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Optimal Warfarin Management for the Prevention of Thromboembolic Events in Patients with Atrial Fibrillation: A Systematic Review of the Clinical Evidence

Supporting Informed Decisions

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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ABBREVIATIONS

AF	atrial fibrillation
CERC	COMPUS Expert Review Committee
CI	confidence interval
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
ER	emergency room
HTA	health technology assessment
INR	international normalized ratio
NVAF	non-valvular AF
POC	point of care
PSM	patient self-management
PST	patient self-testing
RCT	randomized controlled trial
SR	systematic review
TTR	time in therapeutic INR range
UC	usual care

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1 INTRODUCTION

Optimizing drug-related health outcomes and cost-effective use of drugs by identifying and promoting optimal drug prescribing and use is a goal of the Canadian Agency for Drugs and Technologies in Health (CADTH). Where possible, CADTH builds on existing applicable Canadian and international initiatives and research. CADTH goals are achieved through three main approaches:

- identifying evidence-based optimal use in prescribing and use of specific drugs
- identifying gaps in clinical practice, then proposing evidence-based interventions to address these gaps
- supporting the implementation of these interventions.

Direction and advice are provided to CADTH through various channels, including the following:

- the Drug Policy Advisory Committee (DPAC), the DPAC Optimal Use Working Group (OUWG), and the Formulary Working Group (FWG),which include representatives from the federal, provincial, and territorial health ministries and related health organizations
- the COMPUS Expert Review Committee (CERC) (members are listed in Appendix A)
- stakeholder feedback.

1.1 COMPUS Expert Review Committee

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office, and three or more Specialist Experts appointed to provide their expertise in recommending optimal use for one or more specific topics. For this project, five Specialist Experts were appointed; their expertise included cardiology, hematology, and thrombosis. Two of the Core Members are Public Members, who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists, or have other relevant qualifications, with expertise in one or more areas such as, but not limited to, family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization, methodology, affecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. The Core Members, including Public Members, are appointed by the CADTH Board of Directors.

CERC's mandate is advisory in nature and consists of providing recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. The overall perspective of CERC members in producing recommendations is that of public health care policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

2 CONTEXT AND POLICY ISSUES

The DPAC and its working groups, the OUWG and the FWG, have identified warfarin management for prevention of thromboembolic events in patients with atrial fibrillation as being a priority topic for optimal practice initiatives based on the following criteria:

- large deviations from optimal utilization (overuse or underuse)
- size of patient populations
- impact on health outcomes and cost-effectiveness

- benefit to multiple jurisdictions
- measurable outcomes
- potential to effect change in prescribing and use.

Atrial fibrillation (AF) is the most common cardiac arrhythmia.[1] Patients with AF have an elevated risk of stroke, which is a leading cause of death and disability among patients with the condition.[2,3]

Warfarin is an oral anticoagulant in the drug class of vitamin K antagonists. It is often used for stroke prevention in patients with AF at high risk for stroke who have no contraindications. Warfarin and related anticoagulants have consistently been shown to reduce the risk of stroke in patients with AF by more than 60% compared with no treatment, and by 30% to 40% compared with low-dose aspirin.[4,5] Long-term anticoagulation with vitamin K antagonists is typically required for prevention and treatment of thromboembolism in patients with AF and other high-risk groups, such as patients with mechanical heart valves, venous thromboembolism, pulmonary embolism, or peripheral vascular disease.[6,7] However, warfarin use has some disadvantages, including numerous food and drug interactions, the need for frequent laboratory monitoring, and the risk of bleeding complications.

The effectiveness and safety of warfarin depends on maintaining its dose at sufficient levels to keep patient international normalized ratio (INR) within the therapeutic range. Current Canadian guidelines recommend a target INR range of 2.0 to 3.0.[8] The percentage of time spent in the therapeutic range (TTR) depends on the quality of dose management.

TTR can be calculated by different methods. The simplest involves calculating the proportion of INR test results that fall within the therapeutic range, but fails to account for actual time spent in range. The most common method in clinical studies is the Rosendaal linear interpolation method.[9] This method adds each patient's time within the therapeutic range and divides by the total time of observation. This assumes that between-test INR varies linearly. Another common method is the half-time interpolation method, by which the total time of follow-up with INR in range is divided by the total time. Half the time between two tests is allocated to the first INR value, and half to the second. Different studies use different methods to calculate TTR, which should be taken into account when comparing TTR values.

Specialized anticoagulation services have been developed to optimize warfarin dosing management. These services can generally be defined as tertiary or community hospital-based anticoagulation clinics, primary care settings, point-of-care (POC) testing and dose adjustment by community pharmacies, and patient self-testing (PST) and patient self-management (PSM) using a POC device.[10] The primary care anticoagulation setting involves a family practice group or family health team where nurses, pharmacists, or physicians are responsible for managing warfarin therapy.[10] Primary care settings and hospital-based anticoagulation clinics may use computerized decision-support applications or other means to guide warfarin dosing.[7,10] This is in contrast to usual care (UC), which may be defined as warfarin dose adjustment managed by a physician working in a private practice setting that not only addresses anticoagulation management, but also other medical problems.[11] Physicians in this setting use their own judgment without access to specialized anticoagulation tools, or specialized anticoagulation staff and services.[11,12]

The purpose of this report is to compare the clinical effectiveness of different models of warfarin management. A systematic review of the clinical evidence was conducted for this purpose.

3 RESEARCH QUESTIONS

1. What are the clinical benefits and harms associated with the use of individual specialized anticoagulation services, compared with usual care for adult patients receiving long-term warfarin therapy?

2. What are the clinical benefits and harms associated with the use of one type of specialized anticoagulation service compared with another type, for adult patients receiving long-term warfarin therapy?

4 KEY FINDINGS

- Specialized anticoagulation services improve TTR compared with UC.
- Improvement of TTR within the included studies did not necessarily translate into a reduction in hemorrhage, thromboembolism, or need for additional medical care.
- The evidence available that compares different specialized models of care or service components is limited in both quantity and quality.
- The effect of PST or PSM on TTR was mixed, with studies showing either improved TTR with PST/PSM (patient self-testing alone or in combination with patient self-management) or no difference between models of care.
- Effects on clinical outcomes were also mixed, but PST/PSM generally resulted in lower mortality rates and reduced incidence of thromboembolism.
- PST/PSM did not affect the rate of bleeding events.
- PST/PSM may improve quality of life and patient satisfaction.

5 METHODS

5.1 Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946 to present) with in-process records and daily updates via Ovid; Embase (1980 to present) via Ovid; The Cochrane Library (2011, Issue 5) via Wiley; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were warfarin and specialized anticoagulation services. Keywords were searched in title only and controlled vocabulary restricted to major subject headings.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Conference abstracts were excluded from the search results. Where possible, retrieval was limited to the human population. Retrieval was also limited to documents published between January 1, 2006, and May 31, 2011. The initial search was completed on May 31, 2011. Regular alerts were established to update the search until the publication of the final report.

Additionally, a search on warfarin and atrial fibrillation was conducted using the same databases listed above. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and guidelines. Retrieval was also limited to documents published between January 1, 2006, and May 12, 2011. The initial search was completed on May 12, 2011. Regular alerts were established to update the search until the publication of the final report.

Grey literature (literature that is not commercially published) was identified by searching the health technology assessment agencies and guidelines sections of the Grey Matters checklist (www.cadth.ca/resources/grey-matters). Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

The authors of this report also consulted the primary authors of the upcoming 2012 American College of Chest Physicians (ACCP) guidelines on management of anticoagulation therapy.

5.2 Selection Criteria and Method

Two reviewers (CK and AK) independently screened citations and selected health technology assessments (HTAs), systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies regarding specialized anticoagulation services for management of warfarin dosing. The decision to order an article was based on the title and abstract, where available. In cases of insufficient information, the article was ordered. The same two reviewers selected the final articles for inclusion based on full-text publications. An article was included for review according to selection criteria established a priori (Table 1). Any disagreement between reviewers was discussed until consensus was reached.

Table 1: Selection Criteria

Population	Adult patients receiving long-term warfarin treatment (focus on AF, but also mixed populations, including patients with VTE, PE, or DVT)
Intervention	Specialized anticoagulation services (including patient self-testing or self-management)
Comparator	Other specialized anticoagulation services or UC
Outcomes	TTR, TIA, stroke, ischemic stroke, hemorrhagic stroke, systemic embolism, bleeding, minor bleeding, major bleeding, fatal bleeding, ICH, GI bleeding, QoL, mortality
Study designs	Health technology assessments, systematic reviews, meta-analyses, RCTs, and comparative non-randomized studies

AF = atrial fibrillation; DVT = deep vein thrombosis; GI = gastrointestinal; ICH = intracranial hemorrhage; PE = pulmonary embolism; QoL = quality of life; RCTs = randomized controlled trials; TIA = transient ischemic attack; TTR = time in the therapeutic range; UC = usual care; VTE = venous thromboembolism.

5.3 Exclusion Criteria

Studies were excluded if they did not meet the selection criteria; focused only on patients with mechanical heart valves; were narrative reviews or editorials; were performed in a pediatric population; or were included in a selected HTA, systematic review, or meta-analysis. Additionally, systematic reviews were excluded if all reviewed studies were included in a more recent systematic review or meta-analysis.

5.4 Data Extraction Strategy

One reviewer (CK) extracted clinical effectiveness data for each article to tabulate relevant characteristics and outcomes from the included studies. Data extraction was verified by a second reviewer (AK) to confirm accuracy.

5.5 Critical Appraisal of Individual Studies

Two reviewers (CK and AK) independently appraised the included studies. The quality of systematic reviews was evaluated using the AMSTAR instrument.[13] The quality of randomized controlled trials (RCTs) and non-randomized studies was assessed using the Downs and Black instrument.[14] Methodological quality of clinical effectiveness evidence was evaluated based on randomization, adequate concealment of randomization, degree of blinding, use of intention to treat analysis, and description of dropouts and withdrawals, where appropriate. A numeric score was not calculated for each study; instead, strengths and weaknesses are described. Any disagreements were resolved through discussion until consensus was reached.

5.6 Data Analysis Methods

Because of heterogeneity present across the selected studies, a formal meta-analysis was not conducted. Studies were described using a narrative approach.

6 RESULTS

6.1 Quantity of Research Available

The electronic literature search and updates yielded 643 citations. After titles and abstracts were screened, 578 citations were excluded and 65 potentially relevant articles were retrieved for full-text review. An additional 10 potentially relevant reports were identified through grey literature and handsearching. Of the 75 potentially relevant reports, 48 did not meet the inclusion criteria. Twenty-seven publications were included in this review. The study selection process is presented in a PRISMA flowchart (Appendix 2).

One HTA and eight systematic reviews or meta-analyses were identified for inclusion in this report. These will be referred to as SR throughout the report. Of these, six compared specialized anticoagulation services with UC and six examined patient-self testing or self-management (three included reviews addressed both).

Eighteen primary studies, six RCTs, and 12 non-randomized studies met inclusion criteria. Five non-randomized studies compared anticoagulation clinic care with UC.[15-19] One RCT[20] and two non-randomized studies[18,21] compared different models of specialized care. Two RCTs[22,23] and three non-randomized studies[24-26] compared self-testing or self-management with other specialized services, and two non-randomized studies[27,28] compared PST/PSM with UC. Three RCTs[29-31] and one non-randomized study[32] compared computer-assisted anticoagulant dosing with manual dosing by experienced medical staff.

6.2 Study Characteristics

All included systematic reviews[33-41] were published between 2006 and 2011 and included studies published from 1987 to 2010. The number of studies included in each review ranged from 11 to 67. Six systematic reviews[33,34,38-41] were not limited to patients with any one indication (such as atrial fibrillation, deep vein thrombosis, or pulmonary embolism), two

included only studies dealing strictly with atrial fibrillation,[36,37] and one was unclear about the included patient population.[35] Eight included systematic reviews[33,35-41] reported TTR and five[33,34,39-41] reported adverse events, including death, hemorrhage, or thromboembolism. One included systematic review reported quality of life measures.[39]

All included primary studies (RCTs and non-randomized studies) were published between 2006 and 2011. Sample sizes ranged from 40 to 13,052. With the exception of three studies,[15,19,23] TTR was reported. Eleven studies[15,17-20,24,25,28-31] reported adverse events, including death, hemorrhage, or thromboembolism. Two studies[23,28] reported quality of life measures. Two[16,19] reported number of INR measurements in the therapeutic range instead of TTR.

Complete characteristics of each included study are found in Appendices 2 and 3.

6.3 Critical Appraisal of Individual Studies

Nine SRs[33-41] were included in this report. All included systematic reviews were based on a priori design and a comprehensive search of at least two electronic databases. All but one systematic review[37] searched for reports regardless of their publication type. Study selection and data extraction were performed in duplicate by independent researchers in most reviews, although it was not clear in three included studies.[33,37,38] One review[39] provided a list of included and excluded studies, but all included reviews reported characteristics of included trials. Four reviews[35-38] did not perform a critical appraisal of included studies, but the remaining five considered study quality when forming conclusions. All included systematic reviews performed at least partial meta-analysis; five of these[33-35,39,40] performed a test of heterogeneity. Only three included systematic reviews[34,39,40] assessed the likelihood of publication bias.

Six RCTs[20,22,23,29-31] and 12 non-randomized studies[15-19,21,24-28,32] were included in this review. All included studies had clearly stated objectives, and all but one[20] clearly described main outcomes in the introduction or methods. Two studies[15,20] failed to describe patient characteristics. Main findings were clearly described in all included studies. None of the included studies attempted to blind patients or outcome assessors. Although this is reasonable given the nature of the interventions and comparators, it still introduces the risk of bias. Of the six included RCTs, one[22] described the method of randomization. No study reported adequate allocation concealment. Four included RCTs[22,29-31] and five non-randomized trials[19,21,24,25,27] described numbers of patients lost to follow-up, and the reasons. None of the included studies performed an intention to treat analysis, or otherwise accounted for confounders in their analyses. Three studies[19,21,22] performed power calculations to determine sample sizes necessary to detect clinically relevant effects. All others either failed to perform these calculations, or failed to meet the necessary sample size calculated.

6.4 Data Analyses and Synthesis

Specialized anticoagulation clinic care

Six systematic reviews were identified that compared specialized anticoagulation services with UC.[33-38] Results are summarized in Table 2 and Appendix 3.

In 2011, the US Department of Veterans Affairs published a systematic review comparing specialized anticoagulation clinics with UC for long-term anticoagulation.[33] UC was defined as non-specialized clinics, such as primary care clinics or physician offices. Included studies were limited to those involving an adult, outpatient population receiving chronic anticoagulation therapy. Non-English articles, or studies dealing with inpatients, pediatric populations, or

short-term anticoagulation (less than three months) were excluded. The review identified 11 articles (three RCTs and eight cohort studies) that met all inclusion criteria. RCTs and cohort studies were analyzed separately.

