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Efficacy of Direct Acting Oral Anticoagulant Drugs in Treatment of Left Atrial Appendage Thrombus in Patients with Atrial Fibrillation

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Abstract

Direct acting oral anticoagulants (DOACs) are increasingly used for thromboembolic prophylaxis in patients with atrial fibrillation (AF). However, there is limited data to evaluate the use of DOACs for the treatment of pre-existing left atrial appendage thrombus. We aimed to determine the efficacy of DOACs in treatment of left atrial appendage (LAA) thrombus utilizing transesophageal echocardiographic (TEE) and clinical outcomes. In this single-center study, we identified 33 patients that were treated for LAA thrombus with DOAC. 18 were treated with apixaban, 10 with dabigatran, and 5 with rivaroxaban. The primary endpoint was defined as resolution of LAA thrombus (in patients undergoing TEE), or death, major bleeding requiring transfusion, intracranial hemorrhage, ischemic stroke, or peripheral embolization. In this study, 15 of the 16 patients treated with DOACs who underwent follow-up TEE had resolution of LAA thrombus, with a mean duration of 112 days. Of the 15 patients who achieved resolution of the LAA thrombus, 14 had resolution by their first follow-up TEE. In the 17 patients without a follow-up TEE, one died of a retroperitoneal bleed (28 days after DOAC initiation), and one suffered an ischemic stroke (484 days after DOAC initiation). In general, patients without a follow-up TEE were older and had more comorbidities. Although these results are descriptive and limited in number of patients, we believe this is ample evidence that DOACs are relatively safe and efficacious in treatment of patients with AF and concomitant LAA thrombus.

Key words

left atrial appendage; left atrial appendage thrombus; atrial fibrillation; anticoagulation; transesophageal echocardiography; direct acting oral anticoagulants

Atrial fibrillation (AF) predisposes to left atrial (LA) stasis and subsequent formation of left atrial appendage (LAA) thrombus, which can lead to cardioembolic stroke or systemic embolization. Traditionally, warfarin has been used for thromboembolic prophylaxis in patients with AF (1). However, newer direct acting oral anticoagulants (DOAC) are essentially equivalent to warfarin in efficacy, with lower intracranial hemorrhage risk, and are increasingly used for thromboembolic prophylaxis in this patient population. Although there is substantial evidence regarding efficacy of DOACs for thromboembolic prophylaxis in patients with AF, efficacy of treatment in patients with pre-existing left atrial appendage thrombus is limited to a few case reports (2,3) and one registry of modest size in which rivaroxaban was utilized (4). We aimed to determine the efficacy of DOACs in treatment of left atrial appendage thrombus utilizing transesophageal echocardiographic (TEE) and clinical outcomes.

Methods

We conducted this single-center retrospective study at Saint Luke's Mid America Heart Institute in Kansas City. This study was approved by the Institutional Review Board at Saint Luke's Hospital of Kansas City. Between February 19th 2002 and February 24th 2017, 14,924 TEEs were performed at our institution. Of these, 629 study reports identified possible or definite left atrial appendage thrombus. A review of medical records confirmed that 82 of these patients had been subsequently treated with a DOAC. These patients were not on anticoagulation prior to the encounter in which LAA thrombus was diagnosed. To confirm the presence of a definite LAA thrombus, 2 cardiologists (M.L.M. and A.M) with extensive experience in performance and interpretation of TEE separately reviewed each of these TEEs without knowledge of clinical

data. Cases in which both cardiologists independently agreed that a LAA thrombus was present were included in the study group. Cases with only dense spontaneous echo contrast or "sludge" were excluded. Ultimately 36 patients comprised the study group. Clinical and demographic data for these patients was then abstracted from the medical record and entered into a REDCap database for subsequent analysis. REDCap is a HIPAA compliant web application for building and managing online surveys and databases.

The primary endpoint was defined as resolution of LAA thrombus (in patients undergoing TEE), or death, major bleeding requiring transfusion, intracranial hemorrhage, ischemic stroke, or peripheral embolization. One cardiologist (M.L.M) subsequently reviewed all initial and follow-up TEEs in a random and blinded fashion to confirm presence or absence of LAA thrombus, and in cases with thrombus, to measure maximum thrombus area. Of note, 3 of the 36 initial TEEs were deemed by the reviewer at this point not to have a measurable left atrial appendage thrombus, and these were excluded from further analysis.

