Early combination versus initial metformin monotherapy in the management of newly diagnosed type 2 diabetes: An East Asian perspective

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Abstract
Type 2 diabetes (T2D) in the East Asian population is characterized by phenotypes such as low body mass index, an index of β-cell dysfunction, and higher percentage of body fat, an index of insulin resistance. These phenotypes/pathologies may predispose people to early onset of diabetes with increased risk of stroke and renal disease. Less than 50% of patients with T2D in East Asia achieve glycaemic targets recommended by national or regional guidelines, which may be attributable to knowledge and/or implementation gaps. Herein, we review the latest evidence with special reference to East Asian patients with T2D and present arguments for the need to use...
early combination therapy to intensify glycaemic control. This strategy is supported by the 5-year worldwide VERIFY study, which reported better glycaemic durability in newly diagnosed patients with T2D with a mean HbA1c of 6.9% treated with early combination therapy of vildagliptin plus metformin versus those treated with initial metformin monotherapy followed by addition of vildagliptin only with worsening glycaemic control. This paradigm shift of early intensified treatment is now recommended by the American Diabetes Association and the European Association for the Study of Diabetes. In order to translate these evidence to practice, increased awareness and strengthening of the healthcare system are needed to diagnose and manage patients with T2D early for combination therapy.

KEYWORDS
antidiabetic drug, β-cell function, metformin, type 2 diabetes, vildagliptin

1 | INTRODUCTION

Diabetes is a chronic metabolic disorder. Globally, 463 million people were affected by diabetes in 2019 and this number is expected to rise to 700 million by 2045.1 More than 60% of people with diabetes live in Asia,1,2 with China having the highest prevalence (116.4 million) in 2019.1 In East Asia, type 2 diabetes (T2D) accounts for more than 90% of all cases of diabetes.2 It is characterized by varying contributions of insulin resistance and insulin deficiency with considerable intra- and inter-individual variations.3-5 Diabetes is one of the four non-communicable diseases (diabetes, cancer, respiratory and cardiovascular disease), It is also a leading cause of cardiovascular disease, renal failure, blindness, non-traumatic lower extremity amputation and neuropathy, as well as premature death.1

1.1 | Prevalence and trajectory of T2D in East Asia

The incidence, prevalence and progression of T2D varies by ethnic groups because of differences in genetic factors/susceptibility, culture, socioeconomic levels, lifestyle (notably nutrition and physical activity) and geographical features.6-8 In East Asia, the major ethnic groups include Chinese, Koreans and Japanese. The increasing prevalence of T2D and impaired glucose tolerance (IGT) in East Asia are summarized in Table 1. Within East Asia, the prevalence of diabetes and IGT differs between countries and within countries and regions. Furthermore, 36%-64% of people with diabetes are undiagnosed, with China having the highest prevalence of diabetes (Table 1).1

2 | PHENOTYPES OF T2D IN EAST ASIA

The Asian phenotype of T2D is characterized by inadequate β-cell response to insulin resistance. The latter is caused by, but is not limited to, inflammation or body fat. This dual phenotype puts Asians at high risk of developing early-onset diabetes with increased propensity for stroke, renal disease and cancer.3,5,6,9 These phenotypes may be particularly relevant to populations undergoing rapid environmental, lifestyle and cultural transition and may not be unique to Asians who happen to be in the forefront of economic development.6

Obesity reflected by high body mass index (BMI) is closely linked to diabetes risk, albeit this risk association occurs at a much lower BMI in East Asians compared with their Caucasian counterparts.10,11 Most experts accept BMI ≥23 and ≥25 kg/m² to be the cut-off values for defining overweight and obesity, respectively, in East Asian populations.12 Asians are also more probable to accumulate visceral fat than Caucasians for the same BMI and/or waist circumference.11 Compared with Caucasians, Blacks, Hispanics and South East Asians, East Asians have the lowest fat storage capacity in subcutaneous adipose tissue.13 When this capacity for storage is exceeded, lipids accumulate in the visceral adipose tissue, muscle and liver.13 A study has shown that liver fat accumulation is higher in Japanese than Caucasians.14 Compared with Caucasians with similar BMI and fat level, Koreans had pancreas with significantly lower volume yet higher fat content, causing a vulnerability to β-cell damage.15 The accumulation of visceral and ectopic fat, especially in the liver and islets, contributes to insulin resistance, β-cell dysfunction and development of T2D in the East Asian population.6,13 Based on oral glucose tolerance tests, lean East Asians have a low insulin response and are more insulin-sensitive than their European and African counterparts.4,16 However, in the presence of obesity, East Asians have reduced compensatory β-cell capacity resulting in metabolic decompensation at a lower BMI.4,5,16 In prospective studies, β-cell dysfunction with reduced insulin response among progressors to T2D have been consistently reported in the East Asian population.17-20 To this end, Japanese-Americans leading a highly westernized lifestyle displayed an insulin response similar to native Japanese when compared with European-Americans, highlighting the importance of ethnicity in determining insulin secretion.21

In East Asia, one in five adult patients attending medical clinics have young-onset type 2 diabetes (YOD), arbitrarily defined as age of diagnosis before 40 years.2,6,22 The double hit of β-cell dysfunction and visceral adiposity, which might be exacerbated by rapid
The general goals of diabetes management are to avoid acute metabolic decompensation, prevent or delay complications, decrease premature mortality and preserve quality of life. Many East Asian countries have formulated their own national or regional guidelines, often adapted from international guidelines such as those of the American Diabetes Association (ADA), American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) and European Association for the Study of Diabetes (EASD) to suit local needs. Asia, China, Hong Kong, Taiwan, Korea and Japan follow similar guidelines. In this approach, patients are usually initiated on metformin monotherapy in combination with lifestyle modifications at the time of diagnosis unless the patient has poor glycaemic control or metformin contraindication or intolerance. The European Society of Cardiology guidelines developed in collaboration with EASD suggested that SGLT-2is and GLP-1 RAs should be administered as first-line monotherapy in patients with atherosclerotic cardiovascular disease or with high cardiovascular risk. The AACE and ADA/EASD guidelines recommend treatment intensification with an additional drug if monotherapy does not achieve or maintain an HbA1c target after 3 months. The preferred third-line treatment includes insulin initiation or a triple combination of oral blood glucose-lowering drugs.

