# THE EFFECT OF DAPAGLIFLOZIN ON CLINICAL, METABOLIC AND RENAL PARAMETERS IN TYPE 2 DIABETIC PATIENT IN UNIVERSITY OF MALAYA MEDICAL CENTRE: A SINGLE CENTRE EXPERIENCE

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## ABSTRACT

**Aim:** As Asian patients with type 2 diabetes mellitus (T2DM) have significant beta cell dysfunction and increased visceral adiposity, we hypothesize that sodium glucose co-transporter inhibitors which acts independent from insulin dependent mechanisms, are effective in a multi ethnic T2DM population in real-world setting.

**Methods:** A retrospective T2DM cohort (N=110) treated with dapagliflozin for ≥6 months was identified from the electronic pharmacy database. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI 2009 equation. Missing laboratory values were imputed utilizing the "last-observation-carried-forward" method. The 6- and 12-month post-interventional differences in biochemical profiles were examined using linear mixed-effects model or Friedman test.

**Results:** The mean age [±standard deviation] and disease duration [± standard deviation] were 56.2±9.5 and 14.8±8.0 years, respectively; mean $HbA_{1c}$ [±S.D.] was 70±14 mmol/mol (8.6±1.3%), 43.6% were men, and 22.7% had existing cardiovascular disease. The proportions of participants based on ethnicity were Malay 31.8%, Chinese 29.1% and Indian 33.6%. At 12 months, there was a significant decline in $HbA_{1c}$ ($Mdn_{difference}$ -10 mmol/mol [-0.9%], 95% CI -13 to -8 mmol/mol [-1.2 to -0.7%], $P$<0.001), systolic blood pressure (SBP, $Mean_{difference}$ -4.1 mmHg, 95% CI -7.6 to -0.7, $P$=0.013), and body weight ($Mean_{difference}$ -2.01

kg, 95% CI -2.92 to -1.10, $P$=0.013). There are also significant improvements in urinary albumin: creatinine ratio ($Mdn_{difference}$ -0.45 mg/mmol, 95% CI -1.15 to < -0.001, $P$=0.019), square-root transformed eGFR ($P$=0.024), and the proportions of patients attaining $HbA_{1c}$ <7% ($P$<0.001) or SBP <140 mmHg ($P$=0.007).

**Conclusions:** Suboptimally-controlled multi-ethnic Asians with T2DM showed substantial improvements in metabolic and renal parameters with dapagliflozin over a year.

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# INTRODUCTION

The prevalence of Type 2 diabetes mellitus (T2DM) in Malaysia is increasing at an alarming rate(*National Health and Morbidity Survey (NHMS)*, 2015). Phenotypes of Asian are different compared to Caucasian where Asians have significant beta cell dysfunction and increased visceral adiposity. Sodium glucose co-transport 2 (SGLT2) inhibitors, a part of the armamentarium of diabetes treatment acts independent from insulin-dependent mechanisms and may confer additional benefits apart from glucose lowering effects. As there is lack of real- world data in Asian patients on SGLT2 inhibitors, a study of dapagliflozin use in a hospital in Malaysia was carried out to evaluate the effectiveness of dapagliflozin in clinical, metabolic and renal parameters in a multi ethnic population Asian patient with T2DM.

## OBJECTIVE

**GENERAL OBJECTIVE:** To evaluate the effectiveness of dapagliflozin, a SGLT2 inhibitor in a multi ethnic T2DM population in real world setting.

**SECONDARY OBJECTIVES**

: To identify the group of patients that will have greater improvement in clinical, metabolic and renal parameters

: To identify treatment related adverse events

# LITERATURE REVIEW

Type 2 Diabetes Mellitus (T2DM) is a major non-communicable disease. In Malaysia, T2DM prevalence has been on the rise, the latest Malaysia National Heath Morbidity Survey (NHMS 2015) showed the prevalence of T2DM among Malaysian adults age ≥18 years old to be 17.5% (*National Health and Morbidity Survey (NHMS)*, 2015). The prevalence was previously 11.6% in 2006 and 15.2% 5 years later according to the NHMS 2011 study. It is estimated that there are 2.6million adults with T2DM. In Malaysia, compared to global data, where the prevalence is only 8.5% of adult population Malaysia's alarmingly high prevalence needs to be addressed.

It is estimated that global cost of diabetes in 2015 was USD 1.31 trillion or 1.8% of gross domestic product (GDP)(Bommer et al., 2017) and indirect costs accounted for 34.7% of total burden. The same study also noted that nations that are in middle income group are more burdened with diabetes compared to high income countries. The cost of treatment of diabetes is not only limited to the disease but also attributed by its complications both microvascular and macrovascular.

Diabetic nephropathy is the leading cause of end-stage renal disease in developed countries(Tuttle et al., 2014; White S, 2014), with an annual incidence rate of chronic kidney disease (CKD, defined as estimated glomerular filtration rate [eGFR] <60 ml/min/1.73m$^2$) and albuminuria at approximately 2-4% and 8%, respectively (Koye et al., 2017). In a large

T2D database of 7 Asian countries, the corresponding prevalence was much higher at 15.9% and 37.5% respectively (Luk et al., 2016).

Cardiovascular disease (CVD) complications such as coronary heart disease, heart failure, stroke, peripheral arterial disease and cardiomyopathy will be the leading cause of diabetes related morbidity and mortality. Adults with diabetes have twice of developing CVD compared to adults without diabetes(Sarwar et al., 2010). American Heart Association (AHA) & American Diabetes Association (ADA) have considered diabetes as a coronary artery disease risk equivalent rather than a risk factor based on a study which showed risk of myocardial infarction (MI) in people with diabetes is equivalent to the risk of non-diabetic patients with a history of MI (Haffner et al., 1998)

The notion of hyperglycaemia is a major risk factor for macrovascular complications is not entirely true as interventional studies focusing on reducing plasma glucose in T2DM have only a small effect to reduce cardiovascular (CV) risk as compared to reducing microvascular complications such as retinopathy or nephropathy. Diabetes Control and Complications Trial (DCCT) trial showed there is no improvement in CV outcome in the end of the study but benefit of CV reduction is only seen after 10 years in patient in the intensive A1c lowering group. Most T2DM patients have insulin resistance which is associated with multiple metabolic abnormalities i.e. obesity, dyslipidaemia and hypertension and this is the major factor responsible for increased CV risk in diabetics. Consequently, lowering blood pressure and improving lipid profile has greater effect in reducing CV risk than lowering plasma glucose concentration in T2DM. This explains why anti diabetic agents (insulin, sulfonylurea, dipeptidyl peptidases 4 inhibitors) that do not affect metabolic abnormalities

associated with metabolic syndrome has little direct beneficial effect to lower CV risk in T2DM (M. Abdul-Ghani et al., 2016).