The follow-up interval in the RCTs was three months in one study and up to two years in another. The follow-up time for the third RCT was not reported. Pooled analysis of the three RCTs indicated no difference between anticoagulation clinics and UC in rates of mortality (RR 0.81, 95% CI 0.25 to 2.58), major thromboembolic events (RR 1.05, 95% CI 0.36 to 3.12), and major bleeding events (RR 1.29, 95% CI 0.59 to 2.81). The pooled weighted mean TTR was higher for patients treated in an anticoagulation clinic (59.9% versus 56.3% for UC) for a weighted mean difference of 3.6% (range of mean differences, 3.3% to 5%, 95% CI not reported).

Results from cohort studies were not pooled. One included study reported mortality and found no significant difference between clinic and usual care. Four included studies reported major thromboembolic events. One reported a significantly higher incidence with UC, one reported a statistically significant higher incidence with clinic care, and two did not report P-values. The incidence of major bleeding was reported in five studies. One found a significantly higher rate of bleeding incidents with UC, and one found no statistically significant difference. The remaining studies did not report significance. Four studies reported TTR. The pooled weighted mean of TTR was higher with clinic care (63.5% versus 53.5%) for a weighted mean difference of 10% (range of mean differences, 4.3% to 26%, 95% CI not reported). Three included observational studies reported hospital admissions or emergency department visits. One found no difference between clinic and UC groups, while two found significantly fewer anticoagulation-related hospitalizations with clinic care.

A 2010 systematic review and meta-analysis by Saokaew et al.[34] included 24 studies (five RCTs, 19 non-randomized trials) comparing UC with warfarin therapy in which a pharmacist participated. UC was defined as a control group comprising health care professionals other than pharmacists as service providers. In 19 studies, this was a physician. Details of UC were not reported for the other five studies. Results of pooled analysis were reported separately for RCTs and non-randomized studies.

Care in which a pharmacist participated was found to reduce the risk of bleeding events in RCTs (RR 0.51, 95% CI 0.28 to 0.94) and non-randomized (RR 0.71, 95% CI 0.52 to 0.96) studies. When only major bleeding events (based on individual study definitions) were considered, no significant difference was observed in RCTs (RR 0.64, 95% CI 0.18 to 2.36, P = 0.507). A reduction in major bleeding events with pharmacist care was observed in pooled analysis of non-randomized studies (RR 0.49, 95% CI 0.26 to 0.93, P = 0.030). Similarly, RCTs found no statistically significant difference in total thromboembolic events in pharmacist-managed care compared with UC (RR 0.79, 95% CI 0.33 to 1.93, P = 0.610), while a statistically significant reduction was observed with pharmacist-managed care in non-randomized studies (0.37, 95% CI 0.26 to 0.53, P < 0.001). No statistically significant difference in mortality was observed with pharmacist-managed care compared with UC in either RCTs (RR 0.93, 95% CI 0.41 to 2.13, P = 0.867) or non-randomized studies (RR 0.85, 95% CI 0.37 to 1.98, P = 0.711).

In a 2009 systematic review and meta-analysis, Cios et al.[35] evaluated the impact of study setting on INR control in US studies. For the purpose of evaluating the impact of study-level factors on warfarin control, RCTs were considered separately from observational studies. The analysis included 24 studies with 43 study groups performed in an anticoagulation clinic (the

study was not an RCT and was performed in a clinic, or the stated role of clinicians in patient care was limited to anticoagulation management) or community practice (the study could not be classified as anticoagulation clinic or RCT). TTR across all included studies was 57% (95% CI 55% to 59%). Subgroup analysis showed that the overall TTR in the anticoagulation clinic setting was 64% (95% CI 61% to 67%), while in community practice, TTR was 51% (95% CI 48% to 54%). After meta-regression analysis using a multiple-linear, mixed-method model controlling for study-level factors, the adjusted difference (–13, 95% CI –18.1 to –7.9) was statistically significant (P < 0.001). In post-hoc analyses, Canadian warfarin studies were included, with similar results. With Canadian studies included, clinic TTR was 65% (95% CI 61% to 69%) and community practice TTR was 53% (95% CI 50% to 56%), a statistically significant adjusted difference (–11.3, 95% CI –16.2 to –6.3, P < 0.001). Results from Canadian studies were not reported separately.

A systematic review and meta-analysis performed by Baker et al.[36] in 2009 examined the effect of warfarin management setting on TTR in patients with atrial fibrillation. The setting was defined as an anticoagulation clinic if the study took place in a clinic or the stated role of study clinicians was limited to anticoagulation management. All others were classified as community practice. To be included in the meta-analysis, studies had to contain at least one warfarin-treated group with a minimum of 25 patients who had INR monitoring for at least three weeks. No included studies were RCTs. A total of eight studies (four anticoagulation clinic and six community practice; two studies examined both) with 13 study groups (four anticoagulation clinic and nine community practice) were included. With anticoagulation clinic-based warfarin dosing, patients had an average TTR of 63% (95% CI 58% to 68%) compared with an average TTR of 51% (95% CI 47% to 55%) in community practice. Compared with anticoagulation clinics, patients in community practice spent 11% less time in range (95% CI 2% to 20%, n = six studies with nine groups), based on meta-regression analysis. Additionally, five included trials reported the proportion of eligible atrial fibrillation patients receiving warfarin. A definition of eligibility was not provided. The proportion of eligible patients receiving warfarin was higher in the clinic setting (53%, 95% CI 38% to 72%) compared with community-based dosing (47%, 95% CI 41% to 54%), but the significance of this result was not discussed.

In 2008, Dolan et al.[37] published a systematic review and meta-analysis examining the effect of various factors, including management setting, on TTR. A total of 36 studies met inclusion criteria, of which 22 dealt exclusively with patients with AF and had at least one treatment group given oral anticoagulation treatment with a target INR range of 2.0 to 3.0. The remaining 14 studies were conducted in patients with mixed indications and were not included in the primary analysis. These 14 studies were used to conduct sensitivity analysis. Among the AF studies, 18 study groups were judged to have received anticoagulation care in an organized setting (specialized care, including anticoagulation clinics) and 10 study groups were categorized as UC (care delivered in non-specialist settings, including family practice). Patients receiving organized care had a higher TTR (63.6%, 95% CI 61.3% to 65.9%) compared with those receiving UC (52.3%, 95% CI 42.1% to 62.4%). This difference of 11.3% was found to be statistically significant (95% CI 0.1% to 21.7%).

A 2006 systematic review by van Walraven et al.[38] examined the effect of study setting on anticoagulation control. Studies were included if they contained data measuring anticoagulation control in at least one patient group. A total of 67 studies including 123 study groups were classified as being based in an anticoagulation clinic (the authors stated the study was set in a clinic, or the methods stated that the role of study physicians were limited to INR control), a randomized controlled trial, or as community-based practice (all other

studies). Patients treated in randomized controlled trials had a mean TTR of 66.4% (95% CI 59.4% to 73.3%), clinic patients had a mean TTR of 65.6% (95% CI 63.7% to 67.7%), and those treated in a community practice setting had a mean TTR of 56.7% (95% CI 51.5% to 62.0%). There was no significant difference in TTR between the RCT and clinic groups (–3.9%, 95% CI –10.7 to 2.9). However, a decrease in TTR of 12.2% (95% CI 4.8% to 19.5%) was observed in patients treated by their community physicians, compared with RCTs. Community practices had statistically significant lower rates of INR control compared with both anticoagulation clinics and RCTs.

In addition to the included systematic reviews, five studies were identified that compared specialized anticoagulation clinics with UC, which were not included in an included systematic review. The results of these four studies are summarized in Table 2 and Appendix 4.

One cohort study[15] compared patients referred to a nurse-managed anticoagulation clinic (n = 131) with patients managed by physicians (n = 2,266) for long-term anticoagulation therapy (not defined). POC testing was not used. The rate of emergency room (ER) visits was lower for patients receiving care in the nurse-managed clinic compared with usual physician care (1.5% versus 10.9%). Similarly, hospitalization rate was lower with clinic care (2.3% versus 12.8%). Statistical analysis was not done on these figures, but cost savings due to fewer ER visits or hospitalizations were significantly lower in the clinic model (P = 0.0006 and P = 0.0004, respectively).

One retrospective medical record review[16] compared patients receiving usual physician care before and after transfer with a pharmacist-managed anticoagulation clinic using POC INR testing (n = 64). All patients had been established at the clinic for at least one year. TTR was not reported, but the percentage of INR tests within the therapeutic range was reported instead. The number of INR measurements within the therapeutic range was higher after transfer to the pharmacist-managed clinic (81.1% versus 71.1%, P < 0.0001). The estimated variance in therapeutic INR rates was significantly higher for usual physician care (365.7 versus 185.2, P = 0.004).

One retrospective cohort study[17] compared 175 patients receiving usual physician care with the same number managed by a pharmacist-administered anticoagulation service for at least two months. TTR, calculated using the linear interpolation method, was higher in pharmacist-managed care compared with UC (73.7% versus 61.3%, P < 0.0001). The number of ER visits (58 versus 134, P < 0.00001) and hospital admissions (three versus 14, P < 0.00001) were significantly lower with clinic care. Similarly, the anticoagulation-related adverse event rate was lower with clinic care (5.1% versus 15.4%, P < 0.0001) but the nature of these events (thrombosis, hemorrhage, etc.) was not described.

One retrospective chart review[18] compared UC by the patient's primary care provider with either pharmacist- or nurse-managed anticoagulation services. TTR was lowest in patients treated in the primary care model compared with nurse- or pharmacist-managed care (57.4% versus 71.8% versus 83.6% for primary, nurse, and pharmacist care, respectively; P < 0.05 between all models). Hospitalization rate was higher for primary care (13.9 hospitalizations per 100 patient-years) and nurse-managed care (12.3 per 100 patient-years) compared with pharmacist-managed care (5.4 per 100 patient-years, P < 0.05). Similarly, the rate of emergency department visits (expressed as number per 100 patient-years) was higher for primary care (5.6) and nurse-managed clinics (5.6) compared with pharmacist-managed care (1.2, P < 0.05). There was no significant difference in hospitalization or ER visit rate between the nurse-managed model and UC.

A 2008 retrospective study compared the quality of anticoagulation care before and after transition from a pharmacist-managed anticoagulation clinic with physician-managed primary care.[19] In pharmacist-managed care, before transition, 76% of patient INRs were within the target range, compared with 48% after transition to primary care (P < 0.0001). Similarly, the number of INRs within the target range for each patient was lower after transition to primary care (75% versus 36.5%, P < 0.0001). Before transition from the anticoagulation clinic, two emergency department visits for symptoms related to bleeding were reported. After transition to primary care, 13 cases of additional medical care were reported, 12 bleeding related and one thrombosis related. Six resulted in emergency room visits. This was a statistically significant increase in the number of cases requiring medical care after transition from the pharmacist-managed clinic (two versus 13, P = 0.0412). The severity of these events was not reported. The perceived quality of care based on a patient satisfaction survey was higher for pharmacist-managed care.

No systematic reviews were identified comparing different models of specialized clinic care. One RCT[20] and two non-randomized studies[18,21] compared different specialized services. The results of these studies are summarized in Table 3 and Appendix 4.

In a 2006 RCT,[20] patients already on warfarin were randomized to either continue "traditional" hospital-based clinic care or to receive nurse-led primary care using POC testing and a computer decision support system. Patients assigned to nurse-led primary practice care showed a statistically significant improvement in TTR over the study period (initial: 57% [95% CI 50% to 63%], final: 69% [95% CI 66% to 73%], P < 0.01). Improvements were also shown in the control population, but statistical analysis was not provided. At the end of the study period, patients receiving nurse-led primary care had a significantly higher TTR (69%, 95% CI 66% to 73%) compared with those receiving hospital-based care (57%, 95% CI 50% to 63%, P < 0.01). No significant difference was reported in overall death rate or serious adverse events, including transient ischemic attack, stroke, or epistaxis. In the total study population, there were 39.8 minor, 0.4 major, and no fatal hemorrhagic events per 100 patient-years. For thromboembolic events, there were 3.9 serious and 0.79 fatal events per 100 patient-years.

One retrospective chart review[18] compared UC by the patient's primary care provider with either pharmacist- or nurse-managed anticoagulation services. In this comparison, TTR was significantly higher for pharmacist-managed care (83.6% versus 71.8%, P < 0.05). Hospitalization rate was higher for nurse-managed care compared with pharmacist-managed care (12.3 versus 5.4 per 100 patient-years, RR 2.29, 95% CI 1.23 to 4.25). Similarly, the rate of emergency department visits (expressed as number per 100 patient-years) was higher for nurse-managed care compared with pharmacist-managed care (5.6 versus 1.2, RR 4.45, 95% CI 1.42 to 13.98).

A comparison between a secondary care-based anticoagulation clinic and primary care-based practice using POC monitoring and computer-based decision support showed no statistically significant difference in TTR.[21] During 12 months of secondary care management, patients had an average TTR of 76.4%. In 12 months of primary care management, the mean TTR was 72.1%. This reduction of 5.6% from secondary care (a difference of 4.3) was not statistically significant (95% CI –2.7% to +13.9%).

Table 2: Summary of Results for Specialized Clinic Care versus Usual Care											
Study, Year	TTR		Thrombosis		Bleeding		Mortality		ER		QoL
Systematic Reviews											
Bloomfield et al.[33] 2011	RCT +	Obs +	RCT 0	Obs 0*	RCT 0 (major)	Obs 0** (major)	RCT 0	Obs 0†	RCT NR	Obs +‡	+§
Saokaew et al.[34] 2010	NR		RCT 0	Obs +	RCT 0 (major) + (total)	Obs + (major) + (total)	RCT 0	Obs 0	NR		NR
Cios et al.[35] 2009	+		NR		NR		NR		NR		NR
Baker et al.[36] 2009	+		NR		NR		NR		NR		NR
Dolan et al.[37] 2008	+		NR		NR		NR		NR		NR
van Walraven et al.[38] 2006	+		NR		NR		NR		NR		NR
Non-randomized Studies											
Aziz et al.[15] 2011	NR		NR		NR		NR		+††		NR
Garton et al.[16] 2011	+‡‡		NR		NR		NR		NR		NR
Hall et al.[17] 2011	+		NR¶		NR¶		NR¶		+		NR
Rudd and Dier[18] 2010	+		NR		NR		NR		+§§		NR
Garwood et al.[19] 2008	+		0		+ (total)		NR		+		NR

ER = hospitalizations or emergency room visits; INR = international normalized ratios; NR = not reported; Obs = observational study, QoL = quality of life or patient satisfaction; RCT = randomized controlled trial; TTR = time in therapeutic range; UC = usual care; + = clinic superior to usual care; – = clinic inferior to usual care; 0 = no difference between clinic and usual care.
*Meta-analysis not performed; one study favours usual care, one favours specialized clinic, and two did not test significance.
**Meta-analysis not performed; one study favours usual care, one favours specialized clinic, and three did not test significance.
†One study reporting.
‡Meta-analysis not performed; two studies favour specialized clinics, one found no difference.
§Two of three RCTs report significant improvement in patient satisfaction with specialized clinic care.
††Nurse-managed care versus UC; P-values calculated for cost data only.
‡‡Pharmacist-managed care versus UC, TTR not reported, % of INR values within therapeutic range was superior for clinic care.
¶Pharmacist-managed care versus UC; total adverse events were significantly lower with pharmacist care, but details of these events were not described.
§§For pharmacist-managed clinics only (both for hospitalization rate and ER visit rate).

