Frequency, Trend, Predictors, and Impact of Gastrointestinal Bleeding in Atrial Fibrillation Hospitalizations

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Anticoagulation alone or in combination with other treatment strategies are implemented to reduce the risk of stroke in patients with atrial fibrillation (AF). Gastrointestinal bleeding (GIB) is a common complication of oral anticoagulation with a prevalence of 1% to 3% in patients on long term oral anticoagulation. We analyzed the national inpatient sample database from the year 2005 to 2015 to report evidence on the frequency, trends, predictors, clinical outcomes, and economic burden of GIB among AF hospitalizations. A total of 34,260,000 AF hospitalizations without GIB and 1,846,259 hospitalizations with GIB (5.39%) were included. The trend of AF hospitalizations with GIB per 100 AF hospitalizations remained stable from the year 2005 to 2015 (p value = 0.0562). AF hospitalizations with GIB had a higher frequency of congestive heart failure, long term kidney disease, long term liver disease, anemia, and alcohol abuse compared with AF hospitalizations without GIB. AF hospitalizations with GIB had a higher odds of in-hospital mortality (Odds ratio (OR) 1.47; 95% Confidence interval (CI): 1.46 to 1.48, p-value <0.0001), mechanical ventilation (OR 1.69; 95% CI: 1.68 to 1.70, p-value <0.0001), and blood transfusion (OR 7.2; 95% CI: 7.17 to 7.22, P-value <0.0001) compared with AF hospitalizations without GIB. AF hospitalizations with GIB had a lower odds of stroke (OR 0.51; 95% CI: 0.51 to 0.52, p-value <0.0001) compared with AF hospitalizations without GIB. Further, AF hospitalizations with GIB had a higher median length of stay and cost of hospitalization compared with AF hospitalizations without GIB. In conclusion, the frequency of GIB is 5.4% in AF hospitalizations and the frequency of GIB remained stable in the last decade as shown in this analysis. When GIB occurs, it is associated with higher resource utilization. This study addresses a significant knowledge gap highlighting national temporal trends of GIB and associated outcomes in AF hospitalizations. **(Am J Cardiol 2021;146:29−35)**

Atrial fibrillation (AF) is associated with a five-fold increased risk of stroke.[1] Anticoagulation alone or in combination with other treatment strategies are implemented to reduce the risk of stroke in patients with AF. Gastrointestinal bleeding (GIB) is a common complication of oral anticoagulation (OAC) with a prevalence of 1% to 3% in patients on long term OAC.[2] GIB in AF patients leads to discontinuation of anticoagulation, which can increase the risk of ischemic stroke, subject patients to endoscopic procedures, blood transfusions, and related side effects. However, there is not enough literature on the frequency, recent trend, predictors of GIB, and clinical outcomes of GIB in AF hospitalizations. A non-pharmacological method such as left atrial appendage occlusion may require limited or no OAC treatment after the procedure. This procedure provides an alternative to prevent the long-term usage of OAC in patients who are at higher risk of complications.[4,5] We seek to analyze the national inpatient sample (NIS) database to report evidence on the frequency of GIB, recent trends, predictors of GIB, and clinical outcomes of GIB that will help clinicians and policymakers understand the impact of

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GIB in AF hospitalizations and the necessity to look for an alternative non-pharmacological measures.

Methods

The NIS was used for the present analysis which has been described well in other articles. In short, NIS is the largest publicly available all-payor inpatients care database in the United States. It was created by the Healthcare Cost and Utilization Project through a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality. We did not require Institution Review Board approval as the data were de-identified.

