Mortality Associated With Atrial Fibrillation in Patients With Myocardial Infarction

A Systematic Review and Meta-Analysis

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Background—Atrial fibrillation (AF) is a common finding in patients with myocardial infarction (MI). Atrial fibrillation is not generally perceived by clinicians as a critical event during the acute phase of MI; however, its prognostic influence in MI remains controversial. Furthermore, contradictory data exist concerning the risk of death according to AF timing. This article, a systematic review and first meta-analysis, aims to quantify the mortality risk associated with AF in MI patients and its timing.

Methods and Results—A comprehensive search of several electronic databases (1970 to 2010; adults, any language) identified MI studies that evaluated mortality related to AF. Evidence was reviewed by 2 blinded reviewers with a formal assessment of the methodological quality of the studies. Adjusted odds ratios were pooled across studies using the random-effects model. The I^2 statistic was used to assess heterogeneity. In the 43 included studies (278 854 subjects), the mortality odds ratio associated with AF was 1.46 (95% confidence interval, 1.35 to 1.58; I^2=76%; 23 studies). This worse prognosis persisted regardless of the timing of AF; the odds ratio of mortality for new AF with no prior history of AF was 1.37 (95% confidence interval, 1.26 to 1.49), I^2=28%, 9 studies), and for prior AF was 1.28 (95% confidence interval, 1.16 to 1.40; I^2=24%; 4 studies). The sensitivity analysis of new AF studies adjusting for confounding factors did not show a decrease in risk of death.

Conclusions—Atrial fibrillation is associated with increased risk of mortality in MI patients. New AF with no history of AF before MI remained associated with an increased risk of mortality even after adjustment for several important AF risk factors. These subsequent increases in mortality suggest that AF can no longer be considered a nonsevere event during MI. (***Circulation*. 2011;123:1587-1593.**)

Key Words: atrial fibrillation ■ myocardial infarction ■ mortality

Atrial fibrillation (AF) is a common finding in patients who have myocardial infarction (MI). Both conditions have increased frequency with advancing age, and acute MI is associated with a sharp increase in the occurrence of AF. The incidence of AF among MI patients varies between 2% and 22%.[1–7] Compared with severe complications, such as ventricular tachycardia or cardiac failure, AF is generally not perceived by clinicians as a critical event during the acute phase of MI; however, in the literature, the prognostic influence of the presence of AF in MI remains controversial. Some studies illustrated an independent adverse effect on mortality,[2,5,6,8–12] whereas other studies showed no significant effects.[1,3,4,13–15] In 2009, a review of AF in acute MI suggested that AF in patients hospitalized for MI seems to carry adverse prognostic implications for in-hospital and long-term mortality.[16] However, no meta-analysis has been published addressing this question.

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Furthermore, AF may occur as a complication of the MI or be present (diagnosed or not) at the time of the MI. Some studies demonstrated that new AF at the time of MI is associated with an increased risk of mortality, contrasting with a lack of risk with preexisting AF,[10] whereas other studies did not show a different risk of death according to AF timing.[9,17] To address these controversies, we performed a systematic review and a meta-analysis of the data available to date, aiming to quantify the mortality risk associated with the presence of AF in MI patients and its timing.

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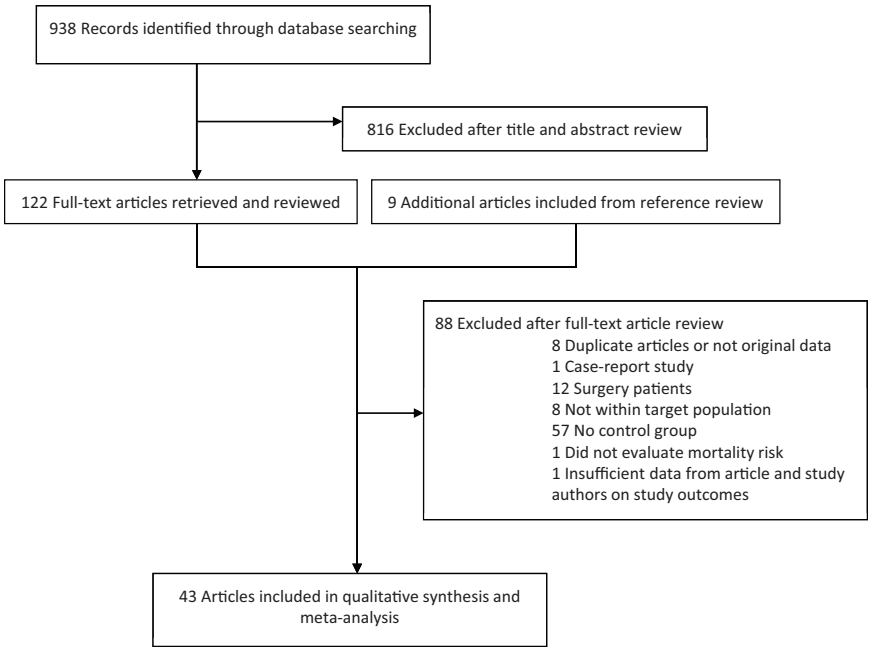

Figure 1. Literature search and study selection.

Methods

This meta-analysis is in adherence with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and the reporting Meta-Analyses of Observational Studies in Epidemiology (MOOSE).[18,19]

Eligibility Criteria

Eligible studies were randomized, controlled clinical trials and observational studies that enrolled patients with acute MI and AF and evaluated the outcome of mortality.

To be considered for inclusion, studies were also required to perform comparisons with a control group of patients without AF and to provide sufficient quantitative data on all-cause mortality or cardiovascular death. We excluded studies that evaluated AF after the first week of MI diagnosis, and those reporting exclusively AF in the context of surgery or catheter ablation. We also excluded abstracts, editorials, reviews, case reports, and case series.

We classified AF in each study as new AF, prior AF, or any AF, according to the authors' classification. New AF was defined by most studies as AF occurring for the first time after the MI with no history of AF before MI. Few studies did not report whether patients had AF preceding their MI, and new AF was defined in these studies as the first occurrence of AF during the infarction period in the absence of AF on admission ECG records. Prior AF was defined as AF preexisting before the MI admission. If no distinction about the first occurrence timing of AF was made, AF was classified as any AF. We classified mortality as all-cause or cardiovascular death if all-cause death was not available.

