Canadian Agency for Drugs and Technologies in Health

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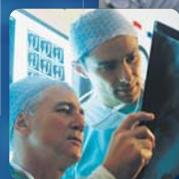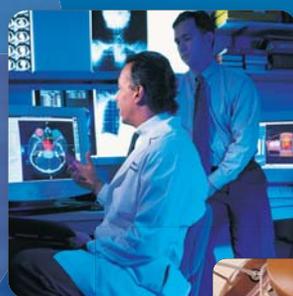
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Point-of-Care Monitoring Devices for Long-Term Oral Anticoagulation Therapy: Clinical and Cost Effectiveness

Supporting Informed Decisions

Canadian Agency for Drugs and Technologies in Health

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

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CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not of its Panel members or reviewers.

Authorship

All authors participated in the development of the protocol, and of the response to reviewers' comments.

Allan Brown is a health economist at CADTH, and was research leader for the project. He developed and coordinated responses to reviewers' comments; assembled and edited the report; wrote the executive summary, the introduction, the issue, the objectives, the economic analysis (review and primary economic evaluation), the health services impact (population impact, budget impact, planning and implementation issues, ethical and psychosocial issues), and the conclusions (except for

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Kaitryn Campbell was an information specialist at CADTH. She was responsible for designing and executing the literature search strategies, writing the methods section and associated appendix on literature searching, and verifying and formatting bibliographic references.

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Conflict of Interest

None of the report authors declared any conflicts of interest.

Point-of-Care Monitoring Devices for 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.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Brown A, Wells P, Jaffey J, McGahan L, Poon M-C, Cimon K, Campbell K. *Point-of-care monitoring devices for long-term oral anticoagulation therapy: clinical and cost effectiveness*

EXECUTIVE SUMMARY

The Issue

New technology makes it possible for patients on long-term oral anticoagulation therapy (OAT) to be monitored with portable devices, sometimes in their homes, rather than having to go to a hospital or laboratory to provide blood by venipuncture. Point-of-care (POC) devices provide the same type of test result as the traditional laboratory test, the international normalized ratio (INR), but may provide it in a more convenient setting and in a less invasive way. Patients or health care professionals take a drop of blood from the finger after a lancet puncture and then use the POC device to measure the blood's clotting tendency. Results are obtained in about one minute. For patients who do not live near a hospital or outpatient laboratory, POC devices allow them to be regularly monitored. The devices have been on the market for the last decade. Those who administer funds for anticoagulation programs need to know how POC devices compare in effectiveness and cost effectiveness with standard laboratory tests.

Objective

The objective of this report is to assess the clinical and economic implications of POC monitoring devices for long-term OAT.

Clinical Review

Methods: We obtained published literature by searching PubMed, the Cochrane Library, DIALOG®'s MEDLINE®, EMBASE®, BIOSIS Previews®, and PASCAL databases. Two reviewers independently assessed quality and extracted data. A meta-analysis was conducted.

Results: POC testing significantly reduced the risk of major thromboembolic events (OR=0.48; 95% CI 0.33 to 0.72) and the risk of death (OR=0.54; 95% CI 0.35 to 0.83), and resulted in better INR control compared with laboratory testing [69% of time INRs in range (95% CI 65% to 72%) versus 61% (95% CI 55% to 66%; p=0.004)]. For major hemorrhage, however, the odds ratio was not significantly different between the POC group and the routine care group (OR=0.75; 95% CI 0.51 to 1.10). Regarding the quality of the 16 articles included for review, no study scored the maximum of five on the Jadad scale, and only eight scored three. The generalizability of results is an issue for several reasons: comparisons to anticoagulation clinics were limited to eight studies; and in general, the duration of patient management with POCs was short, with 10 studies observing patients for a year or less.

Economic Analysis

Methods: We reviewed the economic literature and did a primary economic analysis in Microsoft Excel using a decision analytic Markov model, with a sensitivity analysis in Crystal Ball.

Results: We included seven articles describing six unique studies in the economic review. Their results were generally favourable to POC monitors. The primary economic study found that from a publicly funded health care perspective, including nursing home costs, using POC monitors in anticoagulation clinics was cost-saving compared to conventional therapy for CoaguChek® and ProTime®. Using the same perspective and comparing self-testing by patients using POCs with conventional therapy, the cost per additional QALY gained with CoaguChek® is $57,595. (ProTime

was unavailable for testing in Canada during this analysis.) When a societal perspective is adopted, and travel and time costs to patients and their caregivers are included, self-testing by patients using CoaguChek® is cost-saving.

Health Services Impact

An estimated 209,000 patients in publicly funded drug programs in Canada are on long-term anticoagulation therapy and could potentially benefit from increased availability of POC devices. Of these, 50,160 could be eligible to use a POC device at home for self-testing.

Conclusions

The review of clinical evidence and the quantitative meta-analysis suggest that using POC devices to manage oral anticoagulation therapy results in significantly fewer deaths and thromboembolic events, and better INR control, than conventional laboratory testing. The impact of POC devices on hemorrhagic events, however, is similar to conventional testing. The base results are not altered significantly in subgroup analysis. These conclusions are subject to certain limitations: we could not confirm if thromboembolic events were evaluated in a blinded and objective manner. Also, 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 using 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 willingness to pay 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.

ABBREVIATIONS

ACT	activated whole blood clotting time
APTT	activated partial thromboplastin time (also written as aPTT)
ASA e.V.	German Association for Self-management of Oral Anticoagulation
CVA	cerebrovascular accident
DIN	drug identification number
DVT	deep vein thrombosis
ICER	incremental cost effectiveness ratio
INR	international normalized ratio
mL	millilitre
OACs	oral anticoagulants
OAT	oral anticoagulation therapy
OR	odds ratio
PC	portable coagulometer
PE	pulmonary embolism
POC	point of care
PT	prothrombin time
QALY	quality-adjusted life-year
QoL	quality of life
RBCs	red blood cells
RCT	randomized controlled trial
RevMan	Review Manager systematic review software
RIND	reversible ischemic neurological deficit
RR	relative risk
TE	thromboembolism
TEE	thromboembolic event
TIA	transient ischemic attack
TP	thrombophlebitis
WTP	willingness to pay

GLOSSARY

International normalized ratio: International unit that is used to indicate intensity of oral anticoagulation therapy and that is derived from prothrombin time determination.

Point-of-care testing: Diagnostic testing performed in a clinic, home, or other site of patient care rather than in standard reference laboratory.

Prothrombin time: Test that measures clotting time of plasma (liquid portion of blood).

Self-management or self-controlling: Trained patient uses POC device to do INR test, interprets results, and adjusts dosage of anticoagulant accordingly.

Self-testing or self-monitoring : Trained patient uses POC device to do INR test and informs his or her health care provider of result, then physician or another health care provider adjusts anticoagulant dose using results obtained by patient.

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APPENDICES – available from CADTH's web site www.cadth.ca

1   INTRODUCTION

1.1 Background

Oral anticoagulants (OACs) are widely used for the prevention and treatment of thromboembolic events in various clinical conditions. Long-term use is typically required for high risk groups with particular conditions. OACs are almost always used in patients with mechanical heart valves. Other indications include chronic atrial fibrillation, venous thromboembolism, acute myocardial infarction, stroke, and peripheral arterial occlusion.[1,2] In North America, warfarin is the anticoagulant of choice for long-term (more than three months) oral anticoagulation therapy (OAT). In Canada, it is available under the brand names of Apo®-Warfarin, Coumadin®, Gen-Warfarin, Novo-Warfarin, and Taro-Warfarin. Warfarin is a vitamin K antagonist. Vitamin K is essential for the synthesis of several blood-clotting factors, and warfarin prevents coagulation (blood clots) by suppressing the body's production of the vitamin K-dependent factors that are essential in the coagulation process. For many indications, a person must continue to use vitamin K antagonists for the duration of his or her life.[3,4] Because of the aging population, and an associated increase in the prevalence of atrial fibrillation and venous thromboembolism, it is expected that more patients may need vitamin K antagonists in the future.

Evidence suggests that prophylactic OAT with vitamin K antagonists reduces the incidence of thromboembolic complications (venous and arterial thrombosis), and associated mortality and morbidity in patients with a high risk of blood clots.[5] Warfarin has a narrow therapeutic window. Excessive anticoagulation confers an increased risk of bleeding, while sub-therapeutic anticoagulation is associated with an increased risk of stroke and other thromboembolic events.[6,7] The biological effect of the vitamin K antagonists varies between individuals and in an individual over time.[5] For this reason, patients need frequent monitoring of warfarin's anticoagulation effect. This can be inconvenient in terms of the blood sampling procedure and of the time spent going for a laboratory test.[1,2]

1.2 Overview of Technology

The international normalized ratio (INR) – the unit that is used worldwide to indicate the intensity of OAT – is derived from a prothrombin time determination. The standard practice in Canada for someone needing to monitor his or her INR is to go to a hospital or outpatient facility, and have 4.5 mL of blood drawn from a vein and placed in a tube containing 0.5 mL sodium citrate anticoagulant. An INR is then determined using a calibrated laboratory device with appropriate controls. It costs about $6.50 (Alberta source) for sample handling, transport, and analysis. When staff labour and administration are added, a standard test done in a hospital costs about $14.00 (British Columbia source).[8]

Point-of-care (POC) devices for monitoring long-term OAT were introduced in the 1990s. The technology allows for greater convenience for patients, because the devices are portable and only require a drop of blood from a fingertip. Clinical studies on these devices are widespread. In some countries, such as Germany, self-testing and self-management with POC devices are established therapeutic methods.[9]

Health Canada first licensed the CoaguChek POC monitor in April 1999. It is indicated for use by health professionals or for self-testing by patients. It has been used on a limited basis by health care professionals, health care centres, and patients. The CoaguChek S system includes the CoaguChek S monitor and CoaguChek PT strips. 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 a quality control solution (4×2 mL, $29.00 retail).[10]

The CoaguChek S System is a reflectance photometer, which quantitatively determines prothrombin time (PT) using capillary blood from the fingertip or untreated venous whole blood. The CoaguChek PT strip contains reagents and iron particles, which mix with the blood sample when it is applied. The monitor then starts to measure coagulation time by photometric determination. The iron oxide particles move in response to an oscillating magnetic field. As the blood starts to coagulate, the movement of the iron oxide particles becomes impeded. The monitor then stops the time measurement and displays the result. The monitor converts the measured time into customary coagulation units of INR and PT. If the CoaguChek S is ready for a measurement, the result will be displayed about one minute after application of the sample.[11]

The CoaguChek® XS model, which was released in 2006, has an electrochemical-based detection system. It has comparable results to the CoaguChek S system, but offers additional features, such as a smaller monitor and an on-board quality control on each strip.[11] The suggested retail price is $995.00 for the monitor and $200.88 for 24 test strips.[10]

The ProTime® Microcoagulation System was first licensed in Canada in August 1999, and was available for use by health care professionals.[12] At the time of our analysis, its use was still limited to health care professionals. The ProTime® Microcoagulation System consists of the portable battery-operated ProTime instrument, training video, charger, and instruction booklet. Associated equipment includes the reagent cuvette with built-in quality control, the Tenderlett sample collection system, and a universal charger with a power cord. The system reports results in INR and PT. Up to 30 results can be stored in its memory.[13-16]

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).

