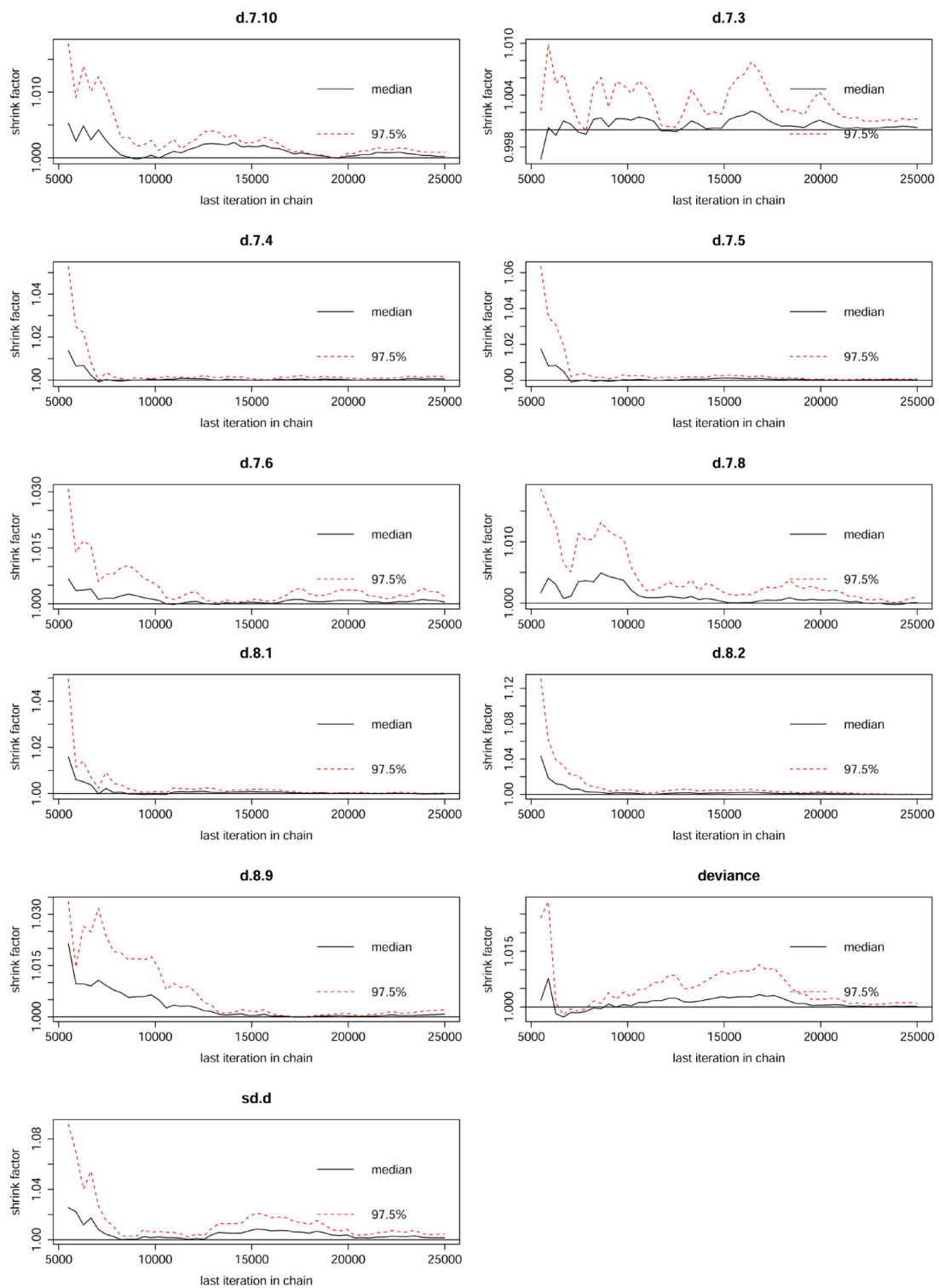


## **Supplementary materials**

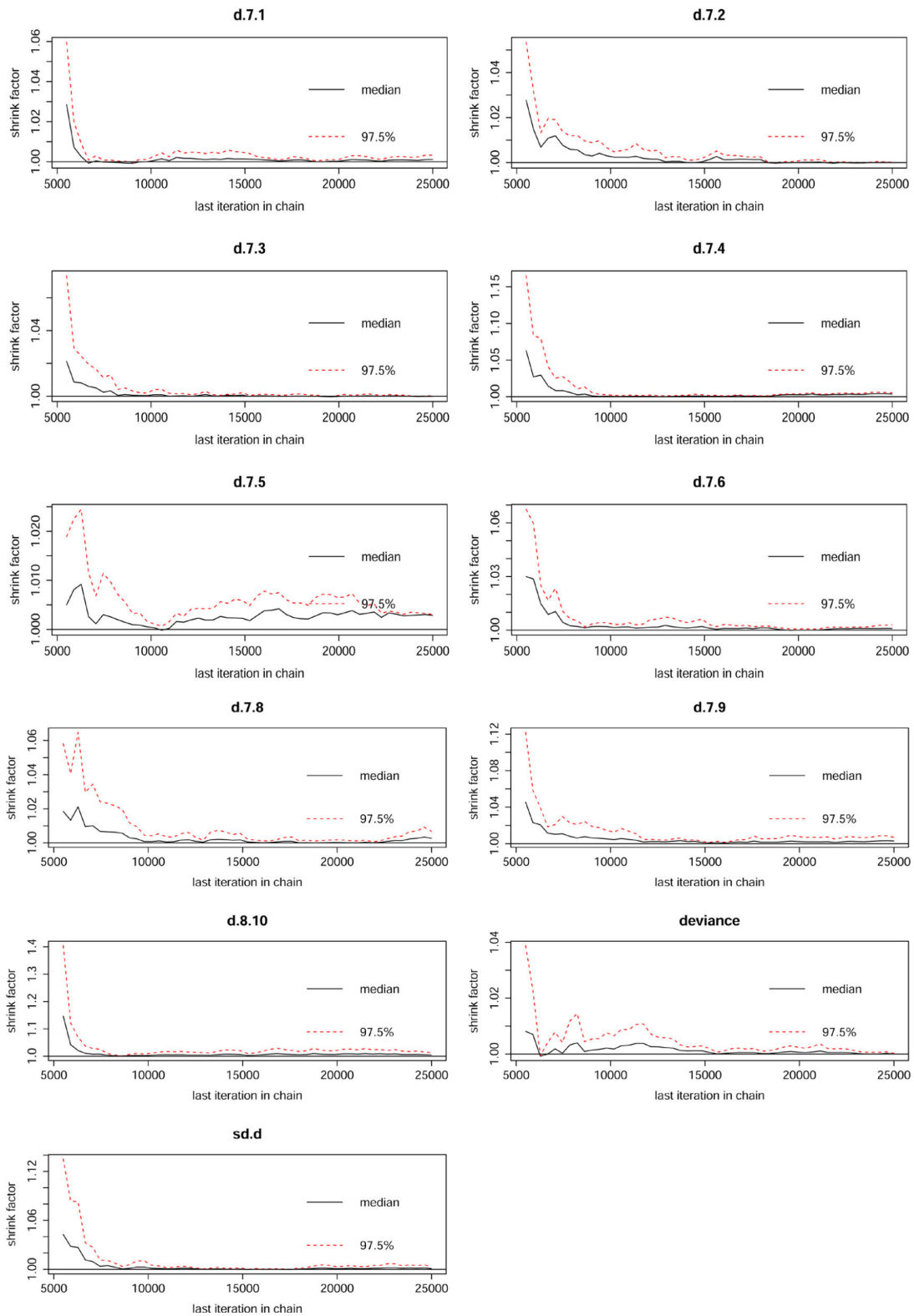
### **Risk analysis of new oral anticoagulants for gastrointestinal bleeding and intracranial hemorrhage in atrial fibrillation patients: a systematic review and network meta-analysis**

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To ensure convergence, we assessed trace plots and the Brooks-Gelman-Rubin statistic as Figs. S1 and S2 show. Analyses were performed using R 3.0.2 (R Language and Environment for Statistical Computing) and WinBUGS software (MRC Biostatistics Unit).