Data Sources and Search Strategies

A comprehensive search of several electronic databases (from 1970 to February 2010; adults, any language, any population) was conducted. The databases searched to identify studies that evaluated mortality related to AF in MI patients included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Health Technology Assessment, and Scopus. The search strategy was designed and conducted by an experienced librarian, with input from the principal investigator of the study. Controlled vocabulary supplemented with keywords was used to define the concept areas—MI, AF/flutter, and mortality—and to limit the search to randomized, controlled studies and observational studies. The detailed search strategy is available from the corresponding author. In addition, we reviewed the reference sections of eligible studies and available reviews. We also requested potentially eligible studies from content experts.

Two reviewers (P.J., A.M.C.), working independently, considered the potential eligibility of each of the abstracts and titles that resulted from executing the search strategy and then reviewed the full text of all potentially eligible studies. The chance-adjusted interreviewer agreement (κ statistic) for study eligibility was 0.82 (95% confidence interval [CI], 0.72 to 0.92). The study selection process is outlined in Figure 1. Disagreements were harmonized by consensus.

Data Collection

Data extraction included full description of participants enrolled, AF timing and evaluation duration, the confounding factors adjusted for, and the outcome measure. Authors were contacted in case of uncertainty about the data. Two reviewers working independently and using a standardized form extracted data from all eligible studies. Data collected included study characteristics, such as author name, year of publication, study size, patient age, AF description, unadjusted and adjusted estimated risk of mortality, and adjustment variables (Appendixes I and II in the online-only Data Supplement and the Table). The Newcastle-Ottawa Scale was used to assess the quality of studies.[28] A quality score was calculated on the basis of 3 major components: selection of the study groups (0 to 4 points), quality of the adjustment for confounding (0 to 2 points), and ascertainment of the exposure and outcome (0 to 3 points). A higher score represents better methodological quality.

Statistical Analysis

We chose to use an odds ratio (OR) as a measure of effect size because it was one of the most commonly used effect measures in our studies. To avoid unnecessary heterogeneity, we formed homogeneous groups of studies according to the adjustment status of the estimated risk. If several estimates were reported in the same article, we chose the most fully adjusted estimate (ie, multivariate regression was selected over univariate regression) corresponding to the longer follow-up. Unadjusted and adjusted ORs with 95% CIs of AF impact on mortality were pooled separately across studies with the use of the random-effects model. Statistical heterogeneity across the studies was tested with the Q statistic, and the I^2 statistic was calculated to quantify inconsistency among studies.[29] I^2 values of $\leq$25%, 50%, and $\geq$75% represent low, moderate, and high inconsistency, respectively. Because therapies for MI have evolved considerably over the

Table. Characteristics of Studies on New Atrial Fibrillation With No History of Atrial Fibrillation Before the Myocardial Infarction

Source	Follow-Up Duration	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Key Prognostic Variables					
				Age	Diabetes Mellitus	Hypertension	Prior MI	Heart Failure	Coronary Revascularization
Randomized trials									
Pedersen et al,[11] 1999	5 y	NR	1.4 (1.2–1.7)	X	X	X	X	X	X
Lehto et al,[9] 2005	3 y	NR	1.8 (1.4–2.4)	X	X			X	X
Nonrandomized trials									
Community studies									
Saczynski et al,[12] 2009	5 y	NR	1.3 (1.2–1.4)	X	X	X	X	X	
Registries									
Behar et al,[1] 1992	6 y	2.2 (1.8–2.8)	1.3 (1.1–1.5)	X	X		X	X	
Eldar et al,[3] 1998	1 y	3.5 (2.6–4.6)	1.3 (1.1–1.7)	X	X		X	X	
Mehta,[10] 2003	Hosp	3.7 (3.1–4.4)	1.7 (1.3–2.1)	X	X	X	X	X	
Lau et al,[20] 2009	1 y	3.3 (2.1–5.3)	1.4 (0.8–2.2)	X			X	X	X
Convenience sample									
Klass and Haywood,[21] 1970	Hosp	4.7 (2.0–10.9)	NR						
Cristal et al,[22] 1976	Hosp	4.6 (2.1–10.0)	NR						
Liem et al,[23] 1976	Hosp	1.8 (1.1–3.1)	NR						
Liberthson et al,[24] 1976	Hosp	0.8 (0.4–1.8)	NR						
Kobayashi et al,[25] 1992	Hosp	2.6 (0.9–7.5)	NR						
Cicek et al,[26] 2003	30 d	7.4 (0.9–70.3)	NR						
Asanin et al,[13] 2005	7 y	2.5 (1.8–3.6)	1.1 (0.7–1.8)	X	X	X	X	X	X
Trappolini et al,[15] 2006	Hosp	2.4 (1.4–4.1)	1.5 (0.8–2.8)	X	X	X	X	X	X
Siu et al,[27] 2007	3 y	0.9 (0.4–2.1)	NR						
Li et al,[14] 2008	Hosp	NR	NR						
Total		2.6 (2.1–3.3)	1.4 (1.3–1.5)						

OR indicates odds ratio; CI, confidence interval; MI, myocardial infarction; NR, not reported; and Hosp, during hospitalization.

time frame of the studies analyzed, we conducted meta-regressions using the effect size as the dependent outcome variable and the year of inclusion in the study as the independent variable. To assess the potential for publication bias, we performed the Begg and Mazumdar rank correlation test.[30] A value of $P<0.05$ (2 sided) was considered statistically significant. Analysis was conducted with Comprehensive Meta-Analysis software (Biostat, Englewood, NJ).

Subgroup and Sensitivity Analyses

Subgroup analyses were conducted by pooling time-specific AF estimates (new AF with no prior history of AF–prior AF) to evaluate the mortality risk of AF according to its timing of development from MI onset. Then, a sensitivity analysis was conducted by excluding new AF studies that did not adjust for age, diabetes mellitus, heart failure, and coronary revascularization. Finally, we conducted a sensitivity analysis on new AF studies that adjusted for age, diabetes mellitus, hypertension, prior MI, heart failure, and coronary revascularization because of the substantial importance of these confounders.

