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Co-existence of Atrial Fibrillation with Myocardial Infarction - Unhealthy Combination

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia with increasing prevalence and incidence. As our population ages, modern treatment options and decreased case-fatality of cardiovascular diseases are likely to increase the number of patients at risk for AF. AF is a frequent co-existing complication ofmyocardial infarction (MI). The onset of AF in the setting of AMI requires immediate intervention which should be individualized for each patient. AF associated with MI influences the in-hospital, medium- and long-term mortality. This brief review, based on 41 reports published between 1970 and 2011, focuses on incidence and mortality in patients with AF in MI setting. Possible mechanisms of AF in MI and treatment options are also discussed.

Introduction

Atrial fibrillation is the most common arrhythmia with increasing prevalence and incidence, affecting approximately 6 million people in the European Union, an estimated 6 million individuals in China and over 2 million patients in the United States.[2] reported during the past two decades.[1] A projected rise in incidence of AF by 12.6% would estimate 25 to 30 million AF cases in Europe and 16 million AF cases in the United States by 2050.[1,3] In patients with manifest AF, survival is markedly reduced, with comparable death rates in both sexes, even after considering co-morbid conditions.[4,5]

Two major reasons for the epidemic of AF are the aging of the population and better survival from cardiovascular diseases (CVD) such as myocardial infarction (MI) and heart failure.[6,7] In these patients, the lifetime risk for development of AF is about 25% for men and women aged 40 years and older. For those without previous or concomitant congestive HF or MI the lifetime risk is still about 16%.[6,7]

Atrial fibrillation is predominant in patients age >60–70 years, and therefore the prevalence of AF is likely to increase further given the global rise in the elderly population.[8] With advancing age and in the presence of concomitant CVD, AF affects nearly 10% of individuals aged 80 years or older.[9] Modern treatment options and decreased case-fatality of CVD are likely to increase the number of patients at risk for AF.[10]

The occurrence of AF in patients with MI is of particular importance. 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.[11] This brief review, based on 41 reports [12-52] published between 1970 and 2011, focuses on incidence and mortality in patients with MI and AF. Possible mechanisms of AF in MI and treatment options are also discussed.

