Evidence-based Synthesis Program (ESP)

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

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Evidence-based Synthesis Program (ESP)

VA Evidence-based Synthesis (ESP) Program Overview

- Sponsored by VA Office of R&D and HSR&D.
- Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers and policy-makers, as they work to improve the health and healthcare of Veterans.
- Builds on staff and expertise already in place at the Evidence-based Practice Centers (EPC) designated by AHRQ. Four of these EPCs are also ESP Centers:
  - Durham VA Medical Center; VA Greater Los Angeles Health Care System; Portland VA Medical Center; and Minneapolis VA Medical Center.

Evidence-based Synthesis Program (ESP)

- Provides evidence syntheses on important clinical practice topics relevant to Veterans, and these reports help:
    - develop clinical policies informed by evidence,
    - the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
    - guide the direction for future research to address gaps in clinical knowledge.
- Broad topic nomination process – e.g. VACO, VISNs, field – facilitated by ESP Coordinating Center (Portland) through online process:

http://www.hsrd.research.va.gov/publications/esp/TopicNomination.cfm

Background

- Long-term anticoagulation indicated for many prevalent conditions (e.g. atrial fibrillation)
- Vitamin K antagonists (e.g. warfarin) have narrow therapeutic window
- Frequent testing and dose adjustment
- Anticoagulation clinics → standardize care
- Portable devices → patient self testing and management

