Is patient self-monitoring (including self-testing and self-management) of oral anticoagulation therapy safe, efficacious and cost-effective?

What is an evidence note
Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision-makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions and are produced in an approximately 1-3 month period. Evidence notes are not comprehensive systematic reviews.

Key points
- Around 1.4% of the 80,000 patients prescribed warfarin in Scotland also receive International Normalised Ratio detection strips for self-monitoring.
- There is considerable heterogeneity in the evidence base for patient self-monitoring with respect to the clinical indications for therapy, patient selection, the intensity of education, training and support provided, the frequency of testing and the duration of follow-up. There is also variation in the format and quality of the ‘usual care’ comparison.
- Meta-analyses of mainly low quality randomised controlled trials in patients receiving long-term oral anticoagulation therapy with vitamin K antagonists report that self-management of INR reduces the incidence of thromboembolic events, compared with usual care, without increasing major bleeding events. The benefit is not seen with self-testing.
- Although there is uncertainty around the beneficial effects as a result of clinical heterogeneity, it is likely that self-monitoring is a safe option for competent and motivated patients.
- Patient satisfaction and quality of life is examined in the literature as a secondary outcome. Where it is reported, the majority of studies record beneficial effects, although these may be small.
- Two recent United Kingdom (UK) economic evaluations concluded that self-monitoring is a cost-effective strategy when compared with usual care. However, further analyses demonstrated that, although self-management was cost-effective, self-testing was not. It is worth noting that cost effectiveness of self-management is based on the assumption that it leads to a reduction in thromboembolic events.
- The findings support the view that the cost effectiveness of self-monitoring is strongly contingent on the patient being able to manage their own oral anticoagulation therapy. By doing so, this helps to ensure that successful patient outcomes are maintained, and that an increase in consumable costs is offset by resource-use savings.
Definitions

**Patient self-testing (PST):** involves patients performing blood sampling and analysis at home using a portable, battery-operated INR testing machine. Results are communicated to a healthcare professional who then decides on dose adjustment.

**Patient self-management (PSM):** here the patient not only performs the blood sampling and analysis but also makes any vitamin K antagonist dose adjustment required.

**Patient self-monitoring:** in this evidence note, patient self-testing (PST) and patient self-management (PSM) are collectively referred to as patient self-monitoring.

Literature search

For this update, a systematic search of the secondary literature was carried out between 17 July–22 July 2015 to identify systematic reviews, health technology assessments (HTAs) and other evidence-based reports.

The primary literature was systematically searched between 17 July–21 July 2015 using the following databases: Medline, Medline in process, Embase, Cinahl. Results were limited to randomised controlled trials (RCTs) and economic evaluations, English language studies, and the time period 2012–2015.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: warfarin, vitamin K antagonist, 4-hydroxy coumarins, anticoagulant. A full list of resources searched and terms used are available on request.

Introduction

Long-term oral anticoagulation therapy (OAT) is indicated for patients with a range of conditions, including venous thromboembolism, atrial fibrillation (AF), and mechanical heart valves (MHV). While newer oral anticoagulant drugs such as direct thrombin inhibitors like dabigatran are being introduced for specific patient groups, the most commonly used agents are the vitamin K antagonists, predominantly warfarin. Warfarin has a narrow therapeutic index and ongoing monitoring of the level of anticoagulation of the blood using the International Normalised Ratio (INR) is required to determine the safest and most effective dose for individual patients.

Treating to a therapeutic target INR for each condition (commonly 2.5) addresses the variability in the action of vitamin K antagonists which is dependent on a range of environmental factors including diet, changes in metabolism and concomitant illness and medication use. Current models of OAT monitoring involve patients attending a hospital outpatient clinic or community-based service.

Health technology description

Patient self-testing (PST) involves patients performing blood sampling and analysis at home using a portable, battery-operated INR testing machine. Results are communicated to a healthcare professional who then decides on dose adjustment. In patient self-management (PSM), the patient not only performs the blood sampling and analysis, but also makes any vitamin K antagonist dose adjustment required.

In this evidence note, these two strategies are collectively referred to as patient self-monitoring.

