

Appendix

Appendix A: Parameters used in model

	Category	Description	References
Risks/Probabilities	Death from other causes	Nonparametric	UK Lifetables. [1]
	Sensitivity and Specificity of TTE in detecting ABN	Jointly estimated from Dirichlet distribution (FN, TP, TN, FP) = (5, 87, 83, 159)	Table 2 of Providencia et al 2012 [2]
	Proportion of patients with ABN	Beta(2.5, 22.5) for CHADS ₂ Beta(0.5, 11.5) for CHA ₂ DS ₂ -VASc (Both with prior of 0.5 added to both cell counts.)	Table 2 of Providencia et al 2012 [2]
	Annual stroke risk by CHADS ₂ score	Annual risks (95% Credible intervals) by CHADS ₂ were reported as follows: 0.6% (0.5% to 0.7%) for CHADS ₂ =0 3.0% (2.9% to 3.2%) for CHADS ₂ =1 4.2% (4.0% to 4.4%) for CHADS ₂ =2 7.1% (6.7% to 7.5%) for CHADS ₂ =3 11.1% (10.4% to 11.8%) for CHADS ₂ =4	Friberg 2012[3]
	Annual stroke risk in those with ABN	In the initial study four out of 50 patients with identified ABN had a stroke. This was used to produce a mean stroke rate of 8.0% and bootstrapped 95% CrIs of 7.2% to 8.2%	Stroke Prevention 1988 [4]

	Relative risk (RR) of stroke in patients receiving dabigatran.	<p>Indirect comparison simulation approach. One thousand simulated values from a lognormal distribution representing the RR of warfarin compared with placebo were multiplied by 1000 simulated values from a lognormal distribution comparing dabigatran with warfarin, to produce 1000 estimates of the RR of dabigatran compared with placebo. Mean RRs and 95% CIs/CrIs are shown below:</p> <p>Reported RR warfarin vs. placebo: 0.33 (0.24 to 0.45)</p> <p>Reported RR dabigatran vs. warfarin: 0.66 (0.53 to 0.82)</p> <p>Derived RR dabigatran vs. placebo: 0.22 (0.15 to 0.32)</p>	<p>Lip et al 2006 for RR of warfarin compared with placebo [5]</p> <p>Eikelboom et al 2011 for RR of dabigatran compared with warfarin[6]</p>
	Annual major bleeding risk for patients receiving dabigatran	<p>Stratified by age. Credible interval calculated using simulation approach. Annual risk reported separately for people under 75 years, and people aged 75 years or older. Credible intervals were calculated by assuming sample sizes of 3618 for people aged under 75 years and 2419 for people aged 75 years or older, then sampling repeatedly and taking the values 2.5% and 97.5% of the way along the distributions. The central estimates</p>	Eikelboom et al 2011 [6]

		(95% CrIs) are as follows: Under 75: 2.1% (1.7 to 2.6%) 75 and older: 5.1% (4.2% to 6.0%)	
	Relative risk (RR) of stroke in patients receiving warfarin	Reported RR warfarin vs. placebo: 0.33 (0.24 to 0.45)	Lip et al 2006 [5]
	Annual major bleeding risk for patients receiving warfarin	Stratified by age. Credible interval calculated using simulation approach. Annual risk reported separately for people under 75 years, and people aged 75 years or older. Credible intervals were calculated by assuming sample sizes of 3618 for people aged under 75 years and 2419 for people aged 75 years or older, then sampling repeatedly and taking the values 2.5% and 97.5% of the way along the distributions. The central estimates (95% CrIs) are as follows: Under 75: 3.4% (2.5 to 3.6%) 75 and older: 4.4% (3.6% to 5.2%)	Eikelboom et al 2011 [6]
	Relative risk (RR) of stroke in patients receiving rivaroxaban	Indirect comparison simulation approach. One thousand simulated values from a lognormal distribution representing the RR of warfarin compared with placebo were multiplied by 1000 simulated values from a lognormal distribution comparing dabigatran with warfarin, to produce 1000 estimates of the RR of dabigatran compared	Lip et al 2006 for RR of warfarin compared with placebo [5] Patel et al 2011 for RR of rivaroxaban compared with warfarin [7]

		<p>with placebo. Mean RRs and 95% CIs/CrIs are shown below:</p> <p>Reported RR warfarin vs. placebo: 0.33 (0.24 to 0.45)</p> <p>Reported RR Rivaroxaban vs. warfarin: 0.88 (0.74 to 1.03)</p> <p>Derived RR Rivaroxaban vs. placebo: 0.30 (0.20 to 0.41)</p>	
	Annual major bleeding risk for patients receiving rivaroxaban	<p>The annual risk of bleeding given rivaroxaban was estimated indirectly by combining estimates of the risk of bleed given warfarin compared with placebo with estimates of the risk of bleed given rivaroxaban compared with warfarin. The central estimates (95% CrIs) were estimated to be as follows:</p> <p>Under 75: 3.2% (2.5% to 4.0%)</p> <p>75 or older: 4.6% (3.6% to 5.7%)</p>	<p>Eikelboom et al 2011 [6]</p> <p>Patel et al 2011 [7]</p>
	Outcome following stroke	<p>Simulation & mapping based approach described in an upcoming report.</p> <p>The proportion dying of a stroke (95% CrI) was estimated to be 0.25 (0.23 to 0.27); the proportion in an independent state was estimated to be 0.56 (0.52 to 0.59); and the proportion in an dependent state following a</p>	<p>Method described in report using results published in Rivero-Arias et al 2010 [8]</p>

