DIABETICMedicine

DOI: 10.1111/dme.13859

Invited Review

Evidence-based diabetes care for older people with Type 2 diabetes: a critical review

A. J. Sinclair[1], A. H. Abdelhafiz[2], A. Forbes[3] and M. Munshi[4]

[1]Foundation for Diabetes Research in Older People, Diabetes Frail Ltd, Droitwich, [2]Rotherham General Hospital, Rotherham, [3]Kings College, London, UK and [4]Harvard Medical School and Joslin Clinic, Boston, MA, USA

Accepted 5 November 2018

Abstract

In our ageing society diabetes imposes a significant burden in terms of the numbers of people with the condition, diabetes-related complications including disability, and health and social care expenditure. Older people with diabetes can represent some of the more complex and difficult challenges facing the clinician working in different settings, and the recognition that we have only a relatively small (but increasing) evidence base to guide us in diabetes management is a limitation of our current approaches. Nevertheless, in this review we attempt to explore what evidence there is to guide us in a comprehensive scheme of treatment for older adults, often in a high-risk clinical state, in terms of glucose lowering, blood pressure and lipid management, frailty care and lifestyle interventions. We strive towards individualized care and make a call for action for more high-quality research using different trial designs.

Diabet. Med. 36: 399–413 (2019)

Introduction and background

It is estimated that in 2017 there were 451 million (age 18–99 years) people with diabetes worldwide, and these figures are expected to increase to 693 million by 2045 [1]. A major shift in the epidemiology of diabetes has been to those aged 60–79 years [2]. Apart from this advancing tide of older people with diabetes, the ageing process itself is increasing the number of people living with the sequelae of ill health, chronic diseases, frailty and injuries, all of which enhance disability and functional decline, and pose real clinical challenges and burdens in those with Type 2 diabetes [3]. Older people with diabetes should be a priority target for focused interventions that bring about improved cardiovascular outcomes, enhanced safety and improved survival if the latter has worthwhile disability-free years and associated quality of life [4]. The important area of Type 1 diabetes in older adults is outside the scope of this review but must be addressed in due course.

We recognize that older people with diabetes can span four decades (ages 60–90 years and older), are not a homogeneous group and range from robust adults still in employment to frail residents of nursing homes. Thus, their cognitive and physical status vary widely, and they often have complex health and social care needs [4]. We therefore consider that our review of the literature in general pertains to those aged 70 years and over because the risks of comorbid illness, frailty and dependency begin to rise after this age, but we accept that other organizations may define being 'old' as less or more than 70 years [5]. It is also important to recognize that to produce valid and evidence-based recommendations for care, it is usually necessary to extrapolate research findings from clinical trials in younger adults, which is a limitation that has implications for developing clinical guidelines [6]. The modern management of older people with diabetes requires an acceptance by clinicians that recommendations of care should be tailored to the individual and take into consideration important factors such as changes in functional status, the comorbid illness profile, whether or not a person is dependent and their estimated life expectancy. These can have a marked influence on management goals, what care model is adapted, and how ongoing and follow-up care is delivered. We call this an 'individualizing care' scheme (Box 1).

Diabetes care for older people is often not straightforward for the reasons cited above, but as advancing age brings about increasing complexity of both the person with diabetes and the management of the illness itself, clinicians face greater challenges to their skills and competence. The different pathway to Type 2 diabetes in older individuals compared with younger individuals reflects changes in body composition, marked changes in insulin resistance in muscle and adipose tissues, a decrease in β-cell capacity and loss of normal insulin pulsatility, and the progressive negative effects on glucose tolerance of comorbid illness, onset of

Correspondence to: Alan Sinclair. E-mail: Sinclair.5@btinternet.com.

What's new?

- This review represents a modern, up-to-date account of published evidence that seeks to examine the significance of previous research relating to the management of diabetes in older people.
- The review also provides a diagrammatic view of the development of the complex illness scenarios seen in ageing people with diabetes, and provides the first detailed algorithm for developing individualized care programmes in this often vulnerable group.
- The evidence review takes us through glucose-lowering trials involving older people, a discussion of important cardiovascular outcome and safety trials relevant to the elderly, in addition to a discussion of insulin therapy, lifestyle interventions and managing frailty.
- This review concludes with a call to action to promote new research in older adults with diabetes with the hope of optimizing clinical outcomes in the future.

frailty and polypharmacy, all of which are superimposed on the ageing process [4,9]. It is inevitable that some alterations or modulation of management goals will be necessary with advancing age as health risk increases and, for convenience, we have used age by decade as a way of demonstrating this. Some of the components of this pathway to diabetes and person–illness complexity are shown in Fig. 1.

Purpose of the review

This review provides an up-to-date summary of the evidence that defines the relationship between glycaemic control and outcome in older people with Type 2 diabetes, what interventions have been undertaken that relate to glucose-lowering and other care outcomes, what clinical guidance is available to enhance quality of care, and what research is needed to assist the clinician in providing evidence-based individualized diabetes care.

Box 1 Modern goals of diabetes care for older adults – generic to the person with diabetes, carers and health professionals [6–9]

- Mandatory individualized management plan that takes into consideration different functional and comorbid categories, and duration of diabetes.
- Evidence-based prescribing for glucose-lowering agents and setting appropriate targets adjusted according to the category and wish of the person with diabetes.
- Proactive shared commitment to reduce the risk of cardiovascular disease and other non-cardiac vascular disorders, renal failure, visual loss, cognitive dysfunction, mobility disorder, functional decline and the development of frailty or disability.
- Minimize the risk of hypoglycaemia and prevent unnecessary hospitalization.
- Proactive monitoring to minimize the threat to independence, self-care capacity and quality of life.

Review methodology

Initial screening was undertaken by each author to remove studies that were not appropriate or had no relevance to their assigned tasks within the writing group. As documented previously [10], we used a model of methodology to conduct a comprehensive and detailed narrative review that minimizes selection bias according to the elements given below.

Data sources and search enquiry

Our detailed literature enquiry also required an assessment of relevant articles/reviews and outputs from key national and international diabetes, endocrine and clinical gerontological societies, and professional bodies. These were: Diabetes UK, American Endocrine Society, International Diabetes Federation (IDF), American Diabetes Association (ADA), Canadian Diabetes Association, European Association for the Study of Diabetes, American Medical Directors Association, British Geriatrics Society, New Zealand Society of Diabetes, Australian Diabetes Society and the American Geriatrics Society.

Databases searched were: Google Scholar, MEDLINE, CINHAL Complete and Embase. We used the following medical subject heading (MeSH) terms: older people, diabetes mellitus, aged, glucose control, guidelines, evidence base, interventions and clinical trials. We limited our selection to English language articles. The titles of all articles were reviewed for relevance. Inclusion criteria were then applied to all articles by examining abstracts, full book texts or a combination of these. A manual review of any further relevant citations was undertaken if they had been overlooked during the database searches. The authors recognize that a limitation of this search strategy is that we may be missing contributions from non-English language scientific resources and journals.

Study selection

We included studies only if the following inclusion criteria were satisfied: (1) randomized clinical trials (RCTs) or smaller clinical studies that contain information about or derived from the generic terms 'older people', 'aged', 'senior citizens' or 'elderly'; (2) they included interventional, observational or descriptive data from studies involving older people with diabetes, or data or reviews of relevant audit, diabetes care policies, or educational programmes for our defined subject population; and (3) described a range of glucose-lowering therapies or other non-pharmacological

