PHARMACIST'S LETTER

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PHARMACIST'S LETTER / PRESCRIBER'S LETTER
May 2016

PRESCRIBER'S LETTER

Comparison of Oral Anticoagulants

The recent proliferation of oral anticoagulants has healthcare professionals questioning how to choose among them. The newest oral anticoagulants are apixaban (*Eliquis*), dabigatran (*Pradaxa*), edoxaban (*Savaysa*, U.S.; *Lixiana*, Canada), rivaroxaban (*Xarelto*), and betrixaban (*Bevyxxa*, U.S.). The following chart compares the indications, clinical benefit, antidotes, washout, switching to/from warfarin, and other therapeutic considerations for these agents.

Abbreviations: A fib = atrial fibrillation; AV = arteriovenous; BID = twice daily; CABG = coronary artery bypass graft; CAD = coronary artery disease; CrCl = creatinine clearance; DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low molecular weight heparin; MI = myocardial infarction; NNT = number needed to treat; PCI = percutaneous coronary intervention; PE = pulmonary embolism; P-gp = p-glycoprotein; PTCA = percutaneous transluminal coronary angioplasty; TIA = transient ischemic attack; VTE = venous thromboembolism.

Apixaban (*Eliquis*) (direct factor Xa inhibitor)	
Approved Indications and Usual Dose	U.S.:[1] • Thromboembolism (e.g., stroke) prevention in nonvalvular A fib (5 mg BID; 2.5 mg BID for patients with two or more of the following: age 80 years and older, weight 60 kg or less, serum creatinine 1.5 mg/dL or greater) • VTE prevention post-hip or knee replacement (2.5 mg twice daily for 35 days [hip] or 12 days [knee] starting 12 to 24 hrs post-op) • DVT/PE treatment (10 mg BID for seven days, then 5 mg BID) • DVT/PE prevention of recurrence (2.5 mg BID after at least six months of treatment) Canada:[2] • Thromboembolism (e.g., stroke) prevention in A fib (in patients with CrCl ≥25 mL/min., 5 mg BID; 2.5 mg BID for patients with two or more of the following: age 80 years and older, weight 60 kg or less, serum creatinine 133 umol/L or greater). Data limited if CrCl 15 to 24 mL/min; no dosing recommendation can be made.[2] • VTE prevention post-hip or knee replacement (2.5 mg twice daily for 32 to 38 days [hip] or 10 to 14 days [knee], starting 12 to 24 hrs post-op, assuming hemostasis achieved) • DVT/PE treatment (10 mg BID for seven days, then 5 mg BID) • DVT/PE prevention of recurrence (2.5 mg BID after at least six months of treatment)
Renal Dosing	• A fib indication, see above. Based on limited data, a dose of apixaban 2.5 mg BID instead of 5 mg BID might be considered in hemodialysis patients.[45,47] Canada: not recommended if CrCl <15 mL/min or on dialysis.[2] • DVT/PE prevention/recurrence indications, Canada: caution if CrCl 15 to 29 mL/min, but no dosage adjustment recommended. Not recommended if CrCl <15 mL/min or on dialysis.[2]

