PRESCRIPTION pad

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Oral Anticoagulants in Atrial Fibrillation

Patients with atrial fibrillation are at an increased risk of stroke and systemic embolism, which can result in death, disability, and impaired quality of life.[1] Warfarin has been used for decades as an effective intervention for reducing the risk of stroke in patients with atrial fibrillation.[2,3] The introduction of new oral anticoagulants provides alternatives to warfarin in select clinical circumstances; however, like warfarin, these anticoagulants are not without risk.[4]

This PAD educational session, *Oral Anticoagulants in Atrial Fibrillation: Update 2014,* aims to provide a balanced discussion of the current evidence on the role of the new oral anticoagulants and the continued need to ensure that adjusted-dose warfarin is managed well.

Learning Objectives

During each PAD session, participants will have the opportunity to discuss:

1. How to apply current evidence for the oral anticoagulants (i.e., warfarin, dabigatran, rivaroxaban, apixaban) in clinical practice.
2. Why warfarin remains the initial therapy for most patients with atrial fibrillation when anticoagulation is considered.
3. Why the Canadian Agency for Drugs and Technologies in Health (CADTH) recommends that the new oral anticoagulants be considered in patients with non-valvular atrial fibrillation who are unable to achieve adequate anticoagulation with warfarin.
4. How to judiciously manage oral anticoagulants, including:
    - initial doses,
    - monitoring and dose adjustments, and
    - the management of drug interactions.
5. Why combined therapy with an oral anticoagulant and an antiplatelet medication is NOT recommended in patients with non-valvular atrial fibrillation except in select coronary heart disease circumstances.

Evidence Considerations: Oral anticoagulant comparisons

A 2013 therapeutic review performed by the Canadian Agency for Drugs and Technologies in Health (CADTH) finds that when oral anticoagulants are compared, **"a conservative interpretation of any apparently statistically significant differences"** is warranted.[1] Evidence considerations identified in CADTH's review and elsewhere include but are not limited to:

- There is **one principal randomized controlled trial (RCT)** comparing each new oral anticoagulant to adjusted-dose warfarin (Appendix 1).[1,5,6] Studies that have not been replicated do not provide information on consistency of the effect.[1,7]
- Perspectives on the **clinical significance** of differences between the new oral anticoagulants and warfarin on stroke and bleeding outcomes are divergent.[1,5,6,8–11] In absolute terms, the differences on most stroke and bleeding outcomes is a difference of less than 10 events per 1,000 patients treated each year or less than 1% per year (Appendix 2).[1,5]
- There are **no direct RCT comparisons** between the new oral anticoagulants. **Clinical and methodological heterogeneity** between the principal RCTs limits reaching firm conclusions regarding differences between the new oral anticoagulants, even when formal indirect comparisons (e.g., network meta-analyses) are performed.[1,5,9,12]
- The duration of follow-up in anticoagulant RCTs is **short (i.e., ≤ 2 years)** and cannot inform of longer-term safety and efficacy.[1,5,8,9] The US Food and Drug Administration (FDA) recently outlined its plans for post-marketing safety surveillance of new oral anticoagulants approved for atrial fibrillation.[13,14]
- There may be limitations to extrapolating the results from large global RCTs to specific **geographic regions**.[5,9,15] Time in therapeutic range (TTR) in the warfarin treatment arms varied by country, with North American sites generally achieving among the higher TTRs relative to other regions of the world; this may reflect differences in standards of overall health care and quality of anticoagulation management.[9,15–19]
- **Methodological limitations** have increased relevance as sources of potential bias in non-inferiority RCTs (the primary design of the **anticoagulant comparison RCTs**).[20] Concerns raised by US FDA medical reviewers, US FDA advisory committees and by others include but are not limited to:
    - open-label design;[15,21–23]
    - suboptimal administration of the standard treatment (i.e., warfarin);[12,24,25]
    - losses to follow-up and incomplete mortality data;[15,25,26]
    - debate regarding the appropriateness of a once daily regimen for rivaroxaban;[24,25]
    - shorter duration of follow-up for some safety outcomes;[12] and
    - concerns regarding trial conduct.[26]
- **Methodological deficiencies** are also identified in the **historical warfarin RCTs** (i.e., when warfarin was compared to placebo or control in superiority RCTs).[2] Consistent reductions in ischemic stroke outcomes for warfarin across multiple RCTs has served to increase confidence in the efficacy of warfarin and also informs the validity of its selection as the standard-of-care comparator in the new oral anticoagulant RCTs.[2,21]

Clinical Practice Gaps: New oral anticoagulants

Current warfarin management recommendations have evolved over decades of clinical experience.[27] **Limited clinical experience** with the new oral anticoagulants means there is less clinical guidance. Clinical practice gaps include but are not limited to:

