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Drug utilization, safety, and effectiveness of exenatide, sitagliptin, and vildagliptin for type 2 diabetes in the real world: Data from the Italian AIFA Anti-diabetics Monitoring Registry

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Abstract *Background and aims:* In Italy, the reimbursed use of incretin mimetics and incretin enhancers was subject to enrollment of patients into a web-based system recording the general demographic and clinical data of patients. We report the utilization data of glucagon-like peptide 1 (GLP1) receptor agonists and dipeptidylpeptidase-4 (DPP4) inhibitors in clinical practice as recorded by the Italian Medicines Agency (AIFA) Monitoring Registry.

Methods and results: From February 2008 to August 2010, 75,283 patients with type 2 diabetes were entered into the registry and treated with exenatide, sitagliptin, or vildagliptin. The treatment was administered to patients in a wide range of ages (≥75 years, $n = 6125$ cases), body mass index (BMI) (≥35 kg/m^2, $n = 22{,}015$), and metabolic control ($HbA_{1c} \geq 11\%$ ((96 mmol/mol), $n = 3151$). Overall, 1116 suspected adverse drug reactions were registered, including 12 cases of acute pancreatitis (six on exenatide). Hypoglycemic episodes mainly occurred in combination with sulfonylureas. Treatment discontinuation for the three drugs (logistic regression analysis) was negatively associated with the male gender and positively with baseline HbA_{1c}, diabetes duration, and, limitedly to DPP-4 inhibitors, with BMI. Treatment discontinuation (including loss to follow-up, accounting for 21–26%) was frequent. Discontinuation for treatment failure occurred in 7.7% of cases (exenatide), 3.8% (sitagliptin), and 4.1% (vildagliptin), respectively, corresponding to 27–40% of all discontinuations, after excluding lost to follow-up. HbA_{1c} decreased on average by 0.9–1.0% (9 mmol/mol). Body weight decreased by 3.5% with exenatide and by 1.0–1.5% with DPP-4 inhibitors.

Conclusions: In the real world of Italian diabetes centers, prescriptions of incretins have been made in many cases outside the regulatory limits. Nevertheless, when appropriately utilized, incretins may grant results at least in line with pivotal trials.

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Introduction

A progressive intensification of treatment is mandatory in type 2 diabetes whenever lifestyle intervention fails to maintain metabolic control [1]. All major guidelines agree on administering metformin as the initial treatment, when tolerated and not contraindicated, but there is no consensus on second-line add-on treatment, in the case of unsatisfactory metabolic control. [2–5].

In the past decade, injectable glucagon-like peptide-1 receptor agonists (GLP-1RAs) and orally administered inhibitors of dipeptidylpeptidase-4 (DPP-4Is) entered the diabetes arena [6,7]. Since the initial marketing authorization as add-on therapies, these drugs have been granted extension of indications to include first-line monotherapy and combination with insulin. However, their best place in therapy remains uncertain [8]. In controlled clinical trials, both GLP-1RAs and DPP-4Is, combined with metformin, produce similar improvements in glycemic control as other second-line treatments, with no negative effects on body weight and overall hypoglycemia [9,10]. However, only a few systematic analyses of long-term clinical data are available on large patients' cohorts [11,12], capturing treatment effects and prescription trends in the community.

In February 2008, the Italian Medicines Agency (AIFA) approved the reimbursed use of exenatide, sitagliptin, and vildagliptin, subject to enrollment of patients into a web-based system to monitor the appropriateness of use, safety profile, and effects on metabolic control and body weight. We report the results of the first 30-month monitoring, as derived from the AIFA Monitoring Registry. Of note, fixed-dose associations of sitagliptin and vildagliptin with metformin were made available along the years; in the present report, their use is considered equivalent to the combination use of the individual compounds. Focus is given to the clinical characteristics of patients, drug safety, and reasons for treatment discontinuation. An analysis of the percentage of patients reaching HbA_{1c} targets over time is also provided, to help clinicians tailor treatment on patients' characteristics.

