Efficacy of Direct Acting Oral Anticoagulants in Treatment of Left Ventricular Thrombus

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Direct acting oral anticoagulants (DOACs) are increasingly used as off-label alternatives to vitamin K antagonists for the treatment of left ventricular (LV) thrombus. However, efficacy data is limited to small case series and one meta-analysis of case reports. We aimed to determine the efficacy and safety of DOACs in treatment of LV thrombus utilizing transthoracic echocardiography (TTE) and clinical outcomes. We identified 52 patients (mean age = 64 years, 71% men) treated with a DOAC for LV thrombus (n = 26 apixaban, n = 24 rivaroxaban, and n = 2 dabigatran). Thirty-five of the 52 patients had a follow-up TTE after DOAC initiation. The primary end point was defined as resolution of LV thrombus (in patients with a subsequent TTE), or death, major bleeding requiring transfusion, intracranial hemorrhage, ischemic stroke, or peripheral embolization. An experienced echocardiographer (M.L.M.) reviewed all TTEs for presence or absence of LV thrombus without knowledge of time point or clinical data. Twenty-nine of the 35 (83%) patients who underwent follow-up TTE had resolution of LV thrombus, with a mean duration of 264 days. Of the total study population, there was 1 cardioembolic event (transient ischemic attack) 52 days after initiating DOAC, 3 gastrointestinal bleeds requiring transfusion, and 1 patient with epistaxis requiring transfusion. All patients with a hemorrhagic complication were receiving concomitant antiplatelet therapy. DOAC therapy appears promising for the treatment of LV thrombus. A larger, prospective study is warranted to confirm these results. **(Am J Cardiol 2019;124:367−372)**

Left ventricular (LV) thrombus is a well-recognized complication of systolic dysfunction, particularly after myocardial infarction. Wall motion abnormalities lead to blood pooling and subsequent thrombus formation, placing the patient at risk for cardioembolic stroke and systemic embolization. Current guidelines recommend vitamin K antagonists (VKA) for treatment of left ventricular thrombus.[1−3] However, the favorable pharmacological and clinical profile of direct acting oral anticoagulants (DOAC) make them increasingly attractive alternatives to VKA. Although there is substantial evidence regarding efficacy of DOACs for thromboembolic prophylaxis in patients with atrial fibrillation, efficacy of treatment in patients with LV thrombus is limited to small case series and one meta-analysis of case reports.[4−7] We aimed to determine the efficacy of DOACs in treatment of left ventricular thrombus utilizing transthoracic echocardiography (TTE) 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 October 7, 2010 and October 12, 2018, 701 patients at our institution had TTEs performed with definite, probable, or possible LV thrombus. A review of medical records confirmed that 73 of these patients had been subsequently treated with a DOAC medication. These patients were not on anticoagulation before the encounter in which LV thrombus was diagnosed. To confirm the presence of a definite LV thrombus, one cardiologist (M.L.M) subsequently reviewed all initial and follow-up TTEs in a random and blinded fashion to confirm presence or absence of LV thrombus, and in cases with thrombus, to measure maximum thrombus area. This was done without knowledge of clinical data. Only cases with discrete, measurable LV thrombus were included. Ultimately 52 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 end point was defined as resolution of LV thrombus (in patients undergoing subsequent TTE), or death, major bleeding requiring transfusion, intracranial hemorrhage, ischemic stroke, or peripheral embolization.

Results

Baseline clinical and demographic characteristics of the 52 patients with a confirmed and measurable LV thrombus are shown in Table 1. Of these patients, 26 were treated

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See page 371 for disclosure information.

