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Abbreviated Class Update: Anticoagulants

Month/Year of Review: March 2013
Last Review: April 2010 (injectable anticoagulants)

End date of literature search:
Source: Provider Synergies

Current Status of PDL Class:

- Preferred Agents: Lovenox (branded product), dalteparin, unfractionated heparin (UFH), warfarin
- Non Preferred Agents: enoxaparin, fondaparinux, rivaroxaban, dabigatran, apixaban

Research Questions:

- Is there evidence of efficacy differences between the different anticoagulant products?
- Is there evidence of safety advantages between the available anticoagulants products?
- Are there indications or subpopulations where one agent may be more effective or safer than other available agents?

Conclusions:

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

- Low-molecular weight heparins (LMWH) demonstrated, with moderate and high strength of evidence, to have a better balance of efficacy and harms compared to unfractionated heparin (UFH) based on deep vein thrombosis (DVT), pulmonary embolism (PE), heparin induced thrombocytopenia (HIT), and major bleeding outcomes when used for prophylaxis in orthopedic surgery.[1]
- LMWHs were found to have a higher incidence of DVT (low strength of evidence for proximal DVT and moderate strength of evidence for DVT) but moderate strength of evidence of less major bleeding compared to factor Xa inhibitors (fondaparinux).[1]
- American College of Chest Physicians (ACCP) guidelines recommend that for venous thromboembolism (VTE) prophylaxis in patients undergoing orthopedic surgery (TKR and THR), LMWH are weakly recommended, based on moderate-quality of evidence, over fondaparinux, apixaban, dabigatran, rivaroxaban, or UFH. LMWH are weakly recommended, based on low-quality of evidence, over vitamin K antagonists (VKA) or aspirin.[2]
- There is low strength of evidence that there are no major differences in the VTE rates between direct thrombin inhibitors (DTI) and LMWH.[3,4]
- All-cause mortality and total bleeding rates were found to be higher with DTI compared to LMWH with moderate and low strength of evidence, respectively.[3]
- There is moderate strength of evidence that UFH are associated with an increased risk of DVT and proximal DVT compared to DTIs.[1]
- There was low strength of evidence that LMWHs were associated with less incidence of DVT compared to VKAs but were associated with more major bleeding, minor bleeding and surgical site bleeding based on high, medium and low strength of evidence, respectively.[1]

- The Drug Effectiveness Review Project (DERP) report found that in patients undergoing orthopedic surgery there was moderate strength of evidence that apixaban, dabigatran and rivaroxaban were similar in preventing symptomatic VTE events. When enoxaparin was compared to newer oral agents, no significant difference was found in the outcomes of all cause mortality and symptomatic PE, based on moderate to high strength of evidence. There was also moderate to high strength of evidence associated with a reduced risk with rivaroxaban compared to enoxaparin for the outcome of symptomatic VTE and evidence that symptomatic DVT was lower with apixaban and rivaroxaban compared to enoxaparin. Symptomatic DVT events favored enoxaparin compared to dabigatran, based on moderate to high strength of evidence.[5]
- For harms the DERP report found moderate strength of evidence that the risk of major bleeding was similar between the newer oral agents, based on indirect comparisons. Rivaroxaban was associated with a higher risk of clinically major bleeding (either major bleeding or clinically relevant minor bleeding) than apixaban based on moderate strength of evidence. For the outcome of clinically major bleeding there was moderate strength of evidence that there was a lower risk with apixaban compared to dabigatran and no difference between rivaroxaban and dabigatran. There was moderate to high strength of evidence that the compared with enoxaparin the risk of clinically relevant bleeding was similar to dabigatran, lower for apixaban and higher for rivaroxaban.[5]
- There is moderate strength of evidence, based on one fair quality trial, that dabigatran is non-inferior to enoxaparin for thromboprophylaxis after THR for the composite endpoint of total VTE and all-cause mortality. There is moderate strength of evidence that there were similar rates of bleeding in both groups.[6]
- There is low strength of evidence for the superiority of apixaban compared to enoxaparin for TKR. This is based on one good quality trial which demonstrated off-label use of apixaban to be superior to enoxaparin and one good quality trial in which apixaban did not meet noninferiority criteria in patients requiring thromboprophylaxis for TKR for the primary composite endpoint of asymptomatic and symptomatic DVT, non-fatal PE and all-cause mortality. There is moderate strength of evidence that rates of bleeding were similar between the two groups.[7,8]
- There is moderate strength of evidence, based on one good quality trial, that the off-label use of apixaban in patients undergoing THR is superior to enoxaparin for the primary composite endpoint of asymptomatic and symptomatic DVT, non-fatal PE and all-cause mortality. There is moderate strength of evidence that rates of bleeding were similar between the two groups.[9]
- The American Heart Association (AHA) gives no preference of anticoagulant for propylaxis.[10]

Table 1. Orthopedic Prophylaxis Summary of Evidence [1-10]

Outcome/Indication	Treatment	Strength of Evidence	Source
Pulmonary Embolism	LMWH favored over UFH	Moderate and High	AHRQ
	No significant difference between enoxaparin, apixaban, dabigatran and rivaroxaban (indirect comparison of symptomatic events)	Moderate to High	DERP
Deep Vein Thrombosis	LMWH favored over UFH	Moderate and High	AHRQ
	Fondaparinux favored over LMWH	Low and Moderate	AHRQ
	DTI favored over UFH	Moderate	AHRQ
	LMWH favored over VKA	Low	AHRQ
	Apixaban* and rivaroxaban favored over enoxaparin (symptomatic events)	Moderate to High	DERP
	Enoxaparin favored over dabigatran* (symptomatic events)	Moderate to High	DERP
Venous Thromboembolism	LMWH equal to DTIs	Low	AHRQ,CADTH
	Apixaban*, dabigatran* and rivaroxaban similar efficacy (indirect comparison of	Moderate	DERP

(VTE)	symptomatic events) Rivaroxaban favored over enoxaparin (symptomatic events)	 Moderate to High	DERP
VTE Prophylaxis	LMWH favored over fondaparinux, apixaban*, dabigatran*, rivaroxaban or UFH No preference	Moderate	ACCP AHA
HIT	LMWH favored over UFH	Moderate and High	AHRQ
Mortality	LMWH favored over DTI No significant difference between enoxaparin, apixaban*, dabigatran* and rivaroxaban	Moderate Moderate to High	Cochrane DERP
Major Bleeding	LMWH favored over UFH LMWH favored over fondaparinux VKAs favored over LMWH Apixaban*, dabigatran* and rivaroxaban similar	Moderate and High Moderate High Moderate	AHRQ AHRQ DERP, AHRQ DERP
Total Bleeds	LMWH favored over DTI	Low	Cochrane
Clinically Major Bleeding (major bleeds or clinically relevant minor bleeding)	Apixaban* favored over rivaroxaban (indirect comparison) Apixaban* favored over dabigatran* (indirect comparison) Rivaroxaban similar to dabigatran* (indirect comparison)	Moderate Moderate Moderate	DERP DERP DERP
Clinically Relevant Bleeding	Enoxaparin similar to dabigatran* (indirect comparison) Apixaban* favored over dabigatran*, rivaroxaban and enoxaparin (indirect comparison) Dabigatran*, apixaban* and enoxaparin favored over rivaroxaban (indirect comparison)	Moderate to High Moderate to High Moderate to High	DERP DERP DERP
Composite of asymptomatic and symptomatic DVT, non-fatal PE and all-cause death	Apixaban* inferior to enoxaparin (30 mg twice daily) for TKR Apixaban* superior to enoxaparin (40 mg once daily) for TKR (ARR: 9.33%/NNT 11) Apixaban* superior to enoxaparin (40 mg once daily) for THR (ARR: 2.5%/ NNT 40)	Moderate Moderate Moderate	Primary Primary Primary
Composite of VTE and all-cause mortality	Dabigatran* 220 mg daily is noninferior to enoxaparin (40 mg daily) for THR	Moderate	Primary
* Not FDA approved for orthopedic prophylaxis ARR - absolute risk reduction, NNT – number needed to treat			

Acute DVT Treatment

- For treatment of acute DVT of the leg, ACCP guidelines recommend LMWH or fondaparinux over SQ UFH with moderate-quality of evidence and low-quality of evidence, respectively.[2]
- There is moderate strength of evidence, based on one fair quality trial, that rivaroxaban is non-inferior to enoxaparin/VKA in the treatment of DVT for treatment up to 12 months.[11]

PE Treatment

- There is low quality of evidence that LMWH is more effective than IV UFH and moderate quality of evidence that LMWH is more effective than SQ UFH for treatment of PE.[1]
- There is moderate quality of evidence that fondaparinux is more effective than IV UFH and low quality of evidence that fondaparinux is more effective than SQ UFH for treatment of PE.[1]
- VKAs are strongly recommended for treatment of acute PE, based on moderate-quality of evidence.[2]
- ACCP guidelines weakly recommend LMWH (moderate-quality of evidence) or fondaparinux (low-quality of evidence) over SQ UFH for initial parenteral anticoagulant for the acute treatment of PE.[2]
- There is moderate quality of evidence in patients with cancer and PE that LMWH are more effective than VKA for long-term treatment.[2]
- In patients with cancer who are not treated with LMWH, there is low quality of evidence that VKA are more effective than dabigatran and rivaroxaban for PE treatment.[2]
- AHA gives no preference of anticoagulant for treatment of acute PE.[10]
- There is moderate quality of evidence that rivaroxaban is noninferior to warfarin for the treatment of symptomatic PE, based on one good quality trial with similar rates of bleeding.[12]

Table 2. Treatment of PE Summary of Evidence [1,2,10,12]

Outcome	Treatments	Strength of Evidence	Source
PE	LMWH favored over IV UFH and SQ UFH Fondaparinux is favored over IV UFH and SQ UFH	Low and Moderate Low and Moderate	AHRQ AHRQ
Acute PE	VKAs strongly recommended LMWH or fondaparinux favored over SQ UFH No preference to agents	Moderate Moderate and Low	ACCP ACCP AHA
Cancer and PE	LMWH favored over VKA VKA favored over dabigatran and rivaroxaban	Moderate Low	ACCP ACCP
Symptomatic Recurrent VTE	Rivaroxaban is noninferior to Enoxaparin/VKA	Moderate	Primary

Long-term Anticoagulation

- In most patients requiring long-term anticoagulation for DVT treatment, VKA are considered to have similar risks and benefits when compared with LMWH but are slightly preferred over LMWH based on low-quality evidence.[2]
- LMWH have similar risks and benefits as new oral agents (dabigatran or rivaroxaban) for treatment of DVT, but are slightly preferred based on low-quality of evidence, if VKA therapy is not used.[2]
- There is moderate quality of evidence in patients with cancer and thrombosis that LMWH are more effective than VKA for long-term treatment.[2]
- High quality trial data shows LMWH to have less incidence of recurrent VTE during treatment compared to VKAs, however, this benefit was reversed in favor of VKAs when only studies with the same initial treatment were analyzed*.[13]

- High quality trial data found LMWH to have less major bleeding than VKAs, which was not statistically different.[13]

