Supplementary Materials

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*Cardiovascular and Bleeding Outcomes with Anticoagulants Across Kidney Disease Stages: Analysis of a National US Cohort*

Supplemental Table S1: ICD-9 codes used to determine combined CVD outcomes, bleeding outcomes, and intracranial bleeding outcomes.

Supplemental Table S2: CHA2DS2-VASC and HAS-BLED score of individuals in OLDW with atrial fibrillation (AF) stratify by CKD stage.

Supplemental Table S3: Hazard ratios for the association of DOAC vs warfarin treatment with cardiovascular combined outcomes in (A) 351,407 individuals in the OLDW in time-varying as-treated analysis across 4 models of adjustment (warfarin as reference group) and in (B) 303,505 non-CKD, 25,503 CKD stage 3, 6,414 CKD stage 4 and 5, and 5,292 ESKD individuals in the OLDW with model 3 and 4 adjustments.

Supplemental Table S4: Hazard ratios for the association of DOAC vs warfarin treatment with bleeding outcomes in (A) 351,407 individuals in the OLDW in time-varying as-treated analysis across 4 models of adjustment (warfarin as reference group) and in (B) 303,505 non-CKD, 25,503 CKD stage 3, 6,414 CKD stage 4 and 5, and 5,292 ESKD individuals in the OLDW with model 3 and 4 adjustments.

Supplemental Table S5: Hazard ratios for the association of anticoagulation treatments with (a) cardiovascular combined and (b) bleeding outcome after matching DOAC patients with warfarin patients using coarsened exact matching in 299,171 non-CKD, 23,012 CKD Stage 3, 4,696 CKD Stage 4-5, and 2,884 ESRD OptumLabs patients (reference: warfarin patients).

Supplemental Figure S1: Study period for treatment cohorts.

Supplemental Figure S2: Cohort construction.

Supplemental Table S1**.** ICD-9 codes used to determine combined CVD outcomes, bleeding outcomes, and intracranial bleeding outcomes.

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| **Cardiovascular disease (CVD) Combined Outcome** |
| Myocardial Infarction (MI)410, I21, I22Ischemic Stroke433, 434, 435, 436, H34, I63, I64 |
| **Bleeding** |
| Non-Cerebral Bleeding Upper Gastrointestinal Tract5307, 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 5780, 5781, K2211, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282 K284, K286, K2901 K31811, K920, K921 Non-Cerebral Bleeding Lower Gastrointestinal Tract5693, 5789, K625, K922Hemoperitoneum56881, K661 Hematuria5997, 53501, 53511, 53521, N020, N021, N022, N023, N024, N025, N026, N027, N028, N029, R310, R311, K226, K250, K252, K254, K256, K260, K262, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625 EpistaxisR040Hemoptysis7863, R042, R048, R049Vaginal hemorrhage6262, N920, N921NOS Hemorrhage4590, R58  |

