ACS: Antiplatelet, Anticoagulant Therapy and Combinations

The Challenge of a High Benefit/Bleeding Ratio

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Professor of Medicine, Harvard Medical School
Disclosures for Dr. Bhatt

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This presentation discusses off-label and/or investigational uses of various drugs and devices.
ACS and Oral Antithrombotic Therapy

Antithrombotic Therapy

- Antiplatelet Agents
- Anticoagulants

Rupture
THROMBUS
PLAQUE

Anticoagulants
Fibrinogen

Prothrombin

Thrombin

Fibrin

ATIII

Factor Xa

Rivaroxaban
Apixaban
Edoxaban

Vorapaxar

PAR-1

TF + FVIIa

Fondaparinux
LMWH
UFH

Bivalirudin
Dabigatran

ACS & Plaque Rupture

TRITON TIMI-38: Net Clinical Benefit

Bleeding Risk Subgroups

Post hoc analysis

Prior Stroke / TIA

Yes

No

Risk (%)

P_{int} = 0.006

+54

-16

Age

>=75

P_{int} = 0.18

-1

< 75

Wgt

< 60 kg

P_{int} = 0.36

+3

>= 60 kg

OVERALL

Prasugrel Better

1

Clopidogrel Better

2

0.5

Intensifying Platelet Inhibition — Navigating between Scylla and Charybdis

Deepak L. Bhatt, M.D.
Potential Relationship Between Bleeding and Mortality

Major Bleeding

Hypotension

Cessation of DAPT

Transfusion

Ischemia

Stent Thrombosis

Inflammation

Mortality

Bhatt DL. In Braunwald: Heart Disease Online 2005.
Primary Efficacy Results (MI/Stroke/CV Death) by Pre-Specified Entry Category

<table>
<thead>
<tr>
<th>Population</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying CAD, CVD or PAD *</td>
<td>0.88 (0.77, 0.998)</td>
<td>0.046</td>
</tr>
<tr>
<td>(n=12,153)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Risk Factors *</td>
<td>1.20 (0.91, 1.59)</td>
<td>0.20</td>
</tr>
<tr>
<td>(n=3,284)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Population†</td>
<td>0.93 (0.83, 1.05)</td>
<td>0.22</td>
</tr>
<tr>
<td>(n=15,603)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A statistical test for interaction showed marginally significant heterogeneity (p=0.045) in treatment response for these pre-specified subgroups of patients
† 166 patients did not meet any of the main inclusion criteria

CHARISMA—Prior MI

N=3,846

Primary Outcome Event Rate (%)

