

ATRIAL FIBRILLATION

WHERE DO THE NEW ANTICOAGULANTS FIT? WHICH IS BETTER, RATE OR RHYTHM CONTROL?



January 2013

GUIDELINES/REVIEWS

CCS^{2010, 2012 update}: http://www.ccsguidelineprograms.ca/index.php/afib/122_afib_guidelines
CADTH²⁰¹²: http://www.cadth.ca/media/pdf/tr0002_New_Oral_Anticoagulants_rec_e.pdf
ESC^{2010, 2012 update}: <http://eurheartj.oxfordjournals.org/content/early/2012/08/24/eurheartj.ehs253.full.pdf+html>
AHA/ASA²⁰¹²: <http://stroke.ahajournals.org/content/early/2012/08/02/STR.0b013e318266722a>
ACCF/AHA/HRS^{2006, 2011 update}: <http://circ.ahajournals.org/content/123/1/104.full.pdf+html>
CHEST²⁰¹²: http://chestjournal.chestpubs.org/content/141/2_suppl/e5315.full.html

RISK CALCULATORS/TOOLS

SPARC <http://www.sparctool.com/>
CCPN SPAF <http://ccpn.ca/tools.php>
Framingham Heart Study www.framinghamheartstudy.org

PATIENT RESOURCES

See On Line Extras for list & links.

RXFILES RELATED

Oral Anticoagulation in AF <http://www.cfp.ca/content/58/8/850.full>
Antiplatelet & Antithrombotics Drug Chart http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht_AntiThrombotics.pdf
Warfarin Tips/Nomograms <http://www.rxfiles.ca/rxfiles/uploads/documents/members/Warfarin%20Management.pdf> also see last page of Newsletter
Does Dabigatran risk of MI http://www.rxfiles.ca/rxfiles/uploads/documents/Dabigatran_MI%20Risk_QandA.pdf
QT Prolongation & Torsades http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht_QA%20TORSADESdePoint.pdf
ACTIVE A & W (ASA clop, vs warf) http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE_A_Trial_Summary.pdf
ARISTOTLE (apixaban vs warfarin) http://www.rxfiles.ca/rxfiles/uploads/documents/ARISTOTLE_AF_Apixaban.pdf
RACE II (lenient vs strict rate control) http://www.rxfiles.ca/rxfiles/uploads/documents/RACE_II_trial.pdf
RELY (dabigatran vs warfarin) http://www.rxfiles.ca/rxfiles/uploads/documents/RELY_Trial_Dabigatran.pdf
ROCKET AF (rivaroxaban vs warfarin) http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET_AF_Rivaroxaban.pdf
PALLAS (dronedaron in permanent AF) http://www.rxfiles.ca/rxfiles/uploads/documents/PALLAS_trial%20summary.pdf

Highlights

Assess stroke CHADS₂, CHA₂DS₂VASc & bleeding HAS BLED risk.
If CHADS₂ = 1, consider using CHA₂DS₂VASc.
If HAS BLED = 3, oral anticoagulant use requires caution.
New oral anticoagulants (NOACs) vs warfarin:
▪ **Advantages:** non inferior for stroke & systemic embolism, no INR monitoring, & fewer drug interactions.
▪ **Disadvantages:** no bleeding antidote, no long term data or real world experience >2 years, limited cardiovascular outcome data, & medication cost.
No significant difference between rate control vs. rhythm control in mortality or stroke risk.

Background Issues

Individuals with atrial fibrillation (AF) have 3 to 5 fold increased risk for ischemic stroke. Key symptom is irregular pulse (may not be rapid).

Approach to Managing AF

Identify & treat precipitating causes, if possible.
Manage thromboembolic risk:
▪ Calculate stroke risk (CHADS₂, CHA₂DS₂VASc)
▪ Calculate bleed risk (HAS BLED)
Manage arrhythmia (rate vs. rhythm control).

CHADS₂ versus CHA₂DS₂VASc for estimating risk of stroke

Both tools help guide antithrombotic therapy & have a similar ability to estimate the risk of stroke in AF.
CHADS₂ score is easier to remember & use.
CHA₂DS₂VASc is better for estimating stroke risk in low or intermediate risk individuals (e.g. CHADS₂ score = 1).
CHADS₂ = 0: AF guidelines recommend considering gender (female), presence of vascular disease & age (> 65 years) to guide therapy (i.e. CHA₂DS₂VASc).

HAS BLED for estimating the risk of major bleeding

Compared to other bleeding risk prediction tools, HAS BLED is easier to use & has a better predictive value for clinically relevant bleeding, including intracranial hemorrhage.
HAS BLED score = 3 = risk of major bleed.
The risk of bleeding must be balanced with the risk of stroke stroke has risk of mortality & morbidity versus bleed.

Role of Oral Anticoagulants (OACs) in AF

OACs include warfarin **COUMADIN**, apixaban **ELIQUIS**, dabigatran **PRADAXA/PRADAX**, & rivaroxaban **XARELTO**.
OACs suggested when CHADS₂ = 1 (most benefit = 2).
In landmark trials, dabigatran^{RELY}, rivaroxaban^{ROCKET} & apixaban^{ARISTOTLE} were as good as or better than warfarin for prevention of stroke & systemic embolism.
Warfarin is preferred in patients with valvular heart disease, advanced renal/liver dysfunction, risk of dyspepsia &/or gastrointestinal bleed, well controlled INRs, concerns about medication cost, ± patients excluded from landmark trials. See Warfarin Tips/Nomograms (last page)

Switching between warfarin & the NOACs

- Switching FROM warfarin apixaban
 - Stop warfarin. Start apixaban when INR <2
- Switching FROM apixaban warfarin
 - Start warfarin. Stop apixaban when INR >2
- Switching FROM warfarin dabigatran
 - Stop warfarin. Start dabigatran when INR <2
- Switching FROM dabigatran warfarin
 - CrCl >50mL/min: start warfarin 3 days before stopping dabigatran.
 - CrCl 31-50mL/min: start warfarin 2 days before stopping dabigatran.
 - CrCl 15-30mL/min: start warfarin 1 day before stopping dabigatran.
- Switching FROM warfarin rivaroxaban
 - Stop warfarin. Start rivaroxaban when INR = 2.5
- Switching FROM rivaroxaban warfarin Start warfarin. Stop rivaroxaban after 2-4 days of overlapping therapy and when INR = 2

Rate versus Rhythm Control

Patients with persistent AF are more likely to benefit from rate control. Choose therapy based on patient's symptoms & preferences. See inside for details.
Rate control drug choices: (alphabetical)
▪ blockers (BB), digoxin, diltiazem, dronedarone, verapamil
▪ Target heart rate < 100 bpm
Rhythm control drug choices: (alphabetical)
▪ Amiodarone, dronedarone, flecainide, propafenone, sotalol

"Pill in the pocket" Strategy

In infrequent recurrences of AF, outpatients can take flecainide 200-300mg x 1 or propafenone 450-600mg x 1 intermittently or as an extra dose. Usually co administration with a BB. See inside for details.

What is the role of Digoxin in AF?

Less effective than non dihydropyridine calcium channel blockers (CCBs) or BBs during exercise.
▪ Digoxin prolongs AV nodal refractoriness by vagal tone; with exercise, vagal tone is withdrawn.
Use digoxin in combination with BBs or non dihydropyridine CCBs in active patients, or as monotherapy in sedentary patients.
▪ mortality risk in AF patients both combo & mono AFFIRM
Titrate dose to effect symptom control, 0.0625-0.25mg po daily. Check levels to avoid toxicity <1.3-2.6 nmol/L.
Toxicity level is pt dependent may occur at <1.3 nmol/L.

