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Abbreviated Class Update: Anticoagulants

Month/Year of Review: July 2014
Last Review: March 2013

End date of literature search: June 2014
Source: OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: lovenox (branded product), dalteparin (Fragmin®), unfractionated heparin (UFH), warfarin
- Non Preferred Agents: enoxaparin, fondaparinux (Arixtra®), rivaroxaban (Xarelto®), dabigatran (Pradaxa®), apixaban (Eliquis®)

Current PA: Oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (apixaban and rivaroxaban) are subject to prior authorization criteria to promote safe and effective use among patients requiring anticoagulation (Appendix 2).

Research Questions:

- Is there any new evidence of efficacy differences between approved anticoagulants in adults requiring treatment or prevention of deep vein thrombosis (DVT) or pulmonary embolism (PE), orthopedic prophylaxis of venous thromboembolism (VTE), or patients with atrial fibrillation (AF)?
- Is there evidence of differences in harms between the available anticoagulants products?
- Are there indications or subpopulations where one agent may be more effective or safe than other available agents?

Conclusions:

- The new oral anticoagulants (dabigatran, apixaban and rivaroxaban) have been shown to be superior or non-inferior to warfarin for the prevention of stroke and systemic embolism in patient with non-valvular AF based on high strength of evidence (SOE)[1], however, clinical differences remain small.[2] Guidelines recommend warfarin in preference to the newer agents or offer that patient characteristics and discussion of the risks and benefits of all treatments be the determining factors in anticoagulant selection.[3,4]
- For the treatment of VTE, apixaban demonstrated non-inferiority to conventional therapy in one good quality study with reduced rates of major bleeding (moderate SOE).[5] For extended VTE treatment, dabigatran proved to be non-inferior to warfarin with less risk of major or clinically relevant bleeding and that dabigatran is superior to placebo (NNT 19) but with increased risk of bleeding (moderate SOE).[6,7] Low molecular weight heparins (LMWH) are preferred for long-term VTE prophylaxis in patients with cancer, based on high SOE.[8]
- Meta-analysis data in patients undergoing total hip or total knee surgery that require VTE prophylaxis, demonstrated that factor Xa inhibitors (apixaban and rivaroxaban) reduced the rate of symptomatic DVT to a greater extent than LMWH (4 fewer events per 1000 patients) based on high SOE, with a higher occurrence of major bleeding compared to LMWH (2 more events per 1000 patients treated), based on moderate evidence.[9] There was no significant difference in efficacy outcomes between LMWH and dabigatran 220mg daily (strength not available).[9]

- Based on low strength of evidence, rivaroxaban was shown to be as effective as enoxaparin at day 10 and superior to enoxaparin at day 35 when used for thrombus prevention in patients who were medically ill. Enoxaparin treatment was associated with less risk of bleeding compared to rivaroxaban based on low strength of evidence. There is insufficient evidence for the use of rivaroxaban long-term in this population.[10]

Recommendations:

- **Atrial Fibrillation:** Recommend warfarin as first-line therapy and offer dabigatran and apixaban as non-preferred agents subject to PA approval. No changes to the PDL are recommended.
- **VTE treatment:** Recommend warfarin or enoxaparin first line with dabigatran, rivaroxaban and apixaban as non-preferred options if clinical criteria are met. Recommend adding apixaban to current PA criteria as a second line option.
- **Orthopedic Prophylaxis:** Recommend LMWH as an appropriate first-line treatment option. Recommend rivaroxaban and apixaban as non-preferred options if clinical criteria are met. Recommend adding apixaban to current PA criteria as a second line option.
- **Medically Ill:** If continued anticoagulation is warranted in medically ill patients recommend warfarin as first-line option. Fourteen day supply of rivaroxaban allows transition to preferred therapy in current PA criteria. No changes to the PDL are recommended.
- Add "difficulty obtaining INR monitoring" to questions #5 and #9 in Oral Direct Factor Xa Inhibitors PA criteria, and questions #3 and #8 in Oral Direct Thrombin Inhibitors PA (Appendix 2).

Reasons for the Review:

As the range of treatment options for patients requiring anticoagulation expands, new evidence becomes available. Data on newer oral anticoagulants (NOA) continues to evolve with the additional FDA approved indications and additions to the literature. The recent Drug Effectiveness Review Project (DERP) scan will be reviewed with applicable literature added. New indications and safety alerts since the last drug class update in 2013 will summarized.

Previous Conclusions and Recommendations:

Atrial Fibrillation

- There is moderate level of evidence that the new oral anticoagulants are superior (dabigatran and apixaban) or non-inferior (rivaroxaban) to warfarin in patients with non-valvular AF as demonstrated by the reduced risk of stroke and systemic embolism.[11-13] The risk of major bleeding was less with the NOAs compared to warfarin based on moderate strength of evidence. There are no studies directly comparing the new oral agents. Treatment beyond two years has not been studied. Concerns over lack of antidote for the new oral anticoagulants, unexplained increases in coronary events with dabigatran and limited clinical experience in the general population remain. Clinical prior authorization criteria are required for the utilization of the new oral anticoagulants while warfarin is available without restrictions.

Acute or Chronic DVT or PE Treatment

- Based on four, fair- good quality studies the NOAs have been shown to be non-inferior to warfarin (±previous enoxaparin therapy) for acute and chronic DVT and PE treatment based on moderate level of evidence.[14-17] Direct comparison among the new agents is lacking. Patients with severe renal disease and those at high risk of bleeding have not been studied. Guidelines favor the use of warfarin followed by LMWH for this indication and these treatments are available without restriction.[18] Dabigatran and rivaroxaban are available upon meeting clinical PA requirements.

VTE Prophylaxis in Orthopedic Surgery (Total Knee Replacement [TKR] and Total Hip Replacement [THR)

- Data from five studies suggested NOAs are non-inferior or superior to enoxaparin when used for orthopedic prophylaxis in patients undergoing THR.[19-23] Studies of the NOAs in patients undergoing TKR have shown conflicting results with evidence suggesting non-inferiority or superiority of the NOAs over enoxaparin when the 40 mg daily dose for enoxaparin is used.[24,25] Studies utilizing the US enoxaparin recommended dose for TKR, 30 mg twice daily, has shown the NOAs to be inferior to enoxaparin with the exception of rivaroxaban which has demonstrated superiority based on moderate strength of evidence.[26-29] No direct comparisons are available, however, indirect data suggests apixaban, dabigatran, and rivaroxaban prevent symptomatic VTEs to a similar extent based on moderate SOE.[30] Guidelines favors LMWH over fondaparinux, apixaban, dabigatran, rivaroxaban, or UFH based on moderate evidence.[18] LMWH are considered an appropriate first-line treatment and are not subject to PA criteria. Rivaroxaban is considered the most appropriate second-line option.

Background:

Anticoagulants are used in the prevention and treatment of a variety of medical conditions. Thrombosis results from damage to the endothelial lining of blood vessels which trigger activation of the coagulation cascade leading to thrombus formation.[30] Injectable anticoagulants work by enhancing antithrombin (AT) which is responsible for inhibiting a variety of clotting factors.[30] Oral anticoagulants exhibit anticoagulant activity through blocking the formation of vitamin K clotting factors (warfarin), direct thrombin inhibition (dabigatran) or factor Xa inhibition (rivaroxaban and apixaban).[32-35] Commonly used oral and injectable anticoagulants are presented in table 1.

Table 1. Anticoagulants – FDA Approved Indications[32-36]

Drug	DVT/PE Prophylaxis	DVT/PE Treatment	Atrial Fibrillation	Cardiac Valve Replacement	Post- MI
Warfarin (Coumadin®)	+	+	+	+	+
Dabigatran (Pradaxa®)	---	+	+ (nonvalvular only)	---	---
Rivaroxaban (Xarelto®)	+ (Studied in THR and TKR)	+	+ (nonvalvular only)	---	---
Apixaban (Eliquis®)	+ (Studied in THR and TKR)	---	+ (nonvalvular only)	---	---
Enoxaparin (Lovenox®)	+	+	---	---	+

* MI- myocardial infarction, DVT – deep vein thrombosis, THR- total hip replacement, TKR- total knee replacement

The most important outcomes in assessing therapy for treatment and prevention of VTE include the occurrence or reoccurrence of VTE, major bleeding and all-cause mortality. Additional relevant outcomes include: minor bleeding, cardiovascular events and withdrawals due to adverse events. Early research relied primarily on symptomatic VTE and fatal PE as measures of antithrombotic prophylaxis efficacy. When evaluating anticoagulation therapies for patients undergoing hip or knee replacement surgeries current literature has incorporated the use of the surrogate outcome, asymptomatic DVT, detected by mandatory

venography.[36] The American College of Chest Physicians (ACCP) guidelines find this outcome "fundamentally unsatisfactory" due to the inability to weigh the risks and benefits of efficacy (knowledge of symptomatic events) compared to serious bleeding.[18] The guidelines provide suggestions to estimate reductions in symptomatic thrombosis, dependent upon available evidence. Many studies that evaluate the effectiveness of anticoagulants in surgery patients rely on asymptomatic DVT events to determine treatment differences and are not powered to detect a difference in the frequency of symptomatic events, due to low occurrence rates.[37]

Rates of stroke, systemic embolisms and mortality are appropriate outcomes in evaluating treatment for AF. Secondary outcomes of interest are rates of ischemic and hemorrhagic strokes and incidence of myocardial infarctions (MI). Important safety outcomes include major bleeds, clinically relevant non-major bleeds and gastrointestinal bleeding.