Methods

The AIFA Anti-diabetics Monitoring registry

A monitoring system has long been operative in Italy to register the use of several therapeutic agents in a wide range of diseases (oncology, neurodegenerative disorders, inflammatory diseases, etc.). The incretin-mimetic and incretin-enhancer AIFA Registry was the first example of a monitoring tool in a highly prevalent disease largely managed by general practitioners (GPs). Access to therapy was allowed through diabetes specialist centers after registration of patients in a web-based system provided by CINECA, a consortium of Italian universities and the National Research Council. The system monitored the registration process all over the country and the uploading of clinical data, and gave access to reimbursement by the National Health Service (NHS). An information letter was sent to the GPs of registered patients to create a flow of information inside the therapeutic network. Follow-up data were uploaded at 3- (vildagliptin) or 4-month (exenatide and sitagliptin) intervals for the first year, and every 6 months thereafter (Supplemental Figure S1).

The case report form included demographic and clinical characteristics, the association with other glucose-lowering agents, and the treatment effects on HbA_{1c} and body weight. The reasons for withdrawal and treatment change were also recorded, and a webpage was available to register adverse drug reactions (ADRs) according to Medical Dictionary for Regulatory Activities (MedDRA) classification. The details of the ADRs were sent to the pharmacovigilance system online or by fax, and the most severe ADRs were locally checked by direct phone interview with specialists.

The AIFA Anti-diabetics Registry was set up in February 2008. In August 2010, exenatide, sitagliptin, and vildagliptin were made available without registration.

Statistical analysis

A descriptive analysis of the population was initially carried out through a multiple-record/-patient approach. To assess the differences in baseline characteristics among patients' groups, Mood's median test was used for continuous variables and the chi-squared test for categorical variables. Combination therapies with other antidiabetic drugs were also recorded.

The safety profiles were assessed by incidence rates (IRs) of ADRs, expressed as 1000 person-years (sum of the duration of exposure from entry to event, discontinuation or data lock in August 2010). The relative risks (RRs) of hypoglycemic events were also calculated in relation to the associated glucose-lowering therapy.

In multivariate logistic regression analysis, all cases with recorded discontinuation (any cause) or lost to follow-up (L-FU) were classified as "treatment discontinuation" (dependent variable, worst-case scenario). The independent variables were the demographic and clinical characteristics at enrollment (gender, age, body mass index (BMI), waist circumference, fasting glucose, HbA_{1c}, fasting C-peptide, and associated glucose-lowering drugs). The waist circumference (less informative than BMI) and fasting glucose or C-peptide (less informative than HbA_{1c}) were excluded. In a sensitivity test, the analyses were repeated in a subset of patients from centers compliant to follow-up >80% (exenatide, $n = 10{,}388$; sitagliptin, $n = 18{,}278$; vildagliptin, $n = 7068$; total L-FU, $n = 2746$ (7.7%)).

The probability of reaching the target value of HbA_{1c} <7% (53 mmol/mol) at the 3–4- and 8–9-month follow-up was tested by logistic regression in separate models for the three different drugs, having HbA_{1c} at baseline as independent variable. In a sensitivity analysis, a less stringent glycemic control of HbA_{1c} <8% (64 mmol/mol) was assessed.

All analyses were performed by CINECA by means of the open-source R Project for Statistical Computing &

Graphics, Version 2.15.0/2012 (www.r-project.org), developed at Bell Laboratories (now Alcatel-Lucent, Paris, France) for multivariate statistics and models, and by means of an SQL developer (Oracle) for the descriptive part of the analysis.

Results

Patient population and baseline characteristics

A total of 77,864 records (38,811 on sitagliptin, 21,064 on exenatide, and 17,989 on vildagliptin), corresponding to 75,283 patients, were registered by 3741 diabetes specialists in 1278 centers, either hospital (n = 790) or community based (n = 488), distributed throughout Italy. On average, 16.5/10,000 inhabitants aged ≥18 were included (from 8.2 to 28.8 in different Italian regions).

The patients belonged to a fairly heterogeneous group, including a high proportion of cases scarcely represented in the trials supporting the marketing authorization of the three medicinal products. Over 50% of cases on exenatide and approximately 20% on DPP4-Is had severe obesity (BMI ≥ 35 kg/m^2); exenatide patients exhibited higher median HbA_{1c} and a greater percentage of cases with very poor metabolic control (HbA_{1c} ≥ 11%, ≥97 mmol/mol). Elderly patients (≥75 years, n = 6125) constituted approximately 10% of the DPP-4I-treated cases (Table 1A; Supplemental Figure S2).

