Worth the risk or clots of trouble?

Yaw B. Owusu, PharmD, MSc Candidate
Ambulatory Care Pharmacy Resident
Blackstock Family Health Center
The University of Texas at Austin College of Pharmacy
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Learning Objectives
1. Review the clotting cascade and the anticoagulant mechanism of warfarin
2. Discuss the indications for long-term warfarin therapy
3. Identify possible indications warranting combination warfarin and aspirin therapy
4. Explain the bleeding risk associated with warfarin therapy
5. Review studies evaluating the use of combined oral anticoagulant and aspirin in atrial fibrillation patients with coexisting indication for aspirin
I. Introduction\textsuperscript{1-6}
   a. Increasing prevalence of oral anticoagulation (OAC)
      i. Warfarin is the most widely used oral anticoagulant in the world
      ii. Out-patient prescriptions for warfarin use in the United States (US) increased from 21 million in 1998 to over 30 million in 2004
      iii. Reasons for increased prevalence of warfarin use in the US include
           1. Aging population
           2. Evidence of effectiveness of OAC in preventing stroke in atrial fibrillation patients. The evidence-based studies were published in the 1990’s.
      iv. The most common indication for OAC in the US is atrial fibrillation (AF)
      v. There are strong recommendations of combined OAC and antiplatelet therapy only for patients undergoing PCI with stents and patients with prosthetic heart valves. The national guidelines are not clear on the appropriateness of using antiplatelet therapy in patients on chronic OAC.
      vi. The annual rates of major bleeding from warfarin in the US is estimated to be 1-5% based on clinical trial data
      vii. Approximately 10% of all major bleeding from warfarin is fatal
      viii. It is estimated that about 4 of 10 patients receiving chronic warfarin therapy are also on an antiplatelet agent

II. Mechanism of thrombus formation\textsuperscript{6-9}
   a. Platelet plug formation
      i. Vascular injury breaches the vessel wall exposing collagen to the subendothelial matrix and tissue factor (factor III) to blood
      ii. Exposed collagen triggers platelet activation and exposed tissue factor initiates generation of thrombin which converts fibrinogen to fibrin
      iii. Platelets adhere to the site of injury via the membrane adhesion receptor, glycoprotein (GP) Ib/IX/V complex, mediated by von Willebrand factor leading to the activation of integrin GP IIb/IIIa
      iv. GP IIb/IIIa on platelet surface binds to its receptor to mediate platelet adhesion, aggregation and spreading
      v. Platelet aggregation is promoted by adenosine diphosphate (ADP) via binding to G-protein coupled receptors P2Y on platelet surface

![Figure 1. Platelet response to vascular injury\textsuperscript{7}](image)
b. Two proposed models of coagulation

i. Coagulation cascade model
   1. This model is useful in interpreting the aPTT and PT tests
   2. Distinct intrinsic and extrinsic pathways that converge at a common pathway at the level of factor Xa leading to the formation of thrombin
   3. This model does not fully explain bleeding tendencies in some clotting deficiencies, e.g., hemophilia. This has led to the hypothesis that both the intrinsic and extrinsic pathways are linked.

![Diagram of the coagulation cascade model](image_url)

Figure 2. The cascade hypothesis: intrinsic and extrinsic pathways

ii. Cell based model of hemostasis
   1. This model proposes that hemostasis occurs in step-wise process regulated by cellular processes in vivo
   2. The cell based model shows the interaction of clotting factors with specific cell surfaces
   3. The cell based model includes cells essential for the hemostasis process, platelets, cellular source of tissue factor and plasma levels of coagulation factors which when deficient can cause bleeding disorders
   4. Coagulation occurs by three different overlapping steps occurring on three different surfaces
      A. Initiation on a tissue factor bearing subendothelial cell leading to the activation of factors X and IX
      B. Amplification leads to platelet activation by thrombin and it sticks to the site of injury to form a plug
      C. Propagation leads to the production of enough factor IIa to support additional platelet activation
Figure 3. The cell based model system of hemostasis in veins\textsuperscript{12}