The NIS starting from January 1, 2005 to September 31, 2015 was utilized for the present analysis. Patients less than 18 years and with a diagnosis of cancer were excluded as they may have different reasons and risk factors for bleeding. All hospitalizations with AF as the primary or secondary diagnosis were included in the present analysis which has been described earlier.[6,7] We further stratified the hospitalizations based on the presence or absence of GIB. The ICD-9-CM codes used in the present study are summarized in **Supplementary Table 1**. ICD-9-CM codes used for assessing Deyo's Modification of Charlson's co-morbidities Index are elaborated in **Supplementary Table 2**. A recommended checklist for studies published using the NIS database has been provided in **Supplementary Table 3.**

The present analysis was performed per the methodological standard laid down by sponsors using SAS version 9.4 (SAS Institute Inc). All analyses used in the present study accounted for NIS clustering (HOSP_NIS), survey nature (SURVEYMEANS, SURVEYFREQ, and SURVEYLOGISTIC), stratification (NIS_STRATUM), and weights (DISCWT)**.** Categorical variables were presented as numbers along with percentages, while continuous variables were presented as mean (with standard deviations [SD]) or median (with interquartile range [IQR]) depending on the data distribution**.** Categorical variables were compared using the Chi-square test, while continuous variables were compared using the Student's *t*-test or Wilcoxon rank-sum test based on the frequency. The trend of GIB frequency per 100 AF hospitalizations from 2005 through 2015 was assessed using the Jonckheere-Terpstra trend test. Further, the Jonckheere-Terpstra trend test was used to assess the trend of percentage mortality stratified based on the presence or absence of GIB. The total cost of each hospital stay was analyzed by merging NIS data with cost-to-charge ratio files available from the sponsor. We estimated the final cost by adjusting the cost for inflation according to the Consumer Price Index data released by the United States Government.[7] Multivariable logistic regression was used to adjust the outcomes for confounders. The variables utilized in the regression analysis were age, gender, race, hypertension, diabetes mellitus, long term lung disease, congestive heart failure, dyslipidemia, long term kidney disease, long term liver disease, obesity, thyroid dysfunction, obstructive sleep apnea, anemia, alcohol abuse, drug abuse, smoking, CHA2DS2VASc Score, region of the hospital, hospital bed size, location of the hospital, payment type and median household income category for patient's zip code.

Results

A total of 34,260,000 AF hospitalizations without GIB and 1,846,259 hospitalizations with GIB (5.39%) were included in the present analysis. The trend of AF hospitalizations with GIB per 100 AF hospitalizations remained stable from the year 2005-2015 (p-value = 0.0562) (**Figure 1**). AF hospitalizations with GIB had a higher mean age compared with AF hospitalizations without GIB (77.9 ± 23.3 years vs 75.6 ± 27 years, p-value <0.0001) (**Table 1**). AF hospitalizations with GIB had a higher frequency of congestive heart failure (36.1% vs 22.9%, p-value <0.0001), long term kidney disease (27.1% vs 21.2%, p-value <0.0001), long term liver disease (4.1% vs 1.9%, p-value <0.0001), anemia (15.4% vs 1%, p-value <0.0001), and alcohol abuse (3.7% vs 2.6%, p-value <0.0001) compared with AF hospitalizations without GIB (**Table 1**). AF hospitalizations with GIB had a lower frequency of dyslipidemia (33.4% vs 38.4%, p-value <.0001), obesity (8.7% vs 11%, p-value <0.0001), and smoking (16.2% vs 20%, p-value <0.0001). There was no significant difference in the frequency of hypertension, diabetes, long term lung disease, thyroid dysfunction, obstructive sleep apnea, and drug abuse between the 2 groups. AF hospitalizations with GIB had a higher frequency of CHA_2DS_2VASc score more than or equal to 3 (81% vs 74.5%, p-value <0.0001) compared with AF hospitalizations without GIB. Further, AF hospitalizations with GIB had a higher frequency of Charlson's Comorbidity Index equal to or higher than 3 (81% vs 74.5%, p-value <0.0001) compared with AF hospitalizations without GIB. AF hospitalizations with GIB had a higher frequency of Medicare and/or Medicaid as the payment type (88.9% vs 83.7%, p-value <0.0001) compared with AF hospitalizations without GIB. AF hospitalizations with GIB had a lower frequency of in-hospital procedures like electro cardioversion (1.4% vs 3.2%, p-value <0.0001), left atrial appendage (LAA) closure (0.1% vs 0.3%, p-value <0.0001), surgical ablation (0.1% vs 0.4%, p-value <0.0001), and catheter ablation (0.2% vs 1.1%, p-

