Supplementary Material A: Study Methods

Methods

Study Design

This study employed a retrospective matched-cohort design and data from four large integrated US private healthcare claims databases—the Truven Health Analytics' MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases (the 'Market-Scan Database'), the IQVIA PharMetrics Plus Database (the 'PharMetrics Database'), the Optum Clinformatics Claims Database (the 'Optum Database') and the Humana Medical, Laboratory and Pharmacy Claims Database (the 'Humana Database'). Data from the four databases were pooled for analyses to increase the power of the study to evaluate study outcomes and to improve the generalizability of study results. A schematic depicting the design of the study follows: dures performed/services rendered and quantity of services (professional-service claims only). Data available for each outpatient pharmacy claim include the drug (class) dispensed, dispensing date, quantity dispensed and number of days supplied. Medical and pharmacy claims also include amounts paid (i.e. reimbursed) by health plans and patients for services rendered by health care providers (MarketScan, PharMetrics, Humana), or standard costs (Optum). Selected demographic and eligibility information (including age, sex, geographic region of residence, dates of plan eligibility) is available for all health plan enrolees in the databases. All data can be arrayed to provide a detailed chronology of medical and pharmacy services used by each plan member over time.

From each data extract, an analytic file comprising all patients and variables required for planned analyses was created from information contained exclusively within the source material. Each of the analytic files was patient-level,



Data Source(s)

The four study databases each comprise medical (i.e. facility and professional service) and outpatient pharmacy claims from a large number of participating U.S. private health plans, and spanned the period from 1 March 2014 through 30 June 2017 herein. Together, these four geographically diverse databases capture health care claims information for > 45 million plan members annually, including enrolees, their spouses and their dependents. Elderly persons who have elected to enrol in an employer-sponsored commercial plan (with or without Medicare supplemental coverage) or a Medicare Advantage Plan—and thus receive their health care coverage through a private health plan—also are included in the data source population.

Data available from each facility and professional-service claim include dates and places of service, diagnoses, proceand included data on patient demographic and clinical characteristics, VTE encounters, anticoagulant therapy and outcomes of interest (e.g. bleeding events, bleeding-related costs); variable names were standardized across analytic files. Variables were created based on information from medical and pharmacy claims, as well as enrolment records, which were linked at the patient level via encrypted identifiers provided by the data vendors.

Once created, the four independent, identically structured analytic files were then integrated (i.e. set or stacked, but not linked in any way), with the end product being one master analytic file that was used for planned analyses. No manipulation of data fields, or linking/appending of information to observations, was performed on the master file. Patient-level information from the four study databases was pooled in a single analytic file to increase the power to address study objectives and to enhance the generalizability of study findings.

Source and Study Populations

The source population included all patients aged \geq 18 years who, between 1 September 2014 and 30 June 2017, had an encounter for the treatment of VTE. Evidence of VTE was ascertained based on encounters in the acute-care inpatient setting or ambulatory-care setting (e.g. emergency department, physician office) with ICD-9-CM/ICD-10-CM diagnosis codes for lower extremity DVT or PE. The earliest such encounter for each patient was designated the 'index encounter'. Outpatient encounters followed by inpatient encounters within 7 days were considered inpatient encounters, unless apixaban or warfarin was initiated between encounters, in which case they were classified as outpatient encounters.

From the source population, all patients who received outpatient treatment with apixaban or warfarin (plus PAC bridging therapy) following their index encounters, and who met all other inclusion criteria, were selected as candidates for matching and thus inclusion in the study population. Outpatient use of apixaban or warfarin from the date of the index encounter (service date, if outpatient VTE; discharge date, if inpatient VTE) through the 30-day period thereafter was ascertained based on National Drug Codes (NDCs) (>Supplementary Material B, ► **Appendix A**). The first treatment (i.e. apixaban or warfarin) received by each patient was designated as the 'index therapy'. Warfarin patients with an index VTE encounter requiring outpatient care only who did not have evidence of PAC use (i.e. bridging therapy) during the period ± 14 days from first receipt of warfarin were excluded. Among warfarin patients who had evidence of PAC use during this period, the sub-set who received it beyond the 14-day period following initiation of warfarin was also excluded. Other inclusion criteria (e.g. \geq 6 months of enrolment prior to index encounter; no evidence of atrial fibrillation/flutter, prior VTE, history of bleeding, active malignancy) are set forth below.

Inclusion Criteria

Patients who met all of the following criteria (#1–#4) were considered for matching and thus inclusion in the study population:

- (1) An acute-care inpatient encounter with a principal or secondary diagnosis of VTE, or an ambulatory-care encounter with any diagnosis of VTE from 1 September 2014 to 30 June 2017. VTE diagnosis codes were based in large part on those recommended in the FDA-sponsored mini-sentinel report on definitions previously employed in studies using administrative data sources (Tamariz 2011):
- ICD-9 415.1x (pulmonary embolism and infarction) and ICD-10 I2692, I2699, T82817A, T82818A (pulmonary embolism and infarction), excluding:
- ICD-9 415.12 (septic pulmonary embolism).
- ICD-10 I2690 (septic pulmonary embolism without acute cor pulmonale).

- ICD-9 451.xx (phlebitis and thrombophlebitis) and ICD-10 I801*, I802*, I803, I809 (phlebitis and thrombophlebitis), excluding:
- ICD-9 451.0 (of superficial vessels of lower extremities), 451.82 (of superficial veins of upper extremities) and 451.89 (other [axillary vein, jugular vein, subclavian vein, thrombophlebitis of breast).
- ICD-10 I800* (of superficial vessels of unspecified lower extremity), I808 (phlebitis and thrombophlebitis of other sites).
- ICD-9 453.xx (other venous embolism and thrombosis) and ICD-10 I821, I82220, I82221, I8240*, I8241*, I8242*, I8243*, I824Y*, I8244*, I8249*, I824Z*, I8281*, I8261*, I8262*, I8260*, I82A1*, I82B1*, I82C1*, I82210, I82290, I82890, I829* (other venous embolism and thrombosis), excluding:
- ICD-9 453.0 (Budd–Chiari syndrome), 453.3 (of renal vein), 453.5 (chronic venous embolism and thrombosis of deep vessels of lower extremity) and 453.7 (chronic venous embolism and thrombosis of other specified vessels).
- ICD-10 I820 (Budd-Chiari syndrome), I823 (of renal vein), I8250*, I8259*, I8251*, I8252*, I8253*, I825Y*, I8254*, I825Z* (chronic venous embolism and thrombosis of deep vessels of lower extremity), I8271*, I8272*, I8270*, I82A2*, I82B2*, I82C2*, I82211, I82291, I82891 (chronic venous embolism and thrombosis of other specified vessels).

Qualifying outpatient encounters followed by qualifying inpatient encounters within 7 days were considered inpatient episodes (unless apixaban or warfarin was initiated between encounters, in which case such episodes would be classified as outpatient encounters).

- (2) An outpatient pharmacy claim for apixaban or warfarin during the 30-day period following the index encounter (i.e. date of service if outpatient, date of discharge if inpatient).
- (3) Continuous and comprehensive medical/drug coverage for ≥6 months preceding the index encounter (i.e. date of service if outpatient, date of admission if inpatient).
- (4) Age ≥ 18 years.

Exclusion Criteria

Apixaban and warfarin patients who met any of the following criteria (#1-#7) were excluded from the source population:

- Evidence of atrial fibrillation/flutter or chemotherapy/ radiation therapy for malignancy (other than non-melanoma skin cancer) during 6-month period preceding first receipt of index therapy.
- (2) Evidence of VTE (VTE event) during 6-month period preceding index encounter.
- (3) Evidence of malignancy (other than non-melanoma skin cancer) during 90-day period preceding first receipt of index therapy.
- (4) Evidence of any OAC/parenteral anticoagulant (PAC) use during the 30-day period preceding the index encounter, or evidence of any OAC/PAC use during the 6-month

period preceding the index encounter (excluding the 30day period immediately preceding the index encounter) unless it is determined that such therapy was administered prophylactically.^a

- (5) Evidence of inferior vena cava (IVC) filter or pregnancy at any time during the study period.
- (6) Evidence of receipt of another OAC on the day of first receipt of the index therapy (or during the period between the index encounter and initiation of the index therapy).
- (7) History of major/clinically relevant non-major (CRNM) bleeding event during 6-month period preceding first receipt of index therapy.

In addition, warfarin patients with an index VTE encounter requiring outpatient care only who did not have evidence of PAC use during the period beginning 14 days before, and ending 14 days after, first receipt of warfarin were excluded from the study population. Among warfarin patients who had evidence of PAC use during this period, the sub-set who received it beyond the 14-day period following initiation of index therapy was excluded. PAC use was identified based on corresponding Healthcare Common Procedure Coding System (HCPCS) Level II Codes on medical claims and NDCs on pharmacy claims; for the latter, therapy-days supplied was used to tally duration of PAC use.

Diagnosis, procedure and drug codes that were used to identify exclusionary conditions (except for bleeding history) and pharmacotherapy are set forth in **Supplementary Material B, Appendix C** (PAC), **Appendix D** (OAC) and **Appendix E** (conditions/procedures). Codes that were used to define a history of major/CRNM bleeding event are set forth in Section "Endpoint(s)/Outcome(s) Assessment."

Matching Procedure

Apixaban patients were matched to warfarin patients based on age, care setting of index encounter (inpatient vs. ambulatory), VTE diagnosis (DVT only vs. PE [with or without DVT]), VTE aetiology (provoked vs. unprovoked) and study database (MarketScan, PharMetrics, Optum, Humana), as well as their estimated propensity score using a fixed 1:1 ratio (without replacement) and nearest-neighbour approach. Provoked VTE was defined as an event that was preceded (within 3 months) by hormone therapy, fracture/ trauma involving lower extremities, pelvic/orthopaedic surgery or hospitalization for medical or surgical reasons (-Supplementary Material B, -Appendix H). Propensity scores for receipt of apixaban versus warfarin-the dependent variable-were estimated using multivariable logistic regression; independent variables included age, gender, comorbidity profile, history of fall(s), history of fracture/ trauma involving lower extremities, history of selected surgeries and outpatient pharmacotherapy.

Definitions

Study Period

The study period spanned from 1 September 2014 to 30 June 2017.

Baseline Period

The baseline period for evaluating demographic and clinical characteristics of patients spanned the 6-month period preceding first receipt of index therapy.

Study Follow-Up Period

Study outcomes were assessed from the day after therapy initiation through the subsequent 6-month period, date of health plan disenrollment, date of death (in hospital), date of index therapy discontinuation,^b date of switch to another OAC, date of initiation of (new) PAC treatment^c or end of study database (30 June 2017), whichever occurred first.

Endpoint(s)/Outcomes(s) Assessment

Major Bleeding. A major bleeding event was defined as an acute-care inpatient admission with:

- A principal or first-listed diagnosis code for:
 - Gastrointestinal (GI) bleeding.
 - Intracranial haemorrhage (ICH).
 - Other selected types/sites of bleeding (as defined below)

OR

• A procedure code for the treatment of bleeding (as defined below).

CRNM Bleeding. A CRNM bleeding event was defined as:

- An acute-care inpatient admission with a secondary diagnosis code for GI bleeding or other non-critical-care types/sites of bleeding (without a principal/first-listed diagnosis code for GI/ICH/other bleeding, or a procedure code for bleeding treatment); or
- An ambulatory-care encounter with a diagnosis code for GI bleeding or other non-critical-care types/sites of bleeding.

Recurrent VTE. A recurrent VTE event was defined as an acute-care inpatient admission with a corresponding principal/first-listed diagnosis as set forth in Section "Inclusion Criteria." Encounters occurring within 7 days of the qualifying VTE event (i.e. index encounter) were not considered in identifying new (i.e. recurrent) events.

^a Prophylactic use of OAC/PAC was determined based on the duration of use and timing of use (e.g., relative to knee/hip replacement surgery or medical inpatient admission); the operational algorithm that was employed to differentiate between prophylactic use and therapeutic use of OAC/PAC is set forth in Appendix B.

^b Discontinuation of index therapy was defined as a gap of 30 days without available drug (based on days supplied from filled prescriptions).

^c Episodes of PAC treatment were differentiated based on a gap in therapy ≥ 2 days that occurred after initiation of index therapy + 14 days.

Bleeding Category	ICD-9-CM Diagnosis Codes	ICD-10-CM Diagnosis Codes	ICD-9-CM Procedure Codes	ICD-10-CM Procedure Codes
Major Bleeding				
Gastrointestinal (GI)	456.0, 456.20, 530.82, 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, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x	K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K661, K625, K920, K921, K922, I8501, I8511, K2901, K2931, K2941, K2951, K2961, K2921, K2971, K2991, K2981, K5711, K5713, K5731, K5791, K5733, K5793, K5521, K31811	44,43	OW3P8ZZ
Intracranial (ICH)	430.xx, 431.xx, 432.0x, 432.1x, 432.9x, 852.0x, 852.2x, 852.4x, 853.0x	1602, 1604, 1606, 1607, 1608, 1609, 161*, 1621, 1629, 1600*, 1601*, 1603*, 1605*, 1620*, 5066X0A, 5066X1A, 5066XA, 5066XA, 5066XA, 5066XA, 5066XA, 5065XA,		
Other	285.1, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 423.0, 596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9, 719.1x, 782.7, 784.7, 784.8, 786.3x, 958.2, 997.02, 998.11	D62, 1312, R31*, N421, N831, N857, N920, N923, N930, N897, N925, N938, N926, N939, R333, R04*, H356*, H210*, H113*, H0289, H431*, M2500, M2508, G973*, D780*, D782*, E360*, G975*, H952*, H954*, I9742, I9762, I956*, K916*, I260*, I262*, N996*, H4431*, H4573*, H3130*, H3131*, H3141*, H0523*, H4702*, M2501*, M2502*, M2503*, M2504*, M2505*, M2506*, M2507*, I9781*, I9782*, H591*, H5931*, H5932*, I9741*, I9761*, J9583*, K9184*, M9681*, M9683*, N9862*, T7920XA	99.04*	30230N1, 30230P1, 30233N1, 30233P1, 30240P1, 30240P1, 30243N1, 30243P1, 302540P1, 30243N1, 3025491, 30253P1, 30253P1, 30260N1, 30260P1, 30263N1, 30263P1
Clinically Relevant Non-N	Aajor Bleeding			
Gastrointestinal (GI)	456.0, 456.20, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.4x, 533.0x, 533.2x, 533.4x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.x	K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K920, K921, K922, IS501, IB511, K2901, K2931, K2941, K2951, K2961, K2921, K2971, K2991, K2981, K5711, K5713, K5731, K5791, K5793, K5793, K5793, K5821, K31811		
Intracranial (ICH)	***	***		
Other	372.72, 374.81, 596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.8, 626.9, 782.7, 784.7, 784.8, 786.3x, 958.2	R31*, N421, N831, N857, N920, N923, N930, N897, N925, N938, N926, N939, R233, R04*, H113*, H0289, H952*, H954*, J956*, K916*, L760*, L767*, J9781*, J9782*, J9583*, K9184*, L792YXA	1.000	

*Hospitalizations with ICD-9-CM procedure code 99.04 and corresponding ICD-10-CM procedure codes will be classified as other bleeding events only in the absence of codes for GI or ICH bleeding events

Other Study Variables

Independent variables used in the estimation of propensity scores included demographic and clinical characteristics of patients that are believed to be associated with the study outcomes and/or choice of index therapy. It was anticipated that demographic characteristics would be available for nearly all study subjects. All other characteristics were defined based on the presence of specific data (e.g. diagnosis codes, procedure codes); the absence of such data was assumed to indicate the absence of the characteristic captured by the variable. All such characteristics were ascertained based on information available during the 6-month period preceding first receipt of index therapy.

Patient and treatment characteristics included: age; gender; geographic region of residence; type of insurance coverage; specialty of physician prescriber (if available); comorbidity profile (e.g. Deyo-Charlson Comorbidity Index [► Supplementary Material B, ► Appendix F], and coagulopathy, ischaemic heart disease, peripheral vascular disease, heart failure, stroke or transient ischaemic attack [TIA], chronic obstructive pulmonary disease [COPD], liver disease, renal disease, thrombocytopaenia, diabetes, anaemia, ulcer disease, dyspepsia, hypertension, thrombophilia, inflammatory bowel disease); recent history of falls, fracture/trauma involving the lower extremities, selected surgeries; and outpatient pharmacotherapy (e.g. recent history of statins, anti-platelet therapy, non-steroidal anti-inflammatory drug [NSAID], hormone therapy) (>Supplementary Material B, ► Appendix G).

Other characteristics that were examined during followup include dose of index therapy (i.e. with first and subsequent prescriptions), switching from index therapy to another oral anticoagulant, amount of index therapy received (i.e. days supplied), use of PAC (between index encounter and initiation of index therapy, and subsequently) and duration of follow-up. These variables were not considered in the estimation of propensity scores.

Data Analysis

Base Case Analysis

The adequacy of the matching procedure in terms of patients' baseline characteristics was evaluated using standardized differences; a value < 0.1 was assumed to indicate a negligible difference in the characteristic between apixaban patients and warfarin patients (Austin 2011, Norman 2001).

