Efficacy and Safety of Anticoagulant Treatment in Acute Cardioembolic Stroke

A Meta-Analysis of Randomized Controlled Trials

Maurizio Paciaroni, MD; Giancarlo Agnelli, MD; Sara Micheli, MD; Valeria Caso, MD, PhD

Background and Purpose—The role of anticoagulant treatment for acute cardioembolic stroke is uncertain. We performed an updated meta-analysis of all randomized trials to obtain the best estimates of the efficacy and safety of anticoagulants for the initial treatment of acute cardioembolic stroke.

Methods—Using electronic and manual searches of the literature, we identified randomized trials comparing anticoagulants (unfractionated heparin or low-molecular-weight heparin or heparinoids), started within 48 hours, with other treatments (aspirin or placebo) in patients with acute ischemic cardioembolic stroke. Two reviewers independently selected studies and extracted data on study design, quality, and clinical outcomes, including death or disability, all strokes, recurrent ischemic stroke, and cerebral symptomatic bleeding. Odds ratios for individual outcomes were calculated for each trial and data from all the trials were pooled using the Mantel-Haenszel method.

Results—Seven trials, involving 4624 patients with acute cardioembolic stroke, met the criteria for inclusion. Compared with other treatments, anticoagulants were associated with a nonsignificant reduction in recurrent ischemic stroke within 7 to 14 days (3.0% versus 4.9%, odds ratio 0.68, 95% CI: 0.44 to 1.06, $P=0.09$, number needed to treat=53), a significant increase in symptomatic intracranial bleeding (2.5% versus 0.7%, odds ratio 2.89; 95% CI: 1.19 to 7.01, $P=0.02$, number needed to harm=55), and a similar rate of death or disability at final follow up (73.5% versus 73.8%, odds ratio 1.01; 95% CI: 0.82 to 1.24, $P=0.9$).

Conclusions—Our findings indicate that in patients with acute cardioembolic stroke, early anticoagulation is associated with a nonsignificant reduction in recurrence of ischemic stroke, no substantial reduction in death and disability, and an increased intracranial bleeding. **(*Stroke*. 2007;38:423-430.)**

Key Words: anticoagulants ■ cardioembolism ■ cerebral bleeding ■ stroke

Emboli arising from the heart account for at least 20% of ischemic strokes. Nonvalvular atrial fibrillation (NVAF) is the most common cause of cardiac embolism, is associated with a 5-fold increased risk of stroke, and accounts for nearly 25% of strokes in patients older than 80 years.[1,2]

The risk of early recurrent ischemic stroke, defined as a new stroke of presumed embolic origin occurring within the first 2 weeks, is higher in patients with NVAF than in patients with stroke resulting from other causes, and the rate varies between 0.1% and 1.3% per day.[3,4] The role of immediate anticoagulation to reduce early recurrence and improve functional outcome in acute cardioembolic ischemic stroke is controversial. However, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or heparinoids are commonly used in routine clinical practice outside clinical trials.

To further clarify the role of anticoagulants (UFH, LMWH, heparinoid) for the treatment of acute cardioembolic stroke, we performed an updated meta-analysis of all randomized trials comparing anticoagulants, started within 48 hours, with other treatments (placebo or aspirin) for the initial treatment of acute cardioembolic stroke. Our outcomes were death or disability, all strokes, recurrent ischemic stroke, and cerebral symptomatic bleeding.

Methods

A protocol was prospectively developed, which detailed the specific objectives, criteria for study selection, the approach to assessing study quality, clinical outcomes, and statistical methodology.

Study Identification

We aimed to identify all relevant published and unpublished randomized trials comparing anticoagulants (UFH, LMWH, heparinoids) with other treatments (placebo or aspirin) for the initial treatment (within 48 hours) of acute cardioembolic ischemic stroke. The following anticoagulant regimens were to be included: subcutaneous and intravenous UFH, subcutaneous LMWHs, and subcutaneous and intravenous heparinoids. We searched electronic databases (MEDLINE and EMBASE) from January 1980 to February

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.
Received April 24, 2006; final revision received August 28, 2006; accepted September 25, 2006.
From the Stroke Unit, Department of Internal Medicine, University of Perugia, Perugia, Italy.
Correspondence to Maurizio Paciaroni, MD, Stroke Unit, Department of Internal Medicine, University of Perugia, Ospedale Santa Maria della Misericordia, Sant'Andrea delle Fratte, Perugia, Italy. E-mail: mpaciaroni@libero.it

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000254600.92975.1f**

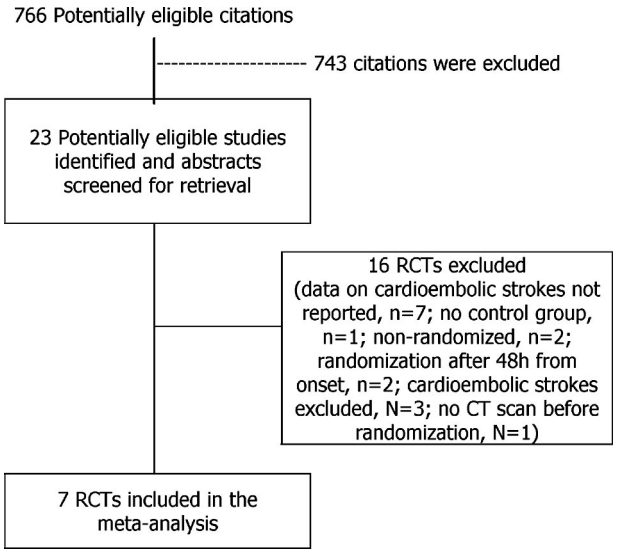

Figure 1. Process of study selection.