		stroke was estimated to be 0.19 (0.16 to 0.23).	
	Outcome following a major bleeding event	Previous estimates	Simpson et al 2010 [9]
Utilities	Baseline utilities by age and gender	Regression based approach, described in full in the reference. HRQoL is estimated as a function of age and gender, using the equation for the general population.	Ara et al 2010 [10]
	Utility multiplier following stroke, utility multiplier following major non-fatal intracranial bleed	Simulation & mapping based approach described in an upcoming report. Utility multipliers (95% CrIs) were estimated to be 0.822 (0.819 to 0.824) for an independent state following a stroke, and 0.482 (0.477 to 0.487) for a dependent state following a stroke.	Method described in report results published in Rivero-Arias et al 2010 [8]
Costs	Annual cost of dabigatran	£920. A fixed cost was assumed.	NICE FAD, 2011 [11]
	Annual cost of rivaroxaban	£767. A fixed cost was assumed.	London New Drugs Group [12]
	Annual cost of warfarin	£252 to £259 including monitoring costs. A uniform distribution was assumed.	BNF [13]
	Cost of TTE	£66	NHS Reference Costs [14]
	Cost of death due to stroke	£7,019 (95% CrI £6,975 to £7,064)	Sandercock et al 2002 [15]
	Costs in stroke survivors	Various. Differing according to dependent and independent states. Subdivided into one-off and continuing costs. Estimates (95% CrIs) are as follows:	NHS Reference Costs [14] NHS Stroke Strategy Impact Assessment [16] Unit Costs of Health and Social Care 2010 [17]

		<p>Dependent stroke, one-off costs: £2830 (£2708 to £2952)</p> <p>Dependent stroke, continuing annual cost: £6386 (£5749 to £7023)</p> <p>Independent stroke, one-off costs: £542 (£513 to £571)</p> <p>Independent stroke, continuing annual cost: £3195 (£2871 to £3518)</p>	
	Costs of fatal bleed	Assumed identical to costs of death due to stroke	
	Costs of nonfatal bleed	<p>Major bleeds subdivided into gastrointestinal (GI) and intracranial (IC). GI bleeds were assumed to incur a one-off cost but no continuing costs. The one-off cost (95% CrI) was £1261 (£1212 to £1310).</p> <p>For IC bleeds, the costs depended on the Glasgow Outcome Scale (GOS) level of disability that they cause, from GOS 2 (most severe) to GOS 5 (least severe).</p> <p>The one-off costs (95% CrIs) used were as follows:</p> <p>GOS 2: £46785 (£40895 to £53250)</p> <p>GOS 3: £10096 (£8849 to £11363)</p> <p>GOS 4: £27419 (£22582 to £32964)</p> <p>GOS 5: £1261 (£1211 to £1309)</p>	NHS Reference Costs [14]

		GOS 4 and GOS 5 states were assumed not to have ongoing costs. The ongoing annual costs (95% CrIs) of the other states were as follows: GOS 2: £50047 (£49645 to £50343) GOS 3: £33949 (£33843 to £33969)	
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Table 1 Parameters used in model

References

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- 15 Sandercock P, Berge E, Dennis M, *et al.* A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. *Health Technology Assessment* 2002;**6**.
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Appendix B: Sensitivity and Specificity tables

W₅₀		Specificity										
0_M		0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Sensitivity	0	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	D	8.4
	0.2	D	D	D	D	D	D	D	D	D	D	5.7
	0.3	D	D	D	D	D	D	D	D	D	70.7	4.9
	0.4	D	D	D	D	D	D	D	D	D	26.2	4.4
	0.5	D	D	D	D	D	D	D	D	>99	17.1	4.2
	0.6	D	D	D	D	D	D	D	D	65.6	13.1	4.0
	0.7	D	D	D	D	D	D	D	D	35.0	10.9	3.8
	0.8	D	D	D	D	D	D	D	>99	24.5	9.5	3.8
	0.9	D	D	D	D	D	D	D	63.9	19.2	8.5	3.7
	1	D	D	D	D	D	D	>99	40.2	16.0	7.8	3.6

