step 4 *continued* Select, implement & monitor stroke prophylaxis

	Dabigatran (Pradaxa®)[20]	Rivaroxaban (Xarelto®)[21]	Apixaban (Eliquis®)[22]
Converting from novel oral anticoagulant to warfarin	From dabigatran to warfarin, based on CrCl:[20] CrCl (mL/min) / Start warfarin "x" days before stopping dabigatran > 50 / 3 days 31-50 / 2 days INR should be assessed just prior to novel oral anticoagulant dose to better reflect the impact of warfarin on INR	Give rivaroxaban or apixaban concurrently with warfarin until the INR is ≥ 2.0 then stop[21,22]	
Laboratory Assessment and Anticoagulation Testing	Monitor CBC at baseline and with any change in health status that may impact haemoglobin, red blood cell count or platelets. Monitor CrCl to assess stability of renal function and ongoing drug dose/use[20-22] Routine anticoagulant monitoring is not required.[20-22,25-27] The INR and aPTT do not quantitatively correlate with drug levels and should not be used for routine monitoring A calibrated diluted TT (namely Hemoclot assay) will provide dabigatran levels. In absence of Hemoclot assay availability, a normal TT rules out presence of clinically important dabigatran levels, aPTT may be used to reflect presence of drug, although a minority of patients (<2%) may have a normal aPTT just prior to their next dose,[20] while chronically taking dabigatran[28]	Rivaroxaban calibrated anti-Xa levels reflect the pharmacodynamic effect in a dose dependent fashion. In the absence of calibrated anti-Xa levels, PT (Neoplastin® reagent) may be useful to reflect presence of drug[21]	Rotachrom® Heparin Anti-Xa assay reflects the pharmacodynamic effect of apixaban in a linear, dose-related fashion. In the absence of calibrated anti-Xa levels, PT/INR is not effective for assessing apixaban[22]
Adverse effects[20-22]	Dyspepsia, bleeding	Bleeding	Bleeding
Antidote	Antidotes currently under clinical development. In case of life-threatening bleed consult local specialist. Limited clinical data is available; options may include activated prothrombin complex concentrates (PCCs), inactivated PCCs or rFVIIa[26,27,29] For dabigatran only, dialysis may be considered, but may not be practical[20]		
Drug-drug interactions[20-22] (see detailed table)	Dabigatran etexilate is a substrate for the efflux P-glycoprotein (P-gp) transporter. Plasma concentrations are affected by strong P-gp inducers and inhibitors	Rivaroxaban is eliminated by CYP 3A4 and P-gp, concomitant strong inhibitors/inducers of both of these pathways will impact rivaroxaban exposure	Apixaban is eliminated by CYP 3A4 and P-gp, concomitant strong inhibitors/inducers of both of these pathways will impact apixaban exposure

Hold Prior to Surgery[25*]

Drug/CrCl	Last intake of drug prior to procedure	
	Standard risk of bleeding †	High risk of bleeding ‡
Dabigatran§		
≥ 80 mL/min	≥ 24 hours	≥ 48 hours
≥ 50 - < 80mL/min	≥ 36 hours	≥ 72 hours
≥ 30 - < 50 mL/min	≥ 48 hours	≥ 96 hours
Rivaroxaban¥		
≥ 30 mL/min	≥ 24 hours	≥ 48 hours
≥ 15-30 mL/min	≥ 36 hours	≥ 48 hours
Apixaban**		
≥ 30 mL/min	≥ 24 hours	≥ 48 hours
≥ 15 – 29 mL/min	≥ 36 hours	≥ 48 hours

* To minimize the risk of ischemic stroke, therapy should be restarted once hemostasis is achieved, and this should be also guided by the risk of bleeding due to the procedure.
† such as cardiac catheterization, ablation therapy, or uncomplicated laparoscopic procedures[27]
‡ such as neurosurgery, major cancer/cardiac/urologic/vascular surgery[27]
§ if CrCl < 30 mL/min (dabigatran is contraindicated), hold at least 5 days[20]
¥ if CrCl < 30 mL/min (rivaroxaban is not recommended),[21] last dose before elective surgical intervention should be > 36 hours if low risk and > 48 hours if high risk[25]
** for CrCl 15-24 mL/min limited clinical data,[22] last dose before elective surgical intervention should be > 36 hours if low risk and > 48 hours if high risk,[22] while if CrCl < 15mL/min apixaban is not recommended and longer intervals are likely necessary (no data)[22]

Drug-Drug Interactions[20-22]

Limited pharmacokinetic drug interaction data is currently available and data below reflects those studies/reports to date.