By its nature, development of hyperglycaemia is a prerequisite for stepwise therapy, which leads to therapeutic inertia. Clinicians may also be reluctant to initiate combination or multidrug therapy early in the disease continuum because of the fear of potentially increased side effects with multiple drugs. As a result, patients may be exposed to prolonged hyperglycaemia before the treatment is intensified, which can lead to an increased risk of microvascular and macrovascular complications. With the onset of complications, therapy intensification can become complex with an increased risk of side effects, notably hypoglycaemia. Failure to prevent disease progression during the early stage of disease often leads to intensive insulin therapy over time.
The AACE treatment algorithm recommends that patients with an HbA1c level of 7.5% or higher (≥59 mmol/mol) should start with a combination therapy of metformin plus an additional blood glucose-lowering drug. Based on evidence from the 5-year Vildagliptin Efficacy in combination with metformin For earY treatment of T2D (VERIFY) study, ADA 2020 Standards of Care suggest that early combination therapy can be considered in some patients at treatment initiation to avoid treatment escalation. In the ADA/EASD 2018 position statement, combination treatment is only recommended if the HbA1c level is more than 17 mmol/mol (1.5%) above the individual target. Supported by the latest evidence, the 2019 update recommended engaging newly diagnosed patients with T2D early to start combination therapy through shared decision-making. In Taiwan, combination therapy of metformin and another blood glucose-lowering drug is recommended for patients with an HbA1c level of 8.5% or higher (≥69 mmol/mol) at diagnosis. In Hong Kong and Korea, combination therapy with metformin is recommended in patients with HbA1c of 7.5% or higher (≥59 mmol/mol).

Nearly all blood glucose-lowering drug classes, for example, metformin, SU, AGi, GLP-1 RA, DPP4-i and SGLT2-i, may be used in combination. Most early combination therapies use metformin as base therapy. The efficacy and safety of different combination therapies have been extensively reviewed and assessed in meta-analyses and are summarized in Table 2. Using monotherapy alone is not probable to maintain HbA1c values below 6.5%. Compared with stepwise therapy, early combination therapy may provide earlier and greater reductions in HbA1c and thus achievement of glycaemic target. Given the widespread phenomenon of clinical inertia, early intensification may be an effective strategy to reduce the glycaemic burden over time. Optimizing glycaemic control from the time of diagnosis can lead to long-term reduction in the risk of microvascular and macrovascular complications. Besides, reducing glucotoxicity during the early stage of disease may also preserve β-cell mass and function as well as improve insulin sensitivity.

Considering the complex pathophysiology of T2D, the combination of different classes of drugs with synergistic actions may be a more appropriate strategy. Combination therapy of metformin and a DPP4-i can suppress hepatic glucagon production while a DDP4-i can additionally improve prandial insulin release. Besides, metformin has been shown to increase circulating levels of GLP-1, which can be further augmented by reducing the degradation of GLP-1 using a DPP4-i. The use of DPP-4is and GLP-RAs can also counteract the elevated glucagon levels induced by SGLT2-is when used in combination.

In terms of safety, compared with metformin monotherapy, early combination of metformin with an SU is associated with a greater risk of hypoglycaemia. On the other hand, combination of metformin with a DPP4-i or SGLT2-i exhibits a similar risk of hypoglycaemia compared with metformin monotherapy. However, early combination therapy may reduce patient adherence because of perceived complex multi-drug regimens, which can be overcome by using a fixed-dose drug combination.

Treatment cost is an important factor to consider while initiating combination therapy. Early combination therapy will be more expensive compared with a single agent in stepwise therapy. However, the reduced risk of complications and glycaemic durability because of superior initial and long-term glycaemic control may offset the initially higher cost of medication. In an economic analysis from Australia, first-line use of dapagliflozin plus metformin was more cost-effective than metformin monotherapy followed by gradual addition of dapagliflozin in patients with T2D. Currently, there are a scarcity of data with which to compare the long-term safety and cost-effectiveness of different early combination therapies in East Asian populations, although these data will be useful to inform practice.

Although insulin therapy has traditionally been recommended as the last option in the sequential treatment algorithm of T2D, several guidelines and consensus statements suggest consideration of insulin as part of a first-line regimen. The AACE/ACE recommend early use of insulin for patients with T2D who are symptomatic and have HbA1c of 9.0% or higher. Practice guidelines from China and Korea also recommend initial insulin therapy if HbA1c is 9% or higher.

Recovery of β-cell function has been reported in newly diagnosed patients with T2D and severe hyperglycaemia who were treated intensively with early insulin therapy.

3.1 | Challenges in the pharmacological management of T2D

Table 3 lists the treatment targets defined by East Asian guidelines and achievement of these targets in East Asia. Despite the availability of an array of glucose-lowering drugs, more than half of East Asian patients with T2D do not achieve glycaemic targets (Table 3). This is attributable to multiple factors including, but not limited to, insufficient guidance from current diabetes treatment recommendations, low adherence, lack of access to care, coverage, education and high costs associated with newer glucose-lowering therapies. Similarly, 49% of patients with T2D in the United States had HbA1c of 7.0% or higher during 2011–2014, while 37% of patients in Europe did not reach glycaemic targets of HbA1c less than 7.0%, as estimated by the PANORAMA survey in nine European countries.

