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# Off-label Use of Direct Oral Anticoagulants Compared With Warfarin for Left Ventricular Thrombi

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## Key Points

**Question** What are the embolic outcomes associated with using direct oral anticoagulants for left ventricular thrombi, and how do they compare with outcomes associated with using warfarin for the same indication?

**Findings** In this cohort study of 514 patients with echocardiographically diagnosed left ventricular thrombi, anticoagulation with direct oral anticoagulants was associated with a higher risk of ischemic stroke and systemic emboli compared with warfarin treatment.

**Meaning** Off-label use of direct oral anticoagulants for left ventricular thrombi should be undertaken with caution until clinical trial data are available to compare their use with warfarin.

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**IMPORTANCE** Left ventricular (LV) thrombi can arise in patients with ischemic and nonischemic cardiomyopathies. Anticoagulation is thought to reduce the risk of stroke or systemic embolism (SSE), but there are no high-quality data on the effectiveness of direct oral anticoagulants (DOACs) for this indication.

**OBJECTIVE** To compare the outcomes associated with DOAC use and warfarin use for the treatment of LV thrombi.

**DESIGN, SETTING, AND PARTICIPANTS** A cohort study was performed at 3 tertiary care academic medical centers among 514 eligible patients with echocardiographically diagnosed LV thrombi between October 1, 2013, and March 31, 2019. Follow-up was performed through the end of the study period.

**EXPOSURES** Type and duration of anticoagulant use.

**MAIN OUTCOMES AND MEASURES** Clinically apparent SSE.

**RESULTS** A total of 514 patients (379 men; mean [SD] age, 58.4 [14.8] years) with LV thrombi were identified, including 300 who received warfarin and 185 who received a DOAC (64 patients switched treatment between these groups). The median follow-up across the patient cohort was 351 days (interquartile range, 51-866 days). On unadjusted analysis, DOAC treatment vs warfarin use (hazard ratio [HR], 2.71; 95% CI, 1.31-5.57; $P = .01$) and prior SSE (HR, 2.13; 95% CI, 1.22-3.72; $P = .01$) were associated with SSE. On multivariable analysis, anticoagulation with DOAC vs warfarin (HR, 2.64; 95% CI, 1.28-5.43; $P = .01$) and prior SSE (HR, 2.07; 95% CI, 1.17-3.66; $P = .01$) remained significantly associated with SSE.

**CONCLUSIONS AND RELEVANCE** In this multicenter cohort study of anticoagulation strategies for LV thrombi, DOAC treatment was associated with a higher risk of SSE compared with warfarin use, even after adjustment for other factors. These results challenge the assumption of DOAC equivalence with warfarin for LV thrombi and highlight the need for prospective randomized clinical trials to determine the most effective treatment strategies for LV thrombi.