**Fig. S1 Trace plot of the Brooks-Gelman-Rubin statistics of Bayesian network meta-analysis on GIB in patients receiving NOACs compared with standard warfarin treatment**



**Fig. S2 Trace plot of the Brooks-Gelman-Rubin statistics of Bayesian network meta-analysis on ICH in patients receiving NOACs compared with standard warfarin treatment**

**Table S1 Characteristics of the included studies**

Study/trial name, year	Study group (n) vs control (n)	Median/mean age, men%	Median follow-up period	GIB	ICH	INR within therapeutic range in warfarin group, median time
Robert P. Giugliano, M.D <i>et al.</i> , ENGAGE AF-TIMI 48,2013[27]	Warfarin (N = 7,036) High-Dose 60 mg/d Edoxaban (N = 7,035) Low-Dose 30 mg/d Edoxaban (N = 7034)	72 y, 62.0%	1022 days	232/190/129	41/61/132	83.1%, 68.4%
Patel <i>et al.</i> , ROCKET-AF, 2011[12]	Rivaroxaban 20 mg qd and warfarin placebo (7131) dose-adjusted warfarin (INR2–3)and rivaroxaban placebo (7133)	73 y, 60%	707 days	124/154	55/84	58%; mean, 55%
Connolly <i>et al.</i> , RE-LY, 2009[28]	Dabigatran 110 mg bid (6015) or 150 mg bid (6076) warfarin INR 2–3 (6022)	72 y, 64%	2.0 y	133/182/120	27/36/84	64%
Granger <i>et al.</i> , ARISTOTLE, 2011[13]	Apixaban 5 mg bid and warfarin placebo (9120) dose-adjusted warfarin (INR 2–3) and apixaban placebo (9081)	70 y, 65%	1.8 y	105/119	52/122	66%; mean, 62.2%
Connolly <i>et al.</i> , AVERROES, 2011[29]	Apixaban 5 mg bid and aspirin placebo (2808) aspirin 81–324 mg qd and apixaban placebo (2791)	70 y, 59%	1.1 y	12/14	11/13	Not applicable
Ogawa <i>et al.</i> , ARISTOTLE-J, 2011[30]	Apixaban 2.5 mg bid (74) Apixaban 5 mg bid (74) Dose-adjusted warfarin (INR 2–3 or 2–2.6 if age > 69 y) (74)	Mean age, 70 y, 61%	Not reported	0/1/0	Not reported	> 60% of patients had INR within range for 60% of the treatment period
Hori, J-ROCKET AF, 2012[31]	Rivaroxaban 15 mg (10 mg for RF) (n=639) Warfarin (n=639)	Mean age, 71.1y, 80.6%	Not reported	6/12	5/10	65.0% of the INR values of warfarin-treated patients were within the prespecified, age-dependent target range.
Yamashita, not reported, 2012[32]	Edoxaban 30 mg qd (131) or 45 mg qd (134), or 60 mg qd (131)vs dose-adjusted	69.0, 82.5%	Not reported	not reported	0/0/1/0, number	Not reported

Study/trial name, year	Study group (n) vs control (n)	Median/mean age, men%	Median follow-up period	GIB	ICH	INR within therapeutic range in warfarin group, median time
	warfarin (INR 2–3) (129)					
Chung <i>et al.</i> , not reported, 2011[33]	Edoxaban 30 mg qd (79) or 60 mg (80) qd Dose-adjusted warfarin (INR 2 – 3) (75)	65 y, 65%	Not reported, total follow - up period, 12 wk	0/0/1	Not reported	45.1% , not reported
Paller Peterson, AFASAK-I, 1989[34]	Dose-adjusted warfarin (335), aspirin 75 mg (336), placebo (336)	74.2 y, 54%	Not reported	4/1/0	1/0/0	42%, not reported
BAATAF, 1990[35]	Dose-adjusted warfarin (212), placebo (208)	68 y, 72.5%	2.3yrs	Not reported	1/0	83%, 2.3yrs
CAFA, 1991[36]	Dose-adjusted warfarin (191), placebo (210)	67.7 y, 74.0%	15.2 months	Not reported	2/0	43.70%, not reported
SPAF-I, 1991[37]	Aspirin (260), placebo (265)	67 y, not reported	1.7yrs	34/23	0/1	not applicable
EAFT, 1993[38]	Dose-adjusted warfarin (335), placebo (369)	63.3 y, 57.9%	19 months	Not reported	3/0	Not applicable
AFASAK-II, 1998[39]	Dose-adjusted warfarin (170), aspirin (169)	74 y, 61%	291 days	Not reported	1/1	Not applicable
PATAF, 1999[40]	Dose-adjusted warfarin (131), aspirin (319)	74.8 y, 44.9%	2.7 yrs	2/9	1/1	48%, not reported
Active W, 2006[41]	Dose-adjusted warfarin (3371), Aspirin+Clopidogrel (3335)	70.2 y, 66.5%	1.28yrs	Not reported	21/11	63.80%, not reported
JAST, 2006[42]	Aspirin (426), placebo(445)	65.1 y, 70.3%	810days	10/0	4/2	Not applicable
Active A, 2006[43]	Clopidogrel + ASA(N = 3772), Aspirin (N = 3782)	71.0 y, 58.2%	3.6yrs	132/68	30/22	Not applicable
BAFTA, 2007[44]	Dose-adjusted warfarin (488), Aspirin (485)	81.5 y, 54.5%	2.7yrs	Not reported	8/6	47%, not reported

