APPENDIX A: PEER REVIEW COMMENTS AND RESPONSES

Reviewer Comment	Author Response
Overall	
You exhaustively synthesize the literature related to the questions you sought to answer. This was extremely professional and the product is truly authoritative.	Thank you
Re: the repeated messages about how warfarin is due to be replaced at any moment 1. I'm not sure this really belongs in an ESP because this is not part of the evidence base you were synthesizing. 2. I suspect we will still be using warfarin, at least for some patients, for at least the next 10 years, if not more. No alternative agent has received FDA approval.	We have deleted many of the messages about potential alternatives to warfarin (see additional responses below).
The report is a comprehensive review of anticoagulation management in the outpatient setting.	Thank you
Objectives, Scope, and Methods Clearly Described	
Each of these areas is clearly described.	NR*
Yes	NR
Yes	NR
a. Yes. Overall, this is a very thoughtful, thorough, and well written report that provides a comprehensive summary of three decades of research on management of oral anticoagulation. b. Although the questions addressed by the review are clinically quite relevant, in certain respects, however, it forces the analysis to address the clinical circumstances in a somewhat unrealistic manner. The management of oral anticoagulation is simplistically divided into two phases: initiation and maintenance. As the authors of this review have found, the highest risk of complications is during this period [initiation]. Once stability is achieved, the maintenance is oriented toward minimizing variation in the INR related to intercurrent illness, administration of drugs, changes in diet, etc. Research suggests the inherent variability during this latter phase also predicts likelihood of complications. The analytic framework adopted in this review treats these phases as one continuous process. It is likely that interventions studies, i.e., AC clinics and PST, and the risk factors for complications might be different according to the phase studied. c. It does not appear that the confounding effects of computerized dosing programs, protocols, or nomograms were considered. My bias is that much of any beneficial effect of ACCs reflect the standard use of protocols. Can you ascertain if some of the "control" clinics related to Question #1 were using such tools?	Thank you. b. We have reviewed the studies cited in the report and have added information about initiation and maintenance phases in the Overview of Included Studies sections for KQ1 and KQ2. c. We have added information about possible processes of care that might have accounted for observed differences under KQ1a.

Bias	
I believe there is significant bias shown in support of the direct thrombin inhibitors class and specially dabigatran which is yet to be approved for release to the US market (*see pages iii, iv, and vi of the Executive Summary for example)*; these statements are all speculative and biased and should not be included in an evidence based report. A more benign and accurate statement to be considered that could be used once in the Executive Summary: "New anticoagulants which may offer the same clinical efficacy and safety profile as warfarin with considerable less monitoring are currently being evaluated for the US market. Final FDA approval of these products may significantly alter the standard for anticoagulation therapy and subsequent monitoring".	Thank you for the suggested wording. We have added a statement to the "Background" section of the Executive Summary and the "Discussion and Recommendations" section of the full report. We have deleted all other statements about direct thrombin inhibitors.
No	NR
There is no evidence in the report to support the conclusions regarding direct thrombin inhibitors and specifically dabigatran (see pages iii, iv, vi, and 46). This drug has not been approved by the FDA for use in the US and the report does not draw on any FDA documents surrounding this drug. There have been several drugs that showed exceptional promise in pre-marketing trials that have either been withdrawn from the market or had their use severely limited due to problems found during post-marketing surveillance. Stating that direct thrombin inhibitors are "poised to become the preferred treatment for long term anticoagulation" shows bias towards this class of drugs that is not supported by evidence in the report. The statement on page 46 ("The long term safety of these new agents is not yet established") is not included in the executive summary. I would recommend removing references to direct thrombin inhibitors from the report. If it is included, I would recommend just stating this class of drugs is currently in clinical trials and the role in therapy has not been defined but may impact the usage of warfarin.	We have added a statement to the "Background" section of the Executive Summary and the "Discussion and Recommendations" section of the full report. We have deleted all other statements about direct thrombin inhibitors.
No	NR
Other Published or Unpublished Studies	
Not that I am aware of	NR
No	NR
None to my knowledge	NR

It is not clear that all studies have been included specifically: 1. Fihn SD et al. Ann Intern Med 1993;118:511-520 (addresses several risk factors presented in Table 12 including variability in INR) 2. Van Leeuwen Y et al. Thromb Haemost 2008;6:451-460 (addresses variability in INR as a risk factor) 3. LeTourneau T. Chest 2009;136:1503-1513 (addressed variability in INR as a risk factor) There is evidence that variability in INR Is important during the maintenance phase and should be acknowledged in the review.	Fihn 1993 was excluded, because it was outside of the search window (1996 or later). Information for both Van Leeuwen 2008 and LeTourneau 2009 has now been added to the KQ3 section.
Additional Comments	
Page 23, paragraph 2 - change THIINRS to THINRS	NR
There are multiple statements diminishing the usefulness of this review with the assumption that direct thrombin inhibitors will replace warfarin for anticoagulation since they do not require intensive monitoring. It seems premature to make this assumption based on recently published RCTs. While these studies report the efficacy of the new drug in clinical trial populations, the effectiveness (or cost-effectiveness) of these therapies in non-clinical trial settings remains to be seen.	We have added a statement to the “Background” section of the Executive Summary and the “Discussion and Recommendations” section of the full report. We have deleted all other statements about direct thrombin inhibitors.
The THINRS final analyses have been completed and the main study paper is planned for submission in February 2010. An inquiry on whether the unpublished results can be included in the tables and meta-analysis could be sent to the CSPCC in Palo Alto.	We have been in contact with the CSPCC and including unpublished data is not an option.

a. Although the literature synthesis showed insufficient evidence to conclude that ACC care leads to fewer deaths, thromboembolic events, or major bleeding events than usual care, several expert reviews have concluded that better quality anticoagulation control typically seen within an ACC can infer better outcomes. This is discussed in Philips and Ansell (2008) and the ACCP Guidelines (2008). This review does discuss other reviews (pg. 46) but this disparity is not discussed in the Executive Summary. b. Other organizations that have focused on quality and safety have supported AC clinics (Joint Commission Sentinel Event Alert Issue 41; AHRQ Report #43, Part III, Chpt. 9). c. For the conclusion on page iv that states "there is insufficient evidence for the VA to actively promote the implementation of ACCs" I would recommend stating further that this has not been the conclusion of other organizations or expand on how the conclusion of the systematic review differs from conclusions of other organizations and experts in the field. d. I would recommend adding that this synthesis of the literature did not consider the cost-effectiveness of ACCs or resource utilization and therefore the conclusion that there is insufficient evidence is based solely on evidence regarding clinical outcomes and does not factor in patient satisfaction, costs, and resource utilization. As the VA does manage a large portion of their patients within AC clinics HSR&D may want to consider a study that looks at AC clinic patient management within the VA system and include these factors.	a. We have chosen to present the results from our review in the Executive Summary leaving comparisons to other studies in the Discussion section. In agreement with the ACCP Guidelines, we have noted the limited nature of the evidence in the Executive Summary. b. We have reviewed these documents. The Joint Commission Alert is based on a few studies (not a comprehensive review). The AHRQ Report was completed in 2001 and therefore does not include many of the studies cited in our review. c. We are limited to reaching conclusions based on the evidence. d. Cost-effectiveness was outside the scope of the report as defined by the Key Questions. We searched for but were unable to identify evidence-based data on resource utilization. Patient satisfaction results are included in our review. We agree that a study that includes costs and resource utilization would be worthwhile and we have added a statement to that effect in the Conclusions and Recommendations for Key Question 1.
In a couple of places, the authors indicate that the review may be of limited value because of the imminent introduction of direct thrombin inhibitors. Although this may well be true, reports of demise of vit K antagonists have been prevalent for 3 decades. Although these drugs have a narrow therapeutic ratio, they have an efficacy in preventing stroke of nearly 75%, higher, perhaps, than almost any other drug in regular therapeutic use. Given the fact that the drug itself is relatively inexpensive, must typically be taken for many years, and has a long track record, it may not be dislodged all that soon.	We have added a statement to the "Background" section of the Executive Summary and the "Discussion and Recommendations" section of the full report. We have deleted all other statements about direct thrombin inhibitors.

