

## Shall We Consider DPP-4-Inhibitors as Cardiovascular Safe Drugs?

Jose Mario F de Oliveira

Department of Medicine, Universidade Federal Fluminense, Brazil

### Opinion

Cardiovascular diseases are by far the most frequent and deadly complications of type 2 diabetes mellitus.

All recent anti-diabetic drugs have been shadowed by signals of more or less severe toxic side-effects, but the DPP-4 Inhibitors (DPP-4) have been gaining the reputation, based on interpretations of short and medium-term randomized clinical trials (RCT), and to pre-marketing rules of regulatory agencies, of being as a whole safe anti-diabetic drugs for type 2 diabetics [1].

The awareness about the safety of recent anti-diabetic drugs has prompted the FDA to issue, since the rosiglitazone saga [2], more restrictive, albeit still liberal rules for the release of these drugs. In a few words, legal approval could be achieved by these kind of drugs as long as they show in pre-marketing RCTs being non-superior to an 80% upper-bound 95% confidence interval (CI) increase in cardiovascular disease risks [3].

Here we argue that indeed there are no direct or indirect reasons to consider DPP-4 as safe drugs at large. And why that? Let's try going on in a step by step mode:

- Is there any clinical trial evidence that DPP-4 prolong life by just 5 minutes, 5 hours, 5 days or 5 months in type 2 diabetics? The answer is No, there isn't one single RCT, short-term, medium-term, or long-term that have shown either one of these.

- Is there any RCT evidence that DPP-4 is superior to placebo for reducing cardiovascular disease such as stroke, coronary heart disease, myocardial infarction or congestive heart failure? The answer still remains a robust No for either one of the above.

Conversely, RCTs namely with saxagliptin and sitagliptin, plus the

recent largest published meta-analysis of pooled trial data has so far shown an absolute excess risk when compared to placebo of admissions for congestive heart failure of being in the magnitude of 16 cases per 1000 patients treated for 10 years providing a number needed to harm of 63 (NNH) patients over these same 10 years, especially for those high risk for cardiovascular disease type 2 diabetics [4]. And what is most worrying is the finding in the TECOS trial of sitagliptin that just with a simple look at the 95% CIs one can see that this DPP-4 studied under the ideal conditions created by Merck, sitagliptin induced a 9% increase in the composite cardiovascular outcomes; 95% CI Hazard ratio of 0.88 to 1.09.

Having said the above, and considering all the uncertainties surrounding a class of drugs that in present diabetes care has not shown any superiority to placebo over hard endpoints type 2 diabetes complications, and with a measurable potential for harms – namely for congestive heart failure we should still keep a red flag on its use and keep a well-shaped memory about the rosiglitazone glory days [5].

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**\*Corresponding author:** Jose Mario F de Oliveira, Department of Medicine, Universidade Federal Fluminense, Brazil, Tel: +55212629-9208; E-mail: [jmariofranco@gmail.com](mailto:jmariofranco@gmail.com)

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