4 | CONSIDERATIONS FOR TREATMENT OF NEWLY DIAGNOSED T2D IN THE EAST ASIAN POPULATION

Because T2D is a complex disorder, therapeutic interventions that target only HbA1c but not the underlying pathogenic abnormalities are improbable to result in an effective and durable treatment response. Thus, modern management of T2D should focus on identification of disease aetiologies and use pathway-targeted interventions aimed at correcting the underlying pathophysiological abnormalities. In patients with IGT, reduced first-phase insulin secretion and non-suppression of glucagon are already evident. Given the East Asian phenotype with dual contributions from increased visceral fat and reduced β-cell function, a combination treatment that targets these pathways
| Combination class | HbA1c reduction efficacy (%) | Weight loss | β-cell protection | CV protection | Side effects |
|-------------------|-----------------------------|-------------|-------------------|---------------|-------------|
| Metformin + DPP4-i vs. BL | −0.99 to −3.00<sup>45</sup> | Neutral<sup>66</sup> | Combination of metformin and DPP4-i improve β-cell function<sup>74,48</sup> | Metformin and DPP4-i have neutral effect on secondary CV outcomes, except there is possible risk of increased HF with alogliptin and saxagliptin<sup>49-51</sup> | Similar safety profile to metformin monotherapy. Rarely side effect<sup>46</sup> |
| vs. Met | −0.44<sup>45</sup> | | | | |
| vs. DPP4-i | −0.88<sup>45</sup> | | | | |
| Metformin + SU vs. BL | −1.53 to −2.27<sup>45</sup> | Gain<sup>46,52</sup> | Metformin does not directly preserve β-cell mass and function. SU does not preserve β-cell mass and function<sup>53</sup> | Metformin has neutral effect on CV outcomes<sup>51</sup> SU is associated with potential ASCVD risk<sup>49,50</sup> | Increased risk of hypoglycaemia (moderate) compared with metformin monotherapy<sup>46</sup> |
| vs. Met | −0.68<sup>45</sup> | | | | |
| vs. SU | −0.49<sup>45</sup> | | | | |
| Metformin + TZD vs. BL | −1.83 to −2.30<sup>45</sup> | Gain<sup>46</sup> | Metformin does not directly preserve β-cell mass and function. TZD prevent β-cell apoptosis, promote β-cell. Proliferation and improve β-cell function<sup>53,54</sup> | Metformin has neutral effect on CV outcome<sup>51</sup> TZD may reduce stroke risk, yet may increase risk of HF<sup>49,50</sup> | Increased risk of hypoglycaemia (low), oedema, heart failure, bone fracture compared with metformin monotherapy<sup>46</sup> |
| vs. Met | −0.44<sup>45</sup> | | | | |
| vs. TZD | −0.83<sup>45</sup> | | | | |
| Metformin + SGLT2-i vs. BL | −1.78 to −2.08<sup>45</sup> | Loss<sup>46,55</sup> | Metformin does not directly preserve β-cell mass and function. SGLT2-i improve β-cell function<sup>43</sup> | Metformin has neutral effect on CV outcome<sup>51</sup> SGLT2-i reduce CV death, HF hospitalization and total mortality (secondary prevention)<sup>49,50</sup> | Increased risk of urogenital infection (low), dehydration, euglycaemic ketoacidosis compared with metformin monotherapy<sup>46</sup> |
| vs. Met | −0.47<sup>45</sup> | | | | |
| vs. SGLT2-i | −0.64<sup>45</sup> | | | | |
| Metformin + GLP-1 RA<sup>+</sup> vs. BL | −1.20<sup>56</sup> | Loss<sup>46,56</sup> | Combination of metformin and GLP-1 RA improve β-cell function<sup>56</sup> GLP-1 RA reduce β-cell apoptosis, increase β-cell mass and improve β-cell function<sup>53,54,57</sup> | Metformin has neutral effect on CV outcome<sup>51</sup> GLP-1 RA was shown to have CV protection (secondary prevention), yet results were not consistent across this class of medication<sup>49,50</sup> | Mild GI symptoms in combination therapy<sup>46</sup> |
| vs. Met | −0.80<sup>56</sup> | | | | |
| DPP4-i + TZD vs. BL | −1.00<sup>58</sup> | Gain<sup>58</sup> | Both TZD and DPP4-i reduce β-cell apoptosis, increase β-cell mass and improve β-cell function<sup>53,54,57,59</sup> | DPP4-i has neutral effect on CV outcome, except there is possible risk of increased HF with alogliptin and saxagliptin. TZD may reduce stroke risk, yet may increase risk of HF<sup>49,50</sup> | Hypoglycaemia (low), oedema (low) in combination therapy. Similar safety profile to individual drug<sup>58</sup> |
| vs. Met | −0.70<sup>58</sup> | | | | |
| SU + AGi vs. BL | −0.60<sup>60</sup> | Neutral<sup>60</sup> | SU and AGi do not preserve β-cell mass and function<sup>53</sup> | SU is associated with potential ASCVD risk, AGi has neutral effect on CV outcome<sup>49,50</sup> | GI side effects, hypoglycaemia in combination therapy<sup>60</sup> |
| vs. AGi | −0.29<sup>60</sup> | | | | |
| vs. SU | −0.19<sup>60</sup> | | | | |
| SU + TZD vs. BL | −2.4 to −2.5<sup>61</sup> | Gain<sup>61</sup> | TZD prevent β-cell apoptosis, increase β-cell mass and improve β-cell function<sup>53,54</sup> SU do not preserve β-cell mass and function<sup>53</sup> | SU is associated with potential ASCVD risk, TZD may reduce stroke risk, yet may increase risk of HF<sup>49,50</sup> | Hypoglycaemia and weight gain in combination therapy<sup>61</sup> |
### TABLE 2  (Continued)