The ProTime instrument is a portable photometer. A plastic cartridge contains an enclosed capillary channel leading to a chamber with dry rabbit brain thromboplastin. This cartridge is inserted into the instrument. Capillary whole blood from a finger stick is allowed to drip into a well in the cartridge. The blood flows by capillary action to mix with the thromboplastin. As the blood clots, the light source detects cessation of flow by sensing variation in light scatter from the red blood cells. The time elapsed is converted into PT and INR.[17]

2   ISSUE

New technology makes it possible for patients on long-term OAT to be monitored with portable devices, sometimes in their homes, rather than having to go to a hospital or laboratory to provide blood by venipuncture. POC devices provide the same type of test result as the traditional laboratory test, the INR, but may provide it in a more convenient setting and in a less invasive way. Patients or health care professionals take a drop of blood from the finger after a lancet puncture. They then use the POC device to measure the blood's clotting tendency. Results are obtained in about one minute. For patients who do not live near a hospital or outpatient laboratory, POC devices allow them to be regularly

monitored. The devices have been on the market for the last decade. Those who administer funds for anticoagulation programs need to know how POC devices compare in effectiveness and cost effectiveness with standard laboratory tests.

3   OBJECTIVES

The objective of this report is to assess the clinical and economic implications of POC monitoring devices for long-term OAT. The following research questions were addressed.

- What is the clinical evidence from randomized controlled trials (RCTs) of the effectiveness of POC monitoring devices compared with the standard laboratory test in long-term oral anticoagulant therapy?
- What is the cost effectiveness of patient self-testing with POC devices and POC testing in anticoagulation clinics compared with the standard laboratory test for long-term oral anticoagulant therapy?

4   CLINICAL REVIEW

4.1 Methods

For the clinical and economic sections of the report, a protocol was written a priori and followed throughout the review process.

4.1.1 Literature search strategy

We obtained published literature by cross-searching DIALOG®'s MEDLINE® (1966 to current), EMBASE® (1974 to current), BIOSIS Previews® (1969 to current), and PASCAL databases. There were no year or language restrictions. A broad search strategy with appropriate descriptors and keywords was used, in combination with a filter, to restrict results to controlled trials, meta-analyses, and systematic reviews. We also ran parallel searches on PubMed and the Cochrane Library. Appendix 1 describes the clinical literature search strategy.

The original search was performed in July 2005. Regular alerts were established on MEDLINE®, BIOSIS Previews®, and EMBASE® databases to capture new studies up to August 11, 2006 and updated searches in the Cochrane Library regularly. The last Cochrane updates for this report were performed on July 20, 2006. We obtained grey literature by searching the web sites of regulatory agencies, and health technology assessment agencies, and near-technology assessment agencies. Specialized databases, such as the University of York's NHS Centre for Reviews and Dissemination and the Latin American and Caribbean Center on Health Sciences Information (LILACS), were also searched. The following professional associations' web and conference sites were searched for additional information: Thrombosis Interest Group of Canada, Canadian Cardiovascular Society, American College of Cardiology, American Society of Hematology, and European Society of Cardiology.

Non-RCTs were included in the literature search because of their potential use in other sections of the report. To support the economic component of the report, we searched relevant literature

(Appendix 2). Google™, Dogpile®, and Yahoo! were used to search for additional web-based information.

4.1.2 Selection criteria and method

Studies that were included met the following selection criteria:
- study design: RCTs in a research or clinical setting
- population groups: patients on OAT for at least three months after the start of the trial (no a priori restrictions on age or mental capacity); originally, there was an additional criterion that patients were on OAT for at least three months before the start of the trial, but this criterion was dropped because there were insufficient details in many of the articles to determine how long patients had been on anticoagulation therapy, and because the studies otherwise met the criteria and provided useful data
- interventions: anticoagulation monitoring by POC device; this could include POC testing at an anticoagulation clinic, POC self-testing by the patient, POC self-testing plus self-management and control, or any other POC management strategy
- comparators: usual care (venipuncture blood draw for an INR lab test and management provided by an anticoagulation clinic or individual practitioner)
- outcomes: for studies to be included, they were required to have reported on at least one of the following:
    - Rates of major hemorrhage, where major was defined as resulting in death, or were clinically overt and showed one of the following: critical site involvement (intra-cranial, retroperitoneal, intra-ocular, intra-spinal, or pericardial), drop in hemoglobin of ≥ 2.0 grams per deciliter, need for transfusion of >2 units of packed red blood cells, or a bleeding index of >2.0.
    - Major thromboembolic event rates, noting whether the study required objective tests for venous and arterial thromboembolic complications of stroke and valve thrombosis. Transient ischemic attacks were considered to be minor thromboembolic events and were included in a secondary analysis to evaluate all thromboembolic events.
    - Percentage of time the patient's blood was within the normal therapeutic INR range according to a method described by Rosendaal *et al*.[18] (The Rosendaal algorithm is used to calculate the time that a patient stayed in a pre-determined INR interval. The algorithm assumes a linear increase or decrease between two consecutive INR determinations.[19])

Reports were excluded if they were duplicate reports, preliminary reports of data presented in full, dose-finding studies, studies in which oral anticoagulants were combined with antiplatelet drugs, and studies that did not follow patients for more than three months. While we had planned to exclude data based on patients who had not been on OAT for three months and who may have had unstable INR results at the start of therapy, we dropped this criterion because of insufficient details in studies regarding the duration of anticoagulation therapy. Analyses were performed with or without these studies.

We assessed the retrieved references for possible inclusion based on an evaluation of the title and the abstract according to the selection criteria. The reviewers pilot-tested the inclusion-exclusion criteria on seven articles and performed a calibration exercise to ensure consistent application. Letters to the editor, review articles, editorials, and commentaries were excluded. The remaining studies were fully assessed.

At least two reviewers independently reviewed each citation from the literature search. At the first stage, abstracts were selected independently by KC and LM. Consensus was reached by discussion. At the second stage, full-text articles were reviewed independently. Agreement on eligibility was achieved by discussion between the two reviewers.

4.1.3 Data extraction

A data extraction form was developed a priori (Appendix 3). Two reviewers (PW, KC) independently extracted data from eligible articles and assessed their quality using a standard electronic form. PW and LM arrived at a consensus on the extracted data and quality values through discussion. The main outcome measures were patient-days below, in, or above the therapeutic range as defined in the studies; rates of major hemorrhage; and rates of thromboembolic events. We extracted data on the length of the observation period, mean age, gender, indication for anticoagulation, minor thromboembolic events, POC device used, sources of potential bias, withdrawals, and deaths.

4.1.4 Strategy for quality assessment

Study quality was assessed using the criteria proposed by Jadad *et al*., and the adequacy of allocation concealment was evaluated as appropriate or inappropriate according to the criteria proposed by Schulz and Grimes.[20,21] If information in the reports was insufficient, these issues were recorded as unclear or unstated. We successfully contacted authors when data were incomplete or missing.

4.1.5 Data analysis methods

For assessing the outcomes of major hemorrhage, major thromboembolic events, and all thromboembolic events, we conducted a meta-analysis by calculating odds ratios 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. Odds ratios (ORs) were calculated. OR will approximate the relative risk when the event is "rare" (some take this as <10%).[22] In our analysis, the event rate is low, so the approximation is good. The OR will always be further from the neutral point ("1") than the relative risk (i.e., less conservative), so the results should be interpreted with this in mind. We used a random-effects model for all comparisons (according to the method described by DerSimonian and Laird[23]), recognizing that its use can reduce the effect of larger studies relative to a fixed-effects model. A random-effects model allows for between-study variation, and was chosen as the more conservative option.

Differences between effects were tested using a Z test, and p values <0.05 were considered to be significant. Our plan was to analyze the differences in patient characteristics and other study differences to evaluate the cause of any heterogeneity. For each comparison group, we estimated the between-study heterogeneity using the Q statistic in the Review Manager (RevMan) software package. Heterogeneity was considered significant for p<0.05. The I^2 statistic, indicating the proportion of total variation due to heterogeneity, was also calculated. For I^2, the cut-points were 25%, 50%, and 75% for low, moderate, and high heterogeneity respectively.[24] The summary measures of rates of major hemorrhage and thromboembolic events were determined using the inverse variance weighted averages. Forest plots were prepared. Funnel plots were generated to assess whether the magnitude of the observed association was related to the variance of each study and whether there was evidence of publication bias.

Patient days below, in, or above the therapeutic range as 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.

Our analysis was performed for five groups:
- all eligible studies
- studies that required patients to be on OACs for >3 months before study entry, analyzed as a subgroup: these are patients more likely to stay on OACs, because they are familiar with what is involved in OAC care; any events in the first three months are less likely to be related to OAC control
- studies that compared POC self-testing and self-management to routine care: these look at patients' use of POCs rather than their use by health care professionals
- studies that described the requirement for objective tests to diagnose major thromboembolic events: these are most likely to have the most accurate data
- studies scoring ≥3 on the Jadad assessment tool: these use better methods, and we can evaluate whether poorly designed studies are driving the results produced when all studies are included.

4.2 Results

4.2.1 Quantity of research available

We identified 439 citations in our initial search. Routine updates yielded an additional 13 citations for a total of 452 (Figure 1.) Of these 452 citations, 409 did not meet the selection criteria and were excluded, leaving 43 (39 from the initial search and four in the updated searches). Two were added for reconsideration after the study criteria were revised to include studies where patients had been on OAT for <3 months at the start of the study. We retrieved 45 potentially relevant articles for further review. Of these, we excluded 29 articles (Appendix 4),[25-53] leaving 16 relevant articles describing 15 unique RCTs.[54-69] One RCT (about mechanical heart valve replacement) was reported in two publications.[60,61] These articles by Koertke *et al.* were not duplicates because they reported different aspects of the RCT. The Gadisseur article provided two sets of data because the authors compared self-test plus self-management and self-test plus clinic management to routine care.[57] The degree of agreement between reviewers was kappa=0.49, which is just shy of moderate agreement. Differences in selection experience may account for some of the differences, but consensus was obtained.

Of the 11 articles that were excluded based on study design, four were reviews.[32-35] Five articles were excluded because the intervention used was inappropriate for our review.[36-39,53] For example, while POC testing was used in some studies, the patients were managed based on results from laboratory testing, not POC testing. As a result, no true comparison could be made with those patients in a group undergoing laboratory testing because this study design may miss results related to management based on POC testing. One article was excluded based on population,[40] one based on outcome measures,[46] and three because they were at the protocol stage.[41-43] Three were duplicates of excluded articles,[44,45,47] and five were duplicates of included articles, so they were also excluded.[48-52]

4.2.2 Study characteristics

Appendix 5 summarizes the characteristics of the studies and demonstrates their variability regarding observation periods, mean age of patients, and indication for anticoagulation. It was not possible to break down study outcomes according to the indication for anticoagulation. Routine anticoagulation control could be performed in a primary care setting, in a specialized anticoagulation clinic, or in

hospital anticoagulation clinics. Of primary interest were self-monitoring plus self-management studies compared to routine anticoagulation control. We found 11 studies that made this comparison. In eight studies, only patients who had been on OAT for ≥3 months were enrolled; in seven studies, patients were enrolled from the time of initiation of anticoagulation.[56,60,61,63,66-69] Two of the latter studies did not state how long patients had been on anticoagulants, so it was assumed that there was no three-month minimum.[63,66] Appendix 6 summarizes the outcome data from eligible trials.

4.2.3 Data analysis and synthesis

The intervention group comprised 2,144.6 patient-years of observation, while the control group comprised 2,316.1 patient-years. For all studies, there were significantly fewer major thromboembolic events in the POC testing group than in the routine care group (OR=0.48; 95% CI 0.33 to 0.72). This statistically significant difference was also observed in all four of the other subgroups (Table 1).

