Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Anticoagulation

April to June 2023

- Indications for ongoing oral anticoagulation (OAC) include atrial fibrillation (AF), mechanical valve replacement, prevention of venous thromboembolism (VTE), left ventricular thrombus, and coronary artery disease (CAD)/ peripheral artery disease (PAD). Not all indications require an indefinite duration of treatment with oral anticoagulants.
- Guidelines for the management of AF recommend OAC for almost all patients aged 65 years and older, but in practice only up to 50% of older adults receive maintenance OAC therapy[2].
- Elderly and frail older adults have a higher risk for adverse outcomes associated with OAC including increased risk for bleeding compared to younger individuals[1]. Due to concerns about the risks associated with anticoagulation in older adults, anticoagulation may be underutilized in this population[2].
- While trials have demonstrated that direct acting oral anticoagulants (DOACs) are safe and effective when compared to warfarin, these trials excluded nursing home residents[12].
- Older individuals receiving a DOAC may not be receiving the appropriate dose, resulting in their dosage being too high or too low.[2] A non-therapeutic dose can result in older adults being at an increased risk of bleeding without their risk of stroke being reduced.

! For the quarterly medication reviews from April to June 2023, reassess all residents on oral anticoagulants and those with an indication for anticoagulation:

- **Assessment**:
  - ◊ Determine the indication for OAC and the appropriate duration of treatment
  - ◊ Assess the resident's benefit and risk with receiving OAC
    - * For resident's older than 65 years of age with atrial fibrillation, assess their risk of stroke by using the CHADS-65 score (see Figure 1 on page 2) and their risk of bleeding by calculating their HAS-BLED Score
  - ◊ Reassess the dose of the anticoagulant based on resident-specific factors (e.g., renal function, indication) to ensure they are receiving the appropriate dose (see Table 2 on page 6)
  - ◊ Assess for any issues with the resident taking the anticoagulant (e.g. warfarin—review recent INR levels; DOACs—taking as per manufacturer's recommendations)
  - ◊ Assess for any potential drug interactions or concomitant medications that may increase the risk of bleeding (e.g. antiplatelets, SSRIs, NSAIDs). Assess if the resident requires GI protection.
- **Recommendations**:
  - ◊ For nonvalvular atrial fibrillation with or without CAD, a DOAC is preferred over warfarin.[3] For residents on warfarin with nonvalvular AF, consider switching to a DOAC.
  - ◊ Reassess residents taking an antiplatelet for CAD and an OAC for AF. If CAD is stable, e.g. at least 12-months post-ACS, consider deprescribing the antiplatelet (see Figure 2 on page 3).
  - ◊ Reassess residents taking an OAC for prevention of DVT or PE. Consider the duration since the DVT/PE occurred and the cause of the DVT/PE, if known, to identify residents who no longer require the OAC (see Table 1 on page 4).
  - ◊ Inappropriate dosing of DOACs (either too high or too low) is common in elderly populations[12]. Ensure residents are on the appropriate dose of their DOAC (see Table 2 on page 6). If CrCl less than 15 mL/min, discuss with nephrology.
  - ◊ Apixaban was associated with superior safety, efficacy, effectiveness, and lower mortality than vitamin K antagonists (e.g. warfarin); superior safety than rivaroxaban and similar safety to dabigatran; and with similar effectiveness when compared with rivaroxaban or dabigatran[11]. Compared to warfarin and rivaroxaban, apixaban is the anticoagulant with the highest benefit-risk ratio for older adults with atrial fibrillation[23].
  - ◊ Apixaban is now available from generic companies so it is the most cost-effective DOAC (see Table 3 on page 7).
  - ◊ **Apixaban is the preferred DOAC for PCH residents so consider switching residents from other DOACs to apixaban.**
  - ◊ Older adults with AF benefit from stroke prevention with anticoagulation even if they are at high risk of falls. Fall risk should not be a deciding factor for withholding anticoagulation in this population.[2]
  - ◊ ASA alone is not sufficient for stroke prevention in older adults with atrial fibrillation. The stroke prevention benefit from apixaban was shown to be greater with no increased risk of hemorrhage (NNT=26 for 75 years and older and NNT=15 for 85 years and older).[15]

Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Anticoagulation

QMR Contents:

Guidelines: Atrial Fibrillation

- The Canadian Cardiovascular Society (CSS) recommends an oral anticoagulant (OAC) should be prescribed to most patients 65 years of age or older and for younger patients with nonvalvular atrial fibrillation (AF) or atrial flutter and 1 or more of the other **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack (CHADS2) risk factors[3].
- The CSS has developed a modified version of the CHADS2 algorithm when choosing therapy for patients 65 years and older with AF called the CHADS -65 (see Figure 1). The CHADS-65 incorporates the substantial risk of stroke conferred with being 65-74 years old, which is not included in the CHADS2 algorithm[3].
- ***A DOAC is preferred over warfarin for nonvalvular AF[3].***
  - ◊ ***Patients with valvular AF should receive warfarin[3]***. Valvular atrial fibrillation includes patients with moderate to severe mitral stenosis and/or presence of mechanical heart valves.

