

The incidence and prognostic significance of new-onset atrial fibrillation in patients with acute myocardial infarction and left ventricular systolic dysfunction: A CARISMA substudy

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BACKGROUND: The incidence and risk associated with new-onset atrial fibrillation (AF) occurring after discharge in patients with acute myocardial infarction (MI) remains unknown.

OBJECTIVE: This study sought to describe the incidence and clinical risk associated with postdischarge new-onset AF in post-MI patients with left ventricular systolic dysfunction.

METHODS: The population included 271 post-MI patients with left ventricular ejection fraction $\leq 40\%$ and no history of previous AF from the Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study. All patients were implanted with an implantable cardiac monitor and followed up every 3 months for 2 years. Major cardiovascular events were defined as reinfarction, stroke, hospitalization for heart failure, or death.

RESULTS: The risk of new-onset AF is highest during the first 2 months after the acute MI (16% event rate) and decreases until month 12 post-MI, after which the risk for new-onset AF is stable. The risk of major cardiovascular events was increased in patients with AF events ≥ 30 seconds (hazard ratio [95% CI] = 2.73 [1.35 to 5.50], $P = .005$), but not in patients with AF events lasting

< 30 seconds (hazard ratio [95% CI] = 1.17 [0.35 to 3.92], $P = .80$). More than 90% of all recorded AF events were asymptomatic.

CONCLUSION: Using an implantable cardiac monitor, the incidence of new-onset AF was found to be 4-fold higher than earlier reported. In the study population, in which treatment with beta-blockers was optimized, the vast majority of AF events were asymptomatic, emphasizing the importance of using continuous monitoring for studies concerning AF in heart failure patients. A duration of 30 seconds or more identified clinically important AF episodes documented by an implantable cardiac monitor.

KEYWORDS Atrial fibrillation; Acute myocardial infarction; Cardiovascular risk; Heart failure; Implantable cardiac monitor

ABBREVIATIONS: AF = atrial fibrillation; AMI = acute myocardial infarction; ECG = electrocardiogram; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; ICM = implantable cardiac monitor; LVEF = left ventricular ejection fraction

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Atrial fibrillation (AF) frequently complicates the clinical course after an acute myocardial infarction (AMI), especially in patients with left ventricular systolic dysfunction.^{1–7} The

incidence of in-hospital new-onset AF occurring in the immediate days after the AMI is 5% to 18%,^{1,2,5,8} and occurs more frequently in older patients with cardiac and extracardiovascular comorbidities such as congestive heart failure, kidney disease, hypertension, diabetes, and pulmonary disease.^{2,4–6,9} Development of AF does not seem to be related to the type of AMI,^{4,10} but is related to a higher right atrial pressure and pulmonary artery wedge as well as low cardiac index and ejection fraction.¹¹ Accordingly, in-hospital AF is associated with increased in-hospital short-term and long-term mortality, even though debate still exists regarding whether new-onset AF per se is an independent predictor of this end point or not.

In contrast, despite the vast amount of studies investigating the risk associated with in-hospital AF, there is a paucity of data regarding new-onset AF occurring after discharge from the hospital in post-AMI patients. Thus,

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most aspects of AF incidence, recurrence, and symptomatic presentation are unknown in this population. Specifically, there are no earlier prospective studies using devices to continuously monitor patients for development of new-onset AF in post-AMI patients with left ventricular systolic dysfunction. In the Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study,¹² patients with AMI and left ventricular ejection fraction $\leq 40\%$ were implanted with an implantable cardiac monitor recorder (ICM) and followed up for 2 years with the purpose of describing the incidence of arrhythmias. The incidence of AF using only the ICM and risk of cardiac death associated with new-onset AF was described in the CARISMA manuscript,¹² and a detailed analysis of the predictors AF have been described in a separate manuscript.¹³ The aim of this study was to provide a detailed analysis of the total incidence and burden of new-onset AF using all devices and the associated risk for relevant major cardiovascular events including heart failure, new myocardial infarction (MI), and stroke using an ICM.

Methods

This study was performed as planned.