Previous paradigm of diabetes treatment focused on the triumvirate of impaired insulin secretion, increased hepatic glucose production and decreased glucose uptake from muscles / liver (Ralph A. DeFronzo, 2009) and current understanding of pathophysiology of diabetes has shifted to the ominous octet where multiple pathophysiology processes are contributing to hyperglycemia state. Thus, a combination therapy will be required. Sodium-glucose transporter 2 (SGLT2) inhibitor, which acts primarily at the kidneys, targeting the kidneys on how glucose level is controlled. Glucose homeostasis via the kidneys are independent from other mechanisms. It works by inhibiting the SGLT2 co transporter which reabsorbs 90% filtered glucose from the lumen in the first part of proximal convulated tubules back into the systemic circulation. The remaining 10% of glucose will be reabsorbed in the more distal part of proximal convulated tubules via SGLT1 protein(Levine, 2017). In diabetic patients, SGLT proteins are upregulated resulting in renal threshold and increased urinary glucose reabsorption despite elevated plasma glucose. Currently, SGLT2 inhibitor available in Malaysia are canagliflozin, dapagliflozin and empagliflozin. As SGLT2i works in the renal, independent from pancreatic beta cell functions, thus it can be used in early and in advanced disease of DM.

One specific SGLT2 inhibitor, empagliflozin in the EMPA-REG trial showed reduction of major adverse cardiac event end point (CV death, nonfatal myocardial infarction, nonfatal stroke) by 14%, 38% reduction in CV mortality with no significant decrease in nonfatal myocardial infarction or stroke. Empagliflozin also results in 35% reduction in

hospitalization for heart failure without affecting hospitalization for unstable angina. It is the first anti-diabetic agent that provides CV benefit. Canagliflozin, in the recently published CANVAS study also conferred similar CV benefit where it showed 14% reduction in composite endpoint of CV mortality, non-fatal myocardial infarction (MI) or non-fatal stroke and 33% reduction in risk of hospitalization for heart failure compared with placebo(S. Lee, 2017). Dapagliflozin is currently undergoing clinical trial (DECLARE- TIMI58)(Sonesson et al., 2016) and results will only be out in 2019. Whether reduction of CV risk is only in empagliflozin and canagliflozin or also with dapagliflozin will only be seen after 2019 but some study has pointed that this might be a class effect (Kosiborod et al., 2017).

Currently most of the data for SGLT2 inhibitor studies are from US and Europe and there is lack of real- world data in Asian populations who have distinct phenotypes from Caucasians namely T2DM develops at a younger age, with lower body mass index, higher visceral adiposity, and more significant beta cell dysfunction. (Lim et al., 2017). Other studies on SGLT2 inhibitors done in Asia showed empagliflozin well tolerated and reduces A1c, weight, blood pressure (Yoon et al., 2016) and the subgroup of Asian patients in EMPA-REG outcome which includes South East Asia countries of Malaysia, Singapore, Indonesia, Thailand, Philippines are similar and consistent with the overall trial population(Kaku et al., 2017). Dapagliflozin has been studied in Asian population as well but studies done in Chinese patients (Yang et al., 2016), but no studies have been done in South East Asia patients before. Thus, this study aims to evaluate the effectiveness of dapagliflozin on clinical, metabolic and renal parameters among multi ethnic Asians in Malaysia, a country in the South-East Asia region which has a heterogenous population in a real-world setting.

## PATIENTS AND METHODS

This was a retrospective observational study, done in University Malaya Medical Centre (UMMC). There were two SGLT2 inhibitors available, dapagliflozin and empagliflozin. Dapagliflozin is available in the centre since March 2014 thus patient on dapagliflozin has longer follow up compared to empagliflozin which is only available in 2016. Eligible patients are those started on dapagliflozin in UMMC, either as monotherapy or as combination therapy with other oral antidiabetic agent or insulin between March 2014 until Dec 2015. and maintained on this antihyperglycaemic agent for at least 6 consecutive months from the index date. The index date was defined as the date of first prescription for dapagliflozin as shown in the electronic pharmacy database. Exclusion criteria included patient with haemoglobinopathies which could render glycated haemoglobin ($HbA_{1c}$) measurements to be inaccurate, incomplete medical records and less than 6 months duration of dapagliflozin therapy. The study flow diagram is shown in Fig. 1.

Patients demographic data, clinical characteristics and results of serial blood and urine tests (renal function test, fasting plasma glucose [FPG], $HbA_{1c}$, total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], fasting triglyceride, urinary albumin (measured by urinary albumin: creatinine ratio [ACR] in mg/mmol) were retrieved from both electronic and paper-based medical records. Microalbuminuria is defined as urinary ACR 2.5-30 mg/mmol in men and 3.5-30 mg/mmol in women and macroalbuminuria as urinary ACR >30 mg/mmol in at least two consecutive samples.

The research protocol was approved by the UMMC Ethics Committee (MECID 20163-2261) and registered at the ClinicalTrials.gov (NCT02966626).

