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

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REVIEW ARTICLE

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.

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.[1] 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/m^2 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

TABLE 1 Prevalence and projection of diabetes in East Asia

Region	Diabetes estimates (20-79 years), Nª (%)			
	Prevalence in 2019	Proportion of undiagnosed cases of diabetes in 2019	IGT prevalence in 2019	Projection of diabetes prevalence in 2045
Global	462 969.9 (8.3)	231 874.0 (50.1)	373 900.0 (8.6)	700 200.0 (9.6)
China	116 446.9 (9.2)	65 179.8 (56.0)	54 545.9 (4.3)	147 235.3 (10.8)
Hong Kong	723.4 (4.5)	466.1 (64.4)	980.7 (7.1)	876.3 (5.7)
Taiwan	1228.8 (6.4)	525.9 (42.8)	2957.2 (14.1)	1372.9 (7.8)
Republic of Korea	3689.4 (6.9)	1333.2 (36.1)	5605.1 (11.0)	4462.9 (8.4)
Japan	7390.5 (5.6)	3441.2 (46.6)	12 097.2 (9.4)	6545.9 (6.6)

Abbreviation: IGT, impaired glucose tolerance.
Note: Data based on International Diabetes Atlas, ninth edition (2019).[1]
ªN in 1000, age-adjusted comparative prevalence were presented.

urbanization characterized by consumption of energy-dense foods, physical inactivity and psychosocial stress, all contribute to the growing prevalence of YOD.[6,8,23] Driven by long disease duration, patients with YOD have a high risk of macrovascular and microvascular complications, hospitalizations and premature mortality compared with their peers with late-onset diabetes (LOD).[22–25] This is compounded by factors such as low levels of awareness, non-adherence or delayed intervention, which may underlie the poor control of risk factors and frequent defaults in young patients.[26] Adding to this challenge is the high proportion of women of childbearing age with obesity and hyperglycaemia who are at risk of developing gestational diabetes, which put both women and their offspring at a high risk of developing diabetes.[6,7]

Additionally, patients with T2D from Asia have a higher incidence of renal complications and ischaemic stroke, but lower rates of coronary heart disease and peripheral vascular disease than their counterparts in eastern Europe and Australia.[27] The pattern of increased renal complications in Asian patients with T2D has been observed across multiple studies and is a major disease burden in Asia.[28,29]

3 | TREATMENT FOR NEWLY DIAGNOSED T2D IN EAST ASIA

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),[30] American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE)[31] and European Association for the Study of Diabetes (EASD)[32] to suit local needs.[33–37] Pharmacological treatment options for T2D are divided into: (a) non-insulin therapies including (i) insulin sensitizers (metformin, thiazolidinediones [TZDs]), (ii) secretagogues (sulphonylureas [SUs]), (iii) incretin-based therapies (glucagon-like

peptide-1 receptor agonists [GLP-1 RAs], dipeptidyl peptidase-4 inhibitors [DPP4-is]) and (iv) insulin-sparing agents such as α-glucosidase inhibitors (AGis) and sodium-glucose co-transporter-2 inhibitors (SGLT-2is); and (b) insulin therapies. Until recently, stepwise and combination therapy have been the two recommendations for pharmacologic approaches in T2D.

Because of a lack of sufficient evidence on the use of early combination therapy, stepwise treatment intensification has been the standard approach with which to achieve glycaemic control, as recommended by ADA/EASD consensus on treatment algorithm.[32] Asia, China, Hong Kong, Taiwan, Korea and Japan follow similar guidelines.[32–36] 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.[38] 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.[31,32]

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.[39] Failure to prevent disease progression during the early stage of disease often leads to intensive insulin therapy over time.[40]

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.[31] Based on evidence from the 5-year Vildagliptin Efficacy in combination with metfoRmIn For earlY 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.[41] 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.[32] Supported by the latest evidence, the 2019 update recommended engaging newly diagnosed patients with T2D early to start combination therapy through shared decision-making.[42] 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.[34] In Hong Kong and Korea, combination therapy with metformin is recommended in patients with HbA1c of 7.5% or higher (≥59 mmol/mol).[36,37]

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[43,44] 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.[71] Optimizing glycaemic control from the time of diagnosis can lead to long-term reduction in the risk of microvascular and macrovascular complications.[72] Besides, reducing glucotoxicity during the early stage of disease may also preserve β-cell mass and function as well as improve insulin sensitivity.[44]

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.[71]

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.[43] 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.[40]

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.[71] 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.[73] 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[31] 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.[33,36] 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.[74]

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,[81] 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.[82]

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.[83] Given the East Asian phenotype with dual contributions from increased visceral fat and reduced β-cell function, a combination treatment that targets these pathways

