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Drug Class Update: Anticoagulants, Oral and Subcutaneous

Date of Review: November 2019

Date of Last Review: November 2017 – Class Scan
July 2017 – Betrixaban NDE
Date of Literature Search: September 2019

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of the anticoagulant class update is to review any new comparative effectiveness literature that has been published since the last review and to ensure the preferred drug list (PDL) aligns with current evidence.

Research Questions:
1. Is there new high-quality comparative evidence on the effectiveness of anticoagulants when used for stroke prophylaxis in atrial fibrillation or prophylaxis or treatment of venous thromboembolism (VTE)?
2. Is there new high-quality comparative evidence on the harms of anticoagulants when used for stroke prophylaxis in atrial fibrillation or prophylaxis or treatment of (VTE)?
3. Is there evidence regarding subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one anticoagulant is more effective or associated with fewer harms than another anticoagulant?

Conclusions:
- There are thirteen systematic reviews, one guideline and eight randomized controlled trials (RCTs) that provided high-quality evidence for the anticoagulant drug class update.

<u>Venous Thromboembolism</u>
- A high quality systematic review found that prophylaxis with anticoagulants, compared to placebo, after major orthopedic surgery reduces the incidence of deep vein thrombosis (DVT) based on high strength of evidence.[1] In patients with total hip replacement (THR), low-molecular weight heparin (LWMH) was associated with less major bleeding compared to factor Xa inhibitors (FXaIs) (ARR 0.5%) based on moderate quality evidence. Factor Xa inhibitors were associated with a 3% reduction in total DVTs compared to LMWH, 3.4% versus 6.4%, respectively. In patients undergoing THR, DTIs were associated with less risk of total DVT compared to LMWH based on moderate evidence (OR range of 1.14 to 1.52) .[1] Moderate evidence demonstrated a reduction in total DVT events with FXaI when compared to LMWH in patients undergoing TKR, 1.2% versus 2.5%.[1]

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- There is moderate strength of evidence that LMWH has a lower risk of mortality compared to unfractionated heparin (UFH) when used as initial treatment for VTE in patients with cancer, followed by oral therapy for 3 months (57 fewer deaths per 1000 patients treated versus 168 deaths per 1000 patients).[2]
- Moderate strength of evidence found no difference in 3 months of LMWH compared to vitamin K antagonists (VKA) for the treatment of VTE for the outcomes of recurrent VTE and mortality.[3]

Stroke Prophylaxis in Atrial Fibrillation

- A high-quality systematic review and meta-analysis evaluated the use of anticoagulants for the prevention of thromboembolism in patients with atrial fibrillation (AF). Warfarin and rivaroxaban were similarly effective for the outcomes of stroke or systemic embolism. Apixaban was found to be more effective than warfarin (HR 0.79; 95% CI, 0.66 to 0.95) (absolute risk reduction was not provided). Edoxaban was also found to more effective than warfarin for hemorrhagic strokes (HR 0.33; 95% CI, 0.22 to 0.50) but not for overall stroke risk. Dabigatran 150 mg demonstrated superiority over warfarin for stroke and systemic embolism (RR 0.66; 95% CI, 0.53 to 0.82). Major bleeding rates were similar between the direct acting oral anticoagulants (DOACs) and warfarin, with the exception of edoxaban and apixaban which were associated with less major bleeding.[4]
- In patients with chronic kidney disease (CKD) and AF, the efficacy of DOACs was similar to warfarin for the outcome of stroke and systemic embolism prevention based on moderate evidence.[5]
- A high-quality review found risk of stroke and systemic embolism to be less in patients with AF who are treated with FXaIs compared to patients treated with warfarin based on high quality of evidence (odds ration [OR] 0.89; 95% CI, 0.82 to 0.97). Actual differences in event rates between FXaIs and warfarin are small, 34 versus 32 events per 1000 patients.[6]
- There is insufficient direct comparative evidence for comparisons of the DOACs in patients with AF or VTE.

Recommendations:

- No changes are recommended to the PDL based on review of the clinical evidence.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- There is insufficient comparative evidence to universally recommend one anticoagulant over another. There is extensive clinical experience using warfarin; however, DOACs have been shown to have a reduced risk of bleeding in some instances. Clinically efficacy comparisons between warfarin and DOACs have demonstrated similar or superior effectiveness with DOAC therapy, dependent on the indication and outcome studied.
- The last review done in May 2017 resulted in no changes to the PDL. A class update in 2015 resulted in removal of the prior authorization (PA) requirement for most DOACs due to concerns of potentially delaying treatment by requiring prior authorization (PA). Betrixaban still requires a PA, as it is indicated for only hospitalized adult patients.
- An internal drug utilization review in 2017 found that the DOACs were being used appropriately within the Oregon Health Authority (OHA) fee-for-service population.
- A majority of the anticoagulants are available without prior authorization. Drugs requiring a PA include: betrixaban, dalteparin vials, fondaparinux and branded enoxaparin. The anticoagulation class results in a fair amount of expenditures to the OHA with over half the utilization due to DOACs.

Background:
Anticoagulants are used for many indications, most commonly VTE or stroke treatment and prophylaxis. In the last year, the number of patients in the fee-for-service population with an indication for anticoagulation (e.g., stroke, AF, DVT, PE, or VTE) was approximately 400. One to two patients per 1000 people are affected by DVT/pulmonary embolism (PE) annually and approximately 100,000 patients die each year from VTE.[7] The United States (US) prevalence of stroke is approximately 800,000 new and secondary strokes a year.[8] An additional new indication for anticoagulants is the use for reduction in risk of major cardiovascular events (CV death, MI and stroke) when used in combination with aspirin for patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD). Low-dose rivaroxaban (2.5 mg twice daily) is the first DOAC to be approved for this indication; however, evidence suggests a marginal clinical benefit with an actual risk reduction (ARR) of 1.3% in favor of rivaroxaban 2.5 mg twice daily + aspirin compared to aspirin + placebo, 4.1% versus 5.4% (**Table 7**).[9]

The pathophysiology of thrombosis results from damage to the endothelial lining of blood vessels which trigger activation of the coagulation cascade leading to thrombus formation.[10] Anticoagulant pharmacotherapy targets aspects of the clotting cascade to exhibit a therapeutic effect. Injectable anticoagulants work by enhancing antithrombin (AT) which is responsible for inhibiting a variety of clotting factors. Oral anticoagulants exhibit anticoagulant activity through blocking the formation of vitamin K clotting factors (warfarin), direct thrombin inhibition (dabigatran) or factor Xa inhibition (apixaban, edoxaban, and rivaroxaban).[10]

Anticoagulants recommended for VTE are: warfarin, LMWH, and DOACs.[11] Some guidelines preference the use of DOACs over warfarin for VTE disease.[11] For patients with VTE and cancer, the use of LMWH is recommended over other anticoagulants.[11] However, there is accumulating data supporting DOACs in this patient population. For patients undergoing THR or TKR, prophylactic anticoagulants are considered standard practice. Low-molecular weight heparins and DOACs are most commonly used for THR or TKR; however, warfarin is a viable alternative.[1] Patients with AF are at increased risk of stroke and systemic embolism. Anticoagulation is recommended for patients with an elevated CHA_2DS_2-VASc score (2 or greater in men and 3 or greater in women) by some guidance and advocated for patients at lower risk by alternate guidelines.[12,13] Warfarin has been traditionally used first-line for stroke prophylaxis; however, recent guidance recommends DOACs as preferred therapy. Evidence has demonstrated equivalent or superior efficacy of DOACs to warfarin with similar or reduced risk of major bleeding.[13]

The most important outcomes in assessing therapy for treatment and prevention of VTE include the occurrence or reoccurrence of VTE and all-cause mortality. Additional relevant outcomes include: major and minor bleeding, cardiovascular events and withdrawals due to adverse events. Early research relied primarily on symptomatic VTE and fatal PE as measures of antithrombotic prophylaxis efficacy. Recent trials evaluating the anticoagulant efficacy in patients undergoing hip or knee replacement often use the surrogate outcome, asymptomatic DVT, detected by mandatory venography.[36] Many studies that 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, which is the more clinically relevant outcome.[37] This limitation should be considered when interpreting findings from trials studying the use of anticoagulants in patients undergoing TKR or THR.

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

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Venous Thromboembolism

AHRQ – Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery
A 2017 review from the Agency for Healthcare Research and Quality (AHRQ) analyzed literature published from January 2010 thru June 2016, which updated the 2012 review.[1] A total of 142 studies were included, 127 of which were randomized controlled trials (RCTs). High risk of bias related to maintaining blinding was found in 52 of the studies, 28 had high risk of bias in maintaining intention-to-treat (ITT) methodology, 8 had high risk of bias for data analysis and 22 had high risk of bias related to attrition bias. Fifty-four percent of the trials were funded by industry.[1] Fifteen non-randomized comparative studies were also included. The following classes of drugs were included: antiplatelet drugs (aspirin), direct thrombin inhibitors (dabigatran and desirudin), FEI (TB402 – not approved in the US), Factor XaI (apixaban, darexaban, edoxaban, eribaxaban, fondaparinux, rivaroxaban and TAK422), Factor Ii (Factor XI antisense oligonucleotide), LMWH (dalteparin, enoxaparin, semuloparin, tinzaparin), mechanical devices, unfractionated heparin, and VKAs (warfarin).[1] Findings for therapies Food and Drug Administration (FDA) approved in the United States (U.S.) on outcomes with moderate to high strength of evidence will be discussed. Evidence for within-class comparisons of thromboprophylaxis was insufficient to draw conclusions.