### *Laboratory assays*

Serum $HbA_{1c}$ level was analysed by ion exchange high-performance liquid chromatography technique (National Glycohemoglobin Standardization Program/Diabetes Control and Complications Trial-aligned; Bio-Rad Variant TM II Turbo; Bio-Rad, Hercules, California, USA). The respective intra- and inter-assay correlations of variance were <2.0 and <2.3%, respectively. Serum FPG level was analysed using glucose oxidase method; urinary ACR was measured using turbidimetric technique (ADVIA Chemistry XPT System; Siemens Healthcare Diagnostics, Tarrytown, New York, USA). Complete blood counts were analysed using fluorescent flow cytometry (XN-10; Sysmex, Kobe, Japan). Renal function test and lipid profiles were measured using colorimetric methods (ADVIA 2400 Chemistry System; Siemens Healthcare Diagnostics, Tarrytown, New York, USA). The estimated glomerular filtration rate was estimated using the creatinine-based CKD-Epidemiology Collaboration (CKD-EPI) 2009 equation.

## DATA ANALYSIS

Patients' baseline characteristics were expressed as mean ± standard deviation (SD), median (interquartile range) or number (percentages), as appropriate. Missing data for FPG, $HbA_{1c}$, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile, body weight, urinary ACR and eGFR were imputed using the "last observation carried forward (LOCF)" method. Data transformations were performed as appropriate to ensure normality of residuals or linearity assumptions were met. The post-interventional differences in metabolic and renal parameters at 6- and 12-month intervals from baseline were evaluated using linear mixed-effects model with maximum likelihood estimation or Friedman test followed by Wilcoxon signed-rank test as post-hoc test, if the continuous variable was in normal or extremely skewed distribution, respectively. Bonferroni correction was applied in post-hoc analysis. The magnitude of the differences in medians were calculated using Hodges–Lehmann estimator. The proportions of patient who achieved treatment targets, defined as either $HbA_{1c}$ ≤53 mmol/mol (7%), SBP ≤140 mmHg, DBP ≤90 mmHg or LDL-C ≤2.6 mmol/L, were compared at 6- and 12-month intervals from baseline using Pearson Chi-square test. A two-sided *P*-value of <0.05 denoted statistical significance. All statistical analyses were performed using SPSS version 24.0 for Windows (IBM Corp., Armonk, New York, USA).

## RESULTS

### *Baseline characteristics*

Table 1 shows the baseline characteristics of 110 patients in the analysis. The mean (SD) age and duration of T2D were 56.2±9.5 and 14.8±8.0 years, respectively. There were 48 (43.6%) men. The proportions of patients based on ethnicity were Malay 31.8%, Chinese 29.1%, Indian 33.6%, and others 5.5%. Notably, approximately 1 in 3-4 patients had pre-existing cardiovascular disease or albuminuria. At baseline, the patients had suboptimal metabolic control, with mean $HbA_{1c}$ and SBP levels of 70±14 mmol/mol (8.6±1.3%) and 134.3±15.7 mmHg, respectively.

The proportions of patients who attained treatment targets are shown in Table 2. Over 90% of patients had a $HbA_{1c}$ level >53 mmol/mol (7%), whilst close to half of them had SBP >140 mmHg at baseline. Most patients had good lipid control, with >70% with baseline LDL-C <2.6 mmol/L.

### *Changes in metabolic and renal parameters after treatment initiation*

Fig. 2 depicts the 1-year post-interventional changes in metabolic parameters. Overall, there are significant improvements in: a) FPG ($Mdn_{difference}$ -1.65 mmol/L, 95% confidence intervals [95% CI] -2.20 to -1.05, $P<0.001$), b) $HbA_{1c}$ ($Mdn_{difference}$ -10 mmol/mol [-0.9%], 95% CI -13 to -8 mmol/mol [-1.2 to -0.7%], $P<0.001$), c) SBP ($Mean_{difference}$ -4.1 mmHg,

95% CI -7.6 to -0.7, $P$=0.013), and d) body weight ($Mean_{difference}$ -2.01 kg, 95% CI -2.92 to -1.10, $P$<0.001). The post-interventional differences of DBP ($P$=0.391), logarithmic-transformed fasting triglyceride ($P$=0.323), logarithmic-transformed HDL-C ($P$=0.070), and logarithmic-transformed LDL-C ($P$=0.880) were not significant.

Post-hoc analyses revealed early and significant decline of metabolic parameters after 6 months of dapagliflozin treatment in: a) FPG ($Mdn_{difference}$ -1.45 mmol/L, 95% CI -2.05 to -0.85, $P$<0.001), b) $HbA_{1c}$ ($Mdn_{difference}$ -9 mmol/mol [-0.9%], 95% CI -12 to -7 mmol/mol [-1.1 to -0.6%], $P$<0.001), and c) body weight ($Mean_{difference}$ -1.47 kg, 95% CI -2.38 to -0.57, $P$<0.001). Use of dapagliflozin tended towards improvement in SBP at 6 months ($Mean_{difference}$ -2.7 mmHg, 95% CI -5.4 to 0.0, $P$=0.054). There are greater response with dapagliflozin in patients with worse metabolic control at baseline. After a year of dapagliflozin treatment, patients with $HbA_{1c}$ >9%, SBP 140-160 mmHg, and body weight >95kg at baseline reduced significantly by 1.9%, 11.7 mmHg, and 3.58 kg, respectively (Table 2).

As shown in Table 3, there was about a 5-fold increase (from 4.5% to 21.8%) in the proportion of patients who attained $HbA_{1c}$ <53 mmol/mol (7%) after 6- and 12-month initiation of dapagliflozin. For SBP control (defined as SBP <140 mmHg), we observed an increase from 64 (58.7%) to 85 (78.0%) at 12 months ($P$=0.007). However, the proportion of patients who attained either DBP <90 mmHg or LDL-C <2.6 mmol/L was not significant. Regarding the effects of dapagliflozin on renal function, there are significant improvements in urinary ACR ($P$=0.005) and square-root transformed eGFR ($P$=0.024) after one year (Fig. 3). The median urinary ACR levels at 6-month and 12-month intervals were significantly lower than the corresponding measurements at baseline.

