SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 5.
Issue: 4.
Page N. 146-154
Year: 2021

Original Article www.wjahr.com

OFF LABEL USE OF DIRECT ORAL ANTICOAGULANTS (DOACS) COMPARED TO VITAMIN K ANTAGONIST (VKA) FOR LEFT VENTRICULAR THROMBUS (LVT): A SYSTEMATIC REVIEW AND META-ANALYSIS

Abdulkareem AlGarni[1,3,4], Abdulmajeed Aljuhiman[2,4] and Dr. Ayman F. Soliman[1,3,4]*

[1]King Saud bin Abdulaziz University for Health Sciences, COAMS-A, Al Ahsa, Saudi Arabia.
[2]Imam Abdulrahman Al Faisal Hospital - Saudi Arabia.
[3]King Abdulaziz Hospital, MNGHA, Al Ahsa, Saudi Arabia.
[4]King Abdullah International Medical Research Center (KAIMRC), Al Ahsa, Saudi Arabia.

Received date: 19 May 2021 **Revised date:** 09 June 2021 **Accepted date:** 29 June 2021

***Corresponding author: Dr. Ayman F. Soliman**
King Abdulaziz Hospital, MNGHA, Al Ahsa, Saudi Arabia.

ABSTRACT

Background: Left ventricular (LV) thrombus is associated with high burden of stroke, systemic embolization and mortality. Direct oral anticoagulants (DOACs) has emerged as an alternative treatment to Vitamin K Antagonist (VKA). In absence of randomized controlled trials, we aim to conduct systematic review and meta- analysis for the available observational studies. **Objective:** to evaluate effectiveness and safety of DOACs Versus VKA in Setting of LV thrombus. **Methods:** We searched Ovid Medline, Embase, PubMed, Google scholar and ClinicalTrials.gov for comparative Observational studies of DOACs Versus VKA in LV thrombus treatment. **Results:** We found 9 eligible observational studies including 2160 patients reported as 4 published studies and 5 abstracts without full report. Meta-analysis showed no difference between two interventions in terms of stroke and systemic embolization (SSE) RR= 1.09, 95% CI (0.90 –1.31), thrombus resolution RR= 1.01, 95% CI (0.62-1.63) and Major bleeding events RR =1.06, 95% CI (0.66-1.71). **Conclusion:** There is no difference between DOACs and VKA in terms of effectiveness and safety for treatment of LV thrombus. Randomized controlled trial is needed to evaluate DOACs in the treatment of LV thrombus.

KEYWORD: DOACs, warfarin, left ventricular thrombus.

INTRODUCTION

Left ventricular (LV) thrombus is a Life-threatening complication of Myocardial infarction (MI) and LV dysfunction associated with high burden of Stroke, Systemic embolization and mortality.

Incidence of LV thrombus in Pre PCI era was up to 40%.[1] However, a prevalence in the current PCI era is ranging between 3% and 9% after MI.[2] Limited Data available on incidence of LV thrombus in Non-ischemic cardiomyopathy with an old report indicated that up to 36% in non-ischemic cardiomyopathy.[3]

Vitamin K antagonist (VKA) is the mainstay of Long-term anticoagulation for LV thrombus, However, Warfarin is still associated with Hemorrhagic stroke and Need for periodic monitoring. Direct oral anticoagulants (DOACs) emerged as an alternative choice of treatment as an off-label use. A few retrospective studies shown that DOACs is as effective as warfarin in rate of thrombus resolution and decrease of systemic embolization.[4,5] On the other hand, a recent Large observational study showed that DOACs are associated with increased risk of stroke and systemic embolization compared to VKA.[6]

In absence of RCTs, we aim to conduct a systematic review for observational studies to evaluate the effectiveness and safety of DOACs in patients with LV thrombus compared to VKA, in terms of stroke and systemic embolization (SSE), thrombus resolution and risk of bleeding.

Methods

Protocol and registration

We aim to establish the review protocol with a plan to register the protocol upon review completion.

Types of studies
There were no available randomized control trials to address the clinical question, therefore we included the observational studies. we have also included all available comparative abstracts that address the clinical question. We excluded non-comparative studies and abstracts.

Type of participants
We included all adult patients (≥18 years of age) diagnosed with Left ventricular thrombus (LVT) by Transthoracic Echocardiograph (TTE) or Cardiac magnetic resonance imaging (CMR) and treated with either DOACs or VKA.

Types of interventions
The intervention being evaluated are DOACS versus VKA. DOACs include Dabigatran, Rivaroxaban, Apixaban, Edoxaban and have been approved for other conditions of deep vein thrombosis and atrial fibrillation, however, their use in LVT is an off-label use and must be discussed with patients . VKA, mainly, Warfarine is the standard of care anticoagulant in patients with LVT and must be overlapped with heparin till achieving the target INR 2-3.

