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REVIEW

Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications

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Atrial fibrillation (AF), the most commonly encountered clinical arrhythmia, often complicates acute myocardial infarction (AMI) with an incidence between 6 and 21%. Predictors of the arrhythmia in the setting of AMI include advanced age, heart failure symptoms, and depressed left ventricular function. The bulk of evidence demonstrates that AF in patients hospitalized for AMI has serious adverse prognostic implications regarding in-hospital, but also long-term mortality. This seems to apply for all patient populations studied without significant differences related to the treatment of AMI (i.e. no reperfusion therapy vs. thrombolysis vs. percutaneous coronary intervention). Mortality is particularly high in patients who have congestive heart failure and/or a reduced left ventricular ejection fraction. Finally, there are persuasive data indicating that AF complicating AMI not only increases the risk for ischaemic stroke during hospitalization but also during follow-up. This seems to apply also for transient AF which has reversed back to sinus rhythm at the time of discharge. These observations emphasize the need for prospective studies evaluating optimal therapeutic approaches for patients with AMI complicated by AF.

Keywords Atrial fibrillation • Acute myocardial infarction • Acute coronary syndrome • Anticoagulation

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in patients with and without structural heart disease with an increasing incidence mainly due to the aging population.[1–4] Data from large epidemiological studies have clearly demonstrated that AF is associated with an increase in mortality and morbidity.[5,6] The combination of AF and congestive heart failure is particularly ominous in that it appears that the development of either condition has a marked detrimental impact upon the mortality of the other.[7–9]

Atrial fibrillation can also complicate acute coronary syndromes, particularly acute ST-segment elevation myocardial infarction (AMI). In this clinical setting, the occurrence of AF is of particular importance since rapid and irregular ventricular rates during the arrhythmia may cause further impairment of the coronary circulation and left ventricular function in addition to the adverse consequences of neurohormonal activation. Atrial fibrillation is associated with a high mortality which may be due in part to the development of AF as a surrogate or marker of heart failure, elevated filling pressures and atrial volume overload.[10]

Atrial fibrillation may also give rise to the occurrence of severe ventricular tachyarrhythmias[11,12] perhaps due to ischaemia, varying R–R intervals, or as a result of activation of the sympathetic nervous system. Despite these clinically important considerations, there are no firm therapeutic guidelines which specifically address critically important issues such as the role of antiarrhythmic drugs, pharmacological rate control, and prevention of thrombo-embolism in patients with AF complicating AMI.

This review, therefore, aims to systematically evaluate the published literature regarding the incidence, clinical features, and implications of AF in the setting of AMI.

Search strategy

A Medline search of the English literature published between 1980 and 2007 was performed using the search terms 'atrial fibrillation and acute myocardial infarction'; 'atrial fibrillation, acute myocardial infarction and treatment', and 'atrial fibrillation, acute myocardial infarction and anticoagulation'. Abstracts of identified papers were reviewed for appropriateness. Reference lists of articles

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Table 1 Studies on AF complicating AMI

