Development of computerized algorithms to classify transitions in cardiometabolic medications in deprescribing studies based on pharmacy dispensing data

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ABSTRACT

Background: More research is needed to deprescribing cardiometabolic medication (i.e. for cardiovascular diseases and diabetes mellitus type 2). To assess whether transitions in medication use are de-intensifications, automated tools are needed that recognise discontinuations, dosage reductions and switches to safer alternative medication as de-intensifications.
Aim: Development of four computerized algorithms that classify transitions in the use of lipid modifying, blood glucose lowering, blood pressure lowering and antithrombotic medication efficiently, using community pharmacy medication dispensing data.
Methods: The algorithms were developed as part of the CO-DEPRESCRIBE study. For all algorithms, first relevant transitions were identified with corresponding classification (being a de-intensification, no de-intensification or requiring individual assessment), based on literature. The transitions were translated into ATC-code based decision rules and were/will be computerized using the programmes R and RStudio. The computerized algorithms were/will be validated using pharmacy dispensing data and adapted till all classifications were correct.
Results: The algorithms for lipid modifying agents and blood glucose lowering agents were computerized and validated. In the algorithm for lipid modifying agents, among others changes in statin equivalence are assessed. For blood glucose lowering agents, switches to safer alternatives were included as de-intensification. In a test with 61 users of lipid modifying agents, 8 out of 15 computerized decision rules applied with 89.1% of the transitions being automatically classified. In a test with 19 users of blood glucose lowering agents, 8 out of 19 computerized decision rules applied with 21.1% of the transitions being automatically classified. Decision rules for blood pressure lowering agents and antithrombotic agents will be computerized and validated in the near future. These focus on the total number of antihypertensives including dose changes and the total number of antithrombotic agents respectively.
Conclusions: All four medication groups required an individual approach due to factors like presence of more and less potent medication, medication with a high or low risk and agents with multiple indications. The algorithms can be used in deprescribing studies in Dutch older people and after adaptation used for deprescribing studies in other settings. The underlying principles can be used to develop algorithms for other medication groups. Further validation of the algorithms is indicated.

Achtergrond: Er is meer onderzoek nodig naar deprescribing van cardiometabole medicatie (gebruikt bij cardiovasculaire ziekten en diabetes mellitus type 2). Om vast te stellen of een medicijntransitie een de-intensivering is, zijn geautomatiseerde hulpmiddelen nodig die stopzettingen, doseringsverlagingen en wisselingen naar een veiliger alternatief herkennen als de-intensivering.
Doel: Het ontwikkelen van vier computergestuurde algoritmes die transities in het gebruik van lipidenverlagende, bloedglucose verlagende, bloeddrukverlagende en antitrombotische middelen efficiënt classificeren, op basis van uitgiftegegevens van openbare apotheken.
Methode: De algoritmes werden ontwikkeld als onderdeel van het CO-DEPRESCRIBE onderzoek. Bij alle algoritmes werden eerst relevante transities geïdentificeerd, met bijbehorende classificatie (wel/geen de-intensivering, of dat individueel beoordelen nodig is) gebaseerd op literatuur. De transities werden vertaald in beslisregels die gebruik maken van de ATC-classificatie, en werden/worden geprogrammeerd met de programma's R en RStudio. De geprogrammeerde algoritmes werden/worden gevalideerd met behulp van apotheekuitgiftegegevens tot alle classificaties correct waren.
Resultaten: De algoritmes voor lipidenverlagende middelen en bloedglucose verlagende middelen werden geprogrammeerd en gevalideerd. In het algoritme voor lipidenverlagende middelen worden onder andere veranderingen in statine-equivalentie beoordeeld. Voor bloedglucose verlagende middelen worden onder andere wisselingen naar een veiliger alternatief geclassificeerd als de-intensivering. In een test met 61 gebruikers van lipidenverlagende medicatie werden 8 van de 15 geprogrammeerde beslisregels toegepast en werd 89,1% van de transities automatisch

geclassificeerd. In een pilot met 19 gebruikers van bloedglucose verlagende middelen werden 8 van de 19 geprogrammeerde beslisregels toegepast en werd 21,1% van de transities automatisch geclassificeerd. Beslisregels voor bloeddrukverlagende middelen en antitrombotische middelen worden in de nabije toekomst geprogrammeerd en gevalideerd. Deze focussen zich respectievelijk op het totaal aantal bloeddrukverlagende middelen inclusief doseringsveranderingen en het totaal aantal antitrombotische middelen.
Conclusies: Alle vier medicijngroepen hadden een andere aanpak nodig vanwege factoren als de aanwezigheid van meer en minder potente middelen, medicijnen met een hoog of laag risico en middelen met meerdere indicaties. De algoritmes kunnen worden gebruikt in deprescribing studies bij Nederlandse ouderen en na aanpassing bij deprescribing studies in een andere setting. De gebruikte principes kunnen worden gebruikt bij de ontwikkeling van algoritmes voor andere medicijngroepen. Verdere validatie van de algoritmes is nodig.

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INTRODUCTION

Research into deprescribing is increasing. Also clinical guidelines pay attention to deprescribing and deprescribing recommendations have been developed for several (classes of) drugs. Deprescribing was initially defined as a process in which inappropriate medication is withdrawn under supervision of a health care provider, amongst others aimed to manage polypharmacy (1). This definition has evolved to additionally encompass that the process is patient-centred and also includes dose reductions and switches to medication with a lower risk of adverse effects (2), (3). Altogether, we call these changes in medication use de-intensifications.

Polypharmacy, usually defined as the concurrent use of 5 or more drugs (2), (4), (5), in older people is increasing in the Western world due to ageing of the population and subsequent increases in the number of patients with multiple chronic diseases simultaneously (5). Though the concurrent use of 5 or more drugs by one patient might be indicated, it increases the risk of adverse drug events and inappropriate medication (5), (6). For example, the risk of drug-drug interactions increases from 10.9% when taking 2-4 drugs to more than 80% when taking 10 or more drugs (5). Further, it is estimated that a quarter of the medications in older people is a Potentially Inappropriate Medication (PIM) (7). Similar findings were reported by Oktora et al. in a population of middle-aged and older people with diabetes (8). Diabetes and cardiovascular diseases are mortal and increasingly prevalent conditions (9), (10). Given the fact that the prevalence of polypharmacy in patients with cardiometabolic conditions is high (6), (11), deprescribing cardiometabolic drugs in this population might be indicated to reduce harmful outcomes.

There are more factors suggesting that deprescribing cardiometabolic medications is needed, especially in older people. Deprescribing might be indicated in older people because changes of the ageing body lead to a different exposure to drugs, requiring adjusted treatment (5). Additionally, guidelines advice to adjust the goals of cardiometabolic treatment towards less intensive control of HbA1c, LDL-cholesterol and blood pressure or to stop medication based on higher age, lower estimated life expectancy, occurrence of annoying side-effects and increasing frailty of the patient (12), (13), (14), (15), (16), (17), (18), (19), (20), (21). It is even plausible that for frail older people higher levels of cholesterol and less strict treatment targets for blood pressure provide preventive effects, findings arising from multiple studies and also suggested in the Dutch General Practitioners (GP) guideline for cardiovascular risk management (12), (22), (23), (24). Further, cardiometabolic drugs like statins often aim to prevent the occurrence of a health event in the future and the relevance of preventive medication reduces when the life expectancy is short (25).

Although these facts illustrate that deprescribing is relevant, deprescribing rates of cardiometabolic medication in diabetes patients older than 65 years who are eligible for deprescribing were reported to remain often low and variable, and more research into deprescribing cardiometabolic medication is needed (26). The US deprescribing network considered the quantification of changes in drug use in deprescribing research essential to assess the effect of a deprescribing intervention and recommended to clearly define this outcome (27). Quantification of deintensification rates is not straightforward. Currently, a variety of approaches is used to establish whether drugs are stopped or reduced in dose. A review from Nizet et al. mentioned a range of different medication outcome measures used in deprescribing studies to quantify changes in drug use between baseline use (before an intervention) and follow-up use (after the intervention) (28). It appeared that in most studies the number of PIMs is taken as a measure of quantifying medication changes and that others use the total number of chronic drugs, Defined Daily Dose (DDD), or some other parameters. To clarify the underlying approaches that have been used to quantify changes in medication use so far, a rather old deprescribing study as well as a few of the studies mentioned in the review of Nizet et al. and also some studies focusing specifically on deprescribing cardiometabolic medication will be

highlighted now. An overview of these studies is given in **Table 1**. A relatively old study from 2003 by Baillargeon et al. used blood samples of patients to verify whether benzodiazepine use was truly

Tabel 1 *Overview of approaches to quantify medication changes used in multiple deprescribing studies*

Study	**Medication**	**Approach to quantify** (data source)	**Level** (discontinuation, reductions, switches)	**Limitations** (mentioned by the authors)
Baillargeon et al. (29)	Benzodiazepines	Patient diaries and blood samples	Discontinuations and dose reductions	-
Aharaz et al., (30)	All (all medication of included patients)	Electronic prescription data in combination with patient reported use	Discontinuations and dose reductions	-
Ashworth et al., (31)	Benzodiazepines	Multiples of DDD calculated based on electronic drug dispensing records	Dose reductions and discontinuations	Switch to substituting drugs not included
Campbell et al., (32)	Anticholinergics	Discontinuation-prescriptions as part of all prescriptions	Discontinuation	Potentially underestimation of deprescribing rate
Cateau et al., (33)	All (all medication of included patients)	Forms reported by NH pharmacists	Discontinuations, dose reductions and switch to more appropriate drug	-
Tannenbaum et al., (34)	Benzodiazepines	Pharmacy renewal profiles	Discontinuations and dose reductions	Potentially not all dose tapering processes were finished after 6 months, giving underestimation of discontinuation. Potential relapses after 6 months are not seen
Nguyen-Soenen et al., (35)	Proton pump inhibitors	PPI reimbursement (healthcare insurances)	Discontinuations and dose reductions	Possible overestimation of PPI use since adherence might be poor. Underestimation possible due to availability of OTC-PPI*
Wouters et al., (36)	All prescribed medications of patients	Electronic pharmacy dispensing records, assessed manually	Discontinuations (and dose reductions of drugs with need of gradual dose reductions) and switches to safer alternatives	Collecting follow-up data after 4 months is short to measure long-term relapse of diseases as result of discontinuation
Crutzen et al. (37)	Cardiometabolic medication	Drug dispensing data + records by pharmacists	Discontinuations, dose reductions and switches to safer alternatives	Collecting follow-up data after 3 months might be too rapid: drug changes might need a longer time to be implemented

Hassan et al. (38)	Antihypertensives	Patient records in GP information systems containing amongst others drug information	Discontinuations and dose reductions	Other studies should use 'more formal ways of data-collection' to ensure 'data validity and limit protocol deviations'
Hart et al. (39)	Blood glucose lowering drugs	Electronic medical records, assessed manually	Discontinuations, dose reductions, switches to drugs with lower risk of hypoglycaemia	-
Koehn et al. (40)	Insulin and sulphonylureas	Electronic health records	Discontinuations and dose reductions	Newer diabetes drugs are not included

*OTC-PPI: over-the-counter proton-pump inhibitor; available without prescription

stopped (29). For dose reductions that were recorded in diaries, no confirmatory blood measurements were drawn. One of the studies mentioned by Aharaz et al. used electronic prescription data from electronic patients records in combination with patient interviews by a clinical pharmacist to verify the theoretical medication use as mentioned in the electronic records (30). In another study, the change in multiples of DDDs of benzodiazepines per patient was calculated based on electronic drug dispensing records (the Pharmaceutical Information Network) one year before and for the duration of one year starting some months after the intervention (31). Further, Campbell et al. used prescription information from a medical records system to assess the proportion of discontinuation prescriptions as part of all prescription orders for anticholinergics (32). Cateau et al. measured as the main outcome the number and dose of PIMs before and after an intervention (33). Tannenbaum et al. investigating benzodiazepine deprescribing, used pharmacy renewal profiles containing information about dosing, date and quantity to determine whether there was de-intensification of benzodiazepine use (34). In this study, switches to other benzodiazepines were taken into account. Others collected data from healthcare insurances to determine based on proton-pump inhibitor (PPI) re-imbursement whether a 50% decrease of PPI use occurred (35). Wouters et al. investigated discontinuation of inappropriate medication and switches to less risky medications in older people based on data from electronic pharmacy dispensing records that was interpreted manually (36). Recent research into deprescribing cardiometabolic medication also shows different approaches that are used to decide whether or not de-intensification of drugs had occurred. Crutzen et al. investigated deprescribing of cardiometabolic drugs in diabetes type 2 patients following a clinical medication review (37). To quantify changes in the use of cardiometabolic medication, reports by the pharmacist as well as drug dispensing data from pharmacy information systems were collected to determine whether cardiometabolic drugs were stopped or reduced in dose. Switching to less potent medication was considered to be de-intensification, being determined only based on the records from the pharmacists and not on the pharmacy drug dispensing data. A study performed by Hassan et al. investigated deprescribing antihypertensives and considered antihypertensives that were stopped and/or reduced in dose as de-intensified (38). Patient records from GP information systems were used for the quantification of changes in medication use. Another study focused on de-intensification of glucose lowering medication in over-treated patients following after a reminder to the treating general practitioner or practice nurse (39). Here, de-intensification included discontinuations, dose reductions and switches drugs with a lower risk of hypoglycemia. The medication changes observed in electronic medical records were assessed manually. As final example, the HypoPrevent study aimed to reduce hypoglycemia in diabetes type 2 patients and measured amongst others changes in the use of insulins and sulphonyl urea derivatives. The data source used for the assessment of medication changes is not clearly specified by the authors, but most likely is electronic health records (40).

To summarize, most studies investigating deprescribing define de-intensifications of drugs as discontinuations, often combined with dose reductions, without including switches to less risky medication as well. As stated earlier, these switches also belong to de-intensifications but currently lack in most studies and require more attention, a finding also concluded earlier (28). Further, studies often investigate only one (class of) drug(s) with a manual quantification of changes in drug use (transitions) and approaches to quantify drug changes are very heterogeneous. To enable deprescribing research in a broader setting than for just one (type of) drug(s) or medical condition(s), quantifying transitions in more than one group of drugs using a rapid and straightforward classification method is essential. Given the urgence for more research in deprescribing cardiometabolic medication, which constitute a range of different drugs that might be used simultaneously, there is a demand for tools that easily and automatically classify whether de-intensification occurred. The aim of this study is therefore to develop and test algorithms that classify whether or not de-intensification of cardiometabolic medication has occurred, based on community pharmacy drug dispensing data of polypharmacy patients of 75 years and older. Separate algorithms will be developed for four medication groups.

Research question:

Which computerized algorithm using medication dispensing data classifies transitions in medication use focusing on de-intensifications correctly and efficiently for the following medication groups:

a) Lipid modifying medication;
b) Glucose lowering medication;
c) Antihypertensive medication;
d) Anticoagulant medication?

METHODS

Setting

The algorithms were developed as part of the CO-DEPRESCRIBE study and more details can be found in the protocol article of the trial (41). In short, the study investigates the effect of healthcare provider (HCP) training on performing cardiometabolic-focused clinical medication reviews (CMRs), which forms the intervention of the study. The CMRs are performed in a population of older people (75 years and older) with polypharmacy and using one or more of the included cardiometabolic drugs. The study takes place in the Dutch community pharmacy setting, where general practitioners (GP's), community pharmacists and sometimes nurse practitioners conduct CMRs together, all having a distinct role. The primary outcome is the percentage of patients for whom cardiometabolic medication is de-intensified. Cardiometabolic medication is defined as lipid modifying, blood glucose lowering, blood pressure lowering and antithrombotic agents. The included medications are mentioned in the section 'Outcome measures and other parameters' in the CO-DEPRESCRIBE protocol article. De-intensification is defined as medication discontinuations, dose reductions, less intensive insulin administration schemes and switches to less risky alternative drugs (for example with a reduced risk of hypoglycemia).

Algorithm characteristics

The algorithms will compare the medication use of individual patients participating in the CO-DEPRESCRIBE study at baseline and at follow-up using dispensing data. Each algorithm constitutes of a set of decision rules that will be computed to classify transitions in the use of cardiometabolic medications automatically as de-intensification, no de-intensification or requiring individual assessment. Four subtypes of de-intensification will be distinguished, namely therapy cessation (meaning absence of therapy at follow-up), discontinuation of one or more drugs (without complete cessation of therapy), dose reductions and a switch to safer alternatives (less risky medication). If a transition can be both therapy cessation or discontinuation, it will be classified simply as de-intensification. The classification individual assessment will be assigned for transitions that are difficult to define in a decision rule because of complexity of the medication regimes or when there is a likelihood of misinterpretation of data by the algorithm. For those cases, a guide will be developed with instructions on how to manually classify medication transitions.

Development of decision rules

The development of the algorithms classifying whether or not cardiometabolic drugs have been de-intensified or switched to safer alternatives, required multiple steps. At first, the cardiometabolic medications were divided into 4 different therapeutic groups, namely lipid modifying medication, blood glucose lowering medication, blood pressure lowering medication and antithrombotic medication. Included patients all used at least one drug of one of these therapeutic groups at the moment of inclusion. The drugs belonging to these therapeutic groups are defined in the protocol for the CO-DEPRESCRIBE mother-study (section 'Outcome measures and other parameters'). These groups were treated subsequently and all underwent the steps as depicted in **Figure 1**.

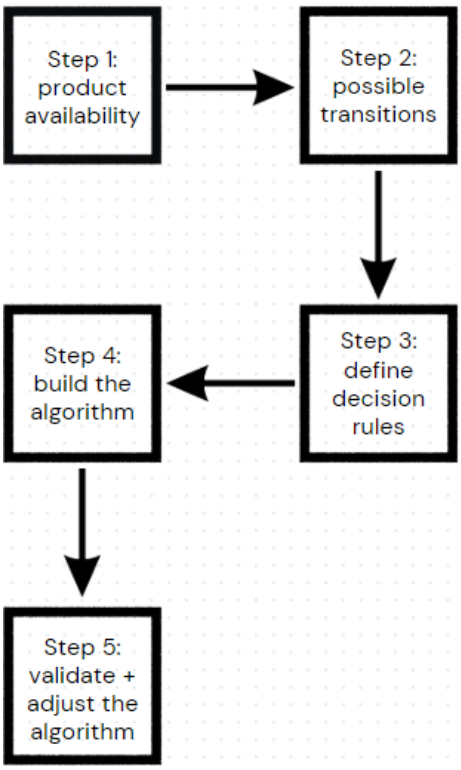

Figure 1 Schematic overview of steps in the development of the computerized algorithm

First of all, for each group of drugs was identified which (combination of) agents were present on the Dutch market, using the website https://www.farmacotherapeutischkompas.nl/. On this Dutch website containing information about medications, each medication having an ATC code according to the World Health Organization (WHO) classification (42) was checked for availability in the Netherlands. When a product or corresponding ATC-code was not found in the website, it did not have to be included in the algorithm. Secondly, guidelines with recommendations on when and how to de-intensify the drugs were consulted as well as the clinical guidelines with recommendations for treatment. Consulted guidelines included Dutch clinical guidelines for GP's, Dutch guidelines for de-intensification (knowledge documents for reducing and stopping drugs) and deprescribing guides from primary health Tasmania. From these, potential de-intensification steps were identified, focusing on medication discontinuations, dose changes and/or switches between medications. Then flowcharts were created in which possible transitions in treatment states between baseline and follow-up drug use are listed. Each transition was classified as a subtype of de-intensification, no de-intensification, or requiring individual assessment. These transitions were translated into a set of decision rules at ATC-code level. These decision rules were discussed with a junior and a senior researcher from the CO-DEPRESCRIBE study team, to ensure that all potential transitions were covered and classified correctly.

Programming the computerized algorithm

The decision rules were or will be translated into Rmarkdown codes by a member of the CO-DEPRESCRIBE study team using the programs Rstudio (RStudio 2024.09) (43) and R (version 4.4.2 (2024-10-31 ucrt)) (44). Together, the Rmarkdown codes form the computerized algorithm of the medication group, also called 'script'. Questions about how to interpret and operationalize decision rules were discussed with all persons involved in the development of the decision rules. The software ChatGPT (45) was used in composing the RMarkdown code.

Data

For the CO-DEPRESCRIBE study, drug dispensing data are extracted from community pharmacy information systems of the included pharmacies for the participating patients. The data includes but is not restricted to drug name and strength, ATC-code, amount, dosing schedule and date of the dispensing. A specific time window is used in which drug dispensing data is collected to establish the baseline and follow-up medicinal treatment. The date at which the CMR is conducted in the CO-DEPRESCRIBE study is called the indexdate. To establish the baseline treatment, the drug dispensing records in a period between 120 and 1 days before the indexdate are collected. To establish the follow-up treatment, drug dispensing records in a period of 120 days are collected around 182 days after the indexdate, meaning a period between 123 days and 242 days after the indexdate.
All medication dispensing data from the participating patients are exported from the pharmacy information systems to Microsoft Excel (version 2409 Build 16.0.18025.20214). Extraction data of participating pharmacies are combined into one Excel document, which forms the input data for the algorithm. Participating pharmacies were at different time points eligible for extraction of dispensing data and the available dispensing data for the development and validation of the algorithm increased as the CO-DEPRESCRIBE trial progressed.

Validation of the decision rules

The dataset with drug dispensing data from multiple participating pharmacies combined was run through the computerized algorithms. For algorithm validation, all different types of classifications as assigned to the medication transitions were individually validated, thereby validating all decision rules that were applied. Decision rules for transitions that did not occur in the dataset and as such could not be validated were labeled. Individual validation was performed by classifying the medication transitions of the corresponding patients manually and comparing these classifications with the classifications assigned by the algorithms. In this way, it was also investigated whether the

right decision rules were used. When discrepancies occurred, the algorithms were adapted and the newer versions were validated again. This process of testing, validating and adapting the algorithms continued till all transitions received the correct classification.

Outcomes

The primary outcome for each algorithm was the percentage of cases being correctly classified, for which the benchmark was set at 100%. As secondary outcome, as a marker of efficiency, the percentage of cases receiving the classification de-intensification or no de-intensification automatically (without requiring individual assessment) will be calculated. For the calculation of the outcomes, descriptive statistics will be used.

RESULTS

Part 1: Lipid modifying agents

1.1 Lipid modifying agents on the Dutch market

All lipid modifying agents (medication with ATC-code starting with C10) available on the Dutch market were listed in **Table A1.1** of **Appendix 1.1** and taken into account for the development of the algorithm. No agents were found on the Dutch market that were a combination of a lipid modifying agent with other classes of drugs (C10BX).

1.2 Possible transitions in lipid modifying agents

For lipid modifying agents, the only available deprescribing recommendations were for statins (19). Recommendations discussing how to deprescribe other available lipid modifying agents were lacking. Therefore, rational de-intensification steps were identified by reversing the treatment intensification steps from the clinical guidelines for Dutch GP's (12,13,46), as summarized in **Figure 2**. The drugs of first choice in the treatment of hypercholesterolemia are statins, which can be intensified by increasing the dose or switching to a more potent statin (see below) if the starting dose appears to be insufficient. When this still remains insufficient, ezetimibe can be added. PCSK9 inhibitors (evolocumab or alirocumab) can be added in secondary care when the therapy remains insufficient or in case of statin intolerance.