Table 3. Long-term Anticoagulation Summary of Evidence [2,13]

Outcome	Treatments	Strength of Evidence	Source
DVT	VKA favored over LMWH LMWH favored over dabigatran and rivaroxaban	Low Low	ACCP ACCP
Recurrent VTE	LMWH favored over VKA (*see above)	High	Cochrane
Cancer and PE	LMWH favored over VKA	Moderate	ACCP

Atrial Fibrillation

- ACCP guidelines weakly recommended dabigatran, based on moderate-quality of evidence, over VKAs. For patients with other types of AF, VKAs are recommended, with and without additional agents.[2]
- The DERP report found that there was moderate strength of evidence in patients with non-valvular AF that there was no difference in all cause mortality between apixaban, rivaroxaban, dabigatran 110 mg and dabigatran 150 mg (indirect comparison). Dabigatran was shown to have a reduced incidence of stroke compared to warfarin, based on moderate to high strength of evidence, and apixaban was shown to have a decreased incidence of stroke or systemic embolism, based on moderate strength of evidence, compared to warfarin.[5]
- When assessing harms in patients with AF, there was moderate strength of evidence that dabigatran 150mg and rivaroxaban had increased risk of major bleeding and gastrointestinal (GI) bleeding compared to apixaban. Compared to warfarin, the newer oral agents were found to have less intracranial bleeds, based on moderate-high strength of evidence. Apixaban was also found to have less risk of major bleeds compared to warfarin (moderate-high strength of evidence). The risk of GI bleeds was found to be higher with dabigatran and rivaroxaban compared to warfarin based on moderate-high strength of evidence.[5]
- There is moderate strength of evidence, based on one good quality study, that apixaban is superior to warfarin for the treatment of AF and is associated with significantly less major bleeding.[14] The ARR is 0.33% favoring apixaban with a number needed to treat (NNT) of 303 per treatment year.
- Canadian Agency for Drugs and Technologies in Health (CADTH)[15]

Table 4. Atrial Fibrillation Summary of Evidence [2,5,14,15]

Outcome/Indication	Treatments	Strength of Evidence	Source
Atrial Fibrillation	Dabigatran favored over VKAs	Moderate	ACCP
Stroke	Dabigatran favored over warfarin Apixaban favored over warfarin Dabigatran favored over warfarin	Moderate to High Moderate	DERP DERP CADTH
Systemic Embolism	Apixaban favored over warfarin	Moderate	DERP
Mortality	Apixaban, dabigatran (110 mg and 150 mg) and rivaroxaban similar (indirect comparison)	Moderate	DERP
Major Bleeds	Apixaban favored over dabigatran 150 mg and rivaroxaban (indirect comparison) Apixaban favored over warfarin	Moderate Moderate to High	DERP DERP

Gastrointestinal Bleeds	Apixaban favored over dabigatran 150 mg and rivaroxaban (indirect comparison) Warfarin favored over dabigatran and rivaroxaban	Moderate Moderate to High	DERP DERP
Intercranial Bleeds	Apixaban, dabigatran and rivaroxaban favored over warfarin	Moderate to High	DERP
Composite of Stroke or Systemic Embolism	Apixaban superior to warfarin (ARR 0.33/NNT 303)	Moderate	Primary
ARR - absolute risk reduction, NNT – number needed to treat			

Recommendations:

- Make apixaban, rivaroxaban, and dabigatran non-preferred with PA criteria to insure appropriate patient selection.
- Add an exclusion for patients with mechanical prosthetic heart valves to the dabigatran PA criteria.

Reason for Review:

The injectable anticoagulant class was reviewed by the Oregon Health Resources Commission (HRC) in April 2010. The comparative effectiveness resource used for this review did not included injectable anticoagulant or oral anticoagulant comparisons to the newly released oral anticoagulant agents.[7] This review will analyze the comparative effectiveness of injectable and oral anticoagulants compared to the new oral anticoagulants, dabigatran and rivaroxaban, and incorporation of important updates related to this class since the last review. New evidence-based guidelines from the ACCP and a systematic review from the DERP were also updated and will be included in this review.

Previous HRC Conclusions/April 2010 (only injectable anticoagulants were evaluated):

- There is no evidence to suggest a difference in the efficacy and harms of LMWHs.
- There is evidence that fondaparinux has superior efficacy compared enoxaparin but with an increased risk of bleeding.
- Fondaparinux has been shown to be non-inferior to dalteparin.

Background:

Anticoagulants are used in the prevention and treatment of thrombosis, including venous thromboembolism (VTE). VTEs are a result of DVT or PE which can be secondary to surgery and other medical conditions. Thrombosis may result from abnormalities in the vascular and coagulation systems.[16] Damage to the endothelial lining of blood vessels trigger activation of the coagulation cascade leading to thrombus formation.[17] Available injectable anticoagulants work by enhancing antithrombin (AT) which is responsible for inhibiting a variety of clotting factors.[17] Oral anticoagulants exhibit anticoagulant activity through blocking the formation of vitamin K clotting factors (warfarin), direct thrombin inhibition (dabigatran) and factor Xa inhibition (rivaroxaban and apixaban).[18-21]

The most important outcomes in assessing therapy for the prevention and treatment of VTE include the occurrence or reoccurrence of VTE, major bleeding and all-cause mortality. Additional relevant outcomes are: hepatopathy, minor bleeding, incidence of HIT, withdrawals due to adverse events and readmission. Early research relied primarily on symptomatic VTE and fatal PE as measures of antithrombotic prophylaxis efficacy. Current literature has incorporated the use of the surrogate outcome, asymptomatic DVT, detected by mandatory venography.[22] The ACCP guidelines finds this outcome "fundamentally unsatisfactory" due to the inability to weigh the risks and benefits of efficacy (knowledge of symptomatic events) compared to serious bleeding.[22] The guidelines provide suggestions to estimate reductions in symptomatic thrombosis, dependent upon available evidence. Many studies that evaluate the effectiveness of anticoagulants in

orthopedic 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.[4]

VTE Prophylaxis

For patients undergoing THR or TKR prophylactic anticoagulants are considered standard practice. ACCP guidelines weakly recommend, based on moderate-quality of evidence, the use of LMWH over other available treatment options.[2] A minimum treatment duration of 10-14 days is strongly recommended, based on moderate-quality of evidence.[2] There is moderate quality of evidence that suggests thromboprophylaxis be continued for up to 35 days from the day of the surgery.[2] 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.[23] This is in contrast to the common European dose of enoxaparin 40 mg given once daily for prophylaxis in patients undergoing knee replacement used in some trial designs.

VTE Treatment

Guidelines recommend the use of LMWH, fondaparinux, I V UFH or subcutaneous SC UFH for the acute treatment of DVT and PE. Long-term anticoagulation is also strongly recommended, ranging from 3 months to extended therapy, depending on the indication.[2] Treatment with VKA is recommended over LMWH for extended anticoagulation in most patients, except those with cancer in which LMWH are preferred.[2]

Atrial Fibrillation

Patients with AF are at increased risk of stroke and systemic embolism, which is estimated based on the $CHAD_2$ Classification Scheme (Table 1). The $CHADS_2$ risk stratification scheme estimates stroke risk in patients with AF based on: presence of heart failure, presence of hypertension, age ≥75 years, presence of diabetes mellitus, and a history of previous stroke or transient ischemic attack.[24] The greater the number of risk factors present, the greater the risk of stroke. CHEST guidelines on antithrombotic and thrombolytic therapy recommend anticoagulation for patients with AF and a $CHAD_2$ score ≥1. Suggested first line therapy is dabigatran 150 mg twice daily and warfarin as an alternative option.[2]

Table 1. $CHADS_2$ Classification Scheme for Stroke Risk[24]

	Risk Factor	Points
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes	1
S_2	History of stroke or TIA	2

Injectable Anticoagulants - FDA-Approved Indications[23,25-28]

Drug	DVT Prophylaxis				DVT Treatment (with warfarin)	Other
	Abdominal Surgery	Hip Replacement	Knee Replacement	Hip Fracture Surgery		

Dalteparin (Fragmin®)	+	+	---	---	---	Unstable angina and non-Q-wave MI, DVT prophylaxis, extended VTE treatment in cancer patients
Enoxaparin (Lovenox®)	+	+	+	----	+ (without PE in outpatient setting, with or without in inpatient setting)	Unstable angina and non-Q-wave MI, DVT prophylaxis, acute STEMI or with subsequent PCI
Fondaparinux (Arixtra®)	+	+	+	+	+ (inpatient setting only, with or without PE)	Acute PE if treated in the hospital with warfarin
Heparin	+				+	- Low-dose for prevention of postoperative VTE and PE in patients undergoing abdominothoracic surgery or for those at risk of developing thrombosis - Prophylaxis and treatment of PE - A-fib with embolization - Acute and chronic consumptive coagulopathies - Prevention of clotting in arterial and cardiac surgery - Prophylaxis and treatment of peripheral arterial embolism

* MI- myocardial infarction, DVT – deep vein thrombosis, VTE- venous thromboembolism, STEMI- ST segment elevation myocardial infarction, PCI-percutaneous coronary intervention

Oral Anticoagulants – FDA Approved Indications[18-21]

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®	---	---	+ (nonvalvular only)	---	---

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

Methods:

Author: Kathy Sentena, Pharm.D. March 2013

A Medline literature search ending in October 2012 for new systematic reviews and randomized controlled trials (RCTs) comparing injectable anticoagulants to each other or to other anticoagulants was performed. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical 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. After review of the citations from Medline and the manual searches, the following were reviewed: three clinical treatment guidelines, six systematic reviews and twelve RCT.

Systematic Reviews:

Cochrane[3] – Prevention of VTE

A recent Cochrane analysis compared the effectiveness of VKA, LMWH and DTI in prevention of VTE in patients undergoing total hip replacement (THR) or total knee replacement (TKR). Fourteen randomized controlled trials were included in the analysis involving 21,642 patients for the efficacy analysis and 27,360 patients for the safety analysis. Four dabigatran and nine ximelagatran studies were included in the DTI analysis and three studies compared warfarin to ximelagatran. Currently, ximelagatran is not available due to hepatic toxicities. The major outcomes of interest were major VTE events (symptomatic and asymptomatic), all-cause mortality, total bleeding events and liver function tests, measured by alanine aminotransferase (ALT) >3 times the upper limit of normal. Included randomized clinical trials were 7-14 days of treatment with the exception of one dabigatran study, which allowed for extended prophylaxis up to 35 days.

When DTI were compared to LMWH there was low strength of evidence that there were no major difference in the rate of major VTE events (OR 0.91, CI 0.69-1.19). A sensitivity analysis of major VTE found that this finding remained true regardless of surgery type or doses studied. When only symptomatic VTEs were included, again there was no difference found between LMWH and DTI. Due to the infrequent nature of symptomatic events, the sample size needed to properly evaluate the differences between treatments would require thousands of patients, which was not attainable in this analysis. The time of initiation of anticoagulation, before compared to after surgery, was shown to impact the efficacy of anticoagulant more than the drug. A sensitivity analysis found that when DTI were initiated before surgery less VTEs resulted compared to LMWH. The opposite effect was true when DTI were started after surgery.

