Apixaban versus warfarin in evaluation of progression of atherosclerotic and calcified plaques (prospective randomized trial)

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Warfarin has been showed to increase vascular calcification. Apixaban, a direct factor Xa inhibitor, has no interaction with vitamin K and its effect on coronary plaques is unknown. We randomized and compared warfarin and apixaban on progression of coronary atherosclerotic plaques measured by coronary computed tomographic angiography in 66 subjects with non-valvular atrial fibrillation over the period of one-year follow up. There was significant higher total, calcified and low attenuation plaque volume in the group randomized to warfarin as compared to apixaban (all $P < .05$). Greater volume of total ($\beta_2 = 28.54$; $P = .03$), low attenuation plaque ($\beta_2 = 3.58$; $P = .02$) and calcified ($\beta_2 = 14.10$; $P = .005$) plaque progression was observed in the VKA_group. (Am Heart J 2019;212:129-33.)

The prevalence of concomitant coronary atherosclerotic disease (CAD) and atrial fibrillation (AF) is high.[1] The coexistence of CAD and AF not only makes the management challenging but also results in poor outcomes.[1] Therefore, it is imperative to accurately assess the progress of CAD and to optimize the treatment of the patients with CAD with coexisting AF.

The progression of atherosclerotic plaques characterized by various anatomic plaque composition changes has been acknowledged to be associated with increased plaque rupture, myocardial infarction and death.[2] Coronary computed tomography angiography (CCTA) has emerged as a novel non-invasive modality with high diagnostic performance for detection and assessment of atheroma compared to invasive coronary angiography (ICA) and intravascular ultrasound (IVUS).[3] Beyond stenosis severity, CCTA also permits anatomic quantification of numerous atherosclerotic plaque phenotypes, plaque burden and ability to differentiate between various plaque types.[2]

Warfarin, a vitamin K antagonist (VKA) and one of the most commonly used oral anti-coagulants, has been showed to increase vascular calcification[4] leading to increased cardiovascular (CV) events.[5] However, apixaban, a direct Factor Xa inhibitor, has no interaction with vitamin K and its effect on the progression of atherosclerotic plaques is still unknown. The potential benefit of avoiding VKA therapy and the favorable effects of factor Xa inhibitors may contribute to a reduction in CV events. We aimed to compare apixaban with warfarin on progression of coronary plaque composition and volume in non-valvular AF patients using CCTA.

Methods

We have published a methods paper discussing the study design and methodology of this trial.[6] Briefly, 66 patients were enrolled and consented with NVAF. Patients were prospectively randomized to warfarin or apixaban, and underwent serial coronary CTA at baseline and 52 weeks. The primary objective was to examine the rate of change in coronary artery calcification in the apixaban vs. warfarin cohorts. The secondary objective was to examine the rate of incident plaque and quantitative changes of different plaque types and volumes in patients. Full methodology is published in online supplemental appendix.

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Table I. Baseline Characteristics among Participants

	Entire Cohort (n = 56)	Warfarin Group (n = 30)	Apixaban Group (n = 26)	*P*
Age, years	57.4 ± 11.4	55.1 ± 12.4	60.1 ± 9.7	.12
Male gender, %	69.6	80	57.7	.07
Body mass index, m^2/kg	32.2 ± 8.6	33.6 ± 1.8	30.6 ± 1.3	.34
Hypertension, n (%)	96.4	28 (93.3)	26, (100)	.18
Dyslipidemia, n (%)	67.9	21(70)	17 (65.4)	.71
Diabetes mellitus, n (%)	35.7	11 (36.7)	9 (34.6)	.87
History of smoking, n (%)	62.5	17 (56.7)	18 (69.23)	.33
Family history of coronary artery disease, n (%)	41.1	10 (33.3)	13 (50)	.21
History of PCI, n (%)	10.7	3 (10)	3 (11.5)	.85
History of CABG surgery, n (%)	3.6	1 (3.33)	1 (3.85)	.92
Use of aspirin, n (%)	28.6	10 (33.3)	6 (23.1)	.39
Use of lipid lowering agents, n (%)	60.7	18 (60.0)	16 (61.5)	.91
eGFR, mL/min per 1.73 m^2	87.9 ± 21.9	90.2 ± 21.9	85.3 ± 22.0	.36
Total cholesterol, mg/dL	156.8 ± 44.9	152.3 ± 36.4	162.2 ± 53.8	.37
High density lipoprotein, mg/dL	47.4 ± 12.1	46.7 ± 12.1	48.3 ± 12.4	.56
Low density lipoprotein, mg/dL	83.4 ± 34.9	78.3 ± 29.5	89.6 ± 40.3	.31
Triglyceride, mg/dL	153.7 ± 86.6	136.5 ± 77.9	174.4 ± 93.5	.13

