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Factors other than body weight predicting heparin loading to acquire optimal activated clotting time in endovascular neurointerventions

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ABSTRACT

Objectives: The aim of this study was to investigate the relationship between the activated clotting time (ACT) and heparin loading based on body weight (BW), and factors other than BW that may contribute to the ACT after heparin loading to establish a more accurate regimen for achieving ACT targets during endovascular neurointerventions.

Patients and Methods: : Japanese patients who underwent endovascular coiling of unruptured intracranial aneurysms or carotid artery stenting in our institution between January 2014 and November 2017 were enrolled. The ACT was measured before (pre–ACT) and 3 min after heparinization (post–ACT). The correlation between ACT and heparin loading based on BW and factors that may contribute to the ACT after heparin loading were analyzed retrospectively.

Results: : A total of 199 cases (109 males, age: 66 ± 12 years) were analyzed. There were positive correlations between the heparin loading per kg of BW and post–ACT, post–ACT – pre–ACT (ΔACT) (Spearman's r = 0.2946, 0.2633, *P*: < 0.0001, 0.0002, respectively). Heparin loading per kg of BW, gender, hematocrit (Ht), estimate glomerular filtration rate (eGFR) were significant confounding factors to ΔACT. The calculated predicted ΔACT based on these significant factors was found to be highly correlated with ΔACT compared with the heparin loading per kg of BW. (Spearman's r = 0.5820, *P* = < 0.0001).

Conclusion: Initial BW–based heparin loading is a simple way in endovascular neurointerventions. ACT after heparin loading based on BW has individual differences greatly, it is possible to estimate more accurately the heparin loading for acquiring the optimal ACT considering not only BW but also gender, Ht and eGFR.

1. Introduction

The infusion of heparin is a useful anticoagulation procedure for preventing perioperative thromboembolic complications during endovascular neurointerventions. The rapid onset of the anticoagulant effects of heparin and the ease with which these effects can be reversed with protamine sulfate contribute to the popularity of heparin. It is known that individual patients respond differently to similar dosages of the drug [1–5]. To reduce the frequencies of thrombotic and hemorrhagic complications, the activated clotting time (ACT) is measured to monitor the anticoagulant effects of heparin loading during endovascular neurointerventions. The therapeutic ACT range for endovascular coiling and carotid artery stenting (CAS) has been proposed to be 200–300 s [6–8,10,11]. As the routine measurement of the ACT is not possible in some laboratories, the optimal heparin loading for achieving a therapeutic ACT in patients undergoing endovascular treatment has yet to be determined. We have decided heparin loading based on body weight (BW) to acquire optimal ACT, but there are some reports that individual differences of ACT are large in determination of heparin loading based only on BW [19,20]. In order to obtain targeted ACT, it is necessary to improve prediction accuracy of heparin loading. The aim of this study was to investigate the relationship between the ACT and heparin loading based on BW, and factors other than BW that may contribute to the ACT after heparin loading to establish a more accurate index for achieving ACT targets during endovascular neurointerventions.

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2. Patients and methods

All this study protocols were approved by the ethics committee of Hiroshima University.

2.1. Study population

We used our date base to identify consecutive 210 Japanese patients who underwent endovascular treatment (endovascular coiling for unruptured intracranial aneurysms or CAS) in our institution between January 2014 and November 2017. We excluded 10 patients who were taking oral anticoagulants and one patient who presented with a prolonged baseline ACT. The 199 patients (111 patients who underwent endovascular coiling of unruptured intracranial aneurysms and 88 patients with CAS) were analyzed retrospectively. All patients were received heparin infusion in the endovascular neurointerventions. The patients' data were collected, including information regarding age, gender, height (cm), BW (kg), hemotocrit (Ht) (%), platelet (PLT) ($\times 10^4$/μL), prothrombin time (PT) (%), activated partial thromboplastin time (APTT) (sec), estimate glomerular filtration rate (eGFR) (ml/min/1.73 m^2), presence or absence of oral administration of multiple antiplatelet drugs, history of thromboembolic and hemorrhagic events. Thromboembolic events were defined as symptomatic cerebral infarction, ischemic heart disease, arteriosclerosis obliterans and deep vein thrombosis, hemorrhagic events were defined as symptomatic intracranial hemorrhage, hemorrhage requiring surgical intervention, and hemorrhage requiring blood transfusion, respectively.

eGFR was calculated based on the following calculation formula.

