Time to treatment intensification in patients receiving metformin+incretin-based medicines *versus* metformin+other hypoglicemics

Protocol version 1.2

Title	Time to treatment intensification in patients with type 2 diabetes receiving metformin+incretin-based medicines versus metformin+other hypoglicemics
Medicinal product(s) / Device(s)	Incretin-based medicines (Glucagon Like Peptyde-1 analogues and Dipeptidyl Peptidase-4 Inhibitors) and other antidiabetic drugs.
Event(s) of interest	Intensification of the pharmacological treatment of diabetes.
Research question and objectives	To compare the time to treatment intensification in patients with type 2 diabetes receiving incretin-based medicines versus other non-insulin antidiabetics as add-on therapy to metformin.
Country(ies) of study	Italy
Protocol author(s)	Giuseppe Roberto, Francesco Barone-Adesi, Stefania Spila Alegiani, Roberto da Cas, Rosa Gini

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Amendments and updates

Version	Description of changes	Study protocol section	Date of effectiveness
1.2	- Three ATC codes were added to Table 1 (i.e. A10BD15, A10BD16, A10BD20)	3.2	27/09/2017
1.2	- Duration of treatment with metformin prior index dispensing was no longer considered among matching criteria	3.3	27/09/2017
1.2	- The list of variariables measured at baseline was updated	3.4	27/09/2017
1.2	- A total of six further sensitivity analyses were added	3.7	27/09/2017
1.2	- Figure 5 was modified	3.9	27/09/2017
1.2	- Five ATC codes were added to the Appendix 2 (i.e. A10BD04, A10BD06, A10BD15, A10BD16, A10BD20)	5	27/09/2017

List of abbreviations and acronyms

ARS	Agenzia Regionale di Sanità della Toscana (Regional Health Agency of Tuscany)
ATC	Anatomical Therapeutic Chemical classification
DPP4i	Dipeptidyl Peptidase-4 inhibitors
DRUGS	Registry of dispensings of prescription drugs intended for outpatient use
EXE	Registry of the exemption from copayment
GLP1a	Glucagon like peptide-1 analogues
HOSP	Hospital discharge record registry
MET	Metformin
OUTPAT	Registry of the utilization ofoutpatient specialistic visits, diagnostic tests or procedures
PERSONS	Population registry
SGLT2i	Sodium-glucose trasporter-2 inhibitors
T2DM	Type 2 diabetes mellitus

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1. Background

Diabetes is a chronic metabolic condition causing sustained hyperglyemia due to a deficit of insulin secretion and/or a reduced response of target tissues to this hormone [1]. In particular, type 2 diabetes (T2DM), in which insulin-resistance is the predominant pathogenetic mechanism, represents the about the 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 micro- and macrovascular complications [1]. Therefore, if diet and life style modification are not sufficient for an adequate glycemic control, pharmacological treatment is strongly recommended [1,3,4].

Current guidelines [3,5] recommend metformin as the initial treatment of T2DM and the subsequent addition (or switch in case of intolerance) of one or more antidiabetic drugs in order to maintain the recommended glycemic target. In fact, due the progressive nature of the disease, antidiabetic drugs tend to lose their efficacy over time so that treatment intensification is required. This phenomenon is referred to as secondary treatment failure [6,7].

In addition to older non-insulin hypoglycemic drugs such as metformin, sulphonylureas, glinides, glitazones and acarbose, in February 2008 the Italian Healthcare Service approved the reimbursement of the first incretin-based medicines [8]. The clinical efficacy of this class of drugs in the treatment of T2DM relies on the potentiation of the activity of the Glucagon-like peptide 1 (GLP-1), an endogenous hormone belonging to the family of incretin hormones that exerts an important role in the glycemic homeostasis [9]. Currently, available incretin-based therapies are distinguished in two main groups: i) GLP-1 analogues (GLP1a), which possess a longer half-life compared to the endogenous GLP-1 hormone and are administered subcutaneously, and ii) the dipeptidyl peptidase-4 inhibitors (DPP4i), which act by reducing the degradation of the endogenous GLP-1 and are administered orally [3,9].

Results from clinical trials have suggested a positive risk/benefit balance of these drugs in the treatment of T2DM [9,10]. However, given the recent commercialization, evidence on treatment durability (i.e. time to secondary treatment failure) of incretin-based therapies in real world setting is still scarce and conflicting [9,11,12].

The identification of secondary treatment failure, which requires periodic measurements of glycated haemoglobin levels, might be challenging in electronic health record (EHR) databases. Nevertheless, treatment intensification, such as progression to insulin or add-on of a non-insulin antidiabetic drug, was shown to be positively associated with a worsening of the glycemic control [6,13-16]. In this contest, EHR databases can be used to perform comparative studies and emulate the ideal target randomized trials that would answer the question of interest [17], leveraging an otherwise inconceivable sample size and follow-up duration.

