ORIGINAL RESEARCH

Antithrombotic Therapy and Outcomes After ICD Implantation in Patients With Atrial Fibrillation and Coronary Artery Disease: An Analysis From the National Cardiovascular Data Registry (NCDR)®

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***Background*—**Management of antithrombotic agents after implantable cardioverter defibrillator implantation is challenging, particularly among patients with atrial fibrillation and coronary artery disease.

***Methods and Results*—**Using data from National Cardiovascular Data Registry® Implantable Cardioverter Defibrillator Registry™ linked with Medicare claims data, we identified 25 180 patients with atrial fibrillation and coronary artery disease who underwent implantable cardioverter defibrillator implantation. Patients were categorized into 5 different groups according to antithrombotic agents prescribed at discharge (any 1 antiplatelet agent [A, n=6538], dual antiplatelet therapy [DA, n=3414], warfarin [n=5264], warfarin+A [n=7994], warfarin+DA [n=1970]). We assessed the primary outcomes occurring within 30 days of hospital discharge. Combinations of DA (adjusted hazard ratio [HR]: 1.39; 95% CI: 1.03 to 1.87), warfarin+A (adjusted HR: 1.32; 95% CI: 1.03 to 1.69), and warfarin+DA (adjusted HR: 2.03; 95% CI: 1.49 to 2.77) were associated with a higher bleeding risk. The risk of major adverse cardiovascular events was higher in patients discharged with A (adjusted HR: 1.69; 95% CI: 1.33 to 2.16), DA (adjusted HR: 2.17; 95% CI: 1.66 to 2.83), and DA+warfarin (adjusted HR: 1.61; 1.16 to 2.24). There was no association between postdischarge antithrombotic agents and thromboembolic events or device-related complications.

***Conclusions*—**Short-term bleeding risk and major adverse cardiovascular events differ with usage patterns of antithrombotic agents, while the risk of thromboembolic events and device-related complications is relatively constant. These data may help clinicians balance risks and benefits when choosing antithrombotic therapy following implantable cardioverter defibrillator implantation. **(*J Am Heart Assoc*. 2015;4:e001331 doi: 10.1161/JAHA.114.001331)**

Key Words: anticoagulants • arrhythmia • complications • defibrillation

Implantable cardioverter-defibrillators (ICDs) improve survival in patients at high risk of sudden cardiac death, but device implantation carries a significant risk of bleeding complications.[1] Although multiple factors influence bleeding risk, postprocedural antithrombotic therapy is likely to play a significant role, particularly among patients who require multiple agents due to atrial fibrillation (AF) and coronary artery disease (CAD).[2,3] However, this may substantially increase the risk of bleeding around the time of the procedure.[2,3] Decisions regarding antithrombotic therapy require balancing the competing risks of bleeding complications and thromboembolic events (TEs). However, currently there are no guidelines for the management of antithrombotic therapy for patients with AF and CAD after ICD implantation. The lack of guidelines may reflect incomplete knowledge about the association between different antithrombotic agents and short-term outcomes after ICD implantation.

At present, patterns of use of postprocedural antithrombotic agents and their association with clinical outcomes have not been described. We therefore set out to determine patterns of utilization of antiplatelet agents and warfarin and the associated early, short-term risks of bleeding, TEs, and

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device-related complications in patients with AF and CAD who are discharged on antithrombotic agents using the National Cardiovascular Data Registry's (NCDR®'s) ICD Registry™. The registry collects data on patients' postdischarge antithrombotic medications and when linked with Medicare claims data, it provides an opportunity to evaluate outcomes associated with antithrombotic agents following ICD implantation.

Methods

Data Source

Patients with ICD implantation were enrolled from the registry. The registry, which is cosponsored by the American College of Cardiology and the Heart Rhythm Society, has been previously described.[4] The registry was established in April 2006 and has been funded by a combination of hospital fees and grants from both device companies and payers. Hospitals are required to submit data on all Centers for Medicare and Medicaid Services patients who receive an ICD for primary prevention of sudden cardiac death.[5] However, more than 75% of hospitals report data on all ICD implantations (irrespective of indication and payer), and these hospitals submit more than 88% of all cases in the registry.[4]

The registry collects more than 130 data elements at the time of initial ICD implantation, device upgrade, and device replacement. Clinical, demographic, procedural information, and discharge medications are collected in addition to information about adverse events until the time of discharge using standardized data elements and definitions. Data are submitted by participating hospitals using certified software. Data quality is examined using a formal Data Quality Reporting and audit process.[4,6] Longitudinal outcomes were obtained by linking registry files with Medicare inpatient fee-for-service claims using probabilistic matching, as previously described.[7]

Patient Population

All admissions from January 2006 through December 2009 that could be matched to Centers for Medicare and Medicaid Services Medicare fee-for-service claims data were identified. We restricted the population to patients with a history of AF and CAD. We defined CAD as having 1 of the following: (1) ischemic heart disease, (2) previous myocardial infarction, (3) coronary artery bypass grafting, or (4) previous percutaneous coronary intervention (PCI). Patients were excluded if they were not enrolled in the Medicare fee-for-service; had a previous ICD or pacemaker; did not have 3 months of follow-up; had unknown medications on discharge; had experienced bleeding complications during the hospitalization for ICD implantation; or were not discharged on any medications under evaluation.

Postdischarge Medication Groups

We divided patients into 5 groups based on the postdischarge antiplatelet and anticoagulant agents. These groups included patients with (1) warfarin, (2) 1 antiplatelet agent (A), (3) dual antiplatelet agents (DA), (4) warfarin and A; and (5) warfarin and DA. The antiplatelet agents included in the analysis were aspirin and clopidogrel/ticlodipine. Patients discharged without any antithrombotic agents or with missing information about discharge medications were not included in our analysis.

