JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 71, NO. 23, 2018
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PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Only Trials Tell the Truth About Treatment Effects*

John J.V. McMurray, MD

With the increasing availability of large datasets, publication of "real-world" analyses of outcomes related to pharmacological therapy is now commonplace in medical journals. In this issue of the *Journal*, the report by Kosiborod et al. (1) is an especially impressive example of such studies, with an initially eligible population of nearly 2.6 million patients with type 2 diabetes mellitus receiving a new prescription for a glucose-lowering drug. The available datasets

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included a remarkable 20% of the whole population of Japan and 80% to 90% of all individuals with diabetes in Australia. Following propensity-score matching, outcomes after 249,348 episodes of initiation of a sodium-glucose cotransporter (SGLT)-2 inhibitor were compared with those after an equal number of episodes of initiation of other glucose-lowering therapies (because some patients were started on both types of treatment, the analysis was by episode of initiation). Compared with other therapies, initiation of an SGLT-2 inhibitor was associated with better clinical outcomes after an approximate mean follow-up of just over 1 year (**Table 1**). Kosiborod et al. (1) concluded that their findings suggest that the known cardiovascular benefits of SGLT-2 inhibitors may extend across racial/ethnic background and from primary to secondary prevention (and that there is a "class effect"). Are these conclusions valid?

The limitations and risks of inferring an effect of treatment from observational data are well known (2–5). The problem with propensity scores and other means of adjusting for differences between groups of patients treated in one way or another is that only measured confounders can be accounted for (and may still not be fully accounted for). Although Kosiborod et al. (1) included an impressive list of patient characteristics in their matching, many prognostically important variables are missing, including urinary albumin creatinine ratio, lipids, blood pressure, C-reactive protein, uric acid, as well as important noncardiovascular comorbidities (e.g., chronic lung disease and history of cancer). Other variables apparently adjusted for are not shown in the after-matching table, so we cannot be sure how similar they were (e.g., duration of diabetes, smoking, body mass index, antiplatelet, and anticoagulant therapy). Other critically important unmeasured confounders include socioeconomic status and the "healthy-user" effect (6). Socioeconomic status is a powerful determinant of cardiovascular and other outcomes and in many societies only the economically advantaged can afford new drugs. The healthy-user effect is thought likely to have at least in part accounted for some of the classic examples of observational findings disproved by randomized trials (e.g., the "benefits" of estrogen replacement therapy and vitamins C and E) (6). Other unmeasured confounders/unknown biases include additional patient and physician factors that influence who is and is not prescribed the treatment of interest (including confounding by indication) (2–5). A glance at the striking differences between individuals prescribed a SGLT-2 inhibitor and those prescribed another

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom. Dr. McMurray has served as a co-principal investigator and Steering Committee member, respectively, for the Harmony-Outcome trial (albiglutide) and ASCEND-D and ASCEND-ND (using daprodustat) and meetings related to these trials (both funded by GlaxoSmithKline) and as principal investigator for the BEST trial (bexagliflozin) and meetings related to this trial (funded by Theracos); and as principal investigator for DAPA-HF (dapagliflozin) and meetings related to this trial (funded by AstraZeneca). GlaxoSmithKline, Theracos, and AstraZeneca have paid his employer, Glasgow University, for his time, but he has not received any payments personally.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2018.04.019

glucose-lowering therapy, before propensity-score matching, highlights the probability of significant unmeasured confounding.

These are the reasons why only random assignment to therapy (in a sufficient number of patients) allows valid assessment of the effect of a treatment. Randomization ensures equal distribution of both known and unknown confounders between treatment groups. The example of the SGLT-2 inhibitors is particularly interesting because 3 large (and several smaller) double-blind randomized placebo-controlled trials have been conducted (7–9). Comparison of the findings of these trials with those of Kosiborod et al. (1) is instructive (**Table 1**). Although the hazard ratios for heart failure hospitalization and myocardial infarction appear similar, those for the other outcomes are not. Examination of death from any cause is most informative. At face value, a hazard ratio of 0.51 in the observational analysis suggests an almost 50% "reduction" in mortality. Clearly, almost no chronic therapy has such an effect after as little as 1 year of follow-up, especially as dosing and adherence are unlikely to be as good in the real world as in clinical trials. We have seen this before. In another large and carefully conducted observational analysis using propensity matching and other methods of adjustment, Go et al. (10) found that statin use was associated with a 30% to 40% lower mortality in patients with heart failure. Two subsequent large randomized controlled trials showed no effect of this treatment on mortality in heart failure (11,12). These and other examples reaffirm the unreliability of observational assessments of treatment "effects" (2–6).

However, it is important to emphasize that observational analyses are still valuable (13,14). They remain an important tool for evaluating and improving the use of evidence-based therapy in routine practice, providing data for economic analyses and for identifying rare and unexpected adverse effects of therapy. They are useful for assessing the external validity of trial populations and in the present report we can see the quite different cardiovascular comorbidity and, especially, background therapy in the countries studied, compared with the large trials. The dataset used by Kosiborod et al. (1) was dominated by South Korean patients, with high rates of use of thiazolidinediones (22%) and dipeptidylpeptidase-4 inhibitors (31%). Observational analyses are also valuable for generating hypotheses and occasionally may provide the best available (but confounded) data on treatments for conditions too rare to be studied in clinical trials and in subsets of patients excluded from trials.

In summary, each of the observational studies and clinical trials are informative and valuable, and they are complementary, but only trials tell the truth about treatment effects.

TABLE 1 Comparison of Outcomes Using Sodium-Glucose Cotransporter-2 Inhibitors in Trials in Individuals With Type 2 Diabetes Mellitus and Observational Data From the CVD-REAL 2 Study

Data Source (Ref. #)	Death	HFh	MI	Stroke
RCT meta-analysis (9)	0.79 (0.70–0.88)	0.67 (0.55–0.80)	0.84 (0.73–0.98)	1.03 (0.86–1.24)
Observational data (1)	0.51 (0.37–0.70)	0.64 (0.50–0.82)	0.81 (0.74–0.88)	0.68 (0.55–0.84)

Values are hazard ratio (95% confidence interval) for each outcome, SGLT-2 inhibitor versus placebo/alternative glucose-lowering therapy.

CVD-REAL = Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors study; HFh = heart failure hospitalization; MI = myocardial infarction; RCT = randomized controlled trial.

ADDRESS FOR CORRESPONDENCE: Dr. John J.V. McMurray, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, United Kingdom. E-mail: john.mcmurray@glasgow.ac.uk. Twitter: @UofGICAMS.

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Diabetes Res Clin Pract 2018 Mar 28 [Epub ahead of print].

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KEY WORDS cardiovascular disease, diabetes mellitus, heart failure, observational studies, randomized controlled trials, sodium glucose cotransporter