Major bleeding, CRNM bleeding and recurrent VTE were compared between patients who received apixaban versus warfarin using shared frailty models (an extension of the Cox proportional hazards model that adjusts for correlation from matching). Kaplan–Meier curves were generated to depict the cumulative incidence of major bleeding, CRNM bleeding and recurrent VTE, respectively, and statistical comparisons were based on the stratified log-rank test (Klein 1997). The proportional hazards assumption was evaluated using published methods (Allison 2010, Pencina 2008). All analyses were performed in SAS 9.4 (SAS Institute, Cary, North Carolina, United States).

Sub-Group and Sensitivity Analyses

Sub-Group Analyses. Analyses of study measures, as described above, were repeated focusing alternatively on each data source—MarketScan Database, PharMetrics Database, Optum Database and Humana Database, respectively. **Sensitivity Analyses.** Use of a cohort design (i.e. without matching) was also employed. In these analyses, all patients who received outpatient treatment with apixaban or

warfarin (plus PAC bridging therapy) following their index encounters, and who met all other inclusion criteria were included in the study population. Bleeding events and recurrent VTE events were compared between patients who received apixaban versus warfarin using a shared frailty model (an extension of the Cox proportional hazards model that adjusts for intra-cluster [i.e. intra-database] correlation), with adjustment of estimated hazard ratios for systematic differences between treatment groups in baseline demographic and clinical characteristics. Patient characteristics were selected for inclusion in the multivariate model using a stepwise selection method (variable entry/retention criterion, *p*-value < 0.10).

In addition, an alternative approach to model specification using inverse proportional treatment weighting (IPTW) was employed to examine the impact of average treatment effect. The probability of receiving apixaban at study baseline was regressed on baseline covariates including VTE diagnosis, VTE care setting and VTE aetiology, as well as demographic and comorbidity profiles. Predicted probabilities were then inverted for apixaban patients and 1 minus predicted probabilities were inverted for warfarin patients. These inverses were then normalized to account for unequal sample sizes between treatment arms and were used as weights in evaluations of study outcomes using Cox proportional hazards models.

Power/Sample Size

Estimation of statistical power was based on the following assumptions, which were in turn based on exploratory analyses of data from earlier releases of the MarketScan and PharMetrics Databases (including data through 30 September 2015) and findings from the AMPLIFY clinical trial (Agnelli 2013):

- There would be at least 8,000 patients who received apixaban as outpatient treatment for VTE and met all other study entry criteria;
- The matched number of patients who received warfarin as outpatient treatment for VTE and met all other study entry criteria would total 8,000;
- Patients who received warfarin as outpatient treatment of VTE would have a 1.9% risk of a major bleeding event during the 6-month follow-up period; and

• Patients who received apixaban as outpatient treatment of VTE would have a 0.8% risk of a major bleeding event during the 6-month follow-up period.

Based on these assumptions and using a test to detect a difference between two proportions (Fleiss 1981), we calculated that β for this evaluation would <20% (two-sided $\alpha = 0.05$), and that the study would have >80% power to detect the assumed difference in risk of major bleeding events between patients who received apixaban versus those who received warfarin.

Bibliography

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Supplementary Material B

Appendix A

Brand Name	Generic Name	NDC Code	Form	Strength	Route
Eliquis	Apixaban	54569-6513-00	TAB	2.5 mg	ORAL
2.5	2	54569-6514-00	TAB	5 mg	ORAL
		00003-0894-21	TAB	5 mg	ORAL
		00003-0893-21	TAB	2.5 mg	ORAL
		00003-0894-31	TAB	5 mg	ORAL
		00003-0893-31	TAB	2.5 mg	ORAL
Coumadin	Warfarin sodium	00056-0173-01	TAB	7.5 mg	ORAL
		00056-0188-01	TAB	3 mg	ORAL
		00056-0173-70	TAB	7.5 mg	ORAL
		00056-0174-01	TAB	10 mg	ORAL
		00056-0174-70	TAB	10 mg	ORAL
		00056-0174-75	TAB	10 mg	ORAL
		00056-0172-01	TAB	5 mg	ORAL
		00056-0172-90	TAB	5 mg	ORAL
		00056-0172-75	TAB	5 mg	ORAL
		00056-0172-70	TAB	5 mg	ORAL
		00056-0170-01	TAB	2 mg	ORAL
		00056-0170-70	TAB	2 mg	ORAL
		00056-0170-75	TAB	2 mg	ORAL
		00056-0170-90	TAB	2 mg	ORAL
		00056-0169-01	TAB	1 mg	ORAL
		00056-0169-75	TAB	1 mg	ORAL
		00056-0169-70	TAB	1 mg	ORAL
		00056-0169-90	TAB	1 mg	ORAL
		00056-0176-01	TAB	2.5 mg	ORAL
		00056-0176-75	TAB	2.5 mg	ORAL
		00056-0176-90	TAB	2.5 mg	ORAL
		00056-0176-70	TAB	2.5 mg	ORAL
		00056-0168-70	TAB	4 mg	ORAL
		00056-0168-75	TAB	4 mg	ORAL
		00056-0168-01	TAB	4 mg	ORAL
		00056-0189-70	TAB	6 mg	ORAL
		00056-0189-75	TAB	6 mg	ORAL
		00056-0189-01	TAB	6 mg	ORAL
		00056-0188-70	TAB	3 mg	ORAL
		00056-0188-75	TAB	3 mg	ORAL
	Minufacia andiam	00056-01/3-/5	TAB	7.5 mg	ORAL
antoven	warrarin sodium	00832-1216-89	TAB	5 mg	ORAL
		00832-1211-00	TAD	1 mg	ORAL
		00832-1216-00	TAD	5 mg	ORAL
		00832-1210-10	TAB	5 mg	ORAL
		00832-1218-01	TAB	7.5 mg	ORAL
		00832-1218-01	TAB	7.5 mg	ORAL
		00832-1218-00	TAB	7.5 mg	ORAL
		00832-1213-00	TAB	4 mg	ORAL
		00832-1215-01	TAB	4 mg	ORAL
		00832-1215-00	TAB	4 mg	ORAL
		00832-1215-10	TAB	4 mg	ORAL
		00832-1217-89	TAB	6 mg	ORAL
		00832-1217-01	TAB	6 mg	ORAL
		00832-1217-00	TAB	6 mg	ORAL
		00832-1217-10	TAB	6 mg	ORAL
		00832-1214-89	TAB	3 mg	ORAL
		00832-1214-01	TAB	3 mg	ORAL
		00822 1214 10	TAD	2 mg	OPAL

Appendix B^d

Operational algorithm for differentiating between prophylactic versus therapeutic use of OAC/PAC agents:

Step 1: Identifying anticoagulation treatment episodes based on OAC and PAC use during the period of interest; an episode was assumed to be terminated when a gap \geq 30 days occurred.

Step 2: Each identified anticoagulation treatment episode was determined as prophylactic use if:

(1) Duration of episode was \leq 42 days; and

(2) Initiation date of anticoagulation in the episode occurred within 2 days before or 7 days after knee/ hip replacement surgery; or

Initiation date of anticoagulation in the episode occurred within 7 days after the admission date of a hospitalization associated with a 'medically ill' primary diagnosis (see below for corresponding codes) and with LOS \geq 3 days.

Step 3: A patient will be excluded from the study if any of his/her 6-month pre-index anticoagulation treatment episodes is determined as non-prophylactic use.

					1
		Preliminary list of ICD-9-CM Codes used	to define and identify "me	dically ill" patient	ls
General Category	ICD-9-CM		General Category	ICD-9-CM	Condition
Infectious diseases	001	Cholera	Infectious diseases	117	Other seycoses
Indections diseases	002	Typhoid and paratyphoid fevers	Infectious diseases	118	Opportunistic mycoses
Infectious diseases	003	Other salmosella infections	Infectious disenses	120	Schestosomianis (billarzianis)
Infectious diseases	004	Negritous Other find entropies (hereinight)	Infectious diseases	121	Other treaslode infections
Informations discourses	005	American Contenting (Internal)	Infectious diseases	122	Other cannot infection
Infortions diseases	007	Other protocoal intentinal diseases	Infectious diseases	124	Trichingia
Infectious diseases	008	Intestinal infections due to other organisms	Infectious diseases	125	Filarial infection and dracostiasis
Infectious diseases	009	Ill-defined intestinal infections	Infectious diseases	126	Ancylestemiasis and necatoriasis
indectious diseases	010	Primary tuberculous infection	Infectious diseases	127	Other intestinal helpsinthiases
Infectious diseases	011	Pulmonary tuberculoaia	Infectious diseases	128	Other and unspecified helminthinses
Indections diseases	011.5	Tuberculous bronchiectasis	Infections diseases	129	Intratinal parasitium, unspecified
Infectious diseases	012	Other respiratory tuberculosis	Infectious diseases	130	Tonoplasmosis
Infectious diseases	013	Tuberculosis of meninges and central nervous system	Infectious diseases	131	Trichononiasis
Infectious diseases	014	Tuberculosis of intestines peritoseun and mesenteric glands	Infectious diseases	132	Pediculosis and phthirus infestation
Infections diseases	015	Tuberculosis of bours and joints	Infectious diseases	133	Acerianis
Infectious diseases	016	Tuberculosis of genitourisary system	Infectious diseases	134	Other infestation
Infectious diseases	017	Tubercadosis of other organs	Infections diseases	135	Barunidosis
Infectious diseases	018	Miliary tuberculosis	Infectious diseases	136	Other and unspecified infectious and parasitic diseases
Indectious diseases	020	Plague	Infectious diseases	137	Late effects of tuberculosis
Infectious diseases	021	Tularenia	Infectious diseases	138	Late effects of acute policesystitis
Indections diseases	022	Anthrax	Infectious diseases	139	Late effects of other infectious and parasitic diseases
Infectious diseases	023	Brucellosis	Cancer	140	Cancer of lip
Infectious diseases	024	Glanders	Capcer	141	Cancer of tongue
Infections diseases	025	Melioidosiv	Callorr	142	Cancer of major salivary glands
Infectious diseases	026	Rat-bite fever	Caporr	143	Cancer of gum
Indections diseases	027	Other zoosotie bacterial diseases	Caser	144	Center of floor of mostly
mecsous diseases	030	Depensy Discourse does not dependent	Caleff	145	Canada of other and anoperated parts of month
marcdous diseases	031	Disking dat to other rejectingering	Caster	140	Cancer of exceptanyas
Information discours	032	When the same	Contraction	140	Cancer of hereithereit
Informations diseases	033	Strationeral area floor and scarles from	Canter	148	Concert of other and ill-defined sizes within the line and environment of
Merculus useeses	034	Englishes	Comme	149	Concer of southants
Information disease-	035	Meximan overal infection	Canver	150	Cancer of strength
Infectious Alanses	037	Tabasa	Conver	157	Cancer of small integring including devicement
Sensis	037	Sectionals	Canad	154	Cancer of roles
acpsis	0.58	A discussion in factories	Caser	155	Cancer of codes
Inflactions discours	040	Oder herteriel diseases	Caser	155	Cancel of Feedball recomplication and anter Cancel of Feedball recomplication hills during
Infectious diseases	041	Barnerial infection in conditions classified elsewhere and of monecified site	Cancer	156	Cancer of callbladder and extrahenatic bile docts
Infactions diseases	047	Maximum mechanism communication consistent and on antipectation and	Carrow	157	Cancel of particular and exception rate doca
Infectious discours	045	Arnte solizentelitia	Cancer	158	Cancer of retroperitonents and peritonents
Infectious diseases	046	Slow virus infection and prior diseases of central nervous system	Cancer	159	Cancer of other and ill-defined sites within the disentive organs and periformum
Indections diseases	047	Meninaltis due to enterovirus	Caporr	160	Cancer of usual cavities middle ear and accessory similes
Infectious diseases	048	Other enterovirus diseases of central nervous system	Caport	161	Casor of larms
Infectious diseases	049	Other non-arthropod-borne viral diseases of central nervous system	Cancer	162	Cancer of traches broacless and lung
Infectious diseases	050	Smallpox	Capter	163	Cancer of plears
Infectious diseases	051	Compox and paravaccinia	Cancer	164	Cancer of thymus heart and mediastimus
Infectious diseases	052	Chickrapos	Capter	165	intrathoracic organs
Infectious diseases	053	Herpes zonter	Cancer	170	Cancer of bone and articular cartilage
Infectious diseases	054	Herpes simplex	Capoer	171	Cancer of connective and other soft tissue
Infectious diseases	055	Measles	Capoer	172	Malignant melanoms of skin
Indectious diseases	056	Rubella	Cascer	174	Cancer of female breast
Infectious diseases	057	Other viral exathemata	Cascer	175	Cancer of male breast
Infectious diseases	058	Other human herpesvirus	Capcer	176	Kaposi's sarcoma
Infectious diseases	059	Other pozvirus infectious	Capter	179	Cancer of sterus, part suspecified
Infectious diseases	060	Yellow fever	Caper	180	Cancer of cervix uteri
Infectious diseases	061	Dengor	Capter	181	Cancer of placenta
Infectious diseases	062	Mosquito-borne viral encephalitis	Cascer	182	Cancer of body of aterus
Infectious diseases	063	Tick-borne viral encephalitis	Caser	183	Cancer of overy and other uterine adaras
Indectiona diseases	064	Viral encephalstis transmitted by other and unspectfied arthropods	Casorr	184	Cancer of other and unspecified frankle genital organs
Indectious diseases	065	Arthropod-borne hemorrhagic fever	Cancer	185	Cancer of prostate
Indections diseases	900	Other arthropod-horne viral diseases	Caser	180	Cancer of Invite
Indectious diseases	070	Viral beparties	Cancer	187	Cancer of peuts and other male genital organs
Infectious diseases	071	Rabies	Cascer	188	Cancer of bladder
Indectoous diseases	072	Stanps Online in	Cabour	100	Cancer of anney and other and unspectived tranky organs
Infection disease-	073	Specific distance due to consuchie view	Capetr	190	Cancer of brain
Infectious diseases	074	Specific diseases due to consactie virus	Cancer	191	Cancer of other and an analified earth of sectors and an
Infections diseases	076	Trachona	Castr	192	Cancer of during aland
Industing diagons	077	Other discusses of configuration due to vieway and chimedian	Constant	194	Cancer of other endorsing shads and school encourses
Infectious diseases	078	Other diseases the to viewes and chlamodian	Caster	195	Cancer of other and ill-defined aims
Inductions diseases	079	suspecified site	Cancer	196	Secondary and unspecified Cancer of lymph nodes
Infections diseases	080	Louise-berrie (epidemic) typhus	Canorr	197	Secondary Cancer of respiratory and digentive systems
Infectious diseases	081	Other typhss	Cascer	198	Secondary Cancer of other specified sites
Infections diseases	082	Tick-borne rickettuioses	Canter	199	Cancer without specification of site
Infectious diseases	083	Other rickettaioses	Caperr	200	lymphatic tiasur
Infectious diseases	084	Malaria	Casser	201	Hodgkin's disease
Infectious diseases	085	Leishmaniasis	Capoer	202	Other Cancers of lymphoid and histiocytic tissue
Infectious diseases	086	Trypanosomiasis	Cancer	203	Multiple myeloma and immunoproliferative neoplasms
Infections diseases	087	Relapsing Sever	Capter	204	Lymphoid leukemia
Indectious diseases	088	Other arthropod-borne diseases	Capter	205	Myeloid leskenia
Infections diseases	090	Congenital syphilis	Caperr	206	Monocytic Indemin
Infectious diseases	.091	Early syphilis symptomatic	Cancer	207	Other specified leukenia
Infections diseases	092	Early syphilis latent	Cascer	208	Leukenia of unpecified cell type
Infections diseases	093	Cardiovascular syphilis	Cancer	209	Neuroendocrine tumors
Indections diseases	094	Neurosyphilis	Neurologic disorders	342	Flaceid humiplagia
Infectious diseases	095	Other forms of late syphilis with symptoms	Neurologic disorders	342.1	Spastic bresiplegia
Infections diseases	096	Late syphilis, latent	Neurologic disorders	342.8	Other specified hemiplegia
Infectious diseases	097	Other and unspecified syphilis	Neurologic disorders	342.9	Hemiplegia suspecified
Infoctions diseases	098	Genecoccal infections	Neurologic disorders	344	Quadriplegia ant quadruparesis
Infectious diseases	099	Other venereal diseases	Neurologic disorders	344.1	Paraplegia
infectious diseases	100	Leptospirosis	Neurologic disorders	344.3	Monoplegia of lower limb
Indectious diseases	101	Vincent's angina	Neurologic disorders	344.6	Cauda equina syndrome
Infectious diseases	102	Yawa	Neurologic disorders	344.8	Other specified paralytic syndromes
Infectious diseases	103	Pinta	Neurologic disorders	344.9	Paralysis, unspecified
Indectious diseases	104	Other spirochetal infection	Cardiovascular conditions	428	Heart failure
lafections diseases	110	Dermatophytosia	Cardiovascular conditions	433	Occlusion and stenosis of precerebral arteries
Infections diseases	111	Demalonycosis other and unspecified	Cardiovascular conditions	434	Occlusion of cerebral america
Infectious diseases	112	Candidianis	Neurologic disorders	438.2	Hemiplegia/hemiparesis
Infections diseases	114	Coecidiosofosycosis	Neurologic disorders	438.4	Monoplegia of lower limb
Indections diseases	115	Histoplasmosis	Neurologic disorders	438.5	Other paralytic syndrome
Infectious diseases	116	Blastomycotic infection			

^d Corresponding ICD-10-CM codes are available upon request.

