Antiplatelet and Antithrombotic Soup

Garrett Wong, MD
May 4, 2013
## Disclosure Statement of Financial Interest

Within the past 12 months, I have had a financial Interest /arrangement or affiliation with the organization(s) listed below

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consulting Fees/Honoraria:</td>
<td>Astra Zeneca</td>
</tr>
<tr>
<td></td>
<td>Bristol-Myers Squibb / Sanofi Aventis</td>
</tr>
<tr>
<td></td>
<td>Daiichi Sankyo / Eli Lilly</td>
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<td>Medicines Company</td>
</tr>
</tbody>
</table>
Outline

- Overview of antiplatelet and antithrombotic therapies
- Update of new drug trials
- Discuss combination therapy
Platelets Role in Thrombosis

1. Adhesion
2. Activation
3. Aggregation

Reproduced with permission from Cannon CP. Atherothrombosis slide compendium. Available at: www.theheart.org.
Platelet shape change and aggregation
Pathways to Clot Formation

AT III = Antithrombin III
Xa = Factor Xa
PAF = Platelet Activating Factor
TXA2 = Thromboxane A2
ADP = Adenosine Diphosphate
LMWH = Low-molecular-weight Heparin

White HD. AM J Cardiol 1997; 80:2B-10B
Schafer A. J Clin Invest 1986; 78:73-79
The critical roles of thrombin

- Thrombin links vessel injury, coagulation, and platelet response
- Thrombin is a powerful platelet activator, and it stimulates multiple responses in platelets and other cells

Heparin/LMWH: Mechanism of action

- Heparin/antithrombin (AT) complex inhibits thrombin and Factor Xa
- Must have adequate AT present for anticoagulant effect

Thrombin inhibition requires “bridging” by heparin chain (at least 18 units)

LMWH has greater activity against Xa than thrombin


LMWH: low molecular weight heparin.
Bivalirudin mechanism of action

- Bivalirudin exhibits direct and reversible binding to thrombin

HORIZONS AMI Trial Design

3,602 patients with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

Randomized 1:1

UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)

Bivalirudin* (± provisional GP IIb/IIIa)

Primary PCI Strategy

3,000 patients eligible for stent randomization

Randomized 1:3

Bare metal stent

paclitaxel-eluting stent

Primary Endpoints: 30-day NACE and non-CABG major bleeding; Follow-up at 1 year, and then yearly through 3 years

UFH=unfractionated heparin; MACE=all-cause death, reinfarction, ischemic TVR, or stroke; NACE=net adverse clinical events=major bleeding + MACE.

Cardiac Mortality
30 days to 3 years*

Cardiac Mortality (%)

1-yr† HR [95%CI] = 0.57 [0.38, 0.84]
P = 0.005

3-yr† HR [95%CI] = 0.56 [0.40, 0.80]
P = 0.001

30-d† HR [95% CI]
0.62; [0.40, 0.96]
P = 0.03

*All cause mortality at 3 years was also consistently lower with bivalirudin (5.9% vs 7.7%),
HR 0.75 [0.58–0.97]; p=0.03
†These timepoints were prespecified analyses

Acute Anterior MI - Angiography
Acute Anterior MI – Final Angiograms
Currently Available Antiplatelet Therapies

**Oral**
- Aspirin
- Dipyridamole
- Cilostazol
- Thienopyridines: P2Y$_{12}$ inhibitor of platelet function
  - Clopidogrel (Plavix)
  - Ticlopidine (Ticlid)
  - Prasugrel (Effient)
- Ticagrelor (Brilinta)

**Intravenous**
- Glycoprotein (GP) IIb/IIIa inhibitor of platelet function
  - ReoPro (abciximab)
  - Integrilin (eptifibatide)
  - Aggrastat (tirofiban)
Target Directed Therapy
Antiplatelet Agents

ADP = adenosine diphosphate, TXA2 = thromboxane A2, COX = cyclooxygenase.
Aspirin

- The simplest drug available in cardiology
  - Old and oral, once a day
- One of the most efficacious
- The cheapest available
- Therefore:
  - The most cost-effective
Dose-Dependence and Aspirin Efficacy

<table>
<thead>
<tr>
<th>Aspirin Dose</th>
<th># Trials</th>
<th>OR* (%)</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>500–1500 mg</td>
<td>34</td>
<td>19</td>
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</tr>
<tr>
<td>160–325 mg</td>
<td>19</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>75–150 mg</td>
<td>12</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>&lt;75 mg</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

ASA Better: 0.5, 1.0, ASA Worse: 1.5, 2.0

BMJ. 2002;324:71-86.

