# POINT-OF-CARE TESTING FOR ORAL ANTICOAGULANT MANAGEMENT WITH PORTABLE PROTHROMBIN TIME SYSTEMS

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# ABBREVIATIONS

| | |
|---|---|
| ACC | anticoagulation clinic |
| AF | atrial fibrillation |
| APTT or aPTT | activated partial thromboplastin time |
| ASA e.V. | German Association for Self-management of Oral Anticoagulation |
| CI | confidence interval |
| CVA | cerebrovascular accident |
| DVT | deep vein thrombosis |
| HCP | health care practitioner |
| INR | international normalized ratio |
| ITT | intention to treat |
| MHV | mechanical heart valve |
| OACs | oral anticoagulants |
| OAT | oral anticoagulation therapy |
| OR | odds ratio |
| PC | portable coagulometer |
| PE | pulmonary embolism |
| POC | point of care |
| POCT | point of care testing |
| PPTS | portable prothrombin time systems |
| PSM | patient self-management |
| PST | patient self-test |
| PT | prothrombin time |
| QALY | quality-adjusted life-year |
| QOL | quality of life |
| RBCs | red blood cells |
| RCT | randomized controlled trial |
| RR | relative risk |
| SMD | standard mean difference |
| TE | thromboembolism |
| TEE | thromboembolic event |
| TIA | transient ischemic attack |
| TP | thrombophlebitis |

# GLOSSARY

**International normalized ratio**: International unit that is used to indicate intensity of oral anticoagulation therapy and that is based on prothrombin time.

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

**Prothrombin time**: Clotting time of plasma.

**Self-management (also referred to as PSM)**: Trained patient uses POC device to do INR test, interprets results, and adjusts dosage of anticoagulant accordingly.

**Self-testing (also referred to as PST)**: 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.

# EXECUTIVE SUMMARY

**Background**

- Atrial fibrillation, venous thrombosis and thromboembolism are common diseases which require oral anticoagulant therapy (OAT).
- 37,000 Albertans are currently tested to optimize their OAT.
- The current gold-standard method for monitoring the international normalized ratio (INR) is laboratory testing of blood obtained by venepuncture.
- Patients may find testing to be time consuming and inconvenient.
- With the development of portable coagulometers it is now possible to measure INR outside the laboratory setting.

**Methods**

- We wished to evaluate the effectiveness of patient self-management (PSM), patient-self testing (PST) and point-of-care testing (POCT) by health care practitioners (HCPs) using portable coagulometers, compared to conventional laboratory testing.
- We identified 22 controlled trials (RCTs), 3 meta-analyses (MAs) and 4 health technology assessments (HTAs) comparing POC INR monitoring to usual care.
- When high variability between studies was noted, a number of study-variables were used in a meta-regression analysis.
- We developed a Markov model to evaluate the costs of PPTS from societal and health system perspectives.

**Results**

- Our quantitative analysis of effectiveness confirmed findings from previous MAs and HTA reports.

- Both the percentage of time spent and percentage of INR measurements in, the INR target range were significantly higher with PPTS than conventional laboratory-based INR testing.
- The POC testing and management of INR provides better INR control, resulting in fewer major complications, deaths and thromboembolic events for patients.
- The quality of life (QOL) measures reported in several trials suggest that patients prefer the PSM/PST method versus laboratory testing.

**Conclusions**

- POC testing is at least as effective as usual care in maintaining an INR in the target range.
- Only approximately 25 percent of OAT patients will be eligible for POC testing.
- The incidence of adverse events is lower in POC testing patients than in usual care patients.
- The use of POC devices should consider patient suitability, patient education and training, health system constraints, and affordability. The percentage of patients who would be eligible for POC testing is dependant on a variety of factors, including age, degree of independence and concurrent illnesses. Determining the actual mix of suitable patients in Alberta would require a field trial.
- The economic analysis performed showed that PPTS testing is cost-effective, with the lowest cost option depending on the mix of testing and payment scheme employed.

# 1 INTRODUCTION

## 1.1 Purpose of Assessment

To review the technology known as portable prothrombin time systems (PPTS) in the monitoring and management of oral anticoagulation therapy (OAT) for the purpose of considering its potential as a publicly funded health service in Alberta.

## 1.2 Intent of Report

1. To review the social and demographic factors relating to the provision of PPTS in the monitoring and management of oral anticoagulation therapy.
2. To review the effectiveness, efficacy and safety of PPTS in the monitoring and management of oral anticoagulation therapy.
3. To review the fiscal and economic factors relating to the provision of PPTS in the monitoring and management of oral anticoagulation therapy.

## 1.3 Research Questions

- What are the prevalence and incidence of patients requiring International Normalization Ratio (INR) monitoring and management of OAT?
- What are the conditions requiring INR monitoring and management of OAT?
- What are risk factors for requiring INR monitoring and management of OAT?
- What is the frequency of INR monitoring for patients requiring management of OAT?
- How do the findings vary by factors such as age, gender, medication, co-morbidity, and other relevant factors?
- What are the current options for INR monitoring and management of OAT?
- What is the current pattern of care?

- What are the trends in INR monitoring across Alberta, and in the use of PPTS for INR monitoring?
- What system supports in Alberta are in place for appropriate provision of INR monitoring, and for PPTS monitoring of INR?
- How do the findings vary by factors such as age, gender, co-morbidity and other relevant factors in Alberta?
- How accessible is INR monitoring, and PPTS monitoring of INR?
- How do the findings vary by factors such as age, gender and geographical location (urban versus rural)?
- What is/are the current/standard protocol(s) for monitoring INR and managing OAT in Alberta?
- How does the use of PPTS differ from the current/standard method(s) of monitoring INR?
- What does PPTS do differently compared to the current/standard testing procedure(s)?
- What are the relative effectiveness, efficacy and safety of PPTS compared to the current/standard method(s) for INR monitoring?
- What are the expected benefits of using PPTS to monitor INR, what are the risks, and do the benefits outweigh the risks?
- Does using PPTS compared to the current/standard method(s) of monitoring INR result in improved attainment/maintenance of therapeutic INR levels and quality of life?
- What are other relevant outcome measures for OAT management and how does PPTS compare with the current/standard procedure(s) with respect to these outcomes?
- Is the use of PPTS more effective/efficacious or safer in certain patients or patient groups, or for certain conditions?

- How do the findings vary by mode of service delivery (physician's office, community pharmacy, and patient self- monitoring/management in the home)?
- What is the cost-effectiveness of PPTS compared to current/standard procedures for INR monitoring and management of OAT?
- How do the findings vary by mode of service delivery (physician's office, community pharmacy, and patient self-testing/management in the home), and factors such as age, gender and co-morbidity?

# 2 BACKGROUND

## 2.1 Technology Definition

The current gold-standard method for monitoring the INR is laboratory testing of blood obtained by venepuncture, using a standardized thromboplastin. In our discussions with laboratory managers we learned that under the best circumstances, testing of INR under emergency conditions, involves a wait of up to one hour for the test results to be available.[1] Routine or standard tests are reported back to the physician within 24 hours as such samples tend to be batched at one of the larger laboratories. The third type of INR monitoring usually takes place in specialized anticoagulation hospital-based or clinic-based laboratories. Patients have to travel regularly to have blood drawn and tested, which may be time-consuming and inconvenient, and consequently, has a negative impact on treatment satisfaction and quality of life.[2] This is particularly pertinent to the large rural population in Alberta. Moreover, the burden on the health care system is increasing alongside the prevalence of conditions requiring long term OAT monitoring due to an ageing population.[1]

The development of portable coagulometers has made possible the measurement of INR outside the laboratory setting, either by a HCP or by the patient. All portable coagulometers

require a drop of blood (capillary blood, obtained by fingerstick or venous blood, obtained by venepuncture) applied on a disposable test strip. For all devices, an INR result is obtained within 3 minutes.[1]

These methods of INR monitoring are included in the definition of point of care (POC) or near patient testing. POC for INR testing eliminates the delay in waiting for the result to be processed by the hospital laboratory and reduces the subsequent delay in informing the patient of their dosing advice.[3] For some patients an appointment with their primary physician is necessary to discuss the dose modification, if any, required. The POC monitoring of INR, among other factors, may decrease the physicians' reluctance to use OAT in elderly patients with no contraindications for OAT.[4] Moreover, the option to use capillary blood instead of venous blood may improve compliance with INR testing. A randomized controlled trial (RCT) reported by Woods et al[5] concluded that patients prefer capillary versus venous INR determination. Further, the option to use capillary blood makes patient self-testing (PST) of INR and patient self-management (PSM) of OAT possible. PSM of OAT involves not only PST but also the adjustment of oral anticoagulant dosage by the patient. PSM offers increased patient empowerment to control their own therapy with a model similar to home glucose monitoring using a portable glucometer.[6]

## 2.2 Condition Definition

### *2.2.1 OAT Definition*

OAT is aimed at inhibiting activation of coagulation factors. The most widely used agents for OAT are vitamin K antagonists, such as warfarin or coumarin derivatives (acenoucoumarol or phenoprocoumon). The use of these drugs has proved to be very effective in preventing and treating thromboembolic events. For the province of Alberta we estimate that the prevalence of OAT is 990-1050 per 100,000 population. The incidence of

OAT is estimated to range between 62.5 to 37.7/100,000 population. (See Table 1) The therapeutic window of vitamin K antagonists is relatively narrow, which may lead to either ineffective inhibition of coagulation (and thrombotic complications as a consequence) or over anticoagulation (and hemorrhagic complications as a consequence).[7] The prothrombin time (PT), expressed as international normalized ratio (INR), is the best indicator of the intensity of anticoagulation. To prevent under-dosing (ineffective inhibition of coagulation) or over-dosing (over-anticoagulation) INR monitoring and drug dose-adjustment have to be performed regularly (every 3 to 5 weeks).[1]

The major side effect of OAT is the risk of bleeding, which is the result of over-anticoagulation (INR higher than 4.5). An INR lower than 2 in patients on OAT (ineffective anticoagulation) increases the risk of thromboembolic events.[8] The INR therapeutic range is determined by the condition the OAT was prescribed for. Generally, the INR therapeutic range with the lowest incidence of adverse events is between 2 and 3 INR units.[9] The dosage of anticoagulant needed to maintain the INR in the therapeutic range may vary from patient to patient, due to drug and diet interactions or genetic factors that may influence the effectiveness of the anticoagulation.[10]

### *2.2.2 Conditions for which long term OAT is indicated*

Long term OAT is manly indicated in patients with chronic atrial fibrillation, venous thromboembolism, coronary artery disease or a mechanical prosthetic heart valve.[1] In Appendix 1, we included a comprehensive list of conditions that require long term OAT (along with the ICD-10 codes for each condition).

Below we present a short description of the main conditions for which long term OAT is indicated.

*Atrial fibrillation (AF)* AF is the most common sustained arrhythmia. The incidence of AF increases with age such that >5% of the adult population over 70 will experience the arrhythmia. As many patients are asymptomatic with AF, it is anticipated that the overall incidence, particularly which noted in the elderly, may be more than double previously reported rates. It is marked by disorganized, rapid, and irregular atrial activation with irregular and rapid ventricular response. OAT is of particular importance in patients who have known risk factors for stroke associated with AF. Factors associated with the highest risk of stroke include a history of stroke, transient ischemic attack or systemic embolism, or the presence of rheumatic mitral stenosis. Other identified risk factors include age >65 years, history of congestive heart failure, diabetes mellitus, hypertension, Left Ventricle (LV) dysfunction, and evidence of marked left atrial enlargement (>5.0 cm). Chronic anticoagulation with warfarin targeting an INR between 2.0 and 3.0 is recommended in patients with persistent or frequent and long-lived paroxysmal AF and risk factors.[11]

It has been estimated that the incidence of AF in Canada is 200/100,000 population (Table 2).

*Venous thromboembolism (VTE)* VTE includes deep venous thrombosis (DVT) and pulmonary embolism (PE). DVT occurs about 3 times more often than PE. The incidence of DVT has varied from 39 to 117/100,000 population in America. The incidence of PE varies from 47-63/100,000 Americans. The major adverse outcome of DVT alone, without PE, is the development of postphlebitic syndrome, which occurs in more than half of patients with DVT. There is no effective medical therapy for this condition, which impairs quality of life and disables. Most patients describe chronic ankle and calf swelling, and aching, especially after prolonged standing. In its most severe form,

postphlebitic syndrome causes skin ulceration. PE can be fatal or can cause chronic thromboembolic pulmonary hypertension, with breathlessness at rest or with mild exertion. Patients with PE are more likely to suffer recurrent VTE than patients with DVT alone. The successful treatment of DVT and PE includes long term OAT. Warfarin is the main oral anticoagulant drug used for long term anticoagulation in patients with VTE. The target INR is usually 2.5, with a range of 2.0–3.0.[12]

*Mechanical heart valve (MHV)* All patients who have undergone replacement of any valve with a valve mechanical prosthesis are at risk of thromboembolic complications and must be maintained permanently on oral anticoagulants.[13] A recent study[14] suggests that for patients with a mechanical heart valve on a oral anticoagulant, an INR between 2.5 and 3.5 should be maintained. It has been suggested by the Heart and Stroke Foundation of Canada that there are 100,000 adults who had surgery during childhood to correct congenital defects, many of whom have had mechanical valve replacement.

*Coronary artery disease (CAD)* In CAD, especially after myocardial infarction (MI), the use of OAT has been controversial because of the relatively narrow "therapeutic window", necessitating close monitoring of the INR and individual dose adjustments.[15] Moderate intensity OAT, with or without aspirin, may be considered in patients with CAD and coexisting AF, large anterior MI, prosthetic heart valves, mural thrombi, or aspirin allergy.[16] The dosage should be aimed at maintaining an INR in the therapeutic range of 2.0–2.5 (3.0), with a target of 2.3 (2.5). When OAT is administered alone, the INR should be between 2.5 and 4.0, with a target of 3.0.[15]

### *2.2.3 Who should be considered for POCT?*

Using data drawn from AHW, it was estimated that 37,000 (2008) individual patients were identified as requiring OAT therapy. It has been suggested that approximately 25% of OAT

patients would be candidates for PST/PSM. Patients require visual acuity, manual dexterity and cognitive abilities to be selected. Another factor for PPTS consideration involves geography and patient motivation. When 800 Dutch patients were offered the chance to participate in PST/PSM trials only 25% accepted the opportunity, which may be due to the close proximity of testing facilities. Alberta, with a large rural population would likely have a different acceptance rate than Holland.

The Thrombosis Interest Group of Canada (TIGC) has published guidelines for the use of POC devices for PST/PSM. They recommend that patients selected for POC INR testing demonstrate good adherence to treatment and participate in three direct comparisons between POC and laboratory INR determination. Patients should also participate in a standardized educational program, the TIGC recommends KIDCLOT©. This program has been developed for children but can be utilized by adults as well. POC patients must have an ongoing relationship with an anticoagulation facility or a primary physician experienced in POC INR testing. Finally ongoing quality assurance programs, with testing every 6-12 months, is mandatory.[18]

### *2.2.4 Drugs used for OAT*

The oral anticoagulants are a class of pharmaceuticals that act by antagonizing the effects of vitamin K. The most common agents used in OAT are warfarin (Coumadin), acenocoumarol and phenprocoumon. In Canada, warfarin is the main drug used for OAT. Warfarin interferes with the hepatic synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and the natural anticoagulant proteins C and S. Warfarin has a very narrow therapeutic window, and managing OAT with warfarin must be coupled with close monitoring of INRs.

There are numerous drugs, herbal medicines and diets that may interfere with warfarin.[17] These interactions make the management of warfarin dosage very difficult, especially in multi-medicated elderly.

# 3 METHODOLOGY

## 3.1 Literature

### *3.1.1 Literature Search*

We searched the following electronic databases: MEDLINE (OVID), Cochrane Library (OVID), EMBASE (OVID), NHS Economic Evaluations Database (OVID), Health Technology Assessment Database - University of York (OVID), DARE Database of Reviews of Effects (OVID), EconLit (EBSCO). These databases were searched for RCTs, systematic reviews/meta-analyses (MAs) and HTA reports published between 1989 and 2009. Observational studies, case reports, animal and in vitro studies, duplicate publications, preliminary reports of data later 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 and with greater than 20% loss to follow-up were excluded. The Search Strategy is presented in Appendix 2. We also searched the gray literature and the reference lists of the studies included in our review. A list of the gray literature sources is presented in Appendix 3. The Expert Advisory Group (EAG) provided expert opinion on the search strategy for this review. No hand searching was required.

### *3.1.2 Selection of Literature*

The titles and abstracts yielded by our search of the literature were reviewed by two independent reviewers and a decision regarding the papers we included in our review was reached by discussion and consensus, based on our inclusion/exclusion criteria. These criteria

have been adapted from the CADTH report on PPTS[18] and were updated after consultation with the members of the EAG formed for this review. A full text review of the papers retrieved after the abstract and title review was conducted using the same procedure. We selected studies including patients on oral anticoagulant therapy (OAT) requiring INR monitoring for at least three months (long term OAT) after the start of the trial and receiving POC monitoring (including POC testing at an anticoagulation clinic, PST self-testing by the patient, PSM self-testing plus self-management and control, or any other POC management strategy). For RCTs, the usual care comparator was venepuncture blood draw for an INR laboratory test and management provided by an anticoagulation clinic or individual practitioner. We included studies that reported on at least one of the following: percentage of time in INR target range, percentage of INR measurements in INR target range, rates of major hemorrhage, major thromboembolic event rates, and quality of life measurements.

