The 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

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Contributions of authors

Pawana Sharma and Moira Cruickshank (Research Fellows) screened the search results, assessed full text studies for inclusion, and undertook data extraction and quality assessment with assistance from Miriam Brazzelli (Senior Research Fellow). Pawana Sharma reviewed the evidence on the clinical effectiveness of the target interventions. Emma Tassie (Research Assistant) reviewed the evidence on the cost-effectiveness of the target interventions and contributed to the economic evaluation under the supervision of Graham Scotland (Senior Health Economist). Graham Scotland developed the economic model and conducted the

economic evaluation. Chris Burton (Senior Lecturer in Primary Care) and Bernard Croal (Director of Laboratory Services) provided expert advice on the clinical aspects of this appraisal. Cynthia Fraser (Senior Information Specialist) developed and ran the literature searches and provided information support to the appraisal. Miriam Brazzelli oversaw and co-ordinated all aspects of this appraisal. Craig Ramsay (Health Care Assessment Programme Director) jointly co-ordinated the appraisal and commented on an early draft of this report. All authors commented on the final report.

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DEFINITION OF TERMS/LIST OF ABBREVIATIONS

AC	Anticoagulant
AHV	Artificial heart valves
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CTEPH	Chronic thromboembolic pulmonary hypertension
DASS	Duke anticoagulation satisfaction scale
DVT	Deep vein thrombosis
EQ5D	European quality of life 5 dimensions
HUI	Health utilities index
INR	International normalized ratio
IQR	Inter quartile range
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NS	Non-significant
OAT	Oral anticoagulation treatment
PE	Pulmonary embolism
PSM	Patient self-management
PST	Patient self-testing
PTS	Post thrombotic syndrome
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk
SC	Standard care
SD	Standard deviation
SEIQoL	Schedule for evaluation of individual quality of life
SEM	Standard error of mean
SF-36	Short form health survey
SIGN	Scottish Intercollegiate Guidelines Network
SM	Self-monitoring
TTR	Time in therapeutic range
UKHVR	United Kingdom heart valve registry
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WMD	Weighted mean difference

1 EXECUTIVE SUMMARY

1.1 Background

There are increasing numbers of people with atrial fibrillation, heart valve disease, or other cardiac conditions who are at high risk of thrombosis, requiring long-term oral anticoagulation therapy (OAT). It is estimated that 1.4% of the population in the UK requires treatment with OAT. The goal of OAT, generally with warfarin (a type of vitamin K antagonist), is to establish a balance between bleeding and clotting. Under-anticoagulation increases the risk of thromboembolism while over-anticoagulation increases the risk of haemorrhage; hence treatment with warfarin requires frequent monitoring. The blood coaguability of people taking warfarin is monitored by the use of the international normalized ratio (INR) which is a standardised unit for measuring the time it takes for blood to clot. As standard practice, warfarin monitoring is managed by health care professionals in anticoagulant clinics based in hospitals using laboratory testing or managed in primary care (with or without the use of laboratory services). The other option for warfarin monitoring is the use of a personal testing machine at home (known as a point-of-care test) which allows people to perform self-testing (when people perform the test themselves and the results of the test are managed by healthcare professionals) or self-management (when people perform the test and alter the dose of anticoagulation therapy themselves according to a personalised protocol). Self-testing and self-management are together referred to as self-monitoring. Self-monitoring is considered as one of the options for warfarin monitoring in the NHS, but there is limited evidence on its effectiveness compared with other ways of delivering services.

1.2 Objectives

This assessment investigates the clinical effectiveness and cost-effectiveness of point-of-care coagulometers for the self-monitoring of coagulation status in people receiving long-term vitamin K antagonist therapy. CoaguChek system (both the S and XS models), INRatio2 PT/INR monitor and ProTime Microcoagulation system coagulometers are being considered in this assessment as an alternative to standard UK anticoagulation therapy services.

1.3 Methods

Clinical effectiveness

Comprehensive electronic searches were undertaken to identify relevant reports of published studies up to May 2013. Evidence was considered from randomised controlled trials (RCTs) evaluating the point-of-care tests under consideration for the self-monitoring of anticoagulation therapy. The population were those with atrial fibrillation or heart valve disease for whom long-term vitamin K antagonist therapy was intended. Self INR monitoring supervised by primary or secondary care using

CoaguChek system (both the S and XS models), INRatio2 PT/INR monitor or ProTime Microcoagulation system were considered in this assessment. The comparator considered was standard clinical practice, which consisted of INR monitoring managed by healthcare professionals in primary care, in secondary care or in a "shared provision" setting.

Data on clinical outcomes, intermediate outcomes and patient-reported outcomes were extracted from the included studies. Dichotomous and continuous data (when possible) were meta-analysed as pooled summary effect sizes using standard inverse variance methods. Apart from the pre-specified subgroup analysis according to the type of anticoagulation therapy management (self-testing and self-management), post-hoc subgroup analyses according to the type of the target clinical condition (i.e. atrial fibrillation, heart valve disease, and mixed clinical indication) and according to the type of service provision for anticoagulation management (i.e. primary care, secondary care, and shared provision) were performed. A post-hoc sensitivity analysis by excluding the studies conducted in the UK was performed. Risk of bias assessment for all included RCTs was performed using the Cochrane Risk of Bias tool.

Cost-effectiveness

A review of existing economic evaluations identified 12 studies of potential relevance to the scope of this assessment. These studies demonstrated mixed results with respect to the cost-effectiveness of self-testing or self-management strategies versus standard primary or secondary care monitoring. Only two studies were directly relevant to the NHS setting, and none addressed all the comparisons set out in the scope for this assessment.

A de novo economic model was developed in TreeAge Pro (TreeAge Software, Williamstown, MA, 2013) to assess the cost-effectiveness of INR self-monitoring (self-testing and self-management) versus standard primary or secondary care clinic monitoring. The alternative point-of-care devices considered for self-monitoring were: CoaguChek XS system; INRatio2 PT/INR monitor; and ProTime Microcoagulation system.

The model simulated the occurrence of thromboembolic and bleeding events over a ten-year period for a cohort of people on long-term vitamin K antagonist therapy. Indications for vitamin K antagonist therapy included atrial fibrillation and artificial heart valves. Baseline risks of events for people with the different underlying conditions (under standard monitoring) were derived from a focused review of existing literature, and the relative effects of self-testing and self-management on these events were derived from the meta-analysis of existing randomised controlled trials. Other parameters including cost and utility inputs were derived from focused literature searches, previous economic models, and routine data sources.

1.4 Results

Clinical effectiveness

In total, 26 RCTs (published in 45 papers) were included in the clinical effectiveness review with mean sample size of 337 participants (range 16 to 2922). Primary analyses were based on data from 21 out of the 26 included trials relevant to the comparisons and outcomes of interest. The majority of trials (85%) investigated the use of the CoaguChek system including model 'XS' (n=414 in four trials), model 'S'/CoaguChek (n=3910 in 17 trials), and CoaguChek Plus (n=1155 in one trial) for the self-monitoring of anticoagulation therapy. Two trials utilised both CoaguChek and INRatio together (n=222) while other two trials utilised ProTime (n=3062). No trials that exclusively assessed the clinical effectiveness of INRatio were identified.

Only four trials were judged at low risk of bias. Three of these trials used either the CoaguChek model 'S' or the model 'XS' for INR measurement while the other trial used CoaguChek XS to measure INR in children.

The results of this assessment indicate that self-monitoring (self-testing or self-management) of anticoagulation therapy leads to significantly fewer thromboembolic events (RR 0.58, 95% CI 0.40 to 0.84, p=0.004) compared with standard primary care or anticoagulation control in specialised clinics. Self-monitoring (self-testing and self-management) did not demonstrate a significant reduction in the number of major and minor bleeding events compared with standard care (RR 0.95, 95% CI 0.74 to1.21, p=0.66). In people with artificial heart valves, self-monitoring almost halved the risk of thromboembolic events (RR 0.56, 95% CI 0.38 to 0.82, p=0.003) and all-cause mortality (RR 0.54, 95% CI 0.32 to 0.92, p=0.02). There was greater reduction in thromboembolic events and all-cause mortality through self-management but not through self-testing. Fewer thromboembolic events were observed among people who self-monitored their therapy compared with those who were managed by their GPs or physicians but not compared with those managed in specialised anticoagulation clinics. The subgroup analysis was not, however, statistically significant.

While no significant differences were found between self-management and standard care for time in therapeutic range (WMD 0.47, 95% CI -1.40 to 2.34, p=0.62), self-testing showed a modest but significantly higher percentage of time in therapeutic range compared with standard care (WMD 4.44, 95% CI 1.71 to 7.18, p=0.02). None of the UK-based trials showed significant difference between self-monitoring and standard care for major complications, deaths or anticoagulation control. Improvements in quality of life in the self-monitoring group were only observed in non-UK based trials.

Cost effectiveness

Self-monitoring (50% self-testing, 50% self-management) was found to increase the INR monitoring costs compared to standard primary/secondary care monitoring. The incremental monitoring costs (incorporating training costs and annuitized device cost) associated with self-monitoring over the ten-year period were £639, £675, and £1923 with INRatio2, CoaguChek XS and ProTime Microcoagulation System respectively. However, applying the pooled relative risks of adverse events to people completing training and continuing with self-monitoring, it was estimated that the cumulative incidence of thromboembolic events at ten years would be 2.4% lower than with standard monitoring. This in turn resulted in quality of life gains and future cost-savings associated with acute and long-term care. Thus, the difference in net health and social care costs was less pronounced after ten years: £7,295 (self-monitoring with INRatio2); £7,324 (standard primary/secondary care monitoring); £7,333 (self-monitoring with CoaguChek XS); and £8,609 (self-monitoring with ProTime). The estimated QALY gain associated with self-monitoring at ten years was 0.03. Assuming the benefits of self-monitoring applied equally to all point-of-care devices, self-monitoring with INRatio2 dominated standard monitoring under the base case assumptions. The incremental cost-effectives ratio for CoaguChek XS and ProTime versus standard monitoring was £319 and £47,604 per QALY gained respectively. Within the base case analysis, self-testing alone was not found to be cost-effective (due to its higher cost and small non-significant effect on thromboembolic events), whilst self-management was found to be less costly and more effective than standard monitoring.

Deterministic sensitivity analysis indicated that the cost-effectiveness results were most sensitive to the estimated effects of self-monitoring on thromboembolic events. Applying relative risks obtained from UK trials only, self-monitoring was not found to be cost-effective at the testing frequency observed in these clinical trials. Self-monitoring with INRatio2 and CoaguChek XS was found to be slightly less costly than standard secondary care monitoring when there was no increase in testing frequency (with no difference in effects assumed), but this finding was sensitive to several other costing assumptions. Applying the based case assumptions, self-monitoring with CoabuCheck XS or INRatio2 had ~80% chance of being cost-effective at a threshold ratio of £20,000 per QALY gained.

Discussion

The included trials varied considerably in terms of clinical indications for anticoagulation therapy, type of control care, reporting structure for the time and/or values in therapeutic range, type and structure of the pre-intervention training and education programme, length of follow up, and methodological study quality. Whilst the meta-analysis results demonstrated low statistical heterogeneity there remains uncertainty that clinical heterogeneity may have over or underestimated the effects. Only limited data were available for people with atrial fibrillation and consequently no reliable conclusions could be drawn in relation to this patient population. The majority of trials

investigated the use of the CoaguChek system for the self-monitoring of anticoagulation therapy and it proved unfeasible to conduct reliable comparisons according to the type of point-of-care device. While the CoaguChek device appears to have the most robust evidence, ProTime and, particularly, INRatio do not.

Generalisability of the findings

All included trials enrolled highly selected samples of people requiring anticoagulation therapy, and so it was uncertain whether there was strong external validity (i.e. applicability of the study results to the entire population of eligible participants). There remains some uncertainty on the applicability of the pooled results to the UK population. In our view, the greatest uncertainty relates to the applicability of the standard care comparators in the trials and not to the participants in the trial.

Conclusions

Based on available evidence, our findings suggest that self-monitoring using point-of-care devices by people at home compared with standard care, is safe and effective for anticoagulation control, especially for people with artificial heart valves. Self-monitoring, and in particular self-management, of anticoagulation status appeared cost-effective when pooled estimates of clinical effectiveness were applied. However, if self-monitoring does not result in significant reductions in thromboembolic events, it is unlikely to be cost-effective from the NHS and personal social services perspective, based on a comparison of annual monitoring costs alone.

The base case cost-effectiveness results are most applicable to self-monitoring strategies using CoaguChek XS. The majority of clinical effectiveness evidence related to a previous version of Coaguchek (CoaguChek S), to which the current version (Coaguchek XS) has been shown to have very similar or slightly superior performance in terms of accuracy and precision.

Implications for research

Trials investigating the longer term outcomes of self-management are needed, and direct comparisons of the various point-of-care coagulometers ought to be incorporated into any future evaluation. The technology related to point-of-care testing devices is constantly changing and future research needs to target larger cohorts of people requiring long-term anticoagulation therapy who may benefit from the use of these new generations of devices.

2 BACKGROUND AND DEFINITION OF THE DECISION PROBLEM(S)

2.1 Conditions and aetiologies

Brief statement describing the health problem

People with certain clinical conditions such as atrial fibrillation or heart valve disease are at high risk of thrombosis (blood clot). Untreated, these may lead to thromboembolism affecting the brain (causing a stroke), the lungs (pulmonary embolism), or other parts of the body. Many people with these conditions are required to take lifelong blood thinning drugs (called vitamin K antagonists) to avoid the risks associated with thrombosis. The treatment of people with blood thinning drugs is termed anticoagulant therapy and it is estimated that 1.4% of the population in the UK require anticoagulant therapy.[1]

Warfarin is the most common vitamin K antagonist drug given to prevent clot formation and stroke. However, serious side effects including bleeding or stroke can result from people being on the wrong dose of warfarin (over- or under- dosing). Therefore it is necessary to ensure that people taking warfarin have ongoing monitoring of their blood coaguability.

Epidemiology and prevalence

There are increasing numbers of people with atrial fibrillation, heart valve replacement, or other clinical conditions requiring long-term oral anticoagulation therapy (OAT).[2] As up to 60% of people with atrial fibrillation may be undiagnosed, screening programs have the potential to increase diagnoses and associated use of OAT.[3] The prevalence of atrial fibrillation has recently been described as "approaching epidemic proportions"[4] and it has been predicted that, by 2050, more than 5.6 million adults in the USA will be diagnosed with atrial fibrillation as compared to 2.3 million in 2001.[5] Increased use of OAT has intensified pressure upon resources, with some haematology services becoming unable to cope.[6]

Atrial fibrillation

In the USA, prevalence of atrial fibrillation has been reported as 0.1% in adults under 55 years of age and 9% in those at least 80 years old.[5] Over 6 million people in Europe have atrial fibrillation[7] and a recent Swedish study reported prevalence of 2.9% in adults older than 20 years.[8] Atrial fibrillation is the most common heart arrhythmia and affects around 800,000 people in the UK, or 1.3% of the population.[9] Prevalence increases with age, affecting 0.5% of people aged 50-59 years and around 8% of people aged over 65 years.[10] Atrial fibrillation is more likely to affect men than women and is more common in people with other conditions, for example, high blood pressure, atherosclerosis or other heart conditions, such as heart valve problems. For people with atrial fibrillation, there is a 5 times

higher risk of stroke and a 3 times higher risk of congestive heart failure.[11] One-fifth of all strokes are as a result of atrial fibrillation.[7] An average proportion of 47% of people with atrial fibrillation currently receive anticoagulation therapy, such as warfarin.[1]

Heart valve disease

Aortic stenosis is the most common type of heart valve disease. It affects one in 20 adults over the age of 65[12,13]. Data from the UK heart valve registry (UKHVR) indicate that approximately 0.2% of the UK population has prosthetic heart valves. Around 6,500 adult heart valve replacements (using mechanical or biological valves) are carried out each year, of which around 5,000 are aortic valve replacements.[14,15]

Impact of health problem: significance for the NHS and burden of disease

The blood coaguability of people taking warfarin is monitored by the use of the international normalized ratio (INR) which is a standardised unit for measuring the time it takes for blood to clot. INR monitoring can be delivered using various options in the NHS. The options include INR monitoring managed by health care professionals in anticoagulant clinics based in hospitals using laboratory testing or managed in primary care (with or without the use of laboratory services). The use of a personal INR testing machine at home (known as a point-of-care test) allows people to perform self-testing (when people perform the test themselves and the results of the test are managed by healthcare professionals) or self-management (when people perform the test and alter the dose of anticoagulation therapy themselves according to a personalised protocol). Self-testing and self-management are together referred as self-monitoring. Self-monitoring is considered as one of the options for INR monitoring in the NHS, but there is limited evidence on the effectiveness compared to other ways of delivering services.

It is believed that the use of point-of-care coagulometers for self-monitoring may avoid unnecessary visits to hospitals while allowing regular INR monitoring and timely adjustment of warfarin dosing to avoid adverse events. For people requiring monitoring of their coagulation status this may result in better quality of life.[16]

Measurement of disease

The goal of anticoagulant therapy is to establish a balance between bleeding and clotting[17] and it is desirable for people on warfarin to remain within a narrow INR therapeutic range, generally between 2.0 and 3.0.[18,19] If the dose of anticoagulation therapy is too low (under-anticoagulation), the risk of thromboembolism increases, while if it is too high (over-anticoagulation) the risk of haemorrhage increases. Individuals reactions to warfarin vary according to modifiable (e.g. diet) and non-modifiable factors (e.g. age, concomitant diseases). Adequate control of INR is necessary to avoid

serious complications such as stroke. Therefore, repeated and regular measurements of INR are required to allow adjustments to size and/or frequency of dosage.[20]

2.2 Description of technologies under assessment

Summary of point-of-care tests

Point-of-care devices for measuring coagulation status in people receiving long-term vitamin K antagonist therapy allow both self-testing and self-management, defined as follows:

- Self-testing: point-of-care test carried out by the patient with test results managed by their healthcare provider (e.g. general practitioner, nurse, specialised clinic).
- Self-management: point-of-care test carried out by trained patient, followed by interpretation of test result and adjustment of dosage of anticoagulant according to a pre-defined protocol.

Self-testing and self-management are together referred to as *self-monitoring* for the purposes of this report.

The purpose of this assessment was to appraise the current evidence for the clinical effectiveness and cost-effectiveness of self-monitoring (self-testing and self-management) using either the **CoaguChek** system (Roche Diagnostics, Basel, Switzerland), the **INRatio**2 PT/INR monitor, (Alere Inc., San Diego CA, USA) or the **ProTime** Microcoagulation system (International Technidyne Corporation, ITC - Nexus Dx, Edison, NJ, USA) compared with standard clinical monitoring in people with atrial fibrillation or heart valve disease for whom long-term vitamin K antagonist therapy is indicated.

All these point-of-care devices, which are currently available for use in the NHS, are CE marked and FDA approved. Point-of-care instruments work basically in the same way: a drop of capillary whole blood is obtained by a finger puncture device, applied to a test strip and inserted into a coagulometer. However, they differ in terms of methods of clot detection and general operational functions.

Summary of CoaguChek system

The CoaguChek system is a point-of-care testing device developed by Roche Diagnostics and measures prothrombin time and INR (the globally recommended unit for measuring thromboplastin time) in people on oral anticoagulation (VKA) therapy. A low INR indicates an increased risk of blood clots, while a high INR indicates an increased risk of bleeding events. CoaguChek S and CoaguChek XS devices are intended for patient self-monitoring. The CoaguChek XS model comprises a meter and specifically designed test strips for blood sample analysis (fresh capillary or untreated whole venous blood). The CoaguChek XS system purports to have the following advantages over the CoaguChek S: i) the thromboplastin used in the prothrombin time test strips is a human

recombinant thromboplastin, which is more sensitive and has a lower ISI of 1.0 compared to 1.6; ii) test strips have onboard quality control that is automatically run with every test, rather than having to perform external quality control; iii) test strips do not have to be refrigerated; iv) a smaller blood sample can be used; v) the meter is smaller and lighter. The CoaguChek XS Plus is an upgraded XS model aimed primarily at healthcare professionals, which is suitable for home testing and possesses additional features to the XS system including increased storage and connectivity for data management.

Summary of INRatio2PT/INR monitor

The INRatio2 PT/INR monitor performs a modified version of the one-stage prothrombin time test using a recombinant human thromboplastin reagent. The clot formed in the reaction is detected by the change in the electrical impedance of the sample during the coagulation process. The system consists of a monitor and disposable test strips and the results for prothrombin time and INR are reported.

Summary of ProTime Microcoagulation system

The ProTime Microcoagulation system is designed for measuring prothrombin time and INR. The test is performed in a cuvette which contains the reagents. Two different cuvettes are available depending on the amount of blood that needs to be collected and tested: the standard ProTime cuvette and the ProTime3 cuvette.

Identification of important sub-groups

There are a number of clinical conditions which require long-term vitamin K antagonist therapy to reduce the risk of thrombosis. These conditions include atrial fibrillation and heart valve disease.

Atrial fibrillation

Atrial fibrillation results in unorganised atrial contraction which can lead to blood stagnating in parts of the atria and as a result forming a clot. This clot may then move from the heart causing thromboembolism, most commonly in the brain where it causes stroke. People with atrial fibrillation are at a 5-6 times greater risk of stroke, with 12,500 strokes directly attributable to atrial fibrillation every year in the UK. Treatment with warfarin reduces the risk by 50–70%.[1,21,22]

Artificial heart valves

Valve disease can affect blood flow through the heart in two ways; valve stenosis, where the valve does not open fully, and valve regurgitation (or incompetence), where the valve does not close properly, allowing blood to leak backwards. The most effective treatment for many forms of valve disease is heart valve replacement. Replacement heart valves are either articficial (mechanical) or

from animals (tissue). People with mechanical heart valves generally require long-term anticoagulant treatment to prevent clotting related to the valve.

Current usage in the NHS

The NICE clinical guideline on atrial fibrillation[23] recommends that self-monitoring of INR should be considered for people with atrial fibrillation receiving long-term anticoagulation, if they prefer this form of testing and if the following criteria are met:

- The patient (or a designated carer) is both physically and cognitively able to perform the self-monitoring test;
- An adequate supportive educational programme is in place to train participants and/or carers;
- The patient's ability to self-manage is regularly reviewed;
- The equipment for self-monitoring is regularly checked via a quality control programme.

2.3 Comparators

In UK clinical practice, INR monitoring is currently managed by a range of healthcare professionals including nurses, pharmacists and general practitioners. INR monitoring can be carried out in primary care and secondary care. Primary care anticoagulant clinics use point-of-care tests or laboratory analysers. In the latter, blood samples are sent to a central laboratory based at a hospital ("shared provision"). In the case of secondary care, INR monitoring can be carried out in hospital-based anticoagulant clinics using point-of-care tests or laboratory analysers.

2.4 Care pathways

The clinical population considered for the purpose of this assessment includes people with atrial fibrillation or heart valve disease for whom long-term vitamin K antagonist therapy is intended. According to the NICE clinical guideline on atrial fibrillation and the SIGN clinical guideline on antithrombotics,[23,24] the most effective treatment considered for the treatment of atrial fibrillation is dose-adjusted warfarin, the most common vitamin K antagonist drug. Lifelong anticoagulation therapy with warfarin is also recommended in all people after artificial valve replacement.[25] Warfarin, especially if taken incorrectly, can cause severe bleeding (haemorrhages). Therefore, it is necessary to ensure that people taking warfarin have ongoing monitoring of their blood coaguability.

The routine monitoring of blood coagulation can take several configurations. The NICE anticoagulation commissioning guide[1] states that UK anticoagulation therapy services can be delivered in a number of different ways, and that mixed models of provision may be required across a local health economy. This could include full service provision in primary or secondary care, shared provision, domiciliary provision, or self-management.

This assessment focuses on the role of point-of-care tests (for the self-monitoring of INR by people at home) as an alternative to standard UK anticoagulation care.

2.5 Outcomes

Outcomes of interest for this review were:

Clinical outcomes:

- Frequency of bleeds or blood clots;
- Morbidity (e.g. thromboembolic and cerebrovascular events) and mortality from INR testing and vitamin K antagonist therapy;
- Adverse events from INR testing, false test results, vitamin K antagonist therapy and sequelae.

Patient reported outcomes:

- People anxiety associated with waiting time for results and not knowing their current coagulation status and risk;
- Acceptability of the tests;
- Health-related quality of life.

Intermediate outcomes:

- Time and values in therapeutic range;
- INR values;
- Test failure rate;
- Time to test result;
- Patient compliance with testing and treatment;
- Frequency of testing;
- Frequency of visits to primary or secondary care clinics.

2.6 Overall aim and objectives of this assessment

The aim of this assessment was to appraise the current evidence for the clinical effectiveness and cost-effectiveness of self-monitoring (self-testing and self-management) using CoaguChek, INRatio2 PT/INR monitor and ProTime Microcoagulation system point-of-care devices compared with standard monitoring in people with atrial fibrillation or heart valve disease receiving long-term vitamin K antagonist therapy.

The specific objectives of this assessment were to:

1. Systematically review the evidence on clinical-effectiveness of self-monitoring (self-testing and self-management) using CoaguChek, INRatio2 PT/INR monitor and ProTime Microcoagulation system point-of-care devices, compared with standard monitoring practice, in people receiving long-term vitamin K antagonist therapy;
2. Systematically review existing economic evaluations on self-monitoring technologies for people receiving long-term vitamin K antagonist therapy;
3. Develop a *de novo* economic model to assess the cost-effectiveness of both self-testing and self-management (using CoaguChek XS system, INRatio2 PT/INR monitor and ProTime Microcoagulation system as self-monitoring technologies) versus standard monitoring practice in people receiving long-term vitamin K antagonist therapy.

3 ASSESSMENT DESIGN AND RESULTS – CLINICAL EFFECTIVENESS

3.1 Methods for standard systematic review of effectiveness

An objective synthesis of the evidence for the clinical effectiveness of self-monitoring in people receiving long-term vitamin K antagonist therapy using either CoaguChek system, INRatio2 PT/INR monitor or ProTime Microcoagulation system compared with current standard monitoring practice has been conducted. The evidence synthesis has been carried out according to the general principles of the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care,[26] the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [27] and the indications of the NICE Diagnostics Assessment Programme Manual.[28]

Identification of studies

Comprehensive electronic searches were undertaken to identify relevant reports of published studies. Highly sensitive search strategies were designed using both appropriate subject headings and relevant text word terms, to retrieve randomised controlled trials (RCTs) evaluating the point-of-care tests under consideration for the self-monitoring of anticoagulation therapy. A 2007 systematic review with similar objectives to those of the current assessment was identified in the Cochrane Library.[29] Since extensive literature searches had already been undertaken for the preparation of this systematic review, the literature searches for the current assessment were run in May 2013 for the period '2007-to date' to identify newly published reports. All RCTs included in the Cochrane review were obtained and included for full-text assessment. Searches were restricted to publications in English. MEDLINE, MEDLINE In Process, Embase, Biosis, Science Citation Index, and Cochrane Controlled Trials Register (CENTRAL) were searched for primary studies while the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE) and the HTA database were searched for reports of evidence syntheses.

Reference lists of all included studies were perused in order to identify additional potentially relevant reports. The expert panel provided details of any additional potentially relevant reports.

Searches for recent conference abstracts (2011-13) were also undertaken and included the annual conferences of the American Society of Hematology (ASH), the European Hematology Association (EHA) and the International Society on Thrombosis and Haemostasis (ISTH) as well as the proceedings of the 12th National Conference on

Anticoagulant Therapy. Ongoing studies were identified through searching Current Controlled Trials, Clinical Trials, WHO International Clinical Trials Registry and NIH Reporter. Websites of professional organisations and health technology agencies were checked to identify additional reports. Full details of the search strategies used are presented in Appendix 1.

Inclusion and exclusion criteria

The initial scoping searches performed for this assessment identified a Cochrane review[29] and a few technology assessment reports [20,30,31] assessing different models of managing oral anticoagulation therapy. These publications focused on several randomised controlled trials, which reported relevant clinical outcomes. In particular, the Cochrane review included both the CoaguChek S and the CoaguChek XS devices. The CoaguChek XS system is the upgraded version of CoaguChek S and uses the same technology as its precursor. Details of the performance of the two CoaguChek models compared with standard INR monitoring are provided in section 3.2.

The studies fulfilling the following criteria were included in this assessment.

Population

People with atrial fibrillation or heart valve disease for whom long-term vitamin K antagonist therapy was required.

Setting

Self INR monitoring supervised by primary or secondary care.

Interventions

The point-of-care devices considered in this assessment were:

- CoaguChek system;
- INRatio2 PT/INR monitor;
- ProTime Microcoagulation system.

Comparators

The comparator considered in this assessment was standard practice, which consisted of INR monitoring managed by healthcare professionals. INR monitoring can be carried out in primary care, in secondary care or in a "shared provision" setting:

- **Primary care -** INR monitoring can be carried out in primary care anticoagulant clinics using point-of-care tests or laboratory analysers. In the latter, blood samples are sent to a central laboratory based at a hospital (**shared provision**);
- **Secondary care -** INR monitoring can be carried out in hospital-based anticoagulant clinics using point-of-care tests or laboratory analysers.

Outcomes

The following outcomes were considered:

Clinical outcomes:

- Frequency of bleeds or blood clots;
- Morbidity (e.g. thromboembolic and cerebrovascular events) and mortality from INR testing and vitamin K antagonist therapy;
- Adverse events from INR testing, false test results, vitamin K antagonist therapy and sequelae.

Patient reported outcomes:

- People's anxiety associated with waiting time for results and not knowing their current coagulation status and risk;
- Acceptability of the tests;
- Health related quality of life.

Intermediate outcomes:

- Time and INR values in therapeutic range;
- Test failure rate;
- Time to test result;
- Patient compliance with testing and treatment;
- Frequency of testing;
- Frequency of visits to primary or secondary care clinics.

Study design

Priority was given to RCTs assessing the effectiveness of the CoaguChek system, the INRatio2 PT/INR monitor, and the ProTime Microcoagulation system. In the absence of RCTs, non-randomised studies (including observational studies) were considered, providing they included relevant outcomes for this assessment. Systematic reviews were used as source for identifying additional relevant studies.

Studies were excluded if they did not meet the pre-specified inclusion criteria and, in particular, the following types of report were not deemed suitable for inclusion:

- Biological studies;
- Reviews, editorials and opinions;
- Case reports;
- Non-English language reports;
- Conference abstracts published before 2012.

Data extraction strategy

Two reviewers (PS, MB) independently screened the titles and abstracts of all citations identified by the search strategies. Full-text copies of all studies deemed to be potentially relevant were obtained and assessed independently by two reviewers for inclusion (PS, MC). Any disagreements were resolved by discussion or arbitration by a third reviewer (MB).

A data extraction form was designed and piloted for the purpose of this assessment (Appendix 2). One reviewer (PS) extracted information on study design, characteristics of participants, settings, characteristics of interventions and comparators, and relevant outcome measures. A second reviewer (MC) crosschecked the details extracted by the first reviewer. There was no disagreement between reviewers.

Assessment of risk of bias in included studies

A single reviewer assessed the risk of bias of the included studies (PS) and findings were crosschecked by a second reviewer (MC). There were few disagreements which were resolved by consensus or arbitration by a third reviewer (MB). The reviewers were not blinded to the names of studies' investigators, institutions, and journals. Studies were not included or excluded purely on the basis of their methodological quality. The risk of bias assessment for all included RCTs was performed using the Cochrane Risk of Bias tool (Appendix 3).[27] Critical assessments were made separately for all main domains: selection bias ('random sequence generation', 'allocation concealment'), detection bias ('blinding of outcome assessor'), attrition bias ('incomplete outcome data') and reporting bias ('selective reporting'). The 'blinding of participants and personnel' was not considered relevant for this assessment due to the nature of intervention being studied (i.e. patient performing the test themselves or under supervision of health care professionals). However, we collected information related to the blinding of outcome assessors, which was considered relevant to the assessment of risk of bias.

We judged each included study as 'low risk of bias', high risk of bias' or as 'unclear risk of bias' according to the criteria for making judgments about risk of bias described in the Cochrane Handbook for Systematic Reviews of Interventions.[27] Adequate sequence generation, allocation concealment, and blinding of outcome assessor were identified as key domains for the assessment of the risk of bias of the included trials.

Data analysis

For dichotomous data (e.g. bleeding events, thromboembolic events, mortality), relative risk (RR) was calculated. For continuous data (e.g. time in therapeutic range), weighted mean difference (WMD) was calculated. Where standard deviations were not given, we calculated them using test statistics wherever possible. The RR and WMD effect sizes were meta-analysed as pooled summary effect sizes using the Mantel-Haenszel method and the inverse-variance method, respectively. Confidence intervals were also calculated (95% CIs). To estimate the summary effect sizes, both fixed effects and random effects models were used with RR and WMD. In the absence of clinical and/or statistical heterogeneity, the fixed effects model was selected as the model of choice while the random effects model was used to crosscheck the robustness of the fixed effects model. However, in the presence of either clinical or statistical heterogeneity, the random effects model was chosen as the preferred method for pooling the effect sizes, as in this latter situation, the fixed effect method is not considered appropriate for combining the results of included studies.[27] Heterogeneity across studies was measured by means of the Chi squared statistic and also by the I-squared statistic, which describes the percentage of variability in study effects that is explained by real heterogeneity rather than chance. It is worth noting that, for bleeding and thromboembolic events, we used the total number of participants who were actually analysed as denominator in the analyses. In contrast, for mortality, we used the total number of participants randomised as denominator because participants could have died due to any causes after randomisation but before entering the self-monitoring programme.

Apart from the pre-specified subgroups analysis according to the type of anticoagulation therapy management (self-testing and self-management), we performed a post-hoc subgroup analysis according to the type of the target clinical condition (i.e. atrial fibrillation, heart valve disease, and mixed clinical indication) and one according to the type of service provision for anticoagulation management (i.e. primary care, secondary care, and shared provision).Where trials had multiple arms contributing to different subgroups, the control group was subdivided into two groups to avoid a unit of analysis error.

Sensitivity analyses were planned in relation to some of the study design characteristics. The methodological quality (low/high risk of bias), and the different models of the CoaguChek system were identified at protocol stage as relevant aspects to explore in sensitivity analyses. In addition to those pre-specified in the protocol, we performed a sensitivity analysis by excluding the studies conducted in the UK.

Review Manager software (Review Manager 5.2, 2012) was used for data management and all relevant statistical analyses for this assessment. Where it proved unfeasible to perform a quantative synthesis of the results of the included stuides, outcomes were tabulated and described in a narrative way.

3.2 Results

Performance of point-of-care devices

A formal evaluation of the performance of the CoaguChek, INRatio, and ProTime point-of-care systems with regard to INR measurement was outside the scope of this assessment. An objective 'true' INR remains to be defined and usually the calculation of INR measurement is based on different assumptions. INR determined in the laboratory is regarded as the gold standard to which all other measurement methods should be compared.[32] Information on the precision and accuracy of these point-of-care devices was gathered from the available literature. Normally, the precision or reproducibility of point-of-care devices is expressed by means of the coefficient of variation (CV) of the variability while the accuracy is the level of agreement between the result of one measurement and the true value and is expressed as correlation coefficient.[33] Table 1 summarises the performance of the target point-of-care devices according to the FDA Self Test documentation and relevant published papers.

Table 1 Summary of point-of-care devices performance data

	PRECISION				ACCURACY
	Mean (SD) INR		CV (%)		Correlation (r)
	Patient	Professional	Patient	Professional	
CoaguChek S[34]	2.42 (0.68)	NR	NR	NR	0.95*
CoaguChek XS [35]	2.57 (0.13)	2.52 (0.13)	5.13	5.36	0.93
CoaguChek XS plus[36]	2.47 (0.135)	2.45 (0.101)	5.47	4.12	0.97
INRatio 2[37]	2.70 (0.153)	2.93 (0.180)	5.68	6.16	0.93
ProTime 3 [38]	4.0 (0.19)**	NR	NR	NR	0.95

*MHRA, 2004[39]; **"within day"; NR Not reported

A systematic review published by Christensen and Larsen in 2012[33] assessed the precision and accuracy of current available point-of-care coagulometers including CoaguChek XS, INRatio and ProTime/ProTime3.The authors found that the precision of CoaguChek XS varied from a CV of 1.4% to 5.9% based on data from 14 studies while the precision of INRatio and ProTime varied from 5.4% to 8.4% based on data from 6 studies. The coefficient of correlation for CoaguChek XS varied from 0.81 to 0.98, while that for INRatio and ProTime varied from 0.73 to 0.95. They concluded that the precision and accuracy of point-of-care coagulometers were generally acceptable compared to conventional laboratory-based clinical testing. The same conclusions were drawn by the Canadian Agency for Drugs and Technologies in Health report published in 2012 on point-of-care testing.[40] Similarly, the international guidelines prepared in 2005 by the international self-monitoring association for oral anticoagulation stated that "Point-of-care instruments have been tested in a number of different clinical settings and their accuracy and precision are considered to be more than adequate for the monitoring of oral anticoagulation therapy in both adults and children".[41]

CoaguChek XS versus CoaguChek S

The CoaguChek S monitor was replaced in 2006 by the XS monitor which offers a number of new technical features such as the use of a recombinant human thromboplastin with a lower ISI and internal quality control included on the test strip. The safety and reliability of

CoaguChek S and CoaguChek XS have been demonstrated in several studies in both adults and children.[42-49] A number of studies have also compared the performance of CoaguChek S with that of CoaguChek XS in relation to conventional INR measurement. Even though a good agreement between the two CoaguChek models and conventional laboratory-based results has been demonstrated, CoaguChek XS has shown more accurate and precise results than its precursor in both adults and children especially for higher INR values (> 3.5).[32,34,50-53]

Quantity of available evidence

A total of 658 records were retrieved for the assessment of the clinical effectiveness of the point-of-care tests under investigation. After screening titles and abstracts, 563 were excluded and full text reports of 120 potentially relevant articles were obtained for further assessment including 25 full-text papers from the18 trials included in the Cochrane systematic review published by Garcia-Alamino and colleagues.[29] In total, 26 RCTs (published in 45 papers) met the inclusion criteria and were included in the clinical effectiveness section of this assessment. Three of the 26 included studies were randomised cross over trials[32, 33,34] while the remaining studies were parallel group randomised controlled trials.

We based the primary analyses on data from 21 out of the 26 included studies relevant to the comparisons and outcomes of interest (see Table 2 for further details).

Of these 21 trials, which provided data for statistical analyses, 15 trials were the same as those included in the Cochrane systematic review by Garcia-Alamino and colleagues[29] and six were newly identified trials, published in or after 2008.

Table 2 Studies considered relevant for this assessment but not included in the meta-analyses

Study ID	Comparisons	Reason for exclusion from meta-analyses	Reason for inclusion in this assessment
Bauman 2010[54]	Compares PSM with PST group (PST was the usual care provided in the study context).	Lack of data on standard care group where people OAT are generally managed by the primary or secondary care.	Only RCT that reported acceptability outcomes on the relevant subgroup of interventions for children.
Gardiner 2005[44]	Compares PST with standard care.	The data collected by the participants were not used for the analysis. Instead monthly data collected by the health care professionals was used.	Reports patient acceptability of self-testing as secondary outcome.
Gardiner 2006[55]	Compares PST with PSM and then historically compares the included sub-groups with the standard care they received for last six months before their enrollment in the study.	Lack of randomised data on standard care group where participants receiving OAT are usually managed by the primary or secondary care.	Provide relevant data on TTR on the subgroup of interventions that were of interest.
Hemkens 2008[56]	Compares PSM with standard laboratory monitoring.	Do not provide data on any relevant clinical outcomes or intermediate outcomes.	Reports patient satisfaction of self-management as secondary outcome.
Rasmussen 2012[57]	Compares PSM with standard care.	Do not provide any relevant clinical outcomes. Data provided for TTR was in median (25 to 75 percentile) which was not possible to be converted into mean (SD).	Provide data on TTR.

OAT: oral anticoagulant therapy; PSM: patient self-management; PST; patient self-testing; TTR: time in therapeutic range

Figure 1 shows a flow diagram of the study selection process. The list of 26 included RCTs (and other linked reports) is given in Appendix 4.

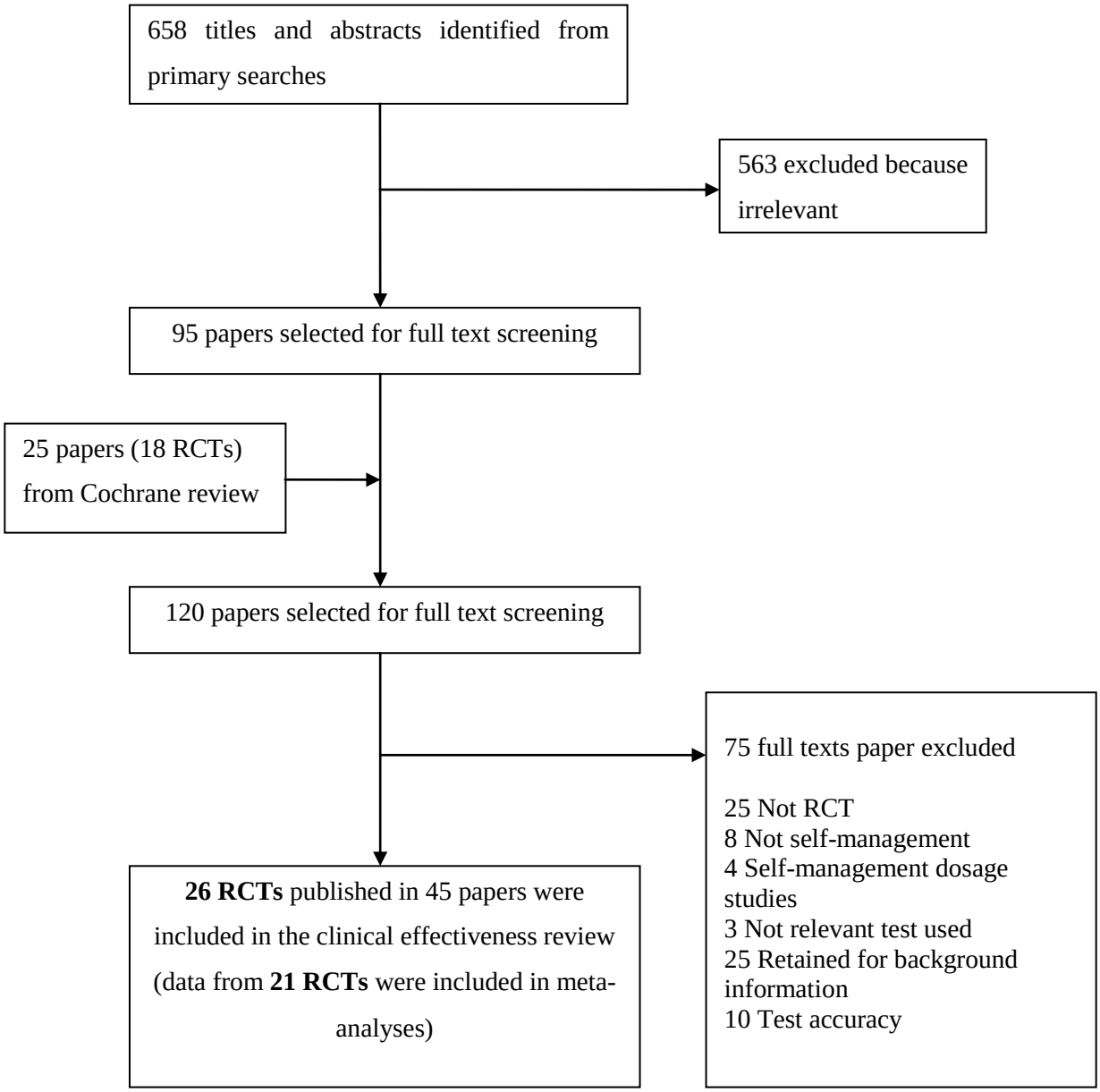


Figure 1 Flow diagram outlining the selection process

Number and type of studies excluded

Appendix 5 lists the number of studies excluded after full-text assessment and the reasons for their exclusion.

Quality of research available

Figure 2 illustrates a summary of the risk of bias assessment for all included studies. The majority of trials were judged at 'unclear' or 'high' risk of bias. One trial was only reported in abstract and hence did not allow for an adequate assessment of the risk of bias.[58] Similarly, one trial was discontinued before the end of the pre-specified follow up due to difficulties in the recruitment process.[59] Overall, 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.[54,60-62] Three of these trials used either the CoaguChek model 'S'[60,62] or the model 'XS'[61] for INR measurement while the other trial used CoaguChek XS to measure INR in children receiving anticoagulation therapy.[54] Appendix 6 provides details of the risk of bias assessment for each individual study. Main findings of the risk of bias assessment for all included studies are described in detail below.

