

BMJ Open Impact of deintensifying hypoglycaemic drugs in older adults with type 2 diabetes: protocol for an emulation of a target trial

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To cite: Christiaens A, Simon-Tillaux N, Thompson W, *et al.* Impact of deintensifying hypoglycaemic drugs in older adults with type 2 diabetes: protocol for an emulation of a target trial. *BMJ Open* 2023;**13**:e073081. doi:10.1136/bmjopen-2023-073081

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2023-073081>).

Received 22 February 2023
Accepted 07 November 2023



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ABSTRACT

Introduction In older adults with type 2 diabetes (T2D), overtreatment with hypoglycaemic drugs (HDs: sulfonylureas, glinides and/or insulins) is frequent and associated with increased 1-year mortality. Deintensification of HD is thus a key issue, for which evidence is though limited. The primary objective of this study will be to estimate the effect of deintensifying HD on clinical outcomes (hospital admission or death) within 3 months in older adults (≥ 75 years) with T2D.

Methods We will emulate with real-world data a target trial, within The Health Improvement Network cohort, a large-scale database of data collected from electronic medical records of 2000 general practitioners in France. From 1 January 2010 to 28 February 2019, we will include eligible patients ≥ 75 years who will have T2D, a stable dose of HDs, glycated haemoglobin A1c (HbA1c) value < 75 mmol/mol (9.0%) and no deintensification in the past year. The target trial will be sequentially emulated (ie, eligibility assessed) every month in the database. Patients will be classified at baseline of each sequential trial in the intervention arm (deintensification of HDs: decrease of $\geq 50\%$ in the total dose of HDs, including complete cessation) or control arm (no deintensification of HDs). The pooled dataset for all sequential emulated trials will be analysed. The primary outcome will be time to first occurrence of hospital admission or death, within 3 months. Secondary outcomes will be hospitalisation, death, appropriateness of glycaemic control and occurrence of HbA1c > 75 mmol/mol within 1 year. Participants will be followed from baseline to 12 months after randomisation, administrative censoring, or death, whichever occurs first. A pooled logistic regression will be used to estimate the treatment effect on the incidence of the outcomes.

Dissemination and ethics No ethical approval is needed for using retrospectively this fully anonymised database. The results will be disseminated during conferences and through publications in scientific journals.

INTRODUCTION

Type 2 diabetes mellitus (T2D) is a chronic condition characterised by hyperglycaemia,

STRENGTHS AND LIMITATIONS OF THE STUDY

- ⇒ This study will focus on the deintensification of hypoglycaemic drugs (HDs), a key issue for which there is limited scientific evidence, and will include older patients, who are usually excluded from randomised controlled trials.
- ⇒ This study will include multicentre real-life data that are routinely collected in West-European primary care practices, for a large set of patients.
- ⇒ This study will be an emulation of a target trial, a methodological design that allows for precisely defining the causal question and estimates the effect of the intervention in an observational setting.
- ⇒ This study will be limited by its observational design, which will induce restrictions to define the criteria of eligibility, unmeasured confounding and missingness on covariates and outcomes.
- ⇒ The database will not include information on patients' willingness or motivation regarding the deintensification of HDs, nor any data about the occurrence of hypoglycaemic events or the patients' functional status.

and its prevalence is estimated at 20.1% in the older population, which includes people ≥ 65 years old in Europe.¹ The treatment of T2D relies on, among other things, restoring appropriate glycaemic control to avoid the acute and chronic consequences of hyperglycaemia leading to significant morbimortality^{2–4} by the use of glucose-lowering therapy.⁵ Among the various available glucose-lowering drug classes, the hypoglycaemic drugs (HDs; ie, sulphonylureas, glinides (oral HDs), and insulins (injectable HDs)⁵) may cause hypoglycaemia.

