Direct oral anticoagulants in patients with atrial fibrillation undergoing percutaneous coronary intervention – PIONEERING the way for a new paradigm?

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Learning Objectives:
1. Describe the significance and management of concomitant atrial fibrillation and acute coronary syndromes requiring percutaneous coronary intervention
2. Provide a basic overview of atrial fibrillation, acute coronary syndromes, percutaneous coronary intervention, and direct oral anticoagulants
3. Discuss the literature pertaining to the use of direct oral anticoagulants in patients with atrial fibrillation undergoing percutaneous coronary intervention
4. Recommend optimal antithrombotic regimens in patients with atrial fibrillation undergoing percutaneous coronary intervention
Acute Coronary Syndromes Requiring Percutaneous Coronary Intervention in Patients with Atrial Fibrillation

I. Significance
   a. Atrial fibrillation (AF) – most common arrhythmia, affecting approximately 2.7-6.1 million Americans (~1-2% of the general population)\textsuperscript{1,2}
      i. Expected to double by 2030
      ii. Contributes significantly to mortality
         1) Underlying cause of death on ~21,000 death certificates in United States (US) in 2013
         2) High risk of death in first four months after diagnosis
         3) Many fatal complications: non-cardiovascular (CV) death, sudden cardiac death, progressive heart failure (HF), and stroke
   b. Acute coronary syndromes (ACS) – acute manifestations of coronary heart disease (CHD), which affect an estimated 15.5 million Americans over age 20\textsuperscript{1,3}
      i. Estimated 18% increase by 2030
      ii. Responsible for greater than 1 million hospitalizations annually in the US – approximately ~660,000 Americans with a new event and ~305,000 with recurrent events
      iii. Most common cause of CV disease death
          1) Decreased mortality in the last 10 years due to:
             a) Primary and secondary prevention
             b) Initial treatment for ACS events or HF
             c) Coronary artery revascularization
             d) Shift in the incidence of different ACS event types

II. Overlap
   a. 20-30% of patients with AF have concomitant CHD\textsuperscript{4}
      i. Incidence of both AF and ACS increases with age\textsuperscript{1,2,4}
         1) Average age of patients with AF: 66.8 years for men and 74.6 years for women
         2) Average age of patients with ACS: 65.1 years for men and 72 years for women
      ii. AF associated with increased mortality in patients with myocardial infarctions (MI)\textsuperscript{1,2}

III. Management
   a. Antithrombotic therapy is a core component of management of both AF and ACS after revascularization with percutaneous coronary intervention (PCI)\textsuperscript{4}
      i. Purposes of antithrombotic therapy
         1) AF: prevent cerebrovascular ischemia or systemic embolism\textsuperscript{2,4}
         2) ACS post-PCI: prevent recurrence of coronary ischemic events and stent thrombosis\textsuperscript{4}
   b. Triple Therapy: dual antiplatelet therapy (DAPT) + oral anticoagulant\textsuperscript{4}
      i. Guiding principles
         1) Anticoagulant used to decrease risk of stroke or thromboembolic events in AF
         2) DAPT used to decrease coronary ischemia and thrombosis after PCI for ACS
            a) DAPT = aspirin + P2Y\textsubscript{12} inhibitor
            b) DAPT + anticoagulant – 2-3x increased risk of bleeding complications\textsuperscript{4,5}
      ii. Historical standard of care for triple therapy: warfarin + clopidogrel + aspirin\textsuperscript{4}
      iii. Direct oral anticoagulants (DOACs) have evidence and indications for use in nonvalvular AF\textsuperscript{6-10}
          1) Until recently, relatively little literature about the use of DOACs in AF after PCI
          2) Guideline recommendations regarding use of DOACs in patients with AF undergoing PCI are inconsistent
c. Obstacle and objective of antithrombotic therapy: balance risk of clot with risk of bleed

![Thrombosis and Bleeding Diagram]

<table>
<thead>
<tr>
<th>Thrombosis</th>
<th>Bleeding</th>
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<tr>
<td>Systemic Embolism</td>
<td>Major Bleeding</td>
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<tr>
<td>Stent Thrombosis</td>
<td>Minor Bleeding</td>
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d. Guideline recommendations:

<table>
<thead>
<tr>
<th>Table 1: Summary of Various Guideline Recommendations for Antithrombotic Therapy in Patients with AF Undergoing PCI²,⁵,¹¹-¹³</th>
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<tbody>
<tr>
<td><strong>Antithrombotic therapy</strong></td>
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<td><strong>Antiplatelet Agents</strong></td>
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<td><strong>Stent Type</strong></td>
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<td><strong>Duration</strong></td>
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Proposed DOAC-based strategy\textsuperscript{14}

i. Rationale
   1) DOACs have lower intracranial hemorrhage risk and noninferior to lower risk of non-gastrointestinal (GI) major bleeding vs. warfarin
   2) Clopidogrel – key to prevention of stent thrombosis and has lower bleed risk than newer P2Y\textsubscript{12} inhibitors
   3) Stopping aspirin does not appear to increase risk of stent thrombosis

ii. Algorithm:
   1) 0-1 months: aspirin + clopidogrel + DOAC
   2) 1-6 months: clopidogrel + DOAC
   3) 6+ months: DOAC

iii. Use lower dosage ranges than approved for clinical use

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### Atrial Fibrillation

I. Definition & Classifications\textsuperscript{2}
   a. Type of supraventricular tachycardia characterized by rapid atrial rate, disorganized atrial activation, and irregularly irregular pulse
   b. Types:
      i. Valvular AF – associated with mechanical or bioprosthetic heart valve, mitral valve stenosis, or mitral valve repair
      ii. Nonvalvular AF (NVAF) – absence of above valvular complications

