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Long-term prognostic outcomes and implication of oral anticoagulants in patients with new-onset atrial fibrillation following st-segment elevation myocardial infarction

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Background New-onset atrial fibrillation (NEW-AF) following ST-segment elevation myocardial infarction (STEMI) is a common complication, but the true prognostic impact of NEW-AF is unknown. Additionally, the optimal treatment of NEW-AF among patients with STEMI is warranted.

Methods A large cohort of consecutive patients with STEMI treated with percutaneous coronary intervention were identified using the Eastern Danish Heart Registry from 1999-2016. Medication and end points were retrieved from Danish nationwide registries. NEW-AF was defined as a diagnosis of AF within 30 days following STEMI. Patients without a history of AF and alive after 30 days after discharge were included. Incidence rates were calculated and multivariate analyses performed to determine the association between NEW-AF and long-term mortality, incidence of ischemic stroke, re-MI, and bleeding leading to hospitalization, and the comparative effectiveness of OAC therapy on these outcomes.

Results Of 7944 patients with STEMI, 296 (3.7%) developed NEW-AF. NEW-AF was associated with increased long-term mortality (adjusted HR 1.48, 95% CI 1.20-1.82, $P<.001$) and risk of bleeding leading to hospitalization (adjusted HR 1.36, 95% CI 1.00-1.85, $P=.050$), and non-significant increased risk of ischemic stroke (adjusted HR 1.45, 95% CI 0.96-2.19, $P=.08$) and re-MI (adjusted HR 1.14, 95% CI 0.86-1.52, $P=.35$) with a median follow-up of 5.8 years. In NEW-AF patients, 38% received OAC therapy, which was associated with reduced long-term mortality (adjusted HR 0.69, 95% CI 0.47-1.00, $P=.049$).

Conclusions NEW-AF following STEMI is associated with increased long-term mortality. Treatment with OAC therapy in NEW-AF patients is associated with reduced long-term mortality. (Am Heart J 2021;238:89–99.)

New-onset atrial fibrillation (NEW-AF) following ST-segment elevation myocardial infarction (STEMI) in patients treated with primary percutaneous coronary intervention (PPCI) is a common complication with an incidence ranging from 3.6 to 5.3%[1-3]. Several risk factors to NEW-AF have been identified including older age, female sex, hypertension, cardiogenic shock, and congestive heart failure[4-6], suggesting that the cause of NEW-AF is multifactorial[7]. The clinical importance of NEW-AF following STEMI is not fully known, as some data suggest that NEW-AF is associated with long-term mortality[6,8], whereas others do not find NEW-AF to be an independent predictor of mortality[1,3,4]. Additionally, some data suggest that NEW-AF may increase the risk of ischemic stroke[6], however the long-term risk of bleeding leading to hospitalization and re-MI have not been evaluated. Thus, due to heterogenicity in current studies evaluating the prognostic impact of NEW-AF, the true prognostic value of NEW-AF following STEMI on long-term mortality, risk of thromboembolic, and bleeding events is unknown, and further analyses are warranted.

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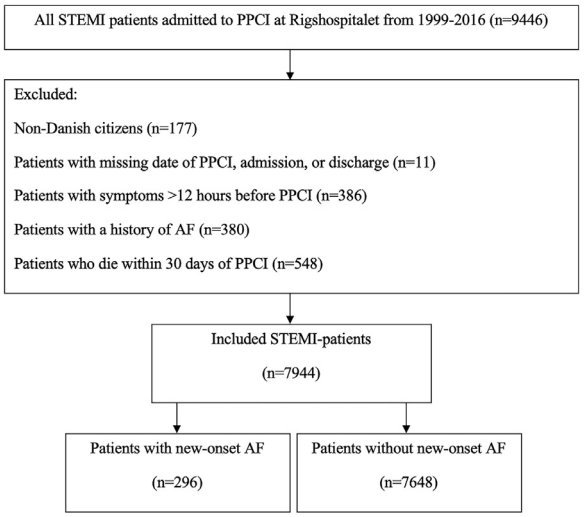
Figure 1



Flowchart of the study population. The selection process of the study population including both inclusion and exclusion criteria. Arrows indicate the order of the population selection. A total of 7944 patients were included of whom 296 developed new-onset atrial fibrillation. AF = atrial fibrillation, PPCI = primary percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction.

The optimal duration and combination of antithrombotic and anticoagulant therapy in patients with STEMI and NEW-AF are unknown[9]. According to recent guidelines, based on low to moderate level of evidence, patients with atrial fibrillation (AF) and myocardial infarction are less likely to receive appropriate antithrombotic therapy and have more adverse outcomes[10]. However, the thromboembolic and bleeding risk of using oral anticoagulant (OAC) therapy in patients with NEW-AF following STEMI is unclear, and no data exists on solely PPCI treated patients with STEMI developing NEW-AF.

In patients with STEMI, we investigated (1) the incidence of NEW-AF, (2) long-term mortality, and incidence of ischemic stroke, recurrent myocardial infarction (re-MI), and bleeding leading to hospitalization of NEW-AF, and (3) the prognostic implication of OAC therapy.

