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HSR&D

# 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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## INTRODUCTION

### BACKGROUND AND TOPIC DEVELOPMENT

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.[1] Typically run by specially trained nurses or pharmacists, these clinics provide intense patient education, provide 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).[2]

As a leader in safety and quality, the Department of Veterans Affairs (VA) is interested in assuring that veterans on long-term anticoagulation receive state-of-the-art care that maximizes efficacy and minimizes complications. Towards that end, this review was commissioned by the VA's Evidence-based Synthesis Program, in conjunction with the Office of Quality and Performance. Rowena Dolor, MD, MHS; Adam Rose, MD, MSc; and Keith Trettin, RPh, MBA agreed to serve on the Technical Expert Panel (TEP) for the project. We conferred with the TEP members and other experts inside and outside the VA to select the parameters of the review, including patient characteristics, interventions, and outcomes (Figure 1, Analytic Framework).

The final key questions are:

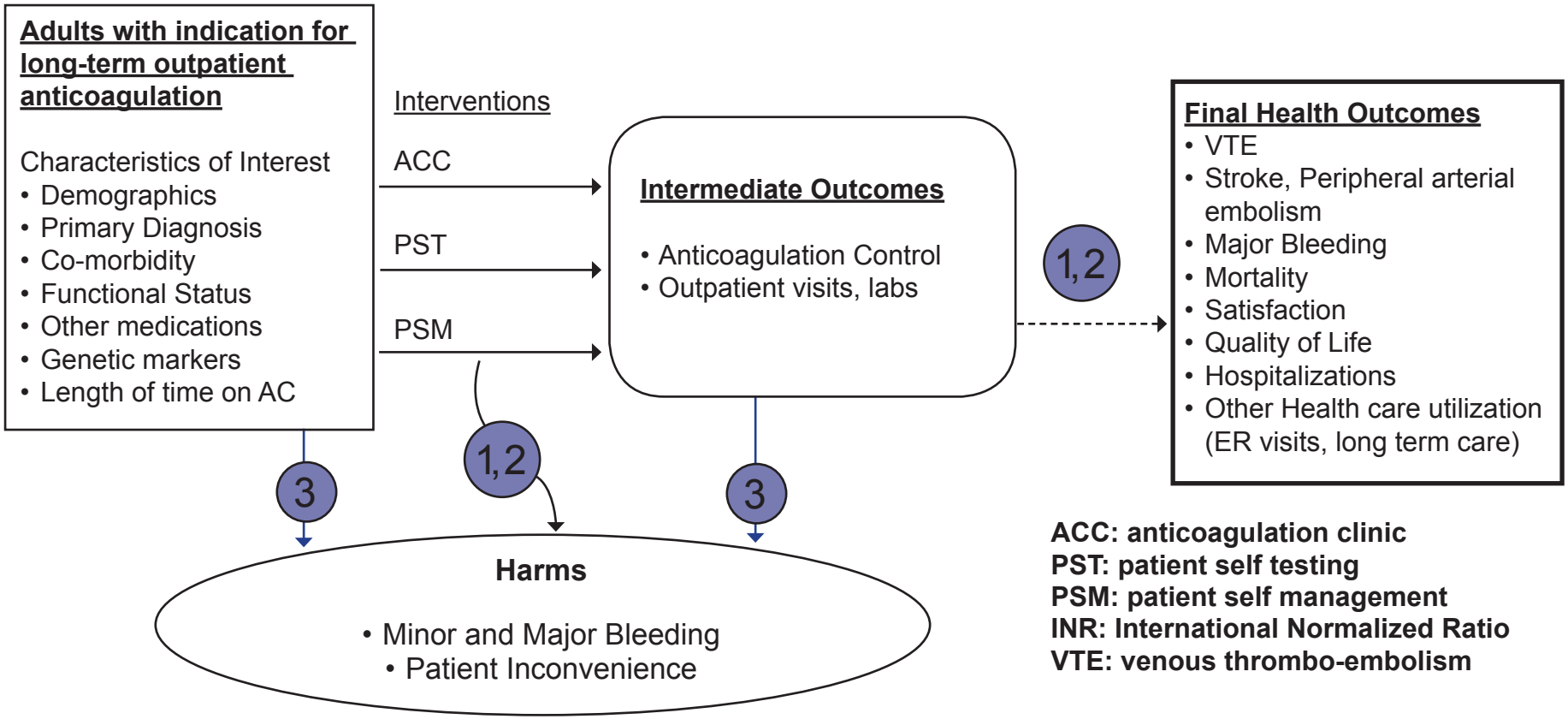
1. For management of long-term outpatient anticoagulation in adults, are specialized anticoagulation clinics (ACC) more effective and safer than care in non-specialized clinics (e.g., primary care clinics, physician offices)?

1a. Which components of a specialized anticoagulation clinic are associated with effectiveness/safety?

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?

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

**Figure 1 Analytic Framework**




**KQ1:** For mangement of long term outpatient anitcoagulation in adults, are specialized anticoagulation clinics, (ACC) more effective and safer than care in non-specialized clinics (e.g., primary care clinics, physician offices)?
**KQ1a:** Which components of a specialized anticoagulation clinic are associated with effectiveness/safety?

**KQ2:** Are patient self testing (PST) and self management (PSM) effective, safe and cost-effective?

**KQ3:** What are the risk factors for serious bleeding in patients on chronic anticoagulant therapy?

# METHODS

## SEARCH STRATEGY

We searched Ovid MEDLINE using the search strategies outlined below. For Key Question 1 we searched the <1950 to 2010> database, downloaded the results and then excluded pre-1996 references. For Key Question 2, we searched the <1950 to 2010> database, limited the results to references from 2005-2010 in the search string and then downloaded the results for further inclusion/exclusion determination. This search was limited to articles published after 2004 because of the availability of a 2007 technology assessment report directly related to this question.[2] For Key Question 3, we searched the <1996 to 2010> database and then downloaded the results for further inclusion/exclusion determination. For all three Key Questions, the initial literature search was completed in 2009. All searches were updated in March 2010 using identical search strategies. The literature search for Key Question 2 was updated again in October 2010. We also searched the Cochrane Library and identified additional citations from reference lists of relevant articles.

### Search Strategy – Key Question #1:

1 warfarin.mp. or exp Warfarin/
2 coumadin.mp.
3 coumarin.mp. or exp Coumarins/
4 exp anticoagulants/ or anticoagul*.mp.
5 or/1-4
6 Ambulatory Care Facilities/
7 Outpatient Clinics, Hospital/
8 6 or 7
9 5 and 8
10 (anticoagul* adj clinic*).mp.
11 9 or 10

### Search Strategy – Key Question #2:

1 exp anticoagulants/
2 (warfarin or coumadin or coumarin).mp.
3 (oral adj anticoagul$).mp.
4 or/1-3
5 self administration/
6 drug administration schedule/
7 international normalized ratio/
8 near patient test$.mp.
9 point of care systems/
10 self test$.mp.
11 self manage$.mp.
12 drug monitoring/
13 primary health care/
14 (primary care or general practice or general practitioner$).mp.
15 or/5-14
16 4 and 15
17 limit 16 to yr=”2005 -Current”

## Search Strategy – Key Question #3:

1 (warfarin or coumadin or coumarin).mp.
2 exp HEMORRHAGE/ or hemorrhag*.mp.
3 exp CEREBROVASCULAR ACCIDENT/
4 exp CEREBROVASCULAR TRAUMA/
5 bleed$.mp.
6 stroke.mp.
7 or/2-6
8 1 and 7
9 risk factor*.mp. or exp Risk Factors/
10 predict*.mp. or exp Risk/
11 9 or 10
12 8 and 11
13 cohort stud*.mp. or exp Cohort Studies/
14 prospective stud*.mp. or exp Prospective Studies/
15 random*.mp. or exp Randomized Controlled Trial/
16 or/13-15
17 12 and 16

Trained researchers reviewed the titles and abstracts identified by the literature search to identify articles published in the English language, in peer-reviewed journals, and related to one of the key questions. For KQ1 and KQ2, we included articles that involved an outpatient, adult population receiving chronic (defined as more than 3 months) anti-coagulation therapy. For KQ3, we further limited the inclusion criteria to studies that involved warfarin therapy, reported results by risk factor status, and had a study population of at least 25 cases of serious bleeding. For all questions, we excluded case series, case reports, qualitative reports, narrative reviews, and editorials or letters. Full-text versions of potentially relevant articles were obtained for further review (see Figures 2, 3, and 4) and trained researchers extracted data from articles that met inclusion criteria.