Self-testing devices evaluated in clinical studies include the CoaguChek® series (Roche diagnostics, Basel, Switzerland), Protime® (International Technidyne Corporation, Edison, USA) and INRatio® (Alere Inc, San Diego, USA). Although each employs a different technology, all use a small volume capillary whole blood sample obtained from a finger prick. Device costs for those available to NHS Scotland are around £300. Test strips and lancets are available on prescription. The gross ingredient cost (before deduction of any discount) of test strips dispensed in the community in 2014/2015 was £187,515 (J Smith, Information Analyst, ISD Scotland. Personal Communication, 5 August 2015). Caution is required when interpreting these data since prescriptions for consumables may relate to point of care use, for example by community healthcare practitioners, rather than self-testing.

Epidemiology

In Scotland, in 2014–2015, around 80,000 individuals were prescribed warfarin. The number of people prescribed warfarin is increasing; in year 2008–2009, around 65,000 patients were prescribed the medication. Approximately 1.4%
(1,100) of people prescribed warfarin also receive detection strips on prescription (J Smith, Information Analyst, ISD Scotland. Personal Communication, 5 August 2015).

Clinical effectiveness

The evidence base for INR self-monitoring was heterogeneous with important differences in patient groups, parameters of the interventions and specification of the usual care comparator. Most studies bring together patients whose clinical indications for oral anticoagulation vary. Mean age of study participants was approximately 65 years. In a systematic review of 26 trials only seven provided adequate information to assess the balance between study groups in important co-morbidities and risk factors such as previous stroke. Study participants were highly selected and required motivation, confidence and sufficient mental and physical capabilities to perform the monitoring. In half of the studies in one systematic review, up to 50% of the patients who met the eligibility criteria did not go on to complete the training and agree to be randomised.

Interventions were heterogeneous in terms of testing protocols and the intensity and quality of education and support provided. Vitamin K antagonists included warfarin, phenprocoumon, acenocoumarol and fluindione. Although 6 months was a common study duration, follow-up periods for trials encompassed in meta-analyses ranged from 4 months to 9.3 years. Usual care interventions included a mix of highly specialised anticoagulation clinics, general outpatient clinics and, in some cases, routine primary care. Around half of the trials in the evidence base reported industry funding.

Primary outcome measures in RCTs examining the clinical effectiveness of self-monitoring of oral anticoagulation therapy included: rates of thromboembolic events such as stroke; rates of severe haemorrhagic events (the precise definition of which varies between studies) and mortality. Secondary outcomes included measures of anticoagulation control such as time spent in therapeutic range (TTR), patient satisfaction and quality of life.

Adults

Three contemporary meta-analyses summarised the evidence base in adults. Unlike previous meta-analyses, all three incorporate data from the largest study of self-testing in adults published in 2010. Two were trial-level analyses which, for the primary outcomes, incorporate data from largely the same group of trials, and one used individual patient data from a subset of 11 of these trials.

The most recent of the meta-analyses provided the evidence base for the National Institute for Health and Care Excellence (NICE) diagnostics guidance on AF and heart valve disease. This guidance recommends ‘self-monitoring of coagulation status in adults and children on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease if the person prefers this form of testing and the person or their carer is both physically and cognitively able to self-monitor effectively’. This was in agreement with the Scottish Intercollegiate Guidelines Network (SIGN) Guideline 129 on Antithrombotics: indications and management, which based on older evidence recommends that ‘self-monitoring and self-dosing is safe and effective and can be considered for some patients’.

Table 1 outlines the findings of the three meta-analyses for effect of self-monitoring on the outcomes of major thromboembolic events, major bleeding events and mortality. Although data from up to 21 trials were incorporated in the meta-analyses, the majority of the included studies were at moderate or high risk of bias due to lack of blinding of outcome assessment, lack of intention to treat analysis or lack of detail on methods of randomisation and allocation concealment. Thus, findings were based on low quality evidence. In addition, for many of the trials, the extent of patient education around INR control was greater for the intervention group than the standard care group.
Table 1 Key findings from contemporary meta-analyses of effects of self-monitoring of oral anticoagulation compared with standard care

