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RESEARCH PAPER

Association between hypoglycaemic drug de-intensification, mortality and hospital admission in older adults with type 2 diabetes: a cohort study emulating a target trial

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Abstract

Background: Hypoglycaemic drugs (sulfonylureas, glinides or insulins) are commonly prescribed for older adults with type 2 diabetes (T2D) but may carry risks of adverse events. Whether de-intensifying hypoglycaemic drugs is associated with clinical benefit in older adults remains unknown.
Objective: To evaluate the association between de-intensification of hypoglycaemic drugs and clinical outcomes in older adults with T2D.
Methods: Cohort study conducted with the target trial emulation approach, using data collected from 2000 French general practises between January 2010 and February 2019 (The Health Improvement Network—THIN database). Eligible participants were ≥75 years old, on stable hypoglycaemic drugs (no change in drug or dose) for at least 6 months, and had an HbA1c value <9%. Hypoglycaemic drug de-intensification (exposure) was defined as cessation or reduction of ≥50% of total dose. The primary outcome was a composite measure of all-cause death or hospital admissions within 3 months, and its association with exposure was assessed using multivariable logistic regression adjusted for potential baseline confounders.
Results: The study included 14 383 unique individuals corresponding to 177 314 trial emulation participants (mean age 80 years; 44.7% female). Of these, 6480 participants were allocated to de-intensification group, and 170 834 to the control group. At 3 months, the primary outcome occurred in 3.96% of the de-intensification group and 2.99% of controls

[adjusted relative risk, 1.33 (95% CI, 1.22–1.43)]. Subgroup analyses showed consistent associations across most participants' profiles.
Conclusions: In older adults with T2D, de-intensification of hypoglycaemic drugs was associated with a higher short-term risk of all-cause death or hospitalisation.

Keywords: type 2 diabetes; glucose-lowering treatment; older adults; general practises; de-intensification older people

Key Points

- This cohort study aimed at assessing association between hypoglycaemic drug de-intensification, mortality and hospital admission.
- Using data from 2000 French GPs, it emulated sequential target trials in a cohort of older adults living with type 2 diabetes.
- It included 14 383 unique individuals corresponding to 177 317 trial emulation participants.
- It found that de-intensifying hypoglycaemic drugs was associated with increased mortality and/or hospital admission.

Introduction

Type 2 diabetes (T2D) is diagnosed in 20% of individuals ≥75 years old in both the United States and Europe [1, 2]. Glucose-lowering treatments (GLTs), including non-hypoglycaemic drugs (e.g. metformin, dipeptidyl-peptidase 4 inhibitors or glucagon-like peptide 1 receptor agonists) and hypoglycaemic drugs (i.e. sulphonylureas, glinides and insulins) [3], are used for glycaemic control and to reduce the risk of complications [4]. However, these treatments, particularly hypoglycaemic drugs, carry a significant risk of side effects, including hypoglycaemia, which is reportedly associated with increased risk of death, falls, hospitalisations and cognitive decline [5–8].

Current clinical guidelines for managing T2D in older adults (e.g. from the European Geriatric Medicine Society, American Diabetes Association or Deprescribing.org network [8–10]) advocate for de-intensification of treatment, particularly hypoglycaemic drugs, i.e 'decreasing the dose or completely discontinuing' the treatment [11]. Recommendations are for de-intensification when the risk of adverse events is too high (e.g. use of hypoglycaemic drugs, frequent hypoglycaemia, multimorbidity and polypharmacy) or when the benefits of treatment are too uncertain, i.e. in patients with limited life expectancy, including those with cognitive impairment, living in nursing home or at end-of-life situations [9, 10, 12]. However, these recommendations are largely based on expert opinion rather than robust empirical evidence, which leads to inconsistencies across guidelines [12, 13].

As the effects of de-intensifying hypoglycaemic drugs in the older population are not yet established, it is worth conducting well-designed studies to improve the understanding of this issue. This study aimed to primarily evaluate the association between de-intensification of hypoglycaemic drugs and all-cause death or hospital admissions in older adults (≥75 years old) with T2D and haemoglobin A1c (HbA1c) value <9% (75 mmol/mol) in general practise (GP) settings.

Methods

This study involved using the target trial emulation framework, a method to estimate associations as close as possible to causal effects of interventions by using observational data [14]. Following a 2-step strategy, we designed a target trial (i.e. the trial that could theoretically answer the causal question), then the trial was explicitly emulated with observational data. The full protocol of this study was previously published [15] (Appendix 1 in Supplementary Data); posthoc modifications were introduced because of various data-related problems (Appendix 2 in Supplementary Data). The reporting of this study followed the RECORD-PE reporting statement, an extension of STROBE guidelines [16] (Appendix 3 in Supplementary Data).

This study involved a retrospective analysis of fully anonymised secondary data for which individual consent or additional ethical approval were not required.