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Table 1
Baseline clinical and demographic characteristics of the 52 patients with left ventricular thrombus

Age	Gender	BMI	CHA_2DS_2 - Vasc	HAS-BLED score	Tobacco abuse	On anti-platelet agents at the time of DOAC	Moderate-severe valvular disease	EF on baseline TTE (%)	DOAC	DOAC total daily dose (mg)
34	Female	30	4	1	+	Aspirin	o	35	Apixaban	10
34	Male	29	1	0	o	No	+(MR)	15	Apixaban	10
37	Male	24	1	0	+	No	o	10	Rivaroxaban	20
42	Male	35	4	2	o	Aspirin	o	19	Rivaroxaban	20
44	Male	33	3	0	+	No	+(MR)	30	Apixaban	10
46	Male	25	1	1	o	Aspirin	o	52	Rivaroxaban	20
46	Female	34	2	0	o	No	o	40	Apixaban	10
50	Female	34	3	2	+	Aspirin	o	12	Rivaroxaban	15
50	Male	31	2	0	o	No	o	20	Rivaroxaban	20
50	Male	34	2	2	o	Aspirin	o	25	Apixaban	10
51	Female	66	4	1	+	Aspirin	o	20	Apixaban	10
52	Female	28	2	1	o	Clopidogrel	o	43	Apixaban	10
56	Male	30	2	1	o	Aspirin	o	39	Rivaroxaban	20
56	Male	28	5	2	o	Aspirin	+(MR)	15	Apixaban	10
57	Male	32	2	1	+	Aspirin	o	35	Rivaroxaban	20
57	Male	21	1	1	+	Aspirin	+(MR)	14	Apixaban	10
57	Female	26	3	1	o	Aspirin	o	18	Apixaban	10
58	Male	41	2	1	o	Aspirin	o	15	Rivaroxaban	15
58	Male	34	1	1	o	Aspirin	o	20	Dabigatran	300
58	Male	33	1	1	o	Aspirin	o	39	Rivaroxaban	20
58	Male	37	1	1	o	Aspirin	o	23	Apixaban	10
60	Male	20	1	0	o	No	o	10	Apixaban	10
60	Female	33	2	1	o	Aspirin/Clopidogrel	o	20	Rivaroxaban	20
61	Female	29	4	1	o	Aspirin	o	36	Apixaban	10
62	Male	38	2	1	+	Aspirin/Clopidogrel	o	55	Rivaroxaban	20
65	Male	28	3	2	+	Aspirin/Prasugrel	o	50	Rivaroxaban	15
66	Male	23	4	3	+	Aspirin	+(MR)	22	Rivaroxaban	20
66	Male	27	4	2	+	Clopidogrel	o	44	Apixaban	10
67	Male	30	3	3	o	Aspirin	o	20	Rivaroxaban	20
67	Male	28	2	2	+	Aspirin	o	55	Apixaban	10
68	Male	35	2	1	o	No	o	25	Dabigatran	300
69	Female	21	4	2	+	Aspirin/Clopidogrel	+(MR)	18	Rivaroxaban	15
70	Male	42	2	2	+	Aspirin/Clopidogrel	+(Bioprosthetic AVR)	62	Rivaroxaban	20
70	Female	25	4	2	o	Aspirin/Clopidogrel	o	41	Rivaroxaban	20
74	Male	28	4	1	o	No	o	50	Rivaroxaban	20
74	Male	32	4	2	o	Aspirin/Clopidogrel	o	60	Apixaban	10
75	Female	32	8	3	+	Aspirin/Clopidogrel	o	29	Apixaban	10
76	Male	35	4	2	o	Aspirin	o	48	Rivaroxaban	20
76	Male	27	6	3	o	Aspirin/Ticagrelor	+(MS)	17	Apixaban	10
76	Male	24	7	3	o	Aspirin	+(Bioprosthetic AVR)	39	Apixaban	10
77	Male	34	3	2	o	Aspirin/Clopidogrel	o	51	Rivaroxaban	20
78	Male	35	8	4	o	Aspirin	o	35	Apixaban	10
79	Male	29	5	3	o	Aspirin	o	38	Rivaroxaban	20
80	Female	21	6	2	+	No	+(MR)	25	Apixaban	5
80	Male	25	5	3	o	Clopidogrel	o	15	Apixaban	5
80	Male	22	4	3	o	Aspirin	o	15	Apixaban	10
81	Male	26	4	2	+	Aspirin	o	35	Apixaban	10
82	Male	32	3	2	o	Aspirin	o	45	Rivaroxaban	20
84	Female	16	6	1	o	No	o	15	Apixaban	5
85	Female	30	4	3	o	Aspirin	o	13	Rivaroxaban	20
85	Male	18	3	2	o	Aspirin	o	30	Rivaroxaban	15
87	Female	22	6	1	o	No	o	60	Apixaban	5

with apixaban, 24 with rivaroxaban, and 2 with dabigatran. Thirty-five of the 52 patients underwent a follow-up TTE (see Figure 1 and Table 2) and 29 (83%) had complete resolution of LV thrombus. The average time to resolution of thrombus was 264 days. Of the 29 patients who achieved resolution of the LV thrombus, 24 had resolution noted on their first follow-up TTE.