<table>
<thead>
<tr>
<th></th>
<th>Major thromboembolic events (N-trials, n-patients)</th>
<th>Major bleeding events (N-trials, n-patients)</th>
<th>Mortality (N-trials, n-patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharma 2015</td>
<td>RR = 0.52; 95% CI 0.34 to 0.80; p=0.003</td>
<td>RR = 1.02; 95% CI 0.86 to 1.22; p=0.80</td>
<td>RR = 0.83; 95% CI 0.63 to 1.10; p=0.20</td>
</tr>
<tr>
<td></td>
<td>I² = 36%</td>
<td>I² = 0%</td>
<td>I² = 11%</td>
</tr>
<tr>
<td></td>
<td>N=21, n=8,394</td>
<td>N=20, n=8,202</td>
<td>N=13, n=6,537</td>
</tr>
<tr>
<td>Bloomfield 2011</td>
<td>OR= 0.58; 95% CI 0.45 to 0.75; p&lt;0.001</td>
<td>OR=0.89*; 95% CI 0.75 to 1.05; p=0.169</td>
<td>OR= 0.74; 95% CI 0.63 to 0.87; p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>I² = 27%</td>
<td>I² = 2%</td>
<td>I² = 51%</td>
</tr>
<tr>
<td></td>
<td>N=14, n=7,759</td>
<td>N=16, n=7,867</td>
<td>N=13, n=6,370</td>
</tr>
<tr>
<td>Heneghan 2012</td>
<td>HR= 0.51; 95% CI 0.31 to 0.85; p=0.01</td>
<td>HR= 0.88; 95% CI 0.74 to 1.06; p=0.18</td>
<td>HR= 0.82; 95% CI 0.62 to 1.09; p=0.18</td>
</tr>
<tr>
<td></td>
<td>I² = 53%</td>
<td>I² = 0%</td>
<td>I² = 37%</td>
</tr>
<tr>
<td></td>
<td>N=11, n=6,417</td>
<td>N=11, n=6,417</td>
<td>N=11, n=6,417</td>
</tr>
</tbody>
</table>

*appears in study report as 0.89 and 0.87
Cl=confidence interval  RR=relative risk, OR=odds ratio, HR=hazard ratio

There was agreement across the three analyses that the use of self-monitoring led to statistically significant and clinically significant reductions of over 40% in major thromboembolic events when compared with standard care, with no concomitant increase in major bleeding events7-9. Pre-specified subgroup analysis showed that the rate of thromboembolic events was reduced with self-management but not with self-testing7,9.

For the mortality outcome, two of the analyses observed no significant difference in all cause mortality between self-monitoring and usual care7,9 whilst one reported a statistically significant mortality benefit with self-monitoring8. Discrepancies in the consistency of how the mortality data were extracted from several of the primary studies into the meta-analyses limited confidence in the findings.

Individual patient data meta-analysis identified that patients younger than 55 years of age and those with MHV who were allocated to self-monitoring had statistically significant reductions in thromboembolic events whilst older patients and those with AF did not9.

All three analyses incorporated the findings of the largest RCT of PST11, The Home International Normalised Ratio Study (THINRS). Published in 2010, THINRS randomised 2,922 patients (98% were males) to weekly home self-testing or to monthly high-quality testing in a specialist clinic. Follow-up was undertaken for a minimum of 2 years (mean follow-up 3 years, range 2.0–4.75 years). There were no statistically significant differences between study groups for the three primary end points: stroke, major bleeding or death. This study was identified by each meta-analysis as a major source of heterogeneity due to it having both a longer follow-up period and higher quality care in the usual care arm compared with other trials in the analyses.

