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Mortality Risk Associated with AF in Myocardial Infarction Patients

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Abstract

Atrial fibrillation (AF) complicating myocardial infarction (MI) has been a controversial topic for the last few decades. It has generated a plethora of debates regarding whether it is a risk indicator of co-morbidities and poor haemodynamic status or independent causal mediator of poor outcomes. The management of this condition has also been idiosyncratic probably due to confusion regarding its prognostic significance. We shall review the literature and attempt to elucidate the prognostic significance as well as evidence available for defining management strategies.

Introduction

AF remains the commonest clinically encountered arrhythmia and continues to beget a considerable morbidity as well as mortality burden. It is well known to be associated with age, heart failure, myocardial ischemia, valvular heart disease amongst other pathologies. The significance and management of this arrhythmia in the setting of MI, have provoked intense debate over the last few decades. AF is generally viewed by clinicians to be a pesky condition that complicates acute MI, whilst foremost efforts are usually being understandably directed towards urgent reperfusion and appropriate secondary prevention therapy. Whilst it is generally agreed that AF in the setting of acute MI portends significant mortality risk as well as increased risks due to stroke and heart failure,[1,2] questions have been raised[3] as to whether it is a bystander marker of co-morbidities that have led to the MI or whether it increases mortality risk on its own.

Epidemiology

The varying incidence of this condition that has been reported in various studies can be attributed to temporal changes in reperfusion (pre-thrombolytic, thrombolytic and PCI) and other management strategies as well as increased prescription of secondary prevention medications for MI. It is interesting to analyse the changing temporal trends of AF incidence complicating acute myocardial infarction, as these trends reflect the changing risk profile of various populations, evolution of improved management strategies for MI such as reperfusion therapy and secondary prevention as well as improved arrhythmia assessment and detection. As many of the predictors of AF are also dependant on the ramifications of acute coronary occlusion, reperfusion strategies clearly have an important bearing upon the risk for development of peri-MI AF. However AF complicating MI in pre-thrombolytic and

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Table 1 Studies of AF Complicating Acute MI Reported Since 2000

Authors	N	Population	AF Incidence	Risk Factors for AF	Outcomes
Siu et al [2]	431	Inferior STEMI patients with preserved LV function Mean age 64±1 y	Transient in-hospital AF-13.7%	Older age, women	1 year incidence of AF and stroke higher but mortality similar in comparison to group without AF
Bahouth et al[3]	1920	Acute MI patients without known AF	New-onset AF in 8.4%	FMR, impaired LVEF<45%, Killip class>1, age≥60y, enlarged left atrium	New onset AF did not independently predict mortality after adjustment for functional mitral regurgitation(FMR) and LV ejection fraction
Wong et al (GUSTO III trial investigators) [5]	13,858	Acute STEMI/ LBBB patients randomised to alteplase or reteplase	New-onset AF -6.5%	Age, systolic BP(SBP), weIght, Killip class, previous bypass, complete heart block, ventricular fibrillation	AF independently predicted in-hospital, 30day and 1 year adverse mortality
Rathore et al [6]	106,780	Acute MI patients aged ≥65y	11.3% new-onset AF	Killip class 4, heart rate , SBP,age, anterior MI, race, previous MI/ cerebrovascular disease, hypertension, time to presentation, current smoking status	New onset AF independently predicted increased in-hospital , 30 day and 1 year mortality
Pizzetti et al (GISSI-3 investigators) [7]	17,749	Acute MI patients (without chronic AF) randomised to lisinopril or no lisinopril	7.8% new-onset AF	Age, Killip class, heart rate, previous MI, hypertension, diabetes, females, lack of thrombolysis, LVEF	AF independently predicts worse in-hospital and long-term mortality Late-onset AF (after days 0-1) predicted hospital mortality but no long-term mortality
Pedersen et al (TRACE Study investigators) [8]	6676	Acute MI patients randomised to trandalopril	5.3% new-onset AF	Age, LVEF, lack of thrombolysis, males, hypertension	AF predicts worse in-hospital and long-term mortality in patients with heart failure
Mcmurray et al (CAPRCORN Trial investigators) [10]	984placebo,975 carvedilol	Acute MI patients, post-hoc analysis of arrhythmias	New-onset AF 5.4 % in placebo group and 2.3% in carvedilol group		Carvedilol treatment significantly reduces risk of post-MI AF
Danchin [12]	3396	Acute MI patients without AF on first ECG	New-onset AF -4.7%	Older age, later statin therapy, higher GRACE score, previous nitrate use, use of loop diuretics during 1st 48h	Early statin therapy led to reduced risk of developing AF
Mrdovic (RISK-PCI Trial) [13]	2096	Primary PCI patients	New onset AF 6.2%	Older age, Killip>1, systolic BP, creatinine clearance, post-procedural TIMI flow<3	AF independently predicts worse 30 day MACE and mortality