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Apixaban, continued	
Clinical Benefit In…[a]	A fib: for every 1000 patients treated per year, apixaban prevents three more strokes, avoids ten major bleeds, and prevents four deaths compared to warfarin.[3] Post-hip/knee replacement: at least as effective as enoxaparin for preventing VTE; comparable bleeding.[4,5] DVT/PE treatment/prevention of recurrence: comparable to enoxaparin/warfarin for prevention of recurrent VTE or VTE death (combined endpoint); less bleeding.[40]
Antidote/pre-op, pre-procedure washout (if indicated)	No specific antidote. See our chart, *Managing Bleeding with the New Oral Anticoagulants*, and commentaries, *Stopping Antithrombotics Before Surgery* and *Managing Antithrombotics Before Minor Procedures*.
Therapeutic Considerations	• Requires BID dosing.[1,2] • Not recommended in patients with prosthetic heart valves.[1,2] Canada: not recommended in hemodynamically significant rheumatic heart disease, especially mitral stenosis.[2] • Severe liver impairment: not recommended (U.S.).[1] Canada: contraindicated in hepatic disease with coagulopathy and clinically significant bleeding risk.[2] • Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement.[17] • For VTE treatment, continue for at least three months.[18] Benefit of extended use may not outweigh risk in patients with high bleeding risk.[18]
Switching To/From Other Anticoagulants	• To switch from warfarin, stop warfarin, then start apixaban when INR <2.[1,2] • To switch to warfarin: apixaban increases INR, thus confounding initial warfarin dosing.[1,2] U.S.: Consider starting a parenteral anticoagulant plus warfarin when the next dose of apixaban would have been due, then discontinuing the parenteral agent when the INR reaches the desired range.[1] Canada: continue apixaban with warfarin until the INR is >2. Use the "usual" initial warfarin dose for the first two days. Thereafter, check INR just prior to the next dose of apixaban to minimize apixaban interference with the INR.[2] • See product labeling for instructions for switching to/from other anticoagulants.
Select Drug Interactions *Continued…*	• U.S.: reduce dose by 50% with strong inhibitors of BOTH CYP3A4 and P-gp (e.g., itraconazole, ketoconazole, ritonavir, clarithromycin). Avoid in patients already taking 2.5 mg BID.[1] Canada: contraindicated. Canadian contraindication also includes posaconazole, voriconazole, and HIV protease inhibitors.[2] • Avoid strong inducers of BOTH CYP3A4 and P-gp (e.g., carbamazepine, phenytoin, phenobarbital, St. John's wort, rifampin).[1,2] • Caution with antiplatelets and anticoagulants (U.S.).[1] Canada: anticoagulants contraindicated; caution with

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Apixaban, continued	
Select Drug Interactions, Continued	antiplatelets. Prasugrel and ticagrelor not recommended.[2] • Dual antiplatelet therapy about doubles bleeding risk.[6]
Cost of 30-day supply[b]	2.5 mg BID or 5 mg BID. U.S.: $359.92, Canada: $103.68
Betrixaban (*Bevyxxa* [U.S.]) (direct factor Xa inhibitor)	
Approved Indications and Usual Dose	• VTE prevention in acutely ill medical, non-surgical patients with moderate or severely limited mobility plus other VTE risk factors (160 mg x 1, then 80 mg once daily **with food**, for 35 to 42 days)[48]
Renal dosing	• For CrCl 15 to <30 mL/min (calculated using actual body weight): 80 mg x 1, then 40 mg once daily **with food** for 35 to 42 days.[48] • Patients with CrCl <15 mL/min, dialysis patients, and patients likely to need dialysis within three months were excluded from the clinical trial used for FDA approval.[49] • It is unknown if betrixaban is removed by hemodialysis.[48]
Clinical Benefit In…[a]	• VTE prevention in acutely ill medical patients: vs about 10 days' treatment with enoxaparin, NNT to prevent one symptomatic event (symptomatic DVT, non-fatal PE, or VTE death) = 167.[48] NNT = 63 to prevent one asymptomatic or symptomatic VTE.[49] Comparable major bleeding, but NNH = 90 for clinically important (but nonmajor) bleeding that may require prescriber contact, intervention (e.g., drug discontinuation), or patient discomfort.[48] NNT = 170 to prevent one VTE-related readmission.[51]
Antidote/pre-op, pre-procedure washout (if indicated)	• No specific antidote. See our chart, *Managing Bleeding with the New Oral Anticoagulants*, for general information. • Half-life 19 to 27 hours.[48] Expect betrixaban's effect to last for at least 72 hours after the last dose.[48] • Do not remove epidural catheter sooner than 72 hours after the last dose, and do not give betrixaban sooner than five hours after catheter removal. Delay betrixaban use for 72 hours in the event of traumatic puncture.[48]
Therapeutic Considerations	• U.S. approval was based on the APEX clinical trial.[48] Enrolled patients were at high risk of VTE. Patients were required to have an elevated D-dimer or be 75 years or older, in addition to having restricted mobility plus decompensated heart failure, acute respiratory failure, infection, ischemic stroke, or acute rheumatic disease.[49] • Notable APEX **exclusion criteria** included body weight <45 kg; dual antiplatelet therapy; recent significant bleeding, trauma, peptic ulcer disease, or major surgery; potential need for major surgery; active lung cancer; or low platelets.[49] • Not indicated for patients with prosthetic heart valves due to lack of data.[48] • Avoid use in hepatic impairment.[48] • Less than 6% of betrixaban patients in the trial used for FDA approval had a CrCl of 15 to <30 mL/min.[49] • Few APEX enrollees had a history of cancer or VTE. Only 18% received a reduced dose due to P-gp interaction.[49]

