Received: 8 February 2019 | Revised: 19 March 2019 | Accepted: 27 March 2019

DOI: 10.1111/dom.13724

ORIGINAL ARTICLE

WILEY

Deintensification in older patients with type 2 diabetes: A systematic review of approaches, rates and outcomes

Samuel Seidu MD[1] | Setor K. Kunutsor PhD[2] | Pinar Topsever MD[3] | Clare E. Hambling MSc[4] | Francesc X. Cos MD[5] | Kamlesh Khunti PhD[1]

[1]Diabetes Research Centre, Diabetes & Metabolic Medicine, University of Leicester, Leicester, UK

[2]Translational Health Sciences, Bristol Medical School, Musculoskeletal Research Unit, NHS Foundation, National Institute for Health Research Bristol, Biomedical Research Centre, University Hospitals Bristol Trust and University of Bristol, Bristol, UK

[3]Department of Family Medicine, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkey

[4]Department of Public Health and Primary Care, School of Clinical Medicine, Cambridge, UK

[5]Diabetes & Metabolic Medicine, Jordi Gol Institute for Research in Primary Care, The Foundation University Institute for Primary Health, Barcelona, Spain

Correspondence
Samuel Seidu, Diabetes Research Centre, Diabetes & Metabolic Medicine, University of Leicester, Leicester, UK.
Email: sis11@leicester.ac.uk

Funding information
This study was initiated and completed independently by the Primary Care Diabetes European Association for the Study of Diabetes with full funding from Primary Care Diabetes Europe (PCDE). PCDE has received corporate sponsorship from Eli Lilly, Novo Nordisk, Astra Zeneca and Roche Diagnostics, but the companies had no input in the study.

Peer Review
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.13724.

Abstract

Aim: To assess deintensification approaches and rates and evaluate the harm and benefits of deintensification with antidiabetic medication and other therapies among older people (≥ 65 years) with type 2 diabetes with or without 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 were extracted on baseline characteristics, details on deintensification and outcomes, and was synthesized using a narrative approach.

Results: Ten studies (observational cohorts and interventional studies) with data on 26 558 patients with comorbidities were eligible. Deintensification approaches included complete withdrawal, discontinuation, reducing dosage, conversion, or substitution of at least one medication, but the majority of studies were based on complete withdrawal or discontinuation of antihyperglycaemic medication. Rates of deintensification approaches ranged from 13.4%–75%. The majority of studies reported no deterioration in HbA1c levels, hypoglycaemic episodes, falls or hospitalizations on deintensification. On adverse events and mortality, no significant differences were observed among the comparison groups in the majority of studies.

Conclusion: Available but limited evidence suggests that the benefits of deintensification outweigh the harm in older people with type 2 diabetes with or without comorbidities. Given the heterogeneity of patients with diabetes, further research is warranted on which deintensification approaches are appropriate and beneficial for each specific patient population.

KEYWORDS
cardiovascular disease, deintensification, deprescribing, medication, older adults, systematic review, type 2 diabetes

1 | 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.[1] Most patients with type 2 diabetes have at least one complication, which includes cardiovascular disease (CVD), stroke, chronic kidney disease (CKD), retinopathy, and neuropathy.[2] Cardiovascular complications are the leading cause of morbidity and death in these patients.[1]

The major goal of managing type 2 diabetes is to achieve appropriate reduction in glucose levels, in order to minimize the risk of

complications, which include adverse vascular events.[3] To achieve appropriate glycaemic targets as set by guideline bodies, antihyperglycaemic medications are usually initiated individually or in combination [4] in a timely manner when appropriate to prevent therapeutic inertia, which is defined as the failure to alter therapy when it is appropriate to do so.[5] At the same time, there needs to be a balance between the relative risks of clinical inertia (i.e. the failure to advance treatment by a healthcare professional when appropriate to do so) versus overtreatment in the management of glycaemia in patients with diabetes.[6] In older patients with type 2 diabetes, achieving glycaemic control is very problematic, with adverse effects such as hypoglycaemia reported to be common in such patients.[7,8] The consequences of hypoglycaemia impact substantially on patients and the healthcare system: these include physical injury, psychological harm, impaired cognition, reduced quality of life, mortality, additional manpower and resource utilization, and the costs of providing emergency assistance.[9–14] The majority of older type 2 diabetes patients have coexisting frailty and comorbidities such as renal and cognitive impairment, and the risk of hypoglycaemia is particularly high in these patients.[7,9,15] Despite recommendations by guideline bodies to individualize glycaemic targets with risk assessments aimed at avoiding overtreatment and hypogycaemia,[16–18] recent data suggest increased hospital emergencies for hypoglycaemia.[19] Indeed, evidence suggests that older people with complex multiple comorbidities are being overtreated with drugs that cause hypoglycaemia.[20–22] Although some evidence suggests the adverse effects of overtreatment with antihyperglycaemic drugs in older patients outweigh the benefits,[20] data on the potential benefits and harm of stopping, reducing or substituting these antihyperglycaemic agents (i.e. deintensification) in the older patients with type 2 diabetes and comorbidities remain uncertain. Deintensification, as defined by a position statement from Primary Care Diabetes Europe, is the de-escalation or down-titration of glucose-lowering therapy by reducing the dose, deprescribing, or substituting one agent for a less potent glucose-lowering therapy.[23] Deintensification also includes deprescribing, which is the process of withdrawal or stopping inappropriate medication, and the ultimate goal is improving outcomes and managing polypharmacy.[24,25] Deintensification approaches are on the increase and it is becoming an established part of the prescribing process, especially in the management of older patients with multiple comorbidities.[26,27] There is emerging evidence on the efficacy of deintensification from several randomized trials and observational studies conducted in other patient populations.[25] In older patients with type 2 diabetes with or without comorbidities, it is uncertain whether the benefits of deintensification outweigh the harm in these patients. In this context, using a systematic review of all available published observational and interventional evidence, our primary aim was to assess deintensification approaches and rates and evaluate the harm and benefits of deintensification with antidiabetic medication and other therapies among older people (≥ 65 years) with type 2 diabetes with or without other cardiometabolic conditions such as CVD, CKD or dementia. Given that the majority of these patients are also on non-diabetic medication (e.g. lipid-lowering drugs, antihypertensives) for their comorbidities, we also included these medications in our evaluation. We also sought to explore if there are gaps in the existing evidence.

