What’s New in Atrial Fibrillation

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Disclosures

• I have received honouraria and/or consulting fees from
  – Boehringer Ingelheim
  – Bayer
  – Pfizer
  – BMS
  – Servier
  – Amgen
  – Sanofi
What IS new?

• Guidelines
• Evidence
  – ANNEXA-4
  – AUGUSTUS
• Drugs
Society Guidelines

2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

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2018 Focused Update

Content

1. Anticoagulation in the context of cardioversion
2. Management of antithrombotic therapy for patients with AF and CAD
3. Investigation and management of subclinical AF
4. Antidotes for NOACs/NOAC reversal agents
5. Acute pharmacological rhythm control
6. Catheter ablation of AF
7. Integrated approach to AF and modifiable cardiovascular risk factors
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Anticoagulation in the context of cardioversion
CCS Recommendations - 1

NEW!

• MOST patients should receive therapeutic anticoagulation for 3 weeks before cardioversion* – STRONG/Moderate

NEW!

• CV without 3 weeks of therapeutic anticoagulation be reserved for patients
  – With clear onset of 12h or less WITHOUT recent stroke or TIA
  – Who present 12-48h of onset with a CHADS$_2$ score of LESS than 2 - WEAK/Low
WHAT ARE THE CONTEMPORARY RATES OF THROMBOEMBOLISM AFTER CV OF AF?

IRRESPECTIVE OF CV

- 4 trials
- 1088 events
- 71,381 pts

- Monthly event rate (%) >48h ADW: 0.14
- Monthly event rate (%) >48h NOAC: 0.12

↑ 329%

AFTER CV

- 6 trials
- 30 events
- 7,653 pts

- Monthly event rate (%) >48h CV ADW: 0.46
- Monthly event rate (%) >48h CV NOAC: 0.31

↑ 258%

IRRESPECTIVE OF CV

FROM 4 NOAC PIVOTAL TRIALS

AFTER CV

FROM 3 NOAC PIVOTAL TRIALS AND 3 NOAC CV RTCs

IS CV WITHIN 48 HOURS A MUCH LOWER RISK FACTOR THAN IS CV AFTER 48 HOURS?

<table>
<thead>
<tr>
<th>Time to cardioversion, h</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-24 vs &lt;12</td>
<td>4.0 (1.7-9.1)</td>
<td>.001</td>
</tr>
<tr>
<td>24-48 vs &lt;12</td>
<td>3.3 (1.3-8.9)</td>
<td>.02</td>
</tr>
</tbody>
</table>

**AFTER CV >48 H**

- >48h CV no AC: 0.79
- >48h CV AC: 0.33


**AFTER CV < 48 H**

- <48h CV no AC: 0.71
- <48h CV AC: 0.13

PARSING THE RISK OF THROMBOEMBOLISM AFTER CV OF ATRIAL FIBRILLATION

<48 Hr AF with CV On AC Versus Off AC by CHA₂DS₂-VASc

<table>
<thead>
<tr>
<th>CVA</th>
<th>Anticoagulated (%)</th>
<th>Not Anticoagulated (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0.00</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.00</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>0.15</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>2.20</td>
<td>1.5% / yr</td>
<td>0.001</td>
</tr>
</tbody>
</table>

significant decrease in TE for CHA₂DS₂-VASc ≥2 if on OAC
0.2% anticoagulated vs. 1.1% not anticoagulated, p=0.001

CCS
Recommendations - 2

• We suggest that for unplanned CV, therapeutic anticoagulation be initiated immediately (preferably before CV) with either a NOAC or heparin followed by adjusted-dose warfarin (ADW) – WEAK/Low
CCS Recommendations - 3

• As an alternative to 3 weeks of therapeutic anticoagulation, TEE (transesophageal echo) may be used to exclude cardiac thrombus – WEAK/moderate

• Consider IMMEDIATE CV for patients whose AF/AFL is the direct cause of hemodynamic instability – STRONG/Low
CCS
Recommendations - 4

• In absence of a strong contraindication, all patients receive at least 4 weeks of therapeutic anticoagulation post CV – WEAK/Low

