

NEW-ONSET ATRIAL FIBRILLATION IN THE POST-PRIMARY PCI SETTING: A SYSTEMATIC REVIEW

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Abstract. Background: Atrial fibrillation is a relatively common complication of acute myocardial infarction with significant impact on the short and long-term prognosis. **Methods:** A systematic literature review was done through Pubmed and CENTRAL to extract data related to new-onset atrial fibrillation following primary PCI. **Results:** Searching resulted in twenty-one matched studies. Extraction of data showed an incidence rate of new-onset atrial fibrillation (2.8%-58%). A negative impact was found on the outcomes of patients treated with primary PCI with increased short and long-term mortality and morbidity. **Conclusion:** New-onset atrial fibrillation is an adverse prognostic marker in patients with acute myocardial infarction treated invasively. Preventive measures and anticoagulant therapy should be considered more intensively in this subset of patients.

Key words: atrial fibrillation, new-onset atrial fibrillation, myocardial infarction, percutaneous coronary intervention, primary PCI

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INTRODUCTION

Atrial fibrillation (AF) is a relatively common complication of acute myocardial infarction with an estimated incidence of new-onset AF (NOAF) ranging from 2.3% to 28% [1, 2]. It is possible that myocardial infarction induces structural and electrophysiological changes in the atrial tissue that act as a substrate for the initiation of AF [3]. The adverse hemodynamic effects of atrial fibrillation are related to tachycardia, which leads to increased oxygen demand and reduced diastolic filling time. Furthermore, the elevated heart rate and decreased blood pressure are associated with ineffective atrial contractions and impaired AV synchrony causing further deterioration in coronary perfusion and exacerbation of the myocardial ischemia.

The impact of NOAF on the acute coronary syndrome patients is significant, with impaired short and long-term prognosis. The Global Registry of Acute Coronary Events (GRACE) substudy reported that patients with NOAF had a higher in-hospital and 6-month mortality and morbidity than patients without AF, equal to the patients with prior AF [4]. A meta-analysis of 43 studies indicated that mortality is higher in acute STEMI patients with NOAF (OR 1.37; 95% CI, 1.26 to 1.49) and the risk remained elevated even after adjustment for age, diabetes mellitus, hypertension, prior MI, heart failure and coronary revascularization [5]. However, confounding effects on the mortality of acute STEMI with NOAF in comparison with those without AF are possible due to baseline LV dysfunction, higher Killip class and cardiogenic shock

[6]. Morbidity is also higher in patients with NOAF due to the increased risk of LV dysfunction, stroke and bleeding events [7].

This review explores the available evidence on the incidence and major predictors of NOAF, and highlights its prognostic significance in invasively treated acute STEMI patients.

SEARCH METHODOLOGY

A literature search through PubMed and Cochrane CENTRAL library was done using the MeSH terms “atrial fibrillation and myocardial infarction” and “atrial fibrillation and primary PCI”. In addition, manual search of relevant references was done. The search was limited to papers in the English language only. The initial search resulted in 5739 matches followed by removal of duplicates, screening of titles and abstracts and finally exploring the full text of relevant papers. Finally, 21 papers, investigating specifically the risk of new-onset AF post primary PCI, were selected for data extraction and inclusion in this systematic review (Fig. 1). The included research types are substudies of prospective trials ($n = 6$), prospective registries and cohorts ($n = 5$), and retrospective analyses ($n = 10$).

NEW-ONSET AF POST PRIMARY PCI

The development of new-onset AF after PCI is defined by the European Society of Cardiology as “the

change from sinus rhythm at admission to AF during/ after PCI” typically occurring during the first four days after acute MI” [8]. Several studies evaluated the clinical impact of NOAF in the contemporary era following the advancements in the management of acute STEMI including reperfusion by the widespread application of invasive coronary catheterization.