Metformin was the background therapy in most cases, with/without concomitant sulfonylureas. Glitazones were rarely used, reflecting the Italian market. Monotherapy with sitagliptin was registered in <1% of cases (Table 1B).

Adverse drug reactions

During the 30-month observation period, 1116 ADRs were registered. The median time to ADR was 2.06, 2.85, and 3.87 months on exenatide, sitagliptin, and vildagliptin, respectively. Complete and partial recovery was observed in 717 and 179 cases, respectively; 103 cases did not recover, and late complications were registered in 13. No follow-up was available in 102 cases and two patients died. ADRs did not lead to treatment discontinuation only in 90 cases; after stopping the treatment, drug use was restarted in 100 cases.

ADRs were classified as severe in 77 cases (6.9%), particularly with exenatide (six acute pancreatitis, seven vomiting/nausea, and four renal failures, corresponding to an IR of 0.334, 0.390, and 0.223/1000 person-years, respectively) (Table 2). Three cases of acute pancreatitis occurred on sitagliptin and three more on vildagliptin (IRs: 0.097 and 0.221/1000 person-years, respectively). In addition, non-severe pancreatitis/elevated pancreatic enzymes were recorded in 48 cases (19 with exenatide, 16 with sitagliptin, and 13 with vildagliptin).

Hypoglycemic episodes were reported in 1085 exenatide-treated patients, 608 on sitagliptin, and 207 on vildagliptin, with IRs of 20.6, 6.3, and 4.6/1000 person-years, respectively. Sulfonylureas, either alone or combined with metformin, increased the risk of hypoglycemia. The RR during add-on to sulfonylureas, compared with add-on to metformin, was 2.96 (95% confidence interval (CI), 2.33−3.50) on exenatide, 2.99 (95% CI, 2.45−3.64) on sitagliptin, and 1.84 (95% CI, 1.20−2.69) on vildagliptin. In add-on to sulfonylurea + metformin, the RRs further increased to 3.76 (95% CI, 3.24−4.36) and 2.94 (95% CI, 2.39−3.61) for exenatide and sitagliptin, respectively (not authorized for vildagliptin).

Treatment switching and discontinuation

Treatment switching (to one of the monitored drug or to other treatments) was recorded in 3.5%, 7.2%, and 7.7% of cases on exenatide, sitagliptin, and vildagliptin, respectively. The most common change was from sitagliptin to exenatide (n = 652).

There were 9608/21,064 discontinuations (including L-FU) on exenatide (45.6%), 13,578/38,811 on sitagliptin (35%), and 7056/17,989 on vildagliptin (39.2%) (Supplemental Figure S3). The rates of L-FU were 26.1%, 21.2%, and 24.5%, respectively. Discontinuation for treatment failure occurred in 7.7%, 3.8%, and 4.1% of cases,

Table 1A Baseline demographic/clinical data of the population with diabetes enrolled in the AIFA Anti-diabetics Monitoring Registry with glucose-lowering agents.

	Exenatide (n = 21,064)		Sitagliptin (n = 38,811)		Vildagliptin (n = 17,989)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	58.9	9.9	61.7	10.4	61.9	10.4
Duration of diabetes (years)	10.0	15.4	9.1	7.1	8.2	6.5
Body mass index (kg/m^2)	36.1	6.8	30.8	5.7	30.5	5.5
Waist circumference (cm)	115.9	14.4	104.6	13.1	104.4	12.6
Fasting glucose (mg/dL)	187.8	49.8	170.8	41.6	171.9	41.1
HbA_{1c} (%) [mmol/mol]	8.8 [73]	1.3 [14]	8.3 [67]	1.1 [12]	8.2 [66]	1.1 [12]
Fasting C-peptide (ng/mL)	3.2	1.6	3.0	1.6	3.3	1.7
	N	***%***	***N***	***%***	***N***	***%***
Male gender	10,109	48.0	20,446	52.7	9741	54.1
Age > 75 years	723	3.4	3666	9.4	1736	9.7
BMI > 35	10,835	51.4	7870	20.3	3300	18.3
HbA_{1c} > 11% (>97 mmol/mol)	1496	7.1	1139	2.9	516	2.9

Table 1B Association with other glucose-lowering agents.

