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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Can patients with infectious endocarditis be safely anticoagulated?

A: Managing anticoagulation in patients with infectious endocarditis requires an individualized approach, using a careful risk-benefit assessment on a case-by-case basis. There is a dearth of high-quality evidence; consequently, the recommendations also vary according to the clinical situation.

Newly diagnosed native valve infectious endocarditis in itself is not an indication for anticoagulation.[1–3] The question of whether to anticoagulate arises in patients who have a preexisting or coexisting indication for anticoagulation such as atrial fibrillation, deep vein thrombosis, pulmonary embolism, or a mechanical prosthetic heart valve. The question becomes yet more complex in patients with cerebrovascular complications and a coexistent strong indication for anticoagulation, creating what is often a very thorny dilemma.

Based on a review of available evidence, recommendations for anticoagulation in patients with infectious endocarditis are summarized below.

AVAILABLE EVIDENCE IS SCARCE AND MIXED

Earlier observational studies suggested a significant risk of cerebral hemorrhage with anticoagulation in patients with native valve endocarditis, although none of these studies were recent (some of them took place in the 1940s), and none are methodologically compelling.[4–8] Consequently, some experts have expressed skepticism regarding their findings, particularly in recent years.

In part, this skepticism arises from studies that showed a lower incidence of cerebrovascular complications and smaller vegetation size in patients with prosthetic valve infectious endocarditis, studies in which many of the patients received anticoagulation therapy.[9,10] The mechanism responsible for this effect is theorized to be that the vegetation is an amalgam of destroyed cells, platelets, and fibrin, with anticoagulation preventing this aggregation from further growth and propagation.

How great is the benefit or the potential harm?

Some experts argue that the incidence of ischemic stroke with hemorrhagic transformation in patients with infectious endocarditis receiving anticoagulation is overestimated. According to this view, the beneficial effects of anticoagulation at least counterbalance the potential harmful effects.

In addition to the studies cited above, recent studies have shown that patients on anticoagulation tend to have smaller vegetations and fewer cerebrovascular complications.[11–13] Snygg-Martin et al[11] and Rasmussen et al[12] found not only that cerebrovascular complications were less common in patients already on anticoagulation at the time infectious endocarditis was diagnosed, but also that no increase in the rate of hemorrhagic lesions was reported.

These were all nonrandomized studies, and most of the patients in them had native valve infectious endocarditis diagnosed at an early stage. Importantly, these studies found that the beneficial effects of anticoagulation were only present if the patient was receiving warfarin before infectious endocarditis was diagnosed and antibiotic therapy was initiated. No benefits from anticoagulation were demonstrated once antimicrobial therapy was begun.

New infectious endocarditis is not an indication for starting anticoagulation

doi:10.3949/ccjm.83a.15027

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TABLE 1

Guidelines for managing anticoagulation in patients with infective endocarditis

American Heart Association[1]

Discontinuing all forms of anticoagulation in patients with mechanical valve infectious endocarditis who have experienced a central nervous system embolic event for at least 2 weeks is reasonable.

Initiating aspirin or other antiplatelet agents as adjunctive therapy in infective endocarditis is not recommended.

Continuing long-term antiplatelet therapy at the time of development of infective endocarditis with no bleeding complications may be considered.

European Society of Cardiology[2]

Interruption of antiplatelet and anticoagulant therapy is recommended in the presence of intracranial hemorrhage or other major bleeding.

In ischemic stroke without hemorrhage, replacement of oral anticoagulant (anti-vitamin K) therapy by unfractionated or low-molecular-weight heparin for 1–2 weeks should be considered under close monitoring.

In patients with intracranial hemorrhage and a mechanical valve, unfractionated or low-molecular-weight heparin should be reinitiated as soon as possible following multidisciplinary discussion.

In the absence of stroke, replacement of oral anticoagulant therapy by unfractionated or low-molecular-weight heparin for 1–2 weeks should be considered in the case of *Staphylococcus aureus* infectious endocarditis under close monitoring.

Thrombolytic therapy is not recommended in patients with infectious endocarditis.

American College of Chest Physicians[3]

In patients with infectious endocarditis, routine anticoagulant and antiplatelet therapy is not recommended unless a separate indication exists.

In patients with a prosthetic valve who are on anticoagulation and who develop infectious endocarditis, it is suggested to discontinue the anticoagulation at the time of initial presentation until it is clear that invasive procedures will not be required and the patient has stabilized without signs of central nervous system involvement. When the patient is deemed stable without contraindications or neurologic complications, reinstitution of anticoagulant therapy is suggested.

Similarly, Anavekar et al[14] showed that embolic events occurred significantly less often in those who were currently on continuous daily antiplatelet therapy, suggesting that receiving antiplatelet agents at baseline protects against cardioembolic events in patients who develop infective endocarditis. However, the only randomized trial examining the initiation of antiplatelet therapy in patients diagnosed with infectious endocarditis receiving antibiotic treatment showed that adding aspirin did not reduce the risk of embolic events and was associated with a trend toward increased risk of bleeding.[15]

A recent large cohort study suggested that infectious endocarditis patients who receive anticoagulation therapy may have a higher incidence of cerebrovascular complications (hazard ratio 1.31, 95% confidence interval 1.00–1.72, $P = .048$), with a particular association of anticoagulation therapy with intracranial bleeding (hazard ratio 2.71, 95% confidence interval 1.54–4.76, $P = .001$).[16]

Another provocative link supported by the same study was a higher incidence of hemorrhagic complications with anticoagulation in patients with infectious endocarditis caused by *Staphylococcus aureus*, an association also suggested by older data from Tornos et al,[8] but not seen in a study by Rasmussen et al.[12]

Continuing anticoagulation is an individualized decision

The benefit or harm of anticoagulation in patients with infectious endocarditis may be determined at least in part by a complex mix of factors including the valve involved (embolic events are more common with mitral valve vegetations than with aortic valve vegetations), vegetation size (higher risk if > 1 cm), mobility of vegetations, and perhaps the virulence of the causative organism.[16,17] The fact that antimicrobial therapy obviates any beneficial effect of anticoagulation speaks strongly against starting anticoagulation therapy in infectious endocarditis patients with the sole purpose of reducing stroke risk.

Without large randomized trials to better delineate the risks and benefits of continuing preexisting anticoagulation in all patients with infectious endocarditis, patients already receiving anticoagulants need a careful, individual-

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ized risk-benefit assessment. Current guidelines agree that newly diagnosed infectious endocarditis per se is not an indication for anticoagulation or aspirin therapy (**Table 1**).[1–3]

TAKE-HOME POINTS

- Starting antiplatelet and anticoagulation therapy for the sole purpose of stroke prevention is not recommended in patients with newly diagnosed infectious endocarditis.
- In most cases, anticoagulation and antiplatelet therapy should be temporarily discontinued in patients with infectious endocarditis and stroke or suspected stroke.
- Patients need careful assessment on a case-by-case basis, and the presence of risk factors predisposing patients to cerebrovascular complications (eg, large or very mobile vegetations, causative pathogens such as *S aureus* or *Candida* spp) may prompt temporary suspension of anticoagulation and antiplatelet therapy.
- If there is a clear preexisting or coexisting indication for these agents and surgery is not anticipated, consider continuing antiplatelet and anticoagulant therapy in patients with infectious endocarditis, provided they lack the risk factors described above and stroke has been excluded.
- If there is a clear preexisting or coexisting indication for these agents and surgery is being considered, consider using a short-acting anticoagulant such as intravenous or low-molecular weight heparin as a bridge to surgery.

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