Effect of race on cardiometabolic responses to once-weekly exenatide: insights from the Exenatide Study of Cardiovascular Event Lowering (EXSCEL)

Timothy M. E. Davis¹*, Anna Giczewska², Yuliya Lokhnygina², Robert J. Mentz², Naveed Sattar³, Rury R. Holman⁴ and for the EXSCEL Study Group

Abstract

Background: To determine whether there were racial differences in short-term cardiometabolic responses to once-weekly exenatide (EQW) in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL).

Methods: EXSCEL enrolled 14,752 patients with type 2 diabetes (hemoglobin A1c (HbA1c) 6.5–10.0% [48–86 mmol/mol]) with or without cardiovascular disease who were randomized double-blind to EQW or placebo. Background glucose-lowering/other cardiovascular therapies were unaltered for 6 months post-randomization unless clinically essential, facilitating comparison of EQW-associated effects in 14,665 evaluable participants self-identifying as White (n = 11,113), Asian (n = 1444), Black (n = 870), or Other Race (n = 1,238). Placebo-adjusted 6 month absolute changes in cardiometabolic variables were assessed using generalized linear models.

Results: Mean 6-month placebo-adjusted HbA1c reductions were similar in the four groups (range 0.54–0.67% [5.9 to 7.3 mmol/mol], P = 0.11 for race x treatment interaction), with no significant difference in Asians (reference) versus other groups after covariate adjustment (all P ≥ 0.10). Six-month placebo-adjusted mean changes in systolic (−1.8 to 0.0 mmHg) and diastolic (0.2 to 1.2 mmHg) blood pressure, serum LDL (−0.06 to 0.02 mmol/L) and HDL (0.00 to 0.01 mmol/L) cholesterol, and serum triglycerides (−0.0 to 0.0 mmol/L) were similar in the racial groups (P ≥ 0.19 for race x treatment interaction and all P ≥ 0.13 for comparisons of Asians with other races). Resting pulse rate increased more in Asians (4 beats/min) than in other groups (≤ 3 beats/min, P = 0.016 for race x treatment interaction and all P ≤ 0.050 for comparisons of Asians with other races).

Conclusions: Short-term cardiometabolic responses to EQW were similar in the main racial groups in EXSCEL, apart from a greater pulse rate increase in Asians.

Trial registration: https://clinicaltrials.gov NCT01144338.

Keywords: Exenatide once weekly, Cardiovascular risk factors, Racial differences

Background

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become established as blood glucose-lowering therapies that should be considered in people with type 2 diabetes if glycemic targets are not met with lifestyle measures and metformin [1], especially in those with, or
at high risk of, cardiovascular disease (CVD) [2]. There is some evidence, based on an initial meta-analysis of three Phase IV cardiovascular outcome trials [3], and further supported by a more recent narrative review [4] and an expanded meta-analysis of seven trials [5], that Asians with type 2 diabetes may have fewer major adverse cardiovascular events (MACE; nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) when treated with GLP-1 RAs than other racial groups. It has been proposed that one of the possible underlying mechanisms for this difference could be a greater improvement in cardiometabolic risk factors resulting from GLP-1 RA therapy in Asian participants [3].

There is, however, inconsistent support for this hypothesis. A systematic review and meta-analysis found that, although there is no evidence of race-specific differences in the pharmacokinetic properties of GLP-1 RAs, the hemoglobin A1c (HbA1c) reduction in Asian-dominant studies (those with ≥ 50% Asian participants) was 0.32% (3 mmol/mol) greater than in non-Asian-dominant studies [6]. Subsequent analyses of pooled individual patient data from phase 3 studies have suggested that twice-daily exenatide has greater glycemic efficacy in Asians with type 2 diabetes than other races [7–9], but that there is no such racial difference in the case of once-weekly exenatide (EQW) [8–10]. Race-specific responses of other CVD risk factors, including blood pressure and serum lipids, to exenatide therapy were also assessed in three of these studies, but no formal statistical comparisons were performed [7, 9, 10].

Since available data relating to the glycemic and non-glycemic CVD risk factor response to GLP-1 RA therapy have come largely from people with type 2 diabetes without CVD or at low CVD risk who have participated in Phase III studies, we examined EQW-related changes in cardiometabolic risk factors in participants in the large-scale Phase IV Exenatide Study of Cardiovascular Event Lowering (EXSCEL) [11], with particular reference to those who were Asian.

Methods
Study participants and design
EXSCEL was a double-blind, placebo-controlled cardiovascular outcome trial that randomized 14,752 patients with type 2 diabetes, with or without previous cardiovascular disease, to the addition of EQW or placebo to usual care. It showed that EQW was noninferior to placebo when added to usual care for type 2 diabetes with respect to the primary 3-point MACE composite endpoint [11]. Adults aged ≥ 18 years with type 2 diabetes were eligible if their usual care HbA1c was 6.5–10.0% (48 to 86 mmol/mol) inclusive. The EXSCEL protocol specified that ~ 70% of enrolled patients should have previous cardiovascular disease. The trial was run jointly by the Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit in an academically independent collaboration with the sponsor, Amylin Pharmaceuticals (a wholly owned subsidiary of AstraZeneca) [11].