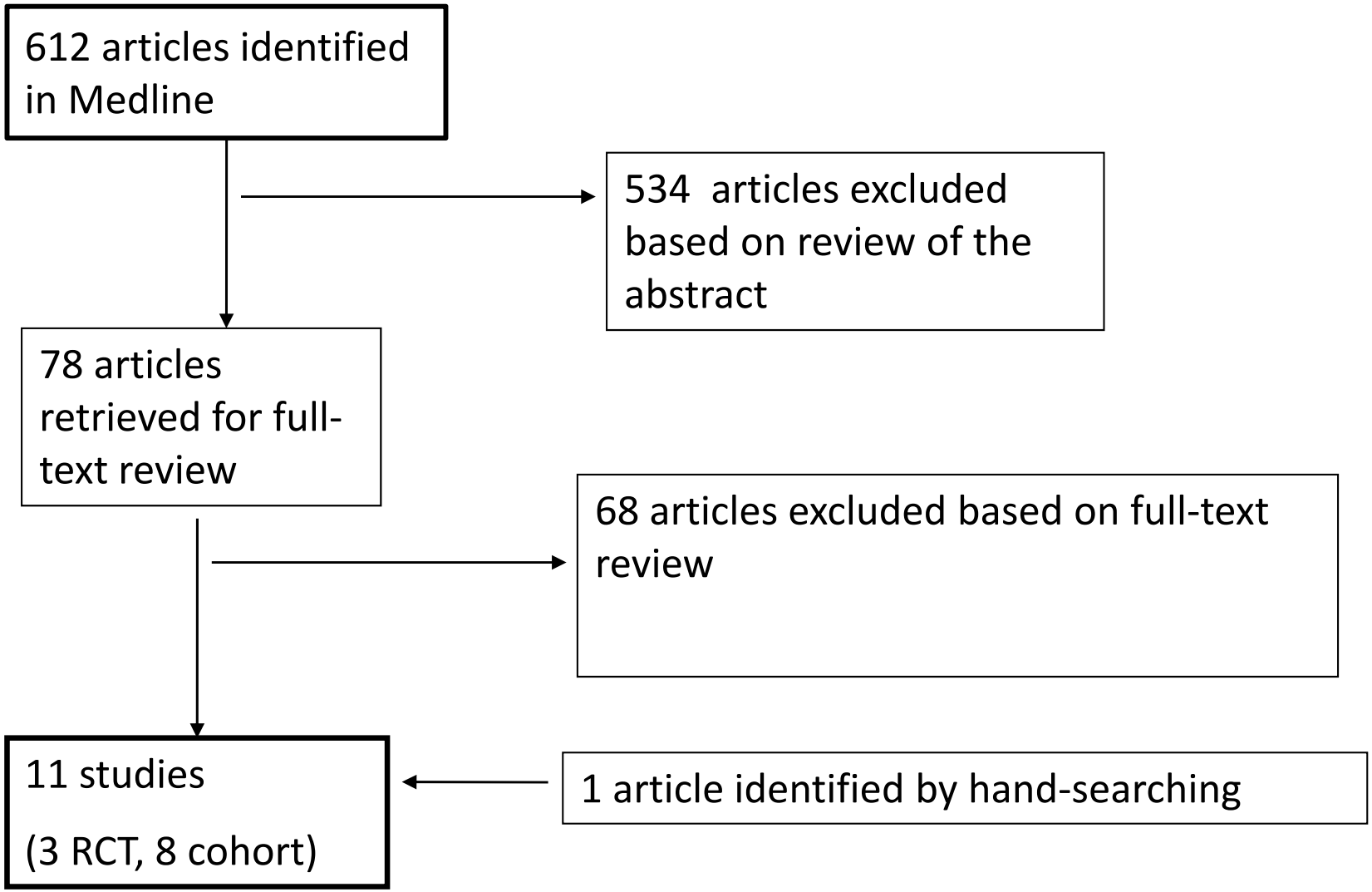
KEY QUESTIONS

1) Are specialized anticoagulation clinics (ACC) more effective and safer than care in non-specialized clinics (e.g., primary care clinics, physician offices) for management of long- term anticoagulation in adults?
2) Is Patient Self Testing (PST), either alone or in combination with Patient Self Management (PSM), more effective and safer than standard care?
3) What are the risk factors for serious bleeding in patients on chronic anticoagulant therapy?

KQ1: Are specialized anticoagulation clinics (ACC) more effective and safer than care in non-specialized clinics?

- Literature Search
  - Included
    - Randomized controlled trials or cohort studies of long-term (>3 months) oral anticoagulation published in English between 1966 and 2010
  - Excluded
    - Studies of inpatient or pediatric populations

Literature Flow Diagram for Key Question 1



Overview of Studies and Subjects

- 3 RCTs (US, China, and Canada)
  - 722 subjects
  - Mean age 68 (range of study means 59 to 76)

- 8 Cohort Studies (5 in US)
  - 3 prospective, 5 retrospective
  - 12,768 subjects
  - Mean age 69 (range of study means, 57 to 74)

Results of RCTs

- Rates of all-cause mortality, major thromboembolic events, and major bleeding did not differ significantly between the two treatment arms in any of the 3 RCTs.
- In the pooled analysis,
  - Total Mortality: 5/181 in ACC and 6/178 in UC all from a single study (RR: 0.81, 95%CI: 0.25 to 2.58)
  - Major Bleeding: 6/353 in the ACC patients and 8/495 in UC patients (RR: 1.05, 95%CI: 0.36 to 3.12)
  - Major thromboembolism: 11/353 in ACC and 14/495 in UC (RR: 1.29, 95%CI: 0.6 to 2.81).

Results of RCTs-2

- Percent time in therapeutic range
  - ACC 59.9%
  - UC 56.3%
  - weighted mean difference of 3.6% (range of mean differences, 3.3 to 5%)

Results of Cohort Studies

- Unable to pool outcomes
- Total mortality (N=1 study)
  - no significant difference between ACC and UC
- Major thromboembolic events (N=4 studies)
  - 1 significantly higher incidence in UC
  - 1 significantly higher incidence in ACC
  - 2 studies, p values were not reported
- Major Bleeding (N= 5 studies)
  - significantly higher in UC in 1
  - not significantly different between groups in 1

Results of Cohort Studies -2

- Percent time in therapeutic range (N=4 studies)
  - ACC 63.5%
  - UC 53.5%
  - weighted mean difference of 10% (range of mean differences, 4.3 to 26%)

Conclusions for KQ1

- Evidence for the safety and efficacy of ACC is limited but *suggests* that ACC *may* lead to better quality anticoagulation control as measured by time in therapeutic range

- There is insufficient evidence to conclude that ACC care leads to fewer deaths, thromboembolic events, or major bleeding events than care provided in UC

- Results from two studies suggest that patients like the convenience and enhanced service provided by these clinics

