Double and Triple Antithrombotic Therapy Update

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Disclosures

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Combining Two Topics into One

- Recent advances in antithrombotic therapy in patients with acute coronary syndromes
- Recent advances in antithrombotic therapy in patients with atrial fibrillation

Antithrombotic therapy in patients with.....

- Acute Coronary Syndromes
- Atrial Fibrillation
Patients with AF and ACS
Common Clinical Scenarios

- Patient with chronic atrial fibrillation who has an acute coronary syndrome event
- Patient with paroxysmal atrial fibrillation and angina undergoes PCI with a drug eluting stent
- Patient with an anterior STEMI develops atrial fibrillation in the setting of his STEMI
- Patient with coronary disease and a prior PCI develops atrial fibrillation
AF and CAD
Overlapping Patient Populations
Overlapping Indications for Antithrombotic Therapy

Challenging

AF
Atrial Fibrillation

CAD (ACS, PCI/Stent, CABG)

Doses
Stent type
Duration
Bleeding
Subgroups
Genetics
Cost

VKA
Antiplatelets
NOACs

Challenging

The art of medicine

Practice guidelines largely based on clinical trials that exclude patients with other diseases / indication

Aspirin (drop?)
Clopidogrel
New P2Y12s
NOACs?
What we know

- AF is a frequent complication of myocardial infarction (MI), with incidence ranging from 5–23%.
- AF is associated with worse outcome.

What we don’t know

- How should we use aspirin, clopidogrel, and warfarin, given high risk of both thrombotic and bleeding outcomes?
Adjusted One-year Mortality

P value <0.001

Mortality %

Days

Duke Clinical Research Institute

From Thought Leadership to Clinical Practice

Lopes RD, Heart 2008
Coronary stenting in patient with AF and high risk of stroke

The problem: You can not simultaneously prevent all three!

Stent thrombosis + Stroke = Major Bleeding
Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data

Rikke Sørensen, Morten L Hansen, Steen Z Abildstrom, Anders Hvelplund, Charlotte Andersson, Casper Jørgensen, Jan K Madsen, Peter R Hansen, Lars Køber, Christian Torp-Pedersen, Gunnar H Gislason

- Over 40,000 patients
- Registries from Denmark
- 2000-2005
- Mean Follow-up 476 days
- 4.6% of patients were admitted to hospital with bleeding

The Lancet. 2009;374(9706):1967-74
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Yearly Incidence of Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2.6%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>4.6%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>4.3%</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>3.7%</td>
</tr>
<tr>
<td>Aspirin plus Warfarin</td>
<td>5.1%</td>
</tr>
<tr>
<td>Warfarin plus clopidogrel</td>
<td>12.3%</td>
</tr>
<tr>
<td><strong>Triple Therapy</strong></td>
<td><strong>12.0%</strong></td>
</tr>
</tbody>
</table>

Hazard Ratios for Bleeding

A Non-fatal and fatal bleeding

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin alone</td>
<td>1.00</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Clopidogrel alone</td>
<td>1.33</td>
<td>1.11</td>
<td>1.59</td>
</tr>
<tr>
<td>Vitamin K antagonist alone</td>
<td>1.23</td>
<td>0.94</td>
<td>1.61</td>
</tr>
<tr>
<td>Aspirin plus clopidogrel</td>
<td>1.47</td>
<td>1.28</td>
<td>1.69</td>
</tr>
<tr>
<td>Aspirin plus vitamin K antagonist</td>
<td>1.84</td>
<td>1.51</td>
<td>2.23</td>
</tr>
<tr>
<td>Clopidogrel plus vitamin K antagonist</td>
<td>3.52</td>
<td>2.42</td>
<td>5.11</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>4.05</td>
<td>3.08</td>
<td>5.33</td>
</tr>
</tbody>
</table>

The Lancet. 2009;374(9706):1967-74
Over 82,000 Danish Patients with AF
National Registry
1997-2006
Mean Follow-up: 3.3 Years
11.4% developed a non fatal or fatal bleeding
How about dropping aspirin, using warfarin plus clopidogrel?
WOEST Study Primary Endpoint Incidence of TIMI Bleeding Events


HR=0.36  95% CI 0.26-0.50
p<0.001
WOEST Study Secondary Endpoint Incidence of Death, MI, Stroke, Stent Thrombosis & Target Vessel Revascularization

Cumulative Incidence of Events (%)

Treatment duration (days)

N at risk: 284 272 270 266 261 252 242 223

Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation (ISAR-TRIPLE Trial)

To evaluate clinical outcomes of a therapy duration of 6 weeks clopidogrel versus 6 months clopidogrel after DES implantation in patients receiving concomitantly aspirin and oral anticoagulation
**ISAR-TRIPLE**

**Trial design:** Patients with an indication for oral anticoagulation (OAC) and undergoing DES PCI were randomized to either 6 weeks or 6 months of triple therapy (aspirin + clopidogrel + OAC initially, aspirin + OAC indefinitely). Patients were followed for 9 months.

