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Comparison of outcomes of direct-acting oral anticoagulants *vs.* vitamin K antagonists in patients with bioprosthetic heart valves or valve repair: a systematic review and meta-analysis

L.-L. TANG, S.-W. LIANG, H.-L. SHI, J.-J. YE

Department of Pharmacy, XinChang County Hospital of Traditional Chinese Medicine, Shaoxing, Zhejiang Province, P.R. China

Abstract. – OBJECTIVE: To compare the outcomes between direct-acting oral anticoagulants and vitamin K antagonists, particularly for risk of stroke and bleeding, among patients with atrial fibrillation (AF) and bioprosthetic heart valve replacement or repair.

MATERIALS AND METHODS: A systematic search was conducted in the PubMed, Scopus, Cochrane Database of Systematic Reviews and Google scholar databases. Studies that were done in patients with AF who underwent bioprosthetic heart valve replacement or repair and that compared the outcomes between the use of direct-acting oral anticoagulants (DOACs) and vitamin K antagonists were eligible for inclusion. Studies that were preferably randomized controlled trials or adopted a cohort approach or retrospective data-based studies were considered for inclusion. The strength of association was presented in the form of pooled hazards risk (HR). Statistical analysis was done using STATA version 16.0.

RESULTS: A total of 8 articles were included in the meta-analysis. There were no significant differences in the risk of "all-cause stroke" [HR 0.72, 95% CI: 0.39, 1.34] and ischemic stroke [HR 0.79, 95% CI: 0.49, 1.29] between the two groups. The risk of "any bleeding" [HR 0.74, 95% CI: 0.64, 0.87], major bleeding [HR 0.60, 95% CI: 0.42, 0.86] and intra-cranial bleeding [HR 0.54, 95% CI: 0.36, 0.81] was much lower in those that received DOAC compared to warfarin. Compared to those receiving warfarin, those on DOACs had substantially reduced risk of any clinical thromboembolic events [HR 0.52, 95% CI: 0.39, 0.70]. No significant differences were noted for all-cause mortality [HR 0.88, 95% CI: 0.74, 1.05], cardiovascular events/myocardial infarction (MI) [HR 0.58, 95% CI: 0.33, 1.04] and and readmission rates [HR 0.85, 95% CI: 0.62, 1.18].

CONCLUSIONS: Findings suggest that the use DOACs in patients with AF with bioprosthetic valve replacement or repair is comparatively better than vitamin K antagonists in reducing the risk of bleeding and thrombo-embolic events. Future studies with a randomized design and larger sample sizes are needed to further substantiate these findings.

Key Words:

Directly acting oral anticoagulants, Vitamin K antagonists, Atrial fibrillation, Bioprosthetic valve, Randomized controlled trials, Meta-analysis.

Introduction

The risk of thromboembolic events, particularly, the ischemic events, tends to increase in patients with atrial fibrillation (AF)[1,2]. Further, AF often occurs in presence of valvular heart disease and both of them, as a standalone medical entity increase the risk of mortality[2-5]. In order to attenuate the risk of thromboembolic events, the role of oral anticoagulants is critical. The commonly used anticoagulant is warfarin, which is a vitamin K antagonist[6,7]. For non-valvular atrial fibrillation, the role of directly acting oral anticoagulants (DOACs) is established[8,9]. However, these DOACs are somewhat contraindicated in patients with valvular AF, especially when there is associated mitral stenosis, because of their possible tendency to increase the risk of thrombo-embolism and bleeding related events[10,11].

DOACs are widely used in the prevention of stoke in non-valvular atrial fibrillation, venous thrombo-embolism and in surgical procedures, especially in the field of orthopaedics[12-14]. The emerging consideration for the use of DOACs in the prevention of thrombo-embolic events is largely due to the fact that these classes of drugs

Corresponding Author: Lingling Tang, MD; e-mail: tang202120212021@163.com

have minimal interactions with other drugs, no interaction with food and most importantly, they do not require frequent observation and monitoring of their anti-coagulant activity[15]. On the other hand, patients on warfarin have to undergone frequent assessment of the international normalized ratio (INR) as the therapeutic window is narrow[16]. Several randomized controlled trials have shown that DOACs are as efficacious as warfarin in the prevention of thrombo-embolic events and have a better safety profile, but these trials had not involved patients with bioprosthetic valves[1,17,18]. Bioprosthetic valves have been commonly used in the treatment of valvular heart disease and while no specific contraindication exists for use of DOACs in place of vitamin K antagonists, the use has been limited due to lack of contemporary data. Recently, few studies have attempted to compare the outcomes between DOAC and vitamin K antagonists in patients with AF and bioprosthetic valve replacement or repair. The aim of the present meta-analysis is to synthesize the findings of these studies to generate pooled estimates of the merits and/or demerits of using DOAC, compared to vitamin K antagonists. The primary outcomes of interest were risk of stroke and bleeding.