**Table S2 Quality assessment of included studies**

Study/trial name, year	Method of randomization	Concealment of allocation	Blinding for treatment	Independent clinical end point committee	Lost to follow-up evaluation of total study population (%)	Intention-to-treat analysis(A/B/C/D)
Robert P. Giugliano, M.D <i>et al.</i> , ENGAGE AF-TIMI 48,2013[27]	A	A	A	A	0.005	A
Patel <i>et al.</i> , ROCKET-AF, 2011[12]	A	A	A	A	0.2	A
Connolly <i>et al.</i> , RE-LY, 2009[28]	A	A	B	A	0.1	A
Granger <i>et al.</i> , ARISTOTLE, 2011[13]	A	C	A	A	0.4	A
Connolly <i>et al.</i> , AVERROES, 2011[29]	A	A	A	A	Not reported	A
Ogawa <i>et al.</i> , ARISTOTLE-J, 2011[30]	A	C	B	A	1.8	A
Hori, J-ROCKET AF, 2012[31]	A	C	B	A	Not reported	A
Yamashita, not reported, 2012[32]	A	C	B	A	2.1	A
Chung <i>et al.</i> , not reported, 2011[33]	A	A	B	A	0.9	A
Paller Peterson, AFASAK-I, 1989[34]	A	A	C	A	not reported	A
BAATAF, 1990[35]	A	A	C	A	0	A
CAFA, 1991[36]	A	C	A	A	1.3	B
SPAF-I, 1991[37]	A	A	C	A	0	A
EAFT, 1993[38]	A	C	C	A	1.9	C
AFASAK-II, 1998[39]	A	A	C	A	0	B
PATAF, 1999[40]	A	A	B	A	0	A
Active W, 2006[41]	A	A	C	A	0.3	B
JAST, 2006[42]	A	A	C	A	Not reported	B
Active A, 2006[43]	A	A	A	A	0.8	A
BAFTA, 2007[44]	A	A	C	A	0.82	B

**Table S3 Effect estimates from multiple treatment meta-analysis compared with direct and indirect estimates, based on node-splitting and pair-wise meta-analyses of GIB**

Abbreviation: Api, apixaban; ASA, aspirin; Clo, clopidogrel; Dab, dabigatran; Riva, rivaroxaban; Edo, edoxaban

	Direct effect		Indirect effect		Network effect		P-value	Pair-wise meta-analysis		
	OR	95% CI	OR	95% CI	OR	95% CI		OR	95% CI	N of trials
ASA vs Warfarin	0.95	0.24 3.63	1.03	0.19 5.53	0.99	0.36 2.68	0.93	0.85	0.37 1.96	2
ASA+clo vs ASA								1.98	1.44 2.66	1
Warfarin vs Placebo								0.66	0.38 1.15	1
Dab 150 mg vs Warfarin								1.52	1.20 1.92	1
Dab 110 mg vs Warfarin								1.11	0.87 1.42	1
Dab 110 vs 150 mg								0.73	0.59 0.92	1
Riva vs Warfarin								1.38	1.13 1.69	2
Api vs Warfarin	0.88	0.30 2.56	0.81	0.12 5.26	0.86	0.36 2.04	0.94	0.88	0.68 1.15	2
Api vs ASA	0.85	0.24 3.03	0.93	0.17 5.26	0.87	0.33 3.06	0.93	0.85	0.39 1.84	1
Edo 30 mg vs Warfarin								1.48	1.18 1.85	2
Edo 60 mg vs Warfarin								1.81	1.46 2.25	2
Edo 30 mg vs Edo 60 mg								0.81	0.67 0.99	2

**Table S4 Effect estimates from multiple treatment meta-analysis compared with direct and indirect estimates, based on node-splitting and pair-wise meta-analyses of ICH**

