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ORIGINAL RESEARCH

Thromboembolic events following cardioversion of acute atrial fibrillation and flutter: a systematic review and meta-analysis

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Abstract

Background Recent studies have presented concerning data on the safety of cardioversion for acute atrial fibrillation and flutter. We conducted this meta-analysis to evaluate the effect of oral anticoagulation use on thromboembolic events post-cardioversion of low-risk acute atrial fibrillation and flutter patients of < 48 h in duration.

Methods We searched MEDLINE, Embase, and Cochrane from inception through February 6, 2020 for studies reporting thromboembolic events post-cardioversion of acute atrial fibrillation and flutter. Main outcome was thromboembolic events within 30 days post-cardioversion. Primary analysis compared thromboembolic events based on oral anticoagulation use versus no oral anticoagulation use. Secondary analysis was based on baseline thromboembolic risk. We performed meta-analyses where 2 or more studies were available, by applying the DerSimonian-Laird random-effects model. Risk of bias was assessed with the Quality in Prognostic Studies tool.

Results Of 717 titles screened, 20 studies met inclusion criteria. Primary analysis of seven studies with low risk of bias demonstrated insufficient evidence regarding the risk of thromboembolic events associated with oral anticoagulation use (RR = 0.82 where RR < 1 suggests decreased risk with oral anticoagulation use; 95% CI 0.27 to 2.47; $I^2 = 0\%$). Secondary analysis of 13 studies revealed increased risk of thromboembolic events with high baseline thromboembolic risk (RR = 2.25 where RR > 1 indicates increased risk with higher $CHADS_2$ or CHA_2DS_2-VASc scores; 95% CI 1.25 to 4.04; $I^2 = 0\%$).

Conclusion Primary analysis revealed insufficient evidence regarding the effect of oral anticoagulation use on thromboembolic events post-cardioversion of low-risk acute atrial fibrillation and flutter, though the event rate is low in contemporary practice. Our findings can better inform patient-centered decision-making when considering 4-week oral anticoagulation use for acute atrial fibrillation and flutter patients.

Keywords Atrial fibrillation · Cardioversion · Thromboembolism · Meta-analysis

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Résumé

Contexte Des études récentes ont présenté des données sur la sécurité de la cardioversion pour la fibrillation auriculaire aiguë et le flutter. Nous avons mené cette méta-analyse pour évaluer l'effet de l'utilisation de l'anticoagulation orale sur les événements thromboemboliques post-cardioversion de patients atteints de fibrillation auriculaire aiguë à faible risque et de flutter de moins de 48 heures.

Les méthodes Nous avons recherché dans MEDLINE, Embase et Cochrane depuis le début jusqu'au 6 février 2020 des études faisant état d'événements thromboemboliques après une cardioversion de la fibrillation auriculaire aiguë et du flutter. Le principal résultat a été des événements thromboemboliques dans les 30 jours suivant la cardioversion. L'analyse primaire a comparé les événements thromboemboliques basés sur l'utilisation de l'anticoagulation orale par rapport à l'absence d'anticoagulation orale. L'analyse secondaire était basée sur le risque thromboembolique de base. Nous avons effectué des méta-analyses lorsque deux études ou plus étaient disponibles, en appliquant le modèle à effets aléatoires DerSimonian-Laird. Le risque de biais a été évalué avec l'outil *Quality in Prognostic Studies*.

Résultats Sur les 717 titres examinés, 20 études ont répondu aux critères d'inclusion. L'analyse primaire de sept études présentant un faible risque de biais a démontré l'insuffisance des preuves concernant le risque d'événements thromboemboliques associés à l'utilisation d'anticoagulation orale (RR = 0,82 où RR < 1 suggère une diminution du risque avec l'utilisation d'anticoagulation orale ; IC 95 % 0,27 à 2,47 ; I2 = 0 %). L'analyse secondaire de 13 études a révélé un risque accru d'événements thromboemboliques avec un risque thromboembolique de base élevé (RR = 2,25 où RR > 1 indique un risque accru avec des scores CHADS2 ou CHA2DS2-VASc plus élevés ; 95 % CI 1,25 à 4,04 ; I2 = 0 %).

Conclusions L'analyse primaire a révélé des preuves insuffisantes concernant l'effet de l'utilisation de l'anticoagulation orale sur les événements thromboemboliques après une cardioversion de fibrillation auriculaire aiguë à faible risque et de flutter, bien que le taux d'événements soit faible dans la pratique contemporaine. Nos conclusions peuvent mieux éclairer la prise de décision centrée sur le patient lorsqu'il s'agit d'envisager l'utilisation de l'anticoagulation orale pendant 4 semaines pour les patients souffrant de fibrillation auriculaire aiguë et de flutter.

Clinicians' capsule

What is known about this topic?

Recent studies have presented concerning data on the safety of cardioversion of acute atrial fibrillation and flutter.

What did this study ask?

What was the effect of oral anticoagulation use on thromboembolic events at 30 days following cardioversion of acute atrial fibrillation and flutter?

What did this study find?

Our meta-analysis found insufficient evidence regarding the effect of oral anticoagulation use on thromboembolic events, however the event rate appears low.

Why does this study matter to clinicians?

