

Drug Class Literature Scan: Anticoagulants

Date of Review: February 2021

Date of Last Review: November 2019
Literature Search: 09/01/19 – 01/04/20

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

Conclusions:

- There were five systematic reviews and meta-analyses, four new guidelines and two randomized controlled trials (RCTs) identified since the last review.
- Results from a 2020 Cochrane review demonstrated moderate evidence of an increased risk of stroke in patients treated with rivaroxaban compared to vitamin K antagonists (VKAs) in adult patients with antiphospholipid syndrome (APS), 14 versus 0 (relative risk [RR] of 14.13; 95% confidence interval [CI], 1.87 to 106.81).¹ Confidence intervals suggest imprecision most likely due the low number of events. There was no difference between groups in risk of thromboembolic events. The incidence in major bleeding was similar between groups (RR 1.10; 95% CI, 0.45 to 2.68) based on moderate evidence.
- Patients with no history of thromboembolism and undergoing knee arthroscopy (KA) were included in a Cochrane review.² In short term studies (30 days to 3 months), there was moderate evidence of no difference between control (no treatment) and low-molecular weight heparin (LMWH) for the outcomes of pulmonary embolism (PE) and there was also no conclusive evidence of differences between adverse events.² Very low quality evidence found no difference between LMWH and controls for symptomatic and asymptomatic deep vein thrombosis (DVT).
- Primary venous thromboembolism (VTE) prophylaxis in adult ambulatory patients with cancer found high strength of evidence that LMWH was more effective at decreasing the risk of any VTE compared to no treatment with moderate evidence of an increased risk of clinically relevant bleeding and major bleeding. There was moderate evidence that all DVT (symptomatic and asymptomatic) rates were decreased with non-vitamin K oral anticoagulants (NOACs) compared to no treatment; reductions in symptomatic DVT, symptomatic PE and VTE with NOACs compared to placebo were based on low strength of evidence. There was moderate evidence of increased clinically relevant bleeding and major bleeding in patients treated with NOACs.
- A Cochrane review found no differences between NOACs and VKAs in death from cardiovascular (CV) causes, myocardial infarction (MI), stroke, death from any cause and stent thrombosis in trials lasting 6 months to 2.2 years, based on very-low to moderate quality of evidence. Risk of major bleeding was less with dabigatran (low dose) compared to VKAs (RR 0.38; 95% CI, 0.21 to 0.70) (moderate quality evidence). All other NOAC comparisons to VKA found no substantial differences in major bleeding between groups.³
- High quality evidence from a Cochrane review on management of distal DVTs found VKAs to prevent more VTEs compared to placebo and treatment for 3 or more months was more effective in VTE reduction compared to 6 weeks of treatment.⁴
- Updated guidance from the National Institute for Health and Care Excellence (NICE) on venous thromboembolism and American Hematology Society (AHS) on the management of VTE were updated in 2020 and support our current policy.^{5,6} The American Heart Association, American College of Cardiology and Heart Rhythm Society (AHA/ACC/HRS) guideline on the management of patients with atrial fibrillation (AF) also supports current policy.⁷ Lastly, an update from the American Society of Clinical Oncology (ASCO) aligns with current policy.⁸

- There were several Food and Drug Administration (FDA) safety updates, including the warning of an increased risk of thrombosis in patients with triple positive antiphospholipid syndrome with NOACs and use is not recommended.

Recommendations:

- No changes to the preferred drug list (PDL) are warranted based on the evidence identified since the last review.
- After evaluation of costs during executive session, dalteparin syringes were made PDL non-preferred.

Summary of Prior Reviews and Current Policy

- The anticoagulant class was last reviewed in November of 2019. New evidence for the treatment of VTE and atrial fibrillation (AF) was presented. No changes were made to the PDL based on clinical evidence or after comparative cost consideration in executive session.
- All anticoagulants are designated as preferred with the exception of: betrixaban, dalteparin, enoxaparin ampules, and fondaparinux.
- There is 100% utilization of preferred products for the anticoagulant class based on the most recent quarter data. There is higher NOAC utilization compared to warfarin.

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), 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:

Cochrane – Antiplatelet and Anticoagulant Agents for the Secondary Prevention of Stroke and Other Thromboembolic Events in People with Antiphospholipid Syndrome

A 2020 Cochrane review evaluated the use of antiplatelets or anticoagulants, alone or in combination, in patients with APS for secondary prevention of thrombosis, in particular ischemic stroke.¹ There were 8 studies that met inclusion criteria which enrolled a total of 811 patients. The average age of patients were 36-50 years. Drugs included rivaroxaban 15-20 mg/day, aspirin (100 mg/day) and warfarin (standard-dose [INR 2.0 to 3.0] and high-dose [INR 3.1 to 4.0]).¹ The outcomes of interest were thromboembolic events, stroke, death and major bleeding.

Three trials compared standard dose VKA (INR 2.0-3.0) to rivaroxaban over a period of 7 months to 35.4 months.¹ There was no difference in the incidence of thrombotic events: VKAs 28 per 1000 patients compared to 115 per 1000 for patients treated with rivaroxaban (RR 4.08; 95% CI, 0.48 to 34.79) based on moderate evidence, which was downgraded due to imprecision.¹ Large confidence intervals suggests imprecision and uncertainty in the findings. The incidence

of major bleeding was similar between groups, 42 per 1000 for VKAs and 47 per 1000 patients taking rivaroxaban (RR 1.10; 95% CI, 0.45 to 2.68) (moderate quality evidence).¹ There was moderate quality of evidence that all-cause mortality rates were 19 per 1000 patients treated with VKAs and 28 per 1000 patients treated with rivaroxaban (RR 1.45; 95% CI, 0.44 to 4.78). There were 14 strokes with rivaroxaban compared to none in patients treated with VKA, (RR of 14.13; 95% CI, 1.87 to 106.81).¹ Confidence intervals suggest imprecision most likely due the low number of events (moderate quality of evidence). There was moderate quality of evidence of no difference in clinically relevant non-major bleeding between VKAs and rivaroxaban, 47 per 1000 and 80 per 1000 (RR 1.70; 95% CI, 0.69 to 4.19).¹