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Betrixaban, continued	
Switching To/From Other Anticoagulants	• No data.
Select Drug Interactions	• Reduce dose to 40 mg once daily (after 80 mg loading dose) with strong P-gp inhibitors (e.g., amiodarone, azithromycin, clarithromycin, ketoconazole, verapamil).[48] Patients with CrCl 15 to <30 mL/min requiring a strong P-gp inhibitor were excluded from the clinical trial used for FDA approval.[49] Avoid in such patients.[48] • Caution with antiplatelets and anticoagulants.[48] Not studied in patients requiring dual antiplatelet therapy.[49]
Cost of 30-day supply[b]	40 or 80 mg once daily. U.S.: $450[c]
Dabigatran (*Pradaxa*) (direct thrombin inhibitor)	
Approved Indications and Usual Dose	U.S.:[7] • Thromboembolism (e.g., stroke) prevention in nonvalvular A fib (150 mg BID) • DVT/PE treatment (following 5 to 10 days' treatment with a parenteral anticoagulant)/prevention of recurrence (150 mg BID). (Start 0 to 2 hours before the next dose of parenteral anticoagulant would have been due, or at the time of discontinuation of heparin drip.) • VTE prevention post-hip replacement (220 mg once daily x 28 to 35 days. If started on day of surgery [1 to 4 hrs post-op, assuming hemostasis achieved], initial dose is 110 mg). Canada:[8] • Thromboembolism (e.g., stroke) prevention in A fib (150 mg BID; 110 mg BID for patients ≥80 years, and for patients at higher risk of bleeding, including patients ≥75 years of age with at least one other bleeding risk factor; also consider for other elderly. • VTE prevention post-hip or knee replacement (220 mg once daily x 10 days [knee] or 28 to 35 days [hip]. If started on day of surgery, normally within 1 to 4 hrs post-op, assuming hemostasis achieved, initial dose is 110 mg. Consider 150 mg once daily for patients over 75 years). • DVT/PE treatment (following 5 to 10 days' treatment with a parenteral anticoagulant)/prevention of recurrence (150 mg BID; 110 mg BID for patients ≥80 years, and for patients at higher risk of bleeding, including patients ≥75 years of age with at least one other bleeding risk factor). (Start 0 to 2 hours before the next dose of parenteral anticoagulant would have been due, or at the time of discontinuation of heparin drip.)
Renal Dosing *Continued…*	• Check renal function at baseline, yearly (Canada), and when clinically indicated.[7,8] • Also see drug interactions section, below. • Canada, contraindicated if CrCl <30 mL/min.[8] • A fib (U.S.): use 75 mg BID if CrCl 15 to 30 mL/min.[7] No dosing information for CrCl <15 mL/min or dialysis.[7] • DVT/PE treatment/prevention and VTE prevention post-hip replacement (U.S.): no dosing information for CrCl ≤30 mL/min or dialysis.[7]

