Randomized Comparison of Progression of Atherosclerotic Plaques and Calcification of Coronary Artery in Atrial Fibrillation Patients Treated With Edoxaban Versus Warfarin (The REPRESENT-AF trial)

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Although the adverse effects of long-term use of vitamin K oral anticoagulant (OAC), warfarin, on the coronary vasculature are well-established, it remains unknown whether nonvitamin K oral anticoagulants play a role in the attenuation of plaque progression and coronary calcification. This study aimed to compare the changes in atherosclerotic plaques and calcification of the coronary arteries in patients with atrial fibrillation (AF) treated with edoxaban and warfarin. A total of 150 OAC-naÿve patients with AF and atherosclerotic lesions on coronary computed tomography angiography (CCTA) were enrolled and randomly assigned to the edoxaban or warfarin treatment groups. All enrolled patients received rosuvastatin 10 mg and 119 patients completed the entire study protocol. A total of 12 months after the assigned OAC treatment, follow-up CCTA was performed and changes in plaque and calcium volumes of the coronary arteries were analyzed. The baseline characteristics of the 2 groups were well-balanced. The percentage of time in therapeutic range in the warfarin group was 61.1%. Compared with the baseline CCTA, there was a significant reduction in plaque volume after 12 months of OAC and rosuvastatin administration in both groups, and the extent of regression did not differ significantly between the groups. The increase in calcium volume was greater in the warfarin group than in the edoxaban group; however, the difference was not significant. In OAC-naÿve patients with AF and atherosclerotic coronary lesions who were treated with moderate-intensity statin, edoxaban use did not have a positive effect on atherosclerotic plaques and coronary calcification compared with warfarin use over a 12-month follow-up period. **(Am J Cardiol 2024;229:56−62)**

Keywords: atrial fibrillation, edoxaban, plaque, warfarin

Coronary artery disease (CAD) and atrial fibrillation (AF) commonly coexist; they facilitate the occurrence and aggravate the prognosis of one another.[1−4] The progression of atherosclerotic plaques is the main mechanism of CAD; therefore, the attenuation of this progression is essential for the management of patients with concomitant CAD and AF.[5,6]

The vitamin K antagonist, warfarin, has been used as a traditional oral anticoagulant (OAC) for stroke prevention in patients with AF for several decades. However, warfarin has been rapidly replaced with nonvitamin K OACs (NOACs) mainly because of greater safety and better adherence with taking the pill. Another important reason NOACs are preferred over warfarin is that warfarin increases vascular calcification.[7,8] Vitamin K is necessary for the production of not only coagulant factors but also proteins involved in anti-inflammatory processes and vascular protection.[9] Previous studies have reported that warfarin intake was associated with an increased risk of cardiac and vascular diseases, whereas vitamin K supplementation slowed the progression of coronary calcification.[10,11]

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See page 61 for Declaration of Competing Interest.

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In this respect, activated factor X (factor Xa) inhibitors have received attention because they inhibit the activation of factor X, which involves a proinflammatory response through protease-activated receptors, and they are not dependent on vitamin K.[12] Recent studies have demonstrated the preferable effects of NOACs to reduce the progression rate of calcified plaque volumes compared with warfarin[13,14]; this may be supported by the numerical reduction in myocardial infarction (MI) occurrence in patients treated with NOACs in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial and the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial.[15,16] To date, however, no data on edoxaban have been reported. The objective of the present study was to compare the changes in atherosclerotic plaques and coronary artery calcification in OAC-naïve patients with AF and atherosclerotic lesions treated with edoxaban and warfarin.

Methods

This prospective, single-center, randomized controlled trial (RCT) included 150 consecutive patients diagnosed with AF and confirmed to have atherosclerotic lesions using coronary computed tomography angiography (CCTA). Patients with any history of OAC use, with preexisting mechanical prosthetic valve, with moderate to severe mitral stenosis, aged <18 years, or refused to participate in the study were excluded. The participants were randomly assigned 1:1 to the edoxaban or warfarin treatment groups. Rosuvastatin 10 mg was administrated once per day to all enrolled patients, regardless of previously prescribed statins or baseline lipid profile level. Medical records were comprehensively reviewed for demographic data, cardiovascular risk factors, laboratory data, transthoracic echocardiography, and CCTA parameters.

