

# **Deprescribing in older patients with type 2 diabetes: a systematic review of deprescribing rates and outcomes**

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## **Abstract**

**Background:** Deprescribing in older patients with cardiometabolic conditions now being recommended, but there is uncertainty whether it is associated with worse outcomes. We conducted a systematic review of published evidence, to assess deprescribing approaches and evaluate the harms and benefits of deprescribing with antidiabetic medication and other therapies amongst older people ( $\geq 65$  years) with type 2 diabetes and other cardiometabolic conditions.

**Methods:** We identified relevant studies in a literature search of MEDLINE, Embase, Web of Science, and Cochrane databases to 30 October 2018. Data was extracted on baseline characteristics, deprescribing methods, and outcomes and was synthesized using a narrative approach.

**Results:** Eleven studies (observational cohorts and interventional studies) with data on 26,925 patients with comorbidities were eligible. Deprescribing approaches included complete withdrawal, discontinuation, reducing dosage, conversion, or substitution of at least one medication. Rates of deprescribing approaches ranged from 13.4% to 75%. Majority of studies reported no deterioration in HbA1c levels, hypoglycaemic episodes falls or hospitalisation on deprescribing. On adverse events and mortality, no significant differences were observed between the comparison groups in the majority of studies. Two studies reported an increased risk of mortality and other vascular events associated with discontinuation of medication.

**Conclusion:** Available evidence suggests deprescribing does not generally lead to harm. There is lack of good quality evidence to guide deprescribing approaches in order to achieve individual targets.

**Keywords:** Deprescribing; medication; elderly; type 2 diabetes; cardiovascular disease; systematic review

**Systematic review registration:** PROSPERO 2018: CRD42018102853

## Introduction

Type 2 diabetes is a chronic disease which is characterized by high levels of blood glucose (hyperglycaemia). It is one of the major causes of death globally.<sup>1</sup> Most patients with type 2 diabetes have at least one complication, which include cardiovascular disease (CVD), stroke, chronic kidney disease (CKD), retinopathy, and neuropathy.<sup>2</sup> Cardiovascular complications are the leading cause of morbidity and death in these patients.<sup>1</sup>

The major goal of managing type 2 diabetes is to achieve appropriate reduction in glucose levels, in order to minimize the risk of complications, particularly the vascular ones.<sup>3</sup> To achieve appropriate glycaemic targets as set by guideline bodies, antihyperglycaemic medications are usually initiated individually or in combination<sup>4</sup> in a timely manner when appropriate to prevent therapeutic inertia.<sup>5</sup> At the same time, there needs to be a balance between the relative risks of clinical inertia versus overtreatment in the management of glycaemia in patients with diabetes.<sup>6</sup> In elderly patients with type 2 diabetes, achieving glycaemic control is very problematic; with adverse effects such as hypoglycaemia reported to be of concern in such patients.<sup>7,8</sup> In elderly type 2 diabetes patients with co-existing frailty and comorbidities such as renal and cognitive impairment, the risk of hypoglycaemia is particularly high.<sup>9,10</sup> Despite recommendations by guideline bodies to individualise glycaemic targets with risk assessments aimed at avoiding overtreatment and hypoglycaemia,<sup>11-13</sup> recent data suggest increased hospital emergencies for hypoglycaemia.<sup>14</sup> Indeed, evidence suggests that older people with complex multimorbidity are being overtreated with drugs that cause hypoglycaemia.<sup>15-17</sup> Consequences of hypoglycemia include physical injury, psychological harm, impaired cognition, reduced quality of life, mortality, with significant impact on the healthcare system.<sup>9,18-22</sup> Though evidence suggests the risks of overtreatment with antihyperglycaemic drugs in older patients outweigh the benefits,<sup>15</sup> data on the potential benefits and harms of stopping or reducing these antihyperglycaemic agents and other medication (i.e., deprescribing) in the elderly with type 2 diabetes and comorbidities remains uncertain. There is also very little information on how to reduce

doses or stop or switch these medications to achieve individual targets. In this context, we conducted a systematic review of all available published observational and interventional evidence, to assess deprescribing approaches and rates and evaluate the harms and benefits of deprescribing with antidiabetic medication and other therapies amongst older people ( $\geq 65$  years) with type 2 diabetes, including those with co-existing cardiometabolic conditions such as CVD, CKD, or dementia. We also sought to explore if there are gaps in the existing evidence.

