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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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 with those in sinus rhythm (SR). We analyzed the "Nationwide Inpatient Sample" database (2004 to 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 (composite of mortality, stroke, and cardiac complications) and its components. 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 major adverse cardiovascular and cerebrovascular events (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.
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The prevalence of atrial fibrillation (AF) in patients with acute coronary syndrome (ACS) is significant, with reported rates of 7% to 21% in previous studies.[1] 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 co-morbidities including hypertension, renal failure, advanced heart failure, and previous history of cerebrovascular disease, ischemic heart disease (IHD), and coronary revascularization (percutaneous coronary intervention [PCI] and/or coronary artery bypass grafting [CABG]) that portend to worse clinical outcomes in patients presenting with ACS.[1−4] The present study sought to examine the differences in clinical characteristics, in-hospital outcomes, and utilization of invasive management between patients with AF 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 period (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] It includes anonymized data on primary and secondary discharge diagnoses and procedures from > 7 million hospitalizations annually. The NIS dataset was designed to approximate 20% stratified sample of US community hospitals and provides sampling weights to calculate national estimates that

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represent >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 NSTE-ACS (NSTE 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 2 groups: SR and 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 codes used to identify patient characteristics, outcomes (except death), and co-morbidities are all listed in Supplementary Table 1. The following co-morbidities were extracted using diagnoses codes: dyslipidemia, smoking status, previous acute myocardial infarction (AMI), previous coronary artery bypass grafting (CABG), history of IHD, previous PCI, previous cerebrovascular accident (CVA), family history of coronary artery disease (CAD), and dementia. Other co-morbidities were identified using existing 29 Agency for Healthcare Research and Quality (AHRQ) Elixhauser co-morbidity 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 postprocedural hemorrhage or hematomas, or bleeding requiring transfusion. Secondary outcomes included the evaluation of their management strategy in the form of receipt of coronary angiography (CA) and revascularization (PCI or CABG).

Statistical analysis was performed using SPSS version 24 (IBM Corp, Armonk, New York). Continuous variables are presented as medians with interquartile range 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-square 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 with 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, gender, 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 intra-aortic balloon pump (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 co-morbidities (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).

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

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 decreased 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 1). In contrast, the rate of stroke remained stable between 2004 and 2014 in both SR (1.5% vs 1.5%) and AF groups (2.8% vs 2.7%; Figure 1).

Table 1
Patient characteristics of study groups

	SR (82.4%)	AF (17.6%)	Total	p value
Number of weighted discharges	3,848,202	820,535	4,668,74	<0.001
Age (years), median (IQR)	67(56,78)	78(69,85)	69(58,80)	<0.001
Men	57.4%	54.7%	56.9%	<0.001
Ethnicity				<0.001
White	73.8%	83.2%	75.5%	
Black	12.0%	6.6%	11.0%	
Hispanic	8.3%	5.4%	7.8%	
Asian/Pacific Islander	2.2%	2.1%	2.2%	
Native American	0.6%	0.4%	0.5%	
Other	3.1%	2.4%	3.0%	
Unstable angina pectoris	9.5%	3.8%	9.3%	<0.001
Elective admission	7.1%	6.6%	7.0%	<0.001
Weekend admission	25.1%	25.2%	25.1%	0.214
Dyslipidemia*	50.9%	38.9%	48.8%	<0.001
Previous/current smoker	33.7%	21.9%	31.6%	<0.001
Previous acute myocardial infarction	9.6%	9.5%	9.6%	<0.001
History of ischemic heart disease	66.3%	61.4%	65.4%	<0.001
Previous percutaneous coronary intervention	10.2%	9.0%	10.0%	<0.001
Previous coronary artery bypass graft	7.3%	8.7%	7.6%	<0.001
Previous cerebrovascular accident	3.1%	4.9%	3.4%	<0.001
Family history of coronary artery disease	6.8%	3.0%	6.2%	<0.001
Acquired immunodeficiency syndrome	0.1%	0.0%	0.1%	<0.001
Alcohol abuse	2.8%	2.1%	2.7%	<0.001
Deficiency anemias**	15.3%	20.8%	16.2%	<0.001
Chronic blood loss anemia†	1.1%	1.6%	1.2%	<0.001
Rheumatoid arthritis/collagen vascular disorders	2.2%	2.5%	2.3%	<0.001
Congestive heart failure	0.7%	1.3%	0.8%	<0.001
Chronic pulmonary disease	21.6%	27.3%	22.6%	<0.001
Coagulopathy	3.7%	6.9%	4.3%	<0.001
Depression	7.2%	6.7%	7.1%	<0.001
Diabetes	30.2%	29.2%	30.0%	<0.001
Diabetes with complications	7.0%	7.3%	7.1%	<0.001
Drug abuse	2.2%	0.7%	1.9%	<0.001
Hypertension	69.9%	69.9%	69.9%	0.563
Hypothyroidism	10.1%	14.0%	10.8	<0.001
Liver disease	1.3%	1.2%	1.3%	<0.001
Lymphomas	0.5%	0.7%	0.5%	<0.001
Fluid and electrolyte disturbances	18.0%	26.8%	19.5%	<0.001
Metastatic cancer	0.9%	1.0%	0.9%	<0.001
Other neurological disorders	5.8%	7.4%	6.1%	<0.001
Obesity‡	13.0%	10.1%	12.5%	<0.001
Paralysis	1.6%	2.4%	1.8%	<0.001
Peripheral vascular disease	11.4%	14.7%	12.0%	<0.001
Psychoses	2.3%	1.9%	2.3%	<0.001
Pulmonary circulation disorder	0.1%	0.2%	0.1%	<0.001
Chronic renal failure	17.6%	26.4%	19.2%	<0.001
Solid tumor without metastases	1.4%	1.9%	1.5%	<0.001
Valvular heart disease	0.2%	0.5%	0.3%	<0.001
Weight loss	2.0%	3.5%	2.2%	<0.001
Dementia	2.3%	3.6%	2.5%	<0.001
Hospital bed size				<0.001
Small	11.1%	11.1%	11.1%	
Medium	25.3%	25.1%	25.2%	
Large	63.6%	63.9%	63.6%	
Hospital region				<0.001
Northeast	20.3%	22.3%	20.6%	
Midwest	22.6%	22.9%	22.7%	
South	40.3%	38.0%	39.9%	
West	16.8%	16.8%	16.8%	
Location/teaching status				<0.001
Rural	11.5%	11.0%	11.4%	
Urban nonteaching	41.7%	42.2%	41.8%	
Urban teaching	46.8%	46.8%	46.8%	

