# **Supplementary Figures and Tables**

# Systematic review with meta-analysis: the association between Non-vitamin K antagonist oral anticoagulants and gastrointestinal bleeding in observational studies

Ying HE<sup>1</sup>, Ian CK WONG<sup>1, 3</sup>, Xue LI<sup>1</sup>, Shweta ANAND<sup>1</sup>, Wai K LEUNG<sup>2</sup>, Chung Wah SIU<sup>2</sup>, Esther W CHAN<sup>1</sup>

<sup>1</sup>Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong; <sup>2</sup>Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong; <sup>3</sup>Research Department of Practice and Policy, School of Pharmacy, University College London, London, UK. Supplementary Table 1 Newcastle-Ottawa scale for assessment of quality of the included

comparative observational studies

Study	Study design	Newcastle- Ottawa		Newcastle-Otta	wa Scale
		Scale Score (Total)	Selection	Comparability	Exposure/Outcome
Abraham 2015[37]	С	9	****	**	***
Chan 2015[38]	С	6	**	**	**
Chang 2015[39]	С	9	****	**	***
Graham 2015[26]	С	7	***	**	**
Hernandez 2015[40]	С	8	***	**	***
Larsen 2014[34]	С	8	***	**	***
Staerk 2015[43]	С	9	****	**	***
Larsen 2013[32]	С	8	***	**	***
Lauffenburger 2015[41]	С	8	***	**	***
Vaughan Sarrazin 2014[36]	С	8	***	**	***
Laliberte 2014[33]	С	7	***	**	**
Bell 2013[31]	CS	2	**	-	-
Choi 2014[60]	CS	2	**	-	-
Sherid 2015[42]	CS	7	***	**	**
Nagao 2015[45]	CS	6	**	**	**
Sherid 2014[35]	CS	5	***	-	**

Abbreviations: C=cohort studies; CS=cross-sectional studies

Supplementary Table 2 Summary of the main characteristics and results of included comparative studies\*

Study	Patient age	CHADS2	NOAC & Warfarin	GIB Rate (per 100 Potient Veens)	Crude OR/IRR/HR	Adjusted OR/RR/HR	Confounding variables
		(mean ±SD)	(GIB/total, patient-years)"	Patient-Years)	(95% CI)	(95% CI)	aujusteu for
Cohort stuc	lies (n=11)						
Abraham 2015[37]	Dabi 67.2 $\pm$ 11.2, 60.8% $\geq$ 65y; Warf matched 67.5 $\pm$ 11.2, 60.7% $\geq$ 65y; Riva 69.0 $\pm$ 10.9, 68.9% $\geq$ 65y; Warf matched 69.1 $\pm$ 10.9, 68.0% $\geq$ 65y	Dabi 45.4% 0-1; Warf matched 44.8% 0-1; Riva & Warf matched both 41.9% 0-1	Dabi NR/7846(7749 matched) Riva NR/5434 (5166 matched) Warf NR/22787 (7749 and 5166 matched for Dabi and Riva respectively) Follow up time NR	Dabi: 2.29 (1.88- 2.79) Warf: 2.87 (2.41- 3.41) Riva: 2.84 (2.30- 3.52) Warf: 3.06 (2.49- 3.77)	IRR: Dabi vs Warf 0.80(0.61-1.04)b Riva vs Warf 0.93 (0.69-1.25)b	Dabi vs Warf (HR): GIB 0.79 (0.61 to1.03) UGIB 0.78 (0.56 to 1.09) LGIB 0.81 (0.53 to 1.24) Riva vs Warf (HR): GIB 0.93 (0.69 to 1.25) UGIB 1.05 (0.72 to 1.54) LGIB 0.77 (0.48, 1.24)	1:1 PS matched for risk factors for GIB, race, age categories, drug classes and controlled for follow- up times by including a categorical variable representing the quarter of treatment duration, Table 1
Chan 2015[38]	Dabi 68.4±12 Riva 66.9±12 Warf 70.6±11	Dabi 2.3±1.0 Riva 2.2±1.0 Warf 2.4±1.0	Dabi 41/281, 123 P-Y Riva 15/244, 72 P-Y Warf 852/8064, 3839 P-Y ASA 593/6469, 3226 P-Y	Major GIB: Dabi: 33.3 (24.5- 45.2)b Riva: 20.8 (12.6- 34.6)b Warf: 22.2 (20.8- 23.7)b ASA: 18.4 (17.0- 19.9)b	Major GIB IRR: ASA vs Warf 0.82 (0.73-0.91) Dabi vs Warf 1.49 (1.08–2.04) Riva vs Warf 0.96 (0.57-1.59) Minor GIB IRR: ASA vs Warf 0.66 (0.53-0.80) Dabi vs Warf 0.85 (0.40-1.79) Riva vs Warf 0.82 (0.31-2.22)	NR	All parameters listed in Table 1 after backward variable selection with an exit criteria of P<0.05
Chang 2015[39]	Dabi 62.0±12.0, 32.8% ≥65y; Riva57.6±9.8,1 7.5% ≥65y;	N/R	Dabi 122/4907, 1354.0 P-Y Riva 4/1649, 117.4 P-Y Warf 632/39607, 9007.1 P-Y	Dabi: 9.01 (7.41- 10.61) Riva: 3.41 (0.07- 6.75) Warf: 7.02 (6.47- 7.56)	HR: Dabi vs Warf 1.20 (0.96-1.52) Riva vs Warf 0.95 (0.31-2.94)	HR: Dabi vs Warf 1.21 (0.96–1.53) Riva vs Warf 0.98 (0.36–2.69)	PS weighting, age, Clinical Classification Software categories, demographics (age groups, sex, and region), renal failure, trauma, or