Hypoglycaemia is harmful in older patients, and is associated with increased risk of mortality, frailty, falls, hospitalisations and cognitive and functional decline, which

worsens the well-being of patients and generates excess costs for healthcare systems.^{6–9} In particular, in some older patients, the risks of morbidity and mortality due to short-term and medium-term hypoglycaemia outweigh the benefits of glucose-lowering drugs.¹⁰ Therefore, tailoring glycaemic management in older adults with T2D has become the gold-standard practice in recent years, as stated by recommendations provided by clinical practice guidelines developed by major scientific societies.¹⁰

As suggested by a systematic review of recent international recommendations, scientific societies recommend deintensifying glucose-lowering drugs (ie, reducing the total dose or the number of drugs, including total discontinuation of the treatment¹¹), in particular limiting the use of HDs, for various profiles of older patients with T2D (eg, those with high risk of hypoglycaemia, those with uncertain benefit of glucose-lowering drugs, and those unable to provide self-care^{12–17}). However, these recommendations are heterogeneous between current clinical practice guidelines, mostly unclear, and based on low-level evidence (expert opinion-based), given the limited evidence available on this topic.^{18–19} Only a few studies focused on deintensifying glucose-lowering drugs in the older population, reporting that deintensifying glucose-lowering drugs may reduce rates of adverse events (two randomised controlled trials and two observational studies between 2015 and 2021, all with low certainty based on a Grading of Recommendations, Assessment, Development and Evaluations assessment).²⁰

This situation highlights the need for well-designed studies investigating the deintensification of glucose-lowering drugs (particularly HDs) in an older general population with T2D.²⁰ The target trial framework was proposed in 2016 by Hernán and Robins.^{21–22} This methodology consists of defining the target randomised trial that would have been conducted in the interventional setting to answer the causal question and emulating its design in observational data. This framework aims to identify the causal estimate of interest and reduce biases through confrontation of the target trial and its emulation.^{21–23–25}

In older people, we hypothesise that deintensification of HDs will be superior to no deintensification in this particular population. This study will aim to assess whether deintensifying HDs affects clinical outcomes (prevents hospital admission or death within 3 months (primary objective), or within 12 months (secondary objectives)) in older people (≥ 75 years old) with T2D.

METHODS AND ANALYSES

Study overview

In this study, we will emulate in real-world data (observational data from a large-scale cohort) a target trial. Table 1 summarises both the specifications of the target trial and its emulation with observational data.^{21–22} This protocol describes how we will emulate the target trial. This study

(ie, the data analysis work) will start on 15 October 2023 and end on 15 January 2024.

Data sources

Data will be extracted from The Health Improvement Network (THIN) database from GERS DATA (Groupe-ment pour l'Elaboration et la Réalisation de Statistiques, Cegedim SA).²⁶ THIN is a large-scale database, collecting fully anonymised real-life longitudinal patient data in several European countries; we will use data from France. THIN has been used in more than 1900 publications since 2012, including pharmacoepidemiological studies.²⁷ Data from France have been collected since 1994 from electronic health records of about 3000 physicians in primary care (2000 general practitioners (GPs)) using the CrossWay software (electronic medical record device from CEGEDIM SA). The French population included in THIN is representative of the whole French population, in terms of age, sex and geographical area. The data encoded by the GP at each visit of a patient include sociodemographic characteristics (age, sex, place of residency), diagnoses (codes of the International Classification of Diseases, 10th Revision), medications prescribed by the GP (codes of the Anatomical Therapeutic Chemical classification system), acts performed by the GP during the patient visit, and laboratory test results (including glycated haemoglobin A1c (HbA1c) values). For each patient, reimbursement data are obtained from the Historique des Remboursements (from the French Health Insurance system) and include reimbursements for medical acts, treatment from the pharmacy and hospitalisations. Patient's vital status was collected from the French National Register.²⁸ Data (from medical records, reimbursement and vital status) are linked for each patient. All dates of measurement of variables are available in a month/year format. The THIN database complies with all current European data protection laws (General Data Protection Regulation) and adheres to the Observational Medical Outcomes Partnership model.

Study timeframe

The inclusion period will be from 1 January 2010 to 28 February 2019. We will limit inclusions up to 28 February 2019 in order to have 1 year of potential follow-up and avoid measurement of outcomes during the COVID-19 pandemic period, which could have affected their incidence. Data will be extracted to span the period from 1 January 2009 to 28 February 2020, to have a 1-year look-back to assess medical history before inclusion and a potential 1 year of follow-up.

Figure 1 presents the timeframe defining the baseline, which is each month in which all eligibility criteria are met.

