Restarting Anticoagulant Therapy After Intracranial Hemorrhage
A Systematic Review and Meta-Analysis

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Background and Purpose—The safety and efficacy of restarting anticoagulation therapy after intracranial hemorrhage (ICH) remain unclear. We performed a systematic review and meta-analysis to summarize the associations of anticoagulation resumption with the subsequent risk of ICH recurrence and thromboembolism.

Methods—We searched published medical literature to identify cohort studies involving adults with anticoagulation-associated ICH. Our predictor variable was resumption of anticoagulation. Outcome measures were thromboembolic events (stroke and myocardial infarction) and recurrence of ICH. After assessing study heterogeneity and publication bias, we performed a meta-analysis using random-effects models to assess the strength of association between anticoagulation resumption and our outcomes.

Results—Eight studies were eligible for inclusion in the meta-analysis, with 5306 ICH patients. Almost all studies evaluated anticoagulation with vitamin K antagonists. Reinitiation of anticoagulation was associated with a significantly lower risk of thromboembolic complications (pooled relative risk, 0.34; 95% confidence interval, 0.25–0.45; Q=5.12, P for heterogeneity=0.28). There was no evidence of increased risk of recurrent ICH after reinstatement of anticoagulation therapy, although there was significant heterogeneity among included studies (pooled relative risk, 1.01; 95% confidence interval, 0.58–1.77; Q=24.68, P for heterogeneity <0.001). No significant publication bias was detected in our analyses.

Conclusions—In observational studies, reinstitution of anticoagulation after ICH was associated with a lower risk of thromboembolic complications and a similar risk of ICH recurrence. Randomized clinical trials are needed to determine the true risk–benefit profile of anticoagulation resumption after ICH. (***Stroke***. 2017;48:1594-1600. DOI: 10.1161/ STROKEAHA.116.016327.)

Key Words: anticoagulation ■ atrial fibrillation ■ myocardial infarction ■ stroke ■ thromboembolism

Atrial fibrillation increases the risk of stroke 3- to 5-fold and is implicated in about 15% of all strokes every year.[1] Anticoagulation therapy has been proven to be efficacious in reducing incident stroke and systemic embolism in patients with atrial fibrillation[2] and mechanical heart valves.[3] However, the benefits of anticoagulation must be carefully weighed against the increased risk of intracranial hemorrhage (ICH) faced by patients receiving anticoagulation therapy.[4,5] Hence, resumption of anticoagulation after ICH poses a clinical conundrum. The absence of evidence-based guidelines to address this issue has led to wide variations in restarting anticoagulation after ICH. Premature reinstatement of anticoagulation could potentially increase recurrent ICH risk, whereas an unnecessary delay in restarting anticoagulation could considerably increase a patient's thromboembolic risk. Furthermore, there is also no consensus on the timing of reinstitution of these medications.[6] Individual studies in the literature have attempted to address this clinical challenge and have been unable to provide clear guidance on this issue because of small sample sizes and conflicting results. We performed a meta-analysis of available studies to evaluate the safety and efficacy of reinitiation of anticoagulant therapy after ICH.

Methods

We performed this study in accordance with the guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[7] and the Meta-Analysis of Observational Studies in Epidemiology[8] statements. This study used publically available, deidentified published data and was exempt from approval by the Institutional Review Board.

Data Sources and Searches

We performed comprehensive searches in Ovid MEDLINE, Ovid Embase, and the Cochrane Library from the inception of each database to September 30, 2016. An English language filter was not applied. After the initial search in Ovid MEDLINE, the search was extended to other databases. Keywords used to query the databases included: intracranial hemorrhage or intracerebral hemorrhage and a combination of anticoagulation, warfarin, atrial fibrillation, heart valve, ischemic stroke, myocardial infarction, and recurrence. Details of the search methodology are listed in the online-only Data Supplement.

Study Selection

We included studies evaluating thromboembolic complications and recurrence of ICH after hospitalization for ICH. The inclusion criteria for our study were (1) studies with nontraumatic ICH as the primary inclusion criteria; (2) studies with documented outcomes of ischemic stroke, myocardial infarction [MI], and ICH recurrence in the follow-up period; (3) studies with clear documentation of whether or not anticoagulation was restarted; (4) adult patients ≥18 years of age; and (5) sample size ≥10 patients to avoid inclusion of case reports or small case series. We only included peer-reviewed publications in scientific journals and not conference proceedings or abstracts because the latter typically do not provide the level of detail needed of rigorous data extraction. In case of ambiguity, we attempted to contact the corresponding author for clarification. In case of multiple publications from a single cohort of patients or institutional database, the study with the largest cohort of patients was selected to avoid duplication of data.

Data Extraction and Quality Assessment

A single investigator (S.B.M.) read the title and abstract produced by the initial search and shortlisted articles for further review. These articles were then independently reviewed by 2 investigators (S.B.M. and A.E.M.) and selected based on the inclusion criteria and quality of data. Any disagreements were resolved by a third investigator. Data were extracted using a prespecified collection template. The following study characteristics were extracted: first author, journal of publication, year of publication, country of study origin, and study design. We also collected patient demographics, including age, sex, and stroke comorbidities such as hypertension, diabetes mellitus, dyslipidemia, smoking history, coronary heart disease, atrial fibrillation, mechanical heart valve, previous stroke, or transient ischemic attack. Timing of restarting of anticoagulation therapy was also recorded. Outcome data included cases of ischemic stroke, MI, and recurrent ICH in the follow-up period.