All participants provided written informed consent. The study protocol was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital and complied with the Declaration of Helsinki. The procedures in this study were performed in accordance with the ethical standards of institutional and national research committees. The study was registered at *cris.nih.go.kr* (unique identifier: KCT0004133).

Follow-up CCTA was performed 12 months after the assigned OAC treatment, unless patients had significantly impaired renal function or allergic reactions to the contrast media. For the warfarin group, the prothrombin time international normalized ratio was regularly checked, with a target range of 2.0 to 3.0. The primary end points were changes in atherosclerotic plaques and calcification of the coronary arteries in the 2 groups. Intragroup analyses were also conducted to compare the baseline plaque volumes and calcification with the 12-month follow-up after the assigned OAC treatment. The secondary safety end point was the occurrence of any major bleeding event, and the efficacy end point was any major adverse cardiovascular event, defined as a composite of stroke or systemic embolism, MI, hospitalization for heart failure, and all-cause mortality.

Coronary artery plaque analysis was performed using Vitrea software version 7.14.4.30 (Canon Medical Systems, Japan). After loading the CCTA case, the cardiac analysis application automatically detected the centerlines of each coronary artery using the auto vessel probe feature. A total of 2 lesions were identified within the 3 main coronary arteries (left anterior descending artery], left circumferential artery, and right coronary artery) where prominent plaques were present, and their dimensions were assessed within a 20-mm length span. Measurements at matched locations were obtained from the baseline and follow-up computed tomography (CT) scans to ensure maximal alignment between the 2 data sets. Once the extent of the lesion was identified, the program automatically analyzed the plaque volume (Figure 1). Changes in plaque volumes were calculated as the difference between baseline and follow-up CT scans. The total plaque was categorized into 3 groups based on the default threshold values in the Vitrea workstation. Plaque 1 had CT attenuation values ranging from −100 to 49 Hounsfield units (HUs), plaque 2 had values ranging from 50 to 149 HU, and the calcified plaque had values ranging from 150 to 1,300 HU. Plaque 1 represented a lipid plaque, whereas plaque 2 corresponded to a fibrous plaque. These threshold values corresponded with those of previously published ex vivo studies on CT attenuation values of atherosclerotic plaques.[17]

Randomization was performed using computer-generated random permutation sequences by study personnel who were blinded to the group assignments. The normally distributed continuous variables were expressed as the mean ± SD. Categorical variables were expressed as numbers and percentages. For intragroup and intergroup comparisons, categorical and continuous variables were compared using Fisher's exact test or Student's *t* test, respectively. A $p < 0.05$ was considered significant. All statistical analyses were performed using SPSS version 21.0 (SPSS Inc, Chicago, Illinois).

Results

Figure 2 shows the present study flow. A total of 150 OAC-naïve patients with AF and atherosclerotic lesions on CCTA were enrolled. Of these, 119 completed the study. The dropout rate was 20.7% (31 of the 150 patients) and was substantially higher in the warfarin group than in the edoxaban group (26.7% vs 14.7%, respectively, $p = 0.070$). Dropouts occurred because of early discontinuation of the assigned OAC (n = 12), study withdrawal (n = 11), lack of follow-up CCTA because of renal function decline (n = 5), or an allergic reaction to the contrast media (n = 3). The reasons for dropping out of the warfarin group included early discontinuation of the assigned OAC (n = 12) because of inconvenience in taking warfarin, study withdrawal (n = 5), lack of follow-up CCTA because of renal function decline (n = 2), or an allergic reaction to contrast media (n = 1).

As listed in Table 1, the baseline characteristics were well-balanced between the 2 groups. The mean age was 61.4 years, and 21.8% were women. The left atrial dimension was 40.6 mm on average, and nonparoxysmal AF accounted for 54.9% of the cases. A total of 2 patients had a history of MI. The percentage of time in therapeutic range

