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Is self-monitoring an effective option for people receiving long-term vitamin K antagonist therapy? A systematic review and economic evaluation

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ABSTRACT

Objectives: To investigate the clinical and cost-effectiveness of self-monitoring of coagulation status in people receiving long-term vitamin K antagonist therapy compared with standard clinic care.

Design: Systematic review of current evidence and economic modelling.

Data sources: Major electronic databases were searched up to May 2013. The economic model parameters were derived from the clinical effectiveness review, routine sources of cost data and advice from clinical experts.

Study eligibility criteria: Randomised controlled trials (RCTs) comparing self-monitoring versus standard clinical care in people with different clinical conditions. Self-monitoring included both self-management (patients conducted the tests and adjusted their treatment according to an algorithm) and self-testing (patients conducted the tests, but received treatment recommendations from a clinician). Various point-of-care coagulometers were considered.

Results: 26 RCTs (8763 participants) were included. Both self-management and self-testing were as safe as standard care in terms of major bleeding events (RR 1.08, 95% CI 0.81 to 1.45, p=0.690, and RR 0.99, 95% CI 0.80 to 1.23, p=0.92, respectively). Self-management was associated with fewer thromboembolic events (RR 0.51, 95% CI 0.37 to 0.69, p≤0.001) and with a borderline significant reduction in all-cause mortality (RR 0.68, 95% CI 0.46 to 1.01, p=0.06) than standard care. Self-testing resulted in a modest increase in time in therapeutic range compared with standard care (weighted mean difference, WMD 4.4%, 95% CI 1.71 to 7.18, p=0.02). Total health and social care costs over 10 years were £7324 with standard care and £7326 with self-monitoring (estimated quality adjusted life year, QALY gain was 0.028). Self-monitoring was found to have ~80% probability of being cost-effective compared with standard care applying a ceiling willingness-to-pay threshold of £20 000 per QALY gained. Within the base case model, applying the pooled relative effect of thromboembolic events, self-management alone was highly cost-effective while self-testing was not.

Conclusions: Self-monitoring appears to be a safe and cost-effective option.

Trial registration number: PROSPERO CRD42013004944.

Strengths and limitations of this study

- The study is the most up-to-date evidence synthesis on this topic, with the largest number of included randomised controlled trials.
- Clinical heterogeneity was observed among included trials.
- The majority of the trials included participants with mixed clinical indications for anticoagulation therapy, which made it challenging to extrapolate the results to specific clinical populations.
- The perspective of the economic modelling was that of the National Health Service (NHS) and personal social services, and did not capture any wider benefit.
- Long-term outcomes data on self-management from larger cohorts of people with different clinical indications are needed.

INTRODUCTION

Approximately 2% of the population are prescribed long-term oral anticoagulant drugs for atrial fibrillation (AF),[1–3] heart valve disease,[4–6] or other conditions with high risk of thrombosis.[7–9] Historically, treatment has been with vitamin K antagonist therapy, with dose-adjusted warfarin the most commonly used drug. Recently, new oral anticoagulants (NOACs) which do not require dose adjustment, such as dabigatran etexilate, rivaroxaban or apixaban, have been proposed as a possible alternative to warfarin for the treatment of AF.[10 11] However, NOACs are unsuitable for people with artificial heart valves

(AHF), people with liver or renal dysfunctions and those who are taking concurrent medication, which may react with this class of anticoagulants. For these people, warfarin remains the long-term treatment of choice. Furthermore, the lack of long-term evidence on these novel anticoagulants compared with vitamin K antagonists induces some caution in their wide prescription.[10]

Typically, dose adjustment of vitamin K antagonist therapy involves a blood test of clotting (international normalised ratio, INR) with dose titration to maintain this within a narrow therapeutic range (TTR).[12 13] Underdosing of anticoagulation therapy increases the risk of thromboembolism, while overdosing increases the risk of bleeding events. Repeated and regular measurements of INR, with dose adjustment when necessary, are necessary to ensure safe and effective anticoagulation therapy.[14]

Monitoring of anticoagulant treatment can be delivered in a number of different ways. These include full service provision in specialist anticoagulation clinics, in physician offices or general practices (either with samples sent to a laboratory or with near-patient testing) or self-monitoring[8] in which patients carry out their own tests at home using approved portable coagulometers, which test a finger-prick blood sample. Self-monitoring includes both self-management, in which patients conduct tests and adjust their treatment according to an algorithm; in self-testing, the patients conduct the tests, but obtain treatment recommendations from a clinician after sending them the results.

Several coagulometers are available, which have CE marketing authorisation and Food and Drug Administration (FDA) approval; these include the CoaguChek system (versions S and XS) (Roche Diagnostics, Basel, Switzerland), the INRatio2 PT/INR monitor, (Alere Inc., San Diego, California, USA) or the ProTime Microcoagulation system (International Technidyne Corporation, ITC—Nexus Dx, Edison, New Jersey, USA). Their precision and accuracy compared with conventional laboratory-based clinical testing have been reported in a number of studies in the literature.[15–17]

The increased use of oral anticoagulants has intensified pressure on healthcare resources.[18] The use of point-of-care coagulometers for self-monitoring may avoid unnecessary visits to hospitals or clinics while permitting more frequent INR monitoring and timely adjustment of warfarin dosing to avoid adverse events.[19] The evidence for the effectiveness of self-monitoring is limited[20] and previously published economic evaluations have produced conflicting results.[14 16] The aim of this study is to assess the current evidence on the clinical and cost-effectiveness of self-monitoring (self-testing and self-management) in people receiving long-term vitamin K antagonist therapy as an alternative to standard anticoagulation monitoring care. We focus mainly on the current generation of point-of-care devices (eg, CoaguChek XS), which utilised the most recent technology to minimise measurement inaccuracies.

METHODS

Clinical effectiveness

The methods of the systematic review of clinical effectiveness were prespecified and detailed in a research protocol (http://guidance.nice.org.uk/DT/16/FinalProtocol/pdf/English), and reported according to standard guidelines.[21–24]

Identification of studies

We identified a relevant systematic review published in the Cochrane Library in 2010 by Garcia-Alamino *et al*,[20] which included studies published up to 2007, and had similar objectives to those of this study. Thus, the literature searches for this study were run in May 2013 for the period '2007-to date' to identify newly published reports. All randomised controlled trials (RCTs) included in the Garcia-Alamino *et al*'s[20] review were obtained and included for full-text assessment. Major electronic databases such as MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Biosis, Science Citation Index, and Cochrane Controlled Trials Register (CENTRAL) were searched for relevant primary studies. Evidence syntheses' reports, conference abstracts (2011–2013), and ongoing studies were sourced from relevant databases. Reference lists of included studies were perused for additional publications and experts in the field contacted for further information on relevant outcomes and ongoing research in the field. Searches were restricted to publications in English. Full details of the search strategies are presented in online supplementary appendix 1.

Inclusion and exclusion criteria

We included RCTs comparing self-testing and/or self-management of anticoagulation control using point-of-care coagulometers with standard monitoring care, which consisted of INR monitoring managed by healthcare professionals. We included studies of both adults and children with heart valve disease (eg, AHV), AF or other clinical indications who required long-term vitamin K antagonist therapy. Main outcomes of interest were: (1) major bleeding and thromboembolic events; (2) all-cause mortality; (3) anticoagulation control measured as time and INR values in TTR, and other intermediate outcomes (including frequency of testing, frequency of visits to clinics, patient compliance with testing).

Study selection and data extraction

Two authors independently screened the results of the literature searches, retrieved full-text copies of selected studies and extracted relevant data (PS, MC). Information on study design, characteristics of participants, settings, characteristics of interventions and comparators, and outcome measures was recorded for all included studies. The Cochrane Risk of Bias tool was used to assess the risk of bias in the included studies.[22] Critical assessments of selection, detection, attrition and reporting biases were

performed initially by one author (PS) and cross-checked by a second author (MC). Studies were not excluded purely on the basis of their potential risk of bias. Any uncertainty or disagreements during the study selection, data extraction and risk of bias assessment was resolved by discussion or arbitration by a third author (MB).

Data analysis

Where appropriate, pooled summary estimates were calculated using Review Manager, software (Review Manager V.5.2, Copenhagen: the Nordic Cochrane Centre, The Cochrane Collaboration, 2012). In the presence of either clinical or statistical heterogeneity, a random effects model was chosen as the preferred method for pooling the effect sizes.[21] Relative risk (RR) together with 95% CIs were calculated for dichotomous data (Mantel-Haenszel method), while weighted mean difference (WMD) together with 95% CI were calculated for continuous data (inverse-variance method). Where SDs were not given, these were extrapolated, if possible, using test statistics. Heterogeneity across studies was explored by means of the χ^2 statistic (with significance level at $p<0.05$) and the extent of inconsistency between studies quantified by means of the I^2 statistic. For trials that had multiple arms contributing to different subgroups, the control group was subdivided into two groups to avoid a unit of analysis error.

Cost-effectiveness analysis

A *de novo* Markov model was developed[25 26] in TreeAge Pro (TreeAge Software, Williamstown, Massachusetts, 2013) to assess the cost-effectiveness of self-monitoring (self-testing and self-management). The model structure was based on previous economic models of INR self-monitoring published in the literature,[14 27–34] including models assessing the cost-effectiveness of NOAC drugs compared with warfarin in people with AF.[11 35] In addition, an unpublished economic model was provided by Roche Diagnostics, the manufacturer of the CoaguChek XS coagulometer (J Craig, York Health Economics Consortium, 2013). The model was built and analysed in accordance with the National Institute for Health and Care Excellence (NICE) reference case for the evaluation of diagnostic tests and devices.[36]

Model framework and method of synthesis

The model was populated using data derived from the systematic review of clinical effectiveness, other relevant reviews to inform key parameters (eg, baseline risks), and routine sources of cost data,[37 38] and information provided by clinical experts. The alternative monitoring pathways were embedded in a Markov model simulating the occurrence of adverse events over time for a hypothetical cohort of people with AF or AHV (figure 1). The model incorporated the pathways of care that individuals currently follow under standard practice in the National Health Services (NHS)—standard monitoring in primary care or in secondary care—as well as proposed pathways for self-testing and self-management. The cost-effectiveness of self-monitoring was assessed as a whole assuming a 50:50 split between self-testing and self-management. The model simulated transitions between the discrete health states on a quarterly (3-month) cycle. Appropriate costs and quality of life weights were attached to modelled events and health states, allowing cumulative health and social care costs and quality adjusted life years (QALYs) to be modelled over time. Full details of the modelling methods are provided in online supplementary appendix 2. The main assumptions made for the base case analysis are summarised in table 1. For the purpose of this study, it was assumed that self-monitoring patients use the CoaguChek XS system.

The results of the model are presented in terms of a cost-utility analysis (ie, costs for and number of QALYs generated by each monitoring strategy). Self-monitoring

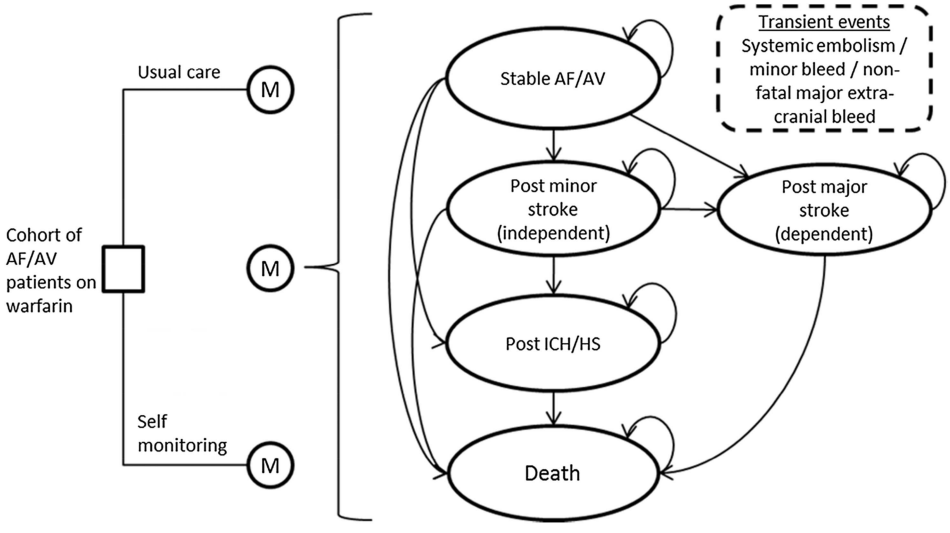

Figure 1 Schematic of the model structure.

Table 1 Main assumptions made for the base case analysis and justification

Assumptions	Justification
66.45% of standard care monitoring occurs in primary care with practice nurses	Based on previous TAR (manufacturers submission for TA256)[70]
60% of the cohort have atrial fibrillation, 40% have an artificial heart valve	In line with the observed proportions of patients with these conditions in self-monitoring trials[68]
Average age of the cohort is 65 years, and 55% are male	In line with the observed mean age of included patients with these conditions in self-monitoring trials[68]
50% of self-monitoring people self-test, 50% self-manage	Self- assumption
The increase in the number of tests performed per year with self-monitoring is 23	In line with the observed frequency of self-testing in self-monitoring trials[68]
Relative treatment effects are estimated and applied separately for self-testing and self-management	Derived from the observed event rates in cohorts of people being managed under current standard models of care. Relative risks of these events resulting from improved/reduced INR control, conferred by self-monitoring, were derived from the meta-analysis of RCTs of self-monitoring versus standard practice. (see section on clinical effectiveness results)
15% of participants do not commence self-monitoring following training	Based on the RCT literature[43] and the expert advisory committee consultation
10% of participants discontinue self-monitoring within a year of commencing	Based on consideration of the views of the expert advisory committee (~5%) and a rate of 14% reported in the largest UK-based trial.[43]
Self-monitoring device costs are annuitized over 5 years to account for the potential for loss and accidental damage	It was assumed that the NHS would pay for devices and loan them out to patients. As such they were annuitized over their expected useful life, to provide an equivalent annual/quarterly cost of use
75% of devices are reused by another patient when a patient discontinues self-monitoring	In line with a previous UK-based economic evaluation[71]

TAR, technology assessment report; INR, international normalised ratio; RCT, randomised control trial; NHS, National Health Service.

strategies were compared to standard care monitoring, to estimate the incremental costs per QALY gained. Both costs and benefits (QALYs) were discounted at a rate of 3.5% per annum, in line with the NICE reference case.[36] Cost are expressed in 2011/2012 Stirling. The model was initially analysed over a 10-year period, but the impact of adopting longer time horizons was explored through sensitivity analyses. Further sensitivity analyses focused on the standard care comparator (primary care, secondary care), the proportional split between the active interventions (self-testing, self-management), the baseline risk of thromboembolic events and the RRs associated with self-testing and self-management. In addition, cost-minimisation scenarios were considered (assuming an equal number of tests with self-monitoring and standard care, and equivalence in effects). Finally, the results of probabilistic sensitivity analyses were used to express the parameter uncertainty surrounding the base estimates of cost-effectiveness.

RESULTS

Clinical effectiveness

Of the 658 records retrieved, 26 RCTs published in 45 papers with a total of 8763 participants met the inclusion criteria. Of the 26 included RCTs, 21 trials with a total of 8394 participants provided suitable data for statistical analyses relevant to the comparisons and outcomes of interest. A flow diagram outlining the selection process is shown in online supplementary appendix 3.

The 26 included trials were conducted in Europe and North America. Seventeen trials (17/26) compared self-management with standard care,[39–55] six assessed self-testing,[56–61] and one evaluated both self-testing and self-management versus either trained or untrained routine care (four arms).[62] The remaining two trials compared self-testing with self-management,[63 64] one of which focused exclusively on children.[63] Two trials enrolled exclusively participants with AF,[55 59] six trials limited inclusion to participants with AHV[41 45 46 50 52 56] and 18 trials[39 40 42–44 47–49 51 53 54 57 58 60–64] included participants with mixed clinical indications. The majority of the included trials (22/26) used the CoaguChek system for INR monitoring. Two trials used either INRatio or the CoaguChek S for INR measurement (but did not present results according to the type of the point-of-care device used),[44 56] while the other two trials used the ProTime system.[53 60]

Table 2 summarises the characteristics of the included trials (full details are shown in online supplementary appendix 4 table S1). The included trials varied in size (16–2922 participants), the length of study duration (3.5–57 months), the age of the included adult participants (16–91 years) and the type of standard care (63.6% of the participants measured INR in secondary care, 27.2% in primary care and 9.2% in mixed care

Table 2 Summary of the characteristics of included trials

Characteristics	Range	Total number (%)	Number of trials
Sample size, n	16–2922	8763	26
Self-monitoring, n		4553 (51.9)	
PSM	14–579	2619 (57.5)	20*
PST	14–1465	1934 (42.5)	9*
Standard care, n		4199 (47.9)	
AC clinic	17–1457	2669 (63.6)	15
GP/physician	26–576	1143 (27.2)	6
AC clinic or GP/physician	49 to103	387 (9.2)	5
Study duration, months	3.5–57†		
<12	16–320	2186 (25)	17
≥12	28–2922	6577 (75)	9
Age, years	1–91		
Mean age groups, years			
Mean age ≤18	1–19	28 (<1)	1
Mean age >18 to <50	22–71	100 (~1)	1
Mean age ≥50 to <70	16–91	8289 (94.6)	21
Mean age ≥70	65–91	85 (~1)	1
Clinical indication, n			
AF	85–202	287 (3)	2
AHV	58–1155	2434 (28)	6
Mixed indication	16–2922	6042 (69)	18
POC devices, n			
CoaguChek	28–1155	5479 (62.5)	22
ProTime	140–2922	3062 (35.0)	2
INRatio2	–	0	0
CoaguChek+INRatio2	16–206	222 (2.5)	2
Outcomes, n			
Thromboembolic events	49–2922	8394 (95.8)	21
Bleeding events	49–2922	8394 (95.8)	21
Mortality	49–2922	6537 (74.6)	13
Time in therapeutic range	28–2922	6245 (71.3)	18
INR values in range	49–1155	4472 (51)	12

*For conversion of study duration reported in week, 4 weeks was considered equivalent to 1 month.
†Three of the 26 trials reported both PSM and PST arms.[62–64]
PSM, patient self-management; PST, patient self-testing; AC, anticoagulation; GP, general practitioner; AF, atrial fibrillation; AHF, artificial heart valves; POC, point-of-care; INR, international normalised ratio.

setting). In approximately 95% of the included participants, mean age was between 50 and 70 years. Nine trials, which includes 75% of the total participants, had study duration of more than or equal to 12 months.[41 43 46 47 50–52 60 63] Three trials recruited participants who were new to anticoagulation therapy,[46 48 51] two trials included participants receiving anticoagulants for the past 1–2 months,[53 61] 12 trials recruited participants who had been on anticoagulants for at least 3 months before randomisation[39 40 42 43 47 54 57–59 62–64] while the remaining trials did not provide this information.