	Warf 57.4±13.5, 22.4% ≥65y						H.pylori infection, prescription of NSAIDs, PPI or steroid
Graham 2015[26]	In both group, all ≥65y; 59% ≥75y	In both group 28% 0-1	Dabi 623/67207, 18205 P-Y Warf 513/67207, 19382 P-Y	Dabi: 3.42 (3.15- 3.69) Warf: 2.65 (2.42- 2.88)	IRR: Dabi vs Warf 1.29 (1.15-1.45)b	HR: Dabi vs Warf 1.28 (1.14-1.44) Dabi75mg 1.01 (0.78–1.31) Dabi150mg 1.51 (1.32–1.73)	PS matched, Table 1: Socio-demographic factors, medical conditions, and medication use
Hernandez 2015[40]	Dabi 75.1±10.2	Dabi 19.1% 0-1;	Dabi NR/1302; Mean follow up time: 117 days (IQR: 89- 256)	NR	NR	HR: Dabi vs Warf 1.85 (1.64-2.07)	PS weighting, characteristics listed in Table 1
	Warf 75.6±9.5	Warf 18.9% 0-1	warf NR/8102; Mean follow up time: 228 days (IQR: 119- 333)				
Larsen 2014[34]	VKA na ïve: Dabi 150 median 67, 63.6% ≥65y; Dabi 110 median 82, 95.3% ≥65y; Warf median 73, 76.8%≥65y	Dabi 150 0.94±1.05 Dabi 110 1.91±1.21 Warf 1.33±1.21	VKA na we: Dabi110mg 12/3045 Dabi150mg 19/4018 Warf 78/14126 VKA experienced: Dabi110mg 21/2038 Dabi150mg 12/2214 Warf 52/8504 Follow up time NR	VKA na we: Dabi 110mg 0.42 (0.24-0.74)b Dabi 150mg 0.49 (0.31-0.77)b Warf 0.58 (0.46- 0.72)b VKA experienced: Dabi 110mg 0.97 Dabi 150mg 0.43 Warf 0.51 CI not calculated	IRR VKA na ive: Dabi110mg: 0.72 (0.39-1.33)b Dabi150mg: 0.84 (0.51-1.40)b VKA experienced: Not calculated	HR VKA na we: Dabi110mg: 0.53 (0.28-0.98) Dabi150mg: 1.37 (0.81-2.31) VKA Experienced HR: Dabi110mg: 1.22 (0.73-2.03) Dabi150mg: 1.03 (0.54-1.93)	Stratified by VKA experience (2 years as cut- off point) adjusted by age, components of CHA2DS2-VASc and HAS-BLED; and months since August 2011 (continuous, cubic spline); and time since the initiation of VKA therapy
Staerk 2015[43]	Dabi 150 65.9±8.7 Dabi 110 80.0±8.7 Warf 70.3±11.3	Dabi 150 1.1±1.1 Dabi 110 2.0±1.2 Warf 1.4±1.2	OAC-na ve: Dabi 110mg NR/1168 Dabi 150mg NR/1844 OAC-experienced: Dabi 110mg NR/1143 Dabi 150mg NR/1748 OAC-na ve Warf: NR/4534 Median follow up: 244 days for all (IQR, 105.0–377.0)	NR	NR	OAC na ive HR: Dabi 110mg: 0.90 (0.32-2.52) Dabi 150mg: 1.43 (0.58-3.52) OAC experienced HR: Dabi 110mg: 0.91 (0.36-2.29) Dabi 150mg: 0.93 (0.38-2.31)	CHF, hypertension, DM, stroke/TIA, vascular disease, age, sex, and treatment with acetylsalicylic acid or NSAIDs

