Original research

Risks of post-colonoscopic polypectomy bleeding and thromboembolism with warfarin and direct oral anticoagulants: a population-based analysis

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ABSTRACT

Background There were limited data on the risk of post-polypectomy bleeding (PPB) in patients on direct oral anticoagulants (DOAC). We aimed to evaluate the PPB and thromboembolic risks among DOAC and warfarin users in a population-based cohort.

Methods We performed a territory-wide retrospective cohort study involving patients in Hong Kong from 2012 to 2020. Patients who received an oral anticoagulant and had undergone colonoscopy with polypectomy were identified. Propensity-score models with inverse probability of treatment weighting were developed for the warfarin-DOAC and between-DOAC comparisons. The primary outcome was clinically significant delayed PPB, defined as repeat colonoscopy requiring haemostasis within 30 days. The secondary outcomes were 30-day blood transfusion requirement and new thromboembolic event.

Results Apixaban was associated with lower PPB risk than warfarin (adjusted HR (aHR) 0.39, 95% CI 0.24 to 0.63, p<0.001). Dabigatran (aHR 2.23, 95% CI 1.04 to 4.77, adjusted p (ap)=0.035) and rivaroxaban (aHR 2.72, 95% CI 1.35 to 5.48, ap=0.002) were associated with higher PPB risk than apixaban. In subgroup analysis, apixaban was associated with lower PPB risk in patients aged ≥70 years and patients with right-sided colonic polyps.

For thromboembolic events, apixaban was associated with lower risk than warfarin (aHR 0.22, 95% CI 0.11 to 0.45, p<0.001). Dabigatran (aHR 2.60, 95% CI 1.06 to 6.41, ap=0.033) and rivaroxaban (aHR 2.96, 95% CI 1.19 to 7.37, ap =0.013) were associated with higher thromboembolic risk than apixaban.

Conclusions Apixaban was associated with a significantly lower risk of PPB and thromboembolism than warfarin, dabigatran and rivaroxaban, particularly in older patients with right-sided polyps.

Significance of this study

What is already known on this subject?
- Direct oral anticoagulants (DOACs) were shown to be associated with a lower risk of GI bleeding than warfarin; however, limited high-quality data were available regarding the risk of post-polypectomy bleeding (PPB) between individual DOAC.

What are the new findings?
- Apixaban was associated with a significantly lower risk of PPB and thromboembolism than warfarin, dabigatran and rivaroxaban.
- High-risk subgroups included older patients aged ≥70 years or those with right-sided polyps.

How might it impact on clinical practice in the foreseeable future?
- With the increasing use of DOACs among patients requiring colonoscopy, our results will inform clinical practice about the choice of oral anticoagulants and their associated risks of post-polypectomy bleeding.
- Patients with high bleeding risks warrant special adjustment in their peri-procedural anticoagulation plan.

INTRODUCTION

Direct oral anticoagulant (DOAC) has led to a paradigm shift in the management of atrial fibrillation (AF) and thromboembolism, due to the rapid onset of action, short half-life, predictable pharmacokinetic effect and better safety profile.[1] Nevertheless, management of anticoagulation in patient undergoing invasive procedure remains challenging due to the limited data available and difficulty in balancing the bleeding and thrombotic risks.

Colonoscopy with polypectomy has shown to reduce colorectal cancer (CRC)-related mortality.[2] However, there is a considerable risk of post-polypectomy bleeding (PPB). Current international guidelines classified colonoscopic polypectomy as a high-risk endoscopic procedure based on the risk of haemorrhage.[3–5] Several independent risk factors for PPB had been identified, including advanced age, underlying cardiovascular or renal diseases, large polyp size, pedunculated polyp morphology, polyp location in right hemi-colon and the use of antiplatelets or anticoagulants.[6–12]

Among all the risk factors, the use of anticoagulants including warfarin and heparin bridging was associated with a substantially higher risk of PPB.[13–17] When compared with warfarin, DOAC had limited and inconclusive results, with the absolute PPB risk reported to be 0.63%–13.7%. Two

retrospective studies demonstrated a similar PPB risk between patients on warfarin and DOAC.[18 19] However, two larger observational cohorts found a higher PPB risk in warfarin than DOAC users.[20 21] The limitations of these studies were either small sample size or lack of certain key factors which may potentially affect the final outcomes, including the specific type of DOAC, location and histopathology of polyps and missing data on concurrent use of aspirin and low-molecular-weight heparin. To date, the risk of PPB among patients on DOAC has never been studied in a head-to-head basis.

In this territory-wide population-based study, we aimed to evaluate the bleeding and thromboembolic risks after colonoscopic polypectomy among warfarin and DOAC users to address the current knowledge gap and unmet clinical need.

MATERIALS AND METHODS

Study design and data source

We performed an industry-independent territory-wide, propensity score (PS)-weighted retrospective cohort study involving patients in all public hospitals in Hong Kong during the period of 1 January 2012 to 30 June 2020. Clinical parameters were retrieved through the Clinical Data Analysis and Reporting System (CDARS) of the Hospital Authority. CDARS is an electronic healthcare database that records patients' demographics, death, diagnoses, procedures, investigation results and drug prescription from all public hospitals in Hong Kong, which serves over 90% of the whole 7.4 million population in Hong Kong. It facilitates the retrieval of good quality computerised clinical data captured from different operational systems for analysis and reporting. All patients are de-identified in CDARS to ensure confidentiality. A number of territory-wide studies were conducted by CDARS previously with the validity of data verified.[22 23]

Clinical parameters including demographic data, details of hospitalisation, endoscopic procedures, relevant diagnoses, laboratory tests, blood product use and concomitant drugs were retrieved and analysed.

Subjects

We identified adult patients who underwent colonoscopy or sigmoidoscopy with polypectomy during the study period by the procedure codes for endoscopic polypectomy of large intestine (45.42) and rectum (48.35) from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Among these patients, we further identified those who received an oral anticoagulant (apixaban, dabigatran, edoxaban, rivaroxaban or warfarin) by their respective drug prescription records. Active drug user was defined as either (a) any endoscopy performed between the start date and end date of current drug prescription, or (b) any endoscopy performed within 7 days after the current prescription end date and within 30 days before next prescription start date. We excluded patients who did not resume their oral anticoagulants within 30 days after the endoscopy.

We retrieved their demographic data (age and gender), baseline laboratory tests (haemoglobin, platelet, activated partial thromboplastin time (aPTT), international normalised ratio (INR), bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), urea, creatinine) and backgound comorbidities based on the ICD-9-CM diagnosis codes. Diagnosis codes of pulmonary embolism (PE), deep vein thrombosis (DVT), AF, valvular heart diseases, cardiac arrhythmia, ischaemic heart diseases (IHD), congestive heart failure, peripheral vascular diseases, cerebrovascular accidents (CVA), hypertension, diabetes mellitus, liver and renal diseases, connective tissue diseases, chronic obstructive pulmonary diseases, peptic ulcers, dementia, immunodeficiency and malignancy (ICD-9-CM 042–044, 250, 279, 290, 294, 331, 390–459, 490–496, 531–534, 570–573, 580–589, 710) were included for analysis. We therefore calculated a Charlson Comorbidity Index for each patient.[24] We also calculated CHA_2DS_2-VASc scores and HAS-BLED scores for relevant patients to estimate their corresponding thrombotic and bleeding risks.[25 26]

The concurrent use of antiplatelet agents and heparin were also retrieved through drug prescription records. Antiplatelet agents included aspirin, clopidogrel, dipyridamole and ticagrelor. Heparin included unfractionated heparin and low-molecular-weight heparin (enoxaprin, nadroparin, tinzaparin). The presence of heparin bridging was defined by any prescription of heparin within 7 days before and after colonoscopy.

The institutes performing the procedures were divided into seven clusters (A–G) according to the geographical location. Additional details of colonoscopy and polypectomy, including the number, location and histopathology of polyps, were also collected. Polyp location was defined right-sided (from caecum to transverse colon) and/or left-sided (from descending colon to rectum). The histopathology was grouped into a low-risk group (benign mucosal or hyperplastic polyps, tubular adenoma, sessile serrated adenoma) and a high-risk group (tubulovillous or villous adenoma, high-grade dysplasia, carcinoma, neuroendocrine tumour).