TABLE 2 The efficacy and safety of combination therapy in type 2 diabetes

Combination class	HbA1c reduction efficacy (%)[a]	Weight loss[a]	β-cell protection[b]	CV protection[b]	Side effects
Metformin + DPP4-i	vs. BL −0.99 to −3.00[45] vs. Met −0.44[45] vs. DPP4-i −0.88[45]	Neutral[46]	Combination of metformin and DPP4-i improve β-cell function[47,48]	Metformin and DPP4-i have neutral effect on secondary CV outcomes, except there is possible risk of increased HF with alogliptin and saxagliptin[49–51]	Similar safety profile to metformin monotherapy. Rarely side effect[46]
Metformin + SU	vs. BL −1.53 to −2.27[45] vs. Met −0.68[45] vs. SU −0.49[45]	Gain[46,52]	Metformin does not directly preserve β-cell mass and function. SUs do not preserve β-cell mass and function[53]	Metformin has neutral effect on CV outcomes[51] SU is associated with potential ASCVD risk[49,50]	Increased risk of hypoglycaemia (moderate) compared with metformin monotherapy[46]
Metformin + TZD	vs. BL −1.83 to −2.30[45] vs. Met −0.44[45] vs. TZD −0.83[45]	Gain[46]	Metformin does not directly preserve β-cell mass and function. TZD prevent β-cell apoptosis, promote β-cell. Proliferation and improve β-cell function[53,54]	Metformin has neutral effect on CV outcome[51] TZD may reduce stroke risk, yet may increase risk of HF[49,50]	Increased risk of hypoglycaemia (low), oedema, heart failure, bone fracture compared with metformin monotherapy[46]
Metformin + SGLT2-i	vs. BL −1.78 to −2.08[45] vs. Met −0.47[45] vs. SGLT2-i −0.64[45]	Loss[46,55]	Metformin does not directly preserve β-cell mass and function. SGLT2-i improve β-cell function[53]	Metformin has neutral effect on CV outcome[51] SGLT2-i reduce CV death, HF hospitalization and total mortality (secondary prevention).[49,50]	Increased risk of urogenital infection (low), dehydration, euglycaemic ketoacidosis compared with metformin monotherapy[46]
Metformin + GLP-1 RA[c]	vs. BL −1.20[56] vs. Met −0.80[56]	Loss[46,56]	Combination of metformin and GLP-1 RA improve β-cell function[56] GLP-1 RA reduce β-cell apoptosis, increase β-cell mass and improve β-cell function.[53,54,57]	Metformin has neutral effect on CV outcome[51] GLP-1 RA was shown to have CV protection (secondary prevention), yet results were not consistent across this class of medication[49,50]	Mild GI symptoms in combination therapy[46]
DPP4-i + TZD	vs. BL −1.00[58] vs. Met −0.70[58]	Gain[58]	Both TZD and DPP4-i reduce β-cell apoptosis, increase β-cell mass and improve β-cell function[53,54,57,59]	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[49,50]	Hypoglycaemia (low), oedema (low) in combination therapy. Similar safety profile to individual drug[58]
SU + AGi	vs. BL −0.60[60] vs. AGi −0.29[60] vs. SU −0.19[60]	Neutral[60]	SU and AGi do not preserve β-cell mass and function[53]	SU is associated with potential ASCVD risk, AGi has neutral effect on CV outcome[49,50]	GI side effects, hypoglycaemia in combination therapy[60]
SU + TZD	vs. BL −2.4 to −2.5[61] vs. TZD −0.73 to −0.77[61] vs. SU −0.63 to −0.66[61]	Gain[61]	TZD prevent β-cell apoptosis, increase β-cell mass and improve β-cell function[53,54] SU do not preserve β-cell mass and function[53]	SU is associated with potential ASCVD risk, TZD may reduce stroke risk, yet may increase risk of HF[49,50]	Hypoglycaemia and weight gain in combination therapy[61]

(Continues)

TABLE 2 (Continued)

Combination class	HbA1c reduction efficacy (%)[a]		Weight loss[a]	β-cell protection[b]	CV protection[b]	Side effects
DPP4-i + AGi	vs. BL	−0.62[62] to −0.76[63]	Loss[63]	DPP4-i reduce β-cell apoptosis, promote β-cell proliferation and improve β-cell function [53,59] There is no evidence of AGi preserving β-cell function	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 [49,50]	GI side effects in combination therapy[62,64]
	vs. AGi	−0.36[62] to −0.62[63]				
	vs. DPP4-i	−0.04[62]				
SGLT2-i + DPP4-i	vs. BL	−1.08 to −1.24[65]	Loss[65]	Combination of SGLT2-i and DPP4-i improves β-cell function[66]	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) [49,50]	Mild adverse events in combination therapy, similar safety profile to individual drug[67]
	vs. SGLT2-i	−0.35[68]				
	vs. DPP4-i	−0.62[68]				
Metformin + TZD + DPP4-i	vs. BL	−2.70[69] to −4.00[70]	Loss[69] Gain[70]	Triple combination therapy with metformin, DPP4-i and TZD improves β-cell function[70]	Metformin has neutral effect on CV outcome[51] 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 [49,50]	Hypoglycaemia (low) and peripheral oedema in combination therapy[69,70]
	vs. conventional stepwise	−0.55[69] to −0.80[70]				

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 one of the components shows β-cell protection, one or more of the components shows CV AE, or causes hypoglycaemia or other side effects.

