Management of Atherosclerotic Cardiovascular Disease Risk Factors in the Older Adult Patient With Diabetes

Mary T. Korytkowski[1] and Daniel E. Forman[2]

Diabetes Care 2017;40:476–484 | DOI: 10.2337/dc16-0815

Older adults with diabetes are at higher risk for atherosclerotic cardiovascular disease (ASCVD) than younger adults with diabetes and older adults without diabetes. The rationale to implement ASCVD risk–lowering therapies in older adults with diabetes is compelling. Recommendations for lifestyle modification, lipid-lowering therapy, blood pressure management, blood glucose control, and aspirin therapy are often based on studies that show their efficacy in younger populations. However, the risks associated with each of these interventions increase with age, and favorable risk-to-benefit ratios demonstrated in younger adults with diabetes are less certain in older populations. The variability in health status among older adults is pertinent. Those with robust health are more likely to tolerate and derive benefit from many therapies when compared with those who have more complex health including frailty. Age- and/or frailty-stratified data to help clarify these relationships are sparse. In this Perspective, current recommendations for modifying ASCVD risk are described with a review of the pertinent literature that guides their application in older adults. A pragmatic approach to the treatment of ASCVD risk factors in older adults with diabetes is presented.

Diabetes is highly prevalent in the aging population, affecting >25% of individuals aged >65 years and 19% of those aged >75 years (1,2). Physiological changes associated with aging increase susceptibility to coronary heart disease and other atherosclerotic cardiovascular disease (ASCVD) processes (3). The incidence and prevalence of ASCVD-related macrovascular events essentially doubles in older adults with diabetes (4–6). The overlap of older age, diabetes, and other ASCVD risk factors enhances risk for microvascular and macrovascular complications, functional disability, and geriatric syndromes (including frailty, multimorbidity, polypharmacy, cognitive impairment, depression, urinary incontinence, and falls) (1,7–10). As the population of older adults grows, the implications of diabetes on ASCVD risk escalate, and insights regarding optimal care become increasingly important (2).

Therapies directed at ASCVD risk factor reduction are important therapeutic priorities for older adults with diabetes as a way of modifying risk for vascular events and improving health-related quality of life (HRQL) (11,12). Therapeutic targets include control of lipids, blood pressure (BP), and blood glucose in combination with antiplatelet agents. The expectation is that these therapies will increase longevity, reduce ASCVD events and need for hospitalizations, and improve HRQL. However, iatrogenic risks and limited life expectancy confound these objectives

[1]*Division of Endocrinology and Metabolism, Department of Medicine, University of Pittsburgh, Pittsburgh, PA*
[2]*Division of Geriatric Medicine and Cardiology, Department of Medicine, University of Pittsburgh, Pittsburgh, PA*

Corresponding author: Mary T. Korytkowski, mtk7@pitt.edu.

Received 14 April 2016 and accepted 15 October 2016.

See accompanying articles, pp. 440, 444, 453, 461, 468, 485, 494, 502, 509, 518, and 526.

among older adults and merit consideration as part of patient-centered management goals (1,9). For example, benefits of cholesterol- or BP-lowering therapies are counterbalanced by higher risk for myalgias and/or hypotension and falls (13,14). Strict glycemic control is counterbalanced by risk for hypoglycemia (15,16). Antiplatelet therapy is associated with higher risk for bleeding (17). Geriatric syndromes and age-related differences in pharmacokinetics and pharmacodynamics of some medications further compound these iatrogenic risks (18).

Despite the marked prevalence of ASCVD in older adults with diabetes, there are no trials that specifically explore the utility of risk factor modification in this population. Instead, benefits are often inferred from study populations who are often younger, healthier, and less complex than those encountered in clinical practice. These indirect analytic methods are problematic in that older adults with diabetes tend to be more heterogeneous and clinically complex than the younger populations (1,7,19). While most trials focus on mortality end points, many seniors may be more concerned with HRQL, functional capacity, and independence (20).

In this Perspective, current recommendations and standards of care for lipid lowering, BP and glycemic management, and use of aspirin for reducing ASCVD are discussed with attention to older adults with diabetes. The age reference for older adult will be defined as >65 years, subdivided by health status as healthy, intermediate, or poor health (Table 1) (1). This approach acknowledges that age alone is not an indicator of impaired health but recognizes that the percentage of individuals who can be classified as healthy decreases with increasing age, especially in those with diabetes (21). In *Standards of Medical Care in Diabetes—2016*, the American Diabetes Association (ADA) replaced the term cardiovascular disease (CVD) with ASCVD as more inclusive of overall vascular disease. For this reason, ASCVD will be used unless CVD is more relevant to a specific citation (22).

STANDARDS OF CARE

The therapeutic goals for any patient with diabetes are to avoid symptoms of hyperglycemia and hypoglycemia, to minimize risk for acute and chronic diabetes-related complications, and to optimize HRQL. A Consensus Report on diabetes in older adults provided a framework for ASCVD risk management according to overall health status (1) (Table 1). This framework addresses lipid, BP, and glucose management in relation to age and one of the following three health categories:

1. Healthy with few coexisting illnesses and intact cognitive and functional status
2. Complex or intermediate health with three or more coexisting chronic illnesses, impairments in two or more activities of daily living (ADL) (Table 2), or mild to moderate impairment in cognitive function
3. Very complex or poor health including those requiring long-term care or who have end-stage chronic illnesses, moderate to severe cognitive impairments, or two or more ADL dependencies

The ADA recommendations for older adults with diabetes are consistent with guidelines developed by the American Geriatrics Society (AGS) (23). Both organizations recommend that functional, cognitively intact older adults who have significant anticipated life expectancy receive similar ASCVD risk reduction strategies as younger adults. However, methods to best achieve stratification that is inclusive of aggregate disease status, function, cognition, and other holistic perspectives remains an ongoing challenge and is not well-integrated with electronic medical records.