| Combination class | HbA1c reduction efficacy (%)<sup>a</sup> | Weight loss<sup>a</sup> | β-cell protection<sup>b</sup> | CV protection<sup>b</sup> | Side effects |
|-------------------|----------------------------------------|------------------------|-------------------------------|--------------------------|--------------|
| DPP4-i + AGi vs. BL | -0.62<sup>62</sup> to −0.76<sup>63</sup> | Loss<sup>63</sup> | DPP4-i reduce β-cell apoptosis, promote β-cell proliferation and improve β-cell function<sup>53,59</sup> | DPP4-i has neutral effect on CV outcome, except there is possible risk of increased HF risk with alogliptin and saxagliptin. AGi has neutral effect on CV profile<sup>49,50</sup> | GI side effects in combination therapy<sup>62,64</sup> |
| vs. AGi | -0.36<sup>62</sup> to −0.62<sup>63</sup> | | There is no evidence of AGi preserving β-cell function | | |
| vs. DPP4-i | -0.04<sup>62</sup> | | | | |
| SGLT2-i + DPP4-i vs. BL | -1.08 to −1.24<sup>65</sup> | Loss<sup>65</sup> | Combination of SGLT2-i and DPP4-i improves β-cell function<sup>66</sup> | DPP4-i has neutral effect on CV outcome, except there is possible risk of increased HF risk with alogliptin and saxagliptin. SGLT2-i reduced CV death, HF hospitalization and total mortality (secondary prevention)<sup>49,50</sup> | Mild adverse events in combination therapy, similar safety profile to individual drug<sup>67</sup> |
| vs. SGLT2-i | -0.35<sup>68</sup> | | | | |
| vs. DPP4-i | -0.62<sup>68</sup> | | | | |
| Metformin + TZD + DPP4-i vs. BL | -2.70<sup>69</sup> to −4.00<sup>70</sup> | Loss<sup>69</sup> Gain<sup>70</sup> | Triple combination therapy with metformin, DPP4-i and TZD improves β-cell function<sup>70</sup> | Metformin has neutral effect on CV outcome<sup>51</sup> DPP4-i has neutral effect on CV outcome, except there is possible risk of increased HF risk with alogliptin and saxagliptin. TZD may reduce stroke risk, yet may increase risk of HF<sup>49,50</sup> | Hypoglycaemia (low) and peripheral oedema in combination therapy<sup>69,70</sup> |
| vs. conventional stepwise | -0.55<sup>69</sup> to −0.80<sup>70</sup> | | | | |

**Abbreviations:** AE, adverse events; AGi, α-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; BL, baseline; CV, cardiovascular; DPP4-i, dipeptidyl peptidase-4 inhibitor; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; Met, metformin; NA, not applicable; SGLT2-i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

**Note:** High HbA1c reduction, or weight loss, or all components show β-cell protection, one or more show CV protection, or minimal side effect.

**Note:** Intermediate HbA1c reduction, or weight neutral, or one component shows β-cell protection, neutral CV profile, or some side effects.

**Note:** Low HbA1c reduction, or weight gain, or none of the components shows β-cell protection, one or more of the components shows CV AE, or causes hypoglycaemia or other side effects.

<sup>a</sup>HbA1c reduction efficacy category (compared with baseline value): (i) high: >1% (>11-22 mmol/mol); (ii) intermediate: >0.5%-1% (>5.5-11 mmol/mol); and (iii) low: ≤0.5% (≤5.5 mmol/mol). Weight loss/gain compares weight at baseline and post-treatment for the combination therapy. As individual component: metformin and DPP4-i are weight neutral; SU and TZD caused weight gain; GLP-1 RA, SGLT2-i and AGi caused weight loss. Results are based on clinical trial results and are influenced by several variables (baseline HbA1c, drug type and dose, duration of treatment, wash-out from other antihyperglycaemic therapies, as well as adherence among participants to study medication and diet and exercise, among other factors), therefore the information must be interpreted with caution.

<sup>b</sup>For β-cell protection and CV protection, effects of individual components were presented if information on combination therapy are not available.

<sup>c</sup>Injectable, other drugs listed are oral medications.
without weight gain and hypoglycaemia may preserve β-cell function with durable glycaemic control. According to the UK Prospective Diabetes Study, every 1% reduction in HbA1c is associated with a reduction in the risk of microvascular complications by 37% and that of death by 21%.84 In a recent meta-analysis, compared with metformin monotherapy, early combination therapy of metformin plus another glucose-lowering drug (SU, TZD, DPP4-i or SGLT2-i) resulted in greater HbA1c reductions (P < .001) than metformin monotherapy.43 This early treatment intensification reduces the risk of clinical inertia, improves glycaemic control and may preserve β-cell mass.71