a) W_{50_0_M}

W₆₅		Specificity										
0_M		0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Sensitivity	0	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	D	8.9
	0.2	D	D	D	D	D	D	D	D	D	29.8	4.9
	0.3	D	D	D	D	D	D	D	D	62.8	13.9	3.6
	0.4	D	D	D	D	D	D	D	>99	25.0	9.3	2.9
	0.5	D	D	D	D	D	D	>99	38.8	15.9	7.1	2.5
	0.6	D	D	D	D	D	>99	56.6	23.4	11.8	5.8	2.3
	0.7	D	D	D	D	D	80.4	32.1	16.9	9.4	5.0	2.1
	0.8	D	D	D	D	>99	42.3	22.6	13.3	7.9	4.4	1.9
	0.9	D	D	D	>99	54.5	28.9	17.5	11.0	6.9	4.0	1.8
	1	D	D	>99	69.3	36.1	22.1	14.4	9.5	6.1	3.6	1.7

b) W_{65_0_M}

W₆₅		Specificity										
0_F		0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Sensitivity	0	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	>99	8.1
	0.2	D	D	D	D	D	D	D	D	>99	24.4	4.6
	0.3	D	D	D	D	D	D	D	>99	39.8	12.9	3.4
	0.4	D	D	D	D	D	D	>99	54.5	21.0	9.0	2.8
	0.5	D	D	D	D	D	>99	68.6	28.8	14.4	7.0	2.5
	0.6	D	D	D	D	>99	82.0	36.5	19.8	11.1	5.8	2.3
	0.7	D	D	D	>99	94.7	44.1	25.1	15.2	9.1	5.0	2.1
	0.8	D	D	>99	>99	51.4	30.3	19.2	12.4	7.8	4.5	2.0
	0.9	D	>99	>99	58.4	35.4	23.2	15.7	10.6	6.9	4.1	1.9
	1	>99	>99	65.4	40.4	27.1	18.9	13.3	9.2	6.1	3.7	1.8

c) W_{65_0_F}

R_65 O_F		Sensitivity										
		0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Specificity	0	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	77.0	7.3
	0.2	D	D	D	D	D	D	D	D	65.3	17.4	4.1
	0.3	D	D	D	D	D	D	>99	61.4	23.9	10.1	3.0
	0.4	D	D	D	D	D	>99	59.5	28.4	14.8	7.3	2.4
	0.5	D	D	D	D	>99	58.3	31.7	18.6	10.9	5.8	2.1
	0.6	D	D	>99	>99	57.5	34.2	21.8	14.0	8.7	4.8	1.9
	0.7	D	>99	>99	57.0	36.3	24.4	16.7	11.3	7.3	4.2	1.7
	0.8	>99	93.2	56.6	37.9	26.6	19.0	13.6	9.5	6.3	3.7	1.6
	0.9	87.0	56.2	39.3	<u>28.5</u>	<u>21.1</u>	15.6	11.5	8.2	5.6	3.4	1.5
	1	56.0	40.4	30.1	<u>22.9</u>	<u>17.5</u>	13.3	10.0	7.3	5.0	3.1	1.5
g) R_65_O_F												
D_65 O_M		Sensitivity										
		0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Specificity	0	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	D	44.1	6.8
	0.2	D	D	D	D	D	D	D	>99	36.0	12.8	3.6
	0.3	D	D	D	D	D	>99	84.7	33.4	16.2	7.6	2.5
	0.4	D	D	D	D	>99	62.0	32.0	18.3	10.5	5.5	1.9
	0.5	D	D	>99	>99	52.3	31.2	19.8	12.7	7.9	4.3	1.6
	0.6	>99	>99	79.3	46.9	30.7	20.9	14.4	9.8	6.3	3.6	1.4
	0.7	>99	66.5	43.5	30.3	21.8	15.8	11.4	8.0	5.3	3.1	1.2
	0.8	58.8	41.1	30.0	22.4	16.9	12.7	9.4	6.7	4.5	2.7	1.1
	0.9	39.3	29.8	22.9	<u>17.8</u>	<u>13.8</u>	10.6	8.0	5.8	4.0	2.4	1.0
	1	29.6	23.4	18.6	<u>14.8</u>	<u>11.7</u>	9.2	7.0	5.2	3.6	2.2	1.0
h) D_65_O_M												
D_65 O_F		Sensitivity										
		0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Specificity	0	D	D	D	D	D	D	D	D	D	D	∞
	0.1	D	D	D	D	D	D	D	D	>99	28.3	6.2
	0.2	D	D	D	D	D	>99	>99	46.8	23.8	11.2	3.3
	0.3	D	D	>99	>99	99.6	57.0	35.4	22.2	13.4	7.1	2.4
	0.4	>99	>99	97.7	63.5	43.6	30.6	21.5	14.7	9.5	5.3	1.9
	0.5	96.6	67.9	49.8	37.2	28.0	21.0	15.5	11.0	7.4	4.3	1.6
	0.6	54.5	42.5	33.5	26.4	20.7	16.1	12.2	8.9	6.1	3.6	1.4
	0.7	38.1	31.0	25.3	20.5	16.5	13.0	10.1	7.5	5.2	3.1	1.3
	0.8	29.3	24.5	20.4	16.8	13.7	11.0	8.6	6.4	4.5	2.8	1.2
	0.9	23.9	20.2	17.1	<u>14.3</u>	<u>11.8</u>	9.5	7.5	5.7	4.0	2.5	1.1
	1	20.1	17.3	14.7	<u>12.4</u>	<u>10.3</u>	8.4	6.7	5.1	3.6	2.3	1.1
i) D_65_O_F												