Potential ↑ in Dabigatran	Potential ↓ in Dabigatran
Amiodarone* Clarithromycin* Cyclosporine* Dronedarone¥ Itraconazole* Ketoconazole‡ Nelfinavir* Posaconazole* Quinidine*§ Ritonavir* Saquinavir* Tacrolimus* Tipranavir* Ticagrelor¥ Verapamil*§ Strong P-glycoprotein inhibitors‡	Antacids§ Atorvastatin** Carbamazepine¥ Proton Pump Inhibitors* Rifampin¥ St John's Wort¥ Tenofovir¥ Strong P-glycoprotein inducers‡

* no empiric dosage adjustment required, however use with caution
§ recommend to give 2 hours after dabigatran
‡ contraindicated
¥ caution advised if co-administering, should be avoided
** no dose adjustment is required

Potential ↑ in Rivaroxaban	Potential ↓ in Rivaroxaban
Clarithromycin* Erythromycin* Fluconazole* Ketoconazole‡ Ritonavir‡ Strong inhibitors of both P-glycoprotein and CYP 3A4‡	Carbamazepine¥ Phenobarbital¥ Phenytoin¥ Rifampin¥ St. John's Wort¥ Strong inducers of both P-glycoprotein and CYP 3A4¥

Potential ↑ in Apixaban	Potential ↓ in Apixaban
Diltiazem* Ketoconazole, itraconazole, voriconazole, posaconazole = azole-antimycotics‡ Naproxen* Ritonavir (all HIV protease inhibitors)‡ Strong inhibitors of both P-glycoprotein and CYP 3A4‡	Carbamazepine¥ Phenobarbitol¥ Phenytoin¥ Rifampin¥ St. John's Wort¥ Strong inducers of both P-glycoprotein and CYP 3A4¥

overview

step 1 Determine your patient's risk of stroke using $CHADS_2$ Score:[2-4]

$CHADS_2$ Score

Congestive heart failure	Hypertension	Age (≥75 years)	Diabetes Mellitus	Stroke/TIA_2	MAX.SCORE
1	1	1	1	2	6

If $CHADS_2$ Score = 0, further risk stratify in accordance with:[2,4,5]
- Age 65 to 75 years
- Vascular Disease

$CHADS_2$ = 0
Stroke risk is 1.9 per 100 patient years (1.2-3.0)

≥ 65 years	Vascular disease (prior MI, aortic plaque, peripheral vascular disease)	< 65 years and no additional risk factors for stroke
OAC*	ASA	No antithrombotic

$CHADS_2$ 1 or More		
$CHADS_2$ Score	Stroke Rate per 100 patient years (95% CI)	Recommended therapy
1	2.8 (2.0 – 3.8)	OAC*
2	4.0 (3.1 – 5.1)	OAC
3	5.9 (4.6 – 7.3)	OAC
4	8.5 (6.3 – 11.1)	OAC
5	12.5 (8.2 – 17.5)	OAC
6	18.2 (10.5 – 27.4)	OAC

* OAC refers to therapeutic (i.e. treatment dose) Oral Anticoagulant Therapy

step 2 Determine your patient's risk of bleeding using the HAS-BLED Score:[6]

High SBP >160 mmHg*	Abnormal renal or liver function	Stroke	Bleeding history	Labile INR*	Elderly age >65 years	Drugs or ETOH*	MAX. SCORE
1	1 or 2	1	1	1	1	1 or 2	9

Score ≥ 3 indicates high risk & warrants some caution/regular patient evaluation of antithrombotic therapy
* These bleeding risk factors may be modifiable and doing so can decrease the risk of bleeding with anticoagulation

