ORIGINAL RESEARCH

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

Robert J. Mentz, MD; M. Angelyn Bethel, MD; Peter Merrill, PhD; Yuliya Lokhnygina, PhD; John B. Buse, MD, PhD; Juliana C. Chan, MD; João S. Felício, MD; Shaun G. Goodman, MD, MSc; Jasmine Choi, MS; Stephanie M. Gustavson, PhD; Nayyar Iqbal, MD; Renato D. Lopes, MD, MHS, PhD; Aldo P. Maggioni, MD; Peter Öhman, MD, PhD; Neha J. Pagidipati, MD, MPH; Neil R. Poulter, FMedSci; Ambady Ramachandran, MD; Barry Reicher, MD; Rury R. Holman, FMedSci; Adrian F. Hernandez, MD, MHS; on behalf of the EXSCEL Study Group

***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.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT01144338. **(*J Am Heart Assoc*. 2018;7: e009304. DOI: 10.1161/JAHA.118.009304.)**

Key Words: glucagon-like peptide-1 receptor agonis • major adverse cardiac event • mortality • type 2 diabetes mellitus

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,

From the Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (R.J.M., P.M., Y.L., R.D.L., N.J.P., A.F.H.); Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, United Kingdom (M.A.B., R.R.H.); Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC (J.B.B.); Department of Medicine & Therapeutics, The Chinese University of Hong Kong, China (J.C.C.); Hospital Universitário João de Barros Barreto—UFPA, Belém, Brazil (J.S.F.); St. Michael's Hospital, University of Toronto, Ontario, Canada (S.G.G.); Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada (S.G.G.); AstraZeneca Research and Development, Gaithersburg, MD (J.C., S.M.G., N.I., P.O., B.R.); ANMCO Research Center, Firenze, Italy (A.P.M.); International Centre for Circulatory Health, Imperial College London, United Kingdom (N.R.P.); India Diabetes Research Foundation and Dr. A. Ramachandran's Diabetes Hospitals, Chennai, India (A.R.).

Accompanying Appendix S1, Tables S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009304

*A complete list of the EXSCEL Study Group members can be found in Appendix S1.

Correspondence to: Robert J. Mentz, MD, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715. E-mail: robert.mentz@duke.edu

Received May 25, 2018; accepted August 14, 2018.

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[4] (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.[1–3] 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 m^2, 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.[3]

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	868/1091 (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	498/1091 (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%)
Hyperlipidemia/ dyslipidemia	878/1091 (80.5%)	10 773/13 660 (78.9%)
Hypertension	995/1091 (91.2%)	11 382/13 660 (83.3%)
Atrial fibrillation/ atrial 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	7/1090 (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%)
Depression	135/1091 (12.4%)	1535/13 660 (11.2%)
BMI, kg/m^2	32.0 (28.0, 36.8)	31.8 (28.3, 36.1)
SBP, mm Hg	135.0 (123.0, 146.0)	135.0 (124.0, 145.0)
DBP, mm Hg	76.0 (69.0, 83.0)	80.0 (71.0, 85.0)
Pulse pressure, mm Hg	59.0 (50.0, 70.0)	56.0 (48.0, 65.0)
HbA1c, %	8.1 (7.4, 8.9)	8.0 (7.3, 8.9)
eGFR by MDRD, mL/min/1.73 m^2	66.7 (53.0, 85.0)	77.0 (62.0, 92.5)
Calculated risk score	1.9 (1.3, 2.4)	1.1 (0.5, 1.6)

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[5] 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 ≈80% 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,[6–10] 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),[8] 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,[6]

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 m^2, under 85	0.76 (0.73, 0.79)	<0.001	0.86 (0.82, 0.90)	<0.001
	Per 1 mL/min/1.73 m^2, 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)	
	Latin America vs North America	0.41 (0.34, 0.49)		0.55 (0.45, 0.67)	
Smoking status	Current vs never	1.30 (1.12, 1.51)	<0.001	1.29 (1.10, 1.52)	0.004
	Former vs never	1.33 (1.21, 1.47)		1.00 (0.90, 1.12)	
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)	
	III vs no HF	3.28 (2.65, 4.05)		2.07 (1.66, 2.60)	
	IV vs no HF	9.01 (4.04, 20.11)		4.31 (1.78, 10.41)	
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)	
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 m^2, under 85	0.82 (0.79, 0.84)	<0.001	0.91 (0.88, 0.94)	<0.001
	Per 10 mL/min/1.73 m^2, over 85	1.00 (0.96, 1.05)		1.04 (1.01, 1.09)	
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)	
DBP	Per 10 mm Hg, under 85	0.75 (0.71, 0.80)	<0.001	0.91 (0.85, 0.98)	0.007
	Per 10 mm Hg, over 85	1.23 (1.08, 1.40)		1.19 (1.03, 1.37)	

Continued

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.

Hong Kong,[7] the United Kingdom,[10] or the United States.[9] 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.[11] 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.[12]