General Category	ICD.9-CM	Condition	General Category	ICD.9-CM	Condition
Infectious diseases	480	Viral pneumonia			
Infectious diseases	481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]			
Infectious diseases	482	Other bacterial pneumonia			
Infectious diseases	483	Pneumonia due to other specified organism			
Infectious diseases	484	Pneumonia in infectious diseases classified elsewhere			
Infectious diseases	485	Bronchopneumonia, organism unspecified			
Infectious diseases	486	Pneumonia, organism unspecified			
Infectious diseases	487	Influenza			
Respiratory conditions	490	Bronchitis, not specified as acute or chronic			
Respiratory conditions	491	Chronic bronchitis			
Respiratory conditions	492	Emphysema			
Respiratory conditions	493	Asthma			
Respiratory conditions	494	Bronchiectasis			
Respiratory conditions	495	Extrinsic allergic alveolitis			
Respiratory conditions	496	Chronic airway obstruction, not elsewhere classified			
Respiratory conditions	518.81	Acute respiratory failure			
Respiratory conditions	518.82	trauma and surgery			
Bowel diseases/obesity	555	Regional enteritia			
Bowel diseases/obesity	556	Ulcerative enterocolitis			
Infectious diseases	680	Carbuncle and furuncle			
Infectious diseases	681	Cellulitis and abscess of finger and toe			
Infectious diseases	682	Other cellulitis and abscess			
Infectious diseases	683	Acute lymphadenitis			
Infectious diseases	684	Impetigo			
Infectious diseases	685	Pilonidal cyst			
Infectious diseases	686	Other local infections of skin and subcutaneous tisane			
Rhuematic disorder	714.0	Rheumatoid arthritis			
Rhuematic disorder	715.15	Osteoarthrosis, localized, primary, pelvic region and thigh			
Rhuematic disorder	715.16	Osteoarthrosis, localized, primary, lower leg			
Rhuematic disorder	715.17	Osteoarthrosis, localized, primary, ankle and foot			
Rhuematic disorder	715.25	Ostcoarthrosis, localized, secondary, pelvic region and thigh			
Rhuematic disorder	715.26	Osteoarthrosis, localized, secondary, lower leg			
Rhuematic disorder	715,27	Ostcoarthrosis, localized, secondary, ankle and foot			
Rhoematic disorder	715.35	pelvic region and thigh			
Rhuematic disorder	715.36	lower leg			
Rhuematic disorder	715,37	ankle and foot			
Rhuematic disorder	724.2	Lumbago			
Rhuematic disorder	724.3	Sciatica			
Rhoematic disorder	733.13	Pathological fracture of vertebrae			
Infectious diseases	730	Osteomyelitis periostitis and other infections involving bone			
Respiratory conditions	748.61	Congenital bronchicctasis			
Neurologic disorders	780.01	Coma			
Sepsis	790.7	Bacteremia			
Sepsis	995.91	Sepsis			
Sepsis	995.92	Severe sepsis			
Infectious diseases	996.6	graft			
Infectious diseases	997.62	Infection (chronic) of amputation stump			
Infectious diseases	998.3	Disruption of operation wound			
Infectious diseases	998.5	Postoperative infection not elsewhere classified			
Infectious diseases	999.3	Other infection due to medical care not elsewhere classified			

Appendix C^e

Table. HCPCS codes for parenteral anticoagulants

Drug	HCPCS Code	
Low Molecular Weight Heparin		
Dalteparin	J1645	
Enoxaparin	J1650	
Tinzaparin	J1655	
Heparin	J1642, J1644	
Fondaparinux	J1652	

^e Codes from the NDC system were also be used to characterize use of PAC.

Appendix D

Brand Name	Generic Name	NDC Code	Form	Strength	Route
Pradaxa	Dabigatran etexilate	00597-0107-54	CAP	75 mg	ORAL
	mesylate	00597-0107-60	CAP	75 mg	ORAL
		00597-0108-60	CAP	110 mg	ORAL
		00597-0135-54	CAP	150 mg	ORAL
		00597-0135-60	CAP	150 mg	ORAL
		00597-0149-54	CAP	75 mg	ORAL
		00597-0149-60	CAP	75 mg	ORAL
		21695-0899-60	CAP	150 mg	ORAL
-		54569-6276-00	CAP	150 mg	ORAL
Xarelto	Rivaroxaban	42254-0376-01	TAB	20 mg	ORAL
		50458-0578-10	TAB	15 mg	ORAL
		50458-0578-30	TAB	15 mg	ORAL
		50458-0578-90	TAB	15 mg	ORAL
		50458-0579-10	TAB	20 mg	ORAL
		50458-0579-30	TAB	20 mg	ORAL
		50458-0579-90	TAB	20 mg	ORAL
		50458-0580-10	TAB	10 mg	ORAL
		50458-0580-30	TAB	10 mg	ORAL
		50458-0584-51	TAB	15 mg; 20 mg	ORAL
Savaysa	Edoxaban	65597-0201-30	TAB	15 mg	ORAL
		65597-0202-05	TAB	30 mg	ORAL
		65597-0202-30	TAB	30 mg	ORAL
		65597-0202-90	TAB	30 mg	ORAL
		65597-0203-05	TAB	60 mg	ORAL
		65597-0203-30	TAB	60 mg	ORAL
		65597-0203-90	TAB	60 mg	ORAL

Table. NDC codes for other oral anticoagulants

Appendix E^f

Table. Codes for exclusionary conditions and procedures

Condition/Procedure	Diagnosis Codes	Procedure Codes
Atrial Fibrillation/Flutter	427.31, 427.32	
Chemotherapy		See below
Radiation Therapy		77280, 77285, 77290, 77295, 77299, 77300,
		77301, 77305, 77310, 77315, 77321, 77326,
		77327, 77328, 77331, 77332, 77333, 77334,
		77336, 77338, 77371, 77372, 77373, 77399,
		77401, 77402, 77403, 77404, 77406, 77407,
		77408, 77409, 77411, 77412, 77413, 77414,
		77416, 77417, 77418, 77421, 77422, 77423,
		77424, 77425, 77427, 77431, 77432, 77435,
		77469, 77470, 77499, 77520, 77522, 77523,
		77525, 77750, 77761, 77762, 77763, 77776,
		77777, 77778, 77785, 77786, 77787, 77789,
		77799, 92.20-92.29
Malignant Neoplasm (excluding non-melanoma	140-209.3	
skin)	(excluding 173)	
IVCF		ICD-9: 38.7x
		CPT: 37191, 37192, 37193, 37620
Pregnancy/Postpartum Care	(20, (70, 1/20, 1/20, 1/21, 1/27)	ICD-9: 72.00-75.99
	630-679, V22, V23, V24, V27, V28, V61.6, V61.7, 792.3, 796.5	CPT: 59000-59350, 59400-59430, 59510-59866, 59870-59899, 76801-76828, 83661-83664

^f Corresponding ICD-10-CM codes are available upon request.

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Chemotherapy Drug/Administration	HCPCS Level II Codes
ALDESLEUKIN	J9015
ALEMTUZUMAB	C9110, S0087
ARSENIC TRIOXIDE	C9012
ASPARAGINASE	J9020
AZACITIDINE	C9218, J9025
BENDAMUSTINE	C9243, J9033
BEVACIZUMAB	J9035, C9214, C9257, Q2024, S0116
BLEOMYCIN	C9417, J9040
BORTEZOMIB	C9207
BRENTUXIMAB	C9287, J9042
BUSULFAN	C1178, J0594, J8510
CABAZITAXEL	C9276, J9043
CAPECITABINE	J8520, J8521
CARBOPLATIN	J9045
CARMUSTINE	C9437, J9050
CETUXIMAB	C9215, J9055
CHEMO unknown	J9999
CHLORAMBUCIL	S0172
CISPLATIN	C9418, J9060. J9062
CLADRIBINE	C9419, J9065
CLOFARABINE	C9129, J9027
CYCLOPHOSPHAMIDE	C9420, C9421, J8530, J9070, J9080, J9090, J9091, J9092, J9093,
CYTARABINE	C1166, C9422, J9098, J9100, J9110
DACARBAZINE	J9130, J9140, C9423
DACTINOMYCIN	19120
DAUNORUBICIN	J9150, J951, C9424
DECITABINE	C9231_J0894
DENILEUKIN DIFTITOX	C1084_J9160
DOCETAXEL	I9170 I9171
DOXORUBICIN	C9415 19000
DOXORUBICIN LIPOSOMAL	19001 19002 02048 02049 02050
FPIRUBICIN	19178 C1167 19180
FRIBULIN	19179 (9280
ETOPOSIDE	19181 19182 09414 09425 18560
EVEROLIMUS	18561
FLOXURIDINE	19200 C9426
FLUDARABINE	10185 C0262 02025 18562
FLUOROURACII	10100
GEEITINIB	18565
GEMCITARINE	10201
GEMTUZUMAD	C0004 10200
HVDPOVVIDEA	\$0176
IPPITIMOMAP	A0542
IDRITOMOMAD	19000
IBRUTINIB	18999
IDARUBICIN	J9211, C9429
IDELALISIB	J8999
IFOSFAMIDE	J9208, C9427
IMATINIB	50088
IPILIMUMAB	J9228, C9284
IKINOTECAN	J9206
IXABEPILONE	J9207, C9240
KADCYLA	C9131, J9354
LEUCOVORIN	J0640
LEVOLEUCOVORIN	J0641
LOMUSTINE	C9017, S0178
MECHLORETHAMINE	J9230
MELPHALAN	J9245, J8600

Chemotherapy Drug/Administration	HCPCS Level II Codes
MERCAPTOPURINE	S0108
METHOTREXATE	J9250, J9260, J8610
MITOMYCIN	J9280, J9290, J9291, C9432
MITOXANTRONE	J9293
NELARABINE	J9261
OFATUMUMAB	J9302
OXALIPLATIN	C9205, J9263
PACLITAXEL	C9127, C9431, J9264, J9265
PANITUMUMAB	C9235, J9303
PEGASPARGASE	J9266
PEMETREXED	C9213, J9305
PENTOSTATIN	J9268
PERTUZUMAB	C9292
PLICAMYCIN	J9270
PRALATREXATE	C9259, J9307
PROCARBAZINE	\$0182
REGORAFENIB	J8999
RITUXIMAB	J9310
ROMIDEPSIN	C9265, J9325
STREPTOZOCIN	J9320
TEMOZOLOMIDE	C1086, C9253, J9328, J8700
TEMSIROLIMUS	C9239, J9330
TENIPOSIDE	Q2017
THIOTEPA	C9433, J9340
TOPOTECAN	J9350, J9351, J8705
TOSITUMOMAB	G3001
TRASTUZUMAB	J9355
TRETINOIN	S0117
VALRUBICIN	J9357
VINBLASTINE	J9360
VINCRISTINE	J9370, J9375, J9380
VINCRISTINE LIPOSOMAL	J9371
VINORELBINE	C9440, J9390
ZALTRAP	J9400

Table.	List o	of chemot	herapy	admistration	codes
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HCDCS I avail I/II Cadaa	Description	
HCPCS Level I/II Codes	Description	
36640	Arterial catheterization for protonged infusion therapy (chemotherapy), cutdown	
01517	Chamatharana a darini intracavitary chemounerapy agent (list separately in addit	
96401	Chemotherapy administration, subcutaneous of intramuscular, non-normonal anti-ne	
96402	Chemotherapy administration, subcutaneous or intramuscular, hormonal anti-neopia	
96405	Chemotherapy administration; intralesional, up to and including / lesions	
96406	Chemotherapy administration; intralesional, more than / lesions	
96409	Chemotherapy administration; intravenous, push technique, single or initial subs	
96411	Chemotherapy administration; intravenous, push technique, each additional substa	
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, singl	
96415	Chemotherapy administration, intravenous infusion technique; each additional hou	
96416	Chemotherapy administration, intravenous infusion technique; initiation of prolo	
96417	Chemotherapy administration, intravenous infusion technique; each additional seq	
96420	Chemotherapy administration, intra-arterial; push technique	
96422	Chemotherapy administration, intra-arterial; infusion technique, up to one hour	
96423	Chemotherapy administration, intra-arterial; infusion technique, each additional	
96425	Chemotherapy administration, intra-arterial; infusion technique, initiation of p	
96440	Chemotherapy administration into pleural cavity, requiring and including thorace	
96445	Chemotherapy administration into peritoneal cavity, requiring and including peri	
96446	Chemotherapy administration into the peritoneal cavity via indwelling port or ca	
96450	Chemotherapy administration, into CNS (eg, intrathecal), requiring and including	
96542	Chemotherapy injection, subarachnoid or intraventricular via subcutaneous reserv	
96549	Unlisted chemotherapy procedure	
99555	Home infuse, chemotheraphy	
Q0083	Chemotherapy administration by other than infusion technique only (eg subcutaneo	
Q0084	Chemotherapy administration by infusion technique only, per visit	
Q0085	Chemotherapy administration by both infusion technique and other technique(s) (e	
S9329	Home infusion therapy, chemotherapy infusion; administrative services, professio	
\$9330	Home infusion therapy, continuous (twenty-four hours or more) chemotherapy infus	
\$9331	Home infusion therapy, intermittent (less than twenty-four hours) chemotherapy i	

Appendix F^g Deyo–Charlson Comorbidity Index

Diagnostic Category	ICD-9-CM codes	Points
Myocardial Infarction	410, 412	1
Congestive Heart Failure	428-428.9	1
Peripheral Vascular Disease	443.9, 441-441.9, 785.4, V43.4; 38.48 (Px)	1
Cerebrovascular Disease	430-438	1
Dementia	290–290.9	1
Rheumatologic Disease	710.1, 710.4, 714.0–714.2, 714.81, 725	1
Peptic Ulcer Disease	531-534.9	1
Mild Liver Disease	571.2, 571.5, 571.6, 571.4–571.49,	1
Diabetes	250–250.3, 250.7	1
Diabetes w/ Complications	250.4–250.6	2
Hemiplegia or Paraplegia	344.1, 342–342.9	2
Renal Disease	582-582.9, 583-583.7, 585, 586, 588-588.9	2
Any Malignancy	140–172.9, 174–195.8, 200–208.9	2
Moderate or Severe Liver Disease	572.2–572.8, 456.0–456.21	3
Metastatic Solid Tumour	196–199.1	6
AIDS	042-044.9	6

^g Corresponding ICD-10-CM codes are available upon request.

ovariate	Variable Type and Definition	Onerational Alcorithm	
emographics	HALFFERT AT ANY AT A SAME A		
Age	Continuous, Categorical: 18-49, 50-64, 65-74, >=75	Based on year of index therapy initiation	
Gender	Categorical: male vs. female		¢
U.S. Geographic Region	Categorical: northeast, south, north central, west, other		200
Physican Specialty	Categorical: based on empirical data		9 IV.
omorbidity Profile			
		The Deyo-Charlson Comorbidity Index will based on information available during the pre-index period:	
		 I point: myocardial infarction. consective heart failure. perioheral vascular 	
These Charless Constitution Lades	P sustineers	disease, dementia, cerebrovascular disease, chronic pulmonary disease,	Case Assessed of
ACTO-COMPANIAN COMPANIA ADDEX	CONTRACTO	recumanylogic disease, peptic user disease, inid river disease, dianyces (inida to moderate)	occurring the second seco
		o 2 points: hemiplegia or paraplegia, renal disease, diabetes with complication, an	-Ar
		 a points: moderate or severe liver disease 	
Acoulted immunodeficiency confrome (AIDS)	Categories, too an	 6 points: malignant tumor, acquired immunodeficiency syndrome (AIDS) 2-1 diamonic during & month baseling needed 	307, 610
Alcohol Abuse	canagorieali yes, no Categoricali yes, no	>=1 diagnosis, procedure, drug during 6-month baseline period	DX: 291, 303, 305.0, 357, 4355, 535, 351.0, 571.1, 571.2, 571.3, PX (ICD-a): 94.46, 94.55, 94.61, 94.67, 94.67, 94.67 PX (ICPT): 94.46, 94.15, 94.61, 94.67, 94.67, 94.69 PX (ICPT): 94.96, 94.96, 00395, 14054, 14056
Anemia	Categorical: yes, no	>=1 diagnosis, procedure, drug during 6-month baseline period	280.x-285.x
			Gastrointestinal bleeding: 455 2, 455 5, 455 8, 456 0x, 456 20, 530 7x, 750 25, 530 7x, 751 0x, 531 0x, 532 0x, 542 0x, 550 0x
Bleeding	Categorical: yes, no	>=1 diagnosis during 6-month baseline period	Intracranial hemorrhage: 430.xx, 431.xx, 432.0x, 432.1x, 432.9x, 852.xx, 853.0x
			Other hemorthage: 078 (x, 246.3x, 285.1, 286.5, 388.69, 360.43, 362.43, 362.44), 362.41, 362.81, 356.1, 350.52, 357.13, 361.41, 375.21, 374.14, 379.21, 423.04, 499.05, 593.1, 565.7x, 599.7x, 602.1x, 620.1x, 621.4x, 626.5x, 626.5x, 626.5x, 626.5x, 667.8x, 991.1x, 782.7x, 784.8x, 786.3x, 790.01, 958.2x, 997.02, 998.11
Central Venous Catheter	Categorical: yes, no	>=1 diagnosis, procedure during 6-month baseline period	DX: 999.31, 999.32, 999.33 PX (ICD-9); 38.95, 38.95, 38.97, 89.62 PX (CPT): 3655-36569, 55520, 55520
Cerebrovascular Disease (stroke and TLA)	Categorical: yes, no	>=1 diagnosis, procedure during 6-month baseline period	DX: 430, 431, 432, x, 434, xx, 435, x, 436, 4371, 4378, 437, 997,02 PX (CP): 5390, 37215, 37216 PX (CP): 5391, 3212, 3212, 3212
Chronic Obstructive Pulmonary Disease	Categorical: yes, no	>=1 diagnosis during 6-month baseline period	DX: 491 xx, 492 x, 496
Coagulopathy	Categorical: yes, no	>=1 diagnosis during 6-month baseline period	DX: 286.6, 286.7, 286.9
Congestive Heart Failure	Calcgorical: yes, no	>=1 diagnosis during 6-month baseline period	DX: 398.9J, 402.0J, 402.1J, 402.9J, 404.0J, 404.03, 404.1J, 404.13, 404.13, 401.52, 425.xx PX (CPT): 3390, 33971, 33975, 33940, 33944, 33945, 33961, 33967, 33968, 33970, 33971, 33972, 33974, 33975, 33978, 33967, 33969, 33981, 33952, 33957, 33974, 33975, 33978, 3761, 37.62, 37.64, 37.64, 37.66, 37.66, 37.67, 37.68

^h Corresponding ICD-10-CM codes are available upon request.