**Results**

- Primary endpoint: Composite of death, MI, stent thrombosis, stroke, TIMI major bleeding at 9 months for 6 weeks vs. 6 months of triple therapy: 9.8% vs. 8.8%, HR 1.14, 95% CI 0.68-1.91, p = 0.63

- Cardiac death, MI, stent thrombosis, ischemic stroke: 4.0% vs. 4.3%, p = 0.87; TIMI major bleeding: 5.3% vs. 4.0%, p = 0.44

- Stent thrombosis: 0.7% vs. 0%

**Conclusions**

- 6-week duration of triple therapy is not superior to a 6-month duration of triple therapy in patients undergoing DES PCI, who also had an indication for OAC use

- Trial was underpowered to assess smaller bleeding differences

Fiedler KA et al, JACC, 2015
New 2014 European joint consensus document on management of NVAF and ACS/PCI

**STEP 1 – Stroke risk**
- **CHA₂DS₂-VASc = 1**
  - Low to intermediate (e.g. HAS-BLED = 0–2)
  - Stable CAD
    - If PCI is performed
      - Triple or dual therapy*
        - O A C
        - or DAPT
        - A C
    - Dual therapy**
      - O A or C
      - or DAPT
      - A C
  - ACS
    - If PCI is performed
      - Triple or dual therapy*
        - O A C
    - Dual therapy**
      - O A or C
  - Stable CAD
    - If PCI is performed
      - Triple or dual therapy*
        - O A C
      - or DAPT
        - A C
  - ACS

**STEP 2 – Bleeding risk**
- **CHA₂DS₂-VASc ≥ 2**
  - High (e.g. HAS-BLED ≥ 3)
  - Low to intermediate (e.g. HAS-BLED = 0–2)
  - Stable CAD
    - If PCI is performed
      - Triple or dual therapy*
        - O A C
    - Dual therapy**
      - O A or C
  - ACS
    - If PCI is performed
      - Triple or dual therapy*
        - O A C
  - Stable CAD
    - If PCI is performed
      - Triple or dual therapy*
        - O A C
  - ACS

**STEP 3 – Clinical setting**
- **Stable CAD**
- **ACS**

**STEP 4 – Antithrombotic therapy**
- **Time from PCI/ACS**
  - 0
  - 4 weeks
  - 6 months
  - 12 months
  - Lifelong

- **Oral anticoagulation**
  - O
- **ASA 75–100 mg daily**
  - A
- **Clopidogrel 75 mg daily**
  - C

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*Dual therapy with oral anticoagulation and clopidogrel may be considered in selected patients; **ASA as an alternative to clopidogrel may be considered in patients on dual therapy (i.e. oral anticoagulation plus single antiplatelet); ***Dual therapy with oral anticoagulation and an antiplatelet agent (ASA or clopidogrel) may be considered in patients at very high risk of coronary events. DAPT = dual antiplatelet therapy; Lip et al Eur Heart J 2014 doi:10.1093/eurheartj/ehu298.

Slide by C. Michael Gibson, M.S., M.D.
### Triple Versus Dual Antithrombotic Therapy in Patients with Atrial Fibrillation and History of Coronary Artery Disease: Insights from the ORBIT-AF Registry

<table>
<thead>
<tr>
<th>Antithrombotic Medication</th>
<th>DT1 N=1347</th>
<th>DT2 N=196</th>
<th>TT N=152</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>89%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>11%</td>
<td>96%</td>
<td>98.7%</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>0.2%</td>
<td>4%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Warfarin</td>
<td>95.5%</td>
<td>0</td>
<td>99.3%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>4.5%</td>
<td>0</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

DT1 = OAC plus an antiplatelet agent  
DT2 = 2 antiplatelet agents  
TT = OAC plus two antiplatelet agents