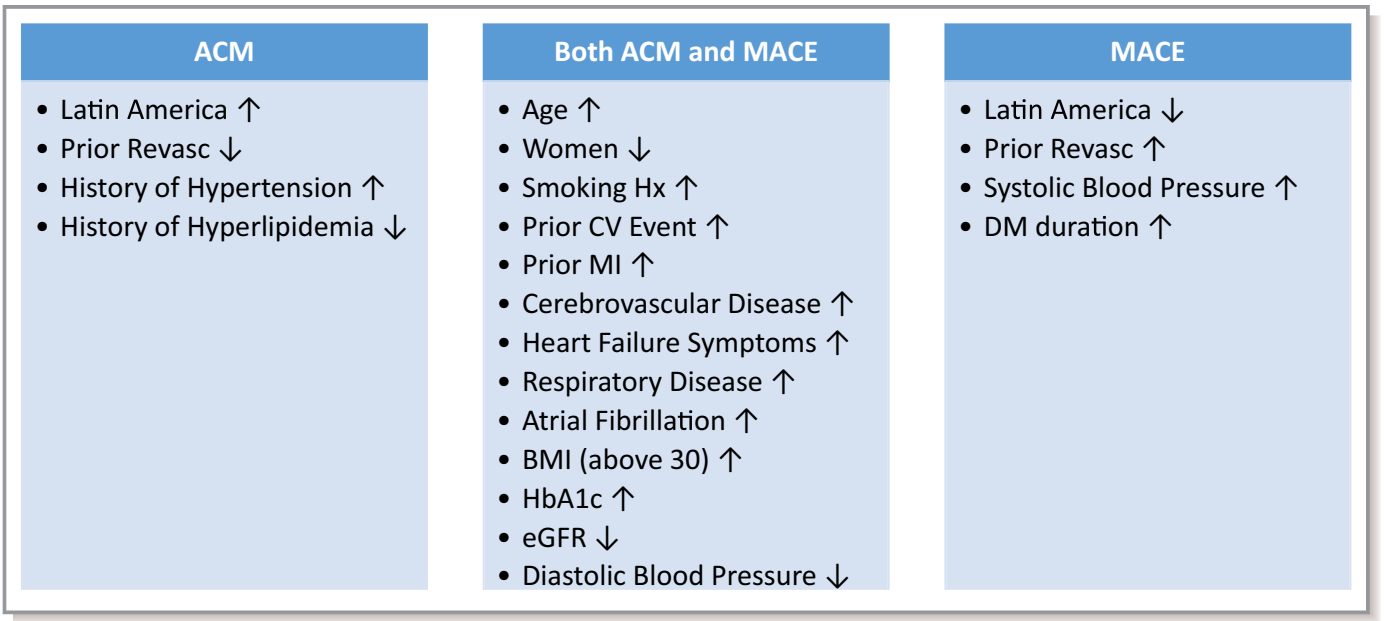

Figure 1. Summary of predictive models for (A) all-cause mortality (ACM) and (B) major adverse cardiovascular events (MACE). BMI indicates body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; hx, history; MI, myocardial infarction; Revasc, revascularization.

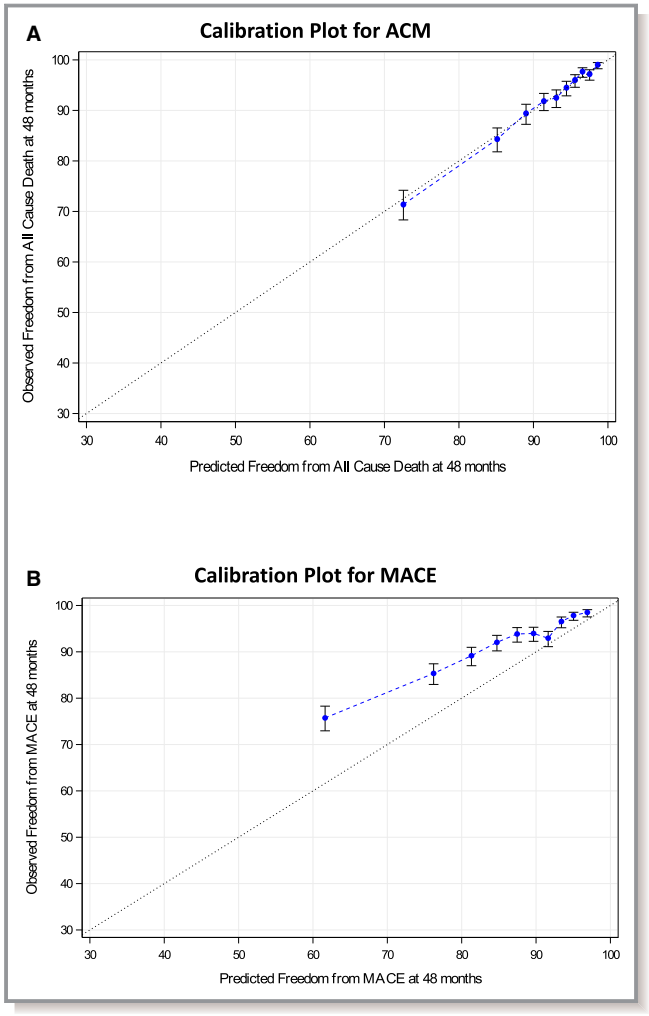

Figure 2. Calibration plots for predictive models for (A) ACM and (B) MACE. ACM indicates all-cause mortality; MACE, major adverse cardiovascular events.

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.[13] Although there were differences in study patient populations and trial designs,[2] 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.[4] 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[14] where robust mortality models are more readily derived compared with clinical composite outcomes that tend to have less discriminatory and prognostic utility.