II. Pathophysiology\textsuperscript{2}
   a. Mechanisms
      i. Atrial structural abnormalities – extracardiac factors, oxidative stress, tachycardic remodeling, genetics, and renin-angiotensin-aldosterone system (RAAS) activation
      ii. Atrial electrical abnormalities – RAAS activation, atrial tachycardic remodeling, genetics, and autonomic nervous system

I. Presentation\textsuperscript{3}
   a. Symptoms
      i. Rapid heartbeat, palpitations
      ii. Worsening HF symptoms – dyspnea or fatigue
      iii. Asymptomatic
   b. Signs
      i. Irregularly irregular rhythm without P waves – ventricular rate of 120-180 beats per minute

III. Risk factors & Complications
   a. Predictors of new onset AF\textsuperscript{1, 2}
      i. Patient factors – advanced age, greater height and body mass index, genetic variants, family history, moderate to heavy alcohol use, and smoking
      ii. CV factors – left ventricular hypertrophy, left atrial enlargement, hypertension, and CV disease including CHD, HF, and valvular heart disease
      iii. Other factors – hyperthyroidism, chronic kidney disease (CKD), diabetes
b. Complications
   i. Self-perpetuating arrhythmia
   ii. Ischemic stroke and other thromboembolic events
   iii. Increased risk of MI and HF

IV. Management
   a. Antiarrhythmic Therapy – refer to guidelines for acute management, including discussion of rate 
      vs. rhythm control strategies
   b. Prevention of Thromboembolism
      i. Individualized based on risk of stroke and bleeding
         1) Stroke risk assessed by CHA2DS2-VASc score (appendix A)
            a) Score of 0 – reasonable to omit oral antithrombotic medications
            b) Score of 1 – consider antiplatelet therapy, oral anticoagulant, or aspirin
            c) Score ≥ 2 – anticoagulant recommended
         2) Bleed risk assessed by HAS-BLED score (appendix A)
            a) Score ≥ 3 – “high risk” for bleeding
      ii. Vitamin K antagonist
         1) Historical standard of care – has the most evidence and a reversal agent
         2) Limitations: genomics, interactions, monitoring, and narrow therapeutic index
      iii. DOACs
         1) Four approved for NVAF (appendix B)
         2) Increased use due to evidence of efficacy in reducing stroke and systemic embolism 
            (SSE), as well as noninferior or lower risk of bleeding
         3) More predictable anticoagulation and no INR monitoring
         4) Limitations: only one has reversal agent and limited evidence with renal dysfunction

Table 2. Summary of Atrial Fibrillation Guideline Recommendations

<table>
<thead>
<tr>
<th>Valvular AF</th>
<th>Warfarin recommended anticoagulant</th>
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<tbody>
<tr>
<td>NVAF</td>
<td>Patients with prior stroke or transient ischemic attack (TIA) or CHA2DS2-VASc score ≥ 2 – warfarin, dabigatran, rivaroxaban, and edoxaban all options</td>
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<tr>
<td></td>
<td>• 2016 European Society of Cardiology guidelines recommend DOACs over warfarin</td>
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<tr>
<td></td>
<td>• 2012 CHEST guidelines suggest dabigatran rather than warfarin based on individual patient factors and preferences</td>
</tr>
<tr>
<td></td>
<td>• DOAC recommended in patients unable to maintain therapeutic INR on warfarin</td>
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<td></td>
<td>• Selection based on renal function</td>
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<tr>
<td></td>
<td>o Moderate to severe CKD – may consider reduced doses of DOACs (no established safety and efficacy), or use warfarin</td>
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<tr>
<td></td>
<td>o End-stage CKD or dialysis – warfarin recommended</td>
</tr>
</tbody>
</table>

*Dabigatran only DOAC approved for NVAF at time of publication
**Reassessed when clinically indicated and at least annually when DOACs selected
Direct Oral Anticoagulants

![Clotting Cascade with Oral Anticoagulant Targets](http://www.nature.com/nrcardio/journal/v10/n7/fig_tab/nrcardio.2013.73_F1.html?foxtrotcallback=true)

**Table 3: Overview of DOACs Approved for NVAF**

<table>
<thead>
<tr>
<th>Name (Brand)</th>
<th>Approved Doses</th>
<th>Mechanism of Action</th>
<th>Monitoring</th>
<th>Adjustments for Renal Function</th>
<th>Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apixaban (Eliquis®)</strong></td>
<td>5 mg BID or 2.5 mg BID if any 2: age ≥ 80, weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL</td>
<td>Factor Xa inhibitor</td>
<td>Renal and hepatic function, bleeding</td>
<td>Avoid use with CrCl &lt;25 mL/min</td>
<td>No specific reversal agent Not dialyzable</td>
</tr>
<tr>
<td><strong>Dabigatran (Pradaxa®)</strong></td>
<td>150 mg BID</td>
<td>Direct thrombin inhibitor</td>
<td>Complete blood count (CBC), renal function, bleeding</td>
<td>CrCl 15-30 mL/min: 75 mg BID Per CHEST: contraindicated in CrCl ≤ 30 mL/min</td>
<td>Idarucizumab (Praxbind®) Dialysis removes ~57% over 4 hours</td>
</tr>
<tr>
<td><strong>Edoxaban (Savaysa®)</strong></td>
<td>60 mg daily</td>
<td>Factor Xa inhibitor</td>
<td>Bleeding, renal function prior to initiation</td>
<td>Do not use if CrCl &gt; 95 mL/min Dose reduce if CrCl 15-50 mL/min: 30 mg daily Not recommended: CrCl &lt; 15 mL/min</td>
<td>No specific reversal agent Not dialyzable</td>
</tr>
<tr>
<td><strong>Rivaroxaban (Xarelto®)</strong></td>
<td>20 mg daily with evening meal</td>
<td>Factor Xa inhibitor</td>
<td>CBC, renal and hepatic function</td>
<td>Dose reduce if CrCl 15-50 mL/min: 15 mg daily Avoid with CrCl &lt; 15-30 mL/min</td>
<td>No specific reversal agent Not dialyzable</td>
</tr>
</tbody>
</table>
Acute Coronary Syndromes

