Intra-arterial treatment in acute ischemic stroke

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Safety of intra-arterial treatment in acute ischemic stroke patients on oral anticoagulants. A cohort study and systematic review

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ABSTRACT

Background

Elevated INR of > 1.7 is a contra-indication for the use of intravenous thrombolytics in acute ischemic stroke. Local, intra-arterial therapy (IAT) is considered a safe alternative. We investigated safety and outcome of IAT in patients with acute ischemic stroke using oral anticoagulants (OAC).

Methods

Data were obtained from a large national Dutch database on IAT in acute stroke patients. Patients were categorized according to International Normalized Ratio (INR): >1.7 and ≤1.7. Primary outcome was symptomatic Intracerebral Hemorrhage (sICH), defined as deterioration in National Institutes of Health Stroke Scale (NIHSS) score of ≥4 and ICH on brain imaging. Secondary outcomes were clinical outcome at discharge and three months. Occurrence of outcomes was compared with risk ratios and corresponding 95% confidence intervals. Further, we performed a systematic review and meta-analysis on sICH risk in acute stroke patients on OAC treated with IAT.

Results

456 patients were included. Eighteen patients had an INR > 1.7 with a median INR of 2.4 (range 1.8-4.1). One patient (6%) in the INR>1.7 group developed a sICH compared with 53 patients (12%) in the INR≤ 1.7 group (RR 0.49, 95% CI 0.07-3.13). Clinical outcomes did not differ between the two groups. Our meta-analysis showed a first week sICH risk of 8.1% (95% CI 3.9-17.1%) in stroke patients with elevated INR treated with IAT.

Conclusion

The use of OAC, leading to an INR>1.7, did not seem to increase the risk of a sICH in patients with an acute stroke treated with IAT.

INTRODUCTION

The most feared complication of intravenous thrombolysis in acute ischemic stroke is symptomatic intracerebral hemorrhage (sICH) which occurs in 7.7% according to the Cochrane review on the use of thrombolytics in acute stroke.[1] Hence, intravenous thrombolysis in patients with acute ischemic stroke on oral anticoagulants (OAC) is restricted to those with an internationalized standard ratio (INR) of ≤1.7.[2] As a result, in our experience, a considerable number of stroke patients is withheld thrombolytic therapy. With the advent of intra-arterial therapy (IAT), it has become possible to treat patients with acute ischemic stroke by applying local thrombolytic therapy only or mechanical thrombectomy – which often requires no additional thrombolytics. Conceivably, these techniques may therefore be less prone to bleeding complications.

Previous reports on IAT in patients with acute ischemic stroke on OAC suggest that there is no increased risk of intracerebral hemorrhages in these patients.[3-9] However, there are only few such studies and the number of patients studied is limited. In addition, these studies report mainly on patients treated with subtherapeutic INR levels (below 2.0),[5,6] on patients who received IAT after reversion of anticoagulants with fresh frozen plasma[7] or on patients with disturbed hemostasis not related to oral anticoagulants.[4] Therefore, risk of developing sICH and the effect on functional outcome in patients on OAC with acute ischemic stroke treated with IAT is still largely unknown.

We investigated safety and outcome of intra-arterial therapy in patients with acute ischemic stroke on OAC in a large Dutch cohort. To this study, we added a systematic review of the literature on the risk of sICH after intra-arterial therapy.

MATERIALS AND METHODS

Patients

Patient data were obtained from a national Dutch database on intra-arterial treatment in acute stroke patients. This database was initiated in preparation of the MR CLEAN trial, a Dutch, national trial on the use of intra-arterial therapy in acute ischemic stroke. All centers that were willing to participate in the MR CLEAN trial had to provide their “pre-trial experience” (see appendix 1 for participating centers). This assembly of data resulted in a database that contained information on all acute ischemic stroke patients treated with IAT from October 2002 until October 2013 in the major Dutch stroke hospitals. Inclusion in this dataset continued until a center started recruiting for MR CLEAN.

Demographic and clinical data were recorded at baseline (age, sex, time of symptom onset, baseline NIHSS, blood pressure on admission, International Normalized Ratio (INR) on admission).
Registration and use of the data was approved by the institutional review board from the coordinating institution (Erasmus MC Rotterdam). The decisions to treat a patient with intra-arterial therapy were decisions made for each patient individually and intra-arterial treatment was performed only after obtaining consent from the patient or his relatives.