Types of outcome measures
The outcomes that were selected are the clinically important outcomes for the patients and the health care providers which include a composite outcome of stroke and systemic embolization (SSE), Major bleeding events. We also included thrombus resolution, an outcome that has been proven as important predictor for stroke and systemic embolization in the previous studies.[7]

Search methods for identification of studies
We searched Medline and Embase Databases based on previous studies and systematic reviews in titles and abstracts from January 1996 till September 2020. We also searched PubMed, Clinicaltrials.gov and Google scholar. The following key words were used for the search: Left ventricular thrombus, LV thrombus, Intracardiac thrombus, Direct oral anticoagulants, Novel oral anticoagulants, DOACs, NOACs, Rivaroxaban, Dabigatran, Apixaban and Edoxaban.

There were no date or language restriction for the search and we contacted the authors as required. Last searched September 28,2020. The search strategy is presented in

Appendix 1-2.

Data collection and analysis
The search result was imported to EndNote X9 and the titles and abstract were screen by two independent authors (AK, AJ) for potentially relevant studies based on the predefined eligibility criteria. The two authors independently assessed the full text of the studies that passed the screening processes. Disagreement through out the screening and assessment process was resolved through discussion.

Data extraction and management
Data extraction was done using an excel sheet that has been designed for the included studies.

We piloted the data abstraction process for one study conducted by two reviewers independently and the difference in the data abstraction or requirement of modification of the data abstraction form was resolved by discussion. Subsequently, we completed data abstractions for all included studies. Our data abstraction form included study design, type (full text versus abstract), author, setting, inclusion criteria, patients' characteristics, sample size, number of participants, reported outcome, follow-up duration. We have planned and tried to contact the author for any missing data or when appeared to be necessary to acquire further information.

Assessment of risk of bias in included studies
The included studies were assessed for the risk of bias of all outcomes by two independents reviewers and any disagreement were resolved by discussion. RONBINS-I tool for assessing the risk of bias in non-randomized studies for interventions was used to evaluate seven risk of bias domains. These domains include bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. Each outcome was assessed across the seven risks of bias domains to judge the overall risk of bias as a low, moderate, serious, critical risk of bias.

Measure of treatment effect and data synthesis
For outcome data synthesis we used Review Manager 5.4 software to conduct the analysis. We expressed results for the outcomes: Stroke and systemic embolization (SSE), Major bleeding events and Thrombus resolution as Risk Ratios (RRs) with 95% Confidence interval (CI).

Dealing with missing data
For studies with missing data we contacted the authors for clarification. As there were three outcomes measured in our study, we analyzed only studies with complete data for each outcome separately.

Assessment of heterogeneity
We assessed the heterogeneity between pooled trials with the Chi-squared test and I^2 statistic.

P less than 0.1 was considered significant. The I^2 value was assessed as low (between 30 and 40%), moderate (30% t 60%), substantial (50% to 90%) or high (75% to 100%). We also considered the qualitative evaluation of heterogeneity.

We also performed visual inspection of graphs.

Assessment of reporting biases
Since we have less than 10 studies it was inappropriate to generate funnel plot to assess risk of bias. We relied on the signaling questions to assess reporting bias and additional comprehensive search strategy.

Data synthesis
We Used Review manager 5.4 to pool results of data of the studies. We used Mantel-Haenszel and random-effects model.

Subgroup analysis
Since we included abstracts to increase our sample size and to capture more events, we planned to do subgroup analysis by publications type, full text versus abstracts.

Sensitivity analysis
No sensitivity analysis was conducted.

Assessment of the certainty of the evidence
For all outcome results we used GRADE approach to evaluate Certainty of Evidence including:
Risk of bias, Inconsistency, Indirectness and impression as: Low, moderate or high guided by GRADE manual. We used GRADEpro Guidelines development tool (software) to generate summary of findings. Table 2

RESULTS

Results of the literature search
245 articles found during the search. We Excluded 85 duplicate studies. Additional 116 Record Were excluded that were case reports and Case series. We also excluded 34 records which were non comparative studies with one arm. The titles and abstracts were screened by two reviewers, which led to 9 articles including abstracts. Figure 1

Included studies
No Randomized controlled trails were found during our search. Total of 9 studies included in our systematic review, 4 Full reports and 5 Abstracts (4,5,6, 8,9,10,11,12,13). All studies were in English language and compared Warfarin to Direct oral anticoagulants in patient with Left Ventricular thrombus. Data of primary outcome (stroke and systemic embolization) were synthesized for 7 studies (4 full studies and 3 abstracts). Data for secondary outcome (thrombus resolution) were available in 7 studies (3 full text articles and 4 abstracts). Data for Safety measures (major bleeding) were available for 7 studies. Total number of patients included in all studies 2160 patients, out of which 756 patients in full text articles and 1433 from Abstracts. In total 1599 patients received Warfarin and 561 patients received DOACs.

Risk of bias in included studies
We assessed risk of bias in all included studies, which showed serious risk of bias in all studies except one study where the risk was moderate. Table 3 shows the summarized risk of bias in various domains.

Effects of interventions and assessment of the evidence
Efficacy
Stroke and systemic embolization
7 studies included in the analysis, 4 full text articles and 3 abstracts. Total number of patients Included in the analysis was 2041. With 528 patients in DOACs group and 1513 patients in VKA group. Figure 4 shows the forest plot of the related meta-analysis. The pooled results of these studies showed no difference between DOACs and VKA
Risk Ratio (RR) = 1.09, 95% Confidence interval (CI) 0.90 – 1.31. There was No significant
Heterogeneity between studies with I^2 = 0%, Chi^2 test P= 0.56.