2006 and the Cochrane Library (2006, Issue 1) using the terms stroke, cardioembolism, heparin, heparinoids, low-molecular-weight heparin, anticoagulants, randomized controlled trial, and controlled clinical trial. Bibliographies of journal articles were manually searched to locate additional studies and abstracts from major international meetings were reviewed to locate any unpublished studies. Relevance of studies was assessed using a hierarchical approach based on title, abstract, and the full manuscript. We included in this review randomized controlled trials that compared anticoagulants with other treatments or placebo in patients with acute stroke resulting from etiologies other than cardioembolism but only when it was possible to extrapolate data regarding patients with cardioembolism. If any of these data were not available in the publications, further information was sought by correspondence with the authors.

Study Selection

Criteria for inclusion were: (1) randomization within 48 hours from stroke onset; (2) inclusion of patients with objectively diagnosed stroke of presumed cardioembolic origin; (3) comparison of anticoagulants (UFH, LMWH, heparinoid) with other treatments (placebo or aspirin) for the initial therapy of cardioembolic ischemic stroke; and (4) use of objective methods to assess one or more of the study outcomes.

Assessment of Study Quality

We adopted the criteria for study quality outlined by Schultz and colleagues[5] in the evaluation of studies included in our meta-analysis. These criteria include: (1) proper generation of the treatment allocation sequence; (2) proper concealment of the allocation sequence; (3) blinding of the patient and the investigator assessing clinical outcomes to treatment allocation; and (4) completeness of follow up.

Data Extraction

Two investigators (M.P., S.M.) independently extracted data on study design, study quality, and the following efficacy and safety outcomes at 14 days: (1) all strokes (ischemic or hemorrhagic); (2) recurrent ischemic stroke; (3) symptomatic intracranial hemorrhage; (4) pulmonary embolism and, at final follow up, (5) death or disability. The data abstracted for each trial were confirmed by a third investigator (V.C.) and any disagreements resolved by consensus.

Outcomes

The efficacy outcomes were the composite of death or disability at final follow up (at least 3 months), all strokes (ischemic and hemorrhagic) within 14 days, early recurrent stroke (within 14 days), and pulmonary embolism; the safety outcome was symptomatic intracranial bleeding.

Study outcomes were analyzed comparing the results from trials with anticoagulants versus aspirin or the results from trials with anticoagulants versus placebo.

Statistical Analysis

Given the presence of possible statistical heterogeneity resulting from clinical diversity of the selected studies, we used a random-effects model based on the Mantel-Haenszel method[6] for combining results from the individual trials. We calculated the odds ratio (OR) and 95% CIs. Tests of heterogeneity were calculated using the Mantel-Haenszel method. A P value <0.05 was considered statistically significant except for heterogeneity testing, in which statistical significance was accepted at a P value of 0.10. All statistical calculations were performed using Review Manager.[7]

TABLE 1. Randomized Trials With Anticoagulants in Patients With Cardioembolic Stroke

	Trials on Cardioembolism		Subgroups From Larger Trials				
Trial	HAEST (2000)	CESG (1983)	Camerlingo et al (2005)	IST (1997)	TOAST (1998)	FISS-bis (1998)	TAIST (2001)
Blinding	Yes	No	Yes	No	Yes	Yes	Yes
Treatment	Dalteparin (LMWH) 100 IU/kg subcutaneous/ twice a day (n=224); aspirin 160 mg/d (n=225)	Heparin intravenously (n=24); no heparin (n=21)	Heparin intravenously 24 000 IU (n=94) Placebo (n=85)	Heparin −12 500 IU subcutaneous/twice a day (n=784); 5000 IU subcutaneous/twice a day (n=773); no heparin (n=1612)	Danaparoid intravenously (n=143); placebo (n=123)	Nadroparin 85 anti-Xa IU/kg subcutaneous once or twice a day (n=86); placebo (n=62)	Tinzaparin 175 anti-Xa IU/kg (n=121); 100 anti-Xa IU/kg (n=135); aspirin (n=112)
Interval to treatment	<30 hours	<48 hours	<3 hours	<48 hours	<24 hours	<24 hours	<48 hours
Duration of treatment	14 days	14 days	5 days	14 days	7 days	10 days	10 days
Loading dose	No	NR	No	No	Yes	No	No
Monitoring of anticoagulation	No	NR	Yes	No	Yes	No	No

NR indicates not reported.