Results

Baseline clinical and demographic characteristics of the 33 patients with a confirmed and measurable LAA thrombus are shown in Table 1. Representative LAA thrombus images are shown in Figure 1. Of these 33 patients, 18 were treated with apixaban, 10 with dabigatran, and 5 with rivaroxaban. Sixteen of the 33 patients underwent a follow-up TEE (see Table 2 and Figure 2) and 15 (94%) had complete resolution of LAA thrombus. The average time to resolution of thrombus was 112 days. Of the 15 patients who achieved resolution of the LAA thrombus, 14 had resolution noted on their first follow-up TEE. The patient without thrombus resolution underwent TEE after 122 days of rivaroxaban therapy with a residual thrombus area of

0.8cm^2, increased from an initial area of 0.5cm^2. None of these 16 patients had cardioembolic or bleeding events.

Overall, 1 of the 33 patients (3%) had a cardioembolic event, which was an ischemic stroke. This event occurred 484 days after initiation of anticoagulation. Two other patients experienced significant ischemic events; one suffered a periprocedural stroke during transcatheter aortic valve replacement, and the other experienced a myocardial infarction. Both of these events occurred during the index hospital admission in which the LAA thrombus was diagnosed. Three of the 33 patients (9%) had a major bleeding event. Two were gastrointestinal hemorrhages requiring transfusion, and one was a fatal retroperitoneal bleed diagnosed at autopsy. In general, patients without a follow-up TEE were older and had more comorbidities. Clinical outcomes in the 18 patients who did not undergo follow-up TEE are shown on Table 3 and Figure 3.

Discussion

Atrial fibrillation is commonly associated with formation of left atrial appendage (LAA) thrombus which can lead to thromboembolic events. Traditionally, warfarin has been the primary anticoagulant used for patients with AF (1). In 2009, the RE-LY trial in patients with AF showed that dabigatran reduced stroke risk in patients with atrial fibrillation without increasing the risk of major bleeding as compared to warfarin (5). In 2011, the ROCKET-AF trial demonstrated that rivaroxaban was non-inferior to warfarin in preventing stroke or other systemic thromboembolism in a similar patient population (6). Also, in 2011, the ARISTOTLE trial showed that apixaban was associated with a lower incidence of stroke and/or thromboembolism, and a decrease in the incidence of bleeding, as compared to traditional anticoagulation therapy with warfarin in patients with atrial fibrillation (7,8). Although these studies demonstrated

efficacy in thromboembolic prophylaxis in patients with AF (9), there is limited data regarding use of these agents to treat patients with pre-existing LAA thrombus (2-4).

In the present study, 15/16 patients treated with DOACs who underwent follow-up TEE had resolution of LAA thrombus (mean of 112 days). In the 17 patients without a follow-up TEE, one died of a retroperitoneal bleed (28 days after DOAC initiation), and one suffered an ischemic stroke (484 days after DOAC initiation). Although these results are descriptive and limited in numbers of patients, we believe this is ample evidence that DOACs are relatively safe and efficacious in treatment of patients with AF and concomitant LAA thrombus.

Our study is limited by the small number of patients (n = 33). However, there is only one other study in this patient population (n= 53), and all patients in that study were treated with a single agent (rivaroxaban) (4). A second limitation is that only about half of our patients underwent a follow-up TEE. However, extensive clinical information was available for all the patients.