The study sponsor had no role in study design, data collection, analysis, or interpretation of data. The sponsor did not participate in the writing of the report or in the decision to submit the paper for publication. All authors had full access to all the data in the study, and all authors agreed to submit the paper for publication.

Results

Study Identification

Nine hundred thirty-eight potentially relevant studies were identified. After title and abstract screening, 816 studies were excluded, and the remaining 122 studies were retrieved for a more detailed evaluation (Figure 1). Nine additional studies were identified through manual review of references. Of these 131 clinical studies, 88 were excluded because they did not meet eligibility. Finally, 43 studies were included in our review: 8 studies[2,5,7,9,11,17,31,32] derived from randomized trials, 31 cohort studies,[1,3,4,6,8,10,12,14,15,20,21,22,24,26,27,33–48] and 4 case-control studies.[13,23,25,49] For the purpose of this study, we dealt with the 8 studies derived from randomized trials as observational studies, with the population being analyzed as a whole without taking into account the randomization process.

Appendix I in the online-only Data Supplement summarizes the characteristics of the 43 eligible studies. Sample size ranged from 100 to 106 780, with a median of 967 patients and a mean age of 65 years. Across the 40 studies that reported participant sex, 30% were women. The years of MI diagnosis ranged from 1972 to 2007. Exposure was poorly described in the included studies; therefore, it was not always clear whether patients with prior AF were included. In these cases, AF was classified as any AF. Additionally, new AF included AF on admission ECG in some studies,[17,21] whereas several studies excluded it.[4–6,31,42] Across the 22 studies that reported the number of participants with any AF, the incidence of AF was 13% (range, 4% to 25%). Across the 30 studies that reported the number of participants with new AF,

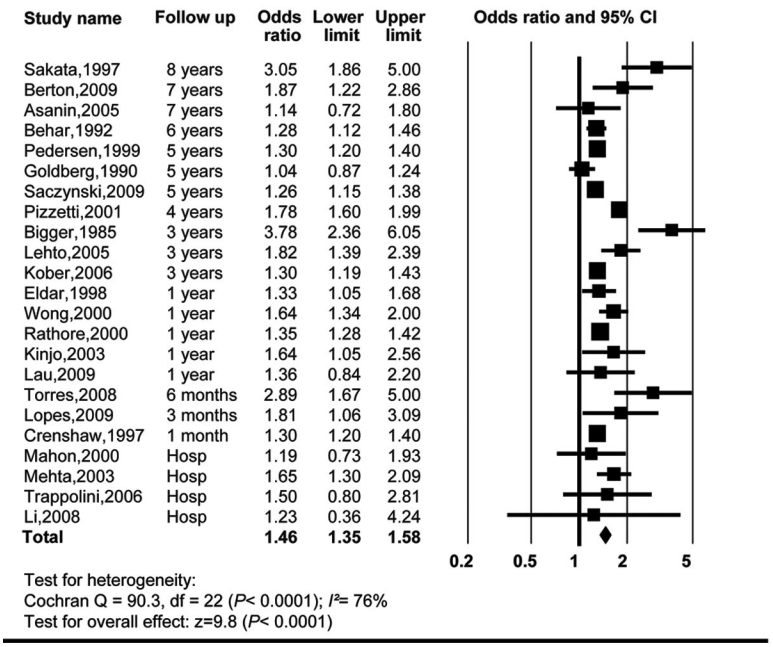

Figure 2. Mortality and atrial fibrillation in myocardial infarction patients. CI indicates confidence interval.

the incidence of AF was 10% (range, 4% to 19%). Across the 11 studies that reported the number of participants with prior AF, the incidence of AF was 7% (range, 1% to 13%). Evaluation of AF occurred mostly during the hospital stay or less, with only 1 study[9] that evaluated AF during a median of 3 years after the qualifying MI. Follow-up time varied widely across studies. In this meta-analysis, the pooled mortality analysis referred to all-cause mortality except for 1 study,[41] which reported only cardiovascular mortality. Loss to follow-up was generally low (<5%). Quality score as evaluated by the Newcastle-Ottawa Scale revealed a median score of 7 (range, 4 to 8; Appendix I in the online-only Data Supplement). The 20 studies that reported only unadjusted ORs had a median score of 5.

Meta-Analysis

After the 43 eligible studies were pooled, there was a significant association between AF and mortality (for both available unadjusted and adjusted ORs). However, the mortality risk estimate was significantly higher for the unadjusted ORs. For this reason, we decided to report only mortality estimates after accounting for the confounding factors. A total of 23 of the 43 studies presented ORs and 95% CIs for mortality after multivariate analysis (Appendix II in the online-only Data Supplement). The mortality OR associated with AF was 1.46 (95% CI, 1.35 to 1.58; I^2=76%; Figure 2). Although the heterogeneity between the analyzed studies was high, almost all of the studies pointed to a positive association. The meta-regression analysis showed no association between the effect size and the year of inclusion in the studies (P=0.38), confirming that our findings were consistent over time. There was no statistical evidence of publication bias among the included studies by the Begg test (P=0.06).

Subgroup and Sensitivity Analyses

The Table summarizes the characteristics of the 17 studies evaluating new AF with no history of AF before MI. The significant association between AF and mortality was similar when analysis was performed for new AF and prior AF subgroups; the OR of mortality for new AF with no prior history of AF was 1.37 (95% CI, 1.26 to 1.49; I^2=28%; 9 studies) and for prior AF was 1.28 (95% CI, 1.16 to 1.40; I^2=24%; 4 studies; Figures 3 and 4). There was no statistical evidence of publication bias (P=0.18 and P=1.00, respectively). The heterogeneity between the analyzed studies decreased substantially compared with the main analysis.

We conducted several sensitivity analyses pooling studies according to their follow-up duration: short-term (≤30 days), midterm (>30 days to 1 year), or long-term (>1 year) mortality. The time frame had relatively little effect on the estimates (data not shown).