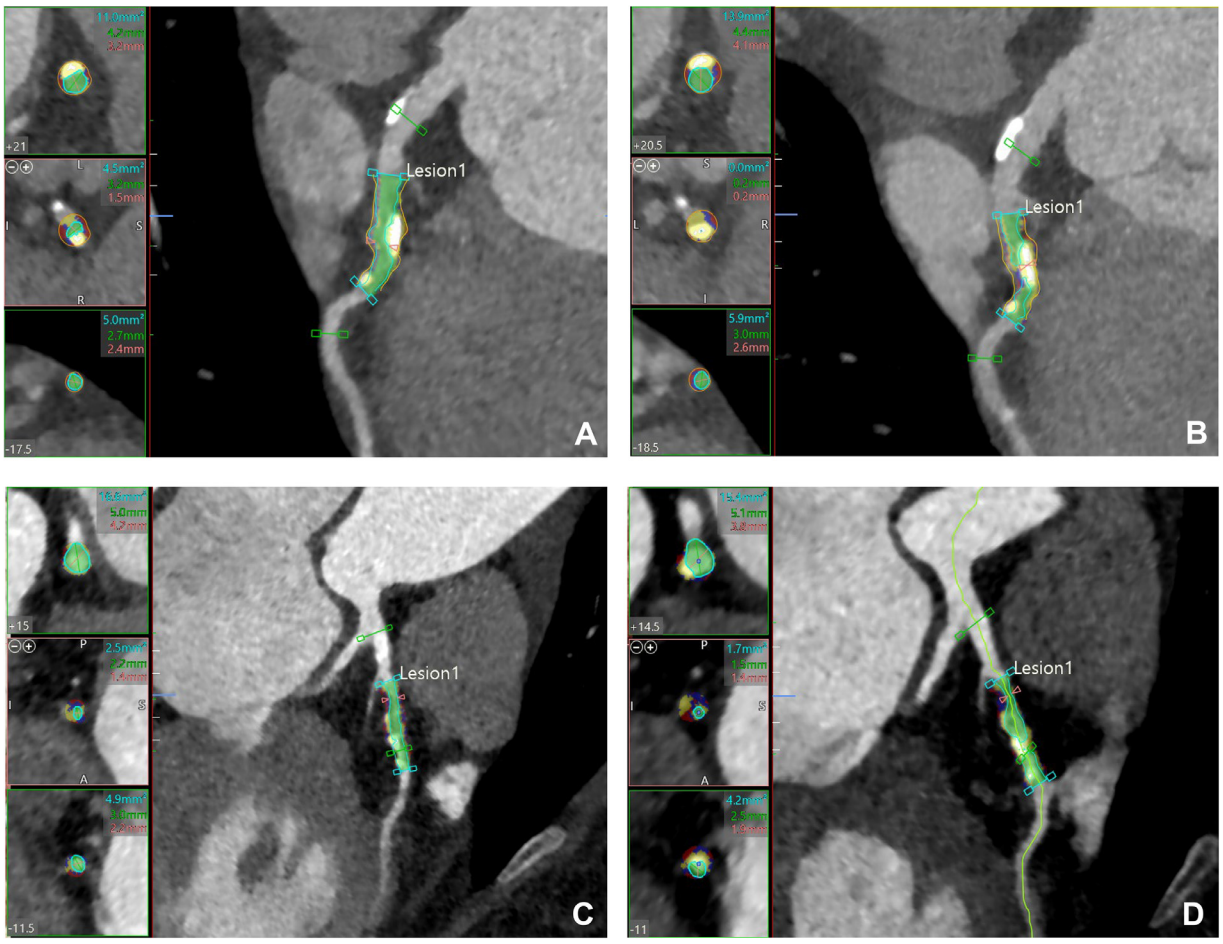

Figure 1. In a patient treated with warfarin, the calcified plaque burden increased over 1 year (*A*−*B*). Computed tomography (CT) scans show the lesion of the left anterior descending artery (LAD) measured at baseline (*A*) and at the 1-year follow-up (*B*). The observed calcified plaque burden increased from 79.5 to 145.5 mm^2. In another case, minimal reduction in the calcified plaque burden was observed in a patient treated with edoxaban (*C*−*D*). CT scans show the LAD lesion measured at baseline (*C*) and the 1-year follow-up (*D*). The observed plaque burden increased minimally from 31.6 to 31.9 mm^2. Green represents the lumen of the coronary artery, red indicates plaque 1, blue signifies plaque 2, and yellow denotes calcified plaque.

(prothrombin time international normalized ratio 2.0 to 3.0) in the warfarin group was 61.1% during the entire study period.

