Impact of Atrial Fibrillation on Acute Coronary Syndrome—Analysis of In-Hospital Outcomes and 30-Day Readmissions

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Abstract: With an aging population and significant overlap of risk factors, the cohort of patients with acute coronary syndrome (ACS) and concomitant atrial fibrillation (AF) is a sizable and growing one, with implications on cardiac reserve, anticoagulation and antiplatelet therapies, and related complications. The present study uses a large national database to analyze the impact of AF on patients admitted with an ACS. We queried the 2012 to 2014 National Readmissions Database to identify patients admitted with an

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ACS using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes. These patients were then subcategorized based on the presence or absence of AF. Analysis of their initial hospitalization, 30-day readmissions and healthcare utilization and the economic burden was performed. Among 1,558,205 patients with ACS, 270,966 (17.4%) were noted to have concomitant AF. At baseline, these patients were older and more likely female, with a significantly higher burden of comorbidities. Patients with AF had longer and more complicated index hospitalizations with significantly higher mortality rates (8.6% vs 4.6%). Coronary artery bypass graft was the preferred method of revascularization in patients with AF as compared to percutaneous coronary intervention. The 30-day readmissions were higher in the AF group (15.6 vs 10.8%), largely driven by noncardiac causes. This was associated with higher healthcare utilization with longer hospitalizations during index admission. Patients admitted with ACS and concomitant AF is a high-risk population with increased in-hospital complications and mortality, as well as short term readmissions. Coronary artery bypass graft appears favored over percutaneous coronary intervention for revascularization in patients with AF. (Curr Probl Cardiol 2021;46:100764.)

Introduction

Atrial fibrillation (AF) shares several common risk factors with acute coronary syndrome (ACS), including advanced age and a high burden of comorbidities.[1,2] Reports indicate poor inpatient outcomes and prognosis compared to their counterparts with normal sinus rhythm.[3,4] Though our understanding of this complex relationship has increased significantly in the preceding decades – the degree to which AF impacts patients in the setting of ACS remains poorly defined. Indeed, the need for anticoagulation and the addition of antiplatelet therapies, both intravenous and oral, may result in heightened complications. In addition, patients with AF may represent a population with more diastolic dysfunction, impaired cardiac output, and resultant heart failure with

poorer cardiac reserve. Accordingly, concomitant AF may result in higher complications periprocedurally and may impact index as well as readmissions. Notably, despite major improvements in ACS management, early readmissions remain a major burden to healthcare systems and more importantly, patient outcomes. Therefore, here we used a large national database to analyze population characteristics, in-hospital outcomes, mortality, and 30-day readmission characteristics in patients with ACS and concomitant AF.

Methods

Data Source

The study was derived from the Healthcare Cost and Utilization Project's (HCUP) National Readmission Database (NRD) 2012-2014. This database, sponsored by the Agency for Healthcare Research and Quality, is one of the largest publicly available inpatient databases in the United States with data from state inpatient databases representing 51.2 % of all US hospitalizations. It longitudinally follows verified patient linkage numbers to track patients across different hospitals and state lines over a given year. Patients were tracked during the same year using variable "NRD_visitlink," and time between 2 admissions was calculated by subtracting the variable "NRD_DaysToEvent." We calculated the time to readmission by subtracting the length of stay (LOS) of index admission from the time between 2 admissions. Further details of NRD data are available online.

Data Selection

We queried the NRD using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for acute myocardial infarction (AMI) in the primary diagnosis field to identify 1,711,084 admissions. The ICD-9 CM code for AMI in administrative databases has demonstrated positive predictive values of 93%.[5] Patients younger than 18 years of age (n = 104), as well as those admitted in December (n = 152,775), were excluded as we lack 30-day follow-up data for these patients. This left a total of 1,558,205 individuals for further study who were then subcategorized based on a secondary diagnosis of AF (427.31 - positive predictive value of 70%-96%).[6] Patients in each arm who were readmitted to any hospital within 30 days of the same calendar year were further evaluated. The inclusion of discharge weights

provided by the NRD for each hospitalization allows extrapolation to calculate expected national hospitalization rates. This resulted in a total of 270,966 patients with AF of whom 38,714 were readmitted within 30 days of the index hospitalization. The non-AF arm comprised 1,287,239 patients, of whom 132,475 were readmitted in the same period. Further details of the ICD codes used are provided in Supplementary Table 1.