Thrombus resolution
We included 7 studies in this analysis: 3 full text articles and 4 abstracts. Total number of patients Included in the analysis was 715 patients with 193 patients in DOACs group and 522patients in VKA group. Figure 5 shows the forest plot of the related meta-analysis. The pooled results of this analysis showed no difference between DOACs and VKA
Risk Ratio (RR)= 1.01, 95% Confidence interval (CI) 0.62 -1.63. There was considerable
Heterogeneity between studies with I^2 = 46%, Chi^2 test P: 0.09.

Safety: Major bleeding events
To assess Safety of the interventions (DOACS and VKA) in term of Major bleeding events, We pooled the data from 6 studies. 3 full texts and 3 abstracts. Total number of patients Included in the analysis was 1982 patients. With 511 patients in DOACs group and 1471 patients in VKA group. Figure 6 shows the forest plot of the related meta-analysis. The pooled results of the studies showed no difference between DOACs and VKA Risk Ratio (RR) =1.06, 95% Confidence interval (CI) 0.66-1.71. The Heterogeneity between studies was low with I^2 =18 %,
Chi^2 test P: 0.30.

Additional analysis
Due to serious risk of bias which was highest among abstracts, we performed subgroup Analysis by pooling Data for full text articles against abstracts. The result remains the same for all the outcomes with the test for subgroup difference revealed P value more than 0.05 for all the assessed outcomes (figure 5, 6, 7)

Risk of bias across studies
Risk of bias in all studies was serious except one study, Austin 2020 (6), where the risk was moderate which was included in the outcomes of SSE and Major bleeding events.

Flow chart

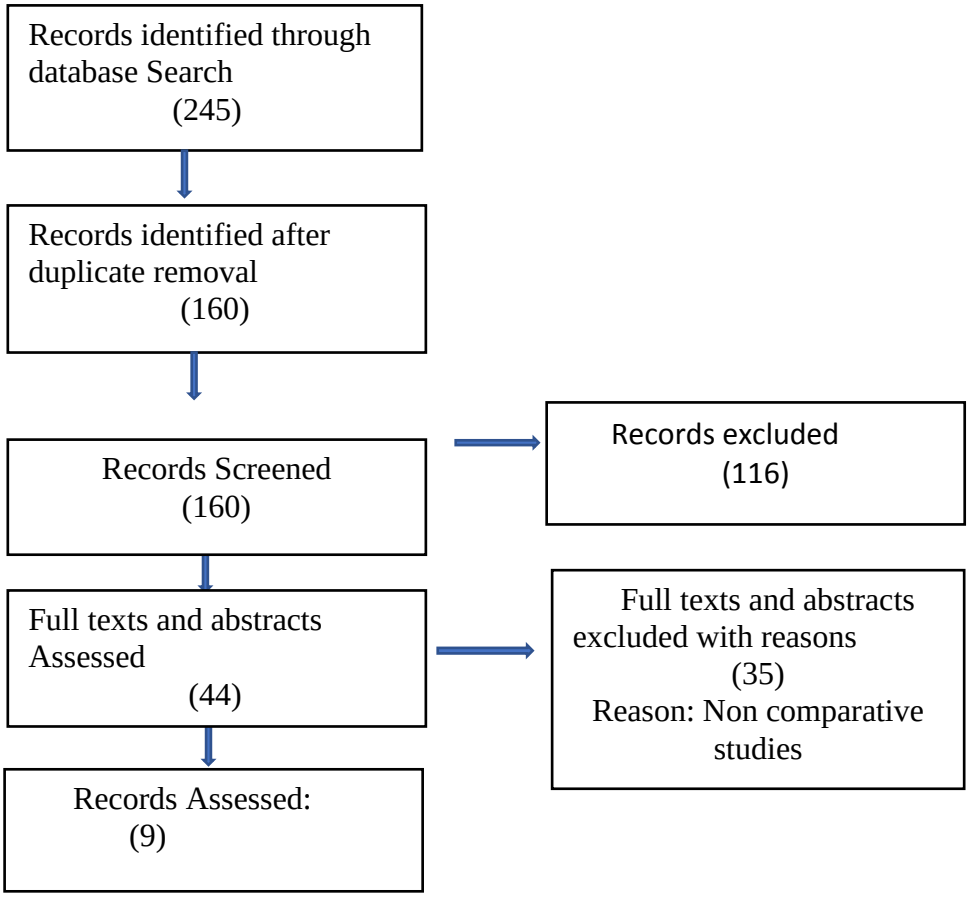

Figure 1: Study flow diagram.

Table 1: Summary of the studies.