We adapted risk of bias assessments in previously published meta-analyses on stroke risk and generated 8 specific questions to evaluate for potential selection, detection, reporting, and confounding bias.[9,10] Two readers assessed for risk of bias using this questionnaire, with disagreements in assessment resolved by a third tie-breaking evaluator.

Definitions of Outcomes

Our outcome measures were thromboembolism, defined as a composite of ischemic stroke or MI, and recurrence of ICH. Most of the studies identified outcomes using International Classification of Diseases (ninth or 10th revision) diagnosis codes. Two studies used mailed questionnaires and semiquantitative telephone interviews to prospectively ascertain the occurrence of thromboembolic complications and ICH recurrence.[11,12]

Data Synthesis and Analysis

We performed a meta-analysis to assess the association between anticoagulation resumption and thromboembolic complications and recurrence of ICH using the pooled relative risk (RR) as the effect parameter. We used a random-effects (DerSimonian–Laird) model to calculate the pooled RR and generated forest plots to display the individual study RR and pooled RR.[13] The rationale of using the more conservative random-effects model was to account for the variability in effect sizes, design, and follow-up between the individual studies. We assessed heterogeneity using the Cochran Q test. If heterogeneity was detected, meta-regression was performed to explore underlying factors.[14] The presence of publication bias was evaluated using the Begg–Mazumdar rank correlation test. Statistical analyses were performed using Stata (version 14.0, College Station, TX). All tests were 2-tailed, and P values <0.05 were considered significant.

Results

Study Selection and Characteristics

We screened a total of 888 titles and abstracts from which 8 studies met the inclusion criteria (Figure I in the online-only Data Supplement). For the evaluation of thromboembolic events after ICH, we were able to include 6 of the 8 studies, as 2 studies focused on ICH recurrence.[15] We were able to calculate a crude RR expressing the association between anticoagulant use and the outcomes of interest in all of the selected studies. Of the included studies, 2 were from Denmark,[15,16] and 1 each from, Germany,[11] Belgium,[17] and the Netherlands,[12] 1 from the United States,[18] and 1 from Canada,[19] whereas 1 study included patient cohorts from Sweden and Canada (Table 1).[20]

Four studies included patients only with intraparenchymal hemorrhage as the index ICH,[11,12,15,18] whereas others widened their selection criteria to include subdural and subarachnoid hemorrhages.[16,17,19,20] The mean age of patients was between 69 and 78 years, with the majority being men (range 56.0–63.1 years; Table I in the online-only Data Supplement). Data on stroke risk factors were not available in 4 studies.[15–17,20]

Oral Anticoagulant Therapy Indications and Reinitiation

The most common indication for anticoagulation treatment before the onset of ICH was atrial fibrillation (34.7%–77.8%), followed by prosthetic heart valve (2.6%–27.8%), venous thromboembolism (7.9%–20.8%), and previous ischemic stroke (3.7%–71.8%). Reinitiation of anticoagulation occurred at a median of 10 to 39 days (Table 2). Four studies did not report the exact timing of resumption of anticoagulation,[12,15,16,19] but the majority of patients were prescribed anticoagulation within the first 3 months after ICH. The anticoagulation of choice was oral vitamin K antagonist (VKA) medications in all studies, with the exception of Ottosen et al[15] and Nielsen et al,[16] in which some patients were administered non-VKA oral anticoagulants (NOACs).

Association Between Anticoagulant Therapy and Thromboembolic Complications

We included 6 studies with 2044 patients with ICH. Among these patients, anticoagulation therapy was restarted in 786

Table 1. Overview of the Characteristics of Studies Included in the Meta-Analysis

Study	Country	Design	Major Inclusion Criteria	No. of Subjects	Mean/Median Follow-Up, mo	Outcomes
De Vleeschouwer et al[17]	Belgium	Retrospective cohort	Patients with all subtypes of ICH—intraparenchymal, subdural, and subarachnoid hemorrhages	108	12	Recurrent ICH; thromboembolic events; functional outcome
Claassen et al[18]	United States	Retrospective cohort	Patients with radiologically documented warfarin-associated intraparenchymal hemorrhage, INR ≥1.5, discharge data	48	43	Recurrent ICH; thromboembolic events
Majeed et al[20]	Sweden and Canada	Retrospective cohort	Patients with any warfarin-associated ICH, data from 3 tertiary care hospitals	234	34	Recurrent ICH; thromboembolic events
Yung et al[19]	Canada	Retrospective cohort	Patients with intraparenchymal or subarachnoid hemorrhages, documented warfarin use, excluded trauma/tumors/surgical interventions	284	12	Primary—all-cause mortality, recurrence or expansion of intracranial bleeding. Secondary—composite of death, bleeding, or thrombotic complications
Gathier et al[12]	the Netherlands	Retrospective cohort	Patients with radiologically documented AC-related intraparenchymal hemorrhage, INR ≥1.1, discharge data	38	42	Primary—fatal or nonfatal radiologically confirmed cerebral infarction and recurrent ICH; Secondary—other thrombotic sequelae
Nielsen et al[16]	Denmark	Retrospective cohort	Patients with nonvalvular atrial fibrillation only, any new incident ICH, AC treatment within 6 mo of ICH	1752	12	Recurrent ICH; thromboembolic events
Kuramatsu et al[11]	Germany	Retrospective cohort	Patients with warfarin-associated intraparenchymal hemorrhage and INR ≥1.5	853	12	Primary—frequency of hematoma enlargement; Secondary—thromboembolic events, recurrent ICH, functional outcomes
Ottosen et al[15]	Denmark	Retrospective cohort	Patients ≥18 y, with first-time acute spontaneous ICH, and surviving the first 30 d	2978	27.6	All-cause mortality, thromboembolic events, major bleeding, recurrent ICH

AC indicates anticoagulation; ICH, intracranial hemorrhage; and INR, international normalized ratio.