Abbreviations: TF: Tissue factor  vWF: von Willebrand factor  TFPI: tissue factor pathway inhibitor
III. Warfarin or Vitamin K antagonist

a. Mechanism of action
   i. Inhibits vitamin K dependent coagulation factors II (prothrombin), VII, IX and X and proteins C and S
   ii. Warfarin interferes with the cyclic interconversion of vitamin K and vitamin K epoxide
   iii. This warfarin interference alters the γ-carboxylation of glutamate residues on the terminal regions of vitamin K dependent proteins
   iv. The vitamin K dependent coagulation factors require γ-carboxylation for their procoagulant activity
   v. Proteins C and S also require γ-carboxylation to exert their effect

Figure 4. Mechanism of warfarin in inhibiting coagulation factors
b. Monitoring anticoagulation intensity
   i. The prothrombin time (PT) test is measured in seconds
   ii. The PT is converted to international normalized ratio (INR) for standardized reporting \[ \text{INR} = \frac{\text{PT}_{\text{patient}}}{\text{PT}_{\text{normal}}} \]
   iii. Optimal target range for INR has been established for various indications
   iv. Bleeding is the major complication and it is closely related to the intensity of anticoagulation. The therapeutic range of INR for most indications requiring OAC is between 2-3 with higher goals increasing the risk of bleeding and lower goals increasing the risk of thromboembolism.

IV. Indications for long-term/chronic warfarin therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Age &gt;75; history of transient ischemic attack (TIA)/stroke/thromboembolism(TE); hypertension (HTN), valve replacement, poor left ventricular function; rheumatic mitral valve disease</td>
</tr>
<tr>
<td>Thromboembolism (DVT, PE)</td>
<td>Recurrent DVT/PE; antiphospholipid antibody syndrome; persistent risk factors (antithrombin, protein C, protein S deficiencies; factor V Leiden; prothrombin gene mutation; malignancy)</td>
</tr>
<tr>
<td>Cerebrovascular disease (TIA, stroke)</td>
<td>Cardioembolic source (atrial fibrillation, heart failure, left ventricular dysfunction, mural thrombus); embolic event despite anticoagulation</td>
</tr>
<tr>
<td>Valvular disease (aortic valve, rheumatic mitral valve)</td>
<td>All patients anticoagulated</td>
</tr>
<tr>
<td>Bioprosthetic valve replacement</td>
<td>Atrial fibrillation; following systemic embolism</td>
</tr>
<tr>
<td>Mechanical valve replacement</td>
<td>All patients anticoagulated</td>
</tr>
</tbody>
</table>

Table 1. Indications for chronic warfarin therapy

V. Aspirin
   a. Aspirin has the following indications in cardiovascular care
      i. Primary prevention of ischemic stroke in low risk AF patients
      ii. Primary prevention of CAD
      iii. Secondary prevention of stroke/TIA
      iv. Secondary prevention of CAD
      v. Prevention of thrombosis post-PCI ± stent
   b. Mechanism of action of aspirin
      i. Aspirin irreversibly inactivates cyclooxygenase (COX) enzyme
      ii. COX-1 catalyzes the formation of thromboxane-A2 (TXA2) from arachidonic acid
      iii. TXA2 is involved in platelet activation
VI. Combination aspirin and warfarin therapy
a. Rational for adding aspirin to warfarin when aspirin is indicated for cardiovascular prophylaxis\textsuperscript{2,16,18-21}
   i. Works by different mechanism of action to inhibit platelet activation
   ii. Patients receiving OAC usually have concomitant comorbidities including coronary artery disease (CAD) or have a high risk for stroke and clinicians believe that aspirin stabilizes the vascular disease with significant reduction in the risk of cardiovascular events
   iii. Combination warfarin and low dose aspirin has shown favorable outcomes in studies of acute coronary syndrome (ACS) patients. Outcomes in these studies included:
      1. death
      2. non-fatal reinfarction
      3. thromboembolic stroke
      4. coronary artery reocclusions
      5. event free survival rate at three months