Overall, 1 of the 52 patients (2%) had a cardioembolic event, which was a transient ischemic attack (TIA). This event occurred 52 days after initiation of anticoagulation. Of the 52 patients, there were 3 patients with gastrointestinal bleed requiring transfusion (hemoglobin nadir 7.4, 5.1, and 7.1 grams/deciliter), and 1 patient with epistaxis requiring transfusion (hemoglobin nadir 6.6 grams/deciliter). All

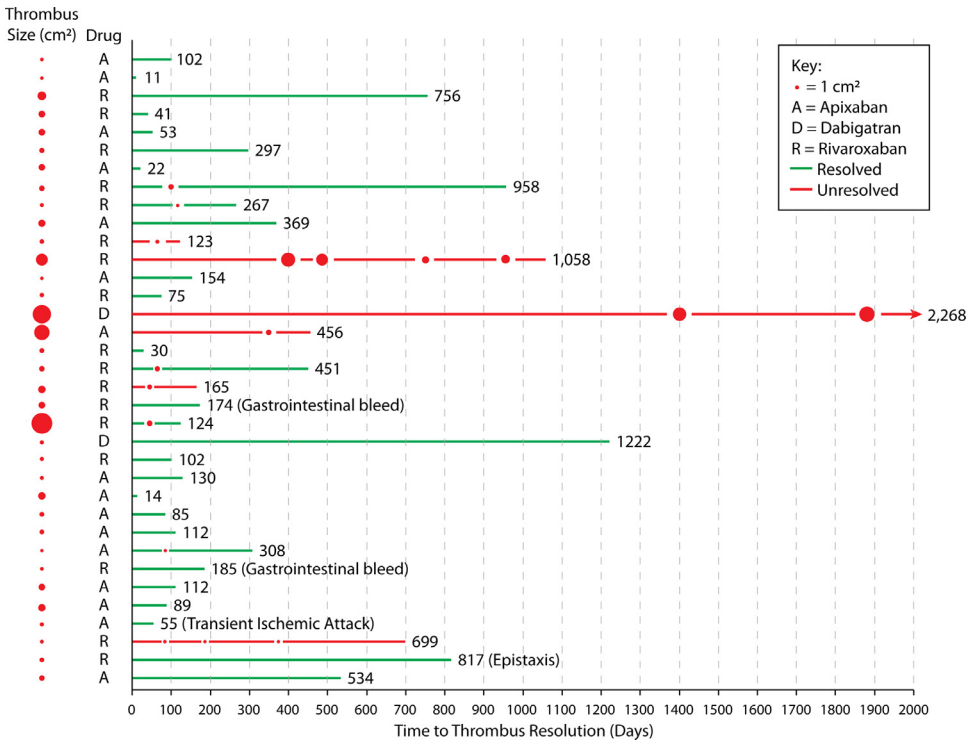

Figure 1. Left ventricular thrombus size and clinical outcomes in the 35 patients with a follow-up transthoracic echocardiogram. The patient order matches that in Table 2.

Table 2
Results in the 35 patients who underwent follow-up transthoracic echocardiography