All-cause mortality and total bleeding events were found to be higher with DTI compared to LMWH with moderate and low strengths of evidence, respectively. When follow up events were included, the difference in all-cause mortality was statistically significantly higher with DTI compared to LMWH (OR 2.06, CI 1.10 to 3.87). There is low strength of evidence to suggest ALT elevations >3 times the upper normal limit occurred less frequently with DTIs compared to LMWH (OR 0.41, CI 0.23-0.72).

Cochrane concluded that there was insufficient evidence to recommend dabigatran for the prevention of VTE in patients undergoing orthopedic surgery.

Cochrane[13]- Treatment of Symptomatic Venous Thrombosis

A second Cochrane Systematic Review was released in October 2012 The long-term treatment of symptomatic venous thrombosis with either VKAs or LMWH was analyzed. A literature search up to February 2012 resulted in fifteen open-label trials involving 3, 197 patients with symptomatic VTE. Trials included four

formulations of VKA (warfarin, coumarin, acenocoumarol and phenprocoumon) and 7 types of LMWH (enoxaparin, fragmin, tinzaparin, dalteparin, nadroparin, and reviparin). Trials were classified based on methodological quality (concealed randomization, double-blinded treatment and blinded assessment of outcomes measures). Category I trials were considered to have high methodological quality and Category II trials had a lower level of methodological quality. Additional analyses were performed for Category I (7 trials) and Category II (8 trials) designations. The primary outcomes of the analysis were recurrent symptomatic VTE, major bleeds and mortality at three months.[6]

The incidence of recurrent VTE during treatment was higher with VKA (5.2%) compared to LMWH (4.5%), (OR 0.82, 95% CI 0.59 to 1.13).[6] Analysis of Category I trials found similar results in favor of LMWH (OR 0.80, 95% CI 0.54 to 1.18). When only Category I trials using the same initial treatment were analyzed (2 trials), treatment favored VKA (OR 1.95, 95% CI 0.74 to 5.19). Thirteen trials found no significant difference between VKA and LMWH in rates of major bleeding. Pooled analysis data of major bleeding showed a significant trend favoring LMWH (OR 0.50, 95% CI 0.31 to 0.79). When considering only Category I trials, major bleeding rates favored LMWH, but were not statistically different, from VKA (OR 0.62, 95% CI 0.36 to 1.07). Mortality was similar for VKA and LMWH, 3.6% and 3.9%, respectively.[6] International normalized ratios (INR) were reported in six trials. Four trials reported 64-69% of patients with mean INRs in therapeutic range and two trials reported patients with INRs that were considered good (30-38%) or acceptable/intermediate (43-56%).[6]

AHRQ - Venous Thromboembolism Prophylaxis in Orthopedic Surgery[1]

A comparative effectiveness review was done to evaluate the role of prophylaxis on VTE in patients undergoing orthopedic surgery. One hundred and seventy seven controlled trials and observational studies were included. Comparative efficacies between classes of agents and of individual agents within classes were evaluated. Approval of rivaroxaban occurred after the completion of this report and therefore data from the RECORD trials were included as an addendum but not in the pooled analyses. There is insufficient evidence to compare the benefits or risk of harms between the different low molecular weight heparin (LMWH) treatments.[1] LMWH were found to have a better balance of efficacy and harms when compared to UFH. This was substantiated with moderate strength of evidence for PE (OR 0.48 [0.24 to 0.95]), DVT (RR 0.80 [0.65 to 0.99]), and HIT (OR 0.12 [0.03 to 0.43)] and with high strength of evidence for proximal DVT (RR 0.60 [0.38 to 0.93]) and major bleeding (OR 0.57 [0.37 to 0.88]). Strong conclusions of benefits and harms of LMWH and oral antiplatelet agents, fondaparinux, injectable or oral DTIs or oral VKAs were not able to be drawn. There was moderate strength of evidence that LMWH may be inferior to factor Xa inhibitors (fondaparinux) when evaluating proximal DVT (RR 1.99 [1.57 to 2.51]) and distal DVT (OR 2.19 [1.52 to 3.16]) but are associated with less risk of major bleeding (OR 0.65 [0.48 to 0.89]). UFH was found to have an increased incidence of DVT and proximal DVT compared to DTI (medium strength of evidence). Observational studies found that LMWH were associated with decreased mortality but this was not supported by RCT findings. UFH was associated with a higher rate of major bleeding and death when compared to fondaparinux.

There were few studies to do a comparative analysis between agents within the same class. Enoxaparin was found to have similar benefits and harms as dalteparin and tinzaparin.

CADTH- Dabigatran or Rivaroxaban Versus Other Anticoagulants for Thromboprophylaxis After Major Orthopedic Surgery: Systematic Review of Comparative Clinical-Effectiveness and Safety[4]

A Health Technology Assessment was performed to compare the clinical effectiveness and safety of the new oral anticoagulants, dabigatran and rivaroxaban, to currently used anticoagulants (LMWH, fondaparinux, UFH and warfarin) in the prevention of thrombosis following orthopedic surgery. A total of nine phase II and phase III trials of patients undergoing TKR and THR were included. No difference in efficacy was found between dabigatran and enoxaparin when the results from the phase III trials (RENOVATE1[15], RE-MODEL[16], and REMOBILIZE[17]) were pooled for a meta-analysis (n=8,210). Rates of bleeding, liver enzyme elevations and acute coronary events were also similar between groups. Rivaroxaban was compared to enoxaparin in three phase III RCTs (RECORD 1[18], RECORD 2[19] and

RECORD 3[20]) using the 40mg once daily enoxaparin dose. Rivaroxaban was shown to be superior to enoxaparin based on the primary endpoint of any DVT, non-fatal PE, and all-cause mortality. Comparable rates of major bleeding, liver enzyme elevation, and acute coronary events were found between treatment groups. RECORD 4[21], comparing rivaroxaban to enoxaparin 30mg twice daily, is ongoing but preliminary results suggest a significantly significant reduction in the primary endpoint events in favor of rivaroxaban with low rates of bleeding in both groups.

DERP – Newer Oral Anticoagulant Drugs (final draft)[5]

A recently released review from DERP analyzes the safety and efficacy of the newer oral anticoagulants in patients with AF, undergoing orthopedic surgery and medically ill. The report included the new oral anticoagulants: apixaban, dabigatran, edoxaban (not approved in US) and rivaroxaban. Clinical evidence was graded from insufficient to high and studies had to meet appropriate inclusion criteria, which left 8 systematic reviews available for analysis. No direct comparisons between new oral agents were available.

Orthopedic Prophylaxis

In patients undergoing orthopedic surgery there was moderate strength of evidence that apixaban, dabigatran and rivaroxaban were similar in preventing symptomatic VTE events. This was based the comparison of apixaban to dabigatran (compared to dabigatran RR, 1.16; 95% CI, 0.31 to 4.28), rivaroxaban compared to dabigatran (RR, 0.68; 95% CI, 0.21 to 2.23) and rivaroxaban compared to apixaban (RR, 0.59; 95% CI, 0.26 to 1.33). Comparison of enoxaparin to newer oral agents for orthopedic prophylaxis showed no significant difference in the outcomes of all cause mortality and symptomatic PE, based on moderate to high strength of evidence. A reduced risk of symptomatic VTE was found with rivaroxaban compared to enoxaparin (RR, 0.48; 95% CI, 0.31 to 0.75)(moderate to high strength of evidence). There was also moderate to high strength of evidence that symptomatic DVT was lower with apixaban and rivaroxaban compared to enoxaparin; enoxaparin compared to apixaban (RR, 0.41; 95% CI, 0.18 to 0.95), enoxaparin compared to rivaroxaban (RR 0.40; 95% CI, 0.22 to 0.72). Symptomatic DVT events favored enoxaparin compared to dabigatran (RR, 0.82; 95% CI, 0.17 to 3.99), based on moderate to high strength of evidence.

When comparing the evidence of harms of the newer oral agents in patients undergoing orthopedic prophylaxis, DERP found moderate strength of evidence that the risk of major bleeding was similar between the groups, based on indirect comparisons. There was moderate strength of evidence for the composite outcome of clinically major bleeding (either major bleeding or clinically relevant minor bleeding) that rivaroxaban had a higher incidence compared to apixaban (RR, 1.52; 95% CI, 1.19 to 1.95). This translates into a clinically relevant bleeding risk increase of 52% with rivaroxaban compared to apixaban, based on indirect comparisons. For the outcome of clinically major bleeding there was moderate strength of evidence that there was a lower risk with apixaban compared to dabigatran and no difference between rivaroxaban and dabigatran. There was moderate to high strength of evidence that the compared with enoxaparin the risk of clinically relevant bleeding was similar to dabigatran. For this same outcome, the risk was lower with apixaban (RR, 0.82; 95% CI, 0.69 to 0.98) compared to enoxaparin and higher with rivaroxaban (RR 1.12; 95% CI 0.94 to 1.35) when compared to enoxaparin.

Atrial Fibrillation

There was moderate strength of evidence in patients with non-valvular AF that there was no difference in all cause mortality between apixaban, rivaroxaban, dabigatran 110 mg and dabigatran 150 mg (indirect comparison). There was moderate strength of evidence that rivaroxaban was associated with an increased incidence of stroke when compared to dabigatran 150 mg (OR, 1.35; 95% CrI, 1.03 to 1.79). However, rivaroxaban was associated with less myocardial infarctions than dabigatran 150 mg (OR, 0.63; 95% CrI, 0.42 to 0.93). When compared to warfarin, there was moderated strength of evidence of reduced risk of stroke and systemic embolism (OR, 0.80; 96% CrI, 0.66 to 0.95) and all cause mortality (OR, 0.90; 95% CrI, 0.80 to 0.998) with apixaban. Dabigatran was also shown to have a reduced risk of stroke when compared to warfarin, based on moderate to high strength of evidence (OR, 0.65; 95% CrI, 0.52 to 0.81).

Subgroup analysis found patients with AF and INRs that were therapeutic at least 66% of the time, the new oral agents were not superior to warfarin. In individuals over the age of 75, the newer agents decreased the risk of stroke/systemic embolism compared to warfarin but this was only true for dabigatran in patients under 75. Apixaban was the only agent that decreased the risk of major bleeds compared to warfarin in patients over 75, however, in patients under 75 years dabigatran and apixaban had less risk of major bleeds compared to warfarin. Patients with a $CHAD_2$ score >2 benefited from apixaban treatment with less strokes and less major bleeds.

When assessing harms in patients with AF, there was moderate strength of evidence that dabigatran 150mg had increased risk of major bleeding compared to apixaban (RR 1.35; 95% CrI, 1.11 to 1.66) and increased risk of gastrointestinal (GI) bleeding compared to apixaban (RR 1.65; 95% CrI 1.16 to 2.38). Rivaroxaban was also shown, based on moderate strength of evidence, to have an increased risk of major bleeding and major GI bleeding compared to apixaban, OR 1.48 (95% CrI, 1.21 to 1.82) and OR 1.83 (95% CrI, 1.30 to 2.57), respectively. Compared to warfarin, there was moderate-high strength of evidence, that apixaban had less risk of major bleeds (OR 0.70; 95% CrI, 0.61 to 0.81) and intracranial bleeds (OR 0.42; 95% CrI, 0.30 to 0.58). Dabigatran 150mg and rivaroxaban were found to have less intracranial bleeds (OR 0.42 and OR 0.66) but increased risk of GI bleeds (OR 1.45 and OR 1.61), compared to warfarin based on moderate-high strength of evidence.