Any rescope for haemostasis was identified by procedure codes of colonoscopy or sigmoidoscopy with control of bleeding (45.43 (1, 2, 7) and 48.35 (1, 5, 8)), which was performed within 30 days after index colonoscopy. Diagnostic colonoscopies or sigmoidoscopies were not included to avoid counting staged procedures unrelated to bleeding. Blood transfusion records within 30 days of endoscopy were captured from the blood bank.

Outcomes

The primary outcome was clinically significant delayed PPB, which was defined as occurrence of repeat colonoscopy with the need of haemostasis to control bleeding within 30 days after the index colonoscopy. The secondary outcomes were blood transfusion requirement within 30 days of endoscopy and new-onset thromboembolic events within 30 days after the index colonoscopy, which was a composite end point of CVA, IHD, PE and DVT.[20]

Statistics

Data were analysed by R software (V.3.5.1; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed in mean (±SD). Categorical variables were presented as number (percentage). All statistical tests were two-sided. The primary and secondary end points were analysed using Cox proportional hazards regression. Statistical significance was taken as $p<0.05$. When multiple testing was taken into account, Bonferroni adjustment would be used.[27] An HR and an adjusted p value (ap) with an upper bound of 1 were generated.

We performed a two-step analysis to evaluate the PPB risk of each DOAC. First, we compared each DOAC with warfarin individually. Second, we performed a three-arm, head-to-head comparison between all three DOACs with multiple testing correction. To minimise the effect of potential confounding variables, we developed PS models between the respective DOAC and warfarin groups for PS weighting using the inverse probability of

Table 1 Imputed patient characteristics after balancing with the inverse probability of treatment weighting method

	Warfarin	Apixaban	SMD	Warfarin	Dabigatran	SMD	Warfarin	Rivaroxaban	SMD
n	2222	510		2222	604		2222	526	
Age (mean (SD))	69.85 (9.76)	72.29 (9.68)	0.250	69.75 (9.7)	72.16 (8.81)	0.260	69.69 (9.72)	71.19 (9.78)	0.154
Male (%)	1360 (61.2)	350 (68.6)	0.157	1369 (61.6)	386 (63.9)	0.049	1364 (61.4)	326 (62.0)	0.014
HAS-BLED (mean (SD))	1.76 (1.26)	1.96 (1.14)	0.163	1.75 (1.25)	1.91 (1.15)	0.135	1.74 (1.25)	1.78 (1.16)	0.032
CHA_2DS_2-VASc (mean (SD))	3.78 (1.97)	3.96 (1.79)	0.100	3.73 (1.95)	3.98 (1.79)	0.130	3.74 (1.95)	3.88 (1.81)	0.072
Laboratory results									
Haemoglobin (mean (SD))	11.97 (2.55)	12.06 (2.36)	0.037	12.02 (2.54)	12.51 (2.47)	0.196	12 (2.54)	12.18 (2.48)	0.073
Platelet (mean (SD))	204.14 (75.81)	218.13 (77.76)	0.182	203.89 (75.17)	210 (66.0)	0.086	204.63 (75.77)	211.88 (75.82)	0.096
aPTT (mean (SD))	34.03 (7.95)	32.69 (5.77)	0.193	34.22 (8.23)	34.3 (9.28)	0.010	34 (7.96)	32.85 (6.34)	0.160
INR (mean (SD))	1.32 (0.34)	1.27 (0.33)	0.138	1.32 (0.34)	1.26 (0.34)	0.180	1.32 (0.34)	1.29 (0.34)	0.097
Bilirubin (mean (SD))	15.11 (10.05)	14.5 (10.11)	0.061	15.15 (10.05)	13.96 (7.79)	0.133	15 (10.01)	13.89 (8.76)	0.118
ALP (mean (SD))	81.03 (42.68)	84.74 (46.78)	0.083	80.59 (42.38)	74.94 (31.89)	0.151	80.81 (42.41)	79.4 (28.92)	0.039
ALT (mean (SD))	21.94 (14.92)	21.25 (15.07)	0.046	22.06 (15.0)	20.33 (12.13)	0.127	21.88 (14.77)	21.18 (12.63)	0.051
Creatinine (mean (SD))	115.53 (111.24)	104.76 (53.58)	0.123	113.4 (106.68)	95.24 (34.95)	0.229	113.71 (107.44)	95.85 (34.78)	0.224
Urea (mean (SD))	7.09 (4.49)	6.8 (3.48)	0.072	6.99 (4.37)	6.14 (2.69)	0.234	7 (4.37)	6.41 (3.17)	0.155
Indication of anticoagulation									
Thromboembolism (%)	229 (10.3)	42 (8.2)	0.072	227 (10.2)	39 (6.4)	0.139	242 (10.9)	85 (16.1)	0.155
Atrial fibrillation (%)	1369 (61.6)	359 (70.4)	0.188	1364 (61.4)	425 (70.3)	0.189	1353 (60.9)	336 (63.8)	0.062
Cardiac arrhythmia (%)	256 (11.5)	79 (15.4)	0.114	253 (11.4)	73 (12.1)	0.023	253 (11.4)	59 (11.3)	0.002
Valvular heart disease (%)	671 (30.2)	38 (7.4)	0.608	662 (29.8)	24 (3.9)	0.739	662 (29.8)	33 (6.3)	0.642
Comorbidities									
CHF (%)	471 (21.2)	119 (23.4)	0.053	460 (20.7)	91 (15.1)	0.148	462 (20.8)	96 (18.3)	0.061
MI (%)	67 (3.0)	32 (6.3)	0.159	62 (2.8)	30 (5.0)	0.113	64 (2.9)	21 (3.9)	0.059
Hypertension (%)	902 (40.6)	266 (52.2)	0.235	891 (40.1)	301 (49.8)	0.194	893 (40.2)	235 (44.6)	0.088
Stroke (%)	253 (11.4)	81 (15.9)	0.131	249 (11.2)	106 (17.5)	0.179	242 (10.9)	63 (12.0)	0.035
ICH (%)	113 (5.1)	11 (2.2)	0.153	111 (5.0)	18 (3.0)	0.100	109 (4.9)	8 (1.5)	0.192
PVD (%)	53 (2.4)	12 (2.3)	0.005	51 (2.3)	2 (0.3)	0.174	51 (2.3)	7 (1.4)	0.072
DM (%)	344 (15.5)	105 (20.6)	0.133	329 (14.8)	101 (16.7)	0.052	331 (14.9)	80 (15.3)	0.010
DM complications (%)	73 (3.3)	20 (3.9)	0.035	69 (3.1)	18 (2.9)	0.011	69 (3.1)	24 (4.5)	0.071
Mild liver disease (%)	16 (0.7)	2 (0.3)	0.062	16 (0.7)	7 (1.2)	0.048	16 (0.7)	0 (0.0)	0.118
Severe liver disease (%)	7 (0.3)	1 (0.1)	0.036	7 (0.3)	4 (0.6)	0.055	4 (0.2)	0 (0.0)	0.071
Renal disease (%)	136 (6.1)	33 (6.4)	0.013	129 (5.8)	5 (0.8)	0.285	129 (5.8)	14 (2.7)	0.152
Peptic ulcer (%)	73 (3.3)	19 (3.8)	0.031	71 (3.2)	12 (2.0)	0.077	73 (3.3)	21 (3.9)	0.036
Pulmonary disease (%)	147 (6.6)	27 (5.3)	0.053	142 (6.4)	33 (5.4)	0.043	151 (6.8)	35 (6.6)	0.009
CT disease (%)	16 (0.7)	3 (0.6)	0.013	16 (0.7)	2 (0.4)	0.045	16 (0.7)	3 (0.6)	0.013
Dementia (%)	13 (0.6)	1 (0.2)	0.057	13 (0.6)	7 (1.2)	0.064	13 (0.6)	0 (0.0)	0.108
Cancer (%)	140 (6.3)	56 (10.9)	0.164	140 (6.3)	47 (7.8)	0.057	140 (6.3)	39 (7.4)	0.046
Metastatic cancer (%)	20 (0.9)	2 (0.4)	0.055	20 (0.9)	4 (0.7)	0.029	20 (0.9)	3 (0.6)	0.026
Drugs									
Aspirin (%)	320 (14.4)	82 (16.1)	0.048	318 (14.3)	106 (17.5)	0.088	316 (14.2)	64 (12.2)	0.060
Other antiplatelets (%)	31 (1.4)	16 (3.1)	0.113	29 (1.3)	10 (1.6)	0.019	29 (1.3)	12 (2.2)	0.066
Heparin bridging (%)	1187 (53.4)	193 (37.8)	0.317	1144 (51.5)	213 (35.3)	0.332	1173 (52.8)	199 (37.9)	0.302
Polyp details									
Polyp number (mean (SD))	1.76 (1.39)	2 (1.68)	0.153	1.75 (1.37)	1.85 (1.44)	0.068	1.76 (1.37)	1.8 (1.36)	0.031
High-risk lesion (%)	502 (22.6)	115 (22.5)	0.003	491 (22.1)	147 (24.4)	0.054	493 (22.2)	93 (17.7)	0.113
Low-risk lesion (%)	2084 (93.8)	494 (96.8)	0.140	2084 (93.8)	566 (93.7)	0.004	2086 (93.9)	503 (95.7)	0.080
Right-sided (%)	1358 (61.1)	343 (67.2)	0.128	1353 (60.9)	375 (62.1)	0.024	1362 (61.3)	349 (66.3)	0.104
Left-sided (%)	1467 (66.0)	344 (67.5)	0.033	1462 (65.8)	381 (63)	0.059	1462 (65.8)	344 (65.4)	0.010
Institute/Cluster (%)			0.240			0.233			0.213
A	256 (11.5)	64 (12.5)		258 (11.6)	86 (14.3)		262 (11.8)	72 (13.7)	
B	398 (17.9)	97 (19.1)		382 (17.2)	80 (13.3)		376 (16.9)	72 (13.6)	
C	293 (13.2)	34 (6.7)		296 (13.3)	53 (8.7)		289 (13.0)	50 (9.6)	
D	182 (8.2)	40 (7.8)		182 (8.2)	71 (11.8)		213 (9.6)	68 (13.0)	
E	420 (18.9)	100 (19.7)		422 (19.0)	106 (17.5)		409 (18.4)	114 (21.6)	
F	416 (18.7)	120 (23.5)		418 (18.8)	132 (21.9)		418 (18.8)	105 (19.9)	
G	260 (11.7)	54 (10.6)		264 (11.9)	75 (12.4)		256 (11.5)	45 (8.6)	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastic time; CHF, congestive heart failure; CT, connective tissue; DM, diabetes mellitus; ICH, intracerebral haemorrhage; INR, international normalised ratio; MI, myocardial infarction; PVD, peripheral vascular disease; SMD, standardised mean difference.

