48th Annual Meeting

Updates in Antithrombotic Therapy

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August 8, 2014

Navigating the Oceans of Opportunity

What's new in antiplatelet therapy?
- Duration of dual antiplatelet therapy (DAPT)
- DAPT after Percutaneous Coronary Intervention (PCI)
- Novel antiplatelet therapy
- Vorapaxar
- Concomitant antiplatelet and anticoagulant combination
- Triple therapy

Disclosure

- We do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

Objectives

- Describe evidence based recommendations for various combination antiplatelet regimens
- Appraise data available for the durations of dual antiplatelet therapies in various situations
- Discuss practical considerations with use of antithrombotic therapies in the acute care setting
- Detail current trends and future developments with the newer antithrombotic therapies

DAPT Duration

Randomized evaluations of DAPT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE/PC</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>I-CURE</td>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>COMMIT</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>CHARISMA</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>PLATO</td>
<td>2009</td>
<td></td>
</tr>
</tbody>
</table>

Informs on management in 12-15 months post-ACS
DAPT Post-PCI

- **ACC/AHA 2011 PCI statement**
  - Class I:
    - Aspirin indefinitely after PCI (LOE: A)
  - ACS setting:
    - P2Y12 for at least 12 months (LOE: B)
    - Non-ACS setting:
      - DES: Discontinue P2Y12 for at least 12 months if not at high bleeding risk (LOE: B)
      - BMS: Discontinue P2Y12 early if risk bleeding > benefit (LOE: C)
  - Class IIa:
    - Discontinue P2Y12 inhibitor early if risk bleeding > benefit (LOE: C)
  - Class IIb:
    - DAPT for >12 months may be considered in patients undergoing DES implantation (LOE: C)

- **ACCP CHEST 2012**
  - After 12 months of DAPT: “Single antiplatelet therapy over continuation of dual antiplatelet therapy” (Grade 1B)

DAPT after stenting

- **Observational benefit with long-term DAPT**
  - Duke Heart Center 2000-2005 (DES pts n=1,501)

<table>
<thead>
<tr>
<th>Status of DAPT</th>
<th>Status of Death event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 vs 24 months</td>
<td>5.5% vs 6.0% (p=0.5)</td>
</tr>
<tr>
<td>12 vs 24 months</td>
<td>4.7% vs 3.6% (p=0.44)</td>
</tr>
<tr>
<td>DES (n=1,501)</td>
<td>3.1% vs 7.2% (p=0.002)</td>
</tr>
<tr>
<td></td>
<td>0% vs 4.5% (p=0.001)</td>
</tr>
</tbody>
</table>

- **PARIS – 2 year registry of DAPT use**
  - 42.7% continued DAPT for 2 years
  - TRITON TIMI-38 follow up (2.1 years) registry
  - 26% continued DAPT

DAPT – PCI Setting

- **2012 Meta-analysis (Cassese et al.)**
  - **DEATH**
    - EXCELLENT: 1.76 (0.51, 6.06)
    - PRODIGY: 6.98 (0.75, 64.2)
    - REZERT: 1.83 (0.79, 3.98)
    - RESET: 1.61 (0.52, 4.95)
  - Total (95% CI): 1.15 (0.85, 1.54)

- **MI**
  - EXCELLENT: 2.01 (0.37, 11.00)
  - PRODIGY: 2.88 (0.14, 68.08)
  - REZERT: 3.82 (0.31, 38.62)
  - RESET: 3.92 (0.61, 14.98)
  - Total (95% CI): 2.64 (1.31, 5.34)

“…the PRODIGY trial represents one more victory against the greatest enemy of drug-eluting stents: the wrongly assumed need for endless dual antiplatelet therapy.”

- Adnan Kastrati, MD (2011 ESC meeting)

Questions Raised About Clopidogrel Duration Poststenting.

- Duke Heart Center 2000-2005 (DES pts n=1,501)

- Second generation DES use is associated with lower incidence of stent thrombosis

- Some patients may benefit from >12 months of DAPT

DAPT – PCI Setting

- **Does the stent type matter?**
  - Second generation DES use is associated with lower incidence of stent thrombosis

- **Dual Antiplatelet Therapy**
  - Some patients may benefit from >12 months of DAPT
  - PRODIGY sub-analysis in patients with PCI for ISR
Vorapaxar

Novel tool for residual risk reduction?