The odds ratios for all thromboembolic events were similar. Death from any cause was significantly less likely in the POC testing group when all eligible studies were pooled (OR=0.54; 95% CI 0.35 to 0.83), and this remained significant in all other analyses except the one that included only three studies (i.e., those that defined the objective diagnostic criteria). For major hemorrhage, the odds ratio was not significantly different between the POC testing group and the routine testing group in any of the analyses (OR=0.75; 95% CI 0.51 to 1.10 for the analysis of all studies).

The percentage of time in range was significantly better for the POC group in all four relevant analyses (Table 1). For the "all studies" analysis, the mean percentage of time in range for the POC testing group was 69% (95% CI 65% to 72%) versus 61% (95% CI 55 % to 66%; p=0.004) for the routine care group. In the analysis comparing self-testing plus self-management with routine testing, the means were 71% (95% CI; 66% to 76%) versus 63% (95% CI; 60% to 66%), p=0.016, respectively.

Figure 1: Selected articles for clinical review

439 citations identified from original electronic search, and 13 from alert searches for a total of 452

409 citations excluded

2 citations reconsidered based on revised study criteria (OAT<3 months initially)

39 (original search) and 4 (updated search) and 2 (revised criteria) potentially relevant articles retrieved for further scrutiny (full text, if available)

45 potentially relevant articles

29 articles excluded due to:
• study design inappropriate for review (11)
• intervention inappropriate for review (5)
• population inappropriate for review (1)
• outcomes inappropriate for review (1)
• protocol only, study incomplete (3)
• duplicates of excluded studies (3)
• duplicates of included studies (5)

16 relevant articles describing 15 unique studies (RCTs) for clinical review

Table 1: Odds ratio for primary and all secondary analyses*					
Analysis	**Major Hemorrhage**	**Major Thromboembolic Events**	**All Thromboembolic Events**	**All Deaths**	**% Time in Range**
All studies	0.75 (0.51 to 1.10)	0.48 (0.33 to 0.72)	0.45 (0.29 to 0.70)	0.54 (0.35 to 0.83)	69% versus 61%
3 months anticoagulation	0.78 (0.47 to1.27)	0.46 (0.26 to 0.80)	0.35 (0.15 to 0.81)	0.35 (0.18 to 0.71)	70% versus 64%
Self-test, self-managed	0.76 (0.47 to 1.24)	0.43 (0.25 to 0.74)	0.35 (0.16 to 0.73)	0.38 (0.19 to 0.74)	71% versus 63%
Used objective definitions for TEE	0.83 (0.36 to 1.88)	0.41 (0.18 to 0.95)	0.33 (0.15 to 0.73)	0.39 (0.15 to 1.02)	ND
Quality scores ≥3**	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%

*Table 1 was calculated using SAS, while figures 4.2a to 4.2d were prepared with RevMan, which accounts for slight discrepancies.
**No studies had a quality score of >3; ND=not done; too few studies; TEE=thromboembolic event.

Figures 2 to 5 show forest plots for major hemorrhage, major thromboembolic events, all thromboembolic events, and death. Figure 6 shows the funnel plot for all thromboembolic events, which appears to be symmetrical and does not give an indication of publication bias. Figure 7 shows a funnel plot for major hemorrhage that suggests the possibility of publication bias. The funnel plots assumed a fixed effect, because the software used does not allow random effects for funnel plots.

Figures 2 to 5 also provide information for assessing heterogeneity using Q and I^2 statistics. This is summarized in Table 2, and indicates only a small effect of heterogeneity on the meta-analysis.

Table 2: Heterogeneity test results				
Outcome	**Number of studies**	**Q**	**p value**	**I^2**
Major hemorrhage	13	8.63	0.73	0
Major thromboembolic events	14	4.13	0.94	0
All thromboembolic events	11	7.24	0.51	0
Death	8	3.87	0.57	0

We had hoped to be able to compare quality of life (QoL) scores between studies, but QoL was not uniformly measured, and when it was, different tools were used. Five studies planned and performed formal evaluations. One used the EuroQol[59] and reported no significant changes or differences between the study groups from study inception to completion. Two used the same 40-item structured questionnaire.[54,63] Cromheeke demonstrated significant differences in five categories, in favour of the self-management group, and Sawicki demonstrated similar findings with the most pronounced improvements in general treatment satisfaction scores and distress scores. Two studies used locally developed satisfaction scales and demonstrated that patients were satisfied using POC devices, but did not do any formal comparisons.[64,69] However, the fact that the QoL evidence was based on the included clinical RCTs is a potential limitation. The focus of the study was on clinical endpoints, and there were resource availability considerations. Nevertheless, the chance of missing significant QoL evidence was slim.

Figure 2: Forest plot for major hemorrhage

Study or sub-category	POC n/N	Laboratory n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
OAT >3 months					
Sawicki 1999	1/90	1/89		1.94	0.99 [0.06, 16.06]
Fitzmaurice 2000	1/122	0/102		1.46	2.53 [0.10, 62.80]
Koertke 2000	17/305	25/295		36.96	0.64 [0.34, 1.21]
Sidhu 2001	1/51	0/49		1.45	2.94 [0.12, 73.93]
Gadisseur 2003	2/47	1/161		2.56	7.11 [0.63, 80.22]
Gadisseur 2003B	0/52	1/161		1.46	1.02 [0.04, 25.40]
Menendez 2004	4/368	7/369		9.84	0.57 [0.16, 1.96]
khan 2004	1/44	0/40		1.44	2.79 [0.11, 70.54]
Fitzmaurice 2005	4/337	4/280		7.73	0.83 [0.21, 3.34]
Voller 2005	1/101	0/101		1.46	3.03 [0.12, 75.26]
Subtotal (95% CI)	1517	1647		66.30	0.83 [0.51, 1.33]
Total events: 32 (POC), 39 (laboratory)					
Test for heterogeneity: chi²=6.30, df=9 (p=0.71), I²=0%					
Test for overall effect: Z=0.78 p=0.43					
OAT <3 months					
Beyth 2000	8/163	17/162		19.87	0.44 [0.18, 1.05]
Sunderji 2004	0/70	1/70		1.45	0.33 [0.01, 8.21]
Claes 2005	5/278	9/556		12.38	1.11 [0.37, 3.35]
Subtotal (95% CI)	511	788		33.70	0.61 [0.31, 1.19]
Total events: 13 (POC), 27 (laboratory)					
Test for heterogeneity: chi²=1.83, df=2 (p=0.40), I²=0%					
Test for overall effect: Z=1.44 (p=0.15)					
Total (95% CI)	2028	2435		100.00	0.75 [0.51, 1.10]
Total events: 45 (POC), 66 (Laboratory)					
Test for heterogeneity: chi²=8.63, df=12 (p=0.73), I²=0%					
Test for overall effect: Z=1.48 (p=0.14)					

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          0.01   0.1      1      10    100
            Favours POC   Favours Laboratory
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Figure 3: Forest plot for major thromboembolism

Study or sub-category	POC n/N	Laboratory n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 OAT > 3 months					
Horstkotte 1998	1/75	3/75		2.91	0.32 [0.03, 3.19]
Sawicki 1999	0/90	2/89		1.63	0.19 [0.01, 4.09]
Cromheecke 2000	0/25	0/25			Not estimable
Fitzmaurice 2000	2/122	6/102		5.78	0.27 [0.05, 1.35]
Koertke 2000	12/305	20/295		28.20	0.56 [0.27, 1.17]
Sidhu 2001	1/51	4/49		3.06	0.23 [0.02, 2.09]
Gadisseur 2003	0/47	0/161			Not estimable
Gadisseur 2003B	0/52	0/161			Not estimable
Menendez 2004	3/368	12/369		9.38	0.24 [0.07, 0.87]
Fitzmaurice 2005	3/337	3/280		5.88	0.83 [0.17, 4.14]
Voller 2005	0/101	1/101		1.47	0.33 [0.01, 8.20]
Subtotal (95% CI)	1573	1707		58.31	0.42 [0.25, 0.70]
Total events: 22 (POC), 51 (Laboratory)					
Test for heterogeneity: Chi² = 2.94, df = 7 (P = 0.89), I² = 0%					
Test for overall effect: Z = 3.31 (P = 0.0009)					
02 OAT < 3 months					
Beyth 2000	13/163	20/162		28.15	0.62 [0.30, 1.28]
Sunderji 2004	0/70	2/70		1.63	0.19 [0.01, 4.12]
Claes 2005	4/278	13/556		11.91	0.61 [0.20, 1.89]
Subtotal (95% CI)	511	788		41.69	0.59 [0.32, 1.07]
Total events: 17 (POC), 35 (Laboratory)					
Test for heterogeneity: Chi² = 0.53, df = 2 (P = 0.77), I² = 0%					
Test for overall effect: Z = 1.73 (P = 0.08)					
Total (95% CI)	2084	2495		100.00	0.48 [0.33, 0.72]
Total events: 39 (POC), 86 (Laboratory)					
Test for heterogeneity: Chi² = 4.13, df = 10 (P = 0.94), I² = 0%					
Test for overall effect: Z = 3.65 (P = 0.0003)					

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       0.001 0.01  0.1     1    10   100  1000
              Favours POC   Favours Laboratory
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Figure 4: Forest plot for all thromboembolism (major and minor)

Study or sub-category	POC n/N	Laboratory n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 OAT > 3 months					
Sawicki 1999	1/90	2/89		3.47	0.49 [0.04, 5.49]
Cromheecke 2000	0/25	1/25		1.92	0.32 [0.01, 8.25]
Fitzmaurice 2000	2/122	10/102		8.53	0.15 [0.03, 0.72]
Gadisseur 2003	0/47	0/161			Not estimable
Gadisseur 2003B	0/52	0/161			Not estimable
Menendez 2004	4/368	20/369		17.29	0.19 [0.06, 0.57]
Fitzmaurice 2005	4/337	3/280		8.96	1.11 [0.25, 5.00]
Voller 2005	0/101	1/101		1.97	0.33 [0.01, 8.20]
Subtotal (95% CI)	1142	1288		42.15	0.30 [0.15, 0.60]

Total events: 11 (POC), 37 (Laboratory)
Test for heterogeneity: Chi² = 4.47, df = 5 (P = 0.48), I² = 0%
Test for overall effect: Z = 3.38 (P = 0.0007)

Study or sub-category	POC n/N	Laboratory n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
02 OAT < 3 months					
Beyth 2000	14/163	21/162		39.78	0.63 [0.31, 1.29]
Sunderji 2004	0/70	2/70		2.18	0.19 [0.01, 4.12]
Claes 2005	4/278	13/556		15.90	0.61 [0.20, 1.89]
Subtotal (95% CI)	511	788		57.85	0.60 [0.33, 1.08]

Total events: 18 (POC), 36 (Laboratory)
Test for heterogeneity: Chi² = 0.55, df = 2 (P = 0.76), I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)

| Total (95% CI) | 1653 | 2076 | | 100.00 | 0.45 [0.29, 0.70] |

Total events: 29 (POC), 73 (Laboratory)
Test for heterogeneity: Chi² = 7.24, df = 8 (P = 0.51), I² = 0%
Test for overall effect: Z = 3.49 (P = 0.0005)