Study	Type	Number of patient	Start dat	End dat	Participants	Setting	Intervention (DOAC	Comparator (VKA)	Follow up
Raviteja R. Guddeti,	full text	99	2012-01-01	2019-03-01	All patients above 18 with LV thrombi	Multicenters	Doacs : 19 (19%)	Warfarin : 80 (81%)	1 year
Jessica Daher	full text	59	2010-01-01	2019-08-01	All patients with LV thrombi	single center	28.8% (17)	71.2% (42)	3 months on ATC
Austin A. Robinson	full text	514	2013-10-01	2019-03-31	All patients with LV thrombi	Multicenters	185	300	351 days
Hansa Iqbal	full text	84	2012-12-01	2018-06-30	All patients above 18 with LVT	single center	22 (26%)	VKAs 62 (74%)	3.0 ± 1.4 years
F. Gama	abstract	66	2009-01-01	2018-12-01	All patients with LV thrombus with HF or MI	single center	13 (1 lost f/u)	VKA 53 (1lost f/u)	similar F/U
K. Durrer-Ariyakuddy	abstract	53	2015-01-01	2018-01-01	All patients with LV thrombi	Multicenters	20	33	20 months
Daniel A Jones,	abstract	101	2015-05-01	2018-12-01	patents undergoing (PCI) for AMI with LVT	single center	41 (40.6%)	VKA 60 (59.4%)	median 2.2 years
Megan Bass	abstract	949	2012-09-01	2018-10-01	All patients with LV thrombi	single center	180 (19%)	769 (81%)	3 months on ATC
Adil Yunis,	abstract	264	2014-01-01	2019-04-01	All patients with LV thrombi	single center	24.2% (n=64)	75.8% (n=200)	24 months

Table 2: Risk of bias assessment.

Non Randomized Studies	Austin 2020	Raviteja 2020	Jessica 2020	Hansa 2020	F. Gama 2019	K. Durrer-Ariyakuddy 201	Megan 2019	Daniel 2020	Adil 2020
Bias due to confounding	moderate	serious	serious	serious	serious	serious	serious	serious	serious
Bias in selection of participant into the study	moderate	moderate	moderate	moderate	serious	serious	serious	serious	serious
Bias in classification of interventions	moderate	moderate	serious	low	serious				
Bias due to deviations from intended interventions	moderate	low	low	low	serious	serious	serious	serious	serious
Bias due to missing data	moderate	low	low	serious	serious	serious	serious	serious	serious
Bias in measurement of outcomes	moderate	serious	moderate	serious	high	high	high	high	high
Bias in selection of the reported result	moderate	moderate	moderate	moderate	serious	serious	serious	serious	serious
Overall*	moderate	serious	serious	serious	serious	serious	serious	serious	serious

Table 3: Summary of finding table.

Author(s):
Question: DOACs compared to Warfarin for left ventricular thrombus (LVT)
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOACs	Warfarin	Relative (95% CI)	Absolute (95% CI)		
Stroke and systemic embolization (SSE)												
7	observational studies	serious [a,b]	not serious	not serious	serious [c]	[d]	104/528 (19.7%)	338/1513 (22.3%)	**RR 1.09** (0.90 to 1.31)	**20 more per 1,000** (from 22 fewer to 69 more)	- [e]	
Bleeding												
6	observational studies	serious [a,f]	not serious	not serious	serious [c]	[d]	34/511 (6.7%)	103/1471 (7.0%)	**RR 1.06** (0.66 to 1.71)	**4 more per 1,000** (from 24 fewer to 50 more)	- [e]	
Thrombus resolution												
7	observational studies	serious [a,f]	not serious	not serious	serious [c]	[d]	38/193 (19.7%)	97/522 (18.6%)	**RR 1.01** (0.62 to 1.63)	**2 more per 1,000** (from 71 fewer to 117 more)	- [e]	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Downgraded one level for serious bias due to unbalanced prognostic factors across all included studies.
b. 6 out of 7 studies did not adjust for potential confounding risk factors
c. The 95% confidence interval (CI) overlaps no effect
d. funnel plot to asess publication bias can not be done for less than 10 studies
e. low Certainty (serious risk of bias and imprecision)
f. all studies did not adjust for potential confounding risk factors

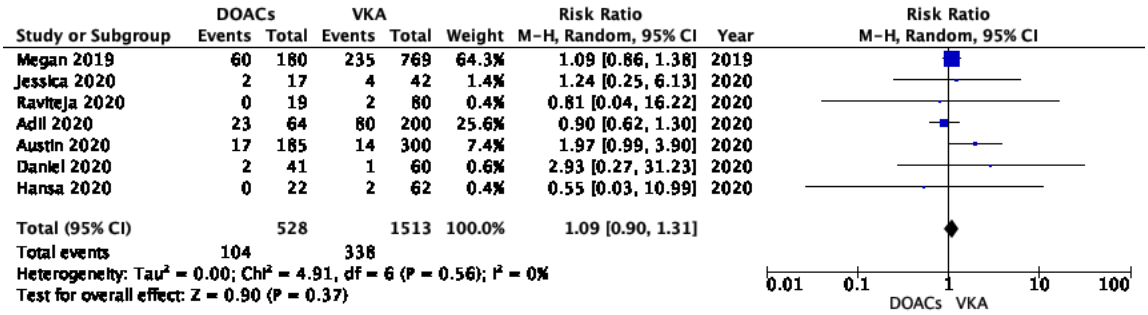

Figure 2: SSE (All studies).