b. Conditions in which adding aspirin to warfarin is preferred
   i. Recommendations by US guidelines (Class I level only)\textsuperscript{22-27}
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation (Class I level only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEST 2008 Guideline for primary and secondary prevention of coronary artery disease</td>
<td>No class I recommendation recommending combination warfarin and aspirin</td>
</tr>
<tr>
<td>ACC/AHA/SCAI 2007 Guidelines update for percutaneous coronary intervention</td>
<td>In patients requiring warfarin, aspirin and/or clopidogrel after PCI, target INR of 2.0-2.5 is recommended with low dose aspirin (75-81 mg) and a 75 mg dose of clopidogrel</td>
</tr>
<tr>
<td>ACC/AHA 2007 Guidelines for the management of patients with STEMI</td>
<td>In patients requiring aspirin, warfarin and clopidogrel after PCI with stent, an INR of 2.0-2.5 is recommended with low dose aspirin (75-81 mg) and 75 mg dose of clopidogrel</td>
</tr>
<tr>
<td>ACC/AHA 2006 Guidelines for the management of patients with valvular heart disease</td>
<td>AVR in high risk (i.e. AF, prior thromboembolism, LV dysfunction, hypercoagulable states), aspirin 75–100 mg/day + warfarin (INR 2.5–3.5)</td>
</tr>
<tr>
<td>MVR, aspirin 75–100 mg/day + warfarin (INR 2.5–3.5)</td>
<td></td>
</tr>
<tr>
<td>AHA/ACC Guidelines for secondary prevention for patients with other atherosclerotic vascular disease: 2006 Update</td>
<td>PCI with stent after MI, maintain warfarin at INR of 2.0 -3.0 when clinically indicated and monitor closely because of increased risk of bleeding from aspirin and/or clopidogrel</td>
</tr>
</tbody>
</table>

Table 2. US Guideline for combined OAC and antiplatelet (Class I level only)

ii. Results of studies and systematic reviews\textsuperscript{19,28}
   1. Cappelleri et al
      a. Meta analysis of five randomized controlled trials (RCTs) totaling 748 patients
      b. Compared the efficacy and safety of combined oral anticoagulant and antiplatelet (aspirin or dipyridamole) therapy versus oral anticoagulant alone after prosthetic valve replacement
      c. The combined regimen reduced embolism and overall mortality by approximately 67% (p=0.0032) and overall mortality by approximately 40% (p=0.11)
2. Dentali et al
   a. Meta analysis of 10 RCTs totaling 4,180 patients
   b. Compared combined OAC therapy with OAC alone in patients at risk for cardiovascular disease
   c. The combined regimen reduced the risk of arterial thromboembolism by about 34% (95% CI, 0.52-0.84)
   d. Benefits were limited to only patients on mechanical heart valve (OR, 0.27; 95% CI, 0.15-0.49)

VII. Bleeding risk associated with warfarin therapy
   a. Rates of bleeding with warfarin alone or in combination with aspirin
      i. Studies have shown that major bleeding is the most common complication of warfarin therapy
      ii. The Subcommittee on Control of Anticoagulation of the Scientific and the Standardization Committee of the International Society on Thrombosis and Haemostasis defines major bleeding in non-surgical patients as:
          1. fatal bleeding and/or
          2. symptomatic bleeding in a critical area (e.g., retroperitoneum) or organ
          3. bleeding causing a fall in hemoglobin level of ≥ 2 mg/dL or leading to a transfusion of 2 or more units of blood
      iii. The rates of major hemorrhage on OAC therapy for various indications is estimated from several trials (table 3)
      iv. The wide variation of the rates of major bleeding is due to different patient populations, different intensities of treatment and inconsistency in the definition of major bleeding

<table>
<thead>
<tr>
<th>Indication for anticoagulation therapy</th>
<th>Rates of major hemorrhage (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic heart valves</td>
<td>1.0 – 19.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0 – 7.0</td>
</tr>
<tr>
<td>Acute ischemic coronary syndrome</td>
<td>0 – 6.8</td>
</tr>
<tr>
<td>Ischemic heart disease, long-term</td>
<td>0.6 – 14.5</td>
</tr>
<tr>
<td>Venous thromboembolism, initial management</td>
<td>0 – 7.0</td>
</tr>
</tbody>
</table>

