Direct Oral Anticoagulants versus Vitamin K Antagonists for Patients with Left Ventricular Thrombus: A Systematic Review and Meta-Analysis

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Direct Oral Anticoagulants versus Vitamin K Antagonists for Patients with Left Ventricular Thrombus: A Systematic Review and Meta-Analysis

Short title: DOACs vs VKAs for Left Ventricular Thrombus treatment

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Conflicts of interest: none declared.
What’s new?

For patients with left ventricular thrombus (LVT), direct oral anticoagulants (DOACs) showed similar efficacy for the prevention of strokes or systemic embolism, thrombus resolution and the risk of any bleedings, as compared with vitamin K antagonists (VKAs).

For LVT treatments, DOAC users acquired lower risk of strokes and clinically relevant bleedings than VKA users.

DOACs are safe and effective alternatives of VKAs and could be considered as primary oral anticoagulants for LVT patients.
Abstract

Introduction: Although vitamin K antagonists (VKAs) are recommended as first-line anticoagulants for patients with left ventricular thrombus (LVT), accumulating evidence suggests direct oral anticoagulants (DOACs) could be safe alternatives for VKAs. Efficacy and safety of DOACs should be assessed to justify their usage for LVT patients.

Objectives: To compare the efficacy and safety of DOACs and VKAs for the treatment of LVT.

Patients and methods: We performed a meta-analysis of observational studies to compare DOACs to VKAs in LVT patients. The PubMed and EMBASE databases were searched for articles published until November 12, 2020. Pooled effects were estimated using Mantel–Haenszel method and presented as risk ratios (RR) using fixed-effect model. Reporting followed the Meta-analyses of observational studies in epidemiology (MOOSE) guideline.

Results: A total of 2467 LVT patients from 13 studies were included. Compared with VKAs, DOACs showed similar efficacy in prevention of stroke or systemic embolism (RR: 0.96, 95% confidence interval [CI]: 0.80-1.16, \( P = 0.68 \)) and thrombus resolution (RR: 0.88, 95% CI: 0.72-1.09, \( P = 0.26 \)), but significantly lower risk of stroke (RR: 0.68, 95% CI: 0.47-1.00, \( P = 0.048 \)). For safety outcomes, DOAC users showed similar risk of any bleedings (RR: 0.94, 95% CI: 0.67-1.31, \( P = 0.70 \)), but lower risk of clinically relevant bleedings (RR: 0.35, 95% CI: 0.13-0.92, \( P = 0.03 \)) compared with VKA users.

Conclusions: Compared with VKAs, DOACs acquired similar efficacy and safety profile for patients with LVT, but could reduce the risk of strokes and clinically relevant bleedings.

Key words: left ventricular thrombus, direct oral anticoagulants, vitamin K antagonists
Introduction

Left ventricular thrombus (LVT) is a rare complication associated with acute myocardial infarction, heart failure, and various cardiomyopathies [1, 2]. Owing to the increased risk of embolic events, oral anticoagulation therapy is required to prevent stroke or systemic embolism (SSE). Current guidelines, which are based on limited evidence from observational studies, recommend vitamin K antagonists (VKAs) for patients with LVT [1-4]. However, off-label use of direct oral anticoagulants (DOACs) for the management of LVT is gaining interest because they provide consistent anticoagulant effects, and do not require continuous monitoring of international normalized ratio (INR) [1, 5-9]. Numerous trials and analyses have already shown that compared with VKAs, DOACs exhibit similar efficacy in SSE prevention and lower bleeding risk in other clinical conditions (e.g., atrial fibrillation and heart failure) [10-12]. Additionally, there have been successful cases that have achieved complete LVT resolution and long-term favorable outcomes using DOACs [13, 14]. However, affirmative evidence for the use of DOACs in patients with LVT is still lacking. Therefore, this study aimed to summarize the evidence from latest clinical studies, while comparing the efficacy and safety of DOACs and VKAs in patients with LVT, in order to offer novel insights for clinical practice and randomized clinical trials (RCTs) on anticoagulation therapy for LVT in the future.

Patient and methods

Strategies for literature search

We performed a comprehensive literature search in the Pubmed and EMBASE databases using the following search terms: “ventricular thrombi” or “ventricular thrombus,” and “direct oral anticoagulants” or “novel oral anticoagulants” or “dabigatran” or “rivaroxaban” or “apixaban” or “edoxaban” and “vitamin K antagonists” or “warfarin” or “dicoumarol” or “phenindione” or
“phenprocoumon” or “acenocoumarol” or “ethyl biscoumacetate” or “fluindione” or “clorindione” or “diphenadione” or “tioclomarol.” The literature search and data extraction process were completed by two researchers, independently (R. Chen and J. Zhou). The final search was conducted on November 12, 2020.

