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Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

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CADTH is funded by Canadian federal, provincial, and territorial governments.

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National Library of Canada
ISSN: 1203-9012 (print)
ISSN: 1481-4501 (online)
H0446 – February 2007

PUBLICATIONS MAIL AGREEMENT NO. 40026386
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Devices for Point-of-Care Monitoring of Long-Term Oral Anticoagulation Therapy: Clinical and Cost Effectiveness

February 2007

We thank Janice Mann for her assistance in creating this overview from a longer report authored by Allan Brown et al.


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Devices for Point-of-Care Monitoring of Long-Term Oral Anticoagulation Therapy: Clinical and Cost Effectiveness

Technology
Point-of-care (POC) devices that measure the international normalized ratio (INR) for monitoring oral anticoagulation therapy (OAT).

Condition
Patients who are at an elevated risk of experiencing thromboembolic events or complications from blood clots, and require long-term (more than three months) OAT.

Issue
The availability of portable POC devices makes it possible for patients on long-term OAT to be monitored without having to visit a hospital or laboratory. This is especially relevant for rural or remote patients not living near a laboratory, or for patients wishing to travel for extended periods. The utility of these devices in the monitoring of OAT is uncertain. To make informed decisions regarding funding, those who administer anticoagulation programs need to know how POC devices used by patients and anticoagulation clinics compare with standard laboratory testing in clinical and cost effectiveness.

Methods and Results
A systematic review of the clinical and economic literature was performed. For the clinical review, multiple databases were searched. Two reviewers independently assessed quality, after extracting data from the 16 eligible articles. A meta-analysis was conducted. In conducting an economic analysis, seven articles describing six unique studies were reviewed, and a primary economic evaluation was performed.

Implications for Decision Making
- **POC devices can improve health.** Using POC devices to manage OAT results in significantly fewer deaths and thromboembolic events, and better INR control than conventional laboratory testing, with no significant difference in hemorrhagic events.
- **POC devices can reduce costs.** Compared to laboratory testing, using POC devices in anticoagulation clinics is cost-saving compared with conventional testing for health care payers. It is also cost effective if society is willing to pay $50,000 for a quality-adjusted life-year (QALY). Self-testing by patients compared to laboratory testing does not seem to be cost effective from a publicly funded health care perspective.
- **Additional resources are required.** Up to 24% of OAT patients in Canada could be eligible for self-testing or self-management with POC devices. The capital outlay for these patients would be $50 million and the annual costs for consumables would be $18 million.

1 Introduction

Oral anticoagulation therapy (OAT) is widely used for the prevention and treatment of thromboembolism, which is commonly known as a blood clot. Treatment can be short or long term, with long-term therapy (more than three months) being required for those at a higher than average risk for complications from blood clots, usually as a result of a chronic health condition. These include people with mechanical heart valves, chronic atrial fibrillation, venous thromboembolism, acute myocardial infarction, stroke, and peripheral arterial occlusion. \(^1\,^2\) Once OAT is started, many continue the treatment for the remainder of their lives. While long-term OAT is already common in Canada, its use is expected to increase, given the aging population who are more likely to experience atrial fibrillation or venous thromboembolism – two of the most common conditions requiring OAT.

In North America, warfarin is the most common choice for long-term OAT. Warfarin, which suppresses the body’s ability to use vitamin K in the clotting process, is known as a vitamin K antagonist. The process for forming clots in the body depends on the presence of vitamin K. Warfarin is available in Canada under the brand names Apo\textsuperscript{®}-Warfarin, Coumadin\textsuperscript{®}, Gen-Warfarin, Novo-Warfarin, and Taro-Warfarin.

Available evidence supports long-term treatment with vitamin K antagonists such as warfarin to reduce the risk of death (mortality) or illness and disability (morbidity) for those at higher risk for blood clots. The appropriate dose must be individualized because all patients react differently to warfarin, and the same patient may react differently over time. If the dose is too low, a patient may be inadequately protected against developing a blood clot. If the dose is too high, the risk of bleeding or hemorrhaging is increased. This creates a need for monitoring the degree of anticoagulation in patients on long-term OAT.

