UCLA
UCLA Previously Published Works

## Title

Off-Label Dosing of Direct Oral Anticoagulants Among Inpatients With Atrial Fibrillation in the United States.

## Permalink

https://escholarship.org/uc/item/2sf90546

## Journal

Circulation: Cardiovascular Quality and Outcomes, 16(12)

## Authors

Sandhu, Amneet
Kaltenbach, Lisa
Chiswell, Karen
et al.

## Publication Date

2023-12-01

## DOI

10.1161/CIRCOUTCOMES.123.010062

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

VA Author Manuscript

VA Author Manuscript

VA Author Manuscript

U.S. Department of Veterans Affairs
Public Access Author manuscript
*Circ Cardiovasc Qual Outcomes*. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:
*Circ Cardiovasc Qual Outcomes*. 2023 December ; 16(12): e010062. doi:10.1161/CIRCOUTCOMES.123.010062.

# Off-Label Dosing of Direct Oral Anticoagulants Among Inpatients with Atrial Fibrillation in the United States

**Amneet Sandhu, MD, MSc**[1,2], **Lisa A. Kaltenbach, MS**[4], **Karen Chiswell, PhD**[4], **Vijay Shimoga, BS**[6], **Carmel Ashur, MD**[2], **Abby Pribish, MD**[2], **Gregg C. Fonarow, MD**[5], **Jonathan P. Piccini Sr, MD**[3,4], **P. Michael Ho, MD, PhD**[1,2], **Paul D. Varosy, MD**[1,2], **Paul L. Hess, MD, MHS**[1,2]

[1]Denver VA Medical Center, Section of Cardiology

[2]University of Colorado, Division of Cardiology

[3]Duke University Hospital

[4]Duke Clinical Research Institute

[5]University of California Los Angeles, Division of Cardiology

[6]University of Colorado, School of Medicine

## Abstract

**Background:** Among patients hospitalized for atrial fibrillation (AF), the frequency of off-label direct oral anticoagulant (DOAC) dosing, associated factors, hospital-level variation, and temporal trends in contemporary practice are unknown.

**Methods:** Using the Get With The Guidelines® Atrial Fibrillation (GWTG-AF) registry, patients admitted from January 1st, 2014 to March 31st, 2020, and discharged on DOAC were stratified according to receipt of under, over, or recommended dosing. Factors associated with off-label dosing (defined as under or overdosing) were identified using logistic regression. Median odds ratio and time-series analyses were used to assess hospital-level variation and temporal trends, respectively.

**Results:** Of 22,470 patients (70.1 +/− 12.1 years, 48.1% female, 82.5% White) prescribed a DOAC at discharge from hospitalization for AF (66% apixaban, 29% rivaroxaban, 5% dabigatran), underdosing occurred among 2006 (8.9%), overdosing among 511 (2.3%), and recommended dosing among 19953 (88.8%). The overall rate of off-label dosing was 11.2%. Patient-related factors associated with off-label dose included age (underdosing: OR 1.06 per 1-year increase [95% CI 1.06–1.07] and overdosing: OR 1.07 per 1-year increase [1.06–1.09]), dialysis dependence (underdosing: OR 5.50 [3.76–8.05] and overdosing: OR 5.47 [2.74–10.88]), female sex (overdosing: OR 0.79 [0.63–0.99]) and weight (overdosing: OR 0.96 per 1-Kg increase [0.95–1.00]). Across hospitals, the adjusted median odds ratio for off-label DOAC dose was 1.45

Address for Correspondence: Amneet Sandhu, MD, MSc, F2-171, 1700 N Wheeling St, Aurora, CO 80045, Phone: 720-723-8461, Fax: 720-723-7839, amneet.sandhu@cuanschutz.edu.

Disclosures:
None

[95% CI 1.34–1.65] (underdosing: 1.52 [1.39–1.76] and overdosing: 1.32 [1.20–1.84]), indicating significant hospital-level variation. Over the study period, recommended dosing significantly increased over time (81.9% to 90.9%, p<0.0001 for trend) with a corresponding decline in under (14.4% to 6.6%, p<0.0001 for trend) and overdosing (3.8% to 2.5%, p=0.001 for trend).

**Conclusion:** Over 1 in 10 patients hospitalized for AF is discharged on an off-label DOAC dose with significant variation across hospitals. While the proportion of patients receiving recommended dosing has significantly improved over time, opportunities to improve DOAC dosing persist.

### Keywords

anticoagulation; atrial fibrillation; off-label; underdosing; overdosing

## INTRODUCTION

Appropriately dosed direct oral anticoagulants (DOACs) reduce the risk of stroke and systemic embolism among select patients with atrial fibrillation (AF).[1–3] The Food and Drug Administration (FDA) specified dosing derived from pivotal phase III trials[1–3] based on factors inclusive of age, weight, kidney function, and concomitant medication use. Unfortunately, use of DOACs at doses not studied in the pivotal trials or recommended in FDA-labeling has been significant, affecting up to 12–20% of patients.[4–7] Off-label DOAC dosing for AF has been observed in the outpatient setting and is associated with increased risk of cardiovascular hospitalization and all-cause mortality.[5,6] Meta-analyses have also shown an increased bleeding risk with DOAC overdosing and higher stroke risk with DOAC underdosing.[8]

The degree to which off-label DOAC dosing occurs in patients hospitalized for AF is unknown. Hospitalizations often are associated with significant changes in health critical to prescription of an optimal DOAC dosage, including weight, kidney function, and concurrent medication use. Temporal trends in off-label DOAC dosage and how use of these agents varies between hospitals is not known. Accordingly, using data from the Get With The Guidelines®-Atrial Fibrillation (GWTG-AFIB) registry, we sought to characterize (1) off-label DOAC dosing rates at discharge among patients requiring hospitalization for AF, (2) patient- and facility-level factors associated with off-label DOAC dosing and (3) temporal changes in the proportion of patients treated with off-label DOAC dosing.

## METHODS

### Data Source

The data used were collected by the American Heart Association's Get With The Guidelines®-AFib registry and may be made available from the corresponding author upon reasonable request. GWTG-AFIB registry was launched in 2013 as a prospective, national, observational initiative tracking hospital encounters for atrial fibrillation. The program and data elements of the GWTG-AFIB registry have been previously described.[9] IQVIA (Parsippany, New Jersey) serves as the data collection and coordination center. A key objective of the GWTG program is to highlight national and institutional-level



VA Author Manuscript VA Author Manuscript VA Author Manuscript

VA Author Manuscript VA Author Manuscript VA Author Manuscript

opportunities for quality improvement. Each participating hospital received either human research approval to enroll cases without individual patient consent under the common rule, or a waiver of authorization and exemption from subsequent review by their institutional review board. The Duke Clinical Research Institute (Durham, NC) serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes. The Institutional Review Board at Duke University Health approved this study. Participating sites were required to adhere to local regulatory and privacy procedures and obtain Institutional Review Board approval if needed. Institutional review board approval was granted to analyze limited data for research purposes.

