

Supplementary Figures and Tables

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

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Supplementary Table 1 Newcastle-Ottawa scale for assessment of quality of the included comparative observational studies

Study	Study design	Newcastle-Ottawa Scale Score (Total)	Newcastle-Ottawa Scale		
			Selection	Comparability	Exposure/Outcome
Abraham 2015[37]	C	9	****	**	***
Chan 2015[38]	C	6	**	**	**
Chang 2015[39]	C	9	****	**	***
Graham 2015[26]	C	7	***	**	**
Hernandez 2015[40]	C	8	***	**	***
Larsen 2014[34]	C	8	***	**	***
Staerk 2015[43]	C	9	****	**	***
Larsen 2013[32]	C	8	***	**	***
Lauffenburger 2015[41]	C	8	***	**	***
Vaughan Sarrazin 2014[36]	C	8	***	**	***
Laliberte 2014[33]	C	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 (mean ±SD)	NOAC & Warfarin (GIB/total, patient-years) ^a	GIB Rate (per 100 Patient-Years)	Crude OR/IRR/HR (95% CI)	Adjusted OR/RR/HR (95% CI)	Confounding variables adjusted for
Cohort studies (n=11)							
Abraham 2015[37]	Dabi 67.2±11.2, 60.8% ≥65y; Warf matched 67.5±11.2, 60.7% ≥65y; Riva 69.0±10.9, 68.9% ≥65y; Warf matched 69.1±10.9, 68.0% ≥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; Riva 57.6±9.8, 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 Warf 75.6±9.5	Dabi 19.1% 0-1; Warf 18.9% 0-1	Dabi NR/1302; Mean follow up time: 117 days (IQR: 89- 256) Warf NR/8102; Mean follow up time: 228 days (IQR: 119- 333)	NR	NR	HR: Dabi vs Warf 1.85 (1.64-2.07)	PS weighting, characteristics listed in Table 1
Larsen 2014[34]	VKA na ÷ve: 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 ÷ve: 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 ÷ve: 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 ÷ve: Dabi110mg: 0.72 (0.39-1.33) ^b Dabi150mg: 0.84 (0.51-1.40) ^b VKA experienced: Not calculated	HR VKA na ÷ve: 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 ÷ve 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

Larsen 2013[32]	VKA na i ve: Dabi 150 67.4±8.5, 68.6% ≥65y; Dabi 110 74.7±11.8, 80.5% ≥65y; Warf 70.4±12.6, 73.0% ≥65y	Dabi 150 0.96±1.07 Dabi 110 1.27±1.27 Warf 1.18±1.17	Dabi150mg: 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.
Lauffenbur ger 2015[41]	Dabi 67.5±12.4, 55.4% ≥65y Warf 71.4±12.2, 68% ≥65y	CHA ₂ DS ₂ - 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
Vaughan Sarrazin 2014[36]	Dabi 69.7±9.0, 69.9% ≥65y; Warf 74.4±10.1, 82.2% ≥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.
Laliberte 2014[33]	Riva: 82.6% >65y Warf: 84.6% >65y	Riva 2.0±1.0, 40.1% 0-1; Warf 2.0±1.0, 37.7% 0-1	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 listed in Tables 1 and 2
Cross-sectional studies (n=5)							

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 m ² , 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

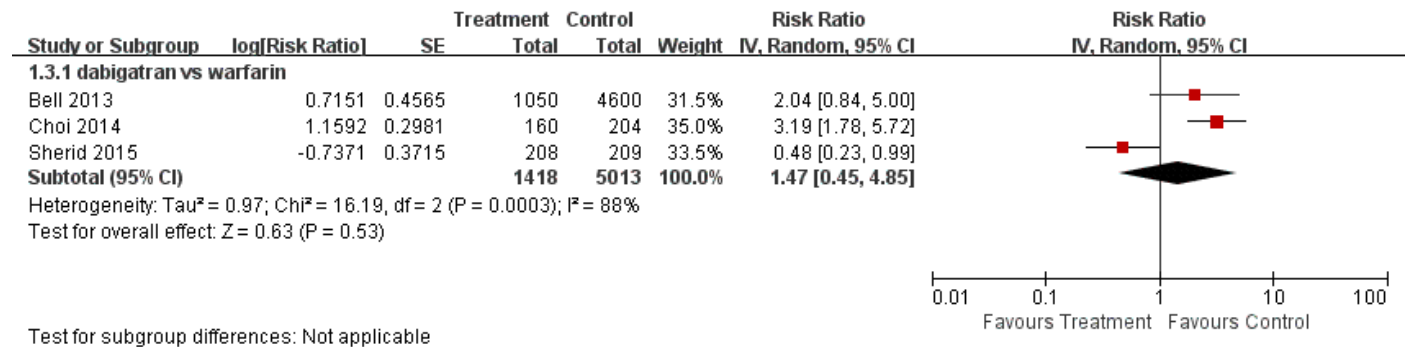
Abbreviations: ACEi=angiotensin converting enzyme inhibitor; AF=atrial fibrillation; Api=apixaban; ARB= angiotensin receptor blocker; ASA=aspirin; CI=confidence interval; CHADS2=congestive heart failure, hypertension, age 75 years or older, diabetes mellitus and stroke; TIA=transient ischemic attack; CHA₂DS₂-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

^a 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;