Although no direct comparison is available regarding the incidence of NOAF between primary PCI and thrombolytic therapy, the rate of NOAF was lower after primary PCI (18%) than that following thrombolytic therapy (33%) [9]. It has been suggested that primary PCI is superior to thrombolytic therapy in lowering the incidence of NOAF, especially when higher TIMI flow grade can be achieved [10]. In a study of patients with inferior MI, transient NOAF was reported in 17% of patients who underwent primary PCI, and in 39% of those who received thrombolytic therapy [11]. Another study showed a 49.8% risk of NOAF with thrombolytic therapy and 25.6% with primary PCI [12].

The studies that enrolled patients treated with primary PCI were heterogeneous, and many of them were non-randomised observational studies with variations in follow-up duration and analysis methodology. There are differences regarding definitions of time of onset and the type and duration of AF attacks resulting in inconsistencies of some of the results. Furthermore, there is insufficient data regarding management strategies and the impact of antithrombotic therapy.

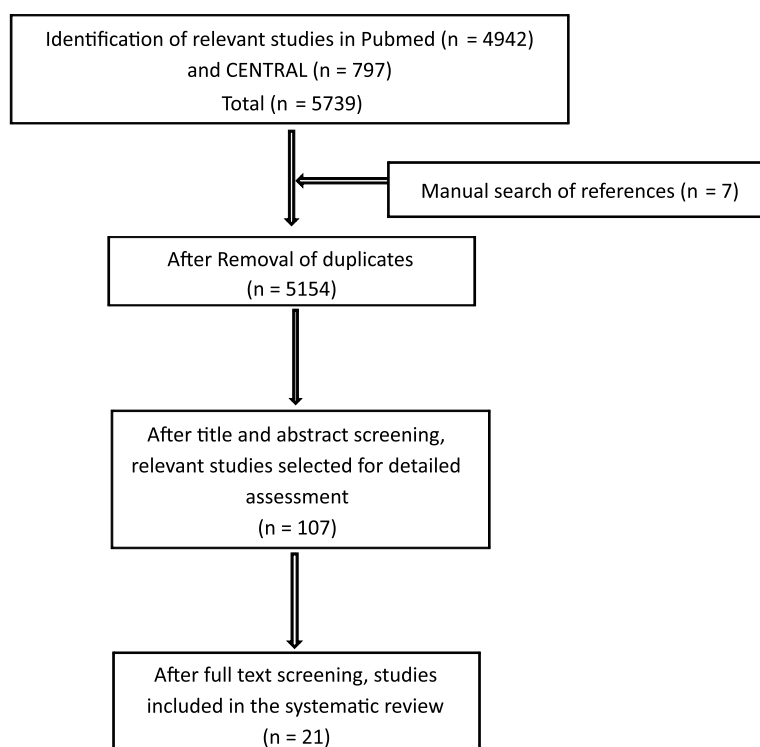


Fig. 1. Overview of the searching process

THE INCIDENCE OF NEW-ONSET AF

Studies of AF in patients with acute STEMI managed by primary PCI showed an incidence rate ranging from 2.8% to 58% (Table 1) [13-33]. The incidence rate of NOAF in the large prospective studies (the OACIS, APEX-AMI, RISK-PCI and HORIZONS-AMI trials) is ranging from 4.0% to 7.7% [13, 14, 18, 19]. Most cases of NOAF are transient or paroxysmal. However, persistent AF at hospital discharge was 5.3% in one study [14].

The variation in the incidence of NOAF can be explained by the lack of standard definitions in the assessment of NOAF. The timing of detection, the intensity of patient monitoring and duration of follow-up were variable between studies. Some studies considered AF on admission without prior history as NOAF

[13, 18], while others estimated the incidence only during hospitalization. Most studies used standard ECG monitoring throughout the period of hospitalization, while investigators of the ARREST study used implantable cardiac monitors for extended periods of time reaching up to 2 years counting all episodes of AF, including short-lived asymptomatic events, which are the reason of a very high rate of NOAF in this study (58%) [31]. In contrast, another study performed a single ECG, 3 hours after primary PCI [16].

