

Comparative effectiveness and safety of non-vitamin K antagonists oral anticoagulants (NOACs) and warfarin in daily clinical practice: A propensity weighted nationwide cohort study.

Supplementary material

Torben Bjerregaard Larsen, MD, PhD^{1,2}, Flemming Skjøth, MSc, PhD^{2,3}, Peter Brønnum Nielsen, MSc, PhD^{1,2}, Jette Kjældgaard Nordstrøm, MSc², Gregory Y.H. Lip, MD^{2,4}

Supplementary Table 1

Definitions on comorbidity and concomitant medication according to ICD-10 codes and ATC-codes. Conditions marked with † was used in the calculation of the CHA₂DS₂-VASc score. Conditions marked with # was used in the calculation of the HAS-BLED score.

Condition	International Classification of Diseases 10th revision (ICD-10) code	Anatomical Therapeutic Chemical (ATC) code
†Congestive heart failure	I11.0; I13.0; I13.2; I42.0; I50	CO3C
†Left ventricular dysfunction	I50.1; I50.9	
†#Hypertension		See specified definition*
†Diabetes mellitus	E10.0; E10.1; E10.9; E11.0; E11.1; E11.9	A10
†#Ischemic stroke	I63; I64	
†Systemic embolism	I74	
†#Transient ischemic disease	G45	
†Aortic plaque	I70.0	
†Peripheral arterial disease	I70.2-I70.9; I71; I73.9	
†Myocardial infarction	I21-I23	
#Moderate/severe renal disease	I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61	
#Moderate/Severe liver disease	B150 B160 B162 B190 K704 K72 K766 I85	
Cancer	C	
Chronic pulmonary disorder	J44	
Mitral stenosis	I05	
Mechanical heart valve	Z952 Z953 Z954	
#Haemorrhagic stroke – intracranial bleeding	I60 I61 I62	
#Extracranial or unclassified major bleeding	D62 J942 H113 H356 H431 N02 N95 R04 R31 R58	
#Gastrointestinal bleeding	K250 K260 K270 K280 K290	
#Traumatic intracranial bleeding	S063C S064 S065 S066	
#Alcohol	E224 E529A F10 G312 G621 G721 I426 K292 K70 K860 L278A O354 T51 Z714 Z721	
Pulmonary embolism	I26	
Deep venous thromboembolism	I801 I802 I803 I808 I809 I819	

	I636	I676	I822	I823	I829
Atrial fibrillation	I48				
Medication					
Apixaban					B01AF02
Dabigatran					B01AE07
Rivaroxaban					B01AF01
Warfarin					B01AA03
Phenprocoumon					B01AA04
#Aspirin					B01AC06
#Clopidogrel					B01AC04
Beta-blockers					C07
Statins					C10
#Non Steroidal Anti Inflammatory Drugs					M01A

* We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive drugs:

I· Alpha adrenergic blockers (C02A, C02B, C02C)

II· Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)

III· Vasodilators (C02DB, C02DD, C02DG, C04, C05)

IV· Beta blockers (C07)

V· Calcium channel blockers (C07F, C08, C09BB, C09DB)

VI· Renin-angiotensin system inhibitors (C09)·

Supplementary table 2.**Risk score definitions**

Risk score	Points if present
CHA₂DS₂VASc^a	
Congestive heart failure or Left Ventricular Dysfunction	1
Hypertension	1
Age ≥ 65 years	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism)	2
Vascular disease (myocardial infarction, peripheral arterial disease, or aortic plaque)	1
Sex category (female)	1
HAS-BLED^b	
Hypertension	1
Abnormal renal function	1
Abnormal hepatic function	1
Stroke (ischemic stroke or transient ischemic attack)	1
Bleeding	1
Labile international normalized ratio ^c	1
Elderly age (≥ 65 years)	1
Drugs (aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs)	1
Alcohol intake	1

^aReflects stroke risk in atrial fibrillation patients not in anticoagulant therapy (Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263-72)

^bReflects bleeding risk in atrial fibrillation patients undergoing anticoagulant therapy (Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5):1093-100)

^cNot included due to unavailable information

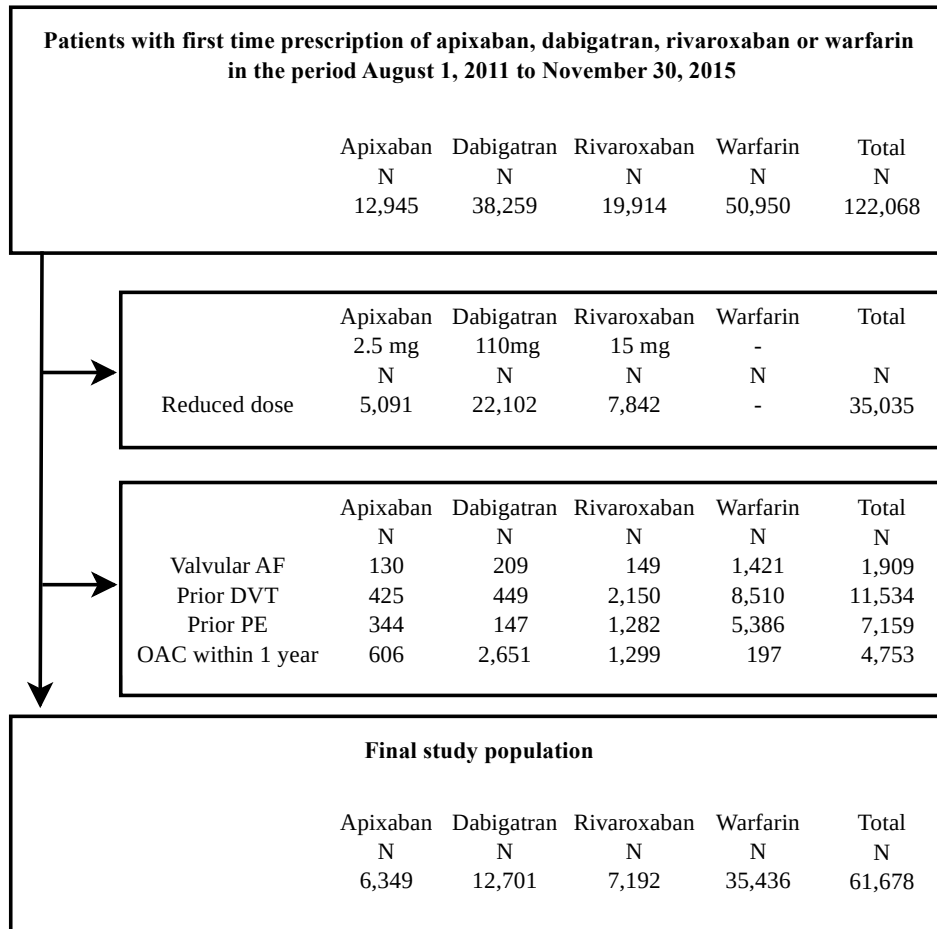
Supplementary Table 3 Odds ratio (OR) for choosing treatment vs any of three alternatives.