### *3.1.3 Results of Literature Search*

A total of 2105 titles and abstracts of potential RCTs, MAs, HTA reports and economic evaluations were retrieved. 52 articles were selected for full text review. In addition, we found four HTA reports. The full CADTH[18] and MSAC[19] and UK[20] reports are available on the internet, the fourth was produced by a private HTA consulting company[21]. We contacted this company, but the report was no longer available because it was older than 2 years. A fifth very recent (9/2009) HTA report[22] was retrieved after the gray literature search and we included it in our literature review. The completeness of the RCT search was confirmed by comparison with the RCTs identified from the most recent HTA. Our review identified 24 studies[23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46] describing 22 original RCTs, 3 MAs[47,48,8] and 4 HTA reports.[18,19,22,20] Economic articles were reviewed by one health

economist. Included in our economic literature review were papers fulfilling the following criteria:

1) Providing sufficient data to contribute to an economic evaluation

2) Analyzing an adult population of patients undergoing long-term OAT

3) Using as an intervention a POC device for testing INR.

4) Using as a comparison a standard laboratory-based testing routine

#### 3.1.4 Data Extraction

Data extraction was performed using a form developed by our team. We extracted the following information: single/multiple site RCT, inclusion/exclusion criteria, intervention/control groups description, device used in the intervention, age of the sample, gender of the sample, sample used in the analysis, loss to follow-up, randomization method, blinding (patients, outcome assessors, treatment providers), target INR, drug used for oral anticoagulation, indications for oral anticoagulation, follow-up period, outcomes and statistical analysis, results at follow-up points, complications and conclusion.

#### 3.1.5 Quality of studies

The quality of RCT studies included in this report was assessed using the CONSORT statement checklist,[49] presented in Appendix 4. The overall quality of a study was classified as high, moderate or low, based on GRADE criteria,[50] included in Appendix 5.

### 3.2 Social Systems and Demographics (S) Approach to Analysis

We included in this section information from published articles retrieved through our literature search, medical specialty books and experts that were consulted for this report. To estimate the potential demand for PPTS in Alberta, we developed a list of conditions requiring long term OAT (reviewed by members of EAG). This list, along with the ICD-10 diagnostic codes, is presented in Appendix 1.

## 3.3 Technology Effects and Effectiveness (T) Approach to Analysis

The RCT studies evaluating the efficacy and effectiveness of INR testing using a portable device and anticoagulation management were analyzed quantitatively and qualitatively.

The clinical outcomes of interest were the mean percentage of time spent in INR target range, the mean percentage of INR measurements in the target range and adverse events odds ratio (OR).

A meta-analysis was performed using published data on the outcomes of interest. We calculated pooled standardized mean differences between intervention and control groups for the percentage of time spent in INR target range and the percentage of INR measurements in the INR target range. We also calculated a summary OR for the adverse events (major hemorrhagic events and major thromboembolic events). A chi-square heterogeneity test was performed to reveal the presence of between-study variance. We compiled a list of study variables that might account for the heterogeneity: patient self management (PSM), patient self-testing (PST), point of care testing (POC), drug used for OAT (warfarin or other), patient education in the control group, indications for OAT in the sample, age of the sample (selected elderly or all ages), gender of the sample. These variables were tested in a meta-regression analysis. The meta-analysis and meta-regression were performed using the *meta* and, respectively, *metareg* packages in STATA version 9.0.[51]

## 3.4 Economic (E) Approach to Analysis

A qualitative review of full economic evaluations from government agencies, and one article that provides a foundation for several of the reports (Lafata et al.[52]), were used as background for the economic approach. As a result, this report undertakes a cost-utility

analysis. By analyzing utility levels, patient quality of life can be better measured, as opposed to analyzing just adverse events avoided (or added) by switching between different anticoagulation therapy options. This will also allow for comparability across the previous literature, specifically the Lafata et al.[52], the Canadian Agency for Drugs and Technologies in Health [CADTH][18], and The Ontario Medical Advisory Secretariat[22] studies. A Markov decision tree model was developed using Matlab 6.5. Four comparators are used, as mentioned in Section 2.1:

1) Laboratory-based testing – this is the current standard of care in Alberta.

2) POC Clinic testing – A POC device is used at a physician's office, or a pharmacist's office.

3) Patient self testing (PST) – a POC device is used at a patient's home, and testing results phoned into a physician or clinic.

4) Patient self management (PSM) – a POC device is used at a patient's home, with self-managing of warfarin or other anticoagulation doses based on the self-test.

The analysis included both the healthcare perspective – costs borne by the province – and society. Societal costs will include travel time to and from testing sites, as well as lost wages due to time testing for caregivers and patients. Medical system costs will include physician consultations, health care practitioner costs, such as time spent training patients, potential adverse events resulting from being outside the normal INR range, and the cost of the POC devices, consumables, monitoring and management. Sensitivity analyses will be completed in which the costs of the POC devices and/or the consumables for testing are borne by the medical system or by the consumer.

The timeframe for economic analysis will be equivalent to the serviceable life of the POC device, which is 5 years. To determine the economic impact, a Markov decision tree model was constructed. The model follows what was previously done in the Lafata[52] and CADTH

reports.[18] The model begins with patients who need OAT. The hypothetical cohort of patients is followed for 5 years – each simulation of the model represents one year, and is calculated a total of five times. Patients move through varying health states, depending on transition probabilities between those states. These probabilities were drawn from previous literature, and are listed, along with other parameter values, in Appendix 6.

Patients who entered the model are assumed to need long-term OAT. Sensitivity analyses included will vary the percentage of patients using each of the four methods of treatment noted above. Patients then receive a Markov draw determining their INR level: above normal, normal, or below normal. Given those ranges, there is potential for an adverse event happening – there could be a bleeding event or a thromboembolic event. Although patients with high INR levels have a higher probability of having a bleeding event, there is also a nonzero probability that these patients could suffer a thromboembolic event. Likewise, patients with low INR levels have a higher probability of having a thromboembolic event, but there is a nonzero probability that these patients could suffer a bleeding event. Individuals with normal INR levels may also have a thromboembolic or bleeding event occur.

These adverse events may be classified as minor events or major events, depending on severity level. In-hospital visits due to the conditions would be classified as a major event. These will have different hospitalization costs depending on the level of the event. Both minor and major events have probabilities of death or permanent injury, which would result in a patient dropping from the cohort. If death does not occur, then either a temporary injury (30 days after the event) or a permanent injury (for the remaining time in the cohort) will result. If a permanent injury results, there will be a probability assigned to the patient not continuing with OAT. A temporary injury, as well as those in the cohort with no injuries, and

those with permanent injuries who continue with OAT, will then cycle back into the model for the next year.

Outcomes are valued using utility levels. A person who is injury free will have higher quality of life than a person who is temporarily or permanently injured due to an adverse event. As in previous literature (for instance, the CADTH[18] and the Ontario Medical Advisory Secretariat[22] reports), temporary disability is given a utility level of 0.75, and permanent disability is given a utility level of 0.5. Those with no disabilities are given a utility level of 1, and those who die are given utility of 0 for the current and future year cycles.

Discounting is done at 5% annually, as recommended by CADTH guidelines.[18] Several sensitivity analyses were done, and will be noted in the results section. These include having the patient incur the cost of the POC device, having a higher probability of below-normal INR due to a mechanical heart valve, having lower compliance due to living in a rural area, and having lower compliance due to being older.

# 4 SOCIAL SYSTEMS AND DEMOGRAPHICS

## 4.1 Patterns of the Condition

### *4.1.1 Burden of the Condition*

As mentioned in Chapter 2.2.2, OAT is indicated for the prevention of embolism in patients with AF or prosthetic heart valves, for the primary prevention of acute myocardial infarction (MI) in patients with peripheral arterial disease, and for the prevention of stroke, recurrent infarction, or death in patients with acute MI. The incidence of these conditions rises with age, especially in patients 60 years or older.[53] Consequently, the need for OAT control is expected to increase in the future, along with the increase in the percentage of seniors in the population. The demographics of OAT patients in Alberta as well as the top ten

diagnosis cited by physicians in Alberta are summarized in Table 3. For prevalence of INR testing in Alberta, see Table 1.

Out-of-range INR levels are a serious consideration in the management of patients on OAT. While INR levels above the target range can cause bleeding, INRs below the target range can increase the risk of thromboembolic events. Seniors at high risk for bleeding complications, benefit the most from adequate coagulation because of their substantially increased thrombotic risk.[54]

**Risks of supra-therapeutic INRs: bleeding complications**

The major complication of OAT therapy is bleeding. Clinical trial data indicate that the intensity of OAT is the most important factor for hemorrhage from any site. Additionally, there is a strong relationship between the intensity of OAT and the risk of bleeding reported in patients with DVT, ischemic stroke, and AF. Several studies have found that INRs above therapeutic level are associated with a fourfold increase in bleeding complications.[54]

The risk factors for bleeding included in the black box warning on the FDA-approved warfarin label are: high intensity of anticoagulation (INR>4), age 65 or older, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs, and a prolonged duration of warfarin therapy.

Bleeding complications associated with OAT have also been related to mortality. Studies showed that an increase of 1 INR unit above 2.5 doubled the risk of death from cerebral bleeding and from any cause. Intracranial hemorrhages are the most feared complication of vitamin K antagonist treatment.[54]

**Risks of sub-therapeutic INRs: thromboembolic complications**

Sub-therapeutic INRs are associated with a significantly higher risk (3.31 times) of a major thromboembolic complication. A sub-therapeutic INR has also been linked with an increased risk of stroke. The importance of adequate anticoagulation, in terms of both intensity and duration, has been shown in patients undergoing rate control or rhythm control for AF.

In addition to primary embolic events, poor quality of anticoagulant control in the first 3 months after an acute unprovoked VTE is shown to be a risk factor for late recurrence.[54]

### *4.1.2 Population Dynamics*

Prevalence and incidence are not measures that have been closely estimated in the previous literature. The CADTH Report[18] extrapolated data for Alberta based on the number of warfarin users (for longer than 3 months) in British Columbia, arriving at a total of 19,557 long-term users for 2005-2006. With an approximate 11% growth in Alberta's population between 2005 and 2009, scaling this number upwards would result in an estimate (for 2009) of 21,708 long-term users. The Ontario Medical Advisory Secretariat[22] uses a clinical expert estimate of 1% of the population receiving OAT for prophylaxis and/or treatment of thrombosis. Thus, using 2009 population estimates for Alberta, results in an estimate of 35,580 long-term users.

Analyzing potential new cases – incidence – will prove to be challenging. The main conditions leading to the need for OAT include:

- Atrial fibrillation (ICD10: I48)
- Prosthetic heart valve (ICD10: Z95.2)
- Pulmonary embolism (ICD10: I26)
- Phlebitis and thromobophlebitis of lower extremities (ICD10: I80.3)

These codes are rough measurements, as for instance, the prosthetic heart valve includes more than just mechanical valves, which will result in overestimation. Not everyone with

these conditions will necessarily need OAT. Hence, using prevalence or incidence to forecast future demand will be imprecise, as noted below.

Using Alberta Health and Wellness observations, patient characteristics can be analyzed for Alberta. These include patients who have a record for physician management of anticoagulation therapy (03.01N) or a record for coagulation defects (ICD-9 diagnostic code 286.*, which matched ICD-10 diagnostic codes D65-D68). From this, approximate incidence and prevalence rates can be calculated for Alberta. Using observations from 2007 and 2008, Table 1 displays approximate prevalence (the proportion of the population needing coagulation treatment) and incidence (the rate of the population between 2006-07 and 2007-08 that need treatment for that year) specifically for Alberta. This leads to an estimate of the potential population for PPTS treatment in Alberta.

There are several precautions that must be accounted for when interpreting this data. The 03.01N billing code was recently introduced, which is why the last complete years of data were taken for analysis. This could also explain the drop in the incidence rate, between 2007 and 2008, as more physicians began to use the new billing code by this time.

The potential population of those needing OAT, based on the four conditions in Table 1, is complicated to calculate. A partial review of the literature gives a wide-range of incidence rates, as shown in Table 2. These numbers are subject to measurement error, and in the case of prosthetic heart valves, are overestimated since mechanical valves alone are not included. All of these are potential risk factors contributing to the need for anticoagulation therapies. Alberta and Canadian specific statistics on the incidence and prevalence of the main conditions leading to OAT were not found. Most estimates cited were based on a population with a specific medical condition, rather than the entire population. The uncertainty in these numbers, with no published literature stating the probabilities of these risk factors – either

alone or in combination – leading to anticoagulation treatment, will result in these numbers not being used in the healthcare system-wide estimation of costs. Based on these figures, the CADTH[18] prevalence (.6% of the population)*, the prevalence from the Ontario[22] estimates (1% of the population), and the estimated number of unique long-term anticoagulation patients in Alberta (37,529 from Table 3), plus 1% of that amount to account for potential measurement error (for a total of 1.1% of the population), is used for analysis.

From the Alberta data, age, location, gender, and underlying diagnoses of the patients undergoing anticoagulation therapy can be estimated. These estimates are given in Table 3. Approximately 64% of patients are from either Calgary or Edmonton. Half of the patients are above 70 years of age. The usage of treatment between males and females is not significantly different, so gender will not be used in further sensitivity analyses. Underlying diagnoses are also given in Table 3, though since these diagnosis codes come from the physician fee-for-service claim database, some caution should be used in assuming the diagnoses represent true underlying conditions.

A variety of other population information was searched for but we were unsuccessful in retrieving any credible data. Specifically, any information relating to how the prevalence and incidence rates varied by patient characteristics (i.e. age, gender, co-morbidities, medications etc.) was sought but was not available. There was also no data on frequency and accessibility to PPTS monitoring and how this may have varied by patient characteristics.

* The .6% of the population is matched by a study from Sweden, which found a prevalence of .67% and an incidence of .17% for warfarin treatment, with chronic atrial fibrillation as the primary diagnosis [Nilsson et al. (2003)].

## 4.2 Patterns of Care

### *4.2.1 Current Standard Procedures*

In Alberta, the current standard for determination of a patient's INR, on long term OAT, is a laboratory-based procedure. The patient regularly (more often at the beginning of therapy, approximately once a month after the optimum dosage has been established) visits a hospital or a community-based setting to provide venous blood samples, obtained by venepuncture. The venepuncture is provided by a trained healthcare provider and the blood sample is sent to a laboratory. Further, the INR determination is sent by the laboratory to the physician who is managing the patient. This step causes a delay to occur, ranging from 1 hour to 24 hours depending on the location (emergency department testing or community routine testing), between the collection of blood samples and the availability of results. Additionally, because the physician contacts the patient, and recommends adjustments in the OAT dosage (if the INR results are out of target range), another time delay occurs between the collection of the blood sample and the actual dosage adjustment.

Most frequently, patients on long-term OAT are managed by their primary care physician. Another option for these patients is to attend anticoagulation clinics (ACC), which coordinate and optimize the delivery of OAT and INR testing. There are five major anticoagulation centers in Alberta (information available at http://www.acforum.org/clinics_canada.htm), each of them coordinating one or more ACCs programs:

- Red Deer, Alberta: Red Deer Regional Hospital Centre
- Edmonton, Alberta: University of Alberta Anticoagulation Management Service (AMS)
- Calgary, Alberta: Peter Lougheed Centre, Foothills Centre
- Medicine Hat, Alberta: Medicine Hat Regional Hospital ACM

- Edmonton, Alberta: Pediatric Thrombosis Team, University of Alberta Hospital

A recently published report[55] evaluated the impact of care at the University of Alberta Anticoagulation Management Service (AMS) on clinical events. This clinic is managed by pharmacists, using a core group of physicians as consultants. The adequacy of anticoagulant control was significantly greater when anticoagulation management was offered at the clinic compared with the period before referral. Specifically, patients were in the target INR range 66.5% versus 48.8% of the time, respectively ($p < 0.0001$). The relative risk of a thromboembolic event before referral to the clinic was significantly higher ($p < 0.0001$), while the relative risk of a hemorrhagic event before referral to the clinic was similar ($p = 0.25$). A telephone survey of a random sample of 75 patients receiving care from the ambulatory AMS, for at least four months, showed that while most patients preferred to remain under AMS care, the majority would accept alternate strategies including self-management.[56]

### *4.2.2 Procedure Overview and Trends*

Portable INR testing devices allow testing at the POC, eliminating travel time for the patient (in-home testing) and/or the time delay between the collection of the sample and the availability of the results (in-home testing, testing by a health care professional in a clinic or pharmacy). Moreover, these devices require only capillary whole blood, which may be obtained by fingerstick. This procedure can be performed by the patient and is better tolerated than venepuncture, which can only be performed by a trained health care professional. Portable INR testing devices measure clotting time mediated by thromboplastin, which is then converted by a microprocessor to a plasma PT equivalent and expressed as INR.[57]

Portable INR testing devices were introduced into the market in five stages.[57] The first was based on the Protime 1000 testing device (Biotrack Inc) and is no longer available. The second included the CoaguCheck devices (Roche Diagnostics), which are licensed in Canada

(Table 4). The third was the ProTime device (International Technidyne Corp), which is also licensed in Canada (Table 4). The fourth was developed by Avocet Inc. (AvoSure PT) and is not currently licensed in Canada. Finally the latest device, INRatio (Hemosense Inc) was introduced; it is also licensed in Canada (Table 4).

