Antiplatelet Therapy in ACS

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DISCLOSURES

None
OBJECTIVES

• Understand platelet physiology in ACS
• Outline options for antiplatelet therapy
• Review of guidelines for ACS
• Review new data for duration of therapy
• Review data for use with anticoagulants (warfarin and NOACs)
Plaque rupture with thrombosis

- Thrombus
- Fibrous cap
- Lipid core
ASPIRIN

• Cyclooxygenase inhibitor
• Permanently disables cyclooxygenase for the life of the platelet
• Reduces thromboxane A2 production and prostaglandin synthesis
• In ACS, aspirin in proven to reduce recurrent ischemic events by 50% in meta-analysis of 197 RCTs with over 135,000 patients
• Loading dose is 325 mg, maintenance 81 mg
• Increases risk of bleeding, particularly in patients with current of history of PUD, ICH, and renal impairment
HEPARIN

- Interacts with anti-thrombin III
- Both UFH and LMWH reduce the risk of recurrent MI
- Heparin plus aspirin superior to aspirin alone in preventing recurrent ischemia (Theroux, 1988, Montreal Heart)
- LMWH equally effective, easier to administer, and avoids HIT
- LMWH therapy of choice in conservatively managed patients
- LMWH should be converted to UFH 12 hours prior to cardiac catheterization
• In the CURE study of 12,562 patients with ACS without ST-segment elevation:
  – clopidogrel demonstrated a 20% relative risk reduction in MI, stroke or cardiovascular death with long-term use† ($P < 0.001$)
  – the Kaplan-Meier curves began to diverge within hours and continued to diverge over the course of 12 months
• Clopidogrel in addition to aspirin and other standard therapy demonstrated an early effect (within hours) and sustained long-term benefit throughout the entire study period of 12 months
PCI-CURE CONCLUSIONS

• For the composite of MI or cardiovascular death in the 2658 patients who underwent PCI in the CURE trial:
  – clopidogrel plus aspirin* demonstrated a 25% relative risk reduction in the composite of MI or cardiovascular death with long-term use† from PCI to end of follow-up ($P = 0.04$)
  – clopidogrel in addition to aspirin and other standard therapy provides early beneficial effects and sustained long-term† benefit in ACS patients requiring PCI

• * In combination with standard therapy
• † Up to 12 months
PCI-CURE CONCLUSIONS

– Long-term† administration of clopidogrel plus aspirin* resulted in an overall 25% relative risk reduction in MI and CV death from PCI to end of follow-up
  • Pretreatment with clopidogrel plus aspirin* resulted in a 30% relative risk reduction in CV death, MI and target vessel revascularization in 30 days post PCI
– There was an increase in minor bleeding, but was no significant difference in major or life-threatening bleeding between the two treatment groups

• † Up to 12 months
• * In combination with standard therapy
Problems with clopidogrel

- Pro-drug: requires 2 CYP450 steps in the liver to convert to active metabolite (so-called CYP2C19 pathway)
- 4-6 hour onset of action
- Irreversible binding of PY2-12 receptor
- Long half-life (11 days)
- Extent of platelet inhibition 45%
- 20% of patients have intermediate loss of function of CYP2C19 allele, so-called “intermediate metabolizers”
- 3-5% of patients have complete loss of function of CYP2C19 allele, so-called “non-metabolizers”; this group of patients has a 2-5 fold risk for in-stent thrombosis
- Drug-drug interactions include omeprazole which affects absorption and CYP2C19 metabolism
Prasugrel

- Onset of action < 1 hour, after 60 mg bolus dose
- Peak action at 4 hours
- Half-life 2-4 days
- Platelet inhibition 60%
- Single step quicker metabolism to active metabolite by CYP450 system
- Absorption and metabolism unaffected by PPIs
- Once daily dosing 10 mg
- Side effects – none except bleeding
Inhibition of Platelet Aggregation (Prasugrel)
Major Events for Prasugrel vs. Clopidogrel - UA/NSTEMI
Major Events with Prasugrel vs. Clopidogrel - STEMI