(38.4%) patients with a total follow-up for incident thromboembolic complications of 861 person-years. Anticoagulation therapy was not restarted in the remaining 1258 patients (61.6%), who were followed for a total of 1328 person-years for thromboembolic complications. The rate of thromboembolic events in patients on anticoagulation therapy was 6.7% compared with a 17.6% for patients not restarted on anticoagulation therapy (Table 3). We observed a significant inverse association between anticoagulation therapy and the risk of thromboembolic events (pooled RR, 0.34; 95% confidence interval, 0.25–0.45) (Figure 1). There was no statistically significant heterogeneity ($Q=5.12$; $P=0.28$) or publication bias ($P=0.55$). The funnel plot for assessment of publication bias is shown in Figure II in the online-only Data Supplement.

Association Between Anticoagulants and ICH Recurrence

Eight studies were eligible for meta-analysis of the relationship between anticoagulation therapy and ICH recurrence. These studies included 5306 ICH patients of whom 1899 (35.8%) were restarted on anticoagulation therapy. The total follow-up for recurrent ICH in this group restarted on anticoagulation therapy was 3494 person-years. Anticoagulation

therapy was not restarted in the remaining 3407 patients (64.2%) who were followed for a total of 7030 person-years. Recurrence of ICH was observed in 166 (8.7%) patients on anticoagulation and in 267 (7.8%) not on antithrombotic agents. We observed no difference in ICH recurrence in the 2 groups (pooled RR, 1.01; 95% confidence interval, 0.58–1.77; Figure 2). There was evidence of significant heterogeneity ($Q=24.68$; $P<0.001$), but no evidence of publication bias (P value for Begg–Mazumdar test=0.55; Figure III in the online-only Data Supplement.).

Sensitivity Analysis

Given the significant heterogeneity in the random-effects model assessing the relationship between resumption of anticoagulation therapy and ICH recurrence, we performed a meta-regression to identify factors that could have resulted in the heterogeneity. Studies were appraised based on different factors such as inclusion of intraparenchymal hemorrhages only, sample size >100 patients, clearly specified time point for resumption of anticoagulation therapy, and reinitiation with anticoagulation therapy other than VKAs. Each of these factors was assessed individually. Subgroup meta-analyses were performed using these specific criteria to evaluate for the

Table 2. Overview of AC Indications and Characteristics

Study	Indications for AC (%)*						Received AC	AC Type	Time to Restarting AC, d
	NVAF	Prosthetic Heart Valve	VTE	Previous Stroke	Recent MI	Other			
De Vleeschouwer et al[17]	56 (51.9)	30 (27.8)	11 (10.2)	4 (3.7)	2 (1.9)	5 (4.6)	25 (23.1)	VKA	11
Claassen et al[18]	23 (47.9)	12 (25.0)	10 (20.8)	N/A	N/A	3 (6.3)	23 (47.9)	VKA (warfarin)	10
Majeed et al[20]	135 (58.0)	35 (15.0)	37 (16.0)	N/A	N/A	27 (11.0)	45 (34.1)†	VKA (warfarin)	39.2
Yung et al[19]	191 (67.3)	37 (13.0)	31 (10.9)	N/A	N/A	N/A	91 (32.0)	VKA (warfarin)	N/A
Gathier et al[12]	10 (40.0)	2 (8.0)	6 (24.0)	8 (32.0)	2 (8.0)	4 (16.0)	12 (48.0)	VKA	Within 2 mo
Nielsen et al[16]	1752 (100.0)	0	0	0	0	0	509 (29.1)	VKA/NOAC	N/A
Kuramatsu et al[11]	664 (77.8)	67 (7.9)	71 (8.3)	N/A	N/A	51 (6.0)	172 (23.9)	VKA	31
Ottosen et al[15]	1032 (34.7)	78 (2.6)	236 (7.9)	2139 (71.8)	264 (8.9)	30 (1.0)	160 (6.3)‡	VKA/NOAC	Within first 6 mo

AC indicates anticoagulation; MI, myocardial infarction; N/A, not available; NOAC, nonvitamin K oral anticoagulant medications; NVAF, non-valvular atrial fibrillation; VKA, vitamin K antagonists; and VTE, venous thromboembolism.

*Sum of all indications may exceed 100% because some patients had multiple indications for AC.

†Data on 132 patients with cardiac indications who were restarted on AC were available.

‡Data were available on 2543 patients who survived.

source of heterogeneity in the overall analysis. Significant heterogeneity was found with the inclusion of studies that used anticoagulation medications other than VKAs (P=0.006). The 2 studies that used NOACs were by Ottosen et al[15] and Nielsen et al.[16] After the exclusion of these studies, we constructed a random-effects model to evaluate the association between reinstitution of anticoagulation medications and ICH recurrence in the remaining studies. We observed a pooled RR of 1.18 (95% confidence interval, 0.83–1.70; heterogeneity P=0.82).