There were 2 studies (n=223) that compared high-dose VKA compared to standard-dose VKA. All evidence was graded as low quality.¹ There was no statistically significant differences between groups for the following outcomes: any thromboembolic events, major bleeding, all-cause mortality, or stroke. There were concerns of incomplete outcome reporting and selective outcome reporting in both studies and one study was underpowered due to poor recruitment, resulting in early termination. The risk for any bleeding was higher with high-dose VKA compared to standard-dose VKA (hazard ratio [HR] 2.03; 95% CI, 1.12 to 3.68).¹

One RCT (n=82) compared standard-dose VKA plus a single antiplatelet agent versus standard-dose VKA and found low to very low quality evidence for all outcomes studied.¹ There was a difference in the number of thrombotic events favoring standard-dose VKA compared to standard-dose VKA plus an antiplatelet agent, 184 per 1000 patients treated compared to 394 per 1000 patients, respectively (RR 2.14; 95% CI, 1.04 to 4.43).¹ There was no statistically significant differences demonstrated between the groups for all other outcomes studied. There was no allocation concealment in the trial, which downgraded the evidence. There was also imprecision due to the low number of events.

Cochrane – Interventions for Preventing Venous Thromboembolism in Adults Undergoing Knee Arthroscopy

Cochrane updated their 2007 review on VTE prevention in patients undergoing KA in 2020.² A literature search ending in August 2019 identified four new studies, bringing the total to 8 studies (n=3818). All studies were at low or unclear risk of bias. Patients were adults with no history of thromboembolism who were scheduled for KA. Drug treatments included: aspirin, LMWH, rivaroxaban 10 mg and aspirin.² All comparisons involved only one study with the exception of LMWH, in which there were 5. Results are limited to patients with no history of thrombosis due to exclusion of secondary prevention patients and patients with risk factors.

There were no deaths in any of the groups and the incidence of PE was low across all studies, which could be attributed to short durations of follow-up lasting from 30 days to 3 months.² In studies of LMWH compared to control (no prophylactic treatment) there was no difference in PE (assessed with CT arteriography) with a RR of 1.81 (95% CI, 0.49 to 6.65) (moderate quality evidence).² Symptomatic and asymptomatic DVT rates were not different between groups based on low to very low quality of evidence. Evidence was downgraded due to imprecision and indirectness. There was moderate quality evidence that the incidence of all adverse events, was not different between those randomized to control and those treated with LMWH, 13 per 1000 and 24 per 1000, respectively (RR 1.85; 95% CI, 0.95 to 3.59).² Major bleeding rates were 1 per 1000 for both control and LMWH (RR 0.98; 95% CI, 0.06 to 15.72) based on moderate quality evidence. Minor bleeding rates were also similar between groups (RR 1.79; 95% CI, 0.84 to 3.84).² There was imprecision in the results for adverse events and minor and major bleeding rates.

A study comparing rivaroxaban to placebo found moderate strength of evidence that the incidence in DVT was not clinically different between the groups (RR 0.16; 95% CI, 0.02 to 1.29).² Evidence was insufficient for data on risk of PE. There were no differences found between minor (RR 0.63; 95% CI, 0.18 to 2.19) and major bleeding rates (none reported in either group).

There was one study comparing aspirin to control; however, there were no events for PE, symptomatic or asymptomatic DVT in either group to inform treatment comparisons.²

Cochrane – Primary Prophylaxis for Venous Thromboembolism In Ambulatory Cancer Patients Receiving Chemotherapy

Primary prophylaxis for ambulatory patients with cancer and receiving chemotherapy were the focus of a 2020 Cochrane review, which updates a 2012 version.⁹ Active treatment was compared to placebo, or no treatment, in 6 (n=3326) newly identified trials. Participants were adult patients with locally advanced or metastatic cancer. Imprecision and high risk of bias resulted in downgrading the evidence for some outcomes.

The use of NOACs compared to placebo or no thromboprophylaxis was studied in 3 trials in high-risk populations with a median follow-up of 6 months. There was low quality evidence that NOACs may decrease the incidence of VTE (RR 0.42; 95% CI, 0.18 to 1.06), symptomatic PE (RR 0.38; 95% CI, 0.10 to 1.47) and symptomatic DVT (RR 0.51; 95% CI, 0.21 to 1.22).⁹ Moderate quality evidence reported an increase in major bleeding with NOACs compared to placebo, 32 per 1000 versus 18 per 1000 patients treated (RR 1.74; 95% CI, 0.82 to 3.68).⁹ The incidence of any DVT was lower with NOACs compared to placebo, 52 per 1000 patients treated versus 95 per 1000 patients treated (RR 0.55; 95% CI, 0.34 to 0.90) (moderate quality evidence).⁹ There was moderate quality evidence that the risk of clinically relevant bleeding was higher with NOACs compared to placebo, 52 per 1000 patients treated versus 32 per 1000 patients treated (RR 1.61; 95% CI, 0.82 to 3.15).⁹

There were 15 studies that evaluated the use of LMWH compared to no thromboprophylaxis. The evidence ranged from low to high with an average follow-up of 10 months (Table 1).⁹ While there was some variability in dosing strategies of LMWH, results were consistent, so there was no downgrading of the evidence due to dosing.

