Effect of Once-Weekly Exenatide on Clinical Outcomes According to Baseline Risk in Patients With Type 2 Diabetes Mellitus: Insights From the EXSCEL Trial

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Background—In the EXSCEL (Exenatide Study of Cardiovascular Event Lowering), exenatide once-weekly resulted in a nonsignificant reduction in major adverse cardiovascular events (MACEs) and a nominal 14% reduction in all-cause mortality in 14 752 patients with type 2 diabetes mellitus (T2DM) with and without cardiovascular disease. Whether patients at increased risk for events experienced a comparatively greater treatment benefit with exenatide is unknown.

Methods and Results—In the EXSCEL population, we created risk scores for MACEs and all-cause mortality using step-wise selection of baseline characteristics. A risk score was calculated for each patient, and a time-to-event model for each end point was developed including the risk score, treatment assignment, and risk-treatment interaction. Interaction P values evaluating for a differential treatment effect by baseline risk were reported. Over a median follow-up of 3.2 years (interquartile range, 2.2, 4.4), 1091 (7.4%) patients died and 1744 (11.8%) experienced a MACE. Independent predictors of MACEs and all-cause mortality included age, sex, comorbidities (eg, previous cardiovascular event), body mass index, blood pressure, hemoglobin A1c, and estimated glomerular filtration rate. The all-cause mortality and MACE risk models had modest discrimination with optimism-corrected c-indices of 0.73 and 0.71, respectively. No interaction was observed between treatment effect and risk profile for either end point (both interactions, P>0.1).

Conclusions—Baseline characteristics (eg, age, previous cardiovascular events) and routine laboratory values (eg, hemoglobin A1c, estimated glomerular filtration rate) provided modest prognostic value for mortality and MACEs in a broad population of patients with type 2 diabetes mellitus. Exenatide’s effects on mortality and MACEs were consistent across the spectrum of baseline risk.

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The EXSCEL (Exenatide Study of Cardiovascular Event Lowering) was an international pragmatic trial that included a broad population of patients with type 2 diabetes mellitus (T2DM) both with and without known cardiovascular disease.1–3 In EXSCEL, once-weekly administration of the glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide,
Clinical Perspective

What Is New?

• We found that the effect of exenatide once-weekly on major adverse cardiac events and all-cause mortality as compared with placebo was consistent across the spectrum of baseline risk in a large, international trial of patients with type 2 diabetes mellitus.

What Are the Clinical Implications?

• Exenatide once-weekly represents a safe and effective choice for patients with type 2 diabetes mellitus across the spectrum of baseline risk.

resulted in a nonsignificant 9% reduction in major adverse cardiovascular events (MACEs; P value for superiority=0.061) and a nominal 14% reduction in all-cause mortality (ACM; P=0.016) versus placebo. Whereas these effects were consistent across prespecified subgroups in univariate analyses (including previous cardiovascular event status), it is unknown whether relative magnitude of treatment effect with exenatide depends on a patient’s overall baseline risk profile. Such data could help clinicians better understand how to optimize use of this therapy to improve patients’ clinical outcomes. We hypothesized that patients at increased risk for ACM and MACE would experience a comparatively greater relative treatment benefit with exenatide than those at lower risk. We were specifically interested in exploring whether the relative treatment benefit would be greater in the higher-risk group, not merely an increased absolute effect size in a group with increased disease severity and higher event rates. This hypothesis was based on potential mechanisms of benefits from GLP-1 receptor agonists related to anti-inflammatory and cardioprotective effects (eg, weight loss, blood pressure reduction, and lipid lowering), which could be more instrumental in those at greater risk for events, and that for a given relative risk reduction the highest absolute risk reduction is usually observed in those at highest baseline risk. Thus, we developed risk scores for clinical end points in EXSCEL based on baseline characteristics and evaluated whether there was a differential treatment effect with exenatide based on a patient’s baseline risk.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. EXSCEL enrolled 14 752 patients at 687 sites in 35 countries between June 2010 and September 2015. Trial design, baseline characteristics, and primary results have been published. In brief, EXSCEL investigated the effects of the once-weekly GLP-1 receptor agonist, exenatide (2-mg injection), on cardiovascular-related outcomes in T2DM. The study included patients with a hemoglobin A1c (HbA1c) of 6.5% to 10% at any level of cardiovascular risk and targeted ≈70% with a previous cardiovascular event, including previous coronary, cerebrovascular, or peripheral vascular events or stenosis. Patients aged <18 years, with type 1 diabetes mellitus, ≥2 episodes of severe hypoglycemia in the previous 12 months, an estimated glomerular filtration rate <30 mL/min/1.73 m², or previous pancreatitis were excluded. Median (interquartile range) age of the population was 62 years (56, 68), 38% were female, and median baseline HbA1c was 8.0% (7.3, 8.9). Median follow-up was 3.2 years (2.2, 4.4), with a median duration of drug treatment exposure of 2.4 years (1.4, 3.8) in the exenatide group and 2.3 years (1.2, 3.6) in the placebo group. The primary composite end point of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke occurred in 11.4% (839 of 7356) of the exenatide group and 12.2% (905/7396) of the placebo group (hazard ratio, 0.91; 95% confidence interval, 0.83–1.00). Exenatide was noninferior to placebo for safety (P<0.001 for noninferiority), but was not superior to placebo with respect to efficacy (P=0.061 for superiority). The secondary outcome of ACM occurred in 6.9% (507 of 7356) of exenatide patients and 7.9% (584 of 7396) of placebo patients (hazard ratio, 0.86; 95% confidence interval, 0.77–0.97; nominal P=0.016).

