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Saxagliptin, Alogliptin, and Cardiovascular Outcomes

TO THE EDITOR: Besides showing futility in the use of dipeptidyl peptidase 4 (DPP-4) inhibitors to reduce cardiovascular outcomes, the studies by Scirica et al.¹ and White et al.² (Oct. 3 issue) have raised concerns regarding increased rates of heart failure associated with these agents. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)—Thrombolysis in Myocardial Infarction (TIMI) 53 (SAVOR-TIMI 53) trial, reported by Scirica et al., showed a 27% increase in hospitalization for heart failure among patients with diabetes who received saxagliptin as compared with patients with diabetes who received placebo (3.5% vs. 2.8%; hazard ratio, 1.27; 95% confidence interval [CI], 1.07 to 1.51; $P=0.007$). Outcomes with respect to heart failure were not mentioned at all in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial reported by White et al., although 28% of patients had congestive heart failure at baseline.² Clinically oriented readers would have wished to see figures for incident (not total) heart failure as an outcome in both trials, as well as rates of cardiovascular events among patients with preexisting heart failure, to clarify this safety aspect of DPP-4 inhibitor therapy, especially since there has been some uncertainty about the use of another DPP-4 inhibitor, vildagliptin, in patients with heart failure.³ Furthermore, interactions of DPP-4 inhibitors with heart failure cannot be totally ruled out, since levels of brain natriuretic peptides, which may be 100 times as high in patients with heart failure as in patients without heart failure, are known substrates of the enzyme DPP-4.⁴

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1. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317-26.
2. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327-35.
3. McMurray J. The Vildagliptin in Ventricular Dysfunction Diabetes (VIVID) trial. Presented at the Heart Failure Congress 2013, Lisbon, Portugal, May 25–28, 2013:99. abstract.
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DR. SCIRICA AND COLLEAGUES REPLY: SAVOR-TIMI 53 showed that saxagliptin neither increased nor decreased the primary end point (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke). As Standl emphasizes, the observed increased risk of hospitalization for heart failure requires additional analysis. Among the 12.8% of patients who had a history of heart failure, the risk of the primary end point and the secondary end point (the primary composite end point plus hospitalization for heart failure, coronary revascularization, or unstable angina) among patients who received saxagliptin was similar to that among patients without a history of heart failure (hazard ratio for the primary end point, 1.13; 95% CI, 0.89 to 1.43 vs. hazard ratio for the primary end point, 0.97; 95% CI, 0.85 to 1.10; $P=0.28$ for interaction; and hazard ratio for the secondary end point, 1.06; 95% CI, 0.89 to 1.27 vs. hazard ratio for the secondary end point, 1.01; 95% CI, 0.91 to 1.11; $P=0.63$ for interaction). Moreover, although the absolute risk of hospitalization for heart failure was highest among patients with a history of heart failure, the relative risk among patients assigned to saxagliptin was similar regardless of the baseline history of heart failure (hazard ratio, 1.21; 95% CI, 0.93 to 1.58 vs. hazard ratio, 1.32; 95% CI, 1.04 to 1.65; $P=0.68$ for interaction).¹ Standl appropriately notes that natriuretic peptides are substrates of the DPP-4 enzyme, and

therefore careful selection of the appropriate assay is an important clinical and research consideration.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Scirica BM, Raz I, Cavender MA, et al. Outcomes of patients with type 2 diabetes and known congestive heart failure treated with saxagliptin: analyses of the SAVOR-TIMI 53 Study. *Circulation* 2013;128:A17503. abstract.

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DRS. WHITE AND ZANNAD REPLY: Standl inquires about findings in the EXAMINE trial regarding incident heart failure, since these exploratory data were not part of the article on our primary results. Because concerns have been raised recently about other DPP-4 inhibitors and increased rates of hospitalization among patients with

heart failure, we have initiated analyses of heart-failure outcomes in our trial. In patients with type 2 diabetes and a recent acute coronary syndrome, including patients with a history of heart failure and those with elevated baseline levels of N-terminal pro-brain natriuretic peptide, cardiovascular outcomes inclusive of hospitalization for heart failure were not increased with alogliptin as compared with placebo. In addition, alogliptin neither induced new-onset heart failure nor worsened heart-failure outcomes in patients with a history of heart failure before randomization. We will continue to analyze results related to this important question in our trial.

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Preparing for Responsible Sharing of Clinical Trial Data

TO THE EDITOR: Mello et al. (Oct. 24 issue)¹ identify ensuring the responsible use of data as a key aspect of any system for expanded access to participant-level data. In their careful framework for considering the legal, ethical, and policy implications of such sharing, however, they omit a powerful mechanism to meet this aim. Open computer code facilitates replication, which both advances knowledge² and holds powerful interests accountable.³

Regardless of which of the four proposed models are adopted, data-use agreements should require data requesters to publish their computer code alongside any analysis. The program should be complete, in that it takes as its input the provided trial data and finishes by providing every table, figure, and summary statistic reported in the final paper.

Just as proposals for an increase in the level of shared clinical trial data use openness as a mechanism to hold data generators accountable, openness can hold data requesters accountable. If scientists can make progress in ensuring the replicability of studies that include the use of

genetically modified mice,⁴ surely the far easier task of ensuring replicable reanalyses can be achieved.

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3. Herndon T, Ash M, Pollin R. Does high public debt consistently stifle economic growth? A critique of Reinhart and Rogoff. PERI Working Paper Series. April 15, 2013 (http://www.peri.umass.edu/fileadmin/pdf/working_papers/working_papers_301-350/WP322.pdf).

4. The sharing principle. *Nature* 2009;459:752.

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TO THE EDITOR: Mello and colleagues outline the potential benefits and risks of participant-level data sharing. They highlight technical and ethical concerns as sponsors and investigators move