**Figure 2. Literature Flow Diagram for Key Question 1**

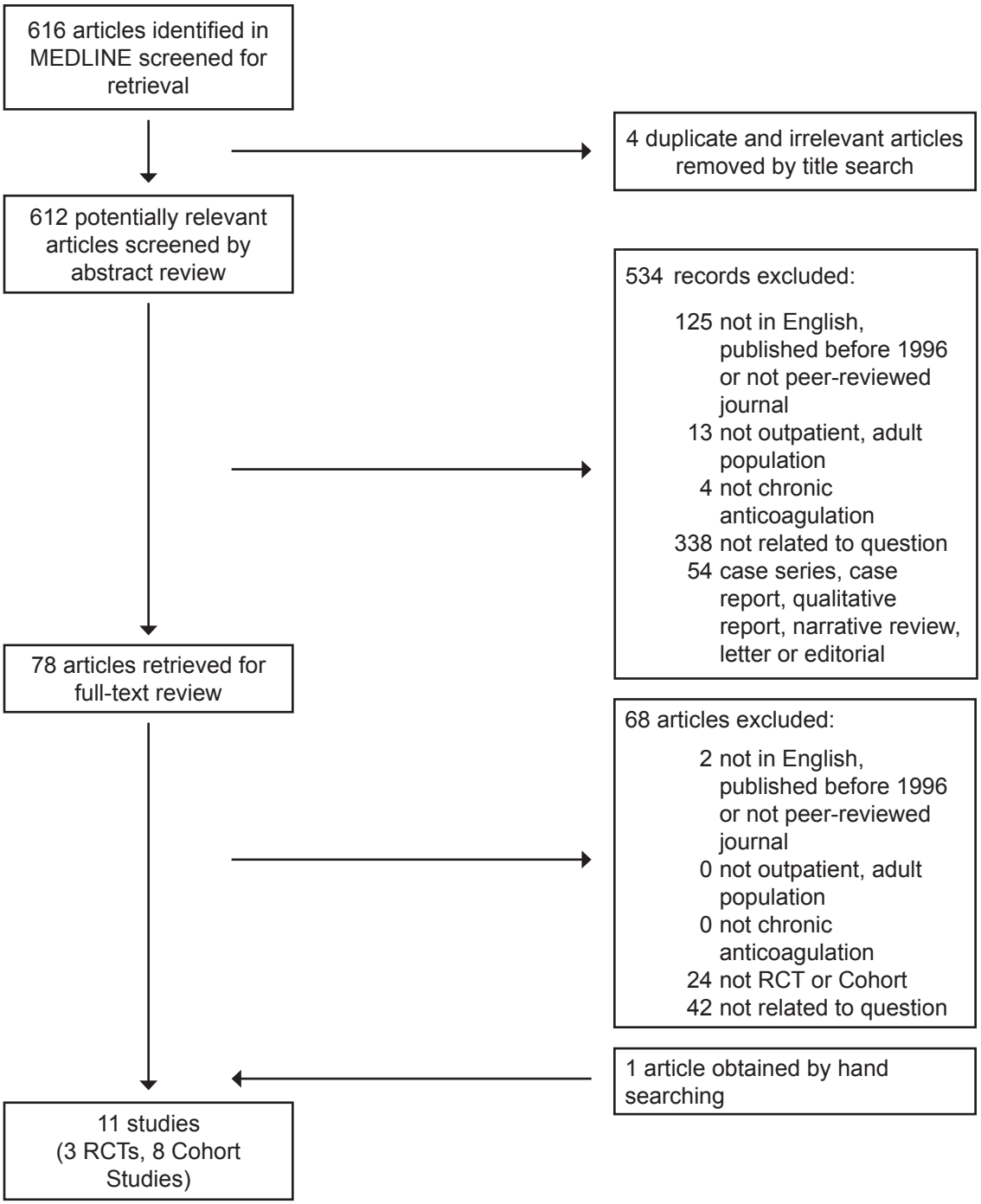


**Figure 3. Literature Flow Diagram for Key Question 2**

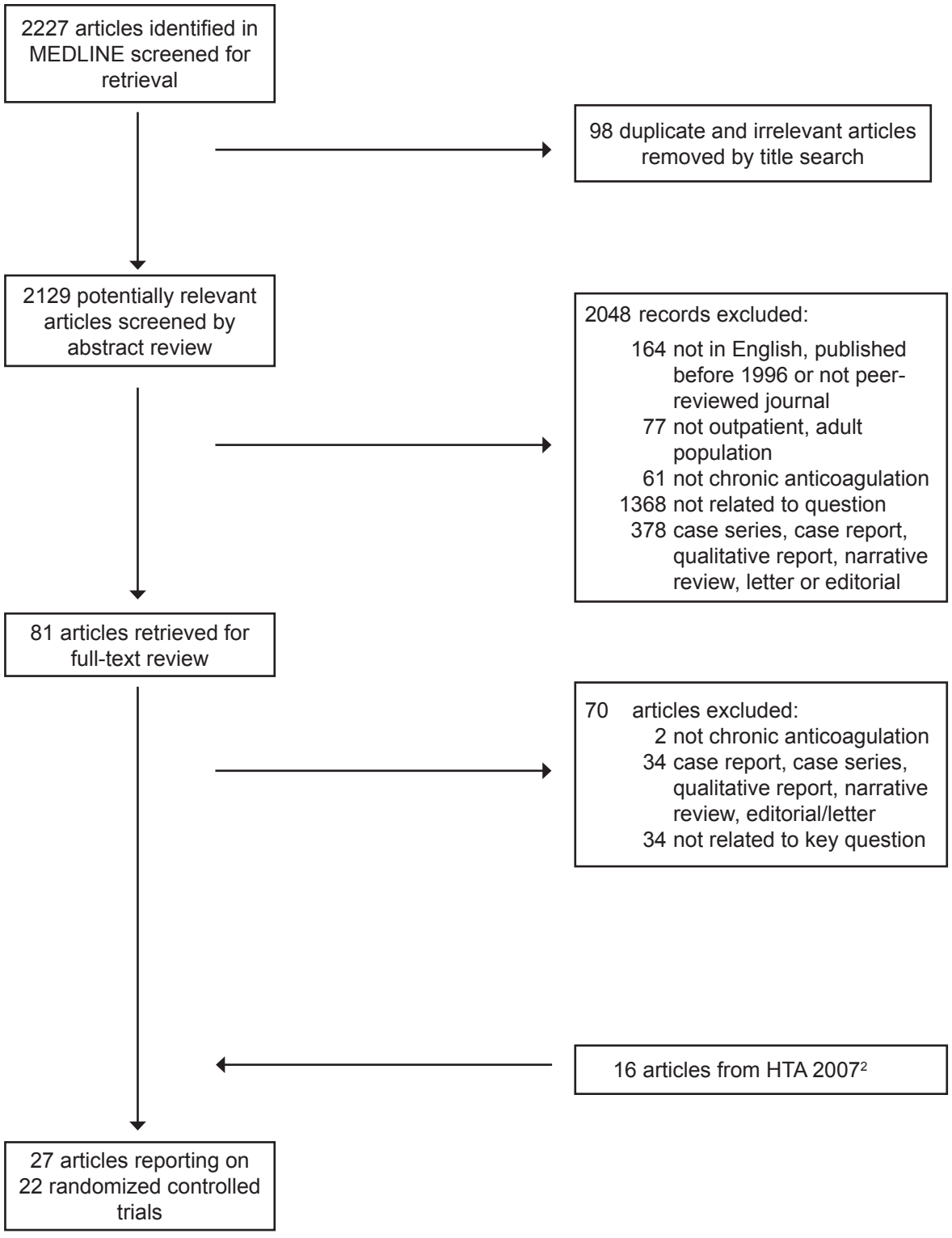
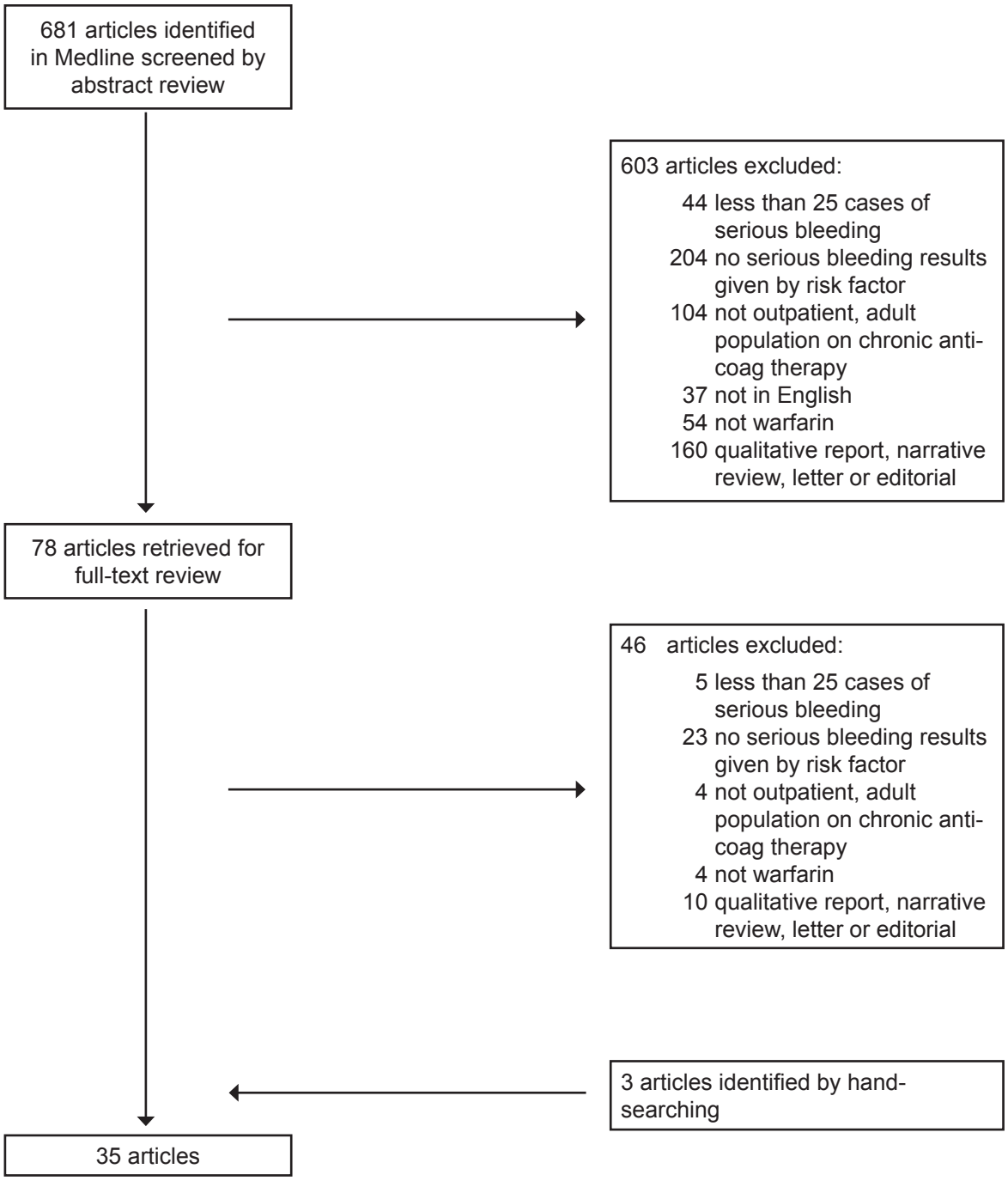


**Figure 4. Literature Flow Diagram for Key Question 3**



## DATA EXTRACTION

For studies related to Key Questions 1 and 2, we extracted data on study design, country of origin, funding source, indications for anticoagulation, sample characteristics, interventions, mortality, thromboembolic events, major bleeding events, patient satisfaction, quality of life, laboratory measures of anticoagulation quality (i.e., percent time within the therapeutic range, percent of INR values within the therapeutic range, and INR variability), hospitalizations, outpatient and emergency room utilization, outpatient laboratory utilization, and long-term care admissions.

For Key Question #1a, we extracted data on ratio of staff to patient load; qualifications of staff and leadership; organizational structure of clinic; frequency and type (e.g., face-to-face versus phone) of contact with patient; frequency and timing of INR checks; use of computer-based algorithms to adjust dosing; timeliness of follow-up of abnormal INRs; patient education; use of genetic information to tailor therapy; protocols for use of vitamin K; clinic volume; hypercoagulation workups (e.g., Factor V Leiden); and use of technologies such as Interactive Voice Recording.

For Key Question #3, we extracted data on study characteristics, patient factors (e.g., age, gender, level of education); indication for anti-coagulation (atrial fibrillation; deep vein thrombosis/pulmonary embolism – either first or recurrent and with or without precipitating factors; mechanical heart valve; TIA/stroke; other); indices measuring severity of illness, functional status, and co-morbidity; time above therapeutic range; type of anticoagulant used; frequency and type of monitoring; concomitant use of anti-platelet agents; concomitant use of other medications; and setting within which patient is monitored (specialized anticoagulation clinic or not).

## QUALITY ASSESSMENT

The quality of the individual randomized studies was assessed by the following: 1) adequate allocation concealment, denoted by central allocation, including telephone, web-based and pharmacy controlled randomization or use of sequentially numbered, opaque, sealed envelopes; 2) blinding of key study personnel (i.e., providers and/or study personnel who adjudicated outcomes blinded to group assignment); 3) analysis by intention-to-treat (i.e., all subjects counted in group to which they were randomized in the outcomes analyses); and 4) reporting of number of withdrawals/dropouts by group assignment.

## DATA SYNTHESIS

*For Key Question #1,* analyses using a DerSimonian and Laird random-effects model, which assumes that the true treatment effects in the individual trials may vary from each other, were conducted in Review Manager Version 5.0.[3] A random-effects model is an analytical approach that incorporates heterogeneity that cannot be readily accounted for. Statistical heterogeneity between trials was assessed using the $I^2$ test. An $I^2$ score of 50 or greater indicates substantial heterogeneity.[4]

*For Key Question #2,* clinical outcomes data were pooled and analyzed in Review Manager

Version 5.0.[3] Because of low event rates for several clinical outcomes, we used Peto odds ratios (fixed effects model). Weighted mean differences were calculated using a random effects model using the Comprehensive Meta-Analysis software© (Biostat, Inc., Englewood, NJ). Statistical heterogeneity between trials was assessed using the $I^2$ test; a score of 50% or greater suggests moderate to substantial inconsistency among studies.[4] In order to explore heterogeneity we performed subgroup analyses and tested for interactions. The extent of publication bias was evaluated through visual inspection of funnel plot asymmetry and the linear regression–based test proposed by Egger.[5]

## PEER REVIEW

A draft version of this report was sent to our Technical Expert Panel members and to three peer reviewers. Reviewer comments were addressed and our responses incorporated into the final report (Appendix A).

# 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)?*

### Literature Search

Using the search strategy outlined in the Methods section, we searched for both randomized clinical trials and cohort studies published after 1996 in peer reviewed journals. We excluded non-English articles and studies that dealt with inpatients, pediatric populations, or short-term anticoagulation (< 3 months). As shown in Figure 2, we reviewed the abstracts of 612 articles of which 78 were selected for more detailed review. Of these, we identified a total of 10 articles. One more was obtained through a hand search for a total of 11 articles reporting on 3 randomized clinical trials and 8 cohort studies that met all inclusion criteria.

### Randomized Controlled Trials

#### *Overview of Included Studies (Table 1; Appendix B - Table 1)*

The 3 trials were conducted in the US, China, and Canada. The Canadian trial randomized 221 subjects with mixed indications for outpatient anticoagulation (OAC) to either an ACC or usual care with a family physician and followed them for 3 months.[6] The Chinese trial randomized 138 subjects with mixed indications for OAC to either a hematologist-led or a pharmacist-led ACC and followed them for up to 2 years.[7] The US trial randomized practice clusters within 6 sites to either access or no access to an ACC; only subjects with atrial fibrillation as their indication for OAC were included.[8] Although 2 of the studies enrolled inception cohorts (i.e., patients new to anticoagulation), neither study was designed to detect differences in outcomes between the early and the maintenance anticoagulation phases.[6,7]

#### *Subject Characteristics in the RCTs (Table 1)*

A total of 722 subjects were enrolled in the 3 RCTs. The mean age of the subjects was 68 (range of study means, 59 to 76 years). Fifty one percent of subjects were male (range in studies, 45 to 58%). In the US study 37% of subjects were non-white;[8] in the Chinese study all subjects were Asian.[7] The Canadian study did not report race/ethnicity.[6] There were 359 patients in the 2 studies that allowed mixed indications for OAC[6,7] and 363 in the one study restricted to subjects with atrial fibrillation.[8]

#### *Study Quality*

The quality of the included studies was generally low. Only the Canadian study met all 4 of the quality indicators (adequate allocation concealment, some attempt at blinding, analyses by intention to treat [partially], and adequate description of study withdrawals).[6]

#### *Interventions in the RCTs*

In the US study,[8] the intervention consisted of an ACC which had responsibility for 3 core functions: management of anticoagulation which involved assigning patients to a medically

qualified mid-level provider; screening administrative files to find eligible patients and offering ACC services to these patients' providers; and educating patients about anticoagulation.

In the Canadian study,[6] all enrolled patients received standard education regarding importance of medication compliance, self monitoring for clinical complications, dietary considerations, and possible medication interactions and were monitored by the ACC until they had achieved a stable dose of warfarin. They were then randomized to continued care in the ACC or with their primary care physician. Details of the procedures employed in the ACC were not included in the report.

In the Chinese study,[7] the intervention consisted of a pharmacist led clinic. The pharmacist received 1 month of training from 2 hematologists and was provided with a management protocol. A hematologist saw patients on their first visit to determine target INR range and duration of therapy. Patients in this arm received "intense education" during visits, written materials, and access to a pharmacist consultation through a telephone hotline.

### *Outcomes in the RCTs*

The outcomes reported in each study are shown in Table 2. As shown in Table 3, there were very few major clinical outcome events and 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 studies. Time within therapeutic range did not differ between intervention and control groups in the US and Canadian studies but was significantly higher in the intervention group in the Chinese study (64% v. 59%, $p<0.05$).

Two of the 3 RCTS evaluated patient satisfaction.[6,7] Using the Patient Satisfaction Questionnaire Short Form (PSQ-18), overall patient satisfaction was significantly higher in the intervention group (pharmacist managed) than in the control group (physician managed) ($P <0.001$).[7] Similar significant results were also found for the sub-scores measuring technical quality, interpersonal manner, communication, time spent with clinician and accessibility but there were no significant differences in the general satisfaction and financial sub-scores. In the second study,[6] patient satisfaction was measured by a "previously validated questionnaire", not referenced. Ninety six percent of patients in ACC reported being satisfied or very satisfied with their overall warfarin care compared with 84% of patients randomized to the family physician group ($p=0.001$). Specifically, patients in the ACC group reported significantly higher satisfaction with teaching, helpfulness of staff, availability of staff in an emergency, and time spent with staff than the subjects randomized to usual care.

In the one RCT that reported resource utilization,[7] there were no significant differences in cost per patient per month between the intervention and control groups for medication use, emergency room utilization, and hospitalizations.

### *Pooled Data*

In the pooled analysis (Figure 5), 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] 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).

### *Laboratory Outcomes*

Percent time in therapeutic range (TTR) by study group is shown in Table 4. In all 3 trials, %TTR was higher for the ACC than the UC group, but in only one was the difference statistically significant.[7] Overall, the pooled weighted mean of 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 usual care, for a weighted mean difference of 3.6 (range of mean differences 3.3 to 5) (Table 5).

## Cohort Studies

### *Overview of Included Studies (Table 1; Appendix B - Table 2)*

Five of the 8 cohort studies were conducted in the US,[9-13] 1 in China,[14] 1 in Sweden,[15] and 1 in multiple countries.[16] Three studies were prospective[9,14,15] and 5 were retrospective cohort studies.[10-13,16] Five studies included subjects with mixed indications for OAC[9-12,15] and 3 included only subjects with atrial fibrillation.[13,14,16] One study enrolled an inception cohort, meaning that subjects had been on OAC for < 3 months,[10] 2 did not,[11,13] and in the other 5 it was unclear.[9,12,14-16] The one study that enrolled an inception cohort did not stratify outcomes by initiation vs. maintenance phases.[10] Follow-up was less than 12 months in 2,[9,12] 12 months in 2,[13,16] >12 months in 1,[15] and not reported in 3 studies.[10,11,14] In 4 studies, the intervention was an ACC run by a pharmacist,[9-12] in one it was an ACC run by a nurse,[13] in one it was defined as care provided in a systematic way by personnel focusing specifically on AC management,[16] and in 2 others the ACC was not described.[14,15]

### *Subject Characteristics in the Cohort Studies (Table 1)*

A total of 12,768 subjects were included in the 8 observational studies. The mean age of subjects was 69 (range of study means, 57 to 74). Fifty five percent of subjects were male (range in studies 42 to 59%). Race/ethnicity was only reported in 2 studies. There were 9946 subjects in the studies that allowed mixed indications for OAC and 2822 in the 3 studies that restricted enrollment to atrial fibrillation.

### *Outcomes in the Cohort Studies*

Reported outcomes are shown in Tables 2 and 3. In the only study in which all-cause mortality was reported, there were 3 deaths (0.09%) in the intervention group and 2 (0.06%) in the control group (p values not reported).[12] Four studies reported major thromboembolic events; in 1 of these the incidence was significantly higher in the control group,[10] in 1 it was significantly higher in the intervention group,[14] and in 2 studies p values were not reported.[12,13] The incidence of major bleeding events was significantly higher in the control group in 1 study,[10] and not significantly different between groups in 1 study.[14] Significance testing was not included for the 3 other studies that reported this outcome.[12,13,15] We were unable to pool major clinical outcomes because outcomes were reported as number of events in only 2 of the 8 studies;[12,14] the other studies reported events per patient- or treatment-year.

### *Laboratory Outcomes*

As shown in Table 4, time within therapeutic range or percent of INR values within the therapeutic range was higher in the intervention group in all 6 studies that reported this

metric.[10-14,16] As shown in Table 5, the weighted mean for percent time within therapeutic range for the 4 studies reporting this metric,[10,12,13,16] was 63.5% for the intervention groups and 53.5% for the control groups, for a difference of 10% (range of mean differences, 4.3 to 26%).