TRIPLE THERAPY WITH ASPIRIN, PRASUGREL AND VKA

Figure 1  Composite of TIMI Major and Minor Bleeding

Saraoff N. J Am Coll Cardiol 2013;61:2060-2066
TRIPLE THERAPY WITH ASPIRIN, PRASUGREL AND VKA

Figure 2

Composite of Death, Myocardial Infarction, Ischemic Stroke, or Stent Thrombosis

Saraoff N. J Am Coll Cardiol 2013;61:2060-2066
**TRIPLE THERAPY (ASA, CLOPIDOGREL+VKA) VS DOUBLE THERAPY (TICAGRELOR +VKA)**

n=107 pts TT, 159 pts DT, major bleeding HAS-BLED

Spontaneous major bleeding

Similar rates of thrombotic and bleeding events in TT and DT with ticagrelor

Case

- 70 year old man with HTN, HF, DM, AF currently on rivaroxaban 20mg/daily presents with NSTEMI
- Undergoes coronary angiography and found to have 90% LAD lesion
  - Treated with a DES

How would you treat this patient at discharge?
Case

1. Aspirin plus clopidogrel plus warfarin (INR around 2) for 3 months
2. Aspirin plus rivaroxaban 2.5mg twice daily plus clopidogrel for 6 months
3. Aspirin plus apixaban 2.5mg plus clopidogrel for 3 months
4. Clopidogrel plus warfarin for 6 months
5. Aspirin plus clopidogrel plus Dabigatran 110 mg twice daily for 3 months
6. Aspirin plus clopidogrel plus warfarin (INR around 2) for 1 month
Bewildering Number of Strategies in the ACS Patient with Atrial Fibrillation

- **ASA Dose:** None, Low, High 2 1+8 = 9
- **ASA Duration (mos):** 1, 3, 6, 12, 4
- **Thienopyridine:** None, Clop, Ticlid, Pras, Ticag 4 1+16 = 17
- **Thienopyridine duration (mos):** 1, 3, 6, 12, 4
- **AC:** None, Warf, Dabi, Riva, Apix, Edox 5 1+10 = 11
- **AC INR/Dose:** Low, High 2

Permutations of Single, Dual or Triple Therapy as *Early Initial Therapy* (0,1,3,6 mos) following ACS: 9 X 17 X 11 = 1,683

Permutations of Single or Dual Therapy *Late After Early Therapy* (0,1,3,6 mos) following ACS: 1,683

Total Permutations *throughout one year:* 2.8 Million

*Slide by C. Michael Gibson, M.S., M.D.*
An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention PIONEER AF-PCI

C. Michael Gibson, MS, MD
on behalf of the PIONEER Investigators
Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI

- 2100 patients with NVAF
- Coronary stenting
- No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

**Primary endpoint:** TIMI major + minor + bleeding requiring medical attention

**Secondary endpoint:** CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

- Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
- Alternative P2Y₁₂ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
- Low-dose aspirin (75-100 mg/d).

Gibson et al. AHA 2016.
Pre-Randomization Choice of Duration of DAPT & Thienopyridine: PIONEER AF-PCI

- 2100 patients with NVAF
- Coronary stenting
- No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

≤ 72 hours
After Sheath removal

Rivaroxaban 15 mg qd*
Clopi 95%, Ticag 4%, Prasugrel 1%

1 mo: 16%
6 mos: 35%
12 mos: 49%

Rivaroxaban 2.5 mg bid
Clopi 95%, Ticag 4%, Prasugrel 1%
Aspirin 75-100 mg qd†

Rivaroxaban 15mg QD
Aspirin 75-100 mg qd

VKA (target INR 2.0-3.0)
Clopi 95%, Ticag 4%, Prasugrel 1%
Aspirin 75-100 mg qd

VKA (target INR 2.0-3.0)
Aspirin 75-100 mg qd
TTR 65%

WOEST Like
ATLAS Like
Triple Therapy

Gibson et al. AHA 2016.
Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events

**Treatment-emergent period:** period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.

Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.

Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15mg QD comparing VKA) two-sided log rank test.

