**ATRIAL FIBRILLATION**

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

January 2013

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### GUIDELINES/REVIEWS
- **CADTH** 2012: [http://www.cadth.ca/media/pdf/tr0029_New-Anti](http://www.cadth.ca/media/pdf/tr0029_New-Anti)
- **ESCC** 2013 update: [http://eurheartj.oxfordjournals.org/content/early/2012/08/02/eurheartj.120.0113](http://eurheartj.oxfordjournals.org/content/early/2012/08/02/eurheartj.120.0113)
- **AHA/ASA** 2012: [http://stroke.ahajournals.org/content/early/2012/08/02/STROKEha011331826621a](http://stroke.ahajournals.org/content/early/2012/08/02/STROKEha011331826621a)
- **ACCF/AHA/HRS** 2006, 2011 update: [http://circ.ahajournals.org/content/121/11/104.full.html](http://circ.ahajournals.org/content/121/11/104.full.html)
- **CHEST** 2012: [http://chestjournal.chestpubs.org/content/141/2_suppl/e531S.full.html](http://chestjournal.chestpubs.org/content/141/2_suppl/e531S.full.html)

### RISK CALCULATORS/TOOLS
- **SPARC** [http://www.sparktool.com/](http://www.sparktool.com/)
- **CCP SPAF** [http://ccsp.ca/tools.php](http://ccsp.ca/tools.php)
- **Framingham Heart Study** [www.framinghamheartstudy.org](www.framinghamheartstudy.org)

### PATIENT RESOURCES
See On-Line Extras for list & links.

### RxFiles RELATED

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### Highlights
- Assess stroke CHADS2, CHA2DS2-VASc & bleeding HAS-BLED risk.
- If CHADS2 ≤1, consider using CHA2DS2-VASc.
- If HAS-BLED ≥3, oral anticoagulant use requires caution.
- New oral anticoagulants (NOACs) vs warfarin:
  - Disadvantages: no bleeding antibiotic, 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, CHA2DS2-VASc).
  - Calculate bleeding risk (HAS-BLED).
- Manage arrhythmia (rate vs. rhythm control).

### CHADS2 versus CHA2DS2-VASc 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.
- CHA2DS2-VASc 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. CHA2DS2-VASc).

### 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 ELIQUIOS dabigatran PRADAXA/PRADAX, & rivaroxaban XARELTO.
- OACs suggested when CHADS2 ≥1 (most benefit ≥2).
- In landmark trials, dabigatran, rivaroxaban, & apixaban were as good 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 & 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 dabigatran → warfarin
  - Stop warfarin. Start dabigatran when INR <2
- Switching FROM dabigatran → rivaroxaban
  - Stop warfarin. Start ribavoxaban when INR ≥2
- Switching FROM dabigatan → rivaroxaban
  - Stop warfarin. Start rivaroxaban when INR <2.5

### 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
- 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
- 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 ≥2 more with dronedarone permanent AF.

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 vary among the indications. Refer to the RxFiles Antithrombotic & Antithrombotic Chart, pages 10-11.
What factors favour Rate vs Rhythm control?  

<table>
<thead>
<tr>
<th>Rate-control (☐) drug choices</th>
<th>Target resting HR&lt;100bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-blocker</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>β-blocker</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>β-blocker</td>
<td>Verapamil</td>
</tr>
<tr>
<td>β-blocker</td>
<td>Digoxin*</td>
</tr>
<tr>
<td>β-blockers preferred in CAD</td>
<td>* Digoxin may be considered as monotherapy in sedentary individuals</td>
</tr>
</tbody>
</table>

Rate-control (☐) drug choices
- Dronedarine
- Flecainide
- Propafenone

β-blockers preferred in CAD
- * Digoxin may be considered as monotherapy in sedentary individuals

Non-pharmacological
- Catheter Ablation
- Electrical more effective than pharmacological esp. when AF>48hr, pre-treat with antiarrhythmic s4 wks & anticoagulant 3 wks <48hr or <8hr to rule out thrombus, post-procedure: anticoagulant warfarin or dabigatran x 4 wks.

