Place of sodium-glucose cotransporter-2 inhibitors in East Asian subjects with type 2 diabetes mellitus: Insights into the management of Asian phenotype

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ABSTRACT

The burden of type 2 diabetes (T2DM) in East Asia is alarming. Rapid modernization and urbanization have led to major lifestyle changes and a tremendous increase in the prevalence of obesity, metabolic syndrome, and diabetes mellitus. The development of T2DM at a younger age, with lower body mass index, higher visceral adiposity, and more significant pancreatic beta-cell dysfunction compared to Caucasians are factors responsible for the increased prevalence of T2DM in East Asians. Sodium-glucose Cotransporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, etc.) reduce renal glucose reabsorption, leading to favorable effects on glycemic, blood pressure, and weight control. The insulin-independent mechanism enables their use as monotherapy or combination therapy with insulin and other oral antidiabetic agents. The role of SGLT2 inhibitors in the management of T2DM among East Asians is an interesting area of research, given that East Asians have been proven to be uniquely different from Caucasians. This review provides comprehensive coverage of the available literature not only on the efficacy and safety, but also on the recent cardiovascular and renal outcomes of SGLT2 inhibitors, focusing among East Asians.

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1. Introduction

There has been an alarming rise in the global prevalence of diabetes, with more than 415 million people afflicted by it worldwide in 2015. This number is expected to increase further to 642 million by 2040. Diabetes has imposed an enormous financial burden on countries and their health systems due to the increased utilization of healthcare services, decrease in productivity, and increased need for long-term management of complications. In the majority of countries, nearly 5% to 20% of total health expenditure is on diabetes, with subsequent impedance on sustainable economic development.

2. Rising diabetes prevalence in East Asia

Currently, Asia is undergoing rapid modernization and urbanization, leading to major lifestyle changes and a substantial increase in the prevalence of obesity, metabolic syndrome, and T2DM (Kong et al., 2013). China, with 113.9 million and 493.4 million adults suffering from diabetes and prediabetes respectively, has emerged to be the country with largest number of affected patients worldwide (Diabetes Atlas, 2015; Xu et al., 2013). (See Table 1) A nationwide survey in China conducted in 1994 reported the prevalence of diabetes to be 2.5% (Pan, Yang, Li, & Liu, 1997). A decade later, this had rapidly increased by four-fold, with the diabetes prevalence estimated at 9.7% and 11.6% in 2008 and 2010 respectively (Xu et al., 2013; Yang et al., 2010).

3. Clinical phenotypes of T2DM: a comparison between Asians and Caucasians

Several biological differences have been identified between Asians and Caucasians that render Asians more vulnerable to T2DM in the presence of external stressors. Several Asian phenotypes pose an elevated risk of adverse T2DM outcomes (Chan, Yeung, & Luk, 2014):

• Low body mass index (BMI)
• Increased visceral fat
• Insufficient beta-cell response to counter insulin resistance
• High rates of central obesity and metabolic syndrome
• High rates of childhood obesity, gestational diabetes, and renal disease
• High rate of young-onset T2DM
• High rate of cancer, especially those with viral causes, e.g. liver cancer
• Increased inflammatory markers
• Low rate of autoimmune type 1 diabetes
• Social disparity and psychosocial stress

3.1. Body mass index and visceral adiposity

The occurrence of T2DM at a lower mean BMI in East Asians is one of the most striking observations across studies (Ma & Chan, 2013; Sone, 2015). In a large multiethnic cohort study, for an equivalent incidence rate of diabetes at a BMI of 30.0 kg/m² in Caucasians, the corresponding cut-off values were 24.0 kg/m², 25.0 kg/m², and 26.0 kg/m² in South Asian, Chinese, and Black subjects respectively (Chiu, Austin, Manuel, Shah, & Tu, 2011). The pooled data analysis from the Asian Cohort Consortium demonstrated a U-shaped association between BMI and cardiovascular (CV) death among East Asians, with an increased risk in the BMI categories of <17.5 kg/m² and ≥25.0 kg/m² (Chen et al., 2013).

The Obesity in Asia Collaboration, involving 263,000 subjects, reported that visceral adiposity is a strong predictor of T2DM and CV disease, independent of BMI, in both East Asians and Europeans (Huxley et al., 2008). Visceral fat, which can be assessed by waist circumference (WC) in the clinical setting, produces adipokines and cytokines that lead to proinflammatory, procoagulant, and insulin-resistant states (Donohoe, Doyle, & Reynolds, 2011; Huxley et al., 2008). For a given BMI, the body fat percent (BF%) in Asians was found to be 3%–5% higher than that in Caucasians, which can be explained by a lower lean muscle mass and higher visceral fat mass (Deurenberg, Deurenberg-Yap, & Guricci, 2002; Huxley et al., 2008). Interestingly, the absolute risk of T2DM in both genders was consistently greater among Asians compared to Caucasians at any given BMI and WC. For instance, at a BMI of 24 kg/m², the prevalence of T2DM among males was 5% and 2% in Asians and Caucasians respectively. The corresponding prevalence among females was 5% and 1% respectively (Huxley et al., 2008).