## **Methods**

### **Data sources and search strategy**

A predefined protocol was used to conduct this review and also in accordance with PRISMA and MOOSE guidelines<sup>23 24</sup> (**Appendix 1-2**) and using a protocol, which has been registered in the PROSPERO prospective register of systematic reviews (CRD42018102853). We searched MEDLINE, Embase, Web of Science, and Cochrane databases from inception to October 2018. The computer-based searches combined free and MeSH search terms and combination of key words related to deprescribing (e.g., “deprescribe”, “discontinue”, “de-intensify” “cessation”); medication (e.g., “prescription”, “antidiabetic”, “hyperglycaemic”); cardiometabolic conditions (e.g., “diabetes mellitus”, “hypertension”); and older patients (“aged”, “ageing”, “geriatric”, “elderly”). There were no restrictions on language. Reference lists of retrieved articles were manually scanned for all relevant additional studies and review articles missed by the original search. Full details on the search strategy are presented in **Appendix 3**.

### **Eligibility criteria**

We searched for observational (cross-sectional, prospective or retrospective case control, prospective cohort, retrospective cohort, case-cohort, or nested-case control) studies and clinical trials (randomised controlled trials (RCTs) including cluster and pragmatic trials and non-randomised controlled trials) that had reported on (i) elderly patients ( $\geq 65$  years) with type 2 diabetes including

those with co-existing cardiometabolic conditions such as CVD, CKD, or dementia who were taking antidiabetic medication plus other therapies for their conditions; (ii) reported deprescribing approaches (stopping drug treatment entirely, reducing dose, gradual tapering, or substitution); and/or (iii) reported outcomes such as admission rates, hospitalisations, complications, mortality, quality of life, and patient satisfaction. The age cut off applied if the average age of study participants age was 65 years or older; more than 75% of study participants were aged 65 years and older; or ability to extract data on participants aged 65 years and older from the study. The following exclusions were applied (i) studies not reporting deprescribing approaches; (ii) those not including patients with type 2 diabetes; (iii) those including patients < 65 years; or (iv) studies that included only terminal or palliative patients.

### **Patient and Public Involvement**

The study was supported by a patient focus group which provided input to the programme of research on the 9<sup>th</sup> of April 2018. Patients partnered with us for the design to refine the population to include other multimorbidities instead of just diabetes. They suggested that the burden of deprescribing could not just be worsening of glycaemic control but admissions and falls. It is our intention to continue to engage the group for the dissemination of the findings

### **Data extraction and quality assessment**

One reviewer (S.K.K.) independently extracted data and performed quality assessments using a standardized predesigned data collection form. A second reviewer (S.S.) checked extracted data with that in the original articles.

The titles and abstracts of all articles identified by the broad literature search were assessed independently by two reviewers (SS and SKK). Studies that did not meet the inclusion criteria were discarded. Full text of selected articles were retrieved and assessed to determine if they met the inclusion criteria. Those studies which met the inclusion were included in the review and the data

were extracted independently by two reviewers (SS and SKK) using standard data extraction form. The quality of the studies were assessed independently by both reviewers. Data was extracted on study, publication date, geographical location, study design, mean age, percentage of males, duration of follow-up, sample size, comorbidities, concomitant medications, doses, frequency, duration, deprescribing regimen (stopping/tapering/switching), and data/risk estimates on benefits and harms of deprescribing. Each article was assessed using the inclusion criteria and any disagreement regarding eligibility of an article was discussed, and agreement reached by consensus with a third reviewer. Authors of eligible studies were contacted to provide additional information where necessary. Additionally, in the case of multiple publications, data on the study with the most up-to-date or comprehensive information was extracted. Methodological quality of observational cohort studies was assessed based on the nine-star Newcastle–Ottawa Scale (NOS),<sup>25</sup> a validated tool for assessing the quality of non-randomised studies, including cohort and case-control studies. It uses three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality. For cross-sectional studies, we assessed quality using the NOS modified for cross-sectional studies (**Appendix 4**<sup>26</sup>). A maximum score of 8 reflected the highest study quality. The Cochrane Collaboration’s risk of bias tool was used to assess the quality of the included trials.