Triton Study

Figure 3: Time to first event of CV death, MI, or stroke (TRITON-TIMI 38)
Bleeding Risk of Prasugrel

- Triton Study

![Graph showing bleeding risk over time for Effient and Clopidogrel](image)
Subgroup analysis
Prasugrel vs. Clopidogrel
Ticagrelor (Brilinta)

- Reversible, direct binder of P2Y12 receptor
- Oral agent, 90 mg BID dosing
- Onset of action 2-3 hours
- Half-life 12 hours
- Inhibition of platelet activity 60% and is consistent throughout all patient groups
- Does not need to be metabolized to active agent
- Drug-drug interactions – full dose aspirin, use 81 mg daily dosing
- Off target effects: dyspnea, bradycardia
Inhibition of Platelet Aggregation (Ticagrelor)
Plato Trial
Ticagrelor vs Clopidogrel
Major CV Events
Plato Trial
Incidence of Bleeding
Ticagrelor vs Clopidogrel

Figure 2. Cumulative Kaplan–Meier Estimates of the Time to the First Major Bleeding End Point, According to the Study Criteria.

The time was estimated from the first dose of the study drug in the safety population. The hazard ratio for major bleeding, defined according to the study criteria, for the ticagrelor group as compared with the clopidogrel group was 1.04 (95% confidence interval, 0.95 to 1.13).
Ticagrelor vs. Clopidogrel

Major end points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ticagrelor Group</th>
<th>Clopidogrel Group</th>
<th>Hazard Ratio for Ticagrelor Group (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)</td>
<td>864/9333 (9.8)</td>
<td>1014/9291 (11.7)</td>
<td>0.84 (0.77–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary end points — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause, MI, or stroke</td>
<td>901/9333 (10.2)</td>
<td>1065/9291 (12.3)</td>
<td>0.84 (0.77–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event</td>
<td>1290/9333 (14.6)</td>
<td>1456/9291 (16.7)</td>
<td>0.88 (0.81–0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td>504/9333 (5.8)</td>
<td>593/9291 (6.9)</td>
<td>0.84 (0.75–0.95)</td>
<td>0.005</td>
</tr>
<tr>
<td>Death from vascular causes</td>
<td>333/9333 (4.0)</td>
<td>442/9291 (5.1)</td>
<td>0.79 (0.69–0.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>125/9333 (1.3)</td>
<td>106/9291 (1.3)</td>
<td>1.17 (0.91–1.52)</td>
<td>0.22</td>
</tr>
<tr>
<td>Ischemic</td>
<td>96/9333 (1.1)</td>
<td>91/9291 (1.1)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>23/9333 (0.2)</td>
<td>13/9291 (0.1)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>10/9333 (0.1)</td>
<td>2/9291 (0.02)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Other events — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>399/9333 (4.5)</td>
<td>506/9291 (5.9)</td>
<td>0.78 (0.69–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from causes other than vascular causes</td>
<td>46/9333 (0.5)</td>
<td>64/9291 (0.8)</td>
<td>0.71 (0.49–1.04)</td>
<td>0.08</td>
</tr>
<tr>
<td>Severe recurrent ischemia</td>
<td>302/9333 (3.3)</td>
<td>345/9291 (3.8)</td>
<td>0.87 (0.74–1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>500/9333 (5.8)</td>
<td>516/9291 (6.2)</td>
<td>0.93 (0.82–1.05)</td>
<td>0.22</td>
</tr>
<tr>
<td>TIA</td>
<td>18/9333 (0.2)</td>
<td>23/9291 (0.3)</td>
<td>0.78 (0.42–1.44)</td>
<td>0.42</td>
</tr>
<tr>
<td>Other arterial thrombotic event</td>
<td>19/9333 (0.2)</td>
<td>31/9291 (0.4)</td>
<td>0.61 (0.34–1.08)</td>
<td>0.09</td>
</tr>
<tr>
<td>Death from vascular causes, MI, stroke — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive treatment planned§</td>
<td>569/6732 (8.9)</td>
<td>668/6676 (10.6)</td>
<td>0.84 (0.75–0.94)</td>
<td>0.003</td>
</tr>
<tr>
<td>Event rate, days 1–30</td>
<td>443/9333 (4.8)</td>
<td>502/9291 (5.4)</td>
<td>0.88 (0.77–1.00)</td>
<td>0.045</td>
</tr>
<tr>
<td>Event rate, days 31–360¶</td>
<td>413/8763 (5.3)</td>
<td>510/8688 (6.6)</td>
<td>0.80 (0.70–0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent thrombosis — no. of patients who received a stent/total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>71/5640 (1.3)</td>
<td>106/5649 (1.9)</td>
<td>0.67 (0.50–0.91)</td>
<td>0.009</td>
</tr>
<tr>
<td>Probable or definite</td>
<td>118/5640 (2.2)</td>
<td>158/5649 (2.9)</td>
<td>0.75 (0.59–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Possible, probable, or definite</td>
<td>155/5640 (2.9)</td>
<td>202/5649 (3.8)</td>
<td>0.77 (0.62–0.95)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* The percentages are Kaplan–Meier estimates of the rate of the end point at 12 months. Patients could have had more than one type of end point. Death from vascular causes included fatal bleeding. Only traumatic fatal bleeding was excluded from the category of death from vascular causes. MI denotes myocardial infarction, and TIA transient ischemic attack.