### *Other Outcomes*

Three observational studies reported hospital admissions and/or emergency department (ED) visits.[9-11] In one there were no significant differences between UC and ACC groups for ED visits or inpatient admissions.[11] In the second,10 there were significantly fewer anticoagulation related hospitalizations (19 v 5) and ED visits (22 v 6) in the ACC group. For hospitalizations unrelated to AC use, there were no differences between the 2 groups but the group randomized to AC had significantly fewer ED visits for reasons deemed unrelated to anticoagulation. The third study,[9] reported warfarin-related hospital admissions in 10 control group patients vs. 3 ACC patients ($p<0.01$).

## KEY QUESTION 1A

*Which components of a specialized anticoagulation clinic are associated with effectiveness/ safety?*

None of the included studies reported the **association** between **specific elements of ACC** (e.g. ratio of staff to patient load; qualifications of staff and leadership; organizational structure of clinic; frequency and type of contact with patient; use of computer-based algorithms to adjust dosing; patient education) and **outcomes**. In one RCT, patients in both arms received algorithm driven dose adjustments,[7] and in the other 2 studies only patients in the intervention arm were managed with dosing algorithms.[6,7] Among the 8 observational studies, 4 commented on possible processes of care that might have accounted for observed differences in outcomes. These included use of both face-to face and telephone interactions with patients,[13] use of a computerized patient monitoring system that identified patients who were delinquent in returning for timely INR determinations;[12] the specialized expertise of the ACC staff;[12] more consistency in ACCs in obtaining regular INRs;[11] and frequency of face-to-face consultations, methods of dosage adjustment, and provision of written dosage instructions.[16]

## SUMMARY – KEY QUESTION 1

The evidence suggests that care provided within ACC may lead to better quality anticoagulation control as measured by time in therapeutic range but 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. Patients were reported to like the convenience and enhanced service provided by these clinics.

**Table 1. Summary of Study Characteristics for Anticoagulation Clinic versus Usual Care Studies (KQ1)**

| | Randomized controlled trials (N=3) | | Observational studies (N=8) | |
|---|---|---|---|---|
| **Characteristic** | **Range or Mean %** | **# studies reporting** | **Range or Mean %** | **# studies reporting** |
| Overall: number of subjects per study | 138 to 363 (722 total) | 3 | 116 to 6645 (12,768 total) | 8 |
| Study dropouts/withdrawals, overall: mean % (range) | 1 (0.7 to 1) | 2 | NA | NA |
| Age of subjects: mean years (range) | 68 (59 to 76) | 3 | 69 (57 to 74) | 6 |
| Gender, male: mean % (range) | 51 (45 to 58) | 3 | 55 (42 to 59) | 8 |
| Race/ethnicity, white: mean % (range) | 45 (0 to 63) | 2 | 73 (0 to 86) | 2 |
| Race/ethnicity, non-white: mean % (range) | 55 (37 to 100*) | 2 | 23 (14 to 100*) | 2 |
| Indication for anticoagulation, mixed indications:** number of subjects per study | 138 to 221 (359 total) | 2 | 116 to 6645 (9946 total) | 5 |
| Indication for anticoagulation, atrial fibrillation: number of subjects per study | 363 | 1 | 204 to 1511 (2822 total) | 3 |
| Non-pharmacy, mixed (RN, NP, PA, PharmD, MD), or unclear managed anticoagulation clinic studies: number of subjects per study | 221 to 363 (584 total) | 2 | 204 to 2731 (5553 total) | 4 |
| Pharmacy-managed anticoagulation clinic studies: number of subjects per study | 138 | 2 | 116 to 6645 (7215 total) | 4† |
| Studies conducted in the United States: number of subjects per study | 363 | 1 | 116 to 6645 (8322 total) | 5 |
| Prospective cohort studies: number of subjects per study | NA | | 136 to 2731 (3071 total) | 3 |
| Retrospective cohort studies: number of subjects per study | | | 116 to 6645 (9697 total) | 5 |

* 1 trial exclusively Asian

** Generally venous thromboembolism; CVA/stroke; heart valve replacement, atrial fibrillation, pulmonary embolus, myocardial infarction, cardiomyopathy or prophylaxis;

† All studies conducted in the United States

**Table 2. Outcomes Reported for Anticoagulation Clinic versus Usual Care Studies (KQ1)**

| Study | Mortality | Thrombo-embolic events | Major bleeding events | Quality of life/patient satisfaction | % Time within therapeutic range | % INR values within therapeutic range | Emergency Room visits | Hospitaliza-tions |
|---|---|---|---|---|---|---|---|---|
| ***Randomized Trials*** | | | | | | | | |
| Matchar 2002[8] | | √ | √ | | √ | | | |
| Wilson 2003[6] | √ | √ | √ | √ | √ | | | √ |
| Chan 2006[7] | √ | √ | √ | √ | √ | | √ | √ |
| ***Observational Studies*** | | | | | | | | |
| Lee 1996[9] | | | | | | | | √ |
| Chiquette 1998[10] | | √ | √ | | √ | √ | √ | √ |
| Chamberlain 2001[11] | | | | | | √ | √ | √ |
| Witt 2005[12] | √ | √ | √ | | √ | | | |
| Du 2005[14] | | √ | √ | | | √ | | |
| Ansell 2007[165] | | | | | √ | √ | | |
| Wallvik 2007[15] | | | √ | | | | | |
| Nichol 2008[13] | | √ | √ | | √ | | | |
| **TOTAL (11)** | 3 | 7 | 8 | 2 | 7 | 4 | 3 | 5 |

**Table 3. Clinical Outcomes Events for Anticoagulation Clinic versus Usual Care Studies (KQ1)**

| Study | # All-cause deaths | | # Thromboembolic events | | # Major bleeding events | |
|---|---|---|---|---|---|---|
| | Intervention | Control | Intervention | Control | Intervention | Control |
| ***Randomized Trials*** | | | | | | |
| Matchar 2002[8] | | | 9/173 (5.2%)† | 11/317 (3.5%) | 3/173 (1.7%)† | 5/317 (1.6%) |
| Wilson 2003[6] | 5/112 (4.5%)† | 6/109 (5.5%) | 1/112 (0.9%)† | 2/109 (1.8%) | 2/112 (1.8%)† | 1/109 (0.9%) |
| Chan 2006[7] | 0/69† | 0/69 | 1/68 (1.5%) † | 1/69 (1.4%) | 1/68 (1.5%) † | 2/69 (2.9%) |
| ***Observational Studies*** | | | | | | |
| Lee 1996[9] | | | | | | |
| Chiquette 1998[10] | | | 3.3% per pt-yr* | 11.8% per pt-yr | 9.7% per pt-yr* | 39.2% per pt-yr* |
| Chamberlain 2001[11] | | | | | | |
| Witt 2002[12] | 3/3323 (0.09%)‡ | 2/3322 (0.06%) | 17/3323 (0.5%)‡ | 41/3322 1.2%) | 29/3323 (0.9%)‡ | 31/3322 (0.9%) |
| Du 2005[14] | | | 19/138 (13.8%)* | 2/66 (3.0%) | 8/138 (5.8%)† | 2/66 (3.0%) |
| Ansell 2007[16] | | | | | | |
| Wallvik 2007[15] | | | | | 13/2292 tx-yrs‡ | 21/2752 tx-yrs |
| Nichol 2008[13] | | | 1.9% per pt-yr‡ | 3.7% per pt-yr | 2.3% per pt-yr‡ | 6.3% per pt-yr |

* $p<0.05$
† Not statistically significant versus control
‡ p value not reported

**Table 4. Laboratory Outcomes by Study Group for Anticoagulation Clinic versus Usual Care Studies**

| Study | % Time within therapeutic range | | % INR values within therapeutic range | | % Time above therapeutic range | | % Time below therapeutic range | |
|---|---|---|---|---|---|---|---|---|
| | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control |
| ***Randomized Trials*** | | | | | | | | |
| Matchar 2002[8] | 55.6%† | 52.3% | | | | | | |
| Wilson 2003[6] | 63% † | 59% | | | | | | |
| Chan 2006[7] | 64%* | 59% | | | | | | |
| ***Observational Studies*** | | | | | | | | |
| Lee 1996[9] | | | | | | | | |
| Chiquette 1998[10] | 45.7%* | 41.4% | 36.6%* | 31.3% | | | | |
| Chamberlain 2001[11] | | | 50.2%‡ | 45.8% | | | | |
| Witt 2002[12] | 63.5%* | 55.2% | | | 11.8%* | 14.5% | 24.7%* | 30.3%* |
| Du 2005[14] | | | 63.6%* | 23.3% | | | | |
| Ansell 2007[16] | 67‡ | 57.9% | 59.1%‡ | 52% | 13% | 17% | 20% | 25% |
| Wallvik 2007[15] | | | | | | | | |
| Nichol 2008[13] | 68.1%* | 42.1% | | | 11.3% | 9.4% | 20.6% | 48.5% |

* $p<0.05$
† Not statistically significant versus control
‡ p value not reported

**Table 5. Weighted Means for the Percentage of Time within Therapeutic Range for Anticoagulation Clinic versus Usual Care Studies**

| Study | AC n | AC, % time within range | UC n | UC, % time within range | Mean difference |
|---|---|---|---|---|---|
| ***Randomized Trials*** | | | | | |
| Matchar 2002[8] | 144 | 55.6%* | 118 | 52.3% | 3.3% |
| Wilson 2003[6] | 112 | 63%* | 106 | 59% | 4% |
| Chan 2006[7] | 68 | 64%** | 69 | 59% | 5% |
| Weighted means | | 59.9% | | 56.3% | Weighted mean difference = 3.6% (range of means 3.3 to 5) |
| ***Observational Studies*** | | | | | |
| Chiquette 1998[10] | 176 | 45.7%** | 142 | 41.4% | 4.3% |
| Witt 2002[12] | 3323 | 63.5%** | 3322 | 55.2% | 8.3% |
| Ansell 2007[16] | 395 | 67%† | 1116 | 57.9% | 9.1% |
| Nichol 2008[13] | 351 | 68.1%** | 756 | 42.1% | 26% |
| Weighted means | | 63.5% | | 53.5% | Weighted mean difference = 10% (range of means 4.3 to 26) |

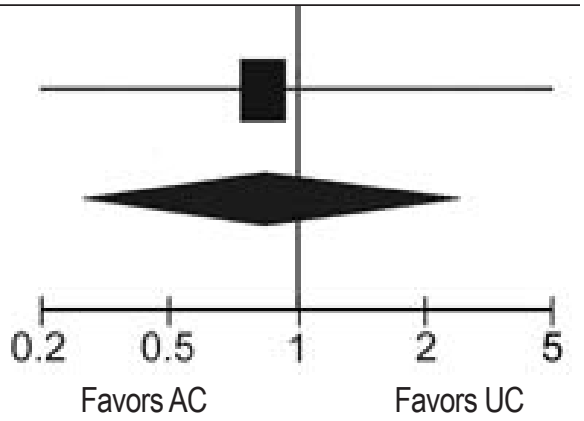
* Not statistically significant versus Usual Care
** p <0.05 versus Usual Care
† p value not reported

**Figure 5. All-cause Mortality, Anticoagulation Clinic versus Usual Care**

| | Anticoagulation Clinic | | Usual Care | | | Risk Ratio | Risk Ratio |
|---|---|---|---|---|---|---|---|
| **Study or Subgroup** | **Events** | **Total** | **Events** | **Total** | **Weight** | **M-H, Random, 95% CI** | **M-H, Random, 95% CI** |
| Chan 2006 (7) | 0 | 69 | 0 | 69 | | Not estimable | |
| Wilson 2003 (6) | 5 | 112 | 6 | 109 | 100.0% | 081 [0.25, 2.58] | |
| **Total (95% CI)** | | **181** | | **178** | **100.0%** | **0.81 [0.25, 2.58]** | |
| Total Events | 5 | | 6 | | | | |

Heterogeneity, Not applicable

Test for overall effect: Z = 0.35 (P = 0.72)



## 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?*

### Literature Search

Using the search strategy shown in the Methods section, we looked for randomized clinical trials published after 1996 in peer reviewed journals. We excluded non-English articles as well as studies that dealt with inpatients, pediatric populations, or short-term anticoagulation (<3 months). As shown in Figure 3, we screened 2129 abstracts and selected 81 for full article review. Of these, we identified a total of 27 articles reporting on 22 distinct randomized clinical trials.

### Overview of Included Studies

An overview of the 22 included studies is shown in Appendix B, Tables 3 and 4. Two studies were conducted in the US,[17,18] 1 in Canada,[19] and 19 in Europe.[20-45] 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 (Table 6). Fourteen studies included patients with a variety of indications for anticoagulation[17-24,26,28-30,32,39-43] and 8 only included patients with mechanical heart valves (6)[31,33-38,44,45] or atrial fibrillation (2).[25,27] Three trials enrolled inception cohorts (i.e., limited enrollment to patients on OAC for < 3 months);[18,35-37,45] 11 trials did not enroll inception cohorts;[17,21-26,28-30,32,39,40,42,43] and in 8 studies the populations were either mixed or it was unclear.[19,20,27,31,33,34,38,41,44] Among the 3 with inception cohorts, outcomes were not analyzed by whether they had occurred in the anticoagulation initiation or maintenance phase.

### Assessments of Quality and Bias

Measures of trial quality are shown in Figure 6 and reported in Appendix B, Tables 3 and 4. Allocation concealment was adequate in 9 trials, some attempt at blinding of endpoint assessors was made in 6, an intention to treat analysis was reported in 8, and number of drop-outs was reported in 18. Five trials met all 4 of these quality indicators.[17,20,24,41-43] Only six trials noted they received no funding from industry.[17,18,28,29,32,39] Egger's test suggested little evidence that small study effects influenced the findings for thromboembolic events (P = 0.513).

### Subject Selection

The percentage of patients screened who met preliminary eligibility criteria, successfully completed the training, and agreed to be randomized was less than 20% in 4 studies,[22,23,30,45] between 20 and 50% in 7 studies,[24,25,28,32,39,41,43] and greater than 50% in 3 studies.[19,20] Eight studies did not report data; THINRS data is presented below. It is difficult to determine how many refusals were due to discomfort being in a trial vs. discomfort with self testing and/or self management of anticoagulation. Among patients who were randomized, the percentage who continued with the intervention throughout the study period ranged from 64-98%.

### Subject Characteristics

The mean age of the subjects was 65 years (range of study means 42 to 75 years) (Table 6). Three studies specifically focused on elderly patients, enrolling only patients over the age of

65[18,25] or 60 years of age.[43] Seventy five percent of subjects were male (range in studies, 43 to 98%). Race/ethnicity was reported only in the 2 US studies, in one of those 8%[17] and in the other 33%[18] of the subjects were non-white. A total of 2911 subjects were enrolled in the 12 studies in which there were multiple indications for anticoagulation; 2074 were enrolled in the 6 studies restricted to a mechanical heart valve indication; 327 in the 2 studies limited to atrial fibrillation; and 3101 in the 2 trials that limited enrollment to mechanical heart valve or atrial fibrillation.