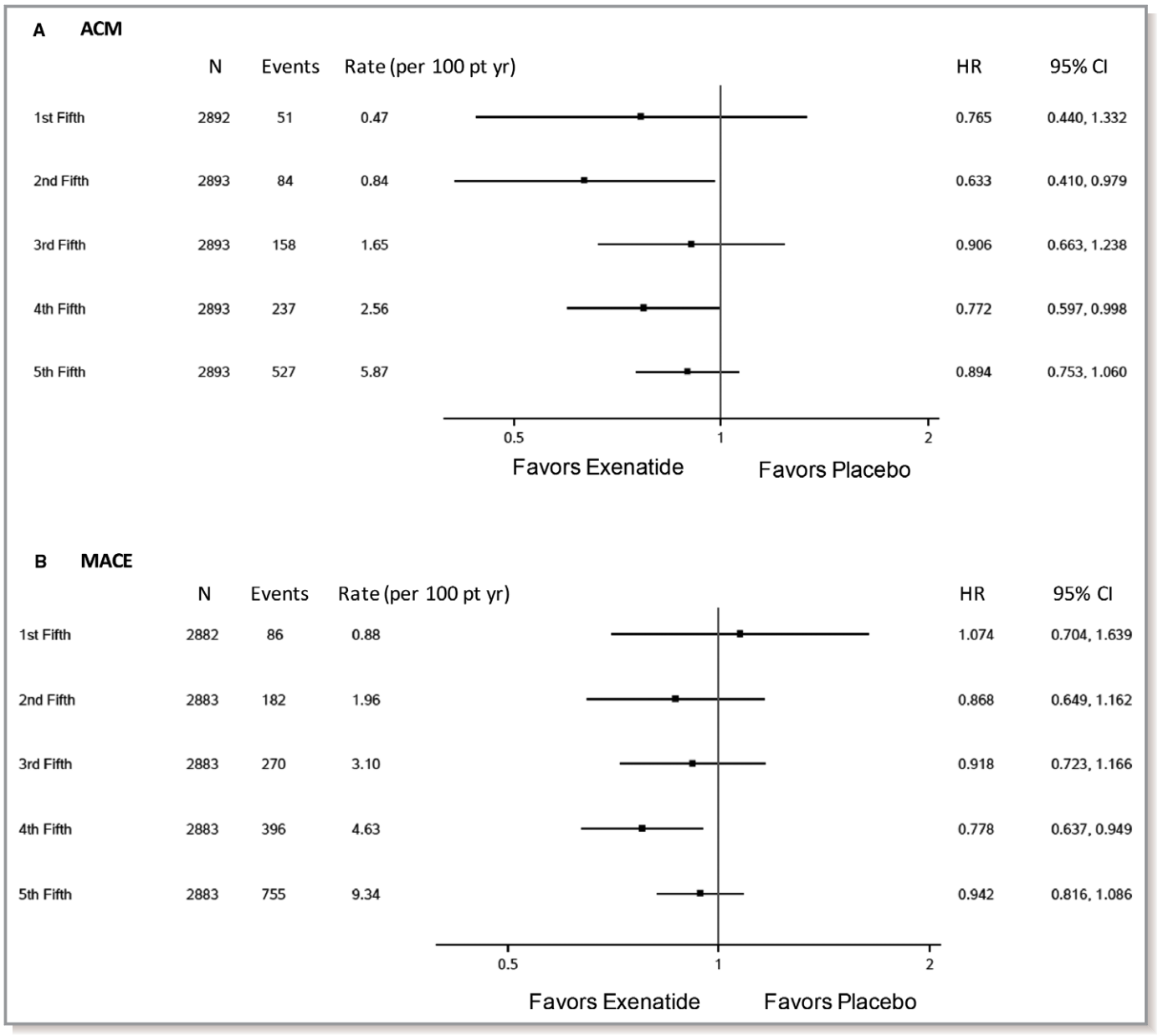

Figure 3. Treatment effect by risk score quintile for (A) ACM and (B) MACE. ACM indicates all-cause mortality; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events.

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.

Sources of Funding

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

Disclosures

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,

Janssen Research & Development, GlaxoSmithKline, and Bayer HealthCare AG outside the submitted work. Buse has received contracted consulting fees, paid to his institution, and travel support from Adocia, AstraZeneca, Dance Biopharm, Dexcom, Elcelyx Therapeutics, Eli Lilly, Fractyl, GI Dynamics, Intarcia Therapeutics, Lexicon, Merck, Metavention, NovaTarg, Novo Nordisk, Orexigen, PhaseBio, Sanofi, Shenzhen HighTide, Takeda, and vTv Therapeutics and grant support from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GI Dynamics, GlaxoSmithKline, Intarcia Therapeutics, Johnson & Johnson, Lexicon, Medtronic, Merck, Novo Nordisk, Orexigen, Sanofi, Scion NeuroStim, Takeda, Theracos, and vTv Therapeutics; he has received fees and holds stock options in Insulin Algorithms and PhaseBio and serves on the board of the AstraZeneca HealthCare Foundation; he is supported by a grant from the National Institutes of Health (UL1TR001111). Chan reports receiving research grants and/or honoraria for consultancy and/or giving lectures from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk, Pfizer, and/or Sanofi (all proceeds have been donated to the Chinese University of Hong Kong to support research and education; the Chinese University of Hong Kong has received research grants and sponsorships from these companies). Felício reports no relevant disclosures. Goodman has received research grant support and/or personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Fenix Group International, Ferring Pharmaceuticals, GlaxoSmithKline, Janssen/Johnson & Johnson, Matrizyme, Merck, Novartis, Pfizer, Regeneron, Sanofi, Servier, and Tenax Therapeutics. Choi, Gustavson, and Iqbal are employees of AstraZeneca. Lopes reports receiving research support from Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, and Pfizer and consulting or advisory board service with Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Medtronic, Merck, Pfizer, and Portola Pharmaceutical. Maggioni reports receiving honoraria from Bayer, Novartis, Cardiorentis, and Fresenius for participation in study committees. Öhman is an employee of AstraZeneca. Pagidipati reports ownership in: Freedom Health, Inc; Physician Partners, LLC; RXAdvance, LLC; and Florida Medical Associates, LLC. Poulter reports receiving personal fees and other support from Novo Nordisk during the conduct of the study; personal fees from Servier, Takeda, Novo Nordisk, and AstraZeneca, grants from Diabetes UK, the NIHR EME, Julius Clinical, and British Heart Foundation outside the submitted work. Ramachandran reports receiving remuneration for advisory board meetings from Merck, Sharp & Dohme, and AstraZeneca; honoraria for lectures from Bayer, Novo Nordisk, Eli Lilly, Merck, Sharp & Dohme, Sanofi-Aventis, and Novartis; and research grant support from AstraZeneca, Merck, Sharp & Dohme, Novartis, and Sanofi-Aventis. Reicher is an employee of AstraZeneca. Holman reports receiving grants from AstraZeneca during the conduct of the study and grants and personal fees from Bayer, Boehringer Ingelheim, and Merck; personal fees from Novartis, Amgen, and Servier; and other support from Elcelyx, GlaxoSmithKline, Janssen, and Takeda outside the submitted work. Hernandez reports receiving research funding from AstraZeneca, GlaxoSmithKline, Merck, and Novartis and consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Merck, Novartis, and Pfizer.

References

1. Holman RR, Bethel MA, George J, Sourij H, Doran Z, Keenan J, Khurmi NS, Mentz RJ, Oulhaj A, Buse JB, Chan JC, Iqbal N, Kundu S, Maggioni AP, Marso SP, Ohman P, Pencina MJ, Poulter N, Porter LE, Ramachandran A, Zinman B, Hernandez AF. Rationale and design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial. *Am Heart J*. 2016;174:103–110.
2. Mentz RJ, Bethel MA, Gustavson S, Thompson VP, Pagidipati NJ, Buse JB, Chan JC, Iqbal N, Maggioni AP, Marso SP, Ohman P, Poulter N, Ramachandran A, Zinman B, Hernandez AF, Holman RR. Baseline characteristics of patients enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL). *Am Heart J*. 2017;187:1–9.
3. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Ohman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:1228–1239.
4. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab*. 2016;24:15–30.
5. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387.
6. De Cosmo S, Copetti M, Lamacchia O, Fontana A, Massa M, Morini E, Pacilli A, Fariello S, Palena A, Rauseo A, Viti R, Di Paola R, Menzaghi C, Cignarelli M, Pellegrini F, Trischitta V. Development and validation of a predicting model of all-cause mortality in patients with type 2 diabetes. *Diabetes Care*. 2013;36:2830–2835.
7. Yang X, So WY, Tong PC, Ma RC, Kong AP, Lam CW, Ho CS, Cockram CS, Ko GT, Chow CC, Wong VC, Chan JC. Development and validation of an all-cause mortality risk score in type 2 diabetes. *Arch Intern Med*. 2008;168:451–457.
8. Wells BJ, Jain A, Arrigain S, Yu C, Rosenkrans WA Jr, Kattan MW. Predicting 6-year mortality risk in patients with type 2 diabetes. *Diabetes Care*. 2008;31:2301–2306.
9. McEwen LN, Karter AJ, Waitzfelder BE, Crosson JC, Marrero DG, Mangione CM, Herman WH. Predictors of mortality over 8 years in type 2 diabetic patients: translating Research Into Action for Diabetes (TRIAD). *Diabetes Care*. 2012;35:1301–1309.
10. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia*. 2013;56:1925–1933.
11. Haas SJ, Vos T, Gilbert RE, Krum H. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. *Am Heart J*. 2003;146:848–853.
12. Steinberg BA, Al-Khatib SM, Edwards R, Han J, Bardy GH, Bigger JT, Buxton AE, Moss AJ, Lee KL, Steinman R, Dorian P, Hallstrom A, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Inoue LY, Sanders GD. Outcomes of implantable cardioverter-defibrillator use in patients with comorbidities: results from a combined analysis of 4 randomized clinical trials. *JACC Heart Fail*. 2014;2:623–629.
13. Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, Pagidipati NJ, Chan JC, Gustavson SM, Iqbal N, Maggioni AP, Öhman P, Poulter NR, Ramachandran A, Zinman B, Hernandez AF, Holman RH. Cardiovascular outcomes with GLP-1 receptor agonists: a meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6:105–113.
14. O'Connor CM, Mentz RJ, Cotter G, Metra M, Cleland JG, Davison BA, Givertz MM, Mansoor GA, Ponikowski P, Teerlink JR, Voors AA, Fiuzat M, Wojdyla D, Chiswell K, Massie BM. The PROTECT in-hospital risk model: 7-day outcome in patients hospitalized with acute heart failure and renal dysfunction. *Eur J Heart Fail*. 2012;14:605–612.

