# Effect of Concomitant Atrial Fibrillation on In-Hospital Outcomes of Non-ST-Elevation-Acute Coronary Syndrome Related Hospitalizations in the United States.

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# Abstract

Atrial fibrillation (AF) is the most common arrhythmia in patients presenting with acute coronary syndrome (ACS). The present study examined the rates and trends of clinical outcomes and management strategies of non-ST-elevation ACS (NSTE-ACS) related hospitalizations in the United States, in patients with concomitant AF compared to those in sinus rhythm (SR). We analyzed the ‘Nationwide Inpatient Sample’ database (2004-2014) for patients with a primary discharge diagnosis of NSTE-ACS, and further stratified the cohort on the basis of diagnoses into SR and AF groups. Multivariate analysis was performed to examine the association between AF and major adverse cardiovascular and cerebrovascular events (MACCE; composite of mortality, stroke and cardiac complications) and its components. Out of 4,668,737 NSTE-ACS hospitalizations, the proportions of SR and AF groups were 82.4% (3,848,202) and 17.6% (820,535), respectively. The incidence of AF increased significantly over time from 16.5% (2004) to 19.3% (2014). The AF group was at a greater risk of adverse outcomes with higher rates and adjusted relative risk (RR) of MACCE (12.9% vs. 5.3%; RR:1.74 [1.72,1.75]), mortality (6.5% vs. 3.3%; RR:1.12 [1.11,1.13]), stroke (2.7% vs. 1.5%; RR:1.32 [1.30,1.34]) and bleeding (14.7% vs. 8.8%; RR:1.42 [1.41,1.43]). Furthermore, the AF group was less likely to receive coronary angiography (47.1% vs. 58%) and percutaneous coronary intervention (18.7% vs. 32.6%) in comparison to SR. (p<0.001 for all outcomes) In conclusion, patients with concomitant AF and NSTE-ACS are less likely to be offered an invasive management strategy for their ACS and are associated with worse complications and higher mortality.

**Key Words:** Atrial fibrillation; NSTE-ACS; acute coronary syndromes; outcomes; management

# Introduction

The prevalence of atrial fibrillation (AF) in patients with acute coronary syndrome (ACS) is significant, with reported rates of 7-21% in previous studies.[1](#_ENREF_1" \o "Schmitt, 2009 #26) In comparison to sinus rhythm (SR), patients with AF who develop non-ST-elevation ACS (NSTE-ACS) are often older with a higher burden of comorbidities including hypertension, renal failure, advanced heart failure and prior history of cerebrovascular disease, ischemic heart disease and coronary revascularization (PCI and/or CABG) which portend to worse clinical outcomes in patients presenting with ACS.[1-4](#_ENREF_1) The present study sought to examine the differences in clinical characteristics, in-hospital outcomes and utilization of invasive management between patients with atrial fibrillation and those in SR in a large national cohort of patients admitted with NSTE-ACS. A temporal analysis of outcomes and management strategies according to concomitant AF status was performed over an 11-year (2004 to 2014).

# Methods

The National Inpatient Sample (NIS), previously known as Nationwide Inpatient Sample until 2012), is the largest publicly available all-payer database of hospitalized patients in the United States and is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project.[5](#_ENREF_5) It includes anonymized data on primary and secondary discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset was designed to approximate 20% stratified sample of United States community hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population. A retrospective observational analysis using the NIS database from 2004 to 2014 was performed. A total of 970,319 records with a primary discharge diagnosis of NSTEACS (non-ST-elevation myocardial infarction (NSTEMI) or unstable angina pectoris (UA)) were extracted from the NIS database using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) codes, which corresponded to a total of 4,668,747 discharges after application of the discharge weight. The cohort was stratified according to the presence or absence of AF, which was also identified using the relevant ICD-9 code, into two groups; sinus rhythm (SR) and atrial fibrillation (AF). All patients ≥18 years of age were included. Records with missing age, gender, admission or discharge date, length of stay and mortality were excluded from the analysis as illustrated in the flow diagram of the cohort selection process (Supplementary Figure 1).