Table 3. Range of rates of major hemorrhage on anticoagulant therapy in percentage per year

v. Bleeding risk increases with the intensity of warfarin therapy and/or the addition of antiplatelet therapy
vi. Table 4 shows the rate of bleeding with warfarin increases when aspirin is added, and the rate is even higher with higher dose of aspirin with all factors held constant
vii. Linkins et al, reported case fatality rate for major bleeding from warfarin of 13.4% (95% CI, 9.4% to 17.4%) in a cohort of 10,757 patients who received 4,734 patient-years of anticoagulation therapy
<table>
<thead>
<tr>
<th>Study/yr</th>
<th>Intervention</th>
<th>Indication</th>
<th>Number of patients (Patient-Years)</th>
<th>Major bleeding (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turpie et al/1993</td>
<td>Warfarin (INR 3.0-4.5) plus placebo</td>
<td>Prosthetic heart valves</td>
<td>186 (~462)</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>Warfarin (INR 3.0-4.5) plus aspirin 100 mg</td>
<td></td>
<td>186 (~462)</td>
<td>5.2</td>
</tr>
<tr>
<td>Laffort et al/2000</td>
<td>VKA (INR 2.5-3.5)</td>
<td>Prosthetic heart valves</td>
<td>120 (120)</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>VKA (INR 2.5-3.5) plus aspirin 200 mg</td>
<td></td>
<td>109 (109)</td>
<td>19.2</td>
</tr>
<tr>
<td>Altman et al/1996</td>
<td>Acenocoumarol (INR 2.0-3.0) plus aspirin 100 mg</td>
<td>Prosthetic heart valves</td>
<td>207 (416)</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Acenocoumarol (INR 2.0 – 3.0) plus aspirin 600 mg</td>
<td></td>
<td>202 (366)</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Table 4. Rates of bleeding with oral anticoagulants increase with intensity of anticoagulation and the addition of antiplatelet agent\textsuperscript{42}

b. Outpatient bleeding risk index (BRI)\textsuperscript{44-46}
   i. Estimates prospectively the probability of bleeding in outpatients on warfarin therapy
   ii. Classifies the risk for bleeding as high, intermediate or low
   iii. Patients receive a score of 1 for each risk factor and based on the total score, they are classified as low- (0 points), intermediate (1 or 2 points) or high-risk (3 or 4 points) for major bleeding (table 4)
   iv. Knowledge of the risk factors can aid in therapy choices involving anticoagulants and antiplatelets

1. What risk factors are present? (check all that apply)
   - Age ≥65 years
   - History of stroke
   - History of GIB
   - Recent MI, Hct<30%
   - Cr>1.5 mg/dl, or
   - Diabetes Mellitus

2. Sum the risk factors:

3. Classify your patient:

4. Estimated Risk for Major Bleeding*
   - in 3 Months
     - Low Risk: 2%
     - Intermediate Risk: 5%
     - High Risk: 23%
   - in 12 Months
     - Low Risk: 3%
     - Intermediate Risk: 12%
     - High Risk: 48%

*based on 1 cohort of 556 patients

Table 5. Example of an outpatient bleeding risk index\textsuperscript{44} GIB = gastrointestinal bleeding; MI = myocardial infarction; Hct = hematocrit; Cr = serum creatinine concentration
VIII. Select studies of combination OAC (INR 2-3) and aspirin

**Flaker and Colleagues. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: An exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials**