† P values were calculated by means of Cox regression analysis.

‡ Statistical significance was confirmed in the hierarchical testing sequence applied to the secondary composite efficacy end points.

§ A plan for invasive or noninvasive (medical) management was declared before randomization.

¶ Patients with any primary event during the first 30 days were excluded.
Subgroup Analysis of Plato

Forest plot of the effect of therapy on the composite end point as a function of various prerandomization and postrandomization characteristics.

Cangrelor (Kengreal)

- Competitive reversible IV agent
- Onset of action immediate
- Half-life 3-5 minutes
- Full recovery platelet function < 30 minutes
- Extent platelet inhibition > 95%
- No need to be metabolized to active agent
- Must be combined with oral antiplatelet agent
Risk of Stent Thrombosis

• High dose Clopidogrel (600 / 150) vs. 300/75)
  – 1.6% vs. 2.3 %  p=.0001
• Prasugrel vs. Clopidogrel
  – 1.1% vs. 2.4 %  p<.001
• Ticagrelor vs. Clopidogrel (600/75)
  – 2.2% vs. 3%  p=.014
• Cangrelor + Clopidogrel vs. Clopidogrel (300/75)
  – 0.2% vs. 0.6%  p=.02
Effect of Morphine on Clopidogrel levels
Morphine reduces platelet deactivation by clopidogrel
Glycoprotein IIbIIIa inhibitors (GPIs)

• Eptifibatide (Integrilin)
• Abciximab (Reopro)

• Binds to IIbIIIa receptor on the platelet to prevent final step in platelet aggregation i.e. fibrinogen binding of platelets.
• May be given before, during, or after coronary intervention.
Bivalirudin (Angiomax)

- Reversible direct thrombin inhibitor
- Anticoagulant for use in unstable angina in patients undergoing PCI
- Heparin alternative (in patients with HIT)
- 3 fold lower rate of bleeding compared with heparin, resulting in significant mortality benefit compared with heparin in Horizons AMI study
- 2 fold higher risk of stent thrombosis without planned use of GPIs
- Should not be used without prolonged pre-treatment with P2Y12 inhibitors or acute administration of GPIs
- Judicious use of heparin, guided by ACT monitoring, less expensive with equivalent outcomes.
Vorapaxar (Zontivity)