Definition of Variables

Demographic characteristics including age, sex, patient-specific characteristics including hospital characteristics (bed size and teaching status), admission type, admission day, and discharge disposition were identified using NRD variables. Comorbidities including hypertension, diabetes mellitus, chronic pulmonary disease, peripheral vascular disease, neurological disorders, coagulopathy, and anemia were identified using ICD-9 CM diagnoses and the diagnosis-related group in effect on the discharge date. Other comorbidities were identified by ICD-9 CM codes for heart failure, chronic kidney disease, ventricular tachycardia/fibrillation, prior coronary artery bypass graft (CABG), prior MI, prior stroke/transient ischemic attack, and prior percutaneous coronary intervention (PCI).[7] We defined the severity of comorbid conditions using the Charlson comorbidity index. This takes into account 17 conditions with differential weights and higher scores corresponding to higher comorbidity burden.[8] We also evaluated LOS and calculated the inflation-adjusted cost of hospitalization using data provided by HCUP.[9]

Statistical Analysis

Analysis was performed using STATA, version 16.0 (StataCorp., College Station, TX). We included a weighted total patient population admitted with ACS during their index admission. Univariable Cox-regression analysis was used to calculate unadjusted hazard ratios for the primary and secondary outcomes. Subsequently, a multivariable Cox regression analysis was used to adjust the results for potential confounders. Multivariable regression models were built by including all confounders that were deemed significant with univariable analysis using a cutoff P value of 0.2. Proportions were compared using Fisher's exact test, and continuous variables were compared using the Student's t test. All P values were 2-sided, with 0.05 used as the threshold for statistical significance. The primary outcome was 30-day all-cause hospital readmissions. A readmission was

TABLE 1. Baseline demographic characteristics of patients with and without atrial fibrillation

Variable	Overall (%) N = 1,558,205	With AF (%) N = 270,966 (17.4%)	Without AF (%) n = 1,287,239 (82.6%)	*P*-value
Age in years ± SD	67.1 ± 14	75.3 ± 12	65.4 ± 14	<0.001
Female	38.7	42	38	<0.001
Discharge (%)				<0.001
Routine	99.2	98.2	99.4	
Skilled nursing facility	0.83	1.8	0.6	
Charlson category (%)				<0.001
0	1.24	0.5	1.4	
1	31.5	18.0	34.4	
2	25.5	23.4	26.0	
3 or more	41.7	58.2	38.0	
Co-morbidities (%)				
Prior stroke	9.1	13.5	8.1	<0.001
Prior MI	12.5	14.1	12.2	<0.001
Prior PCI	15.5	15.8	15.4	0.047
Prior CABG	8.5	11.8	7.8	<0.001
Diabetes	36.8	38.3	36.5	<0.001
PVD	12.3	16.8	11.4	<0.001
Valvular disease	0.4	0.8	0.3	<0.001
HTN	73.2	76.9	72.4	<0.001
Anemia	2.5	3.4	2.3	<0.001
Pulmonary HTN	5.0	10.0	3.9	<0.001
Chronic lung disease	21.0	26.3	19.8	<0.001
Obesity	16.2	14.6	16.5	<0.001
Dyslipidemia	64.0	60.7	64.7	<0.001
Metabolic syndrome	0.5	0.42	0.5	<0.001
CKD	20.8	31.0	18.7	<0.001
ESRD	3.5	4.7	3.24	<0.001
Cocaine use	0.1	0.01	0.05	<0.001
Smoking	41.2	31.6	43.2	<0.001
Alcohol use	3.3	2.7	3.4	<0.001
Coagulation disorder	5.5	9.1	4.7	<0.001
Hypothyroidism	11.3	15.6	10.4	<0.001
Liver disorder	1.6	1.5	1.6	0.49
Electrolyte disorder	22.5	31.7	20.5	<0.001
Depression	8.2	8.3	8.1	0.15