Supplemental Material

Appendix

Trial Organization: EXSCEL Study Group

Principal/Chief Investigators

Rury R. Holman, Diabetes Trials Unit, University of Oxford, UK

Adrian Hernandez, Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA

Former PI

Robert M. Califf, formerly of Duke Translational Medicine Institute, Duke University School of Medicine, Durham, NC, USA (June 2009 – 23 Feb 2015)

Executive Committee

Rury R. Holman (Joint-Chair), Diabetes Trials Unit, University of Oxford, UK

Adrian Hernandez (Joint-Chair), Duke Clinical Research Institute, Duke University School of Medicine, Durham, USA

Juliana C. N. Chan, The Chinese University of Hong Kong, Shatin, Hong Kong

John B. Buse, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Bernie Zinman, Samuel Lunenfield Research Institute, Mount Sinai Hospital and University of Toronto, Toronto, Canada

Aldo P. Maggioni, ANMCO Research Centre, Florence, Italy

Ambady Ramachandran, India Diabetes Research Foundation and Dr A Ramachandran's Diabetes Hospitals, Chennai, India

Neil Poulter, International Centre for Circulatory Health, NHLI, Imperial College London, UK

Steve Marso, HCA Midwest Health, Texas, USA

Peter Ohman, AstraZeneca Research and Development, Gaithersburg, Maryland, USA

Nayyar Iqbal, AstraZeneca Research and Development, Gaithersburg, Maryland, USA

Former Member

Robert M. Califf, formerly of Duke Translational Medicine Institute, Duke University School of Medicine, Durham, NC, USA

Clinical Leads, Study Teams, and Key Statisticians

Clinical Leads

Angelyn Bethel, Diabetes Trials Unit, University of Oxford, Oxford, UK

Robert Mentz, Duke Clinical Research Unit, Duke University School of Medicine, Durham, NC, USA

Neha Pagidipati, Duke Clinical Research Unit, Duke University School of Medicine, Durham, NC, USA

Rishi Patel, Diabetes Trials Unit, University of Oxford, Oxford, UK

Formerly:

Jyothis George, Diabetes Trials Unit, University of Oxford, Oxford, UK (until 2014)

Harald Sourij, Diabetes Trials Unit, University of Oxford, Oxford, UK
Yee Weng Wong, Duke Clinical Research Unit, Duke University School of Medicine, Durham, NC, USA

Study Teams

DCRI

Operations Lead: Karen Hannan (formerly Mary Ann Sellers)
Lead CRA: Pat Gottlieb (formerly Paula Lavender, and Dianne Leloudis)
Onsite Lead CRA: Yolanda Meadows (formerly Dan Larson, and Heidi Anderson)
Lead CEC Coordinator: Mary Elkins
CEC Project Leaders: Lynn Perkins and Matt Wilson
Safety Team: Allegra Stone
Data Management: Andrea Tisch (formerly Lynn Perkins, Kesi Sanders and Curtis Campbell)

DTU:

Project Manager: Irene Kennedy (formerly Paul Heal, Michelle Masterson, Julie Darbyshire)
Clinical Trials Administrator: Lorraine Mumtaz (formerly Rajbir Athwal, Andrea Ferch, Priyanka Batra)

AstraZeneca:

Lynne Durborow
Jennifer Vincent
Andrew Woodall
Terry Flanagan
Stephanie Gustavson
Jasmine Choi
Brian Katona
Barry Reicher

Key Statisticians

DCRI

Vivian Thompson, Yuliya Lokhnygina (from March 2014)

DTU

Emanuela Pozzi, Abderrahim Oulhaj, Ruth Coleman (until October 2014)

Data Safety and Monitoring Committee

Jean Lucien Rouleau, Montreal Heart Institute, Montreal, Quebec, Canada
Stuart J. Pocock, London School of Hygiene and Tropical Medicine, London, UK
Fred Gorelick, Yale School of Medicine, Yale University, Connecticut, USA
John McMurray, University of Glasgow, Glasgow, Scotland
Matt Riddle, Oregon Health and Science University, Portland, Oregon, USA
Robert Gagel, Division of Internal Medicine, University of Texas MD Anderson Center, Houston, Texas

Observer

Tim Collier (Independent Statistician), London School of Hygiene and Tropical Medicine, London, UK

Operations Committee

Asia Pacific

Australia

Tania Markovic, Metabolism and Obesity Services, Royal Prince Alfred Hospital, Camperdown NSW

Hong Kong

Alice Pik Shan Kong, The Chinese University of Hong Kong

Malaysia

Sim Kui Hian, Head of CRC, Jin Hospital Department of Cardiology, Sarawak

New Zealand

Russell Scott, Don Beaven Medical Research Centre, Christchurch

Phillippines

Araceli Panelo, Institute for Studies on Diabetes Foundation Inc., Marikina City

South Korea

Kun-Ho Yoon, The Catholic University of Korea, Seoul St Mary Hospital, Seoul

Taiwan

Wayne Sheu, Taichung Veterans General Hospital, Taichung

Thailand

Piyamitr Sritara, Ramathboi Hospital Cardiology Unit, Rajthevee, Bangkok

China

Ji Linong, Department of Endocrinology & Metabolism, Peking University People's Hospital, Beijing

