ORIGINAL PAPER

Nagoya J. Med. Sci. **83**. 125–133, 2021
doi:10.18999/nagjms.83.1.125

Case-control study of postprocedural arterial puncture site hemorrhage after neuroendovascular treatment

Yosuke Tamari, Takashi Izumi, Masahiro Nishihori, Tasuku Imai, Masashi Ito, Tetsuya Tsukada, Mamoru Ishida and Toshihiko Wakabayashi

Department of Neurosurgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

ABSTRACT

Puncture site hemorrhage following femoral artery catheterization is a significant cause of morbidity. The aim of this case-control study was to identify predictors of postprocedural arterial hemorrhage at the puncture site. We retrospectively reviewed 255 patients who underwent endovascular treatment at our institution over a 23-month period and classified them into a hemorrhage group and a non-hemorrhage group. Puncture site hemorrhage occurred in 15 patients (5.9%). Clinical factors associated with a significantly increased risk of puncture site bleeding included patients whose postoperative activated clotting time of ≥300 seconds before removal of the sheath (9 patients, 11.8%; $P<0.05$), those who received triple antiplatelet therapy (n=4, 17.4%; $P<0.05$) and the group administered heparin postoperatively (7 patients, 13.2%; $P<0.05$). The effects of low on-treatment platelet reactivity, i.e., P2Y12 reaction units <95%, sheath size, hemostasis method used, and operating time were not clinically significant. Our findings suggest an increased risk of puncture site hemorrhage in patients who either had an activated clotting time ≥300 seconds before the postoperative removal of the sheath, had received triple antiplatelet therapy, or were administered heparin postoperatively.

Keywords: neuroendovascular therapy, puncture site hemorrhage, femoral approach, anticoagulant, complications

Abbreviations:
ACT: activated clotting time
PRU: P2Y12 reaction units
HPR: high on-treatment platelet reactivity
LPR: low on-treatment platelet reactivity
VCD: vascular closure device

INTRODUCTION

Endovascular treatment is becoming an increasingly common type of minimally invasive surgery worldwide. The most frequent puncture site is the femoral artery. Puncture site hemor-

Received: April 14, 2020; accepted: August 31, 2020
Corresponding Author: Takashi Izumi, MD, PhD
Department of Neurosurgery, Nagoya University Graduate School of Medicine,
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Tel: +81-52-744-2353, Fax: +81-52-744-2360, E-mail: my-yuzu@med.nagoya-u.ac.jp

rhage following femoral artery catheterization is a significant cause of morbidity, occurring as a complication in 5%–10% of patients and leading to potentially fatal pseudoaneurysm requiring surgical repair in approximately 1.5% of patients with retroperitoneal hematoma.[1] Correlations have been found between the risk of puncture site complications and the number of antiplatelet drugs prescribed and intraoperative heparinization.[1]

Since the introduction of the Seldinger technique almost half a century ago, the gold standard for achieving hemostasis after catheterization of the femoral artery has been manual compression. In recent years, vascular closure devices (VCDs) have been developed and found to have excellent safety and efficacy in several meta-analyses.[2,3,4] However, puncture site hemorrhage may still occur even with bed rest and use of a VCD, and there is no information in the literature on risk factors for postprocedural bleeding at the puncture site after neuroendovascular treatment via the femoral artery. The aim of this case-control study was to identify predictors of postoperative arterial puncture site hemorrhage after neuroendovascular treatment.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Nagoya University Hospital (#2019–0527).

