P-0658 – Effects on endothelial dysfunction with improvement in HbA1c with Dapagliflozin- a 12-week, placebo-controlled trial

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Graph 1: Change in FMD% after 12 weeks of intervention

	DAPA	Placebo	p-value
Baseline	11.22± 8.34	11.49 ± 5.84	0.792
Week 12	11.41± 6.87	9.84 ± 5.25	0.281
Change	0.19± 10.38	-1.36 ± 7.76	0.400
p-value within group	0.91	0.21	

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-blind, 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 Δ FMD and Δ NMD 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 (Δ HbA1c -0.16 ± 1.25 vs. -0.83 ± 1.47 , $p=0.042$ and Δ FBS -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 (Δ ICAM-1, dapagliflozin group vs placebo group, -83.9 ± 205.9 ng/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 Δ FMD within the placebo group whilst the active group had similar values. Similar trends are noted in Δ NMD, in which there is statistical significant difference between both groups at week 12.

Graph 2: Change in glycaemic control after 12 weeks of intervention

Univariate correlation analysis revealed a significant negative correlation between HbA1c and Δ FMD within the active group ($r= -0.31$, $p= 0.02$) which was not seen within the placebo group. In subanalysis study in high CV risk patient with baseline Lp(a) >30 g/L, dapagliflozin group showed significant reductions of Lp(a) levels (-33.55 ± 50.89 g/L, p value = 0.035), which is not seen in placebo group (16.57 ± 214.67 g/L, p value = 0.794)

Change in Lp(a) in high CV risk

Graph 3: Change in Lp(a) after 12 weeks of intervention

		Baseline	12 weeks	Change	
Treatment groups	No	Mean ± SD	Mean ± SD	Mean ± SD	p-values
DAPA	14	102.02 ± 76.33	74.55 ± 104.2	-33.55 ± 50.89	0.028
Placebo	12	100.1 ± 94.64	122.37 ± 104.21	16.57 ± 214.67	0.794

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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