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CLINICAL INVESTIGATION STROKE/NEUROINTERVENTIONS

Periprocedural Heparin During Endovascular Treatment of Tandem Lesions in Patients with Acute Ischemic Stroke: A Propensity Score Analysis from TITAN Registry

François Zhu[1,22] · Michel Piotin[2] · Henrik Steglich-Arnholm[3] · Julien Labreuche[4] · Markus Holtmannspötter[5] · Christian Taschner[6] · Sebastian Eiden[6] · Diogo C. Haussen[7] · Raul G. Nogueira[7] · Panagiotis Papanagiotou[8] · Maria Boutchakova[8] · Adnan H. Siddiqui[9] · Bertrand Lapergue[10] · Franziska Dorn[11] · Christophe Cognard[12] · Monika Killer-Oberpfalzer[13] · Salvatore Mangiafico[14] · Marc Ribo[15] · Marios N. Psychogios[16] · Alejandro Spiotta[17] · Mohammad Anadani[17] · Marc-Antoine Labeyrie[18] · Mikael Mazighi[2] · Alessandra Biondi[19] · Sébastien Richard[20] · René Anxionnat[1] · Serge Bracard[1] · Francis Turjman[21] · Benjamin Gory[1] on behalf of the TITAN (Thrombectomy In TANdem Lesions) Investigators

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Abstract
Background and Purpose Data on safety and efficacy of periprocedural use of heparin are limited during treatment of acute ischemic stroke patients with anterior circulation tandem occlusion. This study aimed to investigate the impact of heparin use during endovascular therapy of anterior circulation tandem occlusions on the functional and safety outcomes.
Methods A retrospective analysis of the multicenter observational TITAN registry was performed. Patients with anterior circulation tandem occlusion and treated with endovascular therapy (EVT) were included, with or without extracranial carotid intervention. We divided patients

A list of TITAN (Thrombectomy In TANdem Lesions) investigators are given in the Appendix section.

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✉ François Zhu
f.zhu@chru-nancy.fr

1 Department of Diagnostic and Therapeutic Neuroradiology, IADI INSERM U1254, University Hospital of Nancy, Nancy, France

2 Department of Interventional Neuroradiology, Rothschild Foundation, Paris, France

3 Department of Neurology, Rigshospitalet, Copenhagen, Denmark

4 EA 2694-Santé Publique: Epidémiologie et Qualité des Soins, Department of Biostatistics, CHU Lille, University of Lille, Lille, France

5 Department of Neuroradiology, Rigshospitalet, Copenhagen, Denmark

6 Department of Neuroradiology, Medical Center, University of Freiburg, Freiburg, Germany

7 Department of Neurology, Emory University/Grady Memorial Hospital, Atlanta, Georgia

8 Diagnostic and Interventional Neuroradiology, Hospital Bremen-Mitte/Bremen-Ost, Bremen, Germany

9 Department of Neurosurgery, State University of New York, Buffalo, USA

10 Department of Neurology, Stroke Center, Foch Hospital, Suresnes, France

11 Department of Neuroradiology, University Hospital of Munich, Munich, Germany

12 Department of Neuroradiology, University Hospital of Toulouse, Toulouse, France

13 Department of Neurology, Paracelsus Medical University Salzburg, Salzburg, Austria

14 Department of Interventional Neuroradiology, Careggi University Hospital, Florence, Italy

15 Department of Neurology, Hospital Vall D'Hebron, Barcelona, Spain

16 Department of Neuroradiology, University Medical Center Göttingen, Göttingen, Germany

into two groups based on periprocedural heparin use (heparin vs. non-heparin). The dose of intravenous unfractionated heparin ranged from 1500 to 2500 I.U. Primary study endpoint was 90-day Modified Rankin Scale (mRS). Secondary study endpoint included angiographic and safety endpoints such as hemorrhagic complications. A propensity-score-matched analysis was performed.

Results Among 369 patients, heparin was used in 68 patients (18.4%). In the propensity-score-matched cohort, favorable outcome (mRS 0–2) occurred in 51.3% in heparin group and 58.0% in non-heparin group (matched OR, 0.76; 95% CI, 0.32–1.78; $P = 0.52$). Similar result was found in propensity-score-adjusted cohort (adjusted OR, 0.72; 95%CI, 0.39–1.32; $P = 0.28$). Likewise, there was no difference in the rate of successful reperfusion (mTICI 2b-3) (propensity-score-adjusted OR, 1.03; 95%CI, 0.50–2.09; $P = 0.93$) neither in safety endpoints between the two groups.