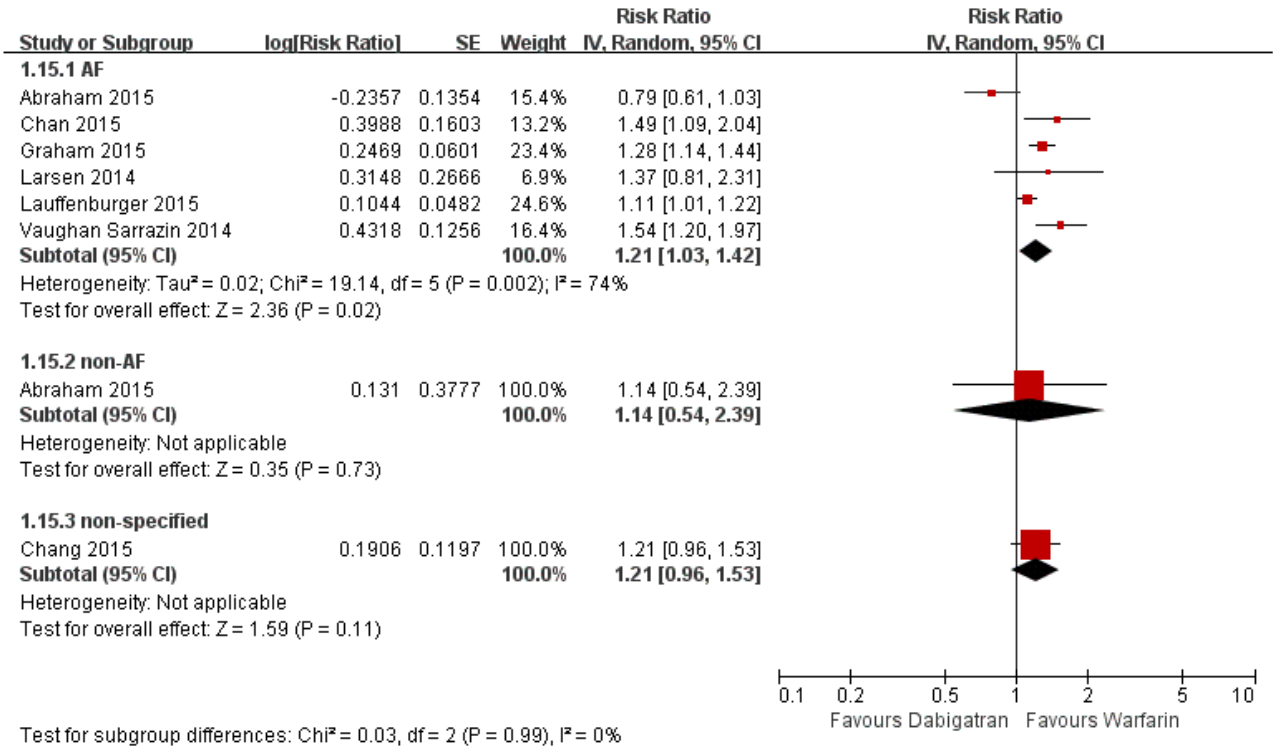
^b If result was not directly reported in original paper, required data and unadjusted result were computed manually

Supplementary Figure 1 Secondary analysis of cross-sectional studies: summarised estimates of GIB risk in NOAC users