The study protocol was approved by ethics committees at participating trial sites. All patients provided written informed consent. A blinded, independent clinical events classification committee adjudicated all the components of the primary composite outcome and secondary outcome, including mortality. These events are defined in the Clinical Event Definitions section in Appendix S1 of the primary trial publication.

For the present analysis, we created risk scores based on baseline characteristics for the end points of ACM and MACE and evaluated whether magnitude of the exenatide treatment effect depended on a patient’s baseline risk profile.

Statistical Analysis

Baseline characteristics were summarized by counts and percentages for categorical variables and by medians with interquartile ranges for continuous variables based on whether patients died or experienced a MACE event during follow-up. For both the primary end point (MACE) and the secondary end point (ACM), predictive models were developed using Cox proportional hazards models with a prespecified set of 26 candidate variables for possible model inclusion. The candidate variables are those listed in Table 1.
### Table 1. Baseline Characteristics by Experience of ACM

| Characteristic               | Died (N=1091) | Alive (N=13 661) |
|-----------------------------|---------------|------------------|
| Age, y                      | 67.0 (61.0, 73.0) | 62.0 (56.0, 68.0) |
| Women                       | 321/1091 (29.4%) | 5282/13 661 (38.7%) |
| Hispanic or Latino          | 176/1091 (16.1%) | 2850/13 659 (20.9%) |
| Race                        |               |                  |
| American Indian or Alaska Native | 4/1091 (0.4%) | 69/13 656 (0.5%) |
| Asian                       | 69/1091 (6.3%) | 1383/13 656 (10.1%) |
| Black                       | 67/1091 (6.1%) | 811/13 656 (5.9%) |
| Native Hawaiian or Pacific Islander | 3/1091 (0.3%) | 32/13 656 (0.2%) |
| Other                       | 80/1091 (7.3%) | 1054/13 656 (7.7%) |
| White                       | 880/1091 (79.6%) | 10 307/13 656 (75.5%) |
| Region                      |               |                  |
| Asia Pacific                | 68/1091 (6.2%) | 1461/13 661 (10.7%) |
| Europe                      | 510/1091 (46.7%) | 6278/13 661 (46.0%) |
| Latin America               | 157/1091 (14.4%) | 2570/13 661 (18.8%) |
| North America               | 356/1091 (32.6%) | 3352/13 661 (24.5%) |
| Diabetes mellitus duration, y | 13.0 (8.0, 20.0) | 11.0 (7.0, 17.0) |
| Smoking status              |               |                  |
| Current                     | 153/1089 (14.0%) | 1568/13 656 (11.5%) |
| Former                      | 479/1089 (44.0%) | 5312/13 656 (38.9%) |
| Never                       | 457/1089 (42.0%) | 6776/13 656 (49.6%) |
| Alcohol consumption         | 348/1086 (32.0%) | 4473/13 651 (32.8%) |
| Previous cardiovascular event* | 927/1091 (85.0%) | 9855/13 661 (72.1%) |
| Previous MI                 | 490/1091 (45.6%) | 4181/13 661 (30.6%) |
| Previous revascularization  | 531/1091 (48.7%) | 5375/13 661 (39.3%) |
| Cerebrovascular disease     | 285/1090 (26.1%) | 2429/13 659 (17.8%) |
| Hypertension                | 878/1091 (80.5%) | 10 773/13 660 (78.9%) |
| Hyperlipidemia/dyslipidemia | 995/1091 (91.2%) | 11 382/13 660 (83.3%) |
| Atrial fibrillation/atral flutter | 157/1091 (14.4%) | 842/13 660 (6.2%) |
| Unstable angina/recurrent ischemia | 84/1091 (7.7%) | 844/13 660 (6.2%) |
| NYHA class                  |               |                  |
| 1                           | 85/1090 (7.8%) | 653/13 659 (4.8%) |
| 2                           | 189/1090 (17.3%) | 1144/13 659 (8.4%) |
| 3                           | 71/1090 (6.5%) | 232/13 659 (1.7%) |
| 4                           | 71/1090 (0.6%) | 6/13 659 (0.0%) |
| No heart failure            | 738/1090 (67.7%) | 11 624/13 659 (85.1%) |
| Chronic liver disease       | 54/1091 (4.9%) | 544/13 660 (4.0%) |
| Chronic respiratory disease | 150/1091 (13.7%) | 1059/13 660 (7.8%) |

Data are presented as median (interquartile range) or n/N (%). ACM indicates all-cause mortality; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; NYHA, New York Heart Association; SBP, systolic blood pressure.

*Previous cardiovascular events were defined as a history of major clinical manifestation of coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease.

The candidate variable list represents a broad range of baseline characteristics, including demographics, region of enrollment, medical history, physical examination parameters, and laboratory values, and was developed based on previous research and clinical relevance. The candidate variables were restricted to intrinsic patient-level characteristics (eg, excluding medications).

