Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors and Stroke

To the Editor:

The large-scale EMPA-REG OUTCOME clinical trial¹ demonstrated for the first time that sodium-glucose cotransporter 2 inhibitors (SGLT2-Is) improved the prognosis for the heart¹ and kidneys² as well as hypoglycemic drugs, although stroke incidence tended to be increased.¹ In fact, a meta-analysis showed stroke increased significantly by SGLT2-Is.³ Recently, it has become clear that SGLT2-Is have a diuretic action,^{4,5} and conventional diuretics are known to effectively suppress stroke⁶ and heart failure.⁶ In the original EMPA-REG,¹ diuretics were combined with SGLT2-Is in 43.7%, probably leading to dehydration and/or hypotension, resulting in cerebral infarction. On the other hand, in an Asian subanalysis⁷ of EMPA-REG, only in 26.7% of participants were diuretics combined with SGLT2-Is, making the incidence of stroke less. As shown in the Figure,⁷ there was no tendency at all that stroke was increased by SGLT2-Is in the Asian group. These findings indicate careful use of combined diuretics and SGLT2-Is is required because SGLT2-Is themselves have a diuretic action.^{4,5} The heart failure subanalysis findings⁸ from EMPA-REG¹ are interesting.^{5,8} The prognostic improvements by SGLT2-Is were not significant under treatment including diuretics such as loop diuretics and aldosterone antagonists, suggesting that the prognostic improvement in heart failure by SGLT2-Is was mostly caused by the diuretic action of the SGLT2-Is.⁵ Because SGLT2-Is have a loop diuretic action,^{4,5} the co-administration of other diuretics may induce dehydration and/or hypotension as discussed next.

To date, diuretics have conventionally prevented stroke,⁶ as just discussed. Therefore, it is important to understand why SGLT2-Is, which have a loop diuretic action,^{4,5} increased stroke incidence. Combined use of different types of diuretics might result in massive diuresis. If loop diuretics (SGLT2-Is) are administered alone, Na reabsorption in the distal tubules (site of action of thiazides), located after the loop of Henle, is enhanced in a compensatory manner.⁵ Therefore, actual diuresis is limited. However, SGLT2-Is use in combination with thiazides may cause massive diuresis. Compensatory Na reabsorption by the distal tubules is dependent on aldosterone.⁵ Therefore, if SGLT2-Is are given with an aldosterone antagonist, not only compensatory reabsorption by distal tubules but also tubular reabsorption in the collecting duct (site of action of aldosterone antagonist) is inhibited, resulting in further massive diuresis. The EMPA-REG data¹ should be re-analyzed regarding whether such combinations were related to stroke (cerebral infarction) or not. We must pay attention to whether combined use of SGLT2-Is and conventional diuretics causes stroke, probably by volume depletion and hypotension.

Details about the types and doses of diuretics administered were unclear in EMPA-REG. I personally expect that SGLT2-Is without other diuretics may suppress the incidence of stroke. EMPA-REG data about stroke must be further analyzed in detail.

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Figure. Stroke incidence (fatal+nonfatal, and fatal) comparison between overall and Asian participants in EMPA-REG trials (modified with permission from Kaku K, et al).⁷ Conventional diuretics were combined in 43.7% and 26.7% of overall participants and Asians, respectively.

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