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Non-Vitamin K Antagonist Oral Anticoagulants Versus Warfarin for Patients With Left Ventricular Thrombus: A Systematic Review and Meta-Analysis

Left ventricular thrombus (LVT) formation is a recognized complication in patients with left ventricular dysfunction, especially following acute myocardial infarction, but may also occur in patients with nonischemic 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.

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 non-vitamin K OAC (NOAC) to vitamin K antagonists (VKA) for the treatment of patients with LVT. We used an advanced search strategy utilizing the terms ([VKA] OR [Warfarin]) AND ([direct OAC] OR [novel OAC] OR [non-VKA OAC]) AND ([LVT] OR [left ventricular thrombi]). Two reviewers (YG and NS) independently performed the search and literature screen, with disputes resolved by consensus following discussion with a third author (MF). 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.

Pooled odds ratios (OR) with 95% confidence interval (CI) were estimated for binary variables using a random-effects model by the method of DerSimonian and Laird. Heterogeneity between individual studies was explored by X^2 statistic and characterized with I^2 statistic. Meta-regression analysis was performed to examine the log transformed OR of embolic events or LVT resolution on OAC and the study reported percentage of ischemic cardiomyopathy. All analyses were performed using RevMan Version 5.4.0 software and Stata version 15.1.

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,[3–5] 1 study did not distinguish between the type of OAC used[6] and the last study only reported echocardiographic findings.[7] The remaining 10 studies were included and they adopted the retrospective observational design.[8–17] Table 1 shows the breakdown of reported baseline characteristics of each study. A total of 2,103 patients were included in the analysis with 524 on NOAC and 1,579 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 to 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 to 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 to 1.56, p = 0.77) (Figure 4A). Furthermore, there was no significant difference in major bleeding (4.4% vs 6.2%, OR 0.86; 95% CI 0.22 to 3.4, p = 0.83) (Figure 4B) or minor bleeding events (1.5% vs 2.2%, OR 0.62; 95% CI 0.25 to 1.51, p = 0.29) between the 2 groups (Figure 4C). Regression analyses showed no relationship between the etiology of LVT and either the occurrence of embolic events (p = 0.13) or LVT resolution with OAC (p = 0.23).

This systematic review and meta-analysis of 10 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. Moreover, there was no difference in rate of LVT resolution or bleeding complications between patients treated with NOAC or warfarin (Figure 5). Furthermore, there was no difference between patients with ischemic and nonischemic etiology of LVT in terms of the efficacy or safety between the 2 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

