

REVIEW

Atrial flutter and the risk of thromboembolism: A systematic review and meta-analysis

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Risk;
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PURPOSE: We conducted a systematic review and meta-analysis of observational studies to assess the risk of thromboembolism associated with atrial flutter.

METHODS: MEDLINE, EMBASE, bibliographies, and consultation with clinical experts were used to identify studies that report the risk of thromboembolism associated with attempted cardioversion and longer-term risk in chronic atrial flutter. The review process and data extraction were performed by two reviewers. Study event rates were assessed graphically, and a chi-squared test was used to assess heterogeneity across studies. Meta-regression with weighted logistic regression was used to assess the association between study-level clinical factors and reported thromboembolic event rates.

RESULTS: We found 13 studies that reported the risk of thromboembolism associated with cardioversion of atrial flutter. Short-term event rates ranged from 0% to 7.3%. A chi-squared test for heterogeneity was significant ($P < 0.001$), so results were not pooled. Instead, a meta-regression analysis was performed, which partly explained the heterogeneity across studies. Studies were more likely to report high event rates when they included patients with a prior history of thromboembolism, and to report lower event rates when at least some patients were anticoagulated or if patients underwent echocardiography before cardioversion. Four studies reported the longer-term risk of thromboembolism, and these suggest a yearly event rate of approximately 3% with sustained atrial flutter.

CONCLUSION: These findings suggest that atrial flutter is indeed associated with an increased risk of thromboembolism, and that clinical factors account for the low event rates reported in some studies.
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The risk of stroke and thromboembolism associated with atrial fibrillation is clearly established, and large well-con-

ducted randomized controlled trials demonstrate that a 65% to 70% relative risk reduction is achievable through anticoagulation.¹⁻³ Further, a review of the literature on the cardioversion of atrial fibrillation⁴ suggests that there is a risk of stroke/thromboembolism of approximately 5% when patients are not anticoagulated in the weeks immediately before and after cardioversion. Management guidelines are consequently quite clear in recommending anticoagulation for atrial fibrillation at the time of planned therapeutic cardioversion, as well as long-term anticoagulation in all

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but low-risk patients when there are no contraindications to long-term anticoagulation.⁵

The evidence surrounding the risk of thromboembolism in patients with atrial flutter is less cogent; hence, recommendations for the management of atrial flutter are also less clear. Even recent commentaries^{6–8} have posed the question of whether atrial flutter is a risk factor for stroke, and whether anticoagulation is required for cardioversion, drawing attention to the discrepant results in the literature. Published recommendations consequently have not been conclusive regarding anticoagulation for atrial flutter.⁵ Rather, most recommendations have pointed to the mechanistic similarities between atrial flutter and atrial fibrillation, and proposed that patients with atrial flutter should, at least for the time being, be managed similarly to patients with atrial fibrillation, unless new evidence appears to suggest otherwise.^{5–8}

The objective of this study was to conduct a systematic review and meta-analysis of observational studies on the risk of thromboembolism associated with atrial flutter. Our findings reveal that there is already a considerable body of evidence on thromboembolism risk, which permits us to conduct a meta-regression of study-level clinical factors associated with reported risk. This analysis reconciles many of the differences among studies and permits stronger assertions regarding the risk of thromboembolism in atrial flutter.

Methods

Search strategy

We identified relevant articles in any language by searching MEDLINE (1966 to present) and EMBASE (1980 to present). Searches were supplemented by scanning bibliographies and contacting experts. The literature search was initially performed late in 2001, and was updated in February 2004 immediately before submission to identify any new studies that might have appeared.