Total Hip Replacement
Direct thrombin inhibitors were found to prevent more DVTs than LMWH based on moderate evidence; however, LMWHs were associated with less major bleeding (**Table 1**).[1] Evidence for the comparison of LMWH to FXaI found less major bleeding with LMWH but efficacy findings were inconsistent. LMWHs were associated with a reduction in VTEs and major bleeding compared to UFH. Comparisons of LMWH and aspirin found similar risk of VTE outcomes and major bleeding between both groups. Patients treated with lower doses of LMWH were found to have less bleeding compared patients treated with higher doses of LMWH based on moderate strength of evidence. Treatment with LMWH two weeks or longer was more effective in reducing total DVT and proximal DVT compared to shorter durations (up to 10 days or to hospital discharge).[1]

Table 1. Outcome Results for Total Hip Replacement for Anticoagulant Class Comparisons[1]

Comparison	Outcome	Results (Summary OR Range of OR Estimates)*	Strength of Evidence
LMWH vs. DTI	DVT, total	Range: 1.14 to 1.52 *Favors DTI*	Moderate
	DVT, proximal	Range: 1.35 to 1.89 *Favors DTI*	Moderate
LMWH vs. FXaI	DVT, total	LMWH: 6.4% FXaI: 3.4% 1.71 (95% CI, 1.22 to 2.39) *Favors FXaI*	Moderate
	DVT, proximal	LMWH: 1.8% FXaI: 0.74% 2.40 (95% CI, 1.23 to 4.69) *Favors FXaI*	Moderate
	Major bleeding	LMWH: 1.2% FXaI: 1.7% 0.74 (95% CI, 0.54 to 0.99) *LMWH is associated with less bleeding*	High
	Serious adverse events	0.95 (95% CI, 0.78 to 1.17) *No difference between treatments*	Moderate
LMWH vs. UFH	PE, total	LMWH: 0.85% UFH: 2.9% 0.29 (95% CI, 0.13 to 0.63) *Favors LMWH*	High
	DVT, total	LMWH: 14.4% UFH: 16.3% 0.84 (95% 0.60 to 1.18) *No difference between treatments*	Moderate
	DVT, proximal	LMWH: 4.9% UFH: 7.9% 0.59 (95% CI, 0.38 to 0.93) *Favors LMWH*	Moderate
	Major bleeding	LMWH: 2.1% UFH: 4.6% 0.46 (95% CI, 0.23 to 0.92)`	Moderate

		LMWH is associated with more bleeding	
LMWH vs. VKA	Major bleeding	LMWH: 1.5% VKA: 0.75% 1.96 (95% CI, 1.14 to 3.38) *VKA is associated with more bleeding*	High
Mechanical devices vs. VKA	DVT, proximal	Range: 2.39 to 4.69 *Favors VKA*	High
LMWH low dose (enoxaparin 20 or 30 mg) vs. high dose (enoxaparin 40 mg)	Major bleeding	LMWH low: 1.6% LMWH high: 5% 0.42 (95% CI, 0.21 to 0.86) *LMWH low dose is associated with less bleeding*	Moderate
LMWH short duration (usually less than 28 days) vs. long duration (usually longer than 28 days)	DVT, proximal	LMWH short: 13% LMWH long: 4.5% 2.94 (95% CI, 1.62 to 5.35) *Favors LMWH long*	Moderate

Key: * ARRs presented when available
Abbreviations: DTI – direct thrombin inhibitor; DVT – deep vein thrombosis; FXaI – factor Xa inhibitor; LMWH – low molecular weight heparin; OR – odds ratio; PE – pulmonary embolism; UFH – unfractionated heparin; VKA – vitamin K antagonist

Total Knee Replacement

Evidence for the use of anticoagulants in patients undergoing TKR are presented in **Table 2**. There was a lower incidence of VTE when treated with FXaI compared to LMWH. Low molecular weight heparin was found to result in a lower incidence of DVT compared to VKAs in patients undergoing TKR.[1] There was high strength of evidence that patients who received higher doses of the DTI, dabigatran 220 to 225 mg (not currently available), had a reduced risk of total DVT and moderate evidence of less proximal DVT than lower doses (i.e., dabigatran 150 mg).[1] Total VTE was reduced in patients taking higher doses of DTIs compared to lower doses based on moderate evidence.

Table 2. Outcome Results for Total Knee Replacement for Anticoagulant Class Comparisons[1]

Comparison	Outcome	Results (Summary OR Range of Estimates)*	Strength of Evidence
LMWH vs. FXaI	DVT, proximal	LMWH: 2.5% FXaI: 1.2% 1.84 (95% CI, 1.07 to 3.16) *Favors FXaI*	Moderate
LMWH vs. VKA	DVT, total	Range: 0.42 to 0.67 *Favors LMWH*	High

DTI low dose (dabigatran 150 mg vs. high dose (dabigatran 220 mg)	DVT, total	Range: 1.54 to 2.08 *Favors high dose*	High
	DVT, proximal	1.57 (95% CI, 0.83 to 2.96) *Favors high dose*	Moderate
FXaI low vs. high dose (twice the lower dose)	VTE, total	FXaI low: 23% FXaI high: 13% 2.06 (95% CI, 1.48 to 2.86) *Favors high dose*	Moderate

Key: * ARRs presented when available
Abbreviations: DVT – deep vein thrombosis; FXaI – factor Xa inhibitor; LMWH – low molecular weight heparin; VKA – vitamin K antagonist

Hip Fracture Surgery

Only six trials were available for analysis and evidence was insufficient for most outcomes. There was moderate evidence that the risk of total DVT was lower with LMWH compared to FXaI.[1]

Findings of this systematic review are limited by total number of DVTs as an outcome for 82% of the included studies, which includes symptomatic and asymptomatic DVTs. Asymptomatic DVTs are not commonly identified in non-study populations, and therefore, the clinically applicability to PE and other vascular outcomes is unknown. Additionally, symptomatic DVTs and other clinically relevant outcomes were only reported in one-third and two-thirds of studies, respectively. The low incidence of PE makes it difficult to determine a correlation with DVT incidence. There was also evidence of selective outcome reporting which has the potential to result in inconsistent conclusions.

Cochrane – Vitamin K antagonists versus Low-molecular-weight Heparin for the Long-term Treatment of Symptomatic Venous Thromboembolism

Symptomatic venous thromboembolism that requires long-term (3 months) therapy with VKAs or LMWH was evaluated by a 2017 Cochrane review.[3] Sixteen trials (n=3299) met criteria for inclusion. Type of VTE was separated into: PE (3 trials), symptomatic DVT and symptomatic PE (1 trial), and symptomatic DVT (12 trials). Seven of the sixteen trials were considered to be of high methodological quality. There was a high risk of performance bias for all included studies and a high risk of allocation bias in a majority of studies. Other domains of bias were low or unclear.

Recurrent VTE rates were similar between LMWH and VKA based on moderate evidence (OR 0.83; 95% CI, 0.60 to 1.15; P=0.27).[3] Moderate quality evidence found no difference in mortality rates between LMWH and VKA with follow-up ranging up to 9 months (OR 1.08; 95% CI, 0.75 to 1.56; P =0.68).[3] There were no differences in bleeding rates between the two therapies. There was imprecision for the outcome of major bleeding preventing strong conclusions favoring either treatment.

There are limitations to the evidence, such as low number of events resulting in imprecision in the data. Different initial treatment of VTE may have also influenced the results. Lack of blinding due to administration differences and settings of administration (inpatient vs. outpatient) introduced a high degree of performance bias. Overall, there are no efficacy and safety differences in using LMWH versus VKA for long-term VTE treatment.

Cochrane – Low Molecular Weight Heparin for Prevention of Venous Thromboembolism in Patients with Lower-Limb Immobilization

A 2017 Cochrane review assessed the effectiveness of LWMH for VTE prevention in ambulatory patients with lower-limb immobilization.[14] LMWH (tinzaparin and dalteparin) use was compared to placebo or no prophylaxis in 8 trials. Risk of bias was low for allocation and blinding. Incomplete outcome data and selective reporting had a high risk of bias in 3 trials. Primary efficacy outcomes were DVT, PE and mortality.

There was moderate evidence of a reduction in DVT in patients receiving LMWH compared to placebo, 87 per 1000 patients versus 174 per 1000 patients (OR 0.45; 95% CI, 0.33 to 0.61) in patients who were receiving therapy during period of immobilization.[14] Findings for all other outcomes were based on low quality evidence and therefore no strong conclusions were able to be drawn. Minor bleeding was rare and not substantially different between groups.

Stroke

AHRQ – Stroke Prevention in Patients with Atrial Fibrillation

A 2018 review done by AHRQ evaluated the comparative effectiveness of vitamin K antagonists (warfarin), DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) and procedural interventions for stroke prevention in patients with AF.[4] This report updates the review from 2013 with the addition of 122 studies. A total of 117 studies contributed to the evidence for prophylactic anticoagulation use. Seventy-five studies were found to be good-quality with a low risk of bias. Bleeding risk and predictive utility of VTE clinical imaging was also investigated.

There was moderate strength of evidence that CHADS2, CHA2DS2-VASc, Framingham score, and Age, Biomarkers (cTnI-hs and NT-proBNP) and Clinical history (ABC) score provide limited prediction of stroke events (moderate strength of evidence).[4] Assessment of predictive factors for bleeding found the HAS-BLED assessment to be effective for predicting major bleeding events in patients taking warfarin for AF based on moderate strength of evidence. Moderate strength of evidence found patients with chronic kidney disease to be at increased risk of bleeding.

Evidence for the use of anticoagulants for the prevention of stroke in patients with nonvalvular AF are presented in **Table 3**.[4] For the majority of therapies superior efficacy is associated with increased risk of bleeding. Warfarin has consistently shown to be more effective than aspirin for stroke prevention and combination therapy of clopidogrel + aspirin is more effective than aspirin alone, for those patients who are not candidates for warfarin or DOACs.[4] Dabigatran 150 mg has been shown to be more effective than warfarin for the outcome of stroke and systemic embolism reduction and associated with similar rates of major bleeding. Mortality benefit and MI risk has been inconsistent in comparisons between dabigatran and warfarin.[4] Apixaban has been shown to be superior to aspirin and superior to warfarin for the outcomes of stroke and systemic embolism with similar or reduced incidence of bleeding. All-cause mortality was also shown to be decreased with apixaban compared to warfarin but this was based on low strength of evidence. Rivaroxaban and warfarin are associated with similar efficacy and major bleeding rates. Edoxaban has demonstrated a lower hemorrhagic stroke risk compared to warfarin but similar overall stroke risk with similar rates of major bleeding.

Limitations to the findings include the lack of direct head-to-head comparisons of the DOACs and high risk of publication bias associated with a majority of included studies being manufacturer funded.