Chanyu Pan, Chinese PLA General Hospital, Beijing

Huo Yong, Heart Center and Department of Cardiology, PKU-1st Hospital, Beijing

Europe

Guntram Schernthaner, Ka Rudolfstiftung Incl. Semmelweis Frauenklinik, Wien, Austria

Chantal Mathieu, UZ Leuven-Campus Gasthuisberg, Leuven, Belgium

Tsvetalina Tankova, University Specialised Hospital for Active Treatment in Endocrinology, Medical University Sofia, Bulgaria

Petr Widimsky, Department of Internal Medicine - Cardiology, University Karlova, Prague, Czech Republic

Markolf Hanefeld, GWT Technical University, Dresden, Germany

Matyas Keltai, Semmelweis University Heart Centre, Budapest, Hungary

Julio Wainstein, The E Wolfson Medical Center, Holon, Israel

Stefano del Prato, PO Cisanello, AOU Pisana, Pisa, Italy

Valdis Pirags, Pauls Stradins Clinical University Hospital. Latvian University, Riga, Latvia

Neli Jakuboniene, UAB Bendrosios medicinos praktika, Kuanas, Lithuania

Adriaan Kooy, Bethesda Diabetes Research Center, Hoogeveen, The Netherlands

Piotr Dziemidok, Instytut Medcyny Wsi Im, Witolda Chodski, Lublin, Poland

Ioan Andrei Veresiu, Emergency County Hospital, Cluj-Napoca, Romania

Alexander V. Dreval, Moscow Regional Scientific Research Clinical Institute, Moscow, Russia

Jan Murin, Univerzitná nemocnica Bratislava, Slovakia

Albert LeCube Torello, Hospital Universitari Arnau de Vilanova, Lleida, Spain

Naveed Sattar, Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK

Olexander Parkhomenko, Inst Kardiologii Strazheska, Kyiv, Ukraine

South Africa

Mohamed Omar, Centre for Diabetes and Endocrinology, Durban, South Africa

Latin America

Argentina

Rafael Diaz, Department of Clinical & Experimental Medicine, Ospedale Cisanello, Santa Fe

Brazil

Renato Lopes, Brazilian Clinical Research Institute, Sao Paulo

Chile

Fernando Lanas, Universidad de La Frontera, Temuco

Colombia

Miguel Urina Triana, Fudación del Caribe para la Investigación Biomédica, Fundacion BIOS, Baranquillar

Mexico

Jose Luis Leiva-Pons, Hospital Central "Dr. Ignacio Morones Prieto", Av. Venustiano Carranza #2395, zona Universitaria, 78290, San Luis Potosi

USA and Canada

David Aguliera, Baylor College of Medicine, Houston, Texas

Richard Bergenstal, International Diabetes Center at Park Nicollet, Minneapolis

Shaun Goodman, Canadian VIGOUR Center, Toronto

Jean Francois Yale, Royal Victoria Hospital, McGill University Medical Center, Montreal, Quebec

Previous OC members

Australia

Ian Caterson, Boden Institute, University of Sydney, Camperdown, NSW

China

Jianping Weng, Department of Endocrinology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou

Dayi Hu, Chief Heart Center, People's Hospital, Peking University

Ge Junbo, Zhongshan Hospital Fudan University, Shanghai *(was removed from DCRI list in Aug 2016 due to lack of interest in EXSCEL)*

France

Faiez Zannad, CIC Institute Lorrain de Coeur et des Visseaux Louis Mathieu, Nancy

India

Misra Anoop, Fortis Hospitals, New Delhi

Mithal Ambrish, Medanta Medicity, Gurgaon, Delhi NCR, Haryana

Peru

John Adaly Gallegos, Hopital Militar Central, AV Faustino Sanchez Carron, Lima

Clinical Events Classification Committee

Jennifer B. Green (chair), Axel Akerblom, Karen Alexander, Sana Al-Khatib, Luciana Armaganijan, Pedro Barros, Maria Batit, Gwen Bernacki, Sabrina Bernandez, Gerald Bloomfield, Emily Clausen, Flavio De Souza Brito, Adam DeVore, Keith Dombrowski, Zubin Eapen, Ziad Gellad, Daniel George, Patricia Guimaraes, Sharif Halim, Rob Harrison, Jodi Hawes, Connie Hess, Kristen Hyland, Larry Jackson, Schuyler Jones, Dedrick Jordan, Marcelo Katz, David Kong, Masaya Koshizaka, Wanda Lakey, Thomas LeBlanc,

Sergio Leonardi, Renato Lopes, Nancy Luo, Ken Mahaffey, Aditya Mandawat, Rajendra Mehta, Chiara Melloni, Robert Mentz, Michael Morse, Neha Pagidpati, Chetan Patel, Keyur Patel, Sean Pokorney, Tom Posvic, Meena Rao, Matthew Roe, Bimal Shah, Hans Tillmann, Adriano Truffa, Yee-Weng Wong, Ana Zazula, Emily Zeitler

Site Investigators: (in site number order)

Argentina

Maximiliano Sicer, Maria Rosa Ulla, Laura Maffei, Maria Isabel Klyver, Pedro Calella, Andrés Alvarisqueta, Ricardo Leon De La Fuente, Diego Aizenberg, Fernando Roque, Adrian Cruciani, Gustavo Frechtel, Elizabeth Gelersztein, Adriana Villarino, Marcelo Mallagray, Lucrecia Nardone, Cesar Zaidman, Leonardo Novaretto, Ines, Bartolacci, Maria de Salvo.

Australia

Candice Delcourt, Denis Crimmins, Richard Jackson, David O'Neal, Peter Colman, William Jeffries, Peak Mann Mah, Gary Wittert, Tania Markovic, Joseph Proietto, John Amerena, Sharon Marks, Ren Tan, David Colquhoun.

Austria

Thomas Pieber, Heinz Drexel, Rudolf Prager, Christoph Schnack, Fredrich Hoppichler, Peter Fasching, Claudia Francesconi, Anton Luger, Hans-Robert Schoenherr, Christoph Ebenbichler, Bernhard Paulweber, Guntram Shernthaner.

