Medication Deprescribing Among Patients With Type 2 Diabetes: A Qualitative Case Series of Lifestyle Medicine Practitioner Protocols

Michael D. Bradley,[1] Matthew E. Arnold,[2] Bradley G. Biskup,[3] Thomas M. Campbell II,[4] Joel Fuhrman,[5] George E. Guthrie,[6,7] John H. Kelly,[7] Salvatore Lacagnina,[8] James F. Loomis,[9] Michelle M. McMacken,[10,11] Caroline Trapp,[12] and Micaela C. Karlsen[13]

This study is a qualitative case series of lifestyle medicine practitioners' protocols for medication de-escalation in the context of reduced need for glucose-lowering medications due to lifestyle modifications. Increasing numbers of lifestyle medicine practitioners report achieving reductions in medications among patients with type 2 diabetes, and in some cases remission, but limited data exist on the clinical decision-making process used to determine when and how medications are deprescribed. Practitioners interviewed here provide accounts of their deprescribing protocols. This information can serve as pilot data for other practitioners seeking examples of how deprescribing in the context of lifestyle medicine treatment is conducted.

KEY POINTS

- De-escalation of glucose-lowering medications is used by lifestyle medicine practitioners when patients with type 2 diabetes have a reduced need for pharmacotherapy after lifestyle interventions.
- Lifestyle medicine practitioners work with a multidisciplinary team of allied health professionals in their process of medication deprescribing.
- Medications known to cause hypoglycemia as an adverse effect are often deprescribed first; most commonly this includes sulfonylureas and insulin, along with any other medication known to cause hypoglycemia.
- During antihyperglycemic medication deprescribing, lifestyle medicine practitioners aim for patients to achieve normoglycemia without incidences of hypoglycemia.

Medication deprescribing is a planned and supervised process of dose reduction or discontinuation of a medication that may be causing harm or no longer providing benefit to a patient (1). The goals of deprescribing are to manage polypharmacy, reduce medication burden, and improve patient outcomes and quality of life. Medication deprescribing is not a new process in the delivery of patient care and has been successfully used during medication changes (2) to reduce polypharmacy in geriatric or hospice patients (3–7), to adjust glucose-lowering medications as necessary after bariatric surgery in patients with type 2 diabetes (8), as part of individualized treatment plans for people with type 2 diabetes (1,5,9–11), to wean patients off of opioids during recovery (12), and in other cases of pharmacotherapy with potentially negative sequalae (13–15). Potential benefits of deprescribing in older populations include reduction in harm from polypharmacy such as hypoglycemia (16,17), cessation of inappropriate medication use, cessation of specific medication classes leading to a reduction in adverse drug reactions, reduction in medication

[1]University of North Texas Health Science Center School of Public Health, Fort Worth, TX; [2]Genesis Quad Cities Family Medicine Residency Program, Genesis Health System, Davenport, IA; [3]UConn Health, Farmington, CT; [4]University of Rochester, Rochester, NY; [5]Nutritional Research Foundation, Flemington, NJ; [6]Advent Health Allopathic Family Medicine Residency, Winter Park, FL; [7]Loma Linda University School of Medicine, Loma Linda, CA; [8]Lee Health System & Concierge Lifestyle Medicine, LLC, Fort Myers, FL; [9]Barnard Medical Center, Washington, DC; [10]New York University Grossman School of Medicine, New York, NY; [11]NYC Health + Hospitals/Bellevue, New York, NY; [12]University of Michigan School of Nursing, Ann Arbor, MI; [13]American College of Lifestyle Medicine, Chesterfield, MO

Corresponding author: Micaela C. Karlsen, mkarlsen@lifestylemedicine.org

https://doi.org/10.2337/cd22-0009

costs, improvement in medication adherence, and increased self-efficacy (18).

Lifestyle medicine uses an evidence-based lifestyle therapeutic approach to treat lifestyle-related chronic disease. The primary domains include a whole-food, predominantly plant-based eating plan, regular physical activity, restorative sleep, stress management, avoidance of risky substances, and positive social connection. In the context of lifestyle medicine and type 2 diabetes treatment, deprescribing is necessary when using intensive, therapeutic lifestyle change (ITLC), as substantial and rapid drops in blood glucose may occur, resulting in hypoglycemia if medications are not adjusted (19). ITLC interventions have been described as including an induction phase that potentiates motivational interviewing and lifestyle coaching and increases in the degree of change that can be achieved by inducing the patient to select bolder personal goals for change (20). Deprescribing glucose-lowering medications for older adults may offer benefits that outweigh harms, even without lifestyle modifications, as summarized in a 2019 systematic review (1).

It is the position of the American College of Lifestyle Medicine (ACLM) that remission of type 2 diabetes should be a clinical goal and may be achieved with a whole-food, plant-based dietary pattern coupled with moderate exercise (20). Remission can be defined as attainment of an A1C <6.5% for at least 3 months with no surgery, devices, or active pharmacologic therapy for the specific purpose of lowering blood glucose (21). Although full remission may not be possible for all patients, outcomes of both remission and substantial reductions in the need for glucose-lowering medications are reported by lifestyle medicine practitioners using a whole-food, plant-based dietary intervention (19), as well as when using energy-restricted dietary interventions and liquid meal replacements such as in the Diabetes Remission Clinical Trial (DiRECT) (22). However, there is limited published guidance on how to practice deprescribing when warranted in this population (23).

There is urgency to pursue lifestyle interventions as a solution to the problem of type 2 diabetes. The Centers for Disease Control and Prevention estimates that >34.2 million Americans are living with type 2 diabetes (24). Type 2 diabetes is the seventh leading cause of death in the United States, with >83,000 individuals losing their lives to the disease in 2017 (25). The total estimated cost of diagnosed diabetes in 2017 was $327 billion, with $237 billion in direct medical costs and an additional $90 billion in decreased productivity (26).

As treatment using lifestyle modifications for type 2 diabetes increases, the need to handle reductions in related medications increases in parallel. Awareness of medication deprescribing is increasing and is considered an important aspect of treatment strategy in the management of chronic disease (2,9), although discussion continues around the relative importance of deprescribing, as underuse of medications also carries risk (27). For example, researchers at the Bruyère Research Institute (Ottawa) and Université de Montréal, through their website (deprescribing.org), provide tools and resources to assist providers with deprescribing proton pump inhibitors, antipsychotics, benzodiazepine receptor antagonists, cholinesterase inhibitors, and memantine (28). They also provide published algorithms for antihyperglycemic medications; however, these resources are specific to older individuals and are not necessarily relevant for a patient population engaging in lifestyle medicine interventions (28).