Selection bias

Of the 26 included trials, only seven trials reported adequate details on both generation of the randomisation sequence generation and concealment of allocation.[54,56,60-64] In 11 trials, the randomisation process proved to be adequate but no information was provided on the way participants were allocated to the study interventions.[57,59,65-73] One trial[74] reported adequate details about the generation of the random sequence but failed to conceal the allocation of participants to study interventions. In contrast, another trial[75] reported adequate information on allocation concealment but failed to provide details on the randomisation process. In six trials, both the randomisation process and the allocation concealment were judged as 'unclear' due to the lack of adequate information.[44,55,58,76-78]

Attrition bias

Seventeen trials were judged to be at low risk of attrition bias. Six of them had limited missing data with similar reasons for discontinuation across intervention groups.[58,68,71,73,75,78] Seven trials relied on an intention-to-treat approach and all dropouts were fully accounted for in the statistical analyses[54,60,62-64,70,74] while the other four reported no missing data.[57,59,61,77] Eight of the 26 included trials were at high risk of attrition bias with more than 5% dropout rate and with missing data not appropriately tackled.[44,55,56,65-67,72,76] In the Early Self-Controlled Anticoagulation Trial (ESCAT),[69] the problem of incomplete outcome data was addressed for the first 600 participants but not for all included participants.

Performance and detection bias

Due to the nature of the interventions being studied (use of point-of-care devices), blinding of participants or personnel was not feasible. Seven trials blinded the outcomes assessor (statistician or clinical outcome assessor).[54,57,60-62,71,76] In six trials, neither the participants nor the personnel involved in delivering the interventions were blinded.[59,64,65,70,73,74] One trial[69] was described as 'double blinded' but no further information was given. Another trial [67] reported that one of the two standard care groups studied (the untrained routine group) was blinded. In addition, this trial revealed that the nurses involved in transferring data on dosing as well as the dosing physicians were blinded. The remaining of the included trials did not provide information on blinding.

Reporting bias

With the exception of three trials,[57,75,78] the outcomes reported in the trials were pre-specified in analysis section and reporting bias was not obvious in the published papers.

Other sources of biases

No other sources of biases were obvious in the included trials.

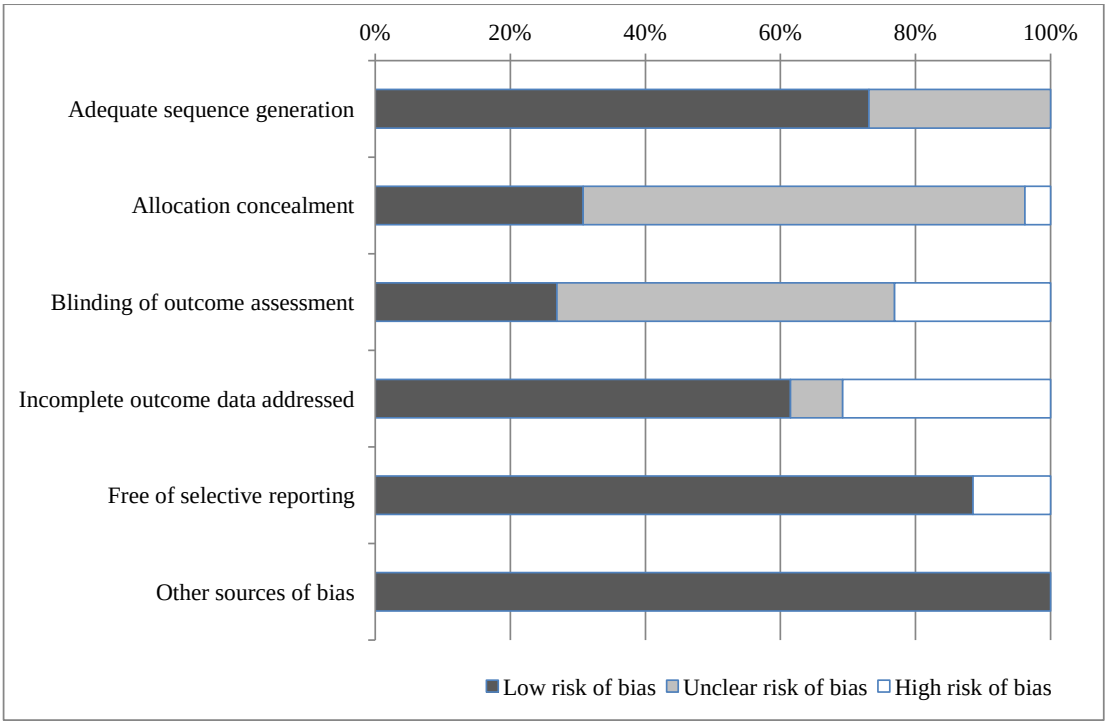


Figure 2 Summary of risk of bias of all included studies

Characteristics of the included studies

Table 3 summarises the main characteristics of the 26 included RCTs. The baseline characteristics of all included trials are described below and tabulated in Appendix 7 (Tables A and B).

Studies details

The majority of included trials were conducted in Europe; six trials were conducted in Germany,[56,58,59,69,71,77] six in the UK,[44,55,63,66,68,72] three in Denmark,[57,65,74] three in the Netherlands,[67,75,78] one in Ireland,[61] one in Austria,[62] one in France,[76] and one in Spain.[60] Three trials were conducted in Canada[54,64,73] and one in the USA.[70] Of the 26 included trials, seven were multicentered,[59,62,63,66,67,70,71] while the remaining 19 were conducted in a single centre.

The length of follow up ranged from 14 weeks[56] to more than 4 years.[62,70] Nine trials reported follow ups equal to or longer than 12 months.[54,60,62,63,65,69,70,72,77,78] One trial, which was originally supposed to run for two years, was discontinued prematurely due to the small number of recruited participants.[59]

Nine of the included trials were funded independently by professional organisations or national/governmental agencies [54,56-58,63-65,68,74] while 13 trials were fully or partly funded by industry. In the remaining four trials the source of funding was not given.[69,75,77,78]

Participants

Most of the included trials (15/26) included participants with mixed indications of which atrial fibrillation, artificial heart valves, and venous thromboembolism were the most common clinical indications,[44,54-56,60-62,64,65,67,70,71,73-75] six trials enrolled exclusively participants with artificial heart valves,[58,69,72,76-78] and two trials limited inclusion to participants with atrial fibrillation.[59,68] Seven trials provided information on risk factors, co-morbidity, and/or previous bleeding and thromboembolic events but did not report significant baseline differences between participants in self-monitoring and those in standard care (see Appendix 7, Table B).[60,62,63,70,71,74,76]

Table 3 Summary of the included RCTs

	CoaguChek XS	CoaguChek S/ CoaguChek	CoaguChek Plus	CoaguChek+INRatio	ProTime
Total no of studies	4	17	1	2	2
PSM	2	14	1	1	1
PST	2	2	0	1	1
PSM and PST	0	1	0	0	0
AC clinic-standard care	4	9	0	2	1
GP/Physician-standard care	0	4	1	0	1
AC clinic or GP/Physician-standard care	0	4	0	0	0
UK	0	6	0	0	0
Non-UK	4	12	1	2	2
AF only	0	2	0	0	0
AHV only	0	4	1	1	0
Mixed only (AF+AHV+others)	4	12	0	1	2
Total sample size	414	3910	1155	222	3062

Note: AC clinic-standard care: In two trials, reporting CoaguChek XS[54] and CoaguChek S[55] PST within AC clinic was the usual care.

AC: Anticoagulant; PSM; Patient self-management; PST:Patient self-testing; AHV: Artificial heart valves; AF:Atrial fibrillation.

The mean sample size among the included trials was 337 participants (range 16[39] to 2922[70] participants). Fifteen trials performed a power analysis and a sample size calculation,[57,59-65,67,68,70,71,73-75] two trials, with very small sample sizes, did not power their studies,[54,56] and the remaining trials did not provide information on how the sample size was determined.[44,55,58,66,69,72,76-78] The age of adult participants ranged from 16 to 91 years.[61] The only trial which assessed children reported a median age of 10 years.[54]

Warfarin was the choice of vitamin K antagonist therapy in half of the included trials.[44,54,55,57,61,63-66,68,72,73,77] In seven trials participants were taking phenprocoumon and/or acenocoumarol and/or fluindione[56,60,62,67,71,75,76] and, in one trial, participants received either warfarin or phenprocoumon.[74] In the remaining four trials, the type of vitamin K antagonist therapy was not reported.[58,59,69,70,78] In nearly half of the included trials (12/26), participants had been on oral anticoagulant therapy for at least 3 months before randomisation.[44,54,55,60,63,65-68,73-75] Three trials included vitamin K antagonist naïve participants for whom long-term anticoagulant therapy was recently indicated but who had not been on anticoagulation therapy before.[57,62,69] In the largest trial, the Home International Normalised Ratio Study (THINRS) [70] randomisation was stratified according to the duration of anticoagulation but no significant differences were found between participants who had started anticoagulation therapy within the previous three months and those who had received anticoagulation therapy for more than three months. In the two remaining trials the included participants received oral anticoagulant therapy for less than three months (1-2 months) before randomisation.[61,64]

Point-of-care tests used for INR measurement

CoaguChek system for INR monitoring was used in 22 of the 26 included trials. Nine trials used the 'S' model,[44,55,57,60,62,63,66,74,77] four the XS model,[54,61,65,73] one[69] the CoaguChek Plus model, and two trials the first model of the CoaguChek series, which was simply referred to as "CoaguChek".[67,71] In six trials it was unclear whether the CoaguChek device was the first model or its later versions.[58,59,68,72,75,78] Either the INRatio or the CoaguChek S were used for INR measurement in two trials (but results were not separated according to the type of the point-of-care device),[56,76] and the ProTime system was used in other two trials.[64,70] In all six trials based in UK, CoaguChek system (either CoaguChek or version 'S') was used for the INR measurement.

In 11 trials, in order to assure accuracy of the point-of-care devices being used, INR results measured directly by participants were compared with those measured in a laboratory.[44,54-57,63-66,68,76]

Eight trials' investigators who did not specify the model of the CoaguChek device (S or XS) used for INR measurement were contacted for further details.[57,59,67,68,71,72,75,76,78] Five of the them provided further information on the model of the CoaguChek point-of-care device.[57,67,71,76,78]

Standard anticoagulant management

The type of standard care varied across trials. In 13 trials, INR was measured by professionals in anticoagulant or hospital outpatient clinics,[44,56,57,60,61,63,65,67,68,70,73,75,78] by a physician or a general practitioner in a primary care setting in six trials,[58,59,64,66,69,77] and either by a physician/general practitioner in a primary care setting or by professionals in anticoagulant/outpatient hospital clinics in five trials.[62,71,72,74,76] In two trials, comparing self-testing with self-management,[54,55] self-testing within anticoagulant clinics was considered as standard care. In the majority of the included trials (17/26), the anticoagulant clinic was led by a clinician (general or specialist), [57-60,62,64,65,67-72,74,76-78] by a nurse in five trials, (three conducted in UK,[44,63, 48] one in Canada[54] and one in Germany,[56] and by a pharmacist in two trials, conducted in Canada[73] and in Ireland[61]

INR measurement was carried out in a laboratory in all but two trials where CoauChek S[66] or another coagulometer[74] was used instead.

Self-monitoring

The majority of the included trials (17/26) compared self-management (participants performed the test and adjusted the dose of anticoagulation therapy themselves) with standard care,[56-60,62-64,66,69,71-75,77,78] six assessed self-testing (participants performed the test themselves with the results managed by health care professionals),[44,61,65,68,70,76] and one evaluated both self-testing and self-management versus either trained or untrained routine care (four arms).[67] It is worth noting that for the subgroup meta-analysis according to type of anticoagulant therapy management, this 4-arm trial contributed to two studies: one on self-testing and one on self-management. The two standard care groups (trained and untrained routine care) were initially combined to produce an overall control group and subsequently subdivided into two groups for the purpose of the subgroup analysis, which was undertaken to assess the effects of self-testing versus self-management.

The remaining two trials compared self-testing with self-management (without standard care as a comparator).[54,55] One of these two trials enrolled exclusively a children population[54] while the other provided a non-randomised comparison of participants in self-testing and self-management with those receiving standard care for a period of six months before study

enrollment.[55] We deemed these two trials suitable for inclusion as they provide relevant outcomes for participants in both self-testing and self-management.

In19 out of 26 included trials, participants received training and education in order to perform self-testing and self-management (see Appendix 7, Table C).[44,54,55,60,61,63-66,68,71-76,78-80] In most of these trials (11/19), the training was provided in group sessions which lasted for around one to two hours[54,60,61,67,68,71,75,76,80] up to a maximum of three hours.[72,73] The training was usually administered by a single member of staff, either a nurse, a practitioner/physician[44,55,60,63,68] or a pharmacist.[73] In a few trials, the training was provided by a team of professionals such as a specialist physician together with paramedical personnel;[79] a research pharmacist coupled with an haematologist[61] or a physician assisted by a nurse.[62,71] In five trials, the personnel responsible for delivering the training was reported to be trained specifically on self-testing and self-management.[55,60,62,63,71]

Clinical effectiveness results

Overview

This section provides evidence from 26 included trials on the clinical effectiveness of self-monitoring using CoaguChek system, INRatio2 PT/INR monitor, and ProTime Microcoagulation system compared with standard practice (Figures 3 to 14, Table 4-6, Appendix 8). For clarity, the results are reported under the broad headings of 'Clinical Outcomes', 'Intermediate outcomes' and 'Patient reported outcomes'. The summary effects of relevant clinical outcomes such as bleeding events, thromboembolic events, and mortality have been described separately within the 'Clinical outcomes' section. Tables 4 and 5 show the main findings of the five trials conducted in the UK and of the four trials using CoaguChek XS. The results of the sensitivity analyses for each point-of-care test are displayed in Table 6.

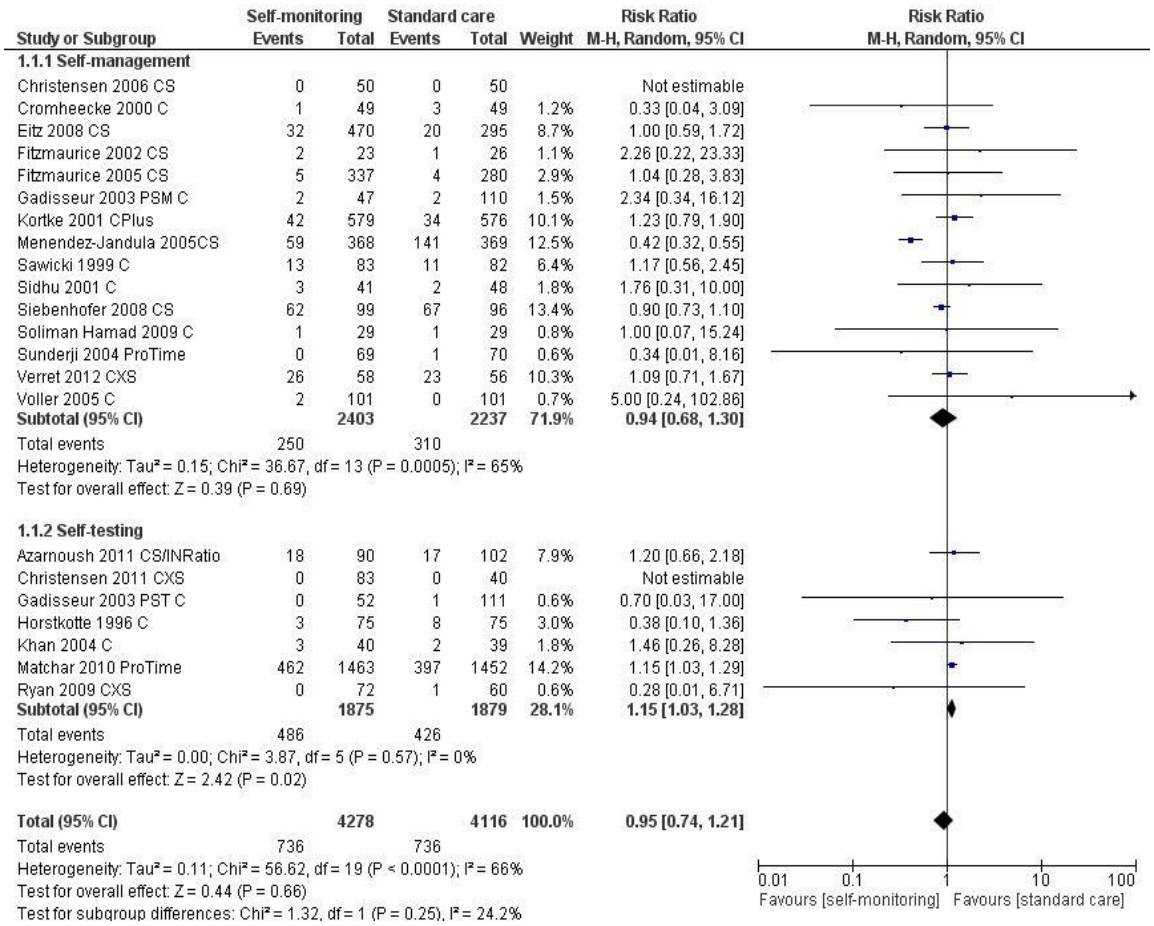
Clinical outcomes

Bleeding

Twenty one trials reported a total of 1472 major and minor bleeding events involving 8394 participants.[58-78] Two trials reported that there were no bleeding events and hence did not contribute to the overall effect size in the related meta-analysis.[65,74] Twenty one trials reported 476 major bleeding events in a total of 8202 participants[58-64,66-73,76-78] while 13 trials reported 994 estimable minor bleeding events in a total of 5425 participants.[60,62,63,66,68,70-73,75,76] No statistically significant differences were observed between self-monitoring participants (self-testing and self-management) and those in standard care for any bleeding events (RR 0.95, 95% CI 0.74 to 1.21, p=0.66) (Figure 3), major bleeding events (RR 1.02, 95% CI 0.86 to

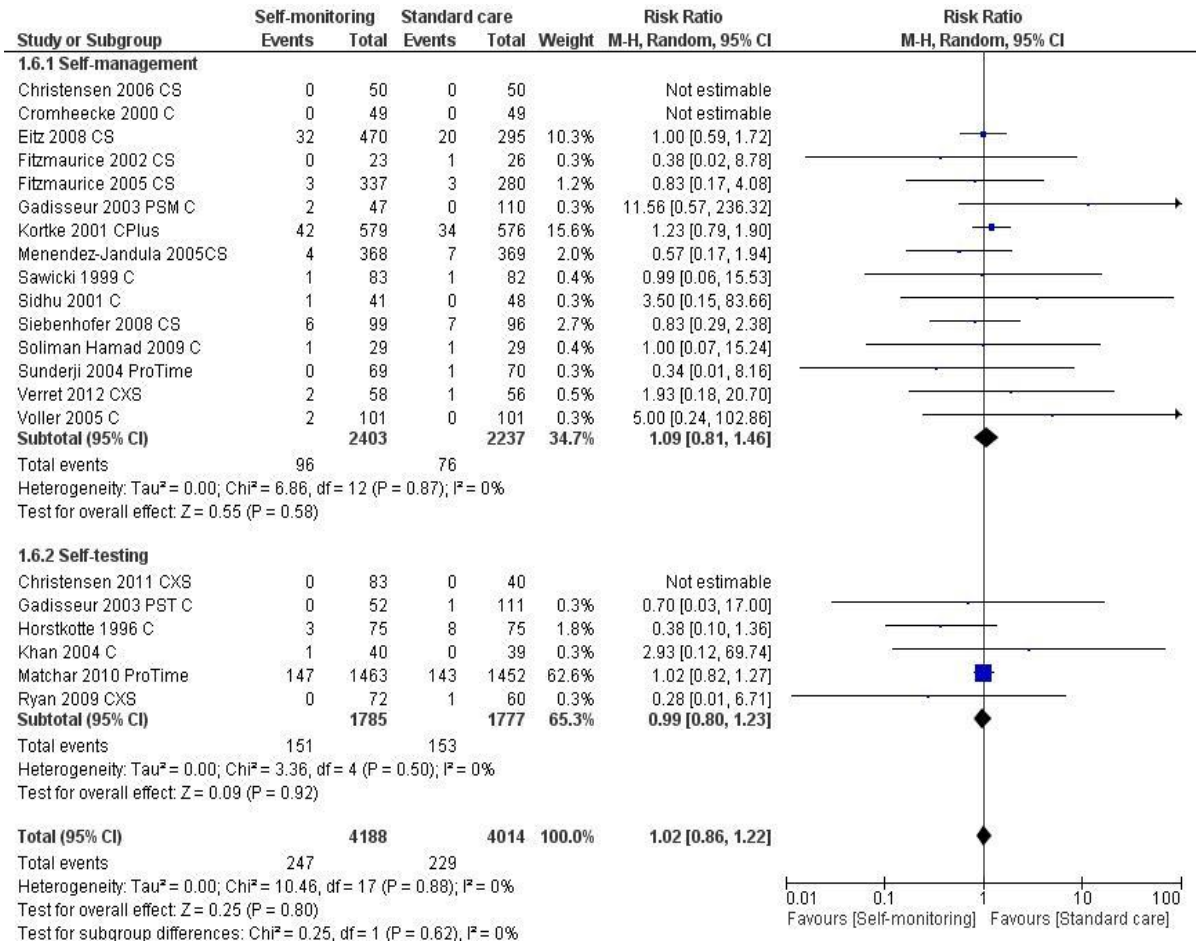
1.22, p=0.80) (Figure 4) and minor bleeding events (RR 0.94, 95% CI 0.65 to 1.34, p=0.73) (Figure 5). The results were not affected by the removal of the UK-based trials (Appendix 8) or by the removal of the trials assessing ProTime and/or INRatio (Table 6 and Appendix 8). Similarly, sensitivity analyses restricted to CoaguChek XS trials demonstrated no differences from the all-trials results (Table 6 and Appendix 8). A sensitivity analysis restricted to trials at low risk of bias slightly changed the estimate of effect but did not significantly impact on the findings (RR 0.59, 95% CI 0.27 to 1.30, p=0.19) (Appendix 8).

The subgroup analysis by type of anticoagulant management therapy did not show any difference between self-management and standard care for any bleeding events (RR 0.94, 95% CI 0.68 to 1.30, p=0.69) but revealed a significant higher risk in self-testing participants than in those receiving standard care (RR 1.15, 95% CI 1.03 to 1.28, p=0.02) (Figure 3). When trials assessing ProTime and INRatio were removed from the analysis, a non-significant trend was observed in favour of self-testing (0.58, 95% CI 0.22 to 1.47, p=0.25) (Table 6 and Appendix 8). No significant differences in the risk of major bleeding were observed between self-management (RR 1.09, 95% CI 0.81 to 1.46, p=0.58) and self-testing (RR 0.99, 95% CI 0.80 to 1.23) versus standard care (Figure 4). When only minor bleeding events were assessed (Figure 5), a significant increased risk was observed in self-testing participants (23%) compared with those in standard care (RR 1.23, 95% CI 1.06 to 1.42, p=0.005) but not in those who were self-managed (RR 0.84, 95% CI 0.53 to 1.35, p=0.47). Two trials enrolled participants with atrial fibrillation, six trials participants with artificial heart valves and 13 trials participants with mixed indication. No statistically significant subgroup differences were found for bleeding events according to the type of clinical indication (Figure 6). Similarly, for bleeding events, no significant differences were detected when trials were grouped according to the type of control care (anticoagulant clinic care RR 0.84, 95% CI 0.50 to 1.42, p=0.52; GP/physician RR 1.09, 95% CI 0.79 to 1.50, p=0.60; mixed care RR 0.94, 95% CI 0.79 to 1.13, p=0.54) (Figure 7).



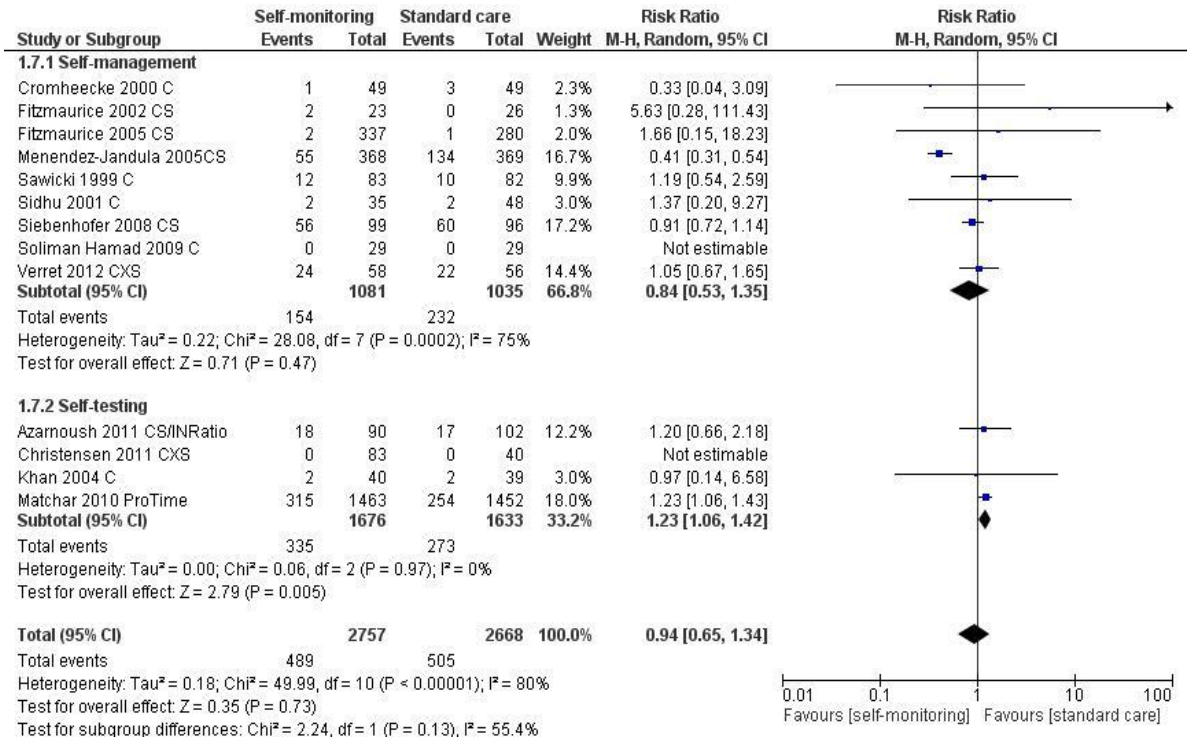
(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

Figure 3 Forest plot of comparison: any bleeding events



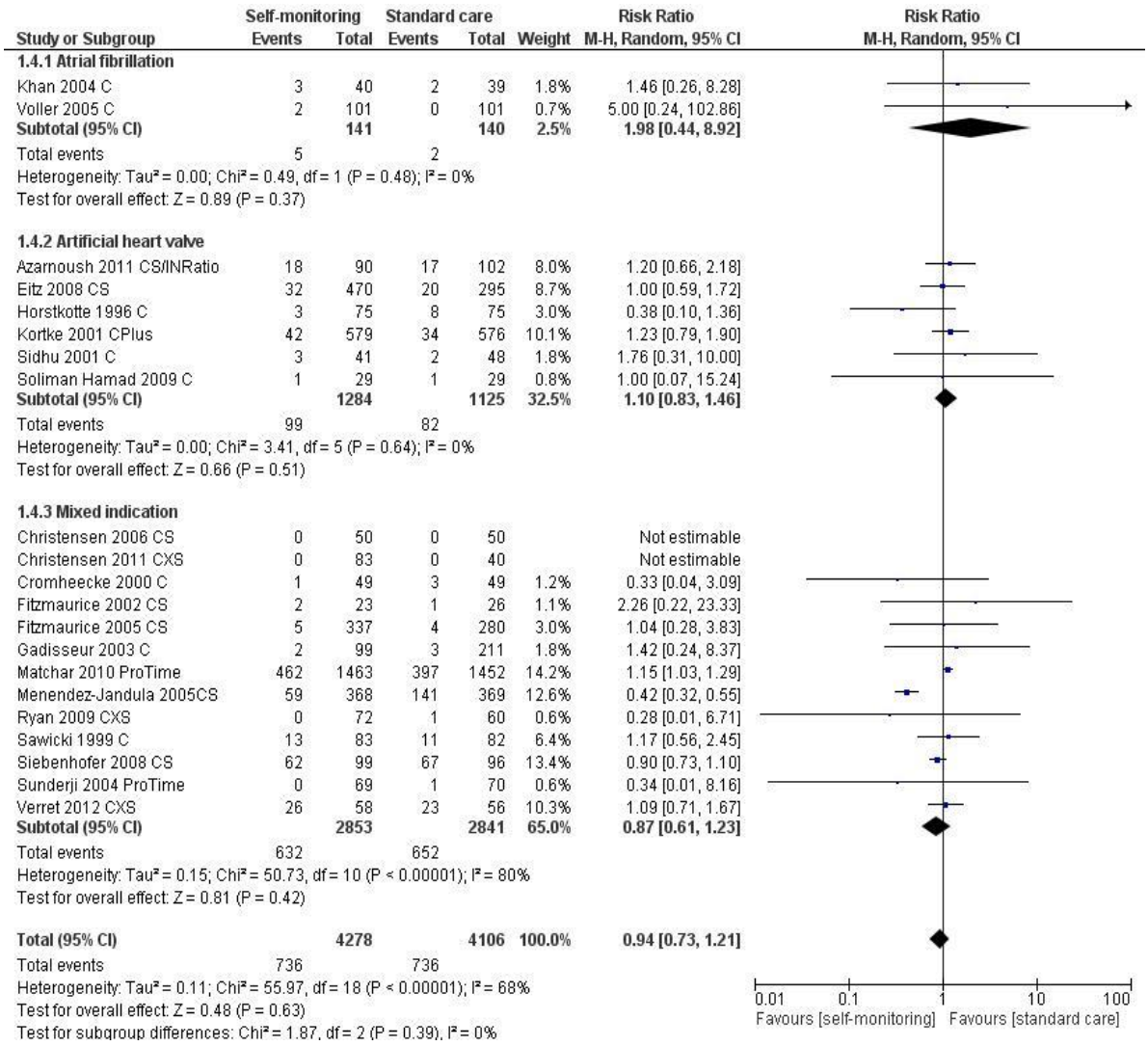
(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

Figure 4 Forest plot of comparison: major bleeding events



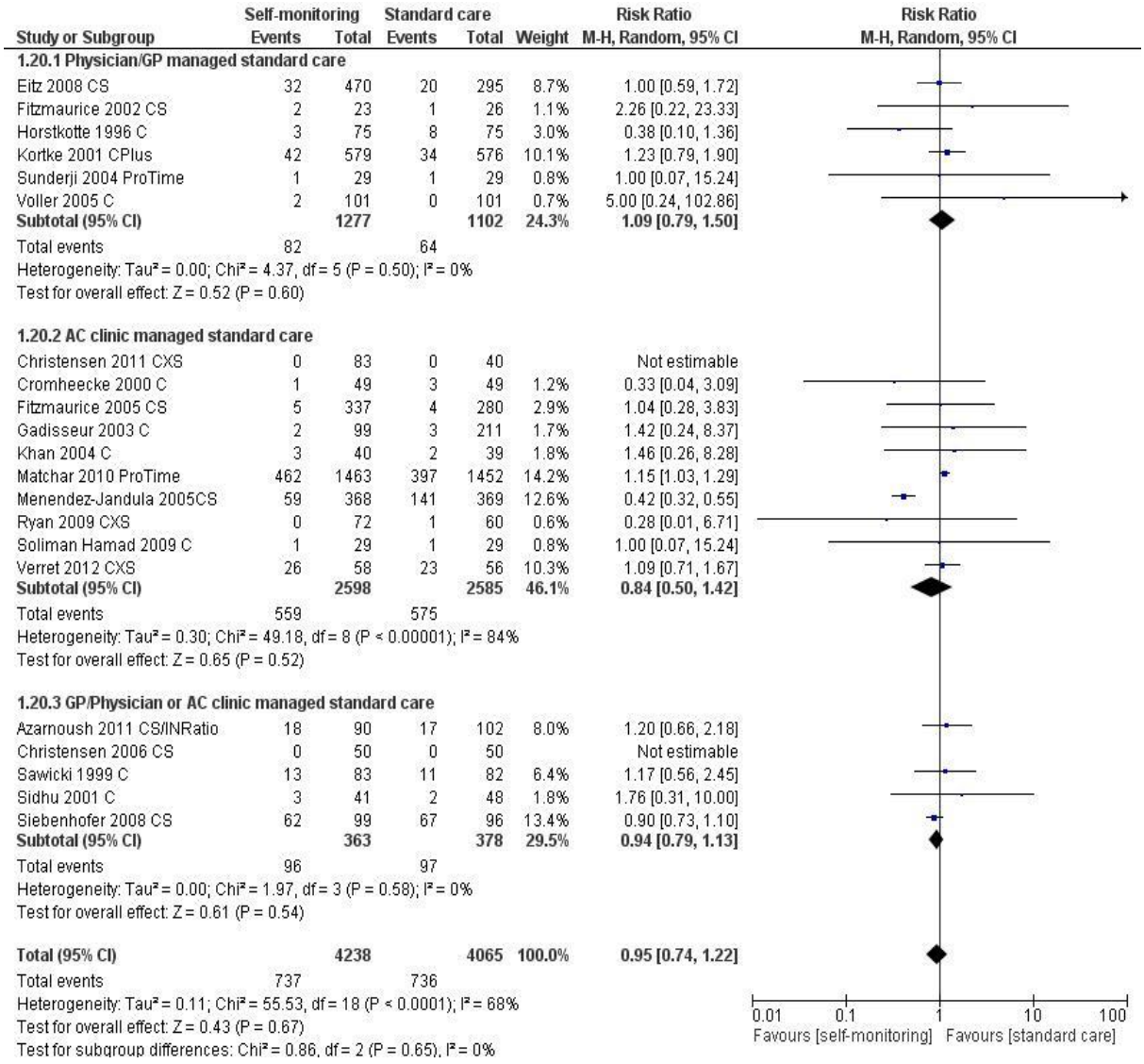
(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

Figure 5 Forest plot of comparison: minor bleeding events



(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

Figure 6 Forest plot of comparison: any bleeding events: clinical indication



(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

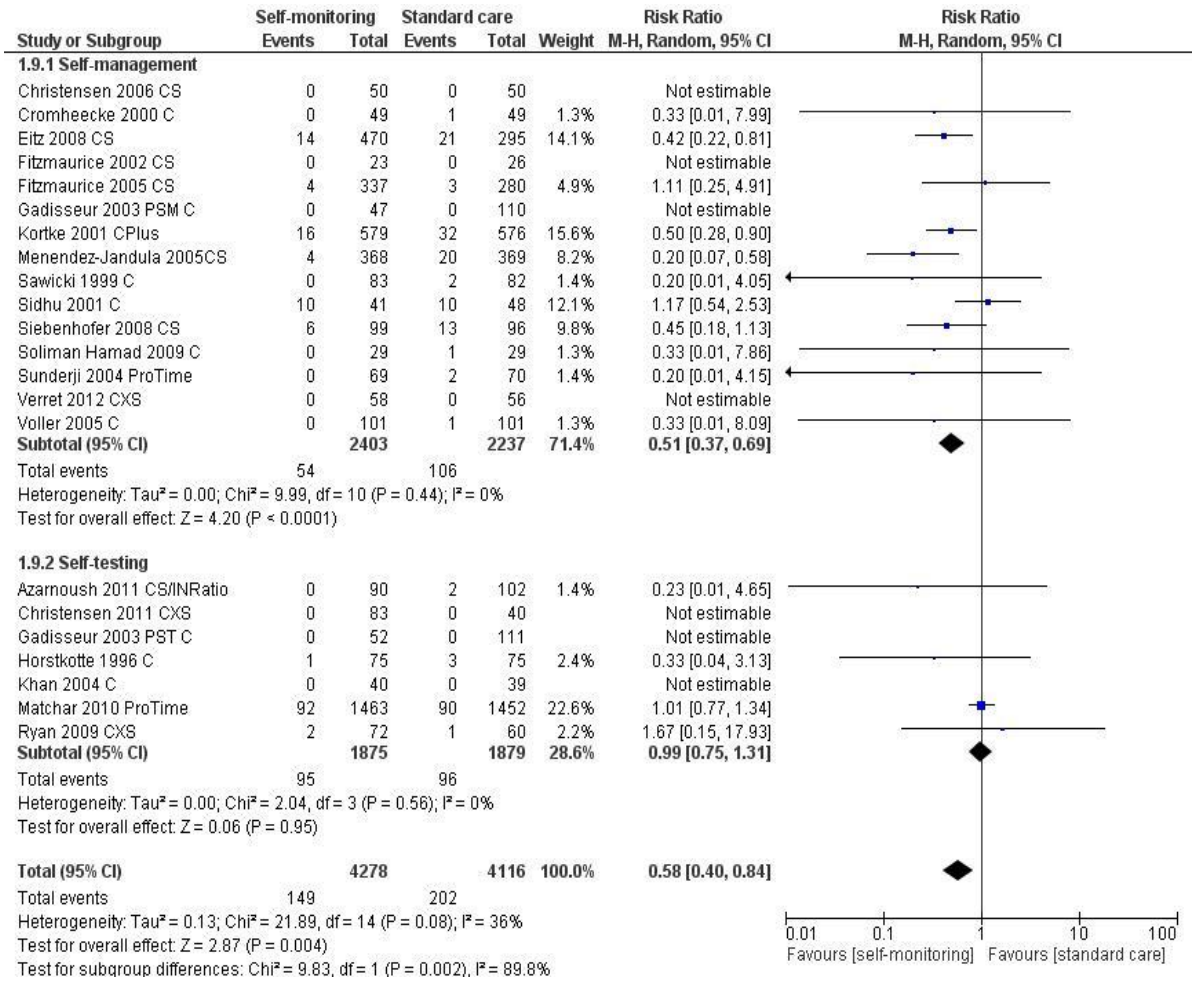
Figure 7 Forest plot of comparison: any bleeding events: type of standard care

Thromboembolic events

Twenty one trials reported 351 major and minor thromboembolic events in a total of 8394 participants.[58-78] Six of these trials did not contribute to the overall estimate of effect as they reported 'zero' events in both groups.[65-68,73,74] Self-monitoring (self-testing and self-management) showed a statistically significant reduction in the risk of thromboembolic events by 42% (RR 0.58, 95% CI 0.40 to 0.84, p=0.004) compared with standard care (Figure 8). The risk reduction further increased to 48% when only major thromboembolic events were considered (RR 0.52, 95% CI 0.34 to 0.80, p=0.003) (Figure 9). The risk of thromboembolic events significantly decreased when the analyses were restricted to non-UK trials (RR 0.50,

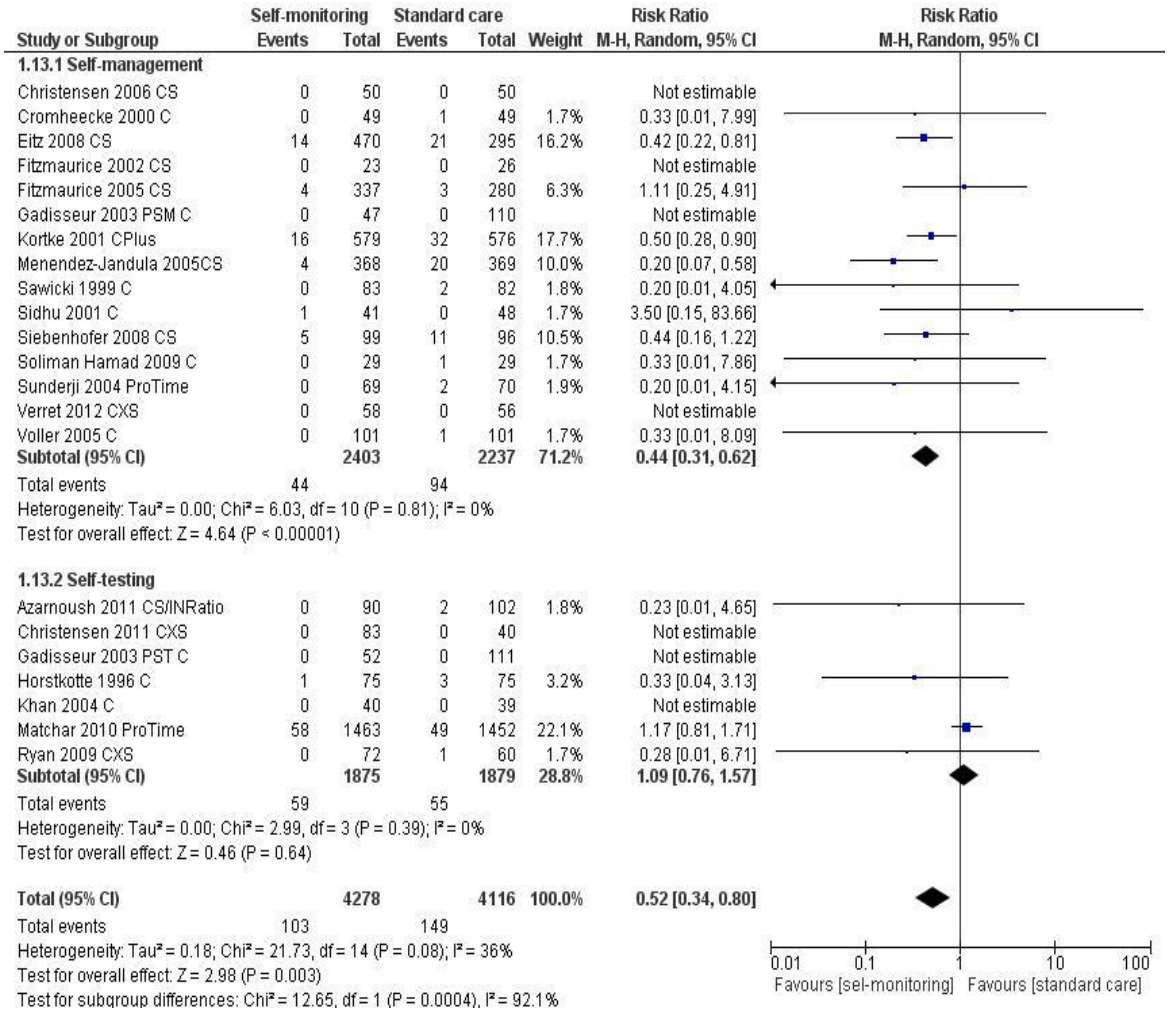
95% CI 0.32, 0.76, p=0.001); to CoaguChek trials (RR 0.52, 95% CI 0.38, 0.71, p<0.0001); and to trials at low risk of bias (RR 0.38, 95% CI 0.16 to 0.92, p=0.03) (Appendix 8).

Self-management compared with standard care halved the risk of thromboembolic events (RR 0.51, 95% CI 0.37 to 0.69, p<0.0001). In contrast, for self-testing participants [58,61,70,76] no significant risk reduction was observed compared with those in standard care (RR 0.99, 95% CI 0.75 to 1.31, p=0.56) (Figure 8). The subgroup difference between self-management and self-testing was statistically significant (p=0.002).When trials assessing the ProTime system were removed from the analysis, the risk reduction increased from 1% to 45% but the summary estimate of effect was not statistically different from the all-trials summary estimate (RR 0.55, 95% CI 0.13 to 2.31, p=0.41) (Table 6 and Appendix 8). Self-monitoring participants with artificial heart valves showed a significant reduction in the number of thromboembolic events compared with those in standard care (RR 0.56, 95% CI 0.38 to 0.82, p=0.003). Among participants with mixed clinical indication (atrial fibrillation, artificial heart valves, or other conditions), the effect was larger but not statistically significant than that observed in participants receiving standard care (RR 0.57, 95% CI 0.30 to 1.09, p=0.09) (Figure 10). The risk of thromboembolic events reduced in self-monitoring participants by 55% when routine anticoagulation control was managed by GP or physician (RR 0.45, 95% CI 0.29 to 0.68, p=0.0002). In contrast, even though less thrombolytic events were observed in participants who self-monitored their therapy compared to those managed in specialised anticoagulation clinics (RR 0.65, 95% CI 0.30 to 1.42, p=0.28) or those in mixed provision managed either by a physician/GP or a specialist (RR 0.66, 95% CI 0.31 to 1.38, p=0.27), no significant subgroup differences were detected (Figure 11).