At a mean follow-up of 377.5 ± 35.7 days after the assigned OAC treatment, the plaque volumes in both groups had significantly regressed in 3 coronary arteries compared with those at baseline (e.g., all plaque volume of left anterior descending artery; 192.2 vs 169.4 mm^3, p <0.001 in the edoxaban group and 195.8 vs 169.5 mm^3, p <0.001 in the warfarin group) (Table 2). The extent of regression did not differ between those on edoxaban and those on warfarin (Figure 3, Table 3). The number of patients with plaque regression was also similar between the 2 groups (64.1% in the edoxaban group vs 74.5% in the warfarin group, p = 0.151). As shown in Figure 3, the change in calcium volume before and after assigned OAC therapy was greater in the warfarin group than in the edoxaban group. However, there were no statistically significant differences between the 2 groups.

Major gastrointestinal bleeding occurred in 2 patients assigned to the warfarin group and none in the edoxaban group. No major adverse cardiac events occurred in either group.

Discussion

This single-center RCT compared the volumes of atherosclerotic plaques and calcification of coronary arteries between edoxaban and warfarin treatment groups. A significant reduction in plaque volume was observed after OAC therapy and administration of rosuvastatin 10 mg; however, there was no significant difference in the amount of reductions between the 2 groups.

Warfarin, a vitamin K antagonist, has been the most used OAC for stroke prevention in patients with AF for the last several decades.[18] Matrix γ-carboxyglutamic acid protein is a small material involved in the inhibition of vascular calcification and it becomes biologically active after vitamin K −dependent carboxylation and phosphorylation.[19] Therefore, vitamin K deficiency or inhibition by a drug such as warfarin is associated with pathologic calcification in systemic arteries.[20] This mechanism is supported by evidence that vitamin K supplementation reduced arterial stiffness and slowed the progression of coronary calcification.[10,21]

It is plausible that NOACs are superior to warfarin with regard to cardiovascular protection because they are not dependent on vitamin K. In addition, it is known that factor