Oral anticoagulants

Patients were grouped based on INR; group1 INR >1.7 and group 2 INR ≤1.7. Oral anticoagulants were not reversed prior to the IAT. No patients on direct oral anticoagulants (DOACs, such as factor Xa and direct thrombin inhibitors) were included in the study.

Intra-arterial treatment (IAT)

Intra-arterial treatment consisted of local intra-arterial thrombolysis, mechanical thrombectomy, thrombosuction, acute carotid stenting or a combination of these techniques. For intra-arterial thrombolysis, alteplase or urokinase was used, often in combination with abciximab or heparin. Mechanical thrombectomy was performed with either a Merci retriever (Concentric Medical, Mountain View, California, USA), Solitaire device (EV3, Irvine, USA), Trevo device (Concentric Medical, Mountain View, California, USA), Revive device (Micrus endovascular, San Jose, California, USA), Catch device (Balt Extrusion, Montmorency, France), "distal access Catheter" (DAC, Concentric Medical, Mountain View, California, USA), Penumbra device (Penumbra Inc, Alameda, California, USA), or a combination of these. Carotid stenting was performed with the Wallstent (Boston Scientific), or comparable dedicated carotid stents. Thombosuction was applied with the Vasco aspiration device (Balt Extrusion, Montmorency, France). The neuro-interventionalist decided which intra-arterial treatment was chosen. Secondary preventive treatment was initiated according to European guidelines.[10]

Radiological characteristics

For each treated patient, site of occlusion or stenosis on CTA, time to intra-arterial treatment (time from start of symptoms until start of angiography), dose of thrombolytics (both intravenous and intra-arterial), devices used and degree of recanalization were recorded. Most patients underwent a CT scan 24 hours after treatment or after any clinical deterioration.

Outcomes

Primary outcome measure was symptomatic intracerebral hemorrhage (sICH). sICH was defined as deterioration in National Institutes of Health Stroke Scale Score (NIHSS) of ≥4 and an ICH on CT or MRI scan according to the ECASS II criteria.[11] Secondary outcome measures were asymptomatic intracerebral hemorrhage (aICH), clinical outcome at discharge and after three months (3 month data from two hospitals only; MC Haaglanden, The Hague and St. Antonius Hospital, Nieuwegein) and recanalization. Clinical outcome was assessed with the modified Rankin Score (mRS).[12,13] Good outcome was defined as a mRS score of 2 or lower. Death from all causes was a separate secondary outcome. Recanalization was assessed with the TICI score [14] by experienced neuro-radiologists blinded for clinical outcome. Recanalization was regarded successful if the TICI score at the end of the intra-arterial procedure was 2b or 3.

Statistical analysis

Descriptive statistics were used for baseline characteristics in the two INR groups. Frequencies of symptomatic intracranial hemorrhage and secondary outcomes were compared between the two groups with risk ratios and 95% confidence intervals. Adjusted risk ratios were calculated with Poisson regression.

Systemic review and meta-analysis

We searched Pubmed for published papers on cohort studies on the risk of sICH in patients with acute ischemic stroke on oral anticoagulation. We combined the concepts "acute ischemic stroke" AND "intra-arterial therapy" AND "oral anticoagulation". We excluded studies containing less than 5 patients on oral anticoagulants and included only studies that were written in English language. Of all publications found, one author (AR) assessed titles for relevance. In case of doubt co-authors were consulted. Reference lists of relevant articles were checked for additional publications.
From each article, number of patients at risk and number of patients with sICH was determined and for each study the one-week risk of sICH with corresponding 95% confidence interval was calculated. For the overall risk assessment, we performed a meta-regression using Poisson regression.

RESULTS

A total of 456 patients were included in the national Dutch database (table 1). Sixty percent of all patients were men and their median age was 62 years. Of these, 18 patients had an INR>1.7 prior to treatment, 438 patients had INRs ≤ 1.7. In the group with INR>1.7, median INR was 2.4 (range 1.8-4.1). The majority of all patients an ischemic stroke in the anterior circulation (72%).

Treatment

Sixty-six percent of all patients were treated with intravenous thrombolysis before intra-arterial therapy was initiated (table 1). However, in the group of 18 patients with elevated INR, only 3 patients (17%) received intravenous thrombolysis before intra-arterial treatment. Their INRs were 1.9, 2.0 and 3.0, respectively. Overall, we were able to retrieve the dose of intravenous alteplase in 160 patients. Of these patients, we were able to retrieve their weight in 136 patients. 91 Patients (67%) received the full-weight-adapted dose and 45 patients (33%) received less of whom 13 patients (10%) received the bridging dose of 0.6mg/kg.