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Dabigatran, continued	
Renal dosing, continued	• DVT/PE treatment/prevention (Canada): for CrCl 30 to 50 mL/min., a dose reduction to 110 mg BID can be considered based on risk/benefit, but is not recommended.[8] • VTE prevention post-hip/knee replacement (Canada): for CrCl 30 to 50 mL/min., dose is 150 mg once daily. If started on day of surgery, normally within 1 to 4 hrs post-op, assuming hemostasis is achieved, initial dose is 75 mg.[8]
Clinical Benefit In…[a]	A fib: prevents about five more strokes per 1000 patients per year than warfarin. Lower rate of hemorrhagic and ischemic stroke, higher rate of major GI bleed, comparable overall bleeding.[10] Post-hip/knee replacement: comparable to enoxaparin for prevention of VTE & mortality (combined endpoint); comparable major bleeding.[11-13] DVT/PE treatment/prevention of recurrence: comparable to warfarin for prevention of recurrent VTE or VTE death (combined endpoint); comparable major bleeding.[14]
Antidote/pre-op, pre-procedure washout (if ind.)	Reversal agent: *Praxbind* (idarucizumab). See our chart, *Managing Bleeding with the New Oral Anticoagulants*, and commentaries, *Stopping Antithrombotics Before Surgery* and *Managing Antithrombotics Before Minor Procedures*.
Therapeutic Considerations	• Requires BID dosing for A fib and DVT/PE treatment/prevention indications.[7,8] • Causes gastrointestinal symptoms in over 10% of patients.[7] • Caution if 75 years or older, poor renal function, or underweight.[7-9] • Contraindicated with mechanical heart valve, and not recommended with bioprosthetic valves (U.S.).[7] Canada: contraindicated in patients requiring anticoagulation for a prosthetic heart valve. Not recommended in patients with hemodynamically significant rheumatic heart disease, especially mitral stenosis.[8] • Dispense/store in original package.[7,8] Once bottle opened, use within 4 months.[7,8] • For VTE treatment, continue for at least three months.[8,18] Benefit of extended use may not outweigh risk in patients with high bleeding risk.[18] • Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement.[17]
Switching To/From Other Anticoagulants	• To switch from warfarin, stop warfarin, then start dabigatran when INR <2.[7,8] • To switch to warfarin, start warfarin three days (if CrCl ≥50 mL/min), two days (if CrCl 30 to 50 mL/min), or one day (if CrCl 15 to 30 mL/min [U.S.]) before discontinuing dabigatran.[7,8] No recommendations are available for patients with CrCl <15 mL/min.[7] • See product labeling for instructions for switching to/from other anticoagulants.

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Dabigatran, continued	

Select Drug Interactions	• P-gp inhibitors may increase dabigatran levels.[7,8]
	  • Ketoconazole and other strong P-gp inhibitors contraindicated (Canada).[8]
	  • A fib indication (U.S.): avoid P-gp inhibitors if CrCl <30 mL/min.[7] Reduce dose to 75 mg BID with ketoconazole or dronedarone if CrCl 30 to 50 mL/min.[7]
	  • VTE/PE treatment/prevention (including post-hip replacement)(U.S.):[7] avoid use of P-gp inhibitors if CrCL <50 mL/min.[7]
	  • VTE prevention post-hip/knee replacement (Canada): use 150 mg once daily with the P-gp inhibitors amiodarone, verapamil, and quinidine. Consider 75 mg once daily in patients taking verapamil who also have moderate renal impairment.[8] Verapamil initiation should be avoided following orthopedic surgery in patients already taking dabigatran.[8]
	  • Give dabigatran 2 hrs before quinidine (A fib) or verapamil (Canada).[8]
	• P-gp inducers could decrease dabigatran efficacy.[7,8] Avoid P-gp inducers per U.S. labeling (Canada: avoid stronger inducers [e.g., rifampin, carbamazepine, phenytoin, St. John's wort]).[7,8]
	• Caution with antiplatelets.[7,8] Ticagrelor or prasugrel not recommended (Canada).[8] Use with aspirin 100 mg or less can be considered.[8] Co-administration with aspirin or clopidogrel about doubles bleeding risk.[8] Caution with anticoagulants (Canada: contraindicated).[7,8]
	• Drugs that increase gastric pH could reduce efficacy. Take dabigatran at least 2 hrs before antacids. Avoid antacids for 24 hrs after hip/knee replacement (Canada).[8]

Cost of 30-day supply[b]	150 mg BID. U.S.: $333.57, Canada: $106.80 (*Pradaxa* savings card can reduce out-of-pocket cost by up to $2400 per year for U.S. patients with private insurance. Other patients can get a free 30-day supply at www.pradaxa.com.)
Edoxaban (*Savaysa* [U.S.], *Lixiana* [Canada]) (direct factor Xa inhibitor)	
Approved Indications and Usual Dose	U.S.:[41] • Thromboembolism (e.g., stroke) prevention in nonvalvular A fib in patients with **CrCl >50 to ≤95 mL/min** (60 mg once daily). • DVT/PE treatment (following 5 to 10 days' treatment with a parenteral anticoagulant) (60 mg once daily; 30 mg once daily if body weight ≤60 kg). Canada:[44] • Thromboembolism (e.g., stroke) prevention in nonvalvular A fib in patients (60 mg once daily; 30 mg once daily if body weight ≤60 kg). • DVT/PE treatment/prevention of recurrence (following 5 to 10 days' treatment with a parenteral anticoagulant) (60 mg once daily; 30 mg once daily if body weight ≤60 kg).