	Exenatide (n = 21,064)		Sitagliptin (n = 38,811)		Vildagliptin (n = 17,989)	
	N	%	*N*	%	*N*	%
No association[a]	0	0	3.87	0.1	0	
Metformin	10,691	50.8	25,116	64.7	15,289	85
Sulfonylureas	1323	6.3	1843	4.7	2062	11.5
Sulfonylureas + metformin	9050	43.0	9824	25.3	–[a]	–[a]
Glitazones	–[a]	–[a]	1624	4.2	638	3.5
Repaglinide	1450	6.9	276	0.7	–[a]	–[a]
Acarbose	260	1.2	225	0.5	72	0.4

In individual cases, background therapy could vary in the course of the observation. Please note that patients could be treated with more than one active principle; therefore, the sum of the percentages of cases may exceed 100%.
[a] Off-label according to marketing authorization.

respectively. It was always less common when exenatide/DPP-4Is were added to metformin as a second-line treatment, compared to third-line treatments. After excluding L-FUs, treatment failure accounted for 27–40% of all discontinuations.

The male gender was associated with a lower risk of discontinuation, while older age was a risk factor for discontinuation on exenatide and a protective factor on DPP-4Is (Table 3). Both baseline HbA_{1c} and diabetes duration were associated with a higher risk of

Table 2 List of all severe ADRs and corresponding IR (in 1000 person-years) reported in the AIFA Anti-diabetics Monitoring Registry.

Event	*Exenatide*			*Sitagliptin*			*Vildagliptin*		
	No.	IR[a]	95% CI	No.	IR[a]	95% CI	No.	IR[a]	95% CI
Acute pancreatitis	6	0.334	(0.157–0.650)	3	0.097	(0.035–0.234)	3	0.221	(0.080–0.533)
Vomiting/nausea	7	0.390	(0.192–0.727)	1	0.032	(0.008–0.119)	0		(0.000–0.185)
Renal failure	4	0.223	(0.090–0.488)	0		(0.000–0.081)	1	0.074	(0.018–0.272)
Colon cancer	1	0.056	(0.013–0.205)	2	0.065	(0.020–0.180)	1	0.074	(0.018–0.272)
Epileptic convulsions	2	0.111	(0.034–0.310)	0		(0.000–0.081)	0		(0.000–0.185)
Abdominal pain	2	0.111	(0.034–0.310)	0		(0.000–0.081)	0		(0.000–0.185)
Severe hypoglycemia	1	0.056	(0.013–0.205)	1	0.032	(0.008–0.119)	0		(0.000–0.185)
Pneumonia	0		(0.000–0.140)	2	0.065	(0.020–0.180)	0		(0.000–0.185)
Breast cancer	1	0.056	(0.013–0.205)	2	0.065	(0.020–0.180)	0		(0.000–0.185)
Visual loss	0		(0.000–0.140)	1	0.032	(0.008–0.119)	0		(0.000–0.185)
Colon adenoma	0		(0.000–0.140)	0		(0.000–0.081)	1	0.074	(0.018–0.272)
Anaphylactic reaction/shock	1	0.056	(0.013–0.205)	1	0.032	(0.008–0.119)	0		(0.000–0.185)
Anemia	0		(0.000–0.140)	0		(0.000–0.081)	1	0.074	(0.018–0.272)
Cardiac failure	1	0.056	(0.013–0.205)	0		(0.000–0.081)	0		(0.000–0.185)
Atrioventricular block	1	0.056	(0.013–0.205)	0		(0.000–0.081)	0		(0.000–0.185)
Renal carcinoma	2	0.111	(0.034–0.310)	0		(0.000–0.081)	0		(0.000–0.185)
Cervix carcinoma	1	0.056	(0.013–0.205)	0		(0.001–0.081)	0		(0.000–0.185)
Coronary disease/Infarction	2	0.111	(0.034–0.310)	0		(0.000–0.081)	0		(0.000–0.185)
Cholecystitis	0		(0.000–0.140)	0		(0.000–0.081)	1	0.074	(0.018–0.272)
Cholestasis	0		(0.000–0.140)	1	0.032	(0.008–0.119)	0		(0.000–0.185)
Acute dermatitis	1	0.056	(0.013–0.205)	0		(0.000–0.081)	1	0.074	(0.018–0.272)
Gastric hemorrhage	0		(0.000–0.140)	1	0.032	(0.008–0.119)	0		(0.000–0.185)
Abdominal hernia	1	0.056	(0.013–0.205)	0		(0.000–0.081)	0		(0.000–0.185)
Atrial fibrillation	1	0.056	(0·013–0.205)	0		(0.000–0.081)	0		(0.000–0.185)
Liver dysfunction	0		(0.000–0.140)	0		(0.000–0.081)	2	0.147	(0.046–0.411)
Acute gastroenteritis	1	0.056	(0.013–0.205)	0		(0.000–0.081)	0		(0.000–0.185)
Congestive gastropathy	1	0.056	(0.013–0.205)	0		(0.000–0.081)	0		(0.000–0.185)
Ictus/cerebral hemorrhage/ischemia	1	0.056	(0.013–0.205)	1	0.032	(0.008–0.119)	1	0.074	(0.018–0.272)
Leukemia/lymphoma	0		(0.000–0.140)	2	0.065	(0.020–0.180)	1	0.074	(0.018–0.272)
Urticaria	2	0.111	(0.034–0.310)	0		(0.000–0.081)	0		(0.000–0.185)
Bladder cancer	0		(0.000–0.140)	0		(0.000–0.081)	1	0.074	(0.018–0.272)
Pericardial effusion	0		(0.000–0.140)	1	0.032	(0.008–0.119)	0		(0.000–0.185)
Gastric ulcer	1	0.056	(0.013–0.205)	0		(0.000–0.081)	0		(0.000–0.185)
Other	2	0.111	(0.034–0.310)	1	0.032	(0.008–0.119)	0		(0.000–0.185)
Total	**43**	**2.397**	(**1.781–3.162**)	**20**	**0.645**	(**0.421–0.960**)	**14**	**1.034**	(**0.619–1.639**)

