sumptions add noise to the measurement. Scoring with item-response theory or Rasch analysis results in precision of measures that is up to 10 times as high as that of summary scoring.[3] We suggest that the authors reanalyze their data using psychometric methods, such as Rasch analysis, that are based on item-response theory; such methods significantly reduce measurement noise and produce interval-level measurement.

Himal Kandel, M.Sc. P.H.E.C.
Jyoti Khadka, Ph.D.
Konrad Pesudovs, Ph.D.

Flinders University
Adelaide, SA, Australia
himal.kandel@flinders.edu.au

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THE AUTHORS REPLY: The VR-12 is a well-established instrument for the assessment of health-related quality of life[1] and has been used in many settings, including the Medicare Advantage Program, quasi-experimental studies, and randomized, controlled trials.[1,2] The VR-12 scoring algorithms involve complex methods with weights that control for the effects of regression toward the mean and for imputation of missing values.[3] Collectively, the literature indicates that the physical and mental summary scores are sensitive to discriminating between clinically relevant groups and are responsive to change in pre–post prospective intervention studies and in randomized clinical trials, and the ceiling effects for the VR-12 have not been found to be substantial.[4] In addition, a previous study that was conducted to develop links between scores on the Patient Reported Outcomes Measurement Information System (PROMIS) 29 and those on the VR-12 indicated that the psychometric properties of the VR-12 performed well in comparison with the PROMIS 29, a measure that is based on item-response theory.[5] Although a Rasch analysis could prove interesting, it is unlikely that it would change our conclusions.

Dan R. Berlowitz, M.D., M.P.H.

Bedford VA Hospital
Bedford, MA
dan.berlowitz@va.gov

Nicholas M. Pajewski, Ph.D.

Wake Forest School of Medicine
Winston-Salem, NC

Lewis E. Kazis, Sc.D.

Bedford VA Hospital
Bedford, MA

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Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

TO THE EDITOR: In the trials of the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program (Aug. 17 issue),[1] patients who had been assigned to receive canagliflozin had significantly lower rates of the primary outcome (a composite of death from cardiovascular causes, nonfatal

myocardial infarction, or nonfatal stroke) than those assigned to receive placebo (hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97). Beyond statistical significance, however, a treatment difference must be clinically significant.[2] On an absolute scale, these results show that more than 200 patients must receive daily canagliflozin for the duration of the trial (mean, 3.6 years; median, 2.4 years) in order for 1 patient to benefit. More importantly, the trials show a risk of amputation that is almost twice as high among patients receiving canagliflozin as among patients receiving placebo (hazard ratio, 1.97; 95% CI, 1.41 to 2.75). Although the risk was primarily at the level of the toes and metatarsals, 29% of the affected participants had a more proximal amputation. Similar to other new medications for type 2 diabetes, canagliflozin is expensive, with a suggested price per tablet of $10.53 (€9.09, £8.03).[3] Economic models[4,5] need to be updated to consider the benefit–harm ratio emerging from these new data.

Piero Baglioni, M.D.

Centre Hospitalier St. Jean d'Angély
St. Jean d'Angély, France
piero.baglioni@ch-angely.fr

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Because of the transparency policy of the *Journal*, readers have access to exhaustive documentation of published trials. In the CANVAS trials, there are some surprising inconsistencies between the statistical analysis section of the trial protocols and the final article, affecting important points concerning the design of the two trials. The primary hypothesis, that "relative to placebo plus standard of care, canagliflozin plus standard of care reduces CV [cardiovascular] risk," is stated as "a test of noninferiority, with the use of a margin of 1.3 for the hazard ratio for the primary outcome with canagliflozin as compared with placebo" in the published article, whereas it is described as just exploratory in the CANVAS–Renal (CANVAS-R) trial. Sample-size calculations in the original protocol are related to changes in the glycated hemoglobin level and not to cardiovascular outcomes and undergo several transformations before they settle down. Methodologic inconsistencies in both design and analysis items that should be clearly prespecified at the beginning of a trial arouse important concerns for the critical reader trying to ascertain the validity of a trial.