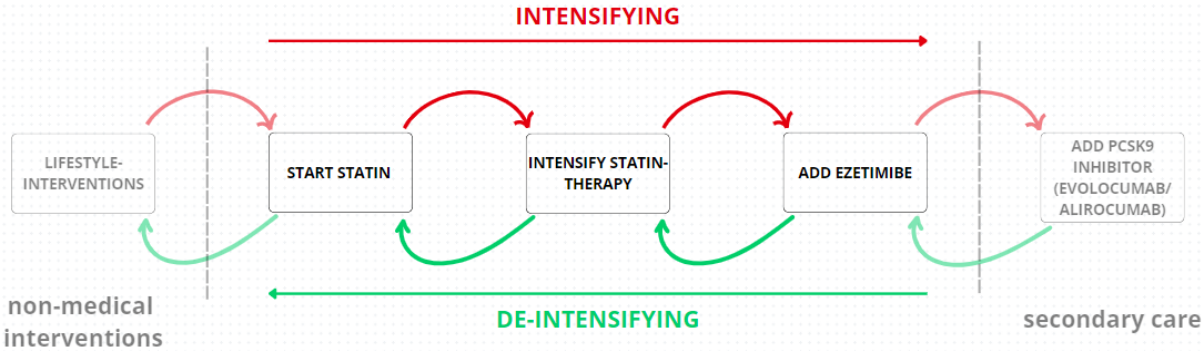

Figure 2 Visual representation of the Dutch guidelines to intensify lipid modifying agents (red), and our proposed route of deintensification (green)

Occurrence of the reversal of the scheme was considered to be a de-intensification of lipid modifying therapy. For example, a patient using at baseline a statin with ezetimibe and at the follow-up measurement only the statin, or a reduction in the intensity of statin therapy. For statins, therapy can be decreased by both decreasing the daily dose of a statin or by switching to a statin that is less potent. Simvastatin 40 mg daily for example has a lower cholesterol lowering effect than atorvastatin 40 mg daily (47). Both a dose reduction of a specific statin as well as a switch to a lower potency statin therefore had to be classified as de-intensification. For this purpose, we developed an equipotency table by which every transition to another dose of the same statin, or a transition to another statin in any dose could be classified easily (see **Table A.1.2**). For each single available statin in each available dose, a potency equivalence value (PEV) was assigned. The PEV was only designed to enable comparisons and therefore had no therapeutic meaning. More potent statins and higher doses of statins received a higher PEV. When the PEV at follow-up was lower than at baseline, it was classified as de-intensification. When there was no change or an increase in PEV, this was classified as no de-intensification. Next to switching to a lower potency statin, medication discontinuation or therapy cessation and dose reduction of any lipid modifying agent were classified as de-intensification. The equipotency table as well as a description of the steps taken in the development of PEVs, can be found in **Appendix 1.2**.

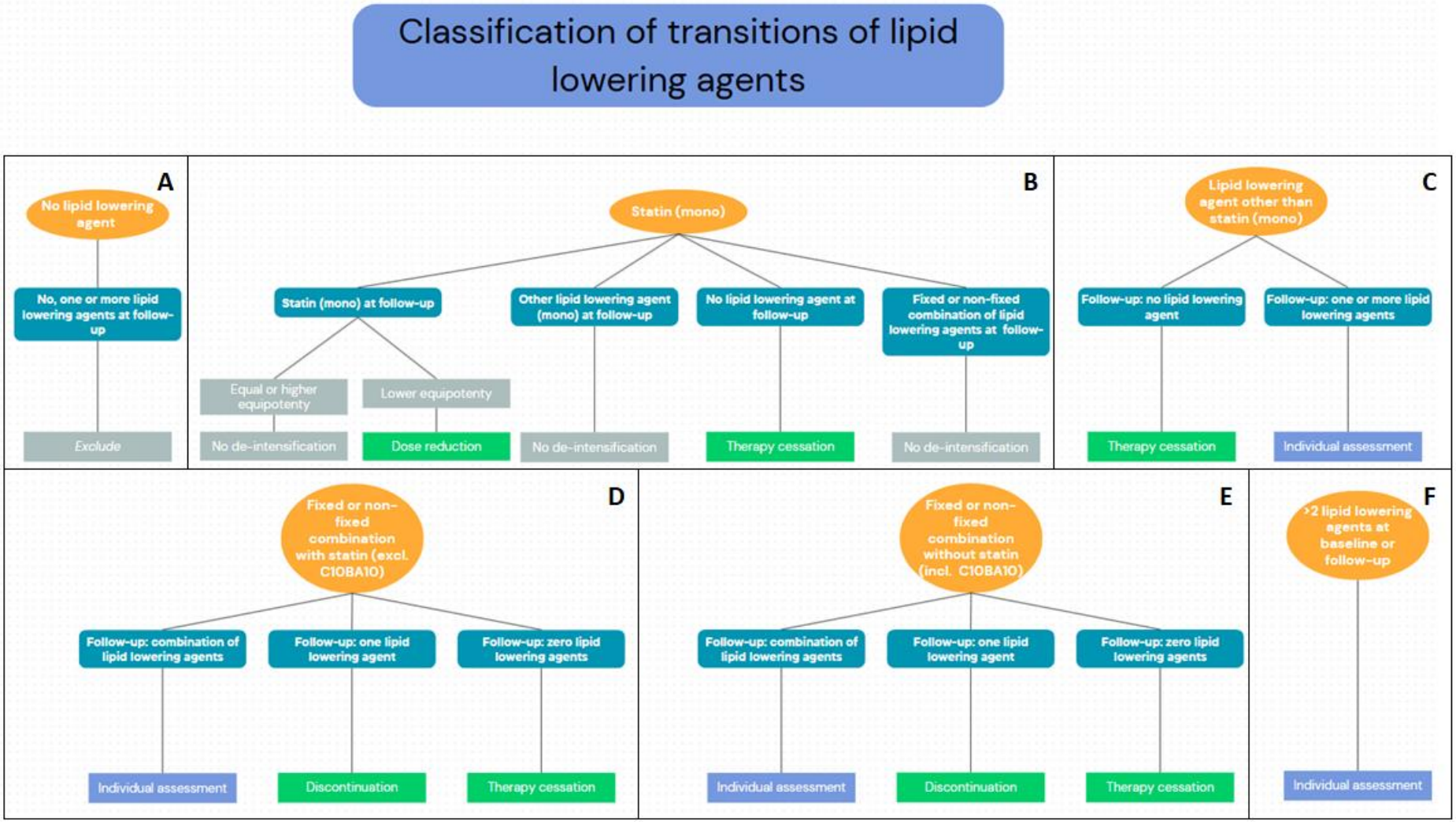

Figure 3 *Overview of (all) possible transitions in treatment states within the lipid modifying agents. Treatment states in orange ovals represent treatment states at baseline, unless specified otherwise. Treatment states in the blue rectangles represent treatment states at follow-up. All forms of de-intensifications are marked green. Transitions requiring individual assessment are marked lilac. Transitions which were no de-intensification are marked grey.*

Transitions in the use of lipid modifying agents were identified and visualized in a flowchart (**Figure 3**) using the aforementioned classifications

no de-intensification, individual assessment and one of the forms of de-intensification. Six different baseline conditions with respect to lipid modifying agents were identified (A-F in **Figure 3**): (A) absence of lipid modifying agents (to be excluded from outcome calculations); (B) statin monotherapy (without other lipid modifying agents); (C) monotherapy of lipid modifying agents other than a statin (excluding combination products); (D) a (non-) fixed combination of lipid modifying agents containing a statin; (E) fixed and non-fixed combinations that only contain other lipid modifying agents (e.g. C10BA10) and (F) more than two lipid modifying agents. Combinations of two lipid modifying agents were called 'fixed' when there is a prescription for a combination product containing two different lipid modifying agents (e.g. having the ATC-code C10BA) and 'non-fixed' when a patient receives separate prescriptions for two or more different lipid modifying agents (for example a statin, C10AA, and ezetimibe, C10AX09). Next, the possible medication transitions were identified for all baseline conditions. Cases with absence of lipid modifying agents at baseline, situation A, were excluded from analysis and did not receive a classification. For situation B with statin monotherapy at baseline, four transitions were identified: use of a statin (requiring calculation of PEV, with a reduction in PEV being only classified as dose reduction, switch to another single lipid modifying agent (classified as no de-intensification), absence of lipid modifying agents (classified as therapy cessation) and presence of a combination of two lipid modifying agents (either being a fixed or a non-fixed combination, classified as no de-intensification). For situation C with a single lipid modifying drug other than a statin, two different conditions at follow-up were identified: absence of lipid modifying agents (classified as therapy cessation) and all other scenarios (requiring individual assessment). For situations D and E with a fixed or non-fixed combination of lipid modifying agents containing a statin respectively exclusive statins, three distinct conditions at follow-up were identified: absence of lipid modifying agents (classified as therapy cessation), use of one lipid modifying agent (so excluding fixed combinations; classified as discontinuation) or the use of a combination of lipid modifying agents (both fixed and non-fixed combinations; which required individual assessment). For all cases in which there were more than two lipid modifying agents, situation F, individual assessment was allocated.

1.3 Development of decision rules for lipid modifying agents

The transitions mentioned above were translated into ATC-code based decision rules, as presented in **Table 2** (legend provided in **Table 2B**). When possible transitions were combined into one decision rule. This was done when the baseline condition was identical and the resulting classifications of the transitions were the same. As example, rule 4 in **Table 2** was formed by combining two transitions mentioned in Figure 3B (namely the transition from monotherapy statin to another single lipid modifying agent and the transition from statin monotherapy to a fixed or non-fixed combination of lipid modifying agents). On the other hand, some transitions as mentioned in **Figure 3** were split into multiple decision rules as shown in **Table 2**. For example, occurrence of more than two lipid modifying agents simultaneously was defined into two rules (1 and 16). The transitions of (non-)fixed combinations of lipid modifying agents were split into three rules for fixed combinations (both with and without a statin), three rules for non-fixed combinations with a statin and three rules for non-fixed combinations without a statin. A total of 17 decision rules with their corresponding classification were the result, among which 3 rules starting with statin monotherapy, 2 starting with other lipid modifying monotherapy, and 9 rules starting with combination treatments. For 6 rules, individual assessment was indicated. One rule (rule 3) required an additional step of calculating the PEV as described in section 1.2. The other 10 rules were automatically classified as no de-intensification or as subtype of de-intensification (see **Table 2**). Five de-intensifications were therapy cessations and three were discontinuations.

Table 2 *Decision rules for the classification of transitions in the use of lipid modifiers*

Decision rule	Baseline	Follow-up	Classification
0	(-) no C10	Any situation	*Exclude*
1	> 2 C10	Any situation	Individual assessment
2	C10AA (mono)	(-)	Therapy cessation
3	C10AA (mono)	C10AA (mono)	Calculation PEV
4	C10AA (mono)	C10AB or C10AC or C10AD or C10AX or C10BA or (C10A* + C10A#)	No de-intensification
5	C10AB/AC/AD/AX (mono)	Any situation except for (-)	Individual assessment
6	C10AB/AC/AD/AX (mono)	(-)	Therapy cessation
7	C10BA	(-)	Therapy cessation
8	C10BA	C10A#	Discontinuation
9	C10BA	C10BA or (C10A* + C10A#)	Individual assessment
10	C10AA + C10A#	(-)	Therapy cessation
11	C10AA + C10A#	C10A#	Discontinuation
12	C10AA + C10A#	C10BA or (C10A* + C10A#) or (C10A* + C10A^)	Individual assessment
13	C10A# + C10A* excl. C10AA	(-)	Therapy cessation
14	C10A# + C10A* excl. C10AA	C10A# or C10A* or C10A^	Discontinuation
15	C10A# + C10A* excl. C10AA	Any situation except for (-) and (C10A# or C10A* or C10A^)	Individual assessment
16	Any situation	> 2 C10	Individual assessment

Table 2B *Legend explaining phrases mentioned in Table 2*

(-)	Absence of C10 prescriptions
(mono)	Monotherapy of that kind of lipid modifying agent; there is just one used
Excl. C10AA	Statins are excluded
Calculation PEV	Here the calculation of the PEV (Potency Equivalence Value) is indicated
Individual assessment	Here the drug dispensing data of the patient has to be evaluated by hand: there is no automatic classification whether it is de-intensification or not

1.4 Development of the computerized algorithm for lipid modifying agents

During the translation of decision rules into Rmarkdown codes, rule 0 of the decision rules was omitted because the use of a lipid modifying agent was a prerequisite for all the codes. Rule 16 was also omitted because transitions leading to more than two lipid modifying agents at follow-up were covered by the other Rmarkdown codes. This resulted in 15 programmed rules. An instruction guide was developed to direct the manual classification of transitions requiring individual assessment (see **Appendix 5**).

1.5 Validation of the script for lipid modifying agents

The first version of the computerized algorithm, also referred to as 'script', that was developed was tested using datasets with dispensing data from 60 patients. All 3 cases in which the script indicated a stop were checked, which were all therapy cessations of statin monotherapy and appeared to be

classified correctly. The classification stop was initially assigned but later specified to therapy cessation and discontinuation. Also 10 cases were checked in which the PEV was calculated, which had been correctly classified. In 9 cases the PEV remained unchanged (according to decision rule 3). One of these was a transition from simvastatin to atorvastatin. The other case was an increase in PEV, correctly classified as no de-intensification. However, some of the cases in which the script indicated that there was no lipid modifying agent appeared to be incorrect. Lipid modifying agents with ATC-codes C10AB, -AC, -AD and -AX had not been recognized as being lipid modifying agents except in one case following rule 15, which was correctly classified as requiring individual assessment. This was the only case requiring individual assessment. Based on these findings, the script for the computerized algorithm was adapted and this second version was also validated. In this second round of validation, all transitions were correctly classified except for a patient using at baseline and follow-up a non-fixed combination of ezetimibe and atorvastatin which was misclassified as using no lipid modifying agents. The algorithm was adjusted a second time and the corresponding third round of validation was performed. At this third round, dispensing data from 61 patients was included and all transitions were correctly classified by the algorithm. Additionally, all patients using lipid modifying agents other than statins were checked on the use of multiple lipid modifying agents simultaneously and for all patients was investigated whether the algorithm recognized the lipid modifying agents and applied the right rules to the transitions. This appeared to be the case. For the final version of the script of the computerized algorithm for lipid modifying agents, see **Appendix 1.3.**

To summarize the results for the 61 patients, 8 out of the 15 programmed decision rules had been applied and validated, namely rules 2, 3, 5, 6, 8, 11, 12 and 15. 100% of the transitions classified by these rules were classified correctly. The other 7 decision rules were developed for transitions that were not present in the data of the 61 patients and therefore could not be validated as well. 55 patients used one or more lipid modifying agents, while the other 6 did not use any lipid modifying agent at baseline. From these 55 cases, in 6 cases individual assessment was indicated (following rules 5, 12 and 15) constituting 10.9% of the cases. Individual assessment revealed that none of these cases was a de-intensification. For the remaining 49 cases (89.1%) the classification was performed fully automated, resulting in six cases of de-intensification and 43 cases of no de-intensification.

Part 2: Blood glucose lowering agents

2.1 Blood glucose lowering agents on the Dutch market

All blood glucose lowering agents (medicines with ATC-code starting with A10) available on the Dutch market were listed (see **Table A.2.1** in **Appendix 2.1**). Within the group A10BD, only fixed combinations with 2 blood glucose lowering agents were available in the Netherlands.

2.2 Possible transitions in blood glucose lowering agents

Deprescribing recommendations for blood glucose lowering agents for patients with diabetes mellitus type 2 focus on the de-intensification of agents with a high risk of hypoglycaemia. Occurrence of steps to de-intensify insulin use as well as switches of SU-derivatives to safer alternatives are considered to be de-intensifications. Additionally, dose reductions and discontinuation or therapy cessation of blood glucose lowering agents are classified as de-intensification.

Multiple recommended strategies are reported for the de-intensification of insulin, depending on the insulin administration scheme that is used by the patient. In general, a reduction of fast-acting insulin, switching from fast-acting to long-acting analogues and reducing the long-acting analogues are considered de-intensifications. De-intensification of insulin is performed step by step. If the total dose of long-acting insulin is less than 20 units, one can try to switch to oral medication (48,49). Other drugs used in diabetes may be gradually reduced in dose or stopped at once (17,20,48,49).

Switches of SU-derivatives to safer alternatives are switches of an SU-derivative with a relatively high risk of hypoglycaemia to blood glucose lowering agents with a lower risk of hypoglycaemia. Also a switch from the high-risk SU-derivatives glibenclamide and glimepiride to the lower-risk SU-derivative gliclazide is considered a de-intensification (17,20,48,49).
Transitions in the use of blood glucose lowering agents that could occur were identified and visualized in a flowchart (see **Appendix 2.2).** Cases in which insulin was discontinued at follow-up received the classification de-intensification (being either therapy cessation or discontinuation) and when insulin was started at follow-up, it received the classification no de-intensification. When insulin was used at both baseline and follow-up, individual assessment was assigned for manual comparison of insulin use. In the pharmacy dispensing data, no information about dosing of insulin was available but only the type of insulin and date of dispensing. Dosing of insulin therefore required individual assessment in which insulin schemes were compared by a healthcare provider of that patient. For cases in which the transitions with insulin did not apply, the flowchart proceeds to transitions of other blood glucose lowering agents. At first, discontinuation of a SU-derivative (regardless of whether it is replaced or not by any non-insulin blood glucose lowering agent) was classified as de-intensification (being either therapy cessation or discontinuation). For the remaining transitions of blood glucose lowering agents, the most important parameter was the total number of different glucose lowering agents. An increase was classified as no de-intensification, a decrease as de-intensification (either therapy cessation or discontinuation) and when the total number remained unchanged, a distinction is made for switches and dose reductions. For medication switches, individual assessment was assigned. For non-switched medications, a de-intensification had occurred if the dose had been reduced. The use of four or more blood glucose lowering agents without use of insulin, as well as a transition from using three agents at baseline to zero at follow-up, were considered potentially misclassified and received the classification individual assessment to ensure manual investigation.

2.3 Development of decision rules for blood glucose lowering drugs

The transitions mentioned above were translated into ATC-code based decision rules, see **Table 3** (legend provided in **Table 3B**). A total of 20 decision rules were defined (when disregarding rule 0 and counting rules 4A and 4B as separate rules). Transitions of insulin were described by rules 1-3, usage of more than three blood glucose lowering agents apart from insulin in rules 4A and B and discontinuation of an SU-derivative in rule 5. Only when rules 1-5 did not apply, rules 6-19 could apply. Transitions of monotherapy were described in four rules, transitions with two or three blood glucose lowering agents were both described in five rules. Agents in the group A10BD counted for 2 blood glucose lowering agents since these are fixed combinations of 2 blood glucose lowering agents (see also **Table A.2.1** in **Appendix 2.1**). 8 of the 20 decision rules required individual assessment, 3 rules required a comparison of the daily dose and the remaining 8 rules were automatically classified as no de-intensification or as subtype of de-intensification. For rules 1 and 5 both therapy cessation and discontinuation are possible, so received the non-specified classification de-intensification.

Table 3 Decision rules for the classification of transitions in the use of blood glucose lowering drugs

Decision rule	Baseline	Follow-up	Classification
0	(-) no A10	Any situation	*Exclude*
1	Any situation with A10A (insulin)	Any situation except for presence of A10A (insulin)	De-intensification (therapy cessation or discontinuation)
2	Any situation with A10A (insulin)	Any situation with A10A (insulin)	Individual assessment
3	Any situation except for presence of A10A (insulin)	Any situation with A10A (insulin)	No de-intensification

4A	>3 A10B present (more drugs than (A10BD + 1 A10B excl. A10BD) or 3 A10B excl. A10BD)	Any situation	Individual assessment
4B	Any situation	>3 A10B present (more drugs than (A10BD + 1 A10B excl. A10BD) or 3 A10B excl. A10BD)	Individual assessment
5	Any situation with A10BB	Any situation without A10BB	De-intensification (therapy cessation or discontinuation)
	When rules 1-5 not apply,	**continue to rules below**	
6	A10B (mono) excl. A10BD	(-)	Therapy cessation
7	A10B (mono) excl. A10BD	2 or 3 A10B (3 A10B excl. A10BD or (A10BD with/without 1 A10B excl. A10BD)	No de-intensification
8	A10B# (mono) excl. A10BD	A10B* excl. A10BD	Individual assessment
9	A10B# (mono) excl. A10BD	A10B# (mono) excl. A10BD	Comparison daily dose
10	(A10B# + A10B* excl. A10BD) or (A10BD#)	A10B? excl. A10BD	Discontinuation
11	(A10B# + A10B* excl. A10BD) or (A10BD#)	(-)	Therapy cessation
12	(A10B# + A10B* excl. A10BD) or (A10BD#)	3 A10B (3 A10B excl. A10BD or (A10BD + 1 A10B excl. A10BD))	No de-intensification
13	(A10B# + A10B* excl. A10BD) or (A10BD#)	(A10B# + A10B” excl. A10BD) or (A10B^ + A10B” excl. A10BD) or A10BD*	Individual assessment
14	(A10B# + A10B* excl. A10BD) or (A10BD#)	(A10B# + A10B* excl. A10BD) or (A10BD#)	Comparison daily dose
15	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD + A10B#)	(-)	Individual assessment
16	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD + A10B#)	(A10B? and/or A10B? excl. A10BD) or A10BD?	Discontinuation
17	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD# + A10B#)	(A10B; + A10B~ + A10B^ excl. A10BD) or (A10BD* +A10B")	Individual assessment
18	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD# + A10B#)	(A10B# + A10B~ + A10B^ excl. A10BD) or (A10B# + A10B* + A10B^ excl. A10BD) or (A10BD^ + A10B#) or (A10BD* + A10B")	Individual assessment
19	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD# + A10B#)	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD# + A10B#)	Comparison daily dose

Table 3B Legend explaining phrases mentioned in Table 3

(-)	Absence of A10 prescriptions
(mono)	Monotherapy of that kind of blood glucose lowering agent; there is just one used
Excl. A10BD	Fixed combinations are excluded
?	Any; A10B? means any A10B
Comparison daily dose	Here the daily dose of the drug(s) needs to be compared to enable classification
Individual assessment	Here the drug dispensing data of the patient has to be evaluated by hand
# or * or ^ or ", etc.	Means a specific product of that group. For example, use of A10B# at baseline and A10B^ at follow-up indicates a switch from product.

2.4 Development of computerized algorithm for blood glucose lowering agents

Decision rules 4A and 4B were translated into one Rmarkdown code. Rule 0 was omitted, because the use of a blood glucose lowering agent was a prerequisite for all the codes. The numbers of the other rules remained unchanged. This resulted in 19 programmed rules classifying transitions of blood glucose lowering agents. An instruction guide was developed to direct the manual classification of transitions requiring individual assessment (see **Appendix 5**).