VTE Prophylaxis

For patients undergoing THR or TKR, prophylactic anticoagulants are considered standard practice. ACCP guidelines recommend the use of LMWHs over other available anticoagulants (moderate evidence).[18] A minimum treatment duration of 10-14 days is recommended (moderate evidence).[18] There is moderate evidence suggesting thromboprophylaxis be continued for up to 35 days from the day of the surgery.[17] The FDA approved doses for subcutaneous enoxaparin prophylaxis in patients undergoing hip replacement surgery is 30 mg every 12 hours or 40 mg once daily and for knee replacement surgery is 30 mg given every 12 hours.[36] This is in contrast to the common European dosing regimen of enoxaparin 40 mg given once daily for prophylaxis in patients undergoing knee replacement, which is used in some trial designs. Dabigatran has demonstrated similar efficacy to LMWH, while rivaroxaban has shown superiority to LMWH in a comparative effectiveness review evaluating patients undergoing orthopedic surgery.[37]

For patients who are medically ill and at risk for VTE, prophylaxis is recommended with one of the following therapies; LMWH, unfractionated heparin (UFH) or fondaparinux.[18]

Acute VTE Treatment

ACCP guidelines recommend the use of LMWH, fondaparinux, intravenous (IV) UFH or subcutaneous UFH for the acute treatment of DVT and PE. The treatment duration is indication dependent, however, long-term anticoagulation is recommended, ranging from 3 months to extended therapy.[17] Treatment with vitamin K antagonists (VKA) are recommended over LMWH for extended anticoagulation in most patients (Grade I, low evidence), except those with cancer in which LMWHs are preferred, based on moderate evidence.[18]

Atrial Fibrillation

Patients with AF are at increased risk of stroke and systemic embolism. Risk estimates are based on the $CHADS_2$ and CHA_2DS_2-VASc Classification Scheme (Table 2).[2] The $CHADS_2$ risk stratification scheme has demonstrated a 2% increase in stroke rate for each one point increase in score. The $CHADS_2$ system designates intermediate risk to those with a score of 1, lacking a clear risk assessment for those at lowest risk.[2] Those with prior history of prior stroke may have their risk underestimated by $CHADS_2$ classification. The CHA_2DS_2-VASc scoring system has a wider scoring system which correlates to better predictability of risk in those with a lower initial stroke risk. CHEST guidelines on antithrombotic and thrombolytic therapy recommend anticoagulation for patients with AF and a $CHAD_2$ score ≥1 and the AHA/ACC/HRS guidelines recommend anticoagulation for those with prior stroke, TIA or CHA_2DS_2-VASc score ≥2.[2,18]

Table2. $CHADS_2$ and CHA_2DS_2-VASc Classification Risk Stratification Scores for Subjects with Nonvalvular AF[2,18]

Definition and Scores for $CHADS_2$ and CHA_2DS_2-VASc			
$CHADS_2$ acronym	**Score**	**CHA_2DS_2-VASc acronym**	**Score**
Congestive HF	1	Congestive HF	1
Hypertension	1	Hypertension	1
Age ≥75yr	1	Age ≥75yr	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA/TE	2	Stroke/TIA/TE	2
Maximum Score	**6**	Vascular disease (prior MI, PAD, or aortic plaque)	1
		Age 65-75 y	1
		Sex category (i.e., female sex)	1
		Maximum Score	**9**

Methods:

A Medline literature search beginning January 2013 (since last anticoagulant drug class update) and ending May 2014 for new systematic reviews and randomized controlled trials (RCTs) of anticoagulant therapies was performed. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Care Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Veterans Affairs - Comparative Effectiveness of New Oral Anticoagulants and Standard Thromboprophylaxis in Patients Having Total Hip or Knee Replacement[9]

A recent systematic review compared the efficacy and harms new oral anticoagulants to standard treatment (LMWH) in patients undergoing THR or TKR. Literature was analyzed and graded using the Assessment of Multiple Systematic Reviews and QUOROM (Quality of Reporting of Meta-analyses) criteria. Six, good-quality reviews were included in the analysis. The new oral anticoagulants studied included: apixaban, dabigatran, rivaroxaban, and edoxaban (not available in the United States [US]). All studies used a LMWH as a comparator. Factor Xa inhibitors were found to reduce the rate of symptomatic DVT to a greater extent than LMWH based on high SOE (4 fewer events per 1000 patients; OR 0.46; 95% CI 0.30-0.70). The risk of non-fatal PE (OR 1.07; 95% CI 0.65 to 1.73) and death (OR 0.95; 95% CI 0.55 to 1.63) were similar. There was moderate SOE that factor Xa inhibitors were associated with a non-significant higher occurrence of major bleeding compared to LMWH (2 more events per 1000 patients treated; OR 1.27; 95% CI 0.98 to 1.65). The direct thrombin inhibitor, dabigatran, was not statistically different from LMWH, regardless of outcome studied (based on low and moderate SOE). Rivaroxaban was shown to reduce the risk of VTE to a greater extent than dabigatran and apixaban, based on indirect comparisons.

COCHRANE – Factor Xa Inhibitors Versus Vitamin K Antagonists for Preventing Cerebral or Systemic Embolism in Patients with Atrial Fibrillation[3]

In a 2013 review, the Cochrane Collaboration evaluated the efficacy and safety of factor Xa inhibitors compared to VKAs in stroke and systemic embolism prevention. Ten, moderate to high quality trials involving 42,084 participants with AF were included. Apixaban and rivaroxaban studies accounted for approximately 80% of the factor Xa inhibitors studied, however, studies of therapies not approved in the US were also included (betrixaban, darexaban, edoxaban and idraparinux). The primary outcome of composite strokes and systemic embolism was reported in nine of the studies. Factor Xa inhibitors were found to be statistically superior to warfarin for the composite primary outcome of stroke and systemic embolic events (OR 0.81, 95% CI 0.72 to 0.91; 9 studies), as well as the individual components. These results translate into of number needed to treat (NNT) of 304 per year for apixaban and 369 for rivaroxaban, when including only larger studies with follow-up of at least a year. Major bleeding was also found to be significantly less with factor Xa inhibitors compared to warfarin (OR 0.81, 95% CI 0.81 to 0.98). Due to high heterogeneity, a second analysis was performed and showed that major bleeds were not significantly less with factor Xa inhibitors (OR 0.92, 95% CI 0.63 to 1.34). Clinically relevant non-major bleeding was not statistically different between the two groups. Intracranial hemorrhage rates and all-cause death were also found be significantly less with factor Xa inhibitors compared to warfarin. Quality of anticoagulation (time in therapeutic range) with warfarin did not effect the efficacy results when compared to rivaroxaban and apixaban. Authors note that while factor Xa inhibitors were shown to be more effective than warfarin the clinical difference between the agents remains very small.

Ruff et al - Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials[39]

Apixaban, dabigatran, edoxaban, and rivaroxaban were included in a recent meta-analysis evaluating the efficacy and safety of these agents in patients with AF. In dabigatran and edoxaban studies, two dosing schemes were used and therefore analyzed in separate analyses: low dose (dabigatran 110mg twice daily and edoxaban 30mg once daily) and high dose (dabigatran 150mg twice daily, edoxaban 60mg once daily, rivaroxaban 20mg once daily and apixaban 5mg twice daily). There were 42,411 patients who received new oral anticoagulants and 29,272 who received warfarin. The mean ages included in the trials ranged from 70-73 with approximately one-third being women. The mean baseline $CHADS_2$ score was 2.1 in studies with dabigatran and apixaban, 2.8 with edoxaban and highest with rivaroxaban with a score of 3.5. Time in therapeutic range (TTR) was 58-68% across the trials. Follow-up ranged from 1.8 to 2.8 years.

The meta-analysis comparative efficacy combined results for stroke and systemic embolism favored high-dose NOAs over warfarin (RR 0.81, 95% CI 0.73 to 0.91, $p < 0.0001$). As in many of the individual trials, the results were driven by reductions in hemorrhagic stroke. All cause mortality rates were also significantly reduced in the patients allocated to the high-dose NOAs compared to those in the warfarin groups (RR 0.90, 95% CI 0.85 to 0.95, $p = 0003$). Safety findings illustrated a reduction in major bleeding (RR 86, 95% CI 0.73 to 1.00, $p = 0.06$) and intracranial hemorrhage (RR 0.48, 95% CI 0.39 to 0.59, $p < 0.0001$). Gastrointestinal bleeding was significantly higher in high-dose NOAs compared to warfarin (RR 1.25, 95% CI 1.01 to 1.55, $p = 0.043$). The efficacy benefits seen with high dose NOAs compared to warfarin were consistent across subgroups (age, sex, diabetes, previous stroke or TIA, creatinine clearance, $CHADS_2$ score, VKA status and center-based TTR). Safety findings were also consistent across subgroups except for the center-based TTR. In centers where TTR was less than 66%, relative reductions in major bleeding were even greater with the NOAs compared to warfarin. The results for the low-dose NOAs comparison to warfarin demonstrated similar efficacy findings as the high-dose, however, ischemic stroke rates were greater in the low-dose NOA groups. More MIs were reported in the low-dose NOAs group compared to warfarin. For the safety analysis, major bleeding and gastrointestinal bleeding rates were not significantly different between groups.