0.001 0.01 0.1 1 10 100 1000
Favours POC   Favours Laboratory

Figure 5: Forest plot for death

Study or sub-category	POC n/N	Laboratory n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 OAT > 3 months					
Sawicki 1999	1/90	1/89		2.43	0.99 [0.06, 16.06]
Fitzmaurice 2000	3/122	6/102		9.47	0.40 [0.10, 1.66]
Sidhu 2001	0/51	4/49		2.17	0.10 [0.01, 1.87]
Shiach 2002	0/23	0/23			Not estimable
Menendez 2004	6/368	15/369		20.56	0.39 [0.15, 1.02]
Fitzmaurice 2005	5/337	11/280		16.50	0.37 [0.13, 1.07]
Subtotal (95% CI)	991	912		51.12	0.38 [0.21, 0.70]

Total events: 15 (POC), 37 (Laboratory)
Test for heterogeneity: Chi² = 1.29, df = 4 (P = 0.86), I² = 0%
Test for overall effect: Z = 3.12 (P = 0.002)

Study or sub-category	POC n/N	Laboratory n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
02 OAT < 3 months					
Beyth 2000	21/163	26/162		48.88	0.77 [0.42, 1.44]
Sunderji 2004	0/70	0/70			Not estimable
Subtotal (95% CI)	233	232		48.88	0.77 [0.42, 1.44]

Total events: 21 (POC), 26 (Laboratory)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.81 (P = 0.42)

| Total (95% CI) | 1224 | 1144 | | 100.00 | 0.54 [0.35, 0.83] |

Total events: 36 (POC), 63 (Laboratory)
Test for heterogeneity: Chi² = 3.87, df = 5 (P = 0.57), I² = 0%
Test for overall effect: Z = 2.80 (P = 0.005)

0.001 0.01 0.1 1 10 100 1000
Favours POC   Favours Laboratory

Figure 6: Funnel plot for thromboembolism

Figure 7: Funnel plot for major hemorrhage

The quality score of the 15 studies varied from one to three, with eight attaining a score of three out of a maximum of five (Appendix 6). Only two studies received a score of one. None of the studies were double-blinded. Because of the nature of the intervention, this was probably not possible, in which case the maximum quality score would be three. Another indicator of quality would be whether investigators evaluated the outcomes of hemorrhage and thromboembolic events without knowing whether patients underwent POC testing or laboratory testing. This approach was followed in four studies.[57,63,67,69] Five studies used adequate allocation concealment.[54,55,62,68,69] It is generally acknowledged that thromboembolic events should be diagnosed using objective tests and a priori definitions. Only three studies stated and defined how thromboembolic events would be diagnosed.[62,64,68] This casts doubt on the accuracy of the recorded number of thromboembolic events. Most studies did define a priori the criteria for major hemorrhage.

To evaluate the potential scope for the use of POC devices, we considered whether they are well tolerated and easily employed. We looked for data on patient eligibility, agreement to consent, and withdrawal from studies. This is most relevant for the 11 studies in which patients were using the POC device for self-management. Three studies did not provide these data.[58,66,68] The studies that did report these data showed the following:

- For the proportion of patients deemed eligible from a group of consecutive patients, eight studies reported that from 16% to 40% of patients were deemed unsuitable to use the POC device, with most studies reporting closer to 40% as unsuitable.
- For the proportion of patients who were randomized but who withdrew after attempting the POC training sessions, six of the 11 studies reported that from 18% to 28% of the patients dropped out after being randomized to the POC device and attempting the training program.
- For the proportion who withdrew after the study began, six studies reported that from 12% to 19% of patients abandoned using the POC device compared with 0% to 6% who withdrew in the routine care groups (Appendix 8).

4.3 Discussion

Our study reviewed 15 RCTs comparing POC testing to routine anticoagulation monitoring care in a hospital or laboratory. Of those, 11 compared using POC devices for self-management and self-monitoring with routine anticoagulation monitoring, the most relevant from the perspective of patient's convenience of care. The data in these trials suggest that POC devices resulted in significantly fewer major thromboembolic events and deaths from any cause. The risk of major hemorrhage was similar between the two groups. These results were unchanged for all subgroup analyses performed. For all analyses, the comparison of percentage time in range between the POC device group and the control group demonstrated superiority with POC use. Three studies described the use of objective tests to diagnose thromboembolic events.

The summary data suggest that POC devices are advantageous. In all studies, the frequency of INR monitoring was higher in the POC group than in conventional testing (Appendix 7). In most cases, the frequency of testing was dictated by the study protocol. It remains unknown whether similar frequent monitoring in routine care would result in similar rates of major thromboembolic events, death, or major hemorrhage, and vice versa. It is also unknown whether this rigorous frequency of monitoring using POC devices would persist outside the study setting. In addition, patients who self-manage lose regular contact with their physician. The implications of this are unknown, but based on the critical endpoint of death, it does not seem to be a disadvantage.

Under usual care, warfarin therapy requires regular laboratory monitoring of the INR, coupled with frequent physician-patient contact for dosage adjustment to ensure efficacy and safety.[8] The usual-care method can be cumbersome and inconvenient for the patient and the physician.[70] There is also a potential for dosing errors due to misinterpretation of information conveyed by the physician or delays in contacting the patient.[8] These factors plus faster test results and more convenience leading to more frequent testing are plausible reasons for the incremental health benefits observed with POC use.

The highest quality score for any of the publications was three. No study was double-blinded. In many studies, it was impossible to categorize what happened to the withdrawals. In all the studies (Appendix 8), the withdrawal rates of the POC testing groups were higher than those of the routine testing group. In most studies, between 16% and 40% of patients did not continue in the study, because they could not master the technique of self-testing or adequately understand the mechanism to self-adjust dose. An additional 18% to 28% dropped out during the study compared with drop-out rates of 0% to 6% in the routine-care group. It seems that the inclusion-exclusion criteria for the individual trials resulted in the exclusion of many patients deemed unsuitable for POC self-testing before randomization, in addition to many such patients declining the invitation to participate. As such, the results of our meta-analysis apply to selected patients.

We performed several subgroup analyses. One included only patients who had been on OAT for ≥3 months. We were initially concerned that including patients who were not yet stable on OAT could bias the results against the use of POC devices, given the known interactions with heparin and the difficulty in first achieving INR control.[71] Our subgroup analysis showed that the results were essentially the same, regardless of the time that patients were on OAT at baseline. The odds ratios were also similar whether we included all studies (i.e., any POC testing compared to routine INR testing) or just self-test plus self-management comparisons. The outcomes were unchanged regardless of who performed the dosing in the POC groups. This raises the possibility that frequency of monitoring or better patient education is more important than the mechanism itself.[71]

While information on QoL and patients' satisfaction with the POC devices was collected, we were unable to provide quantitative summary measures of these factors. A qualitative analysis of the data suggests that, in general, patients were at least as satisfied, and some more so, with self-managing using the POC devices than with receiving care at an anticoagulation clinic. These patients were good candidates for using a POC device, having been self-selected or selected by a health care researcher. The overall proportion of OAT patients who were suitable or willing to use POC self-testing and self-management may be about 24%,[46] which is an upper bound for the uptake of POC for self-monitoring in Canada. This proportion comes from a study conducted using 48 general practices in the West Midlands, UK. In this study, unselected patients were invited to participate, so this can be an indicator for the uptake of POCs in everyday health care.[46] For POC trials conducted in the UK, the comparator population would represent a realistic "best practice," and the results would tend to be valid and generalizable.[55]

This report is not the first systematic review to compare POC testing with laboratory testing for the management of patients on OAT. Five systematic reviews have been published, but all have limitations.[32-34,72,73] The most recent analysis by Heneghan *et al*. suggests that POC testing resulted in significantly fewer major hemorrhages, thromboembolic events, and deaths than conventional INR testing.[72] The Heneghan analysis, which included 14 studies, included three that we considered to be ineligible: one compared POC testing only with other POC testing, one did not use POC test results for OAT management, and the third followed patients for only eight weeks.[31,37,53] Our report also included four articles that were excluded by Heneghan.[55,56,64,68] Finally, the summary data used by

these authors reported events per patient enrolled and not length of follow-up, as we did. Despite this, we came to similar conclusions with respect to two of four outcomes: death and all thromboembolic events. The other authors did not report separately on the more relevant outcome of major thromboembolic events. As for the outcome of major hemorrhage, we did not detect, as they did, a significant difference between groups.

In contrast to our review, the other systematic reviews had a small number of studies[33,34,73] or included non-randomized trials.[32,34] In a meta-analysis of eight RCTs, Odegaard *et al.* found that self-managed anticoagulation was safer and more effective at reducing major clinical events than conventional control for selected patients (OR: 0.62; 95% CI 0.429, 0.895).[33] Self-management resulted in reduced rates of major and fatal bleeds (2.4% versus 3.5%) and thrombosis (2.7% versus 3.9%) compared with conventional control and greater time in therapeutic range. Older patients experienced difficulties due to poor vision, tremor, and thick fingertips. From 50% to 60% of patients were found to be suitable for self-management.[33] A systematic review by Siebenhofer *et al.* comparing four studies concluded that self-management is safe and improves anticoagulation control, but no valid long-term study demonstrates reduced bleeding and thromboembolic events.[32,34]

The safety, effectiveness, and cost effectiveness of POC testing in general practice were evaluated in an assessment by the Medical Services Advisory Committee in Australia.[73] Two studies met the eligibility criteria: a randomized cross-over trial and a case series study. The assessment reported no significant difference in diagnostic performance between POC testing and laboratory testing. There was uncertainty about the diagnostic performance of POC testing at higher INR levels. The authors estimated that POC testing would cost the Australian health care system approximately an extra $44 million annually, based on 2.7 million tests.[73] After considering safety, effectiveness, and cost effectiveness, the report concluded that there was insufficient evidence to support the use of POC testing in general practice at that time.[73]

A recent Canadian multi-centre RCT compared INR conducted by a local laboratory with patient care in a specialized oral anticoagulation clinic or by the patient's family physician. Anticoagulation clinics provided better oral anticoagulation management, but the differences were modest.[74]

To summarize our key clinical results, 16 articles describing 15 unique RCTs met the inclusion criteria. The clinical evidence and quantitative meta-analysis suggest that using POC devices to manage OAT results in significantly fewer deaths and thromboembolic events and better INR control than laboratory INR testing. The effect on hemorrhagic events is similar. The base results were not altered by subgroup analysis, with one exception. For the three studies that defined the objective diagnostic criteria, no difference in death was found between POC testing and routine INR testing. The studies suggest that most patients are unsuitable for self-testing and self-management, but guidelines for selecting appropriate candidates exist.[37] An upper bound of 24% of OAT patients could be eligible for self-testing or self-management with POC.[46]

These findings are subject to certain limitations. We cannot confirm whether thromboembolic events were evaluated in a blinded and objective manner. The INR test frequency is higher in the POC testing strategies. None of the studies is double-blinded. The criteria for patients' eligibility for inclusion into the individual clinical trials and the high withdrawal rates are such that it is difficult to determine generalizability. Definitive conclusions about the clinical benefits of self-testing and self-management with POC devices cannot be made without more rigorously designed randomized trials.

5 ECONOMIC ANALYSIS

5.1 Review of Economic Studies: Methods

5.1.1 Literature Search Strategy

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 parallel searches on PubMed and the Cochrane Library. Appendix 2 describes the economic literature search strategy.

The original search was performed in July 2005. We established regular alerts on MEDLINE®, BIOSIS Previews®, and EMBASE® databases to capture new studies until August 11, 2006 and updated searches in the Cochrane Library regularly. The last Cochrane updates for this report were performed on July 20, 2006. We also ran a parallel search on HEED Health Economic Evaluations Database. We obtained supplementary cost information for the economic model by contacting experts and searching administrative databases.