Our findings can better inform patient-centered decision-making when considering 4-week oral anticoagulation use for acute atrial fibrillation and flutter patients.

Introduction

Background

Acute atrial fibrillation and flutter are the most common arrhythmias requiring care in the emergency department (ED) [1–3]. In recent years, there has been a shift towards increased use of rhythm control in managing episodes of < 48 h in duration [4–11]. Typically, this involves early restoration of sinus rhythm through electrical or pharmacological cardioversion, discharge home, and prescription of oral anticoagulation for patients with risk factors for stroke. Patients presenting with acute atrial fibrillation and flutter of < 48 h in duration have long been considered to be at low theoretical risk of thromboembolism following cardioversion, as demonstrated in various studies evaluating short-term outcomes post-cardioversion of acute atrial fibrillation and flutter [4–9, 12–19].

Importance

Several recent observational studies have presented concerning data on the safety of cardioversion in acute atrial fibrillation and flutter patients with regard to thromboembolic risk [20–25]. Together, these findings have led to various amendments in recent atrial fibrillation and flutter guidelines from major international societies regarding oral anticoagulation use following cardioversion [26–31]. The 2018 Canadian Cardiovascular Society Guidelines recommend all acute atrial fibrillation and flutter patients who undergo cardioversion receive 4 weeks of oral anticoagulation following cardioversion, including those without risk factors for stroke [27]. The 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society Atrial Fibrillation Guidelines recommend patients with a CHA_2DS_2-VASc

[**C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge 65–74, **S**ex (Female)] score of 0 or 1 do not require post-cardioversion OAC [26]. The 2020 European Society of Cardiology Guidelines for the Management of Atrial Fibrillation recommend that 4 weeks of post-cardioversion anticoagulation may be omitted in patients presenting with atrial fibrillation < 24 h and who have low baseline stroke risk (CHA_2DS_2-VASc = 0 in men and 1 in women) [28]. These recommendations are considered Class IIb or "weak based upon low-quality evidence" according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards [32]. With such a recommendation, the decision for prescribing oral anticoagulation post-cardioversion should be patient-centered.

Goals of this investigation

We conducted this meta-analysis to evaluate the effect of oral anticoagulation on thromboembolic events following cardioversion of low-risk acute atrial fibrillation and flutter patients (defined as those presenting with episodes of < 48 h). Specifically, we were interested in comparing oral anticoagulation use versus no oral anticoagulation use with respect to thromboembolic events (i.e. stroke, transient ischemic attack, or systemic thromboembolism) within 30 days post-cardioversion of acute atrial fibrillation and flutter.

Methods

Protocol

This systematic review and meta-analysis were conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and CHARMS (Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies) guidelines for the reporting of systematic reviews [33, 34]. The study protocol was registered with PROSPERO (CRD42019137603).

Data sources and search strategy

The search strategy was developed with guidance from a professional health sciences research librarian. We conducted a comprehensive search of EMBASE, Ovid MEDLINE, and Cochrane Central Register of Controlled Trials from inception to February 6, 2020 (Table S1). Database searches were supplemented by manually screening reference lists of included studies.

Study selection

Studies were eligible if they: (1) included adults ≥ 18 years with acute atrial fibrillation and flutter (i.e. clear symptom onset < 48 h, clear onset < 7 days and receiving appropriate anticoagulation, or clear onset < 7 days with no left atrial thrombus on transesophageal echocardiography) who underwent electrical or pharmacological cardioversion; (2) reported thromboembolic events (i.e. stroke, transient ischemic attack, or systemic thromboembolism) within 30 days following cardioversion; and (3) were observational studies, case series, or randomized controlled trials. Only English records with full-text articles were included. Commentaries, editorials, letters, case reports, systematic reviews, meta-analyses, clinical guidelines, laboratory data, conference abstracts, and studies on patients with valvular heart disease or those without recent-onset atrial fibrillation or flutter (i.e. permanent or persistent) were excluded.

We screened studies using Covidence (Melbourne, Australia) software. Titles were imported into Covidence directly and duplicates removed. Two investigators (B.M.W. and either B.Z. or K.G.) independently reviewed titles and abstracts. Eligible studies were reviewed in full text for potential inclusion. Disagreements were resolved by consensus and did not require third-party adjudication. Investigators were not blinded to study title or authors during the selection process. For studies with incomplete data, a minimum of two attempts were made to obtain further information from the corresponding author, after which the study was excluded if relevant data were not received. The kappa statistic was calculated to determine agreement for full-text review.

Data extraction

Data extraction was conducted by two investigators (B.M.W. and either B.Z. or K.G.) independently using a customized data collection form. The following information was extracted: first author, publication year, study design, setting, study population, number of cardioversions, baseline characteristics, thromboembolic events, oral anticoagulation status, length of follow-up, and $CHADS_2$ (**C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack) or CHA_2DS_2-VASc scores. Any disagreements were resolved by consensus. Of articles that represented duplicated data of the same study population, the study most relevant to our review inclusion criteria and one with the greatest number of cases was selected.

Outcomes

The primary outcome was thromboembolic events (i.e. stroke, transient ischemic attack, or systemic

thromboembolism) at 30 days following cardioversion of acute atrial fibrillation and flutter.