Only four trials were assessed to have adequate sequence generation, concealed allocation and blinded outcome assessment and therefore were judged at low risk of bias.[47 61 63 65] The remaining trials were judged at 'unclear'[40–46 48–50 52 56 58 59 62 64] or 'high'[39 53–55 57 60] risk of bias (figure 2) (full details of the risk of bias assessment are presented in online supplementary appendix 4 table S2).

Major clinical outcomes

Major bleeding and major thromboembolic events were reported in the majority of trials. Definitions varied between the trials and not all trials used well-defined criteria. In general, major events (bleeding or thromboembolic) were defined as complications requiring hospital admission or medical assessment. Fatal bleeding and thromboembolic events were counted as deaths.

Table 3 shows the main findings of self-monitoring (self-testing and self-management) compared with standard clinical monitoring.

Bleeding events

Twenty-one trials reported a total of 1472 bleeding events (major and minor). No statistically significant differences were observed between either self-management or self-testing, and standard monitoring care for major bleeding events (RR 1.08, 95% CI 0.81 to 1.45, p=0.60 and RR 0.99, 95% CI 0.80 to 1.23, p=0.92, respectively) (figure 3 and table 3). Self-testing was associated with a

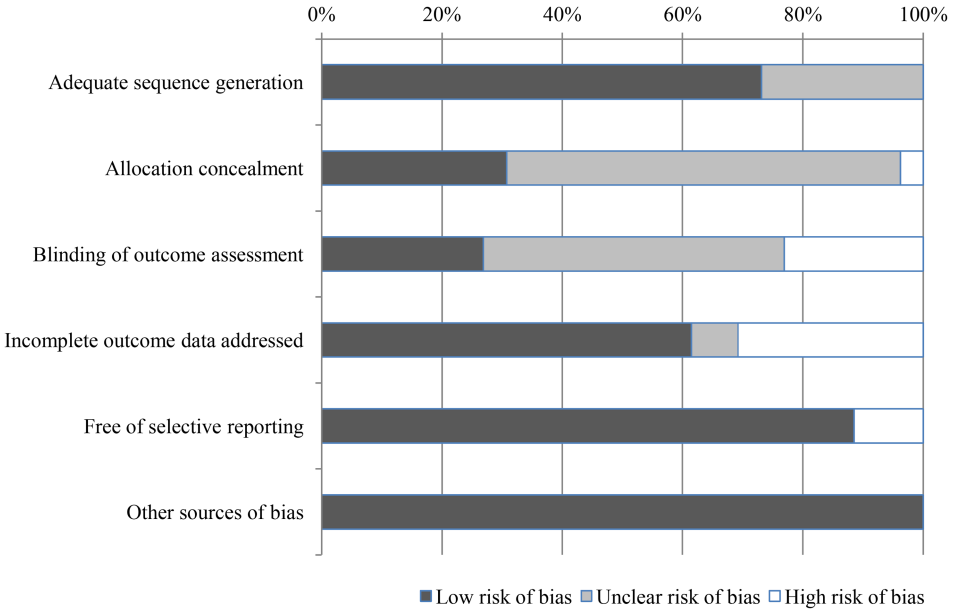

Figure 2 Summary of risk of bias of all included studies.

small increased risk of minor bleeding events (RR 1.23, 95% CI 1.06 to 1.42, p=0.005) and all bleeding events (RR 1.15, 95% CI 1.03 to 1.28, p=0.02) while self-management was not (the RR for minor bleeding events was 0.84, 95% CI 0.53 to 1.35, p=0.47 and for all bleeding events 0.94, 95% CI 0.68 to 1.30, p=0.69).

No statistically significant subgroup differences were found for bleeding events by clinical indication for anticoagulant treatment (AHV only, AF only or mixed) or by the setting for standard care (anticoagulant clinics only, physician/GP offices only, or mixed practices).

Thromboembolic events

Twenty-one trials reported a total of 351 thromboembolic events (major and minor) involving 8394 participants.[39–43 45–57 59–62] Self-monitoring was associated with a statistically significant reduction in the risk of thromboembolic events (RR 0.58, 95% CI 0.40 to 0.84,

Table 3 Meta-analyses results of major clinical outcomes and time in therapeutic range

Outcomes	Self-monitoring		Standard care		RR (95% CI)	p Value	Number of trials
	Number of events	Total number	Number of events	Total number			
All bleeding	736	4278	736	4116	0.95 (0.74 to 1.21)	0.66	22*
Self-management	250	2403	310	2237	0.94 (0.68 to 1.30)	0.69	15
Self-testing	486	1875	426	1879	1.15 (1.03 to 1.28)	0.02	7
Major bleeding	247	4188	231	4014	1.02 (0.86 to 1.21)	0.82	21*
Self-management	96	2403	78	2237	1.08 (0.81 to 1.45)	0.60	15
Self-testing	151	1785	153	1777	0.99 (0.80 to 1.23)	0.92	6
Minor bleeding	489	2757	505	2668	0.94 (0.65 to 1.34)	0.73	13
Self-management	154	1081	232	1035	0.84 (0.53 to 1.35)	0.47	9
Self-testing	335	1676	273	1633	1.23 (1.06 to 1.42)	0.005	4
Thromboembolic events	149	4278	202	4116	0.58 (0.40 to 0.84)	0.004	22*
Self-management	54	2403	106	2237	0.51 (0.37 to 0.69)	<0.0001	15
Self-testing	95	1875	96	1879	0.99 (0.75 to 1.31)	0.95	7
Mortality	197	3323	225	3214	0.83 (0.63 to 1.10)	0.20	13
Self-management	44	1674	68	1619	0.68 (0.46 to 1.01)	0.06	10
Self-testing	153	1649	157	1595	0.97 (0.78 to 1.19)	0.74	3
Time in therapeutic range	NA	2598	NA	2521	WMD 2.82 (0.44 to 5.21)	0.02	11*
Self-management	NA	870	NA	828	WMD 0.47 (−1.40 to 2.34)	0.62	6
Self-testing	NA	1728	NA	1693	WMD 4.44 (1.71 to 7.18)	0.001	5

*For the subgroup meta-analysis according to type of anticoagulant therapy management—, a 4-armed trial, contributed to two studies: one on self-testing and one on self-management.[62]
NA, not applicable; RR, relative risk; WMD, weighted mean difference.

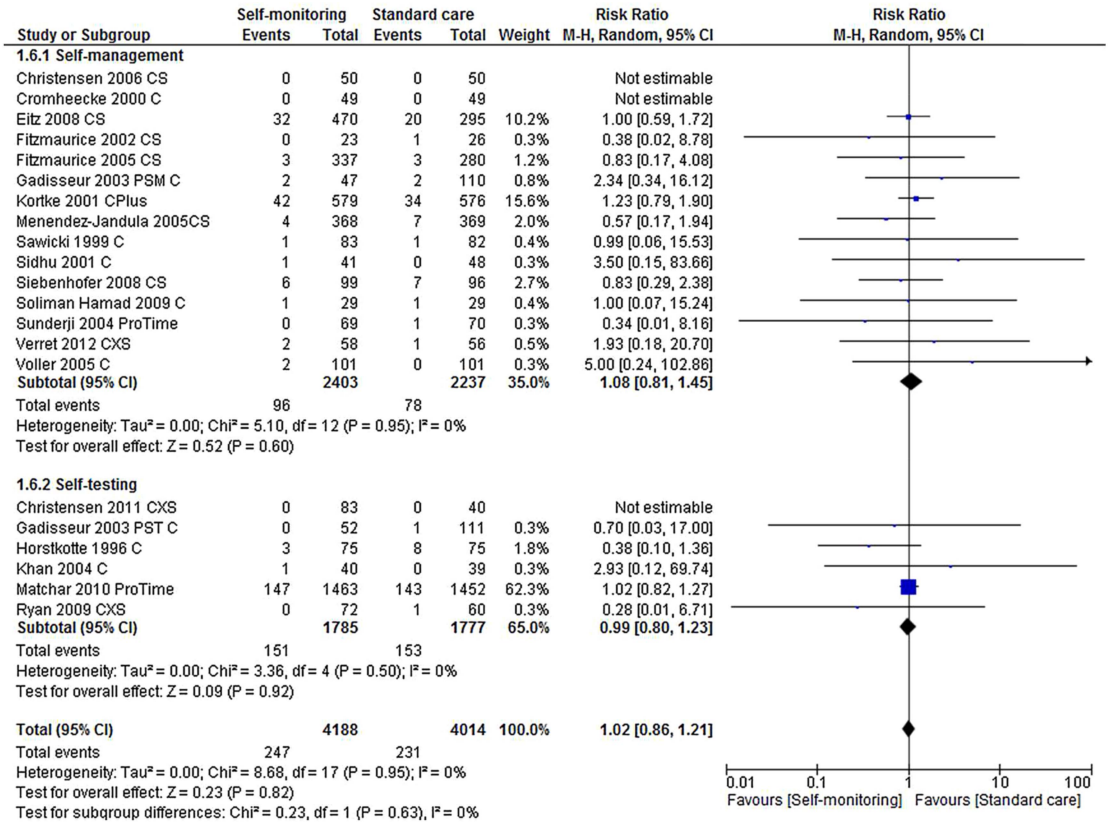

Figure 3 Forest plot of comparison: major bleeding events.

p=0.004) compared with standard care (figure 4). This reduction was still apparent when the analysis was restricted to major thromboembolic events (RR 0.52, 95% CI 0.34 to 0.80, p=0.003). The reduction in thromboembolic events was observed only in studies of patients carrying out self-management (RR 0.51, 95% CI 0.37 to 0.69, p<0.0001). There was no significant risk reduction among trials of self-testing (RR 0.99, 95% CI 0.75 to 1.31, p=0.56).

The observed reduction in thromboembolic events was similar across clinical indications for anticoagulation: AHV (6 studies, RR 0.56, 95% CI 0.38 to 0.82), AF (2 studies, RR 0.33, 95% CI 0.01 to 8.09) and mixed indications (13 studies, RR 0.57, 95% CI 0.30 to 1.09) (test for subgroup differences: p=0.95). Similarly, there were no significant differences in observed reduction in thromboembolic events among studies which conducted standard care in anticoagulant clinics (10 studies, RR 0.65, 95% CI 0.30 to 1.42), physician/GP offices (6 studies RR 0.45, 95% CI 0.31 to 1.38) or mixed practices (5 studies, RR 0.66, 95% CI 0.31 to 1.38) (test for subgroup differences: p=0.55).

Mortality

Thirteen trials reported 422 deaths from any cause in a total of 6537 participants.[39 42 43 46 47 49–52 54 56 57 60] There was no statistically significant difference in all-cause mortality between self-monitoring and standard clinical monitoring (RR 0.83, 95% CI 0.63 to 1.10, p=0.20) (figure 5). Trials of self-management found a reduction in mortality which was close to statistical significance (RR 0.68, 95% CI 0.46 to 1.01, p=0.06), and similar in size and direction to the observed reduction in thromboembolic events. Self-testing had no effect on mortality (RR 0.97 95% CI 0.78 to 1.19, p=0.74).

There was an apparent significant reduction in mortality in trials which restricted entry to patients with AHV (4 trials, RR 0.54, 95% CI 0.32 to 0.92, p=0.02) and no reduction in mortality in trials with mixed clinical indications for anticoagulant therapy (RR 0.95, 95% CI 0.78 to 1.16, p=0.61). As none of the trials reporting mortality specifically excluded patients with AHVs, we could not conclude from the pooled data whether this difference by indication was clinically meaningful.

Deaths directly associated with anticoagulation therapy were reported in five trials.[42 43 47 50 51] In total, six deaths related to anticoagulation therapy occurred among participants receiving usual monitoring care[42 50 51] (1 valve thrombosis, 2 myocardial infarctions, 1 retroperitoneal haemorrhage, 1 cerebral haemorrhage, and 1 gastrointestinal bleeding) and seven deaths occurred among participants who self-managed their coagulation status (1 valve thrombosis, 1 pulmonary embolism, 1 massive ischaemic stroke, 2 myocardial infarctions, 1 cerebral haemorrhage, and 1 gastrointestinal bleeding).[43 47]

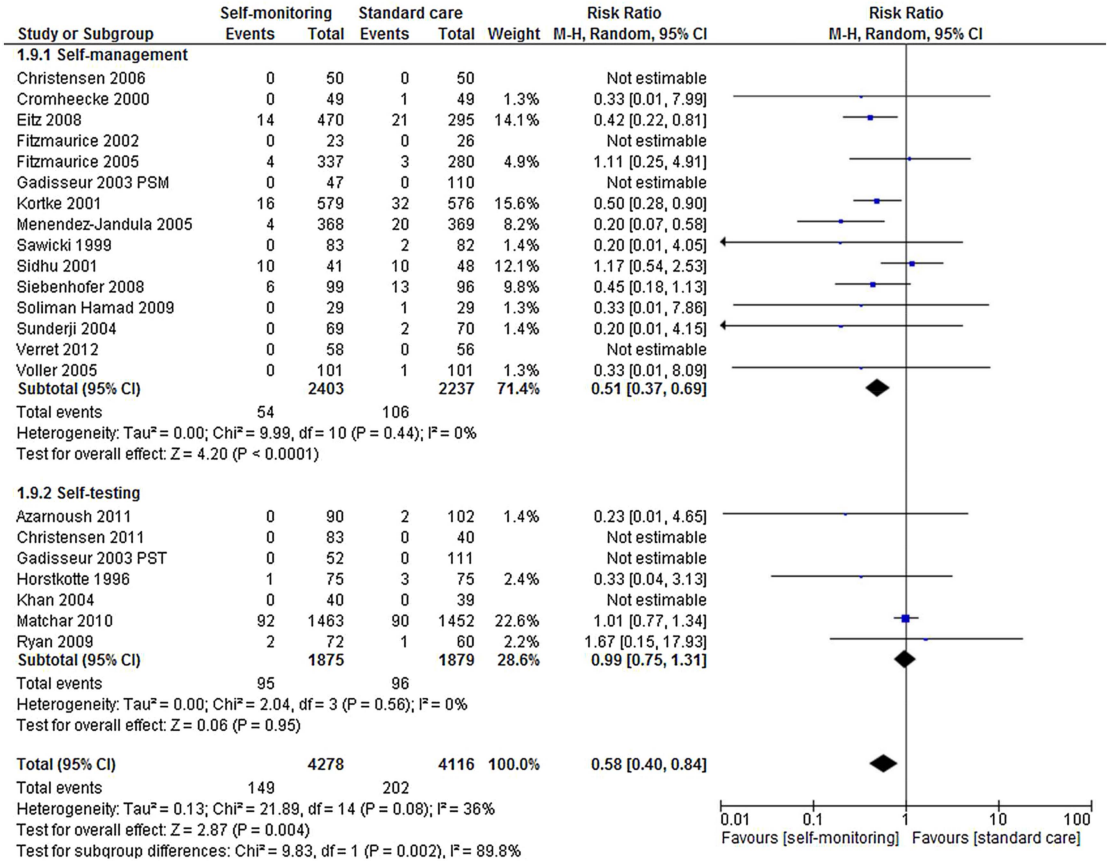

Figure 4 Forest plot of comparison: thromboembolic events.

Anticoagulation control: target range

Table 4 summarises the results of anticoagulation control reported in the included studies. There was a great variation between trials in the measures used to assess INR time and the values in TTR. In general, INR time and INR values in TTR were reported to be higher

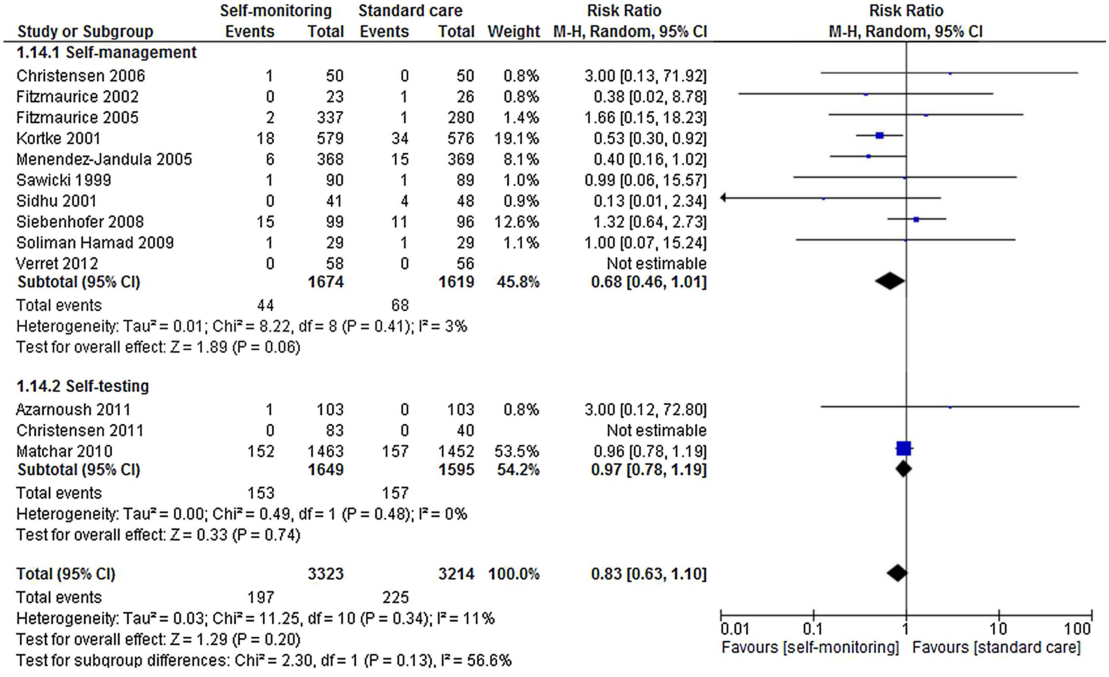

Figure 5 Forest plot of comparison: mortality.