We retrospectively identified 255 patients who had undergone retrograde transfemoral arterial puncture during a neuroendovascular procedure at Nagoya University Hospital in the 23 months from April 2014 to February 2016 (Table 1). Postprocedural puncture site hemorrhage was defined as arterial bleeding occurring after hemostasis with subsequent formation of hematoma. Patients with any degree of ooze were excluded. The patients were divided into a hemorrhage

Table 1 Characteristics of puncture site hemorrhage after neuroendovascular treatment

Parameter	Total	No hemorrhage No. (%)	Hemorrhage No. (%)	P-value
Case	255	240	15	
Age (years; median)		68.2 2–85	62.9 57–80	0.310
Sex				
Female	135	124 (51.7)	11 (73.3)	0.117
Male	120	116 (48.3)	4 (27.7)	
Body mass index (kg/m^2; median)	253	22.5 12.0–56.3	22.9 16.2–26.2	0.803
Past medical history				
Diabetes mellitus	255	42 (17.5)	1 (6.7)	0.478
Hypertension	255	131 (54.6)	11 (73.3)	0.188
Hyperlipidemia	255	65 (25.5)	6 (40.0)	0.372
Cardiovascular disease	255	29 (12.1)	1(6.7)	1.000
Peripheral vascular disease	255	2 (0.8)	0 (0.0)	1.000
eGFR (ml/min; median)	255	72.1 15.9–133.5	64.2 46.8–105.6	0.209
Contrast agent				
Iopamidol 300	213	200 (83.3)	13 (86.7)	1.000
Iohexol 300	6	6 (2.5)	0 (0.0)	1.000
Iodixanol 270	36	34 (14.2)	2 (13.3)	1.000
Dose of contrast agents (ml; median)	252	225 75–285	175 25–362	0.102

eGFR: estimated glomerular filtration rate

group (n=15; 11 male, 4 female, median age 62.9 years) and a non-hemorrhage group (n=240; 124 male, 116 female, median age 68.2 years).

Potential risk factors, including postoperative administration of an anticoagulant, the ACT, number of antiplatelet agents administered, platelet reactivity, sheath size, hemostasis method used, and operating time postoperatively were compared between the two groups.

Argatroban or heparin, or a combination, was used as a postoperative anticoagulant. A comparison was made between the group that was administered heparin and the group that was not administered heparin postoperatively. Patients in whom ACT was not measured after administration of protamine sulfate were excluded. The ACT after neuroendovascular treatment was compared between the non-hemorrhage group (n=229) and the hemorrhage group (n=15).

Platelet function was measured using the VerifyNow assay (Accumetric Inc, San Diego, CA, USA). Aspirin reaction units (ARU) and P2Y12 reaction units (PRU) were measured preoperatively. High on-treatment platelet reactivity (HPR) was defined as an ARU of ≥550 or a PRU of >213. Patients with HPR received cilostazol 200 mg in addition to dual antiplatelet therapy. Hemostasis was achieved by manual compression or use of a VCD (6 Fr/7 Fr Exoseal, Cordis Corporation, Miami Lakes, FL or 6 Fr/8 Fr Angioseal, Terumo Interventional Systems, Somerset, NJ).

A multivariate logistic regression analysis was performed on patients whose ACT was ≥300 seconds before the removal of the sheath after the procedure, on patients who received a triple antiplatelet therapy, and on the group that was administered heparin postoperatively and had a sheath size of 7 Fr or more. Difficulties in achieving hemostasis can occur in patients on anticoagulant or antiplatelet therapy when using large-bore sheaths.[1,5] Therefore, the sheath size is subjected to a multivariate logistic regression analysis.

Categorical variables were evaluated using Fisher`s exact test and continuous variables by the Mann-Whitney test. Multivariate logistic regression analysis was performed. A p-value <0.05 was considered statistically significant. The statistical analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan, version 1.35), which is a graphical interface to R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The postprocedural puncture site hemorrhage occurred in 15 (5.9%) of the 255 patients. There were no significant differences in age, gender, body mass index, diabetes mellitus, hypertension, cardiovascular disease, peripheral vascular disease, renal function, and contrast agent between no hemorrhage group and hemorrhage group. The number of heparinized cases were 12 for single agent and 41 for combined use with argatroban (Table 1). The patients who received heparin postoperatively had significantly more bleeding than those who were not administered heparin (13.2% vs 4.0%; p<0.05). The patients with an ACT of ≥300 seconds before post-procedural sheath removal had significantly more bleeding than those with an ACT of < 300 (11.8% vs 3.6%; p<0.05). There was also a significant difference in bleeding risk between patients who received triple antiplatelet agents and those who received less than two antiplatelet agents (17.4% vs 4.7%; p<0.05) (Table 2 and Table 3). There was no significant difference in the bleeding risk according to clinical characteristics, including a PRU <95, sheath size, hemostasis method used, or operating time (Table 2).

