Comparative Risk Assessment of Severe Abnormal Uterine Bleeding associated with Non-Vitamin K Oral Anticoagulants

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Disclosures

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- The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the FDA

Background

- Higher drug-event reports for menorrhagia with rivaroxaban (n=76) than other oral anticoagulants in the FAERS database
  - Mean age: 40 years, 60% occurring within 1st month of treatment
  - Interventions: Dilation and Curettage or ablation (16), Hysterectomy (3, maybe 4?), Tubal ligation (1), Transfusions (30), Tranexamic acid (1), Hormonal therapy or IUD (10)
- Re-analysis of EINSTEIN trial
  - Women <60 years (acute or symptomatic DVT, PE or both) randomized to oral rivaroxaban or subcutaneous enoxaparin followed by VKA therapy
  - Any abnormal uterine bleeding (HR: 2.13 CI: 1.57-2.89) and uterine bleeding leading to transfusion (19 vs. 3);
    - HR could not be computed due to low events, number of events in rivaroxaban group much larger
    - Calculated RR: 6.6 (CI: 1.9-22.2)

Objectives

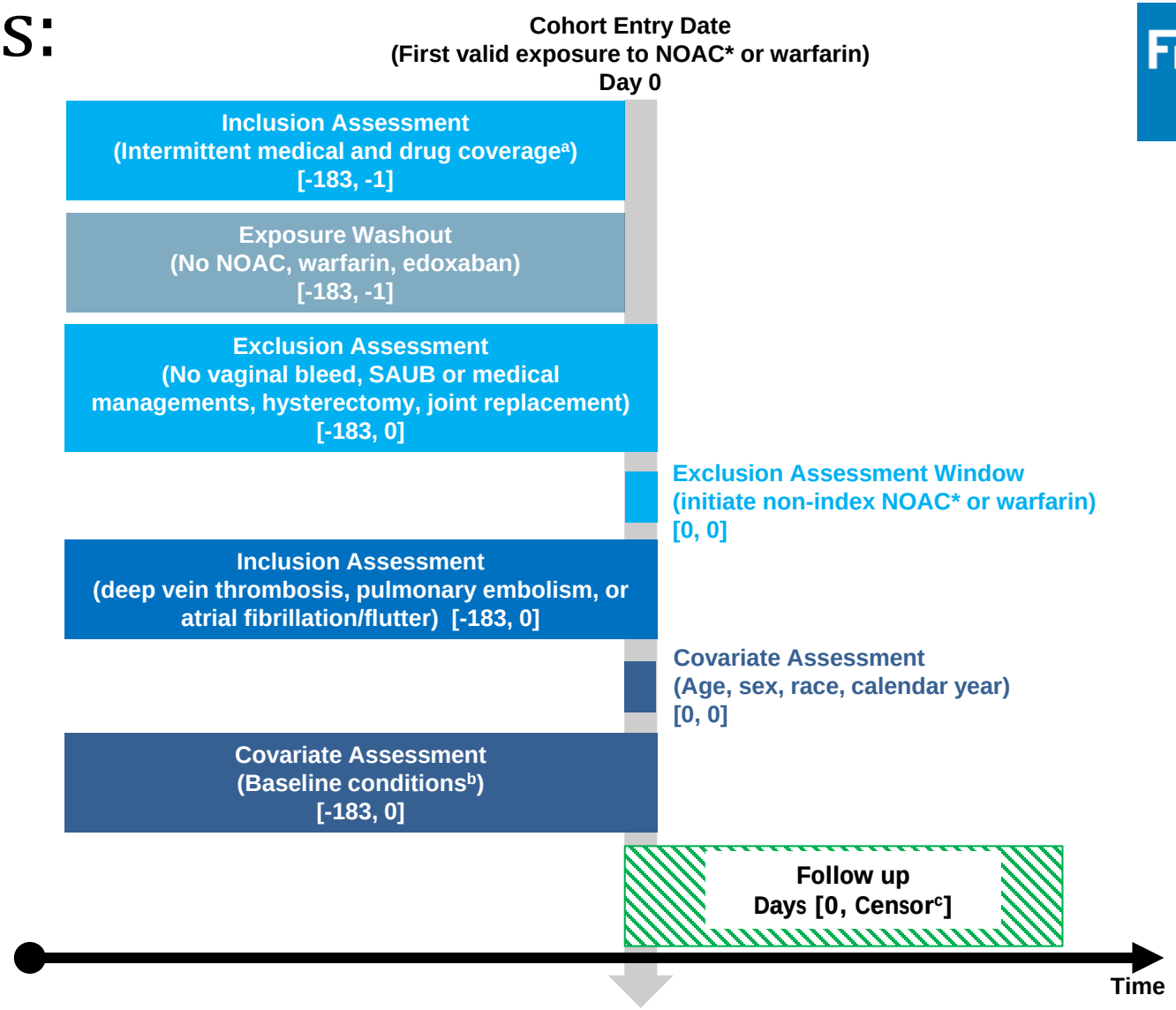
- Determine incidence rates of Severe Abnormal Uterine Bleeding (SAUB)
  - Defined as vaginal bleed diagnosis resulting in same-day transfusion (transfusion outcome) or gynecological surgery* within 60 days after vaginal bleed (surgical outcome)
- Compare rates of SAUB among NOACs and
- Compare rates of SAUB associated with rivaroxaban to the warfarin
  - Undertaken to examine adjustment performance
  - Compare with the randomized trial results

*Hysteroscopic polypectomy, Hysteroscopic laparoscopic or abdominal myomectomy; Other hysteroscopy procedures, uterine embolization, hysterectomy, endometrial ablation [thermal, cryo or resection], dilation and curettage with or without hysteroscopy
SAUB: Severe Abnormal Uterine Bleeding

Methods: Data Source, Study Overview

- Sentinel Distributed Database: 5 national Data Partners included
- Study period: 10/2010 – 9/2015
- Inclusion criteria: females aged 18+ years with venous thromboembolism (VTE) or atrial fibrillation or atrial flutter (AF)
- Exclusion criteria: joint replacement surgery or any of the study outcomes
- New-user cohort design to compare:
  - Rivaroxaban vs. Apixaban
  - Rivaroxaban vs. Dabigatran
  - Dabigatran vs. Apixaban
  - Rivaroxaban vs. Warfarin
- Study outcomes: SAUB by management
  - Vaginal bleed and same-day transfusion
  - Vaginal bleed followed by gynecological surgeries within 60 days

Methods: Study Design



a. Up to 45 day gaps in medical or pharmacy enrollment allowed
b. Baseline conditions included: comorbidity score (Combined Comorbidity Index), health service and drug utilization, cardiovascular and antidiabetic agents, medications that increase bleeding risk, medications that are inducers, inhibitors or substrates listed on label as having clinically significant interactions with warfarin or NOACs, severe anemia, gynecological disorders, Von Willebrand disease, cardiovascular disease, diabetes, hypertension, renal impairment, obesity, smoking, deep vein thrombosis/pulmonary embolism, and atrial fibrillation/flutter.
c. Earliest of: outcome of interest (severe uterine bleed), discontinuation of study drugs, recorded death, disenrollment, end of the study period