There is a need to characterize practitioner protocols specific to glucose-lowering medications used to treat patients with type 2 diabetes regardless of age and in the context of ITLC. Preventing hypoglycemia and resolving drug interactions when medications are changed is essential to upholding a key element of the Hippocratic oath: to "do no harm." The objective of this study is to add to the limited literature published on deprescribing protocols for glucose-lowering medications by documenting the protocols of lifestyle medicine practitioners ($n = 9$) who engage in deprescribing medications after lifestyle interventions delivered with a goal of potential type 2 diabetes remission.

Research Design and Methods

To assess existing research on medication deprescribing, a PubMed literature search was performed using the search strategy "(medication and diabetes) AND (deprescrib* OR deescalat*)" through 18 October 2021, with no date, language, or other restrictions. Table 1 presents the results of this search. Abstracts were screened by a single researcher (M.C.K.) for relevance to medication deprescribing, factors influencing the need for deprescribing (such as polypharmacy), and relevance to deprescribing glucose-lowering medications specifically.

Articles with specific relevance to deprescribing were reviewed by the coauthors to inform this study.

Lifestyle medicine providers with experience treating type 2 diabetes with a goal of remission and supervising

TABLE 1 Results of Formal Search Strategy on Deprescribing

Article Type	Total Articles	Articles Specifically Addressing Deprescribing of Glucose-Lowering Medication for Type 2 Diabetes
Systematic review and/or meta-analysis	4	2
Scoping review	1	1
Randomized controlled trial	2	1
Cohort study	16	3
Retrospective cohort study	6	2
Consensus statement	2	2
Cross-sectional study	4	1
Case report	3	3
Qualitative research	2	0
In vitro study	1	0
Narrative review	11	6

medication deprescribing were purposively sampled and invited to participate in an interview to understand best practices. Qualitative data collection, in the form of in-depth interviews, was performed with each provider. Interview questions assessed their lifestyle medicine practice (intensive vs. nonintensive), use of a documented protocol for medication deprescribing, team members involved in their practice, type 2 diabetes management and reversal, process for patient follow-up, and perceived positive and negative effects of deprescribing.

Each interview lasted between 30 minutes and 1 hour and was recorded with permission. Responses to each question were documented via written notes and/or transcribed in a Microsoft Word document. All interviewees are listed as coauthors of this article and consented to share their responses in this manuscript.

Results

Lifestyle medicine providers ($n = 9$) with expertise in medication deprescribing completed interviews during the period of 21 September 2019 to 10 June 2021 and described their individual decision-making protocols.

Three practitioners reported medication deprescribing in an intensive lifestyle medicine program, two provided care in a nonintensive program, and four provided both intensive and nonintensive care. Description of intensive lifestyle medicine practices varied among practitioners but typically included a process through which individuals received more time with their provider, an increased frequency of interventions, and a higher level of monitoring and care. Nonintensive lifestyle medicine practices were described as a process through which interventions were provided in a manner similar to a standard primary care practice setting. Additionally, the type of lifestyle medicine practice was restricted to each expert's practice setting (i.e., private/independent medical office vs. medical office located within a hospital or health care system).

All but one of the participants reported working with a team of allied health care providers (Table 2). Three practitioners reported having certified diabetes care and education specialists (CDCESs), pharmacists (PharmDs), nurses, and dietitians on their teams. Two reported working with a health coach. Of the nine participating providers, seven reported not using a published, externally documented protocol or algorithm for medication deprescribing (Table 3). For laboratory testing during the medication deprescribing process, five participants reported testing that included a basic metabolic panel (BMP) and comprehensive metabolic panel (CMP), A1C, and C-peptide level; four reported testing that included a fasting lipid panel; three reported monitoring insulin levels; and two reported monitoring HOMA-IR (homeostatic model assessment of insulin resistance), with one of these also including HOMA2-β (updated homeostatic model assessment of β-cell function) (Table 3).

When selecting medications to deprescribe, decision-making seemed most often to be individualized to the practitioner and patient-specific (Table 4). Of the nine practitioners, seven preferred to target sulfonylureas (SFUs), insulin, and any other medications known to cause hypoglycemia first, and six preferred to deprescribe metformin and/or glucagon-like peptide 1 (GLP-1) receptor agonists last or to continue these medication classes in the patient's treatment regimen. The time frame initiation of medication deprescribing is also individualized to the practitioner, is patient-specific, and may be primarily influenced by the perceived risk of hypoglycemia overall at the start of intensive lifestyle interventions and by the use of prescribed medications known to cause hypoglycemia as an adverse effect. The

TABLE 2 Lifestyle Medicine Practice Experience and Identified Team Members

Lifestyle Medicine Practitioner	Type of Practice (Intensive or Nonintensive)*	Other Team Members and Resources
M.M.M.	Both	CDCES nurse, PharmD, chronic disease nurse, dietitian, health coach
J.H.K.	Intensive	Nurses, dietitian/nutritionist
G.E.G.	Both	Dietitian, PharmD†
C.T.	Both	Local plant-based nutrition support group; structured online programs
B.G.B.	Nonintensive	Physicians, advanced practice nurses, CDCESs, and dietitians
J.F.	Both	Intensive program: nurse, psychologist (for food addiction counseling), exercise trainers, and chefs Nonintensive program: psychologist (for food addiction counseling)
S.L.	Nonintensive	PharmD, sleep specialist
J.F.L.	Intensive	Dietitian, health coaches, CDCES, nurse practitioner
T.M.C.	Intensive	None

*Intensive practices involved more time, more frequent intervention, and a higher level of care and monitoring; nonintensive practices were similar to general primary care practice. †Physician was a CDCES.

most common practice among all providers was to first target SFUs, insulin, and other medication known to cause hypoglycemia.

Practitioners identified many factors that are considered in their medication deprescribing process, including the adverse effect profile and costs of medications (Table 5). They reported targeting SFUs first because of concerns about hypoglycemia and the potential to accelerate decline in β-cell function. Thiazolidinediones (TZDs) were commonly targeted because of concerns regarding weight gain and exacerbation of chronic heart failure.