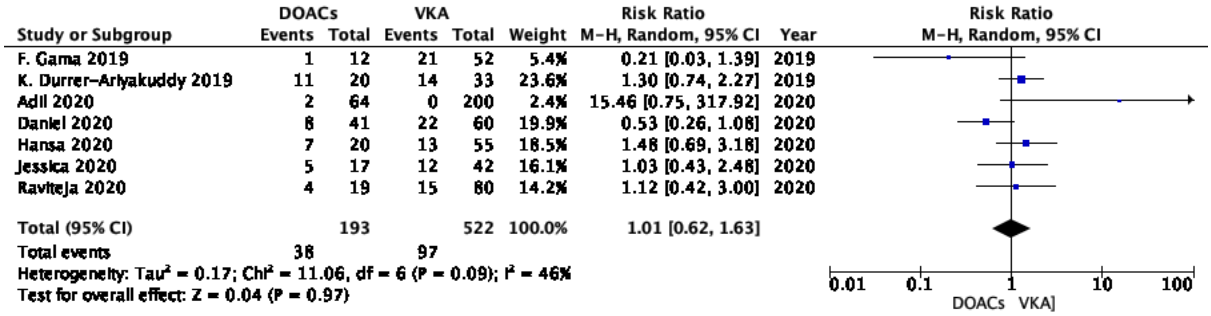

Figure 3: Thrombus resolution (All studies).

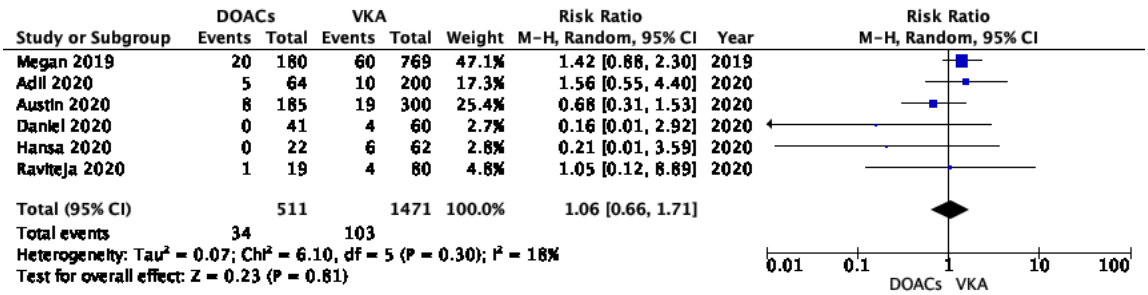

Figure 4: Major bleeding events (All studies).

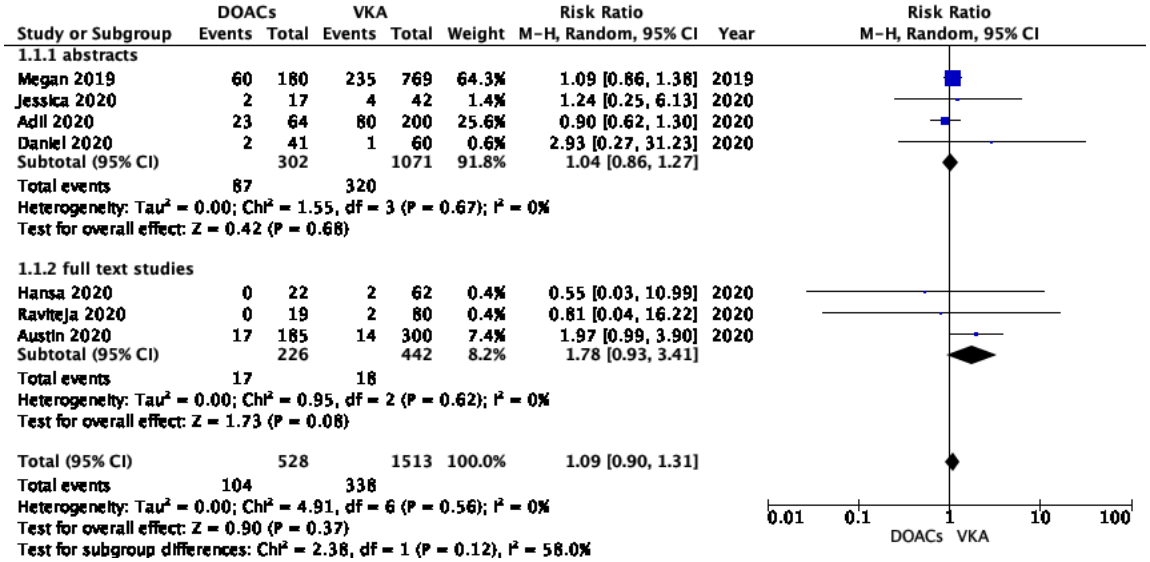

Figure 5: SSE (subgroup analysis abstracts versus full text).