Male: eGFR (ml/min/1.73 m^2) = 194 × Creatinine value$^{-1.094}$ × age$^{-0.287}$

Female: eGFR (ml/min/1.73 m^2) = male eGFR × 0.739

2.2. Sample collection, ACT measurement, and heparin loading protocol

After arterial sheath placement, 2 ml venous blood samples were collected and placed in vacuum–sealed tubes within 10 s, before being rotated continuously in a HEMOCHORON chamber (International Technidyne Corporation, Edison, NJ, USA). The volume of the initial heparin loading was jointly determined by 3 independent interventional physicians considering BW and pre-ACT. The estimated optimal ACT for endovascular coiling and CAS were 250 and 300 s, respectively. Data regarding the total heparin loading were collected for all patients. All of the injected heparin was unfractionated heparin. Three minutes after the heparin loading, the ACT was measured again. The ACT values recorded before and after the heparin loading were defined as the pre–ACT and post–ACT values, respectively. And, difference between post–ACT value and pre–ACT value was defined as the ΔACT (post–ACT – pre–ACT).

2.3. Heparin loading and post–ACT

We retrospectively analyzed the correlation between the heparin loading relative to per kg of BW and the post–ACT. The optimal heparin loading per kg of BW for achieving a therapeutic post–ACT was identified. The achievement rate of the optimal post–ACT (250–300 s) was verified by BW–based heparin loading.

2.4. Heparin loading and ΔACT

We retrospectively analyzed the correlation between the heparin loading relative to per kg of BW and the ΔACT.

2.5. Factors associated with ΔACT

We retrospectively analyzed the association between potential confounders that may contribute to heparin response (e.g., heparin loading per kg of BW (U/kg), age, gender, height (cm), BW (kg), Ht (%), PLT ($\times 10^4$/μL), PT (%), APTT (sec), eGFR (ml/min/1.73 m^2) and presence or absence of oral administration of multiple antiplatelet drugs) and the ΔACT.

2.6. Statistical analyses

Continuous variables are presented as mean ± standard deviation or median and interquartile range (IQR) depending on their distribution. Categorical variables are presented as frequency counts. Linear regression analyses were performed to examine the correlations between the heparin loading per kg of BW and the post–ACT. The relevant linear regression equation was used to identify the optimal heparin loading per kg of BW for achieving a therapeutic post–ACT for endovascular coiling or CAS.

Associations between the ΔACT and each factor were analyzed by multivariate logistic regression analysis. All statistical analyses were conducted using JMP® 13 (SAS Institute Inc., Cary, NC, USA). For all comparisons, *P*–values of < 0.05 were considered to indicate statistical significance.

3. Results

3.1. Patients' characteristics (Table 1)

The characteristics of the 199 patients are shown in Table 1. The patients had a mean age of 65.9 ± 11.9 years and 90 were female.

3.2. Heparin loading and ACT (Table 2)

The total heparin loading, the heparin loading per kg of BW, the pre–ACT, the post–ACT, and the ΔACT are summarized in Table 2.

3.3. Correlations between the post−ACT and the heparin loading relative to BW (Fig. 1)

Regression analysis revealed a positive correlation between the heparin loading per kg of BW and the post–ACT (Spearman's r = 0.2946, *P*: -0.0001). Post–ACT (sec) = 203.92695 + 0.7702437 × heparin loading/BW (U/kg).

Table 1
Characteristics of the patients.