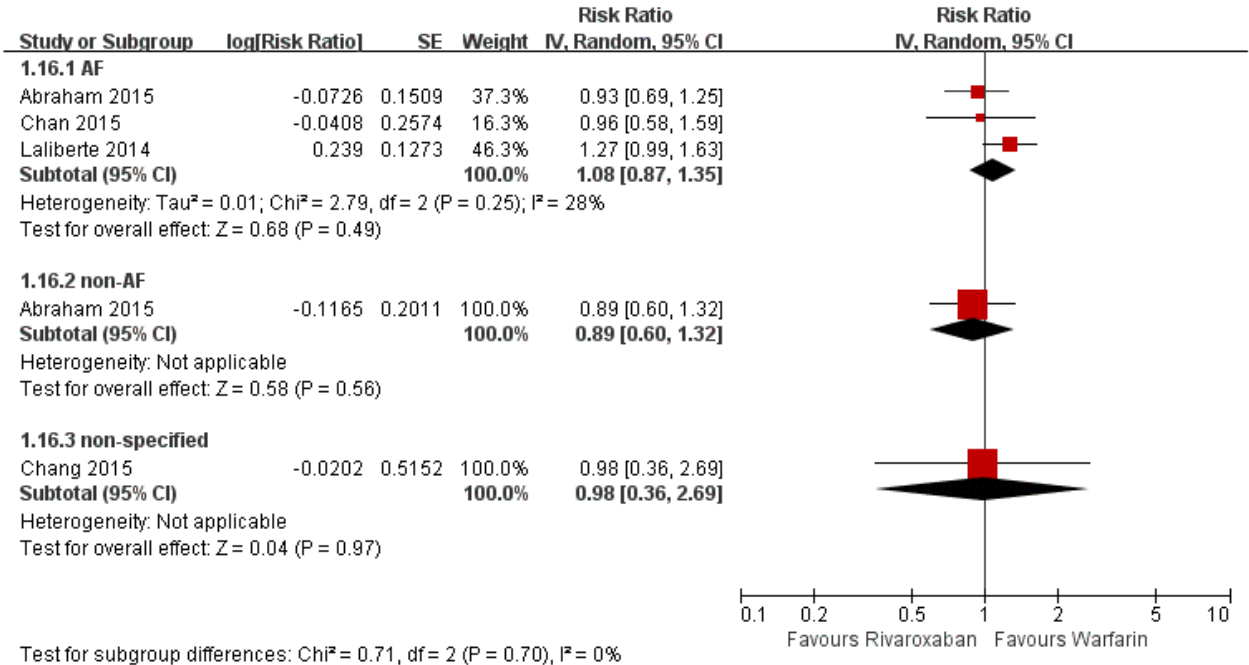


Supplementary Figure 2 Summarised estimates of subgroup analysis by indication

Dabigatran

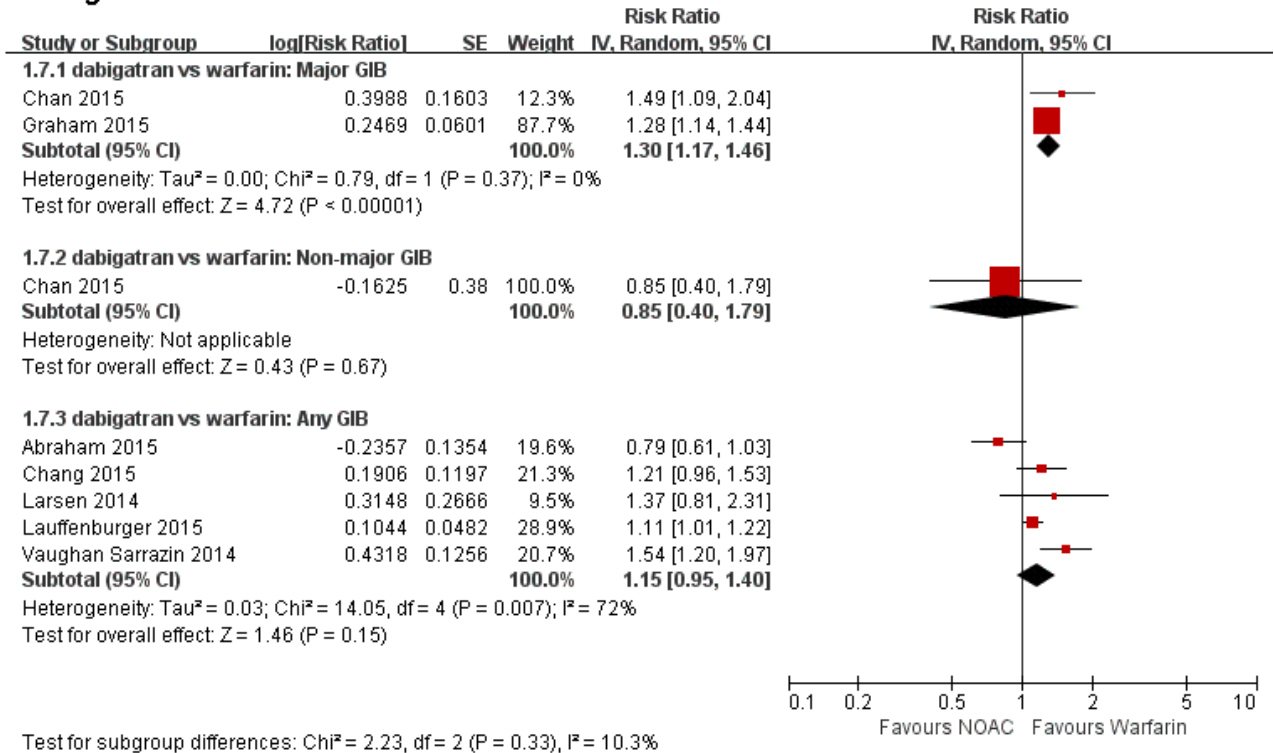


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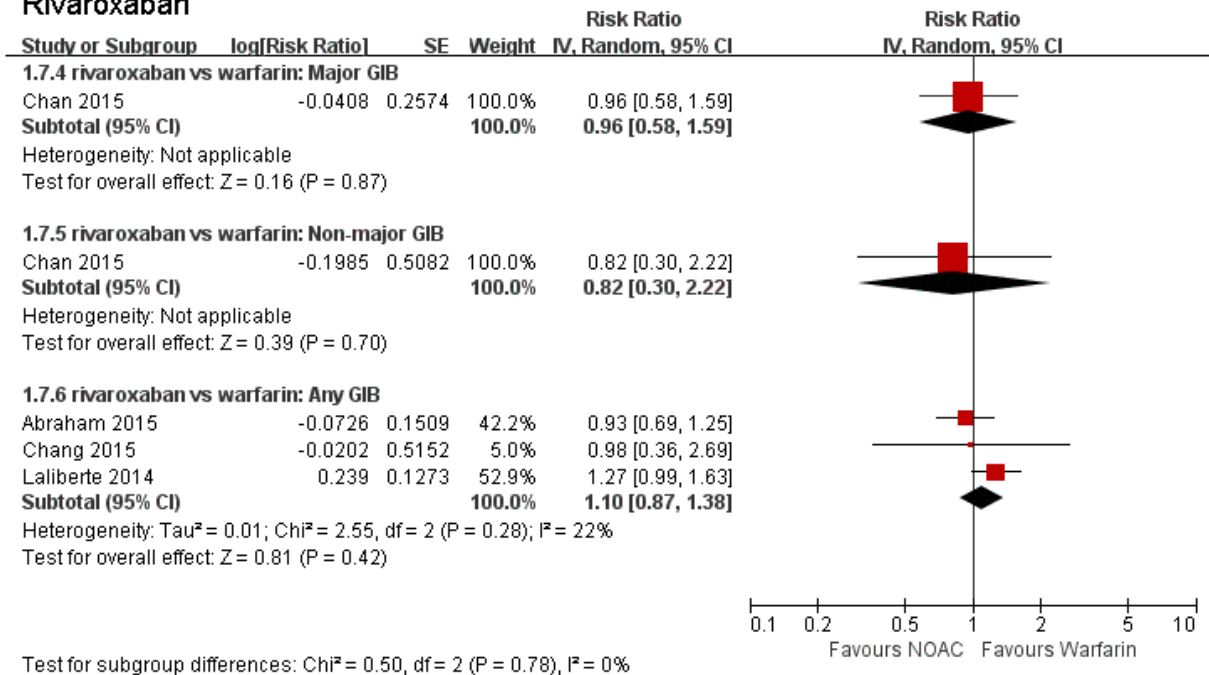


Supplementary Figure 3 Summarised estimates of subgroup analysis by *GIB severity*