CABG, coronary artery bypass surgery; CKD, chronic kidney disease; ESRD, end-stage kidney disease; HTN, hypertension; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

defined as any nontraumatic admission for any principal diagnosis within 30 days after discharge of the index admission. If patients had multiple readmissions within 30 days of discharge, only the first readmission was counted. Patients who died in the index admission were excluded from the denominator. The secondary outcomes were (1) in-hospital mortality rate for index admissions; (2) the most common principal diagnoses for

readmission; (3) resource use associated with readmission: length of hospital stay, total hospitalizations, costs, and charges.

Results

Baseline Characteristics

A total of 1,558,205 patients were identified with an index hospitalization for ACS between 2012 and 2014. Of these, 270,966 (17.4%) had concomitant AF. At baseline, patients with AF were older (75.3 vs 65.4 years, $P < 0.001$) and more likely female (42% vs 38%, $P < 0.001$) with a higher burden of comorbidities as indicated by Charlson indices ≥3 (58% vs 38%). These included significantly higher rates of diabetes, hypertension, hypothyroidism, peripheral vascular disease, chronic kidney, lung, and cerebrovascular diseases ($P < 0.001$). Prior coronary events (14.1% vs 12.2%, $P < 0.001$) as well as interventions including PCI (15.8 vs 15.45, $P < 0.05$) and CABG (11.8% vs 7.8%, $P < 0.001$) were more common in the AF cohort. Smoking, cocaine, and alcohol use was more common among non-AF patients Table 1.

Details of Index Admission

During the index hospitalization, patients with AF had significantly higher rates of CABG than their non-AF counterparts (15% vs 7.6%, $P < 0.001$). PCI (52.8% vs 31.6%, $P < 0.001$) was the preferred revascularization modality among non-AF patients. Patients with AF had a more complicated hospital course with higher rates of heart failure (52% vs 28%, $P < 0.001$) and cardiogenic shock (8.5% vs 5%, $P < 0.001$) mandating increased vasopressor use (2% vs 1%, $P < 0.001$) as outlined in Table 2. This translated to higher rates of acute kidney injury (21% vs 12%, $P < 0.001$) as well as mechanical ventilatory support (3% vs 1.5%, $P < 0.001$). Cerebrovascular disease (2.6% vs 1.4%, $P < 0.001$) as well as hemorrhage (12% vs 7%, $P < 0.001$), were both expectedly higher in the AF cohort. Complete heart block (1.6% vs 1.2%, $P = 0.001$) requiring pacemaker implantation (1.7% vs 0.5%, $P = 0.001$) was more common in patients with AF. Mortality during the index admission was significantly higher in the AF cohort (8.6% vs 4.6%, $P < 0.001$).

Details of Readmission

All-cause readmission rates were significantly higher in AF patients (15.6% vs 10.8%, $P < 0.001$; hazard ratio [HR] 1.11, 95% confidence

TABLE 2. In-hospital outcomes of index admission

Variable	Overall (%)	With AF (%)	Without AF (%)	*P*-value
In-hospital mortality		8.6%	4.6%	<0.001
PCI/PTCA	49.1	31.6	52.8	<0.001
BMS	11	9.5	11.3	<0.001
DES	35.5	19.3	39	<0.001
CABG	8.8	14.8	7.6	<0.001
Cerebrovascular disease	1.6	2.6	1.4	<0.001
Cardiogenic shock	5.5	8.5	4.9	<0.001
Hemorrhage	7.9	12.5	7	<0.001
LVAD	0.04	0.07	0.04	<0.001
Cardiac tamponade	0.1	0.2	0.1	<0.001
Complete heart block	1.3	1.6	1.2	<0.001
Pacemaker implantation	0.7	1.7	0.5	<0.001
AKI	13.9	21.2	12.3	<0.001
Hemodialysis	3.1	4.6	2.8	<0.001
Pressure requirement	1.2	2.0	1.0	<0.001
Mechanical ventilation	1.8	3.0	1.5	<0.001
Coronary dissection	0.6	0.4	0.6	<0.001
Heart failure	32.4	52.5	28.2	<0.001