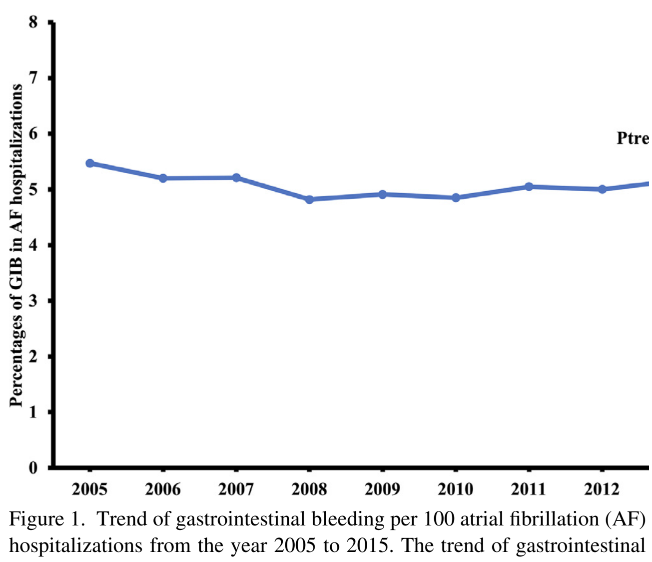

Figure 1. Trend of gastrointestinal bleeding per 100 atrial fibrillation (AF) hospitalizations from the year 2005 to 2015. The trend of gastrointestinal bleeding per 100 AF hospitalizations remained stable from the year 2005 to 2015.

Table 1
Demographics, baseline characteristics and in-hospital outcomes of atrial fibrillation hospitalizations with and without gastrointestinal bleeding events

	GI Bleeding		
Variable	No (N=34,260,000)	Yes (N=1846259)	p Value
Age (years (Mean ± SD))	75.6 ± 27	77.9 ± 23.3	<.0001
18-35	204178 (0.6%)	3617 (0.2%)	<.0001
36-50	927424 (2.7%)	23409 (1.27%)	
51-65	4897475 (14.3%)	184064 (10%)	
66-80	13030000 (38%)	693539 (37.6%)	
>80	15200000 (44.4%)	941630 (51%)	
Men	16810000 (49.1%)	911043 (49.4%)	<0.001
Women	17450000 (51%)	935139 (50.7%)	
White	24630000 (71.9%)	1314979 (71.2%)	
Black	2261271 (6.6%)	136359 (7.4%)	
Other Races	7361238 (21.5%)	394853 (21.4%)	
Hypertension	23110000 (67.5%)	1234374 (66.9%)	<.0001
Diabetes Mellitus	10670000 (31.13%)	576912 (31.3%)	0.001
Long term Lung Disease	9299375 (27.2%)	525641 (28.5%)	<.0001
Congestive Heart Failure	7836435 (22.9%)	665517 (36.1%)	<.0001
Dyslipidemia	13170000 (38.4%)	616150 (33.4%)	<.0001
Long term Kidney Disease	7250742 (21.2%)	499780 (27.1%)	<.0001
Long term Liver Disease	664065 (1.9%)	75960 (4.1%)	<.0001
Obesity	3782378 (11%)	160914 (8.7%)	<.0001
Thyroid Dysfunction	6069630 (17.7%)	299388 (16.2%)	<.0001
Obstructive sleep apnea	2245588 (6.6%)	89757 (4.9%)	<.0001
Anemia	322487 (1%)	283721 (15.4%)	<.0001
Alcohol abuse	904339 (2.6%)	68197 (3.7%)	<.0001
Drug abuse	343195 (1%)	13793 (0.8%)	<.0001
Smoking	6699124 (20%)	299903 (16.2%)	<.0001
In-hospital procedure			
Electrical cardioversion	1109736 (3.2%)	26314 (1.4%)	<.0001
Endoscopy	564184 (1.7%)	495130 (26.8%)	<.0001
Colonoscopy	212876 (0.62%)	277580 (15%)	<.0001
Blood transfusion	2763108 (8.1%)	827171 (44.8%)	<.0001
LAA closure procedure	97946 (0.3%)	1545 (0.1%)	<.0001
Surgical ablation	150597 (0.4%)	2330 (0.1%)	<.0001
Catheter ablation	381538 (1.1%)	3666 (0.2%)	<.0001
Invasive mechanical ventilation	1312990 (3.8%)	128745 (7%)	<.0001
CHA2DS2VASc Score			<.0001
0	932920 (2.7%)	27472 (1.5%)	
1	2578571 (7.5%)	90054 (4.9%)	
2	5131055 (15%)	232690 (12.6%)	
>=3	25620000 (74.8%)	1496043 (81%)	
Charlson's Comorbidity Index <0.001			
0	6473083 (19%)	261997 (14.2%)	
1	8808309 (25.7%)	438997 (23.8%)	
2	7375554 (21.5%)	408251 (22.1%)	
>=3	11600000 (33.9%)	737014 (40%)	
Hospital-level Characteristics			
Region of the Hospital			<.0001
Northeast	7264789 (21.1%)	394155 (21.4%)	
Midwest	8516704 (24.9%)	454055 (24.6%)	
South	12600000 (36.8%)	681385 (37%)	
West	5875050 (17.2%)	316533 (17.2%)	
Hospital Bed Size			<.0001
Small	4915442 (14.4%)	260456 (14.2%)	
Medium	8564980 (25.1%)	477397 (26%)	
Large	20650000 (61%)	1101831 (60%)	
Location of the Hospital			<.0001
Rural	4393675 (12.9%)	243439 (13.2%)	
Urban, Nonteaching	14230000 (41.2%)	785456 (42.7%)	
Urban, Teaching	15500000 (45.4%)	810789 (44.1%)	
Median household income in percentile for patient's zip code			
0-25th	8554227 (25.5%)	473471 (26.1%)	<.0001
26-50th	8862164 (26.4%)	478167 (26.4%)	