Anticoagulation: pre-procedure 1-2mOs to TE to rule out thrombus, post-procedure x 3-6mos [then based on CHADS2; score]. Antiaarrhythmics: 6 wks-3mos post-procedure I AF recurrence. Paroxysmal best success rate.

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 s management, risk if stroke CHADS2 & bleeding has become often.
2. No significant difference between rate vs. rhythm control.
3. Consider an oral anticoagulant (OAC) when CHADS2>2. Most benefit with scores ≥2.
4. If HAS-BLED ≥3, use caution with OAC, & monitor for bleeds.
5. Advantage of new OAC (ie. 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 anticoaguants vs warfarin include no anticoagulation is no anticoagulation for major bleeds, no long-term data ≥ 2 years, limited cardiovascular outcome data & higher direct-cost.

Management of AF
1. Detect & treat precipitating causes (e.g. refer to cardiologist).
2. Manage thromboembolic risk (CHADS2, CHA2DS2-VASC, 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. CHADS2, CHA2DS2-VASC, HAS-BLED) & managed (i.e. stroke prevention, rate or rhythm control) the same as AF pts.

What is the "pill-in-the-pocket" strategy? 

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 (no chronic on therapy)
- Booster dosing: patient on low-dose chronic therapy & requires one extra dose to terminate an episode.

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 abnorms should be observed in hospital during initiation of therapy to observe for extreme PR prolongation or development of dangerous or worrisome arrhythmias.
1. Assess Thromboembolic Risk – CHADS 2, or CHADS 2VASc if CHADS 2 <1
(neither should be used for mechanical heart valves or rheumatic heart disease)

<table>
<thead>
<tr>
<th>CHADS 2 Risk Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure (symptoms in last 3 months)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA (prior)</td>
<td>2</td>
</tr>
</tbody>
</table>

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

**2012 CHADS 2: No drug therapy or ASA 75-325mg daily (Grade B2)**

- CHADS 2 Score 0: No adverse stroke risks
- CHADS 2 Score 1: No additional stroke risk factors: no antithrombotic

1.22 (1-2.4) 12% 0.68

- Female sex or vascular disease: ASA 75-325mg po daily
- Age 65-74 years or female sex & vascular disease: OAC

**2012 CHA2DS2-VASc Score 0: No antithrombotic therapy (Level Ib)**

- CHA2DS2-VASc Score 1: - No additional stroke risks to CHADS 2

- Younger women with CHA2DS2-VASc ≥2, are more likely to benefit from therapy

- CHA2DS2-VASc Score 2: - No increased stroke risk if CHADS 2 <1

- Female age ≥75 yrs, or female sex & vascular disease

- OAC 10-year risk of stroke: 2.7% (Level I)

**2012 CHA2DS2-VASc Score 3: Consider OAC (Level IA)**

- CHA2DS2-VASc Score 4: CHF + AF: CHADS2 ≥3, however a CHADS2 score of ≥2 in patients with atrial fibrillation is generally considered to indicate a high risk of stroke

- OAC 10-year risk of stroke: 4.5% (Level I)

2. Assess Bleeding Risk – HAS-BLED

<table>
<thead>
<tr>
<th>HAS-BLED Risk Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (SBP ≥160mm Hg)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal (transplantation, dialysis, SCr ≥200µmol/L) or liver function (AST/ALT &gt;3xULN, bilirubin &gt;2xULN) (1 point each)</td>
<td></td>
</tr>
<tr>
<td>Stroke (caused by a bleed)</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding (hospitalization, Hgb &gt;20g/L, transfusion)</td>
<td>1</td>
</tr>
<tr>
<td>Label INRs (therapeutic range &lt;0.8%)</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (age ≥65 yrs)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs (ASA/NSAID) or alcohol (≥2drinks/week)</td>
<td>1</td>
</tr>
</tbody>
</table>

**2012 HAS-BLED Score 0: Low bleeding risk (Level I)**

- HAS-BLED Score 1: OAC is reasonable (Level I)

