Effect of Empagliflozin on Endothelial Function in Patients With Type 2 Diabetes and Cardiovascular Disease: Results from the Multicenter, Randomized, Placebo-Controlled, Double-Blind EMBLEM Trial

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Recent large trials on sodium–glucose cotransporter 2 (SGLT2) inhibitors showed that these agents improved cardiovascular outcomes in patients with type 2 diabetes (T2D) with a high risk of cardiovascular events (1). However, the underlying mechanisms of these clinical benefits and vascular effect of SGLT2 inhibitors in that patient group remain uncertain. Endothelial dysfunction is exacerbated by metabolic disorders, such as diabetes, and involved in the pathophysiology of diabetes-related cardiovascular complications (2,3). We therefore investigated whether empagliflozin added to standard therapy, compared with placebo, affected endothelial function in patients with T2D and established cardiovascular disease (CVD). This was a prospective, multicenter, randomized, placebo-controlled, double-blind clinical trial undertaken in 16 centers in Japan (clinical trial reg. no. UMIN000024502, www.umin.ac.jp/ctr/index.htm) (4). A total of 117 adults with T2D and established CVD were randomized (1:1) to receive either empagliflozin 10 mg daily or placebo for 24 weeks. Randomization was performed by using the web-based minimization dynamic allocation method stratified according to HbA_{1c}, age, systolic blood pressure (BP), and smoking status. The placebo was indistinguishable from empagliflozin, and both study drugs were sequentially numbered and concealed. The participants and investigators remained masked to group assignments until the database lock (an action taken to prevent further changes to a clinical trial database). The effects of treatment on endothelial function were assessed by the reactive hyperemia peripheral arterial tonometry index (RHI) (5), with the primary efficacy end point being the change in RHI from baseline to 24 weeks.

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**A complete list of the investigators of the Effect of Empagliflozin on Endothelial Function in Cardiovascular High Risk Diabetes Mellitus: Multi-Center Placebo-Controlled Double-Blind Randomized Trial (EMBLEM) can be found in the Supplementary Data online.*

Ethics approval and informed patient consent were obtained.

Of the 117 patients, 105 were included in the full analysis set. Ten patients dropped out prior to initiation of the study drug, and two patients in the placebo group were excluded due to a serious protocol deviation (lack of data necessary for eligibility assessment). The baseline characteristics were as follows: mean (SD) age 64.9 (10.4) years, BMI 26.4 (5.3) kg/m^2, BP 133.2/75.7 (15.0/10.5) mmHg, diabetes duration 13.2 (10.9) years, and HbA_{1c} 7.2% (0.8%) (55 [9.0] mmol/mol); proportion of the patients who had previously taken dipeptidyl peptidase 4 inhibitors 70%, metformin 51%, thiazolidinedione 24%, and insulin 10%. All patients had at least one CVD (myocardial infarction 24%, angina 31%, stroke 20%, and heart failure 40%), and 77% of patients had been receiving treatment for hypertension (66% on ACE inhibitors or angiotensin receptor blockers, 49% on calcium channel blockers, and 36% on β-blockers) or dyslipidemia (75% on statins).

Twenty-four weeks of empagliflozin treatment significantly improved glycemic control (mean [SD] change volume of HbA_{1c} −0.3% [0.5%] [−2.7 (5.3) mmol/mol] vs. 0.1% [0.7%] [0.7 (7.8) mmol/mol], $P = 0.011$, and of fasting blood glucose −17.9 (22.0) mg/dL vs. −0.8 (37.6) mg/dL, $P = 0.007$). Reductions in BMI in the empagliflozin group were significantly greater than those in the placebo group (mean [SD] −0.8 [1.0] vs. −0.2 [0.8] kg/m^2, $P = 0.002$). There were borderline differences in the changes in BP between the treatment groups (systolic −7.6 [16.5] vs. −2.1 [12.1] mmHg, $P = 0.063$; diastolic −3.7 [8.7] vs. −0.2 [9.9] mmHg, $P = 0.058$).

RHI values at baseline and 24 weeks are shown in Fig. 1. Absolute changes in RHI from baseline to 24 weeks were −0.006 (SD 0.478) in the empagliflozin group and −0.025 (0.454) in the placebo group. The ANCOVA model adjusted for allocation factors demonstrated no significant intergroup difference in the changes in RHI (adjusted mean difference −0.020, 95% CI −0.199 to 0.158, $P = 0.821$). Likewise, in all the prespecified subgroups (e.g., age <65 or ≥65 years, HbA_{1c} <7.0% [53 mmol/mol] or ≥7.0%, systolic BP <140 or ≥140 mmHg, eGFR <60 or ≥60 mL/min/1.73 m^2, history of heart failure, and median RHI at baseline <1.77 or ≥1.77), no significant difference in changes in RHI was observed between the treatment groups.

