Anticoagulants to Prevent Stroke Occurrence and Worsening

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The appropriate use of anticoagulants continues to be one of the most contentious and controversial issues in both Neurology and Medicine. The advent of modern diagnostic technology now enables accurate diagnosis of the cause of most strokes, yet the therapeutics of only a few defined causes have been well studied. The introduction of fractionated low molecular weight heparin and heparinoids has further complicated the issue for clinicians. On the horizon are direct thrombin inhibitors that will undoubtedly replace heparins and warfarin compounds in the future. These direct thrombin inhibitors (e.g., ximelagatran, argabatran, dibigatran) are likely to be much easier to control and are equally or more effective and safer than warfarin. Although these newer compounds have theoretical and practical advantages, most clinicians have had little experience with them and data are insufficient to guide the choice between different pharmaceutical products. Clinicians continue to ask which product should be given to which patients, by what route, with or without an initial bolus, at what dose, how they should be monitored, when treatment should be started, and for how long it should be given. Unfortunately, the data from randomized trials are too scarce to settle any of these queries.

Clots and the theoretical utility of anticoagulants

Thrombi can be divided into red erythrocyte-fibrin clots and white platelet-fibrin clots. Red clots are treated with thrombolytic drugs and heparins, warfarin, and direct thrombin inhibitors. In contrast, white clot formation is prevented by so-called antiplatelet agents (aspirin, clopidogrel, dipyridamole, cilostazole and others) [1].

Red thrombi are composed mostly of red blood cells and fibrin, They tend to form in areas of slowed blood flow. Their formation does not require an abnormal vessel wall or tissue thromboplastin. Red clots are formed by activation of circulating coagulation factors. The final step in the coagulation cascade is conversion of the soluble protein fibrinogen into insoluble polymers called fibrin. Fibrin strands form a network of fibers that entangle the formed blood elements (platelets, erythrocytes, leukocytes) into a clot. Fibrin is quite adhesive and is capable of contracting. The fibrinogen-fibrin reaction occurs when factor II, prothrombin, is converted to thrombin. The amounts of circulating fibrinogen and prothrombin are important in these reactions.

Prothrombin is activated in two different ways. In the so-called extrinsic system of coagulation, a tissue or endothelial injury releases thromboplastic substances – tissue factors, which in turn induce both platelet activation and activation of blood serine protease coagulation factors, especially factors V, VII, and X. Activation of factor X catalyzes the reaction of prothrombin to thrombin. Activation of platelets causes them to agglutinate, to adhere to the injured vessel wall, and to release various intracellular substances, which in turn also activate the coagulation system.

The complementary intrinsic coagulation system refers to blood coagulation factors that circulate in inactive forms (factors V, VIII [antihemophilic globulin], IX, X, XI, XII) and are intrinsic to the blood. Activation of factor XII from an inert precursor form to an activated form triggers a series of reactions, the coagulation cascade, in which the various blood-clotting factors are sequentially converted to their active enzymatic forms. Ultimately, these reactions lead to activation of factor X, which catalyzes the prothrombin-thrombin reaction. Red thrombi are most apt to develop when flow is reduced. Dilated cardiac atria, especially those with inefficient contractility as found with atrial fibrillation, regions of hypokinesia of the cardiac ventricles and frank ventricular aneurysms commonly harbor red clots. Red thrombi are also often formed in heart chambers when ejection fractions are low. Red thrombi tend to form on the surface of myocardial infarcts. Thrombi formed in the leg and pelvic veins that pass through defects in the cardiac atrial and ventricular septa or pass through arteriovenous fistulae in the lungs are nearly always red thrombi. Both red and white thrombi often form along damaged heart valves, especially those made of prosthetic materials.

White clots are composed of platelets and fibrin and do not contain red blood cells. White clots form almost exclusively in areas in which the endothelial surface is abnormal, characteristically in fast-moving bloodstreams. Irregular valvular and endothelial surfaces predispose to platelet-fibrin thrombi forming in areas of irregularities. A thrombus often begins as a white platelet fibrin clot and then a red thrombus is laid down as a cap over the initial platelet mass.

