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Are the cardiovascular properties of GLP-1 receptor agonists differentially modulated by sulfonylureas? Insights from post-hoc analysis of EXSCEL

Kim M. Gooding [a,b,*], Susanna Stevens [c], Yuliya Lokhnygina [c], Anna Giczewska [c], Angela C. Shore [a,b], Rury R. Holman [d]

[a] Vascular Research Centre, University of Exeter Medical School, Barrack Road, Exeter, UK
[b] NIHR Exeter Clinical Research Facility, Royal Devon University Healthcare NHS Foundation Trust, Barrack Road, Exeter, UK
[c] Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA
[d] Diabetes Trials Unit, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

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ABSTRACT

Aims: To examine whether the cardiovascular effects of glucagon-like peptide-1 (GLP-1) receptor agonists are attenuated by concurrent sulfonylurea (SU) therapy in a post-hoc analysis of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL).

Methods: We investigated whether SUs, as a class or by specific type, modulated the effects of once-weekly exenatide (EQW) on EXSCEL cardiovascular outcomes in intent-to-treat analyses of all trial participants, categorized as SU users or nonusers. Marginal structural models were used to evaluate whether there were differential EQW effects by SU category on major adverse cardiovascular events (MACE), depending on duration of SU use (6, 12, and 18 months). EQW-by-SU type interaction p-values and hazard ratios (95 % CIs) for EQW versus placebo for each baseline SU type (glibenclamide, gliclazide, glimepiride, other SUs) were calculated.

Results: Neither SU use nor baseline SU type modified the effect of EQW on time to MACE ($p_{interaction} = 0.88$ and 0.78, respectively), nor did individual SU types, including glibenclamide (a systemically wide-acting SU).

Conclusions: SUs did not modulate the effect of EQW on cardiovascular outcomes, suggesting that SU treatment choices need not be altered to optimize the cardiovascular effects of GLP-1 receptor agonists in people with type 2 diabetes.

1. Introduction

Cardiovascular outcome trials with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown that they have cardiovascular benefits [1]. Likely mechanisms are multifactorial (e.g., weight loss) [2–4] and may include a direct GLP-1 RA effect on the vasculature [5–8]. GLP-1 receptors are expressed in the human vasculature [9–11], but it is uncertain whether they are involved in mediating the vascular actions of GLP-1 RAs [6,8]. Proposed mediators underlying GLP-1 RA vascular actions include nitric oxide, hydrogen sulfide, and potassium channels, particularly K_{ATP} channels [7,12,13] as well as the endothelin pathway [9].

Opening K_{ATP} channels has been shown to mediate the improvement of endothelial function induced by exenatide [7] and by GLP-1 7–36 amide (hereafter referred to as GLP-1) [14]. In healthy individuals, pretreatment with the systemwide sulfonylurea (SU) glibenclamide (glyburide) abolished the incretin-based improvements in endothelial function [7,14]. However, the vascular actions of GLP-1 were not modified by glimepiride, a different SU [14]. A potential explanation is that SUs can act on different K_{ATP} channel subtypes. K_{ATP} channels consist of two subunits, the Kir channel (Kir 6.1/6.2) and the SU receptor subunit (SUR1, SUR2A, SUR2B). The distribution of these subtypes varies between sites—e.g., Kir 6.2/SUR1 is found in the pancreas, while Kir 6.2/SUR2B has been described in the cardiovascular system [15]. The affinity of SU drugs for different K_{ATP} channel subtypes varies—e.g., gliclazide has a high affinity for Kir 6.2/SUR1 and glimepiride for both Kir 6.2/SUR1 and Kir 6.2/ SUR2A, while glibenclamide is a nonspecific K_{ATP} channel closer. Glimepiride has been shown to inhibit K_{ATP}

Abbreviations: EQW, once-weekly exenatide; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; SU, sulfonylurea.

* Corresponding author at: Vascular Research Centre, University of Exeter Medical School, Barrack Road, Exeter EX2 5AX, UK.
E-mail address: K.M.Gooding@exeter.ac.uk (K.M. Gooding).

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channel-dependent vasodilation in rat mesenteric arteries [16], but these studies have not been supported by research in humans [16], possibly reflecting differences in distribution of K_{ATP} channel subtypes between species.

