

# Achieving glycemic control in elderly patients with type 2 diabetes: a critical comparison of current options

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**Abstract:** The prevalence of type 2 diabetes mellitus (T2DM) is increasing in the elderly. Because of the unique characteristics of elderly people with T2DM, therapeutic strategy and focus should be tailored to suit this population. This article reviews the guidelines and studies related to older people with T2DM worldwide. A few important themes are generalized: 1) the functional and cognitive status is critical for older people with T2DM considering their life expectancy compared to younger counterparts; 2) both severe hypoglycemia and persistent hyperglycemia are deleterious to older adults with T2DM, and both conditions should be avoided when determining therapeutic goals; 3) recently developed guidelines emphasize the avoidance of hypoglycemic episodes in older people, even in the absence of symptoms. In addition, we raise the concern of glycemic variability, and discuss the rationale for the selection of current options in managing this patient population.

**Keywords:** glycemic target, glycemic variability, blood glucose, frailty

## Introduction

Diabetes prevalence in older people increases with advancing age. The global prevalence of diabetes in people between the ages of 60 and 79 is 18.6%, which is more than 134.6 million people, and accounts for 35% of all cases of diabetes in adults.<sup>1</sup> Peripheral neuropathy, which is highly prevalent in older people with diabetes, increases the risk of falls and fractures, and consequently, of functional impairment.<sup>2</sup> Diabetes in older people is also associated with dementia and depression.<sup>3,4</sup> Diabetic patients with depressive symptoms may need more attention in treating their condition,<sup>5</sup> particularly women.<sup>6</sup> Age-associated alteration in metabolism and excretion of medication is also a concern in the selection of antidiabetic treatment.<sup>7</sup> Older people are also at increased risk of undernutrition and skeletal muscle loss, which is generally even more evident with the presence of diabetes.<sup>8,9</sup> Older people with diabetes are considered at high cardiovascular risk.<sup>10</sup> Risk of hypoglycemia is also increased due to impaired counterregulatory mechanisms.<sup>11</sup> These biopsychosocial changes increase the complexity in managing diabetes in older adults. Importantly, much attention has been paid to optimal glycemic control in the elderly in the past few years. Guidelines focusing on the elderly with diabetes were developed all over the world in the past decade with increasing focus on cognition and functional capacity.<sup>10,12–18</sup> This review of the literature, in addition to summarizing opinions from recently published guidelines and studies, elucidates the pathophysiological characteristics of elderly patients with type 2 diabetes mellitus (T2DM), and discusses the rationale for selection of current options in managing this patient population.

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Clinical studies included in this article define elderly subgroups chronologically as aged 65 years or more to facilitate the analysis of the data.

## Rationale in determining therapeutic goals for older patients

Heterogeneity of older adults cannot be overemphasized in diabetes care. Some adults were diagnosed with T2DM after age 65 with initial presentation of hyperglycemia crisis and established chronic complications; some were diagnosed from health screening without any complications, and others were diagnosed as young adults or during middle age and sustained till old age with or without microvascular complications.<sup>14</sup> Guidelines developed in recent years all highlight the need to customize therapeutic goals for various older adults with T2DM (Table 1).<sup>10,12,14,19–21</sup> Generally, appropriate therapeutic goals for older patients with T2DM should be determined based on comprehensive evaluation of cognition, functional status, comorbidities including cardiovascular risk, and geriatric syndromes.<sup>22</sup>

In the past decade, glycemic control was focused on glycated hemoglobin (A1C) level and postprandial glucose. Strict glycemic level is aimed at the prevention of development and progression of chronic complications of diabetes, such as nephropathy, retinopathy, and neuropathy. However, to achieve cardiovascular benefits, a prolonged period of around 10 years is needed after intensive control for 6–12 years, as revealed in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study and the United Kingdom

Prospective Diabetes Study (UKPDS).<sup>23,24</sup> These cardiovascular benefits were not observed after intensive glycemic control in long-established T2DM patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation trial, and the Veterans Affairs Diabetes Trial.<sup>25–27</sup> For diabetic patients with limited life expectancy, maintaining independent function, preventing frailty, and preserving cognition integrity are far more important than targeting A1C alone.<sup>17,28</sup> Therefore, it is important to avoid hypoglycemia events and consequent adverse outcomes, such as falls, cognitive decline, autonomic dysfunction, depression, recurrent hypoglycemia, poor compliance, and possible cardiac ischemia or arrhythmia, which may contribute to poor function and poor prognosis.<sup>29–31</sup> Despite the inconsistent relationship between hypoglycemia and falls or fractures, it is still a concern that recurrent hypoglycemia may put elderly people at higher risk for falls.<sup>32–35</sup> Further, this risk may be even more detrimental if the elderly patients live alone. Elders residing in long-term care facilities are at significant risk of poor functional status, frailty, and malnutrition. These frail elders may be vulnerable to hypoglycemia and its serious morbid outcomes.<sup>36</sup> On the other hand, older diabetic patients with low A1C levels may be indicative of reduced food intake and malnutrition rather than good glycemic control.<sup>37</sup> The ACCORD trial is well known for its premature termination after a median duration of 3.5 years because of higher mortality in the intensive group, targeting A1C <6% (42 mmol/mol). Based on these findings, recommendations from some guidelines propose

**Table 1** Categories of older people with type 2 diabetes in different guidelines

Guideline	Year	Category 1	Category 2	Category 3
CHCF <sup>19</sup>	2003	Relatively healthy	Frail, life expectancy <5 years	NA
VA/DoD <sup>20</sup>	2004	Life expectancy >15 years No or minimal microvascular complications	Life expectancy 5–15 years Moderate microvascular complications	Life expectancy <5 years Advanced microvascular complications, advanced age, severe comorbidity
VA/DoD <sup>21</sup>	2010	Life expectancy >10–15 years	DM duration >10 years, comorbid conditions	Life expectancy <5 years Advanced microvascular complications, advanced age, severe comorbidity
EDWPOP <sup>12</sup>	2011	Single system involvement Free of major comorbidities	Frail (dependent, multisystem disease, dementia, care home residents)	NA
ADA/AGS <sup>14</sup>	2012	Healthy (Few coexisting chronic illnesses, intact cognitive and functional status)	Complex/intermediate (Multiple coexisting chronic illnesses or ≥2 IADL impairments or mild to moderate cognitive impairment)	Very complex/poor health (Long-term care or end-stage chronic illnesses or ≥2 ADL dependences or moderate to severe cognitive impairments)
IDF <sup>10</sup>	2013	Functionally independent	Functionally dependent frailty or dementia	End-of-life care

**Abbreviations:** ADA, American Diabetes Association; ADL, activity of daily life; AGS, American Geriatric Society; CHCF, California HealthCare Foundation; EDWPOP, European Diabetes Working Party for Older People; IADL, instrumental activity of daily life; IAGG, International Association of Gerontology and Geriatrics; IDF, International Diabetes Federation; VA/DoD, Veterans Affairs/Department of Defense; NA, not applicable; DM, diabetes mellitus.