I. Definitions & Classification
   a. ACS – acute manifestations of CHD classified according to changes seen on electrocardiogram (ECG) and presence or absence of biomarkers for cardiac necrosis
      i. ST segment elevation myocardial infarction (STEMI) – ischemic injury to full thickness of myocardial wall
         1) Symptoms of myocardial ischemia
         2) ST segment elevation on ECG
         3) Elevated troponin T or I or creatinine kinase-myocardial band (CK-MB)
      ii. Non-ST segment elevation myocardial infarction (NSTEMI) – injury to subendocardial myocardium, usually smaller than STEMI
         1) Symptoms of myocardial injury
         2) Elevated troponin T or I or CK-MB
      iii. Unstable angina (UA) – ischemia that does not produce tissue injury
         1) Symptoms of myocardial ischemia

II. Etiology & Pathophysiology
   a. Disruption of atherosclerotic plaque is the cause of ACS in 90% of patients
      1) STEMI – large plaque fissures → fixed, persistent thrombus → abrupt cessation of myocardial perfusion → transmural myocardium necrosis
      2) NSTEMI – plaque damage → persistent thrombotic occlusion without complete cessation of myocardial perfusion
      3) UA – nonocclusive plaque thrombus, vasoconstriction, mechanical obstruction, inflammation/infection, or secondary UA

III. Presentation
   a. Substernal chest pain or pressure, may radiate to jaw, neck, left arm or shoulder
   b. May be accompanied by nausea, vomiting, diaphoresis, fatigue, or shortness of breath

IV. Risk Factors & Complications
   a. Risk factors: smoking, hypertension, diabetes, hyperlipidemia, obesity, lack of physical activity, family history of heart disease, and prior atherosclerotic ischemic stroke
   b. Complications
      i. Ischemic – angina, reinfarction, or infarct extension
      ii. Mechanical – cardiogenic shock, HF, valve dysfunction, aneurysm, myocardium rupture
      iii. Arrhythmic – node dysfunction, atrial or ventricular arrhythmias
      iv. Embolic – stroke and systemic embolism
      v. Inflammatory – pericarditis

V. Management
   a. Choice of reperfusion therapy by ACS type
      i. STEMI
         1) Primary PCI – treatment of choice within 12 hours of symptom onset and 90-120 minutes of first medical contact
         2) PCI reasonable with ongoing ischemia 12-24 hours after symptom onset
      ii. UA/NSTEMI
1) Choice of therapy based on risk assessment\textsuperscript{21,22}
2) Primary PCI – refractory angina, hemodynamic or electrical instability, absence of major comorbidities or contraindications, and higher risk patients\textsuperscript{21}

b. Pharmacotherapy\textsuperscript{5,20,22}
   i. Aspirin given immediately and continued indefinitely, clopidogrel if patient aspirin intolerant
   ii. Parenteral anticoagulation regardless of treatment strategy
   iii. DAPT started upon presentation in patients in whom early invasive strategy selected

1) P2Y\textsubscript{12} inhibitor loading dose + aspirin loading dose \rightarrow maintenance doses
2) Reasonable to use ticagrelor over clopidogrel, and prasugrel reasonable over clopidogrel in patients at low bleed risk without history of stroke or TIA

Percutaneous Coronary Intervention

I. PCI & Stents
   a. PCI goal: open narrowed or blocked coronary arteries due to atherosclerotic plaques to restore blood flow to the heart, relieve symptoms, and reduce ischemia\textsuperscript{23,24}
      i. Performed during cardiac catheterization
      ii. Tube with balloon or another device inserted into vessel, deployed, and stent placed
   b. Stenting – insertion of a metallic mesh tube to keep the artery open
      i. Stent types: BMS and DES\textsuperscript{24}
      ii. Potential complications: bleeding, vessel damage, thrombosis, arrhythmias, and stroke

II. DAPT Duration Debate – Guideline Recommendations
   a. Older guidelines recommend P2Y\textsubscript{12} inhibitor for 12 months\textsuperscript{21}
      i. \leq 12 months BMS, at least 30 days
      ii. \geq 12 months DES
   b. Newer guidelines provide guidance for shortening or extending DAPT duration\textsuperscript{5}
      i. Shorter duration in patients with higher risk of bleeding
      ii. Longer duration in patients with higher risk of clot and ischemia
   c. In patients on DAPT with high bleed risk, such as those on oral anticoagulation, reasonable to discontinue P2Y\textsubscript{12} inhibitor after 6 months\textsuperscript{5}

Clinical Controversy: DOACs in Patients with AF Undergoing PCI

Past Literature Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban – ARISTOTLE\textsuperscript{25}</td>
<td>Analyzed apixaban vs. warfarin with concomitant aspirin in patients with AF</td>
<td>Higher major bleed rates overall, but even with concomitant aspirin, apixaban showed significantly less bleeding and retained beneficial effects on SSE vs. warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Aspirin + apixaban vs. warfarin – nonsignificantly higher MI</td>
</tr>
<tr>
<td>Dabigatran – RE-LY\textsuperscript{26}</td>
<td>Assessed efficacy and safety of dabigatran vs. warfarin in patients who did and did not</td>
<td>Antiplatelet therapy had little effect on dabigatran’s advantages over warfarin; similar increase in bleed risk seen with dabigatran and warfarin</td>
</tr>
</tbody>
</table>

Table 4: Subgroup Analyses of DOAC AF Trials\textsuperscript{25-28}
receive concomitant antiplatelet therapy