Long-term Anticoagulation

There is moderate strength of evidence of that mortality and recurrent VTE rates are similar between dabigatran and rivaroxaban compared with warfarin.

CADTH – Antithrombotic Agents for the Prevention of Stroke and Systemic Embolism in Patients with Non-Valvular Atrial Fibrillation (draft)[15]

A just released systematic review from CADTH evaluated 12 trials to compare the clinical evidence of antithrombotic agents in patients with AF, which included the following treatments: new oral anticoagulants (NOAC) apixaban, dabigatran and rivaroxaban; warfarin; or ASA ± clopidogrel. The analysis evaluated key endpoints (stroke and systemic embolism, major bleeding, all-cause mortality, extracranial hemorrhage, intracranial hemorrhage and myocardial infarction) as well as subgroup analyses ($CHADS_2$ score, age and TTR) and risk/benefit analysis. Indirect comparisons were used to compare the clinical efficacy of the new NOAC due to lack of direct comparison data.

For stroke and systemic embolism apixaban and dabigatran 150 mg were superior to warfarin (OR 0.8 for apixaban and OR 0.7 for dabigatran). These results translate into 1-6 fewer events per 1,000 patients treated per year with apixaban and 3-9 fewer events per 1,000 patients treated per year with dabigatran. Dabigatran 150 mg was superior to dabigatran 110 mg (dose not available) for stroke and systemic embolism. All anticoagulants were favored over low-dose ASA and the combination of low-dose ASA and clopidogrel. Compared to warfarin, major bleeding rates were lower with apixaban (OR 0.7) and dabigatran 110 mg (OR 0.8). Dabigatran 150 mg and rivaroxaban were associated with higher bleeding rates than apixaban, OR 1.34 and 1.48, respectively. Clopidogrel + low-dose ASA were also found to have significantly higher bleeding rates than apixaban. Mortality rates were significantly less with apixaban compared to warfarin, with 8 fewer events per 1000 patients treated in year. Apixaban was shown to have significantly lower rates of extracranial hemorrhage than warfarin (OR 0.8) and dabigatran 150 mg, rivaroxaban and medium dose ASA all had significantly higher rates compared to apixaban. All NOACs had lower rates of intracranial hemorrhage which were statistically significant and ranged from 1 to 7 fewer events per year and per 1,000 patients treated. NOACs were also superior to low-dose ASA + clopidogrel. Myocardial infarction rates were higher with dabigatran 150 mg compared to warfarin, OR 1.4. Apixaban was found to have lower MI rates compared to dabigatran (110 mg and 150 mg), medium dose ASA and low-dose ASA + clopidogrel.

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The subgroup analyses found that in patients with $CHAD_2$ scores <2 apixaban and dabigatran 110 mg, when compared to warfarin, were found to have significantly lower bleeding rates. In these same patients dabigatran 150 mg proved more effective, based on lower rates of strokes and systemic embolism, than dabigatran 110 mg. NOAC and warfarin were also shown to be more effective than low-dose ASA and low-dose ASA + clopidogrel combination. In patients with a $CHAD_2$ score of ≥2 both dabigatran 150 mg and apixaban were found to have less rates of stroke and systemic embolism compared to warfarin, OR 0.7 and 0.8, respectively. In this same population, NOACs were also more effective than low-dose ASA alone and in combination with clopidogrel. Major bleeding rates were found to be lower with apixaban compared to warfarin, rivaroxaban and dabigatran 150 mg. Dabigatran 150 mg was found to be more effective than warfarin, based on stroke and systemic embolism rates, in patients 75 years or older. Patients in this age group were also found to have lower rates of stroke and systemic embolism when treated with any anticoagulant compared to aspirin. There was no significant difference among treatments in stroke and systemic embolism rates in centers with good INR control (TTR ≥66%). In centers with poor INR control (<66%), dabigatran 150 mg was found to have a reduced rate of strokes and systemic embolisms compared to warfarin and rivaroxaban. In two separate groups, patients younger than 75 years of age and in patients with poor INR control (TTR <66%), apixaban and dabigatran (both doses) were found to have less major bleeding compared to warfarin. In patients with good INR control (TTR ≥66%) apixaban was associated with less major bleeding than warfarin and for those over 75 years old, apixaban was found to have less major bleeding than all the anticoagulants. For patients with poor INR control (TTR <66%) all NOACs were found to be superior to warfarin therapy for major bleeding rates when compared to patients with good control of INR (TTR ≥66%).

The benefit to risk profile, which takes into account stroke and systemic embolism rates compared to major bleeds, found no major differences between the NOACs but demonstrated a positive risk/benefit finding for NOACs when compared to warfarin. However, risk differences were small, mostly under 10 fewer events per 1,000 patients treated per year between NOACs and warfarin. Antiplatelets were shown to lave a less favorable benefit/risk profile compared to NOACs independent of stroke risk, age, or INR control.

New Guidelines:

Antithrombotic Therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines[2]

The ACCP guideline on therapy for VTE updates the 8th edition of the guideline that was released in 2008. Treatment and management of thrombotic events are discussed and graded. Pharmacological classes are recommended for prevention and treatment, however, specific treatments are rarely suggested.

For VTE prophylaxis in patients undergoing orthopedic surgery (TKR and THR), LMWH are weakly recommended, based on moderate-quality of evidence, over fondaparinux, apixaban, dabigatran, rivaroxaban, or UFH. LMWH are weakly recommended, based on low-quality of evidence, over VKAs or aspirin.

In patients requiring treatment of proximal acute DVT of the leg or PE, LMWH and fondaparinux are recommended over IV UFH and SQ UFH based on a weak recommendation with moderate to low-quality evidence. For patients with DVT of the leg or PE, long-term therapy treatment with a VKA is weakly recommended over LMWH. If these same patients decide to not use VKA therapy, then the use of LMWH are weakly recommended over dabigatran or rivaroxaban for long-term use.

In patients with DVT of the leg or PE and cancer, LMWH are weakly recommended over VKA therapy. VKA treatment is preferred (weak recommendation based on low-quality evidence) over dabigatran and rivaroxaban for long-term treatment.

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For patients who have nonrheumatic AF and low risk of stroke, aspirin is weakly recommended, based on moderate-quality of evidence. For patients at intermediate and high risk of stroke ($CHAD_2$ score ≥1), anticoagulation is strongly recommended, based on moderate-quality of evidence and high-quality of evidence, respectively. Dabigatran is weakly recommended, based on moderate-quality of evidence, over VKAs. For patients with other types of AF, VKAs are recommended, with and without additional agents.

* Evidence was analyzed by the expert panel utilizing the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for evaluating outcomes.

Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association[10]

In 2011 The American Heart Association (AHA) published recommendations for treating massive and submassive PE, iliofemoral deep vein thrombosis (IFDVT) and chronic thromboembolic pulmonary hypertension. Recommendations were based on systematically reviewed evidence and given a rating based on the American Heart Association Levels of Evidence. Size of treatment effect was based on class I-III (the lower the class the greater the benefit over risk) and estimate of certainty (precision) of treatment effect (level A-C, with level A having strong evidence and level C having weaker evidence). Therapy recommendations for the treatment of acute massive, submassive, and low-risk PE were similar to other guidelines. Therapeutic anticoagulation with LMWH, IV or SQ UFH or fondaparinux was recommended (Class I; Level of Evidence A). IFDVT involves thrombosis in any part of the iliac vein or the common femoral vein and some evidence suggests that IFDVT presents a greater risk of poor outcomes. Recommendations for initial anticoagulation for IFDVT include IV UFH, LMWH, or fondaparinux (Class I; Level of Evidence A) or SQ UFH (Class I; Level of Evidence B). Direct thrombin inhibitors are recommended for patients with suspected or proven HIT (Class I; Level of Evidence B). Warfarin is recommended for patients without cancer requiring long-term anticoagulation for IFDVT (Class I; Level of Evidence A) and LMWH is preferred for patients with cancer (Class I; Level of Evidence A).

NICE- Venous Thromboembolic Diseases: the Management of Venous Thromboembolic Diseases and the Role of Thrombophilia Testing[29]

NICE released a clinical guideline for VTE management in June 2012. Clinical evidence was evaluated based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method with outcome evidence ratings ranging from very low to high. Treatments included in this review include; UFH, LMWH, synthetic pentasaccharides (fondaparinux) and VKAs. Rivaroxaban is discussed in a separate NICE review. Pharmacological treatment is recommended for DVT and PE based on patient comorbidities, with no specific anticoagulant preferred. Comparisons between fondaparinux and LMWH included only low and very low quality studies with no certainty of a difference in VTE related mortality, recurrent VTE rates and major bleeds. Fondaparinux was compared to UFH in which a clinical important decrease in recurrent VTE favoring fondaparinux was found based on low quality evidence in patients with and without cancer. LMWHs were compared to UFH with uncertain findings favoring LMWH for the outcomes of all cause mortality, recurrent VTE, and major bleeds, based on very low and low quality of evidence. There was moderate quality of evidence that it is unlikely that there is any difference in all cause mortality between LMWH and VKAs. In a study including cancer and non-patients, LMWH was shown to possibly have a clinically important decrease in recurrent VTE rates compared to VKA, based on moderate quality of evidence. This finding was not sustained for a subgroup analysis containing only non-cancer patients but was sustained for the cancer patient group. An option of LMWH or fondaparinux is suggested, with selection dependent upon co-morbidities, contraindications, and costs. UFH and LMWH are preferred for patients with renal failure. For patients with hemodynamic instability and an increased risk of bleeding UFH is recommended. LMWH is recommended for at least six months in patients with cancer with VTE, otherwise VKA treatment is suggested.

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New Safety Alerts, Indications:

DABIGATRAN- FDA Safety Review

Pradaxa (dabigatran etexilate mesylate): Drug Safety Communication- Safety Review of Post-Market Reports of Serious Bleeding Events[30]

On November 2, 2012 the FDA updated a previous report of risk of serious bleeding with dabigatran. The FDA evaluated reports with the new use of dabigatran and warfarin and found that bleeding rates associated with dabigatran did not appear higher compared to warfarin. The FDA is continuing to monitor this safety issue.

FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves[31]

In December 2012, the FDA warned healthcare professionals and patients that a recent study in Europe (RE-ALIGN) demonstrated an increased risk of strokes, heart attacks, and blood clots forming on the mechanical heart valves in patients treated with dabigatran compared to warfarin. Bleeding after valve surgery was also higher in the dabigatran group. A contraindication against the use of dabigatran in patients with mechanical heart valves was added to the prescribing information for dabigatran.