Months Since Randomization

Placebo + ASA
Clopidogrel + ASA

HR=0.774 (95% CI [0.613–0.978])
P=0.031

Timing of Severe or Moderate Bleeding

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

RANDOMIZE DOUBLE BLIND

Ticagrelor 90 mg bid

Ticagrelor 60 mg bid

Placebo

Follow-up Visits
Q4 mos for 1st yr, then Q6 mos

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

Min 12 mos and median 26 mos follow-up Event-driven trial

PEGASUS TIMI 54 – Components of Primary Endpoint

PEGASUS – TIMI 54

Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials

Jacob A. Udell¹,²*, Marc P. Bonaca³, Jean-Philippe Collet⁴, A. Michael Lincoff⁵, Dean J. Kereiakes⁶, Francesco Costa⁷, Cheol Whan Lee⁸, Laura Mauri⁹, Marco Valgimigli⁷, Seung-Jung Park⁸, Gilles Montalescot⁴, Marc S. Sabatine³, Eugene Braunwald³, and Deepak L. Bhatt³*
Primary Endpoint – CV Death, MI, or Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>125</td>
<td>1903</td>
<td>162</td>
<td>1943</td>
<td>0.77 (0.61 - 0.98)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>63</td>
<td>732</td>
<td>69</td>
<td>733</td>
<td>0.91 (0.65 - 1.28)</td>
</tr>
<tr>
<td>ARCTIC-Int’n</td>
<td>3</td>
<td>156</td>
<td>4</td>
<td>167</td>
<td>0.79 (0.18 - 3.51)</td>
</tr>
<tr>
<td>DAPT</td>
<td>59</td>
<td>1805</td>
<td>108</td>
<td>1771</td>
<td>0.52 (0.38 - 0.72)</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>56</td>
<td>1512</td>
<td>66</td>
<td>1551</td>
<td>0.85 (0.60 - 1.21)</td>
</tr>
<tr>
<td>PEGASUS</td>
<td>980</td>
<td>14095</td>
<td>578</td>
<td>7067</td>
<td>0.84 (0.76 - 0.94)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1286</td>
<td>20203</td>
<td>987</td>
<td>13232</td>
<td>0.78 (0.67 - 0.90)</td>
</tr>
<tr>
<td></td>
<td>6.4%</td>
<td></td>
<td>7.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ P = 0.001 \]

Extended DAPT Better

Aspirin Alone Better

Cardiovascular Death

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>53</td>
<td>1903</td>
<td>65</td>
<td>1943</td>
<td>0.82 (0.57 - 1.18)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>31</td>
<td>732</td>
<td>31</td>
<td>733</td>
<td>1.00 (0.61 - 1.64)</td>
</tr>
<tr>
<td>ARCTIC-Int’n</td>
<td>0</td>
<td>156</td>
<td>1</td>
<td>167</td>
<td>0.36 (0.01 - 8.69)</td>
</tr>
<tr>
<td>DAPT</td>
<td>11</td>
<td>1805</td>
<td>16</td>
<td>1771</td>
<td>0.67 (0.31 - 1.44)</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>21</td>
<td>1512</td>
<td>21</td>
<td>1551</td>
<td>1.00 (0.55 - 1.83)</td>
</tr>
<tr>
<td>PEGASUS</td>
<td>356</td>
<td>14095</td>
<td>210</td>
<td>7067</td>
<td>0.85 (0.71 - 1.00)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>472</td>
<td>20203</td>
<td>344</td>
<td>13232</td>
<td>0.85 (0.74 - 0.98)</td>
</tr>
</tbody>
</table>

2.3%  2.6%

P = 0.03

Extended DAPT Better  Aspirin Alone Better

Individual CV Endpoints

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>Extended DAPT</th>
<th>Aspirin Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>6.4</td>
<td>7.5</td>
</tr>
<tr>
<td>CV Death</td>
<td>2.3</td>
<td>2.6</td>
</tr>
<tr>
<td>MI</td>
<td>3.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Stent Thrombosis (Def/Prob)</td>
<td>0.6</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Major Bleeding

<table>
<thead>
<tr>
<th>Study</th>
<th>Extended DAPT</th>
<th>Aspirin Alone</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>Events: 45</td>
<td>Total: 1903</td>
<td>Events: 39</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>Events: 9</td>
<td>Total: 732</td>
<td>Events: 6</td>
</tr>
<tr>
<td>ARCTIC-Int’n</td>
<td>Events: 2</td>
<td>Total: 156</td>
<td>Events: 0</td>
</tr>
<tr>
<td>DAPT</td>
<td>Events: 34</td>
<td>Total: 1805</td>
<td>Events: 14</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>Events: 39</td>
<td>Total: 1512</td>
<td>Events: 31</td>
</tr>
<tr>
<td>PEGASUS</td>
<td>Events: 242</td>
<td>Total: 13946</td>
<td>Events: 54</td>
</tr>
<tr>
<td>TOTAL</td>
<td>Events: 371</td>
<td>Total: 20054</td>
<td>Events: 144</td>
</tr>
<tr>
<td></td>
<td>1.9%</td>
<td>1.1%</td>
<td></td>
</tr>
</tbody>
</table>