- Dabigatran 110 mg – safer for major bleed and equally effective in lowering SSE risk vs. warfarin regardless of antiplatelet therapy
- Dabigatran 150 mg – similar major bleed risk vs. warfarin, but benefit in SSE possibly attenuated by concomitant antiplatelet use

**Edoxaban – ENGAGE AF-TIMI 48**

Evaluates effects of single antiplatelet agent on edoxaban efficacy and safety

- Antiplatelet therapy + edoxaban – significantly greater bleed risk but no alteration in relatively increased safety and efficacy of edoxaban over warfarin

**Rivaroxaban – ROCKET AF**

Assessed DAPT use and associated outcomes in patients who underwent PCI

- Increased event rates of SSE, MI, and bleeding in patients on DAPT + rivaroxaban compared with warfarin

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**Table 5: DOACs in ACS Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Summary</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td><strong>Apixaban</strong></td>
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<tr>
<td>APPRAISE²⁹</td>
<td>Phase II, placebo-controlled, apixaban dose-ranging study in patients with recent ACS on concomitant single or DAPT</td>
<td>Dose dependent increase in major or clinically relevant nonmajor bleeding – not significant for 2.5 mg BID only • More bleeding and ischemic event reduction on DAPT vs. aspirin alone</td>
</tr>
<tr>
<td>APPRAISE-2³⁰</td>
<td>Phase III, placebo-controlled trial of apixaban 5 mg BID vs. placebo + DAPT in high risk recent ACS patients</td>
<td>Discontinued prematurely due to significantly increased major bleeding without a reduction in ischemic events – more intracranial and fatal bleeding with apixaban vs. placebo</td>
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<tr>
<td><strong>Dabigatran</strong></td>
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<tr>
<td>RE-DEEM³¹</td>
<td>Double blind, placebo controlled, dose escalation trial of dabigatran + DAPT vs. placebo post-ACS</td>
<td>Linear increase in major or clinically relevant bleeding with dose, and numerically lower incidence of CV death, nonfatal MI, or non-hemorrhagic stroke composite endpoint with dabigatran vs. placebo • Higher incidence of non-fatal MI with dabigatran • Highest incidence of severe recurrent ischemia with dabigatran 150 mg, and highest incidence of major or clinically relevant bleeding with dabigatran 110 mg</td>
</tr>
<tr>
<td>ATLAS ACS-TIMI 46³²</td>
<td>Phase II, double-blind, multicenter, dose-escalation trial of rivaroxaban in patients post-ACS</td>
<td>Dose dependent increase in clinically significant bleeding but significant reduction in death, MI, or stroke with rivaroxaban • Lowest bleeding with 2.5 mg BID + single or DAPT • Lowest event rates with 2.5 mg BID and 5 mg BID + DAPT</td>
</tr>
<tr>
<td>ATLAS ACS-2-TIMI-51³³</td>
<td>Phase III, placebo-controlled trial of DAPT + rivaroxaban 2.5 mg or 5 mg BID or placebo in patients with recent ACS</td>
<td>Significant reduction in CV death, MI, and stroke, significant increase in major bleed and intracranial hemorrhage rates, and nonsignificant increase in fatal and minor bleeding with rivaroxaban vs. warfarin • Significant decrease in fatal bleeds, minor bleeding, and bleeding requiring medical attention with 2.5 mg BID</td>
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# Major Trials

## I. Rivaroxaban


| Purpose | Compare the safety and efficacy of different treatment strategies after PCI with stent placement in patients with paroxysmal, persistent, or permanent NVAF |
| Study Design | Open-label, randomized, controlled, multicenter, international trial |
| | Duration of DAPT and P2Y₁₂ inhibitor prespecified by investigator prior to randomization |
| | Patients randomized 1:1:1 to groups |

| Group 1 – Low Dose | Group 2 – Very Low Dose | Group 3 – Standard Therapy |
| Rivaroxaban 15 mg daily* + P2Y₁₂ inhibitor | Rivaroxaban 2.5 mg BID + DAPT | Warfarin daily + DAPT |
| • P2Y₁₂ inhibitor for 12 months | • Low dose aspirin for 12 months | • Adjusted to INR 2.0-3.0 |
| | • P2Y₁₂ inhibitor for specified DAPT duration | • Low dose aspirin for 12 months |
| | • Patients in 1 and 6 month groups switched to 15 mg daily for remainder of 12 months* | • P2Y₁₂ inhibitor for specified DAPT duration |

- P2Y₁₂ inhibitors: clopidogrel 75 mg daily, ticagrelor 90 mg BID, or prasugrel 10 mg daily** given for DAPT durations of 1, 6, or 12 months in groups 2 and 3

*10 mg if patient’s CrCl between 30-50 mL/min

** Ticagrelor and prasugrel used in ≤ 15% of patients

### Patient Population

| Inclusion: patients age ≥ 18 years with NVAF who had undergone PCI |
| AF documented within 1 year prior to screening or documented > 1 year prior if patient receiving oral anticoagulation 3 months before PCI |

| Exclusion: |
| History of stroke/TIA |
| Clinically significant GI bleed within 12 months |
| CrCl < 30 mL/min |
| Unknown cause anemia, hemoglobin < 10 g/dL |
| Condition with increased risk for bleeding |

### Endpoints

Primary endpoint: clinically significant bleeding – composite of Thrombolysis in Myocardial Infarction (TIMI) criteria major and minor bleeding and bleeding requiring medical attention

Secondary endpoints:

- Incidence of individual primary endpoint components
- Efficacy endpoints: composite major adverse CV events (composite of death from CV causes, stroke, or MI), individual components of CV event endpoint, and stent thrombosis

### Statistics

Analyses performed on pooled data including all DAPT durations within treatment groups

- Modified intention to treat analyses based on data for all patients who underwent randomization and received at least one dose of trial drug during treatment period
- Cox proportional hazards model: analyze time from first dose to first occurrence of primary safety event, provide hazard ratio (HR) and two-sided 95% confidence interval (CI)
- Kaplan-Meier method: cumulative event rates estimated at 360 days, P values calculated using two-sided log-rank test
### Results