New Antiarrhythmic: Dronedaron MULTAQ

An option for paroxysmal or persistent AF patients with minimal structural heart disease.
AVOID in permanent AF or atrial flutter, heart failure or a left ventricular ejection fraction <40%.
▪ Mortality rates, stroke & hospitalization for heart failure 2x more with dronedaron permanent AF PALLAS

The new oral anticoagulants have been studied for indications other than AF (e.g. venous thromboembolism prevention & treatment, acute coronary syndrome). The dose, duration of therapy & formulary coverage often varies among the indications. Refer to the RxFiles Antiplatelet & Antithrombotic Chart, pages 10-11.

Prevalence of AF: 0.1% <50yr, 10 15% >80yr²
AF Stroke/yr: 5% RCTS; USA: 15% overall, 1.5% 50-59yr, 23.5% 80-89yr
Risk of stroke: see CHADS₂/CHA₂DS₂VASc score (next page)
Risk of bleeding: see HAS BLEED score (next page)
Precipitating Cause(s) of AF:
Cardiac: CAD/MI, HF*, HTN, LVD*, cardiomyopathies hypertrophic, dilated, restrictive, genetic/familial, pacemaker*, pericardial dx, postsurgical cardiac, SSS, SVT WPW syndrome, atrial tachycardia, atrial flutter*, valvular/congenital HD early repair of atrial septal defect*.
Noncardiac: sleep apnea obstructive*, obesity*, electrolyte imbalance, excessive alcohol*, hyperthyroidism*, pulmonary dx pneumonia, COPD, PE, PH, vagally mediated e.g.habitual aerobic training*, medication see list at bottom & drug use recreational.

*Treatment may prevent the development or recurrence of AF
Initial Assessment: (include ECG 12 lead, chest radiograph & echo for possible clot, AF & atrial stretch)

PHYSICAL: Irregular pulse may not be rapid, irregular jugular venous pulse with loss of a wave, & variation in the intensity of the first heart sound. May also uncover causes of AF e.g. HTN, LV systolic dysfunction, HF, valvular/congenital heart disease (HD), hyperthyroidism.

LAB: CBC, lytes Ca&Mg, Scr, BUN, LFT, TSH, lipid fasting, FBG, INR

SELECT INVESTIGATIONS: Chest radiography, ambulatory electrocardiography Holter monitor, event monitor, loop monitor, treadmill exercise test, transesophageal echocardiography, electrophysiological study, sleep study ambulatory oximetry or polysomnography, ambulatory BP monitoring, genetic testing.

Nonpharmacologic Tx: pacemaker, AV junction ablation, cardioversion

What is the predominant pattern of AF?

- First detected AF ⇒ **Three “P” Classification:**
- Paroxysmal:** AF is self terminating within 7 days of recognized onset. Not all patients picked up on ECG.
 - Persistent:** AF is not self terminating within 7 days or is terminated electrically or pharmacologically.
 - Permanent:** AF in which cardioversion has failed or in which clinical judgment has led to a decision not to pursue cardioversion.

PEARLS FOR AF

- A chronic, recurrent & progressive condition. Re evaluate sx management SAF, risk of stroke CHADS₂ & bleeding HAS BLEED often.
- No significant difference between rate vs. rhythm control.
- Consider an oral anticoagulant (OAC) when CHADS₂ 1. Most benefit with scores 2.
- If HAS BLEED 3, use caution with OAC, & monitor for bleeds.
- Advantage of new OAC (i.e. dabigatran, rivaroxaban, apixaban) compared to warfarin include non inferiority for stroke/systemic embolism in patients with nonvalvular AF, no INR monitoring & fewer interactions drug/food.
- Disadvantages of new anticoagulants vs warfarin include no antidote for major bleeds, no long term data > 2 years, limited cardiovascular outcome data & higher direct cost.

Note: warfarin remains more cost effective even after considering INR monitoring³

DRUGS THAT AF: ¹⁶ **Antithrombotics** (anagrelide, clopidogrel), **CV** (acetylcholine, adenosine, arbutamine, atenolol, digoxin, diltiazem, dobutamine, dopamine, dopexamine, flosequinan, isosorbide mononitrate, losartan, perflorbutane, thiazides, verapamil), **Respiratory** (ephedrine, methylprednisolone, phenylephrine, pseudoephedrine, salbutamol, terbutaline, theophylline), **Cytostatics** (5 fluorouracil, cisplatin, docetaxel, etoposide, gemcitabine, ifosfamide, interferon gamma, interleukin 3, interleukin 6, melphalan, proflimer, verteporfin), **CNS** (apomorphine, atropine, bupivacaine, clozapine, donepezil, fluoxetine, physostigmine, sumatriptan, tranylcypromine, trazodone), **Genitourinary** (hexoprenalin, magnesium sulphate, sildenafil, terbutaline), **Antiemetics** (alizapride, benzquinamide), **Miscellaneous** (amphotericin B, amifostine, anabolic steroids, azathioprine, calcium, disulfiram, etanercept, etretinate, fluorescein, flupirtine, gallium nitrate, levocarnitine, nesiritide, niacin, nicotine, pentagastrin, zalcitabine)

HERBALS THAT AF: very limited data: caffeine controversial, ginseng, guarine, ma Huang, yohimbine. Note: many herbals bleeding risk via platelets or INR or clotting risk via INR. Herbal interactions with NOACs: no data; avoid combination until safety known.

NON PHARMACOLOGICAL: **Cardioversion:** Electrical more effective than pharmacological esp. when AF >48hr, pre treat with antiarrhythmic 4 wks & anticoagulant 3 wks unless <48hr or TEE to rule out thrombus, post procedure: anticoagulant warfarin or dabigatran x 4 wks.
Ablation: ^{17,18,19} Anticoagulation: pre procedure 1 2mos or TEE to rule out thrombus, post procedure x 3 6mos [then based on CHADS₂ score]. Antiarrhythmics: 6 wks 3mos post procedure AF recurrence. Paroxysmal best success rate.

Canadian Cardiovascular Society Severity in AF (CCS SAF) & Quality of Life (QOL) 4

CCS SAF scale is recommended at baseline & follow up to assess starting & changing symptom management therapy in AF patients.¹

Step 1 Symptoms	SAF Score	Impact on QOL
Identify the presence of the following symptoms: palpitation, dyspnea, dizziness (presyncope or syncope), chest pain, weakness or fatigue. (frequency, duration & severity of symptoms vary)	Class 0	Asymptomatic with respect to AF
	Class 1	Minimal effect on QOL Minimal ± infrequent Sx, or Single episode of AF without syncope or HF
Step 2 – Association Is AF, when present, associated with the symptoms above? (Ascertain if any of the above symptoms are present during AF or likely caused by AF – as opposed to some other cause)	Class 2	Minor effect on QOL Mild symptom awareness in persistent/permanent AF pts, or Rare episodes (e.g. few/yr) in paroxysmal/intermittent AF pts
	Class 3	Moderate effect on QOL Moderate awareness of symptoms on most days in persistent/permanent AF pts, OR More common episodes (e.g. > few/month) or more severe symptoms, or both in paroxysmal/intermittent AF pts
Step 3 Functionality Determine if symptoms associated with AF (or the treatment of AF) affect the patient’s functionality (subjective QOL). Assign a score from 0 to 4 (Class 0→4).	Class 4	Severe effect on QOL Very unpleasant symptoms in persistent/paroxysmal AF pts, Frequent & highly symptomatic episodes in paroxysmal/intermittent AF pts, Syncope due to AF, HF secondary to AF

Management of AF

- Detect & treat precipitating causes (e.g. refer to cardiologist).
- Manage thromboembolic risk (CHADS₂, CHA₂DS₂VASc, HAS BLEED).
- Manage arrhythmia (rate vs. rhythm control).

