Anticoagulation in acute ischemic stroke: A systematic search

Nayara L. Froio[1], Richard Murdoch Montgomery[1], Elias David-Neto[1], Ivan Aprahamian[1]*

[1]Department of Internal Medicine, Faculdade de Medicina de Jundiaí, Jundiaí, SP, Brazil

Summary

Introduction: Stroke is one of the most important diseases worldwide. Several clinical scenarios demand full dose of anticoagulants primary to stroke etiology or to the treatment of comorbidity. However, controversy exists over many issues regarding anticoagulation treatment in stroke such as time for initiation, efficacy according to stroke etiology, the ideal dose of anticoagulants, and whether novel anticoagulants should be used.

Method: Computerized search for clinical trials and randomized controlled clinical trials was done to the present date at Medline, Scielo, Embase, PsychInfo, and Cochrane Library using MeSH terms and the keywords stroke, ischemic stroke, anticoagulation, anticoagulants, heparin, low-molecular-weight heparin, warfarin, dabigatran, rivaroxaban, apixaban. The PRISMA statement was used to evaluate clinical trials.

Results: Fourteen clinical trials were selected based on inclusion criteria. No evidence was found supporting the early use of heparin, heparinoids or low--molecular-weight heparin (LMWH) early after stroke. No consistent evidence for the use of warfarin and the newer oral anticoagulants were found. Argatroban was the only anticoagulant with significant positive results early after large-artery ischemic stroke.

Conclusion: The ideal time for initiating anticoagulation remains undefined, requiring further investigation. Early anticoagulation for ischemic stroke is not recommended, with few exceptions, such as that of argatroban.

Keywords: acute ischemic stroke, anticoagulation, heparin, warfarin.

Study conducted at Faculdade de Medicina de Jundiaí, Jundiaí, SP, Brazil

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***Correspondence:**
Address: Rua Francisco Telles, 250
Jundiaí, SP – Brazil
Postal code: 13202-550
ivan.aprahamian@gmail.com

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Introduction

Stroke is the second most common cause of mortality and the third cause of disability worldwide. Ischemic stroke leads to 2.9 million deaths and to disabling sequelae in approximately 3.4 million patients globally.[1-3] Among all types of stroke, ischemic stroke accounts for 68% and hemorrhagic stroke for 32% of the cases, having a higher incidence in less developed countries.[4] With regard to the etiology of stroke, 20% of cases are due to intracranial large-artery atherosclerotic disease, 25% to lacunar infarctions, 20% to cardioembolism, and 5% to rare etiologies, while 30% are cryptogenic.[5]

Aspirin, antihypertensives, and statins are the most commonly prescribed drugs for secondary prevention of stroke.[6] Anticoagulation therapy is not routinely indicated for acute stroke management owing to the risks of intra or extra-cranial bleeding although it can offer some benefits. Controversy exists over the timing for initiation of anticoagulation, the efficacy of the treatment in relation to stroke etiology, the ideal dose of anticoagulants, and the use of novel anticoagulants.[3,7] Even the form in which the anticoagulant is administered can influence outcomes. For instance, a study with the administration of a bolus of intravenous heparin at doses of 5,000 IU or less did not increase the risk of complications.[8] However, randomized trials involving a larger number of patients to confirm this finding are needed.[8]

Randomized trials further assessing these issues in large patient cohorts have been suggested. However, heterogeneity among studies and different clinical scenarios justifying anticoagulation hamper a meta-analysis of all the clinical studies available.[3]

The objective of the present review is to critically compile the information on anticoagulation after acute ischemic stroke reviewing debatable issues on anticoagulation treatment. We have searched mainly randomized clinical

trials, and other relevant published information in the literature to achieve a higher grade of evidence.