2. Objectives

The aim of this study is to the analyse routinely collected Italian admistrative data collected from different local and regional health authorities in order to compare the time to treatment intensification in patients with type 2 diabetes receiving incretin-based medicines *versus* other non-insulin antidiabetics as add-on therapy to metformin.

3. Materials and methods

3.1. Data source

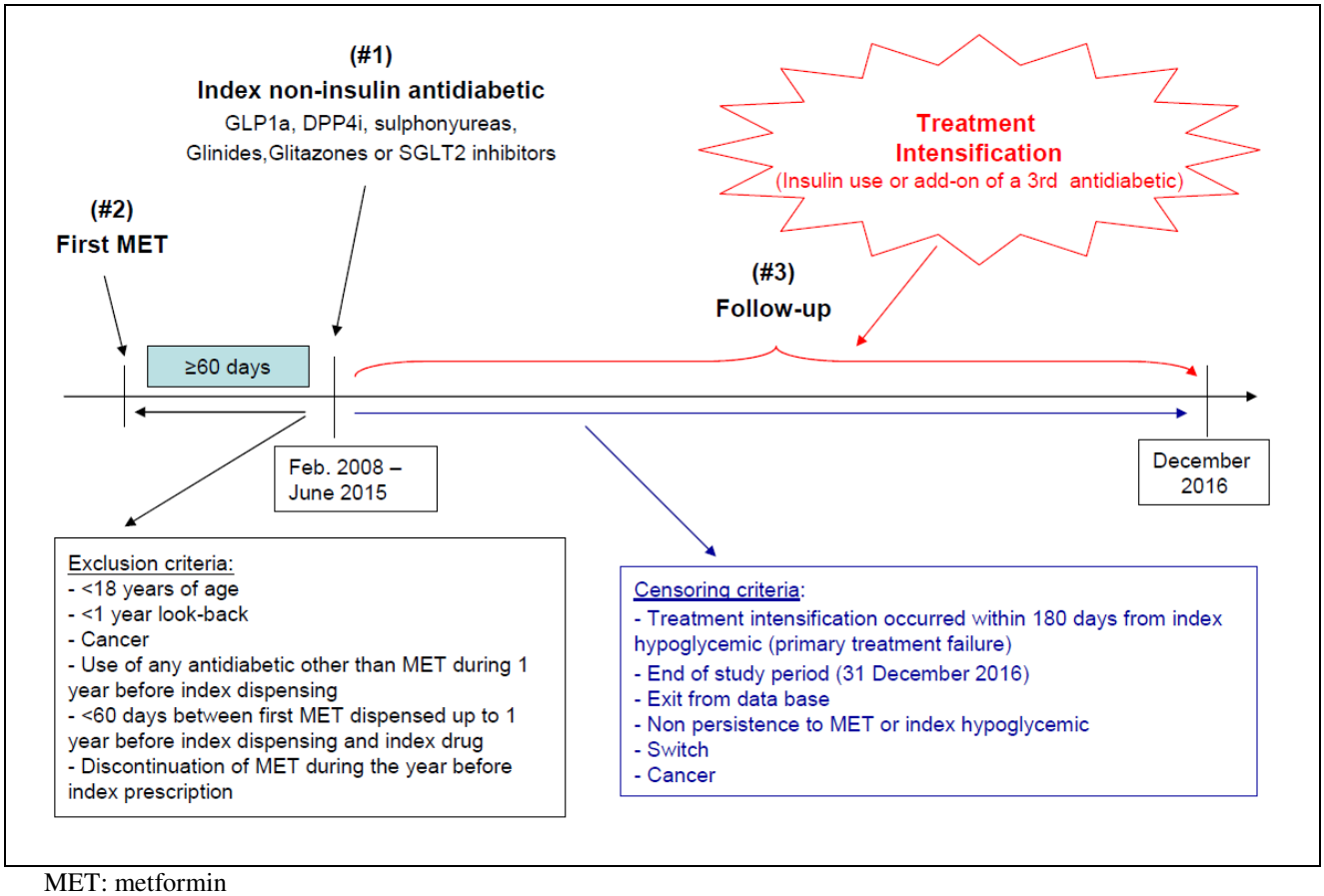
Italy has a tax-based, universal coverage National Health System organised in three levels: national; regional (21 regions); and local (on average 10 Local Health Authorities per region). Healthcare is managed for every inhabitant by the relevant Local Health Authority (LHA).
This study will be based on the analysis of data from three Italian regions, (Northern Italy), Tuscany and Umbria (central Italy), and one LHA, Caserta (South) covering an overall source population of around 10 million people (http://demo.istat.it/bil2015/index.html). The four data sources are based different databases that collect person-level information on the utilization of healthcare services in charge to the National Healthcare Service and dispensed to any subject who is resident and registered with a general practitioner in the relevant catchment areas. Through a pseudoanonymized identification code, information recorded in different databases and concerning the same subject can be linked. For the purposes of this study, data from the following five registries will be used: i) inhabitant registry, ii) hospital discharge records, iii) drug registry, iv) exemption from copayment registry, and v) registry of outpatient visits and diagnostic tests utilization. In specific, the inhabitant registry (PERSONS) contains demographic information (gender, date of birth, date of death, citizenship), with date of registration with a general practitioner or a pediatrician in the region/LHA (for birth or immigration) and date of exit from the region/LHA (for death or emigration). The drug registry (DRUG) records dispensing of prescription drugs intended for outpatient use (e.g. dispensing date, active principle, ATC code, brand name and formulation). The hospital discharge record (HOSP) registry contains information on hospitalization episodes (e.g. date of admission/discharge, discharge diagnoses and procedures code with ICD9CM terminology). The exemption from copayment (EXE) registry records the disease that allows patients to be exempt from copayment of a specific list of healthcare services. The registry of outpatient activities (OUTPAT) records information on the utilization of specialist outpatient visits, diagnostic tests or

