Risk of stroke with reduced dose direct oral anticoagulants vs standard dose anticoagulation after cardioversion of atrial fibrillation: A systematic review and meta-analysis

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BACKGROUND There is consensus on the safety of standard dose direct oral anticoagulants (DOACs) for stroke prevention in patients undergoing cardioversion of atrial fibrillation (AF), but outcomes of reduced dose DOACs in this setting remain unclear.

OBJECTIVE This systematic review and meta-analysis aimed to compare the rate of cardioversion-associated thromboembolic events between patients taking reduced dose DOACs and those receiving standard dose anticoagulation.

METHODS A systematic search was conducted for studies published between January 1, 2009, and February 16, 2024 in PubMed, Embase, and Cochrane Central Register of Controlled Trials. The included studies compared the rate of thromboembolic events in patients with AF undergoing cardioversion on reduced dose DOACs with the rate in those on standard dose anticoagulation. Odds ratios were pooled with a random effects model.

RESULTS We identified 2 randomized controlled trials and 8 cohort studies, which included 5212 patients with AF who underwent cardioversion on anticoagulation (1010 patients on reduced dose DOACs and 4202 patients on standard dose anticoagulation). Follow-up ranged from 3 hours to 90 days after cardioversion. There was a numerically higher rate of thromboembolic events in patients undergoing cardioversion on reduced dose DOACs than in those on standard dose anticoagulation (0.69% vs 0.29%; odds ratio 1.98; 95% confidence interval 0.72–5.45; $P = .19$; $I^2 = 0\%$); however, the difference was not statistically significant.

CONCLUSION Our systematic review and meta-analysis suggests that there is a numerically higher risk of thromboembolic events in patients with AF undergoing cardioversion on reduced dose DOACs than in those on standard dose anticoagulation. However, the difference was not statistically significant. These findings raise concern about the safety of reduced dose DOACs in patients undergoing cardioversion.

KEYWORDS Reduced dose DOACs; Standard dose anticoagulation; Cardioversion; Atrial fibrillation; Thromboembolic events

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KEY FINDINGS

- We identified a numerically higher incidence of thromboembolic events in patients on reduced dose direct oral anticoagulants (DOACs) undergoing cardioversion for atrial fibrillation than in those on standard dose DOACs.
- The lack of statistically significant difference in the odds of thromboembolic events between reduced and standard dose DOAC therapy may be due to insufficient power rather than a true lack of difference.
- Our results raise concern about the safety of reduced dose DOACs in patients undergoing cardioversion.

Introduction

There is an increased risk of thromboembolic events after chemical and electrical cardioversion of atrial fibrillation (AF) and atrial flutter (AFL). The risk of postcardioversion thromboembolic events has been found to significantly drop from 5%–7% to approximately 0.7% with uninterrupted anticoagulation therapy.[1,2] The efficacy of standard dose oral anticoagulation therapy in AF cardioversion has been well studied, and current consensus is that standard direct oral anticoagulants (DOACs) provide a safe and viable alternative to warfarin in this setting.[2–7] However, it is unclear whether reduced dose DOACs sufficiently prevent thromboembolic events in patients with AF undergoing cardioversion. This is particularly important as the prevalence of the use of reduced dose DOACs in patients with AF is approximately 20%.[8]

DOAC therapy at reduced doses is recommended on the basis of factors such as age, weight, and renal function.[1] Major landmark trials have demonstrated the effectiveness of reduced dose regimens in AF compared to warfarin, with lower bleeding risk compared to full dose regimens.[9–12] For patients who qualify for dose reduction, this approach has become the standard of care to minimize bleeding risks. Importantly, off-label underdosing of DOACs has been shown to be associated with an increased risk of stroke and systemic embolism, with no reduction in bleeding risk.[1,6,7,13]

Post hoc analyses of landmark trials investigating the outcomes of cardioversion of patients with AF have highlighted a potential increased risk of thromboembolic events in patients on reduced dose DOACs.[2,3] Subsequent observational studies have revealed efficacy of reduced dose DOACs similar to that of standard dose anticoagulation therapy. Given the lack of consensus, a systematic review of the literature is required to understand the safety of reduced dose DOACs in the setting of cardioversion. The aim of this systematic review and meta-analysis was to compare the rate of thromboembolic events between reduced dose DOACs and standard dose anticoagulation in patients with AF or AFL undergoing cardioversion.