#### *4.2.3 Access to Technology in Alberta*

There are four portable INR testing devices commercialized in Alberta: the CoaguCheck XS, CoguCheck XS plus, ProTime and INRatio. These devices are licensed in Canada (information available at http://www.hc-sc.gc.ca/dhp-mps/md-im/licen/mdlic-eng.php). Details on pricing and characteristics of these devices are presented in Table 4.

# 5 TECHNOLOGY EFFECTS AND EFFECTIVENESS

## 5.1 Current Context

### *5.1.1 New Technology*

Portable devices are now available for monitoring the INR values of patients on OAT, using a sample of whole blood. The drop of blood obtained by fingerstick is placed on a test strip, which is inserted into the monitor. The results are then displayed on-screen in up to 5 minutes.

There are four INR-monitoring portable devices available in Canada. Details of the operating characteristics of these devices are summarized in Table 4.

Not all OAT requires INR monitoring. Two non-vitamin K antagonists are on the market in Alberta (dabigatran and rivaroxaban). These new medications may have a significant role to play in OAT in the future.

### 5.1.2 Procedural Comparison

One of the differences between INR testing using portable devices and laboratory testing is that portable devices permit INR results to be determined immediately without a visit to a laboratory. This reduces the time delay between blood collection and the adjustment of the warfarin dosage. Moreover, with portable devices there is no need for venepuncture (except for quality checks done every 6 months in some clinics), which has to be performed by a trained health professional and creates discomfort for many patients. Another difference is related to the frequency of monitoring. A previous study showed that up to 60% of patients can be expected to stay in their INR target range if their INRs are monitored monthly, up to 85% if monitored weekly and up to 92% if monitored every 3 days.[58] Usually, laboratory INR monitoring is restricted to once a month. Increasing the frequency of laboratory monitoring to every 3 days would create tremendous logistic and costs issues. On the other hand, INR self-monitoring (PST) by patients using portable devices allows for a close to optimal monitoring frequency.

Several studies have evaluated the accuracy of measurement by calculating the correlation coefficient between INRs reported by conventional laboratories and portable devices. The correlation coefficients reported in the literature vary between 0.86 and 0.96 for CoaguCheck, 0.9 and 0.92 for ProTime, and 0.95 and 0.98 for INRatio devices.[57]

### 5.1.3 Health Canada Approval

The CoaguChek S and XS Systems, the ProTime Microcoagulation System, and the INRatio Monitor are licensed by Health Canada as Class 3 medical devices for the quantitative determination of prothrombin time from fingerstick whole blood or untreated venous whole blood and are intended for the management of patients treated with oral anticoagulants. The

CoaguCheck S (no longer available on the market) and the ProTime devices were licensed in 1999, followed by CoaguCheck XS in 2006, and CoaguCheck XS Plus and INRatio in 2007.

## 5.2 Effects/Effectiveness

### *5.2.1 Safety*

The INR-monitoring portable devices are safe to be used by health care professionals or patients trained to use them. The Association of Self Management of Anticoagulation (ASA) based in Germany organizes seminars to train the trainers (physicians and nurses). These seminars cover the theoretical and pharmaceutical aspects of anticoagulation, use of the equipment and a practical session. The trainers who completed these seminars qualify to lead patients through the structured teaching and self management program (SPOG), a course that includes: basic information on blood coagulation, theoretical principles of individual coagulation/drug interactions with oral anticoagulants, practical information on coagulation monitoring with INR-monitoring devices, evaluation of measurements and, if patient is on PSM, dose adjustment, signs of bleeding events (overdose) and thromboembolic events (under dose), information on frequency of INR determination, keeping a patient diary/quality control record keeping, and travel, nutrition, endocarditis prophylaxis, intramuscular injections etc.[59] Elements of these programs were used in designing educational programs for patients and health care professionals in the RCT studies reviewed in this report. At this point in time a formal training program is not in place for the entire province of Alberta.

The main safety concerns regarding the inappropriate use of INR-monitoring portable devices are represented by the risk of bleeding and thromboembolic events. Fourteen RCTs reviewed reported the number of these adverse effects in the intervention (PST, PSM or POC group) and control groups.

### 5.2.2 *Efficacy/Effectiveness*

#### 5.2.2.1 *Qualitative assessment*

**RCT studies**

We reviewed 24 studies reporting on 22 RCTs. From these, 6 were rated high quality, 10 moderate quality, 5 low quality and 1 very low quality. A sensitivity analysis using study quality as a variable demonstrated that this was an important factor in explaining the variability in the analysis.

Details on the follow-up duration, sample characteristics, study groups, main indication(s) for OAT, OAT drug(s), adverse events, outcomes and quality assessment are summarized in Table 5.

There was also variability between studies related to the patient eligibility criteria, baseline patient characteristics, follow-up duration, main indications for OAT, the amount of education control patients received at the beginning of the study and quality of the studies.

Most of the studies reviewed reported no information on the patients' baseline INR values at the beginning of the study, which makes it difficult to evaluate the adequacy of their INR management at baseline. Only one study[44] provided baseline INR values.

The methods used by the authors of the RCTs reviewed were heterogeneous. There was a lack of consistency in the definitions and reporting of clinical outcomes related to anticoagulation control, definitions and reporting of adverse events. Some studies reported anticoagulation control as the time in the therapeutic range, while others reported values in the therapeutic range or proportion of patients in the therapeutic range.

In most studies, the patients in the intervention group performed more frequent INR testing, which may have overestimated the effect of the PSM/PST intervention.

**Meta-analyses**

We included in this review 3 MAs comparing the efficacy of anticoagulation self-testing and/or self-management to routine care. Of note the most recent MA was published in 2007 and the other two in 2006. We summarize below the findings of these studies. Overall, the meta-analyses reviewed varied in statistical power to detect small but significant differences. No obvious flaws were determined by review of the meta-analyses.

*Douketis et al*[47] (2006) This study, published in 2006, does not report details on the methods used to select and review the papers included in the meta-analysis, or on the quality of the papers included. The outcomes reviewed were major and minor complications (hemorrhages and thromboembolic events), mortality, proportion of INRs within the therapeutic range, frequency of INR testing and feasibility of self-monitoring (PST). The authors analyzed the results from 14 RCTs and concluded that self-testing was associated with significant reductions in thromboembolic events and major hemorrhages, while self-management was associated with significantly less thromboembolic events and mortality, but not hemorrhagic events. Another finding of this meta-analysis was that more frequent monitoring of OAT leads to better clinical outcomes. No subgroup analyses were performed.

*Heneghan et al*[8] (2006) This meta-analysis included 14 RCTs. The authors report details on the methods used to evaluate the quality of the papers and to analyze the data extracted. The outcomes pooled were: major hemorrhage, thromboembolic events, death, tests in range, minor hemorrhage, frequency of testing, and feasibility of self-monitoring (PST). The authors concluded that trials of combined self-monitoring and self-adjusted therapy (PSM) showed significant reductions in thromboembolic events and mortality (0·37, 0·16–0·85), but not major hemorrhage. No difference was noted in minor hemorrhage.

*Christensen et al*[48] (2007) This meta-analysis included 10 RCTs with a total of 2724 patients. Adequate methods were used to select, review and analyze the papers included. The results of

the analysis show that self management was associated with a reduced risk of death, major complications and with increasing time within therapeutic INR target range. No clear effect was found regarding minor complications. The authors mention that 8 of the 10 trials were low quality, and recommend caution in interpreting the results.

When summarizing the findings of these three MAs the most definitive data comes from the evaluation of adverse events. All three MAs report that patients who either self-test or self-monitor have lower rates of thromboembolic events, and in some cases, hemorrhagic events as well. Additionally, it appears that the time spent in the INR target range is higher for patients who self-manage. Of note, it was reported that as the frequency of testing increases better clinical outcomes were observed. A moderate level of caution is required for generalizing the results of these analyses, as the studies included in the meta-analyses had a high degree of variability in their quality.

**HTA reports**

*Medical Services Advisory Committee (MSAC), Australia 2005*[19] Two studies were identified that met the inclusion criteria for the assessment of diagnostic performance of POC devices compared with INR laboratory-based testing. One was a RCT (level II evidence) and the other was a case series (level IV evidence). Overall, there was no significant difference in diagnostic performance between PPTS and laboratory-based testing in the two studies, which may have resulted from the small sample sizes employed. The authors of this report concluded that there is insufficient evidence to support the use of INR POCT in general practice at this time. Although it was concluded that insufficient evidence existed, several advantages of PPTS were identified. These included, improved compliance, increased convenience for the patient, more appropriate use of warfarin in rural and remote areas and reduction in difficulties associated with frequent venepuncture.

*Health Technology Assessment, NHS R&D HTA Programme, United Kingdom 2007*[20] This report reviewed 16 RCTs and 8 non-randomized studies. Patient self-testing (PST) was found to be significantly associated with fewer thromboembolic events and deaths. However, a reduction in major complications was not consistently associated with better OAT management. The authors suggested that the reductions in complications and deaths may be due to alternate explanations such as patient education and empowerment. Overall, it was concluded that self-monitoring (PST) is as safe and effective as good-quality specialized anticoagulation clinics in maintaining the quality of OAT for select patients who are successfully trained.

*Canadian Agency for Drugs and Technologies in Health(CADTH), Canada 2007*[18] This report reviewed 15 RCTs. The authors noted that definitive conclusions about the clinical benefits of self-testing and self-management with POC devices cannot be made without more rigorously designed randomized trials. Nevertheless, their analysis of major adverse events showed that using POC devices to manage OAT resulted in significantly fewer deaths and thromboembolic events and better INR control than conventional laboratory testing. Also, the impact of POC devices on hemorrhagic events is similar to that of conventional testing. From a cost perspective, the authors concluded that in a clinical setting POCT is cost saving and cost effective but suggested that PST is not cost effective for Canada's publicly funded health system. This was in large part due to the increased capital and consumable costs associated with PST. However, PST would be cost effective if society was willing to pay $50,000 for a QALY. They also estimated that only 24% of OAT patients would qualify for self-testing or self management programs.

*The Medical Advisory Secretariat (MAS) Ministry of Health and Long-Term Care, Ontario, Canada 2009*[22] This recent report reviewed 17 RCTs. The authors concluded that for a select group of patients who are highly motivated and trained, PSM resulted in significantly fewer

thromboembolic events compared to conventional laboratory-based INR testing. No significant differences were observed for major hemorrhages or all-cause mortality. The PST and POCT by trained health care professionals were just as effective as conventional laboratory-based INR testing for thromboembolic events, major hemorrhages, and all-cause mortality. The authors also noted that the effectiveness of POCT methods (PSM, PST and POC by health care professionals), measured by the proportion of time INR is in the therapeutic range, might also result in better OAT control. An improvement in the quality of life and patient satisfaction and was also noted.

In sum, the HTA reports suggest that patients who had access to PPTS programs had better health, fewer complications and lower costs associated with therapy than patients who had access to conventional laboratory-based testing. Additionally, improved compliance and overall levels of acceptance for PPTS testing will depend on the group of patients selected. The implications for Alberta are challenging, with the growing geriatric component and a significant rural based patient population.

#### 5.2.2.2 *Quantitative assessment*

*Mean percentage of time in INR target range (Table 6)*

The pooled standardized mean difference (SMD) between the intervention (i.e. PPTS) and control groups (i.e. laboratory-based) was 0.156 (95% CI: 0.032-0.280). These results suggest that patients in the intervention group (PSM, PST or POC) spent more time in the INR target range than the patients in the control group, and this difference was statistically significant (p=0.014).

The heterogeneity chi-squared test suggested the presence of between-study variance. The results of the meta-regression suggest that the heterogeneity may be explained by age, in that the difference in the mean percentage of time spent in INR target range, between the

intervention and control groups, differed based on age inclusion. Specifically, it was found that in studies which included only elderly patients there was a clear, statistically significant, benefit of PPTS on time spent in the target INR range. This benefit was still observed in studies which included all ages. Statistical significance was lost for studies which did not specify the ages of included patients (Figure 1).

*Mean percentage of INR measurements in INR target range (Table 7)*

The pooled standardized mean difference (SMD) between the intervention and control groups was 0.317 (95% CI: 0.190-0.444). These results suggest that patients in the intervention group (PSM, PST or POC) had more measurements in the INR target range than the patients in the control group, and this difference was statistically significant ($p < 0.05$).

The heterogeneity chi-squared test suggests the presence of between-study variance. The results of the meta-regression suggest that only the variables PST/PSM may explain the heterogeneity, in that the difference in the mean number of measurements in INR target range, between the intervention and control groups, is larger in the intervention group when patients self-tested or self-managed. Specifically, it was shown that when patients self-tested or self-managed they had a higher percentage of measurements in the target INR range as compared to usual care (Figure 2).

*Adverse events (Tables 5, 6, 8 & 9)*

The pooled OR of major hemorrhagic events was 0.677 (95% CI 0.460-0.995), suggesting that the odds of having a major hemorrhagic event are smaller for patients in the intervention group compared to the control group (Figure 3). This difference was marginally significant ($p=0.047$).

The pooled OR of major thromboembolic events was 0.526 (95% CI 0.377-0.733), suggesting that the odds of having a major thromboembolic event are smaller for patients in

the intervention group compared to the control group (Figures 4). This difference was statistically significant ($p<0.001$).

It is important to note that these adverse events occur on either side of the therapeutic window (Figures 3 & 4 present this data graphically). In conclusion, patients who participate in POCT programs have better health and fewer complications, but the presence of heterogeneity should produce a degree of concern about the findings.

### *5.2.3* Quality of Life and Patient Satisfaction

Quality of life and patient satisfaction measures were used in 8 RCTs. Below we present a summary of the findings.

*Crombheecke et al*[28] used a questionnaire developed by Sawicki et al[41] to evaluate the general treatment satisfaction, self-efficacy, daily anxieties, distress, and strain in both study groups at the beginning and the end of the follow-up period. The authors noted a statistically significant difference in general treatment satisfaction and self-efficacy between the intervention group (i.e. PPTS) and the control group (i.e. laboratory) with the intervention group reporting higher levels of both. Also, scores for daily anxieties, distress, and strain were significantly lower in the intervention group at the end of the trial.

*Jowett et al*[60] reported the results of the QOL assessment done in the SMART trial described by Fitzmaurice et al.[36] The patients were evaluated using the European Quality of Life Questionnaire (Euroqol) at the beginning of the trial, and at 6 months and 12 months follow-up. The authors noted that there was no statistical significant difference in the mean QALYs between the two study groups.

*Gadisseur et al*[53] used the questionnaire developed by Sawicki[41] to evaluate the QOL at the beginning and the end of the study in the 3 study groups (education only, PST and PSM groups). The only significant increase in general treatment satisfaction and self-efficacy, and

decrease in daily anxieties, distress, and strain, from the beginning to the end of the trial, were noted in the patients on PSM of OAT. Nevertheless, comparing the 3 study groups, no significant differences were noted in any aspects of QOL.

*Gardiner et al*[61] reported that 87% of patients in the PST group found self-testing straightforward, 87% were confident in the results they obtained and 77% preferred self-testing to the laboratory testing. The patient acceptability questionnaire was completed only by the patients in the PST group.

*Khan et al*[57] used the Euroqol questionnaire and the UK SF-36 to evaluate the QOL of patients at the beginning, 6, 12 and 24 weeks follow-up. Though the authors did not report any comparison measures between the study groups, they mention in the discussion that only a marginal significant difference in emotional role component of UK SF-36 was noted.

*Sawicki et al*[41] developed a questionnaire containing 40 items that evaluate five aspects of patient satisfaction and QOL: general treatment satisfaction, self-efficacy, daily hassles, distress, and strained social network. For each topic, the minimum sore is 1 and the maximum is 6. The results of the QOL evaluation showed significantly higher improvements in all topics, with the exception of strained social network, from baseline to the end of the 6 month follow-up period, in the intervention group compared to the control group.

*Shiach et al*[42] applied a questionnaire assessing patients' satisfaction with the care they received in the hospital-based versus community-based clinic. Patients were satisfied with all aspects of care in the community-based clinic, while they were satisfied with most aspects of the hospital-based clinic, less the waiting area, communication with the physician and level of information. They also reported a difference in the traveling time to the clinics (20 to 35 minutes longer for the patients attending the hospital-based clinic) and the waiting time (22 minutes longer for the patients attending the hospital-based clinic).

*Soliman Hamad et al*[62] investigated improvement in QOL using the SF-36 questionnaire. Improvement in the physical component summary (PCS) was significantly higher in the intervention group compared to the control group. When different components were analyzed, the improvement in bodily pain, vitality and emotional role functioning were significantly higher in the intervention group.

*Sunderji et al*[45] reported that all the patients in the PSM arm of the study were satisfied with their management of treatment. The authors did not mention the method of evaluation.

When summarizing the QOL findings there appears to be a disconnect between the various scales of QOL employed in the above studies, as such any conclusions on this measure should be interpreted with caution. Overall, five of the eight studies reported showed a positive relationship between PPTS testing and QOL when compared to standard laboratory or hospital-based testing. Of note, measures of overall treatment satisfaction, ease of testing and self efficacy were higher in PPTS than usual care. Three studies reported no significant differences in QOL measures between intervention and control groups.

## 5.3 Delivery Context

### *5.3.1* Delivery Considerations

There are three methods of INR-monitoring using portable devices that are already in use in Alberta:

1. Self-management by patients (PSM). In this case, the selected patients who receive a portable device monitor their INRs and adjust their warfarin dosage. These patients need to be viewed by their primary care physician regularly, but much less often than patients who have their INRs tested in the laboratory.
2. Self-testing by patients (PST). Selected patients monitor their INRs, but they need to report their results to a health care professional (primary care physician, nurse or

pharmacist). Following the analysis of their results, the health care professionals recommend a dose adjustment, if necessary. Contact with the health care professionals can be maintained by phone, eliminating the need to attend a clinic or an office. These patients need to be viewed by their primary care physician regularly, but much less often than patients who have their INRs tested in the laboratory.