Table 3: Summary of Results for Comparison of Specialized Care Models						
Study, Year	TTR	Thrombosis	Bleeding	Mortality	ER	QoL
RCTs						
*Fitzmaurice[20] 2006	+	0	0 (total)	0	NR	NR
Non-randomized Studies						
**Rudd and Dier[18] 2010	–	NR	NR	NR	–	NR
*Edgeworth and Coles[21] 2010	0	NR	NR	NR	NR	NR

ER = hospitalizations or emergency room visits; NR = not reported; QoL = quality of life or patient satisfaction; RCT = randomized controlled trial; TTR = time in therapeutic range; + = favours nurse-led care; – = favours other care; 0 = no difference between specialized care models.
* Study compared nurse-led care with point-of-care testing and computer support to hospital clinic care.
** Study compared nurse-managed anticoagulation service with pharmacist-managed anticoagulation service.

Patient Self-testing and Patient Self-management

Six HTAs, systematic reviews, or meta-analyses were identified that compared PST or PSM with other care.[33,35,38-41] Results are summarized in Table 4 and Appendix 3.

In 2011, the US Department of Veterans Affairs published a systematic review comparing PST, alone or in combination with PSM, with care delivered in specialized or non-specialized clinics.[33] The results of this review were also reported elsewhere.[42] The review identified 27 articles describing 22 distinct RCTs including a total of 8,413 participants.

There was a lower rate of overall mortality (OR 0.74, 95% CI 0.63 to 0.87) and thromboembolic events (OR 0.58, 95% CI 0.45 to 0.75) in patients randomized to PST/PSM compared with other care. Patients assigned to PST/PSM also had a lower rate of major bleeding events (OR 0.89, 95% CI 0.75 to 1.05), but this result was not statistically significant. Mean TTR for patients randomized to PST/PSM was 66.1% (range of means 56% to 76.5%) compared with 61.9% (range 32% to 77%) for patients randomized to other care groups. This difference was not statistically significant. Eleven included studies reported patient satisfaction and quality of life. Measurement and definition varied across the studies but, in general, patients in the PST/PSM group expressed greater treatment satisfaction or quality of life. Three studies reported significantly higher self-efficacy and less distress, fewer daily hassles, and reduced strain on social networks with PST/PSM. One reported improved emotional health and vitality. Four additional studies showed a significant difference in treatment satisfaction in PSM/PST patients. Three included studies reported no significant difference in patient satisfaction or quality of life.

A 2010 systematic review by Garcia-Alamino et al.[39] included 26 papers reporting on 18 RCTs (4,723 participants).

Meta-analysis indicated that patients who self-managed or self-tested were at decreased risk of thromboembolism (RR 0.50, 95% CI 0.36 to 0.69), overall mortality (RR 0.64, 95% CI 0.46 to 0.89), and minor hemorrhage (RR 0.64, 95% CI 0.54 to 0.77). When PST was considered by itself, no significant difference in mortality (RR 0.84, 95% CI 0.50 to 1.41) or thromboembolism (RR 0.57, 95% CI 0.32 to 1.00) was observed compared with other care. Rates of major hemorrhage were not different between PST/PSM patients and other care (RR 0.87, 95% CI 0.66 to 1.16); however, there was a statistically significant reduction in patients

self-testing only (RR 0.56, 95% CI 0.35 to 0.91). Results were also reported based on clinical condition. However, only two included studies examined atrial fibrillation exclusively and event rates were low; therefore, no statistically significant differences in adverse events were reported in this group.

Thirteen included trials reported percentage of INR measurements within the target range. All but one reported improvements in PSM and PST groups, with six of these reporting statistically significant differences. Eleven trials reported TTR. Three of these (n = 554 patients) observed a statistically significant improvement in TTR in the PST and PSM groups, while eight (n = 2,059 patients) showed no significant difference between PST/PSM and other care. Results for these outcomes were not pooled. Eight included studies evaluated quality of life outcomes using various measures and definitions. Five showed a statistically significant improvement in quality of life or treatment satisfaction in PST or PST/PSM patients. The remaining three studies showed no significant difference between the study groups.

In a 2009 systematic review and meta-analysis, Cios et al.[35] evaluated the impact of study setting on INR control in US studies. The analysis included 24 studies (43 study groups) performed in an anticoagulation clinic (the study was performed in a clinic, or the stated role of clinicians in patient care was limited to anticoagulation management) or community practice (the study could not be classified as an anticoagulation clinic or RCT). Subgroup analysis showed PSM is associated with a TTR of 58% (95% CI 47% to 51%), while TTR in the other groups was 57% (95% CI 55% to 59%). After meta-regression using a mixed-method model controlling for study setting, year, design, and other study-level factors, the adjusted difference (–8.9, 95% CI –25.7 to –7.8) was not statistically significant. In a post-hoc analysis, Canadian warfarin studies were included, with similar results. With Canadian studies included, TTR was 65% (95% CI 55% to 76%) with PSM and 59% (95% CI 56% to 61%) without PSM, a non-statistically significant difference (–2.0, 95% CI –15.3 to 11.2).

A 2007 meta-analysis on the safety and effectiveness of POC monitoring devices in anticoagulation therapy included a subgroup analysis of PST/PSM.[40] Patients using a POC device for self-testing and self-management had significantly lower rates of both major thromboembolism (OR 0.48, 95% CI 0.30 to 0.79) and overall thromboembolic events (OR 0.45, 95% CI 0.24 to 0.84) and death (OR 0.48, 95% CI 0.24 to 0.94) compared with patients receiving care from an anticoagulation clinic or individual practitioner without use of a POC device. No significant difference was observed for major hemorrhagic events (OR 0.75, 95% CI 0.47 to 1.20). TTR was higher for PST/PSM patients compared with other care (71% versus 63%, no statistical analysis provided). Analysis separately comparing either clinic or practitioner care with PST/PSM was not performed.

A 2007 HTA[41] included a systematic review of the clinical effectiveness, comparing PST/PSM with other anticoagulation management strategies. The review identified 16 RCTs and eight non-RCTs.

Meta-analysis of RCTs and non-randomized studies was used to calculate risk difference (RD) for major complications and death. PST/PSM was associated with reduced risk of thromboembolic events (RD –0.02, 95% CI –0.03 to –0.01) and death (RD –0.017, 95% CI –0.029 to –0.005), but not hemorrhagic events (RD –0.004, 95% CI –0.015 to 0.007). An odds ratio method was also used for RCTs only, but results did not differ.

Among 12 RCTs that reported TTR, the pooled estimate was 67.4% for PST/PSM and 63.4% for UC. When separated according to type of care used as a control, PST/PSM resulted in a similar TTR to specialized clinics (67.1% versus 66.3%) but a higher TTR compared with primary care

by family doctors (74.8% versus 59.8%). Two non-randomized studies reported TTR, finding significantly better time in range in the PSM group compared with UC. These results were not pooled. Non-RCTs reporting the number of INR measurements within the therapeutic range were pooled and showed better INR control with PSM, compared with UC (82.9% versus 69.5%). Six included studies reported on quality of life, according to different metrics. Three indicated improved quality of life and patient satisfaction with PST/PSM, while three reported no significant difference between PST/PSM and other care.

A 2006 systematic review by van Walraven et al.[38] examined the effect of study group characteristics on anticoagulation control. A total of 67 studies incorporating 123 study groups were included. Of these, seven trial groups involved PSM and 116 had no self-management aspect. Patients who self-managed had a mean TTR of 71.5% (95% CI 65.2% to 77.7%), and those using usual clinic or community practice care without self-management had a mean TTR of 63.1% (95% CI 61.0% to 65.2%). The adjusted effect of 7.0% increase in TTR (95% CI 0.7% to 13.3%) was statistically significant (P = 0.03).

Seven additional studies were identified comparing PST/PSM with other models of anticoagulant care. Five of these compared PST or PSM with other specialized anticoagulation services[22-26] and two compared with UC.[27,28] Results are summarized in Table 4 and Appendix 4.

A 2011 RCT[22] compared patient self-testing using a telemedicine system with treatment in a hospital-based clinic. Patients who self-tested measured INR once or twice a week using a POC device, reporting values to the anticoagulation clinic via an online system. Dose adjustments were made by the clinic and reported using the same system. Patients randomized to traditional clinic care made clinic visits at minimum every four weeks for INR measurement and dose adjustment, but at shorter intervals depending on warfarin dose changes.

TTR was reported for each group. Compared with patients receiving conventional clinic care (72.7%, 95% CI 71.9% to 73.4%), patients had a significantly higher TTR when self-testing either once (79.7%, 95% CI 79.0% to 80.3%) or twice (80.2%, 95% CI 79.4% to 80.9%) per week. The difference in TTR between patients testing once or twice was not significant (P = 0.2516). No patients died during the trial. One adverse event (hospitalization) was reported, but the care group for this patient was not described.

Results of a survey published in 2011[23] examined quality of life changes in patients randomized to receive routine care, either attending a hospital or practice-based anticoagulation clinic, or self-managing with INR testing every two weeks. Questionnaires were sent to participants at the baseline and after 12 months of receiving assigned treatment. Questionnaires used two instruments: one measured anxiety; the other reported on treatment-related quality of life. Overall, a greater improvement in self-efficacy was reported in the PSM group compared with clinic care (1.67 versus 0.43, P = 0.01). This association remained statistically significant after adjusting for age (P = 0.03). No statistically significant differences between PSM and clinic care were observed for changes in daily hassle, psychological distress, treatment satisfaction, or anxiety over the study period.

In 2009, Gardiner et al.[24] examined whether PST is a viable alternative to hospital anticoagulation clinic attendance for anticoagulation management. Patients who self-tested used a POC device to measure INR every two weeks. Results were reported to the anticoagulation clinic where dose adjustment was carried out, using computer dosing software. Patients who did not want to self-monitor received routine care in the

anticoagulation clinic. Details of this care were not described. The median TTR was higher in the PST group (71%, 95% CI 64.1% to 75.3%) compared with those receiving routine care (60%, 95% CI 55.0% to 63.2%, P = 0.003). Among patients who were self-testing, the incidence of major bleeds was 1.7 per 100 patient-years, incidence of minor bleeds was 8.4 per 100 patient-years, and incidence of thrombosis was 3.4 per 100 patient-years. In the routine care group, the incidence of major bleeds, minor bleeds, and thrombosis was 5.4, 16.2, and 1.4 per 100 patient-years, respectively. No statistical analysis was done on adverse event rates.

A 2008 before-after study[25] compared PSM with management provided by an anticoagulation clinic. The PSM group monitored INR every one or two weeks (after an initial three-week training period) and reported measurements using an Internet-based system. A dosing algorithm provided dosing recommendations directly to the patient, or in more extreme INR deviations, to the physician for approval. The mean time in therapeutic range increased from 63.0% during the control period (before introduction of the PSM system) to 74.4% after PSM was introduced, for a mean difference of 11.4% (95% CI, 5.5% to 17.3%, P < 0.004). No hemorrhagic or thromboembolic complications were reported during either study period.

A 2007 retrospective study[26] examined the clinical effectiveness of PSM outside of trial conditions. Patients were selected from a previous RCT comparing PSM with routine care. PSM patients self-managed their warfarin based on INR testing every two weeks. Control patients had their warfarin managed in hospital or practice-based anticoagulation clinics and continued to do so post-trial. In PSM patients, there was no statistically significant difference in TTR between trial and post-trial periods (75% versus 70%, P = 0.12). Similarly, no significant difference was observed in the control arm outside of trial conditions (64% versus 57%, P = 0.09). No significant differences were found between the change in mean TTR in PSM during and post-trial compared with the control arm (P = 0.54).

In a 2011 before-after study,[27] anticoagulation control in patients receiving laboratory INR testing followed by dose adjustment by the lab or general practitioner was compared with the same group of patients after the introduction of a PSM program. There was no significant difference in the overall TTR between the two groups (PSM 81.3% versus UC 72.4%, P = 0.16). In patients with poor control (TTR < 60%) prior to self-management, switching to PSM resulted in a statistically significant improvement in TTR (UC 38.8% versus PSM 71.1%, P = 0.01). There was no significant difference in patients who had good INR control (TTR > 60%) after switching to PSM (UC 83.0% versus PSM 82.5%).

A 2008 study[28] compared PST followed by dose adjustments by a general practitioner using a decision support tool with anticoagulation therapy monitored and controlled by the patient's general practitioner (UC). Mean individual TTR was not significantly different between groups (PST 65.7% versus UC 66.4%, P = 0.85). No statistically significant differences between PST and UC for adverse events, including death (5.5% versus 5.5%, P = 1.0), major hemorrhagic complications (0% versus 1.8%, P = 1.0), minor hemorrhagic complications (7.4% versus 3.7%, P = 0.67), and thromboembolism (1.8% versus 3.7%, P = 1.0), were observed. Compared with results from pre-study questionnaires, PST was associated with greater decreases in dissatisfaction (–0.8 versus 0.2, P = 0.001) and stress (–0.3 versus 0.005, P = 0.003), fewer limitations to daily activities (–0.2 versus 0.3, P = 0.005), fewer social problems (–0.1 versus 0.3, P = 0.03), and decreased anxiety (–2.5 versus 2.3, P = 0.04) over the study period compared with UC.

Table 4: Summary of Results for PST/PSM						
Study, Year	TTR	Thrombosis	Bleeding	Mortality	ER	QoL
Systematic Reviews						
Bloomfield et al.[33] 2011	0	+	0 (major bleed)	+	NR	+*
Garcia-Alamino et al.[39] 2010	0**	+	PST/PSM 0 (major) + (minor) / PST only + (major) 0 (minor)	+	NR	+†
Cios et al.[35] 2009	0	NR	NR	NR	NR	NR
Wells et al.[40] 2007	+	+	0 (major)	+	NR	NR
Connock et al.[41] 2007	0 vs. clinic + vs. UC	+	0 (major)	+	NR	+‡
van Walraven et al.[38] 2006	+	NR	NR	NR	NR	NR
RCTs — PST/PSM versus Clinic Care						
Christensen et al.[22] 2011	+	NR	NR	NR	0	NR
McCahon et al.[23] 2011	NR	NR	NR	NR	NR	0 for anxiety + for self-efficacy
Non-randomized Studies — PST/PSM versus Clinic Care						
§Gardiner et al.[24] 2009	+	–	+ (major and minor)	NR	NR	NR
O'Shea et al.[25] 2008	+	0	0 (total)	NR	NR	NR
McCahon et al.[26] 2007	0¶	NR	NR	NR	NR	NR
Non-randomized Studies — PST/PSM versus Usual Care						
Harper and Pollock[27] 2011	0 overall + in patients with poor control	NR	NR	NR	NR	NR
Salvador et al.[28] 2008	0	0	0 (major and minor)	0	0	+

ER = hospitalizations or emergency room visits; NR = not reported; Obs = observational study; QoL = quality of life; RCT = randomized controlled trial; TTR = time in therapeutic range; + PST/PSM = superior to other care;
– PST/PSM = inferior to other care; 0 = no difference between PST/PSM and other care.