Anticoagulants

Heparins, low molecular weight heparins, and heparinoids act as anticogulants by binding to plasma antithrombin III. This interaction induces a conformational change in antithrombin III that increases its ability to inactivate coagulation enzymes including thrombin and activated factor X (factor Xa). Heparins reduce the formation of red clots in regions of vascular stasis, especially within the heart, in severely stenosed arteries sometimes engrafted on white thrombi, in acute arterial occlusions as fresh tails on existing thrombi, and within extremity, pelvic and dural sinus veins.

Warfarin is a water-soluble coumaric acid derivative that is absorbed by the small intestine and transported in the blood, loosely bound to albumin. Warfarin inhibits the action of vitamin K, which is necessary for the synthesis of factors II (prothrombin), VII, IX and X. Depression of these procoagulant factors affects both the intrinsic cascade and the extrinsic coagulation pathway. Warfarin works quite differently from heparin. Heparin is usually given before beginning warfarin anticoagulation since initiation of therapy with warfarin alone can be associated with an initial period of hypercoagulability, especially in patients with low levels of protein C or protein S. Warfarin anticoagulation is difficult to control because of individual variance in dose and the effect of a variety of foods and other pharmaceutical agents on vitamin K, prothrombin and liver functions. Even during randomized trials optimal control of anticoagulation using warfarin has been difficult. In the community, control is even worse and many patients have prolonged periods of inadequate or too intense anticoagulation.

Direct inhibitors of thrombin offer many potential advantages. Argabatran is an intravenous agent often used in Asia instead of heparin [2,3]. Ximelagatran is an oral agent that has been used in trials and is approved in Europe but not in the United States. It acts quickly so that heparins are not needed. The dose is constant and does not require monitoring by either activated partial thromboplastin time or INR determinations. Foods or other drugs do not have any effect. Ximelagatran is given twice a day; it can cause an elevation of liver enzymes and may potentially cause liver damage in a minority of patients. Other orally administered direct thrombin inhibitors such as dibigitran are now undergoing trials. In the future, direct thrombin inhibitors will likely replace heparins and warfarin for rapid, safe and effective anticoagulation.

Indications for anticoagulation

At present, I believe there are six important potential indications for anticoagulation: a) hypercoagulable states, b) some causes of cardiogenic embolism, c) large protruding and mobile aortic atheromas, d) severe stenosis or occlusion of large cervico-cranial arteries, e) arterial dissection, and f) dural and cerebral venous thrombosis.

Cardiogenic embolism [4]

Table 1 lists the various cardiac sources that are indications for anticoagulation. In many, the relative value of anticoagulants versus other treatments such as platelet inhibitors has not been well studied. The most common and best studied cardiac source is atrial fibrillation; it also serves as a model for the management of anticoagulants in patients with cardiogenic brain embolism. Many randomized trials have shown that anticoagulation decreases the frequency of recurrent brain infarction in patients with atrial fibrillation [5]. A direct thrombin inhibitor, ximelagatran, was shown by the large SPORTIF trials to be safer and at least as effective as warfarin [6-8]. Although clinicians often eclectically choose to anticoagulate atrial fibrillation patients who have not had a stroke, nearly all agree that anticoagulants are indicated in atrial fibrillation patients who have had a cardiac-origin embolic brain infarct. Controversy still exists regarding how soon to anticoagulate. Early anticoagulation of patients with atrial fibrillation-related strokes can be safe and effective [9,10]. In an observational, non-randomized, non-controlled study, Chamorro et al. [11] treated all atrial fibrillation patients who had presumed cardioembolic strokes with either intravenous or subcutaneously administered unfractionated heparin as soon as a computed tomography scan had excluded brain hemorrhage. In 74 patients heparin was given within 6 hours, but between 6 and 48 hours after symptom onset in 157 other patients. Comparing the early-treated and late-treated groups, those treated within 6 hours exhibited more functional recovery at hospital discharge. Treatment with intravenous heparin led to therapeutic and excessive levels of anticoagulation more often than did subcutaneously administered heparin. The rate of serious brain hemorrhage was low. Patients with recurrent strokes had lower mean APTT ratios than those without recurrence, and patients with hemorrhage had higher mean APTT ratios than those without hemorrhage especially when APTT ratios were compared on the day of hemorrhage. Clinicians could conclude that in patients with atrial fibrillation who have cardioembolic strokes: a) early heparin treatment is relatively safe, b) those who are treated early seem to do