A World Health Organization (WHO) expert consultation concluded that Asians have different associations between BMI, BF%, and health risks compared to Caucasians (WHO Expert Consultation, 2004). Hence, the BMI cut-point for overweight among Asians is lower, at 23.0 kg/m² as compared to 25.0 kg/m² for Caucasians (Huxley et al., 2008; WHO Expert Consultation, 2004).

3.2. Insulin secretion and resistance

Insulin resistance (IR) and impaired insulin secretion are important characteristics of T2DM. A cross-sectional study among Japanese T2DM subjects exhibited a larger reduction in insulin secretion and a lower propensity for IR (Fukushima et al., 2004). This association was further confirmed by a recent meta-analysis that measured the insulin sensitivity index and acute insulin response to glucose in three major ethnic groups: Africans, Caucasians, and East Asians. East Asians demonstrated a limited insulin-secreting capacity and lower IR compared to Caucasians and Africans (Kodama et al., 2013). Although East Asians have lower IR, they have greater amounts of visceral fat. A minor increase in IR as sequelae of visceral adiposity can lead to decreased insulin-secretory capacity in East Asians (Yabe, Seino, Fukushima, & Seino, 2015).

3.3. Young-onset T2DM (YOD)

T2DM in Asians is characterized by a younger age of onset compared to Caucasians (Ma & Chan, 2013). The prevalence of diabetes among adults aged 18–44 years in the United States was 13.0%, based on the National Health and Nutrition Examination Survey (NHANES) data (Ali et al., 2013). In contrast, a large Asian T2DM registry reported that as high as one in five adults was diagnosed with T2DM before the age of 40 years old (Yeung et al., 2014). Poorer metabolic control, less adherence to self-care, early insulinization, delayed initiation of cardio-renal protective agents, and lower attainment of treatment targets were the main characteristics of these patients (Chan et al., 2014; Yeung et al., 2014). Moreover, adults with YOD, driven by a longer disease span and prolonged exposure to glucolipotoxicity, were more vulnerable to both cardiovascular and renal complications (Chan et al., 2014; Pavkov, Hanson, Knowler, et al., 2010).

These features pose significant challenges in managing Asians with YOD. Furthermore, young working adults face additional issues in managing diabetes, including acceptance of insulin therapy, complexity of treatment regimen, adherence to blood glucose monitoring, job stress, social stigma, and risk of hypoglycemia at work, etc. (Rusten, Smith, & Fernando, 2013). Thus, antidiabetic agents with sustained glycemic effect, lower rate of hypoglycemia, and ease of administration are particularly useful in them.

3.4. Beta-cell dysfunction

T2DM in East Asians is characterized primarily by beta-cell dysfunction. Lower basal beta-cell function was observed more in Japanese compared to Caucasians (Møller, Dalla Man, et al., 2014). The key determinants of differences in beta-cell response and insulin sensitivity were found to be BMI, WC, android fat, and body weight (Møller, Pedersen, et al., 2014). In the Korean Genome and Epidemiology study involving 4106 participants with normal glucose tolerance (NGT), individuals who progressed to T2DM during 10-year follow-up had a lower 60-min insulinenic index at baseline compared to those who remained NGT. This suggested that decreased beta-cell function and impaired beta-cell compensation for progressive decline in insulin sensitivity play a vital role in the deterioration of glucose tolerance (Ohn et al., 2016).

3.5. Micro- and macrovascular complications

The early onset of T2DM in East Asians increases the risk of micro- and macrovascular complications due to genetic predisposition, longer disease duration, and greater tendency to beta-cell failure (Ma & Chan, 2013). In the WHO Multinational Study of Vascular Disease in Diabetes (WHO MSVDD), American Indians showed an increased incidence of lower-extremity amputation, renal failure, retinopathy, clinical proteinuria, and albuminuria compared to the Caucasians and Asian cohorts (Lee, Lu, Bennett, & Keen, 2001). When vascular complications in Chinese T2DM subjects were compared to cohorts of WHO MSVDD, rates of proteinuria and retinopathy were significantly higher, and large-vessel disease was less frequent among the Chinese (Chi, Lee, Lu, Keen, & Bennett, 2001). The Action in Diabetes and Vascular Disease (ADVANCE) study recorded the incidence of diabetes-related complications in three regions; the incidences of renal complications and ischemic stroke were greater in Asians, with a lower incidence of coronary heart disease (CHD) and peripheral vascular disease compared to subjects in Eastern Europe and established market economies (Clarke et al., 2010). In an 11-year follow-up study of individuals with diabetes in the United Kingdom, South Asians were more likely to report a history of myocardial infarction than Europeans, suggesting a markedly increased risk of CV disease in the former, especially among younger individuals (Mather, Chaturvedi, & Fuller, 1998).

4. SGLT2 inhibitors in T2DM management in East Asians

Sodium-glucose Cotransport-2 (SGLT2) inhibition is a rational approach in T2DM management. SGLT2 inhibitors are a group of oral glucose-lowering agents that prevent renal glucose reuptake, with an
additional weight-loss benefit. Sodium-glucose Cotransporters are a large group of membrane proteins that facilitate the transport of glucose across the intestinal epithelium and proximal renal tubules by means of the electrochemical sodium gradient as the source of energy generated by Na+/K+ - adenosine triphosphatase. While SGLT1, a high-affinity, low-capacity transporter is expressed in the small intestine; SGLT2, a low-affinity, high-capacity transporter is expressed in the proximal renal tubules. In a normal physiological state, SGLT2 and SGLT1 account for 90% and 10% of the renal glucose reabsorption respectively (Fugita & Inagaki, 2014). Evidence has suggested that renal glucose reabsorption is increased as a result of SGLT2 and glucose transport 2 (GLUT2) overexpression among T2D patients (Meyer et al., 1998; Rahmoune et al., 2005).