Method

We performed a broad critical review on anticoagulation in acute ischemic stroke. In November 2015, a computerized search for English written clinical trials and randomized controlled trials was done in Medline, using the following MeSH terms and keywords: stroke, ischemic stroke, anticoagulation, anticoagulants, heparin, low-molecular-weight heparin (LMWH), warfarin, dabigatran, rivaroxaban, apixaban. This initial search yielded a maximum of 469 references. A manual search identified studies against an inclusion criteria for eligibility and relevance that incorporated: ischemic stroke, identification of stroke etiology, randomized controlled trials, outcomes clearly identified, report of adverse effects, report of hemorrhage due to anticoagulation, time of initial, and duration of anticoagulation (n=14). The resulting information was supplemented by extensive manual searching of references included at Medline database or in the primary selected studies, especially for prospective, controlled, systematic reviews, and meta-analysis. Other studies reporting safety and tolerability data not reported in prospective or controlled studies were manually searched. The Cochrane Library was searched to assure that this evidence was not systematic reviewed. Also, Embase, Scielo, and PsychInfo databases were searched for relevant studies not reported at Medline, which yielded no additional findings (Figure 1). Finally, eight studies of anticoagulation in acute stroke were selected (Table 1). Study selection was based on the agreement between two authors using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; www.prima-statement.org) statement checklist and flow diagram as reference for quality analysis (N.F. and I.A.). Two other authors analyzed the information obtained from the selection of studies (R.M.M. and E.D.N.).

Results

The use of heparin for the acute management of ischemic stroke has been assessed in a number of clinical trials, producing conflicting results (both positive and negative) and thus requiring further evaluation.[9-11]

Table 1 provides a brief summary of the findings of the eight most important clinical trials on anticoagulation in acute stroke. Overall, no clear evidence favoring early anticoagulation was found supporting the use of heparin, heparinoids, LMWH or other agents after acute stroke for the secondary prevention of thromboembolic events, disabling sequelae or death.[12-19] Antiplatelet agents remain the first-choice of antithrombotic agents.

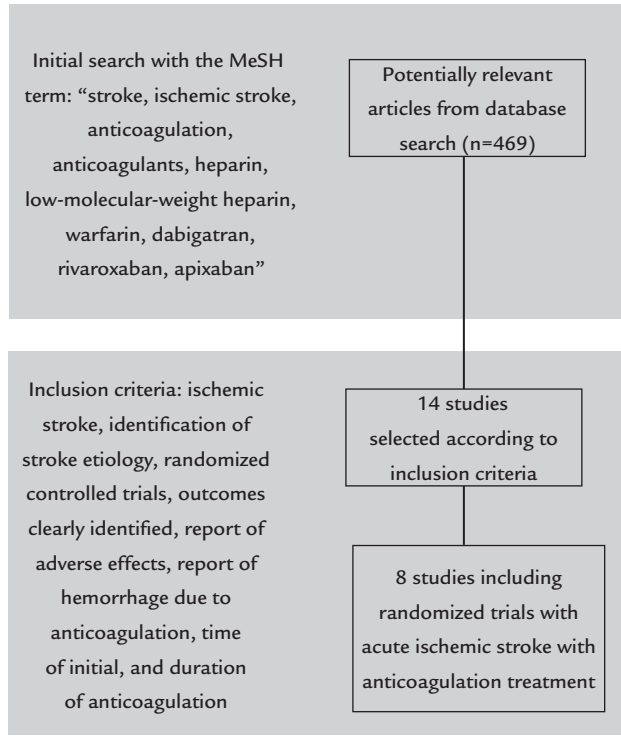

FIGURE 1 Flow diagram of selected studies.

Only two studies showed clinical improvements with anticoagulation.[12,14,20] Kay et al. reported significant dose--dependent reduction in the risk of death or dependency at 6 months with nadroparin.[12] In the TOAST trial there was a significant response observed with anticoagulation using danaparoid at both 7 days and 3 months among subjects with stroke secondary to large-artery atherosclerosis (Table 1).[14] The ARGIS-1 trial used anticoagulation with argatroban safely to subjects with acute stroke also due to large-artery atherosclerosis, but without clinical or functional outcomes between the treatment groups (Table 1).[19]

Non-vitamin K antagonist oral anticoagulants (NOAC) such as dabigatran, rivaroxiban, and apixaban were not properly evaluated in the acute management of ischemic stroke.[20-22] Clinical trials have not included these agents to anticoagulation in the acute stroke phase. Only 44 patients have randomly received apixaban or warfarin within 7 to 14 days of previous stroke in the ARISTOTLE trial, without stroke or systemic embolism in the follow-up and only one major bleed with warfarin.[22]

The main reason to avoid the use of anticoagulants was a variable increase to the risk of bleeding (Table 1). Even at the TOAST trial, a higher bleeding rate was seen in the danaparoid group.[14] However, bleeding rates did not differ between the therapeutic and placebo groups of the ARGIS-1 trial using argatroban.[19]

TABLE 1 Brief description and results of IST, TOAST, HAEST, TAIST, FISS-tris, and ARGIS-1 trials comparing anticoagulation versus aspirin or placebo in the acute management of ischemic stroke (up to 14 days after the event).