2.5 Validation of the script for blood glucose lowering agents

The first version of the computerized algorithm for blood glucose lowering agents, also referred to as 'script', was tested using medication dispensing data from 63 patients. In the first round of validation, all 6 cases in which the script indicated a stop were validated but for 4 cases this was incorrect. For one of these cases, two rules (3 and 5) applied simultaneously according to the computerized algorithm, whereas only one rule should apply per case (here rule 3). For the other three incorrect classified cases, no blood glucose lowering agent was stopped at all. 4 transitions were classified as individual assessment, which was for all correct. 4 other cases were classified as no de-intensification which was correct, but for only one of these cases the classification appeared to be based on the right decision rule. Further, 10 cases were investigated in which the script indicated that no blood glucose lowering agent was present, which was for all 10 cases correct. Based on these findings, the script was adapted and the resulting second version of the script was validated in a second round of validation. At this stage, 2 transitions were classified as a stop and these were classified correctly according to the right rules. The classification 'stop' was initially assigned but later specified into therapy cessation and discontinuation. 7 times individual assessment was assigned to transitions. For one of these cases two rules (13 and 14) applied according to the computerized algorithm while only rule 14 should apply. Two of the cases in which individual assessment was indicated were based on rule 14, which should receive the classification comparison of the daily dose instead of individual assessment. The remaining four cases in which individual assessment was assigned, were correctly classified. For 8 cases, the classification was comparison of the daily dose, which was correct for all cases. Further, 2 cases were classified as no de-intensification which was correct for both transitions. 10 cases for which the script indicated that no blood glucose lowering agent was used (which were also investigated in the first round of validation), were validated again and appeared again to be classified correctly. After the second time the script was adapted, a third validation round was performed. Now the classification of rule 14 was changed to comparison of the daily dose instead of individual assessment and for all cases just one rule applied. In this third validation round, 100% of the classifications were performed correctly by this version of the script. The final version of the computerized algorithm for blood glucose lowering medication can be found in **Appendix 2.3.**
To summarize the results for the 63 patients, 8 rules had been applied and validated (rules 1, 2, 3, 5, 7, 9, 14 and 19). The remaining 11 rules were developed for transitions that did not apply to the data

and could therefore not be validated as well. 44 patients did not use any blood glucose lowering agent at baseline, the remaining 19 patients received all a correct classification. 4 transitions were automatically classified (2 de-intensifications and 2 no de-intensifications), constituting 21.1% of the cases. 4 transitions were classified as individual assessment and 11 transitions were classified as comparison of the daily dose, which all required manual investigation (78.9% of the cases). Since so many cases required manual investigation, an updated version of the decision rules was suggested (see **Appendix 2.4**). These new decision rules have not been programmed and validated yet.

Part 3: Blood pressure lowering agents

3.1 Blood pressure lowering agents on the Dutch market

In the ATC-system, blood pressure lowering agents are spread over different subgroups within the group Cardiovascular system (namely C02, C03, C04, C07, C08 and C09). However, not all agents belonging to these subgroups are indicated for blood pressure lowering (i.e., C03DA04/05, C03XA01) and were therefore excluded in the CO-DEPRESCRIBE study and in this study as well. All included agents that were available on the Dutch market, were collected (see **Table A.3.1** in **Appendix 3.1)**.

3.2 Possible transitions in blood pressure lowering agents

Treatment of hypertension often exists of a combination of blood pressure lowering agents. Intensification of therapy occurs first by addition of another antihypertensive and increasing the dose of antihypertensives occurs only in an advanced stage in the intensifying scheme. A schematic and simplified scheme of the treatment of hypertension is presented in **Figure 4** (12,50). Preferred medications in hypertension are beta blocking agents, calcium channel blockers, diuretics, ACE (angiotensin-converting-enzyme) inhibitors and ARBs (angiotensin receptor blockers) which are all considered equally effective (12,50,51). Therefore, we consider switching from one class of antihypertensive to another to be no de-intensification. Deprescribing recommendations indicate that deprescribing of antihypertensives can consist of dose reductions or discontinuations of the medication depending on experience of adverse effects and co-morbidities (16,49). For both the preferred antihypertensives and other antihypertensives, dose reductions and discontinuations were considered to be de-intensifications.

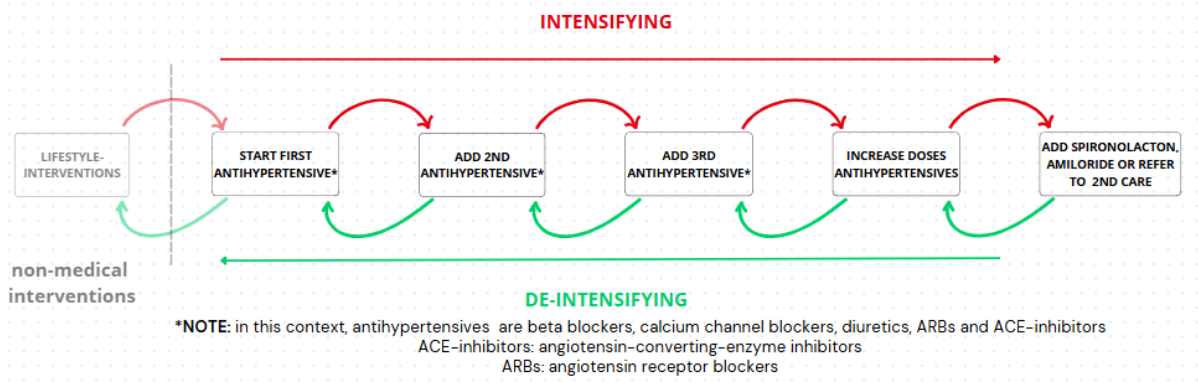

Figure 4 Schematic overview of the treatment of hypertension

All transitions were identified and visualized in a flowchart (see **Figure A.3.3** in **Appendix 3.3**). Agents with ATC-codes starting with C02A, C02C, C02D, C02K, C03C and C03DB potentially have another indication than hypertension (e.g. oedema in case of high ceiling diuretics) and were thus included in separate rules. When the use of these drugs remained unchanged, it was classified as no de-intensification and when these drugs were absent at baseline but started at follow-up, it was classified as no de-intensification. All other transitions including these drugs were to be individually assessed.

If these agents were absent, the total number of blood pressure lowering agents (BPLA) was counted. Agents with only one API (active pharmaceutical ingredient, for example amlodipine) were called 'singles' and counted for 1 BPLA. Fixed combinations of 2 APIs (for example amlodipine/perindopril) were called 'doubles' and counted for 2 BPLA. Fixed combinations consisting of 3 APIs (for example amlodipine/perindopril/indapamide) were called 'triples' and counted for 3 BPLA. An overview of which medication (groups) belong to the groups singles, doubles and triples is given in **Table A.3.2** in **Appendix 3.2**. A total count of BPLA of 5 or higher was considered potentially misclassified and required individual assessment. An increase in the number of BPLA was classified as no de-intensification. A decrease in the number of BPLA by 1 or 2 BPLA was classified as de-intensification (either therapy cessation or discontinuation). A decrease in the number of BPLA by 3 or 4 was considered to be potentially misclassified and required individual assessment. If the total number of BPLA remained unchanged, differentiation was based on medication switches (i.e. a change in the ATC-code). When all BPLA were switched, it was classified as no de-intensification. When one or more BPLA remained unchanged, the daily dose of the unchanged agent was assessed and a decrease in dose was classified as de-intensification.

3.3 Development of decision rules for blood pressure lowering agents

The transitions as depicted in **Figure A.3.3** and described above were translated into decision rules at ATC-code level, as shown in **Table 4** (legend provided in **Table 4B**). In total, 10 decision rules were developed (when disregarding rule 0 and counting rule 2A and B as well as 3A and 3B as separate rules). Rules 1, 2A and 2B were developed for the agents with an indication potentially different from hypertension. Rule 2B, describing a start of one of these agents, was classified as no de-intensification regardless of what transitions were seen in the other blood pressure medications. Rules 3A and 3B covered the cases in which 5 or more BPLA were used. Rules 4 and 5 were developed for transitions with a reduction in the total number of BPLA, rule 6 for an increase in the total number of BPLA and rules 7 and 8 for cases in which the total number of BPLA remained unchanged. Four transitions were automatically classified as individual assessment (rules 2A, 3A, 3B and 5). The other rules were automatically classified as no de-intensification (rules 1, 2B, 6 and 8), de-intensification (therapy cessation or discontinuation, rule 4) and one as comparison of the daily dose (rule 7).

Table 4 Decision rules for the classification of transitions in the use of blood pressure lowering agents

Decision rule	Baseline	Follow-up	Classification
0	(-) no C02, C03 (except C03DA04 and -05 and C03AX01), C07, C08C, C08D,C08E,C08G, C09	Any situation	*Exclude*
1	Presence of C02A#, C02CA#, C02DC#, C02DD#, C02KX#, C03CA# and/or C03DB#	Identical to baseline (same medications, total count, daily dose)	No de-intensification
2A	Presence of C02A, C02CA, C02DC, C02DD, C02KX, C03CA and/or C03DB	Any situation apart from identical to baseline	Individual assessment
2B	Any situation without C02A, C02CA, C02DC, C02DD, C02KX, C03CA and/or C03DB	Presence of C02A, C02CA, C02DC, C02DD, C02KX, C03CA and/or C03DB	No de-intensification
3A	≥ 5 BPLA	Any situation	Individual assessment

3B	Any situation	≥ 5 BPLA	Individual assessment
4	Total count BPLA = X	Total count BPLA < X (X-1 or X-2)	De-intensification (therapy cessation or discontinuation)
5	Total count BPLA = X	Total count BPLA < X (X-3 or X-4)	Individual assessment
6	Total count BPLA = X	Total count BPLA > X	No de-intensification
7	Total count BPLA = X	Total count BPLA = X, ≥ 1 drug unchanged	Comparison of daily dose unchanged drug(s)
8	Total count BPLA = X	Total count BPLA = X, all BPLA switched	No de-intensification

Table 4B Legend explaining phrases of Table 4

≥ 5 BPLA	More than 5 blood pressure lowering agents (singles, doubles and/or triples)
Comparison daily dose	Here the daily dose of the drug(s) at follow-up needs to be compared to baseline to enable classification
Individual assessment	Here the drug dispensing data of the patient has to be evaluated by hand
Total count BPLA = X	The total number of BPLA is equal to X
Total count BPLA < X (X-1 or X-2)	The total number of BPLA is 1 or 2 lower than the value X

3.4 and 3.5 Development and validation of computerized algorithm for blood pressure lowering agents

Within the timeframe of this study, the algorithm was not computerized and therefore not validated as well. An instruction guide was developed to direct the manual classification of transitions requiring individual assessment (see **Appendix 5**).

Part 4: Antithrombotic agents

4.1 Antithrombotic agents on the Dutch market

Antithrombotic agents available on the Dutch market were listed in **Table 4.1** in **Appendix 4.1**. Only anticoagulants and antiplatelet agents were included (B01AA, -AC, -AE and -AF). The only available fixed combination was B01AC30.

4.2 Possible transitions of antithrombotic agents

Clinical guidelines for the treatment of thrombotic disorders as well as deprescribing recommendations for antithrombotic agents indicate that there are different treatment states possible for antithrombotic agents (52–58). Triple therapy consisting of acetylsalicylic acid, a P2Y12-inhibitor and an anticoagulants (with discontinuation of acetylsalicylic acid after max. 6 months); a combination of two antiplatelet agents (duration of combination treatment max 12 months); a combination of an antiplatelet agent with an anticoagulants and an anticoagulants or antiplatelet agent alone are possible treatment states. Deprescribing guidelines only mention complete cessation of antithrombotic agents as de-intensification route (55–58). Dose reductions of antithrombotic agents aim to prevent elevated plasma levels in patients with decreased kidney function and not to de-intensify treatment (57,59). Switches to safer alternatives also do not occur for antithrombotic agents. Therefore, the only de-intensifications were discontinuation and therapy cessation and classification was performed based on the total number of anticoagulants and/or antiplatelet agents only. All transitions were identified and visualized in **Figure 5**. Occurrence of three or more

antiplatelet agents and two or more anticoagulants was a potential misclassification and required individual assessment. Only a reduction in the total number of antithrombotic agents was classified as de-intensification (either therapy cessation or discontinuation).

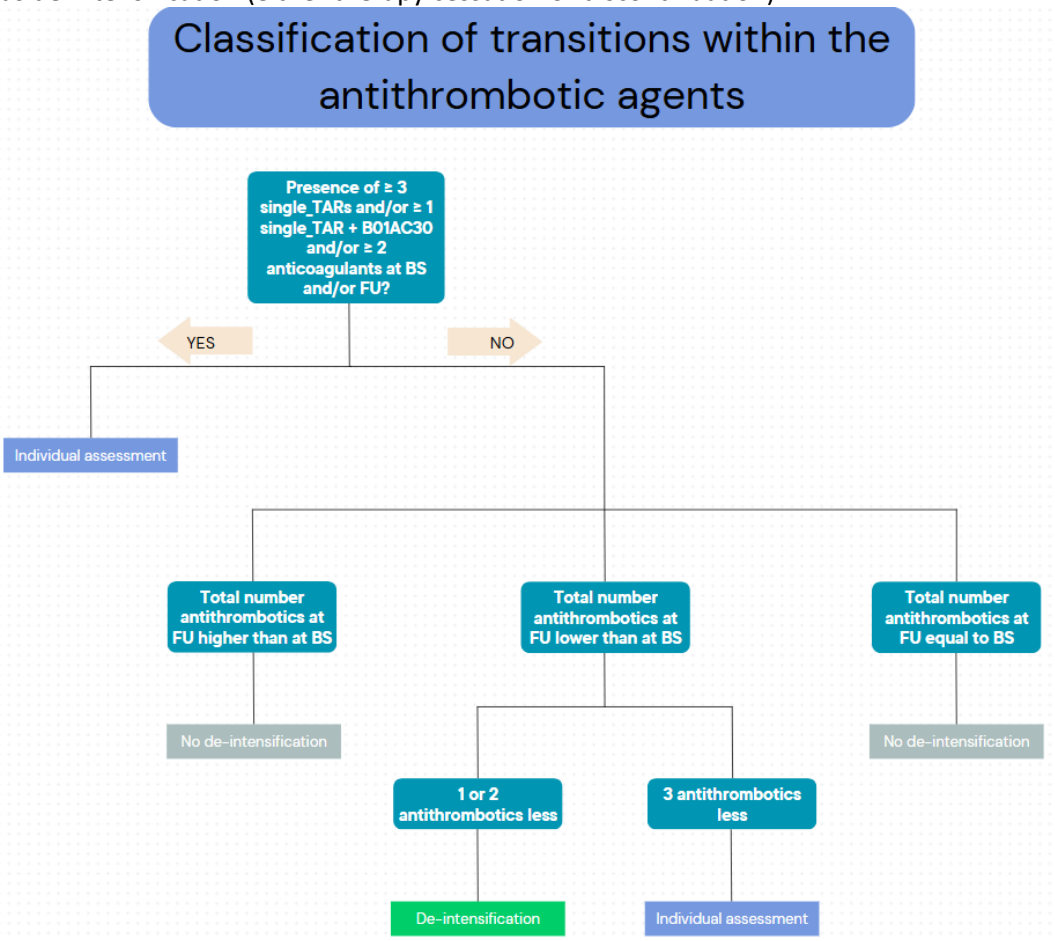

Figure 5 Overview of all possible transitions in treatment states of antithrombotic agents. single_TARs are agents in the group B01AC available on the Dutch market excluding B01AC30. Anticoagulants are products of the groups B01AA, B01AE and B01AF that are available on the Dutch market.

4.3 Development of decision rules for antithrombotic agents

The transitions as depicted in **Figure 5** were translated into ATC-code based decision rules and presented in **Table 5** (legend provided in **Table 5B**). In total 6 decision rules were developed (when disregarding rule 0 and counting rules 1A, 1B, 3A and 3B separately). Rules 2, 3A and 4 received an automatic classification, the other three rules required individual assessment. Only one transition was automatically classified as de-intensification (rule 3A).

Table 5 Decision rules for the classification of transitions in the use of antithrombotic agents

Decision rule	Baseline	Follow-up	Classification
0	(-) no B01AA, -AC, -AE, -AF	Any situation	*Exclude*
1A	≥3 antiplatelets and/or ≥2 anticoagulants	Any situation	Individual assessment
1B	Any situation	≥3 antiplatelets and/or ≥2 anticoagulants	Individual assessment

2	Total number antithrombotic agents = X	Total number antithrombotic agents > X (2 or 3 agents)	No de-intensification
3A	Total number antithrombotic agents = X	Total number antithrombotic agents < X (X-1 or X-2)	De-intensification (therapy cessation or discontinuation)
3B	Total number antithrombotic agents = X	Total number antithrombotic agents < X (X-3)	Individual assessment
4	Total number antithrombotic agents = X	Total number antithrombotic agents = X (1, 2 or 3)	No de-intensification

Table 5B Legend explaining phrases of Table 5

Antiplatelets	Platelet aggregation inhibitors (B01AC)
Individual assessment	Here the drug dispensing data of the patient has to be evaluated by hand
Total number antithrombotic agents = X	The total number of antiplatelets and/or anticoagulants is equal to X
Total number antithrombotic agents < X (X-3)	The total number of antiplatelets and/or anticoagulants is 3 lower than the value X

4.4 and 4.5 Development and validation of computerized algorithm for antithrombotic agents

Within the timeframe of this study, the algorithm was not computerized and as such not validated. An instruction guide was developed to direct the manual classification of transitions requiring individual assessment (see **Appendix 5**).

DISCUSSION

We developed computerized algorithms that automatically classify transitions in the use of cardiometabolic medication as de-intensification, no de-intensification or requiring individual assessment. Medication discontinuations, dose reductions and medication switches to safer alternatives are all taken into account in the classifications. All classifications assigned by the algorithms for lipid modifying agents and blood glucose lowering agents were correct. In total, 9 out of 15 and 8 out of 19 programmed decision rules applied and were validated for these medication classes respectively. The algorithms for blood pressure lowering agents and antithrombotic agents will be programmed and validated in the near future. The algorithm for lipid modifying agents classified 87.8% of tested cases as (no) de-intensification automatically, without requiring individual assessment. This was 21.1% for blood glucose lowering agents, based on a first version of the decision rules.

Interpretation of outcomes and further algorithm development

Since almost 9 out of 10 cases using lipid modifying agents are classified automatically, we see no need for further adaptation of the algorithm in an attempt to increase the number of automatic classifications. The rather poor efficiency of the algorithm for blood glucose lowering agents will be improved by an updated version of the decision rules (see **Appendix 2.4**) but is expected to stay rather low (between 50 and 60%). This is inevitable given the facts that all cases using insulin at baseline and follow-up and cases with medication switches require individual assessment. The poor efficiency forms no major problem because in our dataset of 63 patients only 19 patients used any blood glucose lowering agent and the actual number of cases requiring individual assessment therefore remains relatively low. It is important to realize that without algorithm also non-users of (one of the four groups of) cardiometabolic medication had to be manually investigated, while the algorithm automatically identifies users within a dataset. The percentage of cases requiring individual assessment as marker of the efficiency of the algorithms should therefore be interpreted with nuance. As said, the algorithm for blood pressure lowering agents and antithrombotic agents still need to be computerized and validated. Given their relatively simple structure, assessing changes in the total number of agents used and for blood pressure lowering agents additionally any change in daily dose, no major issues are expected in these algorithms.

What our study adds

The US Deprescribing Network, USDeN, concluded in 2022 that there is a lack of evidence of the effects of deprescribing due to the fact that outcome measures, including medication changes, between deprescribing studies are heterogeneous. Therefore, it was recommended to select clinically meaningful medication outcomes and clearly define these outcomes to enable evidence generation by combining and comparing different studies (27). For the algorithms provided here, we clearly described which transitions are classified as de-intensification and provided guideline or literature-based argumentation of the classifications. We also provided a guide with instructions on how to perform individual assessment of medication transitions (**Appendix 5**). The algorithms were developed for four groups of cardiometabolic medication, thereby enabling automatic classification of medication outcomes for a large number of drugs commonly used by older people. So far, most deprescribing studies only consider medication discontinuation and/or dose reductions of single (classes of) medications when quantifying the effect of an intervention (60) (see table S5). Our algorithms add to this by also including medication switches to safer or less potent drugs as de-intensifications. A recently published algorithm by Min et al. aimed to account for discontinuations, dose reductions and switches by calculating the intensity of antihypertensive treatment based on a standardized hypertension daily dose (HDD) across all antihypertensives (61). The HDD only measures the total intensity of antihypertensives prescribed and therefore changes in the number or type of drugs are disregarded by the algorithm. Another disadvantage is that it is reported that

changes in the prescribed daily dose occur upon switches between antihypertensive medication, without being an intended dose change by the prescriber (62). In the HDD measurement these unintended dose changes will result in an increase or decrease in HDD. We therefore classified switches in blood pressure lowering agents as no de-intensification in our algorithm.

Using dispensing gaps as a proxy of medication discontinuation might result in misclassifications due to factors including poor medication adherence, medication being substituted and medication with 'as needed' use, even when maintaining 90-day dispensing gaps (63).The four algorithms presented here were developed for the CO-DEPRESCRIBE study, where the time between baseline and follow-up medication measurement was set on 123 days. Dispensings within a period of 120 days were used to establish baseline use and follow-up use. These time windows reduce the risk of misclassification due to dispensing gaps as result of, for example, poor medication adherence. Further, the algorithms take medication being substituted into account. Nonetheless, not all cases that are classified as discontinuations and therapy cessations by our algorithms necessarily are true stops of cardiometabolic medication. For example, medication with 'as needed' use such as loop diuretics are prone to misclassification.

All four algorithms were different and required an unique approach in their development due to aspects related to the therapeutic area and available agents in the therapeutic groups, in line with a previous expectation that finding an uniform definition to quantify outcomes is impossible (27). Relevant aspects include clinical aspects, such as differences in potency within a medication class, whether or not dose reductions are relevant, agents with multiple indications, or the option to switch from high to low risk medication classes, but also system-related aspects, such as having to take fixed-combination products into account or the feasibility of extraction dose information. Equipotency of statins had to be taken into account for the algorithm of lipid modifying agents because the lipid lowering effects of high potent statins exceed the effects of statins with a low potency (47,64). For other medication groups, such potency differences did not exist and only dose reductions were taken into account. Statins are present in some fixed combinations and might be present in non-fixed combinations. Therefore, transitions with a combination of lipid modifying agents including a statin had to be assessed on a change of equipotency as well if a statin was used at baseline and follow-up. For antithrombotic agents, dose reductions were even irrelevant and the only discontinuation steps were discontinuations (57,59). Some agents in the classes C02 and C03 could have another indication than hypertension and it is reported that changes in the use of these agents frequently occur (61). Therefore, the algorithm for blood pressure lowering agents treats these agents distinct from other blood pressure lowering agents. For blood glucose lowering agents, a distinction is made between agents with a high and low risk on hypoglycaemia and a switch from insulin or an SU-derivative to an agent with a lower risk of hypoglycaemia is a de-intensification (17,20,48,49). Further, information about insulin use was not available in the dispensing data and

Table 6 Types of de-intensification that applied per medication group

	Lipid modifying agents	*Blood glucose lowering agents*	*Blood pressure lowering agents*	*Antithrombotic agents*
Therapy cessation	X	X	X	X
Discontinuations	X	X	X	X
Dose reductions	X	X	X	
Switch to safer alternative		X		

therefore required individual assessment if used both at baseline and follow-up. Instead of disregarding changes in insulin use as potential de-intensification, as has been done in some other studies (like Crutzen et al. (37)), we used additional information from healthcare providers (i.e.

insulin schemes) to investigate any change in insulin use. Transitions with insulin discontinuation or start of insulin could be classified automatically. For the algorithm of blood pressure lowering agents, the presence of products with one, two or three blood pressure lowering agents forced us to develop a counting mechanism by which changes in the total number of agents could be assessed. So, transitions classified as de-intensifications vary per specific medication group (see **Table 6**).

Implications for future research and practice

The four algorithms can be used without adaptation in the CO-DEPRESCRIBE study and potential similar deprescribing intervention studies in older patients in the Netherlands. However, the aspects discussed above highlight the necessity to explore steps that are considered to be de-intensifications based on evidence prior to applying algorithms in non-identical settings (27). Further a critical investigation of the included medication and inspection of the available medication data should be performed. Steps considered to be de-intensifications might differ between ages. For example, hypoglycaemia has more severe consequences with advanced age and reducing the risk of hypoglycaemia in deprescribing blood glucose lowering agents therefore gets more important with increasing age (65). When used in other countries, a critical investigation of the agents included in this study and available in that country should be performed, as well as a check whether all de-intensification steps as identified here also apply there. Finally, all dispensing information that we used (including ATC-code and strength) should be available when using these algorithms. Additionally, it is important to not only include medication transitions for outcome measurements when using these algorithms for deprescribing intervention studies. Although considered essential, the USDeN suggests to not only include medication but to also include clinical outcomes as quality of life and intervention-specific clinical outcomes to assess a broader effect of an intervention (27).