Kinjo et al [14]	2475	Acute MI patients (Angioplasty <24 hours)	7.7% developed in-hospital AF AF on admission 4.3%	Older age, previous MI or cerebrovascular disease, Killip class 4, male gender,SBP<100 mm Hg Heart Rate>100/mt, multivessel disease,poorer reperfusion of infarct-related artery	AF independent predictor of 1 year but not in-hospital mortality
Lopes et al (APEX-MI investigators) [15]	5466	Primary PCI patients	New onset AF 6.3%	Older, female, lower systolic and diastolic BP, Killip Class 3 and 4, anterior MI, previous heart failure, diabetes, stroke hypertension, higher CK, troponin and BNP	AF independently associated with adverse 90 day mortality, stroke and heart failure.45% AF patients anti-coagulated at discharge including only 39% of those with $CHADS_2$≥2Warfarin use led to lower 90day mortality and strokeTriple therapy led to significantly lower 90day mortality and stroke
Beukema [18]	1728	Primary PCI	AF post-primary PCI 3%	Older, Killip>1, right coronary artery occlusion, TIMI flow 0 before procedure, unsuccessful reperfusion	Only post-primary PCI AF independently predicted worse long-term mortality
Podolecki et al [19]	2980	Acute MI patients treated invasively	Overall AF incidence of 9.46% (pre-hospital only AF -3.09%; new-onset AF-3.66%; permanent AF -2.72%)	Older age, diabetes, impaired renal function, severely impaired LV EF	Only permanent AF and new-onset AF predicted short and long term mortality
Kober et al (from the VALIANT Trial investigators) [20]	14703	Acute MI patients with clinical or radiological signs of heart failure, reduced LV systolic function or both	New-onset AF 12.3%	Older age, higher body mass index, heart rate, SBP, Killip class>1, NSTEMI, renal impairment	Both current and prior AF independently predicted worse long term mortality and major cardiovascular events, magnitude of risk prediction for adverse outcomes similar between these 2 groups
Sankaranarayanan et al [35]	500	Acute MI patients	New-onset AF 11.4%	Older age, LVEF, smoking status	Both AF on admission and new-onset AF predicted increased in-hospital, 1 year and 5.5 year mortality. Only AF on admission was independently associated with VF.
Li et al [37]	967	Acute MI patients aged ≥65 years	New-onset AF 6.51%	Previous MI, cerebrovascular disease, circumflex disease, Killip class 3,4, NSTEMI, inferior MI	AF did not independently predict in-hospital mortality
Bishara et al [47]	2402	Acute MI patients	Transient new-onset AF 7.2%		Transient AF predicted high recurrence rate and risk of stroke or TIA over 1 year

Studies Including Post-Discharge AF					
Lehto et al (OPTIMAAL investigators) [11]	4822	Acute MI patients with clinical heart failure or LVEF<40%	New AF -2% during 1st 3 months and 7.2% overall during median follow-up 3 years	Older age, male, Killip class, diastolic BP, heart rate, history of angina	New-onset AF predicts increased 30 day mortality and stroke as well as long term mortality
Jabre et al [31]	3220	Acute MI patients	New-onset AF 22.6% over a 6.6 year mean follow-up	Older age, female sex, hypertension, diabetes, renal impairment, anterior MI, lower LVEF, higher Killip class	AF independently predicts adverse outcome (and the highest risk is due to AF occurring >30 days post-MI
Jons et al (CARISMA study investigators) [36]	271	Post-MI patients with LVEF≤40% and implantable cardiac monitor	New-onset AF 39.3% during 2 year follow-up		New-onset AF independently predicted major adverse cardiovascular events

thrombolytic studies have been extensively reviewed before.[1,4] Hence this review shall mainly focus upon AF complicating the modern management of MI in the 21st century. The incidence of AF complicating MI has been largely similar among pre-thrombolytic (6-23%) (reviewed in[1,4]) and thrombolytic studies (6.8-21%).[1,4,5,6,7,8] Studies published in the last decade have been detailed in Table 1.Wong et al from the GUSTO 3 Trial reported a 6.5% incidence of new-onset AF or flutter amongst about 14,000 patients whilst evaluating the outcomes of 2 different thrombolytic drugs.[5] One of the highest incidences of new-onset AF (11.3%) amongst these studies was noted by Rathore et al from the Co-operative Cardiovascular Project, the incidence being understandably higher as they analysed the significance of AF in about 107,000 elderly patients (age>65 years) with acute MI.[6] GISSI-3 trial investigators quoted a 7.8% incidence of AF or atrial flutter amongst nearly 18000 acute MI patients.[7] There is considerable variation in the reported incidence of AF even amongst trials conducted during the same era. This could be due to the varying risk profiles of the populations included, different therapies, and detection methods for AF as well as follow-up duration. For instance, the relatively low incidence of AF reported by the GUSTO 3 trial could have been due to the exclusion of patients who were at high risk of AF (such as those with previous stroke).[9]

There have also been a number of trials that have assessed the efficacy of secondary prevention MI drugs and their influence on post-MI AF. The effects of beta-blockers were described in the CAPRICORN trial (AF incidence in placebo group 5.4% versus that in carvedilol group 2.3%-carvedilol/placebo hazard ratio (HR) of 0.41 (95% confidence interval [CI] 0.25 to 0.68; p = 0.0003).[10] The incidence of AF/flutter was 5.3% during in-hospital monitoring and 21% overall amongst nearly 6700 patients in the TRACE study which studied the efficacy of using trandalopril in post-MI patients.[8] The OPTIMAAL trial (which compared use of captopril or losartan in acute MI patients with LV dysfunction) showed an early AF incidence (<3 months) of 2% and overall incidence after follow-up of 7.2%.[11] Danchin et al reported results in nearly 3400 acute MI patients from early use (<48 hours of presentation) of statin which reduced incidence of new onset AF (overall incidence of AF 4.7%, 3.9% in early statin group and 7% in group who did not receive early statin).[12] These trials (other than the statin trial and TRACE study) enrolled acute MI patients associated with left ventricular dysfunction and some of these trials demonstrated a predictably lower incidence of AF presumably due to a higher use of secondary prevention medications.