These observations suggest that the beneficial vascular effects of GLP-1 RAs could be reduced or nullified by concurrent treatment with certain SU types. As SUs are still prescribed globally [17–19], it is important to determine if they might attenuate the beneficial cardiovascular effects of GLP-1 RAs.

We analyzed data from the Exenatide Study of Cardiovascular Event Lowering (EXSCEL; Clinical Trial Registration identifier: NCT01144338) to examine whether the effects of once-weekly exenatide (EQW), a GLP-1 RA, on time to the primary cardiovascular outcome and selected EXSCEL secondary outcomes were modulated by 1) concomitant therapy with any SU or 2) concomitant therapy with different types of SU.

2. Materials and Methods

EXSCEL enrolled 14,752 patients with type 2 diabetes, 73.1 % of whom had previous cardiovascular disease. Key inclusion criteria included an HbA_{1c} of 6.5 % to 10 % (48 to 86 mmol/mol), age $\geq$ 18 years, <2 severe hypoglycemic episodes in the past year, and an estimated glomerular filtration rate (eGFR) $\geq$ 30 mL/min/1.73 m^2. Participants were randomized to receive subcutaneous EQW injections at a dose of 2 mg, or once-weekly matching placebo, and were followed for a median of 3.2 years (interquartile range, 2.2 to 4.4).

The EXSCEL participant baseline characteristics and study results were published in 2017 [20,21]. The major adverse cardiovascular events (MACE) hazard ratio for EQW, compared with placebo, was 0.91 (95 % CI 0.83–1.00) [21]. Hazard ratios for the secondary outcomes were 0.88 (0.76–1.02) for cardiovascular death, 0.97 (0.85–1.10) for fatal or nonfatal myocardial infarction, 0.85 (0.70–1.03) for fatal or nonfatal stroke, 0.94 (0.78–1.13) for hospitalization for heart failure (hHF), and 1.05 (0.94–1.18) for hospitalization for acute coronary syndrome (hACS).

All EXSCEL participants were included in these post-hoc intent-to-treat analyses examining whether SU use modifies the effect of EQW versus placebo on the following predefined EXSCEL time-to-event cardiovascular outcomes: 1) three-point MACE, defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; 2) cardiovascular death; 3) fatal or nonfatal myocardial infarction; 4) fatal or nonfatal stroke; 5) hHF; and 6) hACS.

2.1. SU use versus SU nonuse

Participants were categorized as SU users or nonusers according to their within-trial time-dependent use of SUs. SU categories at any timepoint in the study were determined by whether participants had a report of SU use before that timepoint. Once a participant had reported SU use, they remained in the SU group until the end of follow-up, unless they reported no SU use for a period of at least 2 years. Participants reporting no SU use for a period of 2 years or longer were considered to have stopped SU use at the first visit in the period during which SU use was no longer reported. Where SU use was reported followed by 2 years or more of missed medication assessments, the SU stop date was assumed to be the last reported SU use before the 2 years without information. In effect, this meant there were five possible SU treatment trajectories:

1. Taking SU at baseline and continued during follow-up;
2. Taking SU at baseline but discontinued during follow-up;
3. Not taking SU at baseline and never received it during follow-up;
4. Not taking SU at baseline but commenced SU during follow-up;
5. Not taking SU at baseline but commenced SU during follow-up, which was then discontinued.

In additional sensitivity analyses, participants with 2 or more years of missing information were assumed to have continued the treatment at their last assessment. In these sensitivity analyses, participants who were taking SU at baseline and discontinued its use during follow-up (trajectory 2) were treated as taking SU throughout (trajectory 1). Similarly, participants who started and discontinued SU use (trajectory 5) were treated as starting SU post-baseline and continuing the rest of follow-up (trajectory 4).

2.2. Individual SU type use versus SU nonuse

Participants were categorized into subgroups based on the type of SU they were using at baseline (glibenclamide, gliclazide, glimepiride, other) or a non-SU subgroup for nonuse at baseline. The analyses were performed to evaluate whether the effect of EQW versus placebo on the cardiovascular outcomes was modulated by different types of baseline SU use as compared to no baseline SU use.