Table 1. Cardiac sources of emboli

Anticoagulants indicated	Atrial fibrillation
	Thrombus found in the heart on echocardiography
	Ventricular aneurysm
	Hypokinetic ventricle
	Acute myocardial infarction
	Very low ejection fraction
	Mitral stenosis with large left atrium
	Spontaneous echo contrast and large left atrium
	Prosthetic mechanical valves
Antibiotics indicated	Bacterial endocarditis
Antiplatelets indicated	Fibrotic valve disease in antiphospholipid antibody syndrome
	Non-thrombotic (marantic) endocarditis
	Fibrous strands
Anticoagulants sometimes used	Mitral valve prolapse (with thrombi)
	Mitral annulus calcification (with thrombi)
	Patent foramen ovale especially with atrial septal aneurysm
	Calcific aortic stenosis

APTT = activated partial thromboplastin time

better than those treated later, and c) therapeutic and excessive APTT ratios are more often achieved with intravenous than with subcutaneously administered heparin.

How should clinicians decide on treatment for individual patients with cardiogenic brain embolism? It is worth looking at the reviews published in 1986 and 1989 by the Cerebral Embolism Task Force [12,13]. They analyzed published reports to determine the frequency and timing of stroke recurrence in patients with brain embolism due to a variety of different cardiac lesions and also analyzed the frequency of hemorrhagic complications of heparin treatment. The task force concluded that stroke recurrence during the first 2 weeks after cardiac-origin brain embolism was generally low, especially in patients with non-rheumatic atrial fibrillation, and hemorrhagic complications were relatively common and related to the size of infarction, intensity of anticoagulation, and the presence of hemorrhagic changes on CT scans [12]. On the basis of these findings they advised delaying CT scanning and anticoagulation, but recommended treatment for individual patients by applying aggregate data from large groups of patients to all individuals.

Other investigators also studied the timing of anticoagulation in patients with cardiogenic embolism. The Cerebral Embolism Study Group conducted a randomized trial of immediate vs. delayed anticoagulation in patients with cardiogenic brain embolism and reviewed 30 cases of hemorrhagic infarction or parenchymatous hematomas developing in patients with cardiogenic embolism [14]. Their findings led them to conclude that brain hemorrhage in embolic stroke was most common in large infarcts and that early CT might not estimate infarct size [14]. In contrast, Furlan and team [15], who studied 54 consecutive patients with acute non-septic embolic brain infarcts, demonstrated that hemorrhagic complications were quite rare even in patients with large infarcts and that recurrent strokes were related to inadequate intensity of anticoagulation. They recommended early anticoagulation for all patients with non-septic cardioembolic brain infarcts [15]. Pessin and I and colleagues [16] showed that patients with hemorrhagic infarction on CT scan seemed to have no adverse effects when heparin was continued despite the CT findings. Internists have always anticoagulated patients with pulmonary embolism despite the presence of hemoptysis and hemorrhagic pulmonary infarcts. Chamorro et al. [10] performed a retrospective analysis of the safety of heparin anticoagulation among 83 patients with presumed embolic brain infarcts treated within 72 hours, and found that severity of stroke and infarct size did not predict hemorrhagic changes or clinical worsening.

I urge an eclectic approach to the treatment of individual patients. I urge weighing the benefits versus the risks of any given treatment in the individual patient. With regard to the timing of anticoagulation in patients with cardiac-origin embolism, the risk of early recurrence if the patient is not anticoagulated should be weighed against the risk of early anticoagulation. The probability of early recurrence in atrial fibrillation patients depends on the number of prior embolic events, atrial size, the presence of valve abnormalities, the presence of atrial or auricular appendage thrombi, the presence of ventricular lesions, as well as ventricular function, ejection fraction, and blood and coagulation factors. The risk of hemorrhage with heparin probably depends on the patient's blood pressure, coagulation factors, use of a bolus starting dose, and the route and intensity of anticoagulation. The data are conflicting with regard to the relevance of the size of infarction, the severity of the neurologic deficit, and the presence of hemorrhagic infarction on CT scans. Echocardiography can be helpful when considering the risk of early recurrence.

