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Efficacy and safety of direct oral anticoagulants versus vitamin K antagonists for left ventricular thrombus: an updated systematic review and meta-analysis

Aim	To perform a systematic review and meta-analysis of efficacy and safety of direct oral anticoagulants (DOAC) as compared to vitamin K antagonists (VKA) in the treatment of left ventricular (LV) thrombosis.
Material and Methods	A search was performed in PubMed and Google Scholar for studies that compared DOAC and VKA in the treatment of LV thrombosis with respect of thromboembolic events, hemorrhagic complications, and thrombus resolution. The effect was evaluated with the odds ratio (OR) that was computed using a fixed effects model.
Results	For these systematic review and meta-analysis, 19 studies were selected, including 2 randomized and 17 cohort studies. The articles included into these systematic review and meta-analysis, were published from 2018 through 2021. In total, 2970 patients (mean age, 58.8 лет; 1879 (61.2%) men) with LV thrombus were included into the meta-analysis. Mean follow-up duration was 17.9 months. The meta-analysis showed no significant difference between DOAC and VKA in the incidence of the study outcomes: thromboembolic events (OR, 0.86; 95% CI: 0.67–1.10; p=0.22), hemorrhagic complications (OR, 0.77; 95% CI: 0.55–1.07; p=0.12), thrombus resolution (OR, 0.96; 95% CI: 0.76–1.22; p=0.77). In a subgroup analysis, rivaroxaban compared to VKA significantly (79%) reduced the risk of thromboembolic complications (OR, 0.21; 95% CI: 0.05–0.83; p=0.03) with no significant differences in hemorrhagic events (OR, 0.60; 95% CI: 0.21–1.71; p=0.34) or thrombus resolution (OR, 1.44; 95% CI: 0.83–1.31; p=0.20). The apixaban treatment group had significantly more (4.88 times) cases of thrombus resolution than the VKA treatment group (OR, 4.88; 95% CI: 1.37–17.30; p=0.01); for apixaban, data on hemorrhagic and thromboembolic complications were not available.
Conclusions	The therapeutic efficacy and side effects of the DOAC treatment for LV thrombosis were similar to those of VKA with respect of thromboembolic events, hemorrhage, and thrombus resolution.

Keywords	Vitamin K antagonist; direct oral anticoagulants; left ventricular thrombosis; thromboembolism; hemorrhage; thrombus resolution
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Introduction

Left ventricular thrombosis (LVT), a severe complication most commonly developing in reduced left ventricular (LV) systolic function, occurs in 15% of patients with a history of myocardial infarction (MI) [1]. The incidence of LVT decreased significantly in patients with MI with an era of reperfusion and antithrombotic therapy [2, 3]. Several sources claim that 5%patients with ST segment elevation MI (STEMI) and 9% of patients with anterior STEMI were diagnosed with LVT [3–5]. The 2013 ACC/AHA Guideline for the Management of STEMI recommend using vitamin K antagonists (VKAs) in addition to dual antiplatelet therapy in patients with post-STEMI asymptomatic LVT for at least 3 months [6]. Direct oral anticoagulants (DOACs) have a more favorable safety profile, quicker onset of effect, more reliable therapeutic effect without the need for regular monitoring of the international normalized ratio (INR), and less drug interactions than VKAs [7]. The outcomes of using DOACs in LVT are very limited, which is why the administration of DOACs in LVT is still widely under debate. Many observational showed that DOACs and VKAs have comparable safety and efficacy in LVT [8–10]. However, most of them were single-center studies with small samples and few events. A recent large cohort study identified a higher risk of stroke or systemic embolism during the use of DOACs, and some authors questioned their use in LVT [11].

Objectives of the analysis

The objective of a systematic review and meta-analysis was to compare the safety and efficacy of DOACs and VKAs in the management of LVT

Material and methods

Search for papers and selection of studies

The information search algorithm was developed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [12, 13]. The protocol was prospectively registered in PROSPERO (registration number CRD42022324075).