Table 4 INR time and value in therapeutic range

Study ID	INR time in therapeutic range, mean % (SD)			INR value in target range, % of INR values (95% CI)		
	PSM/PST	Control	p Value	PSM/PST	Control	p Value
Azarnoush *et al* 2011[56]	61.5 (19.3)	55.5 (19.9)	0.0343	NR	NR	NR
Bauman *et al* 2010[63]	PSM: 83 (NR) PST: 83.9 (NR)	–	NR	NR	NR	NR
Christensen *et al* 2006[39]	78.7 (69.2–81.0)*	68.9 (59.3–78.2)*	0.14	NR	NR	NR
Christensen 2011[57]	80.2 (2.3)	72.7 (2.6)	<0.001	80.8 (79.3–82.1)	67.2 (64.1–70.2)	<0.001
Cromheecke *et al* 2000[40]	NR	NR	NS	55 (NR)	49 (NR)	0.06
Eitz *et al* 2008[41]	NR	NR		79 (NR)	65 (NR)	<0.001
Fitzmaurice *et al* 2002[42]	74 (16.2)	77 (23.5)	NS	66 (61–71)	72 (65–80)	NS
Fitzmaurice *et al* 2005[43]	70 (20.1)	68 (23.0)	0.18	70 (64.8–74.8)†	72 (66.3 to 77.1)†	NS
Gadisseur *et al* 2003[62]	PSM: 68.6 (16.8) PST: 66.9 (14.9)	67.9 (19.5)	0.33	66.3 (61–71.5)/ 63.9 (59.8–68)‡	61.3 (55–62.4)/58.7‡	0.14
Gardiner *et al* 2006[64]	PSM: 69.9 (23.1) PST: 71.8 (22.1)	–	0.46	NR	NR	NR
Horstkotte *et al* 1996[45]	NR	NR		43.2 (NR)	22.3 (NR)	<0.001
Khan *et al* 2004[59]	71.1 (14.5)	70.4 (24.5)	NS	NR	NR	NR
Kortke *et al* 2001[46]	NR	NR	NR	79.2 (NR)	64.9 (NR)	<0.001
Matchar *et al* 2010[60]	66.2 (14.2)	62.4 (17.1)	<0.001	NR	NR	NR
Menendez-Jandula *et al* 2005[47]	64.3 (14.3)	64.9 (19.9)	0.2	58.6 (SD 14.3)†	55.6 (SD 19.6)†	0.02
Rasmussen *et al* 2012[48]	52 (33–65)§	55 (49–66)	NR	NR	NR	NR
Ryan *et al* 2009[61]	74 (64.6–81)¶	58.6 (45.6–73.1)¶	<0.001	NR	NR	NR
Sawicki 1999[49]	NR	NR	NR	53 (NR)†	43.2 (NR)†	0.22
Sidhu and O'Kane 2001[50]	76.5 (NR)	63.8 (NR)	<0.0001	NR	NR	NR
Siebenhofer *et al* 2008[51]	75.4 (9.4, 85.0)¶	66.5 (47.1, 81.5)¶	<0.001	NR	NR	NR
Soliman Hamad *et al* 2009[52]	NR	NR	NR	72.9 (SD 11)†	53.9 (SD 14)†	0.01
Sunderji *et al* 2004[53]	71.8 (45.69)	63.2 (48.53)	0.14	NR	NR	NR
Verret *et al* 2012[54]	80 (13.5)	75.5 (24.7)	0.79	NR	NR	NR
Völler *et al* 2005[55]	178.8 (126)**	155.9 (118.4)**	NS	67.8 (SD 17.6)	58.5 (SD 19.8)	0.0061

*Median % (95% CI).
†mean % of individual (95% CI).
‡% (95% CI).
§Median % (25–75 centile).
¶Median % (IQR).
**Mean cumulative days (SD).
INR, international normalised ratio; PSM, patient self-management; PST, patient self-testing; NR, not reported; NS, not significant.

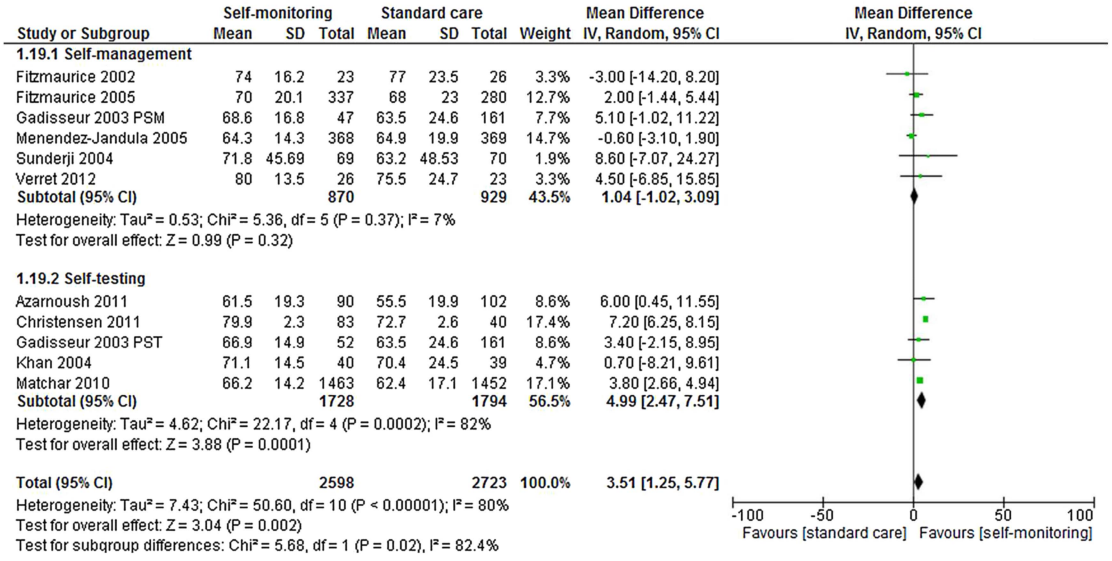

Figure 6 Forest plot of comparison: time in therapeutic range.

among self-monitoring participants compared with those in standard care (table 4). Pooling of INR *values* in TTR across trials proved unfeasible. Eighteen trials[38 39 42 43 47 48 50 51 53–57 59–64] provided data on INR *time* in TTR and pooling of results was possible for 10 trials that provided suitable data.[42 43 47 53 54 56 57 59 60 62] No statistically significant differences were observed between self-management and standard care with regard to TTR (p=0.62) (table 3 and figure 6). Nevertheless, a modest but significantly higher proportion of TTR was found for participants who self-tested compared with those who received standard care (WMD 4.44, p=0.001) (table 3 and figure 6).

The other intermediate outcomes were sparsely reported in the included studies. Two trials reported good patient compliance with self-monitoring (75% and 98%, respectively).[58 59]

Cost effectiveness

Applying the base case assumptions presented in table 1, the results of the cost-effectiveness analyses indicate that over a 10-year period, the introduction of self-monitoring would reduce the proportion of people suffering a thromboembolic event by 2.5%, while slightly increasing the proportion suffering a major haemorrhagic event by 1.2% (table 5). While the predicted monitoring costs are higher with self-monitoring, the total health and social care costs are similar: £7324 for standard care monitoring and £7326 for self-monitoring (table 5). The estimated QALY gain associated with self-monitoring was 0.028. Self-monitoring (50% self-testing, 50% self-management) appears to be cost-effective due to its positive impact on the incidence of thromboembolic events, even though, compared with mixed primary/secondary care, it is likely to increase the INR

Table 5 Mean costs, outcomes and incremental cost-effectiveness over a 10-year time-horizon

Strategy	Mean costs	Cumulative monitoring/ device costs	% with first TE event	% with first major bleed	Mean QALYs	Incremental cost	Incremental QALYs	ICER
Self-monitoring (50% self-management, 50% self-testing) versus standard care								
Standard monitoring	£7324	£1269	14.2	30.2	5.479	–	–	–
Self-monitoring	£7326	£1944	11.7	31.4	5.507	£2	0.028	£71
Base case—100% self-management versus standard care								
Standard monitoring	£7324	£1269	14.2	30.2	5.479	–	–	–
Self-management 100%	£6394	£1717	9.2	32.7	5.535	–£930	0.056	Dominant
Base case—100% self-testing versus standard care								
Standard monitoring	£7324	£1269	14.2	30.2	5.479	–	–	–
Self-testing 100%	£8258	£2171	14.2	30.1	5.479	£934	0	£2 811 298

TE, thromboembolic; QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio.

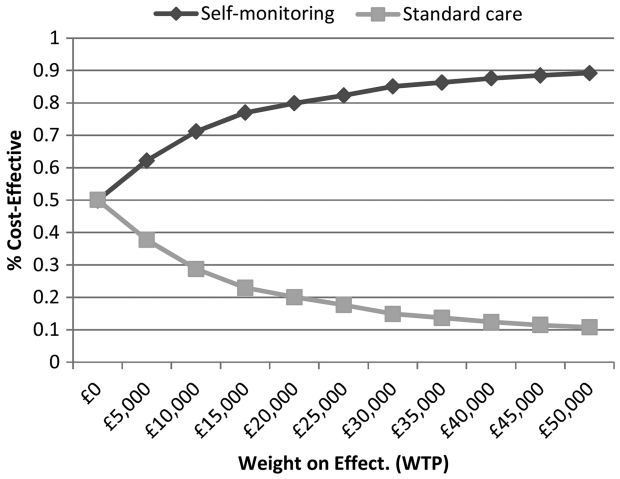

Figure 7 Cost-effectiveness acceptability curves: self-monitoring versus standard care.

monitoring costs. Figure 7 shows that self-monitoring as a whole has an approximately 80% chance of being considered cost-effective at a willingness to pay ratio of £20 000 per QALY gained. However, the pooled relative effect estimate for self-testing on thromboembolic events (figure 4) is small and non-significant (RR 0.99), while the effect estimate for self-management is large (RR 0.51) and significant. Thus, within the base case model, self-management alone is highly cost-effective (ie, dominant), while self-testing is not (table 5).

Further analysis of uncertainty

In an alternative specification of the model, the overall pooled effect estimates obtained from all self-testing and self-management trials were applied to the self-testing and self-management strategies. Under this scenario, self-monitoring as a whole was found to be cost-saving over standard care (see online supplementary appendix 5 table S3).

Two key parameters underpinning the cost-effectiveness findings are the baseline risk of thromboembolic events, and the relative effect of self-monitoring on these events. The model findings were robust to individual changes in these parameters through feasible ranges. However, when a lower baseline risk of thromboembolic events (1.15%) was combined with the upper 95% confidence limit for the RA associated self-management (RR 0.69), the incremental cost-effectiveness ratio (ICER) for self-monitoring as a whole rose above £30 000 per QALY. The same was found when the lower baseline risk of thromboembolic events was coupled with the upper confidence limit of the pooled RA for self-monitoring (RR 0.89). It should be noted, however, that self-management alone remained cost-saving under the former combined scenario. The cost-effectiveness of self-monitoring improved further when the modelled time horizon was extended to 20 and 30 years, dominating standard primary/secondary care based monitoring. The incremental cost per QALY gained for self-monitoring also remained below £20 000 when higher training failure and discontinuation rates were applied, and when higher self-monitoring testing frequencies were applied (with no change in effects).

Alternative scenarios assessed the potential for self-monitoring to be cost-saving if used to replace clinic-based testing without increasing the frequency of testing (see online supplementary appendix 5 table S4). Under these scenarios it was assumed that there would be no effect on the number of thromboembolic or bleeding events, and a cost-minimisation approach was adopted. This showed that, when holding all other base case parameters constant, self-testing and self-management were more costly than standard primary care monitoring (ie, physician offices and general practices), but less costly than standard secondary care monitoring (ie, specialised anticoagulation clinics).

DISCUSSION

Our findings suggest that self-monitoring of anticoagulation at home is at least as safe and effective as standard clinic monitoring. Self-management of anticoagulation is associated with reductions in thromboembolic events and possibly, in all-cause mortality. INR time in TTR was reported to be higher in self-monitoring participants compared with standard clinical care. Self-monitoring, and in particular self-management, of anticoagulation status appeared cost-effective at a willingness to pay threshold of £20 000 per QALY gained when pooled estimates of clinical effectiveness were applied to the economic model. The modelled reduction in thromboembolic events was the key driver of cost-effectiveness.

The differences we observed between self-management and self-testing are difficult to explain. Paradoxically, those who self-tested, rather than self-managed, spent more time in TTR (and had more minor bleeding events), but those who self-managed experienced less thromboembolic events. It is possible that people who self-managed their coagulation status take a more active role in managing their therapy or that self-testing leads to more rapid or frequent dose changes. It is also worth noting that the meta-analyses results on self-testing were dominated by the results of the largest trial published so far, the Home International Normalised Ratio Study (THINRS),[60] which enrolled 2922 people and assessed self-testing versus routine clinical care. This trial had a specialised routine coagulation control and the longest follow-up period (mean 3 years). The high quality of the routine care in the THINRS may exceed current monitoring care for anticoagulation control and could explain the lack of significant differences in major clinical adverse events between self-testing and routine care. When we excluded this trial from the statistical analyses, the risk ratio for thromboembolic events fell from 0.99 to 0.55 among self-testing participants, although the CIs widened (95% CI 0.13 to 2.31).

On the whole, our findings are broadly consistent with those of previously published systematic reviews on self-monitoring using point-of-care devices for the

management of anticoagulation therapy, which found that self-monitoring was associated with a significant reduction in the occurrence of thromboembolic events and all-cause-mortality.[14 16 20 27 29 66–69] Our economic model, in accordance with previous economic evaluations,[29 34] indicates that self-monitoring is likely to be cost-effective. The findings of our economic model are also broadly in line with those of previous UK-based economic assessments, in that self-monitoring (under base assumptions) will increase the monitoring costs to the NHS. However, our base case differs from that of previous UK evaluations in that the pooled relative effects for self-management and self-testing, compared with standard care, were applied. We observed significant future cost savings and quality of life gains as a consequence of a significant reduction in the incidence of thromboembolic events. This, in turn, translated into more favourable estimates of cost-effectiveness. Further differences between the current analysis and the previous UK-based model include the application of higher standard secondary care monitoring costs, lower self-monitoring device costs (in line with current prices), and higher acute treatment costs for stroke and major bleeding events. Our analyses suggest that the cost-effectiveness of self-monitoring is robust to variations in these parameters when pooled clinical effect estimates are applied to the model.

In more general terms, home monitoring, and especially self-management, of anticoagulation therapy may have a substantial impact on the quality of life of patients and their families. It may reduce the anxiety associated with the fear of deviating from the therapeutic target range and boost confidence in the therapy, increase independence and psychological well-being, and allow for the more efficient organisation of time (eg, travelling, social interactions).

Limitations

This study has been conducted as per recommended methodological standards and is the most up-to-date evidence synthesis on this topic with the largest number of included RCTs.[20 66 68]

There are, however, potential limitations. The literature searches were performed in 2013 and were not subsequently updated. While the meta-analysis results demonstrated low statistical heterogeneity, which made it statistically reasonable to combine the studies, uncertainties remain that clinical heterogeneity could have contributed to over or underestimate the effects. The included trials varied in terms of clinical indications for anticoagulation therapy, type of control care, reporting structure for the time and/or values in TTR, the mode and structure of the preintervention training and education programme, length of follow-up, and methodological study quality. The majority of the trials included participants with mixed clinical indications for anticoagulation therapy, which made it challenging to extrapolate the results to specific clinical populations. In particular, only limited data were available for people with AF and consequently, no firm conclusions could be drawn in relation to this patient population is. Nevertheless, it likely that self-monitoring may produce similar clinical benefits in people with AF to those achieved in people with artificial heart valves. A great variation between trials was found in the way both INR time and INR values in TTR were measured, which hampered further analyses.

Assuming there is no interaction between the TTR and the relative treatment effect for self-management on thromboembolic events, our modelling suggests that it will remain cost-effective even where TTR is high and the thromboembolic event rate is low. However, it is possible that the quality of standard care may modify the effectiveness of self-monitoring, and in turn, influence its cost-effectiveness. Where patients are already achieving a very high level of INR control, this may limit the potential for self-monitoring to improve TRR and in turn, reduce thromboembolic event. With regard to the economic model, there is still a certain degree of uncertainty surrounding the pooled clinical effectiveness estimates, especially for self-testing. It is worth noting that the perspective of the cost-effectiveness analysis was that of the National Health Service (NHS) and personal social services. Therefore, our modelling fails to capture any wider benefits or cost-savings to patients and their families, such as a reduction in time spent travelling to and waiting in clinics.

Generally, adherence to self-monitoring was reported to be high in the included trials (more than 90%). However, all included trials enrolled highly selected samples of people requiring anticoagulation therapy, and so it was uncertain whether there was strong external validity. To be enrolled in the trials, participants needed to demonstrate adequate cognitive and physical abilities, as well as dexterity and confidence in using the point-of-care device. In some of the included trials[42 43 47 62] a considerable proportion of eligible participants (up to 50%) ultimately were not considered suitable for inclusion. Despite the enrolment restrictions, results are valid for the patients groups included, which actually represent the population who would be considered for self-monitoring in clinical practices. Six of the trials were conducted in the UK and we could not find any evidence that the UK trial patient cohorts were fundamentally different from those of the rest of the included studies.

Whilst new non-vitamin K antagonist oral anticoagulants were beyond the scope of this assessment, these offer an alternative option for many people with AF who are currently on warfarin. However, these are not suitable for all people who need anticoagulation therapy. Furthermore, due to the potential risk of bleeding, it is unlikely that people receiving warfarin who have stable INR may switch to the NOACs. Therefore, there are still many people who receive warfarin rather than the NOACs for whom self-monitoring is still of clinical relevance.

CONCLUSIONS

Self-monitoring, and in particular self-management, is a safe and cost-effective option for people requiring long-term vitamin K antagonist therapy. Further research assessing the longer-term outcomes of self-management versus standard monitoring care as well as the comparative effectiveness of various point-of-care coagulometers would be useful. The technology related to these devices is constantly changing and future research needs to target larger cohorts of people with different clinical indications requiring long-term anticoagulation therapy. It is worth acknowledging that the modern point-of-care coagulometers are likely to have advanced both in their ease of use and cost, which, in theory, could modify the possible candidates for these devices as well as the magnitude of any economic evaluation.