Anticoagulants are not routinely used as prophylaxis in patients with mitral valve prolapse, mitral annulus calcification, calcific aortic stenosis, and those with fibrotic valve lesions (Libman-Sacks endocarditis in patients with lupus erythematosis and the antiphospholipid antibody syndrome and non-thrombotic marantic endocarditis), cardiac myxomas, and bacterial endocarditis. Anticoagulants are continued in patients with bacterial endocarditis if there was a pre-existing indication such as atrial fibrillation or prosthetic heart valves. Some patients with mitral valve prolapse and mitral annulus calcification have thrombi attached to their mitral valves and anticoagulants are then used.

The choice of anticoagulant and antiplatelet treatments must be individualized, depending on the location, nature and severity of causative cardiac, cerebrovascular and hematologic lesions

The data regarding optimal prophylaxis in patients with atrial septal defects or patent foramen ovale are not conclusive and treatment should also depend on the individual circumstances. Results from three echocardiographic studies indicate a strong association between atrial septal aneurysms and inter-atrial shunts, and that the presence of either atrial septal aneurysms and/or PFOs is strongly associated with the presence of cryptogenic stroke especially among young stroke patients [17-19]. The mechanism by which atrial septal aneurysms contribute to brain embolism has not been satisfactorily clarified, but these lesions can harbor thrombi. Thrombus was seen within an atrial septal aneurysm in one patient [20], and has been found within the base of atrial septal aneurysms at autopsy [21].

The recurrence rate of stroke in patients with PFOs and the effect of various treatments on recurrence have also been studied [22-26]. Bogousslavsky et al. [22] studied stroke recurrence among 140 consecutive patients who had PFOs and brain ischemic events. One-fourth of the patients also had atrial septal aneurysms. During a mean follow-up of 3 years, the stroke or death rate was 2.4% per year; 8 patients had a recurrent brain infarct, 92 (66%) took 250 mg aspirin per day, while 37(26%) were given anticoagulants and 11 (8%) had surgical closure of the

PFO = patent foramen ovale

PFO within 12 weeks of the stroke after anticoagulant treatment. There was no significant difference in the effect of any of the treatments on recurrence. The relatively low rate of recurrence contrasted with the severity of the initial stroke, which left disabling effects in half the patients [22]. In a French multicenter study, 132 patients with PFOs and/or atrial septal aneurysms and cryptogenic stroke were followed for an average of 22.6 months [23]. The recurrence rate was approximately 2–3% at 2 years and was higher in patients with both PFOs and atrial septal aneurysms. Recurrences occurred in four patients who were taking antiplatelet agents and in one treated with anticoagulants [23]. Bridges and co-workers [27] reported the results of transcatheter closure of PFOs among 36 patients with PFOs of whom half had multiple ischemic events. The closure was complete in 28 patients (78%) and nearly complete in another 5. No patient had a recurrent stroke during 8.4 months of follow-up, but four patients had transient ischemic events [24].

The Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) [25] was a substudy of the Warfarin Aspirin recurrent Stroke Study (WARSS) [26]. All patients in WARSS who had undergone transesophageal echocardiography were eligible. In PICSS, 312 stroke patients were treated with warfarin and 318 received aspirin. Large PFOs were much more common in patients with cryptogenic strokes. Among the cryptogenic stroke patients, warfarin treatment was slightly but not significantly better than aspirin with regard to the annual rate of stroke or death (4.75% vs. 8.95%, relative risk 0.53, confidence interval 0.18–1.58) because the numbers were small and the confidence intervals wide [25].

Anticagulants (heparins, warfarin, direct thrombin inhibitors) are used in patients who have red erthrocyte-fibrin clots or lesions that predispose to red clot formation

The available data regarding treatment of PFO-related strokes are inconclusive. The presence of both a PFO and an atrial septal aneurysm substantially increases the risk of stroke recurrence. A large defect, spontaneous right-to-left shunting, and a large number of bubbles shunted may indicate a higher risk of paradoxical embolism. Warfarin and surgical or transcatheter closure are posited to be more effective than drugs that affect platelet functions, but studies have not definitively shown their superiority.

