ORIGINAL RESEARCH

Association of Atrial Fibrillation and Oral Anticoagulant Use With Perioperative Outcomes After Major Noncardiac Surgery

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***Background*—**We examined the association of atrial fibrillation (AF) and oral anticoagulant use with perioperative death and bleeding among patients undergoing major noncardiac surgery.

***Methods and Results*—**A population-based study of patients aged 66 years and older who underwent elective (n=87 257) or urgent (n=35 930) noncardiac surgery in Ontario, Canada (April 2012 to March 2015) was performed. Outcomes were compared between AF groups using inverse probability of treatment weighting using the propensity score. Of 4612 urgent surgical patients with AF, treatments before surgery included warfarin (n=1619), a direct oral anticoagulant (DOAC) (n=729), and no anticoagulation (n=2264). After urgent surgery, the death rate within 30 days was significantly higher in patients with AF compared with patients with no AF (hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.12–1.45). In contrast, among 4769 elective surgical patients with AF treated with warfarin (n=1453), a DOAC (n=1165), or no anticoagulation (n=2151), prior AF was not associated with higher mortality. Comparing patients with AF who were or were not anticoagulated, there was no difference in 30-day mortality after urgent (HR, 0.95; 95% CI, 0.79–1.14) or elective (HR, 0.65; 95% CI, 0.38–1.09) surgery. There was no difference in 30-day mortality between patients with AF treated with a DOAC or warfarin after urgent (HR, 0.91; 95% CI, 0.70–1.18) or elective (HR, 1.64; 95% CI, 0.77–3.53) surgery. Bleeding and thromboembolic rates did not differ significantly among patients with AF prescribed a DOAC or warfarin.

***Conclusions*—**Prior AF was associated with 30-day mortality among patients undergoing urgent surgery. In patients with AF, neither the preoperative use of oral anticoagulants, nor the type of agent (either a DOAC or warfarin) were associated with the rate of 30-day mortality. **(*J Am Heart Assoc*. 2017;6:e006022. DOI: 10.1161/JAHA.117.006022.)**

Key Words: anticoagulation • atrial fibrillation • bleeding • direct oral anticoagulant • mortality • noncardiac surgery • perioperative outcomes • surgery • thromboembolic complications

Since their approval for stroke prevention, prescription rates for direct oral anticoagulants (DOACs) have risen steadily among patients with atrial fibrillation (AF) in North America. At present, they represent over 60% of new prescriptions and over one fifth of all oral anticoagulant prescriptions for such patients.[1–4] Many of these patients will eventually require surgical intervention, as it is estimated that over 50 million surgical procedures are performed yearly in the United States.[5] Among patients undergoing noncardiac surgery in prospective cohort registries, ≈7% have preexisting AF.[6]

While DOACs are being increasingly used, there is a paucity of information on the outcomes of patients with AF who are treated with anticoagulants who subsequently undergo major noncardiac surgery. Subgroup analysis of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation

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Accompanying Tables S1 through S12 are available at http://jaha.ahajournals.org/content/6/12/e006022/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Among patients with atrial fibrillation undergoing major noncardiac surgery, there was no excess risk of 30-day bleeding or death among those prescribed oral anticoagulants, and rates of these outcomes did not differ when a direct oral anticoagulant was compared with warfarin.

What Are the Clinical Implications?

- Although atrial fibrillation is an independent predictor of mortality in patients undergoing urgent noncardiac surgery, use of direct oral anticoagulants or warfarin do not explain their higher perioperative risk.

Therapy) trial[7] suggested that the risks of major bleeding did not differ between those prescribed dabigatran or warfarin, occurring in ≈3% of elective and 20% of urgent surgeries. More recently, an analysis of procedures performed during the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial[8] reported a 30-day major bleeding risk of only 1.6%, with more than one third of patients undergoing procedures without interrupting apixaban. Nonetheless, it is important to note that ≈90% of these surgeries were considered minor.

Outside of the clinical trial arena, there are limited data on perioperative outcomes of patients with AF who are treated with DOAC or warfarin. Accordingly, we examined the postoperative outcomes of patients with and without AF in Ontario, the most populous province of Canada, who subsequently underwent major noncardiac surgery of varying acuity —either elective or urgent procedures. Specifically, we examined the association between prescription of warfarin, a DOAC, or no anticoagulation in patients undergoing major surgery, with the rate of death or bleeding within 30 days. We hypothesized that outcomes among patients with AF would be influenced by the presence or absence of anticoagulation, as well as the specific type of anticoagulant prescribed. Furthermore, we hypothesized that there would be an association between the presence of preoperative AF and outcomes after urgent or elective major noncardiac surgical procedures.

Methods

Data Sources

Using each patient's unique encoded provincial health card number, we linked multiple administrative healthcare databases to create the study cohort. We used the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) to identify all hospitalizations and the CIHI National Ambulatory Care Reporting System Database (NACRS) to identify all emergency department visits. Noncardiac surgical procedures were identified using the Canadian Classification of Interventions codes in the CIHI-DAD and the CIHI Same Day Surgery database (CIHI-SDS). We examined the Ontario Registered Persons Database to ascertain deaths. We also used the Ontario Drug Benefit prescription database to identify funded drug prescriptions filled by individuals aged 65 years and older. Finally, physician billing claims were identified using the Ontario Health Insurance Plan database. The study was approved by the research ethics board of Sunnybrook Health Sciences Centre. There was no need for informed consent since this was an analysis of a population database.

Study Cohort

We included all patients aged 66 years and older who underwent an elective or urgent noncardiac surgical procedure at an acute care hospital in Ontario, Canada, between April 1, 2012 (first date of reimbursement of DOACs by the Ontario Drug Benefit plan), and March 31, 2015. To avoid incomplete medication records, we excluded participants without at least 1 year of eligibility for prescription drug coverage through the Ontario Drug Benefit. Fourteen prespecified major noncardiac surgeries were included: abdominal aortic aneurysm repair, carotid endarterectomy, peripheral vascular surgery, femur and hip surgery, knee replacement, lung resection, gastrectomy or esophagectomy, bowel and rectal surgery, liver resection, pancreaticoduodenectomy, abdominal hysterectomy, radical prostatectomy, nephrectomy, and cystectomy.[9,10] In the event of multiple surgeries performed during the study period, only the first qualifying surgery was used as the index procedure. A complete list of procedure codes is shown in Table S1.

Patients with AF were identified using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada* diagnostic code I48 recorded in any field of the CIHI-DAD, the CIHI-SDS, and the NACRS databases within 5 years before the index surgical procedure date. Code I48 has been previously validated and found to have a positive predictive value of 93.0% (95% confidence interval [CI], 91.6–94.2).[11] Other medical comorbidities were identified by examining secondary diagnosis codes from the index admission and all diagnoses recorded on any hospital admissions within 5 years before the index surgery to enhance sensitivity for detection of comorbidities. A complete list of diagnostic codes for comorbid conditions is shown in Table S2. We excluded from the study cohort patients undergoing dialysis, those with rheumatic heart disease, and those with valve replacements, since DOAC studies have not included these patient groups. We excluded patients who were prescribed both DOACs and warfarin within 30 days and

those with an insufficient medication supply to cover until the index hospitalization. We also excluded patients who were prescribed anticoagulants without a prior diagnosis of AF, as these drugs have alternate indications.

Anticoagulation Categories

Patients with AF were further classified based on their anticoagulation regimen as DOAC (dabigatran, rivaroxaban, or apixaban) users, warfarin users, or nonanticoagulated. We defined DOAC or warfarin users as those who were dispensed a new or refilled prescription for an anticoagulant with a sufficient number of days supplied such that the available days supply would cover the date of the index surgical hospitalization. Patients defined as nonanticoagulated were required to have not filled any prescription for an oral anticoagulant during the 100 days before the index surgical hospitalization. This allowed capture of all new and refilled prescriptions because the maximum duration of a single prescription in Ontario is 3 months supply. Patients who underwent noncardiac surgery with no history of AF and were not taking anticoagulants comprised a reference group.

Surgical Procedures

We categorized surgeries as urgent or elective based on the admission category variable contained within the CIHI-DAD. Surgeries were classified in this way because discontinuation of anticoagulants can be preplanned in patients with elective surgery, but not necessarily in those undergoing urgent/emergent procedures. The date of surgery was determined from the CIHI-DAD and CIHI-SDS databases.

Outcomes

The primary outcome was time to death attributable to any cause within 30 days of the date of the index surgical procedure. The secondary outcome was hemorrhagic events occurring within 30 days after surgery (either during index hospital admission or subsequent emergency visits or hospitalizations), and included intracerebral, intraocular, intraarticular, gastrointestinal, or other postsurgical bleeding, as previously described.[12,13] Diagnostic codes for bleeding have been previously published, found to have 94% sensitivity and 83% specificity in validation studies, and are shown in Table S3.[12] We also examined a related process measure: use of blood products, including transfusion of blood, platelets, or plasma during the index surgical admission or within 30 days after surgery, using the blood transfusion indicator in the CIHI-DAD. Finally, we examined thromboembolic events either occurring as an in-hospital complication or during a subsequent readmission within 30 days after surgery. Thromboembolic events were defined as myocardial infarction, stroke, transient ischemic attack, coronary thromboembolism, arterial embolism and thrombosis, intestinal ischemia, renal ischemia or infarction, vascular myelopathy, and atrial or ventricular thrombosis (see diagnostic codes in Table S4). The secondary outcomes that included hemorrhagic or thromboembolic events were treated as binary outcomes, since the timing of in-hospital bleeding events is not available in the CIHI-DAD.

Statistical Analysis

Categorical data were summarized as percentages, and differences between comparison groups were tested with the χ^2 test. Continuous variables were summarized as medians and interquartile ranges, and were compared using the Wilcoxon rank-sum test. Time to event was determined from the date of the surgical procedure. We used inverse probability of treatment (IPT) weighting using the propensity score to estimate the effect of: (1) anticoagulation versus no anticoagulation in patients with AF; and (2) DOAC versus warfarin among patients with AF who were anticoagulated. In the overall surgical cohort, we compared outcomes of: (1) AF versus no AF; and (2) nonanticoagulated AF versus no AF.[14] Therefore, 4 sets of propensity score weighted analyses were developed. Weighted Cox proportional hazards models were used to estimate the effects of exposure on the rate of mortality in the sample weighted by the IPT weights. We used weighted logistic regression analysis for 30-day bleeding and thromboembolic events because the in-hospital indicator variables for these outcomes were not supplemented with information on the time of the event. For both models, a robust, sandwich-type variance estimator was used to account for the within-subject correlation in outcomes induced by weighting.[15]

All propensity-weighted analyses accounted for the following covariates: age, sex, $CHADS_2$ comorbidities (ie, congestive heart failure, hypertension, diabetes mellitus, stroke, or transient ischemic attack), vascular disease, prior myocardial infarction, Charlson comorbidity score (0 or 1 versus $\geq$2), hospital admission via the emergency department, Johns Hopkins Aggregated Diagnosis Groups categories, and additional administratively coded elements of the HAS-BLED score including renal or liver disease, prior bleeding within the past year, and use of bleeding-relevant drugs (ie, antiplatelet agents, nonsteroidal anti-inflammatory drugs, and proton pump inhibitors). We also included the type of major surgery (eg, orthopedic, vascular, thoracic, abdominal, or urologic/pelvic) and hospital teaching status as covariates in the model. Weighted standardized differences were used to compare baseline covariates between exposure groups in the weighted samples.[16] All statistical analyses were