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REFERENCES

1. DeWilde S, Carey IM, Emmas C, *et al*. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. *Heart* 2006;92:1064–70.
2. Camm AJ, Kirchhof P, Lip GY, *et al*., European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369–429.
3. Cowan C, Healicon R, Robson I, *et al*. The use of anticoagulants in the management of atrial fibrillation among general practices in England. *Heart* 2013;99:1166–72.
4. *Heart valve disease [website on the Internet]*. London: British Heart Foundation, 2013. http://www.bhf.org.uk/heart-health/conditions/heart-valve-disease.aspx (accessed Apr 2015).
5. *Aortic stenosis [website on the Internet]*. Leeds: Patient UK, 2013. http://www.patient.co.uk/health/aortic-stenosis (accessed Apr 2015).
6. *UK Heart Valve Registry [archived webpage on the Internet]*. London: NHS Health and Social Care Information Centre, 2010. http://docdat.ic.nhs.uk/DatabaseList.aspx (accessed Apr 2015).
7. Cayley J. Self-monitoring and self-management of anticoagulation therapy. *Am Fam Physician* 2011;84:266–8.
8. *Anticoagulation therapy service commissioning guide [document on the Internet]*. London: National Insititute for Health and Care Excellence, 2010. URL:http://www.nice.org.uk/usingguidance/commissioningguides/anticoagulationtherapyservice/anticoagulationtherapyservice.jsp (accessed Apr 2015).
9. *Atrial fibrillation [website on the Internet]*. London: British Heart Foundation, 2013. http://www.bhf.org.uk/heart-health/conditions/atrial-fibrillation.aspx (accessed Apr 2015).
10. *SIGN 129 Antithrombotics: indications and management [document on the Internet]*. Edinburgh: Health Improvement Scotland, 2013. http://www.sign.ac.uk/pdf/SIGN129.pdf (accessed April 2015).
11. *Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. NICE Guidance TA249 [document on the Internet]*. London: National Insititute for Health and Care Excellence, 2012. http://guidance.nice.org.uk/TA249 (accessed Apr 2015).
12. Fuster V, Ryden LE, Cannom DS, *et al*. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006;8:651–745.
13. You JJ, Singer DE, Howard PA, *et al*. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl):e531S–75S.
14. Connock M, Stevens C, Fry-Smith A, *et al*. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. *Health Technol Assess* 2007;11:iii–iv, ix–66.
15. Ansell J, Jacobson A, Levy J, *et al*. International Self-Monitoring Association for Oral Anticoagulation. Guidelines for implementation of patient self-testing and patient self-management of oral anticoagulation. International consensus guidelines prepared by International Self-Monitoring Association for Oral Anticoagulation. *Int J Cardiol* 2005;99:37–45.
16. *Point-of-Care Testing: A Review of Systematic Reviews on Testing Accuracy and Cost-Effectiveness [document on the Internet]*. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2012. http://www.cadth.ca/media/pdf/htis/april-2012/RC0345%20Point%20of%20Care%20Testing%20Final.pdf (accessed Apr 2015).
17. Christensen TD, Larsen TB. Precision and accuracy of point-of-care testing coagulometers used for self-testing and self-management of oral anticoagulation therapy. *J Thromb Haemost* 2012;10:251–60.
18. Tamayo AE, Vergara-Mitxeltorena I, Uranga Saez del BE, *et al*. Oral anticoagulation and self-management: Analysis of the factors that determine the feasibility of using self-testing and self-management in primary care. *BMC Cardiovasc Disorder* 2013;13:59.
19. Jones S, Monagle P, Manias E, *et al*. Quality of life assessment in children commencing home INR self-testing. *Thromb Res* 2013;132:37–43.
20. Garcia-Alamino JM, Ward AM, Alonso-Coello P, *et al*. Self-monitoring and self-management of oral anticoagulation. *Cochrane Database Syst Rev* 2010;(4):CD003839. doi:10.1002/14651858.CD003839.pub2.

21. *Systematic reviews: CRD's guidance for undertaking systematic reviews in health care [document on the Internet]*. University of York: Centre for Reviews and Dissemination, 2009. http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm (accessed April 2015).
22. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [document on the Internet]*. The Cochrane Collaboration, 2011. http://www.cochrane-handbook.org/ (accessed April 2015).
23. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal [document on the Internet]*. London: National Institute for Health and Care Excellence, 2013. http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9 (accessed Apr 2015).
24. Moher D, Liberati A, Tetzlaff J, *et al*. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
25. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;13:322–38.
26. Beck JR, Pauker SG. The Markov process in medical prognosis. *Med Decis Making* 1983;3:419–58.
27. *Point-of-Care International Normalized Ratio (INR) Monitoring Devices for Patients on Long-term Oral Anticoagulation Therapy. Ontario Health Asssessment Series 9 (12) [document on the Internet]*. Ontario: Medical Advisory Secretariat Ministry of Health and Long-Term Care, 2009. http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_poc_20090928.pdf (accessed Apr 2015).
28. Brown A, Wells P, Jaffey J, *et al*. *Point-of-Care Monitoring Devices for Long-Term Oral Anticoagulation Therapy: Clinical and Cost Effectiveness. Technology Report no 72 [document on the Internet]*. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2007. http://www.cadth.ca/media/pdf/H0299_anticoagulation-therapy_tr_e.pdf (accessed Apr 2015).
29. Gailly J, Gerkens S, van den Bruel A, *et al*. *Use of point-of-care devices in patients with oral anticoagulation: a Health Technology Assessment. KCE Report 117C [document on the Internet]*. Brussels: Belgian Health Care Knowledge Centre, 2009. https://kce.fgov.be/publication/report/use-of-point-of-care-devices-in-patients-with-oral-anticoagulation-a-health-techn (accessed Apr 2015).
30. Lafata JE, Martin SA, Kaatz S, *et al*. The cost-effectiveness of different management strategies for patients on chronic warfarin therapy. *J Gen Intern Med* 2000;15:31–7.
31. Muller E, Bergemann R, GELIA Study Group. Economic analysis of bleeding and thromboembolic sequelae after heart valve replacement (GELIA 7). *Eur Heart J Suppl* 2001;3(Suppl Q):65–9.
32. Regier DA, Sunderji R, Lynd LD, *et al*. Cost-effectiveness of self-managed versus physician-managed oral anticoagulation therapy. *CMAJ* 2006;174:1847–52.
33. Sola-Morales O. *Portable coagulometers: revision of the scientific evidence and economic assessment of their use in self-control of oral anticoagulant treatment*. Barcelona: Catalan Agency for Health Technology Assessment and Research (CAHTA), 2003.
34. Taborski U, Wittstamm FJ, Bernardo A. Cost-effectiveness of self-managed anticoagulant therapy in Germany. *Semin Thromb Hemost* 1999;25:103–7.
35. *Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation NICE Guidance TA256 [document on the Internet]*. London: National Insititute for Health and Care Excellence, 2012. http://guidance.nice.org.uk/TA256 (accessed Apr 2015).
36. *NICE Diagnostic Assessment Programme manual [document on the Internet]*. London: National Institute for Health and Care Excellence, 2011. http://www.nice.org.uk/media/A0B/97/DAPManualFINAL.pdf (accessed April 2015).
37. *NHS reference costs 2011–12 [website on the Internet]*. UK Department of Health, 2012. https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012 (accessed Apr 2015).
38. Curtis L. *Unit Costs of Health and Social Care 2013 [document on the Internet]*. Canterbury: Personal Social Services Research Unit, 2012. http://www.pssru.ac.uk/project-pages/unit-costs/2012/ (accessed Apr 2015).
39. Christensen TD, Maegaard M, Sorensen HT, *et al*. Self-management versus conventional management of oral anticoagulant therapy: a randomized, controlled trial. *Eur J Intern Med* 2006;17:260–6.
40. Cromheecke ME, Levi M, Colly LP, *et al*. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. *Lancet* 2000;356:97–102.
41. Eitz T, Schenk S, Fritzsche D, *et al*. International normalized ratio self-management lowers the risk of thromboembolic events after prosthetic heart valve replacement. *Ann Thorac Surg* 2008;85:949–54.
42. Fitzmaurice DA, Murray ET, Gee KM, *et al*. A randomised controlled trial of patient self management of oral anticoagulation treatment compared with primary care management. *J Clin Pathol* 2002;55:845–9.
43. Fitzmaurice DA, Murray ET, McCahon D, *et al*. Self management of oral anticoagulation: randomised trial. *BMJ* 2005;331:1057.
44. Hemkens LG, Hilden KM, Hartschen S, *et al*. A randomized trial comparing INR monitoring devices in patients with anticoagulation self-management: evaluation of a novel error-grid approach. *J Thromb Thrombol* 2008;26:22–30.
45. Horstkotte D, Piper C, Wiemer M, *et al*. Improvement of prognosis by home prothrombin estimation In patients with life-long anticoagulant therapy. *Eur Heart J* 1996;17:230.
46. Kortke H, Minami K, Breymann T, *et al*. INR self-management after mechanical heart valve replacement: ESCAT (Early Self-Controlled Anticoagulation Trial). *Z Kardiol* 2001;90(Suppl 6):VI/118–24.
47. Menéndez JB, Souto JC, Oliver A, *et al*. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. *Ann Intern Med* 2005;142:1–10.
48. Rasmussen RS, Corell P, Madsen P, *et al*. Effects of computer-assisted oral anticoagulant therapy. *Thromb J* 2012;10:17.
49. Sawicki PT. A structured teaching and self-management program for patients receiving oral anticoagulation: a randomized controlled trial. Working Group for the Study of Patient Self-Management of Oral Anticoagulation. *JAMA* 1999;281:145–50.
50. Sidhu P, O'Kane HO. Self-managed anticoagulation: results from a two-year prospective randomized trial with heart valve patients. *Ann Thorac Surg* 2001;72:1523–7.
51. Siebenhofer A, Rakovac I, Kleespies C, *et al*., SPOG 6. Self-management of oral anticoagulation reduces major outcomes in the elderly. A randomized controlled trial. *Thromb Haemost* 2008;100:1089–98.
52. Soliman H, van E, van A, *et al*. Self-management program improves anticoagulation control and quality of life: a prospective randomized study. *Eur J Cardiothorac Surg* 2009;35:265–9.
53. Sunderji R, Gin K, Shalansky K, *et al*. A randomized trial of patient self-managed versus physician-managed oral anticoagulation. *Can J Cardiol* 2004;20:1117–23.
54. Verret L, Couturier J, Rozon A, *et al*. Impact of a pharmacist-led warfarin self-management program on quality of life and anticoagulation control: a randomized trial. *Pharmacotherapy* 2012;32:871–9.
55. Völler H, Glatz J, Taborski U, *et al*. Self-management of oral anticoagulation in nonvalvular atrial fibrillation (SMAAF study). *Zeitschrift für Kardiologie* 2005;94:182–6.
56. Azarnoush K, Camilleri L, Aublet-Cuvelier B, *et al*. Results of the first randomized French study evaluating self-testing of the International Normalized Ratio. *J Heart Valve Dis* 2011;20:518–25.
57. Christensen TD. Self-management of oral anticoagulation therapy—methodological and clinical aspects. *Dan Med Bull* 2011;58:B4284.
58. Gardiner C, Williams K, Mackie IJ, *et al*. Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring. *Br J Haematol* 2005;128:242–7.
59. Khan TI, Kamali F, Kesteven P, *et al*. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. *Br J Haematol* 2004;126:557–64.
60. Matchar DB, Jacobson A, Dolor R, *et al*. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med* 2010;363:1608–20.
61. Ryan F, Byrne S, O'Shea S. Randomized controlled trial of supervised patient self-testing of warfarin therapy using an internet-based expert system. *J Thromb Haemost* 2009;7:1284–90.
62. Gadisseur AP, Breukink-Engbers WG, Meer FJ, *et al*. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in the Netherlands: a randomized clinical trial. *Arch Intern Med* 2003;163:2639–46.
63. Bauman ME, Black K, Bauman ML, *et al*. EMPoWarMENT: Edmonton pediatric warfarin self-management pilot study in children with primarily cardiac disease. *Thromb Res* 2010;126:e110–15.
64. Gardiner C, Williams K, Longair I, *et al*. A randomised control trial of patient self-management of oral anticoagulation compared with patient self-testing. *Br J Haematol* 2006;132:598–603.
65. Siebenhofer A, Rakovac I, Kleespies C, *et al*. Self-management of oral anticoagulation in the elderly: rationale, design, baselines and

oral anticoagulation control after one year of follow-up. A randomized controlled trial. *Thromb Haemost* 2007;97:408–16.
66. Bloomfield HE, Krause A, Greer N, *et al*. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med* 2011;154:472–82.
67. Heneghan C, Alonso-Coello P, Garcia-Alamino JM, *et al*. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. *Lancet* 2006;367:404–11.
68. Heneghan C, Ward A, Perera R, *et al*. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet* 2012;379:322–34.
69. Wells PS, Brown A, Jaffey J, *et al*. Safety and effectiveness of point-of-care monitoringdevices in patients on oral anticoagulant therapy: a meta-analysis. *Open Medicine* 2007;1:E131–46.
70. Bayer PLC. *Single Technology Appraisal (STA) of Rivaroxaban (Xarelto®) [document on the Internet]*. London: National Institute for Health and Care Excellence, 2011. http://guidance.nice.org.uk/TAG/274/Consultation/EvaluationReport/ManufacturerSubmissions/Bayer/pdf/English (accessed Apr 2015).
71. Jowett S, Bryan S, Murray E, *et al*. Patient self-management of anticoagulation therapy: a trial-based cost-effectiveness analysis. *Br J Haematol* 2006;134:632–9.

SUPPLEMENTARY INFORMATION

Appendix 1 Details of search strategy

CLINICAL EFFFECTIVENESS

Database: Embase <1980 to 2013 Week 22>, Ovid MEDLINE(R) <1946 to May Week 5 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 05, 2013>
OVID Multi-file Search URL: https://shibboleth.ovid.com/

1 exp 4-Hydroxycoumarins/ use mesz
2 exp coumarin anticoagulant/ use emez
3 antivitamin k/ use emez
4 warfarin.tw
5 vitamin k antagonist$.tw.
6 *anticoagulants/ad use mesz
7 *anticoagulant agent/ad use emez
8 Prothrombin Time/
9 prothrombin time.tw.
10 or/1-9
11 Self Administration/ use mesz
12 Self Care/
13 Self-monitoring/ use emez or Home Monitoring/ use emez
14 point-of-care systems/
15 poc.tw
16 point-of-care.tw.
17 (((patient$ or self) adj1 (monitor$ or manag$ or measur$)) or (self adj1 test$)).tw.
18 or/11-17
19 10 and 18
20 coaguche?k$.tw,dv
21 INRatio$.tw,dv
22 (ProTime$ or pro time$).tw,dv
23 coagulometer$.tw.
24 or/19-23
25 randomized controlled trial.pt.
26 controlled clinical trial.pt.
27 exp clinical trial/ use emez
28 randomization/ use emez
29 randomi?ed.ab.
30 drug therapy.fs.
31 randomly.ab.
32 trial.ab.
33 groups.ab.
34 or/25-33
35 exp animals/ not humans/
36 34 not 35
37 19 and 36
38 limit 37 to yr="2007 -Current"

39 (coaguche?k$ or INRatio$ or ProTime$ or pro time$).tw,dv.
40 38 or 39
41 limit 40 to english language
42 41 not conference abstract.pt
43 41 and conference abstract.pt. and ("2012" or "2013").yr.
44 42 or 43
45 remove duplicates from 44

Science Citation Index (1970 - 5th June 2013)
BIOSIS (1956 –5th June 2013)
Conference Proceedings Citation Index- Science (2012-5th June 2013)
ISI Web of Knowledge URL: http://wok.mimas.ac.uk/

1 TS=anticoagulant*
2 TS=vitamin k antagonist*
3 TS=warfarin
4 TS=prothrombin time
5 #1 or #2 or #3 or #4
6 TS= ((patient* or self) N1 (monitor* or manag* or measur*))
7 TS=(self N1 test*)
8 TS=poc
9 TS=point-of-care
10 #9 or #8 OR #7 OR #6
11 #10 AND #5
12 TS=(CoaguChek* OR CoaguChek*)
13 TS= (INRatio* OR ProTime*)
14 #13 OR #12 OR #11
15 (#14) AND Language=(English) AND Document Types=(Article) Timespan=2007-2013
16 (#14) AND Language=(English) AND Document Types=(Meeting Abstract) Timespan=2012-201
17 #16 OR #15 Timespan=2007-2013

The Cochrane Library Issue 4 2013 (CENTRIAL, CDSR, DARE, HTA Database)
URL: http://www3.interscience.wiley.com/

#1 MeSH descriptor: [4-Hydroxycoumarins] explode all trees
#2 warfarin or vitamin k antagonist*:ti,ab,kw
#3 MeSH descriptor: [Anticoagulants] this term only and with qualifiers: [Administration & dosage - AD]
#4 international normali?ed ratio?:ti,ab,kw
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Self Administration] explode all trees
#7 MeSH descriptor: [Self Care] explode all trees
#8 MeSH descriptor: [Point-of-Care Systems] this term only
#9 poc:ti,ab,kw
#10 (patient near/3 (monitor or manage or measure)):ti,ab,kw
#11 (self near/3 (manage or monitor or measure)):ti,ab,kw
#12 #6 or #7 or #8 or #9 or #10 or #11
#13 #5 and #12
#14 CoaguChek or INRatio or ProTime or coagulometer

#15 #13 or #14

HTA/DARE May 2013
Centre for Reviews & Dissemination URL:http://nhscrd.york.ac.uk/welcome.htm

1 MeSH DESCRIPTOR 4-Hydroxycoumarins EXPLODE ALL TREES
2 (warfarin) OR (vitamin k antagonist*)
3 MeSH DESCRIPTOR anticoagulants EXPLODE ALL TREES WITH QUALIFIER AD
4 #1 OR #2 OR #3
5 MeSH DESCRIPTOR self administration
6 MeSH DESCRIPTOR self care
7 MeSH DESCRIPTOR Point-of-Care Systems
8 (poc) OR (self NEAR3 (monitor* or manag* or measur*)) OR (patient* NEAR3 (monitor* or manag* or measur*))
9 #5 OR #6 OR #7 OR #8
10 #4 AND #9

Additional Conference Proceedings

ASH 2012 54th ASH Annual Meeting and Exposition, Atlanta, GA , Dec 8-11, 2012.
EHA 2012 17th Congress, Amsterdam, 14-17 June 2012.
ISTH 2011 XXIII Congress of the International Society on Thrombosis and Haemostasis 57th Annual SSC Meeting, ICC Kyoto, Kyoto, Japan, July 23-28 2011,
Proceedings of the 12th National Conference on Anticoagulant Therapy, Phoenix, Arizona, May 9-11, 2013 .