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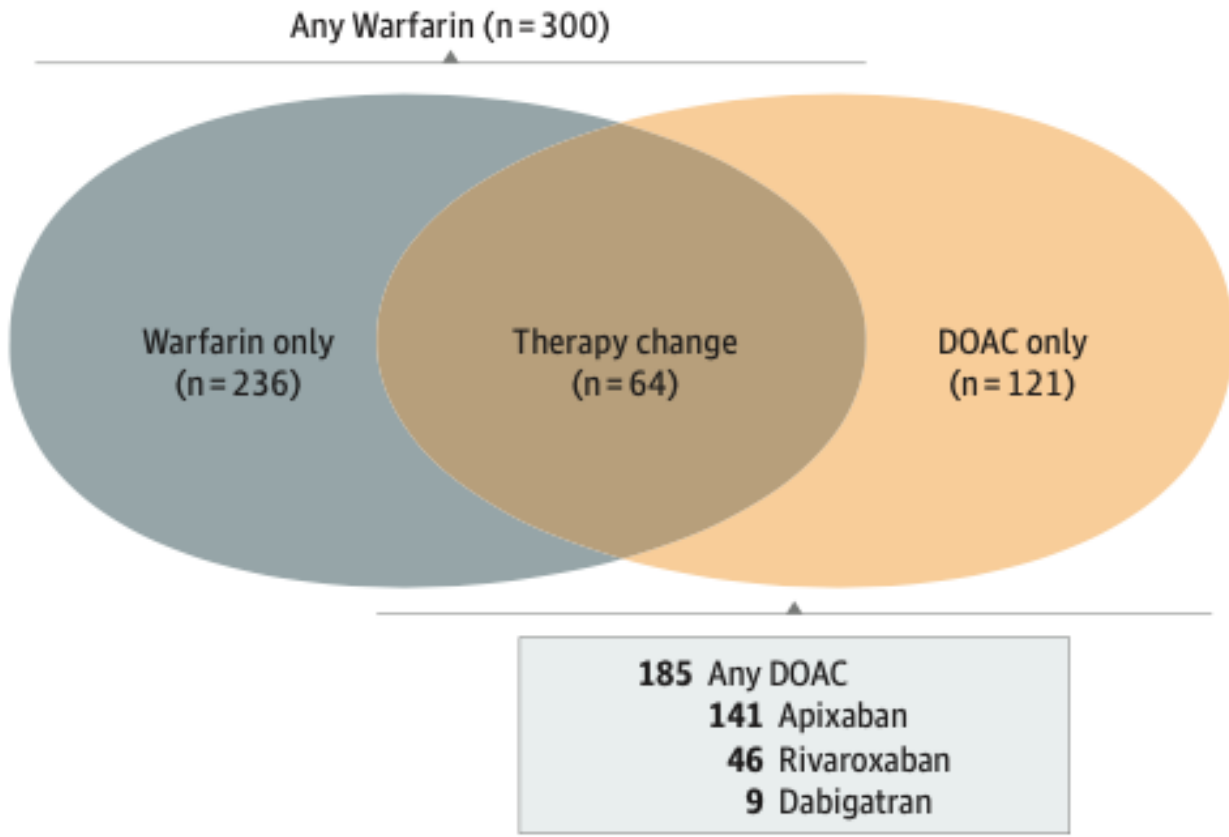
## Figure 1. Oral Anticoagulation Strategies




Of the 514 patients with left ventricular thromb1, 421 were treated with an oral anticoagulant. Three hundred were treated with warfarin at any point during the follow-up period (any warfarin) and 185 were treated with a direct oral anticoagulant (DOAC; any DOAC). These groups included a mixed cohort of 64 patients (therapy change), who switched treatment, such that there were 236 patients treated exclusively with warfarin (warfarin only), and 121 patients treated exclusively with a DOAC (DOAC only). Among the patients treated with a DOAC, 150 were treated with apixaban, 51 with rivaroxaban, and 9 with dabigatran. No patients were treated with edoxaban.

Table 1. Baseline Demographic, Clinical, and Echocardiographic Characteristics of Patients With LV Thrombi[a]

| Characteristic | Patients, No. (%) | | | | *P* value[b] |
|---|---|---|---|---|---|
| | DOAC only (n = 121) | Warfarin only (n = 236) | Therapy change (n = 64) | Neither (n = 93) | |
| Age, mean (SD), y | 58.1 (14.9) | 58.2 (15.1) | 55.5 (12.5) | 61.6 (14.9) | .06 |
| Male sex | 94 (77.7) | 170 (72.0) | 44 (68.8) | 71 (76.3) | .48 |
| White race/ethnicity | 73 (60.3) | 119 (50.4) | 32 (50.0) | 60 (64.5)[c] | .04 |
| Type 1 and 2 diabetes | 36 (29.8) | 92 (39.0) | 26 (40.6) | 41 (44.1) | .21 |
| Hypertension | 86 (71.1) | 177 (75.0) | 47 (73.4) | 66 (71.0) | .99 |
| Hyperlipidemia | 71 (58.7) | 126 (53.4) | 29 (45.3) | 47 (50.5) | .32 |
| Ischemic cardiomyopathy | 66 (54.5) | 148 (62.7) | 36 (56.3) | 60 (64.5) | .34 |
| Venous thromboembolism | 25 (20.7) | 38 (16.1) | 19 (29.7)[c] | 11 (11.8)[d] | .02 |
| Atrial fibrillation | 30 (24.8) | 45 (19.1) | 23 (35.9)[c] | 23 (24.7) | .04 |
| Prior SSE | 33 (27.3) | 51 (21.6) | 15 (23.4) | 12 (12.9) | .09 |
| Presenting embolism | 21 (17.4) | 34 (14.4) | 10 (15.6) | 8 (8.6) | .32 |
| BMI, mean (SD) | 28.2 (6.8) | 28.8 (7.4) | 30.5 (6.6) | 26.8 (5.1)[d] | .01 |
| Estimated GFR, mean (SD), mL/min/1.73 $m^2$ | 80.5 (29.3) | 75.8 (29.8) | 79.4 (25.4) | 75.5 (32.1) | .45 |
| GFR, mL/min/1.73 $m^2$ | | | | | |
| <30 | 5 (4.1) | 18 (7.6) | 1 (1.6) | 6 (6.5) | .24 |
| <15 | 1 (0.8) | 8 (3.4) | 0 | 0 | .07 |
| Echocardiographic contrast use | 46 (38.0) | 86 (36.4) | 25 (39.1) | 29 (31.2) | .70 |
| LV ejection fraction, mean (SD), % | 27.7 (13.8) | 28.2 (12.4) | 25.1 (11.7) | 26.6 (12.0) | .33 |
| Apical thrombus location | 115 (95.0) | 212 (89.8) | 56 (87.5) | 82 (88.2) | .23 |
| Mobile thrombus | 19 (15.7) | 39 (16.5) | 12 (18.8) | 19 (20.4) | .79 |
| Thrombus size, mean (SD), $cm^2$ | 2.8 (2.1) | 2.8 (2.5) | 2.3 (1.5) | 2.9 (2.7) | .43 |
| Protruding or pedunculated thrombus morphologic characteristics | 12 (9.9) | 12 (5.1) | 3 (4.7) | 9 (9.7) | .22 |
| Antiplatelet therapy | 77 (63.6) | 164 (69.5) | 38 (59.4) | 61 (65.6) | .42 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DOAC, direct oral anticoagulant; GFR, glomerular filtration rate; LV, left ventricular; SSE, stroke or systemic embolism.