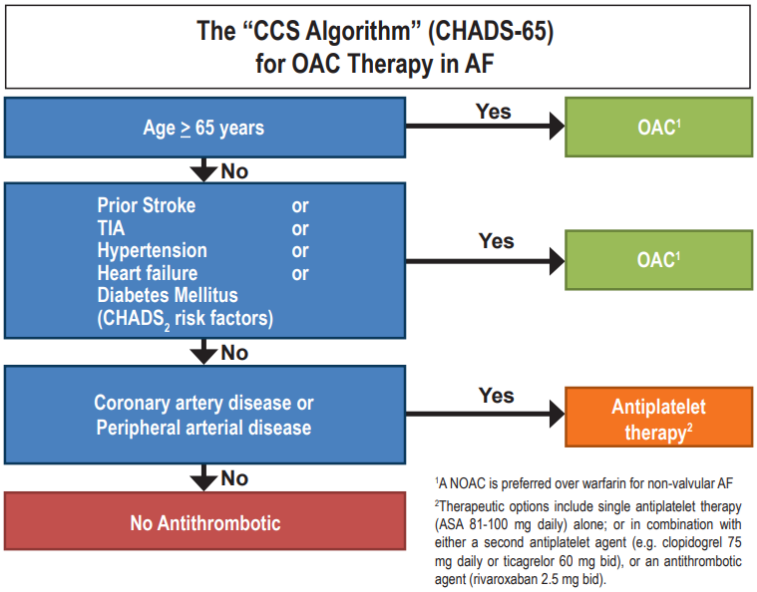

Figure 1: CCS Algorithm (CHADS-65) for Oral Anticoagulant Therapy in Atrial Fibrillation[3]

- ***For residents with renal dysfunction, select a DOAC that can be used with a CrCl 15-30 mL/min. For patients with CrCl less than 15 mL/min, discuss anticoagulant choice with their nephrologist.***
- **For residents with concomitant atrial fibrillation and coronary artery disease (CAD)** (see Figure 2).
  - ◊ Antithrombotic therapy should be based on an assessment of a resident's risk of stroke.
  - ◊ ***When oral anticoagulation is recommended, a DOAC is preferred over warfarin[3]***.
  - ◊ For patients with non-valvular AF, are less than 65 years old, and have no CHADS2 risk factors, guidelines suggest no antithrombotic therapy is required for stroke prevention[3].
  - ◊ For patients with AF who are 65 years or older, or for those who are younger than 65 with a CHADS2 score of greater than or equal to 1 and coronary or arterial vascular disease (peripheral vascular disease or aortic plaque), guidelines recommend long-term therapy with oral anticoagulation alone[3].
    - * Based on the ACTIVE-A trial, for patients who refuse OAC, ASA and clopidogrel may be an alternative option[3]. The addition of clopidogrel or ASA reduced the risk of major vascular events, especially stroke, but increased the risk of major hemorrhage[4]. Bleeding risk of combined antiplatelet therapy may be similar to OAC monotherapy[3].

A DOAC is preferred over warfarin for nonvalvular AF with or without and CAD.[3] For residents on warfarin with nonvalvular AF, consider switching to a DOAC.

Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Anticoagulation

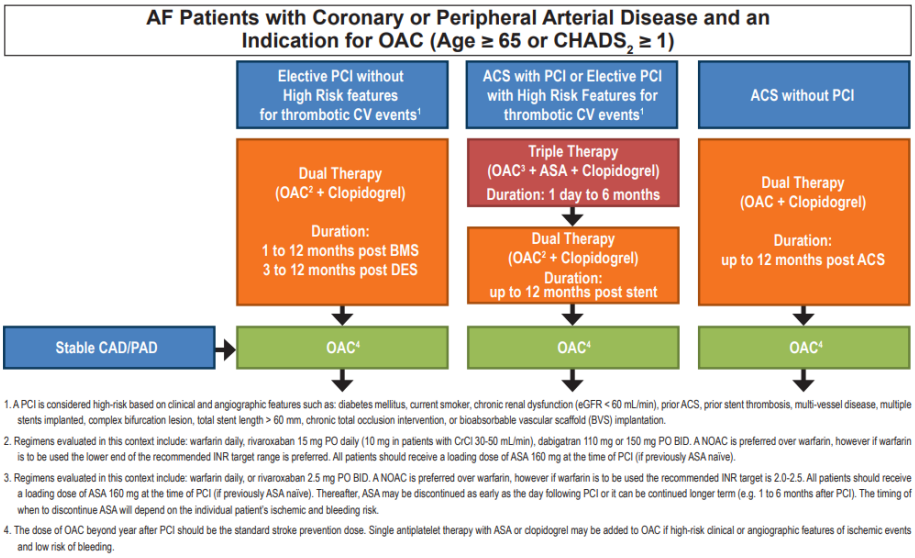

Figure 2: Management of antithrombotic therapy in patients with atrial fibrillation (AF) and coronary artery disease (CAD)/ peripheral artery disease (PAD), who have an indication for an oral anticoagulant (OAC) for stroke prevention.[3]

Reassess residents taking an antiplatelet for CAD and an OAC for AF. If CAD is stable, e.g. at least 12-months post-ACS, consider deprescribing the antiplatelet.