A multivariate analysis was performed when an ACT was ≥300 seconds before postprocedural sheath removal, the group was administered heparin postoperatively, when patients were administered triple antiplatelet agents, and when patients had a sheath size of 7 Fr or more. An ACT

Table 2 Predictors of puncture site hemorrhage after neuroendovascular treatment

Parameter	Total	No hemorrhage No. (%)	Hemorrhage No. (%)	P-value
Postoperative anticoagulant therapy				
Yes	145	135 (93.1)	10 (6.9)	0.583
Heparin	53	46 (86.8)	7 (13.2)	0.019
Argatroban	133	124 (94.0)	8 (6.0)	0.268
No	110	105 (95.5)	5 (4.5)	
Postoperative activated clotting time				
300 ≤	76	67 (88.2)	9 (11.8)	0.018
300 >	168	162 (96.4)	6 (3.6)	
No of antiplatelet agent				
3	23	19 (82.6)	4 (17.4)	0.036
2	129	121 (93.8)	8 (6.2)	1.000
1	36	35 (97.2)	1 (2.8)	0.702
0	67	65 (97.0)	2 (3.0)	0.367
P2Y12 reaction units				
95 ≤	108	99 (92.4)	9 (7.6)	0.523
95 >	38	34 (89.5)	4 (10.5)	
Sheath size				
9 Fr	21	19 (90.5)	2 (9.5)	1.000
8 Fr	27	25 (92.6)	2 (7.4)	0.546
7 Fr	11	9 (81.8)	2 (18.2)	0.132
7 Fr >	196	187 (95.4)	9 (5.6)	0.599
Method of hemostasis				
Manual compression	23	21 (92.3)	2 (8.7)	0.633
Hemostasis device				
7 Fr Exoseal	10	10 (100.0)	0 (0.0)	1.000
6 Fr Exoseal	68	66 (97.1)	2 (2.9)	0.367
8 Fr Angioseal	99	90 (90.9)	9 (9.1)	0.101
6 Fr Angioseal	55	53 (96.4)	2 (3.6)	0.536
Off-label use of a hemostasis device				
8 Fr Angioseal				
On-label	71	74 (91.3)	7 (8.7)	0.634
Off-label	19	17 (90.5)	2 (9.5)	
7 Fr Exoseal				
On-label	9	9 (100.0)	0 (0.0)	
Off-label	1	1 (100.0)	0 (0.0)	
Procedure time (min)				
301 <	29	27 (93.1)	2 (6.9)	0.685
181–300	81	73 (90.1)	8 (9.9)	0.135
180 ≥	143	138 (96.5)	5 (3.5)	0.104

of ≥300 seconds before post-procedural sheath removal and the group that was administered heparin postoperatively were identified to be independent risk factors for postprocedural arterial puncture site hemorrhage (Table 3).

Rates of bleeding in patients with cerebral aneurysm who underwent balloon-assisted coil embolization (5 cases, 10.9%) or stent-assisted coil embolization (4 cases, 11.1%) were high while

Table 3 Predictors of puncture site hemorrhage after neuroendovascular treatment

Parameter	Total	No Hemorrhage No. (%)	Hemorrhage No. (%)	P-value	
				Invariable	Multivariable
Postoperative heparin use					
Yes	53	46 (86.8)	7 (13.2)	0.020	0.047
No	202	194 (96.0)	8 (4.0)		
Activated clotting time					
300 ≤	76	67 (88.2)	9 (11.8)	0.020	0.024
300 >	179	161 (96.4)	6 (3.6)		
No of Antiplatelet therapy					
3drugs	23	19 (92.6)	4 (17.4)	0.036	0.159
2drugs ≥	232	221 (95.3)	11 (4.7)		
Sheath size					
7 Fr ≤	59	53 (89.8)	6 (10.2)	0.121	0.286
7 Fr >	196	185 (94.4)	11 (5.6)		