Conclusions Periprocedural heparin use during EVT of anterior circulation tandem occlusions was not associated with better functional, angiographic or safety outcomes. These findings are applicable for low doses of heparin, and further studies are warranted.

Keywords Heparin · Stroke · Tandem occlusion · Thrombectomy · Endovascular Treatment · Anticoagulation

Introduction

Endovascular therapy (EVT) is the standard of care for anterior circulation tandem occlusion in patients with acute ischemic stroke [1]. Despite the remarkable advances in the endovascular devices, periprocedural pharmacological therapy remains an essential part of endovascular therapy. Periprocedural unfractionated heparin therapy can potentially improve reperfusion and subsequently clinical outcome after endovascular therapy; however, the theoretical risk of hemorrhagic complications makes it a less appealing treatment choice [2]. A post hoc analysis of the MERCI and TREVO-2 trials demonstrated a potential benefit of periprocedural heparin during mechanical thrombectomy with no increased risk of hemorrhagic complications [3, 4].

The aforementioned trials, however, only included patients with intracranial occlusions; therefore, their results may not apply to patients with tandem occlusions. In this study, we aimed to investigate the effect of periprocedural heparin use on the functional, angiographic and safety outcomes of EVT of anterior circulation tandem occlusions.

Materials and Methods

Patients Inclusion

The TITAN (Thrombectomy in Tandem Lesions) international registry pooled individual data from prospectively collected thrombectomy databases across 18 institutions. A total of 11 institutions provided information regarding the periprocedural heparin use and were included in the present study (Fig. 1). The number of patients included in each center is reported in the Supplemental Table 1. Patient eligibility and methods of TITAN collaboration have been previously reported [5]. Patients were included if they presented with acute stroke symptoms due to anterior circulation tandem occlusion and were treated with EVT. Tandem occlusion was defined as a proximal intracranial occlusion (distal intracranial carotid artery [ICA] and/or middle cerebral artery, M1 and/or M2 segment) and an extracranial ICA lesion (complete occlusion or stenosis $\geq 90\%$ North American Symptomatic Carotid Endarterectomy Trial). All mechanical thrombectomies were performed using modern mechanical devices (stent retrievers and/or large bore distal aspiration catheters). Intravenous heparin was administered at the operator discretion during EVT. Heparin dose bolus ranged from 1500 to 2500 I.U. or to target an Activated Clotting Time (ACT) < 250. All patients underwent computed tomography (CT) or magnetic resonance imaging (MRI) at 24 h after treatment onset to assess for hemorrhagic complications. Clinical and angiographic outcomes were reported by local investigators in each institution. The local institutional review boards approved the study. Informed consent was not required as this was a retrospective analysis. All data and materials have been made publicly available in a

[17] Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA

[18] Department of Interventional Neuroradiology, Lariboisière Hospital, Paris, France

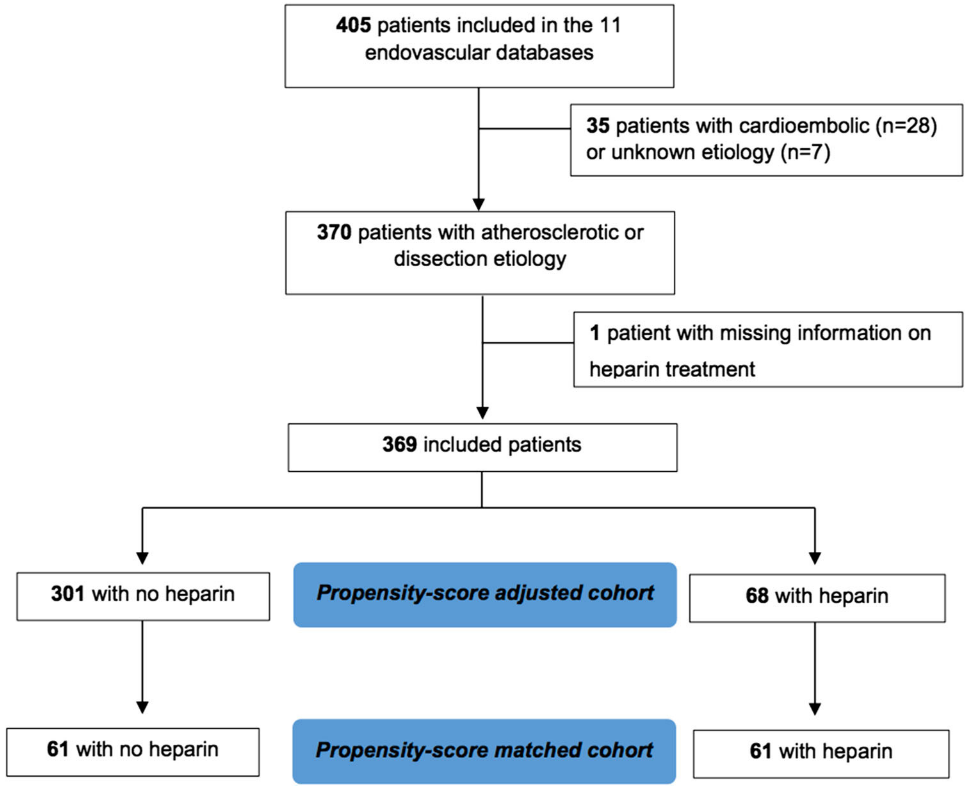
[19] Department of Neuroradiology and Endovascular Therapeutic, University Hospital of Besançon, Besançon, France