TABLE 2. Pooled Estimated of Effects of Anticoagulants versus Placebo or Aspirin on Hemorrhagic Stroke, Recurrent Ischemic Stroke, and Pulmonary Embolism

Outcomes	Anticoagulants vs placebo or aspirin OR (95% CI)	*P*	Anticoagulants vs aspirin OR (95% CI)	*P*	Anticoagulants vs placebo OR (95% CI)	*P*
Hemorrhagic stroke						
Camerlingo	4.94 (1.05–23.23)		...		4.94 (1.05–23.23)	
IST	4.81 (2.12–10.93)		3.28 (1.19–9.06)		7.66 (1.75–33.60)	
HAEST	1.52 (0.42–5.46)		...		...	
TOAST	...		...		...	
FISS bis	...		...		...	
TAIST	6.76 (0.38–119.45)		6.76 (0.38–119.45)		...	
CESG	0.16 (0.01–3.51)		...		0.16 (0.01–3.51)	
Overall	2.89 (1.19–7.01)	0.02	2.62 (1.22–5.64)	0.01	2.94 (0.52–16.60)	0.22
Heterogeneity	*P*=0.17		*P*=0.51		*P*=0.08	
Recurrent ischemic stroke						
Camerlingo	...		...		...	
IST	0.56 (0.39–0.82)		0.74 (0.36–1.50)		0.68 (0.33–1.39)	
HAEST	1.13 (0.57–2.24)		1.13 (0.57–2.24)		...	
TOAST	0.17 (0.01–3.56)		...		0.17 (0.01–3.56)	
FISS bis	...		...		...	
TAIST	0.87 (0.16–4.84)		0.87 (0.16–4.84)		...	
CESG	0.16 (0.01–3.51)		...		0.16 (0.01–3.51)	
Overall	0.68 (0.44–1.06)	0.09	0.92 (0.57–1.48)	0.73	0.59 (0.30–1.17)	0.13
Heterogeneity	*P*=0.31		*P*=0.74		*P*=0.47	
Pulmonary embolism						
IST	...		0.84 (0.31–2.27)		...	
TAIST	...		1.10 (0.21–5.73)		...	
HAEST	...		1.10 (0.21–5.73)		...	
Overall	...		0.94 (0.44–2.00)	0.87	...	
Heterogeneity			*P*=0.94			

Results

Study Selection

The process of study selection is showed in Figure 1. Our search identified 766 potentially eligible citations. After scanning titles and abstracts, 743 citations were excluded and 23 were retained for further evaluation. Eighteen studies were excluded for the following reasons: data on cardioembolic strokes were not reported in 9 trials[8–16]; one trial did not have a control group[17]; 2 trials were nonrandomized[18,19]; randomization was performed after 48 hours from onset in 2 trials[20,21]; cardioembolic strokes were excluded in 3 trials[22–24]; and no computed tomography scan before randomization was performed in one trial.[25] Two studies were reincluded in the analysis because the authors provided us with data on cardioembolic strokes not previously reported in the original published articles.[14,16]

Study Design

The design of 7 studies included[14,16,26–30] in this meta-analysis are summarized in Table 1. All studies included patients with cardioembolic ischemic stroke (n=4624) randomized within 48 hours from stroke onset. Atrial fibrillation was present in 3797 patients and other mixed cardioembolic sources in 827. Three trials used UFH,[16,26,30] 3 trials LMWH (TAIST tinzaparin, HAEST dalteparin, and FISS-bis nadroparin),[14,28,29] and one trial (TOAST) heparinoid (danaparoid).[27] In the CESG trial, the follow up was reported only at 14 days.[30]

Study Quality

Reporting of study quality data was incomplete. Randomized treatment allocation sequences were block-randomized by assignment to sequential numbered packages containing either active drug and corresponding placebo (double-dummy masking) in the HAEST trial[28] and in the TAIST trial[14]; sequentially numbered boxes blinded to doctor, patient, and assessor in the FISS-bis trial[29]; permuted blocks with randomly ordered sizes of 6, 6, and 4 (randomization lists pharmacy controlled) blinded to doctor, patient, and assessor in TOAST[27]; telephone randomization in IST[26], using a computer program from Camerlingo[16] and with sealed envelopes (opaque and sequentially) in CESG.[30] Both patients and investigators were blind to treatment allocation in 5 of the 7 trials. The number of patients lost to follow up was reported in 6 trials included in our meta-