## Interventions

Evaluated interventions included patient self testing only (i.e., dose adjustment made by the clinic, n=5)[17,18,25,32] and patient self-management (i.e. testing and dose adjustment made by patient, n=14).[19-22,25-28,30,31,35,36,38,39,41,43-45] In one study it was unclear if the intervention was PST or PSM.[34] In one study there were 4 arms (PST, PSM, routine care with or without education).[23] In one study there were 3 groups: routine care alone, routine care with education and PSM with education.[25] In one study PSM was compared to PST with no control group.[26,30] In 11 studies warfarin was used in all subjects,[17-19,22,25,26,30,32,38,39,44] other oral anticoagulants (phenprocoumon, acenocoumarol, fluindione) were used in 7,[20,21,23,31,35,36,41,43] in 3 studies the type of oral anticoagulant was not reported,[27,34,45] and in 1 study both warfarin and phenprocoumon were used.[28]

### *Details of PST/PSM Intervention:*

The patient self testing/self management intervention usually included 2-4 small group training sessions of 1-3 hours over several weeks. The sessions, which were led by a nurse, pharmacist or physician, were followed by home practice and a test to ensure competency in all procedures. Training sessions typically included general information on anticoagulation, possible interactions with foods/medicines, how to use the INR testing machine (including demonstrating ability to use the machine correctly and to perform quality control checks), how to dose (usually by algorithm), how often to check INR, and when to call for help. Patients often had access to a 24 hour telephone help line. Two studies had much more intensive training. One of the US studies included one-on-one daily training by a lay educator while patients were still in the hospital followed by a home visit within 3 days of discharge.[18] The second study included a 24 week training program in which responsibility for dosing was gradually transferred from physician to patient,[28,29] A recent study from Ireland[32] employed an internet-based direct to patient expert system in which patients receive advice on dosing from the system after entering their INRs and relevant clinical information (e.g. intercurrent illnesses, dietary changes).

### *Control Intervention:*

The control group received anticoagulation management in an ACC in 11 of the trials,[17,21-23,25,32,39,41,45] in a primary care or other physician office in 7 trials.[18-20,27,31,34-36,44] and in multiple settings in 3 trials.[28,38,42] The other trial compared PST to PSM without another control group.[26,30]

## Outcomes

Reported outcomes are tabulated in Table 7 with details in Tables 8 and 9. All-cause mortality was reported in 16 studies, thromboembolic events in 20, major bleeding episodes in 20, and patient satisfaction and/or quality of life in 11. All studies reported one or more laboratory

measure of quality of anticoagulation, the most common being a measure of time in therapeutic range in 18 studies.

## Clinical Outcomes (Figures 7, 8, and 9)

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%).

### *Sensitivity Analyses:*

There was evidence of inconsistency among the studies, especially for the mortality outcome. In order to explore sources of heterogeneity we conducted subgroup analyses for all 3 clinical outcomes stratifying by the following variables: duration of study (<12 vs. ≥12 months), indication for anticoagulation (mechanical heart valve vs. all other), active intervention (PST vs. PSM), control intervention (ACC vs. physician office), study quality (met all 4 quality domains cited above), and funding source (industry vs. not reported vs. non-industry). Although in the initial analyses there were several significant interactions (i.e., for mortality: indication for anticoagulation, active intervention, control intervention, study quality, and funding source; for bleeding: study duration; and for thromboembolism: active intervention and funding source), only one remained marginally significant after we removed the VA trial, suggesting that the VA trial was a major contributing factor to the observed heterogeneity (see below for further discussion). The marginally significant interaction was for major bleeding by study duration (study duration: ≥ 12 months: Peto OR 1.04 95% CI 0.76 to 1.42; <12 months, Peto OR: 0.44, 0.22 to 0.85, P for interaction=0.02).

### *Effect of Patient Education on Outcomes:*

Subjects enrolled in the PSM or PST arms of a trial receive more extensive training and education than patients assigned to usual care which might explain the difference in outcomes between the 2 groups. In the 2 studies that were designed to explore the independent effect of patient education, one found no effect of patient education on time in therapeutic range.[23,24] The other did find a significant effect on time in therapeutic range using a before-after within group comparison, rather than the more robust between group comparison.[25]

### *Outcome Differences between PST and PSM:*

Two studies[23,30] compared PSM to PST. In neither study (Gadisseur[23] N=99 for this comparison; Gardiner[30] N =104) was there a significant difference in TTR between the 2 groups.

### *Percent Time in Therapeutic Range (TTR) by Study Group (Tables 9 and 10):*

Overall, the pooled weighted mean of TTR for patients randomized to PST/PSM interventions was 66.1% (range of means 56-76.5%), only slightly higher than the 61.9% (range of means 32 to 77%) for the patients randomized to usual care (Table 10). As shown in Figure 10, for the studies we were able to include in a meta-analysis the weighted mean difference of 1.50% was not statistically significant (95% CI: -0.63 to 3.63%, $I^2$=45%, 9 studies, P=0.168).

### *Percent of INRs within Therapeutic Range:*

As shown in Tables 9 and 11, 11 studies reported mean values for this outcome. The pooled weighted mean was 70.5% (range of means 43 to 87%) in the PST/PSM group and 59.3% in the usual care group (range of means 22 to 78%). For the studies we were able to include in the meta-analysis, the weighted mean difference of 5.9% was not statistically significant (Figure 11) with a high level of heterogeneity (95%CI: -0.18 to 12.0%, I2=83%, 6 studies, P=0.057).

### *Patient Satisfaction and Quality of Life:*

There is little uniformity in the measurement or definition of these constructs within the 11 studies that reported them.[17,19-,22,24-26,32,39,45] Three studies that used an instrument developed by Sawicki et al.[20] all found significant differences between the PST/PSM and the UC groups. Specifically, in the German study[20] patients randomized to PSM had significantly higher general treatment satisfaction and self efficacy, and significantly less distress and daily hassles than those in UC. In the cross-over study from the Netherlands,[21] patients in the self management group reported significantly more self-efficacy and general treatment satisfaction, and significantly less distress, social issues and daily worries than those in UC. In the third study, also from the Netherlands,[24] patients were randomized to usual care, PST only, and PSM. This study showed that patients in both intervention arms had significant reductions in daily hassles, distress, and strains in social network and increase in self efficacy and general satisfaction compared to the UC group. There were no statistically significant differences between the 2 intervention arms.

In 3 additional studies, one found that all of the patients who had been randomized to PSM wanted to continue the program after the study ended,[19] in the second, 77% indicated at the end of the study that they preferred self-testing to the hospital clinic,[26] and in the third, 98% expressed a preference for PST.[32] Three studies found no significant difference in patient satisfaction or quality of life between groups.[22,25,40] Patient satisfaction in the VA trial[17] is described below.

## THINRS

This trial[17] is of particular interest since it was conducted in VA and is the largest trial to date comparing patient self-testing with usual care. The trial recruited 3,745 subjects in 28 VAMCs who required long term oral anticoagulation for either atrial fibrillation or a mechanical heart valve. Forty two of these subjects did not meet all entry criteria, 60 did not complete training, 586 did not undergo competency testing, 112 did not pass competency testing, and 23 passed the competency assessment but subsequently withdrew. Thus 78% of screened subjects were enrolled in the trial (N=2922). Subjects were randomized to high quality anticoagulation clinic management or patient self testing. Randomization was centralized and stratified by length of anticoagulation (< 3 months vs. ≥ 3 months) and indication. The primary endpoint was time to first event: stroke, major bleed, or death. Although the investigators and subjects were not blinded to treatment allocation, outcomes were assessed by independent adjudicators. An intention to treat analysis was performed. In both groups, loss to follow up was 1% in and warfarin discontinuation was 7%.

**N**inety eight percent of the patients were male with a mean age of 67 (range of 33 to 99). Ninety two percent were white. Eighty three percent had atrial fibrillation and 24% had a mechanical heart valve. 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.

As indicated above, our results for major thromboembolism and bleeding appear to be robust with negligible heterogeneity, and similar findings have been reported in other reviews.[2,46,47] For mortality, however, there was evidence of inconsistency among studies that was likely attributable to the VA study. There are several possible reasons why the VA results differed from the other studies. First, this trial had substantially longer follow-up than any of the other studies and it may be that over time people assigned to PST stop testing as frequently leading to a lessening of the difference between those who are seen every month in the anticoagulation clinic and those who self test at home. Second, if the VA PST intervention was of lower quality than in other trials, this could explain its lower efficacy. However, this did not appear to be the case as the PST intervention included a rigorous patient education program and ongoing quality control which resulted in high percent time within therapeutic range. Finally, if the VA anticoagulation clinic was of higher quality than in the other trials, there would be less of an observed difference in outcomes between the 2 arms than in studies in which PSM/PST was compared to a lower quality control intervention. This likely was the case as the VA trial employed rigorous criteria to ensure that care in the anticoagulation clinics was state of the art.[17]

## SUMMARY – KEY QUESTION 2

This review confirms that patient self testing with or without self management is at least as effective and safe as routine care for a select group of motivated adult patients requiring long term anticoagulation with Vitamin K antagonists.

**Table 6. Summary of Study Characteristics for Patient Self Testing/Management versus Usual Care Studies**

| Characteristic | Range or Mean % | # studies reporting |
|---|---|---|
| Overall: number of subjects per study | 50 to 2922 (8413 total) | 22 |
| Short-term trials (<12 months): number of subjects per study | 50 to 341 (1935 total) | 13 |
| Long-term trials (≥12 months): number of subjects per study | 62 to 2922 (6478 total) | 9 |
| Study dropouts/withdrawals, overall: mean % (range) | 9 (<1 to 28) | 18 |
| Study dropouts/withdrawals, PST/PSM intervention: mean % (range) | 14 (1 to 43) | 15 |
| Age of subjects: mean years (range) | 65 (42 to 75) | 19 |
| Gender, male: mean % (range) | 75 (43 to 98) | 20 |
| Race/ethnicity, white: mean % (range) | 90 (67 to 92) | 2* |
| Race/ethnicity, non-white/other: mean % (range) | 10 (8 to 33) | |
| Indication for anticoagulation, mixed indications:* number of subjects per study | 50 to 737 (3090 total) | 13 |
| Indication for anticoagulation, MHV replacement: number of subjects per study | 62 to 930 (2074 total) | 6 |
| Indication for anticoagulation, atrial fibrillation: number of subjects per study | 125 to 202 (327 total) | 2 |
| Indication for anticoagulation, MHV replacement and atrial fibrillation: number of subjects per study | 2922 | 1 |
| Studies conducted in the United States: number of subjects per study | 325 to 2922 (3247 total) | 2 |
| **Outcomes Assessed** | | |
| All-cause mortality: number of subjects per study | 56 to 2922 (6820 total) | 16 |
| Event-related mortality: number of subjects per study | 56 to 930 (3302 total) | 9 |
| Thromboembolic events: number of subjects per study | 56 to 2922 (8209 total) | 20 |
| Major bleeding events: number of subjects per study | 56 to 2922 (8209 total) | 20 |
| Percentage of time within therapeutic range: number of subjects per study | 56 to 2922 (6008 total) | 14 |
| Percentage of INR within therapeutic range: number of subjects per study | 50 to 765 (3857 total) | 13 |
| INR variability: number of subjects per study | 67 to 765 (2268 total) | 6 |

PST: patient self-testing; PSM: patient self-management; MHV: mechanical heart valve; INR: international normalized ratio

*Both studies conducted in the United States

**Table 7. Outcomes Reported in Patient Self Testing/Management versus Usual Care Studies**

| Study | All-cause mortality | Event-related mortality | Thrombo-embolic events | Major bleeding events | Patient satisfaction & quality of life | % time within thera-peutic range | % INR values within thera-peutic range | INR variability | % time or INR values above or below range | No. of INR values | Cost-effective-ness |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Short-term (<12 months) randomized, controlled trials*** | | | | | | | | | | | |
| Sawicki 1999[20] | √ | | √ | √ | √ | | | √ | | | |
| Beyth 2000[18] | √ | √ | √ | √ | | √ | | | √ | √ | |
| Cromheecke 2000[21] | | | √ | √ | √ | √ | √ | √ | √ | | |
| Fitzmaurice 2002[22] | √ | | √ | √ | √ | √ | √ | | | √ | √ |
| Gadisseur 2003 & 2004[23,24] | | | √ | √ | √ | √ | √ | | √ | √ | |
| Khan 2004[25] | | | √* | √* | √ | √ | | √ | | | |
| Sunderji 2004[19] | √ | | √ | √ | √ | √ | √ | | √ | √ | |
| Gardiner 2005[26] | √ | | √ | √ | √ | √ | | | | | |
| Voller 2005[27] | √ | | √ | √ | | √** | √ | | √ | √ | |
| Christensen 2006[28] & 2007[28] | √ | | | | | √ | | √ | | √ | |
| Gardiner 2006[30] | | | | | | √ | | | | √ | |
| Dauphin 2008[31] | √ | | √ | √ | | √ | | √ | | | |
| Ryan 2009[32] | | | √ | √ | √ | √ | √ | | | √ | |

| *Long-term (≥12 months) randomized, controlled trials* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Horstkotte 1996[33] & 1998[34] | | | √ | √ | | | √ | | | √ | |
| Koertke 2001[35,36] & 2007[37] | √ | √ | √ | √ | | | √ | | √ | √ | |
| Sidhu 2001[38] | √ | √ | √ | √ | | √ | | | √ | √ | |
| Fitzmaurice 2005[39] & Jowett 2006[40] | √ | √ | √ | √ | √ | √ | | | | | √ |
| Menendez-Jandula 2005[41] | √ | √ | √ | √ | | √ | √ | √ | | √ | |
| Siebenhofer 2007[42] & 2008[43] | √ | √ | √ | √ | | √ | √ | √ | √ | √ | √ |
| Eitz 2008[44] | | | √ | √ | | | √ | √ | √ | √ | |
| Soliman Hamad 2009[45] | √ | | √ | √ | √ | √** | √ | | | | |
| Matchar 2010[17] | √ | | √ | √ | √ | √ | | | | | |
| **TOTAL (20)** | **16** | **6** | **20** | **20** | **11** | **18** | **12** | **8** | **9** | **13** | **3** |

*only recorded in intervention groups **# of days (not % time)