Study selection

Eligible studies were selected based on the following inclusion criteria: (a) diagnosis of LVT was determined using appropriate cardiac imaging techniques (e.g., transthoracic/transesophageal echocardiography, cardiovascular magnetic resonance imaging); (b) an RCT or observational study; and (c) comparing the outcomes of patients using DOACs vs VKAs. Both studies published as full-text and abstract were included in the current meta-analysis. Studies regarding LVT secondary to the implantation of a ventricular assist device, case reports, case series, unpublished studies, and studies not published in English were excluded from the current review. In case of missing data, the authors of the original studies were contacted. The studies in which the data on the specific outcome was unclear, not provided, or could not be acquired after contacting the original authors were excluded from the pooled analysis for that outcome.

Ethics

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

Data extraction and quality assessment

The following data were extracted from the studies that were included: surname of the first author, geographic location, study design, mean/median age or range of age, proportion of male sex, the number of DOAC and VKA users, the number of outcomes, follow-up duration, primary causes of
LVT, and concomitant antiplatelet medications. Outcomes of interest included SSE, stroke, failure of thrombus resolution, any bleeding event, and clinically relevant bleeding event (i.e., life-threatening bleeding and bleeding requiring hospitalization or medical interventions). The quality of the included studies was assessed by two independent authors (R. Chen and L. Song) using the Newcastle-Ottawa Scale (NOS). If there were any discrepancies regarding data extraction and quality evaluation, a third author (J. Zhou) was consulted to reach a consensus. Reporting was done in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines.

**Statistical analyses**

RevMan 5.3 (The Cochrane Collaboration, Oxford, England) and Stata 15.0 (StataCorp, College Station, TX, USA) were used to perform this study. Pooled effects were estimated using the Mantel–Haenszel method and presented as risk ratios (RR) with 95% confidence interval (CI). Heterogeneity across studies was examined using $I^2$ statistics and the chi-square-based Cochran Q test. An $I^2 > 50\%$ or $P$-value < 0.1 for Cochran Q test showed significant heterogeneity. A fixed-effect model was applied if no significant heterogeneity was observed; otherwise, a random-effect model was used. Funnel plots were used to detect potential publication bias. Begg’s rank correlation and Egger’s linear regression tests were performed when an outcome analysis included 10 or more studies. The trim-and-fill method was used to impute the missing studies and correct publication bias, with the `metatrim` command in Stata [15]. The random-effect meta-regression analyses were performed to determine whether age had an impact on various outcomes using the `metareg` command in Stata, with the between-study variance (tau-squared) estimated by the residual maximum likelihood. A $P$-value < 0.05 was considered statistically significant.
Results

Characteristics and quality assessment of the included studies

In the initial literature search, 216 relevant records were identified after removing duplicates (Figure 1). After screening the titles and abstracts, 126 articles were excluded because of irrelevance. Among the 90 eligible articles, 77 studies were further eliminated due to publication type or study design. Finally, thirteen articles were included in the synthetic analysis, two of which were prospective studies[5-9, 16-23].

The average NOS score was 6.2 (Supplementary material, Table S1), which showed that the included studies were of median quality. A total of 2,467 patients with LVT were included. The patients’ mean age ranged from 51.5 to 63.5 years, and the proportion of male patients was over 70 %. The most common cause of LVT was ischemic heart disease. The follow-up duration ranged from 3 months to 3 years. Among DOAC users, apixaban (50.0 %) was most frequently prescribed, followed by rivaroxaban (40.8 %), dabigatran (8.8 %), and edoxaban (0.4 %), whereas warfarin (98.5 %) was predominantly prescribed to VKA users. Concomitant antiplatelet medication was prescribed in over half of the patients, although double antiplatelet treatment was less frequently used.

Clinical outcomes

Stroke and embolic events

Ten studies have shown reports on the occurrence of SSE [5-9, 19-23]. Users of DOACs and VKAs did not show a significant difference in the risk of SSE (RR: 0.96, 95 % CI: 0.80–1.16, \( P = 0.68 \); \( I^2 = 0 \) %, Figure 2). Potential publication bias was detected in the funnel plot (Supplementary material, Figure S1) and the Egger’s test \( (P = 0.029) \), but not by the Begg’s test \( (P = 0.42) \). After using the
trim-and-fill method, the pooled effect remained the same (RR: 0.96, 95 % CI: 0.80–1.16, \( P = 0.68 \)), as no additional studies were imputed (Supplementary material, *Figure S2*). Notably, Robinson et al. reported treatment switches between DOACs and warfarin in 15.2 % of patients (Supplementary material, *Table S2*). The exclusion of this study led to similar results: DOACs exhibited equivalent efficacy in SSE prevention as VKAs (RR: 0.95, 95 % CI: 0.78–1.15, \( P = 0.59 \); \( I^2 = 0 \)). Meta-regression against age did not show a significant impact on the efficacy of DOACs and VKAs (RR: 1.06, 95 % CI: 0.96–1.17, \( P = 0.23 \), Supplementary material, *Figure S3*). Subgroup analysis by follow-up duration (\( P_{\text{interaction}} = 0.07 \)), sample size (\( P_{\text{interaction}} = 0.09 \)), concomitant antiplatelet medication (\( P_{\text{interaction}} = 0.48 \)), primary causes of LVT (\( P_{\text{interaction}} = 0.09 \)), and major types of DOACs being used (\( P_{\text{interaction}} = 0.63 \)) showed consistently similar effects of DOACs and VKAs (Table 2).