NOAC = Non-vitamin K Oral Anticoagulant, *NOAC: rivaroxaban, apixaban or dabigatran depending on the assessment

Methods: Statistical Analysis

- Propensity-Score Stratification to adjust for several covariates
- Propensity-Score Matching (results not shown but consistent with stratification)
- Cox regression model: adjusted HRs for:
  - Overall estimates
  - Subgroup analyses:
    - Age (18-50 vs. 51+ years);
    - Prior gynecological disorder;
    - NOAC dose (high: [dabigatran,150mg; rivaroxaban,15&20mg; apixaban,5mg] and low: [dabigatran,75mg; rivaroxaban,10mg; apixaban,2.5mg];
    - Indication (AF vs. VTE)

Results: Cohort Characteristics

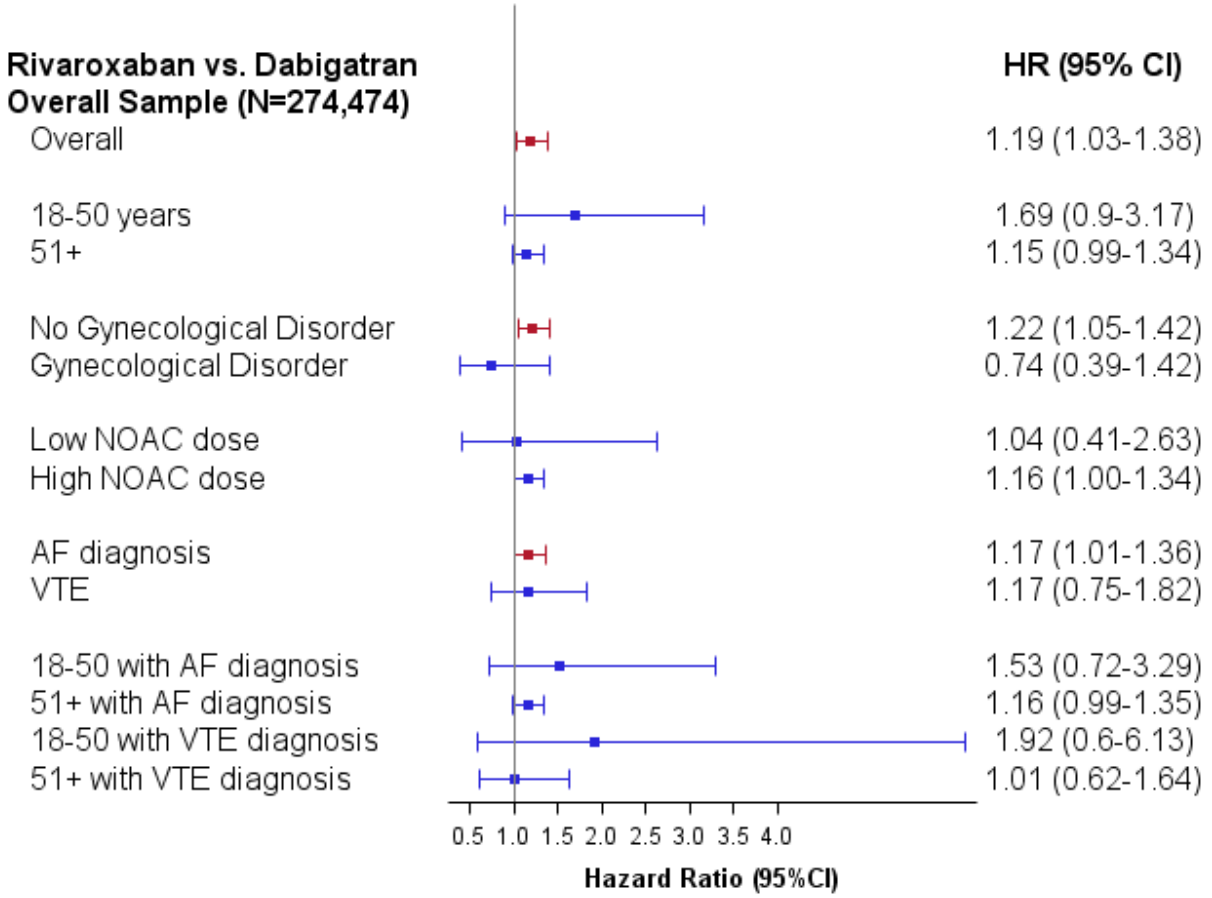
Selected Patient and Clinical Characteristics in the **PS-stratified** Cohorts

Characteristics %	RV 194,400	DB 80,074	SMD	RV 196,090	AP 97,784	SMD	DB 80,179	AP 97,670	SMD	RV 189,015	WF 722,772	SMD
Age: 18-50 years	3.5	3.3	0.01	3.4	2.9	0.03	1.4	1.2	0.02	4.3	5.0	-0.03
Age: 51 years or older	96.5	96.7	-0.01	96.6	97.1	-0.03	98.6	98.8	-0.02	95.7	95.0	0.03
Race (White)	78.0	78.9	-0.02	78.0	80.7	-0.07	80.2	82.2	-0.05	76.4	76.9	-0.01
Anemia	4.4	4.6	-0.01	4.5	4.7	-0.01	3.2	3.3	0.00	8.3	8.8	-0.02
Gynecological disorders	2.6	2.6	0.00	2.6	2.5	0.01	1.8	1.8	0.00	3.0	2.9	0.01
Use of CV agents	93.6	94.0	-0.02	93.5	94.2	-0.03	97.4	97.4	0.00	91.4	91.8	-0.02
CVD	46.9	48.7	-0.04	47.9	49.5	-0.03	52.3	52.3	0.00	51.6	52.1	-0.01
AF	76.5	78.2	-0.04	75.8	77.1	-0.03	94.9	93.7	0.05	61.2	62.0	-0.02
VTE	31.5	30.8	0.02	32.6	31.8	0.02	12.7	13.6	-0.03	50.7	50.4	0.01

