Comparative effectiveness and safety of direct ORal Anticoagulants in patients with atrial fibrillation: a standardiZed Observational data Network study (CORAZON)

Professor Ian Wong (wongick@hku.hk)

5th December 2020

Contents

- A brief introduction to our research team
- Study background and objective
- Methods
- Results
- Discussion

Our team

- Observational studies using population databases from Hong Kong (CDARS) and the UK (IMRD/CPRD)
- Asia Pharmacoepidemiology Network (AsPEN) (Hong Kong, Taiwan, Korea, Australia …)

British Medical Association (BMA) House, London

Li Ka Shing Faculty of Medicine, Hong Kong

Research on direct oral anticoagulants

Research

JAMA | Original Investigation

Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation

Wallis C. Y. Lau, BSc; Esther W. Chan, PhD; Ching-Lung Cheung, PhD; Chor Wing Sing, BSc; Kenneth K. C. Man, MPH; Gregory Y. H. Lip, MD; Chung-Wah Siu, MD; Joanne K. Y. Lam, FHKAM; Alan C. H. Lee, FHKAM; Ian C. K. Wong, PhD

Annals of Internal Medicine ORIGINAL RESEARCH

Association Between Treatment With Apixaban, Dabigatran, Rivaroxaban, or Warfarin and Risk for Osteoporotic Fractures Among Patients With Atrial Fibrillation

A Population-Based Cohort Study

Wallis C.Y. Lau, PhD; Ching-Lung Cheung, PhD; Kenneth K.C. Man, PhD; Esther W. Chan, PhD; Chor Wing Sing, PhD; Gregory Y.H. Lip, MD; Chung-Wah Siu, MD; Joanne K.Y. Lam, MBBS; Alan C.H. Lee, MBBS; and Ian C.K. Wong, PhD

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Sex-Based Differences in Outcomes of Oral Anticoagulation in Patients With Atrial Fibrillation

Sharon W.Y. Law, MPharm,[a] Wallis C.Y. Lau, PhD,[a,b] Ian C.K. Wong, PhD,[a,b] Gregory Y.H. Lip, MD,[c,d] Michael T. Mok, MBBS,[e,f] Chung-Wah Siu, MD,[g] Esther W. Chan, PhD[a]

Gastroenterology

Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study

Esther W. Chan,[1,*] Wallis C. Y. Lau,[1,*] Wai K. Leung,[2] Michael T. C. Mok,[3] Ying He,[1] Teresa S. M. Tong,[2] and Ian C. K. Wong[1]

Comparative effectiveness and safety of direct ORal Anticoagulants in patients with atrial fibrillation: a standardiZed Observational data Network study (CORAZON)

Study background

- Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting 33 million people worldwide and is a leading cause of stroke
- Current guidelines[1,2] recommend direct oral anticoagulants (DOACs) over warfarin for stroke prevention in AF
- No further guidance on how to choose between the DOACs, due to the absence of randomized controlled trials directly comparing the DOACs

1. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation
2. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.

Study background

- Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting 33 million people worldwide and is a leading cause of stroke
- Current guidelines[1,2] recommend direct oral anticoagulants (DOACs) over warfarin for stroke prevention in AF
- No further guidance on how to choose between the DOACs, due to the absence of randomized controlled trials directly comparing the DOACs

	Clinical trials of DOACs vs Warfarin in AF	
	Stroke or systemic embolism	Major bleeding
Dabigatran (Pradaxa)	↓	↔
Rivaroxaban (Xarelto)	↔	↔
Apixaban (Eliquis)	↓	↓
Edoxaban (Savaysa)	↔	↓

↓: reduced in comparison to warfarin;
↔: comparable to warfarin
Adapted from Wadhera RK et al. 2014

Study objective

- To compare the effectiveness and safety outcomes between the four DOACs in patients with AF

  (dabigatran vs rivaroxaban vs apixaban vs edoxaban)

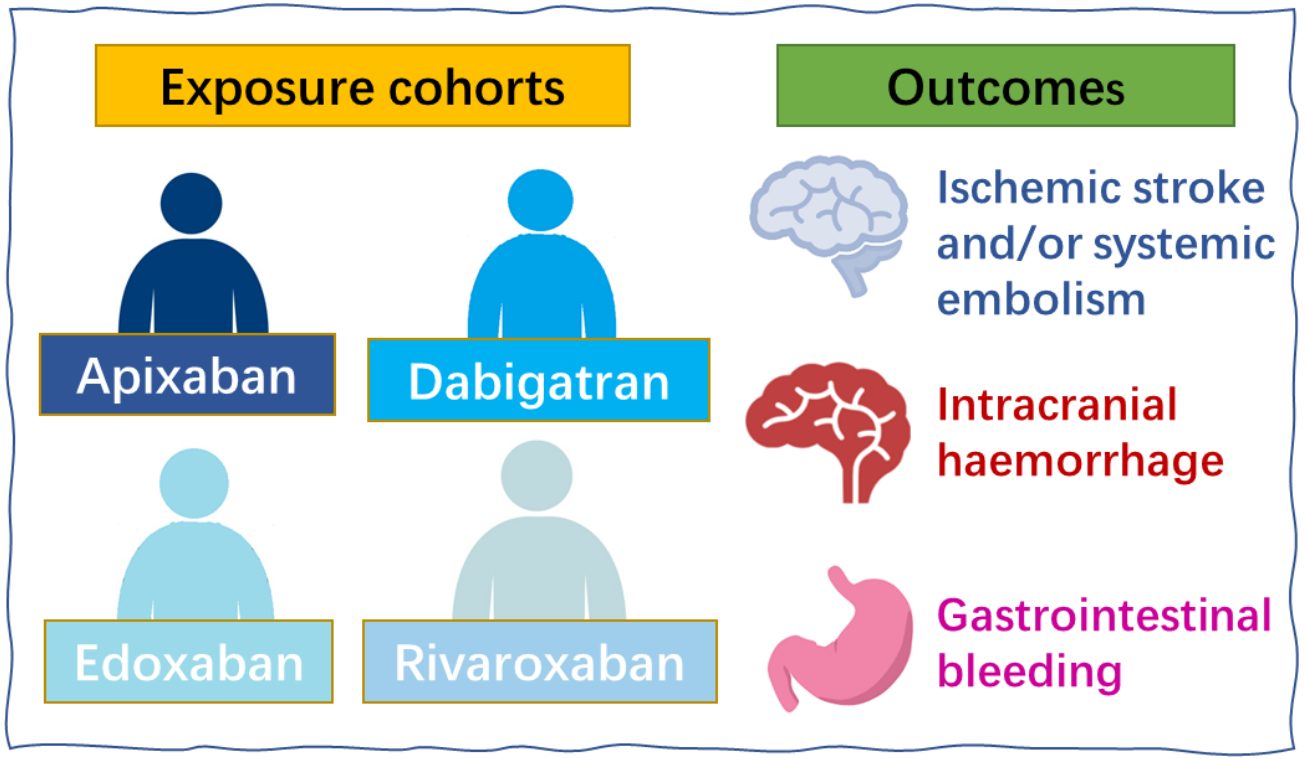
- Outcomes of interest:
  - Ischemic stroke/systemic embolism
  - Intracranial bleeding
  - Gastrointestinal bleeding

