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# Off-label Use of Direct Oral Anticoagulants in Patients Receiving Surgical Mechanical and Bioprosthetic Heart Valves

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## Introduction

In patients with mechanical heart valves, use of direct oral anticoagulants (DOACs) is currently contraindicated, and their use in patients with bioprosthetic heart valves is off-label.[1,2] We sought to determine the current state of use of DOACs in patients with surgical prosthetic heart valves in the US and evaluate differences in preoperative and postoperative profiles among patients discharged while receiving DOACs vs warfarin.

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## Methods

This retrospective cohort study was conducted using data extracted from the Society of Thoracic Surgeons Adult Cardiac Surgery Database risk calculator, version 2.81.[3] Patients who underwent surgical aortic valve replacement or mitral valve replacement with either mechanical heart valves or bioprosthetic heart valves between July 2014 and June 2017 were included. Data were analyzed from May 1 to September 30, 2020. Patients who were not alive at the time of discharge were excluded. Descriptive analyses were performed to summarize variables. The Cleveland Clinic institutional review board determined this study to be exempt from review owing to use of deidentified data, with institutional-determined waiver of informal consent (oral or written). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. Statistical analysis was performed using Python, version 3.6.7 (Python Software Foundation) and Microsoft Excel (Microsoft Corp). Statistical significance was set at 2-tailed $P < .05$.

## Results

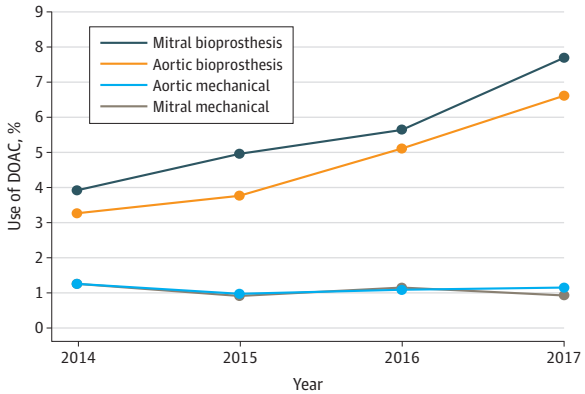
The study population comprised 177 915 patients; 62% were male and 38% were female. The mean (SD) age of the study population was 62.2 (10.8) years. The use of DOACs was observed among 78.6% (858 Of 1092) hospitals and 59.6% (1627 of 2731) physicians captured in the STS database. In patients undergoing aortic valve replacement with mechanical heart valves (n = 18 142), the overall use of DOACs at discharge over the study period was 1.1% (193 of 18 142; 129 patients received factor Xa inhibitors, and 69 patients received thrombin inhibitors): 1.25% in 2014, 0.99% in 2015, 1.09% in 2016, and 1.17% in 2017 for aortic valve replacement ($P = .84$ for trend) (**Figure**). In patients undergoing mitral valve replacement with mechanical heart valves (n = 13 942), the overall use of DOACs at discharge over the study period was 1.04% (139 of 13 942; 94 patients received factor Xa inhibitors, and 46 patients received thrombin inhibitors): 1.25% in 2014, 0.91% in 2015, 1.16% in 2016, and 0.93% in 2017 ($P = .45$ for trend). In patients undergoing aortic valve replacement with bioprosthetic heart valves (n = 116 203), the overall use of DOACs over the study period was 4.66% (5625 of 116 203; 4622 patients received factor Xa inhibitors, and 680 patients received thrombin inhibitors), and the use increased over the study period: 3.30% in 2014, 3.80% in 2015, 5.14% in 2016, and 6.64% in 2017 ($P = .02$ for trend). In patients undergoing mitral valve replacement (n = 39 243) with bioprosthetic heart valves, the overall use of DOACs over the study period was 5.89% (2180 of 39 243; 1906 patients received factor Xa inhibitors, and 289 patients received

thrombin inhibitors), and the use increased over the study period: 3.94% in 2014, 4.97% in 2015, 5.66% in 2016, and 7.72% in 2017 for mitral valve replacement ($P = .03$ for trend).