[20] Department of Neurology Stroke Unit, INSERM U1116, University Hospital of Nancy, Nancy, France

[21] Department of Interventional Neuroradiology, Hospices Civils de Lyon, Lyon, France

[22] Department of Diagnostic and Therapeutic Neuroradiology, CHRU Nancy, Hôpital Central, 29 Avenue du Maréchal de Lattre de Tassigny, 54035 Nancy, France

Fig. 1 Study flowchart



public repository and can be accessed by a request from Dr. Benjamin Gory, MD, Ph.D.

Outcomes

The primary study endpoint was the favorable outcome, defined as 90-day Modified Rankin Scale (mRS) 0–2. Secondary study endpoints included successful reperfusion defined as modified thrombolysis in cerebral infarction (mTICI) 2b-3, complete reperfusion (mTICI 3), all-cause 90-day mortality, any procedural-related complications, any intracranial hemorrhage (ICH), parenchymal hematoma and symptomatic ICH. Symptomatic ICH was defined as any parenchymal hematoma, subarachnoid hemorrhage or intraventricular hemorrhage associated with worsening of the National Institutes of Health Stroke Scale (NIHSS) score by 4 points or more.

Statistical Analysis

Quantitative variables are expressed as means (standard deviation) in the case of normal distribution or medians (interquartile range) otherwise. Categorical variables are expressed as numbers (percentage). Normality of distributions was assessed using histograms and the Shapiro–Wilk test. We assessed the effect of the heparin use on angiographic and clinical outcomes using binary or ordinal (for overall mRS distribution) logistic regression models; odds ratio (OR) and common OR (cOR) for 1-point improvement with their 95% confidence intervals (CIs) were derived from logistic models as effect size using non-heparin group as reference. In order to reduce the effects of potential confounding factors in the between-group comparisons, we used propensity score methods [6]. As the main analysis, propensity score was used to assemble well-balanced groups (propensity-score-matched cohort) and a generalized linear mixed model was used to take into account the matched design. As a secondary analysis, the propensity score was used as a covariate in a logistic regression model to adjust the comparisons (propensity-score-adjusted cohort). The propensity score was estimated using a non-parsimonious multivariate logistic regression model, with the treatment group as the dependent variable and all of the characteristics listed in Table 1 as covariates. Patients from the heparin group were matched 1:1 to patients in the non-heparin group according to propensity score using the greedy nearest neighbor matching algorithm with a caliper width of 0.2 standard deviation of logit for propensity score [7]. To evaluate bias reduction using the propensity-score-matching method, absolute standardized differences were calculated before and after propensity score matching; an absolute standardized difference > 10% indicated a meaningful imbalance in the baseline covariate [8]. Due to missing baseline data (see

Table 1 Baseline characteristics according to heparin use before and after matching