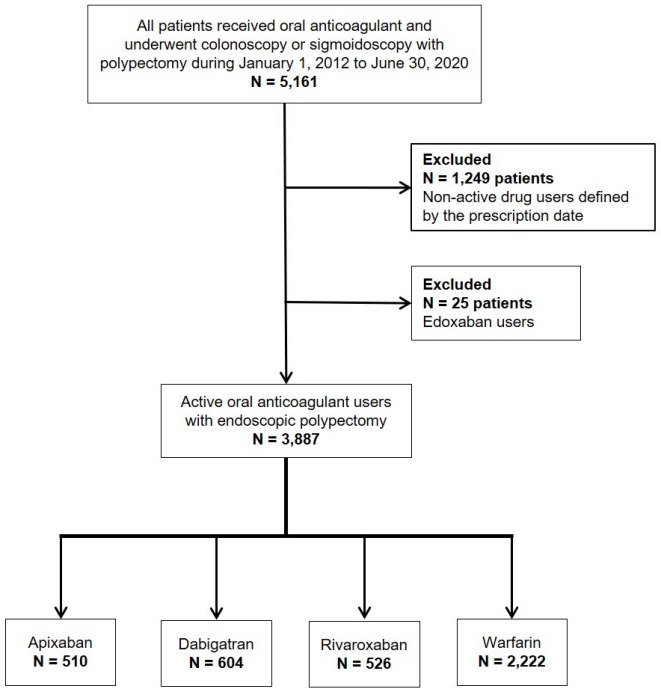

Figure 1 Study flow diagram.

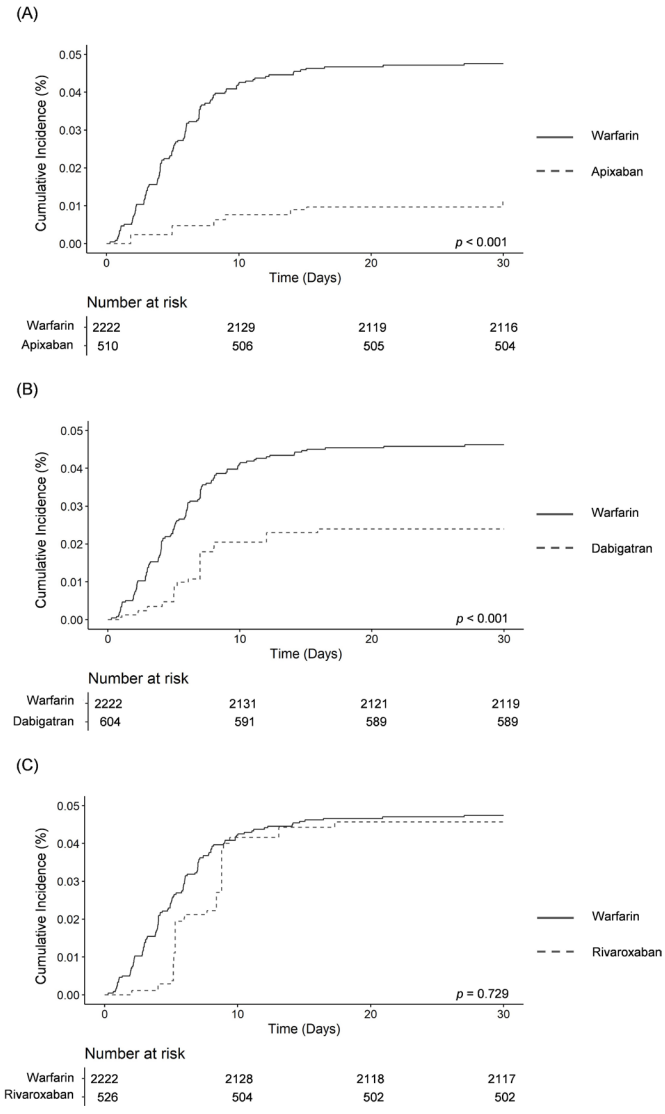

Figure 2 Kaplan-Meier curves for primary outcome (rate of rescope) between warfarin-direct oral anticoagulants (univariate analysis). (A) Warfarin versus apixaban; (B) warfarin versus dabigatran; (C) warfarin versus rivaroxaban.

treatment weighting (IPTW) method.[28] Three separate models were developed for each of the warfarin-DOAC comparisons. Another three-arm model was developed for the between-DOAC comparison. To estimate the respective PS of each patient, we performed generalised boosted models (GBM) incorporating the following patient and endoscopic factors: age, sex, 9 baseline laboratory values, 19 types of background comorbidities, any concurrent use of antiplatelet agents or heparin bridging, polyp characteristics (number, location and histopathology) and institutes/clusters performing the procedures (table 1). We minimised the mean and maximum of absolute standardised mean difference (ASMD) and Kolmogorov-Smirnov statistic as the four stopping rules to determine the corresponding optimal iteration of GBM. The stopping rule with overall the best subgroup balance and effective sample size was adopted. GBM for PS has been proven to have less prediction error and provide more stable weights than logistic regression.[29] In the IPTW analysis between warfarin and DOACs, we applied average treatment effect on the treated weighting to estimate the average treatment effect in the treated cohort, while we used average treatment effect in the IPTW analysis between DOACs.[30]

For both comparisons, the balance in the baseline characteristics between the treatment and control groups were evaluated before and after PS weighting by using ASMD. A value of below 0.1 indicated a good balance. Variables that failed to achieve an ASMD of <0.1 were adjusted in the doubly robust model. Missing baseline data were assumed to be missing at random. They were replaced with substituted values by multiple imputation with chained equations to create 20 complete data sets after the first 10 iterations. The imputed variables, in descending order of missingness, were aPTT (19.5%), INR (15.5%), bilirubin (12.8%), ALP (12.8%), ALT (12.8%), haemoglobin (10.7%), platelet (10.5%), urea (10.5%) and creatinine (10.4%). Imputed values were constrained within plausible ranges.