Approved by FDA May 8, 2014:
Reduction of thrombotic cardiovascular events in patients with a history of MI or PAD, without history of stroke, TIA, ICH, or active pathological bleeding

Vorapaxar – PAR-1 Antagonist

- Rationale
  - Specific inhibition of platelet activation
  - Not involved in collagen-induced platelet function, perhaps decreasing bleeding risk
  - Expressed outside platelets suggesting role in attenuation of atherosclerosis progression, thrombus-mediated ischemic events and restenosis

- Phase III evaluations
  - TRACER
  - NSTEMI-ACS
  - TRA 2°P - TIMI 50

Vorapaxar – MOA

TRA 2°P - TIMI 50

- CAD (2 wks – 12 months post MI)
- CVD (2 wks – 12 months post, presumed thrombotic)
- PAD (intermittent claudication with ABI <0.85 or amputation or revascularization due to ischemia)

Vorapaxar 2.5mg once daily
n=13,225

Placebo
n=13,224

- Primary efficacy endpoint: Composite of CV death, MI or stroke
- Secondary efficacy endpoint: Composite of CV death, MI, stroke or urgent coronary revascularization
- Primary safety endpoint: GUSTO moderate or severe bleeding

TRA 2°P - TIMI 50

Baseline History

<table>
<thead>
<tr>
<th></th>
<th>Vorapaxar (n=13,225)</th>
<th>Placebo (n=13,224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – Median (yrs)</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Age ≥75%</td>
<td>11.4%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Wt &lt;60kg</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Qualifying type of atherosclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>67.3%</td>
<td>67.2%</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>18.4%</td>
<td>18.3%</td>
</tr>
<tr>
<td>PAD</td>
<td>14.3%</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

Antiplatelet Med Use

<table>
<thead>
<tr>
<th></th>
<th>Vorapaxar (n=13,225)</th>
<th>Placebo (n=13,224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>Aspirin 98.1%</td>
<td>98.1%</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>77.9%</td>
<td>78.4%</td>
</tr>
<tr>
<td>PAD</td>
<td>Aspirin 87.8%</td>
<td>88.2%</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>36.8%</td>
<td>36.8%</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>19.5%</td>
<td>19.4%</td>
</tr>
</tbody>
</table>

Antiplatelet Med Use

January 2011 (Enrollment completed 11/2009)

- DMSB recommended discontinue study drug in all subjects with a stroke history or new stroke in trial, continue in others

- Intracranial Hemorrhage*

TRA 2°P - TIMI 50

January 2012

- Database locked

* Percentages are 3 year KM rates
TRA 2°P - TIMI 50

OVERALL TRIAL DATA

Efficacy*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vorapaxar</th>
<th>Placebo</th>
<th>HR (95% CI; p value)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, Stroke</td>
<td>9.3%</td>
<td>10.5%</td>
<td>0.87 (0.80-0.94; &lt;0.001)</td>
<td>83</td>
</tr>
<tr>
<td>CV death, MI, Stroke, UCR</td>
<td>11.2%</td>
<td>12.4%</td>
<td>0.88 (0.82-0.95; 0.001)</td>
<td>83</td>
</tr>
</tbody>
</table>

Safety*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vorapaxar</th>
<th>Placebo</th>
<th>HR (95% CI; p value)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO mod-severe bleeding</td>
<td>4.2%</td>
<td>2.5%</td>
<td>1.66 (1.43-1.93; &lt;0.001)</td>
<td>59</td>
</tr>
<tr>
<td>TIMI clinically significant</td>
<td>15.8%</td>
<td>11.1%</td>
<td>1.46 (1.36-1.57; &lt;0.001)</td>
<td>21</td>
</tr>
<tr>
<td>ICH</td>
<td>1%</td>
<td>0.5%</td>
<td>1.94 (1.39-2.70; &lt;0.001)</td>
<td>200</td>
</tr>
</tbody>
</table>

* Percentages are 3 year KM rates


TRA 2°P - TIMI 50 – PVD Group

No benefit on CV death, MI, or stroke composite

GUSTO mod-severe bleeding: 7.4% vs 4.5% (HR 1.62, 1.21–2.18, p=0.001)


TRA 2°P - TIMI 50 – FDA analysis

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Vorapaxar – Considerations

CYP3A4 substrate

- Rifampin, ketoconazole, erythromycin exclusions in TRA2P-TIMI 50, more extensive list in PI

Terminal elimination 1/5 of ~8 days

- No instructions for dosing in elective/emergency procedures or situations

- No sig increase in CABG bleeding

  - Results of the Phase 2 study in 1030 subjects undergoing coronary angiography and who were candidates for nonemergent PCI demonstrated no clinically meaningful incremental risk of bleeding relative to placebo, even in surgical situations such as CABG

