Dipeptidyl peptidase-4 inhibitors (gliptins) and heart failure: data-mining of spontaneous reports submitted to the FDA Adverse Event Reporting System (FAERS)

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BACKGROUND. The cardiovascular safety of the dipeptidyl peptidase-4 inhibitors (DPP-4-Is) has been recently challenged by results of SAVOR-TIMI and EXAMINE trials, which raised the hypothesis that DPP-4-Is may precipitate and/or exacerbate heart failure (HF) in patients with type II diabetes (Scirica et al., 2013; White et al., 2013). However, recent meta-analyses on clinical trials provided conflicting evidence on whether or not differences exist among agents (Monami et al., 2014). Therefore, we assessed spontaneous reports submitted to the publicly available US-FDA Adverse Event Reporting System (FAERS), which is likely to reflect post-marketing clinical practice, where comorbidities and poly-pharmacotherapy exist.

METHOD. We extracted FAERS reports where DPP4-Is were recorded as suspect (2006Q4 - marketing authorization of the first-in-class agent, sitagliptin - through 2013Q4 - latest available FAERS data). Reports of HF were identified based on the standardized MedDRA Query 'cardiac failure'. Primary disproportionality analysis was carried out by calculating the Reporting Odds Ratio (ROR) with 95%Confidence Interval (95%CI), using the entire FAERS database. A statistically significant ROR was defined by a Lower Limit of the 95%CI>1. Rosiglitazone was used as positive control. Secondary disproportionality analysis was performed by considering reports in which at least one antidiabetic agent was recorded (diabetes represents *per se* a risk factor of HF), correcting for drug-related competition bias (i.e., removal of reports with rosiglitazone) and event-related competition bias (i.e., removal of reports with pancreatitis). Adjustment of ROR (Mantel-Haenszel correction) was also performed for the following concomitant drugs: 1) agents used to treat HF or related risk factors such as atrial fibrillation, as possible indication bias (i.e., selective beta-blockers, carvedilol, ACE inhibitors, angiotensin receptor II antagonists; renin inhibitors, diuretics, antithrombotic agents); 2) agents causing or worsening HF (i.e., anticancer drugs, steroidal and non-steroidal anti-inflammatory drugs for systemic use).

RESULTS. DPP-4-Is were recorded as suspect in 7.342 reports, of which 337 (4.6%) with HF. Sitagliptin received 242 HF reports. In primary analysis, statistically significant ROR emerged for the class (ROR=1.25; 96%CI=1.12-1.40), saxagliptin (1.84; 1.38-2.47), vildagliptin (3.13; 1.76-5.56) and rosiglitazone (14.66; 13.85-15.52). In secondary analysis, the ROR increased for saxagliptin (2.60; 1.92-3.50), vildagliptin (4.07; 2.28-7.27) and sitagliptin (1.61; 1.40-1.86). Pre-specified concomitant drugs were reported in 60% of cases; after adjustment, the ROR maintained statistical significance for saxagliptin (1.97; 1.46-2.66), vildagliptin (2.50; 1.40-4.46), and sitagliptin (1.34; 1.16-1.54).

CONCLUSION. Among antidiabetics, 3 out of 5 marketed DPP-4-Is are associated with disproportionate reporting of HF in FAERS, even after adjusting for different confounders. However, the reporting frequency appears low and similar to previously documented rare events (e.g., pancreatitis). The large proportion of cases with concomitant drugs calls for multi-database post-authorization safety studies to assess actual risk of individual drug and the potential existence of a class effect.

Scirica et al. (2013) *N Engl J Med;* 369: 1317–1326.
White et al. (2013) *N Engl J Med*; 369: 1327-35.
Monami et al. (2014) *Nutrition, Metabolism & Cardiovascular Diseases*; 24: 689-697.