Atrial Flutter (AFL): landmark trial data is primarily based on AF pts; results have been extrapolated to AFL pts. AFL pts can be risk stratified (e.g. CHADS₂, CHA₂DS₂VASc, HASBLEED) & managed (i.e. stroke prevention, rate or rhythm control) the same as AF pts.

What is the “pill in the pocket” strategy?⁵

In relatively infrequent (paroxysmal) recurrences of AF, flecainide or propafenone can be taken **intermittently** (PRN) or as a **booster dose** as an outpatient (**pill in the pocket**).

Intermittent: patient requires dose of flecainide or propafenone to terminate episode (not on chronic therapy)

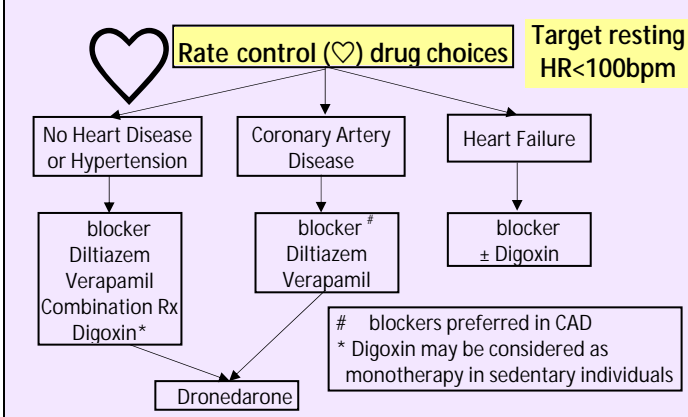
Booster dosing: patient is on low dose chronic therapy & requires one extra dose to terminate an episode⁶

Propafenone or flecainide can the refractory period of the AV node, thereby the ventricular rate consider co administration of BB e.g. metoprolol 50 100mg po x1. AF with structural heart disease or conduction abnormalities should be observed in hospital during initiation of therapy to observe for excessive PR prolongation or development of dangerous or worrisome arrhythmias.^{7,8,9}

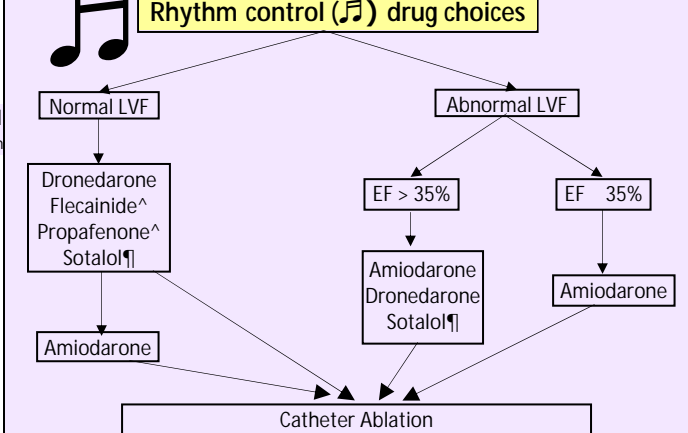
What factors favour Rate vs Rhythm control? 10

Favours Rate Control	Favours Rhythm Control
Persistent AF	Paroxysmal AF or newly detected AF
Less symptomatic	More symptomatic
Aged ≥ 65 years	Aged < 65 years
Hypertension	No hypertension
No history of HF	HF clearly exacerbated by AF
Previous antiarrhythmic drug failure	No previous antiarrhythmic drug failure
Patient preference	Patient preference

No significant difference between rate control vs. rhythm control in mortality or stroke risk.^{11 AFFIRM, 12, 13, 14, 15}
 Choose therapy based on patient symptoms & preferences.¹



Rhythm control (♫) drug choices



^ Class I agents should be **AVOIDED in CAD**; should be combined with AV nodal blocking agents (eg. beta blocker, digoxin, diltiazem, or verapamil).

¶ Sotalol: caution with EF 35 40%; contraindicated in ♀ > 65 yrs taking diuretics.^{CCS}

Selection of Thromboembolic Therapy ²⁰

1. Assess Thromboembolic Risk – CHADS₂, or CHA₂DS₂VASc if CHADS₂ ≤1 (neither should be used for mechanical heart valves or rheumatic heart disease)

CHADS ₂ Risk Criteria		Points	- Easy to remember & use - Moderately effective tool (C-stat) - Initially validated n=1733, 10yr f/u Denmark cohort n=73,538
Congestive Heart Failure (symptoms in last 3 months)		1	
Hypertension (diagnosis)		1	
Age ≥ 75 years		1	
Diabetes mellitus		1	
Stroke/TIA (prior)		2	

CHADS ₂ Score	Stroke Rate, %/yr (95% CI)	Recommended Therapy (Strength of Recommendation)
0	1.9 (1.2 - 3)	2012 CCS: ²¹ (conditional, low-quality) - No additional stroke risk factors: no antithrombotic - Female sex or vascular disease: ASA 75-325mg po daily - Age ≥65 years or female sex & vascular disease: OAC 2012 CHEST: ²² No drug therapy or ASA 75-325mg daily (Grade 2B)
1	2.8 (2 - 3.8)	2012 CCS: OAC Preferred (strong, high-quality) Alternatives: ASA 75-325mg daily (conditional, moderate-quality) 2012 CHEST: OAC Preferred (Grade IB) Alternatives: ASA+ clopidogrel or ASA 75-325mg daily (Grade 2B)
2	4 (3.1 - 5.1)	2012 CCS: OAC (strong, high-quality; Level IA) 2012 CHEST: OAC Preferred (Grade IA) Alternatives: ASA + clopidogrel or ASA 75-325mg daily (Grade IB)
3	5.9 (4.6 - 7.3)	
4	8.5 (6.3 - 11.1)	
5	12.5 (8.2 - 17.5)	
6	18.2 (10.5 - 27.4)	

CHA ₂ DS ₂ VASc Risk Criteria		Points	- Better than CHADS ₂ for low/intermediate risk but more complicated - Moderately effective tool (C-stat) - Initially validated n=1084, 1yr f/u; 10yr f/u Denmark cohort n=73,538 ^{Oleson 11}
Congestive Heart Failure		1	
Hypertension		1	
Age ≥ 75 years		2	
Diabetes mellitus		1	
Stroke/TIA (prior)		2	
Vascular dx (MI, PAD, aortic plaque)		1	
Age 65-74		1	
Sex - female		1	

CHA ₂ DS ₂ VASc Score	Stroke Rate, %/yr	ESC '12 ²³ Recommended Therapy (Strength of Recommendation)
0	0	No antithrombotic therapy (Level IB)
1	1.3	- No antithrombotic tx if ♀ + <65yrs & lone AF (Level IIA, B) - OAC (Level IIA,A) see antiplatelet note below (ASA option if patient refuses OAC) OAC (Level IA) Antiplatelet Therapy If a patient refuses an OAC, consider: (Level IIA, B) - ASA 75-100mg + clopidogrel 75mg daily, or - ASA 75-325mg daily
2	2.2	
3	3.2	
4	4	
5	6.7	
6	9.8	
7	9.6	
8	6.7	
9	15.2	

2. Assess Bleeding Risk – HAS-BLED

HAS-BLED Risk Criteria		Points
Hypertension [SBP>160 mmHg]		1
Abnormal renal (transplantation, dialysis, SCr>200umol/L) or liver function (AST/ALT >3xULN, bilirubin>2x ULN) (1 point each)		1 to 2
Stroke (caused by a bleed)		1
Bleeding (hospitalization, Hgb>20g/L, transfusion)		1
Labile INRs (therapeutic range < 60%)		1
Elderly (age > 65 yrs)		1
Drugs (ASA/NSAID) or alcohol (≥8drinks/week) (1 point each)		1 to 2

HAS-BLED Score	Major bleeds (%/yr)	Score 3 = high risk for bleeding event → use caution & regular evaluation of antithrombotic therapy
0	1.13	
1	1.02	
2	1.88	
3	3.74	
4	8.70	
5	12.50	

²⁴Intracranial, hospitalization, Hgb >20g/L, transfusion Validated only with warfarin (n=7329). Limited value (C-stat). Other tools for predicting warfarin-associated hemorrhage: ATRIA²⁴, RIETE²⁵, HEMORR₂HAGES²⁶ (see On-Line Extras)

3. Assess Benefit vs Risk

e.g. If CHADS₂=1 (2.8%/yr stroke rate) & HAS BLED=4 (8.7%/yr major bleed), stroke risk < bleed rate, consider ASA
 See also SPARC calculator:
<http://www.sparc-tool.com/>

What are the recommendations for the new OAC (apixaban, dabigatran, rivaroxaban) versus warfarin for patients with AF?