Participants could be enrolled if treated with a maximum of three oral blood glucose-lowering drugs, or insulin alone or in combination with up to two oral blood glucose-lowering drugs [12]. As part of baseline assessment, participants were asked to self-identify their racial background as Indian (American) or Alaska Native, Asian, Black, Native Hawaiian or Other Pacific Islander, White, Hispanic, or Other [12, 13].

EXSCEL participants were allocated at random in a 1:1 ratio to receive subcutaneous EQW (Bydureon) 2 mg or matching placebo [12]. Other diabetes therapy (addition or substitution of any blood glucose-lowering therapies, including insulin, but excluding GLP-1 RAs) was adjusted by usual care providers according to local management guidelines. Usual care providers were asked to avoid such changes soon after randomization while HbA1c levels were reflecting the initial effect of allocated study medication. Treatment of non-glycemic cardiovascular risk factors was also left to usual care providers with no post-randomization limitations [12].

In this post hoc analysis, we aimed to determine whether patients who self-identified as Asian had greater initial reductions in HbA1c and blood pressure, pulse rate, and/or improvements in serum lipid profiles, compared with other racial groups in EXSCEL. CVD risk factors were first reassessed 6 months after baseline when the mean HbA1c difference between the active and placebo groups was maximal because of the initial requirement to keep non-trial blood glucose-lowering therapies stable during this period. This was also the case for other CVD risk factors [11], reflecting the small number of participants in whom adjustments in cardiovascular therapy were made during this period.

Statistical analysis
Baseline characteristics included demographics, diabetes duration, baseline medications, and medical history. Continuous variables are presented as median and interquartile range (25th, 75th percentiles) and discrete variables as percentages. Fully conditional regression was used to impute missing follow-up and baseline values. Patients with missing racial identification (N = 5) and those who died before 6 months (N = 82) were not included in analysis. Placebo-adjusted mean absolute changes (mean changes for EQW minus mean change for placebo group) from baseline to 6 months were assessed using generalized linear models with covariates for randomized treatment, race, and race × treatment interaction, adjusted for
the baseline value of the outcome variable and clinically plausible confounders including body weight, height, age, statin therapy, beta-blocker therapy, thiazide therapy, use of other open-label glucose-lowering therapies, and smoking status. Models involving blood pressure and pulse rate were further adjusted for a history of heart failure. Mean placebo-adjusted changes and 95% confidence intervals (CI) are shown. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). P-values < 0.05 were considered statistically significant.

Results
Baseline patient characteristics by racial group
Table 1 summarizes the baseline characteristics of the 14,665 evaluable participants (excluding 5 patients with unspecified race and 82 who died before 6 months), categorized by self-identified race. Because of the small numbers in some groups, four race categories were used—White (N = 11,113; 75.8%), Asian (N = 1444, 9.8%), Black (N = 870; 5.9%), with American Indian, Alaska Native, Native Hawaiian or Other Pacific Islander, Hispanic, and remaining racial groups amalgamated into an Other Race category (N = 1,38; 8.4%). Asian participants comprised the second largest group after White participants. Compared with the other racial groups, Asians tended to be younger, shorter, and to have a lower BMI. They were also more likely to be treated with a sulfonylurea/other insulin secretagogue or an alpha-glucosidase inhibitor, and they were less likely to have a diagnosis of congestive cardiac failure, to be taking diuretics or ACE inhibitors/angiotensin receptor blockers. They had the lowest median systolic blood pressure along with Other Race, but the highest resting pulse rate. Their serum triglyceride concentrations were comparatively low, but their HbA1c levels and other lipid parameters were similar to those in the other racial groups.

Short-term cardiometabolic response to EQW
There were small reductions in use of individual classes of blood glucose-lowering medications and non-glycemic cardiovascular risk reducing therapies over the first 6 months of follow-up that were similar across the racial groups (see Table 2).

The 6-month, placebo-adjusted, absolute mean HbA1c change showed no statistically significant treatment effect differences between the four racial groups (P = 0.10, Table 3). Mean HbA1c reductions ranged from 5.9 mmol/mol (0.5%) in the White group to 7.3 mmol/mol (0.8%) in the Other Race group. There were similarly no race-specific statistically significant differences in changes in systolic or diastolic blood pressure (P ≥ 0.47, Table 3). The 95% CI for the reduction in systolic blood pressure did not include zero for the White, Asian, and Other Race groups, indicating the presence of a treatment effect, but there was no placebo-adjusted reduction in Black participants. There was a consistent mean pulse rate increase of between 2 and 4 beats/min between baseline and 6 months in response to EQW across all racial groups, with the Asians having a significantly greater rise than the other three groups (interaction P = 0.016, Table 3). There were no significant EQW effects on serum LDL cholesterol, HDL cholesterol, or serum triglycerides regardless of racial group. Mean reductions in serum LDL cholesterol and serum triglycerides were most pronounced in the White group with the respective 95% CIs not including zero.