Data source

Data were extracted from The Health Improvement Network (THIN) France database, maintained by GERS DATA SA [17]. THIN France is a representative for large-scale database of anonymised, real-life longitudinal patient data derived from patients' electronic health records from approximately 2000 GPs using the CrossWay software (an electronic medical record system developed by CEGEDIM SA). All medical contacts with the GPs were recorded. For each patient under care of the GP, all diagnoses [coded in the International Classification of Diseases, 10th Revision (ICD-10)], prescribed treatments, and biological measurements were systematically documented. The THIN database adheres to the Observational Medical Outcomes Partnership model, complies with current European data protection laws (General Data Protection Regulation) and was approved by French National Data Protection Authority (CNIL) in 2002. The access to database for research purpose is subject to approval by GERS DATA SA.

Study population, design and baseline definition

We sequentially emulated the target trial each month from January 2010 to February 2019 (i.e. a total of 110 trials), as proposed by Dickerman *et al.* [18]. We defined the baseline of the emulated trial as the first day of each month. Eligible patients were ≥75 years old, had T2D, and had received a GLT including stable hypoglycaemic treatment before baseline for at least 6 months (see below for definition). We excluded patients whose hypoglycaemic drug de-intensification occurred in the year before baseline or with HbA1c level ≥75 mmol/mol (9.0%) in the 6 months before baseline (Appendix 4 in Supplementary Data). The study period was set to include data from the start of their availability, and not to include data after 2019, to avoid any effect of the COVID-19 pandemic.

We identified all patients with T2D when a diagnosis of T2D (according to the ICD-10 code for T2D: E11) was found in the patient's medical record before baseline. We identified GLT (molecules, corresponding doses and duration) from the prescriptions made to the patients, which were electronically structured and coded in the database. Based on this data, we reconstructed the actual duration of treatment exposure. GLTs were separated into hypoglycaemic drugs and nonhypoglycaemic drugs, with doses presented as defined daily dose (DDD) [19]. We defined stability of hypoglycaemic drugs as the same medication(s) and dose(s) of hypoglycaemic drugs prescribed over 6 months, without any changes.

Exposure

In each monthly sequentially emulated target trial, we created a copy of each patient (i.e. a trial emulation participant) and allocated these participants to the two treatment groups according to the treatment that had been prescribed in this particular month (baseline for this trial emulation). To allocate the trial emulation participant in the intervention group (de-intensification of hypoglycaemic drugs), the participant must have experienced at baseline a reduction of 50% or more in total dose of hypoglycaemic drugs (in DDD), including complete cessation (compared to the treatment before baseline). Switching from hypoglycaemic drugs to other hypoglycaemic drugs or nonhypoglycaemic drugs was also considered de-intensification provided that the total dose of hypoglycaemic drugs after de-intensification was reduced by at least 50% of the initial dose. In the control group (no hypoglycaemic drug de-intensification), participants had an increase in total dose of hypoglycaemic drugs, maintained same dose, or had a reduction of <50% in the total dose of hypoglycaemic drugs in that particular month.

Outcomes

The primary outcome was a composite of the occurrence of all-cause death or hospital admissions (i.e. all hospital stays, including visits to the emergency department) at 3 months. Secondary outcomes were the occurrence of all-cause death or hospital admissions (composite outcome), hospital admissions, all-cause death or relaxed glycaemic control [i.e. HbA1c level ≥75 mmol/mol (≥9.0%)] within 12 months. Outcomes were binary.

The exact date of all-cause death was not available in the THIN database. We designed a proxy for the date of death corresponding to the first day of the month following the last recorded medical contact date in the database (including data pharmacy deliverance and any healthcare reimbursement) in the year in which the patient died (confirmed by linkage to the French National Register). The assessment of relaxed glycaemic control involved using all HbA1c measures available within 12 months after baseline.

Directed acyclic graphs and covariates

We constructed causal directed acyclic graphs (DAGs) for each outcome, representing the assumed link between the covariates, the exposure factor (hypoglycaemic drug de-intensification) and the outcome (Appendix 5 in Supplementary Data). A large panel of covariates measured at or before baseline were selected for adjustment (Appendix 4 in Supplementary Data). The analysis was adjusted for the following covariates: age, sex, previous number of GP visits, HbA1c values, total number of drugs prescribed by day, prescribed GLT (drugs and doses in DDD), duration of diabetes (time from diabetes diagnosis), age at diabetes diagnosis, complications of diabetes (i.e. microangiopathy, including diabetic nephropathy, neuropathy and retinopathy), hypertension and other comorbidities (Appendix 6 in Supplementary Data). Comorbidities were coded in ICD-10 codes. We computed the Charlson Comorbidity Index (CCI) [20] (max = 37; high score indicates high number of comorbidities and/or severe comorbidities) and the multimorbidity Frailty Index (mFI) [21] (max = 1.00; high score indicates multiple comorbidities and deficits). Both CCI and mFI are predictors of all-cause death and hospital admission [20–22].

Follow-up

For each sequential emulated target trial, follow-up started at baseline (i.e. date on which all eligible criteria are met, and exposure began) and ended at the occurrence of the outcome of interest, death, up to 12 months, or up to the cut-off date of the database (28 February 2020), whichever occurs first (Appendix 4 in Supplementary Data).