Predictive models were developed using step-wise selection of baseline variables. We used automatic step-wise selection in SAS (PROC PHREG). The selection at each step was based on the Score statistic. A Wald $P<0.05$ was used for both forward and backward steps. Linearity of each covariate was investigated. If a nonlinear relationship was observed, appropriate piece-wise linear splines of the variable were used in models for that covariate. The proportional hazards assumption was evaluated for each covariate using testing and graphical methods (weighted Schoenfeld residuals). The proportional hazards assumption was appropriate for all variables. Models were validated using an optimism-corrected c-index statistic—a statistical tool that allows for internal validation of the model without splitting the data into separate model building and validation cohorts; for interpretation purposes, the closer the c-index is to 1, the better the risk score can distinguish patients with and without events. Additionally, model calibration was examined using decile plots of mean observed versus predicted risks. We report the hazard ratios and 95% confidence intervals for each covariate included in the final predictive model in both the univariate and full model. All analyses were performed with SAS software (version 9.4; SAS Institute Inc, Cary, NC).
Using the parameters of the predictive model, we created a hazard risk score for each patient. A new time-to-event model for each end point was developed including calculated risk score, treatment assignment, and their interaction. We report the \( P \) values of the interaction term. The adjusted hazard ratio and 95% confidence interval for treatment as a function of the risk score are presented. For the analysis, a continuous risk score was assigned to each patient. For presentation purposes, we organized the relationships by quintiles to visually demonstrate the relationships between risk scores and events.

**Results**

Over a median follow-up period of 3.2 years (2.2–4.4), 1091 (7.4%) patients died and 1744 (11.8%) experienced MACEs (including 723 [4.9%] with cardiovascular death). Table 1 presents baseline characteristics for those who died during follow-up versus those who did not. Baseline characteristics by whether patients experienced a MACE event are presented in Table S1. Overall, patients with clinical events tended to be older, were more often men, had a longer duration of diabetes mellitus, had more previous cardiovascular events, and had worse baseline renal function compared with those without clinical events.

Tables 2 and 3 present the association between baseline characteristics and the end points of ACM and MACE, respectively, on uni- and multivariate analyses. Censoring and follow-up time for MACE and ACM end points were similar by treatment assignment (Table S2). Importantly, the trial did not discontinue follow-up after an initial clinical event, reducing the likelihood of informative censoring. Independent predictors of both ACM and MACE included age, sex, smoking history, region of enrollment, and cardiovascular and noncardiovascular comorbidities, body mass index, diastolic blood pressure, HbA1c, and estimated glomerular filtration rate. Baseline variables independently associated with outcomes are summarized in Figure 1. Of note, previous revascularization was associated with reduced mortality risk, but increased risk for MACE. Furthermore, systolic blood pressure during baseline evaluation was observed to be an independent predictor of long-term MACEs, whereas a physician-documented history of hypertension was associated with increased risk for ACM. ACM and MACE risk models had modest discrimination with optimism corrected c-indices of 0.73 and 0.71, respectively. Figure 2 presents the calibration plots for the predictive models over a 4-year period. The ACM model was well calibrated; the predicted probability matched what was observed in the population. The MACE model was not as well calibrated because it overestimated observed risk, particularly in the higher-risk subgroup.

When the new time-to-event models for each end point were developed, including the calculated risk score, there was no evidence of an interaction between treatment and risk profile for either end point (interaction \( P \) value of 0.20 for ACM and 0.79 for MACE). Figure 3 presents the treatment effect by risk score quintile for clinical end points. In terms of study drug adherence by risk profile, median duration of exposure to the trial regimen was 2.5 years (interquartile range, 1.4, 4.1) in the lowest-risk mortality group (lowest quintile) versus 2.1 years (interquartile range, 1.0–3.2) in the highest-risk mortality group (highest quintile). The percentage of patients on treatment at 1 year and at the end of follow-up (Table S3) was similar across quintiles 1 to 3 and was lower in the highest-risk quintiles (quintiles 4–5). For instance, the percentage of patients on treatment at 1 year and at the end of follow-up was \( \approx80\% \) and 60%, respectively, in quintiles 1 to 3 compared with 72% and 44% in the highest risk quintile (ie, quintile 5).

**Discussion**

In this large trial of patients with T2DM and a broad range of cardiovascular risk, we found that routinely available baseline characteristics, including demographics, smoking history, previous cardiovascular events, noncardiovascular comorbidities, and common laboratory values, provided modest prognostic value for ACM and MACE. In contrast to our hypothesis that patients at increased risk for clinical events would experience a comparatively greater treatment benefit with exenatide than those at lower risk, we found that the proportional effects of exenatide on ACM and MACE were consistent across the spectrum of baseline risk.

Given the nominal 14% reduction in ACM observed with exenatide, we were particularly interested in exploring whether higher-risk patients benefited to a greater extent with this therapy. Our first step was to develop a risk model for mortality to better understand which patient characteristics were associated with increased mortality. Relatively few risk models for mortality have been developed for patients with T2DM,\(^a\)–\(^d\) so we developed a new model within our study population. The candidate variable list was based on these previous studies, but also included additional comorbidity data.