Characteristics	Before matching[1]			After matching[1]		
	No heparin (n = 301)	Heparin (n = 68)	ASD, %	No heparin (n = 61)[2]	Heparin (n = 61)[2]	ASD, %
Demographics						
Age, year, mean (SD)	64.0 (12.3)	61.4 (5.5)	20.2	61.5 (17.5)	61.6 (13.2)	0.8
Women	100 (33.4)	28 (41.8)	17.4	25 (41.4)	25 (40.3)	2.2
Medical history						
Hypertension	169 (56.2)	40 (58.8)	5.3	35 (57.3)	35 (57.4)	0.2
Diabetes	44 (14.6)	12 (17.1)	6.7	9 (15.4)	10 (16.3)	2.6
Hypercholesterolemia	116 (38.6)	16 (23.2)	33.8	15 (24.3)	14 (23.7)	1.4
Current smoking	97 (32.3)	20 (29.1)	7.0	18 (29.2)	18 (30.4)	2.5
Admission NIHSS, mean (SD)	16.1 (5.5)	14.0 (7.0)	33.0	15.0 (7.0)	14.6 (6.8)	6.0
Initial imaging modality, MRI versus CT scan	113 (37.6)	36 (53.1)	31.4	32 (51.7)	31 (50.6)	2.0
ASPECTS, median (IQR)	8 (7–9)	8 (6–9)	2.4[3]	7 (6–9)	8 (6–9)	11.6
Extracranial ICA etiology						
Atherosclerosis	232 (77.1)	56 (82.4)	13.1	48 (79.1)	49 (80.4)	3.1
Dissection	69 (22.9)	12 (17.6)		13 (20.9)	12 (19.6)	
Extracranial ICA lesion						
Stenosis ≥ 90%	162 (53.8)	23 (33.8)	41.1	40 (65.2)	39 (64.4)	1.8
Occlusion	139 (46.2)	45 (66.2)		21 (34.7)	22 (35/6)	
Intracranial occlusion, ICA versus MCA	103 (34.2)	17 (25.0)	20.3	17 (27.6)	17 (27.8)	0.04
Treatment characteristics						
Prior use of IV t-PA	201 (66.8)	30 (44.1)	46.8	28 (46.1)	28 (45.6)	1.1
General anesthesia	161 (53.5)	44 (64.7)	23.0	41 (67.5)	39 (64.7)	5.8
Onset to groin puncture, minutes, median (IQR)	245 (182–332)	250 (184–305)	1.6[3]	251 (183–355)	243 (183–305)	9.2
Intracranial thrombectomy devices						
Stent retriever	270 (89.7)	56 (82.4)	21.3	50 (82.3)	51 (82.8)	1.5
ADAPT alone	31 (10.3)	12 (17.6)		11 (17.7)	10 (17.2)	
Extracranial ICA procedure						
None	62 (20.8)	10 (14.1)	18.8	11 (17.8)	9 (15.7)	11.4
Angioplasty alone	37 (12.1)	7 (11.6)		6 (9.3)	7 (11.1)	
Stenting	202 (67.1)	51 (74.3)		44 (72.9)	45 (73.2)	
Antiplatelet drug						
None	122 (27.9)	23 (33.8)	28.1	27 (44.4)	26 (42.3)	13.5
Single agent	95 (31.6)	33 (48.5)		23 (37.1)	24 (39.5)	
≥ 2 agents	84 (27.9)	12 (17.7)		11 (18.5)	11 (18.2)	

Values expressed as numbers (%) unless otherwise indicated

ADAPT a direct aspiration first pass technique, *ASPECTS* Alberta stroke program early CT score, *CT* computed tomography, *ICA* internal carotid artery, *IQR* interquartile range, *IV* intravenous, *MCA* middle cerebral artery, *MRI* magnetic resonance imaging, *NIHSS* National Institutes of Health Stroke Scale, *SD* standard deviation, *ASD* absolute standardized difference

[1]Calculated after handling missing data using multiple imputation procedures (m = 10)

[2]Mean number of matched pairs across the 10 imputed datasets

[3]Estimated using the rank-transformed data

Supplemental Table II), we estimated the treatment effect size in propensity-score-matched and propensity-score-adjusted cohorts after handling missing covariate values by multiple imputations [9], using a regression switching approach (chained equations with $m = 10$ imputations) [10]. Imputation procedure was performed under the missing at random assumption using all variables listed in supplemental Table (i.e., baseline characteristics, outcomes and treatment group) with a predictive mean matching method for continuous variables and logistic regression model (multinomial, ordinal or binary) for categorical variables. In each imputed dataset, we calculated the propensity score and assembled a matched cohort to provide both adjusted and matched ORs. Then, we combined the ORs from each imputed dataset using Rubin's rules [11]. Statistical testing was conducted at the two-tailed α-level of 0.05. Data were analyzed using the SAS software version 9.3 (SAS Institute, Cary, NC).