2.3. Statistical analysis

2.3.1. SU use versus SU nonuse

Marginal structural models [22] were used to evaluate whether EQW effects on cardiovascular events differed depending on the duration of SU use for each of the prespecified EXSCEL cardiovascular outcomes. The models handled the issue of time-dependent confounding of SU by using inverse probability weighting of participants' observed therapies. Weights were determined using the probability of being on SU and the probability of being uncensored on each participant day. Cumulative SU days were set to zero at baseline and incrementing by one day for each day after starting SU. Once an SU was stopped, the cumulative SU duration remained constant. Time-dependent confounders included in the models to obtain treatment and censoring weights were HbA_{1c}, systolic blood pressure, body weight, and heart rate. Baseline covariates used in the models for weights were age, sex, diabetes duration, ethnicity, region, HbA_{1c}, blood pressure, prior cardiovascular event, eGFR, dipeptidyl peptidase IV (DPP-IV) inhibitor use, heart rate, and body weight. After weights were estimated, cardiovascular outcomes were analyzed using weighted pooled logistic regression models with time-dependent intercept, modelled as a restricted cubic spline of day of follow-up, and covariates for randomized treatment (1 = EQW, 0 = placebo), cumulative SU days, and their interaction. Results are presented as hazard ratios with 95 % confidence intervals (CIs) for EQW versus placebo at selected days of cumulative SU use, together with p-values for the interaction of treatment and cumulative days of SU use.

2.3.2. Individual baseline SU type use versus SU nonuse

The hazard ratios with 95 % CIs for EQW versus placebo within each baseline SU group were calculated from the Cox proportional hazards models, together with EQW-by-SU type interaction p-values for each of the EXSCEL prespecified cardiovascular outcomes. These models were stratified by baseline history of cardiovascular disease and adjusted for baseline covariates of age, sex, diabetes duration, ethnicity, region, HbA_{1c}, systolic blood pressure, diastolic blood pressure, eGFR, DPP-IV inhibitor usage, weight, and heart rate.

All analyses were performed using SAS version 9.4 (SAS Institute, Inc. Cary, NC, USA). Statistical comparisons were performed using two-sided tests with an alpha level of 0.05. No adjustments were made for multiple comparisons.

3. Results

3.1. SU use versus SU nonuse

The baseline SU group comprised 5401 participants (n = 3401 who took an SU throughout the study and n = 2000 who took an SU at baseline but discontinued use during follow-up). The baseline non-SU

group comprised 9351 participants (n = 8199 who never took an SU during the study, n = 727 who did not take an SU at baseline but started during follow-up, and n = 425 who did not take an SU at baseline but started and discontinued during follow-up). Baseline characteristics did not differ between the SU and non-SU groups (Table 1).

SU use did not modify the effect of EQW on time to cardiovascular outcomes in the primary or sensitivity analyses (Table 2). The MACE hazard ratios (95 % CI) for exenatide versus placebo were 0.88 (0.78–0.99), 0.88 (0.80–0.98), 0.89 (0.79–0.99), and 0.89 (0.77–1.02) for SU nonuse, 6 months SU, 12 months SU, and 18 months SU use, respectively, with an interaction p value of 0.88. Similarly, there were no significant interactions for the effects of EQW with SU use or nonuse on cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hHF, or hACS.

3.2. Individual baseline SU type use versus SU nonuse

The 5 baseline SU subgroups comprised 1354 participants for glibenclamide, 1641 for gliclazide, 1711 for glimepiride, 695 for other, and 9351 for SU nonusers.

The effects of EQW on cardiovascular outcomes were not modified by different baseline SU types (Table 3). The MACE hazard ratios (95 % CI) for exenatide versus placebo were 0.89 (0.79–1.00), 0.84 (0.58–1.22), 1.09 (0.79–1.50), 0.83 (0.62–1.11), and 0.90 (0.62–1.29) for SU nonuse, glibenclamide, gliclazide, glimepiride and other SU use, respectively, with an interaction p value of 0.78. Similarly, there were no significant interactions for the effects of EQW by type of SU used on cardiovascular death, fatal or nonfatal stroke, hHF, or hACS.