RIVAROXABAN- New Indication

On November 2, 2012 the FDA approved the addition of treatment of DVT, PE and the reduction in the risk of recurrence of DVT and PE to rivaroxaban labeling. For this indication rivaroxaban should be given with food and be dosed at 15 mg twice daily for the first 21 days and then 20 mg once daily for continued treatment. The clinical evidence used for this approval was based on the EINSTEIN-DVT and EINSTEIN-Ext. studies which are presented below.

The EINSTEIN Investigators (See Evidence Table below)[11]

Rivaroxaban was studied in a phase III, parallel group, non-inferiority, open-label, RCT in over 3,400 patients with acute symptomatic DVT without PE in the EINSTEIN-DVT trial. Patients were randomized to rivaroxaban 15mg twice daily for 3 weeks and then 20mg once daily or enoxaparin and a vitamin K antagonist (warfarin or acenocoumarol) for 3, 6, or 12 months.

There was low-strength of evidence that rivaroxaban was non-inferior to standard treatment (enoxaparin plus VKA) for the prevention of recurrent VTE in patients with acute DVT. The primary endpoint was experienced by 2.1% of the rivaroxaban group and 3.0% for the enoxaparin/VKA group (HR 0.68; 95% CI, 0.44-1.04; $p<0.001$ for noninferiority). There was low-strength of evidence of similar rates of major bleeding ,8.1% in both groups. The open-label design of this trial introduces a potential for bias that could influence treatment outcomes.

The EINSTEIN Investigators (See Evidence Table below)[11]

The EINSTEIN-EXTENSION study was a placebo-controlled, double-blind, phase III continuation study in over 1,000 patients with a confirmed symptomatic DVT or PE previously treated with a VKA or rivaroxaban for 6 or 12 months (EINSTEIN-DVT, EINSTEIN-PE), that there was equipoise with respect to the need for continued anticoagulation. Patients were randomly assigned to rivaroxaban 20mg daily or placebo for an additional 6 or 12 months. The average patient was 58 years old with around 40% being female. The primary efficacy analysis was recurrent venous thromboembolism and major bleeding was the primary safety analysis.

There is low-strength of evidence that rivaroxaban is more effective than placebo in preventing VTE with extended treatment (HR 0.18; 95% CI 0.09 to 0.39; p<0.001). There is also low-strength of evidence that rivaroxaban causes more major bleeding than placebo. Extension study design may bias efficacy and safety results based on enrollment of patients already able to tolerate/respond to treatments.

The EISTEIN-PE Investigators (See Evidence Table below)[12]

In a phase III, open-label trial of 4,832 patients, rivaroxaban was compared to enoxaparin followed by warfarin in patients 18 years or older with a confirmed diagnosis of PE (EINSTEIN-PE). Patients were treated for 3, 6 or 12 months determined by treating physician before randomization. Patients were a mean age of 58 years old with equal males and females enrolled. A majority of patients had intermediated anatomical extent of PE and 25% had concurrent symptomatic DVT. An average of 19% of patients has a history of previous VTE and 64% were deemed to have PEs that were unprovoked. The primary outcome was symptomatic recurrent VTE and major or clinically relevant nonmajor bleeding was the primary safety outcome.

The is low strength of evidence that rivaroxaban is noninferior to enoxaparin/VKA treatment for the outcome of symptomatic recurrent VTE when treating PE. The primary outcome occurred in 2.1% of the rivaroxaban group and 1.8% of the enoxaparin group (HR: 1.12, 95% CI 0.75 to 1.68, p=0.003 for noninferiority). There is also low strength of evidence that major bleeding events were significantly lower in the rivaroxaban group compared to enoxaparin/VKA treatment, 1.1% and 2.2%, respectively. The open-label study design may bias treatment results.

New Primary Literature:

Dabigatran vs. Enoxaparin:

Eriksson, et al (See Evidence Table below)[6]

A fair quality phase III, double-blind, RCT compared dabigatran 220mg daily to enoxaparin 40mg SQ daily for thromboprophylaxis after THR (RE-NOVATE II[23]). This study was similar to RE-NOVATE[15] with the exception being that RE-NOVATE II enrolled a more diverse population, only evaluated the 220mg dabigatran dose and included patients from North America (17%). Just over 2,000 patients were randomized to treatment for 28-35 days. Patients were mostly white with an average age of 62. The primary endpoint was the composite of total VTE and all-cause mortality and the main safety outcome was major bleeding. Dabigatran was found to be non-inferior, but not superior, to enoxaparin for the primary endpoint (7.7% for dabigatran and 8.8% for enoxaparin, ARR -1.1%, 95% CI -3.8% to 1.6%). Rates of major bleeds were similar for dabigatran (1.4%) and enoxaparin (0.9%), (RR 1.5, CI 0.67 to 3.6, p=0.40). Limitations to these findings include; results expressed as composites which can overestimate results, evaluation of asymptomatic DVTS which the importance and clinical relevance is unknown, and a large number of patients being excluded from the primary endpoint analysis due to lack of venography.

New Drug Evaluation- Apixaban

FDA Indications:

Apixaban is a factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF.

Potential Off-label Indications:

Apixaban may be used for anticoagulant prophylaxis following orthopedic surgery, treatment of DVT and PE, in medically ill patients and in those with acute coronary syndromes.

Atrial Fibrillation

Clinical Efficacy Data (see evidence table below):

The clinical efficacy of apixaban use in AF was demonstrated in two good quality trials, ARISTOTLE[14] and AVERROES[32]. Both trials were phase III, double-blind, double-dummy design comparing apixaban to warfarin (ARISTOTLE) or aspirin (AVERROES). Both trials allowed for a reduced apixaban dose of 2.5 mg twice daily if they had two or more of the following criteria: ≥80 years old, ≤60 kg weight, or serum creatinine level of 1.5 mg per deciliter (133 µmol/L) or more. Studies enrolled patients with AF and at least one risk factor for stroke. In both trials, patients were on average 70 years old with a $CHAD_2$ score of 2. Populations included warfarin naïve patients and experienced warfarin users. AVERROES was terminated early at 1.1 years of mean follow-up due to a clear benefit of apixaban treatment and ARISTOTLE follow-up was a median of 1.8 years. The primary end point in both trials was the occurrence of stroke or systemic embolism and a key secondary efficacy end point was all-cause mortality. The primary safety outcome was major bleeding.

ARISTOTLE was a good quality, large (n=18,201), multi-center trial enrolling patients with AF from 40 countries.[14] Patients were randomized to apixaban 5 mg twice daily or warfarin (adjusted to an INR goal of 2.0-3.0). Apixaban was superior to warfarin based on the primary outcome rates of 1.27% per year for apixaban compared to 1.60% per year for warfarin (HR 0.79, 95% confidence interval CI 0.66 to 0.95; p= 0.01). The incidence of hemorrhagic stroke was significantly lower with apixaban (0.24%/year) than with warfarin (0.47%/year) (HR 0.51, 95% CI 0.35 to 0.75, p<0.001). The rate of ischemic strokes were also lower with apixaban but not significantly so. All-cause mortality rates were lower with apixaban (3.52%/year) compared with warfarin (3.94%/year), (HR 0.89, 95% CI, 0.80 to 0.998; p=0.47).

AVERROES compared the safety and efficacy of apixaban to aspirin in 5599 patients with AF that were not candidates for warfarin treatment.[32] In this good quality trial, patients were assigned to apixaban 5 mg twice daily or aspirin 81 to 324 mg daily with a mean follow up of 1.1 years. Apixaban was found to be superior to aspirin for the primary endpoint, with incidence rates of 1.6% per year for apixaban and 3.7% per year aspirin (HR 0.45, 95% CI 0.32 to 0.62, p<0.001). Ischemic stroke rates were significantly less with apixaban than with aspirin, 1.1%/year vs. 3.0%/year, respectively. Hemorrhagic stroke rates were also lower for apixaban compared to aspirin but not significantly so. All-cause mortality rates were 3.5%/year for apixaban patients and 4.4%/year for aspirin patients (HR 0.79, 95% CI 0.62 to 1.02, p=0.07).

Clinical Safety:

Safety of apixaban was studied in two phaseIII trials involving 11,886 patients, with the majority taking 5 mg twice daily of apixaban (n=11,284).[14,32] The combined treatment duration of the two studies were ≥24 months for 3,369 patients and ≥12 months for 9,375 patients. Bleeding was the most common reason for treatment discontinuation which occurred more often with warfarin (2.5%/year) than with apixaban (1.7%/year) in ARISTOTLE and more often with apixaban (1.5%/year) than with aspirin (1.3%/year) in AVERROES. Major bleeding rates were significantly higher with warfarin (3.09%/year) than with apixaban (2.13%/year) (HR 0.69, 95% CI 0.60 to 0.80, p<0.0001) in ARISTOTLE. In AVERROES the incidence of major bleeds per year was higher with apixaban than with aspirin, 1.4% and 1.2%, respectively (HR 1.13, 95% CI 0.74 to 1.75, p=0.57).

Conclusion:

There is moderate strength of evidence, based on one good quality study, that apixaban is superior to warfarin for the treatment of AF and is associated with significantly less major bleeding.

Off-label Uses

Orthopedic Prophylaxis

Clinical Efficacy Data (see evidence table below):
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).[7,8,9] Patients were eligible for the trials if they were scheduled for a total knee replacement (TKR) or revision (ADVANCE 1-2)[7,8] or total hip replacement (THR) or revision (ADVANCE 3)[9]. Mean treatment durations were 11-12 days in the TKR trials and 34 days in the THR trial. The primary endpoint in all trials was the rate of symptomatic and asymptomatic DVT, non-fatal PE and all-cause mortality. The primary safety endpoint for all trials was bleeding rates.

ADVANCE-1[7]
ADVANCE-1 was a fair quality ,multi-center trial involving 3,195 patients eligible for thromboprophylaxis after TKR. Patients were randomized to apixaban 2.5 mg twice daily or enoxaparin 30 mg every 12 hours for a mean treatment duration of 11 days. Primary outcome rates were based on venography results which were available for approximately 70% of patients. Apixaban was shown to be inferior to enoxaparin. Rates of the primary outcome occurred in 104 (9.0%) apixaban patients compared to 100 (8.8%) of enoxaparin patients (RR 1.02; 95% CI 0.78 to 1.32, p=0.06 for noninferiority). Symptomatic VTE and VTE related death were also lower in the enoxaparin group. Apixaban was associated with 16 (1.0%) pulmonary embolisms compared to 7 (0.4%) in the enoxaparin group.

ADVANCE-2[8]
In a good quality trial ADVANCE-2 compared apixaban 2.5 mg twice daily to the European TKR dosing regimen of enoxaparin of 40 mg every 24 hours in patients requiring thromboprophylaxis after TKR. In this multi-center (Non-US) trial over 3,000 patients were treated a mean duration of 12 days, which was also the mean length of hospital stay in each group. Approximately 65% of patients were available for the primary efficacy analysis. Apixaban was shown to be noninferior and superior to enoxaparin for the primary outcome. The primary outcome occurred in 147 (15%) of apixaban patients and 243 (24%) of enoxaparin patients (RR: 0.62; 95% CI 0.51 to 0.74, p<0.0001 for superiority). Symptomatic VTE and VTE related death were the same in both groups (n=7). PE rates were slightly higher for apixaban compared to enoxaparin, 4 and 0, respectively.