[a] Additional data on types of antiplatelet regimens are available in eTable 2 in the Supplement.

[b] Calculated from 1-way analysis of variance testing for continuous variables or $\chi^2$ test for categorical variables.

[c] $P < .05$ compared with warfarin only group.

[d] $P < .05$ compared with therapy change group.

**Table 2. Number of SSE Events, Deaths, and Bleeding Events Requiring Cessation in Anticoagulation in Patients With Left Ventricular Thrombi**

| Anticoagulant | Events, No. | | |
|---|---|---|---|
| | SSE | Death | Bleeding event |
| DOAC | 17 | 14 | 8 |
| Warfarin | 14 | 32 | 19 |
| Parenteral agent | 11 | 12 | 4 |
| None | 12 | 57 | NA |
| Total | 54 | 115 | 31 |

Abbreviations: DOAC, direct oral anticoagulant; NA, not applicable; SSE, stroke or systemic embolism.

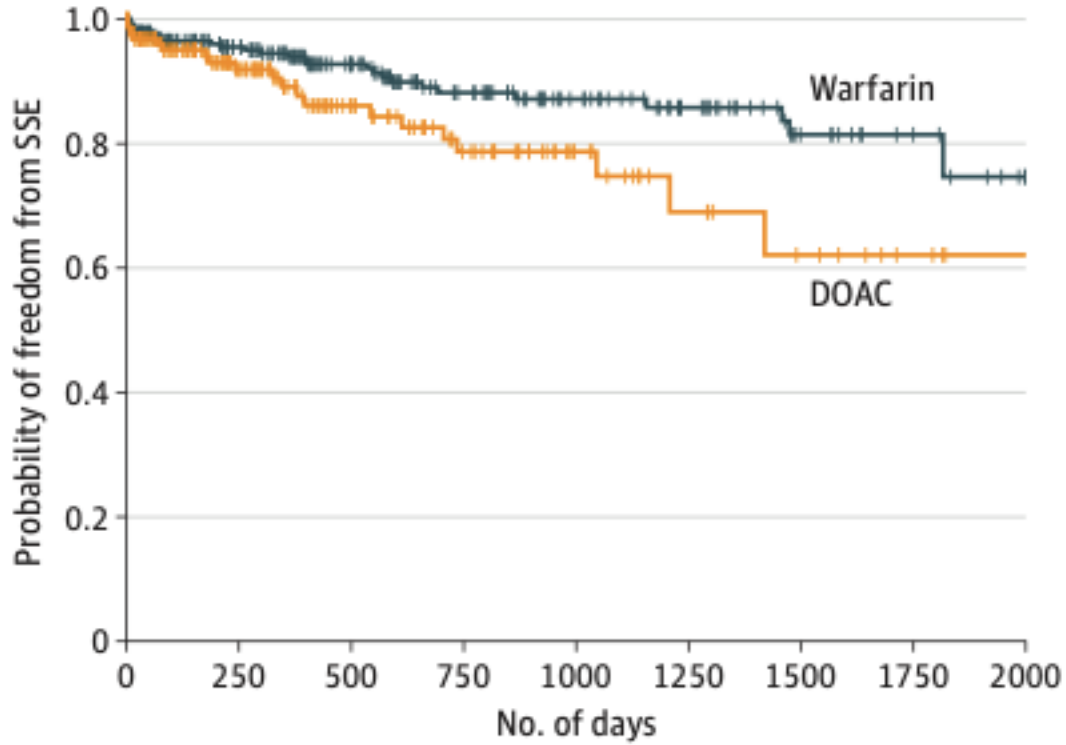
## Table 3. Results of Cox Proportional Hazards Regression Analysis