Clinical Trials (June 2013)
URL: http://clinicaltrials.gov/ct/gui/c/r

CoaguChek OR INRatio OR ProTime OR (("point-of-care" or self) AND anticoagulant OR warfarin))

International Clinical Trials Registry Platform (ICTRP) (June 2013)
World Health Organization URL: http://www.who.int/ictrp/en/
CoaguChek OR INRatio OR ProTime OR (("point-of-care" or self) AND anticoagulant OR warfarin))

COST EFFFECTIVENESS
Database: Embase <1980 to 2013 Week 22>, Ovid MEDLINE(R) <1946 to May Week 5 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 05, 2013>
OVID Multi-file Search URL: https://shibboleth.ovid.com/
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2 exp coumarin anticoagulant/ use emez
3 antivitamin k/ use emez
4 warfarin.tw.
5 vitamin k antagonist$.tw.
6 *anticoagulants/ad use mesz
7 *anticoagulant agent/ad use emez
8 Prothrombin Time/

9 prothrombin time.tw.
10 or/1-9
11 Self Administration/ use mesz
12 Self Care/
13 Self-monitoring/ use emez or Home Monitoring/ use emez
14 point-of-care systems/
15 poc.tw.
16 point-of-care.tw.
17 (((patient$ or self) adj1 (monitor$ or manag$ or measur$)) or (self adj1 test$)).tw
18 or/11-17
19 10 and 18
20 coaguche?k.tw.
21 INRatio.tw.
22 ProTime.tw.
23 coagulometer$.tw
24 or/19-23
25 exp "costs and cost analysis"/ use mesz
26 exp economic evaluation/ use emez
27 economics/
28 health economics/ use emez
29 exp economics,hospital/ use mesz
30 exp economics,medical/ use mesz
31 economics,pharmaceutical/ use mesz
32 exp budgets/
33 exp models, economic/ use mesz
34 exp decision theory/
35 monte carlo method/
36 markov chains/
37 exp technology assessment, biomedical/
38 cost$.ti.
39 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
40 economics model$.tw.
41 (economic$ or pharmacoeconomic$).tw.
42 (price or prices or pricing).tw.
43 (value adj1 money).tw
44 markov$.tw.
45 monte carlo.tw.
46 (decision$ adj2 (tree? or analy$ or model$)).tw.
47 or/25-46
48 24 and 47
49 remove duplicates from 48

Database: HMIC Health Management Information Consortium <1979 to March 2013>
URL: https://auth.athensams.net/
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2 warfarin.tw.
3 vitamin k antagonist$.tw. 4 prothrombin time.tw.
5 or/1-4
6 Self Care/
7 self management/

8 (((patient$ or self) adj1 (monitor$ or manag$ or measur$)) or (self adj1 test$)).tw.
9 point-of-care.tw. (
10 poc.tw.
11 or/6-10
12 5 and 11
13 (coaguche?k$ or INRatio$ or ProTime$ or pro time$).tw.
14 12 or 13

NHS NEED May 2013
Centre for Reviews & Dissemination URL:http://nhscrd.york.ac.uk/welcome.htm
1 MeSH DESCRIPTOR 4-Hydroxycoumarins EXPLODE ALL TREES
2 (warfarin) OR (vitamin k antagonist*)
3 MeSH DESCRIPTOR anticoagulants EXPLODE ALL TREES WITH QUALIFIER AD
4 #1 OR #2 OR #3
5 MeSH DESCRIPTOR self administration
6 MeSH DESCRIPTOR self care
7 MeSH DESCRIPTOR Point-of-Care Systems
8 (poc) OR (self NEAR3 (monitor* or manag* or measur*)) OR (patient* NEAR3 (monitor* or manag* or measur*))
9 #5 OR #6 OR #7 OR #8
10 #4 AND #9

RePEc (Research Papers in Economics)
URL: http://repec.org/
anticoagulation | anticoagulants | warfarin | "vitamin k antagonist"|prothrombin
self management | self-monitoring | self-testing|prothrombin

CEA Registry June 2013
URL https://research.tufts-nemc.org/cear4/default.asp
Oral anticoagulation

WEBSITES CONSULTED

Agency for Healthcare Research and Quality URL: http://www.ahrq.gov/
AHA - American Heart Association URL: http://www.americanheart.org/
Alere URL: http://www.alereINRatio.com/
Belgian Health Care Knowledge Centre (KCE): URL: https://kce.fgov.be/
Canadian Agency for Drugs and Technologies in Health URL: http://www.cadth.ca/
CoaguChek System URL: http://www.CoaguChek.com/uk/
ESC - European Society of Cardiology URL: http://www.escardio.org/
French National Authority for Health (HAS) URL: http://www.has-sante.fr/
Health Information & Quality Authority:URL: http://www.hiqa.ie/
Institute for Clinical and Economic Review URL: http://www.icer-review.org/
Institute for Quality and Efficiency in Health Care URL: https://www.iqwig.de/
ISTH - International Society of Thrombosis and Haemostasis URL: http://www.med.unc.edu/welcome.htm
International Technidyne Corporation (ITC) URL: http://www.itcmed.com/
Medicines and Healthcare Products Regulatory Agency URL: http://www.mhra.gov.uk/
Medical Services Advisory Committee, Australia URL: http://www.msac.gov.au/

National Institute for Health and Care Excellence URL: http://www.nice.org.uk/
NHS Quality Improvement Scotland URL:
http://www.healthcareimprovementscotland.org/
US Food and Drug Administration URL: http://www.fda.gov/default.htm

Appendix 2 Economic modelling methods

A de novo economic model was developed in TreeAge Pro (TreeAge Software, Williamstown, MA, 2013). The model was designed to assess the cost-effectiveness of self-monitoring (self-testing and self-management) using point-of-care devices. Whilst originally designed to assess cost-effectiveness using either the CoaguChek XS system, INRatio2 PT/INR monitor, or ProTime Microcoagulation system, no compelling evidence was identified to suggest significant differences in accuracy or effectiveness between these devices. Therefore, the analysis presented in this paper focuses on cost-effectiveness using CoaguChek XS system, the device to which most of the clinical effectiveness evidence relates.

The model was structured based on a review of published models of INR self-monitoring,[1] and previous models evaluating the cost-effectiveness of new anticoagulant drugs compared to warfarin therapy in people with atrial fibrillation.[2,3] A further unpublished economic model of INR self-monitoring was provided by Roche (the manufacturer of CoaguChek XS), and this model was also used to inform the structure of the new economic model (J Craig, York Health Economics Consortium, 2013).

The model was populated using data derived from the systematic clinical effectiveness review, other focused reviews to inform key parameters (e.g. baseline risks), routine sources of cost data,[4,5] and where necessary some study specific cost estimates based on expert opinion. The model was built and analysed in accordance with the NICE reference case for the evaluation of diagnostic tests and devices.[6]

Methods

Relevant patient population(s)

The model compared the alternative monitoring strategies for a hypothetical cohort of people with atrial fibrillation or an artificial heart valve. These two groups represent the majority of people on long-term vitamin K antagonist therapy. While self-monitoring of INR is relevant to other patient groups, including those with venous thrombotic embolism, there was insufficient data to explicitly model cost-effectiveness for all groups individually. Furthermore, the majority of studies

informing the relative effects of alternative monitoring strategies were derived from trials including predominantly people with atrial fibrillation and/or an artificial heart valve. Therefore, the base case modelling exercise was carried out for a mixed cohort consisting of people with one or other of these two conditions.

Monitoring strategies evaluated

The economic model incorporated the pathways of care that individuals currently follow under standard practice in the NHS, as well as the proposed pathways for self-testing and self-management (informed by a review of current guidelines and expert opinion). Current practice was dichotomised in the model as standard monitoring in primary care and standard monitoring in secondary care. In the base case analysis, the proportional split between standard primary and secondary care INR monitoring was taken from the manufacturers submission for TA256.[7] Based on a survey of providers in England and Wales carried out in 2011, it was estimated that 66.45% and 33.55% of warfarin monitoring appointments were managed in a primary and secondary care setting, respectively. These figures were accepted by the independent evidence review group (ERG) and appraisal committee for NICE TA256.[8]

In terms of self-monitoring, the model incorporated both self-testing and self-management strategies using the alternative devices identified in the scope. However, the cost-effectiveness of self-monitoring was assessed as a whole, and it was assumed in the base case analysis that 50% of people would self-test whilst 50% would self-manage. These proportions were varied in sensitivity analysis. Self-testing and self-management strategies were costed separately for each device based on the assumption that individuals who self-test phone in their results for all tests undertaken, while individuals who self-management group adjust their dosing independently. In reality, some self-monitoring people are likely to fall somewhere in between these two strategies, and several alternative scenarios were also assessed.

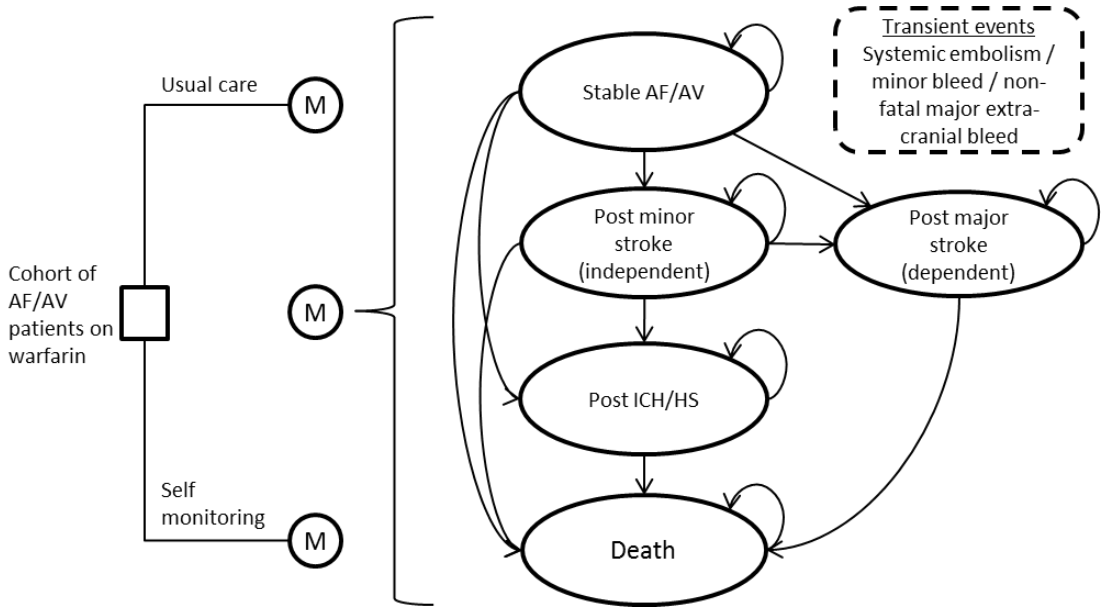
Framework (method of synthesis)

The alternative monitoring pathways, informed by review of previous guidance and expert opinion, were embedded in a Markov model simulating the occurrence of adverse events over time (Figure S1). The adverse events included in the model were

ischaemic stroke (minor, non-disabling, and major disabling or fatal), systemic embolism (SE), minor haemorrhage, and major haemorrhage (intra-cranial haemorrhage (ICH), including haemorrhagic stroke (HS), gastrointestinal (GI) bleed, and others). Systemic embolism was treated as a transient event within the model, such that people surviving this event returned to baseline levels of quality of life and did not incur on-going costs and morbidity. Minor haemorrhage was handled in the same way. Ischemic stroke and ICH were assigned post event states associated with additional ongoing care costs and quality of life decrements.

The model simulated transitions between the discrete health states, and accumulated costs and quality adjusted life years on a quarterly (three monthly) basis. Within each three month cycle, the simulated cohort was exposed to a risk of the aforementioned events as well as death from other causes. A constraint was applied whereby simulated individuals could only experience one event per cycle. A further simplifying structural assumption was applied, such that following a major ischaemic stroke or ICH, no further events were explicitly modelled. However, all-cause mortality was inflated following these events to account for the increased risk of death.

Baseline risks for the modelled events were derived from the observed event rates in cohorts of people being managed under current standard models of care. Relative risks of these events resulting from improved/reduced INR control, conferred by self-monitoring, were derived from the meta-analysis of randomised controlled trials of self-monitoring versus standard practice. Appropriate costs and quality of life weights were attached to modelled events and health states, allowing cumulative health and social care costs and quality adjusted life years to be modelled over time. Further details of the event risks, transitions, costs and quality of life weights applied in the model are provided in the following sections.



Notes: M, Markov process; AF, atrial fibrillation; AV, artificial heart valves; ICH, intracranial haemorrhage; HS, haemorrhagic stroke

Figure S1 Schematic of the model structure

Modelled baseline risks for people with atrial fibrillation

Previous economic models relied on a variety of sources to inform the underlying baseline risks of adverse events, ranging from single centre trials to data pooled from a number of trials. The unpublished model provided by Roche made use of event rates reported by time in therapeutic range,[9-11] based on data from the control arms of large multinational trials comparing new anticoagulant drugs with standard treatment with warfarin for people with atrial fibrillation.

The RE-LY trial of dabigatran etexilate versus warfarin provides a detailed source of event rate data by centre level quartiles of mean time in therapeutic range (TTR).[10,12] The advantage of these data is that they allow underlying event rates to be modelled by the level of anticoagulation control achieved, but there is a question surrounding their generalisability to the atrial fibrillation population on warfarin therapy in the UK. However, a previous study assessed the representativeness of the RE-LY clinical trial population to real-world atrial fibrillation patients in the UK,[13] and found that the majority of patients in the UK (65-74%) would have met the inclusion criteria. Furthermore, to assess the generalisability of the annual risks of stroke derived from RE-LY data, these were compared with those derived from a large cohort of individuals with atrial fibrillation on warfarin in the UK. Gallagher analysed

longitudinal data from the General Practice Research Database on 27,458 warfarin users with atrial fibrillation, and provided a Kaplan Meier plot of the probability of being stroke free by different levels of TTR.[14] Points on these plots were extracted using DigitizeIT software (http://www.digitizeit.de/), and used to estimate the annual risks of stroke by TTR groupings.

These stroke risks were found to be similar to those for people in the corresponding TTR quartiles of the RE-LY trial control arm. Therefore, the control arm of the RE-LY trial was considered to be an appropriate source for estimating baseline risks by level of TTR in the economic model. Gallagher[14] also estimated a mean TTR (INR2-3) of 63% for the UK cohort, so the baseline risks in the model were set to those observed in RE-LY trial centres that achieved a mean TTR between 57.1% to 65.5%.

The analysis of RE-LY trial data by TTR quartiles[10] provided estimated annual event rates for: non-haemorrhagic stroke and systemic embolism; major haemorrhage (including intracranial bleed, haemorrhagic stroke and major gastrointestinal bleeds) and minor haemorrhage. These rates were entered in the model where they were converted into annual risks (Table S1). Following further adjustment where appropriate, with relative risks associated with self-monitoring, the annual risks were converted into quarterly risks using the following equation:

$$Quarterly\ risk = 1 - EXP(Ln(1-annual\ risk) \times 0.25)$$

The events were modelled within each cycle of the model, and were further disaggregated based on the observed numbers of different types of event observed within each composite outcome in the RE-LY trial[10,12] (Table S2).

Further adjustments were applied to the risk of stroke in atrial fibrillation patients, to reflect the importance of age as a risk factor. For this purpose, the same approach as used in the model for NICE TA256 (rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation) was applied.[7] Relative risks of stroke by age, compared with a 70-74 year-old cohort (the average age of participants in RE-LY trial), were derived from a Framingham based risk score calculator for patients with AF,[15] and applied to adjust the risk of stroke and SE by five year age

bands.[7] A similar approach was also used to inflate the risk of bleeding with increasing age, using data from Hobbs and colleagues.[16]

Table S1 Annual baseline event risks for people with AF by level of INR control (TTR)

	Annual risk by INR control (TTR%)			
Event	<57.1%	57.1%-65.5%	65.6%-72.6%	>72.6%
Non-haemorrhagic stroke and systemic embolism	0.0162	0.0162	0.0110	0.0097
Major bleeding	0.0353	0.0405	0.0334	0.0306
Minor bleeding (inferred)	0.1174	0.1323	0.1375	0.1387

Note: The tabulated values were calculated within the model from the average event rates reported by Wallentin et al. The underlying rates were specified as gamma distributions in the model, with variance calculated from the reported event numbers and person-years of follow up.

Table S2 Disaggregation of modelled composite outcomes

Composite event	Proportional disaggregation	Distributional form	Source
Non-haemorrhagic stroke and systemic embolism		Beta	
Non-haemorrhagic stroke	0.909	(α=14; β=140)	Connolly 2009[12]
SE	0.091		Connolly 2009[12]
Major bleeding		Dirichlet	
Intracranial bleed / Haemorrhagic stroke	0.178	α = 89	Connolly 2009[12]
Other major bleed	0.426	α = 183	Connolly 2009[12]
Gastrointestinal bleed	0.396	α = 147	Connolly 2009[12]
Non-haemorrhagic stroke		Beta	
Non-disabling(Rankin 0-2)	0.369	(α=69; β=118)	Connolly 2009[12]
Disabling or fatal (Rankin 3-6)	0.631		Connolly 2009[12]
Intracranial bleed / Haemorrhagic stroke		Beta	
Fatal by 30 days	0.388	(α=36.8; β=58.1)	NICE TA256 [7]
Non-CNS major bleed		Omitted from PSA	
Proportion fatal	0.0155		NICE TA256 [7]
Disabling or fatal stroke (Rankin 3-6)		Beta	
Fatal in hospital	0.06	(α=11; β=177)	Hylek 2003[17]
Fatal by 30 days post discharge	0.159	(α=29; β=151)	Hylek 2003[17]
Non-disabling stroke		Beta	
Fatal by 30 days post discharge	0.01	(α=2; β=176)	Hylek 2003[17]
Systemic embolism		Omitted from PSA	
Fatal	0.004		NICE TA249[18]

Death following stroke was estimated by applying case fatality rates to these modelled events. Death following stroke utilised the same approach as used in the model of dabigatran versus warfarin for NICE technology appraisal TA249.[18] Based on Hylek,[17] the hospital case fatality rate was first applied, followed by the reported 30 day mortality by severity of stroke (Rankin 0-2; 3-5) post discharge (Table S2).

Modelled baseline risks for people with an artificial heart valve

Less extensive data were identified describing the baseline risk of adverse events for people with artificial heart valves by level of INR control. Previous economic models have tended to use overall event risks for mixed cohorts rather than explicit event risks for individual patient groups included in the modelled cohort.

As per the model provided by Roche (J Craig, York Health Economics Consortium, 2013), a recent meta-analysis of individual patient level data from 11 randomised controlled trials of self-monitoring versus standard care provided the source of event data.[19] Heneghan and colleagues presented a subgroup analysis where they presented the estimated pooled hazard ratio and number needed to treat to prevent one major thromboembolic event (ischaemic stroke and systemic embolism) and one major haemorrhagic event by year of follow up (up to 5 years) based on 2243 people with an artificial heart valve. The formula used by Heneghan to estimate the number needed to treat was:

$$NNT = 1/(Sc[t]^h - Sc[t])$$

Where Sc[t] is the survival probability in the control group (standard monitoring) at time t, $Sc[t]^h$ is the corresponding survival probability in the active treatment group (self-monitoring), and h is the hazard ratio. The 5 year probability of experiencing a thromboembolic (0.089) and major haemorrhagic event (0.169) in the control group were back calculated for people with an artificial heart valve, and converted into annual probabilities (Table S3). These were incorporated in the model for subsequent adjustment and conversion into quarterly probabilities for use as baseline risks.

A focused search was undertaken to identify alternative sources of data to inform the baseline risk of thromboembolic events in people with an artificial heart valve. A

previous meta-analysis estimated a pooled annual linearised risk of 1.6% for people with a mechanical aortic valve. A further large Canadian series (including 1622 people with a mechanical heart valve) estimated linearised embolic stroke risks of 1.4% and 2.3% per year for people with an artificial aortic and mitral valve respectively.[20] These figures are generally consistent with the baseline estimates used in the model. However, a smaller series from a single centre in the south west of England, reported a lower rate of 1.15% per patient-year based on two years follow up of 567 people with a Sorin Bileaflet, third generation prosthesis.[21] The impact of applying this lower baseline risk was assessed through sensitivity analysis.