Methods

Study design and study population

This single-center, retrospective cohort study included 9446 consecutive STEMI patients ≥18 years. All patients were admitted to the Heart Centre at Copenhagen University Hospital, Rigshospitalet, Denmark, between 1999 and 2016 (Figure 1). Since 2011, Rigshospitalet has had a catchment area of 2.5 million citizens (45% of the Danish population), corresponding to approximately 1,000 PPCI-procedures per year[11].

Data sources

Data on all STEMI patients was retrieved from the Eastern Danish Heart Registry[12]. This registry holds information on clinical, angiographic, and procedural characteristics. These data have been registered routinely by all interventionalists. Data in this registry was linked via a unique civil registration number to Danish nationwide administrative registries[13]. All Danish residents receive a distinct, personalized, and permanent civil registration number, which enables individual-level linkage between all nationwide registries unambiguously[13]. Date of birth and vital status was retrieved from the Civil Registration Registry. Information on the date of admission, discharge, and diagnoses were collected from the National Patient Registry. This registry comprises information on all hospital admissions and outpatient-contacts according to the International Classification of Disease, Tenth revision (ICD-10)[14]. Information was retrieved for every patient both prior to and after STEMI-admission. All medical prescriptions in Denmark are registered in the Danish National Prescription Registry including type of drug based on the international Anatomical Therapeutic Chemical (ATC) classification system[15], quantity of dispensed drugs, dispensing date, and strength of drug. Blood samples and the exact time of measurement were retrieved from an electronic laboratory database.

Definitions

STEMI was verified by electrocardiogram in adherence to guidelines. Only patients with symptoms ≤12 hours were included. All patients were treated with primary angioplasty according to contemporary guidelines.

Comorbidities were defined according to the modified Ontario Acute Myocardial Infarction Mortality Prediction Rules by diagnoses from hospital admissions or outpatient contacts prior to STEMI admission: Complication to diabetes mellitus, cardiogenic shock, cancer, acute and chronic renal failure, cardiac dysrhythmia, pulmonary edema, cerebrovascular disease, and congestive heart failure[16,17]. To avoid underestimation, complication to diabetes mellitus was replaced with diabetes mellitus. Patients with *a history* of AF were excluded. NEW-AF was defined as a diagnosis of AF within 30 days after STEMI. The diagnosis of AF was retrieved from Danish registries, which has shown to have a validity of 92.6%[18]. To avoid immortal time bias, patients who died within 30 days after STEMI were excluded. Since congestive heart failure has been associated with NEW-AF following STEMI and may be a surrogate hereof[6,19], congestive heart failure was retrieved both as a comorbidity prior to and 30 days after STEMI. To avoid underestimation of the following comorbidities; hypertension, diabetes mellitus, and hypercholesterolemia, these comor-

bidities were identified according to both diagnosis and dispensed medication one year prior to STEMI admission (Supplementary Table 1), as previously described[20]. Dispensed prescriptions were retrieved one year before and within 30 days after STEMI (Supplementary Table I). Use of OAC, antithrombotic, anti-arrhythmic, diuretic, anti-congestive, and anti-hypertensive drugs within 30 days after STEMI were also collected (Supplementary Table 1). Blood levels of creatinine, international normalized ratio (INR), alanine aminotransferase (ALAT), and maximum troponin-T were retrieved. Average levels of creatinine, INR, and ALAT during STEMI-hospitalization were calculated. Only troponin-T levels within 24 hours of STEMI were used to avoid measurements of potential recurrent myocardial reinfarction.

Clinical Outcomes

The primary outcome was long-term all-cause mortality. Long-term mortality was defined as all-cause mortality until end of the follow-up period (the December 31 2018). The secondary outcomes were the association between NEW-AF and the incidence of long-term events including ischemic stroke, re-MI, and bleeding leading to hospitalization. Follow-up started 30 days after STEMI and lasted until occurrence of the outcome of interest, date of emigration, or study end. Finally, we performed analyses on long-term mortality, and incidence of ischemic stroke, re-MI, and bleeding leading to hospitalization among patients with STEMI developing NEW-AF treated with and without OAC therapy within 30 days after STEMI.

Statistical analyses

Baseline characteristics are presented as median and interquartile range (IQR) for continuous variables, and frequencies and percentage for categorical variables. Missing values of the individual variables were annotated (Supplementary Table II). The Wilcoxon rank-sum test was used to evaluate continuous variables and the Chi-Square test or Fisher's exact test (when appropriate) for categorical values. A two-sided *P*-value $\leq$.050 was considered statistically significant. Incidence rates (IR) were calculated and presented as percent per 100 patient year for each outcome. The Kaplan-Meier method was used to make survival curves illustrating differences between patients with and without NEW-AF, and the Log-Rank method was used to test for significant differences between groups.

Hazard ratios (HR) and 95% confidence intervals (CI) were calculated by adjusted Cox proportional hazard analysis to show the association between NEW-AF and long-term mortality, ischemic stroke, re-MI, and bleeding leading to hospitalization. Both the unadjusted and adjusted HR were calculated. Models were adjusted for comorbidities according to the Ontario Acute Myocardial Infarction Mortality Prediction Rules[16,17]. Comorbidities with <10 observations in respective groups were not considered. Average creatinine levels during hospitalization were included as a marker of the renal function. Further, potential confounders using baseline covariates with *P*-values $\leq$.050 for the difference between groups if variables had $\leq$5% missing values and/or >10 observations: continuous age, sex, hypertension, chronic obstructive lung disease, Killip Class at admission, pre- and postprocedural thrombolysis in myocardial infarction (TIMI) flow, and culprit lesion were included in the model. Finally, a prescription of renin-angiotensin-aldosterone system inhibitor, beta-blockers, ASA, OAC, and adenosine diphosphate inhibitors (ADPi) within 30 days after STEMI were included. Missing values of the included variables were calculated (Supplementary Table II). The assumptions of linearity for numeric values, relevant interactions, and proportional hazard were tested, and the models found valid.