Mean age (years) (mean ± SD)	65.9 ± 11.9
Female, n (%)	90 (45.2)
Height (cm) (mean ± SD)	159.1 ± 8.3
Body weight (kg) (mean ± SD)	59.4 ± 10.9
Hematocrit (%) (mean ± SD)	38.0 ± 3.8
Platelet ($\times 10^4$/μL) (median(IQR))	209 (175-240)
PT (%) (median(IQR))	12.1 (11.7-12.5)
APTT (sec) (median(IQR))	29.3 (27.3-31.5)
eGFR (ml/min/1.73 m^2) (mean ± SD)	68.8 ± 19.6
Multiple antiplatelet drugs, n (%)	188 (94.5)
Thromboembolic events, n (%)	59 (29.6)
Hemorrhagic events, n (%)	19 (9.5)

Abbreviation: SD, standard deviation; IQR, interquartile range; PT, prothrombin time; APTT, activated partial thromboplastin time; eGFR, estimate glomerular filtration rate.

Table 2
Heparin loading and ACT.

Index	Value (mean ± SD)
Heparin loading (U)	5325.13 ± 1179.14
Heparin loading/BW (U/kg)	89.96 ± 12.93
Pre-ACT (sec)	120.21 ± 15.58
Post-ACT (sec)	273.22 ± 38.21
Post-ACT - Pre-ACT (ΔACT) (sec)	153.02 ± 37.33

Abbreviation: SD, standard deviation; BW, body weight; ACT, activated coagulation time; Pre-ACT, ACT before heparin loading; Post-ACT, ACT after heparin loading.

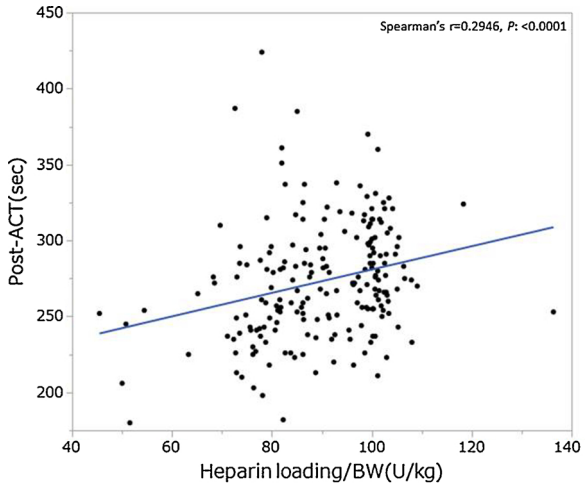


Fig. 1. Correlations between the post − ACT and the heparin loading relative to BW.

3.4. Optimal heparin loading per kg of BW for achieving a therapeutic post − ACT

According to the regression equation for the relationship between the post–ACT and the heparin loading per kg of BW, heparin loads of 59.8 U/kg, 92.3 U/kg and 124.7 U/kg resulted in post–ACT of 250, 275 and 300, respectively.

3.5. Achievement rate of the optimal ACT (250–300 s) by BW–based heparin loading

By heparin loading per kg of BW, the mean post–ACT was 273.22 and the achievement rate of the optimal ACT (250–300 s) was 51.3% (99/193) of the patients.

3.6. Correlations between the ΔACT and the heparin loading per kg of BW (Fig. 2A)

Regression analysis revealed a positive correlation between the heparin loading per kg of BW and the ΔACT (Spearman's r = 0.2633, $P = 0.0002$). ΔACT (sec) = 92.2738 + 0.67517 × heparin loading/BW (U/kg)A.

3.7. Factors associated with the ΔACT (Table 3)

In multivariate regression analysis, the heparin loading per kg of BW, gender, Ht and eGFR were significantly associated with the ΔACT (Table 3).