## DISCUSSION

Findings indicated use of dapagliflozin over a year in suboptimally-controlled multi-ethnic Asians with T2D was associated with 10 mmol/mol (0.9%), 4.1 mmHg, and 2.0 kg reductions in $HbA_{1c}$, SBP, and body weight, respectively. Greater reductions were seen in dapagliflozin-treated patients with worse metabolic control at baseline. In this real-world setting, there are significant improvement in renal function with dapagliflozin. These results corroborated recent cardiovascular outcome trials of SGLT2 inhibitors and The Comparative Effectiveness of Cardiovascular Outcomes (CVD-REAL) study, albeit these studies mainly included non-Asian populations (Kosiborod et al., 2017; Neal et al., 2017; Zinman et al., 2015). Of note, the present cohort was approximately 7 years younger, with similar duration of T2DM (mean age 56.4 years, disease duration 14.7 years) compared to participants recruited in the EMPA-REG OUTCOME trial (Zinman et al., 2015) (mean age 63.1 years, ~57% had >10 years of disease duration) and Integrated Canagliflozin Cardiovascular Assessment Study (CANVAS) program (Neal et al., 2017) (mean age 63.3 years, disease duration 13.5 years). Approximately 1 in 4 patients in the present cohort had established CVD, compared to 13% in the CVD-REAL study (Kosiborod et al., 2017), 99.2% in the EMPA-REG OUTCOME trial (Zinman et al., 2015), and 65.5% in the Integrated CANVAS program (Neal et al., 2017). The latter two trials included higher proportions of participants with CVD than real-world databases, as they were designed to evaluate the cardiovascular safety of SGLT2 inhibitors. Notably, all four study cohorts had poor glycaemic control at baseline with mean $HbA_{1c}$ levels of ≥8%, which highlighted the difficulties in treating to targets in all populations and clinical settings. These differences not only supported previous reports that Asians are more susceptible to develop T2D at a younger age, but also showed

people with young-onset diabetes have poorer metabolic profiles and higher lifetime risk of cardiovascular-renal complications and mortality than their counterparts with late-onset disease (Harding et al., 2016; Kong et al., 2013; Lim et al., 2017; Yeung et al., 2014).

SGLT2 inhibitors are a novel class of oral anti-hyperglycaemic agents that enhance glucosuria and ameliorate glucotoxicity (~7.7-10.9 mmol/mol [0.7-1.0%] $HbA_{1c}$ reduction), leading to sustained improvements in pancreatic beta-cell function and peripheral insulin sensitivity in T2D population (R. A. DeFronzo et al., 2017; Heerspink, Perkins, et al., 2016; Lim et al., 2017). Its associated glycaemic and body weight improvements are greater than DPP-4 inhibitors, especially in people with suboptimally-controlled diabetes (R. A. DeFronzo et al., 2017; Wang et al., 2017). Increasing evidence has also shown SGLT2 inhibitors-treated participants had more durable anti-hyperglycaemic effect with less hypoglycaemia than sulphonylureas, and with additional weight loss benefit consequent to a daily loss of 60-80 grams of glucose (R. A. DeFronzo et al., 2017; Lim et al., 2017; Vasilakou et al., 2013; Wu et al., 2016). In healthy individuals, SGLT2 transporters are responsible for 80-90% of renal glucose reabsorption (M. A. Abdul-Ghani et al., 2008; R. A. DeFronzo et al., 2017). In T2DM, chronic hyperglycaemia upregulates the SGLT2 transporters and elevates the renal threshold for glucosuria, with subsequent worsening of glycaemic control (M. A. Abdul-Ghani & DeFronzo, 2008; R. A. DeFronzo et al., 2017; Lim et al., 2017). Given that sodium and glucose are co-transported by SGLT2, its inhibition causes natriuresis with additional anti-hypertensive effect (~5/2 mmHg reductions in blood pressure), followed by a decrease in cardiac preload, creating an anti-hyperglycaemic agent with a unique mechanism of action (Baker et al., 2014; R. A. DeFronzo et al., 2017). The EMPA-REG OUTCOME trial and Integrated CANVAS program reported the amelioration of central arterial stiffness as sequelae of SGLT2 inhibitors-mediated blood pressure improvement might decrease the

cardiac afterload, left ventricular modelling, and eventually, the risk of heart failure and cardiovascular mortality (M. Abdul-Ghani et al., 2016; Heerspink, Perkins, et al., 2016; Neal et al., 2017; Zinman et al., 2015). In the CVD-REAL Nordic study, which had a similar proportion of patients with CVD as in the cohort, dapagliflozin showed significant associations with 20-50% lower risks of composite cardiovascular events, all-cause mortality, and severe hypoglycaemia, compared to other anti-hyperglycaemic agents (Birkeland et al., 2017). Another favourable effect of SGLT2 inhibition is an approximately 2.5-3.0 kg weight loss, in particular, visceral adipose tissue, which is recognized to cause metabolic perturbation and acts as an independent predictor of all-cause mortality in T2DM population (Kuwahara et al., 2017; S. W. Lee et al., 2017). In the study, the metabolic improvements observed were in line with previous work.

In addition, analysis has revealed significant improvements in both albuminuria and eGFR in dapagliflozin-treated participants. Growing evidence has suggested SGLT2 inhibitors may slow progression of diabetic nephropathy in addition to the use of renin-angiotensin system (RAS) inhibitors, likely driven by several mechanisms. This is of relevance in Asians with T2DM, who are more susceptible to the development and progression of diabetic nephropathy than Caucasians (Kong et al., 2013; Lim et al., 2017). Intrarenal haemodynamic modulation is postulated to play a pivotal role, whereby SGLT2 inhibition augments proximal tubular diuresis, increases sodium delivery to macula densa, activates tubuloglomerular feedback and afferent arteriolar vasoconstriction (R. A. DeFronzo et al., 2017). These result in reduced renal plasma flow and intraglomerular pressure, with subsequent reversal of glomerular hyperfiltration and structural renal damage (R. A. DeFronzo et al., 2017). Consistent with this hypothesis, an initial eGFR decline by approximately 4-5 ml/min/1.73m$^2$ during the first 4 weeks of initiation of SGLT2 inhibitors,