Guidelines: Venous Thromboembolism (Deep Vein Thrombosis or Pulmonary Embolism)

- Thrombosis Canada recommends all patients be treated with anticoagulation for a minimum of 3 months after a DVT or PE[5,6]. Duration may depend on several factors. Choice of DVT treatment should depend on resident specific factors (e.g., renal function, extreme weights, drug interactions, or conditions that may impair oral absorption)[5,6].
- Large phase 3 studies have demonstrated efficacy and safety for DOACs in the acute treatment of DVT/PE (apixaban and rivaroxaban in DVT) as well as for extended treatment[5,6] (usually for a minimum of 3 months) (e.g., apixaban, rivaroxaban, edoxaban, and dabigatran). Warfarin is also an appropriate option for extended treatment of venous thromboembolism[5,6].
- **Appropriate duration of treatment for secondary prevention of VTE (see Table 1):**
  - ◊ Minimum duration for treatment of DVT/PE is 3 months[7] – the risk of recurrent VTE after stopping anticoagulation appears to be similar whether anticoagulant therapy is stopped after 3 months vs. after 6-24 months[7].
  - ◊ Decision to continue should consider balancing risk of recurrence, which depends mainly on whether VTE was provoked by a transient risk factor, unprovoked, or related to a major persistent risk factor such as active cancer[7].
  - ◊ Other considerations[7]:
    - * Type of index events: the risk of VTE recurrence is similar after an episode of proximal DVT vs. PE. However, patients who presented initially with PE are more likely to recur with PE than DVT. The risk of recurrence is lower (by 50%) after an isolated calf (distal) DVT than after proximal DVT or PE[7].
    - * Burden of anticoagulation (financial, functional, and psychological), and quality of life
  - ◊ Long term anticoagulation should be considered with a first unprovoked episode of proximal DVT or PE[7].
  - ◊ 25% risk of recurrence in the first 5 years and 36% in the first 10 years after stopping anticoagulant therapy[7].

Reassess residents taking an OAC for prevention of DVT or PE. Consider the duration since the DVT/PE occurred and the cause of the DVT/PE, if known, to identify residents who no longer require the OAC.

Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Anticoagulation

Table 1: Summary of Recommendations on Duration of Anticoagulant Therapy for Venous Thromboembolism (VTE)[7]

CATEGORIES OF VTE	DURATION OF TREATMENT
First VTE provoked by a transient risk factor	3 months*
Second VTE provoked by a transient risk factor	Same as for first VTE provoked by a transient risk factor*
First unprovoked VTE†	Minimum of 3 months and then reassess.
With low or moderate bleeding risk	Indefinite therapy with periodic reviews¶‡
With high bleeding risk	3 months, especially if recurrent VTE risk is relatively lower and/or bleeding risk factors cannot be mitigated
Second unprovoked VTE	Same as for first unprovoked VTE; this is a strong indication for indefinite anticoagulant therapy unless there is a very high bleeding risk¶‡
Isolated distal DVT	3 months*
Central venous catheter(CVC)-associated VTE	3 months*; longer if CVC remains in place
VTE associated with ongoing non-cancer-related risk factors (e.g. paraplegia or other significant immobility, active inflammatory bowel disease, high risk thrombophilia)	Indefinite therapy with periodic reviews or as long as the risk factor persists¶
Cancer-associated VTE	Minimum 3 months, then reassess and continue if active cancer or patient continuing to receive anticancer therapy

**Although 3 months is the usual length of time-limited treatment, 6 months may be preferred if: (i) the DVT or PE was very large or very symptomatic; or (ii) symptoms of the initial DVT or PE persist; or (iii) the patient is not ready (confident enough) to stop anticoagulant therapy at 3 months; and (iv) the patient does not have a high risk for bleeding.*

† Absence of a transient risk factor, active cancer or other ongoing clinical risk factor for recurrent VTE.

¶ Patients who have been recommended indefinite anticoagulant therapy should be reassessed periodically (e.g. yearly) to re-estimate the VTE versus bleeding risk balance and review patient preferences.