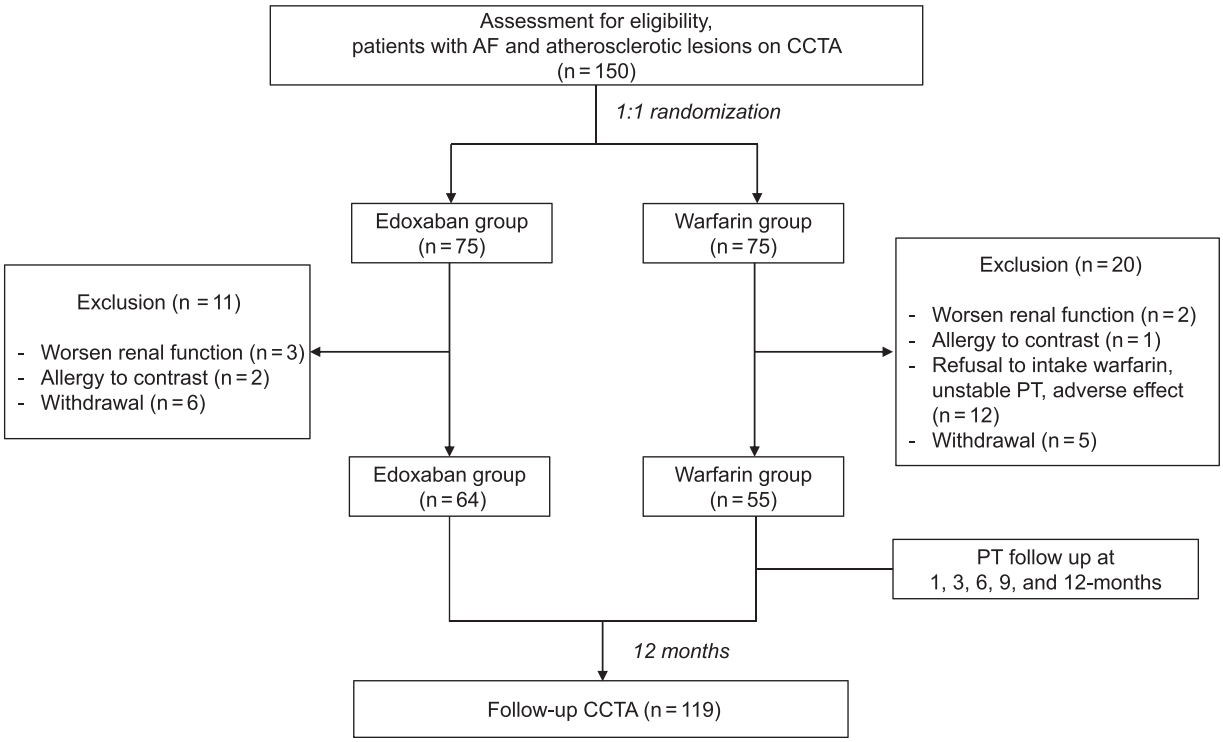

Figure 2. Study flow. Flow diagram describes the study design and the number of patients who were analyzed. AF, atrial fibrillation; CCTA, coronary computed tomography angiography; PT, prothrombin time.

Xa induces an inflammatory response through activation of protease-activated receptors or mediators such as chemokine interleukin-8 and adhesion molecule intercellular adhesion molecule 1.[22] The effect of rivaroxaban, one of the factor Xa inhibitors, on the attenuation of atherosclerotic plaque progression and destabilization was reported in an animal study.[23] In addition, clinical data support the beneficial effects of NOACs on cardiovascular events. In a study of patients with nonvalvular AF and diabetes, rivaroxaban was associated with a 25% reduced risk of major adverse cardiovascular events compared with warfarin.[24]

Table 1
Baseline characteristics

	Edoxaban group (n=64)	Warfarin group (n=55)	*p* value
Age, year	60.1±9.7	62.6±8.8	0.263
Female sex, n (%)	13 (20.3%)	13 (23.6%)	0.662
Body mass index, kg/m^2	24.9±3.2	24.8±2.8	0.312
Paroxysmal AF, n (%)	31 (48.4%)	23 (41.8%)	0.47
Heart failure, n (%)	15 (23.4%)	18 (32.7%)	0.259
Hypertension, n (%)	54 (84.4%)	41 (74.5%)	0.183
Diabetes mellitus, n (%)	25 (39.1%)	17 (30.9%)	0.353
Cerebrovascular accident, n (%)	6 (9.4%)	8 (14.5%)	0.383
Old myocardial infarction, n (%)	0 (0.0%)	2 (3.6%)	0.212
CHA_2DS_2-VASc score	2.3±1.0	2.4±0.9	0.887
Left ventricular EF, %	61.4±5.3	61.0±8.1	0.32
LA diameter, mm	40.3±6.1	40.9±6.3	0.468
Creatinine, mg/dL	0.9±0.2	0.9±0.2	0.743
Creatinine clearance, mL/min	87.0±19.4	83.7±18.3	0.607

AF = atrial fibrillation; EF = ejection fraction; LA = left atrium.

Table 2
Changes in volumes of plaque and calcification of each coronary artery

Edoxaban Group (n=64)	Baseline	Follow-up	p value
LAD plaque 1, mm^3	61.5 ± 21.6	53.5 ± 15.1	<0.001
LAD plaque 2, mm^3	84.3 ± 37.7	67.7 ± 25.6	<0.001
LAD calcium volume, mm^3	46.4 ± 26.9	48.1 ± 28.3	0.458
LAD all volume, mm^3	192.2 ± 66.9	169.4 ± 55.1	<0.001
LCX plaque 1, mm^3	41.6 ± 15.8	42.3 ± 15.5	0.705
LCX plaque 2, mm^3	65.1 ± 28.1	57.9 ± 24.5	0.014
LCX calcium volume, mm^3	55.2 ± 28.6	51.2 ± 31.2	0.239
LCX all volume, mm^3	161.9 ± 59.8	151.5 ± 59.2	0.081
RCA plaque 1, mm^3	59.8 ± 21.1	55.1 ± 19.7	0.073
RCA plaque 2, mm^3	85.9 ± 29.3	70.6 ± 23.4	<0.001
RCA calcium volume, mm^3	31.7 ± 21.1	37.9 ± 26.8	0.032
RCA all volume, mm^3	177.1 ± 59.2	163.7 ± 57.7	0.03
Warfarin Group (n=55)	**Baseline**	**Follow-up**	**p value**
LAD plaque 1, mm^3	59.5 ± 22.3	51.9 ± 17.7	<0.001
LAD plaque 2, mm^3	81.2 ± 30.8	64.1 ± 22.1	<0.001
LAD calcium volume, mm^3	55.3 ± 33.8	53.3 ± 31.7	0.536
LAD all volume, mm^3	195.8 ± 65.9	169.5 ± 54.8	<0.001
LCX plaque 1, mm^3	43.8 ± 17.5	42.4 ± 17.3	0.357
LCX plaque 2, mm^3	66.5 ± 29.8	57.7 ± 21.1	0.002
LCX calcium volume, mm^3	48.2 ± 26.4	61.0 ± 91.4	0.297
LCX all volume, mm^3	158.5 ± 62.6	148.5 ± 55.2	0.044
RCA plaque 1, mm^3	58.1 ± 17.1	53.7 ± 18.2	0.051
RCA plaque 2, mm^3	78.8 ± 24.6	69.6 ± 24.8	0.012
RCA calcium volume, mm^3	36.1 ± 24.1	37.6 ± 23.7	0.584
RCA all volume, mm^3	168.6 ± 52.8	160.8 ± 57.9	0.33

LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

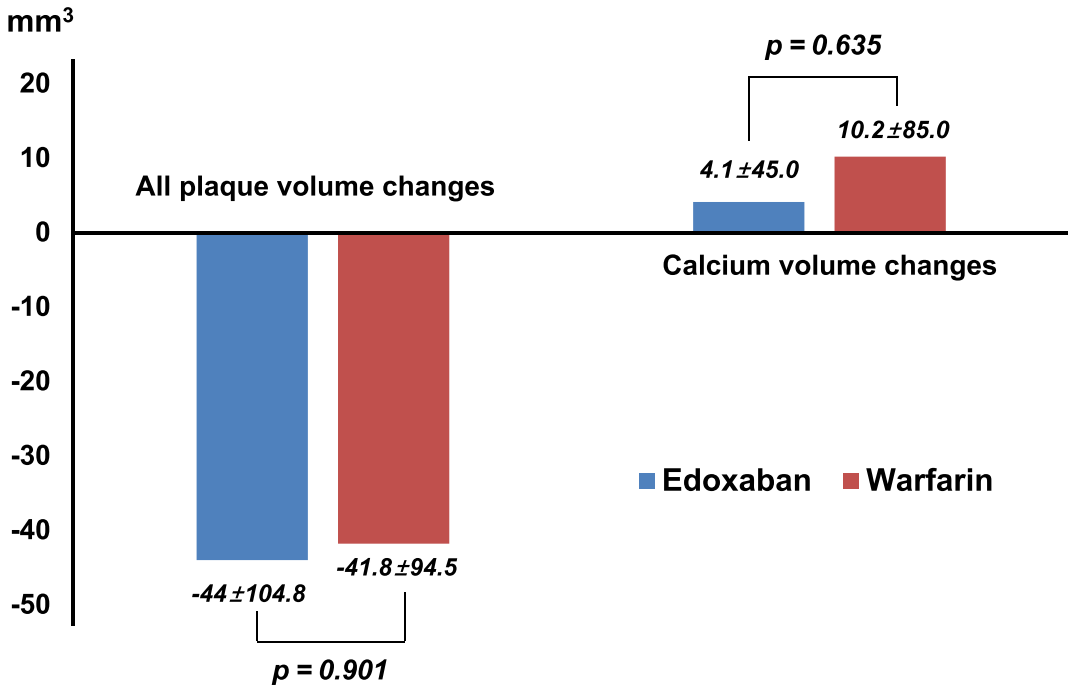

Figure 3. Changes in all plaque and calcium volumes. The extent of volume change was similar between the edoxaban and warfarin groups.

Landmark RCTs of NOACs have shown a trend toward reduced incidence of MI in NOAC treatment groups,[15,16] and the risk of MI was significantly reduced by 16% in a meta-analysis.[25]

