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Duke University Medical Center
Duke Clinical Research Institute
Durham, North Carolina

Improving Patient Outcomes:
Updated Treatment Strategies in
the Management of
Acute Coronary Syndrome

Personal disclosures:
Research grants
Eli Lilly, Daiichi-Sankyo, Gilead Sciences.
Consultant
AstraZeneca, Abiomed, Gilead Sciences, Janssen
Pharmaceutical, The Medicines Company, Merck,
Liposcience, Pozen Medical, WebMD, and Boehringer
Ingelheim

Institutional disclosure for DCRI at www.dcri.duke.edu/research/coi.jsp
Atherosclerosis, Atherothrombosis, and Plaque Rupture

Adapted from Libby P. Circulation. 2001;104;365-372.

Pathophysiologic Differences Between STEMI and NSTEMI ACS

STEMI
- Clot Totally Blocking Channel

NSTEMI
- Clot Partially Obstructing Channel
- Ruptured Plaque

Thrombus formation

Thrombin plays a central role among tissue injury, coagulation, and platelet response.

The Cycle of Clinical Effectiveness

Concept → Clinical Trials → Guidelines → Performance Indicators → Quality

NCDR Registries → Outcomes
Level of Evidence A – From Randomized Clinical Trials
Current ACC/AHA Cardiovascular Guidelines*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>11.7%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>15.3%</td>
</tr>
<tr>
<td>PAD</td>
<td>13.5%</td>
</tr>
<tr>
<td>STEMI</td>
<td>12.0%</td>
</tr>
<tr>
<td>Perioperative</td>
<td>22.9%</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>6.4%</td>
</tr>
<tr>
<td>Stable angina</td>
<td>6.1%</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>23.6%</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>0.3%</td>
</tr>
<tr>
<td>VA/SCD</td>
<td>9.7%</td>
</tr>
<tr>
<td>PCI</td>
<td>11.0%</td>
</tr>
<tr>
<td>CABG</td>
<td>19.0%</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>3.5%</td>
</tr>
<tr>
<td>Radionuclide imaging</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

Quality Matters
Linking Guidelines Adherence and Mortality

Every 10% ↑ in guidelines adherence → 10% ↓ in mortality (OR=0.90, 95% CI: 0.84-0.97)
In-Hospital Mortality by Age and Guidelines Adherence: Observations from CRUSADE

Adjustment OR:
- Age ≥75: 0.71 (0.67-0.75)
- Age <75: 0.79 (0.75-0.83)

- Boden et al, AHA 2005

Duke Clinical Research Institute
Duke University Medical Center

NCDR
National Cardiovascular Data Registry

2500 hospitals
>2000 cardiologists
20 million clinical records

STS/ACC TVT Registry
IMpact Registry
Pinnacle Registry
ACTION Registry-GWTG
CARE Registry
ICD Registry
CathPCI Registry


Helping Cardiovascular Professionals
“Science tells us what we can do;
Guidelines tell us what we should do;
Registries tell us what we are actually doing and how the treatment works in our practice.”

ACS and DAPT: Current Challenges

- The ADP antagonist landscape in ACS
- Is pre-loading anti-platelet therapy important or giving at PCI sufficient?
- Duration of DAPT and switching after ACS is a balance of ischemia and bleeding
- Can dual pathway (anti-platelet and anti-thrombin) therapy be a viable option to improve outcomes?
Controversies and Conundrum Using Anti-Platelet Therapies

- **Clopidogrel**
  - What dose and how long?

- **Ticagrelor**
  - Survival advantage at 1 year post-ACS
  - Trial of long-term safety

- **Prasugrel**
  - Observations from TRITON
  - Dose adjustment to 5mg – what is the data?
  - Long-term safety?