As a sensitivity analysis, we repeated the main analysis with complete case analysis by only including patients without missed baseline data (ie, without imputation). Due to the limitation of electronic database, we also manually reviewed the endoscopy records in hospitals of our institute to capture data on additional endoscopic factors. The data on polyp size, polyp morphology, endoscopic resection method, application of prophylactic clipping and endoscopic stigmata of recent haemorrhage were captured and included in the sensitivity analysis. Subgroup analysis was performed based on advanced age (≥70 years old), high CHA_2DS_2-VASc scores (≥4), high HAS-BLED scores (≥3), concomittant use of antiplatelet drugs or heparin bridging, different locations of polyps and different doses of DOAC.

RESULTS

Patient characteristics

From 1 January 2012 to 30 June 2020, we identified 5161 patients who received an oral anticoagulant (apixaban, dabigatran, edoxaban, rivaroxaban or warfarin) and underwent colonoscopy or sigmoidoscopy with polypectomy. After excluding 1249 non-active drug users and 25 edoxaban users, a total of 3887 patients were included in the final analysis. Among these

Table 2 Primary outcome (postpolypectomy bleeding with rescope), secondary outcomes (blood transfusion and composite outcome of thromboembolic events) for warfarin-direct oral anticoagulants comparisons

Outcome	Comparison	Analysis	Drug	Result (95% CI)	P value
Primary (postpolypectomy bleeding with rescope)*	WA	Univariate	Warfarin	Reference	NA
			Apixaban	0.233 (0.149 to 0.363)	<0.001
		Multivariate	Warfarin	Reference	NA
			Apixaban	0.386 (0.237 to 0.630)	<0.001
	WD	Univariate	Warfarin	Reference	NA
			Dabigatran	0.511 (0.369 to 0.707)	<0.001
		Multivariate	Warfarin	Reference	NA
			Dabigatran	0.908 (0.618 to 1.336)	0.626
	WR	Univariate	Warfarin	Reference	NA
			Rivaroxaban	0.953 (0.727 to 1.251)	0.729
		Multivariate	Warfarin	Reference	NA
			Rivaroxaban	1.664 (1.204 to 2.299)	0.002
Secondary (blood transfusion)†	WA	Univariate	Warfarin	Reference	NA
			Apixaban	0.960 (0.942 to 0.977)	<0.001
		Multivariate	Warfarin	Reference	NA
			Apixaban	0.977 (0.959 to 0.996)	0.020
	WD	Univariate	Warfarin	Reference	NA
			Dabigatran	0.976 (0.958 to 0.994)	0.011
		Multivariate	Warfarin	Reference	NA
			Dabigatran	1.012 (0.993 to 1.032)	0.216
	WR	Univariate	Warfarin	Reference	NA
			Rivaroxaban	0.958 (0.941 to 0.976)	<0.001
		Multivariate	Warfarin	Reference	NA
			Rivaroxaban	0.989 (0.971 to 1.008)	0.246
Secondary (composite outcome of thromboembolic events)*	WA	Univariate	Warfarin	Reference	NA
			Apixaban	0.297 (0.152 to 0.582)	<0.001
		Multivariate	Warfarin	Reference	NA
			Apixaban	0.219 (0.107 to 0.448)	<0.001
	WD	Univariate	Warfarin	Reference	NA
			Dabigatran	1.340 (0.895 to 2.007)	0.155
		Multivariate	Warfarin	Reference	NA
			Dabigatran	1.132 (0.700 to 1.832)	0.613
	WR	Univariate	Warfarin	Reference	NA
			Rivaroxaban	1.045 (0.672 to 1.623)	0.846
		Multivariate	Warfarin	Reference	NA
			Rivaroxaban	1.304 (0.793 to 2.145)	0.296

Results were generated using imputed data.
Primary outcome (rescope) and secondary outcome (composite outcome of thromboembolic events) results are generated using survival analysis and presented in the form of HR, while the secondary outcome (blood transfusion) result is generated using logistic regression and presented in the form of OR.
*Results for the primary outcome (rescope) and secondary outcome (composite outcome of thromboembolic events) are provided in HR.
†Results for secondary outcome (blood transfusion) are provided in OR.
WR warfarin rivaroxaban.NA, not available; WA, warfarin apixaban; WD, warfarin dabigatran.

patients, 510, 604, 526 and 2222 patients received apixaban, dabigatran, rivaroxaban and warfarin, respectively (figure 1).

The baseline characteristics of warfarin and each individual DOAC group are summarised in online supplemental table 1. We performed PS weighting to balance the included variables. A higher proportion of patients with younger age, underlying valvular heart disease and the use of bridging therapy with heparin was found in the warfarin group (table 1). All unbalanced variables were included in the subsequent doubly robust model with Cox regression multivariate analysis.

Outcome analysis

Warfarin versus apixaban

We first compared warfarin with each DOAC individually by respective PS models. For the primary outcome, apixaban was associated with a lower risk of clinically significant PPB requiring rescope for haemostasis (30-day PPB rate: 1.4% in apixaban vs 5.2% in warfarin, median time to event: 9.0 days in apixaban vs 4.9 days in warfarin) compared with warfarin. The adjusted HR (aHR) of apixaban over warfarin was 0.39 (95% CI 0.24 to 0.63, p<0.001) in the doubly robust model (figure 2, table 2). In subgroup analysis, we observed a lower PPB risk for apixaban in patients aged ≥70 years (aHR 0.27, 95% CI 0.14 to 0.53, p<0.001) and those with a HAS-BLED score <3 (aHR 0.37, 95% CI 0.19 to 0.69, p=0.002). Apixaban was associated with a lower PPB risk in either left-sided polyps or right-sided polyps. Apixaban was also associated with a lower PPB risk in patients without concurrent antiplatelets. All doses of apixaban were associated with a lower PPB risk than warfarin in the doubly robust model (figure 3).

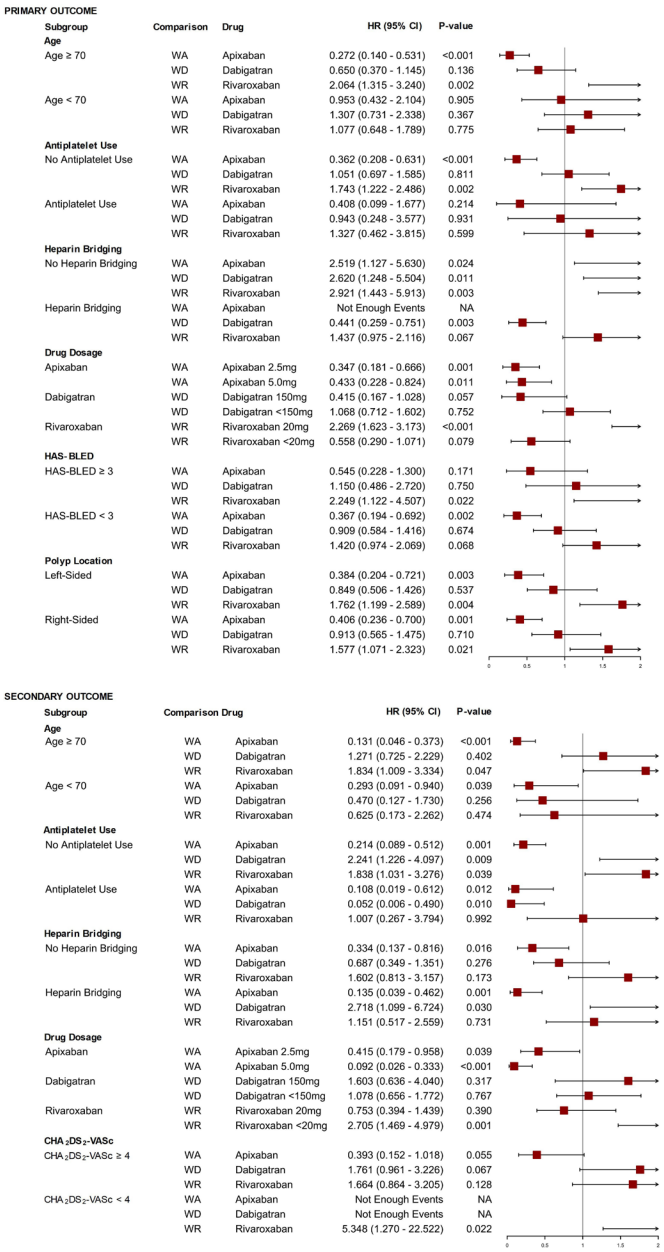

Figure 3 Forest plot comparing primary outcome (rate of rescope) and secondary outcome (rate of the composite outcome of thromboembolic events) among warfarin-direct oral anticoagulants subgroups. WA, warfarin apixaban; WD, warfarin dabigatran; WR warfarin rivaroxaban.