‡ For patients continuing on long term rivaroxaban or apixaban beyond 6 months, dose reduction of rivaroxaban to 10 mg once daily or apixaban to 2.5 mg twice daily can be considered based on the results of the EINSTEIN CHOICE and AMPLIFY Extend studies in which these lower doses were as effective and safe as standard dosing

Efficacy & Safety of Anticoagulation in Elderly & LTC Populations

- Meta-analysis & systematic review of randomized trials of DOACs (including apixaban, rivaroxaban, edoxaban, and dabigatran) for efficacy and DOACs compared to vitamin K antagonists (VKA) in patients 75 years and older[8].
  - ◊ Primary efficacy outcome: each DOAC shown to be at least as effective or superior to VKA in elderly in reducing risk of stroke or systemic embolism in AF, and risk of recurrent thromboembolism in VTE, however, bleeding patterns were distinct[8]. In particular, dabigatran was associated with a higher risk of gastrointestinal bleeding than VKA. Insufficient data for apixaban, edoxaban, and rivaroxaban indicates further work is needed to clarify their bleeding risks in the elderly[8].
  - ◊ 19 studies were eligible for inclusion, but only 11 reported data specifically for elderly patients[8].
  - ◊ Efficacy in managing thrombotic risks for each DOAC was similar or superior to VKA's in elderly populations[8].
  - ◊ A non-significantly higher risk of major bleeding compared to VKA was seen with dabigatran 150 mg (odd ratio 1.18, 95% CI 0.97-1.44) but not with dabigatran 110 mg daily. Significantly higher gastrointestinal bleeding risks were seen with dabigatran 150 mg daily (OR 1.78, 95% CI 1.35-2.35) and dabigatran 110 mg daily (OR 1.40, 95% CI 1.04-1.90)[8]. Lower intracranial bleeding risks compared to VKA were seen with dabigatran 150 mg (OR 0.43, 95% CI 0.26-0.72) and dabigatran 110 mg daily (OR 0.36, 95% CI 0.22-0.610)[8].
  - ◊ For apixaban, a significantly lower major bleeding risk compared to VKAs was observed (OR 0.63, 95% CI 0.51-0.77), edoxaban 60 mg (OR 0.81, 95% CI 0.67-0.98) and 30 mg (OR 0.46, 95% CI 0.38-0.57) while rivaroxaban showed a similar risk[8].

- Low-dose edoxaban in very elderly patients with atrial fibrillation (ELDERCARE-AF) included 984 octogenarian Japanese patients with a mean age of 87 years old[9].
  - ◊ Typical dose of edoxaban is 30 mg or 60 mg daily. This trial compared edoxaban 15 mg daily to placebo[9].
    - ∗ Annual rate of stroke or systemic embolism was 2.3% in the edoxaban group and 6.7% in the placebo group (HR 0.34. 95% CI 0.19-0.61; P<0.001) and the annual rate of major bleeding was 3.3% in the edoxaban group and 1.8% in the placebo group (HR 1.87; 95% CI 0.90-3.89, P=0.09)[9].
    - ∗ No fatal bleeds and no intracranial hemorrhages[9].
    - ∗ No substantial between group difference in death from any cause (9.9% in edoxaban group and 10.2% in the placebo group; hazard ratio, 0.97; 95% CI 0.69-1.36)[9].

Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Anticoagulation

Efficacy & Safety of Anticoagulation in Elderly & LTC Populations continued…

- ◊ A recently published subgroup analysis found that the edoxaban group consistently had fewer stroke or systemic embolism events regardless of frailty status[10].
  - * Objective was to compare very low dose edoxaban (15 mg daily) compared to placebo across frailty status
  - * 944 patients analyzed using data from the ELDERCARE-AF trial. It was found that very low dose edoxaban was associated with a lower incidence of stroke or systemic embolism consistently across frailty status[10]. These findings suggest that edoxaban 15 mg daily is superior to placebo in preventing stroke or systemic embolism in very elderly patients with atrial fibrillation, regardless of frailty status.
  - * Major bleeding and major or clinically relevant nonmajor bleeding events both higher with edoxaban, regardless of frailty compared to placebo[10].
  - * In the placebo group, the estimated event rates for stroke or systemic embolism were 7.1% (1.6%) per patient year in the frail group and 6.1% (1.3%) per patient year in the non-frail group and there was no difference between the groups[10].