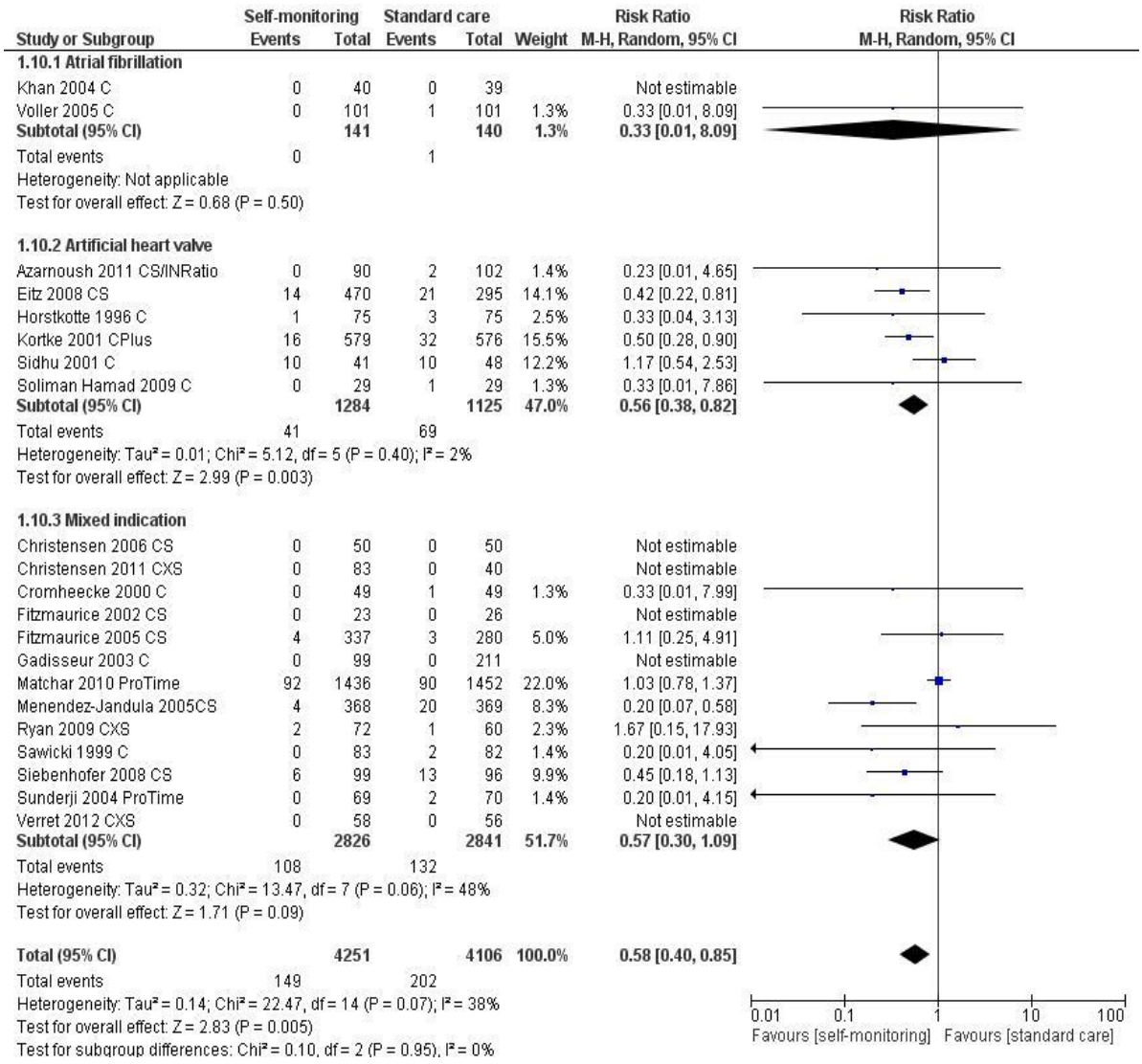
(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

Figure 8 Forest plot of comparison: thromboembolic events



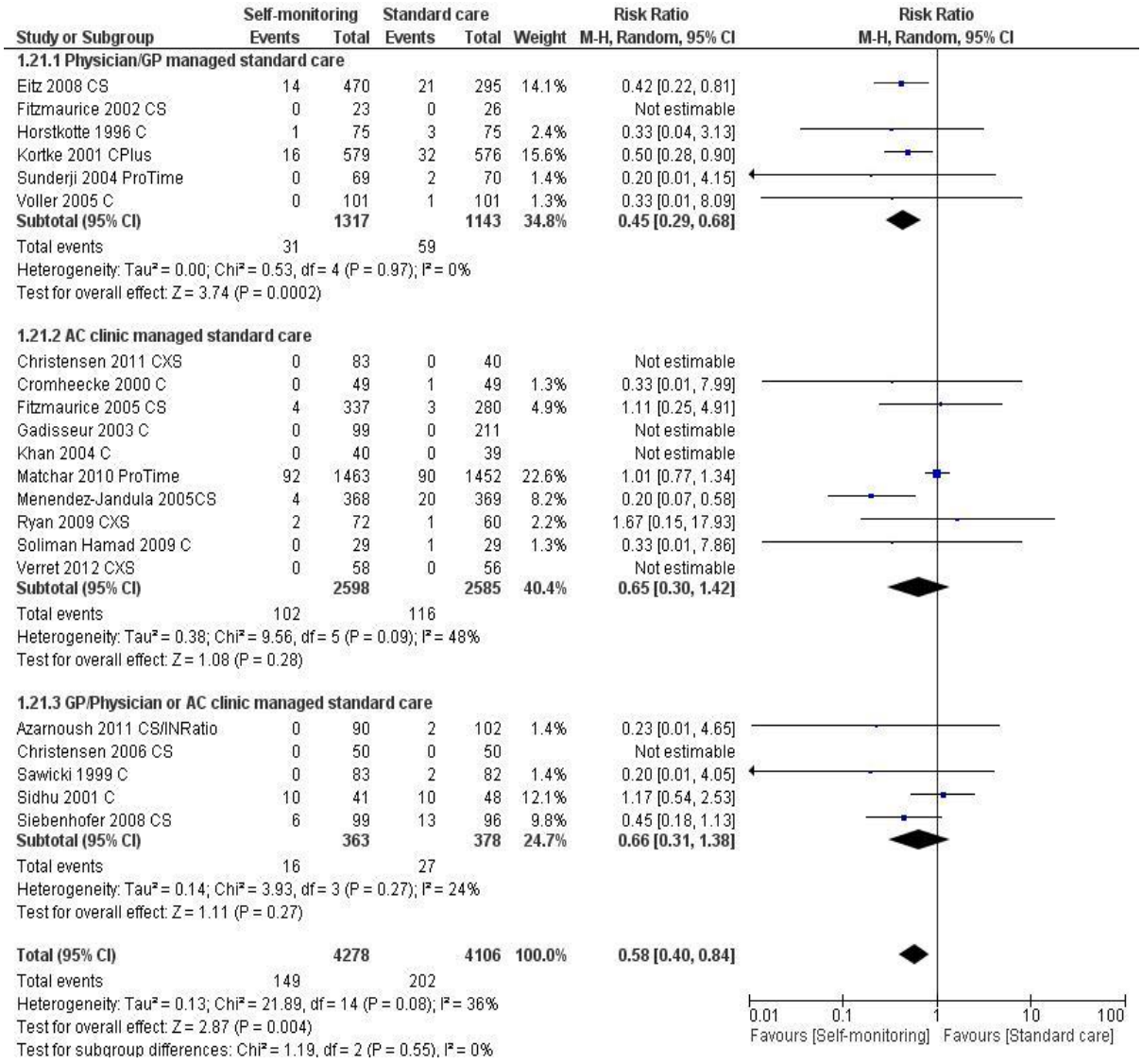
(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

Figure 9 Forest plot of comparison: major thromboembolic events



(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

Figure 10 Forest plot of comparison: any thromboembolic events: clinical indication



(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

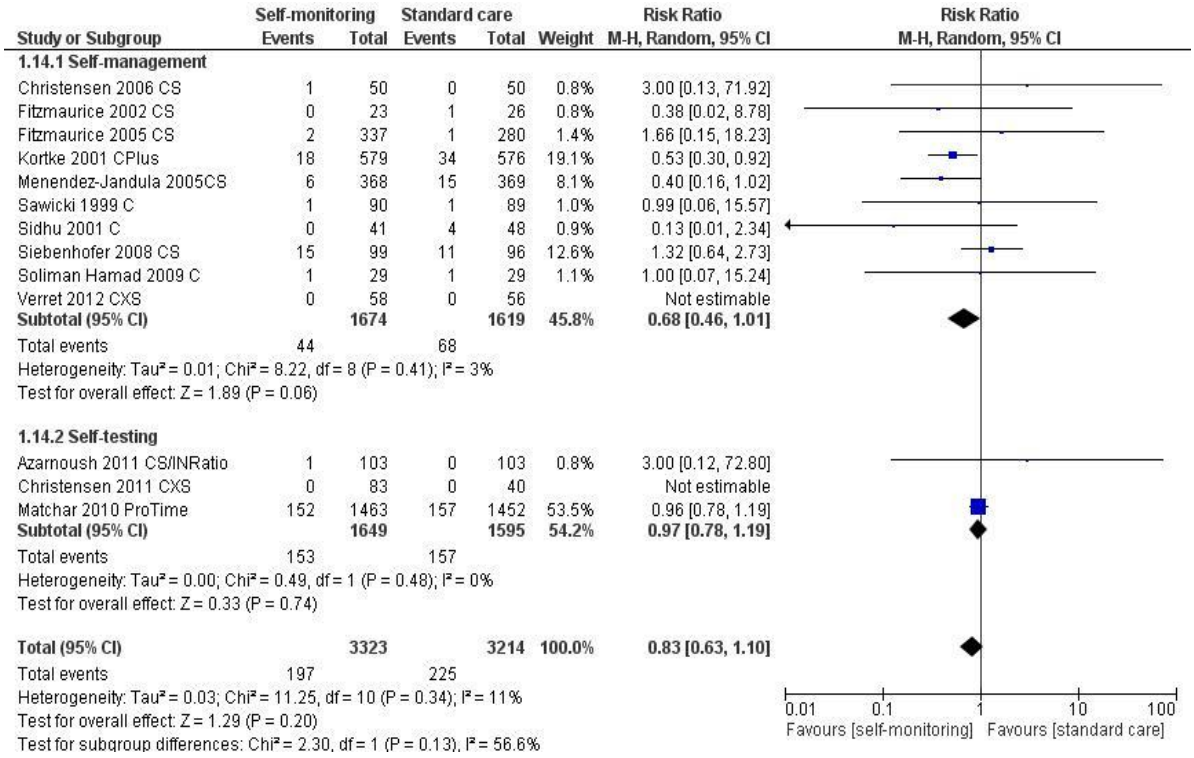
Figure 11 Forest plot of comparison: any thromboembolic events: type of standard care

Mortality

Thirteen trials reported 422 deaths due to all-cause mortality in a total of 6537 participants.[60,62,63,65,66,69-74,76,78] Two trials with zero fatal cases did not contribute to the overall estimate of effect.[65,73] One trial of 1200 participants[69] reported overall mortality data without separating the results for participants self-managed and for those receiving standard care. We contacted the corresponding author of this trial for further information but we did not receive any reply. Therefore, for mortality data, for this particular trial, we relied on the estimates published in the previous meta-analysis by Garcia-Alamino and colleagues[29] and in the HTA by Connock and colleagues,[20] which were based on individual patients' data.

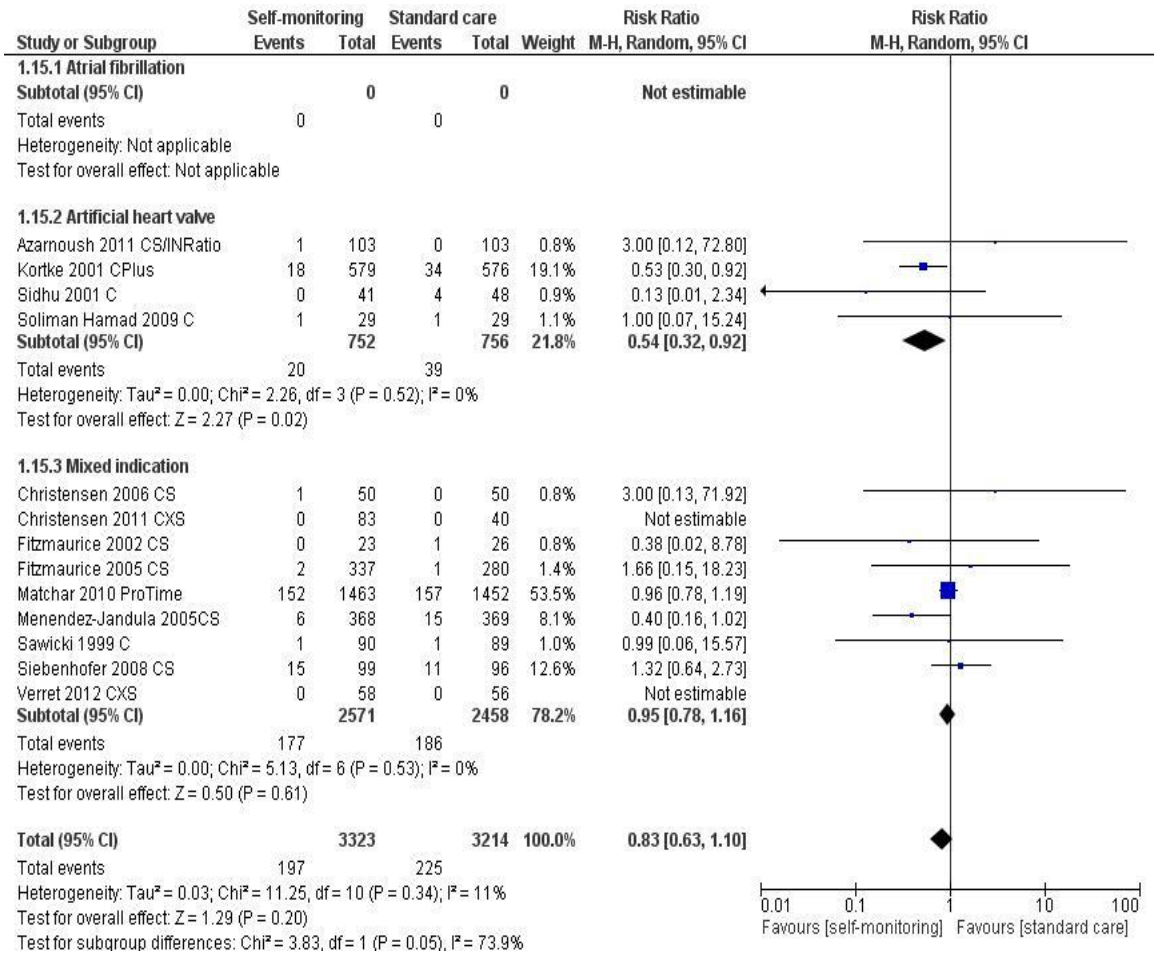
The risk reduction for all-cause mortality was not statistically significant different between self-monitoring (self-testing and self-management) and standard care (RR 0.83, 95% CI 0.63 to 1.10, p=0.20) (Figure 12). The results were not affected by the removal of the UK-based trials or by the removal of trials at high or unclear risk of bias. When the analysis was restricted to trials that used the CoaguChek system, the summary estimate for self-monitoring was not different from the all-trials estimate (RR 0.68, 95% CI 0.46 to1.01, P=0.06) (Table 6 and Appendix 8). Two trials reported six deaths out of a total of 932 participants related to vitamin K antagonist therapy.[60,62]

Risk of death reduced by 32% through self-management (RR 0.68, 95% CI 0.46 to 1.01, p=0.06) but not through self-testing (RR 0.97, 95% CI 0.78 to 1.19, p=0.74) even though the test for subgroup differences was not statistically significant (p=0.13) (Figure 12). Self-monitoring halved the risk of mortality in participants with artificial heart valves (RR 0.54, 95% CI 0.32 to 0.92, p=0.02) but not in those with mixed clinical indication for anticoagulant therapy (RR 0.95, 95% CI 0.78 to 1.16, p=0.61) (Figure 13). The subgroup difference between participants with artificial heart valves and those with mixed indication with regard to the number of deaths was statistically significant (p=0.05). No data were available from trials that enrolled participants with atrial fibrillation. Significantly fewer deaths were recorded among participants who self-monitored their therapy compared with those who were routinely managed by their GP/ physician (RR 0.52, 95% CI 0.30 to 0.90, p=0.02) (Figure 14).



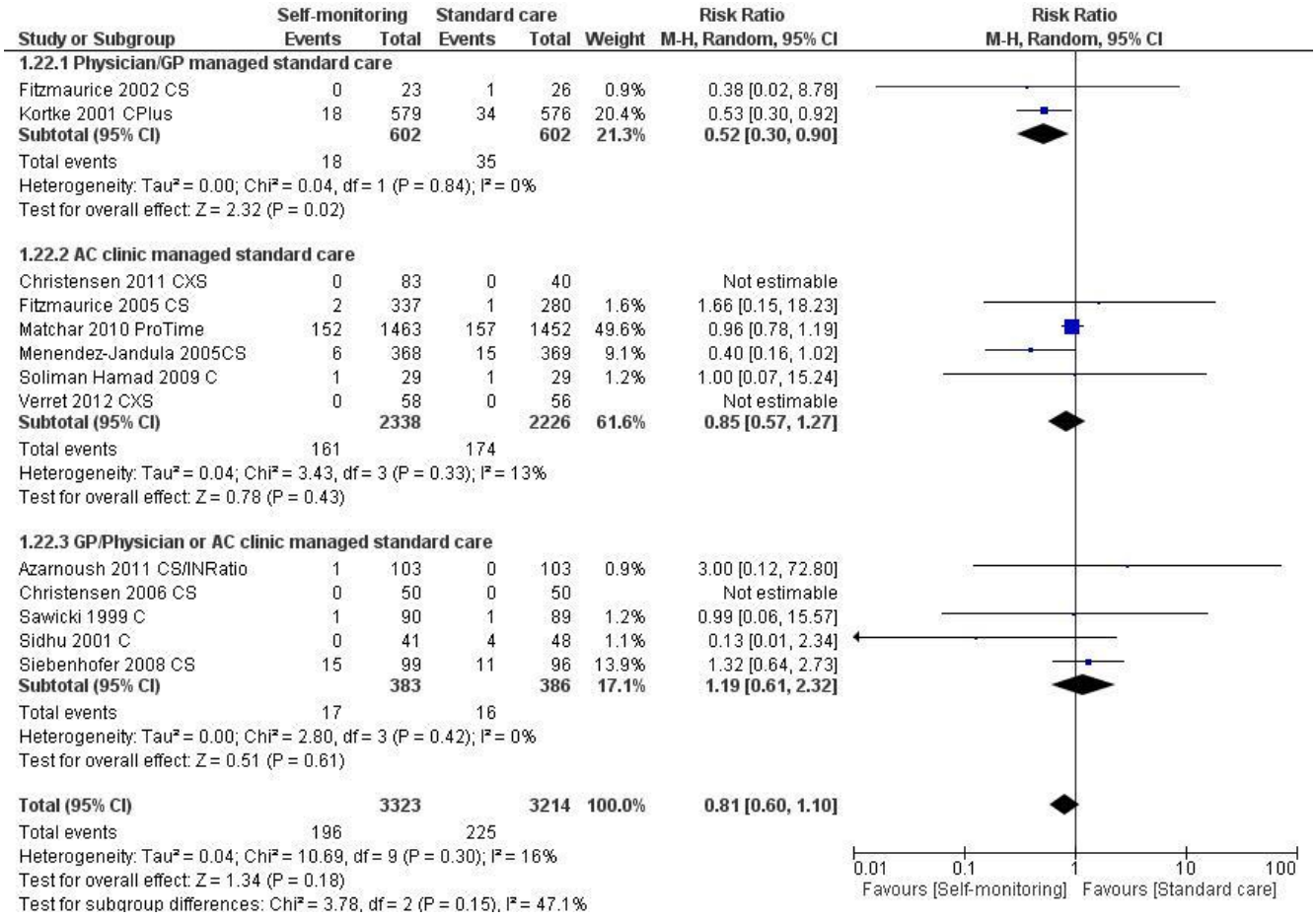
(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

Figure 12 Forest plot of comparison: mortality



(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

Figure 13 Forest plot of comparison: mortality: clinical indication



(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS; CoaguChek 'XS'; CPlus: CoaguChek Plus)

Figure 14 Forest plot of comparison: mortality: type of standard care

Heterogeneity among trials

A significant statistical heterogeneity was observed for any bleeding outcomes (I^2=66%, p<0.0001). In contrast, there was no statistically significant heterogeneity across trials for thromboembolic outcomes (I^2=36%, p=0.08) and for mortality (I^2=11%, p=0.34). The summary estimates of effect were influenced considerably by five large trials: Eitz and colleagues,[77] Kortke and colleagues,[69] Fitzmaurice and colleagues,[63] and Menendez-Jandula and colleagues[60] for self-management and Matchar and colleagues,[70] for self-testing. The trial by Matchar and colleagues,[70] which was the largest trial on self-testing, did not show any significant difference between self-testing and standard care with regard to the incidence of major events. Standard care was provided by means of high quality clinic testing in this trial (a designated, trained staff responsible for participants' visits and follow up; the use of a standard local procedure at each site for anticoagulation management; and the performance of regular INR testing about once a month). The estimated effect of self-testing versus standard

care in the subgroup analysis was dominated by this large trial, and therefore interpretation of this finding requires caution.

Adverse events

No other adverse events from INR testing, false test results, vitamin K antagonist therapy and sequelae were reported in the included trials.

Table 4 Main findings of the five UK trials

Study ID	Type of SM	Type of standard care	Clinical condition	*Sample size		Bleeding events		Thromboembolic events		Mortality		TTR, % (95% CI)		Frequency of self-testing, mean (SD)
				PSM/PST	SC	PSM/PST	SC	PSM/PST	SC	PSM/PST	SC	PSM/PST	SC	
Fitzmaurice 2002[66]	PSM	GP	Mixed	23	26	2	1	0	0	0	1	74 (67-81)	77 (67-86)	1.6 weeks
Fitzmaurice 2005[63]	PSM	Hospital or practice based AC clinic	Mixed	337	280	5	4	4	3	2	1	$70 (68.1-72.4)	$68 (65.2-70.6)	12.4
Gardiner 2006[55]	PSM and PST	PST within AC was the standard care	Mixed	55/49	_	NR	NR	NR	NR	NR	NR	PSM: 69.9 (60.8-76.7) PST: 71.8 (64.9-80.1)		NR
Khan 2004[68]	PST	AC clinic	AHV	44(40)	41(39)	3	2	0	0	NR	NR	#71.1 (14.5)	#70.4 (24.5)	NR
Sidhu 2001[72]	PSM	GP or AC clinic	AHV	51(41)	49(48)	3	2	10	10	0	4	76.5	63.8	NR

* Number in the brackets represents number analysed; AC: anticoagulant clinic; AHV: artificial heart valves; NR: not reported; PSM: patient self-management; PST: patient self-testing; SC: standard care; SM: self-monitoring; TTR: time in therapeutic range;
$ Values in mean
# Values as mean (SD)
Notes:

1. In a trial by Sidhu and colleagues[72] 1/41 had major thromboembolic events and moved to usual care after 3 months.
2. Three of these trials used CoaguChek S[55,63,66] while the other two used CoaguChek[68,72]
3. In a trial by Fitzmaurice and colleagues [66]INR for standard care group was measured using CoaguChek S.
4. Trials by Fitzmaurice and colleagues[63] and Sidhu and colleagues[72] were not funded by industry.
5. The trial by Gardiner and colleagues[44] only provided data on patient acceptability of self-testing and not on relevant clinical outcomes.

Table 5 Main findings of the four trials using CoaguChek XS

Study ID	Country	Type of SM	Type of standard care	*Sample size		Bleeding events		Thromboembolic events		Mortality		TTR, % (95% CI)		Frequency of self-testing, mean (SD)
				PSM/PST	SC	PSM/PST	SC	PSM/PST	SC	PSM/PST	SC	PSM/PST	SC	
Bauman 2010[54] (children population)	Canada	PSM and PST	PST within AC was the standard care	14/14	-	0/0	-	0/0	-	NR	-	#83/83.9	-	NR
Christensen 2011[65]	Denmark	PST	AC clinic, hospital outpatient or GP	OW: 51 (46) TW: 40 (37)	49 (40)	0	0	0	0	0	0	OW 79.7 (79 - 80) TW 80.2 (79.4 - 80.9)	72.7 (71.9-73.4)	OW 7.4 (2.7) TW 4.1 (1.8)
Ryan 2009[61]	Ireland	PST	AC clinic	72	60	0	1	2	1	NR	NR	$74 (64.6-81)	$58.6 (45.6-73.1)	4.6 (0.8)
Verret 2012[73]	Canada	PSM	AC clinic	58	56	26	23	0	0	0	0	# 80 (13.5)	#75.5 (24.7)	NR

AC: anticoagulant clinic; NR: not reported; PSM: patient self-management; PST: patient self-testing; SC: standard care; SM: self-monitoring; TTR: time in therapeutic range; OW: once weekly; TW: twice weekly

* Number in the brackets represents number analysed

Values as mean (SD)

$ Values as median (IQR)

Notes:

1. Significant difference reported between the groups for TTR outcomes in the trials by Christensen and colleagues[65] and Ryan and colleagues[61]
2. All four trials included participants with mixed clinical condition receiving warfarin therapy.
3. A trial by Bauman and colleagues[54] included only children; 50% of them had artificial heart valves and 50% had other clinical condition.
4. Of the total bleeding events reported in a trial by Verret and colleagues[73] 2/26 in PSM group and 2/26 in SC group were major bleeding events.
5. In a cross over trial by Ryan and colleagues[61] median TTR was reported before cross over and after cross over:
   TTR before cross over (from SC to PST) was 72 for PST and 57.6 for SC; TTR after cross over (from PST to SC) was 74.2 for PST and 59.7 for SC; a trial reported that the effect of the order of management on anticoagulation control was not significant (P = 0.412).
6. Trials by Ryan and colleagues[61] and Verret and colleagues[73] were partly funded by industry.
7. A trial by Christensen and colleagues[65] stated that "One patient was admitted to hospital during the trial. The reason for hospitalization was an INR over 9. The next day the patient's INR measured 5.1".

Table 6 Results of sensitivity analyses according to the type of point-of-care device (CoaguChek/INRatio/ProTime)

Outcomes	Main analyses			Sensitivity analyses											
	All included trials			CoaguChek System			CoaguChek XS		ProTime				*CoaguChek/INRatio		
	RR (95% CI)	P value	No. of trials	RR (95% CI)	P value	No. of trials	RR (95% CI)	P value	No. of trials	RR (95% CI)	P value	No. of trials	RR (95% CI)	P value	No. of trials
Bleeding	0.95 (0.74,1.21)	0.66	22	0.90 (0.67,1.23)	0.52	19	1.07 (0.70,1.62)	0.77	3	1.15 (1.03,1.29)	0.01	2	0.93 (0.70,1.23)	0.60	20
PSM	0.94 (0.68,1.30)	0.69	15	0.95 (0.68,1.32)	0.75	14	1.09 (0.71,1.67)	0.69	1	0.34 (0.01,8.16)	0.50	1	0.95 (0.68,1.32)	0.75	14
PST	1.15 (1.03,1.28)	0.02	7	0.58 (0.22,1.47)	0.25	5	0.28 (0.01,6.71)	0.43	2	1.15 (1.03,1.29)	0.01	1	0.97 (0.59,1.61)	0.91	6
Thromboembolic events	0.58 (0.40,0.84)	0.004	22	0.52 (0.38,0.71)	<0.0001	19	1.67 (0.15,17.93)	0.67	3	0.94 (0.48,1.84)	0.86	2	0.51 (0.38,0.70)	<0.0001	20
PSM	0.51 (0.37,0.69)	<0.0001	15	0.51 (0.36,0.72)	0.0001	14	Not estimable		1	0.20 (0.01,4.15)	0.30	1	0.51 (0.36,0.72)	0.0001	14
PST	0.99 (0.75,1.31)	0.95	7	0.71 (0.14,3.63)	0.68	5	1.67 (0.15,17.93)	0.67	2	1.01 (0.77,1.34)	0.92	1	0.55 (0.13,2.31)	0.41	6
Mortality	0.83 (0.63,1.10)	0.20	13	0.68 (0.46,1.01)	0.06	11	Not estimable	—	2	0.96 (0.78,1.19)	0.71	1	0.69 (0.48,1.01)	0.06	12
PSM	0.68 (0.46,1.01)	0.06	10	0.68 (0.46,1.01)	0.06	10	Not estimable	—	1	—	—	—	0.68 (0.46,1.01)	0.06	10
PST	0.97 (0.78,1.19)	0.74	3	Not estimable	—	1	Not estimable	—	1	0.96 (0.78,1.19)	0.71	1	3.00 (0.48,1.01)	0.50	2
TTR	WMD 2.82 (0.44,5.21)	0.02	11	WMD 2.82 (-0.69, 6.33)	0.12	8	WMD 7.18 (6.24,8.12)	<0.00001	2	WMD 3.83 (2.69,4.96)	<0.00001	2	WMD 3.21 (0.04, 6.37)	0.05	9
PSM	WMD 0.47 (-1.40,2.34)	0.62	6	WMD 0.93 (-1.18, 3.03)	0.39	5	WMD 4.50 (6.85,15.85)	0.44	1	WMD 8.60 (-7.07,24.27)	0.28	1	WMD 0.93 (-1.18, 3.03)	0.39	5
PST	WMD 4.44 (1.71,7.18)	0.001	5	WMD 5.41 (1.85, 8.97)	0.003	3	WMD 7.20 (6.25,8.15)	<0.00001	1	WMD 3.80 (2.69, 4.96)	<0.00001	1	WMD 6.23 (4.10, 8.36)	<0.00001	4

* Analysis restricted to all the trials reporting on CoaguChek and one trial reporting on either the INRatio or the CoaguChek S[76] Results were not separated according to the type of the point-of-care device in this trial. There were no other trials that reported on clinical effectiveness of INRatio.

PST: patient self-testing; PSM: patient self-management; RR: relative risk; TTR: time in therapeutic range; WMD: weighted mean difference

Intermediate results

Anticoagulation control: target range

Anticoagulation control can be measured as time INR in therapeutic range or as INR values in therapeutic range. Data on INR time in therapeutic range (TTR) were available from 18 trials.[54,55,57,59-68,70,72-74,76] However, there was variation in the measures used for reporting TTR. Seven trials comparing self-monitoring with standard care reported TTR as mean percentage;[60,63,64,68,70,73,76] three as median percentage,[57,61,74] five as overall percentage[62,65-67,72] and one as cumulative number of days.[59] The two remaining trials, which compared PSM with PST, reported the time in therapeutic range as mean percentage time (one trial)[54] and overall percentage time (other trial).[55] It proved impossible to convert median values into mean values due to the lack of information on the maximum or minimum value required by the conversion formula. Therefore, we were unable to pool the TTR results from the 18 trials which provided this information. The results of these trials are shown in Table 7.

Time in therapeutic range ranged from 52%[57] to 80%[65,73] for self-monitoring and from 55%[57] to 77%[66] for standard care. In all but three trials[57,60,66] TTR was higher in self-monitoring participants compared with those in standard care and, in five of these trials, the difference between intervention groups was statistically significant.[61,65,70,72,76] Three of the UK-based trials reported no significant differences between self-monitoring and standard care.[63,66,68] Pooling of results was possible for ten trials that provided suitable data.[60,63-68,70,73,76] No statistically significant differences were found between self-management and standard care (RR 0.47, 95% CI -1.40 to 2.34, p=0.62). A modest but significantly higher proportion of TTR was found, however, for participants assigned to self-testing compared to those in control care (WMD 4.44, 95% CI 1.71 to 7.18, p=0.001) (Figure 15). It is worth noting that the overall estimate of effect was dominated by the largest included trial on self-testing, the Home International Normalised Ratio Study (THINRS). [70] In two trials, one using CoaguChek XS[65] and the other using ProTime[70] the weighted mean difference between self-testing and standard care for TTR was significantly higher indicating better anticoagulation control among self-testing participants.

Table 7 INR results (TTR and INR values in target range)

Type of point-of-care test	Study ID	Measure	INR time in therapeutic range				INR value in target range				
			PSM/PST	Control	Difference	P value	Measure	PSM/PST	Control	Difference	P value
CoaguChek XS	Bauman 2010[54] Canada (children only)	Mean % (95% CI)	PSM: 83	PST: 83.9	1 (-7.7 to 9.7)		NR				
	Christensen 2011[65] Denmark	*overall days % (95% CI) (SD)	PST-OW 79.7 (79-80.3) (2.3) PST-TW 80.2 (79.4-80.9) (2.3)	72.7 (71.9-73.4) (2.6)	7(6-7.9) (from 73% to 80%)	<0.001	% of INR values (95% CI)	PST-OW 78.3 (76.5-80.1) PST-TW 80.8 (79.3-82.1)	67.2 (64.1-70.2)		<0.001
	Ryan 2009[61] Ireland	Median % (IQR)	74 (64.6-81)	58.6 (45.6-73.1)		<0.001	NR				
	Verret 2012[73] Canada	Mean % (SD)	80 (13.5)	75.5 (24.7)		0.79	NR				
CoaguChek S or CoaguChek	Christensen 2006[74] Denmark	Median % (95% CI)	78.7 (69.2-81.0)	68.9 (59.3-78.2)		0.14	NR				
	Cromheecke 2000[75] Netherlands	Values NR				NS	% of INR values	55	49	OR 1.2 (95% CI 1.0-1.6)	0.06
	Eitz 2008[77] Germany	NR					% of INR values	79	65		<0.001
	Fitzmaurice 2002[66] UK	*% (95% CI) (SD)	74 (67-81) (16.2)	77 (67-86) (23.5)		NS	% of INR values (95% CI)	66 (61-71)	72 (65-80)		NS
	Fitzmaurice 2005[63] UK	*Mean % (95% CI) (SD)	70 (68.1 to 72.4) (20.1)	68 (65.2 to 70.6) (23.0)	2.4 (-1.2 to 6.0)	0.18	mean % of individual (95% CI)	70 (64.8-74.8)	72 (66.3 to 77.1)		NS

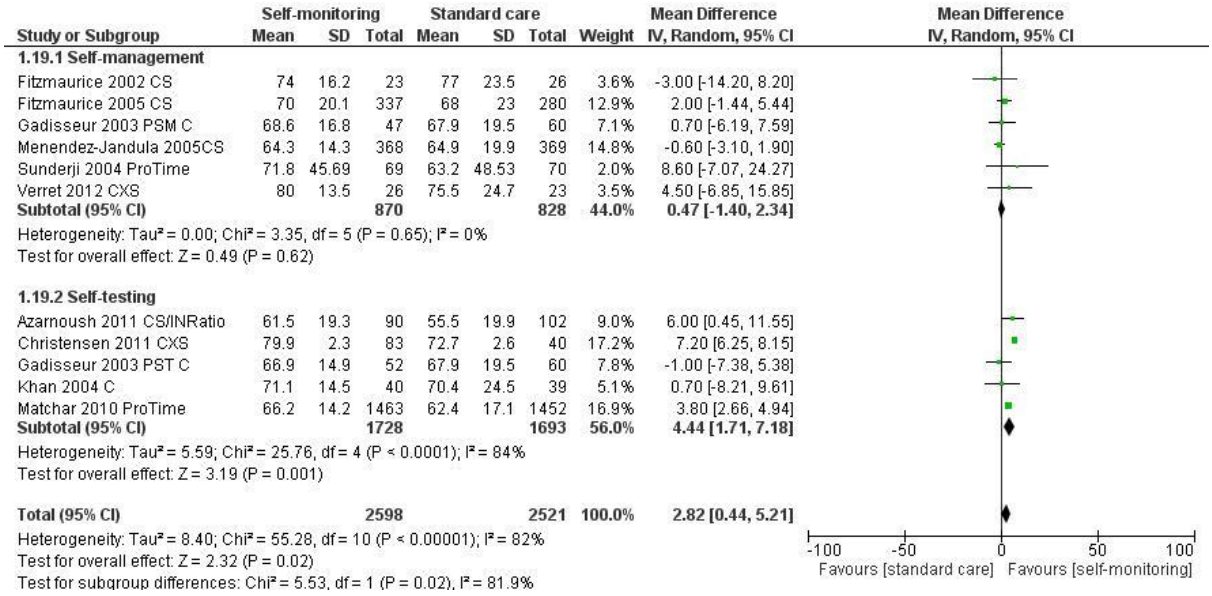
	Gadisseur 2003[67] Netherlands	*% (95% CI) (SD)	PSM; 68.6 (63.7 to 73.6) (16.8) PST: 66.9 (62.7 to 71.0) (14.9)	67.9 (62.9 to 73.0) (19.5)	PST: 3.4 (- 2.7 to 8.9) PSM: 5.1 (-1.1 to 11.3), p<0.5	0.33	% (95% CI)	66.3 (61-71.5)/63.9 (59.8-68)	61.3 (55-62.4)/ 58.7	PST: +5.2 (-1.7 to 12.1) PSM: + 7.6 (0.1 to 14), p<0.5	0.14
	Gardiner 2006[55] UK	% (95% CI) (IQR)	PSM 69.9 (60.8-76.7) (23.1)	PST 71.8 (64.9-80.1) (22.1)	PSM +PST (n=77): 71 (64.7-76.4) (22.5)	0.46	NR				
	Khan 2004[68] UK	Mean % (SD)	71.1 (14.5)	70.4 (24.5)		NS	NR				
	Horstkotte 1996[58] Germany	NR					% of INR values	43.2	22.3		<0.001
	Menendez-Jandula 2005[60] Spain	Mean % (SD)	64.3 (14.3)	64.9 (19.9)		0.2	Mean % of individual (SD)	58.6 (14.3)	55.6 (19.6)	95% CI 0.4 to 5.4	0.02
	Rasmussen 2012[57] Denmark	Median (25-75 percentile) %	52 (33-65)	55 (49-66)			NR				
	Sawicki 1999[71] Germany	NR					% of individual	53	43.2		0.22
	Sidhu 2001[72] UK	%	76.5	63.8		<0.0001	NR				
	Siebenhofer 2008[62] Austria	% (IQR) 6/12 months	70.6 (60.9, 83.9)/75.4 (9.4, 85.0)	57.5 (34.2, 80.3)/66.5 (47.1, 81.5)		<0.001/ 0.029	NR				
	Soliman Hamad 2009[78] Netherlands	NR					Mean % per patient (SD)	72.9 (11)	53.9 (14)		0.01
	Voller 2005[59] Germany	Mean cumulative days (SD)	178.8 (126)	155.9 (118.4)		NS	Mean % of INR values (SD)	67.8 (17.6)	58.5 (19.8)		0.0061

CoaguChek Plus	**Koertke 2001[69] Germany**	NR					% of INR values	79.2	64.9		<0.001
CoaguChek/ INRatio	**Azarnoush 2011[76] France**	Mean % (SD)	61.5 (19.3)	55.5 (19.9)		0.0343	NR				
	Hemkens 2008[56]	NR					NR				
ProTime	**Matchar 2010[70] US**	Mean % (SD)	66.2 (14.2)	62.4 (17.1)	3.8 (95% CI 2.7 to 5.0)	<0.001	NR				
	Sunderji 2004[64] Canada	Mean % (SD)	71.8 (45.69)	63.2 (48.53)		0.14	NR				

* standard deviation was calculated from 95% CI values given in the trials

NR: not reported; NS; not significant; OW: once weekly; TW: twice weekly; PSM: patient self-management; PST; patient self-testing

Note: Gadisseur 2003: TTR for untrained control arm was 63.5% (95% CI 59.7 to 67.3) (SD 24.6)



(Note: C: CoaguChek; CS: Coaguchek 'S'; CXS: CoaguChek 'XS')

Figure 15 Forest plot of comparison: time in therapeutic range

The INR values in therapeutic range were reported in 12 trials.[58-60,63,65-67,69,71,75,77,78] There was great variation between trials in the measures used to assess INR values in therapeutic range and, therefore, the pooling of data across trials proved unfeasible. In eight trials, which reported the proportion of INR measurements in therapeutic range,[58,59,65-67,69,75,77] the values ranged from 43.2%[58] to 80.8%[65] for self -monitoring and from 22.3%[58] to 72%[66] for standard care. In four trials that reported the proportion of participants in therapeutic range instead[60,63,71,78] the values ranged from 53%[71] to 72.9%[78] for self-monitoring and from 43.2%[78] to 72%[63] for standard care. With the exception of two UK-based trials,[63,66] all trials reported higher proportion of INR measurements or larger proportions of participants in therapeutic range for self-monitoring than for standard care. Significant differences between interventions were detected in six of these trials.[59,60,65,69,77,78] The INR values in therapeutic range are summarised in Table 7.

Among participants with artificial heart valves, self-monitoring resulted in a significantly higher INR time in therapeutic range[72,76] or INR values in therapeutic range[58,69,77,78] compared with standard care. In two trials that included participants with atrial fibrillation,[59,68] no TTR differences were found between self-monitoring and standard care.

Test failure rate

Only one trial[44] reported one instrument defect and one test strip problem in the self-testing group. No other failures were mentioned in the remaining included trials.

Time to test result

One trial[73] reported the time for each INR monitoring (i.e. time from INR measurement to test results) and the total time spent for anticoagulant management during the 4-month follow up period. The time spent for each INR monitoring by self-managed participants was significantly lower (mean 5.3 minutes, SD 2.6 minutes) compared with the time spent by participants receiving standard care (mean 158 minutes, SD 67.8 minutes, $p<0.001$). During the 4-months follow up, the total time spent for anticoagulation monitoring by participants in standard care was significantly higher (mean 614.9 minutes, SD 308.8 minutes) than the total time spent by participants who self-managed their therapy (mean 99.6 minutes, SD 46.1 minutes, $p<0.0001$).

Patient compliance with testing

Gardiner and colleagues[44] reported more than 98% compliance with self-testing and stated that participants were conscientious in performing and recording their weekly tests. Of those who did not comply with self-testing, two had difficulties performing the test or experienced disruption due to hospitalisation and one lost the CoaguChek meter. In the trial by Khan and colleagues,[68] 75% (30/40) of participants did not report any problems with the use of the device and expressed willingness to continue with self-monitoring. On the other hand, participants who did not comply (25%) with the testing procedure reported difficulties with the technique or problems placing the fingertip blood drop on the right position on the test strip. This resulted in the need to use multiple strips to achieve a single reading.

Frequency of testing

Even though the frequency of self-testing was pre-planned in 18 of the included trials,[44,55,58,61-68,70-76] only ten trials eventually reported it. [58,61-67,70,75] The frequency of self-testing ranged on average (mean) from every 4.6[61] to every 12.4 days[63] (Table 8).

Frequency of visits to primary or secondary care clinics

Frequency of visits to clinics was reported by twelve trials. Three trials reported three visits in approximately six months;[61,68,71] five trials reported four visits per year;[58,63,66,70,78] three trials reported two visits per year;[62,65,77] and the remaining trial[72] reported that there were no routine clinic visits during the study period (Table 8).

Patient reported outcomes

People's anxiety associated with waiting time for results and with not knowing their current coagulation status and related risk

The trial by Bauman and colleagues,[54] which compared self-management with self-testing in children, reported that one parent (single parent of a 16 years old male child) did not favour self-management because of the increased anxiety related to INR measurements.

Preference and acceptability of the tests

Four trials[44,54,56,61] conducted a questionnaire survey to assess acceptability to participants of self-testing and self-management using point-of-care devices (Table 9). These trials reported high rates of acceptance for both self-management and self-testing (77% to 98%).[44,54,56,61] Two trials[44,61] reported that 77% to 98% of participants favoured self-testing with CoaguChek S over standard care.

Another crossover trial[56] reported that 93% of participants rated their satisfaction with regard to self-monitoring (using either INRatio or CoaguChek S) as high or good. When asked about the overall relative satisfaction with the device, 43% of participants favoured INRatio, 36% CoaguChek S, and 21% both devices in equal way. The trial by Bauman and colleagues,[54] which assessed self-management over self-testing (usual care in this trial) in children, reported that the majority of participants (13 out of 14 participating families, 92%) opted for the use of CoaguChek XS device.