Next to quantifying medication outcomes in deprescribing interventional studies, the four algorithms can also be used to assess to what extent deprescribing of certain types of medication occur in specific populations without interventions. That creates insight into baseline rates of deprescribing for specific populations and medication groups thereby indicating in what populations and medication groups further effort is indicated. For this purpose, the time window between the baseline and follow-up medication use should be adapted to a suitable time scale.

The algorithms provided here for four medication groups can be extended by adding similar algorithms for other medication groups, e.g. agents for gastric acid related disorders and antidepressants. As indicated above, algorithms that are developed here cannot simply be copied and applied for other medication groups, but for new algorithms first deprescribing recommendations need to be consulted and then transitions can be classified. However, general principles as used for the development of the cardiometabolic algorithms will simplify the development of new algorithms: for medication groups with medication with a high and low risk of adverse effects, switches to safer alternatives have to be taken into account. Further, medication groups treating towards a certain effect level (e.g. HbA1c) in general should assess changes in the total number of agents used and, if the total number of drugs remains unchanged, dose changes of unchanged drugs. Medication groups showing dichotomous treatment (like antithrombotic therapy)

Table 7 Forms of de-intensifications requiring additional attention when specific aspects apply

	Differences in risk of adverse event	*Potency differences*	*Combination products*	*Dichotomous treatment*	*Treat to target*
Therapy cessation				X	X
Discontinuation			X	X	X
Dose reduction		X			X
Switch to safer alternative	X				

should only consider changes in the medication count. For all medication groups should be investigated whether the different drugs are equal choices, or that also switches can lead to de-intensifications. Using these principles enables a standardized approach of quantifying medication outcomes, contributing to the comparability of deprescribing studies and the generation of more evidence about the safety and efficacy of deprescribing. A visual representation of subtypes of de-intensification requiring additional attention in several conditions described above, is given in **Table 7**. These principles might form the starting point of new algorithms assessing medication transitions.

Strengths and limitations

This study has strengths and limitations. Some decision rules were developed for transitions that did not occur in the dataset that was used to validate the algorithm. Therefore these decision rules have not been validated yet. These rules are labelled so that transitions following these rules in another dataset will be recognised and validated then. Some rules not being validated were developed for transitions that are not likely to occur (e.g. using five or more antihypertensives simultaneously) and the number of non-validated rules does not indicate that the algorithms are unreliable. The decision rules that were validated, were validated meticulously. Especially for the algorithm of blood glucose lowering agents, there is still in a significant proportion of the transitions individual assessment indicated. Here, the percentage of cases requiring individual assessment might be improved when the updated version of the decision rules are programmed (see **Appendix 2.4**). The algorithms were developed for and based on the Dutch primary care setting, therefore requiring adaptations when using them for other settings.

Furthermore, before applying the algorithm, the correct study population needs to be selected, excluding patients with incomplete follow-up to avoid misclassification of discontinuations. Pharmacy dispensing data is widely available, relatively standardized and easy to obtain, but do not fully reflect actual drug prescribing, since some patients may not collect their prescriptions. For example, a phenomenon called primary non-adherence exists, when a drug is prescribed for the first time but the patient does not fill the drug prescription at the pharmacy (66). On the other hand, a study by Min et al showed that data from pharmacies quite well correlated with the drug prescribing reported by clinicians (61).

The algorithms were developed after thorough investigation of the available literature, including clinical and deprescribing recommendations. However, not all possible transitions were documented in literature and had to be classified by ourselves. For example, we classified a switch from a statin to another lipid modifying agent as no de-intensification since the most rational route for de-intensification is de-intensification of the statin (either by a dose reduction or a switch to a lower potency statin). As another example, cessation of insulin is always classified as de-intensification while in literature it is not explicitly specified whether a switch from insulin to an SU-derivative is also a de-intensification. The algorithms were extensively discussed by a senior and junior researcher but further validation by an expert panel is still recommended, especially for classifications that we assigned ourselves. We provide an instruction guide (**Appendix 5**) to assist the classifications of transitions requiring individual assessment. As such, individual assessment can be performed in a relatively standardized way. However, this guide also needs further validation.

CONCLUSION

The development of computerized algorithms classifying transitions in the use of cardiometabolic medication appeared feasible for lipid modifying and glucose lowering medication. All validated transitions were correctly classified by the computerized algorithm and for the lipid modifying agents 87.8% of the transitions received an automatic classification. For glucose lowering medication, the percentage of transitions receiving an automatic classification was far lower, being 21%, which will be improved. The basis for computerized algorithms for antihypertensive and anticoagulant medication are formed and these algorithms will be computerized and validated in the future. The computerized algorithms can be used in deprescribing intervention studies, such as the CO-DEPRESCRIBE trial, for the investigation of baseline deprescribing and after adaptation also in other populations and countries. The principles used in the development of the algorithms can be used for the development of algorithms assessing de-intensifications in other medication groups.

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APPENDIXES

In this section large documents are appended as well as documents that do not have that high urgence to be placed in the main text, or in order to improve readability. To increase structure in the Appendixes, documents are grouped per treatment group as in the main text.

Content of appendixes:

Appendix 1: lipid modifying agents (C10)

Appendix 1.1 Overview of all lipid modifying agents in the Netherlands

The overview in the table below shows which products with corresponding ATC-code are available on the Dutch market. Products having an ATC-code according to the WHO classification that are not included in the table, are not available on the Dutch market.

Table A.1.1 Overview of all lipid modifying agents that are on the Dutch market

Main group	Subgroup	Products in the Netherlands	Corresponding ATC-code
Lipid modifying agents, plain			
	HMG-CoA reductase inhibitors, C10AA	Simvastatin	C10AA01
		Pravastatin	C10AA03
		Fluvastatin	C10AA04
		Atorvastatin	C10AA05
		Rosuvastatin	C10AA07
	Fibrates, C10AB	Bezafibrate	C10AB02
		Gemfibrozil	C10AB04
		Fenofibrate	C10AB05
		Ciprofibrate	C10AB08
	Bile acid sequestrants, C10AC	colestyramine	C10AC01
		Colesevelam	C10AC04
	Nicotinic acid and derivatives, C10AD	Acipimox	C10AD06
	Other lipid modifying agents, C10AX	Omega-3-triglycerides incl. other esters and acids	C10AX06
		Ezetimibe	C10AX09
		Lomitapide	C10AX12
		Evolocumab	C10AX13
		Alirocumab	C10AX14
		Bempedoic acid	C10AX15
		Inclisiran	C10AX16
		Volanesorsen	C10AX18
Lipid modifying agents, combinations			
	Combinations of various lipid modifying agents, C10BA	Ezetimibe/simvastatin C10BA02	C10BA02
		Pravastatin/fenofibrate	C10BA03
		Atorvastatin/ezetimibe	C10BA05
		Rosuvastatin/ezetimibe	C10BA06
		Bempedoic acid/ezetimibe	C10BA10
	Lipid modifying agents in combination with other drugs, C10BX	*None on the Dutch market*	

Appendix 1.2 Potency equivalence values of statins

Potency equivalence values (PEVs) were assigned for every statin in every dose that was available in the Netherlands. PEVs were assigned based on the potency classification as used by the royal Dutch community for the pharmacy (KNMP) (47). The KNMP distinguished, as many others, three levels of intensity in statin therapy: high intensive statin therapy (>50% LDL reduction, namely atorvastatin 40-80 mg and rosuvastatin 20-40 mg), intermediate intensive statin therapy (30-50% LDL reduction, namely atorvastatin 10-20 mg, fluvastatin 80 mg, pravastatin 40-80 mg, rosuvastatin 5-10 mg and simvastatin 20-40 mg) and low intensive statin therapy (<30% LDL reduction, namely fluvastatin 20-40 mg, pravastatin 10-20 mg and simvastatin 10 mg). We split this division of three levels into a total of six levels of potency to create for every dose of every statin a PEV. Simvastatin 40 mg daily was taken as reference because it was expected to be frequently used and received a PEV of 1. Atorvastatin 20 mg, rosuvastatin 10 mg, pravastatin 80 mg and fluvastatin 80 mg also received a PEV of 1 because these were also in the intermediate-intensity statin therapy range and were all the highest dose in this range (just as simvastatin 40 mg). Therefore, they were regarded as equipotent and received the same PEV. For the other doses, PEVs were calculated by dividing the specific dose of a certain statin by the dose of that statin that belonged to the reference PEV. For atorvastatin 10 mg, the resulting PEV is therefore (10 mg /20 mg=) 0.5. Daily doses higher than the reference dose received a PEV higher than 1 and daily doses lower than the reference dose received a PEV of below 1. For an overview of all statins and the corresponding PEV, see **Table A.1.2** Transitions that led to an increase in PEV or that did not lead to a change in PEV were classified as no de-intensification. The classification 'de-intensification' was only assigned to cases in which the PEV at the follow-up measurement was lower than the PEV at the baseline measurement.

Table A.1.2 Statins with for each dose the assigned PEV. PEV = potency equivalence value

Statin	Daily dose (mg)	ATC code	Calculation PEV	PEV
Atorvastatin	80	C10AA05	80/20	4
Rosuvastatin	40	C10AA07	40/10	4
Atorvastatin	40	C10AA05	80/40	2
Rosuvastatin	20	C10AA07	20/10	2
Atorvastatin	20	C10AA05	*Reference*	1
Rosuvastatin	10	C10AA07	*Reference*	1
Simvastatin	40	C10AA01	*Reference*	1
Pravastatin	80	C10AA03	*Reference*	1
Fluvastatin	80	C10AA04	*Reference*	1
Atorvastatin	10	C10AA05	10/20	0.5
Rosuvastatin	5	C10AA07	5/10	0.5
Simvastatin	20	C10AA01	20/40	0.5
Pravastatin	40	C10AA03	40/80	0.5
Fluvastatin	40	C10AA04	40/80	0.5
Simvastatin	10	C10AA01	10/40	0.25
Pravastatin	20	C10AA03	20/80	0.25
Fluvastatin	20	C10AA04	20/80	0.25
Pravastatin	10	C10AA03	10/80	0.125

Appendix 1.3 Computerized algorithm for the classification of transitions in the use of lipid modifying agents

Below the script is placed as it was used in the programmes R and Rstudio. This final version of the algorithm was validated and appeared to make no misclassifications for the transitions that were validated.

Lipidenverlagers

Peter Stuijt
2025-01-30

```
#setwd("//zkh/appdata/research/KFF/CO-DEPRESCRIBE_ra/R")
#install.packages("knitr")
#install.packages("dplyr")
#install.packages("lubridate")
#install.packages("stringr")
```

Laad de nodige libraries

```
library(readxl)
library(dplyr)
##
## Attaching package: 'dplyr'
## The following objects are masked from 'package:stats':
##
##     filter, lag
## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union
library(lubridate)
##
## Attaching package: 'lubridate'
## The following objects are masked from 'package:base':
##
##     date, intersect, setdiff, union
library(stringr)
library(writexl)
```

Dataset laden

```
data <- read_excel("//zkh/appdata/research/KFF/CO-DEPRESCRIBE_ra/R/data/extr_uitgiftes_combi04022025.xlsx")
# Voeg periodes toe aan de dataset, en zet afleverdatum om naar het juiste format
data <- data %>%
  mutate(Afleverdatum = as.Date(as.character(Afleverdatum)),
         indexdatum = as.Date(indexdatum),
         baseline_start = indexdatum - days(120),
         baseline_end = indexdatum - days(1),
         followup_start = indexdatum + days(123),
         followup_end = indexdatum + days(242))
# APARTE CODE CHUNK VOOR REGEL 5
# Stap 1: Filter voor baseline-periode en identificeer patiënten met relevante ATC's
baseline_data <- data %>%
  filter(Afleverdatum >= baseline_start & Afleverdatum <= baseline_end)

# Stap 2: Filter voor follow-up-periode en identificeer patiënten met een lipidenverlager op FU
followup_data <- data %>%
  filter(Afleverdatum >= followup_start & Afleverdatum <= followup_end, grepl("^C10", ATC)) %>%
  distinct(REDCapID)

# Stap 3: Bereken aantal unieke ATC's die beginnen met C10AB, C10AC, C10AD of C10AX in baseline-periode
unique_atc_baseline <- baseline_data %>%
  filter(grepl("^C10A[B-DX]", ATC)) %>%
  group_by(REDCapID) %>%
  summarise(unique_atc_count = n_distinct(ATC), .groups = "drop")

# Stap 4: Controleer dat er GEEN andere ATC-codes zijn die starten met C10 in de baseline-periode
unique_atc_all_baseline <- baseline_data %>%
  filter(grepl("^C10", ATC)) %>%
  group_by(REDCapID) %>%
  summarise(total_atc_count = n_distinct(ATC), .groups = "drop")

# Stap 5: Combineer de criteria
result_regel5 <- unique_atc_baseline %>%
  inner_join(unique_atc_all_baseline, by = "REDCapID") %>%
  filter(unique_atc_count == 1, total_atc_count == 1) %>%
  inner_join(followup_data, by = "REDCapID") %>%
  inner_join(baseline_data %>% filter(grepl("^C10A[B-DX]", ATC)) %>% distinct(REDCapID), by = "REDCapID") %>%
```

```
  select(REDCapID) %>%
  distinct()

# Print het eindresultaat
print(result_regel5)
## # A tibble: 4 × 1
##   REDCapID
##   <chr>
## 1 8006-6
## 2 8006-7
## 3 8008-2
## 4 8008-9
# APARTE CODE CHUNK VOOR REGEL6
# Stap 1: Controleer of een patiënt een relevante ATC-code heeft in de baseline-periode
baseline_relevant6 <- baseline_data %>%
  filter(grepl("^C10A[B-DX]", ATC)) %>%
  distinct(REDCapID)

# Stap 2: Controleer of een patiënt GEEN ATC-code uit C10 heeft in de follow-up-periode
followup_no_C10 <- data %>%
  filter(Afleverdatum >= followup_start & Afleverdatum <= followup_end, grepl("^C10", ATC)) %>%
  distinct(REDCapID) %>%
  mutate(has_C10_followup = TRUE)

# Stap 3: Bereken het aantal unieke ATC's die beginnen met C10AB, C10AC, C10AD of C10AX in de baseline-periode
unique_atc_baseline_otherll <- baseline_data %>%
  filter(grepl("^C10A[B-DX]", ATC)) %>%
  group_by(REDCapID) %>%
  summarise(unique_atc_count = n_distinct(ATC), .groups = "drop") %>%
  filter(unique_atc_count == 1) %>%
  select(REDCapID)

# Stap 5: Controleer dat er GEEN andere ATC-codes zijn die starten met C10 in de baseline-periode
unique_atc_all_baseline6 <- baseline_data %>%
  filter(grepl("^C10", ATC)) %>%
  group_by(REDCapID) %>%
  summarise(total_atc_count = n_distinct(ATC), .groups = "drop") %>%
  filter(total_atc_count == 1) %>%
```

```
  select(REDCapID)

# Stap 6: Combineer de criteria
result_regel6 <- baseline_relevant6 %>%
  inner_join(unique_atc_baseline_otherll, by = "REDCapID") %>%
  inner_join(unique_atc_all_baseline6, by = "REDCapID") %>%
  anti_join(followup_no_C10, by = "REDCapID") %>%  # Verwijder patiënten die C10 in de follow-up hebben
  select(REDCapID) %>%
  distinct()

# Print het eindresultaat
print(result_regel6)
## # A tibble: 1 × 1
##   REDCapID
##   <chr>
## 1 8023-7
# APARTE CODE CHUNK VOOR REGEL11
# Stap 1: Filter voor follow-up-periode en identificeer patiënten met een C10A... op FU
followup_data <- data %>%
  filter(Afleverdatum >= followup_start & Afleverdatum <= followup_end, grepl("^C10A", ATC)) %>%
  group_by(REDCapID) %>%
  summarise(unique_C10A_followup = n_distinct(ATC), .groups = "drop") %>%
  filter(unique_C10A_followup == 1) %>%  # Zorg ervoor dat er precies 1 unieke C10A-code op follow-up is
  select(REDCapID)

# Stap 2: Identificeer patiënten met een statine (C10AA) in de baseline-periode
baseline_statine <- baseline_data %>%
  filter(grepl("^C10AA", ATC)) %>%
  distinct(REDCapID)

# Stap 3: Identificeer patiënten met een andere lipidenverlager (C10A maar geen C10AA) in de baseline-periode
baseline_other_lipid <- baseline_data %>%
  filter(grepl("^C10A[^A]", ATC)) %>%
  distinct(REDCapID)

# Stap 4: Combineer de criteria
result_regel11 <- baseline_statine %>%
  inner_join(baseline_other_lipid, by = "REDCapID") %>%
```

```
  inner_join(followup_data, by = "REDCapID") %>%
  select(REDCapID) %>%
  distinct()

# Print het eindresultaat
print(result_regel11)
## # A tibble: 1 × 1
##   REDCapID
##   <chr>
## 1 8006-9
# APARTE CODE CHUNK VOOR REGEL12
# Stap 2: Selecteer patiënten die een statine (C10AA) én een andere lipidenverlager (C10A[^A]) op baseline hebben
baseline_both <- inner_join(baseline_statine, baseline_other_lipid, by = "REDCapID")

# Stap 3: Identificeer patiënten die een vaste combinatie (C10BA) in de follow-up hebben
followup_fixed_combo <- data %>%
  filter(Afleverdatum >= followup_start & Afleverdatum <= followup_end, grepl("^C10BA", ATC)) %>%
  distinct(REDCapID)

# Stap 4: Tel het aantal unieke ATC-codes die beginnen met "C10A" in de follow-upperiode
followup_unique_atc <- data %>%
  filter(Afleverdatum >= followup_start & Afleverdatum <= followup_end, grepl("^C10A", ATC)) %>%
  group_by(REDCapID) %>%
  summarise(unique_atc_count = n_distinct(ATC), .groups = "drop") %>%
  filter(unique_atc_count >= 2) %>%
  select(REDCapID)

# Stap 5: Combineer de criteria
result_regel12 <- baseline_both %>%
  inner_join(
    bind_rows(followup_fixed_combo, followup_unique_atc) %>% distinct(REDCapID),
    by = "REDCapID"
  ) %>%
  select(REDCapID) %>%
  distinct()

# Print het eindresultaat
print(result_regel12)
```

```
## # A tibble: 1 × 1
##   REDCapID
##   <chr>
## 1 8003-10
# Controleer per ID welke regels van toepassing zijn
results <- data %>%
 group_by(REDCapID) %>%
 summarize(
  # Regel 1: >2 lipidenverlagers op baseline
  regel1 = (
   # Voorwaarde 1: Minstens 3 unieke ATC-codes die starten met "C10A" in de baselineperiode
   (data %>%
     filter(REDCapID == first(REDCapID),
         Afleverdatum >= baseline_start & Afleverdatum <= baseline_end,
         grepl("^C10A", ATC)) %>%
     distinct(ATC) %>%
     nrow()) >= 3
  ) | (
   # Voorwaarde 2: Minstens één "C10BA" én minstens één "C10A" recept in baselineperiode
   any(grepl("^C10BA", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
   any(grepl("^C10A", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end)
  ),

  # Regel 2: Stop statine monotherapie
  regel2 = any(grepl("^C10AA", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
       !any(grepl("^C10A[^A]", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
       !any(grepl("^C10", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end),

  # Regel 3: Statine op baseline en follow-up equipotentie moet berekend worden
  regel3 = any(grepl("^C10AA", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
       !any(grepl("^C10A[^A]", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
       any(grepl("^C10AA", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end) &
       !any(grepl("^C10A[^A]", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end),

  # Regel 4: statine mono op baseline maar switch of toevoeging op FU
  regel4 = any(grepl("^C10AA", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
       !any(grepl("^C10A[^A]", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
       (
```

```
        any(grepl("^C10A[B-DX]", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end) |
        any(grepl("^C10BA", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end) |
        (data %>%
          filter(REDCapID == first(REDCapID),
                 Afleverdatum >= followup_start & Afleverdatum <= followup_end,
                 grepl("^C10A", ATC)) %>%
          distinct(ATC) %>%
          nrow()) > 1
      ),

# Regel 6: Niet-statine mono, GEEN lipidenverlager op FU (Stop)
#regel6 = any(grepl("^C10A[B-DX]", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
#    !any(grepl("^C10", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end) &
 #(
     # Tel het aantal unieke ATC's die met C10AB, C10AC, C10AD of C10AX beginnen in de baselineperiode
 #    (data %>%
 #      filter(REDCapID == first(REDCapID),
 #             Afleverdatum >= baseline_start & Afleverdatum <= baseline_end,
 #             grepl("^C10A[B-DX]", ATC)) %>%
 #      distinct(ATC) %>%
 #      nrow()) == 1
 # ) &
 #(
     # Controleer dat er in de baseline GEEN andere ATC-codes zijn die starten met C10
 # !(data %>%
 #    filter(REDCapID == first(REDCapID),
 #           Afleverdatum >= baseline_start & Afleverdatum <= baseline_end,
 #           grepl("^C10", ATC)) %>%
 #    distinct(ATC) %>%
 #    nrow()) > 1
 #),

# Regel 7: Combinatiepreparaat op baseline, op FU niets
regel7 = any(grepl("^C10BA", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
      !any(grepl("^C10", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end),

# Regel 8: Combinatiepreparaat op baseline, op FU 1 lipidenverlager
regel8 = any(grepl("^C10BA", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
```

```
        any(grepl("^C10A", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end),

# Regel 9: Combinatiepreparaat op baseline, op FU ook (of losse combi)
 regel9 = any(grepl("^C10BA", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
 (
      any(grepl("^C10BA", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end) |
      (
        # Tel het aantal unieke ATC-codes die starten met "C10A" in de follow-upperiode
        (data %>%
          filter(REDCapID == first(REDCapID),
                 Afleverdatum >= followup_start & Afleverdatum <= followup_end,
                 grepl("^C10A", ATC)) %>%
          distinct(ATC) %>%
          nrow()) >= 2
      )
    ),

 # Regel 10: statine + andere lipidenverlager op baseline naar totale stop lipidenverlagers op FU
 regel10 = any(grepl("^C10AA", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
        any(grepl("^C10A[^A]", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
        !any(grepl("^C10", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end),

# Regel 11: statine + andere lipidenverlager op baseline naar 1 unieke C10A op FU
#regel11 = any(grepl("^C10AA", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
 #        any(grepl("^C10A[^A]", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
  #       any(grepl("^C10A", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end) &
   #      all(duplicated(grep("^C10A", ATC[Afleverdatum >= followup_start & Afleverdatum <= followup_end],
    #     value = TRUE))),

# Regel 12: statine + andere lipidenverlager op baseline naar vaste/losse combi op FU
#regel12 = any(grepl("^C10AA", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
 #        any(grepl("^C10A[^A]", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
  #(
   #     any(grepl("^C10BA", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end) |
    #    (
          # Tel het aantal unieke ATC-codes die starten met "C10A" in de follow-upperiode
     #     (data %>%
      #      filter(REDCapID == first(REDCapID),
```

```
      #          Afleverdatum >= followup_start & Afleverdatum <= followup_end,
       #         grepl("^C10A", ATC)) %>%
        #   distinct(ATC) %>%
         #  nrow()) >= 2
       #)
      #),

 # Regel 13: losse combi 2 NIET-statines op baseline, geen lipidenverlager op FU
 regel13 = n_distinct(ATC[grepl("^C10A[^A]", ATC) & Afleverdatum >= baseline_start &
                    Afleverdatum <= baseline_end]) >= 2 &
        !any(grepl("^C10", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end),

 # Regel 14: losse combi 2 NIET-statines op baseline, 1 unieke C10A op FU
 regel14 = n_distinct(ATC[grepl("^C10A[^A]", ATC) & Afleverdatum >= baseline_start &
                    Afleverdatum <= baseline_end]) >= 2 &
        n_distinct(ATC[grepl("^C10A", ATC) & Afleverdatum >= followup_start &
                    Afleverdatum <= followup_end]) == 1,

 # Regel 15: losse combi 2 NIET-statines op baseline, losse combi op FU
 regel15 = n_distinct(ATC[grepl("^C10A[^A]", ATC) & Afleverdatum >= baseline_start &
                    Afleverdatum <= baseline_end]) >= 2 &
        ((n_distinct(ATC[grepl("^C10A", ATC) & Afleverdatum >= followup_start &
                    Afleverdatum <= followup_end]) > 1) |
        any(grepl("^C10BA", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end)),




) %>%
mutate(
  classification = case_when(
    regel1 ~ "Handmatig te beoordelen",
    regel2 ~ "Stop",
    regel3 ~ "Equipotentie berekenen",
    regel4 ~ "Geen mindering",
    #regel6 ~ "Stop",
    regel7 ~ "Stop",
    regel8 ~ "Stop",
    regel9 ~ "Handmatig te beoordelen",
```

```
    regel10 ~ "Stop",
    #regel11 ~ "Stop",
    #regel12 ~ "Handmatig te beoordelen",
    regel13 ~ "Stop",
    regel14 ~ "Stop",
    regel15 ~ "Handmatig te beoordelen",
    TRUE ~ "n.v.t."
  )
 )
#inpassen van regel5
results <- results %>%
 mutate(regel5 = REDCapID %in% result_regel5$REDCapID) %>%
 relocate(regel5, .after = regel4)  # Zorgt ervoor dat regel5 na regel4 komt

results <- results %>%
 mutate(classification = ifelse(regel5, "Handmatig te beoordelen", classification))
#inpassen van regel6
results <- results %>%
 mutate(regel6 = REDCapID %in% result_regel6$REDCapID) %>%
 relocate(regel6, .after = regel5)  # Zorgt ervoor dat regel6 na regel5 komt

results <- results %>%
 mutate(classification = ifelse(regel6, "Stop", classification))
#inpassen van regel11
results <- results %>%
 mutate(regel11 = REDCapID %in% result_regel11$REDCapID) %>%
 relocate(regel11, .after = regel10)  # Zorgt ervoor dat regel11 na regel10 komt

results <- results %>%
 mutate(classification = ifelse(regel11, "Stop", classification))
#inpassen van regel12
results <- results %>%
 mutate(regel12 = REDCapID %in% result_regel12$REDCapID) %>%
 relocate(regel12, .after = regel11)  # Zorgt ervoor dat regel11 na regel10 komt

results <- results %>%
 mutate(classification = ifelse(regel12, "Handmatig te beoordelen", classification))
# Stap 1: Maak een equipotentie tabel aan
```

```
equipotentie_tabel <- tibble::tibble(
 ATC = c("C10AA05", "C10AA07", "C10AA05", "C10AA07", "C10AA05", "C10AA07", "C10AA01",
         "C10AA03", "C10AA04", "C10AA05", "C10AA07", "C10AA01", "C10AA03", "C10AA04",
         "C10AA01", "C10AA03", "C10AA04", "C10AA03"),
 sterkte = c(80, 40, 40, 20, 20, 10, 40,
             80, 80, 10, 5, 20, 40, 40,
             10, 20, 20, 10),
 equivalentiewaarde = c(4, 4, 2, 2, 1, 1, 1,
                        1, 1, 0.5, 0.5, 0.5, 0.5, 0.5,
                        0.25, 0.25, 0.25, 0.125)
)
# Stap 2: Filter IDs waarvoor regel2 TRUE is
ids_regel3 <- results %>%
 filter(regel3) %>%
 pull(REDCapID)
equipotentievergelijkingen <- data %>%
 # Filter alleen de rijen waarbij ATC begint met "C10" en IDs waarvoor regel3 TRUE is
 filter(REDCapID %in% ids_regel3 & str_starts(ATC, "C10")) %>%
 mutate(
  # Extracteer sterkte uit "Preparaatnaam" kolom
  sterkte = as.numeric(str_extract(Preparaatnaam, "\\d+(?=MG)"))
 ) %>%
 left_join(equipotentie_tabel, by = c("ATC" = "ATC", "sterkte" = "sterkte")) %>%
 group_by(REDCapID) %>%
 summarise(
  # Selecteer de laatste equivalentiewaarde voor baseline
  equivalentiewaarde_baseline = last(na.omit(equivalentiewaarde[Afleverdatum <= baseline_end])),
  # Selecteer de laatste equivalentiewaarde voor follow-up
  equivalentiewaarde_followup = last(na.omit(equivalentiewaarde[Afleverdatum <= followup_end]))
 ) %>%
 mutate(
  classificatie = case_when(
   equivalentiewaarde_baseline > equivalentiewaarde_followup ~ "gereduceerd",
   equivalentiewaarde_baseline < equivalentiewaarde_followup ~ "toegenomen",
   equivalentiewaarde_baseline == equivalentiewaarde_followup ~ "gelijk",
   TRUE ~ NA_character_ # Voor eventuele NA-waarden
  )
 )
```

```
results_na_eqptver <- results %>%
 left_join(equipotentievergelijkingen %>% select(REDCapID, nieuwe_classificatie = classificatie), by = "REDCapID") %>%
 mutate(
  classification = ifelse(classification == "Equipotentie berekenen", nieuwe_classificatie, classification)
 ) %>%
 select(-nieuwe_classificatie)  # Verwijder de tijdelijke kolom
resultaten_per_regel <- colSums(sapply(results_na_eqptver[, 2:16], as.numeric), na.rm = TRUE)
print(resultaten_per_regel)
##  regel1  regel2  regel3  regel4  regel5  regel6  regel7  regel8  regel9 regel10
##      0      3     43      0      4      1      0      1      0      0
## regel11 regel12 regel13 regel14 regel15
##      1      1      0      0      1
table(results_na_eqptver$classification)
##
##              gelijk Handmatig te beoordelen              n.v.t.
##                  42                   6                  13
##                Stop           toegenomen
##                   6                   1
# Bekijk het resultaat
equipotentievergelijkingen
## # A tibble: 43 × 4
##    REDCapID equivalentiewaarde_baseline equivalentiewaarde_follo…¹ classificatie
##    <chr>                        <dbl>                 <dbl> <chr>
##  1 8003-1                           2                     2   gelijk
##  2 8003-2                           1                     1   gelijk
##  3 8003-4                           2                     2   gelijk
##  4 8003-5                           1                     1   gelijk
##  5 8003-6                         0.5                   0.5 gelijk
##  6 8003-7                           2                     2   gelijk
##  7 8003-8                           2                     2   gelijk
##  8 8003-9                           2                     2   gelijk
##  9 8006-2                         0.5                   0.5 gelijk
## 10 8006-4                           1                     1   gelijk
## # ℹ 33 more rows
## # ℹ abbreviated name: ¹equivalentiewaarde_followup
# Maak een object voor "laatste baseline recepten"
laatste_baselinerecepten <- results %>%
 # Filter op REDCapID waarvoor regel2 TRUE is
```

```
  filter(regel3 == TRUE) %>%
  # Selecteer alleen de REDCapID's van interesse
  select(REDCapID) %>%
  # Voeg deze REDCapID's samen met het data-object
  inner_join(data, by = "REDCapID") %>%
  # Filter op regels waar ATC begint met "C10" en Afleverdatum <= baseline_end
  filter(str_starts(ATC, "C10"), Afleverdatum <= baseline_end) %>%
  # Groepeer per REDCapID
  group_by(REDCapID) %>%
  # Selecteer de regel met de Afleverdatum die het dichtst bij baseline_end ligt
  slice_min(baseline_end - Afleverdatum, with_ties = FALSE) %>%
  # Selecteer de relevante kolommen
  select(REDCapID, ATC, Afleverdatum, Preparaatnaam, baseline_end) %>%
  # Maak er een data frame van
  ungroup()

# Inspecteer de resultaten
print(laatste_baselinerecepten)
## # A tibble: 43 × 5
##    REDCapID ATC     Afleverdatum Preparaatnaam              baseline_end
##    <chr>    <chr>   <date>       <chr>                      <date>
##  1 8003-1   C10AA05 2023-12-08   ATORVASTATINE TABL OMH 40MG 2024-01-03
##  2 8003-2   C10AA05 2024-02-06   ATORVASTATINE TABL OMH 20MG 2024-02-07
##  3 8003-4   C10AA05 2023-12-01   ATORVASTATINE TABL OMH 40MG 2024-01-02
##  4 8003-5   C10AA07 2024-01-23   ROSUVASTATINE TABL OMH 10MG 2024-01-24
##  5 8003-6   C10AA01 2023-10-26   SIMVASTATINE TABL OMH 20MG  2024-01-09
##  6 8003-7   C10AA07 2024-03-05   ROSUVASTATINE TABL OMH 20MG 2024-03-12
##  7 8003-8   C10AA05 2024-01-19   ATORVASTATINE TABL OMH 40MG 2024-03-19
##  8 8003-9   C10AA05 2024-02-09   ATORVASTATINE TABL OMH 40MG 2024-05-01
##  9 8006-2   C10AA03 2024-01-29   PRAVASTATINE TABL 40MG      2024-02-26
## 10 8006-4   C10AA05 2024-03-04   ATORVASTATINE TABL OMH 20MG 2024-03-04
## # ℹ 33 more rows
# sterkte extraheren uit Preperaatnaam
laatste_baselinerecepten$sterkte <- as.numeric(str_extract(laatste_baselinerecepten$Preparaatnaam, "\\d+(?=MG)"))
# Maak een object voor "laatste followuprecepten"
laatste_followuprecepten <- results %>%
  # Filter op REDCapID waarvoor regel2 TRUE is
  filter(regel3 == TRUE) %>%
```

```
  # Selecteer alleen de REDCapID's van interesse
  select(REDCapID) %>%
  # Voeg deze REDCapID's samen met het data-object
  inner_join(data, by = "REDCapID") %>%
  # Filter op regels waar ATC begint met "C10" en Afleverdatum <= baseline_end
  filter(str_starts(ATC, "C10"), Afleverdatum <= followup_end) %>%
  # Groepeer per REDCapID
  group_by(REDCapID) %>%
  # Selecteer de regel met de Afleverdatum die het dichtst bij baseline_end ligt
  slice_min(followup_end - Afleverdatum, with_ties = FALSE) %>%
  # Selecteer de relevante kolommen
  select(REDCapID, ATC, Afleverdatum, Preparaatnaam, followup_end) %>%
  # Maak er een data frame van
  ungroup()

laatste_followuprecepten$sterkte <- as.numeric(str_extract(laatste_followuprecepten$Preparaatnaam, "\\d+(?=MG)"))

# Inspecteer de resultaten
print(laatste_followuprecepten)
## # A tibble: 43 × 6
##    REDCapID ATC     Afleverdatum Preparaatnaam            followup_end sterkte
##    <chr>    <chr>   <date>       <chr>                    <date>       <dbl>
##  1 8003-1   C10AA05 2024-06-06   ATORVASTATINE TABL OMH 40… 2024-09-02      40
##  2 8003-2   C10AA05 2024-10-01   ATORVASTATINE TABL OMH 20… 2024-10-07      20
##  3 8003-4   C10AA05 2024-08-29   ATORVASTATINE TABL OMH 40… 2024-09-01      40
##  4 8003-5   C10AA07 2024-09-17   ROSUVASTATINE TABL OMH 10… 2024-09-23      10
##  5 8003-6   C10AA01 2024-07-19   SIMVASTATINE TABL OMH 20MG 2024-09-08      20
##  6 8003-7   C10AA07 2024-10-29   ROSUVASTATINE TABL OMH 20… 2024-11-10      20
##  7 8003-8   C10AA05 2024-11-12   ATORVASTATINE TABL OMH 40… 2024-11-17      40
##  8 8003-9   C10AA05 2024-11-07   ATORVASTATINE TABL OMH 40… 2024-12-30      40
##  9 8006-2   C10AA03 2024-10-14   PRAVASTATINE TABL 40MG     2024-10-26      40
## 10 8006-4   C10AA05 2024-10-28   ATORVASTATINE TABL OMH 20… 2024-11-02      20
## # ℹ 33 more rows
```