- HAS-BLED Score 2: AS or OAC + clopidogrel (Grade 2B)

- HAS-BLED Score 3: AS or ASA + clopidogrel (Grade 2B)

- HAS-BLED Score 4: OAC (Level I)

**Score ≥3 has high risk for bleeding events; use caution & regular evaluation of antithrombotic therapy**

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 risk, 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. CATHD 2012: 1st line: warfarin, 2nd line: new OACs if unable to achieve adequate anticoagulation with warfarin & CHADS 2 score ≥2.
- American CHF 2012: dabigatran preferred over warfarin. ACC/AHA/HRS 2012: dabigatran is an alternative to warfarin. AHA/ASA 2012: new OACs are alternatives to warfarin.
- European ESC 2012: new OACs preferred (Level IIa,A), but note limited experience with these agents. Warfarin is effective in therapy 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 75mg daily
- with poor renal function
- at risk of dyspepsia (gastrointestinal bleeding)
- controlled on warfarin & no concerns with INR monitoring
- excluded from landmark trials, & concerned with cost

**Newer Anticoagulant Agents for Atrial Fibrillation**

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

- Dabigatran at 110mg twice daily
- Rivaroxaban at 20mg daily
- Apixaban at 5mg twice daily

**USUAL DOSE RANGE**

- Dabigatran: 110mg twice daily, 150mg single daily
- Rivaroxaban: 20mg daily
- Apixaban: 5mg b.i.d.

**Major Bleedings:** clinically overt bleeding associated with ≥1 Hgb ≥20 g/dL, clinically overt bleeding leading to transfusion of ≥2 units packed cells or whole blood, fatal, retroperitoneal, intracranial, infrarenal or intracatheter bleeding, bleeding warranting cessation or leading to respiration, included events occurring at the surgical site.

Major Bleedings: clinically overt bleeding associated with ≥1 Hgb ≥20 g/dL, clinically overt bleeding leading to transfusion of ≥2 units packed cells or whole blood, fatal, retroperitoneal, intracranial, infrarenal or intracatheter bleeding, bleeding warranting cessation or leading to respiration, included events occurring at the surgical site.

**Factors which Thrombocytopenia:** platelet count (platelets/cummum), anti-phospholipid antibodies, heparin, tissue plasminogen activator, streptokinase, streptodornase, danaparoid, vincristine, high-dose aspirin, warfarin, low-weight heparin, idarubicin, irinotecan, doxorubicin, clofazimine, dopamine, metoclopramide, cyclophosphamide, ifosfamide, mitomycin-C, methotrexate, vincristine, tamoxifen, doxorubicin, platinum, taxol, cyclophosphamide.
**PLACE IN THERAPY / CONCLUSION / Outcome Evidence / Side effect / Contraindication**

**Beta Blockers (BB)**
- Usual Dose Range: 50-150 mg PO BID
- Contraindication
  - CI: severe/poorly controlled asthma, 2/3rd degree heart block without permanent pacemaker, PR>0.24sec, symptomatic bradycardia (HR<50), SBP<85mmhg, symptomatic hypotension, decompensated HF, or if cocaine user. (Table COPD is not a CI.)
  - Other
  - B/P, HR, dizziness, fatigue-LID, insomnia, dream visual, sexual dysfunctions, PAd, cold extremity, hypoglycemia (hypocaloric, fluid deficiency, paresthesia, hypotension)
  - DR: amiodarone, CCB & digoxin synergistic; antiplatelet drugs; clopidogrel (obs), ibandronate, bisphosphonates, parathyroid or hypothalamichypophyseal
  - ECG
  - Other BBs: Nadolol PO, 50-150 mg BID; propranolol SO, 20-40 mg BID, maximum 480 mg/day.
  - Carvedilol less potent/effective for rate control vs metoprolol.