Endpoints and Definitions

The outcomes for this analysis were bleeding, TEs, major adverse cardiovascular events (MACE), and device-related complications. We focused our primary evaluation on outcomes 30 days postdischarge to minimize the effect of medication changes postdischarge. In our secondary analysis, we evaluated outcomes 90 days following discharge. We identified bleeding, MACE, TEs, and device-related complications based on commonly used ICD-9-CM diagnosis and procedure-related codes (Table 1).[1,5,8,9] Complications that could be attributable to device implantation were considered device-related complications.[1]

Statistical Analysis

Baseline characteristics and outcomes were compared between patients according to postdischarge antithrombotic medication groups using F tests in ANOVA model analysis for continuous variables and χ^2 tests in frequency table analysis for categorical variables. A Cox proportional hazards model was used to estimate the adjusted risk of the antithrombotic medication groups on bleeding, TEs, and device-related complications after accounting for differences in patient and procedural characteristics. Characteristics that we adjusted for included gender, race, New York Heart Association Functional Class, prior myocardial infarction, chronic lung disease, renal failure requiring dialysis, ejection fraction, creatinine, and $CHADS_2VASC$ score. Hazard ratios (HRs) for each postdischarge medication group were calculated after adjusting for the baseline covariates. Multivariable logistic regression model was used to identify factors associated with the decision to discharge patients with warfarin.

We evaluated the association between the treatment groups and outcomes using inverse probability–weighted estimators incorporating propensity scores to compare treatment groups. The propensity scores were calculated based on

Table 1. ICD-9 Codes Used for Defining Thromboembolic and Bleeding Events

Thromboembolic events	
Cerebral occlusion, nonhemorrhagic stroke, or transient ischemic attack	433.x1, 434.x1, 435.x, 436, 437.1x, 437.9x,
Arterial peripheral embolus	444.x, 445.x
Deep vein thrombosis, pulmonary embolism, or other venous thrombosis	415.1x, 451.1x, 451.2, 451.81, 451.9, 452.x, 453.x
Bleeding events	
Gastrointestinal	
Control of hemorrhage and suture of ulcer of stomach or duodenum	44.4x
Esophageal	530.82
Ulcer	531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x
Gastritis and duodenitis with hemorrhage	535.x1
Bleeding of stomach or duodenum due to vascular abnormalities	537.83, 537.84
Bleeding of intestine due to vascular abnormality	569.85, 569.86
Rectum	569.3x
Unspecified	578.x
Cerebrovascular	
Subarachnoid hemorrhage	430.x
Intracerebral hemorrhage	431.x
Intracranial hemorrhage	432.x
Bleeding related to procedure	
Hematoma	998.1x
Tamponade/pericardiocentesis/pericardiotomy	423.3, 37.0, 37.12
Hemopericardium	423.0
Hemarthrosis	719.1x
Hematuria	599.7
Vaginal	626.2, 626.6, 626.8, 627.0, 627.1
Hemoptysis	786.3
Epistaxis	784.7
Hemorrhage not otherwise specified	459.0
Device-related complications	
Other incision with drainage of skin and subcutaneous tissue	86.04
Other skin incision of subcutaneous tissue	86.09
Mechanical complications with system revision	996.0, 996.00, 996.01, 996.02, 996.03, 996.04
System revision	37.75, 37.77, 37.79, 37.97, 37.99, 00.52
Device-related infection	996.61
Pneumothorax/chest tube	512.1, 34.04, 34.06, 34.09
Device-related bleeding	
Hemothorax	511.89
Hematoma	998.1x
Tamponade/pericardiocentesis/pericardiotomy	423.3, 37.0, 37.12
Hemopericardium	423.0
Major adverse cardiovascular events	
Death	
Myocardial infarction	410.X1
Percutaneous coronary intervention	36.00, 36.06, 36.07, and 36.09
Coronary artery bypass grafting	36.10-19

a logistic regression model for the use of warfarin, which was supposed to make the treatment groups more balanced. Inverse probability–weighted estimators require fewer distributional assumptions and handle censored data.[10] Adjusted HRs were calculated according to the inverse probability–weighted approach of Cole and Hernan.[11] Proportional-hazards assumption was tested using the graph of the log (−log [survival]) versus log of survival time and Schoenfeld residuals on the functions of time. No parallel curves or a nonzero slope indicated violation of the proportional-hazards assumption. The assumption of proportionality was tested and met for the Cox proportional hazards analyses.

The statistical significance of differences among strata was tested in survival models accounting for matched groups. We did not account for clustering within hospitals for the final analysis. All statistical tests were 2-sided with a significance threshold of $P<0.05$. All analyses were performed using the statistical packages of SAS version 9.3 (SAS Institute Inc). Analyses of the ICD Registry were approved by the Yale Human Investigation Committee.

Results

The merged data set between the registry and Centers for Medicare and Medicaid Services Medicare claims comprises 185 574 patients between January 2006 and December 2009. Patients were excluded sequentially if they did not have a full 3-month follow-up (n=4840); had a previous ICD (n=55 822), previous pacemaker (n=19 214); unknown medications (n=1025); no history of AF (n=67 536); epicardial leads (n=534); bleeding complications in hospital (n=642); no history of CAD (n=7511); and were not in the considered medication subgroups (n=3270). There were 25 180 patients from 1218 sites who met our inclusion criteria and were included in the study population (Figure 1).

Overall, there were differences in cerebrovascular disease, diabetes, and hypertension among patients discharged with different antithrombotic agent combinations. Baseline characteristics of patients according to medications postdischarge are summarized in Table 2. There was substantial variation in postdischarge medications according to hospital geographic location. There were also differences according to the community served and profit type of hospitals (Table 3).

The proportion of patients discharged on warfarin varied only modestly by the patient stroke risk as assessed by the $CHADS_2VASC$ score (Figure 2). A substantial proportion of patients with $CHADS_2VASC \geq 2$ were not discharged with warfarin (9952/25 180, 39.5%). In multivariable analysis, we assessed factors associated with patients being discharged on warfarin. These included ischemic heart disease, nonischemic cardiomyopathy, sinus node dysfunction, congestive heart failure with New York Heart Association II or III symptoms, previous myocardial infarction, coronary artery bypass grafting or PCI, history of valvular surgery, diabetes mellitus, hypertension, renal failure requiring dialysis, elevated systolic blood pressure, elevated blood urea nitrogen levels, QRS duration, and $CHADS_2VASC$ score. The risk of bleeding assessed by $CHADS_2VASC$ score was not a predictor of discharge warfarin (Figure 3).