Overall: exact role still to be determined due to limited real world experience with the new agents.
Canadian CCS ²⁰¹²: new OACs are **preferred** over warfarin. CADTH^{2012,3}: **1st line**: warfarin, **2nd line**: new OACs if unable to achieve adequate anticoagulation with warfarin & CHADS₂ score is 2.
American CHEST ²⁰¹²: dabigatran **preferred** over warfarin. ACC/AHA/HRS²⁰¹¹: dabigatran is an **alternative** to warfarin. AHA/ASA²⁰¹²: new OACs are **alternatives** to warfarin.
European ESC ²⁰¹²: new OACs **preferred** over warfarin (Level IIA,A), but note limited experience with these agents. Warfarin is effective for stroke prevention when time in therapeutic range >70%.

Warfarin preferred: these documents also list several exceptions where warfarin would be better suited, i.e. patients: with valvular heart dx new OAC not indicated, dabigatran thrombosis/bleed with poor renal function at risk of dyspepsia dabigatran &/or gastrointestinal bleeding controlled on warfarin & no concerns with INR monitoring excluded from landmark trials, &/or concerned with cost

Newer Anticoagulant Agents for Atrial Fibrillation ^{27,28,29}

Refer to pages 10 11 for other oral antiplatelet & antithrombotic agents; & refer to RxFiles trial summaries **RE LY, ROCKET AF, ARISTOTLE**.


Direct Thrombin Inhibitor

Generic/TRADE (Strength, formulation)	Side Effects SE/ Contraindications CI	✓ = therapeutic use / Comments / Drug Interactions DI / Monitor M	Landmark trials excluded recent strokes: ARISTOTLE stroke within 7 days, RELY stroke within 14 days or severe stroke within 6 months, ROCKET-AF stroke within 14 day	USUAL DOSE RANGE	\$/month
Dabigatran AF, PRADAXA / PRADAX 75* ;110,150mg cap  Stable: 4mos in original container Do NOT break or open capsules bioavailability by 75% Contains tartaric acid; prodrug t½ 13hr (27hr if CrCl 30mL/min)	SE Common: Bleed (eg. anemia, GI bleed 1.5%, hematoma, hematuria), GI (eg. abdominal pain, diarrhea, dyspepsia 12 vs 6% ^{RELY} , nausea) Serious: Major Bleed -3.3%/yr ^{RELY} , ICH -0.3% ^{ISMP} : dabi bleeds 5x more fatal vs warfarin (19% vs 4%) ³⁰ CI: prosthetic heart valves thrombosis & bleed ^{REALIGN} renal impairment (CrCl<30mL/min), active bleed, strong P gp inhibitors (e.g.oral ketoconazole) [FDA: ketoconazole + CrCl 30 50mL/min dabi to 75mg BID]	✓ Prevention of stroke/systemic embolism in pts with non valvular AF (e.g. CHADS ₂ 1) ✓ Dabi non inferior 110mg bid / superior 150mg bid vs. warfarin for stroke/systemic embolism ^{RELY31} ☒ No long term (greater than 2 yr) follow up; GI bleeds; ? risk of MI's see RxFiles Q&A ☒ No Antidote for bleeding: ? dialyzable or activated charcoal if 2hr of admin; t½ -13hr, 27hr if CrCl -30 mL/min DI: risk bleed: P gp inhibitors amio & drone darone, quinidine, verapamil; NSAIDs/ASA/clopidogrel. effect: P gp inducers carbamazepine, rifampin, St. John's Wort; Antacids Al, NaHCO ₃ , Ca, Mg, ?PPIs, ?H ₂ RAS M: aPTT (does not reliably assess the activity of dabigatran; aPTT>80 sec at trough is associated with risk of bleeding), SCr & CrCl every 6 12 months Post op: restart 2 5 days based on bleeding risk Pre op: CrCl<50mL/min d/c 1 day pre op or 2 4 days if high bleed risk; CrCl 31 50mL/min d/c 2 days pre op or 4 days if high bleed risk; CrCl 30mL/min d/c 2 5 days pre op or >5 days if high bleed risk.	150mg po BID: < 80 yr 110mg BID: 80yr; >75yr +1 bleeding RF (e.g.CrCl 30 50mL/min) or risk of bleeding CI CrCl<30mL/min: FDA 75mg po bid Switching FROM Warfarin Dabigatran: Stop warfarin. Start dabigatran when INR<2 Switching FROM Dabigatran Warfarin: CrCl<50mL/min: start warf 3 days before d/c dabi CrCl 31 50mL/min: start warf 2 days before d/c dabi CrCl 15 30mL/min: start warf 1 day before d/c dabi	\$110 both doses	
Rivaroxaban AF, XARELTO ^{VFTE} : hip/knee 10 [▼] , (15, 20mg tabs)  t½ -9hr	SE Common: Bleeding, pruritus Serious: Major Bleeding -3.6%/yr ^{ROCKET AF} , hematoma, syncope, ICH -0.5% vs 0.7% warfarin CI: Active major bleeding, hepatic disease, strong CYP3A4 & P gp inhibitors azoles, ritonavir	✓ Prevention of stroke/systemic embolism in pts with non valvular AF ^{AF CDN Jan/12; DVT CDN 12} ✓ Riva non inferior vs warfarin for stroke/systemic embolism ^{ROCKET AF 32} excluded if stroke 14day or TIA 3day prior ☒ No long term (>2 yr) follow up; stroke after rivaroxaban stopped when no overlap with warfarin ☒ No Antidote for bleeding: prothrombin complex concentrate OCTAPLEX / BERIPEX or activated charcoal if 2hr of admin, t½ -9hr DI: CYP3A4 & P gp inhibitors fluconazole, CYP3A4 & P gp inducers rifampin, carbamazepine, phenytoin M: SCr & CrCl every 6 12 months Pre op: stop 1 2day before depending on CrCl & bleeding risk	20mg po daily with food CrCl 30 50mL/min: 15mg daily with food CrCl <30mL/min: not recommended Switching FROM Warfarin Rivaroxaban: Stop warfarin. Start rivaroxaban when INR < 2.5 Switching FROM Rivaroxaban Warfarin: Start warfarin. Stop riva in 2 4days & INR < 2	\$100 both doses	
Apixaban ELIQUIS 2.5,5mg tablet  t½ 12hr	SE Serious: major bleeding 2.1%/yr ^{ARISTOTLE} CI: active bleed, CrCl <15mL/min, hepatic dx, strong CYP 3A4 & P gp inhibitors -azoles, ritonavir, stroke in previous 6 mo. Caution CrCl<30mL/min.	✓ Canada & USA Dec '12 AF approval ☒ No long term (greater than 2 year) follow up ✓ Apixaban superior vs warf in AF non valvular for stroke ^{mortality, bleeds 2.1%/yr but bleed in ACS.} ☒ No Antidote for bleeding: prothrombin complex concentrate OCTAPLEX / BERIPEX , recombinant Factor VIIa, charcoal if 3hr of admin, t½ -12hr DI: CYP3A4 & P gp inhibitors diltiazem & inducers e.g. carbamazepine, St. John's Wort M: SCr & CrCl q6 12 mos	5mg po bid; 2.5mg bid if 2 of: age 80,wt 60kg SCr 133umol/L (CrCl<25mL/min). Avoid: CrCl<15mL/min Switching FROM Warfarin → Apixaban: Stop warfarin. Start apixaban when INR < 2 Switching FROM Apixaban → Warfarin: Start warfarin. Stop apixaban when INR > 2	\$140 both doses	