AHRQ – Stroke Prevention in Atrial Fibrillation[1]

An AHRQ comparative effectiveness review evaluated the efficacy and harms of treatment options for patients with nonvalvular AF. Investigators evaluated studies for quality and applicability and graded the evidence. Ninety-two studies related to bleeding risk, predicting thrombosis, thrombosis prevention and

anticoagulation in patients undergoing procedures were included in the analysis. Dabigatran 150 mg had a significantly lower risk of stroke and systemic embolism than warfarin (RR 0.66; 95% CI 0.53 to 0.82) based on high SOE. There was high SOE that major bleeding was similar between warfarin and dabigatran groups (RR 0.93; 95% CI 0.81 to 1.07). Apixaban was also found to be superior to warfarin for stroke and systemic embolism reduction (HR 0.79; 95% CI 0.66 to 0.95) and major bleeding (HR 0.69, 95% CI 0.60 to 0.80) based on high SOE. All-cause mortality was found to be reduced with apixaban compared to warfarin (HR 0.89, 95% CI 0.80 to 0.998) based on moderate SOE. Apixaban was shown to be superior to aspirin based on high SOE (HR 0.45, 95% CI 0.32 to 0.62). Rivaroxaban was shown to be noninferior to warfarin for stroke and systemic embolism prevention based on moderate evidence with similar rates of major bleeding and death (high SOE). Limitations to the review were the inclusion of a small number of trials and the lack of direct comparisons between the new agents. There was insufficient evidence on patients undergoing invasive procedures, switching among anticoagulant therapies, and starting or restarting anticoagulation after a major bleeding event.

New Guidelines:

2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation[2]

A newly released guideline from the collaborate effort of the American Heart Association (AHA), American College of Cardiology (ACC) and Heart and Rhythm Society (HRS) provides updated guidance on the management of AF. For the purpose of this drug class update, only anticoagulant therapies will be reported. The guidelines incorporate multiple data analysis methods for formulation of recommendations. The Class of Recommendations (COR) is an estimate of the size of treatment effect and the Level of Evidence (LOE) is an estimate of certainty or precision of effect (level A is associated with higher certainty and level C with less certainty). A Class III recommendation is used for those therapies with no benefit or associated with harm. An additional designation of *guideline-directed medical therapy* (GDMT) is used for optimal therapy options. Anticoagulation recommendations are provided by class, as listed below. Additional recommendations not pertaining directly to anticoagulation therapies are provided in table 3.

Class I Recommendations

In patients with mechanical heart valves, warfarin is recommended with an INR goal based on type and location of prosthesis (LOE B). Oral anticoagulants are recommended for all AF patents with prior stroke, transient ischemic attack (TIA) or CHA_2DS_2-VASc score ≥2. Oral anticoagulant options include warfarin (LOE A), dabigatran, rivaroxaban or apixaban (LOE B). INR evaluations for patients on warfarin should be done weekly upon initiation and monthly when stable (LOE A). Direct thrombin or factor Xa inhibitors are suggested for those patients who are unable to maintain a therapeutic INR on warfarin (LOE C). Renal function evaluation should be performed prior to direct thrombin or factor Xa inhibitor initiation and re-evaluate when clinically indicated, and at least annually (LOE B). The recommendations for anticoagulation for atrial flutter are the same as for AF (LOE C).

Class IIa Recommendations

In patients who require anticoagulation with CHA_2DS_2-VASc scores ≥2 and end-stage chronic kidney disease (CrCl <15 mL/min) or on hemodialysis, warfarin is a reasonable choice (LOE B).

Class IIb Recommendations

Consideration may be given to no treatment, anticoagulants, or aspirin therapy in patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1 (LOE C). In patients with a CHA_2DS_2-VASc score of ≥2 who have undergone a coronary revascularization, it may be reasonable to use clopidogrel in combination with oral anticoagulants, but not aspirin (LOE B).

Class III: No benefit
Due to lack of evidence from clinical trials and the balance of risks and benefits, dabigatran and rivaroxaban are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis (LOE C).

Class III: Harm
Dabigatran should not be used in patients with mechanical heart valves (LOE B).

Table 3. AHA/ACC/HRS Guidelines – Non-drug Recommendations for the Prevention of Thromboembolism in Patients with AF[2]

Recommendations	Class of Recommendation	Level of Evidence
Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences	I	C
Antithrombotic therapy selection based on risk of thromboembolism	I	B
Re-evaluate the need for anticoagulation at periodic intervals	I	C
Bridging therapy with LMWH or UFH recommended with mechanical heart valve if warfarin is interrupted. Bridging therapy should balance risks or stroke and bleeding.	I	C
Without mechanical heart valve, bridging therapy decisions should balance stroke and bleeding risks against the duration of time patient will not be anticoagulated	I	C
With nonvalvular AF and CHA2DS2-VAc score of 0, it is reasonable to omit antithrombotic therapy	IIa	B
For percutaneous coronary intervention (see 2011 guideline for specifics on type of stent and duration of dual antiplatelet therapy recommendations) bare-metal stent may be considered to minimize duration of dual antiplatelet therapy	IIb	C

** Table adapted from January CT, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation. J of Amer C of Cardiol 2014, doi: 10.1016/j.jacc.2014.03.022.*

Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update[8]
The 2007 evidence-based guideline produced by the American Society of Clinical Oncology (ASCO) was updated in 2013. Forty-two systematic reviews and randomized controlled trials were included and assessed for risk of bias. Recommendations regarding VTE treatment and prophylaxis will be reported. There was strong evidence to support the use of LMWH over UFH for initial anticoagulation (5-10 days) in patients with cancer with newly diagnosed VTE and no renal impairment. LMWH is preferred for long-term anticoagulation, lasting at least 6 months, over VKAs (strong SOE). However, VKAs are an option if LMWH is unavailable. There is insufficient evidence to recommend anticoagulation beyond 6 months. The use of NOAs for prevention or treatment of VTE is not recommended due to insufficient evidence.

AHA/ASA Guideline – Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack (TIA)[40]
The American Heart Association (AHA) and the American Stroke Association (ASA) released updated guidelines on managing secondary prevention patients with a history of TIA or stroke. The data pertaining to anticoagulation treatment will be summarized. Recommendations are based on two components; the Class of

Recommendations (COR) is an estimate of the size of treatment effect and the Level of Evidence (LOE) is an estimate of certainty or precision of effect (level A is associated with higher certainty and level C with less certainty). A Class III recommendation is used for those therapies with no benefit or associated with harm. The Class of Recommendations (COR) is an estimate of the size of treatment effect and the Level of Evidence (LOE) is an estimate of certainty or precision of effect (level A is associated with higher certainty and level C with less certainty). A Class III recommendation is used for those therapies with no benefit or associated with harm. Table 4 highlights changes from previous recommendations.

Table 4. Updated Recommendations for Stroke Prevention in Patients with Stroke and TIA[40]

Indication	Therapy	Class of Recommendation	Level of Evidence
Nonvalvular AF (paroxysmal or permanent)	VKA Therapy (INR 2.0-3.0)	I	A
	Apixaban	I	A
	Dabigatran	I	B
	Rivaroxaban	IIa	B
Nonvalvular AF and CAD	VKA/Newer Agents and antiplatelet therapy	IIb	C
Ischemic stroke or TIA and MI and Thrombus*	VKA therapy for 3 months	IIb	C
	For patients intolerant to VKAs appropriate alternatives to consider are; LMWH, dabigatran, rivaroxaban or apixaban for 3 months	IIb	C
Ischemic stroke or TIA and Cardiomyopathy*	VKA for ≥3 months for left atrial or left ventricular thrombus	I	C
	VKA therapy for mechanical LVAD	IIa	C
	Dabigatran, rivaroxaban, apixaban therapy for dilated cardiomyopathy, restrictive cardiomyopathy, or mechanical LVAD has uncertain effectiveness compared to VKA treatment	IIb	C
Ischemic stroke or TIA and Valvular Heart Disease	VKA therapy for rheumatic mitral valve disease and AF	I	A
	VKA therapy may be considered for those with rheumatic mitral valve disease or another likely cause for symptoms without AF	IIb	C
Ischemic stroke or TIA and Prosthetic Heart Valve	VKA therapy recommended for mechanical aortic valves in patients with stroke or TIA history before valve insertion	I	B
Pregnancy and High Risk Condition	LMWH, UFH throughout pregnancy or up until the 13th week, followed by a VKA until close to delivery and then LMWH or UFH is resumed	IIa	C
Breastfeeding and High Risk Condition	Warfarin, UFH, or LMWH	IIb	C

* See guideline for specific circumstances regarding therapy recommendations.

