Original Contribution

Intracranial Hemorrhage in Deep Vein Thrombosis/ Pulmonary Embolus Patients Without Atrial Fibrillation

Direct Oral Anticoagulants Versus Warfarin

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Background and Purpose—Deep vein thrombosis (DVTs) is a common disease with high morbidity if it progresses to pulmonary embolus (PE). Anticoagulation is the treatment of choice; warfarin has long been the standard of care. Early experience with direct oral anticoagulants (DOACs) suggests that these agents may be may be a safer and equally effective alternative in the treatment of DVT/PE. Nontraumatic intracranial hemorrhage (ICH) is one of the most devastating potential complications of anticoagulation therapy. We sought to compare the rates of ICH in patients treated with DOACs versus those treated with warfarin for DVT/PE.

Methods—The MarketScan Commercial Claims and Medicare Supplemental databases were used. Adult DVT/PE patients without known atrial fibrillation and with prescriptions for either a DOAC or warfarin were followed for the occurrence of inpatient admission for ICH. Coarsened exact matching was used to balance the treatment cohorts. Cox proportional-hazards regressions and Kaplan-Meier survival curves were used to estimate the association between DOACs and the risk of ICH compared with warfarin.

Results—The combined cohort of 218 620 patients had a median follow-up of 3.0 months, mean age of 55.4 years, and was 52.1% women. The DOAC cohort had 26 980 patients and 8 ICH events (1.0 cases per 1000 person-years), and the warfarin cohort had 191 640 patients and 324 ICH events (3.3 cases per 1000 person-years; $P<0.0001$). The DOAC cohort had a lower hazard ratio for ICH compared with warfarin in both the unmatched (hazard ratio=0.26; $P=0.0002$) and matched (hazard ratio=0.20; $P=0.0001$) Cox proportional-hazards regressions.

Conclusions—DOACs show superior safety to warfarin in terms of risk of ICH in patients with DVT/PE. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.022156.)**

Key Words: anticoagulants ■ intracranial hemorrhages ■ pulmonary embolism ■ venous thrombosis

Venous thromboembolism (VTE), comprising both deep vein thrombosis (DVT) and pulmonary embolism (PE), affects >600 000 persons annually in the United States.[1] Nearly two thirds of VTEs occur in the setting of hospitalization, and they account for ≈300 000 deaths annually.[1,2] In addition to the substantial morbidity and mortality, VTE is also a financial burden to society with estimated annual costs of $4.9 to $7.5 billion for DVT and $8.5 to $19.8 billion for PE in the United States.[3]

Antithrombotic therapy has been shown reduce recurrent VTE and associated mortality and is the standard of care for the acute treatment of VTE.[4,5] Historically, the standard regimen has been the initiation of a parenteral anticoagulant, such as heparin followed by oral therapy with warfarin.[5,6] There are limitations to warfarin therapy, including the need to monitor the international normalized ratio for dose titration and potential for major bleeding complications.[7,8] Intracranial hemorrhage (ICH) is one of the most devastating potential complications of anticoagulation therapy.[9] ICH accounts for ≈10% of major warfarin-associated hemorrhages and for up to 50% of fatal warfarin-associated bleeding complications.[10]

During the past decade, several direct oral anticoagulants (DOACs), including factor IIa (thrombin) and factor Xa inhibitors, have been approved by the Food and Drug Administration. In 2010, based on the results of the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) Trial, the Food and Drug Administration approved dabigatran, a direct thrombin inhibitor, for prevention of stroke in patients with nonvalvular atrial fibrillation (AF).[11,12] Since that time, 3 factor Xa inhibitors—rivaroxaban (2011), apixaban (2012), and edoxaban (2015)—have also received Food and Drug Administration approval for prevention of stroke in nonvalvular AF. Several phase 3 clinical trials demonstrated that these agents are at

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least equivalent to warfarin for prevention of stroke or systemic embolism in patients with AF.[11,13–15] Of note, these trials also demonstrated consistently lower rates of ICH with DOAC therapy compared with warfarin therapy in the AF patient population.[11,13–16] Subsequent studies demonstrated noninferiority of DOACs in prevention of recurrent DVT and PE in the VTE patient population. They also showed a more favorable complication profile of DOACs compared with warfarin therapy in this patient population, including a relative decrease in the risk of ICH.[17–24] There are no postmarketing studies that have reported ICH risk with DOAC therapy in treatment of DVT/PE.[25,26] We evaluate the relative risk of nontraumatic ICH in VTE patients treated with DOACs compared with those treated with warfarin, in a large national database.