(*continued*)

Table 1 (***Continued***)

Variable	GI Bleeding		
	No (N=34,260,000)	Yes (N=1846259)	p Value
51-75th	8383396 (25%)	448783 (24.8%)	
76-100th	7806229 (23.2%)	411768 (22.7%)	
Payment Type			<.0001
Medicare/Medicaid	28640000 (83.7%)	1631471 (88.9%)	
Private insurance	4546116 (13.3%)	171171 (9.3%)	
Self-pay/no charge/others	1025965 (3%)	41283 (3.9%)	
In-hospital Outcomes			
Stroke	1706627 (5%)	47534 (2.6%)	<.0001
In-hospital Mortality	1611997 (4.7%)	142523 (7.7%)	<.0001
Length of Stay (Days (Median, IQR))	4 (2-7)	5 (3-9)	<.0001
Cost ($$ (Median, IQR))	8442 (4852-15914)	9928 (5916-18665)	<.0001

Numerical variables presented as mean (SD) or median (IOR). Categorical variables presented as N (percentages). Obesity was defined as BMI above 30 kg/m^2.

value <0.0001) compared with AF hospitalizations without GIB. AF hospitalizations with GIB had a higher frequency of in-hospital procedures like endoscopy (26.8% vs 1.7%, p-value <0.0001), colonoscopy (15% vs 0.62%, p-value <0.0001), and blood transfusion (44.8% vs 8.1%, p-value <0.0001) compared with AF hospitalizations without GIB. In our multivariate analysis, AF hospitalizations with GIB had a higher odds of mortality (Odds ratio (OR) 1.47; 95% Confidence interval (CI): 1.46 to 1.48, p-value <0.0001), mechanical ventilation (OR 1.69; 95% CI: 1.68 to 1.70, p-value <0.0001), and blood transfusion (OR 7.2; 95%CI: 7.17 to 7.22, p-value <0.0001) compared with AF hospitalizations without GIB (**Table 2**). Further, AF hospitalizations with GIB had a higher median length of stay (5 days (3 to 9) versus 4 days (2 to 7), p-value <0.0001) and cost of hospitalization ($ 9928 ($5916 to $18665), p value <0.0001) compared with AF hospitalizations without GIB. However, AF hospitalizations with GIB had a lower odds of stroke (OR 0.51; 95% CI: 0.51-0.52, p-value <0.0001) compared with AF hospitalizations without GIB. There was a significantly decreasing trend in percentage mortality in both AF hospitalizations, with and without GIB, from the year 2005 to 2015 (p-value <0.0001) (**Figure 2**). There is a significant increase in the use of left atrial appendage closure procedures in the AF hospitalizations during the same period (**Supplementary Figure 1**).