Three sensitivity analyses were performed. First, an analysis including troponin-T max and time from symptom to wire. Second, an analysis, in which patients who had not developed AF within 30 days following STEMI but developed AF *after* 30 days from STEMI were censored at the time of AF, to avoid misclassification of these patients without NEW-AF. Similar multivariate Cox proportional hazard analyses were performed. Third, an unadjusted analysis on all outcomes, excluding all patients admitted with STEMI before 2009, were performed to test for potential chronological bias. Fourth, patients developing NEW-AF following STEMI were considered, and HAS-BLED- and CHA_2DS_2-VASc-scores were calculated (Supplementary Table 3). Since the population consisted of STEMI patients only, all patients gained at least 1 point on the CHA_2DS_2-VASc-score. The association between OAC therapy and long-term mortality, and incidence of re-MI and bleeding leading to hospitalization in NEW-AF-patients was addressed by multivariate Cox proportional hazard analysis adjusted for age, sex, and previous bleeding leading to hospitalization. The association between OAC therapy and ischemic stroke was addressed by similar analysis adjusted for age and previous bleeding leading to hospitalization due to low number of events.

All statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA) and R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Ethical approval

This study was approved by the Danish Data Protection Agency (2007-58-0015/GEH-2014-014 and I-suite number: 02732). The Civil Registration numbers are encrypted which enables anonymity in all included patients. Anonymized data created for this study are available in a persistent repository. Register-based studies in

anonymous setup do not required ethical approval in Denmark.

The authors are solely responsible for the design and conduct of this study, all analyses, drafting and editing of the paper and its final contents. This work was supported by the Alfred Benzon Foundation and the Novo Nordisk Foundation. The funders were not involved in any aspects of the study or the decision to submit for publication. No extramural funding was used to support this work.

Results

A total of 7944 STEMI patients were included in this study with a median follow-up time of 5.8 years (IQR, 3.6-9.3) (Figure 1). Among the 7944 STEMI patients, 296 (3.7%) patients developed NEW-AF within 30 days after STEMI.

Baseline characteristics and pharmacotherapy within 30 days after STEMI

Baseline demographics, pharmacotherapy prior to STEMI admission, and angiographic characteristics are presented in Table I. Patients with NEW-AF were older, more often women, non-smokers, and had more cardiovascular comorbidities (Table I). Patients with NEW-AF were more likely to have lower pre- and post-TIMI flow, and, angiographically, incomplete revascularization, a culprit lesion in the left anterior descending artery as well as a Killip Class ≥2 (Table I).

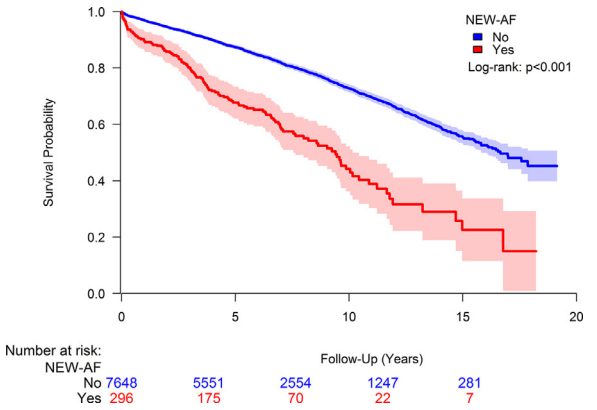
Pharmacotherapy within 30 days after STEMI is presented in Table II.

NEW-AF and long-term mortality, and incidence of ischemic stroke, re-MI, and bleeding leading to hospitalization

During follow-up with a median of 5.8 years (IQR 3.6-9.3), 1778 (22.4%) of all included STEMI patients died, 474 (6.0%) had ischemic stroke, 1575 (19.8%) had re-MI, and 983 (12.4%) had bleeding leading to hospitalization. Patients, who developed NEW-AF, had a significantly shorter median follow-up time of 4.7 years (IQR 2.8-7.4) following STEMI compared with 5.9 years (IQR 3.6-9.4) in patients without NEW-AF. The long-term survival probability was significantly lower among patients with NEW-AF compared with patients without NEW-AF (Figure 2). The IR (percent/100 patient year) of mortality was 44 for NEW-AF patients, and 22 for patients without NEW-AF (Table III). In the adjusted analysis, NEW-AF was associated with a higher long-term mortality (HR 1.48, 95% CI 1.20-1.82, $P < .001$) (Figure 3).

The IR (percent/100 patient year) of ischemic stroke, re-MI, and bleeding leading to hospitalization is presented in Table III. In the adjusted analysis, NEW-AF was associated with increased risk of bleeding leading to hospitalization (HR 1.36, 95% CI 1.00-1.85, P=.050) and non-significant increased rate of ischemic stroke (HR 1.45, 95% CI 0.96-2.19, P=.08) and re-MI (HR 1.14, 95% CI 0.86-1.52, P=.35) (Table III).