ADVANCE-3[9]
ADVANCE-3 was a good quality study in 5,407 patients requiring thromboprophylaxis for THR. Patients from 160 sites primarily based in Europe and North America, received apixaban 2.5 mg twice daily or enoxaparin 40 mg every 24 hours. Patients were treated for a mean duration of 34 days. The primary efficacy analysis involved approximately 70% of randomized patients. Apixaban was associated with 27 (1.4%) occurrences of the primary outcome compared to enoxaparin with a rate of 74 (3.9%), (RR: 0.36 (95% CI 0.22 to 0.54, p<0.001 for noninferiority and superiority). Symptomatic VTE and VTE related death were higher in the enoxaparin group but not significantly different from apixaban. The rate of PE was 4 (0.2%) in the enoxaparin group compared to 0 in apixaban group.

Conclusion:
There is low strength of evidence, based on one fair quality trial, that off-label use of apixaban is superior to enoxaparin in patients requiring thromboprophlaxis for TKR. There is moderate strength of evidence, based on one good quality trial, that the off-label use of apixaban in patients undergoing THR is superior to enoxaparin. There is moderate strength of evidence that rates of bleeding are similar for apixaban and enoxaparin in patients requiring thromboprophylaxis for TKR or THR.

Clinical Safety:
The safety of apixaban inpatients undergoing TKR and THR was evaluated in over 11,000 patients in three phase III trials (ADVANCE 1-3).[7,8,9] Adverse reactions and discontinuations due to adverse events were similar between the groups. The primary safety outcome was bleeding. Major bleeds and clinically relevant non-major bleeds were found to be significantly less with apixaban compared to enoxaparin in ADVANCE-1. The rate of major bleeds in the apixaban group was 0.7% (n=11) compared to enoxaparin which was 1.4% (n=22) (Risk Difference: -0.81; 95% CI -1.49 to 0.14, p=0.05). Major or clinically relevant non-major bleeding occurred in 46 (2.9%) of apixaban patients and 68 (4.3%) of enoxaparin treated patients (Risk Difference: -1.46; 95% CI, -2.75 to 0.17, p=0.03). In ADVANCE-2 and ADVANCE-3 the incidence of major bleeds and the composite endpoint of clinically relevant non-major bleeds or major bleeds were similar in the apixaban and enoxaparin treatment groups.

Medically Ill Patients

Clinical Efficacy Data (see evidence table below):
In one, phase III, fair-quality trial 6,528 medically ill, hospitalized patients were randomized to receive apixaban 2.5 mg twice daily for 30 days or enoxaparin 40 mg once daily for 6-14 days (ADOPT).[33] The trial included acutely ill patients with congestive heart failure (CHF) or respiratory failure or other medical disorders with at least one additional risk factor for VTE. The primary outcome measure was 30-day composite of death related to VTE, PE, symptomatic DVT or asymptomatic proximal-leg DVT which occurred in 2.71% of apixaban patients and 3.06% of enoxaparin patients (RR: 0.87; 95% CI 0.62 to 1.23, p=0.44). The study was underpowered due to high attrition rates, with approximately 36% of patients not included in primary efficacy analysis.

Clinical Safety:
The safety of apixaban in medically ill patients was studied in ADOPT, which included 3,184 patients on apixaban for 30 days.[33] The primary safety outcome was bleeding events. Major bleeds occurred in 15 (0.47%) of patients treated with apixaban and 6 (0.19%) of patients treated with enoxaparin (RR: 2.58; 95% CI 1.02 to 7.24, P=0.04). Major and clinically relevant non-major bleeding events were also lower with enoxaparin compared to apixaban, 2.08% versus 2.67%, respectively.

Conclusion:
There is insufficient evidence for the use of apixaban for thromboprophylaxis in medically ill, hospitalized patients at this time.

Acute Coronary Syndrome

In one phase III, double-blind, placebo-controlled, fair quality trial of 7,392 patients apixaban 5 mg twice daily was found to have increased rates of major bleeds without a counterbalance of reduced ischemic events and for this reason the trial was stopped prematurely.[34]

Extended Treatment of VTE

In one phase III, double-blind, placebo-controlled randomized trial of 2482 patients apixaban 2.5 mg, apixaban 5 mg twice daily compared to placebo were studied (AMPLIFY-EXT)[35]. Patients were included if they had a prior VTE and completed 6 to 12 months of anticoagulation and for whom there was clinical equipoise regarding continuing or discontinuing treatment. Patients were on average 57 years old with slightly more males than females. The primary outcome studied was symptomatic recurrent VTE or death from VTE. The major safety endpoints were major bleeding.

Clinical Efficacy:
There is low strength of evidence, based on one fair quality trial, that both doses of apixaban were superior to placebo for the primary outcome.[35] There were 3.8% of patients with symptomatic recurrent VTE or death from VTE in the apixaban 2.5 mg group (A2.5 vs. placebo: RR: 0.33; 95% CI, 0.22 to 0.48, p<0.001) compared to 4.2% for apixaban 5 mg (A5 vs. placebo: RR: 0.36; 95% CI, 0.25 to 0.53, p<0.001) and 11.6% of placebo patients.

Clinical Safety:
There was low strength of evidence that both doses of apixaban had similar rates of major bleeding and major and clinically relevant non-major bleeding rates.

Conclusion:
There is low strength of evidence to recommend apixaban for extended treatment in patients previously treated for VTE.

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
Medically Ill: Cardiovascular death, myocardial infarction or ischemic stroke
ADVANCE 1-3: Recurrent VTE, clinically relevant bleeding
All studies: bleeding

Evidence Table

RE-NOVATE II[6]									
Eriksson, et al Phase III, RCT, DB, 19 Countries	1. Dabigatran (D 220mg QD * started 1-4 hours after surgery with a half-dose 2. Enoxaparin (E 40mg QD * started the evening before surgery	Age:62 yrs Female: 52% Inclusion: Patients 18 and older undergoing unilateral THR Exclusion: Bleedin disorder, uncontrolled hypertension, surgery, condition or medication predisposing pt. to bleeding, abnormal liver fxn renal insufficiency	1. 1036 2. 1019	Median Tx duration: 32 days Median f/u: 93 days	Total VTE + all-cause mortality : D: 7.7% E: 8.8% ARR: -1.1% (95% CI -3.8 to 1.6%, p<0.0001 for noninferiority) Total DVT: D: 7.6% E: 8.6% ARR: -1.0% (95% CI -3.7 to 1.7%, p=0.48) Symptomatic DVT: D: 0.0% E: 0.4% p=0.06 Symptomatic non-fatal PE: D: 0.1% E: 0.2% p=0.62 VTE Mortality D: 2.2% E: 4.2% ARR: -1.9% (95% CI -3.6 to -0.2%, p=0.03 for superiority)	N/A NS NS NS ARR 1.9% NNT 52	Major Bleeding: D: 1.4% E: 0.9% p=0.40 Withdrawal due to Adverse Events D: 5.9% E: 5.2%	NS NS	**Quality Rating: Fair** **Internal Validity** Selection bias: computer-generated scheme using telephone randomization procedure Performance: double-dummy design used to conceal treatment assignments from patients and clinical monitors Detection: treatment group assignments were concealed from investigators and staff Attrition: large number (21%) excluded from mITT analysis due to lack of venography. The number was similar between groups and is consistent with other similar studies (power estimate took into account expected exclusions). **External Validity** Recruitment: recruited from 108 centers in 19 countries. Patient Characteristics: population was predominately White (90%) and Asian (9%). 2.5% had a DVT or PE history. Setting: Inpatient (avg.8 days) with outpatients follow –up. Outcome: Primary endpoint results expressed as composites can exaggerate outcomes but are included for completeness. Primary endpoint including symptomatic and asymptomatic (venography). The importance and clinical relevance of asymptomatic DVTs is unknown.
EINSTEIN-DVT[11]									
The Einstein	1. Rivaroxaban 15mg twice daily X 3	Age: 56 years Female: 43%/44%	1. 1731	Median Tx duration: 3, 6, or 12 months	Recurrent VTE (composite of DVT, non-fatal PE or fatal PE):		Composite of major or clinically relevant nonmajor bleeding:		**Quality Rating: Fair** **Internal Validity: RofB**

Investigator Phase III, RCT, Open-label, PG, non-inferiority study	weeks then 20mg once daily 2. Enoxaparin + either warfarin or acenocoumarol (vitamin K antagonist)	Inclusion: Acute symptomati DVT Exclusion: Additional VKA indication, CrCl <3(ml/min, significant liver disease, active bleeding, uncontrolled HTN, pregnant/breastfe ding, concomitant CYP-450 3A4 inhibitors	2. 171		R:36 (2.1%) E-VKA: 51 (3.0%) HR: 0.68 (95% CI 0.44-1.04 p<0.001 for noninferiority) Mortality: R: 38 (2.2%) E-VKA: 49 (2.9%) HR: 0.67 (95% CI 0.44 to 1.02, p=0.06)	ARR: 0.9% NNT: 111 NS	R: 139 (8.1%) E-VKA: 138 (8.1%) HR: 0.97 (95% CI 0.76-1.22, p=0.77) Major Bleeding: R: 14 (0.8%) E-VKA: 20 (1.2%) HR: 0.65 (95% CI 0.33 to 1.30, p=0.21)	NS NS	Selection: Patients were randomized via computerized voice-response system. Performance: study was open label allowing for potential bias. Detection: Outcomes were assessed by central adjudication committee that were unaware of treatment assignment. Attrition: Low rates of lost to follow-up. **External Validity:** Recruitment: Details not provided. Patient Characteristics: Patients on warfarin in TTR 58%, which is slightly lower then other similar studies. Included patients with active cancer but not other groups that are unable to take VKAs. Outcomes: Direct outcomes were used to determine treatment effect. Composite outcomes can overestimate treatment effect. Outcomes are unknown beyond 12 months.
EINSTEIN-Extension[11]									
The Einstein Investigators Phase III, DB, PG	1. Rivaroxaban 20mg daily 2. Placebo	Age: 58 yrs Female: 41%/43% Inclusion: objectively confirmed, symptomatic DVT o PE with 12 month prior treatment with warfarin or acenocoumarol Exclusion: additional VKA indication, CrCl <30 ml/min, significant liver disease, active bleeding, uncontrolled HTN, pregnant/ breastfeeding, concomitant CYP-450 3A4 inhibitors	1. 602 2. 594	Tx duration: 6 or 12 months	Recurrent VTE: R: 8 (1.3%) P: 42 (7.1%) HR 0.18; (95% CI 0.09 to 0.39, p<0.001) Morality: R: 1 (0.2%) P: 2 (0.3%)	ARR: 5.8% NNT: 17	Major Bleeding: R: 4 (0.7%) P: 0 (0.0%) p=0.11 Clinically Relevant Non-major Bleeding: R: 32 (5.4%) P: 7 (1.2%)	NS	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via computerized voice-response system. Performance: double-blind design. Placebo comparison limits clinical applicability. Detection: Outcomes were assessed by central adjudication committee that were unaware of treatment assignment. Attrition: Low rates of lost to follow-up. **External Validity:** Recruitment: Patients previously on therapy (EINSTEIN-DVT or routine care) and if there was equipoise to continuing treatment. Patient Characteristics: Patients were previously exposed to treatment. Outcomes: Direct outcomes were used to determine treatment effect. Composite outcomes can overestimate treatment effect.