• Inhibits platelet activation by thrombin; PAR-1 receptor antagonist
• TIMI-50 study April 2012 NEJM: 2.5 mg when added to DAPT reduced incident of recurrent MI, CVA, CV death by 10 % (p<0.001)
• Moderate or severe bleeding risk doubled 2.5% to 4.2%
• ICH risk doubled 0.5% vs 1% (p<0.001)
2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

AHA/ACC NSTE-ACS Guidelines

Initial Oral Antiplatelet Therapy in Patients with Definite or Likely NSTE-ACS Treated with an Initial Invasive or Ischemia-Guided Strategy

• Class I recommendations:
  • A P2Y$_{12}$ inhibitor (either clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with either an early invasive or ischemia-guided strategy. Options include:
    - Clopidogrel (300 mg or 600 mg LD, then 75 mg daily) or ticagrelor* (180 mg LD, then 90 mg twice daily) (LOE: B)
  • Non-enteric-coated, chewable aspirin (162 mg-325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 mg-162 mg daily) should be continued indefinitely (LOE: A)

• Class IIa recommendations:
  • It is reasonable to use ticagrelor in preference to clopidogrel for P2Y$_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy (LOE: B)

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

ACC=American College of Cardiology; ACS=acute coronary syndrome; AHA=American Heart Association; LD=loading dose; LOE=level of evidence; NSTE=non-ST elevation.
AHA/ACC NSTE-ACS Guidelines

Oral Antiplatelet Therapy in Patients Undergoing PCI

- Class I recommendations:
  - A LD of a P2Y\textsubscript{12} receptor inhibitor should be given before the procedure in patients undergoing PCI with stenting (LOE: A). Options include:
    - Clopidogrel 600 mg, prasugrel\* 60 mg, or ticagrelor\+ 180 mg (LOE: B)
  - In patients receiving a stent (BMS or DES) during PCI for NSTE-ACS, P2Y\textsubscript{12} inhibitor therapy should be given for at least 12 months. Options include:
    - Clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor\+ 90 mg twice daily (LOE:B)
  - Patients already taking daily aspirin before PCI should take 81 mg to 325 mg\+ aspirin before PCI and patients not on aspirin therapy should be given aspirin 325 mg\+ as soon as possible before PCI (LOE: B)
    - After PCI, aspirin should be continued indefinitely at a dose of 81 mg to 325 mg daily (LOE: B)
AHA/ACC NSTE-ACS Guidelines

Oral Antiplatelet Therapy in Patients Undergoing PCI (cont’d)

• Class IIa recommendations:
  ▪ It is reasonable to choose ticagrelor over clopidogrel for P2Y$_{12}$ inhibition treatment in patients with NSTE-ACS treated with an early invasive strategy and/or coronary stenting (LOE: B)
  ▪ It is reasonable to choose prasugrel over clopidogrel for P2Y$_{12}$ treatment in patients with NSTE-ACS who undergo PCI who are not at high risk of bleeding complications (LOE: B)
  ▪ After PCI, it is reasonable to use 81 mg per day of aspirin in preference to higher maintenance doses (LOE: B)
  ▪ If the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of P2Y$_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (eg, <12 months) of P2Y$_{12}$ inhibitor therapy is reasonable (LOE: C)

• Class IIb recommendations:
  ▪ Continuation of DAPT beyond 12 months may be considered in patients undergoing stent implantation (LOE: C)

• Class III recommendations (Harm):
  ▪ Prasugrel should not be administered to patients with a prior history of stroke or transient ischemic attack (LOE: B)

DAPT=dual antiplatelet therapy.

This slide includes information regarding ticagrelor that is not found in the currently approved BRILINTA PI.
AHA/ACC NSTE-ACS Guidelines

Oral Antiplatelet Therapy in Relation to Timing of Urgent CABG

- Discontinuation for CABG
  - Class I recommendations:
    - In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery (LOE: B) and prasugrel for at least 7 days before surgery (LOE: C)
    - In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding (LOE: B)
    - Non-enteric-coated aspirin (81 mg-325 mg daily) should be administered preoperatively to patients undergoing CABG (LOE: B)
  - Class IIb recommendations:
    - In patients referred for urgent CABG, it may be reasonable to perform surgery less than 5 days after clopidogrel or ticagrelor has been discontinued and less than 7 days after prasugrel has been discontinued (LOE: C)

CABG=coronary artery bypass graft surgery.