Antithrombotic Trialists’ Collaboration
Clopidogrel (Plavix)

- Requires 2 step metabolism via cytochrome P450
- Platelet aggregation inhibition
  - 75 mg - 3 to 5 days
  - 300 mg - 4 to 6 hours
  - 600 mg – 1 to 2 hours
- Potential resistance mechanisms
- Variability in individual response
- Lower potency - anti-platelet effect (~40%)
CURE - MI/Stroke/CV Death

The primary outcome occurred in 9.3% of patients in the clopidogrel + ASA group and 11.4% in the placebo + ASA group. The cumulative hazard rate for the primary outcome is lower in the clopidogrel + ASA group compared to the placebo + ASA group. The relative risk reduction is 20%, and the difference is statistically significant with a p-value of 0.00009.

Clopidogrel Across Spectrum of CAD

98,809 Patients Enrolled in Randomized Clinical Trials

- **CLARITY**: Acute STEMI
- **CURE**: UA/NSTEMI
- **CREDO**: PCI
- **CAPRIE**: Long-term 2° (1°) prevention
- **CHARISMA**: High-Risk Vascular Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>30 Days</th>
<th>1 Year</th>
<th>1 Year</th>
<th>1-3 Years</th>
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</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>+ Benefit</td>
<td>+ Benefit</td>
<td>+ Benefit</td>
<td>+ Benefit</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>+ Benefit</td>
<td>+ Benefit</td>
<td>+ Benefit</td>
<td>+ Benefit</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI/Stroke/PAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Clopidogrel vs. placebo. †Clopidogrel + ASA. §Clopidogrel vs. ASA.*
Is aspirin and clopidogrel enough for everyone? Do we have a need for newer agents?
Prasugrel (Effient)

- Hydrolysis by intestinal carboxylesterases
- Oxidation by intestinal and hepatic CYP-450
- Increased potency > 75% inhibition
Inhibition of Platelet Aggregation (IPA): Prasugrel and Clopidogrel Loading Dose

The relationship between IPA and clinical activity has not been established.

*Represents healthy subjects in a crossover study who were not on concurrent ASA therapy (n=64).

2. Effient Full Prescribing Information.
Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*
Balance of Efficacy and Safety

- **CV Death / MI / Stroke**
  - Prasugrel: HR 1.32 (1.03-1.68), P=0.03, NNT = 46
  - Clopidogrel: HR 0.81 (0.73-0.90), P=0.0004, NNH = 167

- **TIMI Major NonCABG Bleeds**
  - Prasugrel: ↓ 35 events, HR 1.32 (1.03-1.68), P=0.03
  - Clopidogrel: ↓ 138 events, HR 0.81 (0.73-0.90), P=0.0004
**Net Clinical Benefit**

**Death, MI, Stroke, Major Bleed (non CABG)**

- **ITT** = 13,608
- **Clopidogrel**
  - **13.9**
  - HR 0.87
  - P = 0.004
- **Prasugrel**
  - **12.2**

**Events per 1000 pts**

- MI:
  - Clop: 3.2%
  - Pras: 3.0%
  - P = 0.64
- Major Bleed (non CABG):
  - Pras: +6

All Cause Mortality

- Clop: 3.2%
- Pras: 3.0%
- P = 0.64

**Graph Details**

- **Days** range from 0 to 450
- **Endpoint (%)** scale from 0 to 15
Stent Thrombosis (ARC Definite + Probable)

Any Stent at Index PCI
N= 12,844

HR 0.48
P <0.0001
NNT= 77

Prasugrel
1.1 (68)

Clopidogrel
2.4 (142)
The “Greater Inhibition is Better” Hypothesis In Dual Antiplatelet Therapy

C. Michael Gibson, M.D. 2008
Ticagrelor (Brilinta): an oral reversible P2Y$_{12}$ antagonist

- **Direct acting**
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the P2Y$_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel

- **Reversibly bound**
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets

Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)
ONSET/OFFSET: Pharmacodynamics in Stable CAD Patients

- Loading Dose: 180 mg, 600 mg
- Last Maintenance Dose: 90 mg bid, 75 mg qd

Ticagrelor (n=54) vs. Clopidogrel (n=50)

IPA %

Time (Hours): Onset, Maintenance, Offset

0 0.5 1 2 4 8 24 6 weeks 0 2 4 8 24 48 72 120 168 240

Gurbel P, Circ 2009
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*
Time to first primary efficacy event (composite of CV death, MI or stroke)