Table 3. Anticoagulants for Thromboembolic Prevention in Patients with Nonvalvular AF[4]ǂ

Comparison	Outcome	Results	Strength of Evidence/Notes
Aspirin Vs. Warfarin	Ischemic Stroke	No pooled results *Warfarin superior to aspirin*	Moderate
	Bleeding	No pooled results *Warfarin was associated with more bleeding than aspirin*	Moderate
Warfarin + aspirin Vs. Aspirin	Ischemic stroke	HR 1.27 (95% CI, 1.14 to 1.40) *Increased risk with warfarin + aspirin*	Moderate
	Bleeding	No pooled results *Increased risk with warfarin + aspirin*	Moderate
Clopidogrel + aspirin Vs. Aspirin	Any stroke	HR 0.72 (96% CI, 0.62 to 0.83) *Clopidogrel + aspirin superior to aspirin*	Moderate
	Hemorrhagic stroke	No pooled results *Similar risk between treatments*	Moderate
	Systemic embolism	HR 0.96 (95% CI, 0.66 to 1.40) *Similar risk between therapies*	Moderate
	Major bleeding	HR 1.57 (95% CI, 1.29 to 1.92) *Increased bleeding risk with clopidogrel + aspirin*	Moderate
	Minor bleeding	HR 2.42 (95% CI, 2.03 to 2.89) *Increased bleeding risk with clopidogrel + aspirin*	Moderate
	All-cause mortality	HR 0.98 (95% CI, 0.89 to 1.08) and HR 1.12 (95% CI, 0.65 to 1.90) *Similar risks between treatments*	Moderate Results not pooled
Clopidogrel Vs. Warfarin	Ischemic stroke	*HR 1.86 (95% CI, 1.52 to 2.27)* *Increased risk compared to warfarin*	Moderate
	Bleeding	*HR 1.06 (95% CI, 0.87 to 1.29)* *Similar risk between therapies*	Moderate
Clopidogrel + aspirin Vs. Warfarin	Stroke or systemic embolism	HR 1.56 (95% CI, 1.17 to 2.10) and HR 1.72 (95% CI, 1.24 to 2.37) *Increased risk with clopidogrel + aspirin*	High Results not pooled
	Hemorrhagic stroke	HR 0.34 (95% CI, 0.12 to 0.93) *Increased risk with warfarin*	Moderate
	Major bleeding	HR 1.10 (95% CI, 0.83 to 1.45) *Similar rates between groups*	Moderate
	Minor bleeding	HR 1.23 (95% CI, 1.09 to 1.39) *Increased risk with clopidogrel + aspirin*	Moderate

	All-cause mortality	HR 1.01 (95% CI, 0.81 to 1.26) *Similar risk between therapies*	Moderate
	Death from vascular causes	HR 1.14 (95% CI, 0.88 to 1.48) *Similar risk between therapies*	Moderate
	Myocardial infarction	No pooled results *Similar risk between therapies*	Moderate
Warfarin + clopidogrel Vs. Warfarin	Bleeding	HR 3.08 (95% CI, 2.32 to 3.91) *Increased risk with warfarin + clopidogrel*	Moderate
Warfarin Vs. Warfarin + aspirin + clopidogrel	Bleeding	HR 3.07 (95% CI, 2.89 to 4.76) *Increased risk with triple therapy*	Moderate
Dabigatran 150 mg Vs. Warfarin	Hemorrhagic	RR 0.26 (95% CI, 0.14 to 0.49)* *Dabigatran superior to warfarin*	High
	Stroke or systemic embolism	RR 0.66 (95% CI, 0.53 to 0.82)* *Dabigatran superior to warfarin*	High
	Major bleeding	RR 0.93 (95% CI, 0.81 to 1.07)* *Dabigatran superior to warfarin*	High
	Minor bleeding	RR 0.91 (95% CI, 0.85 to 0.97)* *Dabigatran superior to warfarin*	Moderate
	Intracranial bleeding	RR 0.40 (95% CI, 0.27 to 0.60)* *Dabigatran superior to warfarin*	High
	Death from vascular causes	RR 0.85 (95% CI, 0.72 to 0.99) *Dabigatran superior to warfarin*	Moderate
	Hospitalizations	RR 0.97 (95% CI, 0.92 to 1.03)* *No difference between treatments*	Moderate
	Adverse events (dyspepsia)	Dabigatran: 11.3% Warfarin: 5.8% P<0.001 *Dyspepsia more common with dabigatran*	Moderate
Dabigatran 110 mg Vs. Warfarin	Stroke or systemic embolism	RR 0.91 (95% CI, 0.74 to 1.11)* *No difference between treatments*	Moderate
	Ischemic or uncertain stroke	RR 1.11 (95% CI, 0.89 to 1.40)* *No difference between treatments*	High
	Hemorrhagic stroke	RR 0.31 (95% CI, 0.17 to 0.56)* *Dabigatran superior to warfarin*	High

	Major bleeding	RR 0.80 (95% CI, 0.69 to 0.93)* *Dabigatran superior to warfarin*	High
	Minor bleeding	RR 0.79 (95% CI, 0.74 to 0.84) *Dabigatran superior to warfarin*	Moderate
	Intracranial bleeding	RR 0.31 (95% CI, 0.20 to 0.47)* *Dabigatran superior to warfarin*	High
	Death from vascular causes	RR 0.90 (95% CI, 0.77 to 1.06) *No difference between treatments*	Moderate
	Hospitalizations	RR 0.92 (95% CI, 0.87 to 0.97)* *Dabigatran reduced risk of hospitalizations*	High
	Adverse events (dyspepsia)	Dabigatran: 11.8% Warfarin: 5.8% P<0.001 *Dyspepsia more common with dabigatran*	Moderate
Factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) Vs. Warfarin	Stroke or systemic embolism	HR 0.92 (95% CI, 0.71 to 1.17) *No difference between treatments*	Moderate There was high strength of evidence demonstrating superiority of apixaban to warfarin when analyzed separately
	Ischemic or uncertain stroke	HR 1.06 (95% CI, 0.77 to 1.46) *No difference between treatments*	Moderate to high
	Hemorrhagic stroke	HR 0.48 (95% CI, 0.32 to 0.72) *Factor Xa superior to warfarin*	Low to high
	Systemic embolism	HR 0.87 (95% CI, 0.44 to 1.75) *No difference between treatments*	Moderate for apixaban Moderate for rivaroxaban Moderate for edoxaban
	Major bleeding	HR 0.72 (95% CI, 0.43 to 1.22) *No difference between treatments*	Low to high Apixaban superior to warfarin and rivaroxaban inferior to warfarin*
	Intracranial bleeding	HR 0.45 (95% CI, 0.28 to 0.75) *Factor Xa superior to warfarin*	Moderate to high
	Gastrointestinal bleeding	HR 0.94 (95% CI, 0.78 to 1.12) *No difference between groups*	Low rivaroxaban inferior to warfarin*
	All-cause mortality	HR 0.90 (95% CI, 0.86 to 0.94) *Factor Xa superior to warfarin*	Low to moderate
	Death from CV causes	HR 0.87 (95% CI, 0.84 to 0.90)	Moderate

		Factor Xa superior to warfarin	
	MI	HR 0.96 (95% CI, 0.73 to 1.25) *No difference between treatments*	Moderate to high
	Adverse events	*No difference between treatments*	Moderate for apixaban
	Medication adherence	*Better adherence with rivaroxaban*	Moderate for rivaroxaban
Factor Xa Vs. Dabigatran	Major bleeding	HR 0.91 (95% CI, 0.66 to 1.24) *No difference between treatments*	Apixaban and rivaroxaban superior to dabigatran* Apixaban superior to rivaroxaban*
	Gastrointestinal bleeding	HR 0.84 (95% CI, 0.47 to 1.49) *No difference between treatments*	
Apixaban Vs. Aspirin	Stroke or systemic embolism	HR 0.45 (95% CI, 0.32 to 0.62) *Apixaban superior to aspirin*	Moderate
	Ischemic	HR 0.37 (95% CI, 0.25 to 0.55) *Apixaban superior to aspirin*	Moderate
	Hemorrhagic stroke	HR 0.67 (95% CI, 0.24 to 1.88) *No difference between treatments*	Moderate
	Major bleeding	HR 1.13 (95% CI, 0.74 to 1.75) *No difference between treatments*	Moderate
	Minor bleeding	HR 1.20 (95% CI, 1.00 to 1.53) *Apixaban increased risk*	Moderate
	Death from vascular causes	HR 0.87 (95% CI, 0.66 to 1.17) *No difference between treatments*	Moderate
	Myocardial infarction	HR 0.86 (95% CI, 0.50 to 1.48) *No difference between treatments*	Moderate
	Hospitalizations	HR 0.79 (95% CI, 0.69 to 0.91) *Apixaban reduced risk*	Moderate
	Adverse events	*No difference between treatments*	Moderate

Key: * observational and RCT data combined ł No absolute risk reductions were reported
Abbreviations: CI – confidence interval; CV – cardiovascular; HR – hazard ratio; MI – myocardial infarction; RR – relative risk

Cochrane – Factor Xa Inhibitors versus Vitamin K Antagonists for Preventing Cerebral or Systemic Embolism in Patients with Atrial Fibrillation

Factor Xa inhibitors were directly compared to warfarin for cerebral or systemic embolism prevention in patients with AF in a 2018 Cochrane review.[6] Thirteen randomized controlled trials lasting more than 4 weeks were eligible for inclusion. Warfarin was compared to apixaban, betrixaban, darexaban (discontinued), edoxaban, and rivaroxaban. Follow-up ranged from 12 weeks to 2.8 years. Risk of bias was generally low for all domains except for blinding. Six trials were double-blinded, six were single-blinded studies and one open-label study was included.[6] The primary endpoint was the composite of all strokes (ischemic and hemorrhagic) and systemic embolic events.

Results are presented in **Table 4**. Factor Xa inhibitors were superior to warfarin for all outcomes studied including; stroke and other systemic embolism, all strokes, major bleeding, intracranial hemorrhage, and all-cause death.[6] Additional considerations are that the actual differences between warfarin and factor Xa inhibitors are small and unlikely to be clinically significant for the primary endpoint, all strokes and all-cause death; however, major bleeding is lower with Factor Xa inhibitors. Additionally, NNT values are high for individual study results for edoxaban, apixaban and rivaroxaban for the outcome of overall reduction in stroke and systemic embolism. Findings for major bleeds were associated with high heterogeneity and therefore conclusions are less robust.