It was proposed that the benefits in thromboembolic event rates associated with patient self-management were likely to be mediated by improved anticoagulation control8. A number of measures of this were identified as secondary outcomes in trials. These included TTR, proportion of INR measurements in, or to defined degrees, out of specified therapeutic range and the proportion of study participants with measures in or out of therapeutic range at various time points. This assortment of measures made meta-analysis challenging. One meta-analysis incorporated data from six studies of patients who self-managed oral anticoagulation. Mean TTR varied from 63.2% to 80.0% across all study groups and no significant difference in TTR between study arms was observed (weighted mean difference 0.47%; 95% CI -1.40% to 2.34%; p=0.62)7. Such measures may be confounded by differences between study groups in frequency of testing14. A meta-analysis of individual patient data reported that, after one year, participants with an MHV or AF who were self-monitoring had undertaken over 20 more tests than those receiving standard care9. An RCT
(n=310) examined INR control as primary outcome and used data from monthly blinded laboratory INR testing to compare time outside therapeutic range between patients self-managing with weekly home testing and patients receiving usual care from family doctor or hospital clinic. Over 1 year of follow-up, no statistically significant difference between groups was observed in the proportion of these blinded tests which were outside target range; 35.5% in PSM group and 40.7% in the usual care group (p=0.08). Non-inferiority was satisfied indicating that, with a prespecified 6% margin in rate of out of range values, PSM performed at least as well as usual care in maintaining INR within target range14.

Health-related quality of life was measured in many of the studies incorporated within the systematic reviews, but meta-analysis of the data was not possible. Measurement instruments encompassed a range of domains including satisfaction with treatment, self-efficacy, daily hassles, physical and social functioning, pain and vitality7,8. One systematic review summarised the findings stating that eight of 11 trials measuring such constructs reported that patient satisfaction, quality of life or both was better with self-monitoring when compared with patients receiving usual care8. The inability to blind patients to the intervention may influence such self-report measures. The largest trial in the analyses used the Duke Anticoagulation Satisfaction Scale and found that the degree of patient satisfaction was higher for those in the PST group than for those in the standard care group. The benefit was small (2.4 points on a scale ranging from 25 to 225) but was statistically significant11.

**Children**

A systematic review of studies of INR self-monitoring in children identified 11 studies, all but one of which were small uncontrolled case series with limited follow-up15. One small RCT (n=28) was identified which randomised children undertaking PST to continued PST or to PSM. At 1-year follow-up there was no difference between the groups in time in INR target range, but the PSM group reported higher quality of life. No meta-analysis was possible15.

**Device safety**

A review concluded that portable coagulometers have acceptable accuracy and precision when compared with laboratory measures of INR, but that external quality control is essential10. In the largest RCT of PST (n=1,463 in treatment arm, 4,495 patient years of weekly testing) no participants recorded any adverse event related to operation of the blood testing device11.

**Cost effectiveness**

In 2015, a UK de novo economic model was developed from an NHS perspective to assess the cost effectiveness of self-monitoring (self-testing and self-management) versus usual NHS care7. Although the cost effectiveness of self-monitoring was assessed as a whole, the base case analysis was carried out under the assumption that 50% of patients self-test and 50% of patients self-manage their coagulation status. Within the usual care arm of the model, it was assumed that 66% of warfarin monitoring appointments were managed in primary care, whilst the remaining 34% were managed in secondary care.

The monitoring strategies were compared for patients with AF or an artificial heart valve (AHV). In line with the trial data, within the base case model, 60% of the cohort had AF whilst 40% had an AHV. The average age of the patient cohort was 65 years.

The model, built and analysed to inform the development of NICE diagnostics guidance (DG14)12, simulated the occurrence of adverse events (thromboembolic events and bleeding events) over a 10-year period. Patients transitioned between the discrete health states and accumulated costs and quality-adjusted life years (QALYs), on a quarterly cycle. Baseline risks for the modelled events were derived from cohorts of patients being managed under current standard models of care. Relative risks of events between the treatment arms were derived from the same authors’ meta-analysis of RCTs7 of self-monitoring versus usual care – see Table 2. Appropriate quality of life values were attached to modelled events and health states.
Table 2 Relative effects for self-monitoring versus usual care

<table>
<thead>
<tr>
<th>Event/monitoring strategy</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any thromboembolic event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-management</td>
<td>0.51</td>
<td>0.37 to 0.69</td>
</tr>
<tr>
<td>Self-testing</td>
<td>0.99</td>
<td>0.75 to 1.31</td>
</tr>
<tr>
<td>Self-monitoring (overall)</td>
<td>0.58</td>
<td>0.40 to 0.84</td>
</tr>
<tr>
<td>Major bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-management</td>
<td>1.09</td>
<td>0.81 to 1.46</td>
</tr>
<tr>
<td>Self-testing</td>
<td>0.99</td>
<td>0.80 to 1.23</td>
</tr>
<tr>
<td>Self-monitoring (overall)</td>
<td>1.02</td>
<td>0.86 to 1.22</td>
</tr>
<tr>
<td>Minor bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-management</td>
<td>0.84</td>
<td>0.53 to 1.35</td>
</tr>
<tr>
<td>Self-testing</td>
<td>1.23</td>
<td>1.06 to 1.42</td>
</tr>
<tr>
<td>Self-monitoring (overall)</td>
<td>0.94</td>
<td>0.65 to 1.34</td>
</tr>
</tbody>
</table>

