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Impact of Atrial Fibrillation On Cardiovascular Mortality in the Setting of Myocardial Infarction

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Abstract

Atrial fibrillation (AF) commonly occurs in patient with acute myocardial infarction (AMI). Potential triggers for AF development in this setting includes reduced left ventricular function, advanced diastolic dysfunction and mitral regurgitation leading to elevated left atrial pressures and atrial stretch. Other triggering mechanisms include inflammation and atrial ischemia. Multiple studies have shown that AF in patients with is associated with increased mortality. However, whether AF is a risk marker or a causal mediator of death remains controversial.

There is relative dearth of data with regard to optimal management of AF in the setting of acute coronary syndromes. Patients with AMI who develop AF are at increased risk of stroke. However, the issue of the most appropriate antithrombotic regimens is complex given the need to balance stroke prevention against recurrent coronary events or stent thrombosis and the risk of bleeding. Presently, 'triple therapy' consisting of dual antiplatelet agents plus oral anticoagulants for 3–6 months or longer has been recommended for patients at moderate–high risk of stroke.

Atrial fibrillation (AF), the most common sustained arrhythmia seen in clinical practice, often coincides with acute myocardial infarction (AMI), with a reported incidence ranging between 7% and 21%.[1] The development of atrial fibrillation in the acute phase of AMI may aggravate ischemia and heart failure, lead to clinical instability and adversely affect outcome. In the following we will review the pathophysiology, clinical characteristics and importance, and management of AF occurring in the setting of AMI.

Introduction

Potential Underlying Mechanism Of Atrial Fibrillation In AMI

The mechanisms that promote the development of AF in the AMI setting are complex and often multifactorial. Multiple potential mechanisms have been implicated, including pericarditis, atrial ischemia or infarction, increased catecholamines, metabolic abnormalities, inflammation and increased atrial pressures.[2-4](Figure 1)

Atrial Ischemia

The possibility that atrial ischemia may contribute to the occurrence of AF in the setting of AMI is supported by several clinical and experimental observations. Experimental studies have shown that isolated atrial ischemia causes local atrial conduction slowing and promotes the maintenance of AF.[5] It has been reported that atrial infarction is

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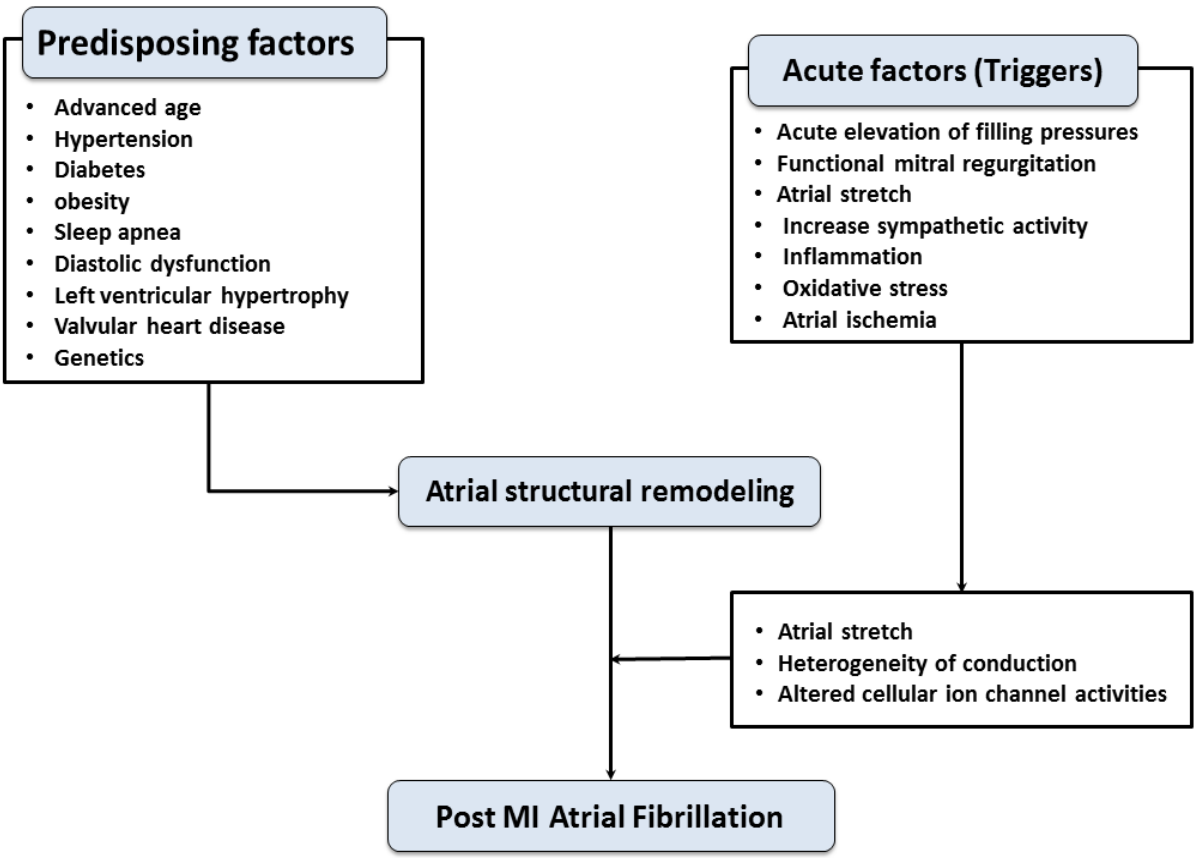
Figure 1: Factors promoting Atrial Fibrillation in Acute Myocardial infarction