Table 4. Factor Xa and Warfarin Comparisons for Cerebral and Systemic Embolism Prevention in Patients with AF*[6]

Outcome	Results (number per 1000 patients)†	Strength of Evidence/Notes	Conclusion
Stroke and other systemic embolism	Warfarin: 34 per 1000 Factor Xa inhibitors: 32 per 1000 OR 0.89; 95% CI, 0.82 to 0.97	High	Factor Xa inhibitors superior to warfarin - actual difference per 1000 patients treated is small
All strokes	Warfarin: 30 per 1000 Factor Xa inhibitors: 28 per 1000 OR 0.89; 95% CI, 0.81 to 0.97	High	Factor Xa inhibitors superior to warfarin - actual difference per 1000 patients treated is small
Major bleeding	Warfarin: 51 per 1000 Factor Xa inhibitors: 41 per 1000 OR 0.73; 95% CI, 0.73 to 0.84	Moderate	Factor Xa inhibitors superior to warfarin
Intracranial hemorrhage	Warfarin: 13 per 1000 Factor Xa inhibitors: 7 per 1000 OR 0.50; 95% CI, 0.42 to 0.59	High	Factor Xa inhibitors superior to warfarin
All-cause death	Warfarin: 67 per 1000 Factor Xa inhibitors: 66 per 1000 OR 0.89; 95% CI, 0.83 to 0.95	Moderate	Factor Xa inhibitors superior to warfarin – actual difference per 1000 patients treated is small
Key: * Majority of data from apixaban, edoxaban, and rivaroxaban studies, † based on assumed risk (median control group risk across studies) for warfarin and corresponding risk (relative effect) for factor Xa inhibitors Abbreviations: CI = confidence interval; OR = odds ratio;			

Cochrane – Direct Oral Anticoagulants versus Warfarin for Preventing Stroke and Systemic Embolic Events Among Atrial Fibrillation Patients with Chronic Kidney Disease

Cochrane reviewed the evidence for the use of DOACs compared to warfarin in patients with chronic kidney disease (CKD) with AF.[5] Anticoagulants included in the review are: apixaban (2.5 mg or 5 mg – dose adjusted based on SrCr), dabigatran (110 mg or 150 mg), edoxaban (30 mg), rivaroxaban (10 mg or 15 mg) and warfarin. Patients with AF were defined as having CKD by a creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) between 15 and 60 mL/min (considered stage G3 or G4 CKD stage). Most of the participants had G3 CKD. Five studies lasting 1.8 to 2.8 years were included in the review. All studies had an unclear risk of bias and a high risk of bias for publication bias.

There is moderate evidence that DOACs decreased the risk of stroke and systemic embolism in patients with CKD to a similar extent as warfarin, 6 less per 1000 patients (RR 0.81; 95% CI, 0.65 to 1.00).[5] Gastrointestinal bleeding was found to be higher with DOACs compared to warfarin with an incidence of 24 per 1000 compared to 17 per 1000 patients (RR 1.40; 95% CI, 0.97 to 2.01) (moderate evidence).[5] There was moderate evidence that warfarin was associated with more risk of intracranial hemorrhage compared to DOACs, 14 versus 6 per 1,000 patients (RR 0.43; 95% CI, 0.27 to 0.69).[5] All-cause mortality was not different between warfarin and DOACs based on moderate evidence (RR 0.91; 95% CI, 0.78 to 1.05).[5]

Limitations to the evidence include the small number of patients with G4 CKD, limiting applicability to this population. In conclusion, the efficacy and safety of DOACs was similar to warfarin in prevention of stroke and systemic embolism in patients with AF who also have CKD.

Cancer

Cochrane – Oral anticoagulation in People with Cancer who Have no Therapeutic or Prophylactic Indication for Anticoagulation

The efficacy and safety of using anticoagulants in ambulatory patients with cancer and otherwise no indication for anticoagulation use was evaluated in a 2017 Cochrane review.[15] Vitamin K antagonists and DOACs were included in the review. Patients eligible for the review were undergoing systemic anticancer therapy and were initiated on anticoagulation within 4 weeks of starting chemotherapy. Anticoagulation was continued during chemotherapy and up to 3 weeks after treatment had ceased. Seven placebo-controlled or no intervention trials were included in the review; 6 warfarin trials and 1 apixaban trial. The risk of bias was low for all domains except for allocation concealment, which was unclear. Primary outcomes of interest were mortality, VTE, symptomatic DVT, PE and bleeding risk.

For the outcome of mortality at 12 months, no clinically meaningful differences were found in the deaths in patients receiving warfarin and those receiving no treatment (RR 0.95; 95% CI, 0.87 to 1.03).[15] There was an increased risk of major and minor bleeding in patients receiving warfarin compared to no prophylaxis, 107 major bleeding events per 1000 patients and 167 minor bleeding events per 1000 patients treated with warfarin ($p<0.05$ for both), respectively (moderate evidence).[15] For the one trial that evaluated apixaban, all outcomes were found to have low strength of evidence and therefore no conclusions of efficacy over no treatment could be made.

Limitations to the evidence include only a small number of trials of short duration. Overall, there was no benefit of warfarin in patients with cancer with no therapeutic or prophylactic indication and anticoagulation was associated with more minor and major bleeding. There was insufficient evidence to make conclusions for the effect of apixaban.

Cochrane – Anticoagulation for the Initial Treatment of Venous Thromboembolism in People with Cancer

A 2018 Cochrane review evaluated the efficacy and safety of anticoagulation therapy in patients with cancer who develop VTE.[2] Therapies included in the review were fixed dosed LMWH, UFH, and fondaparinux. Fifteen studies were included in the review; 13 studies compared LMWH to UFH, one compared fondaparinux to heparin and one compared dalteparin to tinzaparin. Initial parenteral anticoagulation was followed by oral anticoagulation for 3 months in all but one study. Patients were treated as inpatients and outpatients.

The is moderate evidence that after 3 months the use of LMWH, for initial anticoagulation, was associated fewer deaths compared to UFH (57 vs. 168 per 1000 patients 168 deaths per 1000 patients (RR 0.66; 95% CI, 0.40 to 1.10).[2] Recurrent VTE was less frequent with LMWH compared to UFH, 30 vs. 96 per 1000 (RR 0.69; 95% CI, 0.27 to 1.76).[2] Heparin was associated with a mortality benefit over fonadaparinux for initial treatment of VTE in patients with cancer with a RR of 1.25 (95% CI, 0.86 to 1.81).[2] Eight fewer patients taking fondaparinux developed recurrent VTE compared to heparin in which 117 patients per 1000 developed recurrent VTE (moderate evidence). Major bleeding was more common with fondaparinux (RR 0.82; 95% CI, 0.40 to 1.66) compared to more minor bleeding with heparin (RR 1.53; 95% CI, 0.88 to 2.66).[2] Comparison of tinzaparin to dalteparin as initial treatment found no statistically significant differences between groups for relevant efficacy and safety outcomes.

Limitations to the evidence include a high risk of performance bias and publication bias. Direct comparisons to DOACs as initial therapy would also inform decisions on optimal initial therapy in patients with VTE and cancer.

Cochrane – Parenteral Anticoagulation in Ambulatory Patients with Cancer

Ambulatory patients with cancer with no other indication for parenteral anticoagulation beyond cancer treatment were the focus of a 2019 Cochrane review.[16] Nineteen trials were included, all trials evaluated LMWH except one which used unfractionated heparin. Patients who were being treated with chemotherapy, hormonal therapy, immunotherapy, or radiotherapy for a cancer diagnosis were included. All cancer types were eligible for inclusion, most commonly pancreatic cancer, small cell lung cancer, non-small cell lung cancer.[16] The overall risk of bias was low for most studies.

Results at 12 months found no difference in mortality rates between heparin and no therapy, 494 versus 504 per 1000 patients treated (RR 0.98; 95% CI, 0.93 to 1.03), with similar results at 24 months (RR 0.99; 95% CI, 0.96 to 1.01) (moderate evidence).[16] The risk of symptomatic VTE was 38 per 1000 patients given heparin prophylaxis compared to 68 per 1000 in patients not treated with prophylaxis based on high strength of evidence (RR 0.56; 95% CI, 0.47 to 0.68).[16] Major and minor bleeding were higher in patients receiving heparin compared to no prophylaxis based on moderate and high evidence, respectively. There was moderate evidence that patients treated with heparin had a lower risk of thrombocytopenia compared to no prophylaxis; however, results were associated with a high degree of heterogeneity and results were not statistically significant (RR 0.69; 95% CI, 0.37 to 1.27; I^2 = 83%).[16] Quality of life was not different between groups.

Additional evidence directly comparing anticoagulants for prophylaxis in patients with cancer would be helpful. In summary prophylaxis with heparins have to no effect on mortality but reduced the incidence of symptomatic VTE, with an increase in minor and major bleeding, in patients with cancer.

Cochrane – Anticoagulation for Perioperative Thromboprophylaxis in People with Cancer

A 2018 Cochrane review researched the role of anticoagulants (LMWH, UFH, or fondaparinux) for the prevention of mortality, DVT, PE, bleeding and thrombocytopenia in people with cancer undergoing a surgical intervention.[17] Twenty trials were included in the analysis. Trials were at low risk of bias except for the domain of allocation concealment. There was moderate evidence of no difference between LMWH and UFH for outcomes listed in **Table 5.** Comparisons between LMWH and fondaparinux also found no difference between therapies for efficacy and safety outcomes, based on low certainty of evidence. Limitations to the review include the potential for insufficient power to detect a difference between drugs.

Table 5. LMWH Compared to UFH in Patients with Cancer Undergoing Surgery[17]

Outcome*	Results (number per 1000 patients)†	Strength of Evidence/Notes	Conclusion
Mortality	UFH: 51 per 1000 LMWH: 42 per 1000 RR 0.82; 95% CI, 0.63 to 1.07	Moderate	No difference between therapies
Any PE	UFH: 6 per 1000 LMWH: 3 per 1000 RR 0.49; 95% CI, 0.17 to 1.47	Moderate	No difference between therapies
Symptomatic DVT	UFH: 10 per 1000 LMWH: 7 per 1000 RR 0.67; 95% CI, 0.27 to 1.69	Moderate	No difference between therapies
Major bleeding	UFH: 31 per 1000 LMWH: 31 per 1000 RR 1.01; 95% CI, 0.69 to 1.48	Moderate	No difference between therapies
Minor bleeding	UFH: 142 per 1000 LMWH: 143 per 1000 RR 1.01; 95% CI, 0.76 to 1.33	Moderate	No difference between therapies
Wound hematoma	UFH: 86 per 1000 LMWH: 60 per 1000 RR 0.70; 95% CI, 0.54 to 0.92	Moderate	LMWH superior to UFH
Reoperation for bleeding	UFH: 51 per 1000 LMWH: 47 per 1000 RR 0.93; 95% CI, 0.57 to 1.50	Moderate	No difference between therapies
Intraoperative blood loss	MD 6.75 lower in LMWH group	Moderate	No difference between therapies
Postoperative drain volume	MD 30.18 higher with LMWH	Moderate	No difference between therapies
Thrombocytopenia	UFH: 3 per 1000 LMWH: 6 per 1000 RR 3.07; 95% CI, 0.32 to 29.33	Moderate	No difference between therapies

Abbreviations: * Follow-up 1 week to 3 months
Key: CI = confidence interval; DVT = deep-vein thrombosis; LMWH = low-molecular weight heparin; MD = mean difference; PE = pulmonary embolism; RR = relative risk; UFH = unfractionated heparin

Cochrane – Anticoagulation for People with Cancer and Central Venous Catheters

The efficacy and harms of using anticoagulants in people with cancer and central venous catheters (CVC) was reviewed in a 2019 Cochrane report.[18] Anticoagulants in the review included: VKAs, LMWH, UFH and fondaparinux. Seven trials evaluated LMWH compared to no LMWH, six trials compared VKA to no VKA and three trials evaluated LMWH to VKA. Risk for attrition and performance bias was high in all studies. Allocation concealment and reporting bias were unclear for most of the studies.