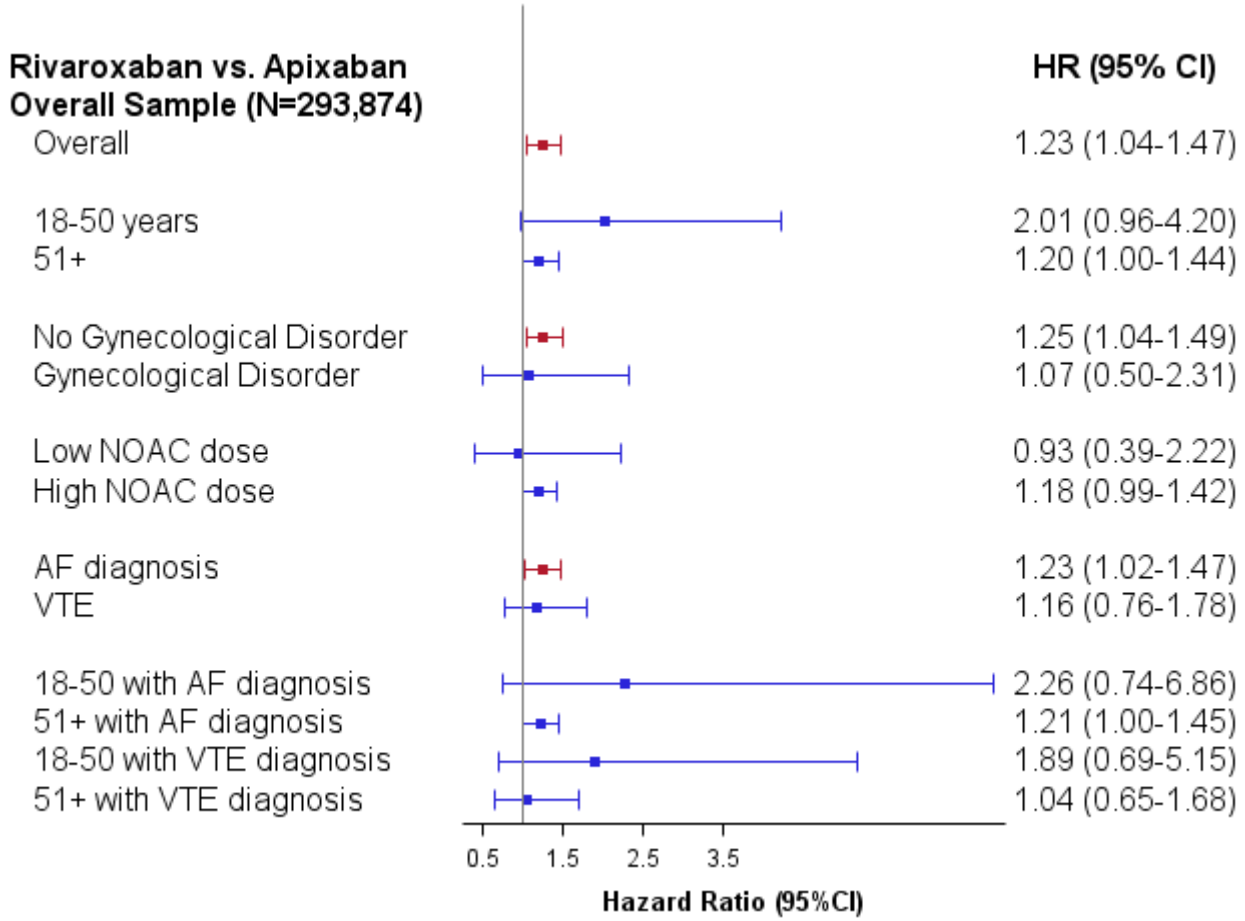
RV: Rivaroxaban; DB: Dabigatran; AP: Apixaban; WF: Warfarin; CV: Cardiovascular; CVD: Cardiovascular Disease; AF: Atrial Fibrillation; VTE: Venous Thromboembolism

RISK ESTIMATES FOR SURGICAL OUTCOME

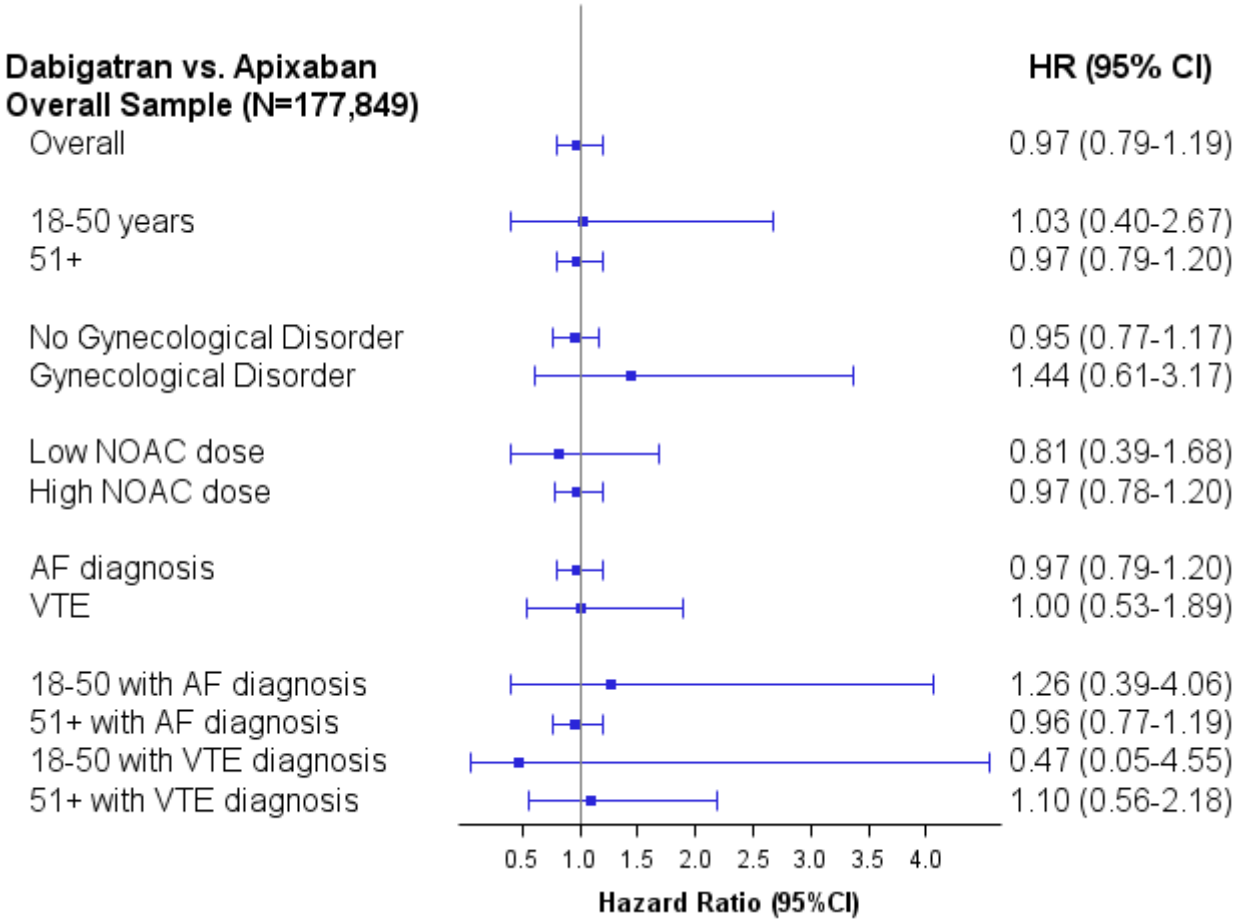
Increased risk of Surgical Outcome with Rivaroxaban compared to Dabigatran