• Values and Preferences
  – Greater emphasis on the benefits of preventing stroke compared with bleeding risk with short course OAC
  – Either NOAC or ADW but NOAC more convenient and faster onset
ANTICOAGULATION PATHWAY: CARDIOVERSION FOR AF OR FLUTTER

1. Valvular AF (any duration), or
2. NVAF Duration <12 hours and recent stroke/TIA, or
3. NVAF Duration 12-48 hours and CHADS$_2$ ≥2, or
4. NVAF Duration >48 hours

**Therapeutic OAC for ≥3 weeks before cardioversion**

- Alternate: TEE to exclude LA thrombus

**CARDIOVERSION**

**ANTICOAGULATION FOR 4 WEEKS POST CARDIOVERSION**

**LONG-TERM ANTICOAGULATION BASED ON THE “CCS ALGORITHM” (“CHADS-65”)**

1. Hemodynamically unstable acute AF$^1$, or
2. NVAF Duration <12 hours and no recent stroke/TIA, or
3. NVAF Duration 12-48 hours and CHADS$_2$ <2

**Initiate OAC as soon as possible (preferably prior to cardioversion)**
Management of antithrombotic therapy for patients with AF and CAD
Balancing Risk…

Factors that Increase Risk of Bleeding

- **Patient Factors**
  - Age (> 65 years)
  - Low body weight (< 60 kg)
  - Hypertension
  - History of bleeding (esp. within 1y)
  - Prior Stroke or intracranial bleed
  - Combined OAC and antiplatelet use
  - Concomitant NSAID or prednisone use
  - Excess alcohol consumption
  - Abnormal liver function
  - CKD (eGFR < 60 mL/min)
  - Anemia (hemoglobin <110 g/L)
  - Labile INR (TTR <60%)

Factors that Increase Risk of Ischemic Coronary Events

- **Patient Factors**
  - Diabetes mellitus treated with OHG or insulin
  - Current smoker
  - CKD (eGFR < 60 mL/min)
  - Prior ACS
  - Prior stent thrombosis

- **Clinical Presentation**
  - ACS (STEMI, NSTEMI, UA)

- **Angiographic factors**
  - Multi-vessel disease
  - Multiple (≥ 3) stents implanted
  - Stenting of a bifurcation lesion
  - Total stent length > 60 mm
  - Left main or proximal LAD stenting
  - Chronic occlusion intervention
  - Bioabsorbable vascular scaffold
Does your patient’s stroke risk warrant OAC?

**AF Patients with Coronary or Peripheral Arterial Disease and an Indication for OAC (Age ≥ 65 years or CHADS\textsubscript{2} ≥ 1)**

**RECOMMENDATION**

9. For patients with AF aged ≥ 65 years or with a CHADS\textsubscript{2} score ≥ 1 and coronary or arterial vascular disease (peripheral vascular disease or aortic plaque), we recommend long-term therapy with an OAC alone (Strong Recommendation, High-Quality Evidence).

**Values and preferences.** For patients with AF and stable coronary or arterial vascular disease, the CCS AF Guidelines Committee believed that routine use of combination therapy (an OAC with a single antiplatelet agent) was not justified because of the increased risk of bleeding without a significant reduction in ischemic coronary and cerebrovascular thrombotic events.

**Practical tip.** For patients with high-risk clinical or angiographic features for ischemic coronary outcomes (Fig. 2) who are at low risk of bleeding, some clinicians prefer a combination of an OAC and single antiplatelet therapy (either aspirin or clopidogrel) in preference to OAC therapy alone.
AF Patients with Coronary or Peripheral Arterial Disease and an Indication for OAC (Age $\geq 65$ years or CHADS$_2 \geq 1$)

**RECOMMENDATION**

10. When an OAC is indicated in the presence of coronary or arterial vascular disease, we suggest a NOAC in preference to warfarin (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. The suggestion for use of a NOAC rather than warfarin places relatively greater weight on the ease of use of NOACs vs warfarin, as well as the data from randomized controlled trials of NOACs vs warfarin for NVAF (eg, equal or greater reduction of stroke, equal or greater reduction in all-cause mortality, equal or less major bleeding, less intracranial bleeding, and no net increase in CAD outcomes).
Does your patient's stroke risk warrant OAC?

