

EDITORIAL COMMENT

Anticoagulation After Anterior Myocardial Infarction

*Primum non Nocere, or First Do No Harm**

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Left ventricular (LV) mural thrombus is a common complication of anterior myocardial infarctions (MIs). Although this incidence has significantly decreased with reperfusion therapies, contemporary studies still note LV thrombus in 3% to 15% of anterior MIs treated with percutaneous coronary revascularization (1,2). Furthermore, pooled analyses suggest a more than 5-fold increased risk for systemic embolism with LV thrombus after anterior MI, and anticoagulation therapy is associated with a significant decrease in this embolic risk (3). As such, the 2013 American College of Cardiology Foundation/American Heart Association ST-segment elevation myocardial infarction (STEMI) guidelines recommend anticoagulation for patients with acute MI and asymptomatic LV mural thrombus (Class IIa, Level of Evidence [LOE]: C) (4). Given the increased risk of bleeding with anticoagulation and dual antiplatelet therapy, these guidelines suggest lower international normalized ratio goals (2.0 to 2.5) in this clinical setting (Class IIb, LOE: C).

Anticoagulation after anterior MI with risk factors for mural thrombus formation is much more controversial, as the risk of clinically-significant thromboembolism in contemporary practice is not well understood. Currently, the 2013 American College of Cardiology Foundation/American Heart Association STEMI guidelines state that anticoagulation therapy may be considered for patients with STEMI and anterior apical akinesis or dyskinesis (Class IIb, LOE: C) (4). However, this recommendation is based

largely on older studies, and it is unknown if the benefits of anticoagulation outweigh the known bleeding risks in current practice. Triple therapy (aspirin, clopidogrel, and warfarin) after percutaneous coronary intervention (PCI) is associated with a 2- to 5-fold greater risk of major bleeding compared with dual antiplatelet therapy (1,5,6).

There are good reasons to consider anticoagulation after anterior MI. Larger infarctions, anterior locations, and lower ejection fractions are associated with higher rates of mural thrombus formation (2,7,8). In addition, a meta-analysis of 307 patients from 4 studies conducted prior to the use of thrombolytics suggests that anticoagulation decreases the incidence of LV thrombus formation by 68% (3). Furthermore, the risk of ischemic stroke is higher following acute MI, with an incidence of about 1.5% to 3.6% (3,9). This risk is greatest in the first month and is also more common in patients with anterior infarctions and lower ejection fractions (9-11). Importantly, anticoagulation has been shown to reduce the incidence of stroke and mortality after acute MI in randomized studies from the pre-thrombolytic era (12,13).

However, not all studies find a link among anterior MI, LV thrombus, and embolic events. In the thrombolytic era, the low molecular weight heparin dalteparin reduced LV thrombus formation by 37% in 517 randomized patients after anterior acute MI. However, this therapy had no impact on early thromboembolic events (14). Similar findings were echoed in a larger observational study of 2,949 patients, in which anticoagulation failed to reduce the incidence of stroke after anterior MI (10).

The study by Le May et al. (15) published in this issue of *JACC: Cardiovascular Interventions* builds on these prior observations and reports the outcomes of anticoagulation in 460 STEMI patients with apical

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dysfunction after PCI. This study is important, as it is the largest study from the PCI era to evaluate anticoagulation in this population, and the authors should be congratulated for investigating a controversial topic for which the best practice is unknown. In this study, patients requiring anticoagulation for LV thrombus, atrial fibrillation, valvular heart disease, or venous

SEE PAGE 155

thromboembolism were excluded. The authors found that anticoagulation was actually associated with an increased incidence of stroke (3.1% vs. 0.3%, $p = 0.02$), major bleeding (8.5% vs. 1.8%, $p < 0.0001$), mortality (5.4% vs. 1.5%, $p = 0.04$), length of stay, and readmissions. Furthermore, after propensity matching, anticoagulation was still associated with a 4-fold greater incidence of net adverse cardiac events. In multivariable analysis, the odds of net adverse cardiac events remained higher in patients treated with anticoagulation. These findings certainly question the routine use of triple therapy in this population.