Because the selection for confounding factors varied widely between studies evaluating new AF and no prior AF (the Table), we conducted sensitivity analyses to assess robustness. Analyses of studies that did adjust for age, diabetes mellitus, heart failure, and coronary revascularization showed a strong association between new AF and mortality (OR, 1.49; 95% CI, 1.26 to 1.76; 4 studies). Finally, the association between new AF and mortality in studies that adjusted for age, diabetes mellitus, hypertension, prior MI, heart failure, and coronary revascularization remained almost similar (OR, 1.39; 95% CI, 1.19 to 1.63; 3 studies).

Discussion

Findings

This is the first meta-analysis of clinical studies on the prognostic impact of AF in the setting of MI. In this meta-analysis of 43 studies involving 278 854 patients, we have demonstrated an increased risk of mortality associated with the presence of AF in the setting of MI. Indeed, AF is associated with at least a 40% increase in the risk of mortality compared with control patients in sinus rhythm. Our analysis

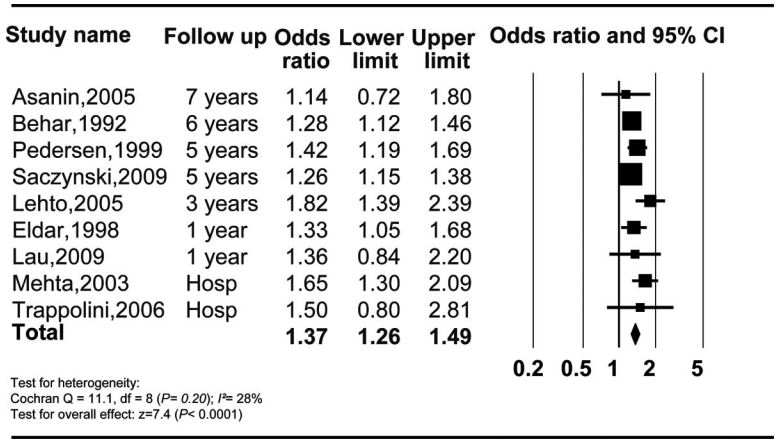

Figure 3. Mortality and new atrial fibrillation after myocardial infarction. CI indicates confidence interval.

further demonstrates that this worse prognosis persists regardless of the timing of AF development. Finally, new AF with no history of AF before MI remained associated with an increased risk of death even after adjustment for age, diabetes mellitus, hypertension, prior MI, heart failure, and coronary revascularization status.

The results of previous studies on the impact of AF on survival in patients with MI were conflicting. Some studies showed no significant adverse effect on mortality,[1,3,4,13–15] and other studies illustrated an independent adverse effect.[2,5,6,8–12]

It is plausible that studies showing no increased risk were imprecise and that the present meta-analysis includes a larger number of events, and thus has increased power. It was also unclear whether the presence of AF before the MI is associated with an adverse prognosis.[6,10,11,20] Our meta-analysis demonstrated that the increased mortality risk seems to be related to AF regardless of its timing of development.

There are several potential explanations for the observed association between increased all-cause mortality and AF in MI patients. New AF may lead to adverse outcomes in patients with MI through adverse hemodynamic effects, such as loss of atrial contraction, rapid ventricular rates, loss of atrioventricular synchrony, and an irregular RR interval, leading to a decrease in cardiac output.[50] Additionally, the combination of AF and heart failure is particularly ominous in that it appears that the development of either condition has a marked detrimental impact on the mortality of the other.[51–53] Pooling selected studies that adjusted for patient characteristics, heart failure, and acute treatment of MI showed the same association between mortality and new AF. The worse prognosis in patients with MI who develop AF seems to be directly correlated with the arrhythmia, in addition to the severity of the clinical conditions of the patients. However, it is still unclear whether AF is a complication of MI or merely demarcates MI severity. Finally, in AF patients with MI requiring percutaneous coronary intervention (PCI) with stent implantation, the optimal association between aspirin, clopidogrel, and oral anticoagulant remains cumbersome and renders the clinical management of MI in the presence of AF more difficult. Aspirin is given systematically during acute MI, and dual antiplatelet therapy (clopidogrel and aspirin) is the gold standard treatment after acute coronary syndrome and percutaneous coronary intervention.[54] In AF patients, triple therapy and dual therapy with aspirin and oral anticoagulant are associated with a high frequency of major bleedings,[55] and the use of clopidogrel and oral anticoagulant combination is associated with a relatively high incidence of fatal stroke.[56] In daily clinical practice, oral anticoagulation is given to only a minority of MI patients with AF, despite the fact that oral anticoagulation is associated with a reduction in 1-year mortality.[31,57] Ongoing and further research is needed to identify ways to prevent the occurrence of AF during MI and to determine the optimal AF therapeutics for patients with MI to reduce mortality.

Strengths and Limitations

Several limitations of this study should be considered. First, we included some randomized trials that were not designed to capture AF; thus, reporting bias is a possibility. However, the incidence rates of AF were consistent with the rates found in the general population, which suggests that AF was adequately ascertained by appropriate surveillance to capture this

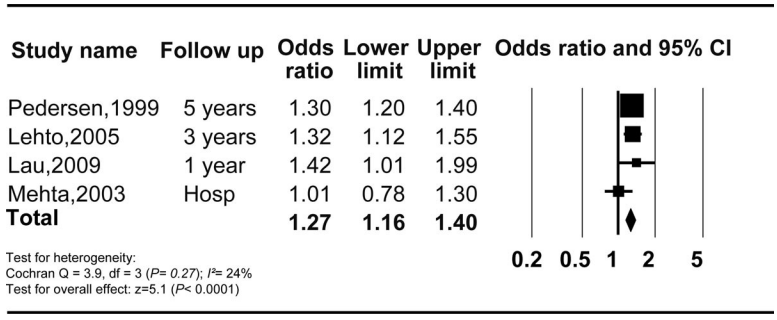

Figure 4. Mortality and atrial fibrillation before myocardial infarction. CI indicates confidence interval.

event. Second, we could not investigate the effects of persistent AF versus paroxysmal AF on mortality because the studies used for our meta-analysis did not investigate this issue. Third, significant heterogeneity between included studies was noted in the main analysis, as is often the case in meta-analyses of large observational studies.[58,59] Potential sources of heterogeneity include patient demographics, follow-up duration, outcome ascertainment, adjustment for confounders, and study quality. Moreover, studies included in the review span several decades (published between 1970 and 2009), during which time great advances were made in the treatment of MI. The use of optimal meta-analytic techniques with random-effects models cannot account for these differences. However, there was virtually no qualitative heterogeneity, and subgroup and sensitivity analyses confirmed robustness by showing results similar to the main analysis. Finally, we did not have patient-level data, the gold standard method to test for interactions at the patient-level covariates.