3. Point-of-care testing (POCT) by health care professionals. In this case, the testing can be performed by primary care physician offices, pharmacies or clinics. The main advantage of this method versus laboratory testing is the elimination of the waiting time for laboratory results. The feedback of health care professionals is delivered without delay. This method does not eliminate patient travel time and the frequency of testing may not be as high as in the other two methods.

### *5.3.2* Implementation Considerations

The most important aspects for implementation of PSM and PST are the careful selection of patients to ensure proper device usage and warfarin dosages. In POCT by health care professionals, the most important aspect for implementation is the training of health care professionals to use these devices. Currently in Alberta there is one standardized training program for health care professionals offered by one of the companies producing portable coagulometers licensed in Canada. To our knowledge, there are no set criteria for selection of patients who want to use the PSM or PST method for INR monitoring. Based on the meta-regression analysis of previous literature, it appears that elderly patients might benefit most from PPTS testing. Specifically, our sensitivity analysis revealed elderly patients spend more time in their target INR range when PPTS testing compared to usual care. This result needs

to be qualified, as the studies that indicated this relationship had very strict inclusion criteria therefore may not be an accurate representation of the entire elderly OAT population.

# 6 ECONOMIC EVALUATION

## 6.1 Literature Review Findings

Relevant economic evaluations fulfilling our criteria for inclusion include:

1. Lafata et al.[52] The study looks at three options for managing long-term OAT: the usual standard of care testing in a laboratory with delayed test results, management at an anticoagulation clinic with immediate test results – equivalent to point-of-care testing – and patient self testing using point-of-care devices with immediate results that are phoned into a clinic. Two perspectives, medical system cost and society cost, were taken in this American study. Cost effectiveness ratios depended on which perspective was analyzed. From the medical system perspective, moving from standard of care testing in a laboratory to clinic testing was cost saving by $3,876 (1997 US$; $6,776 in 2009 CAN$), while moving from clinic testing to patient self-testing cost $24,818 ($43,391 in 2009 CAN$). From the perspective of society, moving from laboratory testing to clinic testing cost $31,237 ($54,615 in 2009 CAN$), while moving from clinic testing to patient self-testing was cost saving by $4,730 ($8,270 in 2009 CAN$). Medical costs include anticoagulation monitoring and adverse events and nursing costs, while societal costs also include costs incurred by patients and caregivers. Cost savings were not directly associated with a specific cause.

2. Regier et al.[63] The study looks at two options for managing long-term OAT: laboratory standard of care testing, and self-management (inclusive of self-adjustment of warfarin doses). One perspective, medical system cost, was taken in this study from Vancouver, B.C. Incremental costs and benefits and a maximum willingness to pay per QALY were evaluated

for moving from physician management to self-management. For a 1-year period, an incremental cost-effectiveness ratio of $236,667 (2003 CAN$; $263,269 in 2009 CAN$) was calculated. This decreased to $14,129 ($15,717 in 2009 CAN$) for a 5-year time horizon, and $2,995 ($3,331 in 2009 CAN$) for a 10-year time horizon. Medical costs included the cost of anticoagulation treatment and monitoring, and costs borne by adverse events.

3. The National Health Service R&D Health Technology Assessment Programme.[20] The study looks at two options for managing long-term OAT: usual care of family physicians and hospital clinic testing, and patient self-management. One perspective, medical system cost, was taken in this United Kingdom study. Incremental costs and utilities, and a threshold incremental cost-utility ratio were evaluated. For a 1-year period, an incremental cost-effectiveness ratio of £577,170 (2005 £; $1,404,988 in 2009 CAN$) was calculated for shifting from usual care to patient self-management. This decreased to £122,365 ($297,869 in 2009 CAN$) for a 5-year time horizon, and £63,655 ($154,953 in 2009 CAN$) for a 10-year time horizon. Medical costs included the costs of anticoagulation therapy, as well as adverse event costs.

4. The Canadian Agency for Drugs and Technologies in Health [CADTH].[18] The study uses a Lafata-style model to compare three options for managing long-term OAT: usual care of laboratory testing, anticoagulation point-of-care clinic testing, and patient self testing using point-of-care devices with results phoned into a clinic or physician. Two perspectives, medical system cost and society cost, were taken in this Canadian study. Cost effectiveness ratios depended on the perspective taken. From the medical system perspective (excluding nursing homes), moving from usual laboratory testing to anticoagulation clinic testing was cost saving by $2,720 per QALY (2005 CAN$; $2,902 in 2009 CAN$), while moving from usual laboratory testing to self testing by the patient cost $72,955 per QALY ($77,837 in 2009

CAN$). From the perspective of society, moving from usual laboratory testing to anticoagulation clinic testing cost $10,808 per QALY ($11,531 in 2009 CAN$), while moving from usual laboratory testing to self testing by the patient was cost saving by $7,104 ($7,579 in 2009 CAN$). Cost savings were not directly attributed, though travel costs for patients and caregivers were likely to cause the savings in the self testing case.

5. The Ontario Medical Advisory Secretariat.[22] The study uses a Lafata-style model to compare four options for managing long-term OAT: standard care of laboratory testing, healthcare staff testing consisting of anticoagulation POCT, patient self-testing, and patient self-management. One perspective, medical system cost, was taken in this Canadian study focusing upon Ontario. Total cost per patient over a 5-year time horizon and incremental cost-effectiveness ratios were calculated. Standard care cost $24,000 (2008 CAN$; $24,317 in 2009 CAN$) per patient over the 5-year horizon. Healthcare staff testing cost $19,000 ($19,251 in 2009 CAN$, while self-testing cost $20,000 ($20,265 in 2009 CAN$) and self-managing cost $15,000 ($15,199 in 2009 CAN$). Compared to standard care, the other three options dominate, while the patient self-management strategy dominates the other three options. Medical costs include the costs of treatment and adverse event costs, from events such as thromboembolic and hemorrhagic events.

The results are summarized in table 10. Costs in the studies were not broken down by gender or other co-morbidities. Major adverse events were included as costs, and in all studies were given as a percentage likelihood of occurring in each cycle. No direct recommendations were given in any of the studies for a targeted population for the different types of anticoagulation therapies. It is important to note that the time spent in normal INR levels differed through the studies. For usual care (i.e. laboratory testing), these range from 50% of the time (Lafata et al.[52]), to 61% of the time (CADTH[18]), to 68.8% of the time (NHS[20]). For

self-management, these range from 69% of the time (CADTH[18]) to 70.4% of the time (NHS[20]). For self-testing, Lafata et al.[52] used 89% as an average time. Our evaluation attempts to balance these studies by using different normal range percentages in differing sensitivity analyses. These are based on whether one has a mechanical heart valve, or is older or lives in a rural population, all of which will reduce the percentage of time spent in normal INR range. These specifications are given in Appendix 6.

The studies show general support for the assertion that self-testing and self-management is cost effective from a system perspective. The NHS study[20] had the highest cost-utility measure, with an incremental medical system cost-utility ratio above $150,000, even with a 10 year time perspective. The Regier et al.[63] study found costs to be significantly less. Different chances of an adverse event occurring, and costs from those events, contribute to the distinct incremental cost-effectiveness ratios. The other studies show that though moving to self-testing will cost the medical system money, the costs will be below $100,000 per QALY. With patient self-testing, the two studies that calculated total costs – societal costs and medical system costs combined – show a potential cost savings compared to standard of care laboratory testing.[18,52] Anticoagulation POC testing is generally cost-saving from the medical system perspective, and is cost effective to the $100,000 per QALY level when societal costs are included.[18,52] Along with self-management, anticoagulation POC testing are generally the less expensive of the four options.[18,22,52]

## 6.2 Economic Analysis

### *6.2.1* Demand Estimates

Due to the imprecision of the number of individuals who will actually need anticoagulation treatment based alone off ICD-9/ICD-10 diagnoses, three estimates will be used: the CADTH estimate of prevalence (0.6% of the population), the estimated prevalence from the

Ontario study (1% of the population), and the estimated prevalence plus a percentage point from the Alberta estimates (1.1% of the population). This results in approximately 21,710 people (0.6% of the Alberta population), approximately 35,580 people (1% of the Alberta population), and approximately 37,902 people (1.1% of the Alberta population) receiving OAT.

### *6.2.2* Results of Economic Evaluation

Basic results from the Markov model we created are presented in Table 11. Cohort sizes were set at 100, with averages taken after each Markov model simulation. The results are sensitive to the specifications chosen in the parameter table in the Methods section. Notably, if home care reduces the time spent outside the optimal INR, system costs will be reduced significantly. If risks due to being outside the INR increase, costs will increase for the system. Sensitivity analyses are shown in Table 12. Sensitivity is done on four factors – the effect on costs from the consumer or healthcare system picking up the cost of the device or the consumables if they self-test; whether mechanical heart valves and the resultant INR changes (higher time spent below the optimal INR) affect costs; whether rural populations (~30% of those tested) and their lower compliance would affect costs; and whether older populations (~60% of those tested are 70 and above) and their lower compliance would affect costs. Estimates for self-management and self-testing were kept below 50% in all sensitivity specifications, due to the older skew of the population that currently is receiving anticoagulation therapy.

It was assumed that the entire cohort would go to 1 lab for tests. More facilities would be available at clinics – hence it was assumed that the cohort of 100 would have 2 clinics to attend. This would reduce driving distances, as noted in the parameter estimates – causing the decrease in society costs. The lowest society cost is for self-testing at home. However, with

the parameter estimates given in the table, society costs do not decrease enough to offset the increased cost of buying each person a testing device. It is sensitive to the cost of the device, and to improvements made in the INR from self-testing – though this would likely be done by more tests, which are not accounted for in the main specification.

Clinic or pharmacy anticoagulation POCT would be the lowest cost option when looking at both the system and the combined system and societal costs. A mix of options, if available, would also provide even lower costs than the current standard of 100% laboratory testing. The estimates are consistent through the sensitivity analyses, suggesting that changes in demographics and recommended INR levels will not change the results significantly. Rather, it will be the price of the tests, machines, as well as how lost wages and time resulting from drives and testing time in clinics and labs are valued that will change the analyses the most. A slight increase is seen in QALYs per patient for most of the tests, though it is an insignificant increase. It is unlikely that there will be a significant difference in quality of life, as measured from medical outcomes, between the different mixes of testing methods.

Overall costs are given in Table 13. Estimates for total (society and healthcare system) costs range from $194-$342 million for 100% laboratory testing, to $129-$226 million for 100% clinic testing, to $180-$318 million for 100% self-testing at home. Though not as cost-saving as 100% clinic testing, other less expensive options involve a mix of all three – laboratory testing, clinic/pharmacy testing, and self-testing, with a small percentage of those self-managing. The cost range for this option – approximately 25% lab testing, 50% POC clinic testing, 20% self-testing, and 5% self-managing, is $152-$267 million. This option also is among the lower cost options when looking at healthcare system costs alone. Outside of 100% POC clinic testing, an option with 75% laboratory testing and 25% POC clinic testing

are also less expensive from the healthcare system perspective, when the healthcare system also pays for the PPTS devices.

There is little change in quality of life – which is dependent upon the number of adverse events – except in groups with lower compliance, as could be hypothesized for rural or older populations. In these scenarios, the Markov model results vary, but generally a slightly higher quality of life is seen when a higher percentage of patients self monitor or self manage. The overall trade-off between higher costs from buying more POC devices and less travel costs for patients, and potentially better compliance in managing or monitoring INR levels, will have to be considered. The latter effect will reduce the number of adverse events that incur high hospitalization costs. Simulations here show that patient costs decrease and healthcare system costs increase as self monitoring and management increase. The cost of POC devices, though, is what drives most of the healthcare system cost increase, with an approximately $800 per patient increase for an additional 25% patients who self test or manage. Specific breakdowns are shown in Table 12.

Generally, effectiveness (in terms of avoiding adverse events), as measured by QALYs, differs little among the options. The lowest system cost (i.e. most cost-effective, as measured from the system perspective) would be to have 100% POC clinic testing. The lowest societal cost (i.e. most cost-effective, measured from exclusively societal costs) would be to have 100% self testing. Excluding the 100% clinical testing option, the next lowest cost perspective tends to be a mix between laboratory testing, POC clinic testing, self-testing and self-management – which has a healthcare system cost slightly higher than a combination of laboratory and POC clinic testing, but a much lower societal cost. These savings, compared to the standard of care laboratory testing, are also seen in the sensitivity analyses for higher risk populations, as well as in the sensitivity analyses where device and consumable costs are allocated differently

between the healthcare system and patients. As more individuals self-test or self-manage, cost savings from the societal viewpoint are outweighed by increased costs from the healthcare system, especially if government incurs the cost of the POC testing device and consumables. Across different payment schemes, patient utility remains relatively constant across the different mixes of PPTS testing, meaning that cost-utility ratios will change only through expected costs. Healthcare system costs are generally higher if device costs are incurred by the system, across different mixes of PPTS testing. Overall system costs, though, are generally lower if the healthcare system pays for the device.

Some notes apply to the cost estimates. Nursing home costs are not included, and estimates of the time spent in normal INR range vary across the literature, so could vary depending on the patient population analyzed. Pharmacy costs were not included, since pharmacists are not currently compensated for performing POC tests. Quality assurance costs were not included. It is unlikely that 100% of all patients will be using one type of test, and with training requirements, the number of individuals self testing or self managing is unlikely to be above 50%.

# 7 DISCUSSION

## 7.1 Assessment Limitations

The RCTs reviewed showed great variability in the methods employed to asses the effectiveness of PSM, PST or POC INR testing by health care professionals. Moreover, the patients included in these studies were highly selected, which may affect the generalizability of the results. We were unable to quantify the difference in QOL between intervention and usual care groups due to the high variability in the measurements used to assess QOL in the papers

reviewed. We noted significant heterogeneity in our study with variation in study quality as a major factor.

Another methodological limitation is the use of "time in INR range" as an outcome variable. The definition is dependant on the condition being treated, for example the range for atrial fibrillation may not be the same as the range for mechanical valve replacement. We are not aware of any studies which have examined a homogeneous group of patients.

The assessment of the demand for the technology in Alberta is limited by the impossibility to determine the exact number of patients who require long term OAT. The list of conditions that require long-term OAT may not be comprehensive. As such we were unable to calculate prevalence and incidence rates for all conditions requiring OAT. However, we were able to determine how many Albertans required OAT in each of the last three years (Table 1). Moreover, the lack of established criteria for the selection of patient's best suited to perform PSM or PST makes the task of assessing the demand even more difficult.

PPTS should be used as an extension of laboratory-based services which will be available to patients regardless of their illness. As such, it is impossible to tell which patients will most benefit from access to this service. While some categories of patients, for example rural patients, would appear to be particularly interested in PPTS only time will tell.

## 7.2 Evolving Developments

Our quantitative analysis of effectiveness confirmed the findings from previous MAs and HTA reports. The POCT and management of INR (either PSM, PST or POCT by health professionals) is at least as effective as the usual care of patients on long-term OAT, both in maintaining the INR in the target range and in reducing the incidence of adverse events. Moreover, the QOL measures reported in several trials seem to confirm that patients prefer the PSM/PST method versus laboratory testing.

Success of the POC approach depends on the selection of suitable patients and the availability of rigorous training programs. Also, the cost of devices and consumables may decrease the present use of these devices by patients who can not afford the long-term costs.

The impact of the next generation of anticoagulants which do not require monitoring cannot be estimated at this time.

The economic analysis we performed showed that for self-testing at home, when societal costs are taken into account, the use of INR-monitoring portable devices has the lowest cost, when compared with usual care. The care system costs depend on the risks of the patient being outside the INR target range: if they are high, the costs for the system increase.

## 7.3 Impacts on Alberta Health System

The implementation of POCT involves creation of an adequate system for patient selection for this type of INR monitoring. It has been suggested that approximately 25% of OAT patients would be candidates for PST/PSM. Patients require visual acuity, manual dexterity and cognitive abilities to be selected. Another factor for PPTS consideration involves geography and patient motivation. Presently it is unclear if PPTS is more effective in any one subgroup of the OAT population, but preliminary evidence would suggest that it may be with elderly patients. Also, standardized training programs need to be put in place to ensure that the risks of using INR-monitoring portable devices are minimized.

The costs for the health system depend on the adverse events avoided by better monitoring of selected patients on long-term OAT. If these risks decrease as a result of POCT, the costs will be lower than usual care in selected patients.

# 8 CONCLUSIONS

According to CADTH, POCT can improve health with fewer deaths and thromboembolic events. Compared to laboratory-based testing, using POC devices in anticoagulation clinics is cost saving. When a cost-effectiveness analysis is performed the cost per QALY is 50,000. POC is at least as effective as usual care in maintaining the INR in the target range. Moreover, the incidence of adverse events seems to be lower in POCT patients than in usual care patients. The use of POC devices should factor patient suitability, patient education and training, health system constraints, and affordability.

