Executive Summary

Safety and Effectiveness of Novel Antithrombotic Agents (Antiplatelet Therapy and Anticoagulants) in Real-World Settings

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▢ Background

Recently, new antithrombotic agents (anticoagulants and antiplatelet agents) have been developed. In Korea, insurance benefits (national health insurance drug prices) were set based on the results of large-scale clinical studies. The use of new anticoagulants (dabigatran; Pradaxa, rivaroxabn; Xarelto, apixaban; Eliquis) in patients with atrial fibrillation and new antiplatelet agents (prasugrel; Effient, ticagrelor; Brilinta) in patients with acute coronary syndrome are increasing rapidly. Although there are many large-scale clinical studies on the safety and efficacy of new anti thrombotic agents, the safety and efficacy studies in real-world patients with various comorbidities and basal characteristics are limited. In particular, most studies published until recently are the results of research on Westerners. In addition, studies of Asians whose side effects and pharmacological effects of antithrombotic agents are somewhat different from Westerners is very limited. Therefore, this study aims to analyze the current status of the use of new antithrombotic agents in Korea and to analyze the safety and effectiveness using the health insurance big data.

▢ Objective

The objective of this study is to compare and analyze the safety and effectiveness of new antithrombotic agents (anticoagulants and antiplatelet agents) in real-world setting.

1. To evaluate the safety and effectiveness of new antiplatelet agents compared to clopidogrel in acute coronary syndromes.
2. To evaluate the safety and effectiveness of new anticoagulants compared with warfarin in atrial fibrillation.

▢ Methods

To analyze the safety and effectiveness of antithrombotic agents, we conducted a retrospective cohort study using National Health Insurance Service's health claim data, health insurance eligibility data, national health checkup data, and Korea National Statistical Office's cause of death data.

Ⅰ. Analytical method of safety and effectiveness for new antiplatelet agents

The study subjects were patients who were diagnosed as acute coronary syndrome (ACS) and were newly prescribed antiplatelet drugs during the study period (July 2012 – Dec 2015). Patients with previous cancer or cardiogenic shock, fibrinolytic therapy, and patients with dual anticoagulant therapy were excluded.

The use of antiplatelet agents was defined as the case in which the antiplatelet agents were prescribed for more than 30 consecutive days. The initial date of medication (index date) was defined as the starting date of the first dose of the medicine on the statement during the study period. The main outcomes of safety included all bleeding requiring outpatient or hospitalization (any bleeding), such as the major bleeding, intracranial bleeding, and gastrointestinal bleeding. Main outcomes of effectiveness were defined as all-cause death, cardiovascular death, stroke, myocardial infarction, and composite measures of cardiovascular death, myocardial infarction and stroke. The definition period of clinical endpoint for safety

and effectiveness was defined as the period from the beginning of the study to December 2015.

The risk of disease by antiplatelet drug usage was suggested using the Cox proportional hazard regression model after matching the propensity score with the consideration of baseline characteristics of the patients. In addition, subgroup analysis based on sex, age, body mass index, hypertension, and diabetes mellitus were used to examine whether the effects of antiplatelet therapy were different in a particular population.

Ⅱ. Analytical method of safety and effectiveness for new anticoagulants

The study subjects were patients who were diagnosed with atrial fibrillation (AF) and were newly prescribed anticoagulant during the study period (July 2015- Dec. 2016). Patients with valvular atrial fibrillation or CHA2DS2-VASc score less than 2, patients with previous thromboembolism or renal dialysis, patients with dual anticoagulant therapy, and patients with anticoagulant usage of less than 30 days were excluded.

The use of anticoagulants was defined as the case in which the anticoagulant was prescribed for more than 30 consecutive days. effectiveness outcomes include all-cause death, cardiovascular death, ischemic stroke, systemic embolism, and myocardial infarction. The primary effectiveness outcome was defined as the composite occurrence of the ischemic stroke or systemic embolism. Safety outcomes included any bleeding, major bleeding, intracranial bleeding, and gastrointestinal bleeding. The safety and effectiveness events were defined as from the beginning of the study to July 2017.

The risk of disease by anticoagulants use, we used the Cox proportional hazards regression model to estimate the hazard ratio (HR), and all risk analysis results were presented after correction of the propensity score. In addition, we analyzed subgroups according to the anticoagulant dosage and presence of history of stroke. The effectivenes and safety of anticoagulant use in patients who were less than 75 years old without chronic kidney disease were analyzed.

▢ Results

Ⅰ. Result of Safety and effectiveness Analysis of New Anti-platelet Agents

The study subjects consisted of 70,715 people, of which 56,216 were in the clopidogrel group, 11,402 in the ticagrelor group and 3,097 in the prasugrel group. After the propensity score matching, the clopidogrel group vs. ticagrelor group were matched 11,402, the clopidogrel group vs. prasugrel group were matched 3,097, and the ticagrelor group vs. prasugrel group were matched 3,097, respectively.