Eligibility criteria

Inclusion criteria

Eligible patients will be ≥ 75 years old and will have T2D, glucose-lowering treatment including stable

Table 1 Summary of the target trial specification and its emulation

	Target trial specification	Target trial emulation
Eligibility criteria	Inclusion criteria: ▶ Older people (≥ 75 years) ▶ Patients with T2D ▶ Receiving glucose-lowering treatment including stable HDs during the past 6 months (ie, same total dose of HDs in DDD and use of the same molecule(s)) ▶ HbA1c value $< 9\%$ Non-inclusion criteria: ▶ Unknown dose of any HD ▶ Deintensification of HD in the past year	Same as for the target trial and additionally: ▶ At least 1 year in the database (to assess previous de-intensification) ▶ At least 1 year of potential follow-up in the database (ie, patients must be eligible up to the date of 28 February 2019) Baseline will be defined each month that all eligibility criteria are met.
Treatment strategies	<i>Deintensification of HDs</i> (ie, decrease in the total dose of HDs ($\geq 50\%$ of the total DDD)), including complete cessation of HD. Switching from HDs to other HDs or non-HDs are considered as deintensification as well, as long as the total dose of HDs (in DDD) after deintensification is decreased of $\geq 50\%$ of the initial dose. <i>No deintensification of HDs</i> (ie, increase of total dose of HDs, same dose of HDs, or decrease of $< 50\%$ in the total dose of HDs).	Same as for the target trial
Assignment to treatment strategies	Participants will be randomly assigned to the treatment strategies and will be aware of their treatment arm.	Participants will be classified at baseline according to the treatment strategy prescribed. Randomisation will be emulated by adjusting at baseline for confounders.
Outcomes	The primary outcome will be time to hospital admission or death, whichever occurs first, at 3 months	Same as for the target trial
Follow-up	Patients will be followed from randomisation to the occurrence of the outcome of interest, death, loss to follow-up, or 1 year after randomisation.	Participants will be followed from baseline to the occurrence of the outcome of interest, death, administrative censoring, or up to 1 year after baseline.
Causal contrast	Intention-to-treat effect Per-protocol effect	Observational analogue of intention-to-treat effect Observational analogue of per-protocol effect
Analysis	Intention-to-treat analysis Per-protocol analysis: follow-up of patients will be censored if they deviate from their assigned treatment arm at randomisation, and a strategy of inverse probability weighting will be implemented to adjust for prandomisation and postrandomisation prognostic factors associated with treatment strategy adherence.	Same as for the target trial. The target trial will be sequentially emulated every month (at the first day of each month) in the database, and the analyses will be additionally adjusted for covariates measured at baseline for each sequential emulated trial.

DDD, defined daily dose; HDs, hypoglycaemic drugs; T2D, type 2 diabetes mellitus.

HDs (ie, sulfonylureas, glinides and/or insulins), and HbA1c level < 75 mmol/mol (9.0%) during the inclusion timeframe (figure 1).

T2D will be defined by a diagnosis of T2D (according to the International Classification of Diseases, 10th Revision code for T2D: E11), and/or a prescription of any glucose-lowering treatment (according to Anatomical Therapeutic Chemical codes). A specific search algorithm will be used to capture all patients with T2D in the database according to this definition (online supplemental file A).

Among the glucose-lowering treatment available, we will distinguish between HDs (that is, sulfonylureas, glinides and/or insulins) and non-HDs (ie, all other glucose-lowering treatment; eg, metformin, glucose-like peptide-1 receptor agonist, dipeptidyl-peptidase 4 inhibitor, etc). The stability of HDs is defined by the prescription of the same medication(s) and dose(s) of HD over 6 months (without any change) (eg, at least two consecutive identical prescriptions 6 months apart, with no change between them). All doses of