Highly significant predictors, with OR>1.1 or OR<0.9 are boldfaced and discussed in text. Below one indicate favour for any alternative; above one indicate favour for treatment.

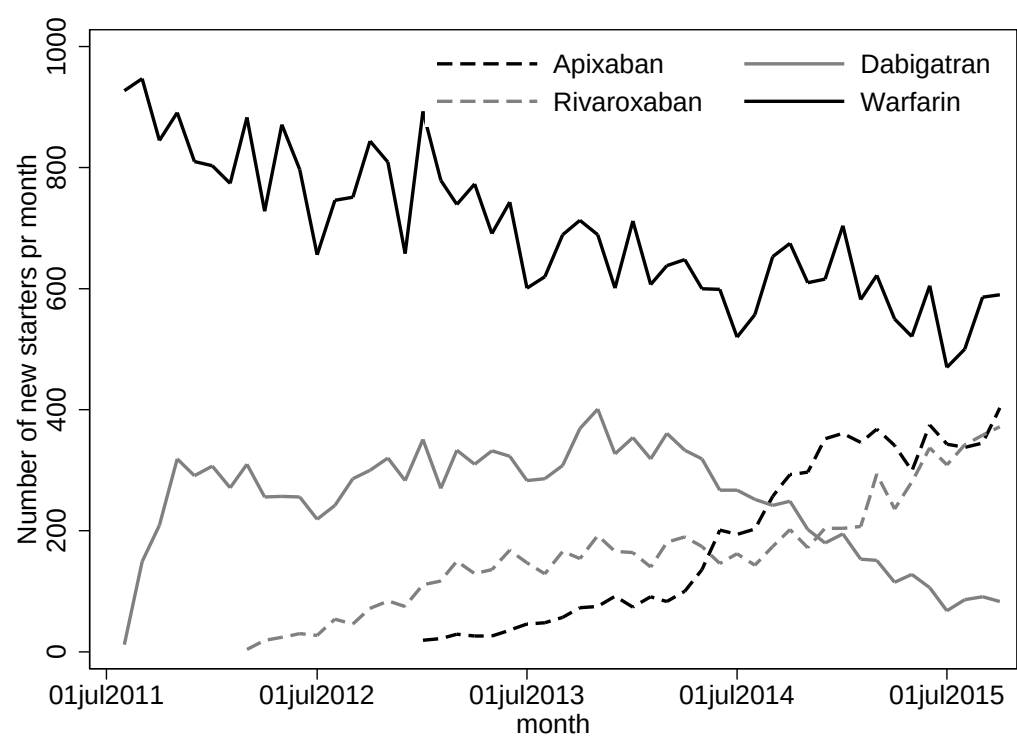
	Apixaban	Dabigatran	Rivaroxaban	Warfarin
Age, 5 years increase*	1.04 (1.03-1.05)	0.85 (0.85-0.86)	1.07 (1.06-1.08)	1.08 (1.07-1.08)
Female sex	1.00 (0.95-1.05)	0.73 (0.70-0.76)	1.17 (1.11-1.23)	1.15 (1.11-1.19)
Prior AF diagnose	1.68 (1.59-1.78)	1.91 (1.83-1.99)	1.11 (1.05-1.16)	0.52 (0.50-0.54)
Cancer	1.05 (0.98-1.13)	0.68 (0.64-0.72)	1.06 (0.99-1.13)	1.22 (1.16-1.27)
Ischemic stroke/SE/TIA	1.55 (1.46-1.66)	0.80 (0.76-0.85)	1.13 (1.06-1.21)	0.91 (0.87-0.95)
Heart failure or LVD	0.92 (0.85-1.00)	0.75 (0.70-0.80)	0.73 (0.67-0.79)	1.41 (1.34-1.48)
Vascular disease	0.88 (0.81-0.94)	0.58 (0.54-0.62)	0.74 (0.69-0.80)	1.66 (1.58-1.74)
Renal dysfunction	0.50 (0.43-0.59)	0.20 (0.17-0.24)	0.36 (0.30-0.43)	4.25 (3.83-4.71)
COPD	1.02 (0.93-1.12)	0.64 (0.59-0.69)	1.01 (0.93-1.11)	1.30 (1.22-1.37)
Prior Bleeding	1.25 (1.16-1.35)	0.79 (0.74-0.84)	1.12 (1.04-1.21)	1.01 (0.96-1.06)
Hypertension	0.97 (0.92-1.02)	0.88 (0.85-0.92)	0.96 (0.91-1.01)	1.12 (1.08-1.15)
Diabetes	1.06 (0.99-1.14)	0.88 (0.84-0.93)	0.91 (0.85-0.98)	1.10 (1.05-1.15)
Aspirin	0.89 (0.84-0.94)	0.89 (0.86-0.93)	0.90 (0.86-0.95)	1.18 (1.14-1.22)
Beta Blocker	0.92 (0.87-0.97)	0.99 (0.95-1.03)	0.94 (0.89-0.99)	1.07 (1.03-1.10)
NSAIDs	0.91 (0.86-0.97)	1.04 (1.00-1.09)	0.89 (0.84-0.94)	1.06 (1.02-1.10)
Statins	1.05 (1.00-1.11)	0.92 (0.88-0.96)	0.95 (0.91-1.00)	1.06 (1.02-1.09)

*Linear effect. SE: Systemic embolism; TIA: Transient ischemic attack; COPD: Compulsive obstructive pulmonary disease; LVD: Left ventricular dysfunction; NSAID's: non-steroidal anti-inflammatory drugs.