4. Discussion

Post-hoc analysis of the EXSCEL trial demonstrated that treatment with SUs, as a therapy class, did not modify the effect of EQW on time-to-event of the 3-point MACE outcome or any of the prespecified secondary cardiovascular outcomes. The SU and non-SU groups were well matched for age, blood pressure, eGFR, and duration of diabetes. Race and sex distribution across both groups was also similar. The proportion of participants with established cardiovascular disease, a known influence [23], varied across the two group (75.8 % SU nonuse group and 68.4 % SU group); however, this was adjusted for in the modelling analysis.

More detailed analysis demonstrated that the impact of the systemically wide-acting SU glibenclamide did not differ from that of the pancreatic-specific SU gliclazide or SU nonuse on the EQW effect on cardiovascular events. Regional variations in the type of SUs prescribed are known [24], but region as well as race were taken into account in the modelling analysis.

With the increasing availability of newer treatments such as DPP-IV inhibitors and SGLT2 inhibitors, SUs have become less popular [25,26]. However, they remain in the guidelines [27] and are still used widely [17–19]. In this study, 36.6 % of the study population were SU users, with considerably smaller sample sizes for those taking individual SUs (9.2 %, 11.1 %, 11.6 %, and 4.7 % for glibenclamide, gliclazide, glimepiride, and other SU use, respectively), limiting the statistical power of this analysis. Despite these relatively small sample sizes, there were no discernible trends to support specific SUs differentially modulating the cardiovascular actions of EQW.

The observation that SUs, particularly glibenclamide, did not modify the cardiovascular outcomes of EQW conflicts with the previous research demonstrating that the vascular actions of GLP-1 and GLP-1 RAs are mediated by K_{ATP} channels [7,14]. Potential reasons for these disparities include differences in study designs (acute mechanistic studies compared to long-term interventional trial), outcomes (modulation of brachial/forearm blood flow compared to hard MACE endpoints), and participant groups (non-diabetes versus diabetes participant groups). Reduced activity of K_{ATP} channels and expression of SUR2B subunit in the cardiovascular system, predominantly affecting

Table 1
Baseline patient characteristics according to baseline sulfonylurea use.

Characteristic	SU users*	SU nonusers	All subjects
N	5401	9351	14,752
Age at randomization (years) - median (25th, 75th percentile)	62 (56, 68)	62 (56, 68)	62 (56, 68)
Female sex	2043/5401 (37.8 %)	3560/9351 (38.1 %)	5603/14752 (38.0 %)
Hispanic or Latino ethnicity	1244/5401 (23.0 %)	1782/9349 (19.1 %)	3026/14750 (20.5 %)
Race			
White	3985/5399 (73.8 %)	7190/9348 (76.9 %)	11175/14747 (75.8 %)
Black	373/5399 (6.9 %)	505/9348 (5.4 %)	878/14747 (6.0 %)
Asian	605/5399 (11.2 %)	847/9348 (9.1 %)	1452/14747 (9.8 %)
Indian (American) or Alaska Native	19/5399 (0.4 %)	54/9348 (0.6 %)	73/14747 (0.5 %)
Native Hawaiian or Other Pacific Islander	16/5399 (0.3 %)	19/9348 (0.2 %)	35/14747 (0.2 %)
Hispanic	401/5399 (7.4 %)	733/9348 (7.8 %)	1134/14747 (7.7 %)
Duration of type 2 diabetes (years) - median (25th, 75th percentile)	11 (7, 16)	12 (7, 19)	12 (7, 18)
Antihyperglycaemic therapy			
No insulin or oral agent use	0/5401 (0 %)	228/9351 (2.4 %)	228/14752 (1.5 %)
Oral agent use	5401/5401 (100.0 %)	7090/9351 (75.8 %)	12491/14752 (84.7 %)
Number of oral agents used			
Monotherapy	601/5401 (11.1 %)	5634/9351 (60.3 %)	6235/14752 (42.3 %)
Dual therapy	3617/5401 (67.0 %)	1304/9351 (13.9 %)	4921/14752 (33.4 %)
≥3 oral agents	1183/5401 (21.9 %)	152/9351 (1.6 %)	1335/14752 (9.0 %)
Insulin use	916/5401 (17.0 %)	5920/9351 (63.3 %)	6836/14752 (46.3 %)
Insulin and oral agent combination			
Insulin alone	0/5401 (0 %)	2033/9351 (21.7 %)	2033/14752 (13.8 %)
Insulin plus one oral agent	166/5401 (3.1 %)	3371/9351 (36.0 %)	3537/14752 (24.0 %)
Insulin plus > 1 oral agent	750/5401 (13.9 %)	516/9351 (5.5 %)	1266/14752 (8.6 %)
DPP-IV inhibitor	943/5401 (17.5 %)	1260/9351 (13.5 %)	2203/14752 (14.9 %)
Biguanides	4565/5401 (84.5 %)	6730/9351 (72.0 %)	11295/14752 (76.6 %)
Medical history			
Coronary artery disease	3692/5401 (68.4 %)	7090/9351 (75.8 %)	10782/14752 (73.1 %)
Prior cardiovascular eligibility criteria			
Coronary artery disease	2554/5401 (47.3 %)	5240/9351 (56.0 %)	7794/14752 (52.8 %)
Cerebrovascular disease	840/5400 (15.6 %)	1669/9350 (17.9 %)	2509/14750 (17.0 %)
Peripheral artery disease	985/5400 (18.2 %)	1815/9351 (19.4 %)	2800/14751 (19.0 %)
Myocardial infarction	1536/5401 (28.4 %)	3143/9351 (33.6 %)	4679/14752 (31.7 %)
Heart failure	828/5401 (15.3 %)	1561/9350 (16.7 %)	2389/14751 (16.2 %)
Smoking status			
Current	614/5400 (11.4 %)	1107/9345 (11.8 %)	1721/14745 (11.7 %)
Former	2083/5400 (38.6 %)	3708/9345 (39.7 %)	5791/14745 (39.3 %)