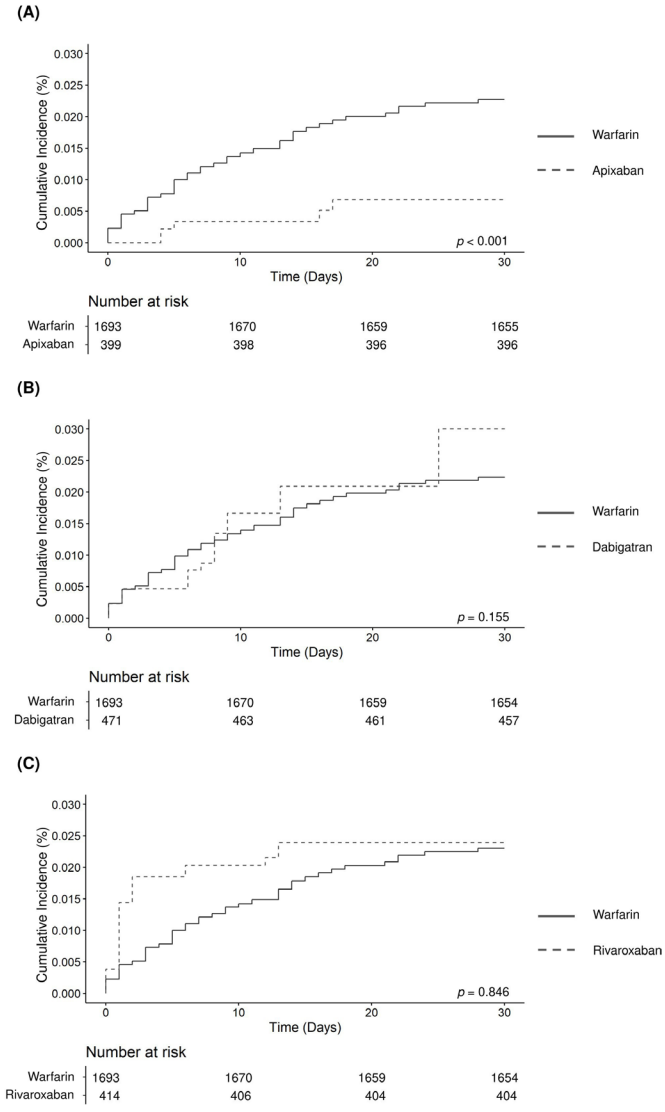

Figure 4 Kaplan-Meier curves for secondary outcome (rate of the composite outcome of thromboembolic events) between warfarin-direct oral anticoagulants (univariate analysis). (A) Warfarin versus apixaban; (B) warfarin versus dabigatran; (C) warfarin versus rivaroxaban.

For the secondary outcomes, apixaban was associated with a lower risk of 30-day blood transfusion requirement. The OR was 0.977 (95% CI 0.959 to 0.996, p=0.02) (table 2). Apixaban was also associated with a lower risk of thromboembolism after colonoscopy than warfarin (30-day thromboembolic event rate: 1.0% in apixaban vs 2.4% in warfarin, median time to event: 10.5 days in apixaban vs 6.5 days in warfarin). The aHR was 0.22 (95% CI 0.11 to 0.45, p<0.001) in the doubly robust model (figure 4, table 2). In subgroup analysis, we observed a lower thromboembolic risk for apixaban in patients of all ages, with or without concurrent antiplatelets and heparin bridging. All doses of apixaban were associated with a lower thromboembolic risk. Apixaban had a trend towards significance (aHR 0.39, 95% CI 0.15 to 1.02, p=0.055) to be associated with a lower thromboembolic risk in patients with high CHA_2DS_2-VASc scores ≥4 (figure 3).

Warfarin versus dabigatran

For the primary outcome, in univariate analysis, dabigatran was associated with a lower PPB risk than warfarin (30-day PPB rate: 2.3% in dabigatran vs 5.2% in warfarin, median time to event: 5.1 days in dabigatran vs 4.9 days in warfarin). The aHR was 0.51 (95% CI 0.37 to 0.71, p<0.001) (figure 2), but the significance was no longer observed in the doubly robust model (aHR 0.91, 95% CI 0.62 to 1.34, p=0.626) (table 2). In subgroup analysis, there was no significant difference observed among different age groups, HAS-BLED scores or polyp locations. We observed a higher risk of PPB in patients using dabigatran without heparin bridging (aHR 2.62, 95% CI 1.25 to 5.50, p=0.011) (figure 3).

For secondary outcome, no significant difference was observed between two groups for 30-day blood transfusion requirement (OR 1.01, 95% CI 0.99 to 1.03, p=0.216). Dabigatran was also similar to warfarin in terms of thromboembolic risk (30-day thromboembolic event rate: 2.1% in dabigatran vs 2.4% in

Table 3 Imputed patient characteristics after balancing with the inverse probability of treatment weighting method