There were similar findings in placebo-adjusted models without further adjustment for confounding variables (see Additional file 1: Table S1), and when absolute changes were analyzed by allocated treatment with and without adjustment for covariates (see Additional file 1: Tables S2 and S3).

Discussion
These EXSCEL data show that Asians with type 2 diabetes had similar 6-month placebo-subtracted glycemic, blood pressure and serum lipid EQW responses as the other three racial groups studied. Our findings, therefore, confirm that EQW can be used as treatment for type 2 diabetes without regard to race, but call into question the suggestion of a race-specific cardiometabolic contribution to the lower incidence of MACE in Asian participants, as suggested by the meta-analysis of data from GLP-1 RA cardiovascular outcome trials including Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER], Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [SUSTAIN-6], and EXSCEL [3, 5]. The rise in pulse rate with EQW therapy was greater among Asians than the other racial groups which might increase their risk of CVD [14], but it might also be a surrogate for greater unmeasured GLP-1 RA responses with CVD benefits in Asians such as anti-inflammatory and antioxidant effects [15].

GLP-1 RAs can be classified as either short-acting with a half-life of a few hours or long-acting with a half-life ≥ 12 h [16]. Long-acting GLP-1 RAs, such as liraglutide, semaglutide, and EQW, are associated with less prandial glucose-lowering efficacy than short-acting compounds such as twice-daily exenatide and once-daily lixisenatide, but they have greater effects on insulin secretion and thus post-absorptive blood glucose concentrations [17]. This distinction was not considered in the meta-analysis, which suggested more potent blood glucose lowering with exenatide in Asians versus non-Asians.
## Table 1  Baseline characteristics of the trial participants categorized by racial group