Indeed, the decline in β-cell mass and function parallels the deterioration of glycaemic control. As such, achieving sustained glycaemic lowering over time (durability) is a key strategy in T2D management. In the ADOPT (A Diabetes Outcome Progression Trial) trial, monotherapy with rosiglitazone improved durable glycaemic control compared with metformin or SU monotherapy.85 SGLT-2is and TZDs have the best glycaemic durability with a projected time to HbA1c neutrality (return of HbA1c to baseline value) of 6-8 years, followed by metformin (5 years), SUs and DPP-4is (3.3 to 4.4 years).86 Other reports indicated that GLP-1 RAs could sustain glycaemic control in a subgroup of patients participating in a clinical trial for up to 7 years.87 In the latest VERIFY study, early combination with a DPP4-i (vildagliptin) and metformin in treatment-naïve newly diagnosed T2D patients with low baseline HbA1c (6.5%-7.5%) provided greater and more durable long-term benefits than initial metformin monotherapy.88 The ongoing TRIPLE-AXEL trial will provide further insights into the long-term durability of triple combination therapy with metformin, SGLT2-is and DPP4-is compared with conventional stepwise therapy in drug-naïve patients with T2D with HbA1c levels of 8.0%-10.5%.89

Among the currently available glucose-lowering drugs, TZDs, GLP-1 RAs, DPP4-is and SGLT-2is are known to have beneficial effects on β-cell function in clinical studies.53 TZDs can restore first-phase insulin response and improve other markers of β-cell function independent of the correction of glucotoxicity. In a 23-week study, pioglitazone monotherapy preserved β-cell function, as indicated by an increase in homeostasis model assessment of β-cell function (HOMA-β).90 A GLP-1 RA increases insulin secretion and reduces postprandial blood glucose. It also suppresses glucagon from the α-cells, leading to a lowering of fasting blood glucose. These dual effects address the key defects in people with diabetes and IGT.53,83

In a meta-analysis of 360 randomized clinical trials, incretin-based therapies (DPP4-i or GLP-1 RA) increased HOMA-β and fasting C-peptide levels while reducing homeostatic model assessment of insulin resistance (HOMA-IR) and fasting plasma glucose compared with placebo. The authors suggested that incretin-based therapies might preserve β-cell function over the long term.91 In an analysis of six phase III studies with a trial duration of 24 weeks, the DPP4-i, linagliptin, displayed a superior effect on HOMA-β versus placebo.92 Similarly, 1-year treatment with vildagliptin increased the β-cell secretory capacity compared with placebo,93 while treatment with saxagliptin versus placebo in a trial with a median follow-up period of 2.1 years showed that saxagliptin prevented reduction in HOMA-β.59

Similarly, SGLT-2is, such as empagliflozin, have been shown to improve β-cell sensitivity and secretion.84 In animal studies, SGLT-2is have been shown to increase pancreatic β-cell mass.95

TZDs are associated with weight gain, mainly from increased fat mass and fluid retention. However, TZD-induced increases in fat mass are mostly limited to subcutaneous fat. Several studies have shown that TZDs can reduce visceral fat through redistribution of fat from visceral to subcutaneous adipose depots accompanied by improved hepatic and peripheral tissue sensitivity to insulin.96,97 Similarly, SGLT-2is have been shown to ameliorate fatty liver, reduce visceral fat mass and increase insulin sensitivity in several in vivo animal studies.95 In patients with T2D, treatment with dapagliflozin sustained glycaemic control for 2 years with reduction in body weight and body fat mass.96 Treatment with DPP4-is and GLP-RAs have also been shown to reduce body fat mass in patients with T2D.99,100

Early drug intervention can rapidly correct the metabolic perturbation and reverse the deleterious effects of excessive glucose (glucotoxicity) and lipid (lipotoxicity) exposure on pancreatic islets, leading to improvement in β-cell function and insulin resistance.40 Using real-world evidence, researchers reported that patients with an HbA1c of 6.5% or higher during the first year after diagnosis had a higher risk of microvascular and macrovascular complications 10 years later compared with those with lower HbA1c levels during the first year of diagnosis.72 In a Korean study of patients with newly diagnosed T2D, early achievement of the HbA1c target was a determinant of long-term glycaemic durability.101 However, it remains debatable as to whether this observation was an intervention effect or selection bias, as patients who responded well to glucose-lowering treatment at an early stage may represent a milder subtype of diabetes, or if it was attributable to other confounders related to patients, providers or care settings.

An optimal treatment regimen for the East Asian T2D population should be safe and effective in achieving durable glycaemic control aimed at reducing β-cell loss and dysfunction as well as improving body fat composition. To this end, SGLT-2is, DPP4-is and GLP-RAs have been shown to improve β-cell function, reduce visceral fat mass without weight gain or muscle loss, and have favourable safety profiles (Table 2). Early combination therapy using these agents may provide rapid, safe and long-term glycaemic control. As shown in Table 2, combination therapies with SUs do not provide benefits in terms of β-cell and cardiovascular protection, contribute to weight gain, and require careful monitoring for hypoglycaemia. However, it is worth noting that SUs are cost-effective and have a high HbA1c-lowering efficacy. The new-generation SUs (such as gliclazide) displayed lower hypoglycaemia and weight gain rates, with improved cardiovascular and renal safety. SUs remain a popular choice of treatment in countries without a well-established healthcare system and where costs are a major issue.102