Appendix G^h

Table. Covariates variable types/definitions, operational algorithm	is, and codes		
Covariate	Variable Type and Definition	Operational Algorithm	Diagnosis/Procedure/Drug Codes
Ishcemic Hear/Coronary Artery Disease	Categorical: yes, no	>=1 diagnosis, procedure during 6-month baseline period	DX: 410.xx, 411.0, 412, 425.71, 435.97, 413.x, 411.1, 411.8x, 414.0x, PX (CPT): 33508, 33510, 33511, 33512, 33514, 33516, 33515, 33518, 33518, 33521, 33521, 33551, 33512, 33538, 33558, 33522, 440.15300, 13500, 35506, 35597, 35508, 35509, 35515, 35601, 35605, 55991, 35669, 35569, 35579, 35795, 25977, 92378, 92978, 92979, 92980, 92381, 92982, 92984 PX (ICC-91, 0066, 1755, 5601, 35605, 5605, 3560, 35607, 35609, 356, 1355, 5601, 3602, 3603, 5606, 356, 35607, 35609, 365, 1356, 3501, 3601, 3603, 3606, 35607, 365, 1356, 3601, 3612, 3613, 3664, 3569, 3607, 0052, 0053, 00.54, 3750, 37791, 37792, 37794, 37795, 37796, 3796, 3797, 3798,
Dementia	Categorical: yes, no	>=1 diagnosis during 6-month baseline period	290.290.9
Diabetes	Categorical: yes, no	>=1 diagnosis, drug during 6-month baseline period	DX: 249.xx, 250.xx, 357.2, 362.0x, 366.41, 648.0, E932.3, V58.67 PX: anticitaloric
Dyspepsia or Stomach Discomfort	Categorical: yes, no	>=1 diagnosis during 6-month baseline period	DX: 787.1, 789.0, 789.4, 789.6, 536.8
Fractures Involving the Lower Extremities	Categorical: yes, no Categorical: yes, no	>=1 diagnosis during 6-month baseline period	DX: 820-828, 835-838, 890-897, 928,0-928,0-928,3, 928.8, 928.9, 945,
Hemiplegia or paraplegia	Categorical: yes, no	>=1 diagnosis during 6-month baseline period	936, 939.0, 939.7 DX: 344.1, 342.342.9
Byperlipidemia	Categorical: yes, no	>=1 diagnosis, drug during 6-month baseline period	DX: 272.2, 272.4
Hypertension	Categorical: yes, no	>=1 diagnosis, drug during 6-month baseline period	DX: 362.11, 401, 402, 403, 405
Inflammatory Bowel Syndrome	Categorical: yes, no	>=1 diagnosis, drug during 6-month baseline period	DX: 555.0, 555.1, 555.2, 555.9, 556.0, 556.1, 556.2, 556.3, 556.5, 556.5, 556.6, 556.8, 556.9
Liver Disease	Categorical: yes, no	>=1 diagnosis, procedure during 6-month baseline period	DX: 070.22, 070.23, 070.32, 070.33, 070.42,070.49, 070.52-070.59, 070.6, 070.7x, 070.9, 277.4, 456.0-456.2, 571.xx, 572.x, 573.x, 751.62, 968.82, v42.7 PX (CPT), 47135, 47136 PX (CPT), 47135, 47136
Malignancy (excluding non-melanoma skin cancer)	Categorical: yes, no	>=1 diagnosis, procedure during 6-month baseline period	DX: 140-172, 174-209.3 PX: see Appendix D
Obesity	Categorical: yes, no	>=1 diagnosis, drug during 6-month baseline period	DX: 278.xx, E66.xx RX: antiobesity agent
Peptic ulcer disease	Categorical: yes, no	>=1 diagnosis, drug during 6-month baseline period	DX: 531 xx, 532 xx, 533 xx, 534 xx RX: antacid therawy
Peripheral Vascular Disease	Categorical: yes, no	>=1 diagnosis during 6-month baseline period	DX: 440, 441, 442, 443, 444, 445
Pneumonia	Categorical: yes, no	>=1 diagnosis during 6-month baseline period	DX: 480.x-486
Renal Disease	Categorical: yes, no	>=1 diagnosis, procedure during 6-month baseline period	DX: 585.xx, 586.xx, 1451, 1x, V56.x, V42.0, 250.4x, 403.00, 403.10, 403.10, 403.00, 404.10, 404.00, 404.10, 404.90, 572.4, 581.xx-583.xx, 588.xx, 291.0 PX (CPT): 36147, 36148, 36800-36821, 3625, 136363, 56356, 36830, 36830, 901549025, 90355, 90959, 90340, 30360, 3056, 54.98, 55.69 PX (ICD-9); 38.95, 39.27, 39.42, 39.42, 39.42, 39.95, 54.98, 55.69
Rheumatologic Disease	Categorical: yes, no	>=1 diagnosis during 6-month baseline period	DX: 710.1, 710.1, 710.4, 714.0-714.2, 714.81, 725
Sleep Apnea	Categorical: yes, no	>=1 diagnosis, procedure during 6-month baseline period	DX: 327.23, 780.57 PX (CPT): G8839, G8841, G8900
Spinal Cord Injury	Categorical: yes, no	>=1 diagnosis during 6-month baseline period	DX: 952 xx
Thrombocytopenia	Categoncal: yes, no	>=1 diagnosis during 6-month baseline period	287.3X, 287.4X, 287.5X, 446.6, 289.84
Varicose Veins	Categorical, yes, no Categorical: yes, no	>=1 diagnosis during 6-month baseline period	454.X 200.2, 207.01
Procedures Abdomínal surgery	Categorical: yes, no	>=1 procedure during 6-month baseline period	PX (ICD-9): 43-47, 50, 51, 54
Hemodialysis	Categorical: yes, no	>=1 procedure during 6-month baseline period	DX: V45.1k, V56.X PX (CPT): 36147, 36148, 5680-3637, 3683, 36830, 36838, 36838, 36870, 90918-90925, 90935, 90939, 39.95, 54.98 PX (ICD-9): 38.95, 39.27, 39.42, 39.43, 39.95, 54.98
Hip replacement	Categorical: yes, no	>=1 procedure during 6-month baseline period	PX (CPT): 27120, 27125, 27136, 27132, 27134, 27137, 27138 PX (fCD-9): 81.51, 81.52, 81.53
Knee replacement	Categorical: yes, no	>=1 procedure during 6-month baseline period	PX (CPT): 27445, 27447, 27486, 27487 PX (ICD-9): 81.54, 81.55
Pelvic or orthopedic surgery Recent surgery (malor)	Categorical: yes, no Categorical: ves. no	>=1 procedure during 6-month baseline period >=1 procedure durine 6-month baseline period	PX (ICD-9): 77.5-77.9, 78.5-78.9, 79.5-79.9, 80.5-80.9, 81 Codes available mon request

Table. Covariates - variable types/definitions, operational	il algorithms, and codes		
Covariate	Variable Type and Definition	Operational Algorithm	Diagnosis/Procedure/Drug Codes
Pharmacotherapy	Committee on an	A strategy of the state of the	by, any constraint of the state
AVE IIIII01015/ANDS	Categorical, yes, no		IAA. MUCS for corresponding unigorials
Antiarrhythmics	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDC's for corresponding drug/drug class
Antiplatelets	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
Aromatase inhibitors	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
Beta blockers	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
Calcium channel blockers	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
Contraceptives (oral)	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
Erythropolesis stimulating agents	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
Gastroprotective agents	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
Hormones	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
NSAIDs	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
SERMS	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
Statins	Categorical: yes, no	>=1 drug during 6-month baseline period	RX: NDCs for corresponding drug/drug class
Healthcare Utilization and Expenditures			
Expenditures for any reason	Continuous	Measures of all-cause health care costs during the 6-month baseline period will be computed for: MD, ED, hospitalizations, and RX (outpatient)	
Expenditures for bleeding-related events	Continuous	Measures of bleeding-related health care costs during the 6-month baseline period will be computed for: MD, ED, hospitalizations	
Utilization for any reason	Continuous, Categorical; 0, 1-3, 4-5, >=6	Measures of all-cause HRU during the 6-month baseline period will be computed for: MID, ED, hospitalizations, and RX (outpatient)	
Utilization for bleeding-related events	Continuous, Categorical: 0, 1-3, 4-5, >=6	Measures of bleeding-related HRU during the 6-month baseline period will be	

Appendix Hⁱ

Table. Factors identifying provoked VTE

Factors	Identifying Strategies
Hormone therapy	
Estrogen Therapy	
	ESTRADIOL CYPIONATE
	ESTRADIOL VALERATE
	ESTRADIOL
	ETHINYL ESTRADIOL
	ESTRADIOL BENZOATE
	ESTRADIOL ACETATE
	ESTRADIOL MICRONIZED
	ESTRONE
	ESTROGENS, CONJUGATED/MEPROBAM
	ESTROGENS, CONJUGATED
	ESTRIOL
	CHLOROTRIANISENE
	QUINESTROL
	DIENESTROL
	ESTROGENS, ESTERIFIED
	ESTROPIPATE
	ESTROGENS, CONJ., SYNTHETIC A
	ESTROGENS, CONJ., SYNTHETIC B
	ESTRIOL MICRONIZED
Combination E+P	ETHINYL ESTRADIOL/NORETH AC
	NORETHIND AC/ETHINYL ESTRADIOL
	ESTRADIOL/NORETH AC
	ESTRADIOL/NORGESTIMATE
	ESTRADIOL/LEVONORGESTREL
	ESTRADIOL/DROSPIRENONE
	ESTROGEN, CON/M-PROGEST ACET
Fracture/Trauma involving the Lower Extremities	ICD-9-CM: 820-828, 835-838, 890-897, 904, 928.0-
na na mana na mana na mana na mana kata kata kata na mana na kata kata na kata kata na kata na kata na kata na Na	928.3, 928.8, 928.9, 945, 956, 959.6, 959.7
Pelvic or orthopedic surgery	ICD-9-CM procedure code: 77.5-77.9, 78.5-78.9,
	79.5-79.9. 80.5-80.9, 81
Any hospitalization	Any acute-care inpatient stay from medical claims

ⁱ Corresponding ICD-10-CM codes are available upon request

Online Supplement Table 1. Selection of patients receiving apixaban or warfarin as outpatient therapy for VTE															
		Humana (n [%])			Market Scan (n [%])			Optum (n [%])			PharMetrics (n [%])		¥.	tal Population (n [%	-
Inclusion/ Exclusion Criteria	Apicaban	Warfarin	Total	Apicaban	Warfarin	Total	Apicaban	Warfarin	Total	Apixaban	Warfarin	Total	Apixaban	Warfarin	Total
Selection of Subjects															
Ind usion criteria:															
Aged 218 years with diagnosis of VTE from September 1, 2014 to June 30, 2017:	!	I	221,647 (100.0%)	I	!	380,035 (100.0%)	I	I	320,098 (100.0%)	1	1	463,551 (100.0%)	1	I	1,385,331 (100.0%)
Setting:															
Acute-Care Inpatient	ł	1	85,120 (38.4%)	1	!	74,195 (19.5%)	I	1	108,014 (33.7%)	I	I	114,683 (24.7%)	I	I	382,012 (27.6%)
A mbulatory Care	ł	1	136,527 (61.6%)	1	1	305,840 (80.5%)	1	ł	212,084 (66.3%)	1	1	348,868 (75.3%)	1	1	1,003,319 (72.4%)
Dia gnosis:															
Diagnosis of PE (with or without DVT)	;		66,428 (30.0%)		!	110,436 (29.1%)		;	96,415 (30.1%)			132,802 (28.6%)			406,081 (29.3%)
Diagnosis of DVT Only	;	1	155,219 (70.0%)	1	1	269,599 (70.9%)	1	ł	223,683 (69.9%)	1	1	330,749 (71.4%)	1	1	979,250 (70.7%)
Presumed aetiology:															
Provoked	ł	ł	67,668 (30.5%)	I	ł	94,836 (25.0%)	I	ł	79,994 (25.0%)	I	I	104,538 (22.6%)	I	I	347,036 (25.1%)
Unprovoked	1	1	153,979 (69.5%)	1	;	285, 199 (75.0%)	1	1	240,104 (75.0%)	1	1	359,013 (77.4%)	1	1	1,038,295 (74.9%)
plus 21 outpatient pharmacy claim for apixaban or warfarin during 30-day period following the index encounter	10,034 (4.5%)	40,709 (18.4%)	50,743 (22.9%)	11,245 (3.0%)	62,640 (16.5%)	73,885 (19.4%)	10,987 (3.4%)	57,337 (17.9%)	68,324 (21.3%)	15,973 (3.4%)	76,117 (16.4%)	92,090 (19.9%)	48,239 (3.5%)	236,803 (17.1%)	285,042 (20.6%)
plus health benefits for a6 months prior to index therapy	8,613 (3.9%)	32,486 (14.7%)	41,099 (18.5%)	10,030 (2.6%)	55,340 (14.6%)	65,370 (17.2%)	7,899 (2.5%)	41,755 (13.0%)	49,654 (15.5%)	11,732 (2.5%)	59,923 (12.9%)	71,655 (15.5%)	38,274 (2.8%)	189,504 (13.7%)	227,778 (16.4%)
Exclusion or iteria:															
plus no ciaims for conditions/procedures:															
No claims for atrial fibrillation/flutter during 6-month period prior to index therapy	6,229 (2.8%)	23,593 (10.6%)	29,822 (13.5%)	8,963 (2.4%)	48,547 (12.8%)	57,510 (15.1%)	6,673 (2.1%)	33,919 (10.6%)	40,592 (12.7%)	10,496 (2.3%)	54,109 (11.7%)	64,605 (13.9%)	32,361 (2.3%)	160,168 (11.6%)	192,529 (13.9%)
No claims for chemotherapy/radiation therapy for malignancy* during 6-month period prior to index therapy	5,710 (2.6%)	22,175 (10.0%)	27,885 (12.6%)	8,392 (2.2%)	46,118 (12.1%)	54,510 (14.3%)	6,242 (2.0%)	32,162 (10.0%)	38,404 (12.0%)	9,923 (2.1%)	51,960 (11.2%)	61,883 (13.3%)	30,267 (2.2%)	152,415 (11.0%)	182,682 (13.2%)
No claims for malignancy* during 90-day period prior to index therapy	4,990 (2.3%)	19,724 (8.9%)	24,714 (11.2%)	7,624 (2.0%)	41,935 (11.0%)	49,559 (13.0%)	5,637 (1.8%)	29,036 (9.1%)	34,673 (10.8%)	9,245 (2.0%)	48,804 (10.5%)	58,049 (12.5%)	27,496 (2.0%)	139,499 (10.1%)	166,995 (12.1%)
No claims for INCF during study period	4,852 (2.2%)	19,068 (8.6%)	23,920 (10.8%)	7,357 (1.9%)	40,503 (10.7%)	47,860 (12.6%)	5,533 (1.7%)	28,148 (8.8%)	33,681 (10.5%)	9,034 (1.9%)	47,399 (10.2%)	56,433 (12.2%)	26,776 (1.9%)	135,118 (9.8%)	161,894 (11.7%)
No claims for pregnancy during study period	4,830 (2.2%)	18,888 (8.5%)	23,718 (10.7%)	7,232 (1.9%)	39,707 (10.4%)	46,939 (12.4%)	5,478 (1.7%)	27,753 (8.7%)	33,231 (10.4%)	8,221 (1.8%)	41,674 (9.0%)	49,895 (10.8%)	25,761 (1.9%)	128,022 (9.2%)	153,783 (11.1%)
plus no evidence of any OAC/PAC use during 30-day period prior to index encounter	4,637 (2.1%)	18,011 (8.1%)	22,648 (10.2%)	6,975 (1.8%)	37,564 (9.9%)	44,539 (11.7%)	5,328 (1.7%)	26,416 (8.3%)	31,744 (9.9%)	7,931 (1.7%)	39,467 (8.5%)	47,398 (10.2%)	24,871 (1.8%)	121,458 (8.8%)	146,329 (10.6%)
plus no evidence of any OAC/PAC use during 6-month period prior to index encounter except prophylactic use **	4,636 (2.1%)	17,996 (8.1%)	22,632 (10.2%)	6,968 (1.8%)	37,516 (9.9%)	44,484 (11.7%)	5,319 (1.7%)	26,371 (8.2%)	31,690 (9.9%)	7,921 (1.7%)	39,409 (8.5%)	47,330 (10.2%)	24,844 (1.8%)	121,292 (8.8%)	146,136 (10.5%)
plus no evidence of receipt of >1 OAC during period between index encounter and index therapy initiation [†]	4,614 (2.1%)	17,957 (8.1%)	22,571 (10.2%)	6,892 (1.8%)	37,373 (9.8%)	44,265 (11.6%)	5,285 (1.7%)	26,262 (8.2%)	31,547 (9.9%)	7,870 (1.7%)	39,292 (8.5%)	47,162 (10.2%)	24,661 (1.8%)	120,884 (8.7%)	145,545 (10.5%)
plus no claims for VTE during 6-month period prior to index encounter	4,566 (2.1%)	12,443 (5.6%)	17,009 (7.7%)	6,656 (1.8%)	23,131 (6.1%)	29,787 (7.8%)	5,247 (1.6%)	18,657 (5.8%)	23,904 (7.5%)	7,820 (1.7%)	28,859 (6.2%)	36,679 (7.9%)	24,289 (1.8%)	83,090 (6.0%)	107,379 (7.8%)
plus evidence of PAC within +/- 14 days of warfarin initiation (ambulatory care only)	4,566 (2.1%)	7,853 (3.5%)	12,419 (5.6%)	6,656 (1.8%)	10,623 (2.8%)	17,279 (4.5%)	5,247 (1.6%)	12,466 (3.9%)	17,713 (5.5%)	7,820 (1.7%)	12,681 (2.7%)	20,501 (4.4%)	24,289 (1.8%)	43,623 (3.1%)	67,912 (4.9%)
plus no claims for bleeding during 6-month period prior to index therapy	3,719 (1.7%)	5,949 (2.7%)	9,668 (4.4%)	5,748 (1.5%)	9,069 (2.4%)	14,817 (3.9%)	4,419 (1.4%)	9,956 (3.1%)	14,375 (4.5%)	6,675 (1.4%)	10,106 (2.2%)	16,781 (3.6%)	20,561 (1.5%)	35,080 (2.5%)	55,641 (4.0%)
Study Population															
All Patients	3,719 (1.7%)	5,949 (2.7%)	9,668 (4.4%)	5,748 (1.5%)	9,069 (2.4%)	14,817 (3.9%)	4,419 (1.4%)	9,956 (3.1%)	14,375 (4.5%)	6,675 (1.4%)	10,106 (2.2%)	16,781 (3.6%)	20,561 (1.5%)	35,080 (2.5%)	55,641 (4.0%)
Matched Patients	3,318 (1.5%)	3,318 (1.5%)	6,636 (3.0%)	4,356 (1.1%)	4,356 (1.1%)	8,712 (2.3%)	4,243 (1.3%)	4,243 (1.3%)	8,486 (2.7%)	5,961 (1.3%)	5,961 (1.3%)	11,922 (2.6%)	17,878 (1.3%)	17,878 (1.3%)	35,756 (2.6%)
DVT: Deep vein thrombosis; NCF: Inferior vena cava filter; OAC: Oral anticoagulants; PAC: Parenteral anticoagulants; PE: Pulmonary embolism	m; VTE: Venous throm	boembolism													
*Other than non-melanoma skin cancer															
**Prophylactic use of OAC/PAC will be determined based on duration and timing of use (See Appendix B)															
Including date of index encounter and date of index therapy initiation															