Given the possibility of large, heavily weighted studies skewing the pooled RR, we performed additional sensitivity analyses. For the assessment of thromboembolic risk, we excluded 2 studies (Kuramatsu et al[11] and Nielsen et al[16]) following which the pooled RR remained significantly in favor of resumption of anticoagulation therapy (RR, 0.40; 95% confidence interval, 0.29–0.83; heterogeneity P=0.13). For the assessment of ICH recurrence, the 2 heavily weighted studies

were by Ottosen et al[15] and Nielsen et al,[16] and the results are as discussed in the meta-regression above.

Assessment of the Quality of Included Studies

The results from the quality assessment questionnaire are shown in Table II in the online-only Data Supplement. Selection bias was minimized in 4 studies either through random selection of patients or recruitment from a community-dwelling population.[11,15,16,20] The investigators were not blinded to the anticoagulant status in any of the included studies. More importantly, only 3 studies corrected for covariate risk factors in assessing the relationship between resumption of anticoagulation therapy and outcomes.[11,15,16]

Discussion

In this systematic review and meta-analysis of studies with >5000 patients with ICH, we found that resumption of anticoagulation therapy was associated with a lower risk of

Table 3. Rates of Thromboembolic Complications and ICH Recurrence

Study	Anticoagulant Medications			No Anticoagulant Medications		
	Stroke+MI (%)	ICH Recurrence (%)	Total Population	Stroke+MI (%)	ICH Recurrence (%)	Total Population
De Vleeschouwer et al[17]	0 (0)	1 (4.0)	25	3 (3.7)	7 (8.6)	81
Claassen et al[18]	6 (26.1)	1 (4.3)	23	8 (32.0)	0 (0)	25
Majeed et al[20]	1 (2.2)	8 (17.8)	45	18 (20.7)	10 (11.5)	87
Yung et al[19]	N/A	14 (15.4)	91	N/A	29 (15.0)	193
Gathier et al[12]	2 (16.7)	1 (8.3)	12	2 (15.4)	0 (0)	13
Nielsen et al[16]	35 (6.9)	36 (7.1)	509	108 (21.4)	72 (14.3)	505
Kuramatsu et al[11]	9 (5.2)	14 (8.1)	172	82 (14.9)	36 (6.6)	547
Ottosen et al[15]	N/A	91 (8.9)	1022	N/A	113 (5.8)	1956
Total events	53 (6.7)*	166 (8.7)	1,899	221 (17.6)*	267 (7.8)	3407

ICH indicates intracranial hemorrhage; MI, myocardial infarction; and N/A, not available.

*Studies by Yung et al[19] and Ottosen et al[15] were excluded because stroke and MI were not reported.
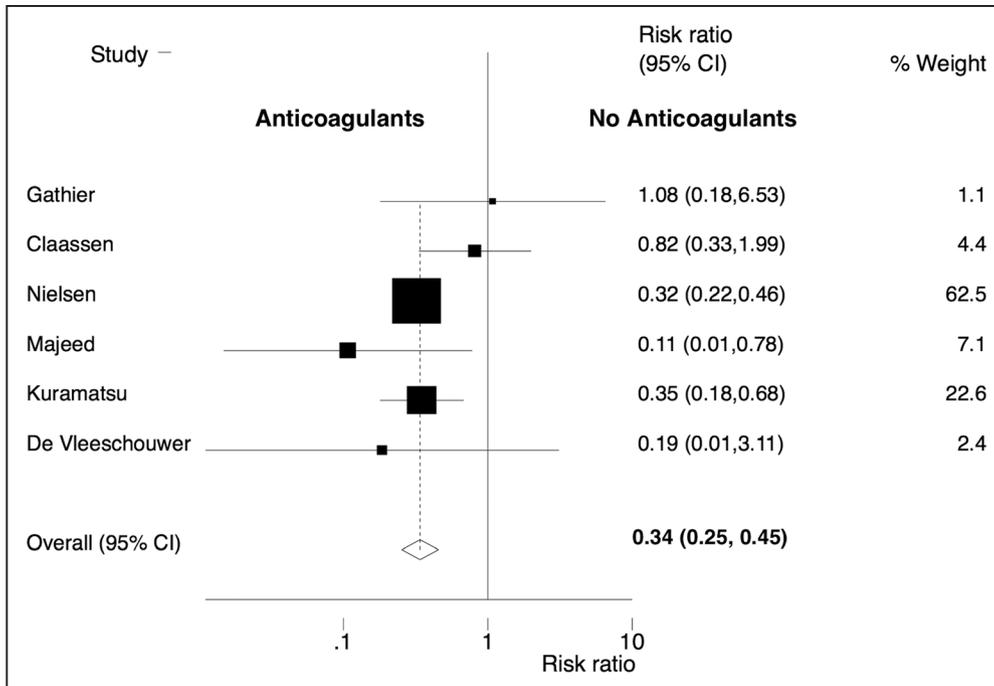
Figure 1. Forest plot of the association between resumption of oral anticoagulation therapy and arterial thromboembolic complications after intracranial hemorrhage. The meta-analysis was calculated using a random-effects model, with the pooled relative risk shown in the forest plot. Each square represents the point estimate of any given study effect size. The size of the squares is proportional to the inverse of the variance of the estimate, whereas the horizontal lines represent each study 95% confidence intervals. The diamond represents the pooled estimate with the width of the diamond representing the pooled 95% confidence interval. Heterogeneity: $Q=5.12$; $P=0.28$. CI indicates confidence interval.

thromboembolic events such as stroke and MI. In addition, there was no apparent heightened risk of ICH recurrence with administration of anticoagulation medications.