THERAPEUTIC LIFESTYLE INTERVENTIONS

Therapeutic lifestyle interventions (TLI) with diet and exercise are important components of ASCVD risk reduction in older as well as younger patient populations (24,25). The efficacy of intensive TLI in older patient populations was demonstrated in the Diabetes Prevention Program (DPP) and Look AHEAD (Action for Health in Diabetes) studies (24–26). In the DPP, participants aged >60 years (range 60–85) achieved greater reductions in risk for progression to type 2 diabetes (T2D) with TLI compared with younger age-groups or those receiving metformin (24,25). In Look AHEAD, older participants receiving TLI experienced greater improvements in physical functioning than younger subjects (27).

TLI components in the DPP and Look AHEAD were similar. Dietary interventions included meal replacements (shakes, food bars) for 1–2 meals a day to achieve caloric restrictions. Exercise prescriptions targeted 150–175 min of weekly physical activity (28). The primary outcome of reductions in ASCVD events in Look AHEAD was not achieved, but there were improvements in ASCVD risk with reduced body weight, waist circumference, and HbA_{1c} and increased physical functioning and fitness (29).

Nutrition counseling is important for older adults who are at risk for undernutrition as well as obesity (30,31). Many older adults focus on food as a source of satisfaction and comfort, potentially viewing meal replacements as interfering with HRQL. Although there is no one optimal diet, the Mediterranean diet with an emphasis on intake of fresh fruit and vegetables, legumes, and nuts may have advantages for some older adults (32). This diet has been demonstrated to be superior to traditional diets in several studies that included seniors aged ≥65 to 90 years for weight loss, lipid lowering, blood glucose control, and CVD outcomes (32,33).

Exercise prescriptions often require modification for elderly populations who may have never performed regular exercise and may be unwilling or unable to do so (34). For some older adults with diabetes, a better strategy may be to reduce sedentary time (35,36) with use of chair exercises, walking in place, or performing arm and leg lifts. These strategies can be safely and effectively used with good adherence even in frailer older adults with complex health (37).

In summary, TLI is an important component of ASCVD management in older adults with diabetes, with the need to individualize recommendations according to health status and ability. Compliance with prescriptions for exercise or increased activity can be achieved by encouraging activities that are enjoyable and can be performed safely and incorporated into daily routines. For those with more frailty or comorbidities (i.e., spinal stenosis, peripheral neuropathy, claudication, or other

Table 1—Summary of current recommendations for control of blood glucose, BP, lipids, and aspirin in older adults with diabetes grouped by health status

	Healthy	Intermediate health	Poor health
HbA_{1c}			
ADA (1)	<7.5% (<58 mmol/mol)	<8.0% (<64 mmol/mol)	<8.5% (<69 mmol/mol)
AGS (23)	7.5–8.0% (58–64 mmol/mol) [7.0–7.5% (53–58 mmol/mol)]*	—	8.0–9.0%
BP (mmHg)			
ADA	<140/90	<140/90	<150/90
AGS		<140/90 (as tolerated)	
JNC 8 (51)		<150/90 for population aged ≥60 years	
Lipids			
ADA	Statin	Statin	Secondary prevention
AGS		Statins, unless contraindicated or not tolerated	
ACC/AHA (38)		Moderate-intensity statin for age 65–75 years without ASCVD; High-intensity statin for age 65–75 years with ASCVD; Moderate-intensity statin for age >75 years with or without ASCVD	
Aspirin			
ADA		Low dose (75–81 mg); Older adults with life expectancy greater than time frame observed in primary or secondary prevention trials	
AGS		Secondary prevention; caution for age >80 years	

*The AGS recommends an HbA_{1c} 58–64 mmol/mol (7.5–8%) for older adults with the added statement that values of 53–58 mmol/mol (7–7.5%) may be appropriate in healthy older adults with few comorbidities and good functional status if this can be safely achieved.

medical problems), intermittent supervision promotes safety and confidence with programs to increase activity (37). A broader social context is relevant for identifying environmental or financial barriers to achieving physical activity and dietary goals (35,37).

LIPID LOWERING

The American College of Cardiology (ACC)/American Heart Association (AHA) lipid-lowering guidelines recommend moderate-intensity statins for patients with diabetes aged 65–75 years without ASCVD and high-intensity statins for those with ASCVD. For adults aged ≥75 years, moderate-intensity therapy is recommended for those with and without ASCVD as it is presumed that this older group would be unable to tolerate higher dosages (38). These recommendations are consistent with those of the ADA and AGS with the added modification that decisions for intensity of therapy be based on health status rather than age alone (1,23) (Table 1). These guidelines counterbalance risk-based therapeutic intensity with recognition of the complexities of care and vulnerabilities associated with aging (5).