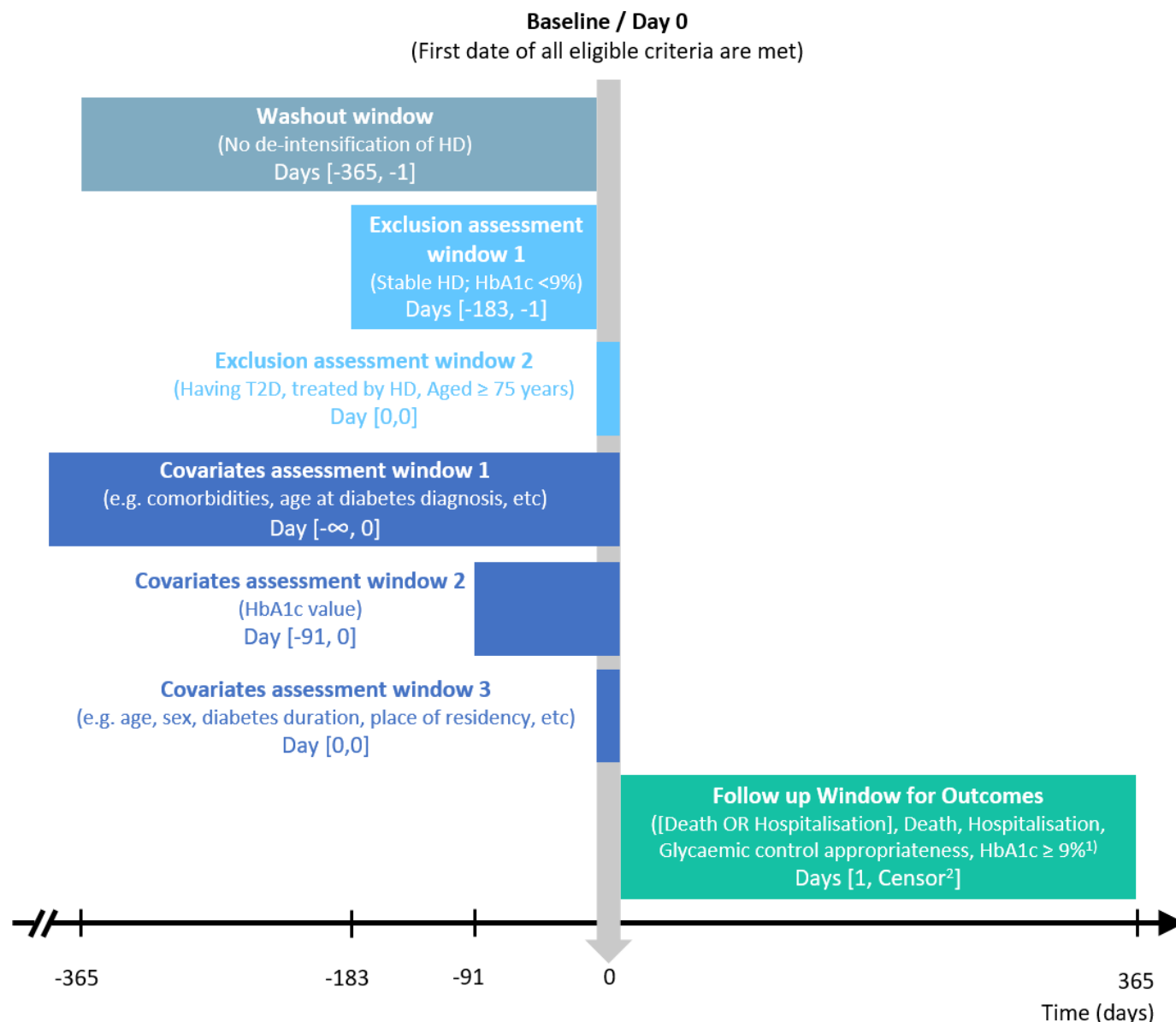


Figure 1 Timeframe for observations in the study.¹Glycated haemoglobin A1c (HbA1c) level ≥ 75 mmol/mol (9.0%) and with an increase greater than or equal to 5% from the HbA1c value at baseline. ²Censored on the occurrence of the outcome of interest, death, administrative censoring (cut-off date on 28 February 2020), or up to 12 months following baseline. HD: hypoglycaemic drugs (sulfonylureas, glinides, and/or insulins); no deintensification of HD: defined according to the treatment strategies (ie, increase of total dose of HD, same dose of HD, or decrease of < 50% of the total dose of HD). Covariates assessed during the first window (during the entire period of data availability up to and including the baseline) will be age at diabetes diagnosis, complications of diabetes (microangiopathy, including diabetic polyneuropathy and diabetic retinopathy), hypertension, other comorbidities (including those of the Charlson Comorbidity Index³⁵: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischaemic attack, severe neurocognitive troubles, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, hemiplegia, moderate-to-severe chronic kidney disease, solid tumour, leukaemia, lymphoma and acquired immunodeficiency syndrome), claim-based frailty index,^{36 37} number of hospitalisation in the year before baseline, and number of general practitioner contacts in the year before baseline. Covariate assessed during the second window (during the 3 months before baseline) will be the HbA1c value. The covariates assessed during the third window (at baseline) will be: age, sex, physician's practice region, place of residence (home vs nursing home), total number of drugs per day and duration of diabetes.