Until recently, monitoring required a visit to a hospital laboratory or outpatient facility. Blood would be drawn from a vein (venipuncture) into a tube and tested in the laboratory to determine the international normalized ratio or INR. The INR is a unit that is used to indicate the OAT intensity. Continued monitoring in this manner presents a challenge for patients, especially for those living in remote locales (who must travel long distances to present for testing) or those wishing to travel for extended periods (making it impossible to present to their hospital laboratory). As with most laboratory tests, there is a delay between the blood sample being taken and the results being available to the physician who is monitoring and prescribing the oral anticoagulation therapy.

Over the last decade, point-of-care (POC) technology has become available for the monitoring of OAT. These portable devices provide the same type of test result (the INR) as does laboratory testing, without a visit to a laboratory and without the need for venipuncture. Instead, a drop of blood from a fingertip is used for testing (similar to the manner in which people with diabetes measure blood sugar levels). Results are available in as little as one minute, allowing any necessary changes in dose to be made immediately after testing.

Several scenarios with POC devices are possible, including use in a clinic, patient’s home, or other patient care setting. If patients self-monitor, they can inform their health care provider of the result, and the health care provider adjusts the anticoagulant dose, if necessary. Alternatively, patients could also self-manage by testing and then adjusting the dose of their anticoagulant themselves.
POC monitoring devices were introduced in April 1999, with Health Canada first licensing the CoaguChek® POC monitor. Since then, health care professionals, health care centres, and patients have used them on a limited basis. In some countries such as Germany, self-testing and self-management with POC devices have become accepted practice.

CoaguChek is indicated in Canada for use by health professionals or for self-testing by patients. The retail price of a CoaguChek S monitor (Roche Diagnostics) is $995.00. Also required are test strips (48 tests at $325.00 retail), lancets (50 for $7.49 retail), and quality control solution (4 × 2 mL, $29.00 retail).

When our analysis was done, ProTime® was only available in Canada for use by health professionals. The retail price of a ProTime Machine (International Technidyne Corporation) is $1,895.00 (pricing subject to change) (Katrin Jung, Sorin Group, Toronto: personal communication, 2006 Aug 18). Also required are ProTime reagent cuvettes and Tenderlett collectors (25 per box: $512.50) (pricing subject to change) (Katrin Jung, Sorin Group, Toronto: personal communication, 2006 Aug 18).

Given the availability of the POC devices for OAT and their potential advantages, it is important for those who administer and fund anticoagulation programs in Canada to know how these devices compare, in clinical and cost effectiveness, with standard laboratory testing.

2 Objective

The objective of this report is to assess the clinical and economic implications of POC monitoring devices for long-term oral anticoagulation therapy. This is done by addressing the following research questions:

- What is the clinical evidence of the effectiveness of POC monitoring devices compared with the standard laboratory test in long-term OAT?
- What is the cost effectiveness of self-testing by patients with POC devices and POC testing in anticoagulation clinics compared with the standard laboratory test for long-term OAT?

3 Clinical and Economic Review Methods

Methods

A protocol was written a priori and followed throughout the review process. The criteria were subsequently revised to include studies of patients who had been receiving OAT for less than three months at the start of the study. This was due to the difficulty in determining the duration of therapy at baseline in many studies. We obtained published literature by searching PubMed, the Cochrane Library, DIALOG®’s MEDLINE®, EMBASE®, BIOSIS Previews®, and PASCAL databases. Parallel searches were run on PubMed and the Cochrane Library. A broad search strategy with appropriate descriptors and keywords was used. Results were restricted to controlled trials, meta-analyses, and systematic reviews. There were no year or language restrictions. We obtained grey literature by searching the web sites of regulatory agencies, health technology assessment agencies, and near-technology assessment agencies. Specialized databases, such as the University of York NHS Centre for Reviews and Dissemination and the Latin American and Caribbean Center on Health Sciences Information (LILACS), were also searched. Web sites of relevant professional associations and their conference sites were searched for additional information.
Selection Criteria
For the clinical review of POC monitoring devices for OAT, randomized control trials (RCTs) were eligible from a research or clinical setting if they included patients on long-term (at least three months) OAT and compared anticoagulation monitoring using a POC device with usual care (laboratory testing). For studies to be included, they must have reported on rates of major hemorrhage, rates of major thromboembolic events, or percentage of time the patient’s blood was in the normal therapeutic INR range. At least two reviewers independently reviewed each citation from the literature search, using the abstract and consensus discussion. This was followed by an independent review of full-text articles by each reviewer, with a second consensus discussion for the final agreement on eligibility.