Materials and Methods

Search Strategy

Through use of electronic search engines, PubMed, Scopus, Cochrane Database of Systematic Reviews and Google academic databases, a thorough systematic search of English language papers published until 30th April 2021 was carried out. **Supplementary Table I** has the specific details of the search strategy used to identify relevant literature for this meta-analysis. The literature search aimed at identifying studies done in patients with atrial fibrillation who underwent bioprosthetic heart valve replacement or repair and had compared the outcomes between use of direct acting oral anticoagulants (DOACs) and vitamin K antagonists, such as warfarin. The primary outcomes of interest were risk of stroke and bleeding. Secondary outcomes were risk of cardiovascular events/myocardial infarction, any clinical thromboembolic events, all-cause mortality and readmission rates. The study processes were in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.

Selection Criteria and Methods

The search strategy was executed in the various databases mentioned above. The studies identified through these databases were compared and duplicates were removed. Subject experts (Name 1, Name 2) from the study team screened the titles and abstracts as an initial step. After removing the articles that were considered not useful for inclusion in the review, the full texts of the remaining articles were reviewed in detail. In case of any disagreements between the two study authors with respect to the inclusion or exclusion of studies, a third senior experienced author was consulted, and consensus was made through discussions. Only those studies were included in the meta-analysis that fulfilled the inclusion criteria. In order to identify additional literature, the reference list of the included studies was also reviewed.

Inclusion criteria: studies that were preferably randomized controlled trials or adopted a cohort approach or retrospective data-based studies were considered for inclusion. For a study to be included, it should have been done in patients with atrial fibrillation who underwent bioprosthetic heart valve replacement or repair. Such studies should have compared the outcomes between use of direct acting oral anticoagulants (DOACs) and vitamin K antagonists such as warfarin. The primary outcomes of interest were risk of stroke ("all-cause stroke" and ischemic stroke) and bleeding ("any" bleeding; major bleeding; clinically relevant non-major bleeding; intracranial and gastrointestinal bleeding).

Exclusion criteria: case-reports or review articles were excluded. Also, those studies that did not provide data on the outcomes of interest or did not compare between DOACs and vitamin K antagonists or involved patients with mechanical heart valves were excluded.

Data Extraction and Quality Assessment

Through use of a pretested data extraction sheet, two study authors separately extracted data from the included studies. The methodological assessment was done independently by two authors using the assessment tool by Cochrane for randomized controlled trials[19]. For one study that was prospective non-randomized in nature, Newcastle-Ottawa Quality Assessment Scale was used[20].

Statistical Analysis

This meta-analysis, using STATA version 16.0, reported effect sizes as pooled hazard's ratio (HR) with 95% CI (confidence intervals). I^2 was used as a measure to denote heterogeneity and in instances where the value of I^2 exceeded 40%, random effects model was used[21]. Sub-group analysis was performed, based on the type of DOACs used and study design, for key outcomes of interest (i.e., all cause stroke, any bleeding, major bleeding and clinically relevant non-major bleeding). For reporting statistical significance, a p-value of less than 0.05 was considered. Egger's test was employed to assess for presence or absence of publication bias.

Results

Selection of Articles, Study Characteristics and Quality of Included Studies

Using the search strategy and after removal of the duplicates, overall, 521 citations were obtained (Figure 1). Screening of the titles led to removal of 428 studies. Out of the remaining 93 citations, 73 were omitted after reading of the abstract. The remaining 20 papers were reviewed in detail and finally, 8 articles were included in the meta-analysis[22-29]. Table I presents the details of the included studies. Three studies were randomized controlled trials (RCT) and one performed secondary analysis of data from a RCT[22,23,28,29]. The remaining 4 studies were either retrospective cohort-based studies or analysed data from a prospectively maintained research database. Majority of the studies were done in USA (n=4/8) followed by Italy (n=2/8). Out of the remaining two studies, one was conducted in South Korea and the other in Brazil. The commonly used DOAC was apixaban (n=4/8) followed by edoxaban (n=2/8). In one study, the DOAC used was dabigatran and in the other, rivaroxaban. In all the studies, the vitamin K antagonist used was warfarin. Majority of the studies has a follow up period of at least 2 years except three studies where the follow up period was 3 months, 6 months and 12 months respectively. The results of the quality evaluation of the included studies are provided in **Supplementary Tables II** and **Supplementary Tables III**. The included studies were of good quality.

Primary Outcomes

There were no significant differences in the risk of "all-cause stroke" [HR 0.72, 95% CI: 0.39,