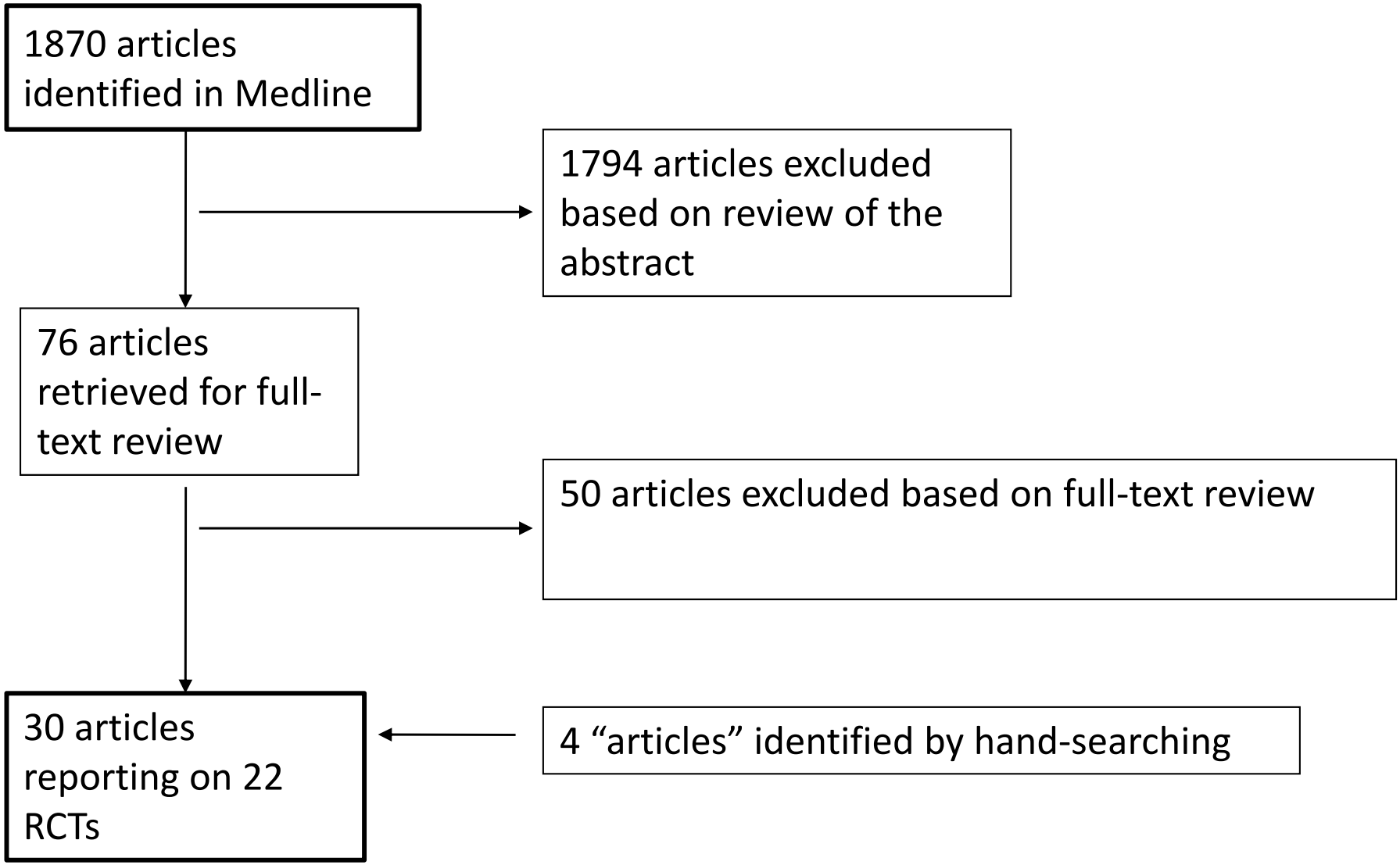
Recommendation for KQ1

- There is insufficient evidence for the VA to actively promote the implementation of ACCs

KQ2: Is Patient Self Testing (PST), either alone or in combination with Patient Self Management (PSM), more effective and safer than standard care?

- Literature Search:
  - Included:
    - Randomized controlled trials of long-term (>3 months) oral anticoagulation published in English between 1966 and 2010
  - Excluded:
    - Studies of inpatient or pediatric populations

Literature Flow Diagram for Key Question 2



Overview of Studies and Subjects

- 22 RCTs
- Only 2 conducted in the US
- 8413 subjects
- Only 3 with inception cohorts
- Duration of follow-up < 12 months in 13 studies

- Mean age 65 (range of means: 42 to 75)
- 3 studies focused on the elderly
- 75% of subjects were male

Interventions

- 4 evaluated PST only; 16 PSM
- PST/PSM
  - Intensive training, 2-4 sessions of 1-3 hours
    - How to use the machine and how often to check
    - How to dose (algorithm)
    - When to call for help
  - Access to telephone “hot line”
- Control
  - Usual clinic care either in an ACC or MD office