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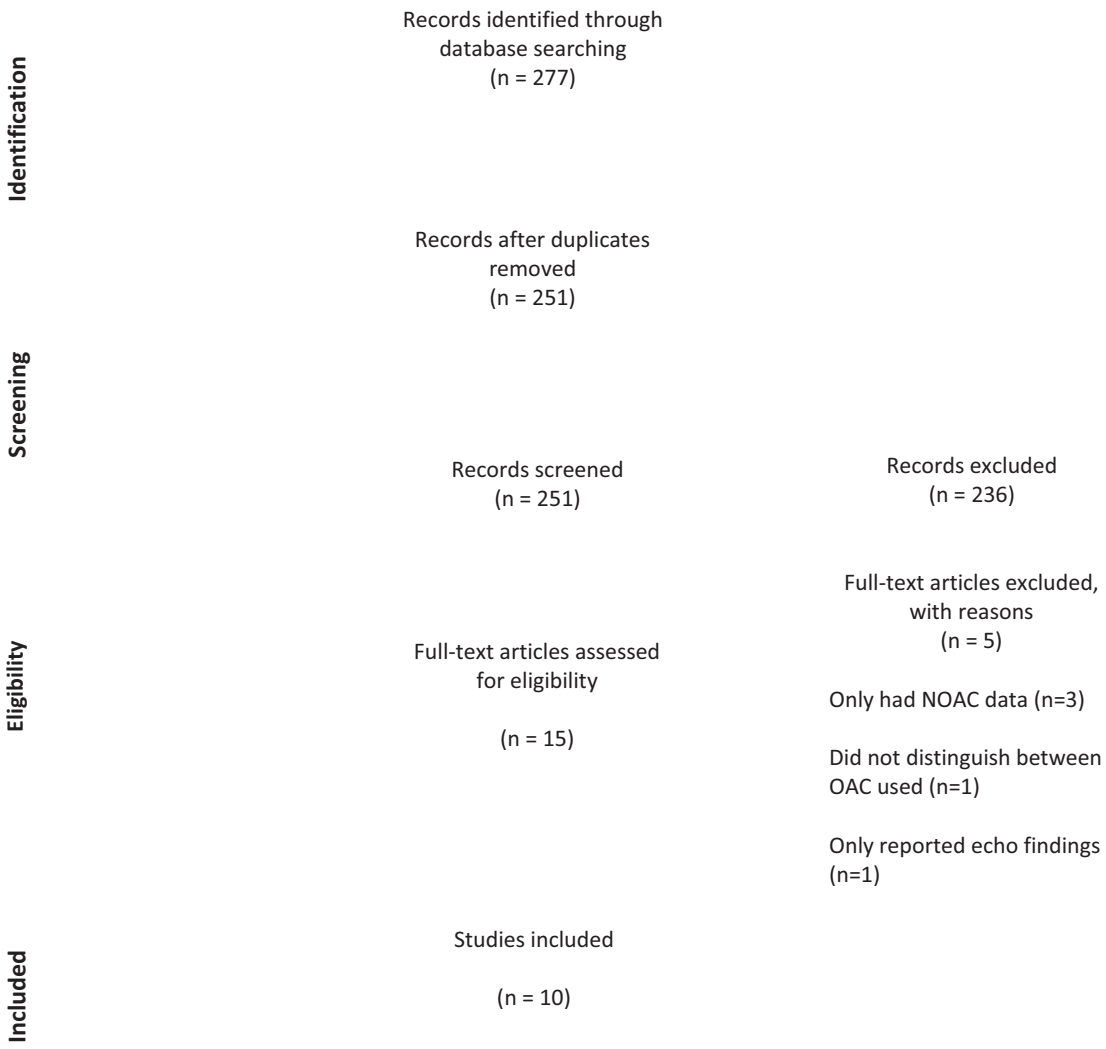


Figure 1. Flow chart of meta-analysis.

Table 1
Baseline characteristics of included studies

	Jaidka et al 2018	Robinson et al 2018	Bass et al 2019	Gama et al 2019	Iqbal et al 2020	Robinson et al 2020	Daher et al 2020	Guddeti et al 2020	Jones et al 2020	Yunis et al 2020
Patients (n)	49	75	949	66	84	357	59	99	101	264
Patients treated with VKA, namely warfarin (n)	37	40	769	53	62	236	42	80	60	200
Patients treated with NOAC (n)	12	35	180	13	22	121	17	19	41	64
Apixaban	NR	26	77	NR	8	NR	12	15	15	NR
Dabigatran	NR	2	28	NR	1	NR	1	2	0	NR
Edoxaban	NR	0	0	NR	0	NR	0	0	2	NR
Rivaroxaban	NR	7	75	NR	13	NR	4	2	24	NR
Age (mean ±SD)	59±11	NR	64*	63±11	62±14	58±15	59±14	61±12	59±14	NR
Men	75%	NR	70%	77%	90%	74.5%	82.6%	74%	82.5%	NR
Diabetes mellitus	13.6%	NR	NR	15.1%	26%	35%	18.6%	38%	17%	NR
Hypertension	33%	NR	NR	58%	32%	72.5%	45.7%	78%	49%	NR
Smoker	42.5%	NR	NR	30%	49%	NR	59.3%	NR	27.1%	NR
Hyperlipidaemia	26%	NR	NR	50%	15%	55%	NR	NR	41%	NR
Ischemic cardiomyopathy	100%	NR	NR	NR	87%	60%	87%	59%	100%	NR
Triple therapy use	87%	NR	NR	51%	38%	NR	NR	NR	69%	NR
Follow up period in months	6	12	3	12	36	12	3	12	26	24
Warfarin TTR	NR	NR	NR	NR	NR	NR	NR	NR	53.3%†	NR
Duration of anticoagulation	NR	NR	NR	NR	667 ± 568 days	NR	NR	NR	3 months	NR

n = numbers; NOAC = non-vitamin K antagonist oral anticoagulants; NR = not reported; SD = standard deviation; TTR = time in therapeutic range; VKA = vitamin K antagonists.