	Apixaban	Dabigatran	SMD	Apixaban	Rivaroxaban	SMD	Dabigatran	Rivaroxaban	SMD
n	510	604		510	526		604	526	
Age (mean (SD))	73.98 (8.73)	73.53 (8.64)	0.052	73.98 (8.73)	73.13 (8.84)	0.097	73.53 (8.64)	73.13 (8.84)	0.047
Male (%)	319 (62.5)	374 (61.9)	0.013	319 (62.5)	324 (61.6)	0.018	374 (61.9)	324 (61.6)	0.005
HAS-BLED (mean (SD))	1.88 (1.07)	1.91 (1.1)	0.033	1.88 (1.07)	1.86 (1.14)	0.011	1.91 (1.1)	1.86 (1.14)	0.043
CHA_2DS_2-VASc (mean (SD))	3.95 (1.78)	4.02 (1.77)	0.037	3.95 (1.78)	3.96 (1.9)	0.005	4.02 (1.77)	3.96 (1.9)	0.031
Laboratory results									
Haemoglobin (mean (SD))	12.22 (2.31)	12.3 (2.44)	0.032	12.22 (2.31)	12.16 (2.49)	0.025	12.3 (2.44)	12.16 (2.49)	0.055
Platelet (mean (SD))	214.55 (71.73)	212.09 (70.2)	0.035	214.55 (71.73)	213.9 (72.29)	0.009	212.09 (70.2)	213.9 (72.29)	0.025
aPTT (mean (SD))	32.28 (5.82)	33.39 (7.87)	0.160	32.28 (5.82)	32.4 (6.34)	0.020	33.39 (7.87)	32.4 (6.34)	0.138
INR (mean (SD))	1.19 (0.27)	1.21 (0.27)	0.059	1.19 (0.27)	1.21 (0.28)	0.056	1.21 (0.27)	1.21 (0.28)	0.003
Bilirubin (mean (SD))	13.66 (8.51)	13.68 (7.45)	0.003	13.66 (8.51)	13.63 (8.71)	0.003	13.68 (7.45)	13.63 (8.71)	0.007
ALP (mean (SD))	78.69 (35.9)	76.75 (34.04)	0.056	78.69 (35.9)	77.04 (27.9)	0.051	76.75 (34.04)	77.04 (27.9)	0.009
ALT (mean (SD))	21.4 (15.38)	20.85 (13.16)	0.038	21.4 (15.38)	20.86 (13.01)	0.038	20.85 (13.16)	20.86 (13.01)	<0.001
Creatinine (mean (SD))	100.13 (50.37)	94.53 (30.6)	0.134	100.13 (50.37)	97.75 (35.02)	0.055	94.53 (30.6)	97.75 (35.02)	0.098
Urea (mean (SD))	6.64 (3.13)	6.28 (2.62)	0.125	6.64 (3.13)	6.59 (3.14)	0.016	6.28 (2.62)	6.59 (3.14)	0.107
Indication of anticoagulation									
Thromboembolism (%)	25 (4.9)	24 (4.0)	0.039	25 (4.9)	40 (7.6)	0.114	24 (4.0)	40 (7.6)	0.152
Atrial fibrillation (%)	360 (70.5)	428 (70.8)	0.008	360 (70.5)	349 (66.3)	0.091	428 (70.8)	349 (66.3)	0.099
Cardiac arrhythmia (%)	72 (14.1)	71 (11.7)	0.070	72 (14.1)	59 (11.2)	0.086	71 (11.7)	59 (11.2)	0.016
Valvular heart disease (%)	21 (4.2)	21 (3.4)	0.042	21 (4.2)	22 (4.2)	0.001	21 (3.4)	22 (4.2)	0.043
Comorbidities									
CHF (%)	102 (20.0)	102 (16.9)	0.080	102 (20.0)	88 (16.7)	0.087	102 (16.9)	88 (16.7)	0.007
MI (%)	24 (4.8)	20 (3.3)	0.074	24 (4.8)	24 (4.5)	0.014	20 (3.3)	24 (4.5)	0.060
Hypertension (%)	252 (49.5)	296 (49.0)	0.009	252 (49.5)	244 (46.3)	0.064	296 (49.0)	244 (46.3)	0.056
Stroke (%)	79 (15.4)	95 (15.7)	0.006	79 (15.4)	60 (11.5)	0.115	95 (15.7)	60 (11.5)	0.121
ICH (%)	14 (2.7)	9 (1.5)	0.085	14 (2.7)	13 (2.4)	0.018	9 (1.5)	13 (2.4)	0.067
PVD (%)	6 (1.2)	2 (0.4)	0.090	6 (1.2)	8 (1.6)	0.026	2 (0.4)	8 (1.6)	0.114
DM (%)	98 (19.3)	101 (16.7)	0.067	98 (19.3)	80 (15.3)	0.106	101 (16.7)	80 (15.3)	0.039
DM complications (%)	14 (2.7)	21 (3.5)	0.046	14 (2.7)	20 (3.8)	0.060	21 (3.5)	20 (3.8)	0.014
Mild liver disease (%)	1 (0.2)	5 (0.8)	0.079	1 (0.2)	0 (0.0)	0.068	5 (0.8)	0 (0.0)	0.127
Severe liver disease (%)	1 (0.1)	1 (0.2)	0.019	1 (0.1)	0 (0.0)	0.051	1 (0.2)	0 (0.0)	0.064
Renal disease (%)	17 (3.3)	4 (0.7)	0.186	17 (3.3)	14 (2.7)	0.033	4 (0.7)	14 (2.7)	0.157
Peptic ulcer (%)	19 (3.7)	8 (1.3)	0.152	19 (3.7)	17 (3.3)	0.020	8 (1.3)	17 (3.3)	0.134
Pulmonary disease (%)	36 (7.1)	40 (6.6)	0.020	36 (7.1)	35 (6.6)	0.020	40 (6.6)	35 (6.6)	<0.001
CT disease (%)	4 (0.8)	3 (0.5)	0.038	4 (0.8)	4 (0.8)	0.007	3 (0.5)	4 (0.8)	0.045
Dementia (%)	1 (0.2)	5 (0.9)	0.099	1 (0.2)	0 (0.0)	0.057	5 (0.9)	0 (0.0)	0.133
Cancer (%)	40 (7.9)	42 (7.0)	0.035	40 (7.9)	26 (4.9)	0.123	42 (7.0)	26 (4.9)	0.088
Metastatic cancer (%)	2 (0.3)	2 (0.4)	0.011	2 (0.3)	4 (0.8)	0.065	2 (0.4)	4 (0.8)	0.055
Drugs									
Aspirin (%)	71 (14.0)	97 (16.1)	0.058	71 (14.0)	69 (13.2)	0.022	97 (16.1)	69 (13.2)	0.081
Other antiplatelets (%)	14 (2.8)	8 (1.3)	0.109	14 (2.8)	13 (2.5)	0.022	8 (1.3)	13 (2.5)	0.088
Heparin bridging (%)	82 (16.0)	74 (12.2)	0.111	82 (16.0)	80 (15.2)	0.022	74 (12.2)	80 (15.2)	0.089
Polyp details									
Polyp number (mean (SD))	1.91 (1.49)	1.77 (1.32)	0.097	1.91 (1.49)	1.78 (1.31)	0.091	1.77 (1.32)	1.78 (1.31)	0.007
High-risk lesion (%)	111 (21.8)	124 (20.5)	0.031	111 (21.8)	106 (20.1)	0.043	124 (20.5)	106 (20.1)	0.012
Low-risk lesion (%)	490 (96.0)	571 (94.5)	0.072	490 (96.0)	497 (94.4)	0.076	571 (94.5)	497 (94.4)	0.004
Right-sided (%)	351 (68.9)	384 (63.6)	0.113	351 (68.9)	349 (66.4)	0.053	384 (63.6)	349 (66.4)	0.060
Left-sided (%)	343 (67.3)	385 (63.8)	0.074	343 (67.3)	352 (67.0)	0.005	385 (63.8)	352 (67.0)	0.069
Institute/Cluster (%)			0.124			0.167			0.138
A	72 (14.2)	87 (14.4)		72 (14.2)	76 (14.4)		87 (14.4)	76 (14.4)	
B	88 (17.3)	91 (15.1)		88 (17.3)	76 (14.5)		91 (15.1)	76 (14.5)	
C	38 (7.4)	50 (8.3)		38 (7.4)	45 (8.6)		50 (8.3)	45 (8.6)	
D	54 (10.5)	77 (12.8)		54 (10.5)	78 (14.9)		77 (12.8)	78 (14.9)	
E	106 (20.8)	112 (18.5)		106 (20.8)	100 (19.0)		112 (18.5)	100 (19.0)	
F	107 (21.0)	122 (20.2)		107 (21.0)	113 (21.4)		122 (20.2)	113 (21.4)	
G	45 (8.9)	65 (10.8)		45 (8.9)	38 (7.2)		65 (10.8)	38 (7.2)	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastic time; CHF, congestive heart failure; CT, connective tissue; DM, diabetes mellitus; ICH, intracerebral haemorrhage; INR, international normalised ratio; MI, myocardial infarction; PVD, peripheral vascular disease; SMD, standardised mean difference.

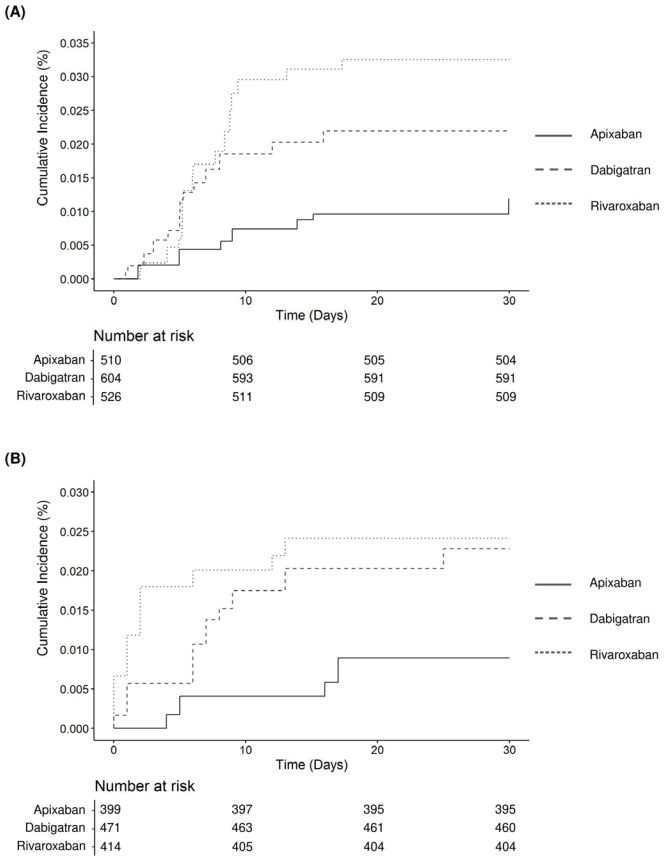

Figure 5 Kaplan-Meier curves for (A) primary outcome (rate of rescope) and (B) secondary outcome (rate of the composite outcome of thromboembolic events) for between-direct oral anticoagulants comparisons (univariate analysis with Bonferroni adjustment). Primary outcome: apixaban versus dabigatran, p=0.126; apixaban versus rivaroxaban, p=0.001; dabigatran versus rivaroxaban, p=0.266. Secondary outcome: apixaban versus dabigatran, p=0.037; apixaban versus rivaroxaban, p=0.022; dabigatran versus rivaroxaban, p=1.000.

warfarin, median time to event: 6.5 days in dabigatran vs 6.5 days in warfarin). The aHR was 1.13 (95% CI 0.70 to 1.83, p=0.613) (figure 4). No significant difference was observed in subgroup analysis of different age groups or CHA_2DS_2-VASc scores. We observed a lower thromboembolic risk in patients using dabigatran with antiplatelets concurrently, and vice versa in patients without antiplatelets (figure 3).