Table 4 shows findings from clinical trials with initial combination therapy conducted in Asian populations. The combination of a DPP4-i and metformin was the most commonly investigated treatment with confirmed efficacy in reducing HbA1c. However, these were short-term studies that included patients with an HbA1c of less than 7.5%.
## Table 3  Summary of the treatment targets of international and East Asian guidelines

| Variable/region                  | China 33 | Hong Kong 37 | Taiwan 34 | South Korea 36,75 | Japan 35 |
|----------------------------------|----------|--------------|-----------|-------------------|---------|
| **Target according to guidelines** |          |              |           |                   |         |
| Target HbA1c (A)                | <7.0% (<53 mmol/mol) | <7.0% (<53 mmol/mol) | <7.0% (<53 mmol/mol) | <6.5% (<48 mmol/mol) | <6.0% (<43 mmol/mol) when aiming for normal glycaemia |
| Target blood pressure (B)       | <130/80  | <130/80      | <140/90   | <130/80 with ASCVD | <130/80 |
| Target LDL cholesterol (C)      | <2.6 without ASCVD | <2.6 without ASCVD | <2.6 if without ASCVD | <2.6 if without ASCVD | <2.6 without ASCVD |
| Fasting blood glucose (mmol/L)  | 4.4-7.0  | 4.0-7.0      | 4.4-7.2   | 4.4-7.2           | 4.4-7.2 |
| Non-fasting/ postprandial blood glucose (mmol/L) | Non-fasting: <10.0 | 2-hour postprandial: 5.0-10.0 | 2-hour postprandial: 4.4-8.9 | 2-hour postprandial: <10.0 | 2-hour postprandial: <10.0 |

### Glycaemic and triple-goal target attainment

|                       | China 33 | Hong Kong 37 | Taiwan 34 | South Korea 36,75 | Japan 35 |
|-----------------------|----------|--------------|-----------|-------------------|---------|
| HbA1c, %              | 47.7<sup>a</sup> | 42.7<sup>b</sup> | 42.2<sup>c</sup> | 25.1<sup>d</sup> | 52.9<sup>e</sup> |
| Triple-goal, % (ABC)<sup>f</sup> | 5.6<sup>a</sup> | 3.8<sup>b</sup> | 12.4<sup>c</sup> | 8.4<sup>d</sup> | 20.8<sup>e</sup> |

### Study population characteristics

|                       | China 33 | Hong Kong 37 | Taiwan 34 | South Korea 36,75 | Japan 35 |
|-----------------------|----------|--------------|-----------|-------------------|---------|
| Mean disease duration, years (mean ± SD) | 8.1 ± 6.8<sup>a</sup> | 4.0 ± 8.0<sup>a</sup> | 11.2 ± 8.5<sup>c</sup> | NA     | 14.0 ± 9.0<sup>f</sup> |
| Age, years (mean ± SD) | 62.6 ± 11.9<sup>a</sup> | 62.8 ± 12.2<sup>b</sup> | 62.3 ± 12.1<sup>c</sup> | NA     | 65.0 ± 12.0<sup>e</sup> |
| Male, %               | 47.0<sup>a</sup> | 48.7<sup>b</sup> | 50.7<sup>c</sup> | NA     | 62.2<sup>e</sup> |

**Abbreviations:** ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; LDL, low-density lipoprotein; NA, not available.

<sup>a</sup>Cross-sectional, multicentre observational study with 25 817 patients enrolled during 2010–2011.

<sup>b</sup>Hong Kong Diabetes Database, a territory-wide electronic medical record of 338 908 patients with diabetes attending public clinics/hospitals during 2000–2012.

<sup>c</sup>Survey conducted with 1661 patients in 2018 in Taiwan.

<sup>d</sup>Data from the 2013–2016 Korea National Health and Nutrition Examination Survey.

<sup>e</sup>Cross-sectional nationwide survey with 9956 patients conducted in 2013.

<sup>f</sup>Control of blood glucose, blood pressure and blood lipids.
| First author, year | Study location/duration | Treatment groups | No. of patients | Mean age (years) | Mean BMI (kg/m²) | Mean baseline HbA1c (%) | HbA1c target (%) | Mean HbA1c reduction (%) | Safety/other findings |
|--------------------|-------------------------|------------------|-----------------|-----------------|-----------------|------------------------|-----------------|------------------------|---------------------|
| Ji, 2016103        | China 24 weeks          | Sitagliptin 50 mg + Metformin 500 mg bid | 122             | 52.6            | 26.1            | 8.5                    | <7.0 and <6.5    | −1.67                  | The incidence of AE was low, and similar, across all treatment groups. The incidences of GI AE were generally higher in high-dose metformin groups than in the placebo group. |
|                    |                         | Sitagliptin 50 mg + Metformin 850 mg bid | 125             | 52.4            | 25.4            | 8.6                    | −1.83           |                        |                     |
|                    |                         | Placebo          | 127             | 53.6            | 25.4            | 9.0                    | −0.59           |                        |                     |
|                    |                         | Metformin 500 mg bid | 126             | 52.6            | 26.0            | 8.7                    | −1.29           |                        |                     |
|                    |                         | Metformin 850 mg bid | 124             | 53.0            | 25.8            | 8.7                    | −1.56           |                        |                     |
|                    |                         | Sitagliptin 100 mg qd | 120             | 51.7            | 26.0            | 8.7                    | −0.99           |                        |                     |
| Mu, 2017104        | China (≥80.0%) 24 weeks | Linagliptin 2.5 mg + Metformin 500 mg bid | 147             | 51.4            | 26.0            | 8.7                    | <7.0 and <6.5    | −2.2                   | Hypoglycaemic AEs were low across groups |
|                    |                         | Linagliptin 2.5 mg + Metformin 1000 mg bid | 147             | 50.7            | 26.0            | 8.7                    | −2.3            |                        |                     |
|                    |                         | Linagliptin 5 mg qd | 147             | 50.8            | 26.2            | 8.7                    | −1.3            |                        |                     |
|                    |                         | Metformin 500 mg bid | 145             | 52.1            | 25.8            | 8.7                    | −1.6            |                        |                     |
|                    |                         | Metformin 1000 mg bid | 144             | 51.4            | 26.1            | 8.6                    | −2.1            |                        |                     |
| Dou, 2018105       | China 24 weeks          | Saxagliptin 5 mg + Metformin 500 mg qd | 210             | 50.8            | 26.7            | 9.4                    | <7.0            | −3.0                   | Hypoglycaemic AEs were infrequent and similar among groups |
|                    |                         | Saxagliptin 5 mg + Placebo qd | 213             | 49.5            | 26.5            | 9.4                    | −2.1            |                        |                     |
|                    |                         | Metformin 500 mg + Placebo qd | 207             | 50.1            | 26.5            | 9.5                    | −2.8            |                        |                     |
| Ji, 2017106        | China, Malaysia South Korea Taiwan 26 weeks | Alogliptin 12.5 mg + Metformin 500 mg bid | 158             | 53.4            | 26.2            | 8.4                    | NA              | −1.53                  | The combination therapy was well tolerated with similar safety to the individual components |
|                    |                         | Placebo          | 161             | 52.2            | 26.6            | 8.2                    | −0.19           |                        |                     |
|                    |                         | Metformin 500 mg bid | 161             | 53.6            | 26.3            | 8.4                    | −1.04           |                        |                     |
|                    |                         | Alogliptin 12.5 mg bid | 162             | 55.4            | 26.2            | 8.5                    | −0.86           |                        |                     |
| Hadjad, 2016107    | 21 countries 22.6%-25% of Asian (Thailand, Korea, Taiwan) 24 weeks | Empagliflozin 12.5 mg bid + Metformin 1000 mg bid | 169             | 53.6            | 30.4            | 8.66                   | <7.0 and <6.5    | −2.08                  | The proportion of patients with confirmed hypoglycaemic AEs was low in all randomized treatment groups |
|                    |                         | Empagliflozin 12.5 mg bid + Metformin 500 mg bid | 165             | 51.0            | 30.2            | 8.84                   | −1.93           |                        |                     |
|                    |                         | Empagliflozin 5 mg bid + Metformin 1000 mg bid | 167             | 52.3            | 30.5            | 8.65                   | −2.07           |                        |                     |
|                    |                         | Empagliflozin 5 mg bid + Metformin 500 mg bid | 161             | 52.2            | 30.1            | 8.68                   | −1.98           |                        |                     |
|                    |                         | Empagliflozin 25 mg qd | 164             | 53.3            | 30.6            | 8.86                   | −1.36           |                        |                     |