With SGLT2 inhibition, the renal glucose excretion threshold is lowered, and glycosuria increases. Therefore, chronic use of SGLT2 inhibitors has the potential to decrease glucotoxicity (Fioretto, Giaccari, & Sesti, 2015, NCT02338921). Evidence indicates that glucocalyx caused by SGLT2 inhibitors improves both beta-cell function and peripheral insulin sensitivity, with subsequent reduction in plasma glucose levels. (Ferrannini et al., 2014; Merovci et al., 2015).

Furthermore, SGLT2 inhibitors have shown promising effects in promoting weight loss and bringing about a modest reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP). The combined effects of SGLT2 inhibitors on hyperglycemia, body weight, and BP suggest a favorable impact on CV risk factors (Araki et al., 2016).

A number of oral SGLT2 inhibitors have been developed; which include canagliflozin, dapagliflozin, empagliflozin,ertugliflozin, ipragliflozin, luseogliflozin, tofogliflozin, etc. (Haas, Eckstein, Pfeifer, Mayer, & Hass, 2014, NCT01958671). Canagliflozin, dapagliflozin, and empagliflozin have been approved for use in the Unites States (US Food and Drug Administration, 2016) and the European Union (EU) (European Medicine Agency, 2016); whilst ipragliflozin, luseogliflozin, and tofogliflozin have been approved for use in Japan (Pharmaceuticals and Medical Devices Agency, Japan, 2016). Several other drugs are in different stages of development and approval (European Medicine Agency, 2016; Pharmaceuticals and Medical Devices Agency, Japan, 2016; US Food and Drug Administration, 2016).

5. Clinical trials of SGLT2 inhibitors

A number of randomized, double-blind, placebo-controlled studies in subjects with T2DM have evaluated the efficacy of SGLT2 inhibitors among East Asians. Glycemic efficacy data from key studies of SGLT2 inhibitors either as monotherapy or as add-on/combo therapy are presented in Table 2.

5.1. Glycemic control

Although different glucose-lowering agents have varying effects in Caucasians and East Asians, SGLT2 inhibitors have demonstrated similar HbA1c lowering effects, independent of ethnicity (Table 2) . The change in HbA1c levels with SGLT2 inhibitors in Caucasians was 0.58%–1.03% from baseline (Fugita & Inagaki, 2014). Among East Asians, different clinical responses were observed with different SGLT2 inhibitors. Dapagliflozin (5 mg and 10 mg) was associated with a significant reduction in HbA1c as monotherapy after 12 weeks (Kaku et al., 2013) and 24 weeks (Ji et al., 2014; Kaku, Kiyosue, et al., 2014); it was also effective as add-on therapy to metformin (Yang et al., 2016), insulin (Araki et al., 2016), SU, glinides, AGI, DPP-4 inhibitors, TZD, or GLP-1 receptor antagonists (Kaku, Maegawa, et al., 2014).

As monotherapy, dapagliflozin has demonstrated long-term benefits in the treatment-naïve T2DM population compared to placebo with low-dose metformin. In this 102-week trial, significant reductions in HbA1c were demonstrated with dapagliflozin 5 mg (−0.53%) and 10 mg (−0.44%) (Bailey et al., 2015, NCT00736879). As an add-on therapy to metformin, the HbA1c reduction was −0.82% with dapagliflozin 10 mg among Chinese with uncontrolled T2DM (Yang et al., 2016). This was comparable to the results in a 102-week study by Bailey et al. (−0.78%) that recruited patients from 80 sites in Argentina, Brazil, Canada, Mexico, and the United States (Bailey et al., 2013, NCT00528879). Dapagliflozin has demonstrated sustained glycemic efficacy compared to glipizide over 2 years (Nauck et al., 2014, NCT00660907) and 4 years (Del Prato et al., 2015) after metformin failure. In both of these long-term studies, dapagliflozin was associated with lower rates of hypoglycemia, and showed greater reductions in body weight and SBP compared to glipizide (Del et al., 2015; Nauck et al., 2014). As an add-on to insulin, dapagliflozin demonstrated an HbA1c reduction of −0.6% in East Asians, after 16 weeks (Araki et al., 2016). This was similar to the reduction obtained in a study by Wilding et al. (2012) that included 800 patients from Europe and North America. After 24 weeks, the HbA1c reductions, with sustained effect till 48 weeks, with dapagliflozin 5 mg and dapagliflozin 10 mg were −0.49% and −0.57% respectively. The reduction in the mean daily insulin dose was 0.72 IU/day among Japanese and 6.28 IU/day among Caucasians (Araki et al., 2016, Wilding et al., 2012, NCT00673231).