Our study has several important strengths. We conducted a comprehensive up-to-date literature search with evidence reviewed by 2 blinded reviewers with adequate interreviewer agreement and formal assessment of the methodological quality of the studies. In addition, our pooled estimates are based on multivariate ORs of studies adjusting for several important AF risk factors. Subgroup analyses and sensitivity analyses confirmed the robustness of our main results. Finally, there was no statistical evidence of publication bias.

Conclusions

The presence of AF is associated with an increased risk of mortality in MI patients, regardless of the timing of AF. This subsequent 40% increase in mortality associated with AF during MI suggests that AF can no longer be considered a nonsevere event. New AF with no history of AF before MI remained associated with an increased risk of mortality even after adjustment for several important AF risk factors. Closer attention should be paid to patients with AF complicating MI, including diligent monitoring during the acute phase of MI.

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Disclosures

None.

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CLINICAL PERSPECTIVE

This is the first systematic review and meta-analysis of studies addressing the prognostic impact of atrial fibrillation in the setting of myocardial infarction. In this meta-analysis of 43 studies involving 278 854 patients, atrial fibrillation was associated with at least a 40% increase in the risk of mortality among patients with myocardial infarction, regardless of the timing of the atrial fibrillation. This worse prognosis persisted even after the studies adjusted for age, diabetes mellitus, hypertension, prior myocardial infarction, heart failure, and coronary revascularization. These findings indicate that atrial fibrillation can no longer be considered a trivial event during the acute phase of myocardial infarction. Research is needed to evaluate potential strategies and interventions to reduce this risk.

Mortality Associated With Atrial Fibrillation in Patients With Myocardial Infarction: A Systematic Review and Meta-Analysis

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLES

Appendix 1. Characteristics of included studies

Source	Mean Age, y	Female %	No. of Patients	Years of Diagnosis	AF Type	AF Incidence Any/New/Prior	AF Evaluation	Mortality Measures	Selection	Comparability	Outcome Ascertainment	Newcastle-Ottawa Scale
Randomized Trials												
Crenshaw,[2]1997	62	25	40891	1990-1993	Any	10%/NR/NR	Hosp	30 d	3	1	2	6
Pedersen,[11]1999*	69	42	6676	1990-1992	Any/New[#]/Prior	21%/17%/4%	Hosp	Hosp, 5 y	3	2	3	8
Wong,[7]2000*	63	27	13858	1995-1997	New	NR/7%/NR	Hosp	30 d, 1 y	3	2	3	8
Pizzetti,[5]2001*	NR	22	17749	1991-1993	New	NR/8%/NR	Hosp	Hosp, 6 m, 4 y	3	2	3	8
Lehto,[9]2005*	67	29	5477	1998-1999	Any/New[#]/Prior	NR/7%/12%	3 y	30 d, 3 y	3	2	3	8
Kober,[17]2006	67	32	14660	1998-2001	Any/New/Prior	15%/12%/2%	10 d	3 y	3	2	3	8
Tangelder,[24]2008	67	31	1883	2001-2002	New	NR/9%/NR	R	6 m	3	0	2	5
Lopes,[23]2009	61	24	5745	2004-2006	Any/New/Prior	11%/6%/5%	14 d	90 d	3	2	2	7
Non Randomized Trials												
Community studies												
Goldberg,[28]1990	66	47	4108	1975-1986	Any/New	16%/9%/NR	Hosp	Hosp, 5 y	3	2	3	8
Saczynski,[12]2009	69	43	7513	1990-2005	New[#]	NR/13%/NR	Hosp	Hosp, 1 y, 5 y	3	2	2	7
Registries												
Behar,[1]1992	64	26	5803	1981-1983	New[#]	NR/10%/NR	Hosp	Hosp, 1y, 6 y	4	2	3	8
Eldar,[3]1998	63	26	2866	1992-1996	New[#]	NR/9%/NR	CCU	30 d, 1y	4	2	3	8
Rathore,[6]2000*	77	50	106780	1994-1996	Any/New/Prior	22%/11%/11%	Hosp	Hosp, 1 y	2	2	1	5
Mehta,[10]2003*	65	32	21785	1999-2001	New[#]/Prior	NR/6%/8%	Hosp	Hosp	3	2	2	7
Kinjo,[4]2003*	64	23	2475	1998-2002	Any/New	12%/8%/NR	Hosp	Hosp, 1 y	3	2	3	8
Lau,[32]2009	65	36	3230	2005-2007	New[#]/Prior	NR/4%/11%	Hosp	Hosp, 1 y	3	2	2	7
Convenience sample												
Klass,[30]1970	66	NR	409	1966-1968	New[#]/Prior	NR/8%/1%	Hosp	Hosp	3	0	1	4
Cristal,[27]1976*	60	24	318	NR	New[#]	NR/11%/NR	CCU	Hosp	3	0	2	5
Liem,[48]1976	68	29	700	1972-1974	New[#]	NR/8%/NR	5 d	Hosp	2	0	2	4
Liberthson,[33]1976	64	NR	917	1968-1974	New[#]	NR/6%/NR	CCU	Hosp	3	0	2	5
Hunt,[29]1978	NR	NR	969	1972-1975	Any	11%/NR/NR	CCU	Hosp, 1y	3	0	3	6
Sugiura,[42]1985	63	39	102	NR	New	NR/18%/NR	3 d	Hosp	3	2	2	7
Bigger,[25]1985	NR	23	504	1974-1980	Any	4%/NR/NR	CCU	3 y	3	2	3	8
Nielsen,[49]1991	60	22	152	1988-1989	Any	9%/NR/NR	CCU	Hosp	3	0	2	5
Petretta,[36]1991	66	25	275	1985-1988	Any	NR/NR/NR	NR	Hosp	3	0	2	5
Kobayashi,[47]1992*	64	14	127	1984-1987	New[#]	NR/18%/NR	CCU	Hosp	2	0	2	4
Suarez,[41]1995	74	30	322	1988-1991	Any	NR/NR/NR	NR	Hosp	3	0	2	5
Madias,[34]1996	64	30	517	NR	Any/New	14%/11%/NR	Hosp	Hosp	3	0	2	5
Sakata,[38]1997	66	25	1039	1985-1995	Any/New/Prior	10%/8%/1%	Hosp	Hosp, 8 y	3	2	2	7
Galcera Thomas,[45]1999	65	23	1239	1992-1994	Any	8%/NR/NR	Hosp	Hosp, 1 y	3	0	2	5