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## **Statistical analysis**

It was planned to synthesise risk ratios for dichotomous outcome data and mean differences for continuous outcomes if consistent outcomes were reported for multiple studies; however, given the limited number of studies, type of measures reported, and the diversity of the study designs and populations, a formal meta-analysis could not be performed. We could also not make effective

comparisons across studies because of the heterogeneity of the data. The characteristics of the deprescribing approaches and outcomes reported for each study were summarized in tables and narrative synthesis was performed.

## **Results**

### **Study identification and selection**

**Figure 1** shows the flow of studies through the review. The literature search identified 8,547 potentially relevant citations. After the initial screen based on titles and abstracts, 59 articles were selected for full text evaluation. Following detailed assessment of the full articles, 48 were excluded because (i) populations were not relevant to review (n=28); (ii) the intervention was not relevant (n=15); (iii) outcomes not relevant to review (n=3); (iv) one article used the same population sample as another study included in the review; and (v) one was a review article. The remaining 11 articles based on 11 unique studies met the inclusion criteria and were included in the review.<sup>28-38</sup>

### **Study characteristics and study quality**

**Table 1** summarizes the key baseline characteristics of the included studies. Studies were published between 2008 and 2017. Overall, the studies involved 26,925 unique participants with type 2 diabetes. The majority of studies (n=4) were conducted in Europe (The Netherlands, Sweden, and UK); three in the United States; and three in Asia (Japan). One study was conducted in 20 countries in Asia, Australasia, Europe, and North America. Only one study, with 98 patients with diabetes, was based on patients in Nursing Homes.<sup>29</sup> The mean/median baseline age of participants ranged from 64.5 to 86.5 years. Study designs comprised of RCTs (n=1); prospective cohorts (n=2); retrospective cohorts (n=2); observational cohorts with controls (n=2); case series (n=2); post-hoc observational analysis of a RCT (n=1); and cross-sectional retrospective sub-analysis of a RCT (n=1). Sample size of studies



ranged from 5 to 11,140 participants. The average follow-up durations for studies providing data ranged from 3 months to 4.3 years. Study populations comprised elderly patients with type 2 diabetes with comorbidities such as coronary heart disease (CHD) and kidney dysfunction and were on antihyperglycemic medication as well as statins or blood pressure medication. Among the observational cohort studies, quality score ranged from 3 to 8. Using the Cochrane risk of bias tool, the only RCT trial included in the review demonstrated low risk of bias in the areas of random sequence generation and blinding of outcome assessment, with high risk of bias in blinding of participants & personnel and incomplete outcome data.<sup>28</sup>

### **Rates of deprescribing**

**Table 2** provides details of the deprescribing approaches reported by each eligible study. The approaches included complete withdrawal, discontinuation, reducing dosage, conversion, or substitution of at least one medication. While the majority of studies were before and after intervention designs, four studies compared deprescribing approaches to usual care.<sup>29-31 37</sup> The rates of deprescribing approaches ranged from 13.4% to 75%. In a pilot study to examine the efficacy and safety of switching from subcutaneous injection of insulin to oral administration of vildagliptin in 20 patients with type 2 diabetes undergoing hemodialysis, 11 (55%) of patients switched successfully.<sup>35</sup> In a study that investigated the withdrawal of all antihyperglycemics or reduction in insulin versus no change in diabetes medication in Swedish nursing home patients, withdrawal of the diabetic medication was successful in 24 (75%) patients 3 months after drug discontinuation.<sup>29</sup> One study reported on the potential for deprescribing in care home residents with type 2 diabetes using the NHS PrescQIPP document 'Optimising Safe and Appropriate Medicine Use' (OSAMU) (now replaced by the Improving Medicines and Polypharmacy Appropriateness Clinical Tool (IMPACT)<sup>39</sup>) an evidence-based tool developed to allow for appropriately stopping or continuing medicines in end of life. Out of 67 potentially inappropriate medications, a physician agreed that 26 (38.8%) of these could be discontinued without further question.<sup>36</sup>