Table 1


<table>
<thead>
<tr>
<th>Country</th>
<th>Diabetes prevalence (%)</th>
<th>Diabetes-related deaths</th>
<th>Mean diabetes-related expenditure per person with diabetes (USD)</th>
<th>Number of cases of diabetes in adults that are undiagnosed (1000 s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>10.6</td>
<td>1,299,670.8</td>
<td>466</td>
<td>57,813.6</td>
</tr>
<tr>
<td>India</td>
<td>8.7</td>
<td>1,027,911.6</td>
<td>94.9</td>
<td>36,061.1</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>14.6</td>
<td>1384.8</td>
<td>215.9</td>
<td>387.2</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>17.6</td>
<td>23,420.8</td>
<td>1145.3</td>
<td>1244.3</td>
</tr>
<tr>
<td>Hong Konga</td>
<td>10.2</td>
<td>–</td>
<td>–</td>
<td>273.8</td>
</tr>
<tr>
<td>Macau*</td>
<td>8.5</td>
<td>–</td>
<td>–</td>
<td>18.6</td>
</tr>
<tr>
<td>Japan</td>
<td>7.6</td>
<td>61,076.0</td>
<td>4084.5</td>
<td>3353.8</td>
</tr>
<tr>
<td>Dem. People’s Republic of Korea*</td>
<td>4.7</td>
<td>19,466.3</td>
<td>–</td>
<td>514.2</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>8.7</td>
<td>31,898.3</td>
<td>2294.2</td>
<td>1559.0</td>
</tr>
<tr>
<td>Mongolia</td>
<td>5.1</td>
<td>2254.4</td>
<td>368.7</td>
<td>50.3</td>
</tr>
<tr>
<td>Taiwan</td>
<td>10.0</td>
<td>–</td>
<td>–</td>
<td>828.3</td>
</tr>
<tr>
<td>USA</td>
<td>12.8</td>
<td>219,413.2</td>
<td>10,941.7</td>
<td>8284.6</td>
</tr>
<tr>
<td>UK</td>
<td>6.2</td>
<td>22,778.4</td>
<td>4372.9</td>
<td>1068.9</td>
</tr>
<tr>
<td>World</td>
<td>8.8</td>
<td>4,960,535.8</td>
<td>1622.1</td>
<td>192,797.8</td>
</tr>
</tbody>
</table>

Adapted from Diabetes Atlas (2015).

* Adult diabetes estimate based on extrapolation of data from similar country.
Canagliflozin was associated with a significant reduction in HbA1c as monotherapy (Inagaki et al., 2014) and as add-on therapy (Kashiwagi et al., 2015) to SU, glinide, AGI biguanide, TZD, or DPP-4i. The greatest benefit was observed with canagliflozin 200 mg as add-on therapy to DPP-4 inhibitors (Kashiwagi et al., 2015). The long-term efficacy of canagliflozin monotherapy has been demonstrated in a 52-week (Stenlöf et al., 2014, NCT01081834) and a 104-week study (Bode et al., 2015, NCT01106651) (patients aged 55–80 years) among T2DM patients. Canagliflozin was generally well tolerated and associated with a sustained reduction in glycemic control and body weight over 52 weeks and 104 weeks (Stenlöf et al., 2014, Bode et al., 2015).

Empagliflozin was associated with a significant reduction in HbA1c as monotherapy across all doses in a 12-week phase II study (Kadowaki et al., 2014); it was also associated with a clinically meaningful reduction in HbA1c (−0.77% to −1.00%) as add-on therapy (Araki et al., 2015). The benefits of glycemic control with SGLT2 inhibitors extended to subjects with mild renal impairment (RI). In the LANTERN trial, ipragliflozin decreased HbA1c and FPG significantly in subjects with mild RI after 24 weeks, although similar benefits were not observed in patients with moderate RI (estimated glomerular filtration rate [eGFR] 30–59 ml/min/1.73 m²) (Kashiwagi et al., 2015). In a recent pooled data analysis of 1326 Asians with T2D, empagliflozin (10 and 25 mg) led to a significant reduction in HbA1c (−0.66%, −0.73%), body weight (−1.6 kg, −1.8 kg), and SBP (−3.5 mmHg, −3.9 mmHg) respectively after 24-weeks of intervention (Yoon et al., 2016).

### 5.2. Effects on body weight, blood pressure, and lipid parameters

SGLT2 inhibitors are associated with a clinically significant weight reduction that can be attributed to glycosuria-induced osmotic diuresis (Fugita & Inagaki, 2014) and, more importantly among Asians, a reduction in visceral adiposity achieved within the first six months of therapy (Bolinder et al., 2012, NCT00855166). In Caucasians, a weight reduction of 2.2–3.4 kg was demonstrated (Fugita & Inagaki, 2014). In a meta-analysis of six studies, SGLT2 inhibitors were associated with a significant body weight reduction ([weighted mean difference [WMD] −1.80 kg, 95% CI −3.5 to −0.11; I² = 97%; five trials] (Vasilakou et al., 2013).

Dapagliflozin, as add-on therapy to metformin, was associated with significant body weight reductions at both 5 mg and 10 mg doses among East Asians (Yang et al., 2016). In a European multicenter study, dapagliflozin 10 mg in addition to metformin was associated with a sustained weight reduction (−4.54 kg) over 102 weeks (Bolinder et al., 2014, NCT00855166).