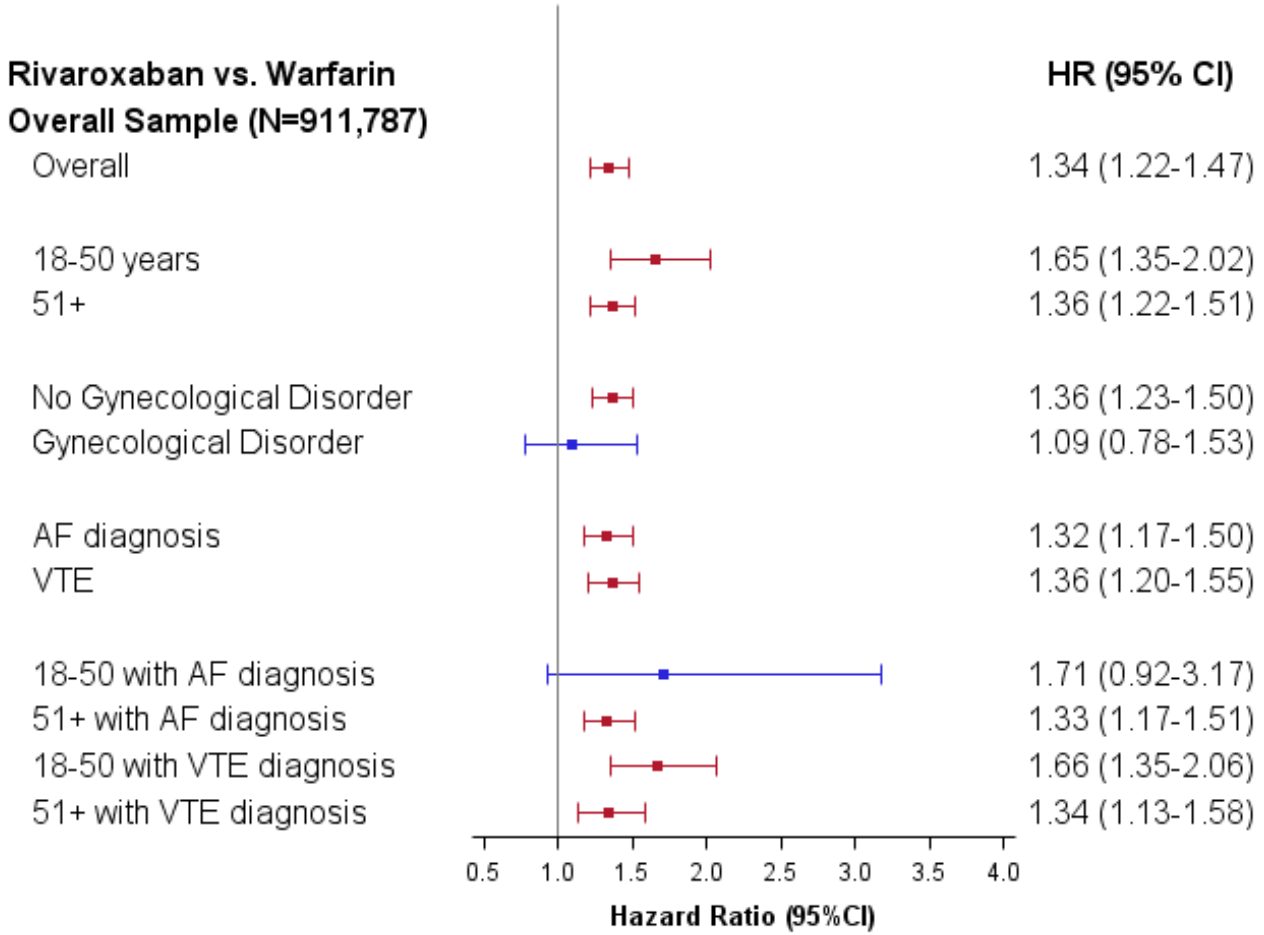
Increased risk of Surgical Outcome with Rivaroxaban compared to Apixaban



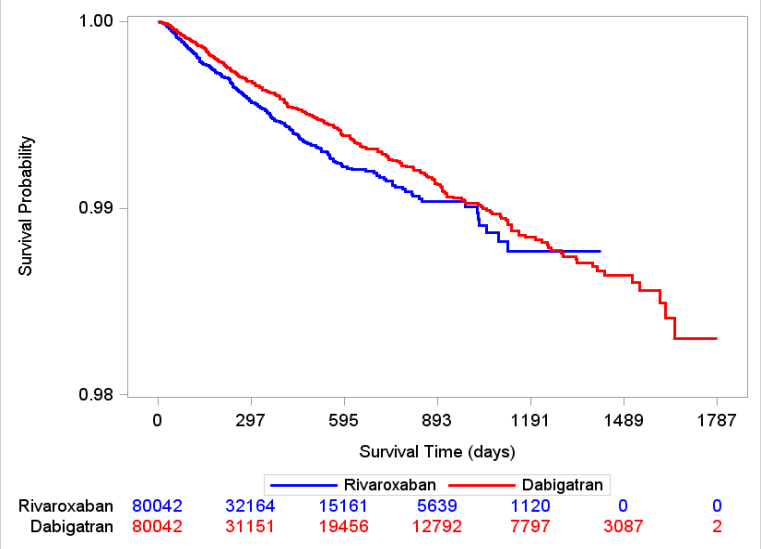
No difference in risk of Surgical Outcome between Dabigatran and Apixaban

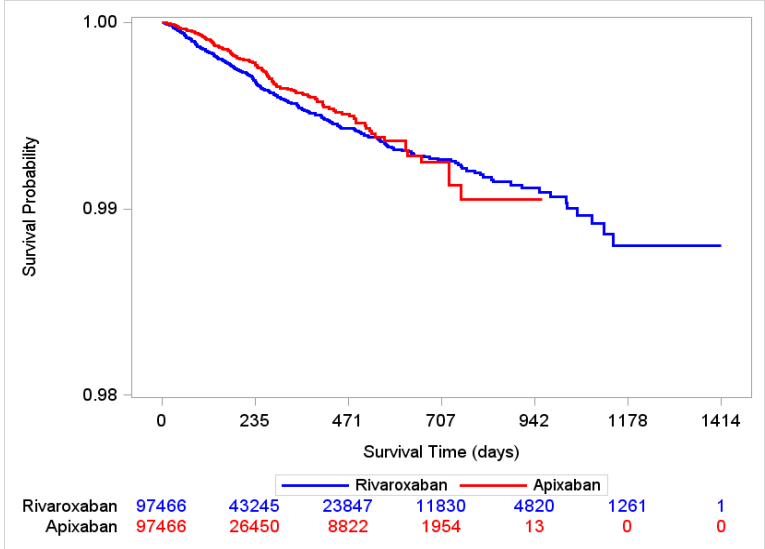


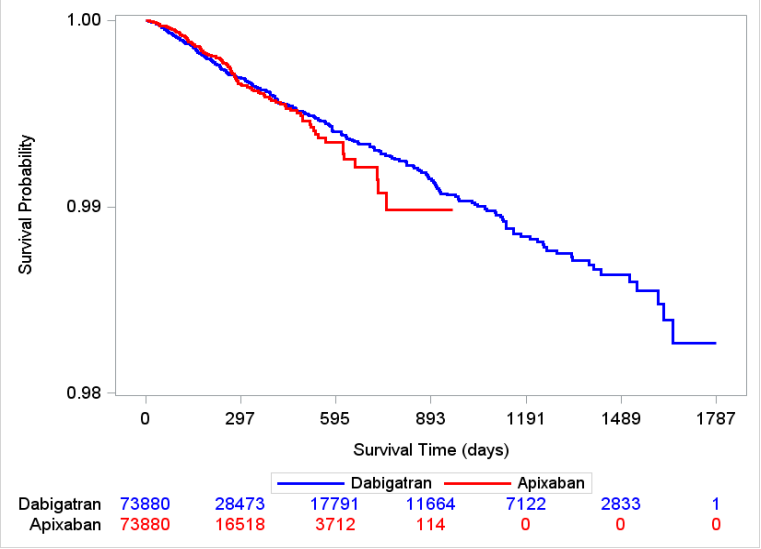
Increased risk of Surgical Outcome with Rivaroxaban compared to Warfarin