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To compare ischemic events and bleeding in SPORTIF III and V trials in post hoc analysis</th>
</tr>
</thead>
</table>
| **Design**    | SPORTIF III: Randomized, open-label, parallel-group study conducted in 23 countries to demonstrate the noninferiority of the oral direct thrombin inhibitor (ximelagatran) relative to warfarin (INR 2.0-3.0) for prevention of all strokes and systemic emboli in patients with atrial fibrillation (AF)  
SPORTIF V: Randomized, double-blind, parallel-group study conducted at 409 North American sites. |
| **METHODS**   | Protocols for SPORTIF III and V were the same except for treatment blinding |
| **Inclusion criteria** | - Permanent or paroxysmal nonvalvular AF with ≥1 of the following risk factors for stroke  
  - Hypertension  
  - Age ≥75 years  
  - Previous stroke, TIA or systemic embolism  
  - LVEF < 40% or symptomatic CHF  
  - Age ≥ 65 years and coronary artery disease  
  - Age ≥ 65 years and diabetes mellitus |
| **Exclusion criteria** | - Continuous aspirin treatment in any dose over 100 mg/d on any other antithrombotic agents  
  - Conditions associated with increased risk of bleeding  
  - History of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding  
  - Overt gastrointestinal bleeding in the previous year  
  - Endoscopically verified ulcer disease in the previous 30 days  
  - Hemorrhagic disorder  
  - Persistent BP > 180/100 mmHg  
  - Major surgical procedure in the previous 30 days  
  - Planned cardiovascular procedure |
| **Study groups** | - Ximelagatran 36 mg bid or warfarin dose adjusted to maintain INR 2.0-3.0 range |
| **Follow-up** | - 1, 4, and 6 weeks, and then at 2, 3, 4, 6, 8, 10, and 12 months, and every 3 months thereafter.  
  - Average treatment exposure was 16.5 months |
| **Endpoints** | - The primary endpoint in each study was the incidence of all strokes and systemic embolic (SE) events  
  - Secondary endpoints are death, acute MI, TIA, major and minor bleeding and discontinuation of treatment |
| **RESULTS** | - 7329 enrolled patients (3407 in SPORTIF III and 3922 in SPORTIF V)  
  - 3120 patients in ximelagatran group and 3172 patients in warfarin group  
  - Aspirin was prescribed to 1012 patients (531 in ximelagatran group and 481 in warfarin group) |
<table>
<thead>
<tr>
<th>Event</th>
<th>Warfarin (n=3172)</th>
<th>Warfarin + ASA (n=481)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1.5% (67/4455)</td>
<td>1.7% (11/642)</td>
<td>0.71</td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>1.6% (69/4454)</td>
<td>1.7% (11/642)</td>
<td>0.78</td>
</tr>
<tr>
<td>MI</td>
<td>1.0% (46/4452)</td>
<td>0.6% (4/463)</td>
<td>0.40</td>
</tr>
<tr>
<td>Death</td>
<td>2.5% (112/4464)</td>
<td>2.6% (17/644)</td>
<td>0.84</td>
</tr>
<tr>
<td>*Major bleeding</td>
<td>2.3% (100)</td>
<td>3.9% (25)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Figures in parenthesis: number of patients with events/patient years
*For major bleeding, figure in parenthesis represent number of patients with events

Conclusions
Adding aspirin to anticoagulant therapy (adjusted dose warfarin) is associated with higher rates of bleeding and no incremental benefits in preventing cerebral, systemic or coronary ischemic events

Critique
- Post hoc analysis
- Large sample size was used in the statistical analysis
- Patients on aspirin in the studies probably had more risk factors for stroke and MI thereby potentially biasing sample analyzed

Comments
- Results add to literature that the combination of aspirin and warfarin may not have any incremental benefit in reducing embolic events, but increase the risk of major bleeding
### Lechat P et al. Anticoagulant (fluindione)-aspirin combination in patients with high-risk atrial fibrillation

<table>
<thead>
<tr>
<th>Design</th>
<th>Multicenter, placebo-controlled, double-blind, randomized trial conducted at 49 investigating centers in France</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To evaluate the preventive efficacy against nonfatal thromboembolic events and vascular deaths in the combination of oral anticoagulant fluindione and aspirin 100 mg in patients with high risk nonvalvular atrial fibrillation</td>
</tr>
</tbody>
</table>

#### METHODS

**Inclusion criteria**
- Permanent or paroxysmal nonvalvular atrial fibrillation with a high risk defined as:
  - History of a thromboembolic event (TIA, nondisabling ischemic stroke or peripheral embolism)
  - Age ≥ 65 years plus at least one of the following:
    - A history of hypertension
    - A recent episode of CHF or LVEF <40%

**Exclusion criteria**
- Mitral stenosis
- Mitral regurgitation
- Interatrial communication
- Heart failure (NYHA class IV)
- Uncontrolled hypo- or hyperthyroidism
- Chronic alcoholism
- Carotid stenosis
- Long-term NSAID
- Coagulation disorders
- History of severe hemorrhages
- History of gastric ulcer

**Study groups and interventions**
- Fluindione adjusted to INR level of 2 – 2.6 plus aspirin 100 mg/day
- Fluindione adjusted to INR of 2.0 – 2.6 plus placebo
- The mean expected follow-up was 42 months