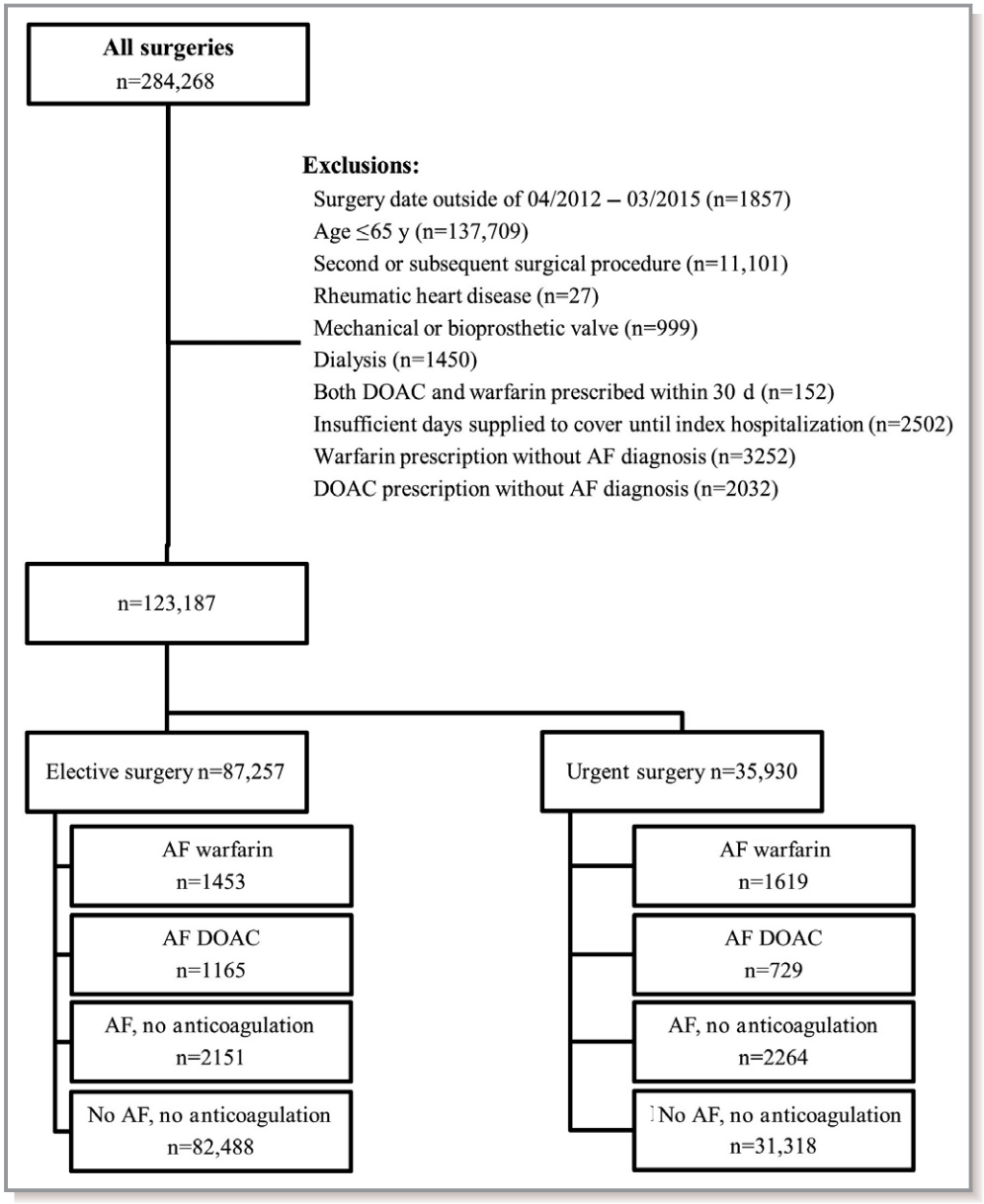

Figure 1. Patient flow diagram. AF indicates atrial fibrillation; DOAC, direct oral anticoagulant.

conducted separately in patients undergoing elective surgery and in those undergoing urgent surgery.

Statistical significance was defined by a 2-sided $P<0.05$. Analyses were performed with SAS software (version 9.4; SAS Institute Inc).

Results

Study Cohorts

A total of 284 268 patients underwent a surgical procedure during the study period. After exclusions, the elective surgery cohort consisted of 87 257 patients while the urgent surgery cohort consisted of 35 930 patients (Figure 1). In the elective surgery cohort, 4769 (5.5%) patients had AF; of these, 1453 (30.5%) were prescribed warfarin, 1165 (24.4%) were prescribed a DOAC, and 2151 (45.1%) were nonanticoagulated. In the urgent surgery cohort, 4612 (12.8%) patients had AF, of whom 1619 (35.1%) were prescribed warfarin, 729 (15.8%) were prescribed a DOAC, and 2264 (49.1%) were nonanticoagulated. Within the DOAC group, dabigatran (n=998, 53%), rivaroxaban (n=687, 36%), and apixaban (n=209, 11%) were prescribed.

Baseline characteristics of patients within the elective cohort are presented in Table 1. Patients undergoing elective surgery with AF treated with warfarin were slightly older and

exhibited higher rates of heart failure, stroke, and diabetes mellitus than patients with AF treated with a DOAC or those who were not anticoagulated. Patients treated with warfarin and nonanticoagulated AF had higher frequency of Charlson index ≥2. However, prior bleeding within 1 year was similar between the 3 AF groups. Baseline characteristics for the urgent surgical cohort are shown in Table 2. Among the urgent surgical cohort, comorbidities were of similar magnitude between anticoagulation categories. Specifically, patients taking warfarin had higher rates of heart failure; patients taking DOAC and warfarin had higher rates of prior stroke, and those who were not anticoagulated exhibited a higher prevalence of coronary disease or myocardial infarction. Overall, however, there was no significant difference in the prevalence of Charlson index ≥2 between the 3 AF groups. Prior bleeding within 1 year was highest among urgent surgical patients receiving a DOAC and those who were not anticoagulated. Patients prescribed warfarin had higher $CHADS_2$ score, followed by those taking DOAC and those who were not anticoagulated. The most common surgical interventions were orthopedic and abdominal surgeries in both elective and urgent AF cohorts.

The majority of the patients with elective surgery underwent surgery on the day of admission, with a median (interquartile range) time from admission to surgery of 0 (0–0) days for all 4 exposure categories: no AF, AF-warfarin, AF-DOAC, and AF-no anticoagulation. The majority of patients in the urgent surgery group (>85%) were admitted via the emergency department and presented to the hospital by ambulance. In the urgent surgical cohort, the median time from admission to surgery for patients with AF was 2 (1–2) days for AF-warfarin, 2 (1–3) days for AF-DOAC, and 1 (1–2) day for AF-no anticoagulation, while those with no AF underwent surgery 1 (0–2) day after admission.

Perioperative Event Rates

Unadjusted outcomes for perioperative mortality are presented in Table 3 and Figure 2. Within the elective surgery cohort, 30-day mortality for patients with AF was 1.7% for those dispensed warfarin, 1.3% for those dispensed a DOAC, and 2.2% for those who were not anticoagulated. Mortality at 30 days was 0.6% in patients without AF who were not anticoagulated.

Within the urgent surgical cohort, 30-day mortality was 14.1% in patients with AF treated with warfarin, 11.7% in patients with AF dispensed a DOAC, and 14.3% in patients with AF who were not anticoagulated. The 30-day mortality rate was 7.8% in patients without AF who were nonanticoagulated. Thromboembolic events are also shown in Table 3. There were significant differences between treatment groups, with the lowest rates of thromboembolic events in patients prescribed a DOAC and patients without AF. The highest rates were observed in patients with nonanticoagulated AF followed by patients treated with warfarin.

The unadjusted 30-day bleeding outcomes are also shown in Table 3. While crude bleeding risks were highest in patients who were prescribed warfarin or a DOAC, the absolute increase in this risk was modest in comparison to patients with AF who were nonanticoagulated. For warfarin, DOAC, and nonanticoagulated AF, the respective bleeding rates were 6.6%, 7.0%, and 5.5% in the elective surgery and 10.1%, 9.1%, and 8.3% in the urgent surgery cohorts. In addition, the absolute increase in bleeding risks among patients prescribed warfarin or a DOAC were only 2% to 3% higher than the low-risk group of nonanticoagulated patients without AF. Irrespective of anticoagulation status, the median length of stay among patients with AF was increased by ≈1 day in the elective surgery group and 2 to 3 days in the urgent surgical cohort, compared with patients without AF (Table 3).

As shown in Figure 2, the incidence of bleeding events exceeded that of mortality in those undergoing elective surgical procedures. However, the opposite effects were observed after urgent surgery, such that death was more common than bleeding (shown in Figure 3).

Perioperative Outcomes of Patients With AF in Relation to Oral Anticoagulant Use

Comparing patients with AF who were anticoagulated versus patients with AF who were not anticoagulated, standardized differences for all covariates in the sample weighted by the IPT weights were <0.10 for both the elective and urgent surgery cohorts (Tables S5 and S6). After adjustment with IPT weighting using the propensity score, the rate of death within 30 days was similar in both patients with anticoagulated and nonanticoagulated AF undergoing elective or urgent surgical major surgery (Figure 4A). There was no significant difference in the odds of 30-day thromboembolic events among patients undergoing elective (odds ratio, 0.88; 95% confidence interval, 0.52–1.50 [*P*=0.645]) or urgent (odds ratio, 0.79; 95% confidence interval, 0.59–1.07 [*P*=0.127]) surgery when patients with anticoagulated AF were compared to patients with nonanticoagulated AF (reference group) after IPT weighting–propensity score adjustment. The 30-day perioperative risk of bleeding was also not significantly different among patients with AF who were or were not anticoagulated.

When comparing patients with AF who were anticoagulated with either a DOAC or warfarin, standardized differences for all covariates were <0.10 in the weighted sample for the elective and urgent surgery cohorts (Tables S7 and S8). After adjustment with IPT weighting using the propensity score, the rate of death within 30 days was not significantly different in

