Erroneous Event Count in a Meta-Analysis (Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes Mellitus)

We identified an erroneous event number in the report by Patil et al[1] entitled "Meta-Analysis of Effect of Dipeptidyl Peptidase-4 Inhibitors on Cardiovascular Risk in Type 2 Diabetes Mellitus," published in the (2012) 110th issue of *The American Journal of Cardiology*. Figures presented in the meta-analysis are not consistent with the data from the report by Chan et al[2] entitled "Safety and Efficacy of Sitagliptin in Patients With Type 2 Diabetes and Chronic Renal Insufficiency" published in the tenth issue of *Diabetes, Obesity and Metabolism* (2008).

In the report by Patil et al, 12 major cardiovascular events were reported in the control group. However, there was only 1 major adverse cardiac event identified in the report by Chan et al. This is confirmed by the clinical register *clinicaltrial.gov* where Chan's trial (NCT00095056) reported only 1 event in the control group.

We performed the same meta-analysis with the corrected number of events for the report by Chan et al using RevMan software. Unfortunately, with this new data set, the results are modified as shown in the forest plot (Figure 1):

The result of the association test becomes not statistically significant ($p = 0.19$), and the conclusion of the safety and efficacy of sitagliptin is misleading.

Marielle Buisson, MD
Catherine Cornu, MD
Patrice Nony, MD, PhD
Bron, France
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1. Patil HR, Al Badarin FJ, Al Shami HA, Bhatti SK, Lavie CJ, Bell DS, O'Keefe JH. Meta-analysis of effect of dipeptidyl peptidase-4 inhibitors on cardiovascular risk in type 2 diabetes mellitus. *Am J Cardiol* 2012;110:826–833.
2. Chan JC, Scott R, Arjona Ferreira JC, Sheng D, Gonzalez E, Davies MJ, Stein PP, Kaufman KD, Amatruda JM, Williams-Herman D. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. *Diabetes Obes Metab* 2008;10:545–555.

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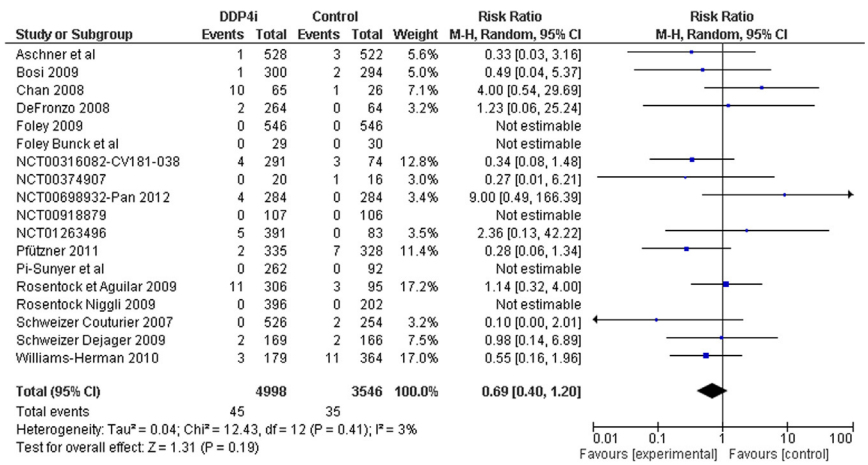

Figure 1. Forest plot for major cardiovascular events, all DPP4 inhibitors versus control.

Reply

We would like to thank Buisson et al[1] for discovering the error in our previous meta-analysis and commend them for their diligence. We have reviewed the raw numbers of major adverse cardiovascular events (MACE) from our previous meta-analysis[2] and confirmed that the MACE we recorded from the report by Chan et al[3] were erroneous. In retrospect, the 2 abstracters recording this information both inadvertently used the events listed in Table 5 of the report by Chan et al, which depicted projected events per 100 patient-years of therapy (10 and 12 for sitagliptin and control groups, respectively), rather than actual events as listed in Table 4 of the report by Chan et al (11 and 1 for sitagliptin and control groups, respectively). After correcting this numerical error, the point estimate for the pooled analysis showed that DPP4 inhibitors no longer had a statistically significant effect on MACE, as pointed out by Buisson et al.[1]

Since the time of our initial analysis, 2 large prospective randomized controlled trials of DPP4 inhibitors have been published. Therefore, we have taken the opportunity to update our meta-analysis by adding in these new data regarding MACE from the SAVOR-TIMI 53 and EXAMINE studies, which evaluated saxagliptin and alogliptin, respectively.[4,5] The updated pooled analysis (Figure 1) shows that DPP4 inhibitors had a neutral effect on MACE (relative risk [RR] 0.98 [0.90 to 1.07], $p = 0.65$), cardiovascular death (RR 0.96 [0.83 to 1.11], $p = 0.57$), and myocardial infarction (RR 0.98 [0.86 to 1.11], $p = 0.70$). The addition of these new randomized trial results markedly improves the power of our previous meta-analysis. Thus, the cumulative randomized trial data suggest that DPP4 inhibitor therapy neither increases nor decreases the risk of adverse cardiovascular events (Figure 2).