procedures (e.g. date, type of specialist visit, test or procedure), however, neither diagnoses nor test results are recorded.

3.2. Selection of study cohort

The study population will be the cohort of patients newly treated with a non-insulin antidiabetic drug among GLP1a, DPP4i, sulfonylureas, glinides, glitazones or the recently marketed sodium-glucose co-transporter 2 inhibitors (SGLT2i), intended as an add-on treatment to metformin monotherapy (Figure 1).

Figure 1. Cohort selection and study design



MET: metformin

All active subjects with at least 1 dispensing of a non-insulin hypoglycemic drug of interest (i.e. GLP1a, DPP4i, sulfonylureas, glinides, glitazones or SGLT2i) recorded between 1st of February 2008 and 30 June 2015 will be identified (see *#1* in Figure 1). The date of the first dispensing of interest will be referred to as the *index prescription*. Patients will be required to be aged 18 or older at index prescription and to have a minimum look-back period of 1 year in all the five registries used for this study (i.e. PERSONS, DRUG, HOSP, EXE, OUTPAT). Given the existing

differences in data availability among the participating data sources, the date of start of the recruitment period will be data source-specific (see Appendix 1). Only patients with ≥1 metformin dispensing before index prescription will be included (see *#2* in Figure 1). During the year preceding index prescription, patients will have to be persistent to metformin monotherapy (see definition of persistence at section 3.9). Patients that received any antidiabetic drugs other than metformin (see Appendix 2) during the year preceding index prescription will be excluded. In order to select patients with similar pattern of antidiabetic pharmacotherapy, we will only include patients who started the index hypoglicemic drug as an add-on to metformin monotherapy. Therefore, we will discard those who received the index hypoglicemic less than 60 days after the first metformin dispensing, that is recommended time interval for the reevaluation of initial metformin monotherapy [18,19], This approach is expected to reduce possible differences of unmeasured baseline characteristics (e.g. HbA1c), both within and across treatment groups. In fact, based on guideline recommendations, patients who start directly with dual antidiabetic pharmacotherapy are likely to be those with more severely uncontrolled T2DM. Moreover, patients with a cancer diagnosis recorded at any time before index prescription will be excluded (ICD9CM codes: 140-239, from HOSP or EXE).

On the basis of the add-on treatment received at index prescription, patients will be classified in one of the following treatment group (see Table 1):

1) MET+DDP4i
2) MET+GLP1a
3) MET+Sulfanylurea
4) MET+Glinides
5) MET+Glitazones
6) MET+SGLT2i

Table 1. Drug classes of non-insulin antidiabetic drug received that will be considered as index prescription.

Pharmacological classes	**ATC codes**

DPP4i	- mono: A10BH01, A10BH02, A10BH03, A10BH04, A10BH05 - fixed combination:A10BD07, A10BD08, A10BD10, A10BD11, A10BD13
GLP1a	- A10BX04, A10BX07, A10BX10, A10BX13, A10BX14 (old ATC codes) - A10BJ* (new ATC codes)
Sulfonylureas	- mono: A10BB* - fixed combination: A10BD02
Meglitinides	- mono: A10BX02; - fixed combination: A10BD14
Glitazones	- mono: A10BG; - fixed combination: A10BD03, A10BD05
SGLT2i	- mono: A10BX09, A10BX11, A10BX12 (new ATC codes); A10BK01, A10BK02, A10BK03 (old ATC codes) - fixed combination: A10BD15, A10BD16, A10BD20

DPP4i: dipeptidyl peptidase-4 inhibitors
GLP1a: Glucagon-like peptide-1 analogues
SGLT2i: Sodium-glucose co-transporter 2 inhibitors

3.3. Study design

Patients in each of the above defined treatment group will be followed starting from the index prescription (see #3 in Figure 1) up to the occurrence of the study outcome, i.e. treatment intensification, or a censoring event, whichever comes first. Events that will be considered as censoring criteria will be: non-persistence to metformin, non-persistence to the index non-insulin antidiabetic drug, switch to a different non-insulin antidiabetic (see section 3.9 for description of operational definitions), end of study period (December 31st, 2016), cancer, death, or emigration from the region/LHU of recruitment.

