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Drug Class Literature Scan: Anticoagulants (oral, injectable)

Date of Review: May 2017

Date of Last Review: March 2015
(Direct-acting Oral Anticoagulants, July 2016)
Literature Search: 01/16/17 – 03/01/17

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

Conclusions:

- Since the last review additional anticoagulation evidence has become available with the publication of 5 new guidelines[1–5], 8 new systematic reviews and meta-analyses[6–13], 5 randomized controlled trials[14–18] and 2 Food and Drug Administration (FDA) labeling changes.[19,20] Evidence directly comparing individual NOACs is insufficient. Recent literature refers to factor Xa inhibitors and direct thrombin inhibitors as non-vitamin K antagonist oral anticoagulants (NOACs) in place of previous direct acting oral anticoagulants (DOACs) nomenclature.
- Consistent with previous findings, low-molecular-weight heparins (LMWH) have the most evidence for venous thromboembolism (VTE) prevention in patients with cancer. A high quality systematic review of anticoagulant use for primary prophylaxis of VTE in patients with cancer receiving chemotherapy found that patients treated for a median of 10 months with LMWH had a reduced incidence of symptomatic deep vein thrombosis (DVT) compared to placebo/no treatment, 2.8% vs. 6%, respectively (ARR 3.2%; NNTB 30).[6] The results were not dependent upon LMWH used, type of cancer, dosage or treatment duration. Risk of major bleeds were not significantly different between groups (RR 1.44; 95% CI, 0.98 to 2.11; p= 0.07). In a second analysis, NOACs were found to have similar efficacy to conventional therapy (LMWH and vitamin K antagonists (VKAs)) for VTE reoccurrence in patients with cancer and VTE with an incidence rate of 3.9% and 6.0%, respectively.[7] Major bleeding occurred in 3.2% of NOAC treated patients and 4.2% of conventional therapy patients, which was not statistically different.
- In an analysis of the safety and efficacy of anticoagulants in patients undergoing orthopedic surgery, fondaparinux, rivaroxaban, and edoxaban had the highest efficacy in VTE prevention with 3.1 -5.1% less risk of VTE compared to enoxaparin (NNT 20 -40).[8] Apixaban and dabigatran were associated with the lowest risk of bleeding and fondaparinux had an 11-fold relative risk (RR) of major bleeding compared to enoxaparin, based on one trial. Limitations to this analysis include varied doses of enoxaparin and shorter duration of enoxaparin exposure versus oral comparators. These factors may bias the results in favor of enoxaparin comparators.
- In patients requiring extended (beyond 3 months) anticoagulation treatment for VTE, NOACs and VKAs were associated with VTE recurrence or death due to VTE in 1.3% of patients compared to 8.0% for placebo (RR 0.17; 95% CI, 0.12 to 0.24; p=0.0001; ARR 7%, NNT = 14). Major bleeding rates were similar in both treatment groups.[9]
- NOACs undergo anywhere from 27-80% renal excretion and are used with caution in patients with renal failure. Additionally, trials often exclude patients with renal failure limiting the evidence available in this population. A systematic review and meta-analysis found that in patients with reduced renal function

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(estimated glomerular filtration rate [eGFR] < 80 mL/min) taking anticoagulants for NVAF had 1.3 times the risk of stroke and systemic embolism and 1.8 times the risk of major bleeds compared to patients with normal renal function (eGFR > 80 mL/min), regardless of anticoagulant used.[10] For patients with mild renal impairment (eCrCl >50 ml/min - 80 ml/min) NOACs were found to have a 2.7% incidence of stroke/systemic embolism compared to 3.9% incidence with warfarin (RR of 0.71; 95% CI, 0.62 to 0.81; ARR 1.2%; NNTB 83) and for moderate renal impairment (eCrCl < 50 ml/min) a 3.8% incidence of stroke/systemic embolism compared to 4.8% with warfarin (RR of 0.79; 95% CI, 0.66 to 0.94; ARR 1%; NNTB 100). Major bleeds occurred in 5.7% patients taking NOACs compared to 6.4% of warfarin treated patients with mild renal impairment (RR 0.88; 95% CI, 0.80 to 0.97) and in 7.2% of NOAC treated patients compared to 9.0% of warfarin treated patients who had moderate renal impairment (RR 0.80; 95% CI, 0.70 to 0.91).[10]

- The risk of major bleeding is a potential risk associated with the use of all anticoagulants. A systematic review and meta-analysis of patients receiving anticoagulation for non-valvular atrial fibrillation (NVAF) or VTE found NOACs to be associated with less risk of major bleeds than VKAs in patients with an eCrCl of > 50 - < 80 mL/min with an incidence of 6.6% vs. 7.6%, respectively (ARR 1.0%; NNH 100) when followed for 0.25 to 2.8 years. Major bleeding was not significantly different between the groups in patients with an eCrCl of < 50 ml/min. An indirect comparison found apixaban to have the lowest major bleeding risk in comparison to other NOACs in patients with an eCrCl of < 50 mL/min. Less risk of hemorrhagic stroke was demonstrated in patients with an eCrCl > 50 mL/min and < 80 mL/min with an incidence rate of 0.5% in patients treated with NOACs compared to 1.05% of patients treated with a VKA (RR 0.43; 95% CI, 0.33 to 0.56) .[11] In patients with an eCrCl of < 50 ml/min hemorrhagic stroke rates occurred in 1.0% of patients treated with NOACs compared to 1.5% of patients treated with a VKAs (RR 0.42; 95% CI, 30 -61; p < 0.00001). In a second analysis of patients with NVAF or VTE the risk of major bleed-related fatalities was reduced by 1-3 patients per 1000 with NOACs compared to VKAs (with or without initial LMWH) in a period of 1.0-2.8 years; however, studies were found to have a high risk of bias for this outcome.[12]
- A moderate quality systematic review and meta-analysis found NOACs to have less risk of mortality related to major bleeds, compared to warfarin, in patients treated for NVAF or VTE (RR 0.53; 95% CI, 0.43 to 0.64).[13] The case-fatality rate was 7.57% for NOACs compared to 11.05% for warfarin.
- The CHEST guidelines recommend NOACs over VKAs for acute DVT or PE treatment in patients without cancer.[1] LMWHs are recommended over NOACs and VKAs for the treatment of DVT or PE in patients with cancer.
- The National Institute for Health and Care Excellence (NICE) issued guidance on the use of edoxaban.[2,3] NICE recommends that edoxaban be considered as an option for the treatment of DVT or PE and for stroke prevention in patients with NVAF.
- Two new guidelines recommend rivaroxaban as an option in patients with non-ST-elevation acute coronary syndrome (ACS), who are also receiving aspirin and clopidogrel, based on evidence from one trial.[4,5] Patients should have no prior stroke or transient ischemic attack (TIA) history and have a low bleeding risk.
- There was insufficient evidence on subgroup populations, including evidence specifically related to Medicaid patients.