Table 1. LMWH Compared to No Thromboprophylaxis in for Primary Prevention of VTE in Ambulatory Cancer Patients at High-Risk⁹

Outcomes	Results	Strength of Evidence	Comments
Symptomatic VTE	RR 0.62; 95% CI, 0.46 to 0.83	High	There is high confidence that LMWH decreases the risk of VTE compared to no treatment
Major Bleeding	RR 1.63; 95% CI, 1.12 to 2.35	Moderate	There is high probability that LMWH increases the risk of major bleeding compared to no treatment
Symptomatic PE	RR 0.60; 95% CI, 0.42 to 0.88	Moderate	There is high probability that the risk of symptomatic PE is reduced with LMWH compared to no treatment
Symptomatic DVT	RR 0.48; 95% CI, 0.35 to 0.67	High	There is high confidence that LMWH decreases the risk of symptomatic DVE compared to no treatment
Any VTE	RR 0.57; 95% CI, 0.46 to 0.71	High	There is high confidence that the LMWH decreases the risk of any VTE compared to no treatment
1-year overall Mortality	RR 0.94; 95% CI, 0.83 to 1.07	Low	There is evidence that LMWH may decrease the incidence of death compared to no treatment
Clinically Relevant Bleeding	RR 3.40; 95% CI, 1.20 to 9.63	Moderate	There is high probability that LMWH increases the incidence of clinically relevant bleeding compared to no treatment

LMWH was compared to aspirin in 2 RCTs with a median follow-up of 18.5 months studied in patients with multiple myeloma.⁹ There was moderate quality evidence that symptomatic VTE rates were reduced with LMWH with an incidence of 20 per 1000 patients versus 39 per 1000 patients treated with aspirin (RR 0.51; 95% CI, 0.22 to 1.17).⁹ There was moderate quality evidence that LMWH reduces the risk of symptomatic PE compared to aspirin resulting in 15 per 1000 fewer events (RR 0.13; 95% CI, 0.02 to 1.03). The risk of symptomatic DVT with LMWH was reduced compared to aspirin by 5 per 1000 fewer events (RR 0.81; 95% CI, 0.32 to 2.04). The evidence for major bleeding was of low quality with an incidence for LMWH of 1 per 1000 treated compared to 7 per 1000 patients treated for aspirin.⁹

LMWH was compared to VKA in one RCT in patients with multiple myeloma patients at high-risk of VTE. There was high quality evidence that LMWH reduced the risk of symptomatic VTE compared to aspirin, 55 per 1000 fewer events (RR 0.33; 95% CI, 0.14 to 0.83).⁹ LMWH probably decreases the incidence of symptomatic DVT compared to VKA, 27 per 1000 versus 64 per 1000 (RR 0.43; 95% CI, 0.17 to 1.10). There was low quality evidence that symptomatic PE rates were reduced more with LMWH compared to VKA with 16 per 1000 fewer events (RR 0.11; 95% CI, 0.01 to 2.06); however, results were not statistically significant.⁹

One randomized controlled trial compared to VKA to aspirin in patients with multiple myeloma at intermediate-risk of VTE. VKA probably increases the risk of VTE compared to aspirin with an incidence of 82 per 1000 compared to 55 per 1000 patients treated with aspirin (RR 1.50; 95% CI, 0.74 to 3.04); however, results are not statistically significant and associated with some uncertainty (moderate quality evidence).⁹ There was moderate quality evidence that the incidence of symptomatic PE with VKAs is similar to aspirin with an incidence of 18 per 1000 patients treated in both groups (RR 1.00; 95% CI, 0.25 to 3.95). Symptomatic DVT incidence was higher with VKAs compared to ASA with 27 per 1000 patients treated (RR 1.75; 95% CI, 0.75 to 4.09); however, differences were not statistically significant (moderate quality evidence).⁹

The evidence for LMWH compared to active control and for VKAs compared to placebo was of low quality and no conclusions on efficacy could be determined. There was very low strength of evidence for outcomes comparing antithrombin versus no thromboprophylaxis.

Cochrane – Non-vitamin K Antagonist Oral Anticoagulants (NOACs) Post Percutaneous Coronary Intervention (PCI)

A recent Cochrane review studied the evidence for the use of NOACs compared to VKAs in patients post-PCI with a need for anticoagulation.³ Results were presented as a direct evidence comparison and as a network meta-analysis (NMA). There were 5 trials with a total of 8373 participants. There were 2 studies comparing apixaban to a VKA, 2 studies comparing rivaroxaban (2.5 mg [low dose] and 10 mg [high-dose]) to a VKA and one study comparing dabigatran (110 mg [low-dose] and 150 mg [high-dose]) to a VKA. Follow-up ranged from 6 months to 2.2 years.³

Evidence from the apixaban trials demonstrated moderate quality of evidence that death from CV causes was similar between apixaban and VKA with one more death per 1000 patients treated with apixaban compared to VKAs (direct: RR 1.06; 95% CI, 0.74 to 1.51 and NMA: 1.06; 95% CI, 0.41 to 2.275).³ The evidence comparing low dose rivaroxaban to VKAs and high-dose rivaroxaban to VKAs was very low quality for the outcome of death from CV causes and found no differences between groups.

There was moderate quality evidence that the incidence of MI was 30 fewer with apixaban compared to VKAs; same relative risk for both direct and NMA (0.89; 95% CI, 0.65 to 1.20); however, not statistically or clinically different.³ The evidence for rivaroxaban (low and high-dose) and dabigatran (low and high-dose) compared to VKAs was of low to very-low quality with no statistically significant findings. The evidence for the incidence of stroke was considered low to very low quality for all comparisons.

For the outcome of major bleeding, as defined by the Thrombolysis In Myocardial Infarction (TIMI) criteria, 7 fewer per 1000 patients experienced an episode if treated with apixaban compared to those treated with VKA (direct and NMA: RR 0.82 (95% CI, 0.55 to 1.21); which suggests no clinically significant differences and is not statistically different (moderate quality evidence).³ There was moderate quality evidence that low-dose dabigatran caused 23 fewer per 1000 cases of major bleeding compared to VKAs (direct and NMA: RR 0.38; 95% CI, 0.21 to 0.70).³ There was low to very low quality evidence for major bleeding outcomes for rivaroxaban (low and high dose) and dabigatran. Evidence was downgraded due to imprecision.

There was moderate quality evidence for the outcome of death from any cause that apixaban was associated with 8 more deaths per 1000 patients treated compared to VKAs, which was not statistically significant (direct and NMA: RR 1.18; 95% CI, 0.74 to 1.87).³ The evidence for rivaroxaban (low and high-dose) and dabigatran (low and high-dose) compared to VKAs was of low quality and demonstrated no clinically meaningful differences.