**Table 8. Clinical Outcomes Events for Patient Self Testing/Management versus Usual Care Studies**

| Study | All-cause mortality | | Event-related mortality (# of deaths) | | # Thromboembolic events | | # Major bleeding events | | Patient satisfaction & quality of life |
|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | |
| ***Short-term (<12 months) randomized, controlled trials*** | | | | | | | | | |
| Sawicki 1999[20] | 1/90 (1.1%)‡, | 1/89 (1.1%) | --- | --- | 1/90 (1.1%)‡ | 2/89 (2.2%) | 1/90 (1.1%)‡ | 1/89 (1.1%) | 40-item questionnaire |
| Beyth 2000[18] | 21/163 (13%)† | 26/162 (16%) | 1/163 (0.6%)‡ | 3/162 (1.8%) | 14/163 (8.6%)† | 21/162 (13.0%) | 8/163 (4.9%)*, | 17/162 (10.5%) | --- |
| Cromheecke 2000[21] | --- | --- | --- | --- | 0/50‡ | 1/50 (2%) | 0/50 | 0/50 | 32-item questionnaire |
| Fitzmaurice 2002[22] | 0/30‡ | 1/26 (3.8%) | 0/30 | 1/26 (3.8%) | 0/30 | 0/26 | 0/30‡ | 1/26 (3.8%) | Patient interview with SEIQoL tool |
| Gadisseur 2003[23] & 2004[24] | --- | --- | --- | --- | *PST:* 0/52 *PSM:* 0/47 | *P/Ed:* 0/60 *PC:* 0/161 | *PST:* 0/52 *PSM:* 2‡, a | *P/Ed:* 2‡, a *PC:* 1/161 (0.6%) | 32-item questionnaire |
| Khan 2004[25] | --- | --- | --- | --- | 0/44 | 0/41 | 1/44 (2.3%)‡ | 0/41 | Surveys with UKSF-36 and EuroQoL |
| Sunderji 2004[19] | 0/70 | 0/70 | 0/70 | 0/70 | 0/70‡ | 2/70 (2.9%) | 0/70‡ | 1/70 (1.4%) | --- |
| Gardiner 2005[26] | 1/44 (2.3%)‡ | 0/40 | --- | --- | 0/44 | 0/40 | 0/44 | 0/40 | --- |
| Voeller 2005[27] | 0/101 | 0/101 | 0/101 | 0/101 | 0/101‡ | 1/101 (1%) | 1/101 (1%) | 0/101 | --- |
| Christensen 2006[28] & 2007[29] | 1/50 (2%) | 0/50 | --- | --- | --- | --- | --- | --- | --- |
| Gardiner 2006[30] | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Dauphin 2008[31] | 1/33 (3%)‡ | 0/34 | --- | --- | 0/33 | 0/34 | 0/33† | 4/34 (11.8%) | --- |
| Ryan 2009[32] | 2 deaths, treatment arm not reported | --- | --- | --- | 2/132 (1.5%) | 1/132 (0.8%) | 0/132 | 1/132 (0.8%) | Patient satisfaction with care |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ***Long-term (≥12 months) randomized, controlled trials*** | | | | | | | | | |
| Horstkotte 1998[33,34] | --- | --- | --- | --- | 0.9* (%/year) | 3.63 (%/year) | 4.49* (%/year) | 10.88 (%/year) | --- |
| Koertke 2001[35,36] & 2007[37] | *At 5 years (est.)* 32/447 (7.2%) *At 12 years* 94/488 (19.3%)‡ | *At 5 years (est.)* 55/395 (13.9%) *At 12 years* 142/442 (32.2%) | 8/488 (1.6%)‡ | 7/442 (1.6%) | 16/579 (2.8%)* | 32/576 (5.6%) | 42/579 (7.3%)‡ | 34/576 (5.9%) | --- |
| Sidhu 2001[38] | 0/51† | 4/49 (8.2%) | 0/51 | 1/49 (2.0%) | 1/51 (2.0%)‡ | 0/49 | 1/51 (2%)‡, | 0/49 | --- |
| Fitzmaurice 2005[39] & Jowett 2006[40] | 5/337 (1.5%)‡ | 11/280 (3.9%) | 2/337 (0.6%)‡ | 1/280 (0.4%) | 4/337 (1.2%)‡ | 3/280 (1.1%) | 5/337 (1.5%)‡, | 4/280 (1.4%) | EQ-5D tool; mean QALYs |
| Menendez-Jandula 2005[41] | 6/368 (1.6%)‡ | 15/369 (4.1%) | 3/368 (0.8%)‡ | 0/369 | 4/368‡ (1.1%) | 20/369 (5.4%) | 4/368‡ (1.1%) | 7/369 (1.9%) | --- |
| Siebenhofer 2007[42] & 2008[43] | 15/99 (15.2%)† | 11/96 (11.5%) | 0/99† | 3/96 (3.1%) | 6/99 (6.1%)†, | 13/96 (13.5%) | 7/99 (7.1%) | 10/96 (10.4%) | --- |
| Eitz 2008[44] | --- | --- | --- | --- | 14/470‡ (3.0%) | 21/295 (7.1%) | 32/470‡ (6.8%) | 20/295 (6.8%) | --- |
| Soliman Hamad 2009[45] | 1/29 (3.4%) | 1/29 (3.4%) | --- | --- | 0/29 | 1/29 (3.4%) | 1/29 (3.4%) | 1/29 (3.4%) | SF-36v2 |
| Matchar 2010[17] | 152/1465 (10.4%)‡ | 157/1457 (10.8%) | --- | --- | 33/1465 (2.3%)‡ | 31/1457 (2.1%) | 180/1465 (12.3%)‡ | 199/1457 (13.7%) | --- |

* p<0.05versus control † not statistically significant versus control ‡ p value not reported § range or deviation not reported
[a] quantity reported as events, not patients; we were therefore unable to determine a proportion since no denominator was available

CI = confidence interval IQR = interquartile range (25-75%) PC = primary care PC/Ed = primary care with education PSM = patient self-management
PST = patient self-testing SD = standard deviation SEM = standard error of the mean

**Table 9. Laboratory Outcomes for Patient Self Testing/Management versus Usual Care Studies**

| Study | Mean % Time within therapeutic range | | Mean % INR values within therapeutic range | | INR variability (method) | |
|---|---|---|---|---|---|---|
| | Intervention | Control | Intervention | Control | Intervention | Control |
| ***Short-term (<12 months) randomized, controlled trials*** | | | | | | |
| Sawicki 1999[20] | --- | --- | --- | --- | 0.65±1.04* (mean squared INR deviation) | 0.83±0.95 |
| Beyth 2000[18] | 56§ | 32 | --- | --- | --- | --- |
| Cromheecke 2000[19] | --- | --- | 55†, § | 49 | 0.1±0.2‡ (mean difference) | 0.12±0.22 |
| Fitzmaurice 2002[22] | 74‡ (95% CI 67-81) | 77 (95% CI 67-86) | 66‡ (95% CI 61-71) | 72 (95% CI 65-80) | --- | --- |
| Gadisseur 2003[23] & 2004[24] | *PST:* 66.9† (95% CI 62.7-71) *PSM:* 68.6† (95% CI 63.7-73.6) | *PC/Ed:* 67.9 (95% CI 62.9-73) *PC:* 63.5 (95% CI 59.7-67.3) | *PST:* 63.9† (95% CI 59.8-68) *PSM:* 66.3† (95% CI 61-71.5) | *PC/Ed:* 61.3 (95% CI 55.4-67.1) *PC:* 58.7 (95% CI 55-62.4) | --- | --- |
| Khan 2004[25] | 71.1‡ (SD 14.5) | *PC/Ed:* 70.4 (SD 24.5) *PC:* 63.2 (SD 25.9) | --- | --- | --- | --- |
| Sunderji 2004[19] | 71.8† (SEM 5.5) | 63.2 (SEM 5.8) | 64.8† (SEM 5.8) | 58.7 (SEM 5.9) | --- | --- |
| Gardiner 2005[36] | 61‡ (SD 20, range 24-96) | 64 (SD 26, range 7-100) | --- | --- | --- | --- |
| Voeller 2005[27] | --- | --- | 67.8* (SD 17.6) | 58.5 (SD 19.8) | --- | --- |
| Christensen 2006[28] & 2007[29] | 78.7 (median)† (95% CI 69.2-81) | 68.9 (median) (95% CI 59.3-78.2) | --- | --- | --- | --- |

| | | | | | | |
|---|---|---|---|---|---|---|
| Gardiner 2006[30] | *PST:* 71.8† (95% CI 64.9-80.1, IQR 22.1) *PSM:* 69.9† (95% CI 60.8-76.7, IQR 23.1) | --- | --- | --- | --- | --- |
| Dauphin 2008[31] | 57† (SD 19) | 53 (SD 19) | | | 41.1±39.3* (mean deviation) | 62.4±72.6 |
| Ryan 2009[32] | 74 (median) (p<0.001) | 58.6 (median) | 87.4 | 78.2 | --- | --- |
| ***Long-term (≥12 months) randomized, controlled trials*** | | | | | | |
| Horstkotte 1998[33,34] | --- | --- | 43.2‡, § | 22.3 | --- | --- |
| Koertke 2001[35,36] & 2007[37] | --- | --- | 78.3*, § | 60.5 | --- | --- |
| Sidhu 2001[38] | 76.5*, § | 63.8 | --- | --- | --- | --- |
| Fitzmaurice 2005[39] & Jowett 2006[40] | 70† (95% CI 68.1-72.4) | 68 (95% CI 65.2-70.6) | --- | --- | --- | --- |
| Menendez-Jandula 2005[41] | 64.3† (SD 14.3) | 64.9 (SD 19.9) | 58.6* (SD 14.3) | 55.6 (SD 19.6) | 0.58±0.18† (INR distance) | 0.59±0.27 |
| Siebenhofer 2007[42] & 2008[43] | 73.4 (median)* (IQR 64.7-82) | 65.5 (median) (IQR 55.4-77.2) | 68.4 (median)* (IQR 61.5-77.8) | 59.1 (median) (IQR 50-70.6) | 0.16*(IQR 0.09-0.25) (squared INR deviation) | 0.23 (IQR 0.16-0.36) |
| Eitz 2008[44] | --- | --- | 79*, § | 65 | 0.35*, § (mean variance) | 0.39 |
| Soliman Hamad 2009[45] | --- | --- | 72.9 (SD 11) (p=0.001) | 53.9 (SD 14) | --- | --- |
| Matchar 2010[17] | **66.2 (SD 14.2)** | **62.4 (SD 17.1)** | **---** | **---** | **---** | **---** |

* p<0.05 † p>0.05 ‡ p value not reported § range or deviation not reported

CI = confidence interval IQR = interquartile range (25-75%) PC = primary care PC/Ed = primary care with education
PSM = patient self-management PST = patient self-testing SD = standard deviation SEM = standard error of the mean

**Table 10. Percentage of Time within Therapeutic Range for Patient Self Testing/Management versus Usual Care Studies***

| Study | PST/PSM group | Standard care group |
|---|---|---|
| ***Short-term studies (<12 months)*** | | |
| Beyth 2000[18] (n=325) | 56 | 32 |
| Fitzmaurice 2002[22] (n=49) | 74 | 77 |
| Gladisseur 2003[23] (n=320) | *PST* 66.9 | *PC/Ed*** 67.9 |
| | *PSM* 68.6 | *PC* 63.5 |
| Khan 2004[25] (n=79) | 71.1 | 70.4 |
| Sunderji 2004[19] (n=139) | 71.8 | 63.2 |
| Gardiner 2005[26] (n=88) | 61 | 64 |
| Dauphin 2008[31] (n=67) | 57 | 53 |
| ***Long-term studies (≥12 months)*** | | |
| Sidhu 2001[38] (n=84) | 76.5 | 63.8 |
| Fitzmaurice 2005[39] (n=617) | 70 | 68 |
| Menedez-Jandula 2005[41] (n=737) | 64.3 | 64.9 |
| Matchar 2010[17] (n=2870) | 66.2 | 62.4 |
| **Pooled weighted mean (range)** | **66.1 (56 to 76.5)** | **61.9 (32 to 77)** |

*Includes only studies that reported *mean* percentage of time
**PC = primary care; PC/Ed = primary care with education

**Table 11. Percentage of INR Values within Therapeutic Range for Patient Self Testing/Management versus Usual Care Studies***

| Study | PST/PSM group | Standard care group |
|---|---|---|
| ***Short-term studies (<12 months)*** | | |
| Cromheecke 2000[21] (n=50) | 55 | 49 |
| Fitzmaurice 2002[22] (n=49) | 66 | 72 |
| Gladisseur 2003[23] (n=320) | *PST* 63.9 | *PC/Ed*** 61.3 |
| | *PSM* 66.3 | *PC* 58.7 |
| Sunderji 2004[19] (n=139) | 64.8 | 58.7 |
| Voeller 2005[27] (n=202) | 67.8 | 58.5 |
| Ryan 2009[32] (n=132) | 87.4*** | 78.2*** |
| ***Long-term studies (≥12 months)*** | | |
| Horstkotte 1998[34] (n=150) | 43.2 | 22.3 |
| Koertke 2001[35,36] (n=575) | 78.3 | 60.5 |
| Menedez-Jandula 2005[41] (n=737) | 58.6 | 55.6 |
| Eitz 2008[44] (n=765) | 79 | 65 |
| Soliman Hamad 2009[45] (n=62) | 72.9 | 53.9 |
| **Pooled weighted mean (range)** | **70.5 (43.2 to 87.4)** | **59.3 (22.3 to 78.2)** |

*Includes only studies that reported *mean* percentage of values
**PC = primary care; PC/Ed = primary care with education
***Within 0.75 units of INR of the target INR