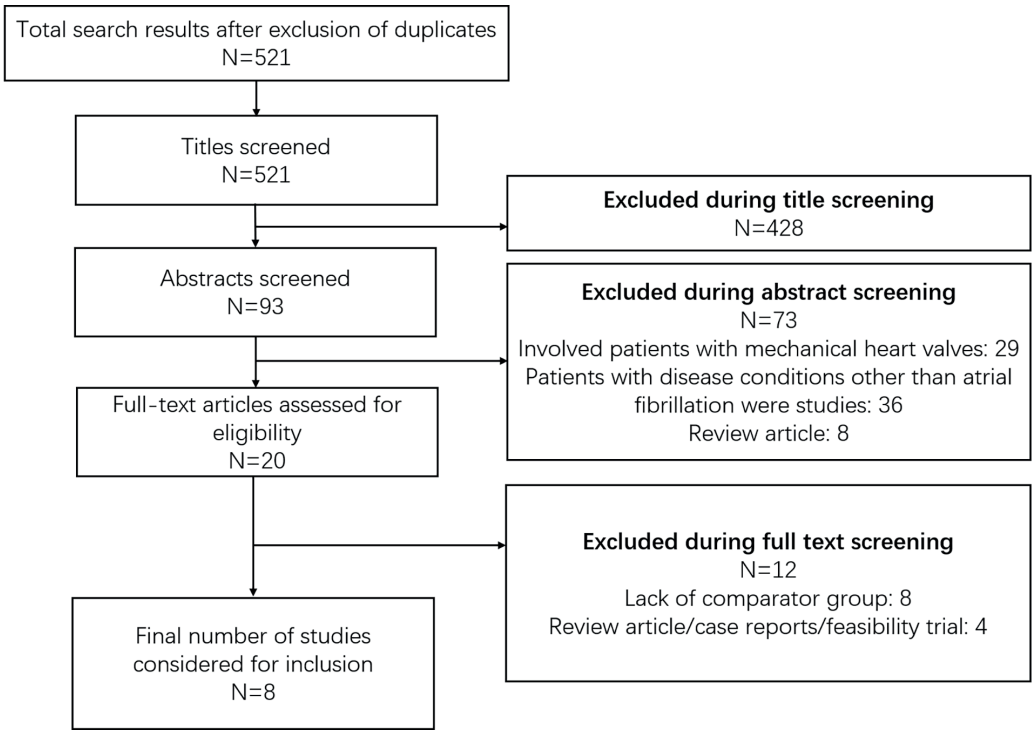

Figure 1. Selection process of the studies included in the review.

Table I. Characteristics of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Participant characteristics	Comparison groups	Sample size	Key outcome (direct-acting oral anticoagulants *vs.* vitamin K antagonists)
Guimaraes et al (2019) [22]	Secondary analysis of data from a randomized controlled trial	USA	Patients with atrial fibrillation and a history of bioprosthetic valve replacement or repair; median age of around 74 yrs; males (60%); history of previous stroke in around one-fifth subjects (20%); > 70% had hypertension	Apixaban *vs.* warfarin	156 (87 Apixaban; 69 warfarin)	Mean follow up period of 2 years. All cause stroke: HR 1.71 (95% CI: 0.31, 9.37) Ischemic stroke: HR 3.28 (95% CI: 0.37, 29.4) Cardiovascular event/Myocardial infarction: HR 0.83 (95% CI: 0.05, 13.2) All-cause mortality: HR 1.02 (95% CI: 0.34, 3.03) Any bleeding: HR 0.87 (95% CI: 0.52, 1.45) Major bleeding: HR 0.88 (95% CI: 0.31, 2.52) Intra-cranial bleeding: HR 0.47 (95% CI: 0.04, 5.19) Gastro-intestinal bleeding: HR 1.24 (95% CI: 0.21, 7.45) Clinically relevant non-major bleeding: HR 0.78 (95% CI: 0.32, 1.93)
Shim et al (2021) [23]	Randomized open label clinical trial	South Korea	Patients who underwent bioprosthetic valve replacement or repair at mitral or aortic positions; mean age of around 67 yrs; around 50% males and 60% of the participants were hypertensives; persistent atrial fibrillation in 35%	Edoxaban *vs.* warfarin	218 (109 Apixaban; 109 warfarin)	Mean follow up period of 3 months Any bleeding: HR 1.57 (95% CI: 0.63, 3.90) Major bleeding: HR 3.0 (95% CI: 0.32, 28.4) Clinically relevant non-major bleeding: HR 1.00 (95% CI: 0.06, 15.8) Any clinical thromboembolic event including intracardiac thrombus: HR 0.11 (95% CI: 0.01, 2.04) Rehospitalization: HR 0.88 (95% CI: 0.33, 2.33) No deaths in either of the two groups
Duan et al (2021) [24]	Retrospective cohort	USA	Patients who underwent bioprosthetic valve replacement or repair; majority older than 75 yrs (>55%); around 60% males; Nearly 55% of the participants were hypertensives; around 76% had history of congestive heart failure	Dabigatran (majority, 82.0%)/ Apixaban/ Rivaroxaban *vs.* warfarin	2672 (439 direct oral anticoagulant; 2233 warfarin)	Mean follow up period of 3 years. All-cause mortality: HR 0.87 (95% CI: 0.72, 1.05) All-cause stroke: HR 1.19 (95% CI: 0.96, 1.48) Ischemic stroke: HR 1.05 (95% CI: 0.82, 1.35) Transient ischemic attack (TIA): HR 1.36 (95% CI: 0.94, 1.98) Any bleeding: HR 0.69 (95% CI: 0.56, 0.85) Intra-cranial bleeding: HR 0.43 (95% CI: 0.25, 0.73) Gastro-intestinal bleeding: HR 0.92 (95% CI: 0.72, 1.17)