Belgium

Ann Verhaegen, Johan Vanuytsel, Chantal Mathieu, Jean-Paul Thissen

Brazil

Pedro Barros e Silva, Renato Lopes, Carolina Gonzaga,Joao Borges, Miguel Hissa, Rosangela Rea, Paulo Rossi, Antonio Chacra, Freddy Eliaschewitz, Benito Garbelini, Joao Felicio, Nelson Rassi, Fabio Rossi, Mayler Nunes dos Santos, Francisco Bandeira e Farias, Hugo Lisboa, Adriana Costa e Forti, José Kerr Saraiva

Bulgaria

Tsvetalina Tankova, Snejina Kovacheva, Georgi Levterov, Galina Sheinkova, Elena Ilieva, Lyudmila Lyubenova, Velichka Damyanova, Valentina Gushterova, Lilyana Mincheva, Dimitar Illiev, Valentin Ivanov, Roza Bobeva, Zahari Nikitov, Rossitsa Shumkova, Ivaylp Nikolov Lefterov, Sabina Zaharieva, Vyara Videva, Andrian Yakov

Canada

Stephen Cheung, Thomas Elliott, Pravinsagar Mehta, Stuart Ross, Ronald Sigal, Vincent Woo, Shahin Jaffer, Robin Kuritsky, Alan Bell, Richard Dumas, Gilbert Gosselin, Yves Robitaille, Allen Greenspoon, Heather Lochnan, Richard Tytus, Jean-Francois Yale, Lawrence Leiter, Amritanshu Pandey. Zubin Punthakee, Bernard Zinman, Francois Dube, John Sigalas, Murray Pearce, Timothy Woodford, Partha Paul, Ronald Bourgeois, Robin Conway, Guiseppe Mazza, Ronald Hatheway, Jack Misterski

Chile

Fernando Lanas, Carlos Raffo, Claudia Olivares, Juan Godoy, Sergio Potthoff, Claudio Santibañez, Gladys Josefina Larenas Yanez

China

Wei Gu, Feixia Shen, Jianhua Ma, Xiaohui Guo, Qifu Li, Yuming Du, Ji Hu, Linong Ji, Yanbing Li, Hongyan Deng, Yingqing Feng, Ling Liu, Yiming Mu, Changsheng Ma, Shen Qu, Jiangzhong Wang, Yong Wang, Zuyi Yuan, Lihui Zhang, Shuxian Zhou, Tao Yang, Youping Dong, Dongfang Liu

Colombia

Julian Coronel Arroyo, German Perez Amador, Rodrigo Botero Lopes, Carlos Jaramilo, Miguel Urina Triana, Alejandro Orozco Linares, Carlos Alberto Cure Cure, Eric Hernandez Triana, Dora Inés Molina de Salazar, Catalina Rua Marin, Carlos Jose Jaramilo Gomez

Czech Republic

Ivana Kellinerova, Vera Adamkova, Pavel Krami, Tomas Brychta, Jana Havelkova, Katarina Pantikova

Germany

Frank Schoper, Wilgard Pohl, Petra-Maria Schumm-Draeger, Ulrich Julius, Diethelm Tschöpe, Andreas Hamann, Jochen Seissler, Sebastian Schellong, Ludger Rose, Bernd Becker, Thomas Linn, Erika-Maria Oerter, Herman Josef Strotmann, Andrea Mölle, Andreas Pfutzner, Thomas Forst,Tim Schäufele, Andreas Mugge, Michael Lehrke, Ulrich Meyer-Pannwitt, Heidrun Mehling, Ilka Simon-Wagner, Isabelle Schenkenberger, Klaus Busch, Stephan Hermes, Karsten Milek, Bernhard Landers, Martin Grueneberg, Martin Braun, Jörg Nothroff, Wolfram Kamke, Gunter Hergdt, Hans-Dirk Duengen, Klaus Kleinertz, Detlev Kuesters, Agnes-Anette Himpel Boenninghoff, Karl-Fredrich Appel, Axel Schaefer, Tasso Bieler

Hong Kong

Risa Ozaki, Andrea On Yan Luk, Daniel Wai-Sing Chu, Michelle Man-Ying Cheung-Wong, David Chung-Wah Siu, Bryan Ping Yen Yan, Kenny Kung, Samuel Yeung Shan Wong, Chiu-Chi Tsang, Vincent Tok-Fai Yeung, Bernard Man-Yeung Cheung, Hung Fat Tse

Hungary

Gabriella Hodi, Karoly Nagy, Jozsef Lippai, Jozsef Takacs, Tibor Fulop, Zsolt Gaal, Zsolt Pauker, Iren Foldesi, Judit Simon, Tamas Oroszan, Laszlo Futo, Katalin Bezzegh, Andras Nagy, Gyozo Vandorfi, Julianna Kiss, Nora Kesmarki, Erno Kis, Janos Takacs, Andras Papp, Aranka Kovacs, Imre Szakal, Attila Palinkas, Zoltan Czegany, Peter Voros, Istvan Reiber, Zsuzsanna Kerenyi, Eniko Dezso, Istvan Wittman, Janos Penzes, Zsolt Ples, Andras Taller, Katalin Farago, János Tibor Kis, Zsolt Zilahi, Marta Molnar, László Barkai, Margit Mileder, Imre Szentpeteri, Eva Peterfai, Orsolva Lovasz

Israel

Ofri Mosenzon, Oscar Minuchin, Anat Jaffe, Victor Vishlitsky, Ilan Shimon, Julio Wainstein, Amir Bashkin, Naftali Stern, Nizar Elias, Tamir Bental, Adi Butnaru, Basil Lewis, Faiad Adawi, William Nseir, Eliezer Klainman, Tommy Herskovits

Italy

Stefano Del Prato, Mauro Cignarelli, Carlo Maria Rotella, Guiseppe Ambrosio, Paolo Pozzilli, Stefano Genovese, Alessandro Cavarape, Alessandro Salvioni

Latvia

Valdis Pirags, Jelena Sokolova, Inese Strautina, Dace Teterovska, Valda Stalte, Sigita Pastare, Inta Leitane, Liga Lagzdina, Ilze Andersone, Ruta Eglite, Indra Stelmane

Lithuania

Neli Jakuboniene, Andrej Levinger, Lina Barsiene, Marijona Sulskiene, Egle Varanauskiene, Evalda Danyte, Egle Urbanaviciene, Vaidotas Urbanavicius, Lina Zabuliene, Rasa Juskiene, Audrone Velaviciene,

Vaida Kakariekiene, Audrone Augusteniene, Dzilda Velickiene, Jurate Lasiene, Dailia Dauksiene, Jonas Čeponis.

Malaysia

Alexander Tong-Boon Tan, Letchuman Ramanathan, Muhammad Radzi Abu Hassan, Florence Tan, Tiong Kiam Ong, Siew Hui Foo, Rohana Abdul Ghani, Wee Kooi Cheah

Mexico

Jose-Luis Leiva-Pons, José Hector Sanchez Mijangos, Ricardo Cabrera Jardines, Margarita Barrientos Perez, Leobardo Sauque Reyna, Marco Antonio Alcocer Gamba, Efrain Villeda Espinosa, Hector Eloy Tamez Perez, Natalia Eloisa De La Garza Hernandez, Sigfrido Miracle Lopes, Santiago Paulino Ramirez Diaz, Roxana Reyes Sanchez, Eduardo Márquez-Rodriguez.

