CCS Focused Update on Atrial Fibrillation New Guidelines for 2016

Canadian Society of Internal Medicine
October 28 2016, Montreal

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Mario Talajic MD: **CCS Focused Update on Atrial Fibrillation New Guidelines for 2016**

Oct 28 2016
Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Implementing GRADE and Achieving Consensus

Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control

2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation
Verma et al. Canadian Journal of Cardiology 2014;30:1114-30

The 2014 Atrial Fibrillation Guidelines Companion: A Practical Approach to the Use of the Canadian Cardiovascular Society Guidelines
Macle et al. Canadian Journal of Cardiology 2015;31:1207-18

2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation
Overview of AF Management

**Detection and Treatment of Precipitating Causes**

- AF Detected
  - Assessment of Thromboembolic Risk (CHADS$_2$)
    - Appropriate Antithrombotic Therapy
  - Management of Arrhythmia
    - Rate Control
    - Rhythm Control

Detection and Treatment of Precipitating Causes
# Atrial Fibrillation

## Etiology/ ‘Reversible’/Actionable Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Obesity</td>
</tr>
<tr>
<td>Structural Cardiac Disease</td>
<td>WPW/SVT</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td>Unnecessary ventricular pacing</td>
</tr>
<tr>
<td>Post Cardiac Surgery</td>
<td>Vagally mediated (over-training)</td>
</tr>
<tr>
<td>Familial/Genetic</td>
<td>Alcohol</td>
</tr>
</tbody>
</table>
HR 1.67 CI (1.49-1.87)

Chamberlain et al, ARIC Study, AHJ 2010
Patients with BMI ≥ 27 (N=825)

Met Exclusion Criteria (N=293)
- Terminal Cancer (N=10)
- Inflammatory Dx (N=20)
- Permanent AF (N=84)
- AV Node ablation (N=12)
- AF ablation (N=90)
- Severe Medical Illness (N=77)

Patients from other States (N=177)

Final Cohort (N=355)

Assessed for Eligibility (N=1415)

Weight Management

≥10%WL (N=135)

3-9%WL (N=103)

<3%WL or WG (N=117)

Pathak et al. JACC 2015
## Impact on Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>&lt;3% Wt Loss Group 3 N=117</th>
<th>3-9% Wt Loss Group 2 N=103</th>
<th>&gt;10% Wt Loss Group 1 N=135</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow Up</td>
<td>Baseline</td>
<td>Follow Up</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>146±17</td>
<td>139±15</td>
<td>144±17</td>
<td>134±14</td>
</tr>
<tr>
<td><strong>Anti-HTN, n</strong></td>
<td>0.8±1.0</td>
<td>1.0±0.7</td>
<td>0.7±0.8</td>
<td>0.7±0.6</td>
</tr>
<tr>
<td><strong>DM with HbA1c≥7, n (%)</strong></td>
<td>34 (29)</td>
<td>23 (20)</td>
<td>28 (27)</td>
<td>15 (15)</td>
</tr>
<tr>
<td><strong>Fasting Insulin (mU/L)</strong></td>
<td>14.5±6.9</td>
<td>17.3±9.6</td>
<td>16.9±6.1</td>
<td>14.8±9.4</td>
</tr>
<tr>
<td><strong>LDL Level (mg/dL)</strong></td>
<td>104±35</td>
<td>108±31</td>
<td>116±35</td>
<td>93±23</td>
</tr>
<tr>
<td><strong>TG Level (mg/dL)</strong></td>
<td>141±62</td>
<td>159±62</td>
<td>141±53</td>
<td>115±53</td>
</tr>
<tr>
<td><strong>Lipid Rx n (%)</strong></td>
<td>56 (48)</td>
<td>54 (46)</td>
<td>45 (44)</td>
<td>38 (37)</td>
</tr>
</tbody>
</table>

*Pathak et al. JACC 2015*
Structural Remodeling

LA Volume (Indexed)

*Group-Time P<0.001

hsCRP Level

*Group-Time P<0.001

Pathak et al. JACC 2015
AF Freedom: Drug & Ablation-Free

**Without AAD or ablation**

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>365</th>
<th>730</th>
<th>1095</th>
<th>1460</th>
<th>1825</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%WL</td>
<td>135</td>
<td>101</td>
<td>72</td>
<td>42</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>3-9% WL</td>
<td>103</td>
<td>62</td>
<td>36</td>
<td>22</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>&lt;3% WL</td>
<td>117</td>
<td>66</td>
<td>44</td>
<td>22</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>

Group

- WL > 10%
- WL > 3-9%
- WL <3% or Gain

Follow up (days)