*No Response Needed

APPENDIX B: EVIDENCE TABLES

Appendix B, Table 1 – Randomized Controlled Trials for Anticoagulation Clinic versus Usual Care (KQ1)

Study **Publication Year** **Country of Origin** **Funding source**	**Indication for anticoagulation** **Entrance criteria** **Duration of follow-up** **Mean age** **% Male** **Inception Cohort/Time on OAC prior to enrollment**	**Intervention Group (n)** **Control Group (n)** **Total sample size (N)**	**Outcomes evaluated***	**Study quality**
Matchar, et al.[8] 2002 USA Agency for Healthcare Research and Quality, DuPont Pharmaceuticals Company	Atrial fibrillation Age ≥ 65, atrial fibrillation, enrolled in 1 of 6 managed care organizations Mean Age: 76+ 7 % Male: 49 A follow-up period of the 9 months immediately after the anticoagulation service had attained the minimum enrollment Inception: unclear	Intervention Cluster: referred to ACC:173, not referred to ACC: 190 Control Cluster: 317 N=680 *2 Practice clusters within each site were randomized to either access or no access to an ACC. The intervention clusters did not HAVE to refer pts to the ACC.*	iii. VTE iv. Bleeding vii. Time in Therapeutic Range	Allocation concealment: NA Blinding: NR Intention-to-treat: NR Dropouts reported: yes
Wilson, et al.[6] 2003 Canada Queen Elizabeth II Health Sciences Centre Research Foundation (Halifax, NS), Physicians' Services Incorporated Foundation (Ottawa, ON), London Health Sciences Centre Internal research Fund (London, ON)	Mixed indications All patients expected to be on warfarin ≥ 3mo Mean Age: 61+ 15 years % Male: 58 Follow-Up: 3 months Inception (< 1 month): 81%	Intervention: ACC: 112 Control: family physician:109 N = 221	i. All cause mortality ii. Event related mortality iii. VTE iv. Bleeding v. Patient Satisfaction vii. Time in Therapeutic Range	Allocation concealment: yes Blinding: clinical event adjudication committee blinded Intention-to-treat: yes Dropouts reported: yes

Chan, et al.[7] 2006 China Health Care and Promotion Fund (Hong Kong)	Mixed indications All patients, age ≥ 18, requiring ≥ 3mo of warfarin therapy Mean Age: 59 + 14 years % Male: 45 Follow-Up: max 2 years, average length cannot be determined Inception cohort: see page 602	Intervention: pharmacist-managed ACC: 69 Control: hematologist-managed ACC: 69 N = 138	i. All cause mortality iii. VTE iv. Bleeding v. Patient Satisfaction vii. Time in Therapeutic Range xi. Hospitalization xii. Outpatient Utilization xiii. ER Utilization	Allocation concealment: unclear Blinding: NR Intention-to-treat: no Dropouts reported: yes

* OUTCOMES

i. All cause mortality
ii. Event related mortality
iii. VTE (venous thromboembolic events)
iv. Bleeding
v. Patient Satisfaction
vi. Quality of Life
vii. Time in Therapeutic Range
viii. % of INRs in Therapeutic Range
ix. INR Variability
x. # of Total INR Values
xi. Hospitalization
xii. Outpatient Utilization
xiii. ER Utilization
xiv. Outpatient Laboratory Utilization
xv. Long-term Care Admission (after related event)

Appendix B, Table 2 – Observational Studies for Anticoagulation Clinic versus Usual Care (KQ1)

Study **Publication Year** **Country of Origin** **Funding Source**	**Study design** **Indication for anticoagulation** **Entrance criteria** **Duration of follow-up** **Mean age** **% Male** **% Inception/time on OAC prior to enrollment**	**Intervention Group (n)** **Control Group (n)** **Total sample size (N)**	**Outcomes evaluated***
Lee, et al.[9] 1996 USA	Prospective Cohort Mixed indications All patients discharged from hospital requiring long term warfarin. Follow-Up: 3 mos Mean Age: 56.9 % Male: 57 Inception: NR	Intervention: Hospital discharges requiring long term anticoagulation referred to anticoagulation clinic. The ACC was led by a pharmacist and included patient education via manuals, videos and compliance aids. (68) Control: Random sample of hospital discharges requiring long term warfarin but not referred to anticoagulation clinic (68) N = 136	xi. Hospitalization
Chiquette, et al.[10] 1998 USA	Retrospective Cohort Mixed Indications All patients, requiring ≥3mo of warfarin therapy, with at least one outpatient visit Follow-Up: NR Mean Age: NR (90% < 65) % Male: 53 Inception: 100%	Intervention: ACC which was led by a pharmacist and included intensive patient education; no dosing algorithm (183) Control: Usual medical care (145) N = 328	iii. VTE iv. Bleeding vii. Time in Therapeutic Range viii. % of INRs in Therapeutic Range xi. Hospitalization xiii. ER Utilization
Chamberlain, et al.[11] 2001 USA Southwest Washington Medical Center	Retrospective Cohort Mixed indications All anticoagulation patients during study period included Follow-Up: NR Mean Age: 63 + 15 % Male: 42 Inception: No/NR	Intervention: Anticoagulation patients during the period 11/1/1996 to 10/31/1997 followed in a pharmacist-run anticoagulation clinic which included POC testing (41) Control: Anticoagulation patients during the period 11/1/1996 to 10/31/1997 followed in a family medicine clinic that did not perform POC testing (75) N = 116	iii. VTE viii. % of INRs in Therapeutic Range xi. Hospitalization xiii. ER Utilization
Witt, et al.[12] 2005 USA	Retrospective Cohort Mixed indications ≥ 18yo, on warfarin, ≥2 INR values during 6 mo evaluation period Follow-Up: 6 months Mean Age: 67.8 % Male: 53 Inception:NR	Intervention: Anticoagulation therapy managed by a centralized, telephonic clinical pharmacy anticoagulation service manned by pharmacists available 24/7; patient education provided (3323) Control: Anticoagulation therapy managed per usual personal physician. (3322) N = 6645	i. All cause mortality ii. Event related mortality iii. VTE iv. Bleeding vii. Time in Therapeutic Range

Du, et al.[14] **2005** **China**	Prospective cohort Atrial fibrillation NVAF on anticoagulation Follow-Up: NR Mean Age: 61.8 % Male: 59 Inception: NR	Intervention: referred to anticoagulation clinic (details not provided) (66) Control: followed by usual care which consists of follow-up by cardiology outpatient clinic (138) N = 204	iii. VTE iv. Bleeding viii. % of INRs in Therapeutic Range
Ansell, et al.[16] **2007** **USA, Sweden, Italy, Spain, France** AstraZeneca Pharmaceuticals	Retrospective Cohort Atrial fibrillation Cross-sectional cohort with chronic NVAF, age >18, minimum 60 days of AC Follow-Up: 12 months Mean Age: NR % Male: NR Inception: NR	Intervention: Patients of anticoagulation clinics using local protocols were followed in Italy and Spain. ACC management was defined as care provided in a systematic way by personnel focusing specifically on AC management (395) Control: Patients of routine medical care using local protocols were followed in the US, Canada and France (1116) N = 1511	vii. Time in Therapeutic Range viii. % of INRs in Therapeutic Range
Wallvik, et al.[15] **2007** **Sweden** Joint Committee of Northern Sweden Health Care Region and Foundation of Medical Research in Skelleftea	Prospective Cohort Mixed indications All patients treated with warfarin in two regions of northern Sweden. Follow-Up: 1.8 years (mean), 4 yrs max Mean Age: 69 % Male: 58 Inception cohort: NR	Intervention: Anticoagulation clinic, no details provided (1537) Control: Primary healthcare centre (1194) N = 2731	iv. Bleeding
Nichol, et al.[13] **2008** **USA** AstraZeneca Pharmaceuticals	Retrospective Cohort Atrial Fibrillation NVAF on anticoagulation Follow-Up: 12 mos Mean Age: NR % Male: 55 Inception: No	Intervention: ACC run by an RN mostly by phone, supervised by a cardiologist; intensive pt education on first visit. (351) Control: Usual care by internists, GPs or cardiologists. (756) N = 1107	iii. VTE iv. Bleeding vii. Time in Therapeutic Range

*OUTCOMES

i. All cause mortality
ii. Event related mortality
iii. VTE (venous thromboembolic events)
iv. Bleeding
v. Patient Satisfaction
vi. Quality of Life
vii. Time in Therapeutic Range
viii. % of INRs in Therapeutic Range
ix. INR Variability
x. # of Total INR Values
xi. Hospitalization
xii. Outpatient Utilization
xiii. ER Utilization
xiv. Outpatient Laboratory Utilization
xv. Long-term Care Admission (after related event)

Appendix B, Table 3 – Overview of individual short-term (<12 months) randomized, controlled trials investigating PST/PSM (KQ2)