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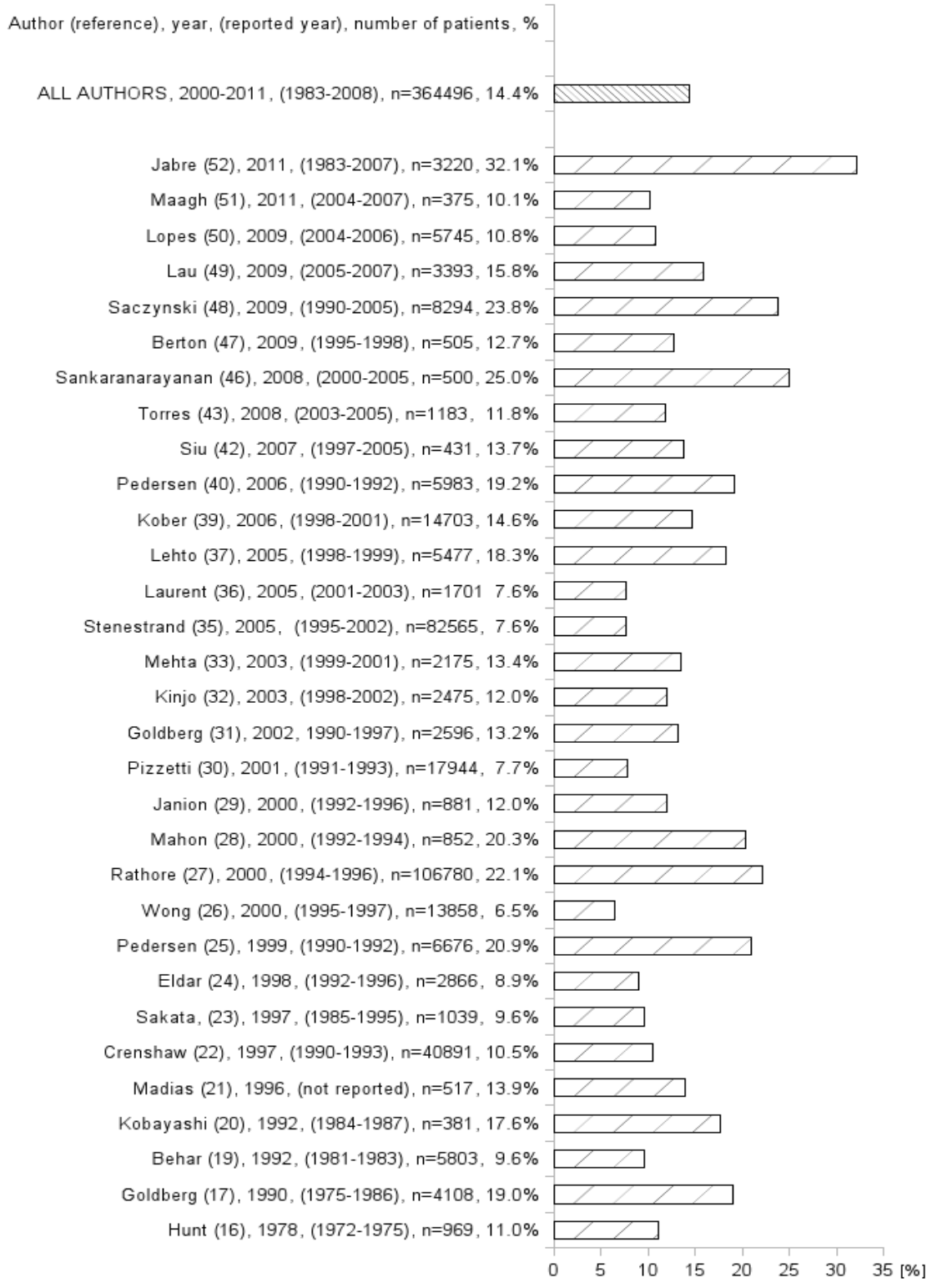
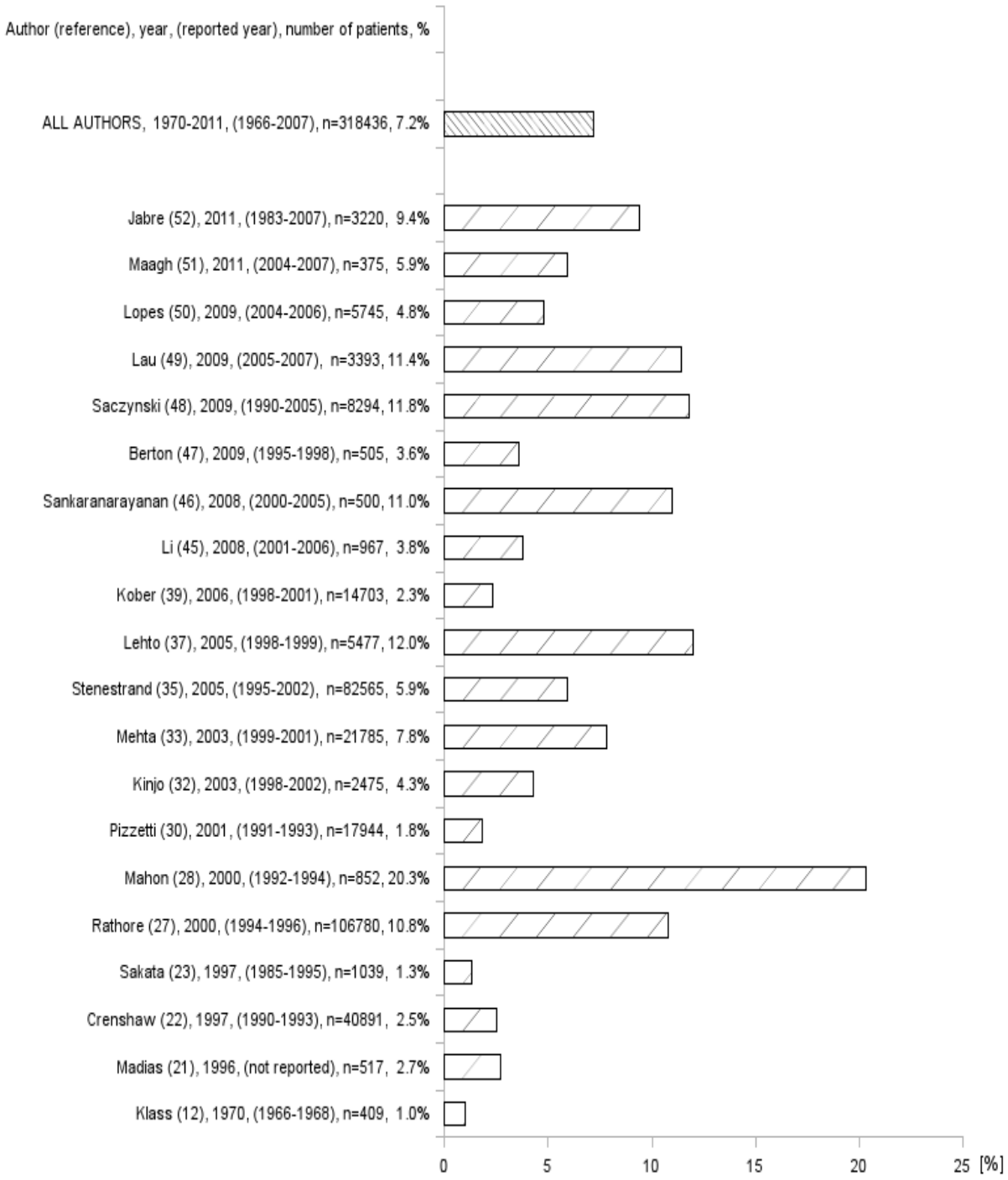
Figure 1: Incidence of any AF in Patients with Myocardial Infarction. Only Studies which Described both AF Diagnosed Prior and During Myocardial Infarction were Included; N – Number of Patients