Major Bleeding=clinically overt bleeding associated with Hgb ≥20 g/L; clinically overt bleeding leading to transfusion of ≥2 units packed cells or whole blood; fatal, retroperitoneal, intracranial, intraocular or intraspinal bleeding; bleeding warranting tx cessation or leading to reoperation. Included events occurring at the surgical site.
 Factors which hemorrhagic risk: renal impairment (CrCl <50mL/min), active ulcerative GI disease, age≥75yr, ASA, bacterial endocarditis, brain/spinal/ophthalmic surgery, clopidogrel, congenital/acquired coagulation disorders, NSAID, P-gp inhibitors co-med (eg. amiodarone, azole antifungals, clarithromycin, cyclosporine, diltiazem, erythromycin, HIV PIs, quinidine, tacrolimus, tamoxifen, verapamil), recent: biopsy/major trauma/GI bleed/ intracranial hemorrhage, steroids & thrombocytopenia.

Generic/TRADE strength/form		Usual Dose Range	Canada \$/30d	PLACE IN THERAPY / COMMENTS / Outcome Evidence /Side effect SE/Contraindication CI
Beta Blockers (BB) ♥ (bisoprolol, metoprolol , selective less with dose) (see pg 3, 13, 16)				✓ BBs recommended as initial therapy for rate control for AF or AFL in pts with MI, LV systolic dysfunction or HF ¹ (see HF chart, pg 12 13) ✓ BBs lower HR at rest and exercise, but no change or a in exercise capacity ³⁷ Useful for exercise induced HR CI: severe/poorly controlled asthma, 2 nd /3 rd degree heart block without permanent pacemaker, PR>0.24sec, symptomatic bradycardia (HR<50), SBP<85mmHg symptomatic hypotension, decompensated HF, ³⁸ or if cocaine user. (Stable COPD is <u>not</u> a CI.) SE: BP/HR, dizziness, fatigue<10%, insomnia, dream vivid, sexual dysfx-4%, PAD, cold extremity, hypoglycemia ?mask,fluid retention?, psoriasis DI: amiodarone, CCB & digoxin synergistic; antidiabetics, cimetidine BB, clonidine hypertensive crisis, NSAIDs BP & phenobarbital BB M: ECG Other BBs: Nadolol ²⁰ 160mg daily BID max 160mg BID, propranolol ⁸⁰ 240mg TID max 320mg LA daily, Carvedilol less potent/effective for rate control vs metoprolol ³⁹
Bisoprolol MONOCOR, g 5, 10mg tab (USA: ZEBETA)	2.5 10mg daily Max 20mg daily	\$10 15	\$10 15	✓ CCBs less effective for exercise induced HR; but may lead to an / in exercise capacity ¹ diltiazem > HR/sx vs verap, meto, carv (n=60) ⁴⁰ ✓ CCBs may be preferred in pts with chronic pulmonary dx & at risk of bronchoconstriction or if paroxysmal SVT eg. AV nodal re entry. ✓ CCBs may be better for younger pts b/c they tend to be less fatiguing than BBs ✗ Avoid in pts after MI or with HF CI: systolic dysfunction HF, SBP<90mmHg, recent MI or pulmonary edema, Sick Sinus Syndrome, 2 nd /3 rd degree AV block SE: BP/HR, constipation verapamil, edema diltiazem M:ECG,HR DI: carbamazepine,cyclosporine,dabigatran,digoxin,grapefruit juice,lova/simva statin
Metoprolol LOPRESOR, g Reg: 25 , 50 , 100 mg tab; SR: 100,200mg tab 10mg/mL susl manufactured at some pharmacies: Vial: 1mg/mL (Atenolol associated with mortality ^{Carbong04})	25 200mg BID Max 200mg BID	\$10 33	\$10 33	
Non dihydropyridine Calcium Channel Blockers (non DHP CCB) ♥				✓ Digoxin is less effective than BBs or CCBs ¹ ; digoxin does <u>not</u> routinely control HR in sympathetic tone states eg. AECOPD,exercise,surgery ✓ Add digoxin to BBs or CCBs in pts whose HR is uncontrolled ✓ Use for rate control in sedentary pts or have LV systolic dysfunction CI: hypersensitivity, ventricular fibrillation. Caution: acute MI, AV block, chronic constrictive pericarditis, HR, thyroid dx. { mortality ^{AFIRM} } SE / Toxicity: anorexia, N/V, weakness, dizziness, visual change (Digoxin less effective if Ca ⁺⁺ ; but toxicity if or K ⁺ , Ca ⁺⁺ , TSH, Mg ⁺⁺) DI: amio /drone darone, azoles, CCB's, clarithro & erythro mycin, cyclosporine & quinidine dig level, BB. M: ECG, Digoxin levels (DIGIBIND if overdose)
Diltiazem CARDIZEM Reg.:30,60 mg tab, CD ₂ : 120,180,240,300mg cap TIAZAC g reg cap XC tab 120, 180, 240, 300, 360mg	120 480mg daily Max 540mg/d	\$25 60	\$25 60	
Verapamil ISOPTIN Reg. 80, 120mg tabs, SR, 120, 180 , 240 mg tab	120mg OD 240mg SR BID Max 480mg/d	\$22 52	\$22 52	
Other ♥				✓ Amiodarone reserved for exceptional cases when other means are not feasible/insufficient since long term toxicity, preferred if EF. ✓ 60 70% efficacy at 1yr ¹⁰ ; Amio more effective than placebo/rate control drug in achieving sinus rhythm RR=3.2, 95% CI (1.9 5.5) ^{Meta analysis,41} CI: Iodine allergy, cardiogenic shock, pulmonary interstitial changes, severe sinus node dysfx, 2 nd /3 rd degree AV block, hepatitis, thyroid dysfx SE: Common: CV bradyarrhythmia, hypotension, DERM blue skin, photo dermatitis/sensitivity wear sunscreen, GI appetite,constipation, N/V, LFTs, Neurologic abnormal gait/coordination, dizziness, paresthesia, peripheral neuropathy, Ophthalmic corneal/micro deposit, visual disturbances, fatigue, tremor, insomnia. Serious: CV cardiac dysrhythmia, HF, vasculitis, ventricular arrhythmia, DERM SIS, TEN, Endocrine hyper/hypo thyroidism or tumour, thyrotoxicosis. Eye blindness, optic neuritis or neuropathy, Lung ARDS, extrinsic allergic alveolitis, interstitial pneumonia, pulmonary fibrosis/toxicity; other hepatic/renal toxicity, lupus, rhabdomyolysis, thrombocytopenia DI: {CYP 3A4, 2C8,1A2, 2C9, 2D6, 3A4, p glycoprotein inhibitor} Warfarin INR by 50%, Digoxin dig level by 50%, protease inhibitors amio level, lova/simva statin statin level, grapefruit juice, BB / CCB HR, cyclosporine cyclo level, antidepressants/TCAs/macrolides/azoles QT, ...etc
Class III – Amiodarone, Dronedaron, Sotalol ♥🎵				✓ May be added for additional rate control despite BBs, CCBs or digoxin; ✓ 40% efficacy at 1 yr ¹⁰ Restricted use only Europe Sep/11 ✗ In patients with permanent AF , risk of CV death, stroke, HF hospitalization; trial stopped early ^{PALLAS 42,43} Dronedaron less efficacious than amiodarone with less serious SE at 1 yr ^{DIONYSOS 44} mortality if decompensated HF ^{ANDROMEDA} CI: Severe HF NYHA IV, 2 nd /3 rd AV block, sick sinus syndrome, bradycardia <50 bpm, QTc 500msec, hepatic impairment severe, strong CYP3A4 inhibitor e.g. azoles, pneumonitis/fibrosis, torsades de pointes eg. phenothiazines, TCA, class I/III antiarrhythmic pg17 SE: Common: Asthenia, GI diarrhea, nausea, abdominal pain, S Cr 10% 5days after tx started, QTc interval prolonged Serious: HF, hepatotoxicity
Amiodarone CORDARONE, g 200 mg tab; 50mg/mL inj: 5, 10, 20mL vials Amiodarone IV/PO Loading Dose (LD) usually initiated in hospital/cardiologist M: ALT/AST baseline & q6 12mos, CXR baseline & q3 12 mos, ECG baseline & q3 6 mos, eye exam funduscopy/slit lamp baseline if possible in hospital & q6 12mos, PFTs = diffusion capacity if symptoms of dyspnea, nonproductive cough, weight loss, ? serum KL 6 levels = indicator for amiodarone induced pulmonary toxicity, normal<500units/mL, TSH/free T4 baseline & q6mos	LD 800 1600mg/d for 1 3 weeks, then 600 800mg/d x 1 month, then 200 400mg/d ^{CPS} Single daily dose, or in pts with severe GI symptoms – bid dose	\$31 55	\$31 55	
Dronedaron MULTAQ 400mg tab ✗	400mg BID For non permanent AF only \$150	\$150	\$150	
M: ECG baseline, & q3mo, S Cr baseline, 1 wk after initiation, AST/ALT baseline, & q3 6mo, then periodically DI: {CYP 3A4, CYP 2D6} Prolong QT interval class I/III antiarrhythmics, phenothiazine, TCAs (see pg 17), bradycardia BBs, non DHP CCBs, dabigatran, digoxin dig level , statin statin level, dronedarone by: 3A4 inhibitors=clar /tel ithromycin, cyclosporine, grapefruit juice, azoles, ritonavir dronedarone by: 3A4 inducers= carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort				
Sotalol SOTACOR g 80 , 160 mg tab useful if CAD & AF CCS AF:CI if CrCl <40mL/min, & in ♀ >65yrs taking diuretics	80mg BID Max 480mg/d CrCl 30 60mL/min → q24H CrCl 10 30mL/min → q36 48H CrCl < 10 mL/min → individualize	\$16	\$16	
Class I – Flecainide, Propafenone 🎵 : if <u>no</u> structural heart disease				✓ Combine with BB, digoxin, non DHP CCB ✓ 30 50% efficacy at 1 yr ¹⁰ ✓ PO may be effective for recent onset/“pill in the pocket” ✓ Given IV 2mg/kg over 10 min, pts with short duration of AF<24h (67 92% at 6hr) convert to sinus rhythm; majority convert within 1 hour ✗ In post MI/asymptomatic ventricular arrhythmias in mortality/nonfatal cardiac arrest rate with flecainide/encainide 19/323=5.8% vs. placebo 7/318=2.2% (NNH=28 in 10 months). ^{47,CAST} ✗ IV rarely effective for termination of AFL or persistent AF CI: 2 nd /3 rd degree AV block, cardiogenic shock; CAUTION: CAD or LV dysfunction SE: Common: nausea, Neurologic asthenia, tremor, dizziness, headache, Ophthalmic blurred vision, corneal deposit, dry eyes, photopsia, anxious, dyspnea Serious rare: cardiogenic shock, chest pain, ECG abnormality, heart block, HF, tachy/ventricular arrhythmia, hepatotoxic, death
Flecainide TAMBOCOR 50, 100 mg tablet	50 150mg PO BID trough=0.2 1ug/mL, toxicity 1ug/mL Pill in the Pocket dose: 200 300mg x1	\$60 85	\$60 85	
Propafenone RYTHMOL g 150, 300 mg tablets	Initial: 150mg/d PO Usual: 150mg q8h Max 600mg/d Pill in the Pocket dose: 450 600mg x1	\$21 \$45	\$21 \$45	
M: ECG, flecainide trough levels if dose>200mg/d, renal/hepatic impairment, children, HF or elderly DI: Digoxin dig levels; (carbamazepine, phenobarbital,phenytoin) flecainide; cimetidine flecainide, BBS negative inotropic effect				
M: CYP 1A2, 2D6, 3A4 Amio proarrhythmic effect, BBS metoprolol/propranolol dose may need , Digoxin, drugs prolong QTc eg., desipramine, etc see page 17, theophylline, venlafaxine, warfarin INR: drugs propafenone grapefruit juice, ritonavir, SSRIs (fluoxetine, fluvoxamine, paroxetine), St. John's Wort; rifampin propafenone				