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Edoxaban (*Savaysa* [U.S.], *Lixiana* [Canada]), continued	
Renal Dosing	U.S.:[41] • A fib: 60 mg once daily for CrCl >50 to ≤95 mL/min, or 30 mg once daily for CrCl 15 to 50 mL/min. Not for use in patients with CrCl >95 mL/min. • DVT/PE treatment: 30 mg once daily for CrCl 15 to 50 mL/min. • Not recommended if CrCl <15 mL/min. Canada:[44] • 30 mg once daily for CrCl 30 to 50 mL/min. • Not recommended if CrCl <30 mL/min.
Clinical Benefit In…[a]	A fib: about as effective as warfarin, with lower risk of major bleeding (six fewer bleeds per 1000 patients per year).[42] (Also see "Therapeutic Considerations," below.) DVT/PE treatment: About as effective as warfarin, with less bleeding (18 fewer bleeds [composite of major plus clinically relevant nonmajor bleeding] per 1000 patients per year).[43]
Antidote/pre-op, pre-procedure washout (if indicated)	No specific antidote. See our chart, *Managing Bleeding with the New Oral Anticoagulants*. Discontinue at least 24 hours before invasive procedures/surgery.[41,44] Canada: consider stopping at least 48 hours if complete hemostasis is desired or in patients at particularly high bleeding risk.[44] See our commentaries, *Stopping Antithrombotics Before Surgery* and *Managing Antithrombotics Before Minor Procedures*.
Therapeutic Considerations	• For A fib, concerns that efficacy may be less than warfarin at higher CrCl is reflected in the U.S. prescribing information, but Canadian labeling does not reflect these concerns. Numerical differences are small and not statistically significant.[41,44] • Not recommended in patients with mechanical heart valves or moderate to severe mitral stenosis (U.S.).[41] Canada: not recommended in patients with prosthetic heart valves or hemodynamically significant rheumatic heart disease, especially mitral stenosis.[44] • For VTE treatment, continue for at least three months.[18] Benefit of extended use may not outweigh risk in patients with high bleeding risk.[18] • Not recommended in moderate or severe hepatic impairment (U.S.).[41] Canada: not recommended in severe hepatic impairment. Contraindicated in hepatic disease with coagulopathy and clinically significant bleeding risk.[44]
Switching To/From Other Anticoagulants	• To switch from warfarin, stop warfarin, then start edoxaban when INR ≤2.5.[41,44] • To switch to warfarin, reduce edoxaban dose by half and start warfarin. Check INR at least weekly, just prior to edoxaban dose. Stop edoxaban once INR is ≥2 and is stable.[41,44] Alternatively, stop edoxaban and "bridge" with a parenteral anticoagulant until INR is ≥2 and is stable.[41,44] • See product labeling for instructions for switching to/from other anticoagulants.

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Edoxaban (*Savaysa* [U.S.], *Lixiana* [Canada]), continued	
Select Drug Interactions	• Use with anticoagulants not recommended (Canada: contraindicated, except when switching).[41,44] Caution with antiplatelets.[41,44] • Avoid rifampin (P-gp inducer).[41] Canadian labeling also recommends avoiding use of other strong CYP3A4 and P-gp inducers (e.g. phenytoin, carbamazepine, phenobarbital).[44] • U.S.: Reduce dose to 30 mg once daily for DVT/PE indication in patients taking certain P-gp inhibitors (e.g., azithromycin, clarithromycin, erythromycin, itraconazole [oral], ketoconazole [oral], quinidine, or verapamil).[41] Canada: reduce dose to 30 mg once daily with certain P-gp inhibitors (e.g., cyclosporine, dronedarone, erythromycin, ketoconazole, quinidine, but NOT amiodarone or verapamil).[44]
Cost of 30-day supply[b]	60 mg or 30 mg once daily. U.S.: $291.30, Canada: $92.02 *Savaysa* savings card can reduce out-of-pocket cost to U.S. patients with private insurance to $4 per month (www.savaysa.com).
Rivaroxaban (*Xarelto*) (direct factor Xa inhibitor)	
Approved Indications and Usual Dose	U.S.:[15] • VTE prevention post-hip or knee replacement (10 mg once daily for 35 days [hip] or 12 days [knee] starting 6 to 10 hrs post-op, assuming hemostasis achieved) • Thromboembolism (e.g., stroke) prevention in nonvalvular A fib (20 mg once daily with evening meal to improve absorption) • DVT/PE treatment/prevention of recurrence (15 mg twice daily x 3 weeks, then 20 mg once daily [**with food** to improve absorption] for six months, then 10 mg once daily) Canada:[16] • VTE prevention post-hip or knee replacement (10 mg once daily for 35 days [hip] or 14 days [knee], starting 6 to 10 hrs post-op, assuming hemostasis achieved) • Thromboembolism (e.g., stroke) prevention in A fib (20 mg once daily **with food** to improve absorption) • DVT/PE treatment/prevention of recurrence (15 mg twice daily x 3 weeks, then 20 mg once daily, **with food** to improve absorption). Treatment duration should last a minimum of 3 months.
Renal Dosing	• Check renal function at baseline, yearly (Canada), and when clinically indicated.[15,16] Canada, monitor if CrCl close to 30 mL/min or potential for worsening renal function.[16] • A fib indication requires renal dosing (15 mg with evening meal for CrCl 15 to 50 mL/min [U.S.], 30 to 49 mL/min [Canada]).[15,16] Pharmacokinetic data suggest rivaroxaban 10 or 15 mg once daily in hemodialysis patients provides levels similar to patients in the pivotal A Fib trial, but there are no clinical outcome data.[15,46] • For DVT/PE prevention and treatment and VTE prevention post-hip/knee replacement, avoid if CrCl <30 mL/min.[15,16]

