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
- CADTH [2012]: 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/ASA [2012]: 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
- CHEST [2012]: http://chestjournal.chestpubs.org/content/141/2_suppl/e531S.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

CFP Article
Oral Anticoagulation in AF
http://www.cfp.ca/content/58/8/850.full

RxFiles Charts
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

RxFiles Q&A
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

RxFiles Trial Summaries
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
RE-LY (dabigatran vs warfarin)
http://www.rxfiles.ca/rxfiles/uploads/documents/RE-LY-Trial-Dabigatran.pdf
ROCKET-AF (rivaroxaban vs warfarin)
http://www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf
PALLAS (dronedarone in permanent AF)
http://www.rxfiles.ca/rxfiles/uploads/documents/PALLAS-trial%20summary.pdf

Highlights

- Assess stroke $CHADS_2$, CHA_2DS_2VASc & bleeding HAS-BLED risk.
- If $CHADS_2$ ≤1, consider using CHA_2DS_2VASc.
- 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 ($CHADS_2$, CHA_2DS_2VASc)
  - Calculate bleed risk (HAS-BLED)
- Manage arrhythmia (rate vs. rhythm control).

$CHADS_2$ versus CHA_2DS_2VASc for estimating risk of stroke

- Both tools help guide antithrombotic therapy & have a similar ability to estimate the risk of stroke in AF.
- $CHADS_2$ score is easier to remember & use.
- CHA_2DS_2VASc is better for estimating stroke risk in low- or intermediate-risk individuals (e.g. $CHADS_2$ score ≤1).
- $CHADS_2$ = 0: AF guidelines recommend considering gender (female), presence of vascular disease & age (≥65 years) to guide therapy (i.e. CHA_2DS_2VASc).

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 $CHADS_2$ ≥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)
  - β-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: Dronedarone 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 dronedarone 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.

Atrial Fibrillation (AF) –Treatment Overview [1]

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Prevalence of AF: 0.1% < 50yr, **10-15%** > 80yr [2]

AF Stroke/yr: 5% RCTs; USA: 15% overall, 1.5% 50-59yr, 23.5% 80-89yr

Risk of stroke: see **$CHADS_2$/CHA_2DS_2VASc** score (next page)

Risk of bleeding: see **HAS-BLED** score (next page)

Precipitating Cause(s) of AF:

Cardiac: CAD/MI, HF*, **HTN**, LVD*, cardiomyopathies hypertropic, 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:

1. **Paroxysmal**: AF is self-terminating within 7 days of recognized onset. Not all patients picked up on ECG.
2. **Persistent**: AF is not self-terminating within 7 days or is terminated electrically or pharmacologically.
3. **Permanent**: AF in which cardioversion has failed or in which clinical judgment has led to a decision not to pursue cardioversion.

PEARLS FOR AF

1. A chronic, recurrent & progressive condition. Re-evaluate sx management SAF, risk of stroke $CHADS_2$ & bleeding HAS-BLED often.
2. No significant difference between rate vs. rhythm control.
3. Consider an oral anticoagulant (OAC) when $CHADS_2$ ≥1. Most benefit with scores ≥2.
4. If HAS-BLED ≥3, use caution with OAC, & monitor for bleeds.
5. 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.
6. 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 monitoring [3]

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]

	SAF Score	Impact on QOL
Step 1 - Symptoms Identify the presence of the following symptoms: **palpitation**, **dyspnea**, **dizziness** (**presyncope** or **syncope**), **chest pain**, **weakness** or **fatigue**. {frequency, duration & severity of symptoms vary} **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} **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 0	Asymptomatic with respect to AF
	Class 1	Minimal effect on QOL • Minimal ± infrequent Sx, or • Single episode of AF without syncope or HF
	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
	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

1. Detect & treat precipitating causes (e.g. refer to cardiologist).
2. Manage thromboembolic risk ($CHADS_2$, CHA_2DS_2VASc, HAS-BLED).
3. 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. $CHADS_2$, CHA_2DS_2VASC, HASBLED) & 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}.**