Figure 2



Long-term survival probability in STEMI patients. Long-term survival probabilities in STEMI patients treated with PPCI conducted using the Kaplan Meier curves. The y-axis presents survival probability and the x-axis presents time in years after STEMI. The red graph presents patients with NEW-AF, and the blue graph presents patients without NEW-AF. The highlighted areas around the graphs present the 95% CI. Number at risk are presented beneath the graph. CI= confidence interval, NEW-AF = new-onset atrial fibrillation, PPCI = primary percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction. (Color version of figure is available online)

OAC therapy in NEW-AF patients and long-term mortality, and incidence of ischemic stroke, re-MI, and bleeding leading to hospitalization

Characteristics of NEW-AF patients according to OAC therapy are presented in Table IV. Out of 296 NEW-AF patients, 113 (38%) patients were treated with OAC therapy within 30 days after STEMI of whom 71 (63%) received triple therapy with OAC, ASA, and ADPi, and 42 (37%) received mono- or dual-therapy with OAC combined with ASA or ADPi.

The IR (percent/100 patient year) of ischemic stroke, re-MI, and bleeding leading to hospitalization is presented in Table V. In adjusted analysis, OAC treatment in NEW-AF was associated with a lower long-term mortality (HR 0.69, 95% CI 0.47-1.00, P=.049). The associations between OAC therapy in NEW-AF patients and ischemic stroke, re-MI, and bleeding leading to hospitalization were non-significant (Table V).

Sensitivity analysis

Similar results were found when including covariates troponin-T max and time from symptom to PCI in the

Table I. Characteristics of the study population

Variables, No. (%)	Without NEW-AF (n=7648)	NEW-AF (n=296)	P-value
Age, median [IQR], years	62 [53, 71]	71 [64, 79]	<.001
Categorical age, years			
<65	4574 (59.8)	86 (29.1)	<.001
65 to 75	1878 (24.6)	95 (32.1)	
≥75	1196 (15.6)	115 (38.8)	
Male sex	5765 (75.4)	207 (69.9)	.033
BMI, kg/m^2			
BMI<25	2206 (36.8)	79 (34.5)	.48
BMI≥25	3787 (63.2)	150 (65.5)	
Family history of IHD	2059 (33.3)	61 (28.0)	.10
CCS			
CCS: Class 1 to 2	817 (11.7)	28 (10.6)	.33
CCS: Class 3 to 4	675 (9.6)	19 (7.2)	
No Angina	5511 (78.7)	217 (82.2)	
Smoking			
Current	3654 (53.4)	84 (35.0)	<.001
Past	1652 (24.1)	80 (33.3)	
Never	1540 (22.5)	76 (31.7)	
Comorbidities prior to STEMI			
Previous myocardial infarction	762 (10.0)	24 (8.1)	.29
Diabetes mellitus	829 (10.8)	36 (12.2)	.47
Hypercholesterolemia	1673 (21.9)	66 (22.3)	.86
Hypertension	2180 (28.5)	130 (43.9)	<.001
Chronic obstructive pulmonary disease	341 (4.5)	24 (8.1)	.003
Chronic ischemic heart disease	872 (11.4)	27 (9.1)	.22
Heart valve disease	80 (1.1)	7 (2.4)	.043*
Peripheral vascular disease	237 (3.1)	14 (4.7)	.12
Acute renal failure	71 (0.9)	4 (1.4)	.36*
Chronic renal failure	77 (1.0)	6 (2.0)	.13*
Congestive heart failure	1872 (24.5)	148 (50.0)	<.001
Cardiogenic shock	7 (0.1)	≤3 (≤1.0)	1.00*
Cancer	581 (7.6)	35 (11.8)	.008
Cerebrovascular disease	432 (5.7)	34 (11.5)	<.001
Pulmonary edema	10 (0.1)	≤3 (≤1.0)	1.00*
Cardiac dysrhythmia besides atrial fibrillation	130 (1.7)	13 (4.4)	<.001
Previous ischemic stroke	246 (3.2)	25 (8.5)	<.001
PCI-related			
Killip class ≥II at admission	478 (6.6)	35 (12.3)	<.001
Pre-PCI TIMI flow 0-1	4868 (64.3)	217 (74.3)	<.001
Post-PCI TIMI flow 3	7116 (94.1)	245 (83.9)	<.001
Symptoms to wire, median [IQR], minutes	180 [126, 270]	185 [127, 280]	.45
Location of culprit lesion			
Left main artery	41 (0.5)	9 (3.1)	<.001
Left anterior descending artery	3301 (43.4)	136 (46.1)	
Circumflex artery	1085 (14.3)	47 (15.9)	
Right coronary artery	3180 (41.8)	103 (34.9)	
Incomplete revascularization	2399 (36.7)	118 (44.5)	.010
Pharmacotherapy 1 year before STEMI			
Beta-blockers	1061 (13.9)	84 (28.4)	<.001
Renin-angiotensin-system inhibitors	1758 (23.0)	85 (28.7)	.022
Statins	1507 (19.7)	59 (19.9)	.92
Antidiabetics	720 (9.4)	31 (10.5)	.54
ASA	1324 (17.3)	85 (28.7)	<.001
OAC therapy	89 (1.2)	17 (5.7)	<.001*
Calcium channel blockers	1230 (16.1)	74 (25.0)	<.001
Anti-adrenergic drugs	79 (1.0)	≤3 (≤1.0)	1.0*
Vasodilators	≤3 (≤1.0)	≤3 (≤1.0)	1.0*
Thiazides	831 (10.9)	56 (18.9)	<.001
Loop diuretics	352 (4.6)	34 (11.5)	<.001
Spironolactone	91 (1.2)	6 (2.0)	.18*
Diuretics (combinational)	568 (7.4)	26 (8.8)	.38
Blood samples during STEMI admission			
Categorical average creatinine, μmolar/L			
<50	165 (2.2)	5 (1.7)	<.001
50-110	6637 (87.5)	222 (76.0)	
>110	780 (10.3)	65 (22.3)	
Troponin-T max, median [IQR], ng/L	2260 [900, 4610]	3530 [1780, 7400]	<.001
Time from symptom to troponin-T max, median [IQR], hours	26 [19; 40]	25 [18; 39]	.75

