Response to Letter Regarding Article, “Anticoagulants for Cerebral Venous Thrombosis: Harmful to Patients?”

I thank Dr Stam1 for the letter rebutting my analysis of anticoagulants for cerebral venous thrombosis (CVT).2 Dr Stam’s letter did not dispute my criticism of the meta-analysis of anticoagulants for CVT randomized controlled trials in the Cochrane Database of Systematic Reviews that he coauthored.3 This meta-analysis included a randomized controlled trial by Einhäupl and colleagues that reported 3 of 10 deaths in the placebo group and 0 of 10 deaths with full-dose heparin. However, the stillbirth of a 38-week-gestation fetus attributed to heparin was not counted as a death in the anticoagulated group. In addition, a placebo group patient that died was heparinized after a clinical diagnosis of pulmonary infarction, and still the death counted in the placebo group. We have learned since the early 1980s, when this trial was conducted, that clinical diagnoses of pulmonary emboli are usually not confirmed by imaging studies or autopsies. The in-hospital survival of CVT patients who received full-dose heparin was not statistically significantly better than without full-dose heparin in this small meta-analysis (n=79). When the 2 errors in allocating deaths are taken into account, it is not even close to a benefit with heparin (in-hospital deaths: full-dose heparin, 3/40; no full-dose heparin, 5/39).

About the case for warfarin post hospitalization, Dr Stam’s meta-analysis was far too small (n=70) and short (3 months) to prove benefit of warfarin (CVT or venous thromboembolism recurrences: placebo group, 2/32; warfarin group, 0/38). Consequently, the additional 60 observational studies and excluded randomized controlled trials on anticoagulants for CVT that I reviewed are of great relevance. The Stroke editor rightly termed my systematic review of anticoagulants for CVT an opinion piece because only 7 of 62 of the corresponding authors of studies gave me missing data on anticoagulation status related to clinical outcomes. Dr Stam and his coauthors of the International Study of Cerebral Venous Thrombosis (ISCVT) declined to send me any unpublished data. Among other things, I asked ISCVT authors about:

1. the survival outcomes of the 476 patients who received an oral anticoagulant after hospital discharge versus the 113 who did not and
2. the bleeding complications in the 439 patients <65 years treated with oral anticoagulants (one ISCVT article disclosed that 2 of 37 warfarinized patients 265 years bled to death).

If reported by ISCVT authors, these data would inform clinicians about the efficacy and safety of warfarin post hospitalization. For example, were there any more warfarin-related bleeding deaths?

Before about 2000 when full-dose heparin became standard treatment of CVT patients, clinicians were understandably reluctant to heparinize CVT patients with intracranial hemorrhages (ICHs). For example, the Cerebral Venous Thrombosis Portuguese Collaborative Study Group (VENOPORT) study (n=142, data accumulated 1980–1998) reported that patients with ICHs were much less likely to receive heparin than patients with no ICHs (P≠0.0009).4 Most of the data after 2000 came from Dr Stam’s ISCVT (n=624). It showed a trend toward higher mortality in heparinized patients (full-dose heparin: 25/520 [4.8%] died versus no full-dose heparin: 2/104 [1.92%]; odds ratio, 2.58; 95% CI, 0.60–11.0; P=0.29). Despite these data from his own study, Dr Stam maintains that heparin benefits CVT patients presenting with ICHs. This is counterintuitive, highly improbable, and unproven.

Given the above odds ratio on in-hospital deaths in the ISCVT (odds ratio, 2.58), to show that heparin halved the ICH incidence-adjusted hospital death rate, the data would have to show that full-dose heparinized patients had ≥5.16× the chance of presenting with ICHs than nonheparinized patients (ie, estimated odds ratio required for presenting with ICH: 2.58 [odds ratio for hospital deaths]×2=5.16). The ISCVT team has the data to test Dr Stam’s claim by publishing baseline prognostic factors of heparinized versus not full-dose heparinized subjects.

Lack of cooperation of CVT study authors prevented my review from more definitively answering whether and to what extent anticoagulants harm CVT patients. However, my analysis does show that anticoagulants are not evidence based to benefit patients.

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Disclosures

None.

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