# The Effect of Atrial Fibrillation on the Long-term Mortality of Patients with Acute Coronary Syndrome - the TACOS Study

Kaari K. Konttila, MD[1], Olli Punkka, BM[1], Kimmo Koivula, MD[1,2], Markku J. Eskola, MD, PhD[3], Mika Martiskainen, MD[1,4], Heini Huhtala, MSc[5], Vesa K. Virtanen, MD, PhD[3], Jussi Mikkelsson, MD, PhD[6], Kati Järvelä, MD, PhD[3], Jari Laurikka, MD, PhD[1,3], Kari O. Niemelä, MD, PhD[3], Pekka J. Karhunen, MD, PhD[1,4], Kjell C. Nikus, MD, PhD[1,3]

[1]Tampere University, Faculty of Medicine and Health Technology, Finnish Cardiovascular Research Center, Tampere, Finland

[2]South-Karelia Central Hospital, Finland

[3]Tampere University Hospital, Heart Center, Tampere, Finland

[4] Fimlab Laboratories Tampere University Hospital, Tampere, Finland

[5]Tampere University, Faculty of Social Sciences, Tampere, Finland

[6]Heart Center, Satasairaala, Pori, Finland

Short Title: Atrial fibrillations effect on long-term mortality after acute coronary syndrome

Corresponding author:
Olli Punkka, BM
Faculty of Medicine and Health Technology, University of Tampere, Finland
Arvo Ylpön katu 34
33520 Tampere, Finland
Tel: +358 50 5294566
E-mail: olli.punkka@fimnet.fi
Orcid: 0000-0001-9760-8474

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**Abstract**

**Introduction:** Atrial fibrillation (AF) is a frequent finding in acute coronary syndrome (ACS), but there is conflicting scientific evidence regarding its long-term impact on patient outcome. The aim of this study was to survey and compare the ≥10-year mortality of ACS patients with sinus rhythm (SR) and AF.

**Methods:** Patients were divided into two groups based on rhythm in their 12-lead ECGs: 1) SR (n=788) at hospital admission and discharge (including sinus bradycardia, physiological sinus arrhythmia and sinus tachycardia) and 2) AF/atrial flutter (n=245) at both hospital admission and discharge, or SR and AF combination. Patients who failed to match the inclusion criteria were excluded from the final analysis. The main outcome surveyed was long-term all-cause mortality between AF and SR group during the whole follow-up time.

**Results:** Consecutive ACS patients (n=1 188, median age 73 years, male/female 58%/42%) were included and followed up for ≥10 years. AF patients were older (median age 77 vs 71 years, p<0.001) and more often female than SR patients. AF patients more often presented with non-ST elevation myocardial infarction (69.8% vs. 50.4%, p<0.001), had a higher rate of diabetes (31.0% vs 22.8%, p=0.009) and were more often using warfarin (32.2% vs. 5.1%, p<0.001) or diuretic medication (55.1% vs. 25.8%, p<0.001) on admission than patients with SR. The use of warfarin at discharge was also more frequent in the AF group (55.5% vs. 14.8%, p<0.001). The rates of all-cause and cardiovascular mortality were higher in the AF group (80.9% vs. 50.3%, p<0.001 and 73.8% vs. 69.6%, p=0.285, respectively). In multivariable analysis AF was independently associated with higher mortality when compared to SR (adjusted HR 1.662; 95% CI: 1.387-1.992, p<0.001).

**Conclusion:** AF/atrial flutter at admission and/or discharge independently predicted poorer long-term outcome in ACS patients, with 66% higher mortality within the ≥10-year follow-up time when compared to patients with SR.

## Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a frequent finding in acute coronary syndrome (ACS) with an incidence ranging between 6.2 % and 21 % [1–5]. AF impacts unfavorably on the hemodynamic state, especially in case of high ventricular response rate [5,6] and also increases the risk of in-hospital complications such as bleeding and ischemic and hemorrhagic strokes [3]. Thus, it would be reasonable to deduce that AF has negative impact on patient outcome in ACS [3,5,7–13]. However, study results are inconclusive and somewhat controversial in this respect [14–16], and there is wide variation in follow-up time from weeks to several years in the different studies. [17].

AF in ACS patients may be pre-existing or new-onset. Previous study reports have come to different conclusions regarding possible differences in outcome between these AF sub-categories [1,4,5,11].

Our goal was to investigate the effect of AF on long-term all-cause mortality in consecutive patients with acute myocardial infarction or unstable angina.