Methods

Registration

The protocol for our study was registered with PROSPERO (CRD42024513348).

Literature search and data sources

A systematic search of the literature was conducted by 2 investigators (T.Q. and E.S.) in PubMed, Embase, and Cochrane Central Register of Controlled Trials for studies published between January 1, 2009, and February 16, 2024. The start date of 2009 was selected as it preceded the approval of DOACs for AF by regulatory bodies. The PubMed search strategy is available in Online Supplemental Appendix S1. Language was restricted to English only. All studies obtained from the search were reviewed manually in duplicate (T.Q. and E.S.) for inclusion. A gray literature search was conducted through databases (Scopus and OpenGrey), manual Web searches, and conference proceedings, in addition to ClinicalTrials.gov for ongoing trials. The reference lists of relevant articles, including systematic reviews and meta-analyses, were hand searched.

Study selection and quality assessment

The following inclusion criteria were applied: (1) studies must compare reduced dose DOACs with standard dose anticoagulation in patients cardioverted for AF or AFL and (2) studies must report on thromboembolic events, including ischemic stroke, transient ischemic attack, or systemic embolism. We excluded noncomparative trials, case reports, case series, systematic reviews, and meta-analyses. Abstracts were included, and although authors were contacted for additional data, no unpublished data were obtained. The selection of studies was assessed independently by 2 investigators (T.Q. and E.S.).

The quality of the primary studies was assessed in duplicate (T.Q. and E.S.). The Newcastle-Ottawa Scale was used to evaluate cohort studies on selection of study groups, comparability of study groups, and measurement of outcomes.[14] The Grading of Recommendations, Assessments, Development and Evaluations approach was used to evaluate the overall evidence of the randomized controlled trials (RCTs) and observational cohort studies for risk of bias, inconsistency, indirectness, imprecision, and publication bias.[15] A summary of the findings is provided in Online Supplemental Table S1.

Data extraction and outcome of interest

Two investigators (T.Q. and E.S.) independently extracted the following data from the included studies: study design, sample size, intervention, patient demographic data, outcome data, and definitions of outcomes. Disagreements were resolved through discussion and, when necessary, consultation with a third author (M.S.).

For our analysis, reduced dose DOACs included apixaban 2.5 mg twice daily, dabigatran 110 mg twice daily, edoxaban

Table 1 Summary of study characteristics

Study	Year	Type	No. of patients		Type of anticoagulation		Follow-up (d)	Definitions
			Reduced dose DOACs	Standard dose OAC	Reduced dose DOACs	Standard dose OAC		
Uziębło-Życzkowska et al[16]	2023	Prospective cohort	113	498	Apixaban 2.5 mg BID: 30 Dabigatran 110 mg BID: 52 Rivaroxaban 15 mg daily: 31	Apixaban 5 mg BID: 76 Dabigatran 150 mg BID: 200 Rivaroxaban 20 mg daily: 222	30	*Stroke:* sudden-onset new focal neurologic deficit in location consistent with the territory of the major cerebral artery, confirmed by imaging, with symptoms that persisted for at least 24 h *Systemic embolism:* acute vascular occlusion of an extremity or organ documented by imaging or surgery *TIA:* Brief episode of focal neurologic deficit with symptoms lasting <24 h
Schaeffer et al[17]	2018	Prospective cohort	93	992	Apixaban 2.5 mg BID: 14 Dabigatran 110 mg BID: 31 Rivaroxaban 15 mg daily: 48	Apixaban 5 mg BID: 41 Dabigatran 150 mg BID: 69 Rivaroxaban 20 mg daily: 292 Warfarin: 375 LMWH: 215	0.125	*Thromboembolic events:* clinically documented thromboembolic events
Russo et al[18]	2018	Prospective cohort	40	310	All dabigatran 110 mg BID	Dabigatran 150 mg BID: 135 Warfarin: 175	30	*Stroke:* clinically documented stroke *TIA:* clinically documented TIA *Systemic embolism:* clinically documented systemic embolism
Shibata et al[19]	2017	Retrospective cohort	87	316	Apixaban 2.5 mg BID: 9 Dabigatran 110 mg BID: 42 Rivaroxaban 15 mg daily: 36	Apixaban 5 mg BID: 25 Dabigatran 150 mg BID: 34 Warfarin: 257	30	Thromboembolic events: ischemic stroke or other embolic event such as renal infarction and acute limb ischemia
Plitt et al[3]	2016	RCT	111	254	All edoxaban 30 mg daily	Edoxaban 60 mg daily: 140 Warfarin: 114	30	*Stroke:* ischemic or hemorrhagic stroke *Systemic embolism:* any type of systemic embolism
Russo et al[20]	2016	Prospective cohort	7	70	All rivaroxaban 15 mg daily	All rivaroxaban 20 mg daily	90	*Stroke:* symptoms or clinical signs of stroke *Peripheral embolism*: symptoms or clinical signs of peripheral embolism
Russo et al[21]	2015	Prospective cohort	19	101	All dabigatran 110 mg BID	All dabigatran 150 mg BID	30	*Stroke:* ischemic or hemorrhagic stroke *Systemic embolism:* not defined