Cumulative incidence (%)

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

<table>
<thead>
<tr>
<th>Days after randomisation</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>360</td>
</tr>
<tr>
<td>No. at risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>9,333</td>
<td>8,628</td>
</tr>
<tr>
<td></td>
<td>8,460</td>
<td>8,219</td>
</tr>
<tr>
<td></td>
<td>6,743</td>
<td>5,161</td>
</tr>
<tr>
<td></td>
<td>4,147</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>9,291</td>
<td>8,521</td>
</tr>
<tr>
<td></td>
<td>8,362</td>
<td>8,124</td>
</tr>
<tr>
<td></td>
<td>6,743</td>
<td>5,096</td>
</tr>
<tr>
<td></td>
<td>4,047</td>
<td></td>
</tr>
</tbody>
</table>

HR 0.84 (95% CI 0.77–0.92)

p=0.0003

NNT=54
Time to major bleeding – Primary safety event

- **Clopidogrel**
  - No. at risk: 9,186
  - Days from first IP dose: 6,930
  - HR: 1.04 (95% CI 0.95–1.13), p=0.434

- **Ticagrelor**
  - No. at risk: 9,235
  - Days from first IP dose: 6,545

K-M estimated rate (% per year)

Days from first IP dose

No. at risk

- Ticagrelor: 9,235
  - 0: 9,235
  - 60: 7,246
  - 120: 6,826
  - 180: 6,545
  - 240: 5,129
  - 300: 3,783
  - 360: 3,433

- Clopidogrel: 9,186
  - 0: 9,186
  - 60: 7,305
  - 120: 6,930
  - 180: 6,670
  - 240: 5,209
  - 300: 3,841
  - 360: 3,479
All-cause mortality

The first and only antiplatelet therapy to demonstrate mortality reduction compared to clopidogrel

K-M estimated rate (% per year)

HR 0.81 (95% CI = 0.68–0.95), p=0.01

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6,732</td>
<td>6,676</td>
</tr>
<tr>
<td>60</td>
<td>6,439</td>
<td>6,376</td>
</tr>
<tr>
<td>120</td>
<td>6,375</td>
<td>6,331</td>
</tr>
<tr>
<td>180</td>
<td>6,241</td>
<td>6,209</td>
</tr>
<tr>
<td>240</td>
<td>5,141</td>
<td>5,114</td>
</tr>
<tr>
<td>300</td>
<td>3,951</td>
<td>3,917</td>
</tr>
<tr>
<td>360</td>
<td>3,233</td>
<td>3,164</td>
</tr>
</tbody>
</table>

Clopidogrel: 5.08%
Ticagrelor: 3.94%
## Comparison of Antiplatelet Agents

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel 600 mg</th>
<th>Prasugrel 60 mg</th>
<th>Ticagrelor ? mg</th>
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<tbody>
<tr>
<td>STEMI indication</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Potency</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Rapidity of onset</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Variable response</td>
<td>Very variable</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CYP2C19 loss of function impact</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Not reversible</td>
<td>Not reversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Hold before CABG</td>
<td>5-7 days</td>
<td>7-10 days</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Clinical experience</td>
<td>++++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Side effects</td>
<td>Rare</td>
<td>Rare</td>
<td>More common</td>
</tr>
</tbody>
</table>
Dual Antiplatelet Therapy (DAPT) Study

- **DES n = 15,245**
- **BMS n = 5,400**

All patients on aspirin + open-label thienopyridine therapy for 12 months

1:1 Randomization at month 12

50% of patients continue on Dual Antiplatelet Therapy

50% of patients receive aspirin + placebo

Total 33 month patient evaluation including additional 3-month follow-up
Platelet Function Testing

No Gold Standard
## An Ideal Anticoagulant

<table>
<thead>
<tr>
<th>Desired Characteristic</th>
<th>Practical Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset of action</td>
<td>No need for overlap with heparin</td>
</tr>
<tr>
<td>Wide therapeutic index</td>
<td>Increased safety</td>
</tr>
<tr>
<td>Minimal side effects</td>
<td>Improved compliance; less monitoring</td>
</tr>
<tr>
<td>Oral formulation</td>
<td>Convenient administration</td>
</tr>
<tr>
<td>Predictable anticoagulant response</td>
<td>Fixed-dose unmonitored treatment</td>
</tr>
<tr>
<td>No food or drug interaction</td>
<td>No need for monitoring</td>
</tr>
<tr>
<td>Availability of antidote</td>
<td>Able to reverse in case of bleeding or urgent surgery</td>
</tr>
<tr>
<td>Cost effective</td>
<td>Accessibility</td>
</tr>
</tbody>
</table>