- Comparative safety and effectiveness of oral anticoagulants in nonvalvular atrial fibrillation (NAXOS Study) analyzed 321,501 patients, 35% (VKAs), 27% (apixaban), 31.1% (rivaroxaban) and 6.6% dabigatran[11].
  - ◊ Mean age was 78.5 years (VKA), 74.7 years (Apixaban), 72 years (rivaroxaban), 72.7 years (dabigatran)
  - ◊ Apixaban was associated with a lower risk of major bleeding compared to VKAs (HR, 0.43 [95% CI, 0.40-0.46]) and rivaroxaban (HR 0.67, [95% CI 0.63-0.72]), but not dabigatran (HR, 0.93 [95% CI, 0.81-1.08])[11].
  - ◊ Apixaban was associated with a lower risk of stroke and systemic thromboembolism compared to VKAs (HR, 0.60 [95% CI, 0.56-0.65]), but not rivaroxaban (HR 1.05 [95% CI 0.97-1.15]) or dabigatran (HR, 0.93 [95% CI 0.78-1.11])[11].
  - ◊ All-cause mortality was lower with apixaban than with VKAs, but not lower than rivaroxaban or dabigatran[11].
  - ◊ Apixaban was associated with superior safety, efficacy, effectiveness, and lower mortality than VKA; superior safety than rivaroxaban and similar safety to dabigatran; and with similar effectiveness when compared with rivaroxaban or dabigatran[11].
- Comparative safety and effectiveness of direct acting oral anticoagulants versus warfarin: a national cohort study of nursing home residents[12]
  - ◊ This retrospective cohort study included nursing home residents 65 years and older with non-valvular atrial fibrillation.
  - ◊ Outcomes included ischemic stroke or TIA, bleeding, other vascular events, and a composite of all outcomes
  - ◊ Overall, apixaban users had higher ischemic cerebrovascular events (HR 1.86, 95% CI 1.00-3.45) and lower bleeding rates (HR 0.66; 95% CI 0.49-0.88) compared to warfarin but outcome rates varied by dosing alignment[12].
    - * Misaligned DOAC dosing was common (33.5% apixaban, 40.9% dabigatran, and 55.6% rivaroxaban) in nursing home residents. Under dosing was associated with higher ischemic cerebrovascular event rates and lower mortality rates (apixaban, dabigatran, and rivaroxaban) and higher than recommended dosing was associated with higher bleeding rates (apixaban and dabigatran)[12].
    - * Subtherapeutic dosing is expected to be associated with lower bleeding and higher ischemic rates[12].
  - ◊ Mortality rates (per 100 person years) were lower for apixaban (absolute rate differences [RDs] - 9.30; 95% CI 13.18-5.42), dabigatran (RDs – 10.79; 95% CI 14.98-6.60), and rivaroxaban (RDs - 8.92; 95% CI 12.01-5.83) compared to warfarin; composite outcome findings were similar[12].
- Rates of potentially inappropriate dosing of direct-acting oral anticoagulants and associations with geriatric conditions among older adults with atrial fibrillation: The SAGE-AF[13]
  - ◊ This study developed an algorithm to analyze dose appropriateness of DOACs to account for drug-drug interactions, age, renal function, and body weight.
  - ◊ Of 1064 participants prescribed anticoagulants, 460 received a DOAC. 23% (105) of participants received an inappropriate DOAC dose, of whom 78% (82) were underdosed, and 22% (23) were overdosed[13].
  - ◊ Older age, higher CHA2DSVASc score, and history of renal failure were associated with inappropriate DOAC dosing, but frailty and other geriatric conditions were not associated with inappropriate DOAC dosing[13].

Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Anticoagulation

Table 2: Optimal Dosing and Durations for DOACs[19,21]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Clinical Indications & doses				
Non-valvular A fib (indefinite duration)	150 mg BID *110 mg BID if 80 years or older or older than 75 with more than 1 bleeding risk factor*	20 mg daily *15 mg daily if CrCl 15-49 mL/min*	5 mg BID *2.5 mg BID if 2 or more of: 80 years or older, 60 kg or less, sCr 133 µmol/L or higher*	60 mg daily *30 mg daily if CrCl 30-50 mL/min, 60 kg or less, drug interactions*
Acute VTE (3-6 months)	150 mg BID (after 5-10 days of LMWH)	15 mg BID x 21 days then 20 mg daily	10 mg BID x 7 days then 5 mg BID	60 mg or 30 mg daily (after 5-10 days low molecular weight heparin)
2˚ prevention of VTE	150 mg BID	20 mg or 10 mg daily	5 or 2.5 mg BID *Consider 2.5 mg BID for treatment beyond 6 months for DVT prevention*[6]	60 mg or 30 mg daily
Stable CAD or PAD	N/A	2.5 mg BID + ASA 81 mg daily	N/A	N/A
Non-valvular AF stoke prevention + PCI with coronary stent	110 mg or 150 mg BID + clopidogrel 75 mg daily	15 mg po daily + clopidogrel 75 mg daily (rivaroxaban 10 mg if CrCl 30-50mL/min)	AF dosing + clopidogrel 75 mg daily	60 mg po daily + clopidogrel 30 mg if CrCl 15-50, 60 kg or less, potent P-gp inhibitor

Efficacy & Safety of Anticoagulation in Elderly & LTC Populations continued...

- Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients with Atrial Fibrillation and Renal Dysfunction[14]
  - ◊ All DOACs have some degree of renal clearance (80% for dabigatran, 50% for edoxaban, 35% for rivaroxaban, and 27% for apixaban) and dose reduction is indicated in patients with significant renal impairment[14].
  - ◊ Failure to reduce the dose in severe renal disease may increase the risk of bleeding, whereas inappropriate dose reduction without a firm indication may decrease the effectiveness of the medication, putting patients with atrial fibrillation at a greater risk of stroke[14].
  - ◊ A total of 14,865 patients with nonvalvular AF were identified who initiated apixaban, dabigatran, or rivaroxaban who have creatinine tests prior to treatment initiation (eGFR less than 15 mL/min were excluded)[14].
  - ◊ 1473 patients were identified to have an indication for a dose reduction. Of these patients, 43% were potentially overdosed with a higher risk of major bleeding (HR 2.19; 95% CI 1.07-4.46) but there was no statistically significant difference in stroke[14].
  - ◊ 13,392 patients were identified as having no indication for dose reduction, and 13.3% of patients were potentially underdosed. Underdosing was associated with a higher risk of stroke (HR 4.87; 95% CI 1.30-18.26) but no statistically significant difference in major bleeding in apixaban-treated patients[14].
  - ◊ There were no statistically significant relationships in dabigatran or rivaroxaban treatment patients without a renal indication[14].