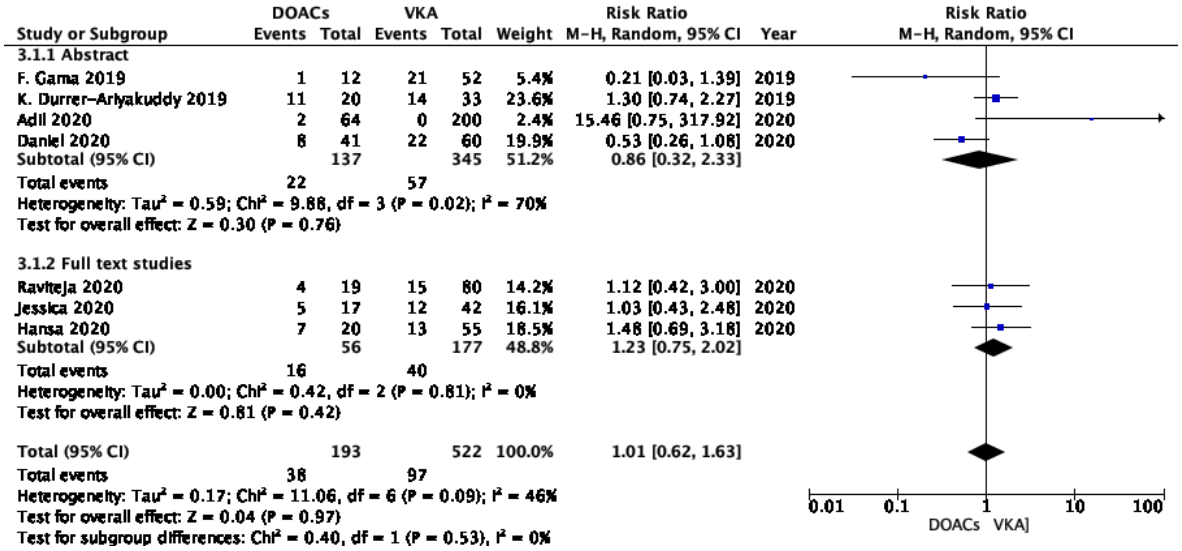

Figure 6: Thrombus resolution (subgroup analysis abstracts versus full text).

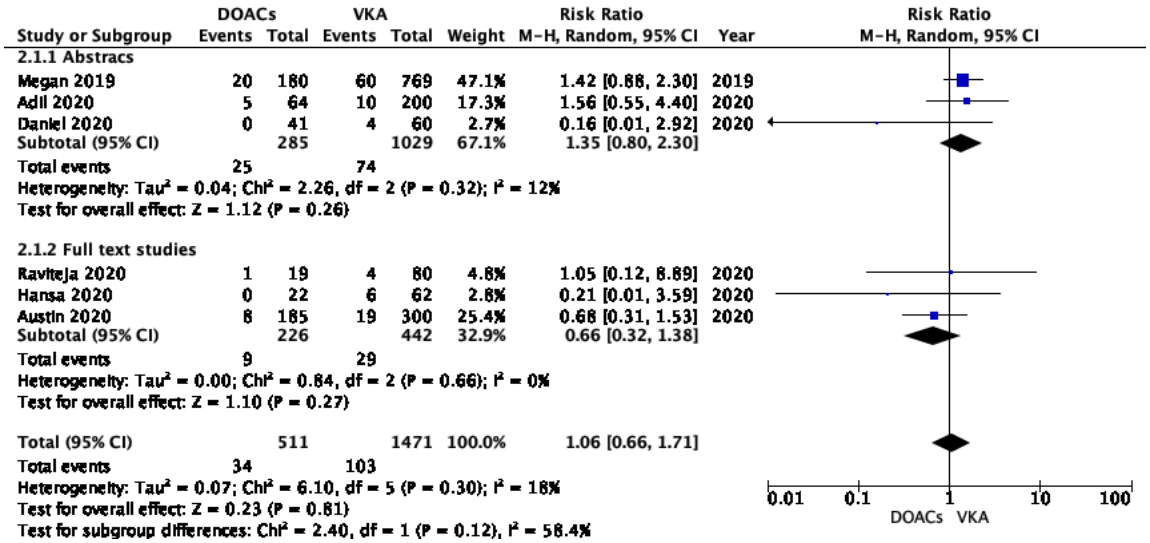

Figure 7: Major bleeding events (subgroup analysis abstracts versus full text).