HD will be converted to a defined daily dose to standardise the doses between the different medications.²⁹

We will restrict inclusion to patients aged ≥ 75 years old because this is a vulnerable population for whom deintensification of HDs is thus more specifically

aimed and for whom there is a profound lack of evidence.¹² We will restrict inclusion to patients with HbA1c level < 75 mmol/mol (9.0%) to allow for exchangeability at baseline across all treatment arms, or in other words, to ensure that patients are

eligible for both treatment strategies at baseline as in a randomised trial.

Non-inclusion criteria

Patients who already had a deintensification of HDs (as defined in the treatment strategies, see below) in the previous year will not be included, to mitigate prevalent user bias. In addition, we will not include patients for whom the dose of HD is missing.

Treatment strategies and assignment

Intervention arm

Deintensification of HDs (ie, insulins, sulfonylureas and glinides): a decrease of the total dose of HDs ($\geq 50\%$ decrease of the total defined daily dose), including complete cessation of all HDs). Switching from HDs to other HDs or non-HDs are considered as deintensification as well, as long as the total dose of HDs (in DDD) after deintensification is decreased of $\geq 50\%$ of the initial dose.

Control arm

No deintensification of HDs (ie, increase of total dose of HDs, same dose of HDs, or decrease of $< 50\%$ of the total dose of HDs).

Outcomes

The primary outcome will be time to hospital admission or death (all-cause mortality), whichever occurs first, at 3 months. This short timeframe was chosen based on the assumption that adverse effects of overtreatment by HDs that should be avoided by deintensification (ie, hypoglycaemic events) are expected to disappear shortly after deintensification, and according to what has been chosen in other studies.¹¹

Secondary outcomes will be time to first hospital admission, time to death (all-cause mortality), the number of hospital admission(s), the appropriateness of glycaemic control, and the occurrence of HbA1c level ≥ 75 mmol/mol (9.0%) (with an increase $\geq 5\%$ from the HbA1c value at baseline), within 1 year.

Appropriateness of glycaemic control will be defined as an HbA1c level $< 8.5\%$ when no HD is prescribed, or an HbA1c between 7.0% and 8.5% when HD is prescribed (at the time of the HbA1c measurement). The assessment of glycaemic control appropriateness will be performed on the first HbA1c value available between 3 months and 12 months after baseline. This definition is adapted (according to the data available in THIN database) from the HbA1c targets suggested by the clinical practice guidelines of the Endocrine Society¹⁴ and used in previous studies.^{30 31}

Follow-up

Participants will be followed from baseline to the occurrence of the outcome of interest, death, exit from the THIN database (lost to follow-up), or up to 12 months, whichever occurs first. Baseline for a given patient is the month in which all eligibility criteria are met (figure 1).

Patients will not be followed up beyond 28 February 2020 (cut-off date of the database).

Covariates

We will consider a large panel of covariates, selected after a review of the literature on this subject.^{3 11 20 31–34} The covariates of interest will be age, sex, physician practice region, patient's place of residence (home vs nursing home), HbA1c value, duration of diabetes (time from diabetes diagnosis), age at diabetes diagnosis, glucose-lowering treatment (drugs and doses in DDD), complications of diabetes (ie, microangiopathy, including diabetic polyneuropathy and diabetic retinopathy), hypertension, other comorbidities (including those of the Charlson Comorbidity Index³⁵: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischaemic attack, severe neurocognitive troubles, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, hemiplegia, moderate to severe chronic kidney disease, solid tumour, leukaemia, lymphoma and AIDS), claim-based frailty index developed by Segal *et al*^{36 37} (computed on the basis of the comorbidities collected in the database), number of hospitalisation in the past year, number of GP contacts in the past year and total number of drugs per day. These covariates will be collected in the database at baseline, or in the 3 months before baseline, or from the beginning of data availability, depending on the type of covariate (figure 1).