In addition, some studies did not differentiate between AF preceding acute STEMI and that occurring later. Two large retrospective registries in the USA and South Korea reported AF in 8.7% and 4.3% of the patients' population, respectively. However, neither studies discriminated between prior AF and post-primary PCI NOAF [24, 25].

Table 1. Summary of studies of NOAF post primary PCI

Study	No. of patients	Incidence of NOAF (n)	Type of study	Duration of follow-up	Country and year of publication
Kinjo (13)	2,475	7.7% (190)	Prospective, part of the OACIS study	1 year	Japan, 2003
Lopes (14)	5,745	6.3% (342)	Prospective, part of the APEX-AMI trial	90 days	Multi-centre, 2009
Lin (15)	783	4.3% (33)	Prospective study	30 days	Taiwan, 2011
Beukema (16)	2,134	3.0% (52)	Retrospective registry	18 months	Netherlands, 2012
Asanin (17)	180	5.0% (9)	Prospective registry	NA	Serbia, 2012
Mrdovic (18)	2,096	4.0% (85)	Prospective, a substudy of the RISK-PCI trial	1 month	Serbia, 2012
Rene (19)	3,281	4.5% (147)	Prospective, sub study of the HORIZONS-AMI trial	36 months	Multi-centre, 2014
Gal (20)	830	8.8% (73)	Prospective, a substudy of the On-TIME II trial	1 month	Multi-centre, 2015
Zehir (21)	1,553	5.8% (90)	Retrospective	NA	Turkey, 2016
Karataş (22)	621	6.4% (40)	Retrospective	22 months	Turkey, 2016
Olsen (23)	373	6% (24)	Prospective single center	5.5 years	Denmark, 2016
Garg (24)	1,493,859	8.7% (129, 354)	Retrospective registry	In-hospital	USA, 2017
Hwang (25)	5,356	4.3% (119)	Retrospective registry	1 year	South Korea, 2017
Karabağ (26)	1,057	5.4% (58)	Retrospective study	33.16 ± 13.2 months	Turkey, 2017
Topaz (27)	1,657	2.8% (47)	Retrospective	3.4 ± 2.1 years	Israel, 2017
Podolecki (28)	4,099	5.5% (225)	Prospective registry	135 months	Poland, 2017
Rencuzogullari (29)	1,565	5.8% (86)	Retrospective	30.8 ± 16.3 months	Turkey, 2017
Rhyou (30)	527	15.4% (81)	Retrospective	1 year	Korea, 2018
Romanov (31)	50	58% (29)	Prospective observational (the ARREST) study	2 years	Netherlands, 2018
Mazzone (32)	1135	7.7% (88)	Retrospective	2 years	Italy, 2018
Modin (33)	373	6% (24)	Prospective (single centre)	5.6 years	Denmark, 2018

PREDICTORS OF NEW-ONSET AF

Several studies aimed at identifying clinical variables that independently predict NOAF in STEMI patients. Analysis of data showed that independent predictors of NOAF following primary PCI were advancing age [13, 16, 18, 19, 21, 22, 27, 29, 30, 32] and signs indicating extensive myocardial damage indicated by tachycardia [13, 22], hypotension [18], cardiogenic shock [30], higher Killip class [13, 16, 18, 21] and poor LV function (represented by LV EF) [21, 22, 29].

The studies found a predictive relationship between laboratory parameters and subsequent incidence of NOAF. A strong association was found with elevated cardiac biomarkers including troponin and BNP [17, 21, 26, 31, 32]. Various hematological indices were regarded as predictors of the NOAF development [21, 22, 32].

Angiographic characteristics of the infarct-related artery including total occlusion, final low TIMI flow [18], the RCA as the culprit artery [16], complexity of coronary artery lesions represented by Syntax score, and the Syntax score II [29] as well as failed PCI procedures [21] were frequently found in patients with NOAF.