The practice of deprescribing GLP-1 receptor agonists was varied. One provider reported disliking GLP-1

TABLE 3 Recommended Laboratory Monitoring

Lifestyle Medicine Practitioner	Use of Deprescribing Protocol/Algorithm?	Laboratory Parameters
M.M.M.	No	A1C, BMP, microalbumin-to-creatinine ratio, fasting lipid panel, and, in certain cases, C-peptide
J.H.K.	No	Insulin level, HOMA-IR, and CMP
G.E.G.	Yes	C-peptide, FBG, HOMA-IR, and HOMA2-β
C.T.	No	FBG, A1C, C-peptide, C-reactive protein, fasting lipid panel, and laboratory tests to assess renal and liver function
B.G.B.	No	Insulin levels, FBG, A1C, fasting lipid panel, fasting insulin, and CMP
J.F.	Yes	Basic laboratory tests (with other laboratory tests individualized)
S.L.	No	Fasting lipid panel, CMP, A1C, thyroid function tests, insulin levels, and C-peptide
J.F.L.	No	A1C, C-peptide, diabetes autoantibodies, and C-reactive protein
T.M.C.	No	A1C, fasting lipid panel, and CMP

Recommendations based on clinical experience and self-developed protocol.

TABLE 4 Recommended Medication Deprescribing Interventions

Lifestyle Medicine Practitioner	Medication Classes and Deprescribing Prioritization
M.M.M.	First priority: SFU and insulin; second priority: TZD; third priority: DPP-4 inhibitor; fourth priority: SGLT2 inhibitor, GLP-1 receptor agonists,* and metformin. Insulin deprescribing is individualized and based on clinical judgment.
J.H.K.	First priority: SFU, insulin secretagogues, and insulin. Almost always deprescribes long-acting insulin. Metformin remains if fasting serum glucose is >100 mg/dL, patient tolerates it, and renal function is good. Deprescribing is individualized to the patient and medication profile.
G.E.G.	First priority: SFU and any medication causing hypoglycemia; second priority: TZD. DPP-4 inhibitors are stopped early because of low cost/benefit profile. Continues GLP-1 receptor agonists until HOMA2-β† normalizes, and continues metformin until HOMA-IR normalizes. Deprescribing is patient-specific.
C.T.	First priority: medications that cause hypoglycemia (i.e., SFU and insulin); second priority: blood pressure medications. Deprescribing is patient-specific. Shared decision-making is key.
B.G.B.	First priority: metformin; second priority: insulin. Considers cost to patient. Deprescribing is patient-specific.
J.F.	First priority: SFU; second priority: insulin.
S.L.	Nonspecific, no priority; will deprescribe all oral medications except metformin. For insulin, reduces dose by 10–20%.
J.F.L.	First priority: SFU and other oral hypoglycemic medications; second priority: statins (primary prevention use only). Deprescribes other medications based on cost. Metformin is deprescribed last. Change in short-acting insulin is individualized per patient need.
T.M.C.	First priority: SFU (if patient is prescribed a high dose, will taper dose by 50% and then assess) and insulin (as appropriate); second priority: TZD and DPP-4 inhibitor (based on glucose control and adverse effects). SGLT2 inhibitor, GLP-1 receptor agonist, and metformin are last for deprescribing consideration.

*Less likely to deprescribe GLP-1 receptor agonists in patients with CKD and/or ASCVD. Comfortable with continuing a GLP-1 receptor agonist if the patient is tolerating it and has obesity. †HOMA2-β is a validated mathematical tool commonly used to estimate β-cell function in type 2 diabetes using fasting glucose and insulin (48).

receptor agonists because of the risk of pancreatitis and stated that two patients in the practice had developed pancreatitis from taking liraglutide. Conversely, other providers were comfortable keeping GLP-1 receptor agonists on board as long as their patients tolerated the therapy.

The same was true for sodium–glucose cotransporter 2 (SGLT2) inhibitors. The rationale for deprescribing medications in this class varied, as well. One provider preferred to deprescribe other agents before SGLT2 inhibitors and reported that they were less likely to deprescribe an SGLT2 inhibitor because of data showing

TABLE 5 Summary of Identified Factors in and Rationale for Medication Deprescribing, Organized by Priority Level

Factor	Rationale
Cost	Medication costs and affordability for the patient
Medications	Consideration includes patient tolerability, patient preferences, and medication adverse effects. Factors for specific medications, listed in order of deprescribing priority, included: 1. SFUs: cause hypoglycemia and weight gain; some providers were concerned about the potential for increased risk of mortality; possibly accelerate loss of β-cell function and cardiac deconditioning. Insulin: causes hypoglycemia and weight gain. 2. TZDs: effects on weight (weight gain) and risk of heart failure exacerbation. 3. DPP-4 inhibitors: no ASCVD risk-reduction benefit. 4. SGLT2 inhibitors: one practitioner noted the importance of confirming use as indicated and reviewing risks (i.e., Does the patient have CKD, heart failure, and/or established ASCVD, and is the patient at higher risk of infection?) 5. GLP-1 receptor agonists: one practitioner reported that two patients on liraglutide developed pancreatitis. 6. Metformin: six practitioners preferred to deprescribe metformin last or to maintain it in the patient's treatment regimen.

independent benefit in patients with atherosclerotic cardiovascular disease (ASCVD) and chronic kidney disease (CKD). Another provider was concerned about the cost and safety of SGLT2 inhibitors, especially when they are prescribed for patients without established CKD, heart failure, or ASCVD. Additoinally, one practitioner preferred to deprescribe dipeptidyl peptidase 4 (DPP-4) inhibitors because no ASCVD risk reduction benefit has been demonstrated with this medication class. No specific rationale was provided for deprescribing metformin.

Table 6 presents the desired target blood glucose range, ultimate blood glucose targets, preferred frequency of self-monitoring of blood glucose (SMBG), and preferences for using continuous glucose monitoring (CGM). Eight of the nine practitioners recommended a target blood glucose range for further deprescribing of <120 mg/dL. Four practitioners recommended ultimate blood glucose targets for fasting blood glucose (FBG) ≤110 mg/dL, and two of the nine experts recommended an ultimate A1C target of <6.5%. When recommending frequency of SMBG, four practitioners preferred patients to test their blood glucose multiple times daily (some up to five to seven times daily), two practitioners individualize their recommendations based on a patient's medication regimen, and six practitioners preferred using data from real-time or intermittently scanned CGM when deprescribing.