step 3 Balance the benefit and risk with available agents

Stroke Prevention	Major Bleeding	Comments
• Compared to warfarin, dabigatran 150 mg BID is superior in preventing stroke, while dabigatran 110 mg BID has similar efficacy[12] • Compared to warfarin, rivaroxaban 20 mg once daily has similar efficacy to prevent strokes[13] • Warfarin is superior to ASA in preventing stroke[11] (Efficacy based on achieving a time in therapeutic range (INR 2-3) at least 60% of the time)[8,9] • Compared to ASA, apixaban 5mg BID is superior in preventing stroke for patients unsuitable for warfarin[14] • Compared to warfarin, apixaban 5mg BID is superior in preventing stroke[15]	• Compared with warfarin, dabigatran 150 mg BID and rivaroxaban 20 mg once daily are associated with similar rates of major bleeding but more GI bleeds[12,13] • Compared with warfarin, dabigatran 110 mg BID is associated with less major bleeding[12] • Compared with ASA, apixaban 5mg BID has similar rates of major bleeding[14] • Compared with warfarin, apixaban 5mg BID is associated with less major bleeding[15] • Dabigatran, rivaroxaban and apixaban are associated with less intracranial hemorrhage (ICH) than warfarin[12,13,15]	• No clinical trials directly comparing the novel/direct acting oral anticoagulants (OACs) (dabigatran, rivaroxaban, apixaban) to each other are available • 2014 Canadian AFib Guidelines do not recommend routine anticoagulation for dialysis pts • Dabigatran and rivaroxaban should be avoided in significant renal dysfunction (i.e. CrCl < 30 mL/min)[20,21] Apixaban is not recommended if CrCl<15mL/min and data are limited for CrCl 15-24mL/min[22] • Dabigatran is contraindicated in combination with strong P-gp inhibitors/inducers.[20] Rivaroxaban and apixaban are contraindicated in combination with strong inhibitors of both P-gp and CYP 3A4.[21,22] Refer to prescribing information for details. • Discuss cost and coverage of novel/direct acting OACs with patient

2014 Canadian AF Guidelines recommend dabigatran, rivaroxaban or apixaban over warfarin[4]

step 4 Select, implement & monitor stroke prophylaxis[16,17,20-22]

Agent	Dose	Routine Monitoring	DI/Food Interactions	Offset	Adverse Effects
ASA	80 – 325 mg daily	No	No	5 – 7 days	Dyspepsia
Apixaban	5 mg BID, 2.5 mg BID*	No	Yes/No	1-3 days†	
Dabigatran	150 mg BID 110 mg BID**	No	Yes/No	1-4 days†	Dyspepsia
Rivaroxaban	20 mg daily, 15 mg daily with food¥	No	Yes/Yes¤	1-3 days†	
Warfarin	As per INR target of 2.5	Yes§	Extensive/ Extensive	3-5 days	

Major bleeding occurs with all anti-thrombotic agents

* If ≥ 2 of the following: age ≥ 80 years, body weight ≤ 60 Kg, or serum creatinine ≥ 133 µmol/L
** Should use Dabigatran 110 mg BID if ≥ 80 years of age and consider for those > 75 years with at least one additional risk factor for bleeding
† Dependent upon renal function
¥ Rivaroxaban 15 mg daily if CrCl 30-49 mL/min
¤ Should be taken with food/main meal of day for complete absorption
§ Efficacy based on achieving a time in therapeutic range of at least 60% of the time[8,9]

For a complete list of References, go to www.ccpn.ca

CCPN RCPC
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RÉSEAU CANADIEN DES PHARMACIENS IMPLIQUÉS EN SOINS CARDIOVASCULAIRES

CCPN SPAF Tool

STROKE PREVENTION IN ATRIAL FIBRILLATION (SPAF): POCKET REFERENCE

Approximately 20% of all strokes are attributable to Atrial Fibrillation (AF).[1] Of these, 20% will result in death and 60% will result in disability. Given this, it is important to ensure that appropriate antithrombotic therapy is provided for those at risk for cardioembolic stroke.

This pocket reference summarizes the therapeutic options for the prevention of stroke in patients with non-valvular AF. It does not address patients with rheumatic heart disease or patients with transient, self-limited AF associated with an acute illness or secondary cause. It is intended only as a general reference to supplement the existing knowledge of healthcare professionals and is NOT a substitute for the sound clinical judgement of the knowledgeable healthcare professional. The authors, editors, or CCPN cannot be held responsible for any harm, direct or indirect, caused as a result of the application of the information contained in this resource.

An electronic application is available at our website:

www.ccpn.ca

step 1

Determine your patient's risk of stroke using $CHADS_2$ Score:[2-4]

$CHADS_2$ Score

	Finding	Points
C	**C**ongestive Heart Failure*	1 point
H	**H**ypertension	1 point
A	**A**ge ≥ 75 years	1 point
D	**D**iabetes	1 point
S	Prior **S**troke or TIA†	2 points

* Defined as history of CHF, clinical findings of CHF, or cardiac imaging showing reduction of LVEF.
† Including other cardioembolic events such as systemic or pulmonary thromboembolism.