Method – data sources

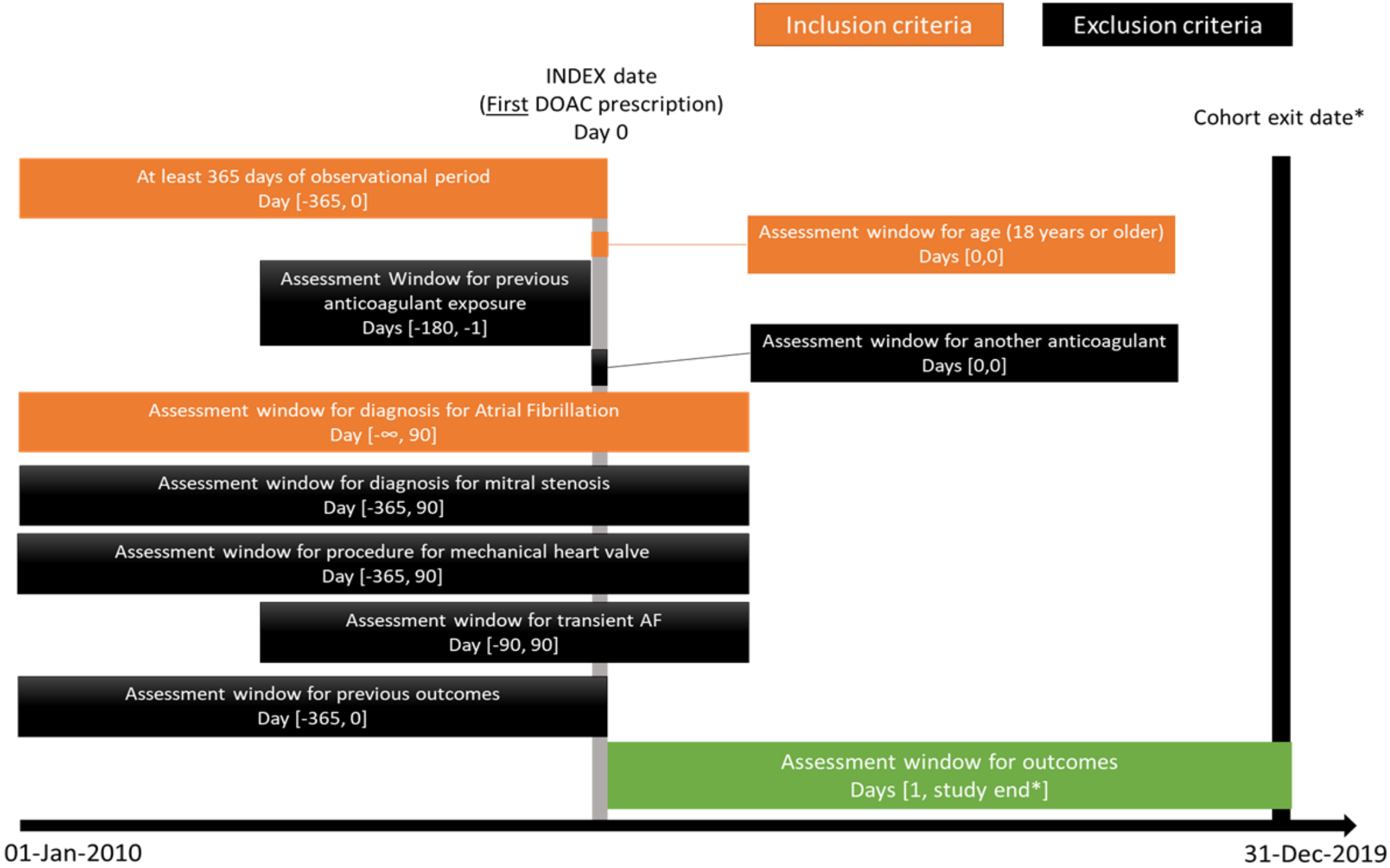
- Five databases from four countries, covering data from hospital and outpatient settings.

Data source	Country	Patient Count	History	Patient Type	Data collection
LPD France EMR	France	30.9 M	2009 -	Outpatient / General population/ Patients seen in the primary care setting	Electronic health records in ambulatory setting
Disease Analyser Germany EMR	Germany	39.2 M	1992 -	Outpatient only / General population/Public and private insurance	Electronic health records in ambulatory setting
UK IMRD	United Kingdom	12.7 M	1994 -	General population / Primary care records with hospitalisation / referral information	Pseudonymised Electronic Medical Records collected from Patient Management software used within UK Primary Care
US Hospital Charge Master	United States	94.5 M	2001 -	Inpatient & outpatient hospital encounters, including Emergency Room visits / General population	Anonymized patient level data are sourced from hospital charge detail masters (CDM) and collected from resource management software within short-term, acute-care and non-federal hospitals
US Ambulatory EMR	United States	75.7 M	2006 –	Outpatient	Electronic health records in ambulatory setting

Method – study design



- A new user cohort Population-Level Estimation (PLE) study
- Four drug exposure cohorts and three outcome cohorts



