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Safe and Effective Anticoagulation in the Outpatient Setting: A Systematic Review of the Evidence

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PREFACE

Health Services Research & Development Service's (HSR&D's) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

HSR&D provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of HSR&D Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of HSR&D field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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EXECUTIVE SUMMARY

BACKGROUND

Long term anticoagulation with Vitamin K antagonists (e.g., warfarin) has been shown to reduce major thromboembolic complications in patients with many common chronic conditions, including atrial fibrillation, history of deep vein thrombosis and pulmonary embolism, and mechanical heart valves. However, Vitamin K antagonists have a very narrow therapeutic window requiring frequent laboratory monitoring to ensure that patients are neither excessively anti-coagulated, which increases the risk for bleeding, or under anti-coagulated, which increases the risk for thromboembolism. Laboratory monitoring consists of measuring the blood's tendency to clot with a test known as the International Normalized Ratio (INR), usually performed every 4-6 weeks. Dosage adjustments are then based on these results.

Since management of long term oral anticoagulation requires frequent testing and dose adjustment, anticoagulation clinics (ACC) have been developed to streamline and standardize this care. Typically run by specially trained nurses or pharmacists, these clinics provide intense patient education and timely follow-up of INR results, use algorithms for dose adjustments, and are easily accessible to patients between visits. More recently, portable devices have become available that are able to accurately measure the INR with a drop of capillary blood. This means that patients can now test themselves at home and either call in the result to their provider who suggests dosage adjustments (known as patient self testing, PST) or adjust their dose of medication themselves (known as patient self management, PSM).

It should be noted that new anticoagulants which may offer the same clinical efficacy and safety profile as warfarin with considerable less monitoring are currently being evaluated for the US market. Final FDA approval of these products may significantly alter the standard for anticoagulation therapy and subsequent monitoring.

OBJECTIVES

The primary objectives of this systematic review were to: 1. Determine whether specialized anticoagulation clinics (ACC) are more effective and safer than care in non-specialized clinics (e.g., primary care clinics, physician offices) for management of long- term anticoagulation in adults; 2. Determine whether patient self testing (PST), either alone or in combination with patient self management (PSM), is more effective and safer than standard care; and 3. Identify the risk factors for serious bleeding in patients on chronic anticoagulant therapy.

METHODS

We searched OVID MEDLINE for relevant articles published in peer-reviewed journals from 1997 to March, 2010 (October, 2010 for Key Question 2) that involved an outpatient, adult population receiving chronic anti-coagulation therapy. We excluded non-English publications and case series, case reports, qualitative reports, narrative reviews, and editorials or letters. Full-text versions of potentially relevant articles were obtained for further review and trained researchers extracted data from articles that met inclusion criteria. The quality of the individual randomized

studies was assessed by standard criteria. Analyses of pooled data using a DerSimonian and Laird random-effects model were conducted for outcomes in Key Question 1. Due to low event rates for several clinical outcomes, Peto odds ratios (a fixed-effects model) were calculated for outcomes in Key Question 2.

RESULTS

Key Question 1

For management of long-term outpatient anticoagulation in adults, are specialized anticoagulation clinics (ACC) more effective and safer than care in non-specialized clinics (e.g., primary care clinics, physician offices)?

Overview of Included Studies

We identified a total of 11 articles reporting on 3 randomized clinical trials (RCTs) and 8 cohort studies that met all inclusion criteria. A total of 722 subjects were enrolled in the 3 RCTs which were conducted in the US, China, and Canada. The mean age of subjects enrolled in the RCTs was 68 years (range of study means 59 to 76). A total of 12,768 subjects were included in the 8 observational studies. The mean age of subjects enrolled in the cohort studies was 69 years (range of study means, 57 to 74). Five of the 8 cohort studies were conducted in the US and 3 in other countries. Three studies were prospective and 5 were retrospective cohort studies.