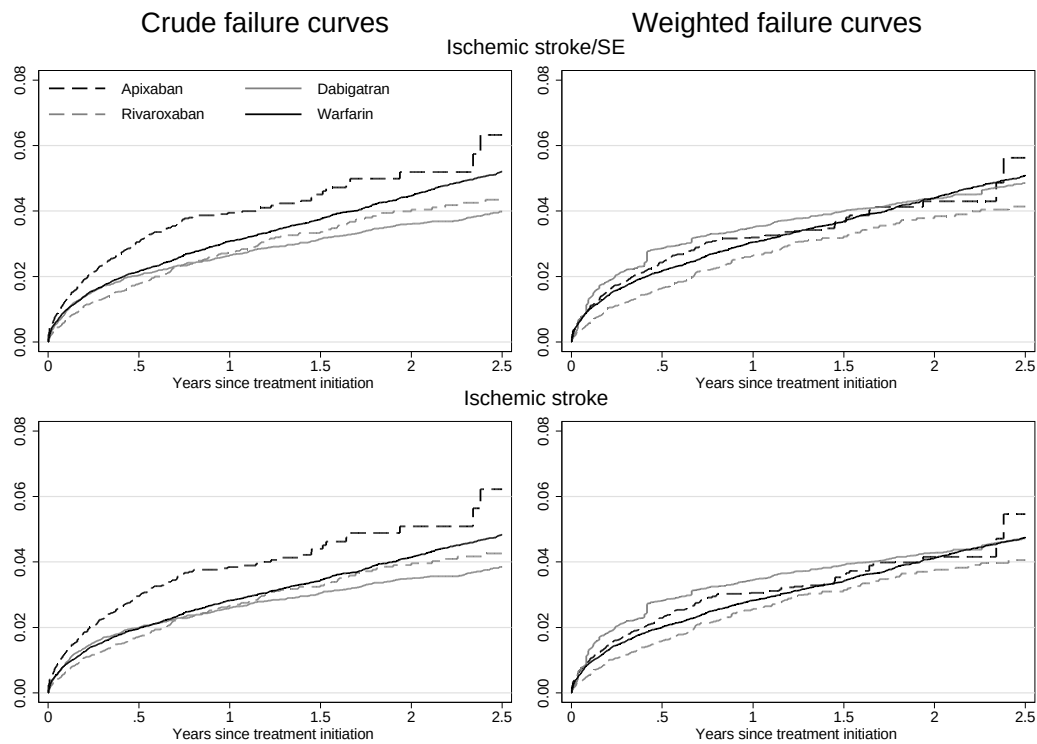
Supplementary Figure 1. Flowchart of patients excluded from study material.



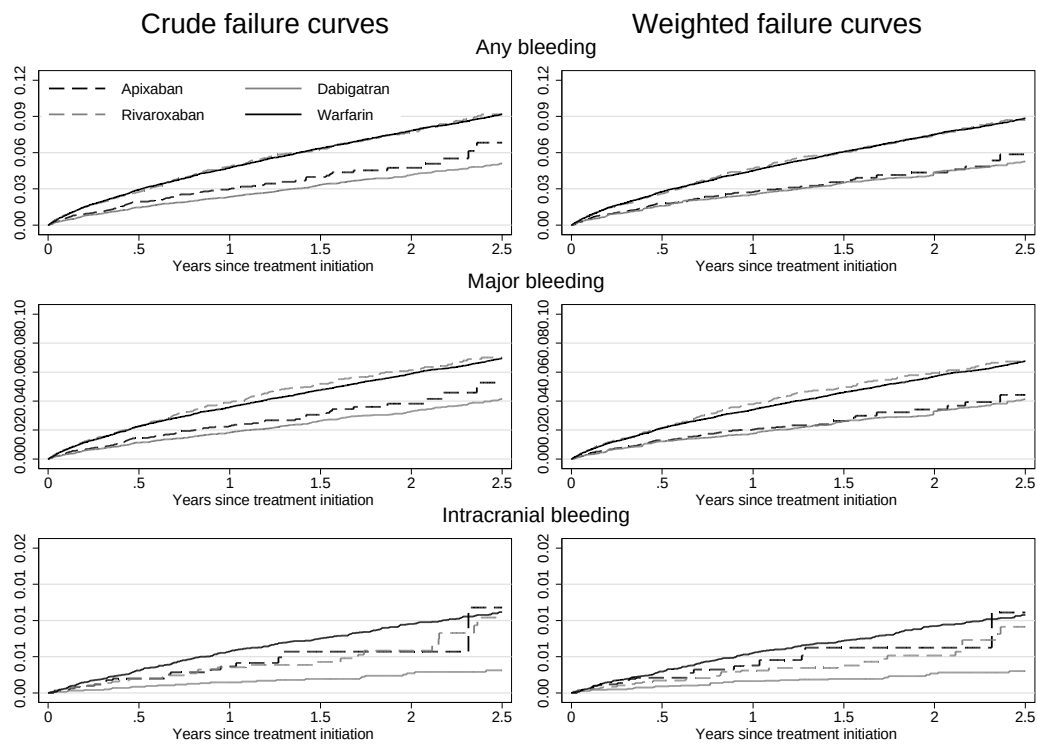
Supplementary Figure 2. Time trends of number of treatment naive patients initiated on anticoagulation, since introduction of dabigatran.