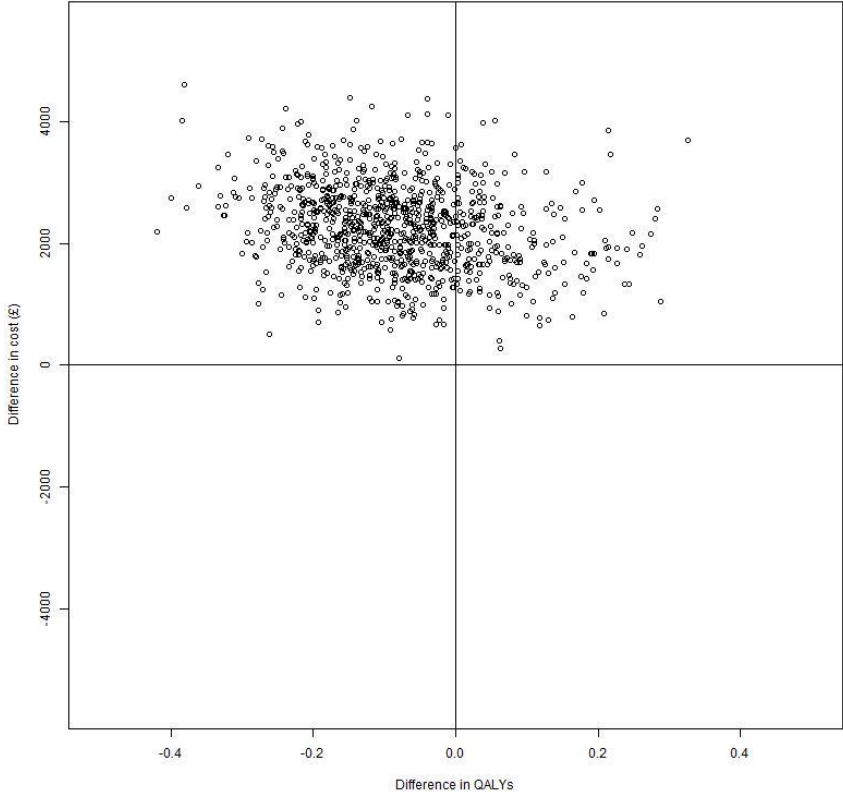
Table 2 Effect of assumed sensitivity and specificity of device on estimated cost effectiveness. D: dabigatran; W: Warfarin; R: rivaroxaban; M: Male; F: Female; 65: 65 years old; 50: 50 years old