Clinical Outcomes

- Significant 25% reduction in all-cause mortality
  (RR: 0.75, 95% CI: 0.57 to 0.99, P=0.04)

- Significant 41% reduction in major thromboembolism
  (RR: 0.59, 95% CI: 0.45 to 0.77, P<0.0001)

- Without any increase in serious bleeding
  (RR 0.91, 95%CI 0.78 to 1.07, P=0.26)

Conclusion for KQ2

- Compared to usual clinic-based models, oral anticoagulation managed with PST/PSM results in fewer deaths and major thromboembolic events without any increase in bleeding for a select group of motivated adult patients requiring long term anticoagulation

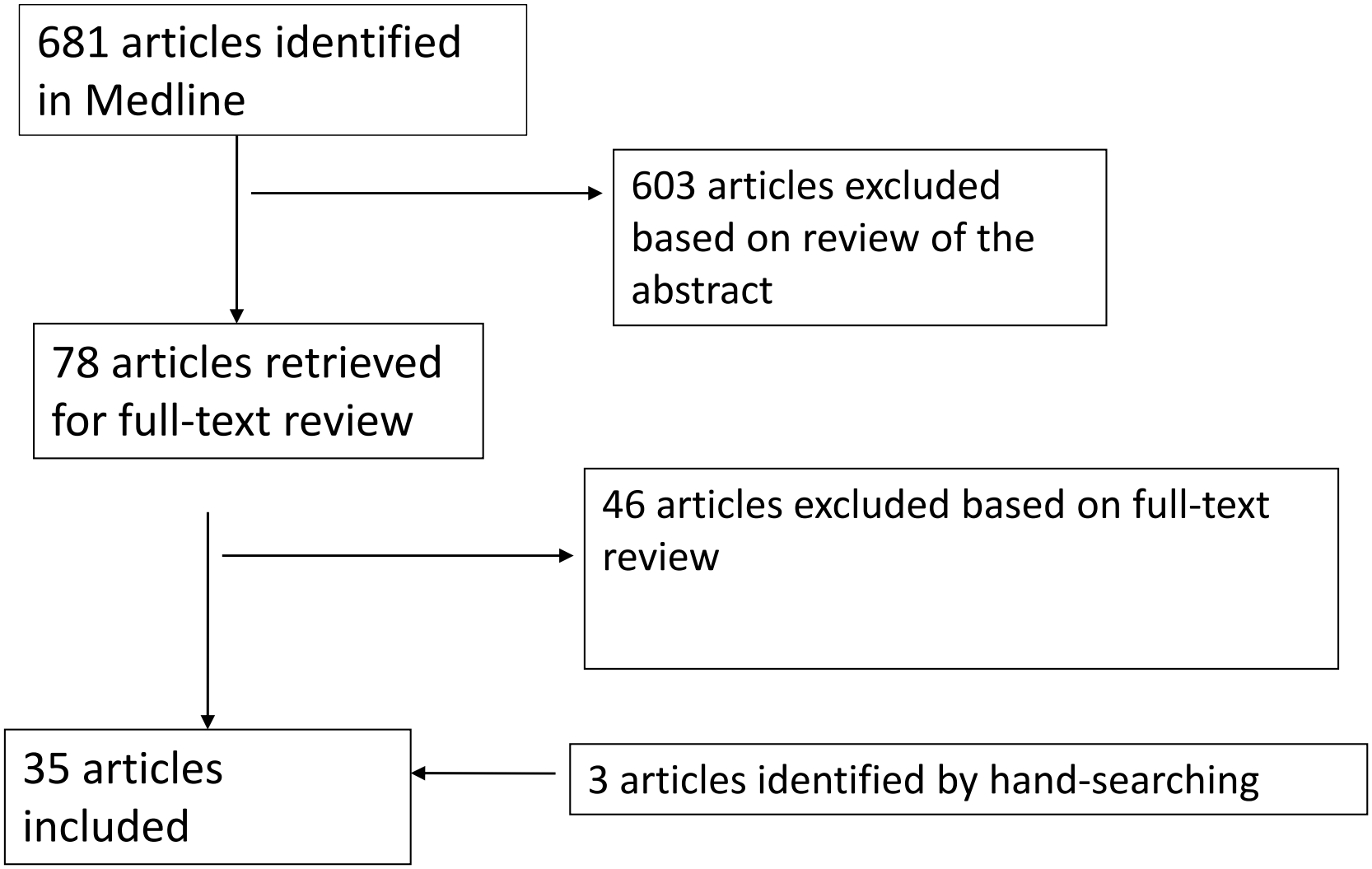
Recommendations for KQ2

- Widespread implementation of this care model in the US should await stronger evidence of effectiveness and cost-effectiveness in typical US health care settings
- THINRS –largest study to date, performed in VA