**Table 2** Glycemic targets according to different categories indicated by guidelines worldwide

Guideline	Year	Category 1	Category 2	Category 3
CHCF <sup>19</sup>	2003	A1C $\leq$ 7% (53.0 mmol/mol)	A1C =8% (63.9 mmol/mol)	NA
VA/DoD <sup>20</sup>	2004	A1C <7% (53.0 mmol/mol)	A1C <8% (63.9 mmol/mol)	A1C <9% (74.9 mmol/mol), avoid symptomatic hyperglycemia
VA/DoD <sup>21</sup>	2010	A1C <7% (53.0 mmol/mol)	A1C <8% (63.9 mmol/mol)	A1C =8%–9% (63.9–74.9 mmol/mol)
EDWPOP <sup>12</sup>	2011	A1C =7%–7.5% (53.0–58.8 mmol/mol) FPG =6.5–7.5 mmol/L	A1C =7.6–8.5% (59.6–69.4 mmol/mol) FPG =7.6–9.0 mmol/L	NA
ADA/AGS <sup>14</sup>	2012	A1C <7.5% (58.5 mmol/mol) FPG =5–7.2 mmol/L Bedtime BG 5–8.3 mmol/L	A1C <8.0% (63.9 mmol/mol) FPG =5–8.3 mmol/L Bedtime BG 5.6–10 mmol/L	A1C <8.5% (69.4 mmol/mol) FPG =5.6–10 mmol/L Bedtime BG =6.1–11.1 mg/dL
IDF <sup>10</sup>	2013	A1C =7%–7.5% (53.0–58.8 mmol/mol)	A1C =7%–8% (53.0–63.9 mmol/mol) up to 8.5% (69.4 mmol/mol)	Avoid symptomatic hyperglycemia
Diabetes UK <sup>36</sup>	2011	Care home residents: A1C =7–8% (53.0–63.9 mmol/mol), FPG =7–8.5 mmol/L, random BG <9 mmol/L		
IAGG/EDWPOP <sup>13</sup>	2012	In general, A1C =7%–7.5% (53.0–58.8 mmol/mol), avoid random BG >11 mmol/L		
Canadian Diabetes Association <sup>15,38</sup>	2013	Limited life expectancy, high level of functional dependency, advanced comorbidities: A1C 7.1%–8.5% (54.0–69 mmol/mol)		
DCPNS/PATH, Canada <sup>16</sup>	2013	Frail older adults: A1C =8%–12% (63.9–107.7 mmol/mol), avoid symptomatic hyperglycemia		

**Abbreviations:** BG, blood glucose; DCPNS/PATH, Diabetes Care Program of Nova Scotia and the Palliative and Therapeutic Harmonization Program; FPG, fasting plasma glucose; ADA, American Diabetes Association; AGS, American Geriatric Society; CHCF, California HealthCare Foundation; EDWPOP, European Diabetes Working Party for Older People; IAGG, International Association of Gerontology and Geriatrics; IDF, International Diabetes Federation; VA/DoD, Veterans Affairs/Department of Defense; NA, not applicable; A1C, glycated hemoglobin.

that higher A1C goals be set for older adults.<sup>10,12,14,16,19–21,36,38</sup> Table 2 presents the glycemic targets according to different categories indicated by guidelines worldwide.

For reasons mentioned previously, less stringent glycemic targets have been suggested from recently developed guidelines.<sup>10,12,14,38</sup> However, when the emphasis is made on less stringent glycemic control, it is likely to exacerbate clinical inertia, promote physician's attempts to withdraw antidiabetic agents, and, in turn, put elderly patients at high risk for sustained hyperglycemia and associated complications, such as incontinence, dehydration, hyperglycemic crisis, cognitive decline, visual disturbances, zinc loss, poor lower extremity performance, reductions in muscle mass, falls, and consequences of dependence.<sup>22,39–42</sup> Physicians should keep in mind that older adults are at higher risk of hyperglycemic hyperosmolar syndrome than younger adults because of the altered perception of thirst that precludes their water intake when dehydrated, impaired functional status that limits their ability to access water, and impaired cognition that restricts their expression of thirst.<sup>43</sup> Preventing incidence of diabetes-related comorbidities is also important in reducing the deterioration in physical disability.<sup>44</sup> Thus, efforts to prevent physical disability should start from early stages, immediately after the diagnosis of diabetes.<sup>45</sup>

Higher glycemic variability, independent of traditional markers for glycemic control, such as A1C, fasting plasma glucose, and postprandial glucose, was associated with

increased oxidative stress, increased inflammatory markers, and impaired cognitive function.<sup>46,47</sup> To prevent frailty and cognitive decline and to prevent sustained hyperglycemia and consequent microvascular complications, minimizing glycemic variability may be equally important as preventing hypoglycemia in elderly diabetic patients.<sup>48</sup>

Is lower A1C really detrimental to the older patients? The ACCORD trial revealed a lesser known aspect that hypoglycemia is found more in individuals with higher A1C levels rather than those with lower A1C levels. Also, it was found that mortality was associated with higher A1Cs and nonimproved patients in the intensive group but not associated with hypoglycemia.<sup>49</sup> Evidence revealed that hypoglycemic episodes are common in older patients with A1C 8.0% (63.9 mmol/mol) or greater. Thus, raising the A1C targets may not prevent hypoglycemia in this population.<sup>50</sup> There is no strong evidence that higher A1C levels were beneficial for older adults. Thus, to achieve benefit from good glycemic control without increasing the risk of hypoglycemia in older adults, it would be better for physicians to follow a safe intensification process with appropriate selection of drugs with low glycemic variability, rather than raising A1C goals.<sup>49,51</sup> If it can be achieved safely without an increase of hypoglycemia or other adverse events, A1C should be as normal as possible. Finally, all biopsychosocial aspects of older patients should be comprehensively evaluated, rather than treating the A1C alone.<sup>52</sup>

## How to select antidiabetic therapies considering the characteristics of older adults

Aging is characterized by a progressive impairment in carbohydrate tolerance, possibly related to disorderly insulin release, reduced insulin production and reduced glucagon-like peptide 1 (GLP-1) secretion, increased adiposity, sarcopenia, and physical inactivity.<sup>14,53,54</sup> Relative contribution of postprandial glucose is higher than that of fasting glucose in older people.<sup>55</sup> These important features provide clues in selecting antidiabetic therapies that are more efficacious in postprandial glucose control for older adults.