Moderate evidence found a reduction in the risk of symptomatic catheter-related VTE at 3 months in patients treated with LMWH compared to no treatment, 38 fewer VTE events per 1000 patients (RR 0.43; 95% CI, 0.22 to 0.81).[18] There was only low quality evidence available for mortality and bleeding comparisons. There was no quality evidence to inform benefits or harms of VKA versus no VKA. Comparisons between LMWH and VKA in adults found no conclusive benefits or risks between therapies when used for patients with CVC.

Most of the evidence for this review was considered low or very-low quality, preventing an accurate assessment of comparative efficacy and safety between therapies and use of no therapy. Overall, there seems to be a benefit of using LMWH in preventing catheter-related VTE in patients with cancer, however; risks of bleeding should be weighed against benefit of anticoagulation.

Cochrane – Prolonged Thromboprophylaxis with Low Molecular Weight Heparin for Abdominal or Pelvic Surgery

A 2019 review evaluated LMWH for extended prophylaxis (at least 14 days) compared to LMWH administration during the inpatient period only, after abdominal or pelvic surgery for the outcome of VTE prevention.[19] Seven trials were included in the analysis all comparing LMWH to placebo for prolonged prophylaxis.

There was moderate quality of evidence that all VTE was reduced with prolonged LMWH compared inpatient hospital treatment only, 5.3% versus 13.2% (OR 0.38; 95% CI, 0.26 to 0.54).[19] The incidence of DVT was reduced with prolonged anticoagulation with LMWH compared to no prolonged anticoagulation with an OR of 0.39 (95% CI, 0.27 to 0.55) (moderate evidence).[19] Proximal DVT and symptomatic VTE rates were also decreased with prolonged LMWH use compared to inpatient treatment alone. Symptomatic VTE, which is the most clinically relevant outcome, was found to be decreased by 7 fewer events per 1000 patients in those individuals treated with prolonged LMWH compared to inpatient therapy (OR 0.30; 95% CI, 0.08 to 1.11).[19] Bleeding rates were not statistically or clinically different between prolonged LMWH prophylaxis compared to none, 3.4% versus 2.8% based on moderate quality of evidence. Moderate quality evidence found no difference in mortality rates between in hospital treatment compared to prolonged treatment, 38 and 43 per 1000 patients, respectively.[19]

Limitations include unclear and high risk of bias in many domains and small, short term trials available for data analysis. Evidence suggest prolonged prophylaxis with LMWH is more effective than in-patient only anticoagulation.

After review, thirty systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

Venous Thromboembolism

NICE – Venous Thromboembolism – Reducing the Risk of Hospital-Acquired Deep Vein Thrombosis or Pulmonary Embolism

A 2018 review by NICE outlined preventative recommendations for VTE and DVT prevention in patients 16 years old and older who are admitted to the hospital.[20] For adults under 18 who require pharmacological VTE prophylaxis, the recommendation is to use apixaban, aspirin, dabigatran, fondaparinux, LMWH or rivaroxaban. Patients whose risk of VTE outweighs their risk of bleeding who take antiplatelet therapies for other conditions should be considered for VTE prophylaxis. Mechanical prophylaxis can be considered if the risk of bleeding outweighs the risk of VTE.

The following patients should be considered for VTE prophylaxis if their risk of VTE outweighs the risk of bleeding:[20]

- Patients who are interrupting anticoagulation therapy and are at increased risk of VTE
- LMWH should be offered first-line for a minimum of seven days to acutely ill medical patients
- Patients with cancer who are receiving cancer modifying treatments should not routinely receive anticoagulation unless they have another indication
- Patients with myeloma who are receiving chemotherapy with thalidomide, pomalidomide or lenalidomide with steroids are candidates for aspirin or LMWH
- Patients with pancreatic cancer who are receiving chemotherapy should get LMWH
- LMWH is recommended first line for patients receiving palliative care (that are not in their last days of life). Fondaparinux is the preferred second-line therapy
- Patients who are admitted into the critical care unit should receive LMWH unless contraindicated
- LMWH is recommended first-line and fondaparinux is recommended second-line for patients admitted to an acute psychiatric ward
- Patients subject to lower limb immobilization, due to orthopedic surgery, are candidate for LMWH or fondaparinux. Consider stopping at day 42 if immobilization continues.
- A month of VTE prophylaxis should be considered in patients with fragility fractures of the pelvis, hip or proximal femur
    - LMWH initiated 6-12 hours post-surgery
    - Fondaparinux initiated 6 hours after surgery if patient is at low risk of bleeding
- Pre-operative VTE prophylaxis should be considered for patients with fragility fractures of the pelvis, hip or proximal femur who has surgery delayed one day beyond the day of admission. LMWH should be discontinued at least 12 hours before surgery and fondaparinux should be stopped at least 24 hours before surgery
- Patients undergoing elective hip replacement surgery should receive VTE prophylaxis:
    - LMWH for 10 days followed by aspirin (75 or 150 mg) for an additional 28 days
    - LMWH for 28 days combined with anti-embolism stockings (until discharge)
    - Rivaroxaban can also be considered an option (evidence of a small efficacy benefit for total DVT of rivaroxaban over the other DOACs when compared to LMWH)
    - Apixaban and dabigatran may be an option if contradictions to the options above
- Options for patients undergoing elective knee replacement include: (any of the following are recommended in no specific order)
    - Aspirin (75 or 150 mg) for 14 days
    - LMWH for 14 days with anti-embolism stockings (until discharge)
    - Rivaroxaban

- Apixaban and dabigatran may be an option if contradictions to the options above

Additional Guidelines for Clinical Context:

ACC/AHA/HRS Guideline on Management of Patients with Atrial Fibrillation

The 2014 American College of Cardiology (ACC), American Heart Association (AHA) and Heart Rhythm Society (HRS) guidelines on management of patients with atrial fibrillation were updated in 2019.[13] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, and the associations themselves funded partially by industry the guideline will not be reviewed in detail or relied upon for policy making decisions.

AHS Guideline for the Management of Venous Thromboembolism Prophylaxis

In 2018 the American Society of Hematology (ASH) provided guideline recommendations for the prophylaxis of VTE in hospitalized and nonhospitalized patients.[21] Many guideline panel members have conflicts of interest with industry and the AHS is heavily funded by pharmaceutical companies. For these reasons the guidelines will not be discussed in detail or relied upon for making policy decisions.

CHEST – Antithrombotic Therapy for Atrial Fibrillation

The 2018 guidelines for the management of patients with atrial fibrillation was published by the American College of Chest Physicians.[12] The chair of the guidelines has multiple ties with industry and only three of the twelve panel members were free from conflicts of interest. Additionally, CHEST obtains industry support which could bias clinical recommendations. Therefore, guideline recommendations will not be presented or relied on for policy decisions.

After review, four guidelines were excluded due to poor quality (e.g., lack of details on methodology, authors with extensive conflicts of interest with industry).[22–25]

New Formulations or Indications:

Indications:

Rivaroxaban (Xarelto®): The FDA approved expanding the indication for rivaroxaban to include the use for reduction in risk of major cardiovascular events (CV death, MI and stroke) when used in combination with aspirin for patients with chronic CAD or PAD (**Table 7**). [9,26]

Rivaroxaban (Xarelto®): In October 2019, rivaroxaban was approved for the prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding.[9] Approval was based on a 2013 study which demonstrated a reduction at day 35 in the composite primary endpoint (asymptomatic proximal DVT in lower extremity, symptomatic proximal or distal DVT in the lower extremity, symptomatic non-fatal PE and death related to VTE) with rivaroxaban 10 mg daily for 35 ± 4 days compared with enoxaparin 40 mg once daily for 10 ± 4 days (followed by placebo), 4.4% versus 5.7% (RR 0.77; 95% CI, 0.62 to 0.96).[9] As with other indications, the dose of rivaroxaban should be decreased in patients with reduced creatinine clearance (less than 30 mL/min) and discontinuation of therapy should be considered in patients who develop acute renal failure.[9]

Dalteparin (Fragmin®): Dalteparin received approval for the treatment of symptomatic VTE to reduce the recurrence in pediatric patients 1 month of age and older.[27]

New FDA Safety Alerts:

Table 6. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Betrixaban[28]	Bevyxxa®	1/2019	Warnings	Reduce the dose for patients on p-glycoprotein inhibitors and avoid concomitant use with p-glycoprotein inducers. Avoid use in patients with moderate or severe hepatic impairment. Store between 59 and 86 degrees Fahrenheit.
Enoxaparin[29]	Lovenox	10/2017	Contraindications	History of immune-mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies
Rivaroxaban[9]	Xarelto®	10/2018	Warnings and Precautions	Increased risk of thrombosis in patients with antiphospholipid syndrome: use is not recommended

Randomized Controlled Trials:

A total of 236 citations were manually reviewed from the initial literature search. After further review, 228 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 8 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 7. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Anderson, et al[30] MC, DB, RCT, Phase 3	Rivaroxaban 10 mg Vs. Aspirin 81 mg All patients received initial rivaroxaban 10 mg till postoperative day 5 Patients were followed for 90 days	Patients undergoing hip or knee arthroplasty N= 3424	Occurrence of symptomatic venous thromboembolism	Rivaroxaban: 12 (0.70%) Aspirin: 11 (0.64%) MD 0.06%; 95% CI, -0.55 to 0.66 P<0.001 for noninferiority and P=0.84 for superiority *Rivaroxaban and aspirin demonstrated similar efficacy*
Calkins, et al[31]	Dabigatran 150 mg twice daily Vs.	Patients scheduled for a catheter ablation	Incidence of major bleeding during and up to 8 weeks after ablation	Dabigatran: 5 (1.6%) Warfarin: 22 (6.9%) MD -5.3%; 95% CI, -8.4 to -2.2