There was a non-significant reduction in stent thrombosis in patients treated with apixaban compared to VKAs based on moderate quality evidence, 6 per 1000 versus 8 per 1000 (direct: RR 0.78; 95% CI, 0.39 to 1.56 and NMA: RR 0.78; 95% CI, 0.39 to 1.56).³ The evidence for rivaroxaban (low and high-dose) and dabigatran (low and high-dose) compared to VKAs was considered low quality.

Cochrane – Treatment of Distal Deep Vein Thrombosis

A 2020 Cochrane review evaluated different treatments for people with distal (below the knee) DVT.⁴ Eight trials (n=1239) were included, five of which compared anticoagulants (e.g., VKAs) to placebo for 3 months and three trials evaluated the use of anticoagulants for different time periods.

There was high quality evidence that VKAs prevented more recurrent VTEs compared to placebo, 31 per 1000 versus 91 per 1000 (RR 0.34; 95% CI, 0.15 to 0.77).⁴ There were a small number of events but a large treatment effect maintaining the high certainty of results. The risk of recurrent DVT with use of VKAs was 20 per 1000 compared to 79 per 1000 on placebo (RR 0.25; 95% CI, 0.10 to 0.67) (high quality of evidence).⁴ There was high quality evidence that clinically relevant non-major bleeding was increased with VKAs compared to placebo by 43 more events per 1000 (RR 3.34; 95% CI, 1.07 to 10.46); however, wide confidence intervals suggest uncertainty in the findings.⁴ The evidence for the outcomes of PE, major bleeding and overall mortality were of low certainty and not statistically significant between groups.

Three trials, with up to 24 months follow-up, evaluated the effect of anticoagulation for 3 months or more compared to anticoagulation for 6 weeks in patients with distal DVT. There was high quality evidence that risk of recurrent VTE was 57 per 1000 for patients treated with 3 months or more of anticoagulation and 135 per 1000 for those treated with 6 weeks (RR 0.42; 95% CI, 0.26 to 0.68).⁴ The risk of recurrent DVT was reduced in patients treated with 3 months or longer compared to 6 weeks of therapy (RR 0.32; 95% CI, 0.16 to 0.64) (high quality evidence).⁴ The evidence for major bleeding, PE, and clinically relevant non-major bleeding was of low quality with large confidence intervals and uncertainty in conclusions. Overall mortality and mortality related to PE were not reported.

After review, 50 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).¹⁰⁻⁶⁰

New Guidelines:

High Quality Guidelines:

NICE – Venous Thromboembolic Diseases

NICE updated their 2015 guidance on the diagnosis and recommendations for treatment of thromboembolic diseases.⁵ Specific treatment recommendations are presented in **Table 2**. Treatment of DVT is focused on the diagnosis of proximal DVT as distal DVT is associated with less risk. Duration of anticoagulation treatment should be for at least 3 months for individuals with confirmed proximal DVT or PE. Patients with active cancer, and confirmed proximal DVT or PE, should be offered anticoagulation treatment for 3 to 6 months, dependent upon clinical need.⁵ There is insufficient evidence comparing inpatient versus outpatient treatment of patients at low-risk and have a confirmed PE and there is no evidence to suggest outpatient treatment is less effective or less safe. NICE recommends outpatient treatment for these patients with intensive monitoring and follow-up. There is insufficient evidence on interim anticoagulation treatment but recommend treatment if diagnostic tests are delayed for than 4 hours. Long-term anticoagulation, treatment beyond 3 months (6 months for patients with active cancer) was deemed most appropriate in patients with an unprovoked DVT or PE and at low risk of bleeding.

Table 2. NICE Recommendations for the Treatment of Thromboembolic Diseases⁵

Indication	Recommendation
Proximal DVT or PE with no relevant comorbidities or significant clinical features	<ul style="list-style-type: none">• Apixaban• Rivaroxaban• If neither of the above are suitable offer the following:<ul style="list-style-type: none">- LMWH for at least 5 days followed by dabigatran or edoxaban OR- LMWH concurrently with a VKA for at least 5 days, or until the INR is at least 2.0 in 2 consecutive readings, followed by VKA on its own• UFH should only be offered to patients with renal impairment or renal failure or an increased risk of bleeding
Proximal DVT or PE with renal impairment (CrCl 15 ml/min and 50 ml/min)	<ul style="list-style-type: none">• Apixaban• Rivaroxaban• LMWH for at least 5 days followed by<ul style="list-style-type: none">- Edoxaban- Dabigatran if estimated CrCL is 30 ml/min or above• LMWH or UFH, given with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by VKA on its own
Proximal DVT or PE with renal failure (CrCl of less than 15 ml/min)	<ul style="list-style-type: none">• LMWH• UFH• LMWH or UFH, given with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by VKA on its own
Proximal DVT or PE with triple positive antiphospholipid syndrome	<ul style="list-style-type: none">• LMWH, given with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings, followed by VKA on its own
Proximal DVT or PE with active cancer	<ul style="list-style-type: none">• Treatment with an anticoagulant for 3-6 months

	<ul style="list-style-type: none"> • Consider a NOAC • If a NOAC is unsuitable consider LMWH alone or LMWH concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in 2 consecutive readings
Treatment failure	<ul style="list-style-type: none"> • Increase dose of anticoagulant or change to an anticoagulant with a different mode of action
Long-term anticoagulation for secondary prevention	<ul style="list-style-type: none"> • Offer continued treatment with current anticoagulant if long-term anticoagulation is deemed appropriate OR • Consider changing patient to apixaban if they are being treated with a NOAC other than apixaban • If patients denies long-term anticoagulation treatment offer aspirin 75 mg daily or 150 mg daily
Proximal DVT or PE in patients with extremes of body weight	<ul style="list-style-type: none"> • Recommend anticoagulation with regular monitoring of therapeutic levels for those who weigh less than 50 kg or more than 120 kg to ensure effective anticoagulation (no specific drug recommendations were provided)
Abbreviations: CrCl – creatinine clearance; DVT- deep vein thrombosis; LMWH – low-molecular-weight heparin; NOACs – non-vitamin K oral anticoagulants; PE – pulmonary embolism; UFH – unfractionated heparin; VKA – vitamin K antagonist	

American Society of Hematology – Management of VTE: Treatment of DVT and PE

In 2020 the ASH updated guidance on the management of VTE, including the treatment recommendations for DVT and PE.⁶ The guideline was deemed good quality according to the AGREE II tool. Recommendations were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and assigned a “strong”, many patients would opt for the recommended treatment or action, or “conditional recommendation”, the majority of patients would want treatment or action but many would not. There are 17 recommendation pertaining to the use of anticoagulants (**Table 3**).