Although various mechanisms of action on atherosclerotic plaques and calcification might explain the cardiovascular protective effects of NOACs compared with warfarin, no large-scale RCT data have yet been reported. Only a few small RCTs have investigated the effect of NOACs versus warfarin on coronary plaque by directly measuring plaque volume. Win et al[14] reported that apixaban was associated with significantly slower total, calcified, and low attenuation plaque progression. In their study, plaque volumes were similar between groups regardless of treatment. However, the change in total plaque volume differed depending on the composition after adjusting for confounding factors, that is, most of the benefit was derived from the calcified plaque, reflecting the protective effect of NOACs against vascular calcification. Lee et al[13] evaluated the effect of rivaroxaban versus warfarin on the progression of coronary atherosclerosis using 2,428 coronary artery segments in 97 patients. They also analyzed the extent of progression in plaque volume according to plaque composition. Changes in absolute and normalized fibrous plaque volume were greater in the warfarin group than in the rivaroxaban group, and warfarin was significantly associated with the progression of total and calcified plaque volumes. However, these findings are inconsistent with the results of the present study. Our study did not show a protective effect of edoxaban on atherosclerotic plaques or calcification of the coronary arteries, although edoxaban is classified as a factor Xa inhibitor similar to apixaban and rivaroxaban. Several factors explain this discrepancy. Statin therapy is the most important consideration. In previous studies on apixaban and rivaroxaban approximately 60% of participants had already been on different statin therapies before randomization, and the proper name or dose of statins was not stated in the papers. Furthermore, statin therapy after study enrollment was not controlled in either group. It is well-known that statin therapy is associated with slowing the progression of coronary atherosclerosis volume and reducing plaques with high-risk features[26] and it is already a guideline-directed medical therapy for patients with CAD.[27] Therefore, any influence of statin use on coronary plaques should be considered when interpreting the results. In our study, all enrolled patients were consistently administered 10 mg of rosuvastatin during the entire study period, regardless of age, presence of diabetes mellitus, low-density baseline lipoprotein cholesterol level, or atherosclerotic cardiovascular disease risk. Therefore, in the present study, the volume of atherosclerotic plaques in the coronary arteries was significantly reduced in both groups after 12 months of statin therapy, and there was no significant difference in the amount of reduction between the edoxaban and warfarin groups. However, in previous studies, plaque volume increased over time despite a lower rate of plaque progression in the NOAC treatment group than in the warfarin treatment group.[13,14]

Another important consideration is the inclusion criteria. In a study by Lee et al,[13] patients with current warfarin use were enrolled; therefore, the adverse effects of long-term warfarin use may have affected the results. The action of warfarin on vascular calcification is dose-dependent.[28] In our study, all enrolled participants were OAC-naïve, and the increase in calcium volume before and after OAC intake were greater in the warfarin group than in the edoxaban group; however, the difference was not statistically significant, which may be because a 12-month period on warfarin is not sufficient to observe the progression of coronary artery calcification. Additional explanation for increased calcium volume of atherosclerotic plaque in both groups might be derived from the effect of the statin. Previous

Table 3
Comparison of changes in volumes of plaque and calcification between two groups

