UNIVERSITI TEKNOLOGI MARA

EFFECTS OF DAPAGLIFLOZIN ON ENDOTHELIAL DYSFUNCTION IN TYPE 2 DIABETES MELLITUS WITH ESTABLISHED ISCHAEMIC HEART DISEASE (EDIFIED)

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of the requirements for the degree of
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CONFIRMATION BY PANEL OF EXAMINERS

I certify that a Panel of Examiners has met on 30th October 2017 to conduct the final examination on Nur Aisyah Zainordin on her Masters in Internal Medicine thesis entitled "**E**ffects of **D**apagliflozin On Endothelial **D**ys**F**unction **I**n Type 2 Diabetes Mellitus With **E**stablished Ischaemic Heart **D**isease (**EDIFIED**)" accordance with Universiti Teknologi MARA Act 1976 (Akta 1973). The Panel of Examiners recommends that the student should be awarded the relevant degree. The panel of examiners was as follow:

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ABSTRACT

Background: SGLT-2 inhibitor has been shown to confer significant cardiovascular (CV) risk reduction in T2DM patients with ischaemic heart disease. However, the mechanism remains unclear. Endothelial dysfunction is a recognized independent predictor of cardiovascular events particularly in T2DM. It is effectively assessed via the measurements of flow-mediated vasodilatation (FMD).

Aims: This study therefore aimed to demonstrate the effect of dapagliflozin on endothelial dysfunction as a possible mechanism in CV risk reductions in high-risk T2DM subjects.

Methods: This was a prospective, double-blinds, placebo-controlled, clinical trial on T2DM patients with underlying ischaemic heart disease who were receiving metformin and insulin therapy (n=81). Subjects were randomised to receive 12-weeks therapy of either dapagliflozin (n=40) or placebo (n=41). Subjects underwent an endothelial function examination measured by ΔFMD and ΔNMD and surrogate markers; ICAM-1, eNOS, hsCRP and Lp(a) of according to the standard protocols. Glycaemic and lipid profiles were also measured as well as metabolic and hemodynamic changes.

Results: After 12 weeks of therapy, dapagliflozin group demonstrated significantly bigger reductions of HbA1c and fasting blood sugar (FBS) compared to the placebo group (ΔHbA1c -0.16±1.25 vs. -0.83±1.47, p=0.042 and ΔFBS -1.90±4.40 vs -0.73±4.55, p=0.015, respectively). There is improvement in ICAM-1 level in dapagliflozin group which showed improvement in endothelial inflammation (ΔICAM-1, dapagliflozin group vs placebo group, -83.9± 205.9ng/mL : $p<0.02$ vs -11.0±169.1 ng/mL p= 0.699) . Albeit no statistical significance, there seemed to be a worsening of ΔFMD within the placebo group whilst the active group had similar values. Univariate correlation analysis revealed a significant negative correlation between HbA1c and ΔFMD within the active group (r= -0.31, p= 0.02) which was not seen within the placebo group.

Conclusion: A 12-week therapy with dapagliflozin, in addition to insulin and metformin, resulted in significant reductions in HbA1c and FBS, which was further associated with improvement in endothelial dysfunction as measured by FMD and ICAM-1. Preservation of endothelial function within the dapagliflozin group could potentially attenuate progression of atherosclerosis in a group of patients with high plaque burden.

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