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Rivaroxaban (*Xarelto*) (direct factor Xa inhibitor), continued	
Clinical Benefit In…[a]	Post-hip/knee replacement: prevents 4 more VTEs compared to LMWH and causes 9 more serious bleeds per 1000 patients treated for 14 days.[17] A fib: comparable to warfarin for preventing stroke or systemic embolism in patients with relatively high stroke risk. Comparable major bleeding, but INR in therapeutic range only 55% of time. Lower rate of hemorrhagic stroke, higher rate of major GI bleed. Increase in events after stopping may reflect poor transition to warfarin, not hypercoagulability.[21] DVT treatment/prevention of recurrence: comparable to enoxaparin/warfarin for prevention of recurrent VTE; comparable major bleeding or clinically relevant nonmajor bleeding (combined endpoint).[22] PE treatment/prevention of recurrence: comparable to enoxaparin/warfarin for prevention of recurrent VTE; lower rate of major bleeding[23]
Antidote/pre-op, pre-procedure washout (if indicated)	No specific antidote. See our chart, *Managing Bleeding with the New Oral Anticoagulants*, and commentaries, *Stopping Antithrombotics Before Surgery* and *Managing Antithrombotics Before Minor Procedures*.
Therapeutic Considerations	• For A fib, some data suggest once-daily dosing insufficient, but BID dosing untested.[24] • Not recommended in patients with prosthetic heart valves,[15,16] or (Canada) patients with hemodynamically significant rheumatic heart disease, especially mitral stenosis.[16] • Avoid in patients with moderate or severe liver impairment or liver disease with coagulopathy.[15] Canada: contraindicated in liver disease with bleeding risk.[16] • For VTE treatment, continue for at least three months.[18] Benefit of extended use may not outweigh risk in patients with high bleeding risk.[18] • Caution in elderly. Underweight patients have slightly increased levels/response.[16] • Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement.[17]
Switching To/From Other Anticoagulants	• To switch from warfarin, stop warfarin, then start rivaroxaban when INR <3 (2.5 or less per Canadian labeling).[15,16] • To switch to warfarin: rivaroxaban increases INR, thus confounding initial warfarin dosing.[15,16] U.S.: consider starting a parenteral anticoagulant plus warfarin when the next dose of rivaroxaban would have been due.[15] Canada: continue rivaroxaban with warfarin until the INR is >2. Use the "usual" initial warfarin dose for the first two days. Thereafter, check INR just prior to the next dose of rivaroxaban to minimize rivaroxaban interference with the INR.[16] • See product labeling for guidance on switching to/from other anticoagulants.