The EMBASE and MEDLINE search strategy used an approach recommended for systematic reviews of observational studies.⁹ We derived three comprehensive search themes that were then combined using the Boolean operator “and.” The first theme, identifying studies that provide information on risk, was created by using the Boolean term “or” to combine exploded versions of specific Medical Subject Headings (MeSH) (*randomized controlled trials* or *clinical trials* or *cohort studies* or *follow-up studies* or *case control studies* or *case reports*) or text words (*risk* or *prognosis* or *course* or *predict*). The second theme, thromboembolism, was created by using the Boolean search term “or” to search for the following terms appearing as both exploded MeSH or text words: *cerebrovascular accident* or *stroke* or *transient ischemic attack* or *Amaurosis fugax* or *transitional blindness* or *retinal artery occlusion* or *throm-*

boembolism. The third theme, atrial flutter, was created by a search using an exploded MeSH and text word search for *atrial flutter*.

Screening of abstracts for eligibility

Abstracts identified from the online literature search were then screened by two reviewers (WG and BW) to determine eligibility for further review. Articles were retained if they reported original data from an original study, and if the article appeared as though it might address the issue of stroke or thromboembolism risk in patients with atrial flutter. The two reviewers were liberal in retaining articles on this initial screen and only discarded articles that clearly did not meet the above criteria. The two reviewers agreed on the inclusion/exclusion status of 88% of the abstracts reviewed, and articles were retained for further review whenever they disagreed.

Full-text review of articles

The same two reviewers then reviewed full-text versions of all retained articles, and all additional articles identified by searching bibliographies and contacting experts. The full-text articles were categorized into five groups: studies that provided estimates of the risk of thromboembolism around the time of therapeutic cardioversion; studies that provided estimates of the risk of thromboembolism over the longer-term; studies that only focused on echocardiographic findings associated with atrial flutter; case reports or case series of stroke/thromboembolism in patients with atrial flutter; and studies that should be excluded because they did not present original data, did not address the issue of thromboembolism risk, or did not clearly identify a subset of patients with atrial flutter. Only articles from the first two groups described above were considered for further detailed analysis.

The two reviewers agreed on group assignments for 88% of the full-text articles reviewed. Disagreements were resolved by consensus.

Data extraction

The two reviewers then independently extracted the following information from all selected studies: the focus of the study (atrial flutter only vs. atrial fibrillation and flutter); management strategy of performing echocardiography before planned cardioversion (yes/no); proportion of patients anticoagulated with vitamin K inhibitors; proportion of patients taking aspirin; total number of patients with atrial flutter; patients with history of prior thromboembolism (yes/no); follow-up time (in days) for ascertainment of thromboembolic events; and number of patients who experienced a thromboembolic event. We also collected information on key indicators of study quality (all yes/no items)⁹: whether consecutive patients were studied, whether explicit criteria

were used to define thromboembolic events, losses to follow-up, and prospective study design. Discrepancies in data extraction between reviewers were resolved by consensus.

Data analysis

Only studies on the risk of thromboembolism surrounding cardioversion were sufficiently similar in study design and data format to permit meta-analysis. Studies on the longer-term risk of thromboembolism in chronic atrial flutter were too methodologically dissimilar to permit meta-analysis, so the studies are reported descriptively.

The proportion of patients experiencing a thromboembolic event around the time of cardioversion was reported for each cardioversion study with exact 95% confidence intervals. Differences in event rates were compared using a chi-squared test, and in the event of significance at $P < 0.05$, heterogeneity was considered to be present. Meta-regression was performed using weighted logistic regression to identify study-level factors associated with the occurrence of thromboembolism. Both fixed- and random-effects analyses were performed, with the latter accounting for random between-study variation. These analyses considered clinical factors (i.e., proportion of patients taking anticoagulants or aspirin, inclusion of patients with prior history of thromboembolism, and use of echocardiography before cardioversion) as variables that may be associated with higher or lower reported rates of thromboembolism. Low event rates and model stability considerations restricted analyses to only one of these factors at a time. Given the exploratory nature of these analyses, the primary focus was on odds ratio point estimates rather than statistical significance in the interpretation of meta-regression results.