abi 150 7.4±8.5, 8.6% ≥65y; abi 110 4.7±11.8, 0.5% ≥65y; 7arf 0.4±12.6, 3.0%≥65y	Dabi 130 0.96±1.07 Dabi 110 1.27±1.27 Warf 1.18±1.17	Dab1150mg: 26/2239, 1749 P-Y; Warf D150 matched: 53/3996, 3661 P-Y; Dabi110: 28/2739,2311 P-Y; Warf D110 matched: 90/4940, 4369 P-Y	Dabi150mg: 1.49 (1.01-2.18)b Warf D150 matched: 1.45 (1.11-1.90)b Dabi110mg: 1.21 (0.84-1.76)b Warf D110 matched: 2.06 (1.68-2.53)b	HR: Warf vs 110 mg dabi: 0.67 (0.43- 0.99) Warf vs 150 mg dabi: 0.81 (0.52- 1.21)	HR: Warf vs Dabi110mg 0.60 (0.37-0.93) Warf vs Dabi150mg 1.12 (0.67-1.83)	PS 1:2 matched, considering baseline characteristics: previous stroke, intracranial bleeding, or TIA; HF; MI; DM; renal disease, and hepatic disease; usage indicators of aspirin, clopidogrel, ARB or ACEi, beta-blocker, amiodarone, statins, PPIs, and H2RAs. All interacted with sex and age categories.
abi 67.5±12.4, 5.4% ≥65y Varf 1.4±12.2, 68% 65y	CHA <sub>2</sub> DS <sub>2</sub> - VASc: Dabi 2.3±1.6, 27.8% 0-1 Warf 2.9±1.7, 16.7% 0-1	Dabi NR/21070, 20652 P-Y Warf NR/43865, 42994 P-Y Mean follow up time since initiation:358days (SD:224)	Dabi 2.18 (1.99- 2.39)b Warf 3.21(3.05- 3.38)b	HR: Dabi vs Warf 0.68 (0.61-0.75)	HR: Dabi vs Warf 1.11(1.02-1.22)	PS weighting, age, gender, region, insurance plan, clinical characteristics. The PS weights were estimated including all variables in Table 2 as covariates
abi 69.7±9.0, 9.9% ≥65y; ⁄arf 4.4±10.1, 2.2% ≥65y;	Dabi 2.21±1.12 26.1% 0-1; Warf 2.08±1.12 30.3% 0-1	Dabi NR/1394, Follow up time: 49470 person-weeks Warf NR/83950, Follow up time:5,391,105person-weeks	Dabi 9.25 (7.51- 11.4)b Warf 5.60 (5.45- 5.74)b	OR: Dabi vs Warf 1.71 (1.36-2.16)	OR: Dabi vs Warf 1.54 (1.20-1.97)	Marginal structural models, adjusting for baseline and time-varying patient covariates.
iva: 2.6%>65y ⁄arf: 4.6% >65y	Riva 2.0±1.0, 40.1% 0-1; Warf 2.0±1.0	Riva NR/3654, Follow up time: mean 83 days (SD:58) Warf: NR/14616, Follow up time: mean 113 days (SD:70) (Warf: 26825 full cohort)	Riva 9.51 (7.64- 11.87)b Warf 7.00 (6.45- 7.59)b	IRR: Riva vs Warf 1.36 (1.06-1.74)b	HR: Riva vs Warf 1.27 (0.99-1.63)	1:4 PS matching: demographics, insurance type comorbidities, and risk factors for bleeding, stroke and VTE events. characteristics included
278 240 703 25 716 29 742 i2 74	abi 150 $.4\pm 8.5$ , $.6\% \ge 65y$ ; abi 110 $.7\pm 11.8$ , $.5\% \ge 65y$ ; arf $.4\pm 12.6$ , $.0\% \ge 65y$ $abi 67.5\pm 12.4$ , $.4\% \ge 65y$ arf $.4\pm 12.2$ , $68\%$ 5y $abi 69.7\pm 9.0$ , $.9\% \ge 65y$ ; arf $.4\pm 10.1$ , $.2\% \ge 65y$ ; va: .6% > 65y	abi 150 .4±8.5, .6% ≥65y; Dabi 110 1.27±1.27 abi 110 .7±11.8, Warf .5% ≥65y; 1.18±1.17 arf .4±12.6, .0%≥65y Abi 67.5±12.4, CHA <sub>2</sub> DS <sub>2</sub> - .4% ≥65y VASc: Dabi arf 2.3±1.6, .4±12.2, 68% 27.8% 0-1 5y Warf 2.9±1.7, 16.7% 0-1 abi 69.7±9.0, Dabi .9% ≥65y; 2.21±1.12 26.1% 0-1; arf .4±10.1, Warf .2% ≥65y; 2.08±1.12 30.3% 0-1 va: .6% >65y Warf .4∪1% 0-1; arf .6% >65y Warf	b) 150 0.96 $\pm$ 1.07 P-Y; Warf D150 matched: .6% $\geq$ 65y; Dabi 110 53/3996, 3661 P-Y; 1.27 $\pm$ 1.27 Dabi110: 28/2739,2311 P-Y; bi 110 Warf D110 matched: .7 $\pm$ 11.8, Warf 90/4940, 4369 P-Y .5% $\geq$ 65y; 1.18 $\pm$ 1.17 arf .4 $\pm$ 12.6, .0% $\geq$ 65y VASc: Warf NR/43865, 42994 P-Y Dabi Mean follow up time since arf 2.3 $\pm$ 1.6, initiation:358days (SD:224) .4 $\pm$ 12.2, 68% 27.8% 0-1 .5y Warf 2.9 $\pm$ 1.7, 16.7% 0-1 bi 69.7 $\pm$ 9.0, Dabi Dabi NR/1394, Follow up .9% $\geq$ 65y; 2.21 $\pm$ 1.12 time: 49470 person-weeks 26.1% 0-1; Warf NR/83950, Follow up time: 5,391,105 person-weeks .4 $\pm$ 10.1, Warf .2% $\geq$ 65y; 2.08 $\pm$ 1.12 .30.3% 0-1 va: Riva Riva NR/3654, Follow up .6% $\geq$ 65y Warf (Warf: NR/14616, Follow up time: to an 113 days (SD:70) .6% $\geq$ 65y Warf (Warf: 26825 full cohort)	bb 150 0.96±1.07 P-Y; (1.10-2.18)b $4\pm 8.5$ , $Warf D150 matched: Warf D150 matched: 1.45 1.27\pm 1.27 Dabi 110 28/2739,2311 P-Y; (1.11-1.90)b bi 110 Warf D110 matched: Dabi 110 matched: 1.45 1.27\pm 1.27 Dabi 110: 28/2739,2311 P-Y; (1.11-1.90)b Varf D110 matched: Dabi 110mg: 1.21 (0.84-1.76)b5\% \ge 65y; 1.18±1.17 Warf D110 matched: 2.06 (1.68-2.53)b4\pm 12.66, 0.0\% \ge 65y VASc: Warf NR/43865, 42994 P-Y 2.39)bDabi Mean follow up time since Warf 3.21(3.05-arf 2.3\pm 1.66, initiation: 358days (SD:224) 3.38)b4\pm 12.2, 68\% 27.8\% 0-15y Warf 2.9\pm 1.7, 16.7\% 0-1bi 69.7±9.0, Dabi Dabi NR/1394, Follow up time: 5,391,105 person-weeks 4.4\pm 10.1, Warf 2.61\% 0-1; Warf NR/83950, Follow up time: 5,391,105 person-weeks 5.74)b4\pm 10.1, Warf 2.3 \pm 1.6, imme: mean 83 days (SD:28) 11.87)b4\pm 10.1, Warf 2.0 \pm 1.12 30.3\% 0-1va: Riva Riva Riva NR/3654, Follow up Riva 9.51 (7.64-11.87)b Warf 7.00 (6.45-3.38 (SD:70) 7.59)b$	bb 150 0.96±1.07 P-Y; (1.01-2.18)b Wart vs 110 mg .4±8.5, Warf D150 matched: Warf D150 dabi: 0.67 (0.43- .6% ≥65y; Dabi 110 53/3996, 3661 P-Y; matched: 1.45 0.99) 1.27±1.27 Dabi110: 28/2739,2311 P-Y; (1.11-1.90)b Warf vs 150 mg Warf D110 matched: Dabi 110mg: 1.21 dabi: 0.81 (0.52- .1.21) dabi: 0.81 (0.52- .1.36 (1.06-1.74) dabi: 0.81 (0.52- .1.36 (1.06-1.74) dabi: 0.82 (1.06- .1.36 (1.06-1.74) dabi: 0.82 (1.12) dabi: 0.82 (1.12) dab	bit 150 0.96±1.07 P-Y: 4±5.5, Warf D150 matched: 1.27±1.27 Dabi110 53/3996, 3661 P-Y: 1.27±1.27 Dabi110 matched: 1.27±1.27 Dabi110: 28/2739,2311 P-Y: 1.27±1.27 Dabi110: 28/2739,2311 P-Y: 1.11.1000b Warf Vs 150 mg Marf Vs 150 mg Dabi110 matched: 1.12 (0.67-1.83) Marf Vs 150 mg Dabi10 matched: 1.21 (0.67-1.83) Marf Vs 150 mg 1.12 (0.67-1.83) Marf Vs 150 mg 1.12 (0.67-1.83) Dabi10.28 (0.52- (0.84-1.76)b 1.21) Warf D110 matched: 2.06 (1.68-2.53)b Marf S2106 Marf S2106 Marf Vs 150 mg 1.12 (0.67-1.83) Marf Vs 16 Marf Vs Warf 0.68 Dabi vs Warf 1.68 Dabi vs Warf 1.14 (1.02-1.22) 1.11 (1.02-1.22) 1.11 (1.02-1.22) 1.11 (1.02-1.22) 1.11 (1.02-1.22) 1.11 (1.02-1.22) 1.11 (1.02-1.22) 1.12 (0.67-1.83) Marf 1.14 (0.61-0.75) 1.11 (1.02-1.22) 1.12 (0.67-1.83) Marf 1.14 (0.61-0.75) 1.14 (0.61-0.75) 1.14 (0.61-0.75) 1.14 (0.61-0.75) 1.14 (0.61-0.75) 1.14 (0.61-0.75) 1.12 (0.61-0.