In patients receiving aortic valve replacement or mitral valve replacement with mechanical heart valves, 88 patients were discharged receiving exclusively DOAC (no warfarin), and 26 474 receiving exclusively warfarin (no DOAC). Of these, patients discharged receiving DOAC were older (mean [SD] age, 60.8 [12.5] years) compared with those discharged receiving warfarin (mean [SD] age, 53 [11.8] years) ($P < .001$), and there was a greater prevalence of preoperative hypertension (83.0% [73 of 88] vs 68.0% [17 974 of 26 398]; $P = .003$), dyslipidemia (69.3% [61 of 88] vs 57.0% [14 926 of 26 351]; $P = .02$), peripheral arterial disease (18.2% [16 of 88] vs 6.6% [1747 of 26 331]; $P < .001$), heparin-induced thrombocytopenia antibody (14.0% [2 of 14] vs 1.9% [86 of 4490]; $P < .001$), and lower mean (SD) international normalized ratio (1.07 [0.15] vs 1.13 [0.4]; $P < .001$) (**Table**). Preoperative use of factor Xa inhibitors was significantly higher for patients discharged receiving DOAC than for those discharged receiving warfarin (3.8% [3 of 80] vs 0.3% [73 of 24 721]; $P < .001$). Postoperative (before discharge) events were also higher in patients discharged receiving DOACs than for those discharged receiving warfarin, such as atrial fibrillation or flutter (43.0% [38 of 88] vs 22.0% [5834 of 26 474]; $P < .001$), reoperation for bleeding (9.1% [8 of 88] vs 3.0% [783 of 26 474]; $P = .001$), venous thromboembolism (3.4% [3 of 88] vs 0.5% [138 of 26 474]; $P = .001$), pulmonary thromboembolism (1.1% [1 of 88] vs 0.04% [11 of 26 474]; $P < .001$), and deep vein thrombosis (3.4% [3 of 88] vs 0.4% [112 of 26 474]; $P < .001$).

In patients receiving aortic valve replacement or mitral valve replacement with bioprosthetic heart valves, 6740 patients were discharged receiving exclusively DOAC (no warfarin), and 48 107 receiving exclusively warfarin (no DOAC). There was a greater prevalence of preoperative arrhythmias (54.8% [3683 of 6725] vs 42.0% [20 109 of 47 947]; $P < .001$), and a lesser prevalence of dialysis (2.0% [132 of 6726] vs 3.2% [1555 of 48 039]; $P < .001$) and heparin-induced thrombocytopenia antibody (3.3% [34 of 1022] vs 2.3% [192 of 8324]; $P < .001$) in patients discharged receiving DOAC. Preoperative use of factor Xa inhibitors (2.6% [165 of 6300] vs 0.5% [220 of 44 853]; $P < .001$) and thrombin inhibitors (0.5% [33 of 6322] vs 0.2% [100 of 44 969]; $P < .001$) was higher in patients discharged receiving DOAC than for those discharged receiving warfarin. Patients discharged receiving DOAC had lesser postoperative (before discharge) events like kidney failure (2.2% [150 of 6740] vs 2.8% [1368 of 48 107]; $P < .001$) and reoperation for bleeding (2.6% [176 of 6740] vs 3.4% [1647 of 48 107]; $P < .001$), but occurrence of postoperative events like atrial fibrillation or flutter (47.7% [3213 of 6740] vs 40.0% [19 239 of 48 107]; $P < .001$), venous thromboembolism (2.5% [168 of 6740] vs 1.8% [870 of 48 107]; $P < .001$), and DVT was higher in patients discharged receiving DOACs (2.1% [143 of 6740] vs 1.5% [717 of 48 107]; $P < .001$).

**Figure. National Trend in Use of Direct Oral Anticoagulants (DOACs) Among Patients With Prosthetic Heart Valves**




There were 2365 (1.33%) patients who received both aortic and mitral mechanical valves, and 7025 (3.94%) patients who received both aortic and mitral bioprosthetic valves.

Table. Differences in Preoperative and Postoperative Profiles Among Patients With Prosthetic Heart Valves Discharged Receiving DOACs vs Warfarin