Table 7 presents practitioners' observations on the frequency of hypoglycemia, describes each practitioner's preferred method to address hypoglycemia management, and reports their considerations in reference to daytime versus nocturnal hypoglycemia. Seven practitioners reported that hypoglycemia occurs infrequently in their practices, one reported that it occurs rarely, and one reported that hypoglycemia frequency varies among their patients. Three providers prescribed commonly recommended hypoglycemia treatment methods (usual care) for treatment of hypoglycemia to their patients. Seven practitioners mentioned avoiding all hypoglycemia as a primary concern in treatment, and, of these, four specifically mentioned additional concerns around avoiding nocturnal hypoglycemia.

Table 8 presents each practitioner's usual patient follow-up process. Responses varied depending on the setting of care. Five practitioners reported patient follow-up intervals of 1–4 weeks, with two of those five using shared medical visits in the process. Two practitioners reported partnering with a CDCES, dietitian, or PharmD for patient follow-up. One practitioner reported that patients follow up with their primary care provider (PCP). Of note, practitioners individualized follow-up based on their patients' needs.

Table 9 presents the practitioners' perceived positive and negative effects of medication deprescribing. Three practitioners reported perceived positive effects related to weight loss and reported cost savings; four reported positive effects associated with reduced medication burden, which included but was not limited to elimination of medication adverse effects and drug interactions. Two reported perceived benefits connected to patient empowerment. Additionally, two experts reported positive effects related to hypoglycemia avoidance. Other than provider and team member access challenges and pushback from insurance companies, no perceived negative effects were reported.

Discussion

As the use of lifestyle medicine grows, the need to practice de-escalation of glucose-lowering medications will also grow, adding to the already identified need for older patients, who may be at risk for adverse events from polypharmacy (29). Both the American Diabetes Association (ADA) (30,31) and the American Association of Clinical Endocrinology (32) recommend lifestyle optimization as part of medical care for type 2 diabetes. To the authors' knowledge, this is the first account published of the medication de-escalation methods used by lifestyle medicine providers when patients demonstrate a decreased need for pharmacotherapy. This study supports the feasibility of de-escalating glucose-lowering medications in this context and provides pilot data on protocols from individual practitioners experienced in deprescribing glucose-lowering medications. Despite differences among providers with regard to laboratory monitoring, prioritization of medication classes to deprescribe, approaches to monitoring blood glucose levels and managing hypoglycemia, and patient follow-up processes, certain themes emerged.

Participants reported practicing de-escalation in both intensive and nonintensive practice settings, but consistently reported involving a multidisciplinary team. Most of the practitioners stated that they did not use a published, externally documented protocol or algorithm for medication deprescribing, but they were able to describe their usual decision-making process in response to interview questions. Laboratory testing varied among providers with regard to A1C, C-peptide, and renal assessment, with the BMP and CMP being the most commonly used laboratory tests. Most of the practitioners targeted normoglycemia in their patients with type 2

TABLE 6 Recommended Target Blood Glucose Range and SMBG Frequency and Use of CGM

Lifestyle Medicine Practitioner	Target Blood Glucose Range for Further Deprescribing, mg/dL	Ultimate Blood Glucose Targets (With or Without Some Continuing Medications)	SMBG Frequency	CGM Use and Corresponding Rationale
M.M.M.	FBG <120, 2-hour postprandial glucose <150	FBG <126 mg/dL, 2-hour postprandial glucose <160 mg/dL, plus A1C <6.5% without medications	Ideally, at least two times per day	No. No or limited coverage for CGM by third-party payers for type 2 diabetes unless the patient is on multiple insulin injections per day.
J.H.K.	FBG <110	FBG <100 mg/dL with no medications or metformin only	Up to five times per day	No. Prefers SMBG for both intensive and nonintensive scenarios. CGM expense is not needed or warranted. For ambulatory patients with poorly controlled glucose, using CGM is more reasonable.
G.E.G.	Glucose 80–120, individualized based on age	FBG 70–99 mg/dL	One to seven times daily	Yes. Real-time CGM can be useful to patients in understanding their glucose response to insulin changes and reaching target glucose ranges. Intermittently scanned CGM can be frustrating for patients who monitor their glucose closely with SMBG when tight glucose control is preferred.
C.T.	If medication is required, average glucose of 154–183 (A1C 7–8%) for most patients, based on American College of Physicians 2018 guidelines (49); lower targets with intensive lifestyle interventions without medication	A1C <6.5%, per 2021 ADA remission consensus (50)	Individualized depending on medication regimen	Yes. Both real-time and intermittently scanned CGM are excellent tools to identify SMBG trends in response to lifestyle interventions and reduce the number of fingersticks needed with SMBG.
B.G.B.	Blood glucose <110	FBG <110 mg/dL without medications or <120 mg/dL with metformin only	Zero to five times per day, depending on medications	Yes. Mostly uses real-time CGM for select patients, depending on third-party payer coverage. Assists patients with understanding the effects of lifestyle changes on glucose control.
J.F.	Blood glucose <120	FBG <120 mg/dL with metformin only and <100 mg/dL without medication	Two times per day, when fasting and at one other varying time of day	No. CGM is not needed with patients who are successfully losing weight and aggressively reversing their diabetes-related parameters (e.g., A1C and SMBG readings)
S.L.	FBG 90–100, 2-hour postprandial glucose <140	FBG <100 mg/dL without medications or <120 mg/dL with metformin	Four times daily	Yes. Uses real-time or intermittently scanned CGM for many patients, with success in reaching target glucose ranges and improving diabetes control. Cost/affordability prohibits use for all patients.

Continued on p. 170 »

« Continued from p. 169

TABLE 6 Recommended Target Blood Glucose Range and SMBG Frequency and Use of CGM (Continued)

Lifestyle Medicine Practitioner	Target Blood Glucose Range for Further Deprescribing, mg/dL	Ultimate Blood Glucose Targets (With or Without Some Continuing Medications)	SMBG Frequency	CGM Use and Corresponding Rationale
J.F.L.	Individualized depending on starting A1C and type/dose of medication(s), but typically FBG <120	A1C <5.7% (normal) and FBG <100 mg/dL without medication	Uses CGM	Yes. Uses both real-time and intermittently scanned CGM. Encourages use for patients with poorly controlled glucose, especially those taking insulin or other hypoglycemic agents.
T.M.C.	Blood glucose in mid-100s range for the first week, then individualized	FBG 70–110 mg/dL with minimal medication	Individualized based on medication regimen	Yes. Uses real-time or intermittently scanned CGM only when patient has been using CGM before initiation of medication deprescribing.

diabetes, and their responses varied with respect to how often patients monitored their blood glucose levels.