Author	Publication date	Patients included	Study characteristics
Behar[39]	1992	5839	Sprint Registry, evaluation of Nifedipine after AMI, analysis of patients with chronic AF.
Behar[20]	1992	5803	Sprint Registry, evaluation of Nifedipine after AMI, analysis of patients with paroxysmal AF.
Madias[37]	1996	517	Prospective study, trandolapril vs. placebo, inclusion 1990–92, sub analysis on AF in AMI.
Crenshaw[19]	1997	40 891	GUSTO I, prospective study on thrombolysis in AMI, streptokinase vs. TPA, subanalysis on AF.
Eldar[18]	1998	2866	Prospective trial in the thrombolytic era vs. retrospective data from pre-thrombolytic era on AF in AMI.
Pedersen[33]	1999	6676	TRACE, prospective study on trandolapril vs. placebo in AMI, inclusion 1990–92, subanalysis on AF and Aflutter.
Rathore[10]	2000	106 780	Retrospective data analysis, inclusion1994–96, Medicare benefitians aged ≥ 65 years with AMI.
Wong[17]	2000	13 858	GUSTO III, prospective trial on reperfusion strategies after AMI, subanalysis on AF.
Pizzetti[28]	2001	17 944	GISSI III, prospective rial, ACE-inhibitors vs. Nitrates in otherwise optimal treated patients after AMI.
Wong [56]	2002	13 858	GUSTO III, prospective trial on reperfusion strategies and antiarrhythmic AF management after AMI.
Goldberg[21]	2002	2596	Retrospective analysis, inclusion 1990–97, comparison of treatment and outcome changes after AMI and AF.
Kinjo[22]	2003	2475	OACIS, prospective study on AF after AMI, all patients were treated with PCI.
Lehto[34]	2005	5477	OPTIMAAL, prospective study on losartan vs. captopril after AMI with LV-dysfunction.
Pedersen[43]	2005	6676	TRACE CHF, prospective study on trandolapril vs. placebo in AMI, subanalysis concerning LV-EF.
Stenestrand[46]	2005	82 565	RIKS-HIA, prospective study using registry data, on anticoagulation in patients with AF after AMI, OAC vs. no OAC.
Laurent[41]	2005	1701	RICO, prospective study, comparing NSTEMI and STEMI, outcome and AF.
McMurray[35]	2005	1959	Capricorn, patients with AMI and reduced LV-EF, carvedilol vs. placebo.
Pedersen[44]	2006	6676	TRACE SCD, prospective study on trandolapril vs. placebo in AMI, subanalysis on mode of death in AF patients.
Fuster[49]	2006		ACC/AHA/ESC guidelines on AF, 2007.
Kober[36]	2006	14 703	VALIANT, prospective study, AMI patients with LVSD and/or heart failure, valsartan vs. placebo, subanalysis on AF.
Siu[40]	2007	431	Retrospective single-centre study, patients with STEMI and normal LVEF, stroke risk evaluation.

AF, atrial fibrillation; AMI, acute myocardial infarction.

were reviewed for additional papers. Data were extracted from original papers published in peer reviewed journals. A total of 20 publications dealing specifically with AF in the setting of AMI were found and constitute the basis of this report. Classification of AMI varied between the studies including criteria such as: ST-segment elevation, CK and CK-MB elevations, typical clinical findings in combination with coronary angiography (*Table 1*).

Incidence of atrial fibrillation in acute myocardial infarction

Over the last three decades, treatment modalities for patients suffering from AMI have been revolutionized by the widespread application of reperfusion therapy with fibrinolytic agents and the rapidly expanding role of primary percutaneous coronary intervention (PCI). The latter is now considered the gold standard of therapy for AMI for those centres with the requisite facilities, logistics, and expertise, but in other areas in which transport delays are a significant factor, the initial preferred therapy is thrombolysis followed by transfer.[13–16] In addition to the development of reperfusion treatments, concomitant drug therapy during the acute phase of AMI has also substantially changed (i.e. wide-spread early administration of β-blockers and ACE-and AT II-inhibitors, and aldosterone antagonists). In the thrombolytic era, the incidence of AF in patients admitted to hospital with AMI varied between 6.8 and 21%.[10,17–20] For instance, in the GUSTO I trial[19] which included 40 981 patients with AMI eligible for thrombolysis, an AF incidence of 10.4% was reported. In a prospective nation-wide survey conducted in the thrombolytic era, Eldar *et al.*[18] reported a 9.8% incidence of paroxysmal AF in a consecutive series of 2866 patients. Wong *et al.*[17] presented data from the GUSTO III study comparing two thrombolytic regiments and found an AF incidence of 6.8%. Goldberg *et al.*[21] and associates conducted a longitudinal study of 2596 patients with an initial AMI and no previous AF. Between 1990 and 1997, the incidence of AF complicating AMI decreased from 18% in 1990 to 11% in 1997, probably as a result of improved therapy including more wide-spread use of thrombolysis. Comparable AF incidences were found in AMI patients undergoing primary PCI. For instance, Kinjo *et al.*[22] published data from the OACIS study which included 2475 patients that were treated with PCI within 24 h. In this study, AF occurred in 12% of patients.