		Humana			MarketScan			Optum			PharMetrics			Total Population	
	Aposban (n=3,318)	Wartarin (n=3,318)	Std. Diff.	Apixaban (n=4,356)	(n=4,356)	Std. Diff.	Apixaban (n=4,243)	Wartarin (n=4,243)	Std. Diff.	Apixeban (n=5,961)	(n=5,961)	Std. Diff.	Aptxaban (n=17,878)	Wartarin (n=17,878)	Std. Diff.
Qualifying VTE Encounter, n (%)															
Setting:	046 501 500 6	100 007 000 0	00000		1 607 160 641	00000	1000 1000 000	1.954 755 756 7	00000	A KEE LAA CALL	100 100 100	0000	100 000 100 000 00	0.000 / 0.000	00000
Ambulatory-care	1,221 (36.8%)	1,221 (36.8%)	0.0000	1,759 (40.4%)	1,759 (40,4%)	0.0000	1.909 (45.0%)	1,909 (45.0%)	0,0000	3,306 (55.5%)	3,306 (55.5%)	0.0000	8,195 (45.8%)	8,195 (45.8%)	0.0000
Diagnosit:	A new yest man	a new and the	A ALAN			100000	a many start many			A new week and	A MARK AND A MARK	a same	and the second second	A LOCAL DESIGNATION	
PE with DVT	268 (19.5%)	292 (21.2%)	0.0260	469 (24.0%)	485 (24.8%)	0.0118	367 (20.6%)	325 (18.2%)	0.0362	551 (24.9%)	533 (24.1%)	0.0105	1,655 (22.6%)	1,635 (22.3%)	0.0039
PE without DVT	1,108 (80.5%)	1,084 (78.8%)	0.0154	1,485 (76.0%)	1,469 (75.2%)	0.0078	1,415 (79.4%)	1,457 (81.8%)	0.0209	1,659 (75.1%)	1,677 (75.9%)	0.0067	5,667 (77.4%)	5,687 (77.7%)	0.0024
DVT only	1,942 (58.5%)	1,942 (58.5%)	0.0000	2,402 (55.1%)	2,402 (55.1%)	0.0000	2,461 (58.0%)	2,461 (58.0%)	0.0000	3,751 (62.9%)	3,751 (62.9%)	0.0000	10,556 (59.0%)	10,556 (59.0%)	0.0000
Presumed actionogy: Provoked	798 (24.1%)	798 (24.1%)	0'0000	1,010 (23.2%)	1.010 (23.2%)	0.0000	892 (21.0%)	892 (21.0%)	0.000	1,369 (23.0%)	1,369 (23.0%)	0.0000	4,069 (22.8%)	4,069 (22,8%)	0:0000
Ungrovoked	2,520 (75.9%)	2,520 (75.9%)	0.0000	3,346 (76.8%)	3,346 (76.8%)	0.0000	3,351 (79.0%)	3,351 (79.0%)	0.0000	4,592 (77.0%)	4,592 (77,0%)	0.0000	13,809 (77.2%)	13,809 (77.2%)	0.0000
Patient Ann honnel															
Mean (SD)	71.5 (13.5)	71.5 (13.5)	0.0000	57.8 (15.8)	57,8 (15.8)	0,0000	65.2 (15.5)	65.2 (15.5)	0.0000	51.4 (12.1)	51.4 (12.1)	0.0000	60.0 (16.0)	60.0 (16.0)	0.0000
Median	72	72	I	52	25	T	63	67	I	ES	53	ł	99	09	t
Age (years), n (%)	Table North Control	10000000000	10000	The second s	1.0000.00000000000000000000000000000000	- 1910 March	And a second second	Characterization of the last	10000		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	1.0000	10 10 10 10 10 10 10 10 10 10 10 10 10 1	11111111111111111111111111111111111111	1.0 0000
18-49 years	130 (5-5%)	186 (5-0%)	000000	1,221 (28.1%)	1,221 (28.1%)	00000	(%5:21) 252	132 (17,5%)	0.0000	2,289 (38.4%)	2,289 (38.4%)	00000	4,428 (24.8%) 6,274 /29 54/	4,428 (24.8%) 6 274 (28 544)	0.0000
65-74 vears	1.162 (35.0%)	1.162 (35.0%)	00000	510 (11.7%)	510(11.7%)	0.0000	1.059 (25.0%)	1.059 (25.0%)	00000	411 (6.9%)	411 (6.9%)	0 0000	3.142 (17.6%)	3.142 (17.6%)	0.0000
275 years	1,307 (39.4%)	1,307 (39.4%)	0.0000	719 (16.5%)	719 (16.5%)	0,0000	1,283 (30.2%)	1,283 (30.2%)	0.0000	121 (2.0%)	121 (2.0%)	0.0000	3,430 (19.2%)	3,430 (19.2%)	0.0000
Missing	ł	1	Ŧ	Ŧ	1	a T	Ĩ	1	I	I	1	I	1	7	ł
Sex, n (%)	A DESCRIPTION OF A DESC	1 1000 1000 1000 P	1.000	1.0000000000000000000000000000000000000	Contraction of the second	Contrast,	A the state of the second	A STREET STREET		Construction of the local	T TOTAL CONTRACTOR	1000000	A NOT THE TWO IS NOT	A second second second	
Male	1,417 (42.7%)	1,469 (44.3%)	0.0316	2,327 (53,4%)	2,301 (52.8%)	07100	2,056 (48,5%)	2,046 (48.2%)	0.0047	3,482 (58.4%)	3,463 (58.1%)	0.0065	9,282 (51.9%)	9,279 (51.9%)	0.0003
-remain Matchar	1455-761 10611	1827-001 64917	9750/0	(warat) (27)/2	1427'/#) ccn/7	1071010	1900 00 1	(NO 010 1477	75000	(WO'Y=) (J+7)	MA.TH 965"7	<0000	100 00 1	0.00.000	
US Geographic Region, n [%]							hanna a								
East	72 (2.2%)	82 (2.5%)	0.0200	724 (16.6%)	731 (16.8%)	0.0043	402 (9.5%)	471 (11.1%)	0.0535	1,080 (18.1%)	1,201 (20.1%)	0.0516	2,278 (12.7%)	2,485 (13.9%)	0.0341
Midwest	603 (18.2%)	744 (22.4%)	0.1058	1,077 (24.7%)	1,175 (27.0%)	0.0514	984 (23.2%)	1,166 (27.5%)	0.0987	1,439 (24.1%)	1,962 (32.9%)	0.1952	4,103 (23.0%)	5,047 (28.2%)	0.1212
South	2,378 (71.7%)	2,138 (64.4%)	0.1556	2,060 (47.3%)	1,650 (37.9%)	0.1912	1,985 (46.8%)	1,606 (37.9%)	0.1815	2,798 (46.9%)	1,822 (30.6%)	0.3409	9,221 (51.6%)	7,216 (40.4%)	0.2265
Other	laun rol core		00000	15 (0.3%)	24 (0.6%)	0.0310	in a way in co		0.0000	factor avenue	-	0:0000	12 (0.1%)	24 (0.15k)	0.0153
Missing	1	6	0.0000	5. 1		0.0000	16 (0.4%)	19 (0.4%)	0.0110	56 (0.9%)	36 (0.5%)	0.0383	72 (0.4%)	55 (0.3%)	0.0160
Comorbidity Profile						1		00, M(x,7)).							
Devo-Charlson Comorbidity Index, mean (SD)	2.0 (2.1)	2.1 (2.1)	0.0141	0.7 (1.2)	0.6 (1.2)	0.0245	13 (1.9)	1.3 (1.8)	0.0163	0.6 (1.2)	0.6 (1.2)	0.0166	(21011)	1.0 (1.7)	0.0001
Connor plotters, m.(?%) Accurrent immunoidaficiance tendrome (A)DS1	12 10 4%	\$ (D 740)	0.0268	1010 243	11 (0) 2451	0.0047	122 01 5501	10/10 4%	0 0103	17100 5411	26 (0.4%)	2000.0	77 10 4%1	64 (0.444)	12000
Alcohol abuse	148 (4.5%)	144 (4.3%)	0.0059	87 (2.0%)	86 [2:0%]	0.0016	151 (3.6%)	128 (3.0%)	0.0304	205 (3.4%)	205 (3.4%)	0.0000	591 (3.3%)	563 (3.1%)	0.0089
Anaernia	811 (24.4%)	795 (24.0%)	0.0113	364 (8.4%)	378 (8.7%)	0.0115	716 (16.9%)	701 (16.5%)	\$600.0	(%ETT) 129	686 (11.5%)	0.0079	2,562 (14.3%)	2,560 (14.3%)	0.0003
Bleeding	66 (2.0%)	47 (1.4%)	0.0443	46 (1.1%)	65 (1.5%)	0.0389	86 (2.0%)	79 (1.9%)	0.0119	79 (1.3%)	72 (1.2%)	0.0105	277 (1.5%)	263 (1.5%)	0.0064
Central venous catheter	152 (4.6%)	137 (4.1%)	0.0222	(155.2) 99	91 (2.1%)	0.0126	183 (4.3%)	187 (4,4%)	0.0046	255 (4.3%)	220 (3.7%)	0.0300	689 (3:9%)	(932 (3.6%)	0.0160
Cereorovascular disease (strowy i M) Chronic obstruction rudinonary disease (POBN)	420 (13.0%) 876 (75.4%)	4/0 (14,330) 888 (35 894)	077000	282 (5.5%)	(ML / M) C02	220010	531 (7.8%)	106271 675	20000	228 (5.5%)	232 (3.378)	0.0015	1,215 (0.6%)	[9/2/4] 767'T	10000
Coagulopathy	38 (1.1%)	49 (1.5%)	16200	38 (0.9%)	3D (0.7%)	0.0209	53 (1.2%)	56 (1.3%)	0.0063	93 (1.6%)	83 (1.4%)	0.0139	222 (1.2%)	218 (1.2%)	0.0020
Congestive heart failure	723 (21.8%)	733 (22.1%)	0.0073	238 (5,5%)	225 (5.2%)	0.0133	623 (14.7%)	567 (13.4%)	0.0380	350 (5.9%)	348 (5.8%)	0.0014	1,934 (10.8%)	1,873 (10.5%)	0.0111
Ischemic heart/coronary artery disease	1,127 (34.0%)	1,114 (33.6%)	0.0083	S35 (12.3%)	463 (10.6%)	0.0519	928 (21.9%)	878 (20.7%)	0.0288	874 (14.7%)	792 (13.3%)	0.0397	3,464 (19,4%)	3,247 (18.2%)	0.0311
Dementia	(%1.7) 752	184 (5.5%)	0.0656	54 (1.2%)	44 (1.0%)	0.0218	192 (4.5%)	180 (4.2%)	0.0138	25 (0.4%)	21 (D.4%)	0.0108	508 (2.8%)	429 (2.4%)	0.0277
Durangetes. Durangeta or stomach discomfort	726 (21 9%)	713 [21 596]	56000	(%0'11'509	605 (13 9%)	0.0027	672 (15.8%)	670 (15, 8%)	E100.0	1000110001	(M. 115, 2%)	0.0037	192 (16:28)	2.892 (16.2%)	21000
Falls	(160.5) 99	1113 (3.4%)	0.0240	118 (2.7%)	93 (2.1%)	6760.0	226 (5.3%)	206 (4.9%)	0.0214	221 (3.7%)	232 (3.9%)	0.0097	664 (3.7%)	644 (3.6%)	0.0060
Fractures involving the lower extremities	170 (5.1%)	211 (6.4%)	0.0531	436 (10.0%)	433 (9.9%)	0.0023	407 (9.6%)	414 (9.8%)	0.0056	682 (11.4%)	754 (12.6%)	0.0371	1,695 (9.5%)	1,812 (10.1%)	0.0220
Hemplegia or paraplegia	76 (2.3%)	67 (2.0%)	0.0187	23 (0.55%)	24 (0.6%)	1500.0	44 (1.0%)	47 (1.1%)	0.0069	44 (0.7%)	53 (0.9%)	0.0168	187 (1.0%)	(%1-1) 161	0.0022
Hubertension	2 680 (80 8%)	2 648 (79.8%)	0.0242	1.906 (43.8%)	1.850 (42.5%)	0.0260	2 583 (60.9%)	2,499 (58,9%)	00000	2,630 (44,1%)	2,470 (41,4%)	0.0543	(M8-C4) 111 0 0 799 (54.8%)	9.467 (53.0%)	0.0373
Inflammatory bowel syndrome	38 (1.1%)	35 (1.1%)	0.0087	32 (0.7%)	37 (0.8%)	0.0129	29 (0.7%)	24 (0.6%)	0.0150	80 (1.3%)	94 (1.6%)	0.0196	179 (1.0%)	(%1-1) 061	0.0061
Liver disease	235 (7.1%)	246 (7.4%)	0.0128	154 (3.5%)	153 (3.5%)	0.0012	248 (5.8%)	267 (6.3%)	0.0188	361 (6.1%)	365 (6.1%)	0.0028	6%9(5)865	1,031 (5.8%)	0.0080
Malignancy (excluding non-melanoma skin cancer)	50 (1.5%)	46 (1.4%)	101010	21 (0.5%)	12 (0.3%)	0.0336	86 (2.0%)	80 (1.9%)	0.0102	59 (1.0%)	62 (1.0%)	0.0050	216 (1.2%)	200 (1.1%)	0.0083
UDESITY Donnie utrae diseases	(965-57) 558 (199-97) 53	(9/9/CZ) 282	OTTOD	(MU.ET) COC	1010421	0,010	(%C/07) 5/2 38 (0.0%)	1942 (JUL 742) 1968	0.0075	1,248 (20.5%) A1 (n 7%)	1,20/ (21.3%) 50/D 8%3	20000	5,251 (1992) (1976) 1501 (1942)	(ME/EL) (PC)	0.00036
Peripheral vascular disease	736 (22, 2%)	766 (23.1%)	0.0216	321 (7.4%)	294 (6.7%)	0.0242	563 (13.3%)	584 (13.8%)	0.0145	417 (7.0%)	408 (6.8%)	0:0059	2,037 (11.4%)	2,052 (11.5%)	0.0026
Pneumonia	479 (14,4%)	461 (13.9%)	0.0156	259 (5.9%)	247 (5.7%)	8110.0	489.01) 158	434 (10.2%)	0.0131	470 (7.9%)	460 (7.7%)	0.0063	1,659 (9.3%)	1,602 (9.0%)	0.0111
Renal disease	944 (28.5%)	968 (29.2%)	00100	342 (7.9%)	355 (8.1%)	0110 0	684 (16.1%)	672 (15.8%)	0.0077	418 (7,0%)	406 (6.8%)	0.0079	2,388 (13.4%)	2,401 (13.4%)	0.0021
Sleep apprease	415 (12 5%)	411 (12 4%)	2500.0	405 (9.3%)	1741 0J 568	0.0079	470 (13 1%)	451 (10.6%)	0.0144	102 (11 200)	624 (10.5%)	0.0222	1 955 (10 9%)	1 881 (10 5%)	0.0134
Spinal cord injury	2 (0.1%)	1 (0.0%)	0.0142	7 (0.2%)	5 (0.1%)	0.0124	4 (0.1%)	1 (0.0%)	0.0291	7 (0.1%)	\$ (0.1%)	0.0106	20 (0.1%)	12 (0.1%)	0.0150
Thrombocytopenia	155 (4.7%)	159 (4.8%)	0.0057	57 (1.3%)	52 (1.2%)	0.0103	135 (3.2%)	127 (3.0%)	6010.0	152 (2.5%)	157 (2.6%)	0.0053	499 (2.8%)	495 (2.8%)	0.0014
Thrombophilla	119 (3.6%)	136 (4.1%)	0.0267	89 (2.0%)	85 (2.0%) 11 10 0401	0.0066	150 (3.5%)	152 (3.6%)	0.0025	352 (5.9%) 200 rt (001)	362 (6.1%)	0.0071	710 (4.0%)	735 (4.1%)	0.0071
Procedures. n [%]	1445.75.76	140.7166	71000	10/ (3.674)	(4.0.2) 571	0000	1107 11 0/1	faco.cl 1c1	00000	(900'C) 662	(%/0°C) CT7	P10074	(%T'+) TH/	14(0.0) 000	00+00
Abdominal surgery	413 (12.4%)	370 (11.2%)	2040.0	428 (9.8%)	402 (9.2%)	0.0203	414 (9.8%)	403 (9.5%)	0.0088	864 (14.5%)	858 (14,4%)	0.0029	2,119 (11.9%)	2,033 (11.4%)	0.0150
Haemodiatysis	42 (1.3%)	57 (1.7%)	0,0373	29 (0.7%)	35 (0.8%)	0.0161	22 (0.5%)	18 (0.4%)	0.0138	38 (0.6%)	40 (0.7%)	0.0042	131 (0.7%)	150 (0.8%)	0.0120
Knee replacement	65 (2.0%)	78 (2.4%)	0.0270	51 (1.2%)	23 (1.2%)	0.0042	74 (1.7%)	76 (1.8%)	0.0035	(%17.1%)	115 (1.9%)	0.0202	289 (1.6%)	322 (1.8%)	0.0142
Pelvic or orthopaedic surgery	1,582 (47,7%)	1,568 (47.3%)	0.0084	1,418 (32.6%)	1,445 (33.2%)	0.0132	1,393 (32.8%)	1,391 (32.8%)	0100.0	(%2'68) 668'2	2,289 (38.4%)	0.0172	6,732 (37.7%)	6,653 (37.4%)	0.0045
Recent surgery (major)	315 (9.5%)	312 (9,4%)	0.0031	368 (8.4%)	381 (8.7%)	0.0106	339 (8.0%)	328 (7.7%)	0.0096	772 (13.0%)	744 (12.5%)	0.0141	1,794 (10.0%)	1,765 (9.9%)	0.0054