The ICD-9 and Clinical Classification Software (CCS) codes used to identify patient characteristics, outcomes (except death) and comorbidities are all listed in Supplementary Table 1. The following comorbidities were extracted using diagnoses codes: dyslipidemia, smoking status, previous acute myocardial infarction (AMI), previous coronary artery bypass grafting (CABG), history of ischemic heart disease (IHD), previous percutaneous coronary intervention (PCI), previous cerebrovascular accident (CVA), family history of coronary artery disease (CAD), and dementia. Other comorbidities were identified using existing 29 AHRQ Elixhauser comorbidity measures.

The primary outcome measures were in-hospital rates of major acute cardiovascular and cerebrovascular events (MACCE), mortality, stroke and all-cause bleeding. In-hospital MACCE was defined as a composite of acute stroke, adverse cardiac complications and mortality. In-hospital cardiac complications included pericardiocentesis, tamponade, hemopericardium and coronary dissection. Bleeding was defined as any post-procedural hemorrhage or haematomas, or bleeding requiring transfusion. Secondary outcomes included the evaluation of their management strategy in the form of receipt of coronary angiography (CA) and revascularization (percutaneous coronary intervention (PCI) or CABG).

Statistical analysis was performed using SPSS version 24 (IBM Corp, Armonk, NY). Continuous variables are presented as medians with interquartile range (IQR) and were compared using the Mann-Whitney test for differences between SR and AF groups and using the Kruskal-Wallis test for trends across years. Categorical variables are presented as percentages and were analyzed using the chi-squared (X2) test.

Multiple logistic regression was used to identify 1) the relative risk (RR [95% confidence interval (CI)]) of adverse events in the AF group compared to sinus group, 2) the trend in RR of adverse events in AF group per study year from 2004 to 2014 and 3) independent predictors of clinical outcomes adjusted for AF status, presented as odds ratios (ORs [95% CI]). The regression models were assessed for fitness using Hosmer–Lemeshow goodness of fit test. The following covariates were adjusted for in all analyses: age, sex, elective admission, weekend admission, primary expected payer, median household income, dyslipidemia, smoking status, previous AMI, previous CABG, history of IHD, previous PCI, previous CVA, family history of CAD, use of assist device or IABP, shock during hospitalization, dementia, receipt of PCI during admission, bed size of hospital, region of hospital, location/teaching status of hospital and 29 AHRQ comorbidities (acquired immune deficiency syndrome, alcohol abuse, deficiency anemias, chronic blood loss anemia, rheumatoid arthritis/collagen vascular diseases, congestive heart failure, chronic pulmonary disease, coagulopathy, depression, diabetes (uncomplicated), diabetes with chronic complications, drug abuse, hypertension, hypothyroidism, liver disease, lymphoma, fluid and electrolyte disorders, metastatic cancer, other neurological disorders, obesity, paralysis, peripheral vascular disorders, psychoses, pulmonary circulation disorders, chronic renal failure, solid tumor without metastasis, peptic ulcer disease excluding bleeding, valvular heart disease, and weight loss).

In order to assess the imbalances in baselines characteristics and crude outcomes between both groups, multiple imputation propensity score matching (mi estimate:teffects psmatch on Stata) was conducted to estimate the average treatment effect (ATE) for each outcome using the aforementioned variables (Supplementary Table 3). ATE are reported as coefficients and 95% confidence intervals.

# Results

A total of 4,668,747 hospitalizations for NTE-ACS (NSTEMI and UA) in the United States from 2004 to 2014 were analyzed of which 3,848,202 patients were in SR (82.4%) and 820,535 (17.6%) were diagnosed with AF. UA comprised 9.3% (n=397,226) of the study cohort and was more prevalent in the SR group than in the AF group (9.5% vs. 3.8%). The prevalence of AF increased over time from 16.5% in 2004 to 19.3% in 2014 (p<0.0001 for trend). The median age of the whole cohort was 69 years (58, 80) with 56.9% men and 75.5% of white ethnicity. Patients’ characteristics are presented according to rhythm group and year of admission in Tables 1 and 2, respectively.