Glucose levels are usually monitored via SMBG or CGM. CGM provides information to patients on both their immediate blood glucose level and its trend (i.e., the direction and rate of blood glucose change) (33). For both patients and practitioners, CGM provides opportunities to understand daytime and nighttime patterns with glycemia, identify causes of glucose fluctuations, and improve overall glycemic control while preventing unwanted hyper- and hypoglycemia (33).

There are two types of user-owned CGM devices. Real-time CGM systems measure and store glucose levels continuously without prompting; intermittently scanned CGM systems also measure glucose levels continuously but require scanning to record glucose values (30). The ADA's *Standards of Medical Care in Diabetes—2022* recommendations support the use of CGM for diabetes management in adults on basal insulin or a multiple daily injection regimen (30). Currently, there is no clinical guidance in the public domain for CGM use when prescribed lifestyle interventions are combined with medication deprescribing in type 2 diabetes. This study highlights a need for clear guidance on the use of CGM during medication de-escalation.

More than half of the practitioners interviewed for this study reported using CGM when deprescribing medications for selected patients or patient groups. Those favoring CGM use reported many patient benefits. Patients can use the immediate blood glucose feedback to assess the effects of medication changes and intensive lifestyle interventions on blood glucose control, understand how stress and poor sleep habits affect blood glucose levels, and assess for hyper- and hypoglycemia. CGM may additionally reduce or eliminate the need for fingerstick blood glucose monitoring, which can be forgotten, become painful over time, or be uncomfortable for patients to use in public settings. Most practitioners expressed that patient expenses associated with CGM use and third-party payer coverage are factors they consider in their decision-making. Health insurance plans often do not cover CGM systems, leaving patients with estimated out-of-pocket costs ranging from $2,500 to $6,000 per year (34,35). Regardless of CGM preference, practitioners identified the need to assess the affordability of CGM systems for patients when de-escalating medications.

There has been increasing attention on the ranking of hypoglycemia and comparison of risk for daytime versus

TABLE 7 Observed Frequency and Recommended Management of Hypoglycemia

Lifestyle Medicine Practitioner	Frequency of Hypoglycemia	Management of Hypoglycemia (Glucose <70 mg/dL)	Considerations for Daytime Versus Nocturnal Hypoglycemia
M.M.M.	Infrequent	Commonly recommended care/treatment (rule of 15*)	Any hypoglycemia, particularly nocturnal, typically prompts de-escalation of insulin and SFUs.
J.H.K.	Infrequent	Educate patients to have ready access to healthy food to raise blood glucose (e.g., dates, an orange, or whole-grain crackers).	Risk of hypoglycemia is avoided during ITLC by holding or greatly reducing doses of diabetes medications. When these medications are deprescribed, there is essentially no risk of hypoglycemia.
G.E.G.	Infrequent	Check blood glucose; consume crackers, glucose tablets, or juice; use glucagon if needed.	Address nocturnal hypoglycemia with evening food and/or lower doses of long-acting insulin to prevent glucose from dropping too low overnight. For patients taking meal-time short-acting insulin, the correct basal dose will allow for more predictable meal-time responses and help to avoid hypoglycemia.
C.T.	Varies among patients	Commonly recommended care/treatment (4 oz fruit juice or glucose tablets and then eat a more substantial snack within 30 minutes; follow up for medication adjustment evaluation)	All hypoglycemia should be avoided. Attention to avoiding nocturnal hypoglycemia should be the first priority in determining which medication to deprescribe.
B.G.B.	Infrequent	Initially, correct blood glucose with 2 oz of a simple carbohydrate or juice, followed by 1 oz of nuts; patients are encouraged to follow up to assess the need to decrease medication	Hypoglycemia is just as important to monitor during the day as at night. I am much more inclined to decrease diabetes medications to allow for brief hyperglycemia into the 150-mg/dL range to prevent hypoglycemia.
J.F.	Rare	Deprescribing at <120 mg/dL (anytime) is emphasized for prevention of hypoglycemia. Patients are advised to have Medjool dates (16 g carbohydrate) available, but these have only been needed in one case in the past decade.	Hypoglycemia is an extremely unusual occurrence, as medications are rapidly discontinued in favor of nutritional therapy and exercise interventions that do not cause hypoglycemia.
S.L.	Infrequent	Educate patients on the importance of having quick access to drinks that can quickly increase blood glucose and notifying someone immediately if hypoglycemia and neurological status worsen.	To properly deprescribe medication, it is imperative to monitor glucose levels and patient symptoms to ensure that no daytime or nighttime hypoglycemic episodes occur.
J.F.L.	Infrequent	Educate patients to have access to something that can raise their blood glucose.	Avoid hypoglycemia in patients as they adopt a healthier lifestyle and we try to deprescribe their medications (especially insulin). I see the most dramatic drops in patients as they transition to a low-fat, high-fiber, whole-food, plant-based diet. I usually stop oral hypoglycemic medications and/or decease insulin doses proactively because I would rather see their glucose run a little high in the short run than have them develop hypoglycemia as their insulin sensitivity starts to improve and/or insulin resistance starts to resolve.
T.M.C.	Infrequent	Usual care/treatment (rule of 15*)	Varies according to patient type, prescribed medications, timing of insulin dosing, meal-time patterns, and baseline blood glucose control when I first meet a patient.

*The "rule of 15," a common guideline for hypoglycemia treatment, includes the following steps: *1*) check blood glucose to confirm that it is <70 mg/dL; *2*) consume 15 g carbohydrate; and *3*) after 15 minutes, recheck blood glucose. If blood glucose is still low, repeat steps 2 and 3 until glucose is >70 mg/dL (51).