Results

Results of literature search

Search of online databases yielded 69 articles from MEDLINE and 76 articles from EMBASE, which when combined represented 113 unique articles. After initial screening of abstracts, it was judged that 39 warranted further full-text review. Twelve additional articles were identified by reviewing bibliographies and contacting experts, yielding a total of 51 articles for full-text review. Among these, 12 were excluded because they only presented echocardiographic findings, and 5 were excluded because they were case reports or case series that did not report the risk of thromboembolism. Another 19 articles were excluded for various reasons (e.g., no original data, no reporting of thromboembolism risk, atrial flutter cases not distinguished from atrial fibrillation), leaving 15 articles for detailed study.^{10–24} An updated scan of the literature in February 2004 revealed one additional study²⁵ that reported the long-term risk of thromboembolism in patients with

chronic atrial flutter; this study was also included. Among these final 16 articles, one by Seidl et al¹⁰ reports both the short-term risk around the time of cardioversion and the longer-term risk. Thus, 13 studies^{10–22} reported the risk of thromboembolism around the time of therapeutic cardioversion, and four^{10,23–25} reported the longer-term risk.

Risk of thromboembolism around the time of cardioversion

The publication dates of the 13 studies that reported the risk of thromboembolism around the time of therapeutic cardioversion ranged from 1992 to 2001 (Table 1), and the number of patients per study ranged from 5 to 615. The follow-up time for ascertaining events around the time of planned cardioversion was typically 28 to 30 days, although three studies^{13,10,19} had shorter follow-up times and one¹¹ had a follow-up of 42 days.

Reported thromboembolism event rates varied, ranging from 0% in seven studies to 7.3% (95% confidence interval [CI]: 1.5% to 19.9%) in another study¹³ (Figure). Notably, four studies reported a risk of more than 2% around the time of cardioversion, and upper 95% confidence intervals were above 10% for five studies. Collectively, these 13 studies reported a total of 19 thromboembolic events among 1546 patients being considered for therapeutic cardioversion. However, a chi-squared test comparing event rates revealed that results were heterogeneous (chi-squared = 40.8, $P < 0.0001$) and thus were not amenable to being combined for the reporting of a pooled event rate.

Among the clinical factors assessed in the fixed-effects analysis (Table 2), the inclusion of patients with a prior history of thromboembolism was associated with a higher risk of thromboembolism (event rate, 2.0% vs. 0.7% when no such patients were included; odds ratio [OR] = 3.0; 95% CI: 1.1 to 8.0), whereas studies that involved a clinical strategy of prescreening patients with echocardiography before cardioversion reported a lower risk (1.0% vs. 2.7% when echocardiography was not used; OR = 0.4; 95% CI: 0.1 to 1.0). Studies with a higher proportion of patients taking anticoagulants also tended to report a lower risk of thromboembolism (OR = 0.5; 95% CI: 0.1 to 2.5). The point estimates of odds ratios for each of these three variables (prior thromboembolism, use of echocardiography, and proportion taking anticoagulants) were similar in the random-effects analyses, although the confidence intervals were wider (Table 2). Meanwhile, analysis of the association between the proportion of patients taking aspirin and event rates revealed markedly inconsistent odds ratios in the fixed-effects versus random-effects analyses (Table 2), thus precluding any conclusions regarding the potential importance of aspirin use on event rates. Similarly, meta-regression of study quality factors as potential predictors of event rate yielded unstable parameter estimates and resulting odds ratios that were on opposite sides of 1.0 in the fixed-effects versus random-effects analyses.