- Optimal and standardized emergency **bleed management strategies** for the new oral anticoagulants are not yet defined (including reversal of anticoagulant activity and standardized laboratory assays for assessing anticoagulant activity).[1,5,8–10,28–31]
- Given the shorter half-lives of the new oral anticoagulants relative to warfarin, the **potential impact of missed doses** on clinical outcomes has been raised as a concern.[8,9,25,31,32]
- **Optimal strategies for switching** between the new anticoagulants and warfarin are uncertain.[8,9,24–26,31]
- **Strategies for the perioperative management** of the new oral anticoagulants are less consistently defined than for warfarin.[8,10,30,33]
- **Optimal dosing** of the new oral anticoagulants in patients with risk factors for an anticoagulant-associated bleed, such as the **frail elderly, low body weight, and those with renal impairment**, is uncertain as is the generalizability of anticoagulant RCT results to those of advanced age and frailty.[10,32,34–39]
- Post-marketing reports of serious bleeding events for dabigatran emphasize the importance of **attention to renal function** at baseline and in clinical circumstances where renal function may deteriorate acutely.[40]
- The new oral anticoagulants are susceptible to **drug interactions with inhibitors or inducers of cytochrome P450 3A4 and P-glycoprotein**.[32,41] Relevant drug interactions exist with other medications often prescribed to patients with atrial fibrillation (Table 2).[32,41] Relative to warfarin, there is limited clinical experience and an absence of laboratory monitoring methods to guide the management of these drug interactions.[32,41,42]

Decision Making: Oral anticoagulants

The Institute for Safe Medication Practices reminds that **all anticoagulants are high-risk medications**.[4] In addition to vigilant prescribing, detailed patient education and attention to patient preferences (including discussion of evidence and the evidence gaps, current clinical practice uncertainties, medication costs and laboratory monitoring requirements), decision making should include:

- Only prescribing an anticoagulant with which you are **highly familiar**.
- **Detailed transfers of information** to other care providers during patient transitions through health care settings while assuring continued access to anticoagulant therapy (e.g., community, inpatient, emergency, long-term care).[43]
- Awareness of clinical circumstances where the use of **warfarin is <u>preferred</u> in patients with atrial fibrillation** or **where a new oral anticoagulant is <u>contraindicated</u>**, including:
    - Patients with prosthetic heart valves or hemodynamically-significant valvular disease.[6,40,44–46]
    - Patients currently well-managed on warfarin.[6,32]
    - Patients with stable coronary heart disease, placement of an intracoronary stent, or acute coronary syndrome.[6,32]
    - Cytochrome P450 3A4 and P-glycoprotein drug interactions that preclude the use of a new oral anticoagulant.[32,41]
- Consideration of **participant inclusion and exclusion criteria** of the principal RCTs (Appendix 1).[42]
- Attention to dosing recommendations and contraindications in patients with **renal impairment or other risk factors for anticoagulant-associated bleeding**.
- **Regular follow-up** to assess for adverse events and medication adherence (note: in the new oral anticoagulant RCTs most patients were assessed at least monthly).[47–49]

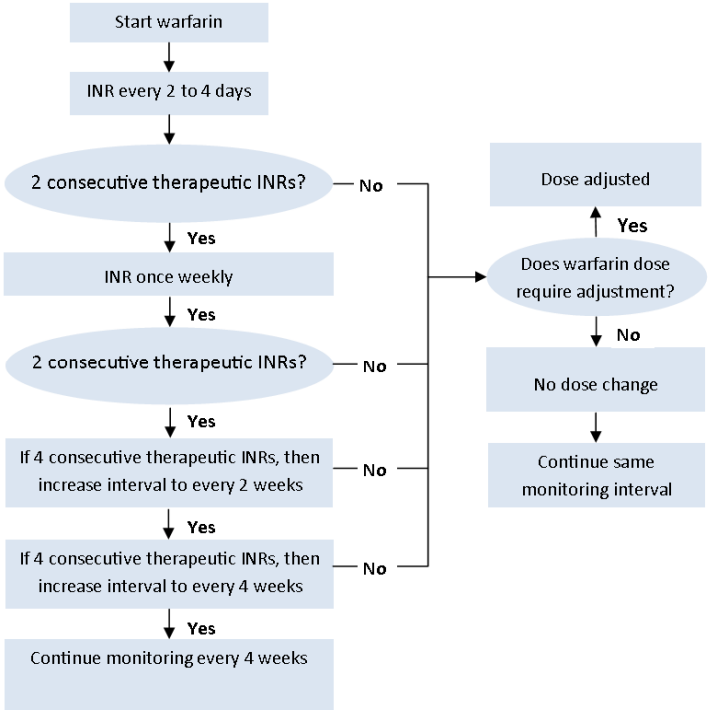
Initiation and Maintenance: Adjusted-dose warfarin