There were 10 669 patients with a history of PCI. A higher proportion of patients were discharged on DA if their PCI had been performed within 3 months of the ICD implantation (36.0%). Among patients whose PCI was performed more than 3 months of the ICD implantation, a higher proportion of patients were treated with warfarin and A (30.7%).

Bleeding, TEs, Device-Related Complications, and MACE

Thirty-day outcomes

Overall, 575 (2.3%) bleeding, 642 (2.5%) MACE, 356 (1.4%) TEs, and 605 (2.4%) device-related complications were observed 30 days following hospital discharge (Table 4). There were 204 (0.8%) device-related bleeding events, which included 176 (0.7%) hematomas. Patients discharged on warfarin+DA had the highest number of bleeding events (3.6%) compared to those discharged on A (2.2%), DA (2.5%), warfarin+A (2.4%), or warfarin (1.7%). Device-related bleeding was more common in patients discharged with warfarin+DA (1.1%) compared to A (0.7%), DA (0.9%), warfarin+A (1.0%), or warfarin (0.6%). Patients discharged on warfarin alone had the lowest rates of MACE (1.8%), compared to those discharged on A (3.0%), DA (3.9%), warfarin+A (2.0%), and warfarin+DA (2.9%). Patients discharged with DA had the highest rates of TEs (2.0%) compared to those discharged on A (1.4%), warfarin (1.5%), warfarin+A (1.2%), or warfarin+DA (1.1%). There were 1970 (7.8%) patients discharged with triple therapy. In multivariable analysis, combinations of DA, warfarin+A, and warfarin+DA were independently associated with higher bleeding risk when compared with warfarin alone (Table 5). Specifically, warfarin+A and warfarin+DA were associated with higher device-related bleeding. Patients discharged with A, DA, and warfarin+DA were associated with a higher risk of MACE. The risk of TEs and device-related complications did not vary across groups. There were no differences in bleeding and TEs, across $CHADS_2VASC$ scores, among patients treated and untreated with warfarin (Table 6).

Ninety-day outcomes

There were 1147 (4.6%) bleeding, 705 (2.8%) TEs, 1072 (4.3%) device-related complications, and 1766 (7.0%) MACE observed 90 days following discharge (Table 4). There were

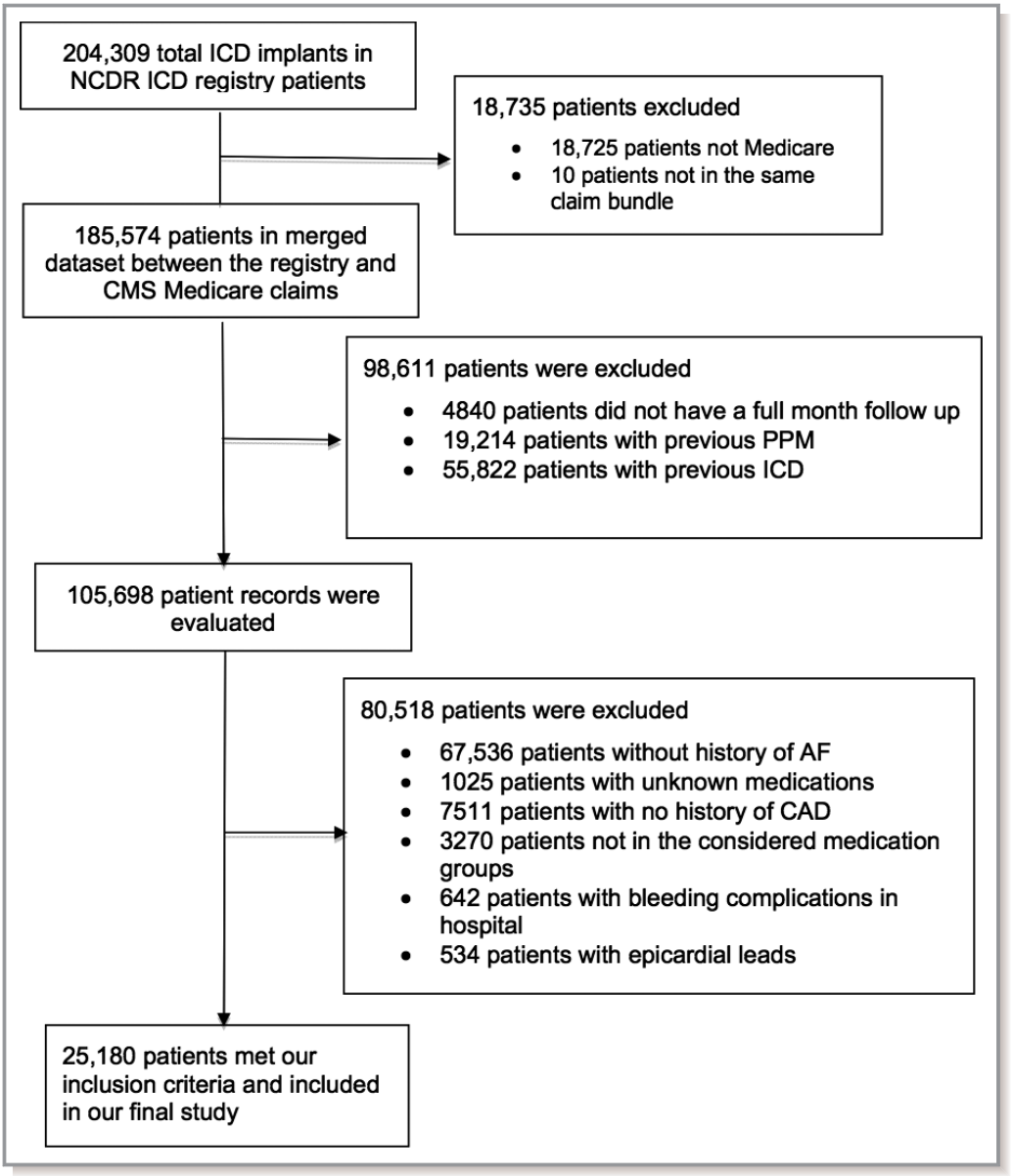

Figure 1. Selection of patients from the NCDR ICD Registry. AF indicates atrial fibrillation; CAD, coronary artery disease; CMS, Centers for Medicare and Medicaid Services; ICD, implantable cardioverter defibrillator; NCDR, National Cardiovascular Data Registry™; PPM, permanent pacemaker.