LMWH- low molecular weight heparin, VKA- vitamin K antagonist, UFH-unfractionated heparin, LVAD-left ventricular assist device , AF-atrial fibrillation

Table adapted from Kernan et al, Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke 2014; 45:00-00. Doi:10.1161/STR.0000000000000024.

Patient specific characteristics such as risk factors, cost, tolerability, patient preference, drug interactions, ability to maintain a therapeutic INR and renal function should be considered when selecting an anticoagulation regimen. Initiation of anticoagulation in patients with a history of TIA or stroke should be considered in most patients within in 14 days of initial symptoms.

AHA/ASA – Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association[41]

Stroke risks and treatments were summarized in a recent guideline from the AHA/ASA pertaining exclusively to women. The guidelines incorporate multiple data analysis methods for formulation of recommendations. The Class of Recommendations (COR) is an estimate of the size of treatment effect and the LOE is an estimate of certainty or precision of effect (level A is associated with higher certainty and level C with less certainty). A Class III recommendation is used for those therapies with no benefit or associated with harm. Data pertaining to anticoagulants will be summarized.

VKAs are recommended for women with acute cerebral venous thrombosis (CVT) for at least 3 months and possibly indefinitely dependent upon etiology. Pregnant women with CVT should receive LMWH during pregnancy, followed by vitamin K antagonists for ≥6 weeks post partum (Class I; Level of Evidence A). For women with paroxysmal or permanent AF with pre-specified risk factors, NOAs are an alternative to VKA therapy in patients without prosthetic heart valves or hemodynamically significant valve disease, severe renal failure, lower weight (<50 kg) or advanced liver disease (Class I; Level of evidence C). Data on NOA use in women is minimal, as none of the studies were powered to determine a difference in efficacy according to sex, but evidence suggests that efficacy is similar to that in men.

NICE – Atrial Fibrillation: the Management of Atrial Fibrillation[4]

June 2014 marked the release of updated guidance from NICE for the management of patients with AF. Evidence was assessed for quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method. Recommendations for anticoagulation will be discussed. Anticoagulation should be considered in patients with a CHA_2DS_2VASc stroke risk score equal to 1 in men and offered to all patients with a CHA_2DS_2VASc score of ≥2. Choice of anticoagulant should be chosen based on patient preference, clinical characteristics and consideration of benefits and risks of all treatments. Evidence comparisons between warfarin and non-vitamin K antagonists have been discussed in single technology appraisals. Bleeding risk, based on the HAS-BLED score, should be taken into account when offering anticoagulation. For patients on VKAs, TTR should be determined every visit and calculated over a maintenance period of at least 6 months. If adequate anticoagulation can't be maintained, other treatment options should be considered. Non-vitamin K anticoagulation options are presented below (table 5). Aspirin monotherapy is not recommended for stroke prevention.

Table 5. Non-vitamin K Antagonists for Patients with Atrial Fibrillation[4]

Treatment	Patient Characteristics
Apixaban	Nonvalvular AF and one or more of the following risk factors: prior stroke, age ≥75 years, hypertension, diabetes or symptomatic heart failure
Dabigatran	Nonvalvular AF and one or more of the following risk factors: previous stroke, TIA, or systemic embolism, left ventricular EF <40%, symptomatic HF of NYHA class ≥2, ≥75 years, ≥65 years with one of the following: diabetes, coronary artery disease or hypertension
Rivaroxaban	Nonvalvular AF and one or more of the following risk factors: CHF, hypertension, ≥75 years or older, diabetes or prior stroke or TIA
AF- atrial fibrillation, TIA – transient ischemic attack, EF – ejection fraction, NYHA – New York heart classification, CHF – congestive heart failure	

New FDA Alerts:

DABIGATRAN- Black Box Warning[35]

Labeling changes were made in April of 2013 to dabigatran. A black box warning was added to alert providers of the increased risk of thrombotic events, including stroke, upon discontinuation of dabigatran. Coverage with a different anticoagulant is recommended unless pathological bleeding is present. Epidural or spinal hematomas may occur in patients treated with dabigatran who are receiving neuraxial anesthesia or undergoing spinal puncture.

RIVAROXABAN- Black Box Warning[42]
In August of 2013 the black box warning for rivaroxaban was changed to include an increased risk of thrombotic events upon premature discontinuation of rivaroxaban, regardless of indication.

Warnings and precautions section was updated to advise against the use of rivaroxaban in patients with prosthetic heart valves as it has not been studied and therefore not recommended.

APIXABAN – Dosing Recommendations[33]
In January of 2014 dosing recommendations for apixaban when used in end-stage renal disease maintained on hemodialysis was updated based on pharmacokinetic and pharmacodynamic studies. Apixaban 5mg twice daily is recommended when undergoing dialysis. As previously recommended, patients $\geq$80 years of age or body weight of $\leq$60 kg should be given 2.5 mg twice daily.

APIXABAN- Black Box Warning[33]
The warning of the risk for epidural or spinal hematoma, potentially causing paralysis, is increased in patient using apixaban and undergoing spinal epidural anesthesia or spinal puncture was added in March 2014.

DABIGATRAN – Drug Safety Communication – Lower risk for Stroke, and Death, but Higher Risk for GI Bleeding Compared to Warfarin[43]
An observational cohort study of 134,000 Medicare patients (65 years and older) was conducted by the FDA to compare dabigatran to warfarin for risk of stroke, major GI bleeding, MI and death. Patients were newly diagnosed with AF within 6 months of medication claim for anticoagulation. Data was derived from administrative and insurance claims data. Adjustments were made for potential confounding variables. Dabigatran (150 mg and 75 mg dose) was found to be associated with a lower risk of ischemic stroke (HR 0.80; 95% CI 0.67 to 0.96), intracranial hemorrhage (HR 0.34; 95% CI 0.26 to 0.46) and death (HR 0.86; 95% CI 0.77 to 0.96) compared to warfarin. Risk for GI bleeding was higher for dabigatran (HR 1.28; 95% CI 1.14 to 1.44) compared to warfarin and MI risk was similar (HR 0.92; 95% CI 0.78 to 1.08). These findings are similar to the RE-LY study with the exception of the MI risk being similar for the two treatments instead of an elevated risk for dabigatran. The increased risk of GI bleeds associated with dabigatran was similar to the RE-LY study but differs from data found in the Mini Sentinel Modular Program analysis which found less risk of GI bleeds with new users of dabigatran compared to warfarin.

New Indications:
APIXABAN-
Apixaban gained a new indication in March 2014 for prophylaxis of DVT which may lead to PE in adult patients who have undergone hip or knee replacement surgery. One fair quality study (ADVANCE-1) and two good quality studies (ADVANCE-2 and ADVANCE-3) were used as evidence for the approval of apixaban for this expanded indication. [22,25,26] The approved dose for prophylaxis is 2.5mg twice daily.

ADVANCE TRIALS – Orthopedic Prophylaxis

The good quality ADVANCE studies were previously evaluated in the Anticoagulant Abbreviated Class Update (Appendix 1), which was presented to the Oregon Health Plan P&T Committee in March 2013.[42] The clinical efficacy and safety of apixaban use in orthopedic prophylaxis was demonstrated in three phase III, randomized, double-blind, double-dummy clinical trials involving 11,659 patients (ADVANCE 1-3).[22,25,26] Patients were eligible for the trials if they were scheduled for TKR or revision (ADVANCE 1-2) or THR or revision (ADVANCE 3). Mean treatment durations were 11-12 days in the TKR trials and 34 days in the THR trial. The primary endpoint was the rate of symptomatic and asymptomatic DVT, non-fatal PE and all-cause mortality. The primary safety endpoint was bleeding rates.

ADVANCE-1 randomized patients undergoing TKR to apixaban 2.5mg twice daily compared to enoxaparin 30mg every 12 hours.[25] Apixaban was show to be inferior to enoxaparin based on primary endpoint occurrence (RR 1.02; 95% Cl 0.78 to 1.32, p=0.06 for noninferiority). In ADVANCE-2 the European dosing regimen of enoxaparin 40mg daily was compared to apixaban 2.5 mg twice daily and was found to be noninferior and superior to enoxaparin (RR 0.62; 95% CI 0.51 to 0.74, p<0.001 for superiority).[26] In ADVANCE-3 patients received enoxaparin 40 mg daily or apixaban 2.5 mg twice daily for THR for a mean duration of 34 days. Apixaban was found to be noninferior and superior to enoxaparin (RR 0.36, 95% CI 0.22 to 0.54, p<0.001).[22]

Pooling data of the ADVANCE trials showed both apixaban and enoxaparin to have a similar rate of adverse reactions and discontinuation due to adverse events. ADVANCE-1 showed apixaban to be associated with significantly less major bleeds and clinically relevant non-major bleeds compared to enoxaparin. These same safety outcomes were found to be similar between apixaban and enoxaparin in ADVANCE-2 and 3.