Discloser

The authors have no disclosures to report

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Fig. 1 A. Transesophageal echocardiographic view of the left atrial appendage in a 72 year-old man with a CHA_2D_2-VASc score = 3. Note the large (1.0 cm^2 maximum area) left atrial appendage thrombus (yellow arrow). Following the TEE, treatment was initiated with rivaroxaban. Fig. 1B: Tranesophageal echocardiographic view of the left atrial appendage (same patient as panel 1A). This study was performed 483 days following identification of the left atrial appendage thrombus, and initiation of rivaroxaban. Note that the thrombus has completely resolved (yellow arrow). Fig. 1C: Tranesophageal echocardiographic view of the left atrial appendage in a 68 year-old man with a CHA_2D_2-VASc score = 5. Note the very large (2.4 cm^2 maximum area) left atrial appendage thrombus. Following the TEE, treatment was initiated with dabigatran. At last clinical follow-up (299 days following the TEE), the patient had not experienced significant bleeding, a stroke, or systemic embolization. Fig. 1D: Transesophageal echocardiographic view of the left atrial appendage in an 81 year-old woman with a CHA_2D_2-VASc score = 4. Note the left atrial appendage thrombus (0.7 cm^2 maximum area) (yellow arrow). Following the TEE, treatment was initiated with rivaroxaban. A repeat TEE was not performed. The patient did not experience significant bleeding complications but suffered an ischemic stroke 484 days following the TEE.

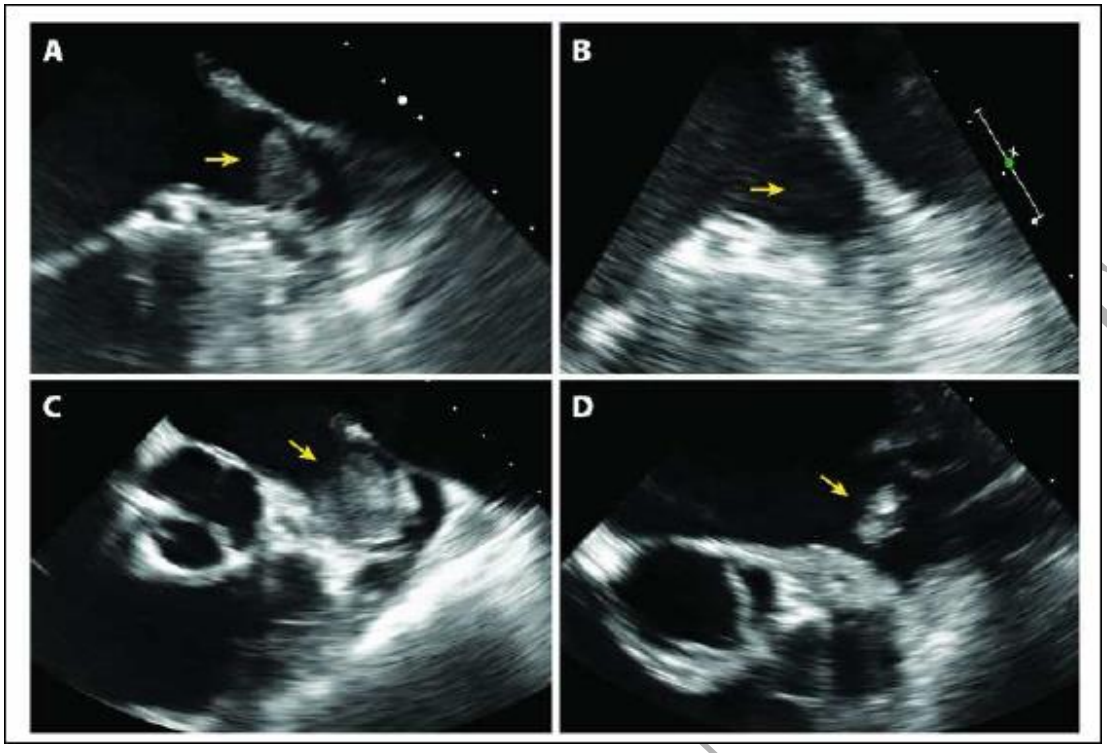

Fig. 2: Outcomes in the patients with a follow-up TEE. Patients order corresponds to Table 2.