*Fisher's Exact Test, two-sided. ASA = acetylsalicylic acid. BMI = body mass index. CCS = Canadian cardiovascular society grading of angina pectoris. IHD = ischemic heart disease. IQR = interquartile range. L= Liter. Ng = nanogram. NEW-AF = new-onset atrial fibrillation. OAC = oral anticoagulant. PCI = percutaneous coronary intervention. STEMI = ST-segment elevation myocardial infarction. TIMI = thrombolysis in myocardial infarction.

Table II. Pharmacotherapy within 30 days after STEMI

Pharmacotherapy, No. (%)	Without NEW-AF (*n*=7648)	NEW-AF (*n*=296)	*P-value*
Beta Blockers	6339 (82.9)	208 (70.3)	<.001
Calcium Channel Blockers	469 (6.1)	15 (5.1)	.45
Digoxin	32 (0.4)	35 (11.8)	<.001*
Amiodarone	54 (0.7)	26 (8.8)	<.001*
Diuretics	1311 (17.1)	123 (41.6)	<.001
ASA	6432 (84.1)	207 (69.9)	<.001
Statins	6674 (87.3)	233 (78.7)	<.001
Renin-angiotensin-aldosterone-system inhibitors	3018 (39.5)	148 (50.0)	<.001
ADPi	7025 (91.9)	237 (80.1)	<.001
Clopidogrel	3301 (43.2)	171 (57.8)	<.001
Prasugrel	1890 (24.7)	34 (11.5)	<.001
Ticagrelor	1920 (25.1)	37 (12.5)	<.001
OAC therapy	161 (2.1)	113 (38.2)	<.001
Vitamin K antagonists	135 (1.8)	84 (28.4)	<.001
Non-Vitamin K antagonists	26 (0.3)	31 (10.5)	<.001*
Mono- or dual-therapy	50 (0.7)	42 (14.2)	<.001*
Triple therapy	111 (1.5)	71 (24.0)	<.001

*Fisher's exact Test, two-sided. ADPi = adenine diphosphate inhibitor. ASA = acetylsalicylic acid. NEW-AF = new-onset atrial fibrillation. OAC = oral anticoagulant. STEMI = ST-segment elevation myocardial infarction.

Table III. IR and multivariate analysis of long-term outcomes in STEMI patients

Outcomes	**Long-term no. of events, IR* (No.)**		**Long-term unadjusted HR**		**Long-term adjusted HR†**	
	NEW-AF (*n*=296)	Without NEW-AF (*n*=7648)	NEW-AF, HR (95% CI)	*P*-value	NEW-AF HR (95% CI)	*P*-value
Mortality	44 (131)	22 (1647)	2.64 (2.21-3.15)	<0.001	1.48 (1.20-1.82)	<.001
Ischemic stroke	11 (33)	6 (441)	2.36 (1.65-3.36)	<0.001	1.45 (0.96-2.19)	.08
Re-MI	22 (65)	20 (1510)	1.28 (1.00-1.64)	0.05	1.14 (0.86-1.52)	.35
Bleeding leading to hospitalization	20 (58)	12 (925)	2.00 (1.53-2.61)	<0.001	1.36 (1.00-1.85)	.050

*Percent per 100 patient year. †Adjusted for NEW-AF, age, sex, culprit lesion, Killip Class, pre- and post-PCI TIMI flow, hypertension, chronic obstructive lung disease, congestive heart failure, cancer, diabetes mellitus, cerebrovascular disease, cardiac dysrhythmia besides atrial fibrillation, average creatinine level during admission, use of beta-blockers, acetylsalicylic acid, renin-angiotensin-aldosterone-system inhibitors, ADP-inhibitors, and OAC within 30 days after STEMI. CI = confidence interval. HR = hazard ratio. IR = incidence rate. NEW-AF = new-onset atrial fibrillation. Re-MI = recurrent myocardial infarction. STEMI = ST-segment elevation myocardial infarction.

models for long-term mortality and NEW-AF with a HR of 1.96 (95% CI 1.47-2.63, *P*<.001).