Data are presented as mean ± standard deviation.
PCI, Percutaneous Coronary Intervention.
CABG, Coronary artery bypass graft.

Table II. CT parameters of segment numbers, length, vessel, lumen and plaque volumes at baseline and 1-year follow-up

	Baseline			Follow-up		
	Warfarin group (n = 30)	Apixaban group (n = 26)	*P*	Warfarin group (n = 30)	Apixaban group (n = 26)	*P*
Segment numbers	12.1 ± 2.2	12.8 ± 2.3	.10	12 ± 2.2	12.7 ± 2.5	.06
*Length, mm	451.8 ± 123.4	461.9 ± 103.0	.34	450.9 ± 119.2	459.7 ± 110.7	.29
*Vessel volume, mm^3	3111.6 ± 1167.4	3643.2 ± 1526.5	.14	3507.9 ± 1394.9	3725.1 ± 1603.6	.71
*Lumen, volume, mm^3	3029.9 ± 1197.0	3530.2 ± 1536.4	.18	3372.4 ± 1434.6	3565.3 ± 1606.8	.78
Absolute PV, mm^3						
Total	81.7 ± 202.1	113.0 ± 178.9	.21	135.5 ± 318.9	159.8 ± 224.1	.19
Non-calcified	50.4 ± 153.0	47.3 ± 70.5	.47	86.4 ± 236.4	78.8 ± 91.5	.29
Fibrous	43.2 ± 123.7	44.1 ± 65.6	.46	72.5 ± 180.5	72.5 ± 83.5	.31
Fibro-fatty	5.6 ± 22.8	2.8 ± 4.5	.30	9.99 ± 37.0	5.56 ± 7.7	.35
Low attenuation plaque	1.6 ± 7.1	0.42 ± 0.9	.25	3.91 ± 19.4	0.74 ± 1.6	.29
Calcified	31.1 ± 61.5	66.0 ± 129.9	.27	49.2 ± 100.6	81.1 ± 156.9	.28
Normalized PV, mm^3						
Total	192.3 ± 447.3	298.2 ± 570.4	.34	311.6 ± 701.5	412.5 ± 689.1	.29
Non-calcified	113.5 ± 328.2	110.9 ± 176.4	.62	192.1 ± 506.3	175.7 ± 218.1	.47
Fibrous	97.6 ± 266.2	104.1 ± 167.2	.62	161.5 ± 388.2	164.8 ± 203.5	.46
Fibro-fatty	12.4 ± 48.1	5.9 ± 9.0	.36	21.2 ± 78.9	11.6 ± 17.8	.38
Low attenuation plaque	3.6 ± 15.1	0.87 ± 1.6	.29	8.3 ± 41.4	1.4 ± 2.6	.27
Calcified	78.2 ± 154.5	188.1 ± 427.4	.35	121.1 ± 247.2	234.7 ± 505.8	.31

PV, plaque volume.
Data are presented as mean ± standard deviation.

design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

This prospective, single-center, randomized, open label trial showed a positive effect of apixaban on the progression of atherosclerotic and calcified plaques by CCTA compared to a traditional oral anticoagulant, warfarin. Given the high prevalence of concomitant coronary artery disease and atrial fibrillation and its associated increase in cardiovascular morbidities and mortalities, it is important to best treat this co-existing condition and to understand the effect of direct oral anticoagulants which have been increasingly use in various clinical settings.