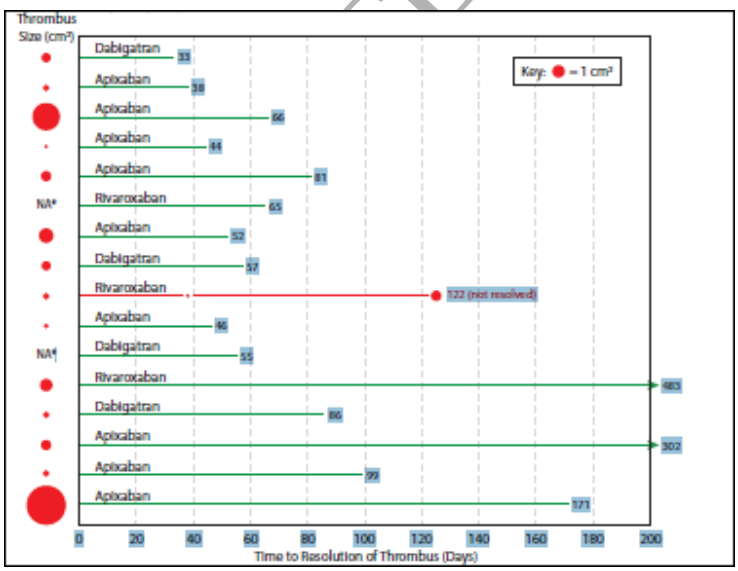

Fig. 3: Outcomes in patients without a follow-up TEE. Patients order corresponds to Table 3.

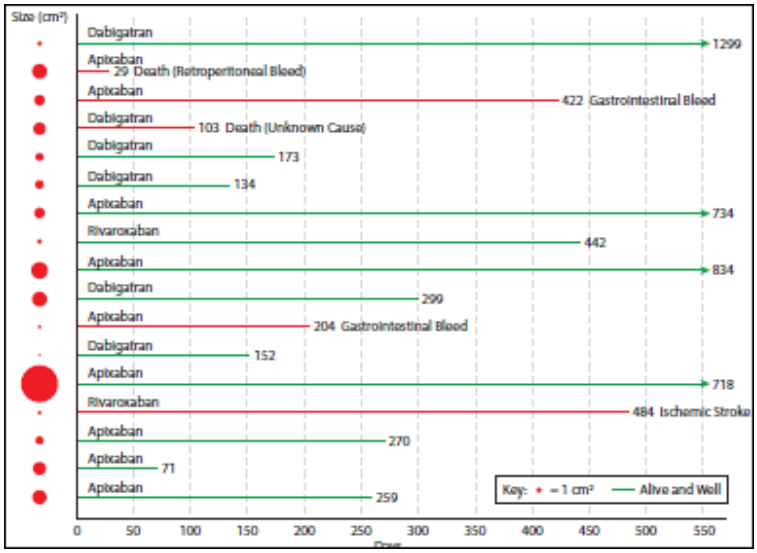

Table 1. Baseline Demographics.

Age (years)	Gender	BMI	CHA_2DS_2-Vasc	HAS-BLED score	Smoker	Anti-Platelet Drugs	Moderate-severe valvular disease	LVEF on baseline TEE (%)	DOAC	DOAC total daily dose (mg)
47	Male	35	1	1	No	Aspirin/Plavix	No	20	Dabigatran	300
49	Female	33	2	0	No	No	No	40	Apixaban	10
54	Male	34	2	1	No	Aspirin	No	20	Dabigatran	300
55	Female	23	7	2	Yes	Aspirin	No	55	Apixaban	10
55	Male	37	2	2	Yes	No	No	20	Apixaban	10
55	Male	26	4	1	No	No	No	65	Apixaban	10
57	Male	45	2	1	No	Aspirin	No	45	Dabigatran	300
57	Male	39	1	0	No	No	No	60	Apixaban	10
58	Male	31	1	1	Yes	Aspirin/Plavix	No	20	Apixaban	10
59	Male	32	2	1	Yes	Aspirin	No	40	Rivaroxaban	20
60	Male	40	3	2	No	No	No	30	Dabigatran	300
60	Female	35	0	0	Yes	No	No	20	Dabigatran	300
61	Male	26	2	0	Yes	No	No	20	Apixaban	10
62	Male	22	3	1	Yes	Aspirin	No	30	Rivaroxaban	20
64	Male	38	2	1	No	Aspirin	MR	20	Apixaban	10
64	Male	42	1	1	No	Aspirin	No	60	Dabigatran	300
65	Male	24	2	2	Yes	Aspirin	No	60	Rivaroxaban	20
66	Male	21	3	1	Yes	No	No	45	Apixaban	10
68	Male	34	5	2	Yes	Aspirin	AS	25	Dabigatran	300