This slide includes information regarding ticagrelor that is not found in the currently approved BRILINTA PI.


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Class I recommendations:

- Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81 mg-325 mg daily in all other patients (LOE: A)

- In addition to aspirin, a P2Y$_{12}$ inhibitor should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. Options include:
  - Clopidogrel (75 mg per day) or ticagrelor* (90 mg twice daily) (LOE: B)

- In patients receiving a stent (BMS or DES) during PCI for NSTE-ACS, P2Y$_{12}$ inhibitor therapy should be given for at least 12 months. Options include:
  - Clopidogrel (75 mg per day), prasugrel (10 mg per day), or ticagrelor* (90 mg twice daily) (LOE: B)

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.
AHA/ACC NSTE-ACS Guidelines

Late Hospital and Posthospital Oral Antiplatelet Therapy (cont’d)

• Class IIa recommendations:
  ▪ It is reasonable to choose ticagrelor over clopidogrel for maintenance \( \text{P}_2\text{Y}_{12} \) treatment in patients with NSTE-ACS treated with an early invasive strategy and/or PCI (LOE: B)
  ▪ It is reasonable to choose prasugrel over clopidogrel for maintenance \( \text{P}_2\text{Y}_{12} \) treatment in patients with NSTE-ACS who undergo PCI who are not at high risk for bleeding complications (LOE: B)
  ▪ It is reasonable to use an aspirin maintenance dose of 81 mg per day in preference to higher maintenance doses in patients with NSTE-ACS treated either invasively or with coronary stent implantation (LOE: B)
  ▪ If the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of \( \text{P}_2\text{Y}_{12} \) inhibitor therapy after stent implantation, earlier discontinuation (eg, <12 months) of \( \text{P}_2\text{Y}_{12} \) inhibitor therapy is reasonable (LOE: C)

• Class IIb recommendations:
  ▪ Continuation of DAPT beyond 12 months may be considered in patients undergoing stent implantation (LOE: C)
AHA/ACC NSTE-ACS Guidelines

Oral Antiplatelet Therapy in Patients with Aspirin Hypersensitivity or GI Intolerance

• Class I Recommendation:

  ▪ In patients with NSTE-ACS who are unable to take aspirin because of hypersensitivity or major GI intolerance, a LD of clopidogrel followed by a daily maintenance dose should be administered (LOE: B)
2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

ACCF/AHA STEMI Guidelines

Oral Antiplatelet Therapy to Support Primary PCI for STEMI

- Class I recommendations:
  - Aspirin 162 to 325 mg should be given before primary PCI (LOE: B)
  - After PCI, aspirin should be continued indefinitely (LOE: A)
  - A LD of a P2Y12 receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include:
    - Clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg (LOE: B)
  - P2Y12 receptor inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:
    - Clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice a day (LOE: B)

- Class IIa recommendations:
  - It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary PCI (LOE: B)

- Class IIb recommendations:
  - Continuation of a P2Y12 inhibitor beyond 1 year may be considered in patients undergoing DES placement (LOE: C)

- Class III recommendations (Harm):
  - Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack (LOE: B)

ACCF=American College of Cardiology Foundation; STEMI=ST elevation myocardial infarction.