299 (1.2%) device-related bleeding events, which included 252 (1.0%) hematomas. Patients discharged on warfarin and DA had the highest number of subsequent bleeding events (7.4%) compared to those discharged on A (4.0%), DA (4.9%), warfarin+A (4.7%), or warfarin (3.7%). Patients discharged with warfarin+A had the lowest rates of MACE (5.7%), compared to those discharged on A (7.7%), DA (9.9%), warfarin (6.0%), and warfarin+DA (7.6%). Patients discharged with DA had the highest number of TEs (3.7%) compared to those discharged on A (3.1%), warfarin (2.7%), warfarin+A (2.4%), or warfarin+DA (2.4%). In multivariable analysis, combinations of DA, warfarin+A, and warfarin+DA were independently associated with higher bleeding risk when compared with warfarin alone (Table 5). The risk of device-related bleeding events was higher in patients discharged with DA, warfarin+A, and warfarin+DA. Furthermore, patients discharged with DA and warfarin+A had a higher risk of device-related complications. Patients discharged with A, DA, and warfarin+DA were associated with a higher risk of MACE. The risk of TEs did not vary across groups. There was a higher risk of TEs in patients with intermediate (3 to 5) and high (≥6) $CHADS_2$-VASC scores who were not treated with warfarin compared to those treated with warfarin (Table 6). Furthermore, there was a higher risk of bleeding in patients with high (≥6) $CHADS_2VASC$ scores who were treated with warfarin (Table 6).

Table 2. Baseline Characteristics

	Total (n=25 180)	A (n=6538)	DA (n=3414)	Warfarin (n=5264)	A+Warfarin (n=7994)	DA+Warfarin (n=1970)
Admission characteristics						
Age: mean (SD)*	75.8±6.1	76.1±6.3	75.5±6.4	76.3±6.1	75.5±6.0	74.9±5.8
Female*	4964 (19.7%)	1375 (21.0%)	800 (23.4%)	1080 (20.5%)	1333 (16.7%)	376 (19.1%)
Race*						
White	23 360 (92.8%)	6022 (92.1%)	3117 (91.3%)	4882 (92.7%)	7509 (93.9%)	1830 (92.9%)
Black	1029 (4.1%)	306 (4.7%)	160 (4.7%)	206 (3.9%)	274 (3.4%)	83 (4.2%)
History and risk factors						
Syncope*	5160 (20.5%)	1494 (22.9%)	795 (23.3)	990 (18.8%)	1511 (18.9%)	370 (18.8%)
Family history of sudden death	866 (3.4%)	223 (3.4%)	124 (3.6%)	176 (3.3%)	272 (3.4%)	71 (3.6%)
Congestive heart failure*	20 631 (81.9%)	5243 (80.2%)	2657 (77.8%)	4464 (84.8%)	6654 (83.2%)	1613 (81.9%)
NYHA class—current status*						
Class I	2253 (8.9%)	640 (9.8%)	366 (10.7%)	370 (7.0%)	700 (8.8%)	177 (9.0%)
Class II	8382 (33.3%)	2227 (34.1%)	1114 (32.6%)	1715 (32.6%)	2636 (33.0%)	690 (35.0%)
Class III	13 223 (52.5%)	3296 (50.4%)	1723 (50.5%)	2931 (55.7%)	4272 (53.4%)	1001 (50.8%)
Class IV	1322 (5.3%)	375 (5.7%)	211 (6.2%)	248 (4.7%)	386 (4.8%)	102 (5.2%)
Ischemic heart disease*	23 672 (94.0%)	6151 (94.1%)	3279 (96.0%)	4820 (91.6%)	7514 (94.0%)	1908 (96.9%)
Previous MI*						
No	6844 (27.2%)	1737 (26.6%)	758 (22.2%)	1630 (31.0%)	2212 (27.7%)	507 (25.8%)
Yes—within 40 days of ICD implant	1942 (7.7%)	524 (8.0%)	440 (12.9%)	215 (4.1%)	540 (6.8%)	223 (11.3%)
Yes—more than 40 days since ICD implant	15 203 (60.4%)	3976 (60.9%)	1945 (57.0%)	3239 (61.6%)	4924 (61.7%)	1119 (56.9%)
Yes—both within or more than 40 days	1163 (4.6%)	293 (4.5%)	269 (7.9%)	173 (3.3%)	310 (3.9%)	118 (6.0%)
Previous CABG*	13 681 (54.3%)	3706 (56.7%)	1614 (47.3%)	2839 (53.9%)	4616 (57.7%)	906 (46.0%)
Previous PCI						
No	14 511 (57.6%)	4167 (63.7%)	1139 (33.4%)	3702 (70.3%)	4976 (62.2%)	527 (26.8%)
Yes—within the past 3 months	2103 (8.3%)	309 (4.7%)	757 (22.2%)	146 (2.8%)	385 (4.8%)	506 (25.7%)
Yes—greater than 3 months	8566 (34.0%)	2062 (31.5%)	1518 (44.5%)	1416 (26.9%)	2633 (32.9%)	937 (47.6%)
Cerebrovascular disease*	5327 (21.2%)	1293 (19.8%)	791 (23.2%)	1075 (20.4%)	1702 (21.3%)	466 (23.7%)
Chronic lung disease*	7055 (28.0%)	1960 (30.0%)	1014 (29.7%)	1447 (27.5%)	2088 (26.1%)	546 (27.7%)
Diabetes*	10 261 (40.8%)	2722 (41.6%)	1509 (44.2%)	1987 (37.7%)	3228 (40.4%)	815 (41.4%)
Hypertension*	20 799 (82.6%)	5416 (82.8%)	2922 (85.6%)	4216 (80.1%)	6576 (82.3%)	1669 (84.7%)