The Cooperative Cardiovascular Project specifically looked at the incidence of AF in elderly patients suffering from AMI.[10] Not unexpectedly, there was a high incidence of AF in this patient group according to a systematic review of records of 106 780 Medicare beneficiaries over the age of 64 years who were treated for AMI between 1994 and 1996.[10] A total of 22.1% of these patients had AF with almost half of the patients developing AF during their hospital stay and the other half presenting already with AF at admission. This high incidence of AF in older AMI patients is consistent with a generally higher prevalence of AF in elderly individuals as documented by several epidemiological studies.[23]

In the last decade, several randomized clinical trials were conducted which evaluated the effects of ACE or AT II-inhibitors on mortality and morbidity in patients with AMI.[24–28] The use of these drugs has previously been found to be associated with a reduction in AF in patients with different cardiovascular diseases.[29–32] In accordance with these findings, there was a lower incidence of AF complicating AMI in the respective randomized trials. For instance, in the TRACE study which compared the use of trandolapril vs. placebo after AMI in 6.676 patients, a 5.3% incidence of AF was found during the initial hospitalization for AMI.[33] An even lower incidence was reported in the OPTIMAAL trial.[34] This trial was performed between 1999 and 2002 and compared the ACE-inhibitor captopril to the AT II antagonist losartan in patients with AMI and congestive heart failure or impaired LVEF. In the first 3 months after AMI and randomization, the incidence of AF was 2% with a subsequent increase to 7.2% during the follow-up period of 3 years. It is likely that the majority of these studies underestimated the true AF incidence since the diagnosis of AF was usually based on a routine ECG, and shorter less symptomatic AF episodes might have been missed. In the CAPRICORN trial, the incidence of AF complicating AMI could be reduced from 5.4 to 2.3% by administering the β-blocker carvedilol (HR 0.41, 95% CI 0.25–0.68, $P = 0.0003$).[35]

In summary, therefore, an AF incidence between 2.3 and 21% complicating AMI has been reported (*Table 2*). The wide-spread use of interventional coronary revascularization (PCI), especially during the acute phase, has been associated with a notable decline in the AF incidence. Not unexpectedly, trials evaluating the effects of ACE, AT II-inhibitors, or β-blockers on mortality and morbidity in patients with AMI reported the lowest incidence rates of AF in the setting of AMI but the major impact of this pharmacological therapy was upon the late development of AF. As our population ages, one can expect that AF will remain a frequent and troublesome complication of AMI.

Clinical variables associated with the development of atrial fibrillation

A number of studies evaluated the clinical characteristics of patients in whom AMI was associated with the occurrence of AF. The largest data set was derived from the Cooperative Cardiovascular Project.[10] Multivariate modelling indicated that advanced heart failure (Killip class IV) was the most significant predictor of the development of AF [odds ratio (OR) 1.58; 95% CI 1.45–1.73]. Other significant predictors included elevated admission heart rate (OR 1.13, 95% CI 1.12–1.13) (probably a surrogate of left-ventricular dysfunction and impaired haemodynamics) and advanced age (OR 1.17, 95% CI 1.16–1.18). Similar findings were reported from the GUSTO I trial, a thrombolysis trial involving almost 40 000 patients.[19] Again, the strongest predictors for the development of AF were the presence of heart failure symptoms on arrival (Killip class IV vs. Killip class I) and increasing age with ORs of 3.28 (95% CI 2.28–4.71) and 3.2 (95% CI 2.99–3.43), respectively. Comparable observations were made in the recently published VALIANT study in 14 703 individuals with AMI.[36] Patients with AF were older, had more heart failure, and received β-blockers and thrombolytics less often than patients in sinus rhythm, perhaps as a result of the presence of increased comorbidities and the severity of underlying left-ventricular dysfunction.

Similar risk predictors for the development of AF were found in more contemporary patient cohorts undergoing PCI for therapy of AMI. For example, data from the prospective Osaka Acute Coronary Insufficiency Study[22] demonstrated that the highest risk for AF development was an admission heart rate $\geq$100/min (OR 3.0, 95% CI 1.94–4.64), Killip class IV (OR 2.06, 95%1.07–3.94), male gender (OR 1.89, 95% 1.23–2.90), and patient age (OR of 1.06, 95% 1.04–1.07).