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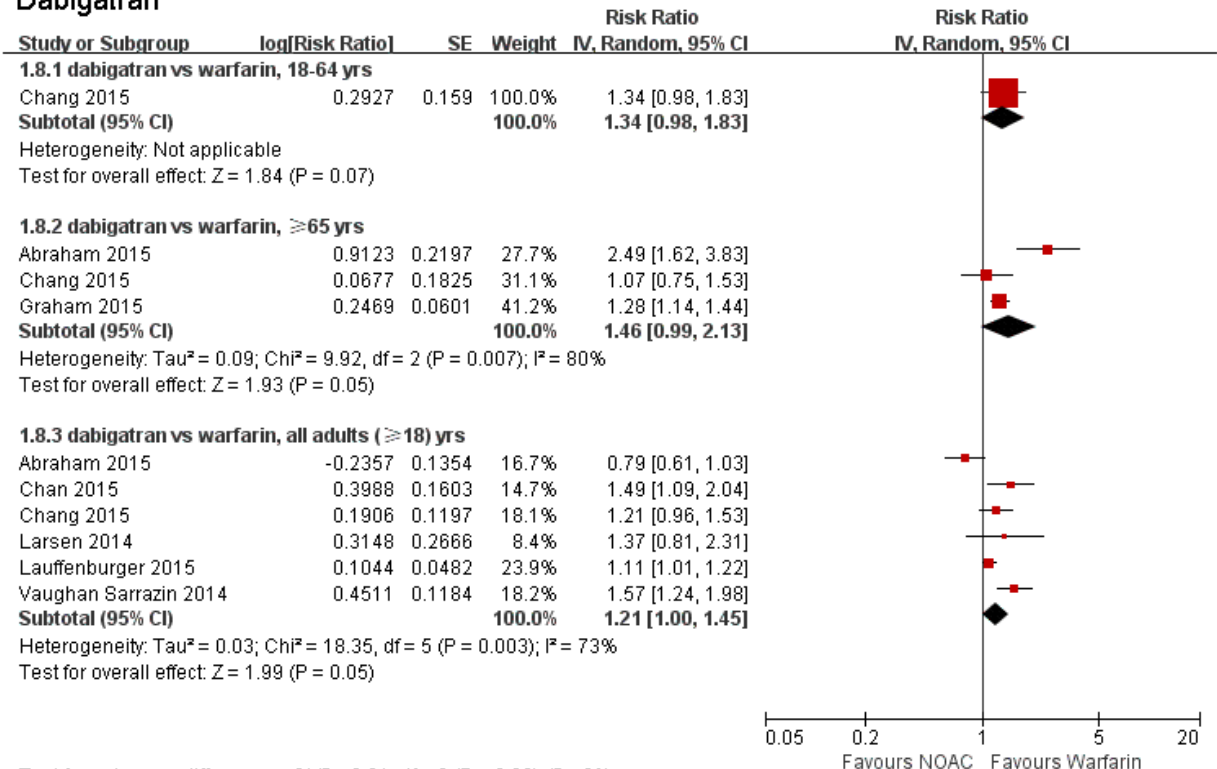


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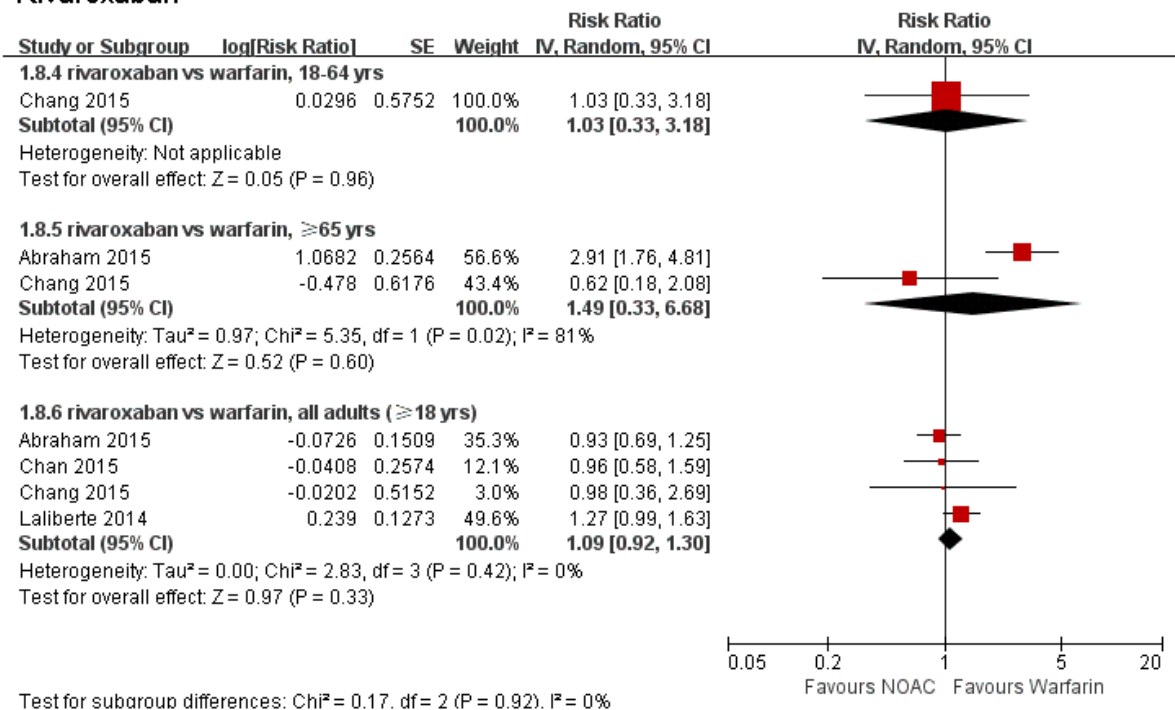


Supplementary Figure 4 Summarised estimates of subgroup analysis *by different age groups*