|                          | Overall (N = 14,665) | White (N = 11,113) | Asian (N = 1444) | Other Race (N = 1238) | Black (N = 870) |
|--------------------------|-----------------------|--------------------|------------------|-----------------------|-----------------|
| Age at randomization (years) | 62 (56, 68)          | 63 (57, 69)        | 60 (54, 66)      | 61 (55, 68)          | 60 (53, 66)     |
| Male                     | 62.0%                 | 63.8%              | 62.3%            | 54.9%                 | 47.6%           |
| Region                   |                       |                    |                  |                       |                 |
| Europe                   | 46.0%                 | 58.9%              | 7.8%             | 1.6%                  | 8.4%            |
| North America            | 25.1%                 | 25.1%              | 8.3%             | 28.6%                 | 49.1%           |
| Latin America            | 18.4%                 | 13.3%              | 0.5%             | 68.5%                 | 42.4%           |
| Asia Pacific             | 10.4%                 | 2.7%               | 83.4%            | 1.3%                  | 0.1%            |
| Diabetes duration (years) | 12 (7, 18)            | 12 (7, 18)         | 11 (7, 18)       | 13 (7, 19)            | 11 (6, 17)      |
| Diabetes therapy (alone/in combination) |                    |                    |                  |                       |                 |
| Metformin                | 76.7%                 | 76.5%              | 76.5%            | 80.5%                 | 73.9%           |
| Sulfonylurea/other secretagogue | 37.9%              | 37.0%              | 44.0%            | 35.5%                 | 43.1%           |
| Alpha-glucosidase inhibitor | 2.0%               | 1.1%               | 11.1%            | 0.7%                  | 0.6%            |
| Thiazolidinedione        | 3.9%                  | 3.8%               | 5.1%             | 3.4%                  | 5.3%            |
| Incretin-based therapies | 15.0%                 | 15.9%              | 17.7%            | 8.6%                  | 7.7%            |
| Insulin                  | 46.2%                 | 46.1%              | 47.5%            | 48.7%                 | 42.1%           |
| Smoking status           |                       |                    |                  |                       |                 |
| Never/former             | 88.3%                 | 88.3%              | 86.6%            | 92.3%                 | 86.6%           |
| Current                  | 11.7%                 | 11.7%              | 13.4%            | 7.7%                  | 13.4%           |
| Prior cardiovascular disease | 73.3%              | 73.0%              | 77.4%            | 72.2%                 | 71.7%           |
| Prior coronary artery disease | 52.7%              | 53.5%              | 58.8%            | 50.5%                 | 36.6%           |
| Prior cerebrovascular disease | 17.0%              | 17.4%              | 20.2%            | 12.0%                 | 13.1%           |
| Prior peripheral arterial disease | 18.9%              | 18.8%              | 19.9%            | 19.0%                 | 12.9%           |
| Prior congestive heart failure | 16.1%              | 18.8%              | 5.4%             | 8.6%                  | 9.3%            |
| Cardiovascular medications |                     |                    |                  |                       |                 |
| Statins                  | 73.5%                 | 74.9%              | 74.7%            | 66.2%                 | 63.9%           |
| ACE inhibitors/angiotensin receptor blockers | 77.3%              | 79.3%              | 67.1%            | 74.6%                 | 71.7%           |
| Diuretics                | 43.6%                 | 47.2%              | 19.9%            | 34.4%                 | 49.9%           |
| Calcium channel blockers | 32.0%                 | 31.7%              | 39.0%            | 25.0%                 | 33.3%           |
| Beta blockers            | 55.7%                 | 58.8%              | 48.0%            | 45.2%                 | 43.4%           |
| Aspirin                  | 63.6%                 | 63.9%              | 61.4%            | 68.6%                 | 55.9%           |
| Other platelet function antagonists | 3.8%               | 3.4%               | 7.3%             | 3.4%                  | 3.2%            |
| Height (cm)              | 168 (160, 175)        | 170 (162, 176)     | 164 (157, 170)   | 163 (155, 170)        | 165 (157, 173)  |
| Weight (kg)              | 90 (77, 103)          | 94 (82, 108)       | 71 (62, 81)      | 80 (69, 93)           | 88 (75, 103)    |
| Body mass index (kg/m²) | 31.8 (28.2, 36.2)     | 32.6 (29.2, 36.9)  | 26.7 (24.2, 29.7) | 30.3 (27.0, 34.2)    | 31.9 (28.5, 36.7) |
| Pulse rate (beats/min)   | 72 (66, 80)           | 72 (66, 80)        | 74 (70, 84)      | 72 (65, 79)           | 72 (65, 80)     |
| Systolic blood pressure (mmHg) | 135 (124, 145)       | 135 (125, 146)     | 130 (120, 142)   | 130 (120, 142)        | 136 (125, 149)  |
| Diastolic blood pressure (mmHg) | 80 (70, 85)           | 80 (70, 85)        | 78 (70, 84)      | 79 (70, 84)           | 80 (73, 86)     |
| Qualifying HbA1c (mmol/mol) | 64 (56, 74)          | 63 (56, 73)        | 65 (57, 74)      | 65 (57, 76)           | 65 (56, 75)     |
| Qualifying HbA1c (%)      | 8.0 (7.3, 8.9)        | 7.9 (7.3, 8.8)     | 8.1 (7.4, 8.9)   | 8.1 (7.4, 9.1)        | 8.1 (7.3, 9.0)  |
| eGFR (mL/min/1.73 m²)    | 75 (61, 90)           | 74 (60, 89)        | 76 (60, 94)      | 75 (61, 92)           | 83 (67, 99)     |
| Urine albumin/creatinine ratio (mg/mmol) | 1.6 (0.5, 5.7)       | 1.5 (0.5, 5.1)     | 2.1 (0.5, 10.1)  | 1.9 (0.4, 7.8)        | 2.5 (0.5, 10.2) |
| Serum LDL cholesterol     | 2.3 (1.7, 3.0)        | 2.2 (1.7, 3.0)     | 2.2 (1.7, 2.9)   | 2.3 (1.7, 2.9)        | 2.5 (2.0, 3.3)  |
| Serum HDL cholesterol     | 1.09 (0.91, 1.29)     | 1.09 (0.90, 1.29)  | 1.09 (0.90, 1.27) | 1.06 (0.91, 1.24)    | 1.16 (0.98, 1.35) |
| Serum triglycerides       | 1.8 (1.3, 2.6)        | 1.8 (1.3, 2.6)     | 1.6 (1.2, 2.3)   | 1.9 (1.3, 2.7)        | 1.5 (1.1, 2.3)  |

Data are percentage or median (interquartile range)
with type 2 diabetes [6]. However, subsequent analyses of pooled patient-level exenatide data from phase 3 studies have indicated that this benefit is seen with twice-daily but not once-weekly administration [7–10], consistent with the present EXSCEL Phase IV data.

The only other relevant meta-analysis compared three studies in Asians (two with once-daily lixisenatide and one with once-daily liraglutide) to 20 involving White participants treated with GLP-1 RAs ranging from once-daily lixisenatide to weekly semaglutide [18]. Although there was no difference between the two racial groups in HbA1c reduction [18], the analysis did not distinguish between short- and long-acting GLP-1 RAs. In addition, the fact that once daily use of the short-acting lixisenatide means that there is minimal or no drug exposure for most of the period between doses [19] may have attenuated a racial difference, since 82% of the Asians versus 21% of Whites treated with GLP-1 RAs in the analysis were allocated this type of GLP-1 RA therapy [18].