Continued

Table I *(Continued)*. Characteristics of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Participant characteristics	Comparison groups	Sample size	Key outcome (direct-acting oral anticoagulants *vs.* vitamin K antagonists)
Pasciolla et al (2020) [25]	Retrospective cohort	USA	Patients with atrial fibrillation who underwent bioprosthetic valve replacement or repair; mean age of around 72 yrs; > 50% males; Nearly 85% of the participants were hypertensives; around 50% had history of atrial fibrillation	Apixaban (majority 68.0%)/ Dabigatran/ Rivaroxaban *vs.* warfarin	197 (127 direct oral anticoagulant; 70 warfarin)	Mean follow up period of 6 months. Major bleeding: HR 2.48 (95% CI: 0.55, 11.2) All-cause stroke: HR 2.77 (95% CI: 0.14, 56.9) Clinical thromboembolic event: HR 1.69 (95% CI: 0.07, 40.9) Readmission: HR 0.74 (95% CI: 0.49, 1.12)
Russo et al (2019) [26]	Analysis of data from prospectively maintained research database	Italy	Patients with atrial fibrillation who underwent bioprosthetic valve replacement or repair; mean age of around 65 yrs; around 44% females; Nearly 33% of the participants were hypertensives; a round 25% had history of stroke	Apixaban (majority 56.0%)/ Dabigatran/ Rivaroxaban/ edoxaban *vs.* warfarin	260 (130 direct oral anticoagulant; 130 warfarin)	Mean follow up period of around 2 years. Clinical thromboembolic event: HR 0.49 (95% CI: 0.19, 1.22) Any bleeding: HR 0.61 (95% CI: 0.36, 1.03) Major bleeding: HR 0.59 (95% CI: 0.15, 2.40) Intra-cranial bleeding: HR 0.33 (95% CI: 0.05, 2.34) All-cause mortality: HR 0.50 (95% CI: 0.05, 5.45) Clinically relevant non-major bleeding: HR 0.68 (95% CI: 0.35, 1.33)
Mannacio et al (2021) [27]	Retrospective cohort study	Italy	Patients who underwent aortic valve replacement with bioprosthetic value; mean age of around 70 yrs; Majority were males; a substantial proportion of participants were hypertensives and/or had a history of stroke	Apixaban (majority)/ Dabigatran/ Rivaroxaban/ edoxaban *vs.* warfarin	1032 (340 direct oral anticoagulant; 692 warfarin)	Average follow up period of around 4-5 years. Clinical thromboembolic event: HR 0.50 (95% CI: 0.37, 0.75) Major bleeding: HR 0.50 (95% CI: 0.33, 0.84) Intra-cranial bleeding: HR 0.84 (95% CI: 0.42, 1.68) All-cause stroke: HR 0.50 (95% CI: 0.34, 0.95) Ischemic stroke: HR 0.50 (95% CI: 0.26, 1.01)

Continued

Table I *(Continued)*. Characteristics of the studies included in the meta-analysis.

Author (year of publication)	Study design	Country	Participant characteristics	Comparison groups	Sample size	Key outcome (direct-acting oral anticoagulants *vs.* vitamin K antagonists)
Carnicelli et al (2017) [28]	Randomized controlled trial	USA	Patients who underwent bioprosthetic valve replacement or repair at mitral or aortic positions; mean age of around 75 yrs; around 64% males; 21% with previous history of stroke or transient ischemic attack	Edoxaban *vs.* warfarin	191 (121 edoxaban; 70 warfarin)	Average follow up period of around 3 years. Major bleeding: HR 0.12 (95% CI: 0.01, 0.95) All-cause stroke: HR 0.53 (95% CI: 0.16, 1.78) Cardiovascular event/ Myocardial infarction: HR 0.36 (95% CI: 0.15, 0.87) Ischemic stroke: HR 0.72 (95% CI: 0.20, 2.57)
Guimaraes et al (2020) [29]	Randomized controlled trial	Brazil	Patients with atrial fibrillation and bioprosthetic mitral valve; mean age of around 59 yrs; around 60% females; 60% with hypertension and 40% with previous congestive cardiac failure	Rivaroxaban *vs.* warfarin	1005 (500 rivaroxaban; 505 warfarin)	Average follow up period of 12 months. All-cause stroke: HR 0.25 (95% CI: 0.07, 0.88) Ischemic stroke: HR 0.43 (95% CI: 0.11, 1.66) Any bleeding: HR 0.83 (95% CI: 0.59, 1.15) Major bleeding: HR 0.54 (95% CI: 0.21, 1.35) Clinically relevant non-major bleeding: HR 1.05 (95% CI: 0.60, 1.87) All-cause mortality: HR 1.01 (95% CI: 0.54, 1.87) Cardiovascular event/Myocardial infarction: HR 0.85 (95% CI: 0.38, 1.90) Readmission: HR 1.15 (95% CI: 0.62, 2.13) Clinical thromboembolic event: HR 0.65 (95% CI: 0.35, 1.20)