Initiation of Warfarin

- There is insufficient evidence to identify the optimal initiation dose of warfarin with respect to the following outcomes: improving time in therapeutic range; predicting time to achieve therapeutic INR; and effect on serious adverse events.[50]
- A reasonable **initial dose for most patients is 5 mg per day**.[51]
- Consider a **lower initial dose (i.e., < 5 mg per day)** for the following patients:[51–53]
  - Age > 70 years
  - Baseline INR > 1.1
  - Hypoalbuminemia (e.g., malnourished, liver disorders, post-operative)
  - Impaired nutrition or weight < 45 kg
  - Congestive heart failure
  - Concurrent medications that increase the effect of warfarin (i.e., ↑ INR)
  - Previously documented increased sensitivity to warfarin
- A therapeutic INR range of 2.0 to 3.0 (target 2.5) is recommended for patients with non-valvular atrial fibrillation.[27]
  - Certain patients, such as those with a mechanical mitral valve, may require a higher therapeutic INR range of 2.5 to 3.5 (target 3.0).[45] Refer to current practice guidelines for comprehensive recommendations.[45]

INR Monitoring

- An INR effect may be noted within the first 2 or 3 days; however, full anticoagulant effect may require up to 5 to 6 days.[51,52]



Increase frequency of INR monitoring to every 2 to 4 days for the following:[51]

- Non-therapeutic INR
- Intercurrent illness
- Any change in concomitant medication (particularly those with warfarin interactions) or change in herbal medication
- Significant change in diet

Adapted from Guidelines and Protocols Advisory Committee: Warfarin Therapy Management (October 1, 2010)[51]

Warfarin Dosing Adjustments

- Managing warfarin therapy should follow a **well-coordinated and structured approach**, including dosing nomograms or decision support tools.[27,54,55]
- Many nomograms are available; use the one that is available in your care setting.[54]
- **Before adjusting warfarin**, evaluate the patient for transient causes (e.g., missed/extra dose, gastroenteritis, antibiotics, recent ↑ alcohol intake) or permanent causes (e.g., lifestyle change, change in chronic medication) of INR changes.[54]
- In patients with a previously stable INR (at least 3 months of consistent therapeutic INRs without requiring a warfarin dose adjustment), **do not adjust warfarin dose based on a single INR within +/- 0.5 of the therapeutic range**.[27] Continue the current warfarin dose and recheck the INR within 1 to 2 weeks.[27]

Table 1: Example of a Dosing Nomogram (for target INR 2.0 to 3.0)

INR	Intervention
Sub-therapeutic INR[51,54]	
< 1.5	**One** extra dose (equal to 20% of weekly dose) ***and*** ↑ weekly dose by **10 to 20%**
1.5 to 1.9	↑ weekly dose by **5 to 10%**
Therapeutic INR[54]	
2.0 to 3.0	No change
Supra-therapeutic INR[27,51,54]	
3.1 to 3.5	**May** consider ↓ weekly dose by **5 to 10%**
3.6 to 4.9 **(without bleeding)**	Hold **one** dose ***and*** ↓ weekly dose by **10 to 20%**
5.0 to 9.0 **(without bleeding)**	Hold **two** doses ***and*** ↓ weekly dose by **10 to 20%**
> 9.0 **(without bleeding)**	Urgent assessment Temporarily **stop** warfarin Consider giving **one** dose of Vitamin K 2.5 mg orally if INR > 9.0; may repeat oral Vitamin K in 24 hours if INR remains > 9.0 Resume warfarin when INR is therapeutic (2.0 to 3.0) ***and*** ↓ weekly dose by **20%**
Increase in the frequency of INR monitoring is recommended when the INR is sub- or supra-therapeutic. If bleeding, or signs/symptoms of stroke or thromboembolism, provide appropriate urgent/emergency care.[54]	

Clinical Considerations for Warfarin Management

Dose Adjustments

- During the maintenance phase, dose adjustments may not be reflected in the INR for 4 to 5 days, therefore **frequent dose changes are not recommended**.[51]

Out-of-Range INRs

- In patients with a previously stable INR (i.e., at least 3 months of consistent therapeutic INRs without requiring a dose adjustment), **do not adjust the dose based on a single INR within +/- 0.5 of the therapeutic range**.[27] Continue the current dose and recheck the INR within 1 to 2 weeks.[27]
- Avoid the routine use of Vitamin K in patients with INRs ≤ 9 if there is no evidence of bleeding.[27]