Table 3. Recommendations for the Management of VTE from the ASH⁶

Condition	Recommendation	Evidence	Strength of Recommendation
Patients with DVT and/or PE*	NOAC use over VKAS	Moderate	Conditional
Patients with DVT and/or PE	No preference in NOAC	Very low	Conditional
Patients with proximal DVT	Anticoagulation therapy alone over thrombolytic therapy and anticoagulation therapy	Low	Conditional
Patients with PE and hemodynamic compromise	Thrombolytic therapy followed by anticoagulation	Low	Strong
Patients with PE and echocardiographic and/or biomarkers compatible with right ventricular dysfunction but without hemodynamic compromise	Anticoagulation alone over use of thrombolysis in addition to anticoagulation	Low	Conditional
Patients with proximal DVT and significant preexisting cardiopulmonary disease as well as patients with PE and hemodynamic compromise	Anticoagulation alone versus anticoagulation plus insertion of an inferior vena cava (IVC) filter	Low	Conditional
Primary treatment of DVT and/or PE (due to TIA, chronic risk factor, or unprovoked)	Shorter courses of anticoagulation for primary treatment (3-6 months) versus longer courses (6-12 months)	Moderate	Conditional

Patients with chronic risk factors who finish primary treatment	Indefinite antithrombotic therapy	Moderate	Conditional
Patients with unprovoked DVT and/or PE who finish primary treatment	Indefinite antithrombotic therapy	Moderate	Conditional
Patients with DVT and/or PE who finish primary treatment and will continue to receive secondary prevention	Anticoagulation is recommended over aspirin	Moderate	Conditional
Patients with DVT and/or PE who have completed primary treatment and will continue with a DOAC for secondary prevention	Standard dose NOAC or a lower-dose DOAC (e.g., rivaroxaban 10 mg daily or apixaban 2.5 mg twice daily)	Moderate	Conditional
For patients with breakthrough DVT and/or PE during therapeutic VKA therapy	Switch to LMWH over a NOAC†	Very low	Conditional
For patients who develop DVT and/or PE provoked by a transient risk and have a history of previous unprovoked VTE or VTE provoked by a chronic risk factor	Indefinite antithrombotic therapy over stopping anticoagulation after completing primary treatment	Moderate	Conditional
Patients who develop DVT and/or PE provoked by a transient risk factor and have a history of previous VTE also provoke by a transient risk factor	Discontinue anticoagulation after completion of primary treatment	Moderate	Conditional
For patients with a recurrent unprovoked DVT and/or PE provoked by a transient risk factor	Indefinite antithrombotic therapy after completion of primary treatment	Moderate	Strong
For patients who develop DVT and/or PE with stable CVD who initiate anticoagulation and were previously taking aspirin for CV risk modification	Suspend aspirin over continuing it for the duration of anticoagulation treatment	Very low	Conditional
<p>Key: * Does not apply to patients with renal insufficiency (CrCl <30 ml/min), moderate to severe liver disease, or antiphospholipid syndrome; † Does not apply to patients with subtherapeutic INRs or those whom a NOAC may be a reasonable option</p> <p>Abbreviations: CrCl – creatinine clearance; CV – cardiovascular; CVD – cardiovascular disease; DVT- deep vein thrombosis; LMWH – low-molecular-weight heparin; NOACs – non-vitamin K oral anticoagulants; PE – pulmonary embolism; TIA – transient ischemic attack; VKA – vitamin K antagonist</p>			

AHA/ACC/HRS – Management of Patients with Atrial Fibrillation

The collaboration of three societies produced a 2019 guideline on the management of atrial fibrillation.⁷ The methods for guideline development and grading of the evidence, resulting in strength of guideline recommendation, are clearly described and presented in **Table 4**. This guideline serves as an update to the 2014 guidance.

Table 4. AHA/ACC/HRS Class Recommendation Definitions and Levels of Evidence (abbreviated)⁷

CLASS (STRENGTH) OF RECOMMENDATION	
Class I (Strong) Benefit >>>Risk	<ul style="list-style-type: none"> • Is recommended • Treatment A is recommended in preference to treatment B
Class IIa (Moderate) Benefit >>Risk	<ul style="list-style-type: none"> • Is reasonable • Treatment A is probably recommended in preference to treatment B
Class IIb (Weak) Benefit ≥Risk	<ul style="list-style-type: none"> • May/might be reasonable • Effectiveness is unknown or not well established
Class III: No benefit (Moderate) Benefit = Risk	<ul style="list-style-type: none"> • Is not recommended
Class III: Harm (Strong) Risk>Benefit	<ul style="list-style-type: none"> • Potentially harmful
LEVEL (QUALITY OF EVIDENCE)	
Level A	<ul style="list-style-type: none"> • High-quality evidence from more than 1 RCT • Meta-analysis of high-quality trials • One or more RCTs corroborated by high-quality registry studies
Level B-R (randomized)	<ul style="list-style-type: none"> • Moderate-quality evidence from one or more RCT • Meta-analysis of moderate quality trials
Level B-NR (not randomized)	<ul style="list-style-type: none"> • Moderate quality of evidence from 1 or more well-designed RCT, observational or registry studies • Meta-analysis of such studies
Level C-LD (limited data)	<ul style="list-style-type: none"> • Randomized or non-randomized observational or registry studies with limitations of design or execution • Meta-analysis of such studies • Physiological or mechanistic studies in human subjects
Level C-EO	<ul style="list-style-type: none"> • Consensus of expert opinion based on clinical experience

Pharmacological recommendations as they pertain to AF will be presented (**Table 5**). An update to the guideline is the use of the CHAD₂DS₂-VASc score, which is more precise. NOACs are recommended over warfarin due to evidence of being non-inferior or superior to warfarin in clinical trials with lower risks of bleeding.