Table S3 Annual baseline event risks for people with an artificial heart valve

Event	Annual risk	Distributional form
Non-haemorrhagic stroke and systemic embolism	0.0185	Beta (α = 19.2; β = 1020.8)
Major bleed	0.0363	Beta (α = 37.3; 977.7)
Minor bleed (assumed)	0.1323	See Table S1

In the absence of more detailed data for people with an artificial heart valve, the same proportional splits used to disaggregate thromboembolic and major hemorrhagic events for people with atrial fibrillation were applied (Table S2). Furthermore, since data on minor bleeds were not available from Heneghan and colleagues[19] for people with an artificial heart valve, the same baseline risk applied for people with atrial fibrillation was adopted. This was justified on the grounds of the two groups facing similar risks of a major bleed (0.405 and 0.363).

Further adjustments to baseline risks

Within the model, a number of simplifying structural assumptions were made. Following the occurrence of a major disabling ischemic stroke or an ICH/HS, no further events were modelled. However, the risk of age/sex specific all-cause mortality was inflated following these events using relative risks estimated by Sundberg and colleagues.[22] Deaths from other causes following minor stroke were

also inflated in the model to account for the observed increased risk of death from all causes following this event.[22,23]

The background risk of death from other causes also was increased for the atrial fibrillation and artificial valve cohorts using SMRs reported by Friberg and colleagues[24] and Kvidal and colleagues[25] (Table S4).

Baseline rates of death from all and other causes were modelled by age and sex based on interim life tables. For other cause mortality, deaths due to stroke, SE, and ICH were removed.[26,27]

Table S4 Parameters used in the model to adjust rates of death from all and other causes

Parameter	Value	SEM	Distributional form	Source
SMR - death from all causes for Atrial fibrillation patients	1.30	0.082	Normal	Friberg 2007[24]
RR - death post minor stroke	2.33*	0.276	Normal	Sundberg 2003[22]
RR - death post disabling stroke	4.11	0.486	Normal	Sundberg 2003[22]
SMR - death from all causes for artificial heart valve patients				Kvidal 2007[25]
≤50 years	4.56	0.861	Normal	
51-60 years	2.66	0.276	Normal	
61-70 years	1.80	0.111	Normal	
≥71 years	1.02	0.071	Normal	

Note: *Figure adjusted to reflect the fact the death from stroke was modelled independently following a minor stroke, and to fit observed survival probabilities following minor stroke.[28]

Incorporation of relative treatment effects

Pooled estimates of relative risk derived from the meta-analysis of randomised controlled trials of self-monitoring versus standard practice were used to adjust the baseline risks of events in the model (Table S5).

For the base case analysis, relative effects were entered separately for the different types of event (any thromboembolic event, major bleed and minor bleed) by type of self-monitoring strategy (self-management and self-testing) (Table S5). While not all effects were significant, the point estimates were applied in the model with appropriate distributions assigned to reflect the uncertainty surrounding them. These relative risks, which represent pooled estimates obtained from trials with follow up periods varying between three and 24 months, were assumed to apply directly to the 12 month risk of an event. Therefore, they were used to adjust the estimated annual baseline risk of events in the model, from which constant three month transition probabilities were derived. The relative risks were only applied to people continuing on self-monitoring in the model.

Table S5 Relative effects for self-monitoring applied in the model

Event/monitoring strategy	RR	Lower 95% CL	Upper 95% CL	Distributional form
Any thromboembolic event				
Self-management	0.51	0.37	0.69	Lognormal
Self-testing	0.99	0.75	1.31	Lognormal
Self-monitoring (overall)	0.58	0.40	0.84	Lognormal
Major bleed				
Self-management	1.08	0.81	1.45	Lognormal
Self-testing	0.99	0.8	1.23	Lognormal
Self-monitoring (overall)	1.02	0.86	1.21	Lognormal
Minor bleed				
Self-management	0.84	0.53	1.35	Lognormal
Self-testing	1.23	1.06	1.42	Lognormal
Self-monitoring (overall)	0.94	0.65	1.34	Lognormal

Resource use estimation

Data on the resource use and costs associated with the alternative monitoring strategies were informed by published literature, existing guidance, expert opinion, manufacturers and suppliers' prices, and other routine sources of unit cost data.[4,5] As noted above, certain costs were informed by expert opinion where suitable data from other sources were not available.

Costs of standard care

Resource use associated with standard monitoring was informed by a number of sources. The model provided by Roche used estimates of monitoring costs (under standard primary and secondary care) based on previous estimates calculated by the independent evidence review group (ERG) for NICE technology appraisal TA249 (dabigatran etixilate for the prevention of stroke and systemic embolism in atrial fibrillation).[29] These estimates of monitoring costs in standard care, which were later applied in the NICE costing template for dabigatran,[30] were derived by the ERG based on previous estimates used in the NICE costing report for clinical guideline CG36 on atrial fibrillation.[31] This report summarised the estimated annual resource use required for monitoring people in primary care, assuming 20 monitoring visits per year. These measures of resource use, per visit, are summarised in Table S6.

Updated unit costs have been applied to provide a total cost per patient monitoring visit in 2011/2012 GBP. When calculating the variable cost per patient associated with monitoring in a secondary care setting, the ERG in their report on dabigatran etexelate assumed that 33% of secondary care monitoring costs would be fixed and not influenced by changes in the number of people being monitored. This assumption was based on the observed proportional split between fixed and variable costs in the bottom-up calculation of the total cost of INR monitoring in primary care.[31] This same assumption was applied in our updated estimates.

When updating the unit costs for practice nurse time in primary care, we used an estimate per hour that incorporates allocated overhead costs (including management and administration) and use of practice space. Some of these allocated costs were not included in previous variable cost estimates for monitoring in primary care. It was considered appropriate to include them here to capture the opportunity cost

associated with use of primary care facilities for INR monitoring.[32] However, since the allocated costs account for administration, additional admin time per patient visit was not costed separately as it was in previous estimates.[3,29,31]

Given the slightly different approach to updating the unit costs for standard monitoring services, our cost estimates based on 20 monitoring visits (£235.20 and £306.94 for primary and secondary care monitoring respectively), differ somewhat from those used in the NICE costing template for dabigatran (£220.90 and £303.43 respectively for monitoring in primary and secondary care in 2009/2010 prices) and also from those applied in the model provided by Roche (£231.33 and £317.90 respectively for primary and secondary care monitoring in 2012/2013 prices).

Table S6 Resource use and updated variable cost estimates per standard primary and secondary care INR monitoring visit

Resource	**Unit costs (2011/2012)**	**Cost per patient per visit (2011/2012)**	**Source/assumtpions**
Primary care			
Reagents	£2.80	£2.80	Roche (assumes point-of-care testing)
lancet	£0.04	£0.04	Roche
Nursing time (15 minutes)	£35.00 (per hour)	£8.75	PSSRU, 2012[5]
Admin time (15 minutes)	Accounted for in allocated costs for nursing time	-	PSSRU, 2012[5]
Office consumables per clinic	£2.52	£0.21	CG36, costing report, inflated to 2011/2012 prices, assumes 12 patients per clinic[30,31]
Use of shared equipment (equivalent annual cost)	£171.65	£0.29	Roche (CoaguChek XS Plus, annuitized over five years, assuming 600 uses per year)
Total variable cost per patient monitoring visit		£11.76	
Total variable cost per year assuming 20 visits		£235.20	

Resource	Unit costs (2011/2012)	Cost per patient per visit (2011/2012)	Source/assumtpions
Total variable cost per year assuming 12 visits		£141.12	
Cost per quarter*		**£35.28**	
Secondary care			
NHS anticoagulation services	£23 (per visit)	£23	NHS reference costs, 2012 (anticoagulation services)[4]
Assumed variable cost component (0.6667)	£15.33 (per visit)	15.33	TA249 ERG report, 2011[3,29]
Total variable cost per patient monitoring visit		£15.33	
Total variable cost per year assuming 20 visits		£306.94	
Total variable cost per year assuming 12 visits*		£184.16	
Cost per quarter*		**£46.04**	

Note: *Standard-care monitoring costs were entered in the model as gamma distributions, with the mean based on 12 monitoring visits per year and the variance reflecting the uncertainty surrounding the annual number of visits.

An alternative source of standard monitoring costs per visit was identified from the largest UK based RCT of self-monitoring.[33] Jowett and colleagues carried out the economic analysis alongside the SMART trial, where people in the control arm received a mix of standard primary and secondary care monitoring.[34] A unit cost per visit (accounting for staff time, equipment, consumables and overheads) was estimated for each care setting from a sample of NHS providers. The resultant cost estimates (per visit) for different types of standard care are presented in the Table S7, inflated to 2011/2012 prices.

Table S7 Alternative unit costs of standard care INR monitoring in different settings, reported by Jowett 2006.[87]

Care setting	Cost per visit (2002/2003)	Inflation factor	Cost per visit (2011/2012)	Annual costs (assuming 20 visits per year)
Hospital clinic	£6.35	1.337	£8.49	£169.79
GP blood sample, hospital analysis and dosing	£9.38	1.337	£12.54	£250.81
GP blood sample and dosing, hospital analysis	£10.69	1.337	£14.29	£285.83
Practice based near patient testing clinic	£14.16	1.337	£18.93	£378.62
Pharmacist led practice clinic	£17.66	1.337	£23.61	£472.20
MLSO-led practice clinic	£11.62	1.337	£15.54	£310.70

For primary care monitoring these unit costs are somewhat higher than those presented in Table S6. However, the cost estimate for monitoring in a secondary care (hospital clinic) is substantially lower. Furthermore, while the proportional mix of standard care service use was not reported in the study by Jowett and colleagues[34] a total mean standard care monitoring cost of only £89.89 (£120.18 in 2011/2012 prices) was reported at 12 months. The actual annual monitoring frequency observed in the control arm of the SMART trial was 37.9 days.[33]

This suggests than an annual number of only ~10 monitoring visits per year was required to achieve the level of control reported for the standard care arm of this pragmatic UK based RCT.

The assumption of 20 visits being the average number of monitoring visits required for people on long-term vitamin k antagonist therapy comes from the NICE costing report for the clinical guideline on the management of atrial fibrillation.[30,31] This was estimated based on the ratio of second to first attendances at anticoagulation clinics (~19 from reported activity in the 2004/2005 NHS reference costs) and a previous study by Jones and colleagues,[35] which reported a median frequency of INR testing of 16 days for people receiving warfarin (equating to ~22 tests per year). A repeat of the calculation based on reference costs activity data for 2011/2012 yielded a ratio of only 9.5. However, this lower value may merely reflect a trend for more people to be followed up in primary care following initiation of therapy.

Given the uncertainty surrounding the average number of monitoring visits for people under standard primary and secondary care, the DAR specialist committee members were consulted on this parameter. Opinion on the frequency of monitoring suggested that 10-12 visits would be required on average in primary and secondary care, but that the number of visits would be highly variable across participants. It was also noted by one member that more monitoring visits may be required for people managed in secondary care, as it tends to be the people with poorer control that are managed in this setting. A further question was raised about the nursing time requirements for routine monitoring visits used in the previous cost estimates informing TA249 (15 minutes of band 5 nurse time per patient visit). One source suggested that 10 minutes would suffice for this.

Based on consideration of the all the above evidence, it was assumed in the base case analysis that on average 12 monitoring visits would be required per year for people under standard primary and secondary care monitoring. To retain consistency with previous analyses used to inform NICE guidance, we applied the unit costs per visit based on the figures in Table S6.

The impact of altering the number of standard care monitoring visits per year was also assessed through sensitivity analysis. We also conducted sensitivity analyses where the updated unit costs in Table S7 were applied to cost monitoring visits, and where we assumed only ten minutes of nurse time per standard care monitoring visit.

Finally, given the reliance of some people on NHS transport for attending secondary care monitoring visits, a cost of transport was applied for a percentage of people modelled to receive this form of monitoring. The percentage of 8.55% was taken from a previous survey of patient pathways used to inform the manufacturer's model for NICE TA256[7] and the return transport cost was taken from the NHS reference costs (£30.96).[4]

Costs of self-monitoring

An average testing frequency of 35 per year (every 10.42 days) was assumed for self-monitoring in the base case analysis. This number was chosen to be consistent with the trials from which the relative effect estimates for self-monitoring were obtained. In a recent meta-analysis of patient level data,[19] 11 of the self-monitoring trials included in our review reported the mean increase in the number of tests performed with self-monitoring versus control. There was an average 24 additional tests by12 months for people with atrial fibrillation and 22 additional tests for people with an artificial heart valve. The average of these two values was added to the estimated 12 tests per year for standard care, to give an estimate of 35 tests per year for self-monitoring. The impact of altering the difference in testing frequency between standard care and self-monitoring, through the 95% confidence intervals reported by Heneghan (13-30 per year), was assessed through sensitivity analysis.[19] Furthermore, we assessed scenarios where self-monitoring was not used to increase the frequency of monitoring as a means to improve INR control, but simply to replace primary and secondary care testing. Under this scenario, we assumed no relative effects of self-monitoring on outcomes. The sections below provide further details on the cost of self-monitoring, with a summary of cost elements provided in Table S8.

Equipment

Self-monitoring device costs were obtained from the manufacturer (Roche Diagnostics). The device costs were treated in the same way that capital investments are normally dealt with in economic evaluation. It was assumed that the NHS would pay for these and loan them out to patients. As such they were annuitized over their expected useful life to provide an equivalent annual / quarterly cost of use. Whilst these devices have a potentially long life-span based on the advice of manufacturers,

their costs were annuitised over a five year period in the base case analysis to account for potential for loss and accidental damage.

There is also a degree of uncertainty about the suitability of the devices for re-use following discontinuation of self-monitoring by participants. In the base case analysis the same assumption that was used in a previous UK based economic modelling study[36] was applied; i.e. three quarters of devices are re-used by another patient in situations where a patient discontinues self-monitoring (see below for details on assumptions about discontinuation).

Consumables

The cost of test strips were provided by the manufacturers, and it was assumed in the base case analysis that the annual cost of test strips would be equal to the number of tests performed annually multiplied by the cost per strip (i.e. that there would be no wastage). It was further assumed that two more test strips would be used annually to cross check each device against a quality assured clinic based machine. This was modelled to take place during bi-annual assessments for self-monitoring participants (see below).

NHS staff time

The staff time input required to oversee self-monitoring relied on expert opinion. People that are self-monitoring can require varying degrees of input from clinical staff to check readings and respond to queries. In the base case it was assumed that all self-testing people would call in each and every test result on a dedicated phone line, and that a nurse would later check and enter each patient's result, and then phone the patient back with instructions to either maintain or alter their warfarin dose. This was assumed to incur 5 minutes of band 5 nurse time per patient (based on the opinion of the specialist advisory committee), which was valued using nationally available unit costs.[5] It was assumed that self-managing people would not require any further support from nursing staff other than biannual routine assessments.

Bi-annual routine assessments

It was assumed that quality control of self-monitoring devices would take place at bi-annual clinic appointments, at the local anticoagulant clinic or practice from where self-monitoring was initiated. It was assumed that this would involve checking the patient's instrument against an externally validated one, and that it would incur 15 minutes of direct face-to-face contact time with a practice nurse (45 per hour) or hospital clinic nurse (£85 per hour).[5] In line with the base case assumption that 34% of people are monitored in secondary care under standard practice, it was assumed that 34% of self-monitoring people would return to this setting for routine assessments, whilst the remainder would return to primary care clinics.

Training

Based on existing literature[37] as well as consultation with members of expert advisory committee, it was assumed that self-testing people would require two hours of one-to-one training while those progressing to self-management would receive four hours of one-to-one training prior to initiation. These assumptions are consistent with those applied in the model that was provided by Roche (J Craig, York Health Economics Consortium, 2013) and the literature on training requirements from RCTs of self-monitoring. Training time was costed using hourly unit costs for direct patient contact time (£45 per hour for practice nurse time and £85 per hour for hospital clinic nurse time).

The RCT literature[33] and the expert advisory committee were also consulted with respect to training success rates and on-going adherence to self-monitoring. In light of this, we incorporated a training failure rate of 15% - the mid-point between 5%, suggested by members of the expert advisory committee, and 24%, a pragmatic UK trial based estimate[33] - and assumed that these people would incur the cost of training but return to standard care without incurring the cost of a monitoring device.

In addition to including a training failure rate in the model, it was considered unrealistic to assume that 100% of participants would continue to self-monitor after initiation. Therefore, we incorporated a discontinuation rate of 10% by 12 months in the model, based on consideration of the views of the expert advisory committee

(~5%) and a rate of 14% reported in the largest UK based trial.[33] Beyond 12 months it was assumed that self-monitoring people would continue to do so unless they experienced a fatal or disabling adverse event.

Warfarin costs

In line with previous evaluations, it was assumed that the quantity and cost of vitamin K antagonist drugs would not vary significantly between self-monitoring and standard monitoring. Therefore, these costs were excluded from the model.

Table S8 Summary of self-monitoring device, training and testing costs

Self-monitoring unit cost	**CoaguChek XS**	
Device cost	£299	
Equivalent quarterly cost for use	£16.56	
Test strips (per unit)	£2.81	
Lancets (per unit)	0.04	
Self-monitoring costs	**Primary care**	**Secondary care**
	CoaguChek XS	**CoaguChek XS**
Training		
Self-testing	£90	£170
Self-management	£180	£340
Annual self-testing costs		
Test strips and lancets (x35)	£99.62	£99.62
External QC twice a year (2 strips + 2 lancets)	£5.69	£5.69
Routine clinic assessment twice per year	£22.50	£42.50
Phone calls (5 minutes of nurse time x 35 per year)	102.08	102.08
Cost per year based on 35 tests	**£229.90**	**£249.90**
Cost per quarter*	**£57.47**	**£62.47**
Annual self-management costs		
Test strips and lancets (x35)	£99.62	£99.62

Self-monitoring unit cost	**CoaguChek XS**	
Device cost	£299	
Equivalent quarterly cost for use	£16.56	
Test strips (per unit)	£2.81	
Lancets (per unit)	0.04	
External QC twice a year (2 strips + 2 lancets)	£5.69	£5.69
Routine clinic assessment twice per year	£22.50	£42.50
Cost per year based on 35 tests	**£127.81**	**£147.81**
Cost per quarter*	**£31.95**	**£36.95**

Note: *Quarterly self-monitoring costs were entered in the model as gamma distributions, with the mean based on 35 monitoring visits per year and variance reflecting the uncertainty surrounding the increased number of tests over standard monitoring (13-30).