Table 1. Elective Surgery: Baseline Cohort Characteristics

Group	No Anticoagulation* No AF	AF With Warfarin	AF With DOAC	AF With No Anticoagulation	*P* Value†
No.	82 488	1453	1165	2151	
Age, median (IQR)	73 (69–78)	78 (73–82)	76 (72–81)	76 (71–81)	<0.001
Men, No. (%)	34 225 (41.5)	774 (53.3)	610 (52.4)	1151 (53.5)	0.814
Teaching hospital, No. (%)	24 885 (30.2)	509 (35.0)	360 (30.9)	724 (33.7)	0.079
Medical history, No. (%)					
Coronary disease	8170 (9.9)	475 (32.7)	331 (28.4)	751 (34.9)	<0.001
Previous MI	3083 (3.7)	170 (11.7)	123 (10.6)	352 (16.4)	<0.001
Congestive heart failure	1498 (1.8)	329 (22.6)	235 (20.2)	315 (14.6)	<0.001
Cerebrovascular disease	2866 (3.5)	178 (12.3)	119 (10.2)	163 (7.6)	<0.001
PVD	3917 (4.7)	151 (10.4)	99 (8.5)	211 (9.8)	0.253
Diabetes mellitus	16 362 (19.8)	450 (31.0)	305 (26.2)	540 (25.1)	<0.001
Hypertension	31 396 (38.1)	942 (64.8)	762 (65.4)	1297 (60.3)	0.003
Hyperlipidemia	6858 (8.3)	256 (17.6)	195 (16.7)	419 (19.5)	0.114
COPD	5652 (6.9)	222 (15.3)	141 (12.1)	294 (13.7)	0.063
Chronic kidney disease	1469 (1.8)	120 (8.3)	41 (3.5)	110 (5.1)	<0.001
Malignancy	3825 (4.6)	84 (5.8)	49 (4.2)	150 (7.0)	0.005
Dementia	844 (1.0)	25 (1.7)	22 (1.9)	72 (3.3)	0.003
Charlson index ≥2	30 168 (36.6)	870 (59.9)	587 (50.4)	1225 (57.0)	<0.001
CHADS 0–2	76 848 (93.2)	1011 (69.6)	876 (75.2)	1725 (80.2)	<0.001
CHADS 3 or 4	5416 (6.6)	407 (28.0)	266 (22.8)	394 (18.3)	
CHADS 5 or 6	224 (0.3)	35 (2.4)	23 (2.0)	32 (1.5)	
Bleeding in past year	6002 (7.3)	214 (14.7)	162 (13.9)	314 (14.6)	0.816
Medications, No. (%)‡					
Antiplatelet	4791 (5.8)	41 (2.8)	14 (1.2)	223 (10.4)	<0.001
ACEI or ARB	34 242 (41.5)	836 (57.5)	633 (54.3)	998 (46.4)	<0.001
β-Blocker	15 514 (18.8)	844 (58.1)	684 (58.7)	976 (45.4)	<0.001
Calcium channel blocker	20 000 (24.2)	531 (36.5)	422 (36.2)	676 (31.4)	0.002
Diuretic	15 888 (19.3)	599 (41.2)	401 (34.4)	537 (25.0)	<0.001
Statin	35 527 (43.1)	872 (60.0)	664 (57.0)	1075 (50.0)	<0.001
NSAID	11 749 (14.2)	66 (4.5)	75 (6.4)	210 (9.8)	<0.001
PPI	21 011 (25.5)	499 (34.3)	404 (34.7)	705 (32.8)	0.452
Surgery, No. (%)					
Abdominal	12 033 (14.6)	270 (18.6)	183 (15.7)	446 (20.7)	<0.001
Orthopedic	51 015 (61.8)	878 (60.4)	724 (62.1)	1218 (56.6)	
Thoracic	3481 (4.2)	58 (4.0)	63 (5.4)	138 (6.4)	
Urologic or pelvic	11 733 (14.2)	124 (8.5)	101 (8.7)	198 (9.2)	
Vascular	4226 (5.1)	123 (8.5)	94 (8.1)	151 (7.0)	
Mini-invasive	9174 (11.1)	185 (12.7)	149 (12.8)	292 (13.6)	0.707

Continued

Table 1. Continued

Group	No Anticoagulation* No AF	AF With Warfarin	AF With DOAC	AF With No Anticoagulation	*P* Value†
Admission characteristics, No. (%)					
Ambulance	556 (0.7)	28 (1.9)	14 (1.2)	49 (2.3)	0.096
Elective admission	80 604 (97.7)§	1420 (97.7)	1138 (97.7)	2102 (97.7)	0.916

ACEI indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PVD, peripheral vascular disease.
*Unless otherwise indicated, all $P<0.001$ for comparison of atrial fibrillation (AF) with no anticoagulation vs AF.
†*P* values for comparison of patients with AF treated with a direct oral anticoagulant (DOAC), warfarin, or no anticoagulation.
‡Medications prescribed within 1 year before admission.
§For comparison of AF with no anticoagulation vs AF, *P*=not significant.

patients who were treated with a DOAC or warfarin preoperatively (Figure 4B), with no significant difference after either elective or urgent major surgical procedures. There was a trend to lower odds of 30-day thromboembolic events after elective surgery (odds ratio, 0.57; 95% CI, 0.29–1.11 [*P*=0.097]) favoring DOACs over warfarin, but there was no difference between drug classes after urgent surgical procedures (odds ratio, 1.01; 95% CI, 0.63–1.64 [*P*=0.958]). Risk of bleeding perioperatively within 30 days was also not significantly different in the comparison between a DOAC and warfarin.

Outcomes Comparing AF Versus No AF

When patients with AF were compared with patients without AF, the comparator groups were well-matched after weighting using the IPT weights (Tables S9 and S10). The rate of death within 30 days was increased only among patients who underwent urgent major surgery (HR, 1.28; 95% CI, 1.12–1.45) (Figure 5A). There was no significant increase in bleeding risk among patients with AF compared to those without AF (Figure 5A).

Patients with AF who were not anticoagulated exhibited standardized differences <0.10 when compared with patients without AF after weighting with the IPT weights (Tables S11 and S12). Again, the rate of mortality was not significantly different when patients with elective surgery were compared. However, the rate of death was higher for patients with AF undergoing urgent surgery who were not anticoagulated when compared with patients without AF (1.34; 95% CI, 1.12–1.59) (Figure 5B). There was no difference in bleeding risk between patients with AF who were not anticoagulated compared with patients without AF (Figure 5B).

Discussion

AF is a prevalent condition that is treated using oral anticoagulation as a cornerstone for the prevention of stroke. In patients with nonvalvular AF, both the European Society of Cardiology and the Canadian Society of Cardiology now recommend DOACs over warfarin as the anticoagulant of choice.[17,18] Surgical procedures are commonly performed in patients who have AF, and the outcomes of these procedures can potentially be impacted by AF and the concomitant use of anticoagulants. In this study of patients undergoing major noncardiac surgery, our findings are 2-fold. First, among patients with AF, regardless of the urgency of surgery, the use of anticoagulation, and specifically DOAC compared with warfarin, was not associated with an increased risk of death or bleeding after propensity score–weighted adjustment. Second, preexisting AF was associated with an increased rate of mortality within 30 days in patients with AF who underwent urgent but not elective surgery. Our findings suggest that AF represents an independent predictor of perioperative mortality in urgent major noncardiac surgery, which appeared not to be mediated by use of oral anticoagulation or hemorrhagic events.

Prior studies examining perioperative outcomes of patients treated with DOAC mainly included elective or minor surgical procedures with lower associated risks. In a post hoc analysis of the RE-LY trial, involving 4591 patients, over 90% of interventions were performed electively and accurate classification of surgery into major/minor categories was only available in 28% of cases. Dabigatran was withheld for at least 24 hours and up to 5 days, depending on the perceived risk of bleeding and patients' renal function. Based on this protocol, the 30-day risk of major bleeding ranged from 6.1% to 7.8%, and was similar among patients treated with dabigatran 110 mg, dabigatran 150 mg, or warfarin.[7] The prospective Dresden registry, which enrolled office- and hospital-based patients on a nonconsecutive basis, reported on 595 DOAC-treated patients (in whom 80% were prescribed for AF indications) who underwent 863 procedures, with ≈10% being major surgery. In this subgroup of DOAC-treated patients who underwent elective major surgery, the all-cause mortality and major bleeding rates at 30 days were 0.7% and

Table 2. Urgent Surgery: Baseline Cohort Characteristics

Group	No Anticoagulation* No AF	AF With Warfarin	AF With DOAC	AF With No Anticoagulation	*P* Value†
No.	31 318	1619	729	2264	
Age, median (IQR)	82 (75–88)	85 (80–89)	83 (78–88)	85 (79–90)	<0.001
Men, No. (%)	9692 (30.9)	594 (36.7)	264 (36.2)	875 (38.6)	0.328
Teaching hospital	8420 (26.9)‡	485 (30.0)	184 (25.2)	670 (29.6)	0.047
Medical history, No. (%)					
Coronary disease	4873 (15.6)	576 (35.6)	238 (32.6)	841 (37.1)	0.084
Previous MI	2627 (8.4)	288 (17.8)	115 (15.8)	482 (21.3)	<0.001
Congestive heart failure	2549 (8.1)	706 (43.6)	278 (38.1)	727 (32.1)	<0.001
Cerebrovascular disease	2386 (7.6)	330 (20.4)	150 (20.6)	350 (15.5)	<0.001
PVD	1971 (6.3)	189 (11.7)	71 (9.7)	240 (10.6)	0.331
Diabetes mellitus	6522 (20.8)	447 (27.6)	207 (28.4)	639 (28.2)	0.890
Hypertension	14 377 (45.9)	1116 (68.9)	503 (69.0)	1499 (66.2)	0.138
Hyperlipidemia	2770 (8.8)	262 (16.2)	120 (16.5)	364 (16.1)	0.971
COPD	3792 (12.1)	379 (23.4)	166 (22.8)	481 (21.2)	0.260
Chronic kidney disease	1487 (4.7)	260 (16.1)	48 (6.6)	290 (12.8)	<0.001
Malignancy	1814 (5.8)‡	65 (4.0)	32 (4.4)	110 (4.9)	0.452
Dementia	5944 (19.0)	310 (19.1)	136 (18.7)	570 (25.2)	<0.001
Charlson index ≥2	12 899 (41.2)	1067 (65.9)	450 (61.7)	1501 (66.3)	0.070
CHADS 0–2	25 941 (82.8)	784 (48.4)	385 (52.8)	1316 (58.1)	<0.001
CHADS 3 or 4	4959 (15.8)	727 (44.9)	295 (40.5)	846 (37.4)	
CHADS 5 or 6	418 (1.3)	108 (6.7)	49 (6.7)	102 (4.5)	
Bleeding in past year	1790 (5.7)	169 (10.4)	96 (13.2)	305 (13.5)	0.014
Medications, No. (%)§					
Antiplatelet	2911 (9.3)	52 (3.2)	24 (3.3)	302 (13.3)	<0.001
ACEI or ARB	11 237 (35.9)	749 (46.3)	335 (46.0)	787 (34.8)	<0.001
β-Blocker	5974 (19.1)	869 (53.7)	406 (55.7)	880 (38.9)	<0.001
Calcium channel blocker	7520 (24.0)	590 (36.4)	230 (31.6)	582 (25.7)	<0.001
Diuretic	6388 (20.4)	795 (49.1)	331 (45.4)	748 (33.0)	<0.001
Statin	10 159 (32.4)	794 (49.0)	364 (49.9)	800 (35.3)	<0.001
NSAID	2057 (6.6)	53 (3.3)	21 (2.9)	93 (4.1)	0.198
PPI	8522 (27.2)	619 (38.2)	296 (40.6)	786 (34.7)	0.006
Surgery, No. (%)					
Abdominal	5774 (18.4)‡	259 (16.0)	138 (18.9)	394 (17.4)	0.136
Orthopedic	23 935 (76.4)‡	1262 (77.9)	548 (75.2)	1744 (77.0)	
Thoracic	153 (0.5)‡	12 (0.7)	7 (1.0)	12 (0.5)	
Urologic or pelvic	208 (0.7)‡	6 (0.4)	6 (0.8)	SC	
Vascular	1248 (4.0)‡	80 (4.9)	30 (4.1)	110 (4.9)	
Mini-invasive	1012 (3.2)‖	51 (3.2)	30 (4.1)	59 (2.6)	0.112

Continued

Table 2. Continued

Group	No Anticoagulation* No AF	AF With Warfarin	AF With DOAC	AF With No Anticoagulation	*P* Value†
Admission characteristics, No. (%)					
Ambulance	23 570 (75.3)	1309 (80.9)	563 (77.2)	1820 (80.4)	0.108
Emergency admission	27 013 (86.3)‖	1402 (86.6)	630 (86.4)	1920 (84.8)	0.241

ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PVD, peripheral vascular disease.
*Unless otherwise indicated, all $P<0.001$ for comparison of atrial fibrillation (AF) with no anticoagulation vs AF.
†*P* values for comparison of patients with AF treated with a direct oral anticoagulant (DOAC), warfarin, or no anticoagulation.
‡For comparison of AF with no anticoagulation vs AF, $P<0.01$.
§Medications prescribed within 1 year before admission.
‖For comparison of AF with no anticoagulation vs AF, *P*=not signficiant.

8.0%, respectively.[19] Our study served to confirm and extend these findings on a population-based level for patients undergoing elective major noncardiac surgery.