Study **Publication year** **Country of origin** **Funding source**	**Indications for anticoagulation** **Entrance criteria** **Duration of follow-up** **Mean age** **% Male** **Length of time on OAC prior to enrollment**	**Intervention group (n)** **Control group (n)** **Total sample size (N)** **Type of vitamin K antagonist**	**Outcomes evaluated***	**Study quality**
Sawicki et al. 1999[20] Germany Industry	Mixed Patients with a disease or condition requiring lifelong OAC 6 months 55±12 years 70% male 2.1±4.8 years (mean) Not clear (pts were not previously treated in THESE clinics)	Intervention: PSM (n=90) Control: PC clinic (n=89) N=179 Phenprocoumon	iii. Thromboembolic events iv. Major bleeding events v. Patient satisfaction/ quality of life vii. INR variability	Allocation concealment: adequate Blinding: lab techs doing the INRs were blinded Intention-to-treat: yes Dropouts reported: yes
Beyth et al. 2000[18] USA NIH, VA HSR&D, American Federation for Aging Research	Mixed Patients aged ≥65 years, residing in Cuyahoga County, OH, starting on OAC with treatment planned for ≥10 days 6 months 75 ± 6.8 years (range 65-94) 43% male 0 years (inception cohort)	Intervention: PST (n=163) Control: PC clinic (n=162) N=325 Warfarin	i. All-cause mortality iii. Thromboembolic events iv. Major bleeding events vii. % time within therapeutic range	Allocation concealment: unclear Blinding: two author-reviewers who were blinded to group assignment adjudicated bleeding events Intention-to-treat: yes Dropouts reported: yes
Cromheecke et al. 2000[21] Crossover trial The Netherlands Not reported	Mixed Self-supporting patients receiving long-term OAC 6 months (each pt followed 3 mos in each treatment) 42 ± 16 years (range 21-71) 59% male 3.9±2.2 years (mean) (not inception)	Intervention: PSM (n=50) Control: AC clinic (n=50) (Total N=50) Phenprocoumon and acenocoumarol	iii. Thromboembolic events iv. Major bleeding events v. Patient satisfaction/ quality of life vi. % time within therapeutic range vii. % INR values within therapeutic range	Allocation concealment: adequate Blinding: NR Intention-to-treat: unclear Dropouts reported: yes

Fitzmaurice et al. 2002[22] United Kingdom Industry	Mixed Patients aged ≥18 years, on long-term OAC for ≥6 months previously, with good vision and manual dexterity, and with INR within 0.5 of target value at least 60% of the time over the prior 12 months 6 months 66 years 76% male Not reported (not inception)	Intervention: PSM (n=30) Control: AC clinic (n=26) N=56 Warfarin	iv. Major bleeding events v. Patient satisfaction/ quality of life vi. % time within therapeutic range vii. % INR values within therapeutic range	Allocation concealment: unclear Blinding: no Intention-to-treat: no Dropouts reported: yes
Gadisseur et al. 2003[23] **& Gadisseur et al. 2004**[24] The Netherlands Industry	Mixed Patients aged 18-75, requiring long-term OAC, with ≥3 months experience on OAC 24.4 weeks (mean) 59 years 71% male Not reported (not inception)	Intervention (1): PST (n=52) Intervention (2): PSM (n=47) Control (1): AC clinic patients aware of the study and receiving education about OAC (n=60) Control (2): AC clinic patients not aware of the study (n=161) N=320 Phenprocoumon and acenocoumarol	iii. Thromboembolic events iv. Major bleeding events v. Patient satisfaction/ quality of life vi. % time within therapeutic range vii. % INR values within therapeutic range	Allocation concealment: adequate Blinding: physicians evaluating and correcting the proposed dosing schedules for group A and group B Intention-to-treat: yes Dropouts reported: yes
Khan et al. 2004[25] United Kingdom BUPA Foundation	Atrial Fibrillation Patients aged ≥65 years without dementia, on warfarin for ≥12 months, with a target INR of 2-3, with an INR standard deviation of ≥ 0.5 over prior 6 months 6 months Median age 73 yrs (range: 65-93) 58% male Not reported (not inception)	Intervention: PST (n=44) Control (1): ACC patients aware of the study and receiving education about OAC (n=41) Control (2): ACC patients not aware of the study (n=40) N=125 Warfarin	iii. Thromboembolic events iv. Major bleeding events v. Patient satisfaction/ quality of life vi. % time within therapeutic range	Allocation concealment: unclear Blinding: NR Intention-to-treat: no Dropouts reported: yes

Sunderji et al. 2004[19] Canada Industry and others	Mixed Patients age ≥ 18 years on warfarin for ≥ 1 month with target INR range 2-3 or 2.5-3.5, without mental incompetence or known hypercoagulable disorders 8 months 60 years 71% male 53.5% with ≥ 6 months OAC	Intervention: PSM (n=70) Control: PC clinic (n=70) N=140 Warfarin	iii. Thromboembolic events iv. Major bleeding events v. Pt Satisfaction vi. % time within therapeutic range vii. % INR values within therapeutic range	Allocation concealment: adequate Blinding: no Intention-to-treat: yes Dropouts reported: yes
Gardiner et al. 2005[26] United Kingdom Industry	Mixed Patients aged ≥18 years attending the anticoagulation clinic at University College London Hospital, on OAC for ≥8 months, with previous record of good compliance 6 months 58 years (range 26-83) (unclear if mean or median) 63% male Not reported (not inception)	Intervention: PST (n=44) Control: AC clinic (40) N=84 Warfarin	iv. Major bleeding events v. Pt Satisfaction vi. % time within therapeutic range	Allocation concealment: unclear Blinding: no Intention-to-treat: unclear Dropouts reported: yes
Voller et al. 2005[27] Germany Industry	Atrial fibrillation Patients on OAC for atrial fibrillation, without alcoholism or other addictions 39± 6 mos 64 ± 9.3years 66% male Not reported	Intervention: PSM (n=101) Control: PC clinic (n=101) N=202 Not reported	iii. Thromboembolic events iv. Major bleeding events vi. % time within therapeutic range (# of days) vii. % INR values within therapeutic range	Allocation concealment: unclear Blinding: no Intention-to-treat: unclear Dropouts reported: unclear
Christensen et al. 2006[28] **& Christensen et al. 2007**[29] Denmark Danish Heart Foundation	Mixed Patients aged ≥18 years on OAC for ≥8 months 182 days (mean) 49 ± 13.7 years 67% male 5.5±4.3 years (mean) Not reported (not inception)	Intervention: PSM (n=50) Control: PC/AC clinic (n=50) N=100 Warfarin and phenprocoumon	i. All-cause mortality iii. Thromboembolic events iv. Major bleeding events vi. % time within therapeutic range viii. INR variability	Allocation concealment: no Blinding: no Intention-to-treat: no Dropouts reported: yes

Gardiner et al. 2006[30] United Kingdom Industry	Mixed Patients aged ≥18 years on long-term OAC for ≥8 months, without history of poor compliance, intellectual impairment, or known drug or alcohol dependency 6 months 60 years (22-88) 61% male Not reported (not inception)	Intervention: PSM (n=55) Control: PST (n=49) N=104 Warfarin	vi. % time within therapeutic range	Allocation concealment: unclear Blinding: no Intention-to-treat: unclear Dropouts reported: yes
Dauphin et al. 2008[31] France Industry	MHV replacement Patients undergoing mechanical valve replacement at Clermont-Ferrand University Hospital 47 ± 12 weeks (mean) 57 ± 9.7 years 67% male Not reported (recruited when undergoing valve replacement)	Intervention: PST (n=33) Control: AC clinic (n=34) N=67 Fluindione and acenocoumarol	i. All-cause mortality iii. Thromboembolic events iv. Major bleeding events vi. % time within therapeutic range vii. % INR values within therapeutic range viii. INR variability	Allocation concealment: unclear Blinding: no Intention-to-treat: unclear Dropouts reported: yes
Ryan et al. 2009[32] Crossover trial Ireland Industry and Health Research Board, Ireland	Mixed Patients on OAC for ≥2 months who had internet access. 6 months 58.7 ± 14.3 years 62% male Not reported (not inception)	Intervention: PSM (n=132 completed both arms,72 initially) Control: AC clinic (n=132,60 initially) N=162 Warfarin	iii. Thromboembolic events iv. Major bleeding events vi. % time within therapeutic range	Allocation concealment: adequate (pharmacy-controlled) Blinding: no Intention-to-treat: no Dropouts reported: yes