Table S4 compares the EXSCEL mortality model with previous T2DM mortality models. In brief, aside from the single-center model developed at the Cleveland Clinic (\(N=33\ 067\)),\(^e\) our model is based on the largest number of patients (>14 700) to date. Moreover, the EXSCEL population included greater geographical representation compared with previous models that were developed exclusively in Italy.\(^e\)
Table 2. All-Cause Mortality Predictive Model Covariates—Univariate and Selection Model ORs

| Baseline Characteristic | OR Comparison                  | Unadjusted OR (95% CI) | Unadjusted P Value | Selection Model OR (95% CI) | Selection Model P Value |
|-------------------------|--------------------------------|------------------------|--------------------|-----------------------------|-------------------------|
| Age, y                  | Per 5 y                         | 1.38 (1.34, 1.43)      | <0.001             | 1.32 (1.26, 1.37)            | <0.001                  |
| Sex                     | Female vs male                  | 0.65 (0.57, 0.74)      | <0.001             | 0.69 (0.60, 0.80)            | <0.001                  |
| Ethnicity               | Hispanic or Latino vs non-Hispanic | 0.93 (0.79, 1.09)   | 0.372              |                             |                         |
| Race                    | American Indian or Alaska Native vs white | 1.01 (0.38, 2.70)   | 0.228              |                             |                         |
|                         | Asian vs white                   | 0.72 (0.57, 0.93)      |                    |                             |                         |
|                         | Black vs white                   | 1.02 (0.80, 1.31)      |                    |                             |                         |
|                         | Native Hawaiian or other Pacific Islander vs white | 1.08 (0.35, 3.34)    |                    |                             |                         |
|                         | Other vs white                   | 0.95 (0.76, 1.20)      |                    |                             |                         |
| Region                  | Asian Pacific vs North America   | 0.64 (0.50, 0.84)      | 0.006              | 0.84 (0.63, 1.11)            | 0.014                   |
|                         | Europe vs North America          | 1.01 (0.88, 1.16)      |                    | 1.10 (0.95, 1.29)            |                         |
|                         | Latin America vs North America   | 0.97 (0.80, 1.17)      |                    | 1.31 (1.05, 1.62)            |                         |
| Smoking status          | Current vs never                 | 1.41 (1.18, 1.69)      | <0.001             | 1.72 (1.41, 2.10)            | <0.001                  |
|                         | Former vs never                  | 1.35 (1.19, 1.53)      |                    | 1.12 (0.97, 1.28)            |                         |
| Alcohol consumption     | Yes vs no                        | 0.90 (0.79, 1.02)      | 0.088              |                             |                         |
| Previous cardiovascular event | Yes vs no                         | 2.90 (2.45, 3.44)      | <0.001             | 1.59 (1.29, 1.95)            | <0.001                  |
| Previous MI             | Yes vs no                        | 2.01 (1.78, 2.27)      | <0.001             | 1.39 (1.21, 1.60)            | <0.001                  |
| Diabetes mellitus duration | Per 5 y                          | 1.16 (1.12, 1.19)      | <0.001             |                             |                         |
| Previous revascularization | Yes vs no                         | 1.57 (1.40, 1.77)      | <0.001             | 0.85 (0.74, 0.99)            | 0.033                   |
| Cerebrovascular disease | Yes vs no                        | 1.74 (1.52, 1.99)      | <0.001             | 1.27 (1.10, 1.48)            | 0.001                   |
| NYHA class              | I vs no HF                       | 2.01 (1.61, 2.52)      | <0.001             | 1.55 (1.23, 1.95)            | <0.001                  |
|                         | II vs no HF                      | 2.57 (2.19, 3.01)      |                    | 1.78 (1.50, 2.12)            |                         |
|                         | III vs no HF                     | 4.31 (3.38, 5.51)      |                    | 2.58 (1.99, 3.36)            |                         |
|                         | IV vs no HF                      | 16.90 (8.03, 35.57)    |                    | 8.27 (3.66, 18.65)           |                         |
| Chronic liver disease   | Yes vs no                        | 1.27 (0.96, 1.66)      | 0.092              |                             |                         |
| Chronic respiratory disease | Yes vs no                        | 1.77 (1.49, 2.10)      | <0.001             | 1.27 (1.06, 1.53)            | 0.010                   |
| Hyperlipidemia          | Yes vs no                        | 1.08 (0.93, 1.25)      | 0.321              | 0.82 (0.70, 0.96)            | 0.016                   |
| Hypertension            | Yes vs no                        | 1.98 (1.61, 2.44)      | <0.001             | 1.35 (1.08, 1.69)            | 0.009                   |
| Atrial fibrillation     | Yes vs no                        | 2.34 (1.98, 2.78)      | <0.001             | 1.33 (1.11, 1.60)            | 0.002                   |
| Unstable angina         | Yes vs no                        | 1.33 (1.06, 1.66)      | 0.013              |                             |                         |
| Depression              | Yes vs no                        | 1.00 (0.84, 1.20)      | 0.990              |                             |                         |
| BMI                     | Per 1 point, under 30            | 0.94 (0.91, 0.97)      | <0.001             | 0.93 (0.91, 0.96)            | <0.001                  |
|                         | Per 1 point, over 30             | 1.01 (1.00, 1.03)      |                    | 1.03 (1.02, 1.05)            |                         |
| HbA1c                   | Per 1%                           | 1.05 (0.99, 1.12)      | 0.131              | 1.13 (1.06, 1.20)            | <0.001                  |
| eGFR                    | Per 10 mL/min/1.73 m², under 85  | 0.76 (0.73, 0.79)      | <0.001             | 0.86 (0.82, 0.90)            | <0.001                  |
|                         | Per 1 mL/min/1.73 m², over 85    | 1.02 (0.96, 1.08)      |                    | 1.07 (1.03, 1.12)            |                         |
| SBP                     | Per 10 mm Hg, under 130          | 0.86 (0.79, 0.93)      | <0.001             |                             |                         |
|                         | Per 10 mm Hg, over 130           | 1.09 (1.04, 1.15)      |                    |                             |                         |
| DBP                     | Per 10 mm Hg, under 85           | 0.73 (0.68, 0.78)      | <0.001             | 0.87 (0.80, 0.94)            | 0.001                   |
|                         | Per 10 mm Hg, over 85            | 1.19 (1.00, 1.41)      |                    | 1.20 (1.00, 1.45)            |                         |
| Pulse pressure          | Per 10 mm Hg, under 50           | 0.96 (0.84, 1.09)      | <0.001             |                             |                         |
|                         | Per 10 mm Hg, over 50            | 1.16 (1.11, 1.22)      |                    |                             |                         |