Table III. Difference/change in plaque volumes per vessel between baseline and follow-up among warfarin and apixaban groups

	Warfarin group (n = 30)	Apixaban group (n = 26)	*P*
Absolute PV, mm^3			
Total	53.8 ± 120.1	46.8 ± 51.7	.40
Non-calcified	36.0 ± 85.5	31.5 ± 33.3	.43
Fibrous	29.4 ± 58.9	28.9 ± 47.2	.42
Fibro-fatty	4.4 ± 14.9	2.8 ± 5.1	.25
Low attenuation plaque	2.3 ± 12.4	0.3 ± 1.3	.97
Calcified	18.1 ± 41.2	15.1 ± 30.3	.45
Normalized PV, mm^3			
Total	119.3 ± 264.4	114.3 ± 58.0	.32
Non-calcified	78.6 ± 183.1	64.8 ± 69.0	.42
Fibrous	63.9 ± 127.7	60.7 ± 57.8	.30
Fibro-fatty	8.8 ± 31.5	5.7 ± 8.9	.15
Low attenuation plaque	4.7 ± 26.5	0.6 ± 2.3	.87
Calcified	42.8 ± 100.2	46.6 ± 98.7	.51

PV, plaque volume.
Data are presented as mean ± standard deviation.

Table IV. Comparison of change in atherosclerotic plaque composition between baseline and one-year follow-up in apixaban vs warfarin groups (Multivariable linear regression analysis)

	Model 1		Model 2		Model 3	
	Difference (95% CI)	*P*	Difference (95% CI)	*P*	Difference (95% CI)	*P*
Total	24.40 (–30.79 to 79.59)	.38	43.70 (–16.40 to 103.80)	.15	28.54 (3.64-53.44)	**.03**
Non-calcified	14.29 (–24.92 to 53.50)	.47	25.93 (–18.83 to 70.68)	.25	15.03 (–6.44 to 36.50)	.17
Fibrous	7.09 (–21.05 to 35.23)	.62	15.47 (–16.69 to 47.62)	.34	7.82 (–8.81 to 24.44)	.35
Fibro-fatty	3.39 (–3.36 to 10.13)	.32	5.39 (–2.16 to 12.95)	.16	3.63 (–0.49 to 7.74)	.08
Low attenuation plaque	3.81 (–1.47 to 9.09)	.15	5.07 (–1.05 to 11.19)	.10	3.58 (0.63-6.53)	**.02**
Calcified	10.71 (–10.14 to 31.57)	.31	18.28 (0.44-36.12)	**.04**	14.10 (4.49-23.72)	**.005**

Model 1, Adjusted for patients' demographic data including age, gender, and BMI.
Model 2, Adjusted for model 1 plus hypertension, diabetes, dyslipidemia, smoking, family history, prior percutaneous coronary intervention, coronary bypass surgery, aspirin use and statin use.
Model 3, Adjusted for model 2 plus baseline plaque volume.
$P < .05$ was considered as statistically significant (as shown in bold font).

The final cohort (those who had two interpretable CTA studies at baseline and 52 weeks) consisted of 56 participants with non-valvular AF (31–85 years old) randomized into VKA_group (n = 30) or Api_group (n = 26). 69.6% of the total study population were male at the mean age of 57.4 years. The baseline clinical and CCTA characteristics were similar in both groups (Table I). We assessed various characteristics of coronary atherosclerotic plaque including total, non-calcified, fibrous, fibrous-fatty, low attenuation, and calcified plaque and demonstrated the plaque change over one-year follow up (Table II). The plaque progression, especially calcified plaque, was substantially higher in the VKA_group as compared with the Api_group. After adjustment for baseline plaque volume in addition to patients' demographic data and clinical variables, in addition to calcified plaque progression, the warfarin was associated with greater total and low attenuation plaque progression (Table III). Additionally, there was a non-statistically significant trend toward greater plaque progression of all plaque types in those on warfarin as compared with those on apixaban (Table IV).