Each patient on MET + DPP4i treatment will be matched to patients in the other treatment groups described above (see section 3.2), by age at index prescription considering 6 age band categories (18-44, 45-54, 55-64, 65-74, 75-84, 85+), sex, and calendar year of index prescription.

On the basis of the actual number of patients per year and geographic area in each treatment group, we will consider the possibility to rearrange treatment categories in order to reach a sufficient number of patients for the study purposes.

3.4. Variables at baseline

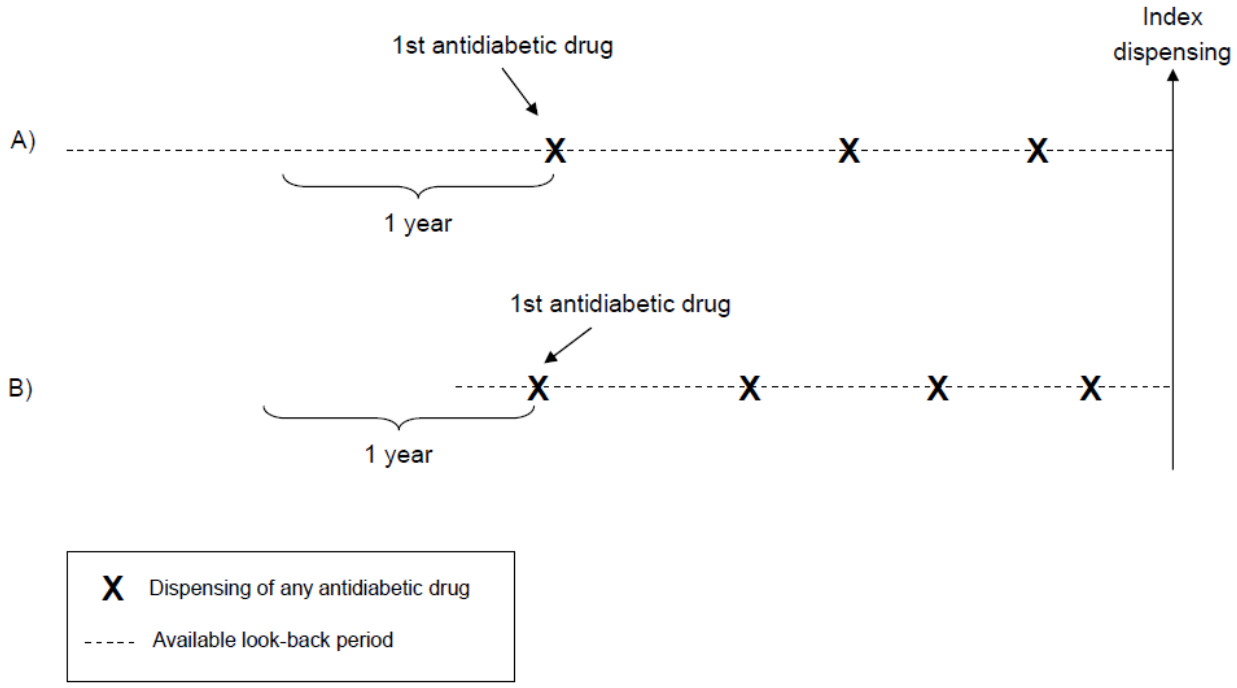
The following variables will be measured at baseline (index prescription): age, sex, calendar year of index prescription, rate of encounters with a diabetologist and rate of measuments of glycated haemoglobin since first metformin dispensing recorded during the year before index prescription. The time from the first record of dispensing of any antidiabetic drug occurred at any time during all the available look-back period and the index dispensing will be measured in years and used as a proxy of disease duration. The estimated time between first antidiabetic drug and index dispensing will be classified either as "definite", for patients with ≥1 year of look-back before the first observed antidiabetic drug, or "uncertain" (see figure 2).

Diabetes complications and comorbidities will be measured through diagnoses recorded, either at hospital discharge or as an exemption from copayment, during one year before index prescription (see Appendix 3).

The use of medications that might affect glycemic control or that might be a proxy of an effect modifier (see Appendix 4) will be measure during one year before index prescription (antidepressants, antipsychotics, corticosteroids for systemic use, lipid-lowering drugs, low-dose aspirin, antihypertensive, thiazides, statins, beta-blockers).

Figure 2. Time between first antidiabetic drug to index dispensing

Two examples of patients for which the time between 1st antidiabetic drug and index dispensing will be respectively classified as "definite" (A) or "uncertain" (B).



3.5. Outcomes

The *primary outcome* will be the occurrence of treatment intensification. It will be defined as either the initiation of insulin treatment (first dispensing of insulin) or the add-on of a third non-insulin antidiabetic (see section 3.9) [6,15,16,20-22]. To avoid the observation of primary treatment failure due to early treatment inefficacy [15], patients experiencing a treatment intensification episode within 180 days from the index prescription will be censored.

As *secondary outcomes,* add-on of a third non-insulin antidiabetic drug, insulin initiation and switch will be considered separately.