Both morbidity and mortality in the elderly are independently predicted by the duration of diabetes and advancing age. Coronary artery disease and hypoglycemia were the most common complications in the elderly, both in short- and long-lasting diabetes.<sup>56</sup> Elderly patients are more vulnerable to hypoglycemia due to age-related impairment of liver and renal function, leading to slightly decreased gluconeogenesis,<sup>18</sup> altered drug elimination, and influence of drug interaction from polypharmacy.<sup>57</sup> The hypoglycemia counterregulatory mechanism is defective in older people. Compared to those of healthy young adults, the responses of glucagon to hypoglycemia are lower in healthy elderly individuals and to a greater degree in older adults with diabetes.<sup>11</sup> However, the response of glucagon to hypoglycemia is similar in middle-aged patients and older patients with diabetes.<sup>58</sup> Older people are aware of hypoglycemia at a variable threshold between 5 mmol/L and 9 mmol/L, which is higher than the usually defined <4 mmol/L. However, the symptoms they present are nonspecific rather than typical

autonomic symptoms, and are generally presented as an unwell feeling.<sup>58,59</sup> These nonspecific symptoms may be misinterpreted in older patients as presentation of coexisting illnesses.<sup>60</sup>

Uncontrolled hyperglycemia, repetitive hypoglycemia, and greater glucose variability are associated with worse cognition.<sup>46</sup> Therefore, choosing effective antidiabetic therapies with relatively low risk for hypoglycemia and low glucose variability is very important in older adults.<sup>15</sup> The principles of medication choice for older patients with T2DM are primarily the same as for younger adults, with special considerations in frailty, sarcopenia, cognition, and functional status. For the diabetic elders with unintentional body weight (BW) loss, sarcopenia, or sarcopenic obesity, the focus should be on avoiding medications with overt gastrointestinal side effects, which may aggravate the condition of malnutrition, worsening the frailty status. For those with cognition problems, efforts should be made to reduce regimen complexity and to avoid overt hyperglycemia and hypoglycemia. For those in end-of-life care, antidiabetic medications are aimed at avoiding symptomatic hyperglycemia with higher tolerable glycemic levels. After risk and benefit evaluations, some experts suggest metformin or dipeptidyl peptidase-4 (DPP4) inhibitors as drugs of choice for the elderly.<sup>12,41</sup> In Table 3, we summarize the antidiabetic drugs with the considerations we mentioned above. Applications of antidiabetic therapies in different categories are summarized in Table 4. Interaction of oral antidiabetic drugs (OADs) and drugs used in common comorbidities are summarized in Table 5 for prescribing reference.<sup>61,62</sup>

**Table 3** Comparisons of current options in glycemic control

Options	Hypoglycemia risks	Glycemic variability	Costs	Treatment complexity	Special considerations
Diet	Low	Reduced	Low	Variable	Balanced between glycemic control and nutrition status
Exercise	Low	Reduced	Low	Low	Individualized planning, muscle strengthening
BW reduction	Low	No data	Low	Variable	Not applicable to frail adults with or without malnutrition
Metformin	Low	No change	Low	Low	Be cautious in advanced CKD, CHF, frailty, malnutrition, and sarcopenia; preserve skeletal muscle
TZD	Low	No change	Moderate	Low	Preserve skeletal muscle; increased risk of fracture, CHF
SU	High	No change	Low	Variable	Avoid glyburide/glibenclamide
Meglitinides	Moderate	Reduced	Moderate	High	Should not combine with SU or AGI, drug interactions
DPP4-i	Low	Lowest	Moderate	Low	Effective with preserved $\beta$ -cell function
GLP1-RA	Low	Lowest	High	Moderate	Effective with preserved $\beta$ -cell function
AGI	Low	Reduced	Moderate	High	Gastrointestinal side effects, social problems
Insulin	High	Variable	Variable	Variable	Long-acting insulin analogs are suggested

**Abbreviations:** AGI, alpha glucosidase inhibitors; BW, body weight; CHF, congestive heart failure; CKD, chronic kidney disease; DPP4-i, dipeptidyl peptidase-4 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonists; SU, sulfonylurea; TZD, thiazolidinediones.

**Table 4** Comparisons of current options in glycemic control based on different categories

Options	Categories				
	Functionally independent		Functionally dependent		End-of-life care
	Newly diagnosed	Long lasting	Frail	Dementia	
Diet	Carbohydrates restriction	Carbohydrates restriction	Adequate calories, proteins	Adequate calories	Adequate calories
Exercise	Muscle strengthening	Muscle strengthening	Muscle strengthening	Activities	Activities
BW	Maintain healthy BW	Maintain healthy BW	Avoid BW loss	Avoid BW loss	Avoid BW loss
Metformin	First-line medication	First-line medication	Potentially beneficial <sup>a</sup> Potentially detrimental <sup>b</sup>	First-line medication	May be considered
TZD	Second-line combination	Potentially beneficial <sup>a</sup> Potentially detrimental <sup>c</sup>	Potentially beneficial <sup>a</sup> Potentially detrimental <sup>d</sup>	Potentially beneficial <sup>e</sup> Potentially detrimental <sup>f</sup>	May be considered
SU	Second-line combination Start low, go slow	May be considered May not be effective	Alternative first line <sup>g</sup> Potential detrimental <sup>h</sup>	May be considered Once daily, start low	May be considered
Meglitinides	Second-line combination	May be considered May not be effective	May be considered	Potentially detrimental <sup>i</sup>	May be considered
DPP4-i	Second-line combination	May be considered May not be effective	May be considered	May be considered, once daily	May be considered
GLP1-RA	Second- or third-line combination	May be considered May not be effective	Potentially detrimental <sup>b</sup>	May not be cost effective	May not be cost effective
AGI	Second-line combination	May be considered May not be effective	Potentially detrimental <sup>b</sup>	May be considered	May be considered
Insulin	Second-line combination, long-acting analogs	May need prandial insulin	Long-acting analogs	Long-acting analogs	NPH may be enough

**Notes:** <sup>a</sup>Potential muscle preservation is good for frail adults. <sup>b</sup>Potential gastrointestinal upsets may be detrimental for malnourished adults with progressive BW loss. <sup>c</sup>Limited use in some comorbidities, such as congestive heart failure. <sup>d</sup>Potential fracture risk should be considered in frail adults with high risk of falling. <sup>e</sup>Pioglitazone exhibited potential cognitive improvement in mild AD. <sup>f</sup>Rosiglitazone is associated with cognitive decline. <sup>g</sup>For elderly not eligible for metformin use, low dose initiated SU may be alternative first line medication. <sup>h</sup>Risk of hypoglycemia and consequent falling may be detrimental for frail adults. <sup>i</sup>For elderly with erratic eating habits, such kind of drug may result in higher risk of hypoglycemia.

**Abbreviations:** AGI, alpha glucosidase inhibitors; BW, body weight; DPP4-i, dipeptidyl peptidase-4 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonists; SU, sulfonylurea; TZD, thiazolidinediones; NPH, neutral protamine Hagedorn.

## Options of therapy in elderly patients

### First line: lifestyle interventions and metformin

#### Lifestyle interventions

The importance of lifestyle interventions cannot be overemphasized. An increase of one healthy behavior was associated with a decrease in A1C level of >1.0 percentage point in older adults with diabetes.<sup>63</sup> Diet and exercise remain the cornerstones of diabetes management. While decreasing the amount of carbohydrates, diet should be designed with adequate calories to maintain ideal BW and lean muscle mass and to prevent sarcopenia or sarcopenic obesity and consequent frailty in the elderly patients. Optimizing weight in adults with diabetes is an important factor in predicting better glycemia.<sup>63</sup> Functionally independent obese elderly patients should be encouraged to maintain a healthy BW. However, compared to those who are overweight or obese, the impact of weight change in those with relatively normal weight may be complicated.<sup>64</sup> Most of the studies reviewed suggest that poor glucose regulation is associated with weight loss.<sup>65</sup> Restricted diet should be avoided in malnourished

elderly patients.<sup>13</sup> Nutrition status should be thoroughly evaluated in elderly diabetic patients, with individualized nutritional planning, focusing on adequate hydration, optimal calories, and protein intake to maintain nutrition and functional status and prevent muscle loss.<sup>8,10,22,36,37</sup> Complex carbohydrates and fiber are good for decreasing glycemic excursions after meals.<sup>39</sup> The average daily protein intake should reach 1.0–1.2 g/kg BW/day to maintain and regain lean body mass and function and to prevent sarcopenia and frailty in older people.<sup>66</sup> Protein-enriched diet with concomitant muscle training may preserve or even enhance muscle mass and strength.<sup>67</sup> This may also improve functional status and muscular glucose uptake.<sup>68</sup>