* No standard deviation reported;

† Good control defined as TTR >65%.

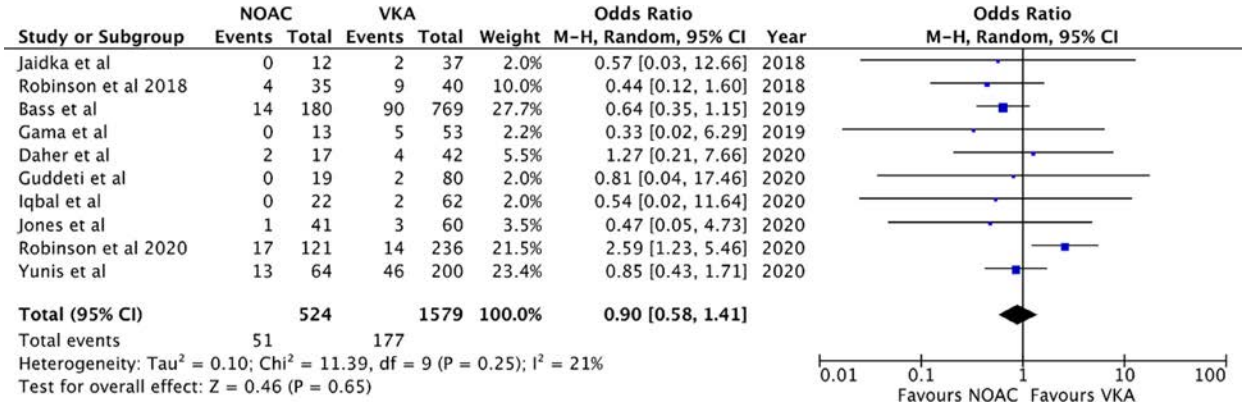


Figure 2. Embolic events with NOAC versus VKA for the treatment of LVT.

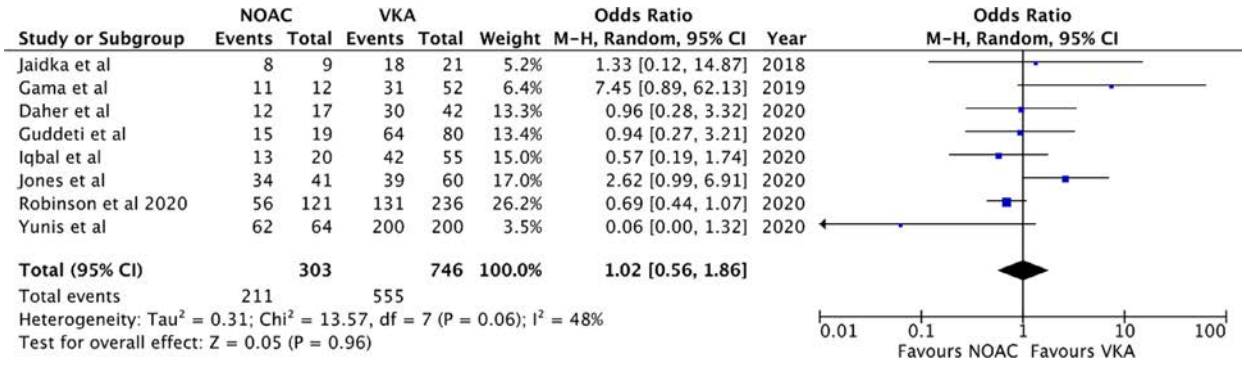
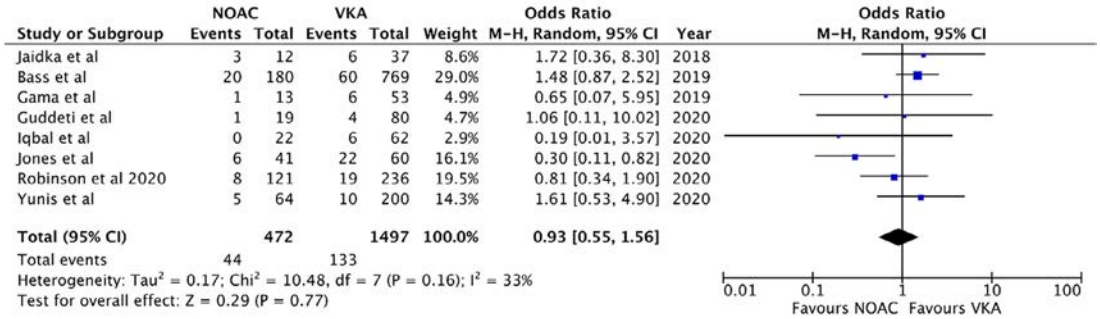
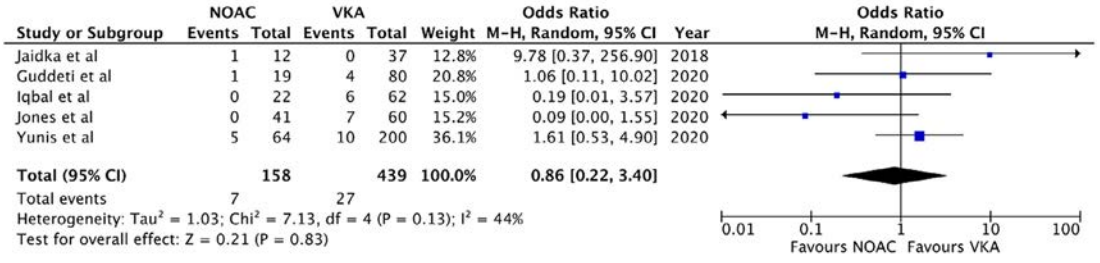