TABLE 8 Patient Follow-Up After Initial Medication Deprescription

Lifestyle Medicine Practitioner	Follow-Up Process
M.M.M.	• Primary care setting: doctor visits every 3–6 months × 20 minutes; CDCES or PharmD visits between doctor visits • Weight management program: once every 4–6 weeks × 30 minutes • Lifestyle medicine program: individual doctor follow-up every 2 weeks if needed; weekly group visits • In all three settings, telephone doctor follow-up between visits, as needed
J.H.K.	None; patients return to PCP for follow-up
G.E.G.	• Shared medical visit weekly, spacing out as patient understands the process • Portal access and insulin adjustment, as needed/desired
C.T.	Individualized based on need; typically, 2–4 weeks, with telephone follow-up as needed
B.G.B.	Every 2 weeks, initially
J.F.	Close contact over the first week and then individualized based on patient need
S.L.	Monthly
J.F.L.	• Once weekly × 4 weeks to see dietitian • Initially, telehealth visits with provider every 2–4 weeks, then every 3–4 months when blood glucose is stable • Monitoring of CGM data monthly, with communication/feedback through portal
T.M.C.	Daily × 3 days after initial interventions (by phone) to monitor glucose control and insulin doses

nocturnal hypoglycemia (36,37). These considerations may not come to the forefront in lifestyle medicine settings; the lifestyle medicine practitioners interviewed in this study did not expect frequent or severe hypoglycemia and shared a variety of strategies they deploy to prevent it from occurring. In the case of any hypoglycemia, particularly nocturnal hypoglycemia, these practitioners reported taking steps to prioritize de-escalating medications known to cause hypoglycemia.

Although medication deprescribing is individualized to each patient, the most common practice among all practitioners was to first target SFUs, insulin, and other medications known to cause hypoglycemia. Practitioners also mentioned targeting SFUs first because of potential acceleration of decline in β-cell function, which has been discussed in the literature (38). Conversely, most practitioners preferred to defer deprescribing medications that have demonstrated cardiovascular and/or renal benefits (i.e., GLP-1 receptor agonists and SGLT2 inhibitors), as well as those with a less severe adverse effect profile (i.e., metformin and GLP-1 receptor agonists) until after other medications are deprescribed.

Some other accounts of medication de-escalation have been published. Previously, the DiRECT study and the Look AHEAD (Action for Health in Diabetes) trial demonstrated the benefits of energy restriction for type 2 diabetes remission; however, neither reported detailed protocols or individualized decision-making processes of medication deprescribing in their methodology (39,40). In the DiRECT study, all glucose-lowering medications were stopped at the outset of the intervention, with a published protocol for individualized reintroduction of antidiabetic medications as needed (22). However, the discontinuation of all medications at the outset of the study was applied to all patients, and no patient monitoring was performed to inform this decision (22). The Look AHEAD study reported that participants were asked to provide blood glucose measurement records so that study staff could make decisions to lower medications as needed, but no other details were provided (39). It is difficult to draw conclusions about general deprescribing practice from these studies. The DiRECT study had a homogenous subject population and a more specific intervention, as it excluded subjects who required insulin and used a very-low-calorie (820–850 kcal/day) diet. The Look AHEAD study had more heterogeneity (with some subjects requiring insulin), which presumably required a more heterogeneous approach to medication deprescribing.

In a recent randomized controlled trial (RCT), investigators evaluated the effect of an intensive lifestyle

TABLE 9 Perceived Positive and Negative Effects of Medication Deprescribing

Lifestyle Medicine Practitioner	Perceived Positive Effects	Perceived Negative Effects
M.M.M.	Weight benefits of decreasing or stopping insulin and SFUs; decreased medication burden and cost; patients feeling empowered	Perception of diabetes medication deprescribing from providers not familiar with lifestyle medicine
J.H.K.	Improved patient morale and sense of empowerment	Need for PCP to reinitiate/recalibrate if recidivism occurs
G.E.G.	Avoidance of hypoglycemia; patients glad to get off medications; improved sense of well-being and hope	No negatives identified
C.T.	Less anxiety about hypoglycemia; reduced out-of-pocket expense; feelings of empowerment	Anger expressed by some patients that they were not told earlier about efficacy of plant-based diet and that less medication is possible
B.G.B.	Educating about ITLC effect on increasing insulin sensitivity to reduce/discontinue medication is empowering to patients	No negatives identified except that ITLC was not discussed with them previously
J.F.	Eliminating medications reduces side effects and enables more effective weight loss and reversal of the health problem	No negatives identified
S.L.	People love the fact that they are getting off of medications; clinical and financial benefits; eliminating complications and drug-drug interactions	Pushback from insurance companies
J.F.L.	Avoidance of hypoglycemia and other medication side effects; weight loss and improved quality of life	No negatives identified
T.M.C.	Weight loss; decreased insulin dose; more energy	Potential mild hypoglycemia and symptoms of hypoglycemia with normal glucose levels

intervention on glycemic control in patients with type 2 diabetes (41). The dose of antihyperglycemic medication was deprescribed (reduced by half or discontinued) almost solely based on A1C results, except in instances of hypoglycemia, for which the endocrinologist assessed the participant and considered whether a medication reduction was necessary (41). No other factors or rationales were considered in the process of deprescribing. In contrast, the clinical practice of the lifestyle medicine practitioners interviewed for this study was generally to evaluate a variety of laboratory assessments (e.g., C-peptide, insulin, and fasting lipid levels), in addition to A1C in their medication deprescribing processes, with treatment decisions regarding dose reductions and medication discontinuation commonly individualized. This finding underscores the need to develop guidance documents and point-of-care tools to assist providers in clinical decision-making when deprescribing medications for type 2 diabetes remission.

Type 2 diabetes is an established risk factor for cardiovascular and renal morbidity and mortality. Several RCTs have been published evaluating the safety and efficacy of agents in the SGLT2 inhibitor and GLP-1 receptor agonist medication classes for reducing the risk of cardiovascular and renal events in individuals with type 2 diabetes (with some studies including subjects with or without a diagnosis of type 2 diabetes) (42–46). The results of many of these studies demonstrated significant cardiovascular and/or renal benefits from these medication classes (42–46). Practitioners interviewed for this study considered this evidence in their decision-making process to continue or deprescribe SGLT2 inhibitors and GLP-1 receptor agonists. Additional evidence from RCTs continues to emerge in this area and will likely remain a consideration in lifestyle medicine practitioners' deprescribing practices.