## **Glycaemic control**

Seven studies reported outcomes of glycaemic control after deprescribing approaches (**Table 2**). In two studies that compared discontinuation or reduction in dose of antihyperglycemic medication with usual care, no significant differences were found in HbA1c levels.<sup>29 31</sup> In one study,<sup>31</sup> there was no significant difference in hypoglycaemia rates between the groups post-intervention. In eight patients who had their hypoglycaemic medications completely withdrawn over 3-6 months and followed up for a year, there was no significant difference between the mean HbA1c at the point of hypoglycaemic medications withdrawal and at 1 year of follow-up.<sup>33</sup> Switching  $\alpha$ -glucosidase inhibitors from acarbose or voglibose to miglitol did not affect levels of HbA1c and fasting glucose in 35 Japanese patients; in addition, glucose fluctuations improved on switching.<sup>34</sup> In 5 patients with type 2 diabetes and on haemodialysis, discontinuation of insulin and other oral hypoglycaemic agents and switching to liraglutide caused reduction in levels of HbA1c and hypoglycaemic episodes.<sup>38</sup> In a retrospective analysis of veterans converted from glyburide to glipizide, mean HbA1c levels increased by 0.34% 1 year after conversion; however, there was a significant reduction in hypoglycaemic events.<sup>32</sup>

## **Other beneficial and adverse outcomes**

In a study that assessed the efficacy of doubling of statin dose or switching to ezetimibe/simvastatin 10/20 mg combination tablet in patients with type 2 diabetes and/or CHD who failed to achieve a low-density lipoprotein cholesterol (LDL-C) target of  $< 2.5$  mmol/l despite treatment with atorvastatin 10 mg or simvastatin 20 mg, no significant difference was observed between the two groups with regards to adverse events.<sup>28</sup> In two studies that evaluated switching from one antihyperglycaemic agent to another, no adverse events were recorded in both studies.<sup>34 35</sup> In a study comparing discharged off antihyperglycaemic therapy to discharged on antihyperglycaemic therapy in Medicare beneficiaries admitted on diabetes medication, rates of readmissions did not differ significantly between the two groups.<sup>30</sup> In a post-hoc observational analysis of an RCT of blood pressure lowering and intensive

glucose control in patients with type 2 diabetes, permanent discontinuation of blood pressure lowering medication during the study period compared to continuing administration of randomised medications was associated with increased risk of macro- and micro-vascular events.<sup>37</sup> When insulin and other oral hypoglycaemic medications were switched to liraglutide in five patients on haemodialysis, there was improved quality of life in more than half of the patients.<sup>38</sup>

## **Mortality**

Four studies reported mortality outcomes after deprescribing approaches (**Table 2**). Two studies reported that discontinuation of antihyperglycaemic or blood pressure lowering therapy was associated with an increased risk of mortality.<sup>30 37</sup> In the study by Sjoblom and colleagues, which compared complete withdrawal or reduction in dose of antihyperglycemic medication with usual care, there was no significant difference in the risk of mortality for the deprescribing group compared to the non-intervention group.<sup>29</sup> In the study assessing the efficacy of doubling of statin dose or switching to ezetimibe/simvastatin, no patient died.<sup>28</sup>

## **Discussion**

### **Key findings**

Deprescribing is a process which involves withdrawal or stopping inappropriate medication; it is supervised by a healthcare professional and the goal is improving outcomes and managing polypharmacy.<sup>40</sup> Deprescribing is on the increase and it is becoming an established part of the prescribing process, especially in the management of elderly patients with multiple comorbidities.<sup>41 42</sup> Using a systematic review, we have summarized deprescribing approaches and rates and the associated benefits and harms from available published observational and interventional studies conducted in older people with type 2 diabetes, including those with comorbidities such as CHD, hypertension, and kidney disease. The rates of deprescribing approaches (complete withdrawal, discontinuation, reducing dosage, conversion, or substitution of at least one medication) ranged from

13.4% to 75%. Two studies reported successful switching or withdrawal of medication in the majority of patients. For studies reporting relevant data on glycaemic control after deprescribing, majority reported no deterioration in HbA1c levels and hypoglycaemic episodes. On adverse events and mortality, no significant differences were observed between the comparison groups in the majority of studies. However, two studies reported an increased risk of mortality and other vascular events associated with discontinuation of medication.<sup>30 37</sup> It is worth noting in these two studies that the reasons for the discontinuation of medications among participants were not well evaluated in these studies.