Recommendations:

- Literature evaluated in this review supports the current preferred drug list (PDL) status of therapies in the anticoagulant class.
- No further review or research is needed at this time. After evaluation of comparative costs in executive session, no PDL changes are recommended.

Previous Conclusions (from July 2016 direct-acting oral anticoagulants [DOACs] summary review)**:**

- There is insufficient evidence for direct comparisons of DOACs. All DOAC efficacy and safety outcome comparisons were based on indirect data.
- There is low strength of evidence that there were no differences in all-cause mortality risks between the DOACs when used in patients with non-valvular atrial fibrillation (NVAF) and in patients undergoing hip or knee replacement surgery. There was insufficient evidence to develop conclusions on all-cause mortality risk between the DOACs when used for VTE prevention during extended treatment. Mortality was not assessed in DOAC treatment for VTE.

- For the composite outcome of VTE and mortality in orthopedic patients undergoing hip or knee surgery, there is low-strength of evidence that apixaban and rivaroxaban were associated with the lowest risk when compared to once daily dabigatran based on low strength evidence. There is low strength evidence that apixaban 2.5 mg twice daily was associated with less major bleeding than rivaroxaban 10 mg daily (OR 0.35; 95% CI, 0.13 to 0.91).
- In patients with NVAF there is low strength evidence that edoxaban 30 mg is associated with a higher risk of the composite outcome of stroke or systemic embolism compared to apixaban 5 mg and dabigatran 150 mg (OR 1.38 and OR 1.64, respectively) twice daily. Rivaroxaban 20 mg daily was found to have a higher risk of stroke and systemic embolism than dabigatran twice daily (OR 1.32, 95% CI, 1.01 to 1.74) based on low strength of evidence. Apixaban and edoxaban were associated with the lowest risk of major bleeds overall compared to the other DOACs.
- For the treatment of VTE there were no differences found for DOAC comparisons based on insufficient evidence for the following outcomes: VTE recurrence, DVT and PE. There is low strength of evidence in this population that major bleeding was less with apixaban compared to edoxaban and dabigatran.
- No differences were found in VTE recurrence, all-cause mortality, acute coronary syndrome, or major bleeding when comparing apixaban, rivaroxaban and dabigatran in patients treated for prevention of recurrent VTE for an extended period (insufficient evidence). Apixaban was associated with less major bleeding than rivaroxaban and dabigatran.
- The evidence of superior efficacy or harms in patient subgroups was insufficient, preventing meaningful conclusions.

Previous Recommendations:
- Evidence supports our current PDL and no changes are recommended.
- Recommend to continue access to all DOACs without prior authorization criteria.

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. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

<u>Safety and Efficacy of NOACs in VTE prevention after Orthopedic Surgery</u>
The efficacy and safety of NOACs in the prevention of VTE after hip and knee arthroplasty was evaluated in a systematic review and meta-analysis.[8] Eighteen trials met the inclusion criteria of being double-blind, RCTs enrolling adult patients scheduled for hip or knee surgery and prescribed anticoagulants. All trials were graded and rated 4-5 on the Jadad scale for quality assessment, indicating high-quality. All trials were funded by the manufacturers. Included trials

evaluated apixaban, dabigatran, rivaroxaban, edoxaban or fondaparinux which were compared to enoxaparin, dosed at 40 mg once daily in most studies. The primary efficacy outcome was VTE occurrence and the primary safety outcome was the composite of major and clinically relevant bleeding.

There was insufficient evidence to perform a meta-analysis to determine mortality differences between anticoagulants due to a low incidence of death. The incidence of VTE was 4.7% with apixaban compared to 7.2% for enoxaparin (RR 0.71; 95% CI, 0.52 to 0.96; p = 0.026); however, there was significantly heterogeneity between the trials due to different dosing regimens for enoxaparin.[8] For the composite bleeding endpoint, the incidence of major/clinically relevant bleeding was 3.8% in the apixaban group compared to 4.6% in the enoxaparin group (RR 0.84; 95% CI, 0.70 to 0.99; p = 0.043). Based on data from four trials, dabigatran was found to have a similar incidence of recurrent VTE as enoxaparin. In comparisons between dabigatran 150 mg daily and enoxaparin the incidence of recurrent VTE was 18% and 15%, respectively (RR 1.19; 95% CI, 0.98 to 1.44). Recurrent VTE was 13% for both groups when dabigatran 220 mg daily was compared to enoxaparin (RR 1.04; 95% CI, 0.87 to 1.24). Incidence of the composite of major and clinically relevant bleeding and major bleeding were similar between groups. Fondaparinux was compared to enoxaparin in four trials. The risk of VTE with fondaparinux was 5% compared to 10.1% for enoxaparin (RR 0.53; 95% CI, 0.45 to 0.63; p < 0.001). No data was available for the composite analysis for bleeding but the incidence of major bleeds was 2.6% in the fondaparinux group compared to 1.71% for enoxaparin (RR 1.64; 95% CI, 0.24 to 11.2; p = 0.62).[6] Four trials were available for the rivaroxaban analysis. Different anticoagulant treatment durations were utilized in the rivaroxaban trials; 31-39 days for rivaroxaban and 10-14 days for enoxaparin. Rivaroxaban was found to have a lower incidence of VTE with a recurrence rate of 3.1% compared to 6.2% for enoxaparin (RR 0.55; 95% CI 0.46 to 0.66; p < 0.001).[8] Risk of major/clinically relevant bleeds was 3.1% for rivaroxaban compared to 2.5% for enoxaparin. Two studies provided data for edoxaban, taking place in Japan and Taiwan, so reduced dosages were used and are less applicable to the US Medicaid population. Edoxaban was shown to decrease risk of VTE compared to enoxaparin in this population.