Literature searches were performed in the PubMed and Google Scholar databases. The following keywords were used to search in PubMed: ((left ventricular thrombus) OR (LV thrombus)) AND ((treatment)) AND ((warfarin) OR (vitamin K antagonist)) AND ((direct oral anticoagulant)). References were also hand searched in several reviews, meta-analyses, and consensus statements. The following queries were used for the search in Google Scholar: left ventricular thrombus, intraventricular thrombus, direct oral anticoagulant, DOAC, NOAC, vitamin K antagonist. Eligible studies for this systematic review and meta-analysis were selected by two authors who examined independently whether abstracts and full-text reports met inclusion and exclusion criteria. The latest search for data to be included in this analysis was performed on April 9, 2022.

Inclusion/exclusion criteria

The criteria for the inclusion of studies in the systematic review with the subsequent meta-analysis were the following: studies comparing DOACs and VKAs in the management of LVT, known outcomes of interest in each group (frequency of thrombus resolution, thromboembolic and hemorrhagic complications). The meta-analysis included randomized and cohort clinical studies. The systematic review included abstracts, as well as full-text articles, if they contained the necessary information on the number of outcomes in each group. The study follow-up periods lasted for at least 3 months. The meta-analysis did not include articles written in languages other than English, case reports, nonclinical studies, reviews, and expert opinions.

Assessment of methodological quality

Risk of bias for randomized clinical trials was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2) [14]. The quality of cohort studies was assessed by the Newcastle-Ottawa scale [15]. The studies were judged using three key criteria: the selection of study groups, the comparability of groups, and the identification of an outcome of interest. All discrepancies were resolved by the discussion between the authors.

Statistical analysis

All statistical analyses were performed in RevMan 5 [16]. The main results are presented as a forest plot. Statistical heterogeneity was assessed using the Pearson's chi-square test and heterogeneity index I2. Statistical heterogeneity was interpreted using the I2 index according to the Cochrane Handbook: insignificant heterogeneity I2=0–40%; moderate heterogeneity I2=30–60%; significant heterogeneity I2=50–90%; high heterogeneity I2=75–100%. The p-value determined using the χ^2 test was also used to assess statistical heterogeneity with $p<0.1$ corresponding to statistically significant heterogeneity and $p\geq0.1$ corresponding to the absence of significant statistical heterogeneity. The intensity of the effect was assessed using an odds ratio (OR) and a 95% confidence interval (CI). The difference was considered statistically significant with the p-value was less than 0.05. A fixed-effect model was used to calculate OR in order to evaluate the effect. Possible bias associated with the publication of mainly positive study outcomes was analyzed by visually assessing a funnel plot.

Results

Results of literature search

A total of 248 papers were found using keyword searches in PubMed and Google Scholar. When duplicates were excluded, the number of papers decreased to 241. After analyzing the headlines and abstracts, 40 eligible papers were left. The most frequent reasons for excluding articles were inconsistency with the object and the lack of data of the number of outcomes of interest in the study groups; reviews, discussions, and opinions were also excluded. Thus, 19 studies were finally selected for our review. The process of selecting relevant studies is shown in Chart 1 (see supplementary materials on the journal's website).

General characteristics of the studies

The total number of patients with left ventricular thrombosis included in our meta-analysis was 2,970, of whom 1,879 were male (74.3%). The selected articles were published from 2018 to 2021. The mean age of patients was 58.8 years, the mean duration of the follow-up period was 17.9 months. Study design, endpoints, and baseline patient characteristics are summarized in Table 1 and Table 2.

Risk of bias in the included studies

Funnel plots for thromboembolic events, bleeding, and thrombus resolutions showed no evidence of publication bias (see Figure 1 in supplementary materials on the journal's website).