Abbreviation: Api, apixaban; ASA, aspirin; Clo, clopidogrel; Dab, dabigatran; Riva, rivaroxaban; Edo, edoxaban;

	Direct effect		Indirect effect		Network effect			Pair-wise meta-analysis						
	OR	95% CI	OR	95% CI	OR	95% CI	P-value	OR	95% CI	N of trials				
ASA vs Placebo								2.10	0.38	11.52	1			
Warfarin vs ASA	1.69	0.79	3.57	2.70	0.98	7.14	2.08	1.11	3.70	0.41	1.90	1.04	3.49	5
ASA+clo vs ASA	1.89	0.77	4.66	0.93	0.26	3.00	1.55	0.71	2.94	0.28	0.73	0.42	1.27	1
Warfarin vs ASA+Clo	1.92	0.65	5.88	0.92	0.29	2.85	1.35	0.65	2.86	0.29	2.97	1.08	8.20	1
Warfarin vs Placebo											0.71	0.18	2.79	3
Dab 150 mg vs Warfarin											0.42	0.28	0.62	1
Dab 110 mg vs Warfarin											0.32	0.21	0.49	1
Dab 110 vs 150 mg											0.76	0.46	1.25	1
Riva vs Warfarin											0.64	0.45	0.88	2
Api vs Warfarin	0.42	0.15	1.18	0.40	0.10	1.75	0.42	0.21	0.85	0.94	0.42	0.31	0.59	2
Api vs ASA	0.84	0.24	2.78	0.87	0.24	2.70	0.87	0.40	1.78	0.97	0.84	0.37	1.88	1
Edo 30 mg vs Warfarin											0.31	0.22	0.44	2
Edo 60 mg vs Warfarin											0.46	0.34	0.62	2
Edo 30 mg vs Edo 60 mg											0.67	0.45	0.99	2



**Table S5 Odds ratios (ORs) and 95% confidence intervals (CIs) for network meta-analyses of GIB for sensitivity test**

Abbreviation: Api, apixaban; ASA, aspirin; Clo, clopidogrel; Dab, dabigatran; Riva, rivaroxaban; Edo, edoxaban

	Edo 30mg	Edo 60mg	Riva	Dab 110mg	Dab 150mg	Api 5mg	Warfarin	Aspirin	Aspirin+Clo	Placebo
<b>Edo 30mg</b>	1(1,1)									
<b>Edo 60mg</b>	1.46(0.37,3.47)	1(1,1)								
<b>Riva</b>	1.01(0.14,4.64)	1.19(0.1,3.97)	1(1,1)							
<b>Dab 110mg</b>	1.26(0.13,8.23)	2.25(0.09,10.87)	2.69(0.17,11.27)	1(1,1)						
<b>Dab 150mg</b>	2.75(0.16,12.33)	2.66(0.14,16.45)	4.27(0.3,13.22)	1.76(0.42,8.56)	1(1,1)					
<b>Api 5mg</b>	0.91(0.15,4.33)	0.86(0.11,3.33)	1.27(0.24,6.94)	3.57(0.15,9.33)	1.46(0.13,5.46)	1(1,1)				
<b>Warfarin</b>	0.94(0.19,3.7)	0.97(0.13,3.39)	1.22(0.41,3.04)	1.47(0.31,4.42)	1.22(0.17,2.68)	1.28(0.36,3.63)	1(1,1)			
<b>Aspirin</b>	0.8(0.26,2.44)	0.73(0.21,2.22)	1.31(0.22,9.78)	2.59(0.17,10.2)	1.03(0.13,3.17)	1.29(0.28,3.59)	1.12(0.29,2.97)	1(1,1)		
<b>Aspirin+Clo</b>	4.86(0.29,37.27)	6.72(0.21,27.08)	9.88(0.31,52.26)	26.83(0.21,72.26)	6.31(0.14,58.73)	4.93(0.27,30.75)	6.57(0.33,13.25)	4.42(0.47,10.21)	1(1,1)	
<b>Placebo</b>	0.97(0.03,3.28)	0.99(0.02,3.37)	0.86(0.06,1.56)	1.2(0.07,2.88)	1.23(0.05,3.62)	1.13(0.05,3.63)	1.12(0.03,2.58)	1.09(0.02,3.45)	<b>0.09(0.03,0.19)</b>	1(1,1)