Conclusion:
Apixaban was found to be superior to the European dosing regimen of enoxaparin, based on one fair quality trial, but not to the US approved dosing regimen of enoxaparin, in patients requiring thromboprophylaxis for TKR (low SOE). One good quality trial found use of apixaban, in patients undergoing THR, to be superior to enoxaparin (moderate SOE). Rates of bleeding were found to be similar for apixaban and enoxaparin in patients requiring thromboprophylaxis for TKR or THR (moderate SOE).

DABIGATRAN – Reduction in Recurrent VTE[6]

Dabigatran recently received approval for the reduction in risk of recurrent DVT and PE in individuals who have already been treated. Dosing recommendations for this indication are dabigatran 150mg twice daily. Evidence for this approval was based on two studies (REMEDY and RESONATE).[6]

Dabigatran was studied in two good quality studies for the extended treatment of VTE in patients previously treated for 3 months with dabigatran or other anticoagulant. In REMEDY 2866 patients were randomized to dabigatran 150 mg twice daily or warfarin (target INR of 2.0 to 3.0) and in RESONATE 1353 patients were assigned to dabigatran 150 mg twice daily or placebo. Both studies had the same design and patient inclusion and exclusion criteria were similar. Patients deemed to be at higher risk for recurrent VTE were enrolled in the active treatment study. Patients were predominately white with a slight majority being male. A higher percentage of patients in the dabigatran group had a history of coronary artery disease, diabetes and hypertension compared to warfarin. DVT was the most common reason for inclusion followed by PE. In the active treatment study therapy ranged from 6 to 36 months and in the placebo study follow-up was to 12 months. The primary efficacy outcomes was recurrent symptomatic and objectively verified VTE or death associated with VTE (or unexplained death in the placebo-control study). Secondary outcomes of importance include symptomatic DVT, non-fatal symptomatic PE, VTE-related death and all deaths. Important safety outcomes included major bleeding, clinically relevant non-major bleeding and acute coronary events.

Dabigatran was found to be non-inferior to warfarin with the primary outcome occurring in 1.8% and 1.3%, respectively (HR 1.44, 95% CI 0.78 to 2.64, p=0.01). Major bleeding was less with dabigatran than warfarin but not significantly so. In the placebo controlled trial primary outcome rates were lower for dabigatran compared to placebo, 0.4% and 5.6%, respectively. Major bleeding was less with dabigatran compared to warfarin but not significantly so. The composite endpoint of major or clinically relevant bleeding was significantly less with dabigatran compared to warfarin (HR 0.54, 95% CI 0.41 to 0.71, p<0.001). As anticipated, major bleeding rates were higher with dabigatran compared to placebo. Major or clinically relevant nonmajor bleeding was also higher with dabigatran than placebo, 5.3% vs. 1.8%. Acute coronary events were found to be higher in the dabigatran group (0.9%) compared with warfarin (0.2%), however event rates were similar in placebo controlled trial. Limitations to the studies include a large noninferiority margin for the hazard ratio (2.85) which proved dabigatran to be noninferior to warfarin even with an increase in risk of almost 3. Most patients enrolled had normal renal function and were Caucasian, limiting extrapolation of results to the general population. The role associated with the increased risk of coronary events seen with dabigatran is still unknown. Future studies including patients with strong indications for continued anticoagulation would be helpful in determining the role of dabigatran for the prevention of VTE long term.

Conclusion: There is moderate SOE that dabigatran is non-inferior to warfarin for the extended treatment of VTE with less risk of major or clinically relevant bleeding and that dabigatran is superior to placebo but with increased risk of bleeding.

RE-COVER II- Dabigatran for the Treatment of VTE[7]

Dabigatran 150 mg twice daily has received FDA approval for use in the treatment of DVT and PE in patients receiving 5to 10 days of parenteral anticoagulation. The RECOVER and RECOVER II studies were used for data to support this indication.[17,7]

In RECOVER II dabigatran was compared to warfarin in 2589 patients, previously treated with LMWH or unfractionated heparin for 5 to 11 days, for the treatment of VTE. In this double-blind, double-dummy, non-inferiority, randomized controlled trial, patients were provided dabigatran 150 mg twice daily or warfarin adjusted to an INR of 2-3 for 6 months. The non-inferiority margin was set at a HR of 2.75 and an absolute risk margin of 3.6 percentage points for the primary outcome. Patients were an average age of 55 years with the majority (61%) being male. Baseline characteristics were well-matched except for a higher percentage of patients in the dabigatran group had prior history of VTE than those in the warfarin group, 19% and 16%, respectively. TTR was 57% for patients randomized to warfarin therapy. The primary efficacy outcomes were recurrent symptomatic and objectively verified VTE or death. Major bleeding was the primary safety endpoint with any bleeding being a secondary safety outcome.

For the primary outcome dabigatran was shown to be non-inferior to warfarin (HR 1.08, 95% CI 0.64 to 1.80, p < 0.001), which was consistent across subgroups. The risk of symptomatic DVT was higher in the dabigatran group compared to warfarin, 2.0% vs. 1.3%, respectively. The reverse was true for symptomatic nonfatal PE, with a lower risk demonstrated in the dabigatran group (0.5%) compared to warfarin (1.0%). Dabigatran was shown to be associated with lower major bleeding than warfarin, 1.2% and 1.7%, respectively (HR 0.69, 95% CI 0.36 to 1.32). Major or clinically relevant non-major bleeding and any bleeding occurred less commonly with dabigatran than with warfarin, with a significant difference found in the latter two outcomes. Dabigatran and warfarin groups were associated with a similar number of deaths and coronary events. A limitation to this study include a large non-inferiority margin which allowed for more than a 3% difference in efficacy . TTR for patients in the warfarin group was less than what has been commonly shown in other studies which would favor dabigatran.

For the pooled analysis of RE-COVER and RE-COVER II patients, recurrent VTE rates were similar with a HR of 1.09 (95%CI, 0.76 to 1.57). Baseline patient characteristics did not influence efficacy results to a significant extent, however, warfarin appeared to be more effective in patients under 60 years of age. For the outcome of clinically relevant bleeding, dabigatran demonstrated a significantly higher risk reduction in younger patients up to the age of 85 years.

Conclusion: There is moderate evidence that dabigatran is non-inferior to warfarin for acute VTE treatment with less major bleeding and significantly less major and clinically relevant non-major bleeds and any bleeding with dabigatran in comparison to warfarin.

NEW EVIDENCE:

Apixaban – VTE Treatment[5]

In AMPLIFY, 5395 patients with objectively confirmed, symptomatic proximal deep-vein thrombosis or pulmonary embolism were randomized to receive apixaban 10 mg twice daily for seven days followed by 5 mg twice daily for 6 months compared to conventional treatment with enoxaparin for at least 5 days and warfarin (target INR 2.0-3.0) for 6 months. The non-inferiority margin was set at a relative risk less than 1.8 and the risk difference below 3.5%. The mean age of included patients was 57 years old and the majority (69%) were males. Patients at high risk of bleeding, those with cancer, patients requiring extended treatment with an anticoagulant, those requiring long-term anticoagulation, or those with additional indications for anticoagulants were excluded. The majority of patients presented with unprovoked DVT. The primary outcome was recurrent symptomatic VTE or death related to VTE. Important secondary outcomes were the individual components of the primary composite outcome. Safety outcomes included major bleeding and the combined outcome of major bleeding plus clinically relevant non-major bleeding.

In this good quality trial, apixaban treatment was shown to be non-inferior to conventional treatment with enoxaparin and warfarin (RR 0.84, 95% CI 0.60 to 1.18, $p<0.001$). Non-fatal PE and DVT risk was lower with apixaban compared to conventional treatment, 1.8% vs. 2.2%, respectively. Major bleeding was found to significantly less in the apixaban group compared to conventional treatment (0.31, 95% CI 0.17 to 0.55, $p < 0.001$). Results were consistent regardless of diagnosis at study entry (DVT or PE). Patients randomized to warfarin were found to have therapeutic INRs 61% of the time, which corresponds to rates found in other studies. Withdrawals due to adverse effects were similar among treatment groups. External validity is limited to patients with normal renal function or mild renal impairment, low risk for bleeds and no cancer diagnosis.

Conclusion: There is moderate SOE that apixaban treatment is non-inferior to conventional therapy for VTE treatment and was found to be superior to conventional therapy for the safety outcome of major bleeding.

RIVAROXABAN – Thromboprophylaxis in Acutely Ill Medical Patients[10]

The MAGELLAN study compared rivaroxaban to enoxaparin in hospitalized, acutely ill, medical patients. In this fair quality study patients were randomized to SQ enoxaparin 40mg once daily for 10±4 days and oral placebo for 35±4 days or rivaroxaban 10 mg daily for 35±4 days and SQ placebo for 10±4 days. There were 8428 patients enrolled in the study which were a median age of 71, predominately white with most having normal renal function. The primary efficacy outcomes were the composite of asymptomatic proximal or symptomatic VTE (asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE and VTE-related death) up to day 10 and up to day 35. Net clinical benefit or harm was an important secondary outcome.