Appendix C: Simulated clinical outcomes

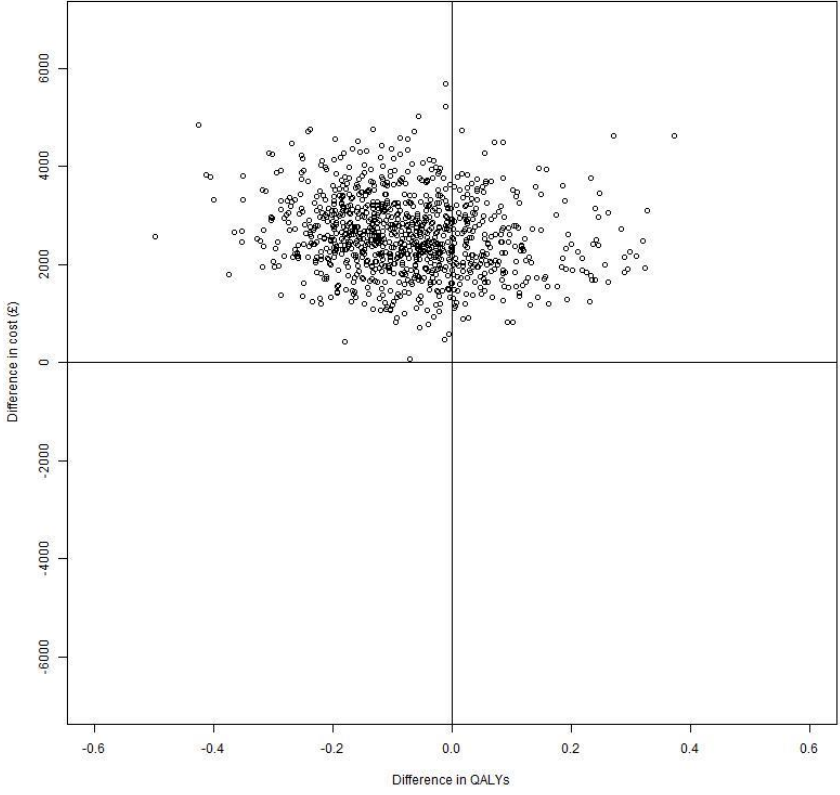
				Cause of Death (%)			Average Number of Events			
<i>OAC</i>	<i>Patient population¹</i>	<i>Strategy</i>	<i>Life Years</i>	<i>Stroke</i>	<i>Bleed</i>	<i>Other</i>	<i>Dependent Strokes</i>	<i>Independent Strokes</i>	<i>ICH</i>	<i>NICH</i>
Warfarin	Male, 50 years old	Without TTE	28.840	11.7	1.3	87.1	0.120	0.242	0.010	0.075
		With TTE	28.928	10.8	1.8	87.4	0.111	0.223	0.014	0.112
	Female, 50 years old	Without TTE	31.633	13.5	1.6	84.9	0.139	0.278	0.012	0.091
		With TTE	31.734	12.6	2.1	85.2	0.130	0.259	0.017	0.130
	Male, 65 years old	Without TTE	17.131	9.0	0.9	90.2	0.087	0.192	0.007	0.052
		With TTE	17.204	8.0	1.3	90.7	0.078	0.172	0.010	0.079
	Female, 65 years old	Without TTE	19.447	10.6	1.1	88.3	0.105	0.225	0.009	0.065
		With TTE	19.531	9.6	1.6	88.8	0.096	0.205	0.012	0.095
Rivaroxaban	Male, 50 years old	Without TTE	28.861	11.5	1.3	87.2	0.117	0.239	0.010	0.075
		With TTE	28.963	10.5	1.8	87.6	0.108	0.219	0.014	0.113
	Female, 50 years old	Without TTE	31.657	13.3	1.6	85.1	0.136	0.275	0.012	0.091
		With TTE	31.772	12.4	2.1	85.5	0.127	0.255	0.017	0.130
	Male, 65 years old	Without TTE	17.141	8.8	0.9	90.3	0.085	0.190	0.007	0.052
		With TTE	17.221	7.8	1.3	90.9	0.076	0.169	0.010	0.080
	Female, 65 years old	Without TTE	19.460	10.5	1.1	88.4	0.103	0.223	0.009	0.066
		With TTE	19.554	9.4	1.6	89.0	0.093	0.201	0.012	0.096
Dabigatran	Male, 65 years old	Without TTE	17.158	8.6	0.9	90.5	0.081	0.188	0.007	0.053
	Female, 65 years old	With TTE	17.251	7.5	1.3	91.2	0.072	0.163	0.010	0.081

¹ All populations had initial CHADS₂ scores of 0

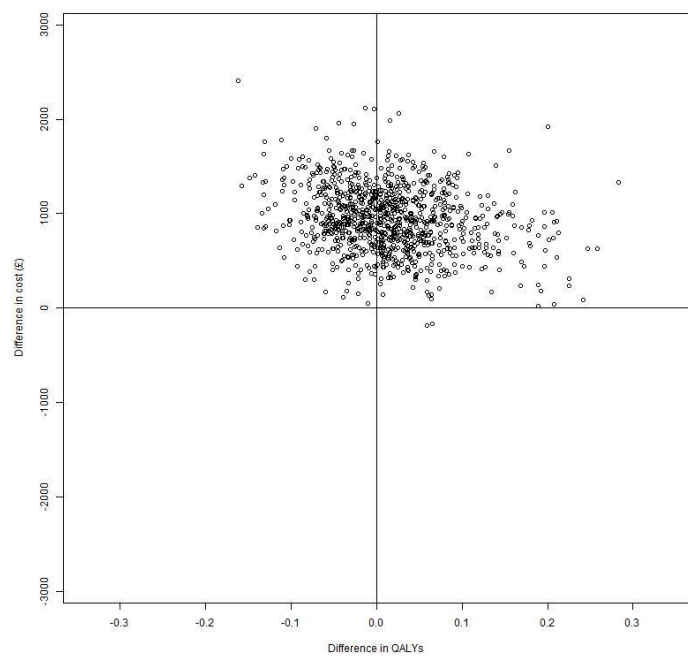
Appendix D: Scatterplots of estimated difference in costs and health outcomes from probabilistic sensitivity analysis