[a]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.

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

[c]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.[94] 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.[98] 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) <6.5% for selected younger individuals with short history of diabetes, long life expectancy and no significant CVD	<7.0% (<53 mmol/mol)	<6.5% (<48 mmol/mol)	<6.0% (<43 mmol/mol) when aiming for normal glycaemia <7.0% (<53 mmol/mol) when aiming to prevent complication <8.0% (<64 mmol/mol) when intensification of therapy considered difficult
Target blood pressure (B) (mmHg)	<130/80	<130/80	<140/90	<130/80 with ASCVD <140/85 without ASCVD	<130/80
Target LDL cholesterol (C) (mmol/L)	<2.6 without ASCVD <1.8 with ASCVD	<2.6 without ASCVD <1.8 with ASCVD	<2.6 if without ASCVD <1.8 with ASCVD	<2.6 if without ASCVD <1.8 with ASCVD	<2.6 without ASCVD <3.1 with ASCVD
Fasting blood glucose (mmol/L)	4.4–7.0	4.0–7.0	4.4–7.2	<6.1	<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					
HbA1c, %	47.7[76a]	42.9[77b]	42.2[78c]	25.1[75,79d]	52.9[80e]
Triple-goal, % (ABC)[f]	5.6[76a]	3.8[77b]	12.4[78c]	8.4[79d]	20.8[80e]
Study population characteristics					
Mean disease duration, years (mean ± SD)	8.1 ± 6.8[a]	4.0 ± 8.0[a]	11.2 ± 8.5[c]	NA	14.0 ± 9.0[e]
Age, years (mean ± SD)	62.6 ± 11.9[a]	62.8 ± 12.2[b]	62.3 ± 12.1[c]	NA	65.0 ± 12.0[e]
Male, %	47.0[a]	48.7[b]	50.7[c]	NA	62.2[80e]

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

[a]Cross-sectional, multicentre observational study with 25 817 patients enrolled during 2010–2011.

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

[c]Survey conducted with 1661 patients in 2018 in Taiwan.

[d]Data from the 2013–2016 Korea National Health and Nutrition Examination Survey.

[e]Cross-sectional nationwide survey with 9956 patients conducted in 2013.

[f]Control of blood glucose, blood pressure and blood lipids.

TABLE 4 Early combination therapy conducted in treatment-naïve East Asian patients

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
Metformin + DPP4-i									
Ji, 2016 [103]	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, 2017 [104]	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, 2018 [105]	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, 2017 [106]	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	
Metformin + SGLT2-i									
Hadjadj, 2016 [107]	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)

TABLE 4 (Continued)

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	The combination therapy was well-tolerated
		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	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; GI, 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/m^2, 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: 36.1 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-β from the VERIFY study will further confirm whether early combination treatment preserved β-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 SUs 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 β-cell dysfunction and insulin resistance. East Asians are predisposed to development of T2D at a comparatively young age, in part because of an insufficient β-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.

CONFLICT OF INTEREST

LJ has received consulting and lecture fees from Eli Lilly, Bristol-Myers Squibb, Novartis, Novo Nordisk, Merck, Bayer, MSD, Takeda, Sanofi, Roche, Boehinger Ingelheim and AZ; and research grants from Roche and Sanofi, MSD, AstraZeneca and Novartis. JCNC has received research grants and/or honoraria for consultancy or giving lectures from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Eli-Lilly, Merck Serono, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer and Sanofi. MY has received honoraria for speaker engagement from MSD, Novo Nordisk, Sanofi, Eli Lilly, Novartis, Servier and AstraZeneca; has served on Advisory boards for Novo Nordisk, Sanofi, MSD and Novartis; and has received research funding from Novo Nordisk. KHY has served as a consultant for Novo Nordisk and MSD; received honorarium as a speaker from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceutical, MSD, Novo Nordisk, Sanofi and Takeda; and received research support from AstraZeneca and Takeda. SGK received consulting and lecture fees from AstraZeneca, Boehringer Ingelheim, MSD, Pfizer, Takeda, Sanofi and Novo-Nordisk; and received research support from AstraZeneca, Novartis and Abbott. SHC has received research grants from Amgen, LG Pharmaceuticals and Chongundang Pharma. CNH has served as an advisor and/or speaker for AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis and Takeda. STT has served as an advisor and/or speaker for AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Eli Lilly and Company, Mitsubishi Tanabe Pharma Corporation, Novartis Pharmaceuticals, Novo Nordisk and Sanofi-Aventis. CYW has nothing to disclose. PMP was employed by Novartis Pharma AG at the time of initial manuscript preparation. WHHS has served as an advisor and/or speaker for AstraZeneca, Bayer HealthCare, Boehringer Ingelheim Pharmaceuticals, Daiichi-Sankyo, Eli Lilly and Company, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, Novartis Pharmaceuticals, Novo Nordisk, Pfizer, Sanofi-Aventis and Takeda.