Several key differences in patient characteristics were observed. In comparison to the SR group, the AF group was older, with a higher prevalence of men and those of white ethnicity. Patients with AF were more likely to present with NSTEMI (96.2% vs. 90.5%) than UA and were generally more comorbid than patients with SR with a higher prevalence of risk cardiovascular factors such as previous CABG, previous CVA, deficiency anemias, chronic blood loss anemia, congestive heart failure, chronic pulmonary disease, coagulopathy, hypothyroidism, fluid and electrolyte disturbances , peripheral vascular disease, chronic renal failure and dementia. (Table 1)

The crude rates of MACCE, mortality and stroke were significantly higher in the AF group than in the SR (12.9% vs. 5.3%, 6.5% vs. 3.3% and 2.7% vs. 1.5% respectively, p<0.001 for all). (Table 3) Although this observation was consistent in all the years, the rates of MACCE and mortality declined from 2004 to 2014 in both SR (MACCE: 5.8% vs. 5.3%, mortality: 3.8% vs. 3.3% respectively) and AF groups (MACCE: 15% vs. 12.9%, mortality: 8% vs. 6.5% respectively) (Figures 1A and 1B). In contrast, the rate of stroke remained stable between 2004 to 2014 in both SR (1.5% vs. 1.5%) and AF groups (2.8% vs. 2.7%) (Figure 1C).

Despite a higher overall adjusted relative risk of adverse events in the AF group (MACCE: 1.74 [1.72, 1.75]; mortality: 1.12 [1.11, 1.13]; stroke: 1.32 [1.30, 1.34], cardiac complications: 5.51 [5.42, 5.60]) (Figure 2), the risk trend remained stable from 2004 to 2014 (MACCE: 1.76 [1.71,1.81] vs. 1.76 [1.71,1.81]; mortality: 1.12 [1.08, 1.16] vs. 1.08 [1.04, 1.12]; stroke: 1.29 [1.22, 1.36] vs 1.25 [1.19, 1.32]) (Supplementary Figure 2).

Several variables other than rhythm status were independently associated with increased odds of MACCE and mortality in our cohort such as shock during admission, metastatic cancer, congestive heart failure, fluid and electrolyte disorders, and renal failure (Supplementary Table 2). Interestingly, women were associated with reduced odds of MACCE and mortality, but they were also at higher odds of stroke (26%).

We observed an overall rate of 9.7% in-hospital bleeding in our cohort with an upward trend in bleeding events from 2004 to 2014. (Tables 3 and 4). The overall rate of bleeding was higher in the AF group in comparison to the SR group (14.7% vs. 8.8%), a finding that persisted in the multivariate analysis (RR 1.42 [1.41, 1.43], p<0.001) (Figure 2). While the annual rate of bleeding events steadily increased from 2004 to 2014 in both SR (7.9% vs. 8.8%) and AF groups (13.1% vs 15.6%) (Figure 1D), the incremental risk was more pronounced in the AF group (RR 2014 vs. 2004: 1.54 [1.50, 1.57] vs. 1.39 [1.35, 1.43], p<0.001) (Supplementary Figure 2).

Several comorbidities were associated with increased odds of bleeding in our cohort, including: chronic anemia (5.86 [5.75, 5.97], p<0.001), coagulopathy (2.85 [2.82, 2.88], p<0.001), congestive heart failure (2.13 [2.08, 2.19], p<0.001), deficiency anemias (1.90 [1.88, 1.91], p<0.001) and previous peptic ulcer excluding bleeding (1.90 [1.68, 2.16], p<0.001).

In comparison to the SR group, patients with AF were less likely to receive CA (47.1% vs. 58.0%, p<0.001) and PCI (18.7% vs. 32.6%, p<0.001) but were more likely to undergo CABG (13.9% vs. 7.6%). (Table 3) In multivariate analysis, AF was independently associated with reduced odds of receipt of CA (OR 0.97 [0.97,0.98]) and PCI (OR 0.64 [0.64,0.64]). Several other factors were associated with reduced odds of receipt of CA and PCI such as age (OR 0.96 [0.96,0.96] and OR 0.98 [0.98,0.98], respectively), female gender (OR 0.92 [0.91,0.92] and OR 0.81 [0.81,0.82], respectively), metastatic cancer (OR 0.38 [0.37,0.39] and OR 0.54 [0.52,0.56], respectively) and renal failure (OR 0.73 [0.73,0.74] and OR 0.85 [0.85,0.86], respectively) (p<0.001 for all).