Clinical outcomes in the RCTs

Rates of all-cause mortality, major thromboembolic events, and major bleeding did not differ significantly between the two treatment arms in any of the 3 RCTs. In the pooled analysis, there were 5 deaths in the ACC group and 6 in the Usual Care (UC) group, all from a single study (RR: 0.81, 95%CI: 0.25 to 2.58); 6 major bleeding events in the ACC patients and 8 in UC patients (RR: 1.05, 95%CI: 0.36 to 3.12); 11 major thromboembolic events in the ACC and 14 in the UC patients (RR: 1.29, 95%CI: 0.59 to 2.81).

The pooled weighted mean of percent time within therapeutic range (%TTR) for patients randomized to ACC was 59.9% (range of means 56-64%), only slightly higher than the 56.3% (range of means 52 to 59%) for the patients randomized to UC, for a weighted mean difference of 3.6% (range of mean differences, 3.3 to 5%).

Clinical Outcomes in the Cohort Studies

In the one study reporting all-cause mortality there was no significant difference between ACC and UC. In the 4 studies reporting major thromboembolic events, 1 reported a significantly higher incidence in UC, 1 a significantly higher incidence in ACC, and in 2 studies, p values were not reported. The incidence of major bleeding events was reported in 5 studies and was significantly higher in UC in 1, and not significantly different between groups in 1. Significance testing was not included for the 3 other studies that reported this outcome. We were unable to pool major clinical outcomes because outcomes were reported as number of events in only 2 of the 8 studies; the other studies reported events per patient- or treatment-year.

The pooled weighted mean of %TTR for the 4 studies reporting this metric, was 63.5% for the intervention groups and 53.5% for the control groups, for a weighted mean difference of 10%

(range of mean differences, 4.3 to 26%).

Conclusion and Recommendation

Evidence for the safety and efficacy of ACC is limited but overall suggests that care provided within ACC may lead to better quality anticoagulation control as measured by time in therapeutic range. There is insufficient evidence to conclude that ACC care leads to fewer deaths, thromboembolic events, or major bleeding events than care provided in usual care settings such as primary care clinics. Results from two studies suggest that patients like the convenience and enhanced service provided by these clinics. There is insufficient evidence for the VA to actively promote the implementation of ACCs.

Key Question 2

Is Patient Self Testing (PST), either alone or in combination with Patient Self Management (PSM), more effective and safer than standard care delivered in either ACCs or non-specialized clinics?

Overview of Included Studies

We identified a total of 27 references reporting on 22 distinct randomized clinical trials. Two studies were conducted in the US, 1 in Canada, and 19 in Europe. Duration of follow-up was less than 12 months in 13 studies and 12 or more months in 9. A total of 8413 subjects were included in the 22 trials, with individual trial sample sizes ranging from 50 to 2922. Five trials met all 4 quality indicators (allocation concealment, blinding, intention to treat analysis, and dropouts reported).

Subjects

The mean age of the subjects was 65 (range of study means 42 to 75 years). The percentage of patients screened who met preliminary eligibility criteria, successfully completed the training, and agreed to enter the study ranged from 10-69%. Among patients who were randomized, the percentage who continued with the intervention throughout the study period ranged from 64-98%.

Interventions

Evaluated interventions included PST only (i.e., dose adjustment made by the clinic) and PST/PSM (i.e., testing and dose adjustment made by patient). The patient self testing/self management intervention usually included 2-4 small group training sessions over several weeks. Training sessions typically included general information on anticoagulation, possible interactions with foods/medicines, how to use the INR testing machine, how to adjust the dose, how often to check INR, and when to call for help. The control group received anticoagulation management in an ACC in 11 of the trials, in a primary care or other physician office in 7 trials, and in multiple settings in 3 trials. The other trial compared PST to PSM without another control group.