[a] Incidence rate (IR) = # event (N)/person-time at risk (T).

Table 3 Factors associated with treatment discontinuation (any reason, including lost to follow-up) for the three drugs in the AIFA Anti-diabetics Monitoring Registry, identified by logistic regression analysis. Data are presented as odds ratio (OR) and 95% confidence interval (95% CI).

	Exenatide		Sitagliptin		Vildagliptin	
	No. events/ **No. at risk**[a]	OR (95% CI)	No. events/ **No. at risk**[a]	OR (95% CI)	No. events/ **No. at risk**[a]	OR (95% CI)
Male sex	4088/9394	0.89 (0.84–0.94)	5236/18,201	0.92 (0.88–0.96)	2898/8613	0.91 (0.86–0.98)
Age (years/10)	8802/19,566	1.14 (1.11–1.17)	10,191/34,421	0.90 (0.88–0.92)	5477/15,841	0.97 (0.94–1.00)
HbA_{1c} at baseline (%)	8802/19,566	1.09 (1.07–1.11)	10,191/34,421	1.13 (1.11–1.15)	5477/15,841	1.13 (1.10–1.17)
Diabetes duration (years/10)	8802/19,566	1.14 (1.10–1.19)	10,191/34,421	1.00 (0.97–1.03)[b]	5477/15,841	1.11 (1.06–1.17)
Body mass index ($kg/m^2/5$)	8802/19,566	0.80 (0.76–0.85)	10,191/34,421	1.03 (1.01–1.05)	5477/15,841	1.03 (1.00–1.06)[b]

[a] No. at risk includes only cases with HbA_{1c} values ranging from ≥7% (≥53 mmol/mol) to 16% at baseline (151 mmol/mol). No. events includes only cases for which a complete description of associated factors was reported.
[b] Not significant ($\alpha = 0.05$).

discontinuation (not statistically significant for sitagliptin). Higher BMI at baseline was associated with a greater risk of discontinuation on DPP-4Is and a lower risk on exenatide. The add-on to metformin was associated with a low risk of discontinuation on exenatide (odds ratio (OR), 0.80; 95% CI, 0.76–0.85) and a high risk on DPP-4i (OR, 1.21; 95% CI, 1.16–1.26). On the contrary, add-on to sulfonylureas, with/without metformin, carried a high risk of discontinuation on exenatide (OR, 1.25; 95% CI, 1.18–1.32) and a low risk on DPP-4i (OR, 0.72; 95% CI, 0.69–0.75).