Figure 3. Thrombus resolution with NOAC versus VKA for the treatment of LVT.

(A)



(B)



(C)

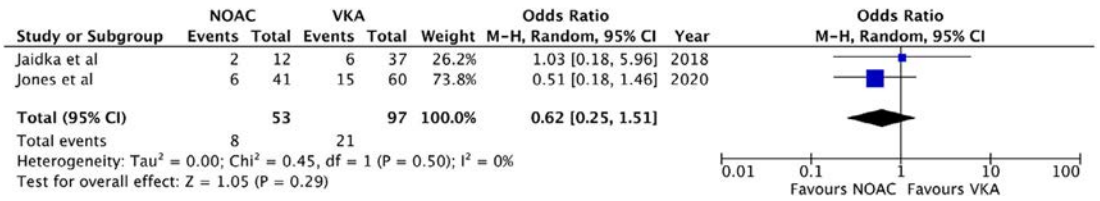


Figure 4. Bleeding events with NOAC versus VKA for the treatment of LVT.

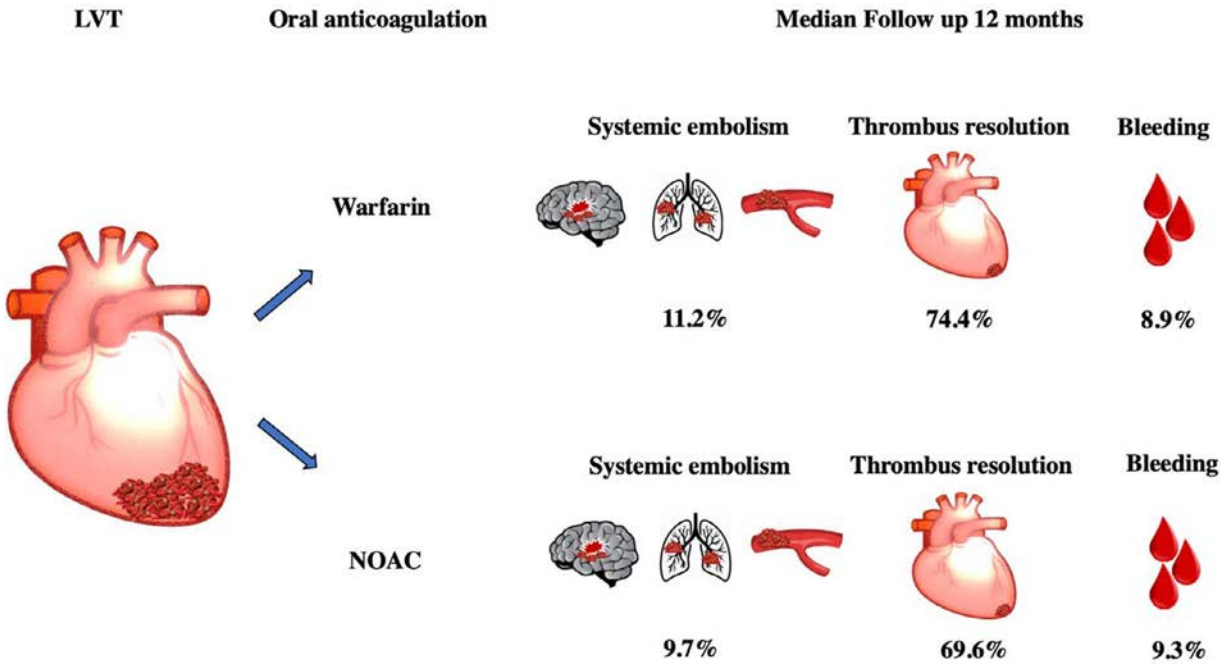


Figure 5. Summary key message. NOAC appear to be as effective as warfarin with similar safety profile. LVT = left ventricular thrombus, NOAC = non-vitamin K antagonist oral anticoagulants.

nonanticoagulated patients, with the highest risk in those with anterior acute myocardial infarction 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.[18] It is important to highlight that case studies have a high potential for publication bias compared with unselected-cohort observational studies. The etiology 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 etiology.

In observational studies of patients with LVT of ischemic and nonischemic etiology, 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.

Ethics

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

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.

Disclosures

The authors have no conflicts of interest to declare.

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Prediction of Incident Heart Failure in *TTR* Val122Ile Carriers One Year Ahead of Diagnosis in a Multiethnic Biobank

Hereditary transthyretin (*TTR*) amyloid cardiomyopathy (hATTR-CM) due to the *TTR* Val122Ile variant is associated with increased heart failure (HF) risk in both African-Americans and Hispanic Americans.[1] However, this variant has incomplete and age dependent penetrance, as not all carriers develop clinical heart failure.[2] Thus, early risk stratification of carriers can potentially inform medical management, especially with widespread genetic testing and available therapies. Here, we use electronic health records on a machine learning framework to predict HF 1-year ahead of diagnosis in African and Hispanic American Val122Ile carriers.