Probable Drug Interactions

- Specific medications, foods, and herbal products may affect the INR, or may increase the risk of bleeding or thromboembolic events.[27,52,56]
- Many reported warfarin interactions are derived from poor-quality studies or single-case reports therefore discordance between drug interaction databases are common.[52,56,57]
- It is **prudent to refer to two drug interaction resources** to determine interaction potential when starting or stopping a medication or herbal product.[57]
- Non-steroidal anti-inflammatory drugs (selective and non-selective NSAIDs), antiplatelet agents, and some antimicrobials are associated with an increased risk of bleeding.[27]
- **Concomitant NSAID use should be avoided and concomitant antiplatelet use is recommended only in select coronary heart disease circumstances**.[6,27]
- Other probable interacting medications include but are not limited to:[27,52,58,59]
    - antimicrobials: amoxicillin-clavulanate, fluoroquinolones, trimethoprim-sulfamethoxazole, macrolides, metronidazole, azole antifungals, tetracyclines, rifampin
    - cardiovascular medications: amiodarone, fenofibrate, propafenone, propranolol, simvastatin
    - central nervous system medications: carbamazepine, selective serotonin reuptake inhibitors, tramadol
- The University of Washington Anticoagulation Services provides an easily accessible online reference for warfarin drug interactions: http://depts.washington.edu/anticoag/home/content/warfarin-drug-interactions.[59]
- **Choose non-interacting alternatives** where possible.[52]
- **Increase the frequency of INR testing to every 2 to 4 days** when changing (i.e., dose change, adding or discontinuing) a concomitant medication or herbal product expected to affect the INR.[51]
- Empiric warfarin dose adjustments are not recommended given an individual's response to warfarin drug interactions is not predictable.[52]

Dietary Management

- Patients should try to **maintain a reasonably consistent diet** to help minimize fluctuations in Vitamin K consumption which may result in more stable INR values.[51,52] In patients with stable INRs, specific avoidance or addition of Vitamin K containing foods is likely unnecessary.[52]

Risk Factors for Anticoagulant-Associated Bleeding

- The assessment of bleeding risk, in addition to stroke risk, provides an opportunity to address **correctable risk factors** for bleeding while ensuring appropriate stroke risk reduction therapy.[27,29]
- Numerous bleeding risk assessment tools are available, offering, at best, a modest estimation of bleeding risk.[31]
- Recent guidance advises that bleeding risk scoring tools should not be used as the single reason for withholding anticoagulant therapy.[27]
- **Risk factors for anticoagulant-associated bleeding** include, but are not limited to:[31,51,52,60]
    - History of or predisposition for bleeding (e.g., gastrointestinal bleeding, thrombocytopenia, platelet dysfunction, active peptic ulcer)
    - Uncontrolled hypertension
    - Renal or hepatic dysfunction
    - Cerebrovascular disease
    - Increasing age
    - Labile or supratherapeutic INRs
    - Concomitant medications (e.g., antiplatelets, NSAIDs)
    - Excessive alcohol consumption
    - Malignancy

Combined Antiplatelet-Anticoagulant Therapy in Non-Valvular Atrial Fibrillation

- Antiplatelet agents (e.g., ASA and/or clopidogrel) are associated with an increased risk of bleeding up to 3 fold in patients receiving a Vitamin K antagonist, such as warfarin.[27]
- In three recent anticoagulant randomized controlled trials (RCTs), concomitant antiplatelet therapy increased the risk of major bleeding in patients receiving warfarin, dabigatran, rivaroxaban, and apixaban.[24,61,62]
- **The combined use of an anticoagulant plus an antiplatelet medication is <u>not</u> recommended in patients with <u>non-valvular</u> atrial fibrillation except in select coronary heart disease circumstances**, such as:[6]
    - Patients with an intracoronary stent
    - Patients with acute coronary syndrome
- Current recommendations:[6]
    - Identify **warfarin** as the preferred anticoagulant when the combined use of an anticoagulant and antiplatelet is indicated;
    - Limit the duration of combination therapy to a **finite** period of time (e.g., depending on the type of intracoronary stent); and
    - Are derived from indirect evidence (i.e., low quality evidence) and may change if higher quality research becomes available.
- For specific details, please refer to antithrombotic guidance.[6]

Table 2: Drug Information for the New Oral Anticoagulants[32,39,41,44,63–67]