Quality Assessment
We assessed study quality using the criteria proposed by Jadad et al., and evaluated the adequacy of allocation concealment as appropriate or inappropriate according to the criteria proposed by Schulz and Grimes.3,4 If the information in the reports was insufficient, these issues were recorded as unclear or unstated. We successfully contacted authors when data were incomplete or missing.

Data Analysis
For assessing the outcomes of major hemorrhage, major thromboembolic events, and all thromboembolic events, we conducted a meta-analysis by calculating odds ratios (ORs) and their 95% confidence intervals (CI) for the event rates, comparing results between POC testing and laboratory testing. A comparison of death rates was also performed, and ORs were calculated. An OR will approximate the relative risk when the event is “rare” (some take this as <10%).5 For all comparisons, we used a random-effects model according to the method described by DerSimonian and Laird.6 Differences between effects were tested using a Z test, and p-values <0.05 were considered to be significant.

Patient days below, in, or above the therapeutic range that was defined in the studies were aggregated to give a percentage of time in range and a percentage of time outside range. We did a paired t-test of mean percentage time in range for the control and intervention groups.

4 Results
A total of 439 citations were identified on the initial search, with an additional 13 citations from routine updates, for a total of 452. Of these, 409 did not meet the selection criteria, leaving 43. Two studies were added after the revision of the study criteria, for a total of 45 potentially relevant articles to be retrieved. Of these, 29 were subsequently excluded, resulting in 16 relevant articles describing 15 unique RCTs.7-22

There was variation among the studies regarding observation periods, mean age of patients, and indication for anticoagulation. We found that 11 studies compared self-monitoring or self-management to routine anticoagulation control. In eight studies, only patients who had been on OAT for at least three months were enrolled, and in seven studies, patients were enrolled from the time of OAT initiation.
The Jadad quality score of the 15 studies varied from one to three, with nine attaining a score of three out of a maximum of five, and two studies receiving a score of one. There was a total of 2,144.6 patient-years of observation for the intervention group and 2,316.1 patient-years of observation for controls across all included studies.

Analyses were performed for five groups. This included all studies and those studies comparing only self-testing or self-management to routine care. In these studies, there were significantly fewer major thromboembolic events, fewer all thromboembolic events, and fewer all deaths in the POC testing group than in the routine care group. For all studies and for the self-testing or self-management studies, the mean percentage of time in the therapeutic INR range was greater than in the routine care group (p=0.004 and p=0.016 respectively). There was not a statistically significant difference in the risk of major hemorrhage between the POC testing group and the routine care groups. The results remained similar when only studies of higher quality were examined.

| Table 1: Odds ratio for all studies* and self-test or self-managed studies** |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Major Hemorrhage| Major Thromboembolic Events | All Thromboembolic Events | All Deaths | % Time in Range |
| All Studies                     | 0.75 (95% CI 0.51 to 1.10) | 0.48 (95% CI 0.33 to 0.72) | 0.45 (95% CI 0.29 to 0.70) | 0.54 (95% CI 0.35 to 0.83) | 69% versus 61%† |
| Studies with Quality Scores of 3 or more | 0.78 (0.48 to 1.28) | 0.53 (0.31 to 0.91) | 0.65 (0.29 to 1.48) | 0.36 (0.14 to 0.93) | 71% versus 64% |
| Self-test, Self-managed         | 0.76 (95% CI 0.47 to 1.24) | 0.43 (95% CI 0.25 to 0.74) | 0.35 (95% CI 0.16 to 0.73) | 0.38 (95% CI 0.19 to 0.74) | 71% versus 63%‡ |

†p=0.004; ‡p=0.016.

Of the 11 studies in which patients were using the POC devices for self-management, three did not report data on patient eligibility, agreement to consent, and withdrawal from studies. Most of the remaining studies reported close to 40% (16% to 40%) of patients being unsuitable to use the POC device. Six of the 11 studies provided information on participants who withdrew after attempting the point-of-care training session, revealing a drop-out rate of 18% to 28%. Six studies reported that 12% to 19% abandoned using the POC device compared with 0% to 6% withdrawing from routine care groups.

5 Economic Analysis

Review of Economic Literature

Methods

We obtained published literature by cross-searching MEDLINE® (1966 to current), BIOSIS Previews® (1969 to current), PASCAL, and EMBASE® (1974 to current) databases, with no year or language restrictions. A broad search strategy with appropriate descriptors and keywords was used,
in combination with an economic filter to restrict results to relevant economic records. We also ran a parallel search on HEED Health Economic Evaluations Database.