*OUTCOMES

i. All cause mortality
ii. Event related mortality
iii. VTE (venous thromboembolic events)
iv. Bleeding
v. Patient Satisfaction
vi. Quality of Life
vii. Time in Therapeutic Range
viii. % of INRs in Therapeutic Range
ix. INR Variability
x. # of Total INR Values
xi. Hospitalization
xii. Outpatient Utilization
xiii. ER Utilization

Appendix B, Table 4 – Overview of individual long-term (≥12 months) randomized, controlled trials investigating PST/PSM (KQ2)

Study **Publication year** **Country of origin** **Funding source**	**Indications for anticoagulation** **Entrance criteria** **Duration of follow-up** **Mean age** **% Male** **Inception cohort/ time on OAC prior to enrollment**	**Intervention (n)** **Control (n)** **Total sample size (N)** **Type of vitamin K antagonist**	**Outcomes evaluated***	**Study quality**
Horstkotte et al. 1998[34], 1996[33] (abstract) Germany Not reported	MHV replacement Entrance criteria not reported 17.7 months (mean) Not reported Not reported Not reported	Intervention: PSM (n=75) (dosing unclear) Control: PC clinic (n=75) N=150 Not reported	iii. Thromboembolic events iv. Major bleeding events vii. % INR measurements within therapeutic range	Allocation concealment: unclear Blinding: NR Intention-to-treat: unclear Dropouts reported: unclear
Koertke et al. 2001 (one in German in Z Kardiol[35] and one in Ann Thor Surg[36]) & Koertke et al. 2007[37] Germany Not reported	MHV replacement Patients undergoing MHV replacement from 2/1994-10/1997 at a German institution Initial f/u: 38 mos Long-term f/u: 9.3 +/- 2.8 years 63 years 66% male Inception Cohort	Intervention: PSM (n=579 in 2001; 488 in 2007) Control: PC clinic (n=576 in 2001; 442 in 2007) N (2001)=1155 N (2007)=930 Phenprocoumon	i. All-cause mortality(2007) ii. Event-related mortality (2007) iii. Thromboembolic events (2001) iv. Major bleeding events (2001) vii. % INR values within therapeutic range (2001)	Allocation concealment: unclear Blinding: NR Intention-to-treat: unclear Dropouts reported: yes
Sidhu et al. 2001[38] United Kingdom Industry	MHV replacement Patients who had undergone MHV replacement by the author and were ≤ 85 yo without visual difficulties 24 months 61 years (range: 26-85) 46% male Not reported	Intervention: PSM (n=51) Control: PC or AC clinic (n=49) N=100 Warfarin	i. All-cause mortality ii. Event-related mortality iii. Thromboembolic events iv. Major bleeding events vi. % time within therapeutic range	Allocation concealment: unclear Blinding: NR Intention-to-treat: unclear Dropouts reported: yes

Fitzmaurice et al. 2005[39] & Jowett et al. 2006[40] United Kingdom United Kingdom Medical Research Council	Mixed Patients aged ≥18 years on warfarin for ≥6 months with treatment indicated for ≥12 months, with a target INR of 2.5-3.5 12 months 65 years 65% male Not reported (not inception)	Intervention: PSM (n=337) Control: AC clinic (n=280) N=617 Warfarin	i. All-cause mortality ii. Event-related mortality iii. Thromboembolic events iv. Major bleeding events v. Patient satisfaction/quality of life vi. % time within therapeutic range	Allocation concealment: adequate Blinding: no Intention-to-treat: yes Dropouts reported: yes
Menendez-Jandula et al. 2005[41] Spain Industry	Mixed Patients aged ≥18 years on long-term OAC for ≥3 months, without severe physical or mental illness 12 months (median f/u) 65 years 53% male 5.1 years (median, IQR 2.0-12.0) % inception NR	Intervention: PSM (n=368) Control: AC clinic (n=369) N=737 acenocoumarol	i. All-cause mortality iii. Thromboembolic events iv. Major bleeding events vi. % time within therapeutic range vii. % INR values within therapeutic range viii. INR variability (INR distance, table 2)	Allocation concealment: adequate Blinding: complications diagnosed and evaluated by a third physician not involved in the trial and unaware of patients' study group Intention-to-treat: yes Dropouts reported: yes
Siebenhofer et al. 2007[42] & Siebenhofer et al. 2008[43] Austria Industry	Mixed Patients aged ≥60 years, on long-term OAC, without severe cognitive problems or terminal illness 2.9 ± 1.2 years (mean) 69 ± 6.3 years 58% male 5.7 ±7.1 years (mean) Not inception	Intervention: PSM (n=99) Control: AC/PC clinic (n=96) N=195 Phenprocoumon and acenocoumarol	i. All-cause mortality ii. Event-related mortality (see table 4 p. 1096) iii. Thromboembolic events iv. Major bleeding events vi. % time within therapeutic range vii % INR values within therapeutic range viii. INR variability	Allocation concealment: adequate Blinding: complications evaluated by two independent physicians not involved in the trial and unaware of patients' study group. Intention-to-treat: yes Dropouts reported: yes

Eitz et al. 2008[44] Germany Not reported	MHV replacement Patients undergoing MHV replacement in a German hospital 2 years 58.7 years 69% male Not reported (randomized at time of valve replacement)	Intervention: PSM (n=470) Control: PC clinic (n=295) (crossovers were allowed) N=765 Warfarin	iii. Thromboembolic events iv. Major bleeding events vii. % INR values within therapeutic range viii. INR variability	Allocation concealment: unclear Blinding: NR Intention-to-treat: no Dropouts reported: no
Soliman Hamad 2009[45] The Netherlands Not reported	MHV replacement Patients undergoing MHV replacement in a Dutch hospital with knowledge of computers and the internet. 12 months 56 years Not reported Inception cohort (randomized at time of valve replacement)	Intervention: PSM (n=29) Control: AC clinic (n=29) N=62 Not reported	i. All-cause mortality iii. Thromboembolic events iv. Major bleeding events v. Pt Satisfaction /quality of life vi. % time within therapeutic range	Allocation concealment: unclear Blinding: NR Intention-to-treat: no Dropouts reported: yes
Matchar (THINRS) 2010[17] USA VA	Mixed Patients with MHV replacement or atrial fibrillation and competent in device use 2 to 4.75 years 67 ± 9 years 98% male Not an inception cohort (mean time on OAT prior to enrollment not reported)	Intervention: PST (n=1,465) Control: AC clinic (n=1,457) N=2922 Warfarin	i. All-cause mortality iii. Thromboembolic events iv. Major bleeding events v. Pt Satisfaction /quality of life vi. % time within therapeutic range	Allocation concealment: adequate Blinding: major outcomes assessed by independent adjudicators Intention-to-treat: yes Dropouts reported: yes

*OUTCOMES
i. All cause mortality
ii. Event related mortality
iii. VTE (venous thromboembolic events)
iv. Bleeding
v. Patient Satisfaction
vi. Quality of Life
vii. Time in Therapeutic Range
viii. % of INRs in Therapeutic Range
ix. INR Variability
x. # of Total INR Values
xi. Hospitalization
xii. Outpatient Utilization
xiii. ER Utilization

Appendix B, Table 5. Overview of Individual Studies – Risk Factors for Serious Bleeding (KQ3)