EINSTEIN-PE[12]									
The EINSTEIN-PE Investigators Phase III, PG, open-label, RCT	1. Rivaroxaban 15 mg twice daily for 3 weeks and then 20 mg once daily 2. Enoxaparin followed by dose-adjusted VKA	Mean Age: 58 years Male: 53% Inclusion: 18 years and older, with acute symptomatic PE with objective confirmation, with or without symptomatic DVT Exclusion: Prior anticoagulation, placement of vena cava, thromboectomy, fibrinolytic agent for current episode, contraindication to anticoagulation treatment, additional indication for anticoagulation, and renal or liver disease.	1. 2419 2. 2413	Tx duration: 3, 6, or 12 months	<u>Symptomatic Recurrent VTE:</u> R: 50 (2.1%) E-VKA: 44 (1.8%) HR: 1.2 (95% CI, 0.75 to 1.68, p=0.003, for noninferiority)	NA	<u>Composite of major or clinically relevant nonmajor bleeding</u>: R: 249 (10.3%) E-VKA: 274 (11.4%) HR: 0.90 (95% CI, 0.76 to 1.07, p=0.23) <u>Major Bleeding:</u> R: 26 (1.1%) E-VKA: 52 (2.2%) HR: 0.49 (95% CI, 0.31 to 0.79, p=0.003) <u>Mortality:</u> R: 58 (2.4%) E-VKA: 50 (2.1%) HR: 1.13 (95% CI, 0.77 to 1.65, p=0.53)	NS NA NS	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via computerized voice-response system. Performance: open-label design lends itself to potential treatment bias. Detection: Details on outcome assessment no described. Attrition: Rates were low. **External Validity:** Recruitment: Patients were from 263 sites in 38 countries. Patient Characteristics: Similar baseline characteristics. Patients in enoxaparin treatment group were treated for a median duration of 8 days. Average TTR for warfarin treated patients was 62.7%. Outcomes: Direct outcomes used.
ARISTOTLE[14]									
Granger, et a Phase III RCT, DB, DD	1. Apixaban 5 mg bid 2. Warfarin (INR adjusted to 2.0-3.0)	Median Age: 70 yrs Female: 35% Mean $CHAD_2$ Score: 2.1 Inclusion: AF or flutter diagnosis and 1 risk factor for stroke Exclusion Criteria: AF with a reversible cause, moderate or severe mitral	1. 9120 2. 9081	Median F/U: 1.8 yrs.	<u>Stroke or Systemic Embolism (per year):</u> A : 212 (1.27%) W: 265 (1.60%) HR 0.79 (95% CI, 0.66 to 0.95, p= 0.01 for superiority) <u>Ischemic Stroke:</u> A: 162 (0.97%) W: 175 (1.05%) HR: 0.79 (95% CI, 0.65 to 0.95, p=0.42) <u>Hemorrhagic Stroke:</u>	ARR: 0.33 NNT: 303 NS	<u>Major Bleeding:</u> A: 327 (2.13%) W: 462 (3.09%) HR 0.69 (95% CI, 0.6 to 0.80) P<0.001		**Quality Rating: Good** **Internal Validity: RofB** Selection: Randomization details not provided Baseline characteristics were well matched. Performance: Patients and investigators were blinded to treatment allocation including encrypted INR device used in DD study design. Detection: Outcomes assessors were blinded to treatment assignment. Attrition: Efficacy data was analyzed based on an ITT analysis which included all patients that were randomized. For safety outcomes, all patients who took at least one dose of study drug were included. Attrition accounted for

		stenosis, other indication for anticoagulation, recent stroke, ASA >165 mg/day or need for both ASA and clopidogrel and renal insufficiency			A: 40 (0.24%) W: 78 (0.47%) HR: 0.51 (95% CI, 0.35 to 0.75, p<0.001) <u>Myocardial Infarction:</u> A: 90 (0.53%) W: 102 (0.61%) HR: 0.88 (95% CI, 0.66 to 1.17, p=0.37) <u>Mortality:</u> A: 603 (3.52%) W: 669 (3.94%) HR: 0.89 (95% CI, 0.80 to 0.998, p=0.047)	ARR: 0.23% NNT: 435 NS ARR: 0.42% NNT: 238			2.1% of patients. **External Validity:** Recruitment: Patients from approximately 40 countries and 1000 centers were included. Patient Characteristics: Study included warfarin naïve users (~43%) and patients with varying degrees of AF risk based on $CHAD_2$ score. Mean time in therapeutic range for warfarin users was 62%. Outcomes: Direct outcomes were used to determine treatment effect. Composite outcomes can overestimate treatment effect.
AVERROES[32]									
Connolly, et al Phase III, RCT DB, DD	1. Apixaban 5 mg bid 2. Aspirin 81-324 mg daily	Age: 70 yrs. old Female: 41% Mean $CHAD_2$: 2 Inclusion Criteria: Patients were 50 yr or older with AF, at least one risk factor for stroke and not receiving or candidates for VKA therapy. Exclusion Criteria: Patient requiring anticoagulation for other indications than AF, serious bleeding in previous 6 months or at high risk of bleeding, alcohol or drug abuse, mental health issues, reduced life	1.2808 2.2791	Mean F/U: 1.1 yrs.	<u>Stroke or Systemic Embolism(per year):</u> A: 51 (1.6%) ASA: 113 (3.7%) HR 0.45 (95% CI, 0.32 to 0.62) P<0.001 <u>Ischemic Stroke:</u> A: 35 (1.1%) ASA: 93 (3.0%) HR: 0.37 (95% CI, 0.25 to 0.55, p<0.001) <u>Hemorrhagic Stroke:</u> A: 6 (0.2%) ASA: 9 (0.3%) HR: 0.67 (95% CI, 0.24 to 1.88, p=0.45) <u>Mortality:</u> A: 111 (3.5%) ASA: 140 (4.4%) HR 0.79 (95% CI, 0.62 to 1.02, p= 0.07)	ARR: 2.1% NNT: 48 ARR: 1.9% NNT: 53 NS NS	<u>Major Bleeding:</u> A: 44 (1.4%) ASA: 39 (1.2%) HR: 1.13 (95% CI, 0.74 to 1.75) P=0.57	ARR: 0.2% NNH: 500	**Study Rating: Good** **Internal Validity: RoB** Selection: Patients randomized via central, computerized, automated voice-response system. Baseline characteristics were well matched. Performance: Use of double-blind, double-dummy design was used to minimize bias. Detection: Outcomes assessors were blinded to treatment assignment. Attrition: Study was stopped early due to clear benefit of apixaban. Data was available on all randomized patients. **External Validity:** Recruitment: Included patients from 36 countries and 522 centers. Patient Characteristics: Patients included warfarin naïve (60%) and those with multiple risk factors for stroke. Most patients randomized to active ASA group received 81 mg of ASA (64%). Nine percent of patients in both groups took ASA in addition, 50% of the time.

		expectancy of less than 1 yr., severe renal insufficiency, increased LFTS/bilirubin or aspirin allergy.							Outcomes: Direct outcomes were used. Composite outcomes can overestimate treatment effect.
ADVANCE-1[7]									
Lassen, et al Phase III, RCT DB, DD	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 hypertension, active hepatobiliary disease, significant renal disease and contraindications to venography.	1. 1599 2. 1596	Mean Treatment: 11 days Mean start of medication: 20 hours	<u>Composite of asymptomatic and symptomatic DVT, non-fatal PE or death from any cause:</u> A: 104 (9.0%) E: 100 (8.8%) RR 1.02 (95% CI 0.78 to 1.32, p=0.06 for noninferiority) <u>Symptomatic VTE and VTE related death:</u> A: 19 (1.2%) E: 13 (0.81%) RR 1.46 (95% CI 0.72 to 2.95) <u>All PE:</u> A: 16 (1.0%) E: 7 (0.4%) <u>Mortality:</u> A: 3 (0.2%) E: 3 (0.2%)	NS NS NS	<u>Major Bleeds:</u> A: 11 (0.7%) E: 22 (1.4%) Risk Difference: -0.81 (95% CI -1.49 to 0.14, p=0.05) <u>Major or clinically relevant non-major bleeding:</u> 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: RoB** Selection: Patients randomized via central, interactive telephone system. Well matched baseline characteristics. Performance: Use of double-blind, double-dummy design was 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 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]									
Lassen, et al Phase III, DB, DD, RCT	1. Apixaban 2.5 mg twice daily (started 12-24 hours post surgery) 2. Enoxaparin	Mean Age: 66.5 years Female: 71.5% Inclusion: Patients ≥ 18 years of age scheduled to have	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%)	ARR: 9.3%	<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,	NS	**Study Rating: Good** **Internal Validity: RoB** Selection: Patients randomized via an interactive, central telephone system. Performance: Double-blind, double-dummy treatment design minimized bias. The

	40 mg once daily (started 12 hours before surgery)	unilateral or bilateral elective knee replacement, including revision. Exclusion: Same as above.			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%)	NNT: 11 NA NA	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	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]									
Lassen, et al Phase III, DD, DB, RCT	1. Apixaban 2.5 mg twice daily (started 12-24 hours post surgery) 2. Enoxaparin 40 mg every 24 hours (started 12 hours before surgery	Mean Age: 60 yrs. Female: 52% Inclusion: Patients ≥ 18 years of age scheduled fo elective total hip replacement or revision of previous inserted hip prosthesis. Exclusion: active bleeding, contraindications to anticoagulation or required ongoing anticoagulation or antiplatelet	1. 1949 2. 1917	Mean treatmen duration: 34 days	<u>Composite of asymptomatic or symptomatic DVT, non-fatal PE or all-cause 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)	ARR: 2.5% NNT: 40 NS	<u>Major Bleeds</u> A: 22 (0.8%) E: 18 (0.7%) Absolute Risk 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 NS	**Study Rating: Good** **Internal Validity: RoB** Selection: Patients randomized via an 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