AF = atrial fibrillation; SR = sinus rhythm.
* Dyslipidemia was defined as any lipid disorder according to Clinical Classification Software code 53.
† Anemia was defined as hemoglobin of <13.5 g/dl in men and <12.0 g/dl in women.
‡ Obesity was defined as body mass index >30.

Table 2
Patient characteristics according to year of admission (SR vs AF)

Group (% within year)	2004		2007		2010		2014		p value (trend)
	SR (83.5%)	AF (16.5%)	SR (82.9%)	AF (17.1%)	SR (82.8%)	AF (17.2%)	SR (80.7%)	AF (19.3%)	
Number of weighted cases	367727	72423	338843	69973	334392	69349	356950	85175	<0.001
Age (years), median (IQR)	67(56,78)	78(71,84)	67(56,78)	79(70,85)	67(56,78)	79(69,85)	67(57,77)	77(68,85)	<0.001
Men	55.9%	53.3%	56.9%	52.6%	57.5%	54.2%	59.0%	57.8%	<0.001
Ethnicity									<0.001
White	74.8%	84.5%	74.6%	83.8%	72.8%	83.3%	72.7%	82.0%	
Black	11.9%	6.6%	11.2%	6.6%	13.9%	6.8%	12.8%	7.3%	
Hispanic	8.0%	5.0%	8.9%	4.6%	7.8%	5.1%	8.4%	5.8%	
Asian/Pacific Islander	2.1%	2.0%	1.7%	2.4%	2.3%	2.4%	2.4%	2.2%	
Native American	0.3%	0.1%	0.6%	0.5%	0.7%	0.3%	0.6%	0.3%	
Other	2.8%	1.8%	3.0%	2.1%	2.5%	2.0%	3.1%	2.4%	
Elective Admission	9.1%	8.2%	8.2%	8.0%	7.1%	7.1%	5.7%	5.5%	<0.001
Weekend admission	24.2%	25.0%	24.2%	24.6%	25.7%	25.6%	25.7%	25.5%	<0.001
Comorbidities									
Dyslipidemia*	40.9%	23.7%	45.7%	32.0%	53.5%	42.7%	58.0%	51.1%	<0.001
Previous/current smoker	23.9%	11.6%	28.5%	15.5%	35.5%	23.0%	43.9%	34.9%	<0.001
Previous acute myocardial infarction	7.9%	6.7%	8.4%	7.6%	10.1%	10.6%	11.4%	12.3%	<0.001
History of ischemic heart disease	59.6%	54.5%	63.6%	57.0%	67.7%	63.8%	70.4%	65.8%	<0.001
Previous percutaneous coronary intervention	6.3%	4.1%	7.6%	6.0%	11.0%	9.9%	14.3%	14.6%	<0.001
Previous coronary artery bypass graft	7.0%	7.0%	6.7%	6.8%	7.3%	9.5%	8.0%	10.9%	<0.001
Previous cerebrovascular accident	-	-	-	0.6%	4.7%	7.0%	5.8%	9.7%	<0.001
Family history of coronary artery disease	4.5%	1.1%	5.3%	1.9%	7.9%	3.6%	9.0%	5.1%	<0.001
Use of assist device or intra-aortic balloon pump	2.0%	3.5%	2.1%	3.7%	2.4%	3.8%	2.6%	3.8%	<0.001
Shock	1.5%	3.0%	1.6%	3.4%	2.2%	4.0%	2.8%	5.2%	<0.001
Acquired immunodeficiency syndrome	0.1%	0.0%	0.1%	0.0%	0.2%	0.0%	0.2%	0.0%	<0.001
Alcohol abuse	2.2%	1.7%	2.5%	1.7%	3.0%	2.0%	3.3%	2.6%	<0.001
Deficiency anemias†	11.1%	13.1%	11.9%	18.1%	16.6%	23.5%	17.2%	24.3%	<0.001
Chronic Blood loss anemia†	1.3%	2.1%	1.3%	2.4%	0.9%	1.4%	0.7%	1.1%	<0.001
Rheumatoid arthritis/collagen vascular disorders	1.7%	1.9%	1.9%	2.3%	2.3%	2.8%	2.6%	3.0%	<0.001
Congestive heart failure	0.9%	1.8%	0.6%	1.4%	0.9%	1.3%	0.6%	1.0%	<0.001