RCT, OL, MC, Phase 4	Warfarin (INR target 2.0 - 3.0) Treatment duration: 12-16 weeks	of paroxysmal or persistent atrial fibrillation N = 704		P<0.001 *Dabigatran was associated with less bleeding compared to warfarin*
Diener, et al[32] MC, DB, RCT, Phase 3	Dabigatran 150 mg or 110 mg twice daily Vs. Aspirin 100 mg daily Median follow-up: 19 months	Patients who had embolic stroke of undetermined source N=5390	Recurrent stroke	Dabigatran: 177 (6.6%) Aspirin: 207 (7.7%) HR 0.85; 95% CI, 0.69 to 1.03 P=0.10 *There was no difference in efficacy between dabigatran and aspirin in stroke prevention*
Eikelboom, et al[26] (COMPASS) MC, DB, DD, RCT, Phase 3	Rivaroxaban 2.5 mg twice daily + aspirin 100 mg daily Vs. Rivaroxaban 5 mg twice daily + placebo Vs. Aspirin 100 mg daily + placebo Mean follow-up: 23 months	Patients with stable vascular disease N=27,395	Composite of cardiovascular death, myocardial infarction or stroke	Rivaroxaban 2.5 mg + aspirin: 4.1% Rivaroxaban 5 mg + placebo: 4.9% Aspirin + placebo: 5.4% Rivaroxaban 2.5 mg + aspirin vs. aspirin: HR 0.76 (95% CI, 0.66 to 0.86) P < 0.001 *Rivaroxaban 2.5 mg + aspirin superior to aspirin alone* Rivaroxaban 5.0 mg vs. aspirin: HR 0.90 (95% CI, 0.79 to 1.03) P = 0.12 *Rivaroxaban 5.0 mg not superior to aspirin alone*
Goette, et al [33] (ENSURE-AF) MC, OL, RCT, Phase 3	Edoxaban 60 mg daily Vs. Enoxaparin - warfarin‡ Follow-up: up to 12 months	Patients with stable vascular disease N=2,199	Composite of stroke, systemic embolic event, myocardial infarction and cardiovascular mortality	Edoxaban: 5 (<1%) Enoxaparin - warfarin: 11 (1%) OR 0.46 (95% CI, 0.12 to 1.43) *Edoxaban had similar efficacy to enoxaparin - warfarin*
Hart, et al[34]	Rivaroxaban 15 mg daily + placebo	Patients with recent ischemic	First recurrence of ischemic or hemorrhagic stroke or systemic	Rivaroxaban + placebo: 172 (5.1%) Aspirin + placebo: 160 (4.8%)

MC, DB, DD, RCT, Phase 3	Vs. Aspirin 100 mg daily + placebo Median follow-up: 11 months	stroke that was presumed to be from a cerebral embolism but without arterial stenosis, lacune or an identified cardioembolic sources N=7,213	embolism in a time-to-event analysis	HR 1.07 (95% CI, 0.87 to 1.33) P = 0.52 *Rivaroxaban was not superior to aspirin and associated with more bleeding (trial was terminated early)*
Lopes, et al[35] RCT, Phase 4, OL* and DB†	Apixaban Vs. Vitamin K antagonist And Aspirin Vs. Placebo Treatment duration: 6 months	Patients with AF and an acute coronary syndrome or undergone PCI and were planning on taking a P2Y12 inhibitor N= 4,614	Major of clinically relevant nonmajor bleeding	Apixaban: 10.5% Vitamin K antagonist: 14.7% HR 0.69; 95% CI, 0.58 to 0.81 P<0.001 *Apixaban caused less bleeding than vitamin K antagonists* Aspirin: 16.1% Placebo: 9.0% HR 1.89; 95% CI, 1.59 to 2.24 P<0.001 *Aspirin was associated with more bleeding than placebo*
Weitz, et al[36] (EINSTEIN CHOICE) MC, DB, RCT, Phase 3	Rivaroxaban 10 mg daily Vs. Rivaroxaban 20 mg daily Vs. Aspirin 100 mg daily Mean follow-up: approximately 1 year	Patients with VTE and previous 6-12 months of anticoagulation therapy who were equipoise regarding the need for continued anticoagulation N=3,396	Symptomatic or recurrent fatal or nonfatal VTE	Rivaroxaban 20 mg: 17 (1.5%) Rivaroxaban 10 mg: 13 (1.2%) Aspirin: 50 (4.4%) Rivaroxaban 20 mg vs. Aspirin HR 0.34 (95% CI, 0.20 to 0.59) P<0.001 *Rivaroxaban 20 mg was more effective than aspirin* Rivaroxaban 10 mg vs. Aspirin HR 0.26 (95% CI, 0.14 to 0.47) P<0.001 *Rivaroxaban 10 mg was more effective than aspirin*

Key: * Apixaban versus warfarin was open-label † Aspirin versus placebo was double-blind (patients received 2 or 3 active treatments dependent upon randomization) ‡ Patients in enoxaparin – warfarin group were started on both and stayed only on warfarin once INR was ≥2
Abbreviations: AF = atrial fibrillation; CAD = coronary artery disease; DB = double-blind; DD = double-dummy; HR = hazard ratio; INR = international normalized ratio; MC = multi-center; OL = open-label; RCT = randomized clinical trial; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; VTE = venous thromboembolism

References:

1. Balk EM, Ellis AG, Di M, et al. Venous thromboembolism prophylaxis in major orthopedic surgery: systematic review update. Comparative Effectiveness Review No. 191. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2015-00002-I.) AHRQ Publication No. 17-EHC021-EF. Rockville MD: Agency for Heatlhcare and Research. June 2017.
2. Anticoagulation for the initial treatment of venous thromboembolism in people with cancer - Hakoum, MB - 2018 | Cochrane Library. https://www-cochranelibrary-com.liboff.ohsu.edu/cdsr/doi/10.1002/14651858.CD006649.pub7/full?highlightAbstract=venous%7Cthromboembol%7Cthromboembolism. Accessed September 3, 2019.
3. Vitamin K antagonists versus low-molecular-weight heparin for the long term treatment of symptomatic venous thromboembolism - Andras, A - 2017 | Cochrane Library. https://www-cochranelibrary-com.liboff.ohsu.edu/cdsr/doi/10.1002/14651858.CD002001.pub3/full?highlightAbstract=venous%7Cthromboembol%7Cthromboembolism. Accessed September 3, 2019.
4. Sanders G, Borre E, Chatterjee R. Stroke prevention in patietns with atrial fibrillation: A systematic review update. Comparative Effectiveness Review No. 214.(Prepared by the Duke Comparative Evidence-based Practice Center under Contract No. 290-2015-00004-I for AHRQ and PCORI). AHRQ Publication No. 18 (19)-EHC018-EF. PCORI Publication No. 2018-SR-04. Rockville, MD: Agency for Healthcare Research and Quality; October 2018. Avialable at: https://doi.org/10.23970/AHRQEPCCER214. Accessed August 30, 2019.
5. Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. *Cochrane Database of Systematic Reviews*. 2017;(11). doi:10.1002/14651858.CD011373.pub2
6. Slot KMB, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. *Cochrane Database of Systematic Reviews*. 2018;(3). doi:10.1002/14651858.CD008980.pub3
7. Centers for Disease Control. Venous thromboembolism data and statistics. Available at: https://www.cdc.gov/ncbddd/dvt/data.html. Accessed September 25, 2019.
8. Ovbiaglel B, Nguyen-Huynh M. Stroke Epidemiology: Advancing Our Understanding of Disease Mechanism and Therapy. Neurotherapeutics. 2011;8; 319-329.
9. Xarelto Prescribing Information. Janssen Pharmaceuticals, Inc. Tutusville NJ; 2011.
10. Carson S, Selph S, Thakurta S. New Oral Anticogulant Drugs. *Drug Effectiveness Review Project Paciric Northwest Evidence-based Practice Center*. 2013.
11. Kearon C, Akl E, Ornelas J, et al. Antithrombotic therapy for VTE disease. CHEST guideline and expert panel report. CHEST. 2016; 149:315-352.
12. Lip G, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation. CHEST guideline and expert panel report. Chest. 2018;154:1121-1201.
13. January C, Wann S, Calkins H, et al. 2019 AHA/ACC/HRS Focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation. 2019;140:e125-e151.

Author: Sentena

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14. Zee AA, Lieshout K van, Heide M van der, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. *Cochrane Database of Systematic Reviews*. 2017;(8). doi:10.1002/14651858.CD006681.pub4
15. Kahale LA, Hakoum MB, Tsolakian IG, et al. Oral anticoagulation in people with cancer who have no therapeutic or prophylactic indication for anticoagulation. *Cochrane Database of Systematic Reviews*. 2017;(12). doi:10.1002/14651858.CD006466.pub6
16. Akl EA, Kahale LA, Hakoum MB, et al. Parenteral anticoagulation in ambulatory patients with cancer. *Cochrane Database of Systematic Reviews*. 2017;(9). doi:10.1002/14651858.CD006652.pub5
17. Matar CF, Hakoum MB, Tsolakian IG, et al. Anticoagulation for perioperative thromboprophylaxis in people with cancer. Cochrane Datatbase of Systematic Reviews. 2018, Issue 7. Art.No.: CD009447.
18. Kahale LA, Tsolakian IG, Hakoum MB, et al. Anticoagulation for people with cancer and central venous catheters. *Cochrane Database of Systematic Reviews*. 2018;(6). doi:10.1002/14651858.CD006468.pub6
19. Felder S, Rasmussen MS, King R, et al. Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery. *Cochrane Database of Systematic Reviews*. 2019;(8). doi:10.1002/14651858.CD004318.pub5
20. National Institute for Health and Care Excellence. Venous thromboembolism in over 16s: reducing the risk of hospital-aquired deep vein thrombosis or pulmonary embolism. NICE Guideline. Published: 21 March 2018. Available at: www.nice.org.uk/guidance/ng89. Accessed September 6, 2019.
21. H Schunemann, Cushman M, Burnett A et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. The American Society of Hematology. 2018. Available at: http://www.bloodadvances.org/content/bloodoa/2/22/3257.full.pdf. Accessed Septeber 10, 2019.
22. Delluc A, Wang T-F, Yap E-S, et al. Anticoagulation of cancer patients with non-valvular atrial fibrillation receiving chemotherapy: Guidance from the SSC of the ISTH. *J Thromb Haemost*. 2019;17(8):1247-1252. doi:10.1111/jth.14478
23. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. August 2019. doi:10.1093/eurheartj/ehz425
24. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. August 2019. doi:10.1093/eurheartj/ehz486
25. Key NS, Khorana AA, Kuderer NM, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. August 2019:JCO1901461. doi:10.1200/JCO.19.01461
26. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. http://dx.doi.org.liboff.ohsu.edu/10.1056/NEJMoa1709118. doi:10.1056/NEJMoa1709118
27. Fragmin Prescribing Information. Pfizer Inc. New York, NY. 2019.
28. Bevyxxa B. Portola Pharmaceuticals Inc. South San Francisco, California; 2017.
29. Lovenox Prescribing Information. Sanofi-aventis U.S. LLC. Bridgewater, NJ. 2018.
30. Anderson DR, Dunbar M, Murnaghan J, et al. Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty. *New England Journal of Medicine*. 2018;378(8):699-707. doi:10.1056/NEJMoa1712746
31. Calkins H, Willems S, Gerstenfeld EP, et al. Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation. *N Engl J Med*. March 2017. doi:10.1056/NEJMoa1701005
32. Diener H-C, Sacco RL, Easton JD, et al. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. *New England Journal of Medicine*. 2019;380(20):1906-1917. doi:10.1056/NEJMoa1813959