Results of trials exploring the significance of AF complicating MI in the PCI era suggest an overall trend towards reduction in incidence of AF (3-12%) in comparison to the pre-thrombolytic and thrombolytic eras [13-19] (Table 1). This is along

expected lines, as primary PCI, being a better reperfusion strategy limits myocardial damage and thereby the incidence of heart failure; both of these factors have been shown to portend AF. The low incidence of AF quoted by Beukema et al who studied nearly 1700 primary PCI patients (AF incidence of 3.3% and 3% pre and 3 hours post-primary PCI respectively), [18] can be explained by the fact that AF incidence post-procedure was calculated based only on an ECG 3 hours post-procedure with no subsequent data on AF incidence. Studies which included both primary PCI and thrombolysis as treatments for STEMI, showed an AF incidence of 12.4 to 13.7% .[2 ,20] There has thus been some decline in the incidence of AF complicating AMI due to improved reperfusion strategies and secondary prevention. However, the extent of the decline seems to be lower than expected and this could be explained by the continued presence of co-morbidities that contribute to AF in MI patients across all treatment eras as well as improved monitoring and detection of the arrhythmia.

Aetiopathogenesis

AF complicating MI is multi-factorial in its aetiopathogenesis. A variety of factors such as haemodynamic disturbance,[6] atrial ischaemia.[21, 22] catecholamine surge or use of sympathomimetic medications,[23] electrolyte imbalance, heart failure, and ventricular remodelling, acute hypoxia, electrolyte disturbances, pericarditis. [24, 25] inflammation [26] and RV infarction – either on their own or in varying combination, have been proposed to initiate AF in the setting of MI.[27-29] Diastolic dysfunction and acute elevation of left atrial pressure that have been shown to accompany MI, have been proposed to be independent factors in potentiating AF in the MI setting.[3, 6, 30] The high(>20%) risk post-discharge recurrence rate of AF with its consequent higher stroke risk[2] could also imply that the peri-MI scenario merely unmasks an underlying predisposition to develop AF.

Table 1 enumerates the various patient co-morbidities and clinical characteristics which are associated with risk of developing AF in the setting of acute MI. Some of the patient characteristics significantly associated with AF include older age, [2 3, 6, 7, 11, 12, 13, 14, 15, 18, 19, 20 ,31, 32, 33 ,34] previous MI [6, 7,35] chronic lung disease,[36] fe,male sex,[2 ,7, 15, 31, 33, 34] hypertension [6 ,7, 15, 31, 32, 34] and diabetes.[7, 16, 19, 31, 33] These studies[3, 30] have also shown that independent clinical predictors of peri-MI AF include higher Killip class, [3 ,5, 6, 7 11, 3, 14, 15, 16, 18, 31, 33, 37] LV ejection fraction, [3, 7, 8, 10, 20, 31] anterior location of MI ,[31] ST elevation MI,[16] lower systolic blood pressure on admission [5, 13] higher heart rate ,[16, 38] creatinine clearance ,[13, 31] poor TIMI flow,[13] left atrial dimension,[3, 36] functional mitral regurgitation[3] and three vessel coronary artery disease [39] But some studies[30] have shown that LV systolic dysfunction as a risk for peri-MI AF is dependant on other variables. Coronary artery disease that affects the atrial branches, has been also shown to be an independent predictor of AF. [21] One of the largest data sets is from Lopes et al who retrospectively analysed pooled data from 10 clinical trials including about 120,000 acute coronary syndrome patients.[16] Based on this study, older age was the strongest clinical predictor (odds ratio OR=1.72 per 10 years; 95% CI 1.68 to 1.76) followed by heart rate ≥85 bpm (OR=1.29 per 10 bpm; 95% CI 1.26 to 1.32), patients receiving medical care in western Europe (vs North America OR=0.63; 95% CI 0.60 to 0.67; p<0.001), Killip class IV versus class I (OR=1.34; 95% CI 1.03 to 1.74), STEMI versus NSTEMI (OR=1.41; 95% CI 1.32 to 1.52), white race (OR=1.65; 95% CI 1.48 to 1.84) and systolic blood pressure >110 mm Hg (OR=0.93 per 10 mm Hg; 95% CI 0.92 to 0.95). This study also reported that AF patients received lesser secondary prevention drugs such as aspirin and beta-blockers whereas NSTEMI patients with AF received more in-hospital cardiac catheterisation.[16] Analyses from this study also elucidated interesting associations of AF with type of MI (i.e, STEMI versus NSTEMI). STEMI patients demonstrated an increase risk of AF in those with increased time (>4 hours) from symptom-onset to treatment initiation and decreased risk associated with increasing systolic blood pressures below 110 mm Hg. NSTEMI patients as opposed to STEMI patients, who were female or had previous cardiac bypass, demonstrated a stronger likelihood of not developing AF in this study. NSTEMI patients with worse Killip class and more chronic heart failure, showed an increased tendency to develop AF; but these associations were not seen in STEMI patients. Another large data set of AF patients