The greater glycemic response of Asians to twice-daily exenatide, compared with EQW, may relate to dietary factors. Compared with Europeans, Asians typically consume more carbohydrates that have a higher glycemic index and which may also lead to a greater subsequent rise in blood glucose [20–22]. This may mean that their response to short-acting GLP-1 RAs with greater postprandial efficacy is also more prominent in type 2 diabetes. An analogous situation is the greater glycemic response of racial groups that have a relatively high carbohydrate intake, including East Asians, to sitagliptin in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in type 2 diabetes [23], albeit to endogenous incretins rather than GLP-1 RA pharmacotherapy.

There were 2-mmHg mean reductions in systolic blood pressure in racial groups in our study, with the exception of the Black group. This pattern has been reported previously for EQW in smaller groups of participants in Phase III studies, most of which were of similar duration to the present study 6-month follow-up [10]. Mean changes in Phase III studies were approximately 3 mmHg greater in White and Asian racial groups than in those observed in our study [9, 10], and there were also significant reductions in diastolic blood pressure which were not evident in EXSCEL participants. We interpret these differences as reflecting greater use of antihypertensive therapies in our Phase IV study participants with, or at high risk of, CVD, the majority of whom were taking combination blood pressure-lowering therapy at baseline.

As is typical of long-acting GLP-1 RA therapy [24], there were 2–4 beats/min increases in mean pulse rate during the first 6 months of EQW therapy in EXSCEL. The increase was greatest in Asian participants, who also started from a 2 beats/min higher baseline. There is some evidence from general population studies that Asians have a higher resting pulse rate [25], which could reflect a reduced vagal contribution to sympathovagal balance [26] and/or increased sympathetic modulation [27], and perhaps even lower physical activity levels. The former neurohormonal mechanisms have been suggested as causes of the increase in heart rate associated with GLP-1 RAs [28, 29], and it is possible that they mediate the increased pulse rate both before and during EQW therapy in Asians. This aspect of CVD risk has not

### Table 2 Medication use of the trial participants at 6 months of follow-up categorized by racial group

|                        | Overall N = 14,665 | White N = 11,113 | Asian N = 1444 | Other races N = 1238 | Black N = 870 |
|------------------------|-------------------|-----------------|----------------|----------------------|--------------|
| **Diabetes therapy**   |                   |                 |                |                      |              |
| Metformin              | 72.7%             | 73.0%           | 70.8%          | 74.6%                | 70.3%        |
| Sulfonylurea/other secretagogue | 34.9%             | 34.5%           | 40.0%          | 31.4%                | 37.6%        |
| Alpha-glucosidase inhibitors | 1.8%             | 1.0%            | 9.7%           | 0.7%                 | 0.2%         |
| Thiazolidinedione       | 3.6%              | 3.4%            | 4.8%           | 3.0%                 | 4.4%         |
| Incretin-based therapies| 14.0%             | 14.8%           | 16.1%          | 8.9%                 | 8.3%         |
| Insulin                | 45.0%             | 45.1%           | 44.7%          | 46.5%                | 41.6%        |
| **Cardiovascular medications** |             |                 |                |                      |              |
| Statins                | 68.6%             | 69.9%           | 69.9%          | 60.7%                | 61.4%        |
| ACE inhibitors or angiotensin receptor blockers | 74.3%             | 76.4%           | 64.1%          | 70.0%                | 71.1%        |
| Diuretics              | 42.3%             | 45.6%           | 20.8%          | 33.5%                | 48.4%        |
| Calcium channel blockers | 30.7%             | 30.3%           | 36.4%          | 24.7%                | 34.5%        |
| Beta blockers          | 53.2%             | 56.1%           | 45.6%          | 43.9%                | 42.2%        |
| Aspirin                | 61.2%             | 61.6%           | 57.2%          | 65.0%                | 58.0%        |
| Other anti-platelet function antagonists | 3.3%              | 2.9%            | 5.6%           | 3.2%                 | 4.4%         |
been examined in the analyses of pooled Phase III data [9, 10], but one study of South Asians with type 2 diabetes treated with liraglutide also suggested an exaggerated pulse rate response to daily liraglutide in this racial group [30].

Although a relatively greater increase in pulse rate resulting from GLP-1 RA treatment would be expected to contribute to an increased CVD risk in Asians versus other racial groups [14], it may also parallel more clinically important enhanced unmeasured responses to GLP-1 RAs that have overriding CVD benefits. There is increasing evidence that GLP-1 may modify CVD risk through direct and indirect actions independent of conventional risk factor changes, including anti-inflammatory and antioxidant activity [15]. It is possible that the greater pulse rate response to EQW in the present study in Asians compared with other racial groups was a surrogate for such larger pleiotropic effects. The limited mediation analyses exploring mechanisms underlying the CVD benefits of GLP-1 RAs performed to date do not appear to have included pulse rate as a candidate variable [31], but this may warrant further consideration.