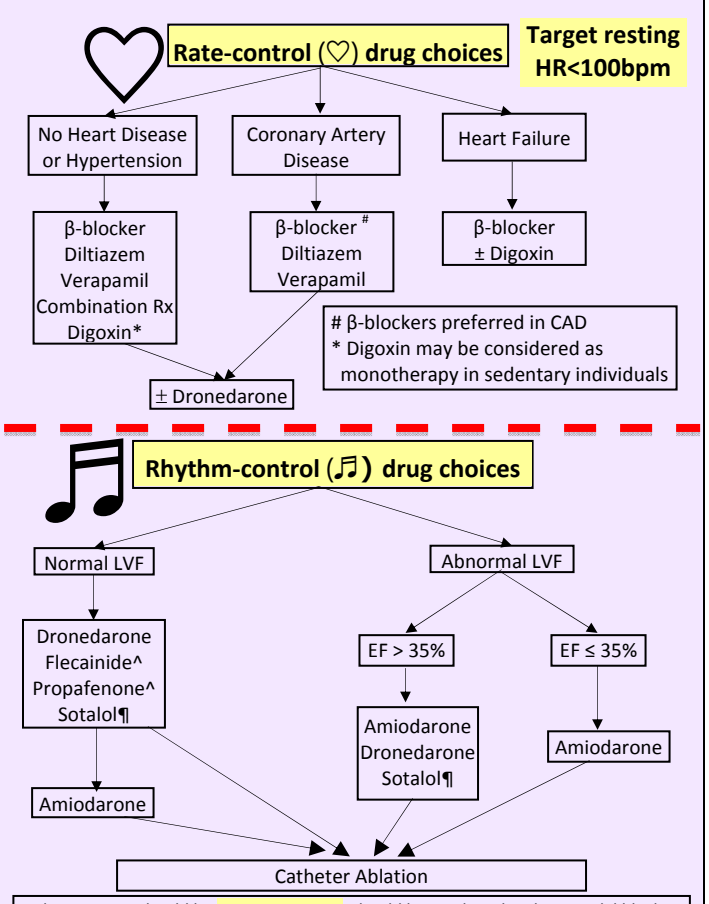
- **Intermittent:** patient requires dose of flecainide or propafenone to terminate episode (not on chronic therapy)
- **Booster dosing:** patient is on low-dose chronic therapy & requires one extra dose to terminate an episode [6]

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]



^ 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

DRUGS THAT ↑AF: [16] Antithrombotics (anagrelide, clopidogrel), CV (acetylcholine, adenosine, arbutamine, atenolol, digoxin, diltiazem, dobutamine, dopamine, dopexamine, flosequinan, isosorbide mononitrate, losartan, perflexane, perfluorbutane, thiazides, verapamil), Respiratory (ephedrine, methylprednisolone, phenylephrine, pseudoephedrine, salbutamol, terbutaline, theophylline), Cytostatics (5-fluorouracil, cisplatan, docetaxel, etoposide, gemcitabine, ifosfamide, interferon-gamma, interleukin-3, interleukin-6, melphalan, profimer, 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 $CHADS_2$ score]. Antiarrhythmics: 6 wks-3mos post-procedure ↓AF recurrence. Paroxysmal best success rate.

Selection of Thromboembolic Therapy [20]

1. Assess Thromboembolic Risk – $CHADS_2$, or CHA_2DS_2VASc if $CHADS_2$ ≤1 (neither should be used for mechanical heart valves or rheumatic heart disease)

$CHADS_2$ Risk Criteria	Points
Congestive Heart Failure (symptoms in last 3 months)	1
Hypertension (diagnosis)	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke/TIA (prior)	2

- Easy to remember & use
- Moderately effective tool (C-stat)
- Initially validated n=1733, 10yr f/u Denmark cohort n=73,538

$CHADS_2$ 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_2DS_2VASc Risk Criteria	Points
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

- 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

CHA_2DS_2VASc 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)
2	2.2	OAC (Level IA)
3	3.2	
4	4	
5	6.7	
6	9.8	
7	9.6	
8	6.7	
9	15.2	

