

Online Appendix to Alonso-Coello et al. ‘Home-monitoring of oral anticoagulation vs. dabigatran. An indirect comparison’ (Thromb Haemost 2012; 108.4)

APPENDIX 1. EVIDENCE PROFILES

Evidence profile 1. Home-monitoring vs. usual management

Trials	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Overall quality	Study event rates (%)		Relative effect (95%CI) ¹	Absolute effect	
							With usual monitoring	With home-monitoring		Risk with usual monitoring	Risk difference with home monitoring (95%CI)
Thromboembolism (CRITICAL OUTCOME)											
12 RCTs 12 months mean follow-up	No serious risk of bias. Lack of information regarding allocation concealment	No serious inconsistency I ² =3%	No serious imprecision	No serious indirectness	Not detected	⊕⊕⊕⊕ High	97/2136 (4.5%)	48/2376 (2.0%)	0.45 (0.32–0.64)	45 per 1000 patients	25 fewer thromboembolic events per 1000 (14 to 35 less)
Death (CRITICAL OUTCOME)											
9 RCTs 12 months mean follow-up	No serious risk of bias. Lack of information regarding allocation concealment	No serious inconsistency I ² =34%	No serious imprecision	No serious indirectness	Not detected	⊕⊕⊕⊕ High	186/1429 (13.0%)	123/1518 (8.1%)	0.62 (0.49–0.78)	130 per 1000 patients	49 fewer deaths per 1000 (26 to 71 less)
Major bleeding (CRITICAL OUTCOME)											
23 RCTs 12 months mean follow-up	No serious risk of bias. Lack of information regarding allocation concealment	No serious inconsistency I ² =0%	Serious imprecision Includes important benefits and harms	No serious indirectness	Not detected	⊕⊕⊕ Moderate	81/2152 (3.7%)	96/2333 (4.1%)	0.96 (0.81–1.13)	37 per 1000 patients	49 fewer major bleeding events per 1000 (71 less to 26 more)

¹Relative risk are those of self-management except for the outcome major bleeding.

RCT: randomised controlled trial, AFIB: atrial fibrillation. ⊕⊕⊕⊕: high quality, ⊕⊕⊕: moderate quality, ⊕⊕: low quality and ⊕: very low quality.

Evidence profile 2. Dabigatran 150 mg vs. usual monitoring Fehler! Verweisquelle konnte nicht gefunden werden.

Trials	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Overall quality	Study event rates (%)		Relative effect (95%CI)	Absolute effect	
							With home-monitoring	With dabigatran		Risk with home-monitoring	Risk difference with home-monitoring (95%CI)
Thromboembolism (CRITICAL OUTCOME)											
1 RCT (18113 patients) 2 years median follow-up	No serious risk of bias. Warfarin administration unblinded	No serious inconsistency. Only one RCT	No serious imprecision	No serious indirectness. Only patients with AFIB included.	Not detected	⊕⊕⊕⊕ High	199/6022 (1.69%)	134/ 6076 (1.11%)	0.66 (0.53–0.82)	16 per 1000 patients	10 fewer thromboembolic events per 1000 (51 to 16 less)
Death (CRITICAL OUTCOME)											
1 RCT (18113 patients) 2 years median follow-up	No serious risk of bias Warfarin administration unblinded	No serious inconsistency. Only one RCT	No serious imprecision	No serious indirectness. Only patients with AFIB included.	Not detected	⊕⊕⊕ Moderate	487/6022 (4.13%)	438/ 6076 (3.64%)	0.88 (0.77–1.00)	41 per 1000 patients	8 fewer deaths per 1000 (0 to 18 less)
Major bleeding (CRITICAL OUTCOME)											
1 RCT (18113 patients) 2 years median follow-up	No serious risk of bias Warfarin administration unblinded	No serious inconsistency. Only one RCT	Serious imprecision Includes important benefits and harms	No serious indirectness. Only patients with AFIB included.	Not detected	⊕⊕⊕ Moderate	397/6022 (3.36%)	375/ 6076 (3.11%)	0.93 (0.81–1.07)	33 per 1000 patients	4 fewer major bleedings per 1000 (12 less to 4 more)
Myocardial infarction (CRITICAL OUTCOME)											
1 RCT (18113 patients) 2 years median follow-up	No serious risk of bias Warfarin administration unblinded	Not applicable	Serious imprecision Includes important benefits and harms	No important limitations	Not detected	⊕⊕⊕ Moderate	-	-	1.38 (1.00–1.91)	7 per 1000 patients	4 more myocardial infarctions per 1000 (0 to 8 more)

