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OPTIMAL USE REPORT

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Recommendations for Optimal Warfarin
Management for Prevention of
Thromboembolic Events in Patients with
Atrial Fibrillation

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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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 ISSUE

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.

2.1 Atrial Fibrillation

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia.¹ It has been estimated that 200,000 to 250,000 Canadians have AF.² This condition is associated with significant morbidity and mortality. Approximately 15% of all strokes are associated with AF; risk is strongly correlated with age, increasing from 6.7% of all strokes in patients aged 50 to 59 years to 36.2% of all strokes for patients aged 80 to 89 years.³

2.2 Technology Description

2.2.1 Vitamin K antagonist anticoagulants

Warfarin is part of the coumarin class of vitamin K antagonists (Table 1). Vitamin K antagonists have been the mainstay of oral anticoagulant therapy for more than 60 years. Their effectiveness has been established by well-designed clinical trials for several thromboembolic indications.⁴ Evidence from several randomized controlled trials (RCTs) shows that long-term anticoagulation therapy with warfarin reduces the risk for ischemic stroke by 68% in patients with non-valvular AF (NVAf).³

However, clinical use of vitamin K antagonists requires vigilance because:

- they have complex pharmacokinetics and pharmacodynamics
- they have a narrow therapeutic window
- they require (and benefit from) regular laboratory monitoring through a standardized blood test [international normalized ratio (INR)]
- the dose response varies among patients
- they are subject to several drug and dietary interactions.⁴

Table 1: Vitamin K Antagonists Available in Canada

Vitamin K Antagonist	Manufacturer	Trade Name
Acenocoumarol (nicoumalone)	Paladin Labs Inc.	Sintrom
Warfarin sodium	Apotex Inc.	Apo-Warfarin
Warfarin sodium	Bristol-Myers Squibb	Coumadin

Table 1: Vitamin K Antagonists Available in Canada		
Vitamin K Antagonist	Manufacturer	Trade Name
Warfarin sodium	Mylan Pharmaceuticals ULC	Mylan-Warfarin
Warfarin sodium	Novopharm Limited	Novo-Warfarin
Warfarin sodium	Sanis Health Inc.	Warfarin
Warfarin sodium	Taro Pharmaceuticals Inc.	Taro-Warfarin

Source: Health Canada Drug Product Database⁵

2.2.2 Vitamin K antagonist anticoagulants management models

The effectiveness and safety of warfarin therapy depend on maintaining the INR in the optimal therapeutic range⁴ (between 2 and 3 for AF⁶). There is a relationship between the time in therapeutic INR range (TTR) and bleeding or thromboembolic events.⁴ The percentage of TTR is used as a marker for the quality of warfarin management. Evidence (from international clinical trials and observational studies on cardiac and other indications) demonstrated a wide spectrum of TTRs, varying from a lower range of 32% to 68% for usual care, to a higher 55% to 92% range for patient self-management (PSM).⁴

Usual care is 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.⁷ Physicians in this setting use their own judgment without access to specialized anticoagulation tools, or anticoagulation clinic staff and services.^{7,8}

Approaches suggested by the literature⁴ to improve anticoagulant therapy include:

- anticoagulant monitoring services
- the use of point-of-care (POC) INR testing that allows patient self-testing (PST) or PSM of dose adjustment (combines self-testing with patient adjustment of their own doses)
- specialized tools to guide warfarin dose adjustment.

Anticoagulation monitoring services include a number of alternatives to usual care, from tertiary or community hospital-based anticoagulation clinics to primary care settings and POC testing and dose adjustment by community pharmacies.⁹ Primary care settings and hospital-based anticoagulation clinics may use computerized decision-support applications or other tools to guide warfarin dosing.^{4,9} 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.⁹ Specialized anticoagulation tools refer to a broad range of products that can be used by clinicians to guide dosing of warfarin in their particular practice setting. These vary from a simple web-based or paper nomogram (e.g., University of Wisconsin dosing protocol¹⁰) to an online warfarin dose calculator (e.g., WarfarinDosing.org¹¹ or Warfdocs version 1.0¹²) to a computer application (e.g., DAWN software¹³).