Antiplatelet Therapy
If a patient refuses an OAC, consider: (Level IIa, B)
- ASA 75-100mg + clopidogrel 75mg daily, or
- ASA 75-325mg daily

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)
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50

Score ≥ 3 = high risk for bleeding event→use caution & regular evaluation of antithrombotic therapy

* Intracranial, hospitalization, ↓ Hgb >20g/L, ± transfusion
Validated only with warfarin (n=7329). Limited value (C-stat).
Other tools for predicting warfarin-associated hemorrhage: ATRIA[24], RIETE [25], $HEMORR_2HAGES$ [26] (see On-Line Extras)

3. Assess Benefit vs Risk

e.g. If $CHADS_2$=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.sparctool.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 & $CHADS_2$ score is ≥2.
- **American CHEST** [2012]: dabigatran **preferred** over warfarin. **ACC/AHA/HRS**[2011]: dabigatran is an **alternative** to warfarin. **AHA/ASA**[2012]: 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 [REALIGN]
- 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**.

	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
Direct Thrombin Inhibitor	**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 & bleeds[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; t ½ ~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_2RAS 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
Direct Factor Xa Inhibitors	**Rivaroxaban** ☎ AF, ⊗ **XARELTO** ☎▼ VTE: 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 [33] ☒ **No Antidote** for bleeding: prothrombin complex concentrate OCTAPLEX / BERIPLEX or activated charcoal if ≤2hr of admin, t ½ ~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[ARISTOTLE 34] ↓mortality, ↓bleeds 2.1%/yr but ↑↑ bleed in ACS. ☒ **No Antidote** for bleeding: prothrombin complex concentrate OCTAPLEX / BERIPLEX, recominbant 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:[1] 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	$/30d	PLACE IN THERAPY / COMMENTS / Outcome Evidence /Side effect SE/Contraindication CI
Beta Blockers (BB) ♡ {bisoprolol, metoprolol β_1-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, 2nd/3rd 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 not 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]
PL **Bisoprolol** MONOCOR, g 5c, 10mg tab [USA: *ZEBETA*]	**2.5-10mg daily** Max 20mg daily	$10-15	
PL **Metoprolol** LOPRESOR, g Reg: 25c, 50c, 100c mg tab; SR: 100, 200mg tab 10mg/mL susp manufactured at some pharmacies; Vial: 1mg/mL	**25-200mg BID** Max 200mg BID	$10-33	
PL **(Atenolol** - associated with ↑ mortality [Carlberg'04])	100mg SR daily; 200mg SR BID	$12; $24	
Non-dihydropyridine Calcium Channel Blockers (non-DHP CCB) ♡			✓CCBs less effective for exercise-induced ↑ HR; but may lead to an ↑ / ↔ in exercise capacity [1] diltiazem > ↓HR/sx vs verap, meto, carv (n=60)[40] ✓CCBs may be preferred in pts with chronic pulmonary dx & at risk of bronchoconstriction or if paroxysmal SVT eg. AV nodal re-entry. ✓CCBs may be better for younger pts b/c they tend to be less fatiguing than BBs ✘ Avoid in pts after MI or with HF **CI**: systolic dysfunction **HF**, SBP<90mmHg, recent MI or pulmonary edema, Sick Sinus Syndrome, 2nd/3rd degree AV block **SE**:↓BP/HR, constipation verapamil, edema dilltiazem **M**:ECG,HR **DI**:carbamazepine,cyclosporine,dabigatran,digoxin,grapefruit juice,lova/simva-statin
PL **Diltiazem** CARDIZEM Reg$_g$:30,60c mg tab, CD$_g$: 120,180,240,300mg cap TIAZAC$_g$ reg cap ,XC tab 120, 180, 240, 300, 360mg	**120-480mg daily** Max 540mg/d	$25-60	
PL **Verapamil** ISOPTIN Reg$_g$ 80, 120mg tabs, SR$_g$ 120, 180c, 240c mg tab	**120mg OD - 240mg SR BID** Max 480mg/d	$22-52	
Other ♡			✓Digoxin is less effective than BBs or CCBs[1]; digoxin does not 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 [AFFIRM]} **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)
PL **Digoxin** TOLOXIN, LANOXIN, g 0.0625c, 0.125c, 0.25c mg tab; 0.05mg/mL elixir; Injectable: 0.25mg/mL amp; 0.05mg/mL amp {AF levels trough or >8hr post-dose: **1.3**-2.6nmol/L}	MD: **0.125-0.25mg po daily** Usual Max in HF: 0.25mg po daily Optional LD:10ug/kg LBW 0.75-1.25mg PO (eg. 0.5mg IV/po x1,then 0.25mg q6h IV/po x2 doses)	$15	