From the clinician's standpoint, the main concern preventing reinstitution of anticoagulation is recurrence of ICH. Although we did not find any significant difference in the rates of recurrent ICH, certain limitations of published literature may have influenced this finding. For instance, 1 possibility is that anticoagulation was more likely to be reinstated in patients with smaller hematomas, but lack of data on baseline hematoma volume precluded further evaluation. Moreover, not all studies provided information on hematoma location or whether the ICH was a first-time bleed or recurrent hemorrhage. Our study, therefore, did not account for lobar hemorrhages, which are more likely to be secondary to amyloid angiopathy and consequently have a higher rate of ICH recurrence. Broadly speaking, these specific factors are instances of confounding by indication in these observational studies, in which patients at higher perceived risk may have been less likely to be restarted on anticoagulation. These factors, in addition to differences
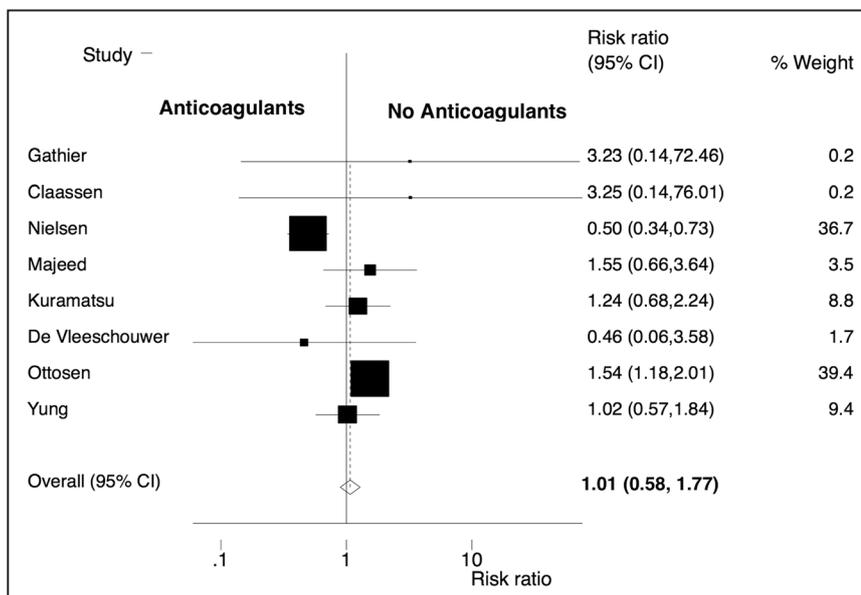

Figure 2. Forest plot of the association between resumption of oral anticoagulation therapy and recurrence of intracranial hemorrhage. The meta-analysis was calculated using a random-effects model, with the pooled relative risk shown in the forest plot. Heterogeneity: $Q=24.68$; $P<0.001$. CI indicates confidence interval.

in study design and timing of resumption of anticoagulation therapy, may have accounted for the significant heterogeneity in our random-effects model. These considerations underscore the importance of future randomized trials to determine optimal antithrombotic strategies after ICH.

It is notable that all studies included in our systematic review used VKAs as the medication of choice. However, a newer class of medications, NOACs, has been shown to have a significantly lower ICH risk compared with warfarin.[21] In addition, emerging data suggest that patients with NOAC-associated ICH have smaller hematomas and better functional outcomes in comparison with warfarin-associated ICH.[22,23] Although recent guidelines recommend using NOACs for non-valvular atrial fibrillation, current research is focused on identifying other potential roles in clinical conditions such as atrial fibrillation associated with valvular heart disease and patients with prosthetic heart valves.[24] Thus, it is possible that the range of indications for NOAC use will expand in the future.[25]

Our study has shed light on additional limitations of the existing body of literature studying anticoagulant use after ICH. First, there are no randomized trials studying resumption of anticoagulation therapy after ICH. Our meta-analysis is hence subject to the intrinsic flaws from the nonblinded, retrospective observational design of the included studies. Second, there was heterogeneity in the follow-up periods in the individual studies. Third, there was variability in the selection criteria of individual studies in that some included only patients with intraparenchymal hemorrhage, whereas others additionally included those with subarachnoid and subdural hematomas. Recurrence of subarachnoid hemorrhage irrespective of anticoagulation status is considered rare after obliteration of the culprit aneurysm,[26] whereas reoccurrence of other forms of ICH may be much higher. For example, recurrence rate for subdural is around 12%,[27] whereas that for intraparenchymal hemorrhage is ≈2%[28,29] in nonanticoagulated patients, which may have significantly affected our results. We also did not have information on blood pressure control, a known predictor of ICH recurrence.[30] Moreover, although warfarin was the drug of choice for anticoagulation in majority of the studies, NOACs were used in 1 study which may have influenced ICH recurrence.[16] Fourth, reasons for reinstitution or continued withholding of anticoagulation involve a complex interplay of clinical and social factors, all of which were not available. Our study is hence subject to confounding by indication of individual studies and may apply to patients who were deemed to be low risk for ICH recurrence. The variation in resumption of anticoagulations may have also accounted for the wide range of thromboembolic complications observed. In addition, the majority of the studies did not adjust for stroke/MI risk factors. As a result, our findings may have been subject to significant confounding bias. Finally, none of the studies characterized stroke subtype. Although cardioembolic strokes are more likely in nonanticoagulated patients with known atrial fibrillation or mechanical heart valves, other subtypes of stroke may have contributed to the stroke incidence.