Unlike the lower-risk surgical spectrum, there are limited data on the outcomes of patients with anticoagulated AF undergoing urgent, unplanned, major noncardiac surgery at a time when DOACs are commonly prescribed. The RE-LY substudy reported the outcomes of 353 patients who underwent urgent surgery, of whom ≈60% were classified as major (orthopedic, abdominal, or vascular) surgery. The remainder included pacemakers, diagnostic procedures, and other same day procedures. In this cohort, the 30-day all-cause mortality and major bleeding rates were 3.3% and 18.9%, respectively. No differences in these outcomes were observed among patients treated with dabigatran (110 or 150 mg) or warfarin.[20] In our urgent surgical AF cohort, consisting of 4769 patients, the 30-day all-cause mortality and major bleeding rates were 13.4% and 8.8%. When compared with the RE-LY subset, the 30-day mortality rate of our urgent surgical cohort was 4-fold higher whereas

Table 3. Thirty-Day Perioperative Outcomes

Elective Surgery	No Anticoagulation No AF	AF With Warfarin	AF With DOAC	AF With No Anticoagulation	*P* Value
No.	82 488	1453	1165	2151	
Length of stay, median (IQR)	3 (3–5)	4 (3–7)	4 (3–6)	4 (3–7)	<0.001
Mortality, No. (%)	509 (0.6)	25 (1.7)	15 (1.3)	47 (2.2)	<0.001
Thromboembolic event, No. (%)	971 (1.2)	29 (2.0)	13 (1.1)	44 (2.0)	<0.001
Ischemic stroke, No. (%)	147 (0.2)	6 (0.4)	SCs	9 (0.4)	0.008
Bleeding, No. (%)	3203 (3.9)	96 (6.6)	81 (7.0)	118 (5.5)	<0.001
Blood transfusion, No. (%)	8590 (10.4)	259 (17.8)	140 (12.0)	372 (17.3)	<0.001
Platelet or plasma products, No. (%)	611 (0.7)	38 (2.6)	17 (1.5)	40 (1.9)	<0.001
Urgent Surgery	**No Anticoagulation No AF**	**AF With Warfarin**	**AF With DOAC**	**AF With No Anticoagulation**	***P* Value**
No.	31 318	1619	729	2264	
Length of stay, median (IQR)	9 (6–16)	11 (7–21)	12 (7–19)	11 (6–19)	<0.001
Mortality, No. (%)	2446 (7.8)	228 (14.1)	85 (11.7)	324 (14.3)	<0.001
Thromboembolic event, No. (%)	1197 (3.8)	75 (4.6)	29 (4.0)	125 (5.5)	<0.001
Ischemic stroke, No. (%)	198 (0.6)	21 (1.3)	10 (1.4)	26 (1.2)	<0.001
Bleeding, No. (%)	2211 (7.1)	163 (10.1)	66 (9.1)	188 (8.3)	<0.001
Blood transfusion, No. (%)	11 104 (35.5)	619 (38.2)	251 (34.4)	922 (40.7)	<0.001
Platelet or plasma products, No. (%)	874 (2.8)	197 (12.2)	35 (4.8)	97 (4.3)	<0.001

AF indicates atrial fibrillation; DOAC, direct oral anticoagulant; IQR, interquartile range; SCs, small cells (unable to report because of privacy regulations).

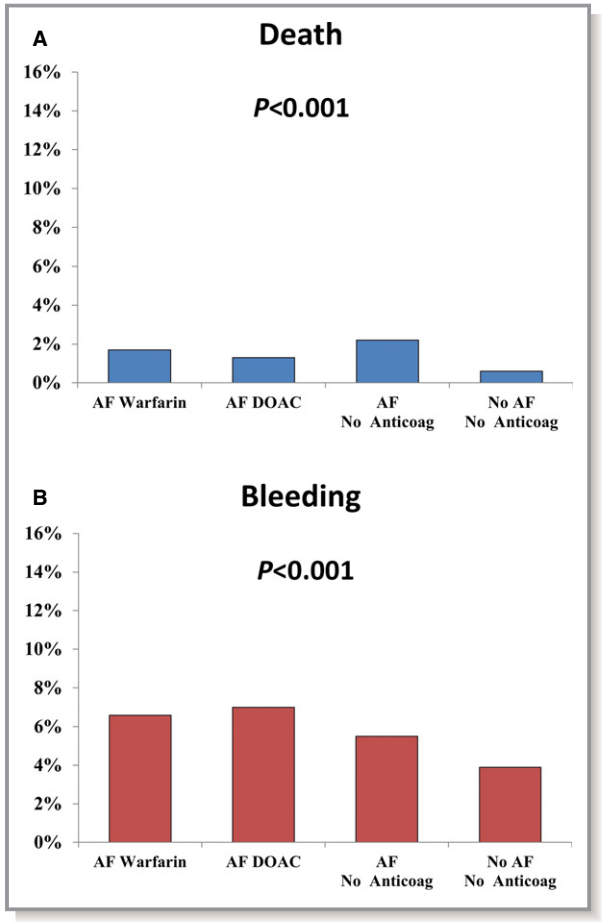

Figure 2. Unadjusted 30-day mortality (A) and bleeding (B) in patients undergoing elective major surgery. AF indicates atrial fibrillation; DOAC, direct oral anticoagulant.

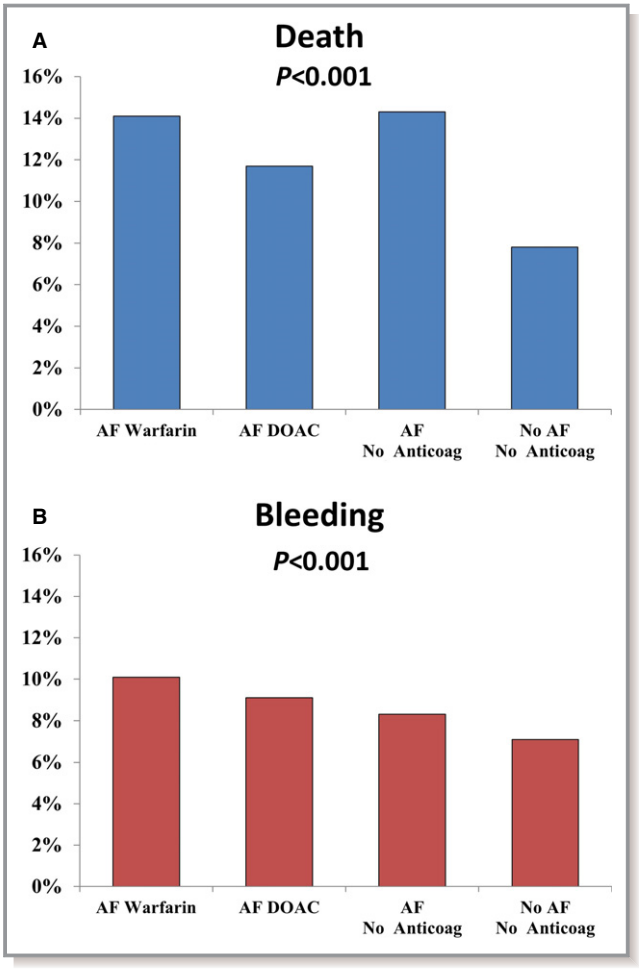

Figure 3. Unadjusted 30-day mortality (A) and bleeding (B) in patients undergoing urgent major surgery. AF indicates atrial fibrillation; DOAC, direct oral anticoagulant.

bleeding rates were lower. These differences may be attributed to the population-based approach, including consecutive patients, limiting participant bias that could impact clinical trials. Furthermore, the majority of patients (≈85%) arrived at hospital via ambulance, reflecting the urgency and unplanned nature of their clinical presentation. Finally, our urgent surgical cohort was on average 10 years older and had greater comorbidity burden than the RE-LY cohort. All of the above factors may have contributed to the greater risk of death than competing bleeding events.

Presently, expert/consensus guidelines recommend that DOAC agents be withheld for 24 to 48 hours before performance of invasive procedures.[21,22] Notably, these recommendations are based on the largely predictable (but not readily measurable) pharmacokinetic profile of DOAC agents. To date, however, there are no published randomized trial data on the optimal timing of DOAC cessation before invasive procedures or surgeries. Although stopping DOACs for patients at 24 to 48 hours before elective surgery is logistically feasible, it is likely much more difficult to implement such recommendations when patients require urgent, unplanned, major noncardiac surgery. In our study, we observed, on average, a 24-hour delay from hospital admission to urgent surgery between patients with AF who were treated with and without oral anticoagulation, which may have been driven by physicians' decision to wait for the effect of anticoagulants to be attenuated between proceeding with surgery. In spite of this time delay, the 30-day mortality and bleeding rates were similar between patients with anticoagulated and nonanticoagulated AF undergoing urgent surgery. Accordingly, our study provided pertinent data on perioperative outcomes of this high-risk cohort during a time when reversal agents for DOAC were not clinically available.[23,24]

Furthermore, our study suggested that patients with a preoperative diagnosis of AF undergoing major noncardiac surgery harbored an intrinsic risk of death, which extended beyond their existing comorbidities, irrespective of anticoagulant use. This finding was observed among patients undergoing urgent but not elective surgery. After extensive

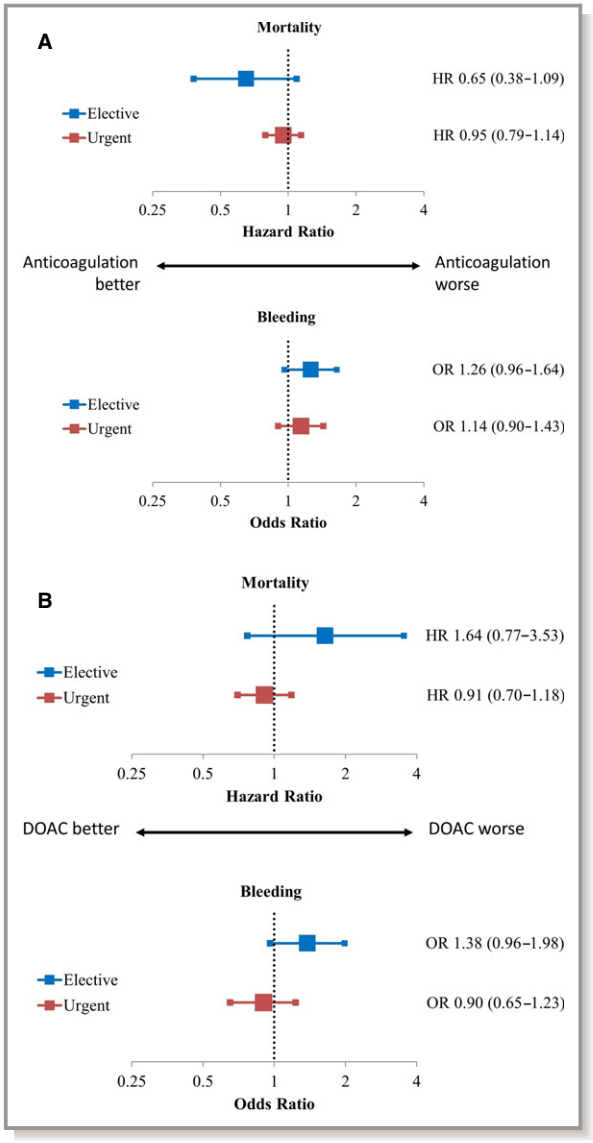

Figure 4. Adjusted mortality and bleeding outcomes when comparing patients with anticoagulated atrial fibrillation (AF) vs nonanticoagulated AF (A) and direct oral anticoagulant (DOAC) AF vs warfarin AF (B). HR indicates hazard ratio; OR, odds ratio.