Emulation of the target trial

The treatment strategies of each cloned copy will be assessed based on prescription data (or the last prescription available) at the beginning of that given month as well as the status for potential confounders (or the last available value for time-varying potential confounders). Then, if the target trial can be emulated (ie, if at least one cloned copy classified in the intervention arm can be compared with at least one cloned copy classified in the control arm), the cloned copies will be retained. To avoid immortal time and selection biases,²² we will create coinciding eligibility, treatment assignment and time zero (or baseline of the sequential nested trial) by restarting the beginning of follow-up at this particular month in the database (first day of the month). These three steps—assessment of eligibility of cloned copy, assignment of treatment strategy and reinitialisation of the follow-up—will be repeated every month in the database. Therefore, a patient can contribute to several sequential nested trials but with potential various treatment assignments and baseline confounders among the different cloned copies (figure 2). All the cloned copies of sequential nested trials will be then stacked in a pooled dataset for analysis.

In this study, the target trial will be emulated several times sequentially. Each calendar month in the database, cloned copies of individuals eligible for the target trial will be created.³⁸ The treatment strategies of each cloned copy will be assessed based on prescription data (or the

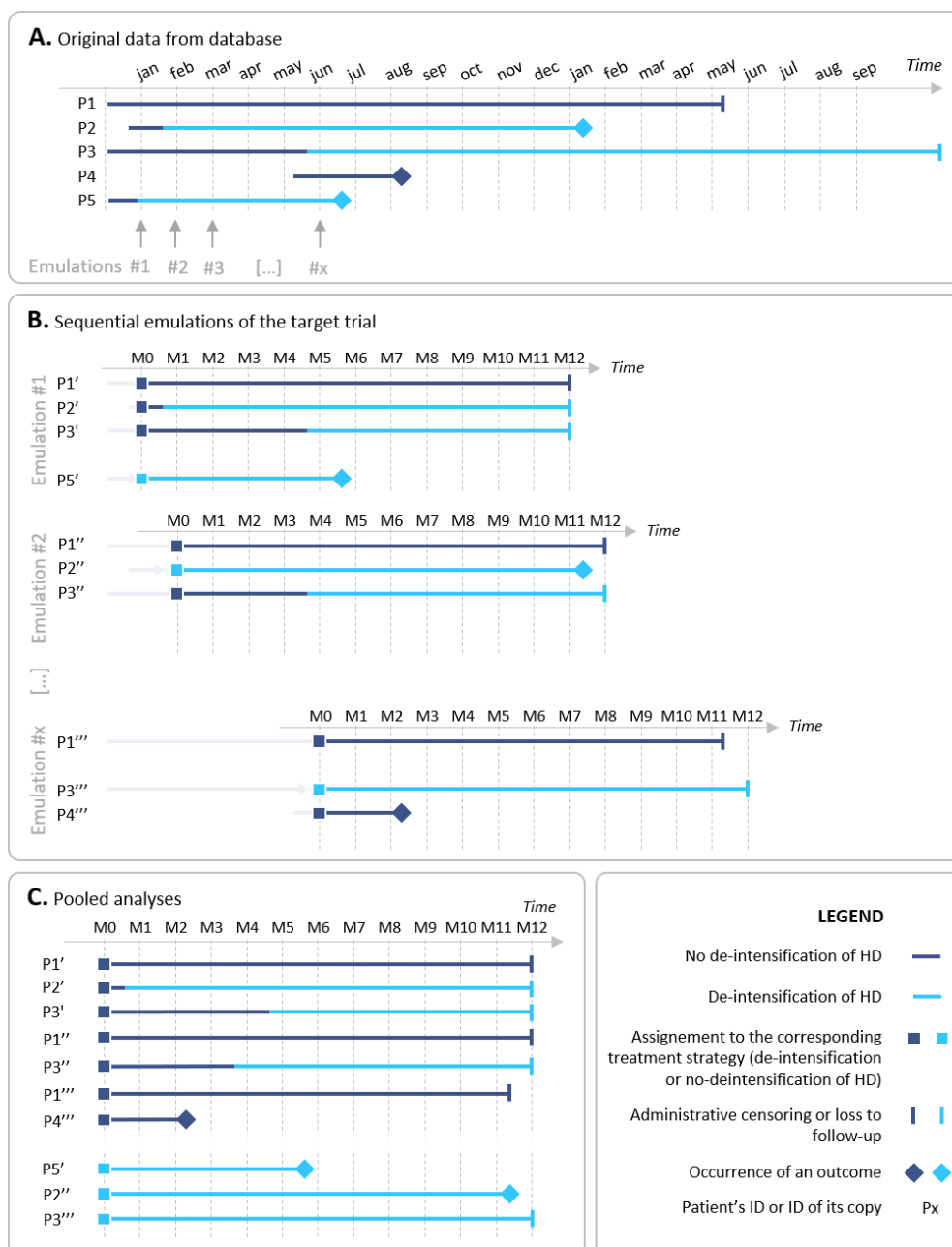


Figure 2 Theoretical example of the sequential emulations of the target trial. (A) In this theoretical example, five patients (P1–P5) were included from the database. Available data for these patients are represented on the timeline. (B) The target trial is sequentially emulated each month, and examples of these sequential emulations are provided for January (emulation #1), February (emulation #2), March (emulation #3), and June (emulation #x). For emulation #1, one cloned copy of patient (P5) started deintensification, which can be compared with three cloned copies of patients (P1, P2 and P3). If the cloned copies meet the eligible criteria of the target trial, they are kept for analysis. Treatment assignment is based on the prescription data compatible with the treatment strategy, and confounders at baseline of the sequential trial (ie, calendar month in the database) are also measured for each cloned copy (eg, comedication). To ensure coinciding of eligibility, treatment assignment and start of follow-up, thus avoiding immortal-time and selection biases,²² the follow-up of each cloned copy is restarted at the beginning of the sequential trial. For emulation #2, one cloned copy of patient P2 that started deintensification can be compared with two cloned copies of patients P1 and P3 that did not. Cloned copies