⚠ = Exception Drug Status in SK ✗ = Non-formulary in SK ☞ = prior approval by NIHB =not covered NIHB ▼=covered NIHB S=retail cost =scored tab ♥=rate control 🎵=rhythm control ACCF=American College of Cardiology Foundation ACS=acute coronary syndrome AECOPD=acute exacerbation of COPD AF=atrial fibrillation AFL=atrial flutter AHA=American Heart Association ALT=alanine aminotransferase AMIO=amiodarone aPTT=activated partial thromboplastin time ARDS=acute respiratory distress syndrome ASA=acetylsalicylic acid AST=aspartate aminotransferase AV=atrioventricular BBB=bundle branch block b/c=because BP=blood pressure bpm=beats per minute BUN=blood urea nitrogen Ca=calcium CAD=coronary artery disease CADTH=Canadian Agency for Drugs in Technology & Health CBC=complete blood count CC=calcium channel blocker CCS SAF=Canadian Cardiovascular Society Severity in AF CI=contraindication CNS=central nervous system COPD=chronic obstructive pulmonary disease CrCl=creatinine clearance CV=cardiovascular CYP=cytochrome CXR=chest x-ray d/c=discontinue DERM=dermatologic DM=diabetes mellitus dx=disease DVT=deep vein thrombosis dysfx=dysfunction ECG=electrocardiogram EF=ejection fraction ESC=European Society of Cardiology FBG=fasting blood glucose f/u=follow-up GI=gastrointestinal H2RAs=histamine2 receptor antagonists HD=heart disease Hgb=hemoglobin HF=heart failure HIV=human immunodeficiency virus HR=heart rate HRS=Heart Rhythm Society HTN=hypertension INR=international normalized ratio K+=potassium LBW=lean body weight LD=loading dose LFT=liver function test LV=left ventricle LVEF=left ventricle ejection fraction LVD=left ventricular dysfunction LVF=left ventricular function M=monitor MD=maintenance dose Mg=magnesium MI=myocardial infarction Na=sodium NNH#-number needed to harm/treat Non-DHP CCB=non-dihydropyridine calcium channel blocker NV=nausea/vomiting NS=not significant NSAIDs=non-steroidal anti-inflammatory drugs NYHA=New York Heart Association OAC=oral anticoagulant PAD=peripheral arterial disease PE=pulmonary embolism PFTs=pulmonary function tests P-gp=permeability glycoprotein PH=pulmonary hypertension PIs=protease inhibitors PPIs=proton pump inhibitors pts=patients QOL=quality of life RR=relative risk RCT=randomized controlled trials Rx=prescription SAF=severity in AF SBP=systolic blood pressure SCR=serum creatinine SE=side effects SJS=Stervens Johnson Syndrome SLE=systemic lupus erythematosus Sx=symptom T½=half life TCAs=tricyclic antidepressants TEE=transesophageal echocardiogram TEN=toxic epidermal necrolysis TIA=transient ischemic attack TSH=thyroid stimulating hormone tx=treatment URTI=upper respiratory tract infection ULN=upper limit of normal VTE=venous thromboembolic event WPW=Wolff-Parkinson-White wt=weight yr=yards

