EVALUATION OF GLYCAEMIC CONTROL COMPARING ORIGINAL VERSUS GENERIC FIXED DOSE GLIBENCLAMIDE/METFORMIN TABLET AMONG DIABETES MELLITUS PATIENTS IN AN OUTPATIENT CLINIC

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By

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DECLARATION OF ORIGINALITY

I hearby declare that this thesis is my own work and none of the contents in this thesis contains substantial proportions of material that has been submitted and accepted for the reward of any other degree or diploma at any tertiary educational institution or organization. The information derived from the previously published work or written by any person has been acknowledged in the text and a full list of references has been included in this thesis.

Lim Phei Ching

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LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
ACER	Average Cost-effectiveness Ratio
ADA	American Diabetes Association
ADOPT	A Diabetes Outcome Progression Trial
AGI	α-glucosidase inhibitor
AUC	Area under the curve
BMI	Body mass index
Cmax	Maximum concentration
CPG	Clinical Practice Guideline
DPP-4	Dipeptidyl peptidase- 4
EASD	European Association for the Study of Diabetes
EMA	European Medicines Agency
FDA	Food and Drug Administration
FFA	Free fatty acid
FLP	Full lipid profile
FPG	Fasting plasma glucose
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide 1
HbA1c	Glycosylated haemoglobin
ICER	Incremental Cost-effectiveness Ratio
ICH-GCP	International Conference on Harmonisation- Good Clinical Practice
IDF	International Diabetes Federation
IGT	Impaired glucose tolerance
LDL-C	Low density lipoprotein cholesterol
MMAS	Morisky Medication Adherence Scale
NHMS	National Health and Morbidity Survey
OAD	Oral antidiabetic agent
PPG	Post prandial glucose
QALY	Quality adjusted life year
RP	Renal profile
SGLT	Sodium-coupled glucose co-transporter
SMBG	Self monitoring blood glucose
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TZD	Thiazolidinedione
UKPDS	UK Prospective Diabetes Study
UMAB	Urine microalbumin

LIST OF APPENDICES

PENILAIAN KAWALAN GLISEMIK MEMBANDINGKAN INOVATOR DENGAN GENERIK DOS TETAP GLIBENCLAMIDE/ METFORMIN DALAM KALANGAN PESAKIT DIABETES MELLITUS DI KLINIK PESAKIT LUAR

ABSTRAK

Ubat generik menyediakan alternatif yang lebih murah dan terbukti setara seperti ubat inovator melalui kajian bioekuivalens tetapi data mengenai keberkesanan dan keselamatan adalah terhad. Kajian ini bertujuan untuk menilai perbezaan dalam kawalan glisemik, pematuhan ubat, kesan sampingan dan keberkesanan kos antara tablet inovator dan generik dos tetap glibenclamide/metformin selepas bertukar dari administrasi bersama gliclazide dan metformin dan selepas bertukar antara satu sama lain. Kajian prospektif rawak bersilang ini dijalankan dari September 2014 hingga Ogos 2015 di kalangan pesakit diabetes jenis 2 yang dirawat dengan dos stabil sekurang-kurangnya 240 mg gliclazide dan 1000 mg metformin. Mereka dibahagikan secara rawak kepada dua kumpulan. Kumpulan A menerima tablet inovator glibenclamide/metformin 2.5/500 mg (Glucovance®) manakala Kumpulan B menerima tablet generik glibenclamide/metformin 2.5/500 mg (Diamide®) selama 12 minggu. Selepas 12 minggu, pesakit dalam Kumpulan A ditukar kepada generik sementara pesakit dalam Kumpulan B ditukar kepada inovator. Ujian asas seperti hemoglobin terglikosilat (HbA1c), kiraan pil, 'Morisky Medication Adherence Scale' (MMAS) dan bilangan episod hipoglisemia diukur. Ujian diulangi pada minggu ke-12 dan ke-24. Nisbah tambahan keberkesanan kos (ICER) dikira. Seramai 84 pesakit (59.5% perempuan; 51.2% dalam Kumpulan A) dengan purata umur 58.01 ± 7.87 tahun dan mempunyai diabetes selama 10 (IQR 9.75) tahun menyertai kajian ini. Tiada perbezaan yang signifikan antara kumpulan dalam ciri-ciri asas.

Purata HbA1c dikurangkan dengan signifikan dalam kedua-dua kumpulan (Kumpulan A -0.76%, $p<0.01$ dan Kumpulan B -0.56%, $p<0.01$) dari minggu ke-0 hingga minggu ke-12 tetapi meningkat dengan signifikan dalam kedua-dua kumpulan (Kumpulan A +0.39%, $p<0.01$ dan Kumpulan B +0.33%, $p<0.01$) dari minggu ke-12 hingga minggu ke-24. Walau bagaimanapun, tiada perbezaan diperhatikan antara dua kumpulan ($p>0.05$). Pertukaran dari administrasi bersama gliclazide dan metformin ke dos tetap glibenclamide/metformin mengurangkan purata HbA1c (-0.30%, $p<0.01$) secara signifikan dari minggu ke-0 hingga minggu ke-24. Kedua-dua kaedah kiraan pil dan MMAS menunjukkan peningkatan secara signifikan dalam kepatuhan kepada ubat-ubatan selepas bertukar kepada tablet inovator atau generik dos tetap glibenclamide/metformin ($p<0.01$). Selain itu, pematuhan Kumpulan B meningkat dengan signifikan, $p<0.05$ apabila ditukar dari generik kepada inovator glibenclamide/metformin. Tiada perbezaan signifikan dalam bilangan episod hipoglisemia selepas bertukar kepada dos tetap glibenclamide/metformin. Walau bagaimanapun, kurang episod hipoglisemia ($p=0.03$) didapati apabila ditukar dari generik kepada inovator glibenclamide/metformin dalam Kumpulan B. Enam pesakit mengadu mengantuk dengan penggunaan generik glibenclamide/metformin. Lebih ramai pesakit mencapai sasaran HbA1c $\leq$ 6.5% dengan tablet inovator berbanding generik (10.7% vs 1.2%, $p<0.05$). ICER menunjukkan tambahan sejumlah RM 282.95 diperlukan untuk merawat pesakit untuk mencapai sasaran HbA1c dengan generik glibenclamide/metformin. Kesimpulannya, pertukaran kepada inovator atau generik dos tetap glibenclamide/metformin meningkatkan kawalan glisemik serta pematuhan ubat dengan signifikan dan ditolerasi dengan baik. Generik glibenclamide/metformin

adalah terapeutik yang setara seperti inovator dalam kawalan glisemik tetapi rawatan dengan inovator adalah lebih kos efektif.