Almost half of all patients (48%) were treated with both intra-arterial thrombolysis and mechanical thrombectomy (Webtable 1, online only). Of these, 79 patients (36%) were treated with a combination of intra-arterial thrombolytics and mechanical thrombectomy and 140 patients (64%) were treated with a combination of intravenous thrombolysis, intra-arterial thrombolytics and mechanical thrombectomy. In 17 (4%) of all 456 patients the endovascular procedure was initiated, but no treatment was performed due to absence of a treatable thrombus or inability to access the site of occlusion (table 1).

Outcome

Intracerebral hemorrhage

Overall, 54 (12%) developed a sICH. In the 18 patients with INR>1.7 one sICHs occurred. This patient was a 49 year old male with a basilar artery thrombosis. He used oral anticoagulants because of atrial fibrillation. His INR previous to treatment was 4.1. Only a mechanical thrombectomy was applied. Two patients (11%) with INR>1.7 developed an aICH compared with 55 (13%) in the group with INR≤1.7 (differences not statistically significant, table 2).

Outcome at discharge and recanalization

In total, 112 patients (25%) died after treatment. Of these, 5 (28%) were in the group with INR >1.7 prior to treatment and 107 (25%) had INRs≤1.7. Of all patients, 99 (22%) had good functional outcome (mRS≤2) at discharge. In the INR>1.7 group

2 patients (11%) had good functional outcome at discharge and in the INR≤1.7 group 97 patients (23%) (differences not statistically significant; table 2, figure 1). Recanalization data were available for 285 patients (63%). Of these 232 (81%) had a complete occlusion (TICI 0) at the start of the intra-arterial procedure. All other patients had a partial occlusion. Recanalization was achieved in 43% of all patients. There were no major differences in recanalization rates between the two groups (table 2). All risk ratios remained essentially the same upon adjustment for age, sex, intravenous treatment, the use of intra-arterial thrombolytics or mechanical thrombectomy (data not shown).

Outcome at three months

Two hospitals (MC Haaglanden, the Hague and St. Antonius hospital, Nieuwegein) also registered functional outcome after three months. Of these 217 patients, 10 had an INR>1.7, 207 had an INR≤1.7. There were no major differences in baseline characteristics between the two groups (Webtable 2, online only).

No additional sICH occurred between discharge and three months follow-up. Functional outcome and death after three months did not differ between INR groups (table 2, figure 1), also after adjustment for covariables (data not shown).

Systematic review and meta-analysis

We identified 5 studies (including our own) that reported on sICH in patients with ischemic stroke treated with intra-arterial therapy who were on oral anticoagulation (table 3).

The number of patients at risk ranged from 7 to 21. The overall incidence of sICH was 8.1% (95% CI 3.9-17.1%) in the first week (figure 2).

DISCUSSION

Our results suggest that patients on OAC might have no increased risk of sICH when applying IAT in acute stroke. Furthermore, we did not find a significant difference in clinical outcome at discharge and after three months. Our meta-analysis review showed an incidence of sICH of 8.1% (95% CI 3.9-17.1%) in the first week after stroke.

These results support the results of previous studies that did not show an increased risk for intracerebral hemorrhage in patients with increased INR treated with intra-arterial treatment.[3-9] However, previous data are limited and heterogeneous. In one study OAC was reversed prior to IAT[7], and two other studies reported on treated patients with subtherapeutic INR levels.[5,6] We were able to present a

substantial number of patients with acute ischemic stroke treated with IAT who used OAC prior to stroke and had an INR within therapeutic range with OAC that was not reversed before treatment. The percentage of 8.1% (95% CI 3.9-17.1%) sICH found in our meta-analysis is comparable with the percentage of symptomatic (including fatal) intracerebral hemorrhage found in a large Cochrane review on thrombolytic therapy for acute ischemic stroke (7.7%).[1] However, it is important to realize that this review represents a heterogenic group of patients from various studies with different definitions of sICH. Previous studies on warfarine treated-patients with acute ischemic stroke treated with intravenous thrombolysis show conflicting results. Smaller, single center, cohort studies report on highly increased risk of sICH in patients on warfarin-treated with intravenous thrombolysis.[14,15,16] On the contrary, a large prospective multicenter by Xian et al report no increased risk of sICH in patients on warfarin.[17] However, all of these studies report on patients on warfarin with subtherapeutic INRs (INR<1.7). Therefore, an adequate comparison between these data and our data is not possible.