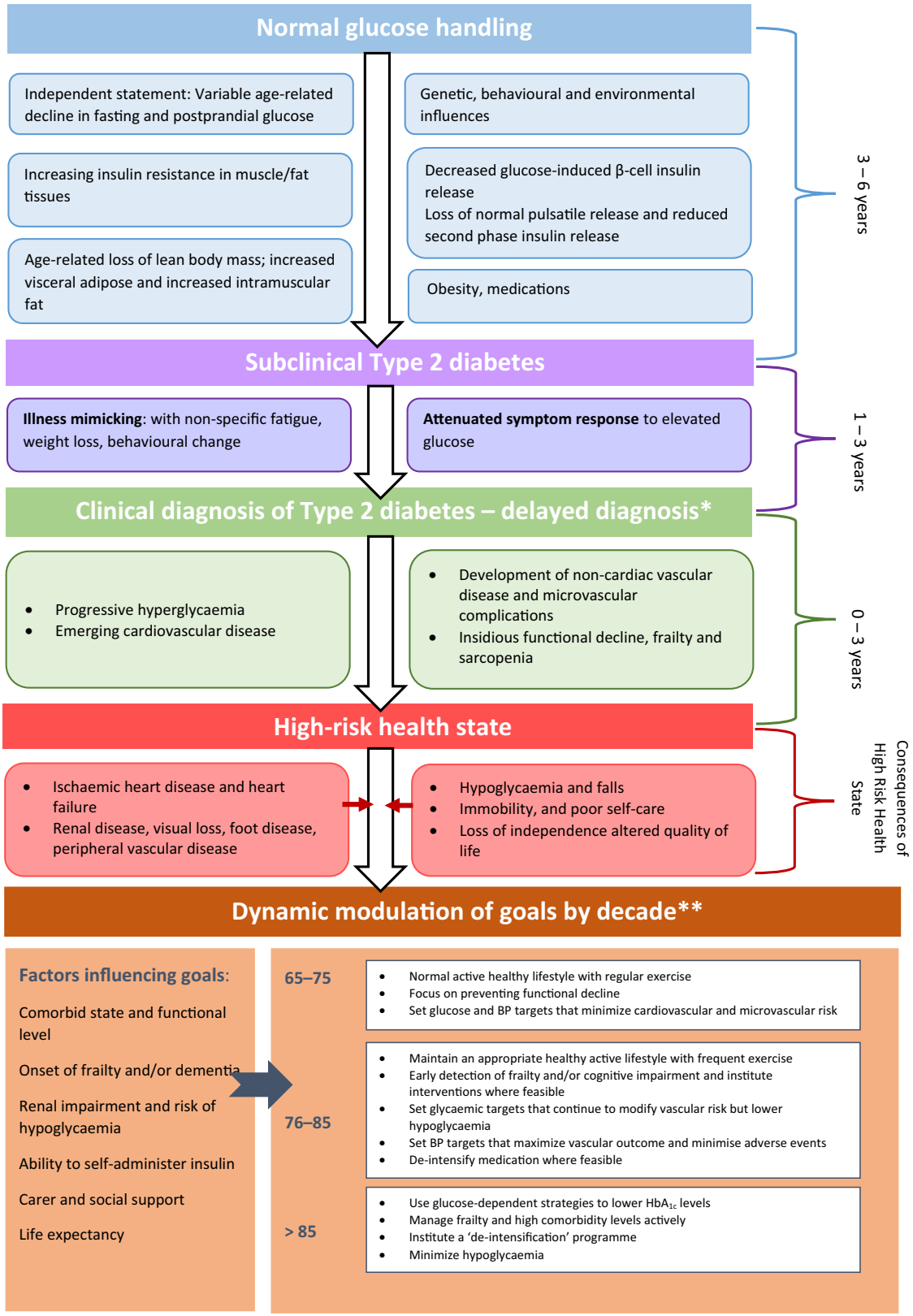

FIGURE 1 Diabetes in older adults – illness complexity leading to modulation of goals. *Provides an opportunity for screening for diabetes in high-risk groups and at opportunistic healthcare encounters. **Chronological age is only one of several factors modulating goals, but this framework represents a guide to decision-making and focusing care

treatments that sought to enhance diabetes care in older people.

Guidelines (and Position Statements) were included if they had clinical relevance to the subject population (e.g. diabetes in older people) or topic area (e.g. cardiovascular outcome), and were written by professional societies or by national or international consensus expert groups. The key issue was that guidance was designed to improve the quality of diabetes care delivered.

Data extraction

All articles/studies derived from the search enquiry were independently examined by two authors (AJS, AHA) and data were extracted using a standardized format according to their relevance to the review subject. AF and MM also independently examined all reference materials relating to glycaemic control in older people, while each intervention study was independently reviewed by the authors according to their writing group tasks. AJS and AHA independently reviewed guidelines and related material. Detailed discussion, review of any conflicts in data interpretation and mutual agreement resolved any disagreements between the reviewers. We have included data relating to the design of studies, the nature of the research question, characteristics of people involved as participants, key findings and outcomes achieved. For the intervention trials, we have included information on study design, nature of participants, the intervention used and main findings. The information obtained for the clinical guidelines reviews summarized the names of the professional organization, the main reason for the guideline development, what was the key methodology involved and how recommendations were framed.

The issue of glycaemic control – what studies tell us?

In Table 1, we summarize the key studies that have examined the role of glycaemic control, the intensity of treatment regimens and their impact on microvascular and macrovascular complications. Although some benefits of intensive glycaemic control were seen in the prevention of microvascular complications, there were no benefits for major cardiovascular events or mortality. Although these studies primarily evaluated middle-aged people (mean age 55–65 years), subgroup analysis in the older age cohort did not show distinct differences in the role of glycaemic control. In recent years, several studies have looked specifically at older adults with diabetes. Almost all of them are observational or retrospective cohort studies.

The common themes emerging from these studies are:

- there are no benefits of tight control below a HbA_{1c} range of 53–59 mmol/mol (7.0–7.5%) in older adults;
- there is a 'J'- or a 'U'-shaped relationship between HbA_{1c} and the risk of diabetic complications including mortality, with an optimal HbA_{1c} around 59–64 mmol/mol (7.5–8%);
- the presence of a high comorbidity burden reduces the benefits of improved glycaemia;
- low (< 42 mmol/mol; <6%) and high (> 75 mmol/mol; >9%) HbA_{1c} levels show more harm than benefit in older adults;
- stable glycaemic control, measured by HbA_{1c} values in the mid-range (42–64 mmol/mol; 6–8%), over time may be more beneficial than lower HbA_{1c} values.

A comprehensive review of care home diabetes, including an examination of interventions undertaken has been published recently [10].

Summary of blood pressure and lipid-lowering studies in older adults with diabetes

The active management of both hypertension and dyslipidaemia in older adults with diabetes is crucial to reduce cardiovascular risk.

People with diabetes have a high baseline cardiovascular risk and for every 1 mmHg fall in blood pressure, additional benefit is seen compared with in those without diabetes, and may be more beneficial overall than lowering of blood glucose [25–27]. Table S1 gives a detailed summary of recent studies on the cardiovascular benefits of blood pressure control in people with diabetes. In people aged ≥ 65 years (but < 85 years) with Type 2 diabetes, the evidence supports the recommendation that the target blood pressure should be < 140/90 mmHg to decrease cardiovascular disease outcomes, including stroke and progressive chronic kidney disease. Lower blood pressure targets (e.g. < 130/80 mmHg may be warranted in higher risk individuals; previous stroke or progressive chronic kidney disease with eGFR < 60 ml/min/1.73^2) but this would require shared decision-making with the clinician and the person with diabetes, with full discussion of the benefits and risks of each target [28]. If lower blood pressure targets are selected, careful monitoring is needed to avoid orthostatic hypotension.

All the major anti-hypertensive drug classes can be used in older people with diabetes and a recent meta-analysis has shown no difference in total or cardiovascular mortality between single drug classes, but drug combinations were superior to monotherapy in reducing blood pressure and achieving better outcomes [29]. The benefits of blood pressure control in older people with diabetes are summarized in Box 2 (a).

There are no large clinical trials of statin therapy specifically designed for older people with diabetes and

Table 1 Key intensive glucose control and other studies – with relevance to older people