Eight studies have reported the outcome of stroke [5, 7, 9, 19-23]. DOAC users showed a lower risk of stroke compared with VKA users (RR: 0.68, 95 % CI: 0.47–1.00, \( P = 0.048 \); \( I^2 = 0 \ %, \) Figure 3). Funnel plots showed no evidence of publication bias (Supplementary material, *Figure S1*). Meta-regression did not show significant impacts of age (RR: 1.01, 95 % CI: 0.82–1.24, \( P = 0.90 \), Supplementary material, *Figure S3*). Subgroup analysis (Table 2) showed consistent results in terms of follow-up duration (\( P_{\text{interaction}} = 0.79 \)), sample size (\( P_{\text{interaction}} = 0.49 \)), concomitant use of antiplatelet agents (\( P_{\text{interaction}} = 0.88 \)), primary etiologies of LVT (\( P_{\text{interaction}} = 0.76 \)), and types of DOACs (\( P_{\text{interaction}} = 0.91 \)).

**Thrombus resolution**

Eleven studies have investigated the outcome of failure in thrombus resolution [5-7, 9, 16-19, 21-23], and the resolution rate was similar between the two groups (RR: 0.88, 95 % CI: 0.72–1.09, \( P = 0.26 \), Figure 4); analysis showed low statistical heterogeneity (\( I^2 = 26 \ %, \) \( P = 0.20 \)) and no significant
publication bias based on the results of the funnel plot (Supplementary material, *Figure S1*) and statistical tests (Begg’s test, $P = 0.48$; Egger’s test, $P = 0.19$). Age did not have substantial impact on thrombus resolution according to the results of meta-regression (RR: 1.08, 95 % CI: 0.95–1.22, $P = 0.22$, Supplementary material, *Figure S3*). The efficacy of thrombus resolution was consistent regardless of variations in follow-up duration ($P_{\text{interaction}} = 0.94$), sample size ($P_{\text{interaction}} = 0.26$), antiplatelet medication ($P_{\text{interaction}} = 0.43$), and types of DOACs ($P_{\text{interaction}} = 0.67$) in the subgroup analysis (Table 2). However, significant interactions were observed in terms of primary causes of LVT (myocardial infarction [MI], RR: 0.57, 95 % CI: 0.38–0.84, $I^2 = 0 \%$, $P = 0.005$; mixed etiologies, RR: 1.09, 95 % CI: 0.85–1.41, $I^2 = 0 \%$, $P = 0.47$; $P_{\text{interaction}} = 0.006$)

*Bleeding events*

Nine studies have shown reports on bleeding events [5, 7, 9, 16, 19-23]. The risk of any bleeding event was similar for DOAC and VKA users (RR: 0.94, 95 % CI: 0.67–1.31, $P = 0.70$; $I^2 = 24\%$, Figure 5), without significant publication bias, as shown in the funnel plot (Supplementary material, *Figure S1*). Meta-regression showed that age did not affect the safety of DOACs or VKAs (RR: 1.03, 95 % CI: 0.81–1.31, $P = 0.76$, Supplementary material, *Figure S3*). Subgroup analysis (Table 2) showed that bleeding risk was similar, regardless of variations in sample size ($P_{\text{interaction}} = 0.21$), etiologies ($P_{\text{interaction}} = 0.14$), and types of DOACs ($P_{\text{interaction}} = 0.91$). However, significant interactions were observed in terms of follow-up duration ($P_{\text{interaction}} = 0.02$) and antiplatelet medications ($P_{\text{interaction}} = 0.006$).

