Adverse reactions to antidiabetic drugs: an overview of Italian spontaneous reporting data

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Introduction
Recently, several antidiabetic agents have been associated with various safety concerns. For instance, rosiglitazone was withdrawn from most countries because of cardiovascular problems, pioglitazone has been implicated in bladder cancer. Nowadays, serious questions raised about the safety of incretin therapies (i.e. pancreatitis, cancer). Additionally, other well-known adverse effects associated with older antidiabetic agents (i.e. hypoglycemia from insulins) have revealed a large impact on health care systems in terms of hospitalizations and costs. In this context, safety evaluation of antidiabetic agents in clinical practice is warranted. The goal of this study was to analyze reported adverse reactions associated with antidiabetic drugs in the Italian spontaneous reporting system (SRS) and to identify their most important features.

Methods
We performed an analysis on the Italian SRS database managed by the Italian Medicines Agency (AIFA). We selected all the adverse drug reaction (ADR) reports collected from 2001 to 2012 attributed to antidiabetic agents.

Results
Overall 148,289 ADR reports have been collected and, of these, 3,416 (2.3%) were related to antidiabetic agents. The reporting rate per DDDs/1000 inhabitants/day based on national consumption estimates of antidiabetics changed from 0.93 in 2003 to 11.8 in 2011.
Serious ADRs, including 43 fatal cases, accounted for 36.6% (N=1,251) of total reports regarding these drugs. The most reported serious ADRs were severe hypoglycemia (about 50% of serious ADR reports), mainly caused by insulins or sulfonylureas, lactic acidosis from metformin, pancreatitis from incretins.
Regarding specific classes, 751 reports (22.0%) were associated with GLP-1 agonists, 561 (16.4%) with combinations of hypoglycemic drugs, 538 (15.7%) with biguanides, 524 (15.3%) with fast-acting insulins/analogues, 390 (11.4%) with long-acting insulins/analogues, 374 (10.9%) with DPP-4 inhibitors and 318 (9.3%) with sulfonylureas.
The most frequently implicated antidiabetic agents were metformin (15.38%), exenatide (15.5%) and insulin glargine (9.0%).
Reported ADRs for sulfonamides and biguanides were essentially metabolic disorders. Regarding alpha-glucosidase inhibitors, GLP-1 mimetics and DPP-4 inhibitors, gastrointestinal system was the most frequently affected site. General disorders and cardiovascular reactions were more commonly reported for glitazones. Some cases of cancer were described with pioglitazone and incretin therapies.

Conclusions
Most of the serious ADRs attributed to antidiabetic agents are hypoglycemic episodes. GLP-1 agonists are the most frequently implicated antidiabetics. Several reports of cancer associated with pioglitazone and incretins have been described. Data have also shown an increased reporting for pancreatitis with GLP-1 based therapies. Taking into account the limitations of SRSs, further research is needed to evaluate these signals.