The Netherlands

Vicdan Köse, Christine Voors-Pette, Adriaan Kooy, P.C Oldenburg-Ligtenberg, Willem Wouter van Kempen, Kevin Cox, Jacqueline Hoogendyk, Lindy Swinkels-Diepenmaat, Gloria Rojas-LinganSusanne Kentgens, Stefanie Schipperen, Harold Wessel de Valk, Henk Swart, B. van Bemmel, P.A.M Hoogslag, Michaela Diamant, E.H Serné.

New Zealand

Russell Scott, Andrew Hamer, Sam Wilson, Nicholas Fisher, Paul Dixon, Owais Chaudhri, Veronica Crawford, Dean Quinn, Kingsley Nirmalaraj, Peter Dunn, John Gillies, Rick Cutfield, Jeremy Krebs, Colin Helm, Jane Kerr, Jason Pryke, Geraldine Ebo

Philippines

Geraldine Ebo, Marian Denopol, Araceli Panelo, Ernesto Ang, Norbert Uy, Cecelia Jimeno, Roberto Mirasoi, Elizabeth Paz Pacheco, Myla Custodio, Nemencio Nicodemus Jr., Elizabeth Anne-Fernando Catindig, Marie Magno, Louie Tirador

Poland

Barbara Cylkowska, Teresa Stasinksa, Teresa Silwinska, Michal Sroka, Marek Piepiorka, Romuald Korzeniak, Piotr Dziemidok, Hanna Mirecka, Roman Zaluska, Danuta Pupek-Musialik, Wojciech Homenda, Anna Grabowska, Boguslaw Okopien, Joanna Niegowska, Hanna Pogorzelska, Anna Mikolajczyk-Swatko, Marcin Sikorski, Dariusz Sowinski

Republic of Korea

Seung Jea Tahk, Yoon-Nyun Kim, Chang-Wook Nam, Se-Joong Rim, Chong-Jin Kim, Kyung Mook Choi, Kun-Ho Yoon, In Kyu Lee, In Joo Kim, June Namgung, Keon-Woong Moon, Kee-Sik Kim, Byung-Hee Oh, Won-Young Lee, Sung-Hee Choi, Eun Sook Kim, Sungdae Moon

Romania

Ioan Andrei Veresiu, Nicoleta Mihaela Mindrescu, Gheorgita Aron, Mariana Graur, Nicolae Hancu, Constantin Mlitaru, Valerica Nafornita, Iosif Szilagyi, Amorin Remus Popa, Liliana Monica Angelescu, Gabriela Doina Negrisanu, Daniela Gabriela Zaharie, Mirela Ioana Culman, Georgeta Vacaru, Mircea Munteanu, Silviana Constantinescu, Simona Tivadar

Russia

Alexander Dreval, Olga Barbarash, Leonid Strongin, Sergey Dogadin. Lyudmila Suplotova, Nadezhda Izmozherova, Vyacheslav Marasaev, Alexander Khokhlov, Alexey Repin, Elena Turova, Irina Bondar, Yulia Samoylova, Alexander Sherenkov, Olga Smolenskaya, Konstantin Zrahevskiy, Olga Koshelskaya, Andrey Obrezan

Slovakia
Jan Murin, Andrej Dzupina, Jan Stevlik, Ingrid Buganova, Daniel Pella, Daniela Vinanska, Jaroslav Jascur, Karol Micko, Dalibor Sosovec, Adriana Philippiova, Peter Olexa, Jan Fedacko, Juraj Selecky

Spain
Joana Nicolau, Juan Mediavilla Garcia, Marta Botella Serrano, Albert Lecube, Iñaki Arguelles, José Sabán, Francisco Gómez Cerezo, Alfonso Soto, Diego Bellido, Nuria Sucunza Alfonso, Joan Vendrell Ortega, Luis Alvarez, Juan Garcia Puig, Mª Angustias Quesada, José Contreras Gilbert, Carlos Alexandre Almeida, Francisco José Tinahones, Luis Garcia Ortiz, Manuel Angel Gómez Marcos, Ismael Aomar, Mercè Fernández Balsells

South Africa
Larry Distiller, Trevenesan Padayachee, Aysha Badat, Iftikar Ebrahim, Puvanesveri Naiker, Naresh Ranjith, Ynez Kelfkens, Hemantkumar Makan, Salphy Mogashoa, Muhammed Fulat, Nazira Carim-Ganey, Mahomed Omar, Kathleen Coetzee, Thirumani Govender, Hendrik Nortje, Agatha Wilhase, Saadiya Seedat, Mashra Gani, Graham Ellis, Paul Rheeder, Jeffrey Wing, Suzanne Blignaut, Hilton Kaplan, Hanlie Lottering, Perumal Pillai, Cheryl Louw, Thomas Coetzer

Taiwan
Wayne Huey Herng Sheu, Jung-Fu Chen, Chwen-Yi Yang, Shih-Ting Tseng, Chih-Yuan Wang, Wen-Ter Lai, Yi-Jen Hung, I-Chang Hsieh, Shih-Li Su, Dee Pei

Thailand
Piyamitr Sritara, Yupin Benjasuratwong

United Kingdom
Naveed Sattar, Tejpal Purewal, Anne Milward, Ioannis Dimitropoulos, Sudhesh Kumar, Thomas Barber, Philip Wiles, Chong Dang, Amanda Adler, Sam Philip, Srikanth Bellary, David Price, Ray Oelbaum, Simon Heller, Thozhukat Sathayapalan, John Clark, Graham Leese, Hamish Simpson, Anne Kilvert, Alison Dawson, Timothy Hall, Amrit Takhar, Charles Bundy, Peter Harvey, Sarah Maxwell, N.Jaimeh Asamoah-Owusu, John McKnight, Sudesna Chatterjee, John Calvert, Anthony Wright, Sandra Macrury, David MacFarlane, Andrew Johnson, Jennifer Litchfield, Benjamin Field

Ukraine
Olena Koval, Oleksandr Larin, Olena Levchenko, Lilya Martynyuk, Vitaliy Maslyanko, Iurii Rudyk, Yevgen Suprun, Vira Tseluyko, Volodymyr Botsyurko, Mykola Vatutin, Ivan Fushtey, Olena Grishyna, Petro Kuskalo, Svitlana Panina, Larys Pererva, Liudmyla Prysupa, Zinaida Teliatnikova, Lyubov Sokolova, Maryna Vlasenko, Vadym Berenfus, Olexander Parkhomenko, Olga Gyrina, Mykola Kopytsya, Vadym Vizir, Myroslava Vayda