- P<0.001

46% without AAD or ablation
Total Arrhythmia-Free Survival

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>365</th>
<th>730</th>
<th>1095</th>
<th>1460</th>
<th>1825</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%WL</td>
<td>135</td>
<td>130</td>
<td>114</td>
<td>86</td>
<td>67</td>
<td>36</td>
</tr>
<tr>
<td>3-9% WL</td>
<td>103</td>
<td>93</td>
<td>83</td>
<td>57</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>&lt;3% WL</td>
<td>117</td>
<td>105</td>
<td>85</td>
<td>53</td>
<td>32</td>
<td>22</td>
</tr>
</tbody>
</table>

With AAD and/or ablation

P < 0.001
Overview of AF Management

- Detection and Treatment of Precipitating Causes
  - AF Detected
  - Management of Arrhythmia
    - Rate Control
    - Rhythm Control
  - Assessment of Thromboembolic Risk (CHADS$_2$)
    - Appropriate Antithrombotic Therapy
Rate or Rhythm Control?

• How do you decide if you are going to pursue rate or rhythm control for a patient with AF?
• No right or wrong answer
• Often, the two are simultaneous:
  – Rhythm control requires good rate control when patient goes back into AF
• Need to continuously re-evaluate the strategy as the AF progresses
  – What may have been a good initial strategy may no longer be warranted

Skanes AC, Healey JS et al., Can J Cardiol 2012 Mar;28(2): 125-136
### Factors Influencing Decision of Rate vs Rhythm Control

<table>
<thead>
<tr>
<th>Favours Rate Control</th>
<th>Favours Rhythm Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent AF</td>
<td>Paroxysmal AF</td>
</tr>
<tr>
<td>Less Symptomatic</td>
<td>More Symptomatic</td>
</tr>
<tr>
<td>&gt; 65 years of age</td>
<td>&lt; 65 years of age</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No Hypertension</td>
</tr>
<tr>
<td>No History of Congestive Heart Failure</td>
<td>Congestive Heart Failure clearly exacerbated by AF</td>
</tr>
<tr>
<td>Previous Antiarrhythmic Drug Failure</td>
<td>No Previous Antiarrhythmic Drug Failure</td>
</tr>
</tbody>
</table>

Rate vs Rhythm Trials
No mortality advantages of sinus rhythm

AFFIRM

AF-CHF

Rate vs Rhythm Decision

- Is AF (despite controlled rate) causing symptoms?
- What is the likelihood of maintaining sinus rhythm?
New Rate/Rhythm Algorithm

Algorithm for Rate vs Rhythm Control for Patients With Symptomatic AF

SYMPTOMATIC AF

Special circumstances in which to consider early rhythm control:
- Highly symptomatic
- Multiple recurrences
- Extreme impairment in QOL
- Arrhythmia-induced cardiomyopathy

ATTEMPT RATE CONTROL:
- β-blocker
- Calcium channel blocker

SYMPTOMS RESOLVE

NO

CONTINUE RATE CONTROL

YES

MODIFY RATE CONTROL CONSIDER RHYTHM CONTROL

Paroxysmal AF
- Low burden recurrence
  - Pill in pocket antiarrhythmic therapy
- High burden recurrence
  - Maintenance anti-arrhythmic therapy
  - Catheter ablation

Persistent AF
- Consider cardioversion
  - Symptoms improve, but AF recurs
  - Symptoms improve, and patient maintains sinus rhythm
  - Symptoms do not change in sinus rhythm and AF recurs

Atrial Fibrillation Guidelines
Overview of Rate Management

Rate Control Drug Choices

Heart Failure

- β-blocker
- ± Digoxin

CAD

- β-blocker*
- CCB#
- Combination Rx

No Heart Failure
or CAD

- β-blocker*
- CCB#
- Digoxin†
- Combination Rx

*β-blockers preferred in CAD
# Non-dihydropyridine calcium channel blockers (diltiazem, verapamil)
†Digoxin may be considered as monotherapy only in particularly sedentary individuals

Drugs are listed in alphabetical order

Skanes AC, Healey JS et al., Can J Cardiol 2012 Mar;28(2): 125-136

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Atrial Fibrillation Guidelines

Overview of Rhythm Management

Rhythm Control Choices
Normal Systolic Function
No Hx of CHF

- Dronedarone+
- Flecainide*
- Propafenone*
- Sotalol#

Catheter Ablation
Amiodarone

Rhythm Control Choices
Hx of CHF or Left Ventricular Systolic Dysfunction

- EF > 35%
- EF ≤ 35%

- Amiodarone
- Sotalol**

Catheter Ablation
Amiodarone

Drugs are listed in alphabetical order

+ Dronedarone should be used with caution in combination with digoxin
  - Class I agents should be AVOIDED in CAD and should be COMBINED with AV-nodal blocking agents
  - Sotalol should be used with caution in those at risk for torsades de pointes VT (e.g. female, age > 65 yr, taking diuretics)