<u>Primary Prophylaxis of VTE in Patients with Cancer</u>

In a 2016 Cochrane review and meta-analysis the effects of primary prophylaxis for VTE in patients with cancer, any age, and undergoing chemotherapy were studied. Five new studies were identified since the last update in 2012.[6] Therefore, a total of 26 RCTs (n=12,352) were included in the current review. Treatments included in the review were the following: semuloparin (not available in the US), LMWH (dalteparin, enoxaparin, certoparin, nadroparin, bemiparin – the last 3 treatments unavailable in the US), UFH, warfarin, antithrombin or apixaban (phase II trial). Eighteen of the studies were comparisons involving LMWH to either placebo/no prophylaxis (n=16), aspirin (n=1) or warfarin (n=1). Doses of LMWH were prophylactic in 16 trials, intermediate in one trial and therapeutic in one trial. The majority of patients had a diagnosis of locally advanced or metastatic cancer and were being treated in an ambulatory care setting. The main outcome was symptomatic VTE, objectively verified DVT or PE.

High quality evidence found thromboprophylaxis with LMWH to reduce the risk of symptomatic VTE with an incidence rate of 2.8% compared to a VTE rate of 6% with placebo/no prophylaxis (RR 0.54; 95% CI, 0.38 to 0.75; p = 0.0003; ARR 3.2%; NNTB 30), based on a pooled analysis of 9 trials with a median follow up of 10 months.[6] Funnel plot analysis found no evidence of bias. Major bleeding was not significantly different between LMWH compared to placebo/no prophylaxis based on low quality evidence (RR 1.44; 95% CI, 0.98 to 2.11; p= 0.07).[4] In an active treatment comparison of LMWH (enoxaparin 40 mg daily) versus warfarin (low dose of 1.25 mg daily) in patients with multiple myeloma, LMWH was found to reduce the risk of VTE more than warfarin (RR 0.33; 95% CI, 0.14 to 0.83).[6] LMWH and warfarin were not associated with any major bleeding. In pooled comparisons between enoxaparin 40 mg daily versus aspirin 100 mg daily, median treatment duration of 18.5 months, there was moderate evidence that enoxaparin decreased VTE more than aspirin (RR 0.51, 95% CI, 0.22 to 1.17). Results were not significantly different and precision was low as indicated by wide confidence intervals. Patients taking aspirin had less than 1% incidence of major bleeds and there were no major bleeds in the enoxaparin group. In one, small (n=328) placebo controlled trial, warfarin (INR of at least 1.5) was found to reduce the risk of symptomatic VTE more than placebo but results were not statistically significant, based on low quality evidence (RR 0.15; 95% CI, 0.02 to 1.2). A trial of semuloparin

was found to reduce the risk of symptomatic VTE compared to placebo (RR 0.36; 95% CI, 0.22 to 0.60) with no increased risk of major bleeding. Subgroup analysis suggests a decreased incidence of VTE in patients with pancreatic or lung cancer without an increased risk of bleeding. Limitations to this analysis is a small number of trials in patients treated with VKAS and doses used for prophylaxis are of unknown efficacy.

NOACs in Patients with VTE and Cancer

A recent systematic review and meta-analysis evaluated the efficacy of NOACs in patients with cancer and VTE.[7] Six studies involving 1,132 patients were included in the meta-analysis. Trial data was available for edoxaban, rivaroxaban, dabigatran and apixaban. The comparator was warfarin for all trials (with initial LMWH). Trial quality was assessed and risk of bias was reported as low (based on analysis of funnel plot inspection). The primary outcome was VTE reoccurrence based on subgroup analysis of patients with cancer that were included in original trials used for approval. This population represented 2.5% to 9.4% of total patients from original trials.

In a pooled analysis of VTE reoccurrence, NOACs were associated with 23 (3.9%) events compared to 32 (6.0%) events with conventional therapy (OR 0.63; 95% CI, 0.37 to 1.10; p = 0.10).[7] Major bleeding risk was 3.2% (n=19/587) for NOACs compared to 4.2% (n=22/527) for vitamin K comparators. Clinical relevant bleeding was seen in 85 (14.5%) patients treated with NOACs compared to 87 (16.5%) patients treated with VKAs. Patients with active cancer at higher risk of VTE may have been treated with LMWH, which represents standard therapy, which may limit the application of this analysis. Additional evidence comparing NOACs to LMWH would help to delineate the optimal treatment for VTE prevention in patients with cancer.

Extended Use of Anticoagulants for VTE

The efficacy and safety of using NOACs in patients with unprovoked VTE was the focus of a systematic review and meta-analysis.[9] Six trials met the criteria for extended anticoagulation. Included treatments were dabigatran, rivaroxaban, apixaban and warfarin. NOACs were compared to placebo (4 trials); warfarin (1 trial of dabigatran compared to warfarin); or treatment discontinuation (warfarin trial). Patients were required to receive at least 6 months of anticoagulation with a NOAC or warfarin, with trial durations lasting 6-36 months. All patients received at least 3 months of previous anticoagulation treatment. Recurrent VTE or deaths related to recurrent VTE was the primary efficacy outcome.