with an eventual return to baseline and stabilization, was observed in people with T2DM (M. Abdul-Ghani et al., 2016; R. A. DeFronzo et al., 2017; Heerspink, Johnsson, et al., 2016; Wanner et al., 2016). In the post-hoc analysis of EMPA-REG OUTCOME trial, an overall eGFR gain of similar magnitude over 3.1 years in the intervention group could be translated into delaying the need for renal replacement therapy by a year, even with a background of high RAS inhibitor use (Wanner et al., 2016). In the CANagliflozin Treatment And Trial Analysis versus SUlphonylurea (CANTATASU), canagliflozin was associated with a slower eGFR decline over 2 years, compared to glimepiride (0.3-0.5 *vs.* 3.3 ml/min/1.73m$^2$/year), which was independent of both glycaemic and blood pressure improvements (Heerspink et al., 2017). As a consequence, to a decrease in intraglomerular pressure, SGLT2 inhibition was significantly associated with 30-40% reduction in albuminuria (Heerspink, Johnsson, et al., 2016; Heerspink, Perkins, et al., 2016). Other proposed mechanisms for this pleiotropic renal benefit include uricosuria, haemoconcentration, and lipolysis with mild ketosis, where the latter two may act via improving renal hypoxia (R. A. DeFronzo et al., 2017; Mudaliar et al., 2016). The on-going CREDENCE trial (NCT02065791), designed to examine the renal outcomes of canagliflozin in T2DM population with stage 2-3 CKD and macroalbuminuria, will offer further insights into the renoprotective effects of SGLT2 inhibitors when it is due to report in 2019.

This study is the first real-world report on the effectiveness of dapagliflozin on metabolic and renal parameters in a relatively young Asian cohort with established T2DM in South East Asia. As the clinical phenotypes of the present cohort differed from the EMPA-REG OUTCOME trial and Integrated CANVAS program, the findings add to the existing evidence on the favourable impacts of SGLT2 inhibitors in a more diverse T2DM population

with broader cardiovascular risk profiles, commonly managed in real-life practice more than clinical trial settings.

As this is a retrospective study with lack of a comparison arm, we could not conclude the renoprotective effect of dapagliflozin or could be confounded by concurrent angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blocker (ARB). Given the variations in timing of clinic visits and completeness of laboratory measurements, the sample size restricted further subgroup analyses by gender, ethnicity, anti-hyperglycaemic regime, and baseline eGFR. The electronic pharmacy database records issuance of prescriptions by attending physicians, but not as medications dispensed or prescription refill. As UMMC is a government-funded hospital and individuals with T2DM are required to self-finance certain medications, including SGLT2 inhibitors, some individuals who are prescribed with SGLT2 inhibitors do not purchase these medications during initiation or refill their prescriptions regularly due to financial constraint. This could explain the discrepancy in the number of individuals being prescribed retrieved from the pharmacy database and the actual number of individuals with ≥6 consecutive months of dapagliflozin treatment. In addition, intention to treat (I.T.T.) analysis was not performed and thus this result might not be comparable to other clinical trials. Lastly, real-world databases face obstacles pertaining to the completeness of documentation, and some data, such as treatment-related adverse events, may not be precisely recorded for analysis. From the patients analysed, there are two cases of balanitis, one case of urinary tract infection and one had nausea. The low incidence of side effects might be under reported. The setback of the current study design curbs the ability of this report to include the safety outcomes of dapagliflozin.

## CONCLUSION

In conclusion, the sustained 1-year benefits on metabolic and renal parameters with dapagliflozin in multi-ethnic Asians with established T2DM are consistent with previous reports, albeit prospective follow-up studies are required to validate the cardio- and renoprotective effects and the safety outcomes of SGLT2 inhibitors in this population. This real-world report provides important clinical implications in guiding future strategic plans to improve diabetes care in Malaysia to halt the growing burden of T2DM and its complications.

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# LIST OF TABLES

**Table 1: Baseline characteristics of participants on dapagliflozin (N=110)**

| Clinical characteristics | Mean ± SD or Mdn (IQR) | Number (%) |
|---|---|---|
| Age, year | 56.4 ± 9.5 | |
| Male gender | | 48 (43.6) |
| Ethnicity | | |
| Malay | | 35 (31.8) |
| Chinese | | 32 (29.1) |
| Indian | | 37 (33.6) |
| Others | | 6 (5.5) |
| Duration of T2D, year | 14.7 ± 8.0 | |
| Weight, kg | 80.1 ± 15.9 | |
| Blood pressure | | |
| SBP, mmHg | 134.3 ± 15.7 | |
| DBP, mmHg | 76.6 ± 10.2 | |
| T2D | | |
| FPG, mmol/L | 8.3 (6.6 - 10.7) | |
| $HbA_{1c}$, IFCC (mmol/L) | 70 (63 - 77) | |
| $HbA_{1c}$, NGSP (%) | 8.6 (7.9 - 9.2) | |
| Dyslipidemia | | |
| Triglyceride, mmol/L | 1.4 ± 0.8 | |
| HDL-C, mmol/L | 1.1 ± 0.4 | |
| LDL-C, mmol/L | 2.2 ± 1.0 | |
| Renal function | | |
| eGFR, ml/min/1.73m$^2$ | 95.8 (78.7 - 107.1) | |
| Urinary ACR$^+$, mg/mmol | 1.90 (0.50 - 9.33) | |
| Microalbuminuria | | 23 (24.4) |
| Macroalbuminuria | | 12 (12.8) |
| Normoalbuminuria | | 59 (62.8) |
| | | |
| Other medical illnesses | | |
| Coronary artery disease | | 21 (19.1) |
| Stroke | | 3 (2.7) |
| Peripheral vascular disease | | 1 (0.9) |
| Cancer | | 4 (3.6) |
| Baseline oral antidiabetic medications | | |
| Biguanide | | 110 (100.0) |
| Sulfonylureas | | 56 (50.9) |
| DPP-4 inhibitors | | 51 (46.4) |
| Baseline use of injectable GLP-1 RA | | 9 (8.2) |
| Baseline insulin therapy | | |
| Basal | | 47 (42.7) |
| Prandial | | 33 (30.0) |
| Premix | | 13 (11.8) |

All continuous variables are expressed as mean ± standard deviation, except FPG, $HbA_{1c}$ and urinary ACR, which are in median (interquartile range). Results of urinary ACR were based on 94

participants.
Abbreviations: ACR, albumin: creatinine ratio; DBP, diastolic blood pressure; DPP4-i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose;

GLP-1 RA, glucagon-like peptide-1 receptor agonist; $HbA_{1c}$, glycated haemoglobin; HDL-C, high-density
lipoprotein cholesterol; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; LDL-C, low-density lipoprotein cholesterol; NGSP, National Glycohaemoglobin Standardization Program;
SD, standard deviation; SBP, systolic blood pressure; T2D, type 2 diabetes.