Results

A total of 405 patients with tandem lesions were enrolled from January 2012 to February 2016 in 11 centers. Of these patients, 28 patients with cardioembolic etiology, 7 patients with undetermined etiology, and 1 patient without information on heparin administration were excluded, yielding 369 patients included in the present analysis. The number of included per center, with information on heparin and stenting treatment are available in the online Supplemental Table I. A total of 203 (83.3%) patients were treated within the first 6 hours after symptom onset (Supplemental Table II). Among included patients, heparin was used during EVT in 68 patients (18.4%) (Fig. 1). 61 of 68 heparin-treated patients were matched using propensity score approach to 61 untreated patients. Table 1 shows the baseline characteristics according to the heparin use before and after propensity score matching and after handling missing values by multiple imputations (see online Supplemental Table II for baseline characteristics before matching and handling missing values). Before matching, several meaningful differences (absolute standardized difference > 10%) were found. These differences were reduced after propensity score matching (Table 1 and Supplemental Figure) with an absolute standardized difference > 10% only for ASPECTS (11.6%), extracranial ICA procedure (11.4%) and number of antiplatelet drugs (13.5%), whereas prior use of IV thrombolysis was not (1.1%), suggesting that the two study groups were well balanced after matching.

In the propensity-score-matched cohort, favorable outcome (pre-specified as primary outcome) occurred in 51.3% in heparin group and 58.0% in non-heparin group without significant difference (matched OR, 0.76; 95% CI, 0.32–1.78; $P = 0.52$) (Fig. 2A). Similar results were found in propensity-score-adjusted cohort (Fig. 2B) or when overall mRS was analyzed (shift analysis, Fig. 3); the common OR for 1 point improvement in mRS was 0.76 (95% CI, 0.36–1.60; $P = 0.47$) and 0.77 (95% CI, 0.36–1.63, $P = 0.50$) in propensity-score-matched and propensity-score-adjusted cohorts, respectively. Regarding angiographic outcomes, successful reperfusion (mTICI 2b-3) was achieved in similar proportion in both groups in propensity-score-matched and propensity-score-adjusted cohorts (Fig. 2A, B). Similarly, there was no significant difference in complete reperfusion (mTICI 3) between the two groups (propensity-score-adjusted OR of 0.56; 95% CI, 0.28–1.10; $P = 0.09$). In both propensity-score-matched and propensity-score-adjusted cohorts, safety outcome rates did not differ between the two groups. In propensity-score-matched cohort (Fig. 2A), any procedural complications (39 emboli to new territories (9.2%), 9 vessel perforations (2.2%), 4 carotid dissections (1.0%) and 6 others complications (1.5%)) occurred in 20.9% in heparin group versus 13.3% in non-heparin group, 90-day all-cause mortality in 17.8% in heparin group versus 14.2% in non-heparin group, and 24-h parenchymal hematoma in 11.1% versus 15.2% in non-heparin group. No intraventricular hemorrhage occurred, and only 15 subarachnoid hemorrhages occurred (11 in heparin group and 4 in no heparin group, see Supplemental Table II).

Discussion

Our analysis of TITAN data demonstrated that the use of periprocedural heparin in patients with tandem occlusions treated with EVT was not associated with angiographic, clinical or safety outcomes.

The data on the safety and efficacy of periprocedural heparin during EVT are scarce [2]. In a post hoc analysis of the TREVO 2 trial that included 173 patients, the use of heparin was independently associated with good functional outcome (90-day mRS 0–2) (OR, 5.30; 95%CI, 1.70–16.48) [3]. A post hoc analysis of the MERCI trial that included 51 patients reported similar results [4]. Both studies concluded that the use of the heparin during EVT may improve functional outcome with no increased risk of hemorrhagic complications. In contrast to the previous reports, we did not find a difference in good outcome between heparin and non-heparin groups. Similar to our study, there was no significant difference in the rate of successful revascularization between heparin and non-heparin groups in the abovementioned post hoc analyses [3, 4].

The lack of the effect of heparin on functional outcome in tandem occlusions could be related to the theoretical fact that most of the tandem occlusions are secondary to atherosclerotic disease with large clot burden rendering heparin less effective. However, our findings are derived from analysis of low doses of heparin; higher therapeutic doses should be further studied but have to be balanced with hemorrhagic risks.