Data Collection

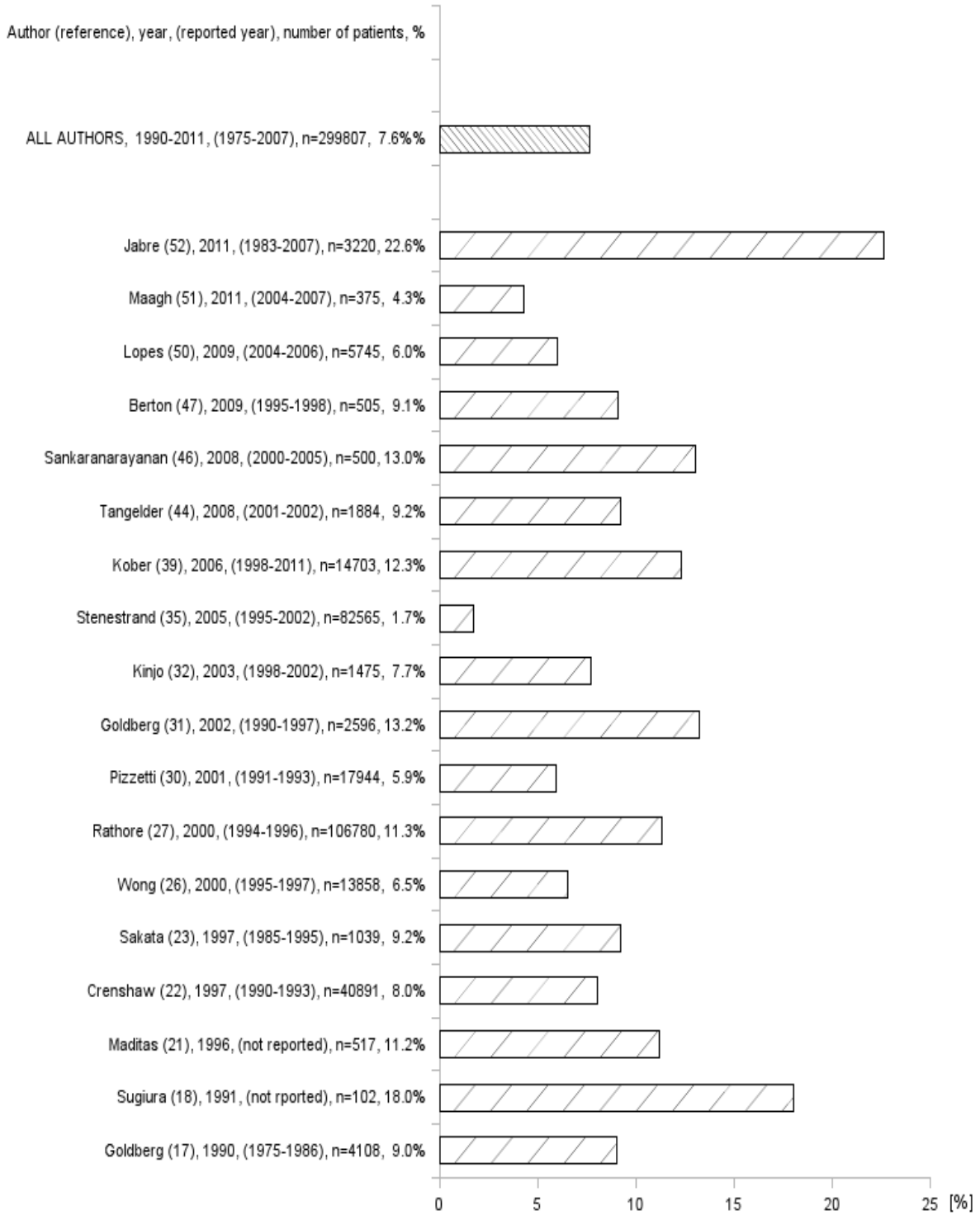
A Medline search of published reports since 1970 was performed using Mesh Database search terms " atrial fibrillation and myocardial infarcion". In addition, the references of eligible reports and available reviews were reviewed. Finally, 41 studies with[12-52]occurence of AF (34

Figure 2: Incidence of known AF in Patients with Myocardial Infarction. Only Studies which Described known AF Prior Myocardial Infarction were Included; N - Number of Patients



studies, n=189513) [13, 20, 25-27, 30, 32-33, 38, 40](AF/AFL; 7 studies, n=181878) [12, 14-19, 21-24, 28-29, 31, 34-37, 39, 41-52] were included which reported any and combined AF and atrial flutter in patients with MI