**Non-dihydropyridine Calcium Channel Blockers (non-DHP CCB)**
- Usual Dose Range: 120-480 mg PO daily
- Contraindication
  - CI: severe/poorly controlled asthma, 2/3rd degree heart block without permanent pacemaker, PR>0.24sec, symptomatic bradycardia (HR<50), SBP<85mmhg, symptomatic hypotension, decompensated HF, or if cocaine user. (Table COPD is not a CI.)
  - Other
  - B/P, HR, dizziness, fatigue-LID, insomnia, dream visual, sexual dysfunctions, PAd, cold extremity, hypoglycemia (hypocaloric, fluid deficiency, paresthesia, hypotension)
  - DR: amiodarone, CCB & digoxin synergistic; antiplatelet drugs; clopidogrel (obs), ibandronate, bisphosphonates, parathyroid or hypothalamichypophyseal
  - ECG
  - Other BBs: Nadolol PO, 50-150 mg BID; propranolol SO, 20-40 mg BID, maximum 480 mg/day.
  - Carvedilol less potent/effective for rate control vs metoprolol.

**Class III – Amiodarone, Dronedarone, Sotalol**
- Usual Dose Range: 500-1000 mg PO daily
- Contraindication
  - CI: severe left ventricular dysfunction, AV block, cardiogenic shock, conduction/congenital/acquired heart block, severe bradycardia, severe heart failure, atrial fibrillation
  - Other
  - B/P, HR, dizziness, fatigue-LID, insomnia, dream visual, sexual dysfunctions, PAd, cold extremity, hypoglycemia (hypocaloric, fluid deficiency, paresthesia, hypotension)
  - DR: amiodarone, CCB & digoxin synergistic; antiplatelet drugs; clopidogrel (obs), ibandronate, bisphosphonates, parathyroid or hypothalamichypophyseal
  - ECG
  - Other BBs: Nadolol PO, 50-150 mg BID; propranolol SO, 20-40 mg BID, maximum 480 mg/day.
  - Carvedilol less potent/effective for rate control vs metoprolol.

**Class I – Flecainide, Propafenone**
- Usual Dose Range: 50-150 mg PO BID
- Contraindication
  - CI: severe left ventricular dysfunction, AV block, cardiogenic shock, conduction/congenital/acquired heart block, severe bradycardia, severe heart failure, atrial fibrillation
  - Other
  - B/P, HR, dizziness, fatigue-LID, insomnia, dream visual, sexual dysfunctions, PAd, cold extremity, hypoglycemia (hypocaloric, fluid deficiency, paresthesia, hypotension)
  - DR: amiodarone, CCB & digoxin synergistic; antiplatelet drugs; clopidogrel (obs), ibandronate, bisphosphonates, parathyroid or hypothalamichypophyseal
  - ECG
  - Other BBs: Nadolol PO, 50-150 mg BID; propranolol SO, 20-40 mg BID, maximum 480 mg/day.
  - Carvedilol less potent/effective for rate control vs metoprolol.

**Flecainide TAMBOCOR**
- Usual Dose Range: 50-150 mg PO BID
- Contraindication
  - CI: severe left ventricular dysfunction, AV block, cardiogenic shock, conduction/congenital/acquired heart block, severe bradycardia, severe heart failure, atrial fibrillation
  - Other
  - B/P, HR, dizziness, fatigue-LID, insomnia, dream visual, sexual dysfunctions, PAd, cold extremity, hypoglycemia (hypocaloric, fluid deficiency, paresthesia, hypotension)
  - DR: amiodarone, CCB & digoxin synergistic; antiplatelet drugs; clopidogrel (obs), ibandronate, bisphosphonates, parathyroid or hypothalamichypophyseal
  - ECG
  - Other BBs: Nadolol PO, 50-150 mg BID; propranolol SO, 20-40 mg BID, maximum 480 mg/day.
  - Carvedilol less potent/effective for rate control vs metoprolol.