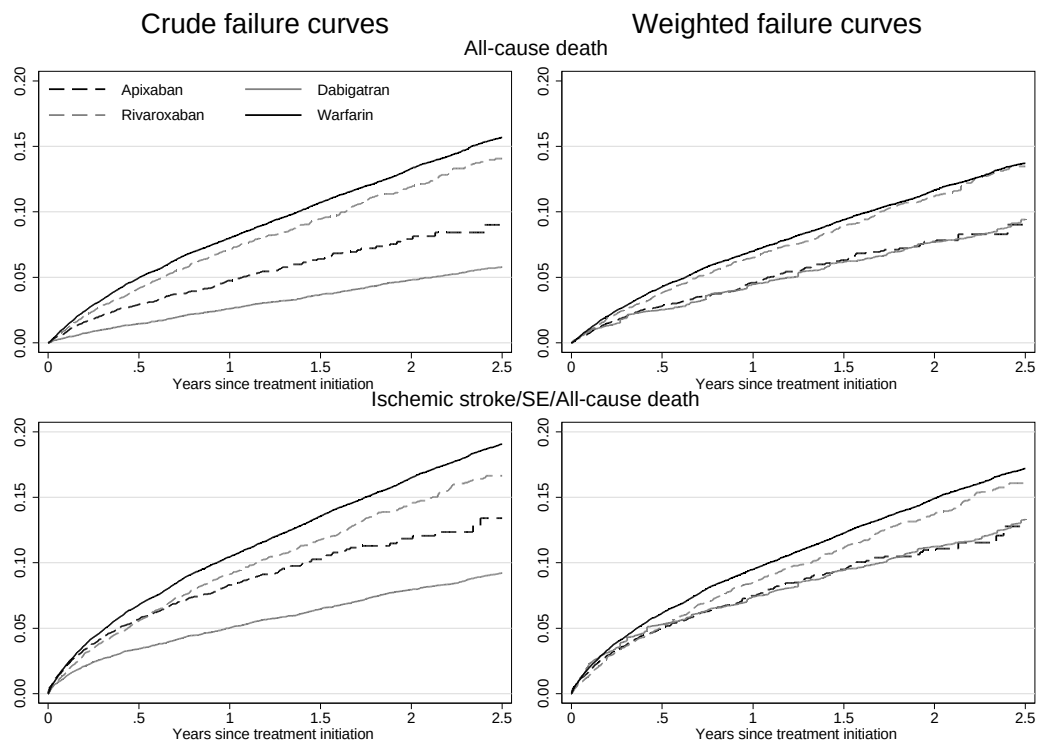
Supplementary Figure 3a. Crude cumulative incidence curves of stroke endpoints according to current treatment.



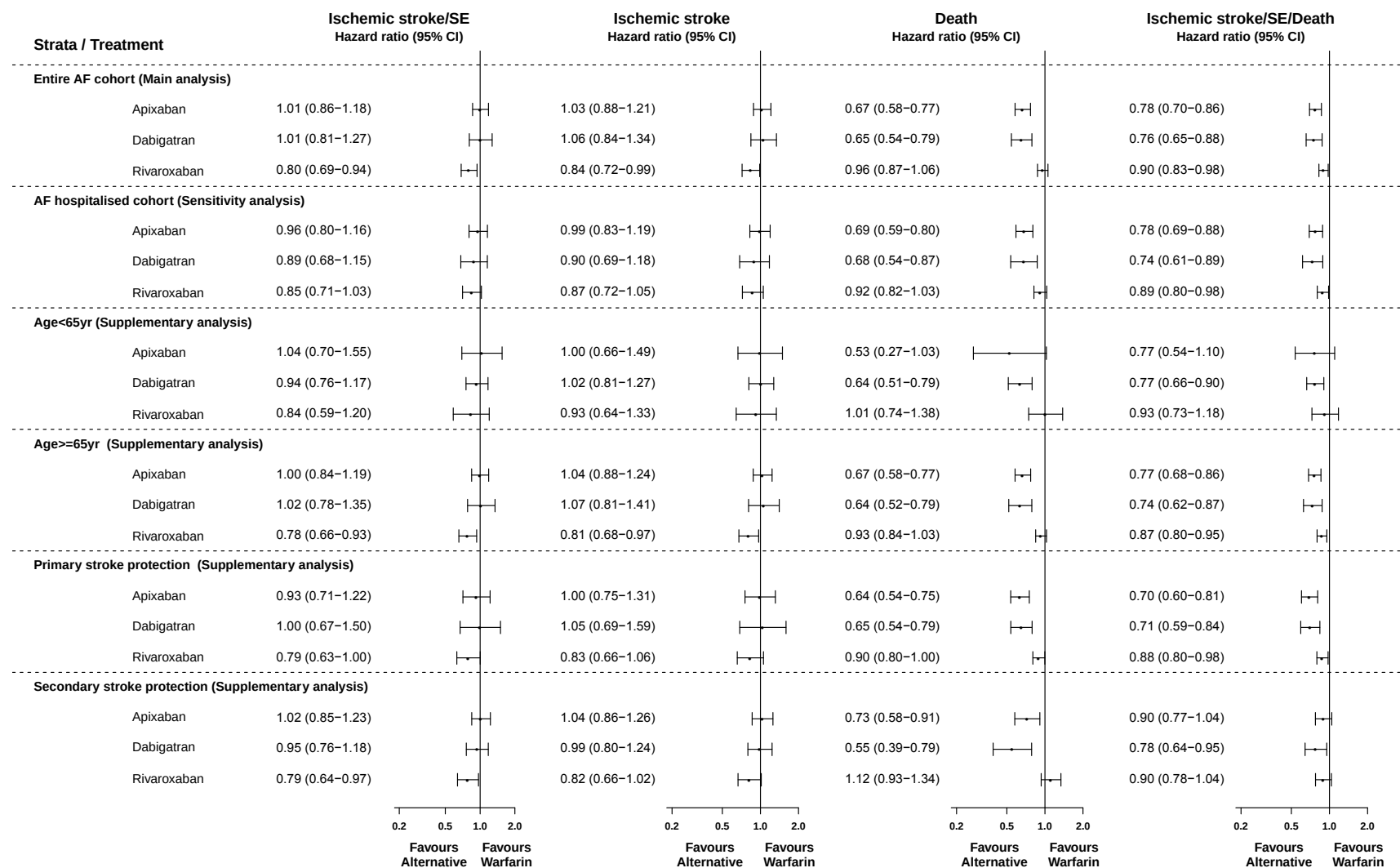
Supplementary Figure 3b. Crude cumulative incidence curves of bleeding endpoints according to current treatment.