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ABSTRACT

Generic drugs provide cheaper alternative and proven to be equal as originator drugs through bioequivalence but the data on the efficacy and safety were limited. This study aimed to evaluate the differences in glycaemic control, adherence, adverse events and cost-effectiveness between original and generic fixed dose glibenclamide/metformin after switched from gliclazide co-administered metformin and after interchanged from each other. This prospective randomized cross over study was conducted from September 2014 to August 2015 among type 2 diabetes patients treated with stable dose of at least 240 mg of gliclazide plus 1000 mg of metformin. They were randomly divided into two groups. Group A received original glibenclamide/metformin 2.5/500 mg tablets (Glucovance®) whereas Group B received generic glibenclamide/metformin 2.5/500 mg tablets (Diamide®) for 12 weeks. After 12-week, patients in Group A were changed to generic while patients in Group B switched to original glibenclamide/metformin. Baseline glycosylated haemoglobin (HbA1c), pill count, Morisky Medication Adherence Scale (MMAS) and number of hypoglycaemic episodes were measured. The tests were repeated at 12-week and 24-week. Incremental cost-effectiveness ratio (ICER) was calculated. Eighty four patients (59.5% females; 51.2% in Group A) with mean age of 58.01 ± 7.87 years and had diabetes for 10 (IQR 9.75) years were included. Baseline characteristics were no significant difference between the groups. Mean HbA1c reduced significantly in both groups (Group A -0.76%, $p<0.01$ and Group B -0.56%,

p<0.01) from 0-week to 12-week but increased significantly in both groups (Group A +0.39%, p<0.01 and Group B +0.33%, p<0.01) from 12-week to 24-week. However, there was no difference between the groups (p>0.05). Nevertheless, the switch from gliclazide co-administered metformin to fixed dose glibenclamide/metformin reduced mean HbA1c (-0.30%, p<0.01) significantly from 0-week to 24-week. Both pill count and MMAS showed significant improvement in adherence after the switch to fixed dose glibenclamide/metformin regardless of original or generic (p<0.01). Besides, adherence improved significantly, p<0.05 when changed from generic to original glibenclamide/metformin in Group B. There was no significant difference in number of hypoglycaemic episodes after switched to fixed dose glibenclamide/metformin. However, significantly less episodes of hypoglycaemia (p=0.03) occurred when changed from generic to original glibenclamide/metformin in Group B. Six patients complained of drowsiness with generic glibenclamide/metformin. More patients achieved target HbA1c ≤ 6.5% with original compared to generic (10.7% vs. 1.2%, p<0.05). The ICER showed an additional RM 282.95 was required to treat patient to achieve target HbA1c with generic glibenclamide/metformin. In conclusion, the switch to original or generic fixed dose glibenclamide/metformin improved glycaemic control and adherence significantly and well tolerated. Generic fixed dose glibenclamide/metformin was therapeutically equivalent as original in glycaemic control but treatment with original was more cost-effective.

CHAPTER 1

GENERAL INTRODUCTION

1.1 Introduction

Diabetes mellitus is a chronic illness that has become a pandemic that affected 382 millions of people worldwide and the prevalence was estimated to increase to 592 millions in 2035 (Aguiree, Brown et al. 2013). The increased in diabetes population was mainly attributed by population growth and aging. With the rising prevalence, the direct healthcare cost of diabetes has increased for those aged between 20 to 79 years and was estimated to be USD 612 billions globally (International Diabetes Federation 2014). Majority of the people (80%) living with diabetes came from low- to middle-income countries (Aguiree, Brown et al. 2013). With the rapid growth and development, the number of diabetes patients increased in Western Pacific region that comprised of the one third of the world diabetes mellitus population (Aguiree, Brown et al. 2013). Thus, Western Pacific region that consisted of Malaysia, China, Japan, Thailand, Korea, Australia, New Zealand and others had the highest number of diabetes patients in the world. Despite being the region with most people living with diabetes, the total health expenditure related to diabetes was only USD 101 billions which was 16% of the total world healthcare expenditure for diabetes in 2013 (International Diabetes Federation 2014).

In Malaysia, the prevalence of type 2 diabetes had increased tremendously with the latest National Health and Morbidity Survey (NHMS) that was done in 2015 reported 17.5% adults aged 18 and above had diabetes compared to 15.2% in 2011 (Institute for Public Health 2011, Institute for Public Health 2015). It was no longer disease of

the elderly as more young people were living with diabetes nowadays. The prevalence of diabetes for those age 20 to 40 years doubled from year 2006 to 2011. For example, for those age between 20 to 24, the prevalence of diabetes mellitus increased from 2.0% in 2006 to 4.9% in 2011 (Letchuman, Wan Nazaimoon et al. 2010). In fact, recently 5.5% of those age 18 to 19 years were living with diabetes and the highest prevalence was among those aged 70 to 74 years that accounted for 39.1% of diabetes population in Malaysia. Higher prevalence was observed in urban area (17.7%) compared to rural area (16.7%) but was not statistically significant (Institute for Public Health 2015). The increased in prevalence might be due to availability of variety of food, unhealthy diet and physical inactivity following the rapid growth in the country. Additionally, the diabetes patients increased in conjunction with higher prevalence of obesity. Malaysia being a developing economy country, has no national public health insurance scheme (OECD , Reinhardt and Cheng 2000). Majority of known diabetes patients (79.3%) seek their treatment in the Ministry of Health Malaysia healthcare facilities (Institute for Public Health 2015). Hence, with the rising prevalence, it would increase the economic pressure on healthcare budgets.