Bell 2013[31]	Dabi 80±3.1 Warf 70±4.3	NR	Dabi 7/1050, Warf 15/4600	N/A	2.04 (0.84, 5.00)b	NR	None
Choi 2014[60]	Dabi 69 ±12 Warf 68 ±9.12	NR	Dabi 21.9%/160 Warf 6.9%/204	N/A	3.19 (1.78, 5.72)b	NR	None
Sherid 2015[42]	Dabi 72.7 yr, 16.8% >85yr; Warf 71.8 yr, 13.9% >85 yr	N/R	Dabi 10/208, Warf 21/209	N/A	RR Dabi vs Warf 0.48 (0.23-0.99)b	OR Warf vs Dabi 2.12 (0.998-4.501)	Age, sex, race, duration, concomitant use with aspirin, thienopyridines, dual antiplatelet, NSAIDs, GFR<=30 ml/min/1.73 m2, previous GIB
Nagao 2015[45]	Api 61±13 Warf 61±3	Api 0.8 ± 1.1 81% 0-1 Warf 0.8 ±0.9 80% 0-1	Api 1/105; Warf 0/237 (105 PS matching)	Only reported P- value	6.73 (0.28, 164.00)b	3.00 (0.12, 72.81)b	PS matching for age, sex, type of AF, and aspirin or clopidogrel use
Sherid 2014[35]	Riva 68.3±15.0, 57.8% ≥65y Dabi 72.7±12.4, 73.1% ≥65y	NR	Riva 7/147; Dabi 12/227	N/A	0.90 (0.36, 2.24)b	OR NR, p=0.8215	None

Abbreviations: ACEi=angiotensin converting enzyme inhibitor; AF=atrial fibrillation; Api=apixaban; ARB= angiotensin receptor blocker; ASA=aspirin; CI=confidence interval; CHADS2=congestive heart failure, hypertension, age 75 years or older, diabetes mellitus and stroke; TIA=transient ischemic attack; CHA<sub>2</sub>DS<sub>2</sub>-VASC=congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years and sex category; Dabi=dabigatran; DM= diabetes mellitus; GFR=glomerular filtration rate; GIB=gastrointestinal bleeding; H2RA=histamine-2 receptor antagonist; HAS-BLED=hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, drugs or alcohol; HR=hazards ratio; IRR=incident rate ratio; LGIB=lower gastrointestinal bleeding; N/A=not applicable; NOAC=non-vitamin K antagonist oral anticoagulant; NR=not reported; NSAID=non-steroidal anti-inflammatory drug; OR=odds ratio; PS=propensity score; PPI=proton pump inhibitor; P-Y=person-years; Riva=rivaroxaban; ROR=reporting odds ratio; RR=risk ratio; SD=standard deviation; IQR= interquartile range; MI=myocardial infarction; CHF=congestive heart failure; HF= heart failure; OAC=oral anticoagulant; UGIB=upper gastrointestinal bleeding; VKA=vitamin K antagonist; Warf=warfarin; Y=years

\* Data are from propensity score matched/adjusted cohort if propensity score method was used in study

<sup>a</sup> The GIB event number, total patient number and patient-years were extracted directly from original papers, NR indicates not reported but the calculated data from secondary analysis manually was not shown here;

<sup>b</sup> If result was not directly reported in original paper, required data and unadjusted result were computed manually

# Supplementary Figure 1 Secondary analysis of cross-sectional studies: summarised estimates

# of GIB risk in NOAC users

			Treatment	Control		Risk Ratio		Risk	Ratio	
Study or Subgroup	log[Risk Ratio]	SE	Total	Total	Weight	IV, Random, 95% Cl		IV, Rando	m, 95% Cl	
1.3.1 dabigatran vs v	warfarin									
Bell 2013	0.7151	0.4565	1050	4600	31.5%	2.04 [0.84, 5.00]		-		
Choi 2014	1.1592	0.2981	160	204	35.0%	3.19 [1.78, 5.72]				
Sherid 2015	-0.7371	0.3715	208	209	33.5%	0.48 [0.23, 0.99]			-	
Subtotal (95% CI)			1418	5013	100.0%	1.47 [0.45, 4.85]				
Heterogeneity: Tau <sup>2</sup> =	= 0.97; Chi <sup>z</sup> = 16.1	9, df = 2	(P = 0.0003)	; I² = 88%						
Test for overall effect:	Z = 0.63 (P = 0.53	3)								
									+ + + + + + + + + + + + + + + + + + +	100
							0.01	U. I	I IU	100
Taat fay ay bayay a dif		liaabla						Favours Treatment	Favours Contr	roi

Test for subgroup differences: Not applicable

#### Supplementary Figure 2 Summarised estimates of subgroup analysis by indication

#### Dabigatran

				Risk Ratio		Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl		IV, Random, 95% Cl
1.15.1 AF						
Abraham 2015	-0.2357	0.1354	15.4%	0.79 [0.61, 1.03]		
Chan 2015	0.3988	0.1603	13.2%	1.49 [1.09, 2.04]		
Graham 2015	0.2469	0.0601	23.4%	1.28 [1.14, 1.44]		+
Larsen 2014	0.3148	0.2666	6.9%	1.37 [0.81, 2.31]		
Lauffenburger 2015	0.1044	0.0482	24.6%	1.11 [1.01, 1.22]		-
Vaughan Sarrazin 2014	0.4318	0.1256	16.4%	1.54 [1.20, 1.97]		
Subtotal (95% CI)			<b>100.0</b> %	1.21 [1.03, 1.42]		◆
Heterogeneity: Tau <sup>2</sup> = 0.02	; Chi <sup>z</sup> = 19.14, df	= 5 (P = 1	0.002); I <b>?</b> :	= 74%		
Test for overall effect: Z = 2	.36 (P = 0.02)					
<b>1.15.2 non-AF</b> Abraham 2015 <b>Subtotal (95% CI)</b> Heterogeneity: Not applica Test for overall effect: Z = 0	0.131 ble .35 (P = 0.73)	0.3777	100.0% <b>100.0</b> %	1.14 [0.54, 2.39] <b>1.14 [0.54, 2.39]</b>		
1.15.3 non-specified						
Chang 2015 <b>Subtotal (95% CI)</b> Heterogeneity: Not applica Test for overall effect: Z = 1	0.1906 ble .59 (P = 0.11)	0.1197	100.0% <b>100.0</b> %	1.21 [0.96, 1.53] <b>1.21 [0.96, 1.53]</b>		
					⊢ 0.1	
						Favours Dabigatran Favours Warfarin