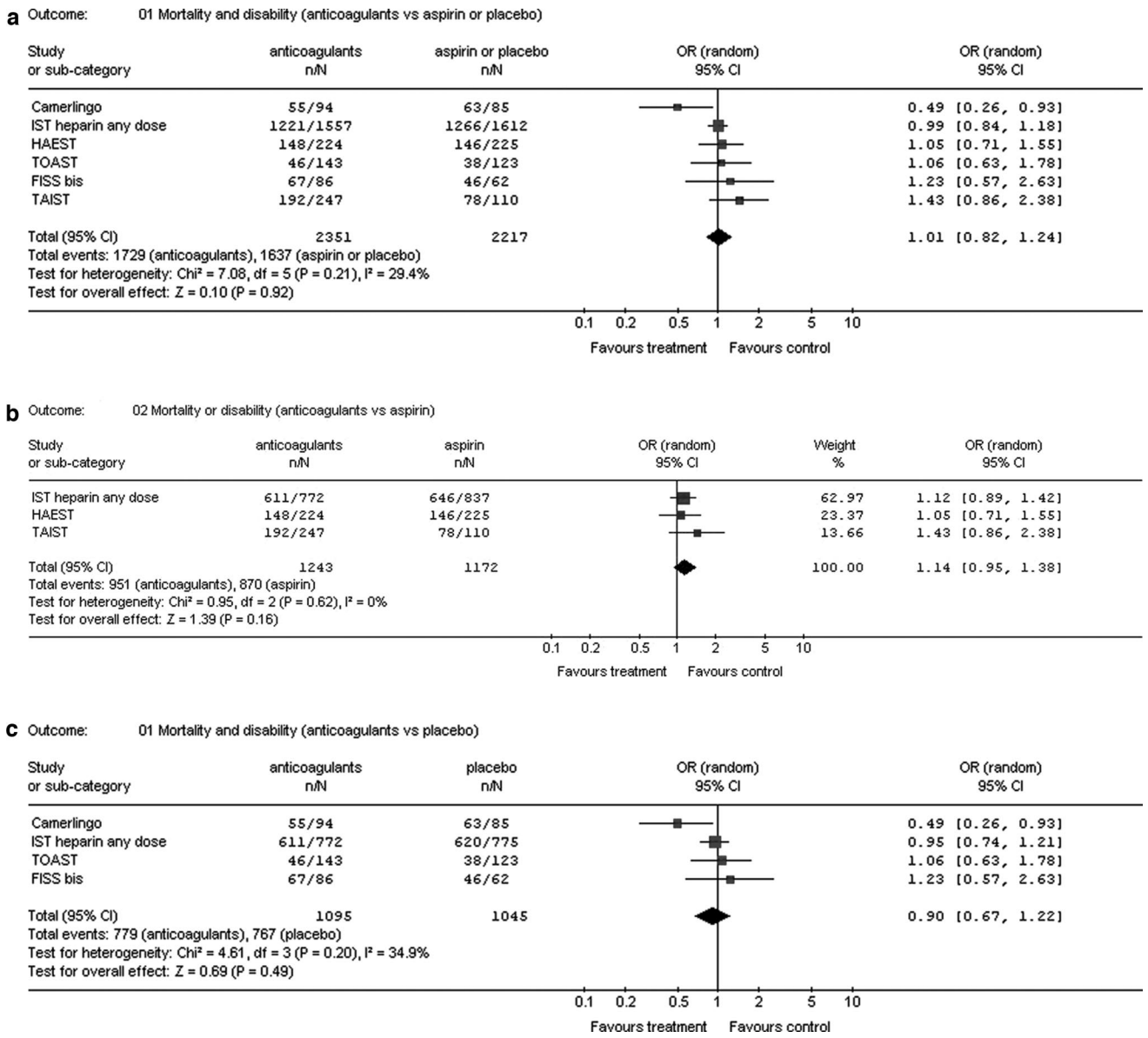

Figure 2. Death or disability in trials comparing anticoagulants with other treatments (a, anticoagulants versus placebo or aspirin; b, anticoagulants versus aspirin; c, anticoagulants versus placebo) for the initial treatment of acute cardioembolic stroke.

analysis (none in CESG, HAEST, and Camerlingo; 11 in TAIST; 25 patients overall in TOAST without specific information about the number of patients with cardioembolic stroke; 99.99% completed for 14 days outcome and 99.2% completed 6-month outcome in IST).

Outcomes

Data on the outcomes are presented in Table 2 and Figures 2 and 3A through C and summary data for individual components of these outcomes are presented in Table 3. Compared with other treatments, anticoagulants were associated with a nonsignificant difference in death or disability at final follow up (73.5% versus 73.8%, OR 1.01; 95% CI: 0.82 to 1.24, $P=0.9$, P for heterogeneity$=0.21$). The difference in death or disability was statistically significant in only one trial[16] (58.5% versus 74.1%, OR 0.49, 95% CI: 0.26 to 0.93). The difference in all strokes (ischemic and hemorrhagic) was not significant (OR 1.18; 95% CI: 0.74 to 1.88, $P=0.49$, P for heterogeneity$=0.25$). Anticoagulants were associated with a nonsignificant reduction in recurrent stroke within 7 to 14 days (3.0% versus 4.9%, OR 0.68; 95% CI: 0.44 to 1.06, $P=0.09$, number needed to treat$=53$) but were associated with a significant increase in symptomatic intracranial bleeding (2.5% versus 0.7%, OR 2.89; 95% CI: 1.19 to 7.01, $P=0.02$, number needed to harm$=55$).

Subgroup Analyses

Compared with placebo, anticoagulants were associated with a nonsignificant difference in death or disability at final follow up (OR 0.90; 95% CI: 0.67 to 1.22). Compared with aspirin, anticoagulants were associated with a nonsignificant trend in favor of aspirin in death or disability at final follow up (OR 1.14; 95% CI: 0.95 to 1.38).