Warfarin versus rivaroxaban

Rivaroxaban was associated with a higher risk for primary outcome than warfarin in the doubly robust model (aHR 1.66, 95% CI 1.20 to 2.30, p=0.002) (30-day PPB rate: 3.2% in rivaroxaban vs 5.2% in warfarin, median time to event: 6.0 days in rivaroxaban vs 4.9 days in warfarin) (figure 2, table 2). In subgroup analysis, we observed a higher risk of PPB in rivaroxaban group in older patients and those without concomittant antiplatelets or heparin bridging. There was a higher PPB risk observed in rivaroxaban group at both right-sided and left-sided colon. High-dose rivaroxaban (20 mg daily) was associated with a higher PPB risk than warfarin in the doubly robust model (figure 3).

For the secondary outcomes, rivaroxaban was similar to warfarin for 30-day blood transfusion requirement (OR 0.99, 95% CI 0.97 to 1.01, p=0.246) and 30-day thromboembolic event rate (2.2% in rivaroxaban vs 2.4% in warfarin, median time to event: 2.0 days in rivaroxaban vs 6.5 days in warfarin, aHR 1.30, 95% CI 0.79 to 2.15, p=0.296) (figure 4). In subgroup analysis, we observed a significantly higher risk of thromboembolic events in those ≥70 years of age or without concurrent antiplatelets. Low-dose rivaroxaban (<20 mg daily) was associated with a higher thromboembolic risk (figure 3).

Apixaban versus dabigatran versus rivaroxaban

With the above findings, we created another separate PS model to evaluate the outcomes among three DOACs as a head-to-head comparison. The baseline patient characteristics before and after balancing with the IPTW method and imputation are summarised in online supplemental table 2 and table 3, respectively. Slightly more patients had renal diseases and peptic ulcers in apixaban and rivaroxaban groups when compared with dabigatran group. Otherwise, the other parameters were closely balanced between individual DOAC groups.

For the primary outcome, apixaban was associated with a lower 30-day PPB rate than dabigatran and rivaroxaban, requiring endoscopic re-intervention (1.4% in apixaban vs 2.3% in dabigatran vs 3.2% in rivaroxaban). Using a doubly robust model with Bonferroni adjustment, the aHR of dabigatran over apixaban was 2.23 (95% CI 1.04 to 4.77, ap=0.035) and the aHR of rivaroxaban over apixaban was 2.72 (95% CI 1.35 to 5.48, ap=0.002) (figure 5, table 4). In the subgroup analysis, apixaban was associated with lower PPB risk than dabigatran and rivaroxaban in patients aged ≥70 years and those without concurrent antiplatelet drugs. Also, we observed a lower PPB risk for apixaban over rivaroxaban in patients with a HAS-BLED score <3 and polyps in both sides of colon (figure 6). On the contrary, we did not observe any significant difference between dabigatran and rivaroxaban (aHR 1.56, 95% CI 0.88 to 2.75, ap=0.186).

For the secondary outcome, 30-day blood transfusion requirement did not differ among three groups. On the other hand, apixaban was associated with a lower 30-day thromboembolic event rate than dabigatran and rivaroxaban (1.0% in apixaban vs 2.1% in dabigatran vs 2.2% in rivaroxaban). The aHR of dabigatran over apixaban was 2.60 (95% CI 1.06 to 6.41, ap=0.033) and the aHR of rivaroxaban over apixaban was 2.96 (95% CI 1.19 to 7.37, ap=0.013). (figure 5) Similar finding was observed in a subgroup of patients aged ≥70 years and high CHA_2DS_2-VASc score ≥4 (figure 6, table 4). There was no significant difference observed between rivaroxaban and dabigatran groups (aHR 1.21, 95% CI 0.62 to 2.34, ap=1.000).

Sensitivity analysis

We repeated complete case analysis by including patients without missed baseline data only (ie, without imputation). We observed similar findings as the main analysis. In complete case analysis of warfarin-DOAC comparisons, apixaban was associated with a lower risk than warfarin in both primary outcome (aHR 0.30, 95% CI 0.17 to 0.54, p<0.001) and secondary outcomes of blood transfusion requirement (OR 0.97, 95% CI 0.95 to 0.99, p=0.008) and thromboembolic events (aHR 0.24, 95% CI 0.11 to 0.53, p=0.001). Rivaroxaban was associated with a higher risk than warfarin for primary outcome (aHR 2.05, 95% CI 1.45 to 2.88, p<0.001) (online supplemental table 3).

For the between-DOAC comparisons, rivaroxaban was associated with a higher PPB risk than apixaban (aHR 3.15, 95% CI 1.26 to 7.90, ap=0.008) in the doubly robust model after Bonferroni adjustment. However, for secondary outcome of

Table 4 Primary outcome (postpolypectomy bleeding with rescope), secondary outcomes (blood transfusion and composite outcome of thromboembolic events) for between-direct oral anticoagulants comparisons

Outcome	Comparison	Analysis	Drug	Result (aHR, 95% CI)*	ap value*
Primary (postpolypectomy bleeding with rescope)†	AD	Univariate	Apixaban	Reference	NA
			Dabigatran	1.859 (0.895 to 3.858)	0.126
		Multivariate	Apixaban	Reference	NA
			Dabigatran	2.228 (1.041 to 4.770)	0.035
	AR	Univariate	Apixaban	Reference	NA
			Rivaroxaban	2.769 (1.386 to 5.530)	0.001
		Multivariate	Apixaban	Reference	NA
			Rivaroxaban	2.722 (1.352 to 5.483)	0.002
	DR	Univariate	Dabigatran	Reference	NA
			Rivaroxaban	1.486 (0.852 to 2.592)	0.266
		Multivariate	Dabigatran	Reference	NA
			Rivaroxaban	1.558 (0.882 to 2.751)	0.186
Secondary (blood transfusion)‡	AD	Univariate	Apixaban	Reference	NA
			Dabigatran	1.009 (0.981 to 1.038)	1.000
		Multivariate	Apixaban	Reference	NA
			Dabigatran	1.013 (0.984 to 1.043)	0.814
	AR	Univariate	Apixaban	Reference	NA
			Rivaroxaban	0.994 (0.968 to 1.021)	1.000
		Multivariate	Apixaban	Reference	NA
			Rivaroxaban	0.995 (0.969 to 1.022)	1.000
	DR	Univariate	Dabigatran	Reference	NA
			Rivaroxaban	0.985 (0.958 to 1.012)	0.532
		Multivariate	Dabigatran	Reference	NA
			Rivaroxaban	0.980 (0.954 to 1.007)	0.236
Secondary (composite outcome of thromboembolic events)†	AD	Univariate	Apixaban	Reference	NA
			Dabigatran	2.566 (1.043 to 6.310)	0.037
		Multivariate	Apixaban	Reference	NA
			Dabigatran	2.602 (1.056 to 6.411)	0.033
	AR	Univariate	Apixaban	Reference	NA
			Rivaroxaban	2.728 (1.115 to 6.672)	0.022
		Multivariate	Apixaban	Reference	NA
			Rivaroxaban	2.960 (1.189 to 7.368)	0.013
	DR	Univariate	Dabigatran	Reference	NA
			Rivaroxaban	1.065 (0.550 to 2.062)	1.000
		Multivariate	Dabigatran	Reference	NA
			Rivaroxaban	1.206 (0.621 to 2.341)	1.000

Results were generated using imputed data. Primary outcome (rescope) and secondary outcome (composite outcome of thromboembolic events) results are generated using survival analysis and presented in the form of HR, while the secondary outcome (blood transfusion) result is generated using logistic regression and presented in the form of OR.
*Adjusted HR and adjusted p value by Bonferroni adjustment.
†Results for the primary outcome (rescope) and secondary outcome (composite outcome of thromboembolic events) are provided in HR.
‡Results for secondary outcome (blood transfusion) are provided in OR.
AD, apixaban dabigatran; aHR, adjusted HR; ap value, adjusted p value; AR, apixaban rivaroxaban; DR, dabigatran rivaroxaban; NA, not available.

thromboembolic events, the findings in main analysis were not reproduced in complete case analysis (online supplemental table 4).