In the subset of centers accurately compliant to follow-up, the analysis did not provide systematically different results (Supplementary Table 1).

Effect on glycemic control and body weight

On exenatide, absolute HbA_{1c} decreased on average by 0.99% (0.9 mmol/mol) and body weight by 3.5% from baseline to the last available follow-up. The corresponding variations for sitagliptin and vildagliptin were −0.88% and −0.94% (0.8–0.9 mmol/mol) for HbA_{1c}, and around −1.0% for body weight. The probability of reaching the HbA_{1c} target of 7% (53 mmol/mol) or the secondary target of 8% (64 mmol/mol), after 3–4 or 8–9 months, decreased rapidly with increasing baseline HbA_{1c}, with <20% probability for baseline values >9% (>75 mmol/mol) (Fig. 1). The number of cases at target with baseline HbA_{1c} >11% was much lower for sitagliptin and vildagliptin than for exenatide, and the confidence interval of the estimate much larger.

In the subset of centers compliant to follow-up, the probability of achieving the desired target was not dependent on age or BMI, but it was inversely related to baseline HbA1c and to the use of incretin mimetics/DPP-4Is as third-line therapy. The add-on to metformin and treatment duration (not on vildagliptin) increased the probability of reaching the target (Supplementary Table 2).

Discussion

The AIFA Monitoring Registry of exenatide, sitagliptin, and vildagliptin, collecting data on the use, safety, and effectiveness of incretin mimetics/DPP-4Is, represents a significant step forward in the post-marketing evaluation of new or innovative medicines.

The safety profiles of exenatide, sitagliptin, and vildagliptin in Italian clinical practice were similar to those recorded in registration trials and recently reviewed [12]. Although favored by online registration, the total number of ADRs was relatively low – but much higher than that usually observed in post-marketing surveillance – despite

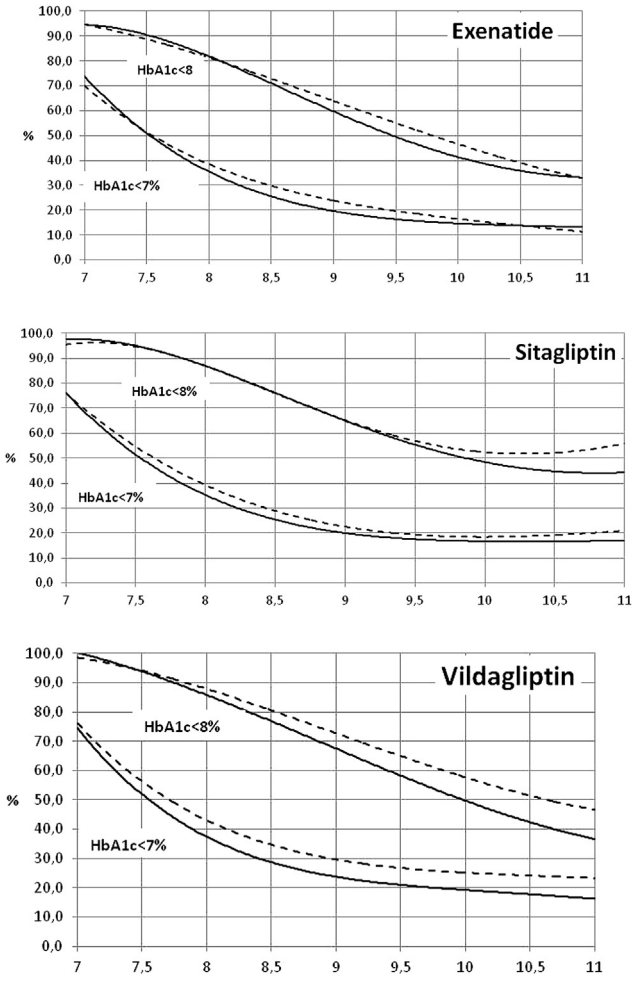

Figure 1 Probability of achieving the targets of metabolic control (HbA_{1c} <7%, lower lines; <8%, upper lines) at 3–4 months (continuous lines) or 8–9 months (broken lines) as function of entry HbA_{1c} values.