	FISS	IST	TOAST	HAEST	TAIST	TOPAS	FISS-tris	ARGIS-1
Drug used	Nadroparin 4,100 IU (aXa), SC, 2x/daily; nadroparin 4,100 IU, once daily, or placebo	UFH 5,000 or 12,500 IU, SC, 2x/daily, with or without aspirin 300 mg	Danaparoid, IV, *in bolus*+ continuous infusion, dose of 0.6-0.8 IU/mL vs. placebo	Dalteparin 100 IU/kg, SC, 2x/daily, vs. aspirin 160 mg, daily	Tinzaparin 175 IU/kg or 100 IU/kg, SC, daily vs. aspirin 300 mg/day	Certoparin 3,000 IU (aXa), SC, daily or 2x/daily, 5,000 IU (aXa), 2x/daily, or 8,000 IU (aXa), 2x/daily	Nadroparin calcium 3,800 IU, SC, 2x/daily, vs. aspirin 160 mg/day	Argatroban (100 µg/kg), IV, followed by continuous infusion of 3 µg/kg/min or 1 µg/kg/min vs. placebo
Duration of anticoagulation	10 days*	14 days*	7 days	14 days	10 days*	12-16 days	10 days*	5 days
Time between onset of symptoms and anticoagulation	Within 48 hours	Within 48 hours	Within 24 hours	Within 30 hours	Within 48 hours	Within 12 hours	Within 48 hours	Within 12 hours
Number of patients involved	308	19,435	1,281	449	1,486	404	603	13,342
Short-term outcomes	No differences at functional or bleeding rates between the groups at 10 days	↓ Ischemic stroke and pulmonary embolism; ↑ Hemorrhagic stroke and extracranial bleeding at 14 days	In general, ↑ bleeding. More favorable outcomes among large-artery atherosclerosis patients at 7 days	↑ Symptomatic intracranial hemorrhaging; Dalteparin showed no benefit in prevention of recurrent stroke at 14 days	↑ Intracranial hemorrhaging, particularly at high doses within 24 hours; ↓ Venous thrombotic events with high dose tinzaparin	No functional difference between groups. Clinical improvement in all groups within 14 days. Severe bleeding more frequent in highest doses	Hemorrhagic transformation and adverse events were similar across groups	Bleeding rates were similar among groups; no major bleeding; neurological scores did not differ among the groups
Long-term outcomes	Significant dose-dependent reduction in risk of death or dependency at 6 months with LMWH	Heparin showed no benefit for disability or death at 6 months ↑ Rate of patients with complete regression of symptoms using aspirin	More favorable outcomes among large-artery atherosclerosis patients at 3 months	No differences between groups for independence or death at 6 months	No differences between groups for independence at 3 or 6 months	Treatment groups were not different with respect to favorable functional outcome at 90 days	Patients with Barthel Index ≥ 85% at 6 months: 73% in use of nadroparin and 69% using aspirin	Neurological scores did not differ among the groups at 90 days

IST: International Stroke Trial; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; HAEST: Heparin in Acute Embolic Stroke Trial; TAIST: Tinzaparin in Acute Ischaemic Stroke Trial; FISS-tris: Fraxiparin in Stroke Study for the treatment of ischemic stroke; IU: international unit; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; IV: intravenous; SC: subcutaneous; 2x/daily: twice daily; aXa: anti-factor X.
*Patients remained on secondary prevention of stroke using antiplatelet therapy after anticoagulation.

Discussion

Only two out of eight studies favored the early anticoagulation for acute stroke. These studies presented different sample selection, anticoagulation agents, outcomes, time of follow-up, and clinical measures. Most studies have used LMWH as the anticoagulant agent and two of them used unfractioned heparin and a particular direct thrombin inhibitor, i.e., argatroban.[23-25] Thus, it is very difficult to include the whole data in a meta-analysis. Three meta-analyses were done regarding the use of anticoagulants for acute ischemic stroke between 2002 and 2008 with different inclusion criteria and studies that were included.[26-28] Thereafter, it is necessary to evaluate each study individually to permit a critical analysis of the results.