Chronic pulmonary disease	20.2%	26.1%	21.1%	28.0%	21.3%	25.9%	22.8%	28.0%	<0.001
Coagulopathy	2.5%	5.2%	2.7%	6.0%	4.0%	7.4%	4.9%	9.2%	<0.001
Depression	5.0%	3.8%	5.8%	5.9%	7.8%	7.4%	9.2%	8.7%	<0.001
Diabetes	27.4%	24.6%	28.4%	27.0%	30.8%	30.3%	32.9%	32.9%	<0.001
Diabetes with complications	5.5%	5.5%	5.7%	6.4%	7.0%	7.4%	8.7%	9.6%	<0.001
Drug abuse	1.4%	0.3%	2.0%	0.5%	2.3%	0.8%	3.1%	1.2%	<0.001
Hypertension	61.5%	57.2%	65.6%	64.2%	72.1%	73.0%	76.4%	78.8%	<0.001
Hypothyroidism	7.7%	9.3%	8.3%	12.3%	10.5%	14.9%	12.2%	16.9%	<0.001
Liver disease	0.9%	0.7%	1.0%	1.0%	1.4%	1.2%	1.9%	1.9%	<0.001
Lymphomas	0.4%	0.6%	0.4%	0.6%	0.5%	0.8%	0.5%	0.8%	<0.001
Fluid and electrolyte disturbances	13.6%	21.2%	14.9%	24.7%	18.8%	27.0%	21.7%	31.3%	<0.001
Metastatic cancer	0.7%	0.9%	0.7%	1.0%	0.9%	1.0%	0.9%	1.0%	<0.001
Other neurological disorders	4.6%	5.4%	5.1%	7.0%	6.0%	8.1%	6.2%	8.2%	<0.001
Obesity‡	8.3%	4.7%	9.3%	6.9%	13.1%	10.6%	18.4%	15.8%	<0.001
Paralysis	1.5%	1.9%	1.4%	2.2%	1.7%	2.5%	1.6%	2.5%	<0.001
Peripheral vascular disease	9.0%	10.7%	9.6%	13.8%	11.5%	15.1%	13.2%	17.9%	<0.001
Psychoses	1.6%	1.2%	1.6%	1.3%	2.6%	2.0%	3.0%	2.5%	<0.001
Pulmonary circulation disorder	0.0%	0.1%	0.0%	0.1%	0.1%	0.3%	0.1%	0.3%	<0.001
Chronic renal failure	8.1%	11.7%	14.9%	26.2%	20.1%	29.8%	22.2%	33.5%	<0.001
Solid tumor without metastases	1.3%	1.7%	1.3%	2.0%	1.5%	1.9%	1.4%	1.9%	<0.001
Peptic ulcer disease	0.1%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%	0.0%	<0.001
Valvular heart disease	0.2%	0.5%	0.2%	0.5%	0.2%	0.5%	0.2%	0.5%	<0.001

(*continued*)

Table 2 (***Continued***)

Group (% within year)	2004		2007		2010		2014		p value (trend)
	SR (83.5%)	AF (16.5%)	SR (82.9%)	AF (17.1%)	SR (82.8%)	AF (17.2%)	SR (80.7%)	AF (19.3%)	
Weight loss	1.0%	2.2%	1.1%	2.8%	2.2%	3.7%	2.6%	4.4%	<0.001
Dementia	2.2%	3.1%	2.3%	3.4%	2.5%	4.0%	1.8%	3.1%	<0.001
Hospital bed size									<0.001
Small	11.6%	11.3%	12.1%	9.4%	10.4%	10.5%	16.3%	16.3%	
Medium	24.2%	24.4%	25.9%	26.0%	22.4%	22.4%	29.8%	29.4%	
Large	64.2%	64.3%	62.1%	64.6%	67.2%	67.0%	53.9%	54.3%	
Hospital region									<0.001
Northeast	23.3%	25.5%	22.3%	23.5%	20.0%	20.6%	18.5%	20.5%	
Midwest	23.5%	22.5%	22.2%	22.7%	24.0%	25.2%	22.6%	23.9%	
South	37.8%	35.6%	40.9%	37.0%	38.7%	37.1%	41.3%	38.2%	
West	15.4%	16.4%	14.6%	16.8%	17.3%	17.1%	17.7%	17.4%	
Location/teaching status									<0.001
Rural	13.9%	11.6%	11.7%	11.0%	12.3%	12.8%	8.8%	9.2%	
Urban nonteaching	44.3%	45.4%	40.5%	44.2%	43.2%	46.1%	28.8%	28.2%	
Urban teaching	41.8%	43.0%	47.8%	44.7%	44.5%	41.1%	62.4%	62.6%	

