Received: 19 November 2020 | Revised: 4 February 2021 | Accepted: 16 February 2021

DOI: 10.1111/dom.14360

BRIEF REPORT

WILEY

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

Subodh Verma MD[1] | Udi Fainberg MD[2] | Mansoor Husain MD[3] | Søren Rasmussen PhD[2] | Lars Rydén MD[4] | Maria Sejersten Ripa MD[2] | John B. Buse MD[5]

[1]St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

[2]Novo Nordisk A/S, Søborg, Denmark

[3]Department of Medicine, Ted Rogers Centre for Heart Research, Toronto General Hospital Research Institute, University of Toronto, Toronto, Ontario, Canada

[4]Department of Medicine K2, Karolinska Institutet, Stockholm, Sweden

[5]University of North Carolina School of Medicine, Chapel Hill, North Carolina

Correspondence
Subodh Verma, MD, PhD, FRCSC, University of Toronto, St Michael's Hospital, 30 Bond St, 8th Floor, Bond Wing, Toronto, Ontario, M5B 1W8, Canada.
Email: vermasu@smh.ca

Funding information
The SUSTAIN 6 (NCT01720446) and PIONEER 6 (NCT02692716) trials were funded by Novo Nordisk

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 semaglutide[2,3] 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

	SUSTAIN 6[3] and PIONEER 6[2]	REWIND[1]
Established CVD	• Prior MI, stroke **or transient ischaemic attack** • History of symptomatic coronary heart disease documented by positive stress test or cardiac imaging • Unstable angina pectoris with ECG changes • Prior coronary, carotid or peripheral arterial revascularization • >50% stenosis on angiography or other imaging of coronary, carotid or lower extremity arteries • Asymptomatic cardiac ischaemia documented by positive nuclear imaging test or exercise test or stress echo or any cardiac imaging • **Chronic heart failure (NYHA class II-III)** • **Chronic kidney disease**	• Prior MI or stroke • History of symptomatic coronary heart disease documented by positive stress test or cardiac imaging • Unstable angina pectoris with ECG changes • Prior coronary, carotid or peripheral arterial revascularization • >50% stenosis on angiography or other imaging of coronary, carotid or lower extremity arteries • Myocardial ischaemia documented by a stress test or with cardiac imaging
CV risk factors	• Persistent microalbuminuria or proteinuria • Hypertension and left ventricular hypertrophy documented by ECG or imaging • Left ventricular systolic or diastolic dysfunction documented by imaging • Ankle-brachial index <0.9	• Persistent microalbuminuria or proteinuria • Hypertension and left ventricular hypertrophy documented by ECG or imaging • Left ventricular systolic or diastolic dysfunction documented by imaging • Ankle-brachial index <0.9 • **Prior transient ischaemic attack or haemorrhagic stroke** • **Chronic heart failure** • **Chronic kidney disease**

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. Patients could not be in both groups. Differences in criteria between trials are in bold.
Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; MI, myocardial infarction; NYHA, New York Heart Association.

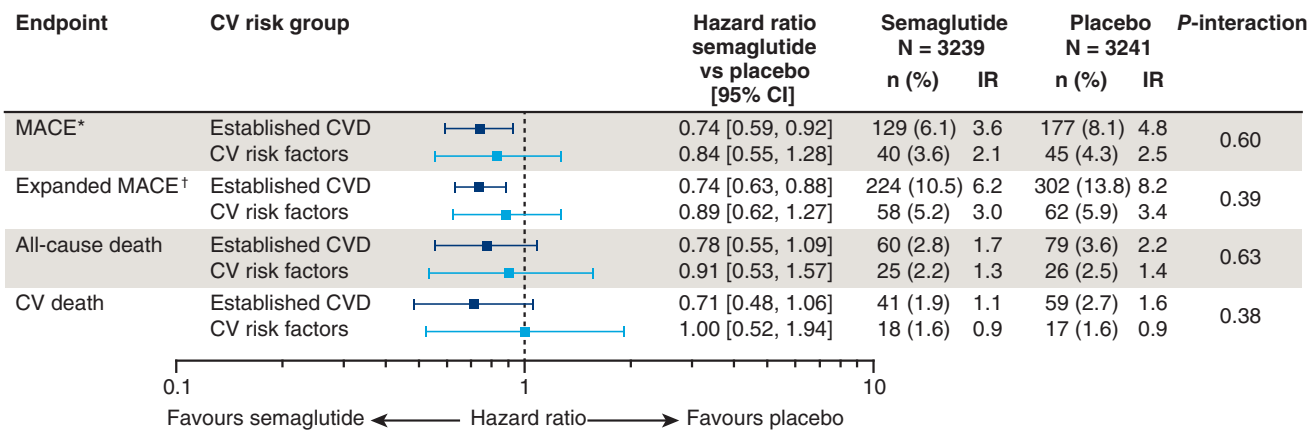

FIGURE 1 Primary and secondary endpoints with semaglutide versus placebo in patients from SUSTAIN 6 and PIONEER 6 re-categorized as having established cardiovascular disease (CVD) or cardiovascular (CV) risk factors using REWIND criteria. Established CVD, n = 4310; CV risk factors, n = 2170. *Major adverse 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.