Table 8 Frequency of self-testing and adherence to self-monitoring

	Type of OAT management	***Total number in SM***	***Number (%) attending training***	***Number (%) completing and start SM***	***Number (%) adherence to SM or completing SM***	***Planned frequency of self-testing***	***Actual frequency of self-testing (mean (SD) days)***	***Clinic visit per year***	***QA per year***
Azarnoush 2011[76]	PST	103	NR	NR	90 (87)	Once weekly	NR	NR	NR
Bauman 2010[54]	PSM vs PST	PSM:14 PST:14	NR	NR	PSM: 12 (86) PST: 14 (100)	NR	NR	NR	Once
Christensen 2006[74]	PSM	50	50 (100)	48 (96)	47 (~98)	Daily for first 3 weeks then once weekly	NR	NR	Once
Christensen 2011[65]	PST: once weekly/twice weekly	51/40	NR	NR	46 (90)/37 (92)	Once weekly Twice weekly	7.4 (2.7)/4.1 (1.8)	Twice	Twice
Cromheecke 2000[75]	PSM	50	NR	NR	49 (98)	Once weekly then once every 2 weeks	8.6	NR	NR
Eitz 2008[77]	PSM	470	NR	NR	NR	NR	NR	Twice	NR
Fitzmaurice 2002[66]	PSM	30	27 (90)	26 (96)	23 (88)	Every 2 weeks	1.6 weeks	4 visits	4 in 6 months
Fitzmaurice 2005[63]	PSM	337	327 (97)	242 (74)	193 (80)	Every 2 weeks	12.4 (95% CI 11.9 to 12.9)	4 visits	4
Gadisseur 2003[67]	PSM	Total 720	184 (25)	180 (98)	NR	Once weekly	NR	NR	NR
Gardiner 2005[44]	PST	44	43 (98)	39 (91)	31 (79)	Once weekly	NR	NR	Once
Gardiner 2006[55]	PST vs PSM	PST:55 PSM:49	NR	NR	PSM: 41(74) PST: 36 (73)	Every 2 weeks	NR	NR	Once
Hemkens 2008[56]	PSM	16	16 (100)	NR	14 (87)	NR	NR	4 visits in 14 weeks	NR

	Type of OAT management	***Total number in SM***	***Number (%) attending training***	***Number (%) completing and start SM***	***Number (%) adherence to SM or completing SM***	***Planned frequency of self-testing***	***Actual frequency of self-testing (mean (SD) days)***	***Clinic visit per year***	***QA per year***
Khan 2004[68]	PST	44	NR	NR	40 (91)	Once weekly	NR	3 visits in 24 weeks	3 in 24 weeks
Koertke 2001[69]	PSM		NR	NR	NR	NR	NR	Twice	NR
Horstkotte 1996[58]	PSM	75	NR	NR	74 (99)	Every 3rd day	Median 3.9 (0.3)	~ 4 visits	NR
***Matchar 2010[70]**	PST	1465	1465 (100)	1465 (100)	1463 (>99%)	Once weekly	7.6 (5.4)	4 visits	NR
Menendez-Jandula 2005[60]	PSM	368	310(84)	300(97)	289(96)	Once weekly	NR	NR	NR
Rasmussen 2012[57]	PSM	54	NR	NR	54 (100)	NR	NR	NR	NR
Ryan 2009[61]	PST	72	NR	NR	72 (100)	Twice weekly then every 2 weeks	4.6 (0.8)	3 visits in 6 months	Every two months
Sawicki 1999[71]	PSM	90	NR	NR	83 (92)	1-2 times per week	NR	3 visits in 6 months	NR
Sidhu 2001[72]	PSM	51	44 (86)	41 (93)	34 (83)	Once weekly	NR	No visits	NR
Siebenhofer 2008[62]	PSM	99	89 (90)	89 (90)	83 (93)	Once weekly	Median = 27 days for first 6 months and 24 days for the following six months	Twice	NR
Soliman Hamad 2009[78]	PSM	29	NR	NR	29 (100)	NR	NR	4 visits	NR

	Type of OAT management	***Total number in SM***	***Number (%) attending training***	***Number (%) completing and start SM***	***Number (%) adherence to SM or completing SM***	***Planned frequency of self-testing***	***Actual frequency of self-testing (mean (SD) days)***	***Clinic visit per year***	***QA per year***
Sunderji 2004[64]	PSM	70	NR	NR	53 (76)	Once weekly for first 4 weeks, every 2 weeks for 2 months and then monthly	9.3	NR	Twice in 8 months
Verret 2012[73]	PSM	58	NR	NR	57 (98)	Once weekly	NR	NR	
Voller 2005[59]	PSM	101	NR	NR	NR	NR	NR	NR	NR

***** Randomization was carried out after the eligible participants were trained and deemed to be competent in self-testing of INR

NR: not reported; PSM: patient self-management; PST: patient self-testing

Table 9 Acceptability of the tests

Study ID	Method	Results
Gardiner 2005[44] PST	Participants in the self- testing group completed a patient acceptability questionnaire after 3–4 months. The acceptability questionnaire included patient's views on ease of use of CoaguChek S, frequency of repeated tests, difficulty of getting an adequate sample, ease of the use of QC materials, confidence in the result and preference for home testing versus hospital testing.	84% initially found it difficult to obtain an adequate sample; 55% subsequently found self-testing very easy; 32% found self-testing easy; one patient found it difficult to use CoaguChek S; 16% still experienced difficulty in obtaining sample; 87% felt confidence in CoaguChek result they obtained; 77% preferred self-testing to attending the anticoagulant clinic
Hemkens 2008[56] PSM	Participants completed a structured questionnaire regarding the ease of use of the point-of-care device.	*Satisfaction with point-of-care testing:* 92% rated satisfaction with INRatio high or good; 86% rated satisfaction with CoaguChek S high or good. *Satisfaction with self-management:* 93% rated satisfaction with self-management high or good *Ease of use of point-of-care:* 62% preferred INRatio and 23% CoaguChek S. *Overall satisfaction with point-of-care:* 43% preferred INRatio and 36% preferred CoaguChek S, 21% reported no difference between the two tests.

Ryan 2009[61] PST	One hundred and seventeen participants (88.63%) completed the satisfaction survey	99.1% found the point-of-care monitor easy to use; most participants (figure not reported) felt confident with the results they obtained; All participants (100%) agreed that the CoagCare questions and dosing instructions were clear and easy to understand; 87.6% felt that they were monitored more closely by the pharmacist during the supervised PST arm of the study; 94.7% felt that their INR was better controlled; 98.3% preferred supervised PST over attendance in the AMS.
Bauman 2010[54] PSM	Open-ended questionnaires (as a platform for semi-structured interviews) and semi-structured interviews were given. A conventional content analysis approach was taken to interpret the semi-structured interviews.	Except for one, all families preferred PSM. Responses to PSM by participants were: • "At first I didn't think I would want to. I thought I would want the protection of the VPaT program but it worked out well" • "I like self management better". • "Made us more aware of why we were changing warfarin dosing and testing more often." • "Inspires cooperation between family members" • "Shared responsibility for managing health." • "More involved." • "Makes things simpler." • "Less stress."

PST: Patient self testing, PSM: Patient self management

Health related quality of life

Nine trials reported on health related quality of life outcomes using one of the following measures:[54,66-68,70,71,73,75,78]

1. Sawicki's tool

   A structured questionnaire containing 32 questions developed and validated by Sawicki and colleagues[71] -. The questionnaire covered five treatment-related aspects including 'general treatment satisfaction', 'self efficacy', 'daily hassles', 'distress' and 'strained social network'. The questions were derived from the sentences formulated by the participants receiving anticoagulation describing their feelings with regard to their treatment. Each item is graded on a scale ranging from a minimum of 1 (total disagreement) to a maximum of 6 (total agreement) as self perceived by participants. Higher scores for self-efficacy and general treatment satisfaction and lower scores for daily hassles, psychological distress, and strained social network are indicative of better quality of life.
2. Short form Health Survey (SF-36) (UK SF-36, SF-36v2)

   SF-36 is a validated tool containing 36 items for the assessment of the --health status and quality of life. SF-36 covered physical functioning, physical role limitation, bodily pain, general health perceptions, vitality, social functioning, emotional role limitation and mental health. United Kingdom Short Form Health Survey (UKSF-36) and SF-36v2 questionnaire have been reported here.
3. Euroqol scores (EQ 5D)

   EQ 5D is a validated tool to assess health status and quality of life.
4. Lancaster's instrument

   Lancaster instrument is designed to measure health beliefs specific to the use of warfarin in anticoagulant treatment.
5. Duke Anticoagulation Satisfaction Scale

   Duke Anticoagulation Satisfaction Scale measures patient satisfaction with anticoagulation. Scores on this scale range from 25 to 225, with lower scores indicating higher satisfaction.
6. Health Utilities Index Mark 3 (HUI Mark 3)

   HUI Mark 3 is a tool to measure quality of life. Scores for the HUI Mark 3 range from −0.36 to 1.00, with a negative score indicating a state worse than being dead and a score of 1.00 indicating perfect health.
7. SEIQoL tool

   The schedule for the evaluation of individual quality of life tool.
8. KIDCLOT PAC QL parent proxy (parents QOL and their assessment of child's' QOL) and child teen KIDCLOT PAC QL©

Four trials reported quality of life using Sawicki's questionnaire (Table 10).[67,71,73,75] Sawicki and colleagues[71] and Verret and colleagues[73] reported improvements in treatment satisfaction and self-efficacy, and reduced level of distress and daily hassles in both the self-management and the standard care groups but the improvements were significantly greater among participants self-managed. Similarly, Cromheecke and colleagues[75] showed significant improvements in treatment satisfaction and self-efficacy, and significant reductions in level of distress and daily hassles for self-management participants compared with those in standard care. Gadisseur and colleagues[67] showed increased treatment satisfaction and self-efficacy, and reduced level of distress and daily hassles among self-monitoring participants (self-testing or self-management). On the other hand, they found an increased level of distress among participants who received education but did not directly monitored their anticoagulation therapy.

Two UK-based trials did not find significant differences in quality of life outcomes between self-management and self-testing participants compared with those receiving standard care (Table 11).[66,68] Khan and colleagues[68] reported quality of life data using the UK SF-36, the Euroqol scores and Lancaster's instrument. No significant differences were observed between self-testing participants and those who received education but did not test themselves, for both the UK SF-36 parameters and the Euroqol scores. Emotional function was the only parameter that showed a significant change at 24 weeks compared with baseline (p=0.04). Fitzmaurice and colleagues[66] assessed participants' attitude towards self-management and quality of life outcomes through a semi-structured interview given to a random sample of 16 participants (8 in self-management and 8 in standard care). Assessed themes were adapted from the Lancaster tool, the SEIQoL tool and a series of focus groups. Five common themes emerged from the interviews conducted on participants in self-management: knowledge and management of condition and self empowerment, increased anxiety and obsession with health, self efficacy, relationship with health professionals, and societal and economic cost. The trial investigators did not find any significant difference in quality of life between participants self-managed and those in standard care. Soliman Hamad and colleagues[78] measured quality of life in participants with artificial heart valves in the Netherlands by means of the SF-36v2. Significant improvements in quality of life scores were observed in participants who self-managed their therapy compared with those in standard care with regard to the physical component summary only. (Table 11)

Matchar and colleagues[70] measured quality of life by means of the Health Utilities Index Mark 3. They reported significant gain in health utilities at the two-year follow up among self-testing participants that used ProTime compared with those managed in high quality

anticoagulant clinics ($p<0.001$). The same investigators[70] measured also anticoagulant satisfaction using Duke Anticoagulation Satisfaction Scale. They found that the degree of satisfaction was higher in self-testing participants compared with those in standard care ($p=0.002$).

Bauman and colleagues[54] assessed self-management versus self-testing in children and provided quality of life data using the KIDCLOT PAC QL© parent- proxy (parents QOL and their assessment of child's' QOL) and the child teen KIDCLOT PAC QL©.

Both tools were completed pre and post-intervention to assess potential changes in quality of life outcomes related to warfarin use. The five common themes identified from the open-ended questionnaires and the semi-structured interviews were: awareness, communication, relationship between parent and child, flexibility, and anxiety. No significant changes in "tasks" related to warfarin use were found between intervention groups.

Table 10 Quality of life measured using Sawicki's tool

Study ID	General treatment satisfaction			Self-efficacy			Daily hassles			Distress			Strained social network		
	PSM/ PST	SC	P value	PSM/ PST	SC	P value	PSM/ PST	SC	P value	PSM/ PST	SC	P value	PSM/ PST	SC	P value
	Mean difference (SD) between baseline and follow up														
Sawicki 1999[71]	+1.54 (1.38)	+0.24 (1.48)	<0.001	+0.83 (0.92)	+0.35 (0.96)	0.003	-0.49 (0.83)	-0.03 (0.53)	0.01	-0.61 (0.87)	-0.21 (0.93)	0.008	-0.40(0.83)	-0.23 (0.79)	0.19
Verret 2012[73]	+1.3 (1.2)	+0.2 (1.1)	<0.001	+0.4 (1.2)	+0.3 (1.1)	0.647	-0.5 (0.6)	-0.2 (0.8)	<0.024	-0.6 (1)	-0.2 (0.8)	<0.029	-0.6 (0.9)	+0.1 (0.7)	<0.001
Gadisseur 2003[67]	+0.49/+0.19	-0.23		+0.32/+0.31	+0.02		-0.31/-0.09	+0.23		-0.44/+0.06	+0.33		-0.21/-0.02	+0.21	
	Mean (SD) at follow up (control group matched for age, sex and indication)														
Cromheeceke 2000[75]	4.8 (1.2)	4.0 (1.5)	0.015	5.4 (0.6)	4.5 (1.0)	<0.001	1.8 (0.5)	2.6 (0.5)	<0.001	2.5 (0.8)	2.9 (1.1)	0.022	1.7 (0.6)	2.7 (0.9)	<0.001

Notes: In a trial by Sawicki and colleagues[71] QoL assessor blinded for the treatment arm

PSM: patient self-management; PST: patient self-testing; SC: standard care;

Table 11 Quality of life measured using SF-36

UK SF-36, Euroqol scores and Lancaster instrument*			
Study ID	***Mean (SD) at 24 weeks***		
Khan 2004[68]	**PST**	**Control**	**P value**
Physical functioning	57 (29)	53 (29)	NS
Physical role limitation	45 (44)	52 (42)	NR
bodily pain	65 (34)	65 (31)	NS
General health perceptions	53 (23)	56 (21)	NR
Vitality	53 (23)	52 (21)	NR
Social functioning	71 (32)	72 (28)	NS
Emotional role limitation	63 (42)	63 (46)	NS
Mental health	78 (18)	76 (20)	NS
Euroquol five dimension score	0.75 (0.27)	0.7 (0.29)	NR
Euroquol percentage	67	66	NR

SF-36v2 questionnaire			
Study ID	***Mean % at 12 months follow up***		
Soliman Hamad 2009[78]	**PSM**	**Control**	**P value**
Physical functioning	13.2	15.8	NS
Role physical	27.4	28.3	NS
Bodily pain	7.3	-2.0	0.02
General health	13.4	9.9	NS
Vitality	25.9	17.6	0.01
Social functioning	13.3	10.8	NS
Role emotional	20	12.1	0.03
Mental health	14.2	9.2	NS
Physical component summary	20.9	9.8	0.03
Mental component summary	13.7	9.1	NS

*Researcher interviewing were blinded

3.3 Summary of the clinical effectiveness results

The evidence of the clinical effectiveness of self-monitoring (self-management and self-testing) of the coagulation status in people receiving vitamin K antagonist therapy compared with standard care was based on the findings of 26 RCTs. Four trials reported on CoaguChek XS (n=414), 17 trials on CoaguChek S/CoaguChek (n=3910), one on CoaguChek Plus (n=1155), two on CoaguChek and INRatio (n=222) and two on ProTime (n=3062). No trials that exclusively assessed the clinical effectiveness of INRatio were identified by this assessment. The main results are summarised below:

- Self-monitoring of anticoagulation therapy showed better control over thromboembolic events compared with standard care. No significant reductions were found in the number of bleeding events and all-cause mortality.
- In participants with artificial heart valves, self-monitoring almost halved the risk of thromboembolic events and all-cause mortality compared with standard care. No differences were observed between intervention groups with regard to the number of bleeding events.
- Self-monitoring significantly reduced the risk of thromboembolic events while self-testing did not.
- Time in therapeutic range varied from 52% to 80% among self-monitoring participants and from 55% to 77% in standard care. Self-testing showed a modest but significantly higher percentage of time in therapeutic range compared with standard care. No significant differences were observed between self- management and standard care. UK-based trials did not find significant differences in the TTR between intervention groups.
- Seventy seven to 93% of participants expressed a preference for self-monitoring (using CoaguChek or INRatio) over standard care.
- Two UK-based trials did not find significant differences in quality of life outcomes between intervention groups.

4 ASSESSMENT OF COST-EFFECTIVENESS

We assessed the cost-effectiveness of self-monitoring (self-testing and self-management) using CoaguChek system and alternative point-of-care testing devices compared with standard monitoring care in people receiving long-term vitamin K antagonist therapy.

4.1 Systematic review of existing cost-effectiveness evidence

Initial scoping searches revealed a number of previous systematic reviews of economic studies evaluating point-of-care testing devices for people receiving long-term vitamin K antagonist therapy.[20,30] Further systematic searches of MEDLINE, MEDLINE In-Process, Embase, Science Citation Index, Health Management Information Consortium (HMIC), NIHR Economic Evaluations Database (NEED) and the HTA Databases were undertaken to identify any further relevant studies. The search strategies are detailed in Appendix 1.

The searches identified 12 economic evaluations of potential relevance to the scope of this assessment. All of these evaluations comparing INR self-monitoring strategies with standard care were appraised against the NICE reference case, and the methods and findings of each study are summarised briefly below in a narrative fashion and tabulated for comparison in Table 12. The studies were assessed against the NICE reference case and their relevance to the scope is shown in Table 13.

***Taborski 1999*[81]**

This German study assessed the cost-effectiveness of patient self-management versus anticoagulation clinic based management by a family physician or specialist. The study included costs relevant to the primary cost carrier, in this case the government-controlled health insurance fund. Information regarding the costs of self-management and clinic management, and the costs of acute treatment and rehabilitation for complications, were acquired from patients and published literature. Quality of life was not considered in the analysis. When costs of complications were included in the analysis, self-management was estimated to be less costly and more effective than clinic managed care - owing to its estimated impact on the incidence of both thromboembolic and bleeding events. However, the estimated effects of self-management on these adverse events were selected from a small number of studies reporting high baseline rates and large beneficial effects of self-management.

***Lafata 2000*[82]**

This study carried out in the United States, constructed a Markov model with a five year time horizon to examine the cost-effectiveness of three anticoagulation management strategies: usual care with a family physician (without a point-of-care) monitoring device), anticoagulation clinic testing with a point-of-care monitor and patient self-testing with a point-of-care monitor. The self-testing strategy required participants to phone their anticoagulation clinic for dosing instructions. For each strategy it was assumed that the time within, above and below the therapeutic range differed and that time out of the target range influenced the risk of complications. Time in range was modelled to be highest for self-testing, followed by point-of-care anticoagulation clinic testing, followed by usual care. The actual estimates were based on a number of cohort studies and clinical trials, but these did not appear to be systematically identified.

The Markov model parameter values were estimated from available literature, routine health service data, and expert opinion where necessary. The analysis was conducted for a hypothetical cohort of participants, aged 57 years, initiating long-term warfarin therapy. Both a health service provider (direct medical care costs only) and wider societal perspective (including costs incurred by participants and their caregivers) were adopted. The patient self-testing strategy assumed the highest number of annual tests (52), compared to anticoagulation clinic testing (23) and usual care (14). The five-year direct health service costs (per 100 participants) were higher for the self-testing strategy ($526,014) than for usual care ($419,514) or anticoagulation clinic testing ($405,560). However, when patient and caregiver costs were included, self-testing accumulated lower 5-year costs than anticoagulation clinic testing ($622,727 versus $645,671). From the health service provider perspective, anticoagulation clinic testing with a point-of-care monitor was considered the most favourable strategy. When patient and caregiver costs were included, self-testing dominated point-of-care antigcogulation clinic testing, but remained more costly and more effective than usual care.

A number of one-way sensitivity analyses were conducted to test key parameter and structural assumptions in the model. Model findings were found to be most sensitive to assumptions regarding the frequency of yearly tests and time spent in the therapeutic range with the different strategies. Given that the setting of this study was the United States, the results cannot be generalised to the UK.

***Muller 2001*[83]**

This economic analysis was conducted to assess the cost-effectiveness of patient self-management compared to standard family physician managed anticoagulation monitoring in people following a mechanical heart valve replacement. The focus was on preventing coagulation related complications. The incidence of stroke was estimated for a hypothetical cohort of 10,000 patients from the German Experience with Low Intensity Anticoagulation (GELIA) study.[84] Data from the US, adapted to German standards, were used to inform lifetime costs of stroke. The study assumed that self-management would reduce the incidence of severe complications by 30%, compared to family physician managed care. The incremental cost-effectiveness ratio was estimated to be DM105, 000 per life year gained for self-management versus physician managed care. The authors concluded that PSM may reduce the incidence of fatal strokes at an acceptable incremental cost-effectiveness ratio.

***Sola-Morales 2003*[85]**

This evaluation was published in Catalan by the Catalan Agency for Health Technology Assessment. It was assessed partially based on a summary in a previous review[20] and using a web-based translation interface to translate key passages.

The study compared several strategies including standard laboratory testing, patient self-management, patient self-testing, point-of-care monitoring by a GP, and point-of-care monitoring in a hospital setting. A Markov model was constructed with a 5 year time horizon. Data to populate the model were acquired from a systematic literature review. The study assumed a higher incidence of adverse clinical outcomes for usual care compared to those strategies utilising a point-of-care monitoring device. It was assumed that all strategies involving the use of a point-of-care monitor had equivalent effects. Based on these assumptions, the results indicated that from a health insurer perspective, the use of point-of-care monitors in a hospital setting was the preferred option on grounds of cost-effectiveness. However, it was not clear what the relative cost-differences were between the monitoring strategies.

***Jowett 2006*[86]**

This cost-utility analysis was conducted alongside the largest UK based randomised controlled trial of patient self-management versus standard primary or secondary care INR monitoring. The follow up period was 12 months. The analysis relied on individual patient level cost and utility data (derived from responses to the EQ-5D), collected alongside the RCT.

The cost-effectiveness of patient self-management (average 30 tests per year with CoaguChek S) versus usual clinic management (average 10 tests per year at a combination of hospital and primary care clinics) was estimated from the perspective of the NHS and also from a wider perspective incorporating patient costs. The trial recruited 617 participants receiving long-term anticoagulation. Quality-adjusted-life-years were derived from participant responses to the EQ-5D at baseline, six weeks and six months. Multiple imputation was used to replace missing EQ-5D data and a regression based approach was used to estimate incremental QALYs associated with self-management.

Costs for patient self-management included training and assessment costs, device and testing strip costs, costs of any phone calls relating to INR or device queries, and costs associated with any adverse events. Costs of standard care clinic monitoring visits were estimated for the various types of standard care on offer (from a sample of participating centres) and applied on a per visit basis. Costs associated adverse events were taken from the NHS reference cost. Wider patient costs included out-of pocket travel costs and the value of time lost from work to attend appointments.

Based on intention to treat, the results indicated that from both the health service and wider perspective, mean costs in the patient self-management arm were significantly higher than those in the usual care arm (+£294 and +£282.93). There was a very small non-significant increase in QALYs in the self-management arm at 12 months (0.009; 95% CI, -0.012-0.030).

From the health service provider perspective the incremental cost-effectiveness ratio (ICER) for PSM was £32,716 per QALY gained, and an ICER of £31,437 per QALY gained was reported from a wider societal perspective. At a ceiling ratio of £20,000 per QALY gained, PSM had a 30% probability of being cost-effective, this probability increased to 46% when the ceiling ratio rose to £30,000 per QALY gained.

The authors concluded that based on the general decision rules for interpreting cost-effectiveness findings in the UK, it was unlikely that self-management would be considered cost-effective compared to usual care. However, it was noted that although patient self-management incurred a higher initial costs, it could reduce the number of people attending outpatient clinics and therefore free up clinician time for other patients. Furthermore, the results were based on only 12 months follow up of a single trial that was not powered to detect a difference in adverse events.

Regier 2006[87]

This Canadian study assessed the cost-effectiveness of patient self-managed and family physician managed (withlaboratory testing) long-term anticoagulation therapy. A Bayesian Markov model was constructed from the perspective of a Canadian health care payer, and analysed over a five year time-horizon. The adopted model structure accounted for the time spent by patients within, above or below the specified INR therapeutic range, and determined patients risks of thromboembolic and haemorrhagic events based on this.

Model input parameter estimates were derived from a number of sources. Time in therapeutic range was obtained from a Canadian trial of self-management versus physician managed warfarin therapy. Event risks for time spent in, above and below therapeutic range were derived from a prospective cohort of 2,745 people with atrial fibrillation, artificial heart valves and venous thromboembolism. Cost and utility parameters were taken from a number of different sources.

It was assumed that under the self-management strategy people would perform 52 tests per year, whilst under physician managed care only 14 tests would be performed each year, with dosing information from the laboratory test being communicated to the patient by telephone.

The mean per patient cost over the five year period was higher for the self-management strategy ($6,116) than for the physician managed strategy ($5,127). In terms of quality of life, self-management resulted in a QALY gain at the five years of 0.07. This was due to a modelled reduction in both the number of thromboembolic events and haemorrhagic events. The reported ICER for self-management versus physician managed care was $14,129 per QALY gained. The authors concluded that self-management was cost-effective for people receiving long-term anticoagulation therapy.

The methods for calculating tyhe costs and outcomes in this study were not transparent and the time spent in the therapeutic range was derived from the results of a single clinical trial conducted in a Canadian setting. Moreover, the perspective adopted was that of a Canadian health care payer, which makes the generalisability of these results to a UK setting difficult. In addition, the comparator in this study was physician managed care relying on laboratory testing, rather than anticoagulation clinic managed care using point-of-care testing. As such, the result may not be less generalisable to contexts where the latter approach is used in standard practice.

***Brown 2007*[30]**

Another Canadian study conducted by Brown et al. adopted a decision analytical modelling approach to assess the cost-utility of patient self-testing (52 tests per year) compared to physician managed laboratory testing (20 tests per year) and physician managed point-of-care testing (23 tests per year). The five-year model presented results from both the health care provider (estimated separately to include and exclude nursing home costs) and a wider societal perspective. The model was similar in structure to other models reported in the literature, with thromboembolic and haemorrhagic events modelled by time spent inside and outside the specified INR therapeutic range. The analysis was conducted for a hypothetical cohort of people on long-term warfarin therapy, with input parameters estimated from the published literature and a meta-analysis of studies assessing time in therapeutic range. It was assumed that self-testing and physician managed point-of-care testing were equivalent in terms of clinical effects. Cost parameters were identified from the published literature and were valued using Canadian sources.

Cumulative Costs and QALYs were estimated over a five-year period. From the health service provider perspective, the results indicated that physician managed point-of-care testing was cost-saving compared to usual care. Self-testing, on the other hand, was not found to be cost-effective in comparison with usual care (ICER $57,595 per QALY gained) and was dominated by physician managed point-of-care testing. However, from a societal perspective self-testing was found to be cost saving over both usual lab testing and physician managed point-of-care testing. A probabilistic sensitivity analysis showed that from the societal perspective, patient self-testing had a 52% probability of being cost-saving compared to usual care. An important limitation of this study was that it did not assess the impact of extending the time horizon beyond five years, which presumably would have improved the cost-effectiveness of self-testing versus usual care (physician managed laboratory testing).

***Connock 2007*[20]**

The objective of this UK based modelling study was to assess the cost-effectiveness of patient self-management of anticoagulation therapy to usual care (a mixture of primary and secondary care testing). A Markov model was constructed and analysed over a 10 year time horizon, adopting a NHS and personal social services perspective. The base-case cohort was aged 65 and was assumed to have an increased risk of death compared to the age/sex matched general population.

Model input parameters were derived from a number of sources. Estimates of time spent in therapeutic range, warfarin monitoring costs, and baseline health state utility (measured using the EQ-5D) were derived from a previous RCT conducted in the UK with an accompanying economic evaluation.[86] The cost of INR devices (assumed to be paid for by the NHS) were annuitized over a three year period, and it was assumed that where patients stopped using these for any reason within three years, 75% would be re-used by another patient. Risks of thromboembolic, major haemorrhagic, and minor haemorrhagic events were estimated from a variety published sources by time spent in, above and below the specified INR therapeutic range. Following major events, patients could either enter a state of permanent disability with associated costs and utility decrements, or have no long-terms consequences.

Following disabling events and minor haemorrhagic events patients were modelled to be at an increased risk of death from all causes. Within the model, it was assumed that there was a non-specific 2.5% reduction in the risk of adverse events with patient self-management - mediated through patient education and empowerment rather than improved INR control. This was based on the finding that self-management was not found to have a significant impact on time in therapeutic range in a pooled analysis of results from eight trials where this outcome was available. This was despite it having a significant beneficial impact on the risk of thromboembolic events and mortality (based on the pooled results from 15 trials).[20]

The base-case results were presented for both a five and ten-year time horizon. Over the five year timeframe the incremental cost per QALY for self-management was estimated to be £122,365. The cost-effectiveness of self-management improved over the longer time horizon, with the incremental cost per QALY gained being £63,655 at 10 years. Cost-effectiveness acceptability curves were generated to characterise the uncertainty surrounding the 10 year estimate. Applying a ceiling ratio of £30,000 per QALY, patient self-management was found to have only a 44% chance of being cost-effective. However, the authors also carried out a sensitivity analysis whereby the pooled estimate of effects (on major complications) from all available trials were applied, and under this scenario found the incremental cost per QALY gained to be £19,617 for self-management at 10 years. The authors concluded that patient self-management of anticoagulation therapy was unlikely to be more cost-effective than usual care in the UK, but that it might offer a cost-effective alternative for patients whose therapy could not be satisfactorily controlled in usual care.

***Gailly 2009*[31]**

The objective of this study was to conduct a cost-effectiveness analysis of the use of point-of-care devices for GP managed care, anticoagulation clinic managed care, patient self-testing

and patient self-management compared with standard laboratory testing. The analysis focused on a cohort of patients on long-term anticoagulation therapy. A decision-tree model, with a 10 year time horizon, was constructed from the perspective of a Belgian healthcare provider. The models input parameters were estimated from a meta-analysis of published studies for clinical effects and Belgian health care databases for baseline risks and resource use.

Since the meta-analysis of clinical effectiveness studies only identified evidence for a significant impact of point-of-care testing on mortality for patient self-management, the cost-effectiveness analysis focused on this modality of monitoring versus usual care (GP managed testing with analysis of the blood sample in a laboratory). Further, the outcome measure was restricted to the number of life-years gained as it was reported that no reliable quality of life data were identified. The annual number of point-of-care tests and the number of GP consultations due to INR tests in usual care and patient self-management were varied in a sensitivity analysis.

Applying the significant beneficial effects of self-management on mortality and thromboembolic events, the results showed self-management to be the dominant strategy compared to usual care, except when 100% of the GP consultations observed in usual care were assumed to be maintained with patient self-management and when the annual number of tests with self-management increased to 52 per year. The probabilistic sensitivity analysis showed patient self-management to have a high chance of being a dominant cost-saving strategy in comparison to usual care.

***Health Quality Ontario 2009*[88]**

This Canadian study assessed the cost-utility of health service point-of-care testing, patient self-testing and patient self-management versus standard care for patients on long-term anticoagulation therapy. A Markov decision analytical model was developed with a five-year time horizon, and was analysed from the perspective of the Ministry of Health and Long-Term care. The model was analysed for a hypothetical cohort of patients and model inputs were derived from a systematic review of effectiveness, other published literature and expert opinion. Time spent within and outside the therapeutic range was used to estimate the likelihood of patients moving from one health state to another. The results indicated that all of the evaluated point-of-care strategies were cost-effective compared to usual care, and that patient self-management appeared to be the most cost-effective strategy.

Other studies

In addition to the above published evaluations, two abstracts were identified for potential relevance. Visnansky and colleagues[89] conducted a rapid health technology assessment to explore the cost-effectiveness of patient self-testing using CoaguChek compared to standard care (laboratory testing). A Markov model was constructed and analysed for hypothetical cohorts (mean age 63 years) on long-term anticoagulation therapy for different indications, applying a lifetime horizon. The authors concluded that patient self-testing was a cost-effective (dominant) strategy compared to usual care for all diagnosis subgroups.

Schmidt and colleagues[90] conducted a cost-utility analysis of patient self-management compared to standard monitoring among long-term oral anticoagulation therapy patients in an Austrian setting. A Markov model was constructed adopting a lifetime horizon with an average baseline age of 67 years. This study found that although self-management incurred higher costs initially, throughout follow up these costs reduced due to the lower number of health care contacts over time. Adopting a life-time perspective, it was found that self-management was the dominant strategy based on both a cost per life-year and cost per QALY analysis.

Summary of findings from identified studies

The above overview of existing economic evaluations illustrates that the cost-effectiveness of patient self-testing and self-management versus usual care is uncertain and largely dependent on a number of key factors.

Firstly, the adopted perspective appears to a significant impact on estimated cost-effectiveness. Existing studies have estimated costs from different perspectives, including those of health service providers, society as whole, health care payers and health insurance funds. When a wider societal perspective has been adopted, self-management and self-testing strategies were generally compared favourably with standard clinic based testing, as a result of lower time costs associated with fewer health service contacts. The initial costs associated with patient self-management and self-testing also appear to be important determinants of cost-effectiveness.

Variation between the studies in terms of the estimated or assumed effects of self-monitoring (on thromboembolic and bleeding events) also helps account for the variable findings and conclusions. The two UK based evaluations of greatest relevance to the scope of this DAR[20,86] estimated or applied effect estimates consistent with small or negligible differences between self-management and usual care with respect to time in therapeutic range and adverse

thromboembolic and haemorrhagic events. They subsequently found there to be a low probability of patient self-management being cost-effective. Contrary to this, several studies applied large effect estimates favouring self-monitoring in terms of time in therapeutic range, thromboembolic events and/or mortality, and subsequently found self-monitoring strategies to be cost-saving or cost-effective.[31,87,88]

In relation to the scope of this assessment, the two most relevant studies are those reported by Jowett and colleagues[86] and Connock and colleagues.[20] These economic evaluations were largely based on the same trial conducted in the UK. Jowett and colleagues adopted an NHS and wider societal perspective and Connock and colleagues[20] adopted a health service and personal social services perspective, which is in line with the NICE reference case. Key outcomes were measured directly within the trial based evaluation, including utility values and complications experienced. Self-testing and self-management strategies do appear to increase the costs of INR monitoring in the short run, as demonstrated by these studies and others. However, other studies have shown that these costs can be offset by future cost saving and quality of life gains, depending on the relative effectiveness of self-monitoring versus usual care in reducing the incidence of mainly thromboembolic events.

The two UK based economic evaluations suggest that for effect estimates consistent with those observed in the largest UK based trial of patient self-management, self-monitoring of INR is unlikely to be cost-effective. However, no UK based trials that have been sufficiently powered to detect a significant difference between standard INR monitoring and patient self-monitoring in terms of major thromboembolic or haemorrhagic events. Given their rarity, meta-analysis of similar trials provides a more powerful means of estimating the true effect of self-monitoring on these clinical outcomes. An updated meta-analysis was described and presented in Chapter 3, and included randomised evidence from a number of recent European trials where standard care is similar to that provided in the UK in terms of approach, frequency and the level of INR control achieved. Therefore, the following section describes the construction and analysis of a new economic model that builds on those described above, and which incorporates all the available evidence on the clinical effectiveness of self-testing and self-monitoring.

Table 12 Summary of identified economic evaluations included in the review

Author	Country	Study design	Cohort	Intervention/ comparators	Study Perspective	Time-frame	Results	Conclusion
Taborski 1999[81]	Germany	Cost-consequence analysis (incidence of thromboembolic and bleeding events)	Data collected from patients to cost treatments and complications	Usual care (monitoring by patient's family physician or specialist) Vs. patient self-management	Government-controlled health insurance fund (INR monitoring costs and acute treatment and rehabilitation costs for adverse events)	Not stated (results expressed as costs and complication rates per 100 patient-years	When complication and direct costs were combined, self-management was estimated to be cost saving (DM 719 per patient per-year)	Self-management results in a decrease in the number of complications compared to usual care. When the costs of complications are included, PSM saves DM719.02 per patient per year
Lafata 2000[82]	U.S.	Cost-effectiveness / cost-utility analysis - Markov model	Hypothetical cohort of patients aged 57 initiating long-term warfarin therapy.	Usual care (14 tests per year) Vs. patient self-testing (52 tests per year) Vs. anticoagulation clinic testing (23 tests per year)	Health service provider and societal perspective	5 years	From a health service provider perspective, anticoagulation clinic testing was cost saving versus standard care. Self-testing had an ICER of $24,818 per event avoided ($153,504 per QALY gained) versus anticoagulation clinic testing but was cost-saving from a societal perspective.	From a health service provider perspective anticoagulation clinic testing is the most cost-effective option. However, the authors concluded that self-testing would be the most cost-effective from a societal perspective.

Muller 2001[83]	Germany	Cost-effectiveness analysis (simple extrapolation model)	Hypothetical cohort of 10,000 patients	Patient self-management versus usual care by a family physician	Not explicitly stated (assumed German healthcare payer)	10 years	Self-management found to cost DM105,000 per life-year gained compared to usual care.	Self-management led to a 30% reduction in severe complications at an acceptable cost-effectiveness ratio.
Sola-Morales 2003[85]	Spain	Cost-effectiveness / minimisation analysis – Markov model	-	Usual hospital care; self-management ; self-testing; use of a portable coagulometer by family physician; use of a portable coagulometer in a hospital setting.	Health insurer	5 years	Assuming equivalent clinical effects for all point-of-care strategies, hospital based coagulometer testing was found to be the lowest cost and therefore most cost-effective option	From a previous translation, hospital based coagulometer testing was reported as being the most efficient strategy.
Regier 2006[87]	Canada	Cost-utility analysis – Bayesian Markov model	Patients receiving long-term anti-coagulation for atrial fibrillation or a mechanical heart valve	Patient self-management; physician management	Canadian health care payer	5 years	The incremental cost-effectiveness ratio for self-management versus physician managed monitoring was $14,129 per QALY gained	Self-management was considered cost-effective with a 95% probability of being cost-effective at a willingness to pay of $23,800 per QALY

Jowett 2006[86]	UK	Cost-utility analysis alongside a RCT	N = 617 (337 self-management, 280 usual care). 65% male. Mean age 65.	Self-management (CoaguChek S; 30 tests per year) vs usual primary or secondary care clinic management (10 tests per year)	National Health Service (NHS) and societal perspective	1 year	The results indicated a very small non-significant increase in QALYs (0.01) associated with self-management for a cost increase of £295 - ICER £32,716 per QALY gained from a health service perspective.	Self-management appeared not to be cost-effective at one year.
Brown 2007[30]	Canada	Cost-utility analysis – Markov model	Hypothetical cohort of patients on long-term warfarin therapy	Usual care (20 tests per year); anticoagulation clinic testing with CoaguChek (23 tests per year); self-testing with CoaguChek (52 tests per year); anticoagulation clinic testing with ProTime (23 tests per year)	Health care provider and societal perspective	5 years	Anticoagulation clinic testing with CoaguChek was cost saving versus usual care. Self-testing had an ICER of $57,595 from a health and social care perspective, but was cost-saving from a societal perspective.	From a health care provider perspective, moving from usual care to self-testing was not considered cost-effective. From a societal perspective, it was cost-saving.

Connock 2007[20]	UK	Cost utility analysis – Markov type model	Mixed cohort of patients aged 65 years.	Patient self-management versus usual primary/ secondary care management	NHS and personal social services perspective	10 years	The incremental cost per QALY gained with self-management versus standard monitoring was £63,655. Self-management was estimated to have a 44% chance of being cost-effective at a threshold of £30,000 per QALY gained.	Self-management is unlikely to be cost-effective over usual care in the UK
Gailly 2009[31]	Belgium	Cost analysis and cost-effectiveness analysis (self-management versus lab testing with GP follow up) – decision tree	Cohort of patients on long-term anticoagulation therapy	Laboratory testing with GP follow up; point-of-care testing by a GP; point-of-care testing by an anticoagulation clinic; patient self-testing; and self-management	Belgian health care payer's perspective	10 years	Self-management was estimated to be the least costly strategy, and dominated usual care with respect to life years gained (the other point-of-care strategies were excluded from the CEA)	Patient self-management resulted in significantly more life-years gained and was on average cost-saving compared to laboratory testing with GP follow up
Health Quality	Canada	Cost-utility analysis –	Patients on long-term anti-	Usual care (lab testing);	Ministry of Health and Long-	5 years	All point-of-care testing strategies	The self-management

Ontario 2009[88]		Markov model	coagulation therapy	healthcare setting point-of-care testing; self-testing; self-management	Term Care		dominated lab testing (usual care). Self-testing was more costly and marginally more effective than point-of-care testing in a clinic setting. Self-management dominated both self-testing and point-of-care clinic testing.	strategy was the most cost-effective strategy

Table 13 Assessment of published economic evaluations against the NICE reference case

Element of health technology assessment	Reference case	Taborski 1999[81]	Lafata 2000[82]	Muller 2001[83]	Sola-Morales 2003[85]	Jowett 2006[86]	Reiger 2006[87]	Brown 2007[30]	Connock 2007[20]	Gailly 2009[31]	Health Quality Ontario 2009[88]
Defining the decision problem	Consistent with the scope for this assessment?	No	No	No	No	Partially	No	No	Partially	No	No
Comparator(s)	As listed in the scope developed by NICE?	Yes	Yes	Yes	-	Yes	Yes	Yes	Yes	Yes	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	No	Yes	Yes	-	Yes	Yes	Yes	Yes	No	Yes
Perspective on costs	NHS and PSS	No	No	No	No	No	No	No	Yes	No	No
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	No	Yes	No	-	Yes	Yes	Yes	Yes	No	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	No	5 years	10 years	-	No	5 years	5 years	10 years	10 years	5 years
Synthesis of evidence on health effects	Based on systematic review	No	No	No	-	No	No	Yes	No (based on trial)	No	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	No	Yes	No	-	Yes	Yes	Yes	Yes	No	Not clear

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	NA	No	NA	-	Yes	Yes	No	Yes	NA	No
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No	No	No	No	Yes	No	No	Yes	No	No
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	NA	Yes	NA	-	Yes	Yes	Yes	Yes	NA	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	No	No	No	No	Yes	No	No	Yes	No	No
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No	No	No	No	Yes	No	No	Yes	No	No

4.2 Independent economic assessment

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 alternative point-of-care devices: CoaguChek XS system; INRatio2 PT/INR monitor; and ProTime Microcoagulation system. The model was structured based on the review of published models of INR self-monitoring, and previous models evaluating the cost-effectiveness of new anticoagulant drugs compared to warfarin therapy in people with atrial fibrillation.[91,92] 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,[93,94] 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.[28]

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 to be evaluated

The economic model incorporated the pathways of care that individuals currently follow under standard practice in the NHS, as well as proposed new 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.[95] 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.[96]

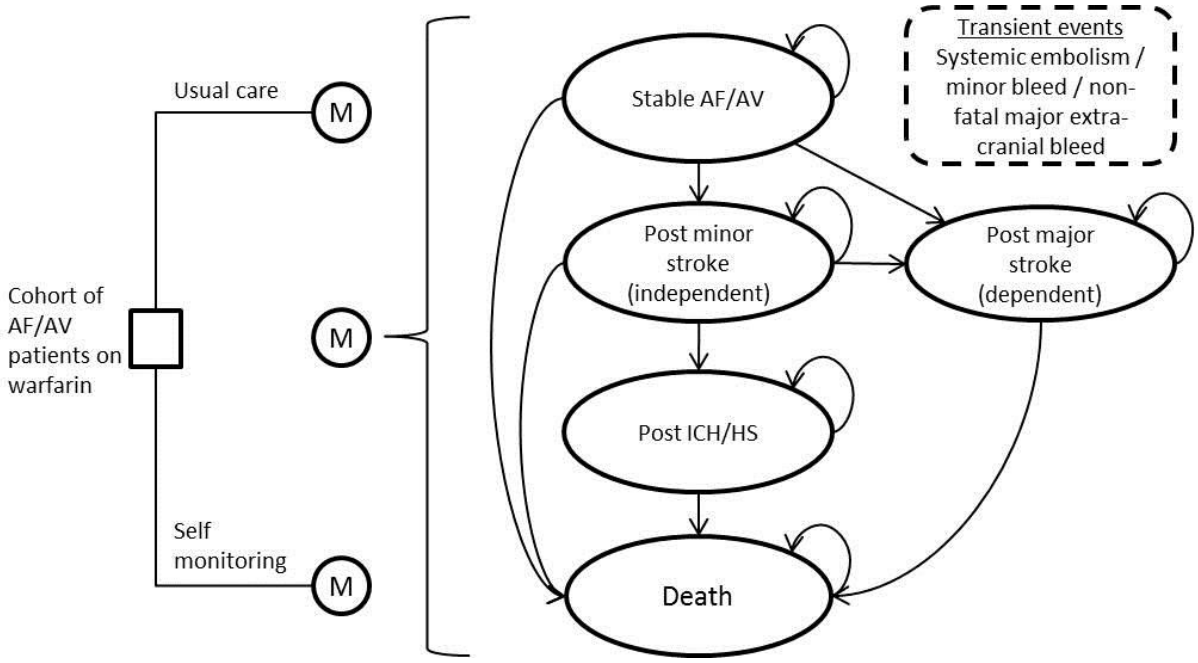
In terms of self-monitoring, the model incorporated both self-testing and self-management strategies using the alternative devices identified in the scope. However, the cost-effectiveness of self-monitoring was assessed as a whole, and it was assumed in the base case analysis that 50% of people would 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 self-testing people phone in their results from all tests undertaken, while self-managing people manage 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 (see below for further details).

