ANSWERING YOUR QUESTIONS ON ANTICOAGULATION IN ATRIAL FIBRILLATION: TREATMENT SELECTION AND COMPLEX CASES

Participant Handout of Some Key Points*

*This handout is a supplemental resource to an educational video activity released on Medscape in October 2014. Please access the activity on Medscape for complete information and content.
SECTION 1: INTRODUCTION

- Atrial fibrillation (AF) is prevalent and projected to increase
- Patients with AF are undertreated, with estimates of about 60% of patients with AF receiving anticoagulation


SECTION 2: OVERVIEW: NEW GUIDELINES AND RISK/BENEFIT

WHAT ARE SOME KEY CHANGES IN AND IMPLICATIONS OF THE NEW AF GUIDELINES?

- Classification of AF: paroxysmal, persistent, longstanding persistent, permanent
- Greater number of patients who should be treated with long-term anticoagulation
- Importance of engaging the patient in shared decision making regarding therapy
- CHA2DS2-VASc scoring system recommended (over CHADS2) to assess stroke risk

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
</tr>
<tr>
<td>A2</td>
<td>Age 65-74</td>
</tr>
<tr>
<td></td>
<td>Age ≥75</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>S2</td>
<td>Prior stroke or TIA</td>
</tr>
<tr>
<td>VA</td>
<td>Vascular disease (previous MI, arterial disease, or aortic plaque)</td>
</tr>
<tr>
<td>Sc</td>
<td>Sex category — female sex</td>
</tr>
</tbody>
</table>

For more on CHA2DS2-VASc, see here.

HOW DO DOCTORS AND PATIENTS DIFFER IN THEIR VIEWS OF RISK AND BENEFIT OF ANTICOAGULATION?

- Patients are undereducated regarding AF and available treatments
- Doctors should consider and assess patients’ health literacy
  - Use visual aids and multimedia education (see figure as example)
  - Use plain language and avoid jargon and terminology
  - Make sure patients understand instructions and plan for treatment
  - Utilize the teach back technique — ask patients to explain in their own words what they understand about treatment plan
- Patients will understand their risk of stroke over time if given enough information
- Patients with AF at high risk for stroke placed more value on the avoidance of stroke and less value on the avoidance of bleeding, compared with physicians who treat patients with AF
- Patients should be given adequate health information, in a form they can understand, so they can reach shared decisions about anticoagulation with their healthcare provider


Figure source: DearPharmacist. Atrial fibrillation screening service. Available at: https://dearpharmacist.info/knowledge-library/atrial-fibrillation-screening-service/?page_name=sre. Accessed October 6, 2014.

SECTION 3: SELECTING THERAPY

IS THERE STILL A ROLE FOR ASPIRIN IN STROKE PREVENTION FOR PATIENTS WITH AF?

- NOACs = novel (or new) oral anticoagulants
  - FDA-approved: apixaban (Eliquis), dabigatran (Pradaxa), rivaroxaban (Xarelto)
  - Currently not FDA-approved: edoxaban (Savaysa)
- Antiplatelets and aspirin are less effective at preventing stroke in patients with AF than anticoagulants
- In new guidelines, the only place for aspirin is as a Class IIb recommendation for patients with CHA$_2$DS$_2$-VASc score of 1: no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered. (Level of Evidence: C)
AHA/ACC/HRS GUIDELINES 2014

Antithrombotic therapy should be individualized based on shared decision making, discussion of risks of stroke and bleeding, and patient preferences (Class I, Level C)

<table>
<thead>
<tr>
<th>RISK CATEGORY</th>
<th>RECOMMENDED THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonvalvular atrial fibrillation with CHA₂DS₂-VASc=0</td>
<td>It is reasonable to omit antithrombotic therapy (Level of evidence: B)</td>
</tr>
<tr>
<td>Nonvalvular atrial fibrillation with CHA₂DS₂-VASc=1</td>
<td>May be considered: No therapy Oral anticoagulant or aspirin (Level of evidence: C)</td>
</tr>
<tr>
<td>Prior stroke, TIA, or CHA₂DS₂-VASc ≥2</td>
<td>Warfarin (Level of evidence: A) Dabigatran, rivaroxaban, or apixaban (Level of evidence: B)</td>
</tr>
</tbody>
</table>


HOW TO DECIDE BETWEEN WARFARIN AND THE NOACS?

- Patient doing well on warfarin: no compelling medical reason to switch to NOAC
- Patient not doing well on warfarin despite being compliant: consider switching to NOAC
- New patients with AF: consider NOACs due to convenience and other potential advantages
- NOAC trials have consistently shown reductions in ICH

## HOW TO DECIDE AMONG THE NOACs?

- **Access**: which agent(s) is covered by patient’s insurance?
- **Cost**: which agent does the health system or insurance cover at a cost reduction?
- **Familiarity**: which agent is the physician or health system most familiar with?
- **Some discriminating factors**
  - Dabigatran: use within certain period of time after opening manufacturer’s packaging (see package insert)
  - Rivaroxaban: take with meal for better absorption
  - See [this medication chart](#) for more information

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>VKORC1</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>T (max)</strong></td>
<td>72-96 hours</td>
<td>2 hours</td>
<td>2.5-4 hours</td>
<td>3 hours</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40 hours</td>
<td>14-17 hours</td>
<td>5-9 hours healthy, 9-13 hours elderly</td>
<td>8-15 hours</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Every 4 weeks or PRN</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Cytochrome P450</td>
<td>80% renal, 20% fecal</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td>PT/INR</td>
<td>Ecarin clotting time*, thrombin time*</td>
<td>Anti-Xa activity*</td>
<td>Anti-Xa activity*</td>
</tr>
</tbody>
</table>

*Not validated/approved for this use.

**LIMITATIONS/CONCERNS WITH AVAILABLE ANTICOAGULANTS**

<table>
<thead>
<tr>
<th>Continuous monitoring</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin overlap often necessary</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited experience with reversal</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Accumulation in renal dysfunction</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of experience treating bleeding</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lack of experience in elderly, obese, African-Americans</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cost</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>


**ARE THERE ANY TESTS THAT MEASURE THE EFFECT OF NOACs?**
- Measure effect of dabigatran using dilute thrombin time or thrombin time
- Measure effect of anti-Xa inhibitors (rivaroxaban, apixaban) using anti-Xa activity test


**HOW TO MITIGATE BLEEDING RISK IN PATIENTS ON LONG-TERM THERAPY**
- Know about use of other medications and alcohol
- Ensure adequate blood pressure control
- Check renal function at least yearly in patients with chronic kidney disease (CKD) stage 3
- Educate patients on importance of telling all healthcare providers of their anticoagulant use
- See later section on aspirin

**WHAT RACIAL DISPARITIES EXIST IN AF, AND WILL THE NOACs AFFECT THESE DISPARITIES?**
- Available data are limited to subgroup analyses and observational cohort or retrospective studies
- AF appears to be less prevalent in racial minority elders
- Black patients with AF are less likely to receive aggressive treatments like ablation and cardioversion
- Racial minorities with AF, especially black patients, appear to be at greater risk for warfarin-related ICH
- Currently, there is no reason to think anticoagulant therapy effects will be different in a particular racial or ethnic group


**WHAT CAN BE DONE TO ADDRESS THE COST OF THE NOACs?**
- Know insurance plan requirements, especially Medicare Part D, regarding prior authorization
- Determine whether Patient Assistance Programs are available from manufacturers
- Assess whether cost effectiveness per quality-adjusted life year (QALY) is within the range of what is paid for in other conditions

Please access the activity at www.medscape.org/viewarticle/833299 for complete information and content.
SECTION 4: HANDLING COMPLEX PATIENTS

A PATIENT WITH RENAL INSUFFICIENCY OR ESRD
- All NOACs are eliminated by the kidneys, to some extent
- Registration trials did not include patients with CrCl <30 mL/min
- Drug insert dosing for these patients is based on pharmacokinetic modeling; some physicians are reluctant to prescribe
- Patients with advanced kidney disease have a higher risk of major anticoagulant-related bleeding
- New approaches to the atrial appendage are needed (e.g., closure device, surgical ligation)

A PATIENT WHO IS OBESE OR UNDERWEIGHT
- NOAC trials included few patients who were >120 kg or <50 kg
- Physicians may prefer warfarin due to ability to monitor in populations at weight extremes

A PATIENT ON ASPIRIN AND AT RISK OF MI
- Adding antiplatelet including aspirin to background anticoagulant therapy substantially increases one’s risk of major hemorrhage
- If annual risk of stroke is much greater than risk of MI and patient is on dual antiplatelet therapy, may be better to prescribe anticoagulant and drop aspirin
- Warfarin and possibly some NOACs likely offer some protection against cardiac events

A PATIENT ON NOACS WITH A MAJOR BLEED: ARE THERE EVIDENCE-BASED REVERSAL STRATEGIES?
- No great clinical outcome-based evidence exists
- Bleeding is infrequent when NOACs are used in properly selected patients
- In the phase III clinical trials, fatal bleeding events were less common in patients on NOACs
- In cases of life threatening, serious bleeding, IV-factor prothrombin complex concentrates (PCCs) might reverse the effect of NOACs

A PATIENT ON A NOAC WHO WILL HAVE A PROCEDURE
- Low bleed risk (single tooth extractions, cutaneous procedures, carpal tunnel repair): no need to stop NOAC
- Medium or high bleed risk (thoracic surgery, renal biopsy, liver biopsy, abdominal procedures):
  - If normal renal function, stop NOAC 2 days before surgery (if impaired, stop earlier)
  - If urgent situation, could probably wait less than 2 days
  - Postprocedure, restart NOAC once hemostasis achieved
- Consider bridging with parenteral agent in special circumstances (e.g., a patient who had GI surgery, is NPO for several days, at high stroke risk, and in AF)

A PATIENT WITH A STENT ON DUAL ANTIPLATELET THERAPY (DAPT)
- Must be decided on a case by case basis
- Current guidelines recommend 1 year DAPT for drug-eluting stents (DES) (latest drug-eluting stents may require less)
- Decision about when to stop DAPT and whether an anticoagulant should be added should be made on individual basis
A PATIENT WITH A STEMI AND ALREADY ON ANTICOAGULANT

- Stop oral anticoagulant and use parenteral anticoagulants (unfractionated heparin or bivalirudin for more rapid response)
- If patient has a very high INR, one could carefully consider simultaneously reversing the effect of warfarin (with plasma or vitamin K) while initiating parenteral anticoagulant
- Resume oral anticoagulation soon, but eventually cut back on DAPT (studies reported since the video recording are suggesting this)
- Choose bare metal stent to allow for stopping DAPT sooner

A PATIENT WITH MALIGNANCY

- Potential drug interactions possible during chemotherapy
- Increased clot risk since cancer is a very prothrombotic condition
- Increased bleed risk due to procedures or to cancer treatments that suppress hematopoiesis and create periods of thrombocytopenia

A GERIATRIC PATIENT

- Decision making is more complicated due to renal/creatinine clearance, overall comorbidities, and polypharmacy
- Rate vs rhythm control decision is more complex
- Risk/benefit ratio becomes more difficult to calculate, but by and large, the benefit of anticoagulation will likely outweigh the risk

SECTION 5: TOOLS AND TECHNOLOGIES

WHAT ARE YOUR FAVORITE TOOLS AND RESOURCES RELATED TO AF AND ANTICOAGULATION?

- TEAManticoag.com
- ACC Anticoag Evaluator app
- Medscape
- Cardiosmart.org
- Calculators and drug interaction protocols built into EMRs

WHAT IS THE LATEST ON WEARABLE TECHNOLOGIES AND DIAGNOSING SUBCLINICAL AF?

- Patients are using more consumer products like pulse oximeters and smart phone applications to track their pulse
- More patients have implanted monitors such as pacemakers, implanted cardiac defibrillators, and implantable loop recorders
- Subclinical AF is common, and it can be associated with cryptogenic stroke


IS AF A REVERSIBLE DISEASE?

- AF is caused by some factors that are potentially reversible (obesity, uncontrolled hypertension, hypertensive heart disease, sleep apnea)
- Don’t neglect the opportunity to reverse these factors
SECTION 6: CLOSING COMMENTS

- **DR. GARCIA:** In patients with AF, anticoagulant therapy should be the default position from which we start

- **DR. DEFRANCO:** The best quality care results from shared decision making centered on the patient’s preferences, values, and goals; when patients have a clear understanding of the risk/benefit ratio of anticoagulation for the prevention of stroke, most patients will choose anticoagulation

- **DR. FLORES:** Consider health literacy, culture, language, and validated tools for patient communication to enhance understanding that allows patients to be a part of shared decision making

GENERIC/TRADE NAME IDENTIFICATION GUIDE FOR DRUGS MENTIONED IN ACTIVITY

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>TRADE NAME*</th>
</tr>
</thead>
<tbody>
<tr>
<td>apixabana</td>
<td>Eliquis®</td>
</tr>
<tr>
<td>aspirin (ASA)</td>
<td>various</td>
</tr>
<tr>
<td>clopidogrel</td>
<td>Plavix®</td>
</tr>
<tr>
<td>dabigatran etexilate</td>
<td>Pradaxa®</td>
</tr>
<tr>
<td>edoxaban</td>
<td>Savaysa™ (not approved)</td>
</tr>
<tr>
<td>enoxaparin</td>
<td>Lovenox®</td>
</tr>
<tr>
<td>heparin</td>
<td>various</td>
</tr>
<tr>
<td>prasugrel</td>
<td>Effient®</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>Xarelto®</td>
</tr>
<tr>
<td>ticagrelor</td>
<td>Brilinta®</td>
</tr>
<tr>
<td>warfarin</td>
<td>Coumadin®, Jantoven®</td>
</tr>
</tbody>
</table>

*Trade names are used for identification purposes only and do not imply endorsement.