AUTHOR CONTRIBUTIONS

All the authors were involved in the conception, drafting and review of the article outline and subsequent drafts. All authors critically reviewed the manuscript and approved the final version for submission.

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REFERENCES

1. International Diabetes Federation. *International Diabetes Federation Atlas*, 9th Edition. 2019https://www.diabetesatlas.org/. Accessed December 4, 2019.
2. Nanditha A, Ma RCW, Ramachandran A, et al. Diabetes in Asia and the Pacific: implications for the global epidemic. *Diabetes Care.* 2016; 39(3):472-485.
3. Hsu WC, Boyko EJ, Fujimoto WY, et al. Pathophysiologic differences among Asians, native Hawaiians, and other Pacific islanders and treatment implications. *Diabetes Care.* 2012;35(5):1189-1198.
4. Kodama K, Tojjar D, Yamada S, Toda K, Patel CJ, Butte AJ. Ethnic differences in the relationship between insulin sensitivity and insulin response. *Diabetes Care.* 2013;36(6):1789-1796.
5. Yabe D, Seino Y. Type 2 diabetes via β-cell dysfunction in east Asian people. *Lancet Diabetes Endocrinol.* 2016;4(1):2-3.
6. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann N Y Acad Sci.* 2013;1281(1):64-91.
7. Chan JCN, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA.* 2009;301(20):2129-2140.
8. Yoon K-H, Lee J-H, Kim J-W, et al. Epidemic obesity and type 2 diabetes in Asia. *Lancet.* 2006;368(9548):1681-1688.
9. Chen Y, Wu F, Saito E, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia cohort consortium. *Diabetologia.* 2017;60(6): 1022-1032.

10. Hsu WC, Araneta MRG, Kanaya AM, Chiang JL, Fujimoto W. BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. *Diabetes Care.* 2015;38(1):150-158.

11. Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr.* 2007;86(2): 353-359.

12. World Health Organization, Regional Office for the Western Pacific. The Asia-Pacific perspective: redefining obesity and its treatment. 2010. https://apps.who.int/iris/handle/10665/206936. Accessed April 12, 2019.

13. Nazare J-A, Smith JD, Borel A-L, et al. Ethnic influences on the relations between abdominal subcutaneous and visceral adiposity, liver fat, and cardiometabolic risk profile: the international study of prediction of intra-abdominal adiposity and its relationship with cardiometabolic risk/intra-abdominal adiposity. *Am J Clin Nutr.* 2012;96 (4):714-726.

14. Azuma K, Kadowaki T, Cetinel C, et al. Higher liver fat content among Japanese in Japan compared with non-Hispanic whites in the United States. *Metabolism.* 2009;58(8):1200-1207.

15. Roh E, Kim KM, Park KS, et al. Comparison of pancreatic volume and fat amount linked with glucose homeostasis between healthy Caucasians and Koreans. *Diabetes Obes Metab.* 2018;20(11):2642-2652.

16. Yabe D, Seino Y, Fukushima M, Seino S. β cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. *Curr Diabetes Rep.* 2015;15(6):602.

17. Yoon KH, Ko SH, Cho JH, et al. Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. *J Clin Endocrinol Metab.* 2003;88(5):2300-2308.

18. Ohn JH, Kwak SH, Cho YM, et al. 10-year trajectory of β-cell function and insulin sensitivity in the development of type 2 diabetes: a community-based prospective cohort study. *Lancet Diabetes Endocrinol.* 2016;4(1):27-34.

19. Qian L, Xu L, Wang X, et al. Early insulin secretion failure leads to diabetes in Chinese subjects with impaired glucose regulation. *Diabetes Metab Res Rev.* 2009;25(2):144-149.

20. Tzeng TF, Chen JH, Hsiao PJ, Hsieh MC, Shin SJ. Insulin action and insulin secretion in newly diagnosed type 2 diabetic patients. *Kaohsiung J Med Sci.* 2001;17(9):468-474.

21. Nakanishi S, Okubo M, Yoneda M, Jitsuiki K, Yamane K, Kohno N. A comparison between Japanese-Americans living in Hawaii and Los Angeles and native Japanese: the impact of lifestyle westernization on diabetes mellitus. *Biomed Pharmacother.* 2004;58(10):571-577.