Age (years)	DOAC	Thrombus size (cm^2)	Thrombus duration (days)	Major bleed	Embolic event	Duration of follow-up (days)	Thrombus resolved
34	Apixaban	0.8	102	o	o	102	+
34	Apixaban	0.7	11	o	o	11	+
37	Rivaroxaban	4.1	756	o	o	756	+
42	Rivaroxaban	2.8	41	o	o	41	+
44	Apixaban	2.8	53	o	o	53	+
46	Rivaroxaban	1.8	297	o	o	297	+
46	Apixaban	2.7	22	o	o	22	+
50	Rivaroxaban	2	958	o	o	958	+
50	Rivaroxaban	1	267	o	o	267	+
51	Apixaban	3.1	369	o	o	369	+
56	Rivaroxaban	1.4	Unresolved	o	o	123	o
57	Rivaroxaban	6.2	Unresolved	o	o	1058	o
57	Apixaban	0.7	154	o	o	154	+
58	Rivaroxaban	1.3	75	o	o	75	+
58	Dabigatran	10.5	Unresolved	o	o	2268	o
58	Apixaban	8.5	Unresolved	o	o	456	o
60	Rivaroxaban	1.6	30	o	o	30	+
62	Rivaroxaban	2	451	o	o	451	+
65	Rivaroxaban	3.3	Unresolved	o	o	165	o
66	Rivaroxaban	2.8	174	GI bleed	o	174	+
67	Rivaroxaban	12.1	124	o	o	124	+
68	Dabigatran	1.1	1222	o	o	1222	+
69	Rivaroxaban	0.2	102	o	o	102	+
74	Apixaban	1	130	o	o	130	+
75	Apixaban	3.3	14	o	o	14	+
76	Apixaban	1.6	85	GI bleed	o	85	+
76	Apixaban	1.5	112	o	o	112	+
78	Apixaban	0.6	308	o	o	308	+

(*continued*)

Table 2 (***Continued***)

Age (years)	DOAC	Thrombus size (cm^2)	Thrombus duration (days)	Major bleed	Embolic event	Duration of follow-up (days)	Thrombus resolved
79	Rivaroxaban	0.8	185	o	o	185	+
80	Apixaban	2.7	112	o	o	112	+
80	Apixaban	3.2	89	o	o	89	+
81	Apixaban	1.1	55	o	TIA	52	+
85	Rivaroxaban	0.9	Unresolved	o	o	699	o
85	Rivaroxaban	1.5	817	Epistaxis	o	816	+
87	Apixaban	2	534	o	o	534	+

patients with a hemorrhagic complication were receiving concomitant antiplatelet therapy. Clinical outcomes in the 17 patients who did not undergo follow-up TTE are shown in Figure 2 and Table 3.

Discussion

The 2013 American College of Cardiology Foundation/American Heart Association STEMI guidelines recommend VKA for the treatment of left ventricular thrombus (Class IIA, Level of Evidence: C).[2] The 2014 American Heart Association/American Stroke Association guidelines on stroke prevention state that DOACs may be considered as alternatives to VKA for LV thrombus in patients who are intolerant to VKA.[3] Therefore, VKA is considered first-line therapy for LV thrombus, albeit with a narrow therapeutic range. A recent study examining patients treated for LV thrombus with VKA showed that 50 of 84 patients spent less than 50% of the time in the effective therapeutic range by serum coagulant testing. Nine embolic events (19%) developed in this group, while only one embolic event (2.9%) occurred in the group which was in the effective therapeutic range over 50% of the time. There was no difference in major bleeding events between these groups (8.5%).[8] DOACs likely offer more consistent levels of anticoagulation with a wider therapeutic range.

Several landmark trials have shown DOACs to be noninferior in efficacy, with up to 50% reduced risk of intracranial hemorrhage, compared with VKA, in the setting of thromboembolic prophylaxis for atrial fibrillation.[9–12] DOACs also appear to be highly efficacious in the treatment of left atrial appendage thrombus.[13] The