	Direct Thrombin Inhibitor	Direct Factor Xa Inhibitors	
	Dabigatran (PRADAXA®)	**Rivaroxaban (XARELTO®)**	**Apixaban (ELIQUIS®)**
Dose (in non-valvular atrial fibrillation) *Doses may differ for other indications*	**150 mg PO BID** OR **110 mg PO BID** if age ≥ 80 years OR for age ≥ 75 years with risk factors for bleeding* Use with caution in patients who weigh < 50 kg. Capsules must be swallowed whole and stored in original blister packaging or bottle to protect from moisture.	**20 mg PO daily with food** OR **15 mg PO daily with food** if CrCl 30-49 mL/min	**5 mg PO BID** OR **2.5 mg PO BID** if ≥ 2 of the following: • Age ≥ 80 years • Body weight ≤ 60 kg • Serum creatinine ≥ 133 µmol/L
Renally compromised patients	CrCl < 30 mL/min: **contraindicated**	CrCl < 30 mL/min: **not recommended**	CrCl < 25 mL/min: **excluded from principal RCT**
Renal elimination	80%	33%	25%
	• Determine CrCl at baseline and annually • Cautious consideration before initiating in patients with a CrCl close to 30 mL/min or with the potential for further deterioration or fluctuation in renal function • In patients > 80 years of age or patients with multiple comorbidities (e.g., diabetes mellitus, heart failure) assess renal function at least every 4 months • Increase frequency of monitoring when renal function is expected to be compromised (e.g., acute myocardial infarction, acute decompensated heart failure, increased use of diuretics, dehydration, hypovolemia) • Discontinue in acute renal failure and reassess when renal function improves		
Elimination half-life in normal renal function‡	11 hours	5 to 9 hours	8 hours
Hepatic impairment	Not recommended in severe hepatic impairment (Child-Pugh C)	Not recommended in moderate to severe hepatic impairment (Child-Pugh B and C)	Not recommended in severe hepatic impairment (Child-Pugh C)
Hemodynamically significant valvular disease	Not recommended	Not recommended	Not recommended
Prosthetic heart valve	Contraindicated[§]	Not recommended	Not recommended
Drug interaction propensity	P-glycoprotein	P-glycoprotein CYP P450 3A4 isoenzyme	P-glycoprotein CYP P450 3A4 isoenzyme
Drug interactions *(not an exhaustive list)* *Current knowledge of drug interactions is limited and likely to change.* *Management of clinical scenarios is best informed by referring to two drug interaction resources (note: some drug combinations are specifically contraindicated).*	**Increased bleeding risk** antiplatelets, NSAIDs (prasugrel, ticagrelor specifically not recommended) **Increased exposure to dabigatran** e.g., ketoconazole, itraconazole, posaconazole, voriconazole, dronedarone, cyclosporine, tacrolimus, amiodarone, azithromycin, clarithromycin, carvedilol, diltiazem, nifedipine, propafenone, propranolol, quinidine, verapamil, grapefruit juice **Decreased exposure to dabigatran** e.g., carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's Wort, medications resulting in ↑ gastric pH (e.g., PPI, antacids)	**Increased bleeding risk** antiplatelets, NSAIDs (prasugrel, ticagrelor specifically not recommended) **Increased exposure to rivaroxaban or apixaban** e.g., ketoconazole, itraconazole, posaconazole, voriconazole, ritonavir, amiodarone, azithromycin, clarithromycin, cyclosporine, diltiazem, dronedarone, felodipine, fluconazole, verapamil, cimetidine, grapefruit juice **Decreased exposure to rivaroxaban or apixaban** e.g., carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's Wort	

Table 2. continued

	Dabigatran (PRADAXA®)	Rivaroxaban (XARELTO®)	Apixaban (ELIQUIS®)
Switching to warfarin *Optimal strategies for switching between the new oral anticoagulants and warfarin are uncertain.*	If CrCl ≥ 50 mL/min: start warfarin at usual starting doses and overlap with dabigatran for 3 days (discontinue dabigatran on day 4) If CrCl 30 to 49 mL/min: start warfarin at usual starting doses and overlap with dabigatran for 2 days (discontinue dabigatran on day 3) Check INR on day 3 of warfarin, just prior to next scheduled dose of dabigatran (patients with CrCl ≥ 50 mL/min will still be receiving dabigatran on day 3 of warfarin) Re-check INR 24 hours after the last dose of dabigatran since dabigatran may have an additional impact on the INR when measured during the overlap phase	Start warfarin at usual starting doses and continue rivaroxaban Check INR on day 3 of warfarin, just prior to the next scheduled dose of rivaroxaban Continue rivaroxaban until INR ≥ 2.0 Re-check INR 24 hours after the last dose of rivaroxaban since rivaroxaban may have an additional impact on the INR when measured during the overlap phase	Start warfarin at usual starting doses and continue apixaban Check INR on day 3 of warfarin, just prior to the next scheduled dose of apixaban Continue apixaban until INR ≥ 2.0 Re-check INR 24 hours after the last dose of apixaban since apixaban may have an additional impact on the INR when measured during the overlap phase
Switching from warfarin *Optimal strategies for switching between the new oral anticoagulants and warfarin are uncertain.*	Discontinue warfarin Start dabigatran when INR < 2.0	Discontinue warfarin Start rivaroxaban when INR ≤ 2.5	Discontinue warfarin Start apixaban when INR < 2.0
Estimated annual cost[≠]	$1426 per year	$1285 per year	$1426 per year
PharmaCare coverage[α]	Requires Special Authority	Requires Special Authority	Requires Special Authority

CrCl = creatinine clearance

*Presence of the following risk factors may increase the risk of bleeding: e.g., age ≥ 75 years, moderate renal impairment (CrCl = 30-50 mL/min), concomitant treatment with P-glycoprotein inhibitors, antiplatelets or a previous gastrointestinal bleed.