M. Mercè Fernández-Balsells, M.D., Ph.D.

Hospital Universitari de Girona Dr. Josep Trueta
Girona, Spain
mercefernandez.girona.ics@gencat.cat

Lidia Sojo-Vega, M.D.

Institut Català de la Salut
Girona, Spain

Wifredo Ricart-Engel, M.D., Ph.D.

CIBERobn
Girona, Spain

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the CANVAS trials, the use of canagliflozin was associated with an increased risk of amputation. The majority of the amputations were minor and occurred distally. Although the mechanisms are still unclear, the fact that the preponderance of events occurred in patients with a history of amputation and peripheral arterial disease may offer some clues. In multivariate analysis, the most important predictor of amputation was previous amputation (hazard ratio, 20.9; 95% CI, 4.2 to 30.8). This raises the possibility that patients in the trial who had critical limb ischemia may have been vulnerable to hemoconcentration and alterations in viscosity, which are well known to occur with sodium–glucose cotransporter 2 (SGLT-2) inhibitors.[1] Patients with critical limb ischemia have seriously impaired perfusion, and even small changes in viscosity

or perfusion may have had a deleterious effect on limb outcomes. Although the prevalence of peripheral-artery disease in the CANVAS trials (21% of all patients) was similar to that in the EMPA-REG OUTCOME trial, the reason why this was not observed in the EMPA-REG OUTCOME trial may have been related to the fact that data regarding events that were related to peripheral-artery disease, such as amputations, were not collected.[2]

Sanjay Rajagopalan, M.D.

Harrington Heart and Vascular Institute
Cleveland, OH
sxr647@case.edu

Robert Brook, M.D.

University of Michigan
Ann Arbor, MI

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Baglioni is concerned about the risks and benefits of canagliflozin. The absolute benefits among the participants of the CANVAS trials were such that, for every 1000 patients who were treated for 5 years, there would be 23 patients (95% CI, 4 to 42) who did not have a primary outcome event (number needed to treat, 43), 16 patients (95% CI, 7 to 25) who were not hospitalized for heart failure (number needed to treat, 63), and 18 patients (95% CI, 8 to 27) who did not have a serious decline in kidney function (number needed to treat, 57). There would also be 15 patients (95% CI, 8 to 22) among whom treatment would lead to an amputation (number needed to treat, 68); 29% of the amputations were more proximal amputations. Clinicians will make tailored decisions about the use of canagliflozin on the basis of the likely balance of benefits and risks in individual patients.

Fernández-Balsells et al. have questions about the design and testing strategy. The hypotheses and testing strategy of the CANVAS Program were designed to maximize the capacity of the trial program to define the efficacy and safety of the compound while minimizing the risk of introducing systematic or random errors. The shift to an analysis strategy on the basis of the combined trial data sets was done primarily to meet guidance that was provided by regulatory bodies.[1] The final analysis strategy underwent extensive review by groups that were independent of the trial sponsor and was documented in detail as both a statistical analysis plan and a peer-reviewed publication, to which we refer readers wishing to ascertain the validity of the approach we used.[2]

Rajagopalan and Brook ask about amputations in our trial. The cause of the increased risk of amputation that was observed in the CANVAS Program remains to be elucidated. Although previous amputation was strongly associated with this risk, most amputations occurred in participants who did not have a history of amputation. Whether amputation risk will be specific to canagliflozin or will also involve other drugs in the class will become apparent only as additional data accrue. There is no detailed report available of the means by which amputation events were recorded in the EMPA-REG OUTCOME trial, and it is unknown whether that could contribute to the difference between the two compounds for this outcome.[3]

Bruce Neal, M.B., Ch.B., Ph.D.
Vlado Perkovic, M.B., B.S., Ph.D.

George Institute for Global Health
Sydney, NSW, Australia
bneal@georgeinstitute.org.au

David R. Matthews, D.Phil., B.M., B.Ch.

University of Oxford
Oxford, United Kingdom

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