Letter Regarding AHA Scientific Statement "Drugs That May Cause or Exacerbate Heart Failure"

To the Editor:

The AHA Scientific Statement "Drugs That May Cause or Exacerbate Heart Failure" by Page *et al.*[1] broadly reviews medications that may impact negatively on heart failure (HF). While we applaud Page *et al.* for taking on this important topic, the statement overlooks key evidence relating to dipeptidyl peptidase-4 inhibitors (DPP4is). Specifically, the review omits consideration of the HF results of the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) published in June 2015,[2] and the recent TECOS secondary analysis by McGuire *et al.*[3] focusing specifically on hospitalization for HF.

Page *et al.* mention the "potential increase in HF hospitalization" indicated by results of the SAVOR-TIMI 53 (saxagliptin) and EXAMINE[4,5] (alogliptin) trials, a claims database analysis of sitagliptin use in a cohort of 7620 patients with type 2 diabetes mellitus and incident HF, and a meta-analysis of randomized trials of DPP4is and HF. In addition, their Table 1 indicates that the "Magnitude of HF induction or precipitation" with sitagliptin is "major" and that this "may be a class effect." However, the TECOS main results and detailed secondary analyses found no impact of sitagliptin on hospitalization for HF with no difference in incidence—3.1% (228/7332) *vs.* 3.1% (n = 229/7339) for sitagliptin and placebo, respectively—or in rates—1.07 *vs.* 1.09 per 100 patient-years, respectively (hazard ratio 1.00; 95% CI 0.83–1.20; P=0.98).[2] McGuire *et al.* also found no increased risk of hospitalization for HF with sitagliptin among patients with a history of HF, and no increased risk of fatal HF events.[3]

Although TECOS showed no effect of sitagliptin on hospitalization for HF, concerns may remain with respect to saxagliptin given the 27% (P=0.007) increased risk of hospitalization for HF in SAVOR-TIMI 53, and alogliptin with a non-significant 19% excess seen in EXAMINE.[4] These saxagliptin and alogliptin results led to an FDA Drug Safety Communication on April 5, 2016, concerning the potential heart failure risk specifically with these two agents (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm494252.htm). The meta-analysis of the hospitalization for HF results from SAVOR-TIMI 53, EXAMINE, and TECOS conducted by McGuire *et al*. is reassuring in that it showed no significant increased risk of HF when the three studies were combined (class hazard ratio 1.14; 95% CI 0.97–1.34; P=0.16, I^2 = 44.9),[3] albeit with moderate heterogeneity.

We respectfully suggest that the section of the statement regarding DPP4is be amended at the earliest opportunity.

Sincerely,

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References

1. Page RL 2nd, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, Spencer AP, Trupp RJ, Lindenfeld J; American Heart Association Clinical Pharmacology and Heart Failure and Transplantation Committees of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association. Circulation. 2016 Jul 11. pii: CIR.0000000000000426. [Epub ahead of print]

2. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015;373(3):232-42.

3. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, Bethel MA, Cornel JH, Lopes RD, Halvorsen S, Ambrosio G, Buse JB, Josse RG, Lachin JM, Pencina MJ, Garg J, Lokhnygina Y, Holman RR, Peterson ED; for the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) Study Group. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial. JAMA Cardiol. 2016;1(2):126-135.

4. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013 Oct 3;369(14):1327-35.

5. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet. 2015 May 23;385(9982):2067-76.

Response:

We very much appreciate the comments by Peterson et al and bringing attention to the findings from the secondary analysis of the Trial Evaluating Cardiovascular Outcomes With Sitagliptin TECOS by McGuire et al which focused specifically on hospitalization for heart failure (HF).[1] As Peterson et al have highlighted, the secondary findings of TECOS demonstrated a neutral effect on the endpoint of hospitalization for HF risk in patients with type 2 diabetes mellitus at high cardiovascular risk (adjusted HF, 1.02; 95% CI, 0.83-1.26). However, it is important to highlight that of those with a history of a first hospitalization for HF (n=457), the majority were New York Heart Association (NYHA) functional class I-II (58.1%) in which 1.6% had NYHA class IV and 23.6% did not have a NYHA reported. Thus, the effect on the risk of HF hospitalization in patients with more serve heart failure will need to be explored.

The data surrounding the use of dipeptidyl peptidase-4 (DPP-4) inhibitor class and their effects on HF hospitalizations in patients with and without HF continues to evolve and unfortunately the findings from the secondary analysis of TECOS were published while our statement was in production. Nonetheless, we agree with Peterson et al that the secondary findings from TECOS does bring reassurance that sitagliptin appears to have a better cardiovascular safety profile within this class. In regards to a "class effect" of these drugs, we will eagerly await the findings from the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) trial. This study is a large, international, randomized trial in subjects with early type 2 diabetes and increased cardiovascular risk or established complications that will determine the long-term cardiovascular safety of linagliptin versus the sulfonylurea.[2] Of note, CAROLINA will also address, through independent adjudication, whether hospitalizations for HF are increased with linagliptin or glimepiride and HF related mortality occurs more frequently.[3] Until the publication of CAROLINA, we recommend caution and close monitoring with the use of DPP-4 inhibitors, particularly with saxagliptin and alogliptin, when used in patients with HF.

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References:

1. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, Bethel MA, Cornel JH, Lopes RD, Halvorsen S, Ambrosio G, Buse JB, Josse RG, Lachin JM, Pencina MJ, Garg J, Lokhnygina Y, Holman RR, Peterson ED; for the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) Study Group. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial. JAMA Cardiol. 2016;1(2):126-135.

2. National Institutes of Health. CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (NCT01243424). Available at: https://clinicaltrials.gov/ct2/show/NCT01243424. Accessed October 1, 2016.

3. Marx N, Rosenstock J, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, Espeland MA, Bluhmki E, Mattheus M, Ryckaert B, Patel S, Johansen OE, Woerle HJ. Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA®). Diab Vasc Dis Res 2015; 12(3): 164-74.