relatively common, observed in up to 17% of autopsy-proven cases of myocardial infarction, with over 20% of cases constituting isolated atrial infarction.[6,7] Isolated atrial infarction is difficult but possible to diagnose clinically, and atrial tachyarrhythmia is a characteristic manifestation.[8]

The pathophysiological role of atrial ischemia in AMI-related AF was recently highlighted by a patient with inferoposterior infarction in whom angioplastic reperfusion of occluded atrial coronary branches led to spontaneous termination of AF.[9] In AMI patients without heart failure,stenosis affecting the atrial branches is a predictor for the development of AF.[10]

By contrast, in the large occluded Coronary Arteries (GUSTO-I) trial, the most important angiographic finding was that AF denoted more extensive coronary artery disease and poorer reperfusion of the infarct-related artery.[11] This study found a weak relationship between right coronary artery involvement, suggesting that actual territories at risk—including the sinoatrial node, the atrioventricular node, and the atria are less important in the pathogenesis of AF.[11]

Inflammation

Current evidence suggests that inflammation plays a prominent role in the initiation and maintenance of AF.[12, 13] In the Women's Health Study, markers of systemic inflammation were significantly related with the risk of incident AF in a female population free of cardiovascular disease at baseline.[14] C-reactive protein (CRP), a sensitive marker of systemic inflammation, is increased in patients with AF compared with patients in sinus rhythm.[15, 16] Elevated CRP levels are associated with increased likelihood of new onset AF,[16, 17] and with recurrence of AF after successful cardioversion.[18] Atrial biopsies in patients with AF have demonstrated inflammatory infiltrates, myocyte necrosis, and fibrosis.[19, 20]

Inflammation may also contribute to the development of AF in the early phase of AMI. AMI is associated with a robust intra myocardial and systemic inflammatory response, resulting in marked elevations of inflammatory markers in peripheral blood.[21-24] The majority of AF events occur during the first few days after AMI, coinciding with the acute phase response to infarction. Interestingly, the acute phase response in AMI resembles the acute phase response after cardiac surgery,[25] in which the temporal course of AF closely follows the CRP-mediated activation of the complement system and release of proinflammatory cytokines.[25, 26] Aronson et al. have shown a graded positive association between elevated CRP and new-onset AF, predominantly due to an increased number of AF events during the first few days after the infarction,[3] akin to the finding that postoperative peak CRP is an independent predictor of the development of AF.[25, 27, 28] In a recent randomized trial, treatment with atorvastatin before elective cardiac surgery significantly decreases postoperative AF.[27]

Acute Elevation of Filling Pressures and Atrial Stretch

Early studies have shown unfavorable invasive hemodynamic measures such as increased pulmonary capillary wedge pressure and right atrial pressure in patients who later developed atrial fibrillation than in those who did not[29,30] Signs and symptoms of heart failure are the most consistent finding in AMI patients who develop AF,[2,31-33] suggesting that acute elevation of filling pressures may play a pathogenic role.