The cost per person with diabetes was estimated to be USD 565.40 annually in Malaysia (Aguiree, Brown et al. 2013). On the other hand, local drug utilization study reported that the cost per patient per year was RM 3747.12 for ambulatory care diabetes patients in the public hospitals (Pharmaceutical Services Division 2014). This drug utilization study involved mostly tertiary hospitals and state hospitals that managed more complicated diabetes cases and 12.5% of patients suffered three or more comorbidities. The diabetes patients had multiple comorbids as diabetes mellitus is a progressive chronic illness that leads to microvascular and

macrovascular complications if poorly controlled (Stratton, Adler et al. 2000). With these complications, it had increased the cost of treatment for diabetes to as much as quadruple (Riewpaiboon, Pornlertwadee et al. 2007, Wang, Fu et al. 2009). For example, in Malaysia, the cost per patient per admission in government hospital for patients with diabetes foot or gangrene was seven times higher compared to the estimated annual cost per patient with diabetes alone (Zawiah 2007). Similarly, in China, the annual direct medical cost significantly increased more than double if the patient had both microvascular and macrovascular diseases compared to diabetes alone (Wang, Fu et al. 2009). Besides the increasing cost of treatment, the underlying comorbids would alter the quality of life and also the productivity of individuals living with diabetes that could indirectly affect the economic development. Therefore, it is essential to control diabetes and also treat with alternatives that are cost-effective.

Intensive glycaemic control is important to decrease microvascular and macrovascular complications such as retinopathy, nephropathy, cardiovascular disease and stroke (Holman, Paul et al. 2008) that will decrease the cost of treatment. However, percentage of diabetes patients achieving target was unsatisfactory in Malaysia as there was a drop of about 50% when comparing year 2003 and 2008. In 2003, 31.2% of patients achieved target glycosylated haemoglobin (HbA1c) of < 6.5% whereas only 11.4% of patients achieved this target in 2008. The mean duration of diabetes patients in Malaysia was 11.5 years. As duration of diabetes was longer, the glycaemic control worsened significantly (Mafauzy, Hussein et al. 2011). Meanwhile, more patients (23.8%) in the primary healthcare clinics in Malaysia were achieving target HbA1c in 2012 as compared to 19.4% in 2009. This might due to the shorter duration of diabetes in the primary healthcare clinics that was median

duration of five years (Feisul and Azmi 2013). In addition, patients in the primary healthcare clinics might be less complicated diabetes cases. The landmark study, UKPDS reported that only 25% of patients had glycaemic control of less than 7% with monotherapy of either insulin, metformin or sulphonylurea over the nine years follow-up period (Turner, Cull et al. 1999). This finding suggested that majority of patients required more than one medication to achieve their glycaemic target.

The Malaysian Clinical Practice Guideline (CPG) and various guidelines available worldwide recommended metformin as the first line oral antidiabetic agent for type 2 diabetes mellitus (Colagiuri, Dickinson et al. 2009, International Diabetes Federation 2012, Garber, Abrahamson et al. 2013, Ministry of Health Malaysia 2015, American Diabetes Association 2016). Metformin is a biguanide that reduces hepatic glucose output and increases the insulin sensitivity (DeFronzo, Barzilai et al. 1991, Johnson, Webster et al. 1993, Stumvoll, Nurjhan et al. 1995). If metformin therapy failed to achieve target glycaemic control after three to six months, guidelines suggested addition of second line agent ranging from oral antidiabetic agents (OADs) to insulin. The Malaysian CPG offered flexibility of sulphonylurea (SU), α-glucosidase inhibitor (AGI), dipeptidyl peptidase- 4 (DPP-4) inhibitor, glucagon-like peptide 1 (GLP-1) agonist, glinides, thiazolidinedione (TZD), sodium glucose co-transporter-2 (SGLT-2) inhibitor or insulin as second line agent (Ministry of Health Malaysia 2015). On the other hand, joint guideline by the American and European associations did not suggested AGI or glinides in the guidelines but suggested addition of other classes of antidiabetic agents similar to Malaysian CPG (American Diabetes Association 2016). As insulin was available in injection, majority of patients were taking oral medication (79.3%) compared to insulin (53.6%) (Mafauzy, Hussein et al. 2011). Besides the patients unwillingness to inject insulin, the physicians also

reluctant to initiate insulin when considering barriers like inconvenient treatment regimen as well as risk factors of hypoglycaemia with insulin therapy (Korytkowski 2002).

Sulphonylurea was usually prescribed as second line agent in Malaysia. Drug utilization study that used defined daily dose (DDD) as its measurement reported that the usage of sulphonylurea was as high as 34.73 DDD/1000 population in 2010 (Pharmaceutical Services Division and Clinical Research Centre 2014). This translated to on average 3.5% of Malaysian populations were prescribed with sulphonylurea every day in a year. Moreover, in the primary healthcare facilities, sulphonylurea (56.9%) was the second most used antidiabetic agents after metformin (82.5%) (Feisul and Azmi 2013). This is the drug class of choice as it was inexpensive and had long term efficacy and safety profile (Holman, Paul et al. 2008). Furthermore, only limited choices of drugs were available in primary healthcare facilities as the doctors available were medical officers or family medicine specialist. Newer generation of drugs such as DPP-IV inhibitors could only be prescribed by consultants. Prospective study comparing addition of either sulphonylurea, DPP-4 inhibitor, GLP-1 agonist or insulin to metformin monotherapy reported that sulphonylurea as second line therapy was equally effective in lowering the blood glucose and comparable in quality adjusted life year with other agents at lower cost (Zhang, McCoy et al. 2014). Besides, studies reported that the combination of sulphonylurea and metformin was the most cost-effective therapy as compared to TZD (Klarenbach, Cameron et al. 2011). It is oral medication and hence, surpasses fear of insulin injection among patients. In addition, combination of metformin and sulphonylurea targeted both insulin resistance and insulin deficiency (DeFronzo 1999). Sulphonylurea is an insulin secretagogue that triggers insulin release from the

pancreatic beta cell. Examples of sulphonylurea are glibenclamide, gliclazide, glimepiride and glipizide (Rendell 2004). All the agents in this group were equally effective (Gangji, Cukierman et al. 2007). A previous randomized double blind controlled trial that involved 289 T2DM patients showed that the efficacy of 40 mg gliclazide was comparable with 2.5 mg glibenclamide with no difference in fasting plasma glucose (FPG) and 2-hour post prandial glucose (Baba, Nakagawa et al. 1983). Addition of sulphonylurea to metformin further reduced HbA1c by 0.8% and more patients achieved target glycaemic control compared to metformin alone (36% vs. 25%) (Hermann, Scherstén et al. 1994, McIntosh, Cameron et al. 2011).