**Selection Criteria**

An economic study was included for review if it satisfied all the following criteria:

- study design: full economic evaluation (cost effectiveness study providing a summary measure of the trade-off between costs and consequences) or partial economic evaluation, such as a cost comparison
- population: adult patients undergoing long-term OAT
- intervention: anticoagulant monitoring with a POC device
- comparator: routine INR laboratory test
- primary outcome: outcome reported as an incremental measure of the implication of moving from the comparator to the intervention (could be expressed as a summary measure such as the incremental cost effectiveness ratio, a cost difference, or a difference in costs and consequences).

One reviewer applied the selection criteria first to the titles and abstract, and then to the full-text articles. A data extraction sheet was used by one reviewer to extract the content of each included study and subsequently checked by a second reviewer.

**Quality Assessment**

A checklist developed for the *British Medical Journal* was used by two reviewers to assess the quality of the included full economic studies; the quality of cost comparison studies was also assessed.

**Results**

From 139 identified articles, seven articles describing six unique studies were eligible for review after applying the selection criteria. Of the six studies, two described full economic evaluations, and four were cost comparisons, with five analyzing the CoaguChek monitor and one the ProTime monitor. The two full economic evaluation studies were judged to be of relatively high quality. The results were generally favourable to POC monitors.

**Primary Economic Evaluation**

**Method**

A cost utility analysis was conducted using a decision analytic approach. We developed the decision tree as a Markov model in Microsoft Excel. Our population consisted of patients on long-term (at least three months) OAT. The three decision options were usual care, anticoagulation clinic testing with a POC device, and self-testing by the patient with a POC device. The model was presented from the perspective of a health care provider and from a societal perspective. The time horizon of the model was five years.

In the decision analytic model, hypothetical cohorts were followed for five years after starting OAT (warfarin). For each monitoring alternative, the time that patients spent in or outside the therapeutic ranges was estimated using results from the meta-analysis with the associated risks of first and recurrent clotting or bleeding, and subsequent risks of temporary or permanent disability. With each year-cycle of the model, patients moved among five possible health states ranging from no clotting or bleeding to death.
Transitions among the states were defined using event probabilities drawn from the meta-analysis and published literature. Key elements of the model include estimates of the time spent in or outside the therapeutic range for each monitoring alternative, the risk of adverse events during these times, and the risk of disability after an adverse event.

The quality-adjusted life-years (QALYs) expected with each decision alternative were estimated using data from several studies.25,26,32-36

**Results**

For CoaguChek, our analysis suggests that from a health provider perspective, moving from usual care to POC devices in an anticoagulation clinic is cost saving (Table 2). For self-testing, the results were not cost effective from a health provider’s perspective at a willingness to pay threshold of $50,000; they were cost saving from a societal perspective.

For ProTime, from a health provider perspective, moving from usual care to POC devices in anticoagulation clinics appears to be favourable. We did not calculate a comparison of usual care with self-testing, because ProTime was unavailable for self-testing by patients in Canada when our analysis was done.
Table 2: Annual anticoagulation monitoring costs per patient and five-year cost effectiveness ratios for CoaguChek and ProTime

<table>
<thead>
<tr>
<th>Monitoring Strategy</th>
<th>Annual Costs</th>
<th>Comparison with Usual Care (Cost per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Health Care System</td>
<td>Patients and Caregivers</td>
</tr>
<tr>
<td>Usual Care</td>
<td>$322</td>
<td>$686</td>
</tr>
<tr>
<td>Anticoagulation Clinic with CoaguChek</td>
<td>$361</td>
<td>$862</td>
</tr>
<tr>
<td>Self-testing with CoaguChek</td>
<td>$807</td>
<td>$274</td>
</tr>
<tr>
<td>Anticoagulation Clinic with ProTime</td>
<td>$392</td>
<td>$862</td>
</tr>
</tbody>
</table>

*Includes costs to patients and their caregivers; NH=nursing home facilities; QALY=quality-adjusted life-year; N/A=not applicable.