Table 1 Characteristics of studies reporting the risk of thromboembolism associated with therapeutic cardioversion for atrial flutter

First author (reference)	No. of patients	Number (%)			Prior embolism	Follow-up (days)	Consecutive patients	Explicit event criteria	Losses to follow-up	Prospective design
		Events	Anticoagulation*	Aspirin*						
Zeiler-Arnold ¹¹	122	0	32 (26)	NR/NA	NR/NA	42	No	Yes	No	No
Black ¹²	7	0	NR/NA	NR/NA	No	30	No	Yes	No	Yes
Mehtha ¹³	41	3 (7)	2 (5)	7 (17)	NR/NA	2	Yes	No	No	Yes
Irani ¹⁴	47	1 (2.1)	7 (15)	23 (49)	Yes	28	No	No	Yes	Yes
Lanzarotti ¹⁵	100	6 (6)	84 (84)	NR/NA	Yes	Unclear	No	Yes	No	No
Kobayashi ¹⁶	5	0	NR/NA	NR/NA	NR/NA	30	Yes	No	No	Yes
Seidl ¹⁰	191	4 (2)	67 (35)	72 (38)	Yes	2	Yes	Yes	No	Yes
Bertaglia ¹⁷	64	0	NR/NA	NR/NA	No	28	No	Yes	No	Yes
Roijer ¹⁸	40	0	NR/NA	NR/NA	No	30	Yes	Yes	No	Yes
Boccaro ¹⁹	41	0	14 (34)	4 (10)	Yes	In-hospital	Yes	No	No	Yes
Corrado ²⁰	134	2 (1.5)	39 (29)	NR/NA	Yes	30	No	No	Yes	Yes
Elhendy ²¹	615	3 (0.5)	415 (67)	238 (39)	NR/NA	30	Yes	No	Yes	No
Schmidt ²²	139	0	NR/NA	NR/NA	Yes	28	No	No	No	Yes

NR/NA = not reported or not available.

*Taking oral anticoagulants or aspirin at the time of cardioversion.

Longer-term thromboembolism risk associated with atrial flutter

Four studies reported the longer-term risk of thromboembolism (Table 3). Shively et al²³ focused on echocardiographic findings in patients with atrial fibrillation or

atrial flutter. Among 28 patients with atrial flutter, only 1 (3.6%) had a stroke. The study's follow-up time was not explicitly reported, although thromboembolic events occurred as late as 68 weeks of follow-up.

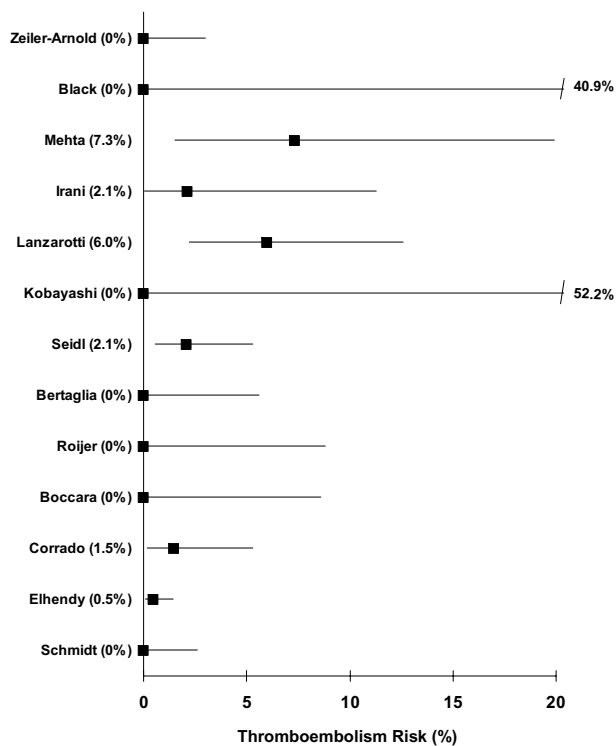


Figure The risk of thromboembolism (with 95% confidence intervals) around the time of cardioversion as reported in 13 studies. Thromboembolism event rates for each study are reported in parentheses beside the lead authors' names.