** Sotalol should be used with caution with EF 35-40% and those at risk for torsades de pointes VT (e.g. female, age > 65 yr, taking diuretics)
### Managing Rhythm Control - Recommended Drugs

<table>
<thead>
<tr>
<th>Drug/Dose</th>
<th>Efficacy</th>
<th>Toxicity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide 50-150 mg BID</td>
<td>30-50%</td>
<td>Ventricular tachycardia, Bradycardia, Rapid ventricular response to AF or atrial flutter (1:1 conduction)</td>
<td>Contraindicated in patients with CAD or LV dysfunction, Should be combined with an AV nodal blocking agent</td>
</tr>
<tr>
<td>Propafenone 150-300 mg TID</td>
<td>30-50%</td>
<td>Ventricular tachycardia, Bradycardia, Rapid ventricular response to AF or atrial flutter (1:1 conduction), Abnormal taste</td>
<td>Contraindicated in patients with CAD or LV dysfunction, Should be combined with an AV nodal blocking agent</td>
</tr>
<tr>
<td>Amiodarone 100-200 mg OD (after 10g loading)</td>
<td>60-70%</td>
<td>Photosensitivity, Bradycardia, GI upset, Thyroid dysfunction, Hepatic toxicity, Neuropathy, Tremor, Pulmonary toxicity, Torsades de pointes (rare)</td>
<td>Low risk of proarrhythmia, Limited by systemic side effects, Most side effects are dose &amp; duration related</td>
</tr>
<tr>
<td>Dronedarone 400 mg BID</td>
<td>40%</td>
<td>GI upset, Bradycardia, Hepatic toxicity</td>
<td>Should not be used for rate control or for rhythm control in patients with a history of CHF or LV EF &lt; 40%, Should be used with caution when added to digoxin, Liver enzyme monitoring required, New agent – limited experience outside clinical trials</td>
</tr>
<tr>
<td>Sotalol 80-160 mg BID</td>
<td>30-50%</td>
<td>Torsades de pointes, Bradycardia, Beta-blocker side effects</td>
<td>Should be avoided in patients at high risk of torsades de pointes VT – especially women &gt;65 years taking diuretics or those with renal insufficiency, QT interval should be monitored 1 week after starting, Use cautiously when EF&lt;40%</td>
</tr>
</tbody>
</table>
Rhythm Control Does Not Replace Anticoagulation

- *No* evidence that AF reduction via antiarrhythmic therapy reduces the risk of stroke/thromboembolism
- *Patients* *must* continue on appropriate anticoagulation according to their individual embolic risk (CHADS$_2$ score)
Tachycardia in Right Veins

ECG Lead II

Right Veins

CS
AF Ablation lesion set

Posterior Left Atrium

LSPV

RSPV

LIPV

RIPV
Tachycardia in Right Veins: Behind Fence

PV Tachycardia

PV Isolation
Why do patients need a repeat procedure?
Contact Force / Cryoablation

Technological Advances
Improved outcomes
Improved sustainability
Improved safety
Atrial Fibrillation Guidelines

Systematic Review of RCTs of Ablation vs Rx

- 9 RCTs / 3 systematic reviews in 1274 patients who have failed ≥ 1 drug
- uniformly demonstrate large differences in recurrence of AF
- (OR 9.74 95% CI, 3.98 to 23.87) in favour of ablation vs AAD

# Worldwide AF Ablation (’03-’06)

<table>
<thead>
<tr>
<th>Type of Complication</th>
<th>No of Pts</th>
<th>Rate%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral pseudoaneurysm</td>
<td>152</td>
<td>0.93</td>
</tr>
<tr>
<td>AV fistulae</td>
<td>88</td>
<td>0.54</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>15</td>
<td>0.09</td>
</tr>
<tr>
<td>Valve damage/requiring surgery</td>
<td>11/7</td>
<td>0.07</td>
</tr>
<tr>
<td>Tamponade</td>
<td>213</td>
<td>1.31</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>115</td>
<td>0.71</td>
</tr>
<tr>
<td>PV stenosis requiring intervention</td>
<td>48</td>
<td>0.29</td>
</tr>
<tr>
<td>Stroke</td>
<td>37</td>
<td>0.23</td>
</tr>
<tr>
<td>Permanent diaphragmatic paralysis</td>
<td>28</td>
<td>0.17</td>
</tr>
<tr>
<td>Death</td>
<td>25</td>
<td>0.15</td>
</tr>
<tr>
<td>Atrium-esophageal fistulae</td>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>741</strong></td>
<td><strong>4.54%</strong></td>
</tr>
</tbody>
</table>