RCT: randomised controlled trial, AFIB: atrial fibrillation. ⊕⊕⊕⊕: high quality, ⊕⊕⊕: moderate quality, ⊕⊕: low quality and ⊕: very low quality.

Evidence profile 3. Self-management vs. dabigatran

Trials	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Overall quality	Study event rates (%)		Relative effect (95%CI)	Absolute effect	
							With home-monitoring	With dabigatran		Risk with home-monitoring ¹	Risk difference with home monitoring (95%CI)
Thromboembolism (CRITICAL OUTCOME)											
12 RCTs of self-management, 1 of dabigatran ²	No serious risk of bias	No serious inconsistency	No serious imprecision	Very serious indirectness. Indirect comparison. Dabigatran trial only includes AFIB patients.	Not detected	⊕⊕ Low	-	-	0.73 (0.48-1.10)	20 per 1000 patients	NS
Death (CRITICAL OUTCOME)											
9 RCTs of self-management, 1 of dabigatran ¹	No serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness. Indirect comparison. Dabigatran trial only includes AFIB patients.	Not detected	⊕⊕ Low	-	-	0.64 (0.40-1.01)	81 per 1000 patients	NS
Major bleeding (CRITICAL OUTCOME)											
23 RCTs of home monitoring, 1 of dabigatran ¹	No serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness. Indirect comparison. Dabigatran trial only includes AFIB patients.	Not detected	⊕⊕ Low	-	-	1.15 (0.83-1.60)	41 per 1000 patients	NS

¹ 12 months of mean follow up in the self-management trials and 24 months median follow up in the dabigatran trial.

² Relative risk are those of self-management except for the outcome major bleeding.

RCT: randomised controlled trial, AFIB: atrial fibrillation. ⊕⊕⊕⊕: high quality, ⊕⊕⊕: moderate quality, ⊕⊕: low quality and ⊕: very low quality.

Appendix 2

Figure A. Risk of publication bias assessed with a funnel plot (outcome: thromboembolic events)