**Practical Tips:**
1. For patients less than 65y with CHADS\(_2\) score of 1 at the lower end of the stroke risk spectrum, some clinicians prefer DAPT
2. OAC “studied” as part of dual pathway therapy are warfarin, rivaroxaban 15mg daily, dabigatran 110mg bid* and dabigatran 150mg bid

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**AF Patients with Coronary or Peripheral Arterial Disease and an Indication for OAC (Age ≥ 65 years or CHADS\(_2\) ≥ 1)**

**RECOMMENDATION**

11. For patients with AF aged ≥ 65 years or with a CHADS\(_2\) score ≥ 1, we suggest dual pathway therapy (an OAC with clopidogrel 75 mg/d) for at least 1 month after BMS implantation and at least 3 months after DES implantation (Weak Recommendation, Moderate-Quality Evidence).
Does your patient's stroke risk warrant OAC?

Practical Tips:

1) All patients should receive ASA 81 mg (or a minimum of 160 mg if ASA-naive) on the day of the PCI procedure.

2) ASA may be continued as part of TT for up to 6 months for patients with a high risk of thrombotic coronary events and low risk of bleeding.

3) OAC "studied" in TT regimens are warfarin and rivaroxaban 2.5mg bid*

4) For patients less than 65y with CHADS² score of 1 at the lower end of the stroke risk spectrum, some clinicians prefer DAPT.

**RECOMMENDATION**

12. For patients with AF aged ≥ 65 years or with a CHADS² score ≥ 1, we recommend an initial regimen of TT (ASA 81 mg/d with clopidogrel 75 mg/d with an OAC) up to 6 months after PCI (Strong Recommendation, Moderate-Quality Evidence). After ASA discontinuation, which may occur as early as the day after PCI, we suggest that dual pathway therapy (an OAC with clopidogrel 75 mg/d) be continued for up to 12 months after PCI (Weak Recommendation, Moderate-Quality Evidence).
Does your patient’s stroke risk warrant OAC?

**Type 1 MI:** pts with thrombotic plaque rupture; medically managed

**Recommendation**

13. For patients with AF aged ≥ 65 years or with a CHADS$_2$ score ≥ 1, we suggest that dual pathway therapy (an OAC with clopidogrel 75 mg/d, rather than prasugrel or ticagrelor) be given without concomitant ASA for 12 months after ACS (Weak Recommendation, Low-Quality Evidence).
AF Patients with Coronary or Peripheral Arterial Disease and an Indication for OAC (Age ≥ 65 years or CHADS₂ ≥ 1)

- Elective PCI without High Risk features for thrombotic CV events
- ACS with PCI or Elective PCI with High Risk features for thrombotic CV events
- ACS without PCI

Dual Therapy
(OAC² + Clopidogrel)
Duration: 1 day to 6 months

Triple Therapy
(OAC³ + ASA + Clopidogrel)
Duration: 1 to 12 months post BMS, 3 to 12 months post DES

Dual Therapy
(OAC² + Clopidogrel)
Duration: Up to 12 months post stent

OAC

Stable CAD/PAD

OAC³

OAC³

OAC³
Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

Renato D. Lopes, M.D., Ph.D., Gretchen Heizer, M.S., Ronald Aronson, M.D., Amit N. Vora, M.D., M.P.H., Tyler Massaro, Ph.D., Roxana Mehran, M.D., Shaun G. Goodman, M.D., Stephan Windecker, M.D., Harald Darius, M.D., Jia Li, Ph.D., Oleg Averkov, M.D., Ph.D., M. Cecilia Bahit, M.D., Otavio Berwanger, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Ziad Hijazi, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Peter Sinnaeve, M.D., Ph.D., Robert F. Storey, M.D., Holger Thiele, M.D., Dragos Vinereanu, M.D., Ph.D., Christopher B. Granger, M.D., and John H. Alexander, M.D., M.H.S., for the AUGUSTUS Investigators*
**INCLUSION**
- Atrial fibrillation (prior, persistent, >6 hr) – Physician decision for OAC
- Acute coronary syndrome (~1/3) or PCI – ≤14 days with planned P2Y$_{12}$ inhibitor for 6 months