Data on resource use and costs associated with the different monitoring strategies were drawn from the published literature, existing guidance, suppliers’ prices, expert opinion, and other routine sources of data. Device costs were annuitised over their expected 5-year use. The accuracy of the cost of testing strips was confirmed with ISD (J Smith, Information Analyst, ISD Scotland. Personal Communication, 10 August 2015).

In terms of resource use, for the usual care arm, it was assumed that 12 monitoring visits per year were required, each requiring 15 minutes of nurse time. For the self-monitoring strategies, the average testing frequency was assumed to be 35 per year based on the trials from which the relative effect estimates were gathered. All self-monitoring patients were assumed to require two routine clinic assessments per year. Self-testing patients were assumed to undertake a 5-minute telephone call with a nurse following each of their 35 tests.

In terms of the key results from the modelling, over the 10-year time horizon, the introduction of self-monitoring would reduce the proportion of people experiencing a first thromboembolic event by 2.5%, from 14.2% to 11.7%, while it would increase the proportion experiencing a first major bleed by 1.4%, from 30.2% to 31.6%. Owing to the additional number of tests, and the higher cost of the testing equipment and consumables, the predicted monitoring costs are higher with self-monitoring. However, these costs are expected to be offset by a reduction in other healthcare costs, including those associated with a reduction in resource use and adverse events.

Following on from this, the mean and incremental costs and effects are presented within Table 3, with the results presented for each of the available testing kits. Compared with usual care, self-monitoring with the INRatio2® kit was the dominant strategy, in that it was associated with a £29 lower cost and a 0.027 QALY gain. Self-monitoring using the CoaguChek® kit, compared with usual care, resulted in a £8 cost increase and a 0.027 QALY gain, leading to an incremental cost-effectiveness ratio (ICER) of £319. As such, self-monitoring using either the INRatio2® or the CoaguChek® kit was concluded to be cost-effective. Probabilistic analysis on the base case found that self-monitoring with INRatio2® or CoaguChek® had an 80% chance of being cost-effective, compared with usual care, at a willingness-to-pay threshold of £20,000 per QALY. The use of the ProTime® kit was not found to be cost-effective. NICE recently confirmed that ProTime® equipment was no longer available to the NHS.
Table 3 Mean and incremental costs and effects

<table>
<thead>
<tr>
<th>Strategy (and testing kit)</th>
<th>Mean cost</th>
<th>Incremental cost</th>
<th>Mean QALYs</th>
<th>Incremental QALYs</th>
<th>ICER</th>
<th>ICER versus usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-monitoring: INRatio2®</td>
<td>£7,295</td>
<td>-</td>
<td>5.507</td>
<td>-</td>
<td>-</td>
<td>Dominant</td>
</tr>
<tr>
<td>Usual care</td>
<td>£7,324</td>
<td>£29</td>
<td>5.479</td>
<td>-0.027a</td>
<td>Dominated</td>
<td>-</td>
</tr>
<tr>
<td>Self-monitoring: CoaguChek®</td>
<td>£7,333</td>
<td>£37</td>
<td>5.507</td>
<td>0</td>
<td>Dominated</td>
<td>£319</td>
</tr>
<tr>
<td>Self-monitoring: ProTime®</td>
<td>£8,609</td>
<td>£1,314</td>
<td>5.507</td>
<td>0</td>
<td>Dominated</td>
<td>£47,604</td>
</tr>
</tbody>
</table>

a not –0.028 owing to rounding

A number of sensitivity analyses were carried out. The most pertinent of these was the modelling of both self-testing and self-management separately. Self-management, regardless of the kit used, was found to dominate usual care (approximately £1,000 lower cost, 0.054 higher QALY). On the other hand, self-testing compared to usual care resulted in ICERs >£2,000,000. This finding stemmed from the aforementioned meta-analysis where no clinical benefit was shown for self-testing, and also the fact that self-testing saves fewer healthcare resources than self-management (that is does not offset the increase in testing equipment and consumables costs). Further sensitivity analysis of note was that under the assumption that 100% of warfarin monitoring appointments are managed in primary care, the base case ICERs increased to £2,749 and £4,108 for the INRatio2® and CoaguChek® kit respectively.