We found no statistically significant 6-month changes in serum lipid parameters between racial groups in this analysis. Paralleling blood pressure changes, available Phase III data suggest that EQW is associated

### Table 3
Placebo-adjusted mean (95% confidence interval) changes in cardiometabolic variables from baseline to 6 months by racial group (adjusted models)

| Cardiometabolic variable | Racial group | Mean change (95% CI) | Racial difference $P$-value vs. Asians | Overall race × treatment interaction $P$-value |
|--------------------------|--------------|----------------------|----------------------------------------|---------------------------------------------|
| HbA1c (%)                | Black        | −0.63 (−0.77, −0.46) | 0.82                                   | 0.10                                        |
|                          | Other Race   | −0.66 (−0.79, −0.54) | 0.80                                   |                                             |
|                          | White        | −0.54 (−0.58, −0.49) | 0.10                                   |                                             |
|                          | Asian        | −0.63 (−0.75, −0.53) |                                        |                                             |
| HbA1c (mmol/mol)         | Black        | −6.8 (−8.5, −5.1)    | 0.82                                   | 0.10                                        |
|                          | Other Race   | −7.3 (−8.7, −5.9)    | 0.80                                   |                                             |
|                          | White        | −5.9 (−6.4, −5.4)    | 0.10                                   |                                             |
|                          | Asian        | −7.0 (−8.3, −5.8)    |                                        |                                             |
| Systolic blood pressure (mmHg) | Black | 0.0 (−2.0, 2.0)    | 0.19                                   | 0.47                                        |
|                          | Other Race   | −1.8 (−3.5, −0.2)    | 0.87                                   |                                             |
|                          | White        | −1.6 (−2.1, −1.0)    | 0.96                                   |                                             |
|                          | Asian        | −1.6 (−3.2, −0.1)    |                                        |                                             |
| Diastolic blood pressure (mmHg) | Black | 1.2 (−0.1, 2.4)    | 0.19                                   | 0.52                                        |
|                          | Other Race   | 0.7 (−0.3, 1.7)      | 0.50                                   |                                             |
|                          | White        | 0.4 (0.1, 0.7)       | 0.73                                   |                                             |
|                          | Asian        | 0.2 (−0.7, 1.2)      |                                        |                                             |
| Pulse rate (beats/min)   | Black        | 2.1 (0.9, 3.3)       | 0.006                                  | 0.016                                       |
|                          | Other Race   | 2.8 (1.8, 3.8)       | 0.048                                  |                                             |
|                          | White        | 2.7 (2.4, 3.1)       | 0.003                                  |                                             |
|                          | Asian        | 4.2 (3.3, 5.1)       |                                        |                                             |
| Serum LDL cholesterol (mmol/L) | Black | 0.02 (−0.08, 0.13)  | 0.27                                   | 0.58                                        |
|                          | Other Race   | −0.05 (−0.13, 0.04)  | 0.89                                   |                                             |
|                          | White        | −0.06 (−0.09, −0.03) | 0.94                                   |                                             |
|                          | Asian        | −0.05 (−0.13, 0.03)  |                                        |                                             |
| Serum HDL cholesterol (mmol/L) | Black | 0.00 (−0.03, 0.04)  | 0.65                                   | 0.83                                        |
|                          | Other Race   | 0.01 (−0.02, 0.03)   | 0.66                                   |                                             |
|                          | White        | 0.00 (−0.01, 0.01)   | 0.36                                   |                                             |
|                          | Asian        | 0.01 (−0.01, 0.04)   |                                        |                                             |
| Serum triglycerides (mmol/L) | Black | 0.0 (−0.2, 0.2)     | 0.92                                   | 0.19                                        |
|                          | Other Race   | 0.0 (−0.1, 0.2)      | 0.99                                   |                                             |
|                          | White        | −0.1 (−0.2, −0.1)    | 0.13                                   |                                             |
|                          | Asian        | 0.0 (−0.1, 0.2)      |                                        |                                             |
with significant ~0.1 mmol/L reductions in serum LDL cholesterol and triglycerides which are independent of race, including for Asians and Whites [9, 10]. Since almost three-quarters of our participants were treated with a statin at EXSCEL entry, we infer that relatively intensive lipid-modifying therapy in our Phase IV participants masked the modest changes seen in Phase III studies. 

There was no evidence of any statistically significant difference in the effect of EQW on the primary MACE endpoint by racial group in EXSCEL [11]. However, in the meta-analyses of LEADER, SUSTAIN-6, and EXSCEL (all involving long-acting analogues), there was a statistically significantly greater CVD benefit of GLP-1 RA therapy in Asians versus Whites (relative risks [95% CI] vs. placebo of 0.35 [0.09, 1.32] and 0.92 [0.73, 1.08], respectively [3], and 0.68 [0.53, 0.84] and 0.87 [0.81, 0.94], respectively [5]). Given the wide confidence intervals and post hoc nature of these meta-analyses, this finding should be considered only hypothesis-generating. Aggregate data were utilized, but patient-level data could improve the power and consistency of analyses through better characterization of subgroups [32]. In addition, some potentially confounding variables were not considered. For example, we incorporated smoking in our adjusted models since smoking rates are relatively high in Asian populations [33]. Although smoking is an independent risk factor for CVD [34], and of relevance to treatments such as exenatide as nicotine increases blood glucose levels in a GLP-1-dependent manner [35], it was not considered in the meta-analysis [3].