Study Country of origin Funding source	Study design Indications for anticoagulation Entrance criteria Duration of follow-up (years)	N (cases) Mean age % Male	Definition of Serious Bleeding	Serious Bleeding Outcomes by Risk Factors
Aspinall 2005[56] United States Public	Retrospective cohort study using Administrative Datasets Patients attending a VA anticoagulation clinic between 2001 and 2002 Follow-up Administrative Data from January 1, 2001 to December 31, 2002	N(cases): 1,269 (42) Mean age: 67.9 (SD=11.4) 92% Male	Patient was hemo-dynamically unstable, required a transfusion, had an intracranial hemorrhage, or died.	***Risk Index*** (Bleeding Risk Index) * *Low:* 0.8% /PYr (95% CI; 0-4.2) *Med:* 2.5%/PYr (95%CI;1.6-3.7) *High:* 10.6% /PYr (95% CI; 6.4-16.6) ***Warfarin Duration*** (p=.08)* *New User* (n/N): 2.2% (11/502) *Prior User* (n/N): 4.0% (31/767)
Battistella 2005[57] Canada Public	Nested case-control study using Administrative Datasets Cohort of continuous warfarin users from April 1, 2000, to March 31, 2001 Follow-up 1 year	N(cases): 1,798 (361) Mean age: 77 (SD=6.8) 49% Male	Patient was admitted to the hospital with any diagnosis of upper GI hemorrhage	***Other Med Use**** NSAID: OR=1.9 (95%CI;1.4-3.7) Cox-2 Inhibitors Celecoxib: OR=1.7 (95%CI;1.2-3.6) Rofecoxib: OR=2.4 (95%CI;1.7-3.6)
Beyth 1998[51] United States Public	2 Prospective cohort studies (derivation and validation cohorts) using data primarily medical records Derivation cohort of patients who started outpatient warfarin therapy upon discharge from hospital between 1977 and 1983 Validation inception cohort of consecutive patients who started warfarin therapy upon discharge from hospital between 1986 and 1987. Follow-up for both groups was presented up to 4 years.	**Derivation cohort:** N(cases): 565 (65) Mean age: 61(SD=14) 47% Male **Validation cohort:** N(cases): 264 (22) Mean age: 60(SD=16) 47% Male	Overt bleeding that led to the loss of at least 2.0 units in 7 days or less, or was otherwise life-threatening (eg, intracranial bleeding)	**Results from Derivation cohort:** ***Risk Index*** (*Outpatient Bleeding Risk Index)** *Risk of major bleeding at 12 months* *Low:* 3% *Intermediate:* 12% *High:* 48% ***Warfarin Duration*** *(follow-up time not time on warfarin)* *Cumulative events at 1 month:* 3% *Cumulative events at 12 months: 11 %* *Cumulative events at 48 months:* 22% **Results from Validation cohort:** ***Risk Index*** (*Outpatient Bleeding Risk Index)** *Risk of major bleeding at 12 months* *Low:* 3% *Intermediate:* 8% *High:* 30% ***Warfarin Duration*** *(follow-up time not time on warfarin)* *Cumulative events at 1 month:* 2% *Cumulative events at 12 months: 8 %* *Cumulative events at 48 months:* 12% **Results from Combined Cohorts:** Stratifying by increased ***Age*** and ***Comorbidity*** (components of OBRI) shows increased the major bleeding

Bousser 2008[68] Multi-national Industry	Prospective Cohort (vitamin K antagonist arm of RCT, warfarin or acenocoumarol) Patients with atrial fibrillation at risk for thromboembolism Follow-up 0.9 years (SD=0.5)	N(cases): 2293(29) Mean age: 70.2 (SD=9.1 65% Male	Bleeding that was fatal, intracranial, or affected another critical anatomical site, or overt bleeding with a drop of hemoglobin ≥20 g/L or requiring transfusion of two or more units of Erythrocytes.	***Risk Index*** (CHADS2 score) * *Low:* 0.8% /PYr *Moderate:* 1.0% /PYr *High:* 2.5% /PYr
DiMarco 2005[58] United States AFFIRM Trial Public	RCT comparing rate-control and rhythm-control strategies in patients with atrial fibrillation All patients were eligible for warfarin at baseline and most continued their warfarin regimen Follow-up average of 3.5 years (range 0 – 5.9 years)	N(cases): 4060 (260) Mean age: 70 (SD=9) 61% Male	Major bleeding was either CNS hemorrhage, or outside the CNS bleeding that required transfusion of ≥2 units of blood, hospitalization in an intensive care unit, and/or discontinuation of anticoagulant or antiplatelet Therapy.	***Age: (****per year):* HR=1.05(95%CI;1.04,1.07)*** ***Comorbidities:*** *CHF:* HR=1.43(95%CI;1.09,1.89)*** *Diabetes:* HR=1.44(95%CI;1.07,1.93)*** *Hepatic or Renal Disease:* HR=1.93(95%CI;1.27,2.93)*** ***Other Med Use:*** *Aspirin Use: HR=2.01(95%CI;1.45,2.77)**** ***Rate Control vs. Rhythm-control strategies*** *No difference (p=0.45)*
Douketis 2006[62] Multinational SPORTIF III & V Trials Industry	Pooled analysis of two large RCTs using just the Warfarin arms of each trial Patients were adults with nonvalvular atrial fibrillation Followed up to 24 months	N(cases): 3665 (136) Mean age: ~71 <65: 22% 65-75: 40% >75: 38% 70% Male	Major bleeding was: fatal bleeding; clinically overt bleeding associated with a reduction in hemoglobin level of 20 g/L or more; clinically overt bleeding requiring transfusion of 2 or more units of whole blood or erythrocytes; intracerebral bleeding; and bleeding involving a critical anatomic site.	***Age: (****Greater 75):* HR=1.26(95%CI;1.03,1.52)*** ***Comorbidities:*** *Hepatic Disease:* HR=4.88(95%CI;1.55,15.39)*** ***Other Med Use:*** *Aspirin Use: HR=2.41(95%CI;1.69,3.43)**** *Statins Use: HR=0.60(95%CI;0.41,0.87)**** ***Warfarin Duration:*** * Cumulative incidence of major bleeding, % (95% CI)* 3 Months: 0.8 (0.5-1.0) 12 Months: 2.6 (2.1-3.2) 24 Months: 4.7 (3.8-5.5)
Douketis 2007[67] Canada Public	Nested case-control study using administrative databases A patients were age 66+ with atrial fibrillation who were prescribed warfarin between April 1, 1994, and December 31, 2001 Follow-up average of 2 years	N(cases): 16,618 (1518) Mean age: 77 (SD=7) 46% Male	Cases were admitted to a hospital with a diagnosis of upper gastrointestinal or intracranial hemorrhage.	***Other Med Use:*** *Long-term Warfarin Users (>6 months)* *Statins Use: OR=0.82(95%CI;0.67,1.00)**** *Recent Warfarin Users (<6 months)* *Statins Use: OR=1.02(95%CI;0. 78,1.34)****

Fang 2006[64] United States ATRIA Study Public	Cohort study using Administrative Datasets Patients with nonvalvular atrial fibrillation Follow-up 2.4 years (IQR=1.8-2.8)	15,300 person years (170 cases) Mean age: 71 (SD=15) 53% Male	Intracranial hemorrhages unless they were associated with major head trauma (e.g., neurosurgical procedure, motor vehicle accident, and skull fracture). Major extracranial hemorrhages defined as fatal, requiring transfusion of two or more units of packed blood cells, or hemorrhage into a critical anatomic site.	***New vs. Prior Warfarin*** *Intracranial hemorrhages* *1st Month*: 0.92% /PYr *Afterward*: 0.46% /PYr RR: 2.0 (95% CI ; 0.6–6.7)* *Major Extracranial hemorrhages* *1st Month*: 1.2% /PYr *Afterward*: 0.61% /PYr RR: 2.0 (95% CI ; 0.7–5.8)* ***Age*** *Intracranial hemorrhages* ≥80 v. <80: RR=1.8 (95%CI;1.1–3.1)*** *Major Extracranial hemorrhages* Per 10 years: RR=1.3 (95%CI;1.1–1.7)***
Fang 2005[59] United States ATRIA Study Public	Cohort study using Administrative Datasets Patients with nonvalvular atrial fibrillation Follow-up 2.4 years (IQR=1.8-2.8)	~15,000 person years (167 cases) Mean age: 71 (SD=15) 53% Male	Intracranial hemorrhages unless they were associated with major head trauma (e.g., neurosurgical procedure, motor vehicle accident, and skull fracture). Major extracranial hemorrhages defined as fatal, requiring transfusion of two or more units of packed blood cells, or hemorrhage into a critical anatomic site.	***Gender:*** *All major hemorrhages* Men 1.1% vs. Women 1.0%* Men: RR=1.25 (95% CI;0.91–1.67)*** *Intracranial hemorrhages* Men 0.55% vs. Women 0.36%* Men: RR=2.0 (95% CI;1.11–3.33)***
Fihn 1996[49] United States - VA National Consortium of Anticoagulation Clinics Government + industry	Combined retrospective and prospective cohort studies Patients attending a combination of VA and university-affiliated clinics anticoagulation clinic between 1980 and 1993 Follow-up: Retrospective study data from 1980 to 1990; prospective study data collected between 1990 and 1993.	N (cases): 2376(259) Mean age: 58.3 73.4% Male	Overt gastrointestinal bleeding; occult gastrointestinal bleeding if endoscopic or radiographic studies were done; gross hematuria prompting cystoscopy or intravenous urography or lasted more than 2 days; hemoptysis.	***Age group**** *Serious Bleeding* *RR(95%CI)** *<50 yrs:* 9.3%/PYr ref *50-59 yrs:* 7.1%/PYr 1.2 (0.9-1.6) *60-69 yrs:* 6.6%/PYr 1.3 (1.0-1.7) *70-79 yrs:* 5.1%/PYr 1.3 (1.0-1.7) *80-89 yrs:* 4.4%/PYr 0.9 (0.5-1.5) *Life-threatening or fatal* *RR(95%CI)** *<50 yrs:* 0.8%/PYr ref *50-59 yrs:* 1.3%/PYr 1.3 (0.4-4.1) *60-69 yrs:* 1.1%/PYr 1.5 (0.5-4.0) *70-79 yrs:* 0.7%/PYr 0.9 (0.3-3.1) *80-89 yrs:* 3.4%/PYr 4.5 (1.3-15.6)
Flaker 2006[63] Multinational SPORTIF III & V Trials Industry	Randomized multicenter study (combined open-label and double-blinded studies) High-risk patients with nonvalvular AF Follow-up: 1.4 years (16.5 months) average treatment exposure	N (cases): 3653(125) Mean age: ~71 70% Male	Fatal; involved a critical anatomical site; or overt and associated with a decrease in hemoglobin level of 20 g/L or transfusion of at least 2 U of blood.	***Warfarin vs Warfarin +aspirin*** (p=.01)* *Warfarin* (n/N): 2.3% (100/3172) *Warfarin + aspirin* (n/N): 3.9% (25/481)