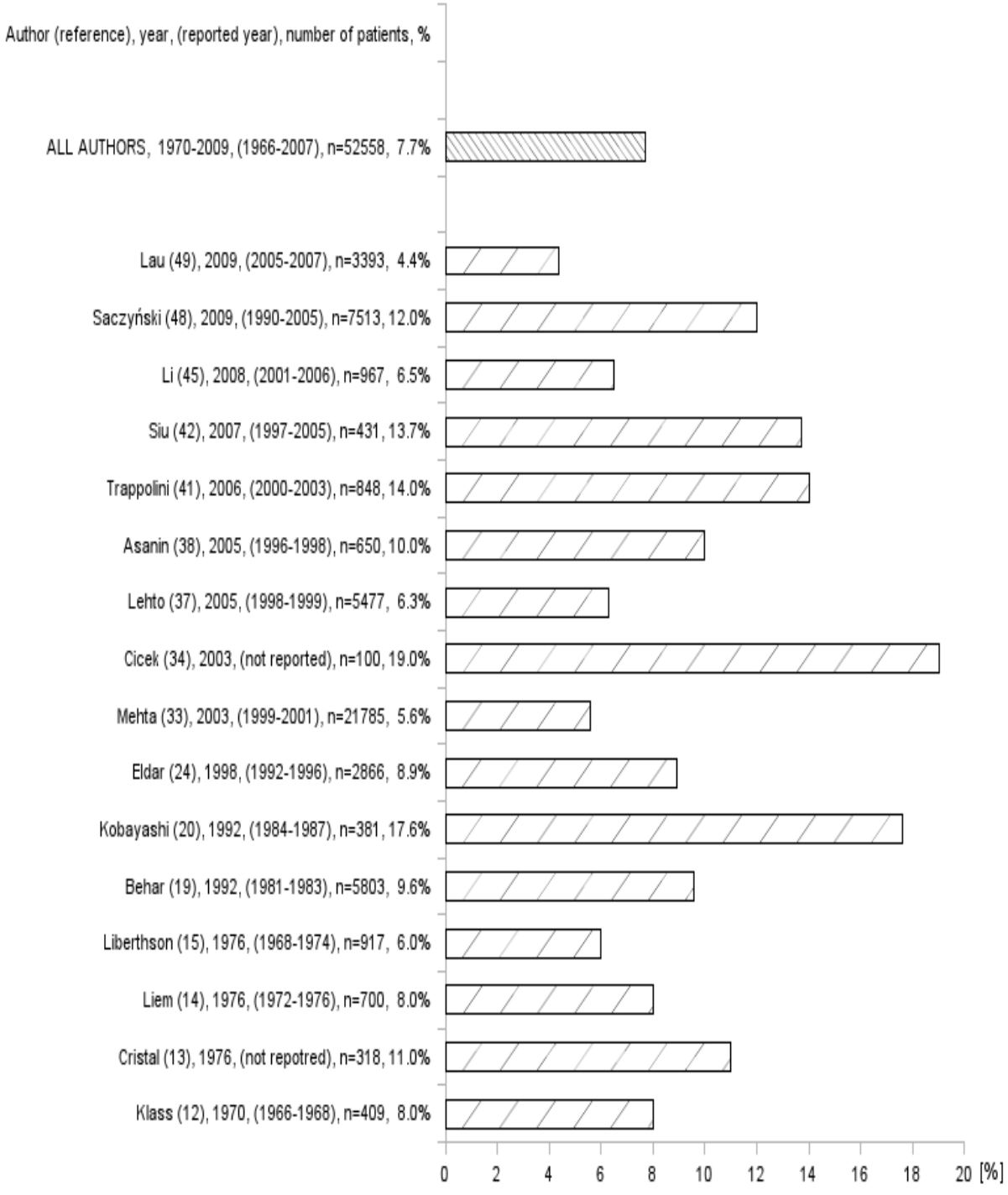
Figure 3: Incidence of New-Onset Atrial Fibrillation in Patients with Myocardial Infarction and Prior History of Atrial Fibrillation. Only Studies which Described New-Onset Atrial Fibrillation During Myocardial Infarction in Patients with known History of Atrial Fibrillation were Included; N - Number of Patients



Incidence of AF in Patients with MI

Patients with AF were predominantly male. They were also older and the AF incidence rose with increasing age.[19] AF diagnosed prior and during MI in patients was 14.4% and varied between 6.5% and 32.1% (Figure 1).[52] The reported incidence of any AF (Studies describing MI in patients

Figure 4: Incidence of New-Onset atrial fibrillation in Patients with Myocardial Infarction and No Prior History of Atrial Fibrillation. Only Studies which Described New-Onset Atrial Fibrillation During Myocardial Infarction in Patients with No Previous History of Atrial Fibrillation were Included; n - Number of Patients



with already diagnosed non-paroxysmal AF)) showed incidence of 7.2% [12, 21-23, 27-28, 30, 32-33, 35, 37, 39, 45-52] between 1% [12] and 20.3%. (figure 2)New onset of AF during MI occured in 7.6% (1.7%-22.6%) of patients with known history of AF (Figure 3). [17-18, 21-23, 23-27, 30-32, 35, 39, 44, 46-47, 50-52]First-ever documented episode of AF was reported in 7.2% (4.4%-19%) of individuals with MI and no previous history of AF (Figure 4). [12-15, 19-20, 24, 33-34, 37-38, 41-42, 45, 48-49] Moreover, transient AF complicating acute MI was associated with higher incidence of AF (22.0% vs 1.3%, p<0.01) at 1 year follow up and shown to be the independent predictor (HR 3.3, 95% CI: 1.2-9.2, p<0.03) of subsequent occurence of AF in the future.[42]

Over the last decades, treatment options and clinical practice has drastically changed as a result of widespread introduction of modern reperfusion and concomitant drug therapy. We went through the era of fibrinolytic agents to current gold standard therapy for MI - primary percutaneous coronary intervention (PCI). Successive consequence of our better understanding of MI was introduction of early administration of beta-blockers, aldosterone antagonists, statins, ACE and AT-II inhibitors. The use of these drugs has previously been found to be associated with a reduction in AF in patients with different cardiovascular diseases.[53-56] They also have the effect on mortality and morbidity in patients with MI. [30, 57-60] Goldberg [31] and Saczynski [48] reported a marked decrease in the proportion of patients who developed AF over time (18% in 1990; 11% in 1997 and 15.5% in 2001; 14.4% in 2005, respectively.). On the contrary, other authors [46, 48-49] found that the AF incidences in MI patients undergoing primary PCI were comparable to the data from the thrombolysis era. Schmitt,[61]in his review which analyzed years 1980-2007, concluded that the above resulted in lower incidence of AF complicating MI in the respective randomized trials and the introduction of PCI led to notable decline in AF occurrence, especially in the acute phase of MI.[61] The figures 1-4 show that it is hard to find definite decrease in AF incidence in subsequent years . As our population ages, one can expect that AF will remain a frequent co-existing complication of MI.