BMI indicates body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MI, myocardial infarction; NYHA, New York Heart Association; OR, odds ratio; SBP, systolic blood pressure.
Table 3. Major Adverse Cardiovascular Events Predictive Model Covariates—Univariate and Selection Model ORs

| Baseline Characteristic | OR Comparison                     | Unadjusted OR (95% CI) | Unadjusted P Value | Selection Model OR (95% CI) | Selection Model P Value |
|------------------------|-----------------------------------|------------------------|--------------------|-----------------------------|------------------------|
| Age, y                 | Per 5 y                            | 1.25 (1.22, 1.28)      | <0.001             | 1.15 (1.11, 1.19)           | <0.001                 |
| Sex                    | Female vs male                     | 0.64 (0.58, 0.71)      | <0.001             | 0.77 (0.69, 0.86)           | <0.001                 |
| Ethnicity              | Hispanic or Latino vs not Hispanic | 0.57 (0.49, 0.66)      | <0.001             |                             |                        |
| Race                   | American Indian or Alaska Native vs white | 1.04 (0.50, 2.20)  | 0.009               |                             |                        |
|                        | Asian vs white                     | 0.84 (0.70, 1.00)      |                    |                             |                        |
|                        | Black vs white                     | 1.02 (0.84, 1.24)      |                    |                             |                        |
|                        | Native Hawaiian or other Pacific Islander vs white | 1.37 (0.62, 3.06)  |                    |                             |                        |
|                        | Other vs white                     | 0.70 (0.57, 0.86)      |                    |                             |                        |
| Region                 | Asian Pacific vs North America     | 0.66 (0.55, 0.78)      | <0.001             | 0.84 (0.69, 1.02)           | <0.001                 |
|                        | Europe vs North America            | 0.72 (0.65, 0.80)      |                    | 0.82 (0.73, 0.92)           | <0.001                 |
|                        | Latin America vs North America     | 0.41 (0.34, 0.49)      |                    | 0.55 (0.45, 0.67)           | <0.001                 |
| Smoking status         | Current vs never                   | 1.30 (1.12, 1.51)      | <0.001             | 1.29 (1.10, 1.52)           | <0.001                 |
|                        | Former vs never                    | 1.33 (1.21, 1.47)      |                    | 1.00 (0.90, 1.12)           | <0.001                 |
| Alcohol consumption    | Yes vs no                          | 0.99 (0.90, 1.10)      | 0.864               |                             |                        |
| Previous cardiovascular event | Yes vs no                       | 3.09 (2.69, 3.55)      | <0.001             | 1.51 (1.27, 1.79)           | <0.001                 |
| Previous MI            | Yes vs no                          | 2.22 (2.02, 2.43)      | <0.001             | 1.51 (1.35, 1.69)           | <0.001                 |
| Diabetes mellitus duration | Per 5 y, under 12.5 y             | 1.28 (1.18, 1.38)      | <0.001             | 1.10 (1.01, 1.20)           | 0.003                  |
|                        | Per 5 y, over 12.5 y               | 1.13 (1.08, 1.17)      |                    | 1.03 (0.99, 1.07)           |                        |
| Previous revascularization | Yes vs no                       | 2.19 (1.99, 2.41)      | <0.001             | 1.23 (1.09, 1.39)           | <0.001                 |
| Cerebrovascular disease | Yes vs no                          | 1.82 (1.64, 2.03)      | <0.001             | 1.48 (1.32, 1.67)           | <0.001                 |
| NYHA class             | I vs no HF                         | 1.55 (1.28, 1.88)      | <0.001             | 1.17 (0.96, 1.42)           | <0.001                 |
|                        | II vs no HF                        | 1.91 (1.66, 2.18)      |                    | 1.41 (1.22, 1.63)           | <0.001                 |
|                        | III vs no HF                       | 3.28 (2.65, 4.05)      |                    | 2.07 (1.66, 2.60)           | <0.001                 |
|                        | IV vs no HF                        | 9.01 (4.04, 20.11)     |                    | 4.31 (1.78, 10.41)          | <0.001                 |
| Chronic liver disease  | Yes vs no                          | 0.89 (0.70, 1.15)      | 0.378               |                             |                        |
| Chronic respiratory disease | Yes vs no                      | 1.80 (1.57, 2.06)      | <0.001             | 1.34 (1.16, 1.55)           | <0.001                 |
| Hyperlipidemia         | Yes vs no                          | 1.49 (1.31, 1.70)      | <0.001             |                             |                        |
| Hypertension           | Yes vs no                          | 1.89 (1.61, 2.22)      | <0.001             |                             |                        |
| Atrial fibrillation    | Yes vs no                          | 2.01 (1.74, 2.32)      | <0.001             | 1.28 (1.10, 1.49)           | 0.002                  |
| Unstable angina        | Yes vs no                          | 1.77 (1.51, 2.07)      | <0.001             |                             |                        |
| Depression             | Yes vs no                          | 1.29 (1.12, 1.47)      | <0.001             |                             |                        |
| BMI                    | Per 1 point, under 30              | 0.98 (0.96, 1.00)      | 0.006              | 0.97 (0.94, 0.99)           | <0.001                 |
|                        | Per 1 point, over 30               | 1.02 (1.01, 1.03)      |                    | 1.02 (1.01, 1.03)           | <0.001                 |
| HbA1c                  | Per 1%                             | 1.08 (1.03, 1.14)      | 0.002              | 1.16 (1.10, 1.22)           | <0.001                 |
| eGFR                   | Per 10 mL/min/1.73 m², under 85    | 0.82 (0.79, 0.84)      | <0.001             | 0.91 (0.88, 0.94)           | <0.001                 |
|                        | Per 10 mL/min/1.73 m², over 85     | 1.00 (0.96, 1.05)      |                    | 1.04 (1.01, 1.09)           | <0.001                 |
| SBP                    | Per 10 mm Hg, under 130            | 0.87 (0.82, 0.93)      | <0.001             | 0.96 (0.89, 1.03)           | <0.001                 |
|                        | Per 10 mm Hg, over 130             | 1.11 (1.07, 1.15)      |                    | 1.10 (1.05, 1.15)           | <0.001                 |
| DBP                    | Per 10 mm Hg, under 85             | 0.75 (0.71, 0.80)      | <0.001             | 0.91 (0.85, 0.98)           | <0.001                 |
|                        | Per 10 mm Hg, over 85              | 1.23 (1.08, 1.40)      |                    | 1.19 (1.03, 1.37)           | <0.001                 |