Experimental and clinical observations demonstrate that increasing atrial pressure and/or causing acute atrial dilatation may trigger AF. Increased atrial stretch induced by increased atrial pressure shortens atrial refractory period and greatly increases the vulnerability to AF.[34,35] The phenomenon of mechanically induced electrical changes (mechanoelectric feedback) is thought to be mediated through stimulation of atrial stretch-activated ion channels which render the atria vulnerable to fibrillation.[34,36,37] In animal models, AF has been shown to be easily inducible when intra-atrial pressure is raised acutely, presumably via the stretch-activated ion channels that are present in cardiac tissue and are activated by increased intra atrial pressure.[4,36-38] At the whole heart level, blockade of stretch-activated channels diminishes AF inducibility.[36,37]

Acute reduction of chronic atrial stretch in mitral stenosis results in favorable effects on atrial electrophysiological characteristics, and some of the stretch-induced electrophysiological changes were abolished immediately after percutaneous mitral balloon valvotomy, suggesting that relief of left atrial stretch underlies these changes.[39-41]

Acute atrial stretch may be relevant to AF episodes occurring during acute changes in hemodynamic conditions such as AMI and acute pulmonary embolism.[42] In patients with AMI and concomitant acute decrease in left ventricular systolic function, the non-compliant left atrium imposes an acute increase in left atrial pressure that predisposes to AF.

Furthermore, in the setting of AMI, incident AF increases markedly with associated complications that result in increased atrial pressures such as functional mitral regurgitation[43] or severe diastolic dysfunction.[44]

Prognostic Significance of Atrial Fibrillation Complicating Acute AMI

The development during hospitalization for AMI has been associated with increased risk of mortality, heart failure and stroke in multiple studies.[1,45-47] The majority of studies have found that AF is an independent predictor of inpatient and longer-term all-cause mortality.[1, 45,47] Several mechanisms have been proposed to explain association between increased all-cause mortality post-AMI in patients who have had AF during the acute event. These include adverse hemodynamic effects due to loss of atrial contraction, rapid ventricular rates, loss of atrioventricular synchrony, irregular RR interval and promoting ischemia and development of heart failure.[48-52]

The concept that AF adversely impacts the outcome of AMI patients implies that patient's outcome will be related to the duration of AF episodes with poorer outcome associated with longer episodes of AF. However, a recent report using

implantable cardiac monitors found the risk for adverse events to be sig`nificantly increased even for a single AF episode lasting ≥30 seconds. Furthermore, the burden of AF, defined as the total number of recorded events, was not significantly predictive of major cardiovascular events.[53] Because a single short episode of AF should not impact patient outcome, these results suggest that AF is a marker rather than a direct mediator of adverse outcome.[54]

Despite the large number of studies investigating the risk associated with AF in the setting of AMI, whether AF is a risk marker or a causal mediator of death remains controversial, as observational reports cannot answer questions of causality.[55] Thus, AF may be an indicator of concomitant comorbidities, excessive neurohormonal activation, inflammation, structural changes and elevation of filling pressures,[3, 43, 56] which both promote the development of AF and increase the risk for mortality. Indeed, a major drawback of almost all studies is the limited adjustments for potential confounders.[54, 55] Most studies adjusted only for patient history and admission findings and some for left ventricular systolic function, with missing information on several important risk factors for both AF and adverse clinical outcomes after AMI. Thus, new-onset AF remains associated with an increased risk of death after adjustment for age, diabetes mellitus, hypertension, prior infarction, heart failure during the index hospitalization, and coronary revascularization status.[47] However, none of the studies accounted for the combined effects of inflammation, left ventricular diastolic dysfunction and functional mitral regurgitation which are both predisposing factors for AF as well as strong independent predictors of mortality after AMI. Thus, there remains a concern of residual confounding due to incomplete adjustments important risk factors. For example, a recent study by Bahouth et al. found that AF was an independent predictor of mortality when the model was adjusted for clinical variables alone. However, after further adjustments for left ventricular systolic function and the degree of functional mitral regurgitation, the relationship between AF and mortality became nonsignificant.[43]