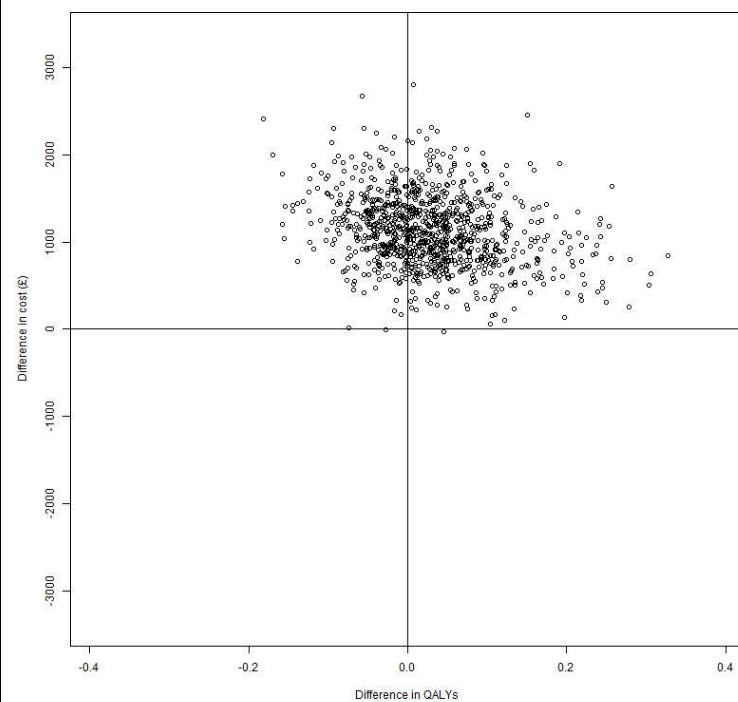
a) Warfarin, 50 years old, males



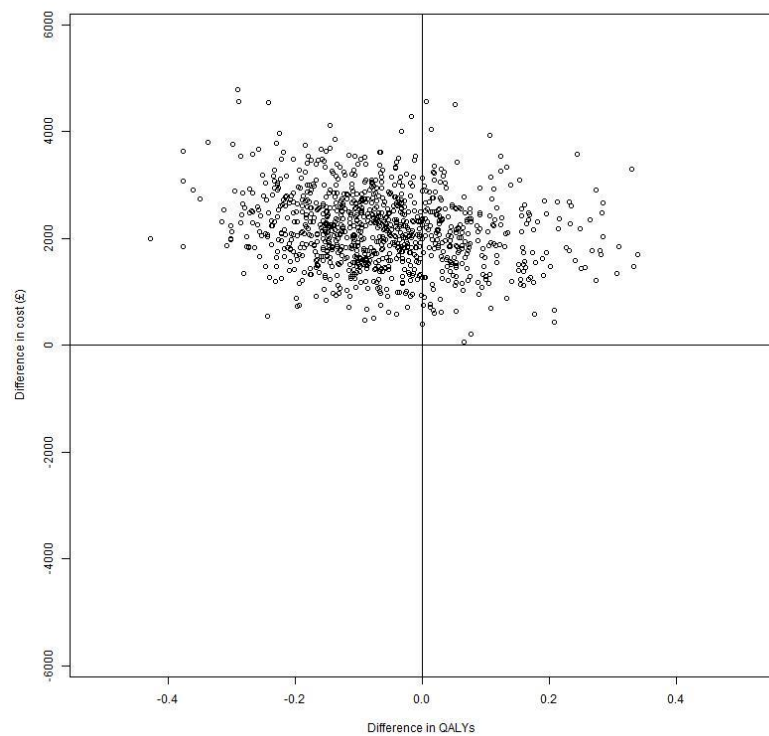
b) Warfarin, 50 years old, females



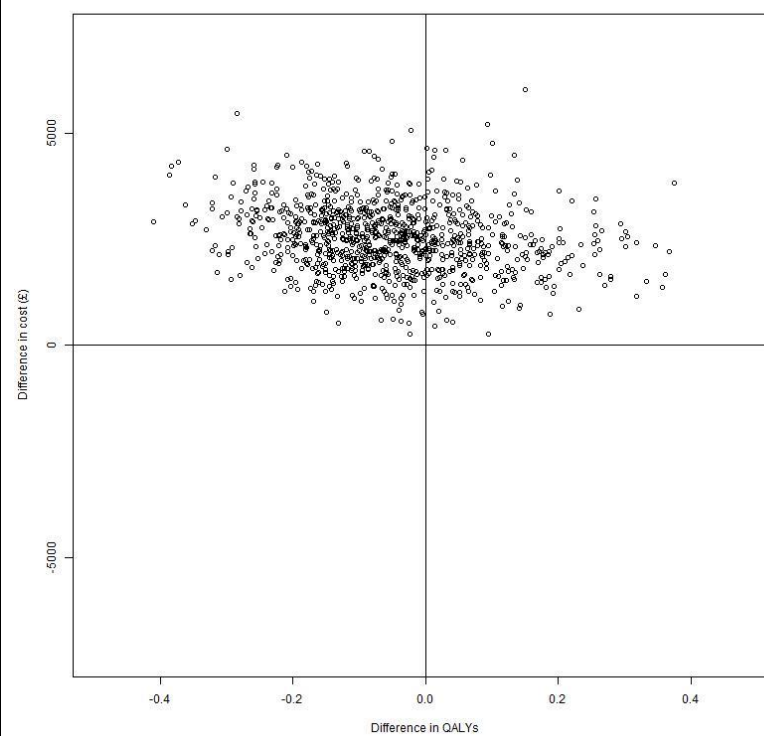
c) Warfarin, 65 years old, males



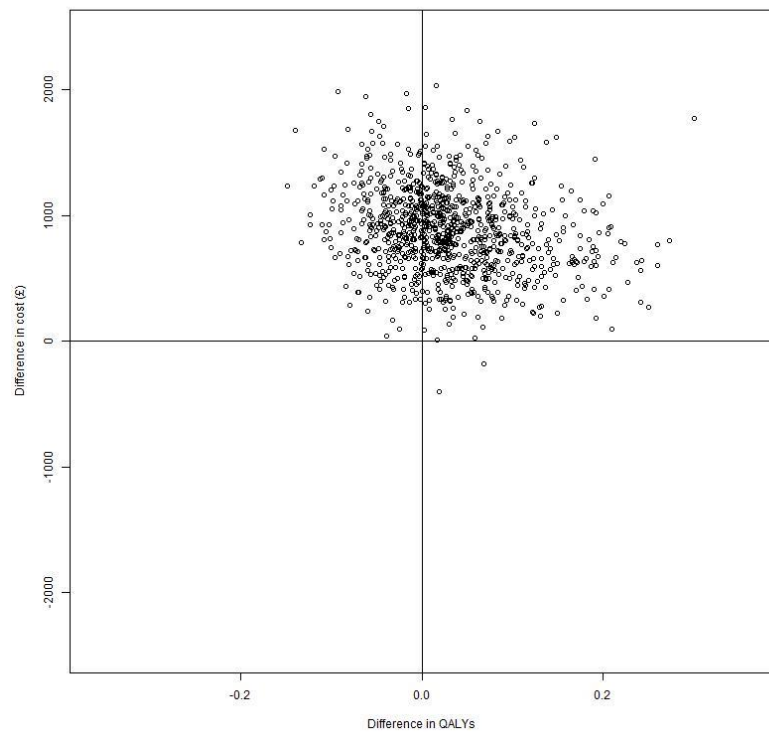
d) Warfarin, 65 years old, females



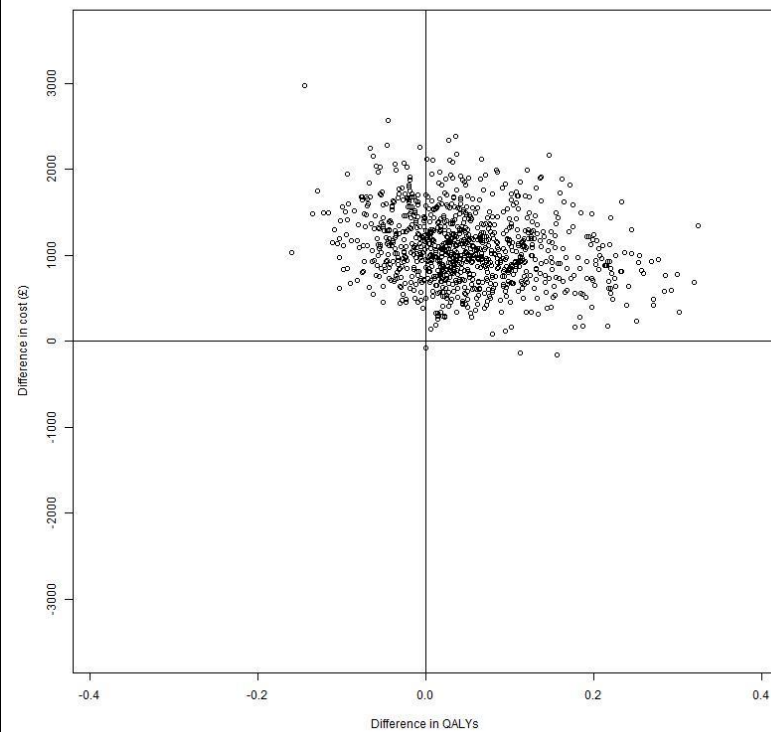
e) Rivaroxaban, 50 years old, males



f) Rivaroxaban, 50 years old, females



g) Rivaroxaban, 65 years old, males



h) Rivaroxaban, 65 years old, females

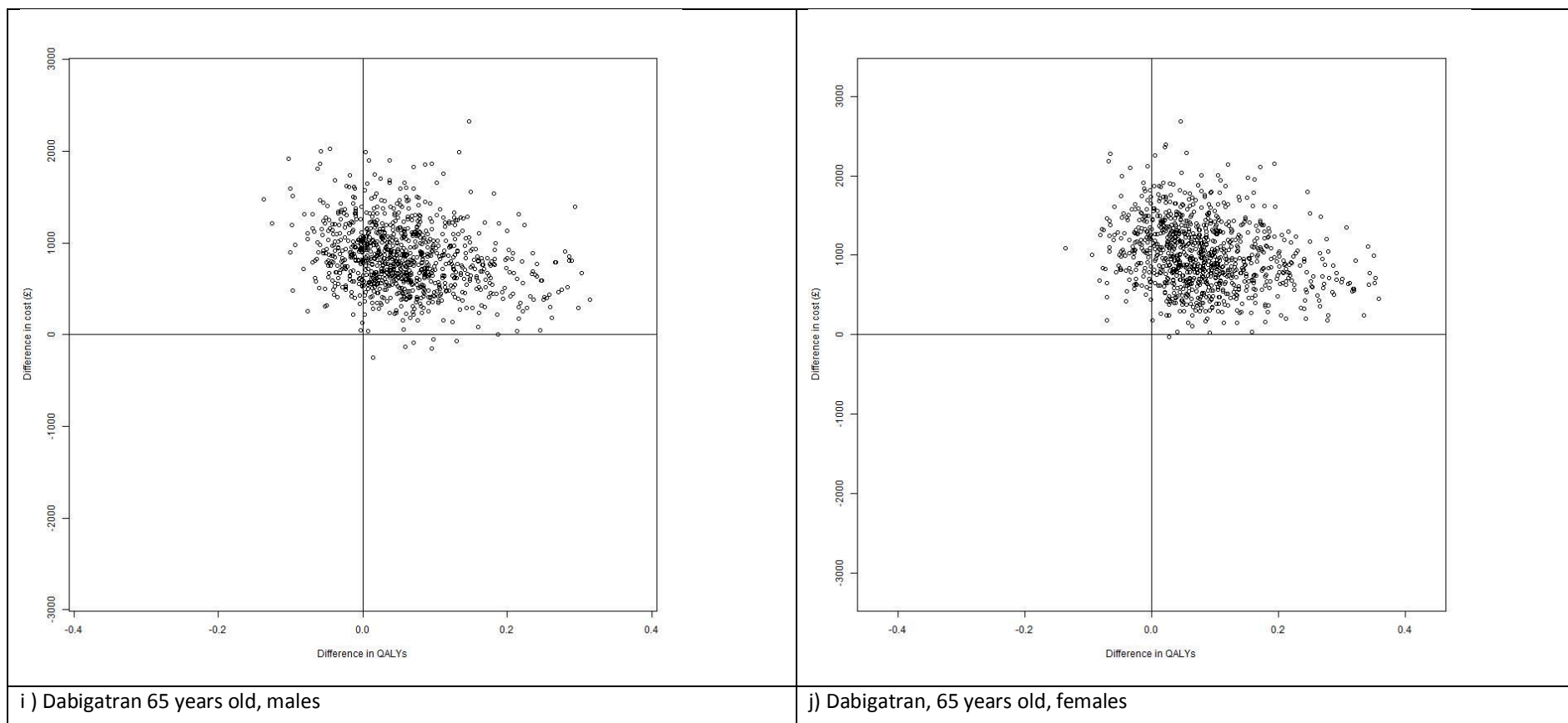


Table 3 Scatterplots of estimated differences in health outcomes (in QALYs) and cost between the TTE and no TTE strategy for the ten populations simulated. QALY: Quality-adjusted life years. TTE: transthoracic echocardiography