Table 2 Results of the meta-regression (weighted logistic regression) analysis assessing the association between study-level clinical factors and the rate of thromboembolic events

Factor	Odds ratio (95% confidence interval)
<i>Fixed-effects analysis</i>	
Inclusion of patients with prior thromboembolism	3.0 (1.1–8.0)
Proportion* of patients taking anticoagulants	0.5 (0.1–2.5)
Echocardiography performed before cardioversion	0.4 (0.1–1.0)
Proportion* of patients taking aspirin	0.4 (0.04–4.0)
<i>Random-effects analysis</i>	
Inclusion of patients with prior thromboembolism	2.5 (0.4–14.9)
Proportion* of patients taking anticoagulants	0.6 (0.1–4.4)
Echocardiography performed before cardioversion	0.5 (0.1–3.6)
Proportion* of patients taking aspirin	6.7 (0.1–362.7)

The corresponding odds ratio presented in the table represent the odds of thromboembolism in a study where all patients were anticoagulated (or taking aspirin) compared with the odds of thromboembolism in a study where none of the patients were anticoagulated.

*The proportions of patients taking anticoagulants (or aspirin) theoretically range from 0 to 1.0.

Table 3 Characteristics of studies reporting the longer-term thromboembolism risk associated with atrial flutter

First author (reference)	No. of patients	Number (%)		Prior embolism	Follow-up	Consecutive patients	Explicit event criteria	Losses to follow-up	Prospective design
		Oral anticoagulant use	Aspirin use						
Shively ²³	28	NR/NA	NR/NA	NR/NA	68 weeks*	NR/NA	Yes	No	Yes
Seidl ¹⁰	191	67 (35)	72 (38)	Yes	780 days	Yes	Yes	No	Yes
Biblo ²⁴	17,413	NR/NA	NR/NA	NR/NA	8 years	No	No	NR/NA	No
Halligan ²⁵	59	13 (22)	28 (47)	Yes	10 ± 6 years	No	No	NR/NA	No

NR/NA = not reported or not available.

*Precise duration of follow-up is not explicitly stated in this study, but 1 patient had a stroke at 68 weeks of follow-up.

The study by Seidl et al¹⁰ also provided information on risk around the time of cardioversion. Among 191 patients with atrial flutter, 4 (2.1%) experienced a thromboembolic event acutely within 2 days after cardioversion, as already reported above. In subsequent follow-up extending to, on average, 26 months, another 9 patients experienced thromboembolic events, for a total event rate (combining early and later events) of 6.8%. This corresponds to an average annual thromboembolism risk of 3.1%.

Halligan et al²⁵ studied 59 patients with chronic lone atrial flutter, and among these, 19 (32.2%) experienced an ischemic cerebrovascular event over an average 10-year follow-up period, for an average annual risk of 3.2%. Over half (56%) of the atrial flutter patients developed atrial fibrillation during follow-up, but this was not a necessary prerequisite for having an ischemic event, as some of the events occurred in patients without intervening atrial fibrillation.

Using a Medicare discharge abstract database, Biblo et al²⁴ identified hospital discharges with a principal or secondary diagnosis of atrial fibrillation (n = 337,428) or atrial flutter (n = 17,413), and ascertained the occurrence of subsequent hospitalizations for stroke. A comparison group was created by selecting a 5% random sample of hospitalizations without coded atrial fibrillation or flutter (n = 395,147). During 8 years of follow-up, more than one third of atrial flutter cases progressed to develop atrial fibrillation. The risk of stroke was increased among patients with atrial fibrillation versus the comparison group (relative risk [RR] = 1.6; 95% confidence interval not reported). The relative risk was also elevated for patients with isolated atrial flutter (RR = 1.4; 95% confidence interval not reported).

Discussion

Our systematic review demonstrates that the reported risk of thromboembolism around the time of cardioversion for atrial flutter varies by study, and that study-level clinical factors contribute to the variability in reported event rates. Collectively, the findings of the 16 studies reviewed in detail suggest that the risk of thromboembolism is not negligible.