Continued
Hong Kong, the United Kingdom, or the United States. In addition, previous models also included medication data that are not intrinsic patient-level variables. Nonetheless, the majority of the independent predictors identified by the EXSCEL model are supported by previous work. For instance, age and sex were independent predictors in most of the other models as were cardiovascular comorbidities (eg, heart failure). Clinical parameters, including body mass index as well as HbA1c and estimated glomerular filtration rate, have also been previously observed to be independent predictors of outcomes. If validated in future work, the EXSCEL model may provide clinicians with a useful tool for prognostication given that all of the variables are commonly available in routine practice. We did not perform additional internal validation of the model (ie, develop the model in half the cohort and validate in the other half), given that our primary intent was to explore the treatment effect across risk in the cohort rather than risk model development.

Following the development of the risk models, we then evaluated whether there was evidence of a differential response to exenatide on clinical outcomes according to baseline risk. We did not observe an interaction between treatment and risk profile for either end point. The consistent treatment effect was clear when presented visually across quintiles of risk.

Although we did not observe differential treatment effects within this diabetic cohort, existing examples of differential treatment effects between diabetic and nondiabetic populations warrant these investigations. For instance, a meta-analysis of beta-blocker therapy in patients with heart failure demonstrated a smaller magnitude of effect on mortality reduction in diabetes mellitus patients versus non–diabetes mellitus patients. Moreover, research has shown that the relative benefits of device-based therapies, such as implantable cardioverter defibrillators, are attenuated with increasing comorbidity burden such as diabetes mellitus.

Table 3. Continued

| Baseline Characteristic | OR Comparison | Unadjusted OR (95% CI) | Unadjusted P Value | Selection Model OR (95% CI) | Selection Model P Value |
|------------------------|--------------|------------------------|--------------------|-----------------------------|-------------------------|
| Pulse pressure          | Per 10 mm Hg, under 50 | 1.03 (0.92, 1.15)      | <0.001             |                             |                         |
|                         | Per 10 mm Hg, over 50   | 1.15 (1.10, 1.19)      |                    |                             |                         |

BMI indicates body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; MI, myocardial infarction; NYHA, New York Heart Association; OR, odds ratio; SBP, systolic blood pressure.

Figure 1. Summary of predictive models for (A) all-cause mortality (ACM) and (B) major adverse cardiovascular events (MACE). BMI indicates body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; hx, history; MI, myocardial infarction; Revasc, revascularization.
Practically, these observations may be related to increased severity of disease and medical complexity that may be less modifiable with specific therapies. On the other hand, even with the potential attenuation of relative risk reduction in patients with T2DM, given that these patients are overall at higher risk for adverse events, the absolute reduction in clinical events may still be substantial.

Clinical Implications

Our findings showed consistent treatment effects of exenatide across the spectrum of cardiovascular risk and might help inform practicing clinicians in their decision-making process. We have recently performed a meta-analysis of the GLP-1 receptor agonist class that supports consistent treatment effects of the different agents in this class (eg, liraglutide, semaglutide, and exenatide) in reducing MACE and mortality. Although there were differences in study patient populations and trial designs, the overall consistent effect of these agents in the context of a favorable safety profile supports shared decision making between the patient and physician to optimize choice of T2DM therapy. For instance, with data supporting consistent relative reductions in MACE, mortality, and cardiovascular death of ≈10% to 13% with GLP-1 receptor agonists, exenatide may be an appropriate choice for some patients based on tolerability, cost, and dosing schedule (ie, weekly with exenatide versus daily with liraglutide). The present data support discussions with patients across the spectrum of baseline risk regarding the potential benefits of exenatide.