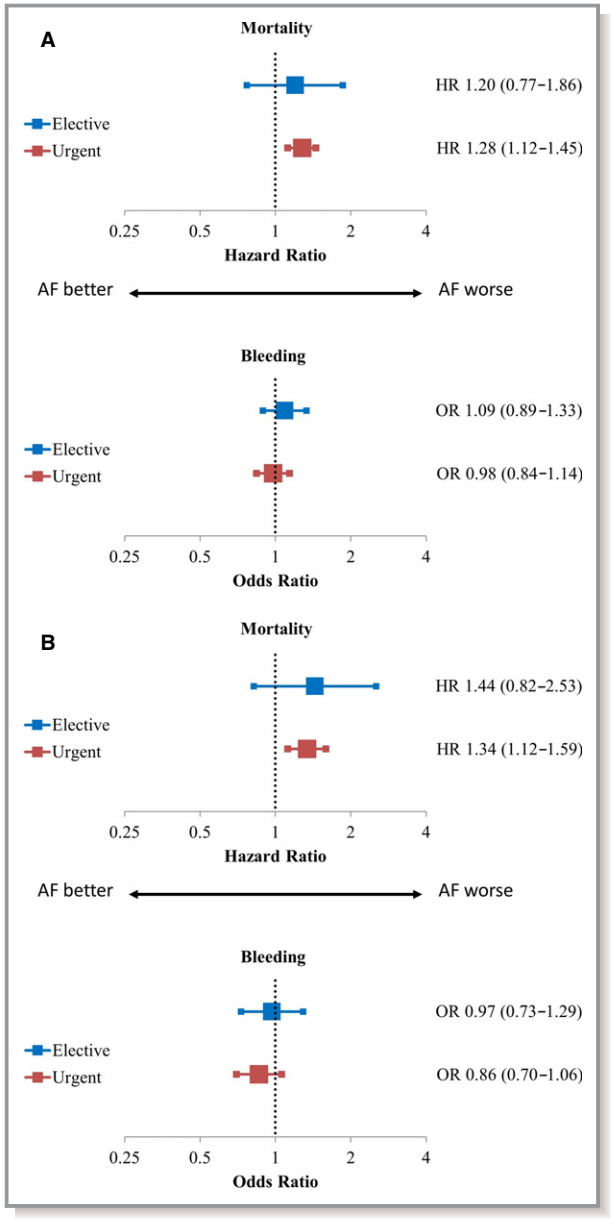

Figure 5. Adjusted mortality and bleeding outcomes when comparing patients with anticoagulated atrial fibrillation (AF) vs patients without AF (A) and nonanticoagulated AF vs patients without AF (B). HR indicates hazard ratio; OR, odds ratio.

adjustment for baseline covariates, we found that patients with AF exhibited an ≈30% increased risk of death at 30 days after urgent, major noncardiac surgery when compared with patients without AF. Furthermore, our study suggested that the higher risk of death in the AF cohort did not appear to be mediated by postoperative bleeding, given the comparable rates between the 2 groups. Increasingly, AF is being recognized as a major risk factor for adverse perioperative outcomes after major noncardiac surgery. In an earlier study, van Diepen et al[10] reported that patients with AF had a 69% increased risk of death when compared with patients with stable coronary artery disease. However, they did not elucidate whether use of oral anticoagulation and associated bleeding events were mechanisms underlying the increased mortality risk. McAlister et al[6] reported a higher risk of cardiovascular death, heart failure, and myocardial injury among 961 patients with AF postoperatively in the VISION (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation) registry. Our study adds to the growing knowledge base on the adverse prognostic impact of patients with AF who undergo noncardiac surgery. Further work, however, is needed to better delineate the mechanisms accounting for worse perioperative outcomes in the AF population.

Study Limitations

A number of limitations of this study should be noted. Because we relied on dispensing data from the provincial pharmacare database to determine anticoagulation status, we were not able to ascertain compliance and adherence of paients who filled their prescriptions, as well as the exact stop date before surgery. We also could not account for out-of-pocket payment of DOACs, although we anticipate that this only involved a small proportion of patients because these medications are covered under the Ontario Drug Benefit formulary. Furthermore, the consistency in bleeding rates in our study with those from clinical trial and registry data suggest that the above were not significant factors in the study. Our study did not capture the use of reversal agents or account for the use of bridging therapy since they were not available during the time of study. The data sources also did not capture medications administered during the inpatient hospitalization, specifically use of oral or parenteral anticoagulation during the early postoperative period. However, any potential differences in postoperative anticoagulation did not translate into significant differences in bleeding between treatment (or nontreatment) groups. In addition, propensity-weighted analyses account for known confounders, and it is possible that some as-yet unmeasured factor may have influenced the effects observed. Urgency was determined using the CIHI-DAD, which indicates whether the hospital admission was elective or urgent and has been validated.[25] However, it could not be further delineated whether urgent procedures were surgical emergencies. Finally, our study identified patients who underwent major surgery as the point of inception. Therefore, it is possible that certain high-risk individuals who were deemed unsuitable for surgery were not represented in this study. However, our study was designed to address the outcomes of patients who underwent noncardiac surgery, and did not intend to examine the outcomes of all patients who might be eligible for major surgery.

Conclusions

Among patients who underwent major noncardiac surgery, patients with preoperative AF who were treated with oral anticoagulation had similar rates of death and bleeding when compared with nonanticoagulated patients. In addition, we found that patients who were treated with DOACs or warfarin had similar death and bleeding outcomes after major noncardiac surgery. Finally, patients with preoperative AF exhibited greater mortality risk after major noncardiac surgery performed on an urgent basis, suggesting the need for further investigations into the mechanisms underlying the adverse outcomes associated with this common arrhythmia.

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References

1. Kirley K, Qato DM, Kornfield R, Stafford RS, Alexander GC. National trends in oral anticoagulant use in the United States, 2007 to 2011. *Circ Cardiovasc Qual Outcomes*. 2012;5:615–621.
2. Xu Y, Holbrook AM, Simpson CS, Dowlatshahi D, Johnson AP. Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis. *CMAJ Open*. 2013;1:E115–E119.
3. Desai NR, Krumme AA, Schneeweiss S, Shrank WH, Brill G, Pezalla EJ, Spettell CM, Brennan TA, Matlin OS, Avorn J, Choudhry NK. Patterns of initiation of oral anticoagulants in patients with atrial fibrillation—quality and cost implications. *Am J Med*. 2014;127:1075–1082.e1.
4. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma CS, Zint K, Elsaesser A, Bartels DB, Lip GY. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry Phase 2. *J Am Coll Cardiol*. 2017;69:777–785.
5. Patel AY, Eagle KA, Vaishnava P. Cardiac risk of noncardiac surgery. *J Am Coll Cardiol*. 2015;66:2140–2148.
6. McAlister FA, Jacka M, Graham M, Youngson E, Cembrowski G, Bagshaw SM, Pannu N, Townsend DR, Srinathan S, Alonso-Coello P, Devereaux PJ. The prediction of postoperative stroke or death in patients with preoperative atrial fibrillation undergoing non-cardiac surgery: a VISION sub-study. *J Thromb Haemost*. 2015;13:1768–1775.
7. Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S, Themeles E, Heidbuchel H, Avezum A, Reilly P, Connolly SJ, Yusuf S, Ezekowitz M. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation*. 2012;126:343–348.

8. Garcia D, Alexander JH, Wallentin L, Wojdyla DM, Thomas L, Hanna M, Al-Khatib SM, Dorian P, Ansell J, Commerford P, Flaker G, Lanas F, Vinereanu D, Xavier D, Hylek EM, Held C, Verheugt FW, Granger CB, Lopes RD. Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing procedures. *Blood*. 2014;124:3692–3698.
9. Wijeysundera DN, Austin PC, Beattie WS, Hux JE, Laupacis A. Outcomes and processes of care related to preoperative medical consultation. *Arch Intern Med*. 2010;170:1365–1374.
10. van Diepen S, Bakal JA, McAlister FA, Ezekowitz JA. Mortality and readmission of patients with heart failure, atrial fibrillation, or coronary artery disease undergoing noncardiac surgery: an analysis of 38 047 patients. *Circulation*. 2011;124:289–296.
11. Atzema CL, Austin PC, Miller E, Chong AS, Yun L, Dorian P. A population-based description of atrial fibrillation in the emergency department, 2002 to 2010. *Ann Emerg Med*. 2013;62:570–577.e7.
12. Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Hellings C, Juurlink DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ*. 2013;185:E121–E127.
13. Maura G, Blotiere PO, Bouillon K, Billionnet C, Ricordeau P, Alla F, Zureik M. Comparison of the short-term risk of bleeding and arterial thromboembolic events in nonvalvular atrial fibrillation patients newly treated with dabigatran or rivaroxaban versus vitamin K antagonists: a French nationwide propensity-matched cohort study. *Circulation*. 2015;132:1252–1260.
14. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424.
15. Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. *Stat Med*. 2013;32:2837–2849.
16. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661–3679.
17. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
18. Verma A, Cairns JA, Mitchell LB, Macle L, Stiell IG, Gladstone D, McMurtry MS, Connolly S, Cox JL, Dorian P, Ivers N, Leblanc K, Nattel S, Healey JS. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2014;30:1114–1130.
19. Beyer-Westendorf J, Gelbricht V, Forster K, Ebertz F, Kohler C, Werth S, Kuhlisch E, Stange T, Thieme C, Daschkow K, Weiss N. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. *Eur Heart J*. 2014;35:1888–1896.
20. Douketis JD, Healey JS, Brueckmann M, Fraessdorf M, Spyropoulos AC, Wallentin L, Oldgren J, Reilly P, Ezekowitz MD, Connolly SJ, Yusuf S, Eikelboom JW. Urgent surgery or procedures in patients taking dabigatran or warfarin: analysis of perioperative outcomes from the RE-LY trial. *Thromb Res*. 2016;139:77–81.
21. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104.
22. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17:1467–1507.
23. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW, Kreuzer J, Levy JH, Sellke FW, Stangier J, Steiner T, Wang B, Kam CW, Weitz JI. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511–520.
24. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J, Bronson MD, Leeds JM, Mar FA, Gold A, Crowther MA. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015;373:2413–2424.
25. Juurlink D, Preyra C, Croxford R, Chong A, Austin PC, Tu JV, Laupacis A. *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study*. Toronto: Institute for Clinical Evaluative Sciences; 2006.