**Propafenone RHYTHMOL**
- Usual Dose Range: 150, 300 mg tablets
- Contraindication
  - CI: severe left ventricular dysfunction, AV block, cardiogenic shock, conduction/congenital/acquired heart block, severe bradycardia, severe heart failure, atrial fibrillation
  - Other
  - B/P, HR, dizziness, fatigue-LID, insomnia, dream visual, sexual dysfunctions, PAd, cold extremity, hypoglycemia (hypocaloric, fluid deficiency, paresthesia, hypotension)
  - DR: amiodarone, CCB & digoxin synergistic; antiplatelet drugs; clopidogrel (obs), ibandronate, bisphosphonates, parathyroid or hypothalamichypophyseal
  - ECG
  - Other BBs: Nadolol PO, 50-150 mg BID; propranolol SO, 20-40 mg BID, maximum 480 mg/day.
  - Carvedilol less potent/effective for rate control vs metoprolol.
**Warfarin Compared to the New Oral Anticoagulants in Atrial Fibrillation (AF)**

**CONSIDERATIONS**

<table>
<thead>
<tr>
<th>WARFARIN</th>
<th>NEW ORAL ANTICOAGULANTS</th>
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<tbody>
<tr>
<td><strong>EXPERIENCE</strong></td>
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<tr>
<td>Approximately 60 years.</td>
<td>Lack long-term safety &amp; efficacy data.</td>
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<tr>
<td>Challenges exist but are well understood.</td>
<td>Landmark AF trials were ~1.5-2 years. Real-world experience ≤2 years.</td>
</tr>
<tr>
<td><strong>EFFICACY</strong></td>
<td></td>
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<tr>
<td>- Only landmark trial for each new OAC versus warfarin in AF</td>
<td>- Apixaban: ELOQUIS &amp; dabigatran: PRADAX 150mg twice daily had less stroke &amp; systemic embolism versus warfarin. NNT ranged from 88 to 167/<del>2 years. Lower mortality rate with apixaban, NNT=132</del>/2 years (p=0.047).</td>
</tr>
<tr>
<td>- Depends on time spent in therapeutic range (TTR) e.g. ≥65% of INRs between 2-3.</td>
<td>- Rivaroxaban: XARELTO &amp; dabigatran 110mg twice daily were no worse than warfarin for the same endpoint.</td>
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<tr>
<td><strong>SAFETY</strong></td>
<td></td>
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<tr>
<td>- Primarily based on RCTs.</td>
<td>- Less intracranial bleeds compared to warfarin. NNT 96-250/&gt;2 years.</td>
</tr>
<tr>
<td>- Post-marketing data will provide sense of real-world safety.</td>
<td>Apixaban had least amount of bleeding. Increased risk of GI bleed with dabigatran &amp; rivaroxaban (NNH=100/year for both drugs).</td>
</tr>
<tr>
<td><strong>REVERSAL AGENT “ANTIDOTE”</strong></td>
<td></td>
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<tr>
<td>Vitamin K:</td>
<td>- Dabigatran also had more dyspepsia &amp; potential increase risk of MI see RxFiles Q&amp;A Does Dabigatran ↑ the Risk of MI <a href="http://www.rxfiles.ca/online/criteria/antithrombic_risk_of_mi_dabigatran.html">http://www.rxfiles.ca/online/criteria/antithrombic_risk_of_mi_dabigatran.html</a></td>
</tr>
<tr>
<td>- If no significant bleeding &amp; INR&gt;10: hold warfarin &amp; give vitamin K 2.5-5mg orally. Reduce weekly warfarin dose by 20% &amp; resume once INR in therapeutic range.</td>
<td>Apixaban &amp; Rivaroxaban: protrombin complex concentrate (PCC) OCTAPLEX, BERIPLEX, recombinant Factor VIIIa, &amp; activated charcoal if ≤2-3 hours of administration.</td>
</tr>
<tr>
<td><strong>FINANCIAL</strong></td>
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<td></td>
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<tr>
<td><strong>MONITORING</strong></td>
<td></td>
</tr>
<tr>
<td>Routine &amp; frequent INR tests.</td>
<td>Serum creatinine and calculated creatinine clearance – every 6-12 months.</td>
</tr>
<tr>
<td>Frequency can be extended to every one-three months once dose stabilized. Can provide reassurance of drug efficacy &amp; safety (i.e. within target range).</td>
<td>[Lack of test for anticoagulation status results in assumptions regarding suitability of empiric dosing for broad populations groups.]</td>
</tr>
<tr>
<td><strong>PHARMACOKINETICS</strong></td>
<td></td>
</tr>
<tr>