**VKA + DAPT**
- No. at risk: 697
- Days: 26.7%

**Riva + DAPT**
- No. at risk: 696
- Days: 18.0%

**Riva + P2Y_{12}**
- No. at risk: 696
- Days: 16.8%

Riva + P2Y_{12} v. VKA + DAPT
- HR=0.59 (95% CI: 0.47-0.76)
- p <0.000013
- ARR=9.9
- NNT=11

Riva + DAPT v. VKA + DAPT
- HR=0.63 (95% CI: 0.50-0.80)
- p <0.00018
- ARR=8.7
- NNT=12

Gibson et al. AHA 2016. 
# Bleeding Endpoints Using TIMI Criteria (Primary Analysis)

<table>
<thead>
<tr>
<th>Kaplan-Meier Estimates</th>
<th>Hazard Ratio (95% CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riva + P2Y&lt;sub&gt;12&lt;/sub&gt; (N=696)</td>
<td>Riva + DAPT (N=706)</td>
<td>Comb. Riva (N=1402)</td>
</tr>
<tr>
<td>Clinically significant bleeding</td>
<td>109 (16.8%)</td>
<td>117 (18.0%)</td>
</tr>
<tr>
<td>TIMI Major</td>
<td>14 (2.1%)</td>
<td>12 (1.9%)</td>
</tr>
<tr>
<td>TIMI minor</td>
<td>7 (1.1%)</td>
<td>7 (1.1%)</td>
</tr>
<tr>
<td>BRMA</td>
<td>93 (14.6%)</td>
<td>102 (15.8%)</td>
</tr>
<tr>
<td>Riva + P2Y&lt;sub&gt;12&lt;/sub&gt; vs. VKA + DAPT</td>
<td>0.59 (0.47-0.76)</td>
<td>0.63 (0.50-0.80)</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Riva + DAPT vs. VKA + DAPT</td>
<td>0.66 (0.33-1.31)</td>
<td>0.57 (0.28-1.16)</td>
</tr>
<tr>
<td>p=0.234</td>
<td>p=0.114</td>
<td>p=0.093</td>
</tr>
<tr>
<td>Combined vs. VKA + DAPT</td>
<td>0.51 (0.20-1.28)</td>
<td>0.50 (0.20-1.26)</td>
</tr>
<tr>
<td>p=0.144</td>
<td>p=0.134</td>
<td>p=0.071</td>
</tr>
</tbody>
</table>

**Treatment-emergent period:** period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

**Clinically significant bleeding** is the composite of TIMI major, TIMI minor, and BRMA events. A subject could have more than one component event. *n* = number of subjects with events, *N* = number of subjects at risk, % = KM estimate at the end of study.

Hazard ratios as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg OD comparing VKA) Cox proportional hazards model. Log-Rank *p*-values as compared to VKA group are based on the (stratified, only for Overall 2.5 mg BID/15 mg OD comparing VKA) two-sided log rank test.

BRMA = Bleeding requiring medical attention, TIMI = Thrombolysis in myocardial infarction, CI = confidence interval, DAPT = dual antiplatelet therapy, HR = hazard ratio, VKA = vitamin K antagonist.

Gibson et al. AHA 2016.

Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke

Cardiovascular Death, Myocardial Infarction, or Stroke (%)

Days

Riva + P2Y₁₂
6.5%
6.0%
5.6%

Riva + DAPT

VKA + DAPT

VKA + DAPT

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Composite of adverse CV events is composite of CV death, MI, and stroke.

Hazard ratios as compared to VKA group are based on the (stratified, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.

Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/115 mg QD comparing VKA) two-sided log rank test.

6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines.

Gibson et al. AHA 2016.

Among stented AF participants, administration of either rivaroxaban 15 mg daily plus P2Y12 monotherapy for one year or rivaroxaban 2.5 mg BID plus 1, 6, or 12 months of DAPT reduced the risk of clinically significant bleeding as compared with standard of care VKA plus 1, 6, or 12 months of DAPT and yielded comparable efficacy with broad confidence intervals.
Interpretation of the PIONEER Results

- PIONEER provides initial important evidence in a field where it has been lacking

- Clear signal of less bleeding with both reduced antithrombotic regimens
  - No aspirin (riva 15 + P2Y12)
  - Very low-dose OAC (riva 2.5 + P2Y12 + aspirin)

- Not powered for efficacy and effects on ischemic events were imprecise with wide confidence intervals
  - Stroke: No Aspirin = HR 1.07, 95% CI 0.39-2.96
    Low-dose OAC = HR 1.36, 95% CI 0.52-3.58
  - Stent thrombosis: No aspirin = HR 1.20, 95% CI 0.32-4.45
    Low-dose OAC = HR 1.44, 95% CI 0.40-5.09