Physical activity is also encouraged in all adults, but should be individualized to fit individual's medical and physical status with special considerations of degenerated joints, diabetic neuropathy, and retinopathy. Both endurance- and resistance-type exercises are recommended as they are safe and tolerable.<sup>66</sup> Cardiovascular risks should be evaluated before introducing an exercise program.<sup>39</sup> Exercise-induced hypoglycemia should be carefully assessed in older diabetic



**Table 5** Drug interactions between antidiabetic agents and drugs used for the most common comorbidities in the elderly

	Metformin	Sulfonylureas	Meglitinides		Pioglitazone		DPP4 inhibitors	Acarbose
Gemfibrozil		IC ↑ effect of glyburide	XX ↑ concentration of repaglinide		ID ↑ concentration of pioglitazone			
Fenofibrate		IC ↑ effect of SU						
Statin		MC ↑ concentration of glyburide (fluvastatin)			IC ↓ concentration of pioglitazone (atorvastatin)			
Aspirin		IC ↑ effect of SU						
Warfarin		IC ↑ effect of both						ID ↑ risk of bleeding
ACE inhibitors	IC ↑ risk of hyperkalemic lactic acidosis						IC ↑ risk of angioedema	
DHP-CCB	MC ↑ absorption of metformin (nifedipine)				SD ↓ exposure to nifedipine IC ↓ efficacy of amlodipine			IC ↓ glucose control (nifedipine)
ND-CCB	SC ↑ effectiveness of metformin (verapamil)						IC ↑ concentration of saxagliptin	
Digoxin	IC ↑ metformin concentration						MC ↑ digoxin level (sitagliptin)	IC ↓ digoxin concentration
Amiodarone		IC ↑ SU concentration	IC ↑ nateglinide concentration		IC ↑ exposure of amiodarone		IC ↑ saxagliptin exposure	
Thiazide	ID ↓ effectiveness of all anti-diabetic agents							
	Metformin	Sulfonylureas	Pravastatin	Ezetimibe	Warfarin	Olmesartan	Diltiazem	Amiodarone
Colesevelam	IC ↑ exposure to metformin-XR	ID ↓ SU absorption	ID ↓ absorption of pravastatin	ID ↓ absorption of ezetimibe	IC ↓ INR	ID ↓ absorption of olmesartan	ID ↓ bioavailability of diltiazem	SD ↓ bioavailability of amiodarone

**Notes:** Severity: X contraindicated; S major; I moderate; M minor. Risk rating: X: avoid combination; D: consider therapy modification; C: monitor therapy.

Reliability rating: ■ good; ■ probable; ■ fair or theoretical.

**Abbreviations:** DHP-CCB, dihydropyridine calcium channel blocker; ND-CCB, non-dihydropyridine calcium channel blocker; SU, sulfonylurea; DPP4, dipeptidyl peptidase-4; ACE, angiotensin-converting enzyme; INR, international normalized ratio.

patients who are prescribed a medication regimen with higher risk of hypoglycemia.<sup>39</sup>

### Biguanides (metformin)

Metformin has gained increasing acceptance as first-line therapy along with lifestyle modification to achieve optimal glycemic goals. It improves insulin resistance, decreases hepatic gluconeogenesis, and induces some BW loss, with low potential for hypoglycemia.<sup>39</sup> A longitudinal cohort study showed that older men with diabetes using metformin or thiazolidinediones (TZDs) lost less lean body mass compared with those with untreated diabetes or treated with other antidiabetic agents.<sup>69</sup> This result is potentially beneficial for older adults, even in the frail elderly patients, whose muscle mass is lost with aging and accelerated with impaired fasting glucose and diabetes.<sup>69</sup>

However, there are still some special considerations that preclude older adults from using metformin as a first-line therapy. The well-known side effects of metformin, namely, gastrointestinal discomfort such as anorexia, nausea, vomiting,

diarrhea, and constipation, are a main concern in older adults who are frail, underweight, anorexic, and malnourished.<sup>10,70,71</sup> Another general concern with metformin is its risk for lactic acidosis, which is still put on the “black-box” warning regarding its use in advanced renal insufficiency (serum creatinine  $\geq 132.6$   $\mu\text{mol/L}$  in men or  $\geq 123.7$   $\mu\text{mol/L}$  in women or estimated glomerular filtration rate  $<30$  mL/min), hepatic disease, congestive heart failure, and advanced age ( $>80$  years old). It is also suggested in the package insert that metformin should be withdrawn in critical illness, persistent diarrhea, hypotension, and two days prior to contrast-enhanced imaging studies for fear of acute kidney injury and consequent accumulation of metformin in these conditions. In clinical practice, controversy exists about the association between lactic acidosis and the use of metformin.<sup>72–76</sup> A Cochrane review of 347 studies in T2DM patients concluded that metformin is not associated with an increased risk of lactic acidosis, or increased levels of lactate, compared to the non-metformin group.<sup>77</sup> The causal relationship of serum concentration of metformin and lactate level is not well established.<sup>78</sup>

A prospective, randomized observational study demonstrated that metformin could be safely continued even in patients with creatinine levels up to 221  $\mu\text{mol/L}$  without increasing the incidence of lactic acidosis.<sup>73</sup> A retrospective cross-sectional study also showed that age per se was not associated with increase of lactate level in metformin users.<sup>79</sup> Based on existing evidence, the benefits of metformin therapy outweigh the potential risks.<sup>74</sup> It is suggested to start metformin from lower doses and reduce the maximum dose by about 50% in patients with  $\text{eGFR} < 60 \text{ mL/min}$ , rather than strictly avoid the drug, even in oldest-old adults.<sup>80</sup>

Patients taking metformin had lower vitamin B<sub>12</sub> (vitB<sub>12</sub>) levels than those not taking metformin.<sup>81</sup> In a multicenter, randomized, placebo-controlled trial, metformin treatment for 4.3 years was associated with decrease in vitB<sub>12</sub> concentration of 19% and decrease in folate concentration of 5%.<sup>82</sup> Regular measurement of vitB<sub>12</sub> and folate level might be necessary in elderly diabetic patients who received long-term metformin therapy. Early recognition of the issue with appropriate supplementation may prevent development of the consequence of vitB<sub>12</sub> deficiency, such as macrocytic anemia and neuropathies.