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 16). 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 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 month) cycle. 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 people 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 16 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,[97-99] 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).[98,100] The

advantage of these data is that they allow underlying risks 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,[101] 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 study of atrial fibrillation patients 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.[102] 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 very 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. The study by Gallagher[102] also estimated a mean TTR (INR2-3) of 63% for the UK cohort of atrial fibrillation people on warfarin, 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[98] 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 14). Following further adjustment, where appropriate, with relative risks, 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[98,100] (Table 15).

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.[95] 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,[103] and applied to adjust the risk of stroke and SE by five year age bands.[95] A similar approach was also used to inflate the risk of bleeding with increasing age, using data from Hobbs and colleagues.[104]

Table 14 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 15 Disaggregation of modelled composite outcomes

Composite event	Proportional disaggregation	Distributional form	Source
Non-haemorrhagic stroke and systemic embolism		Beta	
Non-haemorrhagic stroke	0.909		Connolly 2009[100]
SE	0.091		Connolly 2009[100]
Major bleeding		Dirichlet	
Intracranial bleed / Haemorrhagic stroke	0.178		Connolly 2009[100]
Other major bleed	0.426		Connolly 2009[100]
Gastrointestinal bleed	0.396		Connolly 2009[100]
Non-haemorrhagic stroke		Beta	
Non-disabling(Rankin 0-2)	0.369		Connolly 2009[100]
Disabling or fatal (Rankin 3-6)	0.631		Connolly 2009[100]
Intracranial bleed / Haemorrhagic stroke		Beta	
Fatal by 30 days	0.388		NICE TA256 [95]
Non-CNS major bleed		Beta	
Proportion fatal	0.0155		NICE TA256 [95]
Disabling or fatal stroke (Rankin 3-6)			
Fatal in hospital	0.06	Beta	Hylek 2003[105]
Fatal by 30 days post discharge	0.159	Beta	Hylek 2003[105]
Non-disabling stroke		Beta	
Fatal by 30 days post discharge	0.01		Hylek 2003[105]
Systemic embolism		Beta	
Fatal	0.004		NICE TA249[106]

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.[106] Based on Hylek,[105] 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 15).

Modelled baseline risks for people with an artificial heart valve

Less extensive data was 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. However, the model provided by Roche used a dichotomised cohort with event risks estimated separately for people with atrial fibrillation and an artificial heart valve. This approach is useful for modelling subgroups and cohorts with varying proportions of people with the two conditions. Therefore, the same general approach was adopted.

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.[107] 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 16). 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.[108] 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.[109] The impact of applying this lower baseline risk was assessed through sensitivity analysis.

Table 16 Annual baseline event risks for people with AF

Event	Annual risk	Distributional form
Non-haemorrhagic stroke and systemic embolism	0.0185	Beta
Major bleed	0.0363	Beta
Minor bleed (assumed)	0.1323	Beta

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 15). Furthermore, since data on minor bleeds were not available from Heneghan and colleagues[107] 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 of people 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.[110] 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.[110,111]

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[112] and Kvidal and colleagues[113] (Table 17).

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.[114,115]

Table 17 Parameters used in the model to adjust rates of death from all and other causes

Parameter	Value	Distributional form	Source
SMR - death from all causes for Atrial fibrillation patients	1.30	Normal	Friberg 2007[112]
RR - death post minor stroke	2.33*	Normal	Sundberg 2003[110]
RR - death post disabling stroke	4.11	Normal	Sundberg 2003[110]
SMR - death from all causes for artificial heart valve patients			Kvidal 2007[113]
≤50 years	4.56	Normal	
51-60 years	2.66	Normal	
61-70 years	1.80	Normal	
≥71 years	1.02	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.[116]

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 18). Given the limitations of the available data it was not possible to accurately estimate the relative clinical effectiveness of using the alternative self-monitoring devices. Therefore, in the first instance equivalent effects were assumed on the bases of several studies showing reasonable correlation between the instruments in terms of precision and accuracy. However, it is worth noting that the majority of the clinical effectiveness evidence relates to CoaguChek S, with only one trial included in the systematic review using the INRatio2 PT/INR monitor (although not exclusively), and two trials using the ProTime Microcoagulation system (exclusively).

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 18). 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, assuming constant proportional hazards over time. The relative risks were only applied to people continuing on self-monitoring in the model.

Table 18 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	1.09	0.81	1.46	Lognormal
Self-testing	0.99	0.8	1.23	Lognormal
Self-monitoring (overall)	1.02	0.86	1.22	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.[93,94] 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).[117] These estimates of monitoring costs in standard care, which were later applied in the NICE costing template for dabigatran,[118] were derived by the ERG based on previous estimates used in the NICE costing report for clinical guideline CG36 on atrial fibrillation.[23] 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 19.

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.[23] 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.[119] However, since the allocated costs account for administration, additional admin time per patient visit was not costed separately as it was in previous estimates.[23,92,117]

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 19 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[94]
Admin time (15 minutes)	Accounted for in allocated costs for nursing time	-	PSSRU, 2012[94]
Office consumables per clinic	£2.52	£0.21	CG36, costing report, inflated to 2011/2012 prices, assumes 12 patients per clinic[23,118]
Use of shared equipment (equivalent annual cost)	£171.65	£0.29	Roche (CoaguChek 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	
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)[93]
Assumed variable cost component (0.6667)	£15.33 (per visit)	15.33	TA249 ERG report, 2011[92,117]
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.[63] 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.[86] 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 20, inflated to 2011/2012 prices.

Table 20 Alternative unit costs of standard care INR monitoring in different settings, reported by Jowett 2006.[86]

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 19. 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[86] 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.[63] 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.[23,118] 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,[120] 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 19.

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 20 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[95] and the return transport cost was taken from the NHS reference costs (£30.96).[93]

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,[107] 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.[107] 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 used 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 21.

Equipment

Self-monitoring device costs were obtained from the manufacturers. However, no up-to-date cost could be obtained for ProTime Microcoagulation System. The UK distributor of this device was contacted for information, but stated that the device was not marketed for patient self-monitoring in the UK, and that the device was being superseded by the ProTime InRhythm System, which is being marketed in the UK for professional use only. For completeness, a self-monitoring strategy using the ProTime Microcoagulation System was included in the economic model, by applying an NHS list price from 2008.[121] Finally, a new proportional price (of £195) was provided for INRatio2. The impact of using this price was assessed in a sensitivity analysis.

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 the 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[20] 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.[94] It was assumed that self-managing people would not require any further support from nursing staff other than biannual routine assessments (below).

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).[94] 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[122] 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[63] 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[63] - 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.[63] 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 21 Summary of self-monitoring device, training and testing costs

Self-monitoring unit cost	**CoaguChek XS**	**ProTime**	**INRatio2**
Device cost	£299	£884	£275
Equivalent quarterly cost for use	£16.56	£48.95	£15.23
Test strips (per unit)	£2.81	£4.96	£2.75
Lancets (per unit)	0.04	0.10	0.05

Self-monitoring costs	**Primary care**			**Secondary care**		
	CoaguChek XS	**ProTime**	**INRatio2**	**CoaguChek XS**	**ProTime**	**INRatio2**
Training						
Self-testing	£90	£90	£90	£170	£170	£170
Self-management	£180	£180	£180	£340	£340	£340
Annual self-testing costs						
Test strips and lancets (x35)	£99.62	£177.24	£98.00	£99.62	£177.24	£98.00
External QC twice a year (2 strips + 2 lancets)	£5.69	£10.13	£5.60	£5.69	£10.13	£5.60
Routine clinic assessment twice per year	£22.50	£22.50	£22.50	£42.50	£42.50	£42.50
Phone calls (5 minutes of nurse time x 35 per year)	102.08	102.08	102.08	102.08	102.08	102.08
Cost per year based on 35 tests	**£229.90**	**£311.95**	**£228.18**	**£249.90**	**£331.95**	**£248.18**
Cost per quarter*	**£57.47**	**£77.99**	**£57.05**	**£62.47**	**£82.99**	**£62.05**

Self-monitoring costs	**Primary care**			**Secondary care**		
	CoaguChek XS	**ProTime**	**INRatio2**	**CoaguChek XS**	**ProTime**	**INRatio2**
Annual self-management costs						
Test strips and lancets (x35)	£99.62	£177.24	£98.00	£99.62	£177.24	£98.00
External QC twice a year (2 strips + 2 lancets)	£5.69	£10.13	£5.60	£5.69	£10.13	£5.60
Routine clinic assessment twice per year	£22.50	£22.50	£22.50	£42.50	£42.50	£42.50
Cost per year based on 35 tests	**£127.81**	**£209.87**	**£126.10**	**£147.81**	**£229.87**	**£146.10**
Cost per quarter*	**£31.95**	**£52.47**	**£31.53**	**£36.95**	**£57.47**	**£36.53**

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.[95] 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.[96] These costs were updated for the current analysis using the National Schedules of NHS Reference Cost, 2011-2012, where possible[93], or were otherwise inflated from previously reported 2009/2010 prices using the Hospital and Community Health Services (HCHS) pay and prices index.[94] These costs are presented in Table 22.

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 22).

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 (http://www.hscic.gov.uk/article/2610/HRG4-201112-Reference-Costs-Grouper-Documentation) - from the average length of stay in hospital for people suffering a major stroke (34.4 days based on Saka and colleagues[123]). 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 stoke 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 22 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[93]	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[93]	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 [124] NICE Clinical Guideline CG92[125]	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[93]	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[93]	VC04Z: rehabilitation for stroke (weighted average)	
Post major stroke (Rankin 3-5)	Follow-on care costs per quarter	£2,823	Wardlaw.2006[124] NICE Clinical Guideline CG92[125]	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[93]	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[125]	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[124] 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.[94]

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[96] 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.[126] Alternative values were identified for these states based on the EQ-5D responses of stroke people in the UK. Dorman and colleagues[127] used the EQ-5D to measure the health status of 867 people enrolled in the International Stroke Trial.[128] 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[91,95] 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 trail (0.738).[Jowett, 2006 70 /id} 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 23.

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 well 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 23 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[129]	EQ-5D, UK population norm adjusted for AF/AV
25-34 years	0.888	Kind 1999[129]	EQ-5D, UK population norm adjusted for AF/AV
35-44 years	0.868	Kind 1999[129]	EQ-5D, UK population norm adjusted for AF/AV
45-54 years	0.808	Kind 1999[129]	EQ-5D, UK population norm adjusted for AF/AV
55-64 years	0.758	Kind 1999[129]	EQ-5D, UK population norm adjusted for AF/AV
65-74 years	0.738	Jowett 2006[86]	EQ-5D values for people with AF
≥75 years	0.688	Kind 1999[129]	EQ-5D, UK population norm adjusted for AF/AV
Minor stroke	0.641	Robinson 2001[130]	Standard gamble, UK people
Post minor stroke	0.71	Dorman 2000[127]	EQ-5D, UK stroke people
Major stroke	0.189	Robinson 2001[130]	Standard gamble, UK people
Post major stroke	0.31	Dorman 2000[127]	EQ-5D, UK stroke people
Systemic embolism (decrement)	-0.119	Sullivan 2006 [131]	Based on EQ-5D scores from a US cohort
Minor bleed	0.7757	Sullivan 2006[131]	As above
>75 years	0.7257		As above, adjusted for consistency with UK population norms
Major bleed (decrement)	-0.1814	Sullivan 2006[131]	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.[28] 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). Each strategy was compared incrementally to its next less costly, non-dominated comparator, to estimate its incremental cost per quality adjusted life year gained (QALY). In addition, given the uncertainty surrounding the relative effectiveness of the alternative self-monitoring devices, self-monitoring using each device was also compared incrementally to the standard care monitoring strategy (mixed primary and secondary care monitoring).

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.[132] 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 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 using each device compared to standard practice. Since no direct evidence for the relative clinical effectiveness of the alternative monitoring devices could be identified, the strategies have not been compared simultaneously in the probabilistic analysis. 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.

4.3 Results

Base case analysis

This section presents the results of the base case analysis. The following assumptions were applied:

- 66.45% of standard care monitoring occurs in primary care with practice nurses.
- 60% of the cohort have atrial fibrillation, 40% have an artificial heart valve.
- Average age of the cohort is 65 years, and 55% are male.
- 50% of self-monitoring people self-test, 50% self-manage.
- The increase in the number of tests performed per year with self-monitoring is 23.[107]
- 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 (training failure).
- 10% of participants discontinue self-monitoring within a year of commencing.
- Self-monitoring device costs are annuitized over five years.
- 75% of devices are reused by another patient when a patient discontinues self-monitoring.

Figure 17 indicates the modelled proportion of the cohort (under standard monitoring care) experiencing a stroke, thromboembolic event, major bleeding event, and death by time in years. Figure 18 presents the same outcomes under the self-monitoring strategy. Applying the based case assumptions, the results 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%, whilst slightly increasing the proportion suffering a major haemorrhagic event by 1.4% (Table 24).

While the predicted monitoring costs are higher with self-monitoring (Table 24), the overall net health and social care costs are similar and in some cases lower, and the QALYs gains are greater. Thus under the base case scenario, the self-monitoring strategies compare favourably with standard care, except for with ProTime where the incremental cost per QALY gained is £47,640 (Table 25, Figure 19). Furthermore, due to the lower cost of the INRatio2 device and testing strips, coupled with the assumption of equivalent clinical effectiveness of the alternative self-monitoring devices, INRatio2 dominates CoaguChek XS. However, it should be noted that no direct evidence of clinical effectiveness was identified exclusively for INRatio2 from the systematic review.

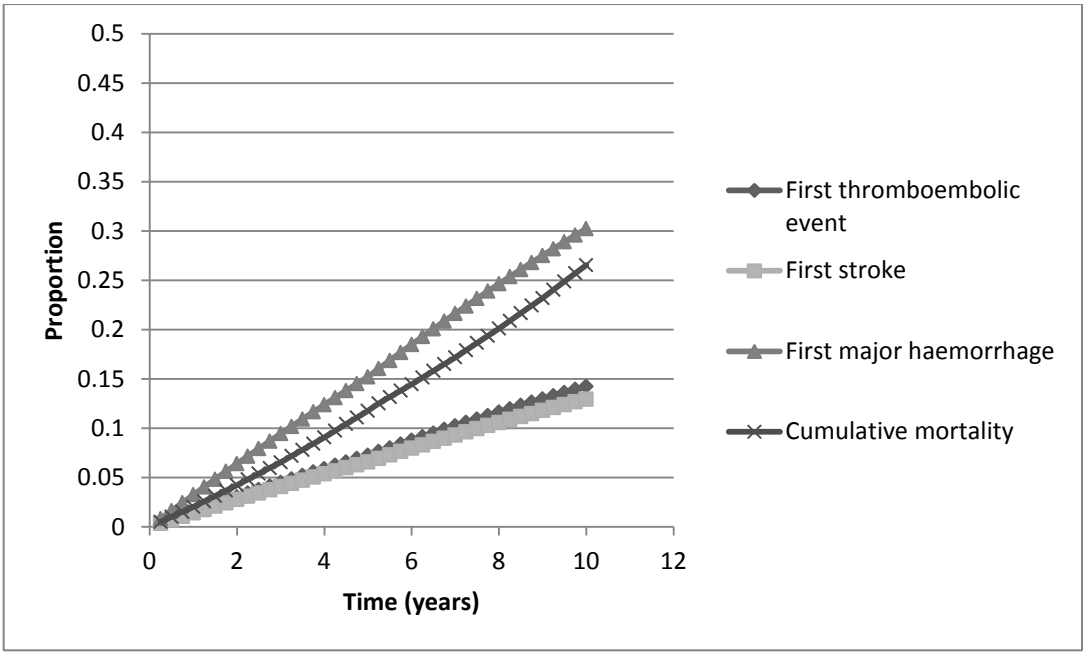


Figure 17 Modelled cumulative probability of a first thromboembolic and major haemorrhagic event, and death from all causes (standard care cohort)

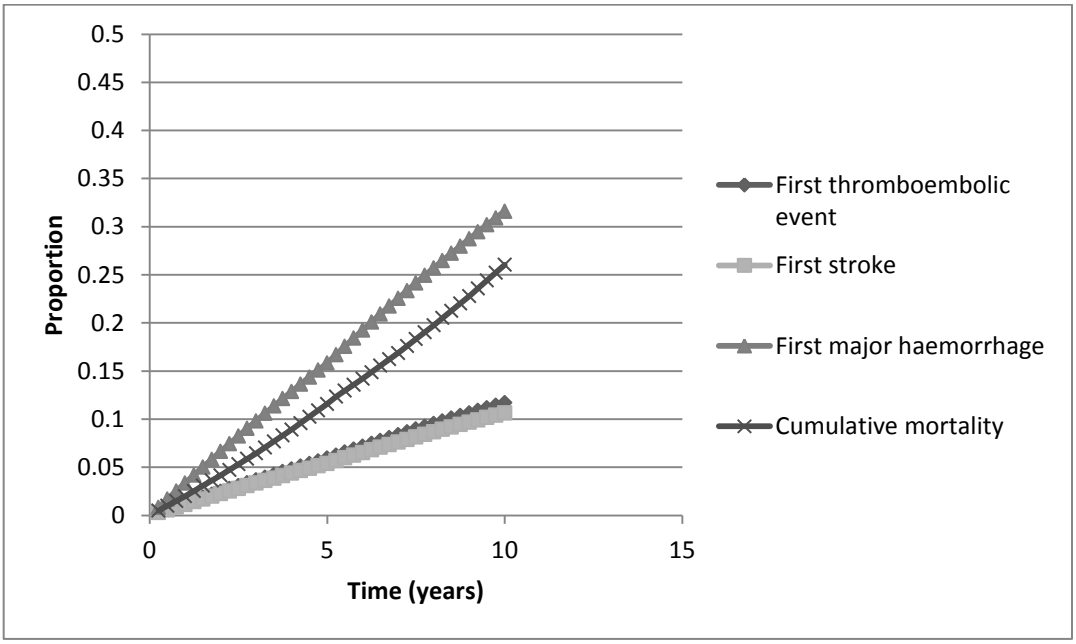


Figure 18 Modelled cumulative probability of a first thromboembolic and major haemorrhagic event, and death from all causes (self-monitoring cohort)

Table 24 Mean costs and outcomes over a 10-year time-horizon

Strategy	Mean costs	Cumulative monitoring /device costs	First thromboembolic event (%)	First major bleed (%)	Mean QALYs
Standard monitoring	£7,324	£1,269	14.2	30.2	5.479
Self-monitoring - INRatio2	£7,295	£1,908	11.7	31.6	5.507
Self-monitoring - CoaguChek XS	£7,333	£1,944	11.7	31.6	5.507
Self-monitoring - ProTime	£8,609	£3,192	11.7	31.6	5.507

Table 25 Mean and incremental costs and effects over a 10-year time-horizon

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER*	ICER Vs. standard care
Self-monitoring - INRatio2	£7,295	£0	5.507	0	-	Dominant
Standard monitoring	£7,324	£29	5.479	-0.027	Dominated	-
Self-monitoring - CoaguChek XS	£7,333	£37	5.507	0	Dominated	£319
Self-monitoring - ProTime	£8,609	£1,314	5.507	0	Dominated	£47,604

Notes: *ICER expressed relative to the next less costly non-dominated alternative, assuming equivalent effects for the alternative self-monitoring devices.

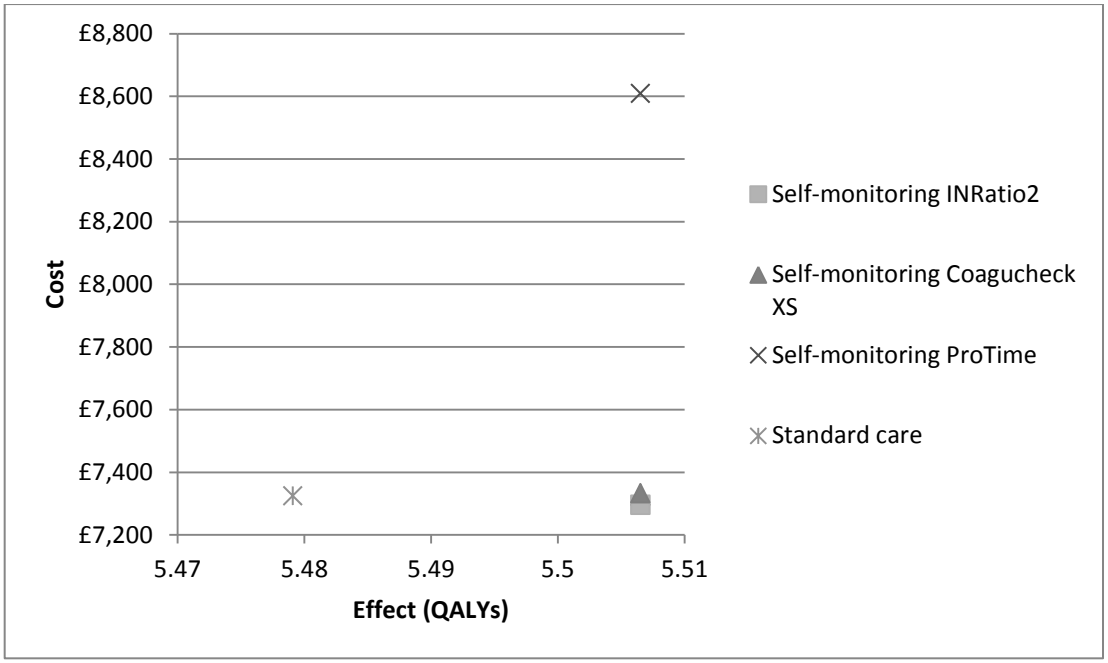


Figure 19 Cost-effectiveness frontier (base case)

Incremental analysis of alternative scenarios

Table 26 shows the results of further scenario analyses: for exclusive self-testing and self-management versus mixed primary/secondary care standard monitoring, and for mixed self-monitoring versus exclusive primary and secondary care clinic testing. Exclusive self-management with INRatio2 and CoaguChek XS was cost-saving under the base case assumptions, whereas self-testing was not cost-effective. The results also showed the mixed self-monitoring strategy (50% self-testing, 50% self-management) to be cost saving with CoaguChek XS and INRatio2 in comparison with exclusive secondary care testing. When applying the pooled relative risk for adverse events (derived from all self-monitoring studies) to both self-testing and self-managing participants, the cost savings and QALY gains associated with self-monitoring increased (Table 26, Scenario 5). This is because under this scenario self-testing becomes independently more effective. The same pattern of results was identified when self-monitoring was compared to exclusive secondary care anticoagulation clinic testing (Table 26, Scenario 6) using the point estimates of relativbe risks derived only from trials making this comparison (See Chapter 3, Figures 6 and 14). Finally, Scenario 7 (Table 26) shows the results when restriciting the comparison to CoaguChek XS versus standard monitoring, using the pooled point estimates of relative risk derived only from trials of CoaguChek versus standard practice.

Table 27 presents the results of alternative non-base case scenarios, assessing the impact of using self-monitoring not to increase the number of tests performed annually, but to replace

standard monitoring tests (average 12 per year). For these analyses it was assumed that no difference in clinical effectiveness exists between self-management, self-testing and standard care. Under most of these scenarios, standard monitoring was found to be less costly than self-monitoring. However, self-testing and self-management with INRatio2 and CoaguChek XS remained cost saving in comparison with exclusive secondary care anticoagulation clinic monitoring.

Table 26 Cost-effectiveness by type of self-monitoring and standard care comparator (primary/secondary care)

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER*	ICER vs. standard care
1. Base case (100% self-management versus standard care)						
Self-monitoring - INRatio2	£6,370	-	5.534	-	-	Dominant
Self-monitoring -CoaguChek XS	£6,407	£37	5.534	0	Dominated	Dominant
Standard monitoring	£7,324	£954	5.479	-0.054	Dominated	-
Self-monitoring -ProTime	£7,691	£1,321	5.534	0	Dominated	£6,797
2. Base case (100% self-testing versus standard care)						
Standard monitoring	£7,324	-	5.479	-	-	-
Self-monitoring - INRatio2	£8,221	£897	5.479	0	£2,699,665	£2,699,665
Self-monitoring -CoaguChek XS	£8,258	£37	5.479	0	Dominated	£2,811,298
Self-monitoring -ProTime	£9,528	£1,306	5.479	0	Dominated	£6,631,414
3. Base case (100% primary care)						
Standard monitoring	£7,132	-	5.479	-	-	-
Self-monitoring - INRatio2	£7,208	£75	5.507	0.027	£2,749	£2,749
Self-monitoring -CoaguChek XS	£7,245	£37	5.507	0	Dominated	£4,108
Self-monitoring -ProTime	£8,522	£1,314	5.507	0	Dominated	£50,689
4. Base case (100% secondary care)						
Self-monitoring - INRatio2	£7,469	-	5.507	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,506	£37	5.507	0	Dominated	Dominant
Standard monitoring	£7,704	£235	5.479	-0.027	Dominated	-
Self-monitoring -ProTime	£8,783	£1,314	5.507	0	Dominated	£39,963

5. 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						
Self-monitoring - INRatio2	£6,753	-	5.53	-	-	Dominant
Self-monitoring -CoaguChek XS	£6,790	£37	5.53	0	Dominated	Dominant
Standard monitoring	£7,324	£571	5.479	-0.051	Dominated	-
Self-monitoring -ProTime	£8,073	£1,321	5.53	0	Dominated	£14,690
6. Self-monitoring (50-50 split between self-testing and self-management) versus secondary care anticoagulation clinic testing, applying pooled relative risk estimates from RCTs where this represented the comparator (Chapter 3, Figures 6 and 11)						
Self-monitoring - INRatio2	£7,064	-	5.532	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,102	£37	5.532	0	Dominated	Dominant
Standard monitoring	£7,704	£639	5.479	-0.053	Dominated	-
Self-monitoring -ProTime	£8,386	£1,321	5.532	0	Dominated	£12,872
7. Self-monitoring with CoaguChek (50-50 split between self-testing and self-management) versus standard care, applying pooled relative risk estimates trials including only CoaguChek (Chapter 3, Table 6)						
Self-monitoring -CoaguChek XS	£7,019	-	5.531	-	-	-
Standard monitoring	£7,324	£305	5.479	-0.052	Dominated	Dominated

Notes: *ICERs expressed relative to the next less costly non-dominated alternative, assuming equivalent effects for the alternative self-monitoring devices.

Table 27 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*	ICER Vs. standard care
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 - INRatio2	£7,423	£99	5.479	0	Dominated	Dominated
Self-monitoring -CoaguChek XS	£7,457	£34	5.479	0	Dominated	Dominated
Self-monitoring -ProTime	£8,435	£978	5.479	0	Dominated	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 - INRatio2	£7,463	£139	5.479	0	Dominated	Dominated
Self-monitoring -CoaguChek XS	£7,498	£34	5.479	0	Dominated	Dominated
Self-monitoring -ProTime	£8,475	£978	5.479	0	Dominated	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 - INRatio2	£7,383	£59	5.479	0	Dominated	Dominated
Self-monitoring -CoaguChek XS	£7,417	£34	5.479	0	Dominated	Dominated
Self-monitoring -ProTime	£8,395	£978	5.479	0	Dominated	Dominated
4. 100% self-test with no increase in number of tests performed compared to standard care (compared to standard monitoring in secondary care)						

Self-monitoring - INRatio2	£7,638	-	5.479	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,672	£34	5.479	0	Dominated	Dominant
Standard monitoring	£7,704	£66	5.479	0	Dominated	-
Self-monitoring -ProTime	£8,650	£1,012	5.479	0	Dominated	Dominated
5. 100% self-manage with no increase in number of tests performed compared to standard care (compared to standard monitoring in secondary care)						
Self-monitoring - INRatio2	£7,557	-	5.489	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,592	£34	5.489	0	Dominated	Dominant
Standard monitoring	£7,704	£146	5.489	0	Dominated	-
Self-monitoring -ProTime	£8,570	£1,012	5.489	0	Dominated	Dominated

Notes: *ICERs expressed relative to the next less costly non-dominated alternative, assuming equivalent effects for the alternative self-monitoring devices.

Differential results for sub-groups

Table 28 presents the results for self-monitoring versus standard care by indication (atrial fibrillation and artificial heart valves) and cohort age. Compared to standard monitoring, self-monitoring in a 65 year-old cohort with atrial fibrillation was estimated to cost £2,574 and £4,160 per QALY gained with INRatio2 and CoaguChek XS respectively. Self-monitoring with ProTime was estimated to cost £58,584 per QALY gained. For a 65 year old artificial heart valve cohort, self-monitoring with INRatio2 and CoaguChek XS was found to be more effective and less costly (dominant) compared with standard monitoring.

A further analysis was carried out for the atrial fibrillation cohort using the baseline risks observed for participants with better INR control in standard care, assuming a constant relative risk reduction for thromboembolic events associated with self-monitoring. As the INR time in therapeutic range (TTR) increased in the control group, and the baseline risk of thromboembolic events consequently dropped, the cost-effectiveness of self-monitoring also decreased. However, the ICERs for CoaguChek XS and INRatio2 only rose above £20,000 per QALY when the baseline TTR was set at >72.6%.

While cost-effectiveness was found to decrease slightly in a younger mixed cohort (due to the lower baseline risk of thromboembolic events), the incremental cost-effectiveness ratios for Coaguchek XS and INRatio2 remained below £20,000 per QALY gained. Self-monitoring was found to be most cost-effective in a 75 year-old cohort.

Table 28 Cost-effectiveness results by patient sub-groups

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER*	ICER Vs. standard care
1. Atrial fibrillation cohort (aged 65 years)						
Standard monitoring	£6,951	-	5.533	-	-	-
Self-monitoring - INRatio2	£7,012	£61	5.557	0.024	£2,574	£2,574
Self-monitoring -CoaguChek XS	£7,049	£37	5.557	0	Dominated	£4,160
Self-monitoring -ProTime	£8,335	£1,323	5.557	0	Dominated	£58,584
2. Mechanical heart valve cohort (aged 65 years)						
Self-monitoring - INRatio2	£7,721	-	5.431	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,758	£37	5.431	0	Dominated	Dominant
Standard monitoring	£7,884	£163	5.398	-0.033	Dominated	-
Self-monitoring -ProTime	£9,020	£1,300	5.431	0	Dominated	£34,449
3. Atrial fibrillation cohort with TTR 65.6%-72.6% (aged 65 years)						
Standard monitoring	£5,522	-	5.608	-	-	-
Self-monitoring - INRatio2	£5,780	£257	5.623	0.016	£16,409	£16,409
Self-monitoring -CoaguChek XS	£5,817	£38	5.623	0	Dominated	£18,817
Self-monitoring -ProTime	£7,117	£1,337	5.623	0	Dominated	£101,677
4. Atrial fibrillation cohort with TTR >72.6% (aged 65 years)						
Standard monitoring	£5,090	-	5.631	-	-	-
Self-monitoring - INRatio2	£5,401	£310	5.645	0.014	£22,768	£22,768
Self-monitoring -CoaguChek XS	£5,438	£38	5.645	0	Dominated	£25,548
Self-monitoring -ProTime	£6,743	£1,342	5.645	0	Dominated	£121,280

5. Mixed cohort (aged 55 years)						
Standard monitoring	£6,956	-	5.945	-	-	-
Self-monitoring - INRatio2	£7,050	£94	5.965	0.02	£4,592	£4,592
Self-monitoring -CoaguChek XS	£7,088	£38	5.965	0	Dominated	£6,465
Self-monitoring -ProTime	£8,411	£1,361	5.965	0	Dominated	£71,262
6. Mixed cohort (aged 75 years)						
Standard monitoring	£6,560	-	4.452	-	-	-
Self-monitoring - INRatio2	£6,563	£4	4.484	0.032	£116	£116
Self-monitoring -CoaguChek XS	£6,598	£35	4.484	0	Dominated	£1,209
Self-monitoring -ProTime	£7,771	£1,208	4.484	0	Dominated	£37,776
7. Mixed cohort (aged 85 years)						
Standard monitoring	£3,705	-	3.008	-	-	-
Self-monitoring - INRatio2	£3,922	£218	3.037	0.029	£7,485	£7,485
Self-monitoring -CoaguChek XS	£3,952	£29	3.037	0	£0	£8,491
Self-monitoring -ProTime	£4,874	£951	3.037	0	£0	£40,169

Notes: *ICERs expressed relative to the next less costly non-dominated alternative, assuming equivalent effects for the alternative self-monitoring devices.

Further analysis of uncertainty (sensitivity analysis)

Deterministic sensitivity analysis was undertaken to test the robustness of the model based findings to various parameter and structural assumptions (Table 29). The findings were found to be most sensitive to the baseline risk of thromboembolic events and the effectiveness of self-monitoring for preventing these events (Table 29, Scenarios 14-16). Appling a baseline risk of 1.15% coupled with the upper 95% confidence limit of the relative risk estimate for self-management (0.69), the ICERs for the mixed self-monitoring strategies rose above £30,000 per QALY gained (Table 29, Scenario 17). The same was found when the lower baseline risk (1.15%) was coupled with the upper confidence limit for the relative risk (for thromboembolic events) associated with self-monitoring as whole (0.84 applied for self-testing and self-management). 100% self-management remained cost-saving under former combined scenario but not the latter.

A final sensitivity analysis was conducted to approximate the cost-effectiveness of self-monitoring for a cohort of children with an artificial heart valve on long-term vitamin K antagonist therapy. For this analysis, the cohort age was set to 10, the baseline risk of thromboembolic events was reduced to 1.4%, and the risk of all cause mortality following a stroke was set at 14.5.[133] Under this scenario, the ICERs for self-monitoring with CoaguChek XS and INRatio2 remained favourable. However, it should be noted that no good data was identified to appropriately adjust the risk of death from all causes in children with an artificial heart valve, and therefore the standardised mortality ratio estimated for an 18-55 year old cohort of artificial heart valve participants was applied.

Table 29 Sensitivity analysis scenarios

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER*	ICER Vs. standard care
1. Assume 10 minutes of nurse time per standard primary care monitoring visit, rather than 15 minutes						
Standard monitoring	£7,146	-	5.479	-	-	-
Self-monitoring - INRatio2	£7,249	£103	5.507	0.027	£3,760	£3,760
Self-monitoring -CoaguChek XS	£7,287	£37	5.507	0	Dominated	£5,119
Self-monitoring -ProTime	£8,563	£1,314	5.507	0	Dominated	£51,699
2. Unit costs of standard care as per Jowett and colleagues 2006						
Self-monitoring - INRatio2	£7,333	-	5.507	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,370	£37	5.507	0	Dominated	Dominant
Standard monitoring	£7,468	£136	5.479	-0.027	Dominated	-
Self-monitoring -ProTime	£8,647	£1,314	5.507	0	Dominated	£43,640
3. Ten standard care visits per year (with no change in the baseline risk of adverse events						
Standard monitoring	£7,112	-	5.479	-	-	-
Self-monitoring - INRatio2	£7,241	£128	5.507	0.027	£4,676	£4,676
Self-monitoring -CoaguChek XS	£7,278	£37	5.507	0	Dominated	£6,035
Self-monitoring -ProTime	£8,555	£1,314	5.507	0	Dominated	£52,616
4. 20 standard care visits per year (with no increase in baseline risk adverse events)						
Self-monitoring - INRatio2	£7,514	-	5.507	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,551	£37	5.507	0	Dominated	Dominant
Standard monitoring	£8,170	£656	5.479	-0.027	Dominated	-
Self-monitoring -ProTime	£8,828	£1,314	5.507	0	Dominated	£24,365

5. Self-monitoring training failure rate 24% and subsequent discontinuation rate 14%						
Standard monitoring	£7,324	-	5.479	-	-	-
Self-monitoring - INRatio2	£7,328	£4	5.503	0.023	£190	£190
Self-monitoring -CoaguChek XS	£7,361	£32	5.503	0	Dominated	£1,563
Self-monitoring -ProTime	£8,459	£1,131	5.503	0	Dominated	£48,488
6. 26 self-monitoring tests per year with the same relative effects						
Self-monitoring - INRatio2	£7,079	-	5.507	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,115	£36	5.507	0	Dominated	Dominant
Standard monitoring	£7,324	£245	5.479	-0.027	Dominated	-
Self-monitoring -ProTime	£8,277	£1,198	5.507	0	Dominated	£35,287
7. 52 self-monitoring tests per year with the same relative effects						
Standard monitoring	£7,324	-	5.479	-	-	-
Self-monitoring - INRatio2	£7,704	£380	5.507	0.027	£13,879	£13,879
Self-monitoring -CoaguChek XS	£7,744	£39	5.507	0	Dominated	£15,309
Self-monitoring -ProTime	£9,237	£1,533	5.507	0	Dominated	£69,814
8. Reduce the increased number of tests with self-monitoring by 50% (+12) and halve the relative effect sizes						
Standard monitoring	£7,324	-	5.479	-	-	-
Self-monitoring - INRatio2	£7,353	£29	5.494	0.015	£1,990	£1,990
Self-monitoring -CoaguChek XS	£7,389	£36	5.494	0	Dominated	£4,440
Self-monitoring -ProTime	£8,522	£1,169	5.494	0	Dominated	£81,724
9. Higher acute costs for major stroke, based on the application of excess bed day costs for each day over the mean HRG length of stay						
Self-monitoring - INRatio2	£7,478	-	5.507	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,515	£37	5.507	0	Dominated	Dominant

Standard monitoring	£7,547	£69	5.479	-0.027	Dominated	-
Self-monitoring -ProTime	£8,792	£1,314	5.507	0	Dominated	£46,101
10. Cost-effectiveness over a 20 year time horizon						
Self-monitoring - INRatio2	£13,002	-	7.711	-	-	Dominant
Self-monitoring -CoaguChek XS	£13,055	£53	7.711	0	Dominated	Dominant
Standard monitoring	£13,417	£415	7.635	-0.076	Dominated	-
Self-monitoring -ProTime	£14,892	£1,890	7.711	0	Dominated	£19,407
11. Cost effectiveness over a 30 year time horizon						
Self-monitoring - INRatio2	£13,877	-	8.156	-	-	Dominant
Self-monitoring -CoaguChek XS	£13,934	£57	8.156	0	Dominated	Dominant
Standard monitoring	£14,300	£424	8.054	-0.102	Dominated	-
Self-monitoring -ProTime	£15,910	£2,034	8.156	0	Dominated	£15,784
12. 60% of self-monitoring patients self-test, 40% self-manage						
Standard monitoring	£7,324	-	5.479	-	-	-
Self-monitoring - INRatio2	£7,480	£157	5.501	0.022	£7,166	£7,116
Self-monitoring -CoaguChek XS	£7,518	£37	5.501	0	Dominated	£8,808
Self-monitoring -ProTime	£8,793	£1,312	5.501	0	Dominated	£66,792
13. 40% of self-monitoring patients self-test, 60% self-manage						
Self-monitoring - INRatio2	£7,110	-	5.512	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,147	£37	5.512	0	Dominated	Dominant
Standard monitoring	£7,324	£214	5.479	-0.033	Dominated	-
Self-monitoring -ProTime	£8,426	£1,315	5.512	0	Dominated	£33,383

14. Baseline risk of thromboembolic events set at 1.15%						
Standard monitoring	£5,999	-	5.537	-	-	-
Self-monitoring - INRatio2	£6,214	£215	5.554	0.017	£12,729	£12,729
Self-monitoring -CoaguChek XS	£6,252	£37	5.554	0	Dominated	£14,944
Self-monitoring -ProTime	£7,538	£1,323	5.554	0	Dominated	£91,005
15. 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 - INRatio2	£7,564	£240	5.495	0.016	£15,318	£15,318
Self-monitoring -CoaguChek XS	£7,601	£37	5.495	0	Dominated	£17,688
Self-monitoring -ProTime	£8,875	£1,311	5.495	0	Dominated	£98,856
16. Relative risk for thromboembolic events associated with self-monitoring = 0.84 for self-testing and self-management						
Standard monitoring	£7,324	-	5.479	-	-	-
Self-monitoring - INRatio2	£7,552	£228	5.495	0.016	£13,964	£13,964
Self-monitoring -CoaguChek XS	£7,589	£37	5.495	0	Dominated	£16,241
Self-monitoring -ProTime	£8,863	£1,311	5.495	0	Dominated	£94,228
17. Baseline risk of thromboembolic events 1.15%, relative risk associated with self-management 0.69						
Standard monitoring	£5,999	-	5.537	-	-	-
Self-monitoring - INRatio2	£6,397	£398	5.546	0.009	£44,308	£44,308
Self-monitoring -CoaguChek XS	£6,434	£37	5.546	0	Dominated	£48,478
Self-monitoring -ProTime	£7,718	£1,321	5.546	0	Dominated	£191,567
18. Baseline risk of thromboembolic events 1.15%, relative risk associated with self-management and self-testing 0.84						
Standard monitoring	£5,999	-	5.537	-	-	-
Self-monitoring - INRatio2	£6,388	£389	5.546	0.009	£41,225	£41,225

Self-monitoring -CoaguChek XS	£6,425	£37	5.546	0	Dominated	£45,193
Self-monitoring -ProTime	£7,709	£1,321	5.546	0	Dominated	£181,371
19. Mechanical heart valve cohort (approximation for children age 10 years)						
Self-monitoring - INRatio2	£7,897	-	7.324	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,936	£39	7.324	0	Dominated	Dominant
Standard monitoring	£7,946	£49	7.291	-0.033	Dominated	-
Self-monitoring -ProTime	£9,296	£1,399	7.324	0	Dominated	£40,906
20. Self-monitoring device costs annuitized over three years						
Standard monitoring	£7,324	-	5.479	-	-	-
Self-monitoring - INRatio2	£7,526	£202	5.507	0.027	£7,387	£7,387
Self-monitoring -CoaguChek XS	£7,584	£57	5.507	0	Dominated	£9,480
Self-monitoring -ProTime	£9,352	£1,826	5.507	0	Dominated	£74,001
21. 50% of devices are reused following patients discontinuing self-monitoring						
Self-monitoring - INRatio2	£7,301	-	5.507	-	-	Dominant
Standard monitoring	£7,324	£23	5.479	-0.027	Dominated	-
Self-monitoring -CoaguChek XS	£7,338	£38	5.507	0	Dominated	£533
Self-monitoring -ProTime	£8,626	£1,326	5.507	0	Dominated	£48,234
22. Lower cost of £195 applied for the INRatio2 PT/INR monitor						
Self-monitoring - INRatio2	£7,185	-	5.507	-	-	Dominant
Standard monitoring	£7,324	£139	5.479	-0.027	Dominated	-
Self-monitoring -CoaguChek XS	£7,333	£147	5.507	0	Dominated	£319
Self-monitoring -ProTime	£8,609	£1,424	5.507	0	Dominated	£47,604

Notes: *ICERs expressed relative to the next less costly non-dominated alternative, assuming equivalent effects for the alternative self-monitoring devices.

Probabilistic sensitivity analysis of the base case

Figure 20 shows the scatter-plot of the estimated mean incremental costs and effects of self-monitoring with CoaguChek XS compared to standard monitoring, derived from 1000 probabilistic iterations of the model. Approximately 50% of the points lie below zero on the cost axis and above zero on the effect axis, indicating a 50% chance of the self-monitoring strategy (50% self-testing, 50% self-managing) dominating standard care monitoring. The acceptability curve (Figure 21) indicates an 80% chance of self-monitoring with CoaguChek XS being cost-effective compared with standard monitoring at a willingness to pay threshold of £20,000 per QALY gained.

Figures 22 and 23 show the corresponding incremental cost and effect scatter-plot and acceptability curve for self-monitoring with INRatio2 versus standard care. This analysis assumes equivalent effects for INRatio2 compared to CoaguChek XS. Self-monitoring with INRatio2 was estimated to have an 81% chance being cost-effective at a threshold of £20,000 per QALY gained under these assumptions. However, it should be noted that no direct RCT evidence was identified for the effect of INRatio2 on long-term adverse outcomes, with the majority of RCT evidence relating to versions of CoaguChek.

Figures 24 and 25 summarise the results of the probabilistic analysis for self-monitoring with ProTime versus standard monitoring. Owing to the higher cost of the device, this strategy was found to have a lower chance of being cost-effective in comparison with standard practice.

Finally, Figures 26 and 27 summarise the uncertainy surrounding the cost-effectiveness of self-monioting with CoaguChek XS versus secondary care anticoagulation clinic testing (applying relative risk distributions based on the pooled estimates from trials making this comparison) and mixed (primary/secondary care) standard monitoring (using relative risks derived from trials using only CoaguChek).