Seven of 13 studies on the risk around the time of cardioversion reported an event rate of 0%. We anticipate that it is such findings that underlie the continuing discussion on the need for anticoagulation of patients with atrial flutter, because they support a strategy of not anticoagulating patients with atrial flutter. Pathophysiologic considerations also provide some rationale for not anticoagulating such patients, as it is recognized that atrial mechanical function is partially preserved in atrial flutter, and that blood flow and atrial emptying velocity are higher than in atrial fibrillation.^{26,27}

However, other studies reported elevated stroke risks in atrial flutter, both around the time of cardioversion and over the longer-term. A parallel can be drawn to the results of an earlier review of 25 studies involving more than 5000 patients on stroke risk surrounding the conversion of atrial fibrillation.⁴ That review, like ours, found that some studies reported a 0% risk of thromboembolism, but that a number of other studies also reported higher event rates. The global conclusion of that study was that the stroke risk in conversion of atrial fibrillation is approximately 5%, and is thus not negligible.⁴

Our meta-regression analyses, although exploratory, provide insights into the reasons for discrepant findings across studies, as some study-level clinical factors appear to influence reported event rates. Further, the findings of these analyses make sense clinically. When studies included patients with a history of prior thromboembolism (a group at higher risk in the context of atrial fibrillation), they tended to report a higher rate of thromboembolism. Meanwhile, studies that included larger proportions of patients taking anticoagulants (a treatment known to protect against thromboembolism) tended to report lower event rates. Similarly, the performance of echocardiography before cardioversion (a management strategy typically intended for detection of thrombi to delay cardioversion when these are present) was associated with a lower thromboembolism risk. Had the 13 studies all included more similar patient samples with prior history of thromboembolism, no antithrombotic drugs, and no echocardiography, we anticipate that the reported risk across studies might have been higher and more homogeneous.

The literature on longer-term stroke risk associated with atrial flutter is relatively sparse, perhaps because chronic isolated atrial flutter is not a common clinical presentation. Many patients with atrial flutter either promptly undergo attempted cardioversion or progress to develop atrial fibrillation or a combination of atrial flutter and fibrillation.^{24,25} Nevertheless, the studies on longer-term thromboembolism risk provided some insights, suggesting that the event risk in patients with atrial flutter is about 3% per year in absolute terms, and in relative terms is higher than for patients in sinus rhythm.

Our systematic review has notable strengths. All steps of the literature review, screening of articles for eligibility, and data extraction were performed in duplicate to enhance reliability and accuracy. We reported our findings using the framework of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria.²⁸ The study is current in its inclusion of eight studies published in 2000 or later. Perhaps most importantly, the data extracted permitted us to perform an exploratory but informative meta-regression that identifies potential reasons for the heterogeneity in event rates across studies, and at least partially reconciles the disagreement across studies.

Our meta-regression analysis provides insights into factors contributing to heterogeneity across studies, and identifies echocardiography before cardioversion as a protective factor. Both transesophageal and transthoracic echocardiography were used in the studies retrieved in our review, and because of low event rates, we were unable to analyze the separate echocardiographic modalities in the meta-regression analysis. We were also unable to analyze formally the specific echocardiographic findings (e.g., atrial thrombus vs. "smoke") that triggered a decision to delay cardioversion in each study, although it appears as though any such finding generally prompted a decision to delay cardioversion.

Collectively, the findings of this systematic review strongly suggest that atrial flutter does indeed impart a risk of thromboembolism. Based on these data, it seems reasonable to recommend anticoagulation around the time of cardioversion for patients without contraindications, as is currently recommended in the context of atrial fibrillation. Due to relatively sparse data on the longer-term risk of thromboembolism associated with atrial flutter, it is more difficult to make firm recommendations on the balance of risk and benefit associated with longer-term anticoagulation. However, the studies reviewed suggest that the risk of thromboembolism is indeed elevated as compared with that among patients in sinus rhythm.

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