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EDITORIAL COMMENT

Should We Give Antithrombotic Therapy to Patients With Infective Endocarditis?

A Serious Question, But Unresolved*

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Embolic events (EEs) are the most frequent complication of infective endocarditis (IE) and are associated with increased morbidity and mortality. The role of antithrombotic therapy (ATT) to improve prognosis in IE has been debated among guidelines.[1,2]

In this issue of *JACC: Advances*, Caldonazo et al[3] proposed a meta-analysis assessing the impact of ATT in IE. The analyzed studies were selected rigorously. The primary outcome selected by the authors was in-hospital cerebrovascular events. Secondary outcomes were in-hospital mortality, intracranial hemorrhage (ICH), EE, and 6-month mortality. To our knowledge, this is the first meta-analysis assessing the effect of both anticoagulants and antiplatelet drugs in IE.

The vegetations observed in IE are thrombi composed of fibrin, platelets, and micro-organisms (**Figure 1**). The first electron microscopy images have clearly demonstrated the role of the cellular players in hemostasis in this process.[4] Although a murine model of IE proposes a dichotomy of cellular organization during the initial phase of *Staph aureus* adhesion, depending on whether the valve is injured or inflamed, platelets and fibrin are the major constituents of the vegetations. This justifies reconsideration of the potential benefits of ATT.[5] Furthermore, the role of platelets in the bacterial response and their ability to interact with microorganisms have been established.[6]

EFFECTS OF ANTIPLATELET THERAPY

The conclusions of Caldonazo et al[3] are important but based on only 7 studies, of which 3 were prospective. Although aspirin was the most frequently administered antiplatelet agent in these studies, several methodological differences, such as the daily dose and the timing of initiation of the drug, and the bacterial species involved should be noted. Caldozano et al[3] found a significant reduction in the risk of EE and, remarkably, an absence of an increase in the risk of ICH. This observation supports the American Heart Association Endocarditis Guidelines, which recommend the continuation of long-term antiplatelet therapy at the time of development of IE.[1] The reduction in the risk of EE with antiplatelet agents agrees with the results obtained in animal models of *Staph aureus* IE, which show that treatment with aspirin reduces the size of vegetations and the risk of EE.[7] Aspirin was able to influence platelet-*Staph aureus* interactions by acting on gene regulation of bacterial virulence factors and decreasing the gene expression of several staphylococcal adherent motifs as well as staphylococcal alpha-toxin,[8] both of which are involved in platelet aggregation.[9]

The benefit of antiplatelet agents in the studies reported by Caldozano et al[3] could be increased if the microbial species were considered. In an in vitro study evaluating the efficacy of different antiplatelet molecules on the aggregation induced by strains of

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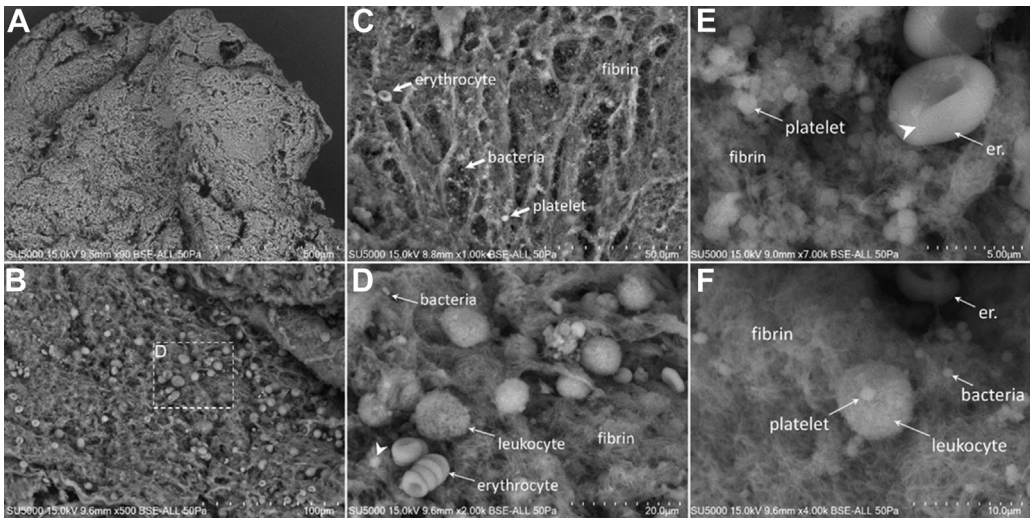
FIGURE 1 Electron Microscopy of *Staph aureus*-Infected Vegetation