Class III – Amiodarone, Dronedarone, Sotalol ♡♬			✓ 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, 2nd/3rd degree AV block, hepatitis, thyroid dysfx **SE**: **Common:** CV bradyarrhythmia, hypotension, DERM blue skin, photo-dermatitis/sensitivity→wear suncreen, 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 SJS, 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
PL **Amiodarone** CORDARONE, g 200c mg tab; 50mg/mL inj: 5, 10, 20mL vials Amiodarone IV/PO Loading Dose (LD) usually initiated in hospital/cardiologist	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	
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			
PL **Dronedarone** MULTAQ 400 mg tab ✘ ⊗ **400mg BID** For non-permanent AF only		$150	✓ 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 Dronedarone less efficacious than amiodarone with less serious SE at 1 yr **DIONYSOS** 44 **↑ mortality if decompensated HF** **ANDROMEDA** **CI**: **Severe HF** NYHA IV, 2nd/3rd 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, ↑SCr≥10% 5days after tx started, QTc interval prolonged **Serious: HF, hepatoxicity**
M: ECG baseline, & q3mo, SCr 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			
PL **Sotalol** SOTACOR g 80c, 160c 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	✓ 30-50% efficacy at 1 yr[4] ✓Sotalol prevents recurrent AF as effective as quinidine-verapamil combination[45] but less effectively than amiodarone[46] **CI**: 2nd/3rd degree AV block without pacemaker, asthma bronchial, cardiogenic shock, congenital/acquired long QT syndrome, HF severe/uncontrolled, hypokalemia, severe sinus node dysfx, sinus bradycardia <50bpm, SSS without pacemaker, **QT**>450ms **M**: ECG esp 1wk after starting, HR, CrCl **SE**: Torsades de pointes, ↓HR, dizzy, weak, see BB SE above **DI**: antiarrhythmics, drugs which ↑QT interval pg 17, see BB above
Class I – Flecainide, Propafenone ♬ : if no 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**: 2nd/3rd 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
PL **Flecainide** TAMBOCOR 50, 100c mg tablet	**50-150mg PO BID** trough=0.2-1ug/mL, toxicity≥1ug/mL Pill in the Pocket dose: 200-300mg x1	$60-85	
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			
PL **Propafenone** RYTHMOL g 150, 300c mg tablets	Initial: 150mg/d PO Usual: **150mg q8h** Max 600mg/d Pill in the Pocket dose: 450-600mg x1	$21 $45	✓Combine with BB, digoxin, non-DHP CCB i.e. AV nodal blocker ✓ 30-50% efficacy at 1 yr [10] ✓PO may be effective for "pill-in-the-pocket" **CI**: cardiogenic shock, AV/intraventricular disorders, bronchospastic disorder, electrolyte balance disorder, hepatic failure, HF severe/uncontrolled, hypotension marked, severe bradycardia <50bpm, sinoatrial, sinus node dysfunction without pacemaker **M**: ECG, HR, CBC, LFTs baseline & if symptomatic for hepatotoxicity **CAUTION: CAD or LV dysfunction** **SE**: **Common:** CV chest pain, edema, palpitations, GI altered taste, constipation, N/V, dizziness, anxiety, dypsnea, fatigue, URTI, headache **Serious: CV** angina, asystole, AF, ↓HR, BBB, HF, AV/heart block, hypotension, sinus arrest, SVT, torsades, ventricular arrhythmia, agranulocytosis, SLE
DI: **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 $=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=acetylsalicyclic acid AST=asparate aminotransferase AV=atrioventricular BB=beta blocker 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 CCB=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 antagonsists 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/T=number needed to harm/treat Non-DHP CCB=non-dihydrophyridine calcium channel blocker N/V=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=permability 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=Stevens Johnson Syndrome SLE=systemic lupus erythematosus SSS=Sick Sinus Syndrome SVT=supraventricular tachycardia 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=years