Currently, the combination oral antidiabetic agents were available in the Ministry of Health medication list. Fixed dose original glibenclamide/ metformin combination therapy (Glucovance®) had been available in the formulary since 2007 (Ministry of Health Malaysia 2010, Lim, Lim et al. 2012). The use of this combination tablet in public healthcare facilities had increased more than doubled in 2010 to 2.0897 DDD/1000 population as compared to 0.7034 DDD/1000 population in 2009 (Minisitry of Health Malaysia 2011). In February 2014, the generic fixed dose glibenclamide/ metformin tablet (Diamide®) had replaced the original glibenclamide/ metformin tablet in government hospitals and health clinics as the price was cheaper.

A multicentre, randomized, double-blind, three-arm parallel group trial reported greater HbA1c reduction with fixed dose glibenclamide/ metformin compared to metformin or glibenclamide monotherapy in type 2 diabetes patients who inadequately controlled with lifestyle intervention (Garber, Donovan Jr et al. 2003). Interestingly, lower dose of fixed dose glibenclamide/ metformin provided a

significant greater reduction of HbA1c than glibenclamide co-administered metformin (2.02% vs. 1.49%, $p < 0.01$). At the same time, adherence to glibenclamide/ metformin tablets was better as compared to glibenclamide co-administered metformin (84% vs. 76%, $p < 0.01$) (Blonde, Wogen et al. 2003). The combination tablets provided convenience and enhanced patients' adherence towards the medication (Cheong, Barner et al. 2008, Schernthaner 2010). This might be attributed to the number of tablets consumed by the patients that were reduced. In a retrospective database analysis of 1815 patients by Melikian et al., the patients' adherence improved by 16% when converting from polytherapy to a single combination tablet (Melikian, White et al. 2002).

A previous retrospective study found that the patients' HbA1c was reduced significantly by 0.83% after six months of switching to lower dose of glibenclamide in fixed dose glibenclamide/ metformin tablets from gliclazide co-administered metformin therapy (10 mg/day of glibenclamide vs. 270 mg/day of gliclazide). This study also concluded a significant reduction in cost of drug acquisition by 44% (Lim, Lim et al. 2012). Randomized controlled studies demonstrated that gliclazide and glibenclamide had similar efficacy in reducing fasting and two hours postprandial glucose as well as HbA1c in type 2 diabetes patients including the elderly (Harrower 1991, Tessier, Dawson et al. 1994). Moreover, a meta analysis of 21 randomized controlled trials that were heterogeneous ($I^2 = 42.1\%$) reported that glibenclamide did not increase the risk of cardiovascular events, death and weight gain when comparing with other sulphonylureas. However, glibenclamide had a higher risk of hypoglycaemia (15.3%) as compared to gliclazide (6.8%) (Gangji, Cukierman et al. 2007). The studies in the meta analysis involved comparison of glibenclamide monodrug to sulphonylurea and did not include the glibenclamide in combination

drug such as fixed dose glibenclamide/ metformin. A prospective randomized controlled trial demonstrated that fasting insulin concentration was lower with fixed dose glibenclamide/ metformin as compared with glibenclamide monotherapy ($p=0.024$) but there was a higher 2-hours post prandial insulin response with glibenclamide/ metformin (Garber, Donovan Jr et al. 2003). With less fasting insulin concentration in fixed dose glibenclamide/ metformin, the risk of hypoglycaemia might be lowered while the higher post prandial insulin response could lead to better glycaemic control. Furthermore, the use of fixed dose glibenclamide/ metformin tablet involved lower glibenclamide dose that might reduce the risk of hypoglycaemia caused by glibenclamide in the glibenclamide/ metformin tablets and enable further upward dose titration in future management. This in return could delay the introduction of third oral antidiabetic agent or insulin.

Fixed dose glibenclamide/ metformin tablet was cheaper that gliclazide tablet and consequently had lower cost than gliclazide co-administered metformin regardless of original or generic. Hence, it had become common practice of switching to fixed dose glibenclamide/ metformin from gliclazide co-administered metformin in the healthcare facilities in the Ministry of Health, Malaysia. The price of original glibenclamide/ metformin 2.5/500 mg was RM 0.10 per tablet whereas generic glibenclamide/ metformin 2.5/500 mg was priced at RM 0.06 per tablet and both were cheaper as compared to generic gliclazide 80 mg that costed RM 0.14 per tablet and generic metformin 500 mg which priced at RM 0.08 per tablet (Ministry of Health Malaysia 2010). The cost of treatment for oral antidiabetic agents for patients treated with fixed dose glibenclamide/ metformin tablets (two tablets twice a day) was RM 0.40/ day and RM 0.24/ day for original and generic respectively whereas for patients treated with gliclazide 240 mg/day co-administered metformin 2000

mg/day, the cost was RM 0.74/ day, which was about two to three times more costly. As there were only retrospective data and small scale studies available to support the switch to fixed dose glibenclamide/ metformin therapy, it is important to conduct a prospective study to evaluate the efficacy and safety of the change in therapy.

Even though generic fixed dose glibenclamide/ metformin tablet was bioequivalence to original and film-coated tablet, it might not have special particle formulation as the originator product. In the originator product, glibenclamide was designed in a range of particle sizes within a freely soluble metformin matrix. When using ANOVA to analyze the log transform value, there were statistically differences between generic and original glibenclamide component in term of area under the curve ($p=0.0159$) and maximum concentration ($p=0.0059$). However, there was no difference between the metformin component in the original and generic fixed dose glibenclamide/ metformin product in term of area under the curve and maximum concentration. As this was a combination tablet, bioequivalence was based on 90% confidence interval of the whole tablet as a component over reference and allowed certain variation in the rate and extend of absorption in the limit of 0.80 – 1.25 to grant the generic drug as equivalence based on US FDA and Malaysia Bioequivalence Guideline (Ministry of Health Malaysia 2000). Hence, generic fixed dose glibenclamide/ metformin was bioequivalence to original glibenclamide/ metformin because the tablet as a whole was within the bioequivalence limit of 0.80 to 1.25 (Yuen, Wong et al. 2008). Even though fixed dose glibenclamide/ metformin passed the bioequivalence study, it might be different in therapeutic equivalence as the original fixed dose glibenclamide/ metformin had special formulation and the variation of glibenclamide in the fixed dose tablet might lead to different therapeutic effect. Besides, the issues around non-therapeutic equivalence among bioequivalence

products were happened among the antiepileptic drugs such as phenytoin and carbamazepine as those drugs had narrow therapeutic index. The change to generic had cause breakthrough seizure and emergence of new adverse events (Van Paesschen, Hauman et al. 2009). It was advisible that epileptic patients maintain with the same brand of antiepileptic drugs regardless of original or generic. Therefore, it is important to evaluate whether the different between generic and originator product especially combination drug or narrow therapeutic index drug will lead to clinically significant impact on the efficacy and safety of the patients. Nevertheless, to the best of our knowledge, currently there was no study comparing the efficacy, adherence and adverse drug reactions between original and generic fixed dose glibenclamide/ metformin tablet product.