<td>Longer t½ (2.5 days)</td>
<td>Shorter t½ (8-17 hours)</td>
</tr>
<tr>
<td>Benefit: therapeutic levels &amp; some sustained protection despite a few missed doses.</td>
<td>Benefit: shorter t½ allows drug to be cleared quicker, but t½ extended with renal impairment.</td>
</tr>
<tr>
<td></td>
<td>Concern: non-compliant patients will lose significant anticoagulation status more quickly with new OAC than with warfarin after missing a dose.</td>
</tr>
<tr>
<td><strong>DRUG INTERACTIONS</strong></td>
<td></td>
</tr>
<tr>
<td>Numerous drug interactions.</td>
<td>Few known drug interactions, but lacking experience to determine clinical significance of these. No way to adjust dose secondary to drug interaction.</td>
</tr>
<tr>
<td>INR monitoring &amp; dosage adjustments; however, useful to accommodate concomitant acute &amp; chronic therapy.</td>
<td>Strong inhibitors of both CYP 3A4 &amp; P-glycoprotein are contraindicated with all three new agents (e.g. azoles, ritonavir).</td>
</tr>
<tr>
<td>Well documented DI:</td>
<td>Caution with CYP 3A4 &amp; P-glycoprotein inducers (e.g. rifampin, phenytoin carbamazepine, St. John’s Wort) &amp; inhibitors (e.g. verapamil, amiodarone, dronedarone, quinidine).</td>
</tr>
<tr>
<td>- antplatelets, NSAIDs, amiodarone, antibiotics (cotrimoxazole, ciprofloxacin).</td>
<td></td>
</tr>
<tr>
<td><strong>FOOD INTERACTIONS</strong></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>Apixaban &amp; dabigatran: none</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban: avoid grapefruit (how much?)</td>
</tr>
<tr>
<td><strong>DOSAGE REGIMEN</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose and frequency depends on the indication. Empiric versus tailored dosing. Stroke prevention regimens are as follows:</td>
</tr>
<tr>
<td></td>
<td>- Apixaban 5mg twice daily, or</td>
</tr>
<tr>
<td></td>
<td>- 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.</td>
</tr>
<tr>
<td></td>
<td>- Dabigatran 150mg twice daily, or</td>
</tr>
<tr>
<td></td>
<td>- 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)</td>
</tr>
<tr>
<td></td>
<td>- Rivaroxaban 20mg once daily with food. (Same question as to whether twice daily might be more optimal given t½.)</td>
</tr>
<tr>
<td><strong>RENAL IMPAIRMENT</strong></td>
<td></td>
</tr>
<tr>
<td>(CrCl &lt;30mL/min)</td>
<td>All require dose reduction or should be avoided with renal impairment (e.g. CrCl &lt;30mL/min). Patients with renal impairment were excluded from trials.</td>
</tr>
<tr>
<td>- No dose adjustment required.</td>
<td>Apixaban: excluded patients with CrCl &lt;25mL/min. Reduce dose to 2.5mg twice daily in patients with two of the following: age ≥80, weight ≤60kg, Scr ≥133umol/L (CrCl &lt;25mL/min). [Official: avoid ≤15mL/min]</td>
</tr>
<tr>
<td>- INR monitoring allows for individual tailoring of dose to patient.</td>
<td>Dabigatran: excluded patients with CrCl &lt;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&lt;30mL/min)</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban: excluded patients with CrCl &lt;30mL/min. Reduce dose to 15mg daily if CrCl 30-49mL/min.</td>
</tr>
<tr>
<td><strong>COST/MONTH</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“$40 (includes INR monitoring cost)</td>
</tr>
<tr>
<td></td>
<td>Warfarin remains a more cost effective 1st line option than the new OAC even after considering the cost of INR monitoring.</td>
</tr>
<tr>
<td></td>
<td>Apixaban $140</td>
</tr>
<tr>
<td></td>
<td>Dabigatran $110</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban $100</td>
</tr>
<tr>
<td></td>
<td>May not be covered by provincial or hospital formularies. Agents on formulary have criteria patient must meet (e.g. failed warfarin, CHADS2&gt;2).</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant Management Clinics may be available. Increases: monitoring efficiency, time in therapeutic range absolute ↑ ~8%. Dosing nomograms are available.</td>
<td>Apixaban: approved by Health Canada for stroke prevention in AF in Dec ’12.</td>
</tr>
<tr>
<td></td>
<td>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%.</td>
</tr>
</tbody>
</table>