Risk/benefit evaluation critical

- Use in elderly and those with weight <60kg largely unknown

Antiplatelet and Anticoagulant Therapies
Combination Antithrombotic Therapy

- 20-30% of patients with indications for anticoagulation have IHD that requires PCI
- Anticoagulant and antiplatelet combination therapy is associated with 4-16% risk of fatal and non-fatal bleeding
- AFib patients with PCI are at higher risk of both stent thrombosis and thromboembolism if not on OAC and DAPT
- ~50% 6 month mortality in patients who have bleed

Summary of Antiplatelet Therapy

- Streamlining of antithrombotic therapy may become part of practice
  - Shorter duration of DAPT after PCI
  - Focused anticoagulant/antiplatelet combinations
  - Careful consideration needed to guide integration of vorapaxar into clinical practice

Dynamic Antithrombotic Effects

- Danish Registry Data – non-fatal & fatal bleeding
- Stroke & Systemic Embolism

Target Specific Oral Anticoagulants (TSOACs)

- Updates in the Acute Care Setting
  1. Acute Coronary Syndrome (ACS)
  2. Periprocedural Use
    - Atrial Fibrillation (AF) Ablation
    - Cardioversion (CVSN)

TSOAC Use in ACS

- Current standard of care
  - Dual antiplatelet therapy (DAPT)
    - Recurrence rate exceeds 11%
  - Warfarin and aspirin for secondary prevention
    - 27% reduction in MI, stroke and all-cause death
    - Significantly increased major bleeding
  - TSOACs for ACS prevention
    - THE GOOD: Rivaroxaban – ATLAS ACS TIMI 46 & 51
    - THE BAD: Apixaban – APPRAISE 1 & 2
    - THE UGLY: Dabigatran – RE-DEEM
VNN1  Finish Editing slide
Verbosky, Natalie N., 7/23/2014
Apixaban in ACS: APPRIASE-2

- High Risk Characteristics
  - Age ≥ 65 years
  - Cerebrovascular disease
  - Diabetes
  - MI < 5 years
  - PVD
  - HF or EF ≤ 40%
  - No revascularization
- Terminated early
  - Bleeding increased 2.5-fold
    HR: 2.59 (1.40–4.46) P=0.001
  - Failed to reduce ischemic events
    HR: 0.95 (0.80–1.11) P =0.50
  - 13.2 vs 14 events per 100 patient-years

Atrial Fibrillation Ablation: Old School and New Tricks

- Historical approach
  - Interrupted warfarin (1)
- COMPARE trial
  - Interrupted vs uninterrupted warfarin (2)
  - Warfarin discontinuation strong predictor of periprocedural thromboembolic events (P>0.001)
- Third approach to periprocedural anticoagulation
  - Minimally interrupted TSOAC (3)

Rivaroxaban in ACS: ATLAS ACS-TIMI 51

- Significantly reduced primary end point
  - 0.84 (0.74–0.96) P=0.002
- At cost of increased major bleeding
  - 3.96 (2.46–6.38 P<0.001)
- Number needed to treat ➔ 56
- Reduced stent thrombosis 31%

Summary of TSOAC

Use in ACS

- Apixaban: Higher risk patients
  - Equivocal dosing to AF
  - Terminated early ➔ underestimating efficacy?
- Rivaroxaban: Lower risk patients
  - Lower dosing than AF with increased bleeding
  - Significant ischemic event benefit

Some unanswered questions
- Who is the proper patient to gain benefit from triple therapy?
- What anti-platelet agent is to be used with aspirin?

Dabigatran in Ablation

- Meta-Analysis of 6 trials
  - 26,731 ACS Patients
  - Clinically significant bleeding
    HR (95%CI) 2.34 (2.06–2.66)
  - MACE
    HR (95%CI) 0.87 (0.80–0.95)
  - NNH 87
  - NNH 24

VNN3

Rivaroxaban in Ablation

- Post-hoc analysis of ROCKET-AF
  - No difference in stroke (1.9% in both) or bleeding observed (18.8% vs 13%) in rivaroxaban and warfarin respectively
- Multi-center, prospective registry, 321 patients
  - Uninterrupted rivaroxaban vs uninterrupted warfarin
  - Embolic complications 0.3% in both groups
  - Major bleeding 1.6% and 2.2% (p=0.772)

“Feasible and safe alternative to uninterrupted warfarin”

- Coming soon… VENTURE-AF
  - Randomized, open-label, active-controlled, multi-center
Summary of TSOAC use in AF Ablation

- Limited available evidence supporting TSOAC use over warfarin
- What is the ideal periprocedural anticoagulation agent?