Author: Sentena

33. Goette A, Merino JL, Ezekowitz MD, et al. Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *The Lancet*. 2016;388(10055):1995-2003. doi:10.1016/S0140-6736(16)31474-X
34. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. *Journal of Medicine*. 2018;378(23):2191-2201. doi:10.1056/NEJMoa1802686
35. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *New England Journal of Medicine*. 2019;380(16):1509-1524. doi:10.1056/NEJMoa1817083
36. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. *N Engl J Med*. 2017;376(13):1211-1222. doi:10.1056/NEJMoa1700518

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
apixaban	ELIQUIS	TAB DS PK	ORAL	Y
apixaban	ELIQUIS	TABLET	ORAL	Y
dabigatran etexilate mesylate	PRADAXA	CAPSULE	ORAL	Y
dalteparin sodium,porcine	FRAGMIN	SYRINGE	SUB-Q	Y
edoxaban tosylate	SAVAYSA	TABLET	ORAL	Y
enoxaparin sodium	ENOXAPARIN SODIUM	SYRINGE	SUB-Q	Y
enoxaparin sodium	LOVENOX	SYRINGE	SUB-Q	Y
enoxaparin sodium	ENOXAPARIN SODIUM	VIAL	SUB-Q	Y
enoxaparin sodium	LOVENOX	VIAL	SUB-Q	Y
rivaroxaban	XARELTO	TAB DS PK	ORAL	Y
rivaroxaban	XARELTO	TABLET	ORAL	Y
warfarin sodium	COUMADIN	TABLET	ORAL	Y
warfarin sodium	JANTOVEN	TABLET	ORAL	Y
warfarin sodium	WARFARIN SODIUM	TABLET	ORAL	Y
betrixaban maleate	BEVYXXA	CAPSULE	ORAL	N
dalteparin sodium,porcine	FRAGMIN	VIAL	SUB-Q	N
enoxaparin sodium	LOVENOX	AMPUL	SUB-Q	N
fondaparinux sodium	ARIXTRA	SYRINGE	SUB-Q	N
fondaparinux sodium	FONDAPARINUX SODIUM	SYRINGE	SUB-Q	N

Appendix 2: Abstracts of Comparative Clinical Trials

Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty.

Anderson DR, Dunbar M, Murnaghan J, Kahn SR, Gross P, Forsythe M, Pelet S, Fisher W, Belzile E, Dolan S, Crowther M, Bohm E, MacDonald SJ, Gofton W, Kim P, Zukor D, Pleasance S, Andreou P, Doucette S, Theriault C, Abianui A, Carrier M, Kovacs MJ, Rodger MA, Coyle D, Wells PS, Vendittoli PA

BACKGROUND:

Clinical trials and meta-analyses have suggested that aspirin may be effective for the prevention of venous thromboembolism (proximal deep-vein thrombosis or pulmonary embolism) after total hip or total knee arthroplasty, but comparisons with direct oral anticoagulants are lacking for prophylaxis beyond hospital discharge.

METHODS:

We performed a multicenter, double-blind, randomized, controlled trial involving patients who were undergoing total hip or knee arthroplasty. All the patients received once-daily oral rivaroxaban (10 mg) until postoperative day 5 and then were randomly assigned to continue rivaroxaban or switch to aspirin (81 mg daily) for an additional 9 days after total knee arthroplasty or for 30 days after total hip arthroplasty. Patients were followed for 90 days for symptomatic venous thromboembolism (the primary effectiveness outcome) and bleeding complications, including major or clinically relevant nonmajor bleeding (the primary safety outcome).

RESULTS:

A total of 3424 patients (1804 undergoing total hip arthroplasty and 1620 undergoing total knee arthroplasty) were enrolled in the trial. Venous thromboembolism occurred in 11 of 1707 patients (0.64%) in the aspirin group and in 12 of 1717 patients (0.70%) in the rivaroxaban group (difference, 0.06 percentage points; 95% confidence interval [CI], -0.55 to 0.66; P<0.001 for noninferiority and P=0.84 for superiority). Major bleeding complications occurred in 8 patients (0.47%) in the aspirin group and in 5 (0.29%) in the rivaroxaban group (difference, 0.18 percentage points; 95% CI, -0.65 to 0.29; P=0.42). Clinically important bleeding occurred in 22 patients (1.29%) in the aspirin group and in 17 (0.99%) in the rivaroxaban group (difference, 0.30 percentage points; 95% CI, -1.07 to 0.47; P=0.43).

CONCLUSIONS:

Among patients who received 5 days of rivaroxaban prophylaxis after total hip or total knee arthroplasty, extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic venous thromboembolism. (Funded by the Canadian Institutes of Health Research; ClinicalTrials.gov number, NCT01720108 .).

Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation.

Calkins H, Willems S, Gerstenfeld EP, Verma A, Schilling R, Hohnloser SH, Okumura K, Serota H, Nordaby M, Guiver K, Biss B, Brouwer MA, Grimaldi M; RE-CIRCUIT Investigators.

BACKGROUND:

Catheter ablation of atrial fibrillation is typically performed with uninterrupted anticoagulation with warfarin or interrupted non-vitamin K antagonist oral anticoagulant therapy. Uninterrupted anticoagulation with a non-vitamin K antagonist oral anticoagulant, such as dabigatran, may be safer; however, controlled data are lacking. We investigated the safety of uninterrupted dabigatran versus warfarin in patients undergoing ablation of atrial fibrillation.

METHODS:

In this randomized, open-label, multicenter, controlled trial with blinded adjudicated end-point assessments, we randomly assigned patients scheduled for catheter ablation of paroxysmal or persistent atrial fibrillation to receive either dabigatran (150 mg twice daily) or warfarin (target international normalized

ratio, 2.0 to 3.0). Ablation was performed after 4 to 8 weeks of uninterrupted anticoagulation, which was continued during and for 8 weeks after ablation. The primary end point was the incidence of major bleeding events during and up to 8 weeks after ablation; secondary end points included thromboembolic and other bleeding events.

RESULTS:

The trial enrolled 704 patients across 104 sites; 635 patients underwent ablation. Baseline characteristics were balanced between treatment groups. The incidence of major bleeding events during and up to 8 weeks after ablation was lower with dabigatran than with warfarin (5 patients [1.6%] vs. 22 patients [6.9%]; absolute risk difference, -5.3 percentage points; 95% confidence interval, -8.4 to -2.2; P<0.001). Dabigatran was associated with fewer periprocedural pericardial tamponades and groin hematomas than warfarin. The two treatment groups had a similar incidence of minor bleeding events. One thromboembolic event occurred in the warfarin group.

CONCLUSIONS:

In patients undergoing ablation for atrial fibrillation, anticoagulation with uninterrupted dabigatran was associated with fewer bleeding complications than uninterrupted warfarin. (Funded by Boehringer Ingelheim; RE-CIRCUIT ClinicalTrials.gov number, NCT02348723 .).

Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source.

Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, Kreuzer J, Cronin L, Cotton D, Grauer C, Brueckmann M, Chernyatina M, Donnan G, Ferro JM, Grond M, Kallmünzer B, Krupinski J, Lee BC, Lemmens R, Masjuan J, Odinak M, Saver JL, Schellinger PD, Toni D, Toyoda K; RE-SPECT ESUS Steering Committee and Investigators.

BACKGROUND:

Cryptogenic strokes constitute 20 to 30% of ischemic strokes, and most cryptogenic strokes are considered to be embolic and of undetermined source. An earlier randomized trial showed that rivaroxaban is no more effective than aspirin in preventing recurrent stroke after a presumed embolic stroke from an undetermined source. Whether dabigatran would be effective in preventing recurrent strokes after this type of stroke was unclear.

METHODS:

We conducted a multicenter, randomized, double-blind trial of dabigatran at a dose of 150 mg or 110 mg twice daily as compared with aspirin at a dose of 100 mg once daily in patients who had had an embolic stroke of undetermined source. The primary outcome was recurrent stroke. The primary safety outcome was major bleeding.

RESULTS:

A total of 5390 patients were enrolled at 564 sites and were randomly assigned to receive dabigatran (2695 patients) or aspirin (2695 patients). During a median follow-up of 19 months, recurrent strokes occurred in 177 patients (6.6%) in the dabigatran group (4.1% per year) and in 207 patients (7.7%) in the aspirin group (4.8% per year) (hazard ratio, 0.85; 95% confidence interval [CI], 0.69 to 1.03; P = 0.10). Ischemic strokes occurred in 172 patients (4.0% per year) and 203 patients (4.7% per year), respectively (hazard ratio, 0.84; 95% CI, 0.68 to 1.03). Major bleeding occurred in 77 patients (1.7% per year) in the dabigatran group and in 64 patients (1.4% per year) in the aspirin group (hazard ratio, 1.19; 95% CI, 0.85 to 1.66). Clinically relevant nonmajor bleeding occurred in 70 patients (1.6% per year) and 41 patients (0.9% per year), respectively.

CONCLUSIONS:

In patients with a recent history of embolic stroke of undetermined source, dabigatran was not superior to aspirin in preventing recurrent stroke. The incidence of major bleeding was not greater in the dabigatran group than in the aspirin group, but there were more clinically relevant nonmajor bleeding events in the dabigatran group. (Funded by Boehringer Ingelheim; RE-SPECT ESUS ClinicalTrials.gov number, NCT02239120.).

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Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease.

Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Störk S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S; COMPASS Investigators.

BACKGROUND:

We evaluated whether rivaroxaban alone or in combination with aspirin would be more effective than aspirin alone for secondary cardiovascular prevention.