Clinical Outcomes

There were 298 deaths in subjects randomized to PST/PSM intervention compared to 369 deaths in the control subjects (Peto OR: 0.74, 95%CI: 0.63 to 0.87, P=0.000), I^2=51%) The intervention group had 283 major bleeding events compared with 300 in the control group (Peto OR: 0.89, 95%CI: 0.75 to 1.05, P =0.169, I^2=2%, There were 99 major thromboembolic events in the

intervention group compared with 149 in the control group (Peto OR 0.58, 95%CI: 0.45 to 0.75, P<0.000, I^2=27%).

The pooled weighted mean of time within therapeutic range for patients randomized to PST/PSM interventions was 66.1% (range of means 56-76.5%), which was not significantly different than the 61.9% (range of means 32 to 77%) for the patients randomized to usual care.

The Home INR Study (THINRS)

This trial is of particular interest since it was conducted in the Department of Veterans Affairs (VA) and is the largest trial to date comparing patient self-testing with usual care. The trial randomized 2,922 patients at 28 VA Medical Centers to high quality anticoagulation clinic management or patient self testing. The primary endpoint was time to first event: stroke, major bleed, or death. The time to event curves did not differ significantly between intervention groups for either the primary endpoint or any of its three individual components. Time in target range and patient satisfaction were significantly higher in the PST group.

Conclusion and Recommendation

This review indicates that compared to usual clinic care, patient self testing with or without self management is associated with significantly fewer deaths and thromboembolic events without any increase in bleeding complications, for a select group of motivated patients requiring long term anticoagulation with Vitamin K antagonists. It should be noted, however, that while the strength of evidence was moderate for the thromboembolism and bleeding, it was low for mortality. Whether this care model is cost-effective and can be implemented successfully in typical US health care settings requires further study.

Key Question 3

What are the risk factors for serious bleeding in patients on chronic anticoagulant therapy?

Overview of Included Studies

We identified a total of 35 articles representing 35 unique studies that provided evidence regarding the impact of various risk factors for predicting serious bleeding events. Each article provided a different set of reported risk factors, in a diverse range of patient populations, using different lengths of follow-up. These differences make statistical pooling of results unreliable, so the evidence is summarized in a narrative format.

Subject Characteristics

A total of 453,918 subjects were included in these studies. Studies ranged in size from a case control study with 26 cases to a large administrative database study of Medicare records that included 353,489 patients. Since any averages of patient characteristics across studies will be mostly driven by the few large administrative studies, the value of overall patient characteristics is somewhat limited. Most studies included primarily elderly populations with an average age of approximately 70 years.

Predictors of Serious Bleeding

Many factors have been shown to predict an increased risk of serious bleeding; however, there is no standard set of variables that is commonly reported. Factors that seemed most consistently associated with increased serious bleeding included: very old age, the first months following warfarin initiation, other medication use (particularly aspirin use), comorbid conditions (such as history of gastrointestinal bleeding events or diabetes), patients whose primary indication for taking warfarin was due to valve conditions, variability in INR values, and genetic factors (ex. variation in the CYP2C gene). There have also been a number of studies of indices that pool together several of the before mentioned risk factors. These studies have shown that patients can, to some extent, be categorized into low, intermediate and higher risk for serious bleeding events based on these indices. Those identified as low risk typically have a several-fold lower risk of bleeding events compared to those identified as high risk. The amount of separation depended, in part, on the population. For example, a population where most of the patients are generally at a low risk of major bleeding will tend to show little separation because there is not much of a range in risk.

Conclusion and Recommendation

Several factors have been shown to predict an increased risk of bleeding and when pooled together a subset of these risk factors has been shown to stratify groups of patients into lower and higher risk groups. Either alone or in combination, these risk factors can likely be used to help clinicians and patients have a dialog about the risks of warfarin therapy. Currently, there is not adequate evidence to suggest that any of the bleeding risk indices are meaningfully superior to the other indices. Future studies might better define the utility of these risk indices by randomizing patients to different bleed risk management strategies that incorporate different combinations of risk factors or bleed risk indices to assess the potential benefits and harms of different anti-coagulation strategies.