		therapy.			All PE: A: 0 (0%) E: 4 (0.2%) Mortality: A: 3 (0.1%) E: 1 (<0.1%)				predominately white and primarily treated in Europe and North America. Mean hospitalization days were 9. Outcomes: Use of composite outcomes may overestimate treatment benefit.
APPRAISE-2[34]									
Alexander, et al Phase III, DB, PC RCT	1. Apixaban 5 mg twice daily 2. Placebo* * In addition to standard anti-platelet therapy	Mean Age: 67 years Females: 32% Inclusion Criteria: Patients with acute coronary syndrome (ACS) at high risk and taking standard treatment for ACS (aspirin or aspirin plus any P2Y12-receptor antagonist) Exclusion Criteria: Severe hypertension, severe renal dysfunction, active bleeding or at high risk of bleeding, known coagulopathy, prior stroke, class IV heart failure, and shortened predicted life expectancy.	1. 3705 2. 3687	Median treatment duration: 175 days for apixaban and 185 days for placebo	Composite of cardiovascular death, myocardial infarction or ischemic stroke: A: 279 (7.5%) P: 293(7.9%) HR: 0.95 (95% CI 0.80 to 1.11, p=0.51) Myocardial Infarction: A: 182 (4.9%) P: 194 (5.3%) HR: 0.93 (95% CI, 0.76 to 1.14, p=0.51) Mortality: A: 155 (4.2%) P: 143 (3.9%) HR: 1.08 (95% CI, 0.86 to 1.35, p=0.51)	NS NS NS	Major Bleeding: A: 46 (1.3%) P: 18 (0.5%) HR: 2.59 (95% CI 1.50 to 4.46, p=0.001) * Trial was stopped early due to excess of clinically important bleeding events	ARR: 0.8% NNH: 125	**Study Rating: Fair** **Internal Validity: RoB** Selection: Patients randomized in a blinded fasion via interactive voice-response system. Performance: Double-blind treatment design minimizes bias. Detection: Blinding of outcome assessors was not described. Attrition: Trial was stopped early due to excess of clinically important bleeding events. **External Validity:** Recruitment: Patients were recruited from 39 countries and 858 sites. Patient characteristics: Patients were high risk with more than half having protocol-defined high-risk characteristic. Most patients were taking aspirin (97%) and a high percent(81%) were also taking aspirin and a P2Y12-receptor antagonist. Outcomes: Composite outcome may overestimate treatment effect.
ADOPT[33]									
Goldhaber, et al Phase III, DB, DD, PC, RCT	1. Apixaban 2.5 mg twice daily for 30 days 2. Enoxaparin 40 mg once	Mean Age: 67 years Males: 49% Inclusion: 40 years or older, hospitalized for	1. 2211 2. 2284	Mean treatment duration: A: 25 days E: 7 days	30-day composite of death related to VTE, PE, symptomatic DVT or asymptomatic proximal-leg DVT: A: 60 (2.71%)	NS	Major Bleeds A: 15 (0.47%) E: 6 (0.19%) RR: 2.58 (95% CI 1.0 to 7.24, P=0.04)	ARR: 0.28% NNH: 357	**Study Rating: Fair** **Internal Validity: RoB** Selection: Patients randomized through a central telephone system with computer-generated randomization list. Trial was

	daily for 6-14 days	CHF, acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or inflammatory bowel disease and had an expected hospital stay of at least 3 days. Except for patients with CHF and respiratory failure, patients also had to have one additional risk factor and be moderately or severely restricted in mobility. Exclusion Criteria: Diagnosis of VTE, disease requiring ongoing anticoagulation, active liver disease, anemia or thrombocytopenia, severe renal disease, taking 2 or more antiplatelets or aspirin at more than 165 mg day, recent surgery, previous anticoagulant prophylaxis within 14 days, actively bleeding or at high risk for bleeding or invasive procedure scheduled.			E: 70 (3.06%) RR: 0.87 (95% CI 0.62 to 1.23, p=0.44) <u>Symptomatic DVT:</u> A: 5 (0.15%) E: 16 (0.49%) <u>Mortality:</u> A: 131 (4.1%) E: 133 (4.1%)	NS NA	<u>Major and clinically relevant non-major bleeding:</u> A: 85 (2.67%) E: 67 (2.08%) RR: 1.28 (95% CI 0.9 to 1.76 P=0.12)	NS	underpowered for primary efficacy outcome. Performance: Different treatment durations makes efficacy comparison difficult. Enoxaparin was given only as an inpatient for a minimum of 6 days. Detection: Primary outcome adjudication done by blinded, independent central adjudication committee. Attrition: Approximately 36% of patients were not included in primary efficacy analysis. **External Validity:** Recruitment: Patients were recruited from 35 countries and 302 sites. Patient Characteristics: Included primarily white patients with CHF or acute respiratory failure. Outcomes: Composite outcome may overestimate treatment effect. Screening of hospitalized patients for VTE with compression ultrasonography not routinely done.
AMPLIFY-EXT									
Agnelli G, et	1. Apixaban 2.5 mg twice daily	Average Age: 56.5 years	1. 840	Tx duration: 12 months	<u>Symptomatic Recurrent VTE or Death from VTE:</u>		<u>Major Bleeds:</u> A2.5: 2 (0.2%)		**Study Rating: Fair**

al Phase III, DB PC, RCT	(A2.5) 2. Apixaban 5 mg twice daily (A5) 3. Placebo	Male: 57.5% DVT initial diagnosis: 65% Inclusion: Patients 18 years or older with objectively confirmed VTE who had competed 6-12 months of anticoagulation therapy and there was clinical equipoise regarding continuing or discontinuing treatment Exclusion: Contraindications to anticoagulant therapy, dual antiplatelet therapy, or aspirin dose greater than 165 mg daily.	2. 811 3. 826		A 2.5: 32 (3.8%) A5: 34 (4.2%) P: 96 (11.6%) A2.5 vs P: RR: 0.33 (95% CI, 0.22 to 0.48, p<0.001) A5 vs. P: RR: 0.36 (95% CI, 0.25 to 0.53, p<0.001)	A2.5- ARR: 7.8% NNT 13 A5- ARR: 7.4% NNT: 14	A5: 1 (0.1%) P: 4 (0.5%) A2.5 vs P: RR 0.49 (95% CI 0.09 to 2.64 A5 vs. P: RR: 0.25 (95% CI 0.03 to 2.24 <u>Major or clinically relevant non-major bleeding:</u> A2.5: 27 (3.2%) A5: 35 (4.3%) P: 22 (2.7%) A2.5 vs P: RR: 1.20 (95% CI 0.69 to 2.10 A5 vs P: RR: 1.62 (95% CI 0.96 to 2.73	NS NS	**Internal Validity: RoB** Selection: Patients randomized through a interactive voice-response system. Performance: Placebo comparison limits clinical applicability. Detection: Details on outcome assessment were not provided. Attrition: There were low levels of attrition (4 patients) **External Validity:** Recruitment: Patients were recruited from AMPLIFY trial (ongoing) in which they have already been accustomed to treatment with either apixaban or enoxaparin and warfarin. Patient Characteristics: Most patients (~90%) had unprovoked VTE, relatively young and were similar at baseline. Outcomes: Composite outcome may exaggerate treatment effect.

[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: Drug Information[19]

Pharmacology: apixaban works by directly inhibiting free and clot-bound factor Xa and prothrombinase activity, resulting in decreased thrombus formation.

Table 1. Pharmacokinetics[19]

Parameter	Apixaban
Half-life	12 hours (chronic dosing)
Metabolism	Metabolized mainly via CYP3A4
Elimination	27% renal and 25% hepatic
Renal Dose Adjustment	Decrease dose to 2.5 mg twice daily if serum creatinine ≥1.5 mg/dL and patient has one of the following: ≥ 80 years or ≤60kg. Not recommended if creatinine clearance is <15 mL/min or on dialysis.
Hepatic Dose Adjustment	No adjustment is needed in mild hepatic impairment.

Contraindications/Warnings[19]**:**

- **Black Box Warning:** Discontinuing apixaban causes patients to be at an increased risk of thrombotic events. An increased rate of stroke was demonstrated in trials when patients were transferred from apixaban to warfarin. It is recommended to strongly consider coverage with another anticoagulant if apixaban is being discontinued for reasons other than bleeding.
- **Contraindications:** apixaban should not be used in patients with active pathological bleeding or severe hypersensitivity to apixaban.
- **Warning:** An increased rate of stroke was demonstrated in trials when patients were transferred from apixaban to warfarin. It is recommended to strongly consider coverage with another anticoagulant if apixaban is being discontinued for reasons other than bleeding. Apixaban increases the risk of bleeding which can be fatal. There is no antidote for apixaban.

Dose[19]

The recommended dose of apixaban is 5 mg twice daily for most patients with AF. The dose should be decreased to 2.5 mg twice daily for patients with any 2 of the following: ≥80 years of age, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL.

Renal Impairment: see above. No data available on those patients with creatinine clearance <15 mL/min or on dialysis.

Hepatic Impairment: No dose adjustment in required in mild hepatic impairment.

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Drug Interactions: The dose of apixaban should be reduced to 2.5 mg twice daily when co-administered with drugs that are strong dual inhibitors of cytochrome P450 3A4 and P-glycoprotein inhibitors. Co-administration of antiplatelet agents, fibrinolytics, heparin, aspirin and chronic NSAID use increases the risk of bleeding.

Switching from warfarin to apixaban: warfarin should be discontinued and apixaban starting when the INR is below 2.0.

Switching from apixaban to warfarin: apixaban will interfere with INR values and therefore INR measurements may not be useful in determining the warfarin dose. For continuous anticoagulation, it is recommended to discontinue apixaban and start a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken.

Switching from apixaban to other anticoagulants other than warfarin: discontinue one being taken and begin the other at the next scheduled dose.

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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

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:** Approve for up to 35 days.	**No:** Go to #2
2. Does the patient have a diagnosis of nonvalvular atrial fibrillation (ICD9 – 427.3x)?	**Yes:** Go to #3	**No:** Go to #6
3. Will the prescriber consider a change to the preferred oral anticoagulant, warfarin?	**Yes:** Approve. Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #4
4. 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	**Yes:** Go to # 5	**No:** Deny with the allowance of a 14 days of rivaroxaban or apixaban (or until patient is deemed adequately anticoagulated)*.

		Recommend trial of warfarin.
5. 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.
6. Does the patient have a diagnosis requiring acute or chronic DVT or PE treatment?	**Yes:** Go to #7	**No:** Deny (Medical Appropriateness)
7. Will the prescriber consider a change to a preferred anticoagulant?	**Yes:** Approve. 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 therapy - drug-drug interactions - intolerable side effects	**Yes:** Go to #9	**No:** Deny with the allowance of a 14 days of rivaroxaban or apixaban (or until patient is deemed adequately anticoagulated)*. Recommend preferred anticoagulant.
9. Is the request for the rivaroxaban?	**Yes:** Approve for up to 1 year.	**No:** Deny with the allowance of a 14 days of apixaban (or until patient is deemed adequately anticoagulated)*. Recommend rivaroxaban trial.

***** 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: 3/28/13 (KS), 8/30/12 (KS), 1/26/12(KS)
Revision(s):
Initiated:

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 #5
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	**Yes:** Go to #4	**No:** Deny. Recommend warfarin trial.

- drug-drug interactions - intolerable side effects		
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:** Approve for up to 1 year.	**No:** Deny (Medical Appropriateness)
5. Does the patient have a diagnosis requiring acute or chronic DVT or PE treatment?	**Yes:** Go to #6	**No:** Deny (Medical Appropriateness)
6. 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 #7
7. 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	**Yes:** Approve for up to 1 year.	**No:** Deny. Recommend trial of preferred anticoagulant.

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