AF = atrial fibrillation; SR = sinus rhythm; - = not available in earlier years.

* Dyslipidemia was defined as any lipid disorder according to Clinical Classification Software code 53.

† Anemia was defined as hemoglobin of <13.5 g/dl in men and <12.0 g/dl in women.

‡ Obesity was defined as body mass index >30.

Table 3
In-hospital clinical outcomes and quality indicators of study groups

	SR (82.4)	AF (17.6)	Total	p value
MACCE	5.3%	12.9%	6.7%	<0.001
Cardiac complications	0.9%	4.3%	1.5%	<0.001
Acute stroke	1.5%	2.7%	1.7%	<0.001
Mortality	3.3%	6.5%	3.9%	<0.001
All-cause bleeding	8.8%	14.7%	9.8%	<0.001
Use of assist device or intra-aortic balloon pump	2.4%	3.8%	2.6%	<0.001
Shock	2.1%	3.9%	2.4%	<0.001
Receipt of coronary angiography	58.0%	47.1%	56.1%	<0.001
Receipt of percutaneous coronary intervention	32.6%	18.7%	30.2%	<0.001
Receipt of coronary artery bypass grafting	7.6%	13.9%	8.7%	<0.001
Length of stay (days), median (IQR)	3 (2, 5)	5 (3, 8)	3 (2, 6)	<0.001
Total charge ($), median (IQR)	35698 (17440, 65288)	39243 (19249, 82123)	36241 (17752, 67618)	<0.001

AF = atrial fibrillation; MACCE = major adverse cardiovascular and cerebrovascular events (composite of mortality, stroke, and cardiac complications); SR = sinus rhythm.

Despite a higher overall adjusted RR 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). Although 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 1), 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 co-morbidities 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),