Dural sinus and cerebral venous thrombosis

Case reports and reviews have shown that patients do not worsen or develop new hemorrhages after heparin anticoagulation. Among 82 heparin-treated patients, there were no deaths and 77% of patients recovered completely [27]. Among 79 patients given anticoagulants, 94% improved and survived while only half of 157 patients not given anticoagulants survived [28]. A meta-analysis of two trials showed an absolute risk reduction in mortality of 14% and a relative risk reduction of 70% in heparin-treated patients [29,30]. Among 102 patients with CVTs (43 with intracerebral hemorrhages), those not treated with heparin fared worse and had a higher mortality [30]. In a double-blind, placebo-controlled multicenter trial, CVT patients treated with low molecular weight heparin had better outcomes than those given placebo [31]. No new symptomatic brain hemorrhages occurred. Prevention of pulmonary embolism is another reason to administer anticoagulants to patients with dural sinus thrombosis [32]. Most clinicians now agree that heparin and anticoagulants are indicated in patients with CVT. The duration of anticoagulation has not been well studied.

Acute arterial occlusions and arterial dissections

The use of anticoagulants in the treatment of stroke patients with non-cardioembolic strokes continues to be controversial. Many neurologists use heparin during the acute phase of stroke and continue with warfarin; others do not use heparin and believe strongly that it should not be used and they seldom use warfarin. Heparin should not be given indiscriminately to all brain ischemia patients. Bleeding complications will outweigh therapeutic benefit. Heparins should theoretically be useful in patients with fresh red erythrocyte-fibrin thrombi within large arteries to prevent intraarterial embolism. Unfortunately, randomized trials have not adequately studied heparins in patients with conditions likely to respond to treatment. Reported trials lumped patients with brain ischemia together without diagnostic investigations defining etiology, stroke subtypes, or vascular lesions.

Worsening and new neurologic deficits can develop when thrombi form, propagate and embolize. Stroke worsening, even when thrombi are present, occurs in about 20–33% of ischemic strokes [33]. Worsening in patients with atherothrombotic large artery occlusive disease is due to perfusion failure and propagation and embolization of occlusive thrombi. Randomized trials in patients with non-cardioembolic brain ischemia to effectively determine heparin utility must be: a) eclectic and include only patients in whom brain and cardiac and vascular imaging show high risk artery-to-artery embolic brain infarcts and patients with documented severe extracranial or intracranial large artery occlusive disease; b) powered to account for clinical worsening and/or new brain infarcts in at least one-third of patients; and c) closely monitored to ensure infrequent bleeding. No available trials even remotely meet these criteria. In the International Stroke Trial (IST), the largest heparin trial, vascular and cardiac imaging were not reported, some patients had no brain imaging before treatment, heparin was given subcutaneously while elsewhere heparins are usually given intravenously, and levels of anticoagulation were not always closely monitored. Heparin effectively prevented pulmonary embolism [34].

In the TOAST trial, the low molecular weight heparinoid ORG 10172 was given within 24 hours of the onset of symptoms of

CVT = cerebral venous thrombosis

an acute ischemic stroke [35]. This heparinoid was then given by continuous intravenous infusion for 7 days with the dose adjusted after 24 hours to maintain the anti-Xa factor activity at 0.6–0.8 anti-factor Xa units/ml. ORG 10172 (danaparoid) is a mixture of glycosaminoglycans with a mean molecular weight of 5500 isolated from porcine intestinal mucosa. The anti-factor Xa activity of danaparoid is attributed to its heparin sulfate component, which has a high affinity for antithrombin III. Although danaparoid treatment was not effective in terms of the entire group of patients with ischemic stroke, effectiveness was shown in the group of patients diagnosed as having large artery atherosclerosis [36]. In this group, heparinoid reduced the number of recurrences of stroke during the 7 days of infusion, and the rates of favorable and very favorable outcomes were significantly higher in patients given heparinoid when compared with placebo. Danaparoid led to a favorable outcome in 68% of patients with large artery atherosclerosis as compared to 54.7% treated with placebo ($P = 0.04$); 43% of patients with large artery atherosclerosis treated with danaparoid had very favorable outcomes vs. 29.1% treated with placebo ($P = 0.02$). Recurrent strokes developed in 6% of danaparoid-treated patients with large artery atherosclerosis vs. 11% of those treated with placebo. Because of the small numbers the figures for recurrent strokes did not reach statistical significance [36].