Recommendations

• We recommend catheter ablation of AF in patients who remain symptomatic following adequate trials of anti-arrhythmic drug therapy and in whom a rhythm control strategy remains desired.
  (Strong Recommendation, Moderate Quality Evidence)

• We suggest catheter ablation to maintain sinus rhythm as first-line therapy for relief of symptoms in highly selected patients with symptomatic, paroxysmal AF.
  (Conditional Recommendation, Low Quality Evidence)

Values and Preferences:
These recommendations recognize that the balance of risk with ablation and benefit in symptom relief and improvement in quality of life must be individualized. They also recognize that patients may have relative or absolute cardiac or non-cardiac contra-indications to specific medications.
Ablation par cathéter de FA: Conseils pratiques

Profil typique d’un patient référé pour envisager la possibilité d’une ablation:

- Age < 80
- Patients avec FA symptomatique
- Échec ou intolérance au traitement antiarythmique
- FA paroxystique ou persistante avec des épisodes de courte durée
- Cardiopathie minime à modérée

L’ablation de FA ne doit pas être considérée comme une alternative à l’anticoagulation orale
Overview of AF Management

AF Detected

Assessment of Thromboembolic Risk (CHADS₂)

Management of Arrhythmia

- Rate Control
- Rhythm Control

Detection and Treatment of Precipitating Causes

Appropriate Antithrombotic Therapy
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td><strong>Maximum Score</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

Stroke rate/100 patient yr

CHADS\textsubscript{2}
Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with AF: a nationwide cohort study

Danish observational cohort; 73 538 non-valvular AF patients not anticoagulated
A NOAC is preferred over warfarin for non-valvular AF.
Stroke or systemic embolic events in large NOAC trials, vs warfarin

RR (95%CI)  p

RE-LY  Dabi 150 mg
0.66 (0.53–0.82) 0.0001

ROCKET AF  Rivaroxaban
0.88 (0.75–1.03) 0.12

ARISTOTLE  Apixaban
0.80 (0.67–0.95) 0.012

ENGAGE AF–TIMI 48  Edox 60 mg
0.88 (0.75–1.02) 0.10

Combined (random)
0.81 (0.73–0.91) <0.0001

Favours NOAC
Favours warfarin

Ruff et al., The Lancet, 2013
Secondary efficacy and safety outcomes in large NOAC trials, vs. warfarin

**Efficacy**
- Ischaemic stroke: RR (0.83–1.02) p 0.10
- Haemorrhagic stroke: RR (0.38–0.64) p <0.0001
- Myocardial infarction: RR (0.78–1.20) p 0.77
- All-cause mortality: RR (0.85–0.95) p 0.0003

**Safety**
- Intracranial haemorrhage: RR (0.39–0.59) p <0.0001
- Gastrointestinal bleeding: RR (1.01–1.55) p 0.043

Ruff et al., The Lancet, 2013
Major bleeding events in large NOAC trials, vs warfarin

RE-LY 150 mg
ROCKET AF
ARISTOTLE
ENGAGE AF –TIMI 48 60 mg
Combined (random)

RR (95% CI) p
0.94 (0.82–1.07) 0.34
1.03 (0.90–1.18) 0.72
0.71 (0.61–0.81) <0.0001
0.80 (0.71–0.90) 0.0002
0.86 (0.73–1.00) 0.06

Favours NOAC
Favours warfarin

Ruff et al., The Lancet, 2013
NOAC preferred over Warfarin because of:

A. Convenience and ease of use for patients and physicians

B. All NOACs are at least as effective and as safe as Warfarin
   -some have greater efficacy for stroke/systemic embolus and mortality
   -some have greater safety for major bleeding

Warfarin indicated over NOAC for patients with:
   Mechanical prosthetic valves
   Rheumatic MS
   Severe renal dysfunction
Independent FDA analysis confirmed the positive safety and efficacy of dabigatran in clinical practice

Medicare\(^1\) >134,000 patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Warfarin</th>
<th>D150 &amp; D75 BID combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.86</td>
<td>1.28</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>0.92</td>
<td>0.80</td>
</tr>
<tr>
<td>Acute MI</td>
<td>0.80</td>
<td>0.34</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>0.92</td>
<td>0.80</td>
</tr>
</tbody>
</table>

RE-LY\(^2–4\) >18,000 patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Warfarin</th>
<th>D110 BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.91</td>
<td>1.07</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>1.29</td>
<td>1.13</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td>0.30</td>
</tr>
</tbody>
</table>

In the USA, the licensed doses for dabigatran etexilate are 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF.