(A and B) Low magnification views of the vegetation. (C) Vegetation rich in platelets and thin fibrin fibers, giving the appearance of a fishing net. (D) Zoom in on the boxed region in (B) showing leukocytes, bacteria, and platelets (arrowhead). (E) Aggregated platelets next to an erythrocyte (er.) enwrapped with fibrin fibers (arrowhead). (F) Platelets on top of a leukocyte.

Staph aureus and *Staph sanguinis*, we found that their efficacy differed depending not only on the species but also on the bacterial strain involved.[10] Moreover, we observed by electron microscopy that the composition and cellular organization of endocardial vegetation differ according to the causative bacterial species.[11]

Finally, the conclusions of Caldozano et al[3] agreed with the meta-analysis performed by Eisen,[12] which demonstrated that aspirin was associated with a significant decrease in EE and a trend toward decreased bleeding risk. However, the mortality rates differed between the 2 studies, with a trend toward increased mortality with antiplatelet drugs in the Eisen's study, whereas Caldozano et al[3] found no significant difference. To understand these different observations, demographic characteristics of population should be considered, with the aspirin group presenting classically with more comorbidities, older age, more frequent diabetes, and coronary disease, which may partly explain a higher mortality rate.

EFFECTS OF ANTICOAGULANT THERAPY

Since vegetations are composed of fibrin, a beneficial effect of anticiagulant therapy (ACT) in reducing EE might be expected. Conversely, their use might be associated with an increased risk of bleeding, particularly ICH. For this reason, discontinuation of ACT in case of IE has been proposed in guidelines.[1]

In the current study, the authors highlight that maintenance of ACT is associated with lower in-hospital mortality without increasing the risk of ICH.

During IE, monocytes, which are rapidly mobilized to the site of infection, and activated endothelial cells will express tissue factor, triggering coagulation and allowing vegetation growth through the formation of fibrin. In addition, the fibrin creates a network to capture platelets and leukocytes, which amplify the inflammation.[5] Given that coagulation mechanisms are the cornerstone of vegetation formation, it is logical to consider the potential role of anticoagulants in inhibiting vegetation growth. Among the 8 studies cited, warfarin was the anticoagulant most widely used. The question of whether to continue or stop this treatment in view of the risk of hemorrhage remains an important clinical issue.

The use of direct-acting oral anticoagulants (DOACS) has not been studied in IE yet. Of the 8 studies cited, only 3 included patients treated with DOAC, representing a very small number of patients. However, many studies have shown that DOACs are associated with a lower risk of ICH than warfarin.[13] We could therefore hypothesize that continued treatment with DOAC could be associated with an even more significant reduction in the risk of ICH compared with warfarin.

Moreover, we have relevant data on the value of dabigatran in an animal model of *Staph aureus* IE. Dabigatran, in addition to being a direct thrombin inhibitor, interferes with the coagulase activity of *Staph aureus*. *Staph aureus* coagulases bypass the coagulation cascade to bind directly with prothrombin and form staphylothrombin, which is directly active on fibrinogen. Thus, dabigatran would serve both as an anticoagulant and an inhibitor of bacterial virulence.[14,15] In a rabbit model, dabigatran reduced the vegetation size, bacterial load, and inflammation in experimental *Staph aureus* IE.[16] The conclusions of Caldonazo et al[3] on the use of anticoagulants during IE are comforting in terms of clinical management. However, their benefit has not been clearly established.

Based on current data and the results of the study by Caldonazo et al,[3] maintenance of daily antiplatelet therapy should be considered for patients already on this therapy when IE is diagnosed. The introduction of an antiplatelet agent in untreated patients is still an open question, which justifies the proposal of prospective multicentric studies, bearing in mind that the administration of an antiplatelet agent does not increase the risk of hemorrhage. Although the data on warfarin presented in this analysis might justify maintaining ACT in patients at high risk of embolism, it is necessary to evaluate the effect of DOACs after an IE since these molecules could have a direct effect on the pathophysiology of IE.

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