An economic study was included for review if it satisfied all of the following criteria:
- study design: a 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 (AB) applied the selection criteria to the title and abstract (if available) of all literature to identify its relevance to our objective. For articles rated as confirmed or undecided, we obtained full-text hard copies. The selection criteria were then applied to the full-text articles. If a study satisfied all the questions on an inclusion-exclusion form based on the criteria, it was included for review.

One reviewer (AB) used a data extraction sheet to extract the principal content of each included study (Appendix 11). As the studies varied in terms of design, data collection, and analysis, no effort was made to pool the results quantitatively. Instead, each study was summarized, and a qualitative comparison was undertaken. Data extracted from included economic studies were checked by a second reviewer (KC).

Two reviewers (LM and KC) used a checklist developed for the *British Medical Journal* to assess the quality of the included full economic studies.[75] The quality of cost comparison studies was also assessed by two reviewers (LM and KC). They considered factors such as inputs included, whether physical measures and unit costs were reported separately, whether there was a defined answerable

question, and timelines of the study.[76] The quality criteria appear in Appendix 9, with the results of the quality assessment.

5.2 Review of Economic Studies: Results

The economic literature search identified 139 potentially relevant articles (137 from Dialog databases and two from Cochrane). After applying the inclusion criteria, seven articles describing six unique studies were included for review. Two articles described the Lafata study.[77,78] Two studies described full economic evaluations (Lafata,[77,78] de Solà-Morales[79]). The other four were cost comparisons.[9,17,80,81] One study analyzed the ProTime monitor.[17] The rest analyzed CoaguChek.

Appendix 9 presents the results for the quality assessment of the two full economic evaluations using the *British Medical Journal* (*BMJ*) checklist.[75] The *BMJ* checklist includes 35 questions under three headings: study design, data collection, and analysis and interpretation of results. Each question is answered with "yes," "no," or "not clear." The "no" and "not clear" responses have been calculated following an approach described by Jefferson.[82] The sum of the "no" and "not clear" answers indicates the extent that issues were not handled. The lower the numerical score, the higher the implied quality. For the two studies, the score was relatively low, suggesting a relatively high quality rating (Lafata[77,78]=4, de Solà-Morales[79]=5). The *BMJ* checklist is appropriate for full economic evaluations, i.e., evaluations that present the costs and consequences of health interventions, and a summary measure of the trade-off between the two. Four partial economic evaluations (all cost comparisons) were included, and their quality was analyzed with an instrument developed for another study.[76] Appendix 10 presents the quality assessment results for Ansell,[17] Cheung,[80] Jacobson,[81] and Taborski.[9]

Table 3 summarizes the characteristics of the included economic studies, and Table 4 summarizes their results.

In the Ansell study,[17] the only included economic study using the ProTime monitor, 20 patients on long-term anticoagulation with warfarin received standard treatment or monitoring with ProTime every other week for eight weeks in a cross-over design. The setting was a US hospital-based anticoagulation clinic. The patients had a variety of indications for anticoagulation, including nine with atrial fibrillation, five with transient ischemic attacks, two with prosthetic aortic valve, and one each with chronic thrombophlebitis, cerebral vascular accident, and mitral valvuloplasty. The patients were managed by the nursing staff. The study found that, relative to standard treatment, the use of ProTime in a large hospital-based anticoagulation clinic reduced the costs associated with therapy. Although the average nursing time per test was greater with ProTime, the increased cost was outweighed by the lower cost associated with the ProTime test relative to the standard test. The Ansell study was partially funded by industry (DuPont).

			Table 3: Characteristics of economic evaluations included in review			
Author	**Industry Sponsorship**	**Study Perspective**	**Interventions and Comparators**	**Study Design**	**Location**	**Outcomes and Source**
Ansell[17]	partial	societal	Laboratory PTT, Coumatrak ProTime Monitor	cost comparison	US	costs ($) and time resource, retrospective administrative database
Cheung[80]	no	societal and health provider	laboratory INR, CoaguChek	cost comparison	US	costs ($), retrospective administrative database
De Solà-Morales[79]	no	health insurer	laboratory INR, CoaguChek under various management strategies	CEA	Spain	major complications, OAT continued, OAT discontinued, death; published literature
Jacobson[81]	no	physician's clinic	laboratory INR, CoaguChek	engineering work flow and cost comparison	US	costs ($) and time resource, two clinics using POC and two clinics using INR laboratory test
Lafata[77,78]	yes	societal and health provider	laboratory INR, CoaguChek in anticoagulation clinic and self-testing by patients	CEA	US	thromboembolic events, hemorrhagic events, no event, death; published literature and retrospective administrative database
Taborski[9]	no	government-controlled health insurance funds	Laboratory INR, CoaguChek	cost comparison	Germany	thromboembolic events, hemorrhagic events complications; published literature

CEA=cost effectiveness analysis; INR=international normalized ratio; OAT=oral anticoagulation therapy; POC=point-of-care device; PTT=plasma prothrombin time

Table 4: Results of economic evaluations included in review			
Author	**Currency Year**	**Estimate of Cost Effectiveness or Relative Cost**	**Conclusions**
Ansell[17]	US$ 1989*	TC per laboratory test: $15.64 TC per test (ProTime): $7.55 nurse-patient time per laboratory test: 8.3 minutes nurse-patient time per test (ProTime): 12.4 minutes overall patient time per laboratory test: 20.0 minutes overall patient time per test (ProTime): 16.2 minutes	In setting of large hospital-based anticoagulation clinic, use of ProTime for oral anticoagulation with management by nursing staff resulted in significant cost savings. Because of immediate availability of results, ProTime should provide improved health care.
Cheung[80]	US$ 1999	cost per laboratory test (societal): $17.30 cost per laboratory test (health provider): $10.67 cost per test (CoaguChek) (societal or health provider perspective): $6.85	CoaguChek by home health nurses gave significant cost saving to society and modest cost saving to home health agency provider. Findings support equipping home health nurses with POCs.
De Solà-Morales[79]	euro 2002 (in 2002, €1=US$1)	TC after 5 years: usual care: €8,997.40 POC and dose in hospital by hematologist: €3,305.30 POC and dose by family doctor: €3,461.50 POC and dose by patient at home: €4,469.50 POC by patient and dose by family doctor: €5,188.50	Overall CoaguChek cost-effective versus usual care. CoaguChek and dose adjustment by hematologist in hospital dominated other options. Given that results are similar among four CoaguChek options, with population perspective due to convenience, preferred option would likely be monitoring with CoaguChek and dose adjustment by patient at home.
Jacobson[81]	US$ 2000*	median turnaround time for POC clinics: 8 minutes (range 4 minutes to 22 minutes) median turnaround time for laboratory testing clinics: 498 minutes (range 22 minutes to 23 days) direct operating costs per test for laboratory testing clinics: $1.12 direct operating costs per test for POC clinics: $7.51	Time from initial blood draw to patient notification of test results faster for POC clinics. Total turnaround time five times more variable for clinics using laboratory test. POC testing resulted in higher direct costs for physician, but this was more than offset by reimbursement potential in US health system under POC testing.
Lafata[77,78]	US$ 1997	health provider perspective: moving from usual care to POC in anticoagulation clinic was cost saving; moving from anticoagulation clinic to patient self-testing gave ICER of $24,818 per avoided event societal perspective: moving from usual care to POC in anticoagulation clinic gave ICER of $31,327 per avoided event, and moving from anticoagulation clinic to patient self-testing was cost saving	From either perspective, POC option more cost-effective than usual care. From health care provider perspective, anticoagulation clinic testing with POC is most cost-effective alternative. From societal perspective (provider organizations and patients), self-testing by patients is most cost-effective alternative.
Taborski[9]	Deutsche Mark (DM) 1999*	TC per patient per year is DM 2,061.48 for usual care, and DM 1,342.46 for self-testing with PC.	Self-testing by patients reduces treatment costs by DM 719.02 per patient annually.

*Currency year not stated, so assumed from publication date; €=euro; DM=Deutsche Mark; ICER=incremental cost effectiveness ratio; OAT=oral anticoagulation therapy; POC=point-of-care device; TC=total cost.

The Cheung study[80] was supported financially by the Agency for Healthcare Research and Quality, United States Department of Health & Human Services. It involved 35 housebound post-hospitalization elderly patients (mean age of 67 years) receiving cardiac home health care and long-term oral anticoagulation with warfarin. The indications for anticoagulation were primarily cardiac. A home health nurse provided management. The study found that using CoaguChek saved on the costs of transporting and processing INR specimens. It could also reduce overall medical expenditures from a societal and a health care provider perspective.

The de Solà-Morales study[79] was a full economic evaluation commissioned by the Catalan HTA agency in Spain. It compared the standard laboratory test with several management strategies involving the CoaguChek POC monitor: use of a POC monitor and dose adjustment in hospital by a hematologist, use of a POC monitor and dose adjustment by a family doctor, use of a POC monitor and dose adjustment by the patient at home, and use of a POC monitor by the patient and dose adjustment by a family doctor. The study assumed that the efficacy for all the POC options was equivalent. The total costs after five years for standard laboratory testing was significantly higher than for all the POC options. The study concluded that CoaguChek was more cost effective than usual care. From a health insurer perspective, the option of providing CoaguChek in a hospital with dose adjustment by a hematologist was the most cost effective option. The authors found that the results were similar among all the CoaguChek options. If a population perspective was taken, they concluded that self-monitoring and self-management in a patient's home was most convenient and therefore preferable.

Jacobson[81] did an engineering work process study including a comparison of direct operational costs, defined as human resource costs plus relevant test costs at each site. The study population consisted of 250 patients on routine OAT. All study patients were ≥18 years of age. Pregnant patients were excluded. Four physicians' offices were included in the study: two used POC monitoring and two referred patients for the standard laboratory test. The physicians' offices had to have specialized software for scheduling, tracking, and documentation. POC testing resulted in decreased clinical turnaround times (from initial blood draw to notification of the patient regarding test results) and decreased variability in clinical turnaround times for warfarin dose adjustments, in comparison with standard laboratory testing.

Jacobson found that turnaround times for POC testing were generally <10 minutes, including time for education and decision support, because patients received their results face to face. The turnaround times for laboratory testing ranged from 22 minutes to >23 days, with no time allotted for education, because these patients usually received their results by telephone. Jacobsen[81] found that direct costs for POC testing were higher than those for the standard laboratory test. Due to the perspective of the study, several cost items were omitted for the physicians' offices using laboratory testing, because the tests were done elsewhere, but were included for the offices doing the testing. These included costs for the blood specimen draw, test supplies, specimen testing, quality control, and equipment. From a health care system or societal perspective, this would bias the costs in favour of the laboratory testing approach. Despite higher direct costs at the physicians' offices, the study concluded that POC testing was economically favourable in this setting, because of the reimbursement opportunities available in the US health care system.

Lafata[77,78] did a full economic evaluation of three management alternatives for long-term anticoagulation therapy: usual care, anticoagulation clinic testing with CoaguChek, and patient self-testing with CoaguChek. The study results indicated that moving from usual care to anticoagulation clinic testing would avoid 1.7 thromboembolic events and 2.0 hemorrhagic events per 100 patients

over five years. Another 4.0 thromboembolic events and 0.8 hemorrhagic events could be avoided by moving to patient self-testing. From a health care system perspective, clinic testing was the most cost effective alternative. From a societal perspective (including patient and caregiver costs), patient self-testing was the most cost effective. The Lafata study was funded by Roche Diagnostics (formerly Boehringer Mannheim).