## Second-line or alternative first-line therapy

In patients contraindicated or intolerable to metformin therapies, all antidiabetic drugs could be used as an alternative first-line therapy, judging by the characteristics of each individual, the regulation of national health insurance, and the specific action of each drug as described below.<sup>83</sup>

### Thiazolidinediones

The TZDs, which are insulin sensitizers and which act through activation of peroxisome proliferator-activated receptors gamma, are effective in lowering fasting glucose level through increased peripheral insulin sensitivity, especially of muscle and adipocytes. Pioglitazone, when prescribed in patients older than 65 years, had similar effectiveness and safety as in younger adults.<sup>84</sup> It was also suggested that a combination of pioglitazone and sitagliptin improved  $\alpha$ -cell and  $\beta$ -cell functions, thus reducing postprandial glucose excursions more than by either treatment alone.<sup>85</sup> Considering the low incidence of hypoglycemia of each class of the drugs, this combination seemed promising in glycemic control for older adults. However, safety profiles of TZDs are still a concern.<sup>86,87</sup> It should not be used in patients with active liver disease. Increased rates of bone fractures was observed in

elderly women taking rosiglitazone but not in men from the A Diabetes Outcome Progression Trial (ADOPT).<sup>88,89</sup> However, increased fractures were observed at the humerus, hand, and foot, rather than the typical osteoporotic sites. A similar finding was also found in the PROactive trial.<sup>90</sup> To date, the mechanism explaining these results is still unclear. The effect of pioglitazone on bone mineral density is reported as a trend of decrease in proximal femur, hip, and lumbar spine in diabetic women, but no effect in prediabetic women. There were no changes in biochemical markers of bone turnover.<sup>91,92</sup> As the clinical and pathophysiological evidence still advises the association between TZDs and fractures, its application in older adults should be made with caution.<sup>93,94</sup>

Another concern is its effect on cognition. As reported in the ACCORD-MIND cohort, exposure to rosiglitazone is associated with greater decline in cognitive performance compared with insulin therapy.<sup>95</sup> Despite the current evidence against the use of rosiglitazone in Alzheimer's disease (AD), pioglitazone exhibited cognitive and functional improvement in mild AD.<sup>96–98</sup> More evidence is needed to make recommendations about the use of pioglitazone in AD.

TZDs are also related to fluid retention. When used in patients with diabetic macular edema, worsening of the condition was reported.<sup>99</sup> Current evidence suggests that TZDs could still be safely continued in patients without macular edema.<sup>100</sup> However, this feature limits its application in patients with class III or IV congestive heart failure.<sup>101–103</sup> The risk of ischemic stroke, myocardial ischemia, and heart failure is still inconclusive in rosiglitazone and pioglitazone.<sup>101,104–108</sup> Prescription of rosiglitazone in some areas is highly restricted now.

Despite the positive effect of TZDs on glycemic control, lean body mass, cognition, and low risk of hypoglycemia, drawbacks such as increased risk of fractures, probable macular edema, heart failure, and fluid retention exist. Application of TZDs in older diabetic adults needs to be carefully evaluated for its risk/benefit ratio. Newer generation TZDs, termed as selective peroxisome proliferator-activated receptors gamma modulators, which may minimize the unwanted effects of current TZDs, are being developed and may be promising in the future.<sup>86</sup>

### Sulfonylureas

Insulin secretagogues, which stimulate insulin release from pancreatic  $\beta$ -cells, have been popular for a long time because of their good efficacy and relatively low cost. As pancreatic  $\beta$ -cell function decreases with aging, insulin secretagogues

are theoretically a good choice to enhance insulin secretion in older adults.<sup>54</sup> Risk of hypoglycemia among elderly patients treated with sulfonylureas (SU), especially glyburide (glibenclamide) and chlorpropamide, is higher than among younger adults, which is associated with more hypoglycemia-related hospitalizations.<sup>109,110</sup> Higher risk of hypoglycemia related to SU use is associated with impaired renal function, impaired hepatic function, recent hospitalization, polypharmacy, alcohol use, and caloric restriction in older adults.<sup>111</sup> Sensitivity to SU may increase, especially in those aged over 80, which makes the oldest-old more vulnerable to hypoglycemia.<sup>36</sup> Despite these drawbacks, there is no need to abruptly withdraw SU from all older adults. Its once-daily dosage form is potentially good for improving compliance of older adults and for minimizing dosing errors.<sup>71</sup> Guidelines developed all over the world suggest avoidance of only glyburide in older adults, which was associated with the most long-lasting, life-threatening hypoglycemic events.<sup>10</sup> The most important thing in prescribing SU in older adults is to follow the principle of starting SU from lowest dose, to slowly titrate to the individualized target, and to closely monitor any hypoglycemia symptoms, especially in elderly patients whose pancreatic  $\beta$ -cell function is only mildly impaired. SUs may still fail to be effective in some patients, as they develop pancreatic  $\beta$ -cell failure, especially in elderly patients with long-lasting diabetes, which makes it an appropriate substitute for insulin in patients whose glycemic targets are not stringent.<sup>18,36</sup>

### Meglitinides (repaglinide and nateglinide)

The meglitinides are rapid-acting insulin secretagogues with a short duration of action, and are aimed at increasing prandial insulin secretion.<sup>112</sup> Nateglinide should not be used with SU because of competitive binding of SU receptors. A randomized, open-label, crossover trial suggested that repaglinide is safe and effective with lower risk of hypoglycemia compared with SU in older patients with borderline poor glycemic control.<sup>113</sup> Hypoglycemia is related to missed meals, so meglitinides should be taken within 30 minutes before meals. Therefore, meglitinides should be prescribed with caution in the elderly patients with cognitive impairment and erratic eating habits.<sup>10</sup> Hepatic and renal insufficiency may prolong the action of repaglinide, resulting in higher risk of hypoglycemia in these conditions.<sup>70</sup> Disadvantages include relatively high cost, frequency of administration, and strict regulation of time of taking medicine, which contribute to the complexity of polypharmacy in older adults.<sup>39,71</sup>

### Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors (AGIs) delay absorption of carbohydrates and result in decreased postprandial glucose excursions, improvement of glycemic variability without increased oxidative stress, and possible improvement of  $\beta$ -cell response.<sup>112,114,115</sup> Maximal antihyperglycemia is achieved with lower doses (25 mg before meals) in elderly patients than their younger counterparts.<sup>116</sup> Moreover, AGIs may increase insulin sensitivity in diabetic elderly patients.<sup>117</sup> They are effective in elderly overweight type 2 diabetic patients.<sup>118</sup> They are well tolerated in older adults even with multiple comorbidities with a low incidence of hypoglycemia as monotherapy. AGIs also reduced the risk of postprandial hypoglycemia and late hypoglycemia in older adults with T2DM who eat rice porridge as main meal, due to impaired chewing function.<sup>119</sup> When hypoglycemia occurs in regimens combined with AGIs, it should be treated with oral glucose because other complex carbohydrates will not relieve the event.<sup>39</sup> Special education should be imparted to the elderly patients and their family members to manage such hypoglycemic conditions. Further, if AGIs are prescribed with prandial insulin, mismatch between peak serum glucose levels and peak prandial insulin levels may occur, placing patients at increased risk for hypoglycemia.<sup>71</sup> The most common adverse events are gastrointestinal disturbances, especially flatulence, abdominal distension, diarrhea, abdominal pain, and abdominal discomfort, which preclude AGIs application in the elderly patients.<sup>118,120–123</sup> The clinical response of AGIs depends on preserved  $\beta$ -cell function. That is, AGIs are more effective in newly diagnosed diabetes and less effective in long-standing diabetes with severely impaired insulin secretion.<sup>112</sup> This feature is important in determining whether AGIs should be prescribed in older adults. Another concern is that AGIs should be taken with meals, which increases the complexity of the medication regimen and may lead to nonadherence.<sup>124</sup>

### Incretin-based therapies

Incretin-based therapies have drawn increasing attention in recent years because of their properties of enhancing glucose-dependent insulin secretion after ingestion of food.<sup>22</sup> Both GLP-1 and glucose-dependent insulinotropic peptide are degraded rapidly by DPP4, resulting in short plasma half-lives. GLP-1 suppresses glucagon secretion, delays gastric emptying, increases satiety, and decreases food intake.<sup>22</sup> There are two classes of drugs focusing on incretin effect, namely, DPP4 inhibitors and GLP-1 receptor agonists.