**Baseline Characteristics:** 2124 patients stratified between May 2013 through July 2015
- Predominantly white males, average age 70 years, most common CHA2DS2-VASc scores 3-5 for all groups – no major between group differences
  - Fewer than 10% enrolled in North America
  - P2Y12 inhibitors: clopidogrel used in ~93-96%
  - Warfarin mean percentage of time in the therapeutic range: 65.0%

**Outcomes:**

<table>
<thead>
<tr>
<th>Safety Outcomes: % of Participants with Events, HR (95% CI)</th>
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<tbody>
<tr>
<td>Low dose (n=696) vs. Standard (n=697)</td>
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<tr>
<td><strong>Primary: Clinically Significant Bleeding</strong></td>
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<td><strong>Major Bleeding</strong></td>
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<td><strong>Minor Bleeding</strong></td>
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<td><strong>Bleeding Requiring Medical Attention</strong></td>
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**Efficacy:** no significance difference for any events with either rivaroxaban group vs. warfarin
- Power to detect 15% lower risk in rivaroxaban group = 11.4%

**DAPT:**

<table>
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<th>Clinically Significant Bleeding by Duration of DAPT:</th>
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<tr>
<td>Event Rates, HR (95% CI)</td>
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<tr>
<td>Very low dose vs. Standard</td>
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<tr>
<td>P value</td>
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<td>------------------------------------------------------</td>
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<tr>
<td>Patients assigned to 1 month DAPT</td>
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<td>Patients assigned to 6 months DAPT</td>
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<td>Patients assigned to 12 months DAPT</td>
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</table>

**Additional Findings:** significantly lower permanent discontinuation rate prior to scheduled termination date with both rivaroxaban groups vs. warfarin (P<0.001, both comparisons)

### Author’s Conclusions

Administration of either low dose rivaroxaban + P2Y12 inhibitor for 12 months or very low dose rivaroxaban + DAPT for 1, 6, 12 months was associated with lower rate of clinically significant bleeding vs. standard therapy warfarin + DAPT for 1, 6, 12 months, with similar efficacy rates

**Limitations:**
- Few secondary efficacy endpoints – not powered for noninferiority or superiority, broad CIs
- Trial underpowered – individual efficacy outcomes power between 5.4-13%, would need ~40,794 patients total to detect 15% event difference
- 2.5 BID ACS CV event prevention indication only in some countries, 15 mg and 10 mg in renal dysfunction daily doses not approved in ACS or AF
- DAPT stratification by clinician choice – baseline characteristics unbalanced
Critique

Strengths:
• First trial directly comparing DOAC with standard therapy in patient with NVAF undergoing PCI
• Well-designed trial evaluating multiple dosing strategies of rivaroxaban

Limitations:
• Little insights regarding efficacy
• No insight on DAPT duration
• Dosages not available or indicated in US
• Excluded high risk patients and those with decreased renal function
• Few US patients

Take Away

Sheds light on bleeding-related safety of two dosing strategies of rivaroxaban with antiplatelet agents, but questions of efficacy of these non-FDA approved dosing strategies remain


Purpose
Assess whether low dose rivaroxaban + P2Y₁₂ inhibitor or very low dose rivaroxaban + DAPT could reduce bleeding and, therefore, favorably impact all-cause mortality or rehospitalization

Study Design
Non-prespecified, post-hoc analysis of patients in the PIONEER AF-PCI trial

<table>
<thead>
<tr>
<th>Group 1 – Low Dose</th>
<th>Group 2 – Very Low Dose</th>
<th>Group 3 – Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 15 mg daily + P2Y₁₂ inhibitor</td>
<td>Rivaroxaban 2.5 mg BID + DAPT</td>
<td>Warfarin daily + DAPT</td>
</tr>
</tbody>
</table>

Patient Population
Same as PIONEER AF-PCI trial – patients with NVAF who had undergone PCI

Endpoints
Primary endpoint: all-cause mortality or recurrent hospitalization for an adverse event (AE)
• AEs classified by investigators using International Conference on Harmonization guidelines
• Those leading to hospitalization included in study and classified as a result of bleeding, CV cause, or other cause blinded to treatment assignment

Statistics
Patients receiving ≥ 1 dose of study drug included – analyzed as-treated, DAPT strata pooled
• Groups compared via two specific, simultaneous pair-wise comparisons without adjustment
• Cox proportional hazard model: HR and 95% CI to compare time from first study drug dose to first occurrence of all-cause death or hospitalization for AE – treatment group covariate
• Kaplan-Meier method: summarize cumulative event rates at 360 days

Results
Baseline characteristics: 2124 patients – well-matched, no significant between group differences

| Risk of All-Cause Mortality or Rehospitalization: % risk, HR (95% CI) |
|-----------------|-----------------|-----------------|-----------------|
| All-Cause Mortality or Rehospitalization for Any Cause | Low dose vs. Standard | P value | Very low dose vs. Standard | P value |
| 34.9 vs. 41.9 | 0.79 (0.66-0.94) | 0.008*, NNT = 15 | 31.9 vs. 41.9 | 0.75 (0.62-0.90) | 0.002*, NNT = 10 |

• Significance retained for all-cause mortality or rehospitalization due to bleeding or CV cause, due to bleeding alone, and due to CV cause alone
• No difference in other all-cause death or recurrent hospitalization, all-cause death alone
• No significant differences between low dose or very low dose rivaroxaban groups
### Author’s Conclusions

Administration of either strategy of rivaroxaban associated with reduced risk of all-cause mortality or recurrent hospitalization for adverse events compared with standard of care.
- Results added strength to PIONEER AF-PCI trial and suggests potential for improved value.
- Rehospitalization greater sensitivity, less specificity than original efficacy endpoints – greater power (90%) to observe 20% difference between groups.
- All-cause death and rehospitalization as endpoints are objective, comprehensive endpoints.