Canagliflozin (100 and 200 mg) was also associated with a marked weight reduction, both as monotherapy and as add-on therapy (Inagaki et al., 2014, 2015). In a 52-week open-label study, the weight reduction was apparent even in subjects treated with SU and TZD, which are known for associated weight gain, although the magnitude of reduction was lesser compared to other groups (Inagaki et al., 2015).

A clinically relevant lowering of SBP and DBP was demonstrated with SGLT2 inhibitors in a few studies among East Asians (Table 2) (Inagaki et al., 2014; Kadowaki et al., 2014). In a meta-analysis of six studies, SGLT2 inhibitors were associated with a reduction in SBP compared to other anti-diabetic agents, with a mean difference of −4.45 mmHg (Vasilakou et al., 2013). Empagliflozin was particularly associated with a sustained reduction in SBP and DBP, both as monotherapy (Kadowaki et al., 2015) (SBP: −2.9 ± 1.7 mmHg and −2.5 ± 1.8 mmHg; DBP: −2.9 ± 1.0 mmHg and −2.0 ± 1.1 mmHg with 10 mg and 25 mg respectively) and as add-on therapy (Araki et al., 2015) (SBP range: −4.5 ± 1.3 to −7.4 ± 1.0 mmHg; DBP range: −2.3 ± 0.7 to −3.6 ± 0.8 mmHg) among East Asians.

SGLT2 inhibitors have been shown to ameliorate some of the lipid parameters in East Asians. In the Japanese study, dapagliflozin 5 mg and 10 mg were respectively associated with mean percent changes of −2.66% and −2.28% in total cholesterol (TC); −19.11% and −16.47% in TG; and +9.55% and +11.52% in HDL-C (Ji et al., 2014). In a post-hoc analysis of Phase 3 placebo-controlled trials (n = 2164) among patients with T2DM and either mixed dyslipidemia or non-mixed dyslipidemia, dapagliflozin was associated with minor changes in HDL-C, non-HDL-C and LDL-C in both groups and a mild decrease in the TG levels. However, there is no subgroup analysis on Asian patients, and the clinical significance of these small changes in lipid parameters remains unclear (Bays, Sartipy, Xu, & Sjöström, 2016).

Canagliflozin demonstrated significant increases in HDL-C and LDL-C as monotherapy in a 24-week study among East Asians (Inagaki et al., 2014). In a pooled data analysis from four 26-week trials, dose-related increases in LDL-C have been observed with canagliflozin (Nauck et al., 2014). With regard to empagliflozin in East Asians, a long-term study reported increases in TC, HDL-C, and LDL-C; and a decrease in TG from baseline after 52 weeks (Araki et al., 2015). Pooled analyses of four placebo-controlled trials on empagliflozin have shown small increases in HDL-C (10 mg: 0.07 mmol/L; 25 mg: 0.07 mmol/L) and LDL-C (10 mg: 0.08 mmol/L; 25 mg: 0.10 mmol/L); and small decreases in TG after 24 weeks (Hach et al., 2014).

### 6. Safety of SGLT2 inhibitors

The risk of hypoglycemia is lower with SGLT2 inhibitors, as compared to sulfonylureas (Fugita & Inagaki, 2014; Vasilakou et al., 2013; Wan Seman et al., 2016; Wu et al., 2016). In a meta-analysis of seven SGLT2 inhibitors trials, the hypoglycemia risk was comparable to metformin/DPP-4 inhibitors (Vasilakou et al., 2013). Moreover, dapagliflozin was associated with fewer events of hypoglycemia compared to placebo when added to insulin (19.5% vs. 23.3%, respectively) (Araki et al., 2016). Among East Asians, the occurrence of hypoglycemia with SGLT2 inhibitors was relatively low and well-tolerated (Yoon et al., 2016).

Although genito-urinary infections are more commonly associated with SGLT2 inhibitors, they are generally mild and self-limiting, with low event rates of urosepsis/pyelonephritis (Canaglifoxin prescribing information, 2016; Dapaglifoxin FDA prescribing information, 2014; Empaglifoxin FDA prescribing information, 2014; Vasilakou et al., 2013; Wu et al., 2016). Hence, it is recommended that clinicians should offer appropriate advice on personal hygiene and monitoring of newly developed symptoms of such infection during consultations. In another recent meta-analysis, incidences of bone fracture, acidosis, kidney disease, venous thromboembolism, and malignancy with SGLT2 inhibitors were not significantly elevated; although a relatively higher risk of volume depletion due to diuretic effect [OR 1.53 (1.27–1.83)] was identified (Wu et al., 2016). A non-significant increasing trend of postural hypotension was also observed with dapagliflozin compared to sulfonylureas (13.8 vs 5.8% respectively) in Asians T2D who fast during Ramadan in a 12-week randomized trial (Wan Seman et al., 2016).

### 6.1. Cardiovascular outcomes

The CV benefits of SGLT2 inhibitors have been studied primarily in Caucasians. Empagliflozin has demonstrated lower rates of CV death (38% relative risk reduction [RRR]), heart failure hospitalization (HF; 35% RRR), and all-cause mortality (32% RRR) in T2DM subjects with established CV disease (Zimman et al., 2015). A meta-analysis of CV outcomes on dapagliflozin (21 studies; n = 9339), which involved 540 Japanese and 393 Chinese patients, suggested a reduction of HF hospitalization in the overall population [HR 0.361 (0.156, 0.838)] and among subjects with CV disease [HR 0.371 (0.155, 0.889)] (Fig. 1) (Sonesson, Johansson, Johnsson, & Gause-Nilsson, 2016).
Table 2
Key studies of SGLT2 inhibitors either as monotherapy or as add-on/combination therapy in T2DM among East Asians.