AKI, acute kidney injury; BMS, bare-metal stent; CABG, coronary artery bypass surgery; DES, drug eluting stent; LVAD, left ventricular assist device; PCI; percutaneous coronary intervention.

interval [CI], 1.08-1.13). This increased readmission rate was largely driven by noncardiac etiologies (46.1% vs 42.6%), with cardiac causes predominating in the non-AF group (54% vs 57%, $P < 0.001$). Among the cardiac causes of readmission, heart failure predominated in patients with AF (52.5% vs 28.2%, $P < 0.001$) while recurrent AMI (9.% vs 14%, $P < 0.001$) and chest pain (2.6% vs 6%, $P < 0.001$) were significantly more common in non-AF patients. Among the noncardiac causes of readmission, pulmonary, cerebrovascular, and renal causes as well as gastrointestinal bleeds were significantly more common in the AF cohort ($P < 0.05$). Higher odds of readmission due to heart failure (HR, 1.24, CI, 1.18-1.30; $P < 0.001$), cerebrovascular disease (HR, 1.60, CI, 1.43-1.80; $P < 0.001$), gastrointestinal hemorrhage (HR, 1.29, CI,1.15-1.45; $P < 0.001$), and thromboembolism (HR, 2.11, CI, 1.41-3.16; $P < 0.001$) were noted as outlined in Table 3 and Table 4 (Fig 1 and Fig 2).

Healthcare utilization and LOS

Patients with AF had longer hospitalizations during their index admission (6.9 days vs 4.4 days, $P < 0.001$) as well as on readmission (5.4 days vs 4.6 days, $P < 0.001$). This translated to significantly higher costs during the index admission in patients with AF ($27,196 vs

TABLE 3. Readmission risk in patients with and without AF

	With AF (%) Number of events, n (%)	Without AF (%) Number of events, n (%)	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
All-cause readmission	38,714 (15.6)	132,475 (10.8)	1.48 (1.45-1.51)	<0.001	1.11 (1.08-1.13)	<0.001
Cardiac readmission	20,862 (8.4)	76,035 (6.2)	1.43 (1.39-1.46)	<0.001	1.56 (0.88-2.77)	0.130
CHF readmission	7,855 (3.2)	17,911 (1.5)	2.28 (2.18-2.39)	<0.001	1.24 (1.18-1.30)	<0.001
CVD readmission	1,245 (0.5)	3,088 (0.2)	2.21 (2.00-2.46)	<0.001	1.60 (1.43-1.80)	<0.001
GI hemorrhage readmission	979 (0.4)	2,739 (0.2)	2.07 (1.86-2.30)	<0.001	1.29 (1.15-1.45)	<0.001
Readmission for thromboembolism	130 (0.05)	217 (0.02)	2.87 (2.00-4.12)	<0.001	2.11 (1.41-3.16)	<0.001

CH, congestive heart failure; CV, cerebrovascular disease; GI, gastrointestinal.

TABLE 4. The relative proportion of cardiac and noncardiac causes of readmission

	With AF (%)	Without AF (%)	*P*-value
Cardiac cause:	53.9	57.4	<0.001
Congestive heart failure	20.3	3.5	<0.001
Cardiac dysrhythmias	9.7	3.2	<0.001
Acute myocardial infarction	9.5	14.1	<0.001
Nonspecific chest pain	2.6	6.1	<0.001
Conduction disorders	0.2	0.2	0.46
Noncardiac causes:			
Pulmonary causes	10.3	8.7	<0.001
Gastrointestinal causes	5.2	5.5	0.17
Renal disorder	4.3	3.8	0.004
Cerebrovascular disorder	3.5	2.7	<0.001
Endocrine, nutritional and metabolic disorder	2.6	3.0	0.014
Gastrointestinal hemorrhage	2.5	2.1	0.001
Hematological disorder	1.3	1.1	0.06
Malignancy	0.9	1.1	0.11
Psychiatric disorder	0.7	1.3	<0.001
Neurologic disorder	0.3	0.5	0.035

$22,167, $P < 0.05$). However, non-AF patients had more expensive readmission stays ($14,100 vs $13,738). With regards to disposition, patients with AF were much more likely to require care at a skilled nursing facility prior to returning home (1.8% vs 0.6%, $P < 0.05$). Mean time to readmission was similar in both groups as described in Table 5.