This slide includes information regarding ticagrelor that is not found in the currently approved BRILINTA PI.
ACCF/AHA STEMI Guidelines

Timing of Urgent CABG in Patients with STEMI in Relation to Use of Antiplatelet Agents

- Class I recommendations:
  - Aspirin should not be withheld before urgent CABG (LOE: C)
  - Clopidogrel or ticagrelor should be discontinued at least 24 hours before urgent on-pump CABG, if possible (LOE: B)

- Class IIb recommendations:
  - Urgent off-pump CABG within 24 hours of clopidogrel or ticagrelor administration might be considered, if the benefits of prompt revascularization outweigh the risks of bleeding (LOE: B)
  - Urgent CABG within 5 days of clopidogrel or ticagrelor administration or within 7 days of prasugrel administration might be considered if the benefits of prompt revascularization outweigh the risks of bleeding (LOE: C)

This slide includes information regarding ticagrelor that is not found in the currently approved BRILINTA PI.
What is the Optimal Duration of DAPT?

**Major Adverse Cardiovascular and Cerebrovascular Events**

- **12–30 mo**
  - Thienopyridine vs. placebo, 4.3% vs. 5.9%; hazard ratio, 0.71; \( P<0.001 \)
- **12–33 mo**
  - Thienopyridine vs. placebo, 5.6% vs. 6.5%; hazard ratio, 0.82; \( P=0.02 \)

![Graph showing cumulative incidence of major adverse cardiovascular and cerebrovascular events over months since enrollment for Thienopyridine and Placebo groups.]
Prolonged DAPT and Stent Thrombosis

Stent Thrombosis

12–30 mo  Thienopyridine vs. placebo, 0.4% vs. 1.4%; hazard ratio, 0.29; P<0.001
12–33 mo  Thienopyridine vs. placebo, 0.7% vs. 1.4%; hazard ratio, 0.45; P<0.001

Cumulative Incidence (%)

No. at Risk
Thienopyridine  Placebo
5020  4941
4934  4845
4870  4775
4828  4721
4765  4651
4686  4603
4642  4556
3110  3105

Months since Enrollment

Table 2. Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Continued Thienopyridine (N = 5020)</th>
<th>Placebo (N = 4941)</th>
<th>Hazard Ratio, Thienopyridine vs. Placebo (95% CI)\textsuperscript{†}</th>
<th>P Value\textsuperscript{†}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis:</td>
<td>19 (0.4)</td>
<td>65 (1.4)</td>
<td>0.29 (0.17–0.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Definite</td>
<td>15 (0.3)</td>
<td>58 (1.2)</td>
<td>0.26 (0.14–0.45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Probable</td>
<td>5 (0.1)</td>
<td>7 (0.1)</td>
<td>0.71 (0.22–2.23)</td>
<td>0.55</td>
</tr>
<tr>
<td>Major adverse cardiovascular and cerebrovascular events:</td>
<td>211 (4.3)</td>
<td>285 (5.9)</td>
<td>0.71 (0.59–0.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death</td>
<td>98 (2.0)</td>
<td>74 (1.5)</td>
<td>1.36 (1.00–1.85)</td>
<td>0.05</td>
</tr>
<tr>
<td>Cardiac</td>
<td>45 (0.9)</td>
<td>47 (1.0)</td>
<td>1.00 (0.66–1.52)</td>
<td>0.98</td>
</tr>
<tr>
<td>Vascular</td>
<td>5 (0.1)</td>
<td>5 (0.1)</td>
<td>0.98 (0.28–3.39)</td>
<td>0.98</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>48 (1.0)</td>
<td>22 (0.5)</td>
<td>2.23 (1.32–3.78)</td>
<td>0.002</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>99 (2.1)</td>
<td>198 (4.1)</td>
<td>0.47 (0.37–0.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>37 (0.8)</td>
<td>43 (0.9)</td>
<td>0.80 (0.51–1.25)</td>
<td>0.32</td>
</tr>
<tr>
<td>Ischemic</td>
<td>24 (0.5)</td>
<td>34 (0.7)</td>
<td>0.68 (0.40–1.17)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>13 (0.3)</td>
<td>9 (0.2)</td>
<td>1.20 (0.50–2.91)</td>
<td>0.68</td>
</tr>
<tr>
<td>Type uncertain</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td>—</td>
<td>0.32</td>
</tr>
</tbody>
</table>

\textsuperscript{a}At 12 months after placement of a drug-eluting stent, patients were randomly assigned to receive either continued thienopyridine therapy plus aspirin or placebo plus aspirin for 18 months. Data are presented for the intention-to-treat population. The primary analysis was performed on data from the period of 12 to 30 months after enrollment, and the study coprimary efficacy end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events. Percentages are Kaplan–Meier estimates.