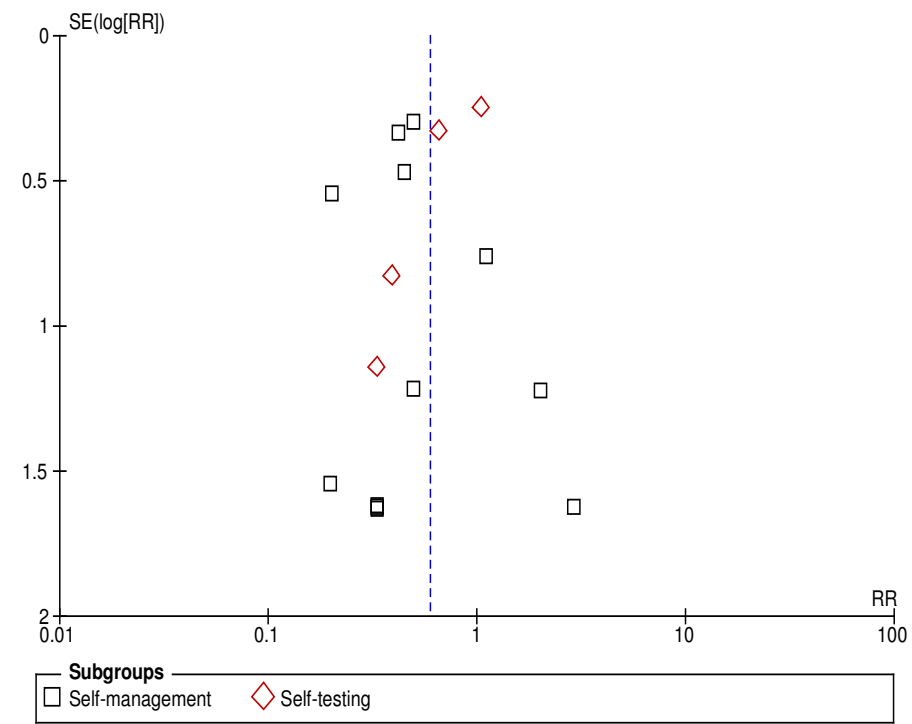
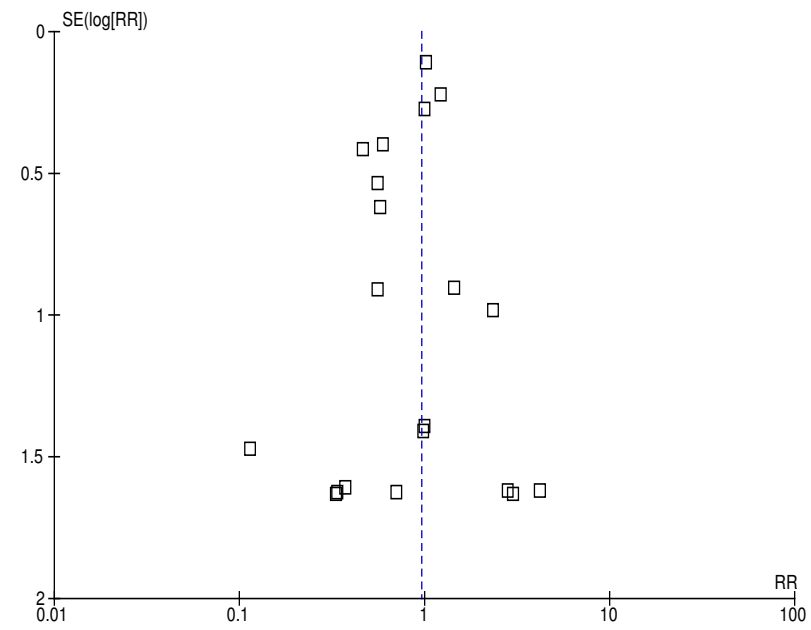


Figure B. Risk of publication bias assessed with a funnel plot (outcome major: major bleeding)



Appendix 3

1. Direct and indirect comparisons of Dabigatran and usual management/home-monitoring

Dabigatran Dose =110mg

Outcomes	Direct comparison (RR, 95%CI)		Indirect comparison (RR, 95%CI, p-value)
	Dabigatran vs. Usual management	Home-monitoring vs. Usual management	Home-monitoring vs. Dabigatran
Thromboembolism	0.91 (0.74-1.11)	0.59 (0.46-0.77)	0.65 (0.47-0.90), 0.01
Mortality	0.91 (0.80-1.03)	0.76 (0.58, 0.99)	0.84 (0.62-1.12), 0.23
Major bleeding	0.80 (0.69-0.93)	0.95 (0.80-1.12)	1.19 (0.95-1.49), 0.13

Dabigatran Dose =150mg

Outcomes	Direct comparison (RR, 95%CI)		Indirect comparison (RR, 95%CI, p-value)
	Dabigatran vs. Usual management	Home-monitoring vs. Usual management	Home-monitoring vs. Dabigatran
Thromboembolism	0.66 (0.53-0.82)	0.59 (0.46-0.77)	0.89 (0.64-1.25), 0.52
Mortality	0.88 (0.77-1.00)	0.76 (0.58, 0.99)	0.86 (0.64-1.16), 0.33
Major bleeding	0.93 (0.81-1.07)	0.95 (0.80-1.12)	1.02 (0.82-1.27), 0.85