Concerning safety endpoints, low-dose heparin therapy was not associated with an increased risk of any ICH, symptomatic ICH or parenchymal hematoma within 24 h

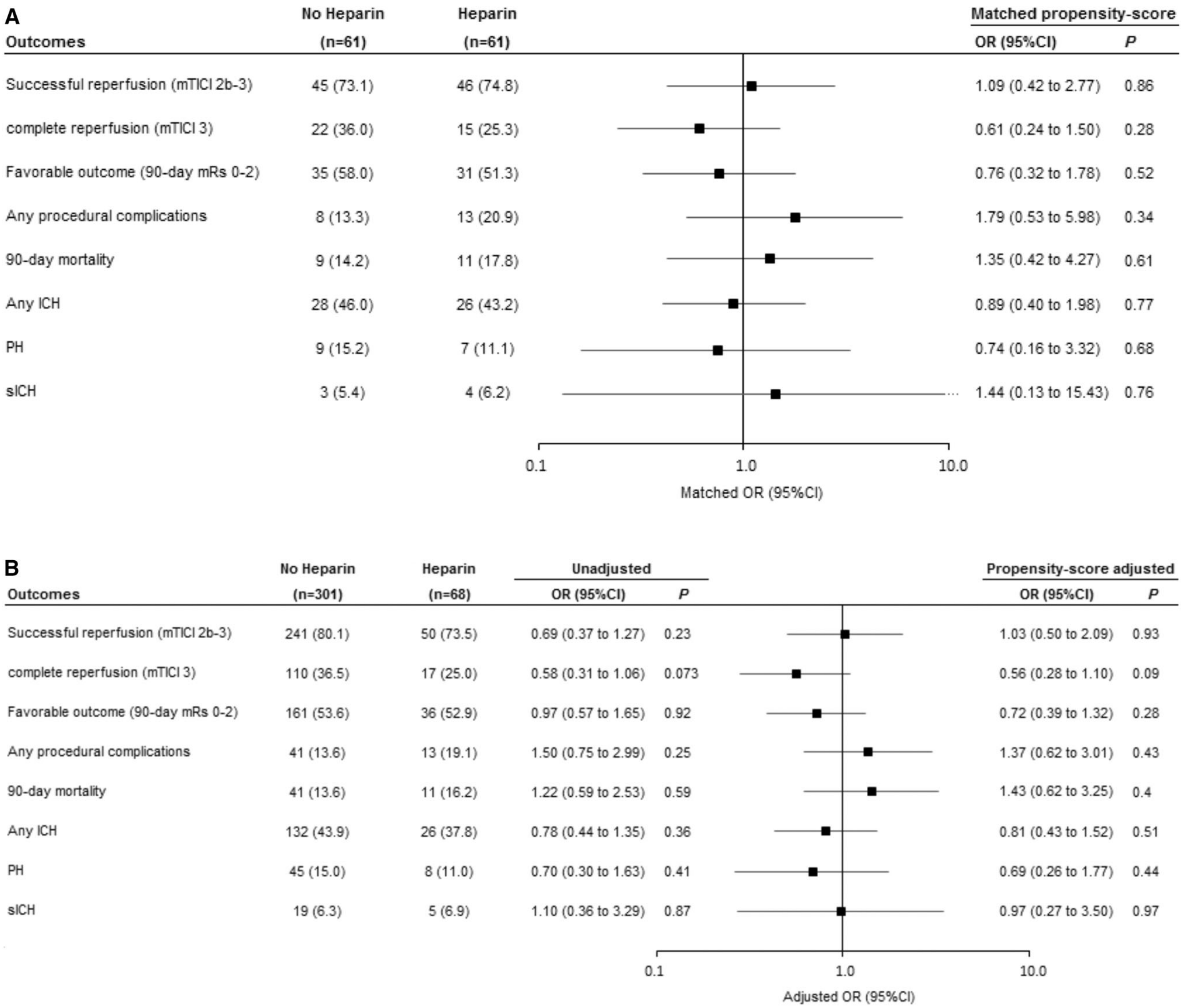


Fig. 2 Angiographic and clinical outcomes according to heparin use in propensity-score-matched (**A**) and propensity-score-adjusted (**B**) cohorts. *CI* confidence interval, *ICH* intracranial hemorrhage, *mTICI* modified thrombolysis in cerebral infarction, *OR* odds ratio, *PH* parenchymal hematoma, *sICH* symptomatic intracranial hemorrhage

in our study a finding that is consistent with previous studies [3–5, 12].

Although we did not find an association between heparin use with the functional and angiographic outcomes, there is still potential benefit of intraprocedural heparin to reduce emboli to new territories and clot extension during endovascular therapy [13]. Concerning its role in the potential benefit to reduce in-stent thrombosis in case of carotid stenting, unfortunately, information regarding stent thrombosis was available only for 50% of the included patients; therefore, no reliable conclusion can be drawn from our study (see Supplemental Table II). In any case, antiplatelet therapy should be administered as the first line treatment rather than heparin [13], deserving further analysis from TITAN registry focusing on anti-aggregation regimen after carotid stenting. Pending the results of the ongoing MR CLEAN-MED (Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands investigating the effect of periprocedural MEDication. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-001466-21/NL) trial, the decision on periprocedural heparin use should be made on a case-by-case basis, depending on multiple factors such as comorbidities, previous antithrombotic use and initial infarct volume.