Methods

Data for this study are commercially available from Truven Health Analytics, and other materials are available from the corresponding author on reasonable request. We extracted insurance claims information from a portion of the MarketScan database, which contains data on millions of patients insured both commercially and through Medicare in the United States from January 2007 to December 2015.[27] Diagnosis information was extracted from inpatient and outpatient records using *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes. Outpatient prescriptions were extracted using National Drug Code numbers. MarketScan is a fully deidentified database, therefore this study was exempt from institutional review board approval.

The primary outcome was a primary or secondary inpatient diagnosis (including overnight Emergency Department encounters) of nontraumatic ICH (*ICD-9*: 430, 431, 432.X), which includes intracerebral, subdural/epidural hemorrhage, subarachnoid hemorrhage, and other ICH. Patients became eligible for inclusion if they had at least 1 period of continuous enrollment for ≥180 day before the date of their first recorded outpatient prescription for a DOAC or warfarin. Prescriptions sufficient for only 1 day of therapy were excluded from index date selection, but otherwise the first prescription date was designated as the index date. Patients with a diagnosis of PE, DVT, or a history of either of these before the index date were included. Patients with a diagnosis of AF, ICH, or an unruptured intracranial aneurysm before the index date (inclusive of the index date in the case of AF) or who were not at least 18 years of age on the index date were excluded. Potential risk factors and other comorbidities were taken from the index period and any prior enrollment periods. The updated Charlson comorbidity index was used.[28] Insurance status was assigned based on the insurance at the index date.

Patients were followed until 1 of 6 end points were reached: (1) the occurrence of the primary outcome (inclusive of the date of first prescription and the date of last follow-up), (2) disenrollment, (3) inpatient death (MarketScan does not record outpatient deaths), (4) discontinuation of anticoagulant therapy for >14 days, (5) switching anticoagulant therapy from DOAC to warfarin or vice versa (but not within the DOAC class), or (6) reaching October 1, 2015 (when International Classification of Diseases, *Tenth Revision* codes began to be implemented).[29] Initial selection was performed separately for the commercial and Medicare cohorts. Only complete cases were used. The selection process is detailed in Figure I in the online-only Data Supplement.

A Cox proportional-hazards (CPH) model was fit on the unmatched cohort to evaluate the association between the treatment (type of anticoagulant) and the risk of the primary outcome, as well as to produce interpretable effect estimates for selected confounding pretreatment variables. The variance inflation factor was calculated for all independent variables to assess multicollinearity. Interactions between the treatment group and all other independent variables were examined for significance one at a time in the context of the other independent variables. The cohort was then matched using Coarsened Exact Matching to balance confounding variables between those prescribed a DOAC and those prescribed warfarin.[30] Confounding variables were selected to balance the demographics and comorbidities between the cohorts. These included sex, age (continuous), insurance type, Charlson comorbidity score (continuous), hypertension, type II diabetes mellitus, heart failure, vascular disease, pulmonary disease, renal disease, liver disease, obesity, and tobacco use. Balance improvement was assessed with the multivariate L1 statistic and by comparing the standardized mean differences of confounding variables between the unmatched and matched cohorts. Differences between demographic and confounding variables were assessed using *t* tests or χ^2tests (weighted versions were used for matched data). Annualized rates were reported as cases per 1000 person-years and were compared using a 2-sided χ^2test.