## Study Population

The study population included patients who required hospital care for management of atrial fibrillation or atrial flutter and were discharged on a DOAC (apixaban, rivaroxaban or dabigatran between January 1st, 2014 and March 31st, 2020). Patient records that were (1) missing key demographic variables or medical history including age, sex, weight or history of atrial fibrillation, (2) missing discharge anticoagulant, dose, or frequency, (3) missing serum creatinine data at the time of discharge, (4) contraindications to DOAC or anticoagulant use or (5) document special circumstances (transition to comfort care or discharged against medical advice) or had missing destination after discharge were excluded (Supplemental Figure 1).

## Study Definition

The designation of “off-label” was defined as deviation from dosing specified by FDA package inserts and used in the seminal DOAC trials.[1–3] They are based on age, weight, kidney function at discharge, and comorbid conditions such as need for dialysis (Supplemental Table 1).[10–12] Recommended dosing of dabigatran varies by creatinine clearance (CrCl >30 ml/min = 150mg orally twice daily and CrCl 15–30 ml/min = 75 mg orally twice daily). For apixaban, recommended dosing is 5 mg twice daily. In the presence of any 2 of 3 factors comprised of age ≥80 years, weight ≤60 kg and a serum creatinine of ≥1.5 mg/dL, recommended dosing is 2.5mg orally twice daily. Recommended rivaroxaban dosing varies by creatinine clearance (>50 ml/min = 20mg orally once daily, 15–50 ml/min = 15mg orally once daily, and <15 ml/min = not recommended).

## Statistical Analysis

Patient characteristics were stratified by discharge DOAC dose characterized as underdosing, recommended dosing, or overdosing. Categorical variables were recorded as counts (percentages) and continuous variables reported as a median (Q1, Q3). Assessments of between-group differences were performed using Pearson $\chi^2$ or Fisher’s exact test as appropriate for the former and Kruskal-Wallis tests for the latter. In sensitivity analyses, rates of off-label dosing were assessed among patients with newly diagnosed AF, those were admitted on DOAC and discharged with a different prescription, and according to weight (≤ 60 kg, 60–120 kg, ≥120 kg or body mass index >40 Kg/m2).

To assess patient- and hospital-level factors associated with off-label dosing, overdosing was compared with recommended dosing and underdosing was compared with recommended

VA Author Manuscript VA Author Manuscript VA Author Manuscript

dosing. In each case, a logistic regression model with stepwise selection was fitted using a significance of 0.10 to enter and remain in the model. Candidate variables were selected based on prior literature[5,6] and clinical judgment which included demographics (age, sex, race and ethnicity), conditions affecting prior health (such as coronary artery disease, prior stroke or TIA, diabetes, hypertension, COPD, OSA, prior myocardial infarction, prior PCI, thyroid disease, prior hemorrhage, PVD, dialysis, liver disease, heart failure), other patient characteristics (such as left ventricular ejection fraction and history of other arrhythmias, smoking, insurance status), and hospital characteristics (region, academic, bedsize, rural). After variable selection, a random intercept for hospital to account for within hospital clustering was added. We assessed whether patient- or hospital-level factors play a larger role in inappropriate dosing using reference effect measures[13], which compare patients at specified percentiles of the random effect of the distribution to patients with the same values for all measured covariates in a reference. Specifically, for all factors as well as patient or hospital factors, 95% ranges and $10^{th}$ and $90^{th}$ percentiles for reference effect measures were analyzed. Wider ranges and differences between the above-mentioned percentiles indicate larger contributions to the overall variation in the outcome. To make comparisons of site variability, variables were scaled such that odds ratios are comparable across variables. Whereas binary variables were dichotomized as in their original form, continuous variables were divided by 2*standard deviation (SD).

To characterize variation across hospitals, the percentage of patients with off-label dosing out of the total number of patients eligible for DOAC dosing was calculated for each hospital. Hospitals with <30 admissions in the study population were excluded. Hospital-level variation use was then graphically displayed using a caterpillar plot. To account for variation in the number of patients per site, a hierarchical logistic regression model with random intercepts for site was fitted. The model was then used to test whether variance components for site were greater than zero and to calculate the median odds ratio (MOR) between sites. The MOR can be interpreted as the median increase in odds of off-label dosing when an individual moves from a lower to a higher-risk hospital. It provides an estimate of the effect size of the hospital variation on the outcome of off-label DOAC dosing. A MOR >1.2 represents significant clinical variation.[14]

To describe temporal trends in percentage off-label DOAC dosing, the percentage of patients with off-label dosing was calculated by calendar quarter beginning in 2014. Trends in percentage of recommended dosing, underdosing, and overdosing over time was graphically displayed. To assess temporal trend significance, unadjusted and adjusted logistic regression models with random intercepts for site were fitted for overdosing versus recommended dosing and underdosing versus recommended dosing. The final clinical variables of the models described as well as random intercepts for site and time in quarters were included. The effect of quarterly trends of off-label DOAC dosing was estimated using odds ratios (95% confidence intervals).

## RESULTS

Among 22,470 patients discharged after a hospital encounter for AF, 2006 (8.9%) received a DOAC that was lower than the recommended dose, 19953 (88.8%) received a DOAC

VA Author Manuscript VA Author Manuscript VA Author Manuscript

at recommended dosing, and 511 (2.3%) received a DOAC that was higher than the recommended dose. Figure 1 displays underdosing, overdosing, and recommended dosing by DOAC type and overall.

Table 1 displays patient-level data for the overall cohort and stratified by underdosed, recommended dosing and overdosed. In the overall population, the mean age was 70.1 +/− 12.1 years old, 48.1% were female, and the mean body mass index was 31.2 +/− 7.9 $Kg/m^2$. The mean CHADS2Vasc score was 3.76 +/− 1.75, 42.0% had paroxysmal AF and 37.6% had chronic kidney disease resulting in an eGFR <60 ml/min while 0.7% were on hemodialysis. Relative to those discharged on DOAC dosing consistent with FDA labeling, patients who received underdosed DOACs were older (77.0 +/− 11.2 years vs. 69.1 +/− 11.9), more commonly on dialysis (2.7% vs. 0.5%), more frequently had a prior hemorrhage (4.7% vs. 2.6%), and more frequently received care at hospitals located in non-rural settings (4.8% vs. 4.4%) or with less than 500 beds (43.4% vs. 33.8%). Relative to FDA-labeled use of DOACs on discharge, those who received overdosed DOACs were older (80.6 +/− 7.8 years vs 69.1 +/− 11.9), more frequently women (66.3% vs. 46.6%), usually had a lower body mass index (25.1 +/− 5.8 vs. 31.5 +/− 5.8), and more frequently were on dialysis (2.4% vs. 0.5%). In sensitivity analyses (Supplemental Table 2), rates of underdosing, recommended, and overdosing among those with newly-diagnosed AF and those with a change in DOAC type (ie. from apixaban to rivaroxaban) from admission to discharge were comparable to the primary analysis. Among 1,380 patients or 9.3% of those who received apixaban at discharge with a weight between 55–65 kg, 16.4% were underdosed, 78.1% received recommended dosing and 5.6% were overdosed. Similarly, among 1,127 patients or 7.6% of those who received apixaban at discharge with a serum creatinine between 1.3–1.7 mg/dL, 10.3% were underdosed, 84.5% received a recommended dose and 5.2% were overdosed

Figure 2 displays all factors, patient and hospital factors associated with overdosing and underdosing relative to recommended dosing in addition to unmeasured site-level variation across hospitals. In multivariable modeling, higher rates of underdosing were associated with patient-level factors such as older age, dialysis dependence, and prior hemorrhage and hospital-level factors such as Western and urban location as well as servicing relatively few beds. Across hospitals, the reference effect measure for random site variation of receipt of underdosed DOAC at discharge ($90^{th}$ percentile in comparison to median hospital) was OR 1.75 (95% CI 1.54–2.00). Higher rates of overdosing were associated with patient-level factors such as older age and dialysis dependence. Hospital-level factors were not significantly contributory. Across hospitals, the reference effect measure for random site variation of receipt of an overdosed DOAC at discharge ($90^{th}$ percentile in comparison to median hospital) was OR 1.46 (95% CI 1.29–1.65).