To our knowledge, this is the first multicenter, randomized, placebo-controlled, double-blind trial to evaluate the effect of empagliflozin on endothelial function in patients with T2D and established CVD as a possible surrogate marker of the cardiovascular benefits from empagliflozin. This observation suggests that 24 weeks of empagliflozin treatment is not associated with an improvement in endothelial function in that population and that cardiovascular benefits observed in large trials (1) may have been attributable, at least in the early phase of treatment, to mechanisms other than amelioration of endothelial dysfunction. One limitation is that participants in our study had relatively well-controlled clinical conditions, such as BP, BMI, and HbA_{1c}, partly differing from those in the large trials. Additionally, we had no measurement of flow-mediated vasodilation, which has been validated against hard outcomes in several studies. Further studies are needed to test whether SGLT2 inhibitors affect endothelial function in other T2D populations.

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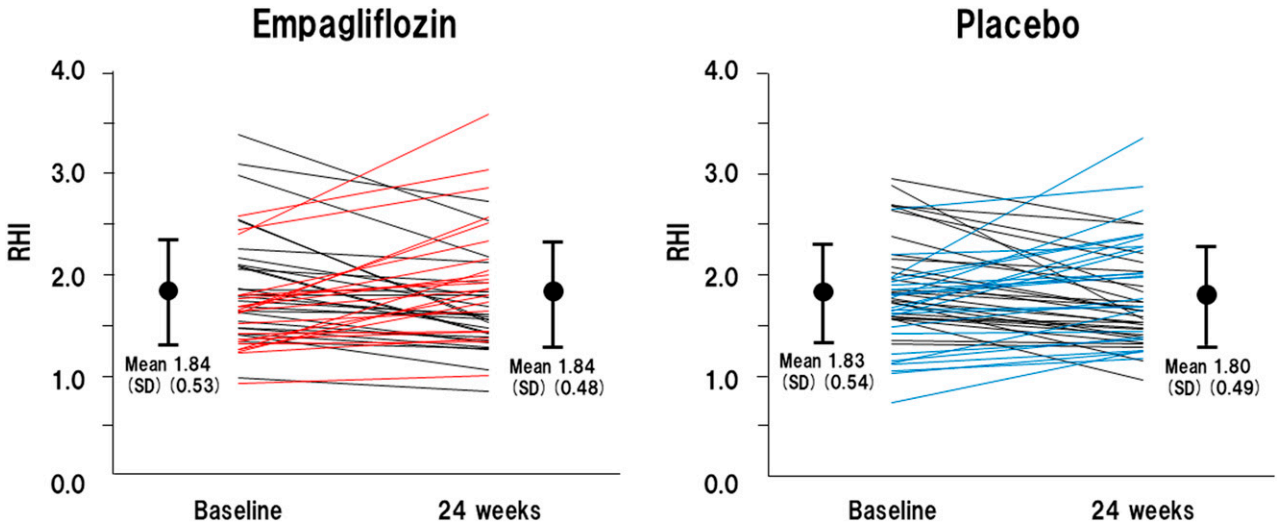

Figure 1—The mean (SD) RHI at baseline and at the 24-week follow-up. RHI values were increased ([RHI at 24 weeks] − [RHI at baseline] > 0) after 24 weeks of treatment in 21 patients (45%) in the empagliflozin group (red lines) and 24 patients (47%) in the placebo group (blue lines).

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Author Contributions. A.T. participated in the study design, operations, and analysis and interpretation of data and drafted the manuscript. M.S. helped to steer the study, collected and analyzed the data, and reviewed and edited the manuscript. N.M., H.T., Y.O., K.R.S., T.T, I.T., I.H., S.T., Y.M., H.T., M.Y.-T., H.Y., Y.S., Y.I., S.U., Y.H., and K.N. contributed to the study concept and design, study operations, data collection, and analysis and interpretation of data and critically reviewed and edited the manuscript. H.Y. contributed to the generation of the scheme for randomization. Y.S. contributed to the statistical analysis. S.U. and Y.H. helped to steer the study as research advisors and reviewed and edited the draft manuscript. K.N. was a principal investigator of the EMBLEM trial. K.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019; 393:31–39

2. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J 2013;34:2436–2443

3. Xu J, Zou MH. Molecular insights and therapeutic targets for diabetic endothelial dysfunction. Circulation 2009;120:1266–1286

4. Tanaka A, Shimabukuro M, Okada Y, et al.; EMBLEM Trial Investigators. Rationale and design of a multicenter placebo-controlled double-blind randomized trial to evaluate the effect of empagliflozin on endothelial function: the EMBLEM trial. Cardiovasc Diabetol 2017;16:48

5. Kuvin JT, Patel AR, Sliney KA, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. Am Heart J 2003;146:168–174