3.8. Correlations between the ΔACT and the predicted ΔACT by the heparin loading per kg of BW, gender, Ht and eGFR (Fig. 2B)

Regression analysis revealed a positive correlation between the ΔACT and the predicted ΔACT by the heparin loading per kg of BW, gender, Ht, eGFR (Spearman's r = 0.5820, $P = < 0.0001$). Predicted ΔACT (sec) = 15.7083 + 0.81288 × heparin loading/BW + 6.2665 × (male as 0 or female as 1) + 2.2990 × Ht – 0.3276 × eGFR

4. Discussion

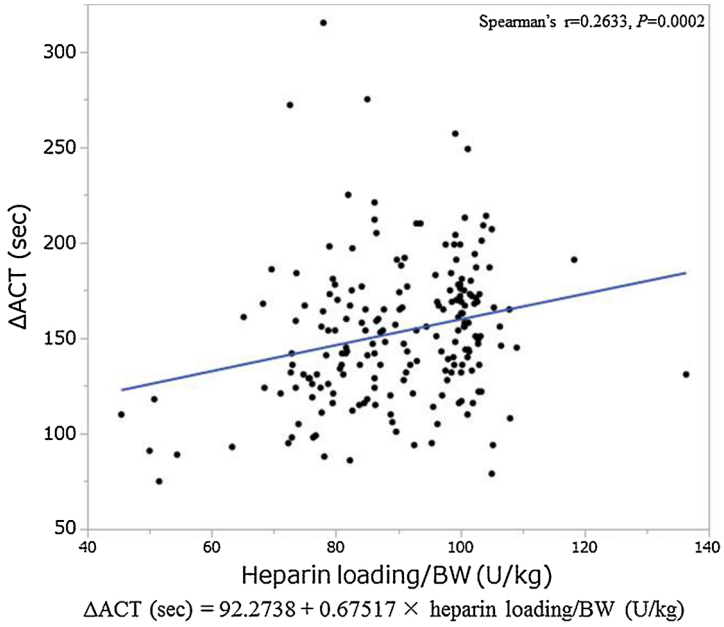
To determine the optimal heparin loading for endovascular neurointerventions, we hypothesized that BW–based heparin dosing would result in prolonged ACT and investigated the correlations between heparin loading based on BW and post–ACT, ΔACT. In addition, factors that may contribute to the ACT after heparin loading were also examined. This study found a positive correlation between the heparin loading per kg of BW and post–ACT, ΔACT. When the estimated optimal ACT was 250–300 s, our regimen suggested that heparin loads of 60–120 U/kg for endovascular neurointerventions were required. BW–based heparin loading is a simple way of achieving ACT targets. However, ACT after heparin loading based on BW has individual differences greatly, it is not sufficient to determine the heparin loading based on only BW. It is possible to estimate more accurately the heparin loading for obtaining optimal ACT considering not only BW but also gender, Ht and eGFR.

Heparin–based anticoagulation therapy is a standard anticoagulation procedure for preventing perioperative thromboembolic complications in patients who undergo endovascular treatment. Anticoagulant underdosing in patients who undergo neurointerventions can result in negative outcomes, including thromboembolic events caused by clot formation or progression, whereas heparin overdosing may give rise to bleeding events. Therefore, it is crucial to adjust the heparin loading appropriately and maintain therapeutic anticoagulation in patients who undergo endovascular neurointerventions.

ACT, which is a measure of the blood clotting time, is widely used to gauge the anticoagulant effects of heparin. In endovascular coiling without stents, the therapeutic range of the ACT has been reported to be 200–250 s [10]. In stent–assisted endovascular coiling and CAS, the recommended therapeutic ACT is over 250 s [6–8,11,12]. In procedures involving the use of stents, the ACT target is higher than in procedures that do not involve stents. Increasing numbers of cases of wide–neck or large aneurysms can be treated with stent–assisted coiling or flow–diverting stents [9,11–15], and careful anticoagulation therapy is needed in such cases to prevent thromboembolic complications.