of patients (P5'') are no longer eligible for the sequential emulated trial, according to eligibility criteria of the target trial: the patient already began deintensification in the past year (or in other words, a new-user design is applied). Assignment to treatment strategy, confounders measurement and follow-up reinitialisation are the same as for emulation #1. For emulation #3, no participant started deintensification in the database, so the comparison between deintensification and no deintensification is not feasible, and the cloned copies are not kept for analysis. These steps are repeated as many times as the target trial can be emulated, that is, each month when at least one eligible cloned copy starts the deintensification strategy and can be compared with a cloned copy belonging to the no-intensification arm. (C) Finally, the cloned copies of all sequential emulated trials are stacked in the final dataset for pooled analysis. HD, hypoglycaemic drug; M, months.

last prescription available) at the beginning of that given month, as well as the status for potential confounders (or the last available value for time-varying potential confounders). Then, if the target trial can be emulated (ie, if at least one cloned copy classified in the intervention arm can be compared with at least one cloned copy classified in the control arm), the cloned copies will be retained. To avoid immortal time and selection biases,²² we will make coincide eligibility, treatment assignment and time zero (ie, baseline of the sequential nested trial) by restarting the beginning of follow-up at this particular month in the database (first day of the month). These three steps (assessment of eligibility of cloned copy, assignment of treatment strategy and reinitialisation of the follow-up) will be repeated every month in the database. Therefore, a patient can contribute to several sequential nested trials but with potential various treatment assignment and baseline confounders among the different cloned copies (figure 2). All the cloned copies of sequential nested trials will be then stacked in a pooled dataset for analysis.

Statistical analysis

A pooled logistic regression will be used to estimate the per-protocol and intention-to-treat risk differences and HRs for the occurrence of the primary outcome.³⁸ The OR from a pooled logistic regression is a good approximation of the HR in a Cox model if the risk of the event is low.³⁹ The pooled logistic regression model will contain an indicator of assigned strategy and a flexible function of months from baseline (linear and quadratic terms). The model will also account for confounders measured at baseline of each sequential trial. The primary analysis will focus on the intention-to-treat estimate, or the effect of assignment to the deintensification strategy or no deintensification strategy at baseline, regardless of adherence to these strategies during follow-up.