## Material and methods

A detailed description of the original research settings has been published earlier [18]. Briefly, the Tampere Acute Coronary Syndrome (TACOS) study included consecutive patients from Tampere University Hospital with a diagnosis of ACS. Overall 1,188 consecutive patients with ST-elevation myocardial infarction (STEMI) (n=343), non-ST-elevation myocardial infarction (NSTEMI) (n=655) or unstable angina (UA) (n=190) were included during the study period 1.1.2002-31.3.2003. The STEMI ECG criteria were: ST- segment elevation in two adjacent leads: in leads $V_{1-6}$ >1.5 mm with >2 mm in at least one lead, in leads II, III, aVF, I and aVL >1 mm. Patients with STEMI had elevated troponin levels and fulfilled the above-mentioned ECG criteria. Patients with NSTEMI had elevated troponin levels and clinical features of ACS, but did not fulfill ECG criteria for STEMI. UA patients

showed no elevation in a minimum of two troponin levels 6-12 hours apart, and the ECG changes were not predefined. Patients with left bundle branch block (LBBB) were categorized as having either NSTEMI (n=60) or UAP (n=11) according to the troponin levels. For the present study, follow-up was set to begin on the day of a patient's first ECG recording used for analysis, and it ended at death or at the end of the follow-up – March 31$^{st}$ 2013.

Data regarding mortality was gathered by linking the personal identity code from the TACOS study to the Causes of Death register, maintained by Statistics Finland, which records 100% of deaths of Finnish citizens at home and nearly 100% abroad [19].

The study complies with the Declaration of Helsinki. The Ethics Committee of the Pirkanmaa Hospital District approved the study protocol (Permission R02100). All subjects gave their written informed consent for participation.

*ECG analysis*

For this study, all the ECGs were analyzed manually by one investigator (OP) to determine the heart rhythm. In case of uncertainty (n = 103 cases), another investigator (KjN) was consulted. For every patient, both the admission and discharge ECG (median interval 6 days, $Q_1$-$Q_3$ 3–9 days; min 1, max 74 days) recorded during the hospital stay were analyzed. The admission ECGs were recorded in the referring health care unit, the ambulance or in the hospital. According to clinical routine during the study, the discharge ECG was recorded on the last day of the hospital stay in most patients. In some patients (n = 103 cases), it was impossible to define the last ECG (discharge ECG) during hospital stay because of missing recording dates from the photocopies of original ECGs; in these cases, an ECG with the last identifiable recording date was used as discharge ECG for 44 patients. In the remaining (n=59) cases, it was impossible to define the discharge ECG due to the following reasons: 1) all ECGs had the same recording date as the admission ECG (n=29), 2) only one ECG was available (n=27) or 3) the death occurred on the day of hospital arrival (n=3).

*ECG rhythm classification*

The ECGs were divided into two categories based on the rhythm in the 12-lead ECG: 1) sinus rhythm including sinus bradycardia, physiological sinus arrhythmia and sinus tachycardia. ECGs with SR and isolated or coupled atrial/ventricular premature complexes extrasystoles or bigeminy were also categorized into the SR group. 2) Atrial fibrillation, including atrial flutter.

Rhythm groups were constructed with the following method; The SR-category (SR, n=788), included patients with SR both in the admission and discharge ECG. In the AF-category (AF, n=245), the first, the last or both ECG's showed AF/flutter. If AF was present in only one of the ECG's, the other ECG's rhythm had to be SR for the patient to be included in the AF group. Of all the patients, 83 failed to satisfy the inclusion criteria because of different other arrhythmias, such as pacemaker rhythm, grade III atrio-ventricular block or ectopic atrial rhythm was present in at least one of the two ECG's analyzed.

Of the original 1 188 consecutive patients, a total of 1 033 patients were included into the final statistical analyses. In addition to the previously mentioned rhythm-based exlusions (n=83), we excluded 13 patients because some major data, such as all of the ECG recordings from the original research setting were missing, and 59 patients because only one ECG-recording was available for the analysis. In total, 155 patients were excluded.

*Causes of death classification*

The classification of death causes was based on the the ICD-10 classification diagnosis codes of each patient's cause of death statement. The information was assessed and linked to each persons personal identity code from the Causes of Death register, maintained by Statistics Finland. The underlying cause of death and immediate cause of death sections were interpreted and used for the classification of death causes. The all cause mortality included all causes of death during the study follow-up time 01.01.2002-31.03.2013. The cardiovascular death included patients with underlying

cause of death or immediate cause of death ICD-10-CM classification code I, “Diseases of the circulatory system”. The ischemic and other forms of heart disease group included ICD-10-CM classification codes I20-25 “Ischemic heart diseases” and I30-52 “Other forms of heart disease” while the Cerebrovascular diseases group included ICD-10-CM classification codes I60-69 with hemorragic, ischemic and unspecified cerebral strokes. Six patients in the SR group and 4 patients in the AF group were included in the cardiovascular death group, but their cause of death diagnosis (e.g. aortitis) did not fit into any of the cause-of-death subgroups. The “Other causes of death” group was created by excluding each one of the formerly presented groups from the all-cause mortality group.