**Table 2: Changes in metabolic parameters stratified by baseline control**

| | Baseline control (N=110) | | |
|---|---|---|---|
| **$HbA_{1c}$ (mmol/mol)†** | **<53 (n=5)** | **53-75 (n=72)** | **>75 (n=33)** |
| Baseline | 46 | 67 | 87 |
| End of study | 51 | 58 | 69 |
| 1-year difference | 2 | -8*** | -21*** |
| **$HbA_{1c}$ (%)†** | **<7.0 (n=5)** | **7.0-9.0 (n=72)** | **>9.0 (n=33)** |
| Baseline | 6.4 | 8.3 | 10.1 |
| End of study | 6.8 | 7.5 | 8.5 |
| 1-year difference | 0.1 | -0.7*** | -1.9*** |
| **SBP (mmHg)** | **<140 (n=64)** | **140-160 (n=40)** | **>160 (n=5)** |
| Baseline | 124.0 | 146.5 | 168.4 |
| End of study | 126.2 | 134.8 | 143.2 |
| 1-year difference | 2.3*** | -11.7* | -25.2 |
| **DBP (mmHg)** | **<90 (n=96)** | **90-100 (n=12)** | **>100 (n=1)** |
| Baseline | 74.4 | 92.7 | 103.0 |
| End of study | 73.9 | 81.8 | 80.0 |
| 1-year difference | -0.4*** | -10.9 | -23.0 |
| **Body weight (kg)** | **Tertile 1 (n=36)** | **Tertile 2 (n=38)** | **Tertile 3 (n=36)** |
| Baseline | 63.57 | 78.66 | 98.22 |
| End of study | 62.66 | 76.41 | 94.64 |
| 1-year difference | -0.91*** | -2.25*** | -3.58*** |
| **LDL-C (mmol/L)†** | **<2.6 (n=80)** | **2.6-3.4 (n=19)** | **>3.4 (n=10)** |
| Baseline | 1.88 | 2.73 | 4.09 |
| End of study | 1.97 | 2.77 | 2.72 |
| 1-year difference | 0.13* | -0.02 | -1.23** |

†Data are expressed as median. Other parameters are expressed as mean. *P*-values are for 1-year difference in each subgroup (*** $P<0.001$, ** $P<0.005$, * $P<0.05$).
Abbreviations: DBP, diastolic blood pressure; $HbA_{1c}$, glycated haemoglobin; LDL-C, LDL-cholesterol; SBP, systolic blood pressure.

**Table 3: Proportions of participants attaining treatment targets or categorized by degree of albuminuria**

| Category | Number (%) | | | |
|---|---|---|---|---|
| | Baseline | 6 months | 12 months | *P*-value |
| **$HbA_{1c}$ <53 mmol/mol (7%)** | 5 (4.5) | 26 (23.6) | 24 (21.8) | 0.000 |
| **SBP <140 mmHg** | 64 (58.7) | 78 (71.6) | 85 (78.0) | 0.007 |
| **DBP <90 mmHg** | 96 (88.1) | 94 (86.2) | 98 (89.9) | 0.705 |
| **LDL-C <2.6 mmol/L** | 80 (72.7) | 85 (77.3) | 81 (73.6) | 0.715 |
| **Normoalbuminuria** | 59 (62.8) | 63 (67.0) | 63 (67.0) | 0.778 |
| **Microalbuminuria** | 23 (24.5) | 19 (20.2) | 19 (20.2) | 0.716 |
| **Macroalbuminuria** | 12 (12.8) | 12 (12.8) | 12 (12.8) | 1.000 |

The proportions of participants in each category of albuminuria were calculated based on 94 participants. Abbreviations: DBP, diastolic blood pressure; $HbA_{1c}$, glycated haemoglobin; LDL-C, LDL-cholesterol; SBP, systolic blood pressure.