Mitamura et al[22]	2015	Retrospective cohort	93	102	All dabigatran 110 mg BID	Dabigatran 150 mg BID: 100 Warfarin: 2	30	*Stroke:* clinically documented stroke
Johansson et al[23]	2015	Retrospective cohort	34	702	All dabigatran 110 mg BID	Dabigatran 150 mg BID: 536 Warfarin: 166	30	*Thromboembolic events:* ischemic stroke and TIA
Nagarakanti et al[2]	2011	RCT	413	857	All dabigatran 110 mg BID	Dabigatran 150 mg BID: 421 Warfarin: 436	30	*Stroke:* sudden-onset focal neurologic deficit in location consistent with the territory of the major cerebral artery *Systemic embolism:* acute vascular occlusion of an extremity or organ documented by means of imaging, surgery, or autopsy

BID = twice daily; DOAC = direct oral anticoagulant; LMWH = low-molecular-weight heparin; OAC = oral anticoagulation; RCT = randomized controlled trial; TIA = transient ischemic attack.

30 mg daily, and rivaroxaban 15 mg daily.[9–12] Standard dose anticoagulation included standard dose DOACs (apixaban 5 mg twice daily, dabigatran 150 mg twice daily, edoxaban 60 mg daily, and rivaroxaban 20 mg daily), vitamin K antagonists, and therapeutic dose low-molecular-weight heparin. Our primary outcome was thromboembolic events, which was defined as ischemic stroke, transient ischemic attack, or systemic embolism, using individual trial outcome definitions (Table 1).

Statistical analysis

The RevMan (version 5) software package provided by the Cochrane Collaboration was used for combining outcomes from the individual studies and for statistical analysis.[24] Outcomes were pooled with the use of a random effects model as described by DerSimonian and Laird.[25] Summary estimates were reported as odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous variables. The heterogeneity between studies was assessed by means of Cochrane X^2 and I^2. $I^2 > 50\%$ was considered to represent significant heterogeneity.[26] Statistical significance was set as $P < .05$.

Results

Literature search and characteristics of the included studies

The literature search yielded 2179 studies (1078 from PubMed, 781 from Embase, 320 from Cochrane Central Register of Controlled Trials, and 21 from other sources, including gray literature and reference lists). Duplicates were removed, and 1333 studies were excluded during title and abstract review. The remaining 98 studies were assessed in full text. Figure 1 summarizes the literature search and study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards.[27]

Ten studies met inclusion criteria and were included in the meta-analysis. We included 2 post hoc analyses of RCTs,[2,3] 5 prospective cohort studies,[16–18,20,21] and 3 retrospective cohort studies.[19,22,23] Four studies compared reduced dose dabigatran with standard dose anticoagulation,[2,18,22,23] 1 compared reduced dose dabigatran with standard dose dabigatran,[21] 1 compared reduced dose rivaroxaban with standard dose rivaroxaban,[20] 1 compared reduced dose edoxaban with standard dose anticoagulation,[3] and 3 compared reduced dose apixaban, dabigatran, and rivaroxaban with standard dose anticoagulation.[17,16,19] Follow-up ranged from 3 hours to 90 days after cardioversion. Studies had variable definitions of outcomes, which are summarized in Table 1. The quality of cohort studies was assessed using the Newcastle-Ottawa Scale in Table 2.[14]