Thromboembolic events

Data on thromboembolic events were found in 17 studies. There was a total 10 (14.7% of 720 patients) and 410 (20.6% of 1994 patients) thromboembolic events in the DOAC group

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and the VKA group, respectively. In the pooled analysis showed no statistically significant difference in the development of thromboembolic events in the DOAC group compared to the VKA group (OR 0.86; 95% CI: 0.67–1.10; p=0.22). The heterogeneity test was not significant, p=0.29, I2=14% (Figure 2A).

Hemorrhagic complications

Data on hemorrhagic events were available in 16 studies. There was a total 50 (7.1% of 703 patients) and 173 (8.9% of 1,952 patients) cases of major bleeding in the DOAC group and the VKA group, respectively. The meta-analysis showed that the incidence of hemorrhagic events decreased in the DOAC group, but the differences were not statistically significant (OR 0.77; 95% CI: 0.55–1.07; p=0.12). The heterogeneity test was not significant, p=0.39, I2=6% (Figure 2B).

LV thrombus resolution

Echocardiographic data on LV thrombus resolution during DOAC treatment compared to warfarin were available in 18 studies. There were 389 (70.0% of 556 patients) and 877 (70.3% of 1,248 patients) patients with thrombus resolution in the DOAC group and the VKA group, respectively. A meta-analysis showed that the comparison of the DOAC group and the VKA group did not reveal a statistically significant difference in the frequency of LV thrombus resolution (OR 0.96; 95% CI: 0.76–1.22; p=0.77). The heterogeneity test was not significant, p=0.69, I2=0% (Figure 2C).

Discussion

Our comparison of two anticoagulant regimens (various DOACs and VKAs for the treatment of LVT) did not identify any statistically significant differences in achieving efficacy and safety endpoints, such as thromboembolic events, bleeding, and thrombus resolution. Our findings support the possibility of using DOACs in this cohort of patients. DOACs are superior to VKAs and have long been receiving the attention of researchers from around the world, they were shown to be effective and safe comparable to VKAs in various diseases requiring anticoagulant treatment. The number of papers on DOACs, including their use for LVT, has increased dramatically in recent years. We analyzed 19 studies including 2,970 patients, which was more than in previous published meta-analyses. Several large meta-analyses on this topic have been published over the past two years. One of the most recent large meta-analyses [32], which included 18 studies (a total of 2,666 patients) also showed no statistically significant differences in the incidence of bleeding, thromboembolism, and thrombus resolution. Interestingly, the use of DOACs, unlike VKAs, was associated with a statistically significant decrease in stroke incidence in this study [32]. However, the results obtained should be interpreted within the limitations of the included studies: only 2 of 18 studies were randomized, the others were cohort studies, that is, they were more susceptible to the effects of confounders and selection bias. Further randomized clinical trials are necessary to draw more substantiated conclusions and increase the level of evidence of recommendations for the use of DOACs in LVT, which is associated with several problems in the study cohort of patients, such as a small number of patients, the inability to perform a blind study due to the need to control INR during the warfarin treatment, difficulties in conducting randomization, and the effect on the outcomes of the concomitant use of antiplatelet drugs.

We conducted a subgroup analysis depending on the type of DOACs. The necessary data could not be extracted from all included studies, but we obtained interesting results that could give ground to studies comparing each DOAC separately, similar to the studies of the administration of DOACs in patients with atrial fibrillation (PIONEER AF-PCI, REDUAL-PCI, RE-LY, AUGUSTUS). For example, rivaroxaban statistically significantly (4.8-fold, compared to VKAs) reduced the risk of thromboembolic events; there were no differences in the frequency of bleeding and thrombus resolution. Only LV thrombus resolution data were available for apixaban in three studies. Thus, there were statistically significantly more (4.88 times) cases of thrombus resolution in the apixaban group than in the VKA group.