$P = 0.004$

## Subgroup Analysis: Primary Endpoint

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>Extended DAPT</th>
<th>Aspirin Alone</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75 years</td>
<td>5.9</td>
<td>6.8</td>
<td>0.83</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>11.1</td>
<td>12.9</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6.6</td>
<td>7.7</td>
<td>0.84</td>
</tr>
<tr>
<td>Female</td>
<td>6.9</td>
<td>7.7</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>DAPT Regimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>5.8</td>
<td>6.9</td>
<td>0.82</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>7.0</td>
<td>8.2</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Index ACS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>3.3</td>
<td>4.6</td>
<td>0.68</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>7.6</td>
<td>8.2</td>
<td>0.88</td>
</tr>
<tr>
<td>STEMI</td>
<td>5.6</td>
<td>7.1</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Time from Index MI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24 months</td>
<td>6.1</td>
<td>7.3</td>
<td>0.76</td>
</tr>
<tr>
<td>≥ 24 months</td>
<td>6.7</td>
<td>7.4</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>History of PCI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.7</td>
<td>6.7</td>
<td>0.78</td>
</tr>
<tr>
<td>No</td>
<td>9.9</td>
<td>11.3</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>6.4</td>
<td>7.5</td>
<td>0.78 (0.67 - 0.90)</td>
</tr>
</tbody>
</table>

All P-interactions >0.05
Abbreviations: NE: no estimate
EXAMINATION:
EES vs BMS in Acute MI

Can 2\textsuperscript{nd} Generation DES Reduce Death?

First generation drug eluting stents  ⟷  Second generation drug eluting stents

\[\downarrow\text{Stent restenosis} \quad \uparrow\text{Stent thrombosis} \quad \downarrow\text{Stent restenosis} \quad \downarrow\text{Stent thrombosis}\]

\[\downarrow\text{Death, MI} \quad \uparrow\text{Death, MI} \quad \downarrow\text{Death, MI} \quad \downarrow\text{Death, MI}\]

\[\uparrow\downarrow\text{Death, MI}\]

OPTIMIZE Trial: NACCE at 1 Year
(All-Cause Death, MI, Stroke, Major Bleeding)

Log-Rank P = 0.84
HR 1.03 (0.77 – 1.38)

Cumulative Incidence of NACCE (%)

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>1563</td>
<td>1520</td>
<td>1504</td>
<td>1468</td>
<td>1384</td>
</tr>
<tr>
<td>No. events</td>
<td>18</td>
<td>25</td>
<td>11</td>
<td>18</td>
<td>21</td>
</tr>
</tbody>
</table>

## Optimal Duration of DAPT?

### Patient-related factors
- **≤12 months DAPT**
  - Patients with stable CAD
  - Patients with a history of bleeding
  - Patients with high risk of bleeding
- **≥12 months DAPT**
  - Patients with ACS
  - Patients with diabetes mellitus
  - Patients with renal dysfunction
  - Patients with CHF
  - Patients with previous ST
  - Patients with PAD

### Anatomy-related factors
- **≤12 months DAPT**
  - Short lesion
  - Single-vessel disease
- **≥12 months DAPT**
  - Long lesion
  - Small vessel
  - Bifurcation lesion
  - Complex anatomy
  - Left-main coronary artery

### Stent-related factors
- **≤12 months DAPT**
  - Second-generation DES
- **≥12 months DAPT**
  - First-generation DES
  - Long stent
  - Multiple stents

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Eisen A, Bhatt DL. Nature Reviews Cardiology. 2015.
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

Prasugrel 30 mg

Placebo

PCI

Coronary Angiography

Coronary Angiography

Prasugrel 30 mg

Prasugrel 60 mg

CABG or Medical Management (no prasugrel)

CABG or Medical Management (no more prasugrel)

n~4100 (event driven)