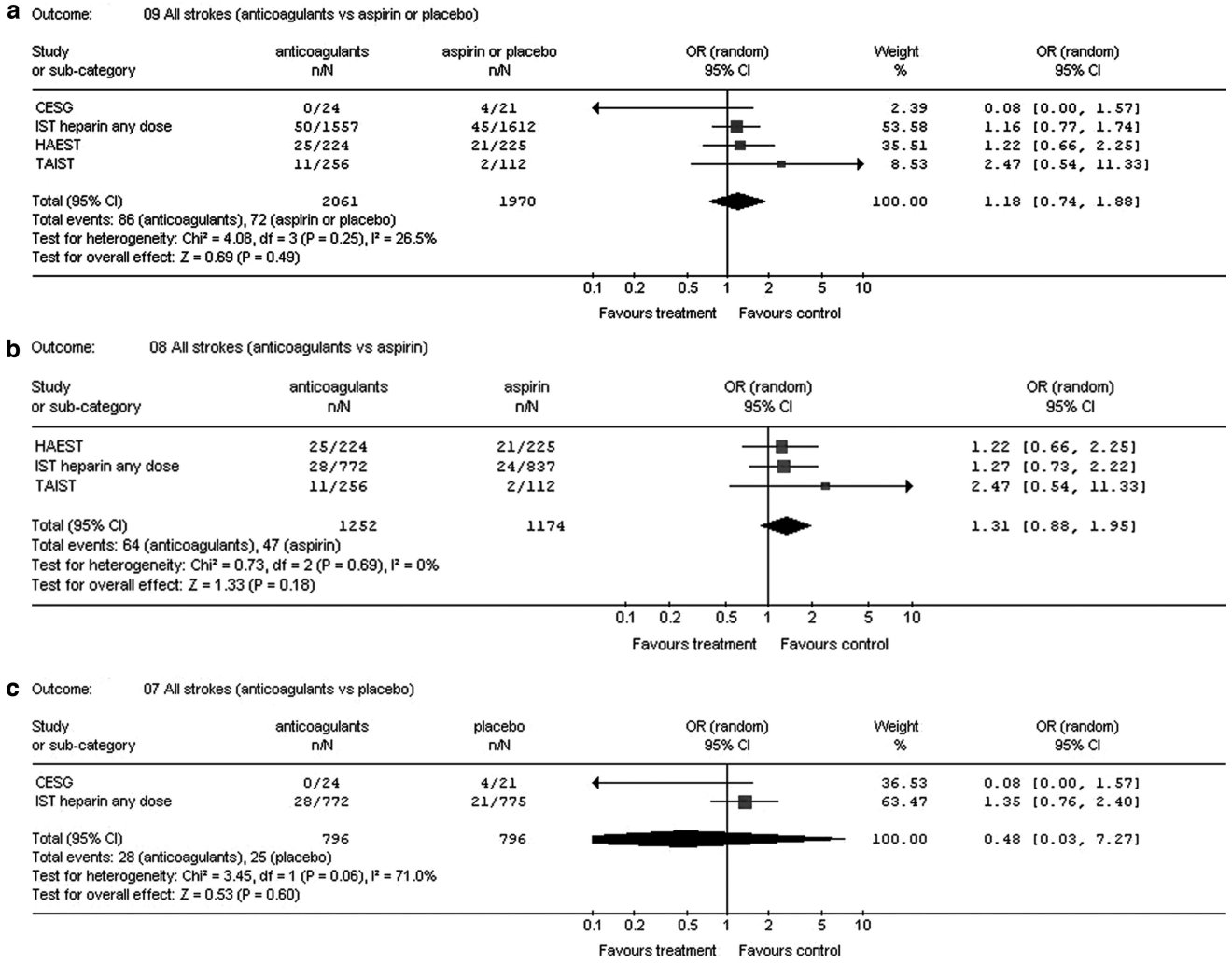

Figure 3. All strokes (ischemic and hemorrhagic) in trials comparing anticoagulants with other treatments (a, anticoagulants versus placebo or aspirin; b, anticoagulants versus aspirin; c, anticoagulants versus placebo) for the initial treatment of acute cardioembolic stroke.

Compared with aspirin, anticoagulants were not associated with a reduction in pulmonary embolism (OR 0.94; 95% CI: 0.44 to 2.00; $P=0.87$, P for heterogeneity=0.94).

Sensitivity Analyses

Sensitivity analyses were conducted to explore the robustness of our results. To identify any study that may have exerted a disproportionate influence on the summary treatment effect, we deleted studies one at a time. Deleting individual studies did not significantly alter the outcomes. The lack of positive trials with a large number of patients (only one small study showed a reduction in death or disability after the scheduled follow-up) and the fact that all the trials demonstrated similar no significant results argue against possible publication bias.

Discussion

This analysis shows that death and disability is not reduced by early anticoagulant treatment in patients with acute ischemic stroke presumably as a result of cardioembolism. Anticoagulants were associated with a nonsignificant reduction in recurrent stroke within 2 weeks as well as with a significant increase in symptomatic intracranial bleeding. With respect to previous systematic reviews,[31–33] this was focused exclusively on patients with cardioembolic stroke, these patients being those who should benefit the most from early anticoagulation and include new unpublished data.