2 | METHODS

2.1 | Eligibility criteria

A predefined protocol was used to conduct this review, which was in accordance with PRISMA and MOOSE guidelines[28,29] (Appendixes S1–S2, see the supporting information) and has been registered in the PROSPERO 2018 prospective register of systematic reviews (CRD42018102853). 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 [randomized controlled trials (RCTs) including cluster and pragmatic trials, and non-randomized controlled trials] that had reported on (i) older patients (≥ 65 years) with type 2 diabetes with or without co-existing cardiometabolic conditions such as CVD, CKD or dementia, who were taking antidiabetic medication with or without other therapies for their conditions; (ii) reported deintensification approaches (stopping drug treatment entirely, reducing dose, gradual tapering, or substitution); and/or (iii) reported outcomes such as measures of glycaemia, admission rates, hospitalizations, complications, mortality, quality of life, and patient satisfaction. The age cut-off applied if the average age of study participants was ≥65 years; more than 75% of study participants were aged ≥65 years; or ability to extract data on participants aged ≥65 years from the study. The following exclusions were applied: (a) studies not reporting deintensification approaches; (b) those not including patients with type 2 diabetes; (c) those including patients <65 years; or (d) studies that included only terminal or palliative patients.

2.2 | Definition of terms

Based on the Population, Intervention, Comparator, and Outcome (PICO) framework, the population included older patients (≥ 65 years) with type 2 diabetes with or without co-existing cardiometabolic conditions such as CVD, CKD or dementia, who were taking antidiabetic medication with or without other therapies for their conditions. The intervention was a deintensification rate, defined as the proportion of patients for whom one medication was stopped, reduced or switched [(n/N)*100], where n denotes number of patients stopping, reducing or switching medication, and N refers to the total number of patients. The comparator included usual care or continuing medications. Outcomes included measures of glycaemia, admission rates, hospitalizations, complications, mortality, quality of life, and patient satisfaction.

2.3 | Data sources and search strategy

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 combinations of keywords related to diabetes and other cardiometabolic conditions (e.g. "diabetes mellitus" and "hypertension"); older patients ("aged", "ageing" and "geriatric"); medication (e.g. "prescription", "antidiabetic" and "hyperglycaemic"); and deintensification (e.g. "deprescribe", "discontinue", "deintensify" and "cessation"). 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 S3 (see the supporting information).

2.4 | 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 against those in the original articles. The titles and abstracts of all articles identified by the broad literature search were assessed independently by two reviewers (S.S. and S.K.K.). Studies that did not meet the inclusion criteria were discarded. Full texts of selected articles were retrieved and assessed to determine if they met the inclusion criteria. Those studies which met the inclusion criteria were included in the review and the data were extracted independently by two reviewers (S.S. and S.K.K.) using a standard data extraction form. The quality of the studies was assessed independently by both reviewers.

Data were 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, deintensification approach (stopping/tapering/switching), and data/risk estimates on benefits and harm of deintensification. 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. Additionally, in the case of multiple publications, data on the study with the most up-to-date or comprehensive information were extracted. Methodological quality of observational cohort studies was assessed based on the nine-star Newcastle–Ottawa Scale (NOS),[30] a validated tool for assessing the quality of non-randomized studies, including cohort and case–control studies. It uses three predefined domains, namely, selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of 4 points for selection, 2 points for comparability, and 3 points for outcome; 9 points on the NOS reflects the highest study quality score. For cross-sectional studies, we assessed quality using the NOS modified for cross-sectional studies (Appendix S4).[31] A maximum score of 8 reflected the highest study quality.

2.5 | Statistical analysis

The characteristics of the deintensification approaches and outcomes reported for each study were summarized in tables and narrative synthesis was performed.