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

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

Days From First Dose

CV Death, MI, Stroke, UR, GPIIb/IIIa Bailout

Effectiveness End Point @ 7 + 30 days

No. at Risk, Primary
Efficacy End Point:
No pre-treatment 1996 1788 1775 1769 1762 1752 1621
Pre-treatment 2037 1821 1809 1802 1797 1791 1616

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

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

Montalescot G et al. NEJM 2013
All TIMI (CABG or non-CABG) Major Bleeding

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

Hazard Ratio, 1.97 (95% 1.26, 3.08)  
P=0.002

No. at Risk, All TIMI Major Bleeding:
No pre-treatment 1,996 1,947 1,328 1,297 1,288 1,284 1,263
Pre-treatment 2,037 1,972 1,339 1,310 1,299 1,297 1,280

Montalescot G et al. NEJM 2013
Studies of pretreatment with oral P2Y12 receptor inhibitors in patients with stable CAD and NSTE-ACS

**Efficacy**

- **Patients**
  - Stable CAD
  - ACS
  - % PCI
- **Drug**
  - Clopidogrel 300 mg
  - Prasugrel 300 mg
- **Follow-up**
  - 28 days
  - 7 days
  - 30 days

**Efficacy endpoint displayed**
- D/MI/Unf
- D/MI/CVA/Rev
- TIMI major bleeding
- All TIMI bleeding

**Safety endpoint displayed**

**Credo**
- Pretreatment: 6.8%
- No pretreatment: 8.3%
- P = 0.23

**Prague 8**
- Pretreatment: 0.8%
- No pretreatment: 1.0%
- P = 0.75

**Accoast**
- Pretreatment: 10.8%
- No pretreatment: 10.8%
- P = 0.98

**Patients**
- 2,115
- 33%
- 67%
- 86%
- 1,028
- 87%
- 13%
- 29%
- 4,033
- No
- All NSTEMI
- 69%

**Safety**

**Credo**
- Pretreatment: 4.8%
- No pretreatment: 3.8%
- P = 0.24

**Prague 8**
- Pretreatment: 3.5%
- No pretreatment: 1.4%
- P = 0.025

**Accoast**
- Pretreatment: 2.6%
- No pretreatment: 1.4%
- P < 0.001

*Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv 2015*
Studies of pretreatment with oral P2Y12 receptor inhibitors in patients with STEMI undergoing Primary PCI

**Efficacy**

- **Patients**
- **Drug**
- **Follow-up**
- Efficacy endpoint displayed
- Safety endpoint displayed

**CIPAMI**
- 337 patients
- Clopidogrel 600 mg
- Hospital discharge
- D/MI/Urev
- TIMI major bleeding

**Load&Go**
- 168 patients
- Clopidogrel 600-900 mg
- 30 days
- CD/MI/CVA/ST
- Major bleeding

**ATLANTIC**
- 1,862 patients
- Ticagrelor 180 mg
- 30 days
- D/MI/CVA/Urev/ST
- All PLATO bleeding

**Safety**

**CIPAMI**
- 9.1%
- P=0.80

**Load&Go**
- 1.8%
- P=0.55

**ATLANTIC**
- 2.5%
- P=0.87

P-values:
- P=0.09
- P=0.91
- P=0.91
- P=0.55
- P=0.87
- P=0.80

Capodanno D & Angiolillo DJ. Circ Cardiovasc Interv 2015
Time from hospital admission or first medical contact to coronary angiography in studies of ACS & STEMI

PCI-CURE 6 days
RITA-3 3 days
CRUSADE 23 hours
ACUITY 20 hours
CHAMPION PLATFORM 7 hours
CURRENT OASIS 7 NSTE-ACS 3 hours
ACCOAST 4 hours


ASSENT-4 PCI 2 hours
PLATO STEMI 1 hour
ATOLL 42 minutes
EUROMAX 50 minutes
HORIZONS AMI 2 hours
CURRENT OASIS 7 STEMI 30 minutes
ATLANTIC 48 minutes

PCI-CLARITY 3 days

Cangrelor

- Direct platelet P2Y\textsubscript{12} receptor antagonist
- ATP analogue MW=800 Daltons
- Parenteral administration
- T1/2 = 3 to 6 minutes
- Offset = 60 minutes

CHAMPION PHOENIX Study Design

CHAMPION PHOENIX
N = 10,900 MITT
SA/ NSTE-ACS/ STEMI Patients requiring PCI
P2Y12 inhibitor naïve

Randomization occurred once suitability for PCI was confirmed either by angiography or STEMI diagnosis. Double blind study medication was administered as soon as possible following randomization.