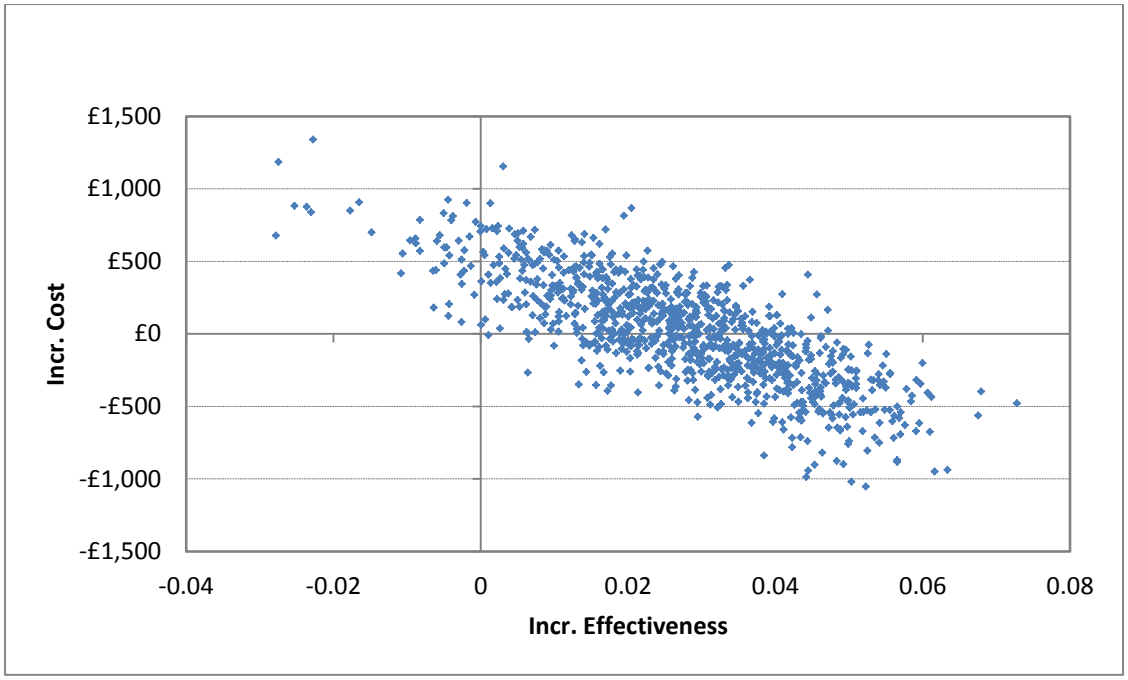


Figure 20 Incremental cost-effectiveness scatter plot – self-monitoring with CoaguChek XS versus standard monitoring

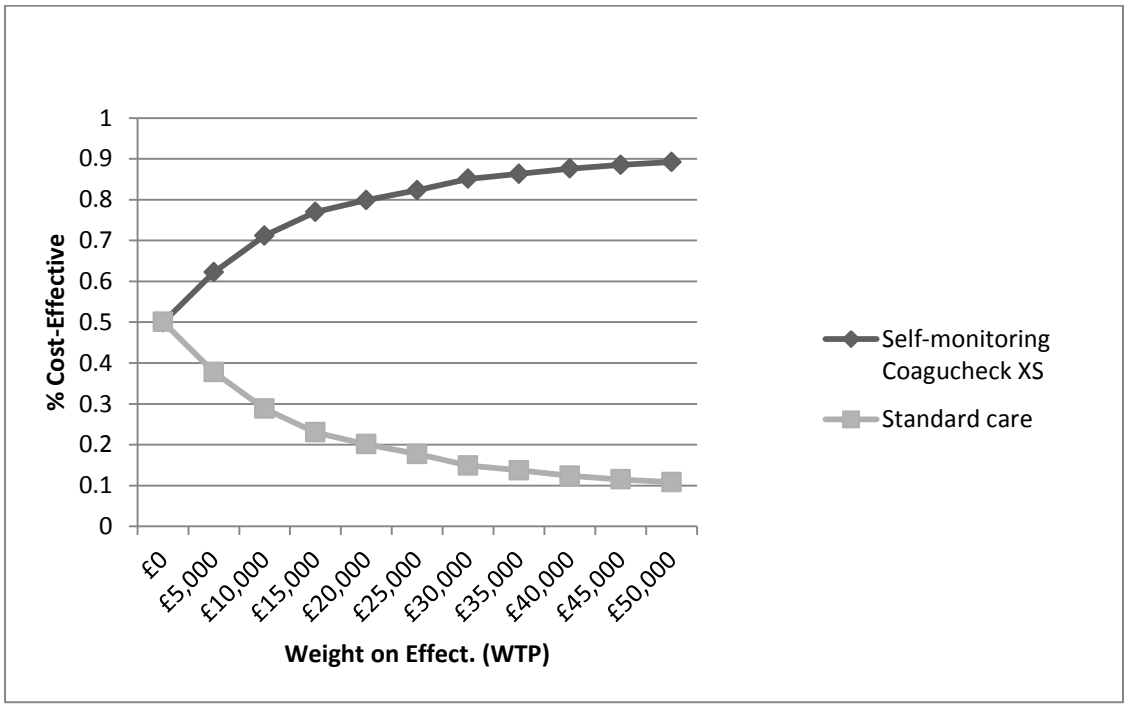


Figure 21 Cost-effectiveness acceptability curves (self-monitoring with CoaguChek XS versus standard care)

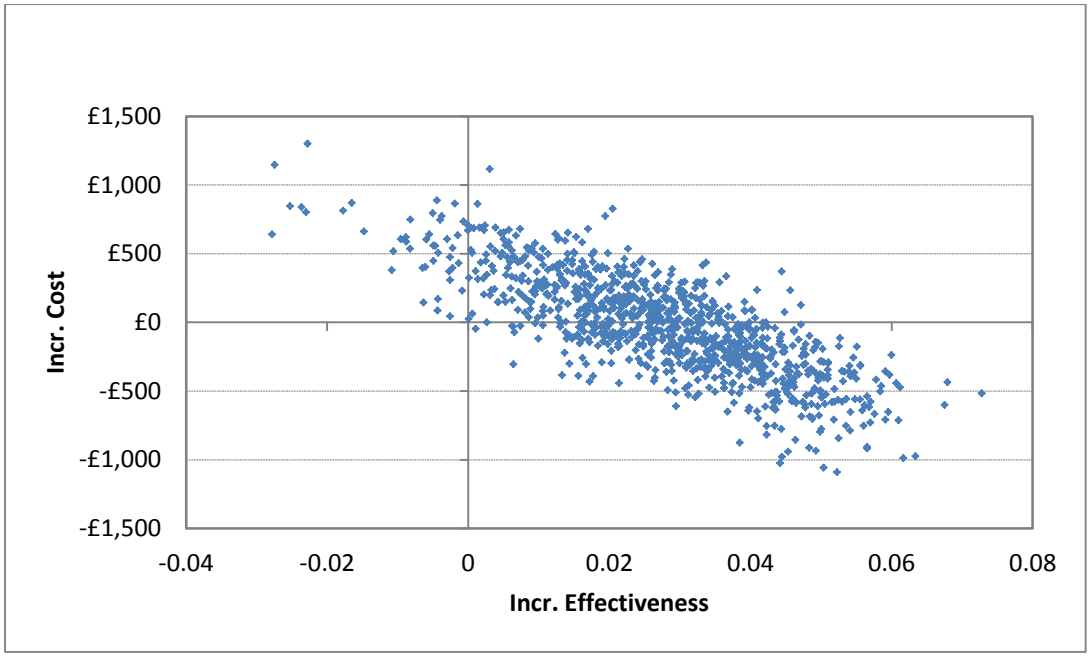


Figure 22 Incremental cost-effectiveness scatter plot – self-monitoring with INRatio2 versus standard monitoring

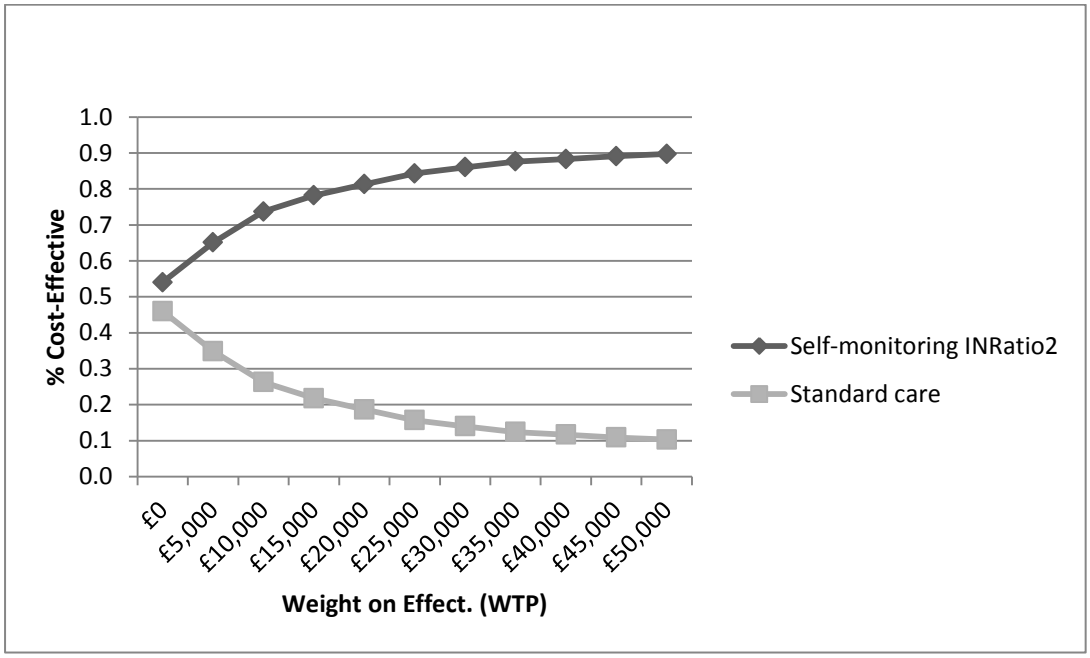


Figure 23 Cost-effectiveness acceptability curves (self-monitoring with INRatio2 versus standard care)

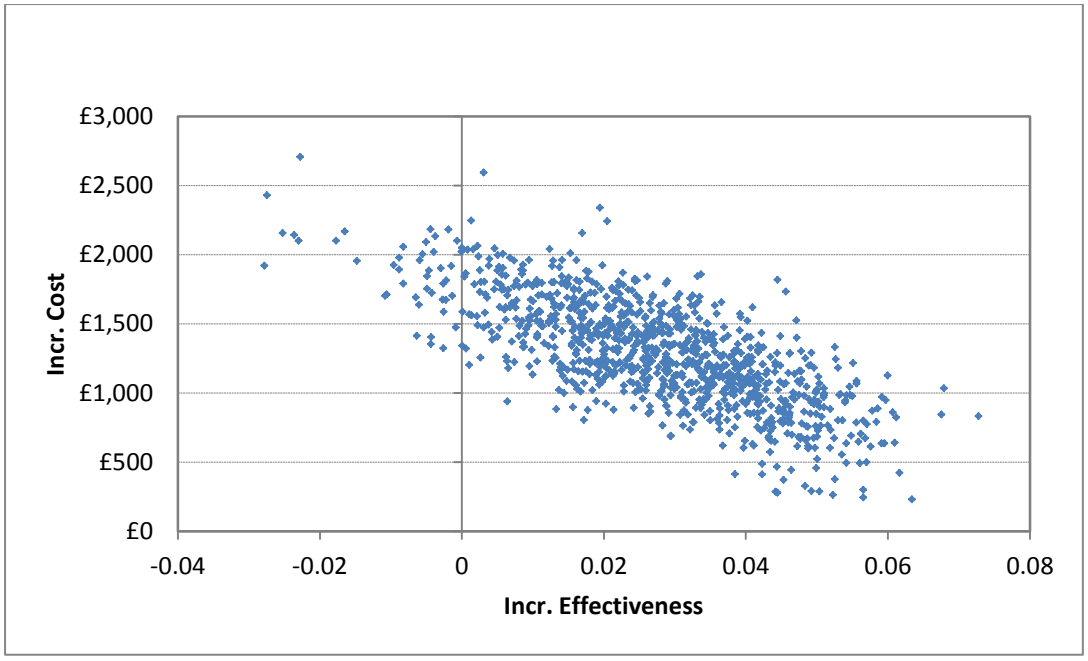


Figure 24 Incremental cost-effectiveness scatter plot – self-monitoring with ProTime versus standard monitoring

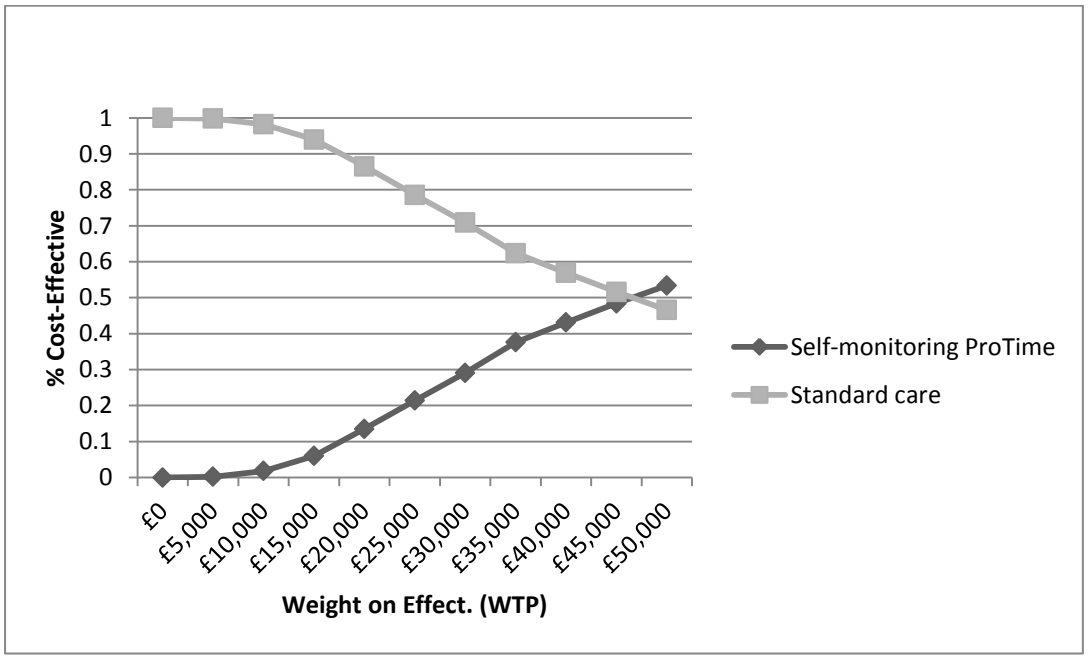


Figure 25 Cost-effectiveness acceptability curves (self-monitoring with ProTime versus standard care)

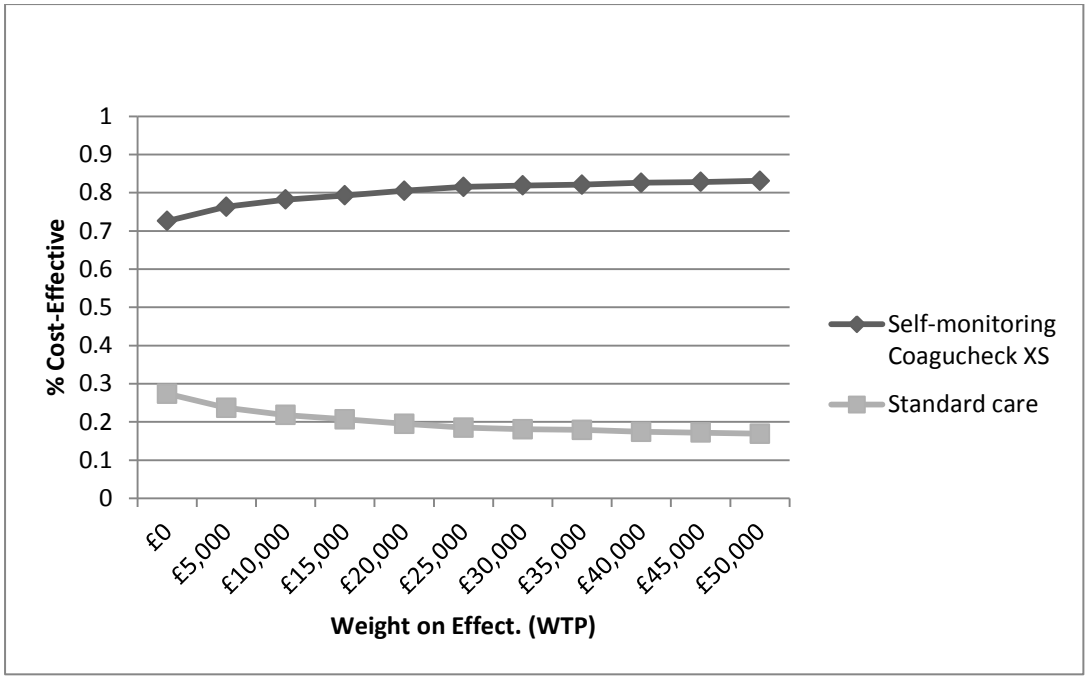


Figure 26 Cost-effectiveness acceptability curves - self-monitoring with CoaguChek XS versus standard monitoring (based on pooled relative risk estimates from CoaguChek studies only)

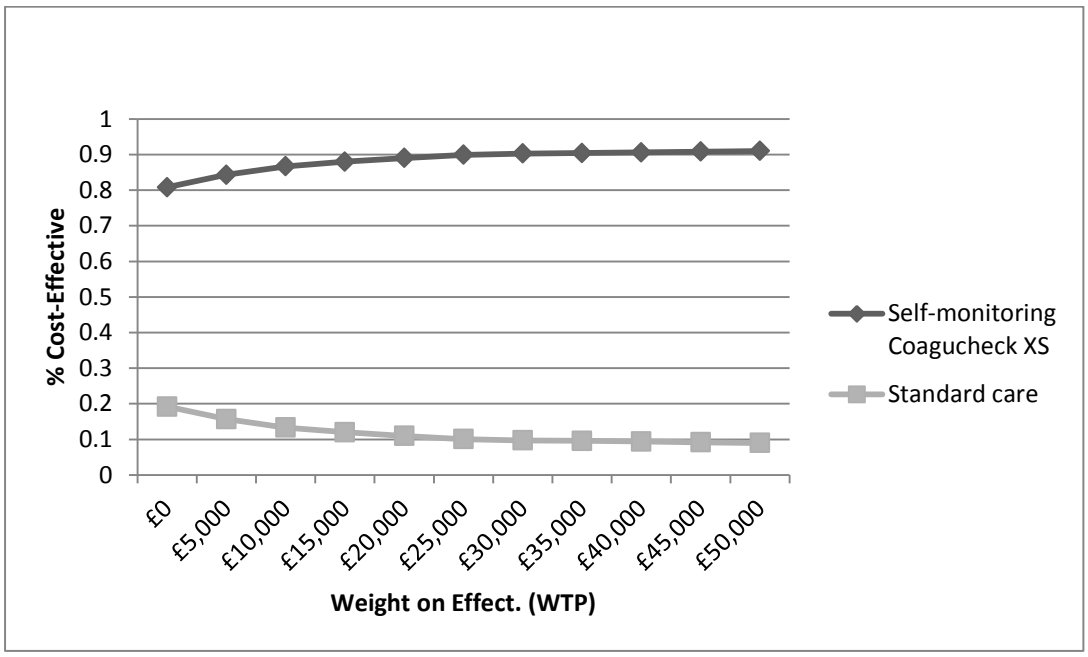


Figure 27 Cost-effectiveness acceptability curves - self-monitoring with CoaguChek XS versus secondary care anticoagulation clinic monitoring (applying relative risks for self-monitoring versus specialised anticoagulation clinic testing)

Summary

Self-monitoring, and in particular self-management, of anticoagulation status appears cost-effective when pooled estimates of clinical effectiveness are applied. However, if self-monitoring does not result in significant reductions in thromboembolic events, it is unlikely to be cost-effective from the NHS and personal social services perspective at the frequency of testing observed in randomised controlled trials.

We are most confident in the applicability of the base case cost-effectiveness findings to self-monitoring strategies using CoaguChek XS. The majority of clinical effectiveness evidence relates to a previous version of Coaguchek (CoaguChek S), to which the current version (Coaguchek XS) has been show to have very similar or slightly superior performance in terms of accuracy and precision (section 3.2). Whilst INRatio and ProTime been shown to have acceptable performance in relation to laboratory testing, very few studies have directly compared CoaguChek XS with the INRatio2 PT/INR monitor and/or ProTime Microcoagulation system. Further studies are needed to assess relative diagnostic and clinical performance.

The main findings and uncertainties are discussed further in Chapter 5.

5 DISCUSSION

5.1 Statement of principal findings

Clinical effectiveness

This assessment is based on 26 RCTs evaluating the use of point-of-care devices for the self-monitoring (self-testing and self-management) of people receiving anticoagulant therapy. The results of this assessment indicate that:

- Self-monitoring (self-testing or self-management) of anticoagulation therapy leads to significantly fewer thromboembolic events compared with standard primary care or anticoagulation control in specialised clinics (RR 0.58, 95% CI 0.40 to 0.84, p=0.004).
- No evidence of a difference in bleeding events (RR 0.95, 95% CI 0.74 to 1.21, p=0.66).
- Self-monitoring almost halved the risk of thromboembolic events in people with artificial heart valves.
- A statistically significantly greater reduction in thromboembolic events was observed among self-managed people compared with those in self-testing.
- Among people who self-monitored their therapy, there was a trend towards fewer thromboembolic events when compared with those who were managed by their GPs or physicians than when compared with those managed in specialised anticoagulation clinic. The subgroup analysis was not, however, statistically significant.
- Self-monitoring significantly reduced the risk of mortality among people with artificial heart valves but not among those with mixed clinical indication. There was lower all-cause mortality through self-management but not through self-testing. In particular, significantly fewer deaths were observed among people who self-managed their anticoagulant therapy compared with those who received primary standard care (control care by a GP or a physician).
- Compared with standard care, self-monitoring (self-testing and self-management) did not demonstrate a significant reduction in the number of major and minor bleeding events.
- In the majority of included trials (23/26), the INR time in therapeutic range was higher in self-monitoring people than in people receiving standard anticoagulation control and in five of these trials there was a statistically significant difference between intervention groups.
- The overall percentage of participants who completed self-monitoring was fairly high (at least 80%) and in the few trials that collected participant views, participants expressed high satisfaction and willingness to continue with the intervention at home.
- Six of the trials were conducted in the UK and there was no evidence that the UK trial populations were importantly different from the rest of the included studies.
- The majority of the trials (22/26) investigated the use of the CoaguChek system, the results are therefore more robust for CoaguChek compared with ProTime and INRatio.

- Four of the 22 trials investigating the CoaguChek system used the CoaguChek XS system. There was insufficient evidence to determine whether the CoaguChek XS outcomes differed from the previous versions of CoaguChek systems.
- A brief overview of diagnostic performance of the various CoaguChek systems demonstrated that across several studies INR results were more accurate in adults and children when comparing CoaguChek XS with other CoaguChek models. We are of the opinion that this provides evidence that the clinical outcomes can be compared across different versions of the CoaguChek system.

Comparison with other studies

Our findings are in line 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 significantly lower incidence of thromboembolic events[20,29,31,88,107,134-136] and deaths.[20,29,31,134-137]

The results of the subgroup analyses according to the type of control care (for thromboembolic events and mortaliy) may be considered broadly in line with the current published evidence which suggests that people managed by their GPs or physicians in primary care settings have poorer anticoagulation control than those managed in specialised anticoagulation clinics.[64,138]

Cost effectiveness

The base case model assessed the impact on costs and outcomes of using self-monitoring to increase the number of INR tests performed annually (by 23), so as to improve INR control and prevent adverse outcomes. The primary findings are detailed below:

- While self-monitoring (50% self-testing, 50% self-management) is likely to increase the INR monitoring cost compared to mixed primary/secondary care standard monitoring, it is likely to be cost-effective as a result of its impact on the incidence of thromboembolic events. This finding assumes that the pooled relative effects of self-testing and self-management, obtained from the meta-analysis of all RCTs, are applicable to the UK setting.
- Underlying this general observation is the finding that the pooled effect estimate for self-testing on thromboembolic events is small and non-significant (RR 0.99), whilst 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 (or dominant), while self-testing is not cost-effective.
- In an alternative specification the overall pooled effect estimates obtained from all self-testing and self-management trials were applied to both the self-testing and self-management strategies in the model. Under this scenario, both self-testing and self-management, with CoaguChek XS or INRatio2, were found to be dominant or highly cost-effective compared with standard monitoring.

- Two key parameters underpinning the above 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 the lower baseline risk of thromboembolic events was combined with the upper confidence limit for the relative risk associated self-management (RR 0.69), the ICERs 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 relative risk for self-monitoring as whole (RR 0.89). It should be noted however that self-management on its own remained saving under the former combined scenario.
- Further uncertainty relates to the applicability of the pooled effect estimates to the UK setting. The few identified UK based trials of self-monitoring versus standard practice did not demonstrate significant effects on thromboembolic or bleeding events. Applying these effect estimates, self-monitoring would not be cost-effective at the self-monitoring testing frequency observed in RCTs.
- Alternative scenarios assessed the potential for self-monitoring to be cost-effective if used to replace clinic based testing without increasing the frequency of testing. 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 based case parameters constant, self-monitoring (50% self-testing, 50% self-managing) was more costly than standard primary care monitoring, but less costly than standard secondary care monitoring. These findings were, however, sensitive to the unit costs applied to standard care monitoring visits. Applying the alternative standard monitoring unit costs estimated by Jowett and colleagues[86] the opposite was observed, with self-monitoring dominating secondary care monitoring but being dominated by primary care monitoring.

Comparison with other economic evaluations

The findings of the model are generally consistent with those of previous evaluations, depending on the assumptions and input values applied. In line with previous models that have assumed or applied significant reductions in thromoembolic events with self-management[31,81,83,87,88] our model suggests that self-monitoring is likely to be cost-effective under this scenario.

Our model also produces findings that are generally consistent with the previous UK based economic evaluations, in that self-monitoring (under base assumptions) will increase the monitoring costs to the NHS. However, our base case differs from previous UK evaluations in that the pooled relative effects for self-management and self-testing, compared to standard care, were applied. This results in significant future cost savings and quality of life gains from a significant reduction in the number of

thromboembolic events. This in turn translates 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 stoke 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.

5.2 Uncertainties from the assessment

Clinical effectiveness

Although our assessment has been conducted according to current standards and recommendations, and is the most up-to-date review undertaken, we need to acknowledge some potential limitations and uncertainties. The areas of uncertainty were:

- The included trials varied considerably in terms of clinical indications for anticoagulation therapy, type of control care, reporting structure for the time and/or values in therapeutic range, type and structure of the pre-intervention training and education programme, length of follow up, and methodological study quality. Whilst the meta-analysis results demonstrated low statistical heterogeneity (which makes it statistically reasonable to combine the studies) there remains uncertainty that clinical heterogeneity may have over or underestimated the effects.
- Quantifying the impact of the potential risk of bias in the estimates was not possible. Only four trials[54,60-62] were judged at low risk of bias. In some trials, outcomes were not assessed blinded, allocation of participants to intervention groups was not concealed, statistical analyses were not conducted according to an intention-to-treat principle, or many methodological details were lacking.
- All included trials enrolled highly selected samples of people requiring anticoagulation therapy, and so it was uncertain whether there was strong external validity (i.e. applicability of the study results to the entire population of eligible participants). 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[60,63,66,67] a considerable proportion of eligible participants (up to 50%) ultimately were not considered suitable for inclusion.
- The frequency of INR testing in the trials was generally weekly for self-monitoring participants and monthly in standard care. It was unclear what the optimal frequency may be, especially at long-term follow up where there was little evidence.
- There remains some uncertainty on the applicability of the pooled results to the UK population. In our view, the greatest uncertainty relates to the applicability of the standard care comparators in the trials and not to the participants in the trial.

- 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 atrial fibrillation and consequently no reliable conclusions could be drawn in relation to this patient population.
- The majority of trials investigated the use of the CoaguChek system (22/26) for the self-monitoring of anticoagulation therapy and it proved unfeasible to conduct reliable comparisons according to the type of point-of-care device. While the CoaguChek device appears to have the most robust evidence, ProTime and, particularly, INRatio do not. Given the broadly similar performance of all the devices compared with the gold standard laboratory test, we are of the opinion that it is not unreasonable to consider pooled estimates of effect across all studies and devices. However, this is an assumption that currently has no direct comparative evidence available and so a degree of caution is necessary.
- The subgroup analysis according to the type of anticoagulation therapy management (self-management versus self-testing) was limited due to the results being dominated by the largest trial published so far, the Home International Normalised Ratio Study (THINRS)[70] which enrolled 2,922 people and assessed PST using the ProTime device versus routine clinical care. The trial results showed similar rates of main clinical outcomes between intervention groups with the exception of a small but significant improvement in the percentage of time in target range for self-testing people. It is worth pointing out that this trial had a highly specialised routine care and the longest follow up period (mean 3 years). It is probable that the quality of the standard care in this trial exceeds current routine care for anticoagulation monitoring and the lack of significant differences between self-testing and routine monitoring could be explained by the rigorous criteria used to ensure high standard care.

Cost effectiveness

The model developed for this assessment has built upon previous models developed to assess the cost-effectiveness of INR self-monitoring strategies and new pharmaceuticals compared to warfarin therapy under standard INR monitoring arrangements. Where possible, input parameter values have been used that have previously been reviewed for NICE submissions by independent evidence review groups and accepted by appraisal committees. A further strength of the model comes through the dichotomisation of indication for warfarin use (atrial fibrillation / artificial heart valves), mode of standard care monitoring (primary / secondary care), and mode of self-monitoring (self-testing / self-management). This allowed assessment of cost-effectiveness by subgroups based on these indicators. Nevertheless the main uncertainties are given below:

- A weakness of the modelling relates to the uncertainty surrounding the pooled clinical effectiveness estimates (for self-testing and self-management) and in particular their applicability to the NHS setting.
- A further weakness relates to the structural assumptions required to estimate cost-effectiveness in younger cohorts; i.e. those below the average age of cohorts used to inform the baseline risks of events and standardized mortality ratios associated with the clinical indications and adverse events. To reflect the importance of age as a risk factor for thromboembolic events, relative risks by 5-year age bands were taken from a previous atrial fibrillation model[91,95,96] and applied. Given a lack of similar evidence relating to people with a mechanical heart valve, the same relative risks were also applied to this subgroup in the model. While this is not ideal, the model results were found to be robust to a range of alternative baseline risks when applied in isolation.
- Owing to data limitations very young cohorts were not formally included in sub-group analyses for the economic modelling. A sensitivity analysis was conducted to aproximate the results for a cohort of children, but the estimates of baseline risk and self-monitoring effects were not well informed.

5.3 Implications for research

Trials investigating the longer term outcomes of self-management are needed, and direct comparisons of the various point-of-care coagulometers ought to be incorporated into any future evaluation. The technology related to point-of-care testing devices is constantly changing and future research needs to target larger cohorts of people requiring long-term anticoagulation therapy who may benefit from the use of these new generations of devices.

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7 APPENDICES

Appendix 1 Search strategies

POINT-OF-CARE TESTS FOR COAGULATION SELF-MONITORING 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))

POfINT-OF-CARE TESTS FOR COAGULATION SELF-MONITORING ACCEPTABILITY

Database: Embase <1980 to 2013 Week 23>, Ovid MEDLINE(R) <1946 to May Week 5 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 07, 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 (197928)
19 10 and 18 (2639)
20 exp patient acceptance of health care/ use mesz
21 exp patient attitude/ use emez
22 consumer satisfaction/ use mesz
23 (patient? adj3 (compliance or participat$ or accept$ or refus$)).tw.
24 (patient? adj2 (attitude? or prefer$ or perception? or satisfaction)).tw.
25 qualitative research/
26 questionnaires/
27 (qualitative or interview$ or focus group? or questionnaire$ or survey$).tw.
28 (ethno$ or grounded or thematic or interpretive or narrative).tw.
29 or/20-28
30 19 and 29
31 remove duplicates from 30

POINT-OF-CARE TESTS FOR COAGULATION SELF-MONITORING 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/

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.
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/

1 anticoagulant agent/

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

POINT-OF-CARE TESTS FOR COAGULATION SELF-MONITORING QUALITY OF LIFE

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 Multifile 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.
21 INRatio.tw.
22 ProTime.tw
23 coagulometer$.tw.
24 or/19-23
25 quality of life/
26 quality adjusted life year/
27 "Value of Life"/ use mesz
28 health status indicators/ use mesz
29 health status/ use emez
30 sickness impact profile/ use mesz
31 disability evaluation/ use mesz
32 disability/ use emez
33 activities of daily living/ use mesz
34 exp daily life activity/ use emez
35 cost utility analysis/ use emez
36 rating scale/
37 questionnaires/
38 (quality adj1 life).tw.
39 quality adjusted life.tw.
40 disability adjusted life.tw.
41 (qaly? or qald? or qale? or qtime? or daly?).tw.
42 (euroqol or euro qol or eq5d or eq 5d).tw.
43 (hql or hqol or h qol or hrqol or hr qol).tw.
44 (hye or hyes).tw
45 health$ year$ equivalent$.tw.
46 (hui or hui1 or hui2 or hui3).tw.
47 (health adj3 (utilit$ or disutili$)).tw.
48 (health adj3 (state or status)).tw.
49 (sf36 or sf 36 or short form 36 or shortform 36).tw.
50 (sf6 or sf 6 or short form 6 or shortform 6).tw.
51 (sf12 or sf 12 or short form 12 or shortform 12).tw.
52 (sf16 or sf 16 or short form 16 or shortform 16).tw.
53 (sf20 or sf 20 or short form 20 or shortform 20).tw.
54 willingness to pay.tw
55 standard gamble.tw.
56 trade off.tw.

57 conjoint analys?s.tw.

58 discrete choice.tw.

59 or/25-58

60 (case report or editorial or letter).pt.

61 case report/

62 (24 and 59) not (60 or 61)

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 Data extraction form

CoaguChek, INRatio and ProTime microcoagulation system for self-monitoring in people taking long-term VKA: data extraction form

Reviewer ID	
Date	

ADMINISTRATION DETAILS	
Study ID	
Publication status	
Papers this study may link with	
AIM OF THE STUDY	
STUDY DETAILS	
Study design	
Country	
Number of centres	
Sample identification	
Method of recruitment	
Allocation method	
Study dates	
Duration of the study	
Length of follow up	
Eligibility criteria for the study	
Inclusion criteria	
Exclusion criteria	
Interventions and comparators	
Comparisons (Intervention versus comparator)	1. 2.
Settings	

Details of the intervention	
Details of the comparator	
Details of education and training provided	
Details of person involved in the study	
Details of point-of-care tests used for INR monitoring	
Details of laboratory analysers used for INR monitoring	
Type of vitamin K anatagonists used by participants	
Time on anticoagulant therapy	
Primary outcomes reported	
Secondary outcomes reported	
Adverse events reported	
Study power and statististical analysis	
Additional information	
Source of funding	

PARTICIPANTS CHARACTERISTICS			
Number of participants, n (%)	**Total**	**Intervention**	**Comparator**
Screened			
Excluded			
Enrolled			
Excluded			
Randomised			
Excluded			
Analysed			
Excluded			
Discontinued study			
Primary analysis data cut-off date			

Patient baseline characteristics	**Total**	**Intervention**	**Comparator**	**Difference between the groups**
Total participants, n				
Adult, n				
Children, n				
Age (years) (mean/median, SD/range)				
Gender (M/F), n (%)				
Reason for anticoagulation				
Atrial fibrillation, n (%)				
Artificial heart valves, n (%)				
Venous thromboembolism, n(%)				
Other indication, n(%)				
INR target range,n(%)				
2 to 3				
2.5 to 3.5				
≥3				
Time on anticoagulant therapy, n(%)				
≥3 months				
≥6 months				
≥12 months				
Receiving treatment with any other blood thinning drugs e,g., clopidogrel, aspirin), n(%)				

Additional information (e.g., comorbidity present, coronary risk factors etc.)				
Feasibility of testing, n (%)				
	Total	**Intervention**	**Comparator**	**Additional information**
Total invited				
Response rate				
Willing to participate				
Provided consent				
Attended training				
Completed training				
Completed intervention				
Reason for the drop-outs, pre randomisation				
Reason for the drop-outs, after randomisation				

OUTCOMES							
Clinical Outcomes/ Adverse events	**Intervention**		**Control**		**Difference between groups**	**p value**	**Additional information**
	Events (n)	**Total (N)**	**Events (n)**	**Total (N)**			
Number of bleeds or blood clots							
Major haemorrhage							
Minor haemorrhage							
Thromboembolic events							
Cerebrovascular events							
Number of deaths							
Number of deaths from INR testing							

Number of deaths from VKA therapy							
Adverse events							
Adverse events from INR testing							
Adverse events from false test results							
Adverse events from VKA therapy and sequelae							

Intermediate Outcomes	**specify measures eg mean (SD)**	**Intervention n=**		**Control n=**		**Difference between groups**	**p value**	**Additional information**
		value	**SD, range etc.**	**value**	**SD, range, etc.**			
Time in therapeutic range for INR (ITT analysis)								
INR values (mean, median/SD, range)								
Test failure rate								
Time to test results								
Patient compliance with testing								
Patient compliance with treatment								
Frequency of testing								

Frequency of visits to primary care clinics								
Frequency of visits to secondary care clinics								

Patient reported outcomes	**specify measures eg, mean (SD)**	**Intervention (n=)**		**Control (n=)**		**Difference between groups values (variance)**	**p value**	**Additional information**
		values	**SD, range etc**	**values**	**SD, range etc**			
People anxiety associated with waiting time for results and not knowing their current coagulation status								
Health-related quality of life								
Acceptability of the tests								

Give details of any other outcomes

Appendix 3 Quality assessment

The Cochrane Collaboration's tool for assessing risk of bias

Domain	**Support for judgement**	**Review authors' judgement**
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and	Attrition bias due to amount, nature or handling of incomplete outcome data.

(or class of outcomes).	exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Appendix 4 List of included RCTs and linked reports

Azarnoush 2011

Azarnoush K, Camilleri L, Aublet-Cuvelier B, Geoffroy E, Dauphin C, Dubray C et al. Results of the first randomized French study evaluating self-testing of the International Normalized Ratio. J Heart Valve Dis 2011;20(5):518-2.

Dauphin C, Legault B, Jaffeux P, Motreff P, Azarnoush K, Joly H et al. Comparison of INR stability between self-monitoring and standard laboratory method: preliminary results of a prospective study in 67 mechanical heart valve patients. Arch Cardiovasc Dis 2008;101:753-61.

Bauman 2010

Bauman ME, Black K, Bauman ML, Bruce AA, Kuhle S, Bajzar L et al. EMPoWarMENT: Edmonton pediatric warfarin self-management pilot study in children with primarily cardiac disease. *Thromb Res* 2010;126:e110-e115.

Bauman ME, Conroy S, Massicotte MP. Point-of-care INR measurement in children requiring warfarin: What has been evaluated and future directions. Pediat Health 2008;2:651-9.

Christensen 2011

Christensen H, Lauterlein JJ, Sorensen PD, Petersen ER, Madsen JS, Brandslund I. Home management of oral anticoagulation via telemedicine versus conventional hospital-based treatment. *Telemedicine Journal & E-Health* 2011;**17**:169-76.

Christensen 2006

Christensen TD, Maegaard M, Sorensen HT, Hjortdal VE, Hasenkam JM. Self-management versus conventional management of oral anticoagulant therapy: A randomized, controlled trial. Eur J Intern Med 2006;17:260-6.

Christensen TD, Maegaard M, Sorensen HT, Hjortdal VE, Hasenkam JM. Self- versus conventional management of oral anticoagulant therapy: effects on INR variability and coumarin dose in a randomized controlled trial. Am J Cardiovasc Drugs 2007; **7**:191-7.

Cromheecke 2000

Cromheecke ME, Levi M, Colly LP, Mol BJ, Prins MH, Hutten BA et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. Lancet 2000;356:97-102.

Eitz 2008

Eitz T, Schenk S, Fritzsche D, Bairaktaris A, Wagner O, Koertke H 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.

Koertke H, Zittermann A, Mommertz S, El AM, Litmathe J, Koerfer R. The Bad Oeynhausen concept of INR self-management. J Thromb Thrombolysis 2005;19:25-31.

Fitzmaurice 2002

Fitzmaurice DA, Murray ET, Gee KM, Allan TF, Hobbs FD. A randomised controlled trial of patient self management of oral anticoagulation treatment compared with primary care management. J Clin Pathol 2002;55:845-9.

Fitzmaurice DA, Hobbs FD, Murray ET, Holder RL, Allan TF, Rose PE. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: a randomized, controlled trial. Arch Intern Med 2000;160:2343-8.

Fitzmaurice 2005

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.

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.

McCahon D, Fitzmaurice DA, Murray ET, Fuller CJ, Hobbs RF, Allan TF et al. SMART: self-management of anticoagulation, a randomised trial. BMC FamPract 2003;4:11

Gadisseur 2003

Gadisseur AP, Breukink-Engbers WG, Meer FJ, Besselaar AM, Sturk A, Rosendaal FR. 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.

Gadisseur AP, Kaptein AA, Breukink-Engbers WG, Meer FJ, Rosendaal FR. Patient self-management of oral anticoagulant care vs. management by specialized anticoagulation clinics: positive effects on quality of life. J Thromb Haemost 2004;2:584-91.

Gardiner2006

Gardiner C, Williams K, Longair I, Mackie IJ, Machin SJ, Cohen H. A randomised control trial of patient self-management of oral anticoagulation compared with patient self-testing. *Br J Haematol* 2006;**132**:598-603.

Gardiner2005

Gardiner C, Williams K, Mackie IJ, Machin SJ, Cohen H. Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring. *Br J Haematol* 2005;**128**:242-7.

Hemkens 2008

Hemkens LG, Hilden KM, Hartschen S, Kaiser T, Didjurgeit U, Hansen R et al. A randomized trial comparing INR monitoring devices in patients with anticoagulation self-management: evaluation of a novel error-grid approach. J Thromb Thrombolysis 2008;26:22-30.

Horstkotte 1996

Horstkotte D, Piper C, Wiemer M, Schulte H.D. Improvement of prognosis by home prothrombin estimation In patients with life-long anticoagulant therapy. Euro Heart J 1996;17:230.

Horstkotte D, Piper C, Wiemer M. Optimal frequency of patient monitoring and intensity of oral anticoagulation therapy in valvular heart disease. J Thromb Thrombolysis 1998;5:19-24.

Khan 2004

Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. 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.

Koertke 2001

Körtke H,Minami k, Breymann T, Seifert D, baraktaris A, Wagner O et al. INR self-management after mechanical heart valve replacement, Z Kardiol 2001;9(Suppl 6):VI/118-VI124.

Koertke H, Minami K, Bairaktaris A, Wagner O, Koerfer R. INR self-management following mechanical heart valve replacement. J Thromb Thrombolysis 2000;9 Suppl 1:S41-S45.

Körtke H, Körfer R. International normalized ratio self-management after mechanical heart valve replacement: is an early start advantageous? Ann Thorac Surg 2001;72:44-8.

Koertke H, Zittermann A, Wagner O, Koerfer R. Self-management of oral anticoagulatin therapy improves long-term survival in patients with mechanical heart valve replacement. *Ann Thorac Surg* 2007;83:24-9.

Matchar 2010

Matchar DB, Jacobson A, Dolor R, Edson R, Uyeda L, Phibbs CS et al. Effect of home testing of international normalized ratio on clinical events. N Engl J Med 2010;363:1608-20.

Matchar DB, Dolor R, Jacobson A, Love S, Edson R, Uyeda L. More Frequent Self-Testing of Prothrombin Time Results in Improved Time in Target Range. Circulation 2012;126(21 Suppl 1): A10606

Matchar DB, Jacobson AK, Edson RG, Lavori PW, Ansell JE, Ezekowitz MD et al. The impact of patient self-testing of prothrombin time for managing anticoagulation: Rationale and design of VA cooperative study #481 - The Home INR Study (THINRS). J Thromb Thrombolysis 2005;19:163-72.

Menendez-Jandula 2005

Menéndez JB, Souto JC, Oliver A, Montserrat I, Quintana M, Gich I et al. Comparing self-management of oral anticoagulant therapy with clinic management: a randomized trial. Ann Intern Med 2005;142:1-10.

Rasmussen 2012

Rasmussen RS, Corell P, Madsen P, Overgaard K. Effects of computer-assisted oral anticoagulant therapy. Thrombosis J 2012;10:17.

Ryan 2009

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 Haemostasis 2009;7:1284-90.

Ryan F, O'Shea S, Byrne S. The 'carry-over' effects of patient self-testing: positive effects on usual care management by an anticoagulation management service. Thromb Res 2010;126:e345-e348.

Sawicki 1999

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.

Sawicki PT, Glaser B, Kleespies C, Stubbe J, Schmitz N, Kaiser T et al. Long-Term Results of Patients' Self-Management of Oral Anticoagulation. J Clin Basic Cardiol 2003;6:2003.

Sidhu 2001

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.