The use of early anticoagulation in ischemic stroke has been a matter of debate for a long time. In the most recent of these debates, Caplan supported the use of UFH in selected patients as those with cardioembolic stroke with a high risk of early recurrence. Sandercock, on the other hand, took the stand that current data from randomized trials are not sufficient to support the use of UFH in acute ischemic stroke.[34,35]

In the IST and CAST studies, patients with atrial fibrillation randomized to aspirin versus control and treated a mean of 20 hours after stroke onset showed trends toward a reduction in early recurrent stroke and an improvement of 6-month functional outcome.[36,37] In our analysis, mortality and disability in patients with cardioembolic stroke treated with aspirin were certainly not worse than in patients treated

TABLE 3. Functional Outcome: Results of Trials With Anticoagulants in Patients With Acute Cardioembolic Stroke

Trial	Recurrent Ischemic Stroke (<7–14 days)	Symptomatic Cerebral Hemorrhage	Death or Disability After 3–6 Months of Follow Up
CESG			
Heparin (n=24)	0% (n=0)	0% (n=0)	NR
No heparin (n=21)	10% (n=2)	10% (n=2)	NR
IST*			
Heparin (n=1557)	2.8% (n=44)	2.1% (n=32)	78.4% (n=1221)
Aspirin (n=837)	2.3% (n=19)	0.6% (n=5)	77.2% (n=647)
Placebo (n=775)	2.5% (n=19)	0.3% (n=2)	80% (n=620)
TOAST			
Dalteparin (n=143)	0% (n=0)	NR	33.2% (n=46)
Placebo (n=123)	1.6% (n=2)	NR	30.1% (n=38)
FISS-bis			
Nadroparin (n=86)	NR	NR	77.0% (n=67)
Placebo (n=62)	NR	NR	74.2% (n=46)
TAIST†			
Tinzaparin (n=256)	1.6% (n=4)	2.7% (n=7)	77.7% (n=192)
Aspirin (n=112)	1.8% (n=2)	0% (n=0)	70.9% (n=78)
HAEST			
Dalteparin (n=224)	8.5% (n=19)	2.7% (n=6)	66.1% (n=148)
Aspirin (225)	7.5% (n=17)	1.8% (n=4)	64.8% (n=146)
Camerlingo et al‡			
Heparin (n=94)	NR	10.6% (n=10)	58.5% (n=55)
Placebo (n=85)	NR	2.4% (n=2)	74.1% (n=63)

* Unpublished data, courtesy of P. Sandercock and S. Lewis; † Unpublished data, courtesy of P. Bath; ‡ Unpublished data, courtesy of M. Camerlingo.
NR indicates not reported.

with anticoagulants. These data combined with the safety and ease of aspirin make early aspirin therapy reasonable for patients with acute stroke and atrial fibrillation.[38]

In the single study in which anticoagulation was started within 3 hours from stroke onset, death or disability was reduced by anticoagulant treatment. These results should be interpreted with caution because other trials did subgroup analyses in hyperacute patients and showed neutral results. Several studies have suggested that besides its antithrombotic effects, UFH also modulates inflammation.[39–43] Thus, the positive effect of early heparin could be the result of either its antithrombotic effects and/or its modulation on the antiinflammatory pathway that appears relevant in the first hours. Whatever the mechanism for improvement, the benefit observed in patients treated within 3 hours suggests the need for further trials on the efficacy of very early administration of anticoagulants in acute cardioembolic stroke. In selecting the study population for these trials, size of ischemia, age, and blood pressure in the acute phase, all known as risk factors for hemorrhagic complications, should be considered.

In clinical trials on thrombolytic therapy for acute ischemic stroke, approximately 20% to 30% of patients had NVAF and thus, a stroke of presumed cardioembolic origin.[38,44–46] The option of treating with thrombolysis patients with acute ischemic stroke and NVAF is limited by the large volume of their brain infarcts, their old age, and the likelihood of symptomatic brain hemorrhage. However, some studies, after adjustment for extent and severity of ischemia, have demonstrated that NVAF is not associated with secondary hemorrhagic transformation after thrombolysis.[47] Furthermore, thrombolysis given within 3 hours of stroke onset appears to offer a benefit for patients with NVAF with acute ischemic stroke. Therefore, further clinical trials in the 3-hour time window need to compare anticoagulant treatment with thrombolysis or to consider anticoagulants for patients in whom thrombolytic therapy is contraindicated.

Deep vein thrombosis and pulmonary embolism are major causes of morbidity and mortality after ischemic stroke.[48,49] Heparin has a role in the prevention of deep vein thrombosis and pulmonary embolism.[50] In the IST, UHF-allocated patients had fewer pulmonary emboli recorded within 14 days (0.5% versus 0.8%; $P=0.02$), but, at 6 months, the rate of deaths or dependent patients was identical. In this analysis, the rates of pulmonary embolism were similar in patients treated with anticoagulants and in patients treated with aspirin.

The optimal timing to initiate oral anticoagulant therapy for secondary prevention was not addressed in this review. It seems reasonable to begin it as soon as the patient is medically and neurologically stable after repeating a computed tomography scan to exclude a hemorrhagic transformation or a large infarct. Empirically if the infarct is large or a hemorrhagic transformation is present, initiation of warfarin should be delayed for 2 to 3 weeks.

Conclusions

Our analysis does not support the early administration of anticoagulants in patients with acute ischemic stroke of cardioembolic origin to prevent early recurrence or to improve functional outcome. Early aspirin followed by vitamin K antagonists for long-term secondary prevention is reasonable. The result of a recent study showing an advantage of the very early administration of heparin (<3 hours from stroke onset) deserves further attention.

Acknowledgments

We thank Phil Bath for the TAIST Investigators, Massimo Camerlingo, and Peter Sandercock, and Stephanie Lewis for the IST Collaborative Group for their availability to provide unpublished data to be included in this analysis.