In placebo controlled comparisons, NOACs and warfarin decreased recurrent VTE or death due to VTE compared to placebo, with a reoccurrence rate of 1.3% compared to 8% for placebo (RR 0.17; 95% CI, 0.12 to 0.24).[9] Warfarin and dabigatran were associated with the lowest risk of VTE reoccurrence or death, 0.03 and 0.08, respectively. Risk of major bleeding was not significantly different with NOACs or warfarin compared to placebo (RR 1.15; 95% CI, 0.40 to 3.31); however, non-major clinically relevant bleeding (NMCRB) was higher in patients treated with NOACs or warfarin compared to placebo (RR 2.12; 95% CI, 1.55 to 2.90).[9] Overall study bias was deemed to be low.

Renal Function Status on Safety and Efficacy of NOACs in Patients with AF

Efficacy and safety data for the use of NOACs in patients with mild to moderate renal dysfunction taking anticoagulants for stroke prevention in patients with NVAF was studied.[10] Patients were divided into 3 groups; normal renal function (eGFR of > 80 mL/min), mild impairment (eGFR 50-80 mL/min) and moderate impairment (eGFR < 50 mL/min). Patients were over the age of 65 years with a CHADS2 score of 2.1 to 3.5. Patients treated with warfarin experienced time in therapeutic range 58-68% of the time. All comparisons were to warfarin and all US approved NOACs (apixaban, dabigatran, edoxaban and rivaroxaban) were included. Four RCTs (58,338 patients) were identified for inclusion. Trials had low degree of bias and were considered high quality. The primary efficacy endpoint was stroke or systemic embolism and the primary safety outcome was major bleeds.

Patients with reduced renal function experienced 1.3 times the risk of stroke/systemic embolism and 1.8 times the risk of major bleeds compared to patients with normal renal function, irrespective of anticoagulant used.[10] Efficacy endpoints were similar for all anticoagulants in patients with normal renal function with an incidence rate of 2% for NOACs and 2.2% for warfarin (risk ratio [RR 0.96; 95% CI, 0.81 to 1.15; p = 0.69); however, NOACs were associated with less major bleeds compared to warfarin, 3.7% vs. 4.3%, respectively (RR 0.86; 95% CI, 0.75 to 0.98; p = 0.03).[8] NOACs were found to have a reduced risk of stroke/systemic embolism compared to warfarin in patients with moderate renal dysfunction, 3.8% and 4.8%, respectively (RR 0.79; 95% CI, 0.66 to 0.94; p = 0.008). The risk of stroke/systemic embolism for patients with mild renal impairment was 2.7% for patients taking NOACs compared to 3.9% for patients taking warfarin (RR 0.71; 95% CI, 0.62 to 0.81; p < 0.00001).[10] Major bleed risk was reduced with NOAC therapy compared to warfarin in patients with mild renal impairment, 5.7% vs. 6.4%, respectively (RR 0.87; 95% CI, 0.79 to 0.95; p = 0.01) and in patients with moderate renal dysfunction with an incidence of 7.2% in the NOAC group compared to 9% in the warfarin group (RR 0.80; 95% CI, 0.71 to 0.91; p = 0.0005). Limitations to the data include high heterogeneity in studies evaluating the risk of major bleeds which can decrease the reliability of the results.

Safety

NOACs and Major Bleeding and Hemorrhagic Stroke in Patients with Renal Failure

The use of NOACs in patients with renal failure has not been extensively studied.[11] This systematic review and meta-analysis evaluated the risk of major bleeding and hemorrhagic stroke in patients with renal failure who were treated with NOACs for NVAF or VTE. Nine RCTS with 94,879 patients that were followed for 0.25 to 2.8 years were included. NOACs included in the analysis were: apixaban, edoxaban, rivaroxaban and dabigatran. All comparisons were to VKAs (warfarin). Patients were analyzed dependent upon renal function; normal renal function (estimated CrCl [eCrCl] > 80 mL/min), eCrCl > 50-< 80 mL/min or eCrCl < 50mL/min. Nine trials were identified which included 94,879 patients. Fifty-eight percent had an estimated CrCl of < 80 mL/min.

In patients with an eCrCl of > 50 mL/min and < 80 mL/min, the NOACs were associated with a decreased risk of major bleeds compared to VKAs. The incidence of major bleeds was 6.6% in the NOAC group compared to 7.6% in the warfarin group (RR 0.87; 95% CI, 0.81 to 0.93; p = 0.0001).[11] Apixaban and edoxaban were the only NOACs associated with this reduced risk in a subgroup analysis. In patients with an estimated CrCl of < 50 mL/min, NOACs were also found to be associated with less risk of major bleeding compared to VKAs with major bleeding occurring in 8.3% and 9.7%, respectively (RR 0.83; 95% CI, 0.68 to 1.02; p = 0.08). Subgroup analysis found that dabigatran and rivaroxaban were not associated with a reduced risk. In patients with an estimated CrCl of < 50 mL/min apixaban was found to have a reduced risk of major bleeding compared with other NOACs.[11] In patients with NVAF there was more risk reduction in major bleeding in patients treated with NOACs compared to VKAs in patients with an estimated CrCl of > 50 mL/min and < 80 mL/min compared to patients with an estimated CrCl of < 50 mL/min. In patients with VTE more benefit was seen with NOACs compared to VKAs in patients with an estimated CrCl of < 50 mL/min compared to patients with an estimated CrCl of > 50 and < 80 mL/min.