The association between AF and subsequent heart failure is particularly difficult to establish because heart failure often coincides with the development of atrial fibrillation during the acute phase of AMI and because of the strong association of AF with elevated filling pressures.[43,44] By contrast, AF in AMI strongly portends subsequent stroke.[11, 57, 58] (seebelow)

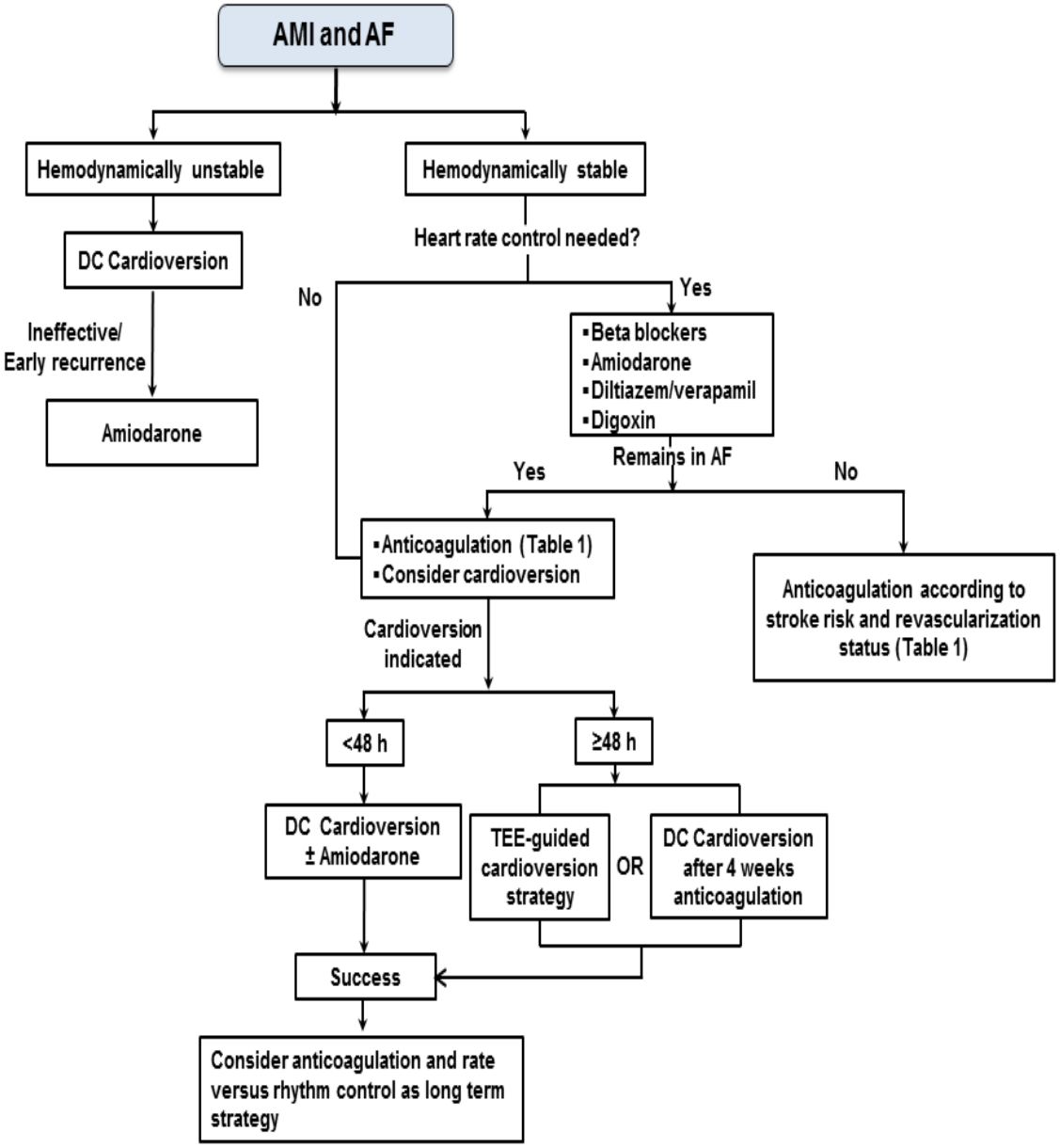
Management of AF in the Acute Phase of Myocardial Infarction