2.6 | Patient and public involvement

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

3 | RESULTS

3.1 | Study identification and selection

Figure 1 shows the flow of studies through the review. The literature search identified 8547 potentially relevant citations. After the initial screening based on titles and abstracts, 59 articles were selected for full text evaluation. Following detailed assessment of the full articles, 49 were excluded because (a) populations were not relevant to review (n = 28); (b) the intervention was not relevant (n = 16); (c) outcomes were not relevant to review (n = 3); (d) one article used the same population sample as another study included in the review; and (e) one was a review article. The remaining 10 articles based on 10 unique studies met the inclusion criteria and were included in the review.[32–41]

3.2 | 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.[32] The mean/median baseline age of participants ranged from 65.8 to 86.5 years. Study designs comprised prospective cohorts (n = 2), retrospective cohorts (n = 2), observational cohorts with controls (n = 2), case series (n = 2), post hoc observational analysis of an RCT (n = 1), and cross-sectional retrospective subanalysis of an RCT (n = 1). No RCT was identified. The sample size of studies ranged from 5 to 11 140 participants. The follow-up duration for studies providing data ranged from 3 months to 4.3 years; however, for the majority of studies, it ranged from 3 to 6 months. Study populations comprised older patients with type 2 diabetes with comorbidities such as coronary heart disease (CHD) and kidney dysfunction, and who were on antihyperglycaemic medication as well as blood pressure medication. Among the observational cohort studies, the quality score using NOS ranged from 3 to 8 and for the cross-sectional study it was 4 (Appendix S5).

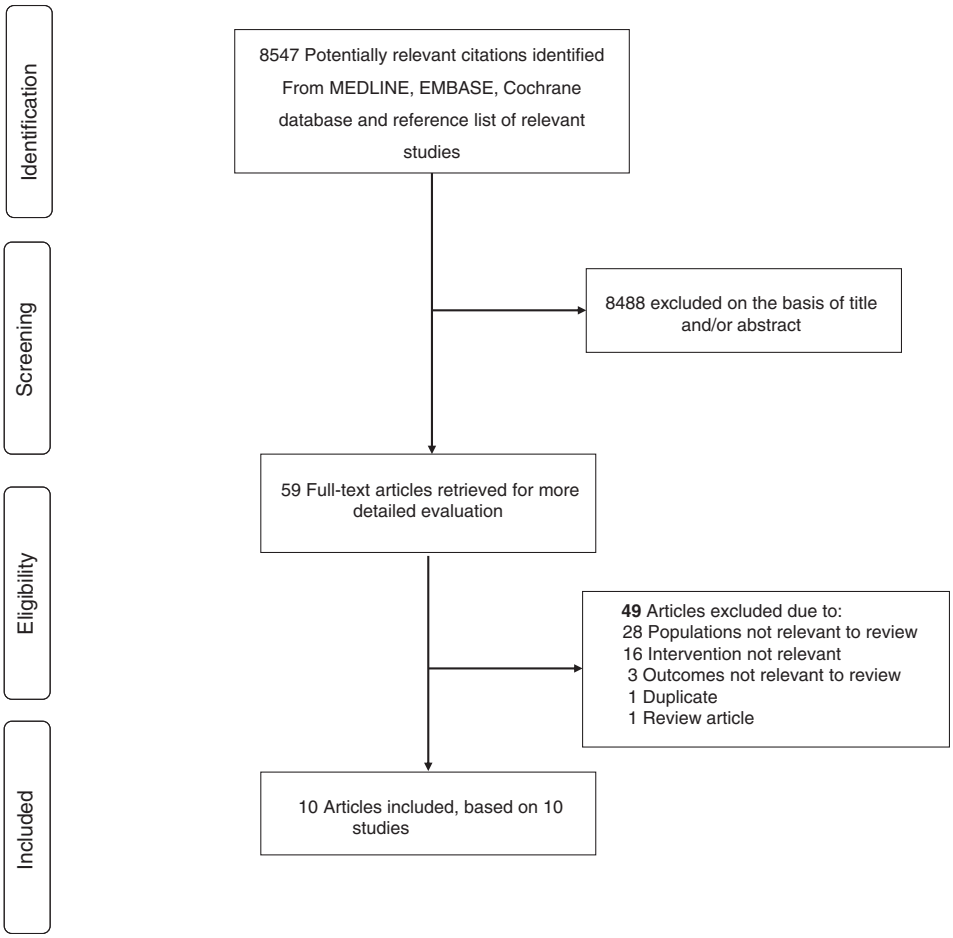

FIGURE 1 Selection of studies included in the review

3.3 | Deintensification approaches and rates

It was planned to synthesize 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.

Table 2 provides details of the deintensification approaches and outcomes reported by each eligible study. The approaches varied and included complete withdrawal, discontinuation, reducing dosage, conversion, or substitution of at least one medication. However, the majority of studies reported on complete withdrawal or discontinuation of therapy. The main reasons for considering deintensification were tight glycaemic control and being at risk of hypoglycaemia, which was reported by five studies.[32,34–36,38] One study reported on the potential for deprescribing in care home residents with type 2 diabetes using a medicines optimization tool, which was validated by a care home physician;[39] although the actual deprescribing was not performed and evaluated in the study, we included it in this review because of its relevance to the topic. Except for one study which was based on blood pressure-lowering therapy,[40] the most common medications that were deintensified were antihyperglycaemic agents comprising sulphonylureas, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, and insulin. The majority of studies were before-and-after study designs, and four studies compared deintensification approaches to usual care.[32–34,40] Lipska and colleagues examined the frequency of discontinuation of antihyperglycaemic agents on discharge among patients with diabetes admitted for acute myocardial infarction on a diabetic regimen;[33] of 8751 patients admitted on at least one antihyperglycaemic agent, 1170 (13.4%) were discharged off antihyperglycaemic therapy. 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 haemodialysis, 11 (55%) patients switched successfully.[38] In a study that investigated the withdrawal of all antihyperglycaemics 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.[32] In the study that 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)[42]], an evidence-based tool developed to allow for appropriately stopping or continuing medicines in end of life care, of the 67 potentially inappropriate medications, a physician agreed that 26 (38.8%) of these could be discontinued without further question.[39]