METHODS:

In this double-blind trial, we randomly assigned 27,395 participants with stable atherosclerotic vascular disease to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). The primary outcome was a composite of cardiovascular death, stroke, or myocardial infarction. The study was stopped for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 months.

RESULTS:

The primary outcome occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (379 patients [4.1%] vs. 496 patients [5.4%]; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; P<0.001; z=-4.126), but major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001). There was no significant difference in intracranial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01; threshold P value for significance, 0.0025). The primary outcome did not occur in significantly fewer patients in the rivaroxaban-alone group than in the aspirin-alone group, but major bleeding events occurred in more patients in the rivaroxaban-alone group.

CONCLUSIONS:

Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. (Funded by Bayer; COMPASS ClinicalTrials.gov number, NCT01776424 .).

Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial.

Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR, Lip GY; ENSURE-AF investigators.

BACKGROUND:

Edoxaban, an oral factor Xa inhibitor, is non-inferior for prevention of stroke and systemic embolism in patients with atrial fibrillation and is associated with less bleeding than well controlled warfarin therapy. Few safety data about edoxaban in patients undergoing electrical cardioversion are available.

METHODS:

We did a multicentre, prospective, randomised, open-label, blinded-endpoint evaluation trial in 19 countries with 239 sites comparing edoxaban 60 mg per day with enoxaparin-warfarin in patients undergoing electrical cardioversion of non-valvular atrial fibrillation. The dose of edoxaban was reduced to 30 mg per day if one or more factors (creatinine clearance 15-50 mL/min, low bodyweight [≤60 kg], or concomitant use of P-glycoprotein inhibitors) were present. Block randomisation (block size four)-stratified by cardioversion approach (transoesophageal echocardiography [TEE] or not), anticoagulant experience, selected edoxaban dose, and region-was done through a voice-web system. The primary efficacy endpoint was a composite of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality, analysed by intention to treat. The primary safety endpoint was major and clinically relevant non-major

(CRNM) bleeding in patients who received at least one dose of study drug. Follow-up was 28 days on study drug after cardioversion plus 30 days to assess safety. This trial is registered with ClinicalTrials.gov, number NCT02072434.

FINDINGS:

Between March 25, 2014, and Oct 28, 2015, 2199 patients were enrolled and randomly assigned to receive edoxaban (n=1095) or enoxaparin-warfarin (n=1104). The mean age was 64 years (SD 10·54) and mean CHA_2DS_2-VASc score was 2·6 (SD 1·4). Mean time in therapeutic range on warfarin was 70·8% (SD 27·4). The primary efficacy endpoint occurred in five (<1%) patients in the edoxaban group versus 11 (1%) in the enoxaparin-warfarin group (odds ratio [OR] 0·46, 95% CI 0·12-1·43). The primary safety endpoint occurred in 16 (1%) of 1067 patients given edoxaban versus 11 (1%) of 1082 patients given enoxaparin-warfarin (OR 1·48, 95% CI 0·64-3·55). The results were independent of the TEE-guided strategy and anticoagulation status.

INTERPRETATION:

ENSURE-AF is the largest prospective randomised clinical trial of anticoagulation for cardioversion of patients with non-valvular atrial fibrillation. Rates of major and CRNM bleeding and thromboembolism were low in the two treatment groups.

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source.

Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, Lavados P, Wang Y, Wang Y, Davalos A, Shamalov N, Mikulik R, Cunha L, Lindgren A, Arauz A, Lang W, Czlonkowska A, Eckstein J, Gagliardi RJ, Amarenco P, Ameriso SF, Tatlisumak T, Veltkamp R, Hankey GJ, Toni D, Bereczki D, Uchiyama S, Ntaios G, Yoon BW, Brouns R, Endres M, Muir KW, Bornstein N, Ozturk S, O'Donnell MJ, De Vries Basson MM, Pare G, Pater C, Kirsch B, Sheridan P, Peters G, Weitz JI, Peacock WF, Shoamanesh A, Benavente OR, Joyner C, Themeles E, Connolly SJ; NAVIGATE ESUS Investigators.

BACKGROUND:

Embolic strokes of undetermined source represent 20% of ischemic strokes and are associated with a high rate of recurrence. Anticoagulant treatment with rivaroxaban, an oral factor Xa inhibitor, may result in a lower risk of recurrent stroke than aspirin.

METHODS:

We compared the efficacy and safety of rivaroxaban (at a daily dose of 15 mg) with aspirin (at a daily dose of 100 mg) for the prevention of recurrent stroke in patients with recent ischemic stroke that was presumed to be from cerebral embolism but without arterial stenosis, lacune, or an identified cardioembolic source. The primary efficacy outcome was the first recurrence of ischemic or hemorrhagic stroke or systemic embolism in a time-to-event analysis; the primary safety outcome was the rate of major bleeding.

RESULTS:

A total of 7213 participants were enrolled at 459 sites; 3609 patients were randomly assigned to receive rivaroxaban and 3604 to receive aspirin. Patients had been followed for a median of 11 months when the trial was terminated early because of a lack of benefit with regard to stroke risk and because of bleeding associated with rivaroxaban. The primary efficacy outcome occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (hazard ratio, 1.07; 95% confidence interval [CI], 0.87 to 1.33; P=0.52). Recurrent ischemic stroke occurred in 158 patients in the rivaroxaban group (annualized rate, 4.7%) and in 156 in the aspirin group (annualized rate, 4.7%). Major bleeding occurred in 62 patients in the rivaroxaban group (annualized rate, 1.8%) and in 23 in the aspirin group (annualized rate, 0.7%) (hazard ratio, 2.72; 95% CI, 1.68 to 4.39; P<0.001).

CONCLUSIONS:

Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding. (Funded by Bayer and Janssen Research and Development; NAVIGATE ESUS ClinicalTrials.gov number, NCT02313909 .).

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Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation.

Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH; AUGUSTUS Investigators.

BACKGROUND:

Appropriate antithrombotic regimens for patients with atrial fibrillation who have an acute coronary syndrome or have undergone percutaneous coronary intervention (PCI) are unclear.

METHODS:

In an international trial with a two-by-two factorial design, we randomly assigned patients with atrial fibrillation who had an acute coronary syndrome or had undergone PCI and were planning to take a $P2Y_{12}$ inhibitor to receive apixaban or a vitamin K antagonist and to receive aspirin or matching placebo for 6 months. The primary outcome was major or clinically relevant nonmajor bleeding. Secondary outcomes included death or hospitalization and a composite of ischemic events.

RESULTS:

Enrollment included 4614 patients from 33 countries. There were no significant interactions between the two randomization factors on the primary or secondary outcomes. Major or clinically relevant nonmajor bleeding was noted in 10.5% of the patients receiving apixaban, as compared with 14.7% of those receiving a vitamin K antagonist (hazard ratio, 0.69; 95% confidence interval [CI], 0.58 to 0.81; P<0.001 for both noninferiority and superiority), and in 16.1% of the patients receiving aspirin, as compared with 9.0% of those receiving placebo (hazard ratio, 1.89; 95% CI, 1.59 to 2.24; P<0.001). Patients in the apixaban group had a lower incidence of death or hospitalization than those in the vitamin K antagonist group (23.5% vs. 27.4%; hazard ratio, 0.83; 95% CI, 0.74 to 0.93; P = 0.002) and a similar incidence of ischemic events. Patients in the aspirin group had an incidence of death or hospitalization and of ischemic events that was similar to that in the placebo group.

CONCLUSIONS:

In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a $P2Y_{12}$ inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens that included a vitamin K antagonist, aspirin, or both. (Funded by Bristol-Myers Squibb and Pfizer; AUGUSTUS ClinicalTrials.gov number, NCT02415400.).

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism.

Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Freitas MCS, Holberg G, Kakkar AK, Haskell L, van Bellen B, Pap AF, Berkowitz SD, Verhamme P, Wells PS, Prandoni P; EINSTEIN CHOICE Investigators.

BACKGROUND:

Although many patients with venous thromboembolism require extended treatment, it is uncertain whether it is better to use full- or lower-intensity anticoagulation therapy or aspirin.

METHODS:

In this randomized, double-blind, phase 3 study, we assigned 3396 patients with venous thromboembolism to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. All the study patients had completed 6 to 12 months of anticoagulation therapy and were in equipoise regarding the need for continued anticoagulation. Study drugs were administered for up to 12 months. The primary efficacy outcome was symptomatic recurrent fatal or nonfatal venous thromboembolism, and the principal safety outcome was major bleeding.

RESULTS:
A total of 3365 patients were included in the intention-to-treat analyses (median treatment duration, 351 days). The primary efficacy outcome occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) receiving 10 mg of rivaroxaban, as compared with 50 of 1131 patients (4.4%) receiving aspirin (hazard ratio for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20 to 0.59; hazard ratio for 10 mg of rivaroxaban vs. aspirin, 0.26; 95% CI, 0.14 to 0.47; P<0.001 for both comparisons). Rates of major bleeding were 0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the aspirin group; the rates of clinically relevant nonmajor bleeding were 2.7%, 2.0%, and 1.8%, respectively. The incidence of adverse events was similar in all three groups.
CONCLUSIONS:
Among patients with venous thromboembolism in equipoise for continued anticoagulation, the risk of a recurrent event was significantly lower with rivaroxaban at either a treatment dose (20 mg) or a prophylactic dose (10 mg) than with aspirin, without a significant increase in bleeding rates. (Funded by Bayer Pharmaceuticals; EINSTEIN CHOICE ClinicalTrials.gov number, NCT02064439 .)

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to September Week 1 2019

Search Strategy:

#	Searches	Results
1	apixaban.mp.	2433
2	dabigatran.mp. or Dabigatran/	4075
3	dalteparin.mp. or Dalteparin/	1214
4	edoxaban.mp.	990
5	enoxaparin.mp. or Enoxaparin/	4572
6	rivaroxaban.mp. or Rivaroxaban/	3960
7	warfarin.mp. or Warfarin/	26192
8	betrixaban.mp.	119
9	fondaparinux.mp. or Fondaparinux/	1692
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	35726
11	limit 10 to (english language and humans and yr="2017 -Current")	3766
12	limit 11 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	236

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Appendix 4: Key Inclusion Criteria

Population	Patients requiring anticoagulation
Intervention	Anticoagulant therapy
Comparator	Active control or placebo
Outcomes	Mortality, stroke, recurrent VTE, DVT, PE, bleeding
Timing	Treatment or prophylaxis
Setting	Inpatient or outpatient