Rivaroxaban was found to be non-inferior to enoxaparin at day 10 (RR 0.97, 95% CI 0.71 to 1.31, p = 0.003 for noninferiority). At day 35 rivaroxaban was shown to be superior to enoxaparin with occurrence of the primary outcome in 4.4% of rivaroxaban patients and 5.7% in those who received enoxaparin (RR 0.77, 95%CI 0.62 to 0.96, p=0.02 for superiority). For the analysis of net clinical benefit (efficacy and harms) enoxaparin was shown to have a benefit over rivaroxaban at day 10 and day 35. For the primary safety outcome of the composite of major or clinically relevant nonmajor bleeding, rivaroxaban was shown to have higher rates at day 10 (RR 2.3, 95% CI 1.63 to 3.17, p < 0.001) and day 35 (RR 2.5, 95% CI 1.85 to 3.25, p < 0.001) compared to enoxaparin. Limitations to this data include the varying treatment durations of study groups and large subgroup of patients not available for ultrasonography (17-25%). The clinical relevance of asymptomatic VTE, included in the composite primary endpoint, is unknown. External validity is limited to elderly patients with normal renal function.

Conclusion: Based on low strength of evidence, rivaroxaban was shown to be as effective as enoxaparin at day 10 and superior to enoxaparin at day 35 when used for thrombus prevention in patients who were medically ill. Enoxaparin treatment was associated with less risk of bleeding compared to rivaroxaban based on low strength of evidence.

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:
Mortality
Thromboembolic events (DVT, PE, stroke)
Cardiovascular events
Bleeding

Primary Study Endpoints:
Surgery Prophylaxis: Total VTE and mortality
DVT/PE Treatment: Recurrent VTE and mortality
AF: Stroke or systemic embolism and mortality
Medically Ill: Cardiovascular death, myocardial infarction or ischemic stroke
All studies: bleeding

Evidence Table

AMPLIFY[5]

Agnelli, et al Phase III, RCT, DB 28 Countries	1. Apixaban (A) - 10mg BID fo 7 days, then 5mg BID for 6 months 2. Conventional Therapy (CT) – SQ enoxaparin for at least 5 days followed by warfarin for 6 months (INR 2.0-3.0)	Age: 57 yrs Male: 59% Inclusion: Patients 18 and older with objectively confirmed, symptomatic proximal deep-vein thrombosis or pulmonary embolism. Exclusion: Bleeding disorder contraindication t warfarin or enoxaparin, cance and use of LMWH was planned, DVT or PE provoked without persistence risk factors for recurrence, less than 6 months of treatment planned, an additional indication for long term anticoagulation, ASA use of >165mg a day, or use of potent cytochrome P-450 3A4 inhibitors.	1. 2691 2. 2704	Median Tx duration: 6 months	<u>Recurrent Symptomatic VTE or Death related to VTE :</u> A: 59 (2.3%) CT: 71 (2.7%) RR: 0.84 (95% CI 0.60 to 1.18, p<0.001 for noninferiority) <u>Fatal PE:</u> A: 1 (<0.1%) CT: 2 (0.1%) <u>DVT:</u> A: 20 (0.8%) CT: 33 (1.3%) <u>Non-fatal PE with or without DVT:</u> A: 27 (10%) CT: 23 (0.9%)	NS NS NS NS	<u>Major Bleeding:</u> A: 15 (0.6%) E: 49 (1.8%) RR: 0.31 (95% CI 0.17 to 0.55, P<0.001 for superiority) <u>Major Bleeding and Clinically Relevant nonmajor bleeding:</u> A: 115 (4.3%) CT: 261 (9.7%) RR: 0.44 (95% CI 0.36 to 0.55, p<0.001) <u>Withdrawal due to Adverse Events</u> A: 162 (6.1%) E: 199 (7.4%)	ARI: 1.2% NNH: 83 ARI: 5.4% NNH: 19 NA	**Quality Rating: Good** **Internal Validity: RofB** Selection: Interactive voice-response system Performance: double-dummy design used to conceal treatment assignments from patients and clinical monitors. INR monitoring was blinded and encrypted. Detection: independent committee, blinded to treatment assignment, adjudicated results Attrition: similar attrition rates were seen in both studies (14-15%). Sensitivity analysis accounting for missing data did not change results. **External Validity** Recruitment: recruited from 358 centers in 28 countries. Patient Characteristics: the majority of patients presented with unprovoked DVT. For patients on warfarin, INRs were therapeutic 61% of the time. Adherence to apixaban was >80% in 96% of patients. Outcomes: Primary endpoint and safety outcomes were appropriate for study.
REMEDY[6]									
Schulman, et al	1. Dabigatran (D) 150 mg daily 2. Warfarin (W)	Age: 54.5 years Female: 39% Duration of prior treatment: 199 days	1. 1430 2. 1426	Median Tx duration: 6-36 months	<u>Recurrent VTE or death:</u> D: 26 (1.8%) W: 18 (1.3%) HR: 1.44 (95% CI 0.78 to 2.64	NA	<u>Major Bleeding</u>: D: 13 (0.9%) W: 25 (1.8%) HR: 0.52 (95% CI 0.27 to 1.02,	NS	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via computerized voice-response system.

Phase III, DB, RCT 33 Countries	with target range of 2.0-3.0	Inclusion: Patients at least 18 years old with objectively confirmed, symptomatic, proximal DVT or PE and 3 months of initial therapy of an approved anticoagulant or dabigatran as part of the RE-COVER or RE-COVER II studies. Exclusion: Symptomatic DVT at screening, patients with PE etiology from source other than legs, use or anticipated use of vena cava filter, patients at excessive risk of bleeding, unstable co-morbidities.			P=0.01 for noninferiority) Recurrent DVT: D: 17 (1.2%) W: 13 (0.9%) HR: 1.32 (95% CI 0.64 to 2.71, p=0.46) Recurrent PE D: 10 (0.7%) W: 5 (0.4%) HR: 2.04 (95% CI 0.70 to 5.98, p=0.19)	NS NS	p=0.77) Major or Clinically Relevant Bleeding: D: 80 (5.6%) W: 145 (10.2%) HR: 0.54 (95% CI 0.41 to 0.71, P<0.001) Acute Coronary Syndrome: D: 13 (0.9%) W: 3 (0.2%) p=0.02 Withdrawal due to Adverse Events D: 145 (10.1%) W: 126 (8.8%)	ARI: 4.6% NNH: 22 ARI: 0.7% NNH: 143 NA	Performance: double-dummy design used to conceal treatment assignments from patients and clinical monitors. INR monitoring was blinded and encrypted. Detection: Outcomes were assessed by central adjudication committee that were unaware of treatment assignment. Large noninferiority margin for the hazard ratio (2.85) allowed for almost 3x the risk to be considered noninferior Attrition: Low rates of lost to follow-up. **External Validity:** Recruitment: Patients recruited from 265 sites from 33 countries. Patient Characteristics: Patients on warfarin in TTR 65% of the time. Patients had previously been exposed to treatments. Outcomes: Direct outcomes were used to determine treatment effect. Large non-inferiority margin was used which could show no difference, even if one exists.
RESONATE[6]									
Schulman, et al Phase III, DB, RCT 21 Countries	1. Dabigatran (D) 150 mg daily 2. Placebo	Age: 56 yrs Female: 44.5% Inclusion: Patients at least 18 years old with objectively confirmed, symptomatic, proximal DVT or PE and 3 months of initial therapy of an approved	1. 681 2. 662	Tx duration: 6 months	Recurrent VTE or death: D: 3 (0.4%) P: 37 (5.6%) HR: 0.08 (95% CI 0.02 to 0.25 P<0.001 for superiority) Recurrent DVT: D: 2 (0.3%) P: 22 (3.3%) Recurrent PE D: 1 (0.1%)	ARR: 5.2% NNT: 19	Major Bleeding: D: 3 (0.3%) P: 0 (0.0%) Major or Clinically Relevant Bleeding: D: 36 (5.3%) P: 12 (1.8%) HR: 2.92 (95% CI 1.52 to 5.60, p=0.001) Acute Coronary	NS ARI: 3.5 NNH: 29	**Quality Rating: Good** **Internal Validity: RofB** Selection: Patients were randomized via computerized voice-response system. Performance: Double-dummy design used to conceal treatment assignments from patients and clinical monitors. INR monitoring was blinded and encrypted. Detection: Outcomes were assessed by central adjudication committee that was unaware of treatment assignment. Attrition: Low rates of lost to follow-up.