Baseline characteristics of patients

The 10 studies included a total of 5212 patients who underwent cardioversion on anticoagulation and were included in our analysis.[2,3,16–23] A reduced dose DOAC was used in 1010 patients. Standard dose anticoagulation was used in 4202 patients. None of our included studies compared

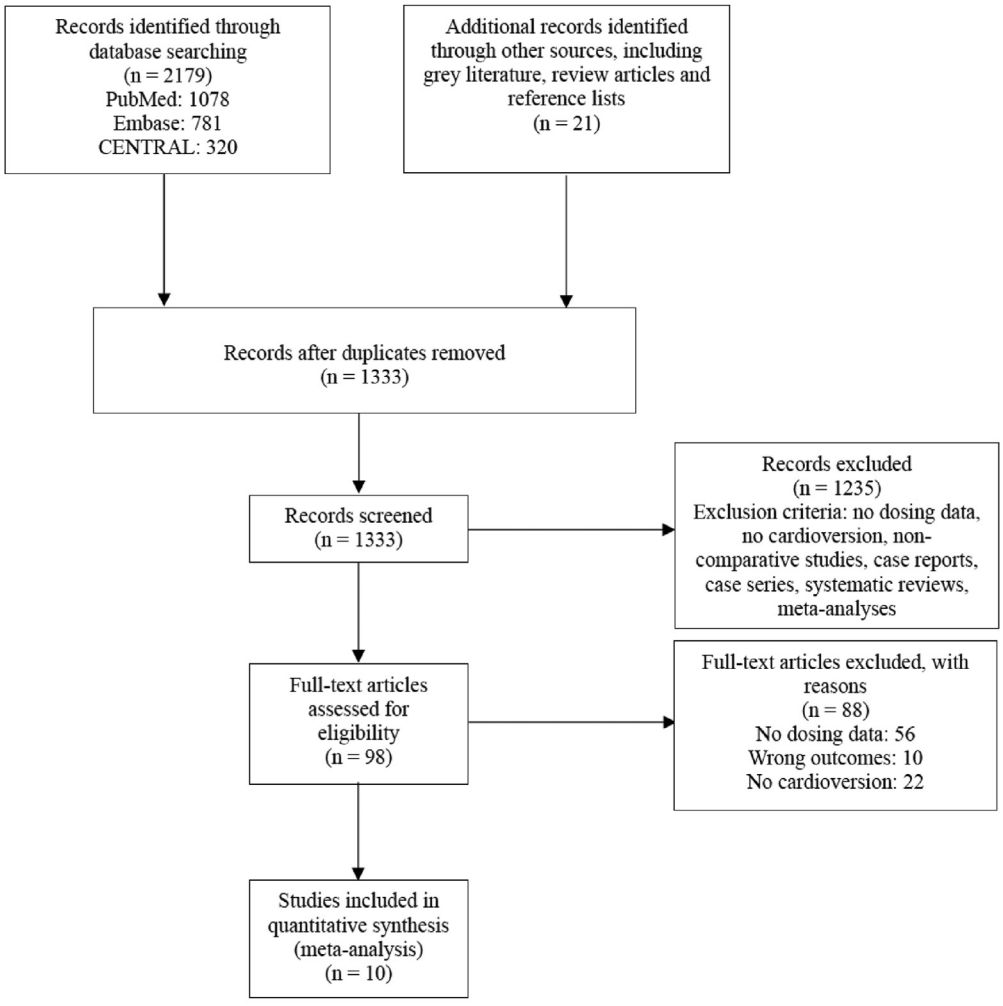

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of literature search and study selection. CENTRAL = Cochrane Central Register of Controlled Trials.

demographic data for patients who underwent cardioversion on reduced dose DOACs vs those on standard dose anticoagulation. Of the included studies, Schaeffer et al[17] reported that the time in therapeutic range for 70.7% of patients on warfarin was 59.8% ± 29.5%.Click or tap here to enter text. The baseline characteristics of patients included in each primary study are summarized in Online Supplemental Table S2.

Outcomes

Thromboembolic events occurred in 7 patients (0.69%) who underwent cardioversion on reduced dose DOACs and 12 patients (0.29%) on standard dose anticoagulation. In comparison to standard dose anticoagulation, there was a numerically higher rate of thromboembolic events in those cardioverted on reduced dose DOACs; however, the difference was not statistically significant (OR 1.98; 95% CI 0.72–5.45; $P = .19$; $I^2 = 0\%$) (Figure 2).