The study conducted by Kay et al. was the first clinical trial to evaluate the use of LMWH nadroparin for the treatment of 308 subjects with acute stroke. Death and dependency were the main outcomes. A significant, dose-dependent reduction in the risk of death or dependency was observed after 6 months among the subjects treated with nadroparin. Bleeding rates were similar among the groups.[12]

After two years, the results of the International Stroke Trial (IST) comparing the administration of subcutaneous unfractionated heparin (UFH) versus aspirin within 48 hours of onset of ischemic stroke symptoms were published. This randomized trial involved 19,435 patients from 467 hospitals in 36 different countries. The study showed that patients treated with heparin had a significantly lower recurrence of ischemic stroke within a 14-day period. However, there was a significant increase in the risk of hemorrhagic stroke and extracranial bleeding in this group. Over a 6-month follow-up, anticoagulation offered no benefits in terms of rates of functional decline or death.[13]

In the following year, results were published for the Acute Stroke Treatment (TOAST), assessing the use of a bolus of intravenous danaparoid, followed by continuous infusion for 7 days, within 24 hours of stroke symptom onset. The trial assessed 1,281 patients and found that early administration was associated with a greater likelihood of bleeding. Ischemic strokes were classified by subtype into the following categories: large-artery atherosclerosis, cardioembolism, small-artery occlusion and other determined or undetermined causes. A significant response to the treatment was observed at both 7 days and 3 months among individuals with stroke secondary to large-artery atherosclerosis.[14]

In the HAEST, anticoagulation with dalteparin was initiated within 30 hours of symptom onset in patients with ischemic stroke and atrial fibrillation. The primary objective was to determine whether the anticoagulant reduced stroke recurrence in 14 days. In all, 449 patients were included and no benefit in the prevention of recurrent stroke compared to aspirin was evident. In addition, patients using anticoagulants had more symptomatic brain hemorrhages. No difference in functional outcomes or deaths was observed at 14 days or at 6 months.[15]

In the TAIST trial, administration of a moderate-to-high dose of tinzaparin was compared to aspirin. In all, 1,484 patients from 100 centers located in Europe and Canada were involved, all treated within 48 hours of symptoms onset. High-dose tinzaparin was associated with lower occurrence of venous thromboembolic events. However, the rate of symptomatic intracranial hemorrhage was significantly higher at the higher doses of the anticoagulant, more frequently when the treatment was started within 24 hours of ischemic stroke. The Rankin scale and Barthel index, measuring the degree of disability acquired by the patient after stroke in their daily living activities, revealed no differences at 3 or 6 months between tinzaparin and aspirin. Given the absence of functional improvement in outcomes and the greater risk of bleeding, high doses of LMWH were not recommended as routine treatment. Possible scaling of treatment was discussed, with initial prescription of aspirin at the time of diagnosis followed by low-dose LMWH as prophylaxis for venous thromboembolism after 1 or 2 days, when the risk of intracranial hemorrhaging has declined.[16]

The TOPAS trial randomized 404 subjects within 12 hours of an acute stroke onset to four different treatment regimens with LMWH certoparin. After three months of follow-up, no significant difference was observed in functional outcome (Barthel index) or neurological recovery (European Stroke Scale). Severe bleeding complications were more frequently observed in the highest-dose group.[17]

Nadroparin calcium was compared with aspirin in the FISS-tris trial, which involved 603 Asian patients with large-artery occlusive disease. The therapy was initiated within 48 hours of onset of symptoms and patients were followed up until six months after the ischemic stroke and assessed by the Barthel index and Rankin scale. The results showed no significant benefit of nadroparin over aspirin in the patients assessed, and further investigation of anticoagulation in large-artery atherosclerosis patients was recommended.[18]

The evidence of benefits from anticoagulation after acute stroke due to large-artery arteriosclerosis is also controversial. As previously outlined, in the TOAST trial a significant response to danaparoid treatment was observed at both 7 days and 3 months among individuals with ischemic stroke secondary to large-artery atherosclerosis.[14]