Patients with a $CHADS_2$ score of 0 could still be at increased risk of stroke and require further risk stratification based on the following characteristics:[2,4,5]

- Age between 65 and 75 years
- Known vascular disease

Next, determine your patient's corresponding risk of stroke and recommended stroke prophylaxis (Canadian Cardiovascular Society 2014 Guidelines):[4]

$CHADS_2$ = 0
Stroke risk is 1.9 per 100 patient years (1.2-3.0)

≥ 65 years	Vascular disease (prior MI, aortic plaque, peripheral vascular disease)	< 65 years with no additional risk factors for stroke
OAC*	ASA	No antithrombotic

$CHADS_2$ = 1 or More		
$CHADS_2$ Score	Stroke Rate per 100 patient years (95% CI)	Recommended therapy
1	2.8 (2.0 – 3.8)	OAC*
2	4.0 (3.1 – 5.1)	OAC
3	5.9 (4.6 – 7.3)	OAC
4	8.5 (6.3 – 11.1)	OAC
5	12.5 (8.2 – 17.5)	OAC
6	18.2 (10.5 – 27.4)	OAC

* OAC refers to therapeutic (i.e. treatment dose) Oral Anticoagulant Therapy

step 2

Determine your patient's risk of bleeding

On the right is the HAS-BLED risk score[6] (tested in a cohort of European patients with AF prescribed warfarin or ASA). Importantly, many risk factors for bleeding are also risk factors for stroke, and sequelae from stroke generally are worse than sequelae from bleeding. Furthermore, a number of bleeding risk factors are potentially reversible (e.g., SBP>160mmHg, concomitant NSAIDs, alcohol abuse, etc) and should be addressed to decrease bleeding risk.

The incidence of major bleeding with a HAS-BLED score

HAS-BLED Score	Major Bleeding Risk
0–1	1.0%/yr
2	1.9%/yr
3	3.7%/yr
4	8.7%/yr
5	12.5%/yr

While certain patient populations may require dual antiplatelet therapy (e.g., ASA + clopidogrel) with anticoagulant therapy (i.e., triple therapy), the risk of bleeding dramatically increases, with population estimates of a 4-fold increased risk compared to warfarin alone.[7]

Letter	Characteristic	Score
H	**H**ypertension (systolic blood pressure > 160 mmHg)	1
A	**A**bnormal Renal (dialysis, transplant or serum Cr > 200 µmol/L) or Liver function (cirrhosis or bilirubin > 2 x upper limit normal with AST/ALT/Alk Phos > 3 x upper limit normal) (1 point each)	1 or 2
S	**S**troke	1
B	**B**leeding (by history or predisposition, e.g., bleeding diathesis, anemia)	1
L	**L**abile INRs (poor time in INR range [< 60% time in range] or frequent unstable or high INRs)	1
E	**E**lderly (> 65 years)	1
D	**D**rugs (concomitant antiplatelet, NSAIDS) or Alcohol abuse (1 point each)	1 or 2
	Maximum Score	**9**

step 3

Balance the benefits and risks with available agents

NOTE: The table provides inter-trial comparative data along with data derived from meta-analyses. Endpoints and definitions along with trial populations differ, and caution must be taken in the interpretation. Data presented provides guidance to readers in understanding the comparative benefits and risks of therapeutic alternatives.

Efficacy with warfarin is only achieved if patients are appropriately anticoagulated (INR 2.0 – 3.0) at least 60% of the time.[8,9] As time in the therapeutic range falls below 60%, there is an increase in mortality, major bleeding, and stroke severity.[8-10]

* Major bleeding defined as a reduction in the hemoglobin level of at least 20 g/L, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ
† Major bleeding defined as a reduction in the hemoglobin level of at least 20 g/L, transfusion of at least 2 units of blood, any critical bleeding which was defined by bleeding that was intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome) or into the retroperitoneum, or fatal bleeding