Limitations

The present study has multiple limitations related to its observational, non-randomized design. First, there was no

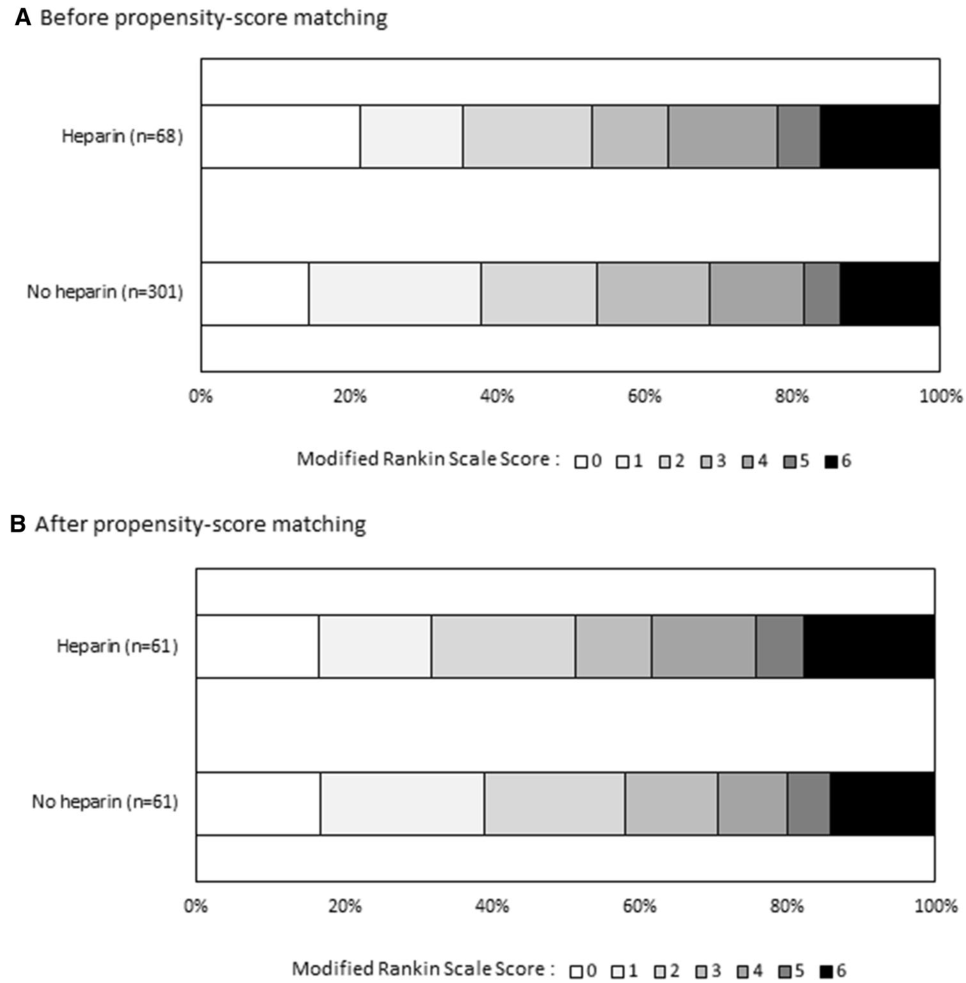


Fig. 3 Distribution of Modified Rankin Scale (mRS) scores according to heparin use before (**A**) and after propensity score matching (**B**). Missing values (on mRS) and baseline characteristics used to calculate propensity score were handled by multiple imputations

independent imaging or clinical assessments. Second, our results could be confounded by unmeasured variables, like prior use of antithrombotic therapy, and initial diffusion-weighted imaging infarct volume. Second, handling data with multiple imputations could have introduced a significant bias in estimates. Third, it is possible that our study was underpowered to detect a difference in functional and safety outcome. Notably, in a posterior power calculation, we calculated the smallest significant between-group difference (expressed as effect size using odd ratio) that our study sample size allowed us to detect with an 80% power. Assuming an incidence of outcome of 20% in no heparin group, we could detect an OR of 3.1 in the propensity-score-matched cohort and 2.3 in propensity-score-adjusted cohort. Assuming an incidence of outcome of 50% in no heparin group, we could detect an OR of 2.9 in the propensity-score-matched cohort and 2.2 in propensity-score-adjusted cohort. Finally, the dose of heparin varied between centers and was not available for this study. Intravenous heparin bolus was below the therapeutic level, with heterogeneous monitoring and without adaptation to the body weight. This study suffers from missing data such as intra-stent thrombosis rates which is a crucial information in this context. Moreover, analyses were performed without considering the different carotid stent used, potentially causing evaluation bias.