**Statistical analysis**

Continuous variables were presented with median and $Q_1$-$Q_3$ range or mean and standard deviation, while categorical variables were presented with numerical values or percentages. Unpaired t-test was used for parametric and Mann-Whitney U-test for non-parametric continuous variables. Chi-Square was applied for the categorical variables. If its assumptions were violated, Fisher’s exact test was used instead. A p-value $<0.05$ was considered statistically significant and 95 % confidence intervals were used. Unadjusted survival data was presented with Kaplan-Meier curves. The hazard ratios (HR) were calculated using Cox Regression analysis. Proportional hazard assumptions were checked on the basis of Schoenfeld residuals. Interactions between age and all other variables used in multivariable analysis were analyzed. In the multivariable analysis, the groups were adjusted for age, gender, diabetes, hypertension, systolic and diastolic blood pressure, ACS category, revascularization during hospital stay, previous revascularization, previous acute myocardial infarction and creatinine level. Of 1 033 patients, in-hospital data regarding ejection fraction was available in 495 cases, of which 402 belonged to the SR group. Due to missing data in a large proportion of patients, ejection fraction was not included in the multivariable analysis. All computations were carried out with SPSS 24.0.

**Results**

The baseline characteristics and in-hospital data of the study patients according to the rhythm categories is shown in Table 1. Of all patients, 788 (76.3%) were in SR and 245 (23.7%) had AF/flutter in at least one of the two analyzed ECG's. At study inclusion, the median age of all patients was 73 years ($Q_1$-$Q_3$ 63-80 years) and the male/female ratio was 58/42%. The AF patients were older (median age 77 vs 71 years, p<0.001) and more often female. The AF patients had a higher rate of diabetes (31.0% vs 22.8%,p=0.009) and more often presented with NSTEMI (69.8% vs. 50.4%, p<0.001), but there was no significant difference in the rate of hypertension between the groups. On admission, patients with AF were more often using diuretic medication (55.1% vs. 25.8%, p<0.001), beta-blocker (62.0% vs. 45.9%, p<0.001) and warfarin (32.2% vs. 5.1%, p<0.001) than SR patients. At the end of hospitalization, AF patients were more often discharged with warfarin (55.5% vs. 14.8%, p<0.001). The number of patients treated with revascularization therapy during hospital stay was higher in the SR group (26.8% vs. 18.8%, p=0.011).

The median survival times for the SR and AF rhythm groups were 9.7 years (95% confidence interval [CI] 8.9-10.6) and 2.3 years (1.7-3.0), respectively. Short-term mortality at 30 days was 8.1% for the SR group and 22.9% for the AF group, while the one-year mortality rates were 15.9% and 39.6%, respectively. The five-year mortality rates for the SR and AF categories were 32.6% and 64.9% while the ten-year mortality rates were 50.3% and 80.8%, respectively. The mortality rate for the whole follow-up period was 51.9% for the SR group and 81.2% for the AF group.

Both survival curves show a steep decline in survival at the beginning of follow-up in the two rhythm categories (shown in Fig. 1). Thereafter the AF rhythm category stays clearly separated from the survival curve of the SR group while both curves show quite parallel decline for the whole follow-up period.

The causes of death according to rhythm group are shown in Table 2. The all-cause mortality within the whole study follow-up period was higher in the AF group than in the SR group (81.2% vs. 51.9%, p<0.001, respectively). Similar results were observed for cardiovascular death (73.9% vs. 69.7%, p=0.285) and cerebrovascular diseases (12.2% vs 10.8%, p=0.671). The rates of ischemic and other forms of heart disease and other causes of death were higher in the SR group than in the AF group (87.0% vs 85.0%, p=0.569 and 30.3% vs 26.1%, p=0.285, respectively).

The influence of the predefined variables to predict mortality at follow-up in the Cox multivariable regression analysis is shown in Table 3. In 26 patients (2.5%), some valuables required for the multivariable analysis were missing; thus a total of 1007 (97.5%) patients were available for the final multivariable analysis. After adjusting for confounding factors, AF was independently associated with increased mortality when compared to patients with SR (adjusted HR 1.662; CI 95%, 1.387-1.992, p<0.001). Of the three ACS categories, patients diagnosed with NSTEMI were associated with the highest hazard ratio of mortality after multivariable analysis (adjusted HR 1.769; CI 95%, 1.327-2.358, p<0.001).