Across participating sites, the median observed percent of off-label DOAC dosage was 10.9% (IQR 6.8 – 15.9%). Figure 3 displays hospital-level variation in the rate of off-label DOAC use in addition to hospital-level variation in rates of underdosing and overdosing. The overall adjusted MOR for off-label DOAC dosage across hospitals was 1.45 (95% CI 1.34–1.65) [REM or random effects model range 0.47–2.14], indicating significant variation across sites. The adjusted MOR for underdosing was 1.52 (95% CI 1.39–1.76)

VA Author Manuscript VA Author Manuscript VA Author Manuscript

[REM range 0.42–2.36] and overdosing 1.32 (1.20–1.84) [REM range 0.56–1.78]. Table 2 shows that in random effects models, while patient factors contributed more to variability than facility-level factors, facility-level factors were nonetheless significantly contributory to both underdosing and overdosing. Figure 4 shows temporal trends in the rates of recommended dosing, underdosing, and overdosing of DOACs. There was a significant increase in recommended dosing from 81.9% in 2014 to 90.9% in 2020, p <0.0001 for trend. There was a significant decline in those receiving underdosing (14.4% in 2014 to 6.6% in 2020, p<0.0001 for trend) and overdosing (3.8% in 2014 to 2.5% in 2020, p=0.001 for trend) dosing over the study period.

## DISCUSSION

In this nationwide analysis of more than 22,000 patients hospitalized for care of atrial fibrillation and discharged on DOACs, there are three key findings. First, 1 of 10 patients hospitalized for AF receive under or overdosed DOACs. Second, significant hospital-level variation exists with regards to use of off-label DOAC dose, with the greatest opportunity for future improvement in hospitals that are Western, urban, or of comparatively small size. Third, over the study period, rates of recommended DOAC dosing increased and off-label dosage decreased. These results characterize favorable national trends in DOAC use while identifying continued opportunities to improve safe and appropriate DOAC dosing at hospital discharge.

Prior work has analyzed rates of off-label DOAC dose in ambulatory outpatients (9.4% are underdosed, 3.4% overdosed and 87% per recommendation) correlating adverse cardiovascular or bleeding events in those who received off-label dosing.[6] Our work extends that of prior analyses by focusing on patients hospitalized with AF and reveals rates of off-label dosage (8.9% underdosed, 2.3% overdosed) similar to that seen among outpatients.[6,15] Encouragingly, rates of recommended dosing remain relatively high and are comparable to prior, smaller analyses in patients with atrial fibrillation warranting long-term anticoagulation.[16] Consistent with prior, smaller studies, we found that several patient characteristics are more common in those treated with an off-label dose, including older age, weight, and dialysis dependence.[6,17] The DOACs studied (apixaban, rivaroxaban and dabigatran) account for the majority of DOAC use in the United States.[18,19] Broadly, these data provide opportunities to address this quality gap, focusing on patient profiles at-risk for off-label DOACs dose, risk of over or underdosing based on type of DOAC utilized. These profiles may prove useful both at the time of hospital discharge as well as during post-hospitalization follow-up clinical encounters.

Significant hospital-level variation of off-label DOACs dosage exists after accounting for measured variables. This finding suggests unmeasured aspects of site-level care may account for a significant proportion of hospital-variation. Such aspects may include variability in formalized structure surrounding quality improvement such as that recommended for dedicated AF Centers of Excellence.[20] In this context, system-level quality improvement efforts may prove fruitful, primarily focusing on reducing rates of underdosing. This may be achieved with the the development of team-based, integrated clinical care pathways developed by relevant stakeholders, including pharmacy, nursing, hospital medicine, and

VA Author Manuscript VA Author Manuscript VA Author Manuscript

cardiology. Key components may include the establishment of pre-discharge medication review processes, enhanced clinical decision support with automated dosing checks accounting for key comorbidities, medications, and up-to-date laboratory values embedded in the electronic medical record, and close outpatient follow-up attentive to the importance of appropriate DOAC dosing.

Nationwide improvement in rates of recommended DOAC use and decline in the use of off-label dosage suggest there may already be some level of recognition of the importance of appropriately-dosed anticoagulation. Nonetheless, the presence of a significant, persistent gap and heterogeneity in performance across hospitals underscores the need for continued, focused mitigation efforts. Endeavors may include not only system-level quality improvement programs described above but also benchmarking of DOAC dosing and the development of performance measures. Benchmarking such as that provided by quality improvement registries like GWTG-AF is likely an effective feedback mechanism to stimulate improvement. In addition, establishment of provider- and facility-level AF performance measures related to appropriate AF dosing may also prove to be an effective a feedback mechanism and policy incentive for continued quality improvement.

Limitations of our work include analysis of hospitals participating in the GWTG-AF Registry, which may select for hospitals choosing to be involved with quality improvement work. Though missing data was the major contributor to patient exclusion, the primary sample size of >20,000 patients allow for meaningful analyses and represents a much greater sample in comparison to other works evaluating off-label dosing. However, despite the low number of centers excluded, we were unable to define the relationship between these sites, who may be more prone to off-label use, and DOAC dose. Factors considered by clinicians such as frailty may influence DOAC dosing and and yet are not captured in the GWTG-AF registry. In addition, in clinical practice, fluctuating renal function and at times, weight, make consistent DOAC dosing recommendations challenging. Weight is only available at a solitary timepoint (at or closest to admission) through the GWTG-AF registry. While dosing adjustment in the context of clinical changes is recommended when feasible, logistical challenges such as distance for regular blood draws and medication adherence may lead clinicians to dose based on historical trends. Though post-discharge management of OAC and long-term clinical outcomes associated with off-label dosing are important considerations in future work, these analyses were not feasible in the current study sample. The intent of our work was to evaluate rates of and factors associated with recommended and off-label DOAC dose in those hospitalized for atrial fibrillation, and as such whether off-label DOAC dosing persisted after discharge was not evaluated. However, this study represents (1) the largest work, to date, analyzing contemporary DOAC dosing and (2) the first to evaluate patients hospitalized for AF and discharged on DOAC therapy.

## CONCLUSIONS

Over 1 in 10 patients hospitalized for AF are discharged on off-label doses of DOAC, with significant variation across hospitals. Over time, rates of underdosing and overdosing declined while the rate of recommended DOAC dosing increased. Owing to persistently elevated rates of off-label DOAC dosing, quality-improvement efforts should be considered.