In summary, our systematic review and meta-analysis suggests that resumption of anticoagulation therapy is associated with a lower risk of arterial thromboembolism after ICH. Moreover, there does not seem to be an increased risk

of ICH recurrence. In the absence of randomized clinical trials, our results help summarize the existing literature and may serve as a guide to clinicians in making informed decisions. Furthermore, our findings will hopefully encourage further studies of the risks and benefits of anticoagulation in this population.

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Disclosures

None.

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Restarting Anticoagulant Therapy After Intracranial Hemorrhage: A Systematic Review and Meta-Analysis

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Restarting Anticoagulant Therapy after Intracranial Hemorrhage
A Systematic Review and Meta-Analysis

Supplemental Methodology

Literature Search Details

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present - Search ran 09/15/2015

1. exp intracranial hemorrhage/
2. ((brain or intracerebral or subdural or subarachnoid) adj4 hemorrhage*).tw.
3. 1 or 2
4. exp antithrombotic/
5. ((atrial fibrillation, mechanical heart valve, antiplatelet, anticoagulant) adj3 antithrombotic.tw.
6. 4 or 5
7. 3 and 6
8. exp stroke/
9. stroke*.tw.
10. Cerebrovascular.tw.
11. ((brain or cerebral or ischemic or lacunar or vascular or venous) adj2 (accident* or attack* or event* or infarct*)).tw.
12. (cva or cvas).tw.
13. or/10-12
14. 7 and 13
15. exp myocardial infarction/
16. 7 and 15
17. recurrent intracranial hemorrhage.tw
18. 7 and 17

The English language filter was not applied. The first search was conducted in Ovid MEDLINE. Subject headings and key words were adapted for the other databases.

Supplementary Table I: Baseline Demographics and Comorbidities of Patients with ICH

| Study	AC Status	Number of Patients	Mean Age (SD)	Males	Hyper-tension	Diabetes Mellitus	Atrial fibrillation	Mechanical Heart Valve	Smoking	Prior Stroke	CAD
De Vleeshouwer[1]	No	81	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Yes	25	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Claassen[2]	No	25	75.3 (14.7)	14 (56)	18 (72)	6 (24)	14 (56)	2 (8)	N/A	8 (32)	10 (40)
	Yes	23	70.8 (25.8)	13 (56.5)	19 (83)	5 (22)	9 (39)	10 (44)	N/A	7 (30)	5 (22)
Majeed[3]	No	87	78 (7.5)	56 (64)	N/A	N/A	79 (91)	6 (7)	N/A	N/A	N/A
	Yes	45	70 (17)	31 (69)	N/A	N/A	22 (49)	22 (49)	N/A	N/A	N/A
Yung[4]	No	193	74.4 (11.9)	110 (57.0)	138 (71.5)	43 (22.3)	89 (46.1)	18 (9.3)	N/A	41 (21.2)	48 (24.9)
	Yes	91	71.8 (12.9)	46 (50.5)	69 (75.8)	21 (23.1)	46 (50.5)	19 (20.3)	N/A	26 (28.6)	27 (29.7)
Gathier[5]	No	13	69 (16)	9 (69)	8 (62)	2 (15)	6 (46)	0	7 (54)	5 (39)	3 (23)
	Yes	12	70 (16)	10 (83)	8 (67)	2 (17)	4 (33)	2 (17)	2 (17)	3 (25)	4 (33)
Nielsen[6]	No	505	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Yes	509	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kuramatsu[7]	No	547	74.5 (8.6)	330 (60.3)	476 (87)	172 (31.4)	456 (83.4)	16 (2.9)	N/A	171 (31.2)	239 (43.7)
	Yes	172	70.6 (9.9)	119	149	48	110	34	N/A	43 (25.0)	77 (44.8)
Ottosen[8]	No	1022	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Yes	1596	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: AC, anticoagulation; CAD, coronary artery disease; N/A, not available; SD, standard deviation
Data are presented as number (%) unless otherwise indicated

Type of Bias	Selection				Detection		Attrition	Confounding
Question:	Was the study sample randomly selected?	Were the inclusion and exclusion criteria adequately described?	Was the primary objective to assess thromboembolic events?	Was the primary objective to assess ICH recurrence?	Was the study prospective in nature?	Were the investigators blinded to the anticoagulation status?	Were losses to follow up systematically reported?	Were the data adjusted for covariate risk?
De Vleeshouwer[1]	-	+	+	+	-	-	+	-
Claassen[2]	-	+	+	+	-	-	+	-
Majeed[3]	+	+	+	+	-	-	+	-
Yung[4]	+	+	-	+	-	-	-	-
Gathier[5]	-	+	+	+	-	-	+	-
Nielsen[6]	+	+	+	+	-	-	+	+
Kuramatsu[7]	+	+	+	+	-	-	+	+
Ottosen[8]	+	+	-	+	-	-	+	+