Table 2—Factors contributing to health status designation in older adults with diabetes

Instrumental ADL
- Ability to use the telephone
- Shopping
- Doing housework
- Doing laundry
- Preparing meals
- Driving
- Taking medications
- Managing money

Comorbidities
- Arthritis
- Cancer
- Chronic heart failure
- Chronic kidney disease
- Emphysema
- Falls
- Hypertension
- Incontinence
- MI
- Stroke

Nonstatin lipid-lowering agents are not generally recommended. Fibrates alone or in combination with statins are not recommended based on the absence of efficacy in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (39) and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (40) trials. In one recent study of adults with ASCVD aged 56–72 years, ezetimibe reduced risk of ASCVD events when used with a statin (41). Subgroup analyses of participants with diabetes (27%) and those >75 years of age (15%) revealed significantly greater reductions in the primary outcome when compared with those without diabetes or <75 years of age, respectively (41). There was no subgroup analysis of subjects with diabetes >75 years of age (41).

Strong evidence supports the ACC/AHA recommendations for adults with diabetes aged <75 years, but data for older adults are more limited. A meta-analysis of studies using statins as primary prevention in 18,686 individuals with diabetes showed a 21% reduction in major vascular events for each mmol/L reduction in LDL cholesterol, with no differences between subjects younger or older than age 65 years (42). The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (43) randomly assigned men and women aged 70–82 years with preexisting ASCVD or one or more CVD risk factors to pravastatin 40 mg or placebo. Significant reductions in the primary outcome (fatal or nonfatal myocardial infarction [MI], stroke) were observed with pravastatin (hazard ratio [HR] 0.85, 95% CI 0.74–0.97) (43), primarily in the secondary prevention group (22% reduction in primary outcome). Subgroup analysis of subjects with diabetes (11%) did not demonstrate a benefit with pravastatin; however, the small numbers limited the ability to interpret these findings.

For patients with diabetes aged ≥80 years, evidence for statin use is limited. In one population-based study of participants aged 66–96 years, all-cause mortality was reduced among those with diabetes receiving statin therapy (HR 0.47, 95% CI 0.32–0.71) compared with nonusers (44). Another retrospective observational study investigated the efficacy of statin therapy in 1,712 community-dwelling adults with diabetes aged ≥65

years (mean 81 ± 7) grouped according to health status (45). Subjects with mild, moderate, and severe impairments in health experienced a similar mortality benefit with statins irrespective of age, underlying clinical complexity, or frailty (45). The authors acknowledged that statin therapy in older individuals with severe health impairments remains controversial. No information was presented regarding adverse side effects in this vulnerable group of patients.

Statins have been associated with a spectrum of muscle concerns in older adults; however, concerns regarding statin-related adverse events in older patients are not substantiated in pooled analyses from clinical trials (46,47). Rhabdomyolysis is rare, but myalgias without creatinine phosphokinase elevations are common (47). This can be especially debilitating in an older population prone to frailty and diminished HRQL. Reports of statin-induced cognitive changes are offset by inconsistent data, with some reports suggesting benefit attributable to reduced inflammation and improved vascular function (48,49). Again, few trials include older adults with intermediate and poor health, indicating a need for further study.

In summary, given the powerful ASCVD risk associated with diabetes, there is strong rationale to use statins, especially in patients with known ASCVD. Although clinical data have clearly demonstrated aggressively lowering LDL as an optimal strategy in younger adults, in older patients these benefits are counterbalanced by risks associated with age, polypharmacy, frailty, other comorbidities, and limited life expectancy (12). A suggested strategy would be to start with low-intensity statin doses and gradually increase dosing as tolerated while monitoring for adverse side effects that prompt dose reductions or discontinuation. There are currently no studies using the new class of humanized monoclonal antibodies that inactivate proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in older populations with diabetes (50).

BP

Hypertension is common among older adults (prevalence rate ~70%), but the associated ASCVD risks are compounded by diabetes (1,51). The ADA, AGS, and Eighth Joint National Committee (JNC 8) provide recommendations regarding benefits of BP-lowering therapy in older adults, emphasizing that goals should be tailored to individual patient characteristics in order to minimize risk for harm (1,23,51) (Table 1). The majority of these recommendations are based on studies focusing on systolic blood pressure (SBP); however, there is evidence that intensive control of diastolic blood pressure (DBP) can be also be associated with harm in older adults with diabetes (52,53). In one study of >34,000 subjects (aged 64.2 ± 12.1 years) with T2D without known CVD at baseline followed for 11 years, an increase in ASCVD events was observed with low as well as high DBP in the older subgroup, with the lowest risk observed with DBP of 80–90 mmHg (53).

Several trials have investigated treatment of hypertension as a way of reducing risk of ASCVD events (3,52,54–56). The observed benefits of BP-lowering therapies have been inferred primarily from larger trials that included only subsets of older subjects with diabetes (12). These trials consistently show that reducing BP from high to moderate levels reduces ASCVD risks. Some trials have demonstrated that more aggressive BP reductions achieve proportionally greater benefits but at the expense of greater iatrogenic risks, particularly in those with poor health or frailty (13,57). Falls and syncope are particularly concerning, as are issues of incontinence, fatigue, and diminished HRQL.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (58) randomized 11,140 adults with T2D (6,601 were aged ≥65 years) to combination perindopril with indapamide or placebo. SBP and DBP were reduced by 5.6 and 2.2 mmHg, respectively, with perindopril–indapamide compared with placebo. There were greater reductions in microvascular and CVD events in the older subgroup (relative risk reduction [RRR] 11% vs. 6% in those aged <65 years).

The UK Prospective Diabetes Study (UKPDS) (59) compared tight (<150/85 mmHg) versus less tight (<180/105 mmHg) therapy in 1,148 patients aged 56.4 ± 8.1 years with newly diagnosed T2D. The mean BP achieved was 144/82 and 154/87 mmHg, respectively. Significant RRR demonstrated with tight control for diabetes-related death, microvascular disease, and stroke at 10 years were not sustained at the posttrial follow-up (56,59). No age-based subgroup analysis was performed; however, the average age of subjects at the posttrial evaluation was 63 ± 8 years, suggesting relevance to older adult populations.