(about 23,500 patients) in an elderly (>65 years) MI population, is obtained from the Co-operative Cardiovascular Project in which Killip Class 4 is found to be the strongest independent risk-predictor for AF [odds ratio (OR) 1.58; 95% CI 1.45–1.73].[6] In a prospective study of about 3,400 patients with acute coronary syndrome, Lau et al studied in detail the differences between chronic AF and new-onset AF.[40] In this study, new onset AF was more associated with STEMI, NSTEMI with high risk, higher peak creatinine kinase levels and left main coronary disease, thereby also leading to a higher incidence of coronary bypass surgery. Surprisingly, however patients with any AF had a lower incidence of coronary angiography even if associated with STEMI. A similar feature was also found in results from the VALIANT trial in which AF patients were less likely to be treated with beta-blockers or thrombolytic agents and the OPTIMAAL trial where these patients received less aspirin, thrombolytics or statins. [11, 41] This is likely to have been due to the associated significant co-morbidities and adverse hemodynamic markers in these patients that could have precluded these treatments.

The clinical risk predictors for AF in contemporary PCI trial have been largely similar to those in previous treatment eras. This is likely to indicate that AF occurrence although reduced by improved reperfusion strategies to some extent, is still dependant on the associated co-morbidities as well as the consequences of MI.

AF-Related Morbidity And Mortality

New onset of AF has been shown to lead to increased in-hospital mortality [6, 8, 38] as well as increased post-discharge deaths.These include medium-term mortality risk up to 1 month,[6 11] three months [15] as well as in the long term (up to 3 years).[8, 11, 14, 20, 42] In addition, it also adds to the morbidity burden by contributing to heart failure,[6, 14, 15] and stroke events.[2, 6, 11, 15, 34] Lopes et al reported in their study of about 120,000 patients with acute coronary syndrome(including both STEMI and NSTEMI) from a pooled database of 10 clinical trials, demonstrating that AF independently increased both short term as well as long term mortality, strokes and bleeding events, irrespective of the type of MI. [16] In addition to these, AF also increased in-hospital complications such as heart failure, cardiogenic shock, re-infarction, acute mitral regurgitation and hypotension. AF conferred a higher risk in NSTEMI patients (when compared to STEMI patients) for outcome measures such as short-term mortality, short or long-term strokes, MI and bleeding events.[16] This was attributed to the fact that NSTEMI patients were associated with more co-morbidities. The GUSTO 1 trial data demonstrated that in-hospital diagnosis of new onset AF post-MI can also delay discharge whereas OPTIMAAL investigators reported the same in patients with baseline AF as well.[11]
There have however also been several studies,[14, 43,44] that have contradicted some of the above findings. In the PCI era, Kinjo et al.[14] reported from their study of MI patients that whilst AF influenced post-discharge mortality, it did not predict in-hospital mortality. Other studies have also provided results that seem to absolve AF of its status as an independent risk-predictor of post MI mortality and instead shifted the blame on to the co-morbidities that cause AF.[37, 43, 44, 45] However, doubts have been also raised whether the adverse consequences of post-MI AF are related to the complications of MI rather than due to AF itself .[46]

A recent large meta-analysis of 43 studies by Jabre et al including a total of nearly 280,000 patients demonstrated that AF independently confers a 40% increase in mortality in acute MI patients and that this risk prediction is irrespective of the timing of onset of the arrhythmia.[4] Mortality odds ratio was calculated only for those studies which reported odds ratio and 95% CI after multivariate analysis. Mortality odds ratio associated with all AF was 1.46 (95% confidence interval, 1.35 to 1.58; I2=76%; 23 studies); for new onset AF OR was 1.37 (95% confidence interval, 1.26 to 1.49), I2=28%, 9 studies), and for prior AF was 1.28 (95% confidence interval, 1.16 to 1.40; I2=24%; 4 studies). Some of the strengths of this comprehensive meta-analysis include increased power due to the inclusion of large numbers of patients. However, it does suffer from limitations such as comparison of heterogeneous populations across 5 decades with varying risk profiles and management strategies. In summary, whilst there are some disagreements between the various studies in terms of the duration of the mortality risk that AF complicating MI seems to confer, the majority of the available evidence seems to concur that especially new-onset

AF in this setting independently increases mortality risk.

Stroke Risk

There is also significant variation amongst various trials in terms of predicted stroke risk as well follow-up for stroke. Many of the older trials do not provide data regarding stroke incidence in relation to AF complicating MI. Bishara et al have recently reported results from their study of a cohort of about 2400 MI patients in which patients with new-onset transient AF (incidence of 7.2%) were more likely to develop persistent AF at 1 year (22.8% versus 2%).[47] Importantly, these patients also had a significantly higher risk of stroke or TIA (9.2% versus 2.5%), the majority of which occurred within 2 months. Lehto et al from the OPTIMAAL trial, report an increased stroke incidence both in patients with baseline AF as well as new onset AF. In new-onset AF patients, the hazard ratio for 1 month risk 14.6; 95% CI 5.87–36.3, p< 0.001) and including the follow-up period adjusted hazard ratio for stroke was 2.79 (95% CI 1.43–3.68, p < 0.001). This trial enrolled MI patients with LV dysfunction, thus explaining the high risk of stroke in concert with AF. In a study of inferior MI patients with transient AF treated with anti-platelets, Siu et al reported a stroke incidence of 10.2% and 7.5 % respectively during the first and second years of follow-up.[2] Asanin et al analysed the long-term (7 year) stroke risk amongst patients with new onset paroxysmal AF complicating AMI. 48 They found a high AF recurrence rate (41%) within 3 months of hospital discharge which independently predicted the highest risk of stroke incidence during this period. They also found that AF duration of >3.5 hours during the first 48 hours after AMI, was most predictive of stroke risk. The primary PCI study by Mrdovic et al,[13] did not show AF to be an independent predictor of stroke risk at 30 days and a large study of ACS patients reported by Lau et al also did not show an association between AF and stroke risk. 40 This is in contrast to a number of previous studies that have shown that AF in the context of MI, significantly increases stroke risk.[216,34]