Test for subgroup differences: Chi<sup>2</sup> = 0.03, df = 2 (P = 0.99), I<sup>2</sup> = 0%

#### Rivaroxaban



Test for subgroup differences: Chi<sup>2</sup> = 0.71, df = 2 (P = 0.70), l<sup>2</sup> = 0%

Favours Rivaroxaban Favours Warfarin

# Supplementary Figure 3 Summarised estimates of subgroup analysis by GIB severity

#### Dabigatran

-				Risk Ratio		Ris	k Ratio		
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl		IV, Rand	lom, 95% Cl		
1.7.1 dabigatran vs war	farin: Major GIB								
Chan 2015	0.3988	0.1603	12.3%	1.49 [1.09, 2.04]					
Graham 2015	0.2469	0.0601	87.7%	1.28 [1.14, 1.44]					
Subtotal (95% CI)			<b>100.0</b> %	1.30 [1.17, 1.46]			•		
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi² = 0.79, df =	1 (P = 0)	.37); I² = 0	)%					
Test for overall effect: Z =	4.72 (P < 0.00001	)							
1.7.2 dabigatran vs war	farin: Non-major G	В				_			
Chan 2015	-0.1625	0.38	100.0%	0.85 [0.40, 1.79]					
Subtotal (95% CI)			100.0%	0.85 [0.40, 1.79]					
Heterogeneity: Not applic	cable								
Test for overall effect: Z =	: 0.43 (P = 0.67)								
1.7.3 dabigatran vs warf	farin: Any GIB								
Abraham 2015	-0.2357	0.1354	19.6%	0.79 [0.61, 1.03]			+		
Chang 2015	0.1906	0.1197	21.3%	1.21 [0.96, 1.53]			+		
Larsen 2014	0.3148	0.2666	9.5%	1.37 [0.81, 2.31]		-	<b></b>		
Lauffenburger 2015	0.1044	0.0482	28.9%	1.11 [1.01, 1.22]			-		
Vaughan Sarrazin 2014	0.4318	0.1256	20.7%	1.54 [1.20, 1.97]					
Subtotal (95% CI)			<b>100.0</b> %	1.15 [0.95, 1.40]			•		
Heterogeneity: Tau <sup>2</sup> = 0.0	03; Chi² = 14.05, df	= 4 (P = I	0.007); l <sup>z</sup> :	= 72%					
Test for overall effect: Z =	1.46 (P = 0.15)								
					<u> </u>		<u> </u>	<u> </u>	
					0.1	0.2 0.5	1 2	5	10
	o			10.00		Favours NOA	Favours Wa	anarin	

Test for subgroup differences:  $Chi^2 = 2.23$ , df = 2 (P = 0.33),  $l^2 = 10.3\%$ 

#### Rivaroxaban

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				Risk Ratio		Risk Ratio	
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl		IV, Random, 95% Cl	
1.7.4 rivaroxaban vs	warfarin: Major G	ыв					
Chan 2015	-0.0408	0.2574	100.0%	0.96 [0.58, 1.59]			
Subtotal (95% CI)			100.0%	0.96 [0.58, 1.59]			
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.16 (P = 0.87	7)					
1.7.5 rivaroxaban vs	warfarin: Non-ma	ajor GIB				_	
Chan 2015	-0.1985	0.5082	100.0%	0.82 [0.30, 2.22]			
Subtotal (95% CI)			100.0%	0.82 [0.30, 2.22]			
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.39 (P = 0.70	))					
1.7.6 rivaroxaban vs	warfarin: Any GIE	3					
Abraham 2015	-0.0726	0.1509	42.2%	0.93 [0.69, 1.25]			
Chang 2015	-0.0202	0.5152	5.0%	0.98 [0.36, 2.69]			
Laliberte 2014	0.239	0.1273	52.9%	1.27 [0.99, 1.63]			
Subtotal (95% CI)			<b>100.0</b> %	1.10 [0.87, 1.38]		-	
Heterogeneity: Tau <sup>2</sup> =	: 0.01; Chi² = 2.55	, df = 2 (P	? = 0.28); I	<b>²</b> = 22%			
Test for overall effect:	Z = 0.81 (P = 0.42	2)					
					0.1 0.2		5 10

Test for subgroup differences:  $Chi^2 = 0.50$ , df = 2 (P = 0.78),  $l^2 = 0\%$ 

Favours NOAC Favours Warfarin

# Supplementary Figure 4 Summarised estimates of subgroup analysis by different age groups

Dabigatran				Risk Ratio		Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV. Random, 95% Cl		IV, Random, 95% Cl
1.8.1 dabigatran vs warf	arin, 18-64 yrs					
Chang 2015	0.2927	0.159	100.0%	1.34 [0.98, 1.83]		+ <b></b>
Subtotal (95% CI)			<b>100.0</b> %	1.34 [0.98, 1.83]		•
Heterogeneity: Not applic	able					
Test for overall effect: Z =	1.84 (P = 0.07)					
1.8.2 dabigatran vs warf	arin, ≥65 yrs					
Abraham 2015	0.9123	0.2197	27.7%	2.49 [1.62, 3.83]		_ <b>_</b>
Chang 2015	0.0677	0.1825	31.1%	1.07 [0.75, 1.53]		
Graham 2015	0.2469	0.0601	41.2%	1.28 [1.14, 1.44]		
Subtotal (95% CI)			<b>100.0</b> %	1.46 [0.99, 2.13]		-
Heterogeneity: Tau <sup>2</sup> = 0.0	)9; Chi² = 9.92, df =	: 2 (P = 0	.007); l² =	80%		
Test for overall effect: Z =	1.93 (P = 0.05)					
1.8.3 dabigatran vs warf	arin, all adults (≥	18) yrs				
Abraham 2015	-0.2357	0.1354	16.7%	0.79 [0.61, 1.03]		
Chan 2015	0.3988	0.1603	14.7%	1.49 [1.09, 2.04]		
Chang 2015	0.1906	0.1197	18.1%	1.21 [0.96, 1.53]		<b>↓</b> ■-
Larsen 2014	0.3148	0.2666	8.4%	1.37 [0.81, 2.31]		
Lauffenburger 2015	0.1044	0.0482	23.9%	1.11 [1.01, 1.22]		•
Vaughan Sarrazin 2014	0.4511	0.1184	18.2%	1.57 [1.24, 1.98]		
Subtotal (95% CI)			100.0%	1.21 [1.00, 1.45]		•
Heterogeneity: Tau <sup>2</sup> = 0.0	)3; Chi² = 18.35, df	= 5 (P =	0.003); I²:	= 73%		
Test for overall effect: Z =	1.99 (P = 0.05)					
					L	
					0.05	0.2 1 5 20
Teet for subgroup differe	neoe: Chi <b>Z</b> = 0.01	df = 270	- 0 6 2 1 8	- 0%		Favours NOAC Favours Warfarin

