
No CKD	92.5
CVD[b] (%)	
Evidence of CVD	23.5
No CVD	76.5

(continued)

CV event, the 50.5% of potentially eligible patients is reduced to 17.9%. If, alternatively, one examines the amended protocol requirement that 70% of patients had a prior CV event, the proportion of eligible patients would be reduced to 15.3%. These results suggest that by omitting the CV inclusion criteria of the EXSCEL study, the authors have included an oversampling of patients with no prior CV event relative to the stated criteria of the EXSCEL trial. As such, the analysis substantially overstates the generalizability of EXSCEL to the overall US T2D population. ■

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TABLE. *(Continued)* NHANES-Weighted Variables Analyzed for Adults With T2D Identified From NHANES Data (for 2013-2014)[1,5,6]

Percentage Fitting EXSCEL Eligibility Criteria, Excluding CVD Criteria	
A1C criteria[c]	56.2
Rx criteria[d]	98.3
Renal function criteria[e]	92.5
A1C, Rx, and renal criteria	50.6
Adding CVD Criteria to A1C, Rx, and Renal Criteria	
Percentage fitting A1C, Rx, and renal criteria who also have CVD[f]	10.7

A1C indicates glycated hemoglobin; CKD, chronic kidney disease; CVD, cardiovascular disease; EGFR, estimated glomerular filtration rate; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; NHANES, National Health and Nutrition Examination Survey; PLATO, Platelet Inhibition and Patient Outcomes; Rx, prescription medication; T2D, type 2 diabetes.

[a]CKD was measured by (1) responding yes to "Have you ever been told you had weak/failing kidneys?", (2) receipt of dialysis in past 12 months, or (3) EGFR score (calculated using Modification of Diet in Renal Disease formula[5]) less than 30 mL/min/1.73^2.

[b]Evidence of CVD measured by responding yes to "Have you ever been told you had congestive heart failure, coronary heart disease, angina/angina pectoris, heart attack, or stroke?"

[c]A1C greater than or equal to 6.5% and less than or equal to 10%.

[d]Taking up to 3 oral antidiabetic medications or insulin (alone or in combination with up to 2 oral antidiabetic medications).

[e]Patients identified as having CKD (as explained in note **a** above) were excluded.

[f]Consistent with Wittbrodt et al,[1] revascularization was proxied by positive response to "Have you ever been told you had angina/angina pectoris or heart attack?" and weighting these responses by estimates of revascularization in PLATO T2D study (71%) and then multiplied by 0.96, because 96% of PLATO participants had T2D.[6]

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Authors' Reply to "Comment on Generalizability of GLP-1 RA CVOTs in US T2D Population"

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We acknowledge the letter to the editor[1] regarding our published analysis of the enrollment criteria for the 7 glucagon-like peptide-1 receptor agonist (GLP-1 RA) cardiovascular outcomes trials (CVOTs) and their generalizability to a well-established, representative, real-world subsample of US individuals (National Health and Nutrition Examination Survey [NHANES]) with type 2 diabetes (T2D).[2] The author specifically addresses our analysis of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial criteria and correctly states that the study protocol was amended partway through the trial to enroll approximately 70% of patients with a prior cardiovascular (CV) event at baseline. CV events were defined as a "history of major clinical manifestation of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease."[3] Coronary artery disease was defined as a prior myocardial infarction, coronary

revascularization, or angiographic evidence of 50% or greater stenosis of a major coronary vessel. Ischemic cerebrovascular disease required either history of ischemic stroke or evidence of carotid artery stenosis. Baseline characteristics from EXSCEL reveal that 73% of participants had a prior CV event at randomization. Ultimately, until the 70% threshold with established cardiovascular disease (CVD) was reached, the protocol states that "patients with any level of CV risk and meeting all other inclusion criteria may be enrolled" into EXSCEL. The broad CV risk eligibility criteria for EXSCEL were reported in a recent meta-analysis of GLP-1 RA CVOTs,[4] and EXSCEL also enrolled the smallest proportion of patients with chronic kidney disease (CKD) at baseline.[5] Of note, EXSCEL enrolled adults 18 years and older and 60% were younger than 65 years, whereas the other CVOTs had a minimum age of 30 (ELIXA), 40 (FREEDOM, HARMONY), or 50 (LEADER, REWIND, SUSTAIN-6) years and all with either established CVD or CKD, or at least 1 or 2 CV risk factors depending on age. The mean age of 63 years in EXSCEL was the lowest of all CVOTs reported to date, and the mean glycated hemoglobin at enrollment was 8.0%, lower than in all CVOTs other than REWIND. The pragmatic design of EXSCEL was more reflective of real-world practice compared with the other CVOTs.[6] These important differences, when evaluated in totality, served to illustrate the broad clinical profile of the EXSCEL trial population extending beyond those of the other CVOTs. For the individual patients enrolled in each trial, the prespecified eligibility criteria for all CVOTs were used for the NHANES analysis and remain an accurate reflection of the intended population. We did not have access to the study population baseline characteristics for all CVOTs at the time of the analysis and, therefore, did not have the option of pursuing that more robust approach. Also, confining the analysis to the eligible trial populations allowed the results to be interpreted in terms of what the study objectives set out to achieve—namely, to identify the intended population most suited to benefit from the intervention. We acknowledge that assessment of the trial population baseline characteristics is an important step in evaluating CVOTs. However, combining analyses of eligibility criteria and trial population characteristics, as the letter author has done, only serves to confuse the reader and cloud the interpretation of the results in terms of their applicability to the general T2D population. ■

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