3.6. Statistical analysis

Survival curves describing the time to treatment intensification will be plotted with the Kaplan-Meier method. The log rank test will be used to test the statistical significance of the difference between treatment groups.

Cox regression models will be applied to estimate hazard ratios, with 95% confidence intervals, and compare the time to treatment intensification from index prescription in patients treated with MET+DPP4i versus those in the other exposure categories. All the variables measured at baseline will be included in the model to account for their potential confounding effect.

3.7. Sensitivity analyses

- Influence of treatment discontinuation as a censoring criteria on study results:

In the preliminary results obtained from the analysis of the Tuscany data bases (*Roberto et al. Time to treatment intensification in patients on dual pharmacotherapy for type 2 diabetes, 34th ICPE, 22-24 August 2018 – Abstract submitted*) a significant imbalance in treatment discontinuation probability was observed when comparing patient treated with MET+DPP4i versus MET+Sulphonilureas, being discontinuation about two fold more frequent in the latter treatment group. For this reason, the protocol was amended to explore the influence of treatment discontinuation on the study outcome and the preliminary results obtained. For this reason, the following additional sensitivity analysis will be performed:

1) Start of follow-up time will be set at 180 days after index prescription. The rationale of this choice is that we noted in the preliminary analysis on the Tuscany data that most of patients on MET+Sulphonylureas discontinued one or the other drug during the first 180 days from cohort entry. Moreover, in the primary analysis, patients experiencing treatment intensification during the first 180 days (i.e. primary treatment failure), which were equally distributed in both MET+DPP4i and MET+ Sulphonylureas group, were censored as well;

2) The analysis will be re-run using a different definition of drug discontinuation. We will consider a discontinuation to occur if the time elapsed from the end of the duration of the last drug dispensing was at least 180 days. This analysis aims to take into account possible exposure misclassification due to private purchase of hypoglicemics, which is expected to be more frequent in MET+ Sulphonylureas because of the lower price of sulphonylureas;

3) The primary analysis will be re-run without censoring patients who discontinue metformin and/or the index drug;

4) In addition to age, sex, calendar year of cohort entry and database, patients will be matched to also by frequency of glycated haemoglobin measurements during the year preceding index date (≥2 versus <2 measurements), intended as a proxy of carefulness toward disease management and treatment adherence.

5) Finally, an intent-to-treat approach will be used censoring neither for discontinuation nor for switch.

- Other sensitivity analyses to test the robustness of the study results:

1) A Propensity Score-matched analysis will be performed. Variables for PS will be selected based on their association with the outcome in order to reduce bias due to measured confounders[23].

2) since disease duration is an important predictor of the durability of the hypoglycaemic efficacy of antidiabetic drugs [24], the primary analysis will be re-run restricting the study cohort to only those patients with "definite" time between first antidiabetic dispensing and index prescription;

3) the subpopulation used to perform sensitivity analysis #1 will be further restricted to patients who did not use any antidiabetic drug other than metformin during all the available look-back period preceding the index dispensing;

4) patients hospitalized during follow-up will be censored to explore the influence of possible differences in prescribing behaviours between inpatient and outpatient setting which could differentially affect the occurrence of censoring or outcome events in the different treatments groups;

5) a different definition of insulin initiation will be tested to distinguish between actual treatment intensification and possible rescue insulin use due to evidence of acute glucose toxicity uses [11,25]. The event date for insulin initiation will correspond to the date of the second insulin dispensing (see section 3.9)