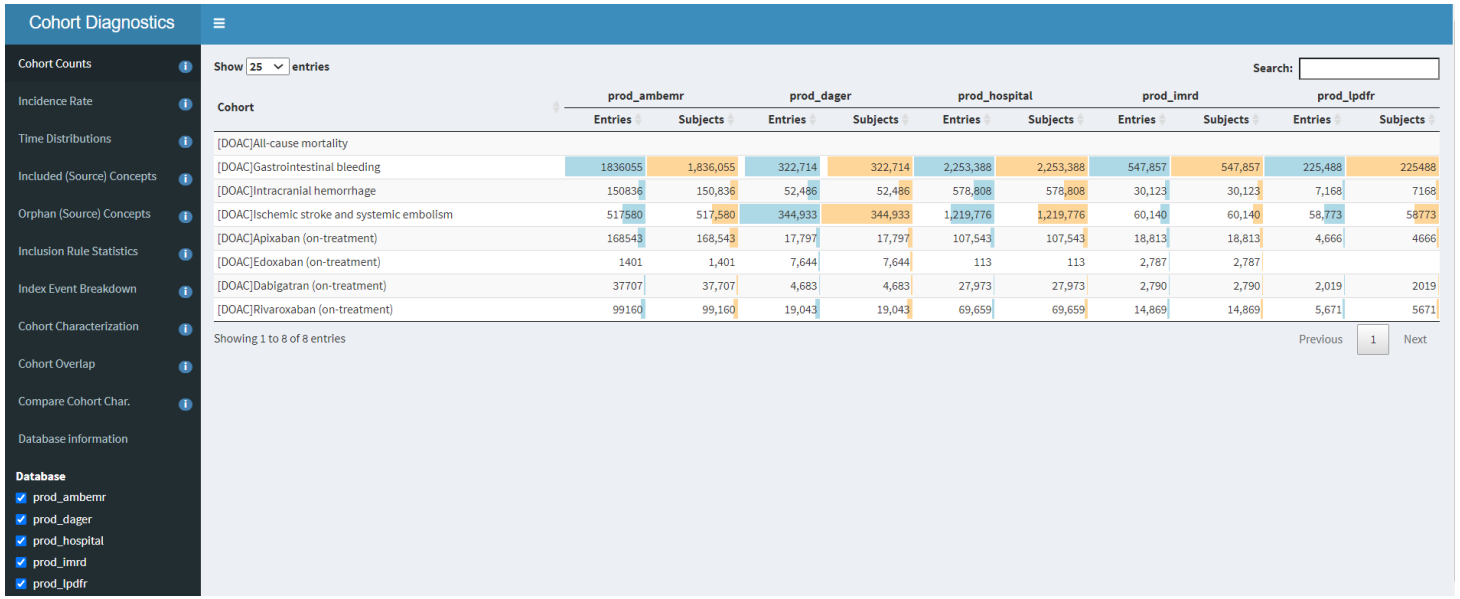
*The earliest of 31-Dec-2019 (study end), date of death, discontinuation of index DOAC (90 days gap), prescription of another anticoagulant

Method – defining concept sets

- The concept sets of the cohorts for defining drug exposure, outcomes, inclusion and exclusion criteria were derived using a combination of methods:
  - Identifying the codes from literature
  - Keyword search in ATHENA
  - Checking the related concepts in the hierarchy of an identified concept to see if its parent or child code(s) should be included instead

Method - CohortDiagnotics

- CohortDiagnotics (https://github.com/OHDSI/CohortDiagnostics) was conducted to assess any potential missing concept sets (orphan concepts) or any abnormalities in the data
- ~100 orphan concepts were added to the concept sets of the cohorts after careful review



Method – Statistical analysis

- **Propensity score** matching with variable target-to-comparator ratio was used to address potential confounding factors between DOAC groups.

- For each patient, propensity scores were estimated using a data-driven, regularized logistic regression model using the Cyclops package (https://ohdsi.github.io/Cyclops), based on a range of baseline covariates including drugs, conditions, procedures, and summary scores such as CHA2DS2-VASc score and Charlson Comorbidity Index.

Method – Statistical analysis

- The outcomes were compared between the cohorts using **Cox proportional hazards regression model**, in terms of **hazard ratios**.
- Negative controls were used for p-value calibration.
- The hazard ratios were pooled across databases in a meta-analysis using a random-effect model.

Method – Statistical analysis

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- Negative controls were used for p-value calibration.
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Method – Additional analyses

- Subgroup analyses were conducted for patients aged 80+ years on the date of DOAC initiation

- Sensitivity analyses:
  - Intention-to-treat
  - Propensity score stratification rather than matching

Method

- The analytic software package is available in GitHub:
  - https://github.com/ohdsi-studies/Corazon

README.md

OHDSI Comparative effectiveness and safety of direct ORal Anticoagulants in patients with atrial fibrillation: a standardiZed Observational data Network study (CORAZON)

Study Status Started

- Analytics use case(s): **Population-Level Estimation**
- Study type: **Clinical Application**
- Tags: **OHDSI, DOAC, AF**
- Study lead: **Wallis CY Lau, PhD, UCL School of Pharmacy, United Kingdom; Carmen Olga Torre, RWS IQVIA, United Kingdom**
- Study lead forums tag: wallislau, CarmenOT
- Study start date: **22/09/2020**
- Study end date: **12/2020**
- Protocol: Word Doc
- Publications: -
- Results explorer: -

Results

Number of patients in each database:

DOACs	Database, no. of patients				
	LPD France EMR	DA Germany EMR	UK IMRD	US Ambulatory EMR	US Hospital Discharge Master
Apixaban	4,666	18,409	18,813	168,543	107,543
Dabigatran	2,019	4,229	2,790	37,707	27,973
Edoxaban	-	8,469	2,787	1,401	-
Rivaroxaban	5,671	17,706	14,869	99,160	69,659
Subtotal	12,356	48,813	39,259	306,811	205,175
Total					**612,414**

LPD France EMR and US Hospital Discharge Master have small (<1000) patient count for edoxaban and were not included in the analyses for edoxaban.