Supplemental Table S2**.** CHA2DS2-VASC and HAS-BLED score of individuals in OLDW with atrial fibrillation (AF) stratify by CKD stage.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   | Total Cohort | Non-CKD | CKD3 | CKD4&5 | ESRD |
| **Variables** | **DOAC** | **Warfarin**  | **DOAC** | **Warfarin**  | **DOAC** | **Warfarin**  | **DOAC** | **Warfarin**  | **DOAC** | **Warfarin**  |
| CHA2DS2-VASC Score |   |  |   |  |   |  |   |  |   |   |
| Total Patients | 83178 (53) | 73594 (47) | 71334 (55) | 57286 (45) | 7255 (48) | 7900 (52) | 1479 (37) | 2543 (63) | 636 (21) | 2424 (79) |
| Mediun (IQR) | 3 (2,5) | 4 (3,5) | 3 (2,5) | 4 (2,5) | 5 (3,6) | 5 (4,6) | 5 (4,6) | 5 (4,6) | 5 (4,6) | 5 (4,6) |
|  Score: 0-2 | 30473 (37) | 18083 (25) | 29048 (41) | 16690 (29) | 890 (12) | 708 (9) | 78 (5) | 147 (6) | 64 (10) | 184 (8) |
|  Score: 3 | 15157 (18) | 12925 (18) | 13512 (19) | 10959 (19) | 1021 (14) | 1017 (13) | 158 (11) | 242 (10) | 83 (13) | 257 (11) |
|  Score: 4 | 12938 (16) | 12897 (18) | 10797 (15) | 9953 (17) | 1356 (19) | 1446 (18) | 215 (15) | 414 (16) | 110 (17) | 444 (18) |
|  Score: 5 | 11545 (14) | 12716 (17) | 8817 (12) | 8902 (16) | 1696 (23) | 1853 (23) | 386 (26) | 671 (26) | 136 (21) | 548 (23) |
|  Score: 6 | 7294 (9) | 8823 (12) | 5258 (7) | 5818 (10) | 1221 (17) | 1433 (18) | 331 (22) | 522 (21) | 103 (16) | 462 (19) |
|  Score: 7 | 3791 (5) | 5179 (7) | 2644 (4) | 3250 (6) | 657 (9) | 879 (11) | 191 (13) | 303 (12) | 80 (13) | 313 (13) |
|  Score: 8 | 1980 (2) | 2971 (4) | 1258 (2) | 1714 (3) | 414 (6) | 564 (7) | 120 (8) | 244 (10) | 60 (9) | 216 (9) |
| HAS-BLED Score |   |  |   |  |   |  |   |  |   |   |
| Total Patients | 83178 (53) | 73594 (47) | 71334 (55) | 57286 (45) | 7255 (48) | 7900 (52) | 1479 (37) | 2543 (63) | 636 (21) | 2424 (79) |
| Mediun (IQR) | 2 (1,3) | 2 (1,3) | 2 (1,2) | 2 (1,3) | 3 (3,4) | 3 (3,4) | 4 (3,4) | 4 (3,4) | 3 (3,4) | 4 (3,4) |
|  Score: 0-2 | 57761 (69) | 44130 (60) | 54645 (77) | 40306 (70) | 1386 (19) | 1379 (17) | 184 (12) | 300 (12) | 106 (17) | 346 (14) |
|  Score: 3 | 15682 (19) | 17048 (23) | 11570 (16) | 11510 (20) | 2721 (38) | 2824 (36) | 536 (36) | 918 (36) | 215 (34) | 790 (33) |
|  Score: 4 | 7196 (9) | 8824 (12) | 4195 (6) | 4492 (8) | 2016 (28) | 2290 (29) | 472 (32) | 802 (32) | 189 (30) | 740 (31) |
|  Score: 5-8 | 2539 (3) | 3592 (5) | 924 (1) | 978 (2) | 1132 (16) | 1407 (18) | 287 (19) | 523 (21) | 126 (20) | 548 (23) |

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease; IQR, interquartile range; OLDW, OptumLabs Data Warehouse
NB: 2% of DOAC and 4% of warfarin patients from the total cohort were missing CKD information

Supplemental Table S3**.** Hazard ratios for the association of DOAC vs warfarin treatment with cardiovascular combined outcomes in (A) 351,407 individuals in the OLDW in time-varying as-treated analysis across 4 models of adjustment (warfarin as reference group) and in (B) 303,505 non-CKD, 25,503 CKD stage 3, 6,414 CKD stage 4 and 5, and 5,292 ESKD individuals in the OLDW with model 3 and 4 adjustments.