Our post hoc analyses have limitations. Baseline differences between racial groups in background blood glucose-lowering therapies may have influenced EQW responses during the first 6 months of the study. However, we are not aware of any clinically important relevant interactions. Despite the request for usual care providers to delay therapeutic initial intensification, there may have been small racial differences in changes in lifestyle and pharmacotherapy post-randomization that influenced group-specific cardiometabolic responses leading up to the 6-month follow-up visit. The grouping of participants may have masked important racial and ethnic differences present within the broad regional assignments we used. In the case of Asian participants, who are from an area that covers more than half of the world's population, we were not able to distinguish between East and South Asians, who are known to have different CVD risks [36].

The strengths of the study are its relatively large number of participants, even relative to previously published meta-analyses, and the incorporation of people with type 2 diabetes at a later stage of their disease compared with participants in Phase III studies from which currently available race-specific comparisons have been made.

Conclusions

This post hoc analysis of EXSCEL data shows that Asians with type 2 diabetes and CVD or at high cardiometabolic risk have similar glycemic, blood pressure, and serum lipid responses to EQW as other racial groups, including the majority White participants, with the exception of a greater increase in resting pulse rate in Asians. Although it has been suggested in recent meta-analyses that Asians may have greater cardiovascular benefit than White people with type 2 diabetes from long-acting GLP-1 RA therapy [3, 5], the present data do not support race-specific differences in key CVD risk factors as an underlying mechanism. Nevertheless, the cause of race-specific differences in pulse rate and their clinical implications merits further study.

**Abbreviations**

CI: Confidence intervals; CVD: Cardiovascular disease; EQW: Once-weekly exenatide; EXSCEL: Exenatide Study of Cardiovascular Event Lowering; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; HbA1c: Hemoglobin A1c; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE: Major adverse cardiovascular events; SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; TECOS: Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12933-022-01555-z.

**Additional file 1.** Table S1. Race effect on an absolute placebo-adjusted change in HbA1c, blood pressure, heart rate, and serum lipids from baseline to 6 months (unadjusted model). Table S2. Race effect on an absolute change in HbA1c, blood pressure, heart rate, and serum lipids from baseline to 6 months by treatment (unadjusted model). Table S3. Race effect on an absolute change in HbA1c, blood pressure, heart rate, and serum lipids from baseline to 6 months by treatment (adjusted model).

**Acknowledgements**

TMED is supported by a Medical Research Future Fund Practitioner Fellowship. RRH is an Emeritus NIHR Senior Investigator. Peter Hoffmann, an employee of DCRI, provided editorial support.

**Author contributions**

TMED and RRH contributed equally to the study design and data analysis and interpretation and edited the manuscript. TMED produced the first draft of the manuscript. AG and YL performed the statistical analysis and edited the manuscript. RJM and NS edited the manuscript. TMED and RRH are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

**Funding**

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

1. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669–701.

2. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43(2):487–93.

3. Kang YM, Cho YK, Lee J, et al. Asian subpopulations may exhibit greater cardiovascular benefit from long-acting glucagon-like peptide 1 receptor agonists: A meta-analysis of cardiovascular outcome trials. Diabetes Metab J. 2019;43(4):410–21.

4. Ghouri N, Javed H, Sattar N. Pharmacological management of diabetes for reducing glucose levels and cardiovascular disease risk: what evidence in South Asians? Curr Diabetes Rev. 2021;17(9):e122820189511.

5. Lee KMY, Ghouri N, McGuire DK, Rutter MK, Sattar N. Meta-analyses of results from randomized outcome trials comparing cardiovascular effects of SGLT2is and GLP-1RAs in Asian versus White patients with and without type 2 diabetes. Diabetes Care. 2021;44(5):1236–41.

6. Kim YG, Hahn S, Oh TJ, Park KS, Cho YM. Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Metab J. 2014;48(1):900–9.

7. Penczek R, Blickensdorfer A, Li Y, Brunell SC, Anderson PJW. Exenatide twice daily: analysis of effectiveness and safety data stratified by age, sex, race, duration of diabetes, and body mass index. Postgrad Med. 2012;124(4):21–32.

8. Shaw JE, Gallwitz B, Han J, Hardy E, Schmehlman G. Variability in and predictors of glycemic responses after 24 weeks of treatment with exenatide twice daily and exenatide once weekly. Diabetes Obes Metab. 2017;19(12):1795–7.