Limitations

First, the duration of follow-up varied significantly across studies in our meta-analysis, which could have affected the findings. Second, all but two of the studies in this meta-analysis were non-randomized and subject to bias. Third, the definition of major bleeding differed in the included studies, because different bleeding criteria were used, such as BARC, GUSTO, and TIMI. Fourth, we did not study the relationship between INR in the therapeutic range and the efficacy and safety of VKAs, which could also affect the results. And finally, many patients took antiplatelet drugs, which certainly increased the risk of bleeding and affected outcomes.

Conclusions

The therapeutic efficacy and side effects of direct oral anticoagulants in patients with left ventricular thrombosis were similar to those of vitamin K antagonists for thromboembolic events, bleeding, and thrombus resolution. Direct oral anticoagulants may be a worthy alternative to vitamin K antagonists in the treatment of LVT.

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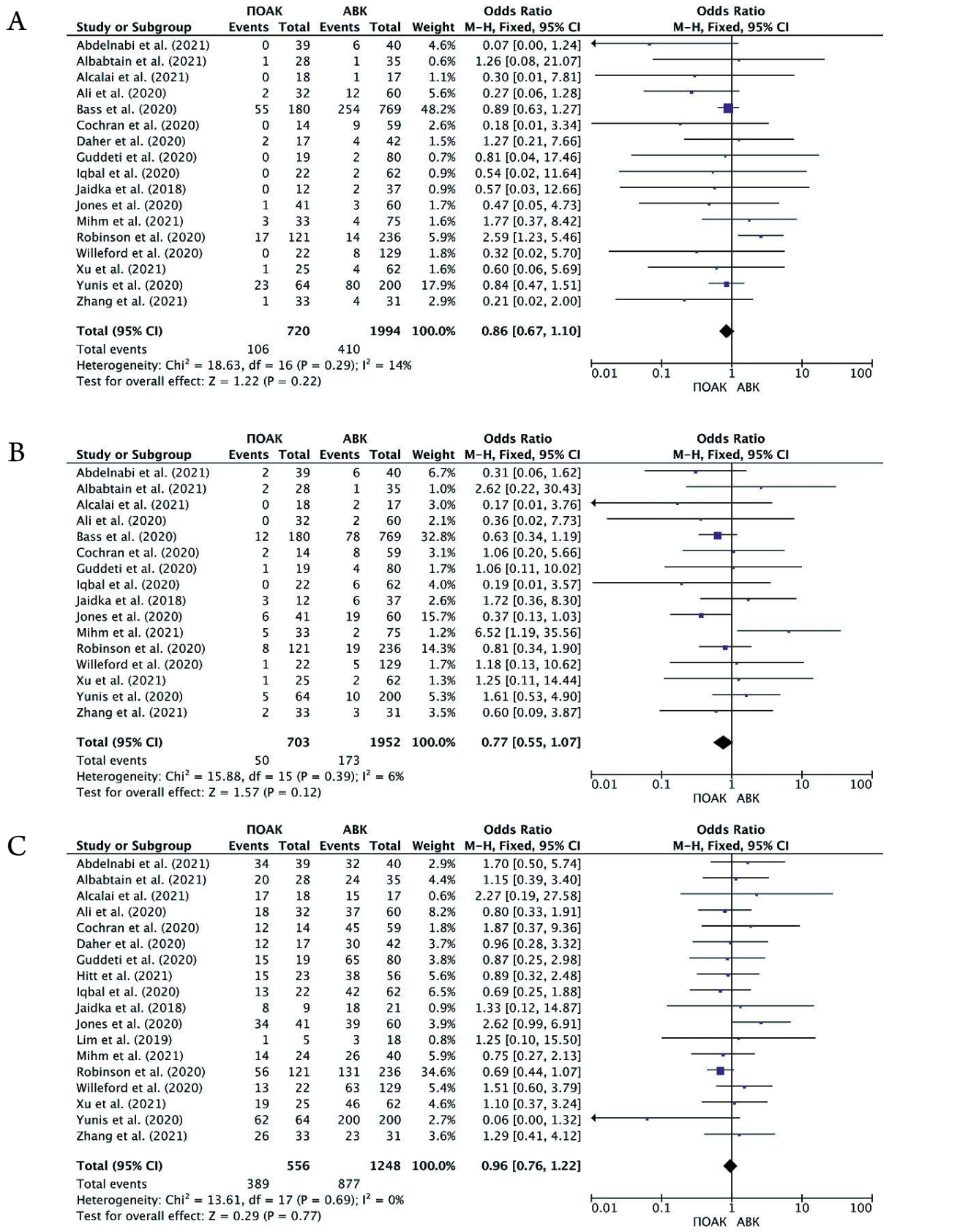
Fugure 2. Forest plot of odds ratio (logarithmic scale) for (A) thromboembolic risks, (B) hemorrhagic complications and (C) thrombus resolution during DOAC therapy compared to VKAs