Table 3 reports the predictors of GIB in AF hospitalizations. Patients over 80 years had a higher odds of GIB during AF hospitalizations (OR 1.48; 95% CI: 1.43 to 1.54, p-value <0.0001) compared with the 18-35 years age group (reference group). Females had a lower odds of GIB during AF hospitalizations (OR 0.94; 95% CI:0.94 0.94, p-value <0.0001) compared with males. Further, Blacks had a higher odds of GIB during AF hospitalizations (OR 1.17; 95% CI:1.17 to 1.18, p-value <0.0001) compared with Whites. Patients with congestive heart failure (OR 1.69; 95%CI:1.68 to 1.69, p-value <0.0001), long term kidney disease (OR 1.23; 95%CI:1.23 to 1.23, p-value <0.0001), long term liver disease (OR 2.07; 95%CI:2.05 to 2.08, p-value <0.0001), alcohol abuse (OR 1.51; 95%CI:1.50 to 1.52, p-value <0.0001) and anemia (OR 17.89; 95%CI:17.79 to 17.98, p-value <0.0001) had a higher odds of GIB during AF hospitalizations. Hospitalizations with a CHA_2DS_2VASc Score more than or equal to 3 had higher odds of GIB during AF hospitalizations (OR 1.1; 95% CI:1.07 to 1.11, p-value <0.0001) compared with hospitalizations with a CHA_2DS_2VASc Score of 0. Hospitalizations with self-pay/no charge/others/private insurance payment type had a lower odds of AF hospitalizations with GIB bleeding compared with Medicare/Medicaid as the payment type.

Table 2
Adjusted outcomes in patient with gastrointestinal bleeding among atrial fibrillation hospitalizations

Outcomes	Odds Ratio With Confidence Interval	p Value
Mechanical Ventilation	1.69 (1.68-1.70)	<0.0001
Mortality	1.47 (1.46-1.48)	<0.0001
Stroke	0.51 (0.51-0.52)	<0.0001
Blood Transfusion	7.2 (7.17-7.22)	<0.0001

Adjusted for age, race, gender, hospital level characteristics, payment and co-morbidities.

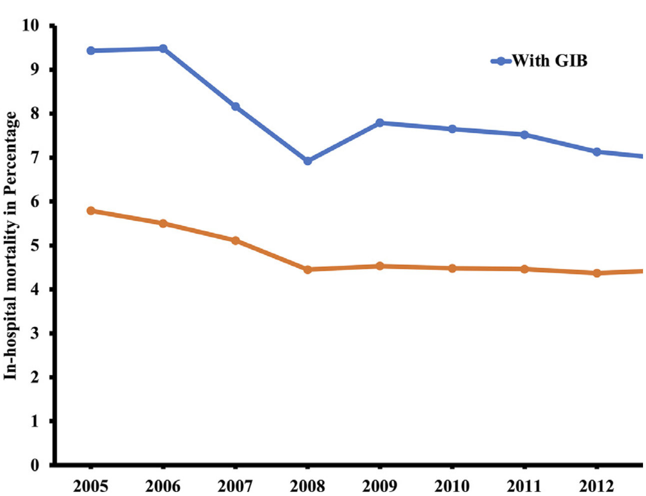

Figure 2. Trend of percentage mortality in AF hospitalizations stratified based on the presence or absence of gastrointestinal bleeding from the year 2005 to 2015. The trend of percentage mortality in AF hospitalizations from the year 2005 to 2015 in both GIB and with GIB decreased significantly.