Previous studies have reported the following information regarding optimal heparin loading doses: endovascular coiling without a balloon or stent: a 3000 U fixed dose [16], stent–assisted endovascular coiling: a 4000–5000 U fixed dose [9,15] or 70–100 U/kg [11,13], and CAS: 70–100 U/kg [7,8]. In addition, a heparin dose of 70–100 U/kg was recommended for achieving the target ACT of 300–350 s in patients who undergo percutaneous coronary interventions (PCI) and are not administered glycoprotein IIb/IIIa inhibitors [17]. For patients with venous or arterial thromboembolisms or unstable angina, Raschke et al. reported that a weight–based nomogram (starting dose: 80 U/kg of BW bolus, 18 U/kg per hour infusion) resulted in a more rapid response than a fixed dose (starting dose: 5000 U bolus, 1000 U per hour infusion) (they measured the activated partial thromboplastin time); however, they did not refer to the prolongation of the ACT [18].

In view of the findings of previous reports, BW–based nomograms have also been adopted for some diseases. In our study, the relationship between the heparin loading per kg of BW and the post–ACT results in similar heparin doses to those described in previous reports about endovascular neurointerventions, PCI, unstable angina, or venous or arterial thromboembolisms. Determining heparin dosage based on BW is a simple and useful nomogram for achieving ACT targets in many



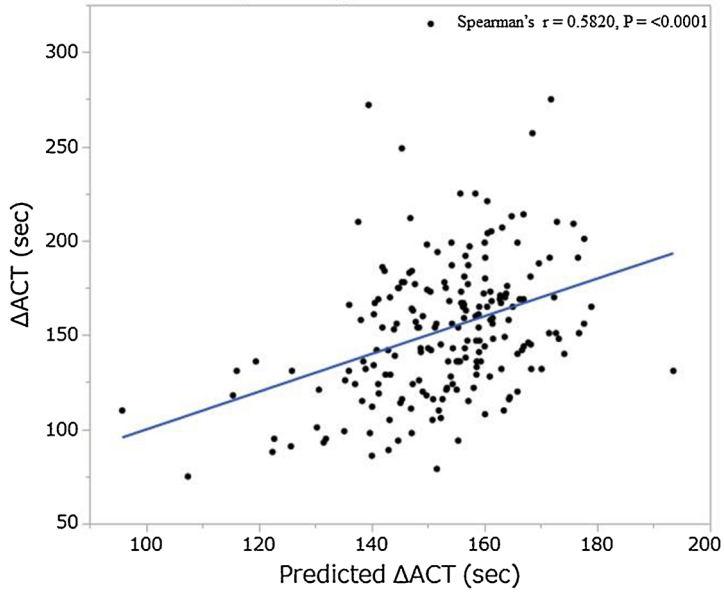


Fig. 2. A: Correlations between the ΔACT and the heparin loading per kg of BW. B: Correlations between the ΔACT and the predicted ΔACT by the heparin loading per kg of BW, gender, Ht and eGFR.

Table 3
Multivariate regression analysis for factors associated with ΔACT.

Index	Estimate	SE	t value	*P* value
Intercept	15.708	33.487	0.470	–
Heparin loading/BW (U/kg)	0.813	0.200	4.060	< .0001
Gender (female)	6.266	2.698	2.320	0.021
Ht (%)	2.299	0.684	3.360	0.001
eGFR (ml/min/1.73 m^2)	−0.328	0.131	−2.510	0.013

Abbreviation: SE, standard error; BW, body weight; Ht, hemotocrit; eGFR, estimate glomerular filtration rate.

procedures involving the use of heparin. In our study, although there was some correlation between the heparin loading per kg of BW and the post–ACT (r = 0.2946), of the cases who administered heparin loading of 70–100 U / kg as previously reported, only 50% showed an estimated optimal ACT of 250–300 seconds. It was thought that determining the heparin loading by BW alone is not necessarily the best. In the previous reports, gender [2,4,21], age [2,4,22], hematocrit [2], platelets [23,24] and renal function [25] were suggested as possible pharmacokinetic variables for heparin. In this study, gender, Ht and eGFI were significant factors that may contribute to the ΔACT after heparin loading. In female and patients with high Ht values and low eGFR, the

anticoagulant effect of heparin tends to be excessive. In female and patients with high Ht values and impaired renal function, refraining heparin loading should also be considered. We consider that determining the heparin loading considering about not only BW but also gender, Ht, and eGFR makes it possible to aquire the optimal ACT more reliably than in the conventional fixed or weight-based methods.