Study/review; year	Design and methods	Principal conclusions	Implications
UKPDS [11,12] Multicentre randomized controlled clinical trial	Participants: middle aged, newly diagnosed Type 2 diabetes (n = 3867). Median age: 54 years (≥ 65 years excluded). Intervention: intensive control (FPG < 6 mmol/l) vs. standard care (best achieved FPG with diet). Median follow-up: 10 years. Primary outcomes: sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal MI, angina, heart failure, stroke, renal failure, amputation, vitreous haemorrhage, retinopathy needing photocoagulation, blindness in any eye, or cataract extraction, diabetes-related death, all-cause mortality.	Median HbA_{1c} in intensive vs. standard arm 53 mmol/mol (7%) vs. 63 mmol/mol (7.9%). Showed benefits of tighter glycaemic control in prevention of microvascular complications (25% risk reduction). Showed persistence in benefits to prevent micro- and macrovascular complications during post-trial follow-up period.	Participants were newly diagnosed without many diabetic complications at the start of the study. Tighter control of diabetes during middle age improves microvascular end points. Tighter control of diabetes during middle age has 'legacy effect' observed at 10 years in older age and improves micro- and macrovascular endpoints even when glycaemic control is not maintained in a tight range in later years.
ACCORD [13,14] Multicentre randomized controlled clinical trial	Participants: middle to older age (mean age 62 years) with high risk of CVD or pre-existing CVD (n = 10 250). Participant age: 40–79 years. Intervention: intensive control [HbA_{1c} goal < 42 mmol/mol (<6%)] vs. standard care [HbA_{1c} goal 53–63 mmol/mol (7–7.9%)]. Median follow-up: 3.5 years (early termination). Primary outcome: non-fatal MI, non-fatal stroke, CVD death	Mean HbA_{1c} in intensive vs. standard arm 46 mmol/mol (6.4%) vs. 59 mmol/mol (7.5%). Excessive deaths in intensive control arm. Trial terminated early after 3 years. No benefits of intensive control on cardiovascular outcomes.	Tighter glycaemic control to near normal levels in middle/old age persons with existing cardiovascular disease or high risk of CVD did not show benefits and may have shown harm. Subgroup analysis show higher mortality in younger age group (< 65 years) but more hypoglycaemia in older age group (> 65 years).
ADVANCE [15] Multicentre randomized controlled clinical trial	Participants: middle to older age (mean 66 years) with pre-existing CVD (n = 11 140). Participant age: ≥ 55 years. Intervention: intensive control [HbA_{1c} goal < 48 mmol/mol (< 6.5%)] vs. standard care (HbA_{1c} goal based on local guidelines). Median follow-up: 5 years. Primary outcomes: non-fatal MI, non-fatal stroke, CVD death.	Mean HbA_{1c} in intensive vs. standard arm 45 mmol/mol (6.3%) vs. 53 mmol/mol (7%). No benefits of intensive control on primary outcomes. Significant reduction in incidence of nephropathy.	Subgroup analysis found no difference in benefits of intensive control by age group (< 65 or > 65 years).
VADT [16–18] Multicentre randomized controlled clinical trial	Participants: middle to older age military veterans in USA (mean 60 years) with suboptimal glycaemic control (n = 1791). Participant age: all adults. Intervention: intensive control vs. standard care (goal for absolute reduction of HbA_{1c} of 1.5%). Median follow-up: 5.6 years. Primary outcomes: non-fatal MI, non-fatal stroke, CVD death, hospitalization for heart failure, revascularization.	Mean HbA_{1c} in intensive vs. standard arm 52 mmol/mol (6.9%) vs. 69 mmol/mol (8.5%). No benefits of intensive control on primary outcomes. Significant reduction in onset and progression of albuminuria.	Post hoc analysis found mortality benefits in participants with diabetes duration < 15 years. No benefits of intensive control in older age group. More recent 15-year review of 1655 participants showed no cardioprotective 'legacy' effect.
Japanese Elderly Diabetes Intervention Trial [19] Randomized controlled, multicentre, prospective intervention trial	Participants: Japanese older adults (n = 1173) with Type 2 diabetes. Participant age: all participants were > 65 years (mean 72 years). Intervention: multifactorial intervention vs. standard care. Median follow-up: 6 years. Primary outcomes: fatal or non-fatal events, composite events.	Mean HbA_{1c} in intervention vs. standard care 63 mmol/mol (7.9%) vs. 65 mmol/mol (8.1%). No difference in primary outcomes between the groups.	Lowering of HbA_{1c} in addition to geriatric-specific interventions was not beneficial in this study of Japanese older adults.
UK General Practice Research Database Observational study [20]	Participants: two cohorts of people with Type 2 diabetes (n = 27 965 using oral therapy and 20 005 using insulin). Participant age: ≥ 50 years (mean 64 years). Intervention: intensification of glycaemic regimen. Period: November 1986 to November 2008. Objective: evaluate relationship between HbA_{1c} and outcomes. Primary outcome: all-cause mortality.	U-shaped relationship seen between HbA_{1c} and mortality risk with lowest hazard ratio at an HbA_{1c} of 59 mmol/mol (7.5%). Higher mortality was seen with higher or lower HbA_{1c}. Hazard ratio (HR) for primary outcome in insulin-treated vs. oral medication-treated people was 1.49.	Too high as well as too low values of HbA_{1c} have higher risk of adverse outcomes.

the evidence is based on data extrapolated from younger trial populations. In Table S2, we give descriptions of the main studies on the cardiovascular benefits of lipid-lowering in older people with diabetes. Evidence of benefit for statin therapy is generally established for those adults up to age 80 years as evidenced by the PROSPER [30] and

Table 1 (*Continued*)

Study/review; year	Design and methods	Principal conclusions	Implications
Diabetes and aging study [21] Retrospective cohort study	Participants: Type 2 diabetes enrolled in Kaiser Permanente Northern California (n = 71 092). Participant age: ≥ 60 years (mean 71 years). Period: 2004–2008. Objective: evaluate relationship between baseline HbA_{1c} and outcomes. Primary outcomes: acute, non-fatal metabolic, microvascular and cardiovascular events and mortality.	U-shaped relationship between HbA_{1c} and mortality with lowest risk of mortality between HbA_{1c} 42 and 75 mmol/mol (6–9%). Higher risk of any outcome at HbA_{1c} ≥ 64 mmol/mol (≥ 8%) and increased risk of mortality when HbA_{1c} < 42 mmol/mol (< 6%). Outcomes were not different between age groups of 60–69, 70–79 and ≥ 80 years.	Authors recommend target HbA_{1c} < 64 mmol/mol (< 8%) in older people.
Italian study [22] Longitudinal observational study	Participants: people with Type 2 diabetes from diabetes outpatient and general practitioner clinics in Italy (n = 3074). Participant age: mean 63 years. Period: November 1986 to November 2008. Median follow up: 5 years. Objective: evaluate benefits of level of glycaemic control < 48 mmol/mol (< 6.5%) or < 53 mmol/mol (<7%) in individuals with high vs. low levels of comorbidities. Primary outcome: total mortality, incident cardiovascular events.	Tighter glycaemic control [HbA_{1c} < 48 mmol/mol (≤ 6.5%) or < 53 mmol/mol (< 7%)] at baseline was associated with lower 5-year incidence of cardiovascular events in those with fewer comorbidities. No benefits seen in group with high number of comorbidities.	Benefits of tighter glycaemic control might be diminished in participants with a high burden of comorbidities.
Retrospective cohort study [23]	Participants: older cohort with Type 1 or Type 2 diabetes, from The Health Improvement Network Database. Data from primary care practices in the UK (n = 54 803) Participant age: ≥ 70 years. Median follow-up: 5 years. Objective: association between mean HbA_{1c} and variability of HbA_{1c} and mortality. Primary outcome: time to all-cause mortality.	J-shaped relationship with most benefits at HbA_{1c} values between 42 and 64 mmol/mol (6–8%). Higher mortality was associated with higher variability in HbA_{1c}.	Not just the HbA_{1c} value, but variability of HbA_{1c} value over time, are important considerations for older adults. Stable glycaemic control in middle range over time might be more beneficial than tighter control in older adults.
The Fremantle Diabetes Study Phase II [24] Prospective cohort study	Participants: adults with Type 2 diabetes recruited between 2008 and 2011 (n = 367). Participant age: ≥ 75 years Study duration: median follow-up 6.7 years. Objective: relationship between tight glycaemic control with different pharmacological agents and outcomes. Primary outcome: all-cause mortality.	Metformin group had higher mortality when HbA_{1c} < 48 mmol/mol (<6.5%). Sulfonylurea and insulin group had higher mortality when HbA_{1c} <53 mmol/mol (< 7%).	Tight glycaemic control, < 48–53 mmol/mol, (< 6.5–7%) is harmful in older adults irrespective of pharmacotherapy but more so when they are treated with sulfonylureas and insulin.

FPG, fasting plasma glucose; CVD, cardiovascular disease.

HPS [31] with similar risk reductions (15–22%) in young and old. Further evidence of cardiovascular benefit in older adults from statin therapy comes from the Cholesterol Treatment Trialists Collaborators (CTTC) systematic prospective meta-analysis [32] and the post hoc analysis of the Collaborative Atorvastatin Diabetes Study (CARDS) trial [33]. Two large RCTs have failed to show any important cardiovascular benefits from adding fenofibrates or niacin to statin therapy in young 'elderly' populations [34,35]. In Box 2(b), we summarize the key messages for lipid lowering and cardiovascular benefit in older adults with diabetes.

Cardiovascular benefits and the safety of older and newer glucose-lowering agents

The cardiovascular safety of glucose-lowering agents is essential in all people with diabetes, particularly older groups who are already at high clinical risk (see Fig. 2). Up to the end of 2017, more than 190 000 people have been studied in nine longer-term cardiovascular outcome trials, and appear to have yielded important information about the benefits and associated risks of the therapies studied. These outcome trials have involved three dipeptidyl peptidase-4 (DPP-4) inhibitor trials, four glucagon-like peptide 1 (GLP-1) receptor agonist trials and two sodium–glucose cotransporter 2 (SGLT2) inhibitor trials [36].

A comprehensive discussion of this area has been published by an expert review group [36] and the results of subgroup analyses relating to event rate by age of various cardiovascular outcome trials has also been recently examined [37]. We summarize the results of the outcome studies for both older and newer blood glucose-lowering agents in Tables S3and S4 in which we also report recently released data from the CARMELINA trial. The data did not identify any safety concerns with linagliptin of the DPP-4 inhibitor class, which provides additional reassurance for clinicians (see Ref. 9 in Table S4).

Box 2 Summary of (a) benefits of blood pressure control and (b) cardiovascular benefits of lipid lowering in older people with diabetes

(a)

- A target systolic blood pressure around 140 mmHg is reasonable.
- Lower target < 130 mmHg may have benefit of reducing stroke risk but is associated with increased adverse events – requires a shared decision approach.
- High risk of adverse events exists in older people with recurrent falls, cognitive dysfunction or frailty.
- Targets are best based on level of function with tight control in the fit but relaxed in frail individuals (145–160/90 mmHg).
- All major anti-hypertensive classes have similar efficacy and achieving target blood pressure is more beneficial than a single class effect.