Interactions between age and all other variables used in the multivariable analysis were analyzed. Statistically significant interaction between age and diabetes was detected. The analysis showed that the younger the patient at the time of ACS, the stronger was the effect of diabetes in mortality. The effect was seen especially within the first year of follow-up, and it diminished with older age; thus mortality rates were quite parallel in the oldest studied patient cohort (>75 years).

**Discussion**

The present study shows that ACS patients with AF or atrial flutter at hospital admission and/or at discharge have significantly worse long-term outcome with higher all-cause mortality compared with patients in SR. The negative impact of arrhythmias on survival is most prominent during the first two years after the index event. Thereafter the groups show similar survival trends implicating the importance of other causes determining survival later. However, the difference between the groups remains.

There was a significant association between AF and ACS category with the strongest negative prognostic impact in NSTEMI patients. NSTEMI patients tend to have a higher proportion of multi-vessel disease than STEMI and UA patients [20]. One could speculate that AF is associated with more diffuse coronary artery disease. The Atherosclerosis Risk in Communities (ARIC) investigators found that AF is associated with an increased risk of incident myocardial infarction, especially in women [21]. The reason for this association is unknown, but the authors discussed the possibility that AF-

induced increase in peripheral prothrombotic risk through systemic platelet activation, thrombin generation, endothelial dysfunction, and inflammation could lead to partial occlusion of the coronary arteries, which is the typical angiographic presentation of NSTEMI. In a study of Taiwanese national health database records, there was an increased risk of ACS in AF patients with a low risk score for stroke [22]. In NSTEMI patients, reduction of coronary blood flow during AF could be the result of a supply/demand mismatch related to high ventricular rate. One study showed that patients with AF had angiographic evidence of slower coronary flow compared with patients in SR, even when controlled for heart rate [23].

In their review article, Kea et al discussed the bidirectional relationship between AF and ACS and possible pathophysiologic explanations for an increased risk of ACS in AF patients [24]. In a small study, STEMI patients with single vessel disease and AF more often had angiographic filling defects suggestive of embolus compared with patients in SR [25]. These findings suggest that cardioembolism may play a role in the pathogenesis of STEMI in patients with AF.

There is a wide range of reported incidence of AF in ACS patients with rates ranging from 6.2 % to 21 % [1–5]. The highest percentages usually count together both pre-existing permanent AF and post-admission new-onset AF while the lowest percentages usually display only new-onset AF. Also, the method of the study, such as the way of searching for AF during hospital stay, affects the overall occurrence rate. However, it should be emphasized, that AF occurring during the acute or the discharge phase might differ with regard to the background pathophysiologic mechanisms. In the acute stage, both changes in the tone of the autonomic nervous system and altered hemodynamic state are important, while in the subacute stage, the degree of myocardial injury and left ventricular function are probably more important. In the present study, the incidence of AF was even higher than in previous studies, 21.5%, reflecting our unique study population with consecutive “real life” patients from all three ACS categories. This is also reflected in the high mean age (76.6 years) of the AF patients. In the very large, nationwide database from the US with STEMI patients, who underwent primary PCI, only 8.7 % had AF, but the mean age was lower (70.6 years) than in our study [12]. In a large registry study from Italy, which also included NSTEMI patients, (mean) age in AF patients (77.1 years in NSTEMI and 74.7 years in STEMI) was comparable to that in our study population

[26]. In that study, 6.1% of the patients had AF on admission. Similar to our study, the ARIAM registry from Spain included ACS patients from all the three ACS categories [11]. The authors reported a 7.3% incidence of AF, of which 55% was new-onset and 45% previously established AF. The mean age of the AF patients was 71.2 years.

The patients in our study were collected in 2002-2003 before the introduction of a standard STEMI protocol and before the wide-spread use of anticoagulants in AF patients, and this could have affected the outcome of our patients. De Luca et al found a 50% decrease in in-hospital mortality in STEMI patients from 2001 to 2014, and at the same time, the incidence of AF showed a clear, although not statistically significant, decrease from 20% to 10.7% [26].

Most previous studies showed that ACS patients with AF are older and have more co-morbidities than patients in SR. This is also the case in our study, where the AF patients were older and more often had diabetes, higher creatinine levels and more often were on medication for cardiovascular disease; for example, diuretic use was more than twice as frequent in AF patients as in patients in SR. The AF patients also had significantly lower ejection fraction.