Supplemental Material

Table S1. Procedure codes

Category	Procedure Name	CCI Code List	Mini-invasive
Vascular	**Carotid Endarterectomy**	1.JE.57 (excludes 1.IJ.76 CABG on same date, excludes 1.JE.57.GQ)	No
	AAA Repair	1.KA.87	No
	All 3 definitions must have ICD-10 code I71.4 or I71.9 on the same admission	1.KA.76	
		1.KA.80 (excludes 1.KA.80.GQ-NR-N)	
	Peripheral vascular surgery	1.KG.76	No
		1.KA.76 without ICD-10 codes I71.3 or I71.4 or I71.9 on the same admission	
		1.JM.76	
		1.KT.76	
		1.KG.80 (excludes 1.KG.80.GQ-NR-N)	
Orthopedic	**Knee Arthroplasty**	1.VG.53	No
	Femur fixation	1.VC.74	
	Hip Arthroplasty	1.VA.53	
		1.VA.74	
Thoracic	**Lobectomy and pneumonectomy**	1.GR.87 (excludes 1.GR.87.DA)	No
		1.GR.89 (excludes 1.GR.89.DA)	
		1.GR.91	
		1.GT.87 (1.GT.87.DA)	
		1.GT.89 (1.GT.89.DA)	
		1.GT.91	
	VATS lobectomy and pneumonectomy	1.GR.87.DA	Yes
		1.GR.89.DA	
		1.GT.87.DA	
		1.GT.89.DA	
Abdominal	**Gastrectomy**	1.NF.87.RP	No
		1.NF.87.RG	
		1.NF.87.RJ	
		1.NF.87.LA	
		1.NF.87.SH	
		1.NF.87.RH	
		1.NF.87.RK	
		1.NF.89.SG	
		1.NF.89.TH	
		1.NF.90	
		1.NF.91	
		1.NF.92	
	Gastrectomy (endoscopic)	1.NF.87.DG	Yes

		1.NF.87.DH	
		1.NF.87.DQ	
		1.NF.87.DA	
		1.NF.87.GX	
		1.NF.87.DJ	
		1.NF.87.DL	
		1.NF.89.GW	
		1.NF.89.DZ	
	Esophagectomy	1.NA.87	
		1.NA.88	
		1.NA.89	No
		1.NA.90	
		1.NA.91	
		1.NA.92	
	Resection of small intestine	1.NK.87.LA	
		1.NK.87.RE	
		1.NK.87.RF	No
		1.NK.87.TF	
		1.NK.87.TG	
	Resection of small intestine (endoscopic)	1.NK.87.DA	
		1.NK.87.DN	
		1.NK.87.DP	Yes
		1.NK.87.DX	
		1.NK.87.DY	
	Colectomy	1.NM.87.LA	
		1.NM.87.RN	
		1.NM.87.RD	
		1.NM.87.RE	
		1.NM.87.TF	
		1.NM.87.TG	
		1.NM.89.RN	No
		1.NM.89.TF	
		1.NM.91.RN	
		1.NM.91.RD	
		1.NM.91.RE	
		1.NM.91.TF	
		1.NM.91.TG	
	Colectomy (endoscopic)	1.NM.87.DA	
		1.NM.87.DF	
		1.NM.87.DE	
		1.NM.87.DN	
		1.NM.87.DX	Yes
		1.NM.87.DY	
		1.NM.89.DF	
		1.NM.89.DX	
		1.NM.91.DF	
		1.NM.91.DE	

		1.NM.91.DN	
		1.NM.91.DX	
		1.NM.91.DY	
	Rectal surgery	1.NQ.87.LA	No
		1.NQ.87.CA	
		1.NQ.87.PF	
		1.NQ.87.RD	
		1.NQ.87.TF	
		1.NQ.87.PB	
		1.NQ.89	
	Rectal surgery (endoscopic)	1.NQ.87.DA	Yes
		1.NQ.87.DE	
		1.NQ.87.DX	
	Liver resection	1.OA.87 (excludes 1.OA.87.DA)	No
	Liver resection (laparoscopic)	1.OA.87.DA	Yes
	Whipple procedure	1.OK.87	No
		1.OK.89	
		1.OK.91	
Urologic / pelvic	**Nephrectomy**	1.PC.87 (excludes 1.PC.87.DA)	No
		1.PC.89 (excludes 1.PC.89.DA)	
		1.PC.91 (excludes 1.PC.91.DA)	
	Nephrectomy (endoscopic)	1.PC.87.DA	Yes
		1.PC.89.DA	
		1.PC.91.DA	
	Cystectomy	1.PM.87.LA	No
		1.PM.89.LA	
		1.PM.90	
		1.PM.91.LA	
	Cystectomy (endoscopic)	1.PM.87.DA	Yes
		1.PM.89.DA	
		1.PM.91.DA	
	Prostatectomy	1.QT.91 (excludes 1.QT.91.DA)	No
		1.QT.87.PK	
		1.QT.87.QZ	
		1.QT.87.PB	
	Prostatectomy (endoscopic)	1.QT.91.DA	Yes
		1.QT.87.DA	
	Hysterectomy	1.RM.89 (excludes 1.RM.89.DA)	No
		1.RM.91 (excludes 1.RM.91.DA)	
	Hysterectomy (endoscopic)	1.RM.89.DA	Yes
		1.RM.91.DA	

Table S2. Comorbidities

Comorbidity	**ICD-10 code**
Heart failure	I50.x
Myocardial infarction	I21.x, I22.x, I25.2
Atrial fibrillation	I48.x
Diabetes	E10.0, E10.1, E10.5, E10.6, E10.9, E11.0, E11.1, E11.5, E11.6, E11.9, E13.0, E13.1, E13.5, E13.6, E13.9, E14.0, E14.1, E14.5, E14.6, E14.9
Hypertension	I10.x, I11.x, I12.x, I13.x, I15.x
Hyperlipidemia	E78.x
Stroke or TIA	I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.9, I61.x, I63.0, I63.1, I63.2, I63.4, I63.5, I63.8, I63.9, I64.x, H34.1, G45.0, G45.1, G45.2, G45.3, G45.8, G45.9
Coronary artery disease	I20.x, I21.x, I22.x, I23.x, I24.x, I25.x
Carotid stenosis	I65.2
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8 K55.9, Z95.8, Z95.9
Rheumatic heart disease	I00.x, I01.x, I02.x, I05.x, I06.x, I07.x, I08.x, I09.x
Cardiac valve replacement	1.HV.90, 1HU.90, 1.HT.90, 1.HS.90
Dialysis	CIHI code: 1.PZ.21 OHIP codes: R849, R850, G323, G325, G326, G330, G331, G332, G860, G333, G083, G091, G085, G295, G082, G090, G092, G093, G094, G861, G862, G863, G864, G865, G866, G294, G095, G096

Table S3. Bleeding and Transfusion Codes

Bleeding (ICD-10)

Intracerebral bleed	I60.x, I61.x, I62.x, S06.3, S06.4, S06.5, S06.6, S06.8
Intraocular bleed	H35.6, H43.1, H45.0
Intraarticular bleed	M25.0
Gastrointestinal bleed	K92.0, K92.1, I85.0, I98.3, K22.10, K22.12, K22.14, K22.16, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K63.80, K31.80, K55.20, K62.5, K92.2
Other bleed	N02.x, K66.1, N93.8, N93.9, N95.0, R04.1, R04.2, R04.8, R04.9, R31.x, R58, D68.3, D62, J94.2, N92.0, N92.1, N92.4
Post surgical hemorrhage	T81.0

Transfusion (Variable within CIHI-DAD)

Blood	BTREDBC
Platelets	BTPLATE
Plasma	BTPLASMA

Table S4. Thromboembolism Codes

Myocardial infarction (MI)	I21
Recurrent MI	I22
Cerebral infarction	I63, I65, I66
Transient ischemic attack	G45
Coronary thromboembolism	I24.0
Arterial embolism and thrombosis	I74
Intestinal ischemia	K55.0
Renal ischemia or infarction	N28.0
Vascular myelopathies	G95.1
Atrial or ventricular thrombosis	I23.6, I51.3

Table S5. Anticoagulated AF vs. Non-anticoagulated AF: Standardized differences before and after IPTW matching in elective surgery cohort

	Before IPTW			After IPTW		
Propensity-weighted covariate	**AF Anticoag**	**AF - No Anticoag**	**Std Diff**	**AF Anticoag**	**AF - No Anticoag**	**Std Diff**
Male sex	52.9%	53.5%	0.013	53.6%	53.5%	0.002
Age, years	77.3	76.3	0.159	76.9	76.9	0.002
Charlson score ≥2	55.7%	57.0%	0.026	56.7%	56.8%	0.002
Johns Hopkins ADG 11-15	41.1%	41.9%	0.017	42.1%	42.0%	0.001
Johns Hopkins ADG 16-20	43.9%	42.6%	0.025	42.8%	42.9%	0.002
Johns Hopkins ADG ≥ 21	6.8%	6.6%	0.009	6.7%	6.8%	0.003
CHADS score 3-4	25.7%	18.3%	0.179	23.5%	22.9%	0.013
CHADS score 5-6	2.2%	1.5%	0.054	1.9%	1.9%	0.001
Congestive heart failure	21.5%	14.6%	0.180	18.8%	18.5%	0.008
Hypertension	65.1%	60.3%	0.099	63.7%	63.6%	0.004
Diabetes	28.8%	25.1%	0.084	28.3%	27.9%	0.010
Stroke or TIA	11.3%	7.6%	0.129	9.7%	10.2%	0.020
Peripheral vascular disease	9.5%	9.8%	0.009	9.8%	9.8%	0.003
Prior MI	11.2%	16.4%	0.151	14.3%	13.9%	0.011
Renal or liver disease	6.4%	5.4%	0.040	6.3%	6.4%	0.005
Previous bleeding 1 year	14.4%	14.6%	0.007	15.1%	14.9%	0.004
PPI	34.5%	32.8%	0.036	34.5%	34.4%	0.002
Antiplatelets	2.1%	10.4%	0.347	5.9%	5.7%	0.004
NSAID	5.4%	9.8%	0.166	7.4%	7.3%	0.004
ACE inhibitor or ARB	56.1%	46.4%	0.195	52.1%	52.0%	0.002
Beta-adrenergic blocker	58.4%	45.4%	0.262	52.9%	53.5%	0.012
Calcium channel blocker	36.4%	31.4%	0.105	35.4%	35.1%	0.007
LMWH	3.2%	1.3%	0.131	2.4%	2.5%	0.008
Diuretics	38.2%	25.0%	0.288	32.5%	32.5%	<0.001
Statins	58.7%	50.0%	0.175	55.0%	55.3%	0.005
Orthopedic surgery	61.2%	56.6%	0.093	59.3%	59.0%	0.006
Thoracic surgery	4.6%	6.4%	0.079	5.5%	5.4%	0.006
Urologic surgery	8.6%	9.2%	0.021	8.5%	8.7%	0.006
Vascular surgery	8.3%	7.0%	0.048	7.9%	8.0%	0.002
Mini-invasive surgery	12.8%	13.6%	0.024	13.0%	13.0%	<0.001
Teaching hospital	33.2%	33.7%	0.010	33.8%	33.3%	0.011
Arrival by ambulance	1.6%	2.3%	0.049	2.0%	1.9%	0.007
Elective admission	97.7%	97.7%	0.001	97.6%	97.8%	0.013

ADG = aggregated diagnosis groups, TIA = transient ischemic attack, MI = myocardial infarction, PPI = proton pump inhibitor, NSAID = non-steroidal anti-inflammatory drug, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, LMWH = low-molecular weight heparin

Table S6. Anticoagulated AF vs. Non-anticoagulated AF: Standardized differences before and after IPTW matching in urgent surgery cohort