**Figure 6. Methodological Quality Summary, Patient Self Testing/Management Studies versus Usual Care Studies**

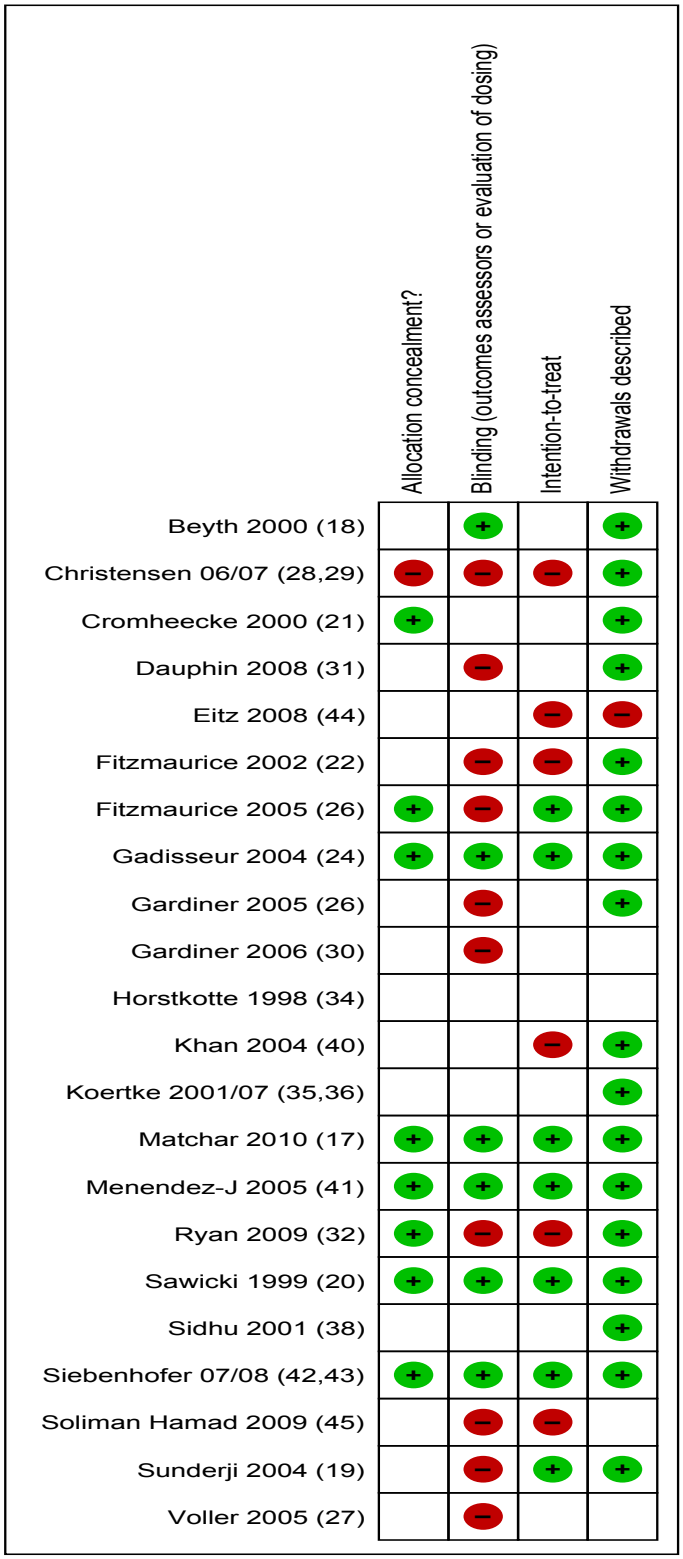


**Figure 7. All-cause Mortality, Patient Self Testing/Management versus Usual Care Studies**

| Study or Subgroup | Patient Self-Testing/Management Events | Total | Usual Care Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.1.1 Short-term trials (<12 months)** | | | | | | |
| Beyth 2000 (18) | 21 | 163 | 26 | 162 | 7.2% | 0.77 [0.42, 1.44] |
| Christensen 2007 (29) | 1 | 50 | 0 | 50 | 0.2% | 7.39 [0.15, 372.38] |
| Dauphin 2008 (31) | 1 | 33 | 0 | 34 | 0.2% | 7.62 [0.15, 384.01] |
| Fitzmaurice 2002 (22) | 0 | 30 | 1 | 26 | 0.2% | 0.12 [0.00, 5.91] |
| Gardiner 2005 (26) | 1 | 44 | 0 | 40 | 0.2% | 6.75 [0.13, 341.54] |
| Sawicki 1999 (20) | 1 | 90 | 1 | 89 | 0.4% | 0.99 [0.06, 15.93] |
| Sunderji 2004 (19) | 0 | 70 | 0 | 70 | | Not estimable |
| Voller 2005 (27) | 0 | 101 | 0 | 101 | | Not estimable |
| **Subtotal (95% CI)** | | **581** | | **572** | **8.2%** | **0.87 [0.49, 1.55]** |
| Total events | 25 | | 28 | | | |
| Heterogeneity: Chi² = 4.52, df = 5 (P = 0.48); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.48 (P = 0.63) | | | | | | |
| **2.1.2 Long-term trials (≥12 months)** | | | | | | |
| Fitzmaurice 2005 (39) | 5 | 337 | 11 | 280 | 2.7% | 0.38 [0.14, 1.03] |
| Koertke 2007 (37) | 94 | 488 | 142 | 442 | 31.2% | 0.51 [0.38, 0.68] |
| Matchar 2010 (17) | 152 | 1465 | 157 | 1457 | 49.1% | 0.96 [0.76, 1.21] |
| Menendez-Jand. 2005 (41) | 6 | 368 | 15 | 369 | 3.6% | 0.42 [0.17, 0.99] |
| Sidhu 2001 (38) | 0 | 51 | 4 | 49 | 0.7% | 0.12 [0.02, 0.89] |
| Siebenhofer 2008 (43) | 15 | 99 | 11 | 96 | 4.0% | 1.37 [0.60, 3.13] |
| Soliman Hamad 2009 (45) | 1 | 29 | 1 | 29 | 0.3% | 1.00 [0.06, 16.39] |
| **Subtotal (95% CI)** | | **2837** | | **2722** | **91.8%** | **0.73 [0.61, 0.86]** |
| Total events | 273 | | 341 | | | |
| Heterogeneity: Chi² = 19.63, df = 6 (P = 0.003); I² = 69% | | | | | | |
| Test for overall effect: Z = 3.63 (P = 0.0003) | | | | | | |
| **Total (95% CI)** | | **3418** | | **3294** | **100.0%** | **0.74 [0.63, 0.87]** |
| Total events | 298 | | 369 | | | |
| Heterogeneity: Chi² = 24.49, df = 12 (P = 0.02); I² = 51% | | | | | | |
| Test for overall effect: Z = 3.61 (P = 0.0003) | | | | | | |
| Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0% | | | | | | |

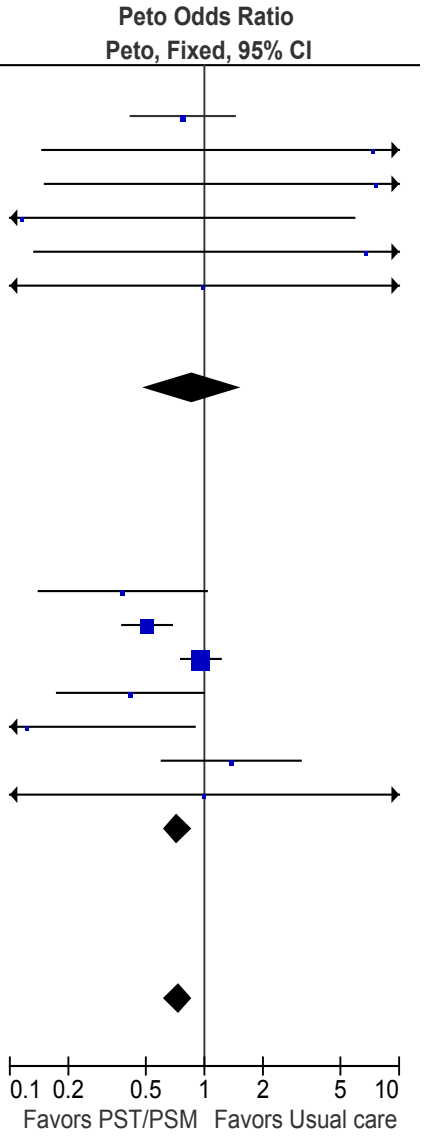


**Figure 8. Major Bleeding Events, Patient Self Testing/Management versus Usual Care Studies**

| Study or Subgroup | Patient Self-Testing/Management Events | Total | Usual Care Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.2.1 Short-term trials (<12 months)** | | | | | | |
| Beyth 2000 (18) | 8 | 163 | 17 | 162 | 4.5% | 0.46 [0.20, 1.03] |
| Cromheecke 2000 (21) | 0 | 50 | 0 | 50 | | Not estimable |
| Dauphin 2008 (31) | 0 | 33 | 4 | 34 | 0.7% | 0.13 [0.02, 0.94] |
| Fitzmaurice 2002 (22) | 0 | 30 | 1 | 26 | 0.2% | 0.12 [0.00, 5.91] |
| Gardiner 2005 (26) | 0 | 44 | 0 | 40 | | Not estimable |
| Khan 2004 (25) | 1 | 44 | 0 | 41 | 0.2% | 6.90 [0.14, 348.69] |
| Ryan 2009 (32) | 0 | 132 | 1 | 132 | 0.2% | 0.14 [0.00, 6.82] |
| Sawicki 1999 (20) | 1 | 90 | 1 | 89 | 0.4% | 0.99 [0.06, 15.93] |
| Sunderji 2004 (19) | 0 | 70 | 1 | 70 | 0.2% | 0.14 [0.00, 6.82] |
| Voller 2005 (27) | 1 | 101 | 0 | 101 | 0.2% | 7.39 [0.15, 372.38] |
| **Subtotal (95% CI)** | | **663** | | **655** | **6.5%** | **0.43 [0.22, 0.85]** |
| Total events | 11 | | 25 | | | |
| Heterogeneity: Chi² = 6.83, df = 7 (P = 0.45); I² = 0% | | | | | | |
| Test for overall effect: Z = 2.43 (P = 0.02) | | | | | | |
| **2.2.2 Long-term trials (≥12 months)** | | | | | | |
| Eitz 2008 (44) | 32 | 470 | 20 | 295 | 8.9% | 1.00 [0.56, 1.79] |
| Fitzmaurice 2005 (39) | 5 | 337 | 4 | 280 | 1.7% | 1.04 [0.28, 3.89] |
| Koertke 2001 (35,36) | 42 | 579 | 34 | 576 | 13.7% | 1.25 [0.78, 1.98] |
| Matchar 2010 (17) | 180 | 1465 | 199 | 1457 | 63.6% | 0.89 [0.71, 1.10] |
| Menendez-Jand. 2005 (41) | 4 | 368 | 7 | 369 | 2.1% | 0.58 [0.18, 1.90] |
| Sidhu 2001 (38) | 1 | 51 | 0 | 49 | 0.2% | 7.10 [0.14, 358.35] |
| Siebenhofer 2008 (43) | 7 | 99 | 10 | 96 | 3.0% | 0.66 [0.24, 1.78] |
| Soliman Hamad 2009 (45) | 1 | 29 | 1 | 29 | 0.4% | 1.00 [0.06, 16.39] |
| **Subtotal (95% CI)** | | **3398** | | **3151** | **93.5%** | **0.93 [0.78, 1.11]** |
| Total events | 272 | | 275 | | | |
| Heterogeneity: Chi² = 3.93, df = 7 (P = 0.79); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.78 (P = 0.43) | | | | | | |
| **Total (95% CI)** | | **4061** | | **3806** | **100.0%** | **0.89 [0.75, 1.05]** |
| Total events | 283 | | 300 | | | |
| Heterogeneity: Chi² = 15.36, df = 15 (P = 0.43); I² = 2% | | | | | | |
| Test for overall effect: Z = 1.38 (P = 0.17) | | | | | | |
| Test for subgroup differences: Chi² = 4.60, df = 1 (P = 0.03), I² = 78.3% | | | | | | |

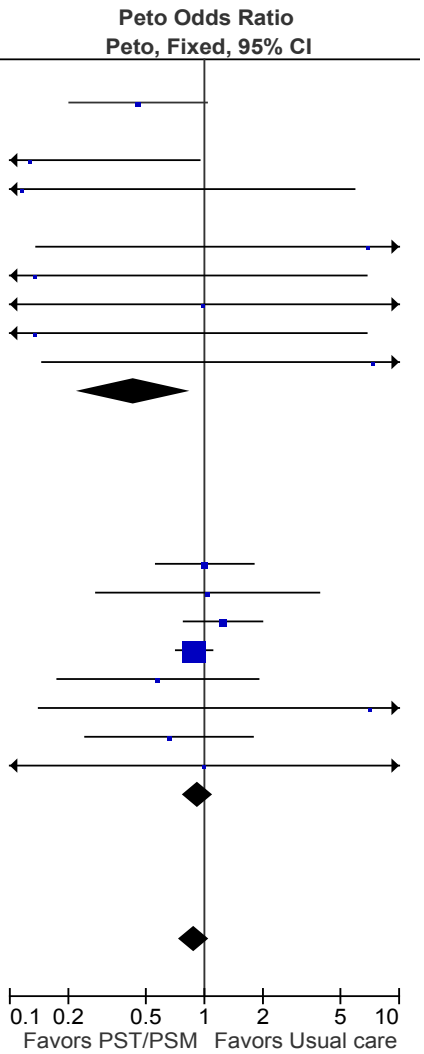


**Figure 9. Major Thromboembolic Events, Patient Self Testing/Management versus Usual Care Studies**

| Study or Subgroup | Patient Self-Testing/Management Events | Total | Usual Care Events | Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.3.1 Short-term trials (<12 months)** | | | | | | |
| Beyth 2000 (18) | 14 | 163 | 21 | 162 | 13.6% | 0.64 [0.32, 1.28] |
| Cromheecke 2000 (21) | 0 | 50 | 1 | 50 | 0.4% | 0.14 [0.00, 6.82] |
| Dauphin 2008 (31) | 0 | 33 | 0 | 34 | | Not estimable |
| Fitzmaurice 2002 (22) | 0 | 30 | 0 | 26 | | Not estimable |
| Gadisseur 2003 (23) | 0 | 99 | 0 | 221 | | Not estimable |
| Gardiner 2005 (26) | 0 | 44 | 0 | 40 | | Not estimable |
| Khan 2004 (25) | 0 | 44 | 0 | 41 | | Not estimable |
| Ryan 2009 (32) | 2 | 132 | 1 | 132 | 1.3% | 1.96 [0.20, 18.98] |
| Sawicki 1999 (20) | 1 | 90 | 2 | 89 | 1.3% | 0.50 [0.05, 4.91] |
| Sunderji 2004 (19) | 0 | 70 | 2 | 70 | 0.9% | 0.13 [0.01, 2.15] |
| Voller 2005 (27) | 0 | 101 | 1 | 101 | 0.4% | 0.14 [0.00, 6.82] |
| **Subtotal (95% CI)** | | **856** | | **966** | **17.9%** | **0.58 [0.32, 1.07]** |
| Total events | 17 | | 28 | | | |
| Heterogeneity: Chi² = 3.31, df = 5 (P = 0.65); I² = 0% | | | | | | |
| Test for overall effect: Z = 1.73 (P = 0.08) | | | | | | |
| **2.3.2 Long-term trials (≥12 months)** | | | | | | |
| Eitz 2008 (44) | 14 | 470 | 21 | 295 | 13.7% | 0.39 [0.19, 0.78] |
| Fitzmaurice 2005 (39) | 4 | 337 | 3 | 280 | 3.0% | 1.11 [0.25, 4.94] |
| Koertke 2001 (35,36) | 16 | 579 | 32 | 576 | 19.9% | 0.50 [0.28, 0.88] |
| Matchar 2010 (17) | 33 | 1465 | 31 | 1457 | 27.1% | 1.06 [0.65, 1.74] |
| Menendez-Jand. 2005 (41) | 4 | 368 | 20 | 369 | 10.1% | 0.25 [0.11, 0.57] |
| Sidhu 2001 (38) | 1 | 51 | 0 | 49 | 0.4% | 7.10 [0.14, 358.35] |
| Siebenhofer 2008 (43) | 6 | 99 | 13 | 96 | 7.5% | 0.43 [0.17, 1.10] |
| Soliman Hamad 2009 (45) | 0 | 29 | 1 | 29 | 0.4% | 0.14 [0.00, 6.82] |
| **Subtotal (95% CI)** | | **3398** | | **3151** | **82.1%** | **0.58 [0.43, 0.77]** |
| Total events | 78 | | 121 | | | |
| Heterogeneity: Chi² = 14.46, df = 7 (P = 0.04); I² = 52% | | | | | | |
| Test for overall effect: Z = 3.79 (P = 0.0001) | | | | | | |
| **Total (95% CI)** | | **4254** | | **4117** | **100.0%** | **0.58 [0.45, 0.75]** |
| Total events | 95 | | 149 | | | |
| Heterogeneity: Chi² = 17.77, df = 13 (P = 0.17); I² = 27% | | | | | | |
| Test for overall effect: Z = 4.17 (P < 0.0001) | | | | | | |
| Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0% | | | | | | |