Appendix 1. Continued

Source	Mean Age, y	Female %	No. of Patients	Years of Diagnosis	AF Type	AF Incidence Any/New/Prior	AF Evaluation	Mortality Measures	Selection	Comparability	Outcome Ascertainment	Newcastle-Ottawa Scale
Mahon,[35]2000	67	40	852	1992-1994	Any	20%/NR/NR	Hosp	Hosp	3	2	2	7
Janion,[46]2001	59	28	881	1992-1996	Any	12%/NR/NR	Hosp	Hosp, 1 y, 6 y	3	1	2	6
Cicek,[26]2003	59	23	100	NR	New[#]	NR/19%/NR	Hosp	30 d	3	0	1	4
Asanin,[13]2005	64	31	650	1996-1998	New[#]	NR/10%/NR	CCU	Hosp, 7 y	1	2	2	5
Rastenyte,[37]2005*	54	25	2008	1983-1992	Any	7%/NR/NR	Hosp	1 y	4	0	2	7
Trappolini,[15]2006	75	25	848	2000-2003	New[#]	NR/10%/NR	CCU	Hosp	3	2	2	7
Siu,[40]2007	64	25	431	1997-2005	New[#]	NR/14%/NR	Hosp	3 y	3	0	3	6
Li,[14]2008	74	36	967	2001-2006	Any/New[#]/Prior	10%/7%/4%	Hosp	Hosp	3	2	2	7
Sankaranarayanan,[39]2008	68	28	500	2000-2001	Any/New/Prior	25%/11%/13%	Hosp	Hosp, 1 y, 6 y	3	0	3	6
Koracevic,[31]2008	64	45	543	2000-2005	Any	11%/NR/NR	NR	Hosp	3	0	2	5
Torres,[43]2008	65	28	1183	2003-2005	Any	12%/NR/NR	2 d	Hosp, 6 m	3	2	2	7
Cui,[44]2008*	63	30	297	2001-2005	Any	11%/NR/NR	10 d	30 d, 6 m	3	0	1	4
Berton,[8]2009*	70	29	505	1995-1998	Any/New	13%/9%/NR	7 d	Hosp, 7 y	3	2	3	8

AF, Atrial Fibrillation; MI, Myocardial Infarction; NR, Not Reported; R, Until randomization; Hosp, during hospitalization; d, days; m, months; y, years; CCU, Coronary Care Unit stay.
Any AF=AF during the MI; New AF=AF occurring after the MI; Prior AF=Pre-existing AF to MI.
*Studies that evaluated Atrial Fibrillation and/or Atrial Flutter
For the purpose of this study, we dealt with studies derived from Randomized Trials as observational studies.
Exposure ascertainment for case-control studies
[#]New AF with no history of AF prior to MI.