Patient characteristics

- The covariates are well-balanced with standardised differences < 0.1 for all comparisons after propensity score matching. The data from US Ambulatory EMR are shown for illustration purpose:

	Before PS			After PS		
Characteristic	Rivaroxaban %	Apixaban %	Std. diff	Rivaroxaban %	Apixaban %	Std. diff
Age group						
25 - 29	0.1	0.1	0.01	0.1	0.1	0.01
30 - 34	0.2	0.1	0.02	0.2	0.1	0.01
35 - 39	0.4	0.2	0.03	0.4	0.3	<0.01
40 - 44	0.8	0.5	0.03	0.7	0.7	<0.01
45 - 49	1.6	1.2	0.04	1.5	1.6	<0.01
50 - 54	3.3	2.4	0.05	3.1	3.1	<0.01
55 - 59	6.4	4.9	0.07	6.1	6.2	<0.01
60 - 64	10.3	8.5	0.06	10.2	10.2	<0.01
65 - 69	15.6	13.9	0.05	15.4	15.5	<0.01
70 - 74	18.2	17.4	0.02	18.3	18.3	<0.01
75 - 79	25.1	20.2	0.12	21.7	21.9	-0.01
80 - 84	18	30.5	-0.29	22.3	21.9	0.01
Gender: female	42.9	46.5	-0.07	43.4	43.2	<0.01

	Before PS			After PS		
Characteristic	Rivaroxaban %	Apixaban %	Std. diff	Rivaroxaban %	Apixaban %	Std. diff
Medical history: general						
Attention deficit hyperactivity disorder	0.2	0.2	0.01	0.2	0.2	<0.01
Chronic liver disease	0.7	0.7	<0.01	0.6	0.7	<0.01
Chronic obstructive lung disease	10	11.3	-0.04	10.2	10.2	<0.01
Crohn's disease	0.3	0.3	<0.01	0.3	0.3	-0.01
Dementia	1.5	1.8	-0.02	1.6	1.6	<0.01
Depressive disorder	9.9	10.1	-0.01	10	10	<0.01
Diabetes mellitus	20.7	22.3	-0.04	21.2	21	<0.01
Gastroesophageal reflux disease	14.8	14.6	0.01	14.6	14.6	<0.01
Human immunodeficiency virus infection	0.1	0.1	-0.01	0.1	0.1	<0.01
Hyperlipidemia	48.4	48.8	-0.01	48.1	48	<0.01
Hypertensive disorder	62.9	66.5	-0.07	64	63.8	<0.01
Lesion of liver	0.8	0.9	-0.01	0.8	0.8	<0.01
Obesity	13.3	13.1	0.01	13.6	13.6	<0.01
Pneumonia	3.9	4.3	-0.02	4	3.9	<0.01
Psoriasis	1	0.9	<0.01	0.9	1	<0.01
Renal impairment	9	13.1	-0.13	9.7	9.6	<0.01
Rheumatoid arthritis	1.4	1.5	<0.01	1.4	1.4	<0.01
Schizophrenia	0.1	0.1	<0.01	0.1	0.1	<0.01
Ulcerative colitis	0.4	0.3	<0.01	0.3	0.3	<0.01
Urinary tract infectious disease	6.1	6.7	-0.03	6.1	6.1	<0.01
Viral hepatitis C	0.4	0.3	<0.01	0.4	0.3	<0.01