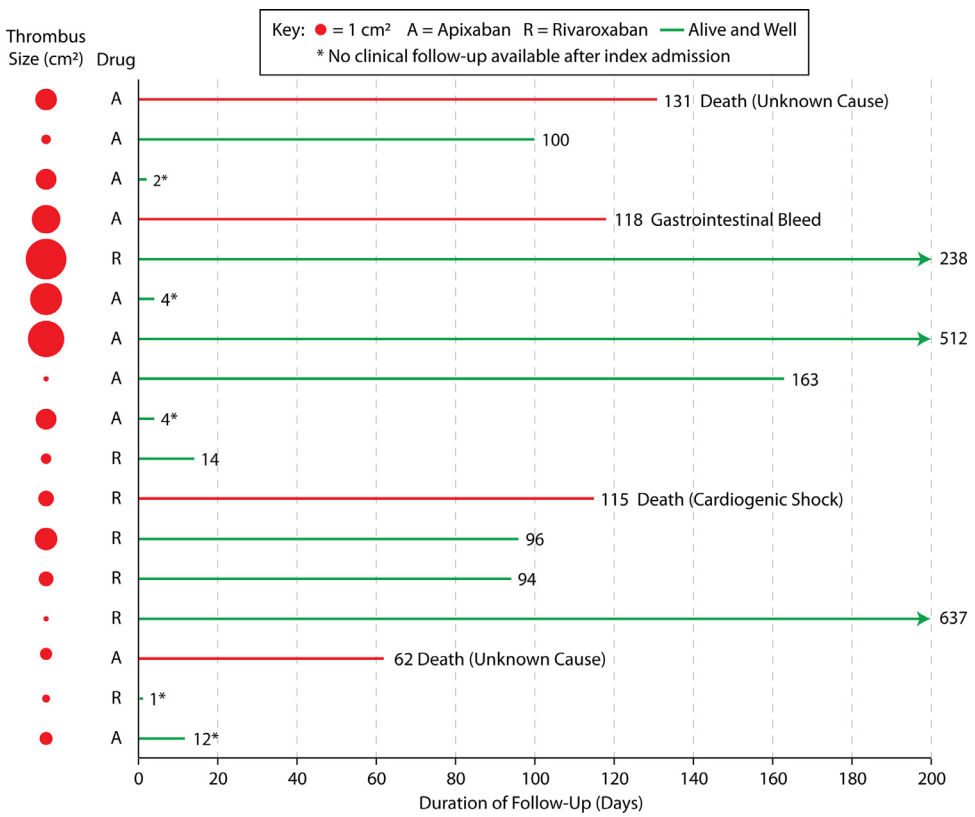

Figure 2. Left ventricular thrombus size and clinical outcomes in the 17 patients without a follow-up transthoracic echocardiogram. The patient order matches that in Table 3.

Table 3
Clinical outcomes in the 17 patients who did not undergo follow-up transthoracic echocardiography

Age (years)	DOAC	Thrombus size (cm^2)	Major bleed	Embolic event	Duration of follow-up (days)	End point
50	Apixaban	2.2	o	o	131	Death
52	Apixaban	0.8	o	o	100	Last clinical f/u
56	Apixaban	2.1	o	o	2	Last clinical f/u
57	Apixaban	3	GI bleed	o	118	GI bleed
58	Rivaroxaban	4.4	o	o	238	Last clinical f/u
60	Apixaban	3.4	o	o	4	Last clinical f/u
61	Apixaban	3.9	o	o	512	Last clinical f/u
66	Apixaban	0.3	o	o	163	Last clinical f/u
67	Apixaban	2.1	o	o	4	Last clinical f/u
70	Rivaroxaban	0.9	o	o	14	Last clinical f/u
70	Rivaroxaban	1.5	o	o	115	Death
74	Rivaroxaban	2.3	o	o	96	Last clinical f/u
76	Rivaroxaban	1.4	o	o	94	Last clinical f/u
77	Rivaroxaban	0.3	o	o	637	Last clinical f/u
80	Apixaban	1.1	o	o	62	Death
82	Rivaroxaban	0.6	o	o	1	Last clinical f/u
84	Apixaban	1.2	o	o	12	Last clinical f/u

formation of LV thrombus is pathologically similar to that of a left atrial appendage thrombus, occurring in a low-flow setting.[1] Given the efficacy of DOACs in thromboembolic prophylaxis for atrial fibrillation and for treatment of left atrial appendage thrombus, it is reasonable to extrapolate their efficacy to the treatment of LV thrombus.