The setting for the Taborski study[9] was Germany, where patients' self-management of anticoagulation has become an established therapeutic method. Taking a government health care insurer perspective, the study concluded that overall therapy costs were significantly lower using self-management with CoaguChek compared with conventional laboratory methods.

5.2.1 Discussion

Of the six included economic studies, one examined ProTime.[17] This study was published in 1989, so more recent models of ProTime devices might give different performance results due to evolution in technology over time.[83] Two of the studies were full cost-effectiveness analyses,[77-79] and the De Solà-Morales study[79] did not look at incremental costs, but total costs. One study (producing two articles) was industry sponsored,[77,78] and another was partially sponsored.[17] Most of the studies were in a US setting,[17,77,78,80,81] with one from Spain[79] and one from Germany.[9] All the studies had the laboratory test as the comparator, but for the POC intervention some studies described one option, while others used a range of POC management strategies. The Cheung[80] and the Taborski[9] studies used a long time span of 10 years for depreciation of the POC devices. Study perspectives varied: one was societal,[17] two were both societal and health provider,[77,78,80] two were health provider,[9,79] and one was physician's clinic.[81] Despite these variations, all the studies found that a POC alternative was more favourable than the usual laboratory test. None of the studies was done in a Canadian setting, so we undertook a primary economic evaluation for Canada.

5.3 Primary Economic Evaluation: Methods

5.3.1 Types of Economic Evaluation

We took a decision analytic approach and modelled a cost utility analysis. Such an analysis was feasible for this report, because it allowed for comparisons among decision options. We developed the decision tree as a Markov model in Excel.

5.3.2 Target Population

Patients on long-term (>3 months) OAT formed the target population.

5.3.3 Comparators

The three decision options are:
- "usual care," consisting of the standard laboratory test with a venipuncture blood draw for an INR
- "anticoagulation (or thrombosis) clinic testing" using the POC monitor for INRs (the CoaguChek or the ProTime portable coagulometer) in an anticoagulation clinic (anticoagulation clinics generally consist of dedicated nursing or pharmacy staff who use explicit protocols and processes to monitor and adjust dosage among patients on warfarin therapy, and seek physician consultation;[77] while

anticoagulation clinics are established in several countries, such as the UK and the Netherlands;[70] they are not widely available in all geographic regions of Canada[8,69])

- "patient self-testing" using the POC monitor for INRs with patients phoning their results to an anticoagulation clinic or family doctor.

5.3.4 Perspective

We presented the model results from two perspectives. The health care provider perspective includes direct medical care costs to the health provider: costs associated with anticoagulation testing, monitoring, costs of adverse thromboembolic and hemorrhagic events, and with or without nursing home costs. The societal perspective includes the provider, plus costs incurred by patients and their caregivers. We included this perspective because time and travel costs can have a negative effect on patients and their caregivers, and can vary between the monitoring approaches.

5.3.5 Time horizon

The time horizon of the model was five years (the serviceable life of a POC monitor).

5.3.6 Modelling

An overview of the decision tree is presented in Figure 8. We followed an approach similar to that of Lafata.[77,78] For each OAT monitoring alternative, the time that patients spend in or outside the therapeutic range is estimated using results from the meta-analysis. There is an associated risk of first and recurrent thromboembolic and hemorrhagic events. Once an event occurs, patients are at risk of temporary and permanent disabilities. Among patients who become permanently disabled, there is a risk of discontinuing anticoagulation therapy and being at increased risk of subsequent thromboembolic events.

In the model, hypothetical cohorts of patients are followed for five years after starting warfarin therapy. With each one-year cycle of the model, patients move among five health states: no prior thromboembolic or hemorrhagic event; prior event, non-disabled, continuing therapy; prior event, permanently disabled, continuing therapy; prior event, permanently disabled, discontinued therapy; or dead.

Transitions among states were defined using event probabilities drawn from the meta-analysis and the published literature. Four elements of the model are estimates of the time spent in or outside the therapeutic range for the monitoring alternatives; the risk of incurring an adverse event associated with these times; the risk of disability after an adverse event; for those permanently disabled, the risk of discontinuing therapy.

For the baseline model, the estimated times spent in and outside the therapeutic range were obtained from our meta-analysis. We assumed that patients receiving usual care spent 39% of their time outside the therapeutic range; and for POC for anticoagulation clinic or self-testing, 31%. For the first thromboembolic event, from our meta-analysis, the event rate per 100 patient years for usual care was 1.55 for a fatal event and 3.9 for a non-fatal event. For the POC groups, it was 0.61 for fatal event and 1.53 for non-fatal. Similarly, event rates for recurrent thromboembolism, and first and recurrent hemorrhagic events, were obtained from our meta-analysis, and these were all recorded using the form in Appendix 3.

We assumed that 60% of all non-fatal thromboembolic events[84-88] and 10% of all non-fatal hemorrhagic events[89] resulted in permanent disability. Among some patients experiencing a disabling event, the risk associated with continued warfarin use most likely outweighs the potential benefits. As a result, the model allows for a proportion of those who were permanently disabled to discontinue warfarin therapy.[77] We assumed that 50% of patients would discontinue therapy after becoming permanently disabled from a thromboembolic event or a hemorrhagic event.[77] For individuals who discontinued therapy, the risk of a subsequent thromboembolic event was 17% and 1%.[90]

The assumptions of the model are:
- for the clinical effectiveness parameters, the values for POC testing in an anticoagulation clinic or for POC use by a patient during self-testing are assumed to be the same
- for CoaguChek and ProTime, the parameter values are assumed to be the same except for the cost of the device and peripheral equipment used with each test
- time for caregivers is assumed to be equal to time for the patient
- caregiver is assumed to travel with the patient.

Figure 8: Model overview
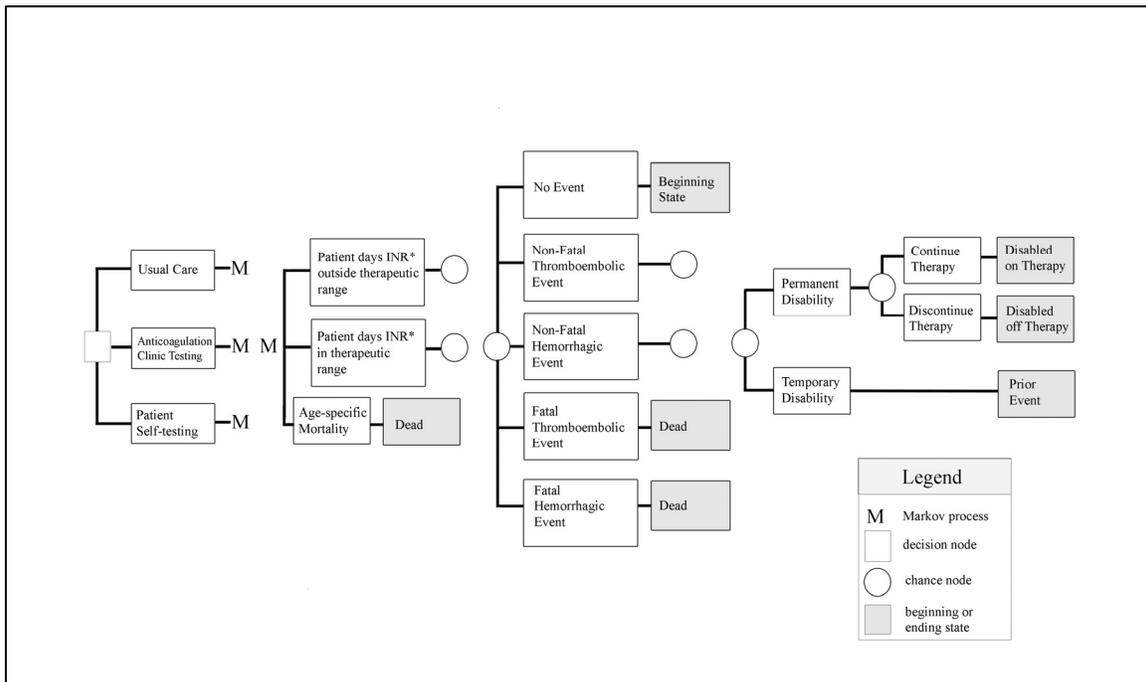
*INR=international normalized ratio.

5.3.7 Data considerations

The parameter values used in the model and their sources are listed in Appendix 12. Where possible, the parameter assumptions favour the standard laboratory test, and this would tend towards a conservative result. The model starts with a hypothetical population cohort of 100 patients on long-term warfarin therapy. The clinical-effectiveness parameters are mostly taken from our meta-analysis and supplemented by information from the published literature. The life-table data used come from Ontario (Appendix 13).

5.3.8 Valuing outcomes

We estimated the quality-adjusted life-years (QALYs) expected with each decision alternative, using data from several studies that have assigned utilities to the adverse events associated with anticoagulation therapy.[77,78,91-95] For patients who had a temporary disabling event, a utility of 0.75 was assigned for the 30 days after the event. For patients who had a permanently disabling event, a utility of 0.50 was assigned from the time of the event until death or the end of the five-year modelling period, whichever came first.

5.3.9 Resource use and costs

Table 5 shows annual anticoagulation monitoring costs for CoaguChek and ProTime with an estimated frequency of testing of 20 times per year for usual care (laboratory test) (PW, unpublished observations, 2006), 23 times per year for anticoagulation clinic testing[96] (with POC device), and 52 times per year for patient self-testing[97] (with POC device). Included in the direct medical care cost of anticoagulation monitoring were the costs of equipment, supplies, and staff (nurse and physician time). The physician's time was two minutes per consult for each strategy, but the frequency of consultation was reduced for an anticoagulation clinic (90% versus 10%).[17] Nursing time was 13 minutes per test for usual care, 15 minutes for each anticoagulation clinic test, and eight minutes for each self-test by a patient.[17] Time and travel costs were included in the costs of anticoagulation management faced by patients and their caregivers. We estimated that 30% of patients were accompanied by a caregiver for clinic-based testing, and 9% received help with home testing.[98] The cost parameters on resource utilization (Appendix 12) come from the published literature. The cost parameters on resource valuation (Appendix 12) come from Canadian sources on wages and prices, and all monetary amounts reflect 2005 dollars.

Table 5: Annual anticoagulation monitoring costs per patient				
Monitoring Strategy	**Number of Tests per Year**	**Costs to Health Care System**	**Costs to Patients and Caregivers**	**Total Costs**
Usual care	20	$322	$686	$1,008
Anticoagulation clinic with CoaguChek	23	$361	$862	$1,223
Self-testing of patient with CoaguChek	52	$807	$274	$1,081
Anticoagulation clinic with ProTime	23	$392	$862	$1,254

Table 6 shows the average cost for adverse events. Included were office visit, emergency department, and hospital administration costs.

Table 6: Average cost per adverse event		
	Thromboembolic Events	**Hemorrhagic Events**
Fatal	$3,208	$6,923
Non-fatal	$18,407	$14,805

5.3.10 Discount rate

All costs and health outcomes were discounted at a base rate of 5%, and a sensitivity analysis was carried out at a 3% and at a 0% rate, as indicated in the CADTH economic guidelines.[99]

5.3.11 Variability and uncertainty

A probabilistic sensitivity analysis was conducted using Crystal Ball. A one-way sensitivity analysis was conducted for the parameters of interest, such as the discount rate and price of the POC monitors and associated materials. A willingness to pay (WTP) per QALY of $50,000 was chosen because it is a commonly used threshold value.[100,101]

5.4 Primary Economic Evaluation: Results

5.4.1 Analysis and 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 7). For self-testing, the results were not cost effective from a health provider perspective at a WTP of $50,000, but cost saving from a societal perspective. Disaggregated results are presented in Appendix 16.