There are a number of uncertainties surrounding the results of the economic evaluation. Not only did the finding of no difference in thromboembolic events lead to the result that self-testing was not a cost-effective strategy, uncertainty surrounding the link between self-management and a reduction in thromboembolic events should also be noted. For example, the clinical-effectiveness section describes how it is likely that many of the studies included in the meta-analysis represented low quality evidence. Also, the applicability of non-UK usual care as a comparator may be limited, especially bearing in mind that the three UK studies found no statistically significant difference in the rate of thromboembolic events between self-management and usual care.

The sensitivity analysis found that, compared with usual care, self-management alone led to a reduction in costs of approximately £1,000. Further analysis demonstrated that when no difference in clinical outcomes was assumed, and even when including the unlikely assumption that self-management led to no extra tests, self-management would result in an overall cost increase compared to usual care. This finding indicates that the overall results of the economic evaluation are driven by the impact on thromboembolic events, not just in terms of quality of life, but also within the adverse events cost calculations.

The two self-monitoring devices of interest are the CoaguChek® system and the INRatio2® system. Of the 26 trials included within the meta-analysis, upon which the economic evaluation is based, 22 tested the use of the CoaguChek® system. There was, however, no direct randomised trial evidence demonstrating the clinical effectiveness of the INRatio2® system. With this in mind, the HTA included a reference to a systematic review by Christensen and Larsen in 2012, where it was concluded that the coagulometers – including the CoaguChek® and INRatio2® devices – were suitably similar in terms of precision and accuracy.

The economic evaluation assumed that there would be zero wastage of test strips, with only two additional test strips used per year to cross check and quality assure the devices. Furthermore, it was assumed that each device would last for 5 years, and that 75% of devices were reused by another patient following any discontinuation of self-monitoring by the initial patient. It is worth noting that any slippage from this efficient use of resources would reduce the cost effectiveness of self-monitoring.

Overall, the results of the economic evaluation show that self-monitoring is cost-effective compared to usual care. Within the group of patients said to be self-monitoring, although
self-management was found to be cost-effective, self-testing was not found to be cost-effective. There are also a number of uncertainties to consider when interpreting the results of the analysis, particularly the potential weaknesses in the clinical data used to inform the model parameters.

In 2014, a UK economic evaluation assessed the cost effectiveness of point of care self-monitoring for warfarin patients compared to clinic setting testing. The economic evaluation was undertaken using a Markov model to compare PST and PSM – using point of care devices – to usual NHS care. The analysis was carried out from an NHS perspective over a 10-year time horizon. The analysis assumed that 66% of patients in the usual care arm were treated in primary care, while the remaining 34% were treated in secondary care. It is not clear what the proportion of patients self-testing and self-managing were, and the results were not broken down by these subgroups.

A hypothetical cohort of 10,000 patients was modelled, where each month patients moved within the model’s seven health states, which ranged from healthy to death whilst incorporating the various adverse events associated with the indications under review. The clinical event rates used to populate the model were drawn from a recent systematic review which included data from 11 trials. Of the patients within these trials, 53% had AF, 35% had an AHV (hereafter ‘mechanical’ HV [MHV]), and 12% had other disorders. The trials assessed either self-management or self-testing, and the usual care arms within the trials were a mixture of monitoring in primary care, anticoagulation clinics, or a combination of both settings.

The model’s base case analysis compared the PST/PSM group to usual care – which meant comparing outcomes for all patients who may use the self-monitoring or self-testing equipment whether they were AF or MHV patients. Analyses were also carried out for AF and MHV subgroups. It is worth noting that for the AF subgroup, owing to the fact that the aforementioned systematic review reported no statistically significant differences in the results for usual care versus PST/PMT, a cost-minimisation approach was taken for the economic evaluation. The comparative 2-year clinical events for the total population, and the MHV and AF subgroups are presented in Table 4.