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| **(A)** |  |  |  |  | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| **CVD Combined** **Outcome** | **n** | **Person Time****(person years)** | **Number****Unique** **Events** | **Incident Rate** **per 100** **person years** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** |
| DOAC | 158,732 | 99,738 | 17,836 | 17.9 (17.6,18.1) | 0.67 (0.66,0.68) | <0.001 | 0.71 (0.70,0.73) | <0.001 | 0.78 (0.77,0.80) | <0.001 | 0.74 (0.73,0.76) | <0.001 |
| Warfarin | 192,675 | 127,527 | 32,436 | 25.4 (25.2,25.7) | reference  | reference  | reference  | reference  |
| Total Cohort | 351,407 | 227,265 | 50,272 | 22.1 (21.9,22.3) |  |  |  |  |  |  |  |

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| **(B)** |  |  |  | **Model 3** | **Model 4** |
|   | **n** | **Person Time** | **Number** | **Incident Rate**  | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** |
| Non-CKD |
| DOAC | 303,505 | 196,474 | 39,716 | 20.2 (20,20.4) | 0.79 (0.77,0.81) | <0.001 | 0.74 (0.72,0.76) | <0.001 |
| CKD 3 |
| DOAC | 25,503 | 17,055 | 5,361 | 31.4 (30.6,32.3) | 0.79 (0.74,0.84) | <0.001 | 0.76 (0.72,0.81) | <0.001 |
| CKD 4-5 |
| DOAC | 6,414 | 3,884 | 1,524 | 39.2 (37.3,41.3) | 0.72 (0.63,0.81) | <0.001 | 0.69 (0.61,0.79) | <0.001 |
| ESKD |
| DOAC | 5,292 | 2,840 | 1,309 | 46.1 (43.7,48.7) | 0.75 (0.64,0.89) | 0.001 | 0.75 (0.63,0.89) | 0.001 |

Note: Cardiovascular disease (CVD) combined outcome defined as a composite outcome of myocardial infarction and ischemic stroke.

Note: Model 1: unadjusted; Model 2: adjusted for demographics (age, gender, and race) and year of the index anticoagulation prescription date; Model 3: adjusted for model 2 plus comorbidities and medications (diabetes, MI, CHF, ischemic stroke, hemorrhagic stroke, and antiplatelet medication use), and CKD stage; Model 4: adjusted for model 3 plus other comorbidities (acute kidney disease, hypertension, atrial fibrillation, pulmonary embolism infarction, deep venous thrombosis, arterial embolism/thrombosis, peripheral vascular disease, hypercoagulable state).

Abbreviations: CI, confidence interval; OLDW, OptumLabs Data Warehouse

Supplemental Table S4**.** Hazard ratios for the association of DOAC vs warfarin treatment with bleeding outcomes in (A) 351,407 individuals in the OLDW in time-varying as-treated analysis across 4 models of adjustment (warfarin as reference group) and in (B) 303,505 non-CKD, 25,503 CKD stage 3, 6,414 CKD stage 4 and 5, and 5,292 ESKD individuals in the OLDW with model 3 and 4 adjustments.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **(A)** |  |  |  |  | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| **Bleeding****Outcome** | **n** | **Person Time****(person years)** | **Number****Unique** **Events** | **Incident Rate** **per 100** **person years** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** |
| DOAC | 158,732 | 102,429 | 18,311 | 17.9 (17.6,18.1) | 0.77 (0.76,0.78) | <0.001 | 0.87 (0.85,0.88) | <0.001 | 0.90 (0.88,0.92) | <0.001 | 0.94 (0.92,0.96) | <0.001 |
| Warfarin | 192,675 | 133,681 | 30,373 | 22.7 (22.5,23.0) | reference  | reference  | reference  | reference  |
| Total Cohort | 351,407 | 236,111 | 48,684 | 20.6 (20.4,20.8) |  |  |  |  |  |  |  |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **(B)** |  |  |  | **Model 3** | **Model 4** |
|   | **n** | **Person Time** | **Number** | **Incident Rate**  | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** |
| Non-CKD |
| DOAC | 303,505 | 203,030 | 38,908 | 19.2 (19,19.4) | 0.92 (0.9,0.94) | <0.001 | 0.96 (0.94,0.99) | 0.002 |
| CKD 3 |
| DOAC | 25,503 | 18,408 | 4,855 | 26.4 (25.6,27.1) | 0.9 (0.84,0.96) | 0.001 | 0.92 (0.86,0.98) | 0.011 |
| CKD 4-5 |
| DOAC | 6,414 | 4,161 | 1,448 | 34.8 (33.1,36.6) | 0.78 (0.69,0.89) | <0.001 | 0.8 (0.71,0.91) | 0.001 |
| ESKD |
| DOAC | 5,292 | 2,973 | 1,264 | 42.5 (40.2,44.9) | 0.81 (0.69,0.96) | 0.013 | 0.81 (0.69,0.95) | 0.012 |

