Don’t Miss Virtual SCAI 2020 Presentations – Online Now!

MHIF FEATURE:
HemoLung Emergency Use of ECCO2R
Dr. Saavedra-Romero

CONTACT:
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Carina Benson - carina.benson@allina.com

20 MHI physicians and MHIF staff participated:
• 28 presentations
• 14 poster presentations
• 14 podium presentations and moderated sessions

A special congratulations to Dr. Brilakis who was the 2020 Scientific Sessions Program Chair!
Find his welcome talk as part of Day 1 presentations [http://www.scai.org/SCAI2020](http://www.scai.org/SCAI2020)

Interested in MHIF Updates During COVID-19?
Visit mplsheart.org/coronavirus/

Thanks to our MHI physician partners who are helping us complete tasks to get patients enrolled in research studies as appropriate during COVID-19!

We appreciate our partnership with you!
Anticoagulation in Patients Who Also Need Antiplatelet Therapy: How Low Can We Go?!

JoEllyn Carol Moore, MD, FACC, FHRS
Cardiac Electrophysiology, Minneapolis Heart Institute
Abbott Northwestern Hospital, part of Allina Health

May 18, 2020
MHIF Grand Rounds

Overview

- Most recent guidelines for oral anticoagulant (OAC) use in atrial fibrillation (AF)
- Brief history of anticoagulants and antiplatelet agents
- AF management guideline update
- Pharmacology of antiplatelet agents and anticoagulants
- Bleeding risk
- Managing “dual” and “triple” therapy
### 2018 North American Guidelines

<table>
<thead>
<tr>
<th>Time from PCI</th>
<th>Default strategy</th>
<th>Patients at high ischemic/thrombotic and low bleeding risk</th>
<th>Patients at low ischemic/thrombotic or high bleeding risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinf-PCI</td>
<td>Triple Therapy (OAC + DAPT)</td>
<td>Triple Therapy (OAC + DAPT)</td>
<td>Triple Therapy (OAC + DAPT)</td>
</tr>
<tr>
<td>1 month</td>
<td></td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td>Double Therapy up to 1 month (OAC + DAPT)</td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>OAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>OAC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OAC: prefer a NOAC over VKA if no contraindications
DAPT: prefer a P2Y12 inhibitor over aspirin
Categorical: the P2Y12 inhibitor of choice depends on the patient's clinical profile and bleeding risk. NOAC: preferred over VKA if no contraindications. Double therapy: preferred over single therapy for patients with high thrombotic risk and low bleeding risk.

Angiolillo et al. (2018) Circulation

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### 2018 European Guidelines

**Figure 3 Management algorithm for all patients presenting with either PCI or ACS undergoing PCI**

- **Concerns about long-term oral anticoagulation**
  - Time from anticoagulation initiation
  - 14 days
  - 30 days
  - 12 months

- **Concerns about high bleeding risk**
  - Time from PCI or ACS
  - 3 days
  - 7 days

Lip et al. (2019) Europace
Scope of the Problem

- 1-4% of the adult population in Australia, Europe and the USA have AF
  - 0.90% in patients 18-64 years old (7% undiagnosed)
  - 9.9% in patients > 65 years old (10% undiagnosed)
  - > 13% in octogenarians
- 20-40% of patients with AF also have CAD
- 20% of patients with AF will go on to need PCI or have ACS
- 5-10% of patients referred for LHC +/- PCI have an indication for an anticoagulant for AF


Did you know?

Aspirin was first distributed:

a) As a powder in 1899
b) As a tablet in 1934
c) As a liquid in 1849
d) As a powder in 1921
Did you know?

Aspirin was first distributed:

a) As a powder in 1899
b) As a tablet in 1934
c) As a liquid in 1849
d) As a powder in 1921

History of Oral Antiplatelet Agents

• 1899: acetylsalicylic acid is distributed as a powder (called Aspirin by Bayer)
• 1991: ticlopidine FDA approved
• 1997: clopidogrel FDA approved
• 2009: prasugrel FDA approved
• 2011: ticagrelor FDA approved
• 2014: vorapaxar FDA approved
Did you know?