Table 4 Two-year clinical events for total population, MHV, and AF by self-monitoring/self-testing versus usual care

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>MHV patients only</th>
<th>AF patients only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PST/PSM</td>
<td>Usual care</td>
<td>PST/PSM</td>
</tr>
<tr>
<td>Major stroke</td>
<td>0.44%</td>
<td>0.84%</td>
<td>0.52%</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>0.67%</td>
<td>1.28%</td>
<td>0.79%</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>0.51%</td>
<td>0.99%</td>
<td>0.61%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.92%</td>
<td>1.76%</td>
<td>1.08%</td>
</tr>
<tr>
<td>Major bleed</td>
<td>1.48%</td>
<td>1.90%</td>
<td>1.57%</td>
</tr>
<tr>
<td>Minor bleed</td>
<td>4.76%</td>
<td>6.10%</td>
<td>5.05%</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.16%</td>
<td>0.31%</td>
<td>0.18%</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>7.44%</td>
<td>9.30%</td>
<td>3.87%</td>
</tr>
</tbody>
</table>
Cost data for warfarin monitoring were drawn from relevant NICE costing templates, with relative resource utilisation informed by the clinical studies. It was assumed that the NHS pays transport costs for 5% of those attending outpatient appointments. For patients who were self-testing or self-monitoring, they were assumed to receive an initial 2, and 4-hour education and training session respectively, from a GP or practice nurse. Patients also received two 15-minute reviews per year, and for those self-testing 10 minutes of telephone calls per month with a GP or practice nurse to review INRs. Device and consumable costs were appropriate and based upon the CoaguChek® device. The device cost was assumed to be paid for by the NHS in the first year and the lifespan of the device was the same as the model’s 10-year time horizon.

Utility values attached to each health state were adopted from a manufacturer’s previous submission to NICE which had been accepted as appropriate. The values were consistent with the values included within the 2015 economic evaluation.

The base case results are presented in Table 5. For the cohort of 10,000 patients, over 10 years, savings of £11.9 million were reported for adopting self-monitoring compared with usual care. This equated to a saving of £1,187 per person. Patients in the self-monitoring arm also had better outcomes, notably 612 fewer deaths and 89 fewer major strokes compared with usual care, and this contributed to the QALY gain in the self-monitoring arm of 0.276 per person. Self-monitoring was said to dominate usual care, as it was cheaper and more effective.

A number of sensitivity analyses were carried out. For all probabilistic sensitivity analysis runs (that is applying distributions to key parameters), self-monitoring was cheaper and more effective than usual care. In terms of deterministic analyses (for example one-way sensitivity analysis), if the device only lasted one year then the incremental cost of self-monitoring was £314 per person. Financial break-even was achieved at just over 2 years. On the other hand, if patients bought their own device, savings of £71 per patient were achieved within the first year. Finally, the cost of usual care was varied between £115 and £414 (base case=£301), and overall savings continued to be demonstrated ranging from £415 and £2,025 respectively.

Scenario analyses for the MHV and AF patients are presented in Table 6 (see page 10).

There are a number of uncertainties associated with the analysis. The first of these relates to the clinical event rates presented in Table 4. For the total population, the clinical data found that there was a difference in stroke events between the two treatment arms. However, the clinical data found no difference for bleed and death end points and, as such, the figures presented in Table 4 appear optimistic in favour of the PST/PSM. This concern also applies to the MHV-only analysis.

The model structure includes a MI health state, although it is not clear where the comparative event rates for MI are drawn from. The 2015 economic evaluation – considered appropriate by NICE – does not include this health state. The inclusion of the MI health state and the assumed benefit that PST/PSM offers may have a large impact upon the model in terms of both costs and effects.