The trend of utilization of CA over the study years according to age categories, gender and hospital location-teaching status is illustrated in Figures 3a, 3b and 3c, respectively, and according to ethnicity in Supplementary Figure 3. The disparity in growth of CA between SR and AF groups increased over the study years across all age groups, although this was less notable in patients aged ≥ 80 years, who were less likely to receive CA regardless of their cardiac rhythm (Figure 3a). The rate of CA was also notably lower in women with AF compared to those in SR throughout the study years (Figure 3b).

While the rate of CA has dramatically improved in both AF and SR groups from 2004 to 2014, the relative increase of CA procedures in the AF group remained modest in women and patients in the upper age group (age ≥ 80 years), and those admitted to rural hospitals compared to the SR group. (Figures 3a, 3b and 3c) Similarly, the trend of utilization of PCI improved throughout the study period in both SR and AF groups, although the AF group was persistently less likely to undergo PCI. (Figure 4) The disparity in rates of utilization of PCI between SR and AF group was more pronounced in the younger groups (age groups ≤60 years and 61-70 years) compared to older groups (age≥80 years) who were much less likely to receive PCI regardless of their rhythm.

 Propensity score matching was performed as a sensitivity analysis for each of the study outcomes (Supplementary Table 3). In line with our findings from the original cohort, patients with AF were found to have greater probability of in-hospital MACCE, mortality, stroke and bleeding as demonstrated by significantly positive coefficients for each of the outcomes (p<0.001 for all).

# Discussion

The present study, drawn from more than 4.6 million discharges, is by far the largest analysis of an unselected NSTE-ACS population according to the presence or absence of concomitant AF. [4](#_ENREF_4),[6](#_ENREF_6),[7](#_ENREF_7) We demonstrate worse clinical outcomes after NSTE-ACS in patients with AF compared to those with. Despite the improvement in in-hospital clinical outcomes over an 11-year period, patients with AF remained at a persistently higher risk of all adverse outcomes in comparison to those with SR throughout the study period. We also find that all-cause bleeding was the most significant adverse event recorded in our cohort, which highlights the complex challenges faced when balancing reductions in ischemic complications with the increase in major bleeding. There were significant disparities in the receipt of invasive management between SR and AF patients, with the latter less likely to receive PCI despite it being associated with reduced odds of MACCE and mortality in our analysis.

AF is the most common supraventricular arrhythmia in patients with ACS.[8-10](#_ENREF_8) AF patients developing ACS represent a higher risk group than those in SR, with a greater burden of comorbidities and a higher incidence of future ischemic and bleeding complications as demonstrated in our analysis.[1](#_ENREF_1),[2](#_ENREF_2),[11](#_ENREF_11) We find that concomitant AF was associated with worse clinical outcomes after NSTE-ACS in our analysis, including MACCE, mortality, stroke and bleeding. Kinjo et al. compared the outcomes of 2475 patients with acute myocardial infarction (AMI) undergoing PCI according to the presence of atrial fibrillation and/or flutter.[6](#_ENREF_6) In their analysis, AF comprised 12% of their study population and was associated with higher in-hospital and one-year mortality, although the hazard of in-hospital mortality was not maintained in a multivariate analysis (1.42[0.88–2.31]).

Despite an improvement in survival and clinical outcomes after ACS in recent years, patients with AF remain at a greater risk of in-hospital adverse outcomes.[3](#_ENREF_3),[12](#_ENREF_12),[13](#_ENREF_13) We demonstrate that AF was persistently associated with a higher risk of in-hospital adverse outcomes in patients with NSTE-ACS throughout the study period, and that the relative risk of bleeding and stroke remained high in this group. More importantly, this group was less likely to receive coronary angiography and PCI despite the well-recognized benefit of an early invasive strategy in NSTE-ACS.[14](#_ENREF_14),[15](#_ENREF_15) Our analysis identifies factors associated with reduced odds of receipt of an invasive management strategy including age, female gender and comorbidities such as renal failure and metastatic cancer. Furthermore, we observe higher rates of CABG in the AF group throughout the study period, which suggests more extensive coronary artery disease in these patients, or a reluctance to treat them with prolonged DAPT and anticoagulation that PCI would require. In a temporal analysis of 2596 AMI hospitalizations based on the presence of AF, Goldberg et al. reported an improvement in in-hospital survival of the AF group (mortality 1990 vs. 1997: 21.3% vs. 18.5%) although the same was true for the SR group (mortality 1990 vs. 1997: 13.2% vs. 10.5%).[13](#_ENREF_13) The AF group was less likely to receive CA and PCI and more likely to undergo CABG in their analysis, in keeping with the present study’s findings. Similarly, a multi-registry analysis by De Luca et al. who studied the effect of concomitant AF separately in 668 NSTEMI and 351 STEMI patients over a 13-year period.[12](#_ENREF_12) revealed a significant underutilization of invasive strategy in patients with concomitant AF.