*In 11 studies reporting QoL or patient satisfaction, four reported significant QoL improvements and four reported increased patient satisfaction. Three reported no significant difference between groups.

**Three of 11 studies (n = 554 patients) reported a statistically significant improvement in TTR with PST/PSM; eight (n = 2059 patients) showed no difference.

†Five of eight studies reporting quality of life outcomes showed an improvement in quality of life or patient satisfaction with PST or PST/PSM.

‡Three of six studies reporting quality of life or patient satisfaction showed significant improvement with PST/PSM. Three reported no significant difference between PST/PSM and other care.

§Statistical significance of clinical outcomes not reported for this study.

¶This study did not directly compare TTR between PSM and control, but rather compared changes in TTR within and outside of trial conditions, finding no difference in the change in mean TTR between groups. TTR was higher with PSM, but statistical significance was not reported.

Other

Four identified studies[29-32] compared computer-assisted with manual anticoagulant dosing by experienced staff. All four studies reported increases in TTR with computerized dosing algorithms, though one[32] did not report the statistical significance of the result. This study examined TTR by indication and found an increase in TTR in AF patients from 46% in 1992 using cardiologist-based manual dosing to 81% in 2006 using computer-assisted dosing in the same practice. Three studies[29-31] reported adverse events and found no significant difference in bleeding events, hemorrhagic events, or deaths between the two groups.

One systematic review[33] identified two studies comparing PSM with PST including clinic care and found no statistically significant difference in TTR between the two groups. One of these studies reported quality of life outcomes and reported greater treatment satisfaction in the PST group compared with PSM.

One meta-analysis[40] compared the use of POC INR testing devices in any setting with "usual care," defined as laboratory INR testing with clinic or primary care management. Seventeen relevant articles reporting on 16 individual trials found no significant difference in major hemorrhage rate with POC testing compared with UC (OR 0.75, 95% CI 0.51 to 1.10). Use of POC devices was associated with a reduction in thromboembolism (OR 0.45, 95% CI 0.29 to 0.70) and mortality (OR 0.54, 95% CI 0.35 to 0.83). TTR was higher with POC device use (69% versus 61%), but no statistical analysis was reported.

7 DISCUSSION

7.1 Summary of Evidence

Results from systematic reviews indicate that specialized anticoagulation clinics result in higher TTR compared with UC, but do not tend to result in significant differences in bleeding events, thromboembolism, or mortality. Two included reviews reported results from RCTs separately from non-randomized studies.[33,34] One of these[34] found a reduction in thromboembolic events and major bleeds with specialized clinic care in non-RCTs, but no difference among randomized controlled trials. This dichotomy may reflect a difference in care in RCT conditions compared with non-randomized trials, which may better reflect actual practice. The two systematic reviews[33,34] reporting clinical outcomes were based on a comprehensive literature search and were generally well conducted, although neither provided a list of included and excluded studies, and one[33] did not attempt to assess the risk of publication bias. Results from the systematic reviews are supported by findings from five additional studies.[15-19] Four of these[16-19] found improvements in TTR with specialized anticoagulation care compared with UC (one[18] found no difference and one[15] did not report this outcome). Four non-randomized studies[15,17-19] found an increase in ER visits or need for additional medical attention with UC, while one RCT[20] reported no significant difference in adverse event rates between nurse-led POC testing and dose management and traditional hospital clinic care. Of the five primary studies reporting clinical outcomes[15,17-20] (including ER or hospital visits), only one[19] took into account loss of patients to follow-up and provided a power calculation. None of these three studies were blinded and one[20] randomized patients to their treatment groups, but did not report the method of randomization. While the additional primary studies are insufficient to identify a trend, their findings reflect the difference between RCTs and non-randomized studies described in the systematic reviews. Clinical practice guidelines produced by the ACCP in 2008 recommend a systematic and coordinated approach to anticoagulation therapy, using specialized anticoagulation management services

as an example.[7] This recommendation was based on a comprehensive literature review that showed a similar discrepancy between RCT and observational studies.

One study[18] compared different models of specialized care and found nurse-managed and pharmacist-managed services to result in a statistically significant increase in TTR compared with UC. When compared with nurse-managed care, pharmacist-managed services were associated with a significantly higher TTR. However, nurse-managed care was not statistically different from UC in the number of hospitalizations or ER visits; both resulted in a significant increase in hospital or ER visits compared with pharmacist-managed services. Two studies[20,21] compared nurse-led POC testing and computer-supported dose adjustment with hospital clinic care. One[20] found an improvement in TTR with nurse-led care, but no difference in rates of thrombosis, hemorrhage, or mortality. One[21] found no difference in TTR but did not report clinical outcomes.

Systematic reviews comparing patient self-testing or self-management with other models of anticoagulation care showed that PST/PSM resulted in lower mortality rates and lower incidence of thromboembolic events, but there was no significant difference in the rates of bleeding events where reported. The four systematic reviews reporting on clinical outcomes[33,39-41] were generally well conducted, based on a comprehensive literature search, and duplicate study selection and data extraction. Two of these reviews[33,41] did not assess the risk of publication bias and three[33,40,41] did not provide lists of included and excluded studies. TTR was similar between PST/PSM patients and those receiving care in anticoagulation clinics, but self-testing or management resulted in better TTR than UC in one HTA. One meta-analysis[40] showed that use of POC monitoring devices in any setting improved INR control. Similar results were shown in a review done for the ACCP guidelines,[7] which showed a trend toward improved TTR for PST or PSM compared with UC, but no difference compared with specialized anticoagulation services. These guideline recommendations suggest that PST or PSM be implemented where suitable. In contrast to the systematic reviews, results from additional primary studies (two RCTs, five non-randomized studies) indicated an increase in TTR with PST/PSM compared with specialized anticoagulation clinic care, but no difference compared with UC. However, one study found, when patients were stratified based on quality of INR control (TTR above or below 60%), that patients with poor control had a significant improvement in TTR when switched to PSM. One of the primary studies[24] showed a trend toward fewer bleeds or thromboembolisms with self-testing, but no statistical analysis was provided.

Quality of life measurements were reported, but not pooled, in three systematic reviews.[39,41,42] Overall, 15 of 25 studies included in the reviews reported quality of life improvements with PST/PSM. Two studies[23,28] found patient-reported improvements to quality of life with self-testing or self-management.

Four articles[29-32] compared the use of computer dosing algorithms with manual dosing by medical staff. These studies found an increase in TTR with computer-assisted dosing, but reported no significant difference in thromboembolism, bleeding, or mortality rates.

7.2 Limitations

This review is limited by mixed indications used in the majority of studies; only two included studies exclusively recruited patients with atrial fibrillation. Additionally, some systematic reviews included studies that would have been excluded from this review (for example, studies exclusively including patients with mechanical heart valve).

Furthermore, because systematic reviews were reviewed, there will be some overlap in included studies. Primary studies will potentially have been captured in more than one systematic review, and will therefore be counted more than once when considering the available evidence on clinical effectiveness of warfarin dosing management strategies.

Definitions of terms, such as major versus minor bleeding or usual care, vary across studies. Implementation of anticoagulation clinics or self-management programs also varies in aspects such as staffing, dose-management algorithms, INR measurement devices, or patient education sessions. This limitation compromises the ability to draw direct comparisons between included studies, and also makes it difficult to determine which specific aspects of organized anticoagulation treatment are beneficial.

Three multicentre trials comparing computer dosing with manual dosing included Canadian centres; however, studies comparing specialized services with UC or examining PST/PSM were conducted primarily in the USA or UK. Care received in these studies may not adequately reflect the Canadian context.

The methodological quality of included systematic reviews was generally good, although most failed to provide a list of excluded studies or assessment of publication bias. There is a risk of bias among the included primary studies. While they were generally well reported, none were blinded, none reported adequate allocation concealment, and only one described the method of randomization. Non-randomized studies are also at risk of bias due to lack of blinding. Additionally, the before-after nature of some of these studies introduces further risk of bias if treatment protocols or standards of care change over the study period.

In studies examining patient self-testing or self-management, participants may not be representative of the general population. Patients in self-testing or self-management arms are typically self-selected, and other eligibility criteria, such as the ability to use a computer and internet-based dosing programs, may select for a particular demographic that is not indicative of the suitability of self-testing or self-management for all patients receiving anticoagulation therapy.

8 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Based on a review of existing systematic reviews and additional primary studies, specialized anticoagulation services improve TTR compared with UC. However, depending on the study design, this improvement in TTR may not translate into a reduction in hemorrhage, thromboembolism, or in need for additional medical care.

Effects of PST or PSM on TTR were mixed, with studies showing either improved time in the therapeutic range, or no difference between models of care. Effects on clinical outcomes were also mixed, but PST or PSM generally resulted in lower mortality rates and reduced incidence of thromboembolism. Self-testing or self-management did not affect rates of bleeding events. PST/PSM may also improve quality of life and patient satisfaction.

Use of computerized dosing algorithms is associated with improved TTR, but not with reductions in adverse event rates, compared with manual dosing by experienced medical staff.

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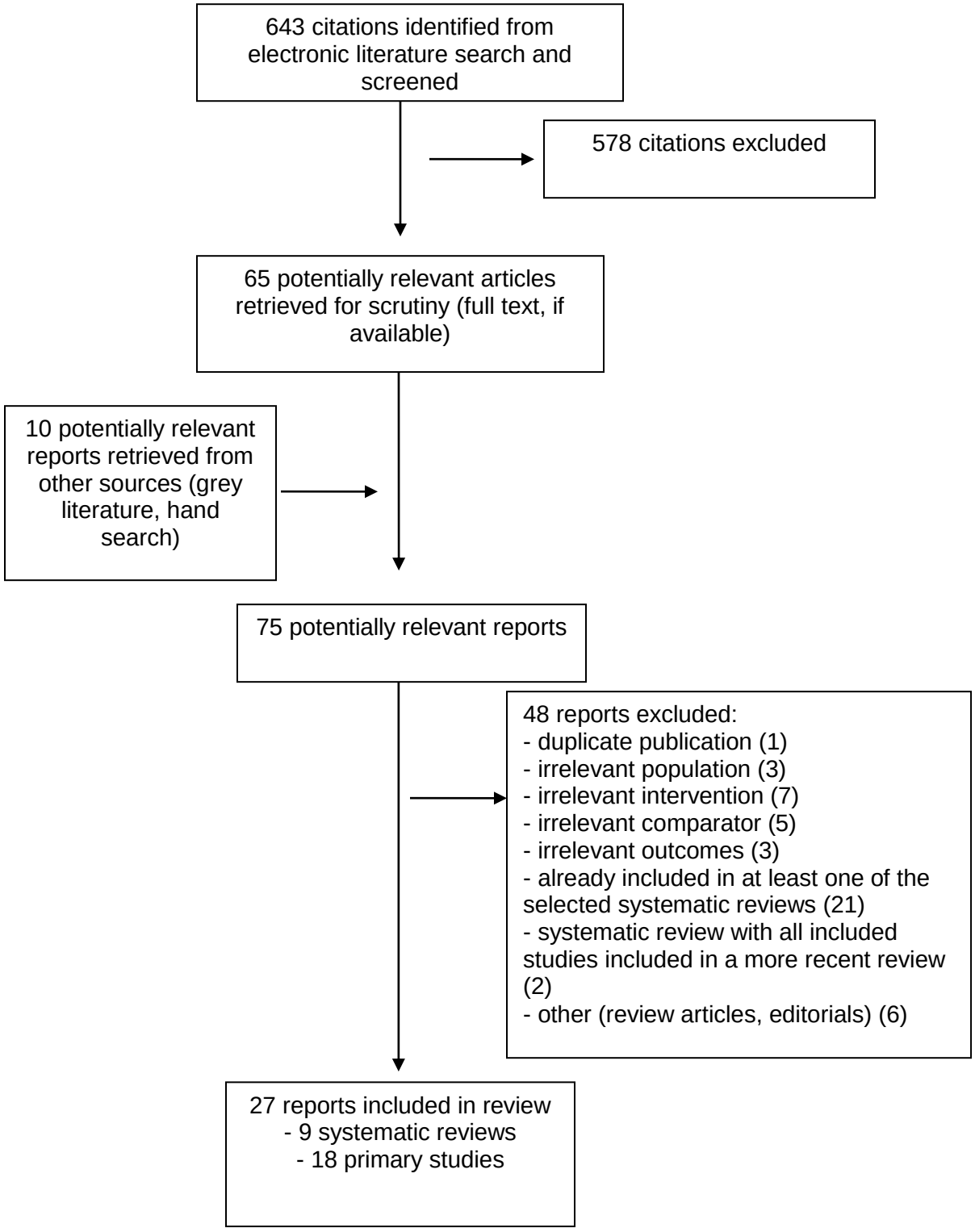
Conflict of Interest

No members declared any conflicts of interest. Conflict of Interest Guidelines are posted on the CADTH website.