Quality assessment

Risk of bias was assessed by two investigators (B.M.W. and either B.Z. or K.G.) using the Quality in Prognostic Studies (QUIPS) tool [35]. This tool identifies six domains when assessing bias in prognostic studies: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting (Table S2). Each domain was rated as having high, moderate, or low risk of bias. Studies with a low risk of bias in four or more domains were considered to be of high quality.

Statistical analysis

We performed pairwise meta-analyses for thromboembolic events where two or more studies were available, by applying a variation of the inverse-variance random-effects model [36]. We implemented analyses stratified based on study design using Open MetaAnalyst and forest plots were generated. The primary analysis compared thromboembolic events based on oral anticoagulation use versus no oral anticoagulation use for studies with a low risk of bias. Specifically, we compared thromboembolic events in patients who were anticoagulated (defined as (1) on oral anticoagulation before and after cardioversion; or (2) started on oral anticoagulation after cardioversion) to those who were non-anticoagulated (neither anticoagulated before nor after cardioversion). Relative risk (RR) comparing oral anticoagulation use versus no oral anticoagulation use for thromboembolic events was determined, with RR > 1 indicating an increased risk of thromboembolic events with oral anticoagulation use and RR < 1 suggesting decreased risk with oral anticoagulation use. The secondary analysis included thromboembolic events based on high versus low baseline thromboembolic risk according to $CHADS_2$ or CHA_2DS_2-VASc scores and duration of acute atrial fibrillation and flutter onset. Studies were excluded from the meta-analysis if they only reported overall thromboembolic events and did not compare oral anticoagulation use versus no oral anticoagulation use, or high versus low $CHADS_2$ or CHA_2DS_2-VASc scores. Low baseline risk for thromboembolism was defined as a $CHADS_2$ score of 0 or a CHA_2DS_2-VASc score of 0 or 1, while high risk was defined as a $CHADS_2$ score ≥ 1 or CHA_2DS_2-VASc score ≥ 2. Heterogeneity was assessed using the I^2 statistic, the Chi-squared test for homogeneity, and visual inspection of the forest plots. In addition, we conducted four sensitivity analyses, two of which were a priori analyses based on study design, and two of which were post-hoc analyses.

Results

Study selection

Our initial search retrieved 717 citations after the removal of duplicates, of which 79 full-text articles were reviewed (Fig. 1). Following full-text review, 59 articles were excluded (Table S3), yielding 20 articles in the final review (Table S4). Agreement between reviewers for full-text review was good (kappa = 0.80).

Study characteristics

Baseline characteristics of the 20 studies (8 prospective cohort, 8 retrospective cohort, and 4 randomized trials) are outlined in Table 1. The majority of studies (i.e. 13/20) exclusively evaluated patients with acute atrial fibrillation and flutter of < 48 h in duration. The remaining 7 studies included both patients with an onset time of < 48 h and > 48 h on anticoagulation, from which 2 studies included an identifiable breakdown of < 48 h versus < 7 days on appropriate anticoagulation. Of the 20 included studies, the number of cardioversions ranged from 23 to 7660, the prevalence of female sex varied from 23.0 to 59.4%, and use of electrical cardioversion ranged from 24.6 to 100%. Overall incidence of thromboembolic events at 30 days post-cardioversion was 0.42% (61 events/14,410 cardioversions). A total of 12 studies reported thromboembolic events based on oral anticoagulation use versus no oral anticoagulation use [9, 13, 16, 19, 22, 37–43]. The remaining eight studies only reported the overall incidence of thromboembolic events and were therefore excluded from the primary meta-analysis [4, 7, 8, 12, 17, 18, 44, 45]. The thromboembolic event rate for these eight studies ranged up to 0.5%. A total of 13 studies reported thromboembolic events based on baseline thromboembolic risk according to $CHADS_2$ and CHA_2DS_2-VASc scores [8, 18, 19, 22, 37–45].

Quality assessment

In total, 60.8% of all domains showed a low risk of bias, 35.8% showed a moderate risk of bias, and 3.3% showed a high risk of bias (Table 2). In the "study participation" domain, five studies [4, 9, 12, 13, 18] had a moderate risk for bias and one study [16] was at high risk. Eleven studies had a moderate risk of bias in the "study attrition" domain [7, 12, 16–18, 22, 37, 38, 40, 41, 45]. In the "prognostic factor measurement" domain, ten studies [4, 8, 9, 12, 13, 17, 22, 37, 43, 45] were at moderate risk and one study [16] was at high risk for bias, due to inadequate reporting of oral anticoagulation or no $CHADS_2$ or CHA_2DS_2-VASc data. In the "outcome measurement" domain, two studies [39, 43]