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Rivaroxaban (*Xarelto*) (direct factor Xa inhibitor), continued	
Select drug interactions	• Avoid use with drugs that are BOTH P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, posaconazole, ritonavir [all contraindicated, per Canadian labeling]).[15,16] Caution with clarithromycin and fluconazole (Canadian labeling).[16] • In patients with CrCl 15 to <80 mL/min., the decision to use a combined P-gp/moderate CYP3A4 inhibitor (e.g., erythromycin) is a risk/benefit determination (U.S.).[15] Canada: use erythromycin with caution in patients with mild to moderate renal impairment.[16] • Drugs that are P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) may decrease efficacy.[15,16] Avoid.[15,16] • Avoid use with other anticoagulants (Canada: contraindicated).[15,16] Antiplatelets increase bleeding risk; co-administer with caution.[15,16]
Cost of 30-day supply[b]	10, 15, or 20 mg once daily U.S.: $333.27, Canada: $92.02 *Xarelto CarePath* savings card can reduce out-of-pocket cost to U.S. patients with private insurance to $0 per month ($3400 maximum annual benefit)(www.xareltocarepath.com).
Warfarin (*Coumadin*) (inhibits formation of vitamin-K dependent clotting factors)	
Approved Indications (**Note**: warfarin dosing variable and patient specific.)	U.S.:[25] • Prevention/treatment of venous thrombosis/PE • Prevention/treatment of thromboembolism due to A fib or prosthetic heart valve • Secondary prevention post-MI Canada:[26] • Prevention/treatment of venous thrombosis/PE • Prevention/treatment of thromboembolism due to A fib • Prevention of reinfarction and thromboembolism (e.g., stroke) post-MI (adjunct) • TIA (adjunct)
Renal Dosing	• Adjust per INR testing. Renal function minor determinant of warfarin response.[25] • Preferred anticoagulant for A fib with CrCl <15 mL/min.[19]

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Warfarin (*Coumadin*) (inhibits formation of vitamin-K dependent clotting factors), continued	
Clinical Benefit In…[a]	A fib: prevents stroke (NNT = 32 vs placebo for one year to prevent one stroke).[27] Post hip/knee replacement: prevents 3 fewer major clots compared to LMWH and causes two more fatal bleeds per 1000 patients treated for 14 days.[17] PE/DVT (with initial use of heparin): reduces risk of recurrence and mortality [Evidence level B; lower quality RCTs][28] Post-MI: reduces reinfarction, stroke, and mortality (INR 2.8 to 4.8);[29] warfarin (INR 2 to 2.5) plus aspirin (75 mg once daily) superior to aspirin alone or warfarin (INR 2.8 to 4.2) alone (combined endpoint).[30] Rheumatic mitral valve disease (off-label): reduces embolic events and mortality in patients with embolic history; reduces embolic events in patients with A fib, promotes resolution of left atrial thrombus [Evidence level B; clinical cohort].[31-33] Mechanical heart valve (off-label, Canada): reduces embolism and valve thrombosis.[34]
Antidote/pre-op, pre-procedure washout (if indicated)	Vitamin K/ **Washout**: five days[35] Also see our commentaries, *Stopping Antithrombotics Before Surgery* and *Managing Antithrombotics Before Minor Procedures*.
Therapeutic Considerations	• INR monitoring required at least every four weeks.[25,26] Goal 2 to 3 for most indications.[18] • Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement.[17] • Not more effective than aspirin for noncardioembolic stroke.[37] • Preferred anticoagulant for A fib with CAD.[39] • For VTE treatment, continue for at least three months.[18] Benefit of extended use may not outweigh risk in patients with high bleeding risk.[18,20]
Select drug interactions	• Many drug and food interactions. • Potential for significant interactions with inducers/inhibitors of CYP2C9, 2C19, 1A2, and 3A4. • Use with antiplatelets increases bleeding risk. Benefit of combo (most data with aspirin or clopidogrel) may outweigh risk in certain patients, such as mechanical heart valve patients, or in A fib plus recent stent or recent CABG.[19,36,38,50]

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Warfarin (*Coumadin*) (inhibits formation of vitamin-K dependent clotting factors), continued	
Cost of 30-day supply[b]	5 mg once daily U.S.: <$5, Canada: $2.15

a. Based on Level A evidence unless otherwise noted.
b. U.S. cost for dose specified (of generic, if available) is wholesale average cost at time of writing unless otherwise specified. Canadian prices are wholesale. Does not include cost of monitoring.
c. Medication pricing by Elsevier, accessed February 2018.

Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

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Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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Cite this document as follows: PL Detail-Document, Comparison of Oral Anticoagulants. Pharmacist's Letter/Prescriber's Letter. May 2016.

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