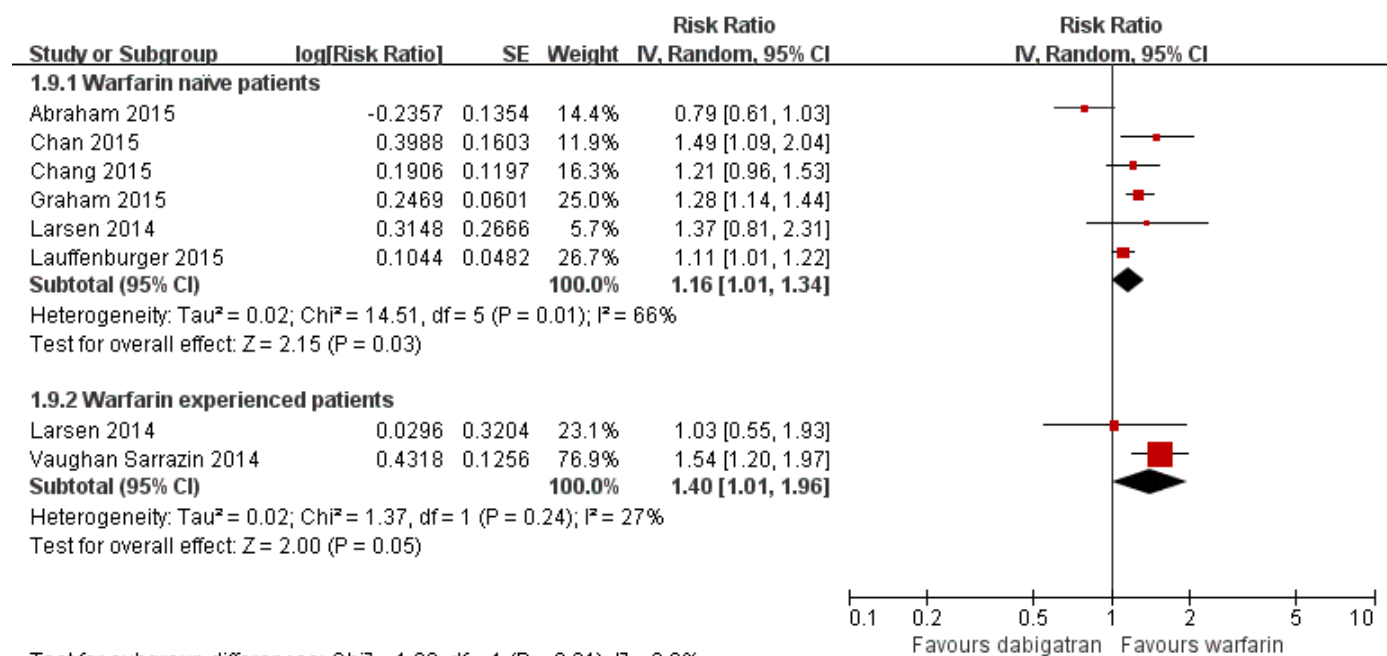
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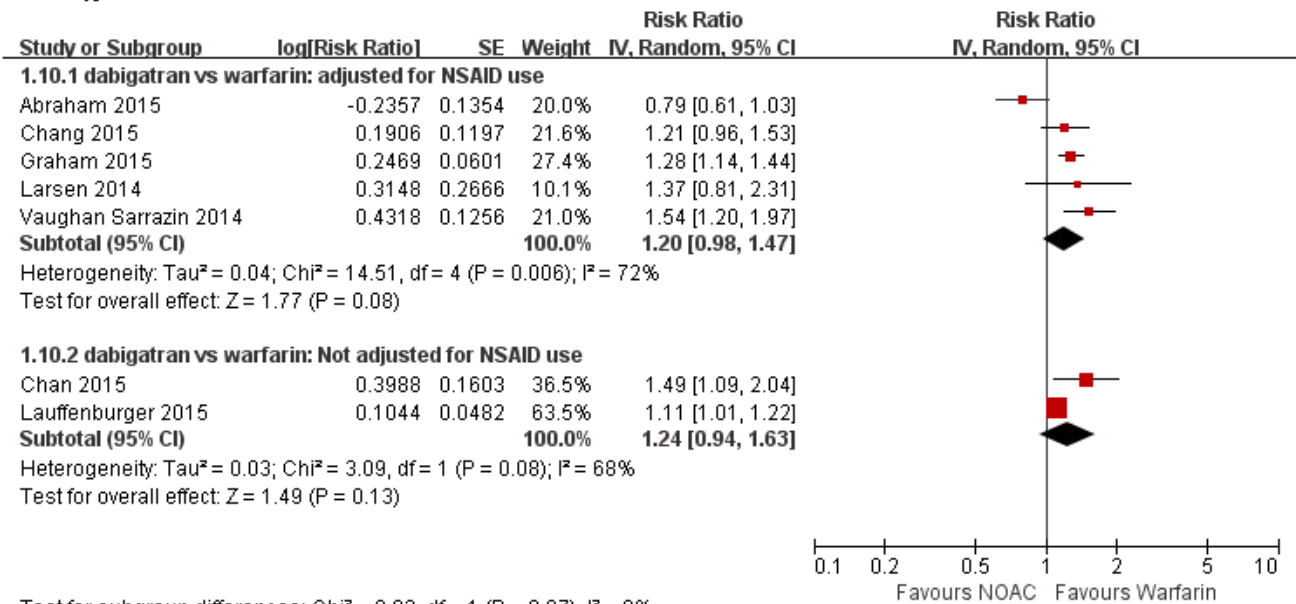


Supplementary Figure 5 Summarised estimates of subgroup analysis *by prior use of warfarin:*
GIB risk among dabigatran users

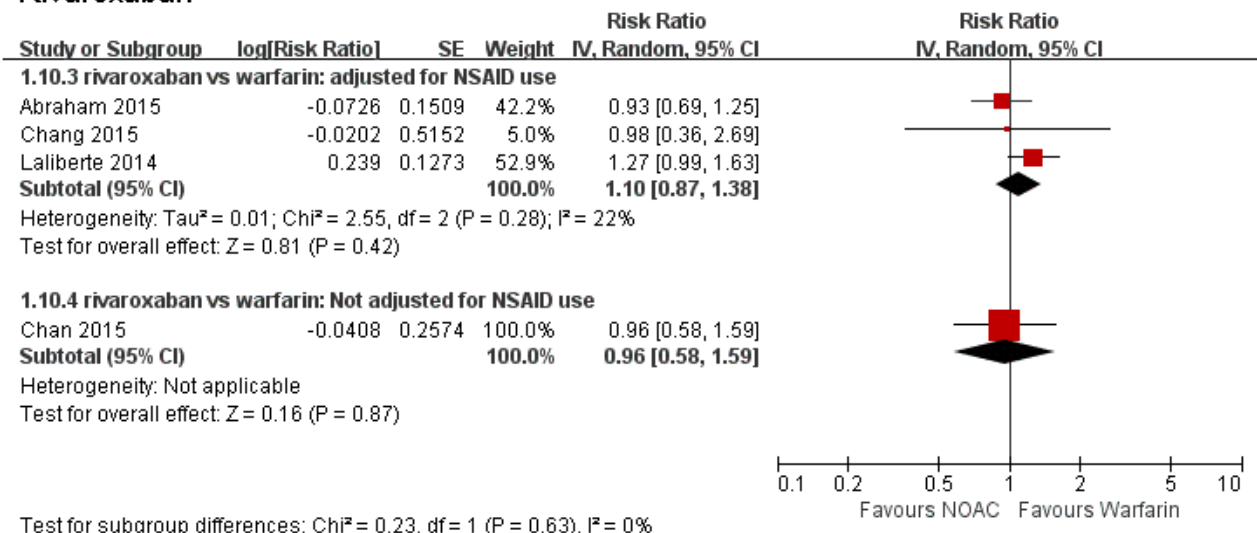


Supplementary Figure 6 Summarised estimates of subgroup analysis *by use of NSAID*