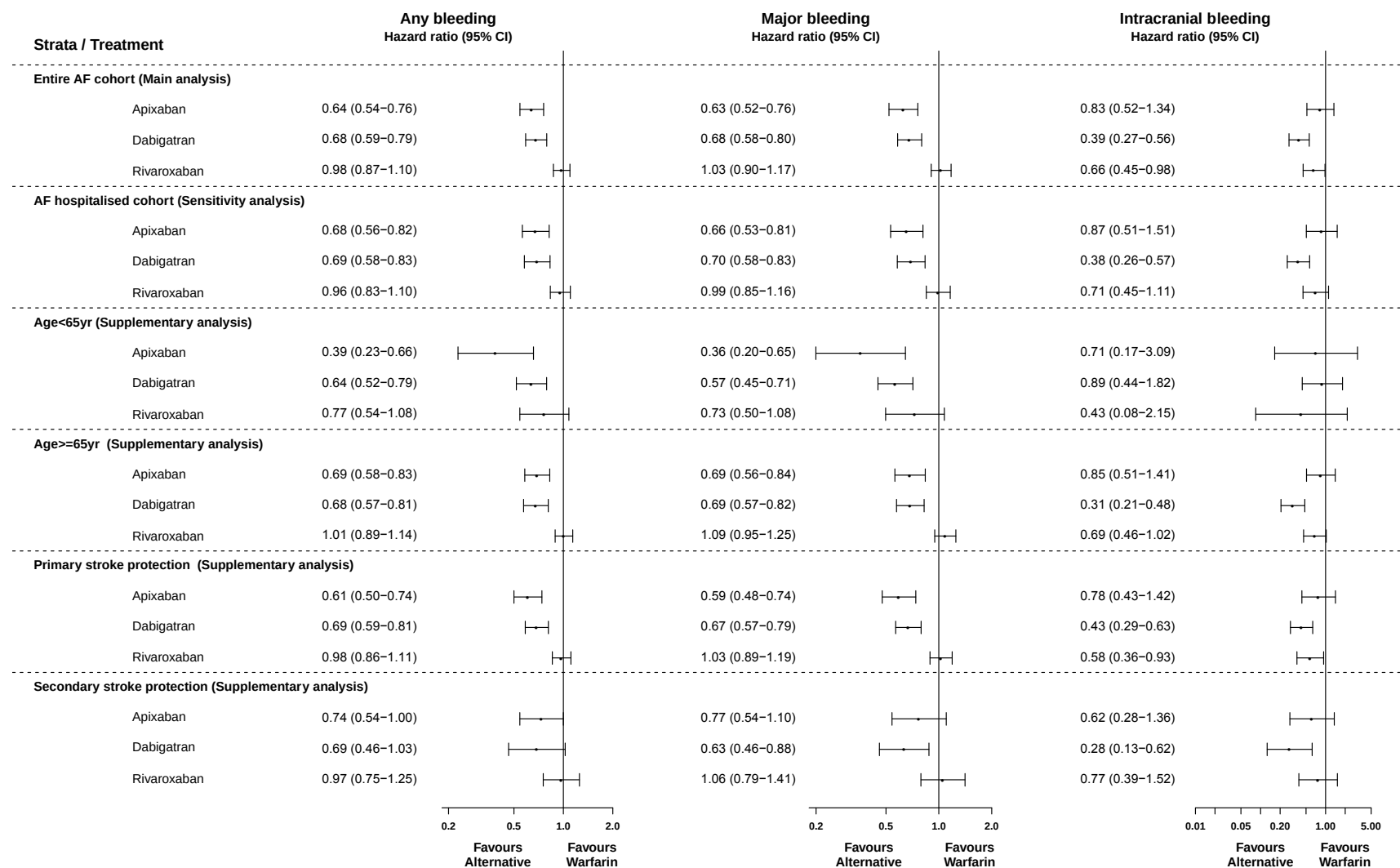
Supplementary Figure 3c. Crude cumulative incidence curves of all-cause death and combined endpoint ischemic stroke/SE or all-cause death according to current treatment.



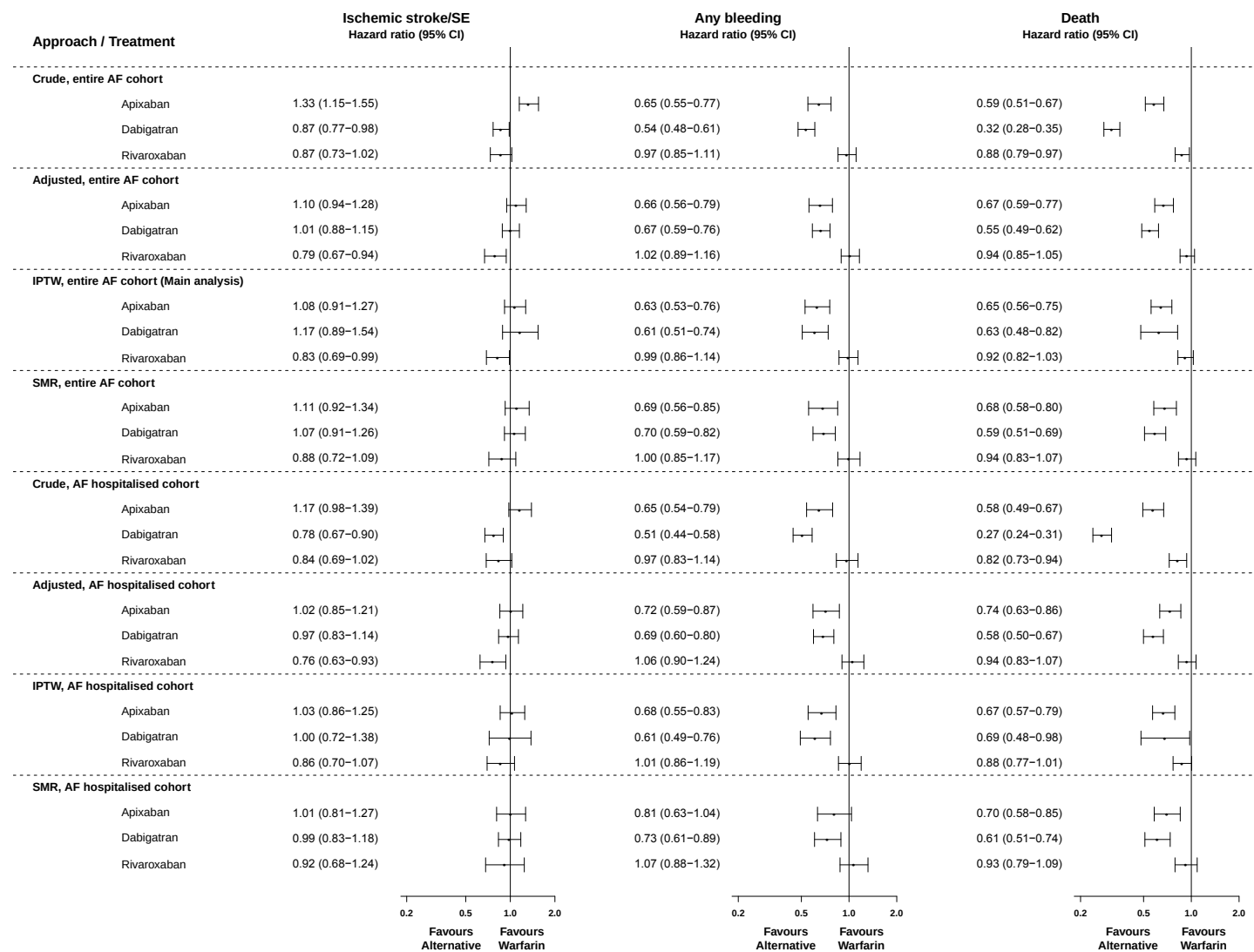
Supplementary Figure 4a. Propensity weighted (IPTW) Cox hazard ratios for 2.5 years follow-up (intension to treat) for NOACs compared to warfarin for stroke and death endpoints.