Costs of adverse events

The costs associated with adverse events were adapted from those used in the model informing NICE TA256 - rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation.[7] These cost estimates were based largely on NHS reference costs, and were considered appropriate by the independent ERG in their critique of the manufacturer's submission.[8] These costs were updated for the current analysis using the National Schedules of NHS Reference Cost, 2011-2012, where possible[4], or were otherwise inflated from previously reported 2009/2010 prices using the Hospital and Community Health Services (HCHS) pay and prices index.[5] These costs are presented in Table S9.

The cost of minor bleed was based on the NHS reference cost for VB07Z: Accident and emergency services, category 2 with category 2 treatment (weighted average). A major non-intracranial bleed was taken as the weighted average reference cost for the HRG codes related to non-elective admissions for gastro-intestinal bleeds (Table S9).

For the cost of a systemic embolism, a weighted average of the reference costs for non-elective admissions relating to the HRG for non-surgical peripheral vascular disease (QZ17A, QZ17B, QZ17C) was applied.

The initial cost of a minor stroke was taken as the weighted average of the 2011/2012 non-elective reference costs for the HRG codes AA22A and AA22B, (Non-Transient Stroke or Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with and without CC). This equates to a cost of £3082.

For major stroke, the cost used in the rivaroxaban submission was also updated, whereby the initial treatment cost was taken as the weighted average of AA22A and AA22B (£3082), with the addition of 10.97 additional bed days costed using the weighted average excess bed day cost (£236.16 per day) for AA22A and AA22B. The excess bed days were estimated by subtracting the length of stay accounted for in the reference costs for AA22A and AA22B - up to 24.43 days[4] - from the average length of stay in hospital for people suffering a major stroke (34.4 days based on Saka and colleagues[38]). In addition, 14 days rehabilitation was added at a cost per day of £313.41 - based on the HRG VC04Z (rehabilitation for stroke) - to estimate the total cost of a major stroke to three months (£10,061). This estimate is lower than that used in the model for NICE TA256 (updated cost of £13,547), since excess bed day costs were only applied to days above the costing trim-point for AA22A and AA22B, rather days above the average length of stay for these codes.

Table S9 Health and social care costs associated with adverse events

Health States/ events	Cost element	Unit costs	Cost source	Assumptions/ description	Total cost
Transient events					
Minor bleed	Acute treatment	£134	National schedule of reference costs 20011/2012[4]	VB07Z: Accident and emergency services. Category 2 with category 2 treatment (weighted average)	£134
Major bleed (non-intracranial)	Acute treatment	£975		Cost of a gastro-intestinal bleeding treatment episode. Weighted average of codes: FZ38D, FZ38E, FZ38F, FZ43A, FZ43B, FZ43C	£975
Systemic embolism	Acute treatment	£1,639		Cost of non-surgical peripheral vascular disease. Weighted average of codes: QZ17A, QZ17B, QZ17C	£1,639
Permanent events					
Minor stroke	Acute treatment	£3,082	National schedule of reference costs 20011/2012[4]	AA22Z: Non-transient Stroke OR Cerebrovascular Accident, Nervous system infections or Encephalopathy	£3,082
Post minor stroke (Rankin 0-2)	Follow-on care costs per quarter	£219	Wardlaw 2006 [39] NICE Clinical Guideline CG92[40]	Annual cost of stroke care per year following an index event, inflated to 2011/2012 prices and quartered	£303

Major stroke	Acute treatment	£3,082	National schedule of reference costs 20011/2012: non elective inpatient[4]	AA22Z: Non-transient Stroke OR Cerebrovascular Accident, Nervous system infections or Encephalopathy - with 10.97 excess bed days	£10,061
	Acute treatment cost per excess bed day	£236			
	Rehabilitation (cost per day) - 14 days	£313	National schedule of reference costs 20011/2012[4]	VC04Z: rehabilitation for stroke (weighted average)	
Post major stroke (Rankin 3-5)	Follow-on care costs per quarter	£2,823	Wardlaw.2006[39] NICE Clinical Guideline CG92[40]	Annual cost of stroke care per year following an index event, inflated to 2011/2012 prices and quartered	£3,906
Intracranial bleed	Acute treatment	£2,250	National Schedule of Reference Costs 20011/12[4]	AA23Z: Haemorrhagic Cerebrovascular Disorders (weighted average)	£6,638
	Rehabilitation (cost per day) - 14 days	£313		VC04Z: rehabilitation for stroke (weighted average)	
Post intracranial bleed /HS	Follow-on care (costs per quarter)	£2,576	Nice Clinical Guideline CG92[40]	Assumed weighted average of quarterly costs following ischemic stroke (assumes 38% of patients dependent, and 62% independent)	£2,576

Note: All costs associated with adverse events (except those occurring post stoke) were specified in the model as gamma distributions, with variance reflecting the lower and upper quartiles reported in the NHS reference costs.

Further costs were applied on a quarterly basis in the years following ischaemic stroke. These costs were adapted from those applied in NICE clinical guideline CG92, which were initially based on costs reported by Wardlaw and colleagues[39] of £11,292 per year for disabling stroke and £876 per year for non-disabling stroke (2001/2002) prices. These costs were inflated to 2011/2012 values using the HCHS pay and prices index.[5]

For the acute treatment costs associated with an intracranial bleed, a weighted average of the non-elective reference costs for HRG AA23Z (Haemorrhagic Cerebrovascular Disorders) was applied. In addition, the same rehabilitation costs as applied following major ischaemic stoke were applied following intracranial haemorrhage, and the following quarterly health and social care costs were taken as the weighted average of those following minor (0.369) and major (0.631) ischemic stroke.

Health measurement and valuation

Time spent in different states of the model was adjusted using utility weights reflecting the desirability of those states on a scale where 0 is equal to death and one is equal to full health. With the model structure similar to that of the model used to inform NICE TA256 (rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation), a number of the utility values used in this previous model were applied (acute major and minor stroke, acute major haemorrhage and ICH). These values were considered appropriate by the independent ERG for NICE TA256[8] and accepted by the appraisal committee. However, the utility values applied to the states "post minor" and "post major stroke" in TA256, were derived from a Norwegian study where values were elicited directly from participants and the general population.[41] Alternative values were identified for these states based on the EQ-5D responses of stroke people in the UK. Dorman and colleagues[42] used the EQ-5D to measure the health status of 867 people enrolled in the International Stroke Trial.[43]

The reported values of 0.31 for dependent health states and 0.71 for independent health states were considered more consistent with the NICE reference case than the directly elicited Norwegian values (0.482, 0.719 respectively) used in TA256. Further,

it was assumed that for people experiencing an ICH or HS, the proportion of people returning to independent living would match that observed for ischaemic stroke, and that the same utilities for minor and major ischaemic stroke would apply to dependent and independent states following ICH. This approach was used as it was noted that the value used in the rivaroxaban submission[2,7] was higher than the age specific UK EQ-5D population norm for people ≥75 years of age. Finally, the baseline utility value for people with atrial fibrillation or mechanical heart valve who were stable was taken as the baseline EQ-5D value of patients enrolled in the SMART trial (0.738).[34] This value was applied to 65-70 year people. The difference between the UK EQ-5D population norm for 65-70 year-olds and the utility estimate from the SMART trial (0.042), was used to estimate age specific baseline utilities in the model. The resultant utility values applied to events and health states are provided in Table S10.

Utilities associated with acute events were applied for the three month period following the event. For post event states with associated on-going morbidity, the appropriate health state utilities were applied for all subsequent cycles spent in these states. Half cycle corrections were applied, by assuming that people experienced events on average at the mid-point of the cycle. Thus a patient starting off in the stable state and experiencing a major stroke in a given cycle of the model, would accrue 6 weeks at the utility value for well and 6 weeks at the utility value for major stroke.

Table S10 Health state utility values applied to modelled events and states in the model

State/event	Utility value / decrement	Source	Description
Stable AF/AV			
<25 years	0.898	Kind 1999[44]	EQ-5D, UK population norm adjusted for AF/AV
25-34 years	0.888	Kind 1999[44]	EQ-5D, UK population norm adjusted for AF/AV
35-44 years	0.868	Kind 1999[44]	EQ-5D, UK population norm adjusted for AF/AV
45-54 years	0.808	Kind 1999[44]	EQ-5D, UK population norm adjusted for AF/AV
55-64 years	0.758	Kind 1999[44]	EQ-5D, UK population norm adjusted for AF/AV
65-74 years	0.738	Jowett 2006[34]	EQ-5D values for people with AF
≥75 years	0.688	Kind 1999[44]	EQ-5D, UK population norm adjusted for AF/AV
Minor stroke	0.641	Robinson 2001[45]	Standard gamble, UK people
Post minor stroke	0.71	Dorman 2000[42]	EQ-5D, UK stroke people
Major stroke	0.189	Robinson 2001[45]	Standard gamble, UK people
Post major stroke	0.31	Dorman 2000[42]	EQ-5D, UK stroke people
Systemic embolism (decrement)	-0.119	Sullivan 2006 [46]	Based on EQ-5D scores from a US cohort
Minor bleed	0.7757	Sullivan 2006[46]	As above
>75 years	0.7257		As above, adjusted for consistency with UK population norms

State/event	Utility value / decrement	Source	Description
Major bleed (decrement)	-0.1814	Sullivan 2006[46]	As above
Post IC bleed	0.461	Assumption	Weighted average of post minor and post major stroke utilities

Note: all utility values and decrements were incorporated in the model as beta distributions with variance derived from the reported source, except for baseline values based on population norms.

Time horizon and discounting of costs and benefits

Both costs and benefits (QALYs) were discounted and 3.5% per annum, in line with the NICE reference case.[6] The model was initially analysed over a 10 year period, but the impact of adopting longer time horizons (including the patient's life time) were explored in sensitivity analyses. It was anticipated that a 10-year time horizon would be sufficient to demonstrate the main health and cost impact of any identified differences in adverse event rates between the alternative monitoring strategies, while avoiding the uncertainty surrounding assumptions about event rates far into the future.

Analysis

The results of the model are presented in terms of a cost-utility analysis (i.e. costs for and number of QALYs generated by each monitoring strategy). The self-monitoring strategies were compared incrementally to standard care, to estimate their incremental cost per quality adjusted life year gained (QALY).

Further analyses were undertaken to assess cost effectiveness by age, indication for anticoagulation therapy (AF, AV), the standard care comparator (primary care monitoring, secondary care monitoring), and the active intervention (self-monitoring, self-management).

To characterise the joint uncertainty surrounding point estimates of incremental costs and effects, probabilistic sensitivity analysis was undertaken.[47] Each parameter was assigned an appropriate distribution as indicated in the preceding parameter tables.

The model was then run iteratively 1000 times, with a value drawn randomly for each input parameter from its assigned distribution for each model run. The results of this probabilistic analysis are presented in the form of incremental cost-effectiveness scatter-plots and cost-effectiveness acceptability curves (CEACs) - for self-monitoring compared to standard practice. Parameters excluded from the probabilistic analysis were: self-monitoring training costs; in hospital fatal stroke costs; post-stroke costs; the proportion of the cohort with atrial fibrillation; the proportion male; the proportional split between primary and secondary standard care monitoring; discontinuation rates; and unit costs of devices, consumables and staff time. Deterministic sensitivity analysis was also undertaken to address other forms of uncertainty.

Summary of base case analysis assumptions

The following assumptions were applied in the base case analysis:

- 66.45% of standard care monitoring occurs in primary care with practice nurses.96
- 60% of the cohort have atrial fibrillation, 40% have an artificial heart valve.108
- Average age of the cohort is 65 years, and 55% are male.108
- 50% of self-monitoring people self-test, 50% self-manage (assumption).
- The increase in the number of tests performed per year with self-monitoring is 23.108
- Relative treatment effects are estimated and applied separately for self-testing and self-management (see Table 10).
- 15% of participants do not commence self-monitoring following training (see text on "training" above).
- 10% of participants discontinue self-monitoring within a year of commencing (see text on "training" above).
- Self-monitoring device costs are annuitized over five years (see text on "equipment" above).
- 75% of devices are reused by another patient when a patient discontinues self-monitoring (see text on "equipment" above).

References

1 Sharma P, Scotland G, Cruickshank M, Tassie E, Fraser C, Burton C et al. *Clinical and cost-effectiveness of point-of-care tests (CoaguChek system, INRatio2 PT/INR monitor and ProTime Microcoagulation system) for the self-monitoring of the coagulation status of people receiving long-term vitamin K antagonist therapy compared with standard UK practice: systematic review and economic evaluation. Diagnostic Assessment Report.* London: National Insititute for Health and Care Excellence; 2013 [accessed April 2015]. http://www.nice.org.uk/guidance/dg14/documents/pointofcare-coagulometers-the-coaguchek-xs-system-and-the-inratio2-ptinr-monitor-diagnostics-assessment-report2.

2 *Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation NICE Guidance TA256 [document on the Internet].* London: National Insititute for Health and Care Excellence; 2012 [accessed April 2015]. http://guidance.nice.org.uk/TA256.

3 *Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. NICE Guidance TA249 [document on the Internet].* London: National Insititute for Health and Care Excellence; 2012 [accessed April 2015]. http://guidance.nice.org.uk/TA249.

4 *NHS reference costs 2011-12 [website on the Internet].* UK Department of Health; 2012 [accessed April 2015]. URL: https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012.

5 Curtis L. *Unit Costs of Health and Social Care 2012 [document on the Internet].* Canterbury: Personal Social Services Research Unit.; 2012 [accessed April 2015]. URL: http://www.pssru.ac.uk/project-pages/unit-costs/2012/.

6 *NICE Diagnostic Assessment Programme manual [document on the Internet].* London: National Institute for Health and Care Excellence; 2011 [accessed April 2015]. http://www.nice.org.uk/media/A0B/97/DAPManualFINAL.pdf.

7 Bayer PLC. *Single Technology Appraisal (STA) of Rivaroxaban (Xarelto®) [document on the Internet].* London: National Institute for Health and Care Excellence; 2011 [accessed April 2015]. http://guidance.nice.org.uk/TAG/274/Consultation/EvaluationReport/ManufacturerSubmissions/Bayer/pdf/English.

8 Edwards S, Hamilton V, Nherera L, Trevor N, Barton S. *Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation STA REPORT [document on the Internet].* London: National Insititute for Health and Care Excellence; 2011 [accessed April 2015]. URL:http://guidance.nice.org.uk/TAG/274/Consultation/EvaluationReport/EvidenceReviewGroupReport/pdf/English.

9 ROCKET AS, I. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism

Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. *Am Heart J* 2010;**159**:340-7.

10 Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;**376**:975-83.

11 Wallentin L, Lopes RD, Hanna M, Thomas L, Hellkamp A, Nepal S et al. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. *Circulation* 2013;**127**:2166-76.

12 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139-51.

13 Lee S, Monz BU, Clemens A, Brueckmann M, Lip GYH. Representativeness of the dabigatran, apixaban and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: A cross-sectional analysis using the General Practice Research Database. *BMJ Open* 2012;**2**:e001768.

14 Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost* 2011;**106**:968-77.

15 Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;**290**:1049-56.

16 Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess* 2005;**9(40)**.

17 Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003;**349**:1019-26.

18 Berhringer Ingelheim. *Atrial fibrillation - dabigatran etexilate: Boehringer Ingelheim submission [document on the Internet].* London: National Insititute for Health and Care Excellence; 2011 [accessed April 2015]. http://guidance.nice.org.uk/TAG/231/Consultation/EvaluationReport/ManufacturerSubmissions/BoehringerIngelheim/pdf/English.

19 Heneghan C, Ward A, Perera R, Self-Monitoring T, Bankhead C, Fuller A et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet* 2012;**379**:322-34.

20 Ruel M, Masters RG, Rubens FD, Bedard PJ, Pipe AL, Goldstein WG et al. Late incidence and determinants of stroke after aortic and mitral valve replacement. *Ann Thorac Surg* 2004;**78**:77-83.

21 Ascione R, Culliford L, Rogers CA, Wild J, Narajan P, Angelini GD. Mechanical heart valves in septuagenarians. *J Card Surg* 2008;**23**:8-16.

22 Sundberg G, Bagust A, Terent A. A model for costs of stroke services. *Health Policy* 2003;**63**:81-94.

23 Bronnum-Hansen H, Davidsen M, Thorvaldsen P, Danish MONICA Study Group. Long-term survival and causes of death after stroke. *Stroke* 2001;**32**:2131-6.

24 Friberg L, Hammar N, Pettersson H, Rosenqvist M. Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). *Eur Heart J* 2007;**28**:2346-53.

25 Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol* 2000;**35**:747-56.

26 *Deaths registered in England and Wales 2011 [webpage on the Internet].* U.K.Office for National Statistics; 2012 [accessed April 2015]. URL:http://www.ons.gov.uk/ons/rel/vsob1/mortality-statistics--deaths-registered-in-england-and-wales--series-dr-/2011/stb-deaths-registered-in-england-and-wales-in-2011-by-cause.html.

27 *Interim life tables, England and Wales, 2009-2011 [webpage on the Internet].* London: UK Office for National Statistics; 2013 [accessed April 2015]. URL:http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2009-2011/stb-2009-2011.html.

28 Slot KB, Berge E, Dorman P, Lewis S, Dennis M, Sandercock P et al. Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. *BMJ* 2008;**336**:376-9.

29 Spackman E, Burch J, Faria R, Corbacho B, Fox D, Woolacott N. *Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: Evidence Review Group Report [document on the Internet].* London: National Insititute for Health and Care Excellence; 2011 [accessed April 2015]. URL: http://guidance.nice.org.uk/TAG/231/Consultation/EvaluationReport/EvidenceReviewGroupReport/pdf/English.

30 *TA249 Atrial fibrillation - dabigatran etexilate: costing template [spreadsheet on the Internet].* London: National Institute for Health and Care Excellence; 2012 [accessed April 2015]. http://guidance.nice.org.uk/TA249/CostingTemplate/xls/English.

31 *Atrial fibrillation: NICE clinical guideline 36 [document on the Internet].* London: National Insititute for Health and Care Excellence; 2006 [accessed April 2015]. URL: http://guidance.nice.org.uk/CG36/NICEGuidance/pdf/English.

32 Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press; 2005.

33 Fitzmaurice DA, Murray ET, McCahon D, Holder R, Raftery JP, Hussain S et al. Self management of oral anticoagulation: randomised trial. *BMJ* 2005;**331**:1057.

34 Jowett S, Bryan S, Murray E, McCahon D, Raftery J, Hobbs FD et al. Patient self-management of anticoagulation therapy: a trial-based cost-effectiveness analysis. *Br J Haematol* 2006;**134**:632-9.

35 Jones M, McEwan P, Morgan CL, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. *Heart* 2005;**91**:472-7.

36 Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. *Health Technol Assess* 2007;**11(38)**:

37 Murray E, Fitzmaurice D, McCahon D, Fuller C, Sandhur H. Training for patients in a randomised controlled trial of self management of warfarin treatment. *BMJ* 2004;**328**:437-8.