- **Inappropriate dosing of DOACs (either too high or too low) is common in elderly populations[12]. Ensure residents are on the appropriate dose of their DOAC (see Table 2).**
- **Apixaban was associated with superior safety, efficacy, effectiveness, and lower mortality than VKA; superior safety than rivaroxaban and similar safety to dabigatran; and with similar effectiveness when compared with rivaroxaban or dabigatran[11]. Apixaban is now available from generic companies so it is the most cost-effective DOAC (see Tables 3 & 4).**
- **Apixaban is the preferred DOAC for PCH residents so consider switching residents from other DOACs to apixaban.**

Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Anticoagulation

Table 3: Cost and Coverage for Warfarin and the DOACs in Manitoba [24-26]

Drug	Cost	Coverage
Warfarin	Approx. $15/month + indirect costs for INR monitoring	Part 1 (full benefit)
Apixaban (Eliquis®)	Generic is available – approx. $26/month	Part 3 EDS approval
Dabigatran (Pradaxa®)	Generic is available – approx. $79/month	Part 3 EDS approval
Rivaroxaban (Xarelto®)	No generic available – approx. $89/month	Part 3 EDS approval
Edoxaban (Lixiana®)	No generic available – approx. $89/month	Part 3 EDS approval

Table 4: Manitoba Pharmacare EDS Criteria for DOACs for Atrial Fibrillation and VTE Prophylaxis [25]

EDS Criteria for DOACs[25]	
Rivaroxaban	For the treatment of DVT & PE for a duration of up to 6 months, excluding: • Patients with clinically significant active bleeding, such as GI bleeding, including that is associated with hemorrhagic manifestations, bleeding diatheses, spontaneous impairment of hemostasis or patients with spontaneous impairment of hemostasis • Patients with severe renal impairment (CrCl less than 30 mL/min)
Apixaban **Edoxaban** **Rivaroxaban** **Dabigatran**	For patient with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism AND: • Anticoagulation is inadequate following a reasonable trial on warfarin OR • Anticoagulation with warfarin is contraindicated or not possible due to inability to regularly monitor INR (no access to INR testing services at a laboratory, clinic, pharmacy, and at home)
Apixaban **Edoxaban**	For the treatment of VTE (DVT & PE) and the prevention of recurrent DVT & PE for a duration of up to 6 months
Rivaroxaban 2.5 mg for CAD & PAD[26] (based on the results of the COMPASS trial)	In combination with ASA (75-100mg) for the prevention of stroke, myocardial infarction, and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with PAD & CAD: See Pharmacare Bulletin #106 (March 2, 2020): https://www.gov.mb.ca/health/mdbif/docs/bulletins/bulletin106.pdf

Fall Risk with DOACs & Warfarin

- Guidelines for managing AF recommend anticoagulation for almost all patients 65 years or older, but in practice up to 50% of patients do not receive maintenance anticoagulation therapy[2]
- The most frequent reason for not prescribing a DOAC in older adults with six or more comorbidities is falls or frailty (31%)[22]
- Older adults with AF benefit from stroke prevention with anticoagulation even if they are at high risk of falls. Fall risk should not be a deciding factor for withholding anticoagulation in this population[2].
- Compared to warfarin and rivaroxaban, apixaban is the anticoagulant with the highest benefit-risk ratio for older adults with atrial fibrillation[23].

How often would a resident need to fall for risk to outweigh the benefit of anticoagulation?

Apixaban 458 times in 1 year[23]

Warfarin 295 times in 1 year[2]

Rivaroxaban 45 times in 1 year[23]

Older adults with AF benefit from stroke prevention with anticoagulation even if they are at high risk of falls. Fall risk should not be a deciding factor for withholding anticoagulation in this population.[2]

Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Anticoagulation

Efficacy & Safety for DOACs versus ASA for Indications Requiring Anticoagulation

- Subgroup analysis from the AVERROES trial included 1989 patients 75 years and older and 366 patients 85 years and old older[15]
  - ◊ In patients 75 years and older, there was a greater relative risk reduction of stroke with apixaban (HR 0.33, 95% CI 0.18-0.56) compared with younger patients (HR 0.68, 95% CI 0.42-1.08)[15].
  - ◊ NNT to prevent a stroke was 26 patients in the 75 years and older group, compared with NNT of 143 in younger patients. The NNT was lower at 15 for the older age group of 85 years and older (see Table 5)[15.]
  - ◊ Relative efficacy of ASA to prevent ischemic stroke decreases as patients with AF age, and appeared to be ineffective as patients enter their eighth decade[15].
  - ◊ The benefit of apixaban with advancing age appears to be due to a rapidly increasing stroke risk on ASA, whereas stroke risk on apixaban is relatively consistent across age groups[15].
  - ◊ Conclusion: older patients with AF are at a higher risk of stroke if given ASA alone and have greater relative and absolute benefits from apixaban compared to younger patients with no greater risk of hemorrhage.[15]