1.2 Rationale of The Study

Prevalence of diabetes mellitus had increased tremendously in conjuction with increased in number of population and aging. Diabetes mellitus was a progressive disease that complicated with microvascular and macrovascular complications. As the population aged, the duration of diabetes was longer and also associated with more complications that decreased the quality of life. Besides, the cost of treatment for diabetes was getting higher as more new generation antidiabetic drugs were available at higher price and treatment of diabetes also included treatment of complications. This implied economic pressure in healthcare since most of the patients seek treatment in the public healthcare facilities. As the result, there was a need for drug that was effective, safe and inexpensive.

Generic drugs provided cheaper alternatives and most of the drugs in the Ministry of Health Malaysia were switched to generic once off patent. However, several studies showed that prescribers had poor perception towards generic drugs as compared to original counterparts. A local study conducted in Hospital Seberang Jaya, Penang had demonstrated that only 35.6% of prescribers had perception that generic drug was equivalence to original drug and 32.2% of prescribers agreed that generic drug was not adequately tested. Majority of the prescribers(86.4%) need more information regarding the efficacy and safety of generic drugs (Leong, Lim et al. 2013). Besides, more than half of the patients (52.6%) preferred original drugs and 28.5% of patients agreed that generics were less effective (Lim, Leong et al. 2014). A study conducted in US also stated that 23% of the physicians had negative perception towards the efficacy and half of them was concerned about the quality of generic drugs (Shrank, Liberman et al. 2011). Similarly, majority of patients in US did not prefer generic drugs (Shrank, Cox et al. 2009).

Therefore, this study enables us to compare the efficacy of original and generic fixed dose glibenclamide/ metformin tablet. So far there was no prospective study being conducted to compare the efficacy between original and generic fixed dose product in Malaysia and other countries. Generic fixed dose product might have different formulation as compared to its original counterpart that would affect the efficacy and safety of the drugs when used in patients. The rate of absorption in the patients might be altered due to underlying disease, organ dysfunction and concomitant medications. Bioequivalence study was done in healthy subjects and might not be enough to demonstrate therapeutic equivalence. Thus, therapeutic equivalence study comparing generic and original fixed dose glibenclamide/ metformin in T2DM patients could provide better evidence. Previous studies were retrospective and had

demonstrated significant greater reduction of HbA1c in fixed dose glibenclamide/ metformin combination compared to sulphonylurea co-administered metformin (Blonde, Wogen et al. 2003, Lim, Lim et al. 2012). Since the study was retrospective, association of better glycaemic control with adherence following treatment with lower dose of fixed dose glibenclamide/ metformin was not captured. Hence, this study enables us to evaluate the adherence and the association with glycemic control. Additionally, in the previous retrospective study conducted in Malaysia, the cost of drugs was evaluated but the issues around adverse drug reactions were not included (Lim, Lim et al. 2012). This study can also evaluate the adverse drug reactions when changing from gliclazide co-administered with metformin to fixed dose glibenclamide/ metformin tablet and the difference between the original and generic arm. Adverse drug reactions are measures for safety of the drug. With this prospective study, the overall cost of the treatment that included cost to treat adverse drug reactions can be evaluated. The true cost-effectiveness of original and generic fixed dose glibenclamide/ metformin tablets can be evaluated.

Confidence of prescribers and patients towards generic will increase if generic fixed dose glibenclamide/ metformin is comparable to original fixed dose glibenclamide/ metformin in terms of efficacy and safety. Besides, the combination drugs with less tablet counts may be a better option in the treatment of T2DM if the efficacy and adverse events when switch to fixed dose glibenclamide/ metformin tablets are comparable or better than gliclazide co-administered metformin therapy, as it may safe the overall treatment cost.

1.3 Objectives of This Study

1.3.1 General Objective

To assess the patients' glycemic outcome, adherence and adverse drug reactions between original and generic fixed dose glibenclamide/ metformin tablet after switching from gliclazide co-administered with metformin and after interchanging from original to generic or generic to original.

1.3.2 Primary Objective

To compare the HbA1c level between original and generic fixed dose glibenclamide/ metformin tablet.

1.3.3 Secondary Objectives

1) To evaluate the difference in HbA1c level after switching from gliclazide co-administered metformin to fixed dose glibenclamide/ metformin.

2) To compare the patients' adherence to medication before and after switching from gliclazide co-administered with metformin to fixed dose glibenclamide/ metformin tablet.

3) To determine the adverse drug reactions including patients reported hypoglycaemia and weight change after switching from gliclazide co-administered with metformin to fixed dose glibenclamide/ metformin tablet.

4) To compare the cost effectiveness between patients under generic and original fixed dose glibenclamide/ metformin tablet group.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview

A systematic literature search was conducted using electronic databases that consisted of ProQuest, Science Direct, Wiley Online Library and Pubmed. Relevant articles from year 1984 to 2015 were identified. Text word, MESH terms and keywords for the search were “diabetes mellitus” or “diabetes mellitus type 2”or “diabetes mellitus type II” combined with “glyburide” or “glibenclamide”, “glyburide/metformin” or “glibenclamide/metformin”, “metformin” and “glibenclamide” or “glyburide” or “gliclazide” or “combination tablet” or “generic” or “original”. In addition, further search was carried out using text word and MESH terms of “diabetes mellitus” or “diabetes mellitus type 2” in combination with “glyburide/metformin” or “glibenclamide/metformin” and “gliclazide” or “generic” and “original”. As for the adherence of the antidiabetic agents, the search included keywords of “diabetes mellitus” and “adherence” or “compliance” or “combination tablet”. Only English language articles were filtered for literature review. Besides, additional search of the references of the articles were also done. All the abstracts were reviewed and appropriate full articles were critically appraised. If there was abundance of abstracts that were almost similar especially on review article, systematic review and meta-analyses, the latest version was selected.

2.2 Type 2 Diabetes Mellitus (T2DM)- Pathophysiology

Understanding the pathophysiology of a disease is utmost important for the management of the disease. As the result, to treat type 2 diabetes mellitus (T2DM) effectively, pathophysiology of this disease was discussed so that treatment was targeted to the mechanism that was responsible to this disease.