The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95 % CI.
The solid vertical line is the OR equal to 1. DOAC, direct oral anticoagulant;
VKA, vitamin K antagonist; OR, odds ratio; CI, confidence interval.

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Table 1. General characteristics of studies included in the systematic review

Title (first author), year	Patients, n	Study design	VKA group, n (%)	DOAC group, n (%)	DOAC type, strength, n (%)	Endpoints	Follow-up period, months
Abdelnabi et al. (2021) [17]	79	Randomized	40 (50.6)	39 (49.4)	Rivaroxaban 20 mg/day, 100 %	Thrombus resolution, thromboembolism, major bleeding	6
Albabtain et al. (2021) [18]	63	Retrospective cohort study	35 (55.6)	28 (44.4)	Rivaroxaban 20 mg/day, 100 %	Thrombus resolution, thromboembolism, major bleeding, mortality	Rivaroxaban 9.5 [6–32.5], warfarin 14 [3–41]
Alcalai et al. (2021) [19]	35	Randomized	17 (48.6)	18 (51.4)	Apixaban 10 mg/day, 100 %	Thrombus resolution, thromboembolism, major bleeding, repeat hospitalization, mortality	3 [2.8–3.1]
Ali et al. (2020) [20]	92	Retrospective cohort study	60 (65.2)	32 (34.8)	Rivaroxaban 18 (56.3 %), apixaban 13 (40.6 %), dabigatran 1 (3.1 %)	Thrombus resolution, thromboembolism, major bleeding, mortality	12
Bass et al. (2020) [21]	949	Retrospective cohort study	769 (81)	180 (19)	Rivaroxaban 77 (42.8 %), apixaban 79 (43.9 %), dabigatran 29 (16.1 %)	Thromboembolism, major bleeding	3
Cochran et al. (2020) [8]	73	Retrospective cohort study	59 (80.8)	14 (19.2)	Rivaroxaban, apixaban, dabigatran, edoxaban	Thrombus resolution, stroke, acute coronary syndrome (ACS), all-cause death, bleeding	12
Daher et al. (2020)* [22]	59	Retrospective cohort study	42 (71.2)	17 (28.8)	Rivaroxaban 15–20 mg/day 4 (23.5 %), apixaban 5 10 mg/day 12 (70.6 %), dabigatran 220–300 mg/day 1 (5.9 %)	Thrombus resolution, thromboembolism	3
Guddeti et al. (2020) [9]	99	Retrospective cohort study	80 (81)	19 (19)	Rivaroxaban 2 (10.5 %), apixaban 15 (78.9 %), dabigatran 2 (10.5 %)	Thrombus resolution, thromboembolism, major bleeding	Median 12, mean 10.4 ± 3.4
Hitt et al. (2021) [23]	76	Retrospective cohort study	56 (73.7)	23 (30.3)	n/a	Thrombus resolution	4.9 [0.3–22.7]
Iqbal et al. (2020) [10]	84	Retrospective cohort study	62 (73.9)	22 (26.2)	Rivaroxaban 20 mg/day 13 (59.1 %), apixaban 10 mg/day. 8 (36.4 %), dabigatran 300 mg/day 1 (4.5 %)	Thrombus resolution, thromboembolism, major bleeding, repeat hospitalization, mortality	36 ± 16.8
Jaidka et al. (2018) [24]	49	Retrospective cohort study	37 (75.5)	12 (24.5)	n/a	Thrombus resolution, thromboembolism, major bleeding	6
Jones et al. (2020) [25]	101	Prospective cohort study	60 (59.4)	41 (40.6)	Rivaroxaban 15–20 mg/day 59 (58.5 %), apixaban 5–10 mg/day 37 (36.5 %), edoxaban 30–60 mg/day 5 (5.5 %)	Thrombus resolution, thromboembolism, major bleeding, mortality	26.4
Lim et al. (2019) [26]	23	Retrospective cohort study	18 (78.3 %)	5 (21.7)	Rivaroxaban 2 (8.7 %), dabigatran 3 (13.0 %)	Thrombus resolution	24
Mihm et al. (2021) [27]	108	Retrospective cohort study	75 (69.4)	33 (30.6)	Rivaroxaban 10 (56.3 %), apixaban 23 (40.6 %)	Thrombus resolution, thromboembolism, major bleeding, mortality	6
Robinson et al. (2020) [11]	514	Retrospective cohort study	300 (58.4)**	185 (36.0)**	Rivaroxaban 46 (24.9 %), apixaban 141 (76.2 %), dabigatran 9 (4.9 %)	Thrombus resolution, thromboembolism, major bleeding,	11.7 [1.7–28.9]
Willeford et al. (2020) [28]	151	Retro spective cohort study	129 (85.4)	22 (14.6)	Rivaroxaban 18 (81.8 %) (17–15 mg/day, 1–20 mg/day), apixaban 4 (18.2 %) (1 to 5 mg/day, 3 to 10 mg/day)	Thrombus resolution, thromboembolism, major bleeding	8.5 [3.3–11.4]