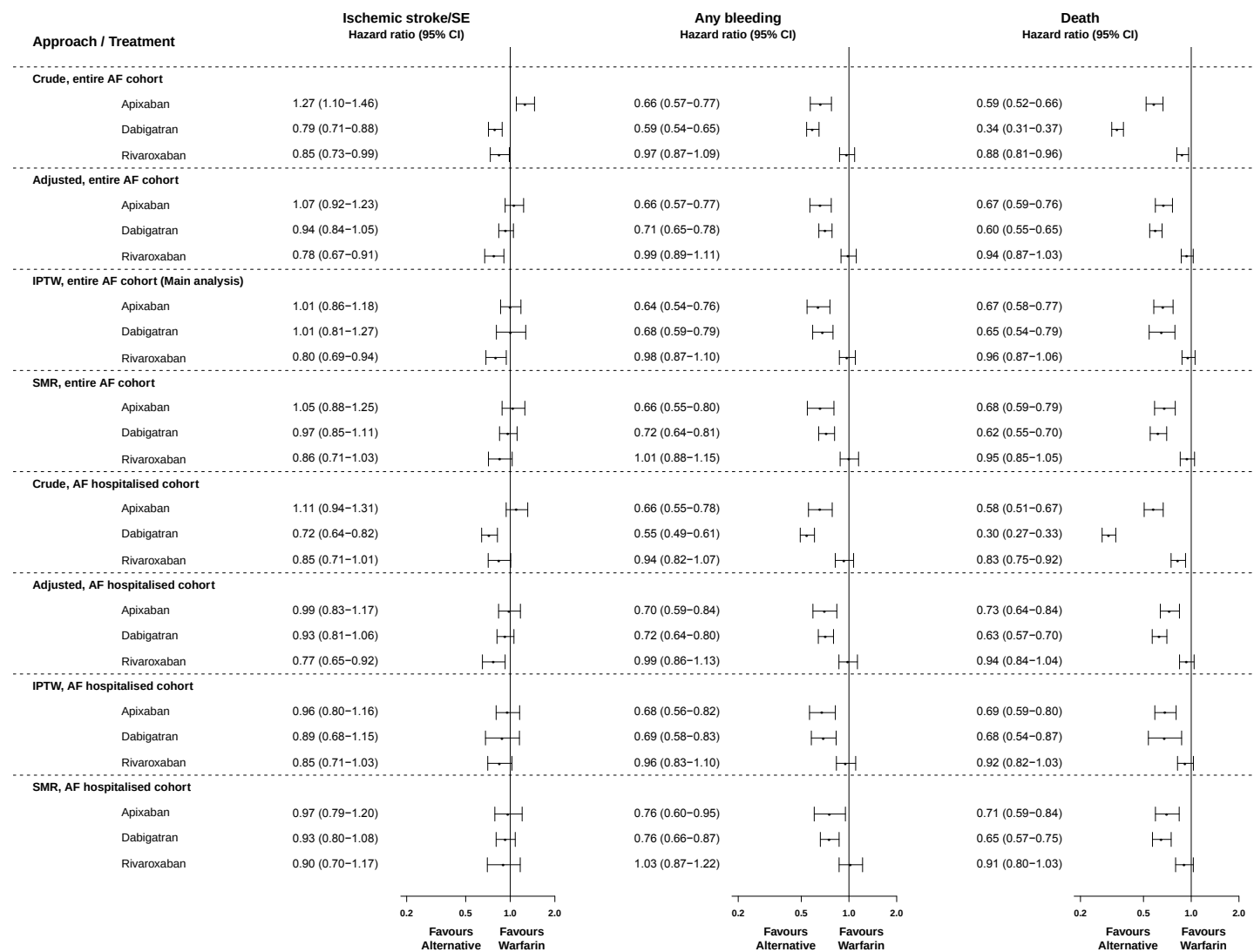
Supplementary Figure 4b. Propensity weighted (IPTW) Cox hazard ratios for 2.5 years follow-up (intension to treat) for NOACs compared to warfarin for bleeding endpoints.