Besides these risk predictors, other studies identified additional clinical characteristics to be associated with the occurrence of AF. Data from the GUSTO III trial indicated that the use of sotalol (OR 3.5, 95% CI 2.6–6.8) or of class 1 antiarrhythmic drugs (OR 2.4, 95% CI 1.3–4.7) during the 2 weeks before an AMI were associated with in-hospital documentation of AF.[17] The study report does not specify the reasons for antiarrhythmic drug therapy but there is a high likelihood that pre-existing AF was the major reason. The presence of left-ventricular hypertrophy was also described as a significant predictor for the development of AF in AMI (OR 2.3, 95% CI 1.65–2.96).[37] Regarding the magnitude of serum creatine phosphokinase elevation as a risk factor for the development of AF, divergent findings have been reported.[37–39] In a very recently published single-centre study no significant differences in the development of AF were observed for different reperfusion regimens (i.e. PCI vs. thrombolysis).[40] The RICO study compared the incidence of AF in AMI with and without ST-segment elevation (STEMI and NSTEMI) in 1701 patients.[41] There was no difference concerning the incidence of AF between both patient groups (7.6 vs. 7.7%, $P = 0.334$).

In essence, predictors of AF in the setting of AMI include increased age, presence of heart failure symptoms, higher heart rates at admission, and left ventricular dysfunction (*Table 2*). These risk factors have been described independently of the type of reperfusion therapy (i.e. none, thrombolysis, PCI). Thus, even with contemporary mechanical reperfusion therapy, AF continues to occur most frequently in those patients with AMI who are particularly at high risk.

Prognostic implications

In-hospital mortality

In the general population, AF has been demonstrated to be associated with increased morbidity and mortality.[5] This is to some

Table 2 Incidence and predictors of AF after AMI

Author/Study	Publication year	AF—incidence after AMI (%)	Predictors of AF in AMI	Treatment modality of AMI
Behar/Sprint Prognosis[20]	1992	9.9	Age >70 years ($P < 0.01$), female gender ($P < 0.01$), diabetes mellitus ($P = 0.01$), CHF on admission ($P < 0.01$)	n.a.
Madias[37]	1996	11.2	Higher age (OR 1.08, 95% CI 1.02–1.06), left ventricular hypertrophy (OR 2.30, 95% CI 1.65–2.96)	n.a.
Crenshaw/GUSTO I[19]	1997	7.9	Older age, increased heart ate, higher Killip class, lower systolic blood pressure	Thrombolysis
Eldar/Sprint[18]	1998	8.9	Age >70 years ($P < 0.01$), female gender ($P < 0.01$), diabetes mellitus ($P = 0.01$), CHF on admission ($P < 0.01$)	Thrombolysis vs. no reperfusion Rx
Pedersen/TRACE[33]	1999	15	Age, female gender, hypertension, diabetes, prior CHF, smoking, no thrombolysis	80% thrombolysis
Rathore[10]	2000	11.3	Age, female gender, hypertension, diabetes, prior AMI or CHF, higher Killip at enrolment	n.a.
Wong/GUSTO III[17]	2000	6	Higher age, female gender, hypertension, diabetes mellitus, higher Killip class, CHF	Thrombolysis
Pizzetti/GISSI III[28]	2001	6.1	Female gender ($P < 0.001$), age >70 years ($P < 0.001$), Killip class >2 ($P < 0.001$), higher heart rate ($P < 0.001$), hypertension ($P < 0.001$), diabetes ($P < 0.01$)	Thrombolysis
Goldberg[21]	2002	13.2	Higher age ($P < 0.001$), hypertension ($P < 0.05$), heart failure ($P < 0.001$)	n.a.
Kinjo/OACIS[22]	2003	7.7	Age (OR 1.06, 95% CI 1.04–1.07), male gender (OR 1.89, 95% CI 1.23–2.90), heart rate ≥100/min (OR 3.0, 95% CI 1.94–4.64), Killip class IV (OR 2.06, 95% CI 1.07–3.94)	PCI
Lehto/OPTIMAAL[34]	2005	7.2	Higher age (per 10 years) (HR 1.66, 95% CI 1.48–1.86), male sex (OR 1.65, 95% CI 1.28–2.12), Killip class III (OR 1.92, 95% CI 1.36–2.72)	n.a.
Stenestrand/RIKS-HIA[46]	2005	1.7	n.a.	n.a.
McMurray/CAPRICORN[35]	2005	2.7–5.5	n.a.	45% thrombolysis or PCI
Laurent/RICO[41]	2005	7.6	Higher age ($P < 0.001$), Killip class >2 ($P = 0.01$), higher heart rate ($P < 0.001$)	n.a.
Kober/VALIANT[36]	2006	12.3	Higher age, prior HF, prior angina, prior MI	n.a.
Siu[40]	2007	13.7	Higher age ($P < 0.01$), female gender $P = 0.02$)	70% thrombolysis and 30% PCI

AF, atrial fibrillation; AMI, acute myocardial infarction.

extent a function of the co-morbidities associated with AF since 'lone' AF in younger patients without structural heart disease is not a predictor of an increased mortality.[42] Nonetheless, in patients with AMI, the presence of AF is well documented as a powerful adverse prognostic factor.