| Variable | Univariable | | Multivariable[a] | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| DOAC use (vs warfarin) | 2.71 (1.31-5.57) | .01 | 2.64 (1.28-5.43) | .01 |
| Prior SSE | 2.13 (1.22-3.72) | .01 | 2.07 (1.17-3.66) | .01 |
| Thrombus mobility | 1.80 (0.96-3.38) | .07 | 1.52 (0.80-2.87) | .20 |
| Patient age | 0.99 (0.97-1.01) | .19 | NA | NA |
| White ethnicity (vs other) | 1.57 (0.91-2.70) | .10 | NA | NA |
| Ischemic cardiomyopathy (vs nonischemic) | 0.89 (0.51-1.55) | .69 | NA | NA |
| Body mass index | 1.02 (0.99-1.06) | .16 | NA | NA |
| Estimated GFR | 1.00 (0.99-1.01) | .61 | NA | NA |
| History | | | | |
| Atrial fibrillation | 0.94 (0.49-1.79) | .85 | NA | NA |
| Venous thromboembolism | 1.03 (0.52-2.06) | .93 | NA | NA |
| Antiplatelet therapy | 0.98 (0.70-1.36) | .90 | NA | NA |
| Bridging anticoagulation | 0.96 (0.45-2.00) | .90 | NA | NA |
| Presenting embolism | 1.46 (0.73-2.91) | .28 | NA | NA |
| Left ventricular ejection fraction | 1.00 (0.97-1.02) | .69 | NA | NA |
| Thrombus size | 1.05 (0.95-1.18) | .35 | NA | NA |
| Pedunculated or protruding thrombus morphologic characteristics | 1.00 (0.31-3.22) | .99 | NA | NA |

Abbreviations: DOAC, direct oral anticoagulant; GFR, glomerular filtration rate; HR, hazard ratio; NA, not applicable; SSE, stroke or systemic embolism.

[a] In multivariable analysis, anticoagulation with DOAC (vs warfarin) and prior SSE were factors significantly associated with SSE. These were included in a multivariable Cox proportional hazards analysis, along with thrombus mobility, which was not a factor significantly associated with SSE in a univariable model but, with $P < .10$, met prespecified criteria for inclusion. In the multivariable model, prior SSE and anticoagulation with a DOAC were significantly associated with subsequent SSE.

## Figure 2. Survival Curves for Freedom From Stroke and Systemic Embolism




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Warfarin | 87 | 193 | 138 | 99 | 73 | 59 | 33 | 28 | 17 |
| DOAC | 64 | 80 | 50 | 37 | 22 | 12 | 9 | 5 | 2 |

Survival curves are shown for freedom from stroke and systemic embolism (SSE) in patients with left ventricular thrombus after index echocardiogram, Mantel-Byar $P < .001$. DOAC indicates direct oral anticoagulant.

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## Conclusions

In this multicenter, retrospective study of more than 500 patients with LV thrombi with 54 SSE events, 43.9% of patients treated with oral anticoagulation used an off-label DOAC for part of their course. Treatment with a DOAC was associated with a higher risk of SSE events compared with warfarin use, even after adjustment for other factors. These findings are limited by the lack of randomization and by the retrospective nature of this analysis. However, the findings argue against the assumption of equivalence of DOACs and warfarin for LV thrombi before outcomes can be compared in a prospective trial. In the interim, off-label use of DOACs for LV thrombi should be undertaken with caution. Randomized clinical trials are needed to determine the most effective treatment strategies for patients with LV thrombi.

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