Statistical analyses

We performed an observational analogue of an intention-to-treat analyses, assessing the effect of prescription of a de-intensification strategy or a no de-intensification strategy at baseline regardless of adherence during follow-up. A multivariable logistic regression model was used to estimate the absolute risk of outcomes according to groups, standardised on the distribution of confounders measured at baseline of each sequential trial (and identified according

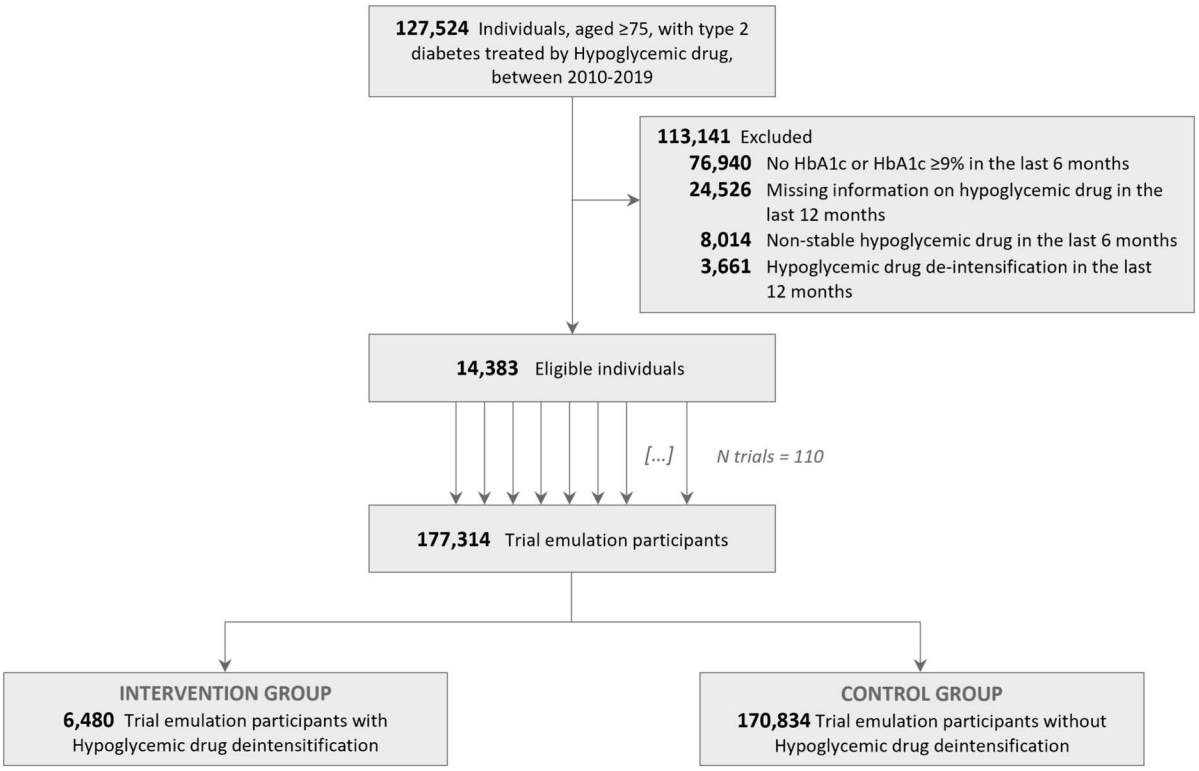


Figure 1. Study Flowchart. Legend: Trial emulation participants correspond to the total number of participants included in all 110 sequential trials. The same individuals could be included several times as different trial emulation participants. Missing information on hypoglycaemic drugs in the last 12 months refers specifically to the partial or total absence of data regarding the doses of hypoglycaemic drugs administered, so the exposure cannot be defined accurately. Abbreviations: HD, hypoglycaemic drugs (insulin, sulfonylureas and/or glinides).

to DAGs, Appendix 5 in Supplementary Data; i.e. age, sex, mFI, CCI, previous contacts with general practitioner, previous hospitalisations, HbA1c value, presence of diabetes complications and polypharmacy), as described elsewhere [18]. Relative risks (RRs) and risk differences (RDs) for the outcomes of interest at 3 and 12 months were computed. The 95% confidence intervals (95% CIs) of estimators were estimated by bootstrapping because of correlation of observations in that patients may participate in several emulated trials.

To evaluate the potential for unmeasured confounding, we computed the E-value, which quantified the minimum strength of association that an unmeasured confounder must have had with both the treatment and the outcome to negate the observed treatment–outcome association, conditional on measured covariates [23].

To further assess residual confounding, we conducted a negative-control outcomes analysis. Specifically, we examined the effect of de-intensification on the risk of pneumonia diagnosis at 3 and 12 months. Indeed, frailty, which may have been not well captured in the data, is a common cause of de-intensification and pneumonia. Therefore, if residual confounding related to frailty is still present, a spurious association between de-intensification and pneumonia would be observed [24]. We also conducted two additional sensitivity analyses to account for potential confounding by proximity to death: one excluding trial emulation participants who died within 3 months of the index date, and one excluding those who died within 12 months.