In the GUSTO I trial[19] randomly assigning 40 891 patients to thrombolytic therapy with either streptokinase or tPA, patients developing AF had a significantly higher in-hospital mortality. In addition, there was a higher incidence of re-infarction, cardiogenic shock, heart failure, and asystole ($P < 0.001$). The 30 day mortality rate demonstrated an OR of 1.3 (95% CI 1.2–1.4) for any AF and of 1.4 (95% CI 1.3–1.5) for AF developing after admission, whereas it was 1.1 (95% CI 0.88–1.3) in those who were admitted with the arrhythmia. No distinction was made regarding the type of AF, i.e. paroxysmal and persistent/permanent AF.

Additional data from the thrombolytic era were presented by Eldar *et al.*[18] who compared their data with that of a historical cohort of patients treated in the pre-thrombolytic era. In this report only patients with paroxysmal AF were included. Patients with paroxysmal AF had a higher 30 day mortality (OR 1.32, 95% CI 0.92–1.87) compared with patients without the arrhythmia. However, patients with AF had relatively lower 30 day mortality rate when they were treated in the thrombolytic era (OR 0.64, 95% CI 0.44–0.94) in comparison to historical controls.

Similarly, in a large database of elderly patients,[10] the development of AF during hospitalization was associated with a higher mortality rate in hospital (OR 1.39, 95% CI 1.28–1.42) and in the first 30 days (OR 1.31, 95% CI 1.25–1.37). In contrast, patients who were in AF at the time of hospital admission had a mortality rate that was not significantly different from that of patients in sinus rhythm, presumably a reflection of persistent or chronic AF as opposed to AF as a manifestation of acute haemodynamic compromise in the AMI setting.

Kinjo *et al.*[22] presented the data from 2475 patients who were treated with PCI. In this study, significantly more in-hospital events (cardiogenic shock, congestive heart failure, ventricular tachycardia, and ventricular fibrillation) ($P < 0.001$) occurred in patients suffering from AF. However after adjustment for possible confounders such as age, gender, diabetes mellitus, hypertension, prior AMI, prior cerebrovascular disease, systolic blood pressure <100 mmHg, heart rate ≥ 100/min, Killip class IV, LAD, multivessel coronary disease, and final TIMI flow grade 3 (OR 1.42, 95% CI 0.88–2.31), in hospital mortality rates were not significantly increased. In this study, whether the patient presented with AF or developed AF during the period of hospitalization appeared to have a similar adverse impact upon outcomes. These data emphasize that much of the morbidity and the mortality associated with AF in AMI is a function not of the arrhythmia *per se* but 'the company it keeps'.

The OPTIMAAL trial[34] differentiated between patients with AF on admission in whom no statistically significant difference in 30 day mortality was found ($P = 0.27$), and patients who presented in sinus rhythm and developed AF during hospitalization. In the latter group of patients, mortality was significantly higher (OR 3.83, 95% CI 1.97–7.43). Importantly, all patients included in this study had left ventricular dysfunction (measured as LVEF $\leq 40\%$) in addition to the diagnosis of AMI.

In summary, studies on in-hospital mortality strongly suggests that the development of AF along with an AMI is an independent predictor of all cause mortality although there is also evidence that AF is in part a surrogate for cardiac failure.

Mortality during follow-up

There are also data on long-term mortality for patients after AMI complicated by AF. For instance in GUSTO I there was[19] a significantly higher 1 year mortality in patients with AF than in those without the arrhythmia. In contrast to the data on in-hospital mortality there was no difference between patients that presented with AF and those who developed AF during hospitalization.[19]

An OR of 1.33 (95% CI 1.05–1.68) concerning 1 year mortality was reported for patients treated in the thrombolytic era with paroxysmal AF during their hospitalization for AMI compared with patients without the arrhythmia. The comparison with pre-thrombolytic era counterparts and AF demonstrated a significant lower mortality in the thrombolytic era (OR thrombolytic era vs. pre-thrombolytic era 0.69, 95% CI 0.54–0.88).[18] The same authors also observed a significantly higher 1 year mortality in those patients from the thrombolytic era who did not receive thrombolytic treatment (26.9 vs. 44.6%, $P = 0.006$).