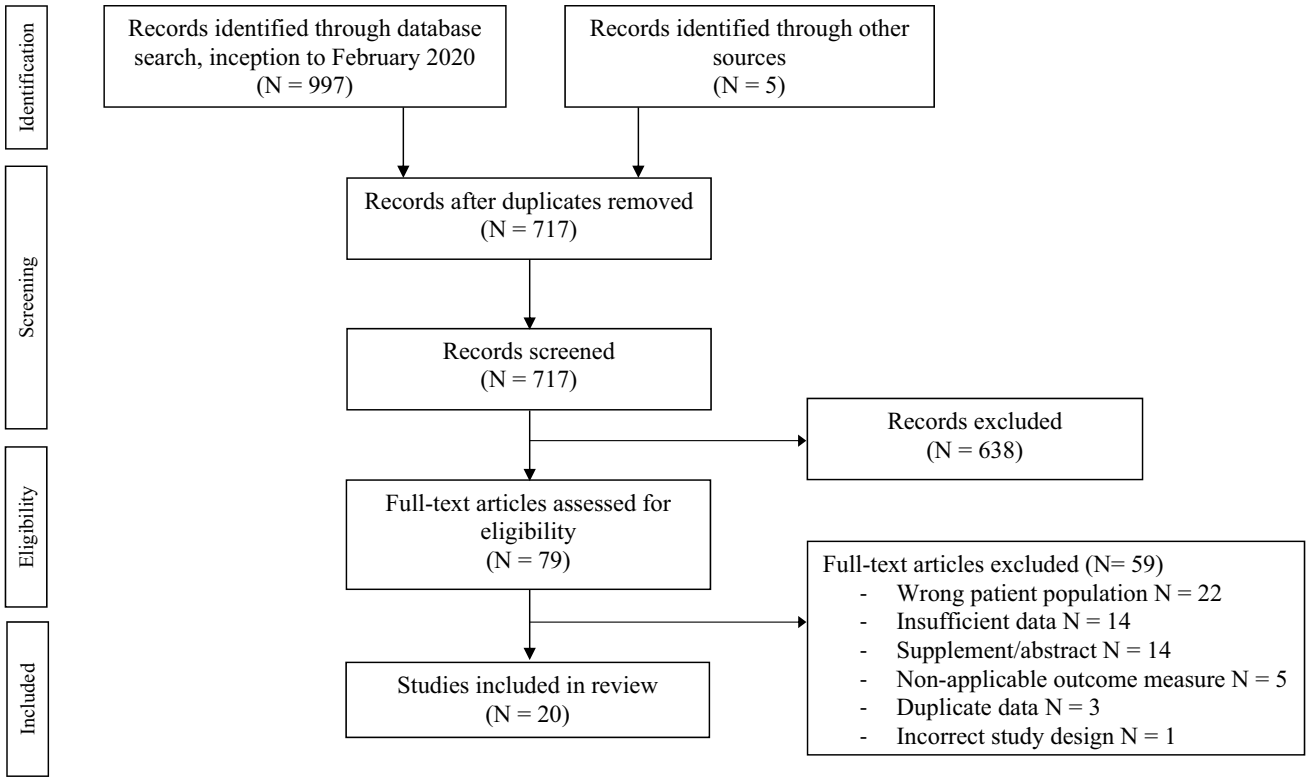

Fig. 1 Flow diagram summarizing database search and study selection

had a moderate risk of bias and one study [16] was at high risk. In the "study confounding" domain, fourteen studies [4, 7–9, 12, 13, 17, 18, 22, 38, 40, 41, 44, 45] had moderate risk and one study [16] had a high risk of bias. All studies except one had a low risk of bias in the "statistical analysis and reporting" domain [16].

Primary analysis

Primary analysis was conducted on seven studies (2 prospective cohort, 2 randomized trials, and 3 retrospective) reporting thromboembolic events at 30 days and considered high-quality according to the QUIPS tool (Fig. 2). Meta-analysis of these seven studies revealed insufficient evidence regarding the effect of oral anticoagulation use on thromboembolic events post-cardioversion (RR = 0.82, 95% CI 0.27–2.47; $I^2 = 0\%$). The rate of thromboembolic events was low in both groups, irrespective of whether oral anticoagulation was used or not. In the oral anticoagulation group, there were 3 thromboembolic events/1380 cardioversions, compared to 6 events/1788 cardioversions in the no oral anticoagulation group. All 9 thromboembolic events in the primary analysis were in patients who had an onset of < 48 h, received electrical cardioversion, and had a CHA_2DS_2-VASc score ≥ 2 (Table S5). Of note, there were no thromboembolic events at 30 days post-cardioversion in 783 cases not receiving oral anticoagulation within the prospective subgroup.

To complement the primary analysis which was restricted to studies with a low risk of bias, we also performed two a priori sensitivity analyses based on the study design of all 12 studies reporting thromboembolic events based on oral anticoagulation use versus no oral anticoagulation use. In Figure S1, meta-analysis of six prospective studies [9, 16, 19, 37–39] also revealed insufficient evidence regarding the risk of thromboembolic events associated with oral anticoagulation use (RR = 2.15, 95% CI 0.50–9.30; $I^2 = 0\%$). In Figure S2, meta-analysis of six retrospective studies [13, 22, 40–43] indicated a statistically significant protective effect of oral anticoagulation use on decreased thromboembolic events (RR = 0.34, 95% CI 0.17–0.72; $I^2 = 0\%$). With the retrospective subgroup, the results were heavily weighted by the results of one study, Gronberg et al. [22], which accounted for many of the total cardioversions and 47 out of the 56 events. Given this study was considered high risk of bias according to the QUIPS tool, we performed a post-hoc sensitivity analysis excluding this study, which did not reveal a significant difference in thromboembolic events according to oral anticoagulation use (RR = 0.50, 95% CI 0.15–1.65; $I^2 = 0\%$) (Figure S3).