(Continues)
| First author, year | Study location/duration | Treatment groups | No. of patients | Mean age (years) | Mean BMI (kg/m²) | Mean baseline HbA1c (%) | HbA1c target (%) | Mean HbA1c reduction (%) | Safety/other findings |
|-------------------|-------------------------|------------------|----------------|-----------------|------------------|------------------------|-----------------|--------------------------|---------------------|
| **Empagliflozin** | **10 mg qd** | 169 | 53.1 | 30.3 | 8.62 | -1.35 | | | |
| **Metformin** | **1000 mg bid** | 164 | 51.6 | 30.5 | 8.58 | -1.75 | | | |
| **Metformin** | **500 mg bid** | 168 | 53.4 | 30.3 | 8.69 | -1.18 | | | |
| **DPP4-i + SGLT2-i** | **Lewin, 2015** | 65 | 22 countries, 9.0%-14.3% of Asian (Philippines, Taiwan) | 24 weeks | | | | | |
| Empagliflozin 25 mg + Linagliptin 5 mg qd | 134 | 54.2 | 31.8 | 7.99 | <7.0 | -1.08 | The combination therapy was well-tolerated | Similar proportions of subjects in every treatment group had one or more AE, most events were mild or moderate in intensity |
| Empagliflozin 10 mg + Linagliptin 5 mg qd | 135 | 55.2 | 31.5 | 8.04 | -1.24 | | | | |
| Empagliflozin 25 mg qd | 133 | 56.0 | 31.2 | 7.99 | -0.95 | | | | |
| Empagliflozin 10 mg qd | 132 | 53.9 | 31.5 | 8.05 | -0.83 | | | | |
| Linagliptin 5 mg qd | 133 | 53.8 | 31.9 | 8.05 | -0.67 | | | | |
| **SU/glinide + AGi** | **Tatsumi, 2013** | 60 | Japan 12 weeks | | | | | | |
| Miglitol 50 mg + Mitiglinide 10 mg tid | 21 | 63.4 | 24.8 | 7.13 | NA | -0.60 | No SAE, transient GI symptoms in arms with miglitol and mild hypoglycaemia in combination group | |
| Miglitol 50 mg tid | 22 | 62.9 | 24.9 | 6.97 | -0.21 | | | | |
| Mitiglinide 10 mg tid | 21 | 65.4 | 25.2 | 7.10 | -0.41 | | | | |
| **DPP4-i + AGi** | **Mikada, 2014** | 62 | Japan 24 weeks | | | | | | |
| Miglitol 150 mg tid + Sitagliptin 50 mg qd | 13 | 60.5 | 28.3 | 7.14 | NA | -0.62 | Total body fat mass and visceral fat mass decreased with the combination therapy | |
| Miglitol 50 mg tid | 14 | 58.7 | 29.5 | 6.90 | -0.26 | | | | |
| Sitagliptin 50 mg qd | 14 | 59.2 | 28.8 | 7.45 | -0.66 | | | | |

**Abbreviations:** AE, adverse event; AGi, α-glucosidase inhibitor; bid, twice a day; BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; GL, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; qd, once a day; SGLT2-i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea; tid, three times a day; TZD, thiazolidinedione.
Until recently, the efficacy of combination treatment in newly diagnosed patients with T2D who often have mild hyperglycaemia was unknown.