	Efficacy Endpoints			Safety Endpoints	
Comparators	Primary endpoint: (95% CI)	Primary endpoint ARR (NNT)	Primary endpoint RRR	Events/year (95% CI)	Intracranial Hemorrhage Events
ASA vs. Placebo[11] (meta-analysis of 5 trials n=2834, 41% secondary prevention)	All Stroke: 6.86%/yr vs 8.77%/yr; RRR 22% (2-39)	1.91%/yr (53)	22%	Major Extracranial hemorrhage: 16 vs 15	8 vs 4
Warfarin vs. Placebo[11] (meta-analysis of 6 trials, n=2900, 20% secondary prevention)	All Stroke: 2.21%/yr vs 6.03%/yr; RRR 64% (49-74)	3.82%/yr (26)	64%	Major Extracranial hemorrhage: 31 vs 17	6 vs 3
Warfarin vs. ASA[11] (meta analysis of 5 trials, n=3647, 21% secondary prevention)	All Stroke: 2.43%/yr vs 3.81%/yr; RRR 38% (18-52)	1.38%/yr (72)	38%	Major Extracranial hemorrhage: 40 vs 22	20 vs 7
Dabigatran 110 mg BID vs warfarin[12] (n=18113)	Stroke/Systemic Embolism: 1.54%/yr vs 1.71%/yr; RR 0.91 (0.74-1.11)	0.13%/yr (769)	9%	Major bleeding:* 2.71%/yr vs 3.36%/yr; RR 0.80 (0.69-0.93)	0.23%/yr vs 0.74%/yr; RR 0.31 (0.20-0.47)
Dabigatran 150 mg BID vs warfarin[12] (n=18113)	Stroke/Systemic Embolism: 1.11%/yr vs 1.71%/yr; RR 0.66 (0.53-0.82)	0.56%/yr (177)	34%	Major bleeding:* 3.11%/yr vs 3.36%/yr; RR 0.93 (0.81-1.07)	0.30%/yr vs 0.74%/yr; RR 0.40 (0.27-0.60)
Rivaroxaban 20 mg daily vs warfarin[13] (n=14264, ITT analysis)	Stroke/Systemic Embolism: 2.1%/yr vs 2.4%/yr; HR 0.88 (0.74-1.03)	0.3%/yr (333)	12%	Major bleeding:† 3.6%/yr vs 3.4%/yr; HR 1.04 (0.90-1.20)	0.5%/yr vs 0.7%/yr; HR 0.67 (0.47-0.93)
Apixaban 5mg BID vs. ASA[14] (N=5599) (Applicable to those not candidates for warfarin)	Stroke/Systemic Embolism: 1.6%/yr vs. 3.7%/yr; HR 0.45 (0.32 – 0.62)	2.1%/yr (48)	55%	Major bleeding:† 1.4%/yr vs. 1.2%/yr; HR 1.13 (0.74 – 1.75)	0.4%/yr vs. 0.4%/yr; HR 0.85 (0.38 – 1.90)
Apixaban 5mg BID vs. warfarin[15] (N=18,201)	Stroke/Systemic Embolism: 1.27%/yr vs. 1.60%/yr; HR 0.79 (0.66-0.95)	0.33%/yr (303)	21%	Major bleeding:† 2.13%/yr vs. 3.09%/yr; HR 0.69 (0.60-0.80)	0.33%/yr vs. 0.80%/yr; HR 0.42 (0.30-0.58)

step 4

Select, implement & monitor stroke prophylaxis

Acetylsalicylic Acid (ASA)[16]

Dosing for Stroke Prophylaxis
80-325 mg daily

Contraindications
Allergy or hypersensitivity, active peptic ulcer disease, ASA plus methotrexate in doses > 15 mg/wk

Adverse Effects
Bleeding (majority occurs within GI tract)
Dyspepsia

Hold Prior to Surgery
5-7 days

Drug-Drug Interactions
May decrease the efficacy of antihypertensives
Ibuprofen may reduce cardioprotective effects of ASA
May increase methotrexate levels/ toxicity particularly at high methotrexate doses

Warfarin (Coumadin®)[17]

Mechanism of Action
Inhibits vitamin K dependent coagulation factors (factors II, VII, IX and X)

Pharmacokinetics
t_{max}: 72–96 hrs
$t_{1/2}$: 40 hrs (range 20-60 hrs)

Dosing for Stroke Prophylaxis and Dose Adjustment
Target INR 2.5 (range 2.0-3.0) for non-valvular AF
- Warfarin initiation doses of 5-10 mg for 1-2 days, with subsequent dosing based on INRs.[18] Choice of initial warfarin dose may be ≤ 5mg for those with liver disease, taking medications likely to pronounce warfarin's effects, are malnourished, debilitated, have heart failure, acutely ill or had recent surgery
- Dosing alteration in the **maintenance phase** of therapy should typically be on the order of 5-15% of the weekly dosage (or average daily dose)