Among 7648 STEMI patients, who did not develop NEW-AF within 30 days after STEMI, 646 (8.4%) developed NEW-AF following 30 days after STEMI until end of follow-up. In Cox proportional analysis accounting for patients developing NEW-AF following 30 days after STEMI, NEW-AF remained associated with an increased long-term mortality with an adjusted HR of 1.31 (95% CI 1.07-1.62, *P*=.011).

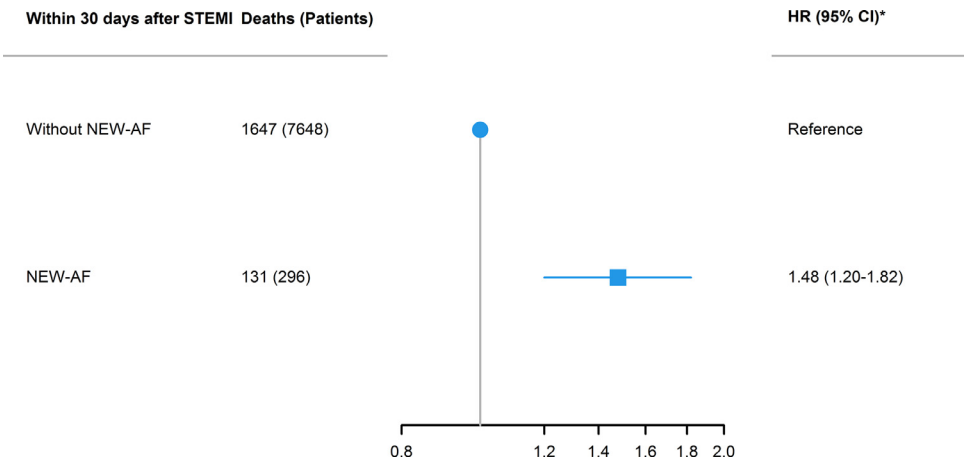
In univariate analysis, excluding patients admitted with STEMI before 2009, NEW-AF was associated with increased long-term mortality (HR 3.21, 95% CI 2.52-4.10, *P*<.001), risk of ischemic stroke (HR 2.90, 95% CI 1.79-4.71, *P*<.001), and bleeding leading to hospitalization (HR 2.21, 95% CI 1.57-3.10, *P*<.001) (Supplementary Table 4).

Discussion

This study has three major findings: (1) the incidence of NEW-AF within 30 days after STEMI was 3.7%, (2) development of NEW-AF was associated with increased long-term mortality and risk of bleeding leading to hospitalization, and non-significant increased long-term risk of ischemic stroke and re-MI, and (3) treatment with OAC among NEW-AF patients was associated with reduced long-term mortality.

Prior observational studies, defining NEW-AF as AF diagnosed based on electrocardiogram during index-hospitalization with no history of AF, have found an incidence of NEW-AF ranging from 3.6% to 5.3% corresponding to the results of our study[1-3]. In contrast, literature review studies found a higher incidence of NEW-AF ranging from 2 to 21%[6,8]. Yet, these literature studies either excluded studies evaluating NEW-AF occurring after the first week of MI or included all acute coronary syndrome (ACS) patients treated with either thrombolysis and/or PCI[6,8]. The differences in the reported incidence of NEW-AF may be due to differences between populations and definitions of NEW-AF. We included solely STEMI patients treated with PPCI that survived 30 days post-STEMI and defined NEW-AF as AF newly developed

Figure 3



Adjusted analysis on long-term mortality in STEMI patients. The figure shows the association between NEW-AF and long-term mortality conducted using multivariate Cox proportional hazard analysis. The adjustments of the multivariate analysis are given in the footnote *. The median follow-up period was 5.8 years. Also, number of deaths and patients in the two groups are presented. The x-axis represents HR, and blue square represents the HR of NEW-AF and long-term mortality. The blue line from the blue square is the 95% CI. The blue circle represents the reference which is patients without NEW-AF. *Adjusted for NEW-AF, age, sex, culprit lesion, Killip Class, pre- and post-PCI TIMI flow, hypertension, chronic obstructive lung disease, congestive heart failure, cancer, diabetes mellitus, cerebrovascular disease, cardiac dysrhythmia besides atrial fibrillation, average creatinine level during admission, use of beta-blockers, acetylsalicylic acid, renin-angiotensin-aldosterone-system inhibitors, ADP-inhibitors, and OAC within 30 days after STEMI. ADP = adenine diphosphate. CI = confidence interval. HR = hazard ratio. NEW-AF = new-onset atrial fibrillation. OAC = oral anticoagulants. PCI = percutaneous coronary intervention. STEMI= ST-segment elevation myocardial infarction. TIMI = thrombolysis in myocardial infarction. (Color version of figure is available online)

within 30 days from STEMI. However, due to asymptomatic or subclinical presentation of AF, NEW-AF may be underestimated. Nevertheless, based on previous studies and the current study, the incidence of NEW-AF after STEMI is probably closer to 5% than 20%.