| | Mechanical | | | | | Bioprosthetic | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | DOAC (n = 88)[a] | | Warfarin (n = 26 474) | | | DOAC (n = 6740)[b] | | Warfarin (n = 48 107) | | |
| Characteristic | Total No.[a] | No. (%) | Total No.[c] | No. (%) | *P* value | Total No.[c] | No. (%) | Total No.[c] | No. (%) | *P* value |
| **Demographic** | | | | | | | | | | |
| Age, mean (SD) y | 88 | 60.8 (12.5) | 26 474 | 53 (11.8) | <.001 | 6740 | 66.3 (7.8) | 48 107 | 65.0 (9.0) | <.001 |
| Female | 88 | 40 (45) | 26 474 | 11 634 (44) | .62 | 6740 | 2384 (35) | 48 107 | 19 115 (40) | <.001 |
| Male | 88 | 48 (55) | 26 474 | 14 827 (56) | .65 | 6740 | 4353 (65) | 48 107 | 28 980 (60) | <.001 |
| Weight, mean (SD), kg | 88 | 88.2 (24.3) | 26 474 | 88.8 (23.8) | .82 | 6740 | 99.6 (22.5) | 48 107 | 88.4 (21.6) | <.001 |
| Height, mean (SD), cm | 88 | 172 (11) | 26 474 | 171 (11.3) | .45 | 6740 | 172 (10.6) | 48 107 | 171 (10.8) | <.001 |
| **Preoperative** | | | | | | | | | | |
| Diabetes | 88 | 26 (29.5) | 26 412 | 6369 (24) | .20 | 6728 | 2405 (35.7) | 48 025 | 15 992 (33) | <.001 |
| Hypertension | 88 | 73 (83) | 26 398 | 17 974 (68) | .003 | 6731 | 5798 (86.1) | 48 035 | 38 728 (81) | <.001 |
| Dyslipidemia | 88 | 61 (69.3) | 26 351 | 14 926 (57.0) | .02 | 6717 | 5135 (76.4) | 47 953 | 34 805 (73) | <.001 |
| Dialysis | 88 | 3 (3.4) | 26 418 | 1210 (4.6) | .46 | 6726 | 132 (2.0) | 48 039 | 1555 (3.2) | <.001 |
| Arrhythmia | 88 | 41 (47) | 26 368 | 8023 (30) | <.001 | 6725 | 3683 (54.8) | 47 947 | 20 109 (42.0) | <.001 |
| Arrhythmia (atrial fibrillation) | 40 | 36 (90) | 7921 | 6686 (84) | .32 | 3658 | 3298 (90) | 19 959 | 17 678 (89) | <.001 |
| Cerebrovascular disease | 88 | 18 (20.5) | 26 251 | 4011 (15.3) | .15 | 6712 | 1492 (22.2) | 47 829 | 9422 (19.7) | <.001 |
| Peripheral arterial disease | 88 | 16 (18.2) | 26 331 | 1747 (6.6) | <.001 | 6714 | 770 (11.5) | 47 906 | 4941 (10.3) | <.001 |
| Endocarditis | 88 | 6 (6.8) | 26 436 | 3585 (13.6) | .06 | 6734 | 511 (7.6) | 48 055 | 4539 (9.4) | <.001 |
| Prior myocardial infarction | 85 | 15 (17.6) | 26 301 | 3294 (12.5) | .13 | 6701 | 1286 (19.2) | 47 823 | 8770 (18.3) | <.001 |
| Thoracic aortic disease | 88 | 3 (3.4) | 26 270 | 1791 (6.8) | .17 | 6687 | 414 (6.2) | 47 862 | 2645 (5.5) | <.001 |
| Liver disease | 88 | 6 (6.8) | 26 234 | 1318 (5.0) | .35 | 6674 | 334 (5.0) | 47 766 | 2312 (4.8) | <.001 |
| Hematocrit, mean (SD) | 88 | 37.6 (6.5) | 26 474 | 38.8 (5.9) | .08 | 6740 | 39.2 (5.7) | 48 107 | 38.7 (5.8) | <.001 |
| Platelets, mean (SD) | 88 | 224 598 (75 325) | 26 474 | 225 494 (76 173) | .91 | 6740 | 211 596 (70 625) | 48 107 | 214 992 (72 966) | <.001 |
| International normalized ratio, mean (SD) | 88 | 1.07 (0.15) | 26 474 | 1.13 (0.4) | <.001 | 6740 | 1.11 (0.21) | 48 107 | 1.15 (0.37) | <.001 |
| Heparin-induce thrombocytopenia antibody | 14 | 2 (14.0) | 4490 | 86 (1.9) | <.001 | 1022 | 34 (3.3) | 8324 | 192 (2.3) | <.001 |
| **Preoperative medication** | | | | | | | | | | |
| Aspirin | 87 | 40 (46) | 26 308 | 11 323 (43) | .49 | 6691 | 3556 (53.1) | 47 834 | 24 679 (52) | <.001 |
| Warfarin | 81 | 0 (0) | 24 782 | 369 (1.5) | .22 | 6323 | 25 (0.4) | 44 934 | 743 (1.7) | <.001 |
| Adenosine diphosphate inhibitors (within 5 d) | 88 | 2 (2.3) | 26 375 | 386 (1.5) | .41 | 6707 | 150 (2.2) | 47 955 | 1018 (2.1) | <.001 |