Numbers on bars denote hazard ratios vs warfarin; MI = myocardial infarction


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Comparison of Main Outcomes: XANTUS versus ROCKET AF

<table>
<thead>
<tr>
<th></th>
<th>ROCKET AF</th>
<th>XANTUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2</td>
<td>3.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Prior stroke*</td>
<td>55%</td>
<td>19%</td>
</tr>
</tbody>
</table>

*Includes prior stroke, SE or TIA

Camm et al. Eur Heart J. 2015
NOAC Antidotes

• Currently available for clinical use
  – Idarucizumab (Praxbind®)
    • Dabigatran-specific reversal agent

• Not available yet for clinical use
  – Andexanet Alpha
    • Factor Xa reversal agent (e.g. apixaban, rivaroxaban, edoxaban)
  – Ciraparantag (PER-977, aripazine)
    • “universal” reversal agent
**RE-VERSE AD™: Multicenter, ongoing, open-label, single-arm phase III study**

**Group A:** Uncontrolled bleeding + dabigatran-treated  
N=51  

**Group B:** Emergency surgery or procedure + dabigatran-treated  
N=39

- 5 g idarucizumab (two separate infusions of 2.5 g)
- 0–15 minutes
- 0–24 hours
- 90 days follow-up

**Primary Endpoint:** Maximum percent reversal based on dTT or ECT  
**Secondary Endpoint:** Proportion with complete normalization of dTT or ECT within 4h

Pollack C et al. Thromb Haemost. 2015 May 28;114 [Epub ahead of print]
RESULTS: Primary endpoint in Group A

Maximum percent reversal 100% dTT (N=40), 100% ECT (N=47)
Complete normalization: dTT: 98%, ECT: 89%
Maximum percent reversal 100% dTT (N=28), 100% ECT (N=34)
Complete normalization: dTT: 93%, ECT: 88%
Safety

• No hypersensitivity observed

• Five thrombotic events occurred
  – 1 early event (DVT + PE) within 72 hours
  – 4 patients had events after 72 hours (DVT, DVT+PE+LA thrombus, MI, ischemic stroke)
    – None of these 5 patients was receiving any antithrombotic therapy when the events occurred

• 18 deaths occurred (9 in each Group)
  – Related to presenting index event and comorbidities
Recommendation

- We recommend administering idarucizimab for emergency reversal of dabigatran's anticoagulant effect in patients with uncontrollable or potentially life-threatening bleeding and/or requiring urgent surgery for which normal hemostasis is necessary
  (Strong Recommendation, Moderate Quality Evidence).

Periprocedural Management of Anticoagulation

OAC Interruption

- Yes
  - When to Stop
  - Bridge or Not
- No
  - When to Restart
Decision to Interrupt Anticoagulation for a Procedure

Bleeding risks of:
1. Procedure
   (High, intermediate, low)
2. Patient
   (HASBLED Score)

Thromboembolic Risks:
1. CHADS2
2. Mechanical valve
3. Thromboembolism <3 m
4. Rheumatic valve disease
Low Risk of Bleeding
Interruption Not Necessary

- Dental extractions (1 or 2 teeth), cleaning, and most dental procedures (including root canal)
- Skin biopsy or skin cancer removal
- Cataract surgery
- Dermatologic procedures (e.g. biopsy)
- Gastroscopy or colonoscopy without biopsy
- Selective invasive procedures: paracentesis, thoracentesis, arthrocentesis
- Coronary angiography
- Cardiac device implantation (pacemaker, ICD)

Practical Tip: http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm
Intermediate Risk of Bleeding

Interruption Necessary

- Certain intraabdominal surgery (including laparoscopic cholecystectomy, and laparoscopic inguinal hernia repair)
- Certain intrathoracic surgery (including breast surgery)
- Bone marrow aspirate and biopsy
- Lymph node biopsy
- Other orthopedic surgery
- Other vascular surgery
High Risk of Bleeding
Interruption Necessary

- Neurosurgery (Intracranial or surgery)
- Neuroaxial procedure (Spinal or epidural anesthesia)
- Cardiac surgery (CABG or heart valve replacement)
- Major vascular surgery (Aortic aneurysm repair, aortofemoral bypass)
- Major urologic surgery (prostatectomy, bladder tumour resection)
- Major lower limb orthopedic surgery (hip/knee joint replacement)
- Lung resection surgery
- Extensive cancer surgery (pancreas, liver resection)
- Intestinal anastomosis surgery
- Selected biopsy procedures (kidney, prostate, and cervical cone)
- Reconstructive plastic surgery
- Pericardiocentesis
- Colonic polypectomy or biopsy
Timing of Antithrombotic Interruption

**Aspirin, Clopidogrel, Prasugrel, Ticagrelor**
Stop 5-7 days before
Very high bleed risk: stop 7-10 days before

**Warfarin**
Stop 5 days before
INR<1.5 for low bleed risk
INR<1.2 for intermediate/high bleed risk

**Apixaban, Rivaroxaban**
Low bleed risk: stop 1-2 days before
Intermediate/high bleed risk: 2-3 days before

**Dabigatran**
CrCl≥80mL/min: stop 1-2 days before for low bleed risk and 2-3 days for intermediate/high bleed risk
CrCl 50-80 mL/min: upper end of ranges above
CrCL 30-50 mL/min: add 1 day
CrCL<30 mL/min, add 2 days
The Bridge Trial: Is Bridging Anticoagulation Necessary for AF Patients?