Test for subaroup differences: Chi<sup>2</sup> = 0.91, df = 2 (P = 0.63), l<sup>2</sup> = 0%

#### Rivaroxaban

				Risk Ratio		Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl		IV, Random, 95% Cl
1.8.4 rivaroxaban vs	warfarin, 18-64 y	rs				<u> </u>
Chang 2015	0.0296	0.5752	100.0%	1.03 [0.33, 3.18]		
Subtotal (95% CI)			<b>100.0</b> %	1.03 [0.33, 3.18]		
Heterogeneity: Not a	pplicable					
Test for overall effect	: Z = 0.05 (P = 0.98	6)				
1.8.5 rivaroxaban vs	warfarin, ≥65 yr	s				
Abraham 2015	1.0682	0.2564	56.6%	2.91 [1.76, 4.81]		│ ── <b>■</b> ──
Chang 2015	-0.478	0.6176	43.4%	0.62 [0.18, 2.08]		
Subtotal (95% CI)			<b>100.0</b> %	1.49 [0.33, 6.68]		
Heterogeneity: Tau <sup>2</sup> =	= 0.97; Chi <sup>2</sup> = 5.35	, df = 1 (F	P = 0.02)(1	P= 81%		
Test for overall effect	Z = 0.52 (P = 0.60	))				
1.8.6 rivaroxaban vs	warfarin, all adul	ts(≥18	yrs)			
Abraham 2015	-0.0726	0.1509	35.3%	0.93 [0.69, 1.25]		
Chan 2015	-0.0408	0.2574	12.1%	0.96 [0.58, 1.59]		
Chang 2015	-0.0202	0.5152	3.0%	0.98 [0.36, 2.69]		
Laliberte 2014	0.239	0.1273	49.6%	1.27 [0.99, 1.63]		t <b>e</b> −
Subtotal (95% CI)			<b>100.0</b> %	1.09 [0.92, 1.30]		◆
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>2</sup> = 2.83	df = 3 (F	P = 0.42)(1	I <sup>2</sup> = 0%		
Test for overall effect	: Z = 0.97 (P = 0.33	3)				
					<b>—</b>	<u>_</u>
					0.05	0.2 1 5 2
To at fay and available	Ferences ObiZ - 0	47 46-4	n = n n	0) IZ - 00/		Favours NOAC Favours Warfarin

Test for subaroup differences:  $Chi^2 = 0.17$ . df = 2 (P = 0.92).  $I^2 = 0\%$ 

# Supplementary Figure 5 Summarised estimates of subgroup analysis by prior use of warfarin:

#### GIB risk among dabigatran users



Test for subgroup differences: Chi<sup>2</sup> = 1.03, df = 1 (P = 0.31), l<sup>2</sup> = 3.0%

# Supplementary Figure 6 Summarised estimates of subgroup analysis by use of NSAID

# Dabigatran

				Risk Ratio		Risk Ratio	
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl		IV, Random, 95% Cl	
1.10.1 dabigatran vs war	farin: adjusted for	NSAID	use				
Abraham 2015	-0.2357	0.1354	20.0%	0.79 [0.61, 1.03]			
Chang 2015	0.1906	0.1197	21.6%	1.21 [0.96, 1.53]		+	
Graham 2015	0.2469	0.0601	27.4%	1.28 [1.14, 1.44]		-	
Larsen 2014	0.3148	0.2666	10.1%	1.37 [0.81, 2.31]		- <b>+-</b>	
Vaughan Sarrazin 2014	0.4318	0.1256	21.0%	1.54 [1.20, 1.97]			
Subtotal (95% CI)			100.0%	1.20 [0.98, 1.47]		◆	
Heterogeneity: Tau² = 0.0	4; Chi <sup>2</sup> = 14.51, df	= 4 (P =	0.006); I <sup>z</sup>	= 72%			
Test for overall effect: Z =	1.77 (P = 0.08)						
1.10.2 dabigatran vs war	farin: Not adjuste	d for NS	AID use				
Chan 2015	0.3988	0.1603	36.5%	1.49 [1.09, 2.04]		<b> </b> − <b>∎</b> −	
Lauffenburger 2015	0.1044	0.0482	63.5%	1.11 [1.01, 1.22]		<b>—</b>	
Subtotal (95% CI)			<b>100.0</b> %	1.24 [0.94, 1.63]		◆	
Heterogeneity: Tau² = 0.0	3; Chi² = 3.09, df =	1 (P = 0	.08); I <sup>2</sup> = 6	68%			
Test for overall effect: Z =	1.49 (P = 0.13)						
					<b>⊢</b> →		—
					0.1 0.1	2 0.5 1 2 5	10
To at fair and superior differen		16 - 4 (D)	0.07) 17	- 001		Favours NOAC Favours Warfarin	

Test for subaroup differences:  $Chi^2 = 0.03$ . df = 1 (P = 0.87). l<sup>2</sup> = 0%

# Rivaroxaban

Trivarozabari							
				Risk Ratio	Risk Ratio		
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% C	1	
1.10.3 rivaroxaban v	s warfarin: adjuste	d for NS	AID use				
Abraham 2015	-0.0726 0	).1509	42.2%	0.93 [0.69, 1.25]			
Chang 2015	-0.0202 0	).5152	5.0%	0.98 [0.36, 2.69]		-	
Laliberte 2014	0.239 0	).1273	52.9%	1.27 [0.99, 1.63]			
Subtotal (95% CI)			100.0%	1.10 [0.87, 1.38]	<b>•</b>		
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi² = 2.55, d	lf = 2 (P	= 0.28); f	<b>²</b> = 22%			
Test for overall effect:	Z = 0.81 (P = 0.42)						
1.10.4 rivaroxaban v	s warfarin: Not adju	isted fo	r NSAID u	ise			
Chan 2015	-0.0408 0	0.2574	100.0%	0.96 [0.58, 1.59]			
Subtotal (95% CI)			100.0%	0.96 [0.58, 1.59]			
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.16 (P = 0.87)						
						5 1	-  0
					Favours NOAC Favours	Warfarin	