‡The anticoagulant effect of the new oral anticoagulants is estimated to diminish within 12 to 24 hours after the last dose. Patient and caregiver education on the importance of strict medication adherence is essential.

§ The RE-ALIGN trial was terminated early because of a significant increase in thromboembolic events and major bleeding with dabigatran as compared to warfarin in patients with recent mechanical heart valve replacement.[68]

≠ Includes drug cost & dispensing fees ($1216 to $1357) and four serum creatinine tests per year ($69) based on estimates in 2013. In comparison, **warfarin costs approximately $394 per year** (drug cost & dispensing fees, $122; INR tests & telephone consultations, $272) assuming 16 INR tests per year.

α Special Authority criteria: Patient has a diagnosis of non-valvular atrial fibrillation **AND** at least one $CHADS_2$ related risk factor (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, or prior stroke/transient ischemic event) **AND** either inadequate anticoagulation (at least 35% of INR results are outside the desired range) after a minimum 2 month warfarin trial **OR** warfarin is contraindicated or not possible due to an inability to regularly monitor via INR testing. Special Authority forms are available at: https://www.health.gov.bc.ca/exforms/pharmacare/5391fil.pdf

Appendix 1: Characteristics of new oral anticoagulant vs. adjusted-dose warfarin, non-inferiority RCTs in atrial fibrillation

	Dabigatran (RE-LY)[16,21,47,69,70]	Rivaroxaban (ROCKET AF)[24,25,48,71–73]	Apixaban (ARISTOTLE)[19,26,49,74]
non-inferiority design	randomized, open-label, blinded adjudication	randomized, double-blind, sham INR	randomized, double-blind, sham INR
# participants / **trial duration**	18,113 / 2.0 years median	14,264 / 1.9 years median	18,201 / 1.8 years median
geography / **Canada, U.S.** / **Canada**	44 countries / 36% / N = 1150	45 countries / 19% / N = 747	39 countries / 25% / N = 1057
funding	Boehringer Ingelheim	Johnson & Johnson, Bayer	Bristol-Myers Squibb, Pfizer
Interventions			
anticoagulant comparisons	dabigatran 110 mg PO BID dabigatran 150 mg PO BID adjusted-dose warfarin PO daily INR 2.0 to 3.0	rivaroxaban 20 mg PO daily rivaroxaban 15 mg PO daily if CrCl 30-49 mL/min adjusted-dose warfarin PO daily INR 2.0 to 3.0	apixaban 5 mg PO BID apixaban 2.5 mg PO BID if 2 or more: age ≥ 80, weight ≤ 60 kg or SCr ≥ 133 µmol/L adjusted-dose warfarin PO daily INR 2.0 to 3.0
Inclusion criteria and baseline patient characteristics *not an exhaustive list; see study protocol for complete list			
inclusion criteria: **ischemic stroke risk factors**	ECG documented atrial fibrillation *plus* at least one of the following: previous stroke, TIA or systemic embolism; LVEF < 40%; symptomatic HF NYHA class ≥ 2 in last 6 months; age ≥ 75; *or* age ≥ 65 plus treated DM, treated HTN, or CAD	ECG documented atrial fibrillation *plus* previous stroke, TIA or systemic embolism *or* at least two of the following: HF; LVEF ≤ 35%; treated HTN or SBP > 140 or DBP > 90; age ≥ 75; *or* DM	ECG documented atrial fibrillation or flutter *plus* at least one of the following: previous stroke, TIA, or systemic embolism; age ≥ 75; symptomatic HF; LVEF ≤ 40%; DM; *or* treated HTN
average participant	72 year old male, 83 kg, CrCl 68 mL/min, $CHADS_2$ = 2.1	71 year old male, 82 kg, CrCl 73 mL/min, $CHADS_2$ = 3.5	69 year old male, 84 kg, CrCl > 50 mL/min, $CHADS_2$ = 2.1
$CHADS_2$ 0 / **$CHADS_2$ 1** / **$CHADS_2$ 2+**	3% / 29% / 68%	0% / 0% / 100%	1% / 33% / 66%
female / **age ≥ 75** / **age ≥ 80**	36% / 40% / 17%	40% / 44% / 18%	35% / 31% / 13%
secondary prevention	22% prior stroke, TIA, or systemic embolism	55% prior stroke, TIA, or systemic embolism	19% prior stroke, TIA, or systemic embolism
HTN / **DM** / **HF**	79% / 23% / 32%	91% / 40% / 62%	87% / 25% / 35%
persistent, permanent / **paroxysmal**	67% / 33%	81% / 18%	85% / 15%
VKA naïve / **moderate renal impair.**	50% / 18% CrCl 30-49 mL/min	38% / 21% CrCl 30-49 mL/min	43% / 15% CrCl 31-50 mL/min
Exclusion criteria *not an exhaustive list; see study protocol for complete list			
exclusion criteria: **hemorrhagic, cardiovascular, renal, hematologic, non-adherence risk factors**	prosthetic heart valve or hemodynamically relevant valve disease; indication for anticoagulation other than atrial fibrillation; active infective endocarditis; reversible causes of atrial fibrillation; recent stroke within 14 days; severe, disabling stroke within 6 months; conditions associated with increased bleeding risk including but not limited to previous intracranial hemorrhage, gastrointestinal bleed within past year, gastroduodenal ulcer disease within 30 days, CrCl < 30 mL/min, SBP > 180 or DBP > 100, active liver disease, Hb < 100 g/L, platelets < 100 x 10^9/L; contraindication to warfarin; substance or alcohol misuse; reduced life expectancy	prosthetic heart valve or hemodynamically significant mitral valve stenosis; indication for anticoagulation other than atrial fibrillation; active endocarditis; reversible causes of atrial fibrillation; recent stroke within 14 days; severe, disabling stroke within 3 months; TIA within 3 days; conditions associated with increased bleeding risk including but not limited to previous intracranial hemorrhage, gastrointestinal bleed within 6 months, CrCl < 30 mL/min, SBP ≥ 180 or DBP ≥ 100, active liver disease, Hb < 100 g/L, platelets < 90 x 10^9/L; contraindication to warfarin; substance or alcohol misuse; reduced life expectancy	prosthetic heart valve or clinically significant mitral valve stenosis; indication for anticoagulation other than atrial fibrillation; active infective endocarditis; reversible causes of atrial fibrillation or flutter; recent ischemic stroke within 7 days; conditions associated with increased bleeding risk including but not limited to prior intracranial hemorrhage, SCr > 221 µmol/L or CrCl < 25 mL/min, SBP > 180 or DBP > 100, active liver disease, Hb < 90 g/L, platelets ≤ 100 x 10^9/L; contraindication to warfarin; substance or alcohol misuse; reduced life expectancy
INR time in therapeutic range (TTR) achieved for adjusted-dose warfarin			
Overall study TTR	64% mean	55% mean	62% mean
TTR Canadian sites	71% mean	66% mean	73% median