Other reported predictors are a previous history of MI [27] and revascularization [21], male gender [13], impairment of renal function [18], body mass index [19, 32], LA size [22, 30] and function [33] by echocardiography, and a higher CHA₂DS₂VASc score [31].

PROGNOSTIC IMPACT AND EFFECT ON OUTCOMES

The effect of NOAF was evident in both the short and long-term outcomes of patients after primary PCI. Although the studies varied in their follow-up duration and discrepancies were noticed in some of the re-

Table 2. Predictors of NOAF post primary PCI

Study	Predictors
Kinjo [13]	Age, male gender, heart rate ≥ 100 bpm, and Killip class IV
Lopes [14]	NA
Lin [15]	NA
Beukema [16]	Age, Killip class > 1 , and occluded RCA
Asanin [17]	BNP ≥ 720 pg/mL
Mrdovic [18]	Age, systolic blood pressure < 100 mm Hg, Killip class $> I$, creatinine clearance < 60 ml/min, occluded infarct-related artery, TIMI blood flow $< III$
Rene [19]	Age and body mass index
Gal [20]	NA
Zehir [21]	Age, Peak Troponin I, Previous CABG, Killip 3/4 on admission, Unsuccessful PCI, LV EF, CRP
Karataş [22]	Age, LV EF, LA volumes, admission heart rate, multivessel disease, increased levels of CRP, mean platelet volume, red cell distribution width, uric acid, neutrophil to lymphocyte ratio and monocyte to high-density lipoprotein ratio
Olsen [23]	Global longitudinal strain by echocardiography
Garg [24]	NA
Hwang [25]	NA
Karabağ [26]	Plasma BNP
Topaz [27]	Age and prior MI
Podolecki [28]	NA
Rencuzogullari [29]	Age, LV EF, Syntax score and Syntax score II
Rhyou [30]	Cardiogenic shock left atrial volume index and age
Romanov [31]	Baseline troponin level and CHA ₂ DS ₂ VASc score of 4
Mazzone [32]	Advanced age, leukocyte count $> 9.68 \times 10^3/\mu\text{L}$, BNP > 80 ng/L and obesity
Modin [33]	Echocardiography parameters: left atrial emptying fraction (LAEF) and left atrial expansion index (LAI)

sults, the overall evidence indicates worse outcomes with the development of NOAF.

A prospective study of 2,475 patients with acute STEMI who underwent primary PCI showed poor long-term outcomes in the patients with NOAF. Although adverse events during hospitalization (LV dysfunction, cardiogenic shock, stroke, and ventricular arrhythmias) were significantly higher in patients with AF, adjusted short-term mortality was not different from the patients without AF. However, a higher long-term mortality at 12 months was reported with NOAF after adjustment for other clinical variables (HR 3.04, 95% CI 1.24 to 7.48) [13].

In the randomized controlled APEX-AMI trial, a three month follow-up of patients after acute STEMI showed higher mortality with NOAF (adjusted HR

1.81; 95%CI 1.06–3.09; P = 0.029). Other short-term complications have been significantly associated with NOAF including congestive heart failure, shock, and stroke [14].

An assessment of outcomes in 2,134 acute STEMI patients was done to detect differences between the patients with prior AF (detected on admission) and those with NOAF following primary PCI (detected 3 hours after admission). A follow-up for 18 months showed that both prior AF and NOAF were associated with increased long-term mortality, 21%, and 23%, respectively. However, the adjusted risk of mortality was significantly elevated only in the presence of NOAF (OR 3.69, 95% CI 1.87–7.29) [16].