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**CURRENT – OASIS 7:**

dose comparison of ASA and Clopidogrel in ACS

Cumulative Hazard Ratios for the Primary Outcome at 30 Days, According to Treatment Group

Double vs standard dose of clopidogrel in ACS
No overall benefit but reduction of CV events in the PCI subset
CV Death, MI or Stroke

- **Clopidogrel Standard**
- **Clopidogrel Double**

<table>
<thead>
<tr>
<th>Days</th>
<th>Cumulative Hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td>6</td>
<td>0.03</td>
</tr>
<tr>
<td>9</td>
<td>0.04</td>
</tr>
<tr>
<td>12</td>
<td>0.04</td>
</tr>
<tr>
<td>15</td>
<td>0.04</td>
</tr>
<tr>
<td>18</td>
<td>0.04</td>
</tr>
<tr>
<td>21</td>
<td>0.04</td>
</tr>
<tr>
<td>24</td>
<td>0.04</td>
</tr>
<tr>
<td>27</td>
<td>0.04</td>
</tr>
<tr>
<td>30</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- **HR 0.85**
- **95% CI 0.74-0.99**
- **P=0.036**

CV Death, MI or Stroke

- **15% RRR**

Main Trial: Primary Results

- **Prasugrel** vs Clopidogrel

<table>
<thead>
<tr>
<th>Days</th>
<th>Endpoint (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>30</td>
<td>2.4</td>
</tr>
<tr>
<td>60</td>
<td>5.1</td>
</tr>
<tr>
<td>90</td>
<td>7.9</td>
</tr>
<tr>
<td>180</td>
<td>12.1</td>
</tr>
<tr>
<td>270</td>
<td>15.5</td>
</tr>
<tr>
<td>360</td>
<td>18.1</td>
</tr>
<tr>
<td>450</td>
<td>20.7</td>
</tr>
</tbody>
</table>

- **CV Death / MI / Stroke**
- **HR 0.81 (0.73-0.90)**
- **P=0.0004**

- **TIMI Major**
- **NonCABG Bleeds**

- **24% reduction in MI**
- **P<0.001**

- **HR 1.32 (1.03-1.68)**
- **P=0.03**
Primary Efficacy Endpoint to 30 Months (Age < 75 years)

HR (95% CI) ≤ 1 Year: 0.99 (0.84, 1.16)
HR (95% CI) > 1 Year: 0.72 (0.54, 0.97)

HR (95% CI): 0.91 (0.79, 1.05) P = 0.21

Interaction P = 0.07

TIMI Major Bleeding to 30 Months (Age < 75 years)

HR (95% CI): 1.31 (0.81, 2.11) P = 0.27

No. at risk:
Prasugrel: 3590 3072 2244 1490 885 427
Clopidogrel: 3590 3116 2363 1652 925 426

Duke Clinical Research Institute
PLATO study design

UA/NSTEMI or STEMI (if primary PCI)
All receiving ASA; clopidogrel-treated or -naive; randomised within 24 hours of index event
(N=18,624)

6–12-month exposure

Clopidogrel
If pre-treated, no additional loading dose; if naive, standard 300 mg loading dose, then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then 90 mg bid maintenance;
(additional 90 mg pre-PCI)

Primary endpoint: • CV death + MI + Stroke
Primary safety: • Total major bleeding

UA = unstable angina; PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid; CV = cardiovascular; TIA = transient ischaemic attack

CV Death, MI, Stroke
“Early” vs. “Late” Risk

Hospital Discharge

Cumulative incidence (%) vs. Days after randomisation

Clopidogrel vs. Ticagrelor

HR 0.88 (95% CI 0.77–1.00), p=0.045

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 days</td>
<td>8,942</td>
<td>8,875</td>
</tr>
<tr>
<td>31-90 days</td>
<td>8,397</td>
<td>8,286</td>
</tr>
<tr>
<td>91-150 days</td>
<td>7,028</td>
<td>6,945</td>
</tr>
<tr>
<td>151-210 days</td>
<td>4,822</td>
<td>4,751</td>
</tr>
</tbody>
</table>

*Excludes patients with any primary event during the first 30 days
Secondary efficacy endpoints over time

**Myocardial infarction**
- Clopidogrel: 6.9%
- Ticagrelor: 5.8%
- HR 0.84 (95% CI 0.75–0.95), p=0.005

**Cardiovascular death**
- Clopidogrel: 5.1%
- Ticagrelor: 4.0%
- HR 0.79 (95% CI 0.69–0.91), p=0.001

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**PLATO Trial: Safety Evaluation of the Elderly Patients (Age >75)**

2,878 Patients (15%) of Total Population

**All-Cause Mortality**
- Age >75 (OR): 0.77, 0.60-0.98

**PLATO Non-CABG Bleeding**
- Age >75 (OR): 1.18, 0.87-1.58

*Husted, Circ Outcomes 2012*
Prevention of Stent Thrombosis
UA/NonSTEMI: Pharmacological Strategies
Rate of Definite/Probable Stent Thrombosis