APPENDIX 2: SELECTION OF INCLUDED STUDIES



APPENDIX 3: CHARACTERISTICS OF INCLUDED SYSTEMATIC REVIEWS

Study Year	No. of Included Studies	Patient Population	Intervention	Comparator	Outcomes
Specialized Anticoagulation Clinics					
Bloomfield et al.[33] 2011	3 RCTs (722 subjects), 8 cohort studies (12,768 subjects)	Mean age: 69 Mixed indications	ACC, various models (6 pharmacist-managed)	Non-specialized primary care clinic, physician office	RCTs *TTR (method not described, 3 RCTs)* Favours ACC 59.9% versus 56.3% *Mortality (2 RCTs)* RR 0.81, 95% CI 0.25 to 2.58 *Major bleeding (not defined, 3 trials)* RR 1.05, 95% CI 0.36 to 3.12 *Major thromboembolism (3 RCTs)* RR 1.29, 95% CI 0.59 to 2.81 Significant improvement in patient satisfaction with ACC care (2 RCTs) Cohort *TTR (method not described, 4 studies)* Favours ACC 63.5% to 53.5% *Mortality (1 study)* No significant difference *Major bleeding (5 studies)* 1 study favours UC, 1 favours ACC, 3 significance not tested *Major thromboembolism* (4 studies) 1 favours UC, 1 favours ACC, 2 significance not described *Hospitalizations, ER visits* 2 studies favour ACC, 1 found no difference

Study Year	No. of Included Studies	Patient Population	Intervention	Comparator	Outcomes
Saokaew et al.[34] 2010	5 RCTs (862 subjects), 19 non-randomized (727,515 subjects)	Mean age: 62.5 Mixed indications Warfarin only	Warfarin management in which a pharmacist participated	Usual physician provided care	RCTs *Major bleeding (definition varies by study, 4 RCTs)* RR 0.64, 95% CI 0.18 to 2.36 *Total bleeding (4 RCTs)* RR 0.51, 95% CI 0.28 to 0.94 *Thromboembolism, any (4 RCTs)* RR 0.79, 95% CI 0.33 to 1.93 *Mortality (3 RCTs)* RR 0.93, 95% CI 0.41 to 2.13 Non-randomized studies *Major bleeding (definition varies by study, 11 trials)* RR 0.49, 95% CI 0.26 to 0.93 *Total bleeding (19 trials)* RR 0.71 95% CI 0.52 to 0.96 *Thromboembolism, any (15 trials)* RR 0.37, 95% CI 0.26 to 0.53 *Mortality (4 trials)* RR 0.85, 95% CI 0.37 to 1.98
Cios et al.[35] 2009	24 non-randomized studies (43 study groups, 26,979 patients)	Mean age: NR Indications: NR Warfarin only	ACC (details not described)	Community care	TTR (mixed interpolation methods, US patients only) ACC: 64%, 95% CI 62% to 67% UC: 51%, 95% CI 48% to 54% Adjusted mean difference: –13%, 95% CI –18.1% to –7.9% TTR (post-hoc inclusion of Canadian studies) ACC: 65%, 95% CI 61% to 69% UC: 53%, 95% CI 50% to 56% Adjusted mean difference: –11.3%, –16.2% to –6.3%

Study Year	No. of Included Studies	Patient Population	Intervention	Comparator	Outcomes
Baker et al.[36] 2009	8 non-randomized studies (22,237 patients)	Mean age: NR AF only Warfarin only US only	ACC — study took place in a clinic, or role of clinicians limited to anticoagulation management	Community practice — study was not an RCT or classified as ACC	TTR (mixed interpolation methods) ACC: 63%, 95% CI 58% to 68% UC: 51%, 95% CI 47% to 55% Meta-regression indicates patients in UC spend 11% (95% CI 2% to 20%, 6 studies, 9 groups) less time in range
Dolan et al.[37] 2008	22 studies (28 study groups; 35,199 patient-years)	Mean age: NR AF only	ACC (details not described, 18 study groups)	Non-specialist setting (including family practice, 10 study groups)	TTR (methods not described) ACC: 63.6%, 95% CI 61.3% to 65.9% UC: 52.3%, 95% CI 42.1% to 62.4% Difference: 11.3%, 95% CI 0.1% to 21.7%
van Walraven et al.[38] 2006	67 studies (123 study groups; 50,208 patients)	Mean age: NR Mixed indications	ACC — study took place in clinic or role of clinicians limited to anticoagulation management (84 study groups)	Community practice — study was not an RCT or classified as ACC (30 study groups) RCT (9 study groups)	TTR (mixed methods) RCT: 66.4%, 95% CI 59.4% to 73.3% ACC: 65.6%, 95% CI 63.7% to 67.7% UC: 56.7%, 95% CI 51.5% to 62% Difference (ACC vs. RCT) –3.9%, 95% CI –10.7% to 2.9% Difference (UC vs. RCT) –12.2%, 95% CI –19.5% to –4.8%
Patient Self-testing or Self-management					
Bloomfield et al.[33] 2011	27 studies reporting on 22 RCTs (8,413 subjects)	Mean age: 65 Mixed indications	PST or PST/PSM	ACC, primary care, or physician office	*TTR (methods not described)* PST/PSM 66.1% vs. other care 61.9% Weighted mean difference: 1.5%, 95% CI –0.63% to 3.63% *Mortality* Favours PST/PSM: OR 0.74, 95% CI 0.63 to 0.87 *Thromboembolism* Favours PST/PSM: OR 0.58, 95% CI 0.45 to 0.75 *Major bleeding* No statistically significant difference:

Study Year	No. of Included Studies	Patient Population	Intervention	Comparator	Outcomes
					OR 0.89, 95% CI 0.75 to 1.05 8 studies reported improvements in quality of life (4 studies) or patient satisfaction (4 studies) out of 11 studies reporting these outcomes
Garcia-Alamino et al.[39] 2010	26 studies reporting on 18 RCTs (4,723 patients)	Mean age: NR Mixed indications	PST or PST/PSM	ACC or personal physician care	TTR (methods not described) 3 of 11 studies reporting TTR report significant improvement with PST/PSM *Mortality* Favours PST/PSM: RR 0.64, 95% CI 0.46 to 0.89 *Thromboembolism* Favours PST/PSM: RR 0.50, 95% CI 0.36 to 0.69 *Major bleeding* No difference: RR 0.87, 95% CI 0.66 to 1.16 *Minor bleeding* Favours PST/PSM: RR 0.64, 95% CI 0.54 to 0.77 PST alone *Mortality* No difference: RR 0.84, 95% CI 0.50 to 1.41 *Thromboembolism* No difference: RR 0.57, 95% CI 0.32 to 1.00 *Major bleeding* Favours PST: RR 0.56, 95% CI 0.35 to 0.91 *Minor bleeding* No difference: RR 0.93, 95% CI 0.72 to 1.20

Study Year	No. of Included Studies	Patient Population	Intervention	Comparator	Outcomes
					5 of 8 studies evaluating quality of life outcomes reported a significant difference in treatment satisfaction or quality of life with PST/PSM
Cios et al.[35] 2009	24 non-randomized studies (43 patient groups, 26,979 subjects)	Mean age: NR Indications: NR Warfarin only	PSM (2 patient groups)	ACC or community care (41 patient groups)	TTR (mixed interpolation methods, US patients only) PSM: 58%, 95% CI 47% to 51% No PSM: 57%, 95% CI 55% to 59% Adjusted mean difference: –8.9%, 95% CI –25.7% to 7.8% TTR (post-hoc inclusion of Canadian studies) PSM: 65%, 95% CI 55% to 76 % No PSM: 59%, 95% CI 56% to 61% Adjusted mean difference: –2.0, 95% CI –15.3% to 11.2%
Wells et al.[40] 2007	17 studies describing 16 RCTs (4,460.7 patient-years)	Mean age: NR Mixed indications	PST or PST/PSM	ACC or primary care	TTR (Rosendaal method) Favours PST/PSM: 71% (95% CI 68 to 78) vs. 63% (95% CI 60 to 65) Mortality (favours PST/PSM, 6 trials) OR 0.48, 95% CI 0.24 to 0.94 Major thromboembolism (favours PST/PSM, 11 trials) OR 0.49, 95% CI 0.30 to 0.79 All thromboembolism (favours PST/PSM, 8 trials) OR 0.45, 95% C 0.24 to 0.84 Major bleeding (no difference, 10 trials) OR 0.75, 95% CI 0.47 to 1.20

Study Year	No. of Included Studies	Patient Population	Intervention	Comparator	Outcomes
Connock et al.[41] 2007	16 RCTs (4,444 patients), 8 non-randomized (1,284 patients)	Mean age: NR Mixed indications	PST or PST/PSM	ACC or primary care/family-doctor managed anticoagulation	TTR (method not described) RCTs (12 studies) 67.4% PST/PSM vs. 63.4% other care when separated by controls used: 67.1% PST/PSM vs. 66.3% ACC 74.8% PST/PSM vs. 59.8% UC P-values not reported *Mortality (favours PST/PSM)* RD –0.017, 95% CI –0.029 to –0.005 *Thromboembolism (favours PST/PSM)* RD –0.02, 95% CI –0.03 to –0.01 *Bleeding (no difference)* RD –0.004, 95% CI –0.015 to 0.007 6 studies reported quality of life outcomes. 3 favoured PST/PSM, 3 reported no significant difference between PST/PSM and other care.
van Walraven et al.[38] 2006	67 studies (123 study groups; 50,208 patients)	Mean age: NR Mixed indications	PSM (7 patient groups)	ACC or community care (116 patient groups)	TTR (mixed methods) No PSM: 63.1%, 95% CI 61% to 65.2% PSM: 71.5%, 95% CI 65.2% to 77.7% Difference: 7%, 95% CI 0.7% to 13.3%

ACC = specialized anticoagulation clinic; NR = not reported; OR = odds ratio; PST = patient self-testing; PSM = patient self-management; RD = risk difference; RR = relative risk; TTR = time in therapeutic range; UC = usual care.

APPENDIX 4: CHARACTERISTICS OF INCLUDED PRIMARY STUDIES

Study Year Country	Study Design Sample Size	Patient Population	Intervention	Comparator	Outcomes
Specialized Anticoagulation Clinics vs. Usual Care					
Aziz et al.[15] 2011 USA	Cohort study (2,397 patients)	Mean age: NR Indication: NR Warfarin only	Nurse-managed anticoagulation service with physician oversight. No POC testing (n = 131)	Usual physician care (n = 2,266)	ER visit: Nurse AMS: 2 patients (1.5%) UC: 247 patients (10.9%) Hospitalization: Nurse AMS: 3 patients (2.3%) UC: 289 patients (12.8%) P-values reported for cost data only
Garton and Crosby[16] 2011 USA	Retrospective medical record review (64 patients)	Mean age: 74 Indication: 81% AF Warfarin only	Pharmacist-managed anticoagulation clinic with POC testing (n = 64)	Usual physician care before clinic referral (n = 64)	Percentage of INR values in range: Pharmacist AMS: 81.1% UC: 71.1% P < 0.0001 Estimated variance in therapeutic INR rates Pharmacist AMS: 185.2 UC: 365.7 P = 0.004
Hall et al.[17] 2011 USA	Retrospective cohort (350 patients)	Mean age: AMS 63.7 UC 65.1 Indication: AMS 68.6% AF UC 60.0% AF Warfarin only	Pharmacist-managed anticoagulation clinic with laboratory INR measurement (n = 175)	Usual physician care (n = 175)	TTR (Rosendaal method): Pharmacist AMS: 73.7% UC: 61.3% P < 0.0001 Adverse events (anticoagulation-related, details not provided): Pharmacist AMS: 14 events in 9 patients (5.1%) UC: 41 events in 27 patients (15.4%) P < 0.0001 ER visits: Pharmacist AMS: 58 UC: 134

Study Year Country	Study Design Sample Size	Patient Population	Intervention	Comparator	Outcomes
					P < 0.00001 Hospitalizations: Pharmacist AMS: 3 UC: 14 P < 0.00001
Rudd and Dier[18] 2010 USA	Retrospective medical record review (996 patients)	Mean age: 72 to 75 (across study groups) Indication: 50% to 56% AF (across study groups) Warfarin only	Pharmacist-managed AMS with POC or laboratory testing (n = 489), or nurse-managed AMS (lab testing only) (n = 307)	Primary care provider with laboratory INR testing (n = 200)	TTR (Rosendaal method) Pharmacist AMS: 83.6% Nurse AMS: 71.8% Primary care: 57.4%, P < 0.05 between all models Hospitalization rate (per 100 patient-years) Pharmacist AMS: 5.4 Nurse AMS: 12.3 Primary care: 13.9, P < 0.05 between pharmacist AMS and other models ER visit rate (per 100 patient-years) Pharmacist AMS: 1.2 Nurse AMS: 5.6 Primary care: 5.6, P < 0.05 between pharmacist AMS and other models
Garwood et al.[19] 2008 USA	Retrospective before-after study (40 patients)	Mean age: 61.7 Indication: 35% AF Warfarin only	Pharmacist-managed anticoagulation clinic	Transition to physician-managed care after INR stabilization	% of INRs in range: Pharmacist: 76% Physician: 48%, P < 0.0001 INRs in range for each patient (median %) Pharmacist: 75% Physician: 36.5%, P < 0.0001 Cases requiring additional medical care (e.g., hospitalization, emergency room visit) Pharmacist: 2 (2 bleeding related) Physician: 13 (12 bleeding related), P =

Study Year Country	Study Design Sample Size	Patient Population	Intervention	Comparator	Outcomes
					0.0412 Perceived quality of care (based on patient satisfaction survey) was higher for pharmacist-managed care
Comparison of Clinic Models					
Fitzmaurice[20] 2006 UK	RCT (224 patients)	Mean age: NR Indication: NR Warfarin only	Nurse-led POC testing and computer-based decision support in primary practice (n = 122)	"Traditional" hospital-based anticoagulation management (n = 102)	TTR (Rosendaal method) Nurse-led: 69%, 95% CI 66% to 73% Hospital: 57%, 95% CI 50% to 63% No significant difference in serious adverse events (3 versus 3, P = NR), including death (1 versus 0, P = NR) between the two groups
Rudd and Dier[18] 2010 USA	See above				
Edgeworth and Coles[21] 2010 UK	Retrospective before-after study (46 patients)	Mean age: 69.7 (at recruitment) Indication: 65.2% AF Warfarin only	Nurse-led POC-testing and computer-based decision support in primary practice	Phlebotomy and secondary care (hospital) anticoagulation service	TTR (method not described) Nurse-led primary care: 72.1% Secondary (hospital) care: 76.4% Mean difference: 4.3 (5.6% reduction), 95% CI –2.7% to +13.9%
Patient Self-testing or Self-management vs. Clinic Care					
Christensen et al.[22] 2011 Denmark	RCT (123 patients)	Mean age: 62 to 66 (across study groups) Indication: 51 to 67% AF (across study groups)	PST once or twice weekly, with hospital clinic adjusted dosing (INR and dose adjustments reported using online system) (n = 83)	Hospital-clinic management with laboratory INR measurements every 4 weeks (n = 40)	TTR (Rosendaal method) PST (1x): 79.7%, 95% CI 79.0% to 80.3% PST (2x): 80.2%, 95% CI 79.4% to 80.9% Clinic: 72.7%, 95% CI 71.9% to 73.4% One hospitalization reported across all groups

Study Year Country	Study Design Sample Size	Patient Population	Intervention	Comparator	Outcomes
McCahon et al.[23] 2011 UK	Survey of RCT participants (SMART trial) (363 responders)	Mean age: NR Indication: NR Warfarin only	PSM with self INR testing every 2 weeks (n = 202)	Hospital or practice-based anticoagulation clinic care (n = 161)	Quality of life: self-efficacy improvement favours PSM: 1.67 versus 0.43, P = 0.01 Social network strain increased with routine care after adjusting for age: 1.36 (clinic) versus 0.34 (PSM), P = 0.02 No significant difference in daily hassle, psychological distress, treatment satisfaction, or anxiety
Gardiner et al.[24] 2009 UK	Prospective cohort study (318 patients enrolled)	Median age (PST): 58 Median age (UC): 68 Indication (PST): 38% AF Indication (UC): 56% AF	PST every 2 weeks with computer dosing performed by specialist nurse (n = 67 in final analysis)	Routine care at a hospital-based anticoagulation clinic (n = 88 in final analysis)	TTR (Rosendaal method): PST: 71%, 95% CI 64.1% to 75.3% Clinic: 60%, 95% CI 55.0% to 63.2% Major bleed (defined as requiring hospitalization or transfusion): PST: 1.7 per 100 patient-years Clinic: 5.4 per 100 patient-years Minor bleed: PST: 8.4 per 100 patient-years Clinic: 16.2 per 100 patient-years Thrombosis: PST: 3.4 per 100 patient-years Clinic: 1.4 per 100 patient-years
O'Shea et al.[25] 2008 USA	Prospective before-after study (58 patients)	Median age: 54.1 (range 27 to 82) Indication: 31% AF Warfarin only	Internet-supervised PSM with self INR testing every 1 or 2 weeks	Routine care at the Duke Anticoagulation Clinic	TTR (Rosendaal method) PST: 74.4% Clinic: 63.0% Mean difference 11.4% 95% CI, 5.5% to 17.3% No bleeding or thrombosis reported during the study period