# FIGURES

## Figure Legends

**Figure 1: Study flow diagram**

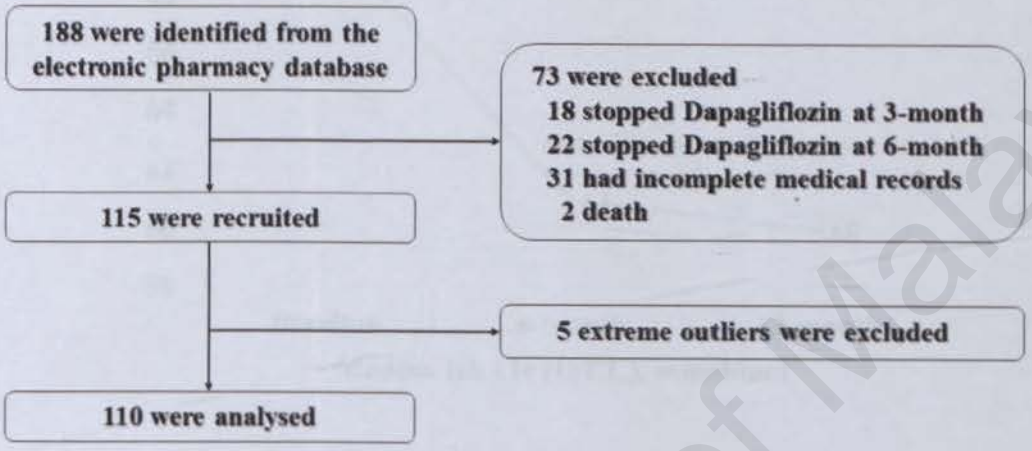
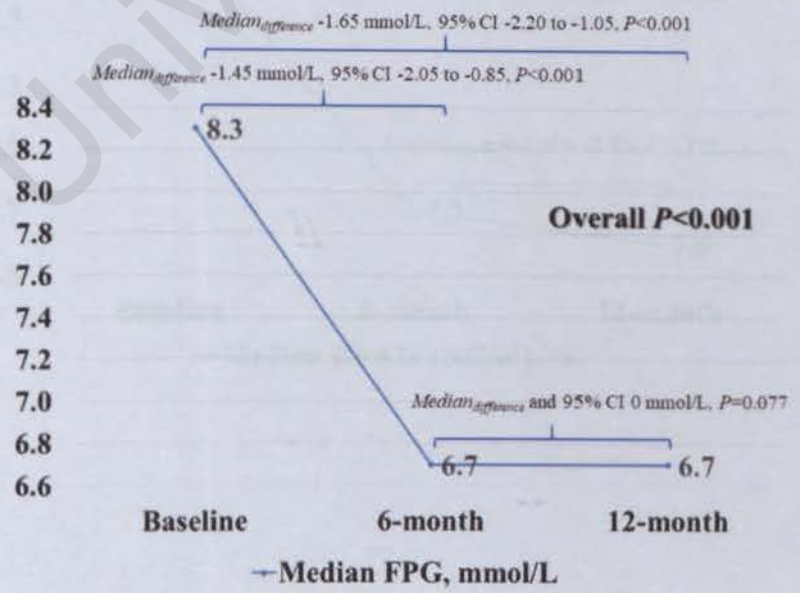
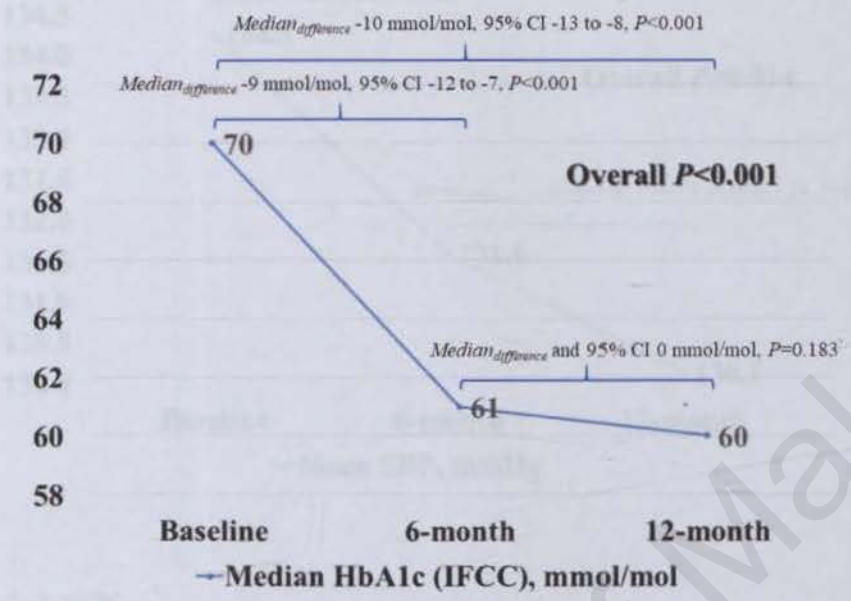



**Figure 2: Changes in metabolic parameters after initiation of dapagliflozin over 1-year follow-up.**

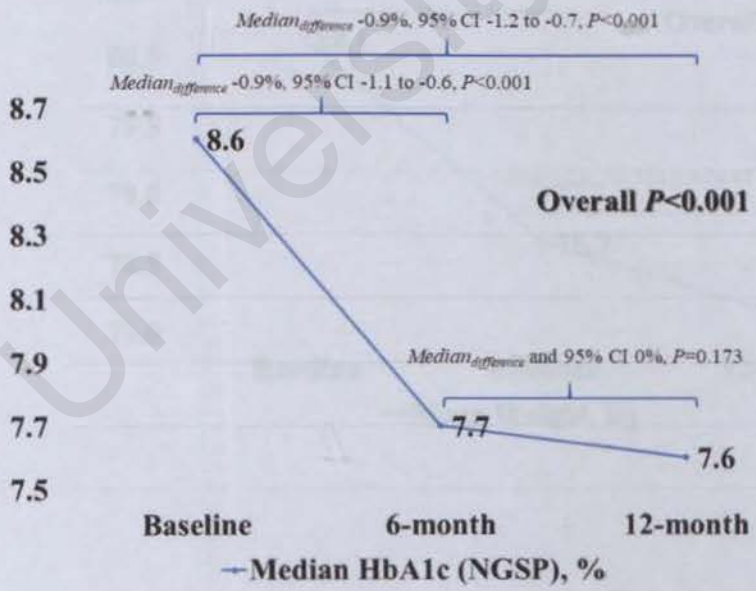
(a) Fasting plasma glucose (FPG);



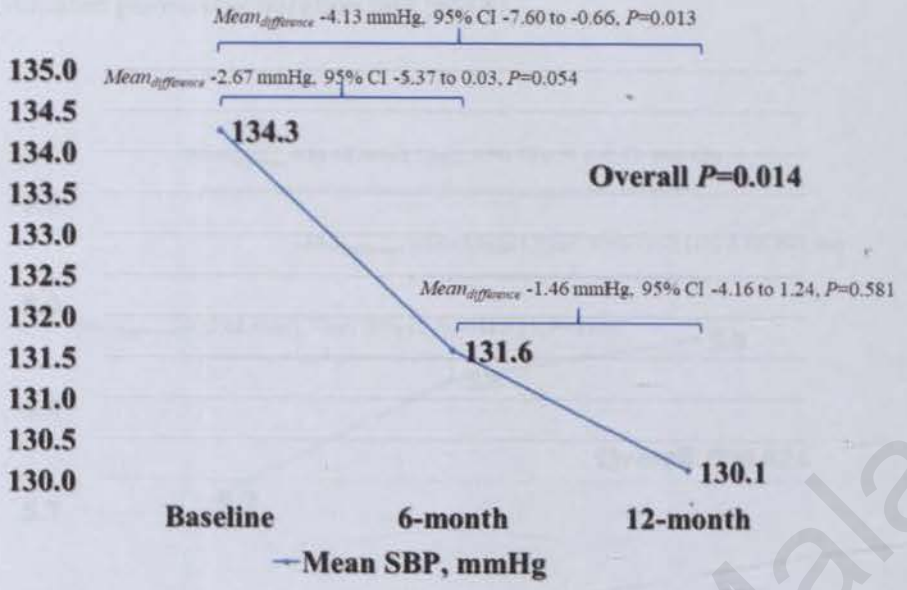
(b) $HbA_{1c}$ (mmol/mol);