When patients were stratified according to whether AF was present on admission or developed during the index AMI hospitalization, the OR for 1 year mortality in those presenting with AF was 1.16 (95% CI 1.11–1.21, $P < 0.05$) in contrast to an OR of 1.51 (95% CI 1.44–1.58, $P < 0.05$) in those who developed AF after admission.[10]

In line with these findings, the 1 year mortality was significantly increased in AMI patients treated by PCI who developed AF after hospital admission (OR 3.04, 95% CI 1.4–7.48). If AF was already present at admission, the arrhythmia carried no prognostic implications.[22]

The OPTIMAAL trial had a particularly long follow-up duration which allowed the investigators to calculate the odds carried by AF in the setting of AMI over 3 years.[34] At baseline, 655/5477 patients (12%) had AF, and 345 (7.2%) developed AF during follow-up. Patients with AF at baseline had an increased mortality risk compared with individuals without the arrhythmia (HR 1.32, 95% CI 1.13–1.56, $P < 0.001$). New-onset AF was associated with increased subsequent 30 day mortality (HR 3.83, 95% CI 1.97–7.43, $P < 0.001$) and over the entire trial period (HR 1.82, 95% CI 1.39–2.39, $P < 0.001$).

A detailed analysis of mortality in AMI patients with and without AF was also derived from the TRACE study, a randomized ACE-inhibitor trial.[43] When patients were classified according to the degree of LVEF impairment, it became obvious that AF was primarily associated with increased in-hospital mortality in heart failure patients. However, long-term mortality was also increased in all subgroups except those with an LVEF ≤ 0.25. This is probably caused by the high mortality rate of subsequent heart failure in any event.

In line with these observations are the findings from the VALIANT study.[36] Among 14 703 patients enrolled, 12 509 were in sinus rhythm, whereas 1812 AMI survivors had AF at randomization (average of 4.9 days after symptom onset). In 339 patients, there was a history of prior AF but these individuals were in

Table 3 Prognostic implication of atrial fibrillation in acute myocardial infarction (in-hospital and long-term)

Study/author	OR [95% CI]	
	In-hospital mortality	Long-term mortality
Behar/Sprint Prognosis[20]	no	1.28 [1.12–1.46]
Madias[37]	no	n.a.
Crenshaw/GUSTO I[19]	1.3 [1.2–1.4]	n.a.
Eldar/Sprint[18]	1.32 [0.92–1.87]	1.33 [1.05–1.68]
Pedersen/TRACE[33]	1.5 [1.2–1.8]	1.3 [1.2–1.4]
Rathore[10]	1.21 [0.99–1.10]	1.34 [1.30–1.39]
Wong/GUSTO III[17]	1.63 [1.31–2.02]	1.64 [1.35–2.01]
Pizzetti/GISSI III[28]	yes	yes
Goldberg[21]	1.71 [1.27–2.31]	1.23 [0.99–1.52]
Kinjo/OACIS[22]	no	1.64 [1.05–2.55]
Lehto/OPTIMAAL[34]	3.83 [1.97–7.43]	1.82 [1.39–2.39]
Pedersen/TRACE CHF[43]	n.a.	n.a.
Stenestrand/RIKS-HIA[46]	n.a.	n.a.
McMurray/ CAPRICORN[35]	n.a.	n.a.
Pedersen/TRACE SCD[44]	n.a.	1.33 [1.19–1.49]
Kober/VALIANT[36]	n.a.	1.32 [1.20–1.45]

sinus rhythm during the index hospitalization. Three year mortality estimates were 20% in patients without AF in the setting of AMI, 37% in those with AF complicating AMI, and 38% in patients with a history AF prior to the AMI.[36] Compared with patients without AF, the multivariable adjusted HR of death was 1.25 (1.03–1.52; $P = 0.03$) for prior AF and 1.32 (1.20–1.45; $P < 0.0001$) for current AF complicating AMI with heart failure or left-ventricular systolic dysfunction.