Regardless of aspirin and statin use, apixaban was associated with a deceleration of plaque progression which might potentially translate into a stabilization of atherosclerotic plaque and a retardation of clinical events. After additional adjustment for clinical variables including hypertension, diabetes, dyslipidemia, smoking, family

history, prior percutaneous coronary intervention, coronary bypass surgery, aspirin use and statin use to model 1, VKA_group was significantly associated with higher calcified plaque volume (β_2 = 18.28; P = .04) as compared with the Api_group (model 2). Greater volume of total (β_2 = 28.54; P = .03), low attenuation plaque (β_2 = 3.58; P = .02) and calcified (β_2 = 14.10; P = .005) plaque progression was observed in the VKA_group after further adjustment for baseline plaque volume in addition to those adjusted in model 2 (model 3).

We have performed reproducibility studies of these measures. The intraclass correlations (ICCs) and coefficients of variation (CVs) were calculated. For plaque volume, the intraobserver CV was 7.8%, the intraobserver ICC was 0.99, and the interobserver ICC was 0.95.[7]

Discussion

Given the high prevalence of concomitant AF and CAD,[1] the appropriate choice of anticoagulation is critically important because it is considerably challenging to manage these overlapping syndromes in clinical practice owing to the need to balance carefully the risk of bleeding against the risk of thromboembolism. Approximately 20% to 30% of patients had CAD in AF registries and trials,[1] and AF was present in about 12.5% of patients in a registry of patients with CAD.[6] Patients with AF and prior CAD are at increased risk for CV events and death.[1,6]

The finding from our pilot study suggests that the use of apixaban was associated with slowed plaque progression independent of aspirin and statin use as compared with VKA. This parallels the event reduction seen with apixaban compared to warfarin in the Aristotle Trial.[8] The novel finding indicates that apixaban alone can be used in managing patients with AF and CAD to prevent AF-related thromboembolic events as well as potentially for secondary prevention of MI with possibly less risk of bleeding as it has been shown that apixaban has lower risk of bleeding as compared to warfarin. This is similar to the results of a parallel study of rivaroxaban that demonstrated slowed plaque progression as compared to warfarin.[4]

Warfarin, a vitamin K antagonist and one of the most widely used oral anti-coagulants, has been showed to increase vascular calcification leading to increased CV events.[9,10] There were several studies indicating that VKA inhibits not only post-translational activation of vitamin K-dependent coagulation factors but also synthesis of functional extra-hepatic vitamin K-dependent proteins; thereby eliciting undesired side-effects.[11] Moreover, several investigations revealed that calcification of the coronary arteries and heart valves was increased in patients on VKA, whereas intake of vitamin K was associated with less progression of coronary artery calcification.[9] One recent study showed vitamin K supplementation retards the aortic valve calcification which is suggestive against the use of VKA due to its association with increased systemic and vascular calcification.[11] The use of warfarin in non-valvular AF has also become less favorable due to its poorer efficacy and safety profiles as compared to direct oral anticoagulants (DOACs),[4,8] However, apixaban, a direct Factor Xa inhibitor, has no interaction with vitamin K.

In ARISTOTLE trial, there were non-significantly fewer MI among patients on apixaban than warfarin.[9] Moreover, among patients with prior coronary disease not on aspirin, the rate of MI was numerically lower with apixaban than with warfarin, suggesting that a strategy of avoiding aspirin for stable coronary disease patients on warfarin might also apply to such patients on apixaban.

Limitation

There are several limitations in the present study. First, it was a prospective randomized open-label design, but all CT readers and statistical analyses were blinded to randomization. The sample size was relatively small and 10 patients were not included due to incomplete CT data or loss to follow up. Despite these limitations, our data provide initial data for future intervention and clinical trials with larger sample sizes and longer follow-up to investigate clinical outcomes of the choice of anticoagulants in patients with atrial fibrillation and co-existing coronary artery disease in order to prevent significant atherosclerotic plaque progression.

Conclusion

Our study shows that apixaban is associated with slow progression or stabilization of coronary atherosclerotic and calcified plaques as compared with warfarin. This novel finding indicates the potential benefit of apixaban in treating patients who have non-valvular atrial fibrillation with co-existing coronary artery disease. The potential to slow atherosclerosis with use of apixaban may possibly lead to stabilization of coronary artery disease. Further investigation to evaluate the clinical outcomes of the use of apixaban in patients with concomitant coronary artery disease and atrial fibrillation is warranted.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.02.014.

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