VA Author Manuscript VA Author Manuscript VA Author Manuscript

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Sources of Funding:

The Get With The Guidelines®–AFIB (GWTG-AFIB) program is provided by the American Heart Association. GWTG-AFIB is sponsored, in part, by BMS Pfizer, Tylenol and Philips Image Guided Therapy.

## Non-standard Abbreviations and Acronyms:

| | |
|---|---|
| **AF** | atrial fibrillation |
| **DOAC** | direct oral anti-coagulant |
| **GWTG-AF** | Get With the Guidelines – Atrial Fibrillation |

## REFERENCES

1. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–891. doi: 10.1056/NEJMoa1009638 [PubMed: 21830957]
2. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–1151. doi: 10.1056/NEJMoa0905561 [PubMed: 19717844]
3. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–992. doi: 10.1056/NEJMoa1107039 [PubMed: 21870978]
4. Brokmeier H, Kido K. Off-label Use for Direct Oral Anticoagulants: Valvular Atrial Fibrillation, Heart Failure, Left Ventricular Thrombus, Superficial Vein Thrombosis, Pulmonary Hypertension-a Systematic Review. Ann Pharmacother. 2021;55:995–1009. doi: 10.1177/1060028020970618 [PubMed: 33148014]
5. Zhang XL, Zhang XW, Wang TY, Wang HW, Chen Z, Xu B, Xu W. Off-Label Under- and Overdosing of Direct Oral Anticoagulants in Patients With Atrial Fibrillation: A Meta-Analysis. Circ Cardiovasc Qual Outcomes. 2021;14:e007971. doi: 10.1161/CIRCOUTCOMES.121.007971 [PubMed: 34932377]
6. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, Kowey PR, Mahaffey KW, Naccarelli G, Reiffel J, et al. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. J Am Coll Cardiol. 2016;68:2597–2604. doi: 10.1016/j.jacc.2016.09.966 [PubMed: 27978942]
7. Sugrue A, Sanborn D, Amin M, Farwati M, Sridhar H, Ahmed A, Mehta R, Siontis KC, Mulpuru SK, Deshmukh AJ, et al. Inappropriate Dosing of Direct Oral Anticoagulants in Patients with Atrial Fibrillation. Am J Cardiol. 2021;144:52–59. doi: 10.1016/j.amjcard.2020.12.062 [PubMed: 33385355]
8. Santos J, Antonio N, Rocha M, Fortuna A. Impact of direct oral anticoagulant off-label doses on clinical outcomes of atrial fibrillation patients: A systematic review. Br J Clin Pharmacol. 2020;86:533–547. doi: 10.1111/bcp.14127 [PubMed: 31631392]
9. Lewis WR, Piccini JP, Turakhia MP, Curtis AB, Fang M, Suter RE, Page RL 2nd, Fonarow GC. Get With The Guidelines AFIB: novel quality improvement registry for hospitalized patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes. 2014;7:770–777. doi: 10.1161/CIRCOUTCOMES.114.001263 [PubMed: 25185244]
10. FDA Package Insert: Dabigatran. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022512s028lbl.pdf.

VA Author Manuscript VA Author Manuscript VA Author Manuscript


11. FDA Package Insert: Rivaroxaban. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215859s000lbl.pdf.
12. FDA Package Insert: Apixaban. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf.
13. Glorioso TJ, Grunwald GK, Ho PM, Maddox TM. Reference effect measures for quantifying, comparing and visualizing variation from random and fixed effects in non-normal multilevel models, with applications to site variation in medical procedure use and outcomes. BMC Med Res Methodol. 2018;18:74. doi: 10.1186/s12874-018-0517-7 [PubMed: 29980180]
14. Chan PS, Maddox TM, Tang F, Spinler S, Spertus JA. Practice-level variation in warfarin use among outpatients with atrial fibrillation (from the NCDR PINNACLE program). Am J Cardiol. 2011;108:1136–1140. doi: 10.1016/j.amjcard.2011.06.017 [PubMed: 21798501]
15. Dawson T, DeCamillo D, Kong X, Shensky B, Kaatz S, Krol GD, Ali M, Haymart B, Froehlich JB, Barnes GD. Correcting Inappropriate Prescribing of Direct Oral Anticoagulants: A Population Health Approach. J Am Heart Assoc. 2020;9:e016949. doi: 10.1161/JAHA.120.016949 [PubMed: 33150804]
16. Luo N, Xu H, Jneid H, Fonarow GC, Lopes RD, Piccini JP, Curtis AB, Russo AM, Lewis WR, Matsouaka RA, et al. Use of Oral Anticoagulation in Eligible Patients Discharged With Heart Failure and Atrial Fibrillation. Circ Heart Fail. 2018;11:e005356. doi: 10.1161/CIRCHEARTFAILURE.118.005356 [PubMed: 30354398]
17. Rose AJ, Lee JS, Berlowitz DR, Liu W, Mitra A, Yu H. Guideline-discordant dosing of direct-acting oral anticoagulants in the veterans health administration. BMC Health Serv Res. 2021;21:1351. doi: 10.1186/s12913-021-07397-x [PubMed: 34922546]
18. Colacci M, Tseng EK, Sacks CA, Fralick M. Oral Anticoagulant Utilization in the United States and United Kingdom. J Gen Intern Med. 2020;35:2505–2507. doi: 10.1007/s11606-020-05904-0 [PubMed: 32514896]
19. Marzec LN, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, Hsu JC, Maddox TM. Influence of Direct Oral Anticoagulants on Rates of Oral Anticoagulation for Atrial Fibrillation. J Am Coll Cardiol. 2017;69:2475–2484. doi: 10.1016/j.jacc.2017.03.540 [PubMed: 28521884]
20. Piccini JP Sr., Allred J, Bunch TJ, Deering TF, Di Biase L, Hussein AA, Lewis WR, Mittal S, Natale A, Osorio J, et al. Rationale, considerations, and goals for atrial fibrillation centers of excellence: A Heart Rhythm Society perspective. Heart Rhythm. 2020;17:1804–1832. doi: 10.1016/j.hrthm.2020.04.033 [PubMed: 32387248]

VA Author Manuscript

VA Author Manuscript

VA Author Manuscript

**What is Known:**

- Among those with atrial fibrillation, use of DOACs at doses not recommended by FDA-labeling, or off-label dosing, is substantial in the outpatient setting and associated with adverse cardiovascular events.
- Inpatient hospitalizations are associated with significant changes in health, the degree to which off-label dosing occurs in those hospitalized for atrial fibrillation remains unknown.

VA Author Manuscript

VA Author Manuscript

VA Author Manuscript

**What this Study Adds:**

- Over 1 in 10 patients hospitalized for atrial fibrillation is discharged on an off-label DOAC dose with significant variation across hospitals.
- There was significant improvement in recommended DOAC dosing over time with a corresponding decline in under and overdosing.