There is thus a significant stroke risk from even transient AF lasting a few hours complicating MI. Assessment of stroke risk in these patients therefore plays an important role in deciding antithrombotic strategies as described in expert consensus recommendations outlined below.

Causes of Death

Other modes of death due to AF include heart failure, cardiogenic shock, stroke and re-infarction .[16] A study by Sankaranarayanan et al demonstrated that VF could be one of the possible mechanisms by which post-MI AF increases mortality, particularly in patients with chronic AF which is associated with a greater irregularity of rhythm.[35] The greater irregularity has been postulated to lead to pro-arrhythmic short-long-short sequences.[35]

Mechanisms of Adverse Consequences due to AF

A number of experimental studies (both canine and human) [49, 50 , 51] have elegantly described the adverse pathophysiological consequences on the coronary circulation, thereby elucidating the mechanisms of worsening outcome in the setting of acute myocardial ischaemia. Due to the irregularity of the ventricular rhythm, the increase in myocardial oxygen demand caused by new onset AF is out of proportion to any increase in coronary blood flow.[49] AF also leads to reduced coronary vascular resistance and reduced diastolic coronary blood flow, thereby worsening ischaemia. Cardiac output is also reduced due to loss of atrial contraction, uncontrolled ventricular rates and atrio-ventricular dyssynchrony.[52] The deleterious haemodynamic effects of AF are compounded by its association with co-morbidities such as heart failure.[53]

Timing and Duration of AF

Distinguishing New-Onset AF from Pre-Existing AF

Many studies have analysed any AF in the setting of MI (for instance by classifying as "AF on admission versus "in-hospital AF") without trying to make a true distinction between new-onset and chronic or pre-existent AF.[16, 7, 14, 35, 54] The definition on "new-onset AF" has been rather confus-

ing as well as some studies have used this term to describe AF on admission [5] whereas others have used this term to describe AF during hospitalisation only.[7, 14, 19, 31] It is important to attempt to make this distinction as accurately as possible as studies have varied in their results of prognostic implications according to timing of AF (as described in the table). Many studies (including GUSTO 3, TRACE and OPTIMAAL trials) have shown that both chronic AF as well as new onset AF independently increased post-MI mortality and stroke-risk.[5, 6 11, 20, 35] Investigators from the OPTIMAAL trial of nearly 5,500 acute MI patients with LV dysfunction reported that both patients with AF at baseline (incidence 12%) and those with new-onset AF (incidence 7.2%) demonstrated an increased risk of death and stroke. [11] However, other studies have led\to contrasting results as below. In a prospective study of about 3,400 MI patients (including both STEMI and NSTEMI) by Lau et al, only new onset AF (incidence 4.4%) led to poor in-hospital outcomes (new onset heart failure, re-infarction, death, acute renal impairment and major bleeding episodes), whereas only chronic AF patients (incidence 11.4%) had worse long-term mortality.[40] New onset AF was more frequent in STEMI patients and more frequently associated with left main stem coronary disease. Length of in-hospital stay was only significantly prolonged amongst the new-onset AF group. Surprisingly neither type of AF significantly increased short term or 1 year stroke risk despite a <41% use of anticoagulation in this study. Maagh et al reported results albeit in a small study that further contradicted the above by showing that chronic AF independently predicted worse short term mortality whereas new onset AF did not.[33] They attributed this to the fact that chronic AF was associated with worse co-morbidities. A study by Sankaranarayanan et al showed in their study that chronic AF was an independent predictor of in-hospital VF whereas new-onset AF was not, as chronic AF was associated with greater irregularity of rhythm.[35] The increased propensity for VF could thus be one of the additional mechanisms whereby chronic AF increases post-MI mortality in comparison to new onset AF.

A study of AF patients post-primary PCI reported recently by Mrdovic et al, showed that new onset AF independently predicted increased one month mortality.[13] This is in contrast to another primary PCI study [15] which showed that AF independently influenced 3 month, but not 1 month mortality. AF duration lasting longer than >30 seconds has been shown to be associated with major adverse cardiovascular events as opposed to those events lasting <30 seconds or the actual number of AF episodes. 36 This is in contrast to stroke risk which is significantly increased by AF of duration≥ 3.5 hours. 48