<table>
<thead>
<tr>
<th>Author; Ethnicity</th>
<th>Study design and population</th>
<th>Intervention</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| Kaku et al. (2013), NCT00972244 Japanese | 12-week, phase II, multicenter, randomized, placebo-controlled study (n = 279) | Dapagliflozin (1, 2.5, 5, or 10 mg) | - Significant reductions in different parameters at all dapagliflozin doses:  
  - HbA1c (−0.11% to −0.44%),  
  - FPG (−15.61 to −31.94 mg/dL),  
  - Body weight (−1.25 to −2.06 kg)  
- Significant increase in HDL-C with dapagliflozin at doses 2.5 mg (4.13%), 5 mg (4.50%), and 10 mg (7.64%)  

| Kaku, Kiyosue, et al. (2014), NCT01294436 Japanese | 24-week, randomized, placebo-controlled study (n = 261) | Dapagliflozin (5 or 10 mg) | - Significantly greater reduction with dapagliflozin (5 mg and 10 mg):  
  - HbA1c (−0.41% and −0.74%),  
  - FPG (−8.6 and −13.7 mg/dL),  
  - Body weight (−2.13 and −2.22 kg)  
- Significant increase in HDL-C with dapagliflozin 5 mg (9.7%)  

| Ji et al. (2014), NCT01095653 Chinese | 24-week, phase III, multicenter, randomized, parallel-group, placebo-controlled, double-blind study (n = 393) | Dapagliflozin (5 or 10 mg) | - Significant reductions with dapagliflozin 5 mg and 10 mg:  
  - HbA1c (−1.04% and −0.74%),  
  - FPG (−25.1 and −31.3 mg/dL),  
  - Body weight (−3.76 and −4.02 kg)  
- Significant reductions in PPG and body weight at all doses  
- Significant reduction in SBP with empagliflozin 10, 25, and 50 mg  

| Inagaki et al. (2014), NCT01413204 Japanese | 24-week, multi-center, randomized, double-blind, placebo-controlled, phase III study (n = 272) | Canagliflozin (100 or 200 mg) once daily | - Significant reductions with canagliflozin 100 mg and 200 mg in:  
  - HbA1c (−0.74% and −0.70%),  
  - FPG (−31.6 and −31.9 mg/dL),  
  - PPG (−84.9 and −79.0 mg/dL),  
  - Body weight (−3.1 kg for both doses)  
- Significant reductions with empagliflozin 5, 10, 25, and 50 mg in HbA1c:  
  - (−0.72%, −0.70%, −0.95%, and −0.91%)  
- Significant reductions with empagliflozin in FPG and body weight at all doses  
- Sustained reduction with empagliflozin 10 and 25 mg in:  
  - HbA1c (−0.67% and −0.86%),  
  - FPG (−24.7 and −31.3 mg/dL),  
  - Body weight (−3.1 kg for both doses)  

| Kadowaki et al. (2014), NCT0193218 Japanese | 12-week, randomized, parallel-group, double-blind, placebo-controlled, phase II study (n = 547) | Empagliflozin (5, 10, 25, or 50 mg) | - Significant reductions with empagliflozin 5, 10, 25, and 50 mg in HbA1c:  
  - (−0.72%, −0.70%, −0.95%, and −0.91%)  
- Significant reductions with empaglifl ozin in FPG and body weight at all doses  
- Sustained reduction with empaglifl ozin 10 and 25 mg in:  
  - HbA1c (−0.67% and −0.86%),  
  - FPG (−24.7 and −31.3 mg/dL),  
  - Body weight (−3.1 kg for both doses)  

| Kadowaki et al. (2015), NCT0193218 Japanese | 52-week, randomized, parallel-group, placebo-controlled, double-blind study (n = 547) | Empagliflozin (5, 10, 25, or 50 mg) | - Significant reductions with empaglifl ozin in:  
  - HbA1c (−0.6% and −0.86%),  
  - FPG (−22.7 mg/dL),  
  - Body weight (−1.21 kg)  
- Placebo-corrected mean daily insulin dose (−0.72 IU/day)  
- Reduction in HbA1c by −0.7% in monotherapy and combination therapy groups  
- Reduction in body weight (−2.6 kg with monotherapy and −2.1 kg with combination therapy)  
- Reduction in SBP (−5.2 mmHg with monotherapy and −3.9 mmHg with combination therapy)  

| **Add-on/combination therapy** |                             |              |              |
| Yang et al. (2016), NCT01095666 Chinese | 24-week, randomized, double-blind, placebo-controlled, parallel-group (n = 444) | Placebo or dapagliflozin (5 or 10 mg) as add-on to metformin | Significant reductions with dapaglifl ozin 5 mg and 10 mg in:  
  - HbA1c (−0.82% and −0.85%),  
  - FPG (−1.2 and −1.5 mmol/L),  
  - PPG (−2.3 and −2.7 mmol/L),  
  - Body weight (−1.1 and −1.8 kg)  