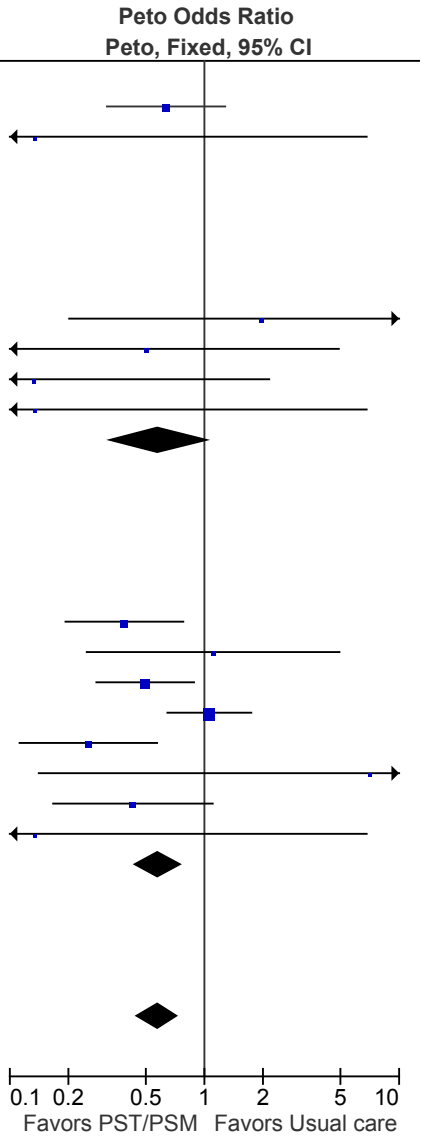


**Figure 10. Percent Time in Therapeutic Range for Patient Self Testing/Management versus Usual Care Studies**

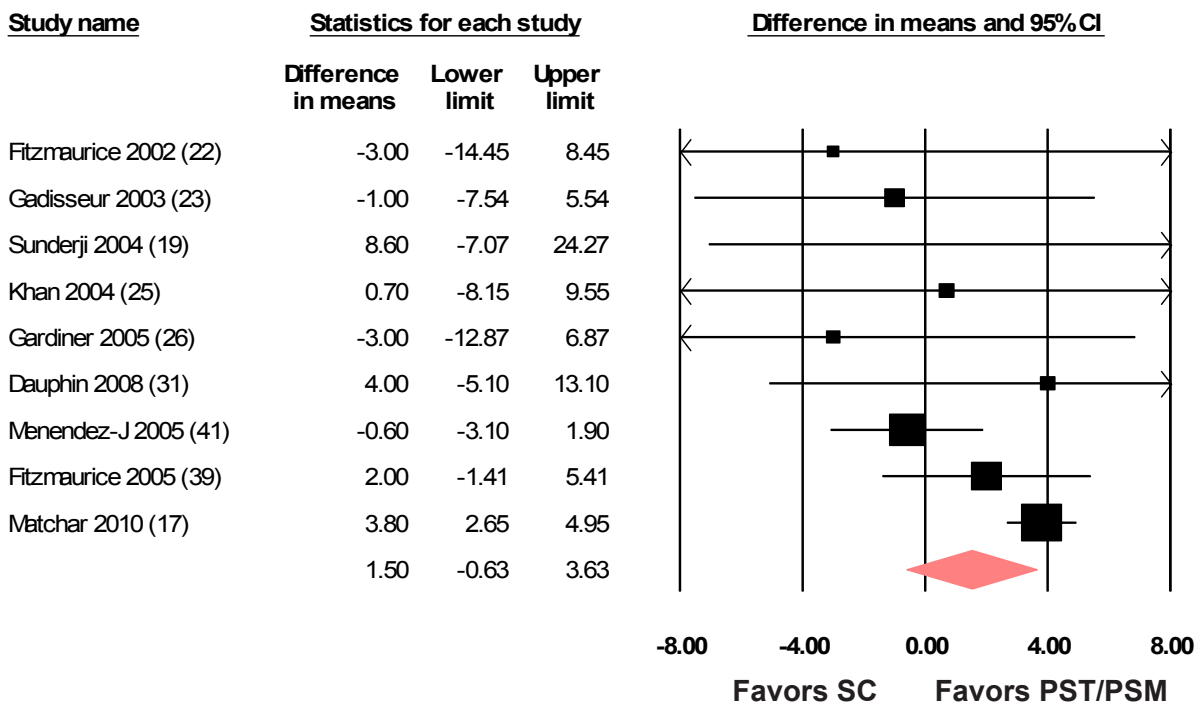
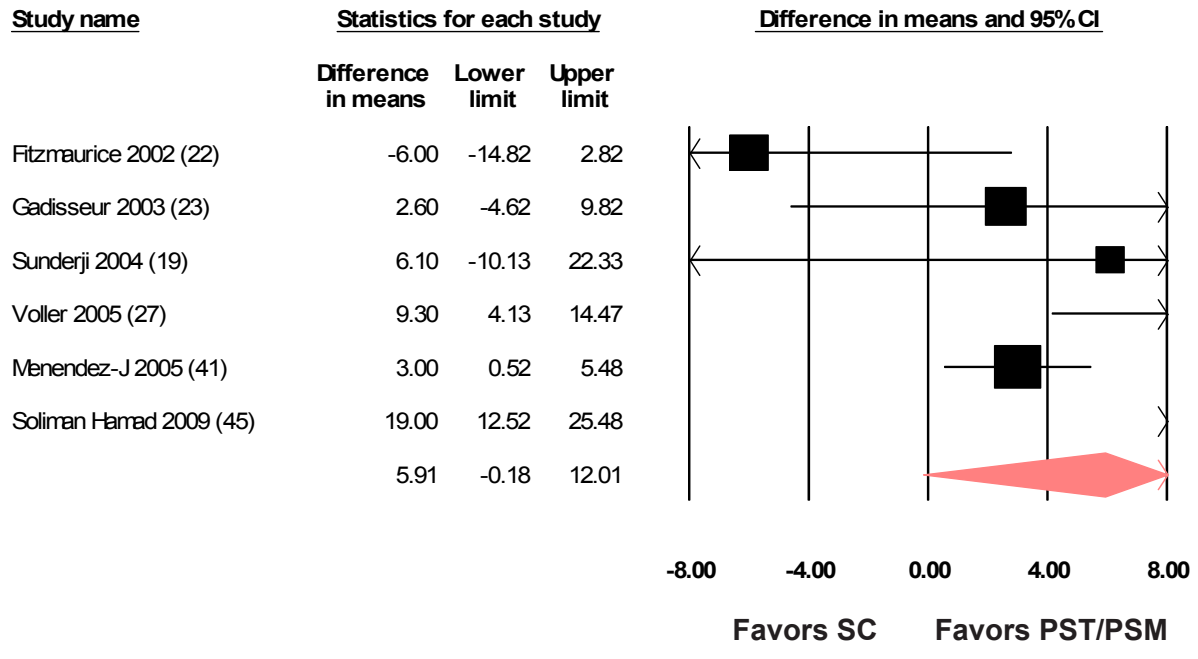



**Figure 11. Percent of INRs within Therapeutic Range for Patient Self Testing/Management versus Usual Care Studies**



# KEY QUESTION 3

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

## Literature Search

Using the search strategy shown in the Methods section, we looked for studies published in English after 1996 in peer reviewed journals. We included studies that provided rates of serious bleeding events in populations who were on warfarin therapy. The rates of serious bleeding needed to either be presented by strata of risk factors (e.g., 1% in people less than 50 years and 1.4% in people over 50 years of age) or using a ratio of risk such as an odds ratio, relative risk or hazards ratio (e.g., HR=1.4 for people over age 50 compared to people under age 50). We excluded studies that did not report at least 25 cases of serious bleeding, since the precision for estimated risk among small studies is limited and observational studies such as those identified in this report are too heterogeneous to pool for formal meta-analysis. We excluded reports that dealt with inpatients, pediatric populations, or non-warfarin anticoagulation. As shown in Figure 4, we screened 681 titles/abstracts and selected 78 for full article review. Of these, we identified a total of 32 articles reporting on 33 distinct studies.[48-79] We also identified three additional articles by hand-searching references cited.[80-82]

## Overview of Included Studies

An overview of the 35 included articles is shown in Appendix B, Table 5. These 35 articles represent 35 unique studies (several studies were reported in multiple articles, 1 article included a development and validation cohort, a series of articles reported on the warfarin arm of two randomized controlled trials, and 1 article reported a meta-analysis of 6 randomized trials). There were three multinational studies, 17 US studies (including 3 studies with a substantial VA population). Study designs included: meta-analyses, RCTs of additional drugs combined with warfarin, warfarin arms of RCTs analyzed as prospective cohort studies, observational retrospective/prospective cohort studies, case-control studies, and case-control studies nested in cohort studies. Within these different study designs various analytical methods were used, ranging from simply reporting frequencies of serious bleeding events by strata of a risk factor to using multivariable models to estimate the independent effect of a risk factor after accounting for many other potential risk factors and follow-up time. Average follow-up times ranged from slightly less than a year to 5 years, with most studies reporting follow-up periods of 1 to 2 years.

## 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 and 56 controls to a large administrative database study of Medicare records that included 353,489 patients. Since any averages of patient characteristics by study 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. The distribution of gender represented in the studies varied widely with a maximum of 98.5% male to a minimum of 23% male.

## Predictors of Serious Bleeding

Of the 35 articles we identified 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 below in a narrative format. All of the quantitative results extracted from the 35 studies are presented in Appendix B, Table 5. The risk factors reported in each study are displayed in Table 12.

### *Age*

Overall, there is evidence that older age is associated with increased risk of serious bleeding in patients on warfarin. The evidence is not completely consistent across studies and also tends to suggest that the association is not linear in that the difference in risk between a 40 and 60 year old is likely not the same as the difference in risk between a 60 and 80 year old.

Sixteen articles from 14 unique studies reported results regarding the impact of increased age on the risk of serious bleeding events in people on warfarin therapy.[48-52,58,61,62,63,65,66,72,74,76,77,79] Increased age was typically found to be associated with increased bleeding risk;[48,48,51,58,62,63,66,76,77,79] however several studies failed to show a significant association between increased age and increased risk of serious bleeding events.[50,52,61,72,74] Furthermore, in the studies that did show a significant age association, the magnitude of the association differed substantially between studies. The amount of increased bleeding attributable to increased age ranged from a few studies reporting several fold higher rates of bleeding events in the oldest age groups (i.e., those over 80) compared to people in their 50s to 60s, while most other studies reported more modest to completely null associations. This suggests that the association between patient age and bleeding is likely complex and dependent on other factors that act as either confounders or effect modifiers. Another difference between studies related to the format in which age was modeled. In some studies results were reported from multivariable adjusted models based estimates of a one year increase in age, while others used dichotomous comparisons of differences above and below an age cut point (e.g., above versus below age 65). Still others simply reported unadjusted rates of bleeding across several age categories.

### *Gender*

Overall, in the studies we identified, gender was not strongly associated with the rate of serious bleeding. Only nine articles reported results regarding the impact of gender on the risk of serious bleeding events in people on warfarin therapy.[48,50,52,59,61,65,66,72,77] Among the studies that reported results by gender, most failed to observe a significant association between gender and risk of serious bleeding.[48,52,59,61,65,77] In a large U.S. study using administrative data, men and women had similar rates of overall hemorrhage (RR: 1.25, 95%CI; 0.91–1.67), but men had a two-fold risk of intracranial hemorrhage (RR: 2.0, 95%CI; 1.11–3.33).[59] Likewise data from two large trials show that the rate of major bleeding on warfarin was not significantly different between men and women (p=0.49) with men having 0.35% more events per year (a non-significant relative difference of approximately 14%).[65] One study from Sweden found men had a 2.8 fold higher rate of severe hemorrhage (95%CI: 1.1-7.3).[72] Conversely, one U.S. study identified a small, but statistically significant increased risk of major bleeding in women.[66] This study was used to develop the bleeding risk index (mentioned below), and this is the one index that incorporates female gender as a predictor of bleeding risk.

### *Aspirin, NSAIDs, and other Medication Use*

Aspirin use has been associated with increased risk of bleeding in patients on warfarin and the relative increase in risk is likely greater than two-fold. Aspirin is the only predictor we investigated for which we identified evidence from randomized controlled trials. A meta-analysis of six RCTs including 3,874 participants, in which 31 cases of intracranial hemorrhage developed, showed a 2.4 fold increased risk (95%CI; 1.2-4.8) among those randomized to aspirin plus warfarin compared to those randomized to only warfarin.[53]

When data are available from randomized trials the value of nonrandomized data is reduced. This is particularly true for drugs where confounding by indication can occur, such that it is difficult to untangle whether it is the drug or the indication for taking the drug that might predispose someone to a higher risk of events. Data from studies that did not randomize patients to aspirin but still compared rates of bleeding by reported aspirin use have also consistently reported increased bleeding in those taking aspirin and the increase has tended to be close to a doubling of the risk of serious bleeding events.[58,60,62,64,70]

The evidence for an increased risk of serious bleeding is not as strong for other medications. NSAIDs have been reported, from observational studies, to be associated with increased risks of serious bleeding events, but these risks are generally weaker in magnitude (less than two-fold increased risk) and less consistently reported than the results from studies of aspirin.[45,52,57,74] We found no randomized controlled trials confirming the association of NSAIDs with serious bleeding events.

In the studies we identified, few other medications were regularly reported with serious bleeding outcomes. A study by Gasse et al. listed several medications which were associated with increased risks of bleeding among patients taking their first ever dose of warfarin.[60] Several medications were associated with increased risk of bleeding some of which were associated with very high risks of bleeding (see Appendix B, Table 5), but most of these medications were either not reported or not assessed in the other studies we identified.

### *Warfarin Duration*

Serious bleeding events tend to occur most frequently during the initiation of warfarin therapy.[51,62,63,72] Among the studies that reported the rate of serious bleeding by the duration of time on warfarin, the most commonly reported first interval was events at 1 month and then typically the rate at 12 months and possibly later was also reported. Only one study reported similar rates of bleeding events during the first month compared to all other months.[74] This same study also found no difference in bleeding rates between new users and chronic warfarin users. All four of the studies showed initial bleeding rates that were two to three times higher in the first one to three months compared to the rest of follow-up. The absolute magnitude of bleeding during the first month varied substantially in magnitude possibly due to differences in the study population and definition of serious bleeding. However there was a clear trend for decreasing rate of bleeding events after the initial few months of warfarin treatment.

INR — We identified only two studies that reported serious bleeding events by INR variability.[81,82] Both studies reported that increased INR variability was associated with an increase in the risk of serious bleeding. However, in one study the impact of INR variability was

only seen among people who spent the greatest amount of time outside of the INR target range of 2.5-4.0.[82]

### *Primary Indication*

We identified only two studies that reported serious bleeding events by the primary indication for taking warfarin.[50,74] Both studies reported that patients taking warfarin because of valve conditions were at significantly increased risk of bleeding compared to other patients. While this may have little impact for patient care since it is not modifiable, it is a relevant factor to consider when evaluating the overall bleeding risk of a population on warfarin.

### *Genetic Factors*

Several recent articles have attempted to predict risk of serious bleeding events using genetic polymorphisms in two genes (CYP2C9 and VKORC1).[54,71,73] These articles represent two unique studies including approximately 631 patients and 75 cases of serious bleeding. Both studies reported participants with variant CYP2C9 genotypes having a roughly three-fold greater rate of serious bleeding events compared to those with the CYP2C9 wild type genotype.[54,71,73] The association between the VKORC1 genotypes and serious bleeding was not significant in either study.[71,73]

### *Co-morbidity*

Twelve studies reported on various co-morbidities and their associations with increased risk of serious bleeding events.[48,50,51,52,55,57,61,62,66,75,79,81] There was not a consistent set of co-morbidities that was reported in the studies we indentified, such that the significance of reported associations may be due, in part, to publication bias; the co-morbidities most strongly associated with events might have been more likely to have been reported. The following factors were all associated with bleeding in at least one of the studies: diabetes, kidney impairment, alcohol abuse, history of GI bleeds, prior stroke, hypertension, psychiatric illness, liver disease, anemia, leukoaraiosis (an age-related change in cerebral white matter), congestive heart failure, cancer, and venous thrombosis. Estimating the actual magnitude of each of these conditions' associations with serious bleeding is beyond the scope of this project and would be difficult given the available data. Particularly important to the task of estimating the impact of these conditions would be untangling the intensity of warfarin therapy and other potential confounding factors that might be mediating the associations with serious bleeding events.