Warfarin Compared to the New Oral Anticoagulants in Atrial Fibrillation (AF) www.RxFiles.ca © Jan 2013

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 see RxFiles Q&A Does Dabigatran ↑ the Risk of MI http://www.rxfiles.ca/rxfiles/uploads/documents/Dabigatran_MI%20Risk_QandA.pdf
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 1st 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 ↑ bioavailability by 75%.

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

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WARFARIN TIPS & DOSING NOMOGRAMS

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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

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

- 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

Option 2: Warf 5mg x 2 Most commonly used

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

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

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

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]

DAY 3 INR	DAY 3 & 4 DOSE (mg)	DAY 5 INR	DAY 5, 6 & 7 DOSE (mg)
<1.3	15, 15	< 2	15, 15, 15
		2 – 3	7.5, 5, 7.5
1.3 - 1.4	10, 10	3.1 – 3. 5	0, 5, 5
		> 3.5	0, 0, 2.5
1.5 - 1.6	10, 5	< 2	7.5, 7.5, 7.5
		2 – 3	5, 5, 5
1.7 – 1.9	5, 5	3.1 – 3.5	2.5, 2.5, 2.5
		> 3.5	0, 2.5, 2.5
2 – 2.2	2.5, 2.5	< 2	5, 5, 5
		2 – 3	2.5, 5, 2.5
2.3 – 3	0, 2.5	3.1 – 3.5	0, 2.5, 0
		> 3.5	0, 0, 2.5
>3	0, 0	< 2	2.5, 2.5, 2.5
		2 – 3	2.5, 0, 2.5
		3.1 – 4	0, 2.5, 0
		> 4	0, 0, 2.5

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-/supratherapeutic 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 NOMOGRAM [9]

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

Anticoagulation in Non-valvular[22] AFib

	COUMADIN / Warfarin	PRADAXA / Dabigatran[150mg]	XARELTO / Rivaroxaban	ELIQUIS / Apixaban
Stroke/Embolism	✓[1]	✓ ✓?[2]	✓?[3]	✓ ✓?[4]
ICH	✖	✓[5]	✓[6]	✓[7]
Major GI Bleed	✓	✖[8]	✖[9]	✓[10]
Major Bleed	✓	✓[11]	✓[12]	✓✓[13]
Manage Bleed	✓[14]	✖ ✖[14]	✖?	✖?
MI	✓	✖?[15]	- ?	- ?
DC Rate /Dyspepsia	-	✖[16] /↑ GI	-	✓
Low renal fx CrCl	✓ ✓[17]	CI<30	CI<30	CI<15 **Trial CI<25**
Cost $40-110-140/mo	✓ ✓[18]	✖	✖	✖ ✖
Half life Pros/Cons[19]	Dosing frequency, impact of missed dose, bleed management			
Monitoring[20]	Need for/ability to monitor INR has pros & cons.			
Certainty vs Un-[21]	✓ ✓	+/-	+/-	+/-

Anticoagulation/AFib: Notes

Warf vs NOACS: pros & cons for each - Loren Regier - www.RxFiles.ca - Oct 2013

Note, the RE-LY trial data for Canada found warfarin had a time in therapeutic range (TTR) >70%.