AF may worsen the outcome in ACS patients by different mechanisms, such as adverse hemodynamic effects, loss of atrial contraction, rapid ventricular rates, and loss of atrioventricular synchrony [27]. Irregular RR intervals may promote ischemia and trigger ventricular arrhythmias. We found that the mortality rate of AF patients during ≥10-year follow-up was at least 60% higher than in the patients in SR after multivariable analysis. Our results are in line with most previous studies and meta-analyses, which showed that AF is an independent predictor of in-hospital and long-term all-cause mortality in ACS patients [3,5,7–13].

Some studies have shown disparate results [14-16]. In some publications, the effect of AF on patient outcome after multivariable analysis was related only to long-term, but not to in-hospital mortality [2,28]. Our results are also quite different from those of the old community study by Goldberg et al, where AF had no independent effect on the short- or long-term mortality after multivariable analysis. We think that differences between the study populations and the time point of patient inclusion (2002-2003 vs. 1970'-1980's in the Goldberg et al study) can explain most of the differences between the results. Meta-analyses concluded that AF occurring in association with MI

was associated with at least 40 % higher risk of mortality compared to patients in SR [10], and in-hospital mortality may be twice as high [13].

In the present study, the length of hospital stay varied greatly between the patients ($Q_1$-$Q_3$ 3-9 days, min 1, max 74 days). Due to this heterogeneity, we decided not to assess the risk estimates for in-hospital mortality.

New-onset and pre-existing AF may have different prognostic impact on mortality. The TRACE-study concluded that AF developing during hospitalization, but not pre-existent AF, was associated with an increased risk of in-hospital mortality, while no significant difference between the two was distinguished for the long-term mortality [5]. According to Crenshaw et al. in the GUSTO-I trial, AF only in the baseline ECG lost its statistical significance on 30-day mortality after multivariable adjustments [1]. In the GRACE-study, the effect of pre-existing and new-onset AF on in-hospital mortality differed [4]. In the large ARIAM registry, only new-onset AF persisted as an independent predictor of mortality after propensity score analysis [11]. Reinfarction, malignant arrhythmias and heart failure were also more frequent in new-onset AF patients compared to those with previous AF or non-AF patients.

There is accumulating study evidence that AF is a common and prognosis-worsening phenomenon in that scenario, and guidelines on antithrombotic therapy in AF associated with ACS were recently published [29,30]. Recent evidence suggests that patients with a first episode of AF during their myocardial infarction had a risk of 13–24% of developing AF after a median follow-up of 1 037 days compared to only 6% of those remaining in SR during their infarction [31]. Decisions regarding anticoagulation therapy need to be tailored according to the thrombotic and bleeding risk of the individual patient [29,32].

**Strengths and limitations**

We consider the fact that our study population represents consecutive “real life” patients from all three ACS categories as a strength of the study. Also, all the ECG’s of the study patients were systematically collected and analyzed. Because the ECG recordings were based on clinical practice,

the number of ECGs collected per patient differed. Therefore, we decided to use only the ECG at admission and the last recording, typically from the day of hospital discharge, for our analyses. Most probably, using diagnostic methods other than the ECG to detect AF, would have affected the study results. Our study did not include comparison of old ECGs or searching for a clinical diagnosis of AF in the health records. Therefore, we were not able to differentiate between new-onset and previously diagnosed or paroxysmal, persistent and chronic AF. However, the relatively small number of patients in the different categories could have been a limiting factor for statistical analysis in that scenario. We were not able to included mode of rhythm conversion (electrical, pharmacological or spontaneous) in our statistical analyses due to incomplete data, and our study protocol did not include attempts to search for new AF episodes after hospital discharge. Also, the fact that heart failure status was not gathered for this study is a major limitation, since majority of patients with atrial fibrillation have concomitant heart failure. Heart failure status would have been an important variable to be included in the multivariable analysis.

In most of the previous studies, the follow-up has varied from in-hospital stay to six years. In this context the long follow-up period, ten years or more, is a strength of the study, as is the fact that our national death register is a reliable source for outcome data.

Finally, it needs to be pointed out that the patients with AF had a clearly higher burden of comorbidity than the SR patients. Multivariable analysis may not correct for all the effect of background factors that could have negative influence on the outcome of the studied patients.

**Conclusions**

AF is a common dysrhythmia during ACS, altering the prognosis with 66% increase in the hazard of mortality during ≥10-year follow-up time compared to patients remaining in SR during hospital care. AF occurring during ACS affects both short and long-term mortality. Thus, future studies to assess effective treatments to diminish the effect of AF are required.

**Statement of Ethics**

The study complies with the Declaration of Helsinki. The Ethics Committee of the Pirkanmaa Hospital District approved the study protocol (Permission R02100). All subjects gave their written informed consent for participation.