In six studies reporting on clinically relevant bleeding events [5, 7, 9, 16, 22, 23], favorable outcomes were seen in DOAC users (RR: 0.35, 95 % CI: 0.13–0.92, $P = 0.03$; $I^2 = 0$, Figure 6), and no significant publication bias was detected using the funnel plot (Supplementary material, *Figure*
Age did not affect the difference in risk of clinically relevant bleeding events between DOAC and VKA users (RR: 0.83, 95% CI: 0.41–1.69, \( P = 0.52 \), Supplementary material, Figure S3). Subgroup analysis showed no significant interactions with follow-up duration (\( P_{\text{interaction}} = 0.09 \)), sample size (\( P_{\text{interaction}} = 0.83 \)), antiplatelet medication (\( P_{\text{interaction}} = 0.20 \)), etiologies (\( P_{\text{interaction}} = 0.23 \)), and types of DOACs (\( P_{\text{interaction}} = 0.28 \)) for the risk of clinically relevant bleeding events in DOAC or VKA users (Table 2).

**Discussion**

The major findings of this systematic review and meta-analysis were as follows: (1) only observational studies have been conducted regarding anticoagulation treatment for LVT, and most of them are retrospective; (2) DOAC users showed similar risk of SSE, failure of LVT resolution, but lower risk of stroke compared to that of VKA users; and (3) DOAC users showed a similar risk of any bleeding event but lower risk of clinically relevant bleeding event as compared with that of VKA users.

**Efficacy of DOACs and VKAs**

According to the current guidelines, warfarin is still recommended as the first-line treatment for LVT, although there is no evidence from RCTs [1, 3, 4]. However, DOACs are gaining interest for LVT treatment as they help achieve consistent anticoagulant effects while reducing bleeding risks [1, 24]. Growing number of cases and clinical studies also show satisfactory outcomes in patients with LVT using DOACs [5-7, 9]. Although the current analysis showed no difference between DOACs and VKAs in terms of their efficacy in SSE prevention, as has been reported in recently published meta-analyses [21, 25], it is definitely of great clinical importance because it showed a 32% risk reduction of stroke in DOAC users. The subgroup analysis also showed a marked homogenous
reduction in the risk of stroke across various confounders. A recently published pooled analysis by Zhou et al. showed no difference in the occurrence of stroke (odds ratio: 0.79, 95 % CI: 0.50–1.23) among DOAC and VKA users [25]; however, the present study included three newly published researches [21-23], which increased the sample size and provided greater power to test the difference between the two medications. Although the interpretation of these findings could be challenging, one of the main reasons could be the fluctuation in INR. Ali et al. report that 71 % of patients with stroke receiving warfarin have exhibited suboptimal control of INR [23]. In a study by Jones et al., nearly half of warfarin users could not sustain an ideal INR for over 65 % of the time during anticoagulation treatment, of whom 75 % are below the target value, while all the thromboembolic events have occurred in these patients with sub-optimally controlled INR. Therefore, physicians should consider initiating treatment with DOACs to provide long-term and consistent anticoagulation for patients with LVT, especially when there are difficulties in monitoring or maintaining INR within an ideal range. Additionally, it should be noted that there are discrepancies among included studies regarding the effects of DOACs. Robinson et al. have reported a substantial increase in the risk of SSE in DOAC users (hazard ratio: 2.67, 95 % CI: 1.31–5.57), which is in contrast with the results of many other studies that were included [8]. However, up to 15 % of their patients switched anticoagulants during the follow-up, making it difficult to estimate the true risk difference between DOACs and warfarin. In two recent studies on the same topic, the impacts owing to this issue are less discussed [21, 25]. In this analysis, wherein we considered an intention-to-treat approach, the inclusion and exclusion of this study did not bring much variation and heterogeneity to the pooled effect, which affirmed the neutral results of the pooled analysis. To summarize, DOACs did not increase the risk
of SSE in patients with LVT, and they effectively reduced the risk of stroke as compared with VKAs, possibly because of its more consistent anticoagulation effects.

Moreover, we showed that the thrombus resolution rate was similar for DOAC and VKA users, which is consistent with the results of previous studies [21, 25]. Notably, patients with MI receiving DOACs showed significantly higher rates of thrombus resolution compared to those using VKAs. These discrepancies could be due to the increased thrombotic burden after MI. In a recent meta-analysis by Low et al., only triple therapy (double antiplatelet treatment + oral anticoagulant) is associated with higher resolution rate of LVT after MI, while the anticoagulation alone is less effective, suggesting a need for more intensive antithrombotic treatment in MI patients complicated with LVT [26]. In patients with MI, LVT is dynamically formed within a few days after the initial cardiac damage [27, 28]. Moreover, the exposure of subendothelial contents because of myocardial necrosis intensifies the prothrombotic states, which could last as long as six months [1, 29]. Therefore, it is reasonable to start effective and consistent anticoagulation therapy as soon as possible to limit the progress of thrombus formation. However, the effects of VKAs peaks in 72 to 96 hours after initial dosage, before the existing clotting factors are depleted, whereas suboptimal control of INR is frequently reported in warfarin users [7, 23]. Such disadvantages could have led to reduced pro-resolutive effect in patients with MI. In this scenario, DOACs could be reasonable alternatives for VKAs to form an effective and safe triple therapy. In a recent study by Jones et al, nearly 70% of patients are on triple therapy at discharge, among whom no embolic events have occurred [7]; in addition, DOAC users have demonstrated earlier resolution of LVT, which could be beneficial as existing thrombus could directly cause SSE [7, 23]. To maximize the antithrombotic effect while controlling the risk of bleeding, triple therapy consisting of aspirin, clopidogrel and
lower dose of DOACs (e.g., dabigatran 110 mg b.i.d., rivaroxaban 15 mg o.d., or apixaban 2.5 mg b.i.d.) has been proved feasible in several cases and endorsed by relevant consensus document for MI patients in need of anticoagulation [7, 30-32]. In sum, DOACs and VKAs showed similar efficacy in thrombus resolution, while DOACs could be more suitable choices for patients with MI.