Despite its frequent occurrence and deleterious influence on outcomes, randomized data regarding management of AF after AMI are scarce. Therefore, specific recommendations for management are based primarily on consensus. The initial management will depend on a rapid assessment of the patient's hemodynamic status (Figure 2). Urgent synchronized direct current (DC) cardioversion should be attempted in patients presenting with AF and intractable ischemia, hypotension, or heart failure. For episodes of AF with hemodynamic compromise that do not respond to electrical cardioversion or that recur after a brief period of sinus rhythm, the use of intravenous amiodarone may help control rate and maintain sinus rhythm.[59] The treatment goals for periinfarction AF and no hemodynamic compromise are identical to those of AF that occur in other settings. These goals include slowing of the ventricular response rate, consideration of conversion and maintenance of sinus rhythm, and prevention of thromboembolic events. Nevertheless, post AMI physiology does have features that favor some therapeutic strategies over others. Each of these goals is discussed separately below

Rate Control

Rate control in the acute MI setting may be challenging. Secondary causes of enhanced AV nodal conduction should be treated aggressively. Attention should be given to pain management, patient arousal and fear, anemia, hypoxia, and intravascular volume status. Addressing these secondary causes of rapid ventricular rate is crucial to successful rate control. When medical therapy is selected, common practice in the critical care setting is to consider the use of intravenous beta-blockers such as esmolol (which has a very short half-life) or metoprolol. Other therapeutic alternatives, used when beta-blocker therapy is ineffective,

Figure 2: The management of new-onset atrial fibrillation in the setting of acute myocardial infarction



poorly-tolerated, or contra-indicated, include a non-dihydropyridine calcium channel blockers (diltiazem, verapamil), digoxin or amiodarome. Amiodarone has both sympatholytic and calcium antagonistic properties, depresses AV conduction, and is effective in controlling the ventricular rate in patients with AF. Although intravenous amiodarone is effective in both the rhythm and rate management of acute AF, its use is associated with significant complications, mainly phlebitis, bradycardia, and hypotension.[60]

Cardioversion and Maintenance of Sinus Rhythm

Randomized trials comparing outcomes of rhythm- versus rate-control strategies in patients with AF found no difference in mortality or stroke rate between patients assigned to one strategy or the other.[61, 62] These studies, however, did not include patients with recent AMI. Thus, it is unclear whether those results extend to the post-AMI patients, a population in whom anti-arrhythmic medications have been associated with a high risk

Table 1 Antithrombotic Strategies Following AMI and Coronary Artery Stenting in Patients with AF at Moderate-to-High Thromboembolic Risk*†

Clinical scenario		Antithrombotic Regimen		
Stent Type	Bleeding Risk	Warfarin + Aspirin + Clopidogrel§	Warfarin + Clopidogrel (or Aspirin)	Warfarin Alone
BMS	Low or intermediate	6 Months	Up to 12 months	After 12 Months
BMS	High	1-3 Months	Up to 12 months	After 12 Months
DSE	Low or intermediate	6 Months	Up to 12 months	After 12 Months
DSE	High	3-6 Months**	Up to 12 months	After 12 Months
None	Any	—	Months 12	After 12 Months

* Modified from references [79, 80, 82]; † Triple therapy: Aspirin dose ≤ 100 mg/day; clopidogrel dose 75 mg/day; warfarin dose adjusted for INR in the 2.0–2.5 range; ‡ Placement of DES is not recommended in this setting, § Prasugrel and ticagrelor are not recommended with warfarin and aspirin given the potential for increased bleeding with such triple therapy;** Triple therapy should be considered for a minimum of 3 months after implantation of a –olimus-eluting stent (e.g. everolimus or zotarolimus) and at least 6 months for a –taxel-eluting stent