**Apixaban 5 mg BID**
Apixaban 2.5 mg BID in selected patients

**Randomize n=4600 patients**

**KEY EXCLUSION**
- Contraindication to DAPT
- Other reason for VKA (prosthetic valve, moderate / severe mitral stenosis)
- History of ICH

**Aspirin for all on the day of ACS or PCI**
Aspirin versus placebo after randomization

**Primary outcome**: ISTH major / CRNM bleeding
**Secondary outcome(s)**: death / hospitalization, death / ischemic events

Lopes et al *Am Heart J* 2018;200:17-23
Antidotes/reversal agents for NOACs
Andexanet Alpha

GLA domain removed to prevent anticoagulant effect

N terminal residues retained to reduce immunogenicity

High affinity

Factor Xa Inhibitor

S419A

Catalytic Domain

Coagulation factor Xa [recombinant], inactivated zhzo
ANNEXA-4 Study Design

### Patient Screening
- Patient with acute major bleeding
- Within 18 hours of last dose of FXa inhibitor
- Assessments:
  - 1 hr
  - 4 hr
  - 8 hr
  - 12 hr
  - Day 1
  - Day 3
  - Day 30

### Bleeding and Laboratory Assessment
- Andexanet
- IV Bolus
- 2-hour IV Infusion
- After end of infusion
- Safety follow-up visit

### Efficacy Outcomes
- Change in anti-FXa activity
- Clinical hemostatic efficacy through 12 hours

### Safety Measurements
- Thrombotic events
- Antibodies to FX, FXa, andexanet
- 30-day mortality

### Dose of andexanet dependent on:
- Agent
- Dose: Low or High
- Timing: less than 8h vs 8h+ since last dose
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Safety Population</th>
<th>Efficacy Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr), mean ± SD</td>
<td>77 (±11)</td>
<td>77 (±12)</td>
</tr>
<tr>
<td>Male</td>
<td>117 (52%)</td>
<td>70 (51%)</td>
</tr>
<tr>
<td>Time from presentation until</td>
<td>4.7 ± 2.8</td>
<td>5.0 ± 3.1</td>
</tr>
<tr>
<td>Andexanet (hrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated CrCl &lt; 30 mL/min,</td>
<td>21 (9%)</td>
<td>13 (10%)</td>
</tr>
<tr>
<td>Indication for anticoagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>178 (78%)</td>
<td>104 (76%)</td>
</tr>
<tr>
<td>Venous Thromboembolic Disease</td>
<td>52 (23%)</td>
<td>38 (28%)</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>32 (14%)</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>47 (21%)</td>
<td>32 (23%)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>52 (23%)</td>
<td>36 (26%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>67 (30%)</td>
<td>42 (31%)</td>
</tr>
</tbody>
</table>
**Efficacy Endpoint:**

**Anti-Factor Xa Activity**

### A Patients Who Received Apixaban

<table>
<thead>
<tr>
<th>Time</th>
<th>Median</th>
<th>Percent Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>149.7</td>
<td></td>
</tr>
<tr>
<td>End of Bolus</td>
<td>11.1</td>
<td>(-93 to -91)</td>
</tr>
<tr>
<td>End of Infusion</td>
<td>11.5</td>
<td>(-93 to -91)</td>
</tr>
<tr>
<td>4 Hr</td>
<td>97.2</td>
<td>(-38 to -29)</td>
</tr>
<tr>
<td>8 Hr</td>
<td>104.6</td>
<td>(-36 to -27)</td>
</tr>
<tr>
<td>12 Hr</td>
<td>91.2</td>
<td>(-41 to -34)</td>
</tr>
</tbody>
</table>

### B Patients Who Received Rivaroxaban

<table>
<thead>
<tr>
<th>Time</th>
<th>Median</th>
<th>Percent Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>211.8</td>
<td></td>
</tr>
<tr>
<td>End of Bolus</td>
<td>14.2</td>
<td>(-94 to -88)</td>
</tr>
<tr>
<td>End of Infusion</td>
<td>16.5</td>
<td>(-93 to -87)</td>
</tr>
<tr>
<td>4 Hr</td>
<td>121.7</td>
<td>(-45 to -36)</td>
</tr>
<tr>
<td>8 Hr</td>
<td>101.4</td>
<td>(-52 to -45)</td>
</tr>
<tr>
<td>12 Hr</td>
<td>85.5</td>
<td>(-65 to -58)</td>
</tr>
</tbody>
</table>
# Hemostatic Efficacy