Our study has several limitations. First, we had limited data on long term follow-up. Three-month data were only available for two of the participating hospitals. However, these hospitals collected almost half of all data. In addition, all ICHs developed in the first week after IAT during hospitalisation which makes a long-term follow-up not crucial for this study. Secondly, our study was retrospective, hence not all data were complete. However, key data on sICH were missing in less than 1% (3/483). Furthermore, our patient groups were rather young (median age 62 years). As most patients that use OAC are older, this limits the generalizability of our results. Another important limitation of our study is that we investigated retrospective collected data of every day clinical practice with no formal inclusion or exclusion criteria defined. We did not have information on how many patients with an elevated INR were not treated. This might result in a rather heterogeneous patient group prone to selection bias. However, this might also be a strength as these results reflect every day clinical practice.

Our results may seem counter-intuitive. One of the possible explanations for our results might be that the use of oral anticoagulants led to direct intra-arterial treatment with shorter waiting times before treatment because intravenous thrombolysis was withheld. Indeed, in our cohort median time to IAT was half an hour shorter in the INR>1.7 group. This shorter time to intra-arterial treatment may have led to less ischemic brain damage resulting in a lower bleeding risk. Another explanation might be that an increased risk of intracerebral hemorrhage in patients on OAC does not lead to worse outcomes because most ICHs remain asymptomatic. However, the percentage of aICH found in the two groups were

essentially the same. Furthermore, the fact that mechanical thrombectomy was the preferred treatment in patients with prolonged bleeding times might explain the low incidence of sICH in our cohort. Nevertheless, 8 patients in the INR>1.7 group were also treated with intra-arterial thrombolytics and 3 also received intravenous thrombolysis.

Our data and those from the meta-analysis do not indicate that patients on OAC are at increased risk of sICH after IAT. However, the results should be considered with caution as our data was limited and our patient groups were rather young. Nevertheless, intra-arterial treatment could be considered in patients on OAC with acute ischemic stroke that would otherwise be excluded from acute treatment.

TABLES

TABLE 1 Baseline Characteristics

	INR > 1.7 (n=18)	INR ≤ 1.7 (n=438)	Total (n=456)
Median age (range)	61.5 (27-80)	62 (12-93)	62 (12-93)
Male sex (%)	16 (89%)	255 (58%)	271 (59%)
NIHSS, median (range)	14.5 (5-38) (n=18)	16 (1-42) (n=434)	16 (1-42) (n=452)
Anterior circulation stroke (%)	12/18 (67%)	314/437 (72%)	326/455 (72%)
Carotid artery occlusion (%)	0 (0%)	10 (2%)	10 (2%)
Carotid T-top occlusion (%)	2 (11%)	26 (6%)	28 (6%)
MCA occlusion (%)	10 (56%)	278 (64%)	288 (63%)
Posterior circulation stroke (%)	6/18 (33%)	123/437 (28%)	129/455 (28%)
Vertebral artery occlusion (%)	1 (6%)	16 (4%)	17 (4%)
Basilar artery occlusion (%)	5 (28%)	104 (24%)	109 (24%)
PCA occlusion (%)	0 (0%)	3 (1%)	3 (1%)
Stroke onset – presentation ER, median in min (range)[a]	52.5 (10-70) n=12	65 (5-590) n=292	65 (5-590) n=304
Time to IVT, median in min (range)[b]	92.5 (65-120) n=2	100 (25-340) n=229	100 (25-340) n=231
Time to IAT, median in min (range)[c]	206 (90-1150) (n=15)	235 (65-1296) (n=304)	235 (65-1296) (n=319)
Intravenous thrombolysis (%)	3 (17%)	299 (68%)	302 (66%)
Intra-arterial thrombolysis (%)	8 (44%)	312 (71%)	320 (70%)
Mechanical (%)	15 (83%)	325 (74%)	340 (75%)
Failed procedure[d]	1 (6%)	16 (4%)	17 (4%)

INR Internationalized standard Ratio, *NIHSS* National Institutes of Health Stroke Scale, *MCA* Middle Cerebral Artery, *IAT* Intra-arterial Treatment. [a] Defined as time from onset of complaints to presentation on the emergency room. [b]Defined as time from onset of complaints to the start of IVT. [c]Defined as time from onset of complaints to start of IAT. [d]Defined as initiated IAT that eventually was not applied.