Test for subaroup differences:  $Chi^2 = 0.23$ . df = 1 (P = 0.63).  $I^2 = 0\%$ 

# Supplementary Figure 7 Summarised estimates of subgroup analysis by use of gastroprotective agents (PPI/H2RA)

# Dabigatran

				Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.11.1 dabigatran vs war	farin: adjusted for I	PPI/H2 (	use		
Abraham 2015	-0.2357 (	0.1354	17.6%	0.79 [0.61, 1.03]	
Chang 2015	0.1906 (	0.1197	19.9%	1.21 [0.96, 1.53]	+
Graham 2015	0.2469 (	0.0601	30.2%	1.28 [1.14, 1.44]	+
Lauffenburger 2015	0.1044 (	0.0482	32.3%	1.11 [1.01, 1.22]	
Subtotal (95% CI)			<b>100.0</b> %	1.11 [0.95, 1.30]	•
Heterogeneity: Tau <sup>2</sup> = 0.03	2; Chi <sup>z</sup> = 11.58, df =	3 (P = 0	0.009); I <sup>z</sup> :	= 74%	
Test for overall effect: Z =	1.33 (P = 0.18)				
1.11.2 dabigatran vs war	farin: Not adjusted	for PPI	/H2 use		
Chan 2015	0.3988 (	0.1603	33.4%	1.49 [1.09, 2.04]	
Larsen 2014	0.3148 (	0.2666	12.1%	1.37 [0.81, 2.31]	
Vaughan Sarrazin 2014	0.4318 (	0.1256	54.5%	1.54 [1.20, 1.97]	
Subtotal (95% CI)			<b>100.0</b> %	1.50 [1.25, 1.80]	•
Heterogeneity: Tau <sup>2</sup> = 0.0	0; Chi <sup>z</sup> = 0.16, df = 2	2 (P = 0.	92); I <sup>z</sup> = 0	1%	
Test for overall effect: Z =	4.39 (P < 0.0001)				
					Eavoure NOAC Eavoure Warfarin
The state of source of the second state of the second		6 4 (D	0.041.17	00.000	

Test for subaroup differences: Chi<sup>2</sup> = 6.16, df = 1 (P = 0.01), l<sup>2</sup> = 83.8%

# Rivaroxaban

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				Risk Ratio	Risk Ratio			
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl			
1.11.3 rivaroxaban vs	s warfarin: adjust	ed for PF	PI/H2 use					
Abraham 2015	-0.0726	0.1509	92.1%	0.93 [0.69, 1.25]				
Chang 2015	-0.0202	0.5152	7.9%	0.98 [0.36, 2.69]				
Subtotal (95% CI)			100.0%	0.93 [0.70, 1.24]	<b>•</b>			
Heterogeneity: Tau <sup>2</sup> =	Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.01, df = 1 (P = 0.92); I <sup>2</sup> = 0%							
Test for overall effect:	Test for overall effect: Z = 0.47 (P = 0.64)							
1.11.4 rivaroxaban vs warfarin: Not adjusted for PPI/H2 use								
Chan 2015	-0.0408	0.2574	19.7%	0.96 [0.58, 1.59]	<b></b>			
Laliberte 2014	0.239	0.1273	80.3%	1.27 [0.99, 1.63]	+			
Subtotal (95% CI)			100.0%	1.20 [0.96, 1.50]	◆			
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); l² = 0%								

Test for overall effect: Z = 1.61 (P = 0.11)



Test for subaroup differences:  $Chi^2 = 1.88$ . df = 1 (P = 0.17).  $I^2 = 46.7\%$ 

Supplementary Figure 8 Summarised estimates of subgroup analysis by use of antiplatelet

agents

# Dabigatran



Test for subaroup differences:  $Chi^2 = 0.63$ . df = 1 (P = 0.43). l^2 = 0%

#### Rivaroxaban

				Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.12.3 rivaroxaban v	s warfarin: adjust	ed for ar	ntiplatele	t agent use	
Abraham 2015	-0.0726	0.1509	46.6%	0.93 [0.69, 1.25]	
Laliberte 2014	0.239	0.1273	53.4%	1.27 [0.99, 1.63]	
Subtotal (95% CI)			100.0%	1.10 [0.81, 1.49]	<b>•</b>
Heterogeneity: Tau <sup>2</sup> =	0.03; Chi <sup>2</sup> = 2.49,	df = 1 (P	<sup>2</sup> = 0.11);	I <sup>2</sup> = 60%	
Test for overall effect:	Z = 0.60 (P = 0.55	6)			
1.12.4 rivaroxaban v	s warfarin: Not ad	ljusted fo	or antipla	telet agent use	$\perp$
Chan 2015	-0.0408	0.2574	80.0%	0.96 [0.58, 1.59]	
Chang 2015	-0.0202	0.5152	20.0%	0.98 [0.36, 2.69]	

0.96 [0.61, 1.51] Subtotal (95% CI) 100.0% Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.00, df = 1 (P = 0.97); l<sup>2</sup> = 0% Test for overall effect: Z = 0.16 (P = 0.87)