To estimate the observational analogue of the per-protocol effect, cloned copies will be additionally censored when they deviate from their assigned strategy (deintensification vs no deintensification). To estimate this analogue of per protocol effect, we will need to account for baseline and time-varying confounding related to adherence to the treatment strategy. Therefore, a strategy of inverse probability weighting will be implemented.³⁸ All treatment effects will be presented with their 95% CI, based on robust variances estimated by bootstrap to account for the duplication of patient observations in the analysis.

To assess the potential effect of unmeasured confounding, several controls will be used. First, we will compute the E-value, or 'the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates'.⁴⁰ Then, to assess residual confounding related to frailty (a condition commonly associated with deintensification and

pneumopathy), that may have been mismeasured in this database, we will assess the effect of deintensifying HDs on the risk of pneumopathy diagnosis at 1 year of follow-up, which is expected to be null (negative control).

In addition, the analyses described above will be repeated in different relevant subgroups. Among these, we will include the different profiles of patients for whom deintensification is suggested by recent clinical practice guidelines¹² (ie, multiple comorbidities (≥ 5 comorbidities), tight glycaemic control ($\text{HbA1c} < 48 \text{ mmol/mol}$ (6.5%)), polypharmacy (≥ 5 drugs/day), impaired renal function (end-stage renal disease), advanced age (≥ 80 years), long duration of diabetes (≥ 20 years), severe neurocognitive troubles, nursing home resident).

Finally, we will conduct sensitivity analyses to assess the robustness of our findings, based on the definition of HDs deintensification (complete cessation of HDs vs decrease of HDs dose $< 50\%$) and the type of HDs deintensified (insulin vs oral HDs).

Patient and public involvement

No patients were involved in the design or development of this protocol.

ETHICS AND DISSEMINATION

The study will be a retrospective analysis of fully anonymised secondary data. Therefore, individual consent is waived, and no ethical approval is needed. The data collection by THIN was approved by the French National Data Protection Authority (CNIL) in 2002, and the database complies with the European general data protection regulations. We will submit the results to a peer-reviewed scientific journal, and will present them during scientific conferences. The reporting of the study will follow the REporting of studies Conducted using Observational Routinely-collected health Data for pharmacoepidemiology (RECORD-PE) reporting guidelines.⁴¹

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Contributors AC, LZ, NS-T, SH, DB-Z and FT conceived the original idea. All authors contributed to design the project. YS-J, BL and AC participated to the reflection on data acquisition. AC, NS-T and LZ drafted the manuscript of the protocol. All authors critically reviewed and revised the manuscript. All authors approved the final version of this manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This work was supported by a Postdoctoral Researcher grant (Antoine Christiaens; no. FC23595) from the Fund for Scientific Research – FNRS (Belgium), and by the “Edouard et Lucie Chaffoteaux” Award – 7th edition from the Société Française de Gériatrie et Gérologie (SFGG), and the Fondation de France (Antoine Christiaens).

Competing interests Antoine Christiaens is employed by the Fund for Scientific Research, as a postdoctoral researcher. He received the “Edouard et Lucie Chaffoteaux” Award – 7th edition – from the Société Française de Gériatrie et Gérologie (SFGG), and the Fondation de France. He received honoraria for a lecture during the Journées de Gériatrie de Nouvelle Aquitaine (Bordeaux, France), from NovoNordisk in April 2022 (This company did not give any guidance, nor did take part in the content of the lecture). He is member of the board of the Belgian Society of Gerontology and Geriatrics (unpaid activity). Florence Tubach is head of the Centre de Pharmacopépidémiologie (Cephepi) of the Assistance Publique – Hôpitaux de Paris and of the Clinical Research Unit of Pitié-Salpêtrière hospital, both these structures have received unrestricted research funding and grants for the research projects handled and fees for consultant activities from a large number of pharmaceutical companies, that have contributed indiscriminately to the salaries of its employees. Florence Tubach is not employed by these structures and did not receive any personal remuneration from these companies. Other authors have no competing interests to declare.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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