Safety and efficacy data of DOACs in the setting of LV thrombus is limited and warrants continued investigation. The results of the present study appear consistent with and add to that from earlier publications. In the present study, 29 of 35 patients (83%) who had follow-up TTE had complete resolution of LV thrombus. A meta-analysis of 33 articles describing 41 patients showed thrombus resolution in 80% of patients.[4] Additionally, a case series of 8 patients showed thrombus resolution in 100% of patients, and another case series showed thrombus resolution in 5 of 6 patients (83%).[6,7] In the present study, the average time to resolution of thrombus was 264 days, the interpretation of which is limited due to the nonstandardized timing of follow-up TTEs. Of the 29 patients who achieved resolution of the LV thrombus, 24 patients had resolution by their first follow-up TTE. Overall, 1 of the 52 patients (2%) had a cardioembolic event, which was a TIA. This event occurred 52 days after initiation of anticoagulation. A TTE performed 3 days after the TIA showed absence of LV thrombus. Of the 52 patients, 4 patients (8%) had major bleeding requiring transfusion. In the previously mentioned meta-analysis and case series, the reported rates of thromboembolic stroke were 2%, 0%, and 0%, respectively.[4,6,7] The reported rates of bleeding events were 2%, 13%, and 10%, respectively.[4,6,7]

The present study essentially doubles the number of investigated patients in the literature and adds the advantage of a blinded expert echo reviewer to verify resolution or change in thrombus over serial TTEs. DOAC therapy appears promising for the treatment of LV thrombus. A larger, prospective study is warranted to confirm these results.

Disclosures

The authors have no disclosures to report.

1. McCarthy CP, Vaduganathan M, McCarthy KJ, Januzzi JL, Bhatt DL, McEvoy JW. Left ventricular thrombus after acute myocardial infarction: screening, prevention, and treatment. *JAMA Cardiol* 2018;3:642–649.
2. O'Gara P, Kushner F, Ascheim D, Casey D, Chung M, de Lemos J, Ettinger S, Fang J, Fesmire F, Franklin B, Granger C, Krumholz H, Linderbaum J, Morrow D, Newby L, Ornato J, Ou N, Radford M, Tamis-Holland J, Tommaso C, Tracy C, Woo Y, Zhao D. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation* 2013;127:362–425.
3. Kernan W, Ovbiagele B, Black H, Bravata D, Chimowitz M, Ezekowitz M, Fang M, Fisher M, Furie K, Heck D, Johnston S, Kasner S, Kittner S, Mitchell P, Rich M, Richardson D, Schwamm L, Wilson J. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:2160–2236.
4. Kajy M, Shokr M, Ramappa P. Use of direct oral anticoagulants in the treatment of left ventricular thrombus: systematic review of current literature. *Am J Ther* 2019;0:1–7.
5. Elikowski W, Malek-Elikowska M, Wroblewski D, Fertala N, Zawodna M, Lachowska-Kotowska P, Skommer K. Apixaban in left ventricular thrombi treatment – a report of seven cases. *Pol Merkur Lekarski* 2018;44:276–279.
6. Smetana K, Dunne J, Parrott K, Davis G, Schmelzer Collier A, Covell M, Smyth S. Oral factor Xa inhibitors for the treatment of left ventricular thrombus: a case series. *J Thromb Thrombolysis* 2017;44:519–524.
7. Shokr M, Ahmed A, Abubakar H, Sayedahmad Z, Rashed A, Afonso L, Cardozo S. Use of direct oral anticoagulants in the treatment of left ventricular thrombi: a tertiary center experience and review of the literature. *Clin Case Rep* 2019;7:135–142.
8. Maniwa N, Fujino M, Nakai M, Nishimura K, Miyamoto Y, Kataoka Y, Asaumi Y, Tahara Y, Nakanishi M, Anzai T, Kusano K, Akasaka T, Goto Y, Noguchi T, Yasuda S. Anticoagulation combined with antiplatelet therapy in patients with left ventricular thrombus after first myocardial infarction. *European Heart J* 2018;39:201–208.
9. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients

with atrial fibrillation: a meta−analysis of randomised trials. *Lancet* 2014;383:955–962.
10. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–1151.
11. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–891.
12. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–992.
13. Fleddermann A, Eckert R, Muskala P, Hayes C, Magalski A, Main M. Efficacy of direct acting oral anticoagulant drugs in the treatment of left atrial appendage thrombus in patients with atrial fibrillation. *Am J Cardiol* 2019;123:57–62.