Important potential indications for anticoagulation include: hypercoagulable states, some causes of cardiogenic embolism, large protruding and mobile aortic atheromas, severe stenosis or occlusion of large cervico-cranial arteries, arterial dissection, and dural and cerebral venous thrombosis

In the WARRS trial, coumadin and aspirin were equally effective in preventing new strokes [26]. The drugs were given within a month of stroke onset, not always acutely, and secondary prevention of new strokes was studied. The number of patients with documented large artery disease was small and vascular studies were not required or reported. Some patients received heparin acutely and then aspirin. Some patients did not receive heparin but were given coumadin within a month. The data do not relate well to the use of heparin/warfarin during the acute stroke.

In the WASID trial of patients with severe intracranial atherosclerosis, there was no difference in the prevention of new strokes between aspirin and warfarin [37]. Again, the study drugs were initiated often weeks after the last ischemic event. Warfarin was difficult to control. In those patients who were maintained within the target therapeutic INR range, warfarin performed better than 1300 mg/day aspirin. More infarcts developed in patients below the target range and more hemorrhages in those above the target INR range [37,38].

I administer heparin to patients with acute arterial dissections Unfortunately, trials have not yielded data on the effectiveness of heparin or any other treatment in patients with arterial dissections. Therapeutics in patients with dissection has not been studied in trials. Although transient ocular and brain ischemia may develop when a dissection causes a complete or near complete arterial occlusion, the great majority of strokes are caused by embolization of thrombi formed in the region of the dissection. Thrombus is often present within the lumen, either as a result of communication of the intramural hematoma with the lumen, or because of stasis of blood flow caused by luminal compromise. Perturbation of the endothelium leads to the release of tissue factors that promote thrombosis. The luminal clot is usually loosely adherent to the intima and can readily embolize distally. In the weeks and months after dissection, the intramural blood is absorbed and the narrowed lumen usually returns to its normal size; if the artery becomes completely occluded, it remains occluded in about 75% of patients. Anecdotally, many neurologists use heparin and follow with warfarin in this situation and believe it to be effective, although initially there was much concern that it could enlarge the intramural clot. The duration of anticoagulation has not been studied.

References

1. Caplan LR. Thrombosis and therapeutic antidotes. In: Bogousslavsky J, Hacke W, eds. Historical Aspects in Thrombolytic and Antithrombotic Therapy for Stroke. Abington, Oxon: Informa UK Ltd, 2006:1–11.
2. Kobayashi S, Tazaki Y. Effectiveness of the thrombin inhibitor argatroban in acute cerebral thrombosis. *Semin Thromb Hemost* 1997;23:531–4.
3. LaMonte MP, Nash ML, Wang DZ, et al., for the ARGIS-1 Investigators. Argabatran anticoagulation in patients with acute ischemic stroke (ARGIS-1). *Stroke* 2004;35:1677–82.
4. Caplan LR, Manning W. Brain Embolism. Boston: Decker, 2006 (in press)
5. Caplan LR. Stroke – A Clinical Approach. 3rd edn. Boston: Butterworth-Heinemann, 2000.
6. Halperin JL, for the Executive Steering Committee, SPORTIF III and V Study Investigators. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). *Am Heart J* 2003;146:431–8.
7. Olsson SB, for the Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003;362:1686–7
8. Albers GW, Diener HC, Frison L, et al., SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA* 2005;293(6):736–9.
9. Cerebral Embolism Study Group. Immediate anticoagulation of embolic stroke: a randomized trial. *Stroke* 1983;14:668–76.
10. Chamorro A, Vila N, Saiz A, Alday M, Tolosa E. Early anticoagulation after large cerebral embolic infarction. *Neurology* 1995;45:861–5.