Discussion

In this retrospective analysis of nearly 1.5 million patients, we analyzed the impact of AF on in-hospital outcomes and short-term readmissions in ACS. Several important observations were noted as outlined below.

Among patients admitted with a primary discharge diagnosis of ACS from 2012 to 2014, 17.4% had concomitant AF indicating a high burden of these 2 disease processes in the real-world population. Patients with ACS and concomitant AF are a high-risk population with a higher burden of comorbidity, in-hospital complications, and mortality during the index hospitalization. In these patients with AF, CABG was the favored modality of revascularization as compared to the non-AF cohort where PCI predominated. AF patients were more likely to be readmitted within 30 days mostly driven by noncardiac causes. Heart failure was the most common cardiac cause of readmission.

Existing literature reports the incidence of ACS with concomitant AF at anywhere between 6% and 22%, with rising incidence in patients older

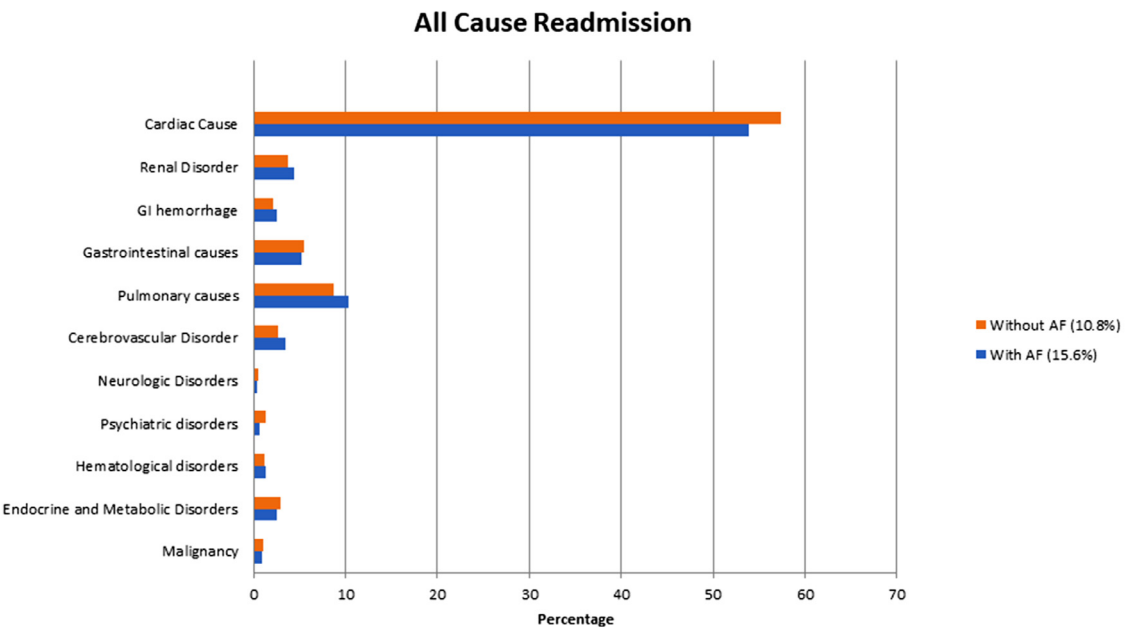

FIG 1. Details of all-cause readmission. GI, gastrointestinal.