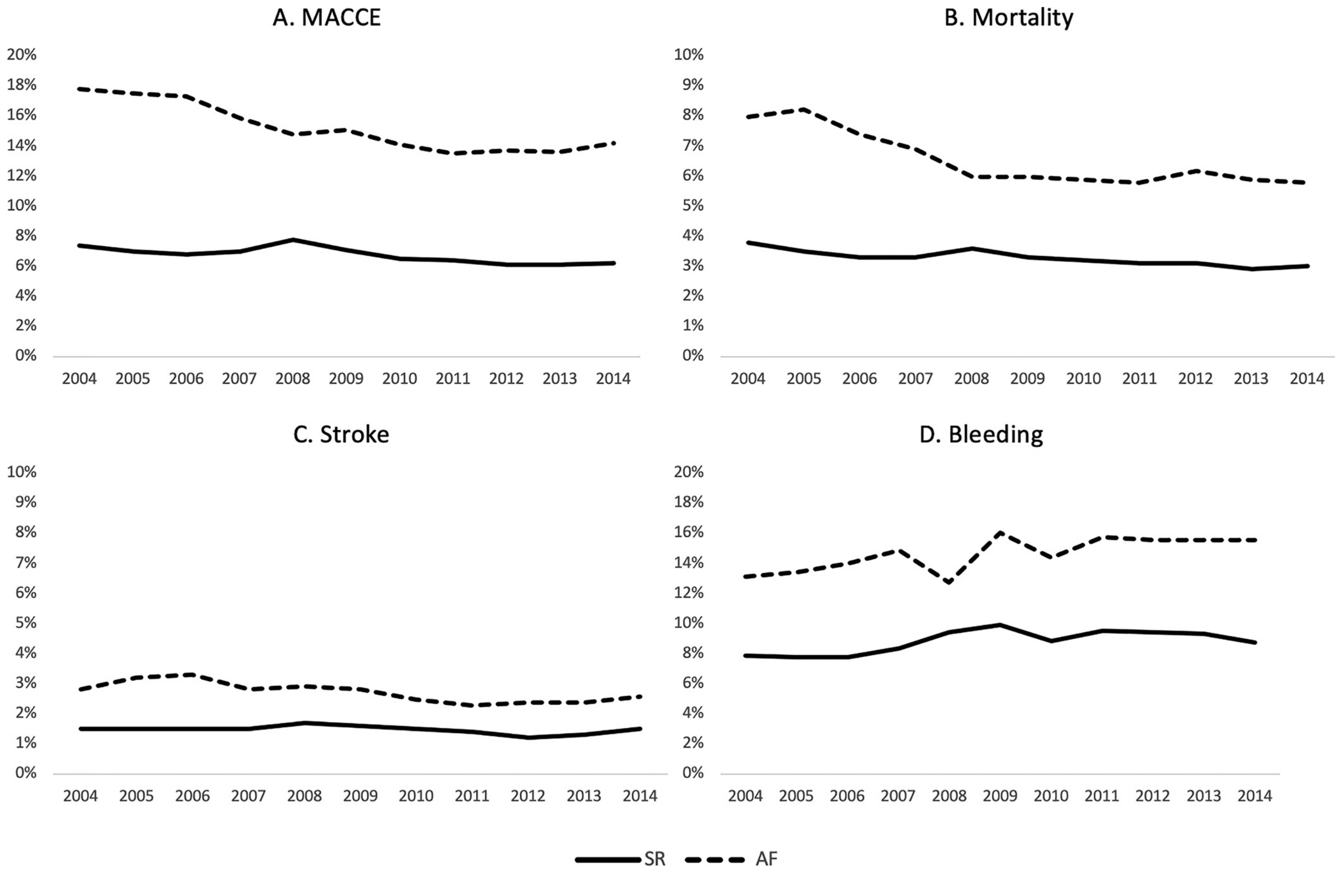

Figure 1. Crude rates of in-hospital adverse events in study groups. *p <0.001 for all trends; AF = atrial fibrillation; SR = sinus rhythm.

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).

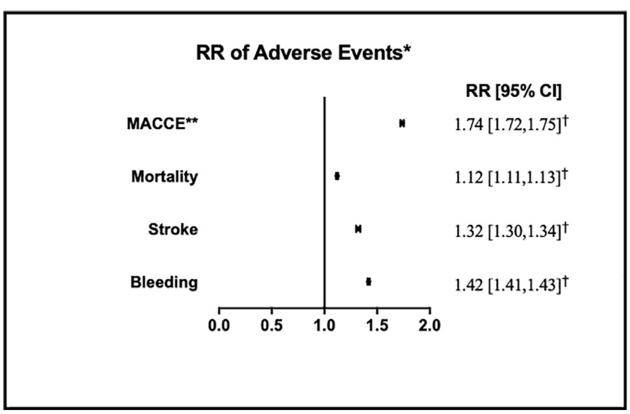

Figure 2. Relative risk (RR) of in-hospital adverse events in AF group. AF = atrial fibrillation; *reference group is sinus rhythm; **MACCE = major adverse cardiovascular and cerebrovascular events (composite of mortality, stroke, and cardiac complications); †p <0.001.

The trend of utilization of CA over the study years according to age categories, gender, and hospital location-teaching status is illustrated in Figure 3 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 3). The rate of CA was also notably lower in women with AF compared with those in SR throughout the study years (Figure 3).

Although 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 with

Table 4
In-hospital clinical outcomes and quality indicators per year of admission (SR vs AF)

	2004		2007		2010		2014		p value (for trend)	Total	
	SR	AF	SR	AF	SR	AF	SR	AF		SR	AF
MACCE	5.8%	15.0%	5.4%	13.4%	5.1%	12.0%	5.1%	12.2%	<0.001	5.3	12.9
Cardiac complications	0.9%	5.1%	0.9%	4.5%	0.8%	4.1%	0.8%	4.3%	<0.001	0.9	4.3
Acute stroke	1.5%	2.8%	1.5%	2.8%	1.5%	2.5%	1.5%	2.6%	<0.001	1.5	2.7
Mortality	3.8%	8.0%	3.3%	6.9%	3.2%	5.9%	3.0%	5.8%	<0.001	3.3	6.5
All-cause bleeding	7.9%	13.1%	8.4%	14.9%	8.9%	14.4%	8.8%	15.6%	<0.001	8.8	14.7
Use of assist device or intra-aortic balloon pump	2.0%	3.5%	2.1%	3.7%	2.4%	3.8%	2.6%	3.8%	<0.001	2.4	3.8
Shock	1.5%	3.0%	1.6%	3.4%	2.2%	4.0%	2.8%	5.2%	<0.001	2.1	3.9
Receipt of coronary angiography	48.9%	42.7%	54.6%	44.6%	59.6%	47.0%	65.7%	52.9%	<0.001	58.0	47.1
Receipt of percutaneous coronary intervention	26.2%	15.1%	29.6%	16.8%	32.6%	18.4%	38.4%	22.5%	<0.001	32.6	18.7
Receipt of coronary artery bypass grafting	7.4%	14.8%	7.3%	13.9%	7.5%	12.8%	8.1%	14.8%	<0.001	7.6	13.9
Length of stay (days), median (IQR)	3 (2, 6)	6 (3, 10)	3 (2, 5)	5 (3, 9)	3 (2, 5)	5 (3, 8)	3 (2, 5)	4 (2, 8)	<0.001	3 (3, 3)	5 (3, 8)

