Applying REWIND cardiovascular disease criteria to SUSTAIN 6 and PIONEER 6: An exploratory analysis of cardiovascular outcomes with semaglutide

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Abstract
In the REWIND trial, dulaglutide reduced cardiovascular (CV) risk versus placebo in patients with type 2 diabetes in both the “established CV disease” (CVD) and “CV risk factor” subgroups. The SUSTAIN 6 and PIONEER 6 trials of semaglutide used different criteria for established CVD from those used in REWIND. The present post hoc analysis assessed the effect of semaglutide on major adverse CV events (MACE) in a pooled population of SUSTAIN 6 and PIONEER 6 patients, re-categorized into CV risk subgroups using the REWIND CVD criteria. In the pooled analysis (n = 6480), a lower percentage of patients were in the established CVD subgroup, when using the REWIND CVD criteria, compared with the original trial CVD criteria (66.5% vs. 83.8%, respectively). After re-categorization, the risk of MACE was significantly lower with semaglutide versus placebo in the established CVD subgroup (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.59, 0.92) and nonsignificantly lower in the CV risk factor subgroup (HR 0.84, 95% CI 0.55, 1.28) (P-interaction = 0.60). These results suggest that the CV effects of semaglutide may extend to patients with type 2 diabetes across the CV risk continuum.

KEYWORDS
antidiabetic drug, cardiovascular disease, GLP-1 analogue, incretin therapy

1 INTRODUCTION

In the cardiovascular (CV) outcomes trial “Researching cardiovascular Events with a Weekly Incretin in Diabetes” (REWIND; NCT01394952), the glucagon-like peptide-1 receptor agonist (GLP-1 RA) dulaglutide reduced CV risk versus placebo in patients with type 2 diabetes.1 This result was seen in the overall trial population, and in both the “established CV disease” (CVD) and “CV risk factor” subgroups.1 In REWIND (9901 patients), a comparatively high proportion of patients were included in the CV risk factor subgroup compared with other GLP-1 RA CV outcomes trials. However, the criteria for established CVD are not consistent across trials. The “Semaglutide in Subjects with Type 2 Diabetes 6” (SUSTAIN 6; NCT01720446) and the “Peptide Innovation for Early Diabetes Treatment 6” (PIONEER 6; NCT02692716) trials of semaglutide2,3 used a broader definition than REWIND for established CVD.1 Key differences in CVD criteria between the trials included patients with chronic kidney disease, chronic heart failure (HF), prior...
### TABLE 1  Criteria for established CVD and CV risk factors in SUSTAIN 6, PIONEER 6 and REWIND

| Endpoint | CV risk group | Hazard ratio semaglutide vs placebo  |
|----------|--------------|----------------------------------|
| MACE*    | Established CVD | 0.74 [0.59, 0.92] |
|          | CV risk factors | 0.84 [0.65, 1.08] |
| Expanded MACE† | Established CVD | 0.74 [0.63, 0.88] |
|          | CV risk factors | 0.89 [0.62, 1.27] |
| All-cause death | Established CVD | 0.78 [0.55, 1.09] |
|          | CV risk factors | 0.91 [0.53, 1.57] |
| CV death | Established CVD | 0.71 [0.48, 1.06] |
|          | CV risk factors | 1.00 [0.52, 1.94] |

Note: Patients needed to meet one or more of the established CVD criteria to be in the established CVD subgroup, and one or more of the CV risk factors criteria to be in the CV risk factors subgroup. Differences in criteria between trials are in bold. Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; MI, myocardial infarction; NYHA, New York Heart Association.