**Safety of DOACs and VKAs**

This analysis showed that DOACs did not reduce the risk of any bleeding events in patients with LVT, but significantly lowered the risk of clinically relevant bleeding events compared with VKAs. These findings were consistent with those of previous studies regarding patients with atrial fibrillation and heart failure [10, 11]. Notably, DOACs showed homogenous reduction in clinically relevant bleeding events across various subgroups, which could be very important for patients with LVT. Although the rate of life-threatening bleeding events was quite low with various anticoagulant agents [5-7, 9], there is still an increasing need for greater reduction in major bleeding events, because oral anticoagulants are frequently prescribed in combination with antiplatelet agents for LVT patients with complex etiologies, which inevitably and substantially increases the bleeding risk [1, 3, 4]. In case of any bleeding events, despite the neutral pooled effects, DOACs still showed lower bleeding rates during long-term follow-ups and in patients taking antiplatelet medications, which could be beneficial for improving the quality of life and adherence of patients in need of long-term anticoagulation or antiplatelet treatments [33, 34]. Another issue to be noticed is the impact of comorbidities. In fact, chronic kidney disease (13.9 %–36.2 %) and cancers (4.8 %–12.9 %) are quite common in patients with LVT [7, 9, 20-22], which might substantially increase bleeding events during anticoagulation [35, 36]. In case of these comorbidities, current evidence generally suggests DOACs are associated with lower risk of bleeding as compared with VKAs, although its clinical
benefit becomes diminished or inconclusive with the advances of underlying diseases [36].

Considering the reduced risk of clinically relevant bleedings, DOACs might be more reasonable choices as primary anticoagulants for LVT patients complicated with relevant comorbidities increasing the bleeding tendency. Moreover, physicians need to come up with individualized anticoagulation for patients of this kind based on careful consideration regarding the risk of SSE, bleeding, and patient preferences. To summarize, DOACs possessed a better safety profile than VKAs because it effectively reduced clinically important bleeding events and showed a potential to reduce overall bleeding rates in patients on long-term and intense antithrombotic treatment.

**Limitations**

The general limitations of this meta-analysis are as follow. Firstly, only observational studies were included in the current analysis. Although baseline characteristics were generally consistent among DOAC and VKA users in most of the included studies, confounding effects could be present due to lack of adjustment from individual data. Besides, some of the included studies are published as abstracts, which might have not undergone strict review. Secondly, the regime and dosage of DOACs were different in each study, which might undermine its comparability with VKAs in pooled analysis. Thirdly, bleeding outcomes were not reported according to standard definitions (like BARC classification). Future well-designed RCTs could be safely initiated to assess efficacy of DOACs and VKAs for LVT patients based on the evidence from current analysis [37].
**Contribution statement**

R.C. and H.Y. contributed to the conception or design of the work. R.C., J.Z., C.L., P.Z., J.L., X.Z., Y.W., Y.C., L.S. and H.Z. contributed to the acquisition, analysis, or interpretation of data for the work. R.C., J.Z. and L.S. drafted the manuscript. R.C., H.Z., H.Y. critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

**Conflicts of interest:** none declared.

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References:


compared with warfarin for left ventricular thrombi. JAMA Cardiol. 2020; 5: 685-692.


Figure 1. PRISMA flow diagram of study selection.

Figure 2. Forest plot for the comparative risk of stroke or systemic embolism with direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs).
Figure 3. Forest plot for the comparative risk of stroke with direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs).

Figure 4. Forest plot for the comparative risk regarding failure of thrombus resolution with direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs).
Figure 5. Forest plot for the comparative risk of any bleeding events with direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs).