Gage 2006[80] United States NRAF Study Public	Cohort study using medical records from the National registry of Atrial Fibrillation data set. Medicare patients with confirmed atrial fibrillation Follow-up to a maximum of 1000 days after baseline hospitalization	N (cases): 1604(67) Mean age: ~80 ~43% Male	Major bleeding defined using ICD-9-CM codes	***Risk Index** (HEMORR$_2$HAGES)* Bleeds per 100 patient-years (95%CI) Score: 0: 1.9 (0.6-4.4) 1: 2.5 (1.3-4.3) 2: 5.3 (3.4-8.1) 3: 8.4 (4.9-13.6) 4: 10.4 (5.1-18.9) ≥5: 12.3 (5.8-23.1) ***Risk Index** (OBRI):* Low: 1.1 (0.3-4.3) Moderate: 4.9 (3.6-6.5) High: 8.8 (5.6-14.0) ***Risk Index** (Kuijer 1999):* Low: 2.9 (1.3-6.5) Moderate: 5.2 (4.0-6.7) High: 7.5 (2.8-19.9) ***Risk Index** (Kearon 2003):* Score: 0: 2.5 (1.1-6.1) 1: 2.5 (1.4-4.3) 2: 6.5 (4.5-9.4) 3: 9.3 (5.7-15.3) ≥4: 15.3 (6.4-36.8)
Gasse 2005[60] UK Government + industry	Longitudinal cohort study plus a nested case-control analysis Patients (from the UK General Practice research Database) who had a first ever warfarin prescription for AF during the study period and continued treatment for more than 90 days Follow-up was approximately 1 year (3740.8 patient-years of warfarin exposure)	N (cases): 4152(46) Age range: ~70 58% Male	Idiopathic bleeds that resulted in hospitalization within 30 days or death within 7 days following bleeding event	***Warfarin +concomitant drug*** [incidence rate = cases/100 PYAR]* *Total:* 1.2 *Warfarin alone:* 0.9 *Concomitant (all):* 1.8 *Allopurinol:* 3.4 *Amiodarone:* 1.2 *Aspirin:* 2.4 *Levothyroxine:* 0.9 *Metronidazole:* 38.5 *Miconazole:* 41.7 *Omeprazole:* 3.2 *Paracetamol:* 3.8 *Paracetamol + Dextropropoxyphene:* 4.1
Gomberg-Maitland 2006[65] Multinational SPORTIF III & V Trials Industry	Randomized multicenter study (combined open-label and double-blinded studies) High-risk patients with nonvalvular AF Followed up to 24 months	N (cases): 3624 (NA) Mean age: ~71 69.7% Male	Major bleeding	***Warfarin arm**** *Women vs men:* -0.35%/yr difference (P=0.491) *Men:* 91 events, 2.57%/yr *Women ≥ 75:* 2.60%/yr *Women < 75:* 1.83%/yr

Hart 1999[53] Meta-analysis	Meta-analysis of 6 randomized trials of warfarin vs aspirin + warfarin. All published prior to 1998 none of which were largest alone to be included Patients with prosthetic cardiac valves (4 trials), men with coronary risk factors (1 trial), patients with AF (1 trial) Follow-up:	N (cases): 3874(31) Mean age: NA NA % Male	Intracranial hemorrhage	***Warfarin vs Warfarin +aspirin*** (p=.08)* *Warfarin* (n/N): 0.46% (9/1947) *Warfarin + aspirin* (n/N): 1.14% (22/1927)
Healey 2008[69] [ACTIVE-W] Multinational Industry	Prospective randomized study (warfarin arm of RCT) Patients with AF and at least 1 additional risk factor for stroke Followed up to 24 months (median 1.3 years)	N (cases): 3371 (93) Mean age: 70.2 (SD=9.5) 66% Male	Bleeding associated with: death; drop in hemoglobin of at least 2 g/dL; significant hypotension with the need for inotropic agents bleeding requiring surgical intervention (other than vascular site repair); symptomatic intracranial hemorrhage; intraocular hemorrhage causing loss of vison; or the requirement for a transfusion of at least 2 U of blood.	***Risk Index*** (CHADS2 score)* *0:* 0.00/100 pt-yrs *1:* 1.48/100 pt-yrs *2:* 2.89/100 pt-yrs *3:* 2.58/100 pt-yrs *4:* 2.92/100 pt-yrs *5:* 0.90/100 pt-yrs *6:* 6.85/100 pt-yrs *CHADS2=1:* 1.36%/yr *CHADS2>1:* 2.75%/yr ***OAC-naïve**** *CHADS2=1:* 1.81%/yr *CHADS2>1:* 3.76%/yr ***OAC-experienced**** *CHADS2=1:* 1.33%/yr *CHADS2>1:* 2.47%/yr
Higashi 2002[54] United States UWMC Clinics Government + industry	Retrospective cohort study Patients attending Univ of Washington Med Ctr anticoagulation clinics Follow-up: 2.2 years (mean)	N (cases): 185(28) Mean age: 59.9 (SD=15.7) 63.8% Male	Serious bleeding: overt gastrointestinal bleeding; occult gastrointestinal bleeding if endoscopic or radiographic studies were performed; gross hematuria that prompted cystoscopy or intravenous urography or lasted more than 2 days; hemoptysis; blood transfusions of 2 units or more.	***CYP2C9 Genotype**** *Variant:* 10.92% /PYr *Wild-type:* 4.89% /PYr
Johnson 2008[70] United States Public	Retrospective longitudinal cohort study: warfarin vs warfarin + antiplatelet combination therapy Patients attending Kaiser Permanente Colorado anticoagulation clinics Follow-up: 4.6 yr (SD=4.0)	N (cases): 4183(55) Mean age: 70.7(SD=12.5 53.3% Male	Major hemorrhage: required the transfusion of two or more units of RBCs; caused a decrease in hemoglobin concentration of ≥ 2 g/dL; or involved any intracranial, intraarticular, intraocular, or retroperitoneal sites	***Warfarin vs Warfarin + antiplatelet*** (p=.003)* *Warfarin* (n/N): 0.9% (23/2560) *Warfarin + antiplatelet* (n/N): 2.0% (32/1623)