		anticoagulant or dabigatran as part of the RE-COVER or RE-COVER II studies Exclusion: Symptomatic DVT a screening, patients with PE etiology from source other than legs, use or anticipated use of vena cava filter, patients at excessive risk of bleeding, unstable co-morbities and cancer.			P: 14 (2.1%)		Syndrome: D: 1 (0.1%) P: 1 (0.2%) Withdrawal due to Adverse Events D: 50 (7.3%) P: 81 (12.3%)		**External Validity:** Recruitment: Patients were recruited from 147 sites in 21 countries. Patient Characteristics: Patients were previously exposed to treatment. Outcomes: Direct outcomes were used to determine treatment effect.
MAGELLAN[10]									
The Cohen, e al Phase III, DB, DD, RCT 52 Countries	1. Rivaroxaban 10mg once daily (R) 2. Enoxaparin 40mg SQ once daily (E)	Median Age: 71 years Male: 55% Median hospital duration: 11 days Inclusion: patients 40 years and older, hospitalized with ar acute medical illness for less than 72 hours with reduced mobility and one additional risk factor for VTE. Exclusion: Elevated risk of bleeding, severe comorbidities, use of medications known to interact with rivaroxaban or enoxaparin, use of	1. 4050 2. 4051	Tx duration: 10 day for enoxaparin /35 days for rivaroxaban	Asymptomatic proximal o symptomatic VTE at day 10: R: 78 (2.7%) E: 82 (2.7%) RR: 0.97 (95% CI, 0.71 to 1.31, p=0.003, for noninferiority) Asymptomatic proximal o symptomatic VTE at day 35: R: 131 (4.4%) E: 175 (5.7%) RR: 0.77 (95% CI, 0.62 to 0.96, p=0.02 for superiority) VTE related death at day 10: R: 3 (0.1%) E: 6 (0.2%) VTE related death at day 35:	NA ARR: 1.3% NNT: 77 NA	Clinically relevant bleeding at day 10: R: 111 (2.8%) E: 49 (1.2%) RR: 2.3 (95% CI, 1.63 to 3.17, p<0.001) Clinical relevant bleeding at day 35: R: 164 (4.1%) E: 67 (1.7%) RR: 2.5 (95% CI, 1.85 to 3.25, p<0.001) Fatal Major Bleed at day 10: R: 5 (0.1%) E: 1 (<0.1%) Fatal Major Bleed at day 35: R: 7 (0.2%) E: 1 (<0.1%)	ARI: 1.6 NNH: 63 ARI: 2.4% NNH: 42 NS	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via computerized voice-response system. Performance: Double-blind, double-dummy design helps to minimize risk of bias. Detection: Outcomes were assessed by centra adjudication committee that was unaware of treatment assignment. Attrition: 17-25% of patients excluded from mITT analysis due to lack of venography. **External Validity:** Recruitment: Patients were from 556 sites in 52 countries. Patient Characteristics: Similar baseline characteristics. Patients were elderly and predominately white. Outcomes: Clinical relevance of asymptomatic VTE is unknown.

		other anticoagulants or compression devices.			R: 19 (0.6%) E: 30 (1.0%)	NA			
RE-COVER II[7]									
Shulman et al. RCT, DD, DB 31 Countries	1. Dabigatran 150 mg twice daily (D) 2. Warfarin (W) – adjusted to INR of 2-3 * Patients in both groups previously treated with LMWH or unfractionated heparin for 5-11 days	Median Age: 55 years Male: 39% <u>Inclusion:</u> Patients 18 or older with acute, symptomatic, objectively verified proximal DVT of the legs or pulmonary embolism whom 6 mo. of anti-coagulation was deemed appropriate. <u>Exclusion:</u> Symptoms >14 days, PE with hemodynamic instability or requiring thrombolytics, additional warfarin indication, high risk of bleeding, unstable CV disease, and renal and liver abnormalities.	1.1279 2.1289	Tx duration: 6 months	<u>Recurrent Symptomatic VTE or death due to VTE:</u> D: 30 (2.3%) W: 28 (2.2%) HR: 1.08 (95% CI 0.64 to 0.1.80 P<0.001 for non-inferiority) <u>Symptomatic DVT:</u> D: 25 (2.0) W: 17 (1.3) HR: 1.48 (95%CI, 0.80 to 2.74) <u>Symptomatic nonfatal pulmonary embolism:</u> D: 7 (0.5) W: 13 (1.0) HR: 0.54 (95% CI 0.21 to 1.35) <u>Death:</u> D: 25 (2) W: 25 (1.9) HR: 0.98 (95% CI, 0.56 to 1.71)	NA NA NA NA	<u>Major Bleeding:</u> D: 15 (1.2%) W: 22 (1.7%) HR: 0.69 (95% CI 0.36 to 1.32) <u>Major or clinically relevant non-major bleeding:</u> D: 64 (5%) W: 102 (7.9%) HR: 0.62 (95% CI 0.4 to 0.84) <u>Any Bleeding:</u> D: 200 (15.6%) W: 285 (22.1%) HR: 0.67 (95% CI 0.56 to 0.81) <u>Dyspepsia:</u> D: 11 (1.0%) W: 3 (0.2%) <u>Acute Coronary Syndrome</u>: D: 4 (0.3%) W: 2 (0.2%) <u>Event Leading to Drug Discontinuation:</u> D: 100 (7.8%) W: 100 (7.8%) HR: 1.00 (95%CI 0.76 to 1.32)	NS NS NS	**Quality Rating: Good** **Internal Validity: RofB** Selection: Patients were randomized via interactive, computerized voice-response system and computer-generated randomization scheme. Performance: Double-blind, double-dummy design minimize risk of bias. Interactive voice-response system provided true or sham INR values. Detection: Outcomes were assessed by centra adjudication committee that was unaware of treatment assignment. Attrition: 17-25% of patients excluded from mITT analysis due to lack of venography. **External Validity:** Recruitment: Patients were from 208 sites in 31 countries. Patient Characteristics: Similar baseline characteristics except for a higher percent of dabigatran treated patients had prior history o VTE. Majority (66%) from Europe and North America. TTR for warfarin treated patients wa 56.9%. Outcomes: Clinical relevance of asymptomatic VTE is unknown.

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.

[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: TTR= time in therapeutic range, SQ-subcutaneous, DVT- deep vein thrombosis, PE-pulmonary embolism, VTE- venous thromboembolism.

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Appendix 1: ADVANCE Studies

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:
Mortality
Thromboembolic events (DVT, PE, stroke)
Cardiovascular events
Bleeding

Primary Study Endpoints:
Recurrent VTE, clinically relevant bleeding
Mortality
Clinically relevant bleeding

Evidence Table

ADVANCE-1[7]								
1. Apixaban 2.5 mg twice daily* 2. Enoxaparin 30 mg every 12 hours* * Treatment started 12-24 hours post surgery	Mean Age: 66 years Female: 60% Inclusion: Patients ≥ 18 years of age scheduled for TKR on one or both knees. Exclusion: active bleeding, contraindications to anticoagulation, required ongoing anticoagulation or antiplatelet therapy, uncontrolled	1. 1599 2. 1596	Mean Treatment: 11 days Mean start of medication: 20 hours	Composite of asymptomatic and symptomatic DVT, non-fatal PE or death from any cause: A: 104 (9.0%) E: 100 (8.8%) RR 1.02 (95% CI 0.78 to 1.32, p=0.06 for noninferiority) Symptomatic VTE and VTE related death: A: 19 (1.2%) E: 13 (0.81%) RR 1.46 (95% CI 0.72 to 2.95) All PE:	NS NS	Major Bleeds: A: 11 (0.7%) E: 22 (1.4%) Risk Difference: -0.81 (95% CI -1.49 t 0.14, p=0.05) Major or clinically relevant non-major bleeding: A: 46 (2.9%) E: 68 (4.3%) Risk Difference: -1.46 (95% CI, -2.75 to 0.17, p=0.03)	NA NA	**Study Rating: Good** **Internal Validity: RofB** Selection: Patients randomized via central, interactive telephone system. Well matched baseline characteristics. Performance: Use of double-blind, double-dummy design wa used to minimize bias. Detection: Outcomes assessment done by blinded, independent central adjudication committee. Attrition: There was a high level of attrition (~30%) which was similar between groups and characteristic for studies dependent upon venography for primary outcome rates. **External Validity:** Recruitment: Included patients from 14 countries and 129 sites. Patient Characteristics: Most patients were white (95%), from North America and under went unilateral knee