Study Year Country	Study Design Sample Size	Patient Population	Intervention	Comparator	Outcomes
McCahon et al.[26] 2007 UK	Retrospective multicentre matched control study (78 patients from SMART trial)	Mean age (PSM): 64 Mean age (control): 66 Indication: 54% AF Warfarin only	PSM with self INR testing every two weeks (n = 38)	Hospital or practice-based anticoagulation clinic care (n = 40)	TTR (Rosendaal method) TTR calculated within and post-SMART trial PSM: trial 75%, post-trial 70%, P = 0.12 Control: trial 64%, post-trial 57%, P = 0.54 No significant difference in change in mean TTR between PSM and control, P = 0.54
Patient Self-testing or Self-management vs. Usual Care					
Harper and Pollock[27] 2011 New Zealand	Prospective before-after study (41 patients)	Mean age: NR Indication: NR Warfarin only	PSM using Internet-based decision support	Laboratory INR tests with dose management by general practitioner or lab staff	TTR (Rosendaal method) Overall PSM 81.3% vs. UC 72.4%, P = 0.16 In patients with poor control (TTR < 60%) prior to PSM PSM 71.1% vs. UC 38.8%, P = 0.01 In patients with good control (TTR > 60%) prior to PSM PSM 82.5% vs. UC 83.0%, P = NS
Salvador et al.[28] 2008 Spain	Prospective cohort study (108 patients)	Mean age (PST): 72.5 Mean age (control): 72.9 Indication (PST): 76% AF Indication (control): 76% AF	PST every 3 weeks with dose adjustment by general practitioner using a decision-support tool (INR and dose adjustments reported using telemedicine system)	Laboratory INR tests with dose management by general practitioner using a decision support tool	TTR (Rosendaal method) PST 65.7% vs. UC 66.4%, P = 0.85 *Mortality*: PST 5.5% vs. UC 5.5%, P = 1.0 *Major bleeding (not defined)*: PST 0% vs. UC 1.8%, P = 1.0 *Minor bleeding*: PST 7.4% vs. UC 3.7%, P = 0.67 *Thrombosis*: PST 1.8% vs. UC 3.7%, P = 1.0 *Hospital admissions*: PST 3 vs. UC 4 Significant improvements in quality of life outcomes were reported with PST

Study Year Country	Study Design Sample Size	Patient Population	Intervention	Comparator	Outcomes
Computer vs. Manual Dosing					
Poller et al.[29] 2009 Multicentre	RCT 2,631 patients	Mean age: 65.9 Indication: 48% AF	Dawn AC dosing program (n = 1,315)	Manual dosing by clinic medical staff (n = 1,316)	TTR (Rosendaal method) Manual dosing: 63.4% Computer dosing: 66.8% Difference: 3.5%, 95% CI 2.3% to 4.9%, P < 0.001 Total adverse events per 100 patient-years (bleeds, thrombosis, death) Manual dosing: 5.8, 95% CI 4.6 to 7.0 Computer dosing: 5.6, 95% CI 4.6 to 6.9 Total adverse events (AF only) Manual dosing: 5.9 per 100 patient-years Computer dosing: 6.1, P = NS
Poller et al.[30] 2008 Multicentre	RCT 10,421 patients	Mean age: 67.1 Indication: 45% AF	Parma-5 dosing program (n = 5,290)	Manual dosing by clinic medical staff (n = 5,131)	TTR (Rosendaal method) Manual dosing: 65.0% Computer dosing: 65.7% Difference: 0.7%, 95% CI 0.1% to 1.3%, P = 0.021 Total adverse events per 100 patient-years (bleeds, thrombosis, death) Manual dosing: 6.0, 95% CI 5.5 to 6.6 Computer dosing: 5.5, 95% CI 4.9 to 6.0 Incidence rate ratio: 0.89, 95% CI 0.78 to 1.01 Total adverse events (AF only) Manual dosing: 5.1 Computer dosing: 4.6, P = NS

Study Year Country	Study Design Sample Size	Patient Population	Intervention	Comparator	Outcomes
Poller et al.[31] 2008 Multicentre	RCT 13,052 patients	Mean age: 66.9 Indication: 46% AF	Dawn AC or Parma-5 dosing program (n = 6,605)	Manual dosing by clinic medical staff (n = 6447)	TTR (Rosendaal method) Manual dosing: 64.7% Computer dosing: 65.9% Mean difference: 1.2%, 95% CI 0.7% to 1.8% TTR (AF patients only, Rosendaal method) Manual dosing: 66.2% Computer dosing: 67.6%, P = NR Total adverse events (bleeds, thrombosis, death) Incidence rate ratio (favours computer dosing): 0.90, 95% CI 0.8 to 1.02, P = NS Total adverse events (AF only) Incidence rate ratio (favours computer dosing): 0.93, 95% CI 0.78 to 1.12, P = NS
Onundarson et al.[32] 2008 Iceland	Retrospective cohort study 1,182 patients	Before (1992): Mean age: 64 Indication: 31% AF After (2006): Mean age: 73 Indication 71% AF	Dawn AC dosing program (n = 941)	Manual dosing by clinic cardiologist (n = 241)	TTR (AF patients, Rosendaal method) Manual dosing: 46% Computer dosing: 81%, P = NR

AF = atrial fibrillation; AMS = anticoagulation management service; NR = not reported; NS = not significant; POC = point of care; PSM = patient self-management; PST = patient self-testing; RCT = randomized controlled trial; UC = usual care; vs. = versus.

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

Optimal Use Report

CADTH

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Optimal Warfarin Management for the Prevention of Thromboembolic Events in Patients with Atrial Fibrillation: Review of Canadian Economic Studies

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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ABBREVIATIONS

AF	atrial fibrillation
CI	confidence interval
ER	emergency room
ICER	incremental cost-effectiveness ratio
INR	international normalized ratio
PMAS	pharmacist-managed anticoagulation service
PT	prothrombin time
QALY	quality-adjusted life-year
RCT	randomized controlled trial
TTR	time in therapeutic INR range

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1 INTRODUCTION

Optimizing drug-related health outcomes and cost-effective use of drugs by identifying and promoting optimal drug prescribing and use is a goal of the Canadian Agency for Drugs and Technologies in Health (CADTH). Where possible, CADTH builds on existing applicable Canadian and international initiatives and research. CADTH goals are achieved through three main approaches:

- identifying evidence-based optimal use in prescribing and use of specific drugs
- identifying gaps in clinical practice, then proposing evidence-based interventions to address these gaps
- supporting the implementation of these interventions.

Direction and advice are provided to CADTH through various channels, including the following:

- the Drug Policy Advisory Committee (DPAC), the DPAC Optimal Use Working Group (OUWG), and the Formulary Working Group (FWG),which include representatives from the federal, provincial, and territorial health ministries and related health organizations
- the COMPUS Expert Review Committee (CERC) (members are listed in Appendix A)
- stakeholder feedback.

1.1 COMPUS Expert Review Committee

CERC consists of eight Core Members appointed to serve for all topics under consideration during their term of office, and three or more Specialist Experts appointed to provide their expertise in recommending optimal use for one or more specific topics. For this project, five Specialist Experts were appointed; their expertise included cardiology, hematology, and thrombosis. Two of the Core Members are Public Members, who bring a lay perspective to the committee. The remaining six Core Members hold qualifications as physicians, pharmacists, or health economists, or have other relevant qualifications, with expertise in one or more areas such as, but not limited to, family practice, internal medicine, institutional or community clinical pharmacy, pharmacoeconomics, clinical epidemiology, drug utilization, methodology, affecting behaviour change (through health professional and/or patient and/or policy interventions), and critical appraisal. The Core Members, including Public Members, are appointed by the CADTH Board of Directors.

CERC's mandate is advisory in nature and consists of providing recommendations and advice to CADTH on assigned topics that relate to the identification, evaluation, and promotion of optimal practices in the prescribing and use of drugs across Canada. The overall perspective of CERC members in producing recommendations is that of public health care policy-makers in pursuit of optimizing the health of Canadians within available health care system resources.

2 CONTEXT AND POLICY ISSUES

The DPAC and its working groups, the OUWG and the FWG, have identified warfarin management for prevention of thromboembolic events in patients with atrial fibrillation as being a priority topic for optimal practice initiatives based on the following criteria:

- large deviations from optimal utilization (overuse or underuse)
- size of patient populations
- impact on health outcomes and cost-effectiveness
- benefit to multiple jurisdictions
- measurable outcomes
- potential to effect change in prescribing and use.

Atrial fibrillation (AF) is the most common cardiac arrhythmia.[1] Patients with AF have an elevated risk of stroke, which is a leading cause of death and disability among patients with the condition.[2,3]

Warfarin is an oral anticoagulant in the drug class of vitamin K antagonists. It is often used for stroke prevention in patients with AF at high risk for stroke who have no contraindications. Warfarin and related anticoagulants have consistently been shown to reduce the risk of stroke in patients with AF by more than 60% compared with no treatment, and by 30% to 40% compared with low-dose aspirin.[4,5] Long-term anticoagulation with vitamin K antagonists is typically required for prevention and treatment of thromboembolism in patients with AF and other high-risk groups, such as patients with mechanical heart valves, venous thromboembolism, pulmonary embolism, or peripheral vascular disease.[6,7] However, warfarin use has some disadvantages, including numerous food and drug interactions, the need for frequent laboratory monitoring, and the risk of bleeding complications.

The effectiveness and safety of warfarin depends on maintaining its dose at sufficient levels to keep patient international normalized ratio (INR) within the therapeutic range. Current Canadian guidelines recommend a target INR range of 2.0 to 3.0.[8] The percentage of time spent in the therapeutic range (TTR) depends on the quality of dose management.

TTR can be calculated by different methods. The simplest method involves calculating the proportion of INR test results that fall within the therapeutic range, but fails to account for actual time spent in range. The most common method in clinical studies is the Rosendaal linear interpolation method.[9] This method adds each patient's time within the therapeutic range and divides by the total time of observation. This assumes that between-test INR varies linearly. Another common method is the half-time interpolation method, by which the total time of follow-up with INR in range is divided by the total time. Half the time between two tests is allocated to the first INR value, and half to the second. Different studies use different methods to calculate TTR, which should be taken into account when comparing TTR values.

Specialized anticoagulation services have been developed to optimize warfarin dosing management. These services can generally be defined as tertiary or community hospital-based anticoagulation clinics, primary care settings, point-of-care testing and dose adjustment by community pharmacies, and patient self-testing and patient self-management using a point-of-care device.[10] The primary care anticoagulation setting involves a family practice group or family health team in which nurses, pharmacists, or physicians are responsible for managing warfarin therapy.[10] Primary care settings and hospital-based

anticoagulation clinics may use computerized decision-support applications or other means to guide warfarin dosing.[7,10] This is in contrast to usual care, which may be defined as warfarin dose adjustment, managed by a physician working in a private practice setting, that not only addresses anticoagulation management, but also other medical problems.[11] Physicians in this setting use their own judgment without access to specialized anticoagulation tools, or specialized anticoagulation staff and services.[11,12]

3 RESEARCH QUESTION

The objective was to review the published literature for Canadian studies that provided information on the following question: What are the costs associated with specialized anticoagulation services?

Specialized anticoagulation services are defined in Appendix 2.

4 KEY FINDINGS

- One cost-utility[13] provided data on patient self-management of anticoagulation, and three costing studies[14-16] provided information on the costs of hospital-based specialized anticoagulation services in Canada.
- The incremental cost-effectiveness ratio of patient self-management compared with physician management of anticoagulation was C$14,000 over a five-year time horizon and from a health payer perspective.[13]
- Hospital-based physician- or pharmacist-managed anticoagulation services were associated with lower costs than community physician-managed care in two costing studies[15,16] and with higher costs in a third study.[14]
- The three-month Ministry of Health costs of anticoagulation were C$108, C$145, and C$199 for hospital-based physician-managed care, hospital-based pharmacist-managed care, and community physician anticoagulation management, respectively.[15]
- The cost-utility[13] estimate was limited by uncertainty in the clinical data. Two costing studies[14,16] had methodological weaknesses that may limit the validity of the findings. In the third costing study,[15] there were differences in the characteristics of patients treated in the hospital compared with the community, which may have affected the costs. The duration of two costing studies was insufficient to capture differences between comparators on the costs related to bleeding or thromboembolic events.[14,15]

5 METHODS

5.1 Literature Search Strategy

A limited literature search was conducted using the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1980–) via Ovid; the National Health Service (NHS) Economic Evaluation Database (2nd Quarter 2011) via Ovid; and PubMed. The main search concepts were warfarin and Canadian publications. For the warfarin concept, keywords were searched in title only and controlled vocabulary restricted to major subject headings. A methodological filter was applied to limit retrieval to economic studies. The search was not limited by date or language. The initial search was completed on June 28, 2011. Regular alerts were established to update the search until the publication of the final report.

5.2 Selection Criteria

Articles were reviewed independently by two researchers (GM, AK) and evaluated for inclusion according to the criteria shown in Table 1.

Table 1: Selection Criteria

Population	Canadian outpatients receiving chronic vitamin K antagonist treatment titrated to an INR of 2.0 to 3.0
Intervention	Specialized anticoagulation monitoring services including patient-managed care
Comparator	Another model of specialized anticoagulation monitoring or usual care
Outcomes	Costs, resource utilization, incremental cost-effectiveness ratio
Study Designs	Cost-consequence, cost-benefit, cost-effectiveness, cost-utility, or cost analyses

INR = international normalized ratio.

Any study consisting completely of patients with mechanical heart valves or pediatric patients, or studies of in-hospital anticoagulation management were excluded.

5.3 Data Extraction and Critical Appraisal Strategy

Data extraction and critical appraisal were completed by one researcher (GM) and verified by a second researcher. The BMJ checklist[17] was used to evaluate the quality of the cost-utility study (Appendix 3). The key limitations were described for the other study types. Study results were described using a narrative approach.