22. Yeung RO, Zhang Y, Luk A, et al. Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE programme): a cross-sectional study of a prospective cohort. *Lancet Diabetes Endocrinol.* 2014;2(12):935-943.

23. Chan JCN, Lau ESH, Luk AOY, et al. Premature mortality and comorbidities in young-onset diabetes: a 7-year prospective analysis. *Am J Med.* 2014;127(7):616-624.

24. Zoungas S, Woodward M, Li Q, et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia.* 2014; 57(12):2465-2474.

25. Ke C, Lau E, Shah BR, et al. Excess burden of mental illness and hospitalization in young-onset type 2 diabetes: a population-based cohort study. *Ann Intern Med.* 2019;170(3):145-154.

26. Chan JCN, Yeung R, Luk A. The Asian diabetes phenotypes: challenges and opportunities. *Diabetes Res Clin Pract.* 2014;105(1): 135-139.

27. Clarke PM, Glasziou P, Patel A, et al. Event rates, hospital utilization, and costs associated with major complications of diabetes: a multicountry comparative analysis. *PLoS Med.* 2010;7(2): e1000236.

28. Young BA, Katon WJ, Von Korff M, et al. Racial and ethnic differences in microalbuminuria prevalence in a diabetes population: the pathways study. *J Am Soc Nephrol.* 2005;16(1):219-228.

29. Chi ZS, Lee ET, Lu M, Keen H, Bennett PH. Vascular disease prevalence in diabetic patients in China: standardised comparison with the 14 centres in the WHO multinational study of vascular disease in diabetes. *Diabetologia.* 2001;44((Suppl 2)):S82-S86.

30. American Diabetes Association. Introduction: Standards of Medical Care in Diabetes—2020. *Diabetes Care.* 2020;43(Supplement 1):S1-S2.

31. American Association of Clinical Endocrinologists. Comprehensive Type 2 Diabetes Management Algorithm (2019) - Executive Summary. 2019. https://www.aace.com/disease-state-resources/ diabetes/clinical-practice-guidelines-treatment-algorithms/ comprehensive. Accessed February 14, 2020.

32. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2018;41(12):2669-2701.

33. Jia W, Weng J, Zhu D, et al. Standards of medical care for type 2 diabetes in China 2019. *Diabetes Metab Res Rev.* 2019;e3158.

34. Diabetes Association of the Republic of China (Taiwan). Executive summary of the DAROC Clinical Practice Guidelines for Diabetes Care - 2018. *J Formos Med Assoc.* 2019;119(2):577–586.

35. Haneda M, Noda M, Origasa H, et al. Japanese Clinical Practice guidelines for Diabetes 2016. *J Diabetes Investig.* 2018;9(3):657-697.

36. Kim MK, Ko S-H, Kim B-Y, et al. 2019 clinical practice guidelines for type 2 diabetes mellitus in Korea. *Diabetes Metab J.* 2019;43(4): 398-406.

37. Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care Settings. 2018. https://www.fhb.gov.hk/pho/english/ resource/files/RF_DM_full.pdf.

38. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J.* 2020;41(2):255-323.

39. Khunti S, Khunti K, Seidu S. Therapeutic inertia in type 2 diabetes: prevalence, causes, consequences and methods to overcome inertia. *Ther Adv Endocrinol Metab.* 2019;10:204201881984469.

40. Cersosimo E, Johnson EL, Chovanes C, Skolnik N. Initiating therapy in patients newly diagnosed with type 2 diabetes: combination therapy vs a stepwise approach. *Diabetes Obes Metab.* 2018;20(3):497-507.

41. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2020. *Diabetes Care.* 2020;43(Supplement 1):S98-S110.

42. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia.* 2020;63(2): 221-228.

43. Cai X, Gao X, Yang W, Han X, Ji L. Efficacy and safety of initial combination therapy in treatment-naïve type 2 diabetes patients: a systematic review and meta-analysis. *Diabetes Ther.* 2018;9(5):1995-2014.

44. Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. *Diabetes Obes Metab.* 2014;16(5):410-417.

45. Cai X, Hu D, Pan C, et al. Evaluation of effectiveness of treatment paradigm for newly diagnosed type 2 diabetes patients in Chin: a nationwide prospective cohort study. *J Diabetes Investig.* 2019;11(1):151–161.

46. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015;38(1):140-149.

47. Williams-Herman D, Johnson J, Teng R, et al. Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. *Diabetes Obes Metab.* 2010;12(5):442-451.

48. Jadzinsky M, Pfützner A, Paz-Pacheco E, et al. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes Obes Metab.* 2009; 11(6):611-622.