We performed separate analyses for RCTs[2,3] and observational studies.[16–23] Similar results were observed in RCTs (OR 2.48; 95% CI 0.25–24.63; $P = .17$; $I^2 = 47\%$) and observational studies (OR 2.11; 95% CI 0.53–8.42; $P = .87$; $I^2 = 0\%$) (Figure 3).

Discussion

In this meta-analysis, there was a numerically higher rate of thromboembolic events in patients with AF undergoing cardioversion on reduced dose DOACs than in those on standard dose anticoagulation; however, the difference was not statistically significant. Moreover, the crude rate of thromboembolic events was overall low.

The current consensus is that standard dose DOACs are comparable with vitamin K antagonists in reducing the risk of cardioversion-associated thromboembolic events in patients with AF.[1,4,28] This is supported by X-VeRT, EMANATE, and ENSURE-AF, which demonstrated rates

Table 2 Risk of bias assessment of cohort studies

Study	Selection					Comparability	Outcome			
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of the study	Comparability of cohorts based on design or analysis	Assessment of the outcome	Follow-up duration adequate	Adequacy of follow-up	*Total score*
Uziębło-Życzkowska et al[16]	*	*	*	*			*	*	*6*
Schaeffer et al[17]	*	*	*	*		*	*	*	*6*
Russo et al[18]	*	*	*	*	**	*	*	*	*9*
Shibata et al[19]	*	*	*			*	*	*	*6*
Russo et al[20]	*	*	*	*			*	*	*6*
Russo et al[21]	*	*	*	*			*	*	*6*
Mitamura et al[22]	*	*	*			*	*	*	*6*
Johansson et al[23]	*		*			*	*	*	*5*

Asterisks indicate the star rating according to the Newcastle-Ottawa Scale for cohort studies. A study can be awarded a maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for outcome.

of thromboembolic events in patients on DOACs similar to those on warfarin. While these 3 RCTs included patients on reduced dose DOACs, outcomes were not reported specifically for the reduced dose groups.[5–7]

RE-LY and ENGAGE-AF-TIMI 48 are the only RCTs that have reported outcomes for patients with AF undergoing cardioversion on reduced dose DOACs.[2,3] The post hoc analysis of RE-LY compared reduced dose and standard dose dabigatran with warfarin. The rate of thromboembolic events was 0.48% in the reduced dose dabigatran group and a combined rate of 0.47% in the standard dose anticoagulation group, including standard dose dabigatran and warfarin.[2] The post hoc analysis of ENGAGE-AF-TIMI 48 compared reduced dose and standard dose edoxaban with warfarin in patients with AF undergoing cardioversion. Cardioversion-associated thromboembolic events occurred in 2 patients on reduced dose edoxaban, whereas none occurred in patients on standard dose edoxaban or warfarin.[3] The low event rates highlight the need for larger studies. Neither study was adequately powered to demonstrate differences in thromboembolic events around the time of cardioversion.[2,3]

Kim et al[29] conducted a single-center cohort study comparing 180 patients on warfarin with 164 patients on DOACs undergoing cardioversion for AF/AFL. All patients underwent transesophageal echocardiography (TEE) before cardioversion. Twenty-two of the patients were on reduced dose DOACs, and the study found a higher prevalence of spontaneous echocardiographic contrast and thrombus on TEE in the reduced DOAC group than in the standard dose DOAC group (68.2% vs 42.5%; $P = .019$).

Our systematic review identified 2 RCTs and 8 cohort studies. We found a numerically higher rates of thromboembolic events in the reduced DOAC group (7 of 1010 [0.69%]) than in the standard dose anticoagulation group (12 of 4202 [0.29%]). Patients prescribed reduced dose DOACs for cardioversion may be exposed to a higher thromboembolic risk, given the higher incidence of thromboembolic events. While the difference did not meet statistical significance, this raises concern regarding the safety of reduced DOACs in the pericardioversion period. Further, the event rate in the reduced DOAC group was comparable to that seen in the Finnish CardioVersion study, where the incidence of cardioversion-associated thromboembolic events was 0.7% in patients not receiving any form of anticoagulation.[30]

While Schaeffer et al[17] reported only outcomes within 3 hours,Click or tap here to enter text. most strokes occur between 2 and 3 days after cardioversion.[1] Only 4 included studies reported on timing of stroke, which ranged from 1 to 26 days postcardioversion. Six of the 11 studies that reported on timing occurred within 3 days of cardioversion.[18,19,22,23]

Given the concern for possible increased thromboembolic events in those on reduced dose DOACs, a risk stratification strategy would be useful. One possible risk stratification tool is the CHADS-VASc score.[31] The Finnish CardioVersion study included 7660 cardioversions for acute (<48 hours) AF, where the majority (71%) were not anticoagulated.