11. Chamorro A, Vila N, Ascaso C, Blanc R. Heparin in acute stroke with atrial fibrillation. Clinical relevance of early treatment. *Arch Neurol* 1999;56:1098–102.
12. Cerebral Embolism Task Force. Cardiogenic brain embolism. *Arch Neurol* 1986;43:71–84.
13. Cerebral Embolism Task Force. Cardiogenic brain embolism. The second report of the Cerebral Embolism Task Force. *Arch Neurol* 1989;46:727–43.
14. Cerebral Embolism Study Group. Immediate anticoagulation of embolic stroke: brain hemorrhage and management options. *Stroke* 1984;15:779–89.
15. Furlan AJ, Cavalier S, Hobbs RE, Weinstein MA, Modic MT. Hemorrhage and anticoagulation after nonseptic embolic brain infarction. *Neurology* 1982;32:280–2.
16. Pessin MS, Estol C, Lafranchise F, Caplan LR. Safety of anticoagulation after hemorrhagic infarction. *Neurology* 1993;43:1298–303.
17. Nater B, Bogousslavsky J, Regli F, Stauffer J-C. Stroke patterns with atrial septal aneurysms. *Cerebrovasc Dis* 1992;2:342–6.
18. Belkin RN, Hurwitz BJ, Kisslo J. Atrial septal aneurysm: association with cerebrovascular and peripheral embolic events. *Stroke* 1987;18:856–62.
19. Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. *Stroke* 1993;24:1865–73.
20. Grosgogeat Y, Lhermitte F, Carpenter A, Facquet J, Alhomme P, Tran T. Aneurysme de la cloison interauriculaire revele par une embolie cerebrale. *Arch Mal Coeur* 1973;66:169–77.
21. Silver MD, Dorsey JS. Aneurysms of the septum primum in adults. *Arch Pathol Lab Med* 1978;102:62–5.
22. Bogousslavsky J, Garazi S, Jeanrenaud X, Aebischer N, Van Melle G. Stroke recurrence in patients with patent foramen ovale: the Lausanne study. *Neurology* 1996;46:1301–5.
23. The French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. Recurrent cerebrovascular events in patients with patent foramen ovale or atrial septal aneurysms and cryptogenic stroke or TIA. *Am Heart J* 1995;130:1083–8.
24. Bridges ND, Hellensbrand W, Latson L, Filiano J, Newburger JW, Lock JE. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. *Circulation* 1982;86:2013–15.
25. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: Patent Foramen Ovale in Cryptogenic Stroke Study. *Circulation* 2002;105:2625–318.
26. Mohr JP, Thompson JLP, Lazar RM, et al., for the Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N *Engl J Med* 2001;345:1444–51.
27. Ameri A, Bousser M-G. Cerebral venous thrombosis. *Neurol Clin* 1992;10:87–111.
28. Jacewicz M, Plum F. Aseptic cerebral venous thrombosis. In: Einhaupl K, Kempkti O, Baethmann A, eds. Cerebral Sinus Thrombosis. Experimental and Clinical Aspects. New York: Plenum, 1990:157–70.
29. Einhaupl KM, Villringer A, Meister W, et al. Heparin treatment in sinus venous thrombosis. *Lancet* 1991;338:597–600.
30. Meister W, Einhaupl K, Villringer A, et al. Treatment of patients with cerebral sinus and vein thrombosis with heparin. In: Einhaupl K, Kempski O, Baethmann A, eds. Cerebral Sinus Thrombosis. Experimental and Clinical Aspects. New York: Plenum, 1990:225–30.
31. de Bruijn SFTM, Stam J, for the Cerebral Venous Sinus Thrombosis Study Group. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral venous sinus thrombosis. *Stroke* 1999;30:484–8.
32. Diaz JM, Schiffman JS, Urban ES. Superior sagittal sinus thrombosis and pulmonary embolism: a syndrome rediscovered. *Acta Neurol Scand* 1992;86:390–6.
33. Caplan LR. Worsening in ischemic stroke patients: is it time for a new strategy? *Stroke* 2002;33:1443–5.
34. International Stroke Trial Collaboration Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute stroke. *Lancet* 1997;349:1569–81.
35. 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;279:1265–72.
36. Adams HP, Bendixen BH, Leira EC, et al. Antithrombotic treatment of ischemic stroke among patients with occlusion or severe stenosis of the internal carotid artery: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 1999;53:122–5.
37. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N *Engl J Med* 2005;352:1305–16.
38. Koroshetz W. Warfarin, aspirin, and intracranial vascular disease. N *Engl J Med* 2005;352:1368–70.

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