5 | INSIGHTS FROM THE VERIFY STUDY

The VERIFY study was conducted across 254 centres in 34 countries. The primary objective was to compare the durability of early combination therapy of metformin plus vildagliptin (a DPP4-i) with a traditional stepwise approach starting with metformin, followed by intensification with vildagliptin, in newly diagnosed T2D patients with mild hyperglycaemia (an HbA1c of 6.5%-7.5% [48-58 mmol/mol]) over a 5-year period.88

One of the major strengths of the VERIFY study is the inclusion of a geographically diverse, multiethnic population, which ensures the generalizability of the trial results. The VERIFY study consisted of 181 (9.0%) Asian patients from Hong Kong, South Korea, Taiwan, Malaysia and the Philippines. In this Asian subgroup, the median disease duration was 1.6 months and the mean age was 52.9 years. The mean BMI, HbA1c and fasting plasma glucose were 26.9 kg/m², 6.9% and 7.0 mmol/L, respectively.108 In summary, East Asians in the VERIFY study were young, overweight with mild hyperglycaemia, and had short disease duration.108

Results from the VERIFY study confirmed that early combination therapy is superior to sequential intensification in these patients with mild hyperglycaemia. Throughout the 5-year study period, the combination treatment group had a lower incidence and a longer time to initial treatment failure (HbA1c ≥7% on two occasions, 3 months apart: incidence: 43.6%, median time to treatment failure: 61.9 months) than the monotherapy group (incidence: 62.1%, median time to treatment failure: 61.1 months) with a hazard ratio of 0.51 (95% CI 0.45-0.58; \(P < .0001\)). The hazard ratio for time to secondary treatment failure was 0.74 (95% CI 0.63-0.86; \(P < .0001\)) in the combination treatment group compared with the monotherapy group.88 The analysis of yearly measurement of HOMA-\(\beta\) from the VERIFY study will further confirm whether early combination treatment preserved \(\beta\)-cell function in newly diagnosed T2D patients.109 From a safety perspective, both treatment strategies were equally well tolerated.

In a preliminary analysis of all geographical subgroups, the effect of early combination therapy was similar to the global population with no heterogeneity.88 In the YOD subgroup population, the time to secondary failure was additionally reduced (RR 0.52, 95% CI 0.34-0.81; \(P = .0035\)) compared with LOD (RR 0.76, 95% CI 0.65-0.89; \(P = .0009\)), supporting the use of early combination therapy in a YOD population who are in need of treatment with long-term durability. There were more patients from Asia with YOD compared with LOD (34.9% vs. 17.0%, respectively).110

The results of the VERIFY study were highlighted in the 2019 update to the ADA/EASD consensus report on the management of hyperglycaemia in T2D. It was suggested that healthcare providers should engage newly diagnosed patients early on the use of combination therapy through shared decision-making.42 Based on class I evidence for early combination therapy from the VERIFY study, the ADA 2020 Standards of Medical Care include a new grade A recommendation that early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure.41

Further studies are required to assess the efficacy of different combinations of drug classes to provide better guidance to healthcare providers. The ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) study, which compares combination of metformin with a DPP4-i, a GLP-1 RA, insulin or SU in newly diagnosed patients with T2D and mild hyperglycaemia (an HbA1c of 6.8%-8.5%) will shed light on the long-term glycaemic durability of different early combination therapies.111

6 | CHALLENGES IN THE MANAGEMENT OF T2D PATIENTS IN EAST ASIA

Besides clinical inertia, one of the major challenges in T2D management is the non-adherence of patients to prescribed therapeutic regimens, which requires patient education, empowerment and engagement.112 To this end, the joint ADA-EASD position statement calls for a patient-centred approach, with an emphasis on shared decision-making, whereby patients’ values and preferences are taken into account while balancing risks and benefits of a treatment in order to improve outcomes.32 In addition, the phenotypic heterogeneity and pluralistic needs of patients with T2D often require data-driven, team-based integrated care in order to stratify risk, assess needs, individualize treatment and promote self-management.112,113 In both developing and developed areas, there are examples of care models which adopt these principles with positive outcomes.112 For example, in Hong Kong, a territory-wide structured risk assessment and management programme for T2D using a multidisciplinary approach has contributed to a 50%-70% risk reduction in all-cause and cause-specific death rates during 2000–2016.114,115 In Taiwan, the Diabetes Shared Care Program for T2D management has resulted in improvement of multiple risk factors including HbA1c, blood pressure and LDL-cholesterol (ABC), and reduction of cardiovascular events, stroke and all-cause mortality.116 These examples are further supported by a meta-analysis where team change, the relaying of information between care providers and patients, as well as patient education/self-management have been confirmed to improve control of cardiometabolic risk factors.113

7 | CONCLUSION

In summary, T2D is an epidemic with a rising disease burden in East Asia. It is a pathophysiologically complex disease caused by varying contributions of \(\beta\)-cell dysfunction and insulin resistance. East Asians are predisposed to development of T2D at a comparatively young age, in part because of an insufficient \(\beta\)-cell response to insulin resistance that is attributable to high body fat, as well as a propensity for developing renal complications and stroke. Among other factors,
delayed diagnosis and intervention often lead to missed opportunities for early treatment intensification with a loss of glycaemic control. There is now strong evidence showing that early combination treatment with metformin and vildagliptin improves glycaemic durability compared with stepwise therapy with metformin in newly diagnosed patients with T2D. Given the comparatively young age of onset in East Asian patients with T2D who face long disease duration, early identification followed by intensive combination treatment may alter the disease trajectory. While formal study will be needed to test this theory, other studies conducted with different classes of an early combination of blood glucose-lowering drugs also allow us to determine the optimal treatment regimen for the East Asian population.

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