Hemorrhagic stroke was reduced in patients taking NOACs compared to VKAs. The incidence of hemorrhagic stroke was 0.5% in patients treated with NOACs compared to 1.1% in patients treated with VKAs in patients with an eCrCl of < 50 to > 80 mL/min (RR 0.43; 95% CI, 0.33 to 0.56; p < 0.00001; ARR 0.6%; NNH 166). Hemorrhagic stroke rates were 1% in patients treated with NOACs and 1.5% of patients treated with VKAs in patients who had an eCrCl of < 50 mL/min (RR 0.42; 95% CI, 0.30 to 0.61; p < 0.00001; ARR 0.5%; NNH 200).[11] The overall risk of bias was low for all included trials; however, there was a high degree of heterogeneity.

NOACs and Major Bleeding Fatalities

In a systematic review and meta-analysis, the risk of major bleeding-related fatalities associated with NOACs compared to VKAs (with or without initial LMWH therapy) was studied.[12] Eleven, phase 3 trials were identified in patients with AF (5 trials) and VTE (6 trials). These types of trials were chosen so that medium-term

to long-term anticoagulation could be accessed. Longer treatment durations are required due to low rates of fatal events. All US approved NOACs were included (dabigatran, apixaban, edoxaban and rivaroxaban). A majority (73%) of patients had an AF diagnosis. The mean age was 71 years for AF patients and 56 for VTE patients. The primary outcome was overall mortality associated with major bleeding events.

Major bleeding fatalities occurred in 121 patients with AF taking NOACs compared to 152 taking VKAs (OR 0.53; 95% CI, 0.42 to 0.68; 3 events avoided per 1000 patients treated over 1-2.8 years).[12] In patients with VTE, the incidence rate of fatalities for NOACs was 7 compared to 22 for VKAs (OR 0.36; 95% CI, 0.15 to 0.85; 1 event avoided per 1000 patients over 6 months). Overall, trials were found to have a low to moderate risk of bias, except for adjusted estimates for fatal bleeding, in which all trials were considered to have a high risk of bias.

Mortality Outcomes with NOACs

A second meta-analysis and systematic review focused on mortality comparisons between NOACS and VKAs.[13] Thirteen trials in patients with NVAF and VTE were included in the analysis. NOAC treatments included: apixaban, dabigatran, edoxaban and rivaroxaban. Trial durations ranged from 6-30 months and 8 were designated as high quality. All trials were at low risk of publication bias based on funnel plot analysis. The primary outcome was case-fatality rate. The case-fatality rate is calculated by the number of fatal bleeds divided by the number of major bleeds expressed as a percentage.

NOACs were associated with a major bleeding case-fatality rate of 7.57% compared to 11.05% for patients taking warfarin based on 12 trials. Fatal bleeding comparisons between NOACS and warfarin demonstrated less fatal bleeds in the NOAC group (RR 0.53; 95% CI, 0.43 to 0.64).[13] Limitations to this analysis include conflicts of interest between the authors and pharmaceutical manufacturers.

New Guidelines:

CHEST Guideline: Antithrombotic Therapy for VTE

The 9th edition of antithrombotic therapy and VTE published by CHEST was updated in 2016. Recommendations are considered strong (Grade 1) or weak (Grade 2) based on the evidence quality, delineated as high (Grade A), moderate (Grade B) or low (Grade C).[1] Recommendations regarding treatment selection and duration of treatment are presented in Table 1.

Table 1. Treatment Recommendations for VTE[1]

Indication	Recommendation	Grade
- Acute proximal DVT or PE and no cancer requiring long-term (first 3 months) anticoagulant therapy	- Dabigatran, rivaroxaban, apixaban or edoxaban over vitamin K antagonists*	Grade 2B
- Proximal DVT or PE and no cancer not treated with dabigatran, rivaroxaban, apixaban, or edoxaban	- Vitamin K antagonists over LMWH*	Grade 2C
- Proximal DVT or PE and cancer requiring long-term (first 3 months) anticoagulant therapy	- LMWH over VKA therapy, dabigatran, rivaroxaban, apixaban or edoxaban*	Grade 2C

- Proximal DVT or PE who receive extended therapy	- Continue current anticoagulant	Grade 2C
- Proximal DVT or PE provoked by surgery	- Treatment for 3 months over treatment for a shorter duration - Treatment over a longer time-limited† period - Extended therapy (no scheduled stop date)	Grade 1B Grade 1B Grade 1B
- Proximal DVT or PE provoked by nonsurgical transient risk factor	- Treatment for 3 months over treatment for a shorter duration - Treatment over a longer time-limited† period - Treatment for 3 months versus a longer time-limited† period if there is a low or moderate bleeding risk - Treatment for 3 months versus extended treatment if there is a high bleeding risk	Grade 1B Grade 1B Grade 2B Grade 1B
- Distal DVT provoked by surgery or by nonsurgical transient risk factor	- Treatment for 3 months over treatment for a shorter duration - Treatment for 3 months over a longer time-limited† period - Treatment for 3 months over extended therapy (no scheduled stop date)	Grade 2C Grade 1B Grade 1B
- Unprovoked DVT (isolated proximal or distal) or PE	- Treatment for at least 3 months over a shorter duration - Treatment for 3 months over treatment of a longer time-limited† duration	Grade 1B Grade 1B
- First VTE that is an unprovoked proximal DVT of the leg or PE	- If low or moderate bleeding risk, extended anticoagulation therapy is recommended - If high bleeding risk, 3 months of anticoagulation therapy over extended therapy	Grade 2B Grade 1B
- Second unprovoked VTE	- If low bleeding risk, extended anticoagulant therapy versus 3 months of therapy - If moderate bleeding risk, extended anticoagulant therapy over 3 months of therapy - High bleeding risk, 3 months of anticoagulant therapy over extended therapy	Grade 1B Grade 2B Grade 2B
- Patients with DVT or PE with active cancer	- If bleeding risk is not high, extended anticoagulation therapy over 3 months of anticoagulation - If high bleeding risk, extended anticoagulation over 3 months of therapy	Grade 1B Grade 2B
- Unprovoked proximal DVT or PE who are stopping anticoagulant therapy	- Aspirin therapy over no therapy if no contraindications to aspirin are present	Grade 2B
- Acute isolated distal DVT without severe symptoms	- Serial imaging of the deep veins for 2 weeks over anticoagulation - Anticoagulation over serial imaging if severe symptoms or risk factors for extension	Grade 2C Grade 2C