49. Paneni F, Lüscher TF. Cardiovascular protection in the treatment of type 2 diabetes: a review of clinical trial results across drug classes. *Am J Med.* 2017;130(6S):S18-S29.

50. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2020 executive summary. *Endocr Pract.* 2020;26(1):107-139.

51. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia.* 2017;60(9):1620-1629.

52. Garber AJ, Donovan DS, Dandona P, Bruce S, Park J-S. Efficacy of glyburide/metformin tablets compared with initial monotherapy in type 2 diabetes. *J Clin Endocrinol Metab.* 2003;88(8):3598-3604.

53. Boughton CK, Munro N, Whyte M. Targeting beta-cell preservation in the management of type 2 diabetes. *Br J Diabetes.* 2017;17(4):134-144.

54. Page KA, Reisman T. Interventions to preserve beta-cell function in the management and prevention of type 2 diabetes. *Curr Diab Rep.* 2013;13(2):252-260.

55. Milder TY, Stocker SL, Abdel Shaheed C, et al. Combination therapy with an SGLT2 inhibitor as initial treatment for type 2 diabetes: a systematic review and meta-analysis. *J Clin Med.* 2019;8(1):45

56. Derosa G, Franzetti IG, Querci F, et al. Exenatide plus metformin compared with metformin alone on β-cell function in patients with type 2 diabetes. *Diabet Med.* 2012;29(12):1515-1523.

57. Bunck MC, Cornér A, Eliasson B, et al. Effects of exenatide on measures of β-cell function after 3 years in metformin-treated patients with type 2 diabetes. *Diabetes Care.* 2011;34(9):2041-2047.

58. Mikhail N. Combination therapy with DPP-4 inhibitors and pioglitazone in type 2 diabetes: theoretical consideration and therapeutic potential. *Vasc Health Risk Manag.* 2008;4(6):1221-1227.

59. Leibowitz G, Cahn A, Bhatt DL, et al. Impact of treatment with saxagliptin on glycaemic stability and β-cell function in the SAVOR-TIMI 53 study. *Diabetes Obes Metab.* 2015;17(5):487-494.

60. Tatsumi F, Hashiramoto M, Hirukawa H, et al. Concomitant use of miglitol and mitiglinide as initial combination therapy in type 2 diabetes mellitus. *Diabetes Res Clin Pract.* 2013;101(1):35-44.

61. Chou HS, Palmer JP, Jones AR, et al. Initial treatment with fixed-dose combination rosiglitazone/glimepiride in patients with previously untreated type 2 diabetes. *Diabetes Obes Metab.* 2008;10(8):626-637.

62. Mikada A, Narita T, Yokoyama H, et al. Effects of miglitol, sitagliptin, and initial combination therapy with both on plasma incretin responses to a mixed meal and visceral fat in over-weight Japanese patients with type 2 diabetes: "the MASTER randomized, controlled trial.". *Diabetes Res Clin Pract.* 2014;106(3):538-547.

63. Wang W, Ning G, Ma J, et al. A randomized clinical trial of the safety and efficacy of sitagliptin in patients with type 2 diabetes mellitus inadequately controlled by acarbose alone. *Curr Med Res Opin.* 2017; 33(4):693-699.

64. Min SH, Yoon J, Hahn S, Cho YM. Efficacy and safety of combination therapy with an α-glucosidase inhibitor and a dipeptidyl peptidase-4 inhibitor in patients with type 2 diabetes mellitus: a systematic review with meta-analysis. *J Diabetes Investig.* 2018;9(4):893-902.

65. Lewin A, DeFronzo RA, Patel S, et al. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. *Diabetes Care.* 2015;38(3):394-402.

66. Ekholm E, Hansen L, Johnsson E, et al. Combined treatment with saxagliptin plus dapagliflozin reduces insulin levels by increased insulin clearance and improves β-cell function. *Endocr Pract.* 2017;23(3): 258-265.

67. Molina-Vega M, Muñoz-Garach A, Fernández-García JC, Tinahones FJ. The safety of DPP-4 inhibitor and SGLT2 inhibitor combination therapies. *Expert Opin Drug Saf.* 2018;17(8):815-824.

68. Cho YK, Kang YM, Lee SE, et al. Efficacy and safety of combination therapy with SGLT2 and DPP4 inhibitors in the treatment of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Metab.* 2018;44(5):393-401.

69. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the efficacy and durability of initial combination therapy for type 2 diabetes (EDICT): a randomized trial. *Diabetes Obes Metab.* 2015;17(3):268-275.

70. Lim S, Ku EJ, Lee SY, et al. Therapeutic efficacy and safety of initial triple combination of metformin, sitagliptin, and lobeglitazone in drug-naïve patients with type 2 diabetes: initial triple study. *BMJ Open Diabetes Res Care.* 2020;8(1):e000807.

71. Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. *Diabetes Care.* 2016;39(Supplement 2):S137-S145.

72. Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the diabetes & aging study). *Diabetes Care.* 2019;42(3):416-426.

73. Chin KL, Ofori-Asenso R, Si S, et al. Cost-effectiveness of first-line versus delayed use of combination dapagliflozin and metformin in patients with type 2 diabetes. *Sci Rep.* 2019;9(1):3256.

74. Chen H-S, Wu T-E, Jap T-S, Hsiao L-C, Lee S-H, Lin H-D. Beneficial effects of insulin on glycemic control and β-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. *Diabetes Care.* 2008;31(10):1927-1932.

75. Diabetes Fact Sheet in Korea 2018.

76. Ji L, Hu D, Pan C, et al. Primacy of the 3B approach to control risk factors for cardiovascular disease in type 2 diabetes patients. *Am J Med.* 2013;126(10):925.e11-e22.

77. Luk AOY, Hui EMT, Sin M-C, et al. Declining trends of cardiovascular-renal complications and mortality in type 2 diabetes: the Hong Kong diabetes database. *Diabetes Care.* 2017;40(7):928-935.

78. Wang C, Tu S-T, Sheu WH-H, et al. National survey of ABC (A1C, blood pressure, cholesterol) of diabetes health promotion institutes in Taiwan: 2002-2018. *J Formos Med Assoc.* 2018;117 (11):952-954.

79. Kim BY, Won JC, Lee JH, et al. Diabetes fact sheets in Korea, 2018: an appraisal of current status. *Diabetes Metab J.* 2019;43(4):487-494.

80. Yokoyama H, Oishi M, Takamura H, et al. Large-scale survey of rates of achieving targets for blood glucose, blood pressure, and lipids and prevalence of complications in type 2 diabetes (JDDM 40). *BMJ Open Diabetes Res Care.* 2016;4(1):e000294.

81. Carls G, Huynh J, Tuttle E, Yee J, Edelman SV. Achievement of glycated hemoglobin goals in the US remains unchanged through 2014. *Diabetes Ther.* 2017;8(4):863-873.

82. de Pablos-Velasco P, Parhofer KG, Bradley C, et al. Current level of glycaemic control and its associated factors in patients with type 2 diabetes across Europe: data from the PANORAMA study. *Clin Endocrinol.* 2014;80(1):47-56.

83. Mitrakou A, Kelley D, Mokan M, et al. Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med.* 1992;326 (1):22-29.

84. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes

(UKPDS 35): prospective observational study. *BMJ.* 2000;321(7258): 405-412.

85. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006;355(23):2427-2443.

86. Cherukuri L, Smith MS, Tayek JA. The durability of oral diabetic medications: time to A1c baseline and a review of common oral medications used by the primary care provider. *Endocrinol Diabetes Metab J.* 2018;2(3).

87. Philis-Tsimikas A, Wysham CH, Hardy E, Han J, Iqbal N. Efficacy and tolerability of exenatide once weekly over 7 years in patients with type 2 diabetes: an open-label extension of the DURATION-1 study. *J Diabetes Complications.* 2019;33(3):223-230.

88. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Prato SD. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. *Lancet.* 2019;394 (10208):1519–1529.

89. Kim NH, Lim S, Kwak SH, et al. Efficacy and tolerability of novel triple combination therapy in drug-naïve patients with type 2 diabetes from the TRIPLE-AXEL trial: protocol for an open-label randomised controlled trial. *BMJ Open.* 2018;8(9):e022448.

90. Rosenblatt S, Miskin B, Glazer NB, Prince MJ, Robertson KE, Pioglitazone 026 Study Group. The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. *Coron Artery Dis.* 2001;12(5):413-423.

91. Wu S, Gao L, Cipriani A, et al. The effects of incretin-based therapies on β-cell function and insulin resistance in type 2 diabetes: a systematic review and network meta-analysis combining 360 trials. *Diabetes Obes Metab.* 2018;975-983.

92. Heise T, Larbig M, Patel S, et al. The dipeptidyl peptidase-4 inhibitor linagliptin lowers postprandial glucose and improves measures of β-cell function in type 2 diabetes. *Diabetes Obes Metab.* 2014;16 (10):1036-1039.

93. Foley JE, Bunck MC, Möller-Goede DL, et al. Beta cell function following 1 year vildagliptin or placebo treatment and after 12 week washout in drug-naive patients with type 2 diabetes and mild hyperglycaemia: a randomised controlled trial. *Diabetologia.* 2011;54(8):1985-1991.

94. Al Jobori H, Daniele G, Adams J, et al. Empagliflozin treatment is associated with improved β-cell function in type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2018;103(4):1402-1407.

95. Kaneto H, Obata A, Kimura T, et al. Beneficial effects of sodium-glucose cotransporter 2 inhibitors for preservation of pancreatic β-cell function and reduction of insulin resistance. *J Diabetes.* 2017;9(3):219-225.