the old age of the population, and no unexpected ADRs were registered, with only one case of heart failure with DPP-4Is [13]. The decision of the regulatory Italian Agency (AIFA) to limit the reimbursement of incretin-based therapies to diabetes specialists in a well-defined monitoring system might have favored an accurate selection of patients also in the community setting, limiting adverse reactions.

Two ADRs are of particular significance: pancreatitis and hypoglycemia. The association of exenatide and sitagliptin with pancreatitis was documented since 2006 and prompted close monitoring [14,15]. Later, the potential risk appeared to be increased by diabetes per se; post-approval studies have documented cases associated with incretin use, but a causal relationship between treatment and pancreatitis was neither proved nor excluded [16–20]. In the registry, a few additional reports of non-severe pancreatitis or simply raised levels of pancreatic enzymes were also recorded, without differences between drugs. When these non-adjudicated ADRs were summed up to severe pancreatitis, the total incidence of pancreatic events was in the range reported in the general population with diabetes and should be considered in the context of the notoriety bias generated by alerts. A 2013 comprehensive review of preclinical and clinical data on pancreatic safety by the European Medicines Agency concluded that the concerns on the risk of pancreatitis should not be minimized [21]. Later, the publication of two large cardiovascular outcome DPP-Is trials [13,22] and epidemiological data [23] stifled the debate; a 2014 joint Food and Drug Administration (FDA)–European Medicines Agency (EMA) assessment concluded with a low-risk [24] but suggested continuous capture of data.

As expected, exenatide and DPP4-I add-ons to metformin were accompanied by low rates of hypoglycemia [25]. On the contrary, a two-to threefold increase in hypoglycemia was observed in combination with sulfonylureas, both with and without metformin, but very few cases were recorded as severe ADRs, requiring hospital admission. These data are in keeping with registration studies and with recent clinical trials showing that DPP4-Is are associated with very low rates of hypoglycemia when combined with metformin [26], despite similar or only moderately inferior glucose-lowering efficacy compared to sulfonylureas.

The analysis of discontinuation rates and metabolic effects may give hints for an appropriate use of these drugs in the community. This approach seems sound, as confirmed by a sensitivity analysis in a subset of selected centers with adherence to follow-up ≥80% (Supplementary Tables 1 and 2). As expected, the discontinuation rates of all drugs increased systematically with higher baseline HbA_{1c}. They also increased with age for exenatide, not for gliptins, indicating a preferential use of oral agents in elderly subjects for whom a less strict metabolic target may be preferred [3,4,27]. On the contrary, weight loss might be the reason for the lower discontinuation rates of exenatide with increasing BMI, despite injections and higher baseline HbA_{1c}.

Two subpopulations, with limited safety data in registration studies, deserve particular attention. The AIFA Registry included many patients aged ≥70; in a few of them, gastrointestinal symptoms associated with exenatide were the precipitating factors of acute renal failure, a side effect to be considered in frail patients. DPP-4Is were demonstrated to be safe in a meta-analysis on patients aged ≥65, as well as in a systematic review, and vildagliptin was shown to be effective and safe also in subjects with diabetes aged ≥75 [6,9,27]. Future analyses of the elderly Italian cohort will throw light on the efficacy of DPP-4I in the elderly. Similarly, the very large group with morbid obesity in the AIFA Registry will offer a unique opportunity to test the effects of incretin-based therapies in these patients, where metabolic control remains difficult and the use of insulin may be critical, because it further increases body weight.