TABLE 2 Risk ratios for primary and secondary outcomes.

	INR > 1.7		INR ≤ 1.7[a]		
Outcome	**n/N[b]**	**(%)**	**n/N[b]**	**(%)**	**RR (95% CI)**
sICH	1/18	(6%)	53/437	(12%)	0.49 (0.07-3.13)
aICH	2/18	(11%)	55/437	(13%)	0.88 (0.23-3.38)
mRS≤2 at discharge	2/18	(11%)	97/430	(23%)	0.49 (0.13-1.84)
mRS≤2 at 3 months[c]	4/10	(40%)	72/207	(35%)	1.15 (0.53-2.51)
Death at discharge	5/18	(28%)	107/430	(25%)	1.12 (0.52-2.39)
Death at 3 months[c]	4/10	(40%)	64/207	(31%)	1.29 (0.59-2.84)
Recanalization[d]	4/10	(40%)	118/275	(43%)	0.93 (0.43-2.02)

INR Internationalized Standard Ratio, *RR* risk ratio, *CI* confidence interval, *sICH* symptomatic ICH, *aICH* asymptomatic ICH. [a] reference; [b]denominators sometimes smaller because of missing data; [c]data from two hospitals only; [d]successful when TICI ≥2B.

TABLE 3 Characteristics of the studies included in the meta-analysis.

	Study Design	N	INR	sICH (N)	IVT (N)	IAT (N)	Mechanical (N)
Brekenfeld[3]	Cohort study	7	[a]	1	0	7	*
De Marchis[5]	Cohort study	20	1.8 (1.4-2.3)[b]	1	0	10	16
Nogueira[4]	Cohort study (MERCI)	20	2.4 (1.8-4.9)[c]	2	0	8	20
Rizos[9]	Prospective observation study	21	1.8 (1.4-2.4)[d]	2	12	9[e]	6[e]
Rozeman	Cohort study	18	2.4 (1.8-4.1)[d]	1	3	8	15

INR International Standardized Ratio, *sICH* symptomatic IntraCerebral Hemorrhage, *IVT* IntraVenous Thrombolysis, *IAT* IntraArterial Treatment. [a] data not supplied in article; [b] median (IQR), [c] mean (min-max); [d] median (min-max); [e]Type of intra-arterial treatment not specified.

SUPPLEMENTARY FILES

WEBTABLE 1: Applied therapies

	N[a]	INR>1.7 (N=18)	Median dosage (range)	INR≤1.7 (N=438)	Median dosage (range)
Intravenous thrombolysis	*456*	3 (17%)		299 (68%)	
Alteplase	*446*	2 (11%)	77mg (77-77mg)	294 (69%)	70mg (8-90mg)
Abciximab	*456*	0 (0%)	-	5 (1%)	300mg (300-300mg)
Heparine	*453*	1 (6%)	5000IU	12 (3%)	2750IU (1000-5000IU)
Intra-arterial thrombolysis	*456*	8 (44%)		312 (71%)	
Alteplase	*453*	4 (22%)	17.5mg (15-23mg)	72 (17%)	19.5mg (2-80mg)
Abciximab	*456*	0 (0%)	-	39 (9%)	8mg (2-10mg)
Heparine	*453*	1 (6%)	5000IU	84 (19%)	5000IU (500-50,000IU)
Urokinase	*453*	3 (17%)	500,000 IU (250,000-1,000,000 IU)	219 (50%)	500,000IU (50,000-1,500,000)
Mechanical treatment	*456*	15 (83%)		325 (74%)	
Retraction	*454*	12 (67%)		158 (36%)	
Aspiration	*453*	1 (6%)		31 (7%)	
Stent placement	*453*	4 (22%)		194 (45%)	
Stent-retriever	*456*	3 (17%)		119 (27%)	
Other	*456*	10 (56%)		123 (28%)	

[a] data missing

WEBTABLE 2: Baseline characteristics of the patients with 3-month outcome data (data from two hospitals only)