Continued

Table 2. Continued

	Total (n=25 180)	A (n=6538)	DA (n=3414)	Warfarin (n=5264)	A+Warfarin (n=7994)	DA+Warfarin (n=1970)
Renal failure—dialysis*	1185 (4.7%)	381 (5.8%)	216 (6.3%)	211 (4.0%)	306 (3.8%)	71 (3.6%)
Diagnostics						
EF %: mean (SD)*	28.0±9.6	28.5±10.0	28.8±10.4	27.3±9.0	27.7±9.3	28.2±9.9
QRS duration: mean (SD)*	125.1±30.6	126.5±31.2	123.6±31.3	125.7±30.3	125.0±30.1	121.4±29.2
Creatinine level: mean (SD)*	1.5±1.0	1.5±1.1	1.5±1.1	1.5±1.0	1.4±1.0	1.4±1.1
ICD indication*						
Primary Prevention	20 413 (81.1%)	5150 (78.8%)	2560 (75.0%)	4526 (86.0%)	6634 (83.0%)	1543 (78.3%)
Secondary Prevention	4767 (18.9%)	1388 (21.2%)	854 (25.0%)	738 (14.0%)	1360 (17.0%)	427 (21.7%)
ICD type*						
Single chamber	5553 (22.0%)	1115 (17.0%)	576 (16.9%)	1424 (27.1%)	1964 (24.6%)	474 (24.1%)
Dual chamber	10 101 (40.1%)	3039 (46.6%)	1708 (50.1%)	1646 (31.3%)	2915 (36.5%)	793 (40.3%)
Biventricular	9491 (37.7%)	2373 (36.4%)	1125 (3.0%)	2184 (41.6%)	3108 (38.9%)	701 (35.6%)

A indicates any antiplatelet agent; CABG, coronary artery bypass grafting; DA, dual antiplatelet therapy; EF, ejection function; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.
*$P<0.05$.

Table 3. Hospital Characteristics Stratified by Medication Group

	Total (n=25 180)	A (n=6538)	DA (n=3414)	Warfarin (n=5264)	A+Warfarin (n=7994)	DA+Warfarin (n=1970)	*P* Value
Geographic location							
New England	1155 (4.6%)	263 (4.0%)	91 (2.7%)	233 (4.4%)	476 (5.9%)	92 (4.7%)	<0.10
Mid-Atlantic	3429 (13.6%)	782 (12.0%)	406 (11.9%)	773 (14.7%)	1157 (14.5%)	311 (15.8%)	
South Atlantic	5929 (23.5%)	1579 (24.2%)	816 (23.9%)	1297 (24.6%)	1794 (22.4%)	443 (22.5%)	
East North Central	5050 (20.1%)	1284 (19.6%)	747 (21.9%)	964 (18.3%)	1641 (20.5%)	414 (21.0%)	
East South Central	1926 (7.6%)	515 (7.9%)	284 (8.3%)	398 (7.6%)	571 (7.1%)	158 (8.0%)	
West North Central	2427 (9.6%)	632 (9.7%)	301 (8.8%)	405 (7.7%)	899 (11.2%)	190 (9.6%)	
West South Central	2525 (10.0%)	743 (11.4%)	382 (11.2%)	561 (10.7%)	669 (8.4%)	170 (8.6%)	
Mountain	990 (3.9%)	230 (3.5%)	146 (4.3%)	212 (4.0%)	320 (4.0%)	82 (4.2%)	
Pacific	1748 (6.9%)	510 (7.8%)	241 (7.1%)	420 (8.0%)	467 (5.8%)	110 (5.6%)	
Profit type							
Government	437 (1.7%)	107 (1.6%)	61 (1.8%)	93 (1.8%)	151 (1.9%)	25 (1.3%)	<0.01
Private/community	21 945 (87.2%)	5789 (88.5%)	3021 (88.5%)	4653 (88.4%)	6798 (85.0%)	1684 (85.5%)	
University	2798 (11.1%)	642 (9.8%)	332 (9.7%)	518 (9.8%)	1045 (13.1%)	261 (13.2%)	
Community							
Rural	3081 (12.2%)	861 (13.2%)	428 (12.5%)	563 (10.7%)	1019 (12.7%)	210 (10.7%)	<0.01
Suburban	7535 (29.9%)	1911 (29.2%)	971 (28.4%)	1709 (32.5%)	2333 (29.2%)	611 (31.0%)	
Urban	14 564 (57.8%)	3766 (57.6%)	2015 (59.0%)	2992 (56.8%)	4642 (58.1%)	1149 (58.3%)	

A indicates any antiplatelet agent; DA, dual antiplatelet therapy.

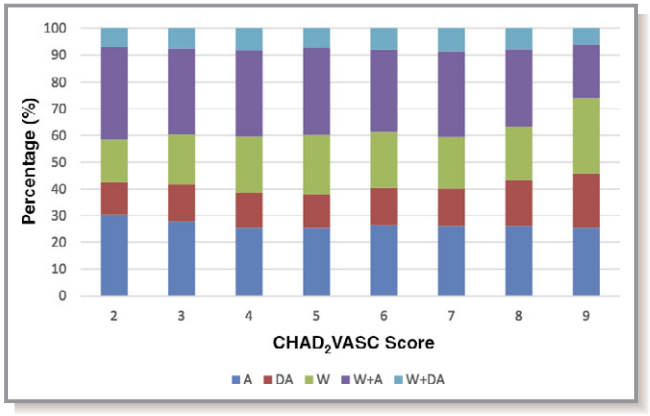

Figure 2. Discharge medications according to $CHADS_2VASC$ score. A indicates any antiplatelet agent; $CHADS_2$ VASC, ; DA, dual antiplatelet therapy; W, warfarin.

Assessment of Outcomes Using Inverse Probability Weights

Comparison of groups using inverse probability–weighted adjustment yielded findings consistent with the adjusted Cox regression models. Patients discharged with DA, warfarin+A, and warfarin+DA were independently associated with higher bleeding risk 30 days following discharge (Table 7). The risk of device-related bleeding was higher in patients discharged with warfarin+A and warfarin+DA. The increased risk of bleeding persisted 90 days following the procedure for patients who were discharged on DA, warfarin+A, and warfarin+DA (Table 7). The risk of device-related bleeding remained elevated in patients discharged with DA, warfarin+A, and warfarin+DA. DA was associated with an increased risk of TEs and device-related complications within 90 days following the procedure (Table 7). The risk of MACE was elevated among patients discharged with A, DA, and DA+warfarin. The elevated risk of MACE in these groups continued 90 days following discharge (Table 7).