Over the decades, two major metabolic defects namely ß-cell dysfunction and insulin resistance in the liver and muscle have been the main causes of T2DM (Buchanan 2003). In fact, the pancreatic ß-cell failure occurred earlier before T2DM was diagnosed (DeFronzo 2009). However, there was a paradigm shift from triumvirate to ominous octet as the pathophysiology of T2DM expanding from ß-cell failure and insulin resistance in the liver and muscle to α-cell, gastrointestinal hormones, kidney, fat cells and brain (Figure 2.1) (DeFronzo 2010).

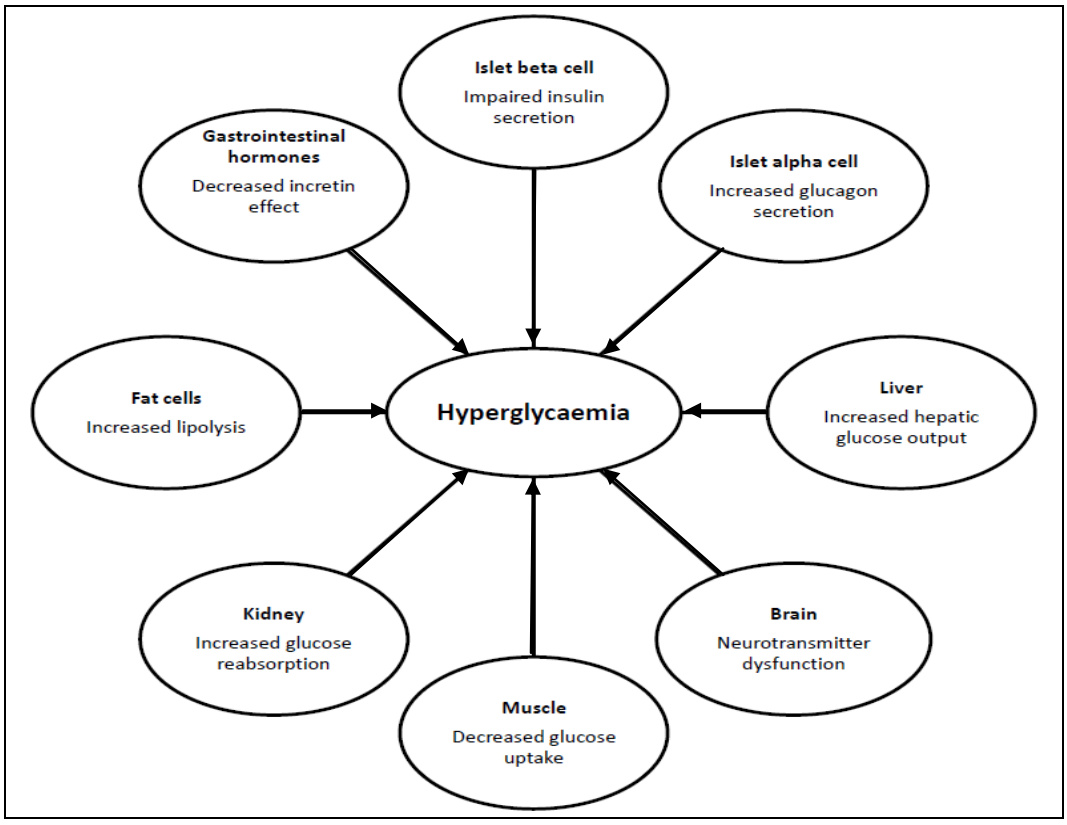

Figure 2.1: Pathophysiology of type 2 diabetes mellitus

2.3 Guidelines for the Treatment of T2DM

There were various guidelines for the treatment of T2DM in the world. However, all these guidelines had a similarity that metformin was the first line agent (Inzucchi, Bergenstal et al. 2012, Garber, Abrahamson et al. 2013, American Diabetes Association 2015, Ministry of Health Malaysia 2015). Metformin was the drug of choice as it is inexpensive and has durable efficacy and safety as well as robust evidence of cardiovascular safety (Holman, Paul et al. 2008, Selvin, Bolen et al. 2008).

In Malaysia, the Clinical Practice Guideline (CPG) was recently updated and published in November 2015. Unlike the previous CPG that had one treatment algorithm, the recent CPG recommended three types of treatment algorithm that consisted of treatment algorithm for newly diagnosed T2DM, patients on clinic follow-up and specific patient profiles (Ministry of Health Malaysia 2009, Ministry of Health Malaysia 2015). The treatment algorithm for newly diagnosed T2DM was almost the same as recommendation for patients on clinic follow-up. The difference was the newly diagnosed algorithm had additional column for HbA1c < 6.5% that recommended lifestyle interventions such as exercise and diet. This algorithm suggested addition of metformin or either one of these drug classes, namely glinides, α-glucosidase inhibitor (AGI) or dipeptidyl peptidase- 4 (DPP-4) inhibitor if post prandial blood glucose was more than 11 mmol/l. Specific patient profiles treatment algorithm were divided into five profiles namely normal weight, overweight, obese, increase risk of hypoglycaemia and chronic kidney disease (CKD) stage three onwards. This algorithm provided a more specific guideline by suggesting definite class of drug after metformin monotherapy failed. It was tailored to certain patients' characteristics as compared to previous guideline that was more generalizable.

Hence, it might aid in faster decision making when choosing the appropriate treatment for the patients.

Metformin was still the preferred first line agent for all three treatment algorithm when HbA1c fell between 6.5% to <7.5% except for CKD stage four and five, metformin was contraindicated. If the patient was unable to tolerate metformin, other agent such as sulphonylurea (SU), α-glucosidase inhibitor (AGI), dipeptidyl peptidase- 4 (DPP-4) inhibitor, glinides, glucagon like peptide-1 (GLP-1) agonist, thiazolidinedione (TZD) or sodium glucose co-transporter-2 (SGLT-2) inhibitor can also be considered as first line second line agent (Ministry of Health Malaysia 2015). The recent Malaysian CPG was more aggressive as smaller range of HbA1c in the algorithm and third agent was suggested to be added in when the HbA1c fell between 8.5% to 10% (Ministry of Health Malaysia 2015). Previous CPG suggested larger range of HbA1c as monotherapy of oral antidiabetic agent (OAD) when HbA1c was between 6.5% to < 8.0% and dual therapy when HbA1c was 8.0% to 10% (Ministry of Health Malaysia 2009). Besides, recent CPG recommended earlier intervention such as addition of second agent was suggested after three months if the HbA1c target was not achieved. Meanwhile previous CPG recommended intervention to be done after three to six months if glycaemic control was not achieving the target. This might be due to the availability of different classes of OAD and also early intensive glycemic control would provide long term benefit in reducing the relative risk of microvascular and macrovascular complications (Holman, Paul et al. 2008).