ACKNOWLEDGMENTS

The authors are grateful to Emre Yildirim, Novo Nordisk, for review of and input to the manuscript. Writing assistance was provided by Alice Singleton, MSc, of Ashfield MedComms, an Ashfield Health Company, part of UDG Healthcare plc (funded by Novo Nordisk), during preparation of this article.

The SUSTAIN 6 (NCT01720446) and PIONEER 6 (NCT02692716) trials were funded by Novo Nordisk, and are registered with clinicaltrials.gov.

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

S.V. has received research grants and/or speaking honoraria from Boehringer Ingelheim/Eli Lilly, AstraZeneca, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Valeant and Amgen. U.F., S.R. and M.S.R. are full-time employees of Novo Nordisk A/S. S.R. also holds stocks in Novo Nordisk A/S. M.H. has received personal fees from Boehringer Ingelheim and Janssen Inc. for advisory panel consultancy and speaker honoraria, grants and personal fees from AstraZeneca and Merck & Co for advisory panel consultancy and investigator-initiated clinical trial grants, personal fees from Roche for advisory panel consultancy, and grants and personal fees from Novo Nordisk for advisory panel consultancy, speaker honoraria and investigator-initiated preclinical study grants. L.R. reports grants from the Swedish Heart Lung Foundation, Stockholm County Council and Boehringer Ingelheim, and fees for consulting and speaking from Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Merck and Bayer. J.B.B.'s contracted consulting fees and travel support for contracted activities are paid to the University of North Carolina by Adocia, AstraZeneca, Dance Biopharm, Dexcom, Eli Lilly, Fractyl, GI Dynamics, Intarcia Therapeutics, Lexicon, MannKind, Metavention, NovaTarg, Novo Nordisk,

Orexigen, PhaseBio, Sanofi, Senseonics, vTv Therapeutics and Zafgen. J.B.B. also reports grant support from AstraZeneca, Eli Lilly, Intarcia Therapeutics, Johnson & Johnson, Lexicon, Medtronic, NovaTarg, Novo Nordisk, Sanofi, Theracos, Tolerion and vTv Therapeutics, is a consultant to Cirius Therapeutics Inc, CSL Behring, Fortress Biotech, Mellitus Health, Neurimmune AG, Pendulum Therapeutics, Stability Health and Zealand Pharma, holds stock/options in Mellitus Health, Pendulum Therapeutics, PhaseBio and Stability Health, and his effort here is also supported by grants from the National Institutes of Health (UL1TR002489, P30DK124723).

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.

ORCID

Subodh Verma https://orcid.org/0000-0002-4018-8533
Mansoor Husain https://orcid.org/0000-0002-3740-6739

REFERENCES

1. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet (London, England)*. 2019;394(10193):121-130.
2. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381(9):841-851.
3. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.
4. Husain M, Bain SC, Jeppesen OK, et al. Semaglutide (SUSTAIN and PIONEER) reduces cardiovascular events in type 2 diabetes across varying cardiovascular risk. *Diabetes Obes Metab*. 2020;22:442-451.
5. Husain M, Bain SC, Holst AG, Mark T, Rasmussen S, Lingvay I. Effects of semaglutide on risk of cardiovascular events across a continuum of cardiovascular risk: combined post hoc analysis of the SUSTAIN and PIONEER trials. *Cardiovasc Diabetol*. 2020;19(1):156.
6. Marsico F, Paolillo S, Gargiulo P, et al. Effects of glucagon-like peptide-1 receptor agonists on major cardiovascular events in patients with type 2 diabetes mellitus with or without established cardiovascular disease: a meta-analysis of randomized controlled trials. *Eur Heart J*. 2020;41(35):3346-3358. ehaa082.
7. 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):487-493.

How to cite this article: Verma S, Fainberg U, Husain M, et al. Applying REWIND cardiovascular disease criteria to SUSTAIN 6 and PIONEER 6: An exploratory analysis of cardiovascular outcomes with semaglutide. *Diabetes Obes Metab*. 2021;23:1677–1680. https://doi.org/10.1111/dom.14360