3 OBJECTIVE

The objective of this report is to provide recommendations for the optimal management of warfarin for the prevention of thromboembolic events in patients with AF. Three specific questions were asked to CERC members:

- Question 1: What is the role of specialized anticoagulation services or other anticoagulation management options for the optimal management of warfarin therapy?
- Question 2: What is the role of patient self-testing and patient self-management for the optimal management of warfarin therapy?
- Question 3: In remote areas, what types of anticoagulation management options can be recommended?

4 PROJECT OVERVIEW

Once a topic is selected, CADTH undertakes activities related to key areas in the procedure. The OUWG and the FWG, will provide advice and guidance throughout the process, through to supporting intervention and evaluation tools. CERC provides expert advice and recommendations on the topic area relating to the identification, evaluation, and promotion of optimal prescribing and use of drugs. A broad range of stakeholders are invited to provide feedback at key stages in the CADTH process.

This report represents the Optimal Use Recommendations step in the process.

5 RESULTS

5.1 Optimal Management Recommendations

Recommendation: CERC recommends that patients with NVAF requiring warfarin be managed by a well-coordinated, structured approach dedicated to their anticoagulation therapy.*

Recommendation: CERC does not recommend self-management for most patients with NVAF requiring warfarin.

Statement: CERC determined that there is no evidence to make a recommendation on the role of warfarin management options in remote areas.

*This does not need to be restricted to specialized anticoagulation clinics

Detailed information regarding these recommendations and statement (i.e., vote results, the rating of overall quality of clinical evidence, underlying values and preferences related to the recommendations and notes from CERC deliberations) is provided in Appendix B and Appendix C.

5.2 Research Gaps

During their deliberations, CERC members identified 13 research gaps. It is not known:

- how warfarin is being managed in Canada (e.g., ease of access to specialized anticoagulation services, number of anticoagulation specialized service centres, number of patients accessing specialized anticoagulation services and for how long, the proportion of patients using PSM in rural versus urban areas)
- why some patients have poor INR control
- what is the impact of specialized anticoagulation services on patient outcomes in Canada (especially where usual clinical care is well managed)
- which components of organized care contribute most to improved patient outcomes
- what is the real cost of different components of specialized anticoagulation services in Canada
- what is the impact of warfarin management care models in remote areas
- whether telehealth is effective as an alternative for managing warfarin therapy in remote areas
- what is the contribution of PST to the effectiveness of PSM for AF
- how often INR should be monitored in relation to the stage of care (i.e., initiation versus maintenance of warfarin therapy) and the intensity of treatment
- what is the most efficient method of providing and the desired amount of patient education needed to optimize patient outcomes
- which POC devices are used in Canada, their accuracy and quality control as used in practice
- how many patients are coming to the emergency room because of bleeding incidences from warfarin treatment or because of stroke due to non-compliance with warfarin therapy
- whether emergency room physicians avoid initiating warfarin therapy because they are unsure if proper INR monitoring and warfarin dosing will be achieved in the outpatient setting.

6 THE EVIDENCE

The evidence for developing recommendations on the optimal management of warfarin for preventing thromboembolic events in patients with AF was derived from the following CADTH science reports. CERC members had access to the bibliographies of these reports early in the process:

- Canadian Agency for Drugs and Technologies in Health. Optimal warfarin management for the prevention of thromboembolic events in patients with atrial fibrillation: a systematic review of the clinical evidence [Internet]. Ottawa: The Agency; 2011 Nov [cited 2011 Nov 21]. (Optimal use report; vol. 1 iss. 2a). Available from: http://www.cadth.ca/media/pdf/OP0508_warfarin-science-report-1_clinical_e.pdf

- Canadian Agency for Drugs and Technologies in Health. Optimal warfarin management for the prevention of thromboembolic events in patients with atrial fibrillation: review of Canadian economic studies [Internet]. Ottawa: The Agency; 2011 Nov [cited 2011 Nov 21]. (Optimal use report; vol. 1 iss. 2b). Available from: http://www.cadth.ca/media/pdf/OP0508_warfarin_science-report-2_cost_e.pdf

7 CONSIDERATION OF THE EVIDENCE

7.1 COMPUS Expert Review Committee Process and Perspective

CERC members consider clinical effectiveness (i.e., benefits and harms), burdens, and cost data when formulating Optimal Use Recommendations. Committee members bring their individual expertise and experience to bear (as experts, general practitioners, interventionists, consumers, and members of the public) and draw upon their own values and preferences to discuss the evidence and reach conclusions.