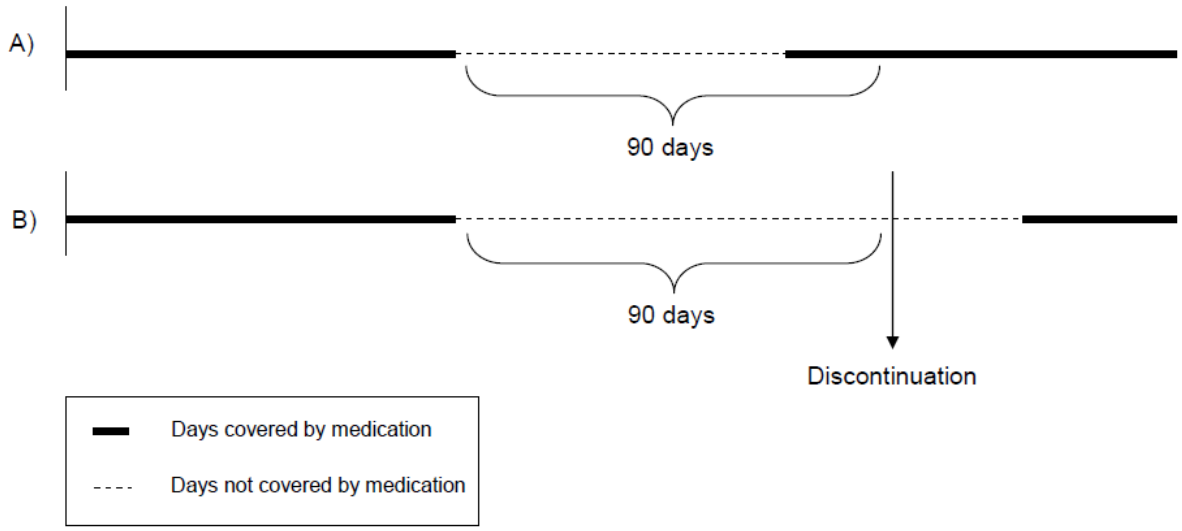
3.8. Data management and analysis

In order to standardize the process of data extraction and management, each study partners will run the open source software TheMatrix (http://thematrix.isti.cnr.it/) locally. As a result an aggregated analytical dataset will be obtained and shared with all the study participants only after local partner's verification and approval. The Regional Agency for Healthcare Services of Tuscany will be responsible for the analyses of the shared analytical dataset. These will be performed with the statistical software STATA (version 14).

3.9. Operational definitions of persistence, insulin initiation, add-on and switch

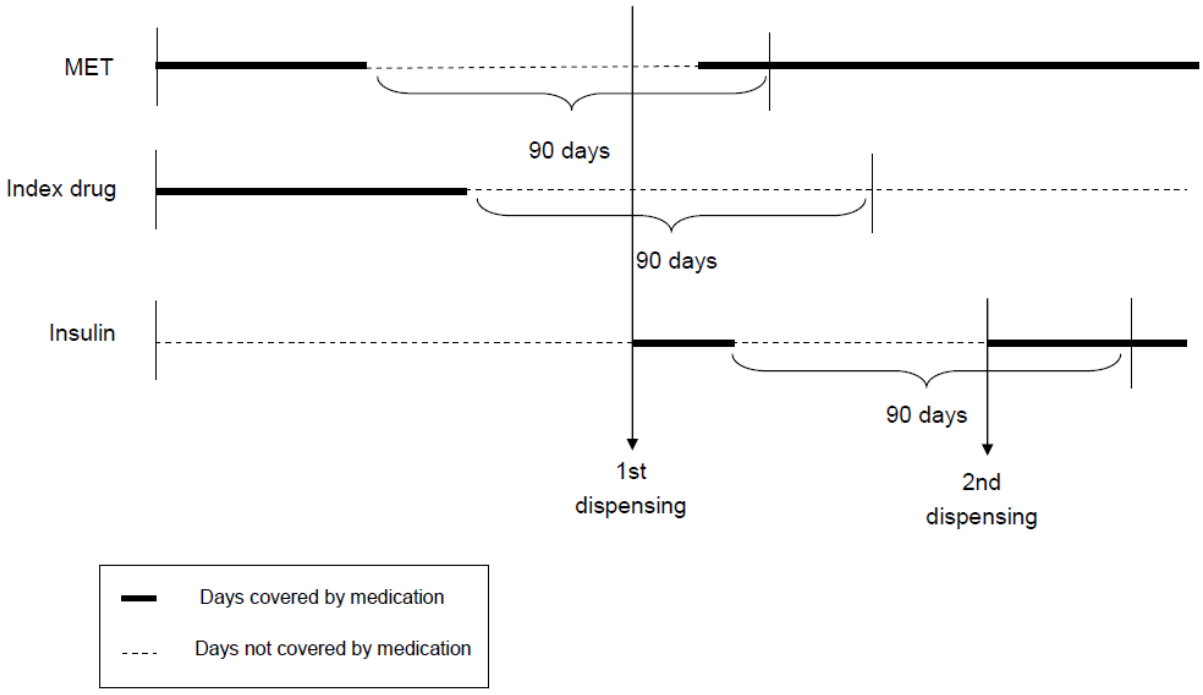
- *Persistence:* it will be defined as the absence of a gap ≥90 days between two treatment episodes [7]. Each dispensing of the drug of interest will correspond to a treatment episode (Figure 2). The duration of each treatment episode (i.e. days covered by the medication) will be estimated as the ratio between the total amount of active principle dispensed and the corresponding Defined Daily Dose (www.whocc.no/atc_ddd_index). The end of a treatment episode will correspond to either i)the date of dispensing plus the estimated duration, or ii)the date of the subsequent dispensing for the prescription refill (i.e. no stockpiling will be allowed) [7].

Figure . Operational definition of persistence.
Two examples of patients that are respectively *persistent* (A) and *non-persistent* (B) to the medication of interest.