The ACCORD–Blood Pressure (ACCORD–BP) trial compared intensive (target SBP <120 mmHg) with standardized (target <140 mmHg) treatment among adults aged 40–79 years with T2D and high risk of ASCVD (60). Intensive therapy did not reduce MI or all-cause mortality, but it was associated with a reduction in strokes (secondary outcome) with the number needed to treat of 89 over 5 years. Results were similar when subjects were grouped according to age (<65 and ≥65 years). Post hoc analysis of the International Verapamil-Trandolapril Study (INVEST) had findings similar to those of ACCORD–BP with no ASCVD benefit with BP targets of <130/85 vs. <140/95 mmHg among patients ≥55 years of age (mean age 66 ± 6 years) (61).

The Systolic Blood Pressure Intervention Trial (SPRINT) (57) is an important trial that renewed interest in intensified BP-lowering therapy that included older adults but excluded those with diabetes. Aggressive BP treatment to achieve SBP <120 vs. <140 mmHg resulted in greater reductions in CVD and non-CVD mortality that was more pronounced in subjects aged ≥75 years (57). These favorable findings are balanced against an almost doubling of serious adverse events with intensive treatment (hypotension, syncope, falls, electrolyte abnormalities, and acute kidney injury), which argues against imposing these more aggressive targets to older adults with diabetes (62).

In summary, pursuing moderate BP control according to ADA recommendations in older adults with diabetes according to health status is an appropriate strategy for reducing ASCVD risk without significantly increasing iatrogenic risks (Table 1).

ASPIRIN

The ADA suggests that aspirin therapy may benefit older adults whose life

expectancy exceeds the time frame for primary or secondary prevention trials (12). The AGS recommends aspirin 75–325 mg a day only for older adults with known CVD unless contraindicated (23) (Table 1). These recommendations are derived primarily from trials of younger populations without diabetes; however, age-specific trials now in progress may help elucidate the extent of potential benefits and risks for older individuals with diabetes in relation to cardiovascular events and mortality as well as subclinical disease associated with microemboli (63).

A study of Japanese individuals with diabetes but no ASCVD demonstrated a benefit of aspirin use on ASCVD events among subjects aged ≥65 years (6.3% vs. 9.2%, $P = 0.047$) but not <65 years (64). The observed benefits were counterbalanced by increases in serious gastrointestinal (GI) bleeding with four participants receiving aspirin and none receiving placebo. Another study showed no benefit from low-dose aspirin in older Japanese adults at high risk for ASCVD, approximately one-third of whom had diabetes (17). Low-dose aspirin again did not significantly reduce the composite outcome of cardiovascular death, nonfatal stroke, and MI but was associated with a reduced incidence of nonfatal MI (HR 0.53, $P = 0.02$) and transient ischemic attack (HR 0.57, $P = 0.04$), again at the expense of an increased risk of extracranial hemorrhage requiring transfusion or hospitalization (HR 1.85, $P = 0.004$).

Overall, data regarding efficacy of aspirin in older adults with diabetes is limited, with some evidence of therapeutic benefits (particularly for those with known ASCVD) that are counterbalanced by notable bleeding risks. A recent publication (65) suggests a new algorithm to help decision making for aspirin use pertinent to older adults (still unvalidated), recommending a highly individualized approach to care that centers on patient preferences and tacitly counters the precept that management can and should be stratified in a standardized manner relative to specific levels of risk.

BLOOD GLUCOSE

The ADA and AGS have similar recommendations for modification of glycemic goals in older adults according to health status (1,23) (Table 1). Although the AGS recommends an upper limit for HbA_{1c} up to 75 mmol/mol (9%), there is evidence that many elderly adults are being treated more aggressively (10). The modified targets for HbA_{1c} in older adults are based in part on the lack of evidence for ASCVD risk reduction as well as concern for harm with tight glycemic targets in older adults (10,66,67). Several large randomized controlled trials with relevance to an elderly population (average age at baseline 60–66 years) were unable to identify any ASCVD benefit with glycemic management strategies targeting HbA_{1c} values of ≤42 to 48 mmol/mol (≤6–6.5%) (68). The ACCORD trial was stopped prematurely because of an observed 22% increase in cardiovascular death with intensive therapy (68). The ADVANCE trial demonstrated neither benefit nor harm with intensive versus conventional therapy (68). Similar to findings in the ACCORD trial, more than 75% of intensively treated participants in the Veterans Affairs Diabetes Trial (VADT) were using thiazolidinediones or insulin, raising questions as to whether the negative results could be ascribed to the glucose-lowering strategies used (68).

The UKPDS legacy study (69) and two recent studies with the sodium–glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin (70) and the glucagon-like peptide 1 receptor agonist (GLP-1RA) liraglutide (71) each demonstrated benefits that have relevance to ASCVD risk management in older adults with T2D (Table 3). In the UKPDS legacy study (69), participants with newly diagnosed T2D at enrollment demonstrated significant reductions for MI and all-cause mortality with a strategy of intensive versus conventional glycemic control. Many participants in this legacy analysis were eligible to be considered older adults based on age >65 years; however, subgroup analysis was not performed.

