CLINICAL RESEARCH STUDY

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Oral Anticoagulation Use in High-Risk Patients Is Improved by Elimination of False-Positive and Inactive Atrial Fibrillation Cases

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ABSTRACT

BACKGROUND: Multiple registries have reported that >40% of high-risk atrial fibrillation patients are not taking oral anticoagulants. The purpose of our study was to determine the presence or absence of active atrial fibrillation and CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 y, Diabetes mellitus, prior Stroke [or transient ischemic attack or thromboembolism], Vascular disease, Age 65-74 y, Sex category) risk factors to accurately identify high-risk atrial fibrillation (CHA_2DS_2-VASc ≥2) patients requiring oral anticoagulants and the magnitude of the anticoagulant treatment gap.

METHODS: We retrospectively adjudicated 6514 patients with atrial fibrillation documented by at least one of: billing diagnosis, electronic medical record encounter diagnosis, electronic medical record problem list, or electrocardiogram interpretation.

RESULTS: After review, 4555/6514 (69.9%) had active atrial fibrillation, while 1201 had no documented history of atrial fibrillation and 758 had a history of atrial fibrillation that was no longer active. After removing the 1201 patients without a confirmed atrial fibrillation diagnosis, oral anticoagulant use in high-risk patients increased to 71.1% ($P < .0001$ compared with 62.9% at baseline). Oral anticoagulant use increased to 79.7% when the 758 inactive atrial fibrillation patients were also eliminated from the analysis ($P < .0001$ compared with baseline). In the active high-risk atrial fibrillation group, there was no significant difference in the use of oral anticoagulants between men (80.7%) and women (78.8%) with a CHA_2DS_2-VASc ≥2, or in women with a CHA_2DS_2-VASc ≥3 (79.9%).

CONCLUSIONS: Current registries and health system health records with unadjudicated diagnoses overreport the number of high-risk atrial fibrillation patients not taking oral anticoagulants. Expert adjudication identifies a smaller treatment gap than previously described.

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KEYWORDS: Anticoagulants; Atrial fibrillation; Electronic medical record; Stroke

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INTRODUCTION

Worldwide, over 33 million individuals have atrial fibrillation.[1] The projected prevalence of atrial fibrillation, given the aging population and newer detection techniques, will more than double over the next 30 years.[2,3] The incidence of all-cause stroke in atrial fibrillation patients is 5%, and ischemic strokes associated with atrial fibrillation are often more severe, more disabling, more likely to be recurrent, and more likely to cause death than stroke from other etiologies.[4]

CLINICAL SIGNIFICANCE

- Registries and databases using unadjudicated electronic medical record diagnoses of atrial fibrillation and stroke risk factors overestimate the oral anticoagulation treatment gap.
- Clinicians should actively adjudicate patient problem list diagnoses to minimize errors in research and quality outcomes that use such data.

Patients with comorbidities, as measured by higher $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 y, Diabetes mellitus, prior Stroke [or transient ischemic attack or thromboembolism]) and CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 y, Diabetes mellitus, prior Stroke [or transient ischemic attack or thromboembolism], Vascular disease, Age 65-74 y, Sex category) scores, have higher stroke, mortality, and re-hospitalization rates.[5,6] In the Stroke Prevention of Atrial Fibrillation (SPAF) trial, warfarin, with a therapeutic international normalized ratio of 2.0 to 3.0, reduced the risk of stroke, compared with placebo, by 66%.[7] Novel/non-vitamin-K-dependent oral anticoagulants have demonstrated similar or better efficacy in reducing stroke and systemic embolic events in large-scale prospective trials.[8-11] In order to treat high-risk patients and avoid oral anticoagulants in low-risk patients, current guidelines recommend anticoagulant treatment in high-risk atrial fibrillation patients with CHA_2DS_2-VASc scores of ≥2 in men and ≥3 in women.[12,13] Despite this recommendation, registries and systemic reviews suggest that >40% of high-risk atrial fibrillation patients are not taking oral anticoagulants.[14-18] This treatment gap has not been significantly reduced with the commercial release of the novel/non-vitamin K-dependent oral anticoagulants.[19] Multiple theories exist as to the reasons for this treatment gap.[18,20]

In reviewing patients diagnosed as having atrial fibrillation as part of a quality-of-care project using our Cerner electronic medical record, we observed that active disease was not present in a large number of patients labeled as having atrial fibrillation, either because of wrong diagnosis or no documented arrhythmia recurrences in the last 5 years. Several prior reports have suggested that the misdiagnosis of atrial fibrillation in the electronic medical record is common,[21-25] and varies by the criteria used. We undertook a systematic retrospective electronic medical record review to determine the presence or absence of active atrial fibrillation to accurately identify high-risk patients who should be treated with oral anticoagulants. We hypothesized that proper identification of such patients would lower the reported treatment gap of patients who should receive oral anticoagulants and more accurately define real-world practices of the use of oral anticoagulants in high-risk atrial fibrillation patients.

METHODS

To identify patients with presumed atrial fibrillation from our electronic medical record, we used diagnosis codes from inpatient, outpatient, and emergency department visits in the Penn State Health system from 2015 thru 2017. Patients were selected if they had 2 or more outpatient visits with a cardiologist or primary care provider. Patients with atrial fibrillation were identified by screening for an International Classification of Diseases, Ninth Revision code of 427.31 (atrial fibrillation) or 427.32 (atrial flutter) coded for 1 inpatient or 2 outpatient or emergency department visits over the last 5 years. Atrial fibrillation was documented by at least one of: billing diagnosis, electronic medical record encounter diagnosis, electronic medical record problem list, or electrocardiogram interpretation.

Based on our criteria, 6514 patients with presumed atrial fibrillation were selected and made up our study group. Figure 1 is a diagram of the patient flow. All patients had their electronic charts manually reviewed by one of the authors to determine if the diagnosis of atrial fibrillation was correct, and also to determine if the diagnosis was still active (occurrences within the last 5 years without rhythm control treatment). In active atrial fibrillation patients, part of the expert review included a recommendation of whether or not the patient should be taking an oral anticoagulant. Patients without active atrial fibrillation were subclassified into no prior history (wrong or inaccurate diagnosis) or inactive (an accurate history of atrial fibrillation that was no longer clinically active in at least the last 5 years without a rhythm control strategy). In addition, all CHA_2DS_2-VASc risk factors were also reviewed for accuracy utilizing data as published by van Doom et al.[26] Based on the timing of this review, those with CHA_2DS_2-VASc risk scores of ≥2 were considered high-risk atrial fibrillation patients. Given changes in the guidelines, at the time of analysis of the data, further analysis of women with scores of 3 or higher are included. A CHA_2DS_2-VASc risk score of 0 was considered low risk and a score of 1, intermediate risk. Patients taking warfarin had their time in therapeutic range calculated using the Rosendaal method.[27]

RESULTS

Active atrial fibrillation was noted in 4555/6514 patients (69.9%) after 1959 patients (30.1%) with no prior history (n = 1201) or inactive atrial fibrillation (n = 789) were withdrawn from further analysis (Figure 1, Table 1). At baseline

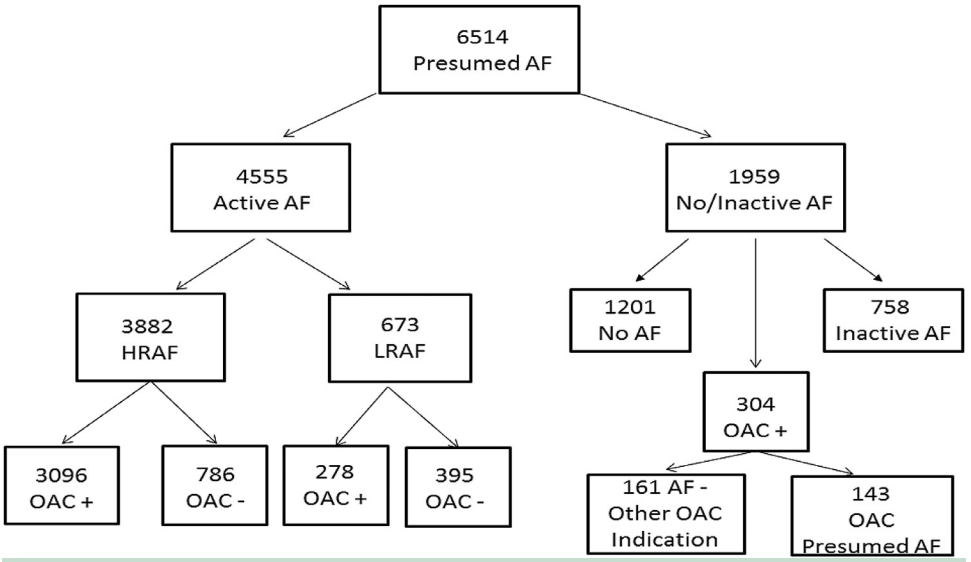

Figure 1 Flow diagram of patient flow. AF = atrial fibrillation; HRAF = high-risk atrial fibrillation; LRAF = low-risk atrial fibrillation; OAC = oral anticoagulation use.

in the presumed atrial fibrillation group, 62.9% of high-risk atrial fibrillation patients were taking an oral anticoagulant. In the postadjudicated active atrial fibrillation group, 3882 had high-risk atrial fibrillation with CHA_2DS_2-VASc ≥2. Oral anticoagulant use in these postadjudication high-risk atrial fibrillation patients (3096/3882 [79.7%]) was statistically higher than oral anticoagulant use (62.9%) in the high-risk atrial fibrillation patients preadjudication ($P < .0001$ by McNemar test) (Figure 2A, Table 2). In the active high-risk atrial fibrillation group, there was no significant difference in the use of oral anticoagulants between men (80.7%) and women (78.8%) with a CHA_2DS_2-VASc ≥2, or in women with a CHA_2DS_2-VASc ≥3 (79.9%). The use of novel oral anticoagulants (51.7%) was numerically but not statistically higher than warfarin (48.3%). Age of 90 years or older was associated with a doubling of oral anticoagulants not being prescribed, from 20% to 40.4% ($P < .05$). In high-risk atrial fibrillation patients taking an oral anticoagulant, expert review agreed in 95% of the cases. In high-risk atrial fibrillation patients not taking an oral anticoagulant (20.3%), expert review disagreed with that recommendation 60% of the time, suggesting that oral anticoagulants can be taken in up to 92% of high-risk atrial fibrillation patients without an absolute contraindication or repeated patient refusal. Table 1 lists the patient characteristics of presumed atrial fibrillation diagnosis at baseline, the active atrial fibrillation group, and the false-positive atrial fibrillation groups (No atrial fibrillation documented, Inactive atrial fibrillation, and the combined false-positive group). The Active high-risk atrial fibrillation group had oral anticoagulants prescribed in 75.0% of the cases, vs only 15% in the false-positive group.

A further analysis after expert adjudication was performed, including the inactive atrial fibrillation group and only removing the 1201 patients without a confirmed atrial fibrillation diagnosis (n = 5313). In this analysis, oral anticoagulant use in high-risk atrial fibrillation patients still significantly increased from 62.9% at baseline to 71.1% ($P < .0001$) (Figure 2B, Table 2).

Expert review of active atrial fibrillation agreed with the problem list 85.6%, encounter diagnosis 83.9%, and positive electrocardiogram in 84.5%, but agreed only 71.4% with the billing diagnosis.

Warfarin use was higher in the false-positive atrial fibrillation group that had another reason for oral anticoagulant use (81.3%), compared with the inactive or misdiagnosed group (60.7%; $P = .0001$). Overall, the time in therapeutic range control was excellent in our warfarin-treated patients, with 68% of patients having a time in the therapeutic range ≥70% using the Rosendaal method. However, this left 32% of warfarin patients with a time in therapeutic range <70%.

In the group of patients with no documented or inactive atrial fibrillation, oral anticoagulant use was low, being used in 304/1959 (15.5%), with 161/1959 (8.2%) patients taking oral anticoagulants for indications not related to atrial fibrillation and only 143/1959 (7.3%) taking an oral anticoagulant for inactive or misdiagnosed atrial fibrillation. Thus, 143/304 (47.0%) nonatrial fibrillation patients were taking an oral anticoagulant for inactive or misdiagnosed atrial fibrillation.

After adjudication, 183 patients had a CHA_2DS_2-VASc = 0 and 60/183 (32.8%) were taking an oral anticoagulant. The majority of those taking anticoagulants were patients in the pericardioversion or ablation time period. In the CHA_2DS_2-VASc = 1 group, 259/490 (56.4%) were taking an oral anticoagulant.

Similar to our findings of verifying active atrial fibrillation, CHA_2DS_2-VASc risk factors were 10% to Table 2 18% inaccurate compared with the chart review of each patient. The positive predictive value, by expert review, of

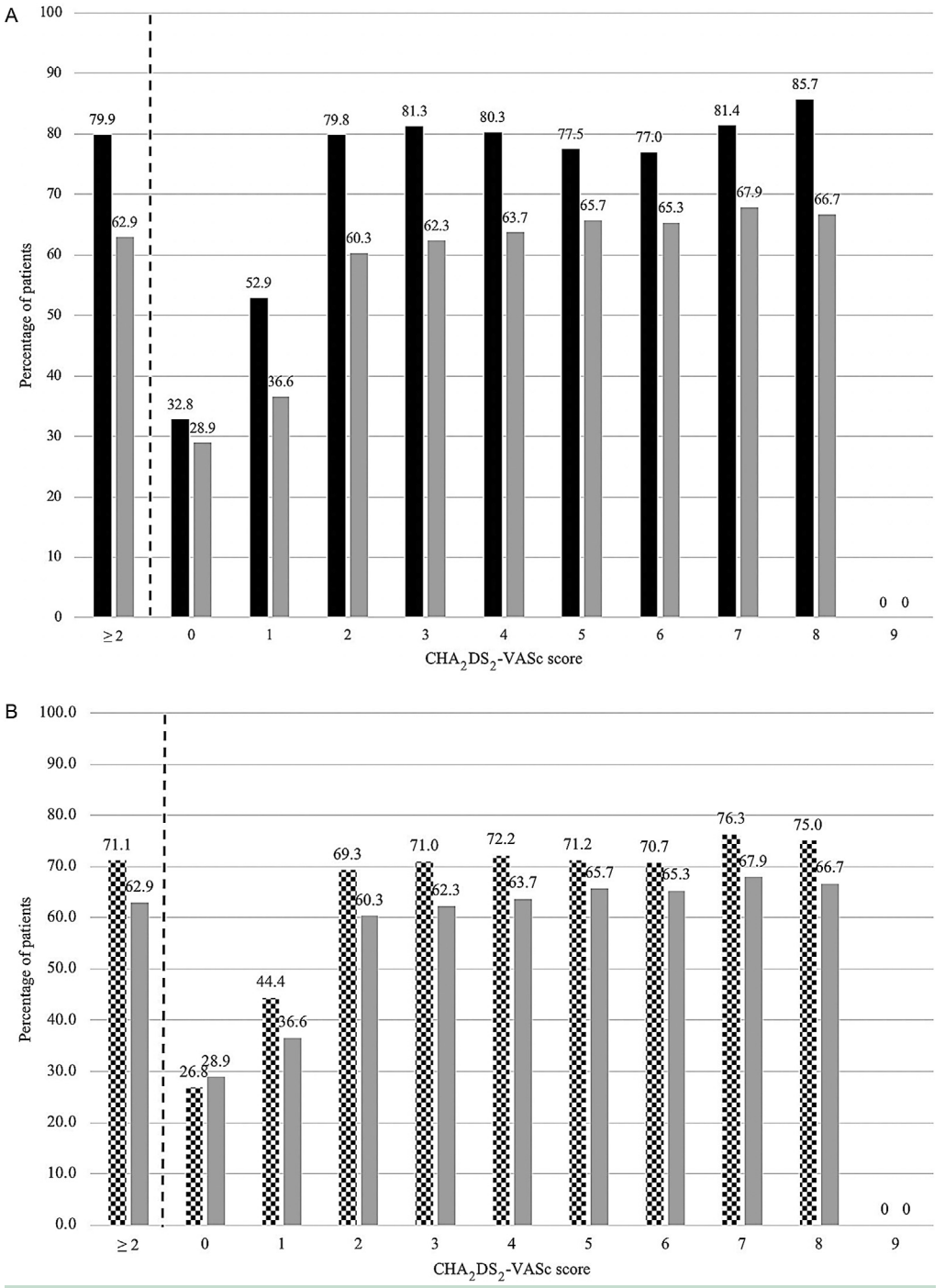

Figure 2 **(A)** OAC use at baseline in preadjudicated AF (gray bars) and after postadjudicated AF (excluding patients with no history of AF and inactive AF) after expert review (black bars) by CHA_2DS_2-VASc score. There was statistically higher OAC use after expert review of active HRAF (CHA_2DS_2-VASc ≥2) status ($P < .0001$). **(B)** OAC use at baseline in preadjudicated AF (gray bars) and after postadjudicated AF (excluding patients with no history of AF but including patients with inactive AF) after expert review (black and white stippled bars) by CHA_2DS_2-VASc score. There was statistically higher OAC use after expert review of active HRAF (CHA_2DS_2-VASc ≥2) status ($P < .0001$). AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 y, Diabetes mellitus, prior Stroke (or transient ischemic attack or thromboembolism), Vascular disease, Age 65-74 y, Sex category; HRAF = high-risk atrial fibrillation; OAC = oral anticoagulation use.

Table 1 Patients' Characteristics

	All Patients Pre-Adj n = 6514	Active AF n = 4555	No AF + Inactive AF n = 1959	NO AF n = 1201	Inactive AF n = 758
Age, mean ± SD	70.8 ± 13.5	72.2 ± 12.7	67.4 ± 14.6	67.3	67.6
Male sex, n (%)	3966 (60.9%)	2760 (60.6%)	1206 (61.6%)	677 (56.3%)	529 (69.8%)
CHA_2DS_2-VASc, mean ± SD	3.1 ± 1.7	3.3 ± 1.6	2.6 ± 1.7	2.7	2.6
Hypertension, n (%)	4296 (66.0%)	3222 (70.1%)	1074 (54.8%)	608 (50.6%)	466 (61.5%)
Diabetes mellitus, n (%)	1606 (24.7%)	1191 (26.1%)	415 (21.2%)	230 (19.2%)	185 (24.4%)
Stroke or TIA, n (%)	821 (12.6%)	611 (13.4%)	210 (10.2%)	138 (11.5%)	72 (9.5%)
Congestive heart failure, n (%)	1534 (23.5%)	1241 (27.2%)	293 (15.0%)	168 (14.0%)	125 (16.5%)
Vascular disease, n (%)	1980 (30.4%)	1414 (31.0%)	566 (28.9%)	297 (24.7%)	269 (35.5%)
Oral anticoagulation use, n (%)	3719 (57.1%)	3415 (75.0%)	304 (15.5%)	219 (18.2%)	85 (7.1%)

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 y, Diabetes mellitus, prior Stroke (or transient ischemic attack or thromboembolism), Vascular disease, Age 65-74 y, Sex category; SD = standard deviation; TIA = transient ischemic attack.

a diagnosis of stroke or transient ischemic attack was 28% lower, congestive heart failure 27% lower, hypertension 11% lower, diabetes mellitus 16% lower, and peripheral artery or coronary artery disease 20% lower than stated in the electronic medical record. Of note, only 7.3% of these corrections led to a change of score large enough to alter an oral anticoagulant recommendation.

DISCUSSION

The main novel finding of our study is that current registries, insurance databases, and health system records, with unadjudicated electronic medical record diagnoses, overreport the number of high-risk atrial fibrillation patients not taking an oral anticoagulant and thus, overestimate the treatment gap in such patients. Our 30% false-positive diagnosis of atrial fibrillation was higher than previous studies,[21-24] however, we included inactive atrial fibrillation patients with no documented atrial fibrillation in the last 5 years. Eliminating this cohort results in a false-positive atrial fibrillation of 18%, consistent with multiple previous reports. The PINNACLE AF registry,[17] at over a hundred study sites, demonstrated a wide range (8%-89%) of proper oral anticoagulants use in atrial fibrillation patients. Dozens of sites from this registry reported anticoagulant use of <30% in high-risk atrial fibrillation patients. The cause of such low oral anticoagulant use in these patients can be explained by the fact that the electronic medical record diagnosis of high-risk atrial fibrillation from these sites was overestimated and consistent with our findings.

Table 2 Oral Anticoagulation (OAC) Use Prior to and After Adjudication in Overall and High-Risk Atrial Fibrillation (HRAF) Groups

	n	%	*P* Value
Baseline AF OAC use	3719/6514	57.1	
Baseline HRAF OAC use	3320/5279	62.9	
Active AF OAC use	3415/4555	75.0	< .0001*
Active HRAF OAC use	3096/3882	79.7	< .0001*
AF minus NO AF OAC use	3500/5313	65.9	
HRAF minus No AF OAC use	3160/4446	71.1	< .0001*
No AF history OAC use	219/1201	18.2	
No HRAF history OAC use	160/833	19.2	
Inactive AF OAC use	85/758	11.2	
Inactive HRAF OAC use	64/585	10.9	

AF = atrial fibrillation.
**P* value calculated by McNemar test compared with baseline.

By excluding patients with absolute contraindications or those who repeatedly refused to take an oral anticoagulant, we found a ceiling of oral anticoagulant use to be 92% of high-risk atrial fibrillation patients similar to the high level of anticoagulant use reported in ORBIT-AF, GARFIELD-AF, and the best performers in the PINNACLE AF Registry.[17,28] Thus, <10% of high-risk atrial fibrillation patients seem to have absolute contraindications to the use of anticoagulants or refuse to take this recommended therapy even after repeated shared-decision making.[29-31] Overall in our study, only 20.3% of high-risk atrial fibrillation patients were not taking an oral anticoagulant, and this number statistically doubled to 40.4% in patients 90 years or older, consistent given the frailty of this patient group. Data have shown that nuisance bleeding and falls are not associated with the feared outcomes that minimize the appropriate use of anticoagulants in high-risk atrial fibrillation patients.[32,33] Many of the remaining patients with absolute contraindications to anticoagulant therapy may be candidates for left atrial occluding devices.[34]

In our data, as in other studies, we took credit for anticoagulant use in all warfarin patients, independent of their time in therapeutic range. However, one-third of our warfarin-treated patients had a time in therapeutic range of <60%, and such patients should be a strategic target for a switch to non-vitamin-K-dependent oral anticoagulants.[35-37] Bonde et al[35] noted in a Scandinavian database that two-thirds of patients had a time in therapeutic range of <70%. and these patients had a higher stroke and major bleeding rate compared with the group who remained in the therapeutic range ≥70% of the time.

Our study also validated the results of other studies[38-42] that the correct diagnosis of all the risk factors may be inaccurate and affect the risk score of such patients. In our study, the inaccuracy of risk-factor diagnosis rarely (7.3%) resulted in a change of risk score large enough to alter the recommendation of whether the patients should take an anticoagulant or not. Improving the accuracy of atrial fibrillation and all risk-factor diagnoses has importance related to quality-improvement projects to improve anticoagulant use[33,43] and for future projects using databases to predict atrial fibrillation for further screening and interventions.[44-51]

We noted no sex difference in appropriate anticoagulant use in patients, similar to some other studies.[52,53] Loikas et al[52] noted that anticoagulant use in women improved and was similar to men by 2015, compared with a lower anticoagulant use in women in 2011. This time-period was when the CHA_2DS_2-VASc scoring system replaced $CHADS_2$, and non-vitamin-K-dependent oral anticoagulants were introduced. Piccini et al[53] also noted no sex difference in oral anticoagulant use in high-risk atrial fibrillation patients in the 2010-2012 timeframe.

Our study found that expert review was concordant with the decision of the practitioner to prescribe an anticoagulant in over 90% of cases. The majority of expert review disagreement was noted in high-risk atrial fibrillation not prescribed an anticoagulant based on perceived risk of bleeding, age, frailty, and falls. Recent registry data[32] noted that over 96% of patients who had minor nuisance bleeding issues continued on oral anticoagulants without any increase in major bleeds.

Based on our findings, all diagnoses may have similar inaccuracies and highlight the limitations of studies with any diagnosis that use unadjudicated Marketscan, Medicare, Department of Defense, insurance, and other electronic medical record databases. Along with an 18% error rate in identifying a diagnosis of atrial fibrillation, other risk factors had a 10% to 18% inaccuracy rate. Prospective registries, such as ORBIT-AF and Garfield AF,[28] can minimize gaps in data and inaccuracies by correction of the data, based on inquiries of the monitoring board.

There are some limitations of our study. Does expert review represent a true gold standard? There is the possibility of inter-reviewer variability. Expert review would not be accurate related to silent occurrences or from atrial fibrillation episodes not documented in our electronic medical record. We tried to minimize this issue by only including patients that frequented our health system so that our database was reasonably complete, including outside scanned records. However, patients may have had silent recurrences, and this may be more of a limitation in the inactive atrial fibrillation group.

Selecting sensitive criteria for entry was done on purpose to minimize missing patients and thus, the loss of some specificity was not surprising. The criteria used in this study are similar to most other studies for enrolling atrial fibrillation patients in registries and clinical trials. As noted above, the magnitude of false positive was higher than previous studies, but this is partially explained by our study including an inactive atrial fibrillation group not included in other prior reports. Even with this wide entry criteria to identify patients, some atrial fibrillation patients were still not identified.

One could argue that our data might be site specific or electronic medical record vendor specific. However, a more likely explanation is that providers who accurately update problem list diagnoses provide the most accurate data, independent of the manual or electronic medical record used. Because the problem list can be edited after the fact, future attempts to accurately define specific diagnoses should concentrate on correcting active problem lists because encounter and billing diagnoses cannot be edited after the fact.

Our study did not exclude the following patients: mechanical valves, postcardiac transplant, adult congenital heart disease, or patients who had undergone an ablation procedure. High-risk atrial fibrillation patients, post ablation procedure, were still considered to need oral anticoagulants as per current recommendations. Our study did not analyze the small number of patients who have indications for oral anticoagulants outside the CHA_2DS_2-VASc scoring system, such as hypertrophic cardiomyopathy or hyperthyroidism. The effect of our findings in subgroups of permanent, persistent, or paroxysmal atrial fibrillation and rate vs rhythm treatment was not analyzed.

Our findings help explain the over-reported underuse of oral anticoagulants in high-risk atrial fibrillation patients and partially explain that even with the approval of the novel anticoagulants, the presumed treatment gap stayed large. Prior reports of oral anticoagulant underuse based on actual or perceived bleeding risk, misperceptions about the efficacy/safety of warfarin, overestimation of aspirin's effectiveness in preventing stroke, adherence issues, especially after stopping an anticoagulant for a procedure and guideline changes over the years, may further explain the current treatment gap. Although our adjudication demonstrated a smaller anticoagulant treatment gap in high-risk atrial fibrillation patients, providing accurate electronic medical record alerts to providers of such patients and developing interventions to improve the education of patients may further decrease the treatment gap in such patients.[44-47] High-risk atrial fibrillation patients, who have major bleeding contraindications or treatment failures with anticoagulants should be screened for other therapies such as left atrial occluding devices.[34] Finally, accurate diagnosis of active atrial fibrillation patients will help improve future predictive models.[48-51]

CONCLUSIONS

Current registries with unadjudicated electronic medical record diagnoses over-report the number of high-risk atrial fibrillation patients not taking oral anticoagulants. Expert adjudication of an active atrial fibrillation diagnosis identifies a significantly smaller oral anticoagulant treatment gap

than previously reported. This issue can be minimized by individual review of patients' medical records and correction of the problem list for the diagnosis of active atrial fibrillation and CHA_2DS_2-VASc risk factors.

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