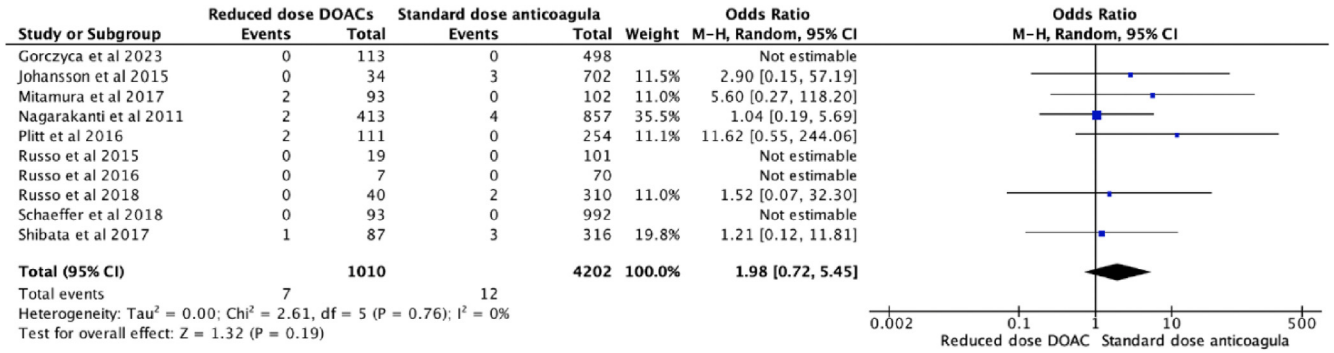

Figure 2 Forest plot of the individual and combined rates of thromboembolic events. CI = confidence interval; df = degree of freedom; DOAC = direct oral anticoagulant; M-H = Mantel-Haenszel.

Age, female sex, heart failure, and diabetes were independent predictors of thromboembolic events after cardioversion.[30] A cohort study of 1299 patients by Garg et al[31] provides additional support for using the CHADS-VASc score to risk stratify patients on reduced dose DOACs around the time of cardioversion.Click or tap here to enter text. No thromboembolic events in patients on no, subtherapeutic, and therapeutic anticoagulation before cardioversion occurred in those with CHADS-VASc scores below 2. Therefore, in patients on reduced dose DOACs before cardioversion, the CHADS-VASc score can be used to inform risk of postcardioversion thromboembolic events. Accordingly, in those on reduced dose DOACs with a high risk of thromboembolic events, it may be reasonable to use a short course (3–4 weeks) of full dose DOACs with or without TEE before cardioversion.[1]

Our meta-analysis has several strengths. To our knowledge, this is the first systematic review and meta-analysis comparing reduced dose DOACs with standard dose anticoagulation for cardioversion of AF/AFL. Our study pooled data from 10 studies and 5212 patients, 1010 of whom underwent cardioversion on reduced dose DOACs. Although several reviews have assessed the efficacy of DOACs in the cardioversion setting, none have specifically reported on outcomes for patients on reduced dose DOACs.[4,13,28]

Limitations

The limitations of our meta-analysis are largely related to the included studies, which reflect the sparsity of the literature on the use of reduced dose DOACs for cardioversion. Most included studies were retrospective studies, which have inherent biases and did not report adjusted events. Consequently, our meta-analysis is limited to unadjusted event rates. Only 2 studies reported on international normalized