However, for treatment to be effective, diagnosis of this stroke subtype must be early and accurate, requiring ancillary exams such as carotid and transcranial Doppler, angioresonance and angiotomography.[14] The FISS-tris trial recommends further investigation of anticoagulants in large-artery atherosclerosis, particularly intracranial.[18]

Argatroban is a direct thrombin inhibitor that, unlike heparin, can bind to thrombin in circulation or adhered to the clot, and does not greatly prolong activated partial thromboplastin time at various doses. In addition, it does not induce the formation of antibodies or interact with heparin-induced antibodies.[23,24] Consequently, the agent causes less bleeding, does not induce or potentialize heparin-induced thrombocytopenia, and is well-tolerated.[23] Its use has proved relatively safe in cases of ischemic stroke and heparin-induced thrombocytopenia and is available in Japan for the treatment of stroke due to large-artery atherosclerosis.[25] Argatroban is short-acting (half-life of 39-51 minutes) and can be monitored by tests such as prothrombin time and activated partial thromboplastin time.[23]

Argatroban anticoagulation in patients with acute ischemic stroke (ARGIS-1) was a randomized trial in an effective population of 13,342 patients from North American centers with up to 12 hours since onset of ischemic stroke symptoms and a National Institute of Health Stroke Scale (NIHSS) of 5 to 22. Patients were divided into three subgroups (high argatroban infusion; low argatroban infusion and placebo) undergoing treatment for five days. An initial intravenous bolus of argatroban (100 μg/kg) was administered, followed by continuous infusion of 3 μg/kg/min (high dose) or 1 μg/kg/min (low dose). Patients received standard care for stroke, including aspirin (81-325 mg) in the first 48 hours of symptom onset. With regard to intracranial hemorrhage, no differences were found among the groups; no major bleeding occurred; minor systemic hemorrhage increased only at high argatroban dose relative to placebo. Neurological scores did not differ among the groups at hospital discharge or at 90 days. Thus, it was concluded that argatroban infusion within 12 hours of symptoms at an average dose of 1.2 to 2.7 μg/kg/min for five days promoted relatively safe anticoagulation in cases of ischemic stroke. Given that argatroban has proven safety, other studies further assessing its efficacy should be performed.[19]

Finally, the utility and safety of the use of NOAC agents for acute cardio-embolic stroke within 7 to 14 days after onset remain unclear according to the best of our evidence. NOAC agents present a more rapid effect and less hemorrhagic complications compared with warfarin, and appear to provide effective anticoagulation for acute cardio-embolic stroke.[29] Future studies like the Triple AXEL can better evaluate the efficacy of NOAC agents in this scenario. The Triple AXEL trial uses rivaroxaban for early anticoagulation of ischemic stroke.[30]

As we focus our attention on anticoagulation treatment after acute ischemic stroke, several particular clinical scenarios were kept out of this review such as cerebral venous thrombosis, arterial dissection, thromboembolism following acute stroke. These topics were not included in our review.

Conclusion

There are numerous controversies over anticoagulation in the management of ischemic stroke. The ideal timing for initiating anticoagulation remains undefined, requiring further investigation. In general, early anticoagulation for ischemic stroke is not recommended, with few exceptions, as might be the case with argatroban, a drug that can bind to thrombin in circulation or adhered to clot and does not prolong activated thromboplastin time at various doses, and used for the treatment of strokes secondary to large artery atherosclerosis. Further studies are still needed to confirm drug efficacy and possible side effects. Other exceptions may be coagulopathies such as idiopathic and familial thrombophilia and acute myocardial infarction with formation of mural thrombus, but the need for weight pros and cons is still warranted. Furthermore, the development of antidotes for these anticoagulants and establishing a means of measuring their therapeutic effect can allow safer clinical practice.[31-33]

Further large-scale trials correlating treatment with factors potentially associated with greater risk of thrombotic events (history of venous thromboembolism, thrombophilia or cancer) or hemorrhagic events (minor cerebral hemorrhages and more in-depth analysis of neuroimaging) are obviously needed, especially considering the escalating incidence of cerebrovascular complications in an aging population and its severe and several sequelae.[34,35]

Therapeutic decisions could be more safely guided by some important factors, such as the volume of acute lesions, etiology, age, gender, and time of occurrence (i.e., how many hours after the ictus is the anticoagulation safe). Future studies correlating this information with anticoagulation in the acute phase could help improve the safety of this practice.[36,37]