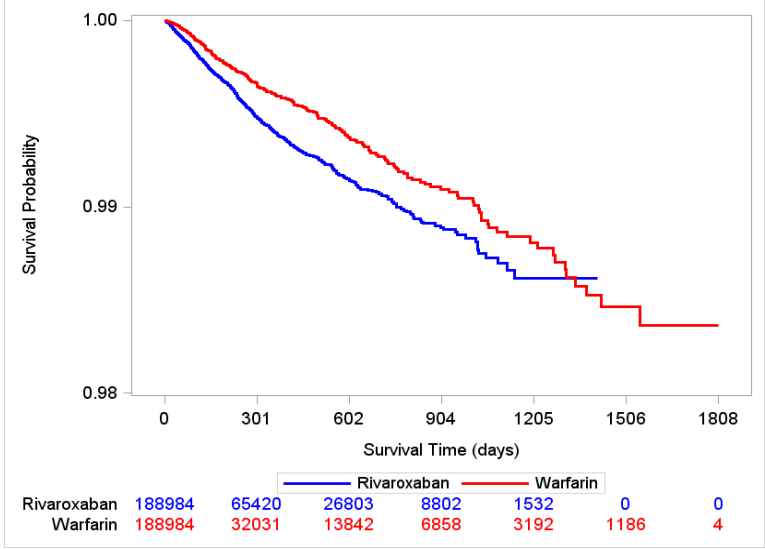


Adjusted Kaplan-Meier plots









Hysteroscopic Polypectomy and Hysterectomy account for more than half of the gynecological surgeries

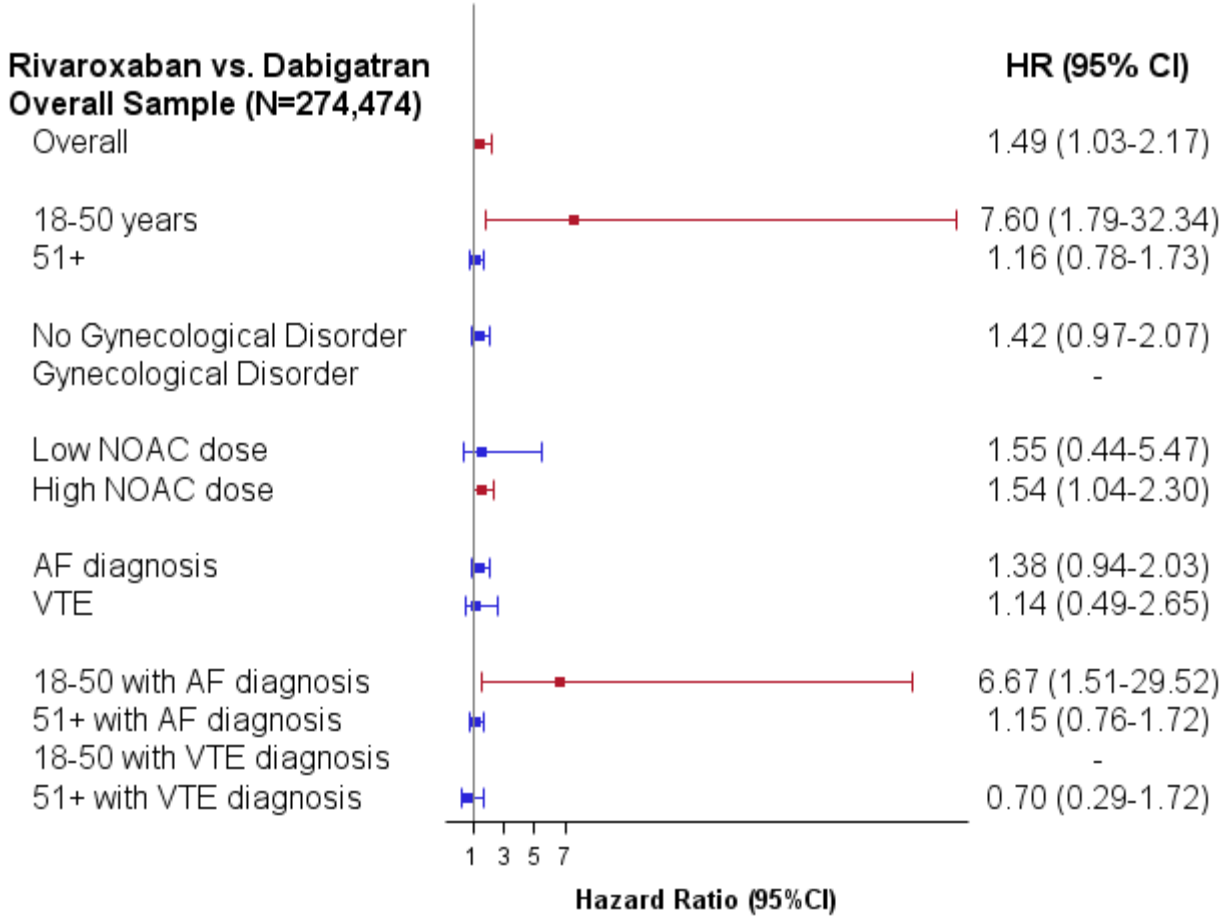
Distribution of the type of Surgical Interventions in **Unmatched** Cohorts

Surgical Management Type %	Rivaroxaban (n=791)	Dabigatran (n=305)	Rivaroxaban (n=791)	Apixaban (n=170)	Dabigatran (n=305)	Apixaban (n=170)	Rivaroxaban (n=793)	Warfarin (n=1344)
Dilation and curettage with or without hysteroscopy	14.7	17.4	14.7	17.1	17.4	17.1	13.6	17.9
Hysterectomy	21.9	22.3	21.9	25.9	22.3	25.9	22.4	25.7
Hysteroscopy (not listed in other surgical managements)	11.9	*****	11.9	*****	*****	*****	18.2	17.3
Hysteroscopic polypectomy	46.1	53.4	46.1	47.1	53.4	47.1	27.2	21.5
Others (endometrial ablation, myomectomy, uterine artery embolization)	5.4	******	5.4	*****	*****	*****	18.6	17.7