Appendix 2: blood glucose lowering agents

Appendix 2.1 Overview of all blood glucose lowering agents in the Netherlands

The overview in the table below shows which agents with corresponding ATC-code are available on the Dutch market. Agents having an ATC-code according to the WHO classification that are not included in the table, are not available on the Dutch market.

Table A.2.1 Overview of all blood glucose lowering agents that are available on the Dutch market

Main group	Subgroup	Products in the Netherlands	Corresponding ATC-code
Insulins and analogues, A10A			
	(…) for injection, fast-acting, A10AB	Insulin (human)	A10AB01
		Insulin lispro	A10AB04
		Insulin aspart	A10AB05
		Insulin glulisine	A10AB06
	(…) for injection, intermediate-acting, 10AC	Insulin (human)	A10AC01
	(…)for injection, intermediate- or long-acting combined with fast-acting, 10AD	Insulin (human)/insulin, isofaan	A10AD01
		insulin lispro/insulin lispro protamine	A10AD04
		insulin aspart/insulin aspart protamine	A10AD05
		insulin degludec/insulin aspart	A10AD06
	(…) for injection, long-acting, 10AE	insulin glargine	A10AE04
		insulin detemir	A10AE05
		insulin degludec	A10AE06
		insulin glargine/ lixisenatide	A10AE54
		insulin degludec/ liraglutide	A10AE56
	(…) for inhalation, 10AF	*None on the Dutch market*	
Blood glucose lowering drugs, excl. insulins, A10B			
	Biguanides, A10BA	Metformin	A10BA02
	Sulfonylureas, A10BB	Tolbutamide	A10BB03
		Gliclazide	A10BB09
		Glimepiride	A10BB12
	Sulfonamides (heterocyclic), A10BC	None	

	Combinations of oral blood glucose lowering drugs, A10BD	Metformin/sulfonylureas	A10BD02
		pioglitazone/metformin	A10BD05
		sitagliptin/metformin	A10BD07
		vildagliptin/metformin	A10BD08
		linagliptin/metformin	A10BD11
		dapagliflozin/metformin	A10BD15
		empagliflozin/metformin	A10BD20
		ertugliflozin/sitagliptine	A10BD24
	A10BE non-existing		
	Alpha glucosidase inhibitors, A10BF	Acarbose	A10BF01
	Thiazolidinediones, A10BG	Pioglitazone	A10BG03
	DPP-4 (dipeptidyl peptidase 4) inhibitors, A10BH	sitagliptin	A10BH01
		Vildagliptin	A10BH02
		Saxagliptin	A10BH03
		Linagliptin	A10BH05
	Glucagon-like peptide-1 (GLP-1) analogues, A10BJ	Liraglutide	A10BJ02
		Dulaglutide	A10BJ05
		Semaglutide	A10BJ06
		Lixisenatide	A10BJ03
	Sodium-glucose co-transporter 2 (SGLT2) inhibitors, A10BK	Dapagliflozin	A10BK01
		Canagliflozine	A10BK02
		Empagliflozin	A10BK03
		Ertugliflozin	A10BK04
	Other blood glucose lowering drugs, excl. insulins, A10BX	Repaglinide	A10BX02
		Tirzepatide	A10BX16
Other drugs used in diabetes, A10X			
	Aldose reductase inhibitors, A10XA	*None on the Dutch market*	
	Other drugs used in diabetes, A10XX	*None on the Dutch market*	

Appendix 2.2 Flowchart with transitions of blood glucose lowering agents

In the figure below, the complete flowchart with transitions of blood glucose lowering agents is shown, subdivided in figures A-D. These subfigures are enlarged shown on the next pages (Figure A.2.2.2 till Figure A.2.2.5) to improve the readability. Green rectangles indicate a form of de-intensification, grey rectangles are no de-intensifications and purple rectangles indicate individual assessment.