Figure 6. Forest plot for the comparative risk of clinically relevant bleeding events with direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs).
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Region</th>
<th>Study design</th>
<th>Sample size</th>
<th>Age (years)</th>
<th>Male sex</th>
<th>Follow-up period</th>
<th>Primary causes of LVT, n (%)</th>
<th>Numbers of DOAC vs VKA users, n (%)</th>
<th>Types of DOACs, n (%)</th>
<th>Types of VKAs, n (%)</th>
<th>Antiplatelet treatment, n (%)</th>
<th>NOS Score</th>
</tr>
</thead>
</table>
| Ali (2020)    | USA    | Retrospective | 92          | 59.0 ±14.0  | 75 (80.6) | 1 year          | *Ischemic cardiomyopathy: 58 %  
Non-ischemic cardiomyopathy: 23 %  
Acute myocardial infarction: 15 %  
Takotsubu cardiomyopathy: 3 %          | DOAC: 32 (34.8)  
vs VKA: 60 (65.2) | Rivaroxaban: 18 (56.2)  
Apixaban: 13 (40.6)  
Dabigatran: 1 (3.1) | Warfarin: 60 (100)  
Aspirin: 60 (65.5)  
P2Y12i: 16 (17.4) | 7          |
| Alizadeh (2019) | UK     | Prospective  | 98          | NA          | NA       | 1.8 years (median) | Acute myocardial infarction: 98 (100) | DOAC: 38 (38.8)  
vs VKA: 60 (61.2) | Rivaroxaban: 22 (57.9)  
Apixaban: 14 (36.8)  
Edoxaban: 2 (5.3) | Warfarin: 60 (100)  
NA | 4          |
| Bass (2019)   | USA    | Retrospective | 949         | 63.5        | 670 (70.6) | ≥ 90 days       | Comorbidities:  
Atrial fibrillation: 463 (48.8)  
Thrombo-embolic stroke: 189 (19.9)  
Myocardial infarction: 520 (54.8)  
Chronic kidney disease: 321 (33.8)  
Heart failure: 696 (73.3)        | DOAC: 180 (19.0)  
vs VKA:769 (81.0) | Rivaroxaban: 77 (41.6)  
Apixaban: 79 (42.7)  
Dabigatran: 29 (15.7) | Warfarin: 769 (100)  
Antiplatelet agents:  
P12 (54.0) | 5          |
| Cochran (2020) | USA    | Retrospective | 73          | VKAs:62.0 (34.0-84.0) DOACs: 51.5 (39.0-73.0) | 56 (76.7) | 12 months | Comorbidities:  
Coronary artery disease: 44 (60.3)  
Congestive heart failure: 58 (79.5)  
Arrhythmia: 13 (17.8)  
Chronic kidney disease: 27 (37.0)  
Type 2 diabetes: 30 (41.1)        | DOAC: 14 (19.2)  
vs VKA: 59 (80.8) | NA | Warfarin: 59 (100)  
NA | 8          |
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study Type</th>
<th>n</th>
<th>Age ± SD</th>
<th>Follow-up</th>
<th>Heart Diseases</th>
<th>Treatments</th>
<th>Differences</th>
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<tbody>
<tr>
<td>Daher (2020)</td>
<td>France</td>
<td>Retrospective</td>
<td>59</td>
<td>62.0 ±14.0</td>
<td>3 months</td>
<td>Ischemic cardiomyopathy: 51 (86.4)</td>
<td>DOAC: 17 (28.8) vs VKA: 42 (71.2)</td>
<td>Rivaroxaban: 4 (23.5)</td>
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<td>49 (83.1)</td>
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<td>Apixaban: 12 (70.6) Dabigatran: 1 (5.9)</td>
<td>Warfarin: 14 (33.3)</td>
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<td>Warfarin: 14 (33.3)</td>