| Araki et al. (2016), NCT02137298 Japanese | Interim analysis of multicenter, randomized, double-blind, placebo-controlled study at 16 weeks (n = 182) | Placebo or dapagliflozin (5 mg) as add-on to insulin, in 2:1 ratio | Significant reductions with dapaglifl ozin in:  
  - HbA1c (−0.6%),  
  - FPG (−22.7 mg/dL),  
  - Body weight (−1.21 kg)  
- Placebo-corrected mean daily insulin dose (−0.72 IU/day)  
- Reduction in HbA1c by −0.7% in monotherapy and combination therapy groups  
- Reduction in body weight (−2.6 kg with monotherapy and −2.1 kg with combination therapy)  
- Reduction in SBP (−5.2 mmHg with monotherapy and −3.9 mmHg with combination therapy)  

| Kaku, Maegawa, et al. (2014), NCT01294436 Japanese | 52-week, open-label, phase III study (n = 728) | Dapagliflozin monotherapy (5 mg titrated to 10 mg) or combination therapy with SU, glinides, MET, AGI, DPP-4i, TZD, or GLP-1 receptor antagonists |  

In another recent meta-analysis of seven different SGLT2 inhibitors, risks of CV death, heart failure, and all-cause mortality were relatively decreased by 37%, 35%, and 29% respectively (Wu et al., 2016). However, these results were driven mainly by the EMPA-REG outcome trial. Of note, an elevated risk of non-fatal stroke [HR 1.30 (1.00, 1.68)] was reported after pooled analysis from canagliflozin and empagliflozin, which was hypothesized to be related to hemococoncentration seen with SGLT2 inhibitors (Wu et al., 2016). Hence, results of on-going CV outcomes trials, i.e. “Dapagliflozin Effect on Cardiovascular Events TIMI-58 [DECLARE]” and CANAgliFlod cardioVascular Assessment Study (CANVAS), are pivotal to substantiate these findings among individual SGLT2 inhibitors (CANVAS study group, 2009, NCT01032629: Yang et al., 2016).

7. Diabetic kidney disease (DKD) in East Asians

The incidence and progression of DKD have been found to be higher in Asians compared to Caucasians (Ma & Chan, 2013). Hispanic and Asian populations showed a higher risk for end-stage renal disease (ESRD) than the African-American and Caucasian populations from a post-hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study (de Zeeuw et al., 2006). Furthermore, South Asians with T2DM demonstrated a greater risk of developing micro- or macroalbuminuria [adjusted odds ratio 3.9 (1.1–14); p = 0.03] and a faster progression of renal disease (loss in GFR ≥ 1.5 times higher) after 5 years of follow-up as compared to European Dutch subjects (Shaw et al., 2006).

7.1. Potential renoprotective role of SGLT2 inhibitors

In the setting of the greater incidence and progression of DKD in East Asians, the potential renoprotective properties of SGLT2 inhibitors, either as direct or indirect effects, are of interest (Górriz et al., 2015). Clinical data on this effect of SGLT2 inhibitors are currently limited, although experimental studies are extensively available. In a 104-week placebo-controlled study of T2DM subjects with moderate RI, the change in eGFR from baseline was similar in the dapagliflozin and placebo groups. Furthermore, dapagliflozin-treated subjects were more likely to regress to the low albumin excretion category than placebo (Kohan, Fioretto, Tang, & List, 2014, NCT00663260).

Recently, a post-hoc analysis of the EMPA-REG outcome trial indicated a significant reduction in the progression of DKD with empagliflozin (median treatment duration: 2.6 years) in T2DM subjects with established CV disease and moderate RI. These positive outcomes were apparent against a background of RAAS inhibitors and well-controlled BP, with a 38% RRR in progression to macroalbuminuria, 44% RRR in doubling of serum creatinine accompanied by eGFR of ≤ 45 ml/min/1.73 m², and 55% RRR in initiation of renal replacement therapy (Wanner et al., 2016, NCT01131676). Furthermore, in the LANTERN study, SGLT2 inhibitors treated subjects were observed to have initial small decrease in eGFR; which was completely reversed after cessation of therapy (Kashiwagi et al., 2015, Wanner et al., 2016). These findings support the potential use of SGLT2-inhibitors in addition to RAAS inhibitors among subjects with DKD. Based on these reassuring data, more long-term studies are crucial to validate the renoprotective effects of SGLT2 inhibitors in East Asians.

A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus (CANVAS-R) is ongoing and aims to assess the renoprotective effect of canagliflozin in T2DM subjects with high CV risk (CANVAS-R study group, 2013, NCT01989754). Two clinical trials on dapagliflozin are under way (DELIGHT and DERIVE) that aim to evaluate glycemic control in T2DM patients with CKD (DELIGHT and DERIVE study group, 2015, NCT02413398). The objective of the DELIGHT study is to determine whether dapagliflozin alone or in combination with saxagliptin can
decrease albuminuria and blood glucose levels in patients with T2DM, albuminuria, and moderate RI. It is currently recruiting participants across different regions, including Japan and Taiwan (DELIGHT study group, 2015, NCT02547935). The DERIVE study aims to evaluate the effect of dapagliflozin on blood glucose and renal safety in patients with T2DM and moderate RI, and will be conducted in 100 centers from countries across North America and Europe (DERIVE study group, 2015).