We also performed sensitivity analysis by reviewing endoscopy records in hospitals of our institute to capture data on additional endoscopic factors. There was no significant difference in polyp size, polyp morphology, endoscopic resection method and rate of prophylactic clipping among warfarin and DOAC subgroups. More warfarin users (6.8%) had PPB with significant stigmata of haemorrhage such as active oozing, non-bleeding visible vessel and adherent clot. All patients with PPB received endoscopic haemostasis including epinephrine injection or mechanical clipping irrespective of the stigmata of haemorrhage (online supplemental table 5). For validation, we also manually reviewed the remaining 515 cases with no PPB event according to the procedure codes. There were only four patients (0.8%) who had minor per rectal bleeding clinically. They received diagnostic colonoscopies subsequently without any bleeding source identified.

In our institute, prophylactic clipping was applied in 41.7%–58.4% of cases in different oral anticoagulant subgroups. Twenty-three out of 298 patients (7.7%) had PPB despite prophylactic clipping, while 9 out of 249 patients (3.6%) had PPB without prophylactic clipping. A multivariate logistic regression model was performed to evaluate the effect of prophylactic clipping on PPB. In this analysis, prophylactic clipping was not an independent risk factor of PPB (OR 1.57, 95% CI 0.71 to 3.75, p=0.287). On the contrary, right-sided polyp location, endoscopic resection method involving electrocautery, use of warfarin and advanced age were independent risk factors of PPB (online supplemental table 6)

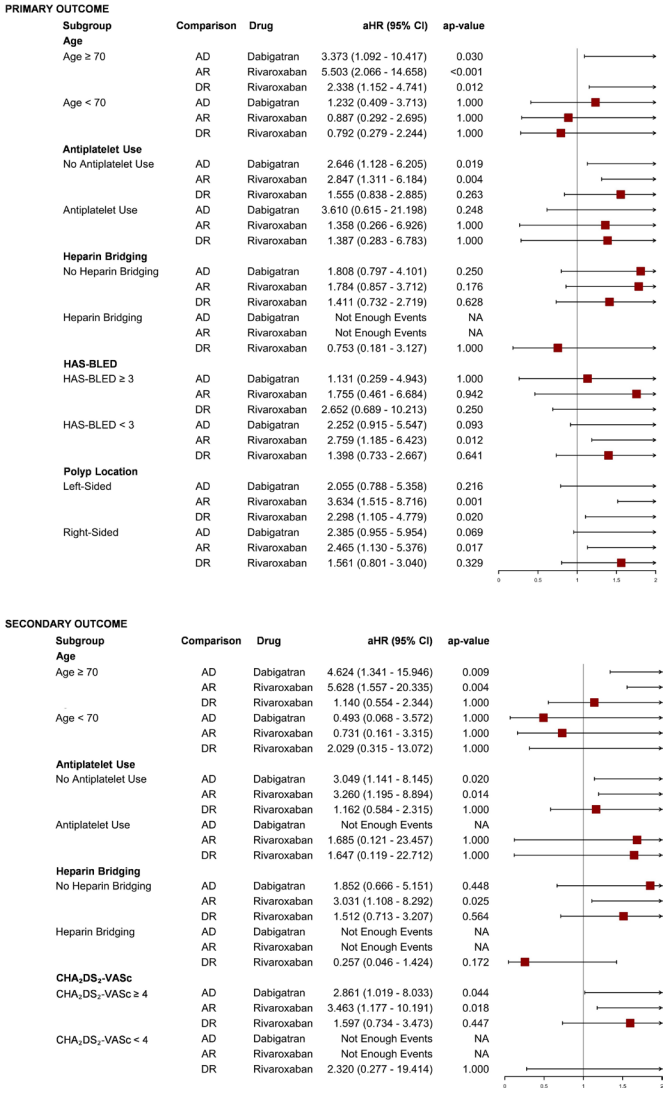

Figure 6 Forest plot comparing primary outcome (rate of rescope) and secondary outcome (rate of the composite outcome of thromboembolic events) among between-direct oral anticoagulants subgroups. aHR, adjusted HR; ap value, adjusted p value; AD, apixaban dabigatran; AR, apixaban rivaroxaban; DR dabigatran rivaroxaban; NA, not available.

DISCUSSION

In this population-based study, we found that compared to warfarin, apixaban was associated with a 61% and 78% relative risk reduction in the 30-day PPB and thromboembolism, respectively. It was particularly important in patients with advanced age or right-sided colonic polyps, who were associated with increased PPB risk independently.[6–9] These high-risk groups may potentially benefit from switching their oral anticoagulant to apixaban if feasible.

Limited retrospective data demonstrated conflicting results of PPB risk comparing warfarin and DOAC.[18–21] Of note, all of the studies combined all types of DOAC as a single group for analysis. However, we observed a possible intrinsic difference between each DOAC in GI bleeding risk.[31] Therefore, we compared each DOAC with warfarin individually, and performed a head-to-head comparison among three DOACs, using separate PS weighting models and IPTW methods. We also included all available potential confounding factors in our doubly robust model, including patient factors (demographics and comorbidities), medication factors (concurrent antiplatelet and heparin bridging) and endoscopic factors (polyp number, location and histopathology). We defined primary end point as clinically significant PPB requiring endoscopic intervention and excluded patients with minor and transient bleeding episodes which could be settled conservatively.

Our research supplemented the previous studies and provided novel data on peri-procedural anticoagulation use with several strengths. First, it was an industry-independent, territory-wide population-based study involving >3800 patients over 8 years. The electronic healthcare database used was highly representative and validated of the 7.4 million population in Hong Kong.[22 23] Second, we carefully balanced potential confounders in each group. We included all available patient, medication and endoscopic factors in the analysis. We performed sensitivity analysis by complete case analysis and internal validation from data of our institute. We also adopted Bonferroni adjustment for multiple testing to reduce type I errors. Third, our study involved a head-to-head comparison among three DOACs with a comparable number of patients. It addressed the current knowledge gap in the individual performance of different DOACs in post-polypectomy settings.

Our findings were consistent with those in the ARISTOTLE trial, which demonstrated a lower rate of bleeding and thromboembolic complications in apixaban than warfarin.[32] On the other hand, we observed a 1.6-fold higher risk of PPB in rivaroxaban than warfarin. Similar results had been reported in ROCKET-AF trial with an increased GI bleeding risk in rivaroxaban group.[33] In the head-to-head comparison by three-arm PS model, we also observed a 2.7-fold increased risk of PPB in rivaroxaban and 2.2-fold higher risk of PPB in dabigatran than apixaban. These findings echoed with the previous observational study showing an overall lower risk of GI bleeding in apixaban users.[31] We therefore concluded that apixaban was associated with better clinical outcomes than warfarin, dabigatran and rivaroxaban, in the post-procedural setting after colonic polypectomy.

There were limitations in our current study. First, despite our effort to include potential confounding factors as many as possible, we failed to match certain endoscopic factors such as polyp size and morphology because of the lack of data and coding in electronic database. Second, we could not retrieve all records of the endoscopic resection technique, which may potentially affect the PPB risks.[34] Third, there was no available data on the application of prophylactic clipping after polypectomy. However, two large randomised trials had conflicting results on the efficacy of prophylactic hemoclips to reduce PPB risk.[35 36] Additionally, in our sensitivity analysis, we found no significant difference in polyp size, polyp morphology, endoscopic resection method and prophylactic clipping rate between warfarin and DOAC groups within our institute. Also, prophylactic clipping was not an independent risk factor of PPB in our multivariate logistic regression model. Fourth, the database did not provide information on the timing of interruption or resumption of anticoagulation. In general, we followed the current international guidelines to withhold and resume anticoagulation for elective procedures in Hong Kong.[3–5] We also excluded patients who did not resume oral anticoagulants within 30 days after endoscopy. Fifth, we excluded edoxaban from the analysis due to its small sample size. Lastly, we could not capture the severity of PPB such as the haemodynamic status and endoscopic stigmata of haemorrhage.

In conclusion, our population-based study with propensity-weighting analysis demonstrated that apixaban was associated with a lower risk of bleeding and thromboembolic events than

warfarin, dabigatran and rivaroxaban after colonoscopic polypectomy. High-risk subgroups including older patients aged ≥70 years or those with right-sided polyps, may warrant special attention in their peri-procedural anticoagulation plan.

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Contributors LHSL was responsible for conception and design of study, data retrieval and drafting of manuscript; CLTG and TCFY were involved in data retrieval and statistical analysis; JWYM, SHW, KLYL, GLHW and SCN provided critical comments and review of manuscript; FKLC was involved in conception and supervision of study.

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