Limitations

These data should be considered in the context of several limitations. First, although the broad inclusion criteria and overall pragmatic design of EXSCEL support generalizability, these observations may not apply to those patients who would not have been included in the trial. For instance, patients with higher baseline HbA1c levels (>10%) were not included in EXSCEL, whereas those at a young age (>18 years) were included. In addition, the EXSCEL trial enrolled ≈70% of participants with known cardiovascular disease at baseline, and thus there may be less applicability to those with newly diagnosed T2DM. On the other hand, these risk models are the first, to our knowledge, that include broad international representation (North America, Latin America, Europe, and Asia Pacific), a wide age range, and a broad range of background T2DM therapies (including sodium-glucose cotransporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors). Importantly, these risk models have not been externally validated in other data sets. Given the pragmatic nature of data capture in EXSCEL, there were certain baseline characteristics (eg, urine albumin-to-creatinine ratio) that were collected, as available, from routine care and for which missing data prevented use of a validated risk model such as the Gargano model. However, given that the EXSCEL models include variables that are routinely available in clinical practice, these models may have more-broad utility for prognostication. Notably, our candidate variable list did not include medications. We decided a priori to focus on intrinsic patient-level characteristics and not include medications given significant regional variation in availability and use of background therapies and a desire to have broader applicability. In addition, the models had only modest discrimination, and whereas the ACM model was well calibrated, the MACE model was not. This is consistent with previous work in other disease states where robust mortality models are more readily derived compared with clinical composite outcomes that tend to have less discriminatory and prognostic utility.
Baseline characteristics, including age, previous cardiovascular events, comorbidity burden, and laboratory values, provided modest prognostic value for mortality and MACEs in a broad population of patients with T2DM. Effects of exenatide on mortality and MACEs were consistent across the spectrum of baseline risk.

**Conclusion**

Baseline characteristics, including age, previous cardiovascular events, comorbidity burden, and laboratory values, provided modest prognostic value for mortality and MACEs in a broad population of patients with T2DM. Effects of exenatide on mortality and MACEs were consistent across the spectrum of baseline risk.

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Mentz reports receiving grants from AstraZeneca during the conduct of the study and grants from GlaxoSmithKline and personal fees from Boehringer Ingelheim outside the submitted work. Bethel reports receiving research support from Merck and AstraZeneca; participating in advisory boards for Boehringer Ingelheim and NovoNordisk; receiving honoraria, personal fees, and other support from Merck, Novo Nordisk, AstraZeneca, and Sanofi; and receiving nonfinancial research support from Bayer and Merck Serono. Merrill reports no disclosures. Lokhnygina reports receiving grants from Amylin Pharmaceuticals Inc (a wholly owned subsidiary of AstraZeneca) during the conduct of the study and grants from Merck,

**Figure 3.** Treatment effect by risk score quintile for (A) ACM and (B) MACE. ACM indicates all-cause mortality; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events.
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Supplemental Material
Appendix

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Table S1. Baseline characteristics by experience of 3-point MACE.

| Characteristic                        | MACE N=1744 | No MACE N=13008 |
|---------------------------------------|-------------|-----------------|
| Age (years)                           | 65.0 (59.0, 72.0) | 62.0 (55.0, 68.0) |
| Women                                 | 511/1744 (29.3%) | 5092/13008 (39.1%) |
| Hispanic or Latino                    | 200/1743 (11.5%) | 2826/13007 (21.7%) |
| Race                                  |             |                 |
| American Indian or Alaska Native      | 7/1743 (0.4%)  | 66/13004 (0.5%)  |
| Asian                                 | 134/1743 (7.7%) | 1318/13004 (10.1%) |
| Black or African American             | 105/1743 (6.0%) | 773/13004 (5.9%)  |
| Native Hawaiian or Pacific Islander   | 6/1743 (0.3%)  | 29/13004 (0.2%)  |
| Other                                 | 96/1743 (5.5%)  | 1038/13004 (8.0%) |
| White                                 | 1395/1743 (80.0%) | 9780/13004 (75.2%) |
| Region                                |             |                 |
| Asia Pacific                          | 149/1744 (8.5%) | 1380/13008 (10.6%) |
| Europe                                | 781/1744 (44.8%) | 6007/13008 (46.2%) |
| Latin America                         | 157/1744 (9.0%)  | 2570/13008 (19.8%) |
| North America                         | 657/1744 (37.7%) | 3051/13008 (23.5%) |
| Smoking status                        |             |                 |
| Current                               | 221/1743 (12.7%) | 1500/13002 (11.5%) |
| Former                                | 772/1743 (44.3%) | 5019/13002 (38.6%) |
| Never                                 | 750/1743 (43.0%) | 6483/13002 (49.9%) |
| Alcohol consumption                   | 586/1742 (33.6%) | 4235/12995 (32.6%) |
| Prior cardiovascular event            | 1508/1744 (86.5%) | 9274/13008 (71.3%) |
| Characteristic                        | MACE N=1744 | No MACE N=13008 |
|--------------------------------------|-------------|-----------------|
| Prior myocardial infarction          | 830/1744 (47.6%) | 3849/13008 (29.6%) |
| Diabetes duration (years)            | 14.0 (8.0, 20.0) | 11.0 (7.0, 17.0) |
| Prior revascularization              | 981/1744 (56.3%) | 4925/13008 (37.9%) |
| Cerebrovascular disease              | 474/1743 (27.2%) | 2240/13006 (17.2%) |
| **NYHA class**                       |             |                 |
| 1                                    | 116/1743 (6.7%) | 622/13006 (4.8%) |
| 2                                    | 249/1743 (14.3%) | 1084/13006 (8.3%) |
| 3                                    | 92/1743 (5.3%) | 211/13006 (1.6%) |
| 4                                    | 6/1743 (0.3%) | 7/13006 (0.1%) |
| No heart failure                     | 1280/1743 (73.4%) | 11082/13006 (85.2%) |
| Chronic liver disease                | 64/1744 (3.7%) | 534/13007 (4.1%) |
| Chronic respiratory disease          | 234/1744 (13.4%) | 975/13007 (7.5%) |
| Hyperlipidemia/dyslipidemia          | 1482/1744 (85.0%) | 10169/13007 (78.2%) |
| Hypertension                         | 1582/1744 (90.7%) | 10795/13007 (83.0%) |
| Atrial fibrillation/atrial flutter   | 212/1744 (12.2%) | 787/13007 (6.1%) |
| Unstable angina/recurrent ischemia   | 169/1744 (9.7%) | 759/13007 (5.8%) |
| Depression                           | 252/1744 (14.4%) | 1418/13007 (10.9%) |
| BMI (kg/m²)                          | 32.4 (28.7, 37.0) | 31.6 (28.2, 36.1) |
| HbA1c (%)                            | 8.1 (7.4, 9.0) | 8.0 (7.3, 8.8) |
| eGFR (mL/min/1.73m²)                 | 69.6 (55.0, 87.5) | 77.0 (62.1, 92.6) |
| Systolic blood pressure (mmHg)       | 135.0 (124.0, 148.0) | 135.0 (124.0, 145.0) |
| Diastolic blood pressure (mmHg)      | 78.0 (69.0, 84.0) | 80.0 (71.0, 85.0) |
| Pulse pressure (mmHg)                | 59.0 (50.0, 69.0) | 55.0 (48.0, 65.0) |
| Calculated risk score                | 1.4 (0.9, 1.9) | 0.8 (0.2, 1.3) |