(b)

- Older people with diabetes up to the age of 80 years will benefit from cholesterol-lowering treatment.
- Older people with diabetes are likely to benefit more than younger people due to their higher baseline risk.
- There is some evidence from observational trials that cholesterol lowering may be beneficial in people aged 80–85 years.
- There is no extra benefit of additional fenofibrate or niacin to statin therapy.
- See Tables S1 and S2.

These studies were undertaken in people with Type 2 diabetes, mainly with pre-existing cardiovascular disease, with more than three-quarters on statins, a high proportion receiving anti-hypertensive and anti-platelet medications, and a mean age of 60–65 years. Overall cardiovascular safety was demonstrated across all classes mainly using the three-point MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) as the main primary composite outcome.

In relation to prescribing glucose-lowering medication to older adults as part of an individualized approach to enhance cardiovascular protection, DPP-4 inhibitors have not shown cardiovascular benefits, whereas empagliflozin and canagliflozin (SGLT2 inhibitors) demonstrated significant reductions in cardiovascular events and renal events, with empagliflozin also reducing hospitalization for heart failure and worsening nephropathy. Time to benefit was short (< 3 months) in the EMPA-REG outcome study [38]. In relation to GLP-1 receptor agonist trials, exenatide (but not liraglutide or semaglutide) showed cardiovascular benefit in older participants (≥ 65 years) but had a 43% discontinuation rate.

A summary of the cardiovascular safety of oral glucose-lowering agents in older people with diabetes is given in Box 3.

Box 3 Summary of cardiovascular safety of hypoglycaemic medications

Older agents

- Metformin: collectively shows modest cardiovascular benefits and evidence of safe use in various organ dysfunctions.
- Sulfonylureas: controversial cardiovascular benefits/risks but likely neutral.
- Glinides and α-glucosidase inhibitors: cardiovascular benefits when added to metformin.
- Thiazolidinediones (TZDs): rosiglitazone has had mixed concerns in terms of cardiovascular risk and remains suspended in Europe; pioglitazone use associated with a reduction in major adverse cardiovascular events and in all-cause mortality, and a lowered risk in recurrent stroke. The increased risk of heart failure remains an important concern.

Newer agents

- Dipeptidyl peptidase-4 (DPP-4) inhibitors: neutral cardiovascular effects. Saxagliptin associated with a significant increase in heart failure hospitalization in the SAVOR-TIMI trial [1.27 (1.07–1.51)] with a trend to an increased risk of heart failure in the alogliptin EXAMINE trial.
- Glucagon-like peptide-1 (GLP-1) receptor agonists: liraglutide demonstrates a significant reduction in three-point MACE in the LEADER Trial but subgroup analysis of people aged 60 years and above showed no benefit; exenatide showed cardiovascular benefits in older participants on subgroup analysis of the EXSCEL trial. Some recent concerns noted about liraglutide in people with chronic heart failure and reduced left ventricular function [39].
- Sodium–glucose cotransporter-2 (SGLT2) inhibitors: empagliflozin (EMPA-REG) and canagliflozin (CANVAS) show significant reductions in the three-point MACE in older participants, and a reduction in hospitalization for heart failure shown in the overall analysis of the studies.

  Note: previous studies in Type 2 diabetes have shown that both insulin glargine [ORIGIN Study [40,41]; people with dysglycaemia, mean age 63.5 years] and insulin degludec [DEVOTE trial [42]; people with a high cardiovascular risk, mean age 65 years] have no effects on MACE outcomes.Also see Cefalu *et al.* [36] and Tables S3 and S4.

Insulin therapy in older adults

In general, several small studies have helped guide therapy recommendations in older adults with diabetes [43]. Insulin therapy has a higher risk of hypoglycaemia in older adults compared with most of the oral hypoglycaemic agents [44,45]. However, it is possible to decrease the risk of hypoglycaemia and associated harm by carefully choosing the insulin preparation to match the timing of hyperglycaemia and by matching the coping ability of the person with diabetes to the complexity of the insulin [46]. The relative contribution of basal hyperglycaemia is lower, and that of postprandial hyperglycaemia higher in older people with diabetes compared with their younger counterparts [47], suggesting that different therapeutic approaches may be required to treat hyperglycaemia effectively in these different age groups. In a small randomized trial of older adults (≥ 65 years), addition of morning daily glargine with oral agents was found to improve hyperglycaemia and decrease the risk of hypoglycaemia compared with mixed insulin twice a day [48].

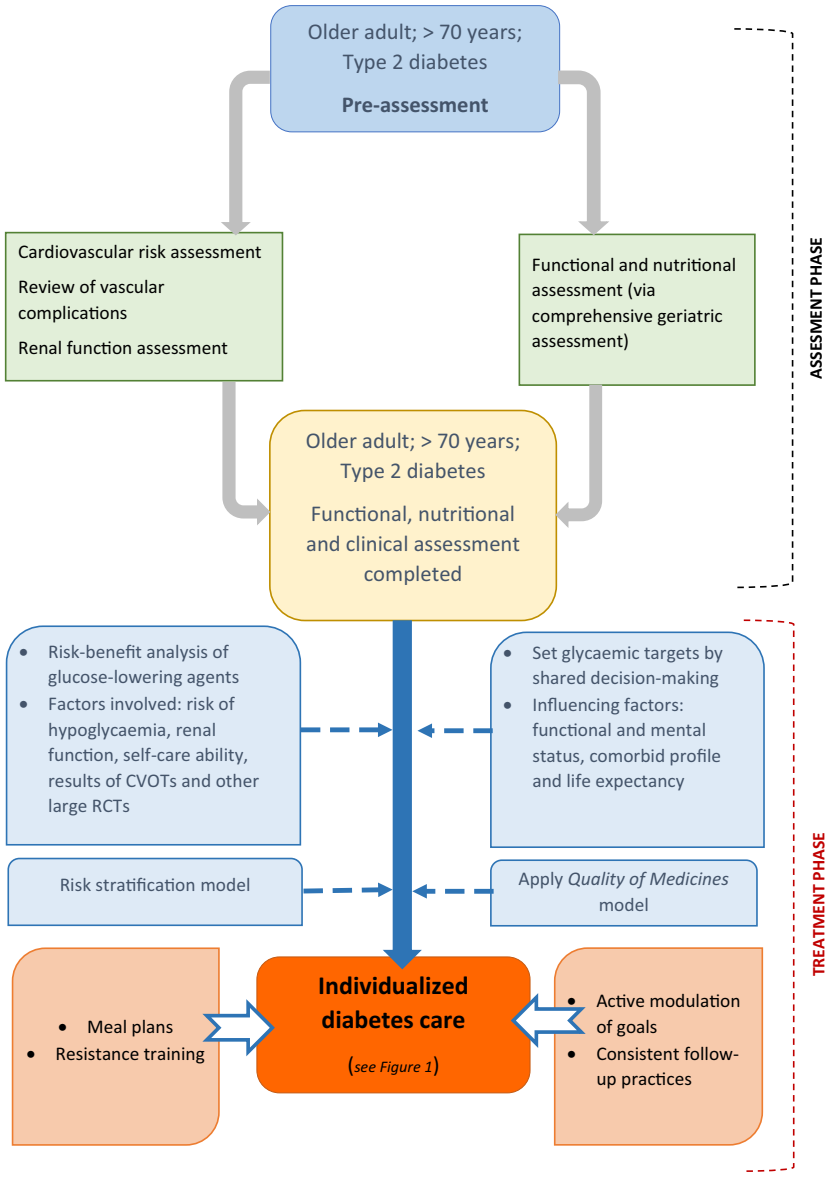

FIGURE 2 A comprehensive management scheme leading to individualized care for diabetes in older adults. CVOT, cardiovascular outcome trial; RCT, randomized controlled trial

The availability of various basal insulin with a half-life of 24 h or longer, including insulin glargine, degludec, glargine U300 and detemir, has provided much needed options to lower baseline glucose levels with a once-a-day injection in addition to non-insulin agents. Comparisons of different types of insulin preparations have shown mostly comparable efficacy in older adults. Some insulins such as degludec and glargine U300 have shown a better risk profile with lower risk of hypoglycaemia and less weight gain compared with glargine [49,50].

Methods of insulin administration have also been a topic of research in older adults. There appear to be no benefits of using a different modality such as an insulin pen, insulin pump or vial/syringe on glycaemic control in older populations. However, vision impairment and low dexterity due to arthritis may impede use of a vial/syringe in frail older adults. It has been long recognized that pre-filled insulin pens are safe and effective for older adults [51,52]. In institution-based diabetes care, various factors related to the institution, staff, person with diabetes and medication lead to the use of pen injectors as a preferred mode of insulin delivery to improve care and cost [53].