CERC develops recommendations and advice to contribute to optimal health outcomes and to foster a sustainable health care system for Canadians. CERC considers the practical needs of policy-makers, health care providers, and consumers in implementing and using the recommendations and advice toward the promotion of optimal practices. To assist with the interpretation of the recommendations and provide commentary relating to the evidence, key statements from CERC deliberations are noted in this report.

8 NEXT STEPS

The Optimal Use Recommendations will be widely disseminated to encourage uptake and implementation by decision-makers at various levels (e.g., policy decision-makers, health care professionals, and patients). Gaps in practice and knowledge related to the use of warfarin will be identified by comparing the final recommendations with information on current practice and utilization of these products in Canada.

Key messages to promote the optimal warfarin management for the prevention of thromboembolic events in patients with atrial fibrillation will be developed to address identified gaps in practice and knowledge. Intervention tools will be populated with the key messages and related evidence for implementation across Canada.

APPENDIX A: EXPERT COMMITTEE AND CONTRIBUTORS

COMPUS Expert Review Committee (CERC) Members

Participating CERC Members

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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 B: COMPUS EXPERT REVIEW COMMITTEE DELIBERATION PROCESS AND INTERPRETATION OF FINDINGS

In developing these recommendations, the COMPUS Expert Review Committee (CERC) considered clinical evidence, economic evidence, and values and preferences.

Question 1: What is the role of specialized anticoagulation services or other anticoagulation management options for the optimal management of warfarin therapy?

Recommendation: CERC recommends that patients with non-valvular atrial fibrillation (NVAF) requiring warfarin be managed by a well-coordinated, structured approach dedicated to their anticoagulation therapy.*

*This does not need to be restricted to specialized anticoagulation clinics.

Clinical Evidence

The committee considered the results of a review of six systematic reviews and five non-randomized studies comparing specialized anticoagulation services to usual care provided in a primary care setting, and one randomized controlled trial (RCT) and two non-randomized studies comparing models of specialized care. The objective of this systematic review was to assess the clinical effectiveness of different models of specialized anticoagulation services in relation to each other or to usual care for prevention of thromboembolic events in patients with atrial fibrillation (AF).

Key findings suggest that:

- Specialized anticoagulation services do not consistently reduce hemorrhages, thromboembolism, or the need for additional medical care. Specialized anticoagulation services improve time in therapeutic international normalized ratio range (TTR) compared with usual care by a modest amount.
- The evidence available comparing different specialized models of care or service components is limited in both quantity and, in particular, quality.

Committee members noted the following:

- Warfarin management by a well-coordinated, structured approach dedicated to anticoagulation therapy does not need to be restricted to specialized anticoagulation clinics.
- The quality of the evidence on the effectiveness of organized management of warfarin therapy is limited, mainly based on low-quality observational studies and few RCTs with design limitations.
- Very few of the studies are in or inclusive of Canadian settings.
- There is heterogeneity in both control and intervention populations in studies.

- There is heterogeneity in how organized services are defined, both in the context of research as well as in clinical practice. There is wide variation in how usual care is defined and in the quality of warfarin management in usual care.
- CERC prefers use of the term “organized care” over the term “specialized care” because organized care of warfarin management has expanded beyond medical specialists and now extends to family physicians, nurses, and pharmacists.
- Organized care involves a structured and systematic approach to international normalized ratio (INR) testing and monitoring as well as warfarin dosing to patients. Such services include a number of specific components: explicit management of frequency of INR testing and response of results, care of all patients on warfarin through a central process such as an anticoagulation clinic, use of dosing decision-support tools (e.g., nomograms, computer-based tools), and patient education. It is acknowledged that evidence is lacking to determine which components contribute to the overall effectiveness of such organized services.
- Current guidelines recommend aiming for an INR range of 2 to 3 on a consistent basis for patients with NVAF, to prevent thromboembolic and bleeding events.
- There were few studies showing improved patient-relevant clinical outcomes with anticoagulation clinics (and mainly from lower-quality evidence). However, organized anticoagulation services do not appear to be worse than usual care.
- While TTR is a surrogate outcome, if TTR can be improved through organized anticoagulation service, it would be desirable to do so but not without considering the cost of each warfarin management option.
- There is a need to look beyond TTR and include hard outcomes such as bleeding and frequency of emergency room visits.