A second CPH model was fit on the matched cohort, again including confounding variables, to produce a doubly robust estimate for the effect size of the treatment on the primary outcome.[31,32] Hazard ratios (HRs) for confounding variables were not reported in the matched regression because of the difficulty of interpreting HRs for variables previously balanced by matching. Statistical significance was set at $P<0.05$. Months were defined as 30-day intervals. Data analyses were conducted in Redivis and R Software.[33,34] This article was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[35]

Results

A total of 218 620 patients (26 980 DOAC and 191 640 warfarin) were selected with an overall median follow-up of 3.0 months (Figure I in the online-only Data Supplement). The DOAC cohort had a shorter mean follow-up time compared with the warfarin cohort (3.8 versus 6.2 months; $P<0001$); It had more patients with ≤1 month of follow-up (31% versus 22%) and fewer patients with >1 year of follow-up (5% versus 12%; $P<0.001$) compared with the warfarin cohort (Table 1). Other demographic differences were accounted for in matching and regression (Table 2). Among patient encounters with ICH in the DOAC cohort, 75% listed *ICD-9* code 431 (intracerebral hemorrhage) as either the primary or secondary diagnosis and 25% listed 432.1 (subdural hemorrhage). In contrast, intracerebral hemorrhage and subdural hemorrhage made up 46% and 36%, respectively, of primary or secondary diagnoses in warfarin cohort ICH patient encounters—*ICD-9* codes 430 (subarachnoid hemorrhage) and 432.9 (unspecified ICH) accounted for another 10% each. The DOAC cohort had a mean age of 53 years compared with 56 years in the warfarin cohort ($P<0.001$) and was composed of 51.5% women compared with 52.2% women in the warfarin cohort ($P=0.04$). A smaller proportion of the DOAC cohort was enrolled in Medicare compared with the warfarin cohort (12% versus 23%; $P<0.001$). The DOAC cohort had a higher prevalence of hypertension (56% versus 55%; $P=0.002$), pulmonary disease (28% versus 26%; $P<0.001$), liver disease (7% versus 5%; $P<0.001$), obesity (26% versus 17%; $P<0.001$), and tobacco use (13% versus 10%; $P<0.001$) and a lower prevalence of type II diabetes mellitus (22% versus 23%; $P=0.05$), heart failure (8% versus 10%; $P<0.001$), vascular disease (16% versus 17%; $P<0.001$), and renal disease (6% versus 7%; $P<0.001$).

The incidence rate of ICH was 1.0 cases per 1000 person-years in the DOAC cohort (95% CI, 0.5–1.9) and 3.3 cases per 1000 person-years in the warfarin cohort (95% CI, 3.0–3.7; $P<0.0001$). The CPH regression fitted before matching revealed several significant associations: treatment with DOAC (HR=0.26; 95% CI, 0.13–0.53; $P=0.0002$), female sex

Table 1. Cohort Characteristics Before Matching

	DOAC		Warfarin			
	n	%	n	%	*P* Value	SMD
Cohort size	26 980		191 640			…
Follow-up, mo (mean, SD)	3.8	4.3	6.2	8.9	<0.001	…
Follow-up, mo (mean, SD)					<0.001	…
(0, 1]	8449	31.3	42 592	22.2		
(1, 3]	7432	27.5	51 052	26.6		
(3, 6]	6025	22.3	40 075	20.9		
(6, 12]	3795	14.1	34 608	18.1		
(12, 100]	1279	4.7	23 313	12.2		
Initial DOAC					…	…
Rivaroxaban	24 250	89.9	…	…		…
Apixaban	1911	7.1	…	…		…
Dabigatran	800	3	…	…		…
Edoxaban	19	0.1	…	…		…
ICH (primary outcome)	8	0	324	0.2	<0.001	…
ICH (by *ICD-9*)*						…
430	0	0	31	9.6	0.761	…
431	6	75	148	45.7	0.199	…
432.0	0	0	3	0.9	1	…
432.1	2	25	115	35.5	0.811	…
432.9	0	0	33	10.2	0.724	…
Matched variables						
Age (mean, SD)	53	13.8	55.9	15.4	<0.001	0.198
Female	13 907	51.5	100 066	52.2	0.04	0.013
Medicare	3310	12.3	44 587	23.3	<0.001	0.291
Charlson (mean, SD)	1.7	2.3	1.7	2.2	0.107	0.010
Hypertension	15 024	55.7	104 784	54.7	0.002	0.020
Type II diabetes mellitus	5979	22.2	43 510	22.7	0.047	0.013
Heart failure	2257	8.4	19 230	10	<0.001	0.058
Vascular disease	4299	15.9	32 672	17	<0.001	0.030
Pulmonary disease	7669	28.4	48 905	25.5	<0.001	0.066
Renal disease	1589	5.9	13 955	7.3	<0.001	0.056
Liver disease	1810	6.7	8939	4.7	<0.001	0.088
Obesity	6867	25.5	31 707	16.5	<0.001	0.220
Tobacco	3652	13.5	20 800	10.9	<0.001	0.082