There are limitations to the current analysis. The study was not randomized, and it is possible that the outcomes of the study were related to differences between groups, even after propensity matching. In addition, the current analysis may not represent current practice, as several recent studies suggest that aspirin can often be omitted when anticoagulation is warranted after PCI. In the 573-patient randomized WOEST (What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting) trial, omission of aspirin decreased major bleeding complications

(44.4% vs. 19.4%, $p < 0.0001$) without any increase in ischemic events (16). These findings were echoed in a larger real-world registry of 12,165 patients undergoing PCI requiring anticoagulation (17). Whether the omission of aspirin would have influenced the results of the current trial is unknown.

In conclusion, the current study by Le May et al. (15) warns against the routine use of anticoagulation in patients with anterior MI with apical dysfunction without evidence of mural thrombus. Given the bleeding risks, triple therapy should probably be avoided in these patients. Whether the combination of clopidogrel and warfarin without aspirin is more effective than dual antiplatelet therapy in these patients is unknown, and randomized studies should be considered to investigate this strategy. Until such a trial is conducted, if anticoagulation is used after anterior MI, clinicians should probably consider omitting aspirin, adding proton pump inhibitors, targeting lower international normalized ratio ranges, shortening the anticoagulation course (3 months), and using radial access. Furthermore, it should be noted that the safety of the novel anticoagulant and antiplatelet therapies in this setting has not been tested. Ultimately, better risk assessment tools are needed to guide therapeutic decisions balancing the risk of LV thrombus formation and thromboembolism with the risk of bleeding.

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REFERENCES

- Nikolsky E, Mehran R, Dangas GD, et al. Outcomes of patients treated with triple antithrombotic therapy after primary percutaneous coronary intervention for ST-elevation myocardial infarction (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI] trial). *Am J Cardiol* 2012;109:831-8.
- Solheim S, Seljeflot I, Lunde K, et al. Frequency of left ventricular thrombus in patients with anterior wall acute myocardial infarction treated with percutaneous coronary intervention and dual antiplatelet therapy. *Am J Cardiol* 2010;106:1197-200.
- Vaitkus PT, Barnathan ES. Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: a meta-analysis. *J Am Coll Cardiol* 1993;22:1004-9.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:485-510.
- Rubboli A, Schlitt A, Kiviniemi T, et al. One-year outcome of patients with atrial fibrillation undergoing coronary artery stenting: an analysis of the AFCAS registry. *Clin Cardiol* 2014;37:357-64.
- Sorensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009;374:1967-74.
- Nayak D, Aronow WS, Sukhija R, McClung JA, Monsen CE, Belkin RN. Comparison of frequency of left ventricular thrombi in patients with anterior wall versus non-anterior wall acute myocardial infarction treated with antithrombotic and antiplatelet therapy with or without coronary revascularization. *Am J Cardiol* 2004;93:1529-30.
- Shacham Y, Leshem-Rubinow E, Ben Assa E, et al. Frequency and correlates of early left ventricular thrombus formation following anterior wall acute myocardial infarction treated with primary percutaneous coronary intervention. *Am J Cardiol* 2013;111:667-70.
- Witt BJ, Brown RD Jr., Jacobsen SJ, Weston SA, Yawn BP, Roger VL. A community-based study of stroke incidence after myocardial infarction. *Ann Intern Med* 2005;143:785-92.
- Udell JA, Wang JT, Gladstone DJ, Tu JV. Anticoagulation after anterior myocardial infarction and the risk of stroke. *PLoS One* 2010;5:e12150.
- Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med* 1997;336:251-7.

- 12.** Turpie AG, Robinson JG, Doyle DJ, et al. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med* 1989; 320:352-7.
- 13.** Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1990;323: 147-52.
- 14.** Kontny F, Dale J, Abildgaard U, Pedersen TR. Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction: the Fragmin in Acute Myocardial Infarction (FRAMI) Study. *J Am Coll Cardiol* 1997;30:962-9.
- 15.** Le May MR, Acharya S, Wells GA, et al. Prophylactic warfarin therapy after primary percutaneous coronary intervention for anterior ST-segment elevation myocardial infarction. *J Am Coll Cardiol Intv* 2015;8: 155-62.
- 16.** Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;381:1107-15.
- 17.** Lamberts M, Gislason GH, Olesen JB, et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. *J Am Coll Cardiol* 2013;62: 981-9.

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