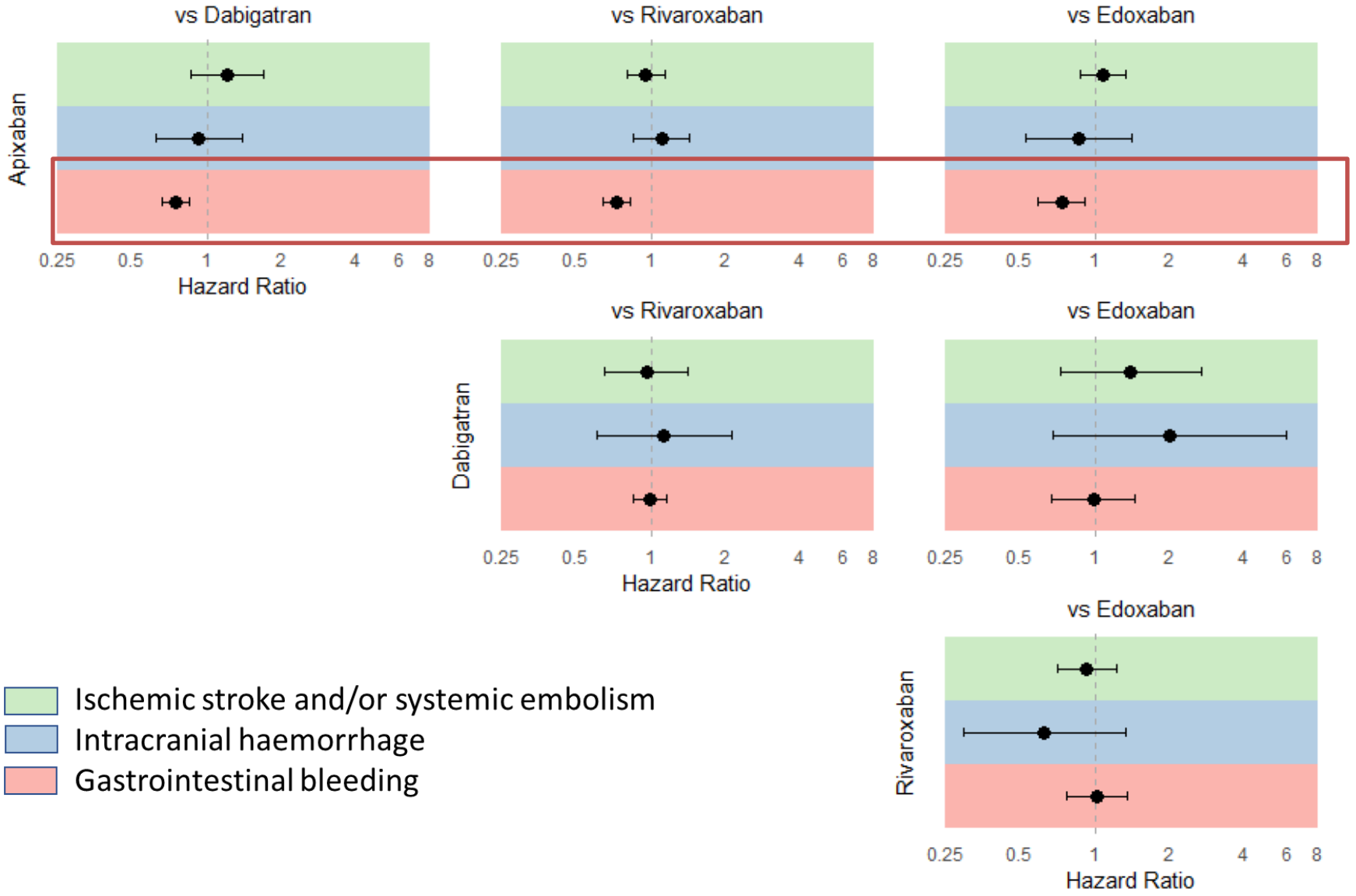
Patient characteristics

- The covariates are well-balanced with standardised differences < 0.1 for all comparisons after propensity score matching. The data from US Ambulatory EMR are shown for illustration purpose:

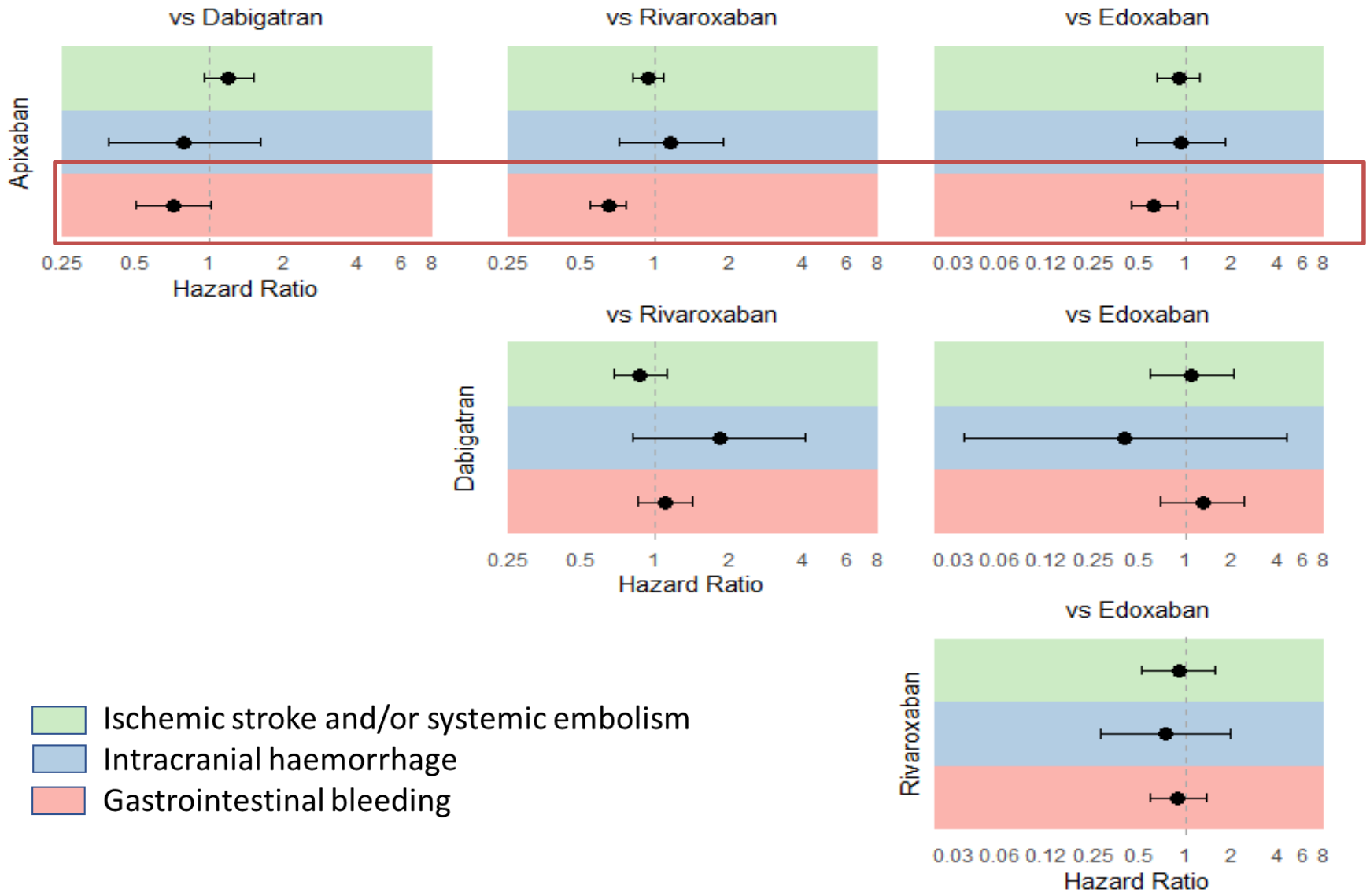
	Before PS			After PS		
Characteristic	Rivaroxaban %	Apixaban %	Std. diff	Rivaroxaban %	Apixaban %	Std. diff
Medical history: Cardiovascular disease						
Cerebrovascular disease	8.4	10.8	-0.08	8.9	8.9	<0.01
Coronary arteriosclerosis	20.3	23.4	-0.08	20.4	20.2	<0.01
Heart disease	47	52.2	-0.1	47.5	47.2	0.01
Heart failure	11.4	14.8	-0.1	11.9	11.8	<0.01
Ischemic heart disease	5.2	5.9	-0.03	5.2	5.1	<0.01
Peripheral vascular disease	4.1	4.8	-0.04	4.1	4.1	<0.01
Pulmonary embolism	1.7	1.2	0.04	1.6	1.6	<0.01
Venous thrombosis	2.6	1.8	0.05	2.3	2.4	<0.01
Medical history: Neoplasms						
Hematologic neoplasm	0.7	0.8	-0.01	0.7	0.7	<0.01
Malignant lymphoma	0.6	0.7	-0.01	0.6	0.6	<0.01
Malignant neoplasm of anorectum	0.1	0.1	<0.01	0.2	0.1	<0.01
Malignant neoplastic disease	10.9	11.2	-0.01	11.1	11	<0.01
Malignant tumor of breast	1.5	1.5	<0.01	1.5	1.5	<0.01
Malignant tumor of colon	0.5	0.5	<0.01	0.5	0.5	-0.01
Malignant tumor of lung	0.7	0.8	-0.01	0.8	0.8	<0.01
Primary malignant neoplasm of prostate	0.9	0.7	0.02	0.8	0.8	<0.01