Table 4 Neuroendovascular treatment and frequency of postprocedural puncture site hemorrhage

Parameter	Total	No hemorrhage No. (%)	Hemorrhage No. (%)
Treatment			
Aneurysm coil embolization			
Simple technique	25	24 (96.0)	1 (4.0)
Balloon-assisted technique	46	41 (89.1)	5 (10.9)
Stent-assisted technique	36	32 (88.9)	4 (11.1)
Double catheter technique	20	19 (7.9)	1 (6.7)
Balloon and double catheter technique	4	4 (100.0)	0 (0.0)
Stent and balloon-assisted technique	4	3 (75.0)	1 (25.0)
Internal trapping	3	3 (100.0)	0 (0.0)
Carotid artery stenting	47	46 (97.9)	1 (2.1)
Intracranial PTA	4	4 (100.0)	0 (0.0)
Extracranial PTA	4	4 (100.0)	0 (0.0)
Thrombectomy	1	1 (100.0)	0 (0.0)
Arteriovenous malformation			
TAE	11	11 (100.0)	0 (0.0)
Dural arteriovenous fistula			
TAE	15	13 (86.7)	2 (13.3)
TVE	15	15 (100.0)	0 (0.0)
TAE and TVE	4	4 (100.0)	0 (0.0)
Spinal arteriovenous malformation			
TAE	4	4 (100.0)	0 (0.0)
Tumor embolization	12	12 (100.0)	0 (0.0)
Operation			
Schedule	252	237 (94.0)	15 (6.0)
Emergency	3	3 (100.0)	0 (0.0)

PTA: percutaneous transluminal angioplasty
TAE: transarterial embolization
TVE: transvenous embolization

those in patients who underwent simple technique coil embolization (1 case, 4.0%) or carotid artery stenting (1 case, 2.1%) were low. The postoperative arterial puncture site hemorrhage rate was not statistically significant after neurovascular treatment (Table 4).

DISCUSSION

Bleeding complication rates reported in the literature range from 0.63% to 9.7%.[6,7] Risk factors identified in patients with acute myocardial infarction include old age, female sex, underweight, renal dysfunction, large sheath size, and use of a VCD.[8,9] The dose and duration of anticoagulants are related factors, and it has been reported that there are fewer bleeding complications after administration of low molecular weight heparin than after use of unfractionated heparin.[9]

Bleeding as a complication of neuroendovascular therapy has not been well described in the literature. Sato et al investigated the incidence of access site complications, which was higher in patients who underwent intraoperative heparinization and were prescribed multiple antiplatelet agents preoperatively.[1] In that study, the incidence of postprocedural arterial puncture site hemorrhage was 5.9%, which is the same as in this present report.

In the present study, the bleeding risk was significantly higher when the ACT was ≥300 seconds before removal of the sheath after the procedure. In the 7F ECLIPSE study, which examined safety and effectiveness of the Exoseal vascular closure device, considered an ACT of ≥300 seconds before removal of the sheath after the procedure as an exclusion criteria.[4] The package insert of Exoseal is stated that safety is not established. Intraoperative heparinization is necessary for prevention of intraoperative thromboembolism. Therefore, an ACT of ≥300 seconds before removal of the sheath could indicate a need for intervention to prevent bleeding at the puncture site.