Until newer findings are available, the use of SGLT2 inhibitors is limited to T2DM adults who are either non-CKD or with stage 1–3A CKD, as the glucose-lowering effect diminishes with deteriorating renal function. Dapagliflozin and empagliflozin are not to be initiated when eGFR falls below 60 and 45 ml/min/1.73 m² respectively; whilst dose of canagliflozin needs to be reduced at eGFR of 45–60 ml/min/1.73 m² and to be discontinued below 45 ml/min/1.73 m² (Canagliflozin prescribing information, 2016; Dapagliflozin FDA prescribing information, 2014; Empagliflozin FDA prescribing information, 2014).

8. Place of SGLT2 inhibitor-based therapy in Asian population

Country-specific T2DM management guidelines are developed based on the local healthcare setting, health resources, and population-based epidemiological data. In general, treatment individualization is widely adopted in selection of appropriate pharmacological therapy, in which the patient's pathophysiological status, presence of any complications or comorbidities, risk of hypoglycemia, drugs' adverse effects, age, and disease duration are taken into consideration (Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care Settings, 2013; Inzucchi et al., 2015; Japan Diabetes Society guidelines 2014/2015). To date, this new class of drug is feasible in most adults with T2D, except in geriatric patients, individuals with stage 3B CKD and below, and those with history of recurrent genitourinary infections (Canagliflozin prescribing information, 2016; Dapagliflozin FDA prescribing information, 2014; Empagliflozin FDA prescribing information, 2014). Most antidiabetic agents, including SGLT2 inhibitors, are contraindicated in pediatric population (<18 years old), pregnant women and nursing mothers as the safety and effectiveness are not established.

The next critical question is the clinical potential of SGLT2 inhibitors in the management of T2DM among East Asians, who have been proven to be phenotypically different from Caucasians as described extensively in previous sections. Table 3 highlighted the main characteristics of this high risk population and the possible benefits offered by SGLT2 inhibitors pertaining to the Asian phenotype.

**Fig. 1.** Four-point major adverse CV event plus unstable angina (4-point MACE) (A), and CV events in the overall population and subgroup of subjects with a history of CVD (B). Adapted from: Sonesson et al. (2016).
9. Conclusion

Clinical trials have proven the combined glycemic, BP, and weight benefits of SGLT2 inhibitors in adults with T2DM, with relatively good tolerability profile. To the best of our knowledge, this is the first review which summarizes the available literature of SGLT2 inhibitors in East Asians. In view of a lack of head-to-head trials, efficacy and safety data of individual SGLT2 inhibitors were not compared. Proper selection of patients who will benefit the most from each treatment strategy (with minimal side effects), together with effective patient–doctor communication, is the key to successful T2DM management. Of note, there is still a paucity of real-world data that focus entirely on East Asians. Furthermore, evidence on the long-term clinical and major safety outcomes of SGLT2 inhibitors, e.g. stroke, diabetic ketoacidosis, hypovolemia, renal impairment etc. is still lacking, warranting an urgent need for robust clinical trials of SGLT2 inhibitors in order to fill in these knowledge gaps. Such effort can be a valuable step towards positioning SGLT2 inhibitors as part of the T2DM treatment armamentarium among East Asians in the future.

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References


Table 3

<table>
<thead>
<tr>
<th>Asian phenotype</th>
<th>SGLT2 inhibitor-based therapy</th>
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<tbody>
<tr>
<td>Young age of onset, resulting in longer duration of diabetes</td>
<td>Sustained long-term glycemic control (4 years) (Del Prato et al., 2015, NCT00660907)</td>
</tr>
<tr>
<td>Diabetes at low BMI and high visceral adiposity</td>
<td>Insulin-independent action ensures longer control (Fugita and Inagaki, 2014)</td>
</tr>
<tr>
<td>Poorer beta-cell function</td>
<td>Lower rate of hypoglycemia that can be an advantage in the working population (Araki et al., 2015, 2016; Inagaki et al., 2014, 2015; Ji et al., 2014; Kadowaki et al., 2014, 2015; Kaku et al., 2013; Kaku, Kiyosue, et al., 2014; Kaku, Maegawa, et al., 2014; Kashiwagi et al., 2015; Yang et al., 2016)</td>
</tr>
<tr>
<td>Higher rates of CV and renal complications</td>
<td>Reduction in visceral fat (Bolinder et al., 2015)</td>
</tr>
<tr>
<td>• Insulin-independent action (Fugita and Inagaki, 2014)</td>
<td>• Reduction in waist circumference (Inuzuchi et al., 2015)</td>
</tr>
<tr>
<td>• Effective reduction of glucose, body weight, and BP, with a possible neutral effect on lipids, thus modifying vital CV risk factors (Araki et al., 2015, 2016; Inagaki et al., 2014, 2015; Kadowaki et al., 2014, 2015; Kaku, Maegawa, et al., 2014; Yang et al., 2016)</td>
<td>• Significant reductions in MAE and hospitalization for heart failure (Sonesson et al., 2016; Zinman et al., 2015)</td>
</tr>
<tr>
<td>• Significant reductions in incident or worsening nephropathy (Wanner et al., 2016)</td>
<td>• Significant reductions in incident or worsening nephropathy (Wanner et al., 2016)</td>
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