	Before IPTW			After IPTW		
Propensity-weighted covariate	**AF Anticoag**	**AF - No Anticoag**	**Std Diff**	**AF Anticoag**	**AF - No Anticoag**	**Std Diff**
Male sex	36.5%	38.6%	0.044	38.1%	38.0%	0.004
Age, years	83.8	83.9	0.014	83.8	83.9	0.004
Charlson score ≥2	64.6%	66.3%	0.036	66.2%	65.7%	0.009
Johns Hopkins ADG 11-15	32.1%	34.3%	0.048	32.0%	32.9%	0.021
Johns Hopkins ADG 16-20	52.4%	51.1%	0.027	52.9%	51.9%	0.019
Johns Hopkins ADG ≥ 21	11.8%	9.9%	0.063	11.2%	10.9%	0.010
CHADS score 3-4	43.5%	37.4%	0.126	40.9%	40.4%	0.009
CHADS score 5-6	6.7%	4.5%	0.095	5.5%	5.6%	0.005
Congestive heart failure	41.9%	32.1%	0.204	37.3%	36.8%	0.011
Hypertension	69.0%	66.2%	0.059	68.8%	68.1%	0.014
Diabetes	27.9%	28.2%	0.008	28.6%	28.4%	0.006
Stroke or TIA	20.4%	15.5%	0.130	17.2%	17.6%	0.012
Peripheral vascular disease	11.1%	10.6%	0.015	11.7%	11.6%	0.003
Prior MI	17.2%	21.3%	0.105	20.0%	19.0%	0.024
Renal or liver disease	13.5%	13.5%	0.000	14.3%	13.6%	0.019
Previous bleeding 1 year	11.3%	13.5%	0.066	13.8%	12.7%	0.032
PPI	39.0%	34.7%	0.088	38.0%	37.2%	0.015
Antiplatelets	3.2%	13.3%	0.373	10.0%	8.3%	0.062
NSAIDs	3.2%	4.1%	0.051	4.0%	3.6%	0.022
ACE inhibitor or ARB	46.2%	34.8%	0.234	41.1%	41.6%	0.011
Beta-adrenergic blocker	54.3%	38.9%	0.313	46.0%	47.3%	0.026
Calcium channel blocker	34.9%	25.7%	0.202	30.5%	31.0%	0.010
LMWH	0.2%	0.7%	0.073	0.5%	0.4%	0.008
Diuretics	48.0%	33.0%	0.307	41.0%	41.2%	0.003
Statins	49.3%	35.3%	0.286	42.9%	43.1%	0.004
Orthopedic surgery	77.1%	77.0%	0.001	77.1%	76.6%	0.011
Thoracic surgery	0.8%	0.5%	0.034	0.7%	0.7%	0.000
Urologic surgery	0.5%	0.2%	0.057	0.4%	0.5%	0.023
Vascular surgery	4.7%	4.9%	0.008	4.9%	4.8%	0.004
Mini-invasive surgery	3.4%	2.6%	0.049	3.0%	3.3%	0.015
Teaching hospital	28.5%	29.6%	0.024	28.2%	29.0%	0.018
Arrival by ambulance	79.7%	80.4%	0.017	79.7%	79.9%	0.005
Emergency admission	86.5%	84.8%	0.050	85.9%	85.7%	0.006

ADG = aggregated diagnosis groups, TIA = transient ischemic attack, MI = myocardial infarction, PPI = proton pump inhibitor, NSAID = non-steroidal anti-inflammatory drug, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, LMWH = low-molecular weight heparin

Table S7. DOAC vs. Warfarin: Standardized differences before and after IPTW matching in elective surgery cohort

	Before IPTW			After IPTW		
Propensity-weighted covariate	**DOAC**	**Warfarin**	**Std Diff**	**DOAC**	**Warfarin**	**Std Diff**
Male sex	52.4%	53.3%	0.018	51.4%	52.5%	0.022
Age, years	76.6	77.9	0.201	77.4	77.3	0.015
Charlson score ≥2	50.4%	59.9%	0.192	56.0%	55.8%	0.003
Johns Hopkins ADG 11-15	41.5%	40.7%	0.018	41.1%	41.2%	0.000
Johns Hopkins ADG 16-20	42.1%	45.3%	0.063	43.8%	44.0%	0.004
Johns Hopkins ADG ≥ 21	6.4%	7.2%	0.035	6.9%	6.8%	0.001
CHADS score 3-4	22.8%	28.0%	0.119	26.2%	25.9%	0.007
CHADS score 5-6	2.0%	2.4%	0.030	2.1%	2.2%	0.009
Congestive heart failure	20.2%	22.6%	0.060	22.8%	21.5%	0.033
Hypertension	65.4%	64.8%	0.012	64.4%	64.9%	0.011
Diabetes	26.2%	31.0%	0.106	28.3%	28.9%	0.013
Stroke or TIA	10.2%	12.3%	0.065	10.9%	11.5%	0.019
Peripheral vascular disease	8.5%	10.4%	0.065	9.4%	9.4%	0.000
Prior MI	10.6%	11.7%	0.036	11.3%	11.2%	0.002
Renal or liver disease	3.8%	8.5%	0.197	6.0%	6.4%	0.017
Previous bleeding 1 year	13.9%	14.7%	0.024	15.2%	14.4%	0.022
PPI	34.7%	34.3%	0.007	34.4%	34.5%	0.002
Antiplatelets	1.2%	2.8%	0.116	1.8%	2.1%	0.021
NSAIDs	6.4%	4.5%	0.083	5.2%	5.4%	0.009
ACE inhibitor or ARB	54.3%	57.5%	0.065	57.6%	56.3%	0.025
Beta-adrenergic blocker	58.7%	58.1%	0.013	59.3%	58.3%	0.021
Calcium channel blocker	36.2%	36.5%	0.007	35.7%	36.3%	0.012
LMWH	0.5%	5.4%	0.293	3.5%	3.3%	0.015
Diuretics	34.4%	41.2%	0.141	38.2%	38.0%	0.004
Statins	57.0%	60.0%	0.061	59.1%	58.7%	0.010
Orthopedic surgery	62.1%	60.4%	0.035	60.3%	61.0%	0.014
Thoracic surgery	5.4%	4.0%	0.067	4.4%	4.6%	0.008
Urologic surgery	8.7%	8.5%	0.005	9.4%	8.8%	0.022
Vascular surgery	8.1%	8.5%	0.014	8.4%	8.3%	0.007
Mini-invasive surgery	12.8%	12.7%	0.002	12.3%	12.8%	0.016
Teaching hospital	30.9%	35.0%	0.088	32.6%	33.3%	0.015
Arrival by ambulance	1.2%	1.9%	0.059	1.6%	1.6%	0.002
Elective admission	97.7%	97.7%	0.003	97.9%	97.8%	0.008

ADG = aggregated diagnosis groups, TIA = transient ischemic attack, MI = myocardial infarction, PPI = proton pump inhibitor, NSAID = non-steroidal anti-inflammatory drug, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, LMWH = low-molecular weight heparin

Table S8. DOAC vs. Warfarin: Standardized differences before and after IPTW matching in urgent surgery cohort

	Before IPTW			After IPTW		
Propensity-weighted covariate	**DOAC**	**Warfarin**	**Std Diff**	**DOAC**	**Warfarin**	**Std Diff**
Male sex	36.2%	36.7%	0.010	37.5%	36.8%	0.015
Age, years	82.8	84.3	0.229	83.9	83.8	0.007
Charlson score ≥2	61.7%	65.9%	0.087	65.1%	64.7%	0.007
Johns Hopkins ADG 11-15	31.3%	32.4%	0.025	32.6%	32.1%	0.010
Johns Hopkins ADG 16-20	53.5%	51.9%	0.031	52.1%	52.5%	0.006
Johns Hopkins ADG ≥ 21	11.0%	12.2%	0.039	11.7%	11.8%	0.004
CHADS score 3-4	40.5%	44.9%	0.090	42.8%	43.4%	0.011
CHADS score 5-6	6.7%	6.7%	0.002	6.8%	6.8%	0.001
Congestive heart failure	38.1%	43.6%	0.112	41.7%	41.8%	0.003
Hypertension	69.0%	68.9%	0.002	68.6%	68.9%	0.007
Diabetes	28.4%	27.6%	0.018	27.8%	27.9%	0.001
Stroke or TIA	20.6%	20.4%	0.005	20.7%	20.6%	0.003
Peripheral vascular disease	9.7%	11.7%	0.063	11.3%	11.1%	0.007
Prior MI	15.8%	17.8%	0.054	17.6%	17.1%	0.012
Renal or liver disease	6.9%	16.5%	0.303	13.6%	13.5%	0.003
Previous bleeding 1 year	13.2%	10.4%	0.085	11.3%	11.4%	0.005
PPI	40.6%	38.2%	0.049	39.7%	39.1%	0.014
Antiplatelets	3.3%	3.2%	0.005	3.1%	3.3%	0.009
NSAIDs	2.9%	3.3%	0.023	3.0%	3.1%	0.006
ACE inhibitor or ARB	46.0%	46.3%	0.006	46.1%	46.1%	0.000
Beta-adrenergic blocker	55.7%	53.7%	0.041	54.2%	54.4%	0.002
Calcium channel blocker	31.6%	36.4%	0.103	33.8%	34.7%	0.018
LMWH	0.0%	0.3%	0.079	0.0%	0.2%	0.065
Diuretics	45.4%	49.1%	0.074	48.0%	47.9%	0.002
Statins	49.9%	49.0%	0.018	50.1%	49.4%	0.015
Orthopedic surgery	75.2%	77.9%	0.066	77.0%	77.1%	0.001
Thoracic surgery	1.0%	0.7%	0.024	0.9%	0.8%	0.007
Urologic surgery	0.8%	0.4%	0.059	0.6%	0.5%	0.002
Vascular surgery	4.1%	4.9%	0.040	4.9%	4.7%	0.008
Mini-invasive surgery	4.1%	3.2%	0.052	3.4%	3.5%	0.002
Teaching hospital	25.2%	30.0%	0.106	28.3%	28.5%	0.005
Arrival by ambulance	77.2%	80.9%	0.089	79.9%	79.6%	0.005
Emergency admission	86.4%	86.6%	0.005	86.7%	86.5%	0.005

ADG = aggregated diagnosis groups, TIA = transient ischemic attack, MI = myocardial infarction, PPI = proton pump inhibitor, NSAID = non-steroidal anti-inflammatory drug, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, LMWH = low-molecular weight heparin

Table S9. AF vs. No AF: Standardized differences before and after IPTW matching in elective surgery cohort

	Before IPTW			After IPTW		
Propensity-weighted covariate	**AF**	**No AF**	**Std Diff**	**AF**	**No AF**	**Std Diff**
Male sex	53.2%	41.5%	0.235	45.2%	42.1%	0.061
Age, years	76.8	74.0	0.442	74.7	74.2	0.082
Charlson score ≥2	56.2%	36.6%	0.402	40.2%	37.8%	0.050
Johns Hopkins ADG 11-15	41.4%	47.8%	0.128	48.9%	47.4%	0.029
Johns Hopkins ADG 16-20	43.3%	23.0%	0.442	27.1%	24.2%	0.068
Johns Hopkins ADG ≥ 21	6.7%	1.9%	0.239	2.3%	2.2%	0.007
CHADS score 3-4	22.4%	6.6%	0.461	9.0%	7.5%	0.052
CHADS score 5-6	1.9%	0.3%	0.157	0.4%	0.4%	0.007
Congestive heart failure	18.4%	1.8%	0.573	3.4%	2.9%	0.033
Hypertension	62.9%	38.1%	0.514	41.3%	39.5%	0.038
Diabetes	27.2%	19.8%	0.173	21.9%	20.3%	0.040
Stroke or TIA	9.6%	3.5%	0.251	4.6%	3.9%	0.036
Peripheral vascular disease	9.7%	4.7%	0.191	6.4%	5.1%	0.057
Prior MI	13.5%	3.7%	0.354	6.5%	4.4%	0.091
Renal or liver disease	6.0%	2.0%	0.205	3.1%	2.2%	0.051
Previous bleeding 1 year	14.5%	7.3%	0.233	7.7%	7.7%	0.001
PPI	33.7%	25.5%	0.181	27.2%	26.0%	0.027
Antiplatelets	6.0%	2.0%	0.205	3.1%	2.2%	0.051
NSAIDs	7.4%	14.2%	0.223	14.9%	13.9%	0.029
ACE inhibitor or ARB	51.7%	41.5%	0.206	45.8%	42.1%	0.073
Beta-adrenergic blocker	52.5%	18.8%	0.752	24.3%	20.7%	0.085
Calcium channel blocker	34.2%	24.2%	0.219	27.1%	24.8%	0.053
LMWH	2.4%	0.2%	0.191	0.3%	0.3%	0.001
Diuretics	32.2%	19.3%	0.300	20.8%	20.0%	0.019
Statins	54.7%	43.1%	0.235	48.0%	43.7%	0.085
Orthopedic surgery	59.1%	61.8%	0.056	61.6%	61.7%	0.001
Thoracic surgery	5.4%	4.2%	0.057	4.1%	4.3%	0.009
Urologic surgery	8.9%	14.2%	0.168	13.8%	13.9%	0.002
Vascular surgery	7.7%	5.1%	0.106	6.3%	5.3%	0.043
Mini-invasive surgery	13.1%	11.1%	0.062	10.5%	11.2%	0.024
Teaching hospital	33.4%	30.2%	0.070	31.1%	30.4%	0.017
Arrival by ambulance	1.9%	0.7%	0.110	1.0%	0.8%	0.029
Elective admission	97.7%	97.7%	<0.001	97.5%	97.7%	0.012