- Acute isolated distal DVT who are managed with anticoagulation	- Same treatment as for acute proximal DVT (outlined above)	Grade 1B
- Acute isolated distal DVT managed with serial imaging	- No anticoagulation if thrombus does not extend - Anticoagulation therapy if thrombus extends but remains confined to distal veins - Anticoagulation therapy if thrombus extends into the proximal veins	Grade 1B Grade 2C Grade 1B
- Subsegmental PE	- Clinical surveillance over anticoagulation if no involvement of proximal pulmonary arteries and no proximal DVT and low risk for recurrent VTE - High risk for recurrent VTE then anticoagulation is recommended over clinical surveillance	Grade 2C Grade 2C
- Upper extremity DVT	- Anticoagulation therapy over thrombolysis	Grade 2C
- Recurrent VTE on VKA or on dabigatran, apixaban, edoxaban or rivaroxaban	- Switch to LMWH at least temporarily	Grade 2C
- Recurrent VTE on LMWH	- Increase dose by one-quarter to one-third	Grade 2C
* Initial parenteral anticoagulation is given before dabigatran and edoxaban but not before rivaroxaban and apixaban and overlapped with VKA therapy. † Time-limited period: 6, 12 or 24 months Abbreviations: LMWH = low-molecular weight heparin;		

NICE: Edoxaban for DVT and PE

NICE reviewed the literature for edoxaban in the treatment of DVT and PE to make a guidance recommendation related to its use.[3] One good quality study found edoxaban associated symptomatic recurrent VTE in 3.2% of patients compared to 3.5% of warfarin treated patients, demonstrating non-inferiority ($p < 0.0001$). NICE recommends edoxaban as an option for the treatment and prevention of DVT and PE in adults.

NICE: Edoxaban for Stroke

The use of edoxaban for the prevention of stroke in patients with NVAF was evaluated for a NICE guidance.[2] Edoxaban is recommended for patients after a discussion on the benefits and risks of such treatment compared with warfarin, apixaban, dabigatran and rivaroxaban. For patients taking warfarin that are considering switching to edoxaban, the benefits and risks as well as the history of INR control should be evaluated.

NICE: Rivaroxaban for ACS

The evidence for the use of rivaroxaban in patients with ACS was reviewed by NICE.[4] After analysis of data from one multi-center, double-blind, manufacturer funded, RCT in over 15,000 patients, guidance recommendations were issued. Rivaroxaban was recommended for the prevention of atherothrombotic events in patients with ACS and elevated biomarkers. Rivaroxaban should be used in this patient population as part of a regimen containing aspirin or aspirin plus clopidogrel.

ESC: Guidelines for the Management of ACS

The ESC provided guidance on managing patients who present with ACS without persistent ST-segment elevation.[5] Evidence level and strength of the recommendation of management strategies were weighed and graded. The recommendation was assigned a class of recommendation with the following: Class I (is recommended and indicated), Class II (conflicting evidence – refer to Class IIa or IIb), Class IIa (should be considered), Class IIb (may be considered), and Class III (is not recommended). The levels of evidence ranged from A (randomized controlled trials or meta-analysis, highest level), B (single RCT or large non-randomized trial) to C (consensus of opinion, lowest level). The Task Force responsible for guideline development did not receive funding from the healthcare industry. The recommendations pertaining to anticoagulation management following the acute phase will be presented below.

ESC recommends the use of rivaroxaban 2.5 mg as an option in patients with non-ST-elevation ACS with no prior stroke or TIA history that are at high risk for ischemia and low risk of bleeding who are also receiving aspirin and clopidogrel (class IIb, level B). Patients should have parenteral anticoagulation discontinued before initiation of rivaroxaban.[5]

New Formulations:

No new formulations identified.

New FDA Safety Alerts:

Apixaban

In July of 2016 the lack of reversal agent for apixaban was noted in the warnings and precautions section.[20] In patients with NVAF, dosing in specific populations was modified to include the dosing regimen of 2.5 mg twice daily in patients with at least two of the following risk factors: age of 80 years or older, body weight of 60 kg or less and serum creatinine of 1.5 mg/dL or less. Recommendations for dosing in patients with end-stage renal disease (ESRD) on dialysis are the same as in patients without ESRD based on pharmacodynamics data. No patients with ESRD, with or without dialysis have been studied. In patients being treated for DVT and PE prevention following hip or knee replacement surgery should not receive a dose adjustment if they have renal impairment or ESRD on dialysis based on pharmacokinetic data. In June of 2015 recommendations for dosing apixaban in patients for renal impairment alone, including those with ESRD on dialysis were updated. Patients should receive the recommended dose without reductions unless they are being treated with NVAF and meet the criteria for dosage reduction. No dose adjustment is required for patients with mild hepatic impairment. Dosing in moderate hepatic impairment has not been studied and therefore dosing cannot be recommended. Apixaban is not recommended in patients with severe hepatic impairment.

Rivaroxaban

Labeling was updated that the use of rivaroxaban with selective serotonin inhibitors and norepinephrine reuptake inhibitors as this combination has the potential to interact and increase the risk of bleeding.[19] Periodic assessment of renal function is also recommended in patients taking rivaroxaban. Patients who have ESRD on dialysis were not included in the rivaroxaban studies. Rivaroxaban doses of 15 mg daily should produce similar concentrations to those included in the ROCKET AF study.