Few studies have evaluated the association between long-term mortality in a vast population of STEMI patients with NEW-AF. They found no association between NEW-AF following STEMI and increased long-term mortality[1,4]. The definition of NEW-AF in one of these studies was similar to the definition of NEW-AF in our study[4], but the two studies may have been underpowered due to a small number of cases ($n<148$)[1,4]. In contrast, other reports show an increased mortality among MI patients with NEW-AF similar to our study[6,8]. Compared with a meta-analysis that found a mortality odds ratio associated with NEW-AF of 1.37 (95% CI 1.26-1.49)[8], our study found NEW-AF among patients with STEMI to be associated with increased long-term mortality (HR 1.48, 95% CI 1.20-1.82, $P < .001$).

Whether NEW-AF is a surrogate of an underlying disease or independently increases mortality remains unknown. NEW-AF may be a surrogate of heart failure[6,8], and the association with outcomes considered multifactorial[7]. Despite relevant statistical adjustments including cardiovascular comorbidities, medication use, and variables associated with risk of heart failure (duration of ischemia, Killip Class, left anterior descending artery as culprit, and maximum levels of troponin T), the increased mortality among NEW-AF patients could be due to residual confounding[19]. Thus, it seems that NEW-AF *per se* is related to poor prognosis. The cause of this is unknown, but a confounding factor may be the association with increased risk of ischemic stroke.

According to guidelines, STEMI patients require dual antiplatelet therapy and in addition, when complicated by AF, OAC may be prescribed[10,21,22]. However, OAC therapy in the setting of NEW-AF patients following STEMI is limited as underlined in current guidelines for the management of patients with ACS complicated by AF. The 2019 focused update on the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines[22] states that the indication for OAC therapy for patients with AF complicating ACS should be based on HAS-BLED and CHA_2DS_2-VASc scores (level of evidence, B). However, adherence to this guidance remains unknown[23]. The 2017 and 2020 European Society of Cardiology (ESC) guidelines[10,21] recommend a similar practice (level of evidence, B and C). Current guidelines[10,21,22] are based on trials, e.g. PIONEER AF-PCI[24], AUGUSTUS[25], WOEST[26], RE-DUAL PCI[27], and ENTRUST-AF-PCI[28] trial, all includ-

Table IV. Characteristics on patients with NEW-AF within 30 days after STEMI according to OAC therapy

Variables, No. (%)	Without OAC therapy (*n*=183)	OAC therapy (*n*=113)	*P*-value
Categorical age, years			
<65	61 (33.3)	25 (22.1)	.11
65 to 75	54 (29.5)	41 (36.3)	
≥75	68 (37.2)	47 (41.6)	
Female sex	59 (32.2)	30 (26.6)	.30
HAS-BLED score ≥3	92 (50.3)	77 (68.1)	.003
CHA_2DS_2-VASc score ≥2	169 (92.4)	105 (92.9)	.86
Comorbidities prior to STEMI			
Diabetes mellitus	22 (12.0)	14 (12.4)	.93
Congestive heart failure	94 (51.4)	54 (47.8)	.55
Hypertension	75 (41.0)	55 (48.7)	.20
Previous ischemic stroke	17 (9.3)	8 (7.1)	.51
Previous myocardial infarction	15 (8.2)	9 (8.0)	.94
Peripheral vascular disease	8 (4.4)	6 (5.3)	.71
Chronic ischemic heart disease	18 (9.8)	9 (8.0)	.59
Previous transient ischemic attack	9 (4.9)	4 (3.5)	.77*
Previous systemic thromboembolism	9 (4.9)	7 (6.2)	.64
Vascular disease	32 (17.5)	19 (16.8)	.88
Renal disease	15 (8.2)	4 (3.5)	.11
Liver disease	5 (2.7)	≤3 (≤1)	.41*
Previous bleeding leading to hospitalization	26 (14.2)	7 (6.2)	.033
Alcohol abuse	≤3 (≤1)	≤3 (≤1)	1.0*
Pharmacotherapy			
ASA	128 (70.0)	79 (69.9)	1.0
ADPi	133 (72.7)	104 (92.0)	<.001
Ticagrelor	32 (17.5)	5 (4.4)	.001
Prasugrel	24 (13.1)	10 (8.9)	.26
Clopidogrel	78 (42.6)	93 (82.3)	<.001
Blood samples during STEMI admission			
Average creatinine >200, μmolar/L	12 (6.6)	≤3 (≤1.0)	.14
Average INR >1.2	50 (27.3)	34 (30.1)	.61
Average ALAT >210, in men or >135 in females, U/L	9 (4.9)	4 (3.5)	.77*

*Fisher's Exact Test, two-side. ADPi = adenine diphosphate inhibitor. ALAT = alanine aminotransferase measured in units per liter. ASA = acetylsalicylic acid. CHA_2DS_2-VASc = Scoring system reflecting the risk of stroke, with values ranging from 0 to 9 and with higher scores indicating greater risk (Supplementary Table 3). HAS-BLED = scoring system reflecting the risk of major bleeding, with values from 0-9 and with higher scores indicating greater risk (Supplementary Table 3). INR = international normalized ratio. L = Liter. NEW-AF = new-onset atrial fibrillation. OAC = oral anticoagulant. STEMI = ST-segment elevation myocardial infarction.