TABLE 1 Baseline characteristics of studies included in the review

Lead author, publication date, reference number	Name of study (population source)	Location	Study design	Baseline population	Year of baseline survey	Baseline mean/median age (years)	% male	Average follow-up	Total participants	Study quality
Sjoblom, 2008[32]	NR (Nursing homes)	Sweden	Prospective cohort with controls	Older patients with T2DM with HbA1c ≤ 6.0%	2006	84.1	41.8	6 mo	98	4
Lipska, 2010[33]	NHCP (Medicare beneficiaries)	United States	Retrospective cohort	Older patients with diabetes after AMIs and on at least 1 antihyperglycaemic agent	1998–2001	76.5	47.2	1 y	8751	8
Aspinall, 2011[34]	Veteran Affairs Database	United States	Retrospective cohort with controls	Community-dwelling veterans	2007–2008	77.0	99.5	5 mo	6254	7
Skoff, 2011[35]	VHA	United States	Retrospective cohort	Older diabetes veterans with renal dysfunction	2008–2010	74.0	99.3	1 y	141	5
Abdelhafiz, 2014[36]	NR (Outpatient health clinic)	UK	Case series	Older patients with diabetes	NR	86.5	25	1 y	8	NA
Hariya, 2014[37]	NR (Healthcare setting)	Japan	Prospective cohort study	Patients with T2DM	2007–2008	65.8	48.6	3 mo	35	3
Yoshida, 2016[38]	NR (Healthcare setting)	Japan	Prospective cohort study	Patients with T2DM on haemodialysis	2010–2011	66.0	55.0	24 wk	20	3
Andreassen, 2016[39]	CAREMED (clinical trial)	UK	Cross-sectional retrospective sub-analysis of a RCT	Older patients with T2DM	NR	86.0	51.4	NA	106	4
Hirakawa, 2016[40]	ADVANCE	20 countries	Post hoc observational analysis of RCT	Patients with T2DM on blood pressure-lowering and intensive glucose control	2001–2003	65.8	57.5	4.3 y	11 140	8
Kondo, 2017[41]	NR (Healthcare setting)	Japan	Case series	Patients with T2DM on haemodialysis	2011–2012	67.6	80.0	3 mo	5	NA

Abbreviations: AMI, acute myocardial infarction; CHD, coronary heart disease; LDL-C, low density lipoprotein cholesterol; NA, not applicable; NHCP, National Heart Care Project; NR, not reported; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; VHA, Veteran's Health Administration.

TABLE 2 Deintensification approaches and outcomes in eligible studies

Lead author, publication date, reference number	Selection of patients for deintensification	Deintensification approach and description	Comparison/control	Intervention/control	Deintensification rate	Glycaemic control	Other outcomes and adverse effects	Mortality
Sjoblom, 2008[32]	Patients with HbA1c ≤ 6.0% and on antidiabetic drugs or insulin, or both in combination, were invited to participate in the diabetes medication withdrawal	Plasma glucose was measured on 3 consecutive days before medication withdrawal. Complete withdrawal of oral antidiabetic drugs, complete insulin withdrawal when doses were 20 units/day and reduced by half in patients on more than 20 units/day	No change in diabetes medication	32/66	Withdrawal of the diabetic medication was successful in 24 (75%) patients 3 mo after drug discontinuation	HbA1c levels: 5.8% (intervention arm), 6.6% (control arm) at 6 mo		5 out of 32 patients (16%) in deprescribing group compared with 14 out of 66 (21%) in the nonintervention group died: 0.74 (0.29–1.87)
Lipska, 2010[33]	Reasons behind the discontinuation of antihyperglycaemic therapy were not evaluated	Discontinuation of antihyperglycaemic agents on discharge. Was based on retrospective analysis of a database	Discharged on antihyperglycaemic therapy	1170/7581	13.4% discharged off antihyperglycaemic therapy	NR	Readmissions did not differ between the 2 groups	Discontinuation of therapy was associated with HR (95% CI) of 1 y mortality of 1.29 (1.15–1.45)
Aspinall, 2011[34]	Patients considered at increased risk of hypoglycaemia were on glyburide with a calculated creatinine clearance of <50 mL/min	Discontinuation of glyburide. Information regarding risk of hypoglycaemia in older persons on glyburide and instructions for switching to alternative agent provided to pharmacists, who could then contact patients' physicians to deprescribe	Received usual care	4368/1886	During the study period, glyburide was discontinued in 71.5% (3123/4368) of the patients in the targeted cohort and in 56.0% (1057/1886) of the nontargeted cohort	No significant difference in HbA1c levels was found between the group of patients who discontinued glyburide and those who continued taking this medication. No significant difference was observed in the rates of hypoglycaemia postintervention between the intervention and control groups	NR	NR

TABLE 2 (Continued)

