Pattern of use of incretin-based drugs in clinical practice

Protocol version 1.1

Title	Pattern of use of incretin-based drugs in clinical practice.
Medicinal product(s) / Device(s)	GLP-1 analogues and Dipeptidyl Peptidase-4 Inhibitors
Event(s) of interest	Not applicable
Research question and objectives	To describe the pattern of use of incretin-based drugs in large sample of the Italian general population.
Country(ies) of study	Italy
Protocol author(s)	Giuseppe Roberto (ARS), Rosa Gini (ARS)

List of abbreviations:

ARS	Agenzia Regionale di Sanità della Toscana (Regional Health Agency of Tuscany)
GLP-1	Glucagon like peptide-1
DPP-4i	Dipeptidyl Peptidase-4 inhibitors
T2DM	Type 2 diabetes mellitus
ATC	Anatomical Therapeutic Chemical classification
ISTAT	Istituto Nazionale di Statistica

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Amendments and updates

Version	Description of changes	Study protocol section	Date of effectiveness
1.1	-Two further data bases will be included (Caserta, Umbria) -Information on the utilization of other drug classes will be used for the study -Two additional descriptive analyses on new incretin drug users with no previous antidiabetic treatment as well as on those previously exposed to insulin will be performed. - The study populations from the three data bases will be standardized by age	Materials and methods	

1. Background

Diabetes is a chronic metabolic condition causing sustained hyperglyemia due to a deficit o insulin secretion and/or a reduced response of target tissues to this hormon [1]. In particular, type 2 diabetes (T2DM), in which insulin-resistance is the predominant pathogenetic mechanism, represents about 90% of all diabetes cases worldwide [2].

In patients with T2DM, the chronic exposure to hyperglycemia can causes the occurrence of serious and potentially fatal metabolic, microvascular and macrovascular complications [1]. Therefore, if diet and life style modification are not sufficient for an adequate glyemic control, pharmacological treatment is necessary [1;3;4].

Current guidelines [3;4] recommend metformin as the initial drug treatment for T2DM and the subsequent addition (or switch in case of intollerance) of one or more antidiabetic drugs in order to maintain the recommended glycemic target.

In February 2008 the Italian Healthcare Service approved the reimbursement of the first incretin-based medicines [5] for the treatment of T2DM. The clinical efficacy of this class of drugs relies on the potentiaton of the activity of the Glucagon-like peptide 1 (GLP-1), an endogenous peptide, belonging to the family of incretin hormones, that exerts an important role in the glycemic homeostasis [3;6;6]. Currently, available incretin-based therapies are distinguished in two main groups: i) GLP-1 analogues, which possess a longer half-life compared to the endogenous GLP-1 hormon and are administered subcutaneously, and ii) the dipeptidyl peptidase-4 inhibitors (DPP-4i), which act by reducing the activity of the enzyme responsible for the degradation of the endogenous GLP-1 and are admistered orally [3;6].

Results from clinical trials have suggested a positive risk/benefit balance of these drugs in the treatment of T2DM [6;7]. However, given the recent commercialization, available literature on the pattern of use of incretin-based therapy in the real world clinical practice is still scarce [5;8-10]. A study based on the administrative data of an Italian Local Health Authority reported a trend of increase of the use of these drugs between 2009 and 2012 [8] however, no specific information was provided with respect of GLP-1 analogues and DDP-4i respectively, as well as for individual molecules belonging to the two groups. Since the effectiveness and safety profile of these drugs cannot be considered completely established yet [7;11], evidence on the exposure of the general population to these medications, as well as the characterization of treated patients, becomes of paramount importance for planning and design large scale observational pharmacoepidemiological studies[12;13].

Therefore, the aim of this study is to describe in greater details the pattern of use of incretin-based drugs through the analysis of routinely collected admistrative data from a large sample of the Italian general population.