1) **Stroke/Embolism**: absolute differences minimal when INR control with warfarin reasonable (TTR=>65%).
2) Stroke/Embolism: Dabi 150mg BID vs Warf; NNT=88/~2yr (no difference with 110mg BID dose, but less bleeding); open label RCT.
3) Stroke/Embolism: Riva 20mg daily vs Warf; non-inferiority trial design (ITT analysis favoured Riva but did not achieve superiority); double-blind RCT
4) Stroke/Embolism: Apix 5mg BID vs Warf; NNT=167/~2yrs; double-blind RCT. Also ↓ death NNT=132/~2yr
5) **ICH**: Dabi vs Warf; NNT=116/~2yr
6) ICH: Riva vs Warf; NNT=250/~2yr
7) ICH: Apix vs Warf; NNT=128/~2yr
8) **GI Bleed**: Dabi vs Warf; NNH=100/~2yr
9) GI Bleed: Riva vs Warf; NNH 100/~2yrs
10) GI Bleed: Apix vs Warf; no difference
11) **Major Bleed**: Dabi 150mg BID vs Warfarin; no difference; however 110mg BID had reduced major bleeding (NNT=77/~2yr) but also less benefit.
12) Major Bleed: Riva vs Warf; no difference
13) Major Bleed: Apix vs Warf; NNT=67/~2yr
14) **Manage Bleeding**: Warfarin - real world experience, & options include PCC & Vitamin K for reversal. New agents have less experience & lack antidote. However shorter half life of new agents means less time till anti-coagulation status returns to normal. Life-threatening/ fatal bleed was less in dabi / riva trials. However, **ISMP Jan 2013** found that **bleeds with Dabi 5x more fatal** than bleeds with warfarin. **Peri-procedural**: less experience & thus more problems in managing NOACs.
15) **MI Risk**: Dabi vs Warf; initial ↑ risk of borderline significance (p=0.048); reanalysis slightly different & non-significant (p=0.06 both doses). {↑rates of bleeding & thrombotic AE in AFib with mechanical valves RE-ALIGN}. Concerns. Controversial. [Warf considered protective.]
16) **Discontinuation** rates vs Warf: lower with Apix (NNT=45/~2yrs); higher with Dabi (NNH=25/~2yr); also more dyspepsia with Dabi (NNH=18/2yr).
17) All new agents lack study & experience in patients with decreased **renal fx**. Dabi & Riva contraindicated (CI) if CrCl <30ml/min. Warfarin can be used. Since AFib patients often older, impaired renal fx an issue.
18) **Economic** review found new anticoagulants more costly than warfarin even after consideration for cost of INR monitoring was built in. However, "soft" indirect costs (e.g. time/travel to the patient) not included & may be assessed individually. Direct cost/month: Warf **$35**, Dabi **$110**, Riva **$100**, Apix 5 BID **$140**.
19) **Half life** of new agents is shorter. "Cons" of this are that Dabi & Apix require BID dosing; poor compliance (missed doses) will result in earlier loss of anticoagulation status; "Pros" are earlier achieve anticoagulation after starting & return to normal after holding if over-coagulated.
20) **INR** "Con" is the inconvenience factor; but "Pro" is ability to assess anticoagulation status stroke/bleed.
21) Warfarin has **60yrs "real world" experience**; new agents have <1-2 yrs & in limited populations. This factor will change with use over the next 3-5+ yrs.
22) **Valvular AFib**: Warf OK, NOACs not indicated; Dabi CI

BEST				Problem
✓ ✓	✓	+/-	✖	✖ ✖

{This editorial synthesis based on interpretation of data from RCTs (RE-LY, ROCKET-AF, ARISTOTLE), CADTH reports, product monographs & clinical consultation. Only direct comparisons of individual NOACs with warfarin have been studied. Comparisons between NOACs have the inherent limitations of indirect comparisons. However, indirect comparisons are often required when decisions need to be made & direct comparisons are not available, nor likely to be done in the near future.}

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FDA Dec/12: Pradaxa (**dabigatran** etexilate mesylate) should **not** be used to prevent stroke or blood clots (major thromboembolic events) in patients with **mechanical heart valves**, also known as mechanical prosthetic heart valves. A clinical trial in Europe (the RE-ALIGN trial) was recently stopped because Pradaxa was more likely to experience strokes, heart attacks, and blood clots forming on the mechanical heart valves than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in the Pradaxa users than in the warfarin users.

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