The RISK-PCI trial found a significant correlation between the incidence of NOAF, the short-term mortal-

Table 3. Outcomes of NOAF post primary PCI

Study	Short-term mortality (vs. patients without AF)	Long-term mortality (vs. patients without AF)
Kinjo [13]	16.0% vs 6.7%, p < 0.001. Adjusted HR 1.42 (95% CI (0.88-2.31), p = 0.153)	18.9% vs 7.9%; p < 0.001. Adjusted HR1.64 (95% CI 1.05-2.55, p = 0.03)
Lopes [14]	Adjusted HR 1.81 (95% CI 1.06-3.09; p = 0.029)	NA
Lin [15]	HR 2.344 (95% CI 0.982-5.596) p (Univariate analysis) = 0.055 p (Multivariate analysis) = 0.530	NA
Beukema [16]	NA	23% vs 4.7%, p = 0.001. Adjusted OR 3.69, (95% CI 1.87-7.29)
Asanin [17]	NA	NA
Mrdovic [18]	22.5% vs 3.5%. Adjusted OR 2.67 (95% CI 1.46-4.89), p<0.001	NA
Rene [19]	NA	11.9% vs 6.3%. HR 1.91 (95% CI 1.16-3.14), p = 0.009.
Gal [20]	14.3% vs 1.4%, p < 0.001. Adjusted OR 13.476, p = 0.006.	NA
Zehir [21]	NA	NA
Karataş [22]	NA	27 vs. 5%, P < 0.001. HR: 2.20 (95% CI 1.03-4.72), P = 0.040
Olsen [23]	NA	NA
Garg [24]	10.3% vs 9.4%. Adjusted OR 1.10 (95% CI 1.06 to 1.16); p < 0.0001)	NA
Hwang [25]	NA	22.7 versus 9.5%, HR 2.51 (95%CI 1.68~3.76), P < 0.001
Karabağ [26]	NA	24.1% vs 7%, p = 0.015
Topaz [27]	6.4% vs. 2.1%, p = 0.08.	17% vs. 9.1%, p = 0.07
Podolecki [28]	7.6%-27.4% vs 4.2%-6.3%, p < 0.05	12%-38.7% vs 9%-12.9%, p < 0.05
Rencuzogullari [29]	NA	23.3% vs. 11%; p = 0.032
Rhyou [30]	NA	NA
Romanov [31]	0.0%	0.0%
Mazzone [32]	NA	HR 2.885 (95% CI 1.146-7.268), P = 0.025
Modin [33]	NA	NA

ity (30 days) (adjusted OR 2.67, 95% CI 1.46–4.89, $p = 0.001$) and the composite MACE rate (adjusted OR 2.39, 95% CI 1.47–3.87) but no significant association was noted with stroke, re-infarction, target vessel revascularization or major bleeding [18].

In the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, a randomized multicenter trial, patients with NOAF post primary PCI had worse outcomes after three years follow-up. The patients with NOAF had a higher mortality in comparison with those without AF (11.9% vs 6.3%, $p = 0.01$). Similarly, the rates of reinfarction (16.4% vs 7.0%, $p < 0.0001$), stroke (5.8% vs 1.5%, $p < 0.0001$), and major bleeding (20.9% vs 8.2%, $p < 0.0001$) were higher. New-onset AF was found to be an independent predictor of long-term mortality (HR 1.74, 95% CI 1.30 to 2.34, $p = 0.0002$) and MACE rate (HR 1.73, 95% CI 1.27 to 2.36). Although there was no report of short-term outcomes, the Kaplan-Meier survival curve showed an early separation in outcomes rates between patients with and without AF, with poor outcomes in the patients with AF [19].

A substudy of the tirofiban in myocardial infarction evaluation (On-TIME) II study, a prospective, multicentre, placebo-controlled, randomized clinical trial with a total of 984 patients evaluated the relation of time of development of NOAF to outcomes. Multivariate analysis indicated that only AF developing within 24-72 hours after primary PCI was significantly associated with increased mortality (adjusted OR 13.476, $p = 0.006$). Older age, hypertension, diabetes, previous MI, blood pressure on admission, LV dysfunction and higher Killip class, < III TIMI flow after PCI and LAD as the culprit's vessel were the main clinical predictors of mortality in patients with NOAF [20].