6 RESULTS

6.1 Quantity of Research Available

The literature search identified 115 articles. One additional article was identified from another source. Of these articles, eight were reviewed in full text and four met the inclusion criteria. Among the included studies were one cost-utility study[13] and three cost analyses (Appendix 4).[14-16]

6.2 Review of Included Studies

A. Patient Self-Management

Study description

Regier et al.[13,18,19] conducted a cost-utility analysis of patient self-managed versus physician-managed anticoagulation from a Canadian health payer perspective. The authors used a Markov model with five health states (no events, minor or major hemorrhagic event, major thromboembolic event, and death) to simulate the costs and health outcomes of patients receiving chronic warfarin treatment. The probability of moving from one state to another depended on the time that the patient's INR was in the therapeutic range. Patients who experienced a major hemorrhage or thromboembolic event could be temporarily or permanently disabled. The time horizon was five years and the primary outcome was the incremental cost-effectiveness ratio (ICER).[13]

The time in the therapeutic range for self- versus physician-managed anticoagulation was taken from a single randomized controlled trial (RCT) conducted at the Vancouver General Hospital that included 140 patients with atrial fibrillation, mechanical heart valve, or venous thromboembolism.[20] The data on the probability of a hemorrhagic or thromboembolic event based on time in the therapeutic range were provided by the Italian Study on Complications of Oral Anticoagulant Therapy (ISCOAT) cohort study of 2,745 patients.[21] Utility values were taken from several published studies in patients who had experienced a stroke or major hemorrhage. The authors conducted deterministic and probabilistic sensitivity analyses to test the robustness of the model.[13]

Results

Regier et al. reported that self-management of anticoagulation prevented 3.5 major thrombotic, 0.79 major hemorrhagic events, and 0.12 deaths per 100 patients compared with physician management, over a five-year time horizon (Table 2).[13] Self-management was associated with an additional C$989, 0.07 quality-adjusted life-years (QALYs), and an ICER of $14,129 per QALY. Almost all estimates from the probabilistic sensitivity analysis were in the upper right-hand quadrant of the cost-effectiveness plane. There was a 95% probability that self-management was cost-effective if the willingness to pay was $23,800 per QALY. In the deterministic sensitivity analyses, the ICER values ranged from $11,428 to $19,514 when the number of physician visits, probability of disability, discount rate, and utility values were varied. The costs for self-management were high in the first year of therapy due to start-up costs of $1,567 per patient for training and support, and this was reflected in the one-year ICER of $236,667 per QALY.[13]

Table 2: Summary of Results from Regier[13]

Expected Incremental Costs and Benefits for Self-managed versus Physician-managed Anticoagulation			
Outcome	**Period**		
	1 year	**5 years (base case)**	**10 years**
Events avoided per 100 patients			
Major thrombotic event	0.72	3.50	5.67
Major haemorrhage	0.17	0.79	1.25
Death	0	0.12	4.1
Mean incremental costs (95% CI)	$1,420 (1,041 to 1,807)	$989 (310 to 1,655)*	$599 (-459 to 1,677)
Mean incremental QALY (95% CI)	0.006 (0.005 to 0.008)	0.07 (0.056 to 0.084)†	0.20 (0.16 to 0.24)
ICER	$236,667	$14,129	$2,995

CI = confidence interval; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
*Mean cost per patient in the self-management strategy: $6,116 (95% CI $5,426 to $6,830); physician-managed strategy: $5127 (95 CI $4390 to 5894)
†QALYs in self-management strategy: 4.28 (95% CI 4.24 to 4.30); physician-managed strategy: 4.21 (95% CI 4.19 to 4.25).

Limitations

The Regier et al.[13] study was limited by the robustness of the clinical outcome data. The authors based the model on a single RCT that reported surrogate outcomes (i.e., time in the therapeutic range). The correlation between time in range and hemorrhagic and thromboembolic events outcomes was extrapolated from a single cohort study. The authors failed to provide detailed descriptions of the patients enrolled or limitations of these studies,

and no deterministic sensitivity analyses were conducted to explore the uncertainty in the clinical data. Reporting of data elements was incomplete for several items on the BMJ checklist (Appendix 3). The source for some cost data was not stated and the utilization of several resources was assumed, and not based on actual patient usage. The generalizability of the findings may be limited due to the strict inclusion criteria in the clinical study used for the model. The authors state that self-management is not suitable for all patients, as it relies on the patients' ability to understand anticoagulation and requires adequate vision and manual dexterity. Thus it may not be possible to extrapolate the findings of this study to the larger population of anticoagulated patients.[13]

B. Hospital-based Anticoagulation Services

Study 1: Schulman et al.[15]

Study description

Schulman et al.[15] conducted a prospective observational costing study comparing four different models of anticoagulation management (Appendix 5). The authors gathered medical, non-medical, patient, and productivity loss costs from 16 sites across Canada, including hospital-based physician- or pharmacist-managed clinics, community-based family physician-managed care (traditional model), and community-based pharmacist-managed care. Data were collected for three months at each site from consecutive eligible patients who were either new users of warfarin (one month or less therapy) or chronic users (three or more months). Adults with atrial fibrillation or previous venous thromboembolism were eligible to participate. Information was collected from each site on the type of setting, services provided, budget, overhead costs, patient volume, staffing, salaries, procedures for laboratory testing and managing warfarin dosing, and point-of-care testing used. Over the three-month study period, the staff recorded the time and complexity of each patient encounter, including communication with the laboratory and administrative (i.e., charting) duties. Patients were asked to provide background information on their indication for warfarin, drug coverage, complications, and concomitant medications. Using a diary, patients recorded the time, travel, and costs (including lost wages) related to anticoagulation. Caregiver's costs and lost income were also collected. The unit costs for resources were obtained from government sources, mainly from Ontario (see Appendix 4). The total costs of anticoagulation management from the Ministry of Health perspective included medical consultations, laboratory tests, hospitalization (if applicable), medications, and overhead. The societal costs included the Ministry of Health costs plus patient costs (medication copayments, personal expenses, caregiver costs, home-care costs, cost of patient, and caregiver workdays lost). The average three-month costs for each care model were presented.[15]

Results

A total of 18 sites were invited to participate in the study and 16 provided data between 2006 and 2008.[15] The data from the one community-based pharmacist-managed clinic were incomplete and were therefore excluded from the results, leaving 15 sites reporting results from the three remaining models of care (Appendix 5). A total of 429 patients were included in the three-month study. The patients from hospital clinics were younger than those in community care (hospital, 63 to 66 years; community, 70 years) and used fewer chronic prescription medications. More patients treated in the community had atrial fibrillation (86%) compared with hospital-based physician-managed (59%) and pharmacist-managed (55%) clinics. Patients treated in hospital clinics had more prothrombin time (PT) tests drawn than in community care. No statistical testing was conducted on patient characteristics to test for differences between care models. During the study period, there were five warfarin-related

complications, but the costs of these events were minimal and they were excluded from the totals.[15]

From the Ministry of Health perspective, the total three-month cost of care per patient was $108, $145, and $199 in the hospital physician, hospital pharmacist and the community physician care models, respectively.[15] In the hospital-based models, PT tests and other health care professional consultations accounted for the highest proportion of costs (physician: 75%; pharmacist: 87%). Physician consultations accounted for 7% and 5% of costs in the hospital physician and pharmacist models. In the community physician model, physician consultations, other health care professional consultations, and PT tests accounted for 42%, 34%, and 20% of costs, respectively. The proportion of costs for warfarin ranged from 4% to 11% among models.[15]

When the societal perspective was taken, the total three-month cost of care per patient was $188, $198, and $244 in the hospital physician, hospital pharmacist, and community physician care models, respectively.[15] In the hospital physician model, PT tests and lost wages by patients accounted for the highest proportion of costs. In the hospital pharmacist model, other health care professional consultations and PT tests had the highest costs, and in the community model, physician and other health care professional consultations were responsible for the highest portion of total costs.[15]

Sensitivity analyses were conducted based on data from other sources. The societal three-month costs of care ranged from $203 to $277 when the number of INR tests was increased to 5.2 tests per three months. If the dispensing fee was increased from the Ontario rate (lowest) to the Nova Scotia rate (highest, $10.13), the three-month costs ranged from $229 to $303, and if non-paid caregivers were paid, the total costs ranged from $309 to $503.

Limitations

The study was limited by the three-month duration, which was insufficient to capture the resources and costs associated with warfarin-related adverse events. There were differences in the patient characteristics between treatment models, which may have had an impact on the total costs of care. The study excluded parking costs, which may be substantial if PT testing was frequent. The authors stated that parking was excluded because these costs were more likely to be related to the size of the municipality than to the anticoagulation service. The authors also state that travel costs may be under-represented, due to the high proportion (~65%) of patients who walked to the laboratory. The authors did not report how sites were selected for inclusion in the study, and whether those that participated were representative of the anticoagulation monitoring services available in Canada. The study excluded patients with more severe comorbidities or non-compliance, who may have higher costs of care. These exclusions may limit the generalizability of the findings.

Study 2: Lalonde et al.[14]

Study description

Two additional studies[14,16] provided some cost data; however, the quality of these estimates may be considered limited. The pragmatic RCT by Lalonde et al.[14] compared the quality of anticoagulation, adverse events, use of health care resources, and direct medical costs for a pharmacist-managed anticoagulation service (PMAS) or family physician-managed care (Appendix 6). Patients were eligible if they required six or more months of warfarin treatment. All patients were initially managed by the community hospital PMAS until their INR

values were stable. They were then randomized to one of the two care models and followed for six months. Physician management of anticoagulation was not standardized.[14]

Costs were estimated from the health care payer perspective, using the resource and outcome data collected from the RCT.[14] Data on health resources and complications requiring an emergency room (ER) visit or hospitalization were collected from a centralized, networked computer system and administrative databases in Quebec. A blinded adjudication committee reviewed hospital charts to determine the severity of bleeding or thromboembolic events. In the PMAS clinic, the authors reported that each INR test required 6.25 minutes of the pharmacist's time and five minutes of the secretary's time. Physicians in Quebec are reimbursed for patient visits but not for telephone follow-up; thus, only the services paid by the government medical insurance plan were included in the estimates. The authors stated that because the number of INR tests and the incidence of treatment complications were similar between groups, these costs were not considered.[14]

Results

A total of 250 patients were randomized, including 122 women (49%). The mean age was 65 years and 60% of patients had atrial fibrillation.[14] The authors reported that both care models provided similar quality of anticoagulation management. There were no statistically significant differences between groups on health-related quality of life measured using two general and one oral anticoagulation-specific questionnaire. Patients in the PMAS group avoided 1.6 family physician visits per year compared with those in the family-physician care group (Appendix 6). The rate of bleeding or thromboembolic events was similar between groups.[14]

The authors reported that PMAS would require an additional $124 per patient per year compared with family physician anticoagulation management, in patients with previously stabilized warfarin dosing.[14] This estimate assumed each patient would require 30 INR tests, 188 minutes of the pharmacist's time ($109), and 38 minutes of the secretary's time ($43), and would avoid 1.6 physician visits per year (–$28).[14]

Limitations

The study was limited by the six-month follow-up time, which was inadequate to capture differences in bleeding or thromboembolic events. This simple cost analysis used the health care payer perspective and therefore excluded the physician's or staff's time spent providing follow-up to patients over the phone. There are opportunity costs associated with these resources that are not captured using the payer perspective. The estimates for the PMAS staff's time to follow up with patients were not referenced. The estimate of 6.25 minutes per INR did not take into consideration the complexity of the patient's clinical condition. No sensitivity analyses were conducted to test whether the results were robust. Overhead costs were ignored, as was the small, non-statistically significant difference between groups on the number of INR tests per patient.

Study 3: Bungard et al.[16]

Study description

The before and after study published by Bungard et al.[16] reported the quality of anticoagulation, adverse events, and hospitalization costs for 125 patients receiving chronic warfarin anticoagulation (Appendix 7). Data were analyzed for four months or more before and after referral to a PMAS in a tertiary hospital. Hospitalization and ER visits were collected from the health region database and classified as hemorrhagic-, thromboembolic-, or non-

anticoagulation-related events. The resource intensity weight, an indicator of typical resources consumed during the hospitalization for a given admission diagnosis, was multiplied by the unit cost of one resource intensity weight (C$3,500) to determine the cost of each event.[16]

Results

Of the patients enrolled, the indication for anticoagulation was atrial fibrillation (40%), mechanical heart valve replacement (24%), venous thromboembolism (19%), or another condition (17%).[16] The patients had a mean age of 63 years and 42% were female. The mean duration of treatment was 10.7 months and 29.3 months in the before and after periods. The quality of anticoagulation was lower in the before period than in the after period, as measured by the time the INR was in the therapeutic range (49% prior, 67% after, P < 0.0001).[16]

The rate of ER visits or hospitalization for thromboembolic events was higher in the before period than in the after period (rate ratio 17.6 [95% CI 6.0 to 51.9]).[16] The difference between before and after periods was not statistically significant for hemorrhagic events (rate ratio 1.6 [95% CI 0.7 to 3.7]). Total costs of ER visits or hospitalization were $18,050 lower for hemorrhagic events, and $104,100 lower for thromboembolic events during the pharmacist-managed care period compared with prior care.[16]

Limitations

This cost analysis[16] was limited to costs of hospitalization and ER visits for PMAS and other anticoagulation management. The authors did not describe the providers or the type of anticoagulation management the patients received prior to their referral to the PMAS, nor did they measure any other health care resources or costs for the before and after periods. The higher rate of thromboembolic events in the before period may be related to how patients were selected for inclusion in the study. Patients with a recent thromboembolic or hemorrhagic event may have been more likely to be referred to a specialized service than those who did not have an event. The authors state that the study patients were representative of the larger population of patients requiring anticoagulation, based on a comparison with 502 non-study patients. Their conclusion, however, was based on similar demographics and time in the therapeutic range, and did not assess the rate of hospitalization or ER visits for the two groups. The use of the before and after study design was limited by the omission of a concurrent control group to provide information on temporal trends.

7 DISCUSSION

7.1 Summary of Evidence

Patient self-management was reported to have an ICER of $14,000 per QALY, compared with physician-managed anticoagulation, from a health payer perspective over a five-year time horizon.[13] The model estimated that self-management prevents 3.5 major thrombotic and 0.8 major hemorrhagic events per 100 patients over five years. The ICER of self-management was $237,000 in the first year of therapy due to the resources involved in training patients, which were not offset by a substantial reduction in warfarin-related complications or thromboembolic events. The cost-effectiveness of self-management improves if patients continue with this type of management for more than one year. Confidence in the ICER values depends on the strength of the clinical data used to populate the model, which in this study[13] may be considered less robust.

A costing study (Schulman et al.[15]) reported that hospital-based physician- or pharmacist-managed anticoagulation was associated with lower three-month costs than community physician-managed care, from the health payer or societal perspective. In contrast, Lalonde et al.[14] reported that pharmacist-managed anticoagulation services were associated with incremental annual costs of $124 per patient compared with family physician-managed care. The differences in the findings of these two studies may be explained, in part, by the costing methods used and the patient population studied. In the Lalonde study,[14] approximately 90% of patients were new users of warfarin, compared with 32% of patients in the Schulman[15] report. In Schulman et al.'s study,[15] patients attending hospital-based clinics were younger, used fewer chronic medications, and were less likely to have atrial fibrillation than those treated by community physicians. The Lalonde study[14] used simple costing methods that may not have captured all relevant costs of care. A third costing study (Bungard et al.[16]) reported cost savings due to reduced hospital and ER visits among patients referred to a pharmacist-managed anticoagulation clinic. This study, however, had methodological issues that may limit the validity of the findings.