**Conflicts of Interest**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Kaari Konttila: Formal analysis, Investigation, Writing – Original Draft
Olli Punkka: Formal analysis, Investigation, Writing – Original Draft
Kimmo Koivula: Review & Editing
Markku Eskola: Project administration, Resources, Supervision
Mika Martiskainen: Review & Editing
Heini Huhtala: Formal analysis, Validation, Review & Editing
Vesa Virtanen: Resources
Jussi Mikkelsson: Project administration, Resources
Kati Järvelä: Supervision, Review & Editing
Jari Laurikka: Supervision
Kari Niemelä: Project administration, Resources
Pekka Karhunen: Project administration, Resources, Review & Editing
Kjell Nikus: Project administration, Conceptualization, Resources, Supervision, Writing Review & Editing

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## TABLE AND FIGURE LEGENDS

**Table 1.** Variables are described with median and $Q_1$-$Q_3$ range or mean and standard deviation.

AF=atrial fibrillation; ACS=acute coronary syndrome; ACE=angiotensin-converting enzyme; ARB=Angiotensin receptor blocker; CAG=coronary angiography; CABG = coronary artery bypass surgery; CCS=Canadian Cardiovascular Society; EF=ejection fraction; MI=myocardial infarction; NSTEMI=non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; Q1= the first quartile; Q3= the third quartile; SR=sinus rhythm; STEMI=ST-elevation myocardial infarction; UAP=unstable angina pectoris. *For plasma creatinine and C-reactive protein, hazard ratio and confidence interval were calculated using values per 10mg/L and 10 ug/L for cTnI. [a]Either isolated or in association with 1-, 2- or 3-vessel disease. [b]Primary PCI was not standard therapy in STEMI patients.

**Table 2**. SR = Sinus rhythm; AF = Atrial fibrillation

**Table 3.** For abbreviations, see Table 1. *For plasma creatinine, hazard ratio and confidence interval were calculated using values per 10mg/L.

**Fig 1**. Kaplan-Meier survival curves for the two rhythm groups. AF=atrial fibrillation; SR=sinus rhythm.

**Table 1. Baseline characteristics for the different rhythm categories (n=1033)**

| | Valid cases | SR n = 788 n (%) | AF n = 245 n (%) | p-value |
|---|---|---|---|---|
| Age, median (Q1-Q3) | 1033 | 71.0 (59.0–78.0) | 77.0 (72.0–83.0) | < 0.001 |
| Female gender | 1033 | 310 (39.3) | 118 (48.2) | 0.014 |
| Active smoking | 949 | 160 (21.6) | 29 (14.0) | 0.016 |
| Ex-smoker | 740 | 269 (47.6) | 71 (40.6) | 0.103 |
| Hypertension | 1027 | 422 (53.8) | 138 (57.0) | 0.372 |
| Systolic BP, mean (SD) | 1032 | 149.9 (30.8) | 143.6 (31.3) | 0.014 |
| Diastolic BP, mean (SD) | 1032 | 80.7 (16.8) | 80.6 (20.8) | 0.923 |
| Diabetes mellitus | 1031 | 179 (22.8) | 76 (31.0) | 0.009 |
| Prior PCI or CABG | 1018 | 94 (12.1) | 37 (15.2) | 0.208 |
| Previous MI | 1018 | 181 (23.4) | 68 (28.0) | 0.143 |
| ACS Classification | 1033 | | | < 0.001 |
| STEMI | | 263 (33.4) | 49 (20.0) | |
| NSTEMI | | 397 (50.4) | 171 (69.8) | |
| UAP | | 128 (16.2) | 25 (10.2) | |
| Plasma creatinine (/10 mg/L)*, median (Q1-Q3) | 1031 | 8.5 (7.0–10.4) | 9.3 (7.7–12.2) | < 0.001 |
| C-reactive protein (/10 mg/L)*, median (Q1-Q3) | 1018 | 1.1 (0.3–4.8) | 2.1 (0.7–8.6) | < 0.001 |
| cTnI (/10 µg/L)*, median (Q1-Q3) | 1033 | 0.6 (0.1–3.2) | 0.4 (0.1–1.5) | 0.047 |
| CCS class | 923 | | | 0.991 |
| 0 | | 392 (53.8) | 106 (54.4) | |
| 1–2 | | 256 (35.2) | 68 (34.9) | |
| 3–4 | | 80 (11.0) | 21 (10.8) | |
| Medication at admission | | | | |
| Aspirin | 1030 | 354 (45.0) | 99 (40.6) | 0.220 |
| Beta-blocker | 1031 | 361 (45.9) | 152 (62.0) | < 0.001 |
| Nitrate | 1031 | 340 (43.3) | 147 (60.0) | < 0.001 |
| Calcium-antagonist | 1031 | 152 (19.3) | 59 (24.1) | 0.108 |
| Diuretic | 1031 | 203 (25.8) | 135 (55.1) | < 0.001 |
| Statin | 1032 | 183 (23.3) | 48 (19.6) | 0.230 |
| ACE-inhibitor | 1030 | 136 (17.3) | 79 (32.4) | < 0.001 |
| ARB | 1031 | 62 (7.9) | 12 (4.9) | 0.113 |
| Warfarin | 1032 | 40 (5.1) | 79 (32.2) | < 0.001 |
| Clopidogrel | 1031 | 8 (1.0) | 1 (0.4) | 0.694 |
| Anticoagulation at hospital discharge | | | | |
| Warfarin | 1033 | 117 (14.8) | 136 (55.5) | < 0.001 |
| EF median (Q1-Q3) | 495 | 57.0 (45.0–70.0) | 49.0 (39.5–69.5) | 0.003 |
| CAG data available | 1033 | 347 (44.0) | 75 (30.6) | < 0.001 |
| Number of diseased vessels | 499 | | | 0.093 |
| < 50 % stenosis | | 50 (12.1) | 12 (13.8) | |
| 1- vessel disease | | 130 (31.6) | 19 (21.8) | |
| 2- vessel disease | | 108 (26.2) | 19 (21.8) | |
| 3- vessel disease | | 124 (30.1) | 37 (42.5) | |
| Left main disease[a] | 499 | 28 (6.8) | 12 (13.8) | 0.029 |
| PCI in hospital[b] | 1033 | 138 (17.5) | 18 (7.3) | < 0.001 |
| CABG in hospital | 1033 | 75 (9.5) | 28 (11.4) | 0.383 |
| Revascularization in hospital | 1033 | 211 (26.8) | 46 (18.8) | 0.011 |