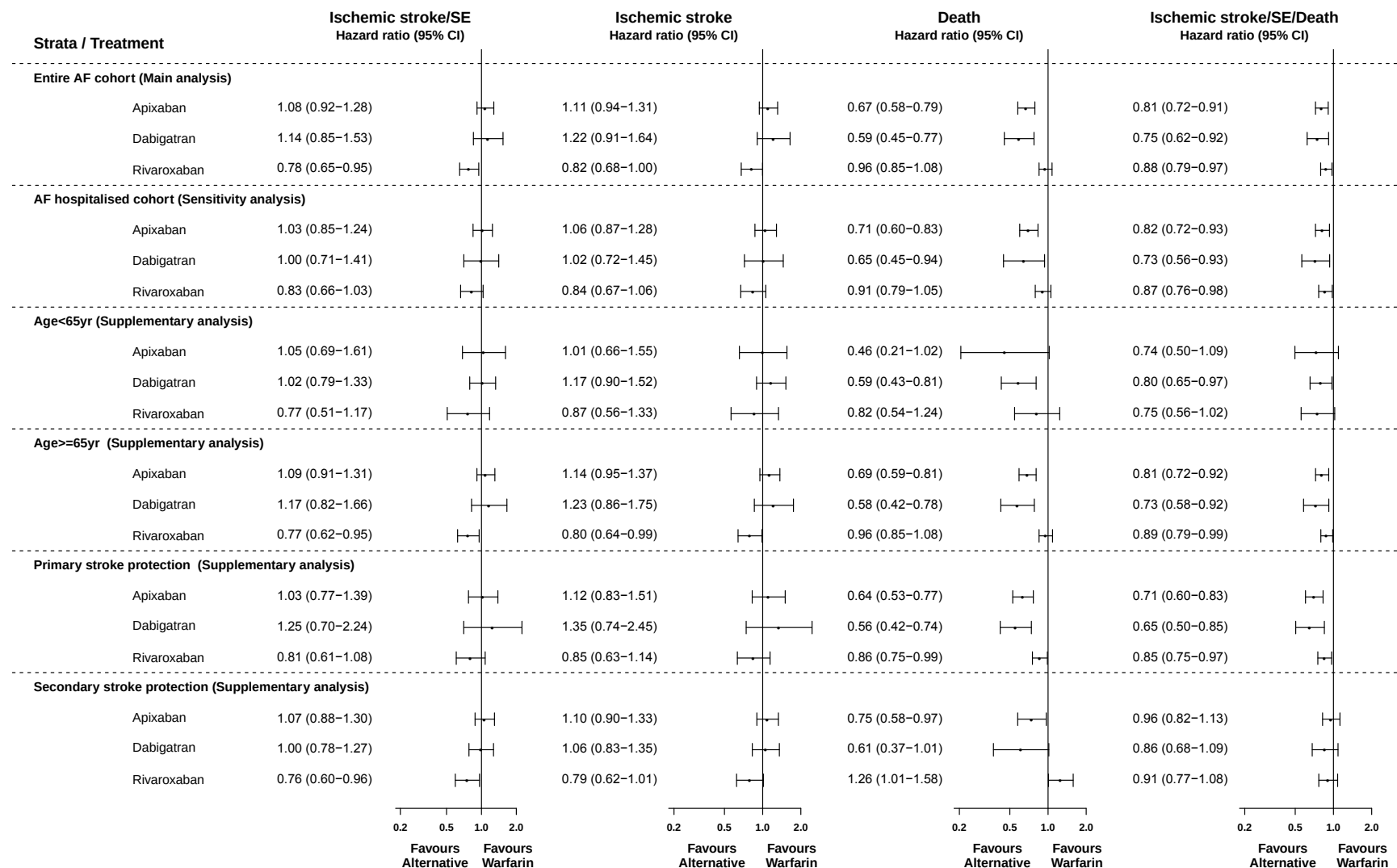
Supplementary Figure 5a. Sensitivity analyses. Cox hazard ratios for 1 year follow-up (intension to treat) for NOACs compared to warfarin for main stroke, bleeding and death endpoints. Four analysis methods and 2 cohort definitions are contrasted.



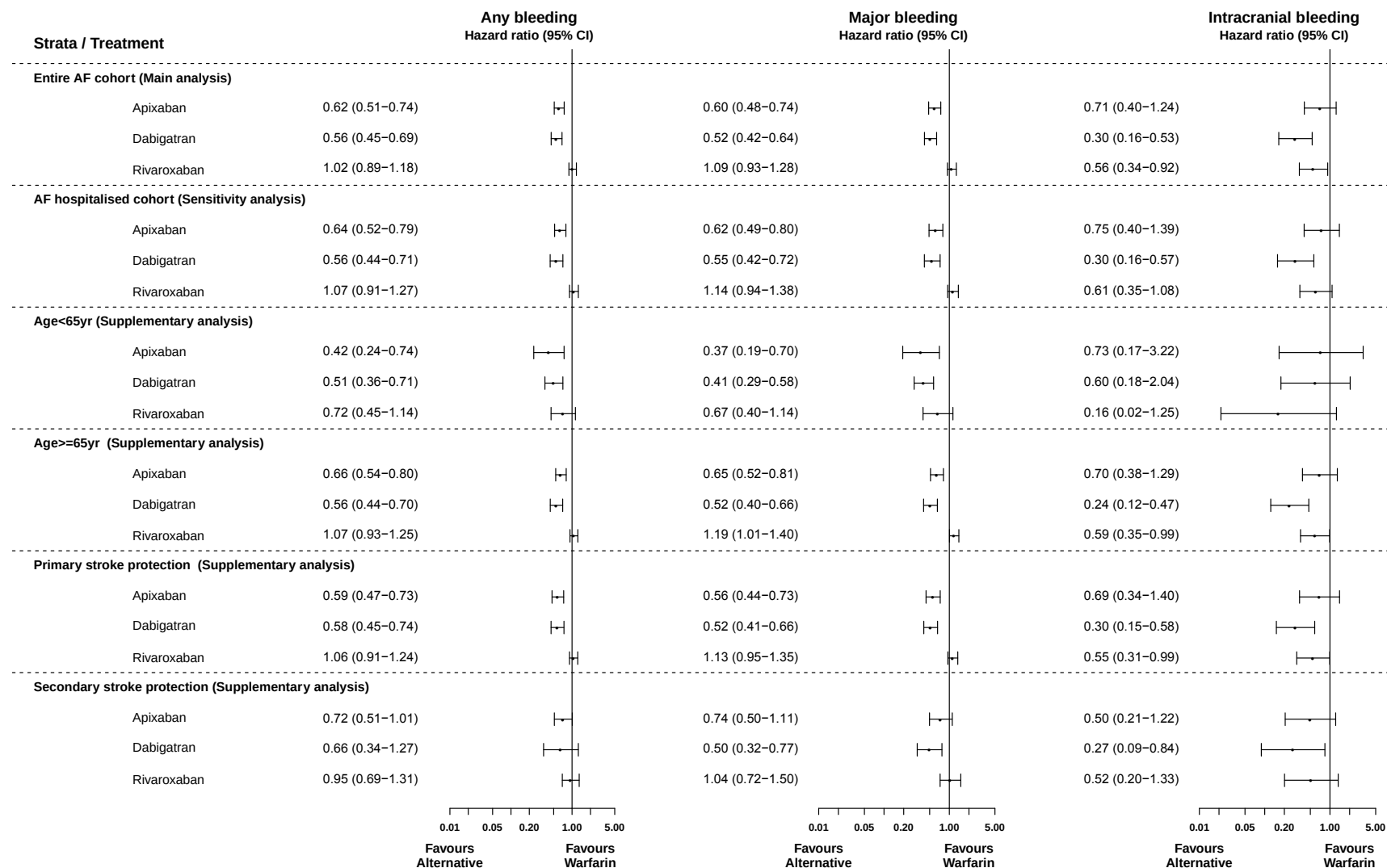
Supplementary Figure 5b. Sensitivity analyses. Cox hazard ratios for 2.5 years follow-up (intension to treat) for NOACs compared to warfarin for main stroke, bleeding and death endpoints. Four analysis methods and 2 cohort definitions are contrasted.