9. Shu WH, Brunell SC, Blase E. Efficacy and tolerability of exenatide twice daily and exenatide once weekly in Asian versus White patients with type 2 diabetes mellitus: A pooled analysis. Diabetes Res Clin Pract. 2016;114:160–72.

10. Penczek R, Blickensdorfer A, Li Y, Brunell SC, Chen S. Exenatide once weekly for the treatment of type 2 diabetes: effectiveness and tolerability in patient subpopulations. Int J Clin Pract. 2012;66(11):1021–32.

11. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228–39.

12. Holman RR, Bethel MA, George J, et al. Rationale and design of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial. Am Heart J. 2016;174:103–10.

13. Mentz RJ, Bethel MA, Gustavson S, et al. Baseline characteristics of patients enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL). Am Heart J. 2017;187:1–9.

14. Seravalle G, Grassi G. Heart rate as cardiovascular risk factor. Postgrad Med. 2020;132(4):358–67.

15. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. Cell Metab. 2016;24(1):115–30.

16. Minambres I, Perez A. Is there a justification for classifying GLP-1 receptor agonists as basal and prandial? Diabetol Metab Syndr. 2017;9:96.

17. Drucker DJ, Buse JB, Taylor K, et al. DURATION-1 Study Group. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet 2008;372(9645):1240–50.

18. Gan S, Dawed AY, Donnellen LA, et al. Efficacy of modern diabetes treatments DPP-4i, SGLT-2i, and GLP-1RA in White and Asian patients with diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care. 2020;43(8):1488–57.

19. Nauck MA, Meier JJ. Management of endocrine disease: Are all GLP-1 agonists equal in the treatment of type 2 diabetes? Eur J Endocrinol. 2019;181(6):R211–34.

20. Burden ML, Samanta A, Spalding D, Burden AC. A comparison of the glycaemic and insulinaemic effects of an Asian and a European meal. Pract Diab Int. 1994;11:208–11.

21. Henry CJ, Lightowler HJ, Newsens K, et al. Glycaemic index of common foods tested in the UK and India. Br J Nutr 2008;99(4):840–5.

22. Hu EA, Pan A, Malik V, Sun Q. White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review. BMJ. 2012;344:e1454.

23. Davis TME, Mulder H, Lokhnygina Y, TECOS Study Group, et al. Effect of race on the glycaemic response to sitagliptin: insights from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Diabetes Obes Metab. 2018;20(6):1427–34.

24. Goud A, Zhong J, Peters M, Brook RD, Rajagopalan S. GLP-1 agonists and blood pressure: a review of the evidence. Curr Hypertens Rep. 2016;18(2):16.

25. Bathula R, Francis DP, Hughes A, Chatuvredi N. Ethnic differences in heart rate: can these be explained by conventional cardiovascular risk factors? Clin Auton Res. 2008;18(2):90–5.

26. Eckberg DL. Physiological basis for human autonomic rhythms. Ann Med. 2000;32(5):341–9.

27. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympathovagal interaction in man and conscious dog. Circ Res. 1986;59(2):178–93.

28. Griffinon KJ, Wan R, Okun E, et al. GLP-1 receptor stimulation depresses heart rate variability and inhibits neurotransmission to cardiac vagal neurons. Cardiovasc Res. 2011;89(1):72–8.

29. Yamamoto H, Lee CE, Marcus JN, et al. Glucagon-like peptide-1 receptor stimulation increases blood pressure and heart rate and activates autonomic regulatory neurons. J Clin Invest. 2002;110(1):43–52.

30. Paiman EHM, van Eijk-HJ, van Aalst MMA, et al. Effect of liraglutide on cardiovascular function and myocardial tissue characteristics in type 2 diabetes patients of South Asian descent living in the Netherlands: a double-blind, randomized, placebo-controlled trial. J Magn Reson Imaging. 2020;52(6):1679–88.

31. Nauck MA, Quast DR, Wefers J, et al. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2020. https://doi.org/10.1016/j/molmet.2020.101102.
32. Tudur Smith C, Marcucci M, Nolan SJ, et al. Individual participant data meta-analyses compared with meta-analyses based on aggregate data. Cochrane Database Syst Rev. 2016;9:MR000007.
33. Yang BY, Dong GH. Tobacco smoking in Asia—a public health threat. JAMA Netw Open. 2019;2(3):e191471.
34. Pan A, Wang Y, Talaei M, Hu FB. Relation of smoking with total mortality and cardiovascular events among patients with diabetes mellitus: A meta-analysis and systematic review. Circulation. 2015;132(19):1795–804.
35. Duncan A, Heyer MP, Ishikawa M, et al. Habenular TCF7L2 links nicotine addiction to diabetes. Nature 2019;574(7778):372–7.
36. Chua A, Adams D, Dey D, et al. Coronary artery disease in East and South Asians: differences observed on cardiac CT. Heart 2022;108(4):251–7.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.