Note: Model 1: unadjusted; Model 2: adjusted for demographics (age, gender, and race) and year of the index anticoagulation prescription date; Model 3: adjusted for model 2 plus comorbidities and medications (diabetes, MI, CHF, ischemic stroke, hemorrhagic stroke, and antiplatelet medication use), and CKD stage; Model 4: adjusted for model 3 plus other comorbidities (acute kidney disease, hypertension, atrial fibrillation, pulmonary embolism infarction, deep venous thrombosis, arterial embolism/thrombosis, peripheral vascular disease, hypercoagulable state).

Abbreviations: CI, confidence interval; OLDW, OptumLabs Data Warehouse

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **(A) CVD Combined Outcome** |  |  | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| **Non-CKD** | **n** | **Person Time****(person years)** | **Number****Unique** **Events** | **Incident Rate** **per 100** **person years** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** |
| DOAC | 139,945 | 89,307 | 17,202 | 19 (19,20) | 0.88 (0.86,0.89) | <0.001 | 0.86 (0.85,0.88) | <0.001 | 0.82 (0.80,0.84) | <0.001 | 0.76 (0.75,0.78) | <0.001 |
| Warfarin | 159,226 | 89,873 | 21,555 | 24 (24,24) | reference  | reference  | reference  | reference  |
| Total Cohort | 299,171 | 179,180 | 38,757 | 22 (21,22) |  |  |  |  |  |  |  |
| **CKD Stage 3** |  |  |  |  |  |  |  |  |  |  |  |
| DOAC | 10,340 | 6,658 | 1,779 | 27 (24,29) | 0.83 (0.78,0.88) | <0.001 | 0.83 (0.79,0.89) | <0.001 | 0.82 (0.77,0.87) | <0.001 | 0.79 (0.74,0.84) | <0.001 |
| Warfarin | 12,672 | 7,460 | 2,549 | 34 (33,36) | reference  | reference  | reference  | reference  |
| Total Cohort | 23,012 | 14,118 | 4,328 | 31 (29,32) |  |  |  |  |  |  |  |
| **CKD Stage 4/5** |  |  |  |  |  |  |  |  |  |  |  |
| DOAC | 1,759 | 953 | 286 | 30 (24,37) | 0.83 (0.72,0.96) | 0.012 | 0.83 (0.72,0.95) | 0.008 | 0.76 (0.66,0.88) | <0.001 | 0.75 (0.65,0.87) | <0.001 |
| Warfarin | 2,937 | 1,635 | 577 | 35 (32,39) | reference  | reference  | reference  | reference  |
| Total Cohort | 4,696 | 2,588 | 863 | 33 (30,37) |  |  |  |  |  |  |  |
| **ESRD** |  |  |  |  |  |  |  |  |  |  |  |
| DOAC | 900 | 375 | 123 | 33 (25,44) | 0.74 (0.60,0.90) | 0.003 | 0.73 (0.59,0.89) | 0.002 | 0.73 (0.60,0.90) | 0.003 | 0.73 (0.60,0.90) | 0.003 |
| Warfarin | 1,984 | 983 | 411 | 42 (37,47) | reference  | reference  | reference  | reference  |
| Total Cohort | 2,884 | 1,358 | 534 | 39 (35,44) |  |  |  |  |  |  |  |