Table 1 Baseline characteristics and thromboembolic events at 30 days following cardioversion in the 20 included studies

Study	Study design	No. of CVs	Age (y), mean ± SD	Female (%)	ECV (%)	Success of CV (%)	Total	OAC use	No OAC use	High risk for TE events[a]	Low risk for TE events[b]
							TE events/Total CVs	TE events/Total CVs	TE events/Total CVs	TE events/Total CVs	TE events/Total CVs
Bonfanti et al. [40]	Retrospective cohort	419	61.1 ± 13.1	31.0	100	96.2	0/419	0/349	0/70	0/209	0/210
Cristoni et al. [17]	Prospective cohort	403	–	56.5	24.6	58.6	1/403	–	–	–	–
Decker et al. [4]	RCT	56	–	–	100	–	0/56	–	–	–	–
Gallagher et al. [13]	Retrospective cohort	443	–	–	100	–	1/443	0/91	1/352	–	–
Garg et al. [41]	Retrospective cohort	1581	–	–	100	–	8/1581	2/898	6/683	8/1084	0/497
Gronberg et al. [22]	Retrospective cohort	7660	62.2 ± 12.3	36.5	90.0	94.5	47/7660	5/2298	42/5362	31/4298[d]	10/3362[d]
Jacoby et al. [16]	Prospective cohort	30	62.7 ± 14.1	36.7	100	97.7	0/30	0/11	0/19	–	–
Knoka et al. [37]	Prospective cohort	23	67.3 ± 12.9	47.8	100	95.7	0/23	0/16	0/7	0/19	0/4
Kriz et al. [44]	Prospective cohort	288	66.8 ± 11.8	56.4	93.8	77.4	1/288	–	–	1/190[e]	0/46[e]
Pluymaekers et al. [45]	RCT	207	65 ± 11	59.4	54.1	82.6	1/207	–	–	1/144[e]	0/75[e]
Scheuermeyer et al. [8]	Retrospective cohort	400	57 ± 14	25.5	100	96.5	0/400	–	–	0/49[f]	0/75[f]
Scheuermeyer et al. [42]	Retrospective cohort	61	–	23.0	75.4	75.4	0/61	0/19	0/42	0/24	0/37
Scheuermeyer et al. [43]	Retrospective cohort	357	–	28.9	60.5	74.5	0/357	0/77	0/280	0/129	0/228
Scheuermeyer et al. [38]	RCT	84	–	38.1	51.1	98.8	0/84	0/14	0/70	0/30	0/54
Stiell et al. [7]	Retrospective cohort	903	64.5	44.4	26.9	78.3	0/903[c]	–	–	–	–
Stiell et al. [19]	Prospective cohort	717	61.4 ± 15.3	35.7	73.2	97.5	0/717	0/200	0/517	0/371	0/346
Stiell et al. [39]	RCT	353	59.3 ± 15.0	33.1	64.9	100	1/345	1/156	0/189	1/151	0/202
Tampieri et al. [18]	Prospective cohort	218	55.2 ± 10.7	29.3	38.9	100	0/211	–	0/211	0/8[e]	0/149[e]

Table 1 (continued)

Study	Study design	No. of CVs	Age (y), mean ± SD	Female (%)	ECV (%)	Success of CV (%)	Total	OAC use	No OAC use	High risk for TE events[a]	Low risk for TE events[b]
							TE events/Total CVs	TE events/Total CVs	TE events/Total CVs	TE events/Total CVs	TE events/Total CVs
Vinson et al. [9]	Prospective cohort	115	64.0 ± 14.4	–	54.8	95.7	1/115	0/14	1/101	–	–
Weigner et al. [12]	Prospective cohort	107	–	–	30.8	–	0/107	–	–	–	–

CV cardioversion, *ECV* electrical cardioversion, *OAC* oral anticoagulation, *RCT* randomized controlled trial, *SD* standard deviation, *TE* thromboembolic

[a]High Baseline Risk for Thromboembolic Events: $CHADS_2 \geq 1$ or CHA_2DS_2-VASc ≥ 2

[b]Low Baseline Risk for Thromboembolic Events: $CHADS_2 = 0$ or CHA_2DS_2-VASc $= 0$ or 1

[c]Study only reported thromboembolic events at 7 days following cardioversion

[d]Based only on definite thromboembolic events (i.e. strokes), does not include probable thromboembolic events (i.e. transient ischemic attacks)

[e]Based on number of patients instead of total cardioversions

[f]Based only on atrial fibrillation patients

Secondary analysis

A total of 13 studies (3 prospective cohort, 3 randomized trials, and 7 retrospective) were included in the analysis comparing high versus low baseline risk of thromboembolism according to $CHADS_2$ and CHA_2DS_2-VASc scores (Fig. 3). The rate of thromboembolic events in those with high baseline thromboembolic risk was 0.63% (42 events/6706 cardioversions). By comparison, the event rate in the low baseline risk group was 0.19% (10 events/5285 cardioversions). There was an increased risk of thromboembolic events in those at high baseline risk with a $CHADS_2$ score ≥ 1 or CHA_2DS_2-VASc score ≥ 2 (RR = 2.25, 95% CI 1.25–4.04; $I^2 = 0\%$).