Le Tourneau 2009[81] United States Public	Population-based retrospective cohort study with chart review Patients in Olmsted County, MN who had mechanical mitral value replacement Follow-up: 8.2 yr (SD=6.1)	N (cases): 112(27) Mean age: 57 (SD=16) 40% Male	Bleeding causing death, hospitalization, permanent injury or transfusion	*Cancer HR 4.01 (95%CI; 1.89-8.52)*** ***INR SD (Variability)*** *HR 2.48 (95%CI; 1.11-5.55)***
Limdi 2008[71] United States POAT Study Public	Prospective cohort study: influence of genotypes on risk for hemorrhagic complications Patients participating in the Pharmacogenetic Optimization of Anticoagulation Therapy (POAT) cohort study Follow-up: 14.9 mo (SD=10.7)	N (cases): 446(44) Mean age: 60.6 (SD=15.6) 51.3% Male 50.9% African American	Major hemorrhage	***Incidence rate by genotype**** *CYP2C9* *Total:* 7.93/100 PYr *Wild type:* 5.67/100 PYr *Variant:* 15.74/100 PYr *VKORC1 1173C/T* *Total:* 8.0/100 PYr *"CC":* 7.4/100 PYr *Any "T":* 8.9/100 PYr
Limdi 2009[75] United States POAT Study Public	Secondary analysis of a prospective cohort study: influence of kidney function on risk for hemorrhagic complications Patients participating in the Pharmacogenetic Optimization of Anticoagulation Therapy (POAT) cohort study Follow-up: 16.2 mo (mean)	N (cases): 565(64) Mean age: 61 (SD=16) 51.1% Male 47.6% African American	Major hemorrhage	***Incidence rate by GFR**** *Overall:* 8.4/100 PYr *GFR≥60:* 6.2/100 PYr *GFR=30-59:* 8.3/100 PYr *GFR<30:* 30.5/100 PYr
Lind 2009[77] Sweden Public	Prospective cohort study Patients with at least at 3 month duration treatment plan were recruited from several warfarin clinics Follow-up: 4.2 years	N(cases): 719(73) Mean age: 70 (SD=11) 63% Male	Fatal bleeding and/or symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more	*Unadjusted* ***Gender:**** Men: RR=0.8 (95% CI;0.5–1.2) *hsCRP:** Per 1 SD: 1.0 (95% CI;0.8–1.3) *MV Adjusted* ***Age***** Per 10 years: RR=1.4 (95%CI;1.1–1.7) Thrombomodulin:*** Per 1 SD: 1.4 (95% CI;1.2–1.7)

Lindh 2008[72] Sweden WARG (Warfarin Genetics) study Public and Industry	Prospective cohort with nested case-control for association of INR and severe bleeding risk No restriction on indication for warfarin treatment Starting warfarin treatment or on anticoagulant for < 2 wks Study period: 12/2001 – 8/2005 1276 patient-years follow-up	N(cases): 1523(33 in 29 patients) Median (interquartile range) age: 66 (57; 74) 63% Male	WHO criteria: lethal, life-threatening, permanently disabling, or leading to hospital admission (ED admissions excluded) or prolongation of hospital stay	*First 165 days of treatment vs. beyond 165* *RR 1.1 (95%CI; 0.5-2.3)* *First treatment month vs. beyond 1 month* *RR 2.4 (95%CI; 1.0-6.0)* ***Age*** *HR 1.02 (95%CI; 0.98-1.06)**** ***Male sex*** *HR 2.8 (95%CI; 1.1-7.3)**** *Target INR HR 1.3 (95%CI; 0.03-50)**** *Aver. Warfarin Dose (mg/d) HR 0.97 (95%CI; 0.79-1.2)**** *Time Outside Ther. INR interval HR 1.2 (95%CI; 0.95-1.5)**** *Interacting drugs at start of tx (yes/no) HR 2.3 (95%CI; 1.1-4.9)**** *INR at time of event (28cases;56 controls) OR 1.9 (95%CI; 1.1-3.4)*
McMahan 1998[52] United States, Veteran's Affairs Medical Center Funding NR	Retrospective cohort No restriction on indication for warfarin therapy Most recent course of treatment (if multiple courses) Followed from start of treatment at VAMC between 3/31/89 and 3/31/94 to end of treatment or 7/1/94; mean duration of follow-up 14.0 mos (range: 1 day to 60 mos)	N(cases): 565(40) Mean Age 65.1 (SD=10.9) 98.5% Male	Landefeld's bleeding severity index – major hemorrhage defined based on patient survival, amount of blood lost, and physical consequences of the hemorrhage	*GI bleeding RR 2.1 (95%CI; 0.93-4.9)**** *Comorbid Condition RR 1.6 (95%CI; 0.86-3.1)**** *Stroke RR 1.2 (95%CI; 0.50-2.9)**** ***Age*** *≥65 yrs RR 1.0 (95%CI; 0.53-1.9)**** *Atrial Fibrillation RR 1.0 (95%CI; 0.47-2.1)**** *Alcohol abuse RR 2.7 (95%CI; 1.4-5.4)**** *Chronic renal insufficiency RR 2.6 (95%CI; 1.3-5.2)**** *Previous GI bleed RR 2.4 (95%CI;1.1-6.0)**** *NOTE: other factor not significant in univariate analyses include: gender(p=.63), NSAID (p=.78), aspirin (p=.56), diabetes (p=.27)*
Meckley 2008[73] United States UWMC Clinics Government + industry	Retrospective cohort of patients attending Univ of Washington Med Ctr anticoagulation clinics No restriction on indication for warfarin therapy; had known *CYP2C9* and *VKORC1* genotype status Attended anticoagulation clinic between 4/3/90 and 4/21/01 with confirmed initial warfarin exposure date and at least 2 clinic visits Excluded Asian or African race	N(cases): 172(31) Mean age: 59.8 64.5% Male	Serious and life-threatening bleeds according to Fihn, 1993 definition	***Genetics***** *CYP2C9 (Variant vs Wild-type)* *HR 3.18 (95%CI; 1.30-7.78)* *VKORC1 (vs. AB)* *AA: HR 1.21 (95%CI; 0.38-3.82)* *BB: HR 0.83 (95%CI; 0.33-2.09)*

Metlay 2008[74] United States Public	Prospective cohort No restriction on indication for warfarin therapy New and continuing users of warfarin; over age 65 Recruited between 5/1/02 and 5/31/03; 24 month follow-up	N(cases): 2370 (111) Mean age: ~78 (all over 65) 23% Male	Any hospitalization due to warfarin-related bleeding (meeting specified criteria and reviewed by independent reviewers)	***Duration of Warfarin Use**** *New users of warfarin: 4.5 /100 PY (95% CI; 2.9-6.8)* *Chronic users of warfain: 4.7/100PY (95%CI; 3.7-5.8)* *First month of follow-up vs. all other months:** RR 0.9 (95%CI; 0.4-1.8) ***Age*** No association*** ***Meds*** *NSAID/ASA (vs. neither)**** RR 1.4 (95%CI; 0.9-2.1) *Number of Current medications (vs. 1-3 meds)**** *4-8 Meds:* RR 1.5 (95%CI; 0.8-3.0) *≥9 Meds:* RR 2.2 (95%CI; 1.0-4.6) ***Primary Indication***** *Valve condition requiring warfarin (vs. other indications): RR 3.02 (95%CI; 1.91-4.78)* *Anticoagulation clinic (vs. non-specialized clinic): RR 1.63 (95%CI 0.84-3.14)*
Poli 2009b[78] Italy Funding NR	Prospective cohort Atrial fibrillation Referred to anticoagulation clinic between 6/98 and 12/07 2,365 pt/years follow-up; median time of follow-up 3.1 years (range: 3 mos-9.5 yrs)	N(cases): 662 (32 with 17 cerebral) Median age: 75 yrs (range: 49-94) 64% Male	Fatal, intracranial, ocular causing blindness, articular, or retroperitoneal; surgery or transfusion of >2 blood units required; hemoglobin reduced 2 g/dl or more	***Risk Index (AFI):**** *Low: 0* *Moderate: 1.3/100 PY* *High: 1.4/100 PY* ***Risk Index (ACCP):**** *Low: 0* *Moderate: 0* *High 1.4/100 PY* ***Risk Index (CHADS2):**** *Low: 0* *Moderate: 1.0/100 PY* *High: 1.9/100 PY* ***Risk Index (NICE):**** *Low: 0* *Moderate: 1.0/100 PY* *High: 1.5/100 PY*
Poli 2009a[76] Italy Funding NR	Prospective cohort Atrial fibrillation Referred to anticoagulation clinic between 6/98 and 12/07 2,567 pt/years follow-up; mean time of follow-up 2.7 years (range: 0.1 -13 yrs)	N(cases): 783 (37 with 20 cerebral) Median age: 75 yrs (range: 37-94) 65% Male	Fatal, intracranial, ocular causing blindness, articular, or retroperitoneal; surgery or transfusion of >2 blood units required; hemoglobin reduced 2 g/dl or more	***Age:**** *Major bleeding* ≥80 v. <80: RR=1.9 (95%CI;1.2–2.8) *Cerebral bleeding* ≥80 v. <80: RR=2.1 (95%CI;0.8–5.5)