Table 5. Recommendations from the AHA/ACC/HRS on Pharmacological Treatments for Patients with Atrial Fibrillation⁷

Condition	Recommendation	Class of Recommendation	Level of Evidence
For patients with AF and an elevated CHAD ₂ DS ₂ -VASc score or 2 or greater in women	<ul style="list-style-type: none"> • Oral anticoagulants are recommended: <ul style="list-style-type: none"> - Warfarin - Dabigatran - Rivaroxaban 	I for all	A B B

	<ul style="list-style-type: none"> - Apixaban - Edoxaban 		B B-R
In NOAC-eligible patients with AF*	<ul style="list-style-type: none"> • NOACs (see above) are recommended over warfarin (except those with mitral stenosis or a mechanical heart valve) 	I	A
In patients treated with warfarin	<ul style="list-style-type: none"> • INR should be determined weekly upon initiation and at least monthly when INR is stable 	I	A
Patients with AF and mechanical heart valves	<ul style="list-style-type: none"> • Warfarin is recommended 	I	B
Anticoagulant therapy selection	<ul style="list-style-type: none"> • Should be based on risk of thromboembolism, irrespective of AF pattern 	I	B
In patients prescribed NOACs	<ul style="list-style-type: none"> • Renal function should be evaluated before initiation and at least annually 	I	B-NR
In patients who anticoagulants are recommended	<ul style="list-style-type: none"> • Absolute risks and relative risk of stroke and bleeding risks should be discussed with the patient 	I	C
For patients with atrial flutter	<ul style="list-style-type: none"> • The same anticoagulant recommendations apply as those with patients with AF 	I	C
Patients on anticoagulant therapy for stroke	<ul style="list-style-type: none"> • Periodic assessment of stroke and bleeding risk with need and choice of anticoagulant should be done 	I	C
Patients who are unable to obtain a therapeutic INR*	<ul style="list-style-type: none"> • NOAC is recommended 	I	C-EO
For patients with AF and an elevated CHAD ₂ DS ₂ -VASC score of 0 in men or 1 in women*	<ul style="list-style-type: none"> • Anticoagulant therapy can be omitted 	IIa	B
For patients with AF and an elevated CHAD ₂ DS ₂ -VASC score of 2 or greater in men and 3 or greater in women and have end-stage chronic kidney disease (CrCl <15 mL/min) or are on dialysis	<ul style="list-style-type: none"> • May be reasonable to prescribe warfarin (INR 2.0-3.0) or apixaban 	IIb	B-NR
For patients with AF and an elevated CHAD ₂ DS ₂ -VASC score with moderate-to-severe CKD*	<ul style="list-style-type: none"> • Treatment with a reduced dose of NOAC may be considered 	IIb	B-R
For patients with AF and an elevated CHAD ₂ DS ₂ -VASC score of 1 in men or 2 in women	<ul style="list-style-type: none"> • Prescribing an oral anticoagulant may be considered 	IIb	C-LD
For patients with AF and end-stage CKD or on dialysis	<ul style="list-style-type: none"> • Rivaroxaban, dabigatran or edoxaban are not recommended 	III	C-EO
In patients with AF and a mechanical heart valve	<ul style="list-style-type: none"> • Dabigatran should not be used 	III	B-R
<p>Abbreviations: AF – atrial fibrillation; CHAD₂DS₂-VASC – congestive heart failure, hypertension, age 75 years or older (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65-74 years, sex category; CKD – chronic kidney disease; CrCl – creatinine clearance; INR – international normalized ratio; NOACs – non-vitamin K oral anticoagulants.</p> <p>Key: * Except with moderate-to-severe mitral stenosis or a mechanical heart valve</p>			

ASCO – VTE Prophylaxis and Treatment in Patients with Cancer

Guidance from the ASCO was updated in a 2020 guideline for the prophylaxis and treatment of VTE in patients with cancer.⁸ The guideline met criteria inclusion outlined in the Drug Use Research and Management methods. Evidence was graded from “insufficient to high” and recommendations were given a “weak to strong” designation. Recommendations pertaining to anticoagulant use are presented in **Table 6**. Recommendations for treatment of incidental PE and DVT are the same as symptomatic VTE.

Table 6. ASCO Recommendations for the Use of Anticoagulants for VTE Prophylaxis and Treatment in Patients with Cancer⁸

Condition	Recommendation	Evidence Quality	Strength of Recommendation
Hospitalized patients with active malignancy and acute medical illness or reduced mobility	Pharmacological thromboprophylaxis in absence of bleeding or other contraindications should be offered	Intermediate	Moderate
Hospitalized patients who have active malignancy without additional risk factors	Pharmacological thromboprophylaxis in absence of bleeding or other contraindications may be offered	Low	Moderate
Patients admitted for the sole purpose of minor procedures or chemotherapy infusion or stem-cell/bone-marrow transplantation	Routine thromboprophylaxis should not be offered	Insufficient	Moderate
Outpatient, ambulatory patients with cancer receiving systemic chemotherapy	Routine thromboprophylaxis should not be offered	Intermediate to high	Strong
High-risk outpatients with cancer*	May be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH if there are no significant risk factors for bleeding or drug interactions	Intermediate to high	Moderate
Patients with multiple myeloma receiving thalidomide or lenalidomide-based regimens with chemotherapy and/or dexamethasone	Pharmacological thromboprophylaxis should be offered with aspirin or LMWH in lower-risk patients and LMWH for higher-risk patients	Intermediate	Strong
Patients with cancer undergoing major surgical intervention	Pharmacological thromboprophylaxis should be offered with UFH or LMWH unless contraindicated (including bleeding)	Intermediate	Strong
Patients with cancer undergoing major surgical intervention	Pharmacological thromboprophylaxis should be started preoperatively	Intermediate	Moderate