Combined antiplatelet therapy is recommended for carotid artery stenting and coil embolization of cerebral aneurysm to prevent perioperative ischemic complications.[10-13] Dual antiplatelet therapy has a significant ability to reduce ischemic complications without an increase in bleeding complications.[10] Hwang et al reported that triple antiplatelet therapy in patients with HPR could lead to oozing at the femoral puncture site or a local groin hematoma without any serious bleeding complications.[14,15] In the present study, the bleeding rate increased as the number of antiplatelet agents administered increased, with a significant difference in the risk of bleeding between patients who received triple antiplatelet treatment and those who received less than two antiplatelet agents. Multivariate analysis did not identify a significant increase in bleeding complications in patients who received triple antiplatelet therapy. The ADAPT-DES study found that a low on-treatment platelet reactivity, i.e., a PRU <95%, was associated with a significantly increased risk of bleeding.[16] However, in the present study, there was no significant increase in postprocedural arterial puncture site hemorrhage in patients with a PRU <95%. The hemorrhagic complication in the ADAPT-DES study was defined as a drop in hemoglobin of > 3 g/dl, need for transfusion, bleeding requiring surgery, or retroperitoneal bleeding. This definition is seemed to include the more cases with intraoperative failure, such as vascular perforation or dissection. In contrast, our study excluded hemorrhage at the intraoperative puncture site and focus on risk factors without technical failure. This difference may affect the association between LPR and bleeding event.

In the present study, there was a significant increase in the bleeding rate in patients who were administered heparin postoperatively. However, Enomoto et al showed that the rate of groin site complications from neuroendovascular therapy was similar between patients treated with postoperative anticoagulant therapy and those who were not (0.7% vs 0.6%, p=0.483). The

hemorrhagic complication rate was also significantly lower in patients who received heparin after neuroendovascular treatment. And the author speculated that postoperative use of heparin may depend on the onset of hemorrhagic or ischemic complications intraoperatively.[17] This study excluded intraoperative puncture site complications. The previous study is different from this study in regard to this definition. It is considered that this study may more accurately reflect the effects of postoperative heparin use. Heparin is an anticoagulant with antithrombin activity; therefore, interpatient variability is wide and it is difficult to accurately predict the response to an anticoagulant dose.[18] In contrast, argatroban is a synthetic direct thrombin inhibitor derived from L-arginine[19] that has been reported to achieve a dose-related steady-state effect within 2 hours of injection.[18] In the present study, there was no increase in the postoperative arterial puncture site hemorrhage rate in patients who received argatroban. When using heparin, it is necessary to confirm an ACT of < 300 seconds before removing the sheath after the procedure and to routinely monitor coagulation ability in the perioperative period. If these cannot be performed, argatroban may be considered as postoperative anticoagulant therapy.

We found that the rate of the postprocedural arterial puncture site hemorrhage was not statistically significant in sheath size. In recent studies, the puncture site complication rate when a VCD was used was not significantly different from that when manual compression was used.[2,3,5,6] In this study, there was no significant difference in bleeding risk according to whether a VCD (Angioseal or Exoseal) or manual compression was used. An 8 Fr Angioseal and 7 Fr Exoseal could be used when the sheath is larger than the recommended size. There were no significant differences between use with and without adaptation. Finally, in these series, the hemostasis method used was not considered to affect the risk of the postprocedural arterial puncture site hemorrhage.

Sato et al reported that the postprocedural puncture site hemorrhage was common with carotid artery stenting and percutaneous transluminal angioplasty[1] and attributed this finding to intraoperative heparinization, preoperative administration of multiple antiplatelet agents, and large sheath size.[1] Although not statistically significant, rates of bleeding with balloon-assisted coil embolization for cerebral aneurysms (5 cases, 10.9%) or stent-assisted coil embolization (4 cases, 11.1%) were high while those of simple technique coil embolization (1 case, 4.0%) or carotid artery stenting (1 case, 2.1%) were low in this study. These findings could be explained by the intraoperative ACT being ≥300 seconds and postoperative administration of heparin in the stent-assisted coil embolization group and inclusion of 2 of 3 patients in whom hemostasis was unsuccessful in the balloon-assisted coil embolization group. The bleeding rate was low when carotid artery stenting and simple coil embolization were performed because heparin was not administered postoperatively.