Population

This study was performed as a prespecified substudy on a subgroup of the CARISMA study population that has been described elsewhere.¹² Briefly, 312 patients were included in 10 Scandinavian centers within the first 3 weeks after experiencing an MI. All patients had a left ventricular ejection fraction (LVEF) $< 40\%$ and a life expectancy > 2 years. The main purposes of the study were to describe the incidence of malignant arrhythmias after acute MI using an implantable loop recorder (ICM) and to risk stratify the study subjects using multiple invasive and noninvasive electrophysiological tests performed at week 6 after MI.

A total of 297 patients were implanted with an ICM (Reveal Plus, Medtronic, Minneapolis, Minnesota). Of these, 10 patients had a history of chronic AF and 16 patients had a history of paroxysmal AF at enrollment. The remaining 271 patients were included in this study. Of the 271 patients, 15 patients were implanted with a pacemaker during the study period and 50 patients received an implantable cardioverter-defibrillator (ICD). When a pacemaker or ICD was implanted, the new device was programmed with parameters similar to the ICM and used to detect arrhythmias. Medical treatment was initiated at the discretion of the treating electrophysiologist.

Implantation and Programming of the loop recorder

The ICM was implanted subcutaneously under local anesthesia in the left parasternal area 5 to 21 days after an AMI. The device was programmed to automatically store tachyarrhythmias at heart rates ≥ 125 beats/min that persist for at least 16 consecutive beats, and to automatically store bradyarrhythmias at heart rates ≤ 30 beats/min, or asystolic

events lasting more than 4.5 seconds. During follow-up, the memory of the loop recorder was interrogated, and the sensitivity of arrhythmia detection was adjusted individually according to the amount of false events at each visit. In a pilot study on the CARISMA population, the ICM was found to document 70% of all supraventricular arrhythmias.¹⁴

Diagnosis of AF

AF diagnosis was started at the time of ICM implant. An episode of AF was defined as: AF episodes documented by the ICM or by pacemaker or ICD lasting more than 16 beats; AF episodes documented by electrocardiogram (ECG) between visits not captured by the ICM, pacemaker, or ICD. If the start or end of an event was not visible on the electrogram (EGM), a new AF event was defined as any automatically activated recording with AF initiated more than 15 minutes after recording of a former AF event or any 2 events separated by a recording containing a non-AF rhythm or a visible termination of an AF event. Only episodes of AF occurring after device implantation were included in this analysis. Patients with new-onset AF during the study period documented by ECG during follow-up but not by a device were excluded from analysis on AF duration and number of events because these factors were unknown in this population subset.

End point

A combined end point of reinfarction, stroke, hospitalization for heart failure, and cardiac death was used for this study. Hospitalizations for reinfarctions, stroke, and heart failure were determined by the responsible physician at the study center, whereas the mode of death was adjudicated by the end point committee.

Statistics

Clinical baseline variables were tested for normality using histogram plotting. Hypothesis testing for significant differences between patients with and without end points were performed using the Student *t*-test, Wilcoxon rank-sum test, or Pearson chi-square test where appropriate. Graphic presentation of the cumulative probability for new-onset AF was illustrated using the Kaplan-Meier method with significance testing using log-rank statistics. Univariate and multivariate hazard ratios (HR) were obtained from Cox proportional hazard regression. Baseline covariates were included in the multivariate models if hypothesis testing revealed a difference between populations with and without the end point at a significance level of $P \leq .05$. Stepwise selection and Pearson score selection was used to create optimized multivariate models containing only significant risk factors for major cardiovascular events. Although the ICM was not implanted on the day of the AMI, the day of the AMI was chosen as the time of origin for this study to ease clinical interpretation.

In the analysis regarding influence of duration and number of AF events on the prognosis of patients with new-