### *Risk Indices*

Several bleeding risk indices are currently available for stratifying patients into "low" and "high" risk groups. We identified seven articles[51,56,66,68,69,78,80] that estimated the risk of serious bleeding events in people on warfarin therapy using one or more of nine different risk indices (OBRI,[51] Shireman,[66] Kuijier,[83] AFI, ACCP, $CHADS_2$,[84] HEMORR2HAGES,[80] Kearon, NICE). Typically, these risk indices place patients into low, intermediate and high risk groups using several risk factors. Four of the risk indices (AFI, ACCP, $CHADS_2$, NICE)[78] were developed to predict risk of stroke, but also provided some evidence about whether or not they also predicted risk of serious bleeding complications. The stroke risk models appeared to be inferior to the bleeding risk models and likely only provide value for risk stratifying in studies that only have the stroke risk indices measured. Therefore, while the results from the stroke models are included in Appendix

B, Table 5, we will focus on the indices developed specifically for bleeding risk.

All of the risk indices included a categorical indicator of age as a component, but they differed in the age cut point with the age ≥60 used by the Kuijers risk index while others used ≥65, ≥70, ≥75, or a two level indicator with some increased risk at ≥65 and more risk ≥75. All of the indices included some increased risk for comorbidities. The comorbidities varied, particularly between the models that were designed specifically to predict stroke versus those designed to predict bleeding. The bleeding models tended to include some marker of prior history of bleeding events while the stroke models focused more on hypertension, history of stroke or TIA, or other vascular diseases. Most included diabetes mellitus as a risk factor and two of three bleeding models included female gender as a risk factor.[66,83]

Risk indices are difficult to compare across different studies. Two articles did however show head-to-head comparisons of different bleeding risk indices within the same study.[66,80] All of the bleeding risk indices were able to separate out groups of people with lower average risks of bleeding from those with higher risks of bleeding. 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. Likewise if age is an important factor in risk stratifying patients, using a tool with an age cut-off at age 65 for the higher risk group will not be very useful in a population where most of the patients are in their 70s or 80s.

Overall, while there have not been a lot of confirmatory studies of individual risk indices, bleeding risk indices were generally successful to some extent in stratifying patients into different risk groups. The choice of risk index might depend in part on the overall risk profile of the patient population (i.e., if many are well over age 65 then indices with older age cut-points might be more useful) and the availability of risk factor information (i.e., information on genotype status and level of detail on prior medical history).

## SUMMARY – KEY QUESTION 3

Several individual risk factors (including very old age, initial warfarin use, INR variability, concomitant medications, comorbid conditions, mechanical heart valve, genetics) and combinations of risk factors (risk indices) can be used to define low and high risk groups for serious bleeding with warfarin use. However, due to the heterogeneity of studies (populations, risk factors assessed, risk factor definitions, etc.), it is difficult to reach definitive conclusions about the value of risk factor assessment.

## Table 12. Risk Factors for Serious Bleeding Reported in the Individual Studies

| Article | Age | Gender | Warfarin Duration | INR | Primary Indication | Asprin/ NSAID | Other Meds | Risk Index | Genetics | Co-morbidity | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Aspinall 2005[56] | | | | | | | | √ | | | |
| Battistella 2005[57] | | | | | | √ | √ | | | | |
| Beyth 1998[51] | √ | | √ | | | | | √ | | √ | |
| Bousser 2008[66] | | | | | | | | √ | | | |
| DiMarco 2005[58] | √ | | | | | √ | | | | √ | |
| Douketis 2006[62] | √ | | √ | | | √ | √ | | | √ | |
| Douketis 2007[67] | | | | | | | √ | | | | |
| Fang 2005[59] | | √ | | | | | | | | | |
| Fang 2006[64] | √ | | √ | | | | | | | | |
| Fihn 1996[49] | √ | | | | | | | | | | |
| Flaker 2006[63] | | | | | | √ | | | | | |
| Gage 2006[80] | | | | | | | | √ | | | |
| Gasse 2005[60] | | | | | | √ | √ | | | | |
| Gomberg-M 2006[65] | √ | √ | | | | | | | | | |
| Hart 1999[53] | | | | | | √ | | | | | |
| Healey 2008[69] | | | | | | | | √ | | | |
| Higashi 2002[54] | | | | | | | | | √ | | |
| Johnson 2008[70] | | | | | | √ | √ | | | | |
| Le Tourneau 2009[81] | | | | √ | | | | | | √ | |
| Limdi 2008[71] | | | | | | | | | √ | | |
| Limdi 2009[75] | | | | | | | | | | √ | |
| Lind 2009[77] | √ | √ | | | | | | | | | √ |
| Lindh 2008[72] | √ | √ | √ | | | | √ | | | | √ |
| McMahan 1998[52] | √ | √ | | | | √ | √ | | | √ | √ |
| Meckley 2008[73] | | | | | | | | | √ | | |
| Metlay 2008[74] | √ | | √ | | √ | √ | √ | | | | √ |
| Poli 2009b[78] | | | | | | | | √ | | | |
| Poli 2009a[76] | √ | | | | | | | | | | |
| Schauer 2005[61] | √ | √ | | | | | | | | √ | √ |
| Schelleman 2010[79] | √ | | | | | | √ | | | √ | |
| Shireman 2006[66] | √ | √ | | | | | √ | √ | | √ | √ |
| Smith 2002[55] | | | | | | | | | | √ | |
| SPAF 1996[48] | √ | √ | | | | √ | √ | | | √ | √ |
| Van Leeuwen 2008[82] | | | | √ | | | | | | | |
| White 1996[50] | √ | √ | | | √ | √ | | | | √ | √ |
| **TOTAL (35)** | 16 | 9 | 5 | 2 | 2 | 11 | 11 | 7 | 3 | 12 | 8 |

# DISCUSSION AND RECOMMENDATIONS

## 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)?*

### Major Clinical Outcomes

The literature available to address this question is limited. We were able to identify 11 studies, of which only 3 were RCTs.[6,7,8] Except for one study,[14] major clinical outcomes occurred more frequently in the control than the intervention group (Table 3b). However, pooled results from the 3 RCTS showed no significant differences between ACC and UC for deaths, thromboembolic events, or major bleeding. Pooling of the observational studies' results was not possible due to heterogeneity among studies in reported outcome metrics.

### Time in Therapeutic Range

All 9 studies that reported this metric (or the related metric, % INRs within therapeutic range) found that subjects receiving care in an ACC spent more time within the therapeutic range than those who received usual care.[6-8,10-14,16] In 4 studies the difference was statistically significant.[7,10,12,14] In the RCTs, the pooled weighted means were only slightly higher for ACC than UC (59.9% v.56.3%). In the observational studies, there was a larger spread with ACC patients spending 63.5% of the time in therapeutic range compared to 53.5% for subjects in usual care.

### Patient Satisfaction

Measured in 2 of the RCTs, patient satisfaction was found to be significantly higher in patients randomized to the ACC intervention than to UC.[6,7]

### Other Reviews

The 2008 ACCP guidelines on *Pharmacology and Management of the Vitamin K Antagonists*[1] included a narrative review of 9 uncontrolled studies, 3 cohort studies, and 2 RCTs. The authors concluded that *"although the literature … is not as robust as one would like, and there is great heterogeneity between studies, the results are almost always consistent, indicating that care provided by an anticoagulation management service results in better outcomes or more stable therapy than UC*" (p 184s[1]). Similarly a systematic review and meta-regression published in 2006[85] found that care provided in community settings resulted in significantly worse anticoagulation control (as measured by TTR) than that provided within ACCs (or within clinical trials). This review included studies of any design as long as the report included original data measuring serial INRs in at least one patient group. A third review and meta-analysis of 36 studies of patients with atrial fibrillation found that significantly more time was spent within the therapeutic range when patients were cared for in organized settings (i.e., ACCs) as compared with usual care.[86] Finally, a very recent meta-analysis investigated the effect of study-level factors (e.g., study design, year of publication, INR interpolation method) on time in therapeutic range and reported that patients managed in ACCs spent significantly more time within the therapeutic range than those managed in usual care.[87] None of these reviews evaluated clinical outcomes.

## KEY QUESTION 1A

*Which components of a specialized anticoagulation clinic are associated with effectiveness/safety?*

None of the included studies reported the association between specific elements of ACC and outcomes. Some possible processes of care that might have accounted for observed differences in outcomes in these studies included use of both face-to face and telephone interactions with patients;[13] use of a computerized patient monitoring system that identified patients who were delinquent in returning for timely INR determinations;[12] the specialized expertise of the ACC staff;[12] more consistency in ACCs in obtaining regular INRs;[11] and frequency of face-to-face consultations, methods of dosage adjustment, and provision of written dosage instructions.[16]

## CONCLUSION AND RECOMMENDATIONS FOR KQ1

The evidence suggests that care provided within ACCs *may* lead to better quality anticoagulation control as measured by time in therapeutic range (a surrogate outcome that has been correlated with clinical events),[50] but 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. Patients reported that they liked the convenience and enhanced service provided by ACCs. There is insufficient evidence for the VA to actively promote the implementation of ACCs. Other organizations have suggested greater benefits with ACCs; future research should include cost and resource utilization outcomes along with clinical outcomes and patient satisfaction measures. Future research should also address whether the benefits from ACC are restricted to the initiation of anticoagulation (a high risk period) or also continue through the maintenance phase.

## 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?

This analysis of 22 randomized, controlled trials (RCTs) indicates that for selected patients, oral anticoagulation therapy delivered through a PST/PSM model results in superior patient outcomes compared with oral anticoagulation therapy delivered through usual clinic based models. Patients randomized to PST/PSM, had a significant 26% lower risk of death and a significant 42% reduction in major thromboembolism without any increased risk of major bleeding events. We included between 4-12 more trials and 3500-5000 more patients than other meta-analyses[2,46,47,88] and to our knowledge we are the first to include the largest trial to date, *The Home INR Study*, a VA cooperative studies trial[17].

The mechanism by which PST/PSM leads to a reduction in thromboembolic events is thought to involve the higher proportion of time spent within the therapeutic range that is achieved with more frequent monitoring and dosage adjustments. This assumption has been predicated on observational data suggesting that the incidence of bleeding and thromboembolism is correlated with the quality of anticoagulation control (i.e., time in therapeutic range or % INR values within therapeutic range).[89-93] The recent VA trial also found a modest but statistically significant

higher percent time within therapeutic range for patients randomized to PST than to usual care (absolute difference 3.8 percentage points).[17] Our study did not confirm this association, possibly because our analysis, which included the largest number of trials to-date, was limited to RCTs whereas other reports were either from single RCTs,[17,91,94] reviews that included both RCTS and observational studies,[89] database analyses[90,92] or retrospective cohort studies.[93]

It is important to note that these trials enrolled highly selected populations. Subjects had to have the desire and confidence as well as the manual dexterity, visual acuity, and mental faculties to use the testing device and either relay those values to their clinic (PST) or perform dose adjustment on their own (PSM). In most of the trials, 50% or fewer patients met preliminary eligibility criteria, successfully completed the training, and agreed to be randomized. Some of the reasons cited for patient unwillingness to participate or continue with the PST/PSM included patient-perceived physical limitations, lack of confidence in their ability to follow the protocol, difficulty performing measurements, and preference for an alternative method.[25,46] However, among the randomized patients, the percentage who continued with the intervention throughout the study was relatively high (64-98%) and patients in the PST/PSM group generally reported higher satisfaction and quality of life than those in usual care.

Several limitations of this analysis should be acknowledged. First, the methodological quality of the included trials was variable; only 5 trials met all of our quality indicators. Second, it is unclear whether the apparent benefits of PST/PSM result from the PST/PSM or simply from the more intense education that these patients receive. Third, the current data do not address the question of whether PST/PSM is safe during the high-risk initiation phase or should only be implemented during the maintenance phase. However, it is reassuring to note that in the VA trial there was no outcome difference between the group who had been randomized within 3 months of starting anticoagulation and the group that had been anticoagulated for more than 3 months.[17] Finally, the data on quality of life and patient satisfaction is difficult to interpret due to the wide range and variable quality of the outcome measures used.

Whether the results of this review can be applied to US health care systems is unclear. Only 2 of the 22 reviewed trials were conducted in the US[17,18] and both investigated PST not PSM. Furthermore, one of these, the VA trial, did not show a significant benefit among patients randomized to PST compared to those randomized to a high quality ACC. The generalizability of results from non-US trials to US health care settings is problematic since half of these trials used vitamin K antagonists not widely used in the US and several of these have markedly different half lives from warfarin.[1] Also, since PST/PSM is a complex multi-component intervention, it is important to have evidence of effectiveness in typical US healthcare settings. Finally, although we did not examine costs, survey data suggest that costs are likely to be a barrier to implementation.[95] Several cost analyses have concluded that implementing PST/PSM may not be cost-effective due to the high cost of the portable monitoring devices and supplies and of patient training.[2,96]

## CONCLUSION AND RECOMMENDATIONS FOR KQ2

This analysis 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?*

### Summary

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 such that coming up with a comprehensive list of independent risk factors is difficult and involves piecing together results from a very heterogeneous group of studies. Factors that seemed most consistently associated with serious bleeding included: very old age, the first months following warfarin initiation, other medication use (particularly aspirin use), comorbid conditions (such as history of GI bleeding events or diabetes), primary indication for taking warfarin was a valve condition, 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 and shown that patients can to some extent be categorized into low, intermediate, and higher risk for serious bleeding events. 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.

### Limitations

Publication bias and the inability to pool results across studies due the heterogeneity of the study designs, analytical methods, and risk factors assessed limit the certainty that can be assigned to the results presented in this section. Publication bias is a concern when looking at lists of predictors of outcomes from observational studies. It is not uncommon for studies to evaluate associations for many more factors than they report results, creating a situation where, positive associations with bleeding may be more often reported than null associations. This may make some factors look artificially more strongly associated than they might be expected to be in real-world circumstances. For this reason, it is important to confirm more novel associations in large prospective studies. The range of uncertainty around the magnitude of effect for any of these risk factors is also necessarily large, since the heterogeneity of the studies precludes anything but a narrative review of the findings.

## CONCLUSION AND RECOMMENDATIONS FOR KQ3

Several factors have been shown to consistently 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. The HEMORR$_2$HAGES index seems to be the most comprehensive

list of potential factors, while the OBRI index has been the most frequently tested model and is more parsimonious. While neither of these is clearly superior, it does seem that there is growing support for the development of more formal methods of risk assessment beyond that of simple clinical intuition or judgment, and the current risk indices provide a means to begin to be develop useful clinical support tools that can be tweaked as new risk factors are identified.

Future studies might better define the utility of these risk indices by randomizing patients to different bleed risk management strategies possibly incorporating different combinations of risk factors or bleeding risk indices to assess the potential benefits and harms of different anti-coagulation strategies.

## FUTURE DIRECTIONS

The questions addressed in this review may become moot within the next several years. Very recent randomized controlled trials suggest that direct thrombin inhibitors, drugs currently being evaluated for the United States market, and which do not require intensive monitoring, may be as safe and efficacious as vitamin K antagonists. Specifically, in large randomized trials, dabigatran has been shown to be equivalent to warfarin for the prevention of thromboembolic events in patients with chronic atrial fibrillation[97] and deep vein thrombosis.[98] The long term safety of these new agents is not yet established. In one trial,[97] myocardial infarction was more common among patients randomized to dabigatran than to warfarin, although this association was only marginally significant. Furthermore, liver function abnormalities were observed with use of an older direct thrombin inhibitor, ximelagatran,[98] although to date this has not been observed with dabigatran. Final FDA approval of these products may significantly alter the standard for anticoagulation therapy and subsequent monitoring.

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