1.34; I^2=68.7%, N=6] and ischemic stroke [HR 0.79, 95% CI: 0.49, 1.29; I^2=41.0%, N=5] among patients that received DOAC, compared to those that received warfarin (Figure 2). Egger's test did not indicate the presence of publication bias (p=0.12 for "all cause stroke; p=0.43 for ischemic stroke). The risk of "any bleeding" was 26% lower [HR 0.74, 95% CI: 0.64, 0.87; I^2=9.1%, N=5] in those that received DOAC compared to warfarin (Figure 3). Similarly, in those that received DOAC, compared to those receiving warfarin, the risk of major bleeding [HR 0.60, 95% CI: 0.42, 0.86; I^2=29.0%, N=7] and intra-cranial bleeding [HR 0.54, 95% CI: 0.36, 0.81; I^2=0.0%, N=4] was much lower. No statistically significant differences were noted between the two groups for gastrointestinal bleeding [HR 0.93, 95% CI: 0.73, 1.18; I^2=0.0%, N=2] and clinically relevant non-major bleeding [HR 0.86, 95% CI: 0.58, 1.26; I^2=0.0%, N=4] (Figure 3). Egger's test did not indicate the presence of publication bias (p=0.22 for "any bleeding"; p=0.14 for major bleeding; p=0.32 for clinically relevant non-major bleeding; p=0.29 for gastrointestinal bleeding and p=0.51 for intracranial bleeding).

Secondary Outcomes

Compared to those receiving warfarin, those on DOACs had substantially reduced risk of clinical thromboembolic events [HR 0.52, 95% CI: 0.39, 0.70; I^2=0.0%, N=5] (Figure 4). No significant differences were noted for all-cause mortality [HR 0.88, 95% CI: 0.74, 1.05; I^2=0.0%, N=4], cardiovascular events/myocardial infarction (MI) [HR 0.58, 95% CI: 0.33, 1.04; I^2=2.9%, N=3] and readmission rates [HR 0.85, 95% CI: 0.62, 1.18; I^2=0.0%, N=3] (Figure 4). Egger's test did not indicate the presence of publication bias (p=0.81 for all-cause mortality; p=0.34 for cardiovascular event/MI; p=0.63 for readmission to hospital and p=0.59 for any clinical thromboembolic event).

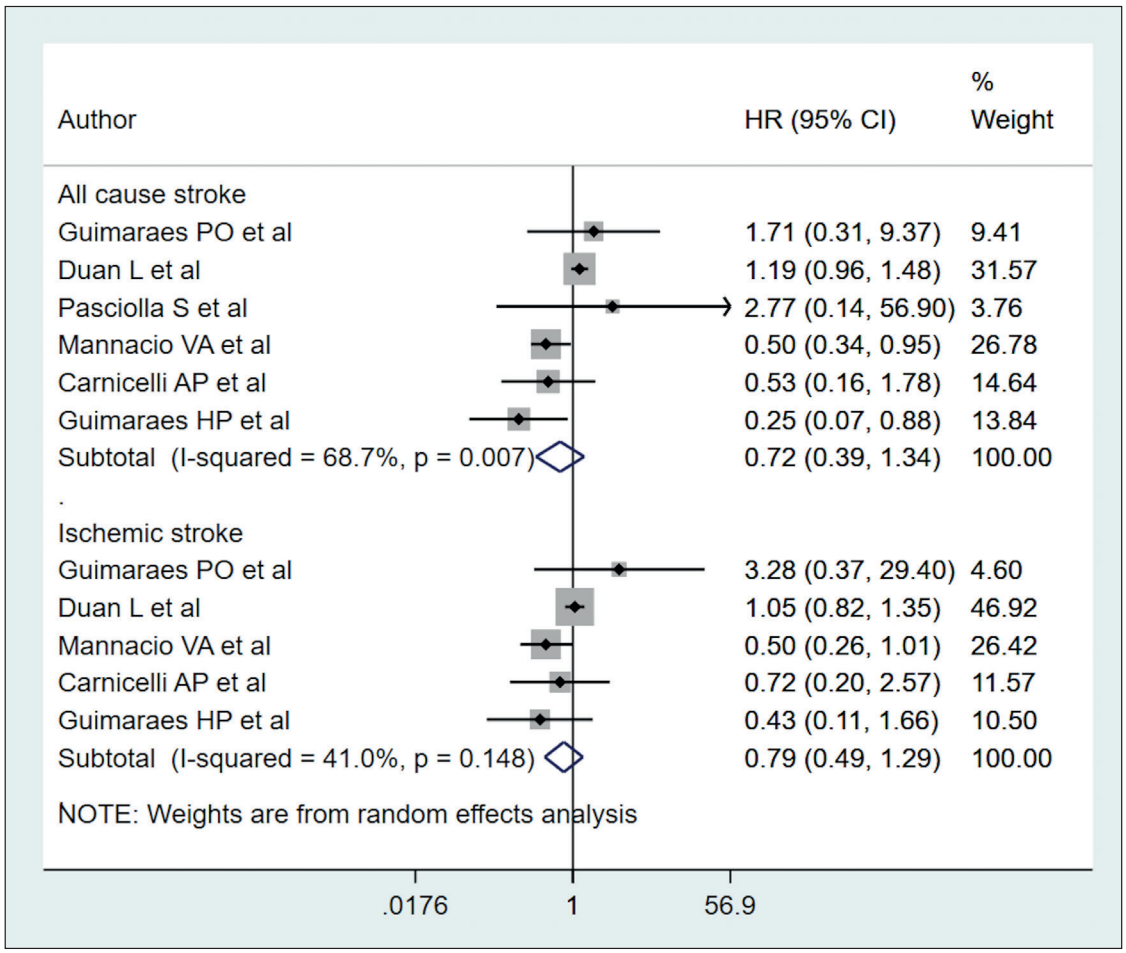

Figure 2. Pooled risk for all cause stroke and ischemic stroke for comparisons between DOACs and warfarin.