Figure S4 displays the post-hoc sensitivity analysis excluding Gronberg et al. [22], which did not show a significant difference in thromboembolic events according to baseline thromboembolic risk (RR = 1.93, 95% CI 0.69–5.38; $I^2 = 0\%$).

Discussion

Interpretation

In the primary analysis, we found insufficient evidence regarding the effect of oral anticoagulation use on thromboembolic events following cardioversion of low-risk acute atrial fibrillation and flutter. We found much of the previous evidence regarding oral anticoagulation post-cardioversion has been derived from low-quality studies, primarily retrospective cohort studies. Our review demonstrated a low rate of thromboembolic events post-cardioversion of acute atrial fibrillation and flutter, irrespective of oral anticoagulation use or no oral anticoagulation use. Of the prospective subgroup, there were no thromboembolic events at 30 days in patients not on oral anticoagulation. Despite a low event rate in the primary analysis, even when pooled together amongst all prospective and retrospective studies, the scarcity of events made it difficult to determine the true value of instituting oral anticoagulation use on thromboembolic events post-cardioversion. We also identified that patients with a $CHADS_2$ score ≥ 1 or CHA_2DS_2-VASc score ≥ 2 had a two-fold increase in the risk of thromboembolic events compared to those with a $CHADS_2$ score of 0 or CHA_2DS_2-VASc score of 0 or 1. Overall, there remains a lack of evidence to provide certainty in the value of oral anticoagulation use, though it appears the rate of thromboembolic events post-cardioversion of low-risk acute atrial fibrillation and flutter is low in contemporary practice.

Table 2 Risk of bias of the 20 included studies based on the Quality in Prognostic Studies (QUIPS) Tool

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Prospective studies						
Cristoni et al. [17]	Low	Moderate	Moderate	Low	Moderate	Low
Decker et al. [4]	Moderate	Low	Moderate	Low	Moderate	Low
Jacoby et al. [16]	High	Moderate	High	High	High	Moderate
Knoka et al. [37]*	Low	Moderate	Moderate	Low	Low	Low
Kriz et al. [44]	Low	Low	Low	Moderate	Moderate	Low
Pluymaekers et al. [45]	Low	Moderate	Moderate	Low	Moderate	Low
Scheuermeyer et al. [38]*	Low	Moderate	Low	Low	Moderate	Low
Stiell et al. [19] *	Low	Low	Low	Low	Low	Low
Stiell et al. [39]*	Low	Low	Low	Low	Low	Low
Tampieri et al. [18]	Moderate	Moderate	Low	Low	Moderate	Low
Vinson et al. [9]	Moderate	Low	Moderate	Low	Moderate	Low
Weigner et al. [12] 1997	Moderate	Moderate	Moderate	Low	Moderate	Low
Retrospective studies						
Bonfanti et al. [40]	Low	Moderate	Low	Moderate	Moderate	Low
Gallagher et al. [13]	Moderate	Low	Moderate	Low	Moderate	Low
Garg et al. [41]*	Low	Moderate	Low	Low	Moderate	Low
Gronberg et al. [22]	Low	Moderate	Moderate	Low	Moderate	Low
Scheuermeyer et al. [8]	Low	Low	Moderate	Low	Moderate	Low
Scheuermeyer et al. [42]*	Low	Low	Low	Low	Low	Low
Scheuermeyer et al. [43]*	Low	Low	Moderate	Low	Low	Low
Stiell et al. [7]	Low	Moderate	Low	Low	Moderate	Low