For ProTime (Table 8), from a health provider perspective, moving from usual care to POC devices again seems 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 7: Cost effectiveness ratios for CoaguChek			
Comparison	**Cost per QALY to Health Care Providers** (excluding nursing home)	**Cost per QALY to Health Care Providers** (including nursing home)	**Societal Cost per QALY***
Usual care to anticoagulation clinic testing	cost saving probability<$0=63%	cost saving probability<$0=99%	$10,808 probability<$50,000=86%
Usual care to self-testing by patient	$72,955 probability<$50,000=2%	$57,595 probability<$50,000=26%	cost saving probability<$0=52%

*Includes costs to patients and their caregivers; QALY=quality-adjusted life-year; probability taken from our probabilistic sensitivity analysis (Appendices 14 and 15).

We performed a probabilistic sensitivity analysis (Appendices 14 and 15) by simulating results for the cost-effectiveness ratios. The results are presented in Tables 7 and 8, indicating the probability of the ICER being <$50,000 or <$0 (cost saving).

To drop the cost per QALY <$50,000 for self-testing with CoaguChek (considering health provider costs, including nursing homes), the price per test of the reagent strips and lancets would need to drop from $6.92 to $6.02. Alternatively, the price of the CoaguChek monitor would need to drop from $995 to $768. Varying the rate of depreciation from the base rate of 5% to 3% and 0% did not significantly affect the results.

Table 8: Cost-effectiveness ratios for ProTime			
Comparison	Cost per QALY to Health Care Providers (excluding nursing home)	Cost per QALY to Health Care Providers (including nursing home)	Societal Cost per QALY*
Usual care to anticoagulation clinic testing	$2,437 probability<$50,000=100%	cost saving probability<$0=94%	$15,966 probability<50,000=82%

*Includes costs to patients and their caregivers; QALY=quality-adjusted life-year; probability taken from our probabilistic sensitivity analysis (Appendices 14 and 15).

5.4.2 Discussion

The economic analysis suggests that from a health care provider perspective, CoaguChek and ProTime, when used in an anticoagulation clinic setting, have potential advantages over usual care. For CoaguChek, our analysis suggests that moving from usual care to using POC devices in an anticoagulation clinic is cost saving. Moving from usual care to self-testing with POC devices falls outside the range of what is usually considered to be cost effective in terms of cost per QALY.

From a societal perspective, the cost effectiveness ratios are favourable and are cost saving or cost effective. CoaguChek is available for self-testing by patients in Canada, while ProTime is not. In a home setting, CoaguChek falls outside the limits of what is generally considered to be cost effective from a health provider perspective. When a societal perspective is used, including travel and time costs for patients and caregivers, CoaguChek for self-testing seems to be cost saving.

Overall, the best results in the economic analysis were obtained for the case of CoaguChek in an anticoagulation clinic with a health provider perspective. The economic results must be interpreted in the proper clinical context. Also, our analysis focused on a comparison of the clinical outcomes from therapy, rather than comparisons of diagnostic accuracy. Some guidelines for health providers note that INR values outside a therapeutic range of 2.0 to 3.0 obtained from POC devices can show bias when compared to plasma-based INR results obtained on laboratory instruments. POC devices predominantly overestimate, but they can go in either direction.[102] Some researchers have recommended periodic internal or external accuracy checks to ensure that results are reliable.[35,65,102] If self-testing is considered, informed decisions need to be made at the individual health provider and patient level to ensure that appropriate candidates are selected.

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 analyzed POC device use in two settings: anticoagulation clinics and patient self-testing in homes; other settings are also possible, for example, the family doctor's office, pharmacies (a review of in-hospital pharmacy-managed anticoagulation concluded that increased pharmacist involvement could enhance the quality of patient care[103]), or a home-care nurse in settings where patients are housebound

- our analysis looked at self-testing by patients; another possible management strategy would have patients also managing their dosage adjustments.[104]

The results of our primary economic study are generally consistent with those in the literature. A study was reported in the *Canadian Medical Association Journal*, but it was too recent to include it in our review of economic studies.[105] This cost-utility analysis by Regier *et al.* compared the cost effectiveness of self-managed versus physician-managed OAT. It concluded that from a health care payer perspective, moving from physician management with the laboratory test to self-management with CoaguChek would cost $14,129 per additional QALY. The Regier patient group is narrower: it only included atrial fibrillation or mechanical heart valve patients, while ours includes all cardiac or thrombotic patients on long-term OAT. Also, their intervention was self-management with POC, including self-testing and self-dosing. Our interventions were POC in a clinic and POC self-testing (excluding self-dosing).

6 HEALTH SERVICES IMPACT

6.1 Population Impact

We estimate that there are 209,000 Canadians in publicly funded drug programs receiving OAT (Table 9) Because they could all potentially be tested using POC devices in clinic, home, or another setting, all of them could be affected if POC devices were more widely available. If the expected uptake of self-testing using a POC device is 24%,[46] that gives a potential market of 50,160 for self-testing. A lower bound of 16% uptake would give a potential market of 33,440.

Table 9: Number of long-term warfarin users in Canadian publicly funded drug programs	
Province, Territory, or Program	**Long-term Warfarin Users**
NIHB*	2,810
DND**	70
Newfoundland and Labrador	3,627
Prince Edward Island	818
Nova Scotia	6,925
New Brunswick	5,541
Quebec	45,095
Ontario	81,709
Manitoba	8,589
Saskatchewan	8,583
Alberta	19,557
British Columbia	25,313
Yukon	185
Northwest Territories	251
Nunavut	180
Total Canada	**209,253**

*NIHB=Non-insured Health Benefits Program, First Nations and Inuit Health Branch, Health Canada; **DND=Canadian Department of National Defence.

We arrived at the overall number of Canadians on OAT in publicly funded drug programs by estimating the number of beneficiaries of Canadian publicly funded drug plans who had their long-term warfarin regimen (defined as ≥3 months duration) reimbursed in fiscal year 2005-2006. (Warfarin forms the majority of OAT. Inhibitors of coagulation factor X_A and direct thrombin inhibitors are in clinical trials).[5] All warfarin brands available in Canada (Apo-Warfarin, Coumadin, Gen-Warfarin, Novo-Warfarin, and Taro-Warfarin) were considered, although some jurisdictions may not list them all or the dosage strengths available. Data for the Non-insured Health Benefits Program, Department of National Defense, British Columbia, Nova Scotia, New Brunswick, Newfoundland and Labrador, Saskatchewan, Manitoba, and Ontario were obtained from the health program providers. In some cases, the data provided did not differentiate long-term from overall warfarin usage, or whether patients were using a combination of warfarin products [drug identification number (DIN) categories are determined by dosage strength and brand], which had the potential for double counting. Double counting could result because patients switch from one brand to another, or from one strength to another, or patients take >1 strength of warfarin concomitantly.

Accordingly, we scaled back those numbers based on information obtained from the BC data, which did not have the double-counting problem: 66% of all warfarin users being long-term users and 77% of long-term individual DIN category users being unique users. Data for the other provinces and territories were extrapolated based on the data from British Columbia and scaled to the population of the province or territory.[106] Data on penitentiary inmates were excluded from the table.

6.2   Budget Impact

If the CoaguChek technology was adopted for widespread use in Canadian anticoagulation clinics, we estimate that the potential capital outlay for the monitors would be about $84,000 ($995.00 for the monitor, with one monitor per clinic, and 81 anticoagulation clinics). The annual consumables cost, for items such as cartridges and lancets would be about $8 million per year ($6.92 per test, 23 tests per year per patient, and 50,160 patients). Similarly, for ProTime technology, we estimate a $160,000 capital outlay ($1,895.00 for each monitor) and an annual cost of consumables of about $9.5 million per year ($8.25 per test, 23 tests per year per patient, and 50,160 patients).

If the CoaguChek technology was adopted for self-testing by patients, the potential capital outlay for the monitors would be about $50 million ($995.00 for the monitor and a population of 50,160). The lower bound with a population of 33,440 would be about $33.3 million for the capital outlay. The annual consumables cost would be about $18 million per year ($6.92 per test, 52 tests per year per patient, and 50,160 patients). Table 10 estimates the provincial or territorial capital budget impact and the annual consumables cost based on the proportion of the total Canadian population.[106]

6.3   Planning and Implementation Issues

The standard approach to managing OAT can be a costly and labour-intensive multi-stage process. Patients usually have blood drawn in a physician's office, at a local laboratory, or at a hospital. Samples may need to be transported to a testing laboratory, depending on where they are drawn. The results must be forwarded to a physician. It is then the physician's responsibility to inform the patient of the results and make any dose adjustment.[17] In northern and remote areas of Canada, many health centres do not have the capacity to perform the test, so they refer coagulation testing to the major centres. Guidelines may specify that a blood sample is good refrigerated for 24 hours unspun. After that, it may need to be separated, and the plasma sent frozen to be processed.

Because of their compactness, portability, speedy results, and relative ease of use, POC devices have the potential to facilitate this multi-stage process. They also have drawbacks for patients and health care professionals. These include the need for training (ongoing with staff turnover in health centres), and the need to make it easy for centres to collect samples and for patients who are self-testing to use the devices.

Province or Territory	CoaguChek Costs ($) Anticoagulation Clinic		CoaguChek Costs ($) Self-test		ProTime Costs Anticoagulation Clinic	
	Capital	Consumables	Capital	Consumables	Capital	Consumables
NL	1,278	126,662	791,062	286,367	2,433	151,007
PE	995*	34,018	212,387	76,911	1,895**	40,556
NS	2,329	230,714	1,442,071	521,614	4,436	275,056
NB	1,867	184,945	1,155,812	418,137	3,555	220,491
QC	18,951	1,877,219	11,733,571	4,244,146	36,093	2,238,013
ON	31,318	3,102,330	19,390,251	7,013,963	59,645	3,698,587
MB	2,928	290,144	1,812,978	655,976	5,577	345,908
SK	2,463	243,996	1,525,179	551,643	4,692	290,891
AB	8,218	814,122	5,088,036	1,840,623	15,651	970,593
BC	10,636	1,053,728	6,585,513	2,382,342	20,257	1,256,251
YT	995*	7,670	47,711	17,341	1,895**	9,144
NT	995*	10,471	66,178	23,674	1,895**	12,484
NU	995*	7,447	46,170	16,837	1,895**	8,879
Total Canada	**83,968**	**7,983,466**	**49,896,919**	**18,049,574**	**159,919**	**9,517,860**

Table 10: Budget Impact by Province or Territory, Capital Costs and Annual Cost of Consumables

*Capital cost for PE, YT, NT, and NU rounded up to one CoaguChek monitor. **Capital cost for PE, YT, NT, and NU rounded up to one ProTime monitor.

If POC devices are being considered for self-testing by patients, good candidates should have a willingness to learn, the incentive to perform the test as required, adequate motor skills to do so, sufficient cognitive abilities and memory, sufficient reading and writing skills, adequate eyesight to see the screen, or a willing caregiver who will take responsibility for monitoring. Patients must then be educated about anticoagulation and be trained in the use of the monitor.[107] A testing schedule can be given to the patient for recording results. Instructions can be reinforced at follow-up visits, with an opportunity for the patient to ask questions and express concerns.[108]

Different models for managing OAT are used in various countries. For example, a UK study[35] notes that self-testing and self-management are credible models for a significant minority of patients if supported by structured training and follow-up.