### **Comparison with previous studies**

We identified only one systematic review which attempted to synthesize evidence on studies evaluating the effects of deprescribing versus continuing antihyperglycemics in older adults with type 2 diabetes. Black and colleagues included only two studies in their review and concluded that there was limited and low-quality evidence on deprescribing antihyperglycaemic medications.<sup>43</sup> We have conducted an updated assessment of the topic which involved the inclusion of 11 studies assessing different deprescribing approaches and their benefits and harms in elderly patients with type 2 diabetes and other comorbidities. Indeed, the evidence is limited and of low quality, but based on the available evidence, our findings show that deprescribing may be feasible but with some studies suggesting harm. We have also shown that there are still gaps in the evidence as there is no information to guide deprescribing approaches in order to achieve individual targets. However, in one of our included studies, Andreassen and colleagues assessed and validated a medicines optimisation tool which was found to be appropriate in allowing pharmacists to identify medicines eligible for deprescribing in care home residents with type 2 diabetes, thus reducing polypharmacy and potentially adverse events.<sup>36</sup>

### **Implications of findings**

There is evidence available showing that older people with type 2 diabetes and other comorbidities are being overtreated with drugs that cause hypoglycaemia.<sup>15-17 44</sup> Hambling and colleagues observed that elderly people, including those with comorbidities such as CKD or dementia, were managed to similar intensive thresholds as those without CKD or dementia.<sup>44</sup> These elderly patients are especially vulnerable to hypoglycaemic episodes and other adverse events such as fractures, head injuries, CVD, or even death,<sup>9 19 20</sup> given predisposing factors such as advanced age, frailty, long duration of diabetes, polypharmacy, and comorbidities such as CKD and cognitive impairment.<sup>9 10 45 46</sup> Intensive treatment with antihyperglycaemic medication in these patients doubles the risk of hypoglycaemia.<sup>47</sup> As a result of increased emergency call-outs and unplanned hospital admissions, the impact on healthcare systems in financial and resource utilization is enormous.<sup>21 22 48</sup> In addition, only few elderly patients with type 2 diabetes and complex comorbidities actually gain substantial benefit from intensive management.<sup>49 50</sup> The need for deprescribing approaches is therefore of substantial relevance in healthcare. Indeed, deprescribing is already becoming an essential part of prescribing when managing patients with multiple conditions and end of life.<sup>41 42 51</sup> Available evidence from our review suggests that deprescribing approaches is feasible and may be of benefit.

### **Strengths and limitations**

Several strengths and limitations of this study merit careful consideration. We have systematically examined and synthesised data in more detail than ever before, evidence on deprescribing approaches and rates and the harms and benefits associated with deprescribing. Our literature review was detailed and spanned multiple databases, yielding 11 articles on the topic. We have also identified several gaps in the research area. There were a number of limitations, but majority were inherent to the included studies and not the actual review. Given limited and heterogenous outcome data, we were unable to pool data as originally planned in our published protocol (CRD42018102853); however, we were able to summarise the evidence according to identified consistent themes. We included a diversity of study designs such as observational cohorts, case series, post-hoc observational analysis of RCTs, and RCTs

and this was because of the limited evidence on the topic. Given the limitations, the conclusions might be limited due to quality of included studies and inability of studies to report the results in a manner that can assist clinicians in making decisions.

In conclusion, based on limited and mixed study designs, the available data suggests deprescribing is feasible and does not generally lead to harm. There is however no information to guide deprescribing approaches in order to achieve safe individual targets. Urgent research is warranted in this area to guide effective decision making. The findings should be interpreted with caution given limitations in the study designs used, the low methodological quality of majority of the studies, and selective reporting of outcomes.

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## **Contribution**

SS conceived the idea for the article, acted as second review and contributed to the writing. He is the guarantor (the contributor who accepts full responsibility for the finished article, had access to any data, and controlled the decision to publish).

SK led to literature search and the writing.

KK was the third reviewer and contributed to the writing.

XC, PT and CEH all contributed to the writing and proof-reading

### **Conflicts of Interest/Disclosures**

None

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## Figure legends

**Figure 1.** Selection of studies included in the review

