Executive Summary

Comparative effectiveness of antihypertensive drugs for preventing diabetic retinopathy in patients with new onset type 2 diabetes

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▢ Background

Diabetes is a metabolic disease characterized by hyperglycemia and is caused by defects in the secretion or function of insulin. Diabetic retinopathy, a diabetes complication caused by damage to microvessels, is a leading cause of impaired vision and blindness in adults. The effective management of hypertension with the adequate use of a blood pressure depressor agent is known to reduce the risk of developing diabetic retinopathy. Of the available hypertension medications, those that belong to the renin-angiotensin system inhibitors (RAS inhibitor) group, including angiotensin converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB), are known to have superior efficacy in the prevention and management of diabetic retinopathy. For this reason, these medications are recommended as first-line drugs for patients with diabetes that is accompanied by hypertension.

▢ Objective

The present study examined the current use of antihypertensive medications among patients with diabetes in Korea to determine the efficacy

of RAS inhibitors (recommended as first-line drugs for hypertension) in the prevention of retinopathy and other eye diseases caused by diabetes. For this purpose, we compared the rates of retinopathy or other eye diseases caused by diabetes between two groups of patients who developed hypertension following a recent diagnosis of type 2 diabetes: a group of patients who were prescribed RAS inhibitors and a group of patients who were prescribed other anti-hypertensive drugs.

□ Methods

The National Health Insurance Service data on health insurance claims, eligibility, and national health screening were analyzed for a retrospective cohort study.

The study subjects included patients newly diagnosed with type 2 diabetes between January 1, 2006, and December 31, 2011, who were prescribed anti-hypertensive medications for the first time in the same period. The point in time at which anti-hypertensive drugs were first prescribed for these individuals was defined as the initiation date (cohort entry date). Subsequently, patients who met the following exclusion criteria were eliminated from the subject pool: history of hospitalization due to cancer, myocardial infarction, or stroke; history of diagnosis of late-stage renal failure, diabetic retinopathy, retinal vein occlusion, renal diseases, other retinal disorders, or intravitreal injections. Patients whose national health screening data before the initiation date were missing were also excluded due to data limitation.

The subjects who were prescribed RAS inhibitors as first-line drugs for hypertension in the study period were defined as the 'RAS inhibitor group', and subjects who were prescribed beta-blockers, calcium channel blockers, alpha-blockers, and vasodilators were defined as the 'no-RAS inhibitor group'. The primary outcome index was diabetic retinopathy, and the secondary outcome index was other diabetic eye diseases (cataract, glaucoma, and retinal artery/vein occlusion).

The patients were followed until the outcome indexes emerged. The minimum follow-up duration was two years. Patients were censored upon death before the end of the study period (December 31, 2013). Patients whose outcome indexes did not emerge nor died during the study period were censored on the study end date.

The incidence rates of outcome indexes were compared among the two groups. The Kaplan-Meier (KM) curves are presented as a summary of the baseline characteristics and trends in incidence in the two groups. A Cox proportional hazard model adjusted for the subjects' baseline characteristics including sociodemographic variables and clinical variables was created to estimate the hazard ratio (HR) for the outcome indexes, and a 95% confidence interval and P-value were also presented. In addition, a Cox proportional hazard model incorporating the Standardized mortality/morbidity ratio (SMR) obtained by a sensitivity analysis was presented. The SMR method was adjusted using a propensity score estimated on the basis of the subjects' baseline characteristics.

□ Results

The study sample included 52,446 patients, of whom 20,916 (40%) belonged to the RAS inhibitor group, and 31,530 (60%) patients belonged to the no-RAS inhibitor group. The rate of diabetic retinopathy (primary outcome index) was 29.9% in the RAS inhibitor group and 27.1% in the no-RAS inhibitor group, indicating a slightly higher rate of diabetic retinopathy in the RAS inhibitor group. However, the opposite result was obtained with the incorporation of SMR, with an incidence of 29.9% in the RAS inhibitor group and 34.0% in the other group. No significant difference in the rate of other diabetic eye diseases (secondary outcome index) was found between the RAS inhibitor group (12.4%) and the no-RAS inhibitor group (13.1%). However, when SMR was incorporated, the incidence rate in the no-RAS inhibitor group was higher than in the RAS inhibitor group (22.3% vs. 15.4%).

The Cox proportional hazard model analysis indicated the following results for the subjects who were prescribed anti-hypertensive medications: before the application of the weighted value method, the no-RAS inhibitor group had a significantly lower HR (0.89; 95% CI: 0.86-0.92; p<0.0001) for developing diabetic retinopathy compared with the RAS inhibitor group. Similarly, the no-RAS inhibitor group had a lower HR (0.96; 95% CI: 0.92-1.01; p=0.1530) for developing other diabetic eye diseases compared with the RAS inhibitor group, although the difference was not statistically significant. On the other hand, the SMR method showed the opposite result. The no-RAS inhibitor group had a significantly higher HR (1.15; 95% CI: 1.11-1.19; p<0.0001) for developing diabetic retinopathy compared with the RAS inhibitor group. Similarly, for other diabetic eye diseases, the HR of the no-RAS inhibitor group was 1.68 (95% CI: 1.60-1.77; p<0.0001) compared with the RAS inhibitor group.

The results of the subgroup analysis indicated that, among subjects in relatively good health, defined by less severe diabetes and absence of vascular diseases, those treated with RAS inhibitors showed a lower risk of developing diabetic retinopathy.

▢ Conclusion

The results of the present study indicated that RAS inhibitors used as first-line drugs by patients who develop hypertension following a recent diagnosis of type 2 diabetes were more effective in lowering the risk of developing diabetic retinopathy or other diabetic eye diseases compared with other anti-hypertensive medications. Nevertheless, anti-hypertensives other than RAS inhibitors are being prescribed as first-line drugs for diabetic patients with hypertension. Therefore, adherence to diabetes management guidelines is necessary. We expect that our results will be employed as useful evidence for the management of diabetes and diabetes complications.

Keywords

Diabetes, diabetic retinopathy, hypertension, antihypertensives, renin-angiotensin system inhibitors (RAS inhibitors)