Table 1 (continuation). General characteristics of studies included in the systematic review

Title (first author), year	Patients, n	Study design	VKA group, n (%)	DOAC group, n (%)	DOAC type, strength, n (%)	Endpoints	Follow-up period, months
Xu et al. (2021) [29]	87	Retrospective cohort study	62 (71.3)	25 (28.7)	Rivaroxaban 46 (24.9 %) (10–20 mg/day), dabigatran 9 (4.9 %) (220–300 mg/day)	Thrombus resolution, thromboembolism, major bleeding, repeat hospitalization, mortality	28.44 ± 25.2
Yunis et al. (2020) [30]	264	Retrospective cohort study	200 (75.8)	64 (24.2)	n/a	Thrombus resolution, thromboembolism, major bleeding	24
Zhang et al. (2021) [31]	64	Retrospective cohort study	31 (48.4)	33 (51.6)	Rivaroxaban 33 (100 %)	Thrombus resolution, thromboembolism, major bleeding	25

* Further analysis included 64 of 108 patients who underwent echocardiographic examination in 6 months.
** These groups also included a mixed cohort of 64 patients, in which anticoagulant therapy was changed.
Thus, the final analysis included 236 patients in the warfarin group and 121 patients in the DOAC group.
VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; n/a, not available.

Table 2. General characteristics of patients included in the systematic review

Title (first author), year	Age, years	Male, n (%)	AH, n (%)	DM, n (%)	AF, n (%)	History of MI, n (%)	Mean LVEF, %	Antiplatelet therapy
Abdelnabi et al. (2021) [17]	49.6±12.5	57 (72.2)	42 (53.1)	42 (53.1)	n/a	n/a	36.6	DAPT 42 (53.1)
Albabtain et al. (2021) [18]	58.6±16.7	58 (92.1)	32 (58)	16 (25.4)	3 (4.8)	41 (65.1)	26.86±7.9	Aspirin 39 (61.9), clopidogrel 33 (52.4)
Alcalai et al. (2021) [19]	57.15±11.55	28 (80)	14 (40)	n/a	n/a	n/a	35.5±6	DAPT 35 (100), in 1 month, monotherapy with clopidogrel 35 (100)
Ali et al. (2020) [20]	59±14	75 (81.5)	n/a	27 (29.3)	27 (29.3)	n/a	23.1±10.3	Aspirin 60 (65.4), clopidogrel 13 (14.55), ticagrelor 1 (0.91), prasugrel 2(1.82)
Bass et al. (2020) [21]	62.5±16	670 (70.6)	n/a	n/a	463 (48.8)	520 (54.8)	n/a	Antiplatelet drugs 512 (54.0)
Cochran et al. (2020) [8]	56.75 (36.5–78.5)	56 (89)	n/a	30 (41.1)	n/a	43 (58.9)	n/a	NR