2. Materials and Methods

2.1 Data sources

Italy has a tax-based, universal coverage National Health System organised in three levels: national; regional (21 regions); and local (on average 10 Local Health Authorities per region). Healthcare is managed for every inhabitant by the Local Health Authority where he/she has her regular address.
This study will be based on the analysis of data from two Italian regions, Tuscany and Umbria (central Italy), and one Local Health Authority, Caserta (South). Overall, the three data sources cover a total source population of almost 6 million people (ISTAT, Istituto Nazionale di Statistica - *http://dati.istat.it/Index.aspx?DataSetCode=DCIS_POPRES1*).
In particular, the databases collect longitudinal pseudonymized patient-level information on the utilization of healthcare services reimbursed by the National Healthcare Service and dispensed to all subjects who are residents and registered with a general practitioner in the relevant catchment areas. For each subject registered in the data bases, demographic data can be linked to different registries in which information on healthcare services delivered are recorded.
For the purpose of this study, information from registries of drug dispensings will be retrieved. This registry collects records of prescription drugs dispensed for outpatient use and include information on active substance name, ATC code, dose, pharmaceutical formulation and date of dispensing.

2.2 Study population and design

This was a descriptive, population-based, pharmacoepidemiological study on the utilization of incretin-based drugs in clinical practice. All subjects registered in the administrative databases of Tuscany, Umbria and Caserta between January 1, 2008 and December 31, 2014 were considered and data from dispensed drug prescriptions will be analyzed. Per each year of observation, the reference study population corresponded to all subjects active into the data base at January the 1st that, at this date, had ≥18 years of age and at least 365 days of look-back period. Within such population, all subjects with ≥1 prescription of any antidiabetic drug (**ATC**: A10*) were identified as well as those with ≥1 prescription containing an incretin-based drug (i.e. GLP-1 analogues- **ATC**: A10BX04, A10BX 07, A10BX10; DPP-4i - **ATC**: A10BH01, A10BH02, A10BH03, A10BH04, A10BH05, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13; see Table 1).

Table 1. **Antidiabetic drugs of interest for the study as available in Italy during the study period.**

Classe farmacologica	ATC	Principio attivo
DDP-4 inhibitor	A10BH01	sitagliptin
	A10BH02	vildagliptin
	A10BH03	saxagliptin
	A10BH04	alogliptin
	A10BH05	linagliptin
	A10BD07	metformin and sitagliptin
	A10BD08	metformin and vildagliptin
	A10BD09	pioglitazone and alogliptin
	A10BD10	metformin and saxagliptin
	A10BD11	metformin and linagliptin
	A10BD13	metformin and alogliptin
GLP-1 analogues	A10BX04	Exenatide
	A10BX07	liraglutide
	A10BX10	Lixisenatide
Biguanides	A10BA01	Fenformin
	A10BA02	Metformin
Sulphanylureas	A10BB01	Glibenclamide
	A10BB02	Chlorpropamide
	A10BB03	Tolbutamide
	A10BB06	Carbutamide
	A10BB07	Glipizide
	A10BB08	Gliquidone
	A10BB09	Gliclazide
	A10BB12	Glimepiride
Thiazolidinediones	A10BG02	Rosiglitazone
	A10BG03	Pioglitazone
Alfa glicosidase inhibitors	A10BF01	Acarbose
Meglitinides	A10BX02	Repaglinide
Insulins	A10A*	Insulin and analogues
Other hypoglicemic drugs in fixed combinations	A10BD01	phenformin and sulfonamides
	A10BD02	metformin and sulfonamides
	A10BD03	metformin and rosiglitazone
	A10BD05	glimepiride and pioglitazone
	A10BD14	metformin and repaglinide

In particular, to describe the pattern of use of incretin-based drugs we observed:

1) the trends of annual prevalence and incidence of use of GLP-1 analogues and DPP-4i both in the general population and among users of antidiabetics (ATC A10*). The prevalence of use will be calculated as the ratio between the total number of prevalent users (subjects with ≥1 prescription of interest during the year) and the total number of subjects in the reference population for that year. The annual incidence of use will be computed by dividing the number of new users of that year (i.e.

patients with ≥1 prescription interest during the year and none during the previous 365 days) for the number of subjects at risk of receiving the drug of interest in the reference population for the same year (i.e. the reference population for that year minus prevalent users of the previous year). The assessment of the exposure categories (i.e. incretin-based drugs, GLP-1 analogues and DPP-4i) will be independent from the other two and non mutually exclusive;

2) the percentage of incident users of GLP-1 analogues and DPP4i among incident users of incretin-based drugs per each year of observation. Patients will be categorized in the relevant exposure category considering the first prescription of interest during the year of reference. Moreover, this analysis will also performed at active substance level (i.e. V° level of the ATC classification, see Table 1).