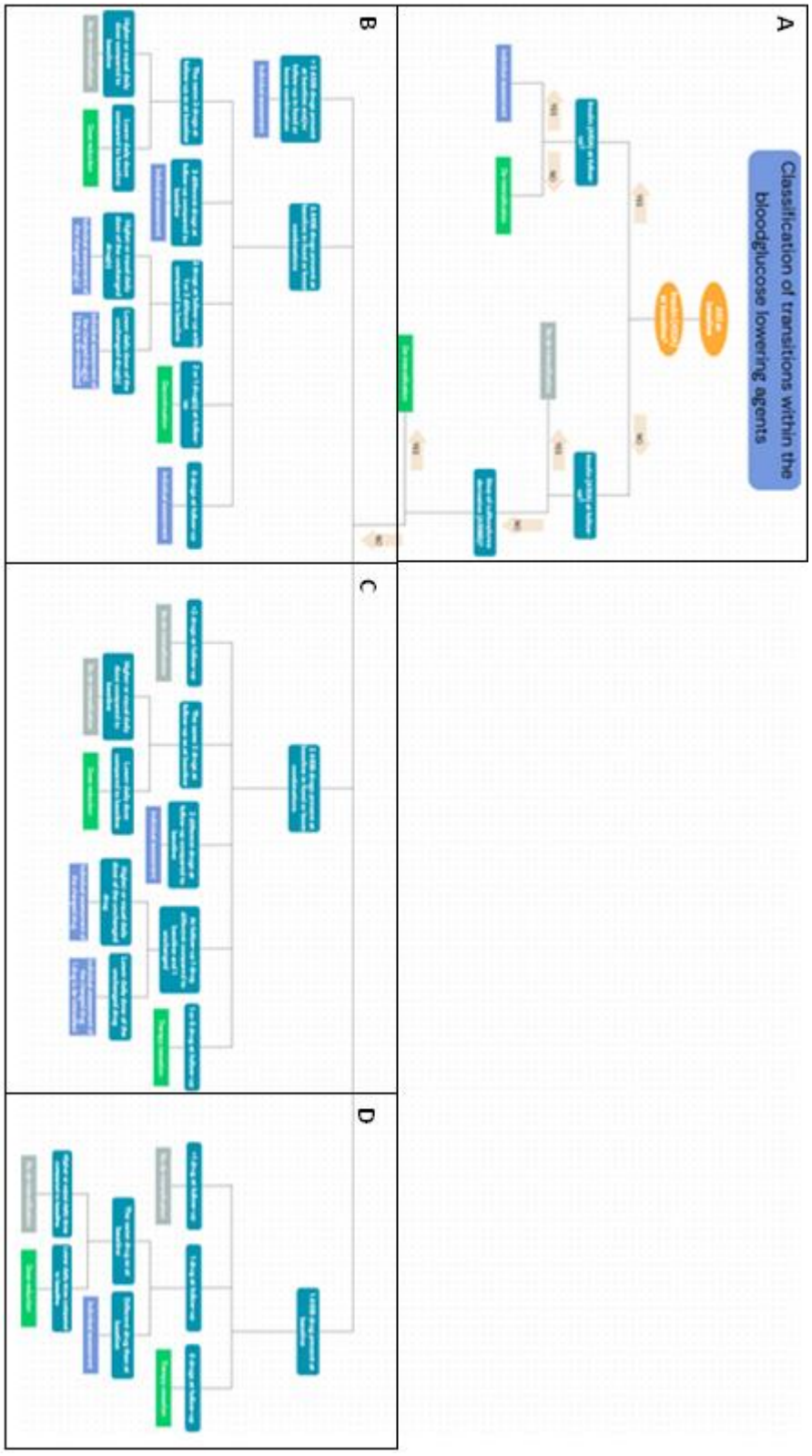

Figure A.2.2.1 Flowchart divided in sub-figures A-D

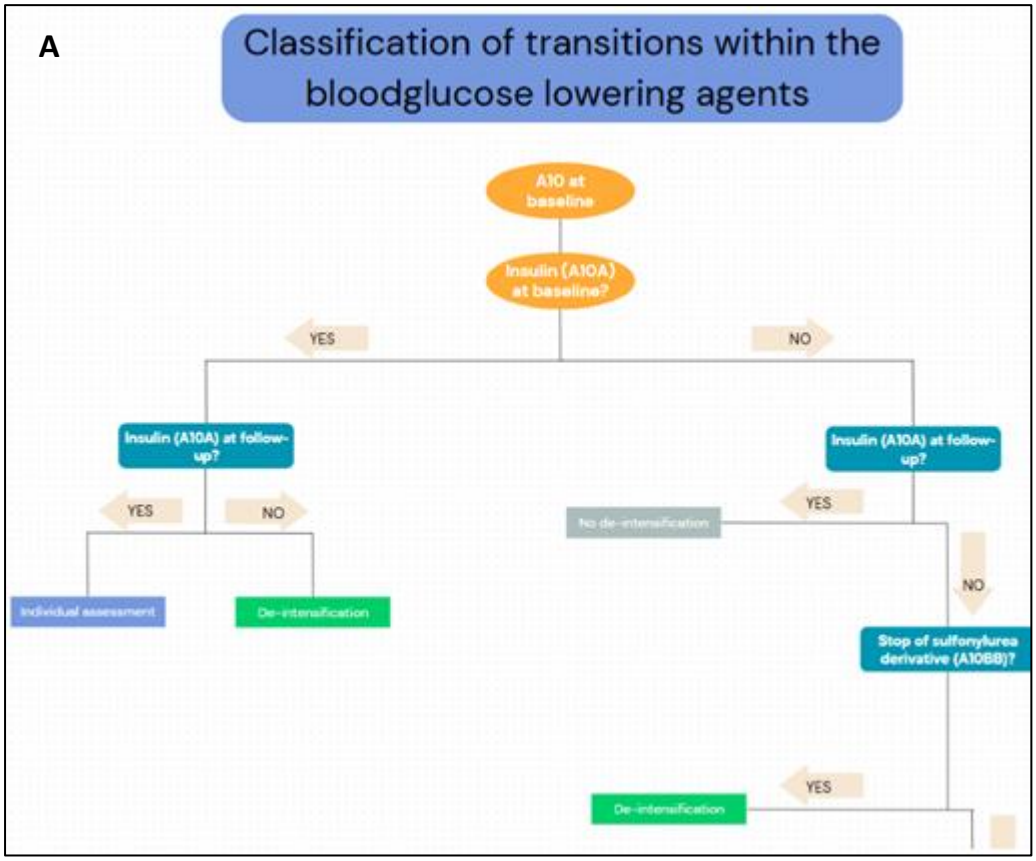

Figure A.2.2.2 Enlargement of part A

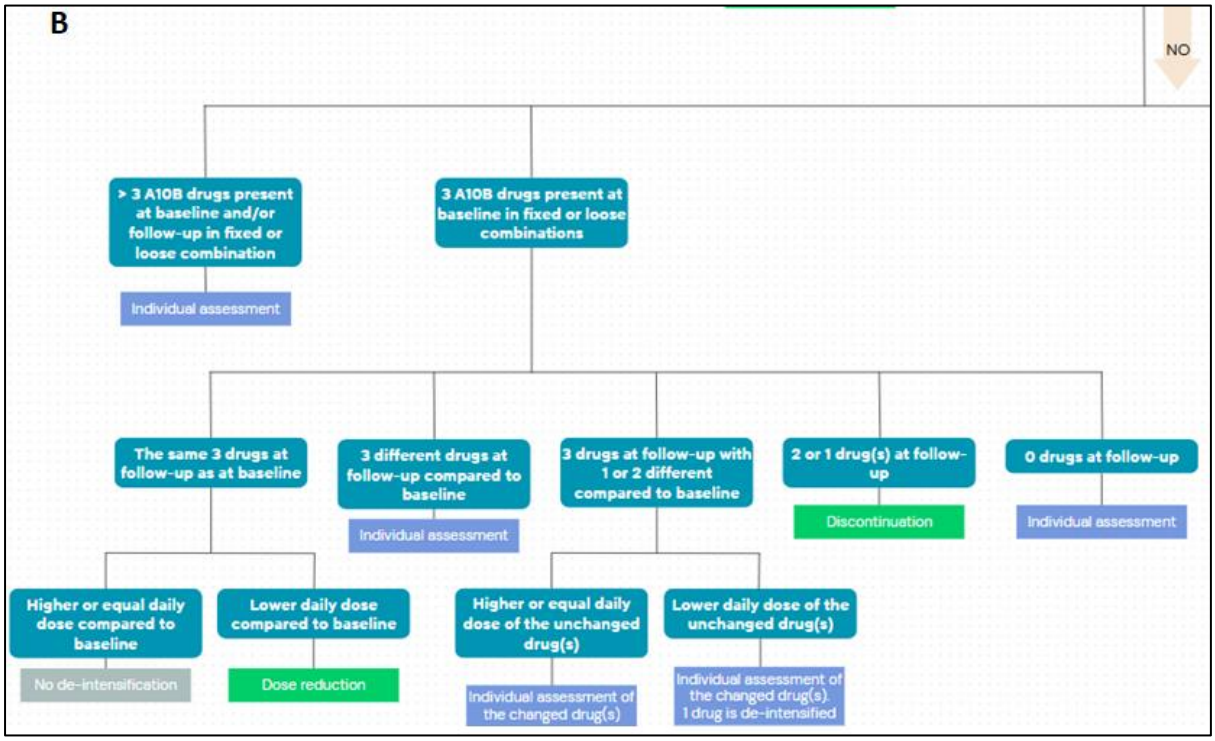

Figure A.2.2.3 Enlargement of part B

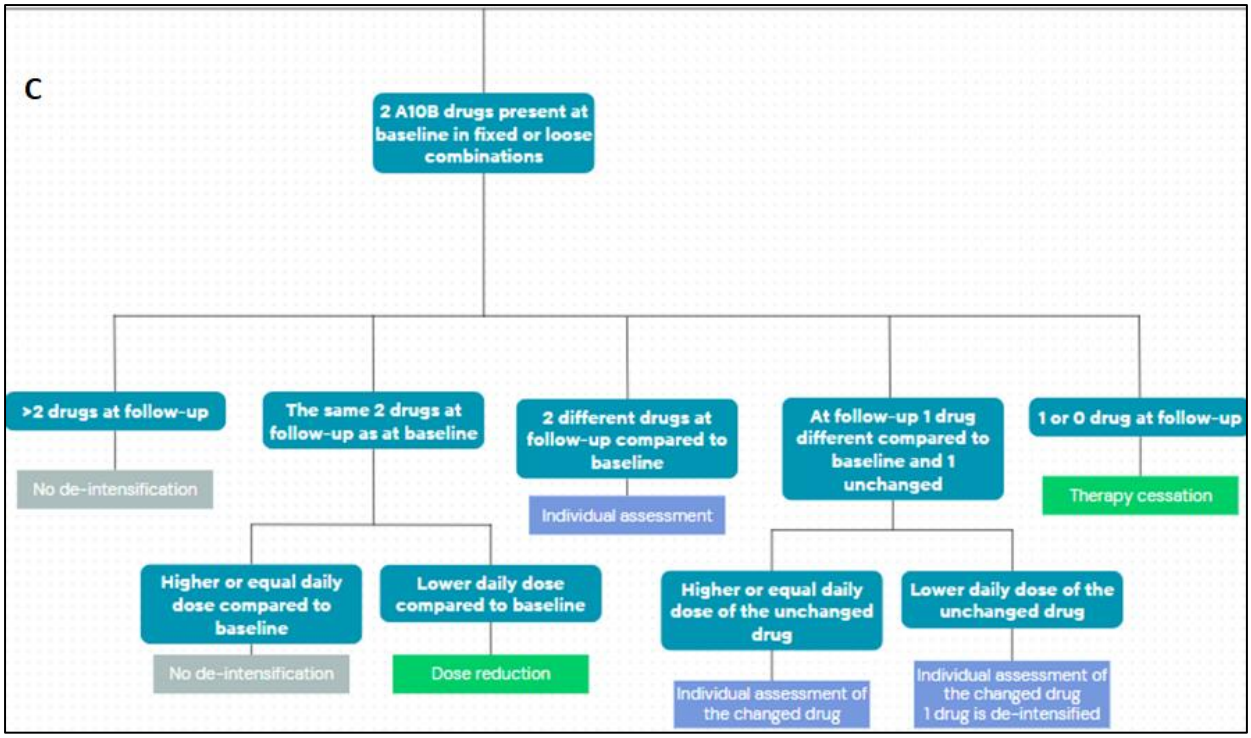

Figure A.2.2.4 Enlargement of part C

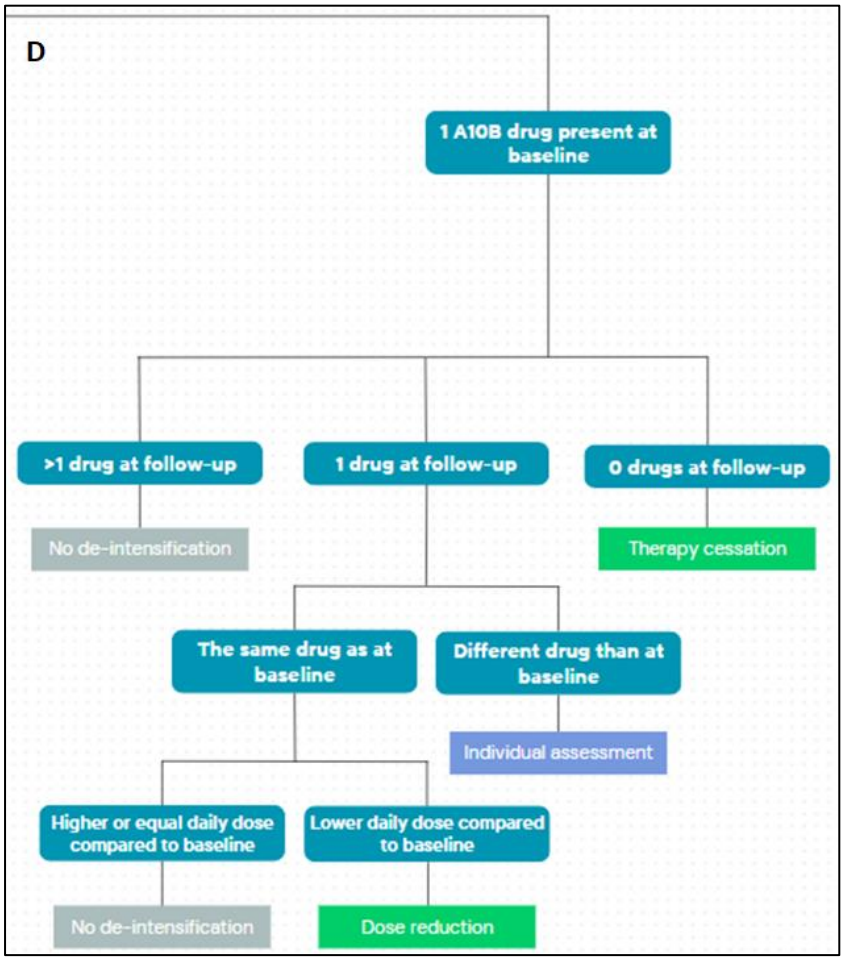

Figure A.2.2.5 Enlargement of part D

Appendix 2.3 Computerized algorithm for the classification of transitions in the use of blood glucose lowering agents

Below the script is placed as it was used in the programmes R and Rstudio. This final version of the algorithm was validated and appeared to make no misclassifications for the transitions that were validated.

antidiabetica

Peter Stuijt
2025-03-04

```
#setwd("//zkh/appdata/research/KFF/CO-DEPRESCRIBE_ra/R")
#install.packages("knitr")
#install.packages("dplyr")
#install.packages("lubridate")
#install.packages("stringr")
#install.packages("tidyr")
#install.packages("purrr")
```

Laad de nodige libraries

```
library(readxl)
library(dplyr)
##
## Attaching package: 'dplyr'
## The following objects are masked from 'package:stats':
##
##     filter, lag
## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union
library(lubridate)
##
## Attaching package: 'lubridate'
## The following objects are masked from 'package:base':
##
##     date, intersect, setdiff, union
library(stringr)
library(tidyr)
library(purrr)
```

```
library(writexl)
```

Dataset laden

```
data <- read_excel("//zkh/appdata/research/KFF/CO-DEPRESCRIBE_ra/R/data/extr_uitgiftes_combi04022025.xlsx")
# Voeg periodes toe aan de dataset, en zet afleverdatum om naar het juiste format
data <- data %>%
  mutate(Afleverdatum = as.Date(as.character(Afleverdatum)),
         indexdatum = as.Date(indexdatum),
         baseline_start = indexdatum - days(120),
         baseline_end = indexdatum - days(1),
         followup_start = indexdatum + days(123),
         followup_end = indexdatum + days(242))
# Controleer per ID welke regels van toepassing zijn
results_1st_round <- data %>%
  group_by(REDCapID) %>%
  summarize(

# Regel 1: Stop insuline
    regel1 = any(grepl("^A10A", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
           !any(grepl("^A10A", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end),

# Regel 2: insuline gecontinueerd
    regel2 = any(grepl("^A10A", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
           any(grepl("^A10A", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end),

# Regel 3: niet-insuline therapie op baseline, wel insuline op followup
    regel3 = any(grepl("^A10B", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
           !any(grepl("^A10A", ATC) & Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) &
           any(grepl("^A10A", ATC) & Afleverdatum >= followup_start & Afleverdatum <= followup_end),

  ) %>%
  mutate(
    classification = case_when(
      regel1 ~ "Stop",
      regel2 ~ "Handmatig te beoordelen",
      regel3 ~ "Geen mindering",
         TRUE ~ "n.v.t."
    )
```

```
 )
#Regel 4
# 1. Filteren van de dataset op de baseline- en followupperiodes
data_baseline <- data %>%
 filter(Afleverdatum >= baseline_start & Afleverdatum <= baseline_end)

data_followup <- data %>%
 filter(Afleverdatum >= followup_start & Afleverdatum <= followup_end)

# 2. Functie om de somscore per periode te berekenen
calculate_somscore <- function(df) {
 df %>%
  filter(str_starts(ATC, "A10B")) %>%  # Selecteer alleen A10B-medicatie
  group_by(REDCapID) %>%
  summarise(
   unique_A10BD = n_distinct(ATC[str_starts(ATC, "A10BD")]),  # A10BD tellen
   unique_A10B_nonBD = n_distinct(ATC[str_starts(ATC, "A10B") & !str_starts(ATC, "A10BD")]),  # A10B maar geen A10BD
   somscore = (unique_A10BD * 2) + unique_A10B_nonBD  # Somscore berekening
  )
}

# 3. Pas de functie toe op baseline en follow-up data
baseline_scores <- calculate_somscore(data_baseline) %>%
 rename(somscore_baseline = somscore)

followup_scores <- calculate_somscore(data_followup) %>%
 rename(somscore_followup = somscore)

# 4. Combineer beide scores per patiënt
final_scores <- full_join(baseline_scores, followup_scores, by = "REDCapID")
# Voeg final_scores toe aan results_1st_round
results_1st_round <- results_1st_round %>%
 left_join(final_scores, by = "REDCapID") %>%
 mutate(
  regel4 = if_else(
   (somscore_baseline > 3 | somscore_followup > 3) & !is.na(somscore_baseline) & !is.na(somscore_followup),
   TRUE,
   FALSE
```

```
  ),
  classification = if_else(regel4 == TRUE, "Handmatig te beoordelen", classification)  # Update classification
 )

# Controleer welke kolommen er daadwerkelijk zijn
print(colnames(results_1st_round))
##  [1] "REDCapID"          "regel1"            "regel2"
##  [4] "regel3"            "classification"    "unique_A10BD.x"
##  [7] "unique_A10B_nonBD.x" "somscore_baseline"   "unique_A10BD.y"
## [10] "unique_A10B_nonBD.y" "somscore_followup"   "regel4"
# Selecteer alle kolommen, behalve de ongewenste (alleen als ze bestaan)
results_1st_round <- results_1st_round %>%
 select(-any_of(c("somscore_baseline", "somscore_followup",
                  "unique_A10BD.x", "unique_A10BD.y",
                  "unique_A10B_nonBD.x", "unique_A10B_nonBD.y")))

# Kolom "regel4" verplaatsen direct achter "regel3"
results_1st_round <- results_1st_round %>%
 relocate(regel4, .after = regel3)
#Regel 5
# 5.1 Baseline-data filteren
baseline_check <- data %>%
 filter(Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) %>%
 group_by(REDCapID) %>%
 summarise(
  has_A10BB_A10BD02 = any(str_starts(ATC, "A10BB") | str_starts(ATC, "A10BD02"))  # Heeft A10BB of A10BD02?
 ) %>%
 mutate(regel5_baseline = has_A10BB_A10BD02)  # Voldoet aan baseline-voorwaarde?

# 5.2. Followup-data filteren
followup_check <- data %>%
 filter(Afleverdatum >= followup_start & Afleverdatum <= followup_end) %>%
 group_by(REDCapID) %>%
 summarise(
  has_A10BB_A10BD02 = any(str_starts(ATC, "A10BB") | str_starts(ATC, "A10BD02"), na.rm = TRUE), # Check op A10BB of
A10BD02
  has_other_A10B = any(str_starts(ATC, "A10B") & !str_starts(ATC, "A10BB") & !str_starts(ATC, "A10BD02"), na.rm = TRUE
) # Check op andere A10B
```

```
 ) %>%
 mutate(
  has_A10BB_A10BD02 = replace_na(has_A10BB_A10BD02, FALSE),  # Zet NA om naar FALSE
  has_other_A10B = replace_na(has_other_A10B, FALSE),  # Zet NA om naar FALSE
  has_A10B_not_BB_BD02 = has_other_A10B & !has_A10BB_A10BD02, # Correcte regel 5 check
  regel5_followup = has_A10B_not_BB_BD02
 )

# 5.3. Combineer baseline- en followup-checks
regel5_data <- full_join(baseline_check, followup_check, by = "REDCapID") %>%
 mutate(regel5 = regel5_baseline & regel5_followup) %>%
 select(REDCapID, regel5)  # Alleen REDCapID en regel5 overhouden

# 5.4. Voeg regel5 toe aan results_1st_round en update "classification"
results_1st_round <- results_1st_round %>%
 left_join(regel5_data, by = "REDCapID") %>%
 mutate(
  regel5 = replace_na(regel5, FALSE),  # Zet NA om naar FALSE
  classification = if_else(regel5 == TRUE, "Stop", classification)  # Update classification als regel5 TRUE is
 ) %>%
 relocate(regel5, .after = regel4)  # Plaats regel5 direct achter regel4
#tweede ronde voor patiënten waarvoor regels 1 t/m 5 niet gelden:
# 1. Baseline-data per patiënt voorbereiden
baseline_data <- data %>%
 filter(Afleverdatum >= baseline_start & Afleverdatum <= baseline_end) %>%
 group_by(REDCapID) %>%
 summarise(
  unique_A10B_baseline = n_distinct(na.omit(ATC[str_starts(ATC, "A10B")])),  # Aantal unieke A10B-codes
  has_A10BD_baseline = any(str_starts(ATC, "A10BD"), na.rm = TRUE),  # Heeft patiënt A10BD?
  unique_A10BD_baseline = first(na.omit(ATC[str_starts(ATC, "A10BD")])),  # Specifieke A10BD-code
  unique_A10B_value_baseline = as.character(first(na.omit(ATC[str_starts(ATC, "A10B")]))),  # Specifieke A10B-code
  unique_A10BD_value_baseline = as.character(first(na.omit(ATC[str_starts(ATC, "A10BD")]))),

  unique_A10B_excl_A10BD_baseline = list(unique(na.omit(ATC[str_starts(ATC, "A10B") &
                                        !str_starts(ATC, "A10BD")]))),
  # Lijst van unieke A10B excl. A10BD
  unique_A10B_excl_A10BD_baseline_str = if_else( # Voor regel14
   lengths(unique_A10B_excl_A10BD_baseline) > 0,
```

```
    paste(sort(unique(unlist(unique_A10B_excl_A10BD_baseline))), collapse = ","), NA_character_)
 )

# 2. Follow-up-data per patiënt voorbereiden
followup_data <- data %>%
 filter(Afleverdatum >= followup_start & Afleverdatum <= followup_end) %>%
 group_by(REDCapID) %>%
 summarise(
  unique_A10B_followup = n_distinct(na.omit(ATC[str_starts(ATC, "A10B")])),  # Aantal unieke A10B-codes
  has_A10BD_followup = any(str_starts(ATC, "A10BD"), na.rm = TRUE),  # Heeft patiënt A10BD?
  unique_A10BD_followup = first(na.omit(ATC[str_starts(ATC, "A10BD")])),  # Specifieke A10BD-code
  has_A10_followup = any(str_starts(ATC, "A10"), na.rm = TRUE),  # Heeft patiënt een A10-code?
  unique_A10B_value_followup = as.character(first(na.omit(ATC[str_starts(ATC, "A10B")]))),  # Specifieke A10B-code
  unique_A10BD_value_followup = as.character(first(na.omit(ATC[str_starts(ATC, "A10BD")]))),

  unique_A10B_excl_A10BD_followup = list(unique(na.omit(ATC[str_starts(ATC, "A10B") &
                                        !str_starts(ATC, "A10BD")]))),
  # Lijst van unieke A10B excl. A10BD
  unique_A10B_excl_A10BD_followup_str = if_else( # Voor regel14
    lengths(unique_A10B_excl_A10BD_followup) > 0,
    paste(sort(unique(unlist(unique_A10B_excl_A10BD_followup))), collapse = ","), NA_character_)
 )

# 3. Combineer baseline- en follow-up gegevens
combined_data <- full_join(baseline_data, followup_data, by = "REDCapID")

# 4. Voeg REDCapIDs toe aan results_2nd_round
results_2nd_round <- results_1st_round %>%
 filter(regel1 == FALSE & regel2 == FALSE & regel3 == FALSE & regel4 == FALSE & regel5 == FALSE) %>%
 select(REDCapID) %>%
 left_join(combined_data, by = "REDCapID") %>%
 mutate(
  regel6 = (unique_A10B_baseline == 1 & !has_A10BD_baseline & !has_A10_followup),

  regel7 = (unique_A10B_baseline == 1 & !has_A10BD_baseline & (has_A10BD_followup | unique_A10B_followup > 1)),

  regel8 = (unique_A10B_baseline == 1 & !has_A10BD_baseline &
      unique_A10B_followup == 1 & !has_A10BD_followup &
```

```
    !is.na(unique_A10B_value_baseline) & !is.na(unique_A10B_value_followup) &
    unique_A10B_value_baseline != unique_A10B_value_followup),

regel9 = (unique_A10B_baseline == 1 & !has_A10BD_baseline &
        unique_A10B_value_baseline == unique_A10B_value_followup &
        unique_A10B_followup == 1 & !has_A10BD_followup),

regel10 = ((has_A10BD_baseline | unique_A10B_baseline == 2) &
         unique_A10B_followup == 1 & !has_A10BD_followup & !has_A10_followup),

regel11 = ((has_A10BD_baseline | unique_A10B_baseline == 2) & !has_A10_followup),

regel12 = ((has_A10BD_baseline | unique_A10B_baseline == 2) &
         ((unique_A10B_followup == 3 & !has_A10BD_followup) |
          (unique_A10B_followup == 1 & has_A10BD_followup))),

regel13 = case_when(
# Optie (a): A10BD op baseline, of exact 2 unieke A10B zonder A10BD op baseline
(has_A10BD_baseline | unique_A10B_baseline == 2) &
# Optie (b): Exact 2 unieke A10B zonder A10BD in follow-up
unique_A10B_followup == 2 & !has_A10BD_followup &
# Baseline ≠ Follow-up → minstens 1 waarde is veranderd
unique_A10B_excl_A10BD_baseline_str != unique_A10B_excl_A10BD_followup_str ~ TRUE,
# Als er geen verschil is, of de voorwaarden kloppen niet → FALSE
TRUE ~ FALSE),

regel14 = case_when(
# Optie (a): A10BD in baseline & exact dezelfde A10BD in follow-up
!is.na(unique_A10BD_baseline) & unique_A10BD_baseline == unique_A10BD_followup ~ TRUE,
# Optie (b): Twee unieke A10B's excl. A10BD in baseline, die exact hetzelfde zijn in follow-up
lengths(unique_A10B_excl_A10BD_baseline) == 2 &
unique_A10B_excl_A10BD_baseline_str == unique_A10B_excl_A10BD_followup_str &
lengths(unique_A10B_excl_A10BD_followup) == 2 ~ TRUE,

# Standaard: als geen van de condities matcht → FALSE
TRUE ~ FALSE),

regel15 = ((has_A10BD_baseline & unique_A10B_baseline == 2) | unique_A10B_baseline == 3) &
```

```
        !has_A10_followup,

regel16 = ((has_A10BD_baseline & unique_A10B_baseline == 2) | unique_A10B_baseline == 3) &
        (has_A10BD_followup | unique_A10B_followup %in% c(1, 2)),

regel17 = ((has_A10BD_baseline & unique_A10B_baseline >= 2) | unique_A10B_baseline == 3) &
    case_when(
      has_A10BD_baseline ~ (
        has_A10BD_followup & unique_A10B_followup == 1 &
        unique_A10BD_value_baseline != unique_A10BD_value_followup &
        unique_A10B_value_baseline != unique_A10B_value_followup
      ),
      unique_A10B_baseline == 3 ~ (
        !has_A10BD_followup & unique_A10B_followup == 3 &
        !setequal(unique_A10B_value_baseline, unique_A10B_value_followup)
      ),
      TRUE ~ FALSE
    ),

regel18 = (
 # Voor baseline: A10BD aanwezig en een andere unieke A10B of 3 unieke A10B zonder A10BD
 (has_A10BD_baseline & unique_A10B_baseline >= 2) | unique_A10B_baseline == 3
 ) & case_when(
   # Als (a) geldt op baseline
   has_A10BD_baseline & unique_A10B_baseline >= 2 ~ (
     # In de followup: 1 A10BD en 1 A10B, en minstens 1 verschilt van baseline
     unique_A10BD_followup == 1 & unique_A10B_followup == 1 &
       (
         unique_A10BD_value_baseline != unique_A10BD_value_followup |
         unique_A10B_value_baseline != unique_A10B_value_followup
         )
     ),
   # Als (b) geldt op baseline
   unique_A10B_baseline == 3 ~ (
     # In de followup: geen A10BD en precies 3 A10B, waarbij 1 of 2 A10B gewijzigd zijn
     !has_A10BD_followup & unique_A10B_followup == 3 &
       sum(!unique_A10B_value_baseline %in% unique_A10B_value_followup) >= 1
     ),
```

```
    TRUE ~ FALSE
    ),

  regel19 = (
   ((has_A10BD_baseline & unique_A10B_baseline >= 2) | unique_A10B_baseline == 3) &
    case_when(
     has_A10BD_baseline & unique_A10B_baseline >= 2 ~ (
     unique_A10BD_followup == 1 & unique_A10B_followup == 1 &
     unique_A10BD_value_baseline == unique_A10BD_value_followup &
     unique_A10B_value_baseline == unique_A10B_value_followup
    ),
    unique_A10B_baseline == 3 ~ (
     !has_A10BD_followup & unique_A10B_followup == 3 &
     setequal(unique_A10B_value_baseline, unique_A10B_value_followup)
    ),
    TRUE ~ FALSE
   )
  )



) %>%
mutate(
  classification = case_when(
   regel6 ~ "Stop",
   regel7 ~ "Geen mindering",
   regel8 ~ "Handmatig te beoordelen",
   regel9 ~ "Dagdosering vergelijken",
   regel10 ~ "Stop",
   regel11 ~ "Stop",
   regel12 ~ "Geen mindering",
   regel13 ~ "Handmatig te beoordelen",
   regel14 ~ "Dagdosering vergelijken",
   regel15 ~ "Handmatig te beoordelen",
   regel16 ~ "Stop",
   regel17 ~ "Handmatig te beoordelen",
   regel18 ~ "Handmatig te beoordelen",
   regel19 ~ "Dagdosering vergelijken",
   TRUE ~ NA_character_  # Als geen van de regels geldt, blijft classification leeg
```

```
  )
 ) %>%
  relocate(classification, .after = last_col())  # Zorg dat classification de laatste kolom is
# Mergen van de datasets obv REDCapID
results_final <- results_1st_round %>%
  select(REDCapID, regel1:regel5, classification) %>%  # Alleen relevante kolommen uit 1st round
  left_join(
    results_2nd_round %>% select(REDCapID, regel6:regel19, classification),  # Relevante kolommen uit 2nd round
    by = "REDCapID"
  ) %>%
  mutate(
    classification = ifelse(!is.na(classification.y), classification.y, classification.x)  # Update classification indien aanwezig in res
ults_2nd_round
  ) %>%
  select(REDCapID, regel1:regel5, regel6:regel19, classification)  # Selecteer juiste volgorde
results_final <- results_final %>% mutate(across(everything(), ~ replace_na(.x, FALSE)))
resultaten_per_regel <- colSums(sapply(results_final[, 2:20], as.numeric), na.rm = TRUE)
print(resultaten_per_regel)
##  regel1  regel2  regel3  regel4  regel5  regel6  regel7  regel8  regel9 regel10
##      1       4       1       0       1       0       1       0       6       0
## regel11 regel12 regel13 regel14 regel15 regel16 regel17 regel18 regel19
##      0       0       0       3       0       0       0       0       2
table(results_final$classification)
##
## Dagdosering vergelijken          Geen mindering Handmatig te beoordelen
##                      11                       2                       4
##                   n.v.t.                    Stop
##                      49                       2
```