Additionally, several subgroups were explored regarding the primary outcome, including patients ≥80 years old, with multiple comorbidities (≥5), high CCI (>6), high mFI (>0.35), polypharmacy (≥5 drugs/day), impaired renal function [severe to end-stage renal disease (estimated glomerular filtration rate < 30 ml/min)], diabetes complications (diabetic neuropathy, retinopathy and nephropathy), diabetes of long duration (≥20 years) and tight glycaemic control [HbA1c value <6.5% (<48 mmol/mol)]. All analyses were conducted with R version 4 [25].

Results

The study included 14 383 unique individuals, corresponding to 177 314 trial emulation participants across 110 sequential trials (Figure 1): 6480 participants were allocated to the intervention group (hypoglycaemic drug de-intensification) and 170 834 to the control group (no de-intensification).

Table 1. Baseline characteristics of trial emulation participants included in the emulated target trials

	Total (n = 177 314)	Intervention group—hypoglycaemic drug de-intensification (n = 6480)	Control group—no hypoglycaemic drug de-intensification (n = 170 834)
Age, in year, median (IQR)	80.0 (77.0–84.0)	80.0 (77.0–84.0)	80.0 (77.0–84.0)
Female sex, No. (%)	79,171 (44.7)	3000 (46.3)	76,171 (44.6)
Comorbidities[a]			
mFI[a], median (IQR)	0.35 (0.25–0.45)	0.40 (0.25–0.50)	0.35 (0.25–0.45)
CCI[b], median (IQR)	6.0 (5.0–8.0)	6.0 (5.0–8.0)	6.0 (5.0–8.0)
Hypertension, No. (%)	141 025 (79.5)	5244 (80.9)	135 781 (79.5)
Stroke, No. (%)	22 645 (12.8)	834 (12.9)	21 811 (12.8)
Peripheral vascular disease, No. (%)	33 196 (18.7)	1245 (19.2)	31 951 (18.7)
Myocardial infarction, No. (%)	24 164 (13.6)	958 (14.8)	23 206 (13.6)
Congestive heart failure, No. (%)	13 183 (7.4)	551 (8.5)	12 632 (7.4)
Severe neurocognitive troubles, No. (%)	4041 (2.3)	169 (2.6)	3872 (2.3)
Atrial fibrillation, No. (%)	16 033 (9.0)	699 (10.8)	15 334 (9.0)
Cancer, No. (%)	32 697 (18.4)	1311 (20.2)	31 386 (18.4)
Chronic kidney disease, stage 4 and 5, No. (%)	10 050 (5.7)	408 (6.3)	9642 (5.6)
Diabetic polyneuropathy, No. (%)	7950 (4.5)	290 (4.5)	7660 (4.5)
Diabetic retinopathy, No. (%)	2502 (1.4)	87 (1.3)	2415 (1.4)
Total number of drugs per day[c], median (IQR)	8.0 (5.0–10.0)	5.0 (2.0–9.0)	8.0 (5.0–10.0)
Use of healthcare system[d]			
Number of general practitioner visits, median (IQR)	8.0 (6.0–12.0)	9.0 (7.0–13.0)	8.0 (6.0–12.0)
Occurrence of ≥1 hospital admission, No. (%)	12 359 (7.0)	524 (8.1)	11 835 (6.9)
HbA1c, in % [mmol/mol][e], median (IQR)	6.80 (6.30–7.40) [51 (45–57)]	6.80 (6.30–7.40) [51 (45–57)]	6.80 (6.30–7.40) [51 (45–57)]
Use of glucose-lowering classes[f], No. (%)			
Hypoglycaemic drugs			
Insulin	24 924 (14.1)	837 (12.9)	24 087 (14.1)
Sulfonylureas or glinides	159 180 (89.8)	5908 (91.2)	153 272 (89.7)
Nonhypoglycaemic drugs			
Metformin	56 760 (32.0)	2129 (32.9)	54 631 (32.0)
DPP4-I	15 751 (8.9)	629 (9.7)	15 122 (8.9)
GLP1RAs	1775 (1.0)	82 (1.3)	1693 (0.9)
Other	24 669 (13.9)	838 (12.9)	23 821 (13.9)
Strategy of GLT, No. (%)			
1 Hypoglycaemic drug alone	91 905 (51.8)	3281 (50.6)	88 624 (51.9)
1 Hypoglycaemic drug + ≥1 nonhypoglycaemic drug	71 888 (40.5)	2714 (41.9)	69 174 (40.5)
2 Hypoglycaemic drugs alone	8055 (4.5)	290 (4.5)	7765 (4.5)
≥2 Hypoglycaemic drugs + ≥1 non-hypoglycaemic drug	4581 (2.6)	161 (2.5)	4420 (2.6)
≥3 Hypoglycaemic drugs alone	885 (0.5)	34 (0.5)	851 (0.5)
Total dose of hypoglycaemic drug, in DDD	1.0 (0.5–1.5)	1.0 (0.5–1.5)	1.0 (0.5–1.5)