Although there are some published examples of deprescribing glucose-lowering medications in patients with type 2 diabetes, there is little in the way of published guidance for clinicians (23,27). One retrospective study evaluated a pharmacist-managed deprescribing program within an integrated health care system (47). The

primary outcome focused on hypoglycemia risk, but there was no mention of any possible dietary interventions, and although an algorithm was used for deprescribing, it was not provided in the publication (47). Another systematic review assessed medication deintensification in type 2 diabetes (1). This study targeted an older population, and its authors described deintensification as medication withdrawal, discontinuation, or dosage reduction. However, this description did not mention lifestyle modifications and also includes conversion or substitution of at least one medication, which was not consistent with the accepted definitions of deprescribing. In these systematic reviews, the authors identified that more data are needed to assist providers with medication deprescribing in type 2 diabetes. Our study also supports the need for clear guidance, given the variations seen among the experts interviewed with respect to rationale, laboratory monitoring, interventions, target blood glucose ranges, and other considerations.

The Bruyère Research Institute's deprescribing.org website offers a publication and an algorithm as a resource for deprescribing antihyperglycemics; however, these resources specifically target elderly patients (>65 years of age) and are not focused on patients undergoing lifestyle interventions and achieving disease reversal or remission (28). The algorithm focuses on a variety of goals, including discontinuation or reduction in the dose of agents that most likely contribute to hypoglycemia, changes to agents with lower risks of hypoglycemia, and reductions in doses of antihyperglycemics that rely on the kidneys for elimination. The authors who were interviewed for this study agreed that avoidance of hypoglycemia is important but also identified other factors influencing their decision-making that are not fully addressed in the resources available at deprescribing.org. Moreover, other classes of medications may require adjustment in patients making intensive lifestyle changes, including various blood pressure medications. The DiRECT study includes mention of this issue in its protocol (22), but data on best practices for this adjustment are limited.

Limitations

Limitations of this study are its small sample size (n = 9) and its design of a case series based on purposive sampling. Although these practitioners have extensive experience in deprescribing glucose-lowering medications, the results are limited to their individual experiences. Because bariatric surgery was not the intervention of interest, we did not include protocols relevant to that procedure. Similarly, we did not include protocols relevant to weaning from other related medications such as blood pressure medications, as they were outside of the scope of the study.

Implications for Future Research

Future research should begin with historical chart reviews of patient data to describe the prevalence, safety, and impact of de-escalation and individualization of therapies; such work is currently in planning with patient panels from several lifestyle medicine practitioners. Future research should also include surveys of larger numbers of lifestyle medicine providers regarding their de-escalation practices, tracking of adverse events among cohorts of patients with type 2 diabetes receiving ITLC, and more detailed, in-depth interviews to develop a more comprehensive framework for decision-making. Furthermore, RCTs comparing the effectiveness of various lifestyle interventions in reducing the need for type 2 diabetes medications, coupled with a variety of approaches to de-escalation of prescription medications, are necessary for the eventual development of clinical practice guidelines. These different deprescribing approaches could also yield important data about safety outcomes and patient experience, satisfaction, and adherence.

Conclusion

This study of lifestyle medicine practitioner protocols demonstrates that a variety of approaches exist to successfully deprescribing glucose-lowering medications in a safe and effective way. Practitioners in this case series worked with interdisciplinary teams and, overall, preferred to deprescribe medications that cause hypoglycemia first, aiming for patients to achieve normoglycemia. Their protocols can serve as examples to other practitioners who may find a need to adjust medications after lifestyle modifications. Future work should advance the field of lifestyle medicine with further research on health outcomes resulting from ITLC interventions and comparisons of deprescribing practices. Pending sufficient research in this area, clinical practice guidelines and point-of-care tools for deprescribing are needed, as well as clinician and patient education materials.

ACKNOWLEDGMENTS

The authors thank Kaitlyn Pauly, MS, RD, DipACLM, and Roman Moretti, BSc (Pharm), of ACLM and Rohit Moghe, PharmD, of Trinity Health Mid-Atlantic for their assistance and participation in the interviewing process, as well as Kara Livingston Staffier, MPH, of ACLM for her assistance in manuscript editing and formatting.

FUNDING

This study was funded by the Ardmore Institute of Health.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

M.D.B. designed the study, conducted the interviews, and wrote the manuscript. M.E.A., B.G.B., T.M.C., J.F., G.E.G., J.H.K., S.L., J.F.L., M.M.M., and C.T. contributed as interviewees and reviewed and edited the manuscript. M.C.K. performed the literature search and screening, and reviewed and edited the manuscript. M.D.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of results.

REFERENCES

1. 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

2. Licata A, Minissale MG, Giannitrapani L, et al. Comorbidities impact and de-prescribing in elderly with HCV-related liver disease: analysis of a prospective cohort. Intern Emerg Med 2022;17:43–51

3. Vu M, Sileanu FE, Aspinall SL, et al. Antihypertensive deprescribing in older adult veterans at end of life admitted to Veteran Affairs nursing homes. J Am Med Dir Assoc 2021;22:132–140.e5

4. Strain WD, Down S, Brown P, Puttanna A, Sinclair A. Diabetes and frailty: an expert consensus statement on the management of older adults with type 2 diabetes. Diabetes Ther 2021;12:1227–1247

5. Niznik JD, Hunnicutt JN, Zhao X, et al. Deintensification of diabetes medications among veterans at the end of life in VA nursing homes. J Am Geriatr Soc 2020;68:736–745

6. Duncan I, Maxwell TL, Huynh N, Todd M. Polypharmacy, medication possession, and deprescribing of potentially non-beneficial drugs in hospice patients. Am J Hosp Palliat Care 2020;37:1076–1085

7. Zueger PM, Holmes HM, Calip GS, Qato DM, Pickard AS, Lee TA. Older Medicare beneficiaries frequently continue medications with limited benefit following hospice admission. J Gen Intern Med 2019;34:2029–2037

8. Vouri SM, Chen J, Sparkman J, Salles A, Micek ST. Order of discontinuation of glucose-lowering medications following bariatric surgery. Diabetes Res Clin Pract 2021;172:108580

9. Oktora MP, Kerr KP, Hak E, Denig P. Rates, determinants and success of implementing deprescribing in people with type 2 diabetes: a scoping review. Diabet Med 2021;38:e14408

10. Naing S, Ramesh G, Garcha J, Poliyedath A, Khandelwal S, Mills PK. Is the stepping-down approach a better option than multiple daily injections in obese patients with poorly controlled type 2 diabetes on advanced insulin therapy? Endocrinol Diabetes Metab 2020;4:e00204

11. Fritsche A, Heni M, Peter A, et al. Considering insulin secretory capacity as measured by a fasting C-peptide/glucose ratio in selecting glucose-lowering medications. Exp Clin Endocrinol Diabetes 2022;130:200–204