Discussion

In a large study of Medicare beneficiaries undergoing first time ICD implantation, we found substantial variation across hospitals in the use of antithrombotic agents. In addition, the risk of postdischarge bleeding events varied by antithrombotic strategy. The combinations of DA, warfarin+A, and warfarin+DA were all associated with an increased risk of bleeding. In contrast, there was no statistically significant difference in the risk of TEs according to antithrombotic strategy used. The findings from our study quantify the risks associated with different approaches to antithrombotic therapy and may identify potential opportunities for reducing complications and improving outcomes among patients undergoing initial ICD implantation.

There have been several studies that have examined anticoagulation strategies in patients receiving heart-rhythm devices. However, the majority of these studies have focused on the perioperative complications related to antithrombotic therapy. There is little data surrounding the role of postdischarge antithrombotic agents and short-term outcomes. Although the majority of risk related to antithrombotic agents is focused on the immediate perioperative period (ie, before hospital discharge), a significant proportion of patients develop complications after discharge. Our study is the first study to demonstrate the risk of bleeding and TEs associated with the choice of antithrombotic agents postdischarge.

Patients with CAD represent a large number of patients who receive ICDs. Atrial fibrillation is common among patients with CAD.[12] The risk of TEs in patients with CAD and AF is often managed by combining low-dose aspirin and warfarin despite little evidence supporting this approach. Therefore, the risk of bleeding must be carefully weighed against the risk of TEs in this population, particularly in the periprocedural period following ICD implantation. In our study, a significant number of patients were on multiple antithrombotic medications, and we observed regional variation in patterns of antithrombotic medications prescribed postdischarge. Furthermore, this variation in antithrombotic medications was not influenced by patients' underlying risk of TEs. There was a large of number of patients being discharged without warfarin despite an elevated risk of TEs. The high risk of TEs evident by $CHADS_2VASC \geq 2$ or higher was not predictive of discharge warfarin, suggesting the possibility that the choice of antithrombotic agents after ICD implantation is mainly driven by the risk of bleeding rather than TEs. In our study, discharge DA was associated with an increase in the risk of bleeding without any associated reduction in TEs. This is consistent with the results of several trials, which have established an increase in the risk of bleeding without a significant reduction in TEs in AF patients treated with DA therapy.[2,13]

Current guidelines recommend the use of "triple-therapy" among patients with AF at moderate or high risk of TEs who also have an indication for DA therapy.[14] In our study, patients discharged with "triple-therapy" were at increased risk of bleeding, TEs, and MACE compared with other strategies. These findings are consistent with previous studies showing a higher rate of bleeding and cardiovascular complications associated with triple therapy.[15] It is likely that many of the patients discharged on "triple-therapy" had a compelling reason justifying the use of multiple agents including the recent implantation of a drug-eluting stent. Consistent with this hypothesis, we found that patients discharged on "triple-therapy" were much more likely to have undergone a PCI within 3 months of device implant. Nevertheless, we found that a substantial number of patients discharged on "triple therapy" had no history of PCI or

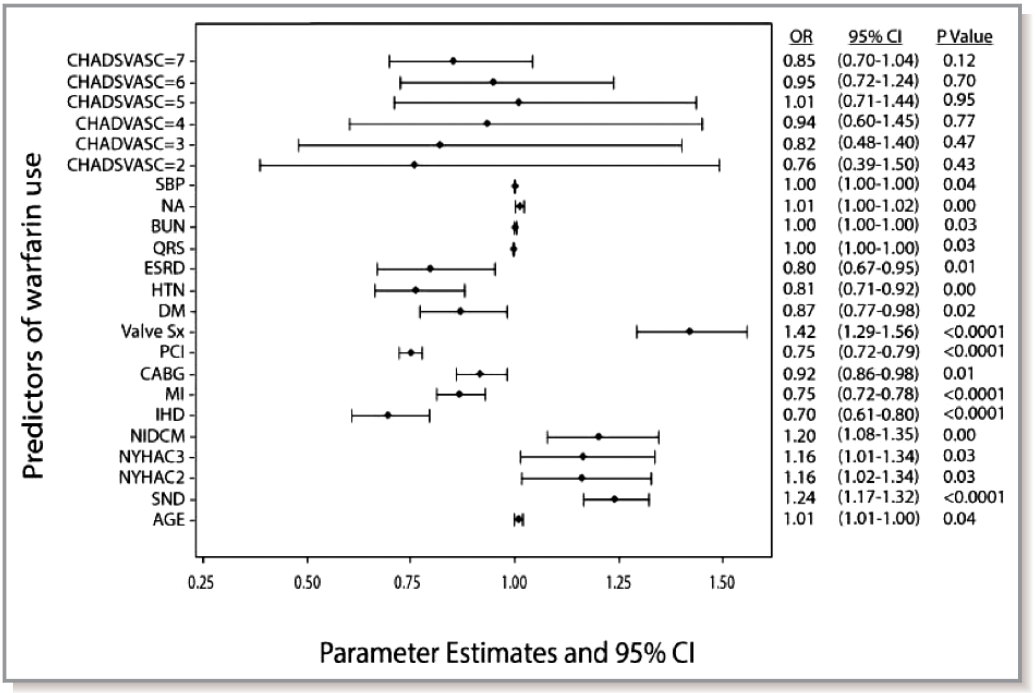

Figure 3. Selected predictors of postdischarge warfarin. BUN indicates blood urea nitrogen; CABG, coronary artery bypass grafting; $CHAD_2SVASC$, ; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; NA, Sodium; NIDCM, nonischemic dilated cardiomyopathy; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SND, sinus node dysfunction; valve Sx, valve surgery.