### DPP4 inhibitors

This drug class inhibits DPP4, and thus prolongs the action of GLP-1 and glucose-dependent insulinotropic peptide in diabetic patients whose incretin response is impaired.<sup>71</sup> Among the currently available DPP4 inhibitors, sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin have been confirmed to be well tolerated in older adults with few gastrointestinal side effects and little effect on BW, with similar efficacy as younger adults, and can be safely used in renal insufficiency with labeled dose adjustment for each drug.<sup>125–131</sup> DPP4 inhibitors resulted in reductions in A1C for patients whose baseline A1C levels were higher.<sup>130</sup> These excellent tolerability profiles, low risk of hypoglycemia, and once-daily dosing make this drug class suitable for frail and debilitated elderly patients.<sup>7,12,22</sup>

DPP4 inhibitors enhance the effect of insulin secretion stimulated by SU, and thus increase the risk of hypoglycemia when used in combinations with SU.<sup>129</sup> This characteristic also indicates that DPP4 inhibitors are efficacious with preserved  $\beta$ -cell insulin secretion, and may be primarily effective early in the course of diabetes with mild hyperglycemia.<sup>132,133</sup> Conversely, DPP4 inhibitors might be ineffective in elderly patients with long-lasting T2DM and poorly preserved  $\beta$ -cell insulin secretion. Another concern is their high expense, which may make them unavailable in some countries.<sup>10</sup>

### GLP-1 receptor agonists

This drug class acts on the GLP-1 receptor directly with long duration due to its resistance to degradation by DPP. GLP-1 receptor agonists are effective in glycemic control and are well tolerated without increasing the risk of hypoglycemia in older patients.<sup>134–136</sup> In addition to their glucose-lowering effects, GLP-1 receptor agonists delay gastric emptying and increase satiety, resulting in weight loss, in particular reductions in subcutaneous fat mass.<sup>137</sup> Liraglutide also resulted in slight reductions of visceral fat mass in pioglitazone users.<sup>137</sup> Both liraglutide and exenatide ameliorate concomitant nonalcoholic fatty liver disease.<sup>137,138</sup> The evidence of their impact on muscle mass is still lacking. However, just as the concern in DPP4 inhibitors, the effect of GLP-1 receptor agonists on A1C reductions was also inversely related to diabetes duration, ie, to the preservation of  $\beta$ -cell function.<sup>139</sup> Thus, the characteristics of GLP-1 receptor agonists might be beneficial to obese diabetic elders if used early in the course of diabetes.<sup>12,140</sup> However, their weight-reducing effect and gastrointestinal side effects may be detrimental for the frail elderly patients with poor caloric intake and poor nutrition status.<sup>10,70,71</sup> These drugs should be used with

caution in diabetic elders who are undergoing unintentional weight loss, and who are malnourished or at high risk for malnutrition. Metabolism and excretion of liraglutide is not affected by renal impairment, even in patients with end-stage renal disease.<sup>141,142</sup> Recommendations for use of liraglutide in patients with more advanced renal impairment are limited.<sup>143</sup> Exenatide is excreted through the kidney, and is not recommended for use in severe renal impairment or end-stage renal disease.<sup>131</sup>

### Bile acid sequestrants

Colesevelam hydrochloride was originally approved for treatment of hyperlipidemia;<sup>144</sup> however, subsequent clinical trials demonstrated an improvement in glycemia for patients with T2DM.<sup>145–147</sup> Colesevelam is a bile acid sequestrant designed to have a high affinity and capacity for binding to bile acids.<sup>148</sup> Colesevelam is nonabsorbable by the body, and its distribution is confined to the digestive tract. Its hydrophilic and water-insoluble nature facilitates binding of bile acids in the intestine and excretion of these complexes in the feces.<sup>149</sup> As a result, the body increases the conversion of cholesterol to bile acids, resulting in an uptake of low-density lipoprotein cholesterol (LDL-C) by the liver to the blood, thereby lowering serum LDL-C. Colesevelam as a monotherapy or add-on therapy for the treatment of T2DM can reduce A1C and LDL-C levels.<sup>150</sup> Further, in T2DM patients aged 65 years and older, colesevelam treatment as an add-on therapy results in similar A1C reductions.<sup>151</sup> Colesevelam is safe and well-tolerated in older adults, with certain mild to moderate gastrointestinal side effects including constipation and dyspepsia.<sup>151</sup> An advantage of prescribing colesevelam to older diabetic patients is the low risk for hypoglycemic events.<sup>150</sup>

### Sodium glucose cotransporter 2 inhibitors

The newest drug class for oral diabetic agents is the sodium glucose cotransporter 2 (SGLT2) inhibitors.<sup>152</sup> SGLT2 inhibitors prevent the reabsorption of renal-filtered glucose levels, resulting in decreased blood glucose levels.<sup>153</sup> SGLT2 inhibitors can be used as a monotherapy or dual and triple therapy for T2DM patients to moderately lower A1C levels (0.5%–1.0%).<sup>154</sup> Further, SGLT2 inhibitors have the added benefits of weight loss and improved blood pressure and lipid parameters.<sup>154–157</sup> SGLT2 inhibitors are generally well tolerated among diabetic patients.<sup>158–161</sup> Common adverse events include urinary tract infections, genital mycotic infections, hypotension/volume depletion, lipid alterations, hypoglycemia, and renal insufficiency.<sup>156,161–165</sup> The efficacy and safety

of SGLT2 inhibitors in elderly patients is consistent with younger patients;<sup>166</sup> however, additional long-term studies are needed. Thus, the risks and benefits of SGLT2 inhibitors should be assessed in older patients on a case-by-case basis given the newness of the drug class.<sup>166</sup>

### Insulin

Insulin therapy is inevitable when  $\beta$ -cell preservation is severely impaired due to advanced age or long-lasting T2DM.<sup>39</sup> Early use of insulin may reduce glucotoxicity and restore function of  $\beta$ -cells.<sup>39</sup> However, insulin is often underutilized in elderly patients due to concerns about hypoglycemia, misconceptions about insulin, social stigma, needle phobia, complexity of injection skills, low adaptation capacity, and, moreover, clinical inertia.<sup>70,167</sup> Before initiating insulin therapy, comprehensive evaluation of psychosocial barriers, functional status (ie, visual acuity and manual dexterity), cognitive status, and financial ability to afford insulin and insulin-delivery supplies should be made to ensure safety, compliance, and effectiveness of insulin use.<sup>70</sup>