Supplementary Table II: Results of Risk of Bias Questions to Assess the Quality of Included Studies

Abbreviations: ICH, intracranial hemorrhage

Supplemental Figure I: Study selection flow diagram
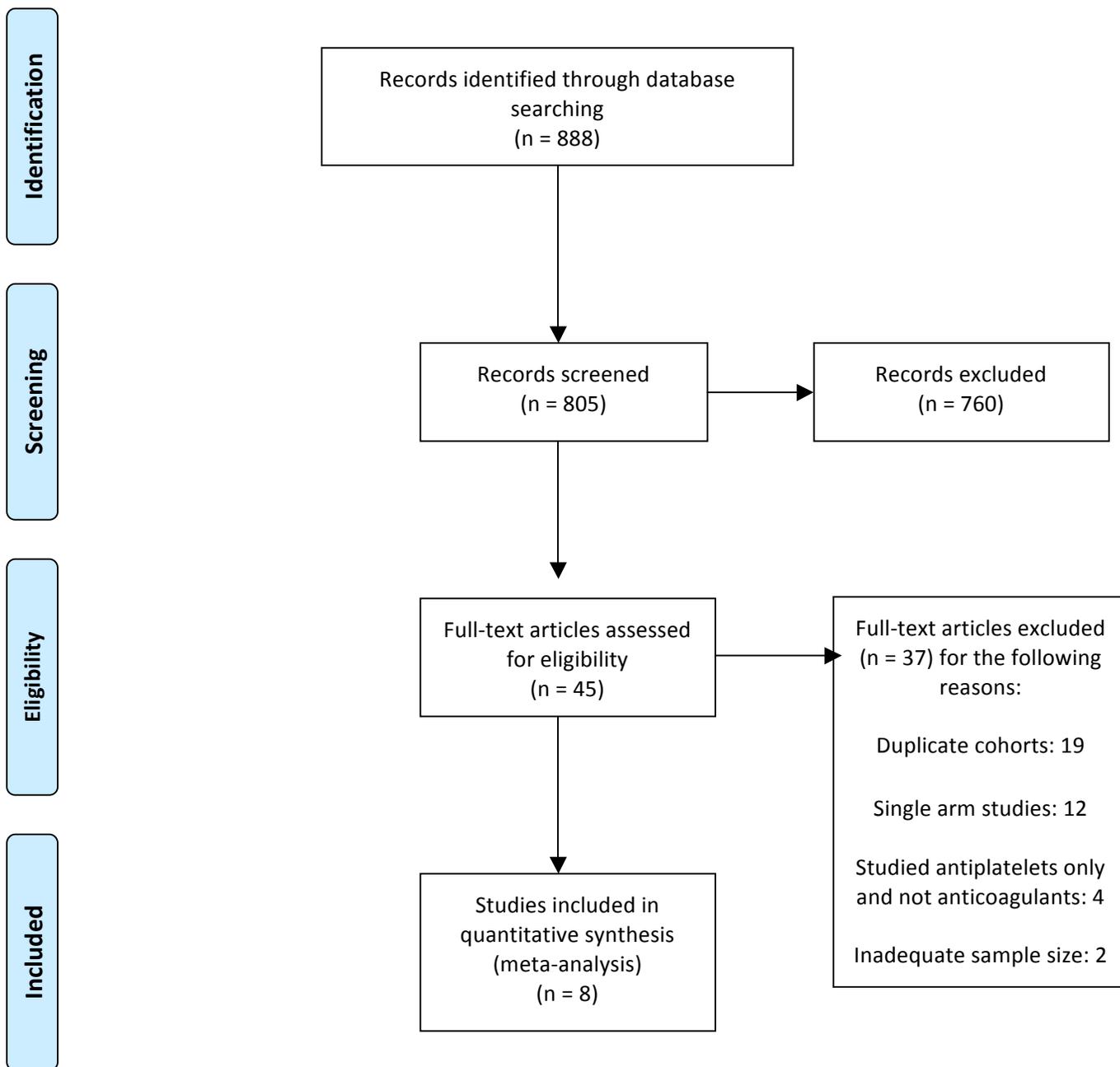
Supplemental Figure II: Funnel Plot to Evaluate Publication Bias of Thromboembolic complications after Intracranial Hemorrhage.