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<td>Durrer-Ariyakuddy (2019)</td>
<td>Switzerland</td>
<td>Retrospective</td>
<td>53</td>
<td>63</td>
<td>20 (6-35 months)</td>
<td>Recent myocardial infarction: 25 (47.2) Ischemic heart disease: 7 (13.2) Non-ischemic cardiomyopathy: 21 (39.6)</td>
<td>DOAC: 20 (37.7) vs VKA: 33 (62.3)</td>
<td>Rivaroxaban: 2 (10.5) Apixaban: 15 (78.9) Dabigatran: 2 (10.5)</td>
</tr>
<tr>
<td>Guddeti (2020)</td>
<td>USA</td>
<td>Retrospective</td>
<td>99</td>
<td>61.0 ± 12.3</td>
<td>10.4 ± 3.4 months</td>
<td>Ischemic cardiomyopathy: 58 (58.6) Others: 41 (41.4)</td>
<td>DOAC: 19 (19.2) vs VKA: 80 (80.8)</td>
<td>Warfarin: 80 (100)</td>
</tr>
<tr>
<td>Iqbal (2020)</td>
<td>UK</td>
<td>Retrospective</td>
<td>84</td>
<td>62.0 ± 14.0</td>
<td>3.0±1.4 years</td>
<td>Ischemic heart diseases: 73 (86.9) Dilated cardiomyopathy: 4 (4.8) Acute myocarditis: 3 (3.6) Myocarditis: 2 (2.4) Unknown: 2 (2.4)</td>
<td>DOAC: 22 (26.2) vs VKA: 62 (73.8)</td>
<td>Rivaroxaban: 13 (59.1) Apixaban: 8 (36.4) Dabigatran: 1 (4.5)</td>
</tr>
<tr>
<td>Jones (2020)</td>
<td>UK</td>
<td>Prospective</td>
<td>101</td>
<td>59.6 ± 14.1</td>
<td>2.2 years (median)</td>
<td>Acute myocardial infarction: 101 (100)</td>
<td>DOAC: 41 (40.6) vs VKA: 60 (59.4)</td>
<td>Rivaroxaban: 24 (58.5) Apixaban: 15 (36.6) Edoxaban: 2 (4.9)</td>
</tr>
<tr>
<td>Lim (2019)</td>
<td>Malaysia</td>
<td>Retrospective</td>
<td>23</td>
<td>55.0 ± 9.6</td>
<td>≥ 3 months</td>
<td>Ischemic heart diseases: 20 (87.0) Thyroid cardiomyopathy: 2 (8.7) Spontaneous coronary dissection: 1 (4.3)</td>
<td>DOAC: 5 (21.7) vs VKA: 18 (78.3)</td>
<td>Rivaroxaban: 2 (40.0) Dabigatran: 3 (60.0)</td>
</tr>
<tr>
<td>Robinson (2020)</td>
<td>USA</td>
<td>Retrospective</td>
<td>421</td>
<td>57.8 ± 14.7</td>
<td>308 (73.2) (51-866)</td>
<td>*Ischemic heart diseases: 59.9 % Non-ischemic cardiomyopathies: 25.3 %</td>
<td>DOAC: 135 (32.1) vs VKA:286 (67.9)</td>
<td>**Rivaroxaban: 24.9% Apixaban: 76.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>351</td>
<td></td>
<td></td>
<td>Warfarin: 300 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aspirin: 191 (45.4) P2Y12i: 88 (20.9)</td>
<td></td>
</tr>
<tr>
<td>Willeford (2020)</td>
<td>USA</td>
<td>Retrospective</td>
<td>151</td>
<td>56 (49-65)</td>
<td>121 (80.1)</td>
<td>254 (98-343) days</td>
<td>Unknown: 7.8 % Others: 7.1 %; Comorbidities: Atrial fibrillation: 27 (17.9) Heart failure: 129 (85.4) Stroke/TIA: 13 (8.6) Myocardial infarction: 39 (25.8) Periperal artery disease: 13 (8.6) Coronary artery disease: 83 (55.0) Chronic kidney disease: 21 (13.9) DOAC: 22 (14.6) vs VKA:129 (85.4) Rivaroxaban: 18 (81.8) Apixaban: 4 (18.2) Dabigatran: 4.9% SAPT: 215 (51.1) DAPT: 64 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Yunis (2020)</td>
<td>USA</td>
<td>Retrospective</td>
<td>264</td>
<td>NA</td>
<td>NA</td>
<td>2 years</td>
<td>NA DOAC: 64 (24.2) vs VKA:200 (75.8) NA Warfarin: 200 (100) NA 7</td>
<td></td>
</tr>
</tbody>
</table>