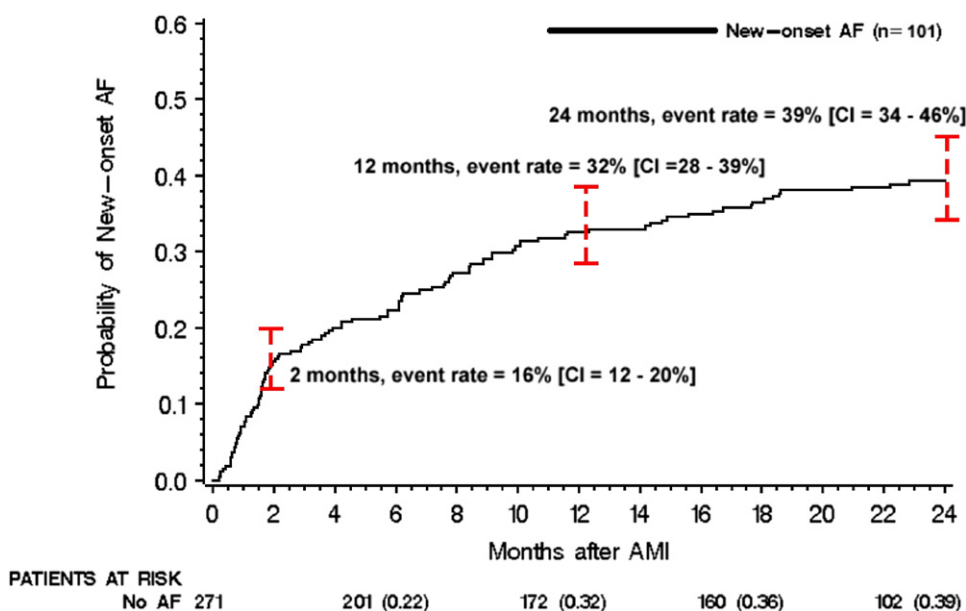


Figure 1 Incidence of new-onset AF after implant of device after index AMI. Kaplan-Meier graph showing the cumulative incidence of ECG-documented new-onset AF during the study period. AF = atrial fibrillation; AMI = acute myocardial infarction; ECG = electrocardiogram.

onset AF patients, patients diagnosed using conventional ECG without events on the implanted devices were excluded (n = 6) because the parameters of interest were unknown for these patients. The cutoff values for clinically significant AF event duration was prespecified according to the current guidelines. In the analysis on the number of AF events, the population of new-onset AF patients was split into tertiles depending on the number of AF events they experienced during the study. In both cases, development of AF events was treated in a time-dependent manner.

Figure 1 displays Kaplan Meier incidences and 95% confidence intervals. Figure 2 was constructed using the

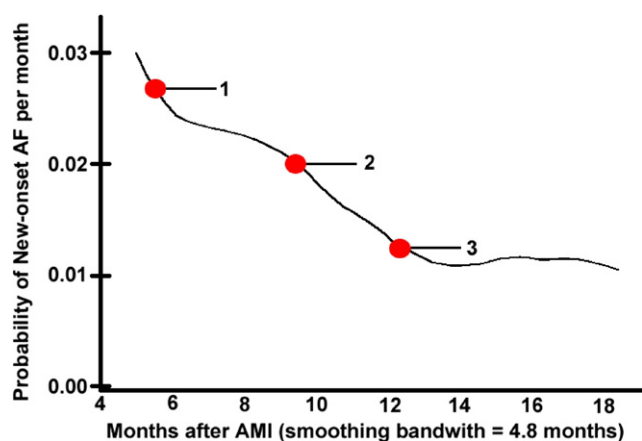


Figure 2 Smoothed hazard function graph. The graph shows the probability of new-onset AF per month at any given time during the study. 1: The risk of new-onset AF is very high in the first 2 months after the AMI, but decreases rapidly in the weeks following. 2: From month 6 to 12, there is a steady decrease in the risk of new-onset AF. 3: Around month 12, the hazard reaches a plateau level, likely reflecting the baseline risk for new-onset AF in this population. AF = atrial fibrillation; AMI = acute myocardial infarction.

SAS macro provided by Allison¹⁵ that implements the method described by Ramlau-Hansen.¹⁶ The figure continuously illustrates the risk for new-onset AF per month during the study period using a smoothing window. The smoothing windows implement the hazard functions obtained during the smoothing period into the current hazard function to allow illustration of larger changes in the hazard function while smaller changes are removed. Generally, a smoothing period of 25% of the entire study period is recommended. Because of the relatively large number of events in this study, a smoothing period of 4.8 months, corresponding to 20% of the study period, was used for a higher resolution of the plot.