Gibson et al. AHA 2016. 
**RE-DUAL PCI**

- **Trial design**
  - **1° End Point**
    - Time to first ISTH major bleeding or clinically relevant non-major bleeding event
    - n= 2,500 patients (approx. 834 patients per arm)

- **Patients >80 years living outside of the USA will be assigned to 110mg dabigatran etexilate (BID) or warfarin in a 1:1 ratio**

- **Screening**
  - 0-120 hours post-PCI

- **Dabigatran etexilate 150 mg BID + P2Y12 inhibitor**
- **Dabigatran etexilate 110 mg BID + P2Y12 inhibitor**
- **Warfarin (INR 2.0 – 3.0) + P2Y12 inhibitor + ASA**

- **Paroxysmal, persistent or permanent NVAF, PCI with stenting [BMS or DES] elective or ACS**

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ACS: Acute Coronary Syndrome; ASA: Acetylsalicylic acid; BMS: Bare Metal Stent; DES: Drug Eluting Stent; ISTH: International Society on Thrombosis and Haemostasis; INR: International Normalized Ratio; NVAF: Non Valvular Atrial Fibrillation; PCI: Percutaneous Coronary Intervention

ClinicalTrials.gov: NCT02164864

https://clinicaltrials.gov/ct2/show/NCT02164864
Apixaban Versus Warfarin in Patients with AF and ACS and/or PCI: The AUGUSTUS Trial

**Inclusion**
- AF (prior, persistent/permanent, paroxysmal)
- Physician decision that oral anticoagulation is indicated
- ACS and/or PCI with planned P2Y12 inhibitor for at least 6 months

**Exclusion**
- Contraindication to DAPT
- Other reason for warfarin (mechanical valve, mod/sev MS)

**Randomize**

\[ n = 4,600 \] Patients

**Apixaban**
- P2Y12 inhibitor for all patients x 6 months
- Aspirin for all on the day of ACS and/or PCI until randomization
- Aspirin versus placebo after randomization

**Warfarin**
- ASA placebo

**Primary outcome:** major/clinically relevant non-major bleeding (through 6 months)

**Secondary objective:** Death, MI, stroke, stent thrombosis, urgent revascularization, re-hospitalization

Renato Lopes. Duke University
Edoxaban Versus Warfarin in Patients with AF and PCI: The ENTRUST-AF-PCI Trial

**Inclusion**
- AF (prior, persistent/permanent, paroxysmal)
- Successful PCI with Stent

**Randomize**

\[ n = 1,500 \]

**Patients**

**Exclusion**
- Contraindication to DAPT
- Other reason for warfarin (mechanical valve, mod/sev MS)

**Edoxaban 60/30 mg QD**

**VKA**

Aspirin & Clopidogrel
(selected patients Prasugrel/Ticagrelor)

**Primary outcome:** major/clinically relevant non-major bleeding
(through 12 months)

**Secondary objective:** CV death, MI, stroke/SE, stent thrombosis
(through 12 months)

*Duke Clinical Research Institute*
The Sweet Spot for Antithrombotics

Ischemic Events
Ischemic stroke
Myocardial infarction
Unstable angina
CV death
Revascularization

Patient Factors

Dose

Combinations

Duration

Bleeding
Intracranial
Major bleeding
Transfusion
Minor bleeding

Duke Clinical Research Institute
From Thought Leadership to Clinical Practice
Conclusions

- Combination antithrombotic therapy with aspirin, a P2Y12 inhibitor, and OAC increases bleeding over the use of any of these therapies alone
  - Benefits of combination therapy are less clear
- Reasonable strategies to mitigate bleeding risk
  - Limit duration of DAPT in pts who require OAC
  - Use clopidogrel rather than more potent P2Y12 inhibitors
  - Use OACs that cause less bleeding (edoxaban, apixaban, dabigatran 110 rather than rivaroxaban, dabigatran 150, VKA) with a single antiplatelet agent
  - Some initial data on NOAC and DAPT for AF patients
- The best current strategy for a patients with an indication for DAPT and OAC is to enroll them in AUGUSTUS.
The Future

- Triple Therapy might not be needed: one antiplatelet plus a new anticoagulant (aspirin out?)

- Duration of Triple and/or Dual Therapy for AF patients is key

- Patient management options will be better clarified:
  - Randomized trials
“In medicine, therapeutic decisions should be based on science; the ‘art’ of medicine is in how you interact with the patient.”

- Robert M. Califf MD
Thank you!