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	CAPSULE	PRADAXA	DABIGATRAN ETEXILATE MESYLATE	Y
ORAL	TAB DS PK	XARELTO	RIVAROXABAN	Y
ORAL	TABLET	COUMADIN	WARFARIN SODIUM	Y
ORAL	TABLET	ELIQUIS	APIXABAN	Y
ORAL	TABLET	JANTOVEN	WARFARIN SODIUM	Y
ORAL	TABLET	SAVAYSA	EDOXABAN TOSYLATE	Y
ORAL	TABLET	WARFARIN SODIUM	WARFARIN SODIUM	Y
ORAL	TABLET	XARELTO	RIVAROXABAN	Y
SUB-Q	SYRINGE	ENOXAPARIN SODIUM	ENOXAPARIN SODIUM	Y
SUB-Q	SYRINGE	FRAGMIN	DALTEPARIN SODIUM,PORCINE	Y
SUB-Q	SYRINGE	LOVENOX	ENOXAPARIN SODIUM	Y
SUB-Q	VIAL	ENOXAPARIN SODIUM	ENOXAPARIN SODIUM	Y
SUB-Q	VIAL	LOVENOX	ENOXAPARIN SODIUM	Y
SUB-Q	SYRINGE	ARIXTRA	FONDAPARINUX SODIUM	N
SUB-Q	SYRINGE	FONDAPARINUX SODIUM	FONDAPARINUX SODIUM	N
SUB-Q	VIAL	FRAGMIN	DALTEPARIN SODIUM,PORCINE	N

Appendix 2: New Comparative Clinical Trials

A total of 449 citations were manually reviewed from the initial literature search. After further review, 444 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The 5 randomized controlled trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 2. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Goette, et al[15] RCT, OL, MC	Edoxaban 60 mg* daily vs. Enoxaparin-warfarin (INR 2.0-3.0) 28-days post procedure	Patients with NVAF undergoing electrical cardioversion N= 2199	Incidence 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
Lee, et al[14] RCT, OL, MC	Tinzaparin (175 IU/kg) vs. Tinzaparin (175 IU/kg)/warfarin (INR 2.0-3.0) 6 months	Patients with active cancer and documented PE or DVT N=900	Recurrent DVT, fatal or nonfatal PE and incidental VTE	Tinzaparin: 31 (7.2%) Tinzaparin/warfarin: 45 (10.5%) HR 0.65; 95% CI, 0.41 to 1.03) P = 0.07
Calkins, et al[17] RCT, OL, MC	Dabigatran 150 mg twice daily vs. Warfarin (INR 2.0 to 3.0) 4-8 weeks pre-procedure and 8 weeks post-procedure	Patients undergoing catheter ablation of atrial fibrillation N = 704	Major bleeding events	Dabigatran: 5 (1.6%) Warfarin: 22 (6.9%) ARR -5.3%; 95% CI, -8.4 to -2.2 P<0.001
Weitz, et al[16] RCT, DB, MC	Rivaroxaban 20 mg or 10 mg daily vs. Aspirin 100 mg daily 12 months	Patients with VTE with a prior 6-12 months of anticoagulation and were equipoise for the need for	Symptomatic recurrent fatal or nonfatal venous thromboembolism	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

		continuing anticoagulation N = 3365		Rivaroxaban 10 mg vs. Aspirin: HR 0.26; 95% CI, 0.14 to 0.47 P<0.001
Ohman, et al[18] RCT, DB, MC	Rivaroxaban 2.5 mg twice daily† vs. Aspirin 100 mg daily† 291 days	Patients with ACS	Thrombolysis in myocardial infarction clinically significant bleeding (not related to coronary artery bypass graft) up to day 390	Rivaroxaban: 80 (5%) Aspirin: 74 (5%) HR 1.09; 95% CI, 0.80 to 1.50 P = 0.5840
* Edoxaban dose was reduced to 30 mg daily if one or more of the following: CrCl 15-50 mL/min, low body weight (≤ 60 kg) or concomitant use of P-glycoprotein inhibitors † Patients also received clopidogrel or ticagrelor				

Abbreviations: ACS = acute coronary syndrome; CI = confidence interval; HR = hazard ratio; INR = international normalized ratio; MC = multi-center; OL = open label; OR = odds-ratio; RCT = randomized clinical trial

Appendix 3: Abstracts of Comparative Clinical Trials

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

Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial
Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA; CATCH Investigators

IMPORTANCE:
Low-molecular-weight heparin is recommended over warfarin for the treatment of acute venous thromboembolism (VTE) in patients with active cancer largely based on results of a single, large trial.
OBJECTIVE:
To study the efficacy and safety of tinzaparin vs warfarin for treatment of acute, symptomatic VTE in patients with active cancer.