A large registry including about 1.5 million acute STEMI patients in the USA assessed retrospectively the impact of AF, both prior and new-onset. The analysis indicated a higher mortality in patients with AF compared to those without AF (10.3% vs. 9.4%, adjusted OR 1.1, CI 1.06-1.16, $p < 0.0001$). Higher rates of complications were reported during hospitalization of patients with AF including acute heart failure (33.0%), cardiogenic shock (17.2%), stroke (1.0%), acute kidney injury (12.8%), vascular complications (1.4%), bleeding (4.0%) and blood transfusion (5.0%) [24].

Similarly, The Korean Acute Myocardial Infarction Registry indicated that presence of AF on admission represented a poor prognostic marker in patients with acute STEMI treated by primary PCI and was significantly associated with a higher 1-year all-cause mor-

tality (HR 2.43, 95% CI 1.28-4.59, $P = 0.006$). The patient outcomes were significantly higher with AF in comparison to sinus rhythm including all-cause mortality (22.7 vs 9.5%, HR 2.51, 95% CI 1.68-3.76, $P < 0.001$), cardiac death (17.7 versus 7.5%, HR 2.49, 95% CI 1.59-3.90, $P < 0.001$) and composite MACE (20.2 versus 13.8%, HR 1.58, 95% CI 1.05-2.39, $P = 0.030$), respectively. However, the registry did not provide data on stroke and bleeding risks [25].

Different results emerged from a retrospective study involving 1,657 patients. The mortality rates with NOAF, both long and short-term, were numerically higher (6.4% vs. 2.1%, $p = 0.08$ and 17% vs. 9.1%, $p = 0.07$, respectively). The study showed that prior AF, but not NOAF, is correlated with short and long-term mortality [27].

The ARREST study, a prospective observational study, followed acute STEMI patients with preserved LV function after primary PCI, using implantable cardiac monitors for a prolonged period (24 months). About 40% of NOAF cases were detected within the first six months after STEMI, and 93% of them were asymptomatic. The results showed that AF was not associated with higher mortality rates, stroke, and bleeding. However, there was an increase in the rate of hospitalization for HF, in the progression of angina and hypertensive crises: 13.8% vs. 4.8% in patients without AF. However, the study sample size was small (51 patients) and not powered to draw conclusions [31].

Evidence extracted from the above studies strongly suggests a significant association of impaired survival and increased adverse events in patients developing AF following acute STEMI managed invasively. However, more information is required regarding the duration and burden of AF attacks, whether it is causing symptoms or not, the profile of thrombotic risk, and the effect of AF management on patients' outcomes.

RISK OF STROKE AND ANTICOAGULATION CHALLENGES

The risk of stroke is significantly elevated in patients developing NOAF secondary to acute STEMI with rates of stroke in the first year about 10.2% [11], significantly associated with the duration of NOAF (≥ 3.5 hours) and with the recurrence of AF following the hospital discharge [34]. Although NOAF can be transient, a high rate of recurrence (22%) was detected in patients with NOAF following acute STEMI [11, 35-37] which may increase the possibility of developing stroke or TIA.

The independent predictors of recurrences are NOAF (adjusted HR 7.84, 95% CI 4.08–10.43, $p < 0.0001$);

advanced age (HR 1.72, 95% CI 1.40–2.11, $p < 0.0001$); LVEF $< 45\%$ (HR 1.89, 95% CI 1.19–3.02, $p = 0.007$) and LA enlargement (HR 1.96, 95% CI 1.16–3.32, $p = 0.01$) [36].

Assessment of MACE events following primary PCI complicated by AF indicated a significantly increased short and long-term risk of stroke. In-hospital stroke rate was found in Kinjo et al., 2.3% with vs. 0.6% without AF, $p = 0.002$ [13], and in the RISK-PCI trial it was 3.1% vs. 0.8%, $p = 0.03$ (18). Mid-term (90 days) stroke rate in the APEX-AMI trial was 9.2 (HR 2.98; 95% CI 1.47–6.04) $p = 0.0024$ (14). In the HO-RIZONS-AMI trial, the long-term (3-year) stroke rate was 5.8% with vs. 1.5% without AF ($p < 0.0001$) [19].