If the target HbA1c was not achieved after three months with dual therapy, triple therapy was recommended. The recent Malaysian CPG recommended that oral agent could be added as third line as well as option of adding insulin unlike the previous guideline that suggested addition of insulin if dual therapy failed to achieve target

HbA1c. This might due to the availability of newer class of OAD. The updated guideline was similar to the American and European professional or regulatory organizations as there was option of addition of third oral agents. (Ministry of Health Malaysia 2009, Inzucchi, Bergenstal et al. 2012, Garber, Abrahamson et al. 2013, Ministry of Health Malaysia 2015).

American Diabetes Association (ADA) recently updated its guideline and there was no difference with the guideline in 2015 (American Diabetes Association 2016). Joint guideline by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) suggested that if the individualized target HbA1c was not met after three months, second line agent such as sulphonylurea, DPP-4 inhibitor, GLP-1 agonist, SGLT-2 inhibitor or insulin could be added (American Diabetes Association 2015). The guideline by ADA/EASD did not have the range of HbA1c as it focused on patient centred approach where target HbA1c was individualized. The Malaysian CPG also suggested the combination therapy of metformin with the same drug as the recommendation of American and European counterparts if the patient's HbA1c level was > 6.5% after three months of monotherapy or the HbA1c level was between 7.5% to <8.5% during the diagnosis of diabetes with additional options of AGI and glinides. However, in the specific patient profiles algorithm, insulin was only suggested as fourth line (Ministry of Health Malaysia 2015). This might due to consideration of weight, risk of hypoglycemia and also patients' preference of oral agents over insulin injection.

Similar to Malaysian CPG, the American Association of Clinical Endocrinologists (AACE) also recommended that metformin was the first line agent for patients with newly diagnosed T2DM or mild hyperglycemia with HbA1c < 7.5%, but it was contraindicated in advance renal impaired patients. Alternatives to metformin

suggested by the AACE was same as the options suggested in latest Malaysian CPG. (Garber, Abrahamson et al. 2013). Both guidelines were more flexible as all classes of OAD were included in the guidelines and provided options that could be considered as first line if the patient was unable to tolerate metformin. AACE also recommended a larger option of second line agent if the patient failed to achieve target HbA1c with metformin alone or if diagnosed with HbA1c > 7.5%. The options included all OADs or insulin as recommended by ADA as well as colesevelam, dopamine receptor agonist such as bromocriptine mesylate or AGI. AACE only recommended addition of insulin in patient with HbA1c > 8% on two or more OADs or patients with entry HbA1c > 9% due to consideration of few factors such as risk of hypoglycemia, patient's motivation, underlying co-morbidities as well as patient well being (Garber, Abrahamson et al. 2013).

All the latest guidelines recommended several OADs classes and insulin as the second line when the patients failed to achieve target of glycaemic control with metformin monotherapy (Garber, Abrahamson et al. 2013, American Diabetes Association 2015, Ministry of Health Malaysia 2015). There was no consensus that recommended a definite class of drug as the second line and provided the flexibility to the healthcare professionals except for the recent updated Malaysian CPG that added of specific patient profiles treatment algorithm (Ministry of Health Malaysia 2015). This specific patient profiles treatment algorithm suggested DPP-4 inhibitor as second line agent as it was weight neutral. However, for overweight and obese patients, SGLT-2 inhibitor and GLP-1 analogue were recommended respectively. Even though, the updated CPG provided convenience in deciding the second or third line agent, consideration of the availability and cost of drug was still needed. The GLP-1 analogue and SGLT-2 inhibitor were not available in the Malaysian

government essential drug list and they were also very expensive (Ministry of Health Malaysia 2010).

With the diverse guidelines, the definite glycaemic target remained controversial as different guidelines recommended different HbA1c target ranging from ≤ 6.5% (Garber, Abrahamson et al. 2013, Ministry of Health Malaysia 2015) to < 7% (American Diabetes Association 2015). The recent Malaysian CPG still maintained with glycaemic target of ≤ 6.5% in general but there was addition of ranges of target HbA1c like ADA/EASD guideline. Irrespective of the variation in the recommended glycaemic target among different guidelines, the best glycemic target should be individualized and consider patients underlying comorbidities, duration of diabetes, life expenctancy and also risk of hypoglycemia. Treatment of T2DM should incorporate patient-centric approach, treat to target and to avoid hypoglycemia. The recent Malaysian CPG considered these factors and suggested for younger and healthier patients with low risk of hypoglycemia, tighter target of 6.0%-6.5% was recommended whereas looser target of 7.1%-8.0% was recommended for elderly, patients with co-morbidities (coronary disease, heart failure, renal failure, liver dysfunction) or hypoglycemia prone patients (Inzucchi, Bergenstal et al. 2012, Ministry of Health Malaysia 2015).

2.4 The Diabetes Control

A previous cross sectional observational study conducted in Malaysia namely DiabCare Malaysia 2008 reported that as the duration of diabetes increased, glycaemic control deteriorated as mean HbA1c increased significantly ($p<0.001$). The mean HbA1c was reported as 7.32 ± 1.5% if the duration of diabetes was less

than a year and it subsequently raised to above 8% as diabetes was longer with 8.34 ± 2.1%, 8.47 ± 1.9% and 8.83 ± 1.9% for the duration of 1-5 years, > 5-10 years and more than 10 years respectively. Only minority patients (11.4%) achieved glycaemic control of less than 6.5% as recommended by the Malaysian CPG (Ministry of Health Malaysia 2009). Besides, only 22% of the patients achieved HbA1c < 7% as of the ADA target as compared to 41% in 2003 (Mafauzy 2006, American Diabetes Association 2011). The blood glucose control deteriorated over the years with mean HbA1c of 8.66 ± 2.09% reported in DiabCare 2008 as compared to 7.80 ± 2.2% in 2003 (Mafauzy, Hussein et al. 2011).