AF = atrial fibrillation; MACCE = major adverse cardiovascular and cerebrovascular events (composite of mortality, stroke, and cardiac complications); SR = sinus rhythm.

the SR group (Figure 3). 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 to 70 years) compared with 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 >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.[4,6,7] We demonstrate worse clinical outcomes after NSTE-ACS in patients with AF compared with those without. 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 with 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] AF patients developing ACS represent a higher risk group than those in SR, with a greater burden of co-morbidities and a higher incidence of future ischemic and bleeding complications as demonstrated in our analysis.[1,2,11] 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[6] compared the outcomes of 2,475 patients with AMI who underwent PCI according to the presence of AF and/or flutter. In their analysis, AF comprised 12% of their study population and was associated with higher in-hospital and 1-year mortality, although the hazard of in-hospital mortality was not maintained in a multivariate analysis (1.42 [0.88 to 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.[3,12,13] 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 RR of bleeding and stroke remained high in this group. More importantly, this group was less likely to receive CA and PCI despite the well-recognized benefit of an early invasive strategy in NSTE-ACS.[14,15] Our analysis identifies factors associated with reduced odds of receipt of an invasive management strategy including age, female gender, and co-morbidities 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 CAD in these patients, or a reluctance to treat them with prolonged dual antiplatelet therapy (DAPT) and anticoagulation that PCI would require. In a temporal analysis of 2,596 AMI hospitalizations based on the presence of AF, Goldberg et al[13] 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%). 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 multiregistry