69	Female	29	4	2	No	Aspirin	No	50	Apixaban	10
70	Male	30	4	2	Yes	Aspirin	No	15	Dabigatran	300
71	Female	25	3	1	Yes	No	MR	55	Apixaban	10
72	Male	26	3	1	No	No	No	60	Rivaroxaban	20
73	Female	29	4	1	No	Aspirin/Plavix	No	65	Dabigatran	300
75	Male	30	4	2	No	Aspirin	No	21	Dabigatran	300
76	Female	32	4	1	No	No	AI/AS	60	Apixaban	10
78	Male	30	8	3	Yes	Plavix	AS	55	Apixaban	10
81	Female	24	4	1	Yes	No	No	60	Rivaroxaban	15
81	Female	33	5	2	No	Aspirin	MR	50	Apixaban	10
85	Male	29	5	2	Yes	Aspirin	No	15	Apixaban	10
86	Male	19	3	2	Yes	Aspirin	No	20	Apixaban	10
90	Male	22	6	3	Yes	Aspirin	No	60	Apixaban	5
94	Female	29	4	1	No	No	MR	65	Apixaban	5

Table 2. Outcomes in Patients with Follow-up TEE.

Age (years)	DOAC	Thrombus size (cm^2)	Resolution of thrombus	Thrombus duration (days)	Major bleed	Embolic event	Duration of follow-up (days)	Endpoint
54	Dabigatran	0.7	Yes	33	No	No	33	Thrombus Resolut
55	Apixaban	0.5	Yes	38	No	No	38	Thrombus Resolut
55	Apixaban	2.4	Yes	66	No	No	66	Thrombus Resolut
57	Apixaban	0.2	Yes	44	No	No	44	Thrombus Resolut
58	Apixaban	0.8	Yes	81	No	No	81	Thrombus Resolut
59	Rivaroxaban	N/A	Yes	65	No	No	65	Thrombus Resolut
64	Apixaban	1.2	Yes	52	No	No	52	Thrombus Resolut
64	Dabigatran	0.7	Yes	57	No	No	57	Thrombus Resolut
65	Rivaroxaban	0.5	No	Unresolved	No	No	2000	Last clinical follow
69	Apixaban	0.3	Yes	46	No	No	46	Thrombus Resolut
70	Dabigatran	N/A	Yes	55	No	No	55	Thrombus Resolut
72	Rivaroxaban	1	Yes	483	No	No	483	Thrombus Resolut
73	Dabigatran	0.5	Yes	86	No	No	86	Thrombus Resolut
76	Apixaban	0.8	Yes	302	No	No	302	Thrombus Resolut
81	Apixaban	0.5	Yes	99	No	No	99	Thrombus Resolut
85	Apixaban	3.5	Yes	171	No	No	171	Thrombus Resolut

Table 3. Outcomes in Patients without Follow-up TEE.

Age (years)	DOAC	Thrombus size (cm^2)	Major bleed	Embolic event	Duration of follow-up (days)	Endpoint	Cause of death

47	Dabigatran	0.8	No	No	1299	Last clinical f/u	
49	Apixaban	2.4	RP bleed	No	29	Death	RP bleed
55	Apixaban	1.7	GI bleed	No	422	GI bleed	
57	Dabigatran	2	No	No	103	Death	Unknown
60	Dabigatran	1.3	No	No	173	Last clinical f/u	
60	Dabigatran	1.4	No	No	134	Last clinical f/u	
61	Apixaban	1.7	No	No	756	Last clinical f/u	
62	Rivaroxaban	0.9	No	No	442	Last clinical f/u	
66	Apixaban	2.7	No	No	834	Last clinical f/u	
68	Dabigatran	2.4	No	No	299	Last clinical f/u	
71	Apixaban	0.6	GI bleed	No	204	GI bleed	
75	Dabigatran	0.4	No	No	152	Last clinical f/u	
78	Apixaban	6	No	Ischemic stroke[1]	718	Last clinical f/u	
81	Rivaroxaban	0.7	No	Ischemic stroke	484	Stroke	
86	Apixaban	1.3	No	MI[2]	270	Last clinical f/u	
90	Apixaban	2.1	No	No	71	Last clinical f/u	
94	Apixaban	2.3	No	No	259	Last clinical f/u	

MI = myocardial infarction. RP = retroperitoneal. GI = gastrointestinal.