Taken together, the bulk of evidence demonstrates that AF in patients hospitalized for AMI has serious adverse prognostic implications regarding in-hospital, but also long-term mortality (*Table 3*). This seems to apply for all patient populations studied without significant differences related to the treatment of AMI.

Causes of death

Information on causes of death in AMI patients with and without AF is available for only one trial. The mode of death in patients who have AF in combination with an AMI was studied by Pedersen *et al.*[44] in the TRACE study. This study was confined to survivors of initial hospitalization and the median follow-up period was 32 months during which 34% (1659) patients died. In the AF group, 482/1149 patients (50%) died compared with 1177/4834 patients (30%) of patients with sinus rhythm ($P < 0.001$). All deaths were classified by an event committee with respect to cause and mode. The adjusted risk ratio of AF for total mortality was 1.33 (95% CI 1.19–1.49, $P < 0.001$) and the risk ratio for sudden cardiac death was 1.31 (95% CI 1.07–1.60, $P = 0.009$). The adjusted risk ratio for non-sudden cardiac death was 1.43 (95% CI 1.21–1.70, $P < 0.001$). The authors concluded that the excess mortality in AMI patients with AF is due to a significant increase in sudden and non-sudden cardiac death. Wang *et al.*[9] described a strong relation of AF and CHF on mortality in the Framingham population. These data although independent of the setting of an AMI illustrates that survival in CHF patients is adversely affected when AF occurs.

Impact of atrial fibrillation upon stroke

Patients with AF are at increased risk for thrombo-embolic complications, particularly for stroke. The individual risk for stroke depends on several comorbid conditions and is clinically most often estimated by the $CHADS_2$ score.[45] Data on AF-associated stroke incidence in the population of AM patients is available from only few investigations. For instance, the GUSTO-I trial with 40 891 patients enrolled, a significantly higher rate for in hospital stroke was documented for patients with AF after AMI.[19] The majority of strokes were ischaemic strokes. During hospital stay, 3.1% of AMI patients with AF suffered from a stroke compared with only 1.3% of patients in sinus rhythm ($P = 0.0001$). This study did not provide data on stroke incidence during follow-up or on antithrombotic therapy.

The most complete data regarding the association of AMI, AF, and stroke stems from the OPTIMAAL trial.[34] New onset AF carried an adjusted hazard ratio for stroke of 14.6 (95% CI 5.87–36.3, $P < 0.001$) for the first 30 days after AMI. Over the entire duration of this randomized trial with 3477 included patients, the adjusted hazard ratio for stroke was 2.79 (95% CI 1.43–3.68, $P < 0.001$). In this *post hoc* analysis, no information on antithrombotic therapy during follow-up in patients with and without AF was provided.

In a recently published retrospective analysis, Siu *et al.*[40] reported on 431 consecutive patients with acute inferior MI and preserved LVEF. Transient AF defined as the occurrence of any new-onset AF during AMI with subsequent spontaneous revision to sinus rhythm prior to hospital discharge was observed in 59 patients (13.9%). At 1 year follow-up, the incidence of AF (22 vs. 1.3%; $P < 0.01$) and, importantly, of ischaemic stroke (10.2 vs. 1.8%, $P < 0.01$) was substantially higher in patients with transient AF compared with those without transient AF. Of note, only antiplatelet agents were prescribed in all patients and no oral anticoagulation (OAC) therapy was used.

In summary, therefore, there are persuasive data indicating that AF complicating AMI not only increases the risk for ischaemic stroke during hospitalization but also during follow-up. This seems to apply also for transient AF which has reversed back to sinus rhythm at the time of discharge. These findings have implications for future therapeutic recommendations.

Anticoagulation

Since the majority of trials discussed were conducted before guidelines on therapy of AF were available, information on antithrombotic treatment of patients with AF during AMI is very limited and not based on controlled studies.