Predictors of AF in MI

Many authors identified different predictors of AF occurrence in patients with MI (Table 1). Age was most consistent predictor in most reports.[19, 21-22, 24-27, 29, 31-32, 36-38, 40-42, 48-49] Older age is the key identified risk factor for AF [62-64] that probably acts through age-related fibrosis. Both heart failure,[19, 24-27, 29, 31, 38, 40-41, 48-49] and higher Killip class [22, 26-27, 30, 32, 36-37] was also widely identified. Several mechanisms operating in heart failure can predispose to AF by creating either a substrate or a trigger for this arrhythmia.[65-66] AF constitutes a strong and independent risk factor for the development of heart failure, and both conditions frequently co-exist,[65] partly because of common risk factors. Heart failure can be both a consequence of AF (e.g. tachycardiomyopathy or decompensation in acute onset AF) and a cause of the arrhythmia due to increased atrial pressure and volume overload, secondary valvular dysfunction, or chronic neurohumoral stimulation.[67] The Framingham Heart Study [63] showed that men had a 1.5 times greater risk of developing atrial fibrillation than women. Bias data are available on influence of gender on AF in MI, with most authors identified female gender as a risk factor. [19, 24, 26-27, 30, 40, 42] Only two papers showed male gender as a predictor of AF in MI.[32, 37] Both hypertension [25-27, 30-31, 40-41, 48] and diabetes mellitus[19,24-27, 38, 40-41, 48] are know risk factors for AF. They contribute to atrial damage, as well as left ventricular hypertrophy [21] and prior MI [25, 27, 29, 38, 41, 48-49]. Fibrosis and apoptosis seen in these patients promote AF. Increased heart rate [22, 30, 32, 36] can be interpreted as sign of higher sympathetic tone which can serve as a AF trigger.

Other single predictors were also identified, like prior angina ,[29] smoking, [40] lower systolic blood pressure [22] and no thrombolysis. [40] All these proposed predictors need to be confirmed in randomized trail focused on co-existence of AF in MI.

In-hospital and long-term mortality

TAF has been demonstrated to be associated with increased morbidity and mortality in the general population.[68] The only exception is 'lone' AF in younger patients without structural heart disease which is not a predictor of an increased mortality.[69] Over last decades many proofs have been collected which show worse in-hospital prognosis in patients with MI and co-existing AF.

Table 1 | **Predictors of Atrial Fibrillation in Patients with Myocardial Infarction**

AF Predictor	Author (Reference)
Age	Behar (19), Madias (21), Crenshaw (22), Eldar (24),Pedersen (25), Wong (26), Rathore (27), Kober (29), Goldberg (31), Kinjo (32), Laurent (36), Lehto (37), Asanin (38), Pedersen (40), Trappolini (41), Siu (42), Saczynski (48), Lau (49)
Heart Failure	Behar (19), Eldar (24), Pedersen (25), Wong (26), Rathore (27), Kober (29), Goldberg (31), Asanin (38), Pedersen (40), Trappolini (41), Saczynski (48), Lau (49)
Higher Killip Class	Crenshaw (22),Wong (26), Rathore (27), Pizzetti (30), Kinjo (32), Laurent (36) Lehto (37)
Female Gender	Behar (19), Eldar (24), Wong (26), Rathore (27), Pizzetti (30), Pedersen (40), Siu (42)
Male Gender	Kinjo (32), Lehto (37)
Hypertention	Pedersen (25), Wong (26), Rathore (27),Pizzetti (30), Goldberg (31), Asanin (38), Pedersen (40), Trappolini (41), Saczynski (48)
Diabetes Mellitus	Behar (19), Eldar (24), Pedersen (25), Wong (26), Rathore (27), Asanin (38), Pedersen (40), Trappolini (41), Saczynski (48)
Left Ventricular Hypertrophy	Madias (21)
Prior Myocardial Infarction	Pedersen (25), Rathore (27), Kober (29), Asanin (38), Trappolini (41), Saczynski (48), Lau (49)
Increased Heart Rate	Crenshaw (22), Pizzetti (30), Kinjo (32), Laurent (36)
Prior Angina	Kober (29)
Smoking	Pedersen (40)
Lower Systolic Blood Pressure	Crenshaw (22)
No Thrombolysis	Pedersen (40)