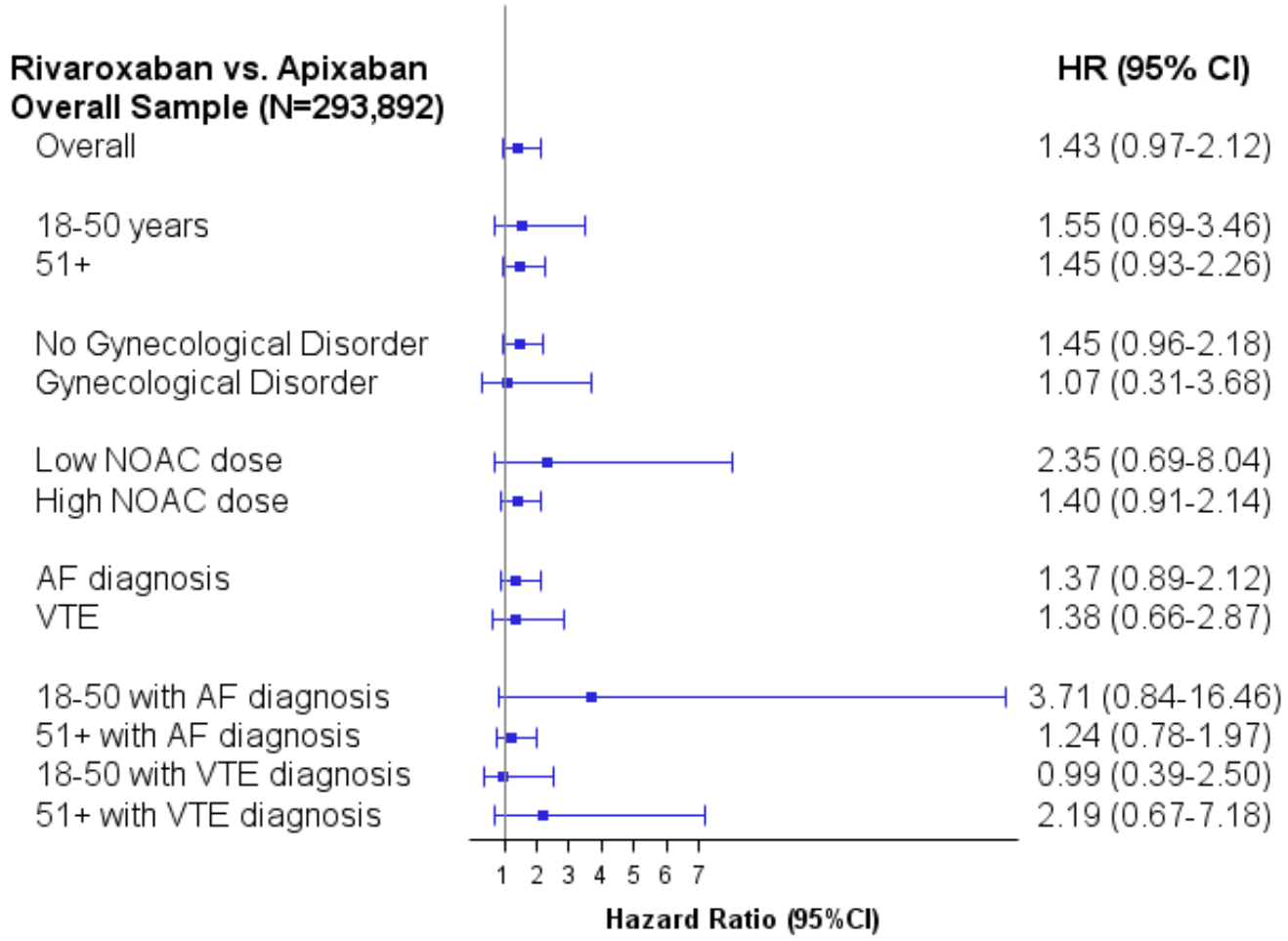
***** *Data are not presented in these cells due to a small sample size or to assure a small cell cannot be recalculated through the cells presented.*

RISK ESTIMATES FOR TRANSFUSION OUTCOME

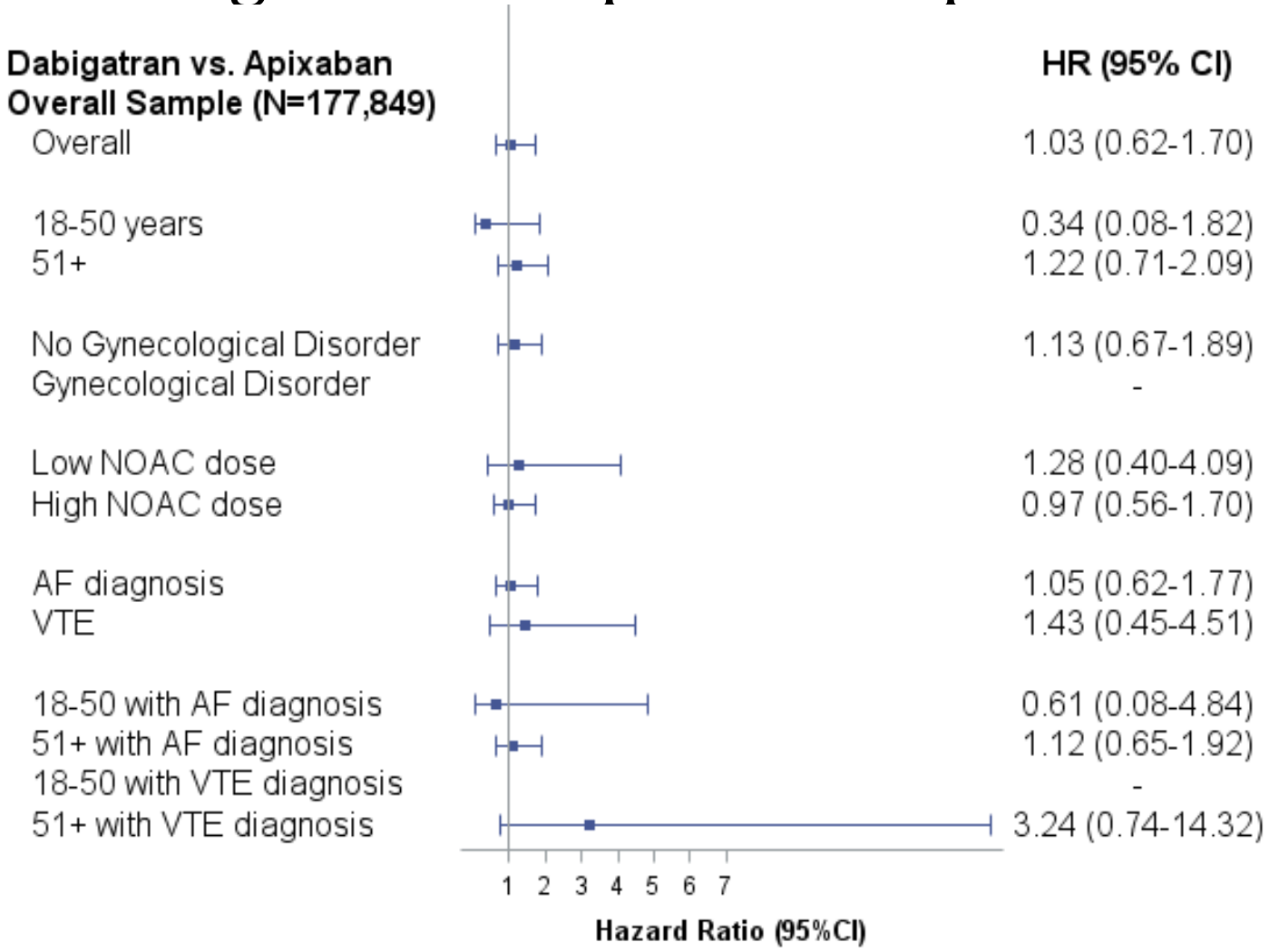
Increased risk of Transfusion Outcome with Rivaroxaban compared to Dabigatran