DOAC indicates direct oral anticoagulants; *ICD-9*, *International Classification of Diseases, Ninth Revision*; ICH, intracranial hemorrhage; and SMD, standardized mean difference.

*May appear in either or both of top 2 diagnoses. Percent calculated out of total ICH *ICD-9* codes.

(HR=0.75; *P*=0.01), age (HR=1.03; *P*<0.0001; continuous variable), Charlson score (HR=1.16; *P*<0.0001; continuous variable), and type II diabetes mellitus (HR=1.32; *P*=0.03; Table 3). The variance inflation factor was <1.5 for all independent variables except age (3.2) and Medicare insurance (3.1). Two significant interactions between treatment group and independent variables were found in the multivariate CPH but were not included in the final model because of the constraint of sample size: age (interaction HR=1.06, *P*=0.03; DOAC HR=0.01, *P*=0.06) and type II diabetes mellitus (interaction HR=6.37, *P*=0.02; DOAC HR=0.10, *P*=0.001).

After matching, the multivariate L1 statistic improved from 0.41 to 0.29, and the standardized mean differences of matched variables between treatment groups were reduced to near zero in the matched cohort (from a maximum of 0.291 to a maximum of 0.002), and no significant differences in matched variables remained (Table 2). The DOAC cohort had a lower hazard of ICH compared with warfarin in the matched CPH regression (HR=0.20; 95% CI, 0.09–0.45; *P*=0.0001; Table 3).

Discussion

The recent introduction of DOACs to the collection of anticoagulant medications has changed clinical practice as class 1a evidence has made DOACs the first-line anticoagulant in many patients. This study used a retrospective insurance claims database to evaluate the relative rates of nontraumatic ICH in VTE (DVT/PE) patients without AF, treated with either DOACs or warfarin. Treatment with DOACs is associated with lower rates of ICH compared with warfarin therapy in this VTE patient population.

Previous Clinical Trials

Phase 3 trials in patients with AF have suggested noninferiority or superiority of DOACs in prevention of thromboembolic complications, with more favorable side effect profiles as compared with warfarin (eg, ICH).[11,13–15,36–38] When ICH does occur, the hemorrhages tends to be smaller, less severe, and less frequently fatal in patients on DOACs compared with patients on warfarin.[39–41] However, >600 000 patients per year in the United States require prolonged anticoagulation therapy for VTE. Other phase 3 trials have demonstrated the noninferiority or superiority of DOACs compared with warfarin for the prevention of recurrent DVT/PE, with more favorable adverse effect profiles. The RE-COVER (2009), RE-COVER II (Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; 2014), and RE-MEDY (Secondary Prevention of Venous Thrombo Embolism)/RE-SONATE (Twice-Daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long-Term Prevention of Recurrent Symptomatic VTE; 2013) trials each demonstrated noninferiority of dabigatran compared with warfarin for prevention of recurrent VTE, with concomitant lower rates of hemorrhagic complications.[17–19] With regard to ICH, a pooled analysis of RE-COVER/RE-COVER II revealed 0.1% rate of ICH in dabigatran group versus 0.2% in the warfarin group (*P* value not reported).[19] RE-MEDY/RE-SONATE did not specifically report on ICH rates; however, dabigatran had a lower rate of major or clinically relevant bleeding