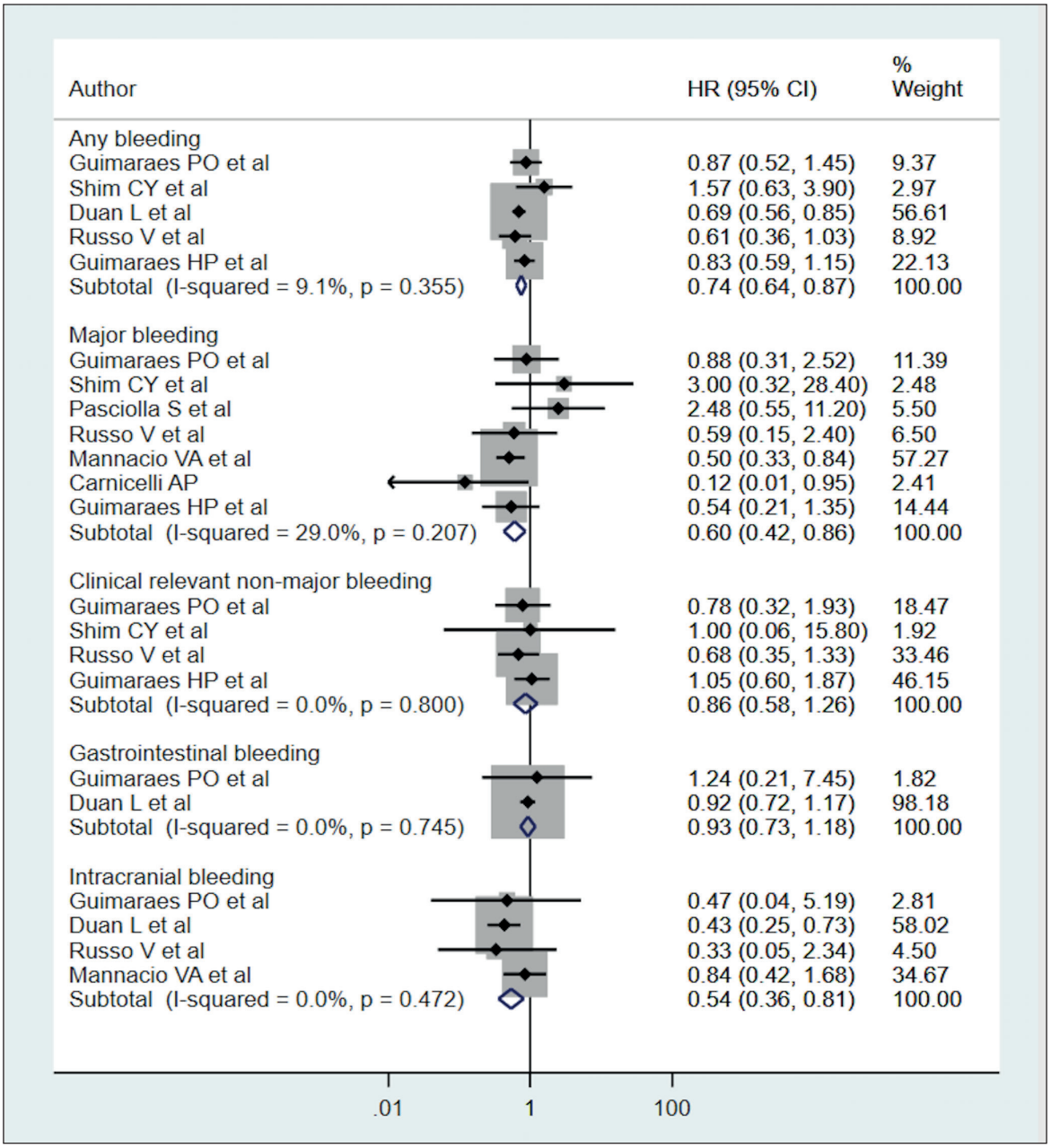

Figure 3. Pooled risk for bleeding related outcomes for comparisons between DOACs and warfarin.