Patients with cancer undergoing major surgical intervention	Pharmacological thromboprophylaxis and mechanical prophylaxis may improve efficacy	Intermediate	Strong
Patients with cancer undergoing major surgical intervention	Pharmacological thromboprophylaxis should be continued for a least 7 to 10 days and up to 4 weeks	High	Strong
Patients with cancer with established VTE	Initial anticoagulation may involve LMWH, UFH, fondaparinux or rivaroxaban For patients initiating parenteral anticoagulation, LMWH is preferred over UFH for the initial 5 to 10 days in patients with a newly diagnosed VTE without severe renal impairment	High	Strong
Patients with cancer with established VTE on long-term anticoagulation	LMWH, rivaroxaban, or edoxaban for at least 6 months are preferred over VKAs VKAs may be used if LMWH or NOACs are not assessible	High	Strong
Patients with cancer (metastatic disease or those receiving chemotherapy) with established VTE on long-term anticoagulation	Anticoagulation beyond 6 months should be offered and assessed on an intermittent basis to ensure a favorable risk-benefit profile	Low	Weak to moderate (consensus recommendation)
Patients with primary or metastatic CNS malignancies and established VTE	Anticoagulation as previously described should be offered; however, uncertainties on choice of agent remain	Low	Moderate
Patients with cancer without established VTE	Anticoagulant use is not recommended	High	Strong
Abbreviations: CNS- central nervous system; LMWH – low-molecular weight heparin; NOACs – non-vitamin K oral anticoagulants; UFU – unfractionated heparin; VKAs – vitamin-K antagonists; VTE – venous thromboembolism Key: * Khorana score of 2 or higher prior to starting a new systemic chemotherapy			

After review, one guideline was excluded due to poor quality.⁶¹

New Formulations:

None identified

New Indications:

Rivaroxaban (Xarelto) – In October 2019 rivaroxaban was approved for use in for prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications in patients not at high risk of bleeding.⁶² Evidence for the new indication for rivaroxaban was from the MAGELLAN study, a multicenter, double-blind, parallel-group RCT which compared rivaroxaban 10 mg daily for 35 days to enoxaparin 40 mg daily for 10 days. Patients were at least 40 years of age with additional risk factors for VTE. The primary endpoint (composite of asymptomatic proximal DVT in lower extremity, symptomatic non-fatal PE, and death related to VTE) measured at day 35 occurred in 4.4% of patients receiving rivaroxaban and 5.7% of patients treated with enoxaparin (RR 0.77; 95% CI, 0.62 to 0.96). Results were not available for 25% of patients due to lack of untrasonographic assessment (13.5%), inadequate assessment (8.1%) or lack of intake of study medication (1.3%).

New FDA Safety Alerts:

Table 7. 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)
Apixaban ⁶³	Eliquis	11/2019	Warnings and Precautions	Increase risk of thrombosis in patients with triple positive antiphospholipid syndrome – use not recommended
Betrixaban ⁶⁴	Bevyxxa	08/2020	Warnings and Precautions	Increase risk of thrombosis in patients with triple positive antiphospholipid syndrome – use not recommended
Dabigatran ⁶⁵	Pradaxa	11/2019	Warnings and Precautions	Increase risk of thrombosis in patients with triple positive antiphospholipid syndrome – use not recommended
Edoxaban ⁶⁶	Savaysa	04/2020	Warnings and Precautions	Increase risk of thrombosis in patients with triple positive antiphospholipid syndrome – use not recommended
Rivaroxaban ⁶²	Xarelto	10/2019	Warnings and Precautions	Increase risk of thrombosis in patients with triple positive antiphospholipid syndrome – use not recommended
Rivaroxaban ⁶⁷	Xarelto	11/2019	Dosage and Administration	Updates to the dosing in patient with renal impairment
Rivaroxaban ⁶⁸	Xarelto	03/2020	Warnings and Precautions	Not recommended for use in patients with prosthetic heart valves

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Appendix 1: Current Preferred Drug List

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

Appendix 2: New Comparative Clinical Trials

A total of 190 citations were manually reviewed from the initial literature search. After further review, 2 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 188 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 8. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Bonaca M, et al ⁶⁹ (VOYAGER PAD)	Rivaroxaban 2.5 mg twice daily + aspirin 100 mg Vs.	Patients 50 years or older with peripheral artery disease who had undergone revascularization	Composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes	Rivaroxaban 2.5 mg twice daily + aspirin: 508 (15.5%) Placebo + aspirin: 584 (17.8) HR 0.85 (95% CI, 0.76 to 0.96) P=0.009

Phase III, DB, PC, MC, RCT	Placebo + aspirin 100 mg Follow-up: 3 years	(n=6564)		
Dangas G, et al ⁷⁰ (GALILEO) Phase III, OL, MC, RCT	Rivaroxaban 10 mg daily (+ Aspirin 75 – 100 mg for the first 3 months) Vs. Aspirin 75 – 100 mg (+ clopidogrel 75 mg for the first 3 months) Median follow-up: 17 months	Patients without and established indication for oral anticoagulation after successful transcatheter aortic-valve replacement (TAVR) (n=1654)	Composite of death or first thromboembolic event	Rivaroxaban: 105 Aspirin: 78 HR 1.35; 95% CI, 1.01 to 1.81 P=0.04

Abbreviations: DB – double-blind; MC – multi-center; OL – open label; PC – placebo controlled; RCT = randomized clinical trial; etc.