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

- Literature Search:
  - Included:
    - Studies published in English after 1996 that provided rates of serious bleeding events in populations who were on warfarin therapy
  - Excluded:
    - Studies <25 cases of serious bleeding
    - Studies with populations primarily composed of inpatients, pediatric populations, or non-warfarin anticoagulation

Literature Flow Diagram for Key Question 3



Overview of Included Studies

- 35 articles represent 35 unique studies (17 US studies)
  - 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
- Analytical methods ranged from frequencies of events by strata of a risk factor to using multivariable models
- Average follow-up times ranged 1 year to 5 years

Subject Characteristics

- Total N for all combined studies = 453,918 subjects
- Wide range in sizes:
  - case control study with 26 cases and 56 controls
  - large administrative database study of Medicare records that included 353,489 patients
- 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.

Narrative Summary of Predictors of Serious Bleeding

- Pooling of statistical results for each predictor was not possible since the study designs and analytical methods varied so widely

- Quantitative results extracted from the 35 studies are presented in the Appendices of the Full Report (App B, Table 5)

Risk Factors for Serious Bleeding Reported in the Individual Studies

Article	Age	Gender	Warfarin Duration	INR	Primary Indication	Asprin/ NSAID	…
Battistella 2005[55]						√	
Beyth 1998[49]	√		√				
DiMarco 2005[56]	√					√	
Douketis 2006[60]	√		√			√	
Douketis 2007[65]							
Fang 2005[57]		√					
Fang 2006[61]	√		√				
Fihn 1996[47]	√						
…							

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Risk Factors for Serious Bleeding Reported in the Individual Studies

Risk Factor	Articles
Age	16
Gender	9
Warfarin Duration	5
INR	2
Primary Indication	2
Aspirin/NSAID	11
Other Meds	11
Risk Index	7
Genetics	3
Comorbidity	12
Other	8

Factors most consistently predicting an increased risk of bleeding

- Very old age (ex. 75+)
- First months following warfarin initiation
- Medication use (particularly aspirin use)
- Comorbid conditions
  - History of GI bleeding events or diabetes
- Primary indication for taking warfarin was a valve condition
- Genetic factors (ex. variation in the CYP2C gene)
- Bleeding Risk Indexes
  - Nine different Indices reported (HEMORR$_2$HAGES and OBRI had the most evidence)

Stratifying Patients by Risk of Bleeding

- For example, In the Outpatient Bleeding Risk Index (OBRI), patients get 1 point for each of the following:
  - 65 years or older, history of GI tract bleeding, history of stroke, and one or more comorbid conditions (recent myocardial infarction, anemia, renal impairment, or diabetes mellitus).
  - Low= score of 0
  - Moderate = score 1 or 2
  - High risk = score 3+

Conclusions for KQ3

- Bleeding risk indices are currently available for stratifying patients into “low” and “high” risk groups.
- However, there is not adequate evidence to suggest that any of the bleeding risk indices are meaningfully superior to the other indices.
- HEMORR$_2$HAGES index seems to be the most comprehensive list of potential factors
- OBRI index has been the most frequently tested model and is more parsimonious.

Conclusions for KQ3

- 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 develop useful clinical support tools that can be tweaked as new risk factors are identified.

Future Research Directions

- Randomizing patients to different levels of treatment based on bleeding risk index measurements prior to or during chronic warfarin treatment would provide clearer evidence of the utility of incorporating risk factor assessment into the clinical encounter
- Decision modeling studies might also provide some information at a lesser cost than a large RCT

Summary of Recommendations

- There is insufficient evidence to recommend active efforts to implement ACCs in VA
- PST/PSM are promising but widespread implementation should await results of studies in US/VA
- Either alone or in combination, risk factors can used to help clinicians and patients have a dialog about the risks of warfarin therapy, but the clinical utility of risk indices is largely untested