	Before PS			After PS		
Characteristic	Rivaroxaban %	Apixaban %	Std. diff	Rivaroxaban %	Apixaban %	Std. diff
Medication use						
Agents acting on the renin-angiotensin system	54.3	55.4	-0.02	54	54.2	<0.01
Antibacterials for systemic use	38.6	38.9	-0.01	37.8	37.9	<0.01
Antidepressants	23.5	24.5	-0.02	23.7	23.6	<0.01
Antiepileptics	15.4	17.1	-0.04	15.9	16	<0.01
Antiinflammatory and antirheumatic products	24.4	23.7	0.02	24	24	<0.01
Antineoplastic agents	2.6	2.7	-0.01	2.6	2.6	<0.01
Antipsoriatics	0.7	1.2	-0.05	0.7	0.7	<0.01
Antithrombotic agents	49.5	52.7	-0.06	49.5	49.3	<0.01
Beta blocking agents	69	70.9	-0.04	69.1	69	<0.01
Calcium channel blockers	39.3	40.5	-0.03	39.1	39.1	<0.01
Diuretics	47.2	50.3	-0.06	47.3	47.2	<0.01
Drugs for acid related disorders	38.1	40.7	-0.05	38.2	38.1	<0.01
Immunosuppressants	3	3.5	-0.03	3.1	3.1	<0.01
Opioids	16.7	16.7	<0.01	16.4	16.4	<0.01