Daher et al. (2020) [22]	62±14	49 (83.1)	27 (45.7)	11 (18.6)	н/д	н/д	37±11	Aspirin 38 (64.4), clopidogrel/tocagrelor/ prasugrel 28 (47.5)
Guddeti et al. (2020) [9]	61±12.3	70 (71)	76 (76.8)	37 (37.4)	n/a	54 (54.5)	25	Aspirin 65 (65.7), clopidogrel 15 (15.2), DAPT 13 (13.1)
Hitt et al. (2021) [23]	n/a	n/a	n/a	n/a	n/a	n/a	36.5	n/a
Iqbal et al. (2020) [10]	62±14	75 (89)	27 (32)	22 (26)	6 (7)	n/a	n/a	Aspirin 48 (57.1), clopidogrel 33 (39.3), ticagrelor 6 (7.1), DAPT 32(38)
Jaidka et al. (2018) [24]	59.25±10.7	37 (75.5)	20 (40.8)	8 (16.3)	n/a	3 (6.1)	28.35±15.4	Aspirin 42 (85.7), clopidogrel 45 (91.8), ticagrelor 3 (6.1)
Jones et al. (2020) [25]	59.61±14.08	n/a	45 (44.6)	17 (16.8)	n/a	16 (15.8)	34.48±15.0	DAPT 70 (69.3), antiplatelet monotherapy 23 (22.8)
Lim et al. (2019) [26]	55±9.6	17 (73.9)	13 (56.5)	12 (52.2)	n/a	n/a	30.8±10.6	n/a
Mihm et al. (2021) [27]	61.8±14.15	77 (71.3)	80 (74.1)	28 (25.9)	28 (25.9)	n/a	25.7±14.5	Aspirin 74 (68.6), clopidogrel 26 (24.1)
Robinson et al. (2020) [5]	58.4±14.8	376 (73.2)	263 (51.2)	128 (24.9)	75 (14.6)	n/a	27.95±13.1	Antiplatelet drugs 241 (46.9)

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Table 2 (continuation). General characteristics of patients included in the systematic review

Title (first author), year	Age, years	Male, n (%)	AH, n (%)	DM, n (%)	AF, n (%)	History of MI, n (%)	Mean LVEF, %	Antiplatelet therapy
Willeford et al. (2020) [28]	56 (49–65)	121 (80.1)	62 (41.1)	41 (27.2)	27 (17.9)	39 (25.8)	n/a	Aspirin 75 (49.7), clopidogrel 39 (25.8)
Xu et al. (2021) [29]	61.5±12.7	66 (75.9)	37 (42.5)	18 (20.7)	70 (80.5)	17 (19.5)	36.2±6.5	Aspirin 38 (43.7)
Yunis et al. (2020) [30]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Zhang et al. (2021) [31]	60.8±11.85	47 (73.4)	34 (53.1)	15 (23.4)	н/д	н/д	42.15±11.95	DAPT 64 (100)

AH, arterial hypertension; DAPT, double antiplatelet therapy;
DM, diabetes mellitus, MI, myocardial infarction, LVEF, left ventricular ejection fraction; n/a, not available.

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