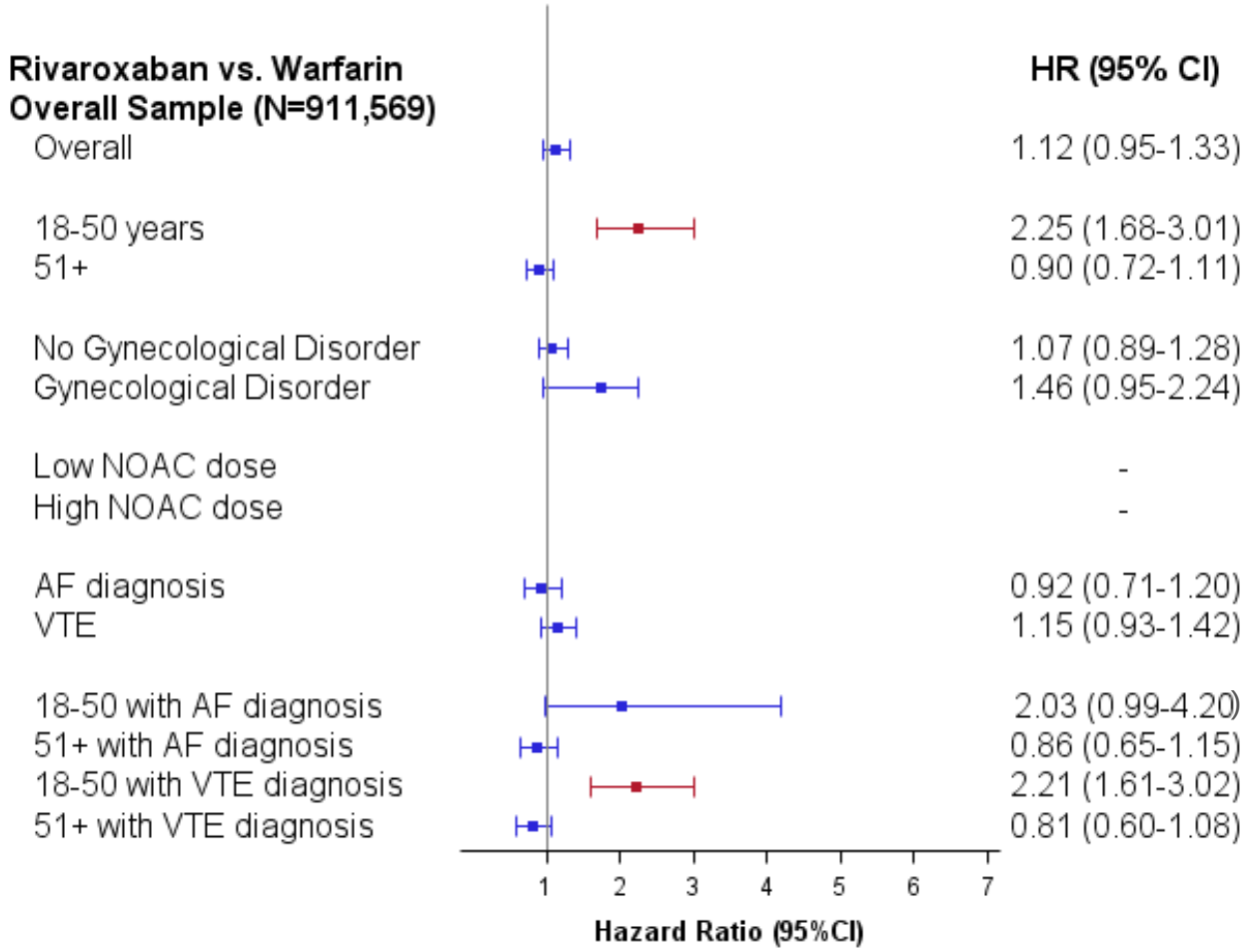
No difference in risk of Transfusion Outcome with Rivaroxaban compared to Apixaban



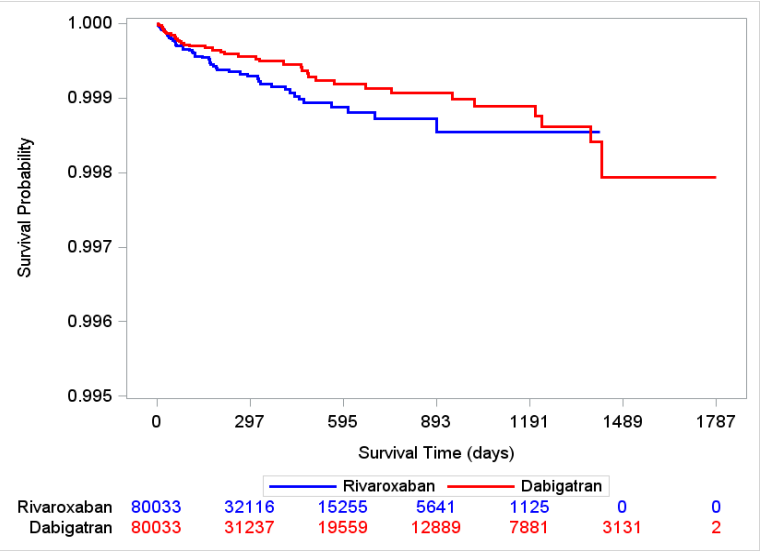
No difference in risk of Transfusion Outcome with Dabigatran compared to Apixaban

