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


Introduction

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

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.

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. 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’s international normalized ratios (INRs) within the therapeutic range. Current Canadian guidelines recommend a target INR range of 2.0 to 3.0. The percentage of time spent in the therapeutic range (TTR) depends on the quality of dose management.

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. 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.

Primary care settings and hospital-based anticoagulation clinics may use computerized decision-support applications or other means to guide warfarin dosing. 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. Physicians in this setting use their own judgment without access to specialized anticoagulation tools, or specialized anticoagulation staff and services.

Objective

The objective of the report was to answer the following 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?
Methods

The literature search was performed by an information specialist using a peer-reviewed search strategy. 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. 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/en/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 with the primary authors of the 2012 American College of Chest Physicians (ACCP) guidelines on the management of anticoagulation therapy (although the draft guidelines themselves were not available for review).

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

Results

Twenty-seven publications were included in this review, which included one health technology assessment and eight systematic reviews or meta-analyses. Of these, six compared specialized anticoagulation services with UC and six examined patient-self testing or self-management (three included reviews addressed both). All included systematic reviews 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.

Eighteen primary studies — six randomized controlled trials (RCTs) and 12 non-randomized studies — met inclusion criteria. All included primary studies (RCTs and non-randomized studies) were published between 2006 and 2011. Sample sizes ranged from 40 to 13,052.

Specialized Anticoagulation Clinic Care

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. 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. This recommendation was based on a comprehensive literature review that showed a similar discrepancy between RCT and observational studies.

Patient Self-Testing and Patient Self-Management

Systematic reviews comparing PST or PSM 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.

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.
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 valves).

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 UC, vary across studies. Implementation of anticoagulation clinics or self-management programs also vary 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.

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 PST or PSM, 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.

Conclusions
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 the 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.

References


Production Notes

CADTH Technology Overviews is produced by:
Canadian Agency for Drugs and Technologies in Health (CADTH)
600-865 Carling Ave.
Ottawa, Ontario, Canada K1S 5S8
Tel.: 613-226-2553
Fax: 613-226-5392
Website: www.cadth.ca

CADTH Technology Overviews contains articles that are based on CADTH Technology Reports and other CADTH reports on health technologies. The information presented in this publication is intended to help Canadian health care decision-makers, 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 publication 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 publication to ensure that its contents are accurate, complete, and up to date as of the date of publication, 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 relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this publication or in any of the source documentation.

CADTH Technology Overviews and the information it provides is prepared and intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter presented in this publication may be different in other jurisdictions and, if used outside of Canada, it is at the user’s risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this publication will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this publication, subject to the limitations noted above. The statements and conclusions in this publication are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government.

Production of CADTH Technology Overviews is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Prince Edward Island, Saskatchewan, and Yukon.

Copyright © CADTH 2012. You are permitted to reproduce this document for non-commercial purposes, provided it is not modified when reproduced and appropriate credit is given to CADTH. You may not otherwise copy, modify, translate, post on a website, store electronically, republish, or redistribute any content from this document in any form or by any means without the prior written permission of CADTH.

Please contact CADTH’s Vice-President of Corporate Services at corporateservices@cadth.ca with any inquiries about this notice or other legal matters relating to CADTH’s services.

Cite as: Canadian Agency for Drugs and Technologies in Health. CADTH Technology Overviews, 2012; 2(3).

ISSN: 1481-4501 (online)