Disclosures

Giancarlo Agnelli received honoraria as a member of the speaker bureau of Astra Zeneca and Bayer.

References

1. Wolf PA, D'Agostino RB, Belanger AJ, Kannwl WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22:312–318.
2. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiological assessment of chronic atrial fibrillation and the risk of stroke: the Framingham Study. *Neurology*. 1978;28:973–977.
3. Hart RG, Coull BM, Hart D. Early recurrent embolism associated with nonvalvular atrial fibrillation: a retrospective study. *Stroke*. 1983;14: 688–693.
4. Kelley RE, Berger JR, Alter M, Kovacs AG. Cerebral ischemia and atrial fibrillation: prospective study. *Neurology*. 1984;34:1285–1291.
5. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408–412.
6. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719–748.
7. *RevMan, Version 4.2 for Windows*. Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration; 2003.
8. Cazzato G, Zorzon M, Mase G, Antonutti L, Iona LG. Il mesoglicano nelle ischemie cerebrali acute a focolaio. *Rev Neurol*. 1989;59:121–126.
9. Adams HP, Woolson RF, Biller J, Clarke W. Studies of ORG 10172 in patients with acute ischemic stroke. *Haemostasis*. 1992;22:99–103.
10. Elias A, Milandre L, Lagrange G, Aillaud MF, Alonzo B, Toulemonde F, Juhan-Vague I, Khalil R, Bayrou B, Serradimigni A. Prevention of deep venous thrombosis of the leg by a very low molecular weight heparin fraction (CY 222) in patients with hemiplegia following cerebral infarction: a randomized pilot study (30 patients). *Rev Med Interne*. 1990;11:95–98.
11. Kwiecinski H, Pniewski J, Kaminska A, Szyluk B. A randomized trial of Fraxiparine in acute ischemic stroke [Abstract]. *Cerebrovasc Dis*. 1995; 5:234.
12. Chamorro A, Busse O, Obach V, Toni D, Sandercock P, Reverter JC, Cervera A, Torres F, Davalos A; for the RAPID Investigators. The rapid anticoagulation prevents ischemic damage study in acute stroke—final results from the writing Committee. *Cerebrovasc Dis.* 2005;19:402–404.
13. Dumas R, Woitinas F, Kutnowski M, Nikolic I, Berberich R, Abedinpour F, Zoeckler S, Gregoire F, Jerkovic M, Egberts JF, et al. A multicentre, double-blind, randomized study to compare the safety and efficacy of once–daily ORG 10172 and twice-daily low dose heparin in preventing deep vein thrombosis in patients with acute ischemic stroke. *Age Ageing*. 1994;23:512–516.
14. Bath PM, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, Marttila R, Olsson J, O'Neill D, Orgogozo J, Ringelstein B, van der Sande J, Turpie AG. Tinzaparin in acute ischemic stroke (TAIST): a randomized aspirin-controlled trial. *Lancet*. 2001;358:702–710.
15. Kay R, Wong KS, Yu YL, Chan YW, Tsoi TH, Ahuja AT, Chan FL, Fong KY, Law CB, Wong A. Low molecular weight heparin for the treatment of acute ischemic stroke. *N Engl J Med*. 1995;333:1588–1593.
16. Camerlingo M, Salvi P, Belloni G, Gamba T, Cesana BM, Mamoli A. Intravenous heparin started within the first 3 hours after onset of symptoms as a treatment for acute nonlacunar hemispheric cerebral infarctions. *Stroke*. 2005;36:2415–2420.
17. Diener HC, Ringelstein EB, von Kummer R, Langohr HD, Bewermeyer H, Landgraf H, Hennerici M, Welzel D, Grave M, Brom J, Weidinger G. Treatment of acute ischemic stroke with the low molecular weight heparin Certoparin: results of the TOPAS trial. *Stroke*. 2001;32:22–29.
18. Massey EW, Biller J, Davis JN, Adams HP, Marler JR, Goldstein LB, Alberts M, Bruno A. Large-dose infusion of heparinoid ORG 10172 in ischemic stroke. *Stroke*. 1990;21:1289–1292.
19. Chamorro A, Vila N, Ascaso C, Blanc R. Heparin in acute stroke with atrial fibrillation. *Arch Neurol*. 1999;56:1098–1102.
20. Prins MH, Gelsema R, Sing AK, van Heerde LR, den Ottolander GJ. Prophylaxis of deep venous thrombosis with a low molecular weight heparin (Kabi 2165/Fragmin) in stroke patients. *Haemostasis*. 1989;19: 245–250.
21. Pambianco G, Orchard T, Landau P. Deep vein thrombosis: prevention in stroke patients during rehabilitation. *Arch Phys Med Rehabil*. 1995;76: 324–330.
22. Duke RJ, Bloch RF, Turpie AG, Trebilcock R, Bayer N. Intravenous heparin for the prevention of stroke progression in acute partial stable stroke. *Ann Intern Med*. 1986;105:825–828.
23. Sandset PM, Dahl T, Stiris M, Rostad B, Scheel B, Abildgaard U. A double-blind and randomized placebo-controlled trial of low molecular weight heparin once daily to prevent deep-vein thrombosis in acute ischemic stroke. *Semin Thromb Hemost.* 1990;16(suppl):25–33.
24. Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, Andrew M, Magnani HN, Hull RD, Gent M. Double-blind randomized trial of ORG 10172 low molecular weight heparinoid in prevention of deep-vein thrombosis in thrombotic stroke. *Lancet*. 1987;1:523–526.
25. McCarthy ST, Turner J. Low-dose subcutaneous heparin in the prevention of deep-vein thrombosis and pulmonary emboli following acute stroke. *Age Ageing*. 1986;15:84–88.
26. Saxena R, Lewis S, Berge E, Sandercock P AG, Koudstaal PJ, for the International Stroke Trial Collaborative Group. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. *Stroke.* 2001;32:2333–2337.
27. 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. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *JAMA.* 1998;279:1265–1272.
28. Berge E, Abdelnoor M, Nakstad PH, Sandset PM, HAEST Study Group. Low molecular-weight heparin versus aspirin in patients with acute ischemic stroke and atrial fibrillation. A double-blind randomised study. *Lancet.* 2000;355:1205–1210.
29. Hommel M for the FISS-bis Investigators Group. Fraxiparine in Ischemic Stroke Study (FISS bis) [Abstract]. *Cerebrovasc Dis.* 1998;8(suppl):19.
30. Cerebral Embolism Study Group (CESG). Immediate anticoagulation of embolic stroke: a randomized trial. *Stroke.* 1983;14:668–676.
31. Adams HP Jr. Emergent use of anticoagulation fro treatment of patients with ischemic stroke. *Stroke.* 2002;33:856–861.
32. Moonis M, Fisher M. Considering the role of heparin and low-molecular-weight heparins in acute ischemic stroke. *Stroke*. 2002;33:1927–1933.
33. Gubitz G, Sandercock P, Counsell C. Anticoagulants for acute ischemic stroke. *Cochrane Database Syst Rev.* 2004;3:CD000024.
34. Caplan LR. Resolved: heparin may be useful in selected patients with brain ischemia. *Stroke*. 2003;34:230–231.
35. Sandercock P. Full heparin anticoagulation should not be used in acute ischemic stroke. *Stroke*. 2003;34:231–232.
36. International Stroke Trial Collaborative (IST) Group. The IST. a randomised trial of aspirin, subcutaneous heparin, both or neither among 19435 patients with acute ischemic stroke. *Lancet*. 1997;349:1569–1581.