Lead author, publication date, reference number	Selection of patients for deintensification	Deintensification approach and description	Comparison/control	Intervention/control	Deintensification rate	Glycaemic control	Other outcomes and adverse effects	Mortality
Skoff, 2011[35]	Patients considered at increased risk of hypoglycaemia were on glyburide with renal dysfunction	Conversion from glyburide to glipizide	NA	NA	NA	Increase in HbA1c level of 0.34% at 1 y after conversion. Hypoglycaemia was confirmed in 44 (31.2%) patients during glyburide treatment and in 18 (12.8%) patients during treatment with glipizide	Liver and renal functions were similar at the point of medication withdrawal compared with their levels at the point of introducing diabetes treatment	NR
Abdelhafiz, 2014[36]	Tight glycaemic control (HbA1c ≤ 6%) was the main reason for medication withdrawal in 2 patients, while recurrent episodes of hypoglycaemia was the main reason in the other 6 patients	Complete withdrawal of hypoglycaemic medication over 3–6 mo	NA	NA	NA	No deterioration of glycaemic control over the 1 y follow-up period. No significant difference between the mean HbA1c at the point of hypoglycaemic medications withdrawal and at 1 y of follow-up	NR	NR
Hariya, 2014[37]	Patients with HbA1c values ranging from 6.9–8.3% being treated with the highest approved doses of alpha-glucosidase inhibitors	Switching alpha-glucosidase inhibitors from acarbose or voglibose to miglitol and continued for 3 mo	NA	NA	NA	Switch did not affect levels of HbA1c and fasting glucose. Glucose fluctuations were improved on switch	No adverse events recorded	NR
Yoshida, 2016[38]	Patients on haemodialysis and receiving subcutaneous insulin injection	Switching from subcutaneous injection of insulin to oral administration of a DPP-4 inhibitor. Oral vildagliptin at a low dose was started on the day	NA	NA	11 (55%) patients switched successfully	Glycated albumin was <1.5% during the post switch	No adverse events recorded	NR

TABLE 2 (Continued)

Lead author, publication date, reference number	Selection of patients for deintensification	Deintensification approach and description	Comparison/control	Intervention/control	Deintensification rate	Glycaemic control	Other outcomes and adverse effects	Mortality
		insulin injections were discontinued						
Andreassen, 2016[39]	NA	Potential for deprescribing	NA	NA	Out of the total of 67 PIMs, the physician agreed that 26 of these could be discontinued without further question (38.8%).	NA	NR	NR
Hirakawa, 2016[40]	Because of adverse effects, inability, or unwillingness to continue with medication	Permanent discontinuation of BP lowering medication. Based on a retrospective analysis of a database	Those who did not discontinue	1557/9583	14%	NR	Discontinuation of BP lowering medication was associated with HR (95% CI) of macrovascular events 3.23 (2.75–3.79); microvascular events 1.38 (1.11–1.71); and combined macrovascular and microvascular events 2.24 (1.96–2.57)	Discontinuation of BP-lowering medication was associated with HR (95% CI) of mortality 7.99 (6.92–9.21)
Kondo, 2017[41]	Patients on haemodialysis	Discontinuation of insulin and switching to liraglutide	NA	NA	NA	Reduction in levels of HbA1c. Reduction in hypoglycaemic episodes	Significant decrease in cardiothoracic ratio on chest radiography. Improved quality of life in more than half of patients	NR

Abbreviations: BP, blood pressure; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; NR, not reported; PIM, potentially inappropriate medicine.

3.4 | Glycaemic control

Seven studies reported outcomes of glycaemic control after deintensification approaches (Table 2). In two studies that compared discontinuation or reduction in dose of antihyperglycaemic medication with usual care, no significant differences were found in HbA1c levels.[32,34] In one study,[34] there was no significant difference in hypoglycaemia rates between the groups postintervention. In eight patients who had their hypoglycaemic medications completely withdrawn over 3-6 months and were 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.[36] Switching α-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.[37] In five 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.[41] 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.[35]

3.5 | Other beneficial and adverse outcomes

In two studies that evaluated switching from one antihyperglycaemic agent to another, no adverse events were recorded in both studies.[37,38] In a study comparing patients whose antihyperglycaemic therapy was discontinued on discharge versus those discharged on antihyperglycaemic therapy, in Medicare beneficiaries admitted on diabetes medication, rates of readmissions did not differ significantly between the two groups.[33] 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 with continuing administration of randomized medications was associated with increased risk of macro- and micro-vascular events.[40] 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.[41]

3.6 | Mortality

Three studies reported mortality outcomes after deintensification approaches (Table 2). Two studies reported that discontinuation of antihyperglycaemic or blood pressure-lowering therapy was associated with an increased risk of mortality.[33,40] In the study by Sjoblom and colleagues, which compared complete withdrawal or reduction in dose of antihyperglycaemic medication with usual care, there was no significant difference in the risk of mortality for the deintensification group compared with the non-intervention group.[32]

4 | DISCUSSION

4.1 | Key findings

Using a systematic review, we have assessed deintensification approaches and rates and the associated benefits and harm 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. Deintensification approaches identified included complete withdrawal, discontinuation, reducing dosage, conversion, or substitution of at least one medication; however, the majority of studies were based on complete withdrawal or discontinuation of antihyperglycaemic medication. Deintensification rates varied based on the approach but generally ranged from 13.4% to 75%. For studies reporting relevant data on glycaemic control after deintensification, the majority reported no deterioration in HbA1c levels or hypoglycaemic episodes in the patient populations. On adverse events and mortality, no significant differences were observed between the comparison groups in the majority of studies.

