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Ischemic Left Ventricular Aneurysm and Anticoagulation: Is It the Clot or the Plot That Needs Thinning?

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All truths are easy to understand once they are discovered; the point is to discover them.
—Galileo Galilei (1564-1642)

In this issue of *Mayo Clinic Proceedings*, Lee et al[1] report a large, nonrandomized, single-center observational study of 648 patients with ischemic left ventricular (LV) aneurysm. Left ventricular thrombus was identified echocardiographically in a modest 13.7% of the patients, and this group had a higher incidence of stroke and systemic embolism during the median follow-up period of just over 3 years. A minority of patients with LV aneurysm (16.4%) and its subgroup with identified LV thrombus (43.8%) received warfarin anticoagulation. An important, but nondefinitive, finding of the study was that warfarin anticoagulation did not change patient outcome, even when adjusted using propensity score hazard regression analysis. Limitations of the study include the low single-digit event rates in the LV thrombus group (such that a type 2 statistical error cannot be excluded), the overall low number of patients who received anticoagulation, and its nonrandomized nature.

In medicine, unintended errors in clinical guidelines can occur when well-intentioned, expert opinion is relied on in the absence of randomized controlled trials. For patients with valvular heart disease, antibiotic prophylaxis against infective endocarditis was advocated for more than 50 years, largely on the basis of expert opinion, supported by experimental animal data but without the benefit of randomized controlled clinical trials—a prophylaxis policy that in retrospect was without meaningful clinical benefit.[2,3]

The use of anticoagulant prophylaxis of systemic thromboembolism in patients with ischemic LV aneurysm may be analogous in that there are no randomized clinical trials to guide therapy. Individual patient risk attendant to brief unneeded antibiotic use to prevent the aforementioned infective endocarditis was vanishingly small; in contrast, the bleeding risk associated with warfarin use in patients with ischemic LV aneurysm, most of whom will also require dual antiplatelet therapy (DAPT), is substantial.

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the management of ST-segment elevation myocardial infarction (STEMI)[4] include a modest class IIa recommendation for "anticoagulant therapy with a vitamin K antagonist in STEMI patients with asymptomatic LV mural thrombi at a level of evidence of C" and a weaker class IIb recommendation for "anticoagulant therapy in STEMI patients who have LV anterior apical akinesis or dyskinesis at a level of evidence of C." (For definitions of these levels of recommendation and evidence, the reader is referred to Table 1 of reference 4.) The weakness of the recommendation and the low level of evidence cited highlight the scientific uncertainty of the clinical guidance.

These 2013 guidelines[4] are much weaker than the earlier 2004 ACC/AHA STEMI guidelines,[5] both in the strength of the recommendation and in the lower level of anticoagulation recommended. The 2004 ACC/AHA guidelines for the management of patients with STEMI recommended oral anticoagulation with a target international normalized ratio (INR) of 2.0 to 3.0 for at least 3 months (class I recommendation, level of evidence B) and perhaps indefinitely in patients who do not have an increased bleeding risk and are post-STEMI with documented LV thrombus (class I recommendation, level of evidence C).[5] The 2013 guidelines recommend a more modest INR of 2.0 to 2.5 in patients receiving DAPT at a level of evidence C.[4] The scientific plot is indeed thinning.

The 2013 ACC/AHA STEMI guidelines[4] are a good-faith effort to provide practical guidance to busy clinicians in an uncertain clinical and legal environment. Their weakness is the nondefinitive scientific data derived from observational studies that date from an earlier era of STEMI management when transmural myocardial infarctions

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were more frequent and ischemic LV aneurysm formation was more common. These studies suggested that patients with ischemic LV thrombus treated with heparin and warfarin had fewer cerebral emboli than did untreated patients. These older data were not definitive, and the possible benefit of warfarin in the prevention of thromboembolism must now be balanced against the considerable and well-documented bleeding risk associated with warfarin anticoagulation in patients who will frequently also require DAPT.

What is the added risk of warfarin in this situation? Best estimates suggest an approximate 2- to 5-fold increase in bleeding risk when warfarin is given in addition to DAPT. Khurram et al[6] reported a significantly higher major bleeding rate (6.6% vs 0%; P=.03) when warfarin and DAPT were given compared with DAPT alone after coronary stenting. Although this bleeding risk may be mitigated by the lower-goal INR, the possible benefit, if any, of warfarin use in addition to DAPT in ischemic LV aneurysm is completely unknown.

Ischemic LV aneurysm formation has become an uncommon finding, yet it remains an important entity because of its association with mural LV thrombus and embolic stroke, particularly among the estimated more than 30% of current patients with STEMI who have suboptimal myocardial reperfusion (due to a number of causes, including failed or delayed STEMI diagnosis, contraindication to thrombolysis, unavailability of emergency percutaneous coronary intervention, and failed reperfusion therapy) and who are at an increased risk of ischemic LV aneurysm.[7-9]

Intuitively, it is surprising that large mural thrombi can form in a damaged yet actively contracting LV with vigorous blood flow, but the pathologic evidence is clear: the necrotic dyskinetic LV anterior wall incites a vigorous inflammatory and prothrombotic response that generates an adherent mural thrombus that is initially at high risk for embolism but matures over time to a state of relatively low embolic risk. The important question is whether the addition of warfarin anticoagulation or possibly one of the new novel anticoagulant agents (currently, no data) will significantly decrease the thromboembolic-embolic risk and whether this decrease is worth the increased bleeding risk.

The historical data on warfarin use in LV aneurysm are inconsistent. In the early 1980s, Reeder et al[10] from Mayo Clinic reported on 100 consecutive patients undergoing LV surgical aneurysmectomy; mural thrombus was present in 48% of the patients and correlated inversely with the duration of previous anticoagulant therapy. In contrast, in the mid-1980s, Lapeyre et al,[11] also from Mayo Clinic, reported on the incidence of embolic events in 76 patients with angiographically defined LV aneurysm who were followed for a median of 5 years. Twenty patients received anticoagulant therapy, whereas 69 patients did not; 13 patients were included in both groups on the basis of their anticoagulation status at the time. A clinical embolic event occurred in only 1 patient who did not receive anticoagulant therapy; accordingly, the incidence was 0.35 per 100 patient-years. The authors concluded that the extremely low incidence of systemic emboli in patients with chronic LV aneurysm did not justify the use of long-term oral anticoagulant therapy.

In 1984, Weinreich et al[12] described 261 patients with acute transmural myocardial infarction, of whom 46 (17.6%) had mural thrombus on cardiac imaging; 43 of these patients were followed for a mean duration of 15 months. None of the 25 patients who received anticoagulation had an embolic event, whereas systemic embolization occurred in 7 (38.8%) of the 18 patients who had not received anticoagulation. All embolic events occurred within 4 months of infarction. A key finding was that although anticoagulation seemed to protect against systemic embolic events, the prevalence of LV thrombi on cardiac imaging was essentially the same whether or not this anticoagulation was used.

In 1993, Vaitkus and Barnathan[13] performed a meta-analysis of then published studies on mural thrombus in ischemic LV aneurysm and reported an odds ratio of 5.45 (95% CI, 3.02-9.83) for the increased risk of emboli in the presence of echocardiographically demonstrated mural thrombus (based on 11 observational studies in 856 patients) and an odds ratio of 0.14 (95% CI, 0.04-0.52) for anticoagulation versus no anticoagulation for preventing embolization (7 studies in 270 patients). The odds ratio of anticoagulation versus control for preventing mural thrombus formation (4 studies in 307