Siebenhofer 2008

Siebenhofer A, Rakovac I, Kleespies C, Piso B, Didjurgeit U, SPOG 6. Self-management of oral anticoagulation reduces major outcomes in the elderly. A randomized controlled trial. Thromb Haemost 2008;100:1089-98.

Siebenhofer A, Rakovac I, Kleespies C, Piso B, Didjurgeit U. 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.

Soliman Hamad 2009

Soliman H, van E, van A, van S. Self-management program improves anticoagulation control and quality of life: a prospective randomized study. Eur J Cardiothorac Surg 2009;35:265-9.

Sunderji 2004

Sunderji R, Gin K, Shalansky K, Carter C, Chambers K, Davies C et al. A randomized trial of patient self-managed versus physician-managed oral anticoagulation. Can J Cardiol 2004;20:1117-23.

Sunderji R, Campbell L, Shalansky K, Fung A, Carter C, Gin K. Outpatient self-management of warfarin therapy: a pilot study. Pharmacotherapy 1999;19:787-93.

Verret 2012

Verret L, Couturier J, Rozon A, Saudrais-Janecek S, St-Onge A, Nguyen 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.

Voller 2005

Völler H, Glatz J, Taborski U, Bernardo A, Dovifat C, Heidinger K. Self-management of oral anticoagulation in nonvalvular atrial fibrillation (SMAAF study). Z Kardiologie 2005;94:182-6.

Völler H, Glatz J, Taborski U, Bernard A, Dovifat C, Burkard G et al. Background and evaluation plan of a study on self-management of anticoagulation in patients with non-valvular atrial fibrillation (SMAAF Study). Z Kardiol 2000;89:284–8.

Appendix 5 List of excluded studies with reasons for exclusion

Study Design not RCT (N=25)

Adedeji-Zakari S, Anthony VP, Honeywell M. The CoaguChek S system. U S Pharmacist 2007;32:

Ansell JE. Empowering patients to monitor and manage oral anticoagulation therapy. Journal of the American Medical Association 1999;281:182-3.

Ansell JE. Is self-management of oral anticoagulation a feasible and safe option? Nature Clinical Practice Cardiovascular Medicine 2005;2:240-1.

Arellano-Rodrigo E. Home monitoring of warfarin effects. N Engl J Med 2011;364:378-9.

Bevan H, Giles M, Heads J, Parker V, Walters J. Point-of-care INR testing in cardiac wards. Australian nursing journal (July;#1993) 2007;#2007.:31.

Biss T, Avery PJ, Walsh PM, Kamali F. Warfarin treatment outcomes in children monitored at home with a point-of-care device. Thrombosis & Haemostasis 2011;105:1103-5.

Coleman B, Patterson D, Long M, Farrell J. Setting quality standards for a community pharmacist-led anticoagulant clinic. Pharmaceutical Journal 2003;270:308-11.

Deom A, Reber G, Tsakiris DA, Hannes FM, Plesch W. Evaluation of the CoaguChek XS Plus system in a Swiss community setting. Thrombosis & Haemostasis 2009;101:988-90.

Ferretti G, Giannarelli D, Carlini P, Felici A, Ciccarese M, Mandala M et al. Self-monitoring versus standard monitoring of oral anticoagulation. [Review] [12 refs]. Thromb Res 2007;119:389-90.

Fitzmaurice DA, Machin SJ. Recommendations for patients undertaking self management of oral anticoagulation. Br Med J 2001;323:985-9.

Ford PW, Close A. Management of warfarin in atrial fibrillation. Med J Aust 2007;187:371.

Heidinger KS, Bernardo A, Taborski U, Muller-Berghaus G. Clinical outcome of self-management of oral anticoagulation in patients with atrial fibrillation or deep vein thrombosis. Thromb Res 2000;98:287-93.

Herijgers P, Verhamme P. Improving the quality of anticoagulant therapy in patients with mechanical heart valves: What are we waiting for? Eur Heart J 2007;28:2424-6.

Kitchen S, Kitchen D, Jennings I, Woods T, Walker I. External quality assessment of CoaguChek point-of-care testing prothrombin time/international ratio monitors. Am J Clin Pathol 2008;129:825-6.

Kitchen S, Kitchen D, Jennings I, Woods T, Walker I. Quality assessment of CoaguChek point-of-care international normalized ratio monitors: a note of caution. Clin Chem 2007;53:1555-6.

Lippi G, Franchini M. Home monitoring of warfarin effects. N Engl J Med 2011;364:378-9.

Martin M. Home and community anticoagulation by GPs and patients. British Journal of Cardiology 1999;6:144-6+150.

Pluddemann A, Thompson M, Wolstenholme J, Price CP, Heneghan C. Point-of-care INR coagulometers for self-management of oral anticoagulation: Primary care diagnostic technology update. Br J Gen Pract 2012;62:e798-e800.

Rodgers G. Patient self-management of oral anticoagulation. Clinical Advances in Hematology and Oncology 2005;3:94-5.

Stafford L, Peterson GM, Bereznicki LR, Jackson SL. A role for pharmacists in community-based post-discharge warfarin management: protocol for the 'the role of community pharmacy in post hospital management of patients initiated on warfarin' study. BMC Health Services Research 2011;11:16,;#2011.:16.

Taborski U, Voller H, Kortke H, Blunt J, Wegscheider K. Self Management of Oral Anticoagulation with the INRatio System: Accuracy and Reliability Following a Two-Day Structured Training Program. Laboratory Medicine 2004;35:303-7.

Thompson JL, Sundt TM, Sarano ME, Santrach PJ, Schaff HV. In-Patient International Normalized Ratio Self-Testing Instruction After Mechanical Heart Valve Implantation. Ann Thorac Surg 2008;85:46-50.

Williams MS. Long-term anticoagulation and home monitoring. Drug Benefit Trends 2000;12:15.

Williams VK, Griffiths ABM. Re: Acceptability of CoaguChek S and CoaguChek XS generated international normalised ratios against a laboratory standard in a paediatric setting: Authors' reply. Pathology (Phila) 2008;40:438-9.

Zimmerman CR. The role of point-of-care anticoagulation monitoring in arterial and venous thromboembolic disorders. J Thromb Thrombolysis 2000;9:187-98.

Not Self Management (N=8)

Claes N, Buntinx F, Vijgen J, Arnout J, Vermylen J, Fieuws S et al. The Belgian Improvement Study on Oral Anticoagulation Therapy: a randomized clinical trial. *Eur Heart J* 2005;**26**:2159-65.

Fitzmaurice DA, Hobbs FD, Murray ET, Bradley CP, Holder R. Evaluation of computerized decision support for oral anticoagulation management based in primary care. The British journal of general practice : the journal of the Royal College of General Practitioners 1996;46:533-5

Jackson SL, Peterson GM, Vial JH, Jupe DM. Improving the outcomes of anticoagulation: an evaluation of home follow-up of warfarin initiation. *J Intern Med* 2004;**256**:137-44.

Lalonde L, Martineau J, Blais N, Montigny M, Ginsberg J, Fournier M et al. Is long-term pharmacist-managed anticoagulation service efficient? A pragmatic randomized controlled trial. *Am Heart J* 2008;**156**:148-54.

Laurence C, Gialamas A, Yelland L, Bubner T, Ryan P, Willson K et al. A pragmatic cluster randomised controlled trial to evaluate the safety, clinical effectiveness, cost effectiveness and satisfaction with point-of-care testing in a general practice setting - Rationale, design and baseline characteristics. *Trials* 2008;**9 ,08**:

Shiach CR, Campbell B, Poller L, Keown M, Chauhan N. Reliability of point-of-care prothrombin time testing in a community clinic: a randomized crossover comparison with hospital laboratory testing. *Br J Haematol* 2002;**119**:370-5.

Wilson SJ, Wells PS, Kovacs MJ, Lewis GM, Martin J, Burton E et al. Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: a randomized controlled trial. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2003;**169**:293-8.

Woods K, Douketis JD, Schnurr T, Kinnon K, Powers P, Crowther MA. Patient preferences for capillary vs. venous INR determination in an anticoagulation clinic: A randomized controlled trial. *Thromb Res* 2004;**114**:161-5.

Self Management Dosage Studies (N=4)

Koertke H, Zittermann A, Wagner O, Ennker J, Saggau W, Sack FU et al. Efficacy and safety of very low-dose self-management of oral anticoagulation in patients with mechanical heart valve replacement. Ann Thorac Surg 2010;90:1487-93.

Kortke H, Secer S. Telemedical based thrombosis service of patients with mechanical heart valve replacement. Vasa - Journal of Vascular Diseases 2012;41. Jahrestagung der Deutschen Gesellschaft fur Angiologie Mainz Germany. Conference Start:25.

Koertke H, Minami K, Boethig D, Breymann T, Seifert D, Wagner O et al. INR self-management permits lower anticoagulation levels after mechanical heart valve replacement. Circulation 2003;108 Suppl 1:II75-II78.

Koertke H, Zittermann A, Tenderich G, Wagner O, El-Arousy M, Krian A et al. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: Final report from the early self-management anticoagulation trial II. *Eur Heart J* 2007;28:2479-84

Excluded Tests (N=3)

Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. Ann Intern Med 2000;133:687-95.

Grunau BE, Wiens MO, Harder KK. Patient self-management of warfarin therapy: pragmatic feasibility study in Canadian primary care. Can Fam Physician 2011;57:e292-e298.

White RH, McCurdy SA, Marensdorff H, Woodruff DE, Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy. A randomized, prospective study. Ann Intern Med 1989;111:730-7.

Background Information (N=25)

Bloomfield HE, Krause A, Greer N, Taylor BC, MacDonald R, Rutks I 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.

Bussey HI. Transforming oral anticoagulation by combining international normalized ratio (INR) self-testing and online automated management. [Review]. Journal of Thrombosis & Thrombolysis 2011;31:265-74.

Cayley J. Self-monitoring and self-management of anticoagulation therapy. Am Fam Physician 2011;84:266-8.

Christensen TD, Larsen TB. Precision and accuracy of point-of-care testing coagulometers used for self-testing and self-management of oral anticoagulation therapy. Journal of Thrombosis and Haemostasis 2012;10:251-60.

Christensen TD, Johnsen SP, Hjortdal VE, Hasenkam JM. Self-management of oral anticoagulant therapy: a systematic review and meta-analysis. [Review] [25 refs]. Int J Cardiol 2007;118:54-61.

Christensen TD. Self-management of oral anticoagulation therapy--methodological and clinical aspects. [Review]. Dan Med Bull 2011;58:B4284.

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. [Review] [95 refs]. Health Technology Assessment (Winchester, England) 2007;11:iii-iiv.

Dolan G, Smith LA, Collins S, Plumb JM. Effect of setting, monitoring intensity and patient experience on anticoagulation control: a systematic review and meta-analysis of the literature. [Review] [42 refs]. Current Medical Research & Opinion 2008;24:1459-72.

Dolor RJ, Ruybalid RL, Uyeda L, Edson RG, Phibbs C, Vertrees JE et al. An evaluation of patient self-testing competency of prothrombin time for managing anticoagulation: pre-randomization results of VA Cooperative Study #481--The Home INR Study (THINRS). J Thromb Thrombolysis 2010;30:263-75.

Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D et al. Self-monitoring and self-management of oral anticoagulation. [Review] [83 refs]. Cochrane Database of Systematic Reviews 2010;CD003839.

Health Q. Point-of-Care International Normalized Ratio (INR) Monitoring Devices for Patients on Long-term Oral Anticoagulation Therapy: An Evidence-Based Analysis. Ontario Health Technology Assessment Series 2009;9:1-114.

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. [Review][Erratum appears in Lancet. 2012 Mar 24;379(9821):1102]. Lancet 2012; 379:322-34.

Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. [Review]. Chest 2012;141:e152S-e184S.

Jennings I, Walker ID, Kitchen S, Kitchen D, Woods TA, Keeling D et al. Management of patients receiving oral anticoagulants using computer dosing software--does everyone agree? Data from a UK NEQAS (blood coagulation) exercise. International Journal of Laboratory Hematology 2012;34:70-80.

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Appendix 6 Quality assessment results 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		
CoaguChek XS										
Bauman 2010[54]	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	14	0	Yes	Low RoB
Christensen 2011[65]	Low RoB	Unclear RoB	High RoB	High RoB	Low RoB	Low RoB	9	18	NR	High RoB
Ryan 2009[61]	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	0	0	NR	Low RoB
Verret 2012[73]	Low RoB	Unclear RoB	High RoB	Low RoB	Low RoB	Low RoB	~2	0	NR	High RoB
CoaguChek S or CoaguChek										
Christensen 2006[74]	Low RoB	High RoB	High RoB	Low RoB	Low RoB	Low RoB	2	2	Yes	High RoB
Cromheecke 2000[75]	Unclear RoB	Low RoB	Unclear RoB	Low RoB	High RoB	Low RoB	2	0	NR	Unclear RoB
Eitz 2008[77]	Unclear RoB	Unclear RoB	Unclear RoB	Low RoB	Low RoB	Low RoB	0	0	NR	Unclear RoB
Fitzmaurice 2002[66]	Low RoB	Unclear RoB	Unclear RoB	High RoB	Low RoB	Low RoB	23.3	0	NR	Unclear RoB
Fitzmaurice 2005[63]	Low RoB	Low RoB	Unclear RoB	Low RoB	Low RoB	Low RoB	41.5	10	Yes	Unclear RoB

Study ID	*Adequate sequence	*Allocation concealment	*Blinding of outcome	Incomplete outcome	Free of selective	Other sources	Dropout rates %		ITT performed	Overall judgement
Gadisseur 2003[67]	Low RoB	Unclear RoB	Unclear RoB	High RoB	Low RoB	Low RoB	13.6		NR	Unclear RoB
Gardiner 2005[44]	Unclear RoB	Unclear RoB	Unclear RoB	High RoB	Low RoB	Low RoB	31.8	2.5	NR	Unclear RoB
Gardiner 2006[55]	Unclear RoB	Unclear RoB	Unclear RoB	High RoB	Low RoB	Low RoB	PSM 25.5, PST 26.5	-	NR	Unclear RoB
Horstkotte 1996[58]	Unclear RoB	Unclear RoB	Unclear RoB	Low RoB	Low RoB	Low RoB	NR	NR	NR	Unclear RoB
Khan 2004[68]	Low RoB	Unclear RoB	Unclear RoB	Low RoB	Low RoB	Low RoB	9.1	4.9	NR	Unclear RoB
Menendez-Jandula 2005[60]	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	21.5	2.4	Yes	Low RoB
Rasmussen 2012[57]	Low RoB	Unclear RoB	Low RoB	Unclear RoB	High RoB	Low RoB	NR	NR	NR	Unclear RoB
Sawicki 1999[71]	Low RoB	Unclear RoB	Low RoB	Low RoB	Low RoB	Low RoB	7.8	7.8	Yes	Unclear RoB
Sidhu 2001[72]	Low RoB	Unclear RoB	Unclear RoB	High RoB	Low RoB	Low RoB	31.4	2	NR	Unclear RoB
Siebenhofer 2008[62]	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB	16	23	Yes	Low RoB

Study ID	*Adequate sequence	*Allocation concealment	*Blinding of outcome	Incomplete outcome	Free of selective	Other sources	Dropout rates %		ITT performed	Overall judgement
Soliman Hamad 2009[78]	Unclear RoB	Unclear RoB	Unclear RoB	Low RoB	High RoB	Low RoB	6.4		NR	Unclear RoB
Voller 2005[59]	Low RoB	Unclear RoB	High RoB	Low RoB	Low RoB	Low RoB	NR	NR	Yes	High RoB
CoaguChek Plus										
Kortke 2001[69]	Low RoB	Unclear RoB	Unclear RoB	Unclear RoB	Low RoB	Low RoB	NR	NR	NR	Unclear RoB
ProTime										
Matchar 2010[70]	Low RoB	Unclear RoB	High RoB	Low RoB	Low RoB	Low RoB	<1	<1	Yes	High RoB
Sunderji 2004[64]	Low RoB	Low RoB	High RoB	Low RoB	Low RoB	Low RoB	24.6	4.3	Yes	High RoB
CoaguChek/INRatio										
Azarnoush 2011[76]	Unclear RoB	Unclear RoB	Low RoB	High RoB	Low RoB	Low RoB	13	1	NR	Unclear RoB
Hemkens 2008[56]	Low RoB	Low RoB	Unclear RoB	High RoB	Low RoB	Low RoB	12		NR	Unclear RoB

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

*Key domain

Appendix 7 Descriptive details of the individual included studies (Tables A-C, these include characteristics, risk factors, training and education)

Table A Baseline characteristics of the individual included studies

Study ID	Geographical location	Study duration,	Sample size, n		Mean age (range) SM/ SC	INR range	SM	Point-of-care test	SC	INR measured	Clinical indication				VKA used	Funding
			PSM/ PST	SC							AF %	AHV %	VTE %	other %		
Azarnoush 2011[76,139]	France	49 weeks*	103	103	55.1/57.5	2-3.5	PST	CoaguChek S and INRatio	AC clinic/ GP	Lab analysis		100			Fluindione, Acenocoumarol	Partly industry
Bauman 2010[54,140]	Canada	12	14/ 14	--	$10 (1-19)	2-3.5	PSM	CoaguChek XS	PST within specialised AC clinic was the usual care	CoaguChek XS		50		50	Warfarin	Non-industry
Christensen 2006[74,141]	Denmark	6	50	50	NR (adult)	2.5	PSM	CoaguChek S	Hospital outpatient 6%, highly specialized AC (1%)/ or GP (93%)	Coagulometer or lab measurement	24	35	8	33	Warfarin, Phenproc oumon	Non-industry
Christensen 2011[65]	Denmark	~5*	91	49	62.5 (21-86)/ 66.0 (49-82)	2-≥3	PST	CoaguChek XS	AC clinic	Lab analysis	*57.7*	*18.7*	*20.3*	*34.1*	Warfarin	Non-industry
Cromheecke 2000[75]	Netherlands	6	50	50	42 (22-71)	2-≥3	PSM	CoaguChek	Thrombosis service	Lab analysis		46	30	24	Acenocoumarol, Phenproc oumon	NR

Eitz 2008[77,142]	Germany	24	470	295	56.4/ 62.4	2.5-4.5	PSM	CoaguChek S	GP	Lab analysis		100			Warfarin	NR
Fitzmaurice 2002[66,143]	UK	6	23	26	63/69	NR	PSM	CoaguChek S	GP	CoaguChek S	55	NR	NR	NR	Warfarin	Partly industry
Fitzmaurice 2005[63,122,144]	UK	12	337	280	65 (18-87)	3.5	PSM	CoaguChek S	Hospital or practice based AC clinics		NR	NR	NR	NR	Warfarin	Non-industry
Gadisseur 2003[67,79]	Netherlands	24.4 weeks*	47/ 52	221	54.35 (24-75)/59 (21-75)	2.5-4	PST and PSM	CoaguChek	AC clinic	Lab analysis	21.2	19.1	20.3	39.4	Acenocoumarol, phenprocoumon	Partly industry
Gardiner 2005[44]	UK	6	44	40	57.9 (26-83)/ 58.4 (31-75)	2-4	PST	CoaguChek S	AC clinic	Lab analysis	27.4	30	28.6	14	Warfarin	Partly industry
Gardiner 2006[55]	UK	6	55/ 49	--	59.0 (30-85)/ 60.9 (22-88)	2-3.5	PSM	CoaguChek S	PST	CoaguChek S	40.4	23.1	19.2	17.3	Warfarin	Partly industry
Hemkens 2008[56]		14 weeks	16		65.8	NR	PSM	CoaguChek S and INRatio	AC clinic	Lab analysis	38		31	31.3	Phenprocoumon	Non-industry
Horstkotte 1996[58,145]	Germany	40607 patient days	75	75	NR	3-4.5	PSM	CoaguChek	Private physician	NR		100			NR	Non-industry
Khan 2004[68]	UK	6	44	41	$71(65-91)/75(65-87)	2-3	PST	CoaguChek	AC clinic	Lab analysis	100				Warfarin	Non-industry

Koertke 2001[69,146-148]	Germany	24	579	576	62.5	2.5-4.5	PSM	CoaguChek plus	Family practitioner	NR		100			NR	NR
Matchar 2010[70,149,150]	US*	36* (24-57)	1465	1457	66.6 (23-89)/ 67.4(33-99)	NR	PST	ProTime microcoagulation	High-quality clinic testing	Lab analysis	76.5	23.4		0.1	Warfarin	Partly industry
Menendez-Jandula 2005[60]	Spain	11.8** (0.3-16.9)	368	369	64.5/65.5	2-≥3	PSM	CoaguChek S	AC clinic	Lab analysis	50.3	37.15	12.5		Acenocoumarol	Partly industry
Rasmussen 2012[57]	Denmark	28* weeks	37	17	[$]68-70/ 69	NR	PSM	CoaguChek S	Specialist clinic	Lab analysis	NR	NR	NR	NR	Warfarin	Non-industry
Ryan 2009[61,151]	Ireland	6	72	60	58.7 (16-91)	2-≥3	PST	CoaguChek XS	AC service	Lab analysis	32.6	37.1	22	8.3	Warfarin	Partly industry
Sawicki 1999[71,152]	Germany	6	90	89	55.0	NR	PSM	CoaguChek	Hospital outpatient or family practitioner	Lab analysis or by the physician	*5*	*84.4*			Phenprocoumon	Industry
Sidhu 2001[72]	UK	24	51	49	61 (32-85)	2.5-3	PSM (51)	CoaguChek	GP or AC clinic (49)	Lab analysis		100			Warfarin	Industry
Siebenhofer 2008[62,80]	Austria	~36*	99	96	69/69	2-≥3	PSM	CoaguChek S	GP or specialised AC clinic	NR	45.6	16.4	28.7	9.2	Phenprocoumon, acenocoumarol	Industry

Soliman Hamad 2009[78]	Netherlands	12	29	29	56.3/ 55.7	2.5-4.5	PSM	CoaguChek	Dutch Thrombosis Service	Lab analysis		100			NR	NR
Sunderji 2004[64,153]	Canada	8	70	70	57.6 (20-79)/ 62.3 (24-85)	2-3.5	PSM	ProTime Microcoagulation	General practitioner	NR	34	59	5	2	Warfarin	Non-industry
Verret 2012[73]	Canada	4	58	56	58.4/ 57.0	2-3.5	PSM	CoaguChek XS	AC clinic	NR	51	42		7	Warfarin	Partly industry
Voller 2005[59,154]	Germany	~5*	101	101	64.3 (9.2)	2-3	PSM	CoaguChek	Family doctor	Lab analysis	100				NR	Partly industry

* Mean study duration

** Median study duration

$ median age

Note:

1. Multicentre RCTs: Fitzmaurice 2002, Fitzmaurice 2005, Gadisseur 2004, Matchar 2010, Sawicki 1999, Siebenhofer 2008, Voller 2005

2. Cross over design: Cromheecke 2000, Eitz 2008, Ryan 2009.

3. Of the total 221participants representing standard care in a trial by Gadisseur and colleagues (2003), 60 were trained while 161 were untrained.

4. Kortke 2001: All participants report including 1200 participants published in German; preliminary reports of 600 participants published in English.

AC: anticoagulant; GP: general practitioner; SM: self-monitoring; SC: standard care; PSM: patient self-management; PST: patient self-testing; AF: atrial fibrillation; AHV: artificial heart valves; VTE: venous thromboembolism; VKA: vitamin K antagonist

Table B Risk factors, co-morbidity or history of previous complications reported in the included studies

Study ID	Risk factors/ co-morbidity				History of previous complications			
		SM	RC	P value		SM	RC	p value
Azarnoush 2011[76]	Systemic HT %	40	38	NS				
	Diabetes %	9	14	NS				
	CABG%	15	20	NS				
	EuroSCORE, mean (SD)	4.2 (2.1)	4.7 (2.0)	NS				
	LVEF @ 3 months, mean (SD)	60 (8.3)	58 (9.5)	NS				
	LVEF @ 6 months, mean (SD)	61 (6.9)	61 (7.9)	NS				
Christensen 2006[74]					Major Thromboembolic events	2	8	NR
					Major bleeding	10	8	NR
Fitzmaurice 2005[63]	HT %	42.43	48.57	NS				
	Hyperlipidaemia %	24.92	21.78	NS				
Matchar 2010[70]	DM %	32.22	33.97	0.31				
	HT %	71.06	69.32	0.31				
	Previous stroke %	9.28	9.61	0.76				
	$CHADS_2$ Score for AF without AHV %			0.42				
	0	11.5	9.79					
	1	29	29					
	2	29.38	31.79					
	3	17.88	18.52					
	4	8.62	7.3					

	5	3.05	3.2					
	6	<1	<1					
	Mean $CHADS_2$ Score	1.94	1.95					
Menendez-Jandula 2005[60] Spain	Arterial HT %	48.6	42.80	NS	Severe bleeding %	11.10	9.8	NS
	DM %	15.40	13.60	NS	Thromboembolic events %	13.50	7.90	NS
	Gastric ulcer %	17.80	15.70	NS				
	Cancer %	9.20	8.70	NS				
	Liver disease %	9.70	8.40	NS				
Sawicki 1999[71]					Minor bleeding %	11.11	11.23	NR
					Major bleeding %	1.11	1.12	NR
Siebenhofer 2008 [62]	cardiovascular disease other than AF or AHV %	78	84	0.24	Thromboembolic events %	45	49	0.624
	HT %	43	49	0.439	Severe bleeding %	4	6	0.484
	DM %	23	25	0.773				
	Pulmonary disease %	13	12	0.895				
	GI tract disease %	12	11	0.886				
	Cancer %	7	8	0.741				
CABG: Concomitant coronary artery bypass graft, LVEF: Left ventricular ejection fraction, HT: hypertension, DM: diabetes mellitus, AF: atrial fibrillation, AHV: artificial heart valves, NS: not significant, NR: not reported								

Table C Description of training and education reported in the included studies

Study ID	Country	Type of OAT management	Care provider	Training		
				Training provider	*Time spent*	*Training description*
Azarnoush 2011[76,139]	France	PST	Cardiologist and or GP	NR	NR	Group session; 3-6 additional practical sessions
Bauman 2010[54,140]	Canada	PSM vs PST	Nurse Practitioner or physician within VPat	NR	1hour	Group session
Christensen 2006[74,141]	Denmark	PSM	Physician	NR	daily for three weeks	NR
Christensen 2011[65]	Denmark	PST	Attending AC clinic doctor	Training on point-of-care test by biomedical laboratory scientists	2 hours	NR
Cromheecke 2000[75]	Netherlands	PSM	NR	NR	2 hours/ session	2 group sessions; 4-6/ group
Eitz 2008[77,142]	Germany	PSM	GP (SC); staff at outpatient clinic (SM)	NR	NR	NR
Fitzmaurice 2002[66,143]	UK	PSM	Nurse led, GP	Research staff, practice staff	1-2 hours/ session	2 sessions
Fitzmaurice 2005[63,122,144]	UK	PSM	Anticoagulant nurse at practice based clinics	Trained AC nurse		2 sessions
Gadisseur 2003[67,79]	Netherlands	PSM	Physician, nurse	Specialised teams including physician and paramedical personnel	90 to 120 minutes/session	3 group sessions: 4-5/ group
Gardiner 2005[44]	UK	PST	Nurse practitioner (SC); clinic staffs (SM)	Trained nurse practitioner		2 sessions
Gardiner 2006[55]	UK	PST vs PSM	clinic staffs (SM)	Trained and experienced nurse		2 sessions
Hemkens 2008[56]	Germany	PSM	Nurse	Skilled teaching nurse	NR	Four weekly sessions
Khan 2004[68]	UK	PST	Study researchers (SM) clinic staffs (SC)	Clinic doctor	2 hours	Group session; 2-3/group
Koertke 2001[69,146-148]	Germany	PSM	Family practitioner	NR	NR	NR
Horstkotte 1996[58,145]	Germany	PSM	Private physician	NR	NR	NR

Study ID	Country	Type of OAT management	Care provider	Training		
				Training provider	*Time spent*	*Training description*
Matchar 2010[70,149,150]	US	PST	Trained clinic staff	NR	NR	NR
Menendez-Jandula 2005[60]	Spain	PSM	Haematologists, trained nurse, physician	Trained nurse	2 hours/ session;	2 group sessions
Rasmussen 2012[57]	Denmark	PSM	Physician	NR	NR	NR
Ryan 2009[61,151]	Ireland	PST	Clinic pharmacist or doctor	Research pharmacists and haematologist	90 mins	1-3/group
Sawicki 1999[71,152]	Germany	PSM	family practitioner or clinic staff at outpatient clinic	Trained nurse and physician (2 days training)	60 to 90 mins/ group	3 group sessions; 3-6/group
Sidhu 2001[72]	UK	PSM	Family physician or AC clinic staff	NR	3 hours /session	2 group session; 2-5/group
Siebenhofer 2008[62,80]	Austria	PSM	GP or specialised AC clinic staff	Trained nurse and physician (2 days training)	90 to 120 minutes/ group	4 group sessions; 3-6/group
Soliman Hamad 2009[78]	Netherlands	PSM	Physician	NR	at least 1 week	NR
Sunderji 2004[64,153]	Canada	PSM	Physician (SC) Clinical pharmacist (SM)	Probably study pharmacist	first session 2-3 hours; second session 1-2 hours	2 sessions
Verret 2012[73]	Canada	PSM	Pharmacist (SM)	Pharmacist	first session- 3 hours; second session- 2 hours	23 sessions held; 1-9/group
Voller 2005[59,154]	Germnay	PSM	Family physician or specialist physician	NR	NR	NR

AC: anticoagulant clinic; NR: not reported; OAT; oral anticoagulation therapy; POC: point-of-care; PSM: patient self-management; PST; patient self-testing; SC: standard care; SM: self-monitoring

Appendix 8 Sensitivity analysis results (Table A, Figures A-T)

Table A Sensitivity analysis results restricted to non-UK trials, UK trials and trials at low risk of bias:

	All included studies	Non-UK trials	UK trials	Trials at low risk of bias
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Any bleeding	**0.95[0.74, 1.21] p=0.66**	0.91 (0.70,1.20), p=0.51	1.40[0.61,3.23] P=0.43	0.72[0.41,1.26] p=0.25
PSM	**0.94 [0.68, 1.30] P=0.69**	0.90 (0.63,1.28), p=0.56	1.38[0.53,3.59] P=0.50	0.74[0.42,1.32] p=0.31
PST	**1.15 [1.03, 1.28] P=0.02**	1.14 (1.02, 1.28) p=0.02	1.46[0.26,8.28] P=0.67	0.28[0.01,6.71] p=0.43
Thromboembolic events	**0.58 [0.40, 0.84] p=0.004**	0.50 [0.32, 0.76] , p=0.001	1.16[0.58,2.29] P=0.68	0.42[0.22,0.77] =0.006
PSM	**0.51 [0.37, 0.69] p<0.00001**	0.40 [0.28, 0.58], p<0.00001	1.16[0.58,2.29] P=0.68	0.38[0.20,0.69] p=0.002
PST	**0.99 [0.75, 1.31] p=0.95**	0.99 [0.75, 1.31] p=0.95	Not estimable	1.67[0.15,17.93] p=0.67
Mortality	**0.83 [0.63, 1.10] p=0.20**	0.83 [0.60, 1.15] p=0.26	0.52[0.11,2.58] P=0.43	0.85[0.40,1.81] p=0.68
PSM	**0.68 [0.46, 1.01] p=0.06**	0.71 [0.43, 1.16] p=0.17	0.52[0.11,2.58] P=0.43	0.85[0.40,1.81] p=0.68
PST	**0.97 [0.78, 1.19] P=0.74**	0.97 [0.78, 1.19] p=0.74	Not estimable	Not estimable

PSM: patient self-management; PST: patient self-testing

Notes:

1) Four of the trials included in meta-analysis were UK based (Fitzmaurice 2002, Fitzmaurice 2005, Khan 2004, Sidhu 2001).
2) Three of trials were judged to be at low risk of bias (Menendez-Jandula 2005, Ryan 2005, Siebenhofer 2008)

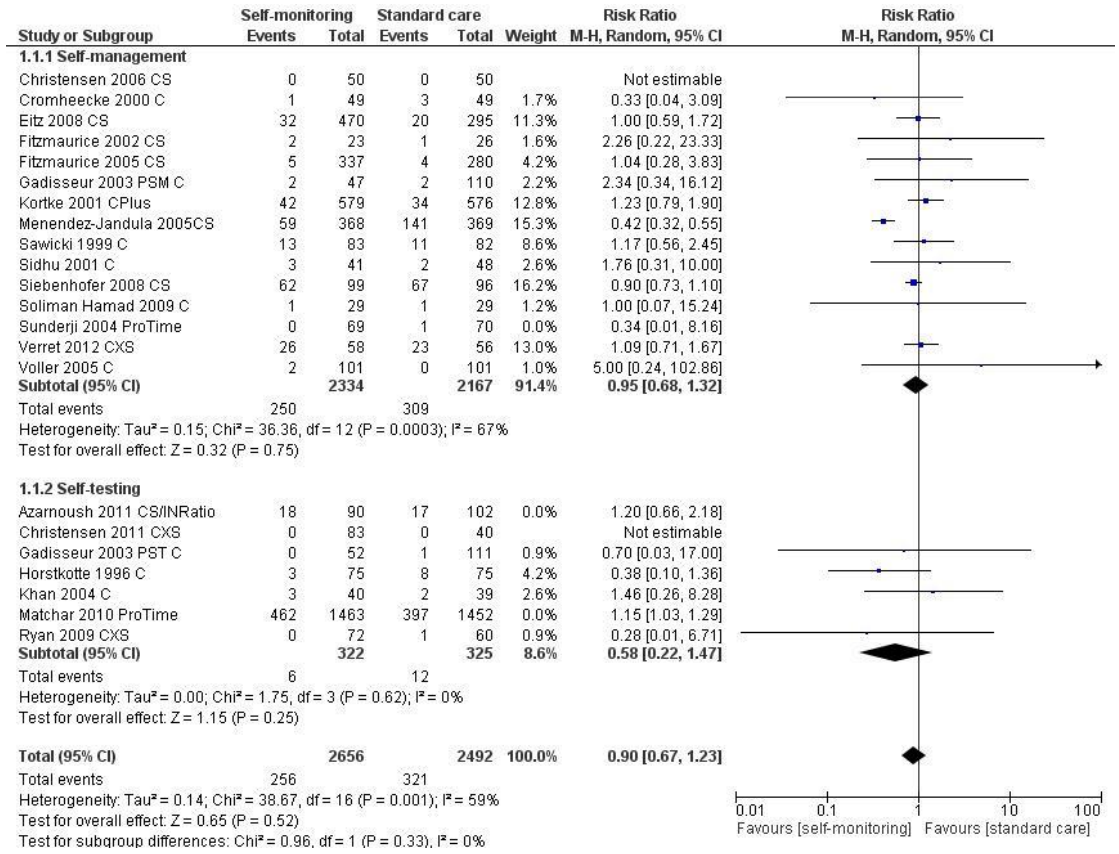

Figure A Forest plot of comparison: Any bleeding: Sensitivity analysis restricted to CoaguChek system trials

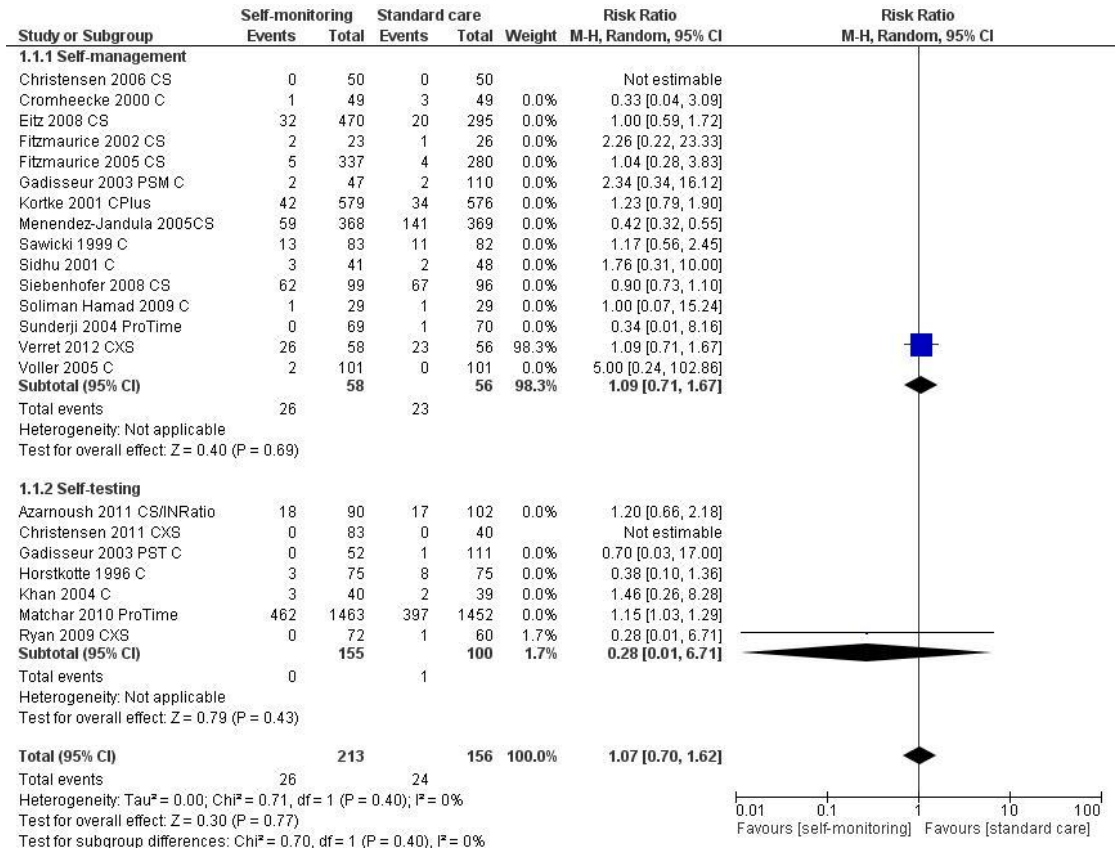

Figure B Forest plot of comparison: Any bleeding: Sensitivity analysis restricted to CoaguChek XS trials

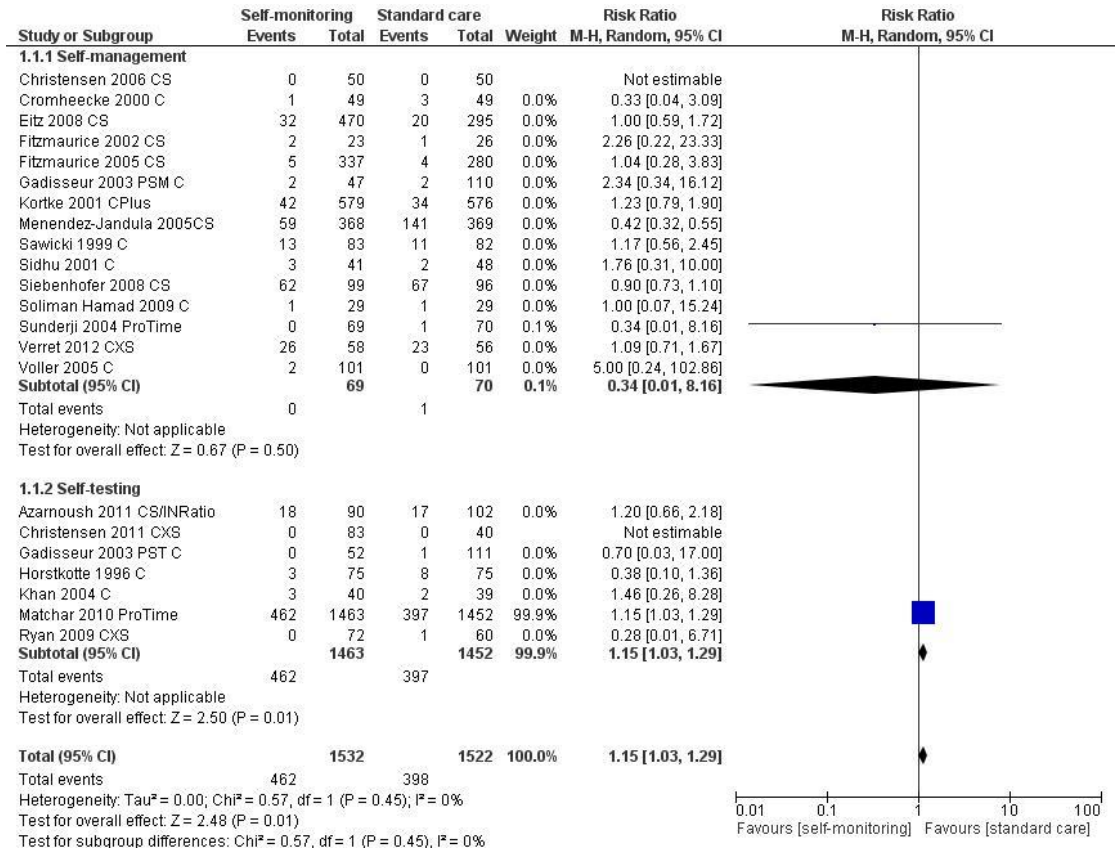

Figure C Forest plot of comparison: Any bleeding: Sensitivity analysis restricted to ProTime trials

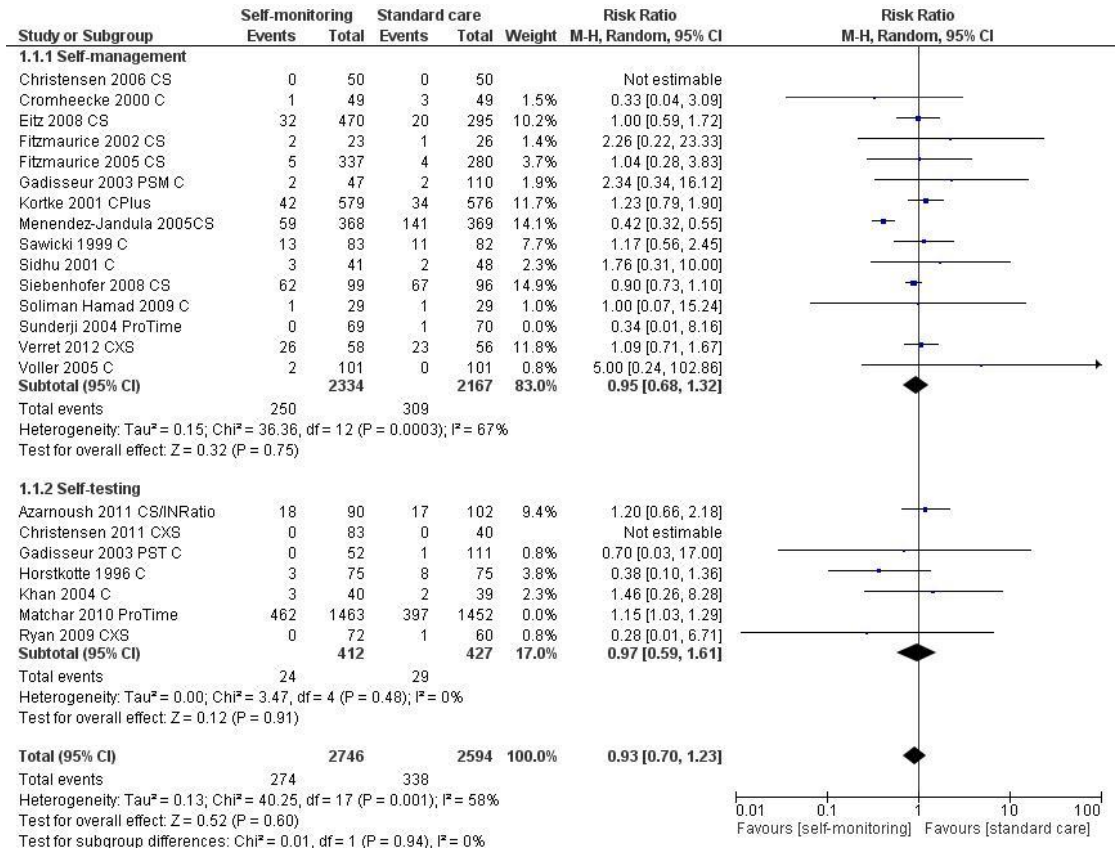

Figure D Forest plot of comparison: Any bleeding: Sensitivity analysis restricted to CoaguChek and INRatio trials