Figure 3 was constructed by starting time at the time of the AMI, where no patients had been diagnosed with AF (No-AF group). If patients developed AF, they were censored from this group, along with patients being terminated from the study without experiencing the end point. If the recorded event of new-onset AF lasted <30 seconds, patients were followed up from the time of the AF events restarting follow-up at time 0 (AF <30 seconds group). If patients later developed AF lasting 30 seconds or longer, they were censored from this group and restarted at time 0 (AF ≥30 seconds group). If the first AF event lasted 30 seconds or more, patients were censored from the “No-AF” group and restarted at time 0 in the “AF ≥30 seconds” group. All analyses were performed using SAS 9.1.3 for Windows (SAS institute, Cary, North Carolina).

Results

Population

The clinical characteristics of the population in those with and without the end point are shown in Table 1. Patients with major cardiovascular events were older, and a higher

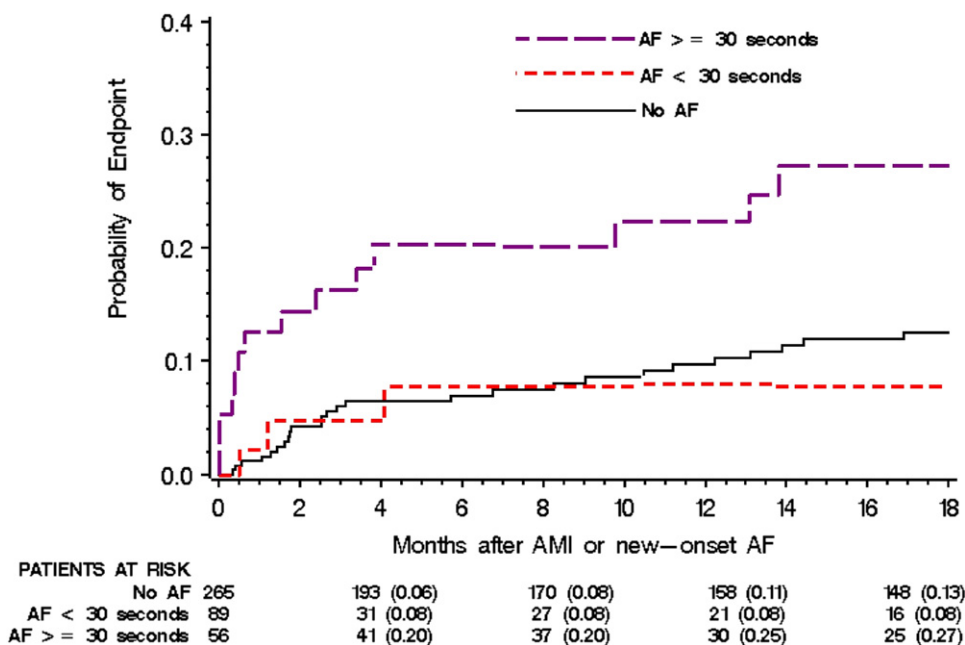


Figure 3 Risk of first major cardiovascular event in patients with AF events <30 seconds and AF events ≥30 seconds. The graph is showing time from MI for all patients (black solid line). If a patient developed an AF event, they were censored from this group and restarted at time 0 in the group corresponding to the duration of the AF event (see Methods section for details on how the graph was constructed). AF = atrial fibrillation; MI = myocardial infarction.

proportion had previous MI, left bundle branch block, wide QRS >120 ms, congestive heart failure, and diabetes. A larger proportion of these patients were in New York Heart Association class II to IV. Medical treatment was balanced in the 2 groups, and more than 90% of patients were treated with beta-blockers and angiotensin-converting enzyme inhibitors. LVEF was equal in the 2 groups, but both left atrial and left ventricular diameters were increased in the group experiencing major cardiovascular events.

Incidence of new-onset AF

A total of 101 patients (event rate = 39.3%, 95% confidence interval [CI] = 33.7% to 45.5%) were diagnosed with AF during the study period, 95 of these using the ICM. Six patients reported AF at follow-up, with no events on the devices implanted at the time of diagnosis (ICM: n = 2, ICD: n = 4). The cumulative incidence of first AF episode is shown in Figure 1. Sixteen percent were diagnosed within 2 months; after 12 months, 32% had been diagnosed with AF. Only 7% of the AF-free population at 12 months was diagnosed with AF between month 12 and month 24 post-MI. To investigate this further, a smoothed hazard function curve was created (Figure 2). This graph shows the hazard function, i.e., the risk of new-onset AF in the population, at any given time during the study period. The hazard is highest just after the AMI and then decreases quickly. The hazard keeps decreasing until 12 months post-MI, where it reaches a plateau level. From month 12 to month 24 post-MI there is no further decrease in the risk for new-onset AF.