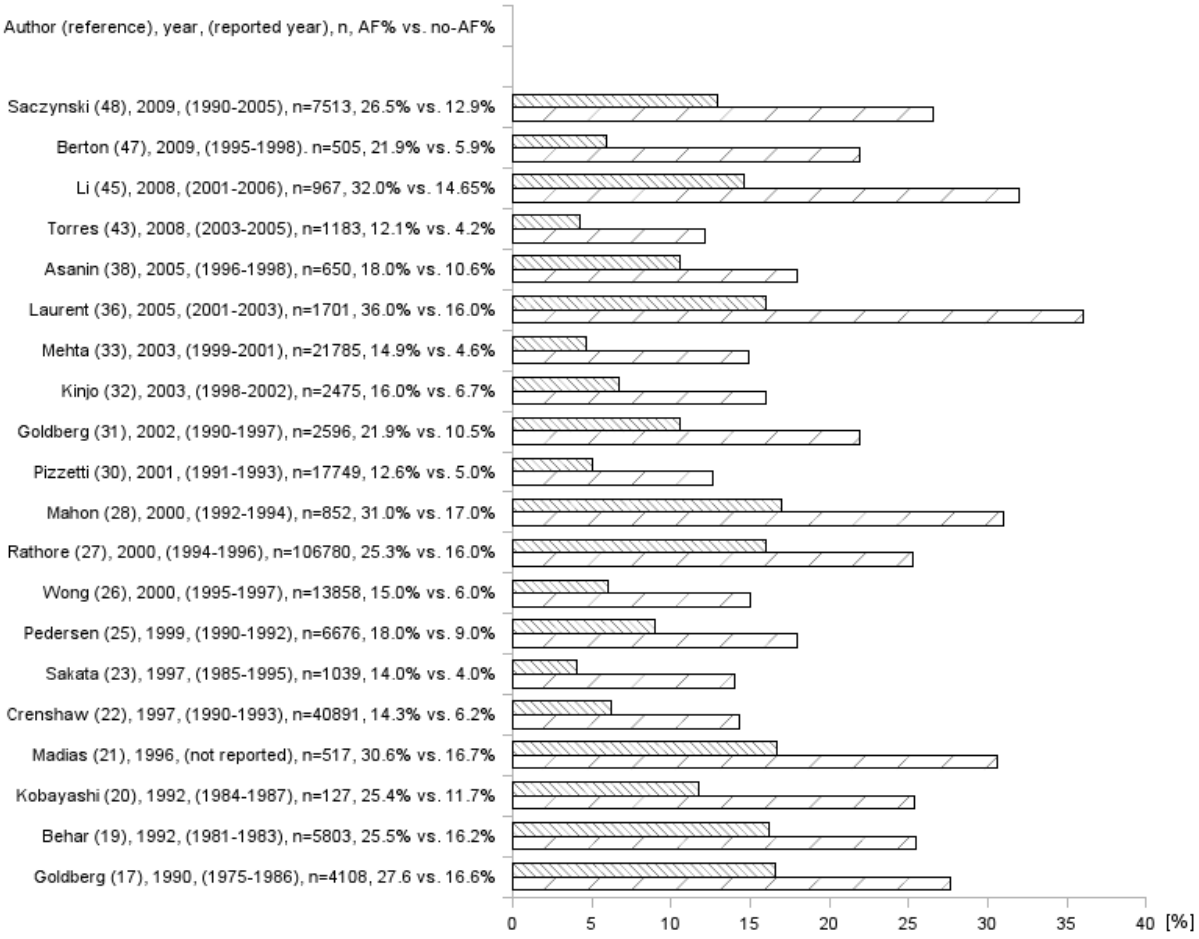
In-hospital mortality among patients with AF varied between 12.1% and 36% as compared with controls (4%-17%, respectively; Figure 5). [17, 19-23, 25-28, 30-33, 36, 38, 43, 45, 47-48] For example, the in- hospital mortality associated with AF was 9.3% higher in the Cooperative Cardiovascular Project which presented data from 106780 patients with MI.[27] Crenshaw[22] and Mehta [33] also described higher mortality in MI patients with AF (8.1% and 10.3%, respectively) but in smaller studied cohorts of 40891 and 21785 MI individuals, respectively.

Medium-term mortality (<=1 year) varied between 15%-48.3% in AF patients and between 6% and 32.7% in controls (Figure 6).[19, 22, 26-27, 30-32, 43, 48] For example, Rathore el al.[27] reported 15.6% higher 1-year mortality associated with AF in 106780 MI patients. Crenshaw,[22] in a smaller series of 40891 MI patients, showed 12.9% higher mortality in 1-year follow up.

Long term mortality(> 1 year) varied between 18.2% and 71.9% in AF patients and between 6.8% and 39% in controls (Figure 7).[19, 25, 31, 37-40, 47, 51] For example, Kober el al.[39] in 14660 MI patients showed 18% higher 3-years mortality associated with AF complicating MI. Pedersen et al.[40] described 22% higher 5-years mortality associated with AF during MI in 6676 patients. Behar et al.,[19] who studied 5803 patients with MI, reported 17.9% higher 6-years mortality in individuals with AF during MI. Berton et al.[47] describe 32.9% higher 7-years mortality associated with AF but in a small group of 505 patients with MI.

In the latest meta-analysis of 43 studies involving 278854 patients, Jabre el al. demonstrated at least 40% increased risk of mortality associated with AF in MI settings[70] The mortality Odds ratio (OR) associated with new and known AF prior MI was 1.46 (95% CI: 1.35-1.58) and 1.27 (95% CI: 1.16-1.40), respectively.[70] They showed that the increased mortality risk was related to AF regardless of its timing of development. [70] Shmitt et al.

Figure 5: In-Hospital Mortality of Patients with Myocardial Infarction and Atrial Fibrillation



[61] in their review concluded that AF in patients hospitalized for MI has serious adverse prognostic implications regarding both in-hospital and long- term mortality in all patients populations regardless differences related to treatment of MI.