		Humana			MarketScan			Optum			PharMetrics			Total Population	
	Apixaban (n=3,328)	Wartarin (n=3,318)	Std. Diff.	Apixaban In=4,356	Wartarin (n=4,356)	Std. Diff.	Apixaban [n=4,243]	Wartarin (n=4,243)	Std. Diff.	Apixaban (1=5,961)	Warfarin (n=5,961)	Std. Diff.	Apoceban (n=17,878)	Warfarin (n=17,878)	Std. Diff.
Outpatient Pharmacotherapy, n (%)															
ACE inhibitors/ARBs	1,405 (42.3%)	1,411 (42.5%)	0.0037	1,257 (28.9%)	1,221 (28.0%)	0.0183	1,296 (30.5%)	1,234 (29.1%)	0.0319	1,217 (20.4%)	1,166 (19.6%)	0.0214	5,175 (28.9%)	5,032 (28.1%)	0.0177
Antiarrhythmics	34 (1.0%)	28 (0.8%)	0.0188	59 (1.4%)	34 (0.8%)	0.0559	64 (1.5%)	31 (0.7%)	0.0740	27 (0.5%)	25 (0.4%)	0.0051	184 (1.0%)	118 (0.7%)	0.0403
Antiplatelets	(%0.6) (8.0%)	263 (7.9%)	0.0369	205 (4.7%)	182 (4.2%)	0.0256	232 (5.5%)	234 (5.5%)	0.0021	138 (2.3%)	115 (1.9%)	0.0268	872 (4.9%)	794 (4.4%)	0.0207
Aromatase inhibitors	16 (0.5%)	14 (0.4%)	060000	14 (0,3%)	14 (0.3%)	0.0000	20 (0.5%)	15 (0.4%)	0.0184	30 (0.5%)	29 (0.5%)	0.0024	80 (0.4%)	72 (0,4%)	0.0069
Beta blockers	1,153 (34,7%)	1,214 (36.6%)	0.0384	1,055 (24.2%)	995 (22.8%)	0.0325	1,200 (28.3%)	1,155 (27.2%)	0.0237	900 (15.1%)	865 (14.5%)	0.0165	4,308 (24,1%)	4,229 (23.7%)	0.0104
Calcium channel tylockers	754 (22.7%)	776 (23.4%)	0,0157	674 (15.5%)	627 (14.4%)	0.0303	762 (18.0%)	695 (16.4%)	0.0419	514 (8.6%)	(%6'2) 02*	0.0268	2,704 (15.1%)	2,568 (14,4%)	0.0215
Contraceptives (oral)	11 (0.3%)	16 (0.5%)	0.0237	201 (4.6%)	216 (5.0%)	0.0161	100 (2,4%)	85 (2.0%)	0.0242	315 (5.3%)	325 (5.5%)	0.0074	627 (3.5%)	642 (3.6%)	0.0045
Erythropoiesis stimulating agents	3 (0.1%)	0.(0.0%)	0.0425	1 (0:0%)	2 (0.0%)	0.0124	S (0.1%)	2 (0.0%)	0.0246	0 (0:0%)	1 (0.0%)	0.0183	9 (0.1%)	\$ {0.0%}	0.0113
Destrogen hormone agents	S7 (1.7%)	52 (1.6%)	6110.0	128 (2.9%)	123 (2.8%)	0.0069	83 (2.0%)	74 (L 7%)	0.0157	185 (3.1%)	139 (2.3%)	0.0475	453 (2.5%)	388 (2.2%)	0.0240
Gastroprotective agents	884 (26.6%)	910 (27.4%)	0.0176	828 (19.0%)	834 (19.1%)	0.0035	867 (20.4%)	861 (20.3%)	0.0035	862 (14.5%)	851 (14.3%)	0.0053	3,441 (19.2%)	3,456 (19.3%)	0.0021
Non-pestrogen hormone agents	1,421 (42.8%)	1,371 (41.3%)	0.0305	1,559 (35.8%)	1,495 (34.3%)	0.0308	1,623 (38.3%)	1,587 (37.4%)	0.0175	1,744 (29.3%)	1,685 (28.3%)	0.0219	6,347 (35.5%)	6,138 (34.3%)	0.0245
NSAID5	628 (18.9%)	580 (17.5%)	0.0375	812 (18.6%)	829 (19.0%)	0.0100	652 (15.4%)	642 (15.1%)	0.0066	1,021 (17.1%)	1,024 (17.2%)	0.0013	3,113 (17.4%)	3,075 (17.2%)	0.0056
SERMS	1	1	1	0 (0:036)	1 (0.0%)	0.0214	1 (0.0%)	3 (0.1%)	0.0217	1	ų,	I	1 (0.0%)	4 (0.0%)	0.0142
Statins	1,450 (43.7%)	1,485 (44.8%)	0.0212	1,252 (28.7%)	1,177 (27.0%)	0.0384	1,437 (33.9%)	1,398 (32.9%)	0.0195	1,142 (19.2%)	1,023 (17.2%)	0.0518	5,281 (29.5%)	5,083 (28,4%)	0.0244

Table 2. C

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Apixaban versus Warfarin in VTE Weycker et al.

Application Marilian Application Application Application Application		Hun	nana	Marki	etScan	Opt	mm	PharN	Aetrics	Total Po	pulation
Interfact <		Apixaban	Warfarin	Apixaban	Warfarin	Apixaban	Warfarin	Apixaban	Warfarin	Apixaban	Warfarin
Mumber of preciption, mean (SD) 35 (3.1) 4.7 (4.1) 5.3 (4.2) 3.6 (2.7) 4.1 (2.1) 4.8 (1.2) Number of preciption, mean (SD) 199.2 (5.0) 13.4 (5.6) 11.2 (6.0) 11.2 (6.0) 11.2 (6.0) 11.3 (6.3) 11.3 (5.7) For ed intersp, n(%) 25 mg 300 (5.3) 406 (5.1) 25 (6.9) 2 (6.9) 2 (6.9) 2 (6.9)	ndex Therapy	lotc'c-iii	lote'e-ii	(acc'+-1))	lacc'+-11	(047'+-11)	10+2'+-11)	1106'6-11	1106'6-11	1010/17-11	(0/0'/T-II)
Number of therapy day, mean (a) 103 (50) 134 (56.4) 172 (60) 132 (60) 151 (95.3) 131 (57.5) Number of therapy day, mean (a) 103 (50.7) 134 (56.4) 172 (60.9) 133 (50) 133 (50) 134 (57.5) 131 (57.5) 132 (57.5) 133 (55.5) </td <td>Mumber of prescriptions mean (SD)</td> <td>3 5 (3 3)</td> <td>11 11 1 1</td> <td>10 10 2</td> <td>C 0 14 71</td> <td>10 01 2 0</td> <td>E 0 14 71</td> <td>11 61 1 1</td> <td>11 0/0 1</td> <td>10 CI C V</td> <td>16 1/ 1 3</td>	Mumber of prescriptions mean (SD)	3 5 (3 3)	11 11 1 1	10 10 2	C 0 14 71	10 01 2 0	E 0 14 71	11 61 1 1	11 0/0 1	10 CI C V	16 1/ 1 3
Numerical contrension 1032 (50.0) 134 (56.8) 113 (60.9) 112.3 (60.9) 112.3 (60.9) 123 (50.3) 131 (57.8) Des of Inder Arreny, n (6) Application 25 mg 3.00 (90.7)		10-21 0-00	(T-+) (++	(7**) C'C	11.410.0	17:71 0.0	12-12/010	(1-2)	(T.C.) 0.4	(6.2) 2.4	(7.4) 1.0
Dose of indextery, n (k) Exercise interaction State Rescription State Rescription<	Number of therapy days, mean (5D)	109.2 (59.0)	134.9 (56.8)	119.6 (62.4)	127.2 (60.9)	112.9 (68.0)	151.9 (99.3)	120.0 (55.2)	131.3 (57.8)	116.2 (61.0)	135.8 (71.0)
Fits prescription Second & Jack (9.1)	Dose of index therapy, n (%)										
Apidation Apidation Apidation Solid (91) The state system (91,1) The state (91,1) The	First prescription										
2.5 mg 300 (6.3)	Apixaban										
5 ng Aprilation 3.010 (90.7) - 4.056 (93.1) - 5,669 (95.1) - 5,669 (95.1) - Aprilation Aprilation Second & subsequent prescriptions 731 (2.3.0) - 233 (5.6) - 733 (5.6) 1 733 (5.6) 1 733 (5.6) 1 <t< td=""><td>2.5 mg</td><td>308 (9.3)</td><td>I</td><td>300 (6.9)</td><td>I</td><td>379 (8.9)</td><td>ł</td><td>292 (4.9)</td><td>I</td><td>1,279 (7.2)</td><td>ţ</td></t<>	2.5 mg	308 (9.3)	I	300 (6.9)	I	379 (8.9)	ł	292 (4.9)	I	1,279 (7.2)	ţ
Scoral & subsequent prescriptions 731 (2.2.0)	5 mg	3,010 (90.7)	I	4,056 (93.1)	1	3,864 (91.1)	1	5,669 (95.1)	1	16,599 (92.8)	1
Apricialin None T31(220) m 860(19.7) m 923(13.8) m T33(15.6) m 5 mg 2.5 mg 2.338(75.1) 2.338(75.4) 3.334(75.4) 3.334(55.6) 3.332(55.6) 3.333(55.6) 3.	Second & subsequent prescriptions										
$\label{eq:relation} \begin{tabular}{c c c c c c c c c c c c c c c c c c c $	Apixaban										
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	None	731 (22.0)	1	860 (19.7)	1	923 (21.8)	1	775 (13.0)	1	3,289 (18.4)	đ
Smg 2,335 (71.1) - 3,284 (75.4) - 3,005 (71.8) - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - 4,980 (83.5) - - - 4,980 (83.5) - - - 2,980 (83.5) - - - 2,980 (83.5) - - - 2,980 (83.5) - - - 2,980 (83.5) - - 2,980 (83.5) - - 2,980 (83.5) - - 2,980 (83.5) - - 2,980 (83.5) - - 2,980 (83.5) - - 2,980 (83.5) - - 2,980 (83.5) - - 2,980 (83.5) - -	2.5 mg	283 (8.5)	I	287 (6.6)	I	374 (8.8)	I	332 (5.6)	B	1,276 (7.1)	Ę
Switch from index therapy to another OAC, n (%) Switch from index therapy to another OAC, n (%) 0 (0.0) 10 (0.0) 10 (0.0) 25 (4.3) Apisaban Dabilistration 0 (0.0) 10 (0.0) 10 (0.0) 0 (0.0) </td <td>5 mg</td> <td>2,359 (71.1)</td> <td>ł</td> <td>3,284 (75.4)</td> <td>I</td> <td>3,045 (71.8)</td> <td>ł</td> <td>4,980 (83.5)</td> <td>I</td> <td>13,668 (76.5)</td> <td>ł</td>	5 mg	2,359 (71.1)	ł	3,284 (75.4)	I	3,045 (71.8)	ł	4,980 (83.5)	I	13,668 (76.5)	ł
Apiraban O(0.0) 126(3.8) 0(0.0) 156(3.8) 0(0.0) 205(3.8) 0(0.0) 255(4.3) Dabligaten 0(0.0) <t< td=""><td>Switch from index therapy to another OAC, n (%)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	Switch from index therapy to another OAC, n (%)										
Dabigatan Dologatan 0 (0.0) 2 (0.1) 1 (0.0) 0 (0.0)	Apixaban	0 (0:0)	126 (3.8)	0 (0.0)	165 (3.8)	0 (0.0)	160 (3.8)	0 (0.0)	255 (4.3)	0 (0.0)	706 (3.9)
Edoxaban Edoxaban 0 (0.0)	Dabigatran	0 (0:0)	2 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Edoxaban	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Warfarin Narfarin	Rivaroxaban	5 (0.2)	2 (0.1)	6 (0.1)	4 (0.1)	4 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	15 (0.1)	9 (0.1)
Use of PAC, n (%) Unfractionated heparin 1 (0.0) 2 (0.1) 1 (0.0) 3 (0.1) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 2 (0.0) 1 (0.0) 2 (0.0) 2 (0.0) 0 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 2 (0.0) 0 (0.0)	Warfarin	87 (2.6)	0 (0.0)	83 (1.9)	0 (0.0)	110 (2.6)	0 (0.0)	152 (2.5)	0 (0.0)	432 (2.4)	0 (0.0)
Between index encounter and initiation of index therapy Unfractionated heparin 1(0.0) 2(0.1) 1(0.0) 3(0.1) 0(0.0)<	Use of PAC, n (%)	and the second se									
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Between index encounter and initiation of index therapy										
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Unfractionated heparin	1 (0.0)	2 (0.1)	1 (0.0)	3 (0.1)	0(0:0)	3 (0.1)	0 (0:0)	0 (0.0)	2 (0.0)	8 (0.0)
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Low molecular weight heparin										
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Dalteparin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0:0)	1 (0.0)	0 (0:0)	2 (0.0)	0 (0.0)	3 (0.0)
Tinzaparin 0(0.0) 0(0	Enoxaparin	40 (1.2)	1,201 (36.2)	84 (1.9)	2,463 (56.5)	105 (2.5)	2,644 (62.3)	147 (2.5)	4,179 (70.1)	376 (2.1)	10,487 (58.7)
Fondaparinux 0(0.0) 8(0.2) 1(0.0) 25 (0.6) 14 (0.3) 2 (0.0) 37 (0.6) Subsequently Unfractionated heparin 8 (0.2) 10 (0.3) 0 (0.0) 6 (0.1) 2 (0.0) 9 (0.2) 0 (0.0) 0 (0.0) Unfractionated heparin 8 (0.2) 10 (0.3) 0 (0.0) 6 (0.1) 2 (0.0) 9 (0.2) 0 (0.0)	Tinzaparin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0) 0	0.0) 0
Subsequently Subsequently Unfractionated heparin 8 (0.2) 10 (0.3) 0 (0.0) 5 (0.1) 2 (0.0) 9 (0.2) 0 (0.0) 0 (0.0) Unfractionated heparin 1 (0.0) 1 (0.0) 1 (0.0) 0 (0.0) 0 (0.0) 3 (0.1) Low molecular weight heparin 1 (0.0) 1 (0.0) 1 (0.0) 0 (0.0) 3 (0.1) Datkeparin 77 (2.3) 1,360 (41.0) 1 (8.0) 2,60 (60.1) 1 (0.0) 0 (0.0) 4,353 (73.0) Fondaparinux 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) Dave of follow-uo. mean (SD) 129 4 (61.3) 124 5 (62.3) 1275 (61.4) 1275 (61.4) 1275 (61.4) 1275 (51.9) 174 5 (22.9) 173 (28.1)	Fondaparinux	0 (0.0)	8 (0.2)	1 (0.0)	25 (0.6)	2 (0.0)	14 (0.3)	2 (0.0)	37 (0.6)	5 (0.0)	84 (0.5)
Unfractionated heparin 8 (0.2) 10 (0.3) 0 (0.0) 6 (0.1) 2 (0.0) 9 (0.2) 0 (0.0) 0 (0.0) Low molecular weight heparin 1 (0.0) 1 (0.0) 1 (0.0) 0 (0.0) 0 (0.0) 3 (0.1) Dalteparin 1 (0.0) 1 (0.0) 1 (0.0) 0 (0.0) 0 (0.0) 3 (0.1) Tinzaparin 77 (2.3) 1,360 (41.0) 118 (2.7) 2,620 (60.1) 120 (2.8) 2,33 (3.9) 4,353 (73.0) Fondaparinux 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) Davs of follow-up. mean (SD) 129 4 (61.3) 145 (63.2) 127 4 (60.9) 127 5 (61.4) 143.6 (55.9) 174 5 (22.9) 173 (28.1)	Subsequently										-
Low molecular weight heparin 1 (0.0) 1 (0.0) 1 (0.0) 0 (0.0) 3 (0.1) Dalteparin 77 (2.3) 1,360 (41.0) 1 (0.0) 0 (0.0) 0 (0.0) 3 (0.1) Enoxaparin 77 (2.3) 1,360 (41.0) 118 (2.7) 2,620 (60.1) 120 (2.8) 2,729 (64.3) 233 (3.9) 4,353 (7.3) Tinzaparin 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) Poindaparinux 2 (0.1) 12 (6.13) 127 (6.1) 12 (0.5) 174 (52.2) 174 (2.2) 173 (28.1) Davs of follow-up. mean (SD) 129 4 (61.3) 145 (65.2) 1275 (61.4) 1275 (61.4) 1275 (51.4) 174 (52.2) 173 (28.1)	Unfractionated heparin	8 (0.2)	10 (0.3)	0 (0.0)	6 (0.1)	2 (0.0)	9 (0.2)	0 (0.0)	0 (0.0)	10 (0.1)	25 (0.1)
Dalteparin 1 (0.0) 1 (0.0) 1 (0.0) 0 (0.0) 3 (0.1) Enoxaparin 77 (2.3) 1,360 (41.0) 118 (2.7) 2,620 (60.1) 12 (0.2) 2,33 (3.9) 4,353 (73.0) Tinzaparin 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) Fondaparinux 2 (0.1) 12 (0.4) 0 (0.0) 37 (0.8) 5 (0.1) 22 (0.2) 51 (0.9) 0 (0.0) Davs of follow-up. mean (SD) 129 4 (51.3) 145.8 (55.0) 124.5 (63.2) 135.4 (60.9) 127.5 (61.4) 143.6 (52.9) 174.5 (22.9) 173.3 (28.1)	Low molecular weight heparin										
Enoxaparin 77 (2.3) 1,360 (41.0) 118 (2.7) 2,620 (60.1) 120 (2.8) 2,3729 (64.3) 4,353 (73.0) Tinzaparin 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) Fondaparinux 2 (0.1) 12 (0.4) 0 (0.0) 37 (0.8) 5 (0.1) 22 (0.2) 51 (0.2)	Dalteparin	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	3 (0.1)	2 (0.0)	6 (0.0)
Tinzaparin 0 (0.0)	Enoxaparin	77 (2.3)	1,360 (41.0)	118 (2.7)	2,620 (60.1)	120 (2.8)	2,729 (64.3)	233 (3.9)	4,353 (73.0)	548 (3.1)	11,062 (61.9)
Fondaparinux 2 (0.1) 12 (0.4) 0 (0.0) 37 (0.8) 5 (0.1) 22 (0.5) 10 (0.2) 51 (0.9) Davs of follow-up. mean (SD) 129.4 (61.3) 145.8 (55.0) 124.5 (63.2) 135.4 (60.9) 127.5 (61.4) 143.6 (55.9) 174.5 (22.9) 173.3 (28.1)	Tinzaparin	0 (0.0)	0 (0:0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0(0:0)	0 (0.0)	0 (0.0)	0.0) 0
Davs of follow-up. mean (SD) 127,5 (61.4) 143,8 (55.0) 124,5 (63.2) 135,4 (60.9) 127,5 (61.4) 143,6 (55.9) 174,5 (22.9) 173,3 (28.1)	Fondaparinux	2 (0.1)	12 (0.4)	0 (0.0)	37 (0.8)	5 (0.1)	22 (0.5)	10 (0.2)	51 (0.9)	17 (0.1)	122 (0.7)
	Days of follow-up, mean (SD)	129.4 (61.3)	145.8 (55.0)	124.5 (63.2)	135.4 (60.9)	127.5 (61.4)	143.6 (55.9)	174.5 (22.9)	173.3 (28.1)	142.8 (56.9)	151.9 (52.1)