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) (70) is the first study demonstrating reductions in ASCVD events with glucose-lowering medication in obese or overweight subjects with T2D and CVD. RRR of 14% for MI and stroke (absolute risk reduction [ARR] 10.5% vs. 12.1%), 38% for cardiovascular death (ARR 3.7% vs. 5.9%), with a 35% decrease in hospitalizations for congestive heart failure (CHF) (2.7% vs. 4.1%) were observed with empagliflozin (70). Subgroup analyses demonstrated more favorable outcomes in subjects aged ≥65 years when compared with younger counterparts. Reductions in ASCVD events were observed early in the study (at 3 months), raising questions regarding the mechanisms for these favorable outcomes. Given the modest differences in HbA_{1c} between the empagliflozin and placebo groups, it is likely that the observed reductions in BP, plasma volume, and weight contributed more to the favorable results than changes in glycemic control. The liraglutide and cardiovascular outcomes study also demonstrated significant reductions in the primary outcome of ASCVD events; however, subgroup analyses based on age demonstrated significance only in subjects <60 but not ≥60 years of age (71) (Table 3). Several large studies with dipeptidyl peptidase 4 inhibitors (DPP-4is) did not show any cardiovascular benefit. An increase in hospitalizations for CHF was observed with saxagliptin (72); however, a meta-analysis suggested no increase in CHF with any of the oral or injectable incretins (73).

TREATMENT STRATEGIES FOR ACHIEVING GLYCEMIC GOALS IN OLDER ADULTS

In addition to insulin, there are several different classes of oral or noninsulin injectable glucose-lowering therapies available for achieving glycemic control (Table 4) (74). There are no absolute contraindications to use of any specific agent; however, there are special considerations for their prescribing and monitoring in older adults. Insulin-providing (IP) therapies with insulin secretogogues or insulin are associated with risk for hypoglycemia, particularly in those with compromised renal function, which is more frequent in older adults with diabetes, emphasizing the need for caution when prescribing these agents (74). Patient education regarding hypoglycemia prevention, recognition, and treatment is important (75). Metformin is no longer contraindicated for individuals aged >80 years or for those who have mild chronic kidney disease (eGFR 45–60 mL/min) (76,77).

Table 3—Selected cardiovascular outcome studies in older adults with diabetes

Drug or strategy tested	*N*	Study population	Age (years), mean ± SD	Primary outcome	Pertinence to older adults
BARI 2D IP vs. IS	2,368	T2D with stable CAD	62.4 ± 8.0 (range <60 to 89.8)	Death and composite of death, MACE, angina, and health status at mean follow-up of 5.3 years	No age-related differences observed between IP and IS on clinical end points in participants grouped by age (<60, 60–69, ≥70 years)
Empagliflozin	7,020	T2D with ASCVD	63 ± 9	Cardiovascular death or nonfatal MI or stroke at median follow-up of 3.8 years	Empagliflozin vs. placebo (10.5% vs. 12.1%, *P* = 0.01); subgroup analysis demonstrated significant benefit in subjects aged ≥65 but not <65 years for primary outcome
Liraglutide	9,340	T2D with ASCVD	64 ± 7	Cardiovascular death or nonfatal MI or stroke at median follow-up of 3.1 years	Liraglutide vs. placebo (13% vs. 14.9%, *P* = 0.01); subgroup analysis demonstrated significant benefit in subjects aged <60 (HR 0.78 [0.62–0.97]) but not ≥60 (HR 0.90 [0.79–1.02]) years
Pioglitazone	3,876	Subjects with insulin resistance with recent stroke or transient ischemic attack (~6% of subjects had diabetes)	64.5 ± 10.6	MI or stroke at 4.8 years	Pioglitazone vs. placebo (9% vs. 11.8%, *P* < 0.01); subgroup analysis demonstrated benefit in subjects aged <65 (HR 0.73 [0.55–0.97]) but not ≥65 (HR 0.79 [0.60–1.03]) years

BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes study; CAD, coronary artery disease; IS, insulin sensitizing; MACE, major adverse cardiac events.

The use of thiazolidinediones in older adults is limited by concerns for weight gain, edema, CHF, reductions in bone mineral density, and increased fracture risk (78,79). In one study, subjects with insulin resistance without diabetes randomly assigned to receive pioglitazone following a stroke experienced significant improvements in insulin sensitivity with a reduction in the combined primary outcome of stroke and MI compared with placebo.

Table 4—Treatment strategies for achieving glycemic goals in older adults

Class	Considerations for use in older adults	Dose adjustment for renal insufficiency	Cost
Sulfonylureas (glyburide, glipizide, glimepiride)	Hypoglycemia (can be prolonged) (particularly with glyburide)	Yes	Low
Glinides (repaglinide, nateglinide)	Hypoglycemia; Require dosing with each meal	Yes	Moderate
Biguanide (metformin)	GI side effects: nausea, diarrhea; Use cautiously if at all with eGFR <45 mL/min; Lactic acidosis rare	Yes	Low
Thiazolidinediones (rosiglitazone, pioglitazone)	Increase in risk for CHF, weight gain; Decrease in bone density, increase risk of fractures in women	No	Low
α-Glucosidase inhibitors (acarbose, miglitol)	GI side effects are common; Require dosing with each meal	No	Low
DPP-4is (sitagliptin, saxagliptin, alogliptin, linagliptin)	Low risk of hypoglycemia when used alone; Low incidence of side effects; Some studies report increases in UTIs, upper respiratory tract infections; Case reports of pancreatitis, increased liver function tests, severe skin reactions, musculoskeletal complaints	Selected agents	High
GLP-1RAs (exenatide, liraglutide, dulaglutide, albiglutide)	Low risk of hypoglycemia; GI side effects common: nausea, vomiting, anorexia (often resolve with continued use); Case reports of pancreatitis, renal insufficiency	Caution advised	High
SGLT2is (empagliflozin, dapagliflozin, canagliflozin)	Cause polyuria and polydipsia; Counsel patients to avoid dehydration; Increased risk for genital infections and UTIs; Cases of euglycemic diabetic ketoacidosis reported	Yes	High