96. Miyazaki Y, Mahankali A, Matsuda M, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab.* 2002;87(6):2784-2791.

97. Ko KD, Kim KK, Lee KR. Does weight gain associated with thiazolidinedione use negatively affect cardiometabolic health? *J Obes Metab Syndr.* 2017;26(2):102-106.

98. Bolinder J, Ljunggren Ö, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab.* 2014;16(2):159-169.

99. Fujita Y, Kubota S, Kuwata H, Yabe D, Hamamoto Y, Seino Y. Glucagon-like peptide-1 receptor agonists predominantly reduce body fat mass in patients with type 2 diabetes. *Diabetes.* 2019;68(Supplement 1):1019–P.

100. Ametov AS, Gusenbekova DG. DPP-4 inhibitors and fat metabolism in patients with type 2 diabetes. *Diabetes and Its Complications.* London, United Kingdom: IntechOpen; 2017.

101. Kim KJ, Choi JH, Kim KJ, et al. Determinants of long-term durable glycemic control in new-onset type 2 diabetes mellitus. *Diabetes Metab J.* 2017;41(4):284-295.

102. Leiter LA. Latest evidence on sulfonylureas: What's new? *Diabetes Ther.* 2020;11(1):15-22.

103. Ji L, Han P, Wang X, et al. Randomized clinical trial of the safety and efficacy of sitagliptin and metformin co-administered to Chinese patients with type 2 diabetes mellitus. *J Diabetes Investig.* 2016;7(5): 727-736.

104. Mu Y, Pan C, Fan B, et al. Efficacy and safety of linagliptin/metformin single-pill combination as initial therapy in drug-naïve Asian patients with type 2 diabetes. *Diabetes Res Clin Pract.* 2017;124:48-56.

105. Dou J, Ma J, Liu J, et al. Efficacy and safety of saxagliptin in combination with metformin as initial therapy in Chinese patients with type 2 diabetes: results from the START study, a multicentre, randomized, double-blind, active-controlled, phase 3 trial. *Diabetes Obes Metab.* 2018;20(3):590-598.

106. Ji L, Li L, Kuang J, et al. Efficacy and safety of fixed-dose combination therapy, alogliptin plus metformin, in Asian patients with type 2 diabetes: a phase 3 trial. *Diabetes Obes Metab.* 2017;19(5):754-758.

107. Hadjadj S, Rosenstock J, Meinicke T, Woerle HJ, Broedl UC. Initial combination of empagliflozin and metformin in patients with type 2 diabetes. *Diabetes Care.* 2016;39(10):1718-1728.

108. Yoon KH, Jimeno C, Marcelo MC, et al. Baseline characteristics of Asians in the VERIFY study. *International Diabetes Federation Congress.* 2019.

109. Del Prato S, Foley JE, Kothny W, et al. Study to determine the durability of glycaemic control with early treatment with a vildagliptin-metformin combination regimen vs. standard-of-care metformin monotherapy-the VERIFY trial: a randomized double-blind trial. *Diabetes Med J Br Diabetes Assoc.* 2014;31(10):1178-1184.

110. Chan JC, Paldánius PM, Mathieu C, Stumvoll M, Del Prato DR. The characteristics and clinical responses of newly-diagnosed adults with young-onset diabetes in the VERIFY study. *International Diabetes Federation Congress.* 2019.

111. Nathan DM, Buse JB, Kahn SE, et al. Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). *Diabetes Care.* 2013;36(8):2254-2261.

112. McGill M, Blonde L, Chan JCN, Khunti K, Lavalle FJ, Bailey CJ. The interdisciplinary team in type 2 diabetes management: challenges and best practice solutions from real-world scenarios. *J Clin Transl Endocrinol.* 2016;7:21-27.

113. Lim LL, Lau ESH, Kong APS, et al. Aspects of multicomponent integrated care promote sustained improvement in surrogate clinical outcomes: a systematic review and meta-analysis. *Diabetes Care.* 2018;41(6):1312-1320.

114. Chan JC, So W-Y, Yeung C-Y, et al. Effects of structured versus usual care on renal endpoint in type 2 diabetes: the SURE study: a randomized multicenter translational study. *Diabetes Care.* 2009;32 (6):977-982.

115. Chan JCN, Lim L-L, Luk AOY, et al. From Hong Kong diabetes register to JADE program to RAMP-DM for data-driven actions. *Diabetes Care.* 2019;42(11):2022-2031.

116. Lee I-T, Hsu C-C, Sheu WH-H, Su S-L, Wu Y-L, Lin S-Y. Pay-for-performance for shared care of diabetes in Taiwan. *J Formos Med Assoc.* 2019;118:S122-S129.