of arrhythmia and sudden cardiac death.[63, 64] The only data available on contemporary treatment strategies in patients with post-MI AF comes from a retrospective analysis of 1131 patients with AF who were enrolled in the Valsartan in Acute Myocardial Infarction Trial (VALIANT). In this observational study, the use of anti-arrhythmic drugs in patients with AF after AMI complicated by HF and/or left ventricular dysfunction was associated with increased early mortality (0-45 days: HR: 1.9, 95% CI 1.2 to 3.0; P = 0.004) but not late mortality (45-1096 days: HR 1.1, 95% CI 0.9 to 1.4; P = 0.45). Interestingly, more than 95% of deaths that occurred in patients receiving anti-arrhythmic drugs occurred in patients taking only amiodarone. No difference was observed in the incidence of stroke (0-45 days: HR 1.2, 95% CI 0.4 to 3.7; P = 0.70). The results of this study, though limited by its retrospective nature, both reinforce previous randomized controlled trials that showed no benefit to a rhythm control strategy and identify a patient population in whom randomized data are needed to determine optimal treatment.[65]

Antithrombotic Therapy

The incidence of an ischemic stroke after AMI ranges from 2% to 5% in the first year.[66-69] The principal mechanism of stroke during this period is embolic cerebral infarction.[68, 70, 71]Although patients with AMI who develop AF are at increased risk of stroke, the optimal anticoagulation strategy for these patients is unknown.

AF in the presence of AMI is frequently perceived by clinicians as a nuisance, and its importance is often overshadowed by the need for revascularization.[72] In these patients, transient AF is frequently attributed to acute hemodynamic changes, elevation of filling pressures and heart failure, inflammation or ischemia.[1, 3, 43, 73] Therefore, AF is often perceived merely a marker that reflects the severity of the underlying ischemic event, and the need for long-term anticoagulation may be ovlooked.[72]

The presence of vascular disease, including myocardial infarction, in patients with pre-existing AF may confer additional risk for ischemic stroke.[74] In a recent study, the mean CHA_2DS_2–VASc stroke risk score was 4.1 (SD 1.8) in patients with AMI and AF. [57] However, in daily practice oral anticoagulants (OAC) are given to only a minority of AMI patients with AF, even to those with $CHADS_2$ scores ≥2.[57,75] In the VALIANT trial, only 4% of patients with AF received 'triple therapy.[58,65] Lopes et al. reported that only 10.6% of patients with AMI and new onset AF received triple therapy, and the use of triple therapy actua ly decreased with increasing $CHADS_2$ score.[76] Thus, the need for anticoagulation in patients with AMI and previously documented AF who are moderate or high risk of thromboembol-

ic event is obvious.[77] However, recent studies demonstrate that even transient new-onset AF complicating AMI is associated with an increased future risk of ischemic stroke in patients treated with antiplatelet agents alone, irrespective of the AF duration.[46,57,78] Moreover, transient AF is associated with high rates of clinically evident AF recurrence rates,[46, 57] further reinforcing the need to consider OAC for stroke prevention

Evidence base for the most appropriate antithrombotic treatment of patients with AMI and AF is limited. Recently, 'triple therapy' consisting of dual antiplatelet agents plus oral anticoagulants for 1 to 6 months has been recommended for patients at moderate–high risk of stroke ($CHADS_2$ score ≥1). These recommendations are summarized in Table1. It is reasonable to use dabigatran or rivaroxaban in place of warfarin in patients who need triple therapy although there is no safety or efficacy data exists on these combinations.[79]

The majority of AMI patients will undergo placement of an intracoronary stent. Thus, the management of AF patients presenting with an acute coronary syndrome (ACS) poses several dilemmas given the need to balance stroke prevention and recurrent coronary events or stent thrombosis against the risk of bleeding.[80, 81]

Conclusions

The understanding of the pathogenesis of AF in the setting of AMI is still evolving. Presently, the management of AF in patients with acute coronary syndromes is driven by consensus-guided recommendations. There are gaps in our knowledge with regard to optimal management of AF in the setting of AMI, and in particular, the optimal antithrombotic regimens. A number of randomized trials on triple therapy are ongoing (ISAR-TRIPLE - NCT00776633; WOEST - NCT00769938; MUSICA-2 - NCT01141153) which may help to refine our knowledge of the optimal antithrombotic management of patients with AMI and AF.

Disclosures

No disclosures relevant to this article were made by the authors.

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