myocardial infarction. Although these findings raise questions about whether "triple-therapy" was in fact necessary, this may simply reflect the fact that the registry may not capture all indications for triple therapy in this population. Nevertheless, our study contributes to our understanding of this issue by characterizing the risks associated with "triple-therapy." Given the excess risk of adverse outcomes associated with use of "triple-therapy" following ICD implantation, practitioners should take every effort to ensure that this risk is clinically justified. Furthermore, our findings highlight the need for additional studies to identify the best strategy for balancing the risks and benefits of different antiplatelet and anticoagulant drug combinations in this population. Recent trials have shown an increase in the risk of bleeding with no

Table 4. Number of Patients With Bleeding, Thromboembolic, and Device-Related Complications

	Total (n=25 180)	A (n=6538)	DA (n=3414)	Warfarin (n=5264)	A+Warfarin (n=7994)	DA+Warfarin (n=1970)	*P* Value
Thirty-day outcomes							
Bleeding	575 (2.3%)	142 (2.2%)	84 (2.5%)	90 (1.7%)	188 (2.4%)	71 (3.6%)	0.0001
Thromboembolic events	356 (1.4%)	89 (1.4%)	67 (2.0%)	79 (1.5%)	99 (1.2%)	22 (1.1%)	0.03
Device-related complications	605 (2.4%)	148 (2.3%)	95 (2.8%)	121 (2.3%)	190 (2.4%)	51 (2.6%)	0.5
Device-related bleeding	204 (0.8%)	44 (0.7%)	31 (0.9%)	30 (0.6%)	77 (1.0%)	22 (1.1%)	0.03
MACE	642 (2.5%)	197 (3.0%)	133 (3.9%)	93 (1.8%)	162 (2.0%)	57 (2.9%)	<0.0001
Ninety-day outcomes							
Bleeding	1147 (4.6%)	260 (4.0%)	166 (4.9%)	197 (3.7%)	379 (4.7%)	145 (7.4%)	<0.0001
Thromboembolic events	705 (2.8%)	201 (3.1%)	126 (3.7%)	142 (2.7%)	189 (2.4%)	47 (2.4%)	0.001
Device-related complications	1072 (4.3%)	257 (3.9%)	163 (4.8%)	202 (3.8%)	360 (4.5%)	90 (4.6%)	0.096
Device-related bleeding	299 (1.2%)	63 (1.0%)	51 (1.5%)	44 (0.8%)	106 (1.3%)	35 (1.8%)	0.001
MACE	1766 (7.0%)	502 (7.7%)	339 (9.9%)	317 (6.0%)	459 (5.7%)	149 (7.6%)	<0.0001

A indicates any antiplatelet agent; DA, dual antiplatelet therapy; MACE, major adverse cardiovascular events.

Table 5. Hazard Ratios for Medication Groups After Discharge

	Warfarin	A	DA	A+Warfarin	DA+Warfarin
Bleeding					
Thirty-day					
Unadjusted	Reference	1.27 (0.98 to 1.66)	1.45 (1.07 to 1.95)	1.38 (1.07 to 1.77)	2.13 (1.56 to 2.91)
Adjusted	Reference	1.25 (0.96 to 1.62)	1.42 (1.05 to 1.91)	1.41 (1.10 to 1.82)	2.18 (1.60 to 2.98)
Ninety-day					
Unadjusted	Reference	1.07 (0.89 to 1.28)	1.31 (1.06 to 1.61)	1.27 (1.07 to 1.51)	2.00 (1.62 to 2.48)
Adjusted	Reference	1.04 (0.87 to 1.26)	1.28 (1.04 to 1.58)	1.31 (1.10 to 1.55)	2.06 (1.66 to 2.55)
Thromboembolic events					
Ninety-day					
Unadjusted	Reference	0.90 (0.67 to 1.23)	1.31 (0.94 to 1.81)	0.82 (0.61 to 1.11)	0.74 (0.46 to 1.19)
Adjusted	Reference	0.88 (0.65 to 1.19)	1.22 (0.88 to 1.69)	0.83 (0.62 to 1.11)	0.73 (0.45 to 1.16)
Ninety-day					
Unadjusted	Reference	1.14 (0.92 to 1.41)	1.37 (1.08 to 1.75)	0.87 (0.70 to 1.09)	0.88 (0.63 to 1.23)
Adjusted	Reference	1.10 (0.88 to 1.36)	1.25 (0.98 to 1.59)	0.89 (0.71 to 1.10)	0.86 (0.62 to 1.19)
Device-related complications					
Thirty-day					
Unadjusted	Reference	0.98 (0.77 to 1.25)	1.22 (0.93 to 1.59)	1.03 (0.82 to 1.30)	1.13 (0.81 to 1.56)
Adjusted	Reference	0.98 (0.77 to 1.25)	1.22 (0.93 to 1.59)	1.05 (0.84 to 1.32)	1.13 (0.81 to 1.57)
Ninety-day					
Unadjusted	Reference	1.02 (0.85 to 1.23)	1.25 (1.02 to 1.54)	1.18 (0.99 to 1.40)	1.19 (0.93 to 1.53)
Adjusted	Reference	1.02 (0.85 to 1.22)	1.24 (1.01 to 1.52)	1.21 (1.01 to 1.43)	1.21 (0.94 to 1.55)
Device-related bleeding					
Thirty-day					
Unadjusted	Reference	1.18 (0.74 to 1.88)	1.60 (0.97 to 2.64)	1.69 (1.11 to 2.58)	1.97 (1.13 to 3.41)
Adjusted	Reference	1.17 (0.74 to 1.86)	1.58 (0.95 to 2.61)	1.74 (1.14 to 2.66)	2.01 (1.16 to 3.49)
Ninety-day					
Unadjusted	Reference	1.15 (0.78 to 1.70)	1.79 (1.20 to 2.68)	1.59 (1.12 to 2.26)	2.13 (1.37 to 3.23)
Adjusted	Reference	1.13 (0.77 to 1.67)	1.74 (1.16 to 2.61)	1.63 (1.15 to 2.32)	2.16 (1.39 to 3.37)
MACE					
Thirty-day					
Unadjusted	Reference	1.72 (1.34 to 2.20)	2.23 (1.71 to 2.90)	1.15 (0.89 to 1.48)	1.65 (1.18 to 2.29)
Adjusted	Reference	1.68 (1.32 to 2.16)	2.16 (1.66 to 2.82)	1.22 (0.94 to 1.57)	1.75 (1.26 to 2.44)
Ninety-day					
Unadjusted	Reference	1.29 (1.12 to 1.49)	1.69 (1.45 to 1.97)	0.95 (0.83 to 1.10)	1.27 (1.04 to 1.54)
Adjusted	Reference	1.26 (1.10 to 1.45)	1.65 (1.41 to 1.92)	1.01 (0.87 to 1.16)	1.35 (1.11 to 1.64)