Table 3
Predictors of gastrointestinal bleeding among atrial fibrillation hospitalizations

Variable	Odds Ratio With Confidence Interval	p Value
Age groups		
18-35	Reference	
36-50	1.48 (1.43-1.54)	<.0001
51-65	2.18 (2.11-2.26)	<.0001
66-80	2.85 (2.75-2.95)	<.0001
>80	3.2 (3.08-3.31)	<.0001
Female vs. Male	0.94 (0.94-0.94)	<.0001
Black vs. White	1.17 (1.17-1.18)	<.0001
Co-morbidities		
Hypertension	0.98 (0.98-0.99)	<.0001
Diabetes Mellitus	0.98 (0.97-0.98)	<.0001
Long term Lung Disease	0.98 (0.97-0.98)	<.0001
Congestive Heart Failure	1.69 (1.68-1.69)	<.0001
Long term Kidney Disease	1.23 (1.23-1.23)	<.0001
Long term Liver Disease	2.07 (2.05-2.08)	<.0001
Obesity	0.86 (0.86-0.87)	<.0001
Alcohol	1.51 (1.5-1.52)	<.0001
Dyslipidemia	0.86 (0.85-0.86)	<.0001
Anemia	17.89 (17.79-17.98)	<.0001
Thyroid Disease	0.88 (0.88-0.89)	<.0001
CHA_2DS_2VASc Score		
0	Reference	
1	1.01 (0.99-1.02)	0.4568
2	1.07 (1.05-1.08)	<.0001
>=3	1.1 (1.07-1.11)	<.0001
Region of the Hospital		
Northeast	Reference	
Midwest	0.94 (0.94-0.95)	<.0001
South	0.97 (0.97-0.98)	<.0001
West	0.96 (0.96-0.97)	<.0001
Hospital Bed Size		
Small	Reference	
Medium	1.07 (1.06-1.07)	<.0001
Large	1.03 (1.03-1.04)	<.0001
Location of the Hospital		
Rural	Reference	
Urban, Nonteaching	1.01 (1.01-1.02)	<.0001
Urban, Teaching	1.00 (1.00-1.01)	0.4412
Payment Type		
Medicare/Medicaid	Reference	
Private insurance	0.89 (0.88-0.89)	<.0001
Self-pay/no charge/others	0.93 (0.9-0.94)	<.0001
Median household income in percentile for patient's zip code		
0-25th	Reference	
26-50th	0.99 (0.98-0.99)	<.0001
51-75th	0.97 (0.97-0.98)	<.0001
76-100th	0.95 (0.94-0.96)	<.0001

Discussion

This largest study-till-date highlights a 5.4% frequency of GIB among AF hospitalizations in the Unites States. The frequency of GIB remained stable from 2005 to 2015. We observed that a higher age group, male gender, anemia, long term kidney disease, long term liver disease, and heart failure were strong GIB predictors in AF hospitalizations. AF hospitalization with private insurance and higher median household income were associated with lower frequency GIB. We observed that electrical cardioversion, catheter ablation, surgical ablation, and LAA closure were performed less frequently among GIB compared with AF hospitalizations without GIB. There was a significantly increasing trend in the utilization of LAA closure procedure done among AF hospitalizations from the year 2005 to 2015. AF hospitalizations with GIB had higher resource utilization, indicated by the occurrence of a higher percentage of endoscopy, colonoscopy, and blood transfusion which eventually requires longer length of stay and higher hospitalization cost. Lastly, we observed a decreasing trend of in-hospital mortality among AF hospitalizations with both with and without GIB.

There are several possible reasons for the observed non-significant trend of GIB in AF hospitalization over the last decade. The reason for this is not known well but might be explained by the following reasons. Firstly, the approval of novel OAC and publication of formalized guidelines on its use[8] during the study period offered physicians a more organized framework for managing AF which could have lowered the bleeding risk compared with warfarin. However, its cost limits its use in lower household income and in patients with Medicare/Medicaid. Previous studies have reported similar disparities in various outcomes between private insurance and Medicaid group in AF and heart failure patients.[23,24] Although the literature does not mention the underlying reason for this discrepancy, the authors believe that regular follow-up and insight on the medical condition due to education level in private insurance groups could be the reason. Secondly, as shown in this article, the trend in the use of LAA occlusion procedures has increased significantly which reduces the required duration of anticoagulation and hence, bleeding.