- High-dose Clopidogrel (600/150mg) vs Clopidogrel (300/75mg)
  1.6% vs 2.3%; OR: 0.69 (95%CI: 0.56-0.87), p=0.001*

- Prasugrel vs Clopidogrel (300/75mg)
  1.1% vs 2.4%; OR: 0.48 (95%CI: 0.36-0.64), p<0.001**

- Ticagrelor vs Clopidogrel (600/75mg)
  2.2% vs 3.0%; OR: 0.73 (95%CI: 0.57-0.94), p=0.014**

- Cangrelor vs Clopidogrel (300/75mg)
  0.2% vs 0.6%; OR: 0.35 (95%CI: 0.11-0.65), p=0.02***

Bivalirudin vs Glycoprotein 2b/3a blocker

- 1.5% vs 1.1%, p=0.37*  *30-day rate
- Bivalirudin requires clopidogrel before PCI (p=0.02)  **48-hour rate

Aoki et al, ACUITY Trial Circ 2009 OASIS-7 PCI, Lancet 2010
CHAMPION-PCI NEJM 2010.

ACS and DAPT: Current Challenges

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- Is pre-loading anti-platelet therapy important or giving at PCI sufficient?
- Duration of DAPT and switching after ACS is a balance of ischemia and bleeding
- Can dual pathway (anti-platelet and anti-thrombin) therapy be a viable option to improve outcomes?
ACCOAST design

NSTEMI + Troponin ≥ 1.5 times ULN local lab value
Clopidogrel naive or on long term clopidogrel 75 mg

Randomize 1:1
Double-blind

n=4100 (event driven)

Prasugrel 30 mg
Placebo

Prasugrel 60 mg

PCI

CABG or Medical Management (no more prasugrel)

Coronary Angiography

PCI

Coronary Angiography

Prasugrel 30 mg

Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

PCI

1° Endpoint: CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days


1° Efficacy End Point @ 7 + 30 days
(All Patients)

CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa Bailout

Pre-treatment 10.0

Pre-treatment 10.8

No Pre-treatment 9.8

Hazard Ratio, 1.02
(95% 0.84, 1.25)
P=0.81

No Pre-treatment 10.8

Hazard Ratio, 0.997
(95% 0.83, 1.20)
P=0.98

No. at Risk, Primary Efficacy End Point:
No pre-treatment
Pre-treatment
1996
10.810.0
9.8
9.8

1788
1821
1775
1809
1769
1802
1762
1797
1752
1791
1621
1618

Days From First Dose

Endpoint (%)

15
10
5
0

0
5
10
15
20
25
30
All TIMI (CABG or non-CABG) Major Bleeding (All Treated patients)

Days From First Dose

Endpoint (%) 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

No. at Risk, All TIMI Major Bleeding:
No pre-treatment 1996 1947 1328 1297 1286 1284 1283
Pre-treatment 3037 1972 1339 1310 1299 1297 1288

Hazard Ratio, 1.97 (95% 1.19, 3.08) P=0.002

Hazard Ratio, 1.90 (95% 1.19, 3.02) P=0.006

Stopping DAPT Prior to CABG: TRITON Trial

Chest tube blood loss All-cause mortality

Guidelines recommend stopping prasugrel 7 days before CABG

Smith et al, JACC 2012
Guidelines recommend stopping either clopidogrel or ticagrelor 5 days before CABG.

**Cangrelor**
- Direct platelet P2Y₁₂ receptor antagonist
- ATP analogue MW=800 Daltons
- Parenteral administration
- T1/2 = 3 to 6 minutes
- Offset = 60 minutes

Platelet Reactivity During Infusion of Cangrelor prior to CABG

No significant increase in bleeding during infusion before CABG

Angiolillo et al., JAMA 2012

CHAMPION Trials Study Designs
Randomised, Double Blind, Controlled Trials of patients undergoing PCI

CHAMPION PHOENIX
n=10,942 mITT
SA / NSTE-ACS / STEMI
P2Y12 naïve
Placebo or clopidogrel before or after PCI

CHAMPION PCI
n=8667 mITT
SA / NSTE-ACS / STEMI
Placebo or clopidogrel before PCI

CHAMPION PLATFORM
n=5301 mITT
SA / NSTE-ACS
P2Y12 naïve
Placebo or clopidogrel after PCI