4.2 | Comparison with previous studies

We identified only one systematic review which attempted to synthesize evidence on studies evaluating the effects of deprescribing versus continuing antihyperglycaemics 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.[43] We have adopted a broader approach, which involved assessing deintensification approaches and their benefits and harm in older patients with type 2 diabetes with or without comorbidities. Indeed, the evidence is limited and of low quality, but based on the available evidence, our findings show that deintensification may be feasible and its benefits generally outweigh the harm. We have also identified some gaps in the evidence. None of the studies provided specific guidance on how patients were identified for the deintensification approach; however, a few studies reported considering deintensification based on patients with tight glycaemic control or at high risk for hypoglycaemia. Although one of the included studies did not specifically evaluate a deintensification approach, the authors assessed and validated a medicines optimization 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.[39] Finally, although discontinuation of therapy was the most common deintensification approach reported, it was difficult to conclude from the findings that a particular approach was associated with more benefits.

4.3 | Implications of findings

For several decades, clinical practice guidelines for glycaemic control have focused on intensifying therapy to achieve target levels of risk

factors, such as reducing HbA1c levels to less than 7.0%.[44,45] However, it appears this overtreatment or treatment intensification is not harmless or associated with more benefits. A number of RCTs have shown that intensive glycaemic control directed at lower HbA1c targets is associated with only minor cardiovascular benefits, but increased adverse events such as mortality.[46] Evidence shows that older people with type 2 diabetes and other comorbidities are being overtreated with drugs that cause hypoglycaemia.[20–22,47] Hambling and colleagues observed that older people, including those with comorbidities such as CKD or dementia, were managed to similar intensive thresholds as those without CKD or dementia.[47] These older patients are especially vulnerable to hypoglycaemic episodes and other adverse events such as fractures, head injuries, CVD, or even death,[9,11,12] given predisposing factors such as advanced age, frailty, long duration of diabetes, polypharmacy, and comorbidities such as CKD and cognitive impairment.[9,15,48,49] Intensive treatment with antihyperglycaemic medication in these patients doubles the risk of hypoglycaemia.[50] In addition, only a few older patients with type 2 diabetes and complex comorbidities actually gain substantial benefit from intensive management.[51,52] The need for deintensification approaches is therefore of particular relevance in healthcare. Indeed, deintensification or deprescribing is already becoming an essential part of prescribing when managing patients with multiple conditions and end of life.[26,27,53] Available evidence from our review suggests that deintensification is associated with more benefits than harm and it is feasible. However, although discontinuation or complete withdrawal of antihyperglycaemic therapy is very commonly used, it is uncertain if it is associated with more benefits compared with other approaches. Furthermore, guidance is needed on how to identify patients for deintensification, and which approaches will be suitable for a particular patient.

4.4 | Strengths and limitations

Some strengths and limitations of this study merit careful consideration. Compared with the only relevant previous review, which only evaluated the effects of deprescribing antihyperglycaemic medications in older adults with type 2 diabetes,[43] our review is more detailed and focuses on deintensification in patients with or without comorbidities. Our literature search was detailed and spanned multiple databases, yielding 10 articles on the topic. There were a number of limitations, but the majority were inherent to the included studies and not the actual review. The data were sparse and heterogenous, hence we were unable to pool data as originally planned in our published protocol (CRD42018102853); however, we were able to summarize the evidence according to identified consistent themes. We included a diversity of study designs such as observational cohorts, case series, and post hoc observational analysis of RCTs, and these were generally not of high methodological quality. The majority of studies were of short follow-up durations of a few months, which precludes inadequate evaluation of the impact of an intervention. Furthermore, studies selectively reported outcomes and did not report results in a manner that could assist clinicians in making decisions. Given these limitations, the findings should be interpreted with caution.

In conclusion, available but limited evidence based on mixed study designs suggests that the benefits of deintensification outweigh the harm in older people with type 2 diabetes with or without comorbidities. The data also suggest deprescribing is feasible. There are still some unanswered questions. There is limited information to guide which deprescribing approaches to use in order to achieve safe individual targets in older patients. The appropriate glycaemic control targets in such patients are also uncertain. Guideline bodies have started to recognize the harm of overtreatment in older patients with diabetes, and several recommendations have been made to reflect the heterogeneity of these patients. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines for diabetes treatment recommend an individualized approach based on the preference of the patient, comorbidities, severity of diabetes-related complications, and life expectancy.[44] In recent guidelines, the ADA, the American Geriatrics Society, and the American Board of Internal Medicine's Choosing Wisely campaign recommend target HbA1c levels of 7.5% or 8.0% for older patients and those with limited life expectancy.[54–56] Given the heterogeneity of patients with diabetes, further research is warranted on which deintensification approaches are appropriate and beneficial for each specific patient population.

ACKNOWLEDGMENTS

S. Seidu and K. Khunti acknowledge support from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – East Midlands (NIHR CLAHRC – EM), the Leicester Clinical Trials Unit and the NIHR Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit, which is a partnership between University Hospitals of Leicester NHS Trust, Loughborough University and the University of Leicester. S.K. Kunutsor is supported by the NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

CONFLICT OF INTEREST

Nothing relevant to declare.