Conventional neutral protamine Hagedorn (NPH) insulin and regular insulin were not recommended due to variable bioavailability and nonphysiological pharmacokinetics that put patients in higher risk of hypoglycemia.<sup>70</sup> Long-acting insulins degludec, glargine, and detemir are safer choices than NPH in older adults because of their lower risk of hypoglycemia, especially nocturnal hypoglycemia, which may contribute to cardiovascular morbidity and falls.<sup>168–172</sup> Insulin degludec resulted in less hypoglycemia than insulin glargine even in long-duration diabetic patients, whose counterregulatory hormone responses were presumed to be weaker.<sup>169</sup> Besides, insulin analogs are mostly delivered through insulin pens, which leads to improved adherence, accuracy of injection, quality of life, and decreased admissions for hypoglycemia.<sup>12,15,173,174</sup>

For elderly diabetic patients with inadequately controlled hyperglycemia, patients with early combinations of basal insulin had better glycemic control and less hypoglycemia than titration of oral antidiabetic drugs.<sup>175</sup> In diabetic elders with poorly controlled glycemia, insulin therapy did not result in higher hypoglycemia events if glycemic targets were less stringent.<sup>176</sup> A once-daily insulin regimen was also more preferred by an older population than more frequent dosing.<sup>177</sup> Prandial insulin supplement in basal bolus regimen or premixed insulin may be appropriate in highly selected elderly patients with good functional reserve.<sup>70</sup> Judicious use of insulin as an add-on therapy may improve mental health, quality of life, social functioning, treatment satisfaction,

and caregiver strain in elderly diabetic patients with poor glycemic control.<sup>178</sup>

### Combinations of antidiabetic agents

Considering the importance of avoiding hypoglycemia and managing postprandial hyperglycemia in elderly patients, some combinations may provide these desirable outcomes better than commonly used metformin plus SU in clinical practice. We summarize the results of randomized controlled trials comparing glycemic effect, hypoglycemia risk, and influence on BW among strategies of each combination in Table 6 and Figure 1. Current trials regarding drugs combination were not planned for the elderly patients except for a few studies including the elderly patients as a subgroup for further analysis.<sup>179–184</sup> As the risk of hypoglycemia is higher in older adults, combination strategies with less hypoglycemia risk in middle-aged adults may be more appropriate for older adults.

#### Metformin plus DPP4 inhibitors

When metformin monotherapy could not achieve glycemic target, DPP4 inhibitor was suggested as first add-on drug compared with SU, TZD, or insulin glargine in the elderly patients. Though not as effective as insulin glargine, combination of metformin with DPP4 inhibitors provided the favorable result of less hypoglycemia incidence.<sup>185</sup> Compared with SU, DPP4 inhibitor results in similar improvement of A1C, but less hypoglycemia incidence and no weight gain.<sup>180–184,186–188</sup> This combination also showed better glycemic variability,<sup>189,190</sup> decrease of glucagon production,<sup>187</sup> better  $\beta$ -cell function,<sup>188</sup> better insulin resistance,<sup>187</sup> and better cost-effectiveness than a combination of metformin with SU.<sup>179,191,192</sup> Compared with TZD, combination with DPP4 inhibitors revealed similar glycemic control and hypoglycemia risk, but less weight gain.<sup>193–195</sup> Compared with metformin plus SU, metformin plus TZD was the more tolerable combination due to less hypoglycemia incidence with similar glycemic control and BW gain.<sup>196–198</sup>

#### Metformin plus SGLT2 inhibitors

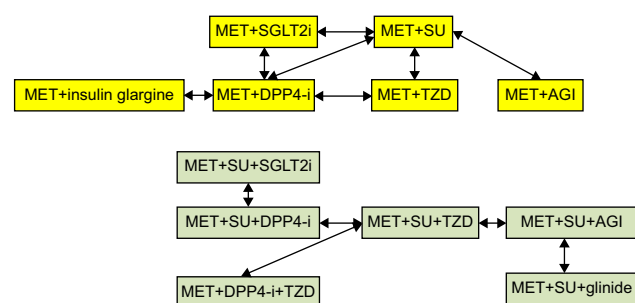
SGLT2 inhibitors are newly approved drugs without experience on long-term effect and safety. Randomized controlled studies demonstrated that combination with canagliflozin is at least not inferior to combination with glimepiride or sitagliptin in glycemic control, but with less hypoglycemia incidence than glimepiride<sup>199</sup> and more BW reduction than sitagliptin.<sup>200</sup> This combination may provide favorable effects for elderly groups, but at the cost of more genitourinary tract