38 Saka O, McGuire A, Wolfe C. Cost of stroke in the United Kingdom. *Age & Ageing* 2009;**38**:27-32.

39 Wardlaw JM, Chappell FM, Stevenson M, De NE, Thomas S, Gillard J et al. Accurate, practical and cost-effective assessment of carotid stenosis in the UK. *Health Technol Assess)* 2006;**10(30)**.

40 *Venous thromboembolism - reducing the risk: NICE clinical guideline 92*. London: National Insititute for Health and Care Excellence; 2010 [accessed October 2013]. http://guidance.nice.org.uk/CG92/NICEGuidance/pdf/English.

41 Hallan S, Asberg A, Indredavik B, Wideroe TE. Quality of life after cerebrovascular stroke: a systematic study of patients' preferences for different functional outcomes. *J Intern Med* 1999;**246**:309-16.

42 Dorman P, Dennis M, Sandercock P. Are the modified "simple questions" a valid and reliable measure of health related quality of life after stroke? United Kingdom Collaborators in the International Stroke Trial. *J Neurol Neurosurg Psychiat* 2000;**69**:487-93.

43 The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet* 1997;**349**:1569-81.

44 Kind P, Hardman G, Macran S. *UK populatioon norms for EQ-5D [document on the Internet]*. University of York: Centre for Health Economics; 1999 [accessed April 2015].

URL:http://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf.

45 Robinson A, Thomson R, Parkin D, Sudlow M, Eccles M. How patients with atrial fibrillation value different health outcomes: a standard gamble study. *J Health Serv Res Policy* 2001;**6**:92-8.

46 Sullivan PW, Arant TW, Ellis SL, Ulrich H. The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. *Pharmacoeconomics* 2006;**24**:1021-33.

47 Briggs A, Sculpher M, Claxton K. *Decision modelling for health economic evaluation.* Oxford: Oxford University Press; 2006.

Appendix 3 Selection process

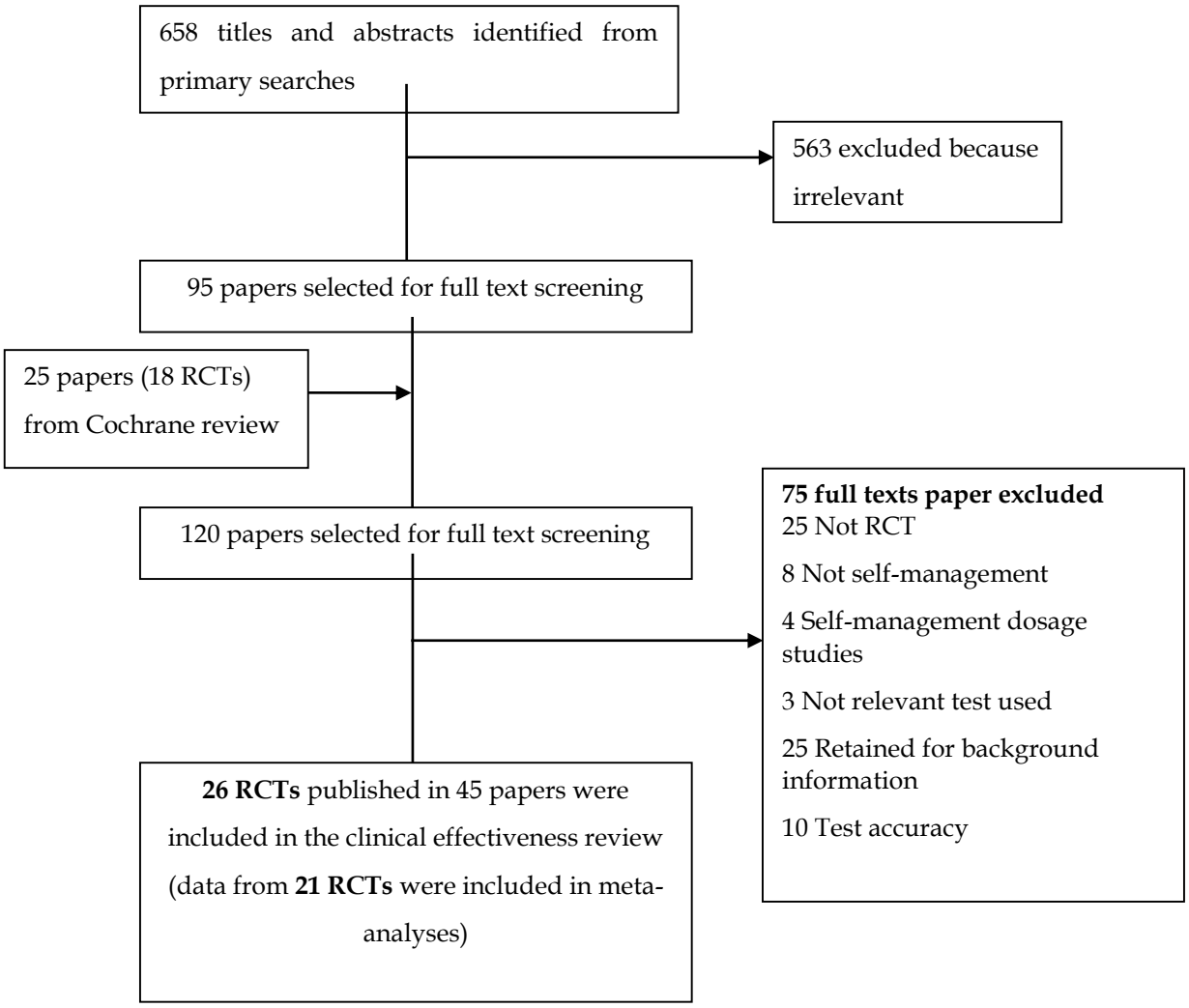


Figure S1 Flow diagram outlining the selection process

Appendix 4 Characteristics and 'risk of bias' assessment of the included studies

Table S1 Characteristics of the included studies

Study ID	Geographical location	SM	Study duration, months	Sample size, n		Mean age (range) SM/ SC	Point-of-care test	SC	Clinical indication				VKA used	Funding
				PSM/ PST	SC				AF %	AHV %	VTE %	other %		
Azarnoush 2011	France	PST	49 weeks*	103	103	55.1/57.5	CoaguChek S & INRatio	AC clinic/ GP		100			Fluindione, Acenocoumarol	Partly industry
Bauman 2010	Canada	PSM	12	14/ 14	-	$10 (1-19)	CoaguChek XS	PST within AC clinic		50		50	Warfarin	Non-industry
Christensen 2006	Denmark	PSM	6	50	50	NR (adult)	CoaguChek S	AC (7%)/ or GP (93%)	24	35	8	33	Warfarin, Phenprocoumon	Non-industry
Christensen 2011	Denmark	PST	~10.8*	91	49	62.5 (21-86)/ 66.0 (49-82)	CoaguChek XS	AC clinic	54	13.4	17	25.6	Warfarin	Non-industry
Cromheecke 2000	Netherlands	PSM	6	50	50	42 (22-71)	CoaguChek	Thrombosis service		46	30	24	Acenocoumarol, Phenprocoumon	NR
Eitz 2008	Germany	PSM	24	470	295	56.4/62.4	CoaguChek S	GP		100			Warfarin	NR
Fitzmaurice 2002	UK	PSM	6	23	26	63/69	CoaguChek S	GP	55	NR	NR	NR	Warfarin	Partly industry
Fitzmaurice 2005	UK	PSM	12	337	280	65 (18-87)	CoaguChek S	Hospital or practice based AC clinics	NR	NR	NR	NR	Warfarin	Non-industry

Gadisseur 2003	Netherlands	PST and PSM	24.4 weeks*	47/ 52	221	54.35 (24-75) /59 (21-75)	CoaguChek	AC clinic	21.2	19.1	20.3	39.4	Acenocoumarol, phenprocoumon	Partly industry
Gardiner 2005	UK	PST	6	44	40	57.9 (26-83)/ 58.4 (31-75)	CoaguChek S	AC clinic	27.4	30	28.6	14	Warfarin	Partly industry
Gardiner 2006	UK	PSM	6	55/ 49	--	59.0 (30-85)/ 60.9 (22-88)	CoaguChek S	PST	40.4	23.1	19.2	17.3	Warfarin	Partly industry
Hemkens 2008	Germany	PSM	14 weeks	16		65.8	CoaguChek S & INRatio	AC clinic	38		31	31.3	Phenprocoumon	Non-industry
Horstkotte 1996	Germany	PSM	40607 patient days	75	75	NR	CoaguChek	Private physician		100			NR	Non-industry
Khan 2004	UK	PST	6	44	41	$71(65-91)/ 75(65-87)	CoaguChek	AC clinic	100				Warfarin	Non-industry
Koertke 2001	Germany	PSM	24	579	576	62.5	CoaguChek plus	Family practitioner		100			NR	NR
Matchar 2010	US	PST	36* (24-57)	146 5	1457	66.6 (23-89)/ 67.4(33-99)	ProTime microcoagulation	AC clinic (high quality)	76.5	23.4		0.1	Warfarin	Partly industry
Menendez-Jandula 2005	Spain	PSM	11.8** (0.3-16.9)	368	369	64.5/65.5	CoaguChek S	AC clinic	50.3	37.2	12.5		Acenocoumarol	Partly industry
Rasmussen 2012	Denmark	PSM	28* weeks	37	17	$68-70/69	CoaguChek S	Specialist clinic	NR	NR	NR	NR	Warfarin	Non-industry
Ryan 2009	Ireland	PST	6	72	60	58.7 (16-91)	CoaguChek XS	AC service	32.6	37.1	22	8.3	Warfarin	Partly industry

Sawicki 1999	Germany	PSM	6	90	89	55.0	CoaguChek	Hospital outpatient or family practitioner	5	84.4			Phenprocoumon	Industry
Sidhu 2001	UK	PSM (51)	24	51	49	61 (32-85)	CoaguChek	GP or AC clinic		100			Warfarin	Industry
Siebenhofer 2008	Austria	PSM	~36*	99	96	69/69	CoaguChek S	GP or specialised AC clinic	45.6	16.4	28.7	9.2	Phenprocoumo, acenocoumarol	Industry
Soliman Hamad 2009	Netherlands	PSM	12	29	29	56.3/55.7	CoaguChek	Thrombosis Service		100			NR	NR
Sunderji 2004	Canada	PSM	8	70	70	57.6 (20-79)/ 62.3 (24-85)	ProTime Microcoagulation	GP	34	59	5	2	Warfarin	Non-industry
Verret 2012	Canada	PSM	4	58	56	58.4/57.0	CoaguChek XS	AC clinic	51	42		7	Warfarin	Partly industry
Voller 2005	Germany	PSM	~5*	101	101	64.3 (9.2)	CoaguChek	Family doctor	100				NR	Partly industry

* Mean study duration, ** Median study duration, $ median age

Note: Kortke 2001: All participants report including 1200 participants published in German; preliminary reports of 600 participants published in English. Cross-over trials: Ryan 2009, Hemkens 2008, Cromheecke 2000, Eitz 2008

AC: anticoagulant; AF: atrial fibrillation; AHV: artificial heart valves; GP: general practitioner; PSM: patient self-management; PST: patient self-testing; SC: standard care; SM: self-monitoring;

Table S2 Details of the risk of bias assessment for the individual included studies

Study ID	*Adequate sequence generation	*Allocation concealment	*Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective reporting	Other sources of bias	Dropout rates %		ITT performed	Overall judgement
							SM	SC		
Azarnoush 2011	Unclear RoB	Unclear RoB	Low RoB	High RoB	Low RoB	Low RoB	13	1	NR	Unclear RoB
Bauman 2010	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	14	0	Yes	Low RoB
Christensen 2006	Low RoB	High RoB	High RoB	Low RoB	Low RoB	Low RoB	2	2	Yes	High RoB
Christensen 2011	Low RoB	Unclear RoB	High RoB	High RoB	Low RoB	Low RoB	9	18	NR	High RoB
Cromheecke 2000	Unclear RoB	Low RoB	Unclear RoB	Low RoB	High RoB	Low RoB	2	0	NR	Unclear RoB
Eitz 2008	Unclear RoB	Unclear RoB	Unclear RoB	Low RoB	Low RoB	Low RoB	0	0	NR	Unclear RoB
Fitzmaurice 2002	Low RoB	Unclear RoB	Unclear RoB	High RoB	Low RoB	Low RoB	23.3	0	NR	Unclear RoB
Fitzmaurice 2005	Low RoB	Low RoB	Unclear RoB	Low RoB	Low RoB	Low RoB	41.5	10	Yes	Unclear RoB
Gadisseur 2003	Low RoB	Unclear RoB	Unclear RoB	High RoB	Low RoB	Low RoB	13.6		NR	Unclear RoB
Gardiner 2005	Unclear RoB	Unclear RoB	Unclear RoB	High RoB	Low RoB	Low RoB	31.8	2.5	NR	Unclear RoB
Gardiner 2006	Unclear RoB	Unclear RoB	Unclear RoB	High RoB	Low RoB	Low RoB	26	-	NR	Unclear RoB
Hemkens 2008	Low RoB	Low RoB	Unclear RoB	High RoB	Low RoB	Low RoB	12		NR	Unclear RoB
Horstkotte 1996	Unclear RoB	Unclear RoB	Unclear RoB	Low RoB	Low RoB	Low RoB	NR	NR	NR	Unclear RoB
Khan 2004	Low RoB	Unclear RoB	Unclear RoB	Low RoB	Low RoB	Low RoB	9.1	4.9	NR	Unclear RoB
Kortke 2001	Low RoB	Unclear RoB	Unclear RoB	Unclear RoB	Low RoB	Low RoB	NR	NR	NR	Unclear RoB
Matchar 2010	Low RoB	Unclear RoB	High RoB	Low RoB	Low RoB	Low RoB	<1	<1	Yes	High RoB
Menendez-Jandula 2005	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	21.5	2.4	Yes	Low RoB
Rasmussen 2012	Low RoB	Unclear RoB	Low RoB	Unclear RoB	High RoB	Low RoB	NR	NR	NR	Unclear RoB
Ryan 2009	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	0	0	NR	Low RoB
Sawicki 1999	Low RoB	Unclear RoB	Low RoB	Low RoB	Low RoB	Low RoB	7.8	7.8	Yes	Unclear RoB
Sidhu 2001	Low RoB	Unclear RoB	Unclear RoB	High RoB	Low RoB	Low RoB	31.4	2	NR	Unclear RoB
Siebenhofer 2008	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	16	23	Yes	Low RoB
Soliman Hamad 2009	Unclear RoB	Unclear RoB	Unclear RoB	Low RoB	High RoB	Low RoB	6.4		NR	Unclear RoB
Sunderji 2004	Low RoB	Low RoB	High RoB	Low RoB	Low RoB	Low RoB	24.6	4.3	Yes	High RoB

Study ID	*Adequate	*Allocation	*Blinding of	Incomplete	Free of	Other	Dropout rates %		ITT	Overall
Verret 2012	Low RoB	Unclear RoB	High RoB	Low RoB	Low RoB	Low RoB	~2	0	NR	High RoB
Voller 2005	Low RoB	Unclear RoB	High RoB	Low RoB	Low RoB	Low RoB	NR	NR	Yes	High RoB

*Key domain
ITT: intention to treat; NR: not reported; RoB: risk of bias; SM: self-monitoring; SC: standard care;

Appendix 5 Sensitivity analysis

Table S3 Deterministic sensitivity analysis

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER
1. Self-monitoring (50-50 split between self-testing and self-management) versus standard care, but applying pooled relative risk estimates for all self-monitoring as a whole					
Standard monitoring	£7,324	-	5.479	-	-
Self-monitoring	£6,790	-£582	5.534	0.054	Dominant
2. 60% of self-monitoring patients self-test, 40% self-manage					
Standard monitoring	£7,324	-	5.479	-	-
Self-monitoring	£7,512	£188	5.502	0.022	£8,401
3. 40% of self-monitoring patients self-test, 60% self-manage					
Standard monitoring	£7,324	-	5.479	-	-
Self-monitoring	£7,140	-£184	5.513	0.033	Dominant
4. Baseline risk of thromboembolic events set at 1.15%					
Standard monitoring	£5,999	-	5.537	-	-
Self-monitoring	£6,245	£246	5.554	0.017	£14,089
5. Relative risk for thromboembolic events associated with self-management = 0.69 (self-testing 0.99 as per base case)					
Standard monitoring	£7,324	-	5.479	-	-
Self-monitoring	£7,595	£271	5.495	0.016	£16,702

6. Relative risk for thromboembolic events associated with self-monitoring as a whole = 0.84 (applied to self-testing and self-management)					
Standard monitoring	£7,324	-	5.479	-	-
Self-monitoring	£7,583	£259	5.496	0.017	£15,350
7. Baseline risk of thromboembolic events 1.15%, relative risk associated with self-management 0.69					
Standard monitoring	£5,999	-	5.537	-	-
Self-monitoring	£6,427	£428	5.546	0.010	£45,012
8. Baseline risk of thromboembolic events 1.15%, relative risk associated with self-monitoring as a whole = 0.84 (applied to self-testing and self-management)					
Standard monitoring	£5,999	-	5.537	-	-
Self-monitoring	£6,419	£419	5.547	0.010	£42,086
9. Cost-effectiveness over a 20 year time horizon					
Standard monitoring	£13,417	-	7.635	-	-
Self-monitoring	£13,043	-£374	7.712	0.077	Dominant
10. Cost effectiveness over a 30 year time horizon					
Standard monitoring	£14,300	-	8.054	-	-
Self-monitoring	£13,922	-£378	8.157	0.104	Dominant

Table S4 Cost-minimisation scenarios assuming of no difference in the number of monitoring tests or clinical effectiveness between patient self-monitoring and standard monitoring

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER
1. Self-monitoring (50% self-test, 50% self-manage) with no increase in number of tests performed compared to standard care (66% primary care, 34% secondary care)					
Standard monitoring	£7,324	-	5.479	-	-
Self-monitoring	£7,457	£133	5.479	0	Dominated
2. 100% self-test with no increase in the number of tests performed compared to standard care (66% primary care, 34% secondary care)					
Standard monitoring	£7,324	-	5.479	-	-
Self-monitoring	£7,498	£174	5.479	0	Dominated
3. 100% self-manage with no increase in number of tests performed compared to standard care (66% primary care, 34% secondary care)					
Standard monitoring	£7,324	-	5.479	-	-
Self-monitoring	£7,417	£93	5.479	0	Dominated
4. 100% self-test with no increase in number of tests performed compared to standard monitoring in secondary care					
Standard monitoring	£7,704		5.479	0	-
Self-monitoring	£7,672	-£32	5.479	0	Dominant
5. 100% self-manage with no increase in number of tests performed compared to standard monitoring in secondary care					
Standard monitoring	£7,704		5.489	0	-
Self-monitoring	£7,592	-£112	5.489	0	Dominant