Too Much: Stroke
Too Little: Bleeding

Cardioversion: What We Know

- Anticoagulation Standard of Care (CHEST 2012)
  - AF >48 hours or unknown duration:
    - Anticoagulation with VKA (INR 2-3) or dabigatran for ≥ 3 weeks prior and ≥ 4 weeks after CVSN

<table>
<thead>
<tr>
<th>Post-Hoc Analysis</th>
<th>Dabigatran vs warfarin RE-LY</th>
<th>Study duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Dabigatran 150mg</td>
<td>Warfarin</td>
</tr>
<tr>
<td>N</td>
<td>672</td>
<td>664</td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>2 (0.3%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>4 (0.6%)</td>
<td>4 (0.6%)</td>
</tr>
</tbody>
</table>

- Dabigatran as effective as warfarin after cardioversion

Cardioversion: Where Do We Go?

- Stay tuned for X-VeRT: rivaroxaban and scheduled cardioversion
- NOACs associated with low risk of embolic complications
- If treated for months prior to CVSN, no justification to switch to warfarin

Unanswered Questions
- Newly diagnosed persistent AF undergoing CVSN
- Should TEE be performed?
- Is 3–4 weeks of NOAC prior to CVSN enough?

Dabigatran and Heart Valve

- RE-ALIGN
  - Population A (80%)
    - Mechanical Valve within 7 days
  - Population B (20%)
    - Mechanical Valve ≥ 3 months ago
  - Dabigatran Dose
    - Renally adjusted
    - 150mg, 220mg & 300mg BID

Outcome Population A Population B

- “Reasons for failure”
  - Doses
  - Mechanisms of action
  - Reporting biases

Baseline Characteristics Dabigatran (N=168) Warfarin (N=84)

| Male Sex - no (%) | 107 (64) | 56 (67) |
| Age (year)        | 56       | 55.7    |
| Creatinine clearance | 107    | 106     |
| Type of Valve Replaced |
| Aortic - no (%)  | 113 (67) | 59 (70) |
| Mitral - no (%)  | 49 (29)  | 22 (26) |
| Both - no (%)    | 6 (4)    | 3 (4)   |
| Thromboembolic Risk |
| Low - no (%)     | 51 (30)  | 23 (27) |
| Moderate/High - no (%) | 117 (70) | 61 (73) |

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Edoxaban: The Next Big Thing?

- Edoxaban
  - Oral, direct factor Xa inhibitor
  - Rapid effect in 1-2 hours
  - T 1/2 ~10 hours
- ENGAGE AF-TIMI 48
  - AF with moderate to high risk of stroke (CHADS2: ≥ 2)
  - 1:1:1 high-dose (60mg) and low-dose (30mg)
  - Edoxaban or warfarin (INR 2-3)
    - Doses halved for CrCl 30-50mL/min, body weight ≤60kg and use of strong P-gp inhibitors
- NDA submitted to FDA January 2014

Edoxaban non-inferior to well-managed warfarin (TTR: 68%)

- Significant reduction in major bleeding, intracranial bleeding, hemorrhagic stroke and CV mortality
- Ischemic stroke similar for high-dose edoxaban
- Risk increased 41% with low-dose edoxaban


TSOAC use in VTE

<table>
<thead>
<tr>
<th>Summary of TSOAC Phase 3 Trials</th>
<th>Acute VTE treatment</th>
<th>Extended VTE treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>RE-COVER</td>
<td>RE-COVER II</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>ENSTEIN DVT</td>
<td>ENSTEIN FE</td>
</tr>
<tr>
<td>Apixaban</td>
<td>AMPLIFY</td>
<td>AMPLIFY-EXT</td>
</tr>
</tbody>
</table>

The Dabigatran RE-VOLUTION

- April 2014: FDA Approved Dabigatran in VTE
  - FDA Approved for treatment of DVT and PE
    - Must have parenteral anticoagulant for 5-10 days
  - FDA Approved to reduce the risk of DVT and PE recurrence