In the previous study with acute myocardial infarction, the old age, female sex, underweight and renal dysfunction were significantly increased bleeding.[8,9] In contrast, Nishi et al found that major bleeds were not associated with advanced age, sex, or low body surface area.[20] In this study, age, female sex and body mass index were not associated with an increased risk of postprocedural arterial puncture site hemorrhage. In our series, if arteriosclerosis or small vessel size was observed at the puncture site on the preoperative CT scan, we changed the puncture site or reduce the sheath size in order to prevent puncture site complications. Renal dysfunction affects the pharmacokinetics of heparin because heparin is renally excreted. Moscucci et al found that this was associated with an increased risk of major bleeding.[7] In this study, estimated glomerular filtration rate was sometimes low in the hemorrhagic group, but the difference did not achieve statistical significance. Rate of major bleeding in postprocedural arterial puncture hemorrhage was low, therefore renal dysfunction may not be associated with the postprocedural puncture site hemorrhage.

As for the limitations of this study, since it is a retrospective study, there is a lack of standard-

ized protocols. First, the duration and dose of the anticoagulant therapy of each patient in the same group was not strictly identical. Second, the data were based on our medical records, so several important piece of information on bleeding could have been omitted. Third, the bleeding complications in the single center were few and limited statistical analysis. Finally, we excluded the patients in whom initial hemostasis had failed, since we examined risk factor of late-onset puncture site hemorrhage.

CONCLUSION

This study investigated the risk factors for puncture site hemorrhage after neuroendovascular therapy. The risk of puncture site hemorrhage was higher in patients whose ACT was ≥300 seconds before removal of the sheath after the procedure, in those who received a triple antiplatelet therapy, and in the group that was administered heparin postoperatively.

ACKNOWLEDGEMENTS

The authors thank all of the staff members at the Department of the Neurosurgery, Nagoya University Graduate School of Medicine for their valuable support.

DISCLOSURE STATEMENT

None of the authors have any conflicts of interest to declare in relation to this work.

REFERENCES

1 Sato M, Matsumaru Y, Sakai N, Yoshimura S, JR-NET Study Group Affiliations. Detailed analysis of puncture site vascular complications in Japanese Registry of Neuroendovascular Therapy (JR-NET) and JR-NET2. *Neurol Med Chir (Tokyo)*. 2014;54 Suppl 2:17–22.

2 Upponi SS, Ganeshan AG, Warakaulle DR, Phillips-Hughes J, Boardman P, Uberoi R. Angioseal versus manual compression for haemostasis following peripheral vascular diagnostic and interventional procedures--a randomized controlled trial. *Eur J Radiol*. 2007;61(2):332–334. doi:10.1016/j.ejrad.2006.09.007.

3 Starnes BW, O'Donnell SD, Gillespie DL, et al. Percutaneous arterial closure in peripheral vascular disease: a prospective randomized evaluation of the Perclose device. *J Vasc Surg*. 2003;38(2):263–271. doi:10.1016/s0741-5214(03)00291-x.

4 Wong SC, Bachinsky W, Cambier P, et al. A randomized comparison of a novel bioabsorbable vascular closure device versus manual compression in the achievement of hemostasis after percutaneous femoral procedures the ECLPISE (Ensure's Vascular Closure Device Speeds Hemostasis Trial). *JACC Cardiovasc Interv*. 2009;2(8):785–793. doi:10.1016/j.jcin.2009.06.006.

5 Das R, Ahmed K, Athanasiou T, Morgan RA, Belli AM. Arterial closure devices versus manual compression for femoral haemostasis in interventional radiological procedures: a systematic review and meta-analysis. *Cardiovasc Intervent Radiol*. 2011;34(4):723–738. doi:10.1007/s00270-010-9981-0.

6 Koreny M, Riedmüller E, Nikfardjam M, Siostrzonek P, Müllner M. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. *JAMA*. 2004;291(3):350–357. doi:10.1001/jama.291.3.350.

7 Moscucci M, Fox KAA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24(20):1815–1823. doi:10.1016/s0195-668x(03)00485-8.

8 Berkowitz SD, Stinnett S, Cohen M, Fromell GJ, Bigonzi F, ESSENCE Investigators. Prospective comparison of hemorrhagic complications after treatment with enoxaparin versus unfractionated heparin

for unstable angina pectoris or non-ST-segment elevation acute myocardial infarction. *Am J Cardiol*. 2001;88(11):1230–1234. doi:10.1016/s0002-9149(01)02082-3.