Supplemental Table S5**.** Hazard ratios for the association of anticoagulation treatments with (a) cardiovascular combined and (b) bleeding outcome after matching DOAC patients with warfarin patients using coarsened exact matching in 299,171 non-CKD, 23,012 CKD Stage 3, 4,696 CKD Stage 4-5, and 2,884 ESRD OptumLabs patients (reference: warfarin patients).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **(B) Bleeding Outcome** |  |  | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| **Non-CKD** | **n** | **Person Time****(person years)** | **Number****Unique** **Events** | **Incident Rate** **per 100** **person years** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** | **Hazard** **Ratio**  **(95% CI)** | **p-value** |
| DOAC | 139,945 | 91,516 | 17,976 | 20 (19,20) | 0.92 (0.90,0.94) | <0.001 | 0.92 (0.90,0.94) | <0.001 | 0.92 (0.90,0.94) | <0.001 | 0.97 (0.95,0.99) | 0.015 |
| Warfarin | 159,226 | 92,591 | 20,811 | 22 (22,23) | reference  | reference  | reference  | reference  |
| Total Cohort | 299,171 | 184,107 | 38,787 | 21 (21,21) |  |  |  |  |  |  |  |
| **CKD Stage 3** |  |  |  |  |  |  |  |  |  |  |  |
| DOAC | 10,340 | 6,789 | 1,925 | 28 (26,31) | 0.93 (0.87,0.98) | 0.014 | 0.94 (0.88,0.99) | 0.029 | 0.93 (0.88,0.99) | 0.021 | 0.96 (0.90,1.02) | 0.174 |
| Warfarin | 12,672 | 7,891 | 2,480 | 31 (30,33) | reference  | reference  | reference  | reference  |
| Total Cohort | 23,012 | 14,680 | 4,405 | 30 (29,31) |  |  |  |  |  |  |  |
| **CKD Stage 4/5** |  |  |  |  |  |  |  |  |  |  |  |
| DOAC | 1,759 | 1,010 | 339 | 34 (26,45) | 0.83 (0.73,0.94) | 0.004 | 0.83 (0.73,0.95) | 0.005 | 0.82 (0.72,0.94) | 0.003 | 0.82 (0.72,0.94) | 0.005 |
| Warfarin | 2,937 | 1,639 | 681 | 42 (38,45) | reference  | reference  | reference  | reference  |
| Total Cohort | 4,696 | 2,649 | 1,020 | 39 (35,43) |  |  |  |  |  |  |  |
| **ESRD** |  |  |  |  |  |  |  |  |  |  |  |
| DOAC | 900 | 384 | 143 | 37 (27,52) | 0.75 (0.62,0.91) | 0.003 | 0.75 (0.62,0.91) | 0.003 | 0.75 (0.62,0.91) | 0.003 | 0.75 (0.62,0.90) | 0.003 |
| Warfarin | 1,984 | 971 | 477 | 49 (45,54) | reference  | reference  | reference  | reference  |
| Total Cohort | 2,884 | 1,355 | 620 | 46 (41,51) |  |  |  |  |  |  |  |

Supplemental Figure S1: Study period for treatment cohorts.

10/1/2010

Index date= first prescription

of DOAC/warf after 10/1/2010

Continuous enrollment
 - no gap>45 days
 - no prescriptions for

DOAC/warf in this period

10/1/2009

Follow up for events:

MI, bleeding, stroke

9/30/2017

Abbreviations: MI, myocardial infarction; warf, warfarin.

Supplemental Figure S2: Cohort construction.

352,404 unique patients with DOACs or Warfarin

prescriptions after 10/1/2010.

Removed 277 patients with more than one date of birth or gender entry (error)

352,127 unique patients

Removed 117 patients with gender unknown

352,010 unique patients

Removed 438 patients who were <18 years of age

351,572 unique patients (age 18-88 years)

Removed 18 patients who had anticoagulation treatments 1 year prior to index date

351,554 unique patients

Removed 126 patients recorded to be on both warfarin and DOAC on index date

351,428 unique patients

351,407 unique patients

Removed 21 patients who had ambiguous anticoagulation treatment status