Besides physical factors, attention should be paid to heparin dosage even when antiplatelet agent is used. According to the 2013 American College of Cardiology Foundation (ACCF) / American Heart Association (AHA) guidelines, for PCI under the use of glycoprotein IIb/IIIa inhibitors (GPIs), the heparin loading of 50–70 U/kg is recommended, and the target ACT value is assumed to be 200–250 seconds [17]. Due to heparin loading loss, there is concern about an increase in thrombotic complications, but in the case of coil embolization of the intracranial unruptured aneurysm treated by stent procedures under the use of aspirin and ticagrelor, the heparin loading of 50 U/kg reduced bleeding and ischemic complications compared with the heparin loading of 70 U/kg [26]. Under the use of antiplatelet drugs, it is also necessary to reduce the heparin loading and set lower targeted ACT.

5. Limitations

Our study was affected by certain limitations. First, we were not able to analyze all potential confounders that might affect the anticoagulant state of heparin. Factors that might lead to heparin resistance, such as the antithrombin III level, heparin clearance, heparin–binding proteins, the factor VIII level, and the fibrinogen level could have influenced our results. In addition, other medications and lifestyle habits might have affected the ACT. Patients who undergo endovascular coiling or CAS can suffer from various disorders, such as diabetes, hyperlipidemia, or hypertension, or use tobacco or consume alcohol. A further multivariate analysis involving these other confounders is needed. Second, since this study is a limited number of retrospective studies in a single center, it is difficult to present specific mathematical formulas. But by increasing the number of studies and conducting multi-center, prospective studies, it may be possible to establish useful mathematical formulas involving factors other than weight.

6. Conclusions

Initial BW–based initial heparin dosing is a simple way of achieving a therapeutic ACT in patients who undergo endovascular coiling or CAS. ACT after heparin loading based on BW has individual differences greatly, it is possible to estimate more accurately the heparin loading for acquiring the optimal ACT considering not only BW but also gender, Ht and eGFR.

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Declaration of Competing Interest