VA Author Manuscript VA Author Manuscript VA Author Manuscript

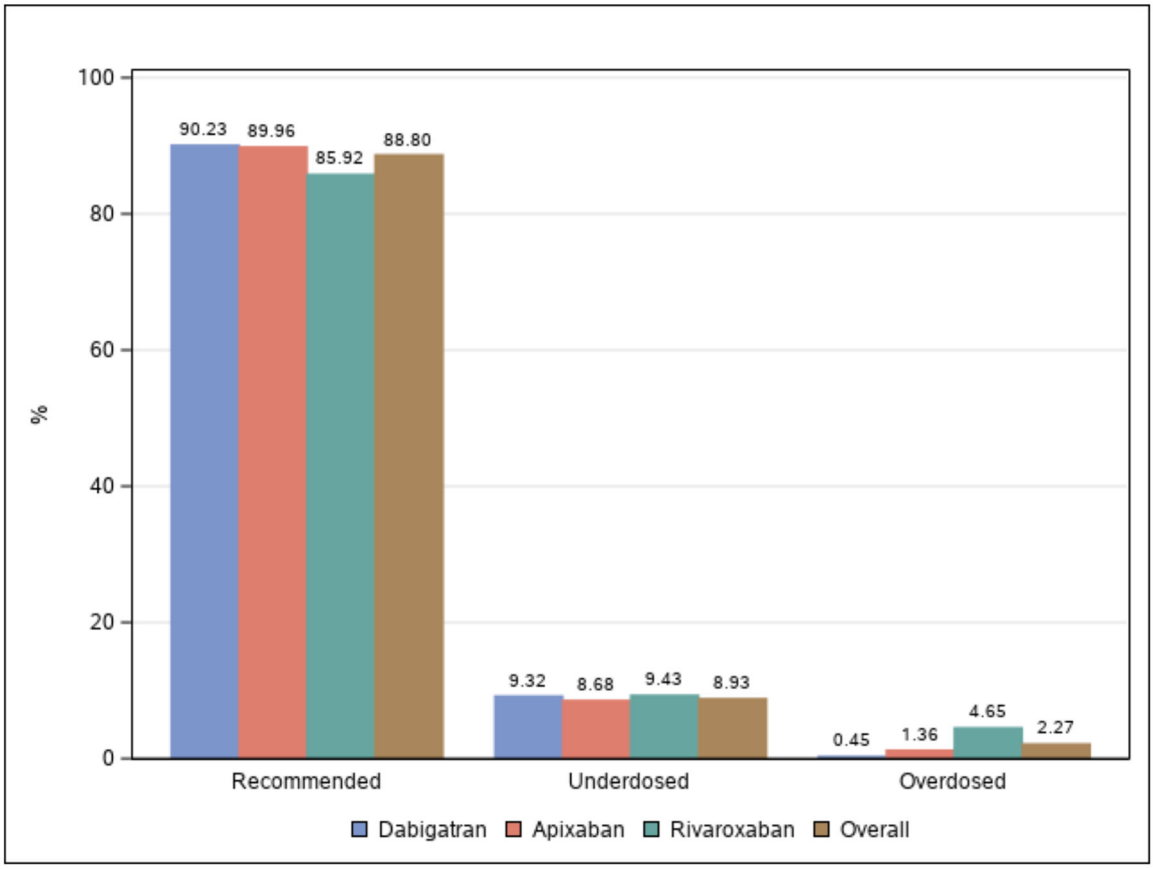


**Figure 1:**
Rates of DOAC dosing at discharge in those hospitalized for atrial fibrillation, stratified by recommended dosing, underdosed or overdosed (percentages displayed).