Early AF Versus Late AF

Differing mechanisms have been deemed to account for the varying manifestation of the timing of new onset AF in the setting of MI and this could also account for the different risks imposed.[22, 55] For instance, Hod et al have proposed that early AF is predominantly caused by acute left atrial ischaemia.[22] Majority of new-onset AF post-MI has been shown to occur within four days of index MI.[15] The definition of "early" and "late-onset" AF has varied considerably amongst various studies.. Jabre et al sub-classified AF in their large population-based study of post-MI AF, into early onset (<2days), intermediate onset (3-30 days) and late onset (>30 days).[31] This study showed that early AF, in comparison with late-onset AF was shown to be more associated with co-morbidities such as older age, female sex, lower body mass index, higher Killip class and chronic kidney disease. Whilst AF at any time after MI was shown to increase mortality risk by the findings of Jabre et al, importantly the timing of AF conferred markedly differing mortality risks. The mortality risks due to early and intermediate onset AF were largely similar but AF occurring more than a month after MI led to 5 fold increased risk of death.[31] AF occurring more than a month after the index MI can lead to a 2.7 times hazard of death in comparison to that occurring within a month which has a mortality hazard of less than 2 fold.[31] Another study by Asanin et al reported that only late onset AF (>24 hours after MI presentation) was independently related to long-term mortality[45] The GUSTO trials defined late-onset AF as that occurring 48 hours after symptom-onset. The CARISMA sub-study [36] excluded patients with chronic AF or known history of paroxysmal AF at time of index MI, whereas other studies included these types of AF as well. The CARISMA sub-study also excluded patients in whom AF was detected by ECG but

missed by the loop recorder.

Investigations To Predict Risk for AF

Investigations which can help predict risk of developing AF in the setting of acute MI are important as these can aid crucial management decisions such as anti-thrombotics. Atrial infarction complicating myocardial infarction, has an incidence varying from 0.7% to 52% and is complicated by AF in 33 to 64% patients.[56] Investigators from the APEX-AMI trial showed that abnormal P wave morphology on baseline surface ECG (M,W, irregular or notched patterns- which was previously identified by Liu et al as a minor criterion to identify atrial infarction [57] independently predicted new-onset AF as well as 90 day mortality .[56] In a small trial of 130 AMI patients (STMI and NSTEMI), Rosiak et al [58] have previously demonstrated that P wave duration>125ms measured using signal averaged ECG, also independently predicts new-onset AF (a finding that is disputed by results from the APEX-AMI trial. [56] Echocardiography is a useful tool to identify causal factors and triggers of AF in the post-MI period. Impaired left ventricular ejection fraction is a well known risk-predictor for AF although this has been questioned.[30] Restrictive filling pattern which is a marker of advanced diastolic impairment (identified by early and late trans-mitral velocities of mitral inflow, their ratio, and E-wave deceleration time), has been identified in many studies to independently predict risk for AF.[30, 59, 60, 60] Functional mitral regurgitation and increased left atrial volume have also been shown to be independent triggers for AF.[3,61] Measurement of total atrial conduction time using tissue Doppler imaging is another echo parameter that helps to assess for risk of AF.[61] Novel risk predictors identified in the CARISMA sub-study include markers of autonomic dysfunction such as heart rate variability and heart rate turbulence which have been shown to independently increase risk for AF post-MI.[62]

Detection and Duration of Monitoring

Studies have varied extensively in terms of the durations of monitoring for detection of AF. Majority of the studies have continuously monitored only during the in-hospital stay and assessed for AF during follow-up using ECGs. However, CARISMA study investigators [36] used an implantable loop monitor (albeit only in post-MI patients with LVEF≤40%) to detect AF for up to 2 years. This method has been shown to reliably detect nearly three-quarters of the AF episodes during the follow-up period.[63] Symptoms alone have been shown to be an unreliable marker of AF as most AF episodes (>90%) are usually asymptomatic [36]. This could have led to the under-estimation of the incidence of post-discharge AF in studies relying only on 12 lead ECG during follow-up to detect AF. [11, 64] The low incidence of AF (5 to 7% in these studies contrast with the incidence of AF in about a third of the study population seen in the CARISMA study which used continuous monitoring to detect AF.[36] Other than the obvious cost-benefit issues, use of continuous monitoring with loop recorders is not without limitations. Whilst their pick-up rate for arrhythmias is known to be high in comparison to intermittent monitoring or symptom-based monitoring,[65] this is also dependant on factors such as the settings for the detection window and memory capacity of the device. Use of an implantable loop recorder to detect post-MI AF such as in the CARISMA sub-study [36] showed that the highest risk for AF incidence was during the first 2 months (with up to a third of cases having been identified within the first 6 weeks) after the event, followed by a steady decrease in risk which ultimately reached a plateau between one to two years. Whilst continuous monitoring of all post-MI patients to detect AF is clearly not feasible, this could be contemplated especially in high-risk patients during the first 6 weeks post-discharge and likely to prove cost-effective.

Management

Management of post MI AF has been in many respects as variant and idiosyncratic as the multi-factorial aetio-pathogenesis of the condition itself.[66 67] To a large extent, this has been due to the confusion regarding whether AF is an independent harbinger of poor outcome or merely a marker of severe co-morbidities in extremely sick patients. The first priority especially in STEMI patients should be to urgently achieve TIMI 3 blood flow in the infarct-related artery and thereby limit myocardial damage. As high ventricular rates are detrimental to the haemodynamic status of these patients by increas-