2. Direct and indirect comparisons of Dabigatran and usual management/self-management /self-testing

Dabigatran Dose =110mg

Outcomes	Direct comparison (RR, 95%CI)		Indirect comparison (RR, 95%CI, p-value)
	Dabigatran vs. Usual management	Self-management vs. Usual management	Self-management vs. Dabigatran
Thromboembolism	0.91 (0.74-1.11)	0.45 (0.32-0.64)	0.49 (0.33-0.74), 0.001
Mortality	0.91 (0.80-1.03)	0.62 (0.49, 0.78)	0.68 (0.52-0.89), 0.004
Major bleeding	0.80 (0.69-0.93)	1.07 (0.79-1.44)	1.34 (0.96-1.87).0.09

Dabigatran Dose =150mg

Outcomes	Direct comparison (RR, 95%CI)		Indirect comparison (RR, 95%CI, p-value)
	Dabigatran vs. Usual management	Self-management vs. Usual management	Self-management vs. Dabigatran
Thromboembolism	0.66 (0.53-0.82)	0.45 (0.32-0.64)	0.68 (0.45-1.03), 0.07
Mortality	0.88 (0.77-1.00)	0.62 (0.49, 0.78)	0.70 (0.54-0.92), 0.01
Major bleeding	0.93 (0.81-1.07)	1.07 (0.79-1.44)	1.15 (0.83-1.60), 0.41

Dabigatran Dose =110mg

Outcomes	Direct comparison (RR, 95%CI)		Indirect comparison (RR, 95%CI, p-value)
	Dabigatran vs. Usual management	Self-testing vs. Usual management	Self-testing vs. Dabigatran
Thromboembolism	0.91 (0.74-1.11)	0.72 (0.51-1.02)	0.79 (0.53-1.18), 0.25
Mortality	0.91 (0.80-1.03)	0.95 (0.78-1.15)	1.04 (0.83-1.32), 0.72
Major bleeding	0.80 (0.69-0.93)	0.90 (0.74-1.09)	1.12 (0.88-1.44), 0.35

Dabigatran Dose =150mg

Outcomes	Direct comparison (RR, 95%CI)		Indirect comparison (RR, 95%CI, p-value)
	Dabigatran vs. Usual management	Self-testing vs. Usual management	Self-testing vs. Dabigatran
Thromboembolism	0.66 (0.53-0.82)	0.72 (0.51-1.02)	1.09 (0.721-1.64), 0.68
Mortality	0.88 (0.77-1.00)	0.95 (0.78-1.15)	1.08 (0.85-1.36), 0.52
Major bleeding	0.93 (0.81-1.07)	0.90 (0.74-1.09)	0.97 (0.76-1.23), 0.79

Appendix 4

Subgroup analyses likelihood criteria (self-management vs. self-testing)

Criteria	Outcomes	
	Mortality	Thrombosis
Design		
1. Is the subgroup variable a characteristic measured at baseline or after randomisation?*	√	√
2. Is the effect suggested by comparisons within rather than between studies?	X	X
√. Was the hypothesis specified a priori?	√	√
4. Was the direction of the subgroup effect specified a priori*	X	X
5. Was the subgroup effect one of a small number of hypothesised effects tested?	√	√
Analysis		
6. Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	√	√
7. Is the significant subgroup effect independent?	√	√
Context		
8. Is the size of the subgroup effect large?	√	√
9. Is the interaction consistent across studies?	√	√
10. Is the interaction consistent across closely related outcomes within the study?*	√	√
11. Is there indirect evidence that supports the hypothesised interaction (biological rationale)?	√	√
Likelihood of subgroup effect	Moderate/High	Moderate/High