(continued on next page)

Table 1 (*continued*)

Characteristic	SU users*	SU nonusers	All subjects
Never	2703/5400 (50.1 %)	4530/9345 (48.5 %)	7233/14745 (49.1 %)
Vitals and labs			
Systolic blood pressure (mmHg) - median (25th, 75th percentile)	135 (124, 145)	135 (124, 145)	135 (124, 145)
Diastolic blood pressure (mmHg) - median (25th, 75th percentile)	80 (71, 85)	79 (70, 85)	80 (70, 85)
Heart rate (bpm) - median (25th, 75th percentile)	72 (66, 80)	72 (66, 80)	72 (66, 80)
Body mass index (kg/m^2) - median (25th, 75th percentile)	31.2 (27.8, 35.4)	32.2 (28.5, 36.7)	31.8 (28.2, 36.2)
Weight (kg) - median (25th, 75th percentile)	88.0 (75.0, 103.0)	91.6 (78.0, 106.0)	90.0 (77.0, 105.0)
HbA_{1c} (%) - median (25th, 75th percentile)	8.1 (7.4, 8.9)	7.9 (7.3, 8.8)	8.0 (7.3, 8.9)
HbA_{1c} (mmol/mol) - median (25th, 75th percentile)	65 (57, 74)	63 (56, 73)	64 (56, 74)
eGFR (mL/min/1.73 m^2) - median (25th, 75th percentile)	77.0 (62.0, 92.0)	76.0 (61.0, 92.0)	76.2 (61.0, 92.0)

Data are n/N (%) unless otherwise indicated. SU = sulfonylurea.
* 1354 glibenclamide, 1641 gliclazide, 1711 glimepiride, and 695 other.

glibenclamide, have been described in diabetes [28,29]. Furthermore, other mediators have been proposed to mediate the vascular effects of GLP-1 and its analogues; these mediators (e.g., nitric oxide and hydrogen sulfide) may also be contributing to, or even compensating for, K_{ATP} channel blockade with glibenclamide in the cardiovascular system [8,12,13].

The main EXSCEL study analysis observed a nonsignificant trend for a reduction in MACE with exenatide [21]. If this mechanistic hypothesis held up, performing this analysis on this population may have revealed a significant decrease in MACE events in certain subgroups, and thus contributed to our understanding of the main study observations. However, there is no suggestion that SUs modify the impact of EQW on MACE events in this analysis. Confirmation of this in another cohort, such as a cardiovascular outcome trial that observed a significant reduction in MACE with a GLP-1 RA, would be advisable.