**Endpoints**
- Primary endpoint was a combination of any of the following events: stroke (ischemic or hemorrhagic), MI, systemic arterial embolism of arterial origin, vascular death, hemorrhagic complications
- Secondary endpoints included hemorrhagic complications, all-cause mortality and cardiovascular mortality

**Statistics**
- A total of 600 patients were planned to be recruited to achieve an 80% power to detect the difference between study groups for the primary endpoint
- Baseline characteristics were compared with the t test or Wilcoxon’s rank sum test and Fisher exact test
- Kaplan Meier survival curves were calculated for primary endpoint and the difference between the treatment groups was assessed with log-rank test
- Analysis of events was performed on an ITT principle and SAS was used for statistical calculations
RESULTS

- Only 157 patients were recruited after an 18-month period and mean follow up was 0.84 years
- Study was stopped prematurely because of the low inclusion rate and financial resources was insufficient for a longer trial
- Seventy five percent of patients were maintained between INR 1.5 – 3.5

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Fludione alone (n=81) n (%)</th>
<th>Combination (n=76) n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>2 (2.87)</td>
<td>5 (7.93)</td>
<td>0.21</td>
</tr>
<tr>
<td>Vascular deaths</td>
<td>3 (4.3)</td>
<td>3 (4.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Deaths secondary to severe hemorrhagic complications</td>
<td>1 (1.4)</td>
<td>2 (3.2)</td>
<td>0.61</td>
</tr>
<tr>
<td>Severe hemorrhagic complications</td>
<td>1 (1.4)</td>
<td>3 (4.8)</td>
<td>0.35</td>
</tr>
<tr>
<td>Nonsevere hemorrhagic complications</td>
<td>1 (1.4)</td>
<td>10 (15.8)</td>
<td>0.0038</td>
</tr>
<tr>
<td>Total number of patients with hemorrhagic complications</td>
<td>2 (2.9)</td>
<td>13 (20.6)</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

Numbers indicate the numbers of patients and the annual incidences per 100 patients each year are in parenthesis

Conclusions
- Study could not meaningfully assess the preventive value of combined aspirin and fluindione against thromboembolic events
- Higher incidence of bleeding complications in the combination therapy group
- Authors do not recommend combination aspirin and vitamin K antagonist in high-risk atrial fibrillation patients because of the potential to increase hemorrhagic complications

Critique
- Randomized, double-blind, multicenter, placebo-controlled trial
- First study to test vitamin K antagonist-aspirin combination with INR of at least 2 in an elderly population with atrial fibrillation
- Lacked adequate power to detect primary endpoint
- Shorter duration of follow-up than planned

Comments
Combination aspirin-vitamin K antagonist significantly increases the risk of bleeding and has no clearly demonstrated benefit in the reduction of thromboembolic complications.

CHF: congestive heart failure; TIA: transient ischemic attack; LVEF: left ventricular ejection fraction; NYHA: New York heart association; NSAID: non-steroidal anti-inflammatory drug; SAS: statistical analysis software; ITT: intention to treat;
VIII. Summary
   a. Literature on this topic is limited
   b. Studies do not suggest incremental benefit of adding aspirin to OAC in patients with an indication for OAC and coexisting indication for ASA
   c. Guidelines recommend the use of combination agents in patients with mechanical heart valves
   d. Several studies of combination OAC (mostly warfarin) and aspirin show increased risk of major bleeding even with warfarin in the therapeutic range, thereby outweighing any benefits of the combination therapy
   e. Most of the patients with an indication for long-term warfarin who have CAD or are at high risk of ACS are also the one’s with high bleeding risk (i.e. >65 years, renal impairment, diabetes mellitus, history of stroke, etc)

IX. Recommendations
   a. Avoid combined OAC and antiplatelet in AF patients with coexisting indication of aspirin because the risk of major bleeding outweighs incremental benefit of adding antiplatelet
   b. Benefits of OAC and antiplatelet may be seen in AF patients with prosthetic heart valves
   c. Avoid combination even in AF patients with concomitant CAD, since the risk of fatality from major bleeding outweighs the benefit of aspirin in preventing reinfarction or reducing mortality
References

9) Jennings LK. Role of platelets in atherothrombosis. Am J Cardiol 2009; 103[suppl]:4A-10A.