Study drug infusion (cangrelor or matching placebo) was continued for 2-4 hours at the discretion of the treating physician. At the end of the infusion patients received a loading dose of clopidogrel or matching placebo and were transitioned to maintenance clopidogrel therapy.

Clopidogrel loading dose (or matching placebo) was administered as directed by the investigator. At the time of patient randomization, a clopidogrel loading dose of 600 mg or 300 mg was specified by the investigator.

MITT=modified intent-to-treat; NSTE-ACS=non-ST-elevation acute coronary syndrome; PCI=percutaneous coronary intervention; SA=stable angina; STEMI=ST-elevation MI.
Death/ MI/ IDR/ Stent Thrombosis within 48 Hours

Patient at Risk
Cangrelor: 5472 5233 5229 5225 5223 5221 5220 5217 5213
Clopidogrel: 5470 5162 5159 5155 5152 5151 5151 5147 5147

Log Rank P Value = 0.006

Stent Thrombosis within 48 Hours

Log Rank P Value = 0.01

Event Rate (%)

- Cangrelor: 0.8%
- Clopidogrel: 1.4%

Patient at Risk
- Cangrelor: 5472 5426 5421 5419 5419 5418 5417 5416 5414
- Clopidogrel: 5470 5392 5389 5388 5386 5385 5385 5383 5383

## Non-CABG Bleeding at 48 Hours, Safety

<table>
<thead>
<tr>
<th>Bleeding Scale</th>
<th>Cangrelor (N=5529)</th>
<th>Clopidogrel (N=5527)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO Severe</td>
<td>9 (0.16%)</td>
<td>6 (0.11%)</td>
<td>1.50 (0.53,4.22)</td>
<td>0.44</td>
</tr>
<tr>
<td>GUSTO Moderate</td>
<td>22 (0.4%)</td>
<td>13 (0.2%)</td>
<td>1.69 (0.85,3.37)</td>
<td>0.13</td>
</tr>
<tr>
<td>GUSTO Severe + Moderate</td>
<td>31 (0.6%)</td>
<td>19 (0.3%)</td>
<td>1.63 (0.92,2.90)</td>
<td>0.09</td>
</tr>
<tr>
<td>TIMI Major</td>
<td>5 (0.1%)</td>
<td>5 (0.1%)</td>
<td>1.00 (0.29,3.45)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>TIMI Minor</td>
<td>9 (0.2%)</td>
<td>3 (0.1%)</td>
<td>3.00 (0.81,11.10)</td>
<td>0.08</td>
</tr>
<tr>
<td>TIMI Major + Minor</td>
<td>14 (0.3%)</td>
<td>8 (0.1%)</td>
<td>1.75 (0.73,4.18)</td>
<td>0.2</td>
</tr>
<tr>
<td>Any Blood Transfusion</td>
<td>25 (0.5%)</td>
<td>16 (0.3%)</td>
<td>1.56 (0.83,2.93)</td>
<td>0.16</td>
</tr>
<tr>
<td>ACUITY Major</td>
<td>235 (4.3%)</td>
<td>139 (2.5%)</td>
<td>1.72 (1.39,2.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACUITY w/out hematoma</td>
<td>42 (0.8%)</td>
<td>26 (0.5%)</td>
<td>1.62 (0.99,2.64)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