**Inclusion:**
- Age ≥18 yrs
- Chronic AF or flutter
- CHADS2≥1

**Exclusion:**
- Mechanical heart valve
- TIA, stroke, systemic embolism <12 weeks
- Major bleeding within the prior 6 weeks
- GFR < 30 ml/min, platelet <100 x 10^9/L
- Planned cardiac, intracranial, or intraspinal surgery

6585 Patients were screened

- 4701 Were excluded
  - 544 Were withdrawn by physician
  - 4155 Did not meet inclusion criteria or met exclusion criteria
  - 2 Had unknown reasons

1884 Were enrolled and underwent randomization

- 950 Were assigned to receive placebo
  - 32 Discontinued study
    - 23 Withdrew consent
    - 3 Were lost to follow-up
    - 2 Were withdrawn by principal investigator
    - 4 Had other reasons
    - 5 Died
  - 913 Completed the study

- 934 Were assigned to receive dalteparin
  - 39 Discontinued study
    - 31 Withdrew consent
    - 3 Were lost to follow-up
    - 1 Was withdrawn by principal investigator
    - 4 Had other reasons
    - 4 Died
  - 891 Completed the study

Douketis et al. NEJM 2015; 373: 823-33
The Bridge Trial: Outcomes and Conclusions

**Findings:**
1. Arterial thromboembolism (No bridge 0.4%, bridge 0.3%; no bridge was non-inferior)
2. Major bleed (No bridge 1.3%, bridge 3.2%; p=0.005 in favor of no bridge)
3. Other events (Death, MI, DVT, PE not significant; Minor bleeding: no bridge 12%, bridge 20.9%; p<0.001 in favor of no bridge)

**Conclusions:**
In patients with AF requiring temporary interruption of warfarin treatment for an elective operation or invasive procedure, a strategy of forgoing bridging was non inferior to perioperative bridging for prevention of arterial thromboembolism and is associated with lower risk of major and minor bleeding.
Bridging for AF / AFL Patients on Warfarin
When Is It Recommended?

- **Recommended for patients at high risk of thromboembolic events**
  - CHADS2 ≥4 (was ≥3 in prior guidelines)
  - Mechanical heart valve
  - Stroke, TIA, thromboembolic events <3 months
  - Rheumatic heart disease

- **Pre-procedure**: when INR is below therapeutic, start LMWH or UFH
  - LMWH should be stopped 24 hours prior to the procedure
  - UFH should be stopped 4-6 hours prior to the procedure

- **Post-procedure**: LMWH or UFH restarted when hemostasis is established
  (~24 hours for a procedure with a low bleeding risk, 48-72 hours for procedures with intermediate/high risk of bleeding). Use prophylactic dosages for the first 24-72 hours and then increase to therapeutic dosages. Continue until INR is therapeutic.

When a decision to interrupt warfarin therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that bridging therapy with LMWH or UFH be instituted when the INR is below therapeutic level only in patients at high risk of thromboembolic events (CHADS2 $\geq 4$, mechanical valve, stroke/transient ischemic attack $< 3$ months, rheumatic heart disease) 

(Conditional Recommendation, Low-Quality Evidence)
No Bridging in Patients on NOACs

Recommendation

We recommend no bridging (LMWH or UFH) for NVAF patients receiving NOACs who undergo elective surgery or invasive procedures requiring interruption of anticoagulation (Strong Recommendation, Moderate-Quality Evidence).