Economic Evidence

The committee considered the results of a review of published literature containing information on Canadian costs associated with specialized anticoagulation services. Three costing studies provided information on the costs of different models of specialized anticoagulation services and usual care in Canadian settings.

Key findings suggest that the literature evaluating the relative costs of hospital-based services (either managed by physicians or pharmacists) compared with community physician-managed care was inconclusive. Anticoagulation services were associated with lower costs in two studies, and higher costs in a third. Not all relevant costs were considered in these studies.

Committee members noted the following:

- There is a lack of economic evidence on organized anticoagulation services versus usual care in Canada.
- CERC acknowledges that provision of organized services does not need to occur in an anticoagulation clinic and could take place through care provided by a family practitioner.
- There is no good evidence that more costly components (e.g., computer-assisted tools) are more or less effective than less costly organized services (e.g., paper nomogram used by family practitioner). The effectiveness and cost-effectiveness of providing various

components is unknown. There is a need for additional costing and economic studies in Canada.

- It is acknowledged that care providers should consider the start-up costs of implementing organized anticoagulation services when deciding for which patients such services should be provided.

Values and Preferences

During their deliberations, committee members identified the following considerations as important (in no order of preference):

- Rate of adoption of warfarin therapy can be limited based on patient beliefs (e.g., stigma associated with “rat poison”) and preferences
- The need for decision aids that outline the frequency and severity of strokes versus bleeds with warfarin therapy for AF, to be more broadly used in practice to enable patients to consider their own preferences regarding the relative importance of preventing stroke and risking bleeds
- Patient convenience and the impact on burden of treatment (e.g., need for laboratory services or clinic visits)
- Personal costs to patient
- Maintenance of continuity of care. Patients on warfarin often have multiple other medical conditions that must be addressed along with AF
- Ability to reach therapeutic range quickly and efficiently
- Role of anticoagulation clinics early versus later in therapy should be considered (e.g., effect on INR and impact on thrombosis and bleeding risk at treatment initiation)
- Need to define coordinated care (e.g., communication between care providers regarding warfarin treatment pre- and post-surgery)
- Equity issues versus patient choice and/or preference
- Use of warfarin is associated with many barriers (some are serious, preventing some patients from electing to use warfarin).

Question 2: What is the role of patient self-testing (PST) and patient self-management (PSM) for the optimal management of warfarin therapy?

Recommendation: CERC does not recommend self-management for most patients with NVAF requiring warfarin.

Clinical Evidence

The committee considered the results of a review of six systematic reviews, two RCTs, and five non-randomized studies comparing PST alone or as part of PSM with specialized anticoagulation services or usual care.

Key findings suggest that:

- The effect of PST or PSM on TTR was inconsistent, with studies either showing improved TTR with PST alone or as part of PSM, or no difference between models of care.
- Effects on clinical outcomes were also inconsistent, but PSM (including PST as part of PSM) generally resulted in lower mortality rates and reduced incidence of thromboembolism.
- Evidence on the efficacy of PST and PSM is not specific to NVAF; most studies included mixed populations (including patients with NVAF).
- One systematic review included a large RCT, with a high enrolment rate among screened patients that showed no difference in clinical outcomes with PST alone, in contrast with the overall meta-analysis of studies on PST alone or as part of PSM that found improvements in thrombosis and mortality, but not bleeding events.
- PST alone or PSM (that includes PST) did not affect the rate of bleeding events.
- PST alone or PSM (that includes PST) may improve quality of life and patient satisfaction.