# TABLES

## Table 1. Approximate Prevalence and Incidence of OAT in Alberta

| | | Prevalence | | Incidence | |
|---|---|---|---|---|---|
| | # unique patients | proportion | per 100,000 population | rate | rate per 100,000 population |
| 2006 | 33,995 | 0.0099 | 990 | | |
| 2007 | 36,190 | 0.0103 | 1030 | 0.000625 | 62.5 |
| 2008 | 37,529 | 0.0105 | 1050 | 0.000377 | 37.7 |

** Rates based on Alberta Health and Wellness physician claims billing data

## Table 2. Prevalence Proportions and Incidence Rates for Potential Conditions Leading to OAT

| Prevalence Proportions | | | | | |
|---|---|---|---|---|---|
| I48 | Atrial fibrillation | 5.50% | Holland | 55 and up | Heeringa et al. (2006)[64] |
| | | 0.95% | US | | Go et al. (2001)[65] |
| Z95.2 | Prosthetic heart valve | 0.10% | US | | Garver et al. (1995)[66] |
| I26 | Pulmonary embolism | 17.50% | Canada | inpatients and outpatients with suspected PE | Wells et al. (1998)[67] |

| Incidence Rates | | | | | |
|---|---|---|---|---|---|
| I48 | Atrial fibrillation | 200 per 100,000 | Canada | | Krahn et al. (1995)[68] |
| | | 438 per 100,000 | Denmark | 40-89 year olds | Frost et al. (2005)[69] |
| Z95.2 | Prosthetic heart valve | 1000 per 100,000 | Holland | 55 and up | Heeringa et al. (2006)[64] |
| I26 | Pulmonary embolism | 47-63 per 100,000 | US | | DeMonaco et al. (2008)[70] |
| I80.3 | Deep vein thrombosis (DVT) | 117 per 100,000 | US | | Ramzi et al. (2004)[71] |
| | | 39 to 83 per 100,000 | US | | Bulger et al. (2004)[72] |

## Table 3. Demographic breakdown of patients currently receiving anticoagulation therapy

| By individual observation (complete January 2004-March 2009 | |
|---|---|
| 30 and below | 1.62% |
| 31 to 40 | 1.73% |
| 41 to 50 | 4.65% |
| 51 to 60 | 9.69% |
| 61 to 70 | 18.25% |
| 71 to 80 | 34.25% |
| 81 to 90 | 26.35% |
| 91 and over | 3.46% |
| n | 1,080,798 |

| By unique patient (as of first record in 2008) | |
|---|---|
| 30 and below | 3.47% |
| 31 to 40 | 3.07% |
| 41 to 50 | 6.27% |
| 51 to 60 | 11.78% |
| 61 to 70 | 18.72% |
| 71 to 80 | 30.52% |
| 81 to 90 | 22.80% |
| 91 and over | 3.37% |
| n | 37,529 |

| By region of patient (unique patients in 2008) | |
|---|---|
| Chinook | 7.92% |
| Palliser | 3.08% |
| Calgary | 30.96% |
| David Thompson | 9.46% |
| East Central | 4.79% |
| Capital | 33.45% |
| Aspen | 6.09% |
| Peace Country | 3.61% |
| Northern Lights | 0.55% |
| Other/unknown | 0.09% |
| n | 37,529 |

**Table 3.(contd)**

| By gender of patient (unique patients in 2008) | |
|---|---|
| Female | 47.58% |
| Male | 52.42% |
| n | 37,529 |

| Top 10 ICD-9 3-Digit Diagnosis Codes for anticoagulation treatment (by unique patient in 2008) | | |
|---|---|---|
| 427 | 37.19% | Cardiac dysrhythmias |
| 286 | 16.61% | Coagulation defects |
| 785 | 5.19% | Symptoms involving cardiovascular system |
| 451 | 3.91% | Phlebitis and thrombophlebitis |
| 289 | 3.44% | Other diseases of blood or blood-forming organs |
| 780 | 3.24% | General symptoms |
| 964 | 3.19% | Poisoning by agents affecting blood |
| 790 | 2.48% | Nonspecific abnormal findings on examination of blood |
| 428 | 1.81% | Heart failure |
| 453 | 1.74% | Other venous embolism and thrombosis |
| Others | 21.20% | |

Others: less than 1.5% of cases for each 3-digit first diagnostic code

## Table 4. Portable INR monitoring devices

| Name | Manufacturer | Licensed in Canada | Target group | Blood sample | Analysis time | Clot detection principle | Memory storage | Quality control | Costs[θ] |
|---|---|---|---|---|---|---|---|---|---|
| COAGUCHEK S*, XS, XS PLUS | Roche Diagnostics GMBH | April 1999 (S)<br>April 2006 (XS)<br>February 2007 (XS plus) | Patient or health professionals (S and XS)<br>Health professionals (XS Plus) | One drop of capillary blood | 1 min | Iron oxide particles/ photoreflection (S)<br>Change in impedance (XS and XS Plus) | 60 tests (S)<br>100 tests (XS)<br>500 tests (XS Plus) | Liquid (S)<br>Internal (XS)<br>Liquid and internal (XS Plus) | Device:<br>$499 (XS)<br>$1,499 (XS Plus)<br>Test strips (per 48):<br>$325 (S)<br>$401.7 (XS) |
| PROTIME MICROCOAGULATION SYSTEM | International Technidyne Corp. | August 1999 | Patient or health professionals | One drop of capillary blood | 3-5 min | Cessation of blood flow | 50 tests | Internal and liquid | Device: $1800<br>Cuvettes (per 25): $145 |
| INRATIO PROTHROMBIN TIME/INR | Hemosense Inc. | January 2007 | Patient or health professionals | One drop of capillary blood | 1-1.5 min | Icon-based LCD and amerometric PT determination | 60 tests | Internal | Device:<br>Professional: $500<br>Self-test: $475<br>Test strips (per 48): $207.9 |

*The CoaguCheck S device is no longer available on the market. The manufacturer continues to supply test strips.

## Table 5. Characteristics of RCTs included in our literature review

| Author, year | FU duration | Sample | | | Description of groups | | Main indication(s) for OAT | OAT drug(s) | Adverse events reported | Outcomes | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Size* | Age (mean) | % female | Intervention | Control | | | | | |
| Beyth 2000 [23] | 6 months | 294 | 75 | 57 | PSM ProTime | Usual care (GP office) | VTE | Warfarin | Major hemorrhages and TE events, mortality | % time in INR target range | Moderate:<br>- no power calculation<br>- no details on randomization |
| Bubner 2009[24] | 18 months | 944 | NS | NS | POC (GP office) | Usual care (GP office) | NS | NS | NS | % measurements in INR target range | Low<br>- no power calculation<br>- no blinding<br>- baseline demographic and clinical data not reported<br>- no ITT analysis |
| Christensen 2007[26] | 6 months | 92 | Int: 52<br>Ctr : 45 | 35 | PSM | Usual care (GP office or anticoagulation clinic) | VTE, AF, other+ | Warfarin and cumarin derivates | NS | Median, IQR of time in INR target range | Moderate<br>- no power calculation<br>- no details on randomization<br>- adverse events not reported |
| Claes 2005[27] | 6 months | 732 | 70 | 26 | POC (GP office) | Usual care (GP office) + education | AF, MHV, VTE | Warfarin and cumarin derivates | Major and minor hemorrhages and TE events, mortality | % time in INR target range | Low<br>- no blinding<br>- baseline demographic and clinical data not reported<br>- adverse events not reported |
| Cromheecke 2000 [28] | 3 months (cross-over design) | 89 | 42 | 40 | PSM | Usual care (anticoagulation clinic) | MHV, AF, other+ | Cumarin derivates | Major and minor hemorrhages and TE events | % measurements in INR target range | Moderate<br>- flow of participants not reported<br>- no blinding |
| Dauphin 2008 [29] | 12 months | 67 | Int: 58<br>Ctr: 55 | 33 | PSM | Usual care (hospital) | MHV | Cumarin derivates | Major and minor hemorrhages, mortality | % time in INR target range | Moderate<br>- no power calculation<br>- no details on randomization<br>- no blinding |
| Eitz 2008 [30] | 2 years | 765 | Int: 56<br>Ctr: 62 | 31 | PSM | Usual care (GP office) | MHV | Warfarin | Major hemorrhages and TE events. | % measurements in INR target range | Moderate<br>- no power calculation<br>- no details on randomization<br>- no blinding |

## Table 5.(contd)

| Author, year | FU duration | Sample | | | Description of groups | | Main indication(s) for OAT | OAT drug(s) | Adverse events reported | Outcomes | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Size* | Age | % female | Intervention | Control | | | | | |
| Fitzmaurice 2000[31] | 12 months | 367 | NS | 45 | POC (nurse) | Usual care (GP office or anticoagulation clinic) | AF, MHV, VTE | Warfarin | NS | % time in INR target range, % measurements in INR target range | Moderate:<br>- eligibility criteria not reported<br>- no blinding<br>- baseline demographic and clinical data not reported |
| Fitzmaurice 2005[36] | 12 months | 617 | 65 | 35 | PSM | Usual care (anticoagulation clinic) | NS | Warfarin | NS | % time in INR target range | High |
| Gadisseur 2003, 2004 [32,33] | 6 months | 320 | 57 | 29 | PST, PSM | Usual care (anticoagulation clinic) + education | VTE, AF, MHV | Cumarin derivates | NS | % time in INR target range, % measurements in INR target range | High |
| Gardiner 2005[34] | 6 months | 69 | Int: 58<br>Ctr: 58 | 45 | PST | Usual care (anticoagulation clinic) | MHV, VTE, AF | NS | Minor hemorrhages | % time in INR target range | Moderate:<br>- no power calculation<br>- no details on randomization<br>- no blinding<br>- no ITT analysis |
| Horstkotte 1998 [35] | 18 months | 150 | NS | NS | PSM | Usual care (GP office) + education | MHV | NS | NS | % measurements in INR target range | Very low:<br>- randomization not stated<br>- eligibility criteria not reported<br>- no details on randomization<br>- no blinding<br>- baseline demographic and clinical data not reported<br>- no ITT analysis<br>- flow of participants not reported |
| Khan 2004[37] | 6 months | 85 | 73 | 40 | PST | Usual care (anticoagulation clinic) + education | AF | Warfarin | NS | % time in INR target range | Moderate:<br>- no blinding<br>- no ITT analysis<br>- dates of recruitment and follow-up not reported |
| Kortke 2001, 2007 [38,39] | 38 months | 600 | 63 | 34 | PSM | Usual care (GP office) | MHV | Cumarin derivates | Major hemorrhages and TE events | % measurements in INR target range | Moderate:<br>- no power calculation<br>- no details on randomization<br>- no blinding |
| Menendez-Jandula 2005 [40] | 12 months | 737 | 66 | 47 | PSM | Usual care (anticoagulation clinic) | AF, MHV, VTE | Cumarin derivates | Major hemorrhages and TE events, mortality | % time in INR target range, % measurements in INR target range | High |

## Table 5.(contd)

| Author, year | FU duration | Sample | | | Description of groups | | Main indication(s) for OAT | OAT drug(s) | Adverse events reported | Outcomes | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Size* | Age | % female | Intervention | Control | | | | | |
| Sawicki 1999 [41] | 6 months | 165 | 55 | 30 | PSM | Usual care (GP office or anticoagulation clinic) | MHV, AF | Cumarin derivates | Major and minor hemorrhages and TE events | Squared INR value deviation, % patients with INR in target, QOL | High |
| Shiach 2002 [42] | 6 months | 39 | NS | NS | PST | Usual care (anticoagulation clinic) | NS | Warfarin | NS | % time in INR target range | Low:<br>- no power calculation<br>- no details on randomization<br>- no blinding<br>- adverse events not reported<br>- baseline demographic and clinical data not reported |
| Sidhu 2001 [43] | 24 months | 82 | 61 | 66 | PSM | Usual care (GP office or anticoagulation clinic) | MHV | Warfarin | Major and minor hemorrhages and TE events, mortality | % time in INR target range | Moderate:<br>- no power calculation<br>- no details on randomization<br>- no blinding<br>- adverse events not reported |
| Siebenhofer 2007 [44] | 36 months | 176 | 69 | 42 | PSM | Usual care (GP office or anticoagulation clinic) | AF, VTE, MHV | Warfarin and cumarin derivates | Major hemorrhages and TE events, mortality | Median, IQR of time in the INR target range and measurements in the target INR range | High |
| Soliman Hamad 2009[62] | 1 year | 58 | Int: 56<br>Ctr: 56 | NS | PSM | Usual care (anticoagulation clinic) | MHV | NS | Major and minor hemorrhages and TE events, mortality | % measurements in INR target range | Low:<br>- no power calculation<br>- no details on randomization<br>- no blinding<br>- no ITT analysis |
| Sunderji 2004 [45] | 8 months | 139 | 60 | 29 | PSM | Usual care (GP office) | MHV, AF, VTE | Warfarin | Major hemorrhages and TE events | % time in INR target range,<br>% measurements in INR target range | High |
| Voller 2005 [46] | 5 months | 202 | 64 | 34 | PSM | Usual care (GP office) | AF | NS | Major hemorrhages and TE events | % measurements in INR target range | Low:<br>- no power calculation<br>- no details on randomization<br>- no blinding<br>- no ITT analysis<br>- adverse events not reported |

* Sample size used in the analysis
\+ Other indication than AF, MHV or VTE

AF = atrial fibrillation
MHV = mechanical heart halve
POC = point of care management

PSM = patient self-management
PST = patient self-testing
VTE = venous thromboembolism

## Table 6. Pooled SMD of percentage time spent in INR target range

| Study | SMD | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Fitzmaurice | 0.131 | -0.086 | 0.348 | 7.74 |
| Beyth | 0.523 | 0.289 | 0.756 | 7.47 |
| Sidhu | 0.258 | -0.183 | 0.699 | 4.45 |
| Shiach | -0.101 | -0.737 | 0.535 | 2.77 |
| Gadisseur (1) | -0.056 | -0.427 | 0.316 | 5.32 |
| Gadisseur (2) | 0.150 | -0.163 | 0.463 | 6.17 |
| Gadisseur (3) | 0.037 | -0.345 | 0.419 | 5.18 |
| Gadisseur (4) | 0.220 | -0.106 | 0.546 | 5.97 |
| Sunderji | 0.182 | -0.151 | 0.516 | 5.86 |
| Gardiner | -0.127 | -0.604 | 0.349 | 4.07 |
| Khan | 0.035 | -0.390 | 0.461 | 4.63 |
| Fitzmaurice | 0.092 | -0.067 | 0.251 | 8.71 |
| Claes | -0.197 | -0.411 | 0.017 | 7.80 |
| Menendez-Jandula | -0.035 | -0.179 | 0.110 | 8.93 |
| Siebenhofer | 0.435 | 0.136 | 0.734 | 6.39 |
| Christensen | 0.968 | 0.535 | 1.400 | 4.55 |
| Dauphin | 0.211 | -0.270 | 0.691 | 4.03 |
| D+L pooled SMD | 0.156 | 0.032 | 0.280 | 100.00 |

Heterogeneity chi-squared = 47.09 (d.f. = 16) p = 0.000
I-squared (variation in SMD attributable to heterogeneity) = 66.0%
Estimate of between-study variance Tau-squared = 0.0395

Test of SMD=0 : z= 2.47 p = 0.014

## Table 7. Pooled SMD of percentage INR measurements in INR target range

| Study | SMD | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Fitzmaurice | 0.084 | -0.133 | 0.301 | 7.45 |
| Gadisseur (1) | 0.131 | -0.240 | 0.503 | 5.24 |
| Gadisseur (2) | 0.234 | -0.079 | 0.548 | 6.03 |
| Gadisseur (3) | 0.236 | -0.147 | 0.619 | 5.10 |
| Gadisseur (4) | 0.332 | 0.006 | 0.659 | 5.84 |
| Sunderji | 0.125 | -0.208 | 0.458 | 5.76 |
| Siebenhofer | 0.771 | 0.465 | 1.078 | 6.12 |
| Sidhu | 0.199 | -0.242 | 0.639 | 4.44 |
| Menendez-Jandula | 0.175 | 0.030 | 0.319 | 8.48 |
| Cromheecke | 0.385 | -0.035 | 0.804 | 4.67 |
| Horstkotte | 0.457 | 0.133 | 0.781 | 5.87 |
| Kortke | 0.380 | 0.218 | 0.541 | 8.25 |
| Eitz | 0.321 | 0.174 | 0.467 | 8.45 |
| Bubner | -0.036 | -0.167 | 0.094 | 8.65 |
| Voller | 0.496 | 0.216 | 0.777 | 6.51 |
| Soliman Hamad | 1.509 | 0.923 | 2.095 | 3.15 |
| D+L pooled SMD | 0.317 | 0.190 | 0.444 | 100.00 |

Heterogeneity chi-squared = 60.10 (d.f. = 15) p = 0.000
I-squared (variation in SMD attributable to heterogeneity) = 75.0%
Estimate of between-study variance Tau-squared = 0.0440

Test of SMD=0 : z= 4.89 p = 0.000

## Table 8. Pooled OR of major hemorrhagic events

| Study | OR | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Fitzmaurice | 1.039 | 0.276 | 3.907 | 8.46 |
| Sunderji | 0.333 | 0.013 | 8.325 | 1.43 |
| Claes | 1.374 | 0.323 | 5.842 | 7.08 |
| Siebenhofer | 1.590 | 0.259 | 9.758 | 4.51 |
| Beyth | 0.550 | 0.230 | 1.319 | 19.42 |
| Sidhu | 0.459 | 0.018 | 11.608 | 1.42 |
| Menendez-Jandula | 0.568 | 0.165 | 1.958 | 9.69 |
| Dauphin | 0.055 | 0.003 | 1.001 | 1.76 |
| Sawicki | 0.988 | 0.061 | 16.063 | 1.91 |
| Kortke | 0.637 | 0.337 | 1.207 | 36.42 |
| Eitz | 0.416 | 0.069 | 2.504 | 4.60 |
| Voller | 3.030 | 0.122 | 75.263 | 1.44 |
| Soliman Hamad | 1.000 | 0.060 | 16.791 | 1.86 |
| Cromheecke | (Excluded) | | | |
| D+L pooled OR | 0.677 | 0.460 | 0.995 | 100.00 |