Legend: The data presented in this table correspond to the compilation of trial emulation participants included in all sequential trials. Hypoglycaemic drugs include sulfonylureas, glinides or insulins; nonhypoglycaemic drugs include other glucose-lowering drugs than sulfonylureas, glinides or insulins. Abbreviations: DDD, defined daily dose; DPP4-I, dipeptidyl-peptidase 4 inhibitors; GLP1RA, glucagon-like peptide 1 receptor agonist; IQR, interquartile range [a]max score = 1 [b]max score = 24 [c]The different drugs prescribed in the months before baseline [d]In the year before baseline [e]Most recent value before baseline [f]GLT before baseline [g]Comorbidities were registered in electronic records in the year before baseline (detailed definitions of covariates available in Appendix 6 in Supplementary Data)

Baseline characteristics of the cohort

At baseline, the median age of the full cohort was 80.0 years [interquartile range (IQR): 77.0–84.0], and 44.7% were female (Table 1). Main comorbidities included hypertension (79.5%), history of myocardial infarction (13.6%), stroke (12.8%), peripheral vascular disease (18.7%),and cancer (18.4%). The median CCI was 6.0 (IQR, 5.0–8.0), and median mFI 0.35 (IQR, 0.25–0.45). The median number of drugs taken daily was eight (IQR, 5–10). Diabetes-related complications were present in 7.7% of the participants. The median HbA1c value was 6.8% (IQR, 6.3%–7.4%) [51 mmol/mol (IQR, 45–57)]. In terms of healthcare use, trial emulation participants had a median of 8 GP contacts (IQR, 6–12), and 7% had at least one hospital admission in the year before baseline.

At baseline, the GLT included sulfonylureas (89.8%), insulin (7.1%), metformin (32.0%), dipeptidyl-peptidase 4 inhibitors (8.9%) and other nonhypoglycaemic drugs (13.9%) (Table 1). At baseline, all trial emulation participants were prescribed at least one hypoglycaemic drug, the median DDD of which was 1.0 (IQR, 0.5–1.5). Several therapeutic combinations of glucose-lowering agents were observed, the most frequent being the use of a hypoglycaemic drug alone (monotherapy: 51.8%), the use of one hypoglycaemic drug associated with at least one nonhypoglycaemic drug (40.5%), and the use of two

Table 2. Estimated association between HD de-intensification and clinical outcomes at 3 and 12 months

Outcomes	Intervention group—hypoglycaemic drug de-intensification (n = 6480)		Control group—no hypoglycaemic drug de-intensification (n = 170,834)		RD, % (95% CI)[a,b]	Adjusted RR (95% CI)[a,b]
	n events	Risk[a], %	n events	Risk[a], %		
All-cause death or hospital admissions, 3 months[c]	277	3.96	5084	2.99	0.97 (0.68–1.29)	1.33 (1.22–1.43)
All-cause death or hospital admissions, 12 months	766	11.10	16,007	9.39	1.71 (1.05–2.13)	1.18 (1.11–1.22)
All-cause death, 12 months	151	2.09	1728	1.02	1.08 (0.98–1.44)	2.06 (2.04–2.56)
Hospital admissions, 12 months	628	9.08	14,335	8.41	0.67 (−0.12–0.91)	1.08 (0.99–1.11)
Relaxed glycaemic control, 12 months	17	0.25	210	0.12	0.12 (0.05–0.20)	2.00 (1.43–2.73)

Legend: Hypoglycaemic drugs include sulfonylureas, glinides or insulins; estimates were computed by multivariable logistic regression; [a]Risks and RDs were standardised on age, sex, mFI, CCI, previous contacts with general practitioner, previous hospitalisations, HbA1c value, presence of diabetes complications, and polypharmacy, and RRs were adjusted for age, sex, mFI, CCI, previous contacts with general practitioner, previous hospitalisations, HbA1c value, presence of diabetes complications and polypharmacy; [b]95% CIs were computed by boostrapping; [c]Primary outcome. Abbreviations: Std., standardised; RD, risk difference; RR, relative risk; 95% CI, 95% confidence interval.

different hypoglycaemic drugs without nonhypoglycaemic drugs (4.5%). Table 1 details these characteristics at baseline for participants of the intervention and control groups.

Exposure

Amongst the 6480 trial emulation participants in the intervention group, exposure (hypoglycaemic drug de-intensification) consisted of cessation of all hypoglycaemic drugs (88.8%) or a reduction of >50% in total dose of hypoglycaemic drugs (11.2%). The de-intensification of hypoglycaemic drugs consisted of different modifications of the GLT strategy, and the glucose-lowering agents used (Appendix 7 in Supplementary Data). The main changes were lower use of sulfonylureas and insulins and greater use of nonhypoglycaemic drug agents. The cessation of all hypoglycaemic drugs resulted from full cessation of all GLT agents (76.6%) or from a switch to nonhypoglycaemic drugs (23.4%). The reduction of hypoglycaemic drugs >50% was accompanied by a switch to other nonhypoglycaemic drugs or no change.

