The clinical effectiveness 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

Pawana Sharma,[1*] Graham Scotland,[1,2] Moira Cruickshank,[1] Emma Tassie,[2] Cynthia Fraser,[1] Chris Burton,[3] Bernard Croal,[4] Craig R Ramsay[1] and Miriam Brazzelli[1]

[1]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[2]Health Economics Research Unit, University of Aberdeen, Aberdeen, UK
[3]Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK
[4]Department of Clinical Biochemistry, University of Aberdeen, Aberdeen, UK

*Corresponding author

Declared competing interests of authors: none

Published June 2015
DOI: 10.3310/hta19480

Scientific summary

The effectiveness of point-of-care tests for vitamin K antagonist therapy

Health Technology Assessment 2015; Vol. 19: No. 48
DOI: 10.3310/hta19480

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

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. Underanticoagulation increases the risk of thromboembolism, while overanticoagulation 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 normalised 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). Another 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 health-care 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 clinical effectiveness compared with other ways of delivering services.

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 the XS models) (Roche Diagnostics, Basel, Switzerland), INRatio2® PT/INR monitor (Alere Inc., San Diego CA, USA) and ProTime Microcoagulation system® (International Technidyne Corporation, Nexus Dx, Edison, NJ, USA) coagulometers are being considered in this assessment as an alternative to standard UK anticoagulation therapy services.

Methods

Clinical effectiveness

Comprehensive electronic searches were undertaken to identify relevant reports of published studies up to May 2013. We searched major electronic databases (e.g. MEDLINE, MEDLINE In Process & Other Non-Indexed Citations, EMBASE, Bioscience Information Service, Science Citation Index and Cochrane Central Register of Controlled Trials) from 2007 to May 2013. Reports published before 2007 were identified from the existing Cochrane review (major databases searched from inception to 2007). 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 the XS models), INRatio2 PT/INR monitor or ProTime Microcoagulation system was considered in this assessment. The comparator considered was standard clinical practice, which consisted of INR monitoring managed by health-care 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 prespecified 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 of the comparisons set out in the scope for this assessment.

A de novo economic model was developed in TreeAge Pro (TreeAge Software 2013, Inc Williamstown, MA, USA) 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 10-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 (AHVs). 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 RCTs. Other parameters including cost and utility inputs were derived from focused literature searches, previous economic models and routine data sources.

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 16–2922 participants). 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 another 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.

Major clinical events

The results of this assessment indicate that self-monitoring (self-testing or self-management) of anticoagulation therapy leads to significantly fewer thromboembolic events [relative risk (RR) 0.58, 95% confidence interval (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 AHVs, 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 general practitioner or physicians but not compared with those managed in specialised anticoagulation clinics. The subgroup analysis was not, however, statistically significant.

Intermediate outcomes

While no significant differences were found between self-management and standard care for time in therapeutic range (TTR) [weighted mean difference (WMD) 0.47, 95% CI –1.40 to 2.34; $p = 0.62$], self-testing showed a modest but significantly higher percentage of TTR than 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.

Patient-reported outcomes

Improvements in quality of life in the self-monitoring group were observed in six of the nine trials that reported quality-of-life outcomes. Two UK-based trials reporting quality-of-life data did not show significant difference between self-monitoring and standard care. Four trials that assessed the patient's acceptability for point-of-care devices reported high rates of preference for both self-testing and self-management (77% to 98%).

Cost-effectiveness

Self-monitoring (50% self-testing, 50% self-management) was found to increase the INR monitoring costs, compared with standard primary/secondary care monitoring. The incremental monitoring costs (incorporating training costs and annuitised device cost) associated with self-monitoring over the 10-year period were £639, £675, and £1923 with INRatio2, CoaguChek XS and ProTime Microcoagulation System, respectively. However, applying the pooled RRs of adverse events to people completing training and continuing with self-monitoring, it was estimated that the cumulative incidence of thromboembolic events at 10 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 total health and social care costs was less pronounced after 10 years: £7295 (self-monitoring with INRatio2); £7324 (standard primary/secondary care monitoring); £7333 (self-monitoring with CoaguChek XS); and £8609 (self-monitoring with ProTime).

The estimated quality-adjusted life-year (QALY) gain associated with self-monitoring at 10 years was 0.03. Assuming that the benefits of self-monitoring were applied equally to all point-of-care devices, self-monitoring with INRatio2 dominated standard monitoring under the base-case assumptions. The incremental cost-effectiveness 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), while self-management was found to be less costly and more clinically 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 RRs 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 base-case assumptions, self-monitoring with CoaguChek XS or INRatio2 had $\approx 80\%$ 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 preintervention training and education programme, length of follow-up and methodological study quality. While the meta-analysis results demonstrated low statistical heterogeneity, there remains uncertainty around the fact that clinical heterogeneity could 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 has 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 or not 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 clinically effective for anticoagulation control, especially for people with AHVs. 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 versus usual care are needed. Future trials should include direct comparisons of the various point-of-care coagulometers. The technology related to point-of-care testing devices is constantly changing and future research needs to target larger cohorts of people with different clinical indications requiring long-term anticoagulation therapy who may benefit from the use of these new generations of devices.

Study registration

This study is registered as PROSPERO CRD42013004944.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 13/06/01. The protocol was agreed in June 2013. The assessment report began editorial review in December 2013 and was accepted for publication in March 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).