Heterogeneity chi-squared = 6.88 (d.f. = 12) p = 0.865
I-squared (variation in OR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000

Test of OR=1 : z= 1.99 p = 0.047

## Table 9. Pooled OR of major thromeboembolic events

| Study | OR | [95% Conf. | Interval] | % Weight |
|---|---|---|---|---|
| Fitzmaurice | 1.109 | 0.246 | 4.998 | 4.87 |
| Sunderji | 0.197 | 0.009 | 4.182 | 1.18 |
| Claes | 0.814 | 0.200 | 3.311 | 5.61 |
| Siebenhofer | 0.889 | 0.286 | 2.761 | 8.60 |
| Beyth | 0.797 | 0.388 | 1.635 | 21.33 |
| Sidhu | 0.459 | 0.018 | 11.608 | 1.06 |
| Menendez-Jandula | 0.173 | 0.059 | 0.508 | 9.54 |
| Sawicki | 0.193 | 0.009 | 4.079 | 1.18 |
| Cromheecke | 0.319 | 0.013 | 8.036 | 1.06 |
| Kortke | 0.563 | 0.270 | 1.174 | 20.46 |
| Eitz | 0.401 | 0.200 | 0.801 | 23.00 |
| Voller | 0.330 | 0.013 | 8.199 | 1.07 |
| Soliman Hamad | 0.322 | 0.013 | 8.237 | 1.05 |
| D+L pooled OR | 0.526 | 0.377 | 0.733 | 100.00 |

Heterogeneity chi-squared = 9.22 (d.f. = 12) p = 0.684
I-squared (variation in OR attributable to heterogeneity) = 0.0%
Estimate of between-study variance Tau-squared = 0.0000

Test of OR=1 : z= 3.79 p = 0.000

**Table 10. Characteristics of economic evaluations in literature review**

| | Medical costs | All costs | Outcome |
|---|---|---|---|
| Lafata et al.[52] | | | |
| Standard of care laboratory test to anticoagulation POC test | -$6,776 | $54,615 | cost per event |
| Anticoagulation POC test to patient self-test | $43,391 | -$8,270 | cost per event |
| Regier et al.[63] | | | |
| Standard of care laboratory test to self-management | $263,269 | | incremental cost-effectiveness ratio over 1 year (with QALYs) |
| Standard of care laboratory test to self-management | $15,717 | | incremental cost-effectiveness ratio over 5 years (with QALYs) |
| Standard of care laboratory test to self-management | $3,331 | | incremental cost-effectiveness ratio over 10 years (with QALYs) |
| National Health Service R&D Health Technology Assessment Programme[20] | | | |
| Standard of care laboratory test to self-management | $1,404,988 | | incremental cost-effectiveness ratio over 1 year (with QALYs) |
| Standard of care laboratory test to self-management | $297,869 | | incremental cost-effectiveness ratio over 5 years (with QALYs) |
| Standard of care laboratory test to self-management | $154,953 | | incremental cost-effectiveness ratio over 10 years (with QALYs) |
| Canadian Agency for Drugs and Technologies in Health [CADTH][18] | | | |
| Standard of care laboratory test to anticoagulation POC test | -$2,902 | $11,531 | cost per QALY |
| Standard of care laboratory test to patient self-test | $77,837 | -$7,579 | cost per QALY |
| Ontario Medical Advisory Secretariat[22] | | | |
| Standard of care laboratory test | $24,317 | | cost per patient over 5 years |
| Anticoagulation POC test | $19,251 | | cost per patient over 5 years |
| Self-testing | $20,265 | | cost per patient over 5 years |
| Self-management | $15,199 | | cost per patient over 5 years |

All costs are in Canadian dollars

## Table 11. Basic results of the Markov model

| With device costs and supply costs incurred by the healthcare system | | | | Total system cost | Total society cost | Total cost per patient | Total QALYs per patient |
|---|---|---|---|---|---|---|---|
| 100% laboratory testing | | | | 4466 | 4468 | 8934 | 4.358 |
| 100% clinic testing | | | | 3264 | 2663 | 5927 | 4.3459 |
| 100% self-testing at home | | | | 8109 | 203 | 8312 | 4.3401 |
| Mix | | | | | | | |
| Lab | POC Clinic | Self testing (PST) | Self manag-ing (PSM) | | | | |
| 75 | 25 | 0 | 0 | 4035 | 3918 | 7953 | 4.2928 |
| 50 | 25 | 25 | 0 | 4873 | 2879 | 7752 | 4.3141 |
| 50 | 25 | 20 | 5 | 4871 | 2954 | 7825 | 4.3466 |
| 25 | 50 | 25 | 0 | 4835 | 2292 | 7127 | 4.2768 |
| 25 | 50 | 20 | 5 | 4620 | 2361 | 6981 | 4.3968 |
| 25 | 25 | 50 | 0 | 5833 | 1995 | 7828 | 4.378 |
| 25 | 25 | 35 | 15 | 5702 | 1790 | 7492 | 4.424 |

**Table 12. Sensitivity results of the Markov model**

With device costs incurred by the patient instead of government

| With device costs incurred by patient and supply costs incurred by the healthcare system | | | | Total system cost | Total society cost | Total cost per patient | Total QALYs per patient |
|---|---|---|---|---|---|---|---|
| 100% self-testing at home | | | | 5567 | 2365 | 7932 | 4.2552 |
| Mix | | | | | | | |
| Lab | POC Clinic | Self testing (PST) | Self manag-ing (PSM) | | | | |
| 50 | 25 | 25 | 0 | 4450 | 3441 | 7891 | 4.3156 |
| 50 | 25 | 20 | 5 | 4317 | 3430 | 7747 | 4.3258 |
| 25 | 50 | 25 | 0 | 4067 | 2923 | 6990 | 4.2682 |
| 25 | 50 | 20 | 5 | 3890 | 2832 | 6722 | 4.3296 |
| 25 | 25 | 50 | 0 | 4386 | 2787 | 7173 | 4.2951 |
| 25 | 25 | 35 | 15 | 4280 | 2736 | 7016 | 4.3157 |

Note: Since device and supply costs are changed only for PST and PSM scenarios, analyses with only lab and/or POC clinic patients are dropped.

With device and consumable costs incurred by the patient instead of government

| With device costs and supply costs for PST and PSM incurred by the patient. | | | | Total system cost | Total society cost | Total cost per patient ($) | Total QALYs per patient |
|---|---|---|---|---|---|---|---|
| 100% self-testing at home | | | | 4847 | 3508 | 8355 | 4.3323 |
| Mix | | | | | | | |
| Lab | POC Clinic | Self testing (PST) | Self manag-ing (PSM) | | | | |
| 50 | 25 | 25 | 0 | 4208 | 3772 | 7980 | 4.3501 |
| 50 | 25 | 20 | 5 | 4149 | 3713 | 7862 | 4.3322 |
| 25 | 50 | 25 | 0 | 3849 | 3246 | 7095 | 4.2869 |
| 25 | 50 | 20 | 5 | 3815 | 3228 | 7043 | 4.3609 |
| 25 | 25 | 50 | 0 | 4212 | 3447 | 7659 | 4.2908 |
| 25 | 25 | 35 | 15 | 4161 | 3488 | 7649 | 4.3721 |

Note: Since device and supply costs are changed only for PST and PSM scenarios, analyses with only lab and/or POC clinic patients are dropped

With consumable costs incurred by the patient instead of government

| With device costs incurred by the healthcare system and supply costs incurred by the patient for PST and PSM. | | | | Total system cost | Total society cost | Total cost per patient ($) | Total QALYs per patient |
|---|---|---|---|---|---|---|---|
| 100% self-testing at home | | | | 7277 | 1057 | 8334 | 4.314 |
| Mix | | | | | | | |
| Lab | POC Clinic | Self testing (PST) | Self manag-ing (PSM) | | | | |
| 50 | 25 | 20 | 5 | 4528 | 3025 | 7553 | 4.3331 |
| 25 | 50 | 25 | 0 | 4454 | 2669 | 7123 | 4.3090 |
| 25 | 50 | 20 | 5 | 4090 | 2644 | 6734 | 4.2696 |
| 25 | 25 | 50 | 0 | 5541 | 2305 | 7846 | 4.3184 |
| 25 | 25 | 35 | 15 | 5243 | 2091 | 7334 | 4.2996 |

Note: Since device and supply costs are changed only for PST and PSM scenarios, analyses with only lab and/or POC clinic patients are dropped

With higher probabilities of below-normal INR from having a mechanical heart valve

| **INR levels (sensitivity 1 -- mechanical heart valves)** | | | | Total system cost | Total society cost | Total cost per patient | Total QALYs per patient |
|---|---|---|---|---|---|---|---|
| 100% laboratory testing | | | | 4477 | 4568 | 9045 | 4.2898 |
| 100% clinic testing | | | | 3183 | 2597 | 5780 | 4.2462 |
| 100% self-testing at home | | | | 7955 | 200 | 8155 | 4.2735 |
| Mix | | | | | | | |
| Lab | POC Clinic | Self testing (PST) | Self manag-ing (PSM) | | | | |
| 75 | 25 | 0 | 0 | 4080 | 3957 | 8037 | 4.3685 |
| 50 | 25 | 25 | 0 | 5186 | 2519 | 7705 | 4.2135 |
| 50 | 25 | 20 | 5 | 4727 | 2675 | 7402 | 4.3213 |
| 25 | 50 | 25 | 0 | 4554 | 2524 | 7078 | 4.3173 |
| 25 | 50 | 20 | 5 | 4388 | 2258 | 6646 | 4.3498 |
| 25 | 25 | 50 | 0 | 6022 | 1616 | 7638 | 4.2899 |
| 25 | 25 | 35 | 15 | 5343 | 1964 | 7307 | 4.3658 |

With lower compliance (higher probabilities of below-average or above-average INR) due to a rural population

| **INR levels (sensitivity 2 -- worse compliance by rural)** | | | | Total system cost | Total society cost | Total cost per patient | Total QALYs per patient |
|---|---|---|---|---|---|---|---|
| 100% laboratory testing | | | | 4468 | 4517 | 8985 | 4.335 |
| 100% clinic testing | | | | 3223 | 2630 | 5853 | 4.2566 |
| 100% self-testing at home | | | | 7890 | 198 | 8088 | 4.185 |
| Mix | | | | | | | |
| Lab | POC Clinic | Self testing (PST) | Self manag-ing (PSM) | | | | |
| 75 | 25 | 0 | 0 | 3993 | 3836 | 7829 | 4.3719 |
| 50 | 25 | 25 | 0 | 4965 | 2593 | 7558 | 4.2544 |
| 50 | 25 | 20 | 5 | 4745 | 2790 | 7535 | 4.2833 |
| 25 | 50 | 25 | 0 | 4762 | 2594 | 7356 | 4.4504 |
| 25 | 50 | 20 | 5 | 4190 | 2371 | 6561 | 4.3437 |
| 25 | 25 | 50 | 0 | 5576 | 1795 | 7371 | 4.2128 |
| 25 | 25 | 35 | 15 | 5495 | 1711 | 7206 | 4.2641 |

With lower compliance (higher probabilities of below-average or above average INR) due to an older population

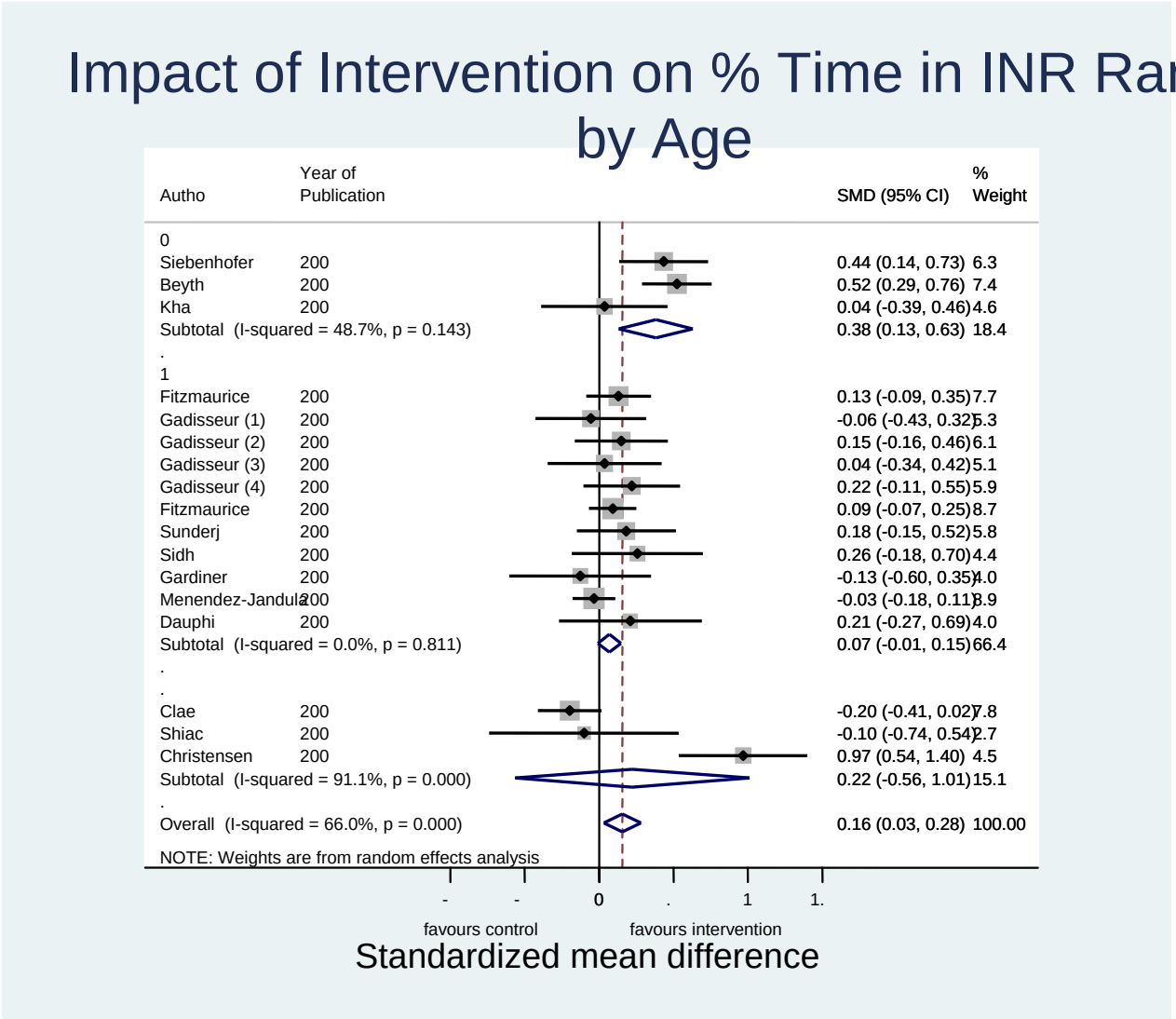
| **INR levels (sensitivity 3 -- worse compliance by age)** | | | | Total system cost | Total society cost | Total cost per patient | Total QALYs per patient |
|---|---|---|---|---|---|---|---|
| 100% laboratory testing | | | | 4402 | 4451 | 8853 | 4.1912 |
| 100% clinic testing | | | | 3157 | 2576 | 5733 | 4.1788 |
| 100% self-testing at home | | | | 7885 | 198 | 8083 | 4.1705 |
| Mix | | | | | | | |
| Lab | POC Clinic | Self testing (PST) | Self manag-ing (PSM) | | | | |
| 75 | 25 | 0 | 0 | 3912 | 3797 | 7709 | 4.183 |
| 50 | 25 | 25 | 0 | 4762 | 2924 | 7686 | 4.2185 |
| 50 | 25 | 20 | 5 | 4563 | 3093 | 7656 | 4.1793 |
| 25 | 50 | 25 | 0 | 4403 | 2223 | 6626 | 4.0705 |
| 25 | 50 | 20 | 5 | 4266 | 2519 | 6785 | 4.3098 |
| 25 | 25 | 50 | 0 | 5759 | 1799 | 7558 | 4.2695 |
| 25 | 25 | 35 | 15 | 5303 | 1903 | 7206 | 4.248 |

