An Association Between Aspirin Use in Human Cases of Infective Endocarditis and Reduced Systemic Embolism Is Shown in Meta-analysis of Observational Studies

To the Editor—Animal studies such as published recently in this journal [1] show benefits of antiplatelet agents in experimental models of Staphylococcus aureus infective endocarditis (IE). It is, therefore, important to consider how these experimental data translate into clinical practice. A number of human studies have considered this area, concentrating almost exclusively on long-term aspirin usage. We have performed a meta-analysis of these 9 published studies [2–10] to assess whether the data may provide a basis for future trials and possibly change Infectious Diseases Society of America guidelines that recommend that aspirin should not be used in IE.

Studies assessing potential benefits of aspirin have been mostly observational, involving patients taking aspirin at the time of IE diagnosis. Two studies were randomized controlled trials (RCTs) of aspirin commenced after the diagnosis of IE, 1 of which (n = 115) [4] was terminated prematurely because of concerns of increased bleeding in aspirin-treated patients. The other RCT was a small study (n = 9) [2]. These 9 human studies, performed between 1980 and 2008, include data on 5400 patients, 1230 of whom were pretreated with aspirin. Four studies [5–10] were of antiplatelet therapy broadly, but ≥96% of the treated patients in these studies were taking aspirin. The other studies were of patients taking aspirin only. In the observational studies, summary statistics show that patients who had been taking aspirin were older with more diabetes and coronary vascular disease. The outcomes studied were major emboli, death, and bleeding. Emboli were either defined as embolic stroke alone or were inclusive of other major systemic emboli. Bleeding was measured by the presence of hemorrhagic stroke in 3 studies [7–9] along with other major hemorrhage in the larger RCT [4]. Because of study heterogeneity, meta-analysis was performed using a random effects model within Stata12 (StatCorp, College Station, Texas), using the metan package.

The risk of major systemic emboli was shown to be significantly reduced in patients either pretreated with aspirin or begun on it at the time of IE diagnosis (odds ratio [OR], 0.66; 95% confidence interval [CI], .54–.81). The most important result was a trend to increased risk of death that approached the level of significance (OR, 1.20; 95% CI, .97–1.50). There was a trend to a decreased risk of bleeding in aspirin-treated patients (OR, 0.71; 95% CI, .44–1.14). Importantly, only 4 studies reported bleeding events.

Use of pooled results in our meta-analysis has limitations. We are unable to assess for confounders directly impacting on the observed differences in embolic risk, hemorrhage, and death in aspirin-treated patients, as only summary statistics were available for analysis.

Our meta-analysis of available data of clinical outcomes in patients, almost all of whom were pretreated with aspirin prior to the diagnosis of IE, shows that the risk of major emboli appears to be reduced. However, there may be up to a 20% increased risk of death associated with aspirin treatment in IE. This is despite a trend to reduced bleeding in the minority of studies where this was reported. The aspirin-treated group has more comorbidities, with greater age, higher rates of diabetes, and coronary vascular disease that may account for some of the effect on mortality seen in this meta-analysis. Nonetheless, we conclude that, despite the reduction in emboli observed, the increased risk of death is sufficient to dissuade further investigation of aspirin in this setting. More retrospective data will likely not further aid in this area, as study designs have not been harmonized to date, and are unlikely to be in the future. The benefits of reduced emboli with aspirin pretreatment, while supported by this meta-analysis, are probably insufficient to proceed to further trials.

The results from Veloso et al [1] describe the superiority of abciximab over other antiplatelet agents, including aspirin, in preventing IE. No bleeding events were found in the experimental animals treated with abciximab, which bodes well for human treatment with such an agent. This is relevant given our demonstrated trend to increased mortality in aspirin-treated IE patients, most likely due to cerebral hemorrhage. Abciximab has neither been studied in humans in relation to IE prevention nor is it suitable, as Veloso et al point out, given the necessity for its parenteral administration. The suggestion by Veloso et al that other antiplatelet agents that share abciximab’s action may be effective in IE prevention is a fascinating one worthy of ongoing attention.

Note

Potential conflict of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Reply to Eisen and McBryde

To the Editor—Eisen and McBryde [1] support the conclusion of our experimental study on antiplaulette prophylaxis of experimental infective endocarditis (IE) and the need to further investigate new drugs of the anti-GPIIb/IIa receptor class (eg, abciximab) that could be given orally. Their argument is based on both the greater ability of abciximab than more classic aspirin-plus-ticlopidine regimen to prevent experimental IE caused by both streptococci and staphylococci, and on their meta-analysis showing that classical antiplaulette therapy given in established IE provided a benefit in terms of embolus prevention, which was counterbalanced by a risk of increased overall mortality. Thus, there is a concept for a benefit of antiplaulette regimens in both IE prevention and therapy, but improved drugs and drug formulations must be sought.

We support the argument of Eisen and McBryde that further development on anti-GPIIb/IIa drugs could represent an improvement for IE prevention in selected at-risk patients. However, we would not entirely discard a potential benefit from more classical antiplaulette regimens, as they did show a significant protective effect against experimental IE caused by both Streptococcus gordonii and Staphylococcus aureus experimental IE, although abciximab was more effective.

Eisen and McBrye’s arguments are based on the relatively limited (although not null) efficacy of classical antiplaulette regimens (mainly aspirin) to prevent embolism in established IE. They also emphasize that antiaggregant therapy should be given before the onset of IE rather than after IE establishment. Indeed, early antiaggregant therapy may decrease the size of nascent vegetations and impede their further enlargement, whereas late antiaggregant therapy might favor vegetation dislodgment and bleeding in embolized areas [2].

The fact that antiaggregant given before IE is not a risk factor for increased embolism in case of later IE development is critical, as it does not prohibit antiaggregants as a prophylactic measure in at-risk patients, at least with classical drugs. The question, however, is whether or not chronic use of aspirin or other antiplaulette drugs might protect patients from IE development. We sought to determine whether existing human data could provide some clues to answer this question. Unfortunately, neither the Framingham Heart Study cohort nor the International Collaboration on Endocarditis database could provide definitive information on this specific issue. Therefore, we are currently planning a prospective observational study in patients with bioprosthetic heart valves receiving or not receiving thrombosis prophylaxis with antiplaulette drugs.

We also would like to emphasize the protective effect of the new-generation thrombin inhibitor dabigatran against S. aureus experimental IE. Control acenocoumarol did not protect against either streptococcal or staphylococcal experimental IE, whereas dabigatran specifically protected against S. aureus IE. This is likely associated with the observation that dabigatran inhibits not only thrombin, but also the S. aureus coagulase, which can bypass thrombin and polymerize fibrinogen into fibrin, even in acenocoumarol or citrate-anticoagulated blood. The dual anticoagulant and anti-S. aureus activity of dabigatran would be ideal in patients with prosthetic valves, in whom S. aureus IE is lethal in close to 50% of cases [3, 4]. Unfortunately, dabigatran did not do well in such patients [5, 6]. While further pharmacologic development is required before dabigatran can be used in prosthetic valves, it opens yet another strategy for S. aureus IE prevention.

We agree with Eisen and McBryde that more developments are needed regarding the prevention and treatment of IE. Regarding prevention, we have abandoned antibiotic prophylaxis overkill, which was based on intuitive rather than evidence-based medicine [7, 8]. Yet, IE is a persistent Damocles sword in at-risk patients, as it can happen at any time during their life. Simple alternatives are needed for these patients, and chronic use of antiplaulette drugs could be one of them. Regarding therapy, 2–6 week courses of parenteral antibiotics are still the standard.