Table 2. Cohort Characteristics After Matching

	DOAC		Warfarin			
	n	%	n	%	*P* value	SMD
Cohort size	25 480	…	159024	…	…	…
Age (mean, SD)	52.7	13.7	52.8	13.7	0.79	0.002
Female	13 131	51.5	81 952	51.5	1	<0.001
Charlson (mean, SD)	1.5	2	1.5	2	1	<0.001
Medicare	2958	11.6	18 461	11.6	1	<0.001
Hypertension	13 965	54.8	87 157	54.8	1	<0.001
Type II diabetes mellitus	5206	20.4	32 491	20.4	1	<0.001
Heart failure	1764	6.9	11 009	6.9	1	<0.001
Vascular disease	3609	14.2	22 524	14.2	1	<0.001
Pulmonary disease	6869	27	42 870	27	1	<0.001
Renal disease	1167	4.6	7283	4.6	1	<0.001
Liver disease	1321	5.2	8245	5.2	1	<0.001
Obesity	6136	24.1	38 296	24.1	1	<0.001
Tobacco	3138	12.3	19 585	12.3	1	<0.001

DOAC indicates direct oral anticoagulants; and SMD, standardized mean difference.

complications as compared with warfarin.[18] The EINSTEIN-DVT (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis; 2010) and EINSTEIN-PE (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; 2012) trials compared rivaroxaban to standard therapy (low-molecular-weight heparin plus warfarin) in acute DVT and PE, respectively, and found that rivaroxaban was noninferior to standard therapy for prevention of recurrent VTE, with lower rates of major and clinically relevant bleeding complications.[20,21] The rate of ICH in the EINSTEIN-PE trial was 0.1% for the rivaroxaban group versus 0.4% for the warfarin group (*P* value not reported). ICH rates were not specifically reported in the EINSTEIN-DVT trial. The AMPLIFY trial (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; 2013) compared apixaban to standard therapy (low-molecular-weight heparin/warfarin) in acute VTE and reported equivalent efficacy of DOACs for prevention of recurrent symptomatic VTE or death related to VTE, as well as lower rates of bleeding complications, including ICH (0.1% with apixaban versus 0.2% with warfarin, *P* value not reported).[22] Similarly, the Hokusai-VTE (2013) trial reported that edoxaban was noninferior to warfarin for prevention of recurrent VTE, with lower associated ICH (0.1% with edoxaban versus 0.4% with warfarin, *P* value not reported).[24]

Table 3. Cox Proportional-Hazards Models

	HR	95% CI	*P* Value
Matched			
DOAC	0.20	0.09–0.45	0.0001
Unmatched			
DOAC	0.26	0.13–0.53	0.0002
Female	0.75	0.6–0.94	0.01
Age	1.03	1.02–1.04	<0.0001
Medicare	0.72	0.49–1.06	0.10
Charlson score	1.16	1.11–1.22	<0.0001
Hypertension	0.96	0.75–1.23	0.75
Type II diabetes mellitus	1.32	1.04–1.69	0.03
Congestive heart failure	0.89	0.64–1.23	0.48
Vascular disease	0.93	0.7–1.23	0.61
Pulmonary disease	0.84	0.65–1.09	0.19
Renal disease	1.08	0.75–1.54	0.69
Liver disease	1.26	0.81–1.95	0.31
Obesity	0.78	0.55–1.1	0.15
Tobacco	0.97	0.66–1.44	0.90

DOAC indicates direct oral anticoagulants; and HR, hazard ratio.

Results of This Study

In this article, we used a large, commercial database to demonstrate that DOACs are associated with a lower hazard of ICH in DVT/PE patients without AF as compared with warfarin (HR=0.26; *P*=0.0002). This finding was confirmed in the matched cohort (HR=0.20; *P*=0.0001), which was the primary study objective. The matching procedure reduced the differences in confounding variables between cohorts to nonsignificant levels. In fact, all standardized mean differences were near zero after matching. Sensitivity analysis with the Medicare cohort recapitulated the direction of the DOAC cohort hazard. It did not achieve significance, but this was likely because of the relatively small proportion of Medicare patients in our cohorts.