A indicates any antiplatelet agent; DA, dual antiplatelet therapy; MACE, major adverse cardiovascular events.

difference in the risk of TEs or MACE in patients receiving triple therapy compared to those receiving warfarin and clopidogrel.[15,16] These results are consistent with our findings and suggest that double therapy may be an alternative to triple therapy in patients receiving ICDs. There is a need for randomized controlled trials that explore the role of different combinations of antithrombotic drugs in patients following ICD implantation.

Several aspects of our study warrant further consideration. Our study cohort was limited to Medicare patients older than 65, and this population may not be representative of all patients undergoing ICD implantation. However,

Table 6. Bleeding and Thromboembolic Events in Patients Treated and Not Treated With Warfarin

	Warfarin	No Warfarin	*P* Value
Thirty-day outcomes			
$CHAD_2VASC \geq 2$			
Bleeding	19 (1.5%)	15 (1.7%)	0.79
Thromboembolic events	11 (0.9%)	9 (1.0%)	0.77
$CHAD_2VASC=3$ to 5			
Bleeding	254 (2.2%)	170 (2.3%)	0.60
Thromboembolic events	128 (1.1%)	91 (1.2%)	0.41
$CHADSVASC \geq 6$			
Bleeding	76 (3.1%)	41 (2.4%)	0.16
Thromboembolic events	61 (2.5%)	56 (3.3%)	0.15
Ninety-day outcomes			
$CHAD_2VASC \geq 2$			
Bleeding	41 (3.3%)	28 (3.1%)	0.83
Thromboembolic events	19 (1.5%)	15 (1.7%)	0.79
$CHAD_2VASC=3$ to 5			
Bleeding	539 (4.7%)	323 (4.4%)	0.40
Thromboembolic events	237 (2.0%)	202 (2.7%)	<0.01
$CHAD_2VASC \geq 6$			
Bleeding	141 (5.8%)	75 (4.4%)	0.04
Thromboembolic events	122 (5.1%)	110 (6.4%)	0.06

Table 7. Hazard Ratios for Medication Groups Using Inverse Probability Weights

	Warfarin	A	DA	A+Warfarin	DA+Warfarin
Bleeding					
Thirty-day	Reference	1.21 (0.93 to 1.57)	1.39 (1.03 to 1.87)	1.32 (1.03 to 1.69)	2.03 (1.49 to 2.77)
Ninety-day	Reference	1.04 (0.86 to 1.25)	1.29 (1.04 to 1.58)	1.24 (1.05 to 1.47)	1.96 (1.58 to 2.42)
Thromboembolic events					
Thirty-day	Reference	0.88 (0.65 to 1.19)	1.29 (0.93 to 1.79)	0.79 (0.59 to 1.06)	0.72 (0.44 to 1.15)
Ninety-day	Reference	1.10 (0.89 to 1.36)	1.35 (1.06 to 1.71)	0.83 (0.67 to 1.03)	0.84 (0.60 to 1.17)
Device-related complications					
Thirty-day	Reference	0.97 (0.76 to 1.23)	1.19 (0.90 to 1.56)	1.03 (0.82 to 1.29)	1.10 (0.79 to 1.53)
Ninety-day	Reference	1.03 (0.85 to 1.23)	1.25 (1.01 to 1.54)	1.18 (1.00 to 1.41)	1.19 (0.93 to 1.53)
Device-related bleeding					
Thirty-day	Reference	1.17 (0.74 to 1.86)	1.57 (0.95 to 2.61)	1.73 (1.14 to 2.63)	1.96 (1.13 to 3.40)
Ninety-day	Reference	1.17 (0.80 to 1.72)	1.79 (1.19 to 2.69)	1.63 (1.15 to 2.32)	2.18 (1.39 to 3.40)
MACE					
Thirty-day	Reference	1.69 (1.33 to 2.16)	2.17 (1.66 to 2.83)	1.11 (0.86 to 1.43)	1.61 (1.16 to 2.24)
Ninety-day	Reference	1.27 (1.10 to 1.46)	1.66 (1.42 to 1.93)	0.92 (0.80 to 1.07)	1.24 (1.02 to 1.51)

A indicates any antiplatelet agent; DA, dual antiplatelet therapy; MACE, major adverse cardiovascular events.

this population is representative of the majority of patients implanted with ICDs in the United States. We did not have information about changes in medical regimens or medication compliance during the follow-up period. As such, we restricted our primary analysis to short-term outcomes after discharge. It is possible that unmeasured confounders may have affected the results of our analysis, but we employed rigorous analytical techniques in order to minimize the effects of confounding on our results. The data regarding the perioperative management of antithrombotic therapy and International Normalized Ratio levels were not available through the National Cardiovascular Data Registry™. Therefore, we were not able to assess the role of perioperative management of antithrombotic therapy and International Normalized Ratio levels on outcomes. The data needed to calculate the bleeding risk (ie, ATRIA bleeding risk score) were not available through the ICD registry. Therefore, we were not able to confirm high bleeding risk as the reason for lack of postdischarge warfarin in patients with high risk for TEs. Finally, our analysis did not include newer anticoagulant and antiplatelet agents; therefore, these results cannot be generalized to patients discharged with novel antithrombotic agents.

In conclusion, we found that patients discharged with warfarin alone have the lowest risk of bleeding after ICD implantation. The concomitant use of antiplatelet therapy with warfarin is associated with increased risk of bleeding without a concomitant reduction in the risk of TEs. These data underscore challenges associated with anticoagulation and antiplatelet therapy following ICD implantation and suggest the need for novel strategies to reduce the risk of complications in this population.

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