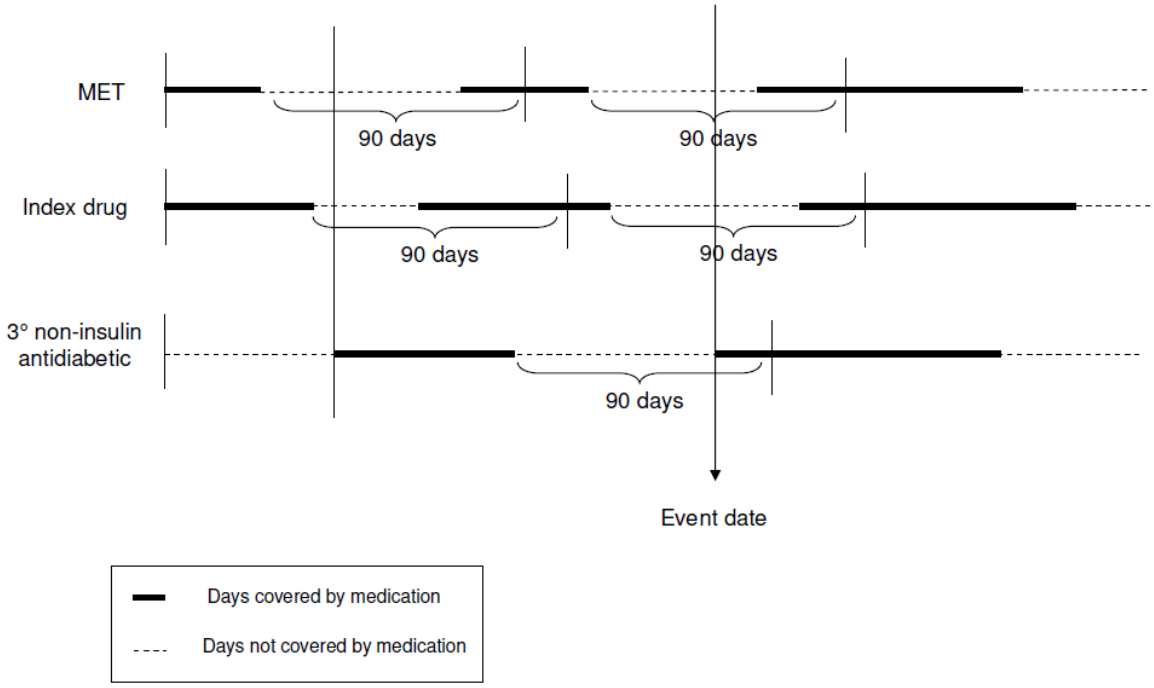
- *Insulin initiation:* it must occur before discontinuation (see the definition of persistence) of anyone of the two hypoglicemic agents corresponding to the index dual therapy. For the primary analysis the event date will be the date of *first* insulin dispensing, while for the sensitivity analysis the event date will be the date of *second* insulin dispensing occurred without insulin discontinuation between the *first* and the *second dispensing* (the other drugs may also be discontinued after the first insulin). In case discontinuation of insulin will occur before the second insulin dispensing, tha patients will be censored at the time of insulin discontinuation (i.e day 90 after the end of the duration of the first insulin dispensing).

Figure 4. Operational definition of insulin initiation.



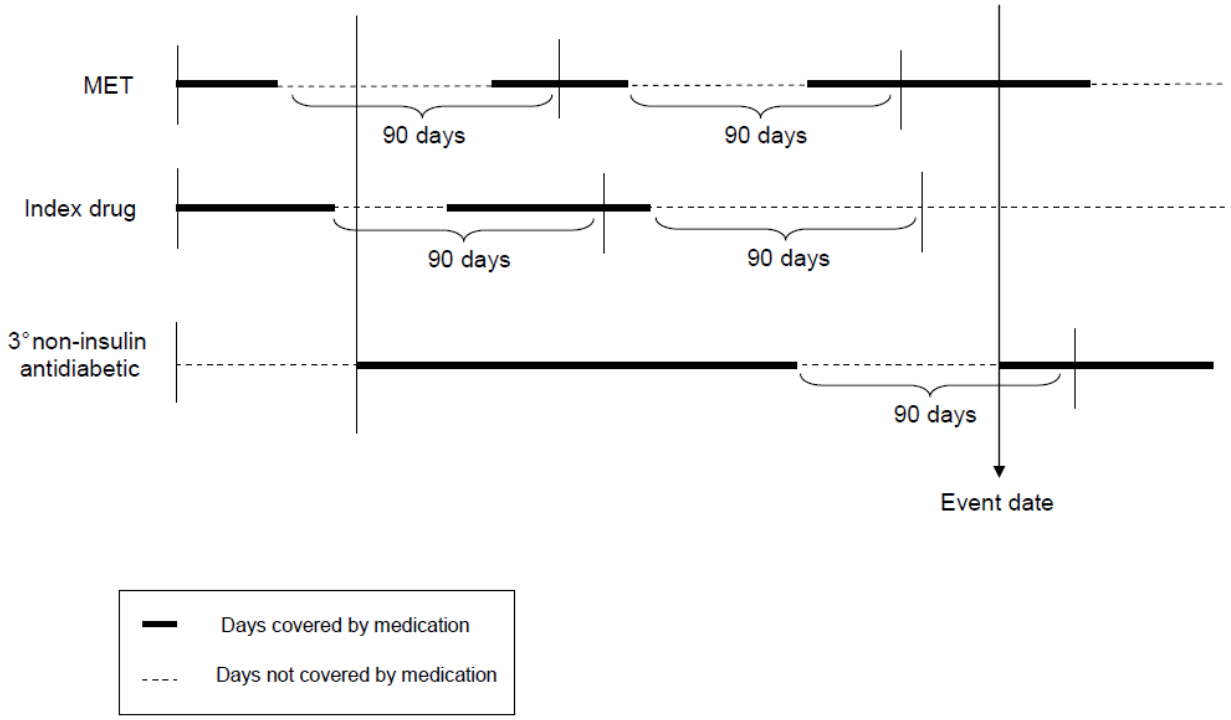
- *Add-on of the third non-insulin antidiabetic drug:* it must occur before discontinuation (see the definition of persistence) of anyone of the two hypoglicemic agents corresponding to the index dual therapy. There must be a second dispensing for all the three drugs after the first dispensing of the third hypoglicemic agent. The latest of these dispensings will correspond to the *event date*.