Dabigatran

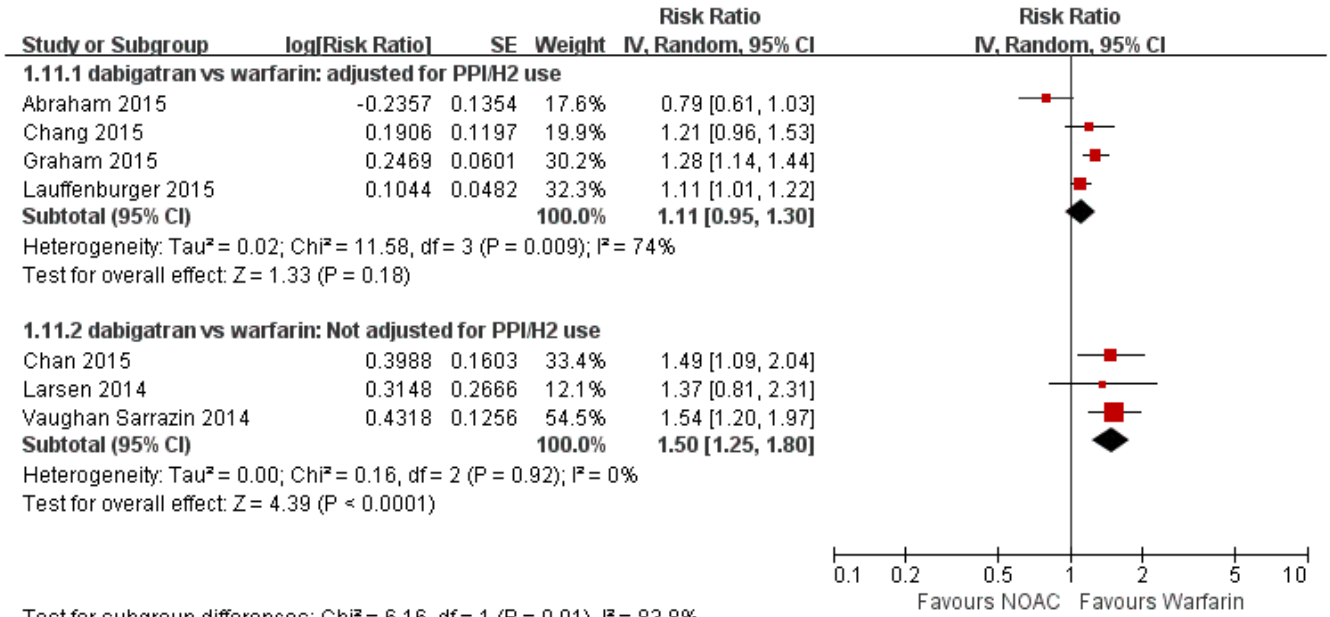


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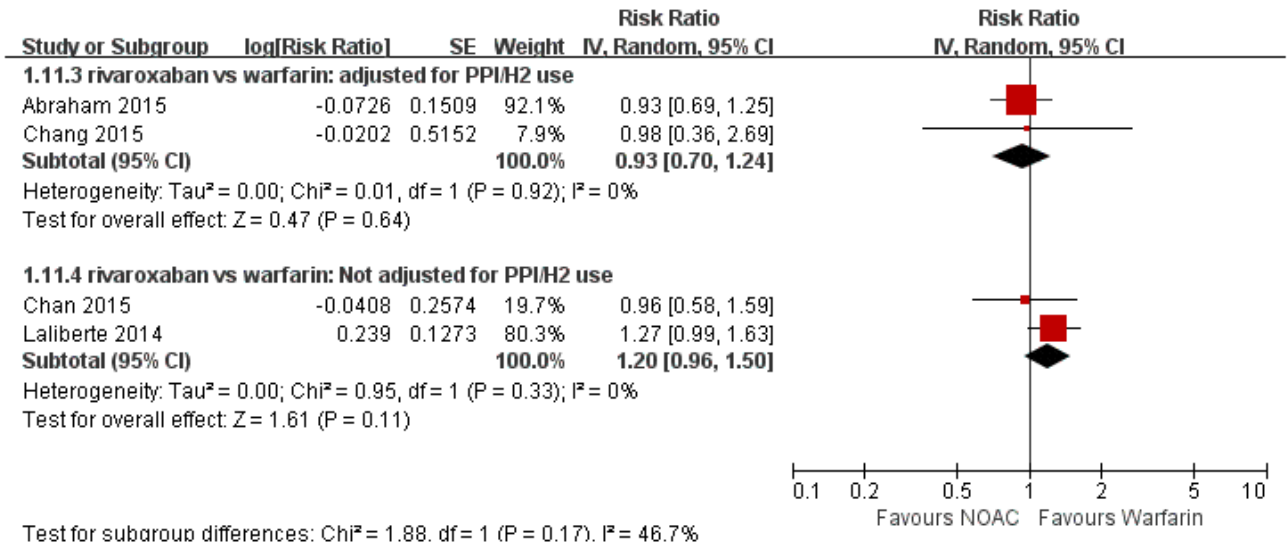


Supplementary Figure 7 Summarised estimates of subgroup analysis *by use of gastroprotective agents (PPI/H2RA)*