In our database, the effectiveness of incretin-based add-on therapies on HbA_{1c} and body weight was similar to that reported in a review of head-to-head trials [28], but these results should be taken with caution, considering that the high rate of L-FUs inflates effectiveness. HbA_{1c} was reduced on average by 0.9–1.0% (9 mmol/mol) in the general dataset, also in relation to HbA_{1c} at baseline, with much larger effects in subjects with poor metabolic control. In the AIFA Registry, exenatide and DPP-4Is were also prescribed to subjects with very poor metabolic control, above the levels where insulin is recommended by international guidelines [4]. Such prescribing approach may be explained by the opportunity to test these new drugs across the whole spectrum of disease, or as an extreme attempt before prescribing insulin. Fig. 1 provides an immediate picture of the possibility of attaining specific HbA_{1c} targets with incretin-based therapies in clinical practice, emphasizing the predictive value of baseline metabolic control. This figure may help clinicians forecast the results of treatment in their next patient, as modulated by other variables (i.e., age, BMI, diabetes duration, and background treatment), as reported in Supplementary Table 2. The observation that several patients with HbA_{1c} in the range 9–11% (75–97 mmol/mol) may reach an acceptable metabolic control with a low incidence of adverse reactions, including hypoglycemic events, is clinically relevant. Drug effectiveness should always be considered in the context of existing therapies [29], safety, cost, therapeutic inertia [30], and the beneficial effects of intensive lifestyle counseling, which remains mandatory at any step of intensified treatment. Notably, in frail patients, a patient-centered approach and progressively less challenging targets are proposed by international guidelines, to avoid the risk of adverse events. [4].

Our study presents limitations and strengths. First, the major limitation is an observation period of only 30 months, too short to draw definite conclusions on long-term efficacy (i.e., effects on diabetic complications). Second, due to its observational nature, baseline differences, and high rates of L-FU, any comparisons of safety, discontinuation, and effect on metabolic and weight

control among the three drugs should be made with extreme caution. Third, given the purpose of the AIFA Registry, there was no comparator-treated group. Conversely, the main strength is the very large and heterogeneous diabetes cohort, including the complete dataset from an entire European nation, where drugs were used under strict regulatory access, requiring online registration for reimbursement.

In conclusion, data on the compliance, safety, and effectiveness of incretin-based therapies derived from the AIFA Registry, while not capturing any new safety signal, provide a comprehensive framework for health-care providers to regulate the use of these drugs in the community. These data might be useful to address several important points, including the independent effect of baseline HbA_{1c} on its decline, the safety and effectiveness in subjects with diabetes over 75, and the effectiveness of incretins – also including liraglutide and saxagliptin from August 2010 – in the large cohort of obese subjects with BMI >35. These analyses will be carried out when the monitoring data will be available in the new and updated in-house web platform currently being developed. Whenever effective strategies of lifestyle changes preliminary to any further step in treatment intensification fail, the implementation of new treatments, including incretin-based therapies, should be dictated by solid data on long-term safety and effectiveness in the context of available drugs for type 2 diabetes, favoring a patient-centered approach. [4].

Author contributions

S.M., G.M., D.M., and L.P. conceived the study and interpreted the results from the AIFA Registry. S.M., G.M., D.M., A.S., P.D.S., and M.P.T. wrote the first draft of the manuscript. Data analysis was performed by CINECA. All the named authors critically reviewed and commented on multiple drafts of the report, approved the final version of the manuscript, and read and met the ICMJE criteria for authorship.

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Guarantor's name

S.M. takes the responsibility for the contents of the article.

Conflicts of interest

S.M., A.S., P.D.S., C.T. and D.M. declare that no competing interests exist.

G.M. has been involved in studies on anti-diabetic drugs sponsored by Boehringer Ingelheim, Eli Lilly, NovoNordisk, and Sanofi; and has received honoraria for lectures from pharmaceutical companies producing anti-diabetics: Merck Sharp & Dome, Eli Lilly, Sanofi, and Novartis. These potential conflicts did not affect the given contributions to this article.

M.P.T., in the previous years, has received honoraria for speaking at scientific meetings and workshops from several pharmaceutical companies, including Abbott Labs, Boehringer Ingelheim, Bristol Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen Cilag, Merck, Roche, Schering-Plough, and ViiV Healthcare. None of these companies produces the antidiabetics studied in the paper, and these potential conflicts did not affect the given contributions to this article.

L.P. in the previous years has received honoraria for lectures at continuing medical education programs for healthcare professionals not focused on specific products.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2014.07.014.

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