Main analysis

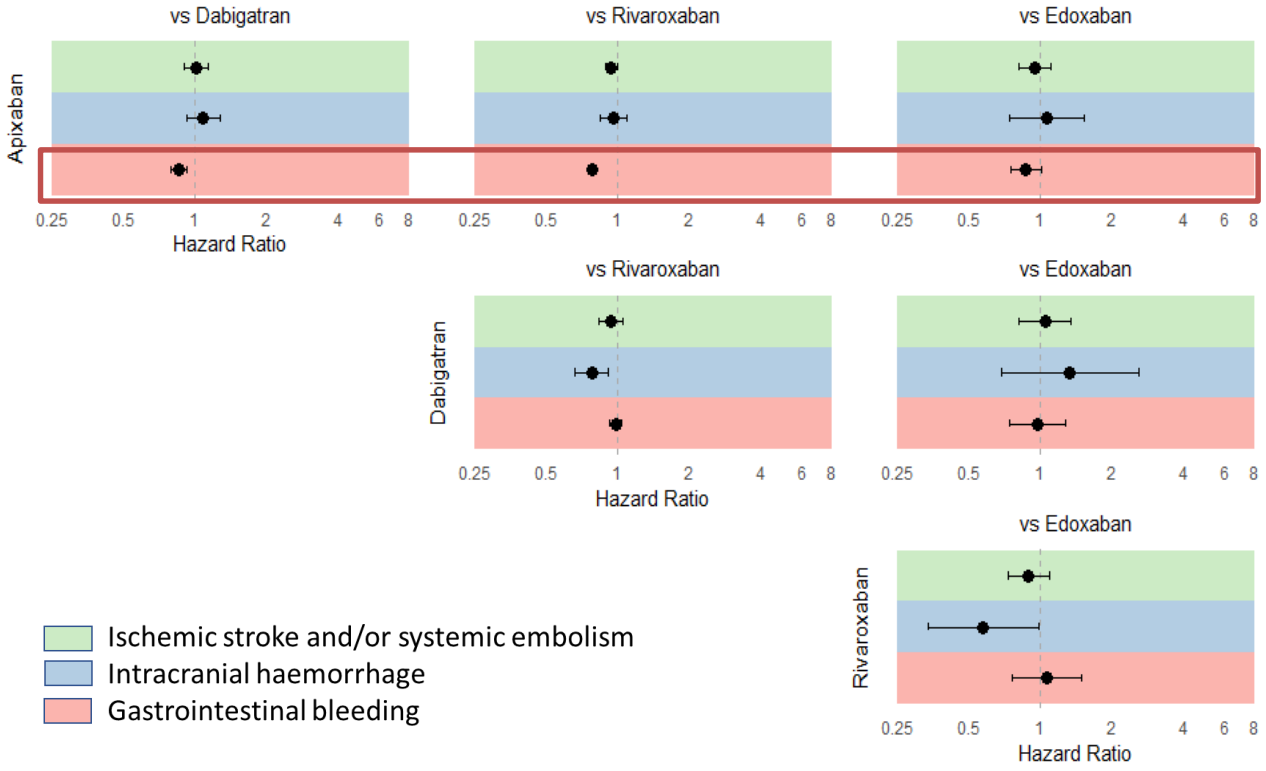


Subgroup: aged >80 years

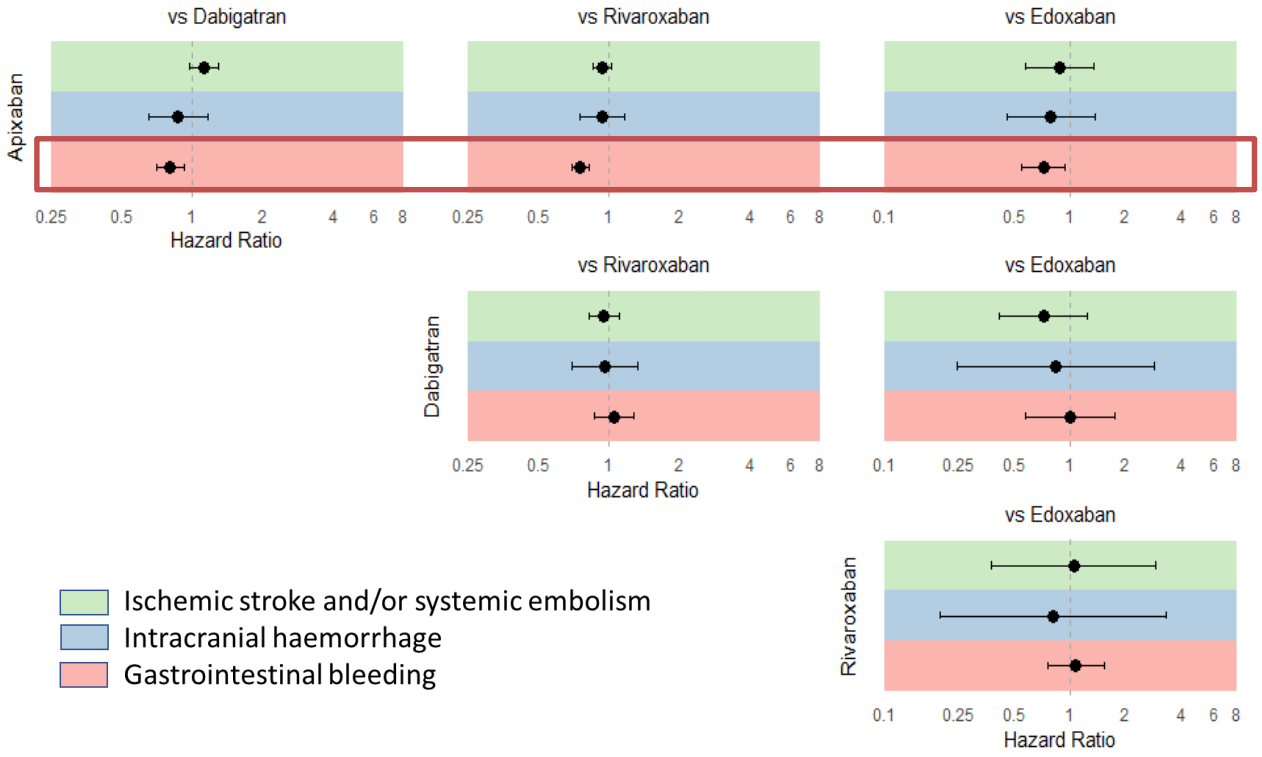


Sensitivity analyses – intention to treat

Main analysis

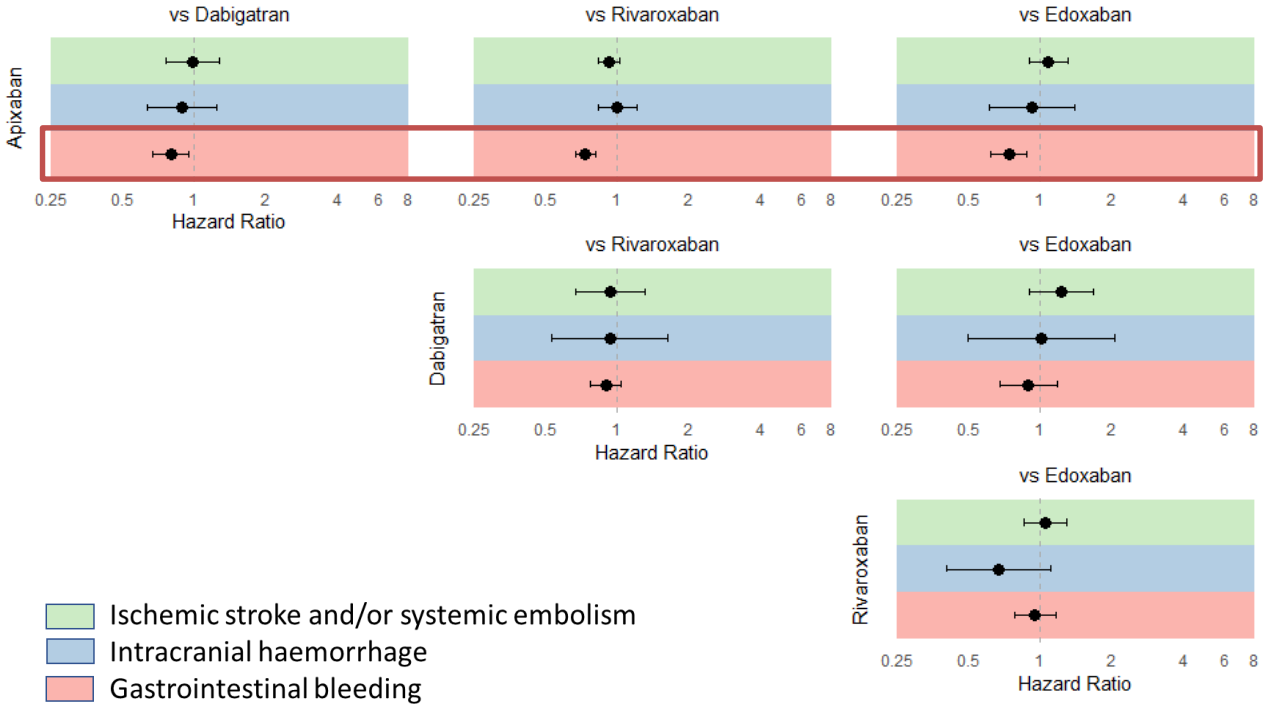


Aged 80+ years



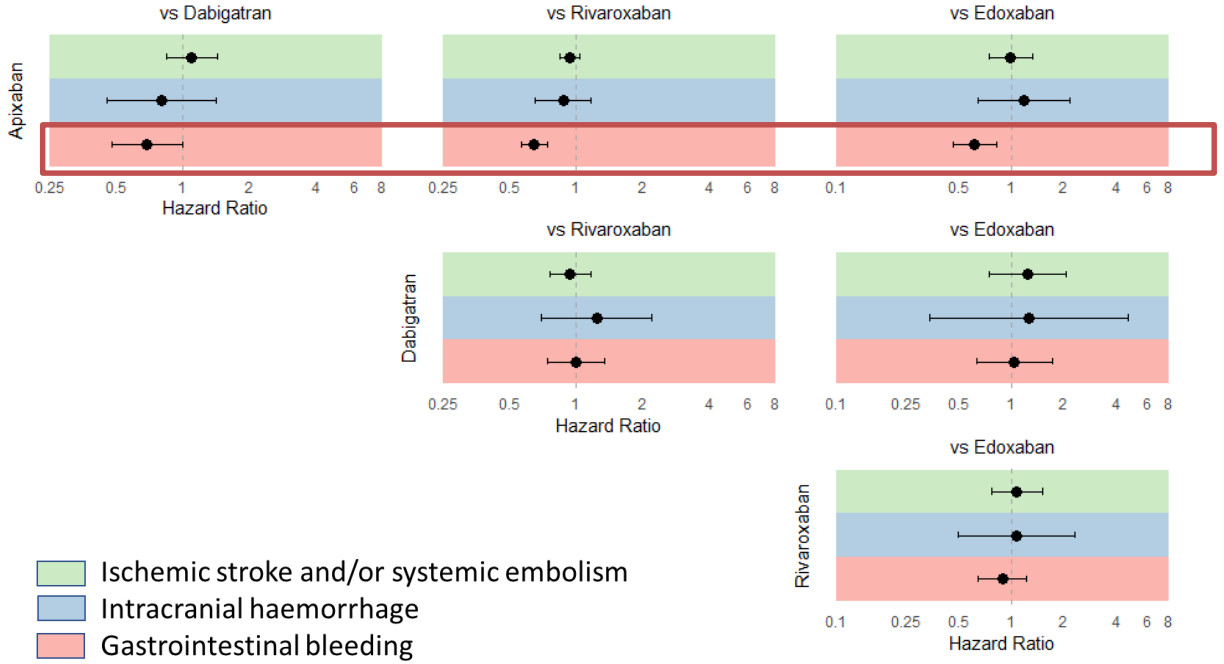
Sensitivity analyses – propensity score stratification

Main analysis



Ischemic stroke and/or systemic embolism
Intracranial haemorrhage
Gastrointestinal bleeding

Aged 80+ years



Ischemic stroke and/or systemic embolism
Intracranial haemorrhage
Gastrointestinal bleeding

Discussion

- This is the largest direct comparison between DOACs involving >600,000 patients with atrial fibrillation in four different countries.
- We found that apixaban is less likely to cause gastrointestinal bleeding compared to dabigatran, edoxaban, and rivaroxaban, with similar risks of ischemic stroke and intracranial hemorrhage.
- The results are consistent for patients aged 80+ years.

Discussion

- There has been no RCTs directly comparing DOACs to guide the choice of DOACs, especially in the older age group who are often excluded from RCTs

- The current study has provided important data to inform the optimal choice of DOACs among patients with atrial fibrillation

- Further studies are warranted to study the use of DOACs for other short-term indications (e.g. venous thromboembolism)