The place of recent international clinical guidelines

There is a paucity of clinical intervention trials in older people with diabetes and optimal metabolic targets in this

age group are still not very clear. Initially, guidelines recommended a target HbA_{1c} of ≤ 53 mmol/mol (< 7.0%) for all people without consideration of age or comorbidities [54]. This was based on results from the UKPDS study, which included relatively younger people with fewer comorbidities and a new diagnosis of diabetes [55]. However, the more recent ACCORD, ADVANCE and VADT studies, which included a cohort of older people with more comorbidities and longer duration of diabetes, failed to demonstrate that tight glycaemic control will reduce cardiovascular mortality and in fact, significantly increase the risk of hypoglycaemia [13,15,16].

In 2011, the European Diabetes Working Party for Older People (EDWPOP) published a comprehensive set of guidelines that were evidence-based as far as possible, set glycaemic targets that were later adopted by many later guidelines and gave the first algorithm for glucose-lowering for frail people with Type 2 diabetes [7]. This was followed by the ADA and the European Association for the Study of Diabetes proposing a person-centred approach with individualization of targets based on the age of the person with diabetes and any comorbidities [56]. Other international guidelines followed [6,8,57–60] (Table 2). The International Diabetes Federation global guidance on managing older people with Type 2 diabetes provided, for the first time, care recommendations for those with different categories of functional status and dependency including frailty [6]. The recent publication of an international Position Statement focusing on the management of frailty in diabetes provides clinicians with recommendations that may assist in the clinical management of a wide range of ill health-associated functional impairment characteristic of frailty [59]. Table S5 gives a general descriptive account of the guidelines shown in Table 2.

Lifestyle interventions in older people with diabetes

Maintaining a healthy diet and activity level are important elements of diabetes care in older age, as in earlier life phases.

Table 2 Summary of main guidelines in older people with diabetes – metabolic targets

Organization	HbA_{1c}	Blood pressure	Lipids
EDWPOP, 2011 [7]	A. Independent: 53–59 mmol/mol (7–7.5%). B. Dependent: 60–69 mmol/mol (7.6–8.5%).	A. Independent: < 140/80 mmHg. B. Non-frail > 80 years old: < 140–145/90 mmHg. C. Dependent: < 150/90 mmHg.	A. Statins generally recommended. B. Fibrates can be considered for high triglyceride in spite of statin therapy.
AGS, 2012 [7]	A. Healthy: < 59 mmol/mol (< 7.5%). B. Moderate morbidity: < 64 mmol/mol (< 8.0%). C. Severe morbidity: < 69 mmol/mol (< 8.5%).	A. Healthy: < 140/80 mmHg. B. Moderate morbidity: < 140/80 mmHg. C. Severe morbidity: < 150/90 mmHg.	A. Healthy: statins recommended. B. Moderate morbidity: statins recommended. C. Severe morbidity: statins considered.
IAGG-EDWPOP-ITFED, 2012 [57]	A general target of 53 59 mmol/mol (7–7.5%) is recommended.	A. Independent: < 140/80 mmHg. B. Dependent or ≥ 75 years old: < 150/90 mmHg.	No recommendations.
IDF 2013 [6]	A. Independent: 53–59 mmol/mol (7–7.5%). B. Dependent: 53–64 mmol/mol (7–8%). C. Frail/dementia: < 69 mmol/mol (< 8.5%). D. End of life: symptomatic, HbA_{1c} not recommended.	A. Independent: < 140/90 mmHg. B. Dependent: < 140/90 mmHg. C. Frail: < 150/90 mmHg. D. Dementia: < 140/90 mmHg. E. End of life: blood pressure control is not recommended.	A. Statins recommended for most. B. Not recommended for those with limited life expectancy.
Diabetes Canada, 2018 [58]	A. Independent: ≤ 53 mmol/mol (≤ 7.0%). B. Dependent: < 64 mmol/mol (< 8.0%). C. Frail/dementia: < 69 mmol/mol (< 8.5%). D. End of life: symptomatic, HbA_{1c} not recommended.	A. Independent: < 130/80 mmHg. B. Dependent: individualized targets.	A. Statins recommended for most. B. Not recommended for those with limited life expectancy.
IPS, 2018 [59]	A. Mild–moderate frailty: 53–64 mmol/mol (7–8.0%). B. Severe frailty: 59–69 mmol/mol (7.5–8.5%).	A. < 140/90 mmHg for all. B. All anti-hypertensive drug classes can be used.	A. Statins recommended for all unless contraindicated. B. Addition of fibrates or niacin to statins is not recommended.
ADA, 2018 [60]	A. Healthy: < 58 mmol/mol. B. Morbidity: < 64 mmol/mol. C. Limited life expectancy: < 69 mmol/mol.	A. Healthy: < 140/90 mmHg. B. Morbidity: < 140/90 mmHg. C. Limited life expectancy: < 150/90 mmHg.	A. Healthy: statins recommended. B. Morbidity: statins recommended. C. Limited life expectancy: statins considered.

EDWPOP, European Diabetes Working Party for Older People; AGS, American Geriatrics Society; IAGG, International Association of Geriatrics and Gerontology; ITFED, International Task Force of Experts in Diabetes; IDF, International Diabetes Federation; IPS, International Position Statement; ADA, American Diabetes Association.

The limited number of studies that have been conducted on dietary interventions targeting older people have shown that nutritional education incorporating portion control, carbohydrate and lipid intake, meal spacing and nutritional awareness can improve metabolic outcomes [61,62]. There is some limited evidence to show that in fitter older people, weight-reducing interventions with calorific restriction may also result in metabolic improvements [63,64], although compensatory exercise to ensure fat rather than muscle deposition needs to be considered [65]. It has also been noted that in older frailer people, intentional weight loss leads to bone and mineral depletion [66].

The nutritional needs of older people vary across groups and may be striking in those with co-morbid frailty, those with loss of the ability to prepare a meal or loss of appetite, and those with poor oral health [67]. These deficits may accelerate problems such as sarcopenia and reduce metabolic well-being [68]. Hence, the diet in the older person should be nutritionally dense, have an optimal protein intake, and be balanced in respect of micro- and macronutrients, which helps to preserve lean body mass [69].

Body mass and physical stature may decline in older age making BMI a less reliable indicator of weight-related hazard [70]. A decline in body weight should be considered a significant risk factor, as it is associated with elevated mortality in the general and diabetes older populations [71,72]. The ADA guideline advocates the use of the Mini-Nutritional Assessment scale which has been used to assess older people with diabetes [61]. Weight and waist circumference has been suggested as a more useful indicator in older people in assessing visceral fat and associated metabolic hazards [73].

Evidence from the large diabetes prevention studies such as the US Diabetes Prevention Programme [74], emphasized how an integrated lifestyle programme can have an enduring benefit. At 15 years post intervention, the lifestyle group had a 27% lower incidence of diabetes compared with the control group. The lifestyle cohort from the US Diabetes Prevention Programme have a mean age of 67 years, emphasizing the importance of exercise and weight reduction in the middle years to realize benefits in older age.

In terms of exercise intervention in older people with diabetes, a systematic review of these studies showed some benefits on skeletal muscle mass and diabetes outcomes [75]. Larger studies in the wider older age population have shown that structured physical activity intervention can significantly decrease age-related mental and physical disability [76]. In 2013, The Look AHEAD (Action for Health in Diabetes) trial [77] was the largest randomized trial evaluating a lifestyle intervention in obese or overweight older adults (aged 45–76 years) with Type 2 diabetes compared with a diabetes support and education control group. Unfortunately, no significant difference in cardiovascular events rates was observed. In 2016, the ADA published a Position Statement on physical activity and exercise in diabetes [78], which concluded that both resistance training and aerobic exercise are required for optimizing glycaemic and other health outcomes.

Studies have also shown that inactivity in older age can contribute to metabolic dysfunction and accelerate the ageing process [79,80]. Hence, continuing to provide older people with targeted lifestyle intervention is important to improve both their physical health and functioning.

Interventions for frailty in diabetes

Frailty is a dynamic condition that can worsen or improve over time [81]. Preventing sarcopenia may in turn prevent frailty [82], but once frailty is established, the treatment requires regular functional assessments followed by timely multimodal interventions including adequate nutrition, physical exercise, managing glycaemia and the use of hypoglycaemic agents that have a high benefit to risk ratio. In the Women's Health and Aging Study II [83], a HbA_{1c} $\geq$ 64 mmol/mol ($\geq$ 8%) vs. < 37 mmol/mol (< 5.5%) was associated with an approximately threefold increased risk of incident frailty and three- to fivefold increased risk of lower extremity mobility limitations (all $P < 0.05$) measured at baseline in participants aged 70–79 years.

In the NHANES study [84], up to 85% of the disability excess identified in those with diabetes was explained by the presence of comorbidities (mainly cardiovascular disease and obesity), and poor glucose regulation ($HbA_{1c} \geq 8\%$). However, the aim in managing older people with diabetes is to identify frailty early enough to stop disability developing in the first place.