**Table 1.** Variables are described with median and $Q_1$-$Q_3$ range or mean and standard deviation.
AF=atrial fibrillation; ACS=acute coronary syndrome; ACE=angiotensin-converting enzyme; ARB=Angiotensin receptor blocker; CAG=coronary angiography; CABG = coronary artery bypass surgery; CCS=Canadian Cardiovascular Society; EF=ejection fraction; Q1=the first quartile; Q3= the third quartile; MI=myocardial infarction; NSTEMI=non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; SR=sinus rhythm; STEMI=ST-elevation myocardial infarction; UAP=unstable angina pectoris. *For plasma creatinine and C-reactive protein, hazard ratio and confidence interval were calculated using values per 10mg/L and 10 ug/L for cTnI. [a]Either isolated or in association with 1-, 2- or 3-vessel disease. [b]Primary PCI was not standard therapy in STEMI patients.

**Table 2. Causes of death according to rhythm group.**

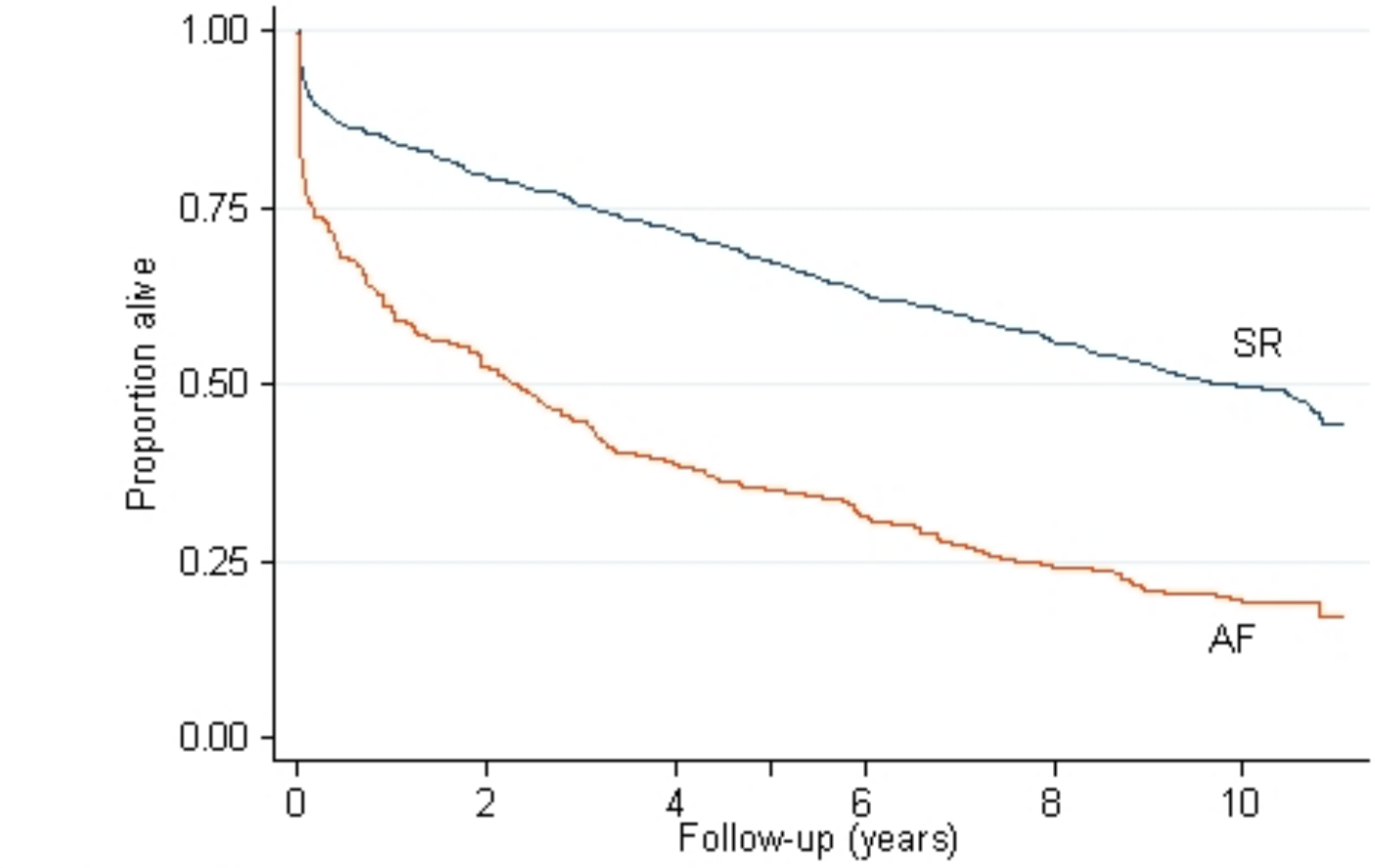
| **Cause of death** | SR n=788 | % | AF n=245 | % | p-value |
|---|---|---|---|---|---|
| All cause mortality | 409/788 | 51.9 | 199/245 | 81.2 | <0.001 |
| Other than cardiovascular death | 124/409 | 30.3 | 52/199 | 26.1 | 0.285 |
| Cardiovascular death | 285/409 | 69.7 | 147/199 | 73.9 | 0.285 |
| Ischemic and other form of heart disease | 248/285 | 87.0 | 125/147 | 85.0 | 0.569 |
| Cerebrovascular diseases | 31/285 | 10.8 | 18/147 | 12.2 | 0.671 |