ing myocardial oxygen demand, attempts should also be made to reduce the ventricular rate using beta-blockers. Early use of routine secondary prevention drugs for MI such as beta-blockers, ACE inhibitors and statins also reduce the incidence of new-onset AF in the peri-MI setting. [10, 12, 32,68] Meticulous attention should also be directed towards restoration of stable haemodynamic status as well as electrolyte balance (i e correction of serum potassium and magnesium). A retrospective analysis of the VALIANT trial by Nilsson et al, which compared rate versus rhythm control strategies to treat post-MI AF, showed that a rhythm control strategy (using intravenous amiodarone) led to a higher mortality up to 45 days post-MI (HR 1.9, 95% CI 1.2 to 3.0). [41] Use of amiodarone in an elderly population with AF following MI, has also previously been shown to portend a trend towards increased 1 year mortality. [42] There is therefore not enough evidence to justify use of amiodarone for a rhythm control strategy in this setting. The GUSTO 3 trial showed that use of sotalol predicted a trend towards improved 3 months and 1 year mortality whereas use of amiodarone or electrical cardioversion did not. [54] Dronedarone is recommended as one of the first line drugs to treat AF in presence of coronary artery disease but there is a paucity of trials exploring its use in the treatment of peri-infarct AF. While its use in presence of heart failure is contraindicated, there is also evidence in animal experiments of increased mortality due to brady-arrhythmias secondary to the negative inotropic action of dronedarone. [69] As AF in the context of MI is frequently paroxysmal and complicated by recurrences, DC cardioversion probably has a minor role in stable patients as it does not predict sinus rhythm upon discharge. [54] However urgent DC cardioversion should be considered in patients with AF and haemodynamic compromise in line with Adult Life Support guidelines.

Anti-Thrombotic Therapy

Devising safe as well as effective anti-thrombotic therapy in MI patients with AF especially if requiring PCI, has been a controversial topic due to the complex issue of balancing the risk-benefit ratio (i.e, preventing strokes and stent thrombosis but minimising bleeding complications in doing so). The ACTIVE-W trial illustrated the inferiority of aspirin-clopidogrel combination in comparison to warfarin alone, in terms of stroke-reduction especially in high risk patients. [70] Similarly, anti-platelets alone have been shown to be inferior to warfarin in preventing cerebrovascular ischemicevents.[47]The efficacy of warfarin in reduction of stroke and mortality has been demonstrated in contemporary PCI trials for ACS. [15, 71] However warfarin alone or in combination with aspirin has been shown to be inferior to the aspirin-clopidogrel combination in preventing adverse vascular outcomes and stent thrombosis post-PCI.[72-74] The differing efficacies are due to the different mechanisms of thrombogenesis due to AF (fibrin-rich hypercoagulable state) versus that seen post-PCI in ACS (largely platelet driven thrombogenesis) .[74] Ruiz-Nodar et al retrospectively analysed a series of patients with AF ($CHADS_2$ score≥2 in 69% patients, ≥1 in 93% patients) who required PCI, the indication being ACS in >80% of the study patients.[71] Whilst this study showed significant variation in the type of anti-thrombotic regiment prescribed (dual anti-platelet therapy versus triple therapy or warfarin plus aspirin and clopidogrel), treatment with warfarin on discharge independently decreased major adverse cardiac events and non-significantly increased major bleeding events. The APEX-AMI trial also showed that warfarin on discharge for post-MI AF led to lower 90 day mortality and stroke.[15] However of patients with AF at discharge, less than half receive warfarin[15 75] and less than a third received triple therapy. Patients at highest risk of stroke ($CHADS_2$≥2) were paradoxically least likely to receive warfarin at discharge in this trial.

"Triple therapy" usually refers to the combination of aspirin, clopidogrel and warfarin and in comparison to aspirin alone, this combination led to four-times higher bleeding risk in a retrospective analysis of Danish registry data.[76] A meta-analysis of 10 studies has shown that this combination leads to a high incidence of major bleeding episodes (2.2% at 1 month increasing to 4-12% at 1 year) thereby causing significant morbidity and mortality.[77] The HORIZONS-AMI trial reported 30 day and 1 year outcomes of approximately 4% out of 3320 primary PCI who required triple therapy.[78] This showed that the ischemic outcomes were similar between the dual anti-platelet versus triple

Table 2

Recommendations by European Consensus Group [75]
Patients with ACS, AF and low/intermediate bleeding risk (bare metal /drug eluting stent) • Until 6 months- triple therapy (warfarin (INR 2.0–2.5) + aspirin ≥100 mg/day + clopidogrel 75 mg/day) • 6-12 months – warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day* (or aspirin 100 mg/day and then • Lifelong – (INR 2.0–3.0) alone
Patients with ACS, AF and high bleeding risk (bare metal stent only) • Until 4 weeks – triple therapy of warfarin (INR 2.0–2.5) + aspirin ≥100 mg/day +clopidogrel 75 mg/day • 1-12 months -combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day*(or aspirin 100 mg/day); mg/day) and then • lifelong: warfarin (INR 2.0–3.0) alone.
Recommendations of North American Consensus Group [77]
Low stroke risk ($CHADS_2$=0) and any stent thrombosis or bleeding risk • BMS – Dual antiplatelet therapy with aspirin and clopidogrel or prasugrel for one month and preferably for 12 months • DES – Dual antiplatelet therapy with aspirin and clopidogrel or prasugrel for 12 months or longer
Moderate/high stroke risk ($CHADS_2$>1), low stent thrombosis risk and low bleeding risk • BMS – Triple therapy for at least one month then oral anticoagulation (OAC) + single antiplatelet (AP) for 12 months • DES – Triple therapy for at least six months then OAC +single AP for 12 months
Moderate/high stroke risk and high stent thrombosis risk and low bleeding risk • BMS -Triple therapy for at least six months then OAC +single AP for 12 months • DES – Triple therapy for 12 months