(c) $HbA_{1c}$ (%);



(d) Systolic blood pressure (SBP);




(e) Body weight

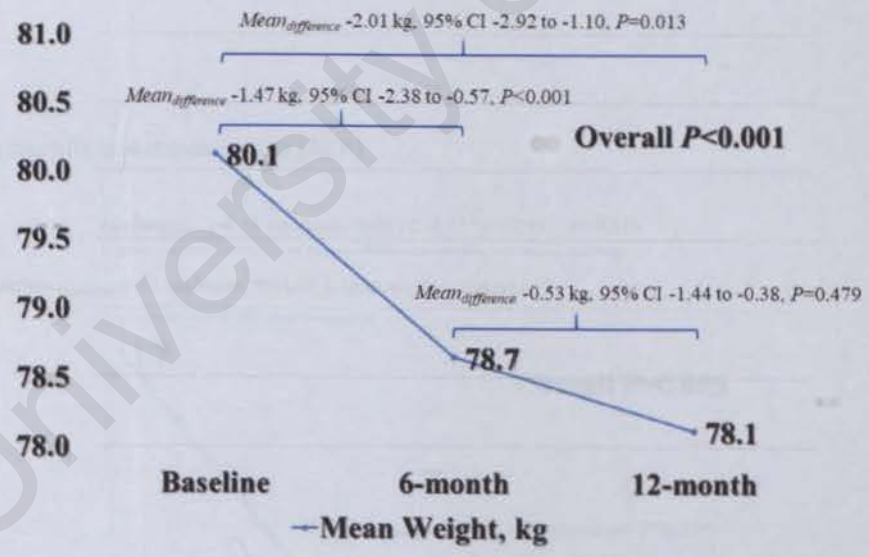
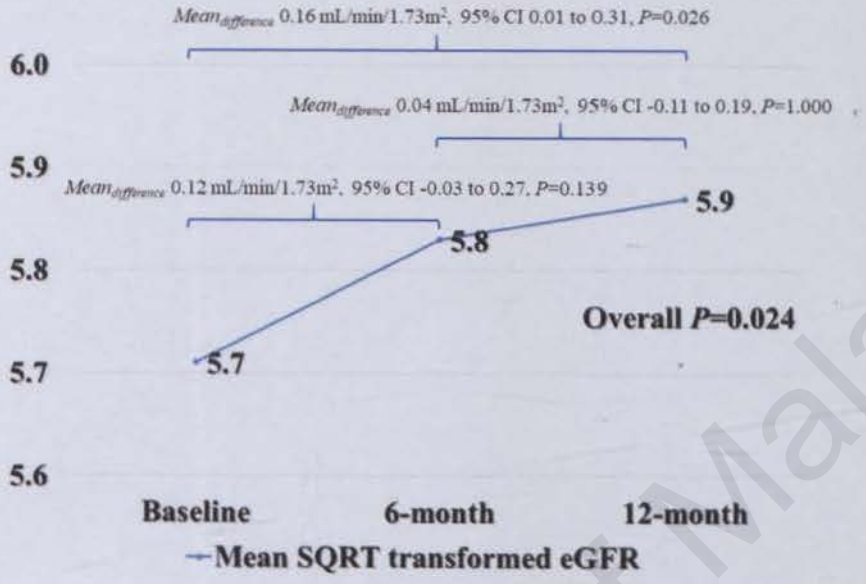
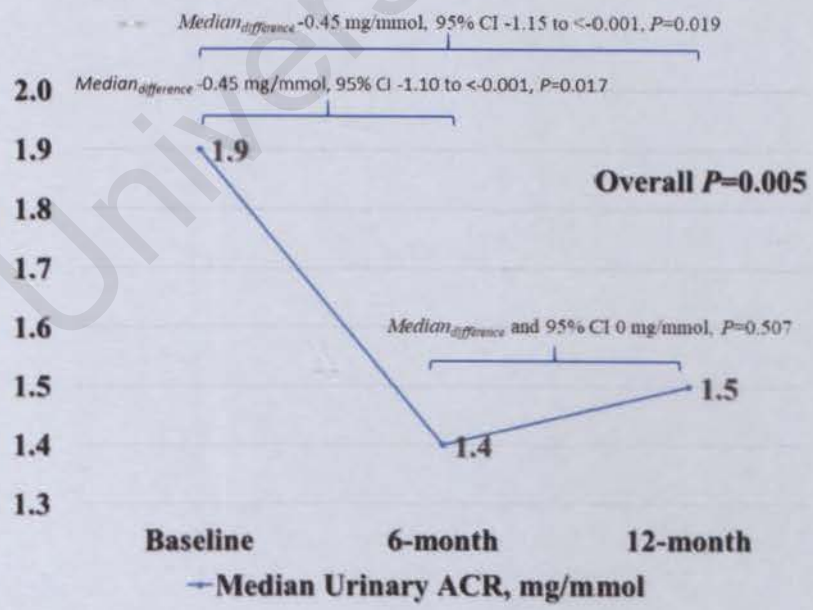


**Figure 3: Changes in renal function after initiation of dapagliflozin over 1-year follow-up.**

(a) Estimated glomerular filtration rate (eGFR)




(b) Urinary albumin: creatinine ratio (ACR)




Abbreviation: SQRT, square-root transformed.