Our study has several limitations. SU use was not randomly assigned, and although we attempted to account for both baseline and time-dependent confounders, we cannot rule out the possibility of unobserved confounders affecting the results. For participants who reported use of SU, continuous use of SU was assumed unless there was no reported SU use for a period of 2 or more years. This assumption may not hold true in reality, but it was necessary in order to reduce the complexity of the models.

In summary, previous mechanistic studies suggest that the cardiovascular actions of GLP-1 RAs may be modulated by certain SUs—e.g., being attenuated by concurrent treatment with glibenclamide but not being affected by concurrent treatment with gliclazide or glimepiride. If this were the case, then patients with type 2 diabetes being treated with glibenclamide would see fewer cardiovascular benefits with GLP-1 RAs, and should have their medications switched to alternative treatment. However, post-hoc analysis of the EXSCEL trial suggests that SUs, and in particular glibenclamide, do not modulate the cardiovascular effects of the GLP-1 RA EQW.

5. Ethics approval and consent to participate

The EXSCEL study protocol was approved by the ethics committee at each participating site, and the statistical analyses were performed by the Duke Clinical Research Institute, independent of the sponsor, Amylin Pharmaceuticals (a wholly owned subsidiary of AstraZeneca). All patients provided written informed consent.

Table 2
Modification of the effect of exenatide on time to cardiovascular events according to sulfonylurea use.

	Primary analyses		Sensitivity analyses*	
Cardiovascular event and duration of sulfonylurea use	**Hazard ratio (95 % CI) for exenatide v. placebo**	**Interaction (exenatide by duration of sulfonylurea use) p-value**	**Hazard ratio (95 % CI) for exenatide v. placebo**	**Interaction (exenatide by duration of sulfonylurea use) p-value**
MACE (CVD/MI/stroke)		0.88		0.95
Sulfonylurea nonuse	0.88 (0.78, 0.99)		0.88 (0.79, 0.99)	
6 months of sulfonylurea	0.88 (0.80, 0.98)		0.89 (0.80, 0.98)	
12 months of sulfonylurea	0.89 (0.79, 0.99)		0.89 (0.79, 0.99)	
18 months of sulfonylurea	0.89 (0.77, 1.02)		0.89 (0.77, 1.02)	
Cardiovascular death		0.64		0.88
Sulfonylurea nonuse	0.80 (0.66, 0.96)		0.82 (0.68, 0.99)	
6 months of sulfonylurea	0.81 (0.69, 0.95)		0.82 (0.69, 0.96)	
12 months of sulfonylurea	0.82 (0.69, 0.98)		0.81 (0.69, 0.96)	
18 months of sulfonylurea	0.84 (0.68, 1.02)		0.81 (0.66, 0.98)	
Fatal or nonfatal MI		0.93		0.77
Sulfonylurea nonuse	0.94 (0.81, 1.10)		0.95 (0.82, 1.11)	
6 months of sulfonylurea	0.94 (0.82, 1.08)		0.94 (0.82, 1.08)	
12 months of sulfonylurea	0.94 (0.81, 1.09)		0.93 (0.80, 1.08)	
18 months of sulfonylurea	0.93 (0.77, 1.13)		0.92 (0.77, 1.11)	
Fatal or nonfatal stroke		0.95		0.88
Sulfonylurea nonuse	0.82 (0.65, 1.05)		0.82 (0.65, 1.05)	
6 months of sulfonylurea	0.83 (0.67, 1.02)		0.83 (0.67, 1.03)	
12 months of sulfonylurea	0.83 (0.65, 1.06)		0.84 (0.66, 1.06)	
18 months of sulfonylurea	0.83 (0.61, 1.14)		0.85 (0.62, 1.15)	
Hospitalization for HF		0.76		0.76
Sulfonylurea nonuse	0.92 (0.73, 1.16)		0.92 (0.73, 1.15)	
6 months of sulfonylurea	0.91 (0.74, 1.11)		0.91 (0.74, 1.11)	
12 months of sulfonylurea	0.89 (0.71, 1.12)		0.89 (0.71, 1.12)	
18 months of sulfonylurea	0.88 (0.66, 1.17)		0.88 (0.66, 1.16)	
Hospitalization for ACS		0.68		0.55
Sulfonylurea nonuse	1.03 (0.90, 1.19)		1.04 (0.90, 1.20)	
6 months of sulfonylurea	1.02 (0.90, 1.15)		1.02 (0.90, 1.16)	
12 months of sulfonylurea	1.01 (0.88, 1.15)		1.00 (0.87, 1.15)	
18 months of sulfonylurea	0.99 (0.84, 1.18)		0.98 (0.83, 1.17)	