As a result of the antiplatelet safety analysis, the risk of any bleeding was 30% higher and the risk of major bleeding was 23% higher in the ticagrelor group than in the clopidogrel group, but there was no statistically significant difference in intracranial bleeding. The risk of any bleeding in the prasugrel group was 1.19 times higher than that in the clopidogrel group (95% CI 1.03-1.38), but there was no statistically significant difference in the risk of major bleeding and intracranial hemorrhage. There was no statistically significant difference in all safety outcome variables between the ticagrelor group and prasugrel group. As a result of the antiplatelet agents use, there was no significant difference in the risk of major cardiovascular composite measures (cardiovascular death, myocardial infarction, or stroke) between the two groups compared with clopidogrel group, but cardiovascular death was significantly lower in the ticagrelor group (HR 0.68, 95% CI 0.51-0.89). The risk of cardiovascular death and stroke was also lower in the ticagrelor group than in the clopidogrel group. In contrast, the prasugrel group had no statistically significant difference in all effectiveness outcomes compared to the clopidogrel group.

Ⅱ. Result of Safety and effectiveness Analysis of New Anticoagulants

The study subjects consisted of 56,504 people, of which 10,409 were in the warfarin group, 12,593 in the dabigatran group and 21,000 in the rivaroxaban group. The use of warfarin, an conventional anticoagulant, was gradually decreased and the use of new anticoagulants (non-vitamin K

antagonist oral anticoagulants, NOAC) increased year by year. In particular, after expansion of health insurance coverage as the primary drug, the use of warfarin has declined sharply and the use of new anticoagulants has increased rapidly.

All NOAC were associated with lower risk of all-cause death (HR 0.75, 95% CI 0.68~0.82), cardiovascular death (HR 0.65, 95% CI 0.57~0.74), ischemic stroke (HR 0.77, 95% CI 0.74~0.81), systemic embolism (HR 0.36, 95% CI 0.31~0.42), and myocardial infarction (HR 0.70, 95% CI 0.63~0.77), as well as the primary effectiveness outcome such as ischemic stroke or systemic embolism (HR 0.72, 95% CI 0.65~0.81), compared to warfarin. These effectiveness outcomes were observed to be particularly favorable in patients with standard dose than those in low dose groups. Especially, when the low doses of apixaban were used in relatively young patients with normal renal function, it was confirmed that the benefits of effectiveness were lost. In terms of safety, NOAC also had a lower risk of major bleeding compared to warfarin (HR 0.82, 95% CI 0.72-0.93). In the safety of each drug, rivaroxaban group showed a slightly higher bleeding tendency than the other NOAC, but rivaroxaban also showed a similar or more safe risk of bleeding than warfarin. Therefore, all types of NOAC tend to be safer than warfarin respectively.

▢ Conclusions

This study analyzed the current use status of Korean antithrombotic agents using the national health insurance big data and evaluated the effectiveness and safety of new antithrombotic drugs (antiplatelet agents and anticoagulants). The use of the existing antithrombotic agents has gradually decreased by year and the use of new antiplatelet agents and new anticoagulants (NOAC) has increased. In particular, the use of NOAC has been rapidly increasing since NOAC was expanded its health insurance coverage as a primary drug. The new antiplatelet agents were similar to the conventional drugs (clopidogrel) in terms of effectiveness such as mortality

risk, but with slightly different results in terms of safety. For some antiplatelet agents, the risk of bleeding was 19 to 110% higher than for conventional drugs. This suggests that appropriate drug selection is required depending on the characteristics and risk of the patient. In addition, the three NOAC showed superior effectiveness and safety outcomes in patients with nonvalvular atrial fibrillation in Korea compared to warfarin. These effectiveness and safety were better showed when using standard dose NOAC compared to low dose NOAC groups. Therefore, the use of an proper dose of NOAC according to the guidelines for drug use is expected to ultimately maximize the effectiveness of the drug. This study has limitations as a retrospective cohort study, so it is necessary to pay attention to interpretation. However, it is meaningful that many results of clinical studies already known in western countries have been confirmed in actual large Korean cohort.

In addition, by evaluating the safety and effectiveness of new antithrombotic agents through the big data study for Koreans based on the National Health Insurance System for all citizen, it raises awareness about applying existing foreign guidelines. Furthermore, the clinical significance of the study is very significant because it poses the necessity to fully examine the safety and effectiveness not found in the development of new drugs after the commercialization of new drugs.

In the future, further investigation of the effectiveness and safety on the use of anti thrombotic agents by the detailed characteristics and risk factors of patients will be needed, and other prospective studies using Korean patient data should be reviewed. It is expected that the study results based on real world data in Korea can be utilized as an important basis for future clinical guidelines for the use of Korean antithrombotic agents.

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Key words

Antiplatelet agents, anticoagulants, acute coronary syndromes, atrial fibrillation