Appendix 1

Ovid MEDLINE(R) <1996 to September 28, 2020>			
#	**Searches**	**Results**	**Type**
1	Left ventricular thrombus.ti,ab.	433	Advanced
2	LV thrombus.ti,ab.	136	Advanced
3	Intracardiac thrombus.ti,ab.	349	Advanced
4	1 or 2 or 3	827	Advanced
5	Novel oral anticoagulants.ti,ab.	755	Advanced
6	NOACs.ti,ab.	1246	Advanced
7	Direct oral anticoagulants.ti,ab.	1798	Advanced
8	DOACs.ti,ab.	1126	Advanced
9	Rivaroxaban.ti,ab.	3889	Advanced
10	Apixaban.ti,ab.	2374	Advanced
11	Edoxaban.ti,ab.	1007	Advanced
12	Dabigatran.ti,ab.	3774	Advanced
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	8882	Advanced
14	4 and 13	36	Advanced
15	4 and 13	36	Advanced

Appendix 2

Search history sorted by search number ascending			
#	**Searches**	**Results**	**Type**
1	Left ventricular thrombus.ti,ab.	1297	Advanced
2	LV thrombus.ti,ab.	642	Advanced
3	Intracardiac thrombus.ti,ab.	1100	Advanced
4	1 or 2 or 3	2727	Advanced
5	Novel oral anticoagulants.ti,ab.	2581	Advanced
6	NOACs.ti,ab.	4790	Advanced
7	Direct oral anticoagulants.ti,ab.	6422	Advanced
8	DOACs.ti,ab.	4415	Advanced
9	Rivaroxaban.ti,ab.	14553	Advanced
10	Apixaban.ti,ab.	9240	Advanced
11	Edoxaban.ti,ab.	3391	Advanced
12	Dabigatran.ti,ab.	13298	Advanced
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	31814	Advanced
14	4 and 13	173	Advanced

DISCUSSION

There was total of 9 studies (4 full text articles and 5 abstracts) evaluating the effectiveness and Safety of DOACs compared to VKA for Left ventricular thrombus (LVT). In terms of efficacy, There was no difference between the two interventions in preventing Stroke and systemic Embolization (SSE) or thrombus resolution. The risk of bleeding appears to be similar between the two Groups.

Although off label Use of DOACs is common now in the clinical practice, there was no Randomized controlled trials conducted to compare it with current standard of Care which is VKA. There have been Multiple case reports, case series and retrospective studies comparing DOACs VS VKA with conflicting results. There was one systematic review, sedhom et al.[14] Which included Case reports, Case series and cohort studies which found that studies have reached conflicting results. However, the systematic review was not comparative for DOACs VS VKA and No metanalysis was conducted. We had to include few abstracts in our systematic review due to low number of studies and patients in the full text articles to increase the sample size and event rate.

Overall, for primary outcome stroke and systemic embolization (SSE) the risk was not different among the two arms. Same applies for Thrombus resolution and bleeding risk. Since the risk of bias was highest among abstracts (missing data, unclear definition of outcomes etc.) We performed Additional subgroup analysis by pooling data from full articles versus abstracts.

The results remained not significant Between DOACs and VKA. Robinson et al included the largest number of participants and event rates among full textarticles. They performed multiple sensitivity analysis to adjust for Most of the confounders.

In their study the risk of stroke and systemic embolization was higher among DOACs group compared to VKA (HR, 2.71; 95% CI, 1.31-5.57; *P* = .01). The difference persisted

On multivariable analysis was performed with HR, 2.07; (95%CI, 1.17-3.66) *P* = .01.

However, baseline characteristics in DOACs group had more baseline risk factors for stroke and systemic embolization Including higher number of: Atrial fibrillation, Venous thrombosis and prior stroke and systemic embolization. Additionally, the probability of freedom from stroke and systemic embolization were the same at 3 months and graph separated beyond 6 months. It is well known that risk of stroke and systemic embolization due to LV thrombus is highest in the first 3 months, which raised the concern about other risks being the cause of high events.

LIMITATIONS

The nature of included studies in our systematic review which is observational studies are at high Risk of bias in many domains especially the risk of bias due confounding in many Studies. Some of the included studies include abstracts with missing data which increased risk of Bias. The assessment of LV thrombus was variable among studies including different modalities of imaging (Echo, MRI). In term of the Intervention, different DOACs type used at different doses and different definitions of bleeding were used among studies. additionally, variable time for assessment of outcomes, duration of anticoagulation and follow up. Also, the adherence to anticoagulation assessment was lacking among studies which is a very important factor affecting the outcomes.

The major limitation for many studies was the missing data for the outcomes, although we have tried to contact the authors there was no response, subsequently, we have decided to exclude these studies from the analysis for the missing outcome. Stroke is more important patient outcome, however, few studies reported this outcome separately, we have used SSE as a composite outcome which may represent other limitations to our study.

Authors conclusion

In our systematic review and meta-analysis of the comparative studies of DOACs and warfarin in LV thrombus did not show difference between the two interventions in terms of SSE, Thrombus resolution and major bleeding events. Even with presence of many limitations in our study, Given the lack of Randomized controlled trials conducted to compare DOACs to VKA in LV Thrombus, our study adds to the growing body of evidence necessitating urgently for a well-designed and adequately powered Randomized control trail. Worth mentioning, our search revealed two registered RCTs addressing same question.[15,16]

Funding

No funding was received for this project.

ACKNOWLEDGEMENTS

Thank you to the tutors of the systematic review course.