6 Limitations

For the clinical analysis, we could not determine whether thromboembolic events were evaluated in a blinded and objective manner. The INR test frequency was higher in the POC testing strategies. None of the studies was double-blinded. The eligibility criteria for the inclusion of patients in the individual clinical trials and the high withdrawal rates made it difficult to determine generalizability. Conclusions about the clinical benefits of self-testing or self-management with POC devices cannot be made without more rigorously designed randomized trials.

Limitations to the economic analysis include the following:
- the meta-analysis did not allow us to draw a distinction between the clinical outcomes of CoaguChek and those of ProTime; we assumed that the effectiveness was equivalent
- other than cost for the device and peripherals, CoaguChek and ProTime were treated equally in the model
- information on resource utilization data for portable coagulometers and the standard laboratory test specific to Canada is scarce
- we were able to analyze POC device use in two settings: anticoagulation clinics and self-testing by patients at home; other settings are also possible, for example, the family doctor’s office, pharmacies, or settings where patients are housebound and being assisted by a home-care nurse
- our analysis looked at self-testing by patients; another possible management strategy would have patients also managing their own dose adjustments.37

7 Health System Implications

An estimated 209,000 patients in publicly funded drug programs in Canada are on long-term OAT and could potentially benefit from an increased availability of POC devices. Of these, 50,160 could
be eligible to use POC devices at home for self-testing. The capital outlay for CoaguChek monitors for these patients would be approximately $50 million and the annual consumable costs would be about $18 million per year.

If the CoaguChek technology was adopted for widespread use in Canadian anticoagulation clinics, the estimated capital outlay for monitors would be approximately $84,000, and the annual consumable costs would be about $8 million per year. For the ProTime technology, the estimated capital outlay would be approximately $160,000, and the annual consumable costs would be about $9.5 million per year.

A review of clinical articles 7,8,12,13,15-18,20-22,38-41 for ethical and psychosocial issues indicated that most of the interventions in the included studies involved self-testing or self-management with monitoring devices at home. There is evidence, however, that patients prefer POC testing at an anticoagulation clinic to standard laboratory testing in a hospital.

Most of the studies looking at quality of life suggested that patients who continued with POC self-testing and self-management preferred it to the standard laboratory test. There is a need for careful selection and training of patients for self-testing or self-management. Care must be taken to select patients who have the physical and cognitive abilities required for training and for using the monitors and associated equipment. Many patients on long-term anticoagulation therapy, through self-exclusion or through a lack of cognitive or physical abilities, would be unable to participate in POC self-testing or self-management. The review suggests that about half the patients in a self-monitoring program would require the assistance of a caregiver. A need for adequate training of health care professionals in the use of POC monitoring devices was also identified.

8 Conclusions

The review of clinical evidence and the quantitative meta-analysis suggest that using POC devices to manage OAT results in significantly fewer deaths and thromboembolic events, and better INR control, than conventional laboratory testing. The impact of POC devices on hemorrhagic events is similar to that of conventional testing. The base results are not altered significantly by subgroup analysis. These conclusions are subject to limitations. We could not confirm if thromboembolic events were evaluated in a blinded and objective manner. In addition, the test frequency was higher in POC strategies than in conventional testing.

Up to 24% of OAT patients in Canada could be eligible for self-testing or self-management with POC devices. Visual acuity, cognitive ability, and manual dexterity are key factors when determining who is capable of self-testing. About half the patients involved in a self-testing program may require caregiver assistance. The ethical-psychosocial review also identified the importance of patient and health care provider education in the use of POC devices.

Our primary economic analysis found that from a publicly funded health care perspective and including nursing-home costs, using CoaguChek or ProTime in anticoagulation clinics is cost saving relative to conventional testing. From a societal perspective, POC devices are cost effective in clinics, using a willingness to pay (WTP) of $50,000 per QALY. The capital cost of a clinic program with CoaguChek would be approximately $84,000, and the annual cost for consumables (for
example, cartridges, lancets) would be about $8 million per year. For ProTime, the estimates are $160,000 for the capital cost and $9.5 million per year for consumables.

From a publicly funded health care perspective, CoaguChek does not seem to be cost effective for self-testing by patients based on a WTP of $50,000 per QALY. From a societal perspective, when time and travel costs to patients and their caregivers are considered, CoaguChek seems to be favourable. ProTime was unavailable in Canada for self-testing when our analysis was done. The capital outlay for a self-testing program with CoaguChek would be about $50 million, and the annual costs for consumables would be about $18 million.

9 References