37. Chinese Acute Stroke Trial (CAST) Collaborative Group. Randomized placebo-controlled trial of early aspirin use in 20 000 patients with acute ischemic stroke. *Lancet.* 1997;349:1641–1649.
38. Hart RG, Santiago P, Lesly AP. Atrial fibrillation, stroke, and acute antithrombotic therapy: analysis of randomized clinical trials. *Stroke*. 2002;33:2722–2727.
39. Yu H, Munoz EM, Edens RE, Linhardt RJ. Kinetic studies on the interactions of heparin and complement proteins using surface plasmon resonance. *Biochim Biophys Acta*. 2005;1726:168–176.
40. Pevni D, Frolkis I, Shapira I et al. Heparin added to cardioplegic solution inhibits tumor necrosis factor-alpha production and attenuates myocardial ischemic–reperfusion injury. *Chest*. 2005;128:1805–1811.
41. Esmon CT. Inflammation and thrombosis. *J Thromb Haemost*. 2003;1: 1343–1348.
42. Vignoli A, Marchetti M, Balducci D, Barbui T, Falanga A. Differential effect of the low-molecular-weight heparin, dalteparin and unfractionated heparin on microvascular endothelial cell hemostatic properties. *Haematologica*. 2006;91:207–214.
43. Cervera A, Justicia C, Reverter JC, Planas AM, Chamorro A. Steady plasma concentration of unfractionated heparin reduces infarct volume and prevents inflammatory damage after transient focal cerebral ischemia in rat. *J Neurosci Res*. 2004;15:565–572.
44. National Institute of Neurological Disorder and Stroke (NINDS) rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581–1587.
45. Yoneda Y, Mori E, Uehara T, Tabuchi M. Non valvular atrial fibrillation in acute ischemic stroke candidates for thrombolytic therapy. *Cerebrovasc Dis*. 1997;7:357–358.
46. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke. *JAMA*. 2000;283:1145–1150.
47. Jaillard A, Cornu C, Durieux A, Moulin T, Boutitie F, Lees KR, Hommel M. Hemorrhagic transformation in acute ischemic stroke: the MAST-E Study. *Stroke*. 1999;30:1326–1332.
48. Bath PM, Iddenden R, Bath FJ. Low-molecular-weight heparins and heparinoids in acute ischemic stroke: a meta-analysis of randomized controlled trials. *Stroke*. 2000;31:1770–1778.
49. Lensing AW. Anticoagulation in acute ischemic stroke: deep vein thrombosis prevention and long-term outcomes. *Blood Coagul Fibrinolysis*. 1999;10(suppl 2):S123–S127.
50. Kamphuisen PW, Agnelli G. What is the optimal pharmacological prophylaxis for the prevention of deep-vein thrombosis and pulmonary embolism in patients with acute ischemic stroke? *Thromb Res.* 2006 May 2; Epub ahead of print.