Appendix 3: Abstracts of Comparative Clinical Trials

Rivaroxaban in Peripheral Artery Disease after Revascularization

Marc Bonaca, Rupert M Bauersachs, Sonia S Anand, E Sebastian Debus, Mark R Nehler, Manesh R Patel, Fabrizio Fanelli, Warren H Capell, Lihong Diao, Nicole Jaeger, Connie N Hess, Akos F Pap, John M Kittelson, Ivan Gudz, Lajos Mátyás, Dainis K Krievins, Rafael Diaz, Marianne Brodmann, Eva Muehlhofer, Lloyd P Haskell, Scott D Berkowitz, William R Hiatt

Abstract

Background: Patients with peripheral artery disease who have undergone lower-extremity revascularization are at high risk for major adverse limb and cardiovascular events. The efficacy and safety of rivaroxaban in this context are uncertain.

Methods: In a double-blind trial, patients with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin or placebo plus aspirin. The primary efficacy outcome was a composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes. The principal safety outcome was major bleeding, defined according to the Thrombolysis in Myocardial Infarction (TIMI) classification; major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) was a secondary safety outcome.

Results: A total of 6564 patients underwent randomization; 3286 were assigned to the rivaroxaban group, and 3278 were assigned to the placebo group. The primary efficacy outcome occurred in 508 patients in the rivaroxaban group and in 584 in the placebo group; the Kaplan-Meier estimates of the incidence at 3 years were 17.3% and 19.9%, respectively (hazard ratio, 0.85, 95% confidence interval [CI], 0.76 to 0.96; P = 0.009). TIMI major bleeding occurred in 62 patients in the rivaroxaban group and in 44 patients in the placebo group (2.65% and 1.87%; hazard ratio, 1.43; 95% CI, 0.97 to 2.10; P = 0.07). ISTH major bleeding occurred in 140 patients in the rivaroxaban group, as compared with 100 patients in the placebo group (5.94% and 4.06%; hazard ratio, 1.42; 95% CI, 1.10 to 1.84; P = 0.007).

Conclusions: In patients with peripheral artery disease who had undergone lower-extremity revascularization, rivaroxaban at a dose of 2.5 mg twice daily plus aspirin was associated with a significantly lower incidence of the composite outcome of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes than aspirin alone. The incidence of TIMI major bleeding did not differ significantly between the groups. The incidence of ISTH major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone. (Funded by Bayer and Janssen Pharmaceuticals; VOYAGER PAD ClinicalTrials.gov number, NCT02504216.)

A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement

George D Dangas, Jan G P Tijssen, Jochen Wöhrle, Lars Søndergaard, Martine Gilard, Helge Möllmann, Raj R Makkar, Howard C Herrmann, Gennaro Giustino, Stephan Baldus, Ole De Backer, Ana H C Guimarães, Lars Gullestad, Annapoorna Kini, Dirk von Lewinski, Michael Mack, Raúl Moreno, Ulrich Schäfer, Julia Seeger, Didier Tchéché, Karen Thomitzek, Marco Valgimigli, Pascal Vranckx, Robert C Welsh, Peter Wildgoose, Albert A Volkl, Ana Zazula, Ronald G M van Amsterdam, Roxana Mehran, Stephan Windecker, GALILEO Investigators

Abstract

Background: Whether the direct factor Xa inhibitor rivaroxaban can prevent thromboembolic events after transcatheter aortic-valve replacement (TAVR) is unclear.

Methods: We randomly assigned 1644 patients without an established indication for oral anticoagulation after successful TAVR to receive rivaroxaban at a dose of 10 mg daily (with aspirin at a dose of 75 to 100 mg daily for the first 3 months) (rivaroxaban group) or aspirin at a dose of 75 to 100 mg daily (with clopidogrel at a dose of 75 mg daily for the first 3 months) (antiplatelet group). The primary efficacy outcome was the composite of death or thromboembolic events. The primary safety outcome was major, disabling, or life-threatening bleeding. The trial was terminated prematurely by the data and safety monitoring board because of safety concerns.

Results: After a median of 17 months, death or a first thromboembolic event (intention-to-treat analysis) had occurred in 105 patients in the rivaroxaban group and in 78 patients in the antiplatelet group (incidence rates, 9.8 and 7.2 per 100 person-years, respectively; hazard ratio with rivaroxaban, 1.35; 95% confidence interval [CI], 1.01 to 1.81; $P = 0.04$). Major, disabling, or life-threatening bleeding (intention-to-treat analysis) had occurred in 46 and 31 patients, respectively (4.3 and 2.8 per 100 person-years; hazard ratio, 1.50; 95% CI, 0.95 to 2.37; $P = 0.08$). A total of 64 deaths occurred in the rivaroxaban group and 38 in the antiplatelet group (5.8 and 3.4 per 100 person-years, respectively; hazard ratio, 1.69; 95% CI, 1.13 to 2.53).

Conclusions: In patients without an established indication for oral anticoagulation after successful TAVR, a treatment strategy including rivaroxaban at a dose of 10 mg daily was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet-based strategy. (Funded by Bayer and Janssen Pharmaceuticals; GALILEO ClinicalTrials.gov number, NCT02556203.).

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) ALL 1946 to December 31, 2020

Search Strategy:

#	Searches	Results
1	apixaban.mp.	4039
2	dabigatran.mp. or Dabigatran/	5684
3	dalteparin.mp. or Dalteparin/	1359
4	edoxaban.mp.	1688
5	enoxaparin.mp. or Enoxaparin/	5542
6	rivaroxaban.mp. or Rivaroxaban/	6291
7	warfarin.mp. or Warfarin/	30958
8	betrixaban.mp.	191
9	fondaparinux.mp. or Fondaparinux/	2000
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	44098
11	limit 10 to (english language and humans and yr="2019 -Current")	2683
12	limit 11 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	190

Appendix 5: Key Inclusion Criteria

Population	Patients with an indication for anticoagulation
Intervention	Anticoagulants
Comparator	Placebo or active treatment comparisons
Outcomes	Incidence of venous thromboembolism, deep vein thrombosis, or pulmonary embolism; stroke, mortality, bleeding
Timing	Prophylaxis or treatment
Setting	Inpatient or outpatient