Table 5: Risk of Stroke or Systemic Embolism in Patients Treated with Apixaban versus ASA[15]

Age	NNT to prevent stroke or systemic embolization for apixaban vs ASA
Less than 75 years	**143**
75 years and older	**26**
85 years and older	**15**

- Warfarin versus Aspirin for stroke prevention in an elderly community population with atrial fibrillation included 973 patients 75 years and older[16]. Patients randomly assigned to warfarin (INR 2-3) or Aspirin (75 mg daily)
  - ◊ Primary endpoint was fatal or disabling stroke (ischemic or hemorrhagic), intracranial hemorrhage, or clinically significant arterial embolism
  - ◊ Mean follow up was 2.7 years
  - ◊ There were 24 primary events in the warfarin group, and 48 primary events in ASA groups[16].
  - ◊ Warfarin was shown to be more effective than ASA in prevention of stroke in people with atrial fibrillation aged 75 and older. There was no evidence that anticoagulants were more hazardous than ASA therapy in this age group[16].

ASA alone is not sufficient for stroke prevention in older adults with atrial fibrillation. The stroke prevention benefit from apixaban was shown to be greater with no increased risk of hemorrhage (NNT=26 for 75 years and older and NNT=15 for 85 years and older).[15]

Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

Optimizing Anticoagulation

References

1. Damanti S, Braham S, Pasina L. (2019). Anticoagulation in frail older people. *J Geriatr Cardiol. 16(11):*844-846. doi: 10.11909/j.issn.1671-5411.2019.11.005.
2. Hagerty T, Rich MW. (2017). Fall risk and anticoagulation for atrial fibrillation in the elderly: A delicate balance. *Cleve Clin J Med. 84(1)*:35-40. doi: 10.3949/ccjm.84a.16016.
3. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, Cox JL, Dorian P, Gladstone DJ, Healey JS, Khairy P, Leblanc K, McMurtry MS, Mitchell LB, Nair GM, Nattel S, Parkash R, Pilote L, Sandhu RK, Sarrazin JF, Sharma M, Skanes AC, Talajic M, Tsang TSM, Verma A, Verma S, Whitlock R, Wyse DG, Macle L. (2020). The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol. 36(12):*1847-1948. doi: 10.1016/j.cjca.2020.09.001.
4. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. (2009). Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med. 14;360(20)*:2066-78. doi: 10.1056/NEJMoa0901301.
5. Thrombosis Canada. (2022). Pulmonary Embolism (PE): Treatment. https://thrombosiscanada.ca/wp-uploads/uploads/2022/12/5.-Pulmonary-Embolism-Treatment_01December2022.pdf
6. Thrombosis Canada. (2023). Deep Vein Thrombosis (DVT): Treatment. https://thrombosiscanada.ca/wp-uploads/uploads/2023/02/3.-Deep-Vein-Thrombosis-Treatment_20February2023-2.pdf
7. Thrombosis Canada (2021). Venous Thromboembolism: Duration of Treatment. https://thrombosiscanada.ca/wp-content/uploads/2021/09/7.-VTE-Duration-of-Treatment_27Sept2021-2.pdf
8. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. (2015). Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism: Systematic Review and Meta-Analysis. *Circulation. 21;132(3)*:194-204. doi: 10.1161/CIRCULATIONAHA.114.013267.
9. Okumura K, Akao M, Yoshida T, Kawata M, Okazaki O, Akashi S, Eshima K, Tanizawa K, Fukuzawa M, Hayashi T, Akishita M, Lip GYH, Yamashita T. (2020). Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation. *N Engl J Med. 383(18)*:1735-1745. doi: 10.1056/NEJMoa2012883.
10. Akashi S, Oguri M, Ikeno E, Manita M, Taura J, Watanabe S, Hayashi T, Akao M, Okumura K, Akishita M, Yamashita T. (2022). Outcomes and Safety of Very-Low-Dose Edoxaban in Frail Patients With Atrial Fibrillation in the ELDERCARE-AF Randomized Clinical Trial. *JAMA Network Open. 5(8)*:e2228500. doi: 10.1001/jamanetworkopen.2022.28500.
11. Van Ganse E, Danchin N, Mahé I, Hanon O, Jacoud F, Nolin M, Dalon F, Lefevre C, Cotté FE, Gollety S, Falissard B, Belhassen M, Steg PG. (2020). Comparative Safety and Effectiveness of Oral Anticoagulants in Nonvalvular Atrial Fibrillation: The NAXOS Study. *Stroke. 51(7):*2066-2075. doi: 10.1161/STROKEAHA.120.028825.