Outcomes

Hypoglycaemic drug de-intensification was associated with increased risk of all-cause death or hospital admissions at 3 months [adjusted RR, 1.33 (95% CI, 1.22–1.43)]. This corresponded to a standardised RD of 0.97% (95% CI, 0.68%–1.29%) between the risk of the outcome in participants with hypoglycaemic drug de-intensification (standardised risk, 3.96%) and the risk in participants without hypoglycaemic drug de-intensification (standardised risk, 2.99%) (Table 2).

Regarding secondary outcomes (all measured at 12 months), there were significant associations between exposure and outcomes, with varying strengths of association. For all-cause death or hospital admission (composite), the adjusted RR was 1.18 [95% CI, 1.11–1.22; RD, 1.71% (95% CI, 1.05%–2.13%)]. For all-cause death, the adjusted RR was 2.06 [95% CI, 2.04–2.56; RD, 1.08% (95% CI, 0.98%–1.44%)]. For hospital admissions, the adjusted RR was 1.08 [95% CI, 0.99–1.11; RD, 0.67% (95% CI, −0.12%–0.91%)], and for relaxed glycaemic control, the adjusted RR was 2.00 [95% CI, 1.43–2.73; RD, 0.12% (95% CI, 0.05%–0.20%)] (Table 2).

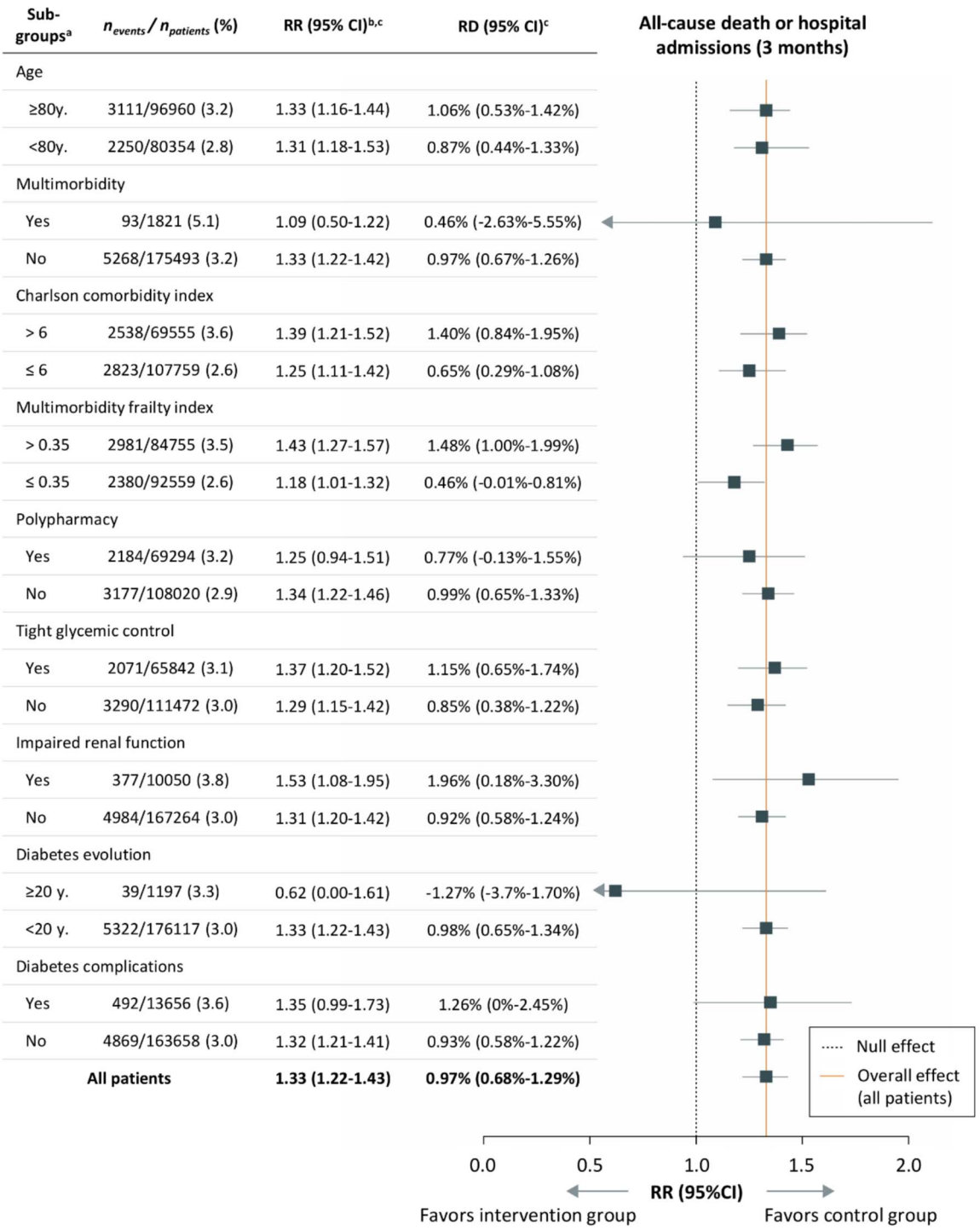
Subgroup analyses

The association between hypoglycaemic drug de-intensification and the primary outcome (all-cause death or hospital admissions) was explored at 3 months in different subgroups (Figure 2). The associations across all subgroups were in the same direction to that seen in the overall population, with nonsignificant associations only in subgroups with the largest 95% CIs (Figure 2).