Another cross sectional study conducted in a tertiary hospital in Malaysia that included T2DM patients aged 18 years and above and on diabetic medication for at least 3 months, also reported that only 17.4% (95% CI, 13.7-21.1%) of patients achieved target HbA1c of < 6.5% based on patients medical records. The main aim of this study was to assess patients adherence based on self reporting questionnaire. The mean age of the patients was 60.3 ± 10.3 years and the mean duration of T2DM was 13.2 ± 8.9 years. More than half of the patients (56.5%) were taking six to 10 type of drugs with 76.5% of patients taking more than one antidiabetic agent and 49.9% of patients injecting insulin. Metformin was the most commonly used antidiabetic agent (68.6%), followed by gliclazide (42.5%) (Chua and Chan 2011). Similar to DiabCare 2008, duration of diabetes also affected the glycemic control besides adherence and use of complementary medicines (Chua and Chan 2011, Mafauzy, Hussein et al. 2011). The patients who were adherence to medications [p=0.035, OR 2.0 (1.1-3.7)], using complementary medicines [p<0.01, OR 0.4 (0.2-0.8)] and those who had shorter duration of T2DM ≤10 years [p<0.01, OR 2.3 (1.2-4.3)] were more likely to achieve target HbA1c (Chua and Chan 2011). These

findings had demonstrated that majority of patients were not achieving the targets even though on diabetes treatment. Besides, this was a single center survey study and the adherence was based on self-report that might over reporting. Therefore, reassessment of current practice plus measures such as addition or alteration of drugs, patients' empowerment and education as well as adherence should be instigated.

The glycaemic control in European countries and United Kingdom was reported to be better than Malaysia in the retrospective prevalence based study, CODE-2 that collected data from November 1998 to May 1999. The CODE-2 study consisted of seven countries in Europe and United Kingdom whereas the DiabCare 1998 was a cross sectional study from 10 centres in Malaysia. The mean HbA1c in CODE-2 study was 7.5% whereas in DiabCare 1998, the mean HbA1c was 8.4%. The percentage of patients achieving HbA1c $\leq$ 6.5% was 31% in CODE-2 study (Liebl, Mata et al. 2002, Mafauzy 2006). This was more than doubled of the amount of patients in Malaysia as only 14% of patients achieved HbA1c < 6.5% in DiabCare 1998. The patients in Malaysia was younger (56 ± 11.7 years) but had longer duration of diabetes (11 ± 7.4 years) and this might be the factor leading to poorer HbA1c control in the Malaysian study as compared to the patients in CODE-2 (mean duration of diabetes = 9.3 years; mean age = 69.5 years) (Mafauzy 2006). This was consistent to the disease progression over the duration of diabetes. In CODE-2 study, 59% of the patients were on OADs and 24% on insulin alone or in combination with oral agents. However, patients on insulin alone or in combination with other drug had poorer glycemic control (mean HbA1c 8.1%) as compared to OADs (mean HbA1c 7.5%) or diet and exercise alone (mean HbA1c 6.7%). Insulin might be added to maintain adequate glycaemic control especially for those with longer duration of

diabetes (Jönsson 2002). Meanwhile, for DiabCare 1998, there was no information on the drug use specifically for Malaysia but there was information based on grouping of six Asian countries. Majority of the patients were on OADs (81%) and only 6% of patients were on diet and 19% were on insulin with or without OADs. More than half (52%) of the patients were on oral combination therapy and more patients were taking SU (35%) than biguanide (12%) (Chuang, Tsai et al. 2002). Most of the patients required combination therapy as they were unable to achieve target HbA1c with monotherapy.

On the other hand, in the United States, data from National Health and Nutrition Examination Survey (NHANES) was used to determine the prevalence, treatment and management of diabetes. Approximately half of the diabetes patients (50.9%) achieved HbA1c of < 7% from 1999 to 2006 (Cheung, Ong et al. 2009). Contrary to Malaysia, HbA1c improved over the years in the United States with 7.82% in 1999 to 2000 and it dropped to 7.47% and 7.15% in 2001 to 2002 and from year 2003 to 2006 respectively (Koro, Bowlin et al. 2004, Hoerger, Segel et al. 2008, Cheung, Ong et al. 2009). The improvement in glycaemic control in the United States might be attributed to awareness campaigns organized by ADA and also availability of multiple drugs. This might be ideal as it was almost achieving the target of HbA1c < 7% as recommended by ADA and further reduction of glycaemic control might not show additional benefit to cardiovascular outcome (Skyler, Bergenstal et al. 2009).

2.5 Second Line Agent

In the UKPDS study, after nine years of follow-up in the intensive arm, only 25% of patients achieved HbA1c < 7% with monotherapy of either metformin, sulphonylurea

or insulin (Turner, Holman et al. 1998). This suggested that majority of patients require more than one medication to achieve their glycaemic target. There was no consensus that recommended a definite class of drug as the second line and provided the flexibility to the healthcare professionals. Thus, drug that was efficacious, safe and economical should be suggested as the choice for second line agent considering the rising prevalence in T2DM (Aguiree, Brown et al. 2013) and its impact towards economic burden (International Diabetes Federation 2014).

The latest drug class, SGLT-2 inhibitor targeted a different pathway that was inhibiting the reabsorption of glucose in the kidney independent of insulin (Bays 2009, Brunton and Reid 2014). Dapagliflozin by Astra Zaneca® was the first SGLT-2 inhibitor approved by the European Medicines Agency (EMA) at the end of 2012 and it was launched in Malaysia at early 2014 (Haas, Eckstein et al. 2014). On the other hand, canagliflozin was the first SGLT-2 inhibitor granted marketing in the United States as dapagliflozin had safety concern on increased risk of bladder and breast cancer (Burki 2012). The evidence on the safety of this drug class was still ongoing (Neal, Perkovic et al. 2013). Recently, 13 episodes of euglycaemic diabetic ketoacidosis and ketosis were reported among type 1 diabetes and type 2 diabetes patients taking SGLT-2 inhibitors (Peters, Buschur et al. 2015). Indeed, EMA and US Food and Drug Administration (FDA) were following the post-marketing surveillance on its cardiovascular, renal safety and cancer risk (Haas, Eckstein et al. 2014). In Malaysia, the use of SGLT-2 inhibitor was limited to the private sector as it was not included in the government essential drug list. Although the Malaysian CPG, AACE and ADA recommended addition of SGLT-2 inhibitor as second line agent, the International Diabetes Federation (IDF) did not recommend the use of SGLT-2