Committee members noted the following:

- There is insufficient evidence to make a recommendation about PST alone. PST alone could be considered as part of a coordinated care strategy.
- Available evidence for PSM for patients with NVAF is limited; some subgroup analyses suggest no benefit. Accounting for limitation of the evidence, PSM should be considered for carefully selected patients only (e.g., patients who are able and willing to self-test and adjust warfarin dose on their own).
- In many studies, only a small proportion of patients could successfully manage PST, and a smaller proportion was able to learn the additional PSM component.
- Relative to organized care, the quality of evidence was higher for PST alone or as part of PSM, and there was more information available on patient-relevant outcomes. The evidence was limited, with respect to generalizability, to “real-world” patients with NVAF (e.g., age difference [included patients tended to be younger], criteria for qualifying for PST [high exclusion rate], and the lack of differentiation between PST and PSM).
- Correlation of TTR with clinical outcomes was also an issue for PST alone or as part of PSM; PSM may be driving the effect.
- There is a notable dearth of evidence on the reliability and accuracy of PST devices available in Canada.
- Studies reported a higher rate of INR testing in patients performing PST alone or as part of PSM (at least 20 more tests per year) versus control groups. The difference in testing rate may affect quality of care and associated costs.
- An upcoming, unpublished patient level meta-analysis may provide new evidence and potentially have an impact on the CERC recommendation.
- PSM, and the distinction with PST, is defined according to what was in the trials. In the trials, PSM was done with PST (using a point of care [POC] device and training). Other strategies for PSM could be considered (e.g., accessing INR lab test results online).

Economic Evidence

The committee considered the results of a review of published literature containing information on Canadian costs associated with PST or PSM. One cost-utility analysis provided information on patient self-management versus physician-managed anticoagulation from a Canadian health payer perspective.

Key findings suggest the following:

- The incremental cost-effectiveness ratio of PSM compared with physician management of anticoagulation was C\$14,000 over a five-year period.
- Costs for PSM were high in the first year due to start-up costs of C\$1,567 per patient for training and support.
- Mean incremental costs were C\$1,420 more for PSM versus usual care for the first year, C\$989 per year after five years, and C\$599 per year after 10 years. These are aggregate costs. Costs in the PSM strategy were partially offset by a reduction in costs associated with clinical events (hemorrhage, thromboembolic event) compared with physician management.

Committee members noted the following:

- Cost-effectiveness data were considered to be unreliable, as the estimate for effectiveness was not based on the overall, limited evidence for clinical benefit. The costing studies also did not report all costs of establishing a program.
- There was no specific economic evidence for patients with NVAf.
- There was no long-term evidence.
- The economic analysis was based on low-quality clinical evidence.
- A higher cost versus limited evidence of additional benefits for patients with NVAf suggests the intervention is not cost-effective.
- Because the subgroup who could eventually manage PST with PSM for AF is likely to be small, the costs of setting up a PSM program, screening patients, maintaining quality control of the devices, and providing extended hours back-up support need to be considered.

Values and Preferences

During their deliberations, committee members identified the following considerations as important (in no order of preference):

- There may be a niche for PST or PSM as part of a well-coordinated and structured approach to anticoagulation therapy with some patients (e.g., remote areas).
- There is a need to provide a choice between organized care and PST or PSM to patients.
- Carefully selected patients may be considered for PST or PSM. Access issues could make the costs acceptable.

Question 3: In remote areas, what types of anticoagulation management options can be recommended?

Statement: CERC determined that there is no evidence to make a recommendation on the role of warfarin management options in remote areas.

Clinical Evidence

No clinical evidence was available for the effectiveness of different warfarin management options in remote areas.

Economic Evidence

No economic evidence was available regarding the costs associated with different warfarin management options in remote areas.

Values and Preferences

During their deliberations, committee members identified the following considerations as important (in no order of preference):

- There is no evidence available to support a recommendation on this question.
- Access to warfarin management services may be limited due to cost associated with distance in remote areas.
- Remote areas are an example where PST testing may be considered.
- There may be a niche for PST or PSM as part of a well-coordinated and structured approach to anticoagulation therapy with some patients (e.g., remote areas).
- Carefully selected patients may be considered for PST or PSM. Access issues could make the costs acceptable.
- The lack of evidence regarding warfarin management options in remote areas is a major research gap.