Exercise interventions have beneficial effects on glycaemic control, muscle insulin sensitivity, intra-abdominal adipose tissue, muscle fat infiltration and on attenuating cardiovascular risk factors associated with diabetes [85]. In relation to older adults with diabetes, combined resistance and endurance training appears to serve as an effective exercise intervention to promote overall physical fitness [75,86] and may even have a positive influence in those with dementia [87]. It is suggested that the exercise prescription for resistance training must be a frequency of one to six sessions per week, training volume of one to three sets of 6–15 repetitions, with an intensity of 30–70% one repetition maximum to promote significant enhancements in muscle strength, muscle power and functional outcomes [88].

Two studies reported in the *Lancet* [89,90] were important attempts to study the short-term benefits of glucose-lowering using DPP-4 inhibitors in 'frail' populations of older people with Type 2 diabetes. The first study was a randomized, double-blind, parallel-group phase 3 study [89] that examined the outcomes in terms of HbA_{1c} using linagliptin 5 mg or matching placebo in a group of highly comorbid older adults (n = 241; mean age 74.9 years). Tolerability was good and safety was similar in both groups, but at week 24,

compared with placebo, the linagliptin group has a significant fall in HbA_{1c} of 0.64% (95% confidence interval: −0.81 to −0.48); unfortunately, despite this being a high-risk population, no objective measures of frailty were undertaken. The second study [90] was a similar double-blind, placebo-controlled, 24-week investigation of vildagliptin in adults aged ≥ 70 years (n = 278; mean age 75 years) with Type 2 diabetes, who were drug naïve or inadequately controlled (HbA_{1c} 53–86 mmol/mol; 7–10%), and ~ 1 in 10 were described as frail using a modified Fried's criteria assessment tool [91]. Each had been set individualized targets based on age, baseline HbA_{1c}, comorbidities and frailty status. This study showed that, compared with 27% in the placebo group, more than half (52.6%) of all those receiving vildagliptin met their set individualized targets ($P < 0.0001$) and had a between-group difference in HbA_{1c} fall of 0.6% ($P < 0.0001$), with a similar tolerability and safety.

More recently, the EU-funded multinational MID-FRAIL Trial [92] has been completed. Unpublished observations of this cluster randomized trial of resistance exercise and nutritional education (vs. usual care) in pre-frail and frail older people (n = 964; > 70 years) show a significant improvement in physical performance at 1 year (measured by changes in Short Physical Performance Battery scores) associated with reduced healthcare costs [93].

Management strategies

Although diabetes management strategies for robust and high-functioning older adults should be similar to those for their younger counterparts [4,6], a safer, risk-stratification approach is required for those who are highly comorbid and/or frail. The focus and main goals are described above (Box 1) but also require a quality use of medicines approach to be achieved [4,6]. All treatment strategies require a risk–benefit analysis and the use of glucose-dependent strategies is preferred because they are less likely to cause unwanted hypoglycaemia, particularly in those with renal impairment [37]. A UK national stakeholder group has recently released a statement of the key principles of modern-day management of frail older adults with diabetes which focuses on the identification of frailty, reducing the vascular complications of diabetes and improving quality of life [94].

Once functional, cardiovascular and diabetes-related complications assessments have been completed (post-assessment stage), and the treatment phase modulators have been applied, the individualized care approach can be realized, including setting glycaemic goals and blood pressure targets according to a multifactorial strategy (see Fig. 2). Although we indicate that life expectancy is an important influence in modulating goals, we accept that we have not discussed end of life as a specific management approach and how decisional capacity can affect planning care. Management of people with diabetes at end of life has been reviewed previously in detail by the lead author and others [6].

Box 4 Future research

Longer term observational studies

- To assess cardiovascular risk with modern-day glucose-lowering treatment classes, particularly dipeptidyl peptidase-4 (DPP4) inhibitors, sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in different participant functional categories or complexities of illness as part of large prospective cohort studies.
- To assess: the impact of HbA_{1c} variability in the development of microvascular disease and frailty.
- Determine which HbA_{1c} and blood pressure targets provide the greatest benefit in different functional categories.

Development of clinical trial methodology

- Instigate randomized clinical trials in primary care to examine the benefits of structured assessment and management pathways using appropriate primary and secondary outcome measures such as disability, cognitive dysfunction, frailty and quality of life.
- Apply comparative effectiveness research techniques to create new innovative clinical trial designs.

Randomized clinical trials of glucose lowering to a specific HbA_{1c} range

- In high cardiovascular risk older people with Type 2 diabetes.
- In older people with Type 2 diabetes and stage 3 renal disease.

Randomized trials of multicomponent interventions

- In people with sarcopenia to prevent frailty and disability.
- In people with functional loss, frailty and lower limb physical restrictions to improve physical performance and prevent immobility and loss of independence.

Influencing commissioners of clinical diabetes and geriatric services

- Health economic analyses of interventions.
- Study designs that allow relevant and appropriate cost comparisons.

For example, the clinician will balance the potential side-effects of SGLT2 inhibitors or GLP-1 receptor agonists in older people with evidence relating to their proven cardiovascular benefits. The choice of using DPP-4 inhibitors will be a balance between minimal hypoglycaemia, lack of weight gain and broad use in renal impairment against neutral cardiovascular benefits. Insulin treatment can also be based on the use of NPH (wide experience, low cost, but higher hypoglycaemia risk) or the newer insulins such as glargine (U100/U300) or deglutec (U100/U200) – less glycaemic variability, lower hypoglycaemia risk, flexible timing but more expensive.

Preventing severe cardiovascular or renal disease and delaying the onset of frailty and disability require frequent review of nutritional status, exercise involvement, pharmacovigilance and the application of a deintensification programme where appropriate (Fig. 2) [95]. A recent Veteran Affairs Health System study of people with diabetes aged ≥ 70 years found that as many as one in five older people may be overtreated as evidenced by low HbA_{1c} levels (< 48 mmol/mol; < 6.5%) [96]. Deintensification (de-prescribing)

has thus become an important strategy for reducing the risks of overtreatment and hypoglycaemia, particularly in frail older people with Type 2 diabetes and multiple comorbidities, and may be achieved without undue harm and no loss of glycaemic control [95,97–99].

Future research: a call for action

In Box 4, we indicate key areas for future research that will address current shortfalls and gaps in evidence, and provide a framework for investment by pharmaceutical companies, medical research organizations, and diabetes and geriatric societies nationally and worldwide. New research directions must take into account the characteristics of older people with diabetes (increased risk of cardiovascular disease, renal impairment, polypharmacy and frailty), the likely complexity of illness management (see Fig. 1) and the inherent vulnerability to strict glucose lowering in terms of hypoglycaemia and premature mortality.

Research into the associations between functional class/category of individuals (e.g. moderate or severe frailty) and HbA_{1c} and blood pressure targets, and their influence on clinical outcome are encouraged. We also recognize the need to study the effects of treatments on both traditional cardiovascular and functional outcomes, as shown in Box 4. What is becoming evident is that RCTs are becoming inefficient, complex, time-consuming and expensive, and the exclusion of various subgroups such as the 'elderly' imposes many restrictions on how healthcare policies can be reliably applied. Hence, a move to observational studies and more innovative clinical designs is encouraged.

Future research may need to focus on comparisons of effective interventions among people in typical care settings, with decisions tailored to individual needs, sometimes referred to comparative effectiveness research [100], an initiative that requires new partnerships with industry, major pharma, private institutions and the public.

Summary of key conclusions

Compilation of this review has been challenging but immensely rewarding. It is obvious that there is increasing interest among clinical researchers, the pharmaceutical industry and government in how older people with Type 2 diabetes should be effectively managed to reduce excessive healthcare costs, and the impact on the individual with diabetes and their family and carers. There is now sufficient evidence and guidance available to present a framework of diabetes care that places an important emphasis on individualized care and how targets of care should be influenced by other factors such as functional status, the presence of frailty or cognitive impairment, and life expectancy. Further research into more innovative trail designs and the benefits of multicomponent interventions should also be encouraged.

Funding sources

None.

Competing interests

None declared.