12. Hopkins RE, Bui T, Konstantatos AH, et al. Educating junior doctors and pharmacists to reduce discharge prescribing of opioids for surgical patients: a cluster randomised controlled trial. Med J Aust 2020;213:417–423

13. Vinuesa-Hernando JM, Gimeno-Gracia M, Malo S, et al. Potentially inappropriate prescriptions and therapeutic complexity in older HIV patients with comorbidities. Int J Clin Pharm 2021;43:1245–1250

14. Thorpe CT, Sileanu FE, Mor MK, et al. Discontinuation of statins in veterans admitted to nursing homes near the end of life. J Am Geriatr Soc 2020;68:2609–2619

15. Pasina L, Novella A, Elli C, Nobili A, Ianes A. Inappropriate use of antiplatelet agents for primary prevention in nursing homes: an Italian multicenter observational study. Geriatr Gerontol Int 2020;20:828–832

16. Nguyen JV, Roseberry S, Rivas JA, Cauthon KAB. Hypoglycemia in older people with type 2 diabetes: prevention and treatment strategies for outpatient and long-term care facility settings. Sr Care Pharm 2021;36:112–123

17. Li J, Chattopadhyay K, Xu M, et al. Prevalence and predictors of polypharmacy prescription among type 2 diabetes patients at a tertiary care department in Ningbo, China: a retrospective database study. PLoS One 2019;14:e0220047

18. Reeve E, Wiese MD. Benefits of deprescribing on patients' adherence to medications. Int J Clin Pharm 2014;36:26–29

19. Karlsen M, Panigrahi G, Kelly J. Intensive lifestyle interventions for treatment towards remission of type 2 diabetes: a case series [Abstract]. Diabetes 2021;70 (Suppl. 1):503-P

20. Kelly J, Karlsen M, Steinke G. Type 2 diabetes remission and lifestyle medicine: a position statement from the American College of Lifestyle Medicine. Am J Lifestyle Med 2020;14:406–419

21. Rosenfeld RM, Kelly JH, Agarwal M, et al. Dietary interventions to treat type 2 diabetes in adults with a goal of remission: an expert consensus statement from the American College of Lifestyle Medicine. Am J Lifestyle Med 2022;16:342–362

22. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol 2019;7:344–355

23. 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

24. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. Health and economic costs of chronic diseases. Available from https://www.cdc.gov/chronicdisease/about/costs/index.htm. Accessed 11 May 2022

25. Centers for Disease Control and Prevention. Leading causes of death. Available from https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm. Accessed 10 February 2022

26. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018;41:917–928

27. 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

28. Farrell B, McCarthy L, Thompson W, Tannenbaum C. Our vision and mission. Available from https://deprescribing.org/about. Accessed 23 November 2021

29. Niehoff KM, Rajeevan N, Charpentier PA, Miller PL, Goldstein MK, Fried TR. Development of the Tool to Reduce Inappropriate Medications (TRIM): a clinical decision support system to improve medication prescribing for older adults. Pharmacotherapy 2016;36:694–701

30. American Diabetes Association Professional Practice Committee. 7. Diabetes technology: *Standards of Medical Care in Diabetes—2022*. Diabetes Care 2022;45(Suppl. 1):S97–S112

31. Burant CF, Young LA, Eds. *Medical Management of Type 2 Diabetes*. 7th ed. Alexandria, VA, American Diabetes Association, 2012

32. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2020 executive summary. Endocr Pract 2020;26:107–139

33. Edelman SV, Argento NB, Pettus J, Hirsch IB. Clinical implications of real-time and intermittently scanned continuous glucose monitoring. Diabetes Care 2018;41:2265–2274

34. Robertson SL, Shaughnessy AF, Slawson DC. Continuous glucose monitoring in type 2 diabetes is not ready for widespread adoption. Am Fam Physician 2020;101:646

35. Oser TK, Litchman ML, Allen NA, et al. Personal continuous glucose monitoring use among adults with type 2 diabetes: clinical efficacy and economic impacts. Curr Diab Rep 2021;21:49

36. Klonoff DC, Wang J, Rodbard D, et al. A glycemia risk index (GRI) of hypoglycemia and hyperglycemia for continuous glucose monitoring validated by clinician ratings. J Diabetes Sci Technol. Online ahead of print on 29 March 2022 (doi: 10.1177/19322968221085273)

37. Leonard CE, Han X, Brensinger CM, et al. Comparative risk of serious hypoglycemia with oral antidiabetic monotherapy: a retrospective cohort study. Pharmacoepidemiol Drug Saf 2018;27:9–18

38. Meier JJ. Beta cell mass in diabetes: a realistic therapeutic target? Diabetologia 2008;51:703–713

39. Gregg EW, Chen H, Wagenknecht LE, et al.; Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489–2496

40. Leslie WS, Ford I, Sattar N, et al. The Diabetes Remission Clinical Trial (DiRECT): protocol for a cluster randomised trial. BMC Fam Pract 2016;17:20

41. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an intensive lifestyle intervention on glycemic control in patients with type 2 diabetes: a randomized clinical trial. JAMA 2017;318:637–646

42. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–130

43. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Optimizing the analysis strategy for the CANVAS Program: a prespecified plan for the integrated analyses of the CANVAS and CANVAS-R trials. Diabetes Obes Metab 2017;19:926–935

44. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844

45. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322

46. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128

47. Hui RL, Chang CC, Niu F, et al. Evaluation of a pharmacist-managed antidiabetic deprescribing program in an integrated health care system. J Manag Care Spec Pharm 2019;25:927–934

48. Felton JL, Cuthbertson D, Warnock M, et al.; Type 1 Diabetes TrialNet Study Group. HOMA2-B enhances assessment of type 1 diabetes risk among TrialNet Pathway to Prevention participants. Diabetologia 2022;65:88–100

49. Qaseem A, Wilt TJ, Kansagara D, et al.; Clinical Guidelines Committee of the American College of Physicians. Hemoglobin A1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. Ann Intern Med 2018;168:569–576

50. Riddle MC, Cefalu WT, Evans PH, et al. Consensus report: definition and interpretation of remission in type 2 diabetes. Diabetes Care 2021;44:2438–2444

51. Diabetes Self-Management. Treating hypoglycemia: the rule of 15. Available from https://www.diabetesselfmanagement.com/managing-diabetes/treatment-approaches/understanding-insulin/treating-hypoglycemia. Accessed 31 January 2022