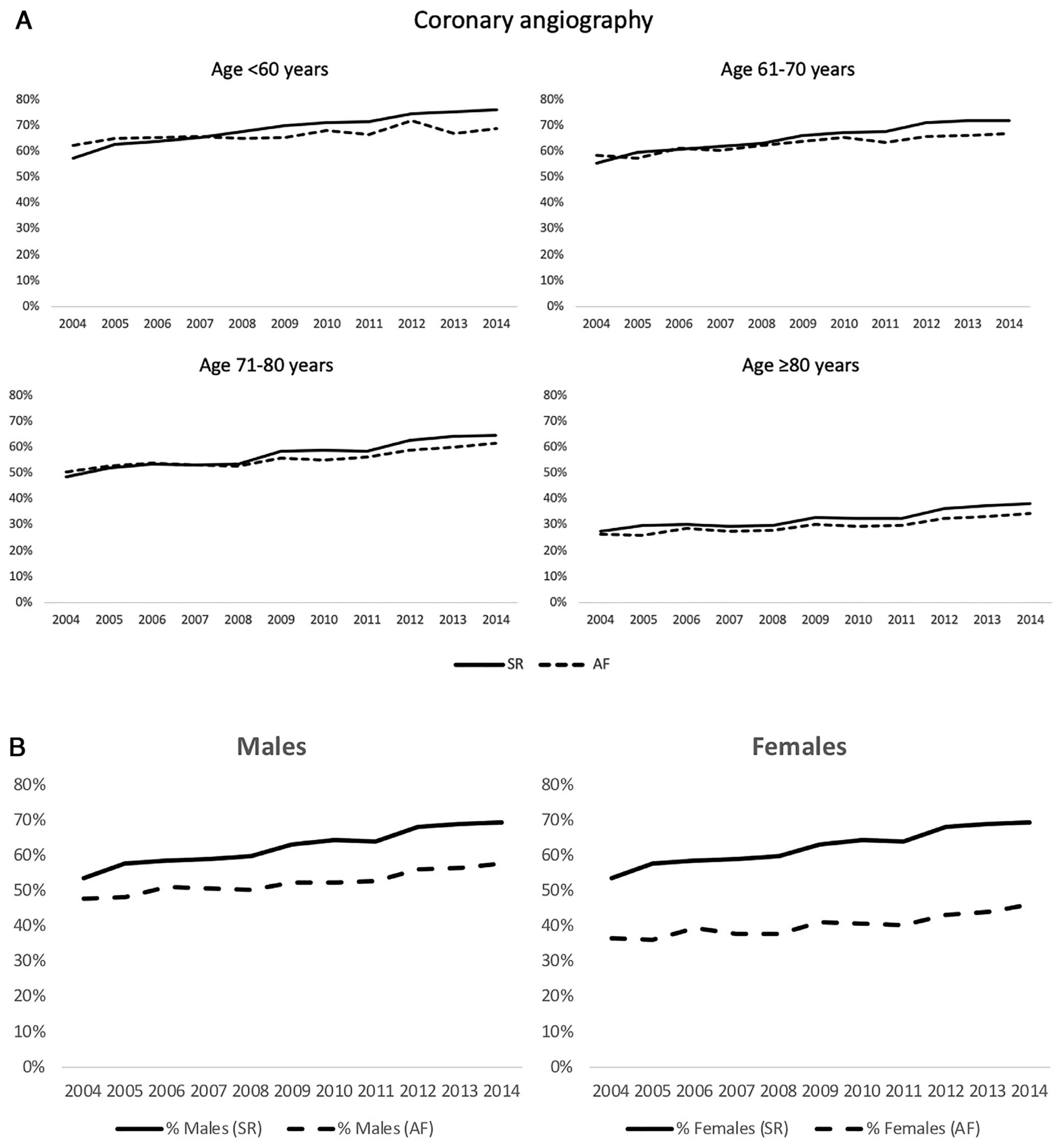

Figure 3. Trend of utilization of coronary angiography according to *(A)* age group, *(B)* gender, and *(C)* hospital location and teaching status in SR and AF groups.*p <0.001 for all trends; AF = atrial fibrillation; SR = sinus rhythm.

analysis by De Luca et al[12] who studied the effect of concomitant AF separately in 668 NSTEMI and 351 STEMI patients over a 13-year period 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] The significant rate of bleeding events in the AF group in the present study carries important clinical implications. Although the increased RR is unadjusted for the use of antiplatelet and anticoagulant

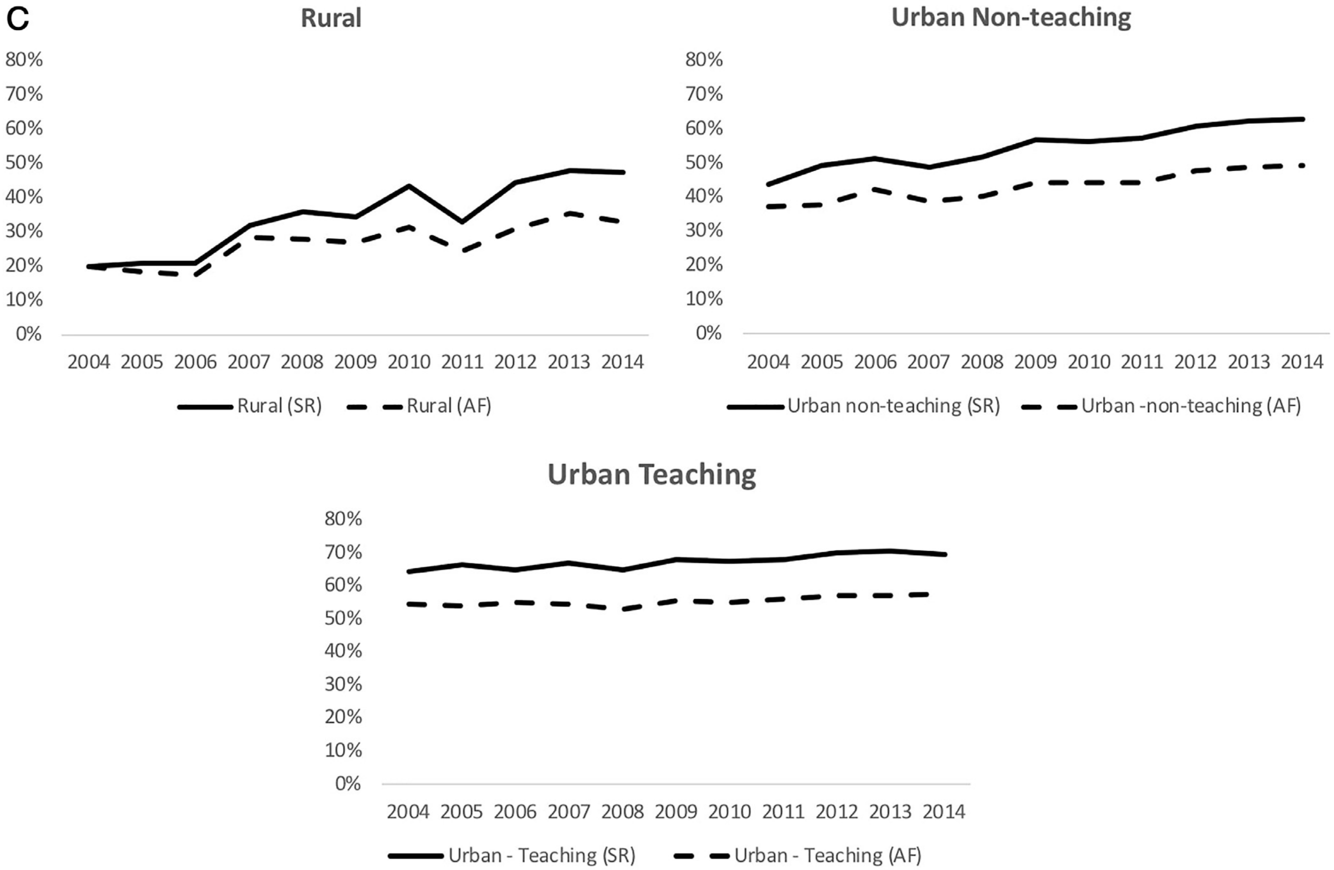

Figure 3. Continued

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.[16,17] Second, we were unable to determine (and adjust for) the onset (preadmission vs postadmission) 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 before admission and/or enrollment was not fully ascertained.[7,18–20] Third, the NIS dataset does not capture pharmacotherapy and, therefore, we were unable to determine differences in antithrombotic therapy between the 2 cohorts, or stratify bleeding risk according to HAS-BLED score as recommended by current guidelines,[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 compared with dual antithrombotic therapy.[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 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 increase 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 with 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.