Stenestrand *et al.*[46] analysed patients that were included in the Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) between 1995 and 2002. Data from a total of 6275 patients discharged alive after AMI and who had AF were analysed. At discharge, 29% of these patients were treated with OAC, 60% were treated with ASA and/or thienopyridines,

and 11% did not receive any antithrombotic therapy. In the OAC group, 26% received additional antiplatelet therapy. All-cause mortality was significantly lower in patients treated with OAC alone (RR 0.74, 95% CI 0.62–0.88) and was also lower in those treated with OAC in combination with antiplatelet therapy (RR 0.70, 95% CI 0.55–0.90) compared with patients receiving only ASA/thienopyridine. The risk for non-fatal bleeding complications was similar in the groups (1.3% non-OAC vs. 1.5% OAC), no fatal bleeding occurred. These registry data thus confirm the high mortality and morbidity associated with AF in the setting of AMI. Furthermore, they indicate that only a minority of patients receive OAC. Notably, this therapy resulted in a 29% relative and 7% absolute reduction in 1 year mortality after adjustment for confounding variables.

Rubboli *et al.*[47] treated 104 patients with AF and AMI with a triple therapy of ASA, clopidogrel, and warfarin after reperfusion therapy with PCI and stenting. No cardiac or peripheral thrombo-embolic events were observed in 1 month follow-up but 5 (4.8%) periprocedural haemorrhages occurred, three of them needed blood transfusion or surgery. The overall bleeding rate in this small group was 20% with triple therapy (ASA and thienopyridine+warfarin/heparin) compared with 4.5% with dual antiplatelet therapy (OR 5.25 95% CI 0.53–51.63, n.s.). One sub-acute stent thrombosis occurred in a patient treated with warfarin and ASA. Ruiz-Nodar *et al.*[48] recently published data of a retrospective analysis on anticoagulation treatment in patients with AF after coronary artery stenting. Of 426 patients, 64%were treated for acute coronary syndromes (including 20.1% AMI). A total of 213 received triple therapy with coumadins, aspirin, and clopidogrel. Non-anticoagulation with coumadin was associated with a significant increase in major cardiovascular events (38.7 vs. 26.5% $P = 0.01$) and all-cause mortality 27.8 vs. 17.8%, $P = 0.02$) at a median follow-up of 594 days.[48]

The ACC/AHA/ESC 2006 guidelines for the management of patients with AF[49] recommend in the acute phase of AMI the administration of unfractionated heparin aiming at a 1.5–2-fold increased in aPTT (class1, level C). Long-term treatment after PCIs with or without AMI is based on expert consensus recommending OAC (INR 2.0–3.0) in combination with 75 mg of clopidogrel for 9–12 months. Thereafter, monotherapy with oral anticoagulants is advised.

Treatment of atrial fibrillation in acute myocardial infarction

High-ventricular rates associated with AF may further impair haemodynamics in patients with AMI by increasing oxygen demand. Thus, adequate rate control represents the most important first therapeutic approach in this setting. In many cases, this can be promptly accomplished by administration of β-blockers, either orally or intravenously. In AMI patients with extensive myocardial damage, however, the negative inotropic effect of β-blockers or calcium antagonists may result in further compromise of pump function. In these patients, rate control may be achieved with intravenous administration of digoxin with or without concomitant administration of intravenous amiodarone.[49,50] Unfortunately, there are no data stemming from controlled clinical trials regarding this clinically important issue. However, it has been demonstrated that intravenous amiodarone is effective and well tolerated in patients with life-threatening ventricular arrhythmias.[51,52] Importantly, this drug seems to not further impair left-ventricular function.[53,54]

Direct current cardioversion is recommended for patients with severe haemodynamic compromise, intractable ischaemia, or if rate control could not be achieved pharmacologically.[49] Despite the high success rate of DC cardioversion, there is a high recurrence rate of AF, particularly in patients who need catecholamine therapy for circulatory support. Although there are no studies examining the effects of intravenous amiodarone in this setting, this therapeutic approach seems to be the most reasonable one for these severely ill patients.[55]

Summary and future directions

The bulk of evidence demonstrates that AF in patients hospitalized for AMI carries adverse prognostic implications regarding in-hospital, but also long-term mortality. Particularly in the setting of congestive heart failure and left ventricular dysfunction, mortality seems to be further elevated when AF is present. Atrial fibrillation complicating AMI not only increases stroke risk during hospitalization but also after discharge. Our review of the available literature emphasizes the need for better data on the issue of AF associated with AMI. There is a lack of data concerning optimal treatment modalities of AF in this setting. Therefore, randomized trials evaluating effects of antithrombotic and/or antiarrhythmic management should be designed and executed.

Conflict of interest: S.H.H. is an advisor to sanofi aventis, BI, BMS, and to Cardiome.

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