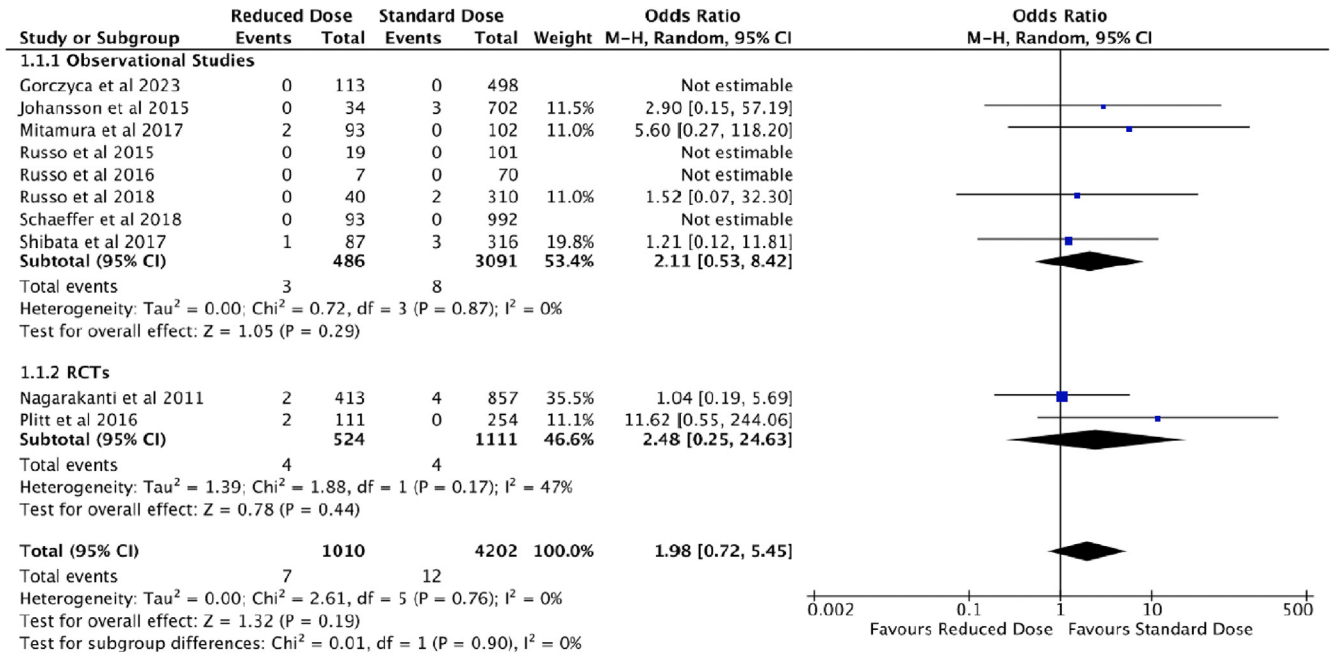

Figure 3 Forest plot of the individual and combined rates of thromboembolic events for observational studies and RCTs. CI = confidence interval; df = degree of freedom; M-H = Mantel-Haenszel; RCT = randomized controlled trial.

ratio levels in the pericardioversion period for patients on warfarin. This is an important consideration as 2 of the 3 patients with a primary outcome in the warfarin group had an international normalized ratio of less than 2.[17,19] In addition, the studies did not report baseline characteristics for standard dose vs reduced dose DOACs specifically, but rather for all patients on DOACs instead. Only 2 of the included observational studies reported details on the appropriateness of reduced dose DOAC use.[17,19] Of these, Shibata et al [19] is the only study in which all patients were dosed according to drug manufacturer labels. In the other study, 58% of patients were prescribed reduced dose dabigatran on the basis of manufacturer labels; however, the remaining 42% were prescribed a reduced dose on the basis of physician preference.[17] Therefore, the appropriateness of reduced dosing remains unclear, and the higher rate of thromboembolic events in the reduced dose DOAC group could be a result of off-label use of reduced dose therapy. Furthermore, TEE was used inconsistently, and this could affect our results. All included patients underwent elective cardioversion, and hence the results may not apply to those undergoing acute cardioversion. Finally, given the very low event rates and small sample size, the negative statistical findings may be due to insufficient power rather than a true lack of difference. A future study with a large sample size and adequately powered analysis should be considered to examine whether there is any true difference in clinical outcomes.

Conclusion

This meta-analysis identified a numerically higher rate of thromboembolic events in patients with AF/AFL undergoing cardioversion on reduced dose DOACs compared to standard dose anticoagulation; however, the difference was not statistically significant. This finding raises possible concern regarding the use of reduced dose DOACs in the cardioversion period. Given low event rates, larger studies are required to evaluate this further.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Ethics Statement: The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards.

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