OAC: Oral anticoagulant; PAC: Parenteral anticoagulant *Use during 6-month follow-up period

	No.	No.	%	Risk per			
	Patients	Events	Evented	100 PY	HR	95% CI	p-value
otal Population							
Major Bleeding Event							
All							
Apixaban	17,878	295	1.7%	4.2	0.75	0.64 - 0.87	< 0.001
Warfarin	17,878	412	2.3%	5.5		-	
Gastrointestinal							
Apixaban	17,878	111	0.6%	1.6	0.72	0.57 - 0.92	0.009
Warfarin	17,878	160	0.9%	2.2			
Intracranial							
Apixaban	17,878	24	0.1%	0.3	0.97	0.56 - 1.69	0.920
Warfarin	17,878	26	0.1%	0.3		1	144) 1441)
Other							
Apixaban	17,878	160	0.9%	2.3	0.74	0.60 - 0.90	0.003
Warfarin	17,878	226	1.3%	3.0			
CRNM Bleeding Event	21						
All							
Apixaban	17,878	1,257	7.0%	18.0	0.77	0.71 - 0.83	< 0.001
Warfarin	17,878	1,688	9.4%	22.7			
Gastrointestinal							
Apixaban	17,878	385	2.2%	5.5	0.88	0.76 - 1.00	0.053
Warfarin	17,878	460	2.6%	6.2			
Other							
Apixaban	17,878	874	4.9%	12.5	0.73	0.67 - 0.79	< 0.001
Warfarin	17,878	1,238	6.9%	16.7		722	
lumana							
Major Bleeding Event							
All							
Apixaban	3,318	99	3.0%	8.4	0.77	0.60 - 1.00	0.049
Warfarin	3,318	140	4.2%	10.6			
Gastrointestinal							
Apixaban	3,318	43	1.3%	3.7	0.74	0.50 - 1.09	0.123
Warfarin	3,318	64	1.9%	4.8		5 	
Intracranial							
Apixaban	3,318	6	0.2%	0.5	0.96	0.32 - 2.85	0.935
Warfarin	3,318	7	0.2%	0.5		8 	
Other							
Apixaban	3,318	50	1.5%	4.3	0.79	0.55 - 1.14	0.207
Warfarin	3,318	69	2.1%	5.2		2 <u>44</u>	
CRNM Bleeding Event							
All							
Apixaban	3,318	233	7.0%	19.8	0.79	0.67 - 0.94	0.007
Warfarin	3,318	316	9.5%	23.9		877	
Gastrointestinal	15						
Apixaban	3,318	77	2.3%	6.5	0.76	0.57 - 1.01	0.062
Warfarin	3,318	110	3.3%	8.3	1.12	244	1440) 1440)
Other	6 4.5 CO 50000						
Apixaban	3,318	156	4.7%	13.3	0.81	0.66 - 0.99	0.042
Warfarin	3,318	209	6.3%	15.8			

Online Supplement -- Table 4a. Risks and hazard ratios for bleeding events among patients receiving apixaban and warfarin as

Online Supplement -- Table 4a. Risks and hazard ratios for bleeding events among patients receiving apixaban and warfarin as outpatient therapy for VTE -- matched-samples analysis

	No	No	%	Risk nor			
	Patients	Events	70 Evented	100 PV	HR	95% CI	n-value
MarketScan	ratients	Events	Evented	10011	TIK	5570 CI	pvalue
Major Bleeding Event							
All							
Apixaban	4.356	45	1.0%	3.0	0.94	0.63 - 1.40	0.760
Warfarin	4,356	51	1.2%	3.2			
Gastrointestinal	1.100						
Apixaban	4,356	19	0.4%	1.3	1.20	0.62 - 2.30	0.590
Warfarin	4,356	17	0.4%	1.1		-	++**
Intracranial							
Apixaban	4,356	3	0.1%	0.2	0.65	0.15 - 2.70	0.549
Warfarin	4,356	5	0.1%	0.3			***.*
Other							
Apixaban	4,356	23	0.5%	1.5	0.84	0.49 - 1.45	0.534
Warfarin	4,356	29	0.7%	1.8		-	
CRNM Bleeding Event							
All							
Apixaban	4,356	310	7.1%	20.9	0.76	0.66 - 0.88	<0.001
Warfarin	4,356	424	9.7%	26.3			
Gastrointestinal							
Apixaban	4,356	96	2.2%	6.5	0.93	0.71 - 1.23	0.617
Warfarin	4,356	109	2.5%	6.8			77.
Other							
Apixaban	4,356	214	4.9%	14.4	0.71	0.59 - 0.84	< 0.001
Warfarin	4,356	317	7.3%	19.6		-	77 -1
Optum							
Major Bleeding Event							
All							
Apixaban	4,243	92	2.2%	6.2	0.80	0.61 - 1.05	0.102
Warfarin	4,243	124	2.9%	7.4			
Gastrointestinal				1.00 C 1.00	1100100-001		
Apixaban	4,243	35	0.8%	2.4	0.71	0.47 - 1.10	0.124
Wartarin	4,243	53	1.2%	3.2	1997.0	877 X	. 77
Intracranial		-	0.004		1.00		
Apixaban	4,243	/	0.2%	0.5	1.30	0.44 - 3.88	0.636
wartarin	4,243	6	0.1%	0.4	-		
Other		50	1 20/	2.4	0.02	0.57 4.40	0.000
Apixaban	4,243	50	1.2%	3.4	0.83	0.57 - 1.19	0.308
	4,243	65	1.5%	3.9			
Ali	4 242	264	6 29/	17.0	0.90	0.69 0.04	0.005
Warfarin	4,243	204	9.1%	21.5	0.80	0.08 - 0.94	0.005
Gastrointestinal	4,245	550	0.470	21.5	-		
Anixahan	4 243	91	2 1%	6.1	0.97	0.73 - 1.29	0.838
Warfarin	4 243	103	2.4%	6.2			
Other	7,243	105	2.7/0	0.2			
Apixaban	4,243	174	4.1%	11.7	0.73	0.61 - 0.89	0.002
Warfarin	4.243	256	6.0%	15.3			

outpatient therapy for VT	E matched-sai	mples analysis					
	No.	No.	%	Risk per			
	Patients	Events	Evented	100 PY	HR	95% CI	p-value
PharMetrics							
Major Bleeding Event							
All							
Apixaban	5,961	59	1.0%	2.1	0.60	0.44 - 0.83	0.002
Warfarin	5,961	97	1.6%	3.4			
Gastrointestinal							
Apixaban	5,961	14	0.2%	0.5	0.53	0.28 - 1.02	0.059
Warfarin	5,961	26	0.4%	0.9		(1 77 7)	
Intracranial							
Apixaban	5,961	8	0.1%	0.3	0.99	0.37 - 2.64	0.987
Warfarin	5,961	8	0.1%	0.3			
Other							
Apixaban	5,961	37	0.6%	1.3	0.58	0.39 - 0.87	0.009
Warfarin	5,961	63	1.1%	2.2		· ++ :	
CRNM Bleeding Event							
All							
Apixaban	5,961	450	7.5%	15.8	0.75	0.66 - 0.84	<0.001
Warfarin	5,961	590	9.9%	20.9		1 	
Gastrointestinal							
Apixaban	5,961	121	2.0%	4.2	0.87	0.68 - 1.11	0.267
Warfarin	5,961	138	2.3%	4.9			
Other							
Apixaban	5,961	330	5.5%	11.6	0.71	0.62 - 0.82	<0.001
Warfarin	5,961	456	7.6%	16.1	- 22	10.000	2201

Online Supplement -- Table 4a. Risks and hazard ratios for bleeding events among patients receiving apixaban and warfarin as outpatient therapy for VTE -- matched-samples analysis

CRNM: clinically relevant non-major; VTE: venous thromboembolism

	No.	No.	%	Risk per			
	Patients	Events	Evented	100 PY	HR	95% CI	p-value
Total Population							
Major Bleeding Event							
All							
Apixaban	20,561	320	1.6%	4.0	0.71	0.62 - 0.81	<0.001
Warfarin	35,080	953	2.7%	6.6			
Gastrointestinal							
Apixaban	20,561	118	0.6%	1.5	0.72	0.58 - 0.90	0.004
Warfarin	35,080	337	1.0%	2.3		(, .)	
Intracranial							
Apixaban	20,561	28	0.1%	0.3	0.71	0.46 - 1.10	0.125
Warfarin	35,080	85	0.2%	0.6			
Other							
Apixaban	20,561	174	0.8%	2.2	0.70	0.59 - 0.84	<0.001
Warfarin	35,080	532	1.5%	3.7			~~
CRNM Bleeding Event							
All							
Apixaban	20,561	1,452	7.1%	18.1	0.77	0.72 - 0.82	<0.001
Warfarin	35,080	3,354	9.6%	23.2			(*** `
Gastrointestinal							
Apixaban	20,561	440	2.1%	5.5	0.90	0.80 - 1.01	0.086
Warfarin	35,080	920	2.6%	6.4			<u>22</u> 2
Other							
Apixaban	20,561	1,014	4.9%	12.6	0.73	0.68 - 0.79	<0.001
Warfarin	35,080	2,452	7.0%	17.0	22	<u>See</u> 8	22
Humana							
Major Bleeding Event							
All							
Apixaban	3,719	106	2.9%	8.1	0.74	0.59 - 0.93	0.010
Warfarin	5,949	273	4.6%	11.6		-	
Gastrointestinal							
Apixaban	3,719	46	1.2%	3.5	0.76	0.54 - 1.08	0.124
Warfarin	5,949	111	1.9%	4.7		\$(<u>5-5</u>)()	
Intracranial							
Apixaban	3,719	7	0.2%	0.5	0.61	0.26 - 1.44	0.262
Warfarin	5,949	21	0.4%	0.9		81 00 33	
Other							
Apixaban	3,719	53	1.4%	4.0	0.70	0.51 - 0.96	0.029
Warfarin	5,949	141	2.4%	6.0		5 77 51	77
CRNM Bleeding Event							
All							
Apixaban	3,719	261	7.0%	19.9	0.80	0.69 - 0.92	0.002
Warfarin	5,949	562	9.4%	23.8			
Gastrointestinal							
Apixaban	3,719	87	2.3%	6.6	0.86	0.67 - 1.11	0.253
Warfarin	5,949	178	3.0%	7.5			
Other							
Apixaban	3,719	174	4.7%	13.2	0.79	0.66 - 0.95	0.010
Warfarin	5,949	389	6.5%	16.5			<u>22</u>