Current guidelines recommend a similar revascularization strategy for NSTE-ACS patients with or without AF, in addition to the use of ‘triple therapy’ in patients with AF and NSTE-ACS in the form of anticoagulation and a variable duration of dual antiplatelet therapy depending on patients’ bleeding risks.[14](#_ENREF_14) The significant rate of bleeding events in the AF group in the present study carries important clinical implications. Although the increased relative risk is unadjusted for the use of antiplatelet and anticoagulant agents, the findings emphasize the importance of using validated scoring systems to objectively stratify the risk of future bleeding and guide the choice and duration of antithrombotic therapy as recommended by current guidelines.

There are several limitations to our present study. First, the NIS is an administrative dataset that is susceptible to coding inaccuracies, although both the use of ICD-9 codes and the NIS database have been previously validated for the purpose of cardiovascular research.[16](#_ENREF_16) [17](#_ENREF_17) Second, we were unable to determine (and adjust for) the onset (pre-admission vs. post admission) or type (paroxysmal vs. permanent vs. chronic) of AF. However, this limitation has been evident in several studies in which the timing of AF onset prior to admission and/or enrolment was not fully ascertained.[7](#_ENREF_7),[18-20](#_ENREF_18) Third, the NIS dataset does not capture pharmacotherapy and, therefore, we were unable to determine differences in antithrombotic therapy between the two cohorts, or stratify bleeding risk according to HAS-BLED score as recommended by current guidelines,[14](#_ENREF_14) which may in part contribute to the adverse outcomes we report in our findings. For example, the use of triple therapy in AF undergoing PCI has been recently shown to increase bleeding complications when compared to dual antithrombotic therapy.[21](#_ENREF_21) Finally, the NIS only reports in-hospital outcomes and, therefore, our study findings should be interpreted in this context. It is possible that the disparity in clinical outcomes between AF and SR groups is becomes less significant over a longer follow-up period. Nevertheless, we believe that our findings provide insight into the ‘real world’ in-hospital clinical outcomes of a large and unselected contemporary NSTE-ACS cohort.

The present study of an unselected nationwide cohort of NSTE-ACS hospitalizations according to supraventricular rhythm demonstrates a significant rise in the prevalence of concomitant AF in recent years. Our analysis reveals that patients with NSTE-ACS and concomitant AF are a high-risk group associated with worse in-hospital adverse outcomes and mortality, and a more conservative management strategy for their ACS, compared to those without concomitant AF. These findings emphasize the prognostic implications of concomitant AF in the context of NSTE-ACS and would support cardiologists in their decision-making process when assessing and managing this high-risk group.

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**Figure Legends:**

**Figure 1. Crude rates of in-hospital adverse events in study groups**

Legend: \* p<0.001 for all trends; AF: atrial fibrillation; SR: sinus rhythm

**Figure 2. Relative risk (RR) of in-hospital adverse events in AF group**

Legend: AF: atrial fibrillation; \*Reference group is sinus rhythm; \*\*MACCE: major adverse cardiovascular and cerebrovascular events (composite of mortality, stroke and cardiac complications); † p<0.001

**Figure 3a. Trend of utilization of coronary angiography according to age group in SR and AF groups\***

Legend: \* p<0.001 for all trends; AF: atrial fibrillation; SR: sinus rhythm

**Figure 3b. Trend of utilization of coronary angiography according to gender in SR and AF groups**

Legend: \* p<0.001 for all trends; AF: atrial fibrillation; SR: sinus rhythm

**Figure 3c. Trend of utilization of coronary angiography according to hospital location and teaching status in SR and AF groups\***

Legend: \* p<0.001 for all trends; AF: atrial fibrillation; SR: sinus rhythm

**Figure 4. Trend of utilization of percutaneous coronary intervention in SR and AF groups according to age group\***

Legend: \* p<0.001 for all trends; AF: atrial fibrillation; SR: sinus rhythm

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