Table 5 Base case results

<table>
<thead>
<tr>
<th></th>
<th>PST/PSM</th>
<th>Usual care</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost</td>
<td>£19,128,390</td>
<td>£30,998,975</td>
<td>-£11,870,585</td>
</tr>
<tr>
<td>Total cost per patient</td>
<td>£1,913</td>
<td>£3,100</td>
<td>-£1,187</td>
</tr>
<tr>
<td>Total QALYs per patient</td>
<td>4.470</td>
<td>4.194</td>
<td>0.276</td>
</tr>
<tr>
<td>Including cost per QALY</td>
<td></td>
<td></td>
<td>Dominant</td>
</tr>
<tr>
<td>Major stroke events</td>
<td>139</td>
<td>228</td>
<td>-89</td>
</tr>
<tr>
<td>MI events</td>
<td>292</td>
<td>480</td>
<td>-188</td>
</tr>
<tr>
<td>Major bleed events</td>
<td>579</td>
<td>672</td>
<td>-93</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>51</td>
<td>84</td>
<td>-33</td>
</tr>
<tr>
<td>Died</td>
<td>3,169</td>
<td>3,781</td>
<td>-612</td>
</tr>
</tbody>
</table>
It is reported that the economic evaluation is based upon 66% of patients in the usual care arm being treated in primary care as opposed to secondary care. However, Table 4 within the economic evaluation suggests that only 20% of patients are assigned the primary care usual care cost. This may impact upon the results since the cost of a primary care appointment is lower than secondary care, and therefore the overall costs of usual care are artificially high – which results in bias in favour of the PST/PSM arm.

It is worth noting some cost inconsistencies between this 2014 economic evaluation and the 2015 assessment. In this 2014 model, the costs of both primary and secondary care within the usual care arm are higher than the equivalent costs used in the 2015 economic evaluation. The cost of major stroke is assumed to be £15,594, compared with £10,061 in the 2015 model. Further – notwithstanding the device costs – the annual costs of self-monitoring are lower in this model (£162 for self-testing and £96 for self-managing) compared to the 2015 economic evaluation (approximately £240 and £140 respectively). Each of these assumptions favours the PST/PSM arm, and contributes the relatively improved cost effectiveness conclusions here relative to the 2015 economic evaluation.

More general uncertainties are as follows.

- The economic evaluation was based upon a systematic review that incorporated only one study based in the UK. In this study, there were only 97 patients with an MHV.

- The trials used to inform the model had relatively short time duration – with the longest trial being of 2 years duration. This inevitably leads to uncertainty when extrapolating the trial results over the 10-year time horizon of the model.

- The author notes that the outcomes modelled are dependent on the motivation and competency of the patients who carry out self-testing or self-monitoring. Therefore it is important to ensure high quality and appropriate training.

As a final point, it is worth reiterating that this economic evaluation did not break down the results by self-management and self-testing. Looking at the data from the systematic review used to populate the economic model, for self-testing compared to usual care, no difference was found between the key end points: stroke, bleed and death. For self-management, a significant difference was found for the stroke end point. These results are consistent with the findings used
to populate the 2015 economic model discussed previously; that although self-management may be cost-effective, self-testing is less likely to be.

In summary, the results of the 2014 economic evaluation show self-monitoring to be both less costly and more effective than usual care. However, there are a number of uncertainties within the analysis that undermine the findings – particularly in relation to the optimistic assumptions surrounding improved bleed, MI and death outcomes for PST/PSM patients compared to usual care.

**Conclusion**

Meta-analysis of mainly low quality RCTs are consistent in finding that self-management of INR in patients using long-term oral anticoagulation therapy with vitamin K antagonists leads to fewer thromboembolic events without increasing the incidence of major bleeding events when compared with usual care. It is proposed that this benefit is mediated by improved control of anticoagulation, but there are insufficient data to inform this.

Two UK economic evaluations found that patient self-monitoring was cost-effective compared to usual care. The first of these economic evaluations provided subgroup analysis to show that within the self-monitoring patients, although self-management was found to be cost-effective, self-testing was not found to be cost-effective. The conclusions of both studies were based on the assumption that self-monitoring leads to fewer thromboembolic events. Furthermore, particularly associated with the second of the economic evaluations, there are a number of other uncertainties that undermine the cost effectiveness results.

For motivated and competent patients, self-management of INR has the potential to be an effective, safe and cost-effective option where this can be appropriately supported.

**Equality and diversity**

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.
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References


References continued