N=249

Excellent: 171 (69%)

Good: 33 (13%)

Poor: 45 (18%)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients/ Total No.</th>
<th>Percent with Excellent or Good Hemostasis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>204/249</td>
<td>82 (77–87)</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>79/99</td>
<td>80 (72–88)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>109/131</td>
<td>83 (77–90)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>13/15</td>
<td>87 (69–100)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>101/127</td>
<td>80 (73–87)</td>
</tr>
<tr>
<td>Female</td>
<td>103/122</td>
<td>84 (78–91)</td>
</tr>
<tr>
<td>Site of bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>51/60</td>
<td>85 (76–94)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>135/168</td>
<td>80 (74–86)</td>
</tr>
<tr>
<td>Other</td>
<td>18/21</td>
<td>86 (71–100)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>23/28</td>
<td>82 (68–96)</td>
</tr>
<tr>
<td>65–75 yr</td>
<td>57/66</td>
<td>86 (78–95)</td>
</tr>
<tr>
<td>&gt;75 yr</td>
<td>124/155</td>
<td>80 (74–86)</td>
</tr>
<tr>
<td>Andexanet dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>172/208</td>
<td>83 (78–88)</td>
</tr>
<tr>
<td>High</td>
<td>32/41</td>
<td>78 (65–91)</td>
</tr>
</tbody>
</table>
Safety

- Patients with thrombotic events:
  - Within 3 days: 11 (3%)
  - Within 30 days: 34 (10%)

- Oral Anticoagulation was restarted in 100 patients (28%):
  - 34 patients had a thrombotic event before restart
  - 0 patients had a thrombotic event after restart

- 49 deaths occurred by 30 days (14%), of which 35 were cardiovascular

- 2 patients with infusion-related reactions
Vernakalant

• Blocks Na and K channels in all phases of the atrial action potential
• Little effect on ventricular repolarization
• Pharmacokinetics
  – Half life: 3h
  – Metabolized by CYP 2D6
    • Competitively inhibits 2D6 but not 3A4, P-gp
• Administration
  – 3mg/kg over 10 min; if no response after 15 min, give second 2mg/kg dose

Vernakalant

• Efficacy:
  – AF: <7d, 50-75% >7d, <10%
    • Patients reported symptom relief
  – A Flutter: NO (not really)

• Adverse Effects
  – Hypotension (5-7%; ~15% in HF patients)
  – Bradycardia – associated with AF termination
  – NSVT in HF patients (7% vs 1% with placebo)
  – Taste alterations (20-30%)
  – Sneezing (10-20%)
  – Paresthesia (8%)
  – Nausea (6%)
Vernakalant

• Indications
  – Rapid conversion of recent onset AF
    • 7d or less for non-surgical AF
    • 3 days or less for post cardiac surgery patients

• Contraindications
  – Severe AS, SBP <100mmHg
  – NYHA III or IV HF, or recent decompensation
  – Long QT
  – Use of Class I or III IV AAD within 3h
Clinical Studies

• **Phase 2**
  – CRAFT – AF 3h to 72h

• **Phase 3 – vs placebo**
  – ACT I - AF 3h to 45d
  – ACT II - AF 3h to 3d - 24h to 7d post CV surgery
  – ACT III - 3h to 7d
  – ACT V - 3h to 7d
  – Scene 2 – Atrial flutter

  *Doesn’t work!*

• **Phase 3 – vs active comparator**
  – AVRO (vs amiodarone)
  – Simon at al (vs ibutilide)
  – Vogiatzis et al (vs ibutilide)

• **Phase 4**
  – ACT IV
  – SPECTRUM*
Overall Efficacy

Cardioversion to NSR within 90 minutes

McIntyre WF. Eur Heart Journal 2018;39S:458-459
Serious adverse events were as defined by individual investigators and included, but were not limited to: tachyarrhythmias, bradycardia, heart failure, thromboembolic events and death.