Dabigatran

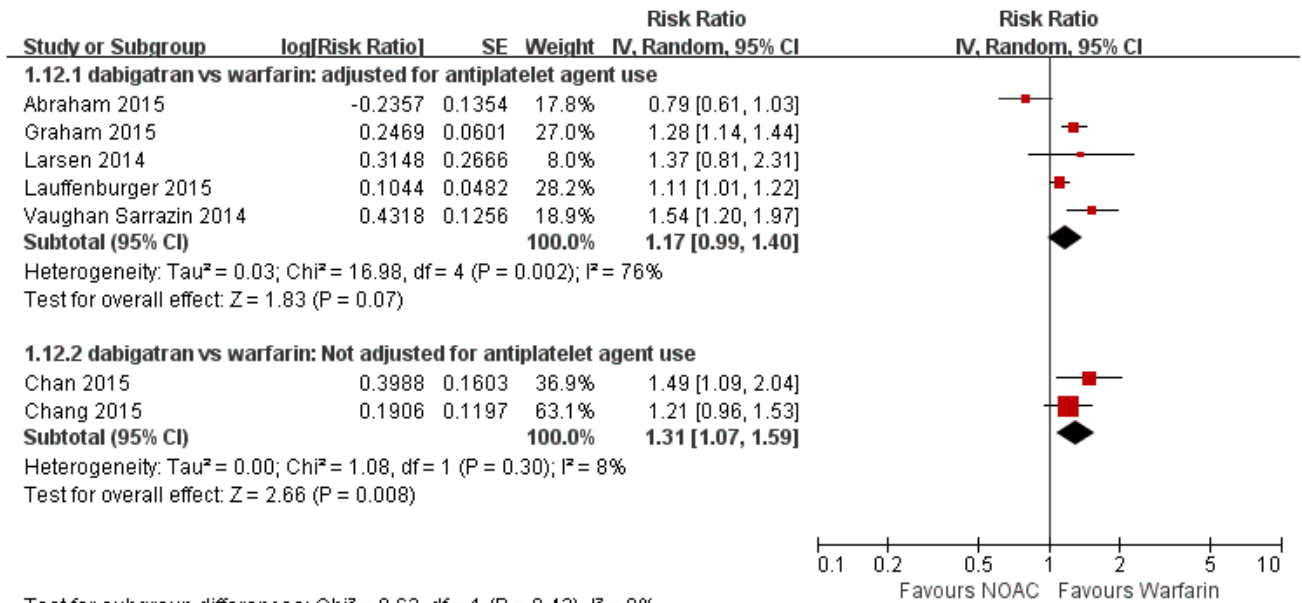


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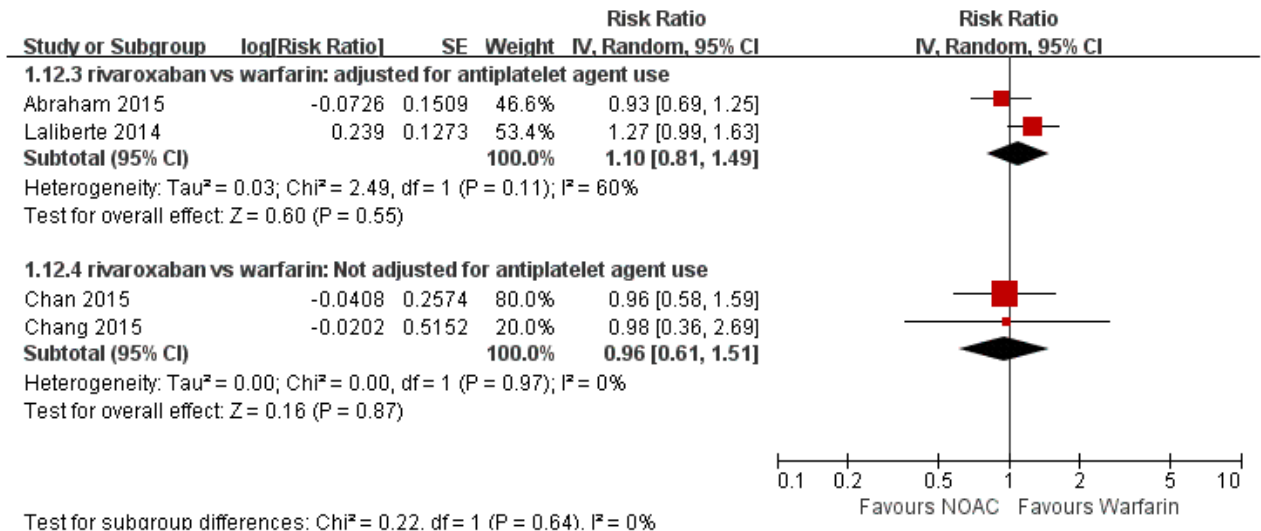


Supplementary Figure 8 Summarised estimates of subgroup analysis *by use of antiplatelet agents*

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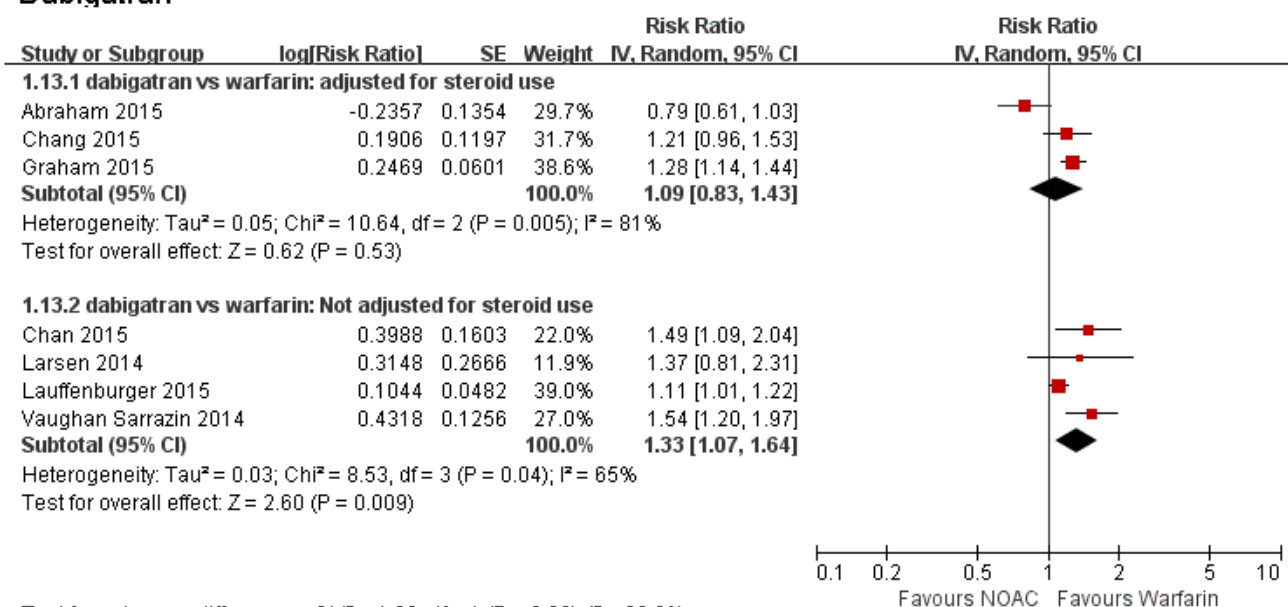