Online Supplement -- Table 4b. Risks and hazard ratios for bleeding events among patients receiving apixaban and warfarin as outpatient therapy for VTE -- unmatched-samples analysis with multivariable Cox proportional hazards models

outpatient therapy for VTE	unmatched-	samples analys	is with multivari	iable Cox propor	tional hazard	s models	
41 	No.	No.	%	Risk per			
	Patients	Events	Evented	100 PY	HR	95% CI	p-value
MarketScan							
Major Bleeding Event							
All							
Apixaban	5,748	55	1.0%	2.8	0.76	0.55 - 1.07	0.114
Warfarin	9,069	137	1.5%	4.1			
Gastrointestinal	ath						
Apixaban	5,748	22	0.4%	1.1	0.88	0.52 - 1.50	0.641
Warfarin	9.069	39	0.4%	1.2			
Intracranial	0						
Apixaban	5.748	5	0.1%	0.3	0.52	0.19 - 1.43	0.205
Warfarin	9.069	15	0.2%	0.4			
Other	5,005		0.270	0.1			
Anivahan	5 748	28	0.5%	14	0.72	0.46 - 1.14	0 161
Warfarin	9,069	83	0.9%	2.5	0.72	0.40 1.14	0.101
CRNM Bleeding Event	5,005	65	0.578	2.5			
All							
An	E 749	412	7 20/	20.9	0.77	0.60 0.87	<0.001
Warfarin	3,748	412	10.0%	20.8	0.77	0.09 - 0.87	<0.001
Castrointesting	9,069	911	10.0%	27.1			
Anivohan	E 749	120	2 10/	C 1	0.95	0.69 1.07	0 174
Apixaban	5,748	120	2.1%	5.1	0.85	0.68 - 1.07	0.174
wartarin	9,069	263	2.9%	7.8			
Other			F 444		0.70		0.004
Apixaban	5,748	292	5.1%	14.8	0.78	0.68 - 0.90	<0.001
Warfarin	9,069	653	7.2%	19.4	- 22		
Optum							
Major Bleeding Event							
All			-				
Apixaban	4,419	93	2.1%	6.0	0.74	0.59 - 0.94	0.013
Warfarin	9,956	350	3.5%	8.9			
Gastrointestinal							
Apixaban	4,419	35	0.8%	2.3	0.76	0.52 - 1.11	0.152
Warfarin	9,956	132	1.3%	3.4		5/ <u>5-2</u> 53	
Intracranial							
Apixaban	4,419	7	0.2%	0.5	0.60	0.27 - 1.37	0.229
Warfarin	9,956	32	0.3%	0.8			
Other							
Apixaban	4,419	51	1.2%	3.3	0.76	0.55 - 1.03	0.079
Warfarin	9,956	187	1.9%	4.7		5 74 3	
CRNM Bleeding Event							
All							
Apixaban	4,419	284	6.4%	18.4	0.81	0.70 - 0.92	0.002
Warfarin	9,956	839	8.4%	21.3			
Gastrointestinal							
Apixaban	4,419	98	2.2%	6.4	1.11	0.88 - 1.41	0.386
Warfarin	9,956	229	2.3%	5.8			
Other							
Apixaban	4,419	187	4.2%	12.1	0.71	0.60 - 0.84	<0.001
Warfarin	9,956	613	6.2%	15.6		2440	42

Online Supplement -- Table 4b. Risks and hazard ratios for bleeding events among patients receiving apixaban and warfarin as outpatient therapy for VTE -- unmatched-samples analysis with multivariable Cox proportional hazards models

	No.	No.	%	Risk per			
	Patients	Events	Evented	100 PY	HR	95% CI	p-value
PharMetrics							
Major Bleeding Event							
All							
Apixaban	6,675	66	1.0%	2.1	0.64	0.48 - 0.85	0.002
Warfarin	10,106	193	1.9%	4.0		5. 55 0	
Gastrointestinal							
Apixaban	6,675	15	0.2%	0.5	0.54	0.30 - 0.97	0.038
Warfarin	10,106	55	0.5%	1.1		(1 77 7)	
Intracranial							
Apixaban	6,675	9	0.1%	0.3	1.06	0.46 - 2.41	0.897
Warfarin	10,106	17	0.2%	0.4			
Other							
Apixaban	6,675	42	0.6%	1.3	0.63	0.44 - 0.91	0.013
Warfarin	10,106	121	1.2%	2.5		(##)	
CRNM Bleeding Event							
All							
Apixaban	6,675	495	7.4%	15.5	0.73	0.65 - 0.81	<0.001
Warfarin	10,106	1,042	10.3%	21.7			
Gastrointestinal							
Apixaban	6,675	135	2.0%	4.2	0.88	0.71 - 1.09	0.226
Warfarin	10,106	250	2.5%	5.2			
Other							
Apixaban	6,675	361	5.4%	11.3	0.69	0.61 - 0.79	<0.001
Warfarin	10,106	797	7.9%	16.6	1222	17 <u>112</u> 17	221

Online Supplement -- Table 4b. Risks and hazard ratios for bleeding events among patients receiving apixaban and warfarin as outpatient therapy for VTE -- unmatched-samples analysis with multivariable Cox proportional hazards models

CRNM: clinically relevant non-major; VTE: venous thromboembolism

outputent inclupy for the	No	No	%	Risk per			
	Patients	Events	Evented	100 PY	HR	95% CI	n-value
Total Population	ratients	Lvents	Lventeu	100 11	TIK	5578 CI	p-value
Major Bleeding Event							
All							
Apixaban	20.561	320	1.6%	4.0	0.71	0.63 - 0.80	<0.001
Warfarin	35.080	953	2.7%	6.6		-	
Gastrointestinal	/			17,455			
Apixaban	20,561	118	0.6%	1.5	0.75	0.61 - 0.91	0.004
Warfarin	35,080	337	1.0%	2.3	1994 - 19		
Intracranial	1999 1 999 - 1997 - 19						
Apixaban	20,561	28	0.1%	0.3	0.73	0.48 - 1.09	0.121
Warfarin	35,080	85	0.2%	0.6	19 44 (1		++-
Other	1.438034-55						
Apixaban	20,561	174	0.8%	2.2	0.68	0.58 - 0.81	<0.001
Warfarin	35,080	532	1.5%	3.7		-	
CRNM Bleeding Event							
All							
Apixaban	20,561	1,452	7.1%	18.1	0.76	0.71 - 0.81	< 0.001
Warfarin	35,080	3,354	9.6%	23.2			
Gastrointestinal							
Apixaban	20,561	440	2.1%	5.5	0.90	0.80 - 1.00	0.058
Warfarin	35,080	920	2.6%	6.4	- -		77.
Other							
Apixaban	20,561	1,014	4.9%	12.6	0.71	0.66 - 0.76	< 0.001
Warfarin	35,080	2,452	7.0%	17.0		-	70 -3
Humana							
Major Bleeding Event							
All							
Apixaban	3,719	106	2.9%	8.1	0.77	0.62 - 0.96	0.021
Warfarin	5,949	273	4.6%	11.6		1.55	
Gastrointestinal							
Apixaban	3,719	46	1.2%	3.5	0.84	0.60 - 1.16	0.292
Warfarin	5,949	111	1.9%	4.7	-		
Intracranial							
Apixaban	3,719	7	0.2%	0.5	0.76	0.33 - 1.71	0.500
Warfarin	5,949	21	0.4%	0.9			
Other							
Apixaban	3,719	53	1.4%	4.0	0.73	0.53 - 1.00	0.047
Warfarin	5,949	141	2.4%	6.0		1.21	
CRNM Bleeding Event							
All		100-035		1210-10	2012-51	10110-000	14 (14) (1
Apixaban	3,719	261	7.0%	19.9	0.80	0.69 - 0.92	0.003
Warfarin	5,949	562	9.4%	23.8		5 4 4 7	
Gastrointestinal							
Apixaban	3,719	87	2.3%	6.6	0.80	0.62 - 1.04	0.092
Warfarin	5,949	178	3.0%	7.5		· · · · ·	443
Other	1212020	12000	1.200			22,021,32,221	100.000.000
Apixaban	3,719	174	4.7%	13.2	0.79	0.66 - 0.95	0.011
Warfarin	5,949	389	6.5%	16.5			++-

Online Supplement -- Table 4c. Risks and hazard ratios for bleeding events among patients receiving apixaban and warfarin as

outpatient therapy for the	No. No.	%	Risk per				
	Patients	Events	Evented	100 PY	HR	95% CI	p-value
MarketScan	rationts	270/10	Erented	10011		3070 0	produc
Maior Bleeding Event							
All							
Apixaban	5.748	55	1.0%	2.8	0.78	0.58 - 1.06	0.111
Warfarin	9.069	137	1.5%	4.1			
Gastrointestinal	-,		2.2.7				
Apixaban	5.748	22	0.4%	1.1	0.97	0.59 - 1.60	0.896
Warfarin	9.069	39	0.4%	1.2			
Intracranial	- 4						
Apixaban	5.748	5	0.1%	0.3	0.61	0.23 - 1.62	0.321
Warfarin	9.069	15	0.2%	0.4			
Other	0,000	77					
Apixaban	5.748	28	0.5%	1.4	0.71	0.47 - 1.08	0.112
Warfarin	9,069	83	0.9%	2.5			
CRNM Bleeding Event	5,005	00	0.570	2.0			
All							
Anixaban	5 748	412	7.2%	20.8	0.77	0 69 - 0 87	<0.001
Warfarin	9,069	911	10.0%	27.1		0.05 0.07	
Gastrointestinal	3,003	511	10.070	27.1			
Anixahan	5 748	120	2 1%	61	0.84	0.68 - 1.04	0 1 1 4
Warfarin	9,069	263	2.1%	7.8	0.04	0.00 - 1.04	0.114
Other	5,005	205	2.570	7.0			
Anivahan	5 7/8	202	5 1%	14.8	0.75	0.65 - 0.86	<0.001
Warfarin	9,069	653	7.2%	19.0	0.75	0.05 - 0.80	-0.001
Ontum	5,005	000	7.270	13.4			
Major Bleeding Event							
All							
Anixahan	4 4 1 9	93	2 1%	6.0	0.73	0 58 - 0 91	0.005
Warfarin	9,956	350	3.5%	8.9	0.75	0.50 0.51	0.005
Gastrointestinal	5,550	550	5.570	0.5			
Aniyahan	4 419	35	0.8%	23	0.70	0.49 - 1.01	0.058
Warfarin	9,956	132	1.3%	3.4	0.70	0.45 - 1.01	0.050
Intracranial	5,550	152	1.570	3.4			
Anivahan	1 110	7	0.2%	0.5	0.59	0.26 - 1.32	0 108
Warfarin	9,956	32	0.2%	0.5	0.55	0.20 - 1.52	0.158
Other	3,350	52	0.576	0.8		1770	
Anivahan	1 110	51	1 7%	2.2	0.77	0 57 - 1 02	0.078
Warfarin	9,956	197	1.2%	17	0.77	0.57 - 1.05	0.078
CRNM Bloeding Event	5,550	107	1.570	4.7	- 117	1773	-85°
All							
Anivahan	1 110	284	6 1%	19.4	0.83	0.72 . 0.94	0.005
Marfarin	4,419	204	0.4%	21.2	0.85	0.72 - 0.94	0.005
Castrointectinal	9,950	039	0.470	21.5			
Anivahan	4 410	00	2 20/	6 4	1 14	0.00 1.42	0.279
Marfarin	4,419	30	2.2%	5.4	1.14	0.90 - 1.45	0.278
Other	9,920	229	2.3%	5.8			
Anivahan	4 410	107	1 20/	12.1	0.72	0.61 0.94	<0.001
Apixaban	4,419	18/	4.2%	12.1	0.72	0.61 - 0.84	<0.001
wartarin	9,956	613	6.2%	15.6			

Online Supplement -- Table 4c. Risks and hazard ratios for bleeding events among patients receiving apixaban and warfarin as outpatient therapy for VTE -- unmatched-samples analysis with IPTW-ATE

	No.	No.	%	Risk per			
	Patients	Events	Evented	100 PY	HR	95% CI	p-value
PharMetrics							
Major Bleeding Event							
All							
Apixaban	6,675	66	1.0%	2.1	0.65	0.50 - 0.84	0.001
Warfarin	10,106	193	1.9%	4.0			
Gastrointestinal							
Apixaban	6,675	15	0.2%	0.5	0.58	0.34 - 0.98	0.043
Warfarin	10,106	55	0.5%	1.1		3 0	
Intracranial							
Apixaban	6,675	9	0.1%	0.3	1.08	0.51 - 2.29	0.847
Warfarin	10,106	17	0.2%	0.4			
Other							
Apixaban	6,675	42	0.6%	1.3	0.62	0.44 - 0.86	0.005
Warfarin	10,106	121	1.2%	2.5			
CRNM Bleeding Event							
All							
Apixaban	6,675	495	7.4%	15.5	0.69	0.62 - 0.77	<0.001
Warfarin	10,106	1,042	10.3%	21.7			
Gastrointestinal							
Apixaban	6,675	135	2.0%	4.2	0.86	0.70 - 1.06	0.171
Warfarin	10,106	250	2.5%	5.2	- 22		227
Other							
Apixaban	6,675	361	5.4%	11.3	0.64	0.57 - 0.73	<0.001
Warfarin	10,106	797	7.9%	16.6		-	

Online Supplement -- Table 4c. Risks and hazard ratios for bleeding events among patients receiving apixaban and warfarin as outpatient therapy for VTE -- unmatched-samples analysis with IPTW-ATE

CRNM: clinically relevant non-major; IPTW-ATE: inverse probability of treatment weighting-average treatment effect; VTE: venous thromboembolism

Online Supplement -- Table 5a. Risks and hazard ratios for recurrent VTE among patients receiving apixaban and warfarin as outpatient therapy for VTE -- matched-samples analysis

	No.	No.	%	Risk per			
	Patients	Events	Evented	100 PY	HR	95% CI	p-value
Total Population							
Apixaban	17,878	403	2.3%	5.8	0.80	0.70 - 0.91	<0.001
Warfarin	17,878	521	2.9%	7.0			77 1
Humana							
Apixaban	3,318	86	2.6%	7.3	0.72	0.55 - 0.94	0.017
Warfarin	3,318	127	3.8%	9.6			
MarketScan							
Apixaban	4,356	74	1.7%	5.0	0.90	0.66 - 1.23	0.506
Warfarin	4,356	87	2.0%	5.4		2 <u>22</u>	220
Optum							
Apixaban	4,243	92	2.2%	6.2	0.81	0.62 - 1.06	0.129
Warfarin	4,243	122	2.9%	7.3			
PharMetrics							
Apixaban	5,961	151	2.5%	5.3	0.81	0.65 - 1.00	0.051
Warfarin	5,961	185	3.1%	6.5	na 17666 199 1	Constanti Unitaria T ata	973-93337) 111

VTE: venous thromboembolism

	No.	No.	%	Risk per			
	Patients	Events	ts Evented	100 PY	HR	95% CI	p-value
Total Population							
Apixaban	20,561	440	2.1%	5.5	0.72	0.65 - 0.81	< 0.001
Warfarin	35,080	1,218	3.5%	8.4			77
Humana							
Apixaban	3,719	92	2.5%	7.0	0.68	0.54 - 0.87	0.002
Warfarin	5,949	247	4.2%	10.5			
MarketScan							
Apixaban	5,748	92	1.6%	4.7	0.90	0.69 - 1.16	0.408
Warfarin	9,069	203	2.2%	6.0		2-10 	22
Optum							
Apixaban	4,419	95	2.1%	6.2	0.69	0.55 - 0.87	0.002
Warfarin	9,956	385	3.9%	9.8			
PharMetrics							
Apixaban	6,675	161	2.4%	5.0	0.70	0.58 - 0.85	< 0.001
Warfarin	10,106	383	3.8%	8.0		5	

Online Supplement -- Table 5b. Risks and hazard ratios for recurrent VTE among patients receiving apixaban and warfarin as outpatient therapy for VTE -- unmatched-samples analysis with multivariable Cox proportional hazards models

VTE: venous thromboembolism

Online Supplement -- Table 5c. Risks and hazard ratios for recurrent VTE among patients receiving apixaban and warfarin as outpatient therapy for VTE -- unmatched-samples analysis with IPTW-ATE

	No.	No.	%	Risk per			
	Patients	Events	Evented	100 PY	HR	95% CI	p-value
Total Population							
Apixaban	20,561	440	2.1%	5.5	0.73	0.66 - 0.81	<0.001
Warfarin	35,080	1,218	3.5%	8.4			775
Humana							
Apixaban	3,719	92	2.5%	7.0	0.72	0.57 - 0.91	0.005
Warfarin	5,949	247	4.2%	10.5			
MarketScan							
Apixaban	5,748	92	1.6%	4.7	0.88	0.69 - 1.12	0.298
Warfarin	9,069	203	2.2%	6.0	<u></u>	200	920
Optum							
Apixaban	4,419	95	2.1%	6.2	0.74	0.60 - 0.91	0.004
Warfarin	9,956	385	3.9%	9.8			<u></u>
PharMetrics							
Apixaban	6,675	161	2.4%	5.0	0.69	0.57 - 0.82	< 0.001
Warfarin	10,106	383	3.8%	8.0			

IPTW-ATE: inverse probability of treatment weighting-average treatment effect; VTE: venous thromboembolism