DESIGN, SETTINGS, AND PARTICIPANTS:
A randomized, open-label study with blinded central adjudication of study outcomes enrolled patients in 164 centers in Asia, Africa, Europe, and North, Central, and South America between August 2010 and November 2013. Adult patients with active cancer (defined as histologic diagnosis of cancer and receiving anticancer therapy or diagnosed with, or received such therapy, within the previous 6 months) and objectively documented proximal deep vein thrombosis (DVT) or pulmonary embolism, with a life expectancy greater than 6 months and without contraindications for anticoagulation, were followed up for 180 days and for 30 days after the last study medication dose for collection of safety data.
INTERVENTIONS:
Tinzaparin (175 IU/kg) once daily for 6 months vs conventional therapy with tinzaparin (175 IU/kg) once daily for 5 to 10 days followed by warfarin at a dose adjusted to maintain the international normalized ratio within the therapeutic range (2.0-3.0) for 6 months.
MAIN OUTCOMES AND MEASURES:
Primary efficacy outcome was a composite of centrally adjudicated recurrent DVT, fatal or nonfatal pulmonary embolism, and incidental VTE. Safety outcomes included major bleeding, clinically relevant nonmajor bleeding, and overall mortality.
RESULTS:
Nine hundred patients were randomized and included in intention-to-treat efficacy and safety analyses. Recurrent VTE occurred in 31 of 449 patients treated with tinzaparin and 45 of 451 patients treated with warfarin (6-month cumulative incidence, 7.2% for tinzaparin vs 10.5% for warfarin; hazard ratio [HR], 0.65 [95% CI, 0.41-1.03]; P = .07). There were no differences in major bleeding (12 patients for tinzaparin vs 11 patients for warfarin; HR, 0.89 [95% CI, 0.40-1.99]; P = .77) or overall mortality (150 patients for tinzaparin vs 138 patients for warfarin; HR, 1.08 [95% CI, 0.85-1.36]; P = .54). A significant reduction in clinically relevant nonmajor bleeding was observed with tinzaparin (49 of 449 patients for tinzaparin vs 69 of 451 patients for warfarin; HR, 0.58 [95% CI, 0.40-0.84]; P = .004).
CONCLUSIONS AND RELEVANCE:
Among patients with active cancer and acute symptomatic VTE, the use of full-dose tinzaparin (175 IU/kg) daily compared with warfarin for 6 months did not significantly reduce the composite measure of recurrent VTE and was not associated with reductions in overall mortality or major bleeding, but was associated with a lower rate of clinically relevant nonmajor bleeding. Further studies are needed to assess whether the efficacy outcomes would be different in patients at higher risk of recurrent VTE.

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism.
Weitz JI, Lensing AW, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Freitas MC, 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 .).

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 .)

Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial.
Ohman EM, Roe MT, Steg PG, James SK, Povsic TJ, White J, Rockhold F, Plotnikov A, Mundl H, Strony J, Sun X, Husted S, Tendera M, Montalescot G, Bahit MC, Ardissino D, Bueno H, Claeys MJ, Nicolau JC, Cornel JH, Goto S, Kiss RG, Güray Ü, Park DW, Bode C, Welsh RC, Gibson CM

BACKGROUND:
Dual antiplatelet therapy (DAPT), aspirin plus a P2Y12 inhibitor, is the standard antithrombotic treatment following acute coronary syndromes. The factor Xa inhibitor rivaroxaban reduced mortality and ischaemic events when added to DAPT, but caused increased bleeding. The safety of a dual pathway antithrombotic therapy approach combining low-dose rivaroxaban (in place of aspirin) with a P2Y12 inhibitor has not been assessed in acute coronary syndromes. We aimed to assess rivaroxaban 2·5 mg twice daily versus aspirin 100 mg daily, in addition to clopidogrel or ticagrelor (chosen at investigator discretion before randomisation), for patients with acute coronary syndromes started within 10 days after presentation and continued for 6-12 months.
METHODS:
In this double-blind, multicentre, randomised trial (GEMINI-ACS-1) done at 371 clinical centres in 21 countries, eligible patients were older than 18 years with unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI), with positive cardiac biomarkers and either ischaemic electrocardiographic changes or an atherosclerotic culprit lesion identified during angiography. Participants were randomly assigned (1:1) within 10 days after admission for the index acute coronary syndromes event to either aspirin or rivaroxaban based on a computer-generated randomisation schedule. Randomisation was balanced by using randomly permuted blocks with size of four and was stratified based on the background P2Y12 inhibitor (clopidogrel or ticagrelor) intended to be used at the time of randomisation. Investigators and patients were masked to treatment assignment. Patients received a minimum of 180 days of double-blind treatment with rivaroxaban 2·5 mg twice daily or aspirin 100 mg daily. The choice of clopidogrel or ticagrelor during trial conduct was not randomised and was based on investigator preference. The primary endpoint was thrombolysis in myocardial infarction (TIMI) clinically significant bleeding not related to coronary artery bypass grafting (CABG; major, minor, or requiring medical attention) up to day 390. Primary analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT02293395.
FINDINGS:
Between April 22, 2015, and Oct 14, 2016, 3037 patients with acute coronary syndromes were randomly assigned; 1518 to receive aspirin and 1519 to receive rivaroxaban. 1704 patients (56%) were in the ticagrelor and 1333 (44%) in the clopidogrel strata. Median duration of treatment was 291 days (IQR 239-354). TIMI non-CABG clinically significant bleeding was similar with rivaroxaban versus aspirin therapy (total 154 patients [5%]; 80 participants [5%] of 1519 vs 74 participants [5%] of 1518; HR 1·09 [95% CI 0·80-1·50]; p=0·5840).
INTERPRETATION:
A dual pathway antithrombotic therapy approach combining low-dose rivaroxaban with a P2Y12 inhibitor for the treatment of patients with acute coronary syndromes had similar risk of clinically significant bleeding as aspirin and a P2Y12 inhibitor. A larger, adequately powered trial would be required to definitively assess the efficacy and safety of this approach.
FUNDING:
Janssen Research & Development and Bayer AG.

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2017
Search Strategy:

#	Searches	Results
1	apixaban.mp.	1427
2	rivaroxaban.mp. or Rivaroxaban/	2320
3	dabigatran.mp. or Dabigatran/	2736
4	edoxaban.mp.	515
5	warfarin.mp. or Warfarin/	17078
6	enoxaparin.mp. or Enoxaparin/	3830
7	dalteparin.mp. or Dalteparin/	1065
8	fondaparinux.mp.	1505
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	24153
10	limit 9 to (english language and humans and yr="2015 -Current")	2573
11	limit 10 to (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	457

Author: Sentena

Date: May 2017