9 Sinnaeve PR, Alexander JH, Bogaerts K, et al. Efficacy of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: one-year follow-up results of the Assessment of the Safety of a New Thrombolytic-3 (ASSENT-3) randomized trial in acute myocardial infarction. *Am Heart J*. 2004;147(6):993–998. doi:10.1016/j.ahj.2003.12.028.

10 McKevitt FM, Randall MS, Cleveland TJ, Gaines PA, Tan KT, Venables GS. The benefits of combined antiplatelet treatment in carotid artery stenting. *Eur J Vasc Endovasc Surg*. 2005;29(5):522–527. doi:10.1016/j.ejvs.2005.01.012.

11 Dalainas I, Nano G, Bianchi P, Stegher S, Malacrida G, Tealdi DG. Dual antiplatelet regime versus acetyl-acetic acid for carotid artery stenting. *Cardiovasc Intervent Radiol*. 2006;29(4):519–521. doi:10.1007/s00270-005-5288-y.

12 Nishikawa Y, Satow T, Takagi T, Murao K, Miyamoto S, Iihara K. Efficacy and safety of single versus dual antiplatelet therapy for coiling of unruptured aneurysms. *J Stroke Cerebrovasc Dis*. 2013;22(5):650–655. doi:10.1016/j.jstrokecerebrovasdis.2012.02.008.

13 Lee SJ, Cho YD, Kang HS, Kim JE, Han MH. Coil embolization using the self-expandable closed-cell stent for intracranial saccular aneurysm: a single-center experience of 289 consecutive aneurysms. *Clin Radiol.* 2013;68(3):256–263. doi:10.1016/j.crad.2012.07.017.

14 Hwang G, Kim JG, Song KS, et al. Delayed ischemic stroke after stent-assisted coil placement in cerebral aneurysm: characteristics and optimal duration of preventative dual antiplatelet therapy. *Radiology*. 2014;273(1):194–201. doi:10.1148/radiol.14140070.

15 Hwang G, Huh W, Lee JS, et al. Standard vs Modified Antiplatelet Preparation for Preventing Thromboembolic Events in Patients With High On-Treatment Platelet Reactivity Undergoing Coil Embolization for an Unruptured Intracranial Aneurysm: A Randomized Clinical Trial. *JAMA Neurol*. 2015;72(7):764–772. doi:10.1001/jamaneurol.2015.0654.

16 Stone GW, Witzenbichler B, Weisz G, et al. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet*. 2013;382(9892):614–623. doi:10.1016/S0140-6736(13)61170-8.

17 Enomoto Y, Yoshimura S, Sakai N, Egashira Y,Japanese Registry of Neuroendovascular Therapy (JR-NET) investigators. Current perioperative management of anticoagulant and antiplatelet use in neuroendovascular therapy: analysis of JR-NET1 and 2. *Neurol Med Chir (Tokyo)*. 2014;54 Suppl 2:9–16. doi:10.2176/nmc.oa2013-0160.

18 S K Swan, J V St Peter, L J Lambrecht, Hursting MJ. Comparison of Anticoagulant Effects and Safety of Argatroban and Heparin in Healthy Subjects. *Pharmacotherapy*. 2000;20(7):756–770. doi:10.1592/phco.20.9.756.35194.

19 Klingele M, Enkel J, Speer T, Bomberg H , Baerens L , Schäfers HJ. Bleeding complications after cardiac surgery, before anticoagulantion start and then with argatroban or heparin in the early postoperative setting. *J Cardiothorac Surg*. 2020 ;15(1):27. doi:10.1186/s13019-020-1059-8.

20 Nishi H, Nakahara I, Matsumoto S, et al. Platelet reactiveity and hemorrhage risk in neurointerventional procedures under dual antiplatelet therapy. *J NeuroInterv Surg*. 2016;8(9):949–953. doi:10.1136/neurintsurg-2015-011844.