Potential effect of unmeasured confounding and sensitivity analyses

The E-value for all-cause death or hospital admissions at 3 months (primary outcome) was 1.99. Regarding secondary outcomes (at 12 months), the E-value was 1.64 for all-cause death or hospital admissions, 3.54 for all-cause death, 1.37 for hospital admissions and 3.41 for relaxed glycaemic control (Appendix 8 in Supplementary Data).

Regarding the association of hypoglycaemic drug de-intensification with pneumopathy at 3 and 12 months, the adjusted RR was 0.99 (95% CI, 0.96–1.02) at 3 months and 0.99 (95% CI, 0.96–1.02) at 12 months (Appendix 9 in Supplementary Data). Results remained broadly consistent after exclusion of individuals who died at 3 or 12 months post-index date, although mortality outcomes could not be evaluated in the latter. Associations between deintensification and hospital admissions or glycaemic outcomes persisted (Appendices 10 and 11 in Supplementary Data).



Sub-groups[a]	n_{events} / $n_{patients}$ (%)	RR (95% CI)[b,c]	RD (95% CI)[c]
Age			
≥80y.	3111/96960 (3.2)	1.33 (1.16-1.44)	1.06% (0.53%-1.42%)
<80y.	2250/80354 (2.8)	1.31 (1.18-1.53)	0.87% (0.44%-1.33%)
Multimorbidity			
Yes	93/1821 (5.1)	1.09 (0.50-1.22)	0.46% (-2.63%-5.55%)
No	5268/175493 (3.2)	1.33 (1.22-1.42)	0.97% (0.67%-1.26%)
Charlson comorbidity index			
> 6	2538/69555 (3.6)	1.39 (1.21-1.52)	1.40% (0.84%-1.95%)
≤ 6	2823/107759 (2.6)	1.25 (1.11-1.42)	0.65% (0.29%-1.08%)
Multimorbidity frailty index			
> 0.35	2981/84755 (3.5)	1.43 (1.27-1.57)	1.48% (1.00%-1.99%)
≤ 0.35	2380/92559 (2.6)	1.18 (1.01-1.32)	0.46% (-0.01%-0.81%)
Polypharmacy			
Yes	2184/69294 (3.2)	1.25 (0.94-1.51)	0.77% (-0.13%-1.55%)
No	3177/108020 (2.9)	1.34 (1.22-1.46)	0.99% (0.65%-1.33%)
Tight glycemic control			
Yes	2071/65842 (3.1)	1.37 (1.20-1.52)	1.15% (0.65%-1.74%)
No	3290/111472 (3.0)	1.29 (1.15-1.42)	0.85% (0.38%-1.22%)
Impaired renal function			
Yes	377/10050 (3.8)	1.53 (1.08-1.95)	1.96% (0.18%-3.30%)
No	4984/167264 (3.0)	1.31 (1.20-1.42)	0.92% (0.58%-1.24%)
Diabetes evolution			
≥20 y.	39/1197 (3.3)	0.62 (0.00-1.61)	-1.27% (-3.7%-1.70%)
<20 y.	5322/176117 (3.0)	1.33 (1.22-1.43)	0.98% (0.65%-1.34%)
Diabetes complications			
Yes	492/13656 (3.6)	1.35 (0.99-1.73)	1.26% (0%-2.45%)
No	4869/163658 (3.0)	1.32 (1.21-1.41)	0.93% (0.58%-1.22%)
All patients		**1.33 (1.22-1.43)**	**0.97% (0.68%-1.29%)**

Figure 2. Estimated association between hypoglycaemic drug de-intensification and all-cause death or hospital admissions at 3 months (primary outcome) by trial emulation participants subgroups. Legend: [a]Subgroups were defined on covariates at baseline or on the last available measure/value in the 6 months before baseline; [b]Estimates (RRs and RDs) were computed by multivariable logistic regression. RRs were adjusted for age, sex, mFI, CCI, previous contacts with general practitioner, previous hospitalisations, HbA1c value, presence of diabetes complications, and polypharmacy. RDs were standardised for the same variables; [c]95% CIs were computed by boostrapping; multimorbidity corresponds to ≥5 different comorbidities from the list of comorbidities of the CCI; polypharmacy corresponds to ≥5 different drugs prescribed by day; tight glycaemic control corresponds to HbA1c value <6.5% (<48 mmol/mol); impaired renal function corresponds to severe to end-stage renal disease (stages 4 and 5, i.e. estimated glomerular filtration rate <30 ml/min); diabetes complications include diabetic neuropathy, retinopathy and nephropathy. See Appendix 6 in Supplementary Data for detailed information on covariates. Abbreviations: RR, relative risk; 95% CI, 95% confidence interval; RD, risk difference; y, years; HbA1c, haemoglobin A1c.