Anticoagulation treatment for transient NOAF is associated with a lower rate of stroke and TIA (6.3% vs. 9.9% with antiplatelet therapy) [36]. Anticoagulation treatment on discharge after acute STEMI can reduce the composite endpoint of death and non-fatal stroke (HR 0.33, 95% CI 0.11–0.96, $p = 0.041$) [35].

A limited number of studies evaluated the effect of anticoagulation on the prognosis of NOAF after primary PCI. In the APEX-AMI trial, the use of triple therapy (warfarin plus DAPT) was associated with lower mortality (0.0% vs. 5.1% with no antithrombotic therapy) and stroke rates (2.7% vs. 5.1 without antithrombotic therapy) [14].

However, management of AF in acute coronary syndrome patients with coronary artery stenting is a clinical challenge as a reduction of ischemic events can be complicated by increased bleeding risk. A meta-analysis of 18 studies enrolling more than 20,000 patients with AF and PCI showed that triple therapy (including DAPT and an anticoagulant) in ACS increased the risk of bleeding (OR 0.68, 95% CI 0.56–0.82, $P < 0.0001$) while the risk of MI, MACE, stroke and the all-cause mortality were similar to those receiving DAPT without anticoagulation [38].

Two large randomized controlled studies, the PIONEER AF-PCI trial and the RE-DUAL PCI trial assessed the bleeding risk in patients with non-valvular AF who underwent PCI using NOAC therapy. About 50% of patients in both studies were labelled as ACS patients. In the PIONEER AF-PCI trial, the bleeding risk was similar between triple therapy (rivaroxaban 2.5 mg twice daily plus DAPT) and dual therapy (rivaroxaban 15 mg once daily plus a P2Y12 inhibitor) – 18.0% vs. 16.8%, respectively. Bleeding risk with both regimens using rivaroxaban was lower than warfarin plus DAPT (26.7% with warfarin). The MACE rate (death from cardiovascular causes, MI or stroke) showed no significant differences between the three regimens [39]. In the RE-DUAL PCI trial, lower bleed-

ing event rates were found with dual therapy (dabigatran plus a P2Y12 inhibitor) in comparison with triple therapy (warfarin plus DAPT) [40].

Based on the available evidence, we suggest consideration of using anticoagulants in high-risk patients with NOAF after primary PCI to lower the risk of mortality and morbidity in this patients' subset. High-risk features include advanced age, LV dysfunction, and higher Killip class on admission with a high CHADS2VASc score and low bleeding risk. Bleeding risk can be minimized by the application of the recent recommendations of the European Society of Cardiology in patients with PCI and an indication for anticoagulation. These include shortening of triple therapy duration or alternatively using dual therapy, use of low dose aspirin and clopidogrel as the P2Y12 inhibitor of choice and considering NOACs (rivaroxaban 15 mg or dabigatran 150 mg) as a substitute to warfarin [8].

EVIDENCE GAP AND FUTURE DIRECTIONS

The currently available evidence is far from providing definite recommendations. Many confounding factors exist including, but not limited to, the patients' heterogeneity, disease burden, relation of AF and NOAF to the pathophysiology of STEMI and primary PCI, impact and necessity of rhythm control, factors (clinical, homeostatic, and angiographic) that determine prognosis, the type and duration of anticoagulation if needed, and risk of bleeding. Having in mind these burning issues, properly designed studies are still needed.

CONCLUSION

The impact of NOAF and its treatment poses a significant burden on the outcomes of primary PCI. Based on data currently available in the literature, it can be concluded that the recognition of NOAF as an adverse prognostic factor is important for risk stratification of patients with acute STEMI. Intensification of preventive measures in high-risk patients and consideration of anticoagulation are needed in the management of patients with NOAF with more intensive short- and long-term follow-up and frequent follow-up visits aiming at improved morbidity and mortality.

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