Dabigatran and Acute VTE Treatment: RE-COVER

<table>
<thead>
<tr>
<th>Body</th>
<th>RE-COVER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Double blind, non-inferior RCT</td>
</tr>
<tr>
<td>Treatment</td>
<td>Initial Tx: mean duration 10 days</td>
</tr>
<tr>
<td></td>
<td>Parenteral anticoag 5 days AND therapeutic INR</td>
</tr>
<tr>
<td></td>
<td>Maintenance 6 months</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150mg BD</td>
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<tr>
<td></td>
<td>Warfarin INR 2-3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>Dabigatran</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>2.4%</td>
<td>2.1%</td>
<td>1.1 (0.65-1.84)</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>1.8%</td>
<td>1.9%</td>
<td>0.92 (0.45-1.88)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.6%</td>
<td>1.7%</td>
<td>0.98 (0.53-1.79)</td>
</tr>
</tbody>
</table>

Dabigatran non-inferior to warfarin for prevention of recurrent of fatal VTE (p<0.001)

Conclusion: Dabigatran is as effective with similar safety profile as warfarin for treatment of acute VTE
Dabigatran and extended VTE
RE-SONATE & RE-MEDY

<table>
<thead>
<tr>
<th>Required Treatment prior to enrollment</th>
<th>RE-SONATE</th>
<th>RE-MEDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-18 mos prior to VTE</td>
<td>No need for continued anticoagulation</td>
<td>3-12 mos prior to VTE</td>
</tr>
<tr>
<td>Considered at increased risk of VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Dabigatran 150mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>Warfarin (INR 2-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Duration</td>
<td>6 mos</td>
<td>(plus 12 mos follow-up)</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>0.08 (0.02-0.25)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Major or CRNMB</td>
<td>2.92 (1.32-5.6)</td>
<td>0.54 (0.41-0.71)</td>
</tr>
</tbody>
</table>

Summary of TSOAC Use in VTE

- Acute VTE Treatment
  - TSOACs shown to be noninferior to adjusted dose VKA therapy for prevention of recurrent VTE
  - Similar bleeding rates with dabigatran and lower with apixaban
- Extended VTE Treatment
  - TSOACs shown to be superior to placebo
  - Clinically relevant bleeding similar to placebo with apixaban and higher with dabigatran
  - Dabigatran noninferior to warfarin

Apixaban and acute VTE Treatment: AMPLIFY

<table>
<thead>
<tr>
<th>Study</th>
<th>AMPLIFY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Double blinded, non-inferiority RCT</td>
</tr>
<tr>
<td>Treatment</td>
<td>Initial Tx: APIX 10BID for 7 days</td>
</tr>
<tr>
<td>- Enox 1mg/kg BID + Warfarin for ≥ 5 days</td>
<td></td>
</tr>
<tr>
<td>Maintenance Tx: 6 mos</td>
<td></td>
</tr>
<tr>
<td>APIX 5mg BID</td>
<td></td>
</tr>
<tr>
<td>Warfarin (INR 2-3)</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>Apixaban</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>2.3%</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>0.6%</td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

- Non-inferior to conventional therapy (p<0.001)
- Significantly lower rates of major bleeding (p<0.001)

Apixaban and extended VTE Treatment: AMPLIFY-EXT

<table>
<thead>
<tr>
<th>Study</th>
<th>AMPLIFY-EXT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Double-blind, superiority, Placebo-Control</td>
</tr>
<tr>
<td>Required Treatment prior to enrollment</td>
<td>6-12 mos prior to VTE</td>
</tr>
<tr>
<td>Treatment</td>
<td>Apixaban 2.5mg BID, Apixaban 5mg BID</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Treatment Duration</td>
<td>12 mos (plus 1 mos follow-up)</td>
</tr>
<tr>
<td>Results</td>
<td>Apixaban</td>
</tr>
<tr>
<td>Primary endpoints</td>
<td>2.5mg: 1.7%</td>
</tr>
<tr>
<td>5mg: 1.7%</td>
<td>0.20 (0.11-0.34)</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>2.5mg: 0.2%</td>
</tr>
<tr>
<td>5mg: 0.2%</td>
<td>0.23 (0.03-2.24)</td>
</tr>
<tr>
<td>Major or CRNMB</td>
<td>2.5mg: 3.2%</td>
</tr>
<tr>
<td>5mg: 4.3%</td>
<td>1.62 (0.96-2.73)</td>
</tr>
</tbody>
</table>

- Extended use with treatment or prophylaxis dose reduced risk of recurrent VTE (p<0.001)
- No increase in rate of major bleeding
- FDA accepts application for review Dec 2013

Summary of Antithrombotic Therapy

- More information needed to answer questions for TSOAC use in ACS, AF ablation and CVSN
- New indications for TSOAC agents in acute and extended VTE treatment
- Keep an eye out for future indications of TSOAC agents
- FDA decision on endoxaban