AUTHOR CONTRIBUTIONS

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). SKK led the 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 proofreading.

ORCID

Setor K. Kunutsor https://orcid.org/0000-0002-2625-0273
Kamlesh Khunti https://orcid.org/0000-0003-2343-7099

REFERENCES

1. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018; 14:88-98.
2. Patel P, Macerollo A. Diabetes mellitus: diagnosis and screening. *Am Fam Physician*. 2010;81:863-870.
3. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95 783 individuals followed for 12.4 years. *Diabetes Care*. 1999;22:233-240.
4. Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. *Diabetes Care*. 2010;33:1859-1864.
5. Khunti K, Davies MJ. Clinical inertia-Time to reappraise the terminology? *Prim Care Diabetes*. 2017;11:105-106.
6. Khunti K, Davies MJ. Clinical inertia versus overtreatment in glycaemic management. *Lancet Diabetes Endocrinol*. 2018;6:266-268.
7. Abdelhafiz AH, Rodriguez-Manas L, Morley JE, Sinclair AJ. Hypoglycemia in older people - a less well recognized risk factor for frailty. *Aging Dis*. 2015;6:156-167.
8. Lee SJ, Boscardin WJ, Stijacic Cenzer I, Huang ES, Rice-Trumble K, Eng C. The risks and benefits of implementing glycemic control guidelines in frail older adults with diabetes mellitus. *J Am Geriatr Soc*. 2011;59:666-672.
9. Rajendran R, Hodgkinson D, Rayman G. Patients with diabetes requiring emergency department care for hypoglycaemia: characteristics and long-term outcomes determined from multiple data sources. *Postgrad Med J*. 2015;91:65-71.
10. Nicolucci A, Pintaudi B, Rossi MC, et al. The social burden of hypoglycemia in the elderly. *Acta Diabetol*. 2015;52:677-685.
11. Hsu PF, Sung SH, Cheng HM, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: a nationwide population-based study. *Diabetes Care*. 2013;36:894-900.
12. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. *Diabetes Care*. 2015;38:316-322.
13. Farmer AJ, Brockbank KJ, Keech ML, England EJ, Deakin CD. Incidence and costs of severe hypoglycaemia requiring attendance by the emergency medical services in South Central England. *Diabet Med*. 2012;29:1447-1450.
14. Newton CA, Adeel S, Sadeghi-Yarandi S, et al. Prevalence, quality of care, and complications in long term care residents with diabetes: a multicenter observational study. *J Am Med Dir Assoc*. 2013;14:842-846.
15. Mattishent K, Loke YK. Bi-directional interaction between hypoglycaemia and cognitive impairment in elderly patients treated with glucose-lowering agents: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2016;18:135-141.
16. World Health Organization. *International Classification of Diseases*, 9th revision (ICD-9). Geneva, Switzerland: World Health Organization; 1977.
17. *International Statistical Classification of Diseases*, 10th revision (ICD-10). Geneva, Switzerland: World Health Organization, World Health Organization; 1992.
18. NIH Consensus Development Panel on Physical Activity and Cardiovascular Health. Physical activity and cardiovascular health. *JAMA*. 1996;276:241-246.
19. Zaccardi F, Davies MJ, Dhalwani NN, et al. Trends in hospital admissions for hypoglycaemia in England: a retrospective, observational study. *Lancet Diabetes Endocrinol*. 2016;4:677-685.
20. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. *JAMA Intern Med*. 2015;175:356-362.
21. Penfornis A, Fiquet B, Blickle JF, Dejager S. Potential glycemic overtreatment in patients >/=75 years with type 2 diabetes mellitus and renal disease: experience from the observational OREDIA study. *Diabetes Metab Syndr Obes*. 2015;8:303-313.
22. Thorpe CT, Gellad WF, Good CB, et al. Tight glycemic control and use of hypoglycemic medications in older veterans with type 2 diabetes and comorbid dementia. *Diabetes Care*. 2015;38:588-595.
23. Hambling CE, Khunti K, Cos X, et al. Factors influencing safe glucose-lowering in older adults with type 2 diabetes: a PeRsOn-centred ApproaCh To IndiVidualisEd (PROACTIVE) Glycemic Goals for older people: a position statement of primary care diabetes Europe. *Prim Care Diabetes*. 2019. pii:S1751-9918(18)30300-0. https.//doi.org./10.1016/j.pcd.2018.12.005.
24. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging definition of 'deprescribing' with network analysis: implications for future research and clinical practice. *Br J Clin Pharmacol*. 2015;80:1254-1268.
25. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med*. 2015;175: 827-834.
26. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. *Arch Intern Med*. 2010;170:1648-1654.
27. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med*. 2006;166:605-609.
28. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of Observational Studies in Epidemiology. *JAMA*. 2000;283:2008-2012.
29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
30. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2011. www.ohri.ca/programs/clinical_epidemiology/oxford.asp.; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 10, 2015.
31. Kunutsor SK, Apekey TA, Laukkanen JA. Association of serum total osteocalcin with type 2 diabetes and intermediate metabolic phenotypes: systematic review and meta-analysis of observational evidence. *Eur J Epidemiol*. 2015;30:599-614.
32. Sjoblom P, Anders T, Lofgren UB, et al. Can diabetes medication be reduced in elderly patients? An observational study of diabetes drug withdrawal in nursing home patients with tight glycaemic control. *Diabetes Res Clin Pract*. 2008;82:197-202.
33. Lipska KJ, Wang Y, Kosiborod M, et al. Discontinuation of antihyperglycemic therapy and clinical outcomes after acute myocardial infarction in older patients with diabetes. *Circ Cardiovasc Qual Outcomes*. 2010;3:236-242.
34. Aspinall SL, Zhao X, Good CB, et al. Intervention to decrease glyburide use in elderly patients with renal insufficiency. *Am J Geriatr Pharmacother*. 2011;9:58-68.
35. Skoff RA, Waterbury NV, Shaw RF, Egge JA, Cantrell M. Glycemic control and hypoglycemia in Veterans Health Administration patients converted from glyburide to glipizide. *J Manag Care Pharm*. 2011;17: 664-671.
36. Abdelhafiz AH, Chakravorty P, Gupta S, Haque A, Sinclair AJ. Can hypoglycaemic medications be withdrawn in older people with type 2 diabetes? *Int J Clin Pract*. 2014;68:790-792.