	Edoxaban group (n=64)	Warfarin group (n=55)	p value
CT follow-up duration, days	376.6 ± 27.5	378.4 ± 43.9	0.794
Baseline volume, mm^3			
LAD plaque 1	61.5 ± 21.6	59.5 ± 22.3	0.625
LAD plaque 2	84.3 ± 37.7	81.2 ± 30.8	0.62
LAD calcium volume	46.4 ± 26.9	55.3 ± 33.8	0.124
LAD all volume	192.2 ± 66.9	195.8 ± 65.9	0.763
LCX plaque 1	41.6 ± 15.8	43.8 ± 17.5	0.514
LCX plaque 2	65.1 ± 28.1	66.5 ± 29.8	0.81
LCX calcium volume	55.2 ± 28.6	48.2 ± 26.4	0.204
LCX all volume	161.9 ± 59.8	158.5 ± 62.6	0.778
RCA plaque 1	59.8 ± 21.1	58.1 ± 17.1	0.657
RCA plaque 2	85.9 ± 29.3	78.8 ± 24.6	0.161
RCA calcium volume	31.7 ± 21.1	36.1 ± 24.1	0.308
RCA all volume	177.1 ± 59.2	168.6 ± 52.8	0.42
Follow-up volume, mm^3			
LAD plaque 1	53.5 ± 15.1	51.9 ± 17.7	0.614
LAD plaque 2	67.7 ± 25.6	64.1 ± 22.1	0.411
LAD calcium volume	48.1 ± 28.3	53.3 ± 31.7	0.35
LAD all volume	169.4 ± 55.1	169.5 ± 54.8	0.991
LCX plaque 1	42.3 ± 15.5	42.4 ± 17.3	0.984
LCX plaque 2	57.9 ± 24.5	57.7 ± 21.1	0.956
LCX calcium volume	51.2 ± 31.2	61.0 ± 91.4	0.491
LCX all volume	151.5 ± 59.2	148.5 ± 55.2	0.798
RCA plaque 1	55.1 ± 19.7	53.7 ± 18.2	0.691
RCA plaque 2	70.6 ± 23.4	69.6 ± 24.8	0.819
RCA calcium volume	37.9 ± 26.8	37.6 ± 23.7	0.936
RCA all volume	163.7 ± 57.7	160.8 ± 57.9	0.794
Changes of volume, mm^3			
changes of LAD plaque 1	−7.9 ± 16.8	−7.5 ± 14.6	0.879
changes of LAD plaque 2	−16.6 ± 29.1	−17.1 ± 23.9	0.92
changes of LAD Ca volume	1.7 ± 17.9	−1.9 ± 22.9	0.348
changes of LAD all volume	−22.8 ± 48.9	−26.4 ± 46.9	0.686
changes of LCX plaque 1	0.7 ± 13.7	−1.4 ± 10.4	0.38
changes of LCX plaque 2	−7.1 ± 20.4	−8.8 ± 18.1	0.668
changes of LCX Ca volume	−4.0 ± 24.7	12.9 ± 82.6	0.188
changes of LCX all volume	−10.5 ± 42.9	−9.9 ± 32.6	0.945
changes of RCA plaque 1	−4.6 ± 19.7	−4.4 ± 16.2	0.956
changes of RCA plaque 2	−15.3 ± 23.8	−9.2 ± 25.5	0.192
changes of RCA Ca volume	6.2 ± 21.9	1.4 ± 19.0	0.219
changes of RCA all volume	−13.8 ± 47.8	−7.8 ± 57.6	0.553

Ca = calcium; CT = computed tomography; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

studies demonstrated that statin therapy promoted coronary atherosclerotic calcification.[26,29] However, it is considered to be a result of plaque stabilizing effect because dense calcium is associated with a more stable plaque phenotype, whereas patchy calcification is associated with ongoing inflammation and plaque vulnerability[30,31] Further large-scale, long-term follow-up RCTs are required to clarify these points.

There are several limitations in the present study. First, the dropout rate in our study was somewhat high (20.7%). The main reason was the early discontinuation of OAC (38.7%, 12 of 31 subjects) because of the inconvenience of taking warfarin, whereas none of the patients in the edoxaban group discontinued their assigned OAC. Second, the confounding effect of statin therapy on plaque progression/regression cannot be completely excluded, although all enrolled patients were administered the same moderate-intensity statin (rosuvastatin 10 mg) to control the dominant effect of statins on atheromatous plaques. Nevertheless, our findings showed that even this dose dominated the plaque progression/regression process. Third, the 12-month follow-up period after the assigned OAC treatment may not be sufficient to differentiate between the edoxaban and warfarin treatment groups; the progression of atherosclerotic plaques or coronary calcification may occur as a result of a long-term process. In addition, because the adverse effects of warfarin are markedly augmented in cases of renal impairment,[32] the number of patients with vascular calcification caused by warfarin intake may have been small because most of the patients in the present study had normal renal function. Finally, we cannot conclude that our findings stem from the class effect of all NOACs because there is an idiosyncratic drug-related effect depending on which NOAC is used.

In conclusion, in OAC-naïve patients with AF and atherosclerotic coronary lesions, plaque volume significantly decreased in the coronary artery 12 months after receiving the assigned OAC and moderate-intensity statin; however, the extent of regression did not differ statistically between the edoxaban and warfarin treatment groups. The increase in calcium volume was greater in the warfarin group than in the edoxaban group; however, this difference was also not statistically significant.

Declaration of competing interest

The authors have no competing interest to declare.

CRediT authorship contribution statement

Jinhee Ahn: Writing − original draft, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yoon Seong Lee:** Methodology, Formal analysis, Data curation. **Whal Lee:** Investigation, Formal analysis, Data curation. **BaRen Jeong:** Software, Data curation. **Eue-Keun Choi:** Writing − review & editing, Resources, Conceptualization. **Dong Geum Shin:** Methodology, Conceptualization. **Sang-Jin Han:** Writing − review & editing, Resources, Investigation. **Hong Euy Lim:** Writing − review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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