USA
Michael Shanik, Dana Headapohl, Jorg Pahl, Stephen Aronoff, Anthony Bartkowiak Jr., Anna Chang, Linda Gaudiani, David Kayne, Michelle Look, Naynesh Patel, Joseph Moran, Elmer Stout, John Tsao, Russell Struble, Norman Fishman, Helena Rodbard, Kathryn Lucas, Pamela Dugano-Daphnis, Bryan Merrick, Venkatesh Nadar, Larry Severa, Chris Sorli, Mark Chang, John Reed III, George Grunberger, Catherine Bain, William Bestermann Jr., Emily Morawski, Judith White, Masoud Azizad, Philomena Ukwade, Adolphus Anekwe, Arthur Jimenez, Daniel Weiss, Sinikka Green, Jeffrey Overcash, Charles Eaton, Hal Roseman, Norman Soler, Frank Mikell, Paul Manos, Lawrence Levinson, Edmund Claxton Jr., Robert Weiss, Georges Argoud, Lauren Bickel, Jonathan Wilson, Brian Short, Brian Webster, Robert McNeill, Adrian Schnall, Rex Force, Lawrence Phillips, Kevin Bybee, Alan Forker, Steven Marso, Douglas Denham,

Thomas VonderHaar, John Pullman, Davida Kruger, Fred Whitehouse, Carol Wysham, Mira Baron, Alan Kravitz, Holly Dushkin, Mary Beth Manning, Alan Wine, Naseem Jaffrani, Chhavi Chadha, JoAnn Sperl-Hillen, Robert Busch, Roger Estevez, David Robbins, Negah Rassouli, Tim Garvey, Suzanne Oparil, Robert Eckel, Michael McDermott, Neda Rasouli, Janet McGill, Clinton Corder, David Klonoff, Richard Mills, John Earl, John Kessel, Richard Bergenstal, Robert Cuddihy, Robert Zimmerman, Priya Dayamani, Anne Chang, Elif Oral, Mark Zimering, Jennifer Marks, Kent Farnsworth, Danny Sugimoto, Philip Toth, Anuj Bhargava, Darren McGuire, Anand Rohatgi, Mark Davies, Eric Peden, Kathleen Wyne, Luis Alfonso, Berhane Seyoum, Basil Akpunonu, Mark Feinglos, Peter Reaven, Jeremy Soule, Louis Luttrell, Brian Schactman, Rafael Canadas, Bruce Boggs, Lisa Abbott, Charles Herring, Lon Roberts, Elie Hage-Korban, Ulrich Schubart, Alain Taylon, Alan Tannenbaum, Jeffrey Kingsley, James Lenhard, Mihaela Biscoveanu, Joshua Cohen, Daniel Donovan, Blandine Laferrere, Novelette Thompson, Thomas Wade, Robert Detweiler, Bruce Henson, Anthony White, Arvind Cavale, Chaitanya Ravi, Asha Thomas, Herbert Goodman, Vicki Kalen, Donald Fox, Ira Dauber, Syed Rizvi, Alan Marcus, Mim Mulford, Alexander Higgins, Majed Chane, Veita Bland, Abayomi Osunkoya, Damodhar Suresh, Salman Khan, Lawrence Anastasi, Mandeep Bajaj, Howard Eisen, Sunder Raj Mudaliar, Stephanie Powell, Kenneth Carr, Devjit Tripathy, Nasrin Azad, Paul Wakefield, Roger Acheatel, Peter Bressler, Julius Dean, Mahfouz El Shahawy, John Gilbert, Ihsan Haque, Daniel Humiston, Rodney Ison, Dennis Karounos, Michael Lillestol. Norman Ferrier, Ajay Labroo, Anthony Vo, Ronald D'Agostino, Michael Dulin, Andrew McWilliams, Joseph Hargrove, Edwin Blumberg, Bruce Jackson, Cezar Staniloae, Abraham Salacata, Horacio Hidalgo Jr., Philip Nicol, Michael DiGiovanna, Joseph Soufer, Vahid Mahabadi, Olakunle Akinboboye, Carlos Arauz-Pacheco, Joel Neutel, Kathleen Dungan, Mark Benson, Talessa Powell, Winston Gandy, Sergio Rovner, Martin Berk, Asma Khan, Gilbert Ledesma, Ivy Madu, Bernard Erickson, Mark Radbill, Mark Graves, Gregory Kaczmarek, Son Giep, Caryn Baldauf, Gordon Golden, Kurt Lesh, Cedrice Davis, Narendra Godbole, William Kirby, Naveed Razzaque, Bankim Bhatt

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/m^2)	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 ($mL/min/1.73m^2$)	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	**Placebo**
	N=7356	**N=7396**
MACE endpoint		
Number censored	6517 (88.6%)	6491 (87.8%)
Median (25^{th}, 75^{th}) 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 (25^{th}, 75^{th}) 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.

	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 Model[1]	Yang X, *et al*[2]	Wells BJ, *et al*[3]	TRIAD[4]	UKPDS Model[5]
Population	Trial	Italian Cohort	Hong Kong	Cleveland Clinic	US Centers	United Kingdom
Sample size	14,752	Derivation: 679 Validation: 936	7,583	33,067	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 fibrillation; 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.

Supplemental References:

1. De Cosmo S, Copetti M, Lamacchia O, Fontana A, Massa M, Morini E, Pacilli A, Fariello S, Palena A, Rauseo A, Viti R, Di Paola R, Menzaghi C, Cignarelli M, Pellegrini F, Trischitta V. Development and validation of a predicting model of all-cause mortality in patients with type 2 diabetes. *Diabetes Care*. 2013;36:2830-2835.

2. Yang X, So WY, Tong PC, Ma RC, Kong AP, Lam CW, Ho CS, Cockram CS, Ko GT, Chow CC, Wong VC, Chan JC. Development and validation of an all-cause mortality risk score in type 2 diabetes. *Arch Intern Med*. 2008;168:451-457.

3. Wells BJ, Jain A, Arrigain S, Yu C, Rosenkrans WA Jr, Kattan MW. Predicting 6-year mortality risk in patients with type 2 diabetes. *Diabetes Care*. 2008;31:2301-2306.

4. McEwen LN, Karter AJ, Waitzfelder BE, Crosson JC, Marrero DG, Mangione CM, Herman WH. Predictors of mortality over 8 years in type 2 diabetic patients: Translating Research Into Action for Diabetes (TRIAD). *Diabetes Care*. 2012;35:1301-1309.

5. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia*. 2013;56:1925-1933.