Cangrelor bolus then infusion
Clopidogrel 600 mg or 300 mg oral

OR

Clopidogrel 600 mg oral

PCI ~30'
## Demographics, mITT

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor (N= 12,475)</th>
<th>Clopidogrel (N= 12,435)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>72%</td>
<td>72%</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>29%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Patient Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>57%</td>
<td>58%</td>
</tr>
<tr>
<td>STEMI</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Loading Dose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg clopidogrel</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>600 mg clopidogrel</td>
<td>89%</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Timing of clopidogrel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PCI start</td>
<td>56%</td>
<td>56%</td>
</tr>
<tr>
<td>During PCI</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Within 1 hour post PCI</td>
<td>31%</td>
<td>30%</td>
</tr>
</tbody>
</table>

*Figures pertain to clopidogrel placebo loaded according to stratification at the time of randomisation.

## Primary Efficacy Outcomes at 48 Hours, mITT

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor (N=12,475)</th>
<th>Clopidogrel (N=12,435)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/IDR/ST</td>
<td>473/12,459 (3.8%)</td>
<td>579/12,422 (4.7%)</td>
<td>0.81 (0.71-0.91)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

## Secondary Efficacy Outcomes at 48 Hours, mITT

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor (N=12,475)</th>
<th>Clopidogrel (N=12,435)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis</td>
<td>62/12,459 (0.5%)</td>
<td>105/12,422 (0.8%)</td>
<td>0.59 (0.43-0.80)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Death/MI/IDR</td>
<td>446/12,459 (3.6%)</td>
<td>543/12,422 (4.4%)</td>
<td>0.81 (0.71-0.92)</td>
<td>0.0014</td>
</tr>
<tr>
<td>MI</td>
<td>387/12,459 (3.1%)</td>
<td>453/12,422 (3.6%)</td>
<td>0.85 (0.74-0.97)</td>
<td>0.0182</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>19/12,459 (0.2%)</td>
<td>36/12,422 (0.3%)</td>
<td>0.53 (0.30-0.92)</td>
<td>0.0211</td>
</tr>
<tr>
<td>IDR</td>
<td>66/12,459 (0.5%)</td>
<td>92/12,422 (0.7%)</td>
<td>0.71 (0.52-0.98)</td>
<td>0.0363</td>
</tr>
<tr>
<td>Death</td>
<td>33/12,459 (0.3%)</td>
<td>45/12,422 (0.4%)</td>
<td>0.73 (0.47-1.15)</td>
<td>0.1694</td>
</tr>
</tbody>
</table>

Stent Thrombosis within 48 Hours

Event rate (%)

No. patients at risk
Cangrelor: 12,475, 12,420, 12,406, 12,403, 12,395, 12,387, 12,384, 12,377, 12,371
Clopidogrel: 12,435, 12,327, 12,319, 12,318, 12,308, 12,306, 12,304, 12,297, 12,291

Log-rank p value = 0.0008

Non-CABG Bleeding at 48 Hours, Safety

Bleeding Scale	Cangrelor (N=12,565)\tClopidogrel (N=12,5425)\tOR (95% CI)\tP Value
---	---	---	---	---
GUSTO Severe	28 (0.2%)\t23 (0.2%)\t1.22 (0.70, 2.11)\t0.4875
GUSTO Moderate	76 (0.6%)\t56 (0.4%)\t1.36 (0.96, 1.92)\t0.0828
GUSTO Severe + Moderate	103 (0.8%)\t79 (0.6%)\t1.30 (0.97, 1.75)\t0.0762
TIMI Major	32 (0.3%)\t28 (0.2%)\t1.14 (0.69, 1.90)\t0.6101
TIMI Minor	77 (0.6%)\t51 (0.4%)\t1.51 (1.06, 2.15)\t0.0218
TIMI Major + Minor	109 (0.9%)\t79 (0.6%)\t1.38 (1.03, 1.85)\t0.0290
Any Blood Transfusion	90 (0.7%)\t70 (0.6%)\t1.29 (0.94, 1.76)\t0.1154
ACUITY Major	534 (4.2%)\t353 (2.8%)\t1.53 (1.34, 1.76)\t<0.0001
ACUITY w/out hematoma	169 (1.3%)\t123 (1.0%)\t1.38 (1.09, 1.74)\t0.0071
ACS and DAPT: Current Challenges

- The ADP antagonist landscape in ACS
- Is pre-loading anti-platelet therapy important or giving at PCI sufficient?
- Duration of DAPT and switching after ACS is a balance of ischemia and bleeding
- Can dual pathway (anti-platelet and anti-thrombin) therapy be a viable option to improve outcomes?