# Pivotal Randomized AF Trials Compared

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF-TIMI 48</th>
<th>AVERROES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT Comparison</strong></td>
<td>Dabigatran (110, 150) vs. warfarin</td>
<td>Rivaroxaban vs. warfarin</td>
<td>Apixaban vs. warfarin</td>
<td>Edoxaban (30, 60) vs. warfarin</td>
<td>Apixaban vs. aspirin</td>
</tr>
<tr>
<td><strong>Size (approx.)</strong></td>
<td>18,000</td>
<td>14,000</td>
<td>18,000</td>
<td>21,000</td>
<td>5,600</td>
</tr>
<tr>
<td><strong>Valve Exclusion</strong></td>
<td>Severe valve disorder</td>
<td>Significant MS; Any prosthesis</td>
<td>Mod/Sev MS; Mechanical</td>
<td>Mod/Sev MS; Mechanical</td>
<td>Req surgery; mechanical</td>
</tr>
<tr>
<td><strong>Renal Exclusion</strong></td>
<td>CrCl&lt;30 mL/min</td>
<td>CrCl&lt;30 mL/min</td>
<td>Cr&gt;2.5 mg/dL or CrCl&lt;25 mL/min</td>
<td>CrCl&lt;30 mL/min</td>
<td>Cr&gt;2.5 mg/dL or CrCl&lt;25 mL/min</td>
</tr>
</tbody>
</table>

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Apixaban versus warfarin: stroke/SE and major bleeding in patients with and without valvular heart disease: findings from the ARISTOTLE study

Excluded Valvular AF in ARISTOTLE:
“Moderate or severe mitral stenosis, or prosthetic mechanical heart valve”

4808 (26.4%) / 18,197 patients:
• Any mitral valve disease (3578): At least moderate mitral regurgitation (3526); Mitral Stenosis (131)
• Any aortic valve disease (1150): Aortic regurgitation (887); Aortic stenosis (384)
• Tricuspid regurgitation (2124)
• Valve surgery (251)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>No Valvular Heart Disease</th>
<th>Valvular Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apixaban %/yr</td>
<td>Warfarin %/yr</td>
</tr>
<tr>
<td>Stroke / SE</td>
<td>1.20 %</td>
<td>1.43 %</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>2.01 %</td>
<td>3.07 %</td>
</tr>
</tbody>
</table>
NOACs and Valvular Heart Disease
Survey of CCS panelists

NOAC use is contra-indicated
- Mechanical Heart Valve (100% agreement)
- Rheumatic mitral stenosis
  - Mild (47% agreement)
  - Moderate-severe (88% agreement)
  - After commissurotomy (42% agreement)

NOAC use is reasonable
- Bioprosthetic heart valve
  - Aortic position (82% agreement)
  - Mitral position (73% agreement)
- Mitral annuloplasty with or without prosthetic ring (88% agreement)
- Nonrheumatic mitral stenosis : Mild (97% agreement)
- Mitral regurgitation
  - Mild (97% agreement)
  - Moderate-severe (>90% agreement)
- Tricuspid regurgitation Any severity (98% agreement)
- Aortic stenosis or regurgitation
  - Mild (98% agreement)
  - Moderate to severe (80% agreement)
Sub-clinical AF
Time to First Device-Detected AT> 6 min, >190 bpm: ASSERT Trial
Healey JS; NEJM 2012

ASSERT : Time to Adjudicated AHRE(>6 minutes,>190/minute)

Cumulative Hazard Rates

# at Risk Year 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
2580 2059 1842 1663 1371 1008 706 446 243

3 month Visit
<table>
<thead>
<tr>
<th>Event</th>
<th>Device-Detected Atrial Tachyarrhythmia</th>
<th>Device-Detected Atrial Tachyarrhythmia Present vs. absent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent N=2319</td>
<td>Present N= 261</td>
</tr>
<tr>
<td></td>
<td>events %/year</td>
<td>events %/ year</td>
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<tr>
<td>Ischemic Stroke or Systemic Embolism</td>
<td>40 0.69</td>
<td>11 1.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR 2.49, 95% CI 1.28 – 4.85, p 0.007</td>
</tr>
<tr>
<td>Vascular Death</td>
<td>153 2.62</td>
<td>19 2.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR 1.11, 95% CI 0.69 – 1.79, p 0.67</td>
</tr>
<tr>
<td>Stroke / MI / Vascular Death</td>
<td>206 3.53</td>
<td>29 4.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR 1.25, 95% CI 0.85 – 1.84, p 0.27</td>
</tr>
<tr>
<td>Clinical Atrial Fibrillation or Flutter</td>
<td>71 1.22</td>
<td>41 6.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR 5.56, 95% CI 3.78 – 8.17, p &lt;0.001</td>
</tr>
</tbody>
</table>
Relation between AF and Stroke

ASSERT Trial
Healey JS
NEJM 2012
RECOMMENDATION

10. We suggest that it is reasonable to prescribe OAC therapy for patients with age ≥ 65 years or CHADS₂ score ≥ 1 ("CCS algorithm") who have episodes of SCAF lasting > 24 hours, or for shorter episodes in high-risk patients (such as those with a recent cryptogenic stroke) (Conditional Recommendation, Low-Quality Evidence).
ACC AHA Guideline Recommended Therapy