Resumo

Anticoagulação no acidente vascular cerebral: uma revisão sistemática

Introdução: O acidente vascular cerebral (AVC) é uma das doenças mais importantes no mundo. Vários cenários clínicos exigem dose completa de anticoagulantes para tratar a etiologia primária do AVC ou para o tratamento de uma comorbidade. Contudo, existem inúmeras controvérsias em relação ao tratamento com anticoagulação no AVC, como tempo para o início, eficácia de acordo com a etiologia do AVC, dose ideal de anticoagulante e utilização de novos anticoagulantes.
Método: Busca computadorizada de ensaios clínicos controlados e randomizados foi feita até a presente data nas bases Medline, Scielo, Embase, PsychInfo e Cochrane Library, usando termos MeSH e as palavras-chave acidente vascular cerebral, acidente vascular cerebral isquêmico, anticoagulação, anticoagulantes, heparina de baixo peso molecular, heparina, varfarina, dabigatran, rivaroxaban, apixaban. O modelo PRISMA foi utilizado para avaliar os ensaios clínicos.
Resultados: Catorze ensaios clínicos foram selecionados de acordo com critérios de inclusão. Não foram encontradas evidências que apoiam o uso precoce de heparina, heparinoides ou heparina de baixo peso molecular (HBPM) precocemente após o AVC. Nenhuma evidência consistente para o uso de warfarina e anticoagulantes orais mais recentes foi encontrada. Argatroban foi o único anticoagulante com resultados positivos significativos para AVC isquêmico precoce não embólico.
Conclusão: O momento ideal para iniciar a anticoagulação continua mal definido, exigindo uma investigação mais aprofundada. Anticoagulação precoce para AVC isquêmico não é recomendada, com exceção para o argatroban.

Palavras-chave: acidente vascular cerebral isquêmico, anticoagulação, heparina, varfarina.