VA Author Manuscript VA Author Manuscript VA Author Manuscript

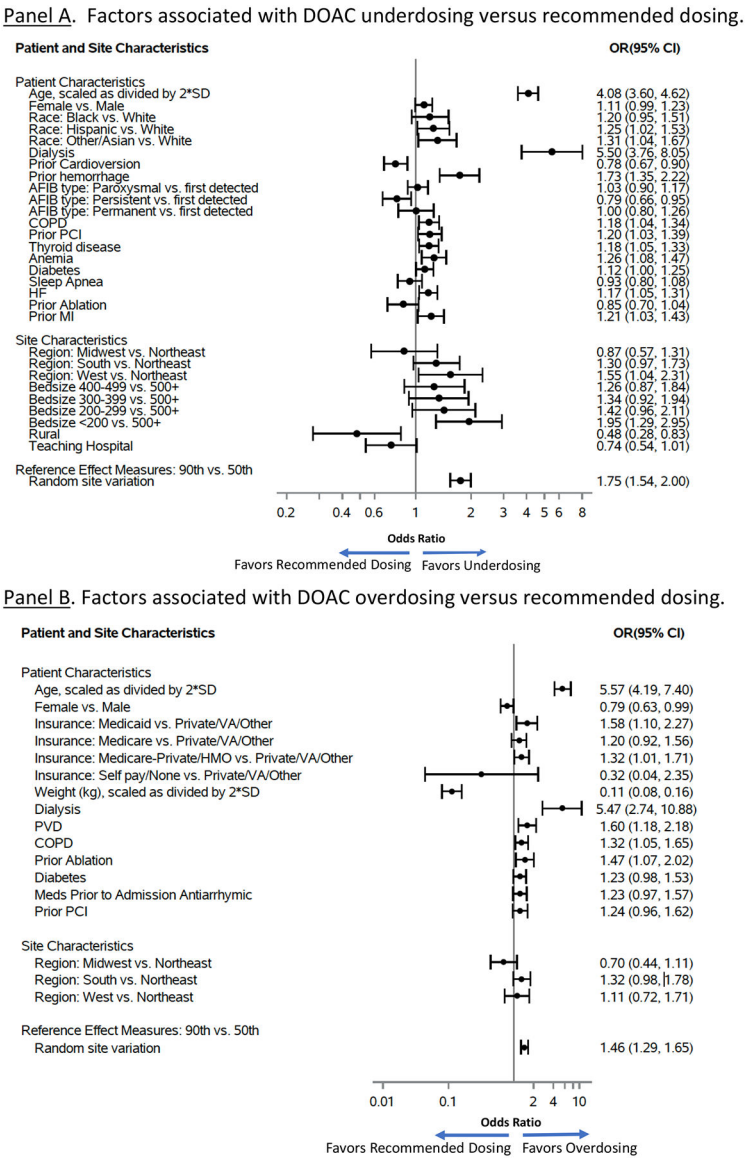


**Figure 2:**
Factors associated with off-label dosing.

VA Author Manuscript

VA Author Manuscript

VA Author Manuscript

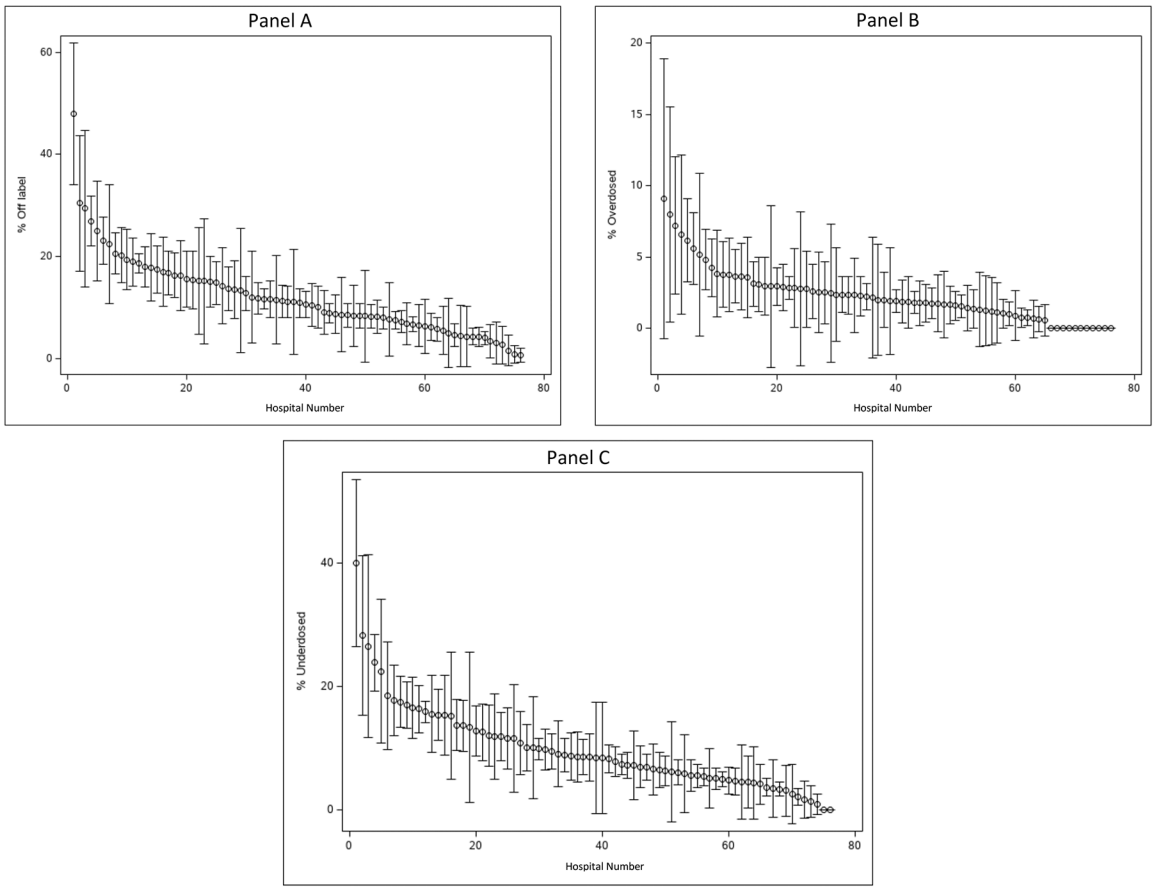


**Figure 3:**

Hospital-level variation in the rate of off-label DOAC dosage (panel A), overdosing (panel B) and underdosing (panel C) at discharge.

VA Author Manuscript

VA Author Manuscript

VA Author Manuscript

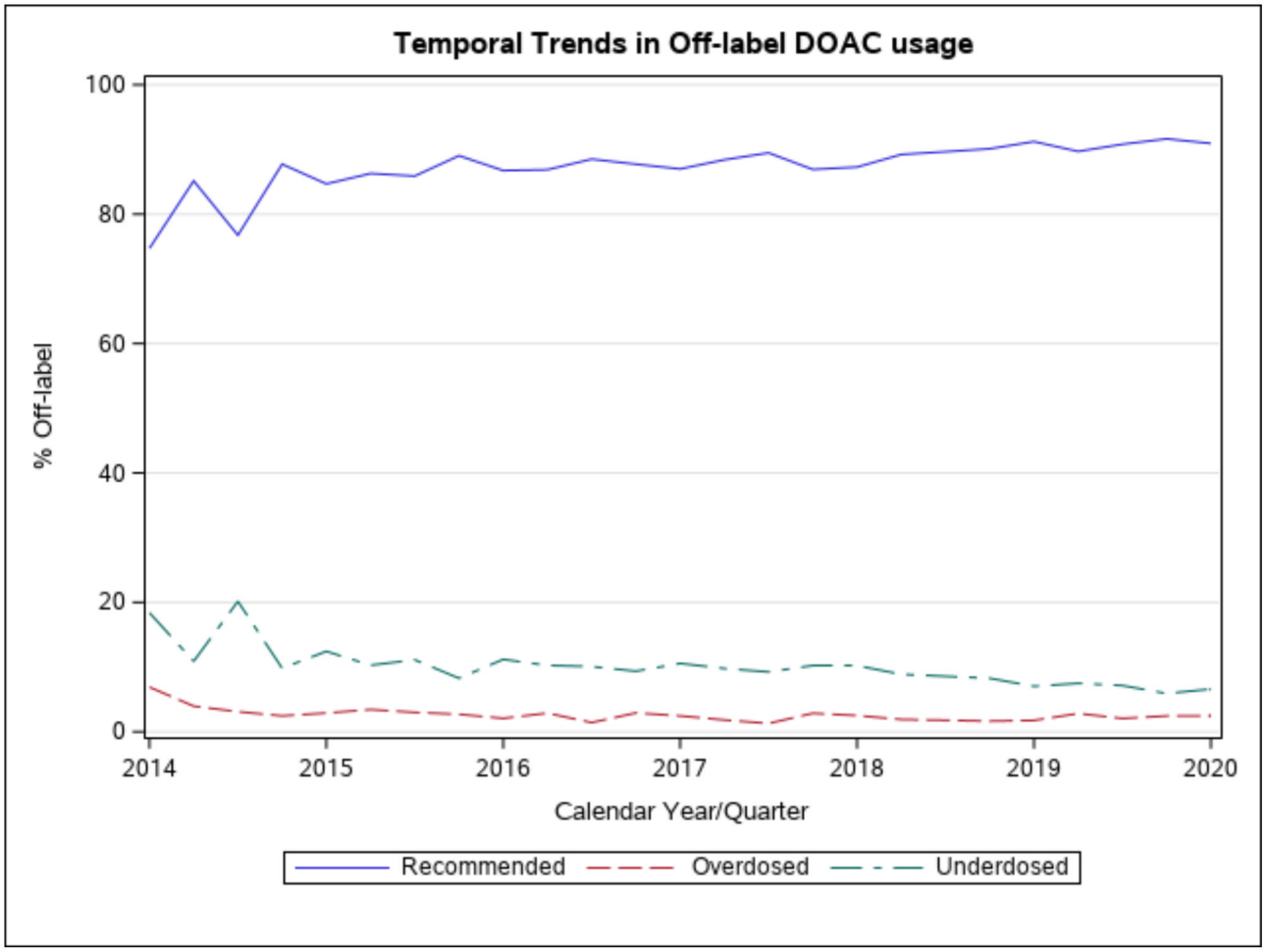


**Figure 4:**
Trends, from 2014–2020, in the rates of recommended dosing, underdosing, and overdosing of DOACs.

VA Author Manuscript

VA Author Manuscript

VA Author Manuscript

**Table 1:**

Summary of DOAC information, patient-level and hospital characteristics stratified by underdosed, recommended dose, overdosed and the overall cohort.