therapy sub-groups but triple therapy independently predicted higher 30 day as well as 1 year incidence of major bleeding, minor bleeding as well as a greater hazard of stroke. The risks of bleeding secondary to triple therapy are higher in patients with co-morbidities such as advanced age, renal or hepatic impairment. Fosbol et al reported that amongst NSTEMI patients with AF aged>65 years from the CRUSADE Registry, the triple therapy sub-group experienced a 4.1% incidence of major bleeding at 30 days and 14.9% incidence of hospitalisation due to bleeding at 1 year.[79] In addition, cardiovascular outcomes were also similar between the triple therapy subgroup and the sub-group on aspirin alone. The rather surprising lack of benefit from triple therapy on cardiovascular outcome in the HORIONS-AMI trial and CRUSADE Registry was contrasted by the significantly lower mortality and stroke incidence seen in the triple therapy sub-group in the APEX-AMI trial.[15] Use of scoring systems such as HAS-BLED score ((Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly- Score≥3 considered to represent high risk of bleeding) which allow an objective assessment of bleeding risk prior to initiation of anti-coagulation, can also guide therapy in post-MI AF.[80] Bare metal stents should therefore be used whenever possible. This is paramount as most of the co-morbidities that portend an increased risk of AF, also predict an increased bleeding risk. Limiting the duration of triple therapy appropriately is crucial to minimise major bleeding events. Publications of a European Consensus Document by Lip et al [74] and a North American Consensus document by Faxon et al[81] have offered recommendations regarding management of anti-thrombotic therapies in patients with ACS and AF undergoing PCI. In brief, the recommendations are listed in Table 2.

The publication of expert opinion in the form of these 2 consensus documents, has attempted to clarify what has been a thorny subject for many years. However, several newer generation anticoagulant alternatives to warfarin such as dabigatran, rivaroxaban and apixaban, have been studied more recently. They possess obvious advantages over warfarin such as lack of need for coagulation monitoring or frequent dose adjustments, reduced interactions with other medications or food and also lower risk of intra-cranial haemorrhage. These newer anticoagulants have also been studied (as described below) in placebo controlled phase II and phase III trials including patients with STEMI and NSTEMI; majority of these patients were also treated with dual anti-platelet therapy with aspirin and clopidogrel. Dabigatran (a direct thrombin inhibitor) was studied in the RE-DEEM Trial which was a double blinded placebo controlled dose escalation phase II trial and this trial showed a clinically significant bleeding events (gastrointestinal bleeds and epistaxis) with the currently approved doses for AF (110 mg and 150 mg BD).[82] Rivaroxaban (a Factor Xa inhibitor), was studied in compari-

son to placebo in phase II (ATLAS)[83] and phase III trials (ATLAS-2)[84 85] and showed a significant reduction in cardiovascular death, myocardial infarction or stroke but also a significant increase in non-fatal TIMI major bleeding. Apixaban (another Factor Xa inhibitor) didn't show improved efficacy in the phase III trial but also showed a significant increase in major bleeding including intracranial haemorrhage and fatal bleeds [86]. The role of these newer anticoagulants in managing AF complicating MI remains far from established especially as they do not have specific anti-dotes for reversal in case of significant bleeding. Further complicating matters is the recent emergence of more efficacious anti-platelets such as prasugrel and ticagrelor (P2Y12 inhibitors) which are recommended by the European Society of Cardiology guidelines as anti-platelets of choice for NSTEMI along with aspirin and Class1B recommendations for STEMI and NSTEMI as per ACC/AHA guidelines.[87 88] There is a glaring lack of data for the use of newer anti-platelets as well as the newer anticoagulants as a part of "triple therapy". In summary, whilst newer anticoagulant alternatives to warfarin are clearly advantageous and approved for the management of non-valvular AF, their role in the management of AF complicating MI is uncertain at the moment and requires further large scale studies especially in combination with the newer anti-platelet agents such as prasugrel and ticagrelor.

Conclusions

Despite achieving remarkable strides in MI management, AF remains a significant complication in MI with wide ranging adverse consequences. Whilst the prognostic significance of AF complicating MI has been controversial for many the last few decades, review of the majority of the evidence especially from new studies, leads us to the conclusion that AF is indeed an independent predictor of poor prognosis. This necessitates that all attempts be made to identify this condition and manage it appropriately to prevent the poor outcomes associated with it. Anti-thrombotics are the most crucial treatment that can alter the adverse prognosis due to post-MI AF. Expert opinion in the form of consensus documents recommending anti-thrombotic management strategies such as triple therapy, have set the stage to standardise AF treatment in MI. However, triple therapy can be associated with significant bleeding risks which seem to overweigh any benefits in the elderly and therefore a dual anti-thrombotic strategy (anticoagulant+anti-platelet) may be more appropriate in this population. It is also important therefore to use bare metal stents where appropriate to minimise the duration of triple therapy There is a need to monitor and minimise bleeding complications amongst other patient sub-groups by using bleeding risk prediction scores such as the HAS-BLED score in order to guide risks versus benefits of anti-thrombotic strategy. With the advent of newer anticoagulants and anti-platelets in the setting of MI, there is a pressing need for further randomised controlled trials to assess their role in the anti-thrombotic strategy for post-MI AF.

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