**FIGURE 1** Primary and secondary endpoints with semaglutide versus placebo in patients from SUSTAIN 6 and PIONEER 6 re-categorized as having established cardiovascular disease (CVD) or cardiovascular (CV) risk factors using REWIND criteria. Established CVD, n = 4310; CV risk factors, n = 2170. *Major adverse CV events (MACE) = death from CV causes, nonfatal myocardial infarction (MI), nonfatal stroke. †Expanded MACE = MACE plus coronary or peripheral revascularization and hospitalization for unstable angina (UA) or heart failure (HF). Established CVD = MI, ischaemic stroke, UA, coronary heart disease or asymptomatic cardiac ischaemia, arterial revascularization and >50% stenosis of coronary, carotid or lower extremity arteries. CV risk factors = microalbuminuria/proteinuria, hypertension and left ventricular hypertrophy, left ventricular dysfunction, ankle-brachial index <0.9, chronic kidney disease, HF or transient ischaemic attack/haemorrhagic stroke. CI, confidence interval; IR, incidence rate (events/100 patient-years of observation); n, number of patients with event.
transient ischaemic attack, or prior haemorrhagic stroke being categorized with established CVD in SUSTAIN 6 and PIONEER 6, but as having CV risk factors only in REWIND (Table 1).1–3 Statistical testing showed no evidence of heterogeneity in treatment effects of semaglutide across CV risk subgroups in SUSTAIN 6 and PIONEER 6; however, the reduction in major adverse CV events (MACE) in patients with CV risk factors only was not significant in either trial.2,3 The present post hoc exploratory analysis aimed to assess the impact of semaglutide on CV outcomes in a pooled population of SUSTAIN 6 and PIONEER 6 patients, re-categorized into CV risk subgroups using the REWIND CVD criteria.

2 | METHODS

The primary endpoint for this analysis was a composite of MACE, defined as CV death, nonfatal myocardial infarction or nonfatal stroke. Secondary endpoints comprised CV death, all-cause death and expanded MACE, which included MACE plus coronary or peripheral revascularization, and hospitalization for unstable angina or HF. Treatment effects were estimated using a Cox proportional hazards model stratified by trial group. Pooled treatment group, CV risk group and the interaction between both as fixed factors were included in the model. No adjustment for multiple comparisons was performed.

3 | RESULTS

In total, 6480 patients were included in the pooled analysis (SUSTAIN 6: 3297; PIONEER 6: 3183). Using REWIND CVD criteria, 66.5% of patients were re-categorized as having established CVD and 33.5% as having CV risk factors, compared with 83.8% and 16.2% using the original SUSTAIN 6 and PIONEER 6 criteria. The majority of patients re-categorized from the established CVD to the CV risk factor subgroup had chronic kidney disease, chronic HF or prior transient ischaemic attack.

After re-categorization, the risk of MACE was significantly lower with semaglutide versus placebo in the established CVD subgroup [hazard ratio (HR) 0.74, 95% confidence interval (CI) 0.59, 0.92] and nonsignificantly lower in the CV risk factor subgroup (HR 0.84, 95% CI 0.55, 1.28; P-interaction = 0.60 [Figure 1]). Consistent effects of semaglutide were observed across subgroups for other endpoints (P-interaction >0.05 for all endpoints; Figure 1). Sensitivity analyses applying age criteria from SUSTAIN 6 and PIONEER 6, and re-categorizing patients with >50% stenosis on diagnostic imaging as having CV risk factors rather than established CVD showed similar results across subgroups (P-interaction >0.05 for all endpoints for both analyses).

4 | DISCUSSION

In this pooled post hoc analysis, semaglutide significantly reduced MACE in patients with established CVD and was associated with a nonsignificant risk reduction in those with CV risk factors only, as defined by REWIND CVD criteria. These findings reinforce other post hoc analyses of the SUSTAIN and PIONEER CV outcome and glycaemic efficacy trials, in which semaglutide appears to reduce the risk of MACE across a broad continuum of CV risk.4,5 Indeed, in a recent meta-analysis of CV outcomes trials of GLP-1 RAs, which included 56 004 patients, the reduction in risk of MACE was not significantly different between patients with established CVD and patients with CV risk factors only,6 demonstrating a favourable protective effect of the GLP-1 RA class across the CV risk continuum. These findings underpin the 2019 update to the American Diabetes Association and the European Association for the Study of Diabetes consensus report, which recommends GLP-1 RAs as first-line therapy in patients with either high/very high CV risk or established CVD.7

A limitation of the present analysis is that, with different inclusion criteria between the trials, definitive re-categorization of SUSTAIN 6 and PIONEER 6 patients was difficult to achieve.

In conclusion, the results of this analysis suggest that the CV effects of semaglutide may extend to patients with type 2 diabetes across the CV risk continuum, consistent with the GLP-1 RA meta-analysis and dulaglutide results from REWIND.

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Parts of these analyses have been presented previously at the American College of Cardiology 2020 Scientific Session (Verma S et al. J Am Coll Cardiol 2020:75:1922;supplement 1).

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS
S.R. performed the statistical analyses. All authors were responsible for the content and editorial decisions, were involved at all stages of manuscript development, and approved the final version. S.V. is the guarantor of the article, had full access to all data presented and takes responsibility for its integrity and analysis.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author.

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