Funnel plot with pseudo 95% confidence limits
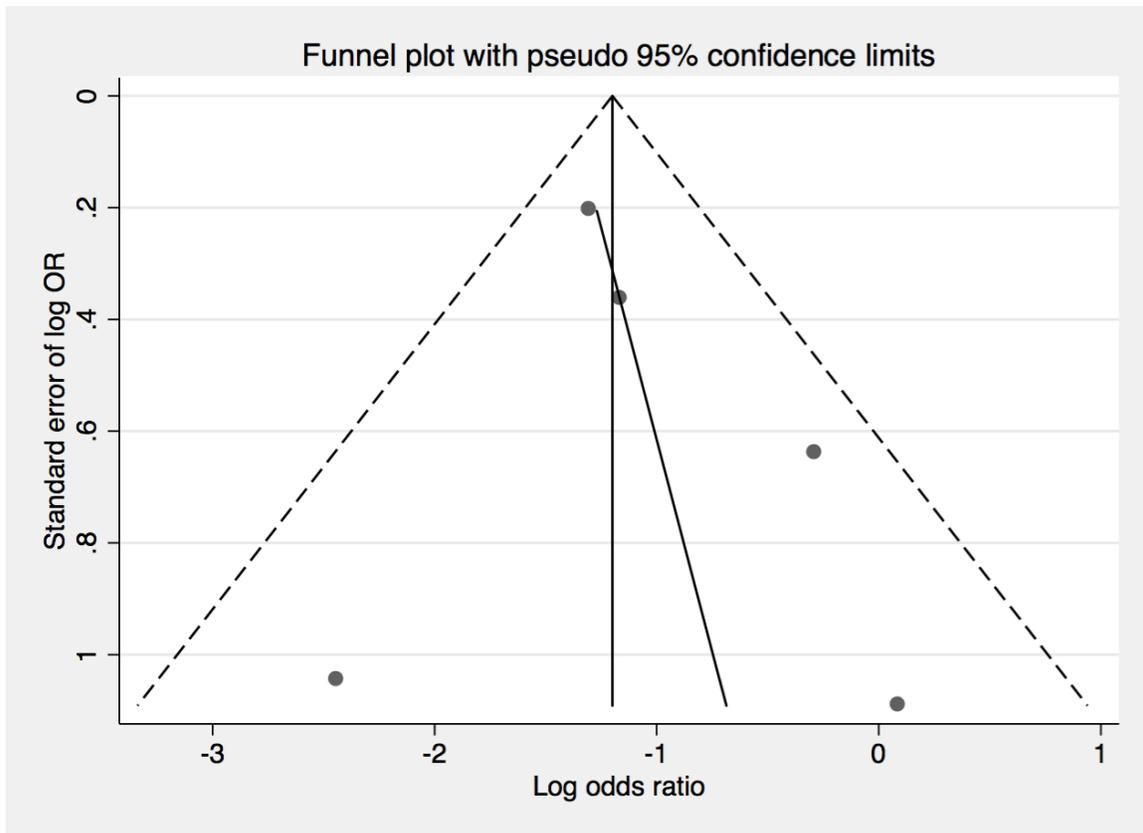
Supplemental Figure III: Funnel Plot to Evaluate Publication Bias of Recurrence of Intracranial Hemorrhage.
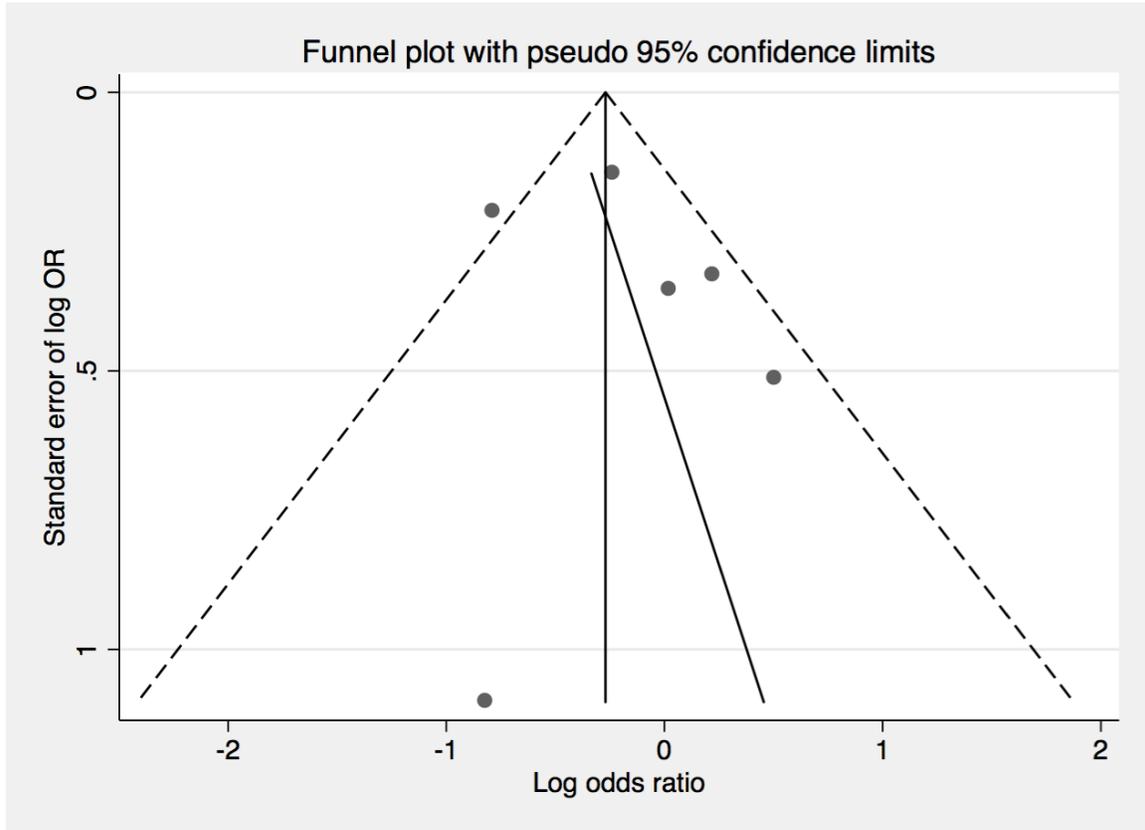
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