Appendix E: Summary of cost-effectiveness results of TTE compared with no TTE strategies for the 10 patient populations under consideration

OAC	Patient Population	Strategy	Mean Cost (£)	Mean QALY	ICER (95% CrI), £/QALY	TTE dominated?
Warfarin	Male, Aged 50	No TTE	2459	13.60	-26 489 (-26 552 to -26 408)	Yes
		TTE	4712	13.51		
	Female, Aged 50	No TTE	2815	14.27	-34 078 (-34 175 to -33 952)	Yes
		TTE	5405	14.19		
	Male, Aged 65	No TTE	1527	9.12	66 793 (66 217 to 67 599)	No
		TTE	2467	9.13		
	Female, Aged 65	No TTE	1974	9.94	39 485 (39 291 to 39 754)	No
		TTE	3106	9.97		
Rivaroxaban	Male, Aged 50	No TTE	2449	13.61	-34 060 (-34 170 to -33 910)	Yes
		TTE	4614	13.54		
	Female, Aged 50	No TTE	2779	14.27	-47 535 (-47 773 to -47 271)	Yes
		TTE	5315	14.22		
	Male, Aged 65	No TTE	1510	9.12	30 310 (30 179 to 30 487)	No
		TTE	2393	9.15		
	Female, Aged 65	No TTE	1955	9.95	22 751 (22 681 to 22 844)	No
		TTE	3039	9.99		
Dabigatran	Male, Aged 65	No TTE	1487	9.13	14 728 (14 693 to 14 782)	No
		TTE	2321	9.18		
	Female, Aged 65	No TTE	1942	9.95	12 314 (12 290 to 12 348)	No
		TTE	2946	10.01		

Table 4 Summary of cost effectiveness results. ICER: Incremental cost effectiveness ratio. TTE: transthoracic echocardiography; QALY: Quality-adjusted life year. Dominated: the strategy is both more expensive and less effective than the strategy to which it is compared