References

1 Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW *et al*. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 2018; **138**: 271–281.
2 Whiting DR, Guariguata L, Weil C, Shaw J. IDF Diabetes Atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011; **94**: 311–321.
3 GBD 2015 Child Mortality Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**: 1545–1602.
4 Sinclair A, Dunning T, Rodriguez-Mañas L. Diabetes in older people: new insights and remaining challenges. *Lancet Diabetes Endocrinol* 2015; **3**: 275–285.
5 Avila-Funes JA, Helmer C, Amieva H, Barberger-Gateau P, Le Goff M, Ritchie K *et al*. Frailty among community-dwelling elderly people in France: the three city study. *J Geront A Biol Sci Med Sci* 2008; **63**: 1089–1096.
6 Dunning T, Sinclair A, Colagiuri S. New IDF Guideline for managing type 2 diabetes in older people. *Diabetes Res Clin Pract* 2014; **103**: 538–540.
7 Sinclair AJ, Paolisso G, Castro M, Bourdel-Marchasson I, Gadsby R, Rodriguez Mañas L; European Diabetes Working Party for Older People. European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. *Diabetes Metab* 2011; **37**(Suppl 3): S27–S38.
8 Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB *et al*.; Consensus Development Conference on Diabetes and Older Adults. Diabetes in older adults. *Diabetes Care* 2012; **35**: 2650–2664.
9 Gambert S, Pinkstaff S. Emerging epidemic: diabetes in older adults: demography, economic impact, and pathophysiology. *Diabetes Spectr* 2006; **19**: 221–228.
10 Sinclair AJ, Gadsby R, Abdelhafiz AH, Kennedy M. Failing to meet the needs of generations of care home residents with diabetes: a review of the literature and a call for action. *Diabet Med* 2018; **35**: 1144–1156.
11 Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 854–865.
12 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**: 1577–1589.
13 Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB *et al*. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545–2559.
14 Miller ME, Bonds DE, Gerstein HC, Seaquist ER, Bergenstal RM, Calles-Escandon J *et al*. ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and

glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ* 2010; **340**: b5444.
15 ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M *et al*. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560–2572.
16 Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD *et al*.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**: 129–139.
17 Duckworth WC, Abraira C, Moritz TE, Davis SN, Emanuele N, Goldman S *et al*.; Investigators of the VADT. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. *J Diabetes Complications* 2011; **25**: 355–361.
18 Gerstein HC, Reaven P. VADT Investigators. VADT at 15 Years: No Legacy Effect From Intensive HbA_{1c} Control. American Diabetes Association, 22–26 June 2018, Orlando, Florida. Available at https://www.medscape.com/viewarticle/898634 Last accessed 15 November 2018.
19 Araki A, Iimuro A, Sakurai T, Umegaki H, Iijima K, Nakano H *et al*. Japanese Elderly Diabetes Intervention Trial Study Group. Long-term multiple risk factor interventions in Japanese elderly diabetic patients: the Japanese Elderly Diabetes Intervention Trial–study design, baseline characteristics and effects of intervention. *Geriatr Gerontol Int* 2012; **12**(Suppl 1): 7–17.
20 Currie C, Peters JR, Tynana A, Evans M, Heine RJ, Bracco OL *et al*. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. *Lancet* 2010; **375**: 481–489.
21 Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. *Diabetes Care* 2011; **34**: 1329–1336.
22 Greenfield S, Billimek J, Pellegrini F, Franciosi M, De Berardis G, Nicolucci A *et al*. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes: a cohort study. *Ann Intern Med* 2009; **151**: 854–860.
23 Forbes A, Murrells T, Mulnier H, Sinclair AJ. Mean HbA_{1c}, HbA_{1c} variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. *Lancet Diabetes Endocrinol* 2018; **6**: 476–486.
24 Bruce DG, Davis WA, Davis TM. Glycaemic control and mortality in older people with type 2 diabetes: The Fremantle Diabetes Study Phase II. *Diabetes Obes Metab* 2018. https://doi.org/10.1111/dom.13469 [Epub ahead of print].
25 Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H *et al*. Effect of diuretic based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 1996; **276**: 1886–1892.
26 Tuomilehto J, Rastenyte D, Birkenhager WH, Thijs L, Antikainen R, Bulpitt CJ *et al*. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 1999; **340**: 677–684.
27 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317**: 703–713.
28 Brook RD, Rajagopalan S. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ and ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Soc Hypertens* 2018; **12**: 238.
29 Remonti LR, Dias S, Leitão CB, Kramer CK, Klassman LP, Welton NJ *et al*. Classes of antihypertensive agents and mortality in hypertensive patients with type 2 diabetes – network meta-analysis of randomized trials. *J Diabetes Complications* 2016; **30**: 1192–1200.
30 Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM *et al*. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; **360**: 1623–1630.
31 Collins R, Armitage J, Parish S, Sleigh P, Peto R. Heart Protection Study Collaborative Group. Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361**: 2005–2016.
32 Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C *et al*. The Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**: 1267–1278.
33 Neil HAW, DeMicco DA, Luo D, Betteridge DJ, Colhoun HM, Durrington PN *et al*. Analysis of efficacy and safety in patients aged 65–75 years at randomisation: Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetes Care* 2006; **29**: 2378–2384.
34 Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P *et al*. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1563–1574.
35 Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K *et al*. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; **365**: 2255–2267.
36 Cefalu WT, Kaul S, Gerstein HC, Holman RR, Zinman B, Skyler JS *et al*. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a *Diabetes Care* Editors' expert forum. *Diabetes Care* 2018; **41**: 14–31.
37 Schernthaner G, Schernthaner-Reiter MH. Diabetes in the older patient – heterogeneity requires individualisation of therapeutic strategies. *Diabetologia* 2018; **61**: 1503–1516.
38 Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S *et al*.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373**: 2117–2128.
39 Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hänselmann A *et al*. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE) – a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail* 2017; **19**: 69–77.
40 Trial Investigators ORIGIN, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, Maggioni AP *et al*. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Eng J Med* 2012; **367**: 319–328.
41 ORIGIN Trial Investigators. Cardiovascular and other outcomes postintervention with insulin glargine and omega-3 fatty acids (ORIGINALE). *Diabetes Care* 2016; **39**: 709–716.
42 Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR *et al*.; DEVOTE Study Group. Efficacy and safety of deglutec versus glargine in type 2 diabetes. *N Eng J Med* 2017; **377**: 723–732.
43 Tanwani LK. Insulin therapy in the elderly patient with diabetes. *Am J Geriatr Pharmacother* 2011; **9**: 24–36.
44 Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med* 2011; **365**: 2002–2012.

45 Umpierrez GE, Cardona S, Chachkiani D, Fayfman M, Saiyed S, Wang H *et al*. A randomized controlled study comparing a DPP4 inhibitor (linagliptin) and basal insulin (glargine) in patients with type 2 diabetes in long-term care and skilled nursing facilities: Linagliptin-LTC Trial. *J Am Med Dir Assoc* 2018; **19**(399–404): e3.
46 Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Simplification of insulin regimen in older adults and risk of hypoglycemia. *JAMA Intern Med* 2016; **176**: 1023–1025.
47 Munshi MN, Pandya N, Umpierrez GE, DiGenio A, Zhou R, Riddle MC. Contributions of Basal and prandial hyperglycemia to total hyperglycemia in older and younger adults with type 2 diabetes mellitus. *J Am Geriatr Soc* 2013; **61**: 535–541.
48 Janka HU, Plewe G, Busch K. Combination of oral antidiabetic agents with basal insulin versus premixed insulin alone in randomized elderly patients with type 2 diabetes mellitus. *J Am Geriatr Soc* 2007; **55**: 182–188.
49 Munshi MN, Gill J, Chao J, Nikonova EV, Patel M. Insulin glargine 300 U/ml is associated with less weight gain while maintaining glycemic control and low risk of hypoglycemia compared with insulin glargine 100 U/ml in an aging population with type 2 diabetes. *Endocr Pract* 2018; **24**: 143–149.
50 Ritzel R, Harris SB, Baron H, Florez H, Roussel R, Espinasse M *et al*. A randomized controlled trial comparing efficacy and safety of insulin glargine 300 units/ml versus 100 units/ml in older people with type 2 diabetes: results from the SENIOR Study. *Diabetes Care* 2018; **41**: 1672–1680.
51 Coscelli C, Lostia S, Lunetta M, Nosari I, Coronel GA. Safety, efficacy, acceptability of a pre-filled insulin pen in diabetic patients over 60 years old. *Diabetes Res Clin Pract* 1995; **28**: 173–177.
52 Wright BM, Bellone JM, McCoy EK. A review of insulin pen devices and use in the elderly diabetic population. *Clin Med Insights Endocrinol Diabetes* 2010; **3**: 53–63.
53 Pandya N, Nathanson E. Managing diabetes in long-term care facilities: benefits of switching from human insulin to insulin analogs. *J Am Med Dir Assoc* 2010; **11**: 171–178.
54 Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R *et al*. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2009; **52**: 17–30.
55 Prospective UK Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**: 837–853.
56 Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M *et al*. Management of hyperglycaemia 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). *Diabetologia* 2012; **55**: 1577–1596.
57 Sinclair A, Morley JE, Rodriguez-Mañas L, Paolisso G, Bayer T, Zeyfang A *et al*. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts. *Diabetes* 2012; **13**: 497–502.
58 Canada Diabetes Clinical Practice Guidelines Expert Committee, Meneilly GS, Knip A, Miller DB, Sherifali D, Tessier D, Zahedi A. Diabetes in older people. *Can J Diabetes* 2018; **42**: S283–S295.
59 Sinclair AJ, Abdelhafiz A, Dunning T, Izquierdo M, Rodriguez Manas L, Bourdel-Marchasson I *et al*. An international position statement on the management of frailty in diabetes mellitus: summary of recommendations 2017. *J Frailty Aging* 2018; **7**: 10–20.
60 American Diabetes Association. 11. Older adults: Standards of Medical Care in Diabetes—2018. *Diabetes Care* 2018; **41**: S119–S125.
61 Miller CK, Edwards L, Kissling G, Sanville L. Nutrition education improves metabolic outcomes among older adults with diabetes mellitus: results from a randomized controlled trial. *Prev Med* 2002; **34**: 252–259.
62 Redmond EH, Burnett SM, Johnson MA, Park S, Fischer JG, Johnson T. Improvement in A_{1c} levels and diabetes self-management activities following a nutrition and diabetes education program in older adults. *J Nutr Elderly* 2006; **26**: 83–102.
63 Lean ME, Powrie JK, Anderson AS, Garthwaite PH. Obesity, weight loss and prognosis in type 2 diabetes. *Diabet Med* 1990; **7**: 228–233.
64 Williamson DF, Thompson TJ, Thun M, Flanders S, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care* 2000; **23**: 1499–1504.
65 Hsieh CJ, Wang PW. Effectiveness of weight loss in the elderly with type 2 diabetes mellitus. *J Endocrinol Invest* 2005; **28**: 973–977.
66 Shapses SA, Riedt CS. Bone, bodyweight, and weight reduction: what are the concerns? *J Nutr* 2006; **136**: 1453–1456.
67 Kirkman SM, Briscoe VJ, Clark N, Florez H, Haas LB, Haler JB *et al*.; Consensus Development Conference on Diabetes and Older Adults. Diabetes in older adults: a consensus report. *J Am Geriatr Soc* 2012; **60**: 2242–2256.
68 Umegaki H. Sarcopenia and frailty in older patients with diabetes mellitus. *Geriatr Gerontol Int* 2016; **16**: 293–299.
69 Rahi B, Morais JA, Gaudreau P, Payette H, Shatenstein B. Energy and protein intakes and their association with a decline in functional capacity among diabetic older adults from the NuAge cohort. *Eur J Nutr* 2016; **55**: 1729–1739.
70 Villareal DT, Banks M, Siener C, Sinacore DR, Klein S. Physical frailty and body composition in obese elderly men and women. *Obes Res* 2004; **12**: 913–920.
71 Newman AB, Yanez D, Harris T, Duxbury A, Enright PL, Fried LP. Weight change in old age and its association with mortality. *J Am Geriatr Soc* 2001; **49**: 1309–1318.
72 Nilsson G, Hedger P, Ohrvik J. Survival of the fattest: unexpected findings about hyperglycaemia and obesity in a population based study of 75-year-olds. *BMJ Open* 2011; **1**: e000012.
73 Visscher TL, Seidell JC, Molarius A, van der Kuip D, Hofman A, Witteman JC. A comparison of body mass index, waist-hip ratio and waist circumference as predictors of all-cause mortality among the elderly: the Rotterdam study. *Int J Obes Relat Metab Disord* 2001; **25**: 1730–1735.
74 Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* 2015; **3**: 866–875.
75 Hovanec N, Sawant A, Overend TJ, Petrela RJ, Vandervoort AA. Resistance training and older adults with type 2 diabetes mellitus: strength of the evidence. *J Aging Res* 2012; **2012**: 284635.
76 Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS *et al*. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA* 2014; **311**: 2387–2396.
77 Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M *et al*. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369**: 145–154.
78 Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC *et al*. Physical activity/exercise and diabetes: a