Figure 5. Operational definition of add-on of a third non-insulin antidiabetic drug.



- *Switch to third non-insulin antidiabetic:* it will occur when a third non-insulin antidiabetic agent will be dispensed before discontinuation (see the definition of persistence) of anyone of the two hypoglicemic agents corresponding to the index dual therapy. The date of second dispensing of the third non-insulin antidiabetic drug will be the *event date*. At this date anyone of the two hypoglicemic agents corresponding to the index dual therapy must be discontinued (see the definition of persistence).

Figure 6. Operational definition of therapeutic switch to a third non-insulin antidiabetic drug.



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5. Appendices

Appendix 1. Start of data availability

Registry	Piedmont	Tuscany	Umbria	Caserta
PERSON	2000	2004	2000	2000
HOSP	2011	1997	2000	2006
DRUGS	2012	2003	2011	2006
EXE	2000	1999	NA*	2006
OUTPAT	2011	2002	NA*	2009

NA: not available at the moment
*This information will be updated when available.

Appendix 2. Antidiabetic drugs 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#	A10BJ01	exenatide
	A10BJ02	liraglutide
	A10BJ03	lixisenatide
	A10BJ04	albiglutide
	A10BJ05	dulaglutide
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
	A10BD04	glimepiride rosiglitazone
	A10BD06	glimepiride 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
Sodium-glucose co-transporter 2 (SGLT2) inhibitors#	A10BK01	dapaglifozin
	A10BK02	canaglifozin
	A10BK03	empaglifozin
	A10BD15	metformina dapagliflozin
	A10BD16	metformina canagliflozin
	A10BD20	metformina empagliflozin

#ATC/DDD alterations 2017
(https://www.whocc.no/atc_ddd_index/updates_included_in_the_atc_ddd_index/atc_ddd_alterations_2017/)

New ATC level name or new
ATC level

A10BJ Glucagon-like peptide-1 (GLP-1) analogues
A10BK Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Previous ATC code	ATC level name	New ATC code
A10BX04	exenatide	A10BJ01
A10BX07	liraglutide	A10BJ02
A10BX09	dapagliflozin	A10BK01
A10BX10	lixisenatide	A10BJ03
A10BX11	canagliflozin	A10BK02
A10BX12	empagliflozin	A10BK03
A10BX13	albiglutide	A10BJ04
A10BX14	dulaglutide	A10BJ05

Appendix 3. Hospitalization for diabetes complications or other comorbidities[1]

Complications or other comorbidities		ICD-9 code
Cardiovascular diseases	Acute myocardial infarction	410
	Acute ischemic heart disease	411
	Angina pectoris	413
	Operations on vessels of heart	Procedure code: 36
Cerebrovascular diseases	Cerebrovascular diseases	430-436
Retinopathy	Retinopathy	362.0, 362.1, 362.2
	Diabetes with ophthalmic manifestations	250.5
Nephropathy	nephropathy	583
	Diabetes with renal manifestations	250.4
	Acute kidney failure	584
Neuropathy	Peripheral neuropathy	356
	Diabetes with neurological manifestations	250.6
Peripheral vascular disorders	Diabetes with peripheral circulatory disorders	250.7
	Amputation of lower limb	Procedure code: 84.11-84.19
	Ulcer of lower limbs, except pressure ulcer	707.1
	Peripheral angiopathy	443.81

[1]Diagnoses either in primary or secondary position recorded during 1 year before index prescription.

Appendix 4. Pharmacotherapies measured at baseline

Pharmacotherapy*	ATC code
Antidepressants	N06A
Corticosteroids for systemic use	H02
Lipid lowering drugs	C10
Anticoagulants	B01, excl B01AC
Antiplatelets	B01AC
Beta blockers	C07
Antihypertensives and/or diuretics	C02-C03
Dihydropyridine CCB	C08CA
Non Dihydropyridine CCB	C08D
Angiotensin receptor blockers and ACE-I	C09
Antipsychotics	N05A

*≥2 dispensings during 1 year before index prescription
ICD: international classification of diseases; ATC: anatomic therapeutic chemical; CCB: calcium channel blocker; ACE-I: angiotensin converting enzyme inhibitor;