Demographic factors such as older age, male gender, black race were associated with higher odds of GIB in AF hospitalization. The study by Sherwood et al., and Lauffenburger et al., reported similar findings that the risk of GIB was highest after the age of 75.[2,3] Renal impairment,[9] the presence of multiple co-morbidities, and polypharmacy may be the attributed reason for an increased risk of GIB among elderly patients.[10,11] The results based on gender were inconsistent among different studies. Our results of higher odds in males were in agreement with few studies like ROCKET AF trial showed higher odds among male,[2] however, a study by Chan et al. did not demonstrate any difference between gender.[12]

Co-morbidities such as anemia, congestive heart failure, long term kidney disease, long term liver disease, alcoholism, and higher CHA_2DS_2VASc score were associated with higher odds of GIB in our analysis. Our results are consistent with the study by Lauffenberger et al.[3] Another study highlighted anemia to be associated with a higher risk of GIB,[13] and was associated with the 2.5-fold increase in GIB even after adjustment for HAS-BLED.[14,15] A former study reported that patients with heart failure (irrespective of ejection fraction) had a higher comorbidity burden leading to higher CHA_2DS_2VASc, and HAS-BLED scores than patients without HF,[16] which makes them high risk for GIB. In long term kidney disease, deteriorating kidney function and accumulation of uremic toxins contribute to platelet activation and recruitment abnormalities, which is an integral part of hemostasis.[17,18] Previous studies reported similar findings,[19] and the greatest risk factor for bleeding in the first thirty days after initiation of anticoagulation was long term kidney disease.[20] There is decreased production of vitamin K-dependent and independent clotting factors, anticoagulants, platelet production abnormalities, and hypersplenism with platelet consumption in long term liver disease.[21] Alcohol has been shown to cause exfoliation of gastric epithelium and injury to different gastric wall layers due to the overproduction of free radicals and decreased prostaglandin synthesis,[22] causing GIB.

We observed a decreasing trend yet higher odds of in-hospital mortality in GIB as compared with those without GIB. The exact reason is unknown. The GIB frequently needs procedures like endoscopy and colonoscopy, as seen in this study. These procedures itself are associated with higher morbidity and mortality. Fatal bleeding from the brain or gastrointestinal tract itself can lead to excess mortality. The decreasing trend of mortality might be ascribed to the rising use of the LAA procedures which has shown to reduce mortality compared with warfarin. Reddy et al. analyzed pooled data from 2 major trials over 5 years and found that LAA closure was a cost-effective and life-saving alternative to long-term oral anticoagulation.[25−28]

This study has several limitations related to its observational nature. Information on the type of anticoagulation, dose, medication compliance, and other co-morbidities such as previous history GIB was not available. We also did not have information on medications or possible polypharmacy and food habits that may have been associated with increased risk of bleeding, specifically in patients taking warfarin. There was no information on patient preference which also plays a major role in AF management.

In conclusion, this study of a nationwide database demonstrated a 5.4% incidence of GIB in AF hospitalizations. The trend of GIB in AF hospitalization was did not change in the last decade. The mortality trend associated with GIB and AF hospitalization was decreasing from 2005 to 2015. Further, GIB was associated with higher rates of morbidity, mortality, and resource utilization.

Credit Author Statement

Mihir Dave: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Writing - Review & Editing; Ashish Kumar: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Writing - Review & Editing; Monil Majmundar: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Writing - Review & Editing; Devina Adalja: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing; Mariam Shariff: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Palak Shah: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Rupak Desai: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Krunalkumar Patel: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Gowthami Sai Kogilathota Jagirdhar: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Saraschandra Vallabhajosyula: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Supervision, Funding acquisition; Nageshwara Gullapalli: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Supervision; Rajkumar Doshi: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Supervision.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.01.020.

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