% = proportion of originally-randomized participants; **N** = number of originally randomized participants

Appendix 2: Outcomes reported in new oral anticoagulant vs. adjusted-dose warfarin, non-inferiority RCTs in atrial fibrillation

The **absence of direct comparisons** between the new oral anticoagulants and the **heterogeneity** of the three principal RCTs limits reaching firm conclusions regarding differences between the new oral anticoagulants.[1,5,9,12] **Methodological limitations** have increased relevance as sources of potential bias in non-inferiority RCTs.[20]

	Dabigatran (RE-LY)[47,75]		Rivaroxaban (ROCKET AF)[48,76]	Apixaban (ARISTOTLE)[49]
	D110 versus WARF	**D150 versus WARF**	**RIVA versus WARF**	**APIX versus WARF**
Primary composite outcome				
stroke or systemic embolism [i]	D110 1.54% per year WARF 1.71% per year **0.90 (0.74, 1.10)**	D150 1.11% per year WARF 1.71% per year **0.65 (0.52, 0.81) ↓ 0.60% per year**	RIVA 2.1% per year WARF 2.4% per year **0.88 (0.75, 1.03)**	APIX 1.27% per year WARF 1.60% per year **0.79 (0.66, 0.95) ↓ 0.33% per year**
Secondary outcomes [ii] (not an exhaustive list of all outcomes)				
total mortality	D110 3.75% per year WARF 4.13% per year **0.91 (0.80, 1.03)**	D150 3.64% per year WARF 4.13% per year **0.88 (0.77, 1.00)**	RIVA 4.5% per year WARF 4.9% per year **0.92 (0.82, 1.03)**	APIX 3.52% per year WARF 3.94% per year **0.89 (0.80, 1.00)** vital status missing 2.1% patients
major bleed [iii]	D110 2.87% per year WARF 3.57% per year **0.80 (0.70, 0.93) ↓ 0.70% per year**	D150 3.32% per year WARF 3.57% per year **0.93 (0.81, 1.07)**	RIVA 3.6% per year WARF 3.4% per year **1.04 (0.90, 1.20)***	APIX 2.13% per year WARF 3.09% per year **0.69 (0.60, 0.80)* ↓ 0.96% per year**
intracranial hemorrhage [iv]	D110 0.23% per year WARF 0.76% per year **0.30 (0.19, 0.45) ↓ 0.53% per year**	D150 0.32% per year WARF 0.76% per year **0.41 (0.28, 0.60) ↓ 0.44% per year**	RIVA 0.5% per year WARF 0.7% per year **0.67 (0.47, 0.93)* ↓ 0.2% per year**	APIX 0.33% per year WARF 0.80% per year **0.42 (0.30, 0.58)* ↓ 0.47% per year**
major gastrointestinal bleed	D110 1.15% per year WARF 1.07% per year **1.08 (0.85, 1.38)**	D150 1.56% per year WARF 1.07% per year **1.48 (1.18, 1.85) ↑ 0.49% per year**	RIVA 2.00% per year WARF 1.24% per year **1.61 (1.30, 1.99)* ↑ 0.76% per year**	APIX 0.76% per year WARF 0.86% per year **0.89 (0.70, 1.15)***