**Limitations:**
- Post-hoc analysis, no multiplicity testing adjustment, method of event allocation not a priori.
- Only generalizable to PIONEER AF-PCI population and clopidogrel.
- Rivaroxaban 2.5 mg not available/indicated in all countries, including US.
- Bias to admit more patients on open-label warfarin therapy.

### Critique

**Strengths:**
- Adequately powered, more sensitive endpoints.
- Analyzed relevant rehospitalization causes.
- Sought to demonstrate clinical significance of previous findings.

**Limitations:**
- Non-prespecified analysis, inclusion of DAPT analysis questionable.
- Justification for lack of original efficacy and new endpoints.
- Limited generalizability.

### Take Away

Provides insight into clinical relevance of bleeding reduction with rivaroxaban but little in the way of understanding efficacy of these lower doses of rivaroxaban in reducing thrombosis risk – true balance in bleeds vs. clots remains uncertain.

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### Dabigatran


#### Purpose

Compare use of two regimens of dual antithrombotic therapy with dabigatran etexilate (DE) with warfarin triple antithrombotic therapy among patients with AF undergoing PCI.

#### Study Design

Randomized, open-label, multicenter, international, controlled noninferiority trial.
- Patients randomized by permuted blocks, stratified by age and region 1:1:1 ratio to:
  - **Group 1 – DE 110 Dual Therapy**: DE 110 mg BID + P2Y12 inhibitor* ≥ 12 months
  - **Group 2 – DE 150 Dual Therapy**: DE 150 mg BID + P2Y12 inhibitor* ≥ 12 months
  - **Group 3 – Triple Therapy**: Warfarin** daily + P2Y12 inhibitor for ≥ 12 months + aspirin discontinued after 1 month with BMS and 3 months with DES

- Continued until patients had ≥ 6 month of follow up, target number of events reached

* Clopidogrel 75 mg daily or ticagrelor 90 mg BID
** Adjusted to INR 2.0-3.0
Patient Population

Inclusion – patients ≥ 18 years with NVAF who underwent PCI in previous 120 hours
- Eligible regardless of whether or not on oral anticoagulant prior to PCI
- ACS or stable CAD as PCI indications

Exclusion
- NVAF due to reversible disorder without anticipated long-term anticoagulation
- Severe renal insufficiency (CrCl < 30 mL/min)
- Other major coexisting conditions

Endpoints

Primary Safety Endpoint: first major or clinically relevant nonmajor International Society on Thrombosis and Haemostasis (ISTH) bleeding event

Secondary:
- Composite efficacy: thromboembolic events (MI, SSE), death, unplanned revascularization
- Combined endpoint of thrombotic events or death, individual events, and stent thrombosis

Statistics

Primary analysis: intention-to-treat for all patients randomized
- Noninferiority margin: upper limit (UL) of 95% confidence interval = 1.38
- Estimated sample size: 2500 patients – assumed primary endpoint 14% event rate per group, 83.6% power for noninferiority, one-sided alpha of 0.025
- Cox proportional-hazards model for primary endpoint
Initial protocol: planned for coprimary endpoint comparison of thromboembolic event rates
- Changed to secondary, sample size changed from 8520 to 2500

Results

Baseline characteristics: 2725 patients randomized between July 2014 through October 2016
- Mean age 70.8, predominantly male, average CHA2DS2-VASc score 3.6 and HAS-BLED 2.7
  - Warfarin group – higher rate of previous stroke
  - P2Y12 inhibitor: 88% clopidogrel
  - Warfarin mean percentage of time with therapeutic INR: 64%

Outcomes:

Safety: Event Rate %, HR (95% CI)

<table>
<thead>
<tr>
<th>Event</th>
<th>DE 110 (n=981) vs. Triple (n=981)</th>
<th>P value</th>
<th>DE 150 (n=763) vs. Triple (n=764)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First major or clinically relevant nonmajor bleeding event</td>
<td>15.4 vs. 26.9 0.52 (0.42-0.63)</td>
<td>&lt;0.001* noninferiority and superiority</td>
<td>20.2 vs. 25.7 0.72 (0.58-0.88)</td>
<td>&lt;0.001* noninferiority, &lt;0.002* superiority</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.3 vs. 1.0 0.30 (0.08-1.07)</td>
<td>0.06</td>
<td>0.1 vs. 1.0 0.12 (0.02-0.98)</td>
<td>0.047*</td>
</tr>
</tbody>
</table>

Efficacy: Event Rate %, HR (95% CI)

Main composite efficacy endpoint: DE 110 and DE 150 (n=1744) vs. triple (n=981): 13.7 vs. 13.4, 1.04 (0.84-1.29), P=0.005 for noninferiority, P=0.74 for superiority
Secondary composite efficacy endpoint: thromboembolic events or death – DE 110 and DE 150 vs. triple: 9.6 vs. 8.5, 1.17 (0.90-1.53), P=0.11 for noninferiority, P=0.25 superiority