	hypertension, active hepatobiliary disease, significant renal disease and contraindications to venography.			A: 16 (1.0%) E: 7 (0.4%) <u>Mortality:</u> A: 3 (0.2%) E: 3 (0.2%)	NS			replacement. Mean hospital stay was 6 days. Outcomes: Use of composite outcomes can overestimate treatment effect. Endpoints were driven mostly by asymptomatic events, which clinical relevance is still unknown.
ADVANCE-2[8]								
1. Apixaban 2.5 mg twice daily (started 12-24 hours post surgery) 2. Enoxaparin 40 mg once daily (started 12 hours before surgery)	Mean Age: 66.5 years Female: 71.5% Inclusion: Patients ≥ 18 years of age scheduled to have unilateral or bilateral elective knee replacement, including revision. Exclusion: Same as above.	1. 1528 2. 1529	Mean treatment: 12 days	<u>Composite of asymptomatic and symptomatic DVT, non-fatal PE and all-cause death:</u> A: 147 (15.1%) E: 243 (24.4%) RR: 0.62 (95% CI 0.51 to 0.74, p<0.0001 for superiority) <u>Symptomatic VTE or VTE-related death:</u> A: 7 (0.46%) E: 7 (0.46%) RR: 1.00 (95% CI 0.35 to 2.85) <u>All PE:</u> A: 4 (0.26%) E: 0 (0%) Mortality: A: 2 (0.13%) E: 0 (0%)	ARR: 9.3% NNT: 11 NA NA	<u>Major Bleeds</u> A: 9 (0.6%) E: 14 (0.9%) P= 0.30 Absolute Risk Difference: -0.33% (95% CI -0.95 to 0.29, p=0.301) <u>Major or clinically relevant non-major bleeding:</u> A: 53 (3.5%) E: 72 (4.8%) Absolute Risk Difference: -1.24% (95% CI -2.66 to 0.18, p=0.088)	NS NS	**Study Rating: Good** **Internal Validity: RofB** Selection: Patients randomized via an interactive, central telephone system. Performance: Double-blind, double-dummy treatment design minimized bias. The European dosing regimen of enoxaparin 40 mg daily was used as the comparator. Detection: Outcome assessment done by assessors blinded to treatment assignment. Attrition: Approximately 35% of patients in both groups were not included in primary efficacy analysis. This rate is consistent with other studies with a similar design, however, higher than projection of 30%. **External Validity:** Recruitment: Patients were recruited from 27 countries and 125 sites. Patient Characteristics: Patients were recruited from non-US sites and majority of patients were white females. Mean hospital stay and treatment duration was 12 days, therefore, majority of drug treatments were done as an inpatient. Outcomes: Use of composite outcomes may overestimate treatment benefit. More clinically relevant symptomatic VTE rates were the same, however, trial was not powered to determine superiority.
ADVANCE-3[9]								
1. Apixaban 2.5 mg twice daily (started 12-24 hours	Mean Age: 60 yrs. Female: 52% Inclusion:	1. 1949	Mean treatment duration: 34 days	<u>Composite of asymptomatic or symptomatic DVT, non-fatal PE or all-cause</u>		<u>Major Bleeds</u> A: 22 (0.8%) E: 18 (0.7%) Absolute Risk	NS	**Study Rating: Good** **Internal Validity: RofB** Selection: Patients randomized via an

post surgery) 2. Enoxaparin 40 mg every 24 hours (started 12 hours before surgery)	Patients ≥ 18 years of age scheduled for elective total hip replacement or revision of previous inserted hip prosthesis. Exclusion: active bleeding, contraindications to anticoagulation or required ongoing anticoagulation or antiplatelet therapy.	2. 1917		<u>mortality:</u> A: 27 (1.4%) E: 74 (3.9%) RR: 0.36 (95% CI 0.22 to 0.54, p<0.001 for noninferiority and superiority) <u>Symptomatic VTE and VTE-related death:</u> A: 4 (0.1%) E: 10 (0.4%) RR: 0.40 (95% CI 0.01 to 1.28, p=0.11) <u>All PE:</u> A: 0 (0%) E: 4 (0.2%) Mortality: A: 3 (0.1%) E: 1 (<0.1%)	ARR: 2.5% NNT: 40 NS	Difference: 0.1 (95% CI -0.3 to 0.6, p=0.54) <u>Major or clinically relevant non-major bleeding:</u> A: 129 (4.8%) E: 134 (5.0%) Absolute Risk Difference: 0.2 (95% CI -1.4 to 1.0 p=0.72)	NS	interactive telephone system. Performance: Double-blind, double-dummy treatment design minimized bias. Detection: Blinding of outcome assessors was not described. Attrition: There were 28% of apixaban treated patients and 29% of enoxaparin treated patients that had venograms that could not be evaluated and were excluded from the analysis. **External Validity:** Recruitment: Patients were recruited from 21 countries and 160 sites. Patient Characteristics: Patients were predominately white and primarily treated in Europe and North America. Mean hospitalization days were 9. Outcomes: Use of composite outcomes may overestimate treatment benefit.

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: TTR= time in therapeutic range, SQ-subcutaneous, DVT- deep vein thrombosis, PE-pulmonary embolism, VTE- venous thromboembolism.

APPENDIX 2:
Suggested PA Criteria

Oral Direct Factor Xa Inhibitors (Rivaroxaban and Apixaban)

Goal(s):

- Promote safe and effective use of oral direct factor Xa inhibitors.

Length of Authorization: 1 year

Author: Kathy Sentena July 2014

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
What diagnosis is the factor Xa being prescribed for?	Record the ICD9 code:	
1. Does the patient have a diagnosis requiring short-term (<45 days) anticoagulation (i.e. total knee replacement: ICD9 - 81.54 or 81.55) or total hip replacement: ICD9 – 81.51 or 81.52)?	**Yes**: Go to #2	**No:** Go to #3
2. Will the prescriber consider a change to a preferred product LMWH?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Approve for up to 35 days.
3. Does the patient have a diagnosis of nonvalvular atrial fibrillation (ICD9 – 427.3x)?	**Yes:** Go to #4	**No:** Go to #7
4. Will the prescriber consider a change to the preferred oral anticoagulant, warfarin?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #5
5. Is the patient unable to tolerate the preferred oral anticoagulants due to one of the following: - unstable INR - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects - Difficulty obtaining routine INR monitoring	**Yes:** Go to # 6	**No:** Deny with the allowance of a 14 days of rivaroxaban or apixaban (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.
6. Is the request for the second line agent, apixaban?	**Yes:** Approve for 1 year.	**No:** Deny with the allowance of a 14

		days of rivaroxaban (or until patient is deemed adequately anticoagulated)*. Recommend trial of apixaban.
7. Does the patient have a diagnosis requiring acute or chronic DVT or PE treatment?	**Yes:** Go to #8	**No:** Deny with the allowance of a 14 days of rivaroxaban or apixaban (or until patient is deemed adequately anticoagulated)*.
8. Will the prescriber consider a change to a preferred anticoagulant?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #9
9. Is the patient unable to tolerate the preferred anticoagulant due to one of the following: - unstable INR - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects - Difficulty obtaining routine INR monitoring	**Yes:** Approve for up to 1 year.	**No:** Deny with the allowance of a 14 days of rivaroxaban or apixaban (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.
***** Patients switching from rivaroxaban or apixaban to other anticoagulants have been shown to have an increased risk of thrombotic events. Adequate anticoagulation is recommended during the switch from rivaroxaban or apixaban to another anticoagulant. Rivaroxaban and apixaban effect INR measurements, therefore, the appropriate dose of warfarin based on INR can not be used. Adding a parenteral anticoagulant, in addition to warfarin, at the time the next dose of rivaroxaban or apixaban is due is recommended.		

P&T Action: 7/24/14 (KS), 3/28/13 (KS), 8/30/12 (KS), 1/26/12(KS)
Revision(s):
Initiated: 4/9/12

Oral Direct Thrombin Inhibitors (Dabigatran)

Goal(s):

- Promote safe and effective therapies for oral direct thrombin inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis of nonvalvular atrial fibrillation?	**Yes:** Go to #2	**No:** Go to #6
2. Will the prescriber consider a change to a preferred product warfarin?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #3
3. Is the patient unable to take warfarin therapy due to one of the following: - unstable INR - warfarin allergy - contraindications to warfarin therapy - drug-drug interactions - intolerable side effects - Difficulty obtaining routine INR monitoring	**Yes:** Go to #4	**No:** Deny with the allowance of a 14 days of dabigatran (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.
4. Does the patient have normal renal function (CrCl >30 mL/min) and is prescribed dabigatran 150mg twice daily or reduced renal function (CrCl 15-30 mL/min) and is prescribed dabigatran 75mg twice daily?	**Yes:** Go to #5	**No:** Deny with the allowance of a 14 days of dabigatran (or until patient is deemed adequately anticoagulated)*.

		Recommend trial of warfarin.
5. Does the patient have a mechanical prosthetic heart valve?	**Yes:** Deny (Contraindicated)	**No:** Approve for up to 1 year.
6. Does the patient have a diagnosis requiring acute or chronic DVT or PE treatment?	**Yes:** Go to #7	**No:** Deny with the allowance of a 14 days of dabigatran (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.
7. Will the prescriber consider a change to the preferred anticoagulant?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #8
8. Is the patient unable to tolerate the preferred anticoagulant due to one of the following: - unstable INR - allergy - contraindications to warfarin therapy - drug-drug interactions - intolerable side effects - Difficulty obtaining routine INR monitoring	**Yes:** Approve for up to 1 year.	**No:** Deny with the allowance of a 14 days of dabigatran (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.
***** Patients switching from dabigatran to other anticoagulants have been shown to have an increased risk of thrombotic events. Adequate anticoagulation is recommended during the switch from dabigatran to another anticoagulant. Dabigatran can increase INR measurements. See package insert for dosing recommendations.		

DUR Board Action: *7/24/14 (KS), 3/28/13(KS), 1/26/12(KS)*
Revision(s):
Initiated: *1/26/12 (KS)*