Disclosures

PK receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation and has received honoraria from several such companies in the past. PK is listed as inventor on 2 patents held by University of Birmingham (Atrial

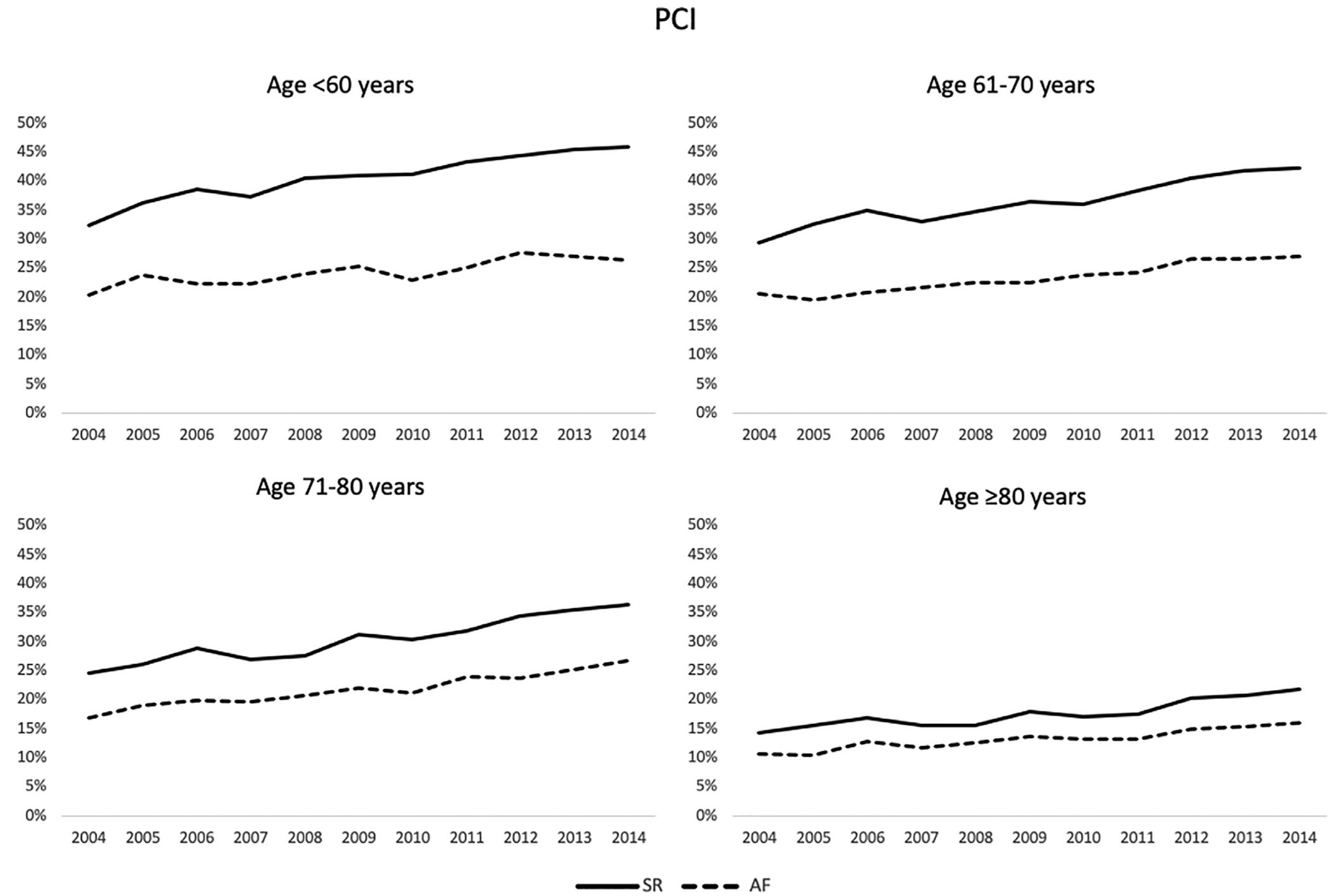

Figure 4. Trend of utilization of percutaneous coronary intervention in SR and AF groups according to age group. *p <0.001 for all trends; AF = atrial fibrillation; SR = sinus rhythm.

Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). All other authors have no disclosures and no relationships with the pharmaceutical industry.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.040.

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