D110 = dabigatran 110 mg PO BID; **D150** = dabigatran 150 mg PO BID; **RIVA** = rivaroxaban 20 mg (15 mg) PO daily; **APIX** = apixaban 5 mg (2.5 mg) PO BID; **WARF** = adjusted-dose warfarin PO daily INR 2.0 to 3.0
black bolded values = relative risk with 95% confidence interval; **blue bolded values** = absolute risk reduction or increase if statistically significant
*truncated follow-up: events occurring more than 2 days after treatment discontinuation were not counted

Notes:

[i] Includes ischemic stroke, hemorrhagic stroke, unclassified stroke, or non-CNS systemic embolism; 2013 therapeutic review judged the event definitions to be similar between the RCTs.[1]

[ii] Appropriate methodology for statistical significance testing of secondary outcomes in non-inferiority RCTs is uncertain.[26]

[iii] Includes decrease Hb ≥ 20 g/L, ≥ 2 unit transfusion whole blood or packed cells, bleed in a critical site, or fatal outcome; 2013 therapeutic review judged the event definitions to be similar between the RCTs;[1] 2012 Ontario population-based cohort study, 125 195 adults aged ≥ 66 with atrial fibrillation prescribed warfarin, found a major bleed rate of 3.8% per person-year.[77]

[iv] Includes hemorrhagic stroke and other intracranial bleeds; 2012 Ontario population-based cohort study, 125 195 adults aged ≥ 66 with atrial fibrillation prescribed warfarin, found an intracranial hemorrhage rate of 0.2% per person-year.[77]

Additional Comments:

1. **Increase in stroke or systemic embolism after discontinuation of study drug**: US FDA medical reviews noted excess stroke or systemic embolism in participants originally randomized to rivaroxaban and apixaban compared with warfarin during the time period when patients were transitioned off of assigned study drug to usual care (e.g., VKA antagonist) at the end of study.[24–26]
2. **Myocardial infarction**: US FDA medical review noted an increased risk of myocardial infarction of 0.2% per year in participants receiving dabigatran compared with warfarin;[21] 2012 meta-analysis (7 RCTs, 30 514 participants, dabigatran vs. various comparators including warfarin), dabigatran increased the risk of myocardial infarction or acute coronary syndrome (OR 1.33, 95% CI 1.03 to 1.71).[78]
3. **Syncope**: US FDA medical review noted numerically more serious syncopal events (i.e., syncope, vertigo, dizziness, presyncope) in participants receiving apixaban compared with warfarin (apixaban = 1.4%, warfarin = 1.0% over the course of the study).[26]
4. **Major bleed events older adults:** significant treatment by age interaction for major bleeding in participants receiving dabigatran compared with warfarin (P for interaction < 0.001);[79] older adults aged ≥ 75 dabigatran 110 mg vs. warfarin RR 1.01 (0.83, 1.23), dabigatran 150 mg vs. warfarin RR 1.18 (0.98, 1.42).[79]
5. **Discontinuations due to adverse events:** US FDA medical review noted participants were more likely to discontinue dabigatran due to adverse events compared with warfarin (dabigatran 110 mg = 19%, dabigatran 150 mg = 20.5%, warfarin = 15.7% over the course of the study);[21] gastrointestinal disorders (e.g., dyspepsia, gastrointestinal hemorrhage) were the most common adverse events leading to dabigatran discontinuation.[21]

Summary of Main Points

1. **Warfarin** remains the initial oral anticoagulant choice in most patients with atrial fibrillation who choose anticoagulation for stroke risk reduction.
2. CADTH recommends that new oral anticoagulants only be considered in patients with non-valvular atrial fibrillation if warfarin fails to achieve adequate anticoagulation.
3. Current evidence for the new oral anticoagulants compared to adjusted-dose warfarin is limited to a single, non-inferiority randomized-controlled trial for each new oral anticoagulant (each with methodological limitations) and by an absence of long-term clinical experience.
4. Combination therapy with an oral anticoagulant and an antiplatelet medication is NOT recommended in patients with non-valvular atrial fibrillation except in select coronary heart disease circumstances (e.g., placement of an intracoronary stent, acute coronary syndrome).

References are available upon request.

Materials are designed to be used in conjunction with an academic detailing session provided by PAD pharmacists. For more information, or to schedule an academic detailing session, please contact:

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