Maintenance Dosing Adjustments for INR of 2.0 – 3.0*

INR	Action
< 1.5	Reload† 0 – 2 doses, ↑ weekly dose by 5 – 15%
1.5 – 1.9	Reload† 0 – 1 dose, ↑ weekly dose by 0 – 10%
2.0 – 3.0	No Change
3.1 – 3.5	Hold 0 – 1 dose, ↓ weekly dose by 0 – 10%
3.6 – 4.9	Hold 0 – 2 doses, ↓ weekly dose by 5 – 15%
5.0 – 9.0‡	Hold warfarin, consider Vitamin K_1 1 - 2.5 mg PO
> 9‡	Hold warfarin and give Vitamin K_1 2.5 – 5 mg PO

* Guidelines are to be used as a general framework for dosage adjustment – to be modified as individual needs dictate
† Reload refers to giving the patient up to twice the daily maintenance dose
‡ Appropriate in patients with no significant bleeding

Contraindications
Hepatic impairment: monitor INR closely as may potentiate response
Active bleeding

Adverse Effects
Bleeding

Hold Prior to Surgery
Amongst stable patients it is likely that the INR will be < 2 after 2 days of withholding warfarin, and ≤ 1.3 with 5 days of holding warfarin. If warfarin is held greater than 2 days, consider bridging if patient is at high thromboembolic risk

Drug-Drug Interactions
Numerous drug interactions are evident with warfarin, and are beyond the scope of this tool. Clinicians should note some of these interactions are delayed, and management of warfarin doses will vary. For a detailed list of drug interactions with management tips, please refer to a published practice tool (www.cpjournal.ca/doi/pdf/10.3821/1913-701X-144.1.21)[19]

	Dabigatran (Pradaxa®)[20]	Rivaroxaban (Xarelto®)[21]	Apixaban (Eliquis®)[22]
Mechanism of Action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Pharmacokinetics t_{max} / $T_{1/2}$ / Elimination	0.5-2 hrs 12-14 hrs Renal 80%	2-4 hrs 7-12 hrs Renal 33% active (inactive renal 33%)	3-4 hrs 8.3 hrs Renal 27%
Dosing for Stroke Prophylaxis[20-22] (Prior to initiation, establish baseline renal function. Assess renal function annually or during clinical situations when renal function may decline throughout therapy.)	• 150mg BID • 110mg BID for patients ≥ 80 yrs of age; consider this dose for those > 75 yrs with at least one risk factor for bleeding (e.g., CrCl 30–50 mL/min, P-glycoprotein inhibitor co-medication, concomitant antiplatelet therapy, diseases/procedures with special hemorrhagic risks) • Contraindicated if CrCl < 30 mL/min	• 20 mg daily with main meal if CrCl ≥ 50 mL/min • 15 mg daily with main meal if CrCl 30 – 49 mL/min • Not recommended if CrCl < 30 mL/min	• 5 mg BID • 2.5 mg BID if ≥ 2 of the following: age ≥ 80 years, body weight ≤ 60 Kg, or serum creatinine ≥ 133 µmol/L (these patients at higher risk of bleeding). • Not recommended if CrCl<15 mL/min
Administration	Do not chew, break or open capsules. Take with or without food	Take with food, preferably main meal of day. Can be crushed and administered by NG[22]	Take with or without food, can be crushed and administered NG[24]
Contraindications[20-22]	Active bleeding; Lesions at risk of clinically significant bleeding (eg., hemorrhagic or ischemic stroke within 6 months [note: for apixaban – *recent* cerebral infarction], active peptic ulcer disease with recent bleeding); Use in pregnancy and nursing is not recommended		
	Treatment with strong P-glycoprotein inhibitors or inducers (eg., ketoconazole, rifampin)	Concomitant treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein (eg., ketoconazole, ritonavir); *strong inducers should be avoided*	
	CrCl < 30 mL/min	Use in patients with CrCl < 30 mL/min is not recommended	Not recommended in patients with CrCl < 15 mL/min, clinical data are very limited in patients with CrCl 15-24 mL/min
	Patients with prosthetic heart valves requiring anticoagulation due to valvular status	*Not recommended in patients with prosthetic heart valves*	*Not recommended in patients with prosthetic heart valves*
	Not recommended in patients with hepatic enzymes > 3X upper limit of normal	Hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and with clinically relevant bleeding risk. *Use with caution in moderate hepatic impairment*	Hepatic disease with coagulopathy and clinically relevant bleeding risk. Not recommended in severe hepatic impairment. *Use with caution for mild or moderate hepatic impairment*
Converting from warfarin to novel OAC[20-22]	Stop warfarin and start dabigatran when INR < 2.0	Stop warfarin and start rivaroxaban once INR is < 2.5	Stop warfarin and start apixaban when INR < 2.0