7.2 Limitations

Overall, the data on costs of specialized anticoagulation services in Canada were limited. Four studies met the inclusion criteria, including one cost-utility study[13] and three costing studies.[14-16] All studies included a mixed population and did not provide cost data specific to patients with atrial fibrillation.

Two costing studies were based on up to six months of follow-up of patients, which was insufficient to capture differences between comparators on the costs and health resources related to clinical outcomes such as bleeding or thromboembolic events.[14,15] Lack of a concurrent control group, selection bias, and an analysis restricted to hospitalization and ER visit costs limited the validity of the before and after study.[16]

The cost-utility analysis[13] was based on clinical outcomes extrapolated from a single RCT reporting surrogate outcomes, and therefore the cost-effectiveness estimates should be interpreted with caution.

8 CONCLUSIONS

The costs of specialized anticoagulation services in Canada are uncertain.

Four studies reported data on the costs, health care resources, or cost-effectiveness of specialized anticoagulation services or patient self-management. These studies were limited by the duration of observation (six months or less), selection bias, incomplete capture of relevant costs, or use of a model based on uncertain clinical data.

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Conflict of Interest

No members declared any conflicts of interest. Conflict of Interest Guidelines are posted on the CADTH website.

APPENDIX 2: DEFINITIONS OF ANTICOAGULATION MANAGEMENT SERVICES

Usual care may be defined as warfarin dose adjustment managed by a physician working in a private practice setting that not only addresses anticoagulation management, but also other medical problems.[11] Physicians in this setting use their own judgment without access to specialized anticoagulation tools, or specialized anticoagulation staff and services.[11,12]

Specialized anticoagulation services are an approach to improving anticoagulant control. These services can generally be defined as tertiary or community hospital-based anticoagulation clinics, primary care settings, point-of-care testing and dose adjustment by community pharmacies, and patient self-testing or patient self-management using a point-of-care device.[10] The primary care anticoagulation setting involves a family practice group or family health team where nurses, pharmacists, or physicians are responsible for managing warfarin therapy.[10] Primary care settings and hospital-based anticoagulation clinics may use computerized decision-support applications or other means to guide warfarin dosing.[7,10]

Of note, based on the above definitions, the following categories of specialized anticoagulation services were developed for the purpose of conducting the environmental scanning:

- Hospital-based anticoagulation clinics (tertiary care and community hospitals)
- Primary care settings (family practice group or family health team, in which RN/NP [nurses], RPh/Pharm D [pharmacists], or MD [physicians] may be responsible for managing warfarin therapy)
- Point-of-care testing and dose adjustment by community pharmacies.

APPENDIX 3: QUALITY ASSESSMENT USING BMJ CHECKLIST[17]

	Study Design	**Regier [13]**
1	Research question stated	1
2	Economic importance of research question stated	1
3	Viewpoint(s) of analysis clearly stated and justified	1
4	Rationale for alternative interventions stated	1
5	Alternatives clearly described	1
6	Form of EE used is stated	1
7	Choice of EE justified in relation to question addressed	0.5
	Data Collection	
8	Source(s) of effectiveness estimates stated	1
9	Details of design and results of effectiveness study given (if based on single study)	0
10	Details of method of synthesis or meta-analysis of estimates (if based on a number of effectiveness studies)	NA
11	Primary outcome measures for EE clearly stated	1
12	Methods to value health states and other benefits stated	0.5
13	Details on subjects from whom valuations obtained stated	0.5
14	Productivity changes (if included) reported separately	NA
15	Relevance of productivity change to study relevance discussed	0
16	Resource quantities reported separately from unit costs	0
17	Methods for estimating resources and unit costs described	0.5
18	Currency and price data recorded	1
19	Details of currency of price adjustment for inflation or currency conversion given	0
20	Details of any model used given	1
21	Choice of model and key parameters on which based justified	0
	Analysis and Interpretation of Results	
22	Time horizon of costs and benefits stated	1
23	Discount rate(s) stated	1
24	Choice of rate(s) justified	0
25	Explanation given if costs/benefits not discounted	NA
26	Details of statistical tests and CIs given for stochastic data	0.5
27	Approach to sensitivity analysis given	1
28	Choice of variables for sensitivity analysis justified	0.5
29	Ranges over which variables are varied are stated	1
30	Relevant alternatives compared	1
31	Incremental analysis reported	1
32	Major outcomes presented disaggregated and aggregated	0.5
33	Answer to study question given	1
34	Conclusions follow from data reported	1
35	Conclusions accompanied by appropriate caveats	0.5

1 = reported; 0.5 = partially reported; 0 = not reported; CI = confidence interval; EE = economic evaluation; NA = not applicable.

APPENDIX 4: SUMMARY OF INCLUDED STUDIES

Study, Location, Funding	Study Design, Outcomes	Perspective, Time Horizon, Discounting, Dollar	Population	Comparators	Data Sources
Regier et al.[13] Canadian Funding: Heart and Stroke Foundation	Markov decision-analytic model (Bayesian) Incremental costs and health benefits (QALY), ICER	Health care payer perspective 5-year time horizon 3% discount rate 2003 Canadian dollars	Patients receiving chronic warfarin treatment	Patient self-managed care Physician-managed care	Clinical data, transition probabilities, self-management training costs, resource utilization for a major TEE and utility values from published RCTs and observational studies; frequency of INR testing in self-managed group and some other interventions were assumed. Cost of major hemorrhage from Health Costing in Alberta. Other data from CIHI, Statistics Canada.
Schulman et al.[15] BC, AB, ON, QC, NB Funding: AstraZeneca/ McKesson Specialty	Prospective observational costing study Direct medical, direct non-medical, direct patient, and productivity loss costs	Health care payer and societal perspective 3-month time horizon No discounting 2008-2009 Canadian dollars	New and chronically treated patients on warfarin for AF, VTE, aged ≥ 18 years Excluded patients with history of frequent hospitalization, planned surgery or invasive procedure, geographic inaccessibility, poor compliance	Hospital-based physician-managed anticoagulation Hospital-based pharmacist-managed care Community-based family physician-managed care Community-based pharmacist-managed care	Cost and resource data collected from each site and patient diaries. Unit costs of health care professional consultations, drugs, lab tests, ER visits, patient and caregiver wage, and travel from Ontario Schedule of Benefits, Ontario Drug Benefit, Ontario government; Statistics Canada, Health Costing in Alberta, and CIHI.

Study, Location, Funding	Study Design, Outcomes	Perspective, Time Horizon, Discounting, Dollar	Population	Comparators	Data Sources
Lalonde et al.[14] QC Funding: CIHI, Taro Pharmaceuticals/Optima Pharma	RCT and costing study Incremental direct medical costs, quality of anticoagulation, adverse events, HRQL	Health care payer perspective 1-year time horizon for costs (6-month RCT) No discounting Canadian dollars, year NR	New and chronic warfarin-treated patients with stable INR values	Pharmacist-managed anticoagulation service Family physician-managed care	Resource utilization and clinical outcome data from administrative and hospital databases. Unit costs from Quebec government and Quebec Association of Hospital Pharmacists.
Bungard et al.[16] AB Funding: Alberta Health and Wellness	Before and after study Hospitalization costs, adverse events, quality of anticoagulation	Perspective NR (presumed to be health payer) Time horizon NR No discounting Canadian dollars, year NR	Patients referred to pharmacist-managed anticoagulation service who have received ≥ 4 months of warfarin therapy	Pharmacist-managed anticoagulation service Other anticoagulation management	Health resource data and costs from Capital Health Region hospital database and CIHI.

AB = Alberta; AF = atrial fibrillation; BC = British Columbia; CIHI = Canadian Institute of Health Information; ER = emergency room; HRQL = health-related quality of life; ICER = incremental cost effectiveness ratio; INR = International Normalized Ratio; NR = not reported; ON = Ontario; PT = prothrombin time; QALY = quality-adjusted life-year; QC = Quebec; RCT = randomized controlled trial; NB = New Brunswick; TEE = thromboembolic event; VTE = venous thromboembolism.

APPENDIX 5: SUMMARY OF SCHULMAN ET AL.[15]

Outcome	Hospital-based Physician-managed	Hospital-based Pharmacist-managed	Community Physician-managed
Site Characteristics	N = 4	N = 5	N = 6
Number of patients managed per year, mean (range)	1,475 (511 to 3,000)	678 (102 to 1,282)	92 (5 to 250)
Number of patient visits per month, mean (range)	610 (125 to 1,800)	310 (8 to 800)	393 (18 to 900)
Number of full-time staff, mean	12.4	3.0	2.9
Estimated overhead costs, mean $ per patient*	$29	$10	$18.5
Patient Characteristics	N = 188	N = 145	N = 96
Age, mean (SD)	63 (15)	66 (14)	71 (11)
Female, %	44	43	52
Indication for warfarin, % AF/DVT/PE	59/32/13	55/38/15	86/8/7
Number of chronic prescription medications, mean (SD)	4.3 (3.5)	4.8 (3.2)	6.1 (3.0)
Hemorrhagic event in last 6 months, %	2	4	0
New warfarin user (< 1 month therapy), %	16	7	8
Employed (full- or part-time), %	43	36	14
No drug insurance coverage, %	4	1	3
Patients using a caregiver, %	29	21	26
Resource Utilization during 3 Months of Treatment			
Patient contacts, mean (SD)	2.5 (3.0)	3.9 (2.8)	2.4 (1.6)
Physician consultations per patient, mean (SD)	1.1 (1.7)	0.1 (0.4)	1.4 (1.2)
Other health care professional consultations per patient, mean (SD)	4.1 (6.0)	5.8 (5.3)	2.6 (2.8)
Time per patient contact, mean min Routine contact/intermediate contact/extended contact**	6.1/9.8/25.0	5.2/8.6/40.0	6.7/ 3.8/28.7
Number of PT tests per patient, mean (SD)	4.1 (2.7)	4.7 (2.0)	2.8 (1.4)
ER visits per patient, mean (SD)	0.04 (0.2)	0.09 (0.4)	0.03 (0.2)
Number of warfarin prescriptions filled per 3 months, mean (SD)	4.0 (7.8)	3.4 (7.0)	4.2 (8.0)
Mode of transportation to laboratory, % Vehicle/public transit/walk	29/7/65	34/2/64	38/1/61
Time missed from work by patient, mean min/week (SD)	15.2 (41.3)	6.2 (28.6)	3.1 (14.1)
Time missed from work by caregivers, mean min/week (SD)	133.4 (146.3)	82.5 (66.5)	3.0 (13.4)

Outcome	Hospital-based Physician-managed	Hospital-based Pharmacist-managed	Community Physician-managed
Costs, Mean CAD per Patient during 3 Months of Treatment			
Total Ministry of Health costs	108.24	144.79	198.75
Total societal costs	187.76	197.71	243.74

AF = atrial fibrillation; CAD = Canadian dollars; DVT = deep vein thrombosis; ER = emergency room; min = minutes; PE = pulmonary emboli; PT = prothrombin time; SD = standard deviation.

*Overhead costs were calculated by dividing the total site costs by the total number of warfarin patients. Total hospital costs included administration, equipment, equipment rental, energy, depreciation, and staff. Total community costs included administration, equipment rental, energy, depreciation, and rent.

**Routine contact = routine dosing with no change; intermediate contact = change in warfarin dose; extended contact = in cases of symptoms related to warfarin therapy.

APPENDIX 6: SUMMARY OF LALONDE ET AL.[14]

Outcome	PMAS	Physician-managed Care	Difference (95% CI)
Patient Characteristics	N = 128	N = 122	--
Age, mean years (SD)	65 (12)	66 (12)	--
Female, %	51	47	--
Indication for warfarin, %* AF/DVT/PE/other	59/28/9/19	61/26/12/13	--
New warfarin user, %	88	92	
Resource Utilization			
Bleeding or TEE requiring hospitalization or ER visit, events per PY (SD)	0.12 (0.84)	0.07 (0.56)	0.05 (–0.12 to 0.23)
INR tests per PY (SD)	30.7 (19.4)	27.8 (17.7)	2.9 (–1.7 to 7.5)
Family physician visits per PY (SD)	5.1 (6.0)	6.7 (6.4)	–1.6 (–3.1 to –0.1)
Specialist visits per PY (SD)	4.3 (14.4)	2.5 (4.4)	1.9 (–0.8 to 4.6)
Costs, C$ per Patient per Year			
Pharmacist costs (based on 30 INR tests per year)	$109.38	NA	--
Secretarial costs	$42.50	NA	--
Physician visit costs	$89.51	$117.59	–$28.08
Total direct health care costs	$241.39	$117.59	$123.80[†]

AF = atrial fibrillation; CI = confidence interval; DVT = deep vein thrombosis; ER = emergency room; INR = International Normalized Ratio; NA = not applicable; PE = pulmonary emboli; PMAS = pharmacist-managed anticoagulation service; PY = patient-year; SD = standard deviation: TEE = thromboembolic events.

*Patients may have more than one indication for anticoagulation therapy.

[†]Incremental direct health care costs = (INR tests per year * 6.25 minutes * pharmacist salary) + (number of INR tests per year * 1.25 minutes * secretary salary) – (number of physician visits avoided * physician fees).

APPENDIX 7: SUMMARY OF BUNGARD ET AL.[16]

Outcome	Baseline Characteristics		
Patient Characteristics	N = 125	--	--
Age, mean years (SD)	63 (15)	--	--
Female, %	42	--	--
Indication for warfarin, % AF/MVR/VTE/other	40/24/19/17	--	--
Resource Utilization and Costs	**Before PMAS**	**During PMAS**	**RR (95% CI)**
ER visit or hospitalization for hemorrhage, events/100 PY	25.1	15.3	1.6 (0.7 to 3.7)
ER visit or hospitalization for thromboembolism, events/100 PY	49.2	3.6	17.6 (6.0 to 51.9)
ER visit or hospitalization for other reason, events/100 PY	391.9	166.6	2.8 (1.7 to 4.5)
Hospitalization costs*	**Before PMAS**	**During PMAS**	**Difference**
Hemorrhagic	$28,598	$10,550	$18,048
Thromboembolic	$106,312	$2,216	$104,097
Other	$864,913	$338,908	$526,005
Total	$999,824	$315,673	$648,150

AF = atrial fibrillation; ER = emergency room; MVR = mechanical valve replacement; NR = not reported; PMAS = pharmacist-managed anticoagulation service; PY = patient-year; RIW = resource intensity weight; RR = rate ratio; SD = standard deviation; VTE = venous thromboembolism.
*Hospitalization costs calculated by multiplying the total RIW by the cost per RIW (C$3,500). Total time of follow-up assumed to be 111.75 PY before PMAS and 111 PY during PMAS.