Strengths and Limitations

- **Strengths**
  - Large study population from multiple countries
  - A new-user cohort study design was used to eliminate the residual effect of previous drug exposure on the outcomes
- **Limitations**
  - Due to the observational nature of the study, we cannot exclude the possibility of residual confounding factors.
    - To overcome this potential limitation, all known confounding variables for which there is adequate information available were included in the study.
    - Also, we used propensity score modelling with p-value calibrations were used to address potential confounding factors and ensure the robustness and validity of the study results.

Summary

- This large, multi-national, OHDSI network study found that among patients with AF, apixaban is associated with a lower risk of gastrointestinal bleeding compared to any other DOAC, with a comparable risk of stroke and intracranial hemorrhage.

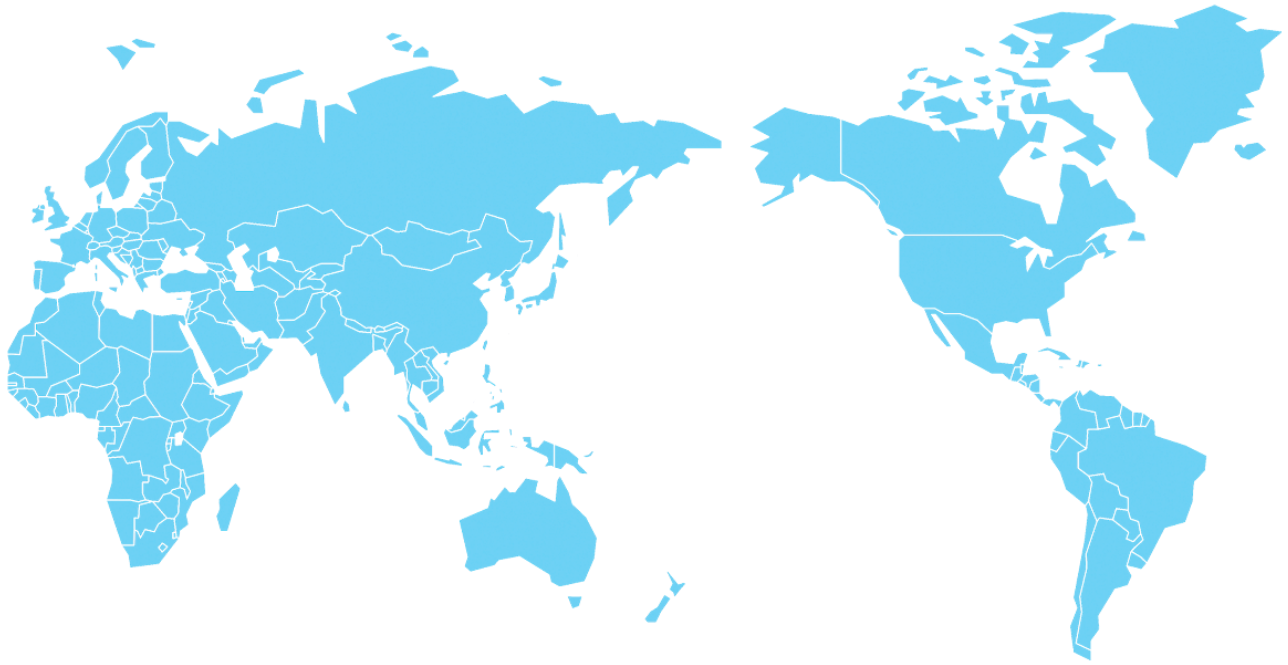
- Similar results were observed among the older age group (80+ years).

- Apixaban may be a safer option over other DOACs with comparable effectiveness for stroke prevention.

Join CORAZON!

We are seeking collaborators to conduct this study in the Asian population

GitHub: [ohdsi-studies/Corazon]



-Thank you -