References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(859):2095-128.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2014 update: a report from the American Heart Association. Circulation. 2014; 129(3):e28-e292.
3. Whiteley WN, Adams Jr HP, Bath PMW, Berge E, Sandset PM, Dennis M, et al. Targeted use of heparin, heparinoids, or low-molecular weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. Lancet Neurol. 2013; 12(6):539-45.
4. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al.; Global Burden of Diseases, Injuries, Risk Factors Study 2010 (GBD 2010); GBD Stroke Experts Group. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health. 2013; 1(5):1-11.
5. Cavaco R, Fonseca T, Gorjão CJ. Terapêutica antitrombótica para prevenção primária e secundária do acidente vascular cerebral isquêmico cardioembólico – pontos de interesse na orientação terapêutica. Med Intern. 2010; 17(21):118-23.
6. Gijn J, Algra A. Anticoagulation in ischemic stroke: opportunities in arterial disease. Cerebrovasc Dis. 2005; 20(Suppl. 2):101-8.
7. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. Stroke. 2007; 38(2):423-30.
8. Toth C. The use of a bolus of intravenous heparin while initiating heparin therapy in anticoagulation following transient ischemic attack or stroke does not lead to increased morbidity or mortality. Blood Coagul Fibrinolysis. 2003; 14(5):463-8.
9. Toth C, Voll C. Validation of weight-based nomogram for the use of intravenous heparin in transient ischemic attack or stroke. Stroke. 2002; 33(3):670-4.
10. Rödén-Jüllig A, Britton M. Effectiveness of heparin treatment for progressing ischaemic stroke: before and after study. J Intern Med. 2000; 248(4):287-91.
11. Chamorro A, Busse O, Obach V, Toni D, Sandercock P, Reverter JC, et al. The rapid anticoagulation prevents ischemic damage study in acute stroke- final results from the writing committee. Cerebrovasc Dis. 2005; 19(6):402-4.
12. Kay R, Wong KS, Yu YL, Chan YW, Tsoi TH, Ahuja AT, et al. Low molecular weight heparin for the treatment of acute ischemic stroke. N Engl J Med. 1995; 333:1588-94.
13. Sandercock P, Collins R, Counsell C, Farrell B, Peto R, Slattery J, et al. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. Lancet. 1997; 349(9065):1569-81.
14. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid, Org 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. JAMA. 1998; 279(26):1265-72.
15. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. Lancet. 2000; 355(9211):1205-10.
16. Bath PMW, Lindenstrom E, Boysen G, Deyn P, Friis P, Leys P, et al. Tinzaparin in acute ischaemic stroke (TAIST): a randomized aspirin-controlled trial. Lancet. 2001; 358(9283):702-10.
17. Diener HC, Ringelstein EB, von Kummer R, Langohr HD, Bewermeyer H, Landgraf H, et al. Treatment of acute ischemic stroke with the low-molecular-weight heparin certoparin. Results of the TOPAS trial. Therapy of Patients With Acute Stroke (TOPAS) Investigators. Stroke. 2001; 32(1):22-9.
18. Wong KS, Chen C, Ng PW, Tsoi TH, Li HL, Fong WC, et al.; FISS-tris Study Investigators. Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomized study. Lancet Neurol. 2007; 6(5):407-13.
19. LaMonte MP, Nash ML, Wang DZ, Woolfenden AR, Schultz J, Hursting MJ, et al. Argatroban anticoagulation in patients with acute ischemic stroke (ARGIS-1): a randomized, placebo-controlled safety study. Stroke. 2004; 35:1677-82.
20. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361(12):1139-51.
21. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365(10):883-91.
22. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al.; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365(11):981-92.
23. Ikoma H. Development of argatroban as an anticoagulant and antithrombin agent in Japan. Pathophysiol Haemost Thromb. 2002; 32(Suppl 3):23-8.
24. Lewis BE, Wallis DE, Leya F, Hursting MJ, Kelton JG; Argatroban-915 Investigators. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med. 2003; 163(15):1849-56.
25. LaMonte MP, Stallmeyer B. Acute ischemic stroke successfully treated using sequenced intravenous and intra-arterial thrombolysis and argatroban anticoagulation: a case study. J Thromb Thrombolysis. 2004; 17(2):151-6.
26. Berge E, Sandercock P. Anticoagulants versus antiplatelet agents for acute ischemic stroke. Cochrane Database Syst Rev. 2002; (4):CD003242.
27. Gubitz G, Sandercock P, Counsell C. Anticoagulants for acute ischemic stroke. Cochrane Database Syst Rev. 2004; (3):CD000024.
28. Sandercock PA, Counsell C, Kamal AK. Anticoagulants for acute ischaemic stroke. Cochrane Database Syst Rev. 2008; (4):CD000024.
29. Yamagami H, Toyoda K. Timing of anticoagulation therapy in patients with acute cardioembolic stroke. Circ J. 2015; 79(4):763-5.
30. Hong KS, Choi YJ, Kwon SU; Triple AXEL Investigators. Rationale and design of Triple AXEL: trial for early anticoagulation in acute ischemic stroke patients with nonvalvular atrial fibrillation. Int J Stroke. 2015; 10(1):128-33.

31. Lewis WR, Fonarow GC, Grau-Sepulveda MV, Smith EE, Bhatt DL, Hernandez AF, et al. Improvement in use of anticoagulation therapy in patients with ischemic stroke: results from get with The Guidelines-Stroke. Am Heart J. 2011; 162(4):692-9.
32. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182.678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Europ Heart J. 2012; 33:1500-10.
33. Turakhia MP, Hoang DD, Xu X, Frayne S, Schmitt S, Yang F, et al. Differences and trends in stroke prevention anticoagulation in primary care vs cardiology specialty management of new atrial fibrillation: The Retrospective Evaluation and Assessment of Therapies in AF (TREAT-AF) study. Am Heart J. 2013; 165(1):93-101.
34. Kirshner HS. Antiplatelet and anticoagulation strategies in the prevention and treatment of ischemic stroke. Curr Pharm Des. 2012; 18(33):5261-72.
35. Robinson AA, Ikuta K, Soverow J. Anticoagulation for acute management of ischemic stroke. Yale J Biol Med. 2014; 87(2):199-206.
36. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al.; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014; 45(7):2160-236.
37. Nomura E, Ohshita T, Imamura E, Wakabayashi S, Kajikawa H, Matsumoto M. Can early effective anticoagulation prevent new lesions on magnetic resonance imaging in acute cardioembolic stroke? J Stroke Cerebrovasc Dis. 2014; 23(8):2099-104.