AF=atrial fibrillation CrCl=creatinine clearance DI=drug interaction GI=gastrointestinal INR=International normalized ratio MI=myocardial infarction NNT=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/38/8/850.full.pdf?sid=65b5856d-5f6f-4e22-9311-9167c95e95

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WARFARIN TIPS & DOSING NOMOGRAMS

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 PEALS
• Use a validated nomogram for initiating & maintaining warfarin. Nomograms have been shown to ↑ time in therapeutic range (TRR) 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, 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 5–12 ± 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 disposing 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 1.5–2.5 or give either 3mg or 6mg).
  2) Warfarin 5mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs

<table>
<thead>
<tr>
<th>TABLE 1: INITIATING WARFARIN - EXAMPLE OF A VALIDATED NOMOGRAM FOR 5mg DAY 1 &amp; DAY 2 (INR 2-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 3</strong></td>
</tr>
<tr>
<td>INR</td>
</tr>
<tr>
<td>&lt;1.5</td>
</tr>
<tr>
<td>1.5–1.9</td>
</tr>
<tr>
<td>2–3</td>
</tr>
<tr>
<td>&gt;3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>TABLE 2: INITIATING WARFARIN - VALIDATED NOMOGRAM FOR 10mg DAY 1 &amp; DAY 2 (INR 2-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 3 INR</strong></td>
</tr>
<tr>
<td>&lt;1.3</td>
</tr>
<tr>
<td>1.3–1.4</td>
</tr>
<tr>
<td>1.5–1.6</td>
</tr>
<tr>
<td>1.7–1.9</td>
</tr>
<tr>
<td>&gt;2</td>
</tr>
<tr>
<td>&gt;3</td>
</tr>
</tbody>
</table>

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 3

<table>
<thead>
<tr>
<th>TABLE 3: MAINTENANCE OF WARFARIN – EXAMPLE VALIDATED NOMOGRAM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TARGET INR 2–3</strong></td>
</tr>
<tr>
<td>&lt;1.5</td>
</tr>
<tr>
<td>1.5–1.9</td>
</tr>
<tr>
<td>2–3</td>
</tr>
<tr>
<td>3.1–3.5</td>
</tr>
<tr>
<td>3.6–4.9</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>9</td>
</tr>
</tbody>
</table>

FREQUENCY OF INR MONITORING
• Initiating warfarin: week 1: Day 3 & 5, week 2: 2 INRs, then weekly INRs until stable x 2 wks, then q2wks until stable x 1 month, then monthly INRs. If stable x 3 months → INR up to q12 weeks. 3,4
• 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 T1/2 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), gastrointestinal, 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).

Managing Warfarin Drug Interactions see RxFiles Antiplatelet & Antithrombotic & Herbs 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, antplatelets. Balance the risk of bleeding/clotting with the benefit of therapy.