*Included in primary analysis

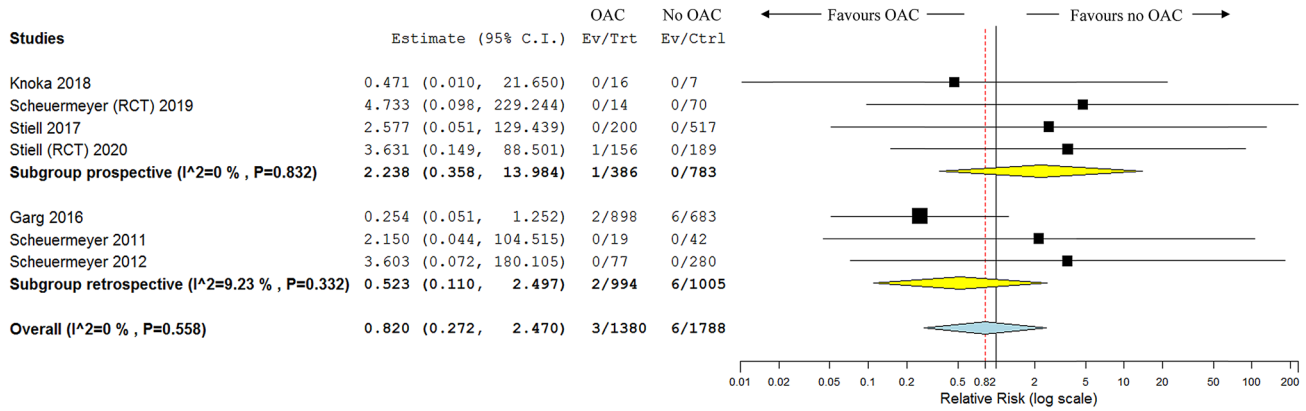

Fig. 2 Primary analysis—forest plot for 7 prospective and retrospective studies of high quality (≥4 domains of low risk of bias based on the QUIPS tool) reporting thromboembolic events at 30 days following cardioversion, with versus without oral anticoagulation (OAC) use. Top: prospective studies (including randomized controlled trials), bottom: retrospective studies. *CI* confidence interval, *Ctrl* control group, *Ev* number of thromboembolic events, *OAC* oral anticoagulation, *RCT* randomized controlled trial, *Trt* treatment group

Previous studies

Several systematic reviews have evaluated the risk of thromboembolism associated with atrial fibrillation and flutter and the role of oral anticoagulation for cardioversion [46–50]. None have specifically evaluated thromboembolic events following cardioversion for episodes of acute atrial fibrillation and flutter < 48 h in duration. A systematic review

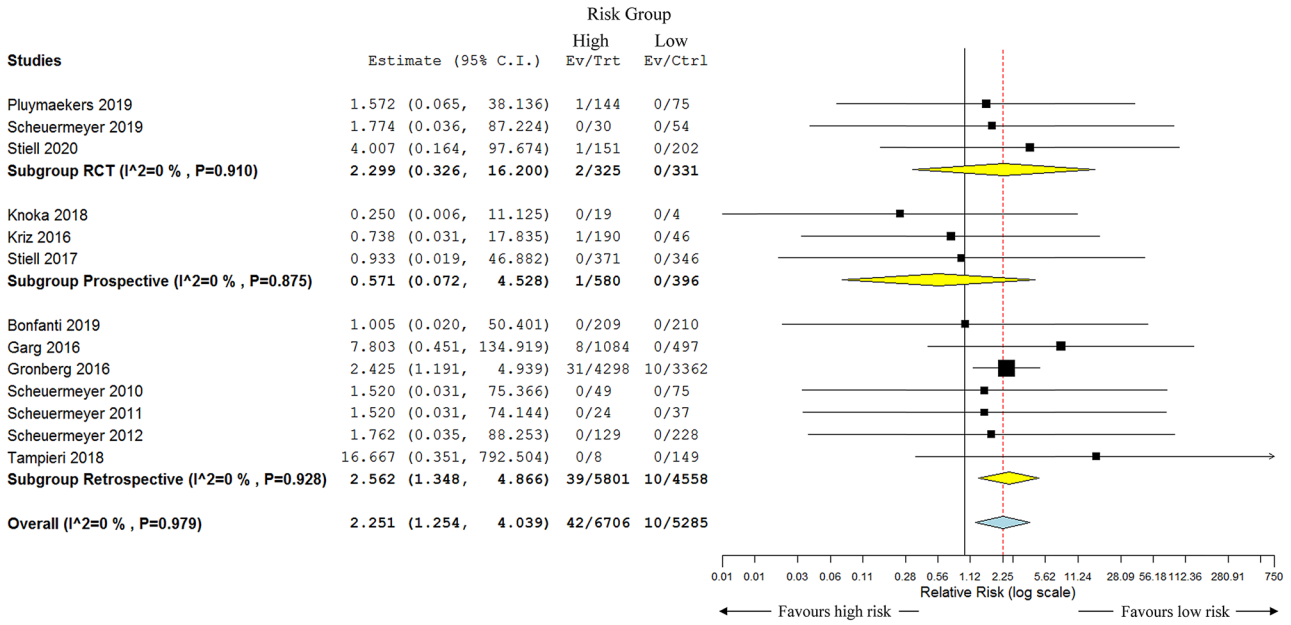

Fig. 3 Secondary analysis—forest plot for 13 prospective and retrospective studies reporting thromboembolic events at 30 days following cardioversion, based on high versus low baseline risk for thromboembolism. Top: randomized controlled trials; middle: prospective cohort studies; bottom: retrospective cohort studies. *CI* confidence interval, *Ctrl* control group, *Ev* number of thromboembolic events, *RCT* randomized controlled trial, *Trt* treatment group. High Baseline Risk: $CHADS_2 \geq 1$ or CHA_2DS_2-VASc ≥ 2. Low Baseline Risk: $CHADS_2 = 0$ or CHA_2DS_2-VASc $= 0$ or 1

by Coll-Vinent et al. [51] was conducted on the method of cardioversion in recent-onset atrial fibrillation. They found that cardioversion in the ED had an overall high rate of conversion and few embolic complications. However, no meta-analysis was conducted and only articles between 2000 and 2011 were included. Another review article by Rankin et al. evaluated the risk of thromboembolism associated with cardioversion of acute atrial fibrillation [52]. Thromboembolism following cardioversion with onset < 48 h was low, though risk varied depending on CHA_2DS_2-VASc score. This was not a systematic review nor was there any pooled analysis. The strength of our study is that, to our knowledge, it is the first to evaluate the effect of oral anticoagulation use on thromboembolic events within 30 days post-cardioversion of acute atrial fibrillation and flutter.