MACE = major adverse cardiovascular event. CVD = cardiovascular disease. MI = myocardial infarction. HF = heart failure. ACS = acute coronary syndrome.
* 280 patients with 2 years or more of missed medication assessments without indication of stopping are assumed to have continued taking sulfonylurea during the time period sulfonylurea was not assessed.

Table 3
Association between baseline sulfonylurea-type-by-exenatide interaction and clinical events.

Event and Type of SU	Hazard ratio (95 % CI), exenatide v. placebo	Interaction (exenatide by type of SU) p-value
MACE (CVD/MI/ stroke)		0.78
SU nonuse	0.89 (0.79, 1.00)	
Glibenclamide	0.84 (0.58, 1.22)	
Gliclazide	1.09 (0.79, 1.50)	
Glimepiride	0.83 (0.62, 1.11)	
Other	0.90 (0.62, 1.29)	
Cardiovascular death		0.63
SU nonuse	0.84 (0.70, 1.01)	
Glibenclamide	0.80 (0.47, 1.36)	
Gliclazide	1.19 (0.76, 1.88)	
Glimepiride	0.84 (0.54, 1.30)	
Other	0.71 (0.40, 1.27)	
Fatal or nonfatal MI		0.67
SU nonuse	0.94 (0.81, 1.10)	
Glibenclamide	1.31 (0.75, 2.30)	
Gliclazide	1.05 (0.66, 1.67)	
Glimepiride	0.81 (0.55, 1.19)	
Other	1.05 (0.67, 1.65)	
Fatal or nonfatal stroke		0.71
SU nonuse	0.86 (0.67, 1.08)	
Glibenclamide	0.49 (0.22, 1.05)	
Gliclazide	0.84 (0.42, 1.71)	
Glimepiride	0.97 (0.50, 1.88)	
Other	0.78 (0.38, 1.61)	
Hospitalization for HF		0.73
SU nonuse	0.91 (0.73, 1.14)	
Glibenclamide	1.23 (0.49, 3.12)	
Gliclazide	1.25 (0.63, 2.49)	
Glimepiride	0.78 (0.39, 1.55)	
Other	0.69 (0.34, 1.40)	
Hospitalization for ACS		0.66
SU nonuse	1.02 (0.88, 1.17)	
Glibenclamide	1.41 (0.87, 2.27)	
Gliclazide	1.03 (0.68, 1.56)	
Glimepiride	0.93 (0.66, 1.32)	
Other	1.19 (0.78, 1.79)	

MACE = major adverse cardiovascular event. CVD = cardiovascular disease. MI = myocardial infarction. HF = heart failure. ACS = acute coronary syndrome.

6. Declarations of interest

R.R.H. reports personal fees from Anji Pharmaceuticals, AstraZeneca and Novartis. No other potential conflicts of interest relevant to this article were reported.

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Author contributions

K.M.G. conceived and contributed to the post-hoc analysis plan, and took the lead in writing the manuscript. S.S., Y.L, and A.G developed the post-hoc analysis plan and performed statistical analysis. A.C.S contributed to the post-hoc analysis plan and reviewed the manuscript. R.R.H. co-chaired the original EXSCEL trial and contributed to planning the post-hoc analysis plan and writing the manuscript. R.R.H. is the guarantor of the study and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CRediT authorship contribution statement

Kim M. Gooding: Writing – original draft, Formal analysis, Conceptualization. **Susanna Stevens:** Formal analysis. **Yuliya Lokhnygina:** Formal analysis. **Anna Giczewska:** Formal analysis. **Angela C. Shore:** Writing – review & editing, Formal analysis. **Rury R. Holman:** Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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