Atrial Fibrillation

CHADS$_2$ > 1

Class IA

Oral Anticoagulant

Coronary Stent

Dual Antiplatelet Tx

Triple Therapy

The Problem = Increased Bleeding
Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation

- Registre Danois
- 82k patients
- 1997-2006
- F-up moyen – 3.3 ans
- Incidence saignements (non-fatal ou fatal): 11.4%

Hansen ML et al. Arch Intern Med 2010;170:1433-41
For patients with AF with an indication for primary CAD prevention or stable CAD/arterial vascular disease:

- Age < 65 and CHADS₂ = 0, No CAD / vascular disease: No antithrombotic therapy
- Age < 65 and CHADS₂ = 0, Stable CAD / vascular disease: ASA
- Age ≥ 65 or CHADS₂ ≥ 1, Stable CAD / vascular disease: OAC* alone

*A NOAC is preferred over warfarin for non-valvular AF

† Primary CAD prevention with ASA may be considered in selected high-risk patients

Concomitant AF and CAD – CCS Guidelines Update 2016
WOEST Trial
Randomized Trial of Triple vs Dual Therapy

573 pts on OAC undergoing PCI (excluded CNS or major bleed)

Randomized

279 OAC + Clopidogrel
284 OAC + DAPT

Clopidogrel for 1 month minimum after BMS and 1 y after DES

Primary EP= All bleeding events (TIMI) at one year
Secondary EP= Stroke, death, MI, ST and TVR

Dewilde, Lancet 2013
WOEST

Primary Endpoint: Total TIMI bleeding events

Cumulative incidence of bleeding

- Triple therapy group
- Double therapy group

44.9%
64%
19.5%

p<0.001
HR=0.36  95%CI[0.26-0.50]

Dewilde Lancet 2013
WOEST: Secondary endpoints

P = 0.027

- **Death**: 6.4%
- **MI**: 4.7%
- **TVR**: 6.8%
- **Stroke**: 2.9%
- **ST**: 3.2%

**Triple therapy group**

**Double therapy group**

Dewilde W et al. Lancet 2013
For patients with AF and recent elective PCI

- Age < 65 and CHADS₂ = 0
  - ASA + Clopidogrel for 12 months
  - ASA alone after 12 months

- Age ≥ 65 or CHADS₂ ≥ 1
  - OAC* + Clopidogrel for 12 months
  - OAC* alone after 12 months

* A NOAC is preferred over warfarin for non-valvular AF
For patients with AF in association with NSTEMI or STEMI:

- **Age < 65 and CHADS₂ = 0**
  - No PCI
    - ASA + Ticagrelor or Clopidogrel for ± 12 months
      - ASA alone after ± 12 months
  - PCI
    - ASA + Ticagrelor or Prasugrel or Clopidogrel for 12 months
      - ASA alone after 12 months

- **Age ≥ 65 or CHADS₂ ≥ 1**
  - No PCI
    - OAC* + Clopidogrel for ± 12 months
      - OAC* alone after ± 12 months
  - PCI
    - OAC* + Clopidogrel + ASA for 3 to 6 months
      - OAC* alone after ± 12 months

*A NOAC is preferred over warfarin for non-valvular AF*
<table>
<thead>
<tr>
<th>trial</th>
<th>n</th>
<th>experimental arm</th>
<th>control arm</th>
<th>clinicaltrials.gov</th>
<th>primary endpoint</th>
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</thead>
<tbody>
<tr>
<td>PIONEER AF-PCI</td>
<td>2,100</td>
<td>rivaroxaban P2Y12</td>
<td>warfarin P2Y12 aspirin</td>
<td>01830543</td>
<td>bleeding</td>
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<tr>
<td>RE-DUAL PCI</td>
<td>2,500</td>
<td>dabigatran* P2Y12</td>
<td>warfarin P2Y12 aspirin</td>
<td>02164864</td>
<td>bleeding</td>
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<tr>
<td>AUGUSTUS**</td>
<td>4,600</td>
<td>apixaban/warfarin P2Y12</td>
<td>warfarin P2Y12 aspirin</td>
<td>02415400</td>
<td>bleeding</td>
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<tr>
<td>ENTRUST AF-PCI</td>
<td>1,500</td>
<td>edoxaban P2Y12</td>
<td>warfarin P2Y12 aspirin</td>
<td>n.a.</td>
<td>bleeding</td>
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<tr>
<td>MANJUSRI²</td>
<td>296</td>
<td>warfarin ticagrelor</td>
<td>warfarin clopidogrel aspirin</td>
<td>02206815</td>
<td>bleeding</td>
</tr>
</tbody>
</table>

* 150mg bid or 110 mg bid
**ACS with or without PCI only

1 Am Heart J 2015;169:472-478
2 Contemp Clin Trials 2015;40:166-171
MERCI!