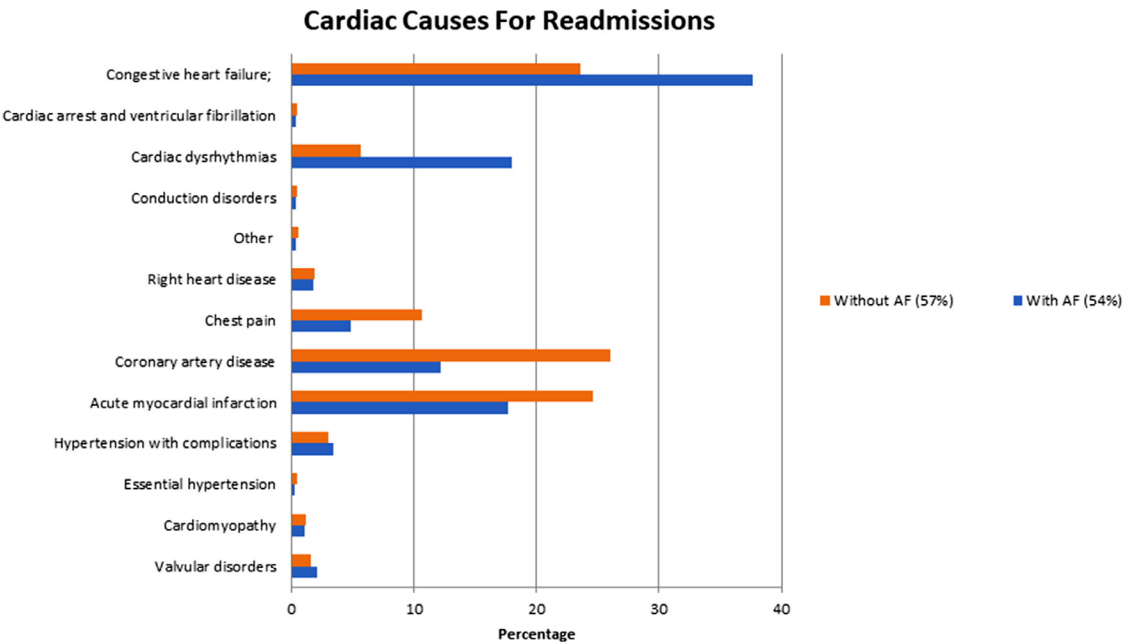

FIG 2. Details cardiac readmission. AF, atrial fibrillation.

TABLE 5. Details of healthcare utilization and LOS

Variable	With AF	Without AF	*P*-value
Mean cost per patient ($)			<0.001
Index admission	27,196	22,167	
Readmission	13,738	14,100	
Total cost (in millions)			
Index admission	270,966	1,287,239	
Readmission	494	1,750	
Mean LOS in days			
Index admission	6.9 ± 8	4.4 ± 5.8	<0.001
Readmission	5.4 ± 6	4.6 ± 5.6	<0.001
Total deaths			
Index admission	23,206	59,356	
Readmission	2,863	6,166	
Mean time to readmission (days)	11.65 ± 9	11.46 ± 9.1	0.02

AF, atrial fibrillation; LOS, length of stay.

than 60 years.[1,10-12] Higher rates of co-existent AF were noted among females, which is in accordance with previously reported figures.[1,10]

During their index admission, patients with AF had significantly longer and more complicated hospital stays with nearly double adjusted mortality rates (8.6% vs 4.6%). The advanced age and higher burden of comorbidities in the AF cohort undoubtedly contributed to the higher mortality. Patients with AF had significantly higher rates of heart failure and cardiogenic shock during their index admission, which would be expected in patients of older age, with more hypertension and diastolic dysfunction, in whom the presence of AF markedly reduces stroke volume. Similar findings were reported in the APEX-AMI trial, where AF was found to be independently associated with increased risks of cardiogenic shock and congestive heart failure.[1,13]