CONSIDERATIONS	WARFARIN	NEW ORAL ANTICOAGULANTS
EXPERIENCE	Approximately 60 years. Challenges exist but are well understood.	Lack long term safety & efficacy data. Landmark AF trials were ~1.5 2 years. Real world experience 2 years.
EFFICACY Only 1 landmark trial for each new OAC versus warfarin in AF	the relative risk of stroke by 64%. Depends on time spent in therapeutic range (TTR) e.g. 65% of INRs between 2 3.	Apixaban ELIQUIS & dabigatran PRADAX 150mg twice daily had less stroke & systemic embolism versus warfarin. NNT ranged from 88 to 167/-2 years. Lower mortality rate with apixaban, NNT=132/-2 years (p=0.047). Rivaroxaban XARELTO & dabigatran 110mg twice daily were no worse than warfarin for the same endpoint.
SAFETY Primarily based on RCTs. Post marketing data will provide sense of real world safety.	Risk of: non hemorrhagic stroke when INR <2 bleed when INR >3, particularly with an INR >4.5	Less intracranial bleeds compared to warfarin. NNT 96 250/-2 years. Apixaban had least amount of bleeding. Increased risk of GI bleed with dabigatran & rivaroxaban (NNH=100/year for both drugs). Dabigatran also had more dyspepsia & potential increase risk of MI <small>see RxFiles Q&A Does Dabigatran the Risk of MI http://www.rxfiles.ca/rxfiles/uploads/documents/Dabigatran_MI%20Risk_QandA.pdf</small>
REVERSAL AGENT "ANTIDOTE"	Vitamin K: If no significant bleeding & INR>10: hold warfarin & give vitamin K 2.5 5mg orally. Reduce weekly warfarin dose by 20% & resume once INR in therapeutic range. Vitamin K 5 10mg IV for serious bleeds.	No established antidote or procedure for reversal. Potential options: Apixaban & Rivaroxaban: prothrombin complex concentrate (PCC) OCTAPLEX , BERIPLEX , recombinant Factor VIIa, & activated charcoal if <2 3 hours of administration. Dabigatran: dialysis, & activated charcoal if 2 hours of administration. See SK Guideline on Dabigatran & Bleeding http://www.health.gov.sk.ca/dabigatran_guideline .
MONITORING	Routine & frequent INR tests. Frequency can be extended to every one three months once dose stabilized. Can provide reassurance of drug efficacy & safety (i.e. within target range).	Serum creatinine and calculated creatinine clearance – every 6 12 months. [Lack of test for anticoagulation status results in assumptions regarding suitability of empiric dosing for broad populations groups.]
PHARMACOKINETICS	Longer t½ (2.5 days) Benefit: therapeutic levels & some sustained protection despite a few missed doses.	Shorter t½ (8 17 hours) Benefit: shorter t½ allows drug to be cleared quicker, but t½ extended with renal impairment. Concern: non compliant patients will lose significant anticoagulation status more quickly with new OAC than with warfarin after missing a dose.
DRUG INTERACTIONS	Numerous drug interactions. INR monitoring & dosage adjustments; however, useful to accommodate concomitant acute & chronic therapy. Well documented DI : antiplatelets, NSAIDs, amiodarone, antibiotics (cotrimoxazole, ciprofloxacin).	Fewer known drug interactions, but lacking experience to determine clinical significance of these. No way to adjust dose secondary to drug interaction. Strong inhibitors of both CYP 3A4 & P glycoprotein are contraindicated with all three new agents (e.g. azoles, ritonavir). Caution with CYP 3A4 & P glycoprotein inducers (e.g. rifampin, phenytoin carbamazepine, St. John's Wort) & inhibitors (e.g. verapamil, amiodarone, dronedarone, quinidine).
FOOD INTERACTIONS	Need to be mindful of foods high in vitamin K, but dose may be adjusted to reflect dietary intake. Consistency versus avoidance of these foods is encouraged.	Apixaban & dabigatran: none Rivaroxaban: avoid grapefruit (how much?)
DOSAGE REGIMEN	Once daily Target: – Most: INR 2 3 – Mechanical mitral valve: INR 2.5 3.5 May require more than one pill per day or alternating dosing schedule	Dose and frequency depends on the indication. Empiric versus tailored dosing. Stroke prevention regimens are as follows: Apixaban 5mg twice daily, or Apixaban 2.5mg twice daily in patients with two or more of the following criteria: age 80 years, body weight of 60kg, SCr 133umol/L. Dabigatran 150mg twice daily, or Dabigatran 110mg twice daily in patients who are 80 years, or 75 79 years of age with 1 bleeding risk factor (e.g. CrCl 30 50mL/min) Rivaroxaban 20mg once daily with food. (Some question as to whether twice daily might be more optimal given t½.)
RENAL IMPAIRMENT (CrCl <30mL/min)	No dose adjustment required. INR monitoring allows for individual tailoring of dose to patient.	All require dose reduction or should be avoided with renal impairment (e.g. CrCl <30mL/min). Patients with renal impairment were excluded from trials. Apixaban: excluded patients with CrCl <25mL/min. Reduce dose to 2.5mg twice daily in patients with two of the following: age 80, weight 60kg, SCr 133umol/L (CrCl <25mL/min). [Official: avoid <15mL/min] Dabigatran: excluded patients with CrCl <30mL/min, and this degree of renal impairment is considered a contraindication in Canada. Consider 110mg twice daily in patients with CrCl 30 50mL/min. (FDA 75mg po BID if CrCl<30mL/min) Rivaroxaban: excluded patients with CrCl <30mL/min. Reduce dose to 15mg daily if CrCl 30 49mL/min.
 COST/MONTH	~\$40 (includes INR monitoring cost) Warfarin remains a more cost effective 1 st line option than the new OAC even after considering the cost of INR monitoring.	Apixaban \$140 Dabigatran \$110 Rivaroxaban \$100 May not be covered by provincial or hospital formularies. Agents on formulary have criteria patient must meet (e.g. failed warfarin, CHADS ₂ 2).
OTHER	Anticoagulant Management Clinics may be available. Increases: ▪ monitoring efficiency, ▪ time in therapeutic range absolute ~8% Dosing nomograms are available.	Apixaban: approved by Health Canada for stroke prevention in AF in Dec'12. Dabigatran: capsules, packaged in blister packs or bottles, must be stored in original container (i.e. cannot be pill/compliance packaged). Capsules from bottles must be used within 4 months of opening. Do not break or open capsules <small>bioavailability by 75%.</small>

AF=atrial fibrillation CrCl=creatinine clearance DI=drug interaction GI=gastrointestinal INR=international normalized ratio MI=myocardial infarction NSAIDs=non steroidal anti inflammatory drugs NNT/H=number needed to treat/harm OAC=oral anticoagulant SK=Saskatchewan SCr=serum creatinine t½=half life

Adapted from RxFiles case in CFP Journal, Aug 2012 http://www.cfp.ca/content/58/8/850.full.pdf?sid=b5585b9d_5fa6_4ce2_9311_9167c965ef95

Warfarin has been used for over 60 years & is approved for multiple indications e.g. stroke prevention in atrial fibrillation, heart valve disease/replacement, venous thromboembolism prophylaxis & treatment, post myocardial infarction/acute coronary syndrome, etc. When appropriately managed in compliant stable patients, warfarin is safe & effective safety & effectiveness as time in therapeutic range .