The analysis took a doubly robust approach to balance confounding variables between treatment cohorts. Matching confounders between treatment cohorts and then including

them as covariates in the subsequent CPH regression allowed the removal of confounding effects that 1 method in isolation may have missed. However, this methodology only allows for the practical interpretation of the treatment hazard. Thus, an identical CPH regression was performed on the unmatched data to allow interpretation of confounding variable hazards. In addition, it demonstrated that, with or without matching, the treatment hazard is in the same direction and remains statistically significant. Indeed, the treatment hazard became larger after matching. It should be noted that, before matching, the DOAC cohort had slightly more liver disease (6.7% versus 4.7%; $P<0.001$) and slightly less renal disease (5.9% versus 7.3%; $P<0.001$) compared with the warfarin cohort—both diseases can result in reduced clearance of anticoagulants. In addition, the DOAC cohort was slightly younger than the warfarin cohort (53 versus 56 years; $P<0.001$) and thus would be at slightly lower risk of ICH. These differences were accounted for in matching and regression.

The findings of this study are consistent with previous studies on DOACs in the VTE patient population. The DOAC cohort had a lower risk of ICH compared with the warfarin cohort in all of our analyses. To our knowledge, this is the first phase 4 (ie, post-marketing, nonclinical trial experience) report of DOAC-associated ICH rates in the literature. Future studies should focus on the long-term complications of DOACs compared with warfarin and should stratify according to the DOAC agent prescribed if sample size allows.

Limitations

Limitations of this study are the same as any retrospective claims database study. The treatment cohorts had a relatively short follow-up time (median, 3.0 months). Previous reports indicate that bleeding complications, including ICH, are clustered at the start of anticoagulation therapy.[10,42] Nonetheless, the short follow-up period in the present cohort must be considered when interpreting the results of this report. The majority of the cohort were commercially insured patients, who may go in and out of insurance coverage, resulting in premature termination of database-captured follow-up. In addition, the index period for which risk factors and other variables were collected extended only to 2007 at most. Thus, it is possible that patients diagnosed with AF before 2007 were included in the study despite the intended exclusion of patients with AF from the cohort.

The way in which inclusion criteria and outcomes were coded is vulnerable to bias. Patients with a diagnosis of DVT/PE in their index period were assumed to be prescribed anticoagulants for that diagnosis, which is not necessarily true. For ICH, only primary and secondary inpatient diagnoses were considered, so patients with a tertiary or lower diagnosis of ICH were not captured. Some events may have been missed if a patient was diagnosed in the Emergency Department but not admitted. It was not possible to determine the pathogenesis or severity of the ICH events outside of details contained in *ICD-9* codes. A systematic review has shown that at least half of administrative databases have a positive predictive value of 89% for ICH (*ICD-9* 431) and 93% for subarachnoid hemorrhage.[43] The overall negative predictive value for cerebrovascular disease in general was at least 95%. MarketScan specifically has been validated for the identification of postoperative complications in spinal surgery, for which it achieved results similar to prospective studies.[44] MarketScan does not capture over-the-counter medications, so the contribution of aspirin and dual antiplatelet therapy could not be assessed. The proportion of warfarin patients with poor therapeutic range control is unknown, which may be an additional factor in the relative benefits of DOACs compared with warfarin. Finally, almost all patients in the DOAC cohort were initially prescribed rivaroxaban—possibly because of its earlier Food and Drug Administration approval for recurrent VTE compared with other DOACs and its convenient once daily dosing—which limits the generalizability of our results to all DOACs.

Conclusions

This report provides evidence that treatment with DOACs is associated with lower rates of nontraumatic ICH compared with warfarin therapy in the VTE patient population. This result requires further validation in prospective postmarketing studies that can better capture relevant confounding factors outside of the clinical trial setting.

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Disclosures

None.