Table 5—Suggested areas for future research into ASCVD risk management in older adults with diabetes

- Are risk predictors (e.g., lipids, BP, glucose) the same for older as in younger adults for primary prevention?
- When do medications directed at risk lowering cause more harm than benefit?
- Subgroup analyses according to age and diabetes status of ASCVD and other outcomes from large clinical trials are recommended.
- Incorporate frailty and multimorbidity in subgroup analyses from these outcomes trials, recognizing that this becomes complex in an elderly heterogeneous population.
- What levels of HbA_{1c} should be targeted for initiation and progression of glucose-lowering pharmacologic therapy in older adults with newly diagnosed and established diabetes?
- A Diabetes Control and Complications Trial for older adults with diabetes stratified into prevention of onset and progression of complications is recommended.
- Address the necessity of ongoing process measures, such as albumin creatinine ratios, for older adults with diabetes.

However, this was at the expense of more weight gain, CHF, and fractures (78). If a decision is made to use these agents, close monitoring for adverse effects is recommended.

DPP-4is have a low incidence of side effects, do not cause hypoglycemia when used alone, and appear to be neutral in regard to ASCVD risk. Injectable GLP-1RAs can be associated with gastrointestinal side effects but do not have specific contraindications in the elderly. Despite the favorable results in EMPA-REG OUTCOME, preventive monitoring of older adults for dehydration, genital infections, and urinary tract infections (UTIs) with use of the SGLT2is is important.

In summary, although there are no absolute contraindications to use of any of the oral or injectable agents available for treating diabetes, there are special considerations for prescribing and monitoring of these agents in older adults that can impact cardiovascular safety, including risk for hypoglycemia and patient preference (10,20).

HYPOGLYCEMIA AS A CARDIOVASCULAR RISK FACTOR

Despite recommendations to modify glycemic goals for older adults, particularly those with intermediate or poor health status, there is evidence that older adults may be treated too aggressively, increasing risk for hypoglycemia and associated adverse events including falls and cardiac and neurological events (10,16). In one study, >50% of participants aged ≥65 years with intermediate or poor health had HbA_{1c} <53 mmol/mol (<7%) (15). IP therapy was the most frequently used glucose-lowering therapy and has been observed to account for the majority of emergency department visits for hypoglycemia among adults aged ≥65 years (15,80).

Older adults with diabetes are particularly vulnerable to hypoglycemia because of impaired counterregulatory responses that interfere with the ability to detect and recover from hypoglycemia (7). Questions regarding the contribution of hypoglycemia to adverse outcomes were raised in the ACCORD, ADVANCE, and VADT studies, where severe hypoglycemia occurred more frequently in intensively treated subjects; however, the relationship between these events and mortality has been the subject of debate (81,82). In ACCORD, severe but not mild hypoglycemia was associated with an increase in mortality that was more pronounced with standard therapy (81). In ADVANCE, severe hypoglycemia was associated with an increased incidence of microvascular and macrovascular events as well as CVD and non-CVD mortality (83). In VADT, severe hypoglycemia was associated with progression of coronary artery calcifications in those receiving standard but not intensive glycemic management (84).

There are several suggested mechanisms for the contribution of hypoglycemia to risk for microvascular and macrovascular events (75,85). In studies using continuous glucose and cardiac monitoring devices, hypoglycemia was associated with an increase in arrhythmias and prolonged QT intervals (75). Enhanced sympathetic nervous system activation, catecholamine excess, and abnormal cardiac repolarization observed with hypoglycemia can potentially contribute to ASCVD risk and events (85,86).

Together, this information emphasizes the importance of minimizing risk for hypoglycemia among older adults with diabetes through patient education and use of therapies that are associated with low risk for hypoglycemia when possible (75).

CONCLUSIONS

In summary, older adults with diabetes are at high risk for ASCVD, warranting consideration of strategies that reduce this risk. Approximately 50% of adults aged 64–75 and >75 years fall in the category of those with good to intermediate health for whom targeted risk-factor management is reasonable (21). The remaining population requires careful consideration of any potential benefit or risk with therapies targeting specific numbers for lipid, BP, or glycemic parameters. There is a need for additional research that addresses the risk-to-benefit ratio of strategies among older adults according to aggregate health status (Table 1). There is growing appreciation of the contribution of hypoglycemia to ASCVD risk, warranting caution with use of IP therapy in this vulnerable population, particularly in those with compromised renal function. The approaches suggested by the ADA and AGS provide a framework for approaching risk-reduction strategies in this age-group; however, there is a need for further investigation into this growing population of older adults to guide clinical practice (Table 5).

Acknowledgments. The authors would like to thank Justin Kanter in the Division of Endocrinology at the University of Pittsburgh Medical Center for assistance with manuscript preparation.

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

Author Contributions. M.T.K. reviewed the literature and wrote the first draft of the following sections: INTRODUCTION, THERAPEUTIC LIFESTYLE INTERVENTIONS, BLOOD GLUCOSE, HYPOGLYCEMIA AS A CARDIOVASCULAR RISK FACTOR, and CONCLUSIONS. D.E.F. reviewed the literature and wrote the first draft of the following sections: LIPID LOWERING, BP, and ASPIRIN. D.E.F. also contributed his expertise to areas related to frailty and aging based on his extensive expertise in this area. Both authors reviewed, critiqued, and edited all sections in preparation for resubmission.