Table V. IR and multivariate analyses on long-term outcomes in patients with NEW-AF

Outcomes	**Long-term no. of events, IR*(No.)**		**Long-term unadjusted HR**		**Long-term adjusted HR†**	
	OAC therapy (*n*=113)	Without OAC therapy (*n*=183)	OAC therapy, HR (95% CI)	*P*-value	OAC therapy, HR (95% CI)	*P*-value
Mortality	36 (41)	49 (90)	0.79 (0.55-1.15)	.22	0.69 (0.47-1.00)	.049
Ischemic stroke	9 (10)	13 (23)	0.65 (0.31-1.36)	.25	0.70 (0.33-1.49)‡	.35
Re-MI	27 (31)	19 (34)	1.54 (0.95-2.52)	.08	1.50 (0.91-2.49)	.11
Bleeding leading to hospitalization	21 (24)	19 (34)	1.15 (0.68-1.95)	.59	1.31 (0.75-2.27)	.34

*Percent per 100 patient year. †Adjusted for use of OAC within 30 days after STEMI, age, sex, and prior bleeding leading to hospitalization. ‡Adjusted for use of OAC within 30 days after STEMI, age and prior bleeding leading to hospitalization. CI = confidence interval. HR = hazard ratio. IR = incidence rate. NEW-AF = new-onset atrial fibrillation. OAC = oral anticoagulant. Re-MI = recurrent myocardial infarction. STEMI = ST-segment elevation myocardial infarction.

ing patients with known AF and combining elective and urgent PCI for ACS. In addition to this, more focus on the ACS subgroups is needed, as the lack hereof may cloud the judgement on how to treat the highest risk patients[23].This study, including only STEMI patients, found an association between OAC treatment in NEW-AF patients and reduced risk of long-term mortality, but no association between NEW-AF patients treated with OAC and a thromboembolic risk (neither ischemic stroke nor re-MI), or bleeding leading to hospitalization. This non-significant impact of OAC in NEW-AF patients on bleeding and thromboembolic risks could be due to a relatively low event rate of these outcomes. Yet, the findings of our study could indicate that the long-term mortality in

NEW-AF patients may decrease if treated with OAC. Also, our study found an increased inherent risk of bleeding based on HAS-BLED scores in NEW-AF patients treated with OAC therapy compared to patients without OAC therapy, which could suggest that the protective effect of OAC may overcome bleeding risk. Unfortunately, our study was not powered to assess the importance of the CHA_2DS_2-VASc to guide OAC treatment. Hence, our findings indicate that OAC therapy could be an important addition to standard treatment of STEMI patients when complicated by NEW-AF, as it is associated with a lower long-term mortality. However, larger clinical studies are needed to evaluate the merits of OAC for STEMI patients with NEW-AF.

Strengths and limitations

The strength of this study is the link between clinical data and Danish nationwide registries, which enables completeness of data. This was a large cohort of consecutive STEMI patients ensuring specificity of the phenotype and focus on the most acute patients. Additionally, this study had a complete and long follow-up with a median time of 5.8 years, which enabled evaluation on long-term mortality, ischemic stroke, re-MI, and bleeding leading to hospitalization. Further, several sensitivity analyses were performed to validate the main results.

Left ventricular dysfunction has shown to be correlated to both AF and increased risk of mortality[6,19]. In this study, the main analysis was adjusted for the ICD-10 code diagnosis of congestive heart failure, however, the left ventricular ejection fraction was not included due to high number of missing values. Maximum troponin-T levels have been suggested as a biochemical signature for heart failure[29]. Adjusting for maximum troponin-T levels in a sensitivity analyses showed similar results on long-term mortality.

The analysis of OAC therapy in NEW-AF patients may be affected of confounding by indication as adjustment of heart failure was not included in the model due to lack of power. Further, the non-significant findings upon ischemic stroke, re-MI, and bleeding leading to hospitalization may be, due to a low event rate, affected by lack of power and differences between patients in the two groups. Also, this study had no information on cause of death.

Another limitation is that some patients, due to asymptomatic events, may have had undiagnosed previous paroxysmal atrial fibrillation leading to an underestimated incidence.

Conclusion

A total of 3.7% of 7944 STEMI patients developed NEW-AF within 30 days after STEMI. NEW-AF following STEMI was associated with increased long-term mortality and rate of bleeding leading to hospitalization, and non-significant increased rate of ischemic stroke and re-MI. NEW-AF patients treated with OAC therapy had reduced long-term mortality compared with NEW-AF patients not treated with OAC.

Author Contributions

Miss JM. Madsen and Dr. MR. Jacobsen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final version for submission.

Conceptualization: Miss Madsen, Drs. Jacobsen, Jabbari, Glinge, Sørensen, Engstrøm, and Lønborg.

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Formal analysis: All authors.

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Resources: All authors.

Software: Miss Madsen, Drs. Jacobsen, Jabbari, Glinge, Køber, Torp-Pedersen, Engstrøm, and Lønborg.

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Validation: All authors.

Visualization: All authors.

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Writing – review and editing: All authors.

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Conflict of Interest

Dr. Engstrøm has received speakers- /advisory board fee from Abbot Vascular, Boston Scientific, Bayer, and Novo Nordisk. Dr. Torp-Pedersen has received grants for research from Bayer and Novo Nordisk. Dr. Køber has received speaker's honorarium from Novo, AstraZeneca, Boehringer and Novartis, unrelated to this topic. The remaining authors have no disclosures to report.

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The authors are solely responsible for the design and conduct of this study, all analyses, drafting and editing of the paper and its final contents.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.04.012.

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