Risk of major cardiovascular events in patients with new-onset AF

Univariately, new-onset AF was associated with an increased risk of major cardiovascular events (HR [95% CI] = 2.04 [1.10 to 3.78], P = .024). Results from the multivariate Cox model are shown in Table 2. Adjusted for significant baseline covariates (QRS width >120 ms and previous MI), new-onset AF remained a risk factor for major cardiovascular events. Adjustment for time-dependent medical treatment, including coumadin and amiodarone, did not affect the results. A breakdown of the combined end point is shown in Table 3.

A total of 564 individual events with AF were recorded on devices, most of these on the ICM: ICM = 546 (97%) in 95 patients, pacemaker (PM) = 6 (1%) in 2 patients, ICD = 11 (2%) in 5 patients. All ICD patients had events on an ICM before ICD implantation. The AF events were largely triggered by tachycardia (69%) with a heart rate of ≥125 beats/min. Four percent of events (n = 25) were associated with a heart rate ≤30 beats/min. Twenty-seven percent of new-onset AF events were detected at average heart rates outside the programmed detection window of the device, but 88 (93%) of the detected AF patients were diagnosed with an event with an average heart rate ≥125 beats/min. Just 49 events (9%) in 20 patients were symptomatic. Most frequent symptoms included palpitations (73%), dyspnea (53%), chest pain (12%), dizziness (10%), and syncope (2%). AF triggered short-lasting nonsustained ventricular tachycardia 7 times in 5 patients, but no episodes of sustained ventricular tachycardia or ventricular fibrillation.

Table 1 Baseline characteristics of the study population†

Parameter	No primary end point (N = 222)	Had primary end point (N = 49)
Demographics		
Age (y)	62.6 (±10.8)	66.7 (±11.5)*
Male gender	171 (77%)	40 (82%)
Body mass index	27.4 (±4.4)	28.3 (±4.5)
Medical history		
Prior MI	66 (30%)	28 (57%)*
Prior CHF	12 (5%)	9 (18%)*
Diabetes mellitus	37 (17%)	16 (33%)*
Hypertension	94 (42%)	21 (43%)
COPD	10 (5%)	3 (6%)
Renal insufficiency	9 (4%)	4 (8%)
NYHA class II to IV	159 (73%)	45 (94%)*
Medical treatment at enrollment		
Beta-blockers	214 (96%)	49 (100%)
ACE inhibitor/AT-II blocker	212 (96%)	47 (96%)
Statins	185 (82%)	41 (84%)
Antiplatelet	216 (97%)	48 (98%)
Oral anticoagulants	45 (20%)	11 (23%)
Class I or III antiarrhythmic drugs	3 (1%)	0 (0%)
Characteristics of AMI and treatment		
Q-wave AMI	148 (67%)	25 (52%)
Anterior location	134 (60%)	26 (53%)
PTCA	81 (36%)	9 (18%)*
Thrombolysis	85 (38%)	16 (33%)
ECG characteristics, inclusion		
Heart rate, enrollment (24-h average)	69.3 (±11.5)	68.2 (±14.2)
LBBB	18 (8%)	6 (12%)
RBBB	16 (7%)	9 (18%)*
QRS width (ms)	100 (±23)	115 (±31)*
Echocardiography, inclusion		
Ejection fraction	31.8 (±6.3)	30.9 (±6.3)
LA diameter	40.3 (±6.2)	43.3 (±6.0)*
LV end diastolic diameter	56.8 (±8.3)	59.5 (±8.1)*
Mitral valve insufficiency > grade I	108 (48%)	12 (23%)

MI = myocardial infarction, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, NYHA = New York Heart Association, ACE = angiotensin-converting enzyme, AT-II = Angiotensin II receptor blocker, AMI = acute myocardial infarction, PTCA = percutaneous transluminal angiography, ECG = electrocardiogram, LBBB = left bundle branch block, RBBB = right bundle branch block, LA = left atrium, LV = left ventricle.