## Table 13. Overall costs from different therapies

| | | | | Total system cost | 1.1% of population (n=~37,902) | 1% of population (n=~35,580) | 0.6% of population (n=~21,710) | Total cost per patient ($) | 1.1% of population (n=~37,902) | 1% of population (n=~35,580) | 0.6% of population (n=~21,710) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 100% laboratory testing | | | | 4466 | $ 170,963,035 | $ 160,112,442 | $ 96,956,860 | 8934 | $ 342,002,633 | $ 320,296,586 | $ 193,957,140 |
| 100% clinic testing | | | | 3264 | $ 124,949,249 | $ 117,019,035 | $ 70,861,440 | 5927 | $ 226,891,606 | $ 212,491,366 | $ 128,675,170 |
| 100% self-testing | | | | 8109 | $ 310,420,791 | $ 290,719,165 | $ 176,046,390 | 8312 | $ 318,191,838 | $ 297,997,003 | $ 180,453,520 |
| Mix | | | | | | | | | | | |
| Lab | Clinic | PST | PSM | | | | | | | | |
| 75 | 25 | 0 | 0 | 4035 | $ 154,463,916 | $ 144,660,480 | $ 87,599,850 | 7953 | $ 304,448,952 | $ 285,126,343 | $ 172,659,630 |
| 50 | 25 | 25 | 0 | 4873 | $ 186,543,410 | $ 174,703,970 | $ 105,792,830 | 7752 | $ 296,754,467 | $ 277,920,208 | $ 168,295,920 |
| 50 | 25 | 20 | 5 | 4871 | $ 186,466,848 | $ 174,632,267 | $ 105,749,410 | 7825 | $ 299,548,982 | $ 280,537,362 | $ 169,880,750 |
| 25 | 50 | 25 | 0 | 4835 | $ 185,088,732 | $ 173,341,616 | $ 104,967,850 | 7127 | $ 272,828,830 | $ 255,513,070 | $ 154,727,170 |
| 25 | 50 | 20 | 5 | 4620 | $ 176,858,312 | $ 165,633,560 | $ 100,300,200 | 6981 | $ 267,239,801 | $ 250,278,763 | $ 151,557,510 |
| 25 | 25 | 50 | 0 | 5833 | $ 223,293,190 | $ 209,121,333 | $ 126,634,430 | 7828 | $ 299,663,825 | $ 280,644,916 | $ 169,945,880 |
| 25 | 25 | 35 | 15 | 5702 | $ 218,278,376 | $ 204,424,797 | $ 123,790,420 | 7492 | $ 286,801,402 | $ 268,598,839 | $ 162,651,320 |
| | | | Means | 5061 | $ 193,732,586 | $ 181,436,866 | $ 109,869,968 | 7613 | $ 291,437,233 | $ 272,940,446 | $ 165,280,401 |

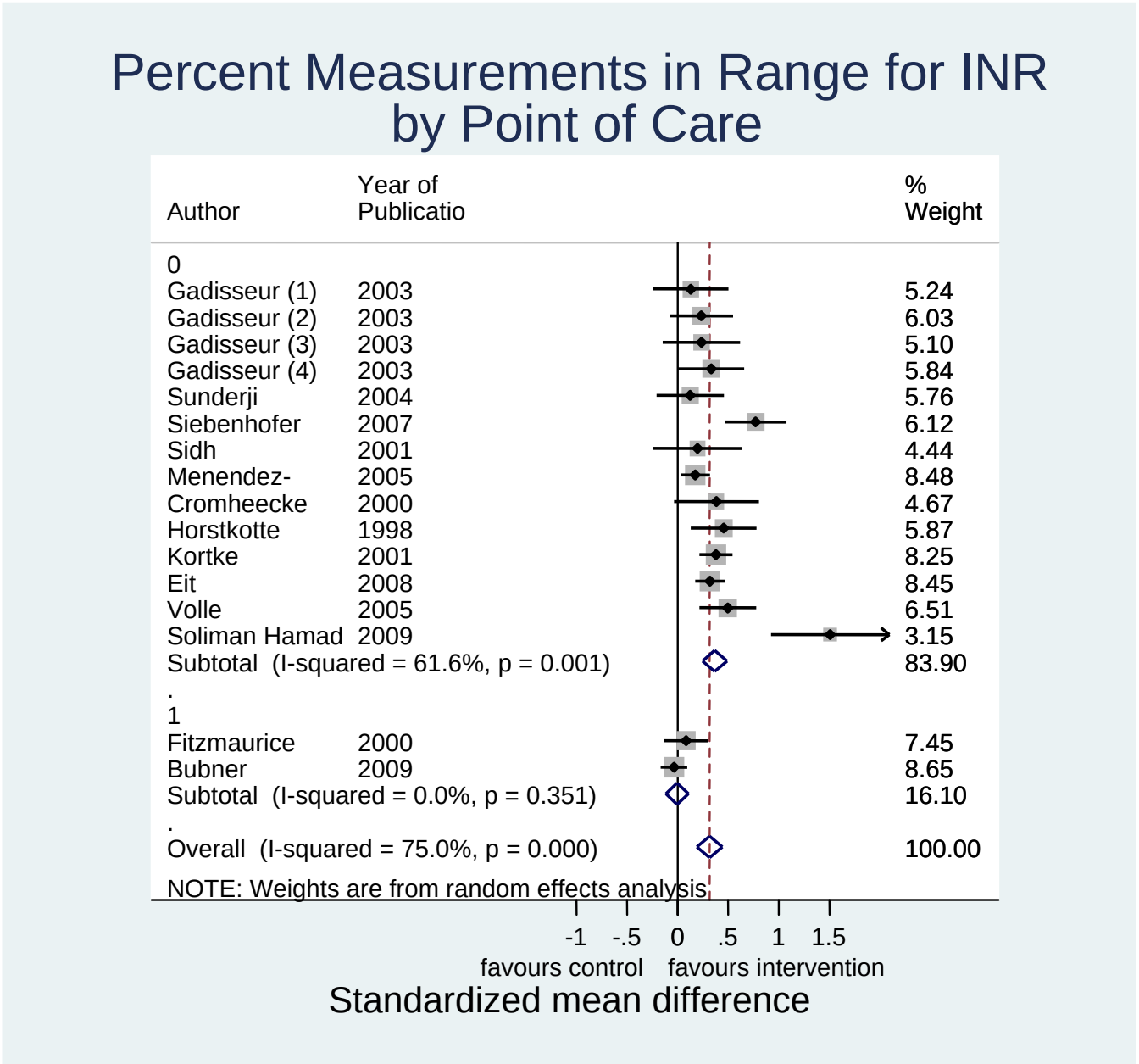
# FIGURES

**Figure 1. Effect of age on SMD of percentage time spent in INR target range**




0 = Studies limited to elderly patients
1 = Studies with no age limits
- = Studies not indicating ages of patients included

**Figure 2. Effect of POC on SMD of percentage INR measurements in INR target range**




0 = PST/PSM
1 = POC (Family physicians office, pharmacist)

**Figure 3. Pooled OR of major hemorrhagic events**

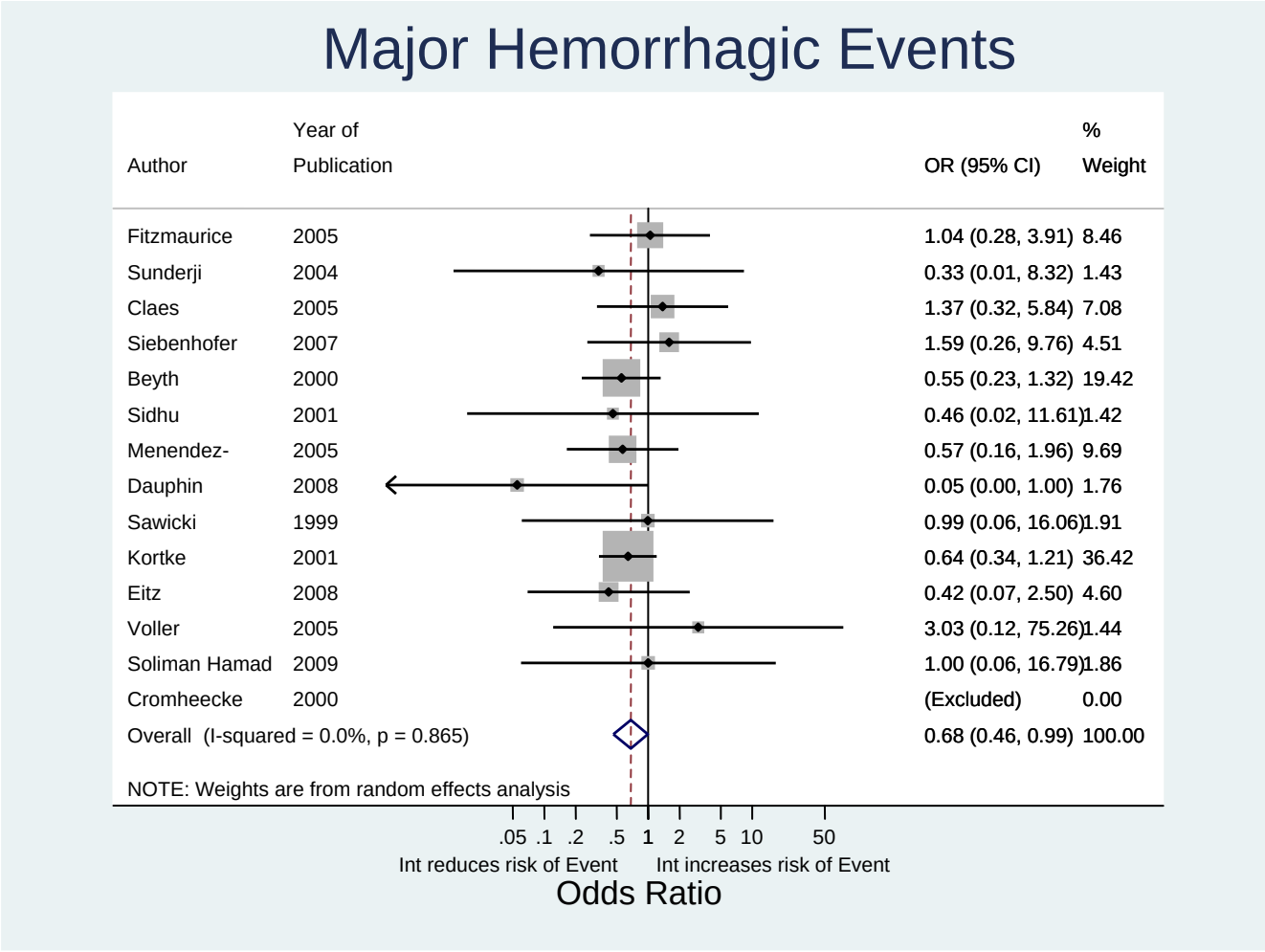
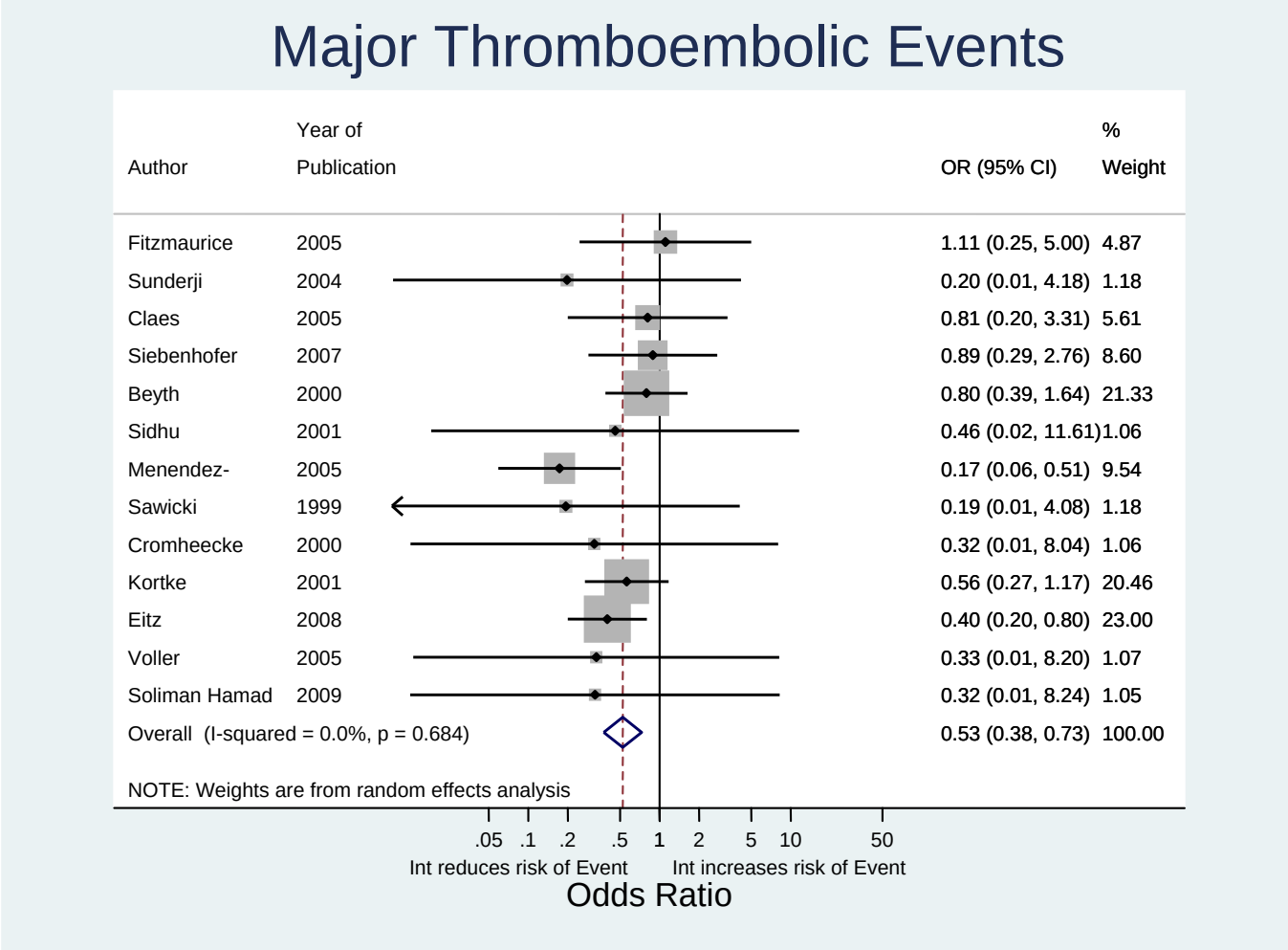


**Figure 4. Pooled OR of major thromboembolic events**



# APPENDICES

# Appendix 1: Conditions requiring long-term OAT, ICD-10 codes

| ICD-10 code | Conditions requiring long-term OAT |
|---|---|
| **(I80-I89)** | **Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified** |
| I80.1 | Phlebitis and thrombophlebitis of femoral vein |
| I80.2 | Phlebitis and thrombophlebitis of other deep vessels of lower extremities<br>Deep vein thrombosis NOS |
| I80.3 | Phlebitis and thrombophlebitis of lower extremities, unspecified<br>Embolism or thrombosis of lower extremity NOS |
| I80.8 | Phlebitis and thrombophlebitis of other sites |
| I80.9 | Phlebitis and thrombophlebitis of unspecified site |
| I81 | Portal vein thrombosis<br>Portal (vein) obstruction |
| I82 | Other venous embolism and thrombosis |
| I82.0 | Budd-Chiari syndrome |
| I82.1 | Thrombophlebitis migrans |
| I82.2 | Embolism and thrombosis of vena cava |
| I82.3 | Embolism and thrombosis of renal vein |
| I82.8 | Embolism and thrombosis of other specified veins |
| I82.9 | Embolism and thrombosis of unspecified vein<br>Embolism of vein NOS<br>Thrombosis (vein) NOS |
| **(I26-I28)** | **Pulmonary heart disease and diseases of pulmonary circulation** |
| I26 | Pulmonary embolism<br>*Includes:* pulmonary (artery)(vein):<br>· infarction<br>· thromboembolism<br>· thrombosis |
| I26.0 | Pulmonary embolism with mention of acute cor pulmonale<br>Acute cor pulmonale NOS |
| I26.9 | Pulmonary embolism without mention of acute cor pulmonale<br>Pulmonary embolism NOS |
| Other | venous embolism and thrombosis (of):<br>· cerebral ( I63.6 , I67.6 )<br>· mesenteric ( K55.0 ) |
| **I48** | **Atrial fibrillation and flutter** |
| **Z95.2** | **Presence of prosthetic heart valve** |
| **Z95.4** | **Presence of other heart-valve replacement** |

# Appendix 2: Search Strategy

Electronic Databases Searched
MEDLINE (OVID)
Cochrane Library (OVID)
EMBASE (OVID)
NHS Economic Evaluations Database (OVID)
Health Technology Assessment Database - University of York (OVID)
DARE Database of Reviews of Effects (OVID)
EconLit (EBSCO)

MEDLINE (OVID)
Cochrane CENTRAL Register of Controlled Trials (OVID)

1. exp anticoagulants/ or exp warfarin/
2. exp vitamin k/ai [antagonists & inhibitors]
3. 81 81 2 warfarin.rn.
4. 81 81 2.tw.
5. (vitamin adj1 k adj1 antagonist*).tw.
6. (anticoagula* or (anti adj1 coagula*) or (anti adj1 vitamin adj1 k) or coumadin or coumarin or warfarin).tw.
7. exp blood coagulation tests or exp international normalized ratio/ or exp prothrombin time/ or exp whole blood coagulation time/
8. ((international adj1 normali* adj1 ratio*) or inr or prothrombin* or (PT adj1 (monitor* or system* or measure* or test or tests or testing or device*)) or coagulomet*).ti,ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp ambulatory care/ or exp ambulatory care facilities/ or family practice/ or home care services/ or long term care/ or exp monitoring, ambulatory/ or outpatients/ or physicians, family/ or physicians' offices/ or point of care systems/ or primary health care/ or exp self care/
11. (general practi* or gp or primary care or primary health or family physician*).tw.
12. (self adj1 (test or tests or testing or tested or monitor* or manage* or managing or control$ or administer*).tw.
13. (home adj1 (test or tests or testing or tested or monitor* or manage* or managing or control* or administer* or device*)).tw.
14. (point adj1 of adj1 care).tw.
15. (poc adj1 (test or tests or monitor*or device*)).tw.
16. (near adj1 patient adj1 test).tw.
17. ((ambulatory adj1 monitor*) or (ambulatory adj1 care) or (outpatient* adj1 monitor*) or (outpatient* adj1 control) or (outpatient* adj2 care) or (outpatient adj1 health adj1 service*) or (home adj2 care)).tw.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 9 and 18
20. (protime or (pro adj1 time) or coaguchek* or (coagu adj1 chek) or inratio or avocet* or (tas adj1 pt adj1 nc) or (harmony adj1 inr) or (rubicon adj3 prothrombin)).tw.