* Etiologies for left ventricular thrombus was only presented in percentages, as original authors only report concrete numbers for each etiology for the whole cohort, including those not receiving anticoagulants or excluded from the original study. ** Authors report treatments switches between anticoagulants, and concrete numbers of patients using various types of DOACs are not reported and could not be calculated.

DAPT = double antiplatelet therapy, LVT = left ventricular thrombus, NA = not available, DOACs = direct oral anticoagulants, NOS = Newcastle-Ottawa Scale, P2Y12i = P2Y12 inhibitors, SAPT = single antiplatelet therapy, TIA = transient ischemic attack, VKAs = vitamin K antagonists.
Table 2. Subgroup analysis of various outcomes for users of direct oral anticoagulants and vitamin K antagonists.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>SSE</th>
<th>Stroke</th>
<th>Failure of thrombus resolution</th>
<th>Any bleedings</th>
<th>Clinically relevant bleedings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>RR (95% CI)</td>
<td>P</td>
<td>P int</td>
<td>N</td>
</tr>
<tr>
<td>All</td>
<td>10</td>
<td>0.96 (0.80-1.16)</td>
<td>0%</td>
<td>0.68 -</td>
<td>8</td>
</tr>
</tbody>
</table>

Follow-up duration

| ≥ 1 year | 5 | 0.73 (0.52-1.05) | 0% | 0.09 0.07 | 5 | 0.72 (0.42-1.25) | 0% | 0.25 0.79 | 7 | 0.88 (0.69-1.13) | 54% | 0.32 0.94 | 6 | 0.59 (0.35-1.00) | 16% | 0.05 0.02 | 4 | 0.18 (0.04-0.77) | 0% | 0.02 0.09 |
| < 1 year | 5 | 1.08 (0.86-1.34) | 0% | 0.51 - | 3 | 0.65 (0.39-1.10) | 0% | 0.92 - | 4 | 0.90 (0.59-1.35) | 0% | 0.52 - | 3 | 1.39 (0.88-2.19) | 0% | 0.16 - | 2 | 1.11 (0.25-4.96) | 0% | 0.89 - |

Sample size

| ≥ 100 | 5 | 1.02 (0.84-1.23) | 0% | 0.85 0.09 | 4 | 0.72 (0.48-1.08) | 0% | 0.11 0.49 | 3 | 0.75 (0.52-1.07) | 60% | 0.12 0.26 | 4 | 1.04 (0.72-1.50) | 61% | 0.83 0.21 | 3 | 0.27 (0.07-1.05) | 16% | 0.06 0.83 |
| < 100 | 5 | 0.46 (0.19-1.12) | 0% | 0.09 - | 4 | 0.47 (0.15-1.46) | 0% | 0.19 - | 8 | 0.97 (0.74-1.26) | 0% | 0.81 - | 5 | 0.54 (0.21-1.40) | 0% | 0.21 - | 3 | 0.48 (0.11-2.02) | 0% | 0.31 - |

Concomitant antiplatelet medication

| Complete | 2 | 0.51 (0.09-3.04) | 0% | 0.46 0.48 | 2 | 0.59 (0.10-3.60) | 0% | 0.57 0.88 | 2 | 0.76 (0.50-1.17) | 76% | 0.22 0.43 | 2 | 0.37 (0.17-0.81) | 0% | 0.01 0.006 | 2 | 0.14 (0.02-1.00) | 0% | 0.05 0.20 |
| Incomplete | 8 | 0.97 (0.81-1.17) | 0% | 0.77 - | 6 | 0.69 (0.47-1.01) | 0% | 0.06 - | 9 | 0.93 (0.73-1.19) | 9% | 0.56 - | 7 | 1.25 (0.85-1.85) | 0% | 0.26 - | 4 | 0.61 (0.19-1.97) | 0% | 0.41 - |

Primary causes of LVT

| MI | 2 | 0.34 (0.10-1.25) | 0% | 0.11 0.09 | 1 | 0.49 (0.05-4.53) | - | 0.63 0.76 | 2 | 0.57 (0.38-0.84) | 0% | 0.005 0.006 | 2 | 0.22 (0.03-1.67) | 0% | 0.14 0.14 | 2 | 0.14 (0.02-1.03) | 0% | 0.05 0.23 |
| Mixed | 8 | 1.00 (0.83-1.21) | 0% | 0.96 - | 7 | 0.69 (0.47-1.01) | 0% | 0.96 - | 9 | 1.09 (0.85-1.41) | 0% | 0.47 - | 7 | 1.02 (0.72-1.44) | 26% | 0.91 - | 4 | 0.57 (0.18-1.85) | 0% | 0.35 - |

Types of DOACs

| Apixaban ≥ 50% | 3 | 1.11 (0.59-2.08) | 0% | 0.75 0.63 | 1 | 0.81 (0.04-16.22) | - | 0.89 0.91 | 2 | 1.02 (0.51-2.04) | 0% | 0.96 0.67 | 1 | 1.05 (0.12-8.89) | - | 0.96 0.91 | 1 | 1.05 (0.12-8.89) | - | 0.96 0.28 |
| Apixaban < 50% | 7 | 0.94 (0.78-1.15) | 0% | 0.56 - | 7 | 0.68 (0.46-1.00) | 0% | 0.048 - | 9 | 0.87 (0.70-1.09) | 40% | 0.22 - | 8 | 0.93 (0.66-1.31) | 34% | 0.69 - | 5 | 0.28 (0.09-0.86) | 0% | 0.03 - |

# Complete medication indicates all patients of a study receive at least one antiplatelet agent along with anticoagulants; incomplete medication indicates studies with some of patients receiving no antiplatelet agents or not reporting data of antiplatelet medications. CI = confidence interval, LVT = left ventricular thrombus, N = number of studies in the subgroup, DOACs = direct oral anticoagulants, MI = myocardial infarction, P int = P for interaction, RR = risk ratio, SSE = stroke or systemic embolism.