Why Switch DAPT after Discharge?

- To improve compliance
  - Reasonable as any DAPT is better than aspirin alone
- To reduce side-effects
  - Reasonable as patients are not compliant with therapy that causes side-effects
- To save money
  - Ischemic events very costly – will not save $
- As routine practice
  - You got to be kidding.....
Primary endpoint: CV death, MI or stroke

These results were achieved without switching after discharge!

K-M estimated rate (% per year) HR: 0.84 (95% CI = 0.75–0.94), p=0.0025

THIENOPYRIDINE SWITCHING

Timing of ADP receptor inhibitor switch

<table>
<thead>
<tr>
<th></th>
<th>1st to 2nd gen (n=669)</th>
<th>2nd to 1st gen (n=271)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6 hours before PCI</td>
<td>3 (0.4%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>0-6 hours before PCI</td>
<td>16 (2.4%)</td>
<td>7 (2.6%)</td>
</tr>
<tr>
<td>During PCI</td>
<td>64 (9.6%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>After PCI</td>
<td>410 (61.3%)</td>
<td>133 (49.1%)</td>
</tr>
<tr>
<td>Time of discharge</td>
<td>176 (26.3%)</td>
<td>128 (47.2%)</td>
</tr>
</tbody>
</table>

Bagai et al. Circulation 2012; 126: A15573
Factors associated with in-hospital switch from \(2^{nd}\) to \(1^{st}\) generation ADP receptor inhibitor

<table>
<thead>
<tr>
<th></th>
<th>Chi-Square</th>
<th>OR</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10y) above 65</td>
<td>24.9</td>
<td>2.54</td>
<td>1.76</td>
<td>3.66</td>
</tr>
<tr>
<td>Anticoagulant on d/c</td>
<td>23.7</td>
<td>3.72</td>
<td>2.19</td>
<td>6.31</td>
</tr>
<tr>
<td>Private insurance</td>
<td>17.9</td>
<td>0.56</td>
<td>0.42</td>
<td>0.73</td>
</tr>
<tr>
<td>Discharge EF (per 5%) above 45</td>
<td>16.1</td>
<td>1.21</td>
<td>1.10</td>
<td>1.32</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>14.9</td>
<td>3.40</td>
<td>1.83</td>
<td>6.33</td>
</tr>
<tr>
<td>South region</td>
<td>6.6</td>
<td>0.65</td>
<td>0.47</td>
<td>0.90</td>
</tr>
<tr>
<td>Current/recent smoker</td>
<td>4.9</td>
<td>1.37</td>
<td>1.04</td>
<td>1.81</td>
</tr>
</tbody>
</table>

Bagai et al. Circulation 2012; 126: A15573

MACE and Bleeding rates from Discharge to 6 weeks

<table>
<thead>
<tr>
<th></th>
<th>Initial 1(^{st}) generation ADP inhibitor (n=6077)</th>
<th>Initial 2(^{nd}) generation ADP inhibitor (n=2072)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Switch Switch to 2(^{nd}) gen No Switch Switch to 1(^{st}) gen</td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>2.3 2.0 1.4 3.1</td>
<td></td>
</tr>
<tr>
<td>MACE*</td>
<td>Reference HR 0.92 (95%CI 0.52-1.63) Reference HR 1.95 (95%CI 0.88-4.32)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for Bleeding</td>
<td>1.3 0.9 0.7 0.4</td>
<td></td>
</tr>
</tbody>
</table>

MACE: death, myocardial infarction, stroke, unplanned revascularization; *Adjusted

Bagai et al. Circulation 2012; 126: A15573
Some Reflections on DAPT

- Duration of DAPT after ACS is a balance of ischemia and bleeding
  - Cost and compliance
  - Desire to switch
  - Side-effects
- After PCI in ACS DAPT is essential to prevent stent thrombosis and other ischemic events
  - Typically 9 months to 1 year
- Duration of DAPT greater than 1 year for
  - Recurrent stent thrombosis – lifetime
  - High-risk PCI (UPLM PCI or equivalent)