37. Hariya N, Mochizuki K, Inoue S, et al. Switching alpha-glucosidase inhibitors to miglitol reduced glucose fluctuations and circulating cardiovascular disease risk factors in type 2 diabetic Japanese patients. *Drugs R D*. 2014;14:177-184.
38. Yoshida N, Babazono T, Hanai K, Uchigata Y. Switching from subcutaneous insulin injection to oral vildagliptin administration in hemodialysis patients with type 2 diabetes: a pilot study. *Int Urol Nephrol*. 2016;48:1349-1355.
39. Andreassen LM, Kjome RL, Solvik UO, Houghton J, Desborough JA. The potential for deprescribing in care home residents with Type 2 diabetes. *Int J Clin Pharm*. 2016;38:977-984.
40. Hirakawa Y, Arima H, Webster R, et al. Risks associated with permanent discontinuation of blood pressure-lowering medications in patients with type 2 diabetes. *J Hypertens*. 2016;34:781-787.
41. Kondo M, Toyoda M, Kimura M, Ishida N, Fukagawa M. Favorable effect on blood volume control in hemodialysis patients with type 2 diabetes after switching from insulin therapy to liraglutide, a human glucagon-like peptide-1 analog--results from a pilot study in Japan. *Tokai J Exp Clin Med*. 2017;42:52-57.
42. Avenell A, MacLennan GS, Jenkinson DJ, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). *J Clin Endocrinol Metab*. 2012;97:614-622.
43. Black CD, Thompson W, Welch V, et al. Lack of evidence to guide deprescribing of antihyperglycemics: a systematic review. *Diabetes Ther*. 2017;8:23-31.
44. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140-149.
45. Mosenzon O, Pollack R, Raz I. Treatment of Type 2 Diabetes: from "Guidelines" to "Position Statements" and Back: recommendations of the Israel National Diabetes Council. *Diabetes Care*. 2016;39:S146-S153.
46. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ*. 2011;343:d4169.
47. Hambling CE, Seidu SI, Davies MJ, Khunti K. Older people with Type 2 diabetes, including those with chronic kidney disease or dementia, are commonly overtreated with sulfonylurea or insulin therapies. *Diabet Med*. 2017;34:1219-1227.
48. Abdelhafiz AH, Koay L, Sinclair AJ. The effect of frailty should be considered in the management plan of older people with Type 2 diabetes. *Future Sci OA*. 2016;2:FSO102.
49. Giorda CB, Ozzello A, Gentile S, et al. Incidence and risk factors for severe and symptomatic hypoglycemia in type 1 diabetes. Results of the HYPOS-1 study. *Acta Diabetol*. 2015;52:845-853.
50. McCoy RG, Lipska KJ, Yao X, Ross JS, Montori VM, Shah ND. Intensive treatment and severe hypoglycemia among adults with type 2 diabetes. *JAMA Intern Med*. 2016;176:969-978.
51. Blaum C, Cigolle CT, Boyd C, et al. Clinical complexity in middle-aged and older adults with diabetes: the Health and Retirement Study. *Med Care*. 2010;48:327-334.
52. Cigolle CT, Kabeto MU, Lee PG, Blaum CS. Clinical complexity and mortality in middle-aged and older adults with diabetes. *J Gerontol A Biol Sci Med Sci*. 2012;67:1313-1320.
53. Todd A, Holmes HM. Recommendations to support deprescribing medications late in life. *Int J Clin Pharm*. 2015;37:678-681.
54. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35:1364-1379.
55. Workgroup AGSCW. American Geriatrics Society identifies five things that healthcare providers and patients should question. *J Am Geriatr Soc*. 2013;61:622-631.
56. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults: a consensus report. *J Am Geriatr Soc*. 2012;60:2342-2356.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Seidu S, Kunutsor SK, Topsever P, Hambling CE, Cos FX, Khunti K. Deintensification in older patients with type 2 diabetes: A systematic review of approaches, rates and outcomes. *Diabetes Obes Metab*. 2019;21:1668–1679. https://doi.org/10.1111/dom.13724