21. 19 or 20
22. limit 21 to yr="1989 to 2009"
23. limit 22 to english language
24. (randomized controlled trial or controlled clinical trial or meta analysis).pt.
25. (placebo or randomized or randomly).ti,ab.
26. trial.ti.
27. "clinical trials as topic".sh.
28. ((met$ adj1 analy$) or metaanaly$ or metanaly$ or (health adj1 technology adj1 assessment$) or (meta adj1 regression$) or meta-regression$ or (mega adj1 regression$) or (systematic$ adj1 (review$ or overview$)) or (methodologic$ adj1 literature adj1 (review$ or overview$)) or (quantitative adj1 (review$ or overview$ or synthes$)) or (research adj1 (integration$ or overview$)) or ((integrative or collaborative) adj2 (review$ or overview$)) or (pool$ adj1 analy$) or (data adj1 (synthes$ or extraction or abstraction))).ti,ab.
29. 24 or 25 or 26 or 27 or 28
30. 23 and 29
31. exp "costs and cost analysis"/
32. (cost benefit* or cost effective* or cost minimi* or cost utility* or economic evaluation*).tw.
33. 31 or 32
34. 23 and 33
35. 30 or 34

*Note: the search terms above will be adapted as needed when searching other electronic databases*

EMBASE (OVID)

1. antivitamin K/ or anticoagulant agent/ or anticoagulant protein/ or anticoagulant therapy or anticoagulation/ or warfarin/
2. 81 81 2.rn.
3. 81 81 2.ti,ab.
4. (vitamin adj1 k adj1 antagonist*).ti,ab.
5. (warfarin or coumadin or coumarin or anticoagula* or (anti adj1 coagula* or (anti adj1 vitamin adj1 k)).ti,ab.
6. international normalized ratio/ or prothrombin time/ or blood clotting test/ or blood clotting time/ or prothrombin/
7. ((international adj1 normali* adj1 ratio*) or inr or prothrombin* or (PT adj1 (monitor* or system* or measure* or test or tests or testing or device*)) or coagulomet*).ti,ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. ambulatory care/ or ambulatory monitoring/ or autoregulation/ or drug monitoring/ or drug self administration/ or general practice/ or general practitioner/ or home care/ or home monitoring/ or long

term care/ or outpatient/ or outpatient care/ or exp outpatient department/ or “point of care testing”/ or primary health care/ or primary medical care/ or exp self care/ or self monitoring/

10. (general practi* or gp or primary care or primary health or family physician*).tw.
11. (self adj1 (test or tests or testing or tested or monitor* or manage* or managing or control$ or administer*)).ti,ab.
12. (home adj1 (test or tests or testing or tested or monitor* or manage* or managing or control* or administer* or device*)).ti,ab.
13. (point adj1 of adj1 care).ti,ab.
14. poc adj1 (test* or monitor* or device*)).ti,ab.
15. (near adj1 patient adj1 test).ti,ab.
16. (ambulatory* adj1 monitor*).ti,ab.
17. (outpatient* adj2 monitor*).ti,ab.
18. ((ambulatory adj1 care) or (outpatient* adj1 control) or (outpatient* adj2 care) or (outpatient adj1 health adj1 service*) or (home adj2 care)).ti,ab.
19. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 8 and 20
21. (protime or "pro time" or coaguchek* or "coagu check" or inratio or avocet* or "tas pt nc" or "harmony inr" or rubicon).dv.
22. (protime or (pro adj1 time) or coaguchek* or (coagu adj1 check) or inratio or avocet* or (tas adj1 pt adj1 nc) or (harmony adj1 inr) or (rubicon adj3 prothrombin)).ti,ab.
23. 20 or 21 or 22
24. limit 23 to yr=”1989 to 2009”
25. limit 24 to english language
26. Randomized Controlled Trial/
27. (random$ or factorial$ or crossover$ or cross over$ or placebo$ or ((singl$ or doubl$ or tripl$ or trebl$) adj1 (blind$ or mask$ or dumm$)) or rct$ or assign$ or allocat$ or volunteer$).ti,ab.
28. Double Blind Procedure/ or Single Blind Procedure/ or crossover-procedure/ or Meta Analysis/ or "systematic review"/
29. ((met$ adj1 analy$) or metaanaly$ or metanaly$ or (health adj1 technology adj1 assessment$) or (meta adj1 regression$) or meta-regression$ or (mega adj1 regression$) or (systematic$ adj1 (review$ or overview$)) or (methodologic$ adj1 literature adj1 (review$ or overview$)) or (quantitative adj1 (review$ or overview$ or synthes$)) or (research adj1 (integration$ or overview$)) or ((integrative or collaborative) adj2 (review$ or overview$)) or (pool$ adj1 analy$) or (data adj1 (synthes$ or extraction or abstraction))).ti,ab.

30. 26 or 27 or 28 or 29
31. 25 and 30
32. exp economic evaluation/
33. (cost benefit* or cost effective* or cost minimi* or cost utility* or economic evaluation*).tw.
34. 32 or 33
35. 25 and 34
36. 31 or 35

Cochrane Database of Systematic Reviews (OVID)
Health Technology Assessment Database (OVID)
NHS Economic Evaluation Database (OVID)
DARE Database of Reviews of Effects (OVID)

1. 81 81 2.tw.
2. (vitamin adj1 k adj1 antagonist*).tw.
3. (anticoagula* or (anti adj1 coagula*) or (anti adj1 vitamin adj1 k) or coumadin or coumarin or warfarin).tw.
4. ((international adj1 normali* adj1 ratio*) or inr or prothrombin* or (PT adj1 (monitor* or system* or measure* or test or tests or testing or device*)) or coagulomet*).tw.
5. 1 or 2 or 3 or 4
6. (self adj1 (test or tests or testing or tested or monitor* or manage* or managing or control$ or administer*).tw.
7. (general practi* or gp or primary care or primary health or family physician*).tw.
8. (home adj1 (test or tests or testing or tested or monitor* or manage* or managing or control* or administer* or device*)).tw.
9. (point adj1 of adj1 care).tw.
10. (poc adj1 (test or tests or monitor*or device*)).tw.
11. (near adj1 patient adj1 test).tw.
12. ((ambulatory adj1 monitor*) or (ambulatory adj1 care) or (outpatient* adj1 monitor*) or (outpatient* adj1 control) or (outpatient* adj2 care) or (outpatient adj1 health adj1 service*) or (home adj2 care)).tw.
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. (protime or (pro adj1 time) or coaguchek* or (coagu adj1 chek) or inratio or avocet* or (tas adj1 pt adj1 nc) or (harmony adj1 inr) or (rubicon adj3 prothrombin)).tw.
15. 13 or 14
16. limit 15 to yr="1989 to 2009"
17. limit 16 to english language

EconLit (EBSCO)

1. 81 81 2.[Search Fields]
2. (vitamin adj1 k adj1 antagonist*)[Search Fields]
3. (anticoagula* or (anti adj1 coagula*) or (anti adj1 vitamin adj1 k) or coumadin or coumarin or warfarin)[Search Fields]

4. ((international adj1 normali* and ratio*) or inr or prothrombin* or (PT and (monitor* or system* or measure* or test or tests or testing or device*)) or coagulomet*)[Search Fields]
5. 1 or 2 or 3 or 4
6. (self and (test or tests or testing or tested or monitor* or manage* or managing or control$ or administer*)[Search Fields]
7. (home and (test or tests or testing or tested or monitor* or manage* or managing or control* or administer* or device*))[Search Fields]
8. (point and of and care)[Search Fields]
9. (poc and (test or tests or monitor*or device*))[Search Fields]
10. (near and patient and test)[Search Fields]
11. ((ambulatory and monitor*) or (ambulatory and care) or (outpatient* and monitor*) or (outpatient* and control) or (outpatient* and care) or (outpatient and health and service*) or (home and care))[Search Fields]
12. (general practi* or gp or primary care or primary health or family physician*)[Search Fields]
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 5 and 13
15. (protime or (pro adj1 time) or coaguchek* or (coagu adj1 chek) or inratio or avocet* or (tas adj1 pt adj1 nc) or (harmony adj1 inr) or (rubicon adj3 prothrombin))[Search Fields]
16. 14 or 15
17. limit 16 to yr="1989 to 2009"
18. limit 17 to english language

## Appendix 3: Gray Literature Sources

AHRQ http://www.ahrq.gov/

National Research register http://www.nrr.nhs.uk/

Medical Services Advisory Committee http://www.health.gov.au/internet/msac/publishing.nsf/Content/home-1

HTAi Vortal http://216.194.91.140/vortal/

NICHSR http://nlm.nih.gov/nichsr

ICES http://www.ices.on.ca/webpage.cfm

McGill TAU http://www.mcgill.ca/tau/

MAS (Ontario) http://health.gov.on.ca/english/providers/program/mas/mas_mn.html

NCCHTA http://www.hta.nhsweb.nhs.uk/

NICE http://www.nice.org.uk/

BCBS TEC http://www.bcbs.com/betterknowledge/tec/tec-assessments.html

VATAP http://www.va.gov/VATAP/

EuroScan http://www.euroscan.bham.ac.uk/

AHTA http://www.health.adelaide.edu.au/ahta/

# Appendix 4: CONSORT Statement 2001 Checklist[49]

| *PAPER SECTION* And topic | Item | Descriptor | Reported on Page # |
|---|---|---|---|
| *TITLE & ABSTRACT* | 1 | How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned"). | |
| *INTRODUCTION* Background | 2 | Scientific background and explanation of rationale. | |
| *METHODS* Participants | 3 | Eligibility criteria for participants and the settings and locations where the data were collected. | |
| Interventions | 4 | Precise details of the interventions intended for each group and how and when they were actually administered. | |
| Objectives | 5 | Specific objectives and hypotheses. | |
| Outcomes | 6 | Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors). | |
| Sample size | 7 | How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules. | |
| Randomization -- Sequence generation | 8 | Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification) | |
| Randomization -- Allocation concealment | 9 | Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned. | |
| Randomization -- Implementation | 10 | Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups. | |
| Blinding (masking) | 11 | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated. | |
| Statistical methods | 12 | Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses. | |
| *RESULTS* Participant flow | 13 | Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons. | |
| Recruitment | 14 | Dates defining the periods of recruitment and follow-up. | |
| Baseline data | 15 | Baseline demographic and clinical characteristics of each group. | |
| Numbers analyzed | 16 | Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%). | |
| Outcomes and estimation | 17 | For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval). | |
| Ancillary analyses | 18 | Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory. | |
| Adverse events | 19 | All important adverse events or side effects in each intervention group. | |
| *DISCUSSION* Interpretation | 20 | Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes. | |
| Generalizability | 21 | Generalizability (external validity) of the trial findings. | |
| Overall evidence | 22 | General interpretation of the results in the context of current evidence. | |

*From* Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357(9263):1191-1194.

## Appendix 5: GRADE system[50]

Type of evidence
 Randomized controlled trial (RCT): given a high GRADE level to start
 Observational study: given a low GRADE level to start
 Any other evidence: given a very low GRADE level to start

Decrease GRADE level if:
 Serious limitation to study quality (-1, reduce GRADE level by 1 so a high GRADE level will become a moderate GRADE level) or very serious limitation to study quality (-2, reduce GRADE level by 2 so a high GRADE level will become a low GRADE level)
 Important inconsistency (-1, reduce GRADE level by 1)
 Some (-1) or major (-2) uncertainty about directness
 Imprecise or sparse data (-1)
 High probability of reporting bias (-1)

Increase GRADE level if:
 Strong evidence of association-significant relative risk of > 2 (< 0.5) based on consistent evidence from 2 or more observation studies, with no plausible confounders (+1, increase GRADE level by 1, so a moderate GRADE level will become high. However a high GRADE level will remain high)
 Very strong evidence of association-significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2, increase GRADE level by 2, so a low GRADE level will become a high GRADE level)
 Evidence of a dose response gradient (+1)
 All plausible confounders would have reduced the effect (+1)

Overall GRADE Level definitions

High: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low: Any estimate of effect is very uncertain.

# Appendix 6: Parameters, usage and cost estimates used in the economic model

| INR levels | Lab | Clinic | Home (self-test) | Home (self-manage) | |
|---|---|---|---|---|---|
| Below Normal (% of time) | 0.2 | 0.17 | 0.17 | 0.15 | The NHS R&D HTA Programme.[20] |
| Normal (% of time) | 0.64 | 0.68 | 0.68 | 0.72 | |
| Above Normal (% of time) | 0.16 | 0.15 | 0.15 | 0.13 | |
| | INR levels | | | | |
| **Adverse events** | Below | Normal | Above | | |
| Minor clot event | 0.0272 | 0.0073 | 0.0081 | | The NHS R&D HTA Programme.[20] |
| Major clot event | 0.0136 | 0.0036 | 0.004 | | half of minor clot event |
| Minor bleed event | 0.061 | 0.0475 | 0.1129 | | The NHS R&D HTA Programme.[20] |
| Major bleed event | 0.0117 | 0.0092 | 0.0337 | | The NHS R&D HTA Programme.[20] |
| **Death risk** | | | | | |
| Clot | 0.21 | | | | The National Health Service R&D Health Technology Assessment Programme.[20] |
| Bleed | 0.14 | | | | The National Health Service R&D Health Technology Assessment Programme.[20] |
| **Permanent injury risk** | | | | | |
| Clot | 0.1 | | | | The Canadian Agency for Drugs and Technologies in Health [CADTH].[18] |
| Bleed | 0.6 | | | | The Canadian Agency for Drugs and Technologies in Health [CADTH].[18] |
| **Drop OAT if permanently injured** | 0.5 | | | | The Canadian Agency for Drugs and Technologies in Health [CADTH].[18] |
| **Tests** | | | | | |
| Lab (per year) | 23 | | | | Approximately twice per month |
| Clinic (per year) | 23 | | | | |
| Self-test (per year) | 23 | | | | |
| Self-manage (per year) | 23 | | | | |
| **Costs** | | | | | |
| Device cost (home) | $499.00 | | | | communication from Roche Diagnostics. |
| Device cost (clinic) | $1,499.00 | | | | communication from Roche Diagnostics. Assume 200 patients use clinic; 1000 use lab; 1 uses home |
| Test strip (1 test) | $8.37 | | | | communication from Roche Diagnostics. |
| Lab test (E43) | $13.34 | | | | From the Schedule of Medical Benefits |
| Physician consult (03.01N) | $16.95 | | | | From the Schedule of Medical Benefits |
| | | | | | |
| Patient driving to lab (km, r-t) | 41.6 | | | | Double distance of drive to clinic |
| Patient driving to lab (min, r-t) | 52 | | | | Double distance of drive to clinic |
| Patient driving to clinic (km, r-t) | 20.8 | | | | Lafata et al.[52] |

| | | |
|---|---|---|
| Patient driving to clinic (min, r-t) | 26 | Lafata et al.[52] |
| Patient cost to drive (per km) | $0.52 | Treasury Board of Canada |
| Patient time at lab (min) | 17 | |
| Patient time at clinic (min) | 20 | |
| Patient time at home (min) | 15 | |
| Patient lost wages to drive (hr) | $19.99 | Statistics Canada SLID wage data. |
| | | |
| Nursing time at lab (min) | 13 | Lafata et al.[52] Also tested with 6 minutes. |
| Nursing time at clinic (min) | 15 | Lafata et al.[52] Also tested with 6 minutes. |
| Nursing time for home training (min) | 75 | |
| Nursing wages (per hr) | $31.15 | $28 in 2003 according to SLID. Adjusted for inflation. |
| | | |
| Minor adverse event cost | $3,408.00 | inflated from 2006 costing data; CMG 709 (coagulation disorders) |
| Major adverse event cost | $15,528.00 | inflated from 2006 costing data; CMG 709 (coagulation disorders) |

Sensitivity Level 1

| **INR levels (sensitivity 1 -- mechanical heart valves)** | Lab | Clinic | Home (self-test) | Home (self-manage) |
|---|---|---|---|---|
| Below Normal (% of time) | 0.3 | 0.26 | 0.26 | 0.23 |
| Normal (% of time) | 0.57 | 0.61 | 0.61 | 0.66 |
| Above Normal (% of time) | 0.13 | 0.13 | 0.13 | 0.11 |

Sensitivity Level 2

| **INR levels (sensitivity 2 -- worse compliance, e.g. rural or older)** | Lab | Clinic | Home (self-test) | Home (self-manage) |
|---|---|---|---|---|
| Below Normal (% of time) | 0.33 | 0.29 | 0.29 | 0.26 |
| Normal (% of time) | 0.41 | 0.46 | 0.46 | 0.52 |
| Above Normal (% of time) | 0.26 | 0.25 | 0.25 | 0.22 |

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