Appendix 2.4 Updated but non-validated decision rules blood glucose lowering agents

Decision rule	Baseline	Follow-up	Classification
0	(-) no A10	Any situation	*Exclude*
1	Any situation with A10A (insulin)	Any situation except for presence of A10A (insulin)	De-intensification (therapy cessation or discontinuation)
2	Any situation with A10A (insulin)	Any situation with A10A (insulin)	Individual assessment
3	Any situation except for presence of A10A (insulin)	Any situation with A10A (insulin)	No de-intensification
4A	>3 A10B present (more drugs than (A10BD + 1 A10B excl. A10BD) or 3 A10B excl. A10BD)	Any situation	Individual assessment
4B	Any situation	>3 A10B present (more drugs than (A10BD + 1 A10B excl. A10BD) or 3 A10B excl. A10BD)	Individual assessment
5	Any situation with A10BB	Any situation without A10BB	De-intensification (therapy cessation or discontinuation)
	When rules 1-5 not apply,	**continue to rules below**	
6	A10B (mono) excl. A10BD	(-)	Therapy cessation
7	A10B (mono) excl. A10BD	2 or 3 A10B (3 A10B excl. A10BD or (A10BD with/without 1 A10B excl. A10BD)	No de-intensification
8	A10B# (mono) excl. A10BD	A10B* excl. A10BD	Individual assessment
9A	A10B# (mono) excl. A10BD	A10B# (mono) excl. A10BD and increased or unchanged daily dose	No de-intensification
9B	A10B# (mono) excl. A10BD	A10B# (mono) excl. A10BD and decreased daily dose	Dose reduction
10	(A10B# + A10B* excl. A10BD) or (A10BD#)	A10B? excl. A10BD	Discontinuation
11	(A10B# + A10B* excl. A10BD) or (A10BD#)	(-)	Therapy cessation
12	(A10B# + A10B* excl. A10BD) or (A10BD#)	3 A10B (3 A10B excl. A10BD or (A10BD + 1 A10B excl. A10BD))	No de-intensification
13	(A10B# + A10B* excl. A10BD) or (A10BD#)	(A10B# + A10B” excl. A10BD) or (A10B^ + A10B” excl. A10BD) or A10BD*	Individual assessment
14A	(A10B# + A10B* excl. A10BD) or (A10BD#)	Identical to baseline (A10B# + A10B* excl. A10BD) or (A10BD#) and unchanged daily dose	No de-intensification
14B	(A10B# + A10B* excl. A10BD) or (A10BD#)	(A10B# + A10B* excl. A10BD) or (A10BD#) but daily dose changed	Individual assessment

15	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD + A10B#)	(-)	Individual assessment
16	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD + A10B#)	(A10B? and/or A10B? excl. A10BD) or A10BD?	Discontinuation
17	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD# + A10B#)	(A10B; + A10B~ + A10B^ excl. A10BD) or (A10BD* +A10B")	Individual assessment
18	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD# + A10B#)	(A10B# + A10B~ + A10B^ excl. A10BD) or (A10B# + A10B* + A10B^ excl. A10BD) or (A10BD^ + A10B#) or (A10BD* + A10B")	Individual assessment
19A	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD# + A10B#)	Identical to baseline (A10B# + A10B* + A10B" excl. A10BD) or (A10BD# + A10B#) and unchanged daily dose	No de-intensification
19B	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD# + A10B#)	(A10B# + A10B* + A10B" excl. A10BD) or (A10BD# + A10B#) but daily dose changed	Individual assessment

Appendix 3: blood pressure lowering agents

Appendix 3.1 Overview of all blood pressure lowering agents in the Netherlands

Table A.3.1 contains an overview of blood pressure lowering agents that are available in the Netherlands. Not all agents possibly lowering blood pressure are included. Agents marked brown/orange are fixed combinations of 2 active pharmaceutical ingredients in one dosage form (i.e. 2 different blood pressure lowering agents). Agents marked red are fixed combinations of 3 active pharmaceutical ingredients in one dosage form (i.e. 3 different blood pressure lowering agents).

Table A.3.1 Overview of blood pressure lowering agents that are available on the Dutch market

Main group	Subgroup	Products in the Netherlands	Corresponding ATC-code
Antiadrenergic agents, centrally acting, C02A	Rauwolfia alkaloids, C02AA	*None on the Dutch market*	
	Methyldopa, C02AB	Methyldopa	C02AB01
	Imidazoline receptor agonists, C02AC	Clonidine	C02AC01
		Guanfacine	C02AC02
		Moxonidine	C02AC05
Antiadrenergic agents, peripherally acting, C02C	Alpha-adrenoreceptor antagonists, C02CA	Doxazosin	C02CA04
		Urapidil	C02CA06
Arteriolar smooth muscle, agents acting on, C02D	Pyrimidine derivatives, C02DC	Minoxidil	C02DC01
	Nitroferricyanide derivatives, C02DD	Nitroprusside	C02DD01
Other antihypertensives, C02K	Antihypertensives for pulmonary arterial hypertension, C02KX	Bosentan	C02KX01
		Ambrisentan	C02KX02
		Macitentan	C02KX04
		Riociguat	C02KX05
		Macitentan and tadalafil	C02KX54
Low-ceiling diuretics, thiazides, C03A			
	Thiazides plain, C03AA	Hydrochlorothiazide	C03AA03
Low-ceiling diuretics, excl. thiazides, C03B	Sulfonamides, plain, C03BA	Chlortalidone	C03BA04
		Indapamide	C03BA11
High-ceiling diuretics, C03C	Sulfonamides, plain, C03CA	Furosemide	C03CA01
		Bumetanide	C03CA02
Aldosterone antagonists and other potassium-sparing agents, C03D	Aldosterone antagonists, C03DA	Spironolactone	C03DA01
	Other potassium-sparing agents, C03DB	Triamterene	C03DB02

Diuretics and potassium-sparing agents in combination, C03E	Low-ceiling diuretics and potassium-sparing agents, C03EA	Hydrochlorothiazide and potassium-sparing agents (triamterene/ hydrochlorothiazide and amiloride/ hydrochlorothiazide	C03EA01
Beta blocking agents, C07A	Beta blocking agents, non-selective, C07AA	Propranolol	C07AA05
		Sotalol	C07AA07
	Beta blocking agents, selective, C07AB	Metoprolol	C07AB02
		Atenolol	C07AB03
		Acebutolol	C07AB04
		Bisoprolol	C07AB07
		Celiprolol	C07AB08
		Esmolol	C07AB09
		Nebivolol	C07AB12
		Landiolol	C07AB14
	Alpha and beta blocking agents, C07AG	Labetalol	C07AG01
		Carvedilol	C07AG02
Beta blocking agents and thiazides, C07B	Beta blocking agents, non-selective, and thiazides, C07BA	*None on the Dutch market*	
	Beta blocking agents, selective, and thiazides, C07BB	Metoprolol and thiazides (methoprolol/ hydrochlorothiazide)	C07BB02
		Bisoprolol and thiazides (bisoprolol/ hydrochlorothiazide)	C07BB07
	Alpha and beta blocking agents and thiazides, C07BG	*None on the Dutch market*	
Beta blocking agents and other diuretics, C07C	Beta blocking agents, non-selective, and other diuretics, C07CA	*None on the Dutch market*	
	Beta blocking agents, selective, and other diuretics, C07CB	Atenolol and other diuretics (atenolol/chlortalidone)	C07CB03
	Alpha and beta blocking agents and other diuretics, C07CG	*None on the Dutch market*	
Beta blocking agents, thiazides and other diuretics, C07D	Beta blocking agents, non-selective, thiazides and other diuretics, C07DA	*None on the Dutch market*	
	Beta blocking agents, selective, thiazides and other diuretics, C07DB	*None on the Dutch market*	
Beta blocking agents and vasodilators, C07E		*Non-existing*	

Beta blocking agents, other combinations, C07F	Beta blocking agents and calcium channel blockers, C07FB	*None on the Dutch market*	
	Beta blocking agents, other combinations, C07FX	*None on the Dutch market*	
Selective calcium channel blockers with mainly vascular effects, C08C	Dihydropyridine derivatives, C08CA	Amlodipine	C08CA01
		Felodipine	C08CA02
		Nicardipine	C08CA04
		Nifedipine	C08CA05
		Nimodipine	C08CA06
		Nitrendipine	C08CA08
		Lacidipine	C08CA09
		Barnidipine	C08CA12
		Lercanidipine	C08CA13
		Clevidipine	C08CA16
	Other selective calcium channel blockers with mainly vascular effects, C08CX	*None on the Dutch Market*	
Selective calcium channel blockers with direct cardiac effects, C08D	Phenylalkylamine derivatives, C08DA	Verapamil	C08DA01
	Benzothiazepine derivatives, C08DB	Diltiazem	C08DB01
Non-selective calcium channel blockers, C08E	Phenylalkylamine derivatives, C08EA	*None on the Dutch market*	
	Other non-selective calcium channel blockers, C08EX	*None on the Dutch market*	
Calcium channel blockers and diuretics, C08G	Calcium channel blockers and diuretics, C08GA	Amlodipine and diuretics (amlodipine/indapamide)	C08GA02
ACE inhibitors, plain, C09A	ACE inhibitors, plain, C09AA	Captopril	C09AA01
		Enalapril	C09AA02
		Lisinopril	C09AA03
		Perindopril	C09AA04
		Ramipril	C09AA05
		Benazepril	C09AA07
		Fosinopril	C09AA09
		Zofenopril	C09AA15
ACE inhibitors, combinations, C09B	ACE inhibitors and diuretics, C09BA	Enalapril and diuretics (enalapril/hydrochlorothiazide)	C09BA02
		Lisinopril and diuretics (lisinopril/hydrochlorothiazide)	C09BA03
		Perindopril and diuretics (perindopril/indapamide)	C09BA04

		Ramipril and diuretics (ramipril/hydrochlorothiazide)	C09BA05
		Quinapril and diuretics (quinapril/hydrochlorothiazide)	C09BA06
		Fosinopril and diuretics (fosinopril/hydrochlorothiazide)	C09BA09
	ACE inhibitors and calcium channel blockers, C09BB	Enalapril and lercanidipine	C09BB02
		Perindopril and amlodipine	C09BB04
		Trandolapril and verapamil	C09BB10
	ACE inhibitors, other combinations, C09BX	Perindopril, amlodipine and indapamide	C09BX01
Angiotensin II receptor blockers (ARBs), plain, C09C	Angiotensin II receptor blockers (ARBs), plain, C09CA	Losartan	C09CA01
		Eprosartan	C09CA02
		Valsartan	C09CA03
		Irbesartan	C09CA04
		Candesartan	C09CA06
		Telmisartan	C09CA07
		Olmesartan medoxomil	C09CA08
Angiotensin II receptor blockers (ARBs), combinations, C09D	Angiotensin II receptor blockers (ARBs) and diuretics, C09DA	Losartan and diuretics (losartan/hydrochlorothiazide)	C09DA01
		Eprosartan and diuretics (eprosartan/hydrochlorothiazide)	C09DA02
		Valsartan and diuretics (valsartan/hydrochlorothiazide)	C09DA03
		Irbesartan and diuretics (irbesartan/hydrochlorothiazide)	C09DA04
		Candesartan and diuretics (candesartan/hydrochlorothiazide)	C09DA06
		Telmisartan and diuretics (telmisartan/hydrochlorothiazide)	C09DA07
		Olmesartan medoximil and diuretics (Olmesartan/hydrochlorothiazide)	C09DA08
	Angiotensin II receptor blockers (ARBs) and calcium channel blockers, C09DB	Valsartan and amlodipine	C09DB01
		Olmesartan medoxomil and amlodipine	C09DB02
	Angiotensin II receptor blockers (ARBs), other combinations, C09DX	Valsartan, amlodipine and hydrochlorothiazide	C09DX01
		Olmesartan medoxomil, amlodipine and hydrochlorothiazide	C09DX03
		Valsartan and sacubitril	C09DX04

Appendix 3.2 Overview of agents indicated as singles, doubles and triples

This appendix gives an overview of the included medication that is referred to as singles, doubles and triples. When the ATC-code given is not specified to the deepest level (i.e. the level of a specific drug), all underlying groups and drugs are included as long as they are available on the Dutch market. For example, C07A encompasses drugs in the groups C07AA, C07AB and C07AG.

Table A.3.2 Agents in ATC-groups referred to as singles, doubles and triples.

Singles (1 BPLA)	**Doubles (fixed combinations of 2 BPLA)**	**Triples (fixed combinations of 3 BPLA)**
C03A	C03EA	C09BX
C03B	C07BB	C09DX01
C03DA01	C07CB	C09DX03
C07A	C08GA	
C08C	C09BA	
C08D	C09BB	
C09A	C09DA	
C09C	C09DB	
	C09DX04	

Appendix 3.3 Flowchart with transitions of blood pressure lowering agents

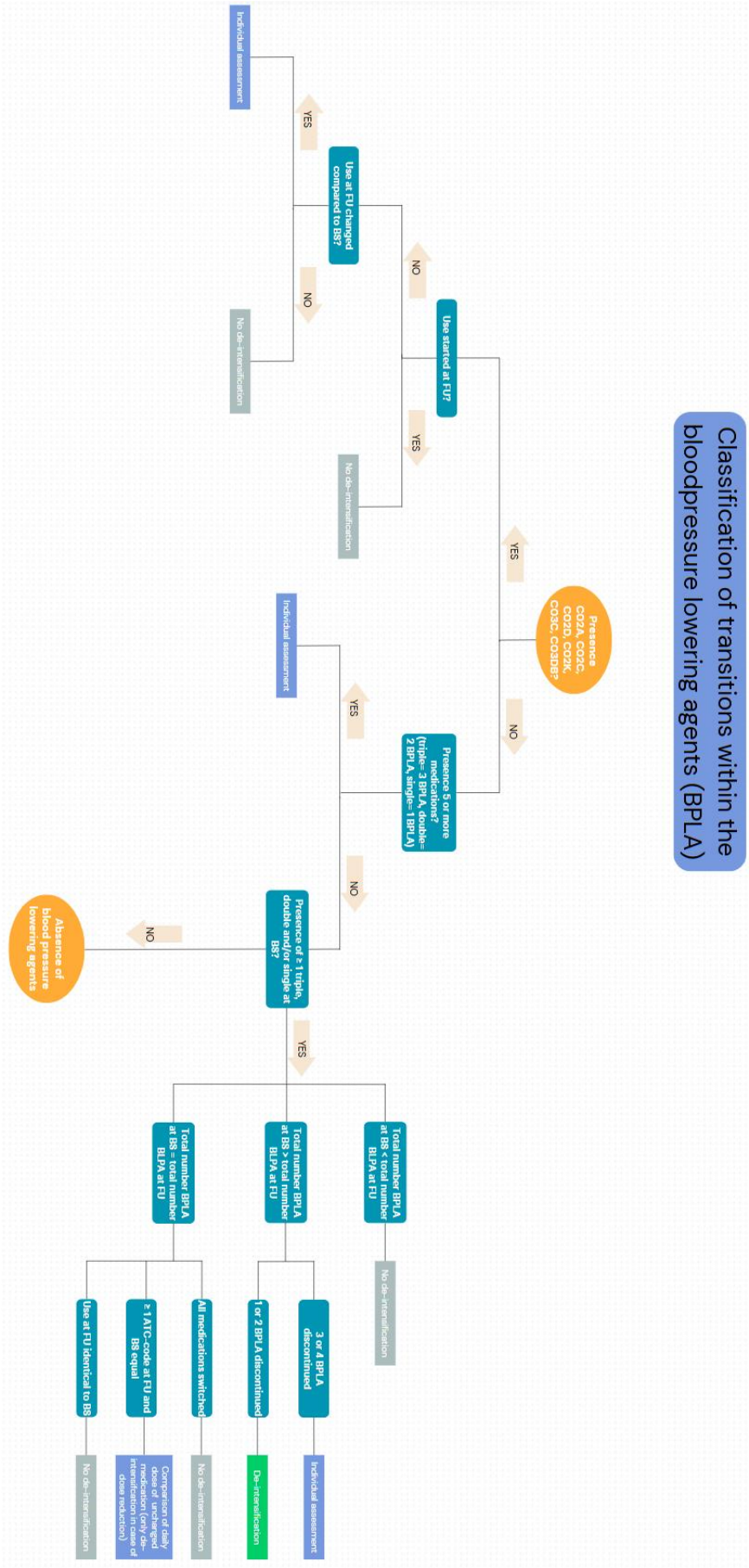

Figure A.3.3 Flowchart classifying all potential transitions of treatment states with blood pressure lowering agents. BPLA = Blood Pressure Lowering Agent. Triple = fixed combination of 3 BPLA, double = fixed combination of 2 BPLA, single = 1 BPLA

Appendix 4: antithrombotic agents

Appendix 4.1 Overview of all antithrombotic agents in the Netherlands

Table A.4.1.1 contains an overview of antithrombotic agents that are available in the Netherlands. Not all agents possibly lowering blood pressure are included but only vitamin K antagonists, platelet aggregation inhibitors excl. heparin, direct thrombin inhibitors and direct factor Xa inhibitors. The agent B01AC30 is marked brown/orange because it is a fixed combination of 2 active pharmaceutical ingredients in one dosage form (i.e. 2 different antithrombotic agents).

Table A.4.1 Overview of blood pressure lowering products that are available on the Dutch market

Main group	Subgroup	Agents in the Netherlands	Corresponding ATC-code
Antithrombotic agents, B01A			
	Vitamin K antagonists, B01AA	Phenprocoumon	B01AA04
		Acenocoumarol	B01AA07
	Platelet aggregation inhibitors excl. heparin, B01AC	Clopidogrel	B01AC04
		Acetylsalicylic acid	B01AC06
		Dipyridamole	B01AC07
		Carbasalate calcium	B01AC08
		Epoprostenol	B01AC09
		Iloprost	B01AC11
		Eptifibatide	B01AC16
		Tirofiban	B01AC17
		Treprostinil	B01AC21
		Prasugrel	B01AC22
		Ticagrelor	B01AC24
		Cangrelor	B01AC25
		Selexipag	B01AC27
		Combinations Clopidogrel/Acetylsalicylic acid	B01AC30
		Acetylsalicylic acid, combinations with proton pump inhibitors	None on the Dutch market
	Direct thrombin inhibitors, B01AE	Argatroban	B01AE03
		Bivalirudin	B01AE06
		Dabigatran etexilate	B01AE07
	Direct factor Xa inhibitors, B01AF	Rivaroxaban	B01AF01
		Apixaban	B01AF02
		Edoxaban	B01AF03

Appendix 5: Instruction guide for manual assessment

Handleiding voor individueel (handmatig) beoordelen medicatietransities

Doel: het doel van dit document is om aanwijzingen te geven in situaties waarbij er individueel en handmatig moet worden beoordeeld of er sprake is van de-intensivering van cardiometabole medicatie of niet. Door middel van deze handleiding kan individuele beoordeling relatief gestandaardiseerd kunnen verlopen.
Setting: Dit document maakt onderdeel uit van de CO-DEPRESCRIBE studie (41), waarbij voor de primaire uitkomst wordt gekeken welke cardiometabole middelen worden geminderd of gestopt (de-intensivering). Hiervoor zijn algoritmes ontwikkeld waarbij de uitkomst van sommige transities in medicijngebruik is dat er individueel moet worden beoordeeld. Dat gebeurt aan de hand van de principes in dit document die tevens ten grondslag liggen aan het ontwerpen en classificeren van transities die het algoritme afhandelt. Per transitie waarin individueel beoordelen nodig is, worden in dit document aanwijzingen geven hoe dat beoordelen vorm te geven. Classificatie gebeurt op basis van uitgiftegegevens van openbare apotheken. Vanuit de literatuur rondom minderen en stoppen en inzichten vanuit de CO-DEPRESCRIBE onderzoeksgroep worden aanwijzingen gegeven en handreikingen gedaan die in lijn zijn met de systematiek van de algoritmes.
Werkwijze: zoek in alle gevallen waarin er individueel moet worden beoordeeld de uitgiftegegevens van die patiënt op (bijvoorbeeld middels de RedCAPID). Filter alle uitgiftes van de patiënt op de uitgiftes van de geneesmiddelgroep die het algoritme (waarbij de classificatie individueel beoordelen werd gegeven) classificeert. Bepaal aan de hand van deze uitgiftes handmatig het baseline-gebruik en het follow-up-gebruik volgens de definities die het script daar ook voor hanteert. Noteer voor het baseline en follow-up gebruik van recepten van de geneesmiddelgroep in ieder geval de betreffende patiënt en de (laatste) baselinerecepten van de verschillende middelen die in gebruik zijn inclusief middel, dosering en datum. Doe dit ook voor de follow-up recepten. Vergelijk nu het gebruik bij de follow-up met het gebruik op baseline en ken een classificatie toe (een vorm van de-intensivering of geen de-intensivering). De verschillende vormen van de-intensivering zijn: therapie stop (afwezigheid van recepten bij de follow-up), discontinuering (stop van 1 of meer middelen, waarbij bij de follow-up ten minste nog 1 middel in gebruik is), doseringsverlaging en wisseling naar een alternatief met lager risico op ernstige bijwerkingen.
Disclaimer: dit document dekt mogelijk niet alle transities. Er bestaat de mogelijkheid dat er een transitie in medicijngebruik wordt gevonden die hier niet (volledig) wordt behandeld. In dat geval moet er zelf worden bepaald (voor zover mogelijk via de voor het algoritme en deze handleiding gebruikte principes) of er sprake is van een de-intensivering of niet.

