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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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APPENDIX 1: EXPERT COMMITTEE AND CONTRIBUTORS

COMPUS Expert Review Committee (CERC) Members

Participating CERC Members

Dr. Lisa Dolovich, Chair
Research Director and Associate Professor
Department of Family Medicine
McMaster University
Ambulatory Care Pharmacotherapy Specialist
St. Joseph's Healthcare Hamilton
Associate Director
Centre for Evaluation of Medicines

Members

Dr. Michael Allen
Associate Professor
Director, Evidence-based Programs
Continuing Medical Education
Dalhousie University

Dr. Michael Evans
Director, Patient Self-Management and Knowledge Support
Centre for Effective Practice
Department of Family and Community Medicine
University of Toronto

Dr. Scott Klarenbach
Associate Professor, Department of Medicine, Division of Nephrology
University of Alberta
Fellow, Institute of Health Economics

Ms. Cathy MacNutt
Public Member

Mr. Panos Petrides
Public Member

Dr. Jim Silvius
Senior Medical Director, Seniors' Health
Alberta Health Services
Associate Professor
Division of Geriatric Medicine
Department of Medicine
University of Calgary

Dr. Adil Virani
Director, Pharmacy Services
Fraser Health Authority
Associate Professor
Faculty of Pharmaceutical Sciences
University of British Columbia

Specialist Members

Dr. Marc Carrier
Associate Scientist, Clinical Epidemiology
Ottawa Hospital Research Institute
Physician, Hematology (Thrombosis)
The Ottawa Hospital
Assistant Professor, Department of Medicine
University of Ottawa

Dr. Agnes Y. Lee
Associate Professor of Medicine
Division of Hematology
University of British Columbia
Medical Director, Thrombosis Program
Vancouver Coastal Health
Diamond Health Care Centre

Dr. Jafna Cox
Heart and Stroke Foundation Endowed Chair in Cardiovascular Outcomes
Director of Research, Division of Cardiology
Professor, Departments of Medicine and of Community Health and Epidemiology
Dalhousie University
Staff Cardiologist, Capital Health

Dr. Anne Holbrook
Professor and Director, Division of Clinical Pharmacology and Therapeutics
Department of Medicine
McMaster University
Senior Scientist, Centre for Evaluation of Medicines
Staff Physician, St. Joseph's Healthcare Hamilton
Staff Physician, Hamilton Health Sciences

Dr. Mario Talajic
Cardiac electrophysiologist
Director, Cardiac Genetics Centre
Montreal Heart Institute
JC Edwards Professor of Medicine
Director, Specialty Training Programs
Department of Medicine
University of Montreal

Dr. Leslie Zypchen — designated backup for Dr. Agnes Lee (sharing votes)
Clinical Assistant Professor
Division of Hematology
University of British Columbia
Staff Hematologist
Vancouver General Hospital

Contributors from Canadian Agency for Drugs and Technologies in Health (CADTH)

Mr. Chris Kamel
Clinical Research Officer

Ms. Agnieszka Kus
Clinical Research Assistant

Ms. Heidi Staples
Clinical Research Officer

Ms. Kasia Kaluzny
Knowledge Exchange Officer

Dr. Mohammed Jabr
Health Economist

Mr. Michel Boucher
Theme Lead, Cardiovascular and Cerebrovascular

Dr. Chander Sehgal
Director, Formulary Reviews
Acting Director, Optimal Use and Health Technology Assessment

Ms. Gaetanne Murphy
Clinical Research Officer

Ms. Kelly Farrah
Information Specialist

Dr. Janice Mann
Knowledge Exchange Officer

Ms. Andra Morrison
Environmental Scanning Officer

Dr. Vijay Shukla
Senior Advisor, Advancing the Science

Dr. Srabani Banerjee
Manager, Clinical Research

Mr. Denis Belanger
Director, Impact, Partnership and Outreach

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.