We obtained whole exome sequencing data of *TTR* Val122Ile for self-reported 213 (14% cases) African-Americans & 114 (15% cases) Hispanic Americans from a multiethnic quaternary care biobank (Bio*Me*).[1] 46 HF cases identified by diagnostic codes were stratified in 3 timeframes before diagnosis: <6, 6 to 12, and >12 months. We removed continuous (labs/vitals) features with more than 60% of missing values, then imputed using a random forest-based algorithm. Between all 2 highly correlated features (>0.8 in Pearson's correlation coefficient), the feature with the highest overall correlation was removed; the remaining were normalized. Medications and diagnostic codes were treated as binary data.

We ensured robustness by splitting cases and controls in train and test sets (60:40). The 40% test set was kept blind to feature selection, normalization, and fitting the model. We performed feature selection 100 times using a random subset of the train set for each iteration. To do so, a random forest model is trained using all features in the train set. Discarded features will be those who do not impact on the models' performance when removed. The union of all selected features, including age, gender, and ethnicity, were then used to fit 100 models using support vector machine.[3] For each iteration, a random subset of controls was sampled from the train set to generate a balanced dataset (Figure 1). A subset of the test set was used to evaluate predictive power 1 year before HF diagnosis. Standard performance metrics, namely sensitivity (recall), specificity, accuracy, and area under receiver operating characteristic (AUROC) curve were used to assess the performance of each model. Results are reported as the

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