REFERENCES

1. Nihoyannopoulos, P., G. C. Smith, A. Maseri and R. A. Foale "The natural history of left ventricular thrombus in myocardial infarction: a rationale in support of masterly inactivity." J Am Coll Cardiol, 1989; 14(4): 903-911.
2. Robinson, A. A., A. Jain, M. Gentry and R. L. McNamara "Left ventricular thrombi after STEMI in the primary PCI era: A systematic review and meta-analysis." Int J Cardiol, 2016; 221: 554-559.
3. Gottdiener, J. S., J. A. Gay, L. VanVoorhees, R. DiBianco and R. D. Fletcher "Frequency and embolic potential of left ventricular thrombus in dilated cardiomyopathy: Assessment by 2-dimensional echocardiography." American Journal of Cardiology, 1983; 52(10): 1281-1285.
4. Daher, J., A. Da Costa, C. Hilaire, T. Ferreira, R. Pierrard, J. B. Guichard, C. Romeyer and K. Isaaz "Management of Left Ventricular Thrombi with Direct Oral Anticoagulants: Retrospective Comparative Study with Vitamin K Antagonists." Clinical Drug Investigation, 2020; 40(4): 343-353.
5. Guddeti, R. R., M. Anwar, R. W. Walters, D. Apala, V. Pajjuru, O. Kousa, N. R. Gujjula and V. M. Alla "Treatment of Left Ventricular Thrombus With Direct Oral Anticoagulants: A Retrospective Observational Study." American Journal of Medicine, 2020.
6. Robinson, A. A., C. R. Trankle, G. Eubanks, C. Schumann, P. Thompson, R. L. Wallace, S. Gottiparthi, B. Ruth, C. M. Kramer, M. Salerno, K. C. Bilchick, C. Deen, M. C. Kontos and J. Dent "Off-label Use of Direct Oral Anticoagulants Compared with Warfarin for Left Ventricular Thrombi." JAMA Cardiology, 2020; 5(6): 685-692.
7. Lattuca, B., N. Bouziri, M. Kerneis, J. J. Portal, J. Zhou, M. Hauguel-Moreau, A. Mameri, M. Zeitouni, P. Guedeney, N. Hammoudi, R. Isnard, F. Pousset, J. P. Collet, E. Vicaut, G. Montalescot and J. Silvain. "Antithrombotic Therapy for Patients With Left Ventricular Mural Thrombus." Journal of the American College of Cardiology, 2020; 75(14): 1676-1685.
8. Iqbal, H., S. Straw, T. P. Craven, K. Stirling, S. B. Wheatcroft and K. K. Witte "Direct oral anticoagulants compared to vitamin K antagonist for the management of left ventricular thrombus." ESC Heart Failure, 2020; **7**(5): 2032-2041.
9. Gama, F., P. Freitas, M. Trabulo, A. Ferreira, M. J. Andrade, D. Matos, C. Strong, R. Ribeiras, J. Ferreira and M. Mendes "Direct oral anticoagulants are an effective therapy for left ventricular thrombus formation." European Heart Journal, 2019; 40 (Supplement 1): 166.
10. Durrer-Ariyakuddy, K., F. Moccetti, S. F. Stampfli, B. W. De Boeck, M. Brinkert, M. Wolfrum, Y.

Suter, J. Nossen, S. Toggweiler, R. Kobza, F. Cuculi and M. Bossard "Direct oral anticoagulans versus vitamin K-antagonists for treatment of left ventricular thrombus-Insights from multicenter registry." Kardiovaskulare Medizin. Conference: Joint Annual Meeting, 2019; 22(3).

11. Jones, D. A., P. Wright, M. A. Alizadeh, S. Fhadil, K. S. Rathod, O. Guttmann, C. Knight, A. Timmis, A. Baumbach, A. Wragg, A. Mathur and S. Antoniou "The Use of Novel Oral Anti-Coagulant's (NOAC) compared to Vitamin K Antagonists (Warfarin) in patients with Left Ventricular thrombus after Acute Myocardial Infarction (AMI)." European heart journal. Cardiovascular pharmacotherapy, 2020; 30.
12. Bass, M., R. L. Page, T. H. Kiser, C. K. McIlvennan, L. A. Allen, G. Wright and C. Shakowski "Comparative Effectiveness of Direct Oral Anticoagulants and Warfarin for the Treatment of Left Ventricular Thrombus." Journal of Cardiac Failure, 2019; 25(8 Supplement): S26-S27.
13. Yunis, A., L. Seese, B. Stearns, M. Genuardi, F. Thoma and A. Kilic "Direct Oral Anticoagulants Are Effective Therapy in Treating Left Ventricular Thrombi." Journal of the American College of Cardiology, 2020; 75(11): 948.
14. Sedhom, R., P. Abdelmaseeh, M. Megaly and R. Asinger "Use of Direct Oral Anticoagulants in the Treatment of Left Ventricular Thrombi: A Systematic Review." The American Journal of Medicine, 2020; 133(11): 1266-1273.e1266.
15. Apixaban versus warfarin in patients with left ventricular thrombus. NCT03232398. Available at: https://clinicaltrials.gov/show/ nct03232398. Accessed May 5, 2020.
16. Apixaban versus warfarin in patients with left ventricular thrombus. NCT02982590. Available at: https://clinicaltrials.gov/show/ nct02982590. Accessed May 5, 2020.