<table>
<thead>
<tr>
<th>Event</th>
<th>DE 110 (n=981) vs. Triple (n=981)</th>
<th>P value</th>
<th>DE 150 (n=763) vs. Triple (n=764)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite efficacy endpoint</td>
<td>15.2 vs. 13.4 1.13 (0.90-1.43)</td>
<td>0.30</td>
<td>11.8 vs. 12.8 0.89 (0.67-1.19)</td>
<td>0.44</td>
</tr>
<tr>
<td>Thromboembolic events or death</td>
<td>11.0 vs. 8.5 1.30 (0.98-1.73)</td>
<td>0.07</td>
<td>7.9 vs. 7.9 0.97 (0.68-1.39)</td>
<td>0.88</td>
</tr>
<tr>
<td>MI</td>
<td>4.5 vs. 3.0 1.51 (0.94-2.41)</td>
<td>0.09</td>
<td>3.4 vs. 2.9 1.16 (0.66-2.04)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Trend favoring triple therapy
- No significant difference in DE groups for death, stroke, or definite stent thrombosis
### Other findings:
- Serious AEs: 42.7% DE 110, 39.6% DE 150, and 41.8% triple therapy
- Fatal serious AEs: 3.9% DE 110, 3.2% DE 150, and 4.3% triple therapy
- Premature discontinuation: 13.3% DE 110, 13% DE 150, and 16.6% triple therapy

### Author’s Conclusions
**Risk of bleeding lower with dual therapy with dabigatran + P2Y₁₂ vs. triple therapy with warfarin + P2Y₁₂ + aspirin; dual therapy noninferior for risk of thromboembolic events – reaffirms safety and net clinical benefit of DE regimens and supports changes in guidelines**
- DE 110 significantly lower major bleeding, nonsignificantly higher thromboembolic events
- DE 150 significantly lower major bleeding, nonsignificantly lower thromboembolic events

**Limitations:**
- Not powered for individual endpoints and amended protocol
- Combined DE groups for efficacy to get 83.6% power
- Noninferiority margin used for SSE in AF trials
- Can only speculate on impact of aspirin omissions in safety and efficacy outcomes

### Critique
**Strengths:**
- Tested multiple dosing strategies with NVAF approved doses
- Tested omission of aspirin and found higher bleeding rates even with shortened duration of aspirin
- Slightly more efficacy insight to be gleaned vs. PIONEER AF-PCI

**Limitations:**
- Combined DE groups to show composite efficacy endpoint noninferiority
- MI rates higher with DE, especially DE 110
- Lack of power for individual endpoints
- Questionable claims about DE 110 clinical benefit, effectiveness, and safety

### Take Away
DE dual therapy superior to classic triple therapy with warfarin for bleeding
Questions about effectiveness and even safety of DE 110 dual therapy
Ultimately favors DE 150 dual therapy for superior bleeding and noninferior efficacy

### Future Studies – Apixaban and Edoxaban

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design &amp; Endpoints</th>
</tr>
</thead>
</table>
| **Apixaban – AUGUSTUS**<sup>37</sup> | An open-label, 2 x 2 factorial, randomized controlled trial evaluating safety of apixaban 5 mg or 2.5 mg BID vs. warfarin, as well as aspirin vs. placebo in patients with AF and ACS or PCI  
*Primary*: time to first occurrence of major or clinically relevant nonmajor bleeding with apixaban vs. warfarin, with no aspirin vs. aspirin  
*Secondary*: apixaban vs. warfarin superiority for major and clinically relevant nonmajor bleeding, composite endpoints of death and ischemic events, and first any cause rehospitalization |
| **Apixaban – SAFE-A**<sup>38</sup> | Multicenter, prospective, randomized, open-label, blinded-endpoint, parallel-group, comparative study of safety and efficacy of 1-month and 6 months of P2Y₁₂ inhibitor plus 12 months of aspirin and apixaban 5 mg BID in patients with NVAF undergoing PCI with DESs  
*Primary*: incidence of bleeding occurrences in 12 months  
*Secondary*: composite of all-cause death, MI, SSE, net clinical benefit, and individual endpoints |
| **Edoxaban – ENTRUST-AF-PCI**<sup>39</sup> | Open-label, randomized clinical trial to evaluate safety and efficacy of edoxaban-based antithrombotic regimen (60 mg daily) vs. warfarin-based antithrombotic regimen in patients with AF post-PCI with stent placement  
*Primary*: incidence of major or clinically relevant nonmajor ISTH-defined bleeding  
*Secondary*: composite of CV death, SSE, MI, and stent thrombosis events |
Summary, Conclusion, and Recommendations

I. Summary:
   a. In patients with AF undergoing PCI, goal is balance between thrombosis and bleed risk
   b. Triple therapy with warfarin + aspirin + clopidogrel is the historical standard of care
   c. Triple therapy holds an inherently increased risk of bleeding
   d. Shifting paradigms are increasing the use of DOACs in the management of NVAF – ease of use and reduction in risk of bleeding compared to warfarin
      i. Increasing number of patients coming into the hospital on a DOAC requiring PCI
      ii. Increased push from clinicians to utilize these newer medications as literature accumulates

II. Conclusions & Recommendations:
   a. Is it time to change our paradigm?
      i. No overall, definitive conclusion to move to utilization of DOACs in all patients with NVAF undergoing PCI can be made based on evidence available to date
         1) Good evidence for decreased bleeding, noninferior efficacy with single strategy of single DOAC – dabigatran 150 dual therapy
            a) Requires additional research into trend towards increased MI
            b) Only generalizable to patient population used in RE-DUAL
         2) Insufficient evidence to recommend any other DOAC
      ii. Certain situations exist in which a DOAC, specifically dabigatran, should be considered
   b. Recommendations
      i. Patients admitted therapeutic on warfarin – consider patient’s lifestyle, compliance, preferences, and bleed risk and history
         1) Patient prefers warfarin, no compliance or lifestyle barriers, and has lower bleed risk – continue warfarin targeting INR between 2.0-2.5
         2) Patient would prefer less monitoring, has lifestyle barriers, and has higher bleed risk – dabigatran 150 dual therapy
      ii. Patients not therapeutic on warfarin or with difficulty complying with INR monitoring – dabigatran 150 dual therapy
      iii. Patients admitted on DOAC for PCI – depends on DOAC
         1) Edoxaban: not enough data to recommend continuation – change anticoagulant
         2) Apixaban: increased risk of bleeding with apixaban + DAPT in ACS trials and questionable trend towards increased MI in patients on aspirin + apixaban in ARISTOTLE subgroup analysis leaves questions of safety – change anticoagulant
         3) Rivaroxaban: based on lack of efficacy conclusions from PIONEER – change anticoagulant
         4) Dabigatran: based on RE-DUAL’s safety and noninferior efficacy – continue dabigatran 150 mg and start clopidogrel
      iv. Initiating new anticoagulant post-PCI
         1) Assess patient’s stroke, bleed, and ACS event risks, as well as preference, likely compliance, and lifestyle
            a) Patient with higher bleed risk – dabigatran 150 dual therapy or warfarin + clopidogrel with decision based on patient factors and preference
            b) Patient with lower bleed risk – dabigatran 150 dual therapy or warfarin triple therapy with decision based on patient factors and preference
      v. Patients with renal dysfunction, either stable or recent onset – warfarin triple therapy targeting INR between 2.0-2.5
References