CHARISMA Trial: 3-Year Outcomes Among Patients with Prior MI

![Graph showing outcomes](https://example.com/graph.png)

- N = 3,846
- Primary outcome event rate
- Placebo + ASA vs Clopidogrel + ASA
- HR: 0.774 [95% CI: (0.813, 0.978)]
- p = 0.0031

Bhatt, JACC 2007
Trial Schema

N = 21,000

**Stable pts with history of MI 1-3 yrs prior**

+ ≥1 additional atherothrombosis risk factor*

**RANDOMIZE**

**DOUBLE BLIND**

Ticagrelor

90 mg bid

Placebo

Ticagrelor

60 mg bid

Follow-up Visits

Q4 mos for 1st yr, then Q6 mos

Min 12 mos and median 26 mos follow-up

Primary Efficacy Endpoint: CV Death, MI, or Stroke

Primary Safety Endpoint: TIMI Major Bleeding

* Age >65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction

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

ADAPT-DES

**Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents**

Up to 11,000 pts prospectively enrolled

No clinical or anatomic exclusion criteria

11 sites in US and Germany

**PCI with ≥1 non-investigational DES**

Successful and uncomplicated

(IVUS/VH substudy; Up to 3000 pts enrolled)

Assess platelet function after adequate DAPT loading and GPI washout: Accumetrics VerifyNow Aspirin, VerifyNow P2Y12, and VerifyNow IIb/IIIa assays (results blinded)

**Clinical FU at 30 days, 1 year and 2 years**

Angio core lab assessment all STs w/1:2 matching controls

clinicaltrials.gov NCT00638794
2-Year Kaplan-Meier Plot of Any DAPT Cessation

Cumulative Incidence, %

Time From PCI, Months

- 30 Days (2.9%)
- One Year (23.3%)
- Two Years (57.3%)

Incidence rates calculated over entire study population. Patients censored at last known contact, death or study end.

DAPT Cessation and MACE*

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-DAPT</td>
<td>1.00 (Ref)</td>
<td></td>
<td>413</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>0.63 (0.46, 0.86)</td>
<td>0.004</td>
<td>52</td>
</tr>
<tr>
<td>Interruption</td>
<td>1.41 (0.94, 2.12)</td>
<td>0.101</td>
<td>26</td>
</tr>
<tr>
<td>Disruption</td>
<td>1.50 (1.14, 1.97)</td>
<td>0.004</td>
<td>67</td>
</tr>
<tr>
<td>0-7 Days</td>
<td>7.04 (3.31, 14.95) &lt;0.001</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>8-30 days</td>
<td>2.17 (0.97, 4.88)</td>
<td>0.06</td>
<td>6</td>
</tr>
<tr>
<td>31+ days</td>
<td>1.30 (0.97, 1.76)</td>
<td>0.083</td>
<td>54</td>
</tr>
</tbody>
</table>

*Cardiac Death, Def/Prob ST, Spontaneous MI, Clinically Driven TLR.

All Cox Models adjusted for age, gender, region, ACS presentation, type of stent, number of stents implanted.
**ACS and DAPT: Current Challenges**

- The ADP antagonist landscape in ACS
- Is pre-loading anti-platelet therapy important or giving at PCI sufficient?
- Duration of DAPT and switching after ACS is a balance of ischemia and bleeding
- Can dual pathway (anti-platelet and anti-thrombin) therapy be a viable option to improve outcomes?

### The New Era of Secondary Prevention after ACS: ATLAS Trial

**Death, MI or Stroke**

93% on ASA + Clopidogrel

**CV Death**

TIMI Major Non-CABG Bleeding - HR 3.5 p<0.001

*Mega et al, NEJM 2011*
Rivaroxaban Use in Patients With AF Undergoing PCI: PIONEER AF-PCI

- Primary objective: TIMI major, minor, and bleeding requiring medical attention
- Secondary objectives: CV death, MI, stroke, and stent thrombosis

2100 patients with NVAF
- No prior stroke/TIA
- PCI with stent placement

End of treatment at 12 months

ACS and DAPT: Current Challenges

- Dual anti-platelet therapy is now a cornerstone of ACS management
  - Ticagrelor is superior to clopidogrel with a survival advantage in all ACS
  - Prasugrel is superior to clopidogrel limited to PCI patients

- DAPT for 1 year is current standard
  - Longer may be better – need more trials

- Switching DAPT after ACS may be problematic