	INR > 1.7 (n=10)	INR≤1.7 (n=207)	Total (n=217)
Median age (range)	58.5 (46-80)	63 (23-91)	62 (23-91)
Male sex (%)	9 (90%)	149 (64%)	158 (65%)
NIHSS (median)	12.5 (5-38) (n=10)	16 (1-42) (n=206)	15.5 (1-42) (n=216)
Anterior circulation stroke (%)	6 (60%)	142 (69%)	148 (68%)
Carotid artery occlusion (%)	0 (0%)	2 (1%)	2 (1%)
Carotid T-top occlusion (%)	1 (10%)	13 (6%)	14 (7%)
MCA occlusion (%)	5 (50%)	126 (61%)	131 (60%)
Posterior circulation stroke (%)	4 (40%)	65 (31%)	69 (32%)
Vertebral artery occlusion (%)	1 (10%)	15 (7%)	16 (7%)
Basilar artery occlusion (%)	3 (30%)	48 (23%)	51 (24%)
PCA occlusion (%)	0 (0%)	2 (1%)	2 (1%)
Stroke onset – presentation ER, median in min (range)[a]	81 (45-170) (n=5)	61.5 (5-149) (n=120)	62 (5-419) (n=125)
Time to IVT, median in min (range)[b]	120 (n=1)	103 (27-315) (n=97)	104 (27-315) (n=98)
Time to IAT, median in min. (min-max)[c]	205.5 (90-458) (n=8)	210 (65-1111) (n=121)	210 (65-1111) (n=129)
Intravenous thrombolysis (%)	2 (20%)	131 (63%)	133 (61%)
Intra-arterial thrombolysis (%)	3 (30%)	159 (77%)	162 (75%)
Mechanical	8 (80%)	170 (82%)	178 (82%)
Failed procedure[d]	1 (10%)	2 (1%)	3 (1%)

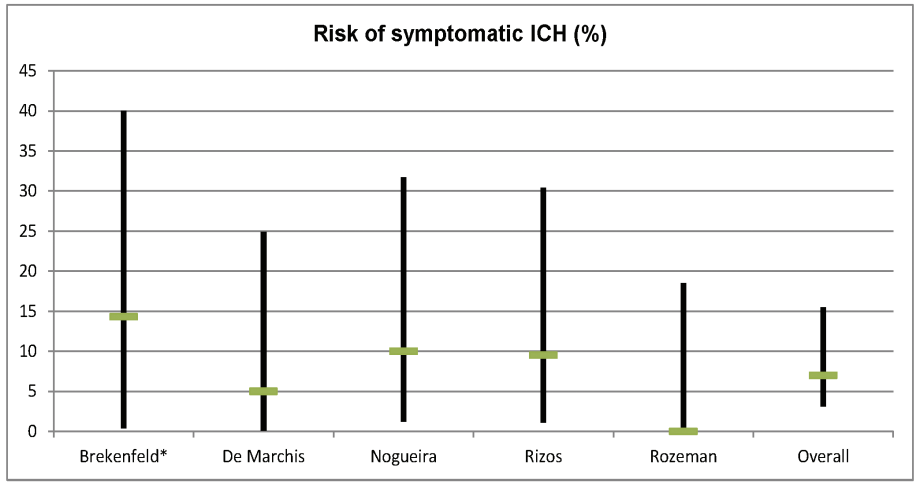
INR Internationalized standard Ratio, *NIHSS* National Institutes of Health Stroke Scale, *IAT* Intra-arterial Treatment. [a] Defined as time from onset of complaints to presentation on the emergency room. [b]Defined as time from onset of complaints to the start of IVT. [c]Defined as time from onset of complaints to start of IAT. [d]Defined as initiated IAT that eventually was not applied.

FIGURES

FIGURE 1 Clinical Outcomes at discharge (A) and after 3 months (B)

FIGURE 2 Meta-analysis: first-week sICH risk after IAT in patients on OAC

* upper limit confidence interval truncated at 40%.



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APPENDICES

Appendix 1 Participating centers

AMC Amsterdam, Rijnstate hospital Arnhem, UMC Groningen, MC Haaglanden The Hague, HAGA The Hague, LUMC Leiden, MUMC Maastricht, St. Antonius hospital Nieuwegein, UMC Nijmegen, Erasmus MC Rotterdam, St. Elisabeth hospital Tilburg, UMC Utrecht, Isala hospitals Zwolle, Atrium MC Heerlen, Medical Spectrum Twente Enschede, Reinier de Graaf hospital Delft.