Warfarin was first distributed:

a) As an insect repellent in 1944
b) As a household cleaner in 1952
c) As a rodenticide in 1952
d) As a sleep aid in 1954
History of Oral Anticoagulants

- 1954: warfarin approved for human use (approved as rodenticide in 1952)
- [digoxin also FDA approved in 1954]
- 2010: dabigatran FDA approved
- 2011: rivaroxaban FDA approved
- 2012: apixaban FDA approved
- 2015: edoxaban FDA approved
- 2017: betrixaban FDA approved

New AF

Mr. Smith is a 50 year old male with past medical history of HL who presents in clinic to discuss management of a new diagnosis of PAF with a recent cardioversion in the ED. He is otherwise healthy with a structurally normal heart by echo. You recommend:

a) No anticoagulation required
b) ASA 81 mg daily
c) Rivaroxaban 15 mg daily X 1 month (take with food)
d) Rivaroxaban 20 mg daily X 1 month (take on an empty stomach)
New AF

Mr. Smith is a 50 year old male with past medical history of HL who presents in clinic to discuss management of a new diagnosis of PAF with a recent cardioversion in the ED. He is otherwise healthy with a structurally normal heart by echo. You recommend:

a) No anticoagulation required
b) ASA 81 mg daily
c) Rivaroxaban 15 mg daily X 1 month (take with food)
d) Rivaroxaban 20 mg daily X 1 month (take on an empty stomach)

Stroke Risk in Atrial Fibrillation (NOT including MS or Mechanical Valve)

- CHA2DS2-VASc score of \(0 \text{ in men or 1 in women}\): reasonable to omit anticoagulant therapy (IIa, B)
- CHA2DS2-VASc score of \(1 \text{ in men and 2 in women}\): oral anticoagulant may be considered (IIb, C)
- CHA2DS2-VASc score of \(2 \text{ or greater in men or 3 or greater in women}\): oral anticoagulants are recommended (I, A-B)

“CHA2DS2-VA score”
Risk of Stroke or Death in the WHI Women with Atrial Fibrillation

Table 2: Annualized Rates of Stroke/TIA by CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc Scores

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} Score</th>
<th>n</th>
<th>Events</th>
<th>Annual %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1760</td>
<td>71</td>
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<tr>
<td>1</td>
<td>2879</td>
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<tr>
<td>2</td>
<td>922</td>
<td>106</td>
<td>1.17</td>
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<tr>
<td>3</td>
<td>299</td>
<td>38</td>
<td>1.49</td>
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<tr>
<td>4+</td>
<td>121</td>
<td>23</td>
<td>2.43</td>
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</tbody>
</table>

Table 6: Annualized Rates of Death by CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc Scores

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} Score</th>
<th>n</th>
<th>Events</th>
<th>Annual %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1760</td>
<td>179</td>
<td>0.87</td>
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<tr>
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<td>2879</td>
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<td>299</td>
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<td>3.49</td>
</tr>
<tr>
<td>4+</td>
<td>121</td>
<td>63</td>
<td>6.13</td>
</tr>
</tbody>
</table>

CHADS\textsubscript{2} score:
1. Congestive heart failure (CHF)
2. Hypertension
3. Age ≥ 75 years
4. Diabetes
5. Stroke

CHA\textsubscript{2}DS\textsubscript{2}-VASc score:
1. Congestive heart failure (CHF)
2. Hypertension
3. Age ≥ 75 years
4. Diabetes
5. Stroke
6. Vascular disease
7. Age 65–74 years

TIA = Transient Ischemic Attack

Moore et al. (2017) Journal of MHIF

Bleeding Risk Scores

Table 2: Bleeding risk scores.

<table>
<thead>
<tr>
<th>Hepatic or Renal Disease</th>
<th>Alcohol/Drug Abuse</th>
<th>Malignancy</th>
<th>Age</th>
<th>Reduced Platelet Count</th>
<th>Hypertension</th>
<th>Anemia</th>
<th>Genetic Factors</th>
<th>Fall Risk</th>
<th>Prior Stroke</th>
<th>Female Sex</th>
<th>History of Blending</th>
<th>Diabetes</th>
<th>Labile INR</th>
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</thead>
<tbody>
<tr>
<td>HEMOPHILIA</td>
<td>x</td>
<td>x</td>
<td>x**</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sickle Cell Anemia</td>
<td>x</td>
<td>x</td>
<td>x**</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>VWD</td>
<td>x</td>
<td>x</td>
<td>x***</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>ATRA</td>
<td>x</td>
<td>x</td>
<td>x****</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

* >75 years
** ≥70 years
*** Antiprotein Case
**** >65 years
***** Glomerular filtration rate <30 ml/min or on hemodialysis
****** >75 years

Reprinted from Heart Failure Reviews, Abraham et al., 2014;19:305-313 with permission from Springer.
Highlights of 2019 AF Guidelines

- “Valvular AF” definition: moderate-severe mitral stenosis or mechanical heart valve
- Class IA recommendation for DOAC use over warfarin
- Annual renal and hepatic function for DOAC monitoring
- It might be reasonable to prescribe apixaban for patients with ESRD
- Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term AC
- Implantable loop recorder to evaluate for AF in patients with cryptogenic stroke

Watchman

Ms. Roberts is an 85 year old female with past medical history of persistent atrial fibrillation who had recurrent GI bleeding on OAC leading to a Watchman placement > 6 months ago. She has had ongoing diastolic heart failure despite rate-controlled AF on metoprolol and desires a rhythm control strategy if possible. You recommend:

a) AVN ablation with a MICRA pacemaker
b) Change her rate-controlling medication to diltiazem
c) Tell her that her symptoms have no solution
d) TEE-guided cardioversion
Ms. Roberts is an 85 year old female with past medical history of persistent atrial fibrillation who had recurrent GI bleeding on OAC leading to a Watchman placement > 6 months ago. She has had ongoing diastolic heart failure despite rate-controlled AF on metoprolol and desires a rhythm control strategy if possible. You recommend:

a) AVN ablation with a MICRA pacemaker  
b) Change her rate-controlling medication to diltiazem  
c) Tell her that her symptoms have no solution  
d) TEE-guided cardioversion??

DCCV with Watchman

Abstract 10866: Cardioversion Outcomes After Left Atrial Appendage Occlusion With the Watchman Device


See full abstract:

33 DCCV in 19 patients  
40% off OAC  
TEE on only 30% off OAC  
No CVA/TIA at median 459 day follow-up  
2 Bleeding events in patients on ASA only

Kaur et al. (2019) Abstract 10866, Circulation
**DCCV with Watchman**

**Indirect Current Cardioversion of Atrial Fibrillation in Patients With Left Atrial Appendage Occlusion Devices**

Sharan Prakash Sharma, MD, Mohit K. Tunduga, MD, Rohit Gopinathannair, MD, Vivek Boldy, MD, Suhail Ra’i, MD, Sarangmitu Mohanty, MD, Xi Cheng, MD, David H. Holmseth, Jr., MD, Lars Søndergaard, MD, Andrea Natale, MD, Dhanunjaya Lakkireddy, MD

- DCCV in 146 patients
- 100% had a TEE
- 2.7% had LA thrombus on TEE
- 43% without OAC after DCCV
- 3 TIAs at median 1/3 of 12.8 months (none within 4 weeks of DCCV)
- 6 bleeding events (one proximate to DCCV-related AC)

**AC with Watchman**

- Warfarin with therapeutic INR at implant
- Warfarin + ASA 325 mg daily → 45 days (TEE at 45 days to evaluate for leak around Watchman) then switch to clopidogrel and ASA
- Clopidogrel 75 mg daily and ASA 325 mg daily → 6 months
- ASA 325 mg daily thereafter
Proposal for DCCV with Watchman

<table>
<thead>
<tr>
<th>&lt; 6 months post Watchman:</th>
<th>&gt; 6 months post Watchman:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DCCV</strong> if therapeutic on warfarin for 3 consecutive weeks</td>
<td><strong>TEE-guided DCCV</strong> if TEE with no thrombus on device or in left atria AND no significant watchman leak (≤5 mm)</td>
</tr>
<tr>
<td><strong>TEE-guided DCCV</strong> if sub-therapeutic warfarin or on ASA/Plavix only regimen</td>
<td>Anticoagulation: daily ASA</td>
</tr>
</tbody>
</table>

Anticoagulation per protocol:
- Warfarin (goal INR 2.5, range 2-3) + ASA x 45 days
- ASA 325mg plus Plavix 75mg daily day 46 through 6 months

What is Next in AC for AF?

- DOACs pre/post Watchman
- DOACs post-TAVR/bioprosthetic AVR
- AC after surgical left atrial appendage ligation
- Watchman with antiplatelet agents only
- DCCV after Watchman without AC
- DCCV with Cardiac CT in place of TEE to exclude LAA thrombus
- Device-detected AF (how much/when??)
Thank you!
Risk and Benefit of Different Antithrombotic Therapies (Focus on AF)

Nedaa Skeik, MD, FACC, FACP, FSVM, RPVI
Associate Professor of Medicine
Section Head, Vascular Medicine
Medical Director, Thrombophilia/Anticoagulation Clinic
Medical Director, Vein Practice
Medical Director, Vascular Laboratory
Minneapolis Heart Institute® Abbott Northwestern Hospital

Disclosures

Consulting and speaking for Pfizer, BMS, J&J, B.I. and BSC
No financial conflict related to this talk
Slides were shared prior to the presentation
Learning Objectives

- Discuss different antithrombotic therapies
- Mechanism of action
- General comparison
- Bleeding risk
- Summary

Coagulation Cascade
Decision Making is More Complicated

Targets for Anticoagulation

- Oral: Vitamin K antagonists, Factor Xa, Factor II
- Parenteral: Fondaparinux, LMWH

Tissue factor–Factor VIIa (extrinsic pathway)
Prothrombinase complex
- AT
- Hirudin
- Argatroban
- Bivalirudin
- Fibrinogen
- Fibrin

Ther Drug Monit. 2019 Dec;32(6):673-9
Dabigatran (Pradaxa)
Only Oral Direct Thrombin Inhibitor

Approved Indications:

1. **NVAF**
   - The only DOAC superior to warfarin to reduce ischemic stroke risk
   - More major bleed (extra cranial) in patients ≥75 years of age
   - More GI side effects and bleeding

2. **Treatment for DVT and or PE:**
   - Requires 5-10 days of parenteral anticoagulation

3. **Risk reduction of VTE after initial therapy**

4. **DVT prophylaxis in patient going for hip replacement**
   - Not approved for patients needing knee replacement

---

Factor Xa Inhibitors

- Rivaroxaban (J&J) Xarelto
- Apixaban [Bristol-Myers Squibb, Pfizer] Eliquis
- Edoxaban (Daiichi) Savaysa
- Betrixaban (Portola Pharma) Bevyxxa

- YM150 (Astellas)
- LY517717 (Lilly)
- TAK-442 (Takeda)
- PD0348292 (Pfizer)
Apixaban (Eliquis)

Approved Indications:

1. NVAF
   - Superior to warfarin, stroke and SE, major bleeding and all-cause mortality
   - Only DOAC studied vs. ASA (AVEROS Trial):
     - Superior for stroke/SE and no significant difference in major bleeding
2. Treatment of DVT and/or PE
   - Superior to enoxaparin/warfarin for major bleed
3. Risk reduction of recurrent VTE after initial therapy
   - Not significantly different from placebo for major bleed
4. DVT prophylaxis following hip or knee replacement

Rivaroxaban (Xarelto)

Approved Indications:

1. NVAF (ROCKET-AF, mean CHADS2: 3.5)
   - Can be given once daily with food for the NVAF indication
   - More GI bleeding and need for transfusion versus warfarin
2. Treatment of DVT and/or PE
   - Superior to enoxaparin/warfarin for major bleed
3. Risk reduction of recurrent VTE after initial therapy
   - 10mg dose has similar major bleeding risk to ASA (EINSTEIN CHOICE Trial, only DOAC compared to ASA for this indication)
4. DVT prophylaxis following hip or knee replacement
5. DVT prophylaxis in medically ill patients (not at high bleeding risk!)
6. MACE risk reduction in patients with chronic CAD/PAD in addition to ASA 81mg daily
Edoxaban (Savaysa)

Approved Indications:

1. NVAF
   - Superior to warfarin for major bleeding
   - Once daily dosage
   - Lower GI bleed with 30 mg dosage vs. warfarin

2. Treatment of DVT and or PE
   - Requires 5-10 days of parenteral anticoagulation
   - Superior to warfarin for major and CRNM bleed

• Not indicated for secondary VTE prevention after initial therapy
• Not indicated for DVT prophylaxis after THR or TKR

Betrixaban (Bevyxxa)

• Approved Indications:

1. VTE prophylaxis in adults hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
   - Superior to enoxaparin with similar major but more CRNM bleedings
**Antiplatelet Agents**

- **Aspirin (NSAID and sulfinpyrazone):** blocks cyclooxygenase, thereby inhibits the biosynthesis of PGs and TXs from arachidonic acid. TXA2 is a potent stimulator of PLT aggregation.

- **The platelet P2Y12 inhibitors** (clopidogrel, ticlopidine, ticagrelor, prasugrel, and cangrelor): block the binding of ADP to P2Y12 receptor, thereby inhibiting PLT activation and aggregation.

- **Vorapaxar:** antagonist of the protease-activated receptor-1 expressed on PLT. It inhibits thrombin-induced PLT aggregation.

- **Glycoprotein IIb/IIIa inhibitors:** bind GP IIb/IIIa receptor inhibiting PLT aggregation.

---

**Antiplatelet Therapies**

- **Aspirin (NSAID and sulfinpyrazone):**
  - PLT aggregation

- **The platelet P2Y12 inhibitors:**
  - PLT activation and aggregation

- **Vorapaxar, PAR 1 antagonist:**
  - PLT aggregation

- **Glycoprotein IIb/IIIa inhibitors:**
  - PLT aggregation
Assess stroke risk with CHA2DS2-VASc score
- Score 1 in men & 2 in women: Annual stroke risk 1%-2%, oral anticoagulants or aspirin may be considered
- Score ≥2 in men & ≥3 in women: Annual stroke risk 2%-15%, oral anticoagulants are recommended

& Balance stroke risk reduction benefit vs. bleeding risk

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Score in Men</th>
<th>CHA2DS2-VASc Score In Women</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>No anticoagulant</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>Aspirin (81-325 mg daily) or oral anticoagulants may be considered</td>
</tr>
<tr>
<td>≥ 2</td>
<td>≥ 3</td>
<td>Oral anticoagulants are recommended*</td>
</tr>
</tbody>
</table>

*DOACS (dabigatran, rivaroxaban, apixaban, and edoxaban) recommended over warfarin in DOAC-eligible patients

2019 ACC/AHA/HRS Focused Update on Atrial Fibrillation

4.4. Nonpharmacological Stroke Prevention
4.4.1. Percutaneous Approaches to Oclude the LAA

Recommendation for Percutaneous Approaches to Oclude the LAA
Referenced studies that support the new recommendation are summarized in Online Data Supplement 4.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>1. Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation (S4.4.1-1–S4.4.1-5).</td>
</tr>
</tbody>
</table>

NEW: Clinical trial data and FDA approval of the Watchman device necessitated this recommendation.

“Oral anticoagulation remains the preferred therapy for stroke prevention for most patients with AF and elevated stroke risk. However, for patients who are poor candidates for long-term oral anticoagulation (because of the propensity for bleeding or poor drug tolerance or adherence), the Watchman device provides an alternative.”
AF Related Major Ischemic Stroke

Anticoagulant Therapy Carries Risk of Intracerebral Hemorrhage or Death
### CHA2DS2-VASc: Scoring Systems to Assess Stroke Risks

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C  Congestive Heart Failure/LV Dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>H  Hypertension (SBP &gt; 160)</td>
<td>1</td>
</tr>
<tr>
<td>A1 Age ≥ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>D  Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S2 Prior Stroke, TIA, or Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>V  Vascular Disease (PAD, MI)</td>
<td>1</td>
</tr>
<tr>
<td>A  Age 65-74 Years</td>
<td>1</td>
</tr>
<tr>
<td>Sc Sec Category (Female)</td>
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</table>

<table>
<thead>
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<th>CHA2DS2-VASc Score</th>
<th>Annual % Stroke Risk</th>
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<td>0</td>
</tr>
<tr>
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</tr>
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<td>6</td>
<td>9.8</td>
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</table>


### HAS-BLED: Scoring Systems to Assess Bleeding Risks

<table>
<thead>
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<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H  Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A  Abnormal Renal/Liver Function (1 pt each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S  Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B  Bleeding History or Disposition</td>
<td>1</td>
</tr>
<tr>
<td>L  Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E  Elderly</td>
<td>1</td>
</tr>
<tr>
<td>D  Current Drugs (Medication) or Alcohol Use (1 pt each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HAS-BLED Score</th>
<th>Annual % Major Bleeding Risk</th>
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</thead>
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<td>5.8</td>
</tr>
<tr>
<td>4</td>
<td>8.9</td>
</tr>
<tr>
<td>5</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Lip. JACC. 2011; 57(2): 173-180
Bleeding Risk Compounds Over Patients’ Lifetime

![Graph showing annual and expected bleeding risk](image)

Antithrombotic Options for Atrial Fibrillation

- **Aspirin:**
  - Meta-analysis (8 trials, 4876 participants), reduced stroke by 22% (CI, 6% to 35%)
  - Major bleeding risk 0.23% / year

- **Warfarin:**
  - Meta-analysis (6 trials, 2900 participants), reduced stroke by 64% (95% CI, 49% to 74%)
  - Major bleeding risk ~ 1-6%

- **Aspirin and Plavix:**
  - Pooled analysis (5 studies involving 24,084 patients) reduced stroke vs. aspirin alone (p<0.05)
  - Increased risk of major bleeding (p<0.05)
Direct Oral Anticoagulants (DOACs)

- Compared to warfarin:
  - Dabigatran: lower ischemic stroke
  - Apixaban and edoxaban: lower hemorrhagic stroke and major bleeding
  - All DOACs: lower ICH
- Do not require monitoring
- Less drug to drug and drug to food interactions
- Maximum concentration in plasma within hours
- Short half-life
- Antidotes are now approved (idarucizumab and andexanet alfa)

- Bleeding complications!
- Compliance, adherence and dosing issues!
- Antidote cost!

Meta-Analysis of Efficacy and Safety of DOACs (Dabigatran, Rivaroxaban, Apixaban) vs. Warfarin in Patients with AF

Forest plot for (A) all-cause stroke and SE, (B) ischemic and unspecified stroke, and (C) hemorrhagic stroke, DOAC vs. warfarin in patients with AF
Meta-Analysis of Efficacy and Safety of DOACs (Dabigatran, Rivaroxaban, Apixaban) vs. Warfarin in Patients with AF

Forest plot for (A) all-cause stroke and SE, (B) ischemic and unspecified stroke, and (C) hemorrhagic stroke, DOAC vs. warfarin in patients with AF

Ruff CT et al. Lancet 2014; 383: 955-962
Meta-Analysis of Efficacy and Safety of DOACs (Dabigatran, Rivaroxaban, Apixaban) vs. Warfarin in Patients with AF

Forest plot for (A) major bleeding, (B) intracranial bleeding, and (C) GI bleeding, DOAC vs. warfarin in patients with AF.

Ruff CT et al. Lancet 2014; 383: 955-962
Meta-Analysis of Efficacy and Safety of DOACs (Dabigatran, Rivaroxaban, Apixaban) vs. Warfarin in Patients with AF

Forest plot for (A) major bleeding, (B) intracranial bleeding, and (C) GI bleeding, DOAC vs. warfarin in patients with AF.

Rates of Bleeding with DOACs

<table>
<thead>
<tr>
<th></th>
<th>Major Bleed (% / year)</th>
<th>ICH (% / year)</th>
<th>GI Bleed (% / year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (RE-LY)</td>
<td>3.11</td>
<td>0.30</td>
<td>1.51</td>
</tr>
<tr>
<td>Apixaban (ARISTOTLE)</td>
<td>2.13</td>
<td>0.33</td>
<td>0.76</td>
</tr>
<tr>
<td>Rivaroxaban (ROCKET-AF)</td>
<td>3.6</td>
<td>0.50</td>
<td>3.2</td>
</tr>
<tr>
<td>Edoxaban (ENGAGE AF-TIMI 48)</td>
<td>2.75</td>
<td>0.39</td>
<td>1.51</td>
</tr>
</tbody>
</table>
Hospitalization and Life Threatening Bleed Related to Anti-Xa Inhibitors

- Annual Hospitalization for Major Bleed: 117,000
- Annual Death Related to Major Bleed: 20,000

Truven Health Analytics, 12 months ending December 31, 2016 for Commercial, Medicare and Medicaid pts.

Skaistis J, et al. Plos One. 2015;10(9);e0137444.

All Cause and ICH Mortality

ROCKET AF Trial
- Rivaroxaban: 20%
- ICH-Related Mortality: 48%

ARISTOTE Trial
- Apixaban: 50%
- All-Cause Mortality: 50%

ACS and AF

- DAPT (aspirin plus P2Y12 inhibitor) prevents MACE after PCI for ACS or stable disease.
- Current debate regarding optimal duration of DAPT!
- Approximately 5-10% of patients undergoing PCI have AF.
- The CV benefits gained by using triple therapy could be offset by higher risk for bleeding.
- Withdrawal of aspirin might lead to higher rates of stent thrombosis and ischemic events.

Bleeding Complications
Dual (DOAC+P2Y12i) vs Triple (warfarin+P2Y12i+ASA)

<table>
<thead>
<tr>
<th>Study</th>
<th>CRNM or Major</th>
<th>Major bleeding</th>
<th>REDUA-PCI (Dabigatran)</th>
<th>CRNM or Major</th>
<th>Major bleeding</th>
<th>PIONEER-AF-PCI (Rivaroxaban)</th>
<th>CRNM or Major</th>
<th>Major bleeding</th>
<th>AGUSTUS (Apixaban)</th>
<th>CRNM or Major</th>
<th>Major bleeding</th>
<th>ENTRUST-AF-PCI (Edoxaban)</th>
<th>CRNM or Major</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dual%</td>
<td></td>
<td>20.2</td>
<td>5.6</td>
<td>26.9</td>
<td>26.7</td>
<td>2.1</td>
<td>3.3</td>
<td>10.5</td>
<td>3</td>
<td>14.7</td>
<td>17</td>
<td>6.7</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>Triple %</td>
<td></td>
<td>26.9</td>
<td>8.4</td>
<td>26.7</td>
<td>3.3</td>
<td>3.3</td>
<td>4.6</td>
<td>14.7</td>
<td>4.6</td>
<td>4.6</td>
<td>20</td>
<td>7.2</td>
<td>7.2</td>
</tr>
</tbody>
</table>
Decision Making!

Antithrombotic therapies have different indications and bleeding risk

DOACs have lower bleeding complications than warfarin in general

Combinations of antithrombotic therapies carry higher bleeding risk

Bleeding Complications: DOAC+P2Y12i < warfarin+P2Y12i+ASA

Summary

Sunset, Gaza City

Thank You!

Nedaa Skeik

Questions at the End?
Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention

Mario Goessl, MD PhD
Interventional Cardiology

Circulation
WHITE PAPER
Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention
A North American Perspective–2018 Update
Table 1. Summary of the PIONEER AF-PCI and RE-DUAL PCI Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Indication for PCI</th>
<th>Primary Safety End Point</th>
<th>Secondary Safety End Point</th>
<th>End Points</th>
<th>Treatment Arms and Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-DUAL PCI</td>
<td>AF with PCI and stem (92%, 82-84%)</td>
<td>CABG ≤30 mL/min No major bleed within 1 mo No stroke within 1 mo n=27/5</td>
<td>ACS, 50.5%</td>
<td>ST major or clinically relevant non-ST major myocardial infarction</td>
<td>Death, MI, stroke, SIC, or unplanned revascularization</td>
<td>Warfarin 110 mg twice daily and P2Y12 inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIONEER AF-PCI</td>
<td>AF with PCI and stem (92%, 88-91%)</td>
<td>CABG ≤30 mL/min No major bleed within 1 mo No Gb bleed within 12 mo No prior stroke or TIA n=27/5</td>
<td>ACS, 51.6%</td>
<td>Any clinically significant bleeding</td>
<td>CV death, MI, stroke</td>
<td>Warfarin with ASA and P2Y12 inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Circulation. 2018;138:527–536. DOI: 10.1161/CIRCULATIONAHA.118.034722

A North American Perspective–2018 Update

I. Pre-procedural Considerations
   - Define appropriateness of PCI procedure
   - Ischemic/thrombotic and bleeding risk stratification
   - Vascular access (i.e., radial)
   - Stent selection (i.e., new-generation DES)

II. Procedural Considerations
   - Close monitoring with re-assessment of risk profile
   - Recommend use of PPIs and avoid NSAIDs

III. Post-procedural Considerations

Antithrombotic Management

- OAC:
  - A NOAC should be preferred in most patients and used at established stroke prevention doses; lower doses are not recommended unless specifically tested.
  - If VKA is chosen, maintain INR at the lower end of the therapeutic range (i.e., 2.0–2.5).
  - Maintain OAC life-long.

- APT:
  - Aspirin in the peri-PCI phase and continued through hospital discharge.
  - Clopidogrel is the P2Y12 inhibitor of choice; ticagrelor may be a reasonable alternative in high ischemic and low bleeding risk patients; avoid prasugrel.
  - Discontinue SAPT at 1 year in most patients; consider earlier SAPT discontinuation (e.g., 6 months) in patients at low ischemic or high bleeding risks and prolonging SAPT (≥1 year) for select patients with high ischemic and low bleeding risks.

Strategy (double vs triple therapy):
- A double-therapy regimen (OAC plus P2Y12 inhibitor) immediately after hospital discharge for most patients.
- Consider triple-therapy by extending aspirin use for a limited period of time (e.g., 1 month) only in patients at high ischemic and low bleeding risks.


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Any Acute Coronary Syndrome

PCI with
- $\geq 3$ stents implanted
- $\geq 3$ lesions treated, and/or
- $3$ coronary vessels treated; and/or
- bifurcation with $2$ stents implanted
- total stent length $>60$ mm, and/or
- treatment of a chronic total occlusion (CTO)

What is high ischemic risk?

What is high bleeding risk?

Precise DAPT

*very low risk:* score $\leq 10$; *low risk:* score $11$ to $17$; *moderate risk:* score $18$ to $24$; and *high risk:* score $\geq 25$)
The Risk / Benefit Tradeoff of Antithrombotic Therapy in Patients with Atrial Fibrillation Early and Late After an Acute Coronary Syndrome or Percutaneous Coronary Intervention: Insights from AUGUSTUS

Severe Bleeding and Ischemic Outcomes
Randomization to 30 Days
### Severe Bleeding and Ischemic Outcomes
30 Days to 6 Months

#### Fatal, ICH, Major Bleeding

<table>
<thead>
<tr>
<th>Days since Start of Randomization</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1.0%</td>
<td>0.5%</td>
</tr>
<tr>
<td>60</td>
<td>2.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>90</td>
<td>3.0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>120</td>
<td>4.0%</td>
<td>3.5%</td>
</tr>
<tr>
<td>150</td>
<td>5.0%</td>
<td>4.5%</td>
</tr>
<tr>
<td>180</td>
<td>6.0%</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

#### CV Death, Stroke, MI, Stent Thrombosis

<table>
<thead>
<tr>
<th>Days since Start of Randomization</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>0.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td>60</td>
<td>1.0%</td>
<td>0.5%</td>
</tr>
<tr>
<td>90</td>
<td>1.5%</td>
<td>0.7%</td>
</tr>
<tr>
<td>120</td>
<td>2.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>150</td>
<td>2.5%</td>
<td>1.3%</td>
</tr>
<tr>
<td>180</td>
<td>3.0%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

---

#### Time from PCI

<table>
<thead>
<tr>
<th>Per-PCI</th>
<th>Default strategy</th>
<th>Patients at high ischemic/thrombotic and low bleeding risks</th>
<th>Patients at low ischemic/thrombotic or high bleeding risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>Triple Therapy (OAC + DAPT)</td>
<td>Triple Therapy up to 1 month (OAC + DAPT)</td>
<td>Double Therapy up to 6 months (OAC + SAPT)</td>
</tr>
<tr>
<td>3 months</td>
<td>Double Therapy up to 12 months (OAC + DAPT)</td>
<td>Double Therapy up to 12 months (OAC + SAPT)</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 months</td>
<td></td>
<td></td>
<td>OAC</td>
</tr>
</tbody>
</table>

OAC: prefer a NOAC over VKA if no contraindications
SAPT: prefer a P2Y_12 inhibitor over aspirin
Clopidogrel is the P2Y_12 inhibitor of choice; ticagrelor may be considered in patients at high ischemic/thrombotic and low bleeding risks; avoid prasugrel
Consider SAPT in addition to OAC after >12 mo; only in select patients at high ischemic/thrombotic and low bleeding risks

---

Polymer-based or Polymer-free Stents in Patients at High Bleeding Risk


CONCLUSIONS
Among patients at high bleeding risk who received 1 month of dual antiplatelet therapy after PCI, use of polymer-based zotarolimus-eluting stents was noninferior to use of polymer-free drug-coated stents with regard to safety and effectiveness composite outcomes. (Funded by Medtronic; ONYX ONE ClinicalTrials.gov number, NCT03344653.)
Summary

- Double vs Triple antithrombotic therapy is an individualized decision but
  - **DON’T** use DAPT + OAC/NOAC >1 mo post PCI
  - **DON’T** use Prasugrel

- **ONYX ONE** shows that even shorter (1 mo) DAPT may be possible
Thank you

We are happy to take your questions now …

---

**Table 3. Summary of Randomized Trials of NOACs Compared With Warfarin Therapy in Patients With AF, With Relative Risk Reductions of Major Clinical Events**

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Dalteparin</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial acronym</td>
<td>RE-LY</td>
<td>ROCHE-OF</td>
<td>ARISTOLE</td>
<td>ENGAGE-AF</td>
</tr>
<tr>
<td>CHADS2 score (mean)</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>TTR (median), %</td>
<td>67</td>
<td>56</td>
<td>66</td>
<td>68</td>
</tr>
<tr>
<td>Approved dose</td>
<td>150 mg twice daily*</td>
<td>110 mg twice daily*</td>
<td>20 mg once daily (15 mg once daily in selected patients†)</td>
<td>5 mg twice daily (2.5 mg twice daily in selected patients†)</td>
</tr>
<tr>
<td>Stroke or SE, HR (95% CI)</td>
<td>0.66 (0.53-0.82)</td>
<td>0.91 (0.74-1.11)</td>
<td>0.88 (0.74-1.03)</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td>Ischemic stroke, HR (95% CI)</td>
<td>0.76 (0.60-0.96)</td>
<td>1.11 (0.89-1.40)</td>
<td>0.94 (0.75-1.17)</td>
<td>0.92 (0.74-1.13)</td>
</tr>
<tr>
<td>Hemorrhagic stroke, HR (95% CI)</td>
<td>0.25 (0.14-0.49)</td>
<td>0.31 (0.17-0.56)</td>
<td>0.59 (0.27-0.93)</td>
<td>0.51 (0.35-0.75)</td>
</tr>
<tr>
<td>All-cause mortality, HR (95% CI)</td>
<td>0.88 (0.77-1.00)</td>
<td>0.91 (0.80-1.03)</td>
<td>0.85 (0.70-1.02)</td>
<td>0.89 (0.80-0.998)</td>
</tr>
<tr>
<td>Major bleed, HR (95% CI)</td>
<td>0.93 (0.81-1.07)</td>
<td>0.80 (0.69-0.93)</td>
<td>1.04 (0.90-1.20)</td>
<td>0.69 (0.50-0.90)</td>
</tr>
<tr>
<td>GI bleeding, HR (95% CI)</td>
<td>1.50 (1.19-1.88)</td>
<td>1.10 (0.86-1.41)</td>
<td>1.39 (1.19-1.61)</td>
<td>0.89 (0.70-1.15)</td>
</tr>
</tbody>
</table>

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