*Significant differences between patients with and without cardiac events ($P < .05$).

†Significant differences between patients with AF at enrollment and study population without AF at enrollment ($P < .05$).

AF burden: duration and number of AF events recorded

Although 95 patients developed AF detected by a device, only 58 (56% of new-onset AF patients, 22% of study population) developed AF events lasting ≥ 30 seconds. Of

these, 18 (32%) initially presented with short AF events (AF <30 seconds). The risk of major cardiovascular events was highly increased in patients when they developed AF events ≥ 30 seconds, but was not increased in patients with AF events lasting <30 seconds (Figure 3, Table 2). In contrast, the number of AF events recorded by the ICM did not predict cardiovascular risk because the risk was found to be significantly increased in patients after the recording of just 1 AF event (Table 2).

Discussion

This study is the first to describe the incidence and risk of AF in post-MI patients with left ventricular systolic dysfunction using continuous monitoring with an implantable cardiac monitor. A high proportion of the study population was diagnosed with new-onset AF, almost half of these patients within 2 months. Importantly, most of the AF events recorded were nonsymptomatic (91%). AF events lasting ≥ 30 seconds was an independent risk factor for major cardiovascular events, whereas shorter AF events did not increase the risk. These results show that AF is much more frequent in this population than earlier anticipated and is a strong risk factor for major cardiovascular events. Future studies are warranted to investigate whether preventive treatment will decrease the incidence of cardiovascular events in this high-risk population.

Incidence of AF

In 2 previous studies on similar populations, the incidence of new-onset AF occurring after discharge from hospitalization after an AMI has been reported to be just 5% to 7%,^{17,18} a somewhat lower incidence than reported during hospitalization after the MI.¹⁹ These low estimates may reflect the fact that patients prone to the arrhythmia develop AF early after AMI and the more healthy part of the population stays free of AF during long-term follow-

Table 2 Results from Cox proportional hazards regression

	HR	95% confidence limits	P
Previous MI	2.47	1.38–4.40	.0023
QRS >120 ms	2.27	1.20–4.28	.012
New-onset AF	1.95	1.02–3.73	.042
Duration of AF*			
≥ 30 s	2.73	1.35–5.50	.0050
<30 s	1.17	0.35–3.92	.80
Number of AF events recorded*			
1 event	2.52	1.09–5.83	.031
2–4 events	0.52	0.07–3.83	.12
5 events or more	3.28	1.35–7.98	.0090

Covariates excluded from the model were age >70 years, congestive heart failure, and diabetes.

HR = hazard ratio, MI = myocardial infarction, AF = atrial fibrillation. *Involves only 265 patients; 6 patients with AF diagnosed at follow-up using conventional electrocardiogram but not detected by implantable cardiac monitor, PM, or implantable cardioverter-defibrillator were excluded from this analysis.

Table 3 Number and distribution of risks associated with each part of the combined end point (only crude hazard ratios are shown)

	Number of events	AF <30 s		AF ≥30 s	
		HR	CI	HR	CI
Stroke	5	—	—	3.55	0.55–22.91
Reinfarction	23	0.53	0.07–4.01	1.17	0.34–4.06
Hospitalization for heart failure	15	2.12	0.44–10.28	3.22	0.94–11.02
Cardiac death	22	1.12	0.24–5.19	3.01	1.13–8.06

AF = atrial fibrillation; HR = hazard ratio; CI = confidence interval.

up. However, these studies relied on conventional 12-lead ECGs recorded during follow-up, and more likely, the incidence of AF is highly underestimated in these studies. In our study, the incidence of clinically important AF events was found to be 4 times more frequent. Also, more than 90% of the AF events were asymptomatic, probably because of the high frequency of beta-blocker treatment. We thus confirm the findings from previous reports, in which regular patient follow-up and short-lasting monitoring with regular intervals were found to highly underestimate the incidence of AF compared with continuous monitoring,²⁰ and underlines the importance of using continuous monitoring in trials concerning AF and in the follow-up of patients at high risk for AF.