Conclusion

Periprocedural heparin use during endovascular therapy of anterior circulation tandem occlusion strokes was not associated with higher functional, angiographic or safety outcomes in our multicenter observational study. These findings are, however, only applicable to low doses of heparin; further studies are warranted to determine the utility and safety of periprocedural antithrombotic therapy.

Funding This work was supported by Stryker.

Compliance with Ethical Standards

Conflict of interest Dr. Piotin reports grants from penumbra, personal fees from Medtronic, other from Stryker, other from

Microvention, other from Balt, outside the submitted work. Dr. Taschner reports grants and non-financial support from Microvention, personal fees and non-financial support from Stryker, non-financial support from Acandis, personal fees and non-financial support from Neuravi, non-financial support from Medtronic, outside the submitted work. Dr. Nogueira reports non-financial support from Stryker, non-financial support from Medtronic, non-financial support from Penumbra, outside the submitted work. Dr. Papanagiotou reports grants from Medtronic, non-financial support from Penumbra Inc., non-financial support from Johnson & Johnson, outside the submitted work. Dr. Siddiqui reports grants from National Institutes of Health/NINDS/NIBIB, University at Buffalo, personal fees from Hotspur, Intratech Medical, StimSox, Valor Medical, Blockade Medical and Lazarus Effect;, non-financial support from Codman & Shurtleff, Inc, Concentric Medical, ev3/Covidien Vascular Therapies, GuidePoint Global Consulting, Penumbra, Stryker, Pulsar Vascular, Microvention, Lazarus Effect, Blockade Medical, other from null, outside the submitted work. Dr. Lapergue reports non-financial support from Medtronic, non-financial support from Penumbra, outside the submitted work. Dr. Cognard reports personal fees from Medtronic, personal fees from Microvention, personal fees from Stryker, outside the submitted work. Dr. Spiotta reports non-financial support from Penumbra, non-financial support from Pulsa Vascular, non-financial support from Microvention, non-financial support from Stryker, outside the submitted work. Dr. Mazighi reports non-financial support from Medtronic, non-financial support from Boehringer Ingelheim, non-financial support from Bayer, non-financial support from Servier, outside the submitted work. Dr. Biondi reports non-financial support from Balt, non-financial support from Medtronic, non-financial support from Microvention, non-financial support from Stryker, non-financial support from Phenox, outside the submitted work. Dr. Turjman reports grants from Stryker, during the conduct of the study, non-financial support from Stryker, non-financial support from Medtronic, non-financial support from Johnson & Johnson, non-financial support from Balt, outside the submitted work. Dr. Gory reports grants from Stryker, personal fees from Medtronic, non-financial support from Balt, during the conduct of the study. François Zhu, Dr Steglich-Arnholm, Julien Labreuche, Dr Holtmannspötter, Dr Eiden,Dr Haussen, Dr Boutchakova, Dr Dorn, Dr Killer, Dr Mangiafico, Dr Ribo, Dr Psychogios, Dr Anadani, Dr Labeyrie, Dr Richard, Dr Anxionnat, Dr Bracard have nothing to disclose.

Informed Consent The local institutional review boards approved the study. Informed consent was not required as this was a retrospective analysis. All data and materials have been made publicly available in a public repository and can be accessed by a request from Dr. Benjamin Gory, MD, Ph.D.

Appendix: TITAN (Thrombectomy in TANdem Lesions) Investigators

Andreas Kastrup, Jonathan Andrew Grossberg, Adrien Guenego, Julien Darcourt, Isabelle Vukasinovic, Elisa Pomero, Jason Davies, Leonardo Renieri, Corentin Hecker, Maria Muchada, Arturo Consoli, Georges Rodesch, Emmanuel Houdart, Raymond Turner, Aquilla Turk, Imran Chaudry, Johanna Lockau, Raphaël Blanc, Hocine Redjem, Daniel Behme, Hussain Shallwani, Maurer Christopher, Anne-Laure Derelle, Romain Tonnelet, Liang Liao, Lisa Humbertjean, Gioia Mione, Jean-Christophe Lacour.

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