MANAGEMENT PEARLS

Use a validated nomogram for initiating & maintaining warfarin. Nomograms have been shown to time in therapeutic range (TTR) see Tables 1, 2 & 3. ^{CADTH, CHEST '12, 3}
 Extend the frequency of international normalized ratio (INR) monitoring to q12wks in pts who have had stable INRs for 3 mons, ^{CHEST '12} ensure pt will report any drug changes between INRs.
 Do not adjust warfarin doses based on an asymptomatic, single, unexplained e.g. no drug/dietary changes, out of range maintenance INR 0.5 target; recheck INR in 1 2 wks. ^{2,4}
 If concomitant use of a drug that alters INR cannot be avoided, INR monitoring & reactively (not proactively) adjust the dose in response, except if can predict response based on past DI.

INITIATING WARFARIN see Tables 1 & 2

Collect INR on Day 1 **only if no baseline available**; INR on Day 2 **usually not needed**.

Target INR for most: 2.5 (acceptable range = 2 3)
 for mechanical mitral valve replacement: 3 (acceptable range 2.5 3.5)

Consider dispensing in strengths that accommodate dose changes e.g. 1 & 2mg, 1 & 5mg.
 Use one of the following regimens **when starting** warfarin; consider the patient's risk factors for **clotting** or extension of existing clot & **bleeding**.^{5,6}

1) Warfarin 2 3mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs

Consider in patient populations such as **elderly, debilitated, malnourished, heart failure, liver disease, risk of bleeding or taking medications known to INR**.
 There is no validated nomogram for this regimen, but can use same % or as outlined in Table 1 (e.g. 3mg Day 1 & 2, with a Day 3 INR of <1.5 give either 3mg or 6mg).

2) Warfarin 5mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs

TABLE 1: INITIATING WARFARIN EXAMPLE OF A VALIDATED NOMOGRAM FOR 5mg DAY 1 & DAY 2 (INR 2 3)⁶

DAY 3		DAY 4 (OPTIONAL INR)		DAY 5		DAY 6 (OPTIONAL INR)	
INR	DOSE(mg)	INR	DOSE(mg)	INR	DOSE (mg)	INR	DOSE (mg)
< 1.5	5 – 10	< 1.5	10	< 1.5	10	< 1.5	7.5 – 12.5
1.5 – 1.9	2.5 – 5	1.5 – 1.9	5 – 7.5	1.5 – 1.9	7.5 – 10	1.5 – 1.9	5 – 10
2 – 3	0 – 2.5	2 – 3	0 – 5	2 – 3	0 – 5	2 – 3	0 – 7.5
> 3	0	> 3	0	> 3	0	> 3	0

3) Warfarin 10mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs

TABLE 2: INITIATING WARFARIN VALIDATED NOMOGRAM FOR 10MG DAY 1 & DAY 2 (INR 2 3)⁷

DAY 3 INR	DAY 3 & 4 DOSE (mg)	DAY 5 INR		DAY 5, 6 & 7 DOSE (mg)	
		< 2	2-3	< 2	2-3
<1.3	15, 15	< 2	2-3	< 2	2-3
1.3 - 1.4	10, 10	2-3	> 3.5	2-3	> 3.5
1.5 - 1.6	10, 5	< 2	> 3.5	2-3	> 3.5
1.7 - 1.9	5, 5	2-3	> 3.5	2-3	> 3.5
2 - 2.2	2.5, 2.5	< 2	> 3.5	2-3	> 3.5
2.3 - 3	0, 2.5	2-3	> 3.5	2-3	> 3.5
>3	0, 0	< 2	> 3.5	2-3	> 3.5

Warfarin 10mg x Day 1 & Day 2:
 -likely safe & effective for outpatients not at high risk of bleeding ^{CHEST '12}

-may achieve therapeutic INR faster ⁷

FREQUENCY OF INR MONITORING

Initiating warfarin: week 1: Day 3 & 5, week 2: 2 INRs, then weekly INRs until stable x 2 weeks, then q2weeks until stable x 1 month, then **monthly INRs**. If stable x 3 months **INR up to q12 weeks**, ^{CHEST '12} ensure pt will report any changes in drug therapy between INRs.

Warfarin dose changes: check INR weekly until stable.

Starting, stopping or changing the dose of an interacting drug: check INR in 4 6 days after the change. monitoring duration for drugs with long t½ or onset e.g. amiodarone.

MANAGEMENT OF SUB /SUPRATHERAPEUTIC INRS see Figure & Table 3

Interpretation of INR requires many considerations:

- trend & time since last INR, duration of current dose full therapeutic effect may take 5 7 days
- changes in medications starting, stopping & changes in doses of interacting medications
- factors that may INR: acute illnesses e.g. diarrhea, fever, in alcohol intake
- factors that may INR: edema, vitamin K intake, physical activity level
- patients with heart failure, diabetes & acute GI illness may experience INR instability ⁸

FIGURE: STEPWISE APPROACH FOR SUB /SUPRATHERAPEUTIC INRS

Step 1: Note indication for warfarin & target INR. Is the patient symptomatic for the INR?
 If the INR is high, is the patient exhibiting signs &/or symptoms bleeding?
 If the INR is low, is the patient exhibiting signs &/or symptoms of a stroke or VTE?
 If **yes**, provide appropriate emergent/urgent care. If **no**, proceed to Step 2.

Step 2: Is the patient at risk of becoming symptomatic for the INR?
 If the INR >10: hold warfarin, give vitamin K 2.5 5mg ampule po x1. weekly warfarin dose by 20% & resume once INR in therapeutic range. Re check INR in ~2 days.
 If the INR is low, consider bridging with LMWH if the patient is at high risk of a clot.

Step 3: Identify if sub /suprathereapeutic INR is a result of a permanent or transient cause.
Transient causes: e.g. missed/extra dose, gastroenteritis, course of antibiotics, recent alcohol intake
 - Consider dose correction e.g. hold or give extra dose & INR monitoring frequency
Permanent causes: e.g. lifestyle change, change with a chronic medication
 - Consider a change in weekly dose see Table 3 below & INR monitoring frequency

Vitamin K 100 200 mcg po daily may help stabilize INR in pts with unexplained fluctuating INRs, but lacks evidence for routine use. Tablets are available at health food stores (e.g. GNC).

TABLE 3: MAINTENANCE OF WARFARIN – EXAMPLE VALIDATED NOMOGRAM⁹

TARGET INR 2 – 3	ACTION	TARGET INR 2.5 3.5
< 1.5	Extra dose, weekly dose by 10 20%	< 2
1.5 – 1.9	weekly dose by 5 10%	2 – 2.4
2 – 3	No Change	2.5 – 3.5
3.1 – 3.5	weekly dose by 5 10%	3.6 – 4
3.6 – 4.9	Hold 1 dose, weekly dose by 10 20%	4.1 – 4.9
5 – 9	Hold 2 doses, weekly dose by 10 20%	5 – 9
> 9	Urgent evaluation	> 9

Do not adjust warfarin dose based on 1 asymptomatic, unexplained, out of range maintenance INR 0.5 target. Recheck INR in 1 2 weeks.

Managing Warfarin Drug Interactions see RxFiles Antiplatelet & Antithrombotic & Herbal DI charts

Interactions that alter INR: e.g. amiodarone, antimicrobials. If combination cannot be avoided, INR monitoring & reactively adjust dose in response. Empiric dosage adjustments rarely necessary & are less predictable than the interaction itself.

Interactions that risk of bleed or clot without affecting INR: e.g. NSAIDs, antiplatelets. Balance the risk of bleeding/clotting with the benefit of therapy.

See On line Extras for more information on warfarin: <http://www.rxfiles.ca/rxfiles/uploads/documents/members/Warfarin%20Management.pdf>

Option 1: Warf 2 3mg x 2 Elderly, high bleed risk, etc

Option 2: Warf 5mg x 2 Most commonly used

Option 3: Warf 10mg x 2 Younger, low bleed risk patients

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