ADG = aggregated diagnosis groups, TIA = transient ischemic attack, MI = myocardial infarction, PPI = proton pump inhibitor, NSAID = non-steroidal anti-inflammatory drug, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, LMWH = low-molecular weight heparin

Table S10. AF vs. No AF: Standardized differences before and after IPTW matching in urgent surgery cohort

	Before IPTW			After IPTW		
Propensity-weighted covariate	**AF**	**No AF**	**Std Diff**	**AF**	**No AF**	**Std Diff**
Male sex	37.6%	30.9%	0.140	33.4%	31.9%	0.032
Age, years	83.9	81.7	0.287	82.3	82	0.042
Charlson score ≥2	65.4%	41.2%	0.501	46.9%	44.5%	0.048
Johns Hopkins ADG 11-15	33.2%	43.8%	0.220	41.5%	42.3%	0.016
Johns Hopkins ADG 16-20	51.8%	32.6%	0.396	36.9%	35.1%	0.039
Johns Hopkins ADG ≥ 21	10.9%	4.0%	0.267	5.5%	5.0%	0.023
CHADS score 3-4	40.5%	15.8%	0.570	20.3%	19.2%	0.027
CHADS score 5-6	5.6%	1.3%	0.235	2.0%	1.9%	0.008
Congestive heart failure	37.1%	8.1%	0.738	13.1%	12.1%	0.030
Hypertension	67.6%	45.9%	0.449	50.3%	48.8%	0.029
Diabetes	28.0%	20.8%	0.168	23.5%	21.8%	0.040
Stroke or TIA	18.0%	7.6%	0.314	9.5%	9.0%	0.017
Peripheral vascular disease	10.8%	6.3%	0.163	7.2%	6.9%	0.012
Prior MI	19.2%	8.4%	0.317	11.9%	10.0%	0.060
Renal or liver disease	13.5%	5.2%	0.289	7.2%	6.5%	0.030
Previous bleeding 1 year	12.4%	5.7%	0.233	6.9%	6.6%	0.011
PPI	36.9%	27.2%	0.208	29.9%	28.6%	0.029
Antiplatelets	8.2%	9.3%	0.039	11.2%	9.2%	0.064
NSAIDs	3.6%	6.6%	0.134	6.7%	6.2%	0.022
ACE inhibitor or ARB	40.6%	35.9%	0.097	37.0%	36.5%	0.012
Beta-adrenergic blocker	46.7%	19.1%	0.616	26.1%	22.9%	0.075
Calcium channel blocker	30.4%	24.0%	0.144	28.2%	25.0%	0.072
LMWH	0.5%	0.3%	0.031	0.4%	0.3%	0.009
Diuretics	40.6%	20.4%	0.451	25.3%	23.2%	0.049
Statins	42.5%	32.4%	0.208	34.8%	33.7%	0.024
Orthopedic surgery	77.1%	76.4%	0.015	76.2%	76.5%	0.008
Thoracic surgery	0.7%	0.5%	0.024	0.6%	0.5%	0.010
Urologic surgery	0.3%	0.7%	0.045	0.9%	0.6%	0.029
Vascular surgery	4.8%	4.0%	0.038	4.2%	4.1%	0.006
Mini-invasive surgery	3.0%	3.2%	0.011	3.0%	3.2%	0.011
Teaching hospital	29.0%	26.9%	0.048	27.4%	27.2%	0.005
Arrival by ambulance	80.1%	75.3%	0.115	76.6%	75.9%	0.016
Emergency admission	85.7%	86.3%	0.016	85.0%	86.1%	0.034

ADG = aggregated diagnosis groups, TIA = transient ischemic attack, MI = myocardial infarction, PPI = proton pump inhibitor, NSAID = non-steroidal anti-inflammatory drug, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, LMWH = low-molecular weight heparin

Table S11. Non-anticoagulated AF vs. No AF: Standardized differences before and after IPTW matching in elective surgery cohort

	Before IPTW			After IPTW		
Propensity-weighted covariate	**AF - No Anticoag**	**No AF**	**Std Diff**	**AF - No Anticoag**	**No AF**	**Std Diff**
Male sex	53.5%	41.5%	0.242	44.7%	41.8%	0.058
Age, years	76.3	74.0	0.343	74.5	74.1	0.061
Charlson score ≥2	57.0%	36.6%	0.417	39.2%	37.1%	0.044
Johns Hopkins ADG 11-15	41.9%	47.8%	0.119	47.7%	47.6%	0.002
Johns Hopkins ADG 16-20	42.6%	23.0%	0.428	26.2%	23.5%	0.062
Johns Hopkins ADG ≥ 21	6.6%	1.9%	0.234	2.1%	2.0%	0.006
CHADS score 3-4	18.3%	6.6%	0.362	7.8%	6.9%	0.035
CHADS score 5-6	1.5%	0.3%	0.131	0.3%	0.3%	0.005
Congestive heart failure	14.6%	1.8%	0.480	2.7%	2.2%	0.036
Hypertension	60.3%	38.1%	0.456	40.1%	38.6%	0.029
Diabetes	25.1%	19.8%	0.127	20.7%	20.0%	0.019
Stroke or TIA	7.6%	3.5%	0.180	4.5%	3.6%	0.046
Peripheral vascular disease	9.8%	4.7%	0.196	5.6%	4.9%	0.031
Prior MI	16.4%	3.7%	0.430	5.4%	4.1%	0.061
Renal or liver disease	5.4%	2.0%	0.184	2.6%	2.1%	0.033
Previous bleeding 1 year	14.6%	7.3%	0.236	6.7%	7.5%	0.030
PPI	32.8%	25.5%	0.161	26.3%	25.7%	0.015
Antiplatelets	10.4%	5.8%	0.168	7.2%	5.9%	0.051
NSAIDs	9.8%	14.2%	0.138	14.3%	14.1%	0.005
ACE inhibitor or ARB	46.4%	41.5%	0.099	43.6%	41.6%	0.040
Beta-adrenergic blocker	45.4%	18.8%	0.594	22.7%	19.5%	0.077
Calcium channel blocker	31.4%	24.2%	0.161	25.7%	24.4%	0.030
LMWH	1.3%	0.2%	0.124	0.3%	0.3%	0.006
Diuretics	25.0%	19.3%	0.138	19.8%	19.4%	0.010
Statins	50.0%	43.1%	0.139	45.8%	43.2%	0.051
Orthopedic surgery	56.6%	61.8%	0.106	61.7%	61.7%	<0.001
Thoracic surgery	6.4%	4.2%	0.098	4.0%	4.3%	0.013
Urologic surgery	9.2%	14.2%	0.157	14.6%	14.1%	0.014
Vascular surgery	7.0%	5.1%	0.080	5.8%	5.2%	0.027
Mini-invasive surgery	13.6%	11.1%	0.075	11.2%	11.2%	0.001
Teaching hospital	33.7%	30.2%	0.075	31.6%	30.3%	0.029
Arrival by ambulance	2.3%	0.7%	0.133	1.2%	0.7%	0.047
Elective admission	97.7%	97.7%	<0.001	97.5%	97.7%	0.017

ADG = aggregated diagnosis groups, TIA = transient ischemic attack, MI = myocardial infarction, PPI = proton pump inhibitor, NSAID = non-steroidal anti-inflammatory drug, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, LMWH = low-molecular weight heparin

Table S12. Non-anticoagulated AF vs. No AF: Standardized differences before and after IPTW matching in urgent surgery cohort

	Before IPTW			After IPTW		
Propensity-weighted covariate	**AF - No Anticoag**	**No AF**	**Std Diff**	**AF - No Anticoag**	**No AF**	**Std Diff**
Male sex	38.6%	30.9%	0.162	34.3%	31.5%	0.059
Age, years	83.9	81.7	0.287	81.9	81.8	0.007
Charlson score ≥2	66.3%	41.2%	0.520	43.9%	42.9%	0.020
Johns Hopkins ADG 11-15	34.3%	43.8%	0.196	41.8%	43.1%	0.026
Johns Hopkins ADG 16-20	51.1%	32.6%	0.382	35.7%	33.8%	0.038
Johns Hopkins ADG ≥ 21	9.9%	4.0%	0.236	5.1%	4.4%	0.033
CHADS score 3-4	37.4%	15.8%	0.503	18.7%	17.4%	0.034
CHADS score 5-6	4.5%	1.3%	0.189	1.5%	1.5%	<0.001
Congestive heart failure	32.1%	8.1%	0.627	10.8%	9.8%	0.031
Hypertension	66.2%	45.9%	0.418	48.2%	47.3%	0.018
Diabetes	28.2%	20.8%	0.173	22.6%	21.3%	0.031
Stroke or TIA	15.5%	7.6%	0.247	8.9%	8.2%	0.026
Peripheral vascular disease	10.6%	6.3%	0.155	7.4%	6.6%	0.030
Prior MI	21.3%	8.4%	0.369	11.3%	9.3%	0.064
Renal or liver disease	13.5%	5.2%	0.289	6.5%	5.8%	0.029
Previous bleeding 1 year	13.5%	5.7%	0.266	5.9%	6.2%	0.016
PPI	34.7%	27.2%	0.163	28.5%	27.7%	0.017
Antiplatelets	13.3%	9.3%	0.128	11.0%	9.6%	0.047
NSAIDs	4.1%	6.6%	0.110	6.7%	6.4%	0.013
ACE inhibitor or ARB	34.8%	35.9%	0.023	36.0%	35.8%	0.004
Beta-adrenergic blocker	38.9%	19.1%	0.447	23.5%	20.5%	0.072
Calcium channel blocker	25.7%	24.0%	0.039	27.3%	24.1%	0.072
LMWH	0.7%	0.3%	0.062	0.3%	0.3%	0.004
Diuretics	33.0%	20.4%	0.289	22.5%	21.3%	0.029
Statins	35.3%	32.4%	0.061	34.3%	32.7%	0.035
Orthopedic surgery	77.0%	76.4%	0.014	75.2%	76.5%	0.030
Thoracic surgery	0.5%	0.5%	0.006	0.6%	0.5%	0.019
Urologic surgery	0.2%	0.7%	0.075	0.5%	0.6%	0.020
Vascular surgery	4.9%	4.0%	0.043	4.3%	4.0%	0.011
Mini-invasive surgery	2.6%	3.2%	0.037	3.5%	3.2%	0.020
Teaching hospital	29.6%	26.9%	0.060	27.5%	27.1%	0.008
Arrival by ambulance	80.4%	75.3%	0.124	75.5%	75.6%	0.002
Emergency admission	84.8%	86.3%	0.041	85.4%	86.1%	0.022

ADG = aggregated diagnosis groups, TIA = transient ischemic attack, MI = myocardial infarction, PPI = proton pump inhibitor, NSAID = non-steroidal anti-inflammatory drug, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, LMWH = low-molecular weight heparin