Onderdeel 1: individueel beoordelen bij lipiden verlagende middelen (C10)
Belangrijk voor de lipidenverlagers is dat de meeste patiënten statines gebruiken en dat er bij statines verschillen in potentie zijn: simvastatine 40 mg per dag geeft een lagere cholesterolverlaging dan rosuvastatine 40 mg per dag. Om de verschillende doseringen van de verschillende middelen toch allemaal met elkaar te kunnen vergelijken, is er een equipotentietabel opgesteld. Zie Tabel 1 en uitleg de een pagina. Een verlaging in equipotentiewaarde is een vorm van de-intensivering (geclassificeerd als doseringsverlaging).
Situaties waarbij een middel wordt toegevoegd ten opzichte van het baseline gebruik, zijn geen de-intensivering maar een escalatie van lipidenverlagende therapie. Hierbij is het van belang op te merken dat een middel met ATC-code C10BA telt voor 2 middelen, aangezien dit combinatiepreparaten zijn.
Als laatste opmerking vooraf: controleer bij onzekerheid over het classificeren van een transitie in REDCap of er sprake is van een bewuste stopzetting/doseringsverlaging/escalatie van lipidenverlagende middelen, zoals gerapporteerd door een zorgverlener (bij 'anamnesegesprek', de 'farmacotherapeutische analyse', 'opgesteld FBP' of 'overleggen van FBP met patiënt').

Principes voor classificatie bij individuele beoordeling:

- De middelen in de groepen **C10AB, C10AC, C10AD en C10AX** zien we als gelijkwaardig. Deze middelen vallen buiten de standaardtherapie en zullen naar verwachting weinig worden gebruikt (afgezien van ezetimibe). Wanneer deze middelen aanwezig zijn in monotherapie en er individueel moet worden beoordeeld, moeten de volgende aandachtspunten in acht worden genomen:
    - Wanneer de dosering op baseline hoger is dan bij de follow-up is er sprake van een de-intensivering.
    - Wanneer er van monotherapie op baseline naar gebruik van 2 middelen op follow-up wordt gegaan, is er geen sprake van de-intensivering.
    - Als een van de bovengenoemde middelen wordt vervangen door een ander middel uit deze groepen, dan is dat een sterke aanwijzing dat de transitie niet is bedoeld als afbouwen, maar om een alternatief middel te vinden. Dit is hoogstwaarschijnlijk geen de-intensivering.
- De middelen in de groep **C10BA** zijn zogenoemde 'vaste combinaties', waarmee wordt bedoeld dat dit combinaties zijn waarin beide middelen in één product (bijvoorbeeld een tablet) zitten. Deze middelen worden grotendeels individueel beoordeeld (tenzij er bij de follow-up geen of een enkele lipidenverlager aanwezig is). Bij het individueel beoordelen dienen de volgende aspecten in acht genomen te worden:
    - Allereerst moet worden gekeken of er op baseline en bij de follow-up dezelfde middelen worden gebruikt. Als dat zo is, moet de dagelijkse dosering worden vergeleken en alleen bij een lagere dagdosering/equipotentie bij de follow-up meting is er sprake van een de-intensivering.
    - Wanneer er bij de follow-up andere middelen in het spel komen, kan door middel van de equipotentietabel worden gekeken of er een lagere equipotentie wordt bereikt door de transitie (wat een de-intensivering zou betekenen) of niet/geen verandering in equipotentie wordt bereikt (wat géén de-intensivering zou betekenen).
    - Belangrijk om te realiseren, is dat een 'vaste combinatie (C10BA)' kan worden omgezet in een 'niet-vaste combinatie' en vice versa. Dit kan een vertekend beeld van de werkelijkheid geven aangezien er in het geval van een vaste combinatie slechts 1 ATC-code aanwezig is, terwijl het 2 werkzame stoffen betreft. Houd daarom ALLE C10-recepten in het oog bij de classificatie.
- Zogenoemde '**niet-vaste combinaties**' zijn weergegeven door verschillende codes, zoals C10AA + C10A#, wat betekent dat er een statine met een willekeurige andere enkelvoudige

lipidenverlager wordt gecombineerd. Bij de niet-vaste combinatie met code 'C10A# + C10A* mits geen C10AA' zijn er twee willekeurige enkelvoudige lipidenverlagers gecombineerd die beide géén statine zijn. In het geval van 3 of meer lipidenverlagers (oftewel 3 of meer enkelvoudige lipidenverlagers OF een combinatiepreparaat (C10BA) en een of meer enkelvoudige middelen) zijn er veel mogelijke situaties bij de follow-up. In deze situaties moet er individueel moeten beoordeeld of er sprake is van de-intensivering. Daarbij gelden de volgende aandachtspunten:

- Wanneer er bij baseline een of meer middelen méér worden gebruikt dan bij de follow-up, dan is er sprake van de-intensivering. Let hierbij wel op of er niet tegelijkertijd (sterke) dosisverhogingen zijn van andere middelen of veranderingen in de gebruikte middelen, die erop kunnen wijzen dat het gestaakte middel wordt gecompenseerd door ophoging van de dosering van andere lipidenverlagers. Deze compensatie kan ook worden gerealiseerd door een verhoging van equipotentie van statines.
- Belangrijk om te realiseren, is dat een 'vaste combinatie (C10BA)' kan worden omgezet in een 'niet-vaste combinatie' en vice versa. Dit kan een vertekend beeld van de werkelijkheid geven aangezien er in het geval van een vaste combinatie slechts 1 ATC-code aanwezig is, terwijl het 2 werkzame stoffen betreft. Houd daarom ALLE C10-recepten in het oog bij de classificatie.
- Wanneer er op baseline en follow-up dezelfde middelen worden gebruikt, moet worden beoordeeld of de dagdosering is veranderd. Wanneer de dagdosering is verlaagd ten opzichte van baseline zónder gelijktijdige doseringsverhoging(en) van (een) andere lipidenverlager(s), is er sprake van de-intensivering. Bij een gelijk gebleven of gestegen dagdosering van alle/een van de middelen is er uiteraard géén sprake van de-intensivering. Dat is ook niet het geval wanneer de de-intensivering van het ene middel wordt gecompenseerd door een dosisverhoging van een ander middel.
- Wanneer er op baseline en follow-up niet (allemaal) dezelfde middelen worden gebruikt, moet worden gekeken of de dosering van een eventueel onveranderd middel hetzelfde is gebleven, of dat het is gestegen of gedaald. Vervolgens moet worden gekeken of het/de middel(en) die veranderd is/zijn equipotent is/zijn aan het baseline gebruik. Gebruik daarvoor de equipotentietabel. Mocht de dosering van het eventuele onveranderde middel (of middelen) zijn gedaald en het veranderde middel naar een meer potent middel is geswitcht, valt dit niet te zien als de-intensivering. De middelen van de groepen C10AB, -AC, -AD en -AX zien we als vergelijkbaar en switches van een van deze middelen naar een ander zien we dus niet als de-intensivering.

Equipotentie statines

Tabel 1 maakt het mogelijk om elke willekeurige dosering van een bepaalde statine te vergelijken met elke willekeurige dosering van een andere statine, en om daarbij meteen te zien of er een de-intensivering in lipidenverlagende therapie optreedt of niet. Het werkt als volgt: wanneer de equivalentiewaarde bij de follow-up hoger is dan bij baseline, dan is er een intensivering van de therapie (namelijk doseringsverlaging). Wanneer de equivalentiewaarde bij de follow-up juist lager is dan op baseline, is er sprake van de-intensivering. Wanneer de equivalentiewaarde bij de follow-up en op baseline hetzelfde is, is er sprake van ongewijzigde intensiteit van de therapie (ook wanneer er bij de follow-up meting een andere statine in gebruik is). Voorbeeld: een transitie van atorvastatine 80 mg naar simvastatine 40 mg betekent een verlaging van equivalentiewaarde van 4 naar 1. Dit is een de-intensivering (geclassificeerd als doseringsverlaging).
Tabel 1 is gebaseerd op de indeling van statine-potentie van de KNMP (47).

Tabel 2 Overzicht van de statines in hun beschikbare doseringen inclusief equivalentiewaarde

Middel	**Dagdosering (mg)**	**ATC code**	**Berekening equivalentie-eenheid**	**Equivalentiewaarde**
Atorvastatine	80	C10AA05	80/20	4
Rosuvastatine	40	C10AA07	40/10	4
Atorvastatine	40	C10AA05	80/40	2
Rosuvastatine	20	C10AA07	20/10	2
Atorvastatine	20	C10AA05	*Referentie*	1
Rosuvastatine	10	C10AA07	*Referentie*	1
Simvastatine	40	C10AA01	*Referentie*	1
Pravastatine	80	C10AA03	*Referentie*	1
Fluvastatine	80	C10AA04	*Referentie*	1
Atorvastatine	10	C10AA05	10/20	0.5
Rosuvastatine	5	C10AA07	5/10	0.5
Simvastatine	20	C10AA01	20/40	0.5
Pravastatine	40	C10AA03	40/80	0.5
Fluvastatine	40	C10AA04	40/80	0.5
Simvastatine	10	C10AA01	10/40	0.25
Pravastatine	20	C10AA03	20/80	0.25
Fluvastatine	20	C10AA04	20/80	0.25
Pravastatine	10	C10AA03	10/80	0.125

Onderdeel 2: individueel beoordelen bij bloedglucoseverlagende middelen (A10)
Voor het handmatig beoordelen van bloedglucose verlagende middelen (BGVM) is het van belang het stroomschema helder te hebben van de aanpak van het classificeren van transities van BGVM. Alle casussen met insuline worden als eerst behandeld: wanneer er bij baseline en follow-up insuline in gebruik is, moet er handmatig worden beoordeeld. Wanneer insuline wordt gestopt, wordt het automatisch geclassificeerd als de-intensivering. Wanneer insuline wordt gestart bij de follow-up, is de classificatie automatisch geen de-intensivering.
Dan wordt bekeken of er sprake is van stopzetting van een sulfonylureum-derivaat (A10BB). Wanneer dit allemaal **niet** het geval is, wordt de classificatie gebaseerd op het aantal middelen dat bij de baseline in gebruik is (dus exclusief insuline). Situaties waarbij 4 of meer verschillende BGVM worden aangetroffen op baseline of bij de follow-up, worden individueel beoordeeld. Verder worden situaties waarbij er teveel verschillende mogelijkheden zijn om af te vangen in geautomatiseerde regels ook individueel beoordeeld (bijvoorbeeld wanneer er van twee of drie middelen tegelijkertijd op baseline naar meerdere middelen bij de follow-up wordt geswitcht).
Onderstaande principes dienen in acht genomen te worden bij het individueel beoordelen.
Als laatste opmerking vooraf: controleer bij onzekerheid over het classificeren in REDCap of er sprake is van een bewuste stopzetting/doseringsverlaging/escalatie van bloedglucoseverlagende middelen, zoals gerapporteerd door een zorgverlener (bij 'anamnesegesprek', de 'farmacotherapeutische analyse', 'opgesteld FBP' of 'overleggen van FBP met patiënt').

Principes voor classificatie bij individuele beoordeling:

- Voor **insuline (A10A)** moet het toedieningsschema (spuitschema) helder zijn om een beeld te krijgen van de dosering op baseline en bij de follow-up. Belangrijke punten voor de classificatie van transities zijn:
    - Als het aantal eenheden dat gespoten wordt, wordt verminderd, is er sprake van de-intensivering (namelijk doseringsverlaging).
    - De aanbevelingen (49) voor minderen en stoppen van insuline geven bij het **basaal-bolus regime** als eerste stap aan om de eventueel aanwezige kortwerkende insuline af te bouwen of te stoppen (afhankelijk van het aantal gespoten eenheden per gift). De tweede geadviseerde stap is het omzetten van een eventuele middellang-werkende insuline in een langwerkende insuline en afbouwen van de langwerkende insuline.
      Wanneer deze stappen worden gezien in de uitgiftegegevens, is er sprake van de-intensivering.
    - Aanbevolen bij minderen en stoppen van insuline bij het **mixregime** wordt om de totale dagelijkse dosering van insuline te halveren en dit 's ochtends te geven als langwerkende insuline. Dit is dus een de-intensivering (doseringsverlaging).
    - Wanneer er een combinatie is van een (middel)lang werkende insuline Voor Slapen (VS) en orale BGVM, dan wordt als eerste aanbevolen een eventueel aanwezig sulfonyl-ureum derivaat (SU derivaat) te stoppen en in een tweede stap de eenheden insuline te halveren en dit toe te dienen als langwerkende variant. Dit kan zo nodig weer wat worden opgehoogd. Deze transities zijn te classificeren als de-intensivering.
    - Houd tegelijkertijd de overige BGVM in de gaten die de patiënt mogelijk gebruikt! Wordt daarvan nog een dosering verlaagd, of een middel gestopt? Dan telt dat ook als de-intensivering. Behandel deze overige BGVM volgens de principes zoals gehanteerd in dit deel van de handleiding (zie onderstaande aanwijzingen).
    - (Wanneer iemand < 20 eenheden langwerkende insuline gebruikt, kan geprobeerd worden over te gaan op orale BGVM of een GLP1-agonist (49),(20). Deze transitie wordt automatisch afgehandeld aangezien een stopzetting van insuline altijd een de-intensivering is)

    - (Als een middel wordt vervangen door **insuline** of als er insuline wordt toegevoegd, wordt dit automatisch geclassificeerd als intensivering van therapie)
- Wanneer er **sulfonylureum derivaten** worden geswitcht naar een ander middel, is er sprake van de-intensivering wanneer er wordt geswitcht van glimepiride of glibenclamide (alleen verkrijgbaar in een combinatiepreparaat met metformine) naar gliclazide of een ander middel met een lagere kans op hypoglycemie (bijv. een DPP4-remmer), maar ook wanneer gliclazide wordt vervangen door een middel met lagere kans op hypoglycemie (bijv. een DPP4-remmer). Een verlaagde dosering van een SU-derivaat of een stopzetting is uiteraard ook een de-intensivering.
  Let ook op situaties met een combinatiepreparaat dat een SU-derivaat bevat (in geval van **A10BD02**)!
  Wanneer echter een sulfonylureum derivaat wordt gestart bij de follow-up meting ten opzichte van de baseline meting, geldt dit vanwege het risico op hypoglycemie als een escalatie van therapie en dus níét als de-intensivering.
- Wanneer er **4 of meer BGVM** (insuline niet meegeteld) worden gevonden op baseline en/of follow-up, moet er handmatig worden gecontroleerd of het algoritme geen leesfout heeft gemaakt: 4 of meer BGVM zijn therapeutisch niet rationeel als insuline niet is geïncludeerd.
    - Controleer allereerst of er daadwerkelijk 4 verschillende middelen worden gebruikt door één patiënt en of dit *tegelijkertijd* wordt gebruikt of dat een of meerdere recepten zijn vervallen zodat niet alle middelen op hetzelfde moment worden gebruik. Het is bijvoorbeeld mogelijk dat iemand op de proef een middel heeft gebruikt en dat niet is bevallen, en toen is geswitcht naar een ander middel terwijl er theoretisch gezien nog voorraad van het eerste middel aanwezig was en het algoritme daarbij concludeert dat er meer middelen in gebruik zijn dan daadwerkelijk het geval is.
    - Mocht het toch blijken dat er 4 of meer middelen tegelijkertijd worden gebruikt, controleer dan of er een verschil is in aantal middelen en dosering tussen het gebruik op baseline en bij de follow-up, en classificeer dit met de gebruikelijke principes (1 receptregel minder, lagere dagdosering of middelen met een lager risico op hypoglycemie bij de follow-up gelden als de-intensivering).
    - Wees erg kritisch bij het behandelen van deze situaties! Vraag eventueel een collega om assistentie.
- Bij situaties waarbij er teveel verschillende mogelijkheden zijn om te vangen in geautomatiseerde regels, gelden ook de gebruikelijke principes zoals hierboven ook herhaaldelijk aangegeven:
    - Wanneer het aantal middelen of de dagdosering vermindert bij de follow-up ten opzichte van baseline (zonder dat er gelijktijdig andere BGVM worden verhoogd in dosering), is er sprake van de-intensivering.
    - Er is tevens sprake van de-intensivering wanneer er wordt geswitcht van een middel met een hoog risico op hypoglycemie naar een middel met een laag risico op hypoglycemie.
    - Wees alert op combinatiepreparaten (A10BD): deze tellen voor 2 middelen! Zoek daarom per casus op welke middelen (productnamen) diegene gebruikt op baseline en bij de follow-up.
- Wanneer er **3 BDVM worden gestopt**, controleer dan of het algoritme de data dan goed heeft gelezen en of de uitgiftedata compleet zijn. Kijk kritisch na of er écht geen middelen meer zijn bij de follow-up en of daar een reden voor is. Deze situatie is therapeutisch gezien namelijk niet rationeel. Kijk goed of er niet iets bijzonders aan de hand is (bijvoorbeeld dat er geen follow-up gebruik is vastgesteld omdat de patiënt is overleden).

Onderdeel 3: individueel beoordelen bij bloeddrukverlagende middelen
Bij de bloeddrukverlagende middelen (BDVM) geldt dat niet alle middelen die een verlaging van bloeddruk zouden kunnen geven ook daadwerkelijk zijn geïncludeerd. Dit zijn alleen de zogenaamde singles, doubles en triples, en een aantal middelen die mogelijk voor hypertensie worden gebruikt (namelijk middelen met codes C02A, C02C, C02D, C02K, C03C en C03DB), maar die mogelijk ook een andere indicatie hebben.
Aangezien BDVM vergelijkbaar zijn (12), worden wisselingen van medicatie niet als de-intensivering geclassificeerd en is er sprake van de-intensivering bij discontinuering van een of meer middelen en bij doseringsverlagingen(21).
Onderstaande principes dienen in acht genomen te worden bij het individueel beoordelen.
Als laatste opmerking vooraf: controleer bij onzekerheid over het classificeren in REDCap of er sprake is van een bewuste stopzetting/doseringsverlaging/escalatie van bloeddruk verlagende middelen, zoals gerapporteerd door een zorgverlener (bij 'anamnesegesprek', de 'farmacotherapeutische analyse', 'opgesteld FBP' of 'overleggen van FBP met patiënt').

Principes voor classificatie bij individuele beoordeling:

- Bij middelen met een onduidelijke indicatie (ATC-codes codes C02A, C02C, C02D, C02K, C03C en C03DB) waarbij er *niet* gestart of gestopt wordt met het middel/de middelen maar de dosering wordt veranderd, moet individueel worden beoordeeld. In deze gevallen moet kritisch worden bekeken of a) er sprake is van een verhoogde dosering (wat afgedaan kan worden als zijnde geen de-intensivering) of b) een verlaagde dosering. In het geval van een verlaagde dosering, moet kritisch worden gekeken of er aanwijzingen zijn dat deze middelen zijn ingezet als bloeddrukverlager of in gebruik zijn voor een overige indicatie. Kijk hierbij of de middelen continu of intermitterend zijn ingezet. Een 'zo nodig' of onderbroken gebruik wijst op een indicatie anders dan hypertensie, aangezien er bij hypertensie continu moet worden behandeld. Wanneer de dagdosering en de gebruikte middelen onveranderd blijven, is er *geen* sprake van de-intensivering. Wanneer de dosering wordt verlaagd en de middelen voor hypertensie worden gebruikt, is er sprake van de-intensivering (doseringsverlaging).
    - NB. C02KX54 is een combinatiepreparaat, bestaand uit 2 middelen.
- Bij aanwezigheid van 5 of meer BDVM dient kritisch gekeken te worden of er inderdaad 5 middelen tegelijkertijd worden gebruikt. Er kan sprake zijn van vroegtijdige stopzetting van het ene middel en gelijktijdige start van een ander middel; dat een middel bijvoorbeeld vanwege bijwerkingen wordt gestopt voordat de voorraad 'oude' medicijnen theoretisch gezien op is en dat er als alternatief meteen een ander middel wordt gestart; dan kan het lijken alsof iemand een middel meer gebruikt dan daadwerkelijk zo is. Wanneer er echt 5 of meer middelen worden gebruikt, dan geldt dat er sprake is van een de-intensivering bij een stop van een of meer middelen (zie ook het volgende aandachtspunt) of een doseringsverlaging die niet wordt gecompenseerd door een doseringsverhoging van een ander middel. Een switch van medicatie is geen de-intensivering.
- Discontinuering van 3 of 4 BDVM is therapeutisch gezien irrationeel. Controleer goed of het algoritme de data goed heeft gelezen en of de uitgiftedata compleet zijn. Kijk hierbij kritisch of er geen andere verklaringen zijn, zoals overlijden van de patiënt. Mocht blijken dat er tóch 3 of 4 middelen zijn gestopt, dan is er sprake van de-intensivering.
- In het geval het aantal BDVM op baseline en follow-up gelijk is, maar het gebruik niet identiek is en niet alle middelen zijn geswitcht, moet de dagdosering van het middel dat niet is geswitcht worden vergeleken. Hierbij geldt dat een eventueel geswitcht middel nooit een de-intensivering is. Er is sprake van de-intensivering (doseringsverlaging) wanneer de dagdosering van een of meer BDVM wordt/worden verlaagd zonder dat er een gelijktijdige doseringsverhoging is van een ander middel (wat tot een netto onveranderde behandeling van hypertensie leidt).

Onderdeel 4: individueel beoordelen bij antitrombotische middelen (B01)
Antitrombotische middelen worden onderverdeeld in TARs (trombocytenaggregatieremmers, ATC-code B01AC) en anticoagulantia (B01AA, -AE en -AF).
Doseringen en wisselingen naar alternatieven met een lager risico op bijwerkingen spelen geen rol bij de-intensivering van antitrombotische middelen, dus de indeling vindt uitsluitend plaats op basis van het totaal aantal middelen dat in gebruik is (55,56).
Het middel B01AC30 is het enige combinatiepreparaat binnen deze groep, bestaande uit twee TARs. De overige middelen met ATC-code B01AC zijn enkelvoudige preparaten, single_TARs genoemd.
Onderstaande principes dienen in acht genomen te worden bij het individueel beoordelen.
Als laatste opmerking vooraf: controleer bij onzekerheid over het classificeren in REDCap of er sprake is van een bewuste stopzetting/doseringsverlaging/escalatie van antitrombotische middelen, zoals gerapporteerd door een zorgverlener (bij ‘anamnesegesprek’, de ‘farmacotherapeutische analyse’, ‘opgesteld FBP’ of ‘overleggen van FBP met patiënt’).

Principes voor classificatie bij individuele beoordeling:

- Aanwezigheid van 3 of meer TARs tegelijkertijd en/of 2 of meer anticoagulans is therapeutisch gezien niet rationeel. Ga bij deze situaties na of de middelen inderdaad tegelijkertijd in gebruik zijn: het kan zijn dat het ene middel wordt gestopt en vervangen door een nieuw middel maar dat er nog voorraad van het oude middel is en het lijkt alsof ze tegelijkertijd worden gebruikt. Wanneer de middelen echt gelijktijdig in gebruik zijn, dan is er alleen sprake van de-intensivering wanneer er een middel wordt gestopt.
- Stopzetting van 3 antitrombotische middelen is ook niet therapeutisch rationeel. Controleer goed of het algoritme de data goed heeft gelezen en of de uitgiftedata compleet zijn. Kijk hierbij kritisch of er geen andere verklaringen zijn, zoals overlijden van de patiënt. Mocht het toch blijken dat er 3 middelen zijn gestopt, dan is er sprake van de-intensivering.

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