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References

[1] C. D'Errico, J.R. Shayevitz, S.J. Martindale, Age – related differences in heparin sensitivity and heparin – protamine interactions in cardiac surgery patients, J. Cardiothorac. Vasc. Anesth. 10 (1996) 451–457.
[2] T.K. Rosborough, In unfractionated heparin dosing, the combination of patient age and estimated plasma volume predicts initial antifactor Xa activity better than patient weight alone, Pharmacotherapy 18 (1998) 1217–1223.
[3] J. Hirsh, R. Raschke, Heparin and low molecular weight heparin: the seventh ACCP conference on antithrombotic and thrombolytic therapy, Chest 126 (2004) 188S–203S.
[4] S. Verma, S. Kato, R. Blum, I. Shapira, P. Friedmann, M. Varma, Association of age, gender, and weight on maintenance dose of intravenous unfractionated heparin, Am. J. Hematol. 85 (2010) 624–626, https://doi.org/10.1002/ajh.21751.
[5] X. Hong, P.R. Shan, W.J. Huang, Q.L. Zhu, F.Y. Xiao, S. Li, H. Zhou, Influence of body mass index on the activated clotting time under weight – based heparin dose, J. Clin. Lab. Anal. 30 (2016) 108–113, https://doi.org/10.1002/jcla.21823.
[6] J. Saw, C. Bajzer, I.P. Casserly, E. Exaire, C. Haery, R. Sachar, D. Lee, A. Abou – Chebl, J.S. Yadav, Evaluating the optimal activated clotting time during carotid artery stenting, Am. J. Cardiol. 97 (2006) 1657–1660.
[7] E. Stabile, G. Sorropago, T. Tesorio, G. Popusoi, V. Ambrosini, M.T. Mottola, G. Biamino, P. Rubino, Heparin versus bivalirudin for carotid artery stenting using proximal endovascular clamping for neuroprotection: results from a prospective randomized study, J. Vasc. Surg. 52 (2010) 1505–1510, https://doi.org/10.1016/j.jvs.2010.06.098.
[8] P. Geisbüsch, B.T. Katzen, C. Peña, J.F. Benenati, H. Uthoff, Bivalirudin used as alternative anticoagulant in carotid artery stenting: a single center observational study, J. Interv. Cardiol. 25 (2012) 197–202, https://doi.org/10.1111/j.1540 – 8183.2011.00684.x.
[9] S. Meckel, T.P. Singh, P. Undrén, B. Ramgren, O.G. Nilsson, C. Phatouros, W. McAuliffe, M. Cronqvist, Endovascular treatment using predominantly stent – assisted coil embolization and antiplatelet and anticoagulation management of ruptured blood blister – like aneurysms, AJNR Am. J. Neuroradiol. 32 (2011) 764–771, https://doi.org/10.3174/ajnr.A2392.
[10] J.C. Park, D.H. Lee, J.K. Kim, J.S. Ahn, B.D. Kwun, D.Y. Kim, C.G. Choi, Microembolism after endovascular coiling of unruptured cerebral aneurysms: incidence and risk factors, J. Neurosurg. 124 (2016) 777–783, https://doi.org/10.3171/2015.3.JNS142835.
[11] M. Möhlenbruch, C. Herweh, L. Behrens, L. Jestaedt, H. Amiri, P.A. Ringleb, M. Bendszus, M. Pham, The LVIS Jr. microstent to assist coil embolization of wide – neck intracranial aneurysms: clinical study to assess safety and efficacy, Neuroradiology 56 (2014) 389–395, https://doi.org/10.1007/s00234 – 014 – 1345 – z.
[12] W. Weber, M. Bendszus, B. Kis, T. Boulanger, L. Solymosi, D. Kühne, A new self – expanding nitinol stent (Enterprise) for the treatment of wide – necked intracranial aneurysms: initial clinical and angiographic results in 31 aneurysms, Neuroradiology 49 (2007) 555–561.
[13] J.C. Gentric, A. Biondi, M. Piotin, C. Mounayer, K. Lobotesis, A. Bonafé, V. Costalat, French SENAT Investigators, Safety and efficacy of neuroform for treatment of intracranial aneurysms: a prospective, consecutive, French multicentric study, AJNR Am. J. Neuroradiol. 34 (2013) 1203–1208, https://doi.org/10.3174/ajnr.A3379.