NYHA indicates New York Heart Association; BMI, body mass index; eGFR, estimated glomerular filtration rate.
Table S2. Number censored and follow-up time for censored subjects by treatment assignment for MACE and all-cause death endpoints.

| Assigned Treatment | Exenatide N=7356 | Placebo N=7396 |
|--------------------|------------------|----------------|
| **MACE endpoint**  |                  |                |
| Number censored    | 6517 (88.6%)     | 6491 (87.8%)   |
| Median (25th, 75th) follow-up for censored subjects (months) | 37.9 (26.8, 51.8) | 36.9 (26.6, 51.6) |
| **All-cause death** |                  |                |
| Number censored    | 6849 (93.1%)     | 6812 (92.1%)   |
| Median (25th, 75th) follow-up for censored subjects (months) | 41.8 (28.1, 53.9) | 41.3 (28.3, 53.7) |
Table S3. Number of participants on treatment at 1 year and end of follow-up by risk quintile groups.

| Quintile | On treatment at 1 year | On treatment at end of follow-up |
|----------|------------------------|----------------------------------|
| 1st Quintile | 2352/2882 (81.6%) | 1769/2882 (61.4%) |
| 2nd Quintile | 2340/2883 (81.2%) | 1763/2883 (61.2%) |
| 3rd Quintile | 2311/2883 (80.2%) | 1698/2883 (58.9%) |
| 4th Quintile | 2257/2883 (78.3%) | 1556/2883 (54.0%) |
| 5th Quintile | 2080/2883 (72.2%) | 1274/2883 (44.2%) |
Table S4. Comparison of the EXSCEL mortality model with previously published models.

|                        | EXSCEL       | Gargano Model¹ | Yang X, et al² | Wells BJ, et al³ | TRIAD⁴ | UKPDS Model⁵ |
|------------------------|--------------|----------------|----------------|-----------------|--------|--------------|
| Population             | Trial        | Italian Cohort | Hong Kong      | Cleveland Clinic| US Centers | United Kingdom|
| Sample size            | 14,752       | Derivation: 679| Validation: 936| 7,583           | 8,334   | 5,102        |
| Demographics           | Age, sex, region| Age           | Age, sex       | Age, sex, race  | Age, sex, race, lower income | Age, sex |
| PMH                    | Smoking, MI, NYHA class, CV event, HTN, HLD, AF, revascularization, cerebrovascular disease, respiratory disease | - | PAD, cancer | Smoking, HF, heart disease, new DM | Smoking, CAD, HF, Charlson Index, nephropathy, dyslipidemia, Smoker; history of AF, PVD, IHD, MI, HF, renal disease, amputation, DM duration; clinical events: amputation, IHD, MI, renal event or stroke |
| Medications            | -            | BP, insulin    | Insulin        | DM and CV meds  | Insulin, ASA, BB, diuretic | -         |
| Exam                   | BMI, DBP     | BMI, DBP       | BMI            | BMI, DBP, SBP   | -       | BMI, HR      |
| Labs                   | HbA1c, eGFR  | LDL, TG, HDL, ACR | eGFR, Hgb, ACR | A1c, GFR, HDL, LDL, TG | LDL     | HDL, WBC, albuminuria |

MI indicates myocardial infarction; NYHA, New York Heart Association; CV, cardiovascular; HTN, hypertension; HLD, hyperlipidemia; AF, atrial fibration; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; ACR, albumin-to-creatinine ratio; PAD, peripheral arterial disease; Hgb, hemoglobin; HF, heart failure; DM, diabetes mellitus; SBP, systolic blood pressure; CAD, coronary artery disease; ASA, aspirin; BB, beta-blocker; IDH, ischemic heart disease; HR, heart rate; WBC, white blood cell count.
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