3) the characteristics of incident users of GLP-1 analogues and DPP4i will be respectively described per year of observation, in terms of percentage of women, mean age, age band distribution (18-44, 45-64, 65-84, 85+) and drug utilization (i.e. cardiac therapy ATC: C01*, vasodilators ATC: C01D*, Antithrombotics ATC: B01A*, and corticosteroids for systemic use ATC: H02*) as measured by at least 2 prescriptions during 1 year preceding the first incretin-containing prescription. As for antidiabetic drugs, patients will be classified in the following mutually exclusive categories (see Table 2):

a) No previous antidiabetic treatment,

b) Insulin with or without hypoglicemic drugs (i.e. ≥1 insulin prescription),

c) hypoglycemic drugs in monotherapy (i.e. drugs belonging to one pharmacological class of hypoglycemics excluding insulin and fixed combinations),

d) Politherapy with hypoglycemic drugs (drugs belonging to more than one class of hypoglycaemic medicines or fixed combination).

Patients in the categories a) and b) mentioned above will be further characterized as follows:

a) in order to describe possible patterns of inappropriate prescribing, new users of GLP1 analogues and DPP4 inhibitors with no previous antidiabetic treatment will be respectively described, per each year, in terms of percentage of women, mean age, age band distribution and drug utilization (as above). Moreover, those patients with ≥365 days of follow up starting from the first prescription of GLP1 analogues/DPP4 inhibitors will be classified in *persistent user* (no prescription gap ≥90 days starting from the end of the duration of each prescription), *non persistent users* (prescription gap ≥90 days) or *switchers* (switch or add-on of one or more antidiabetic drug). Duration of prescriptions will be calculated dividing the total amount of active substance contained in each prescription by the relevant *Defined Daily Dose* (DDD);

b) new users of GLP1 analogues and DPP4 inhibitors with previous insulin prescriptions will be respectively described, per each year, in terms of percentage of women, mean age, age band distribution and classified according to previous antidiabetic treatments in: *insulin without hypoglicemics, insulin with hypoglicemic monotherapy, insulin with hypoglicemic polytherapy*. Moreover, those patients with ≥365 days of follow up starting from the first prescription of GLP1 analogues or DPP4 inhibitors, will be followed for the first year of incretin-based therapy and classified according to the observed use of insulin: *past users* (no insulin prescription), *persistent user* (no gap ≥90 days between two insulin dispensings), *non persistent users* (at least one gap ≥90 days)

Table 2. Exposure categories for the caracterization of incident incretin-based drug users.

Exposure categories	**Description (ATC)***
Insulin with or without hypoglicemic drugs	≥1 insulin prescription (A10A*)
hypoglycemic drugs in monotherapy	Drugs belonging to only one of the following groups: - Biguanides (A10BA*) or - Suphanylureas or Glitinides (A10BB01, A10BB02, A10BB03, A10BB06, A10BB07, A10BB08, A10BB09, A10BB12, A10BX02) or - Tiazoledindiones (A10BG*) or - Alfa glucosidase inhibitors (A10BF01)
Politherapy with hypoglycemic drugs	- Drugs belonging to more than one groups among those reported above or: - Fixed combination (A10BD01, A10BD02, A10BD03, A10BD05, A10BD14)

*drugs dispensed during the 365 days before the first dispensing of a incretin-based drug.

2.3 Statistical analysis

Both prevalence and incidence of use, the latter intended as the incident risk of receiving the drug of interest, will be reported as proportions per 1000 subjects. The study populations from the three data sources will be standardized by age using the Italian population 2011 (ISTAT - http://dati.istat.it/Index.aspx?DataSetCode=DCIS_POPRES1).

3. Data management and processing

Data will be analyzed using the software TheMatrix (http://thematrix.isti.cnr.it/) and statistical software STATA version 12.1.

4. Limitations of study methods

The data source used for this study cannot track prescription drugs used in inpatent setting. Given the design and the descriptive nature of the study this limitation is unlikely to have any significant impact on the study results.

4. Ethical considerations

The study was approved by the governance board of ARS.

5. Disseminations and communication strategy

Data generated through this research will be shared among all study participants before June 2016. A study report summarizing all main results will be produced and shared with data partners before July 2016.
The findings from this study will be submitted to a peer-review international journal before September 2016.

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