Findings of Subgroup Analysis

Subgroup analysis was done for the primary outcomes, i.e., risk of stroke and bleeding. Further, this analysis was done based on the type of DOAC used and the study design (RCT or observational). For the "all-cause stroke", only apixaban [HR 0.58, 95% CI: 0.36, 0.94; N=3] and rivaroxaban [HR 0.25, 95% CI: 0.07, 0.88; N=1], compared to warfarin, were associated with reduced risk (Table II). No differences in the effect sizes were noted based on the study design. For "any bleeding", the reduced risk was noted only for dabigatran [HR 0.69, 95% CI: 0.56, 0.85; N=1] and observed only in studies that were observational/cohort in design [HR 0.68, 95% CI: 0.56, 0.82; N=2] (Table II). For "major bleeding", the reduced risk was observed for apixaban [HR 0.61, 95% CI: 0.41, 0.91; N=4] and in studies that were observational/cohort in design [HR 0.58, 95% CI: 0.38, 0.88; N=3]. In the subgroup analysis, a 49%

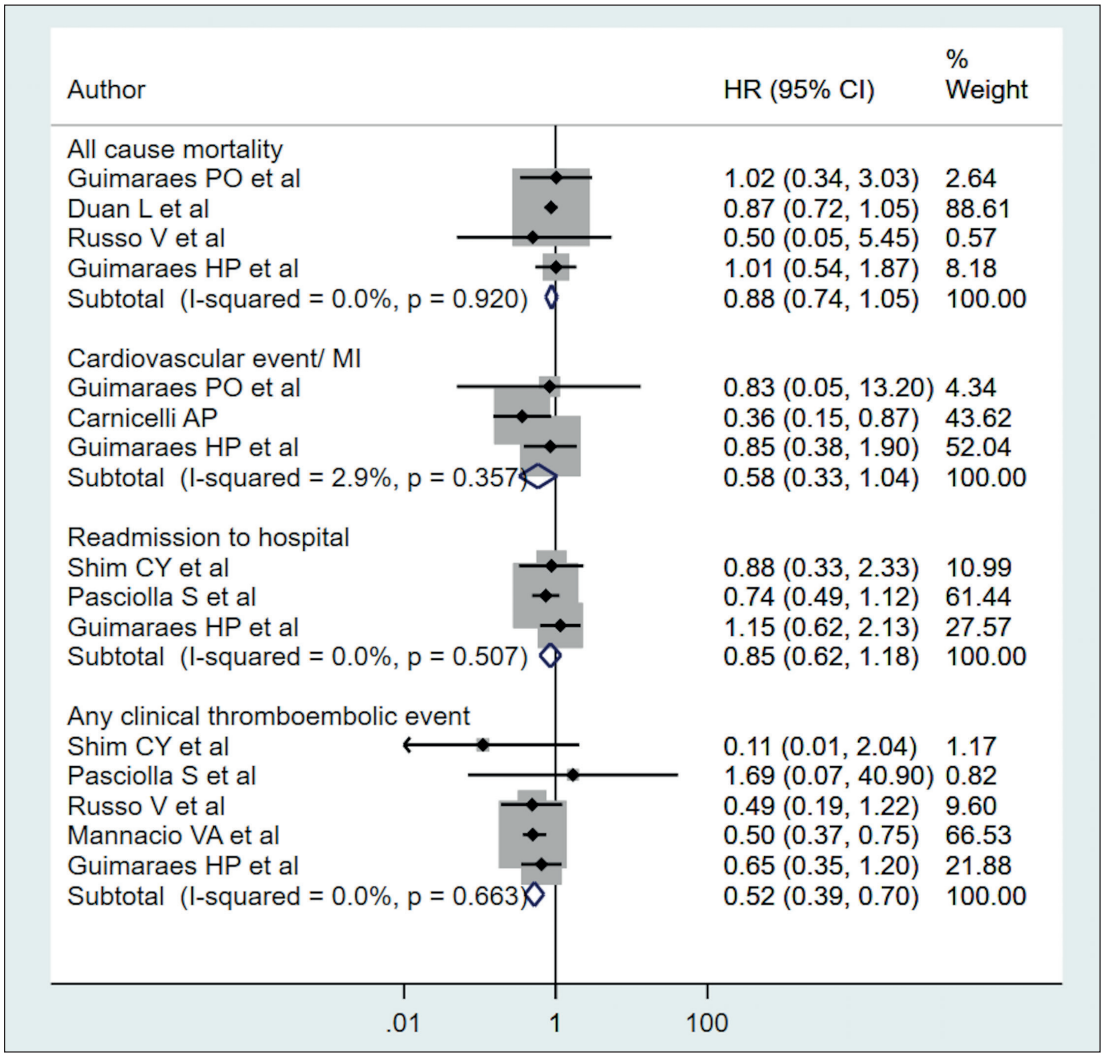

Figure 4. Pooled risk for all-cause mortality, cardiovascular events, readmission to hospital and clinically relevant thromboembolic events for comparisons between DOACs and warfarin.

Table II. Findings of the subgroup analysis.

