Surrogate markers to monitor efficacy of anticoagulants or antiplatelet drugs in atrial fibrillation

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Thromboembolic events are an important possible sequel of atrial fibrillation (AF). In a cross-sectional study Kamath et al.[1] examined the effects of antithrombotic (dose-adjusted warfarin) or antiplatelet therapy (75–325 mg aspirin q.d.) on coagulation markers (D-dimer) and on platelet activation markers (beta thromboglobulin [β-TG] and soluble glycoprotein V [sGPV]).

D-dimer levels were about two-fold higher in patients with AF as compared to controls, β-TG levels were 40% higher and sGPV levels were 40–80% higher in AF patients. As compared to warfarin-treated patients, D-dimer levels were three–four-fold
and six-fold higher in AF patients without treatment and those on aspirin, respectively. Aspirin use was only associated with decreased epinephrine-induced aggregation, but aspirin had no effect on markers of in vivo platelet activation.

Whether the aspirin-induced decrease in prostaglandin formation directly enhanced fibrin formation (as measured by D-dimer levels) cannot be exactly defined due to the study design. Yet, the unchanged β-TG levels confirm that inhibition of thromboxane formation does not mitigate alpha granule release or shedding of GPV into plasma, which could, at least in part, be due to thrombin action.

As neither drug affected platelet activation markers, the authors postulate that the benefit of warfarin in AF is not mediated through a reduction in platelet activation. Similarly, the lack of aspirin effect on platelet activation markers is in keeping with the equivocal effects of aspirin in AF.

In a broader sense, the widespread, but potentially useless, practice of treating AF patients with aspirin instead of with warfarin should be discouraged. Further, it is a fact that coumarin derivatives are under used in AF, particularly the elderly who are at increased risk of thromboembolism. This malpractice is potentially due to concerns of severe bleeding in patients on warfarin.

The benefit/risk ratio of treatment with coumarin derivatives is determined to a great extent by the difficulties inherent in the process of maintaining the therapeutic range of anticoagulation. Thus, it is desirable that novel oral anticoagulants replace coumarin derivatives in the near future. These new classes of anticoagulants, including orally active direct thrombin and factor X inhibitors, will have to be compared against the current standard treatment with coumarin derivatives. Dose finding or efficacy studies in AF patients with thromboembolic disease are time consuming, expensive and carry a potential risk of deleterious consequences in those patients randomized to a relatively ineffective treatment arm. To avoid such deleterious effects, proof of concept studies are necessary to examine the efficacy of novel anticoagulants and show their non-inferiority on suitable surrogate markers such as D-dimer levels. Alternatively, similar efficacy could be established in safe experimental human models of coagulation using adequate surrogate markers to establish proof of concept that comparable anticoagulant efficacy is achieved, before anticoagulants are tested in patients.

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References