12. Alcusky M, Tjia J, McManus DD, Hume AL, Fisher M, Lapane KL. (2020). Comparative Safety and Effectiveness of Direct-Acting Oral Anticoagulants Versus Warfarin: a National Cohort Study of Nursing Home Residents. *J Gen Intern Med. 35(8)*:2329-2337. doi: 10.1007/s11606-020-05777-3.
13. Sanghai S, Wong C, Wang Z, Clive P, Tran W, Waring M, Goldberg R, Hayward R, Saczynski JS, McManus DD. (2020). Rates of Potentially Inappropriate Dosing of Direct-Acting Oral Anticoagulants and Associations With Geriatric Conditions Among Older Patients With Atrial Fibrillation: The SAGE-AF Study. *J Am Heart Assoc. 9 (6)*:e014108. doi: 10.1161/JAHA.119.014108.
14. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. (2017). Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. *J Am Coll Cardiol. 13;69(23):*2779-2790. doi: 10.1016/j.jacc.2017.03.600.
15. Ng KH, Shestakovska O, Connolly SJ, Eikelboom JW, Avezum A, Diaz R, Lanas F, Yusuf S, Hart RG. (2016). Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial. *Age Ageing. 45(1)*:77-83. doi: 10.1093/ageing/afv156.
16. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E. (2007). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet. 370(9586):*493-503. doi: 10.1016/S0140-6736(07)61233-1.
17. Shmyr D, Van der Merwe V, Yakiwchuk E, Barry A, Kosar L. (2017). Triple antithrombotic therapy for atrial fibrillation and coronary stents. *Can Fam Physician. 63 (5)*:375-381.
18. Matsumura-Nakano Y, Shizuta S, Komasa A, Morimoto T, Masuda H, Shiomi H, Goto K, Nakai K, Ogawa H, Kobori A, Kono Y, Kaitani K, Suwa S, Aoyama T, Takahashi M, Sasaki Y, Onishi Y, Mano T, Matsuda M, Motooka M, Tomita H, Inoko M, Wakeyama T, Hagiwara N, Tanabe K, Akao M, Miyauchi K, Yajima J, Hanaoka K, Morino Y, Ando K, Furukawa Y, Nakagawa Y, Nakao K, Kozuma K, Kadota K, Kimura K, Kawai K, Ueno T, Okumura K, Kimura T. (2019). Open-Label Randomized Trial Comparing Oral Anticoagulation With and Without Single Antiplatelet Therapy in Patients With Atrial Fibrillation and Stable Coronary Artery Disease Beyond 1 Year After Coronary Stent Implantation. *Circulation. 139(5)*:604-616. doi: 10.1161/CIRCULATIONAHA.118.036768.
19. RxFiles: Oral Antithrombotic Agents (page 16)
20. https://www.mdcalc.com/calc/807/has-bled-score-major-bleeding-risk (HASBLED scoring tool for patients with atrial fibrillation)
21. Thrombosis Canada. (2023). DOACs: Comparisons and frequently asked questions. https://thrombosiscanada.ca/wp-uploads/uploads/2023/01/21.-DOACs-Comparison-and-FAQs_05Jan2023.pdf
22. Dalgaard F, Xu H, Matsouaka RA, Russo AM, Curtis AB, Rasmussen PV, Ruwald MH, Fonarow GC, Lowenstern A, Hansen ML, Pallisgaard JL, Alexander KP, Alexander JH, Lopes RD, Granger CB, Lewis WR, Piccini JP, Al-Khatib SM. (2020). Management of Atrial Fibrillation in Older Patients by Morbidity Burden: Insights From Get With The Guidelines-Atrial Fibrillation. *J Am Heart Assoc. 9(23)*:e017024. doi: 10.1161/JAHA.120.017024.
23. Wei W, Rasu RS, Hernández-Muñoz JJ, Flores RJ, Rianon NJ, Hernández-Vizcarrondo GA, Brown AT. (2021). Impact of Fall Risk and Direct Oral Anticoagulant Treatment on Quality-Adjusted Life-Years in Older Adults with Atrial Fibrillation: A Markov Decision Analysis. *Drugs Aging. 38(8)*:713-723. doi: 10.1007/s40266-021-00870-6.
24. Falk J, Friesen K, and Bugden S. (2022). Price Comparison of Commonly Prescribed Medications in Manitoba. https://medsconference.org/resources/
25. Manitoba Health. (2023). Exception Drug Status. www.gov.mb.ca/health/mdbif/docs/edsnotice.pdf
26. Manitoba Health. (2023). Manitoba Drug Interchangeability Formulary. https://residents.gov.mb.ca/forms.html?d=details&pub_id=10542&filter_keyword=interchangeability
27. Thrombosis Canada. (2020). Direct Oral Anticoagulation Clinician Follow up Checklist. https://thrombosiscanada.ca/wp-content/uploads/2020/02/ENG-Clinician-Checklist-Feb-2020.pdf