\textsuperscript{†}The hazard ratios and P values were stratified according to geographic region (North America, Europe, or Australia and New Zealand), thienopyridine drug received at the time of randomization, and presence or absence of risk factors for stent thrombosis. P values were calculated with the use of a log-rank test.

\textsuperscript{‡}Definite and probable stent thrombosis were determined according to the criteria of the Academic Research Consortium.

\textsuperscript{§}The end point of major adverse cardiovascular and cerebrovascular events was a composite of death, myocardial infarction, or stroke.
**Trial Design**

Stable pts with history of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor

**RANDOMIZED DOUBLE BLIND**

- Ticagrelor 90 mg bid
- Ticagrelor 60 mg bid
- Placebo

**Follow-up Visits**

Q4 mos for 1st yr, then Q6 mos

**Planned treatment with ASA 75 – 150 mg/d & Standard background care**

**Minimum 1 year follow-up Event-driven trial**

Bonaca MP et al. *Am Heart J* 2014;167:437-44
Primary Endpoint

N = 21,162
Median follow-up 33 months

Placebo (9.0%)
Ticagrelor 90 (7.8%)
Ticagrelor 60 (7.8%)

Ticagrelor 90 mg
HR 0.85 (95% CI 0.75 – 0.96)
P=0.008

Ticagrelor 60 mg
HR 0.84 (95% CI 0.74 – 0.95)
P=0.004

CV
Death
MI, or
Stroke
Bleeding

Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo

P<0.001

3-Year KM Event Rate (%)

<table>
<thead>
<tr>
<th></th>
<th>TIMI Major</th>
<th>TIMI Minor</th>
<th>Fatal bleeding or ICH</th>
<th>ICH</th>
<th>Fatal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor 90</td>
<td>2.6</td>
<td>1.3</td>
<td>0.6</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Ticagrelor 60</td>
<td>2.3</td>
<td>1.2</td>
<td>0.7</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.1</td>
<td>0.4</td>
<td>0.6</td>
<td>0.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School
Summary

- Adding ticagrelor to low-dose aspirin in stable patients with a history of MI reduced the risk of CV death, MI or stroke.

- The benefit of ticagrelor was consistent:
  - For both fatal & non-fatal components of primary endpoint
  - Over the duration of treatment
  - Among major clinical subgroups

- Ticagrelor increased the risk of TIMI major bleeding, but not fatal bleeding or ICH.

- The two doses of ticagrelor had similar overall efficacy, but bleeding and other side effects tended to be less frequent with 60 mg bid dose.
Management of Patients with ACS and Atrial Fibrillation

- 10% of ACS patients have Afib
- 30% of patients with Afib have IHD
- No available data for prasugrel, ticagrelor with warfarin or NOACs, studies are ongoing
- DES stents are reasonable options
- Woest trial (570 patients) concluded that clopidogrel and warfarin without aspirin reduced incidence of bleeding from 40% to 19% without increased risk of stent thrombosis or MI, and improved survival (p=.027)
- Larger studies of double-drug therapy are necessary
- Best practice – use warfarin keeping INR 2-2.5, clopidogrel 75 mg daily, and discontinue aspirin after 30 days from stent implantation.
- Use of NOAC with clopidogrel alone currently being studied and is a reasonable approach in warfarin intolerant patients or patients unwilling to take warfarin.
Conclusions

• With respect to optimal duration of anti-platelet therapy and optimal antiplatelet/oral anticoagulant regimen in patients with atrial fibrillation....

USE GOOD JUDGEMENT AND FOLLOW YOUR PATIENT CLOSELY.
THANK YOU