Appendix 2. Factors adjusted for in the included studies

Source	Adjustment Variables
Randomized Trials	
Crenshaw,[2] 1997*#	Age-Gender-Heart Rate-Killip class-Current smoker-Former smoker-Systolic Blood Pressure-Diastolic Blood Pressure-Hypertension-Previous MI-Diabetes-Weight-Height-MI location-Peak Creatine Kinase level-Time to Thrombolytic therapy-Thrombolytic therapy
Pedersen,[11] 1999*#	Age-Gender-Wall Motion Index-Thrombolytic therapy-Previous MI-Hx Angina Pectoris-Hx Hypertension-Hx Diabetes Mellitus-Congestive Heart Failure-Ventricular Fibrillation-Ventricular Tachycardia
Wong,[7] 2000	Age-Systolic Blood Pressure-Weight-Killip class-Heart Rate-Infarct location-Hypertension-Diabetes Mellitus-Prior angioplasty-Prior Cerebrovascular Disease-Prior bypass surgery-Recurrent Angina-Reinfarction-Worsening Heart Failure-Hypotension-Shock-Third degree Heart Block-Ventricular Fibrillation-Severe Bleeding
Pizzetti,[5] 2001	Age-Gender-MI location-Previous MI-Hx Hypertension-Hx Diabetes Mellitus-Killip class-Systolic Blood Pressure-Hx Angina-Time from onset of symptoms-Heart Rate-Antiarrhythmics-Randomised treatment
Lehto,[9] 2005*	Age-Heart Rate-Prior MI-Smoking-Diabetes Mellitus-Hx Hypercholesterolemia-Hx chronic Heart Failure-Killip class-Thrombolytic use-Statin use
Kober,[17] 2006*	Age-Pulse Pressure-Baseline Creatinine-Heart Rate-Weight-Anterior MI-New Left Bundle Branch Block-Smoking status-Killip class at qualifying MI-Hx Angina-Hx Heart Failure-Hx Unstable Angina- Hx Peripheral Arterial Disease- Hx Alcohol abuse-Hx Stroke- Hx Chronic Obstructive Pulmonary Disease-Prior MI-Prior Percutaneous Transluminal Coronary Angioplasty, Coronary Artery Bypass Graft or Thrombolytics-Previous Hospitalizations-Renal function-Diabetes Mellitus-Country of enrollment-Randomized treatment
Tangelder,[24] 2008	NR
Lopes,[23] 2009*#	Age-Gender-US patients-Height-Weight-Systolic Blood Pressure-Diastolic Blood Pressure-Heart Rate-Killip class-MI location-Hx MI-Hx Coronary Artery Disease-Hx Congestive Heart Failure-Hx Diabetes-Hx Hypertension-Hx Stroke-Hx Transient Ischaemic Attack-Prior Percutaneous Coronary Intervention-Prior Coronary Artery Bypass Grafting-Current smoking-Creatinine clearence-Creatine Kinase level-Creatine Kinase MB level-Troponin-Brain Natriuretic Peptide-Intraaortic Balloon Pump-Automatic Implantable Cardioverter Defibrillator-Percutaneous Coronary Intervention-Cardiac Surgery-Red Blood Cell Transfusion-Recatheterization-RePercutaneous Coronary Intervention-Stents-Moderate or severe Bleed-Congestive Heart Failure-Shock-Cardiac Arrest-Deep Vein Thrombosis-Acute Ventricular Septal Defect-Recurrent MI-Recurrent ischemia-Renal Failure-Pulmonary Embolism-Stroke-Cardiac Tamponade-Ventricular Fibrillation-Ventricular Tachycardia-Ventricular Rupture-Pericarditis-Acute Mitral Regurgitation-Asystole-Acute Atrioventricular Block
Non Randomized Trials	
Community studies	
Goldberg,[28] 1990	Age-Gender-MI order-Congestive Heart Failure-Cardiogenic Shock-Ventricular Tachycardia-Ventricular Fibrillation-Drug therapy
Saczynski,[12] 2009	Age-Gender-Hx Angina-Hx Hypertension-Hx Diabetes Mellitus-Hx Stroke-Hx Heart Failure-Previous MI-Q wave-Anterior MI-ST segment elevation-Heart Failure-Cardiogenic Shock-Stroke- Length of hospital stay
Registries	
Behar,[1] 1992	Age-Gender-Hx MI-Diabetes Mellitus-Congestive Heart Failure-Serum LDH level > 4 times the upper normal limit at the respective participating centre
Eldar,[3] 1998	Age-Gender-Previous MI-Diabetes Mellitus-Congestive Heart Failure
Rathore,[6] 2000	Age-Race-Gender-Heart Rate-Systolic Blood Pressure-Killip class-Hypertension-Time to presentation-Current smoker-Anterior MI-Prior Cerebrovascular Disease-Prior MI-Antiarrhythmic use
Mehta,[10] 2003	Age-Gender-ST segment elevation-Non ST segment elevation-Unstable Angina-US patients-Medical Hx-Prior Angina-Prior MI-Prior Stroke-Prior Congestive Heart Failure-Prior Percutaneous Coronary Intervention-Prior Coronary Artery Bypass Surgery-Current smoker-Hypertension-Diabetes Mellitus-Hyperlipidemia-Medications used-Heart Rate-Systolic Blood Pressure-Diastolic Blood Pressure-Serum Creatinine-Cardiac Arrest-Killip class-Q waves-Left Bundle Branch Block
Kinjo,[4] 2003	Age-Gender-Diabetes Mellitus-Hypertension-Current smoking-Previous MI-Previous Cerebrovascular Disease-Systolic Blood Pressure < 100 mm Hg-Heart Rate ≥ 100 beats/min-Killip class IV-Left Anterior Descending Artery-Multivessel Disease-TIMI flow grade 3
Lau,[32] 2009	Age-Increased Heart Rate-Elevated Cardiac Biomarkers-ST segment changes-Cardiogenic Shock-Impaired Renal function-Hx Ischemic Heart Disease or Heart Failure-Absence of Percutaneous Coronary Intervention

Appendix 2. Continued

Source	Adjustment Variables
Convenience sample	
Klass,[30]1970	NR
Cristal,[27]1976	NR
Liem,[48]1976	NR
Liberthson,[33]1976	NR
Hunt,[29]1978	NR
Sugiura,[42]1985	NR
Bigger,[25]1985	Age-Hx MI-Hx Angina pectoris-Cigarette smoking-Diabetes Mellitus-Left Ventricular Failure-Enlarged heart (x-ray)-Anterior MI-Creatine Kinase > 1000-Pulmonary vascular congestion-Diuretic therapy-Antiarrhythmic drugs-Beta Blocker therapy-Digitalis
Nielsen,[49]1991	NR
Petretta,[36]1991	NR
Kobayashi,[47]1992	NR
Suarez,[41]1995	NR
Madias,[34]1996	NR
Sakata,[38]1997	Age-Gender-Peak Creatine Kinase levels-Left Ventricular Ejection Fraction-Hypertension-Diabetes Mellitus-Hypercholesterolemia-Hx MI-Smoking
Galcera Thomas,[45]1999	NR
Mahon,[35]2000*#	Age-Gender-ST depression-ST elevation-T wave inversion-Left Bundle Brunch Block-Q wave-Smoking-Hypertension-Diabetes Mellitus-Family Hx-Previous MI-Thrombolysis-Coronary Care Unit-Left Ventricular Failure-Cardiogenic Shock
Janion,[46]2001	NR
Cicek,[26]2003	NR
Asanin,[13]2005*#	Age-Gender-Hx Hypertension-Hx Diabetes Mellitus-Previous MI-Hx Angina Pectoris-Thrombolysis-Peak Creatine Phosphokinase level-Beta Blocker therapy-Heart Failure during hospitalization
Rastenyte,[37]2005	NR
Trappolini,[15]2006*#	Age-Gender-Ischemic Events-Coronary Risk Factors-Killip class-Thrombolytic therapy-Pericarditis
Siu,[40]2007	NR
Li,[14]2008	Age-Killip class III/IV-Failure of revascularization
Sankaranarayanan,[39]2008	NR
Koracevic,[31]2008	NR
Torres,[43]2008*#	Age-Gender-Hx Diabetes Mellitus-Smoking-Hx Dyslipidemia-Hx Hypertension-Obesity-Hx Angina-Hx MI-Prior Percutaneous Transluminal Coronary Angioplasty or Coronary Artery Bypass Graft-Heart Failure-Coronary angiography-Reperfusion therapy-Severe Left Ventricular Dysfunction
Cui,[44]2008	NR
Berton,[8]2009*	Age-Diabetes Mellitus-Peak Creatine Kinase-Killip class > 1-Estimate Glomerular Filtration Rate-Thrombolysis-Left Ventricular Ejection Fraction