Position Statement of the American Diabetes Association. *Diabetes Care* 2016; **39**: 2065–2079.
79 Amati F, Dube JJ, Coen PM, Stefanovic-Racic M, Toledo FG, Goodpaster BH. Physical inactivity and obesity underlie the insulin resistance of aging. *Diabetes Care* 2009; **328**: 1547–1549.
80 Landi F, Abbatecola AM, Provinciali M, Corsonello A, Bustacchini S, Manigrasso L *et al*. Moving against frailty: does physical activity matter? *Biogerontology* 2010; **11**: 537–545.
81 Lee JSW, Auyeung TW, Leung J, Kwok T, Woo J. Transitions in frailty states among community-living older adults and their associated factors. *J Am Med Dir Assoc* 2014; **15**: 281–286.
82 Morley JE, Malmstrom TK, Rodriguez-Manas L, Sinclair AJ. Frailty, sarcopenia and diabetes. *J Am Med Dir Assoc* 2014; **15**: 853–859.
83 Kalyani RR, Tian J, Xue Q-L, Walston J, Cappola AR, Fried LP *et al*. Hyperglycemia and incidence of frailty and lower extremity mobility limitations in older women. *J Am Geriatr Soc* 2012; **60**: 1701–1707.
84 Kalyani RR, Saudek CD, Brancati FL, Selvin E. Association of diabetes, comorbidities, and A_{1c} with functional disability in older adults: results from the National Health and Nutrition Examination Survey (NHANES), 1999–2006. *Diabetes Care* 2010; **33**: 1055–1060.
85 Ibañez J, Izquierdo M, Argüelles I, Forga L, Larrión JL, García-Unciti M *et al*. Twice-weekly progressive resistance training decreases abdominal fat and improves insulin sensitivity in older men with type 2 diabetes. *Diabetes Care* 2005; **28**: 662–667.
86 Cadore EL, Casas-Herrero A, Zambom-Ferraresi F, Idoate F, Millor N, Gomez M *et al*. Multicomponent exercises including muscle power training enhance muscle mass, power output, and functional outcomes in institutionalized frail nonagenarians. *Age (Dordr)* 2013; **36**: 773–785.
87 Cadore EL, Moneo AB, Mensat MM, Muñoz AR, Casas-Herrero A, Rodriguez-Mañas L *et al*. Positive effects of resistance training in frail elderly patients with dementia after long-term physical restraint. *Age (Dordr)* 2014; **36**: 801–811.
88 Lopez P, Pinto RS, Radaelli R, Rech A, Grazioli R, Izquierdo M, Cadore EL. Benefits of resistance training in physically frail elderly: a systematic review. *Aging Clin Exp Res* 2018; **30**: 889–899.
89 Barnett AH, Huisman H, Jones R, von Eynatten M, Patel S, Woerle H-J. Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial. *Lancet* 2013; **382**: 1413–1423.
90 Strain WD, Lukashevich V, Kothny W, Hoellinger MJ, Paldánius PM. Individualised treatment targets for elderly patients with type 2 diabetes using vildagliptin add-on or lone therapy (INTERVAL): a 24 week, randomised, double-blind, placebo-controlled study. *Lancet* 2013; **382**: 409–416.
91 Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J *et al*. Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56**: M146–M156.
92 Rodríguez-Mañas L, Bayer AJ, Kelly M, Zeyfang A, Izquierdo M, Laosa O *et al*.; MID-Frail Consortium. An evaluation of the effectiveness of a multi-modal intervention in frail and pre-frail older people with type 2 diabetes–the MID-Frail study: study protocol for a randomised controlled trial. *Trials* 2014; **15**: 34.
93 Final Report Summary – MID-FRAIL STUDY (a randomised clinical trial to evaluate the effectiveness of a multi-modal intervention in older people with Type 2 diabetes on frailty and quality of life: the MID-FRAIL STUDY. ID: 278803. Available at https://cordis.europa.eu/search/result_en?q=midfrail. Last accessed 15 November 2018.
94 Strain WD, Hope SV, Green A, Kar P, Valabhji J, Sinclair AJ. Type 2 diabetes mellitus in older people: a brief statement of key principles of modern day management including the assessment of frailty. A national collaborative stakeholder initiative. *Diabet Med* 2018; **35**: 838–845.
95 Abdelhafiz AH, Sinclair AJ. Deintensification of hypoglycaemic medications-use of a systematic review approach to highlight safety concerns in older people with type 2 diabetes. *J Diabetes Complications* 2018; **32**: 444–450.
96 McCoy R, Lipska K. Physicians frequently fail to de-intensify treatment in older patients with diabetes and very low haemoglobin A1c or blood pressure. *Evid Based Med* 2016; **21**: 158.
97 Thorpe CT, Gellad WF, Good CB, Zhang S, Zhao X, Mor M *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.
98 Tseng CL, Soroka O, Maney M, Aron DC, Pogach LM. Assessing potential glycemic over treatment in persons at hypoglycemic risk. *JAMA Intern Med* 2014; **174**: 259–268.
99 Arnold SV, Lipska KJ, Wang J, Seman L, Mehta SN, Kosiborod M. Use of intensive glycemic management in older adults with diabetes mellitus. *J Am Geriatr Soc* 2018; **66**: 1190–1194.
100 Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med* 2009; **151**: 203–205.

Supporting Information

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

Table S1. Recent studies on cardiovascular benefits of blood pressure control in people with diabetes and implications for older people.

Table S2. Main studies on cardiovascular benefits of lipid lowering treatment in older people with diabetes.

Table S3. Main studies on cardiovascular safety of hypoglycaemic medications – older agents.

Table S4. Main studies on cardiovascular safety of hypoglycaemic medications – newer agents.

Table S5. Summary of main clinical guidelines in older people with diabetes – general recommendations.