Z Dumont BSP, L Kosar MSc www.RxFiles.ca © Jan 2013
**Anticoagulation in Non-valvular AFib**

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/Embolism</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>ICH</td>
<td>x</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Major GI Bleed</td>
<td></td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Major Bleed</td>
<td></td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Manage Bleed</td>
<td>14</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>DC Rate</td>
<td>/Dyspepsia</td>
<td>-</td>
<td>x 16</td>
</tr>
<tr>
<td>Low renal fx</td>
<td>CI&lt;30</td>
<td>CI&lt;30</td>
<td>CI&lt;15</td>
</tr>
<tr>
<td>Cost</td>
<td>$40</td>
<td>$110</td>
<td>$140/mo</td>
</tr>
<tr>
<td>Half life</td>
<td>Pros/Cons</td>
<td>Dosing frequency, impact of missed dose, bleed management</td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>Need for/ability to monitor INR has pros &amp; cons.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certainty vs Un</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

**Anticoagulation/Afib: Notes**

- **Stroke/Embolism**: absolute differences minimal when INR control with warfarin reasonable.
- **ICH**: Dabigatran 150mg BID vs Warf; NNT=68/-2yr (no difference with 110mg BID dose, but less bleeding), open label RCT.
- **Major GI Bleed**: Dabigatran 150mg BID vs Warf; NNT=167/2yr; double-blind RCT. Apix 50mg BID vs Warf; NNT=132/-2yr.
- **MI Risk**: Dabi vs Warf; initial risk of borderline significance (p=0.0488); reanalysis slightly different & non-significant (p=0.06 with doses); (Rates of bleeding & thrombotic AE in Afib with mechanical valves & Warf concerns. Controversial: Warf considered protective.)
- **Discontinuation**: rates vs Warf; lower with Apix (NNH=45/-2yr); higher with Dabi (NNH=25/-2yr); also more dyspepsia with Dabi (NNH=18/-2yr).
- **Economic**: new agents lack study & experience in patients with increased renal fx; less experience & thus more problems in real world experience, & options include POC & vitamin K for reversal. New agents have less experience & lack antidote. However, shorter half-life, less time till anticoagulation status returns to normal. Life-threatening/fatal bleed was less in dabi, riva costs. However, 10Y Jan 2013 to use trial bleed trials with Dabi vs Warf, no difference.
- **Major Bleed**: Dabigatran 150mg BID vs Warf; no difference; however, 110mg BID had reduced major bleeding (NNT=77/-2yr) but also less benefit.
- **GI Bleed**: Dabigatran 150mg BID vs Warf; NNT=90/-2yr.
- **GI Bleed**: Riva vs Warf; NNT=104/-2yr.
- **GI Bleed**: Apix vs Warf; no difference.
- **ICH**: Dabigatran 150mg BID vs Warf; NNT=116/-2yr; double-blind RCT. Apix 50mg vs Warf; NNT=128/-2yr.
- **ICH**: Dabigatran 150mg BID vs Warf; NNT=250/-2yr.
- **GI Bleed**: Riva vs Warf; NNT=116/-2yr.
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### Best
- **Pradaxa**
- **Xarelto**
- **Apixaban**

### +/-
- **Coumadin**

### Problem
- **Warfarin**

---

(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 have been made. 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.)
REFERENCES FOR WARFARIN TIPS & DOSING NOMOGRAMS


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References: RxFiles Atrial Fibrillation

Additional references:
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Char I, Setti I, Ziegler P, et al. Dronedarone doubles their risk for cardiovascular death, stroke, and heart failure, the agency announced after reviewing data from the PALLAS trial. 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. Fragaris N, Koskinas K, Katsritis DG, et al. Comparison of Effectiveness of Ranolazine Plus Amiodarone Versus Amiodarone Alone for Conversion of Recent-Onset...


Health Canada Mar 12 The Pradaxa (dabigatran etexilate) product package has been updated to include in elderly to assess renal function initially & at least once a year. Use of Pradaxa in patients with hemodynamically significant raficulair valvular heart disease, especially mitral stenosis, or in pacients with prothethic heart valves is not recommended. Heist EK, Mansour M, Raskin JN. Rate control in atrial fibrilation: targets, methods, resynchronization considerations. Circulation. 2011 Dec;124(24):2746-55.


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