AF, Atrial Fibrillation; MI, Myocardial Infarction; Hx, History; NR, Not Reporting multivariate analysis

* Studies adjusting for Age, Diabetes, Heart Failure and Coronary Revascularization

Studies adjusting for Age, Diabetes, Hypertension, Prior MI, Heart Failure and Coronary Revascularization

심근경색 환자에서 동반된 심방세동, 사망률을 증가시킨다

최 기 준 교수 서울아산병원 심장내과

Summary

배경

심방세동은 심근경색 환자에서 흔히 관찰할 수 있으나, 일반적으로 급성기 심근경색에서 심방세동은 그리 중요한 질환으로 생각되지 않으며 예후적인 중요성은 확실히 밝혀지지 않았다. 더욱이 심방세동의 발생시기에 따른 사망의 위험도에 대해서는 상반된 결과를 보여주었다. 본 연구에서는 심근경색 환자에서 심방세동의 발생과 그 시점에 따른 사망률에 대해 체계적인 검토와 메타분석을 시행하였다.

방법 및 결과

1970-2010년 사이에 성인을 대상으로 시행된 여러 전자 데이터베이스들을 조사하여, 심근경색 관련 연구 중에서 심방세동과 관계된 사망률을 분석한 연구들을 구분하였다. 자료들은 두 명의 결과를 모르는 검열자에 의해 검토되었고, random-effects 모델을 이용하여 각 연구에서의 보정된(adjusted) odds ratio를 취합하였다. 비균질성 평가는 I^2 통계분석을 이용하였다. 조건에 맞는 43개의 연구(278,854명)에서 심방세동과 연관된 사망률 odds ratio는 1.46이었다(95% CI, 1.35-1.58; I^2=76%, 23개 연구). 이러한 사망률 증가 위험도는 심방세동의 발생 시점과 무관하였다. 과거 심방세동의 병력이 없었던 환자에서 발생한 새로운 심방세동의 사망률에 대한 odds ratio는 1.37이었고(95% CI, 1.26-1.49; I^2=28%, 9개 연구), 과거의 심방세동 병력이 있는 환자들에 대한 사망률 odds ratio는 1.28이었다(95% CI, 1.16-1.40; I^2=24%, 4개 연구). 새로운 심방세동 환자에 대해 복합변수를 보정한 민감도 분석에서도 사망률의 위험도는 감소하지 않았다.

결론

심근경색 환자에서 심방세동은 사망률의 위험 증가와 연관이 있다. 심근경색 이전에는 심방세동이 없었던 새로운 심방세동 환자에서, 여러 가지 주요 심방세동 위험인자로 보정을 하여도 심방세동은 사망률의 증가와 연관이 있었다. 이러한 사망률 증가는 심방세동이 심근경색과 연관된 중요하지 않은 합병증 중 하나가 아님을 시사한다.

Commentary

급성 심근경색 환자에서 심방세동은 자주 발견되는 현상으로, 발병률이 2-22% 정도로 보고된다. 하지만 이러한 심방세동의 중요성이나 사망률과의 연관성은 확실하지 않다. 몇몇 연구에서 심방세동을 사망률의 위험인자로 보고한 것에 반해, 일부 연구에서는 유의하지 않은 것으로 보고되었다. 또한, 심방세동을 원래 가지고 있던 환자에서의 심근경색과 심근경색과 동반된 새로운 심방세동 환자에서의 심방세동의 사망률과의 연관성에 대해서도 연구에 따라 결과가 상이하다. 따라서 본 연구에서는 이러한 의문점에 대한 해답을 얻기 위하여 이전의 심근경색 관련 연구들 중 심방세동에 관한 데이터가 충분한 환자들을 대상으로 심방세동과 사망률과의 연관성, 그리고 새로운 심방세동과 기존에 심방세동을 가지고 있었던 환자에서의 연관성이 다른지를 체계적인 검토와 메타분석을 이용하여 분석한 최초의 연구이다. 43개의 연구에서 278,854명의 심근경색 환자들을 분석한 결과 심방세동은 심근경색 환자의 사망률을 40% 이상 증가시키는 것으로 나타났다. 또한, 원래 심방세동을 가지고 있던 환자에서 사망률이 높았을 뿐 아니라, 심근경색과 동반되어 새로운 심방세동을 보였던 환자에서도 다른 위험인자(연령, 당뇨병, 고혈압, 심근경색의 병력, 심부전, 관상동맥 재관류 상태 등)에 대해 충분히 보정을 한 후에도 사망률의 증가를 보였다.

그렇다면 왜 심방세동 환자가 더 높은 사망률을 보일까? 심근경색과 동반되어 생기는 심방세동의 경우, 심방의 수축이 없어져 심방-심실 동기화가 소실되고 심박수가 빨라지는 등의 혈역학적 변화가 생겨 심박출량이 감소되는 것이 하나의 원인일 수 있겠으며, 심방세동과 심부전과의 악순환적인 연관성도 생각해 볼 수 있다. 하지만 이 연구 결과만으로는 심방세동이 심근경색의 합병증으로 발생하는 것인지, 심한 심근경색증에서 주로 발생하는 중증도의 표지자인지는 확실히 구분할 수 없다. 심근경색과 심방세동이 같이 있는 환자에서의 또 한가지 문제점은 항응고제와 항혈소판제의 병용 문제이다. 심근경색 환자에서 관상동맥 성형술과 함께 스텐트 시술을 한 경우에 아스피린이나 클로피도그렐과 같은 항혈소판제를 주로 사용하게 되는데, 와파린과의 병용 시 주요 출혈의 위험도가 증가하며 치명적인 뇌경색도 증가한다.

이 연구의 제한점으로는 심방세동의 발생을 주 목적으로 하는 연구가 아니었으므로 보고 오류(reporting bias)가 있을 수 있으며, 지속성 심방세동과 발작성 심방세동의 구별이 없었다는 점이다. 향후 심근경색 환자에서 심방세동의 발생을 줄일 수 있는 방법이 개발된다면 환자의 예후를 개선시킬 수 있을 것으로 기대되며, 또한 심근경색과 심방세동이 같이 있는 환자에서의 적절한 치료지침이 연구되어야 할 것으로 생각된다.