Table 6 Comparisons of combination strategies in glycemic control

Study	n(D1/D2)	Age (years)	DM duration (years)	Preexisting drug(s)	Added-on drug 1 (D1)	Added-on drug 2 (D2)	Study period	A1C (%)	ΔA1C (%)	ΔBW (kg)	Hypoglycemia
Ferrannini et al <sup>180</sup>	1396/1393 Elderly 712	57.5	5.7	Metformin	Vildagliptin	Glimepiride	1 year	7.3	-0.44/-0.53	-0.2/+1.5*	0/10 events*
Matthews et al <sup>181</sup>	1562/1556 Elderly 789	57.5	5.7	Metformin	Vildagliptin	Glimepiride	2 years	7.3	-0.10/-0.10	-0.3/+1.2	2.3%/18.2% 2.1%/17.5%
Filozof and Gautier <sup>182</sup>	513/494 Elderly 390	59.5	6.6	Metformin	Vildagliptin	Gliclazide	1 year	8.5	-0.81/-0.85 -0.98/-0.91	+0.08/+1.36*	6/11 events
Göke et al <sup>183</sup>	428/430 Elderly 219	57.6	5.4	Metformin	Saxagliptin	Glipizide	1 year	7.7	-0.74/-0.80	-1.1/+1.1	3%/36.3%*
Gallwitz et al <sup>184</sup>	776/775 Elderly 506	59.8	Variable	Metformin	Linagliptin	Glimepiride	2 years	7.7	-0.16/-0.36	-1.4/+1.3	7%/36%
Arechavaleta et al <sup>186</sup>	516/519	56.3	6.8	Metformin	Sitagliptin	Glimepiride	30 weeks	7.5	-0.47/-0.54	-0.8/+1.2*	7%/22%*
Nauck et al <sup>186</sup>	588/584	56.7	6.3	Metformin	Sitagliptin	Glipizide	1 year	7.7	-0.67/-0.67	-1.5/+1.1*	5%/32%*
Takihata et al <sup>193</sup>	58/57	60.5	NA	Metformin and/or SU	Sitagliptin	Pioglitazone	24 weeks	7.4	-0.86/-0.58*	-0.3/+1.7*	3.4%/3.5%
Bolli et al <sup>194</sup>	295/281	56.6	6.4	Metformin	Vildagliptin	Pioglitazone	24 weeks	8.4	-0.88/-0.98	+0.3/+1.9*	1/0 episode
Bolli et al <sup>195</sup>	295/281	56.6	6.4	Metformin	Vildagliptin	Pioglitazone	1 year	8.4	-0.60/-0.60	+0.2/+2.6*	1/1 episode
Umperrez et al <sup>196</sup>	96/107	53.7	5.4	Metformin	Glimepiride	Pioglitazone	26 weeks	8.4	-1.30/-1.23	+1.7/+1.8	33%/0.9%*
Matthews et al <sup>197</sup>	313/317	56.5	5.7	Metformin	Gliclazide	Pioglitazone	1 year	8.6	-1.01/-0.99	+1.4/+1.5	11.2%/1.3%*
Charbonnel et al <sup>198</sup>	313/317	56.5	5.7	Metformin	Gliclazide	Pioglitazone	2 years	8.6	-0.76/-1.07*	+1.1/+2.3	11.5%/2.2%*
Ceriello et al <sup>207</sup>	62/54	56.3	7.4	Metformin	Gliclazide	Pioglitazone	1 year	8.5	-1.00/-0.80	+0.6/+1.3	NA
Pfützner et al <sup>208</sup>	288	59.0	6.1	Metformin	Glimepiride	Pioglitazone	24 weeks	7.3	-1.00/-0.80	+0.7/+0.7	5/2 events
Wang et al <sup>114</sup>	28/23	53.8	6.8	Metformin	Acarbose	Pioglitazone	24 weeks	8.4	-0.70/-1.20	-1.5/+0.8	0/3 events
Cefalu et al <sup>199</sup>	483/482	56.3	6.6	Metformin	Canagliflozin 100 mg	Glibenclamide	1 year	7.8	-0.82/-0.81	-3.7/+0.7*	6%/34%*
Lavalle-	485/482	56.1	6.7	Metformin	Canagliflozin 300 mg	Glimepiride	1 year	7.8	-0.93/-0.81*	-4.0/+0.7*	5%/34%*
González et al <sup>200</sup>	368/366	55.5	6.7	Metformin	Canagliflozin 100 mg	Sitagliptin	1 year	7.9	-0.73/-0.73	-3.3/-1.2*	4.2%/4.7%
Aschner et al <sup>185</sup>	367/366	55.4	6.9	Metformin	Canagliflozin 300 mg	Sitagliptin	1 year	7.9	-0.88/-0.73*	-3.7/-1.2*	5.0%/4.7%
Charbonnel et al <sup>209</sup>	227/253	53.6	4.5	Metformin	Insulin glargine	Sitagliptin	24 weeks	8.5	-1.72/-1.13*	+0.44/-1.08*	46%/13%*
Kim et al <sup>112</sup>	285/262	57.3	7.8	Metformin	Sitagliptin ± SU	Liraglutide	26 weeks	8.2	-1.30/-1.40	-0.4/-2.8*	12.0%/4.0%*
<b>Triple combination</b>	28/30	56.9	9.6	Insulin glargine	Acarbose	Nateglinide	2 weeks	8.3	NA	NA	3%/5%
Schemthaner et al <sup>201</sup>	378/377	56.7	9.6	Metformin, SU	Canagliflozin 300 mg	Sitagliptin	1 year	8.1	-1.03/-0.66*	-2.5%/+0.3%*	43.2%/40.7%
Derosa et al <sup>202</sup>	52/51	54.0	3.5	Metformin, SU	Acarbose	Repaglinide	15 weeks	8.1	-1.4/-1.1	-1.9%/+2.3%	0/1 events
Derosa et al <sup>203</sup>	175/178	56.0	1.1	Metformin, SU	Acarbose	Pioglitazone	24 weeks	8.6	-1.5/-2.1*	-1.2/+1.4	2/3 events
Derosa et al <sup>204</sup>	225/228	NA	NA	Metformin, pioglitazone	Sitagliptin	Glibenclamide	1 year	7.2	-0.7/-1.1	-2.5/+4.5*	NA
Osonoi et al <sup>205</sup>	14/15	64.4	Variable	Metformin, acarbose	Sitagliptin	Mitiglinide	4 weeks	7.0	-0.39/-0.18	NA	0.4%/0.9%*

**Notes:** \*Reached significance,  $P < 0.05$ . <sup>a</sup>Assessed by continuous glucose monitoring, percentage of blood glucose levels  $< 70$  mg/dL.

**Abbreviations:** BW, body weight; DM, diabetes mellitus; n, number of patients; NA, not available; SU, sulfonylurea; A1C, glycated hemoglobin.



**Figure 1** Comparison of combination therapies, studies including two drugs combination, and three drugs combination.

**Abbreviations:** AGI, alpha glucosidase inhibitors; DPP4-i, dipeptidyl peptidase-4 inhibitors; SU, sulfonylurea; TZD, thiazolidinediones; SGLT2i, sodium glucose co-transporter 2 inhibitor; MET, metformin.

infection. This risk should be balanced with other benefits during clinical practice.

### Metformin plus acarbose

Effective on reduction of postprandial glucose excursion with low hypoglycemia risk makes AGIs an attractive second-line therapy in elderly patients, at least theoretically. However, there was only one study with a small sample size comparing acarbose and glibenclamide as second-line combination therapy. Though not significant, AGIs seemed less effective than SU in glycemic control but had a favorable effect on BW.<sup>114</sup> Evidence was not adequate to make a suggestion due to limited studies.

### Triple combinations

Studies on triple combinations were limited. Most of the dual combinations in clinical practice are metformin plus SU. Some randomized controlled trials enrolled patients in poor control with metformin plus SU and compared the effect of the third drug. Combination with canagliflozin 300 mg/day was superior to sitagliptin in glycemic control and BW reduction without increased incidence of hypoglycemia.<sup>201</sup> Acarbose had similar effects as repaglinide<sup>202</sup> but was less effective than pioglitazone added on, despite favorable effect on BW control.<sup>203</sup>

### Metformin and pioglitazone plus DPP4 inhibitors

If metformin and pioglitazone combinations were used as the first two OADs, DPP4 inhibitors and SU decreased A1C to a similar degree. DPP4 inhibitors had a neutral effect on BW compared with BW gain in SU group. This combination was more tolerable than combination with SU, such that no patients withdrew from the study due to hypoglycemia as compared with eleven patients in the SU arm. This combination also demonstrated better protection

of  $\beta$ -cell secretion.<sup>204</sup> These features were desirable for elderly patients.

### Metformin and acarbose plus DPP4 inhibitors or mitiglinide

Despite the theoretical concern of the mismatch between peak glucose absorption and peak prandial insulin secretion in combination of acarbose with mitiglinides, a prospective randomized study revealed that daily blood glucose fluctuations were significantly improved without increase in incidence of hypoglycemia.<sup>205</sup> For elderly patients poorly controlled with metformin monotherapy, a combination of AGIs plus DPP4 inhibitors or AGIs plus mitiglinide may be an attractive add-on choice.

## Conclusion

The target of glycemic management in elderly patients with T2DM has been focused on preventing frailty and preserving functional independence. Recommendations from guidelines worldwide suggest higher A1C targets than younger adults. However, evidence suggests that better glycemic control in older adults is equally important in maintaining functional independence and cognition in order to prevent hypoglycemia in such populations. Thus, a safe intensification process and selection of antidiabetic drugs with lower glycemic variability may achieve this goal. Recent developments in incretin-based therapies and long-acting insulin analogs follow this principle, and demonstrate lower hypoglycemia risk than traditional therapies such as SU and human insulin. Some combination therapies have demonstrated desirable effects in middle-aged adults and thus may be appropriate for older patients. Future research is needed to explore the best combination of antidiabetic therapies for achieving glycemic control in elderly patients safely and effectively.

## Disclosure

The authors report no conflicts of interest in this work.

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