**Table 2**. SR = Sinus rhythm; AF = Atrial fibrillation

**Table 3. Multivariable Cox regression analysis with all-cause mortality as the end point**

| | Valid cases | Hazard ratio | 95% CI | p-value |
|---|---|---|---|---|
| Age | 1007 | 1.057 | 1.047-1.068 | <0.001 |
| Male gender | 1007 | 1.057 | 0.848-1.211 | 0.881 |
| Diabetes | 1007 | 1.398 | 1.168-1.674 | <0.001 |
| Plasma creatinine (/10 mg/L)* | 1007 | 1.039 | 1.027-1.052 | <0.001 |
| Hypertension | 1007 | 0.880 | 0.741-1.047 | 0.149 |
| Systolic blood pressure | 1007 | 0.998 | 0.994-1.001 | 0.216 |
| Diastolic blood pressure | 1007 | 0.999 | 0.994-1.005 | 0.858 |
| ECG rhythm category | 1007 | | | <0.001 |
| SR | 767 | 1 | | |
| AF | 240 | 1.662 | 1.387-1.992 | <0.001 |
| History of myocardial infarction | 1007 | 1.294 | 1.076-1.556 | 0.006 |
| Previous revascularization | 1007 | 0.872 | 0.677-1.124 | 0.291 |
| PCI or CABG in hospital | 1007 | 1.764 | 1.405-2.215 | <0.001 |
| Category of ACS | 1007 | | | <0.001 |
| UAP | 143 | 1 | | |
| STEMI | 308 | 1.476 | 1.077-2.024 | 0.016 |
| NSTEMI | 556 | 1.769 | 1.327-2.358 | <0.001 |

**Table 3.** For abbreviations, see Table 1. *For plasma creatinine, hazard ratio and confidence interval were calculated using values per 10mg/L.




Number at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| SR | 788 | 625 | 565 | 495 | 441 | 329 |
| AF | 245 | 129 | 95 | 77 | 59 | 40 |