[14] C. Iosif, Y. Camilleri, S. Saleme, F. Caire, C. Yardin, S. Ponomarjova, M.P. Boncoeur-Martel, C. Mounayer, Diffusion – weighted imaging – detected ischemic lesions associated with flow – diverting stents in intracranial aneurysms: safety, potential mechanisms, clinical outcome, and concerns, J. Neurosurg. 122 (2015) 627–636, https://doi.org/10.3171/2014.10.JNS132566.
[15] M. Negrotto, R. Crosa, W. Casagrande, Assisted coiling using LEO Baby or LVIS Jr stents: report of six cases, Interv. Neuroradiol. 21 (2015) 566–574, https://doi.org/10.1177/1591019915590098.
[16] M.J. Kim, Y.C. Lim, S.Y. Oh, B.M. Kim, B.S. Kim, Y.S. Shin, Thromboembolic events associated with electrolytic detachment of guglielmi detachable coils and target coils: comparison with use of diffusion – weighted MR imaging, J. Korean Neurosurg. Soc. 54 (2013) 19–24, https://doi.org/10.3340/jkns.2013.54.1.19.
[17] P.T. O'Gara, F.G. Kushner, D.D. Ascheim, Chung M.K. Casey DE Jr, J.A. de Lemos, S.M. Ettinger, J.C. Fang, F.M. Fesmire, B.A. Franklin, C.B. Granger, H.M. Krumholz, J.A. Linderbaum, D.A. Morrow, L.K. Newby, J.P. Ornato, N. Ou, M.J. Radford, J.E. Tamis-Holland, C.L. Tommaso, C.M. Tracy, Y.J. Woo, D.X. Zhao, J.L. Anderson, A.K. Jacobs, J.L. Halperin, N.M. Albert, R.G. Brindis, M.A. Creager, D. DeMets, R.A. Guyton, J.S. Hochman, R.J. Kovacs, F.G. Kushner, E.M. Ohman, W.G. Stevenson, C.W. Yancy, American college of cardiology Foundation/American heart association task force on practice guidelines, 2013 ACCF/AHA guideline for the management of ST – elevation myocardial infarction: a report of the american college of cardiology Foundation/American heart association task force on practice guidelines, Circulation 127 (2013) e362–425, https://doi.org/10.1161/CIR.0b013e3182742cf6.
[18] R.A. Raschke, B.M. Reilly, J.R. Guidry, J.R. Fontana, S. Srinivas, The weight – based heparin dosing nomogram compared with a "standard care" nomogram, A randomized controlled trial, Ann Intern Med. 119 (1993) 874–881.
[19] A. Poisik, E.J. Heyer, R.A. Solomon, D.O. Quest, D.C. Adams, C.M. Baldasserini, D.J. McMahon, J. Huang, L.J. Kim, T.F. Choudhri, E.S. Connolly, Safety and efficacy of fixed – dose heparin in carotid endarterectomy, Neurosurgery. 45 (1999) 434–441.
[20] S. Mottillo, K.B. Filion, L. Joseph, M. Eberg, V. Forgetta, J.G. Mancini, M.J. Eisenberg, Effect of fixed – Bolus (5,000 units) unfractionated heparin before primary percutaneous coronary intervention on activated clotting time, time flow, and all – Cause mortality, Am. J. Cardiol. 119 (2017) 178–185, https://doi.org/10.1016/j.amjcard.2016.09.039.
[21] S. Monte, G. Lyons, In vitro evidence of gender – related heparin resistance, Int. J. Obstet. Anesth. 13 (2004) 91–94.
[22] V. Ignjatovic, J. Furmedge, F. Newall, A. Chan, L. Berry, C. Fong, K. Cheng, P. Monagle, Age – related differences in heparin response, Thromb. Res. 118 (2006) 741–745.
[23] E. Marciniak, Factor – Xa inactivation by antithrombin III, Evidence for biological stabilization of factor Xa by factor V – phospholipid complex, Br. J. Haematol. 24 (1973) 391–400.

[24] F.J. Walker, C.T. Esmon, The effects of phospholipid and factor Va on the inhibition of factor Xa by antithrombin III, Biochem. Biophys. Res. Commun. 90 (1979) 641–647.
[25] N. Thorevska, Y. Amoateng – Adjepong, R. Sabahi, I. Schiopescu, A. Salloum, V. Muralidharan, C.A. Manthous, Anticoagulation in hospitalized patients with renal insufficiency: a comparison of bleeding rates with unfractionated heparin vs enoxaparin, Chest 125 (2004) 856–863.
[26] A.P. Narata, A. Amelot, R. Bibi, D. Herbreteau, D. Angoulvant, Y. Gruel, K. Janot, Dual antiplatelet therapy combining aspirin and ticagrelor for intracranial stenting procedures: a retrospective single center study of 154 consecutive patients with unruptured aneurysms, Neurosurgery 84 (2019) 77–83, https://doi.org/10.1093/neuros/nyy002.