| Glycoprotein IIb/IIIa inhibitor | 88 | 0 (0) | 26 389 | 44 (0.2) | .51 | 6711 | 21 (0.3) | 47 992 | 94 (0.2) | <.001 |
| Factor Xa inhibitors | 80 | 3 (3.8) | 24 721 | 73 (0.3) | <.001 | 6300 | 165 (2.6) | 44 853 | 220 (0.5) | <.001 |
| Antiplatelets (within 5 d) | 81 | 2 (2.5) | 24 794 | 446 (1.8) | .50 | 6323 | 91 (1.4) | 44 974 | 975 (2.2) | <.001 |
| Thrombolytics | 88 | 0 (0) | 26 379 | 37 (0.14) | .52 | 6714 | 10 (0.15) | 47 993 | 42 (0.1) | <.001 |
| Thrombin inhibitors | 81 | 0 (0) | 24 784 | 43 (0.17) | .52 | 6322 | 33 (0.5) | 44 969 | 100 (0.2) | <.001 |
| **Postoperative event** | | | | | | | | | | |
| Kidney failure | 88 | 3 (3.4) | 26 474 | 648 (2.4) | .43 | 6740 | 150 (2.2) | 48 107 | 1368 (2.8) | <.001 |
| Atrial fibrillation or flutter | 88 | 38 (43.0) | 26 474 | 5834 (22.0) | <.001 | 6740 | 3213 (47.7) | 48 107 | 19 239 (40.0) | <.001 |
| Anticoagulant events | 88 | 2 (2.3) | 26 474 | 275 (1.0) | .21 | 6740 | 120 (1.8) | 48 107 | 824 (1.7) | <.001 |
| Reoperation for bleeding | 88 | 8 (9.1) | 26 474 | 783 (3.0) | <.001 | 6740 | 176 (2.6) | 48 107 | 1647 (3.4) | <.001 |
| Stroke | 88 | 3 (3.4) | 26 474 | 330 (1.2) | .06 | 6740 | 135 (2.0) | 48 107 | 819 (1.7) | <.001 |
| Tamponade | 88 | 0 (0) | 26 474 | 59 (0.2) | .49 | 6740 | 8 (0.11) | 48 107 | 60 (0.1) | <.001 |
| Transient ischemic attack | 88 | 1 (1.1) | 26 474 | 58 (0.2) | .06 | 6740 | 25 (0.37) | 48 107 | 159 (0.3) | <.001 |
| Venous thromboembolism | 88 | 3 (3.4) | 26 474 | 138 (0.5) | .001 | 6740 | 168 (2.5) | 48 107 | 870 (1.8) | <.001 |
| Reoperation for valve dysfunction | 88 | 0 (0) | 26 474 | 48 (0.2) | .50 | 6740 | 5 (0.07) | 48 107 | 69 (0.1) | <.001 |
| New dialysis requirement | 88 | 2 (2.3) | 26 474 | 403 (1.5) | .43 | 6740 | 89 (1.3) | 48 107 | 888 (1.8) | <.001 |
| Pulmonary thromboembolism | 88 | 1 (1.1) | 26 474 | 11 (0.04) | <.001 | 6740 | 25 (0.37) | 48 107 | 124 (0.3) | <.001 |
| Deep vein thrombosis | 88 | 3 (3.4) | 26 474 | 112 (0.4) | <.001 | 6740 | 143 (2.1) | 48 107 | 717 (1.5) | <.001 |

Abbreviation: DOAC, direct oral anticoagulants.

[a] A total of 67 patients received factor Xa inhibitor and 22 received thrombin-inhibitor.

[b] A total of 5993 patients received factor Xa inhibitor and 769 received thrombin-inhibitor.

[c] Number of patients with data available.

## Discussion

The main limitation of this study is the lack of follow-up data to compare outcomes of DOACs vs warfarin in patients with prosthetic valves. Despite this limitation, our study suggests a prevailing off-label use of DOACs in patients with prosthetic heart valves without satisfactory safety data. Until the completion of randomized clinical trials that provide sufficient evidence for DOAC use, physicians may wish to exercise caution with regard to DOAC prescription for patients with prosthetic heart valves.

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**Author Contributions**: Dr Kalra had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Kalra and Raza contributed equally.

*Concept and design:* Kalra, Raza, Jafry, King, Lahorra.

*Acquisition, analysis, or interpretation of data:* Kalra, Raza, Jafry, Svensson, Kapadia.

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