Risk of major cardiovascular events

In this study, the duration of the individual AF events was found to be more clinically important than the number of AF events. This is in concordance with earlier studies, mostly involving patients with pacemakers, in which duration of individual AF events longer than 5 minutes,²¹ 7 hours,²² or even 1 day²³ were found to identify clinically important AF. Because the ICM as well as several other implantable cardiac monitoring devices are only capable of storing shorter-lasting events, these cutoff values cannot be used here. The current guidelines define a clinically important AF event as lasting 30 seconds or more.²⁴ However, this definition has until now not been justified empirically. In this study, the cardiac risk was not increased in patients with AF events unless the AF event duration was longer than 30 seconds. Using a cutoff of 60 seconds increased the risk insignificantly in the short-AF group and was found to be less efficient. It is important to note that although patients with AF events <30 seconds were at the same risk for cardiac events as patients without AF, 32% of patients with AF ≥30 seconds initially presented with AF events <30 seconds. Thus, short AF events are a strong risk factor for development of longer-lasting and thereby clinically significant AF.

The burden of AF as measured by the ICM, defined as the total number of recorded events separated by at least 15 minutes, was not significantly predictive for major cardiovascular events. The ICM has been found to inadequately describe AF burden in smaller series²⁵ of patients with lone AF, and this may explain our results. However, it is also possible that the duration is more important because a min-

imum duration of AF events is required to create the substrate that increases the risk for cardiovascular events, or because short AF events signify a less diseased myocardium. Thus, uninterrupted AF burden rather than total amount of time in AF from multiple AF episodes may be a more clinically significant measure. However, this should be tested in future studies.

Study limitations

The ICM as cardiac monitor is subject to several limitations. First, arrhythmias occurring outside the diagnostic window (30 beats/min ≤ heart rate ≤ 125 beats/min) were not systematically detected. In a heart failure population in which beta-blockers are uptitrated to a maximal tolerance threshold, it is rational to believe that most AF will occur at well-controlled heart rates below 125 beats/min and that these normo-frequency AF episodes will be significantly underreported in the current study. However, more than one quarter of all recorded AFs occurred at mean heart rates below 125 and were stored at the ICM because of short-lasting bursts in heart rate or short-lasting T-wave oversensing. Twenty-one of the 26 patients (81%) patients with normo-frequency AF events experienced AF events with fast heart rates occurring within the diagnostic window. Also, only 2 patients were diagnosed clinically during follow-up or Holter monitoring without an event on the ICM. Thirdly, all known clinical and demographic risk factors were reproduced in this population using 12-lead ECG.¹³ Thus, we believe the proportion of patients with undiagnosed AF events was relatively limited in this study. Although recordings containing artifacts and sinus tachycardia tended to be more frequent in patients without new-onset AF than in patients with AF, the proportion of patients with full memory at follow-up was similar between AF and non-AF patients, indicating that the higher proportion of artifacts did not affect the diagnostic efficacy of the device. Another important limitation was the memory capacity of the ICM. The memory of the ICM contains 13 slots for automatic recordings. When the memory is filled up, the oldest recording is deleted when a new event is stored. Thus, important arrhythmias occurring shortly after the previous follow-up could have been deleted in patients with frequent events. Also, setting the threshold for triggering of the ICM to heart rates at 125 beats/min or higher, a much lower rate than used in patients with syncope, increases the

risk for storing inappropriate activation of the device because of t-wave oversensing, sinus tachycardia, or similar.

Conclusion

The risk for new-onset AF is increased in the first 12 months after AMI in patients with left ventricular systolic dysfunction. Using an ICM, we documented a 4-fold higher incidence of clinically significant AF in post-MI patients with reduced LVEF than in earlier trials. Correspondingly, only 21% of the patients with new-onset AF experienced any symptoms in conjunction with the AF events. Patients with new-onset AF events lasting 30 seconds or more were at higher risk for major cardiovascular events. These results underline the importance of using continuous monitoring in trials on AF patients and in clinical follow-up of patients at high risk for AF. Future trials are warranted to investigate whether early preventive treatment of post-MI patients at high risk for new-onset AF will reduce the high incidence of major cardiovascular events in this population.

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