Emerging Therapies
Factor Xa Inhibitors and Direct Thrombin Inhibitors

Tissue Factor/VIIa

X

IX

IXa

VIIIa

Idrabiotaparinux

Va

Xa

Rivaroxaban
Betrixaban
Apixaban
YM150
DU-176b

Dabigatran
AZD-0837

II

IIa

Fibrinogen

Fibrin

AF Prevalence is Increasing Rapidly

Projected Number of Persons With AF (millions)

Year


5.1 5.9 6.7 7.7 8.9 10.2 11.7 13.1 14.3 15.2 15.9

Current age-adjusted AF incidence

Mayo Clinic

Increased age-adjusted AF incidence

Cardioembolic Stroke
CHADS<sub>2</sub> - Risk for stroke in AF per year without anticoagulation

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
</tbody>
</table>

[Graph showing the CHADS<sub>2</sub> score and stroke rate]
Stroke Risk Stratification in AF

**CHADS<sub>2</sub>**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>1</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
</tbody>
</table>

**CHA<sub>2</sub>DS<sub>2</sub>-VASc**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac failure</td>
<td>1</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (MI, peripheral arterial disease, aortic atherosclerosis)</td>
<td>1</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>

HTN = hypertension; MI = myocardial infarction.

Antithrombotic therapy in Atrial Fibrillation

SAVE THE BRAIN

- Stroke is responsible for most of the morbidity and mortality associated with atrial fibrillation

- 15% of all strokes are due to Atrial Fibrillation
# Characteristics of New Oral Anticoagulants (NOAC)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Betrixaban</th>
<th>Edoxaban</th>
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</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Thrombin inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>14-17 hours</td>
<td>5-9 hours</td>
<td>12 hours</td>
<td>19-24 hours</td>
<td>6-12 hours</td>
</tr>
<tr>
<td>Regimen</td>
<td>BID</td>
<td>QD, BID</td>
<td>BID</td>
<td>QD</td>
<td>QD</td>
</tr>
<tr>
<td>Peak to trough</td>
<td>2</td>
<td>12 (QD)</td>
<td>3-5</td>
<td>~3</td>
<td>~3</td>
</tr>
<tr>
<td>Renal excretion of absorbed drug</td>
<td>~80%</td>
<td>36%-45%</td>
<td>25%-30%</td>
<td>~15%</td>
<td>35%</td>
</tr>
<tr>
<td>Potential for drug interactions</td>
<td>P-glycoprotein inhibitor</td>
<td>CYP3A4 substrate and P-glycoprotein inhibitor</td>
<td>CYP3A4 substrate and P-glycoprotein inhibitor</td>
<td>Not substrate for major CYPs</td>
<td>CYP3A4 substrate and P-glycoprotein inhibitor</td>
</tr>
</tbody>
</table>

CYP3A4 = cytochrome P450 3A4

The NEW ENGLAND JOURNAL of MEDICINE

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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RE-LY - Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group

![Graph showing cumulative hazard rate over months for different treatment groups.]

<table>
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<th>Months</th>
<th>Warfarin</th>
<th>Dabigatran, 110 mg</th>
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Prevention of Stroke and non-CNS Embolism with Rivaroxaban Compared with Warfarin in Patients with Non-valvular Atrial Fibrillation and Moderate Renal Impairment
**Primary Endpoint:** Stroke or non-CNS Systemic Embolism

**Atrial Fibrillation**

**Rivaroxaban**
- 20 mg daily
- 15 mg for Cr Cl 30-49 ml/min

**Warfarin**
- INR target - 2.5 (2.0-3.0 inclusive)
- Randomize Double Blind / Double Dummy (n ~ 14,000)

**Risk Factors**
- CHF
- Hypertension
- Age ≥ 75
- Diabetes
- Stroke, TIA or Systemic embolus

At least 2 or 3 required*

**Monthly Monitoring**
- Adherence to standard of care guidelines

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*Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%
Primary Efficacy Outcome
Stroke and non-CNS Embolism

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

No. at risk:
Rivaroxaban 6958 6211 5786 5468 4406 3407 2472 1496 634
Warfarin 7004 6327 5911 5542 4461 3478 2539 1538 655

HR (95% CI): 0.79 (0.66, 0.96)
P-value Non-Inferiority: <0.001
• Noninferior trial
• 1º efficacy endpoint: confirmed ischemic or hemorrhagic stroke, or systemic embolism
• 1º safety endpoint: time to first occurrence of confirmed major bleeding
• Follow-up: up to 4 years
  – Stratified by warfarin-naïve status

*At least 2 of the following: age ≥80 years, weight ≤60 kg, or serum creatinine ≥0.5 mg/dL.