## Results: Sensitivity analyses for composite endpoints

<table>
<thead>
<tr>
<th>Protocol-defined primary endpoint</th>
<th>Cangrelor (N=5472)</th>
<th>Clopidogrel (N=5470)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/MI/IDR/ST</td>
<td>4.7% (257/5470)</td>
<td>5.9% (322/5469)</td>
<td>0.79 (0.67, 0.93)</td>
</tr>
</tbody>
</table>

### Sensitivity Analyses

#### Removal of IPST

<table>
<thead>
<tr>
<th>Death/MI/IDR/ARC-ST</th>
<th>Cangrelor (N=5470)</th>
<th>Clopidogrel (N=5469)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2% (230/5470)</td>
<td>5.2% (286/5469)</td>
<td>0.80 (0.67, 0.95)</td>
<td></td>
</tr>
</tbody>
</table>

#### Removal of IPST and MIs solely identified by CK-MB >3xULN but <10xULN

<table>
<thead>
<tr>
<th>Death/MI≥10xULN or Symptoms or ECG/IDR/ARC-ST</th>
<th>Cangrelor (N=5470)</th>
<th>Clopidogrel (N=5469)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9% (106/5470)</td>
<td>2.9% (161/5469)</td>
<td>0.65 (0.51, 0.83)</td>
<td></td>
</tr>
</tbody>
</table>

#### Removal of IPST and all MIs solely identified by biomarkers

<table>
<thead>
<tr>
<th>Death/MI with Symptom or ECG/IDR/ARC-ST</th>
<th>Cangrelor (N=5470)</th>
<th>Clopidogrel (N=5469)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6% (86/5470)</td>
<td>2.4% (130/5469)</td>
<td>0.66 (0.50, 0.86)</td>
<td></td>
</tr>
</tbody>
</table>
Early P2Y_{12} inhibition in ST-segment elevation myocardial infarction:

Bridging the gap.

Alexopolous D, Bhatt DL, Hamm CW, Steg PG, Stone GW. Am Heart J 2015;170:3-12
CHAMPION PHOENIX
Overall and STEMI outcomes, 48 h

Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mITT (N=10,942)</td>
<td>257/5470 (4.7%)</td>
<td>322/5469 (5.9%)</td>
<td>0.78 (0.66-0.93)</td>
</tr>
<tr>
<td>STEMI (n=1,991)</td>
<td>27/961 (2.8%)</td>
<td>38/1030 (3.7%)</td>
<td>0.75 (0.46-1.25)</td>
</tr>
</tbody>
</table>

Stent Thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mITT (N=10,942)</td>
<td>46/5470 (0.8%)</td>
<td>74/5469 (1.4%)</td>
<td>0.62 (0.43-0.90)</td>
</tr>
<tr>
<td>STEMI (n=1,991)</td>
<td>12/961 (1.2%)</td>
<td>20/1030 (1.9%)</td>
<td>0.64 (0.31-1.31)</td>
</tr>
</tbody>
</table>

GUSTO sev/mod bleeding

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall safety (N=11,056)</td>
<td>31/5529 (0.6%)</td>
<td>19/5527 (0.3%)</td>
<td>1.63 (0.92-2.90)</td>
</tr>
<tr>
<td>STEMI (n=2,070)</td>
<td>12/1000 (1.2%)</td>
<td>7/1070 (0.7%)</td>
<td>1.84 (0.72-4.70)</td>
</tr>
</tbody>
</table>

Oral Pretreatment in STEMI

Courtesy of Ghobrial J, Gibson CM, Pinto DS.
Oral Pretreatment in STEMI

Courtesy of Ghobrial J, Gibson CM, Pinto DS.
All NOACS: Stroke or SEE

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY [150 mg]</td>
<td>0.66 (0.53 - 0.82)</td>
<td>p=&lt;0.0001</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.88 (0.75 - 1.03)</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.80 (0.67 - 0.95)</td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 [60 mg]</td>
<td>