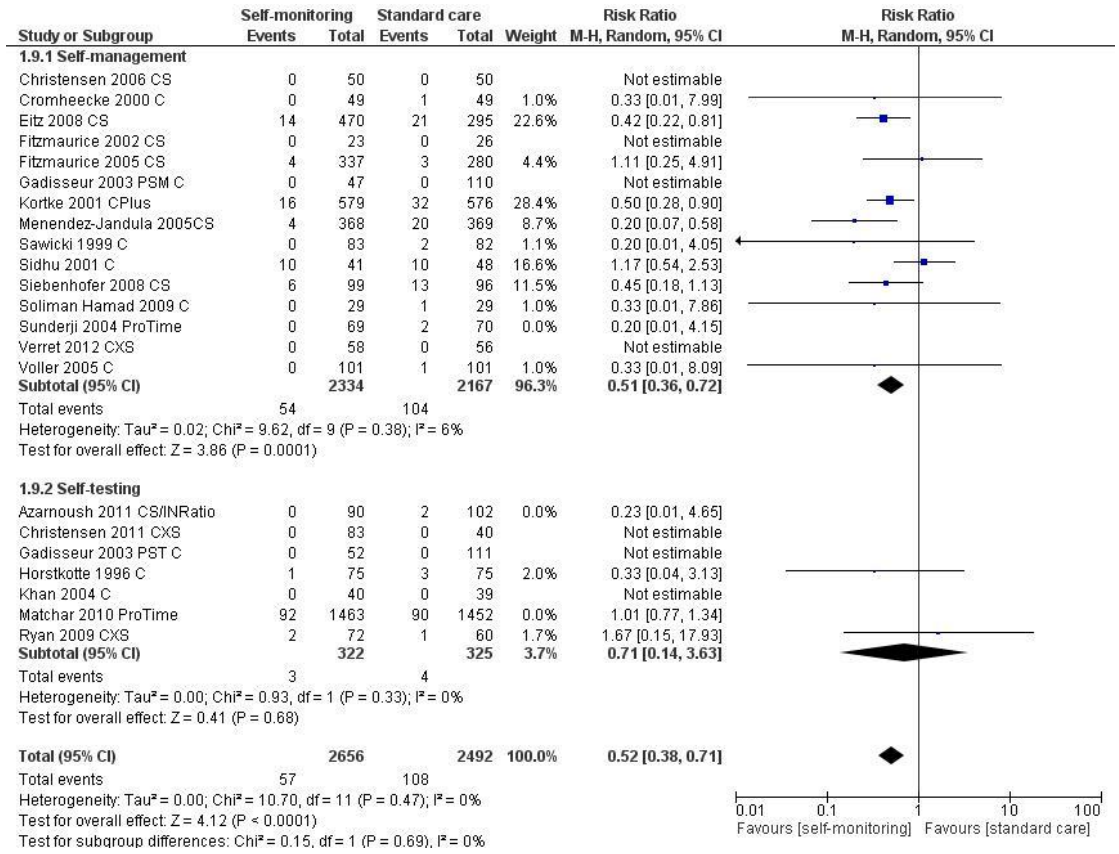

Figure E Forest plot of comparison: Thromboembolic events: Sensitivity analysis restricted to CoaguChek system trials

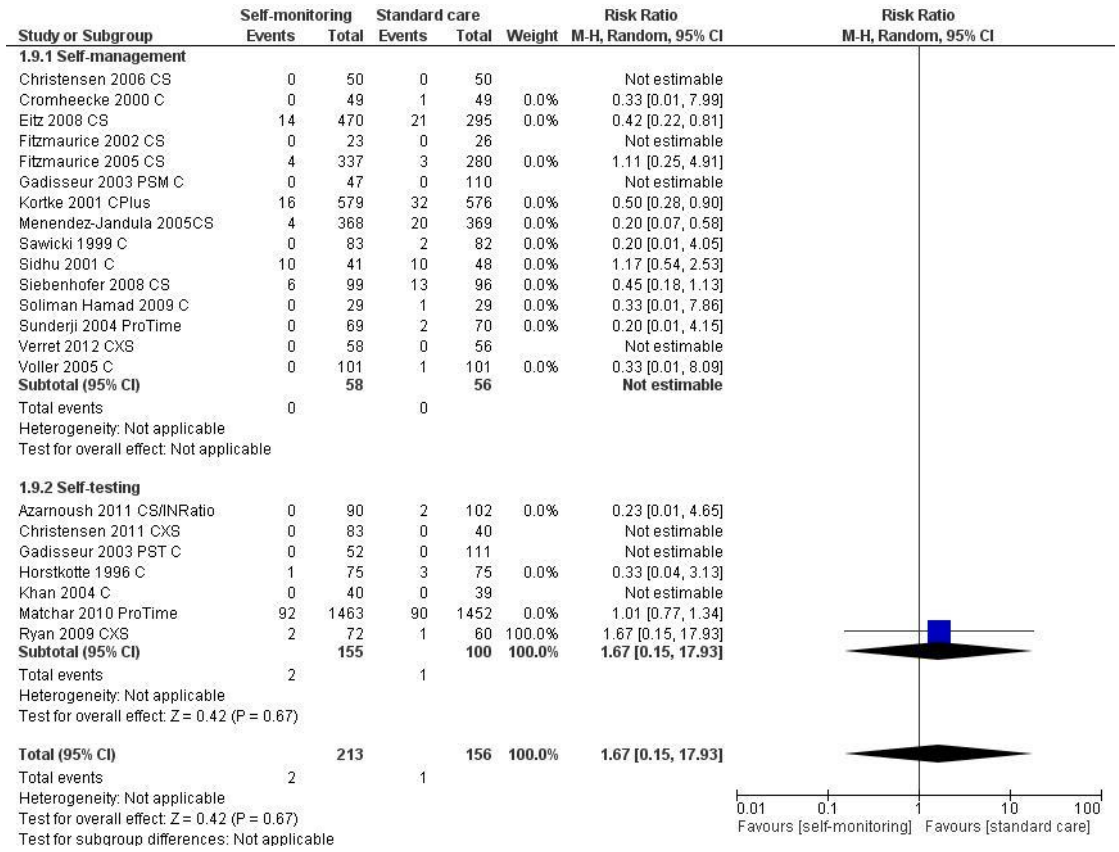

Figure F Forest plot of comparison: Thromboembolic events: Sensitivity analysis restricted to CoaguChek XS trials

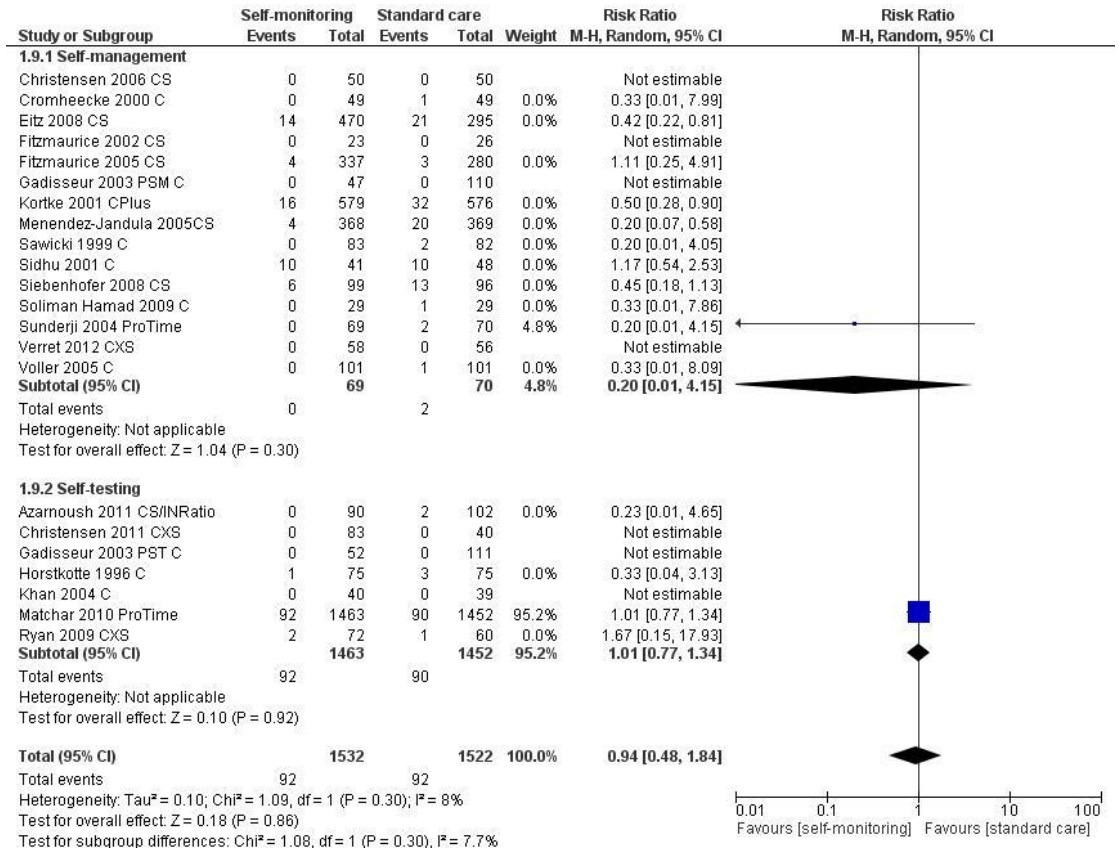

Figure G Forest plot of comparison: Thromboembolic events: Sensitivity analysis restricted to ProTime trials

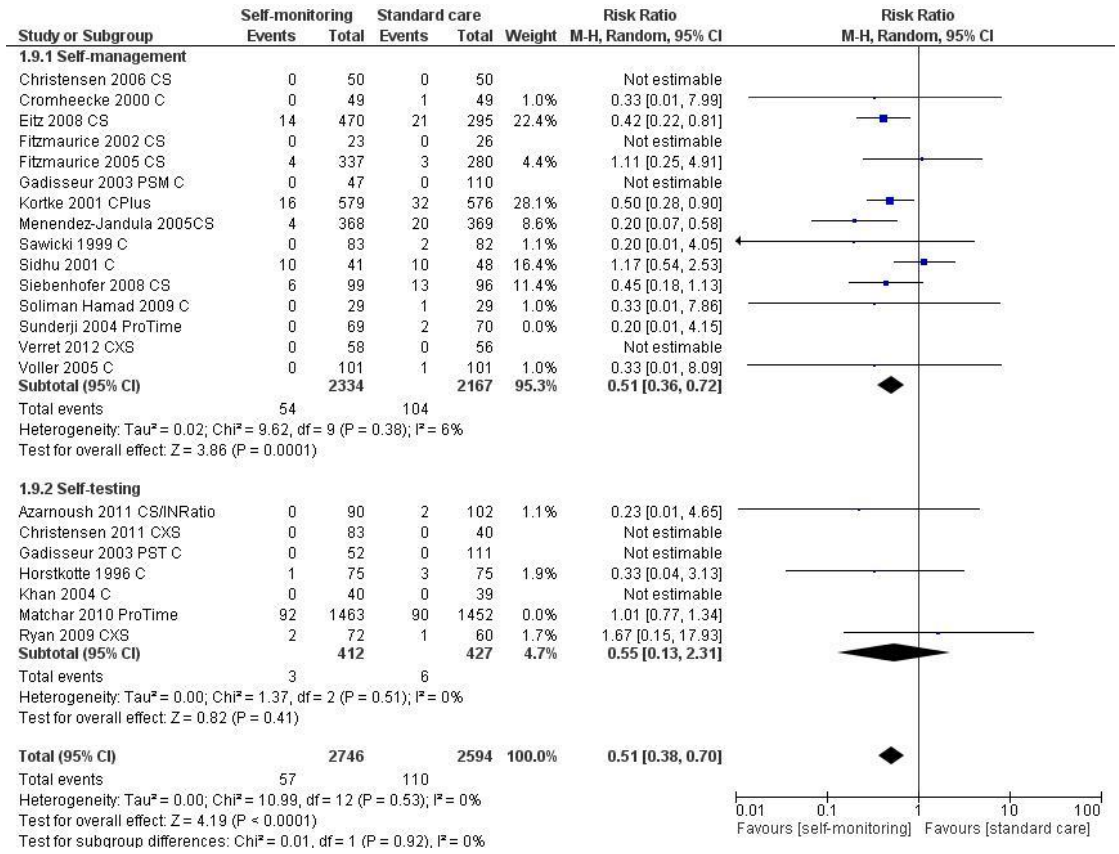

Figure H Forest plot of comparison: Thromboembolic events: Sensitivity analysis restricted to CoaguChek and INRatio trials

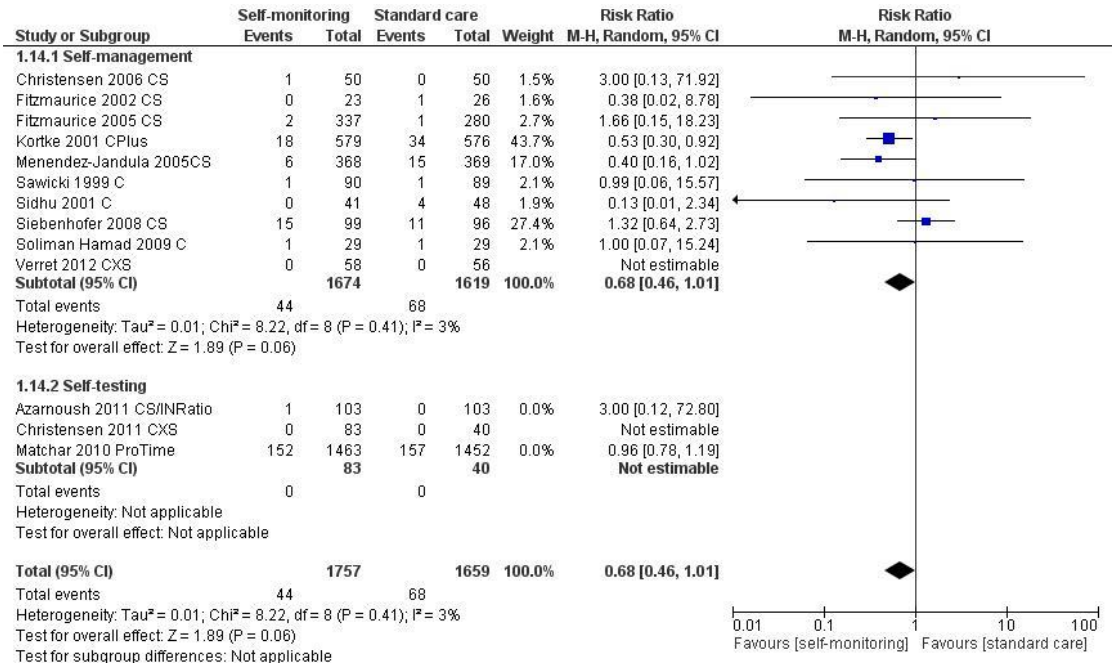

Figure I Forest plot of comparison: Mortality: Sensitivity analysis restricted to CoaguChek system

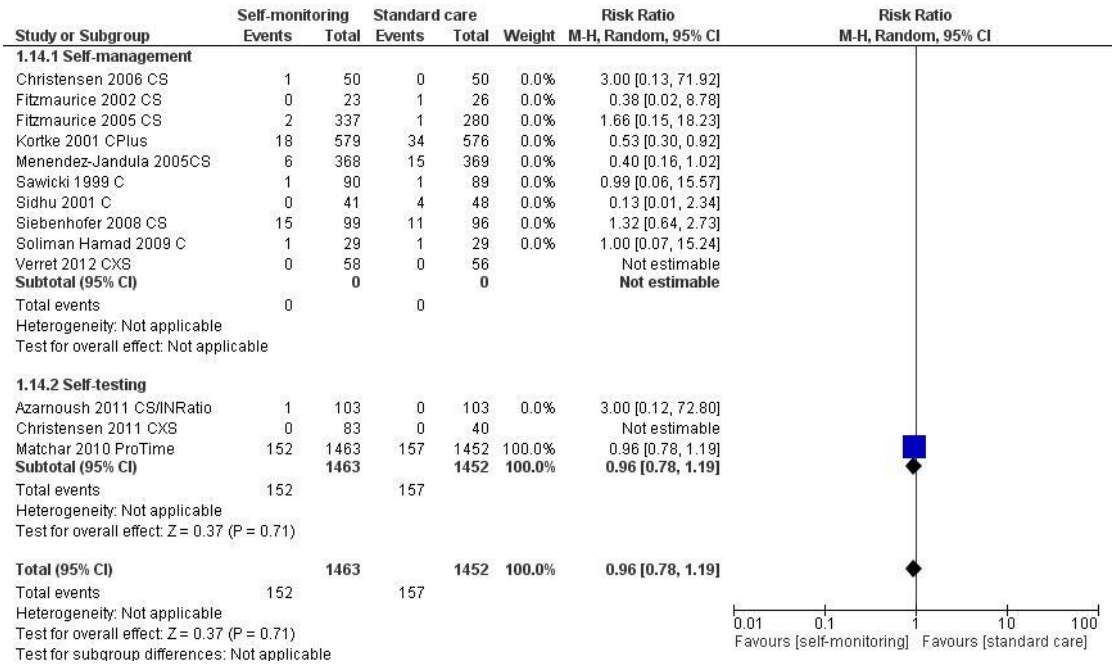

Figure J Forest plot of comparison: Mortality: Sensitivity analysis restricted to ProTime

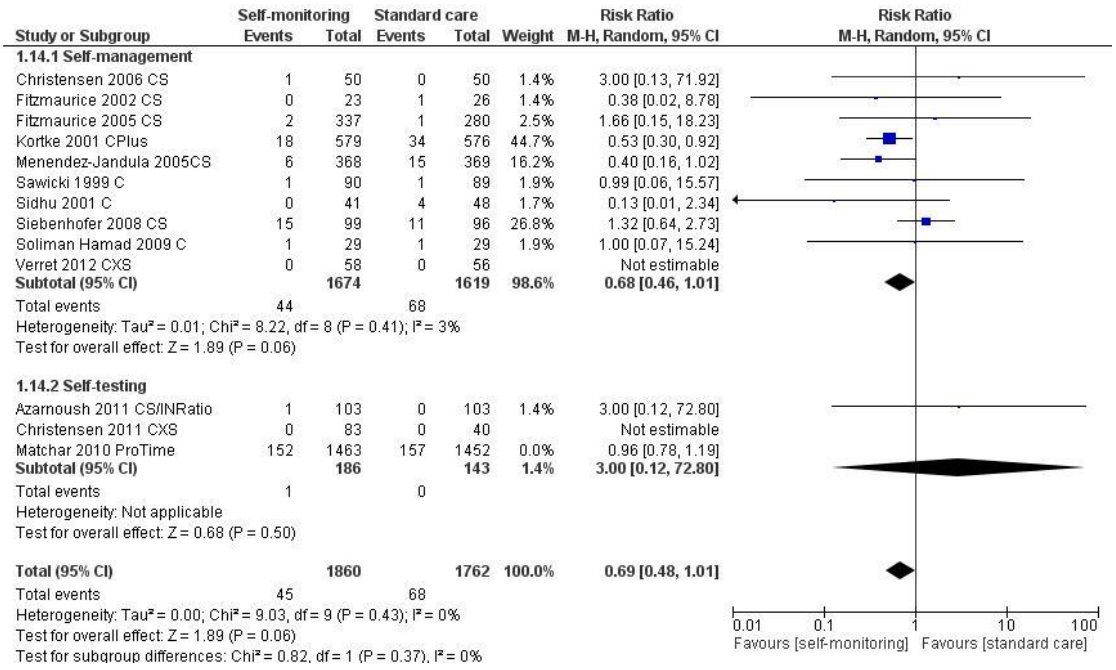

Figure K Forest plot of comparison: Mortality: Sensitivity analysis restricted to CoaguChek and INRatio

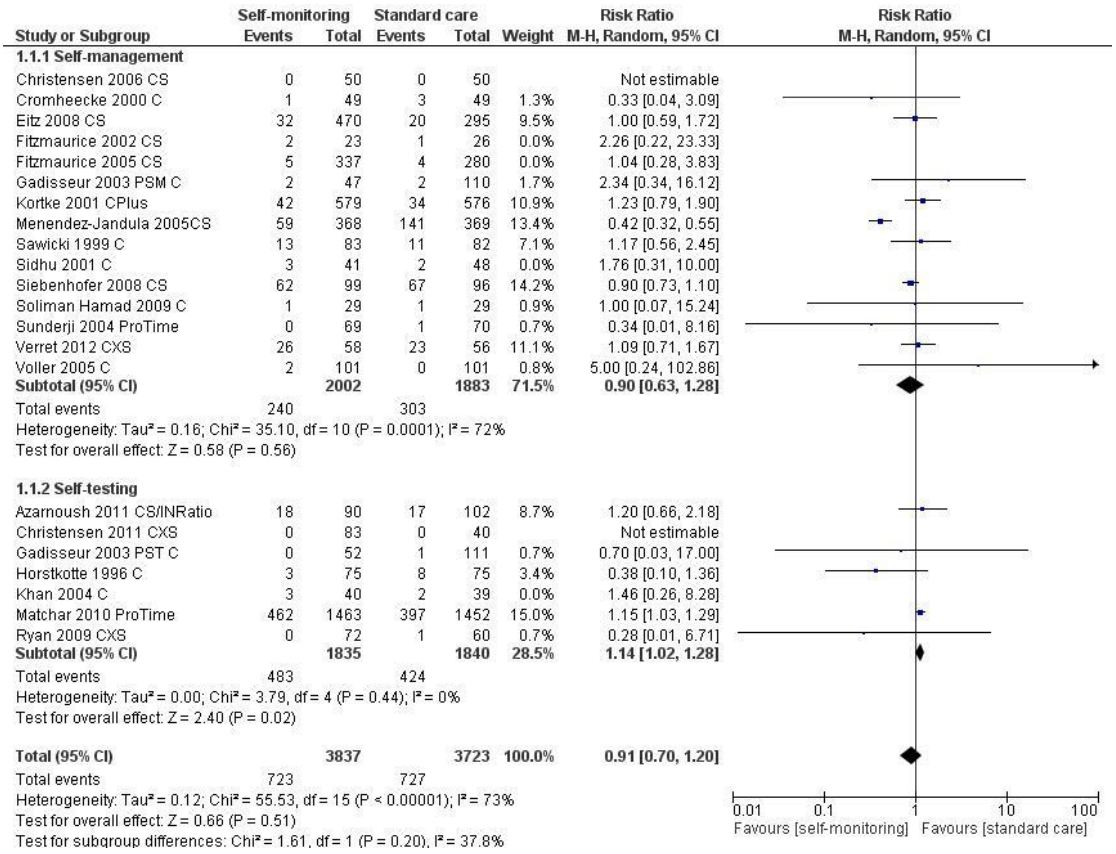

Figure L Forest plot of comparison: Any bleeding: Sensitivity analysis restricted to non-UK trials

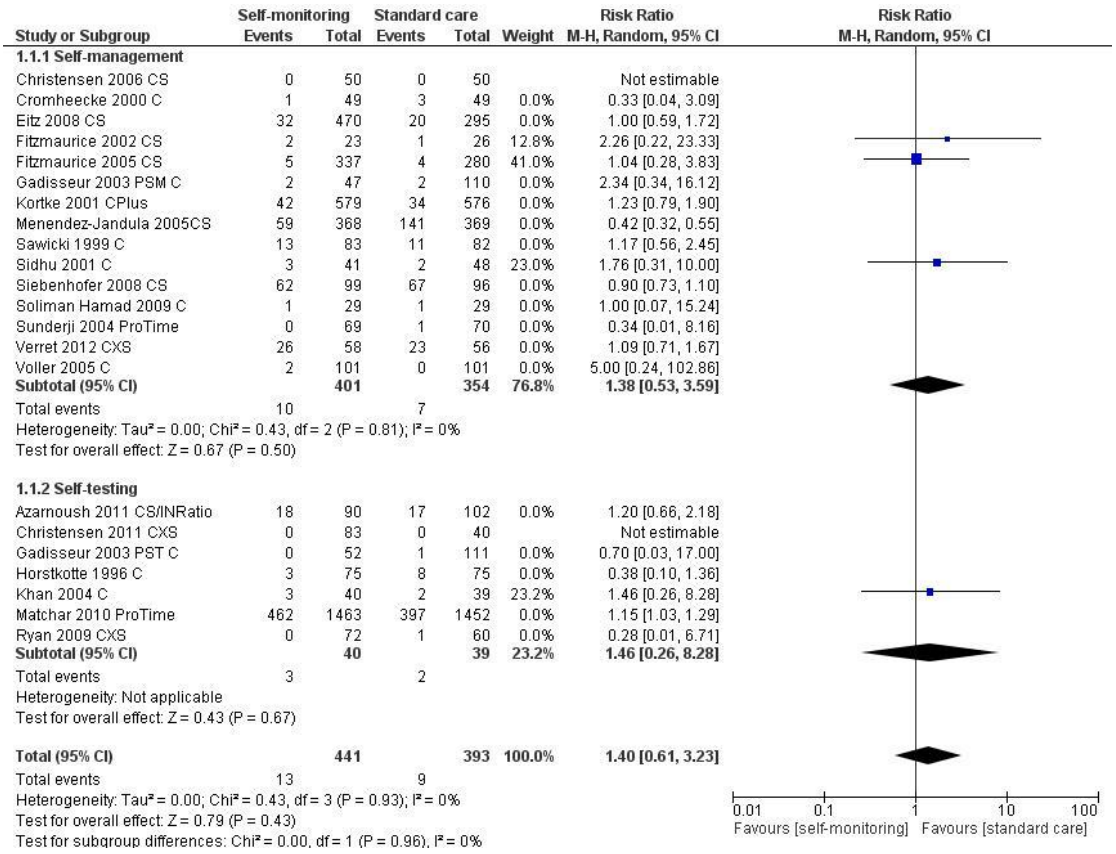

Figure M Forest plot of comparison: Any bleeding: Sensitivity analysis restricted to UK trials

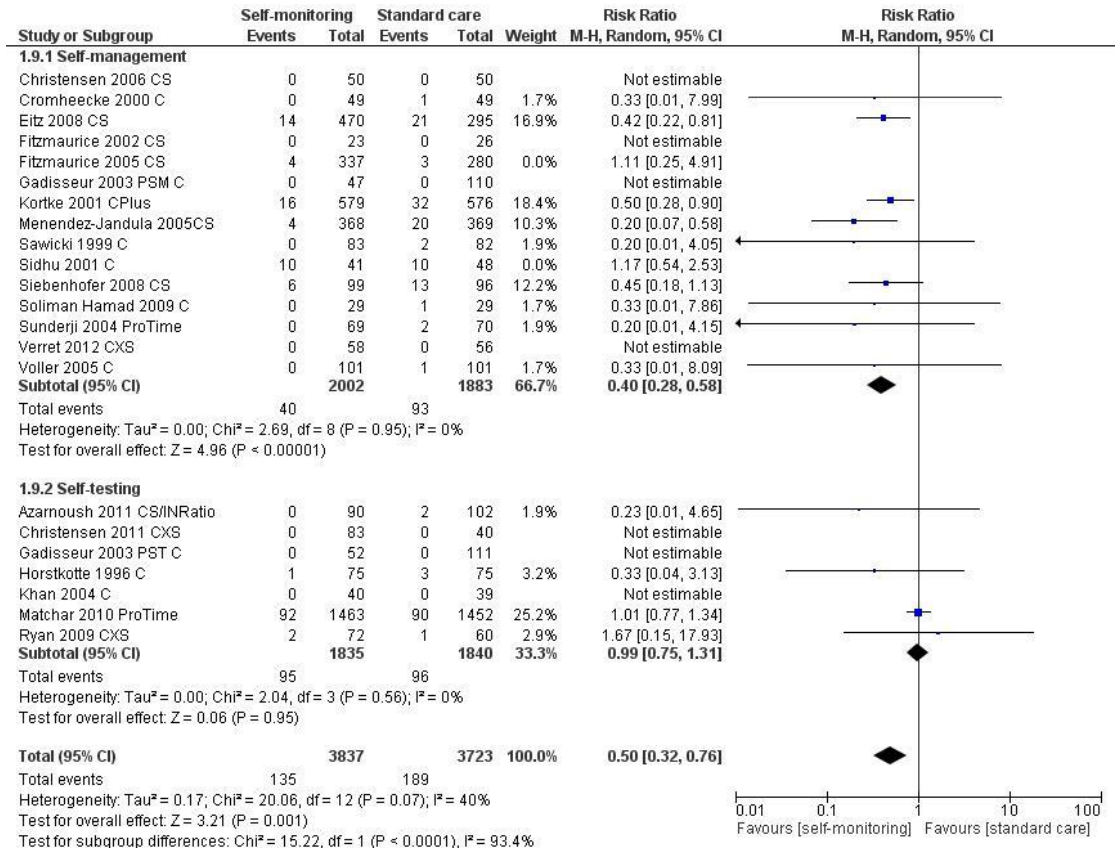

Figure N Forest plot of comparison: Thromboembolic events: Sensitivity analysis restricted to non-UK trials

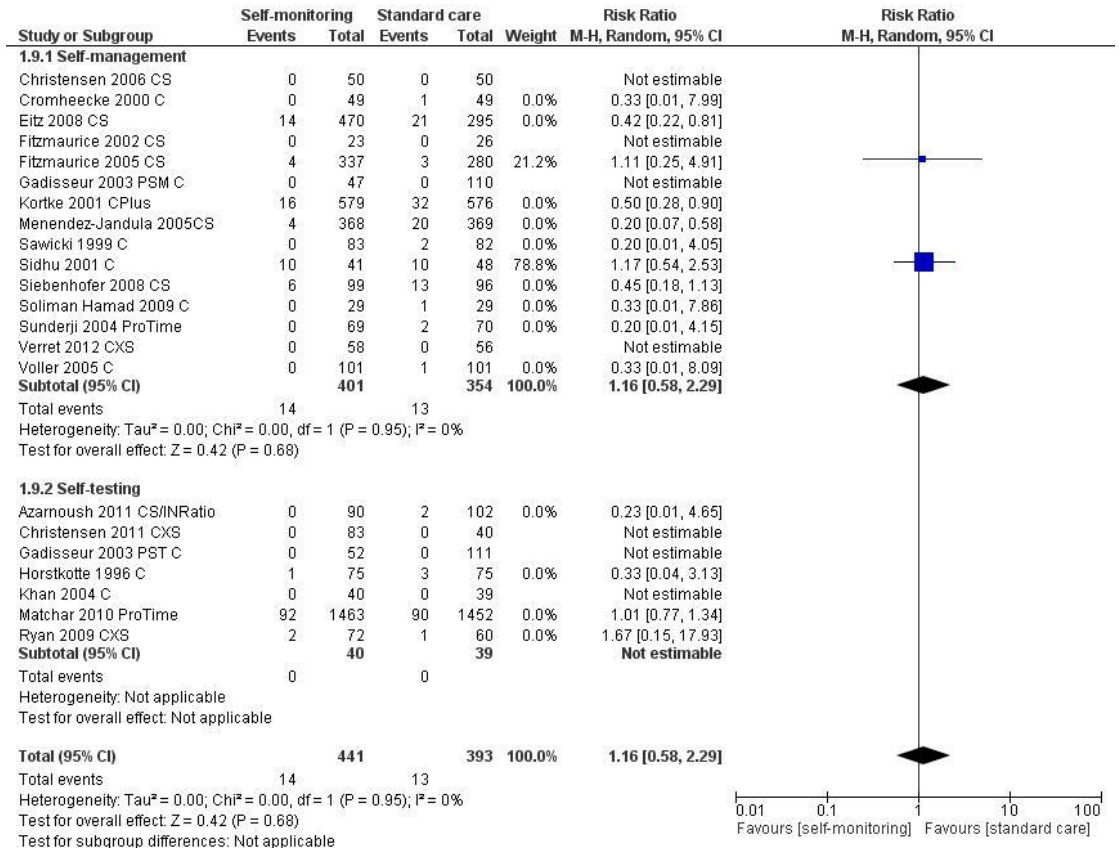

Figure O Forest plot of comparison: Thromboembolic events: Sensitivity analysis restricted to UK trials

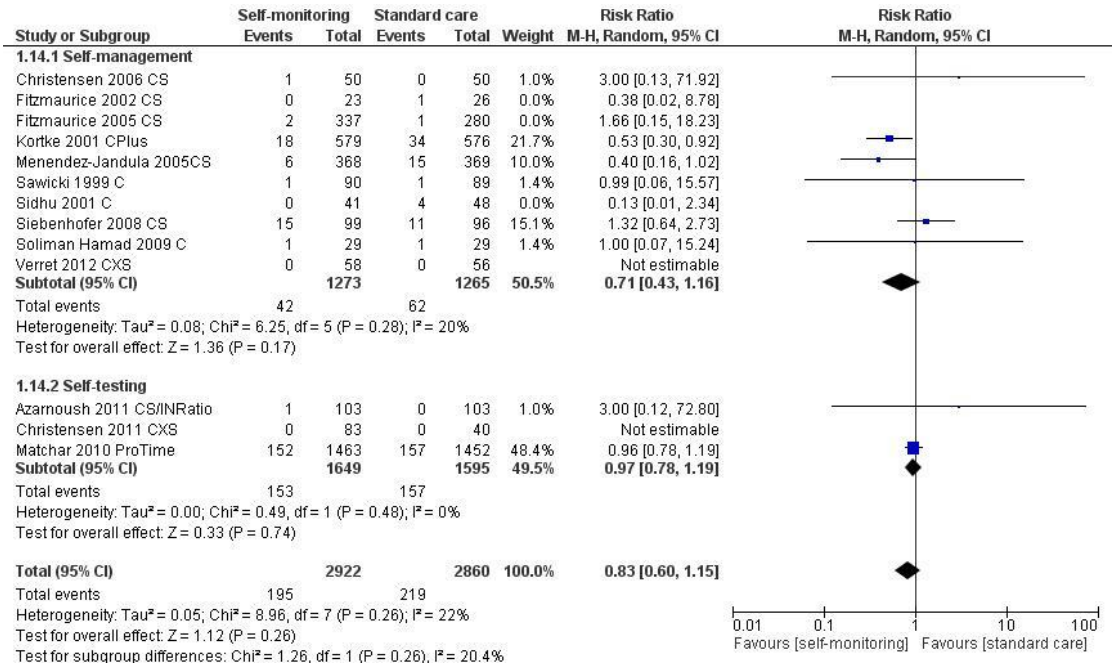

Figure P Forest plot of comparison: Mortality: Sensitivity analysis restricted to non-UK trials

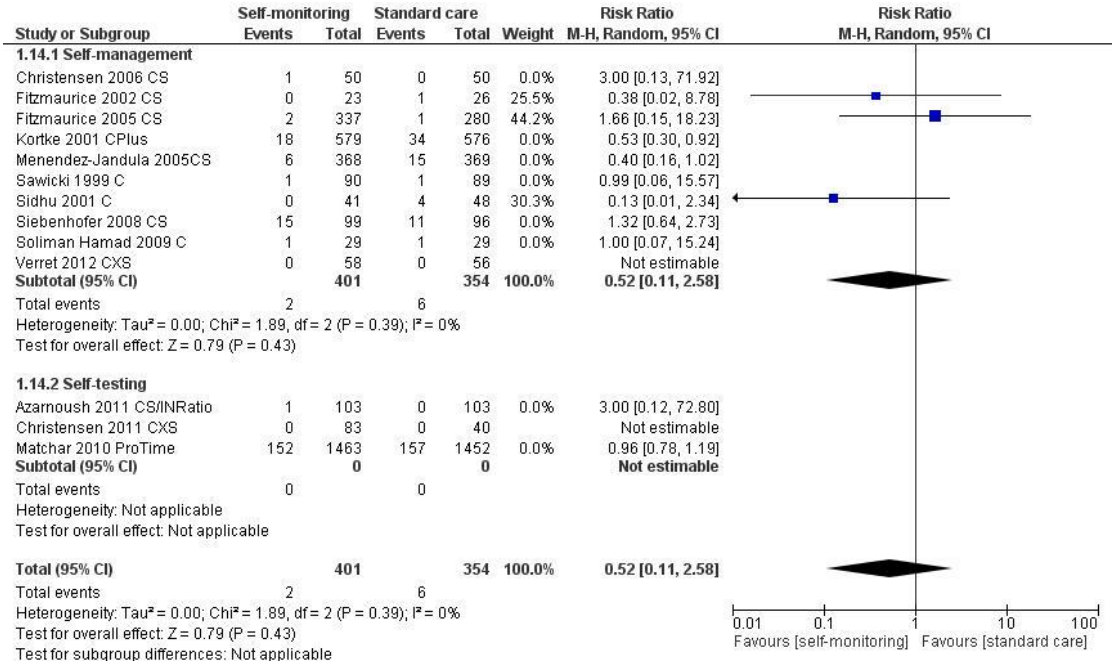

Figure Q Forest plot of comparison: Mortality: Sensitivity analysis restricted to UK trials

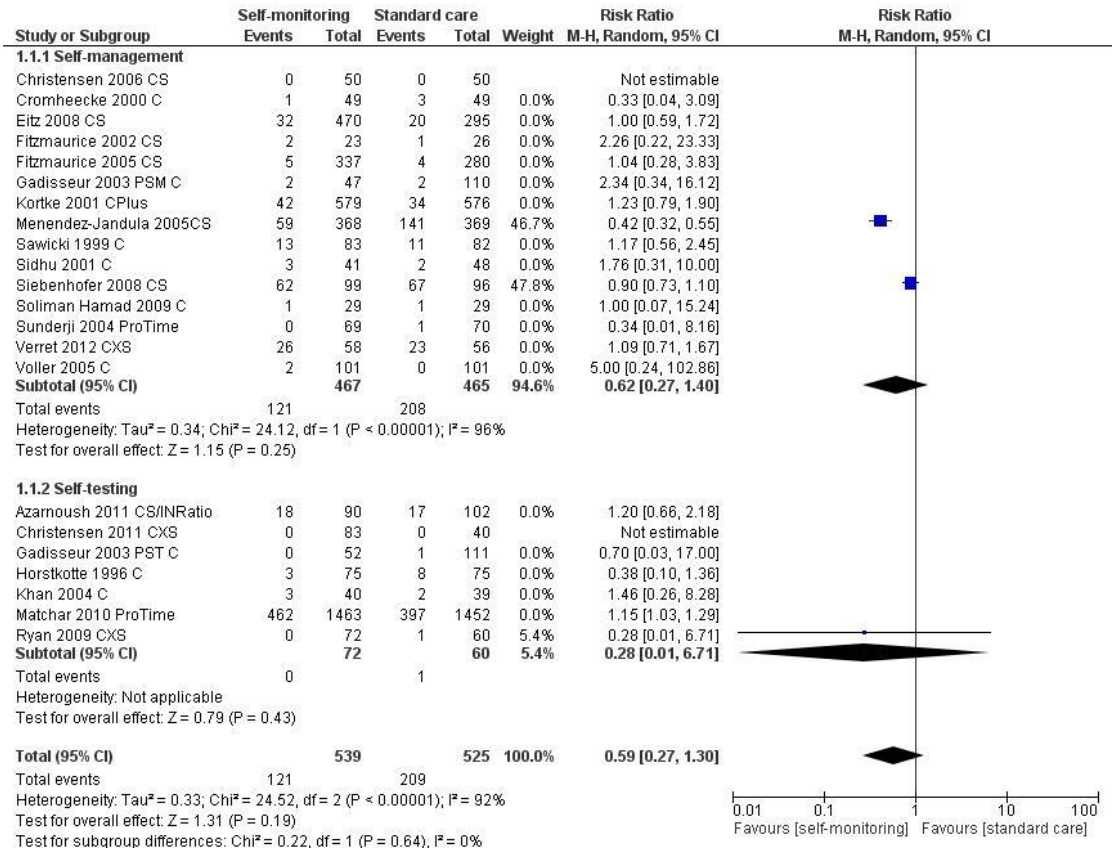

Figure R Forest plot of comparison: Any bleeding: Sensitivity analysis restricted to low risk of bias trials

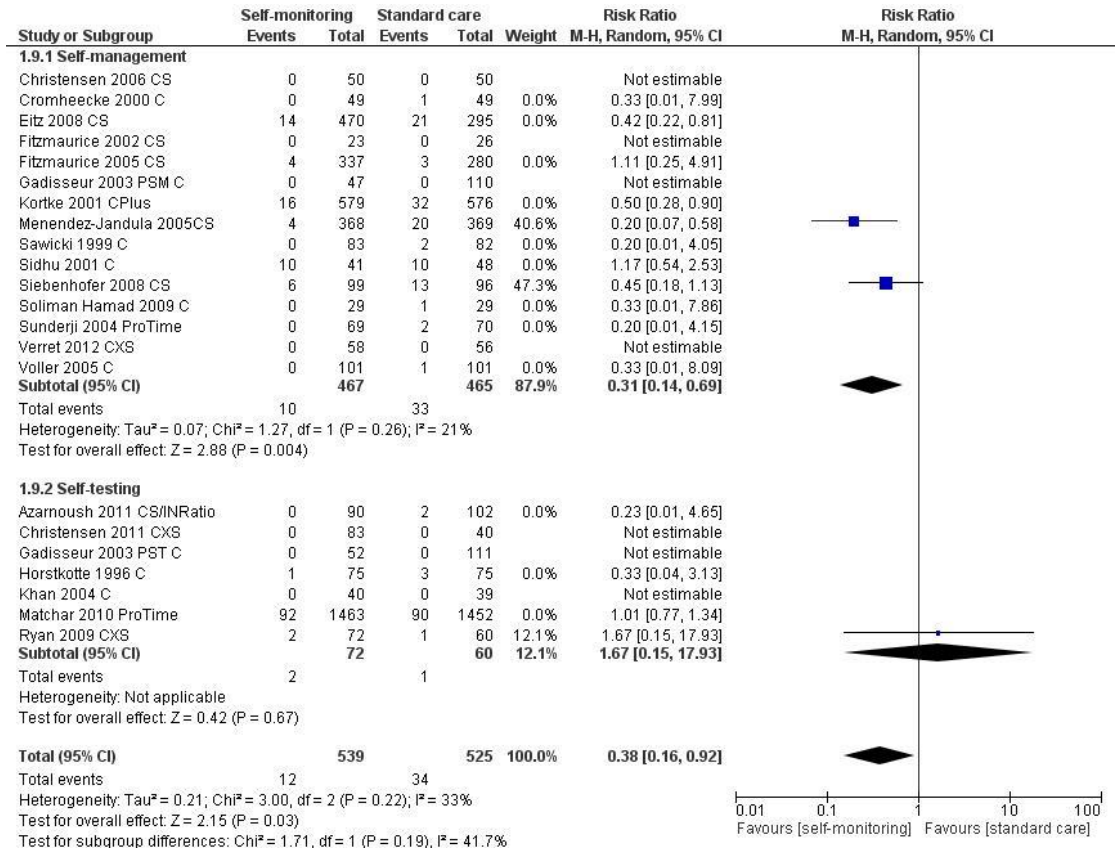

Figure S Forest plot of comparison: Thromboembolic events: Sensitivity analysis restricted to low risk of bias trials

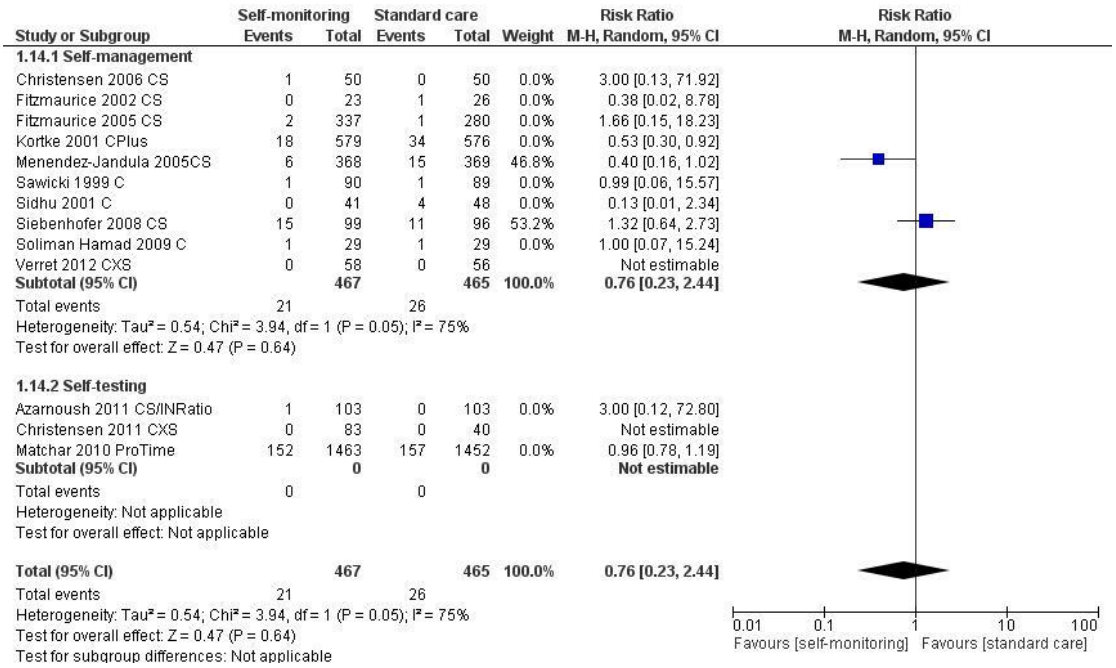

Figure T Forest plot of comparison: Mortality: Sensitivity analysis restricted to low risk of bias trials