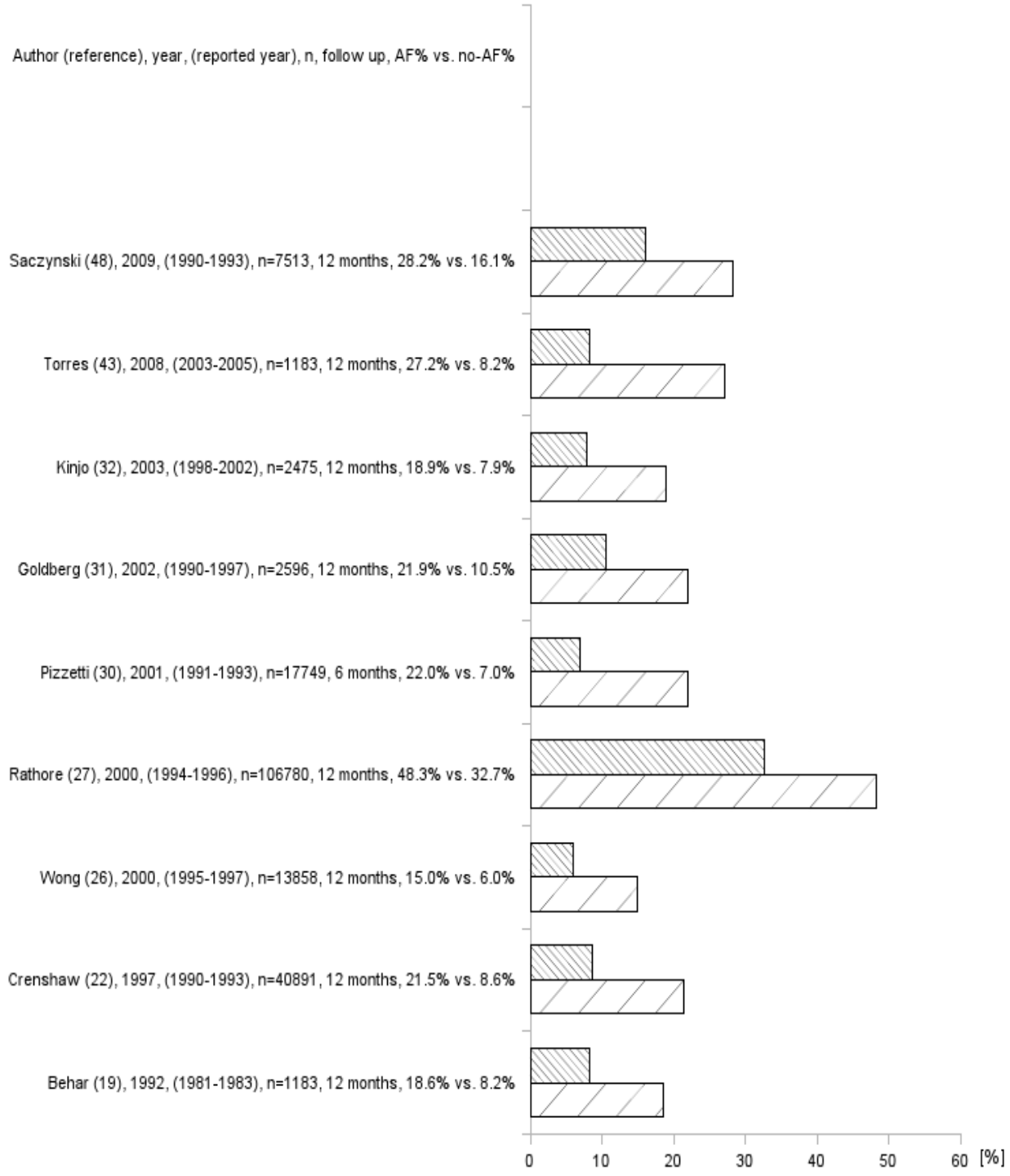
Mechanism of AF in MI

Several mechanisms of new-onset AF in MI settings were proposed:atrial ischaemia or infarction, right ventricular infarction, pericardial inflammation, increased vagal stimulation, acute hypoxia or hypokalaemia, and haemodynamic impairment secondary to left ventricular (LV) dysfunction.[18, 20, 71-74] Endogenous or exogenous catecholamines may also precipitate AF. These factors can be found alone or in combination, and may superimpose on predisposing diseases.[75]

In patients presenting with acute STEMI and simultaneous AF, atrial ischemia has been proposed as the most likely cause.[72] During the reperfusion era, Hod et al.[72] demonstrated that AF resolved minutes to hours after administration of thrombolytics. Recently, Blanton et al.[76] clearly demonstrated the immediate termination of AF with restoration of blood flow to the left atrium in a patient with STEMI. This provided direct evidence to support the hypothesis that left atrial ischemia could result in AF during acute MI and that mechanical reperfusion of occluded atrial branches could result in conversion to sinus rhythm.[76]