6.4 Ethical and Psychosocial Issues

6.4.1 Methods

Three reviewers (LM, KC, and AB) selected papers identified in the clinical review that would be relevant for a review of ethical and psychosocial issues relating to long-term OAT. Papers were included if they met the following criteria:

- study design: RCT
- population: adult patients undergoing long-term OAT
- intervention: anticoagulant monitoring with a POC device
- comparator: routine INR laboratory test
- outcome measures describing informed consent, service availability, knowledge and training, psychological impact, social and family context, effect of cognitive or physical factors on treatment eligibility.

We searched the included clinical studies for ethical and psychosocial content based on the data extraction form established a priori. In addition, three studies excluded from the clinical review were included because they covered these issues. Two had been excluded from the clinical review because they focused on QoL measures[49,60] and one because it focused on a training program.[46] Two reviewers (KC and PW) extracted information regarding ethical and psychosocial issues (Appendix 3).

6.4.2 Results

Fourteen articles met the criteria for ethical and psychosocial content.[34,46,49,53-55,59,60,62-65,67-69] Two[53,65] addressed the area of knowledge and training, two[55,60] addressed compliance, nine[46,49,54,63-65,67-69] addressed satisfaction, four[53,54,59,63] addressed anxiety, and three[59,60,62] addressed social issues associated with testing (Table 11).

A study by Shiach[64] found 98% of enrolled patients preferred POC testing at a community-based anticoagulation clinic versus standard testing at a hospital laboratory. A study by Claes[68] concluded that general practitioners in Belgium should be formally trained and supported in the supervision of OAT. Several studies found that knowledge and management of OAT by patients led to empowerment, convenience, and a desire to continue self-management,[46,53,63,65,69] but in some cases, increased anxiety.[53]

The Beyth[67] study was conducted in Cleveland OH and focused on prevention of major bleeding in older patients receiving warfarin. The POC intervention involved one-to-one patient training by a lay educator lasting 30 minutes to one hour, covering warfarin indications and interactions, signs and symptoms of bleeding, effective communication with health personnel, and how to self-monitor using the ProTime device. The mean age of patients was 75 years. Of the 163 patients who were randomly assigned to the POC intervention group, 19% declined to participate and 22% reverted to conventional monitoring. Of those who reverted, 20 had physical limitations, such as severe arthritis or decreased vision; 12 felt more comfortable with venipuncture; three stopped warfarin therapy during index hospitalization; and one was discharged to a nursing home that precluded the use of a POC. The 59% of the intervention group who continued with ProTime for the study period comprised 28% who practised self-monitoring and 31% who had the help of a caregiver such as a spouse, relative, or visiting nurse.

Table 11: Ethical and Psychosocial Results	
Article	**Key Points**
Beyth[67]	among PT users, half practised self-monitoring, and half had help of caregiver
Claes[68]	general practitioners should be supported in supervision of OAT
Cromheecke[54]	patients preferred self-management with CC over conventional treatment
Fitzmaurice[53]	management of OAT by patients can lead to anxiety and positive feelings such as empowerment
Fitzmaurice[55]	self-management with CC particularly effective for treating patients with poor INR control (population difficult to manage and at risk of adverse events)
Gadisseur[49]	self-monitoring at home with CC increased treatment satisfaction; self-management increased it, increasing self-efficacy, and decreased daily hassles
Khan[59]	with self-monitoring with CC, patient satisfaction mostly unchanged compared to standard care
Koertke[60]	all patients with indication for long-term OAT may be considered to be candidates for self-management with CC regardless of education level
Menendez-Jandula[62]	old age and low educational level not obstacles to CC use.
Murray[46]	standardization and dissemination of training needed for POC use
Sawicki[63]	when OAT based on self-monitoring and self-management with CC, most aspects of treatment-related QoL improve
Shiach[64]	98% of enrolled patients preferred CC at anticoagulation clinic to standard testing at hospital laboratory
Sidhu[65]	participation in OAT by patients offers convenience, and leads to empowerment and desire to continue self-management
Sunderji[69]	patients who used PT preferred to continue with that strategy

CC=CoaguChek; INR=international normalized ratio; OAT=oral anticoagulation therapy; POC=point of care; PT=ProTime; QoL=quality of life.

Other studies that focused on evaluating ethical and psychosocial outcomes all used CoaguChek as the intervention. Murray[46] reported on the effectiveness of a training program for self-management (SMART self-management of anticoagulation: a randomized trial) compared with routine care for long-term warfarin treatment. Patients were from 48 general practices in the West Midlands, UK. Training sessions for the self-management group were provided by nurses and were adapted from a German national program. The objective of the training was to ensure the patients had an understanding of oral anticoagulation and INR monitoring, that they or their caregivers were able to measure INR reliably with CoaguChek, and that they were able to interpret the INR in terms of the appropriate warfarin dose. Of 2,586 patients invited to participate, 608 (24%) did, and 1,978 (76%) declined. The authors thought that this could be an indicator of expected uptake for self-management because the study invited unselected patients to self-manage warfarin.

Of those agreeing to participate in Murray's study,[46] 281 patients were randomized to usual care, and 327 to self-management. Of the latter group, 85 (26%) did not complete the training, 67 excluded themselves, and 18 were excluded by the researchers. Of the 67 self-excluders, 54 were generally unhappy with the procedure, and 30 of the 54 said that they had difficulty obtaining sufficient capillary blood and placing the sample on the test strip. Of 327 patients, 242 (74%) passed the training assessment and started self-management, and of those, 212 (88%) completed 12 months of self-management. Participants who completed training were significantly younger (61 years versus 71 years) and more highly educated than those who did not. The study concluded that if self-management by patients is to become established, standardization and dissemination of training are needed.

The Gadisseur[49] study took place in the Netherlands, where a national network of specialized anticoagulation clinics is responsible for the management of OAT. Routine care for OAT patients in the Netherlands consists of monitoring in an anticoagulation clinic with the standard INR laboratory test. This QoL study was done in a larger study looking at anticoagulation treatment. In total, 720 patients were contacted, and 184 consented to participate. Patients were randomized to three treatment groups: routine care, weekly self-measurement of INR with the CoaguChek POC device at home, and weekly self-measurement and self-management with the POC device at home. After 26 weeks, general treatment satisfaction, measured using a QoL questionnaire, was high under routine care (5.11 on a scale of 1 to 6) and increased through self-monitoring (+0.19, p=0.10) and full self-management (+0.49, p=0.01). For full self-management, there was a significant increase in feelings of self-sufficiency (+0.32, p=0.014) and a significant decrease in the perception of daily difficulties (−0.31, p<0.01) and distress (−0.44, p<0.001).

The Cromheecke study[54] took place in the Netherlands. All 50 patients underwent a randomized cross-over comparison of oral anticoagulation self-management with a CoaguChek monitor and management at a specialized anticoagulation clinic using laboratory testing. Patients underwent a structured educational program on self-testing with a POC device and training on how to devise an oral anticoagulation dosing scheme. A patient satisfaction assessment showed that patients preferred self-management over conventional care. The questionnaire measured general treatment satisfaction, self-efficacy, daily worries, distress, and social issues. There were significant differences in all five categories of the questionnaire in favour of the self-management group. Of the 50 patients in the trial, one patient was unable to self-manage anticoagulation because of progressive visual impairment. This study was unable to establish a relationship between better control of anticoagulation and age, educational level, or indication for anticoagulation. Limiting factors for self-measurement with the CoaguChek were mainly physical, such as visual impairment. Contributing factors were ongoing training and counselling.

Sawicki[63] studied a structured teaching and self-management program for patients in Germany receiving OAT. The control group received usual care with blood drawn by the physician or the laboratory to determine the INR value. Of 179 patients who were enrolled in the study, 165 were followed for six months: 83 in the self-managed group and 82 in the control group. The self-managed group used the CoaguChek monitor and received three training sessions of 60 to 90 minutes. Outcomes included five categories of treatment-related quality of life (QoL) measures. Results were significantly higher in the intervention group compared to controls. The QoL categories were general treatment satisfaction, self-efficacy, strained social network, daily hassles, and distress. The authors noted that patients receiving OAT often worried about complications, dietary limitations, restrictions when travelling, frequent and sometimes difficult venous punctures, and regular visits to physicians and laboratories. The authors concluded that when OAT is based on self-monitoring and self-management, most aspects of treatment-related QoL improved.

Khan[59] studied the value of training older patients with unstable anticoagulation to self-monitor in the management of their warfarin therapy. This UK study involved patients ≥65 years old, with atrial fibrillation, and taking warfarin for >12 months. Of 249 eligible patients, 55 were excluded for such reasons as general frailty, poor hearing or eyesight, impairment of hand function due to disabling arthritis, stroke or tremor, dementia, or living in an institutional care facility that included use of a CoaguChek system. Of the remaining patients, 154 were approached for the intervention arm, and 69 declined because of fear of self-testing, fear of needles, or preference for usual care. Ten patients had difficulty with the technique and required the use of multiple strips to obtain a reading. One patient was unable to perform self-monitoring competently at home. Perceived health status and QoL were

assessed using the UK Short Form Health Survey (UKSF-36), the European Quality of Life questionnaire (EuroQol), and an instrument designed to measure QoL in anticoagulation patients. The intervention group used self-testing with CoaguChek, while the control group underwent standard laboratory testing. Both groups received the same training sessions regarding OAT. The authors concluded that QoL measurements and health beliefs about warfarin were mostly unchanged between the control and intervention groups. For both groups, the time in therapeutic range improved after the education program, and the authors further concluded that patient education regarding anticoagulation therapy could be cost effective and is worthy of more study.

The Koertke study[60] examined patients' compliance with INR self-management immediately after mechanical heart valve replacement, and the extent to which compliance is associated with education level. It was part of a single-centre clinical trial conducted in Germany (ESCAT Early Self-Controlled Anticoagulation Trial). Twelve hundred OAT patients were randomized to use the CoaguChek POC device in self-management or undergo conventional management by family practitioners. Data from the first 600 patients to complete the two-year follow-up were evaluated.

About 92% of the 305 patients randomized to undergo self-management were able to continue with that during follow-up. Another 25 patients (about 8%) who were trained in INR self-management did not continue and returned their coagulometers. The most frequently cited reasons were problems taking blood samples (30%), family practitioners who were opposed to INR self-management (21%), patients who trusted their practitioners more than themselves for INR management (21%), and difficulty in handling the coagulometer (16%). The study found a difference in therapeutic compliance based on education levels, but concluded that all patients with an indication for long-term OAT may be considered to be candidates for self-management, regardless of education.

6.4.3 Discussion

The review of clinical papers for ethical and psychosocial issues showed mixed results and some common trends. Most of the interventions in the included studies involved self-testing or self-management with POC devices at home, although there is evidence that patients prefer POC testing at an anticoagulation clinic to standard laboratory testing in a hospital.

Most of the QoL studies suggested that patients who continued with POC self-testing and self-management preferred this to the standard laboratory test. Some caveats appeared in the review. If self-testing or self-management with POC devices is to be used, care must be taken that the eligible patients have the required physical and cognitive abilities required for training and using the monitors and associated equipment. Many OAT patients, through self-exclusion or 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 a caregiver's assistance. A need for adequate training of health care professionals in the use of POC devices was also identified.

7   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.

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APPENDICES

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