APPENDIX C: COMPUS EXPERT REVIEW COMMITTEE VOTING PROCESS

During their deliberations, COMPUS Expert Review Committee (CERC) members were asked to make recommendations for each question, based on clinical evidence, economic evidence, and values and preferences. CERC members were also asked to rate the quality of evidence for each question. Recommendations were first formulated based on consideration of the clinical evidence, followed by a round of voting. Recommendations were then revised based on economic evidence and values and preferences, followed by a final round of voting.

Question 1: What is the role of specialized anticoagulation services or other anticoagulation management options for the optimal management of warfarin therapy?

Recommendation 1 (clinical evidence)

CERC recommends that patients with non-valvular atrial fibrillation (NVAf) requiring warfarin be managed by a well-coordinated, structured approach dedicated to their anticoagulation therapy.

Vote 1:

- I) Recommendation:
 - a. Agree: 8
 - b. Disagree: 0
 - c. Abstention: 0

- II) Quality of the evidence:
 - a. High: 0
 - b. Intermediate: 1
 - c. Low: 7

Recommendation 1 (clinical and economic evidence)

CERC recommends that patients with NVAf requiring warfarin be managed by a well-coordinated, structured approach dedicated to their anticoagulation therapy.

Recommendation 1 (clinical, economic, values and preferences)

CERC recommends that patients with NVAf requiring warfarin be managed by a well-coordinated, structured approach dedicated to their anticoagulation therapy.

Vote 2:

- I) Recommendation:
 - a. Agree: 8
 - b. Disagree: 0
 - c. Abstention: 0

- III) Quality of the evidence:
 - a. High: 0
 - b. Intermediate: 0
 - c. Low: 7
 - d. Abstention: 1

Question 2: What is the role of patient self-testing and patient self-management for the optimal management of warfarin therapy?

Recommendation 2 (clinical evidence)

CERC recommends that carefully selected patients with NVAF requiring warfarin be given the option to use self-management strategies.

Vote 3:

- I) Recommendation:
 - a. Agree: 7
 - i. Quality of the evidence:
 - 1. High: 0
 - 2. Intermediate: 3
 - 3. Low: 4
 - b. Disagree: 1
 - i. Quality of the evidence:
 - 1. High: 0
 - 2. Intermediate: 1
 - 3. Low: 0
 - c. Abstention: 0
- II) Driving effect: PSM (not PST) may be driving the effect.

Recommendation 2 (clinical and economic evidence)

After considering both clinical and economic evidence, the recommendation was changed to: CERC does not recommend self-management for most patients with NVAF requiring warfarin.

Recommendation 2 (clinical, economic, values and preferences)

CERC does not recommend self-management for most patients with NVAF requiring warfarin.

Vote 4:

- I) Recommendation:
 - a. Agree: 7
 - i. Main drivers:
 - 1. High costs: 3
 - 2. Limited or lack of evidence of clinical benefit (for NVAF): 3
 - 3. Cost-effectiveness, opportunity costs, clinical benefits: 1
 - ii. Quality of the evidence:
 - 1. High: 0
 - 2. Intermediate: 0
 - 3. Low: 7

- c. Disagree: 1
 - i. Main driver:
 - 1. Demonstrated clinical benefits: 1
 - ii. Quality of the evidence
 - 1. High: 0
 - 2. Intermediate: 1
 - 3. Low: 0
- d. Abstention: 0

Question 3: In remote areas, what types of anticoagulation management options can be recommended?

Statement 3 (clinical evidence)

Based on the lack of evidence, CERC members determined that a recommendation was not possible and elected to develop a statement. No vote was held.

Statement 3 (clinical and economic evidence)

No recommendation.

Statement 3 (clinical, economic, values and preferences)

CERC determined that there is no evidence to make a recommendation on the role of warfarin management options in remote areas. No vote was held.

APPENDIX D: ABBREVIATIONS

AF	atrial fibrillation
CERC	COMPUS Expert Review Committee
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
INR	international normalized ratio
NVAF	non-valvular AF
POC	point of care
PSM	patient self-management
PST	patient self-testing
RCT	randomized controlled trial
TTR	time in therapeutic INR range

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