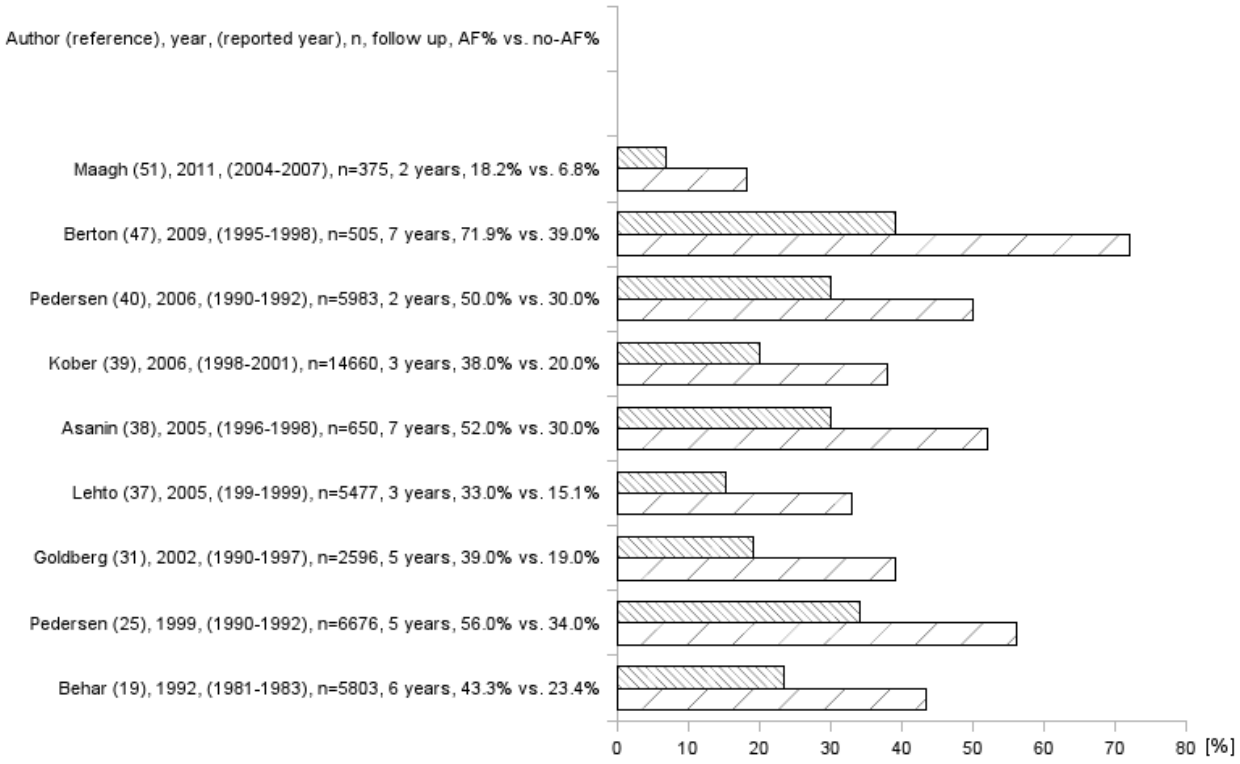
According to Coumel´s triangle of arrhythmogenesis,[77] three cornerstones are required in the onset of clinical arrhythmia – the arrhythmogenic substrate, the trigger factor and the modulation factors such as autonomic nervous system or in-

Figure 6: Medium-Term (6-12 months) Mortality of Patients who had Atrial Fibrillation During Myocardial Infarction; N– Number of Patients



flammation. In patients with history of AF prior MI, i.e. with already existing (electrical or structural) substrate for AF, acute MI may : 1.further (permanently or transiently) modify the substrate (for example: direct ischemia and disturbances in blood pH and electrolytes), 2.be a trigger for new AF onset (for example: increased left atrial pressure, disturbances in blood pH and electrolytes,

Figure 7: Long-Term (>1 year) Mortality of Patients who had Atrial Fibrillation During Myocardial Infarction; n – Number of Patients



hemodynamic imbalance) and 3.act as a modulation factor (increased vagal tone, for example). In patients with no prior history of AF, MI may become any and all factors described by Coumel.[77]

Treatment of AF in MI

Early reperfusion and anticoagulation are the cornerstones strategies in MI patients and are likely to reduce , probably by ≥50%, the risk of developing AF and to protect against associated embolic risk.[57] Administration of B-blockers, ACE and AT-II inhibitors may further limit the risk of AF.[56,78]

Compensation of hemodynamic imbalance as well as disturbances in blood pH, pCO2, pO2 and electrolytes can not only reduce the risk of developing AF but also, once AF has occured, may favour both spontaneous restoration of sinus rhythm and maintenance of sinus rhythm following electrical or pharmacological cardioversion.

The prognostic implication of selecting "rhythm versus rate control" strategy in MI settings has not been investigated.[75] In patients with permanent AF and in new-onset AF without hemodynamic compromise, ventricular rate control (amiodarone, B-blockers, nondihydropyridine calcium antagonist in individuals without left ventricular dysfunction, bronchospasm or A-V block, and alternatively digitalis, in case of severe left ventricular dysfunction and heart failure) is an acceptable alternative.[79] In patients with severe hemodynamic compromise or intractable ischemia or when adequate rate control cannot be achieved with pharmacological agents, direct-current cardioversion should be performed.[79] Nevertheless, expected benefit and possible risk of thromoembolic events, especially in patients with AF>48hours without anticoagulation, should be balanced. If possible, trans-esophageal echocardiography may be useful for evaluation the risk. In addition to electrical cardioversion, amiodarone can be administered for restoration of sinus rhythm. Still, the decision must be cautious , as both pharmacological and electrical cardioversion carry the same risk of throboembolic event. The usage of other antiarrhythmics than amiodarone is restricted,as administration of class

IC is not recommended in such circumstances.[79]

Protection from early and late thromboembolic risk is currently left to unfractioned heparin and to oral anticoagulant in addition to clopidogrel, respectively.[75] However, the risk of bleeding must be considered and evaluated with HAS-BLED score.[80] The need for long-term oral anticoagulant, especially in patients after PCI who need double antiplatelets therapy, should be estimated with $CHADS_2$[81-82] and, in applicable, $CHA2DS_2$-VASc[83] score system.

Further trials are warranted to investigate the role of antiarrhythmic medications and invasive methods (ablation procedures) as a secondary prevention of AF after MI.

Conclusions

AF is a frequent co-existing complication of MI and can no longer be considered as benign event. As our population ages, and despite new therapeutic options, one cannot expect that AF incidence in MI settings will decrease. AF associated with MI increases the in-hospital, medium- and long- term mortality in these patients, regardless of the timing and type of AF. Therefore the onset of AF in the setting of AMI requires immediate intervention which should be individualized for each patient. Furthermore, AF complicating MI should be documented and taken into account as a marker of worse prognosis. Long-term follow-up in these patients is required.

Randomized prospective studies should be addressed to identify risk markers, find prevention modes , define optimal surveillance methods and propose treatment strategy in this population of patients.

Disclosures

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