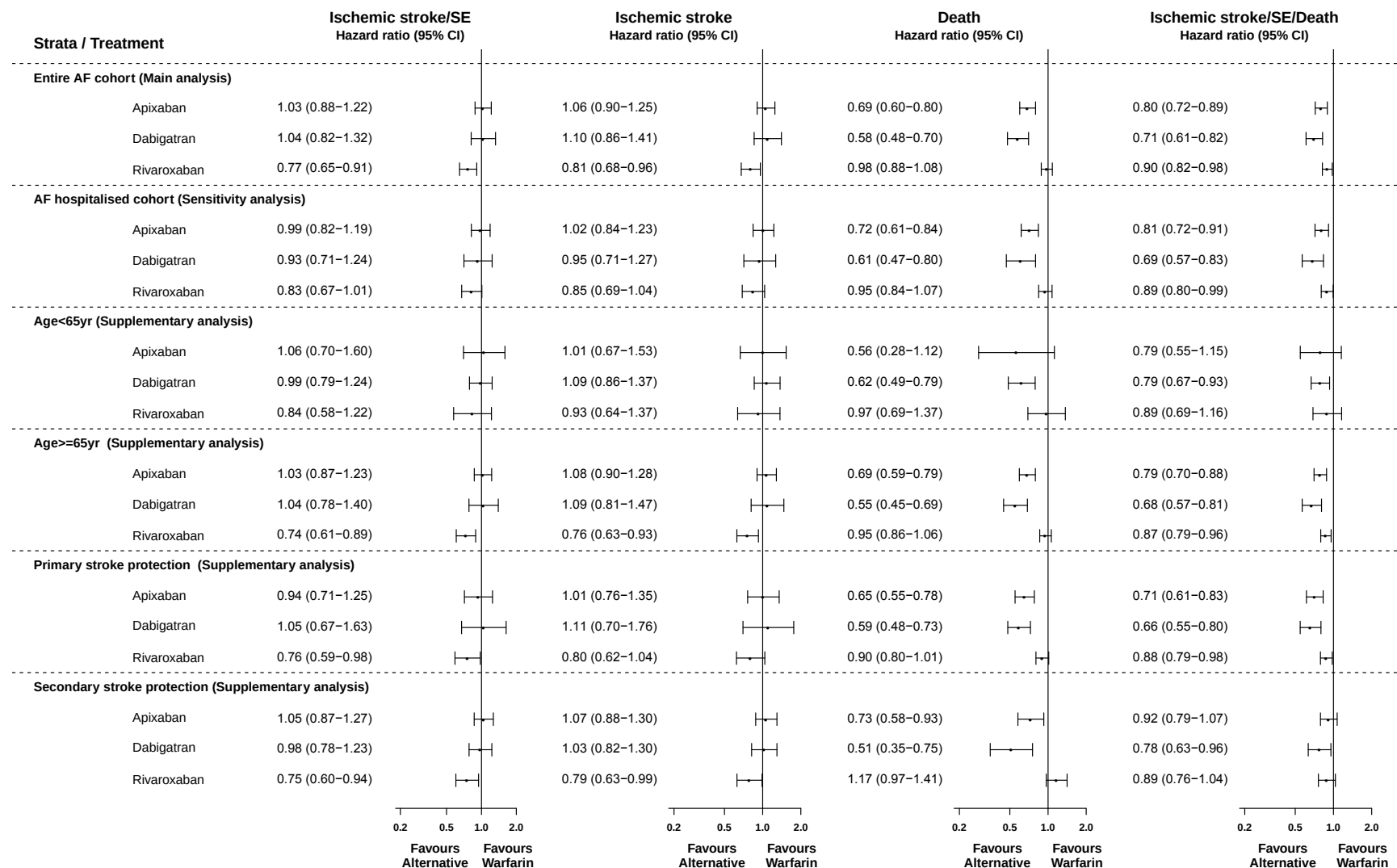
Supplementary Figure 6a. Propensity weighted (IPTW) Cox hazard ratios for 1 years follow-up (continuous treatment) for NOACs compared to warfarin for stroke and death endpoints.



Supplementary Figure 6b. Propensity weighted (IPTW) Cox hazard ratios for 1 years follow-up (continuous treatment) for NOACs compared to warfarin for bleeding endpoints.



Supplementary Figure 7a. Propensity weighted (IPTW) Cox hazard ratios for 2.5 years follow-up (continuous treatment) for NOACs compared to warfarin for stroke and death endpoints.



Supplementary Figure 7b. Propensity weighted (IPTW) Cox hazard ratios for 2.5 years follow-up (continuous treatment) for NOACs compared to warfarin for bleeding endpoints.