Discussion

This study, which aimed to assess the association between de-intensification of hypoglycaemic drugs and clinical outcomes in older adults with T2D, found hypoglycaemic drug de-intensification associated with a significant increase in modest risk of hospital admissions or all-cause death at 3 and 12 months, as well as an increased risk of all-cause death and a relaxation of glycaemic control at 12 months. No significant association was found with hospital admissions at 12 months. Subgroup analyses suggested that these associations were consistent across most trial emulation participants' profiles.

Prior observational studies have reported either a null or nonsignificant association between hypoglycaemic drug de-intensification and hospital admission or all-cause mortality in older individuals with specific characteristics, such as cognitive impairment, or in particular settings, such as nursing homes [11, 13, 26]. Our study, which is, to the best of our knowledge, the first to use a target trial emulation framework to answer this question in a wide general population from primary care, produced results that diverge slightly from previous findings. These results could be interpreted as suggesting a potential harmful effect of de-intensification and therefore suggest that enthusiasm for de-intensifying hypoglycaemic treatment in older adults with T2D should be tempered.

However, this raw interpretation should be nuanced due to the observational, retrospective nature of the data, which introduces potential biases in defining exposure, outcomes and confounders. In particular, these results might be explained, at least in part, by potential confounding by indication (e.g. when hypoglycaemic drug de-intensification is more likely to be used for patients in very poor health or other end-of-life conditions, which may also increase the risk of hospital admissions and death) [27]. Despite the rigorous study design and extensive adjustments for known confounders (aimed at compensating the absence of randomisation), confounding by indication is likely difficult to fully mitigate, as descriptions of 'end-of-life' conditions are not available in database. This issue was already reported in previous studies [26]. While sensitivity analyses excluding participants who died at 3 and 12 months showed consistent results with the primary analyses, negative outcome analyses and E-values suggested that the presence of an unmeasured confounder (that would have caused both exposure and outcomes) cannot be excluded [24].

Then, regarding the association between the exposure and the moderate increase in the risk of relaxed glycaemic control, we also believe that this observation should be interpreted with caution. Although the deterioration in glycaemic control might theoretically elevate the risk of symptomatic hyperglycaemia and hyperglycaemia-related adverse events, such as all-cause death or hospital admissions [8, 28–30], it is important to consider that this observation is limited by a very small number of events. This analysis is therefore very likely underpowered and should thus be interpreted with circumspection. Nevertheless, this is an opportunity to recall that the recommendations for GLT de-intensification in older people suggest closely monitoring glycaemia (and/or HbA1c value) after treatment modification, to avoid unwanted hyperglycaemia [9, 10, 12]. Moreover, they emphasise that although de-intensification may be appropriate in certain clinical contexts, complete discontinuation of hypoglycaemic drugs, particularly if they are intended solely to avoid hypoglycaemia, is not always appropriate. Switching from hypoglycaemic drugs to nonhypoglycaemic drugs (e.g. metformin or dipeptidyl-peptidase 4 inhibitors) might offer a safer alternative [8, 10]. Additionally, treatment simplification, particularly for complex insulin regimens, represents an excellent strategy for de-intensification, aligning with the 'less is better' approach [31–33].

This study was limited by several factors, including confounding by indication (i.e. frailer patients or those at the end of life are more likely to be de-prescribed), unmeasured confounding and limited statistical power (particularly for relaxed glycaemic control at 12 months, all-cause death at 12 months, potentially all-cause death and/or hospital admission at 3 months and subgroup analyses), as detailed above. These biases are primarily inherent to the nature of the data used—i.e. observational data—which the target trial emulation framework, while particularly rigorous and effective in preventing other types of bias (such as immortal time bias), cannot fully address in this context [34]. Therefore, there is a strong rationale for pursuing further investigations on this clinical question through an interventional study involving standard randomisation, which would help to minimise these biases. This is all the more important given that, to date, no definitive conclusion can be drawn regarding the effects of hypoglycaemic treatment de-intensification in the older population.

In conclusion, this cohort study using target trial emulation observed that de-intensification of hypoglycaemic drugs in older adults with T2D in GP was associated with an increased risk of all-cause death or hospital admission. These results could be partially explained by a deleterious effect of hypoglycaemic drug de-intensification but should be interpreted with caution, particularly due to the potential for residual confounding by indication, as de-intensification is more likely to occur in patients who are frail or approaching the end of life.

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member of the board of the Belgian Society of Gerontology and Geriatrics (unpaid activity). FT is head of the Centre de Pharmacoépidémiologie (Cephepi) of the Assistance Publique—Hôpitaux de Paris and 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. FT is not employed by these structures and did not receive any personal remuneration from these companies. Other authors have no competing interests to declare.

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