Limitations

Our study has several limitations. Of the 20 studies that were included in the review, 5 were identified through other sources, specifically by a manual search of reference lists. We recognize that a significant portion of the included studies were identified by manual screening, however, our librarian-assisted search was run multiple times and we believe it is unlikely any relevant articles were missed with our literature search. Additionally, these 5 studies were older studies and were not included in the meta-analysis portion as they did not compare thromboembolic events based on oral anticoagulation versus no oral anticoagulation use. Second, we had two reviewers (one consistent reviewer and one wild-card reviewer) for the study selection, data extraction, and quality assessment process. The limitation of this approach is that with the second reviewer being a wild card, there is potential for inconsistencies in study selection, data extraction, and quality assessment. To ensure consistency between all reviewers, all of our study selection, data extraction, and quality assessment criteria were very clearly outlined and thoroughly defined, and we are confident the systematic review was conducted consistently across all reviewers. Third, our primary analysis consisted of few thromboembolic events in both the oral anticoagulation and no oral anticoagulation groups, even when pooling both prospective and retrospective studies together. The scarcity of events made it difficult to evaluate the true effect of oral anticoagulation use. It does appear though that the event rate in those not receiving oral anticoagulation post-cardioversion is very low. Fourth, of the 12 studies meeting inclusion criteria for the primary analysis, nearly half were considered low-quality according to the QUIPS tool. Given the variation in study quality, our primary analysis was restricted to only high-quality studies. The limitation with this approach is that while our analysis may be at low risk

of bias, excluding studies further limits the data presented, especially in an area of clinical interest that is already lacking. To address this, we did provide two a priori sensitivity analyses stratified by study design in Figures S1 and S2 demonstrating our results if all studies, both high-quality and low-quality, were included. Finally, we were unable to perform any pooled analyses based on the duration of acute atrial fibrillation and flutter onset because of insufficient data. A few studies did provide a further breakdown of atrial fibrillation onset within the 48-h mark (e.g. patients with onset < 12 h or < 24 h), however, thromboembolic events were not reported according to onset time.

Clinical implications

Within the GRADE framework, a "weak recommendation" involves balancing the best available evidence with patient preferences through shared decision-making [53]. The decision for oral anticoagulation or no oral anticoagulation post-cardioversion of acute atrial fibrillation and flutter should weigh the risk of thromboembolism with bleeding risk. High baseline thromboembolic risk should push the decision towards oral anticoagulation, while it may be reasonable to forgo oral anticoagulation in those without comorbidities. Current evidence does not provide clear guidance for low-risk acute atrial fibrillation and flutter of < 48 h and thereby clinicians are left to undertake a patient-centered approach. There remains insufficient evidence to provide certainty on the effect of oral anticoagulation use. Even with a low event rate, the clinical relevance of stroke remains large. Within the "weak recommendation", our findings can better inform patient-centered decision-making in the ED when considering 4 weeks of oral anticoagulation following cardioversion. The low event rate should provide greater reassurance for patients who elect not to undergo 4 weeks of oral anticoagulation. Until the evidence base evolves further, the decision for oral anticoagulation in low-risk acute atrial fibrillation and flutter patients should continue to be patient-centered.

Research implications

The challenge moving forward is that with a low event rate, there remains insufficient power to determine the true effect of oral anticoagulation use, even when pooled together among all studies. Only retrospective studies can provide a sample size large enough to evaluate differences in oral anticoagulation use on stroke rates but should be methodologically sound with a low risk of bias. There remains a lack of high-quality data to evaluate the impact of oral anticoagulation use. Future studies, both prospective and retrospective, are needed to further evaluate the effect of oral anticoagulation use on thromboembolic events, with a focus on the cohort of patients with episodes of < 48 h. Additional research is also needed to evaluate the impact of duration of acute atrial fibrillation and flutter onset and baseline comorbidities on the risk of thromboembolic events post-cardioversion, to further guide therapeutic decision-making.

Conclusion

Within the primary analysis, we found insufficient evidence to provide certainty regarding the value of oral anticoagulation use following cardioversion in low-risk acute atrial fibrillation and flutter. The rate of thromboembolic events in contemporary practice appears to be remarkably low, irrespective of whether oral anticoagulation is used or not. Our findings can better inform patient-centered decision-making when considering 4-week use of oral anticoagulation in the ED for low-risk acute atrial fibrillation and flutter patients. This should reassure patients who elect not to undergo oral anticoagulation treatment post-cardioversion.

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Author contributions BMW, JJP, and IGS conceived the study idea and developed the study protocol. BMW, JJP, WC, BZ, KG, and IGS coordinated the systematic review. BMW, BZ, and KG screened abstracts and full texts, acquired the data, and assessed risk of bias in the studies. WC performed all the statistical analyses. BMW prepared the manuscript. All authors critically revised the manuscript for intellectual content and provided their permission to publish the manuscript. BMW is guarantor.

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Compliance with ethical standards

Conflict of interest All of the authors have no conflicts of interest to declare.

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