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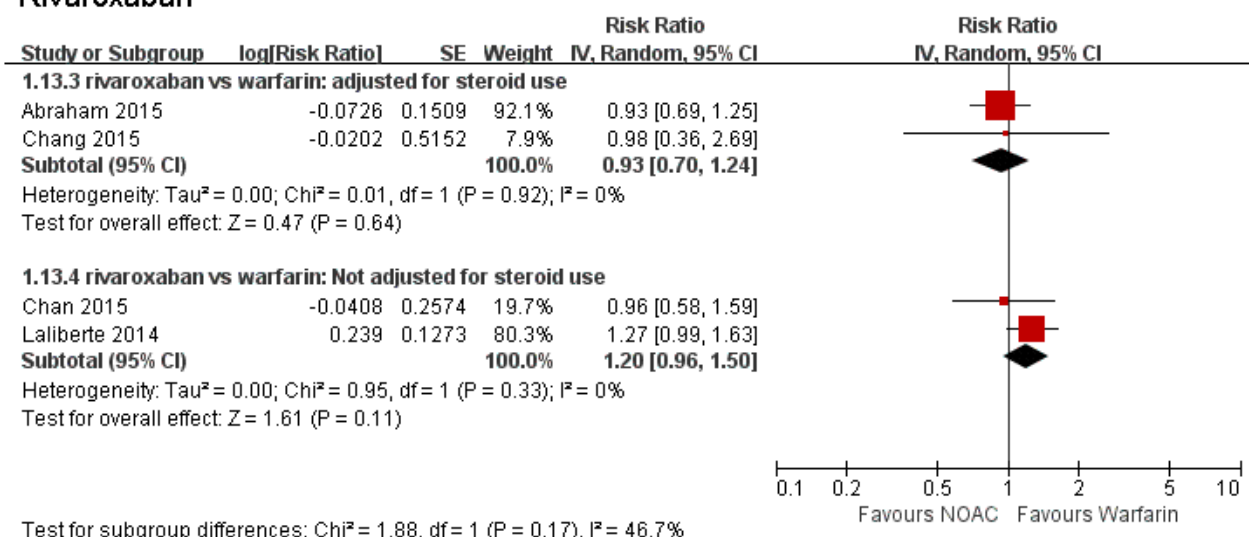


Supplementary Figure 9 Summarised estimates of subgroup analysis *by use of steroids*

Dabigatran

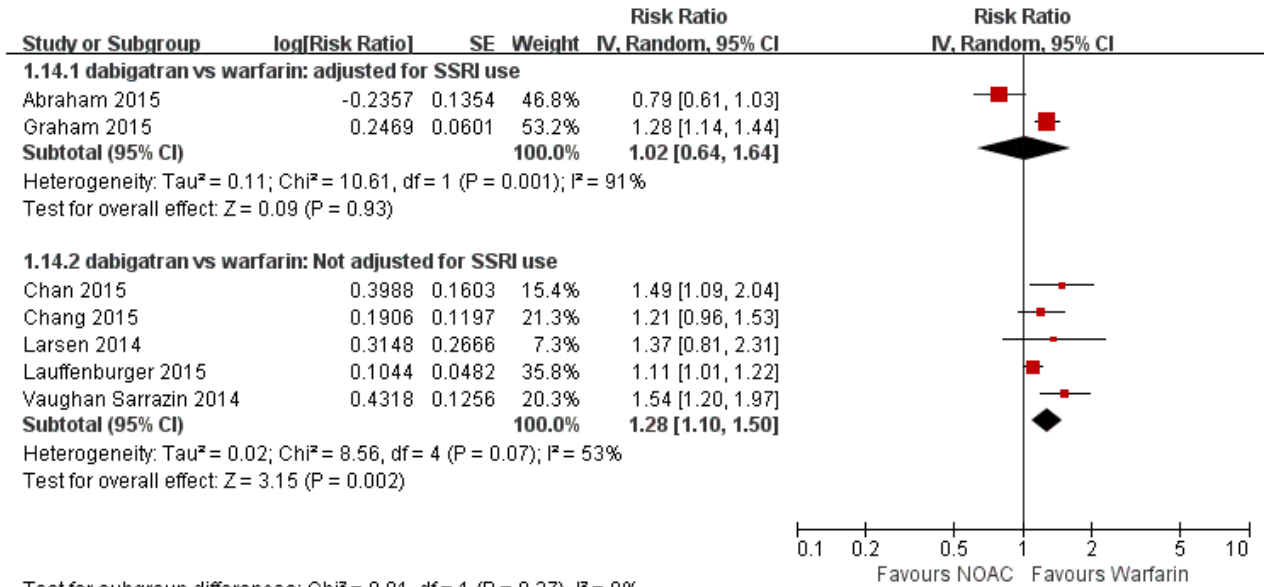


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Supplementary Figure 10 Summarised estimates of subgroup analysis *by use of SSRI*

Dabigatran



Rivaroxaban