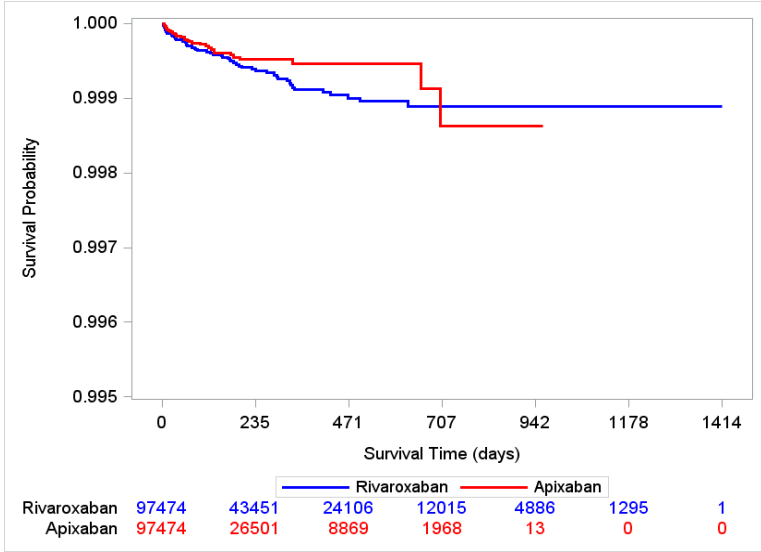


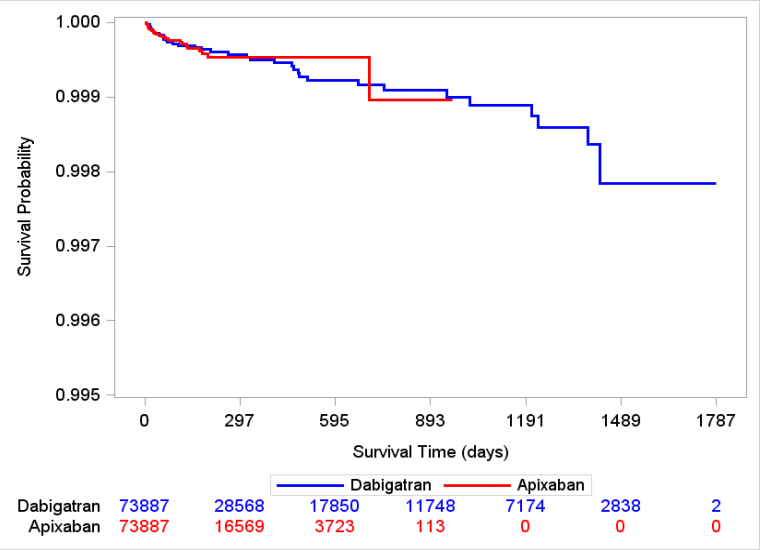
Increased risk of Transfusion Outcome with Rivaroxaban compared to Warfarin

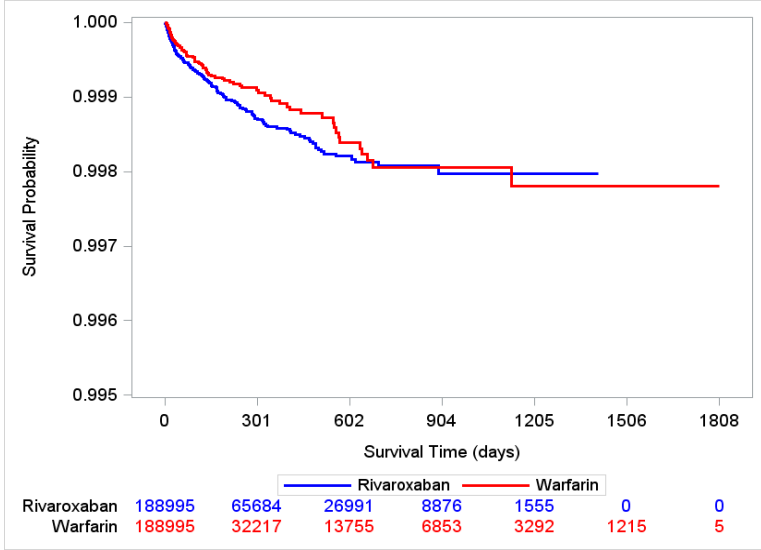


Adjusted Kaplan-Meier plots









Discussion

- Increased risk of SAUB (surgical and transfusion outcomes) with Rivaroxaban compared to other NOACs
- Relative risk consistent with re-analysis of EINSTEIN trial for Rivaroxaban vs. warfarin comparison
  - Among women <50 years with VTE, rivaroxaban vs. warfarin: 2.21 (1.61 – 3.02) for transfusion outcome
  - Re-analysis of clinical trials: 2.13 (95% CI: 1.57-2.89)

SAUB: Severe Abnormal Uterine Bleeding

Discussion

- Increased Risk of SAUB with rivaroxaban, among those with no underlying Gynecological Disorder
  - For the surgical outcome, increased risk associated with rivaroxaban occurred in patients without any gynecological disorder
    - Dabigatran (HR: 1.22 [CI: 1.05-1.42])
    - Apixaban (HR: 1.25 [CI: 1.04-1.49])
    - Warfarin (HR: 1.23 [CI: 1.36-1.50])
  - Similar trends for the transfusion outcome but statistical significance not achieved
    - Dabigatran (HR: 1.42 [CI: 0.97-2.07])
    - Apixaban (HR: 1.45 [CI: 0.96-2.18])
    - Warfarin (HR: 1.07 [CI: 0.89-1.28])

Conclusion

- Increased risk of severe uterine bleeding leading to transfusion associated with rivaroxaban observed in the clinical trials replicated in observational study
- Observed increased risk of severe uterine bleeding leading to surgical intervention associated with rivaroxaban
  - Hysteroscopic polypectomy and hysterectomy account for more than half of gynecological surgeries
- Women who have no associated gynecologic uterine disorder (e.g. fibroids) that would put them at risk for uterine bleeding still appear to have an increased risk with rivaroxaban than other NOACs or warfarin

Limitations

- Possible residual confounding
  - Probably minimal
- Low events (especially for transfusion outcomes) could have affected power
- Algorithm for outcome, not validated
  - Reviewed patients claims around the date of the outcome to ascertain if outcome truly occurred
  - Not expecting that performance of the algorithm will be differential with respect to exposure
- Used age as a surrogate for menopausal age

Thanks to

Data Partners who provided data used in the analysis

Sentinel Operations Center members: Andrew Petrone, Rajani Rajbhandari, Elizabeth Dee, Joy Kolonoski, Judith C Maro, and Anita Wagner for their programming, operational, and clinical review assistance

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Table 2. Incidence Rates for Surgical Management of Severe Abnormal Uterine Bleeding (per 1,000 person-years) in Propensity Score-Stratified Cohorts

Pairwise Comparison	Exposure	Overall	Age at index date, years		Gynecological Disorder		Anticoagulant Indication	
			18-50	51+	Yes	No	AF	VTE
R vs. D	Rivaroxaban	5.33	39.25	4.32	13.65	5.09	4.30	7.37
	Dabigatran	3.61	18.85	3.48	11.59	3.47	3.57	4.23
R vs. A	Rivaroxaban	5.32	40.82	4.32	13.50	5.07	4.32	7.35
	Apixaban	3.59	17.76	3.45	11.05	3.46	3.49	4.32
D vs. A	Dabigatran	3.65	21.08	3.49	13.43	3.50	3.62	3.99
	Apixaban	3.60	18.38	3.47	11.15	3.47	3.51	4.31
R vs. W	Rivaroxaban	5.38	39.41	4.37	14.81	5.14	4.33	7.59
	Warfarin	3.72	21.27	2.98	13.83	3.46	3.01	4.49

Incidence Rates for Transfusion Management for Severe Abnormal Uterine Bleeding (per 1,000 person-years) in Propensity Score-Stratified Cohorts
*Number of events are less than 11

Pairwise Comparison	Exposure	Overall	Age at index date, years		Gynecological Disorder		Anticoagulant Indication	
			18-50	51+	Yes	No	AF	VTE
R vs. D	Rivaroxaban	1.31	19.64	0.80	7.41	1.13	0.75	2.55
	Dabigatran	0.49	2.87*	0.47	0	0.50	0.49	1.13
R vs. A	Rivaroxaban	1.33	20.79	0.81	7.98	1.15	0.75	2.61
	Apixaban	0.77	15.46	0.55	3.62	0.64	0.62	1.44
D vs. A	Dabigatran	0.51	3.46	0.49	0	0.52	0.50	1.14
	Apixaban	0.70	15.94	0.56	3.65	0.65	0.63	1.44
R vs. W	Rivaroxaban	1.32	18.36	0.81	8.48	1.14	0.76	2.60
	Warfarin	1.70	10.26	1.34	8.99	1.50	1.17	2.43