ARISTOTLE = Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation.

Apixaban versus Warfarin in Patients with Atrial Fibrillation

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for the ARISTOTLE Committees and Investigators*
ARISTOTLE Main Trial Results

Stroke (ischemic or hemorrhagic) or systemic embolism

- **Warfarin**
  - 212 patients, 1.27% per year
  - Median TTR 66%

- **Apixaban**
  - 327 patients, 2.13% per year
  - HR 0.69 (95% CI, 0.60–0.80); P<0.001

Major Bleeding ISTH definition

- **Warfarin**
  - 265 patients, 1.60% per year
  - Median TTR 66%

- **Apixaban**
  - 462 patients, 3.09% per year
  - HR 0.79 (95% CI, 0.66–0.95); P=0.011

Granger et al NEJM 2011
**AVERROES Trial**

- 1° efficacy endpoint: confirmed ischemic or hemorrhagic stroke or systemic embolism
- 1° safety endpoint: major bleeding
- Study stopped early because predefined interim analysis revealed clear evidence of a reduction in stroke and systemic embolism

*At least 2 of age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

**AVERROES = Apixaban Versus ASA to Reduce the Risk of Stroke.**


Presented at: European Society of Cardiology; August 28 to September 1, 2010; Stockholm, Sweden.
AVERROES:
Stroke or Systemic Embolic Event and Major Bleeding

Patients on Oral Anticoagulation and PCI

- Atrial Fibrillation
  - 5% - 7% of the overall population referred for stenting have atrial fibrillation
  - Incidence of AF is increasing as the population ages

- Prosthetic heart valves

- Systemic or venous thromboembolism

- Left ventricular thrombus
The WOEST Trial:
First randomized trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting

What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting
The WOEST Trial - Study Design

Inclusion criteria:

1. Indication for OAC for at least 1 year
2. One coronary lesion eligible for PCI
3. Age over 18

1:1 Randomization:

Double therapy group
OAC + 75mg Clopidogrel qd
1 month minimum after BMS
1 year after DES

Triple therapy group
OAC + 75mg Clopidogrel qd + 80mg Aspirin qd
1 month minimum after BMS
1 year after DES
Primary Endpoint: Total number of TIMI bleeding events

Cumulative incidence of bleeding

**Triple therapy group**
- 44.9%
- $p<0.001$
- HR = 0.36, 95% CI [0.26-0.50]

**Double therapy group**
- 19.5%

Days

- 0
- 30
- 60
- 90
- 120
- 180
- 270
- 365

$n$ at risk:

- 284
- 210
- 194
- 186
- 181
- 173
- 159
- 140

- 279
- 253
- 244
- 241
- 241
- 236
- 226
- 208
Secondary Endpoint (Death, MI, TVR, Stroke, ST)

Cumulative incidence

Days

n at risk:

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<tr>
<th>Days</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
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p = 0.025
HR = 0.60 95% CI [0.38-0.94]
Bleeding associated with warfarin, aspirin, clopidogrel in patients with AF

n=82,854

Hazard Ratio (95% CI)

- Warfarin monotherapy: 1.00 (Reference)
- Aspirin monotherapy: 1.06 (0.87-1.29)
- Clopidogrel monotherapy: 1.66 (1.34-2.04)
- Aspirin + clopidogrel: 1.83 (1.72-1.96)
- Warfarin + aspirin: 3.08 (2.32-3.91)
- Warfarin + clopidogrel: 3.70 (2.89-4.76)
- Triple therapy: 2.50 (2.09-3.00)
WATCHMAN LAA Closure Device
Take Home Points

- **Aspirin is safe and effective for all CV pts**
- **Safety of clopidogrel has been confirmed in a broad range of pts with stable and unstable CAD**
- **Compared with clopidogrel, prasugrel and ticagrelor provide a significant reduction in ischemic events and in stent thrombosis (both BMS and DES)**
- **Newer oral anticoagulants offer superior reduction in stroke and systemic embolization compared to warfarin**
- **No increased risk of bleeding compared to warfarin**
- **Ongoing trials for broader indications**
Thank You