Pooled effect size (Hazard ratio; HR) (95% Confidence Interval)						
	Direct-acting oral anticoagulants				Study design	
	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	RCT	Observational/ cohort based
All cause stroke	N = 3 0.58 (0.36, 0.94)*	N = 1 1.19 (0.96, 1.48)	N = 1 0.53 (0.16, 1.77)	N = 1 0.25 (0.07, 0.88)*	N = 3 0.54 (0.20, 1.45)	N = 3 0.86 (0.39, 1.89)
Any bleeding	N = 2 0.73 (0.51, 1.06)	N = 1 0.69 (0.56, 0.86)*	N = 1 1.57 (0.63, 3.91)	N = 1 0.83 (0.59, 1.15)	N = 2 0.89 (0.68, 1.16)	N = 2 0.68 (0.56, 0.82)*
Major bleeding	N = 4 0.61 (0.41, 0.91)*	---	N=2 0.61 (0.12, 3.04)	N=1 0.54 (0.21, 1.35)	N=4 0.66 (0.35, 1.25)	N=3 0.58 (0.38, 0.88)*
Any clinical thrombo-embolic event	N = 3 0.51 (0.36, 0.70)*	---	N = 1 0.11 (0.01, 1.57)	N = 1 0.65 (0.35, 1.20)	N = 2 0.59 (0.33, 1.08)	N = 3 0.51 (0.36, 0.70)*

*Denotes statistically significant.

reduction [HR 0.51, 95% CI: 0.36, 0.70; N=3] in the risk of clinically relevant thromboembolic event was noted for apixaban and only when cohort studies were pooled (Table II).

Discussion

While the safety and efficacy profile of DOACs is established through several studies[17,18,30,31], their role in patients with prosthetic valve, thrombi in left ventricle and in those with mitral stenosis is not studied well. For these patients, the main stay of treatment is still warfarin. However, a recent study[32], though retrospective in design, has shown that in patients with mitral stenosis, the use of DOACs, compared to warfarin, resulted in lower incidence of thromboembolic events and haemorrhagic episodes. The findings call for more clinical trials to test and document the efficacy and safety of DOACs, compared to warfarin, in patients where they are currently contraindicated. Currently, there is no indication of DOACs in the management of patients with prosthetic valve. The mainstay of medical management is the use of vitamin K antogonists along with low dose aspirin[33,34].

The current meta-analysis was conducted to compare the efficacy of DOACs, compared to vitamin K antagonists, in reducing the risk of stroke, thromboembolic events and bleeding in patients with atrial fibrillation and underwent bioprosthetic valve replacement or repair. The observed findings were supportive of use of DOACs in these patients. The risk of all-cause stroke, ischemic stroke, gastrointestinal bleeding, clinically relevant non-major bleeding, all-cause mortality and readmission rates were similar between the two groups i.e., DOACs and warfarin. On the other hand, use of DOACs led to a reduction in the risk of "any bleeding", major bleeding, intra-cranial bleeding, and any clinically relevant thrombo-embolic events. The findings are useful as they may increase the use of DOACs in clinical practice for patients with bioprosthetic valves and these patients may not need frequent monitoring, as is required with use of warfarin.

The subgroup analysis also provides some additional useful insights. The use of apixaban was associated with 42% reduced risk of stroke and 39% reduced risk of major bleeding. Similarly, dabigatran was associated with 31% reduced risk of "any" bleeding. A 49% reduction in the risk of clinically relevant thromboembolic event was noted for apixaban. It is important to note that all significant effect sizes were noted only when observational studies were pooled and not when randomized trials were pooled. Further, the number of studies for the subgroup analysis was very small. These may reduce the reliability of the evidence as there remains an uncertainty whether the adjusted analysis took into account all the potential confounders and addressed all the relevant biases. This calls for methodologically robust and large RCTs to be conducted to provide reliable evidence on this issue.

The current AHA/ACC guidelines recommend use of warfarin in patients with bioprosthetic valve mainly because the evidence on efficacy and safety profile for other anticoagulants in not available[35]. In general, DOACs have been known to have a better safety profile, less interaction with other drugs and food and their use does not necessarily require drug monitoring[15]. However, their efficacy for prevention of stroke, major bleeding and other thromboembolic events in patients with AF and bioprosthetic valve is not known. In this sense, the findings of the current meta-analysis are critical and lend support for the use of DOACs. There were certain limitations of this meta-analysis. Majority of the includes studies were observational in nature, some degree of bias in expected. Further, it is unclear whether the studies reported the adjusted effect sizes after adjustment for all potential confounders. For some of the included studies, the baseline comparability of the two groups was not established and therefore, the final outcomes could have been influenced by these baseline differences. For some of the outcomes, we observed a modest degree of heterogeneity. However, we attempted to understand the reasons for this by doing subgroup analysis. One of the critical limitations was that the meta-analysis protocol was not registered at PROSPERO or another dataset agency. Doing that would have brought more credibility to this review as the readers would have had the opportunity to compare this meta-analytic report with the elements of the registered protocol.

Conclusions

The findings of this meta-analysis, obtained through pooling of mostly observational studies, suggest that the use DOACs in patients with AF with bioprosthetic valve replacement or repair is comparatively better than vitamin K antagonists

in reducing the risk of bleeding and thrombo-embolic events. However, this evidence is mostly from observational studies with small sample sizes and therefore, future studies with a randomized design and larger sample sizes are needed to further substantiate these findings.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Not applicable.

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Availability of Data and Materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution
LT conceived and designed the study. SL, HS and JY collected the data and performed the literature search. LT was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethical Approval
Not applicable.

Patients Consent
Not applicable.

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