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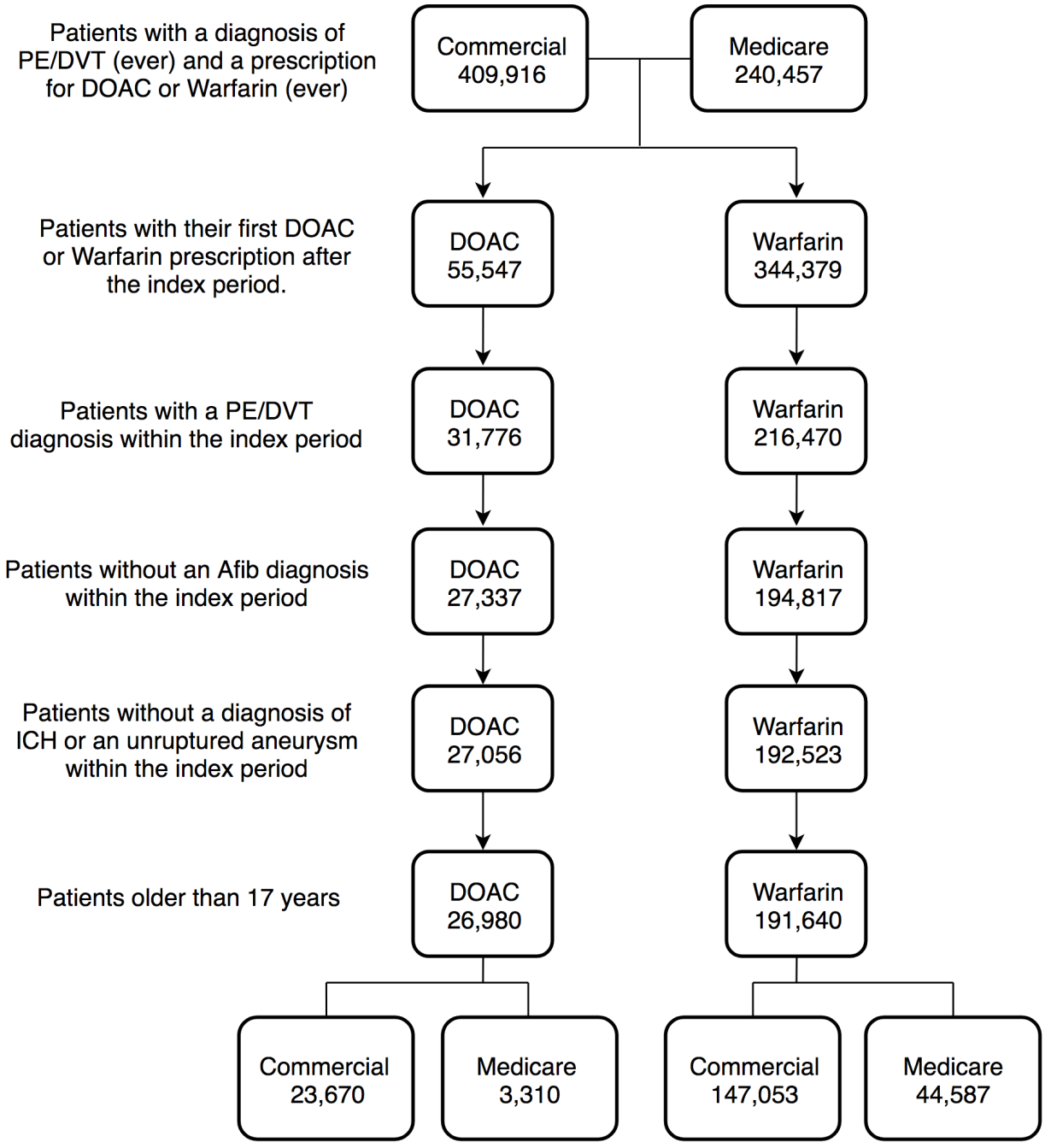
SUPPLEMENTAL MATERIAL



Supplementary Figure I.
Flow diagram of patient selection (cohort size is indicated at each step).