The relationship between AF, ACS, and heart failure is a complicated one. Whether AF contributes to heart failure or if ACS and heart failure themselves lead to AF is beyond the scope of this paper as we lack the data regarding the proportion of patients with pre-existing AF. However, in clinical practice AF is rarely due to acute ischemia and is more likely present prior to ACS either persistently or paroxysmally. Heart failure itself is a risk factor for AF, with previous studies demonstrating a linear relationship between left ventricular end-diastolic pressure, and left atrial stretch which contributes to the development of a proarrhythmic substrate.[14-16] Atrial ischemia through the involvement of the sinoatrial or proximal left circumflex branch has been reported to contribute to the development of AF in the setting of an ACS, and therefore, it is also

possible that concomitant AF in this study was a sequelae to ACS.[17] The resulting atrial scarring and remodeling contribute to the formation of a substrate conducive for re-entry and consequent more persistent AF, which may also affect readmission.[18] Sympathetic hyperactivity in the acute phase of MI likely facilitates this process as well.[19] The consequent loss of atrial contraction or the "atrial kick" with the onset of AF can decrease cardiac output by up to 25% in patients with underlying heart failure.[20,21] Rapid ventricular rates shorten diastole while raising ventricular end-diastolic pressures. These changes negatively impact coronary perfusion gradients while simultaneously increasing myocardial oxygen demand.[22]

AF patients had higher rates of bleeding complications, which is possibly a consequence of increased anticoagulant in addition to antiplatelet use, in those who received stenting, in the setting of advanced age and higher documented rates of renal and hepatic dysfunction.

In terms of revascularization, CABG (15% vs 7.6%, $P < 0.001$) was the favored modality in patients with AF while PCI (31.6% vs 53%) was preferred among the non-AF cohort. A similar trend has been reported in prior studies and has a few possible explanations.[23-25] History of prior coronary interventions in patients with AF as well as presence of diabetes mellitus, hypertension, and smoking increase the odds of having triple vessel coronary artery disease. Multivessel coronary artery disease in patient with AF might influence clinicians' decision to perform CABG over PCI, both anatomically and due to a likely higher proportion with left ventricular systolic dysfunction as a consequence of severe multivessel disease.

Higher 30-day readmission rates were noted in patients with AF (15.6 vs 10.8%, $P < 0.05$). Though cardiac causes predominated overall – they were significantly more common among non-AF patients (57% vs 54%). Heart failure (20% vs 14%, $P < 0.05$) was the most common cause of readmission in AF patients as shown in other studies.[26] This is likely due to the unfavorable impact of AF on a compromised myocardium as outlined earlier. Noncardiac causes of readmission predominated in AF patients (46.11% vs 42.6%), likely a consequence of advanced age and increased comorbidities that closely compete with cardiac issues in terms of severity.

From a healthcare utilization standpoint, AF patients had significantly longer index hospitalizations (6.9 days vs 4.4 days) and readmission stays (5.4 vs 4.6 days) leading to higher overall costs ($40,934 vs $36,267). These healthcare costs continued to rise after discharge with AF patients requiring higher rates of skilled nursing or rehabilitation on discharge (1.8% vs 0.6%, $P < 0.05$).

Among non-AF patients, readmissions for recurrent AMI (9.5 vs 14%, $P < 0.05$) and chest pain (2.5% vs 6%, $P < 0.05$) predominated. We hypothesize that this could be related to the higher rates of PCI in these patients leading to increased short-term stent-related complications. Future studies are required to assess the long-term impact and benefits of revascularization as well as to develop strategies to reduce readmission rates and healthcare utilization in this high-risk population.

Limitations

Our study must be interpreted in the context of multiple limitations inherent to any large data registry. First, all our findings are subject to the accuracy of coding of procedures and complications. Second, the database does not offer details regarding the type of (paroxysmal vs chronic vs permanent) or duration of AF (pre-existing vs new onset) which have been shown to have prognostic implications. Third, we have no angiographic data available to comment on the distribution of disease and the extent of involvement of arterial vasculature. Fourth, the NRD does not provide information on pharmacological therapy in terms of anticoagulation, antiplatelet, or antiarrhythmic therapy. Fifth, we offer a relatively short follow-up period of 30 days. It is possible that over the long term, benefits of revascularization may emerge, leading to a decrease in the disparity between groups in terms of coronary complications.

Conclusions

Patients admitted with ACS, and concomitant AF comprises a high-risk population with increased in-hospital complications and mortality. Higher short-term readmission rates in these patients are largely driven by noncardiac etiologies. CABG is the favored revascularization technique in these real-world patients with AF, with PCI preferred in the non-AF cohort.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2020.100764.

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