# Non-Vitamin K Antagonist Oral Anticoagulants versus Warfarin for Patients with Left Ventricular Thrombus: A Systematic Review and Meta-analysis

Running title: NOAC versus warfarin for left ventricular thrombus

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# Abbreviations

AMI – Acute myocardial infarction

LVT – Left ventricular thrombus

NOAC – Non-vitamin K antagonist oral anticoagulants

OAC – Oral anticoagulation

TT – Triple therapy

TTR – Time in therapeutic range

VKA – Vitamin K antagonists

Left ventricular thrombus (LVT) formation is a recognised complication in patients with left ventricular dysfunction, especially following acute myocardial infarction (AMI), but may also occur in patients with non-ischaemic cardiomyopathy.

The importance of LVT is that it is frequently associated with systemic embolism, which can be life-threatening. A meta-analysis of observational studies demonstrated that patients with mural thrombus exhibit an increased risk of embolic events when compared to patients without (11% vs. 2%).[1] Treatment with systemic anticoagulation reduces embolic event rates by 33% compared to untreated patients[1]. This has led to the international recommendations for the treatment of LVT with oral anticoagulation (OAC).[2] However, due to the lack of prospective randomized data, the choice and duration of OAC remain unclear.

Owing to the ease of use, more predictable and stable anticoagulation, freedom from dietary restrictions and reduced requirements for monitoring, there has been an increase in the use of non-vitamin K antagonist oral anticoagulants (NOAC) as a substitute for conventional vitamin K antagonists (VKA) for both licensed indications, such as the treatment of venous thromboembolism and thromboprophylaxis of stroke in patients with atrial fibrillation, as well as other off-label use including in patients with LVT. Whilst the commonly used VKA, warfarin, has been the standard of care for the management of LVT, the convenience of NOAC makes this an attractive alternative. Nonetheless, the efficacy and safety of NOAC use has not been evaluated in a randomized controlled trial setting in patients with LVT.[3] We therefore performed a systematic review and meta-analysis of available observational studies comparing NOAC and VKA for the treatment of LVT.

We performed a systematic search of online databases PubMed, Embase, Cochrane Central Register of Controlled Trials and Scopus until 31 August 2020 for studies comparing NOAC to VKA for the treatment of patients with LVT. We used an advanced search strategy utilising the terms ((vitamin k antagonist) OR (Warfarin)) AND ((Direct oral anticoagulation) OR (Novel oral anticoagulation) OR (Non-vitamin K antagonist oral anticoagulation)) AND ((Left ventricular thrombus) OR (Left ventricular thrombi)). Two reviewers (Y.G. and N.S.) independently performed the search and literature screen, with disputes resolved by consensus following discussion with a third author (M.F.). We included studies that met all of the following inclusion criteria: 1) all studies comparing NOAC to VKA in patients with LVT, and 2) reporting clinical outcomes that included embolic events, and if available, bleeding events and/or documented LVT

resolution. We excluded individual case reports or series or studies not reporting on the clinical outcomes of interest.

The study primary outcome was the occurrence of embolic events. Secondary outcomes were the occurrence of LVT resolution and bleeding events, including major and minor bleeding.

Our initial search yielded a total of 277 potential studies, of which 15 studies were retrieved and screened for eligibility (Figure 1). Of these, 3 studies were excluded as only single-arm studies,[4–6] one study did not distinguish between the type of OAC used[7] and the last study only reported echocardiographic findings.[8] The remaining 10 studies were included and they adopted the retrospective observational design [9–18]. Table 1 shows the breakdown of reported baseline characteristics of each study. A total of 2103 patients were included in the analysis with 524 on NOAC and 1579 patients on VKA, namely warfarin. All 10 studies reported the primary outcome of the occurrence of embolic events. There was no significant difference in the occurrence of embolic events between patients taking NOAC and warfarin (9.7% vs. 11.2%, OR 0.9; 95% CI 0.58-1.4, P=0.65) (Figure 2).

Eight studies reported the incidence of LVT resolution and bleeding. There was no significant difference in the occurrence of LVT resolution between NOAC and warfarin treated patients (69.6% vs. 74.4%, OR 1.02; 95% CI 0.56-1.86, P=0.96) (Figure 3). Similarly, there was no significant difference in all bleeding events between patients taking NOAC and those taking warfarin (9.3% vs. 8.9% OR 0.93; 95% CI 0.55-1.56, P=0.77) (Figure 4-A). Furthermore, there was no significant difference in major bleeding (4.4% vs. 6.2%, OR 0.86; 95% CI 0.22-3.4, P=0.83) (Figure 4-B) or minor bleeding events (1.5% vs. 2.2%, OR 0.62; 95% CI 0.25- 1.51, P=0.29) between the 2 groups (Figure 4-C).

Regression analyses showed no relationship between the aetiology of LVT and either the occurrence of embolic events (P=0.13; Supplemental Figure 1) or LVT resolution with OAC (P=0.23; Supplemental Figure 2).

This systematic review and meta-analysis of ten observational studies demonstrates no significant difference between patients treated with NOAC or warfarin for LVT with respect to the occurrence of embolic events over a median follow up of 12 months. Furthermore, there was no difference in rate of LVT resolution or bleeding complications between patients treated with NOAC or warfarin (Figure 5). Subgroup analysis shows no difference between patients with ischaemic and non-ischaemic aetiology of LVT in terms of the

efficacy or safety between the two OAC approaches. In the absence of randomized studies, our meta-analysis therefore lends support to the use of NOAC in the treatment of LVT.

In the current meta-analysis, an embolic rate of 10.8% was documented with OAC, whereas historical papers from the 1990s report embolic event rates of around 11% in non-anticoagulated patients, with the highest risk in those with anterior AMI associated with severe wall motion abnormality.[1] This discrepancy between current and earlier event rates could simply reflect advances in imaging modalities for detecting LVT, including contrast echocardiography and cardiac magnetic resonance imaging, as well those for the detection of embolic events, compared with those available at the time of earlier studies. The rate of thrombus resolution on NOAC in our study was approximately 70%, with no significant difference between patients treated with NOAC or warfarin. However, this is much lower than the documented rate of >80% in prior case studies [19]. It is important to highlight that case studies have a high potential for publication bias compared with unselected-cohort observational studies. The aetiology of the LVT did not have a significant impact on either embolic event rate or thrombus resolution rate. This suggests that both NOAC and warfarin are equally effective for the treatment of LVT regardless of the aetiology.

In terms of safety, there does not appear to be any significant difference in bleeding event rates between the two OAC approaches. When exploring NOAC and warfarin comparison studies in other indications such as AF, there appears to be a reduction in intracranial haemorrhage with NOAC with similar rates of ischaemic stroke and systemic embolism[20]. Contemporary evidence shows increased bleeding risk when comparing NOAC to warfarin in the context of AF and AMI requiring antiplatelet combination therapy, thereby favouring the use of NOAC over VKA in such circumstances, owing to their observed less bleeding rates in real-world practice.[21]

In observational studies of patients with LVT of ischaemic and non-ischaemic aetiology, treatment with NOAC appears to be as effective as warfarin with a similar safety profile. Whilst awaiting future randomized clinical trials comparing different OAC approaches, NOAC seem to be a reasonable current alternative to VKA.

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## Ethics

No ethical approval was required for the study as this review was performed using data available in the literature.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author contribution

YXG and NS was involved in the data collection and analysis, wrote the first draft, and worked on subsequent revisions.

ME and DG was involved in the conception, review of the draft and final version of the manuscript

MF responsible for conception and design, critical review and revision of manuscript.

## Data availability

There are no new data associated with this article.

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