Schauer 2005[61] United States Public	Retrospective cohort Nonvalvular atrial fibrillation Ohio Medicaid patients; 1/1/97 to 5/31/02 Mean follow-up 740 days	N(cases): 9,345 (1022) Mean age: 72 (SD=13.8) 32% Male	Intracranial hemorrhage, and gastrointestinal bleeding requiring hospitalization	***Intracranial Hemorrhage:*** HR (95% CI) Substance abuse 2.4 (1.4, 4.0)*** Psychiatric illness 1.5 (1.0, 2.1) *** Social risk factors 0.9 (0.7, 1.3) * Hypertension 1.4 (0.9, 2.2) * CHF 0.9 (0.6, 1.2) * Diabetes mellitus 0.9 (0.7, 1.3) * Liver disease 0.9 (0.4, 2.0) * Renal disease 1.3 (0.9, 1.9) * DVT 0.9 (0.6, 1.5) * **Age** (per decade) 1.0 (0.9, 1.2) * **Sex, male** 1.1 (0.8, 1.5) * Race, white 0.8 (0.6, 1.2) * ***GI Bleeding:*** HR (95% CI) Substance abuse 1.4 (1.1, 1.9)*** Psychiatric illness 1.2 (1.0, 1.4) *** Social risk factors 1.3 (1.1, 1.5) *** Hypertension 1.1 (1.0, 1.3) * CHF 1.3 (1.1, 1.6) *** Diabetes 1.0 (0.9, 1.2) *** Liver disease 1.3 (1.0, 1.7) *** Renal disease 1.6 (1.4, 1.9) *** DVT 1.2 (1.0, 1.5) *** **Age** (per decade) 1.0 (1.0, 1.1) * **Sex, male** 1.1 (0.9, 1.2) * Race, white 0.9 (0.7, 1.0) *

Schelleman 2010[79] United States Non-profit	Case-control study nested within the Medicaid programs Evaluating new antihyperlipidemic prescriptions in patients on warfarin for at least 90 days California, Florida, New York, Ohio, and Pennsylvania Medicaid patients from 1999 to 2003 Average follow-up appears to be nearly 1 year	Total N=353,489 Cases=12,193 Mean age: ~69 33% Male	ICD-9 code indicating hospitalization for gastrointestinal bleeding.	**GI Bleeding** ***New Prescription*** OR (95% CI)*** Fenofibrate No data Gemfibrozil 1.96 (1.19-3.24) Fluvastatin 1.45 (0.68-3.09) Simvastatin 1.33 (1.00-1.78) Atorvastatin 1.29 (1.04-1.61) Pravastatin 0.66 (0.38-1.14) ***3rd to 4th Prescription*** OR (95% CI)*** Fenofibrate 1.31 (0.62-2.79) Gemfibrozil 1.23 (0.61-2.48) Fluvastatin No data Simvastatin 1.10 (0.79-1.53) Atorvastatin 0.62 (0.46-0.85) Pravastatin 0.54 (0.29-1.01) OR (95% CI)* **Male sex** 0.95 (0.92-0.99) Age, (ref=<50) 50-59 1.43 (1.32-1.56) 60-69 1.81 (1.68-1.96) 70-79 2.14 (1.99-2.30) 80+ 2.34 (2.18-2.51) Prior GI bleed 3.12 (3.00-3.24) Diabetes 1.62 (1.56-1.68) Liver disease 1.79 (1.72-1.87) CKD 2.57 (2.47-2.68)

Shireman 2006[66] United States Non-profit	Retrospective Cohort Atrial fibrillation All patients ≥ 65 years old; discharged from hospital receiving warfarin therapy between 4/98 and 3/99 and between 7/00 and 6/01	Total N=26,345 (~415) Development cohort n=19,875 (~318) Validation cohort n=6,470(~97) Mean age: 88% 70 years or older 47% Male	Hospitalized for major acute bleeding event (GI hemorrhage, intracranial hemorrhage) (NOTE: only included events within 90 days of discharge from index AF admission and only the first event for a subject)	***Results from Development Cohort*** *Age ≥ 70 yrs: HR 1.63 (95%CI; 1.08-2.48* *Male gender: HR 0.73 (95%CI; 0.58-0.92)* *Remote bleeding event: HR 1.79 (95%CI; 1.36-2.37)* *Recent bleeding event: HR 1.85 (95%CI; 1.41-2.44)* *Alcohol or drug abuse: HR 2.03 (95%CI; 1.07-3.83)* *Diabetes: HR 1.31 (95%CI; 1.04-1.66)* *Anemia: HR 2.36 (95%CI: 1.76-3.17)* *Antiplatelet drug: HR 1.38 (95%CI 1.07-1.78)* ***Results from Validation Cohort*** ***Risk Index** (Shireman 2006): (p<0.0001)* *Low: 0.9% (cases=35)* *Moderate: 2.0% (cases=48)* *High: 5.4% (cases=12)* ***Risk Index** (Kuijer 1999): (p=0.74)* *Moderate: 1.5%* *High: 1.8%* ***Risk Index** (OBRI): (p<0.0001)* *Moderate: 1.0%* *High: 2.5%*
Smith 2002[55] United States Public	Case-control Cases: history of stroke, taking warfarin, and hospitalized for warfarin-related ICH; age ≥ 60 Controls: history of stroke, taking warfarin, age ≥ 60 80% of each group treated with warfarin as a result of previous stroke or TIA	N(cases): 82(26) Mean age: 75 53.% Male	Intracranial hemorrhage	***Comorbidity*** *Leukoaraiosis: OR 12.9 (95%CI;2.8-59.8); adjusted OR 8.4 (95%CI; 1.4-51.5)* *Severe (grade 3 or 4) leukoaraiosis: OR 24.9 (95%CI;4.5-137.4) vs. absence of leukoaraiosis*
Stroke Prevention in Atrial Fibrillation (SPAF) Investigators 1996[48] United States SPAF II study Public	Warfarin arm of RCT comparing warfarin and aspirin Non-valvular atrial fibrillation Candidates for warfarin anticoagulation Mean follow-up 2.6 years	N(cases): 555(34) Mean age: 70 for all patients 69% Male	Bleeding involving the central nervous system; requiring hospitalization, blood transfusion, and/or surgical intervention; or resulted in permanent functional impairment to any degree	*Univariate Risk of Bleeding During Warfarin Treatment:** ***Age** > 75 yr: RR 2.6 (p=0.009)* ***Male gender**: RR 0.9* ***Comorbidities*** *Thromboembolism: RR 1.9* *CHF: RR 2.0 (p=0.05)* *Diabetes: RR 1.9 (p=0.09)* *GI bleeding: RR 1.6* *Hypertension: RR 1.1* ***Other Meds*** *NSAIDs: RR 1.3* *Other prescriptions: RR 1.2/drug (p=0.003)* ***Other*** *Tobacco Use: RR 1.9 (p=0.1)* *Alcohol: RR 1.0*

Van Leeuwen 2008[82] The Netherlands LAVA study Funding NR	Case–control study nested within a cohort of patients with prosthetic heart valves treated in four anticoagulation clinics between 1985-1993 Cases had a hemorrhagic event during follow-up. Controls were matched 2 per case on age and sex.	N(cases): 460(154)	Hemorrhagic events included: intracranial and spinal hemorrhage; or major extracranial hemorrhage leading to death or hospitalization (except hemorrhage that led to hospital admission for diagnostic procedures only).	***INR Time in Range and Variability:***** In range & stable = Reference In range & unstable: OR 1.0 (0.5-2.0) Outrange & stable: OR 1.6 (0.9-3.1) Outrange & unstable: OR 2.7 (1.4-4.9)
White 1996[50] United States - VA National Consortium of Anticoagulation Clinics Government + industry	Retrospective review of patients followed in clinics during 4/89 Prospective follow-up of all patients with life-threatening bleeding during retrospective review AND all patients between 6/90 and 4/93 Patients treated with warfarin for at least 6 weeks No restriction on indication for warfarin therapy 3,865 PY of follow-up	N(cases): 1,999 (32) Mean age: 58.79 (SD=14.3) 75.3% Male	Life-threatening: cardiopulmon-ary arrest, surgical or angio-graphic intervention to stop the bleeding, irreversible sequelae (including MI, ICH, blindness, or fibrothroax), or any 2 of the following: transfusion of ≥ 3 U of blood, hypotension, critical anemia, or acute bleeding	***Male gender**:* 21 of 32 bleeding cases (66%) vs. 75.3% of study population* ***Primary Indication**** *Mechanical valve: 17/32 (53%) vs. 20% of study population* *VTE: 5/32 (16%) vs. 23.9% of study population* *Atrial fibrillation: 6/32 (19%) vs. 16.9% of study population*

Risk Factor categories (* = Unadjusted; **= Adjusted for Age and/or basic demographics like gender; ***=multivariable adjustment for other covariates thought to be related to serious bleeding).
/PYr =per patient year