Test for subaroup differences:  $Chi^2 = 0.22$ , df = 1 (P = 0.64),  $I^2 = 0\%$ 

# Supplementary Figure 9 Summarised estimates of subgroup analysis by use of steroids

# Dabigatran

				Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.13.1 dabigatran vs wai	rfarin: adjusted fo	r steroid	use		
Abraham 2015	-0.2357	0.1354	29.7%	0.79 [0.61, 1.03]	
Chang 2015	0.1906	0.1197	31.7%	1.21 [0.96, 1.53]	+
Graham 2015	0.2469	0.0601	38.6%	1.28 [1.14, 1.44]	-
Subtotal (95% Cl)			100.0%	1.09 [0.83, 1.43]	<b>+</b>
Heterogeneity: Tau² = 0.0	)5; Chi² = 10.64, df	= 2 (P =	0.005); I <sup>z</sup>	= 81%	
Test for overall effect: Z =	0.62 (P = 0.53)				
1.13.2 dabigatran vs wai	rfarin: Not adjuste	d for ste	roid use		
Chan 2015	0.3988	0.1603	22.0%	1.49 [1.09, 2.04]	
Larsen 2014	0.3148	0.2666	11.9%	1.37 [0.81, 2.31]	
Lauffenburger 2015	0.1044	0.0482	39.0%	1.11 [1.01, 1.22]	<mark>■</mark>
Vaughan Sarrazin 2014	0.4318	0.1256	27.0%	1.54 [1.20, 1.97]	
Subtotal (95% CI)			100.0%	1.33 [1.07, 1.64]	◆
Heterogeneity: Tau <sup>2</sup> = 0.0	)3; Chi <sup>z</sup> = 8.53, df =	3 (P = 0	.04); I <sup>2</sup> = 6	65%	
Test for overall effect: Z =	2.60 (P = 0.009)				
					`0.1 0.2 0.5 1 2 5 10`
			· ·		Favours NOAC Favours Warfarin

Test for subaroup differences:  $Chi^2 = 1.26$ , df = 1 (P = 0.26),  $l^2 = 20.9\%$ 

# Rivaroxaban

				Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.13.3 rivaroxaban v	s warfarin: adjust	ed for st	eroid use	e	
Abraham 2015	-0.0726	0.1509	92.1%	0.93 [0.69, 1.25]	
Chang 2015	-0.0202	0.5152	7.9%	0.98 [0.36, 2.69]	
Subtotal (95% CI)			100.0%	0.93 [0.70, 1.24]	<b>•</b>
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>2</sup> = 0.01,	df = 1 (F	<sup>o</sup> = 0.92);	I² = 0%	
Test for overall effect:	Z = 0.47 (P = 0.64	)			
1.13.4 rivaroxaban v	s warfarin: Not ad	justed fo	or steroid	use	
Chan 2015	-0.0408	0.2574	19.7%	0.96 [0.58, 1.59]	<b>+</b> _
Laliberte 2014	0.239	0.1273	80.3%	1.27 [0.99, 1.63]	
Subtotal (95% CI)			100.0%	1.20 [0.96, 1.50]	►
Heterogeneity: Tau² =	= 0.00; Chi <sup>2</sup> = 0.95,	df = 1 (F	<sup>o</sup> = 0.33);	I <sup>2</sup> = 0%	
Test for overall effect:	Z = 1.61 (P = 0.11	)			
					Favours NOAC Favours Warfarin
To at fair authorization diff	foronada: Chiž – 1	00 df = 4	1/D = 0.4	7) 12 - 46 704	

Test for subaroup differences:  $Chi^2 = 1.88$ . df = 1 (P = 0.17).  $I^2 = 46.7\%$ 

# Supplementary Figure 10 Summarised estimates of subgroup analysis by use of SSRI

# Dabidatran

			Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE Weig	ht IV, Random, 95% Cl	IV, Random, 95% Cl
1.14.1 dabigatran vs wa	rfarin: adjusted for S	SRI use		
Abraham 2015	-0.2357 0.	1354 46.8	% 0.79 [0.61, 1.03]	
Graham 2015	0.2469 0.	.0601 53.2	% 1.28 [1.14, 1.44]	
Subtotal (95% Cl)		100.0	% 1.02 [0.64, 1.64]	
Heterogeneity: Tau <sup>2</sup> = 0.1	l1; Chi² = 10.61, df = 1	I (P = 0.001);	I <sup>z</sup> = 91%	
Test for overall effect: Z =	0.09 (P = 0.93)			
1.14.2 dabigatran vs wa	rfarin: Not adjusted f	or SSRI use		
Chan 2015	0.3988 0.	1603 15.4	% 1.49 [1.09, 2.04]	_ <b></b> -
Chang 2015	0.1906 0.	1197 21.3	% 1.21 [0.96, 1.53]	
Larsen 2014	0.3148 0.	2666 7.3	% 1.37 [0.81, 2.31]	
Lauffenburger 2015	0.1044 0.	.0482 35.8	% 1.11 [1.01, 1.22]	<b>-</b>
Vaughan Sarrazin 2014	0.4318 0.	1256 20.3	% 1.54 [1.20, 1.97]	
Subtotal (95% CI)		100.0	% 1.28 [1.10, 1.50]	◆
Heterogeneity: Tau <sup>2</sup> = 0.0	02; Chi <sup>z</sup> = 8.56, df = 4 (	(P = 0.07); l <sup>2</sup>	= 53%	
Test for overall effect: Z =	3.15 (P = 0.002)			
				U.1 U.2 U.5 1 2 5 10
Test for outpressed differen	nana: ObiZ - 0.04. df-	4 (0 - 0.27)	17 - 00	Favours NOAC Favours Waitarin

Test for subaroup differences:  $Chi^2 = 0.81$ . df = 1 (P = 0.37).  $I^2 = 0\%$ 

#### Rivaroxaban

			Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE Weigh	t IV, Random, 95% Cl	IV, Random, 95% Cl
1.14.3 rivaroxaban v	s warfarin: adjusted	for SSRI use		
Abraham 2015	-0.0726 0.	1509 100.0%	6 0.93 [0.69, 1.25]	
Subtotal (95% CI)		100.09	% 0.93 [0.69, 1.25]	<b>•</b>
Heterogeneity: Not ap	oplicable			
Test for overall effect	Z = 0.48 (P = 0.63)			
1.14.4 rivaroxaban v	s warfarin: Not adjus	sted for SSRI	use	
Chan 2015	-0.0408 0.	2574 18.79	6 0.96 [0.58, 1.59]	
Chang 2015	-0.0202 0.	5152 4.79	6 0.98 [0.36, 2.69]	
Laliberte 2014	0.239 0.	1273 76.69	6 1.27 [0.99, 1.63]	
Subtotal (95% CI)		100.09	% 1.19 [0.96, 1.48]	◆
Heterogeneity: Tau² =	= 0.00; Chi <sup>2</sup> = 1.10, df	= 2 (P = 0.58)	; I² = 0%	
Test for overall effect	Z = 1.57 (P = 0.12)			
				0.1 0.2 0.5 1 2 5 10
				Favours NOAC Favours Warfarin

Test for subaroup differences:  $Chi^2 = 1.73$ , df = 1 (P = 0.19), l<sup>2</sup> = 42.4%