References

1. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care 2012;35:2650–2664
2. Geiss LS, Wang J, Cheng YJ, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. JAMA 2014;312:1218–1226
3. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part II: the aging heart in health: links to heart disease. Circulation 2003;107:346–354
4. Bethel MA, Sloan FA, Belsky D, Feinglos MN. Longitudinal incidence and prevalence of adverse outcomes of diabetes mellitus in elderly patients. Arch Intern Med 2007;167:921–927
5. Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: the Health and Retirement Study. J Am Geriatr Soc 2009;57:511–516
6. Halter JB, Musi N, McFarland Horne F, et al. Diabetes and cardiovascular disease in older adults: current status and future directions. Diabetes 2014;63:2578–2589
7. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the Diabetes and Aging Study. JAMA Intern Med 2014;174:251–258
8. Li CL, Chiu YC, Chang HY, Hsu KH, Bai YB, Wang HH. Association of geriatric conditions and cardiovascular diseases with disability in older adults with diabetes: findings from a nationally representative survey. Geriatr Gerontol Int 2013;13:563–570
9. Sinclair AJ, Rodriguez-Mañas L. Diabetes and frailty: two converging conditions? Can J Diabetes 2016;40:77–83
10. Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the aging patient: a review of glycemic control in older adults with type 2 diabetes. JAMA 2016;315:1034–1045
11. Chung S-C, Hlatky MA, Faxon D, et al.; BARI 2D Study Group. The effect of age on clinical outcomes and health status BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes). J Am Coll Cardiol 2011;58:810–819
12. American Diabetes Association. Older adults. Sec. 10. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016;39(Suppl. 1):S81–S85
13. Williamson JD, Supiano MA, Applegate WB, et al.; SPRINT Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. JAMA 2016;315:2673–2682
14. Bhardwaj S, Selvarajah S, Schneider EB. Muscular effects of statins in the elderly female: a review. Clin Interv Aging 2013;8:47–59
15. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Intern Med 2015;175:356–362
16. Huang ES. Potential overtreatment of older, complex adults with diabetes. JAMA 2015;314:1280–1281
17. Ikeda Y, Shimada K, Teramoto T, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA 2014;312:2510–2520
18. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2015;63:2227–2246
19. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the U.S. Diabetes Care 2006;29:2415–2419
20. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. JAMA Intern Med 2014;174:1227–1234
21. Blaum C, Cigolle CT, Boyd C, et al. Clinical complexity in middle-aged and older adults with diabetes: the Health and Retirement Study. Med Care 2010;48:327–334
22. American Diabetes Association. Cardiovascular disease and risk management. Sec. 8. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016;39(Suppl. 1):S60–S71
23. Moreno G, Mangione CM, Kimbro L, Vaisberg E; American Geriatrics Society Expert Panel on Care of Older Adults with Diabetes Mellitus. Guidelines abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 Update. J Am Geriatr Soc 2013;61:2020–2026
24. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
25. Knowler WC, Fowler SE, Hamman RF, et al.; Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677–1686
26. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–154
27. Rejeski WJ, Bray GA, Chen S-H, et al.; Look AHEAD Research Group. Aging and physical function in type 2 diabetes: 8 years of an intensive lifestyle intervention. J Gerontol A Biol Sci Med Sci 2015;70:345–353
28. Delahanty LM, Nathan DM. Implications of the diabetes prevention program and Look AHEAD clinical trials for lifestyle interventions. J Am Diet Assoc 2008;108(Suppl. 1):S66–S72
29. Korytkowski MT. Lessons from the Look Action for Health in Diabetes Study. Indian J Endocrinol Metab 2013;17(Suppl. 3):S650–S653
30. Alfonso-Rosa RM, Del Pozo-Cruz B, Del Pozo-Cruz J, Del Pozo-Cruz JT, Sañudo B. The relationship between nutritional status, functional capacity, and health-related quality of life in older adults with type 2 diabetes: a pilot explanatory study. J Nutr Health Aging 2013;17:315–321
31. Kaiser MJ, Bauer JM, Rämsch C, et al.; Mini Nutritional Assessment International Group. Frequency of malnutrition in older adults: a multinational perspective using the mini nutritional assessment. J Am Geriatr Soc 2010;58:1734–1738
32. Estruch R, Ros E, Salas-Salvadó J, et al.; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–1290
33. Tourlouki E, Matalas AL, Panagiotakos DB. Dietary habits and cardiovascular disease risk in middle-aged and elderly populations: a review of evidence. Clin Interv Aging 2009;4:319–330
34. Simpson KA, Mavros Y, Kay S, et al. Graded Resistance Exercise And Type 2 Diabetes in Older adults (the GREAT2DO study): methods and baseline cohort characteristics of a randomized controlled trial. Trials 2015;16:512
35. Lewis LK, Rowlands AV, Gardiner PA, Standage M, English C, Olds T. Small steps: preliminary effectiveness and feasibility of an incremental goal-setting intervention to reduce sitting time in older adults. Maturitas 2016;85:64–70
36. Patel AV, Bernstein L, Deka A, et al. Leisure time spent sitting in relation to total mortality in a prospective cohort of US adults. Am J Epidemiol 2010;172:419–429
37. Clegg A, Barber S, Young J, Iliffe S, Forster A. The Home-based Older People's Exercise (HOPE) trial: a pilot randomised controlled trial of a home-based exercise intervention for older people with frailty. Age Ageing 2014;43:687–695
38. Stone NJ, Robinson JG, Lichtenstein AH, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(25 Pt B):2889–2934
39. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574
40. Tonkin A, Hunt D, Voysey M, et al.; FIELD Study Investigators. Effects of fenofibrate on cardiovascular events in patients with diabetes, with and without prior cardiovascular disease: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Am Heart J 2012;163:508–514
41. Cannon CP, Blazing MA, Giugliano RP, et al.; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387–2397
42. Kearney PM, Blackwell L, Collins R, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117–125
43. Shepherd J, Blauw GJ, Murphy MB, et al.; PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–1630
44. Olafsdottir E, Aspelund T, Sigurdsson G, et al. Similar decline in mortality rate of older persons with and without type 2 diabetes between 1993 and 2004 the Icelandic population-based Reykjavik and AGES-Reykjavik cohort studies. BMC Public Health 2013;13:36

45. Pilotto A, Panza F, Copetti M, et al.; MPI_AGE Project Investigators. Statin treatment and mortality in community-dwelling frail older patients with diabetes mellitus: a retrospective observational study. PLoS One 2015;10:e0130946
46. Fleg JL, Forman DE, Berra K, et al.; American Heart Association Committees on Older Populations and Exercise Cardiac Rehabilitation and Prevention of the Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Lifestyle and Cardiometabolic Health. Secondary prevention of atherosclerotic cardiovascular disease in older adults: a scientific statement from the American Heart Association. Circulation 2013;128:2422–2446
47. Iwere RB, Hewitt J. Myopathy in older people receiving statin therapy: a systematic review and meta-analysis. Br J Clin Pharmacol 2015;80:363–371
48. Joosten H, Visser ST, van Eersel ME, et al. Statin use and cognitive function: population-based observational study with long-term follow-up. PLoS One 2014;9:e115755
49. Blum A. HMG-CoA reductase inhibitors (statins), inflammation, and endothelial progenitor cells-New mechanistic insights of atherosclerosis. Biofactors 2014;40:295–302
50. Robinson JG, Farnier M, Krempf M, et al.; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1489–1499
51. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–520
52. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016;352:i717
53. Sundström J, Sheikhi R, Ostgren CJ, et al. Blood pressure levels and risk of cardiovascular events and mortality in type-2 diabetes: cohort study of 34,009 primary care patients. J Hypertens 2013;31:1603–1610
54. Cheng S, Xanthakis V, Sullivan LM, Vasan RS. Blood pressure tracking over the adult life course: patterns and correlates in the Framingham Heart Study. Hypertension 2012;60:1393–1399
55. Soldatos G, Jandeleit-Dahm K, Thomson H, et al. Large artery biomechanics and diastolic dysfunction in patients with type 2 diabetes. Diabet Med 2011;28:54–60
56. Holman RR, Paul SK, Bethel MA, Neil HAW, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med 2008;359:1565–1576
57. Wright JT Jr, Williamson JD, Whelton PK, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–2116
58. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–840
59. 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
60. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
61. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al.; INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. the International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 2003;290:2805–2816
62. Ortiz E, James PA. Let's not SPRINT to judgment about new blood pressure goals. Ann Intern Med 2016;164:692–693
63. ASPREE Investigator Group. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial. Contemp Clin Trials 2013;36:555–564
64. Ogawa H, Nakayama M, Morimoto T, et al.; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134–2141
65. Mora S, Ames JM, Manson JE. Low-dose aspirin in the primary prevention of cardiovascular disease: shared decision making in clinical practice. JAMA 2016;316:709–710
66. Brown A, Reynolds LR, Bruemmer D. Intensive glycemic control and cardiovascular disease: an update. Nat Rev Cardiol 2010;7:369–375
67. 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
68. Skyler JS, Bergenstal R, Bonow RO, et al.; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association [published correction appears in Diabetes Care 2009;32:754]. Diabetes Care 2009;32:187–192
69. 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
70. 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
71. 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
72. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–1326
73. Filion KB, Azoulay L, Platt RW, et al.; CNODES Investigators. A multicenter observational study of incretin-based drugs and heart failure. N Engl J Med 2016;374:1145–1154
74. Frye RL, August P, Brooks MM, et al.; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503–2515
75. Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol 2016;12:222–232
76. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA 2014;312:2668–2675
77. Miles JM, Rule AD, Borlaug BA. Use of metformin in diseases of aging. Curr Diab Rep 2014;14:490
78. Kernan WN, Viscoli CM, Furie KL, et al.; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016;374:1321–1331
79. Lipscombe LL, Gomes T, Lévesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA 2007;298:2634–2643
80. Geller AI, Shehab N, Lovegrove MC, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. JAMA Intern Med 2014;174:678–686
81. Seaquist ER, Miller ME, Bonds DE, et al.; ACCORD Investigators. The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. Diabetes Care 2012;35:409–414
82. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ 2011;343:d4169
83. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
84. Saremi A, Bahn GD, Reaven PD; Veterans Affairs Diabetes Trial (VADT). A link between hypoglycemia and progression of atherosclerosis in the Veterans Affairs Diabetes Trial (VADT). Diabetes Care 2016;39:448–454
85. Leong A, Berkowitz SA, Triant VA, et al. Hypoglycemia in diabetes mellitus as a coronary artery disease risk factor in patients at elevated vascular risk. J Clin Endocrinol Metab 2016;101:659–668
86. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738–1747