Appendices

Appendix A – CHA2DS2-VASc13 and HAS-BLED scores

<table>
<thead>
<tr>
<th>CHA2DS2-VASc risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>+1</td>
</tr>
<tr>
<td>Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+1</td>
</tr>
<tr>
<td>Resting blood pressure &gt;140/90 mmHg on at least two occasions or current antihypertensive treatment</td>
<td>0</td>
</tr>
<tr>
<td>Age 75 years or older</td>
<td>+2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>+1</td>
</tr>
<tr>
<td>Fasting glucose &gt;125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin</td>
<td>0</td>
</tr>
<tr>
<td>Previous stroke, transient ischaemic attack, or thromboembolism</td>
<td>+2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>+1</td>
</tr>
<tr>
<td>Previous myocardial infarction, peripheral artery disease, or aortic plaque</td>
<td></td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>+1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>+1</td>
</tr>
</tbody>
</table>

CH A2DS2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).

### HAS-BLED

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal Liver or Renal Function</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (age &gt; 65)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or Alcohol</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Maximum Score: 9

### Table 1: Summary of Direct Oral Anticoagulant NVAF Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Apixaban</strong></td>
<td><strong>ARISTOTLE</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Double blind, double dummy noninferiority trial of apixaban 5 mg BID vs. warfarin (N=18,201)</td>
</tr>
<tr>
<td></td>
<td>Primary efficacy: SSE</td>
<td>Primary efficacy outcome: apixaban superior</td>
</tr>
<tr>
<td></td>
<td>Primary safety: major bleeding</td>
<td>Major bleeding: apixaban superior</td>
</tr>
<tr>
<td></td>
<td>Other: death from any cause, MI UL 95% CI for noninferiority: 1.38</td>
<td>Death from any cause: apixaban superior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MI: numerically lower event rate with apixaban</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td><strong>RE-LY</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Blinded noninferiority trial of DE 110 mg or 150 mg vs. warfarin in SSE prevention (N=18,113)</td>
</tr>
<tr>
<td></td>
<td>Primary efficacy: SSE</td>
<td>Primary efficacy outcome: DE 110 mg noninferior, DE 150 mg superior</td>
</tr>
<tr>
<td></td>
<td>Primary safety: major hemorrhage</td>
<td>Major hemorrhage: DE both doses superior</td>
</tr>
<tr>
<td></td>
<td>Secondary: SSE and death MI, bleeding</td>
<td>MI: DE 110 mg nonsignificantly and DE 150 mg significantly higher</td>
</tr>
<tr>
<td></td>
<td>Upper limit 95% CI for noninferiority: 1.46</td>
<td>Bleeding: significantly lower rate of major bleed with DE 110 mg, and significantly lower rates of life-threatening bleeding, intracranial bleeding, and major or minor bleeding with DE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose comparison: Greater SSE reduction with DE 150 mg</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td><strong>ENGAGE AF-TIMI 48</strong>&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Double-blind, double-dummy noninferiority trial of edoxaban 60 mg or 30 mg daily vs. warfarin (N=21,105)</td>
</tr>
<tr>
<td></td>
<td>Primary efficacy: SSE</td>
<td>Primary efficacy outcome: edoxaban 60 mg superior, edoxaban 30 mg noninferior</td>
</tr>
<tr>
<td></td>
<td>Principle safety: major bleeding</td>
<td>Major bleeding: significantly lower in both edoxaban groups</td>
</tr>
<tr>
<td></td>
<td>Other: death from CV cause, ischemic stroke, GI bleeding UL 97.5% CI for noninferiority: 1.38</td>
<td>Death from CV causes: lower rates with edoxaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemic stroke: equal with edoxaban 60 mg, significantly higher with edoxaban 30 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI bleeding: significantly higher with edoxaban 60 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparison of doses: edoxaban 60 mg lower primary outcome</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td><strong>ROCKET AF</strong>&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Double blind noninferiority trial of rivaroxaban 20 mg daily vs. warfarin (N=14,264)</td>
</tr>
<tr>
<td></td>
<td>Primary efficacy: SSE</td>
<td>Primary efficacy outcome: per protocol annual event rate with rivaroxaban noninferior</td>
</tr>
<tr>
<td></td>
<td>Principle safety: composite of major and nonmajor clinically relevant bleeding events</td>
<td>ITT efficacy: rivaroxaban noninferior, not superior</td>
</tr>
<tr>
<td></td>
<td>Other: other bleeding measures UL 95% CI for noninferiority: 1.46</td>
<td>Safety population efficacy for superiority: rivaroxaban superior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Principle safety: rivaroxaban numerically higher than warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: similar rates of major bleeding, significant reductions in intracranial hemorrhage and fatal bleeding, significantly more major GI bleeding, significantly greater decrease in hemoglobin ≥2 g/dl, and significantly higher transfusion rates with rivaroxaban</td>
</tr>
</tbody>
</table>