| Variable | Overall | Recommended | Off-Label | | P-value+ |
|---|---|---|---|---|---|
| | | | Underdosed | Overdosed | |
| | (N=22470) | (N=19953) | (N=2006) | (N=511) | |
| **Demographics** | | | | | |
| Age, Mean (years) +/− STD | 70.1 +/− 12.1 | 69.1 +/− 11.9 | 76.9 +/− 11.2 | 80.6 +/− 7.8 | <.0001 |
| Sex, Female (%) | 10818 (48.1%) | 9295 (46.6%) | 1184 (59.0%) | 339 (66.3%) | <.0001 |
| BMI, Mean +/− STD | 31.2 +/− 7.9 | 31.5 +/− 7.9 | 29.7 +/− 7.0 | 25.1 +/− 5.8 | <.0001 |
| **Race/Ethnicity** | | | | | |
| White, N (%) | 18530 (82.5%) | 16516 (82.8%) | 1591 (79.3%) | 423 (82.8%) | <.0001 |
| Black, N (%) | 1398 (6.2%) | 1268 (6.4%) | 106 (5.3%) | 24 (4.7%) | |
| Asian, N (%) | 286 (1.3%) | 246 (1.2%) | 35 (1.7%) | 5 (0.9%) | |
| Other, N (%) | 739 (3.3%) | 650 (3.3%) | 73 (3.6%) | 16 (3.1%) | |
| **Insurance** | | | | | |
| Missing, N (%) | 216 (1.0%) | 201 (1.0%) | 11 (0.6%) | 4 (0.8%) | <.0001 |
| Private/HMO/Other, N (%) | 9397 (41.8%) | 8584 (43.0%) | 668 (33.3%) | 145 (28.4%) | |
| Medicaid, N (%) | 2219 (9.9%) | 1974 (9.9%) | 198 (9.9%) | 47 (9.2%) | |
| Medicare, N(%) | 5260 (23.4%) | 4556 (22.8%) | 557 (27.8%) | 147 (28.8%) | |
| Medicare - Private/HMO/Other, N (%) | 4894 (21.8%) | 4184 (21.0%) | 544 (27.1%) | 166 (32.5%) | |
| No Insurance, N (%) | 484 (2.2%) | 454 (2.3%) | 28 (1.4%) | 2 (0.4%) | |
| **Comorbid Conditions** | | | | | |
| Anemia, N (%) | 2095 (9.3%) | 1747 (8.8%) | 283 (14.1%) | 65 (12.7%) | <.0001 |
| COPD, N (%) | 3698 (16.5%) | 3175 (15.9%) | 406 (20.2%) | 117 (22.9%) | <.0001 |
| Coronary Artery Disease, N (%) | 6319 (28.1%) | 5440 (27.3%) | 703 (35.0%) | 176 (34.4%) | <.0001 |
| CRT-D, N (%) | 307 (1.4%) | 267 (1.3%) | 30 (1.5%) | 10 (2.0%) | 0.4298 |
| CRT-P, N(%) | 57 (0.3%) | 49 (0.3%) | 4 (0.2%) | 4 (0.8%) | 0.0513 |
| Prior Stroke or TIA, N (%) | 2795 (12.4%) | 2399 (12.0%) | 320 (16.0%) | 76 (14.9%) | <.0001 |
| Diabetes, N (%) | 6524 (29.0%) | 5750 (28.8%) | 647 (32.3%) | 127 (24.9%) | 0.0006 |
| Dialysis, N (%) | 158 (0.7%) | 92 (0.5%) | 54 (2.7%) | 12 (2.4%) | <.0001 |
| Heart Failure, N (%) | 6570 (29.2%) | 5724 (28.7%) | 670 (33.4%) | 176 (34.4%) | <.0001 |
| Hypertension, N (%) | 17744 (79.0%) | 15666 (78.5%) | 1663 (83.0%) | 415 (81.2%) | <.0001 |
| ICD Only, N (%) | 723 (3.2%) | 639 (3.2%) | 71 (3.5%) | 13 (2.5%) | 0.4902 |
| Left Ventricular Hypertrophy, N (%) | 312 (1.4%) | 280 (1.4%) | 23 (1.2%) | 9 (1.8%) | 0.4946 |
| Liver Disease, N (%) | 220 (1.0%) | 193 (1.0%) | 22 (1.1%) | 5 (1.0%) | 0.8543 |
| Mechanical Prosthetic Heart Valve, N (%) | 82 (0.4%) | 68 (0.3%) | 12 (0.6%) | 2 (0.4%) | 0.1891 |
| Mitral Stenosis, N (%) | 103 (0.5%) | 95 (0.5%) | 5 (0.3%) | 3 (0.6%) | 0.3253 |
| Obstuctive Sleep Apena, N (%) | 4523 (20.1%) | 4200 (21.1%) | 265 (13.2%) | 58 (11.4%) | <.0001 |
| Pacemaker, N (%) | 1597 (7.1%) | 1338 (6.7%) | 194 (9.7%) | 65 (12.7%) | <.0001 |
| Peripheral Vascular Disease, N (%) | 1327 (5.9%) | 1108 (5.6%) | 163 (8.1%) | 56 (11.0%) | <.0001 |
| Prior Hemorrhage, N (%) | 627 (2.8%) | 518 (2.6%) | 94 (4.7%) | 15 (2.9%) | <.0001 |

VA Author Manuscript VA Author Manuscript VA Author Manuscript

| Variable | Overall | Recommended | Off-Label | | P-value+ |
|---|---|---|---|---|---|
| | | | Underdosed | Overdosed | |
| | (N=22470) | (N=19953) | (N=2006) | (N=511) | |
| Prior MI, N (%) | 2236 (10.0%) | 1945 (9.8%) | 243 (12.1%) | 48 (9.4%) | 0.0031 |
| Prior PCI, N (%) | 2793 (12.4%) | 2394 (12.0%) | 320 (16.0%) | 79 (15.5%) | <.0001 |
| Rheumatic Heart Disease, N (%) | 43 (0.2%) | 36 (0.2%) | 7 (0.4%) | 0 (0%) | 0.1562 |
| Sinus Node Dysfunction, N (%) | 939 (4.2%) | 786 (3.9%) | 114 (5.7%) | 39 (7.6%) | <.0001 |
| Smoker, N (%) | 2257 (10.0%) | 2065 (10.4%) | 159 (7.9%) | 33 (6.5%) | <.0001 |
| Thryoid Disease, N (%) | 4206 (18.3%) | 3595 (18.0%) | 487 (24.3%) | 124 (24.3%) | <.0001 |
| **Atrial Fibrillation Type** | | | | | |
| First Detected Atrial Fibrillation, N (%) | 4664 (20.8%) | 4102 (20.6%) | 465 (23.2%) | 97 (19.0%) | <0.0001 |
| Paroxysmal Atrial Fibrillation, N (%) | 9445 (42.0%) | 8388(42.0%) | 832 (41.2%) | 225 (44.0%) | |
| Persistent Atrial Fibrillation, N (%) | 5011 (22.3%) | 4629 (23.2%) | 290 (14.5%) | 92 (18.0%) | |
| Permanent or long standing Persistent Atrial Fibrillation, N (%) | 1217 (5.4%) | 1026 (5.1%) | 147 (7.3%) | 44 (8.6%) | |
| Unable to Determine, N (%) | 2132 (9.5%) | 1807 (9.1%) | 272 (13.6%) | 53 (10.4%) | |
| **Cardiomyopathy Type** | | | | | |
| Ischemic, N (%) | 785 (3.5%) | 677 (3.4%) | 88 (4.4%) | 20 (3.9%) | <.0001 |
| Non-Ischemic, N (%) | 1458 (6.5%) | 1364 (6.8%) | 71 (3.52%) | 23 (4.5%) | |
| Both, N (%) | 23 (0.1%) | 22 (0.1%) | 0 (0%) | 1 (0.2%) | |
| Missing, N (%) | 793 (3.5%) | 721 (3.6%) | 55 (2.7%) | 17 (3.3%) | |
| **Other Risk Factors** | | | | | |
| CHADS2Vasc Score, Mean +/− STD | 3.76 +/− 1.75 | 3.65 +/− 1.74 | 4.59 +/− 1.6 | 4.81 +/− 1.41 | <.0001 |
| ORBIT Score, Mean +/− STD | 1.93 +/− 1.53 | 1.82 +/− 1.5 | 2.74 +/− 1.47 | 2.90 +/− 1.39 | <.0001 |
| CKD with eGFR < 60 ml/min, N (%) | 8456 (37.6%) | 6950 (34.8%) | 1149 (57.3%) | 357 (69.9%) | <.0001 |
| Prior Major Bleeding, N (%) | 2146 (9.6%) | 1781 (8.9%) | 304 (15.2%) | 61 (11.9%) | <.0001 |
| Prior AF Ablation Procedure, N (%) | 2797 (12.5%) | 2590 (13.0%) | 155 (7.7%) | 52 (10.2%) | <.0001 |
| **Admission Creatinine Clearance** (Cockcroft Gault, Mean (ml/min) +/− STD) | 86.39 +/− 46 | 90.01 +/− 46.12 | 61.69 +/− 35.45 | 42.82 +/− 16.33 | <.0001 |
| **Discharge Creatinine Clearance** (Cockcroft Gault, Mean (ml/min) +/− STD) | 90.6 +/− 47.43 | 94.38 +/− 47.6 | 65.7 +/− 35.13 | 40.88 +/− 12.18 | <.0001 |
| **Anti-arrhythmic Medication Use Prior to Admission**, N (%) | 4445 (19.8%) | 3990 (20.0%) | 355 (17.7%) | 100 (19.6%) | 0.0473 |
| **Hospital Characteristics** | | | | | |
| Academic / Teaching Hospital, N (%) | 18355 (81.7%) | 16406 (82.2%) | 1541 (76.8%) | 408 (79.8%) | <.0001 |
| Teaching Status Missing, N (%) | 984 (4.4%) | 841 (4.2%) | 109 (5.4%) | 34 (6.7%) | |
| Rural Location, N (%) | 1073 (4.8%) | 952 (4.8%) | 88 (4.4%) | 33 (6.5%) | 0.1204 |
| Location Missing, N (%) | 985 (4.4%) | 841 (4.2%) | 109 (5.4%) | 34 (6.7%) | |
| Adult Cardiac Electrophysiology Hospital, N (%) | 2044 (9.1%) | 1746 (8.8%) | 229 (11.4%) | 69 (13.5%) | <.0001 |
| Missing, N (%) | 3031 (13.5%) | 2541 (12.7%) | 379 (18.9%) | 111 (21.7%) | |
| Bed Size, Missing, N (%) | 984 (4.4%) | 841 (4.2%) | 109 (5.4%) | 34 (6.7%) | <.0001 |
| 25–49 Hospital Beds, N (%) | 24 (0.1%) | 20 (0.1%) | 2 (0.1%) | 2 (0.4%) | |
| 50–99 Hospital Beds, N (%) | 500 (2.2%) | 445 (2.2%) | 39 (1.9%) | 16 (3.1%) | |
| 100–199 Hospital Beds, N (%) | 2289 (10.2%) | 1901 (9.5%) | 318 (15.9%) | 70 (13.7%) | |

VA Author Manuscript

VA Author Manuscript

VA Author Manuscript

| Variable | Overall | Recommended | Off-Label | | P-value+ |
|---|---|---|---|---|---|
| | | | Underdosed | Overdosed | |
| | (N=22470) | (N=19953) | (N=2006) | (N=511) | |
| 200–299 Hospital Beds, N (%) | 1969 (8.8%) | 1691 (8.5%) | 218 (10.9%) | 60 (11.7%) | |
| 300–399 Hospital Beds, N (%) | 3143 (14.0%) | 2810 (14.1%) | 261 (13.0%) | 72 (14.1%) | |
| 400–499 Hospital Beds, N (%) | 4064 (18.1%) | 3601 (18.1%) | 381 (19.0%) | 82 (16.1%) | |
| 500+ Hospital Beds, N (%) | 9497 (42.3%) | 8644 (43.3%) | 678 (33.8%) | 175 (34.3%) | |
| Hospital Location, Missing, N (%) | 30 (0.1%) | 26 (0.1%) | 4 (0.2%) | 0 (0%) | <.0001 |
| Northeast, N (%) | 6529 (29.1%) | 5974 (29.9%) | 423 (21.1%) | 132 (25.8%) | |
| Midwest, N (%) | 3478 (15.5%) | 3197 (16.0%) | 225 (11.2%) | 56 (11.0%) | |
| South, N (%) | 9402 (41.8%) | 8156 (40.9%) | 997 (49.7%) | 249 (48.7%) | |
| West, N (%) | 3031 (13.5%) | 2600 (13.0%) | 357 (17.8%) | 74 (14.5%) | |

STD = standard deviation; COPD = chronic obstructive pulmonary disease; CRT-P = cardiac resynchronization therapy – pacemaker; CRT-D = cardiac resynchronization therapy – defibrillator; PCI = percutaneous coronary intervention; MI = myocardial infarction; ICD = implantable-cardioverter defibrillator; AF = atrial fibrillation; HMO = heatlh maintenance organization

VA Author Manuscript

VA Author Manuscript

VA Author Manuscript

**Table 2:**

Contribution to Hospital-Level Variation by Groups of Factors: All Factors, Patient-Level Factors, and Hospital-Level Factors

| Outcome | Variables | Reference Effect Measures* ranges and percentiles | | |
|---|---|---|---|---|
| | | Range | 10th | 90th |
| Underdosed† | All factors | [0.147, 5.496] | 0.289 | 3.224 |
| | Patient factors | [0.172, 4.325] | 0.328 | 2.826 |
| | Hospital factor | [0.669, 2.159] | 0.77 | 1.698 |
| Overdosed† | All factors | [0.017, 13.797] | 0.082 | 6.606 |
| | Patient factors | [0.017, 12.794] | 0.085 | 6.34 |
| | Hospital factors | [0.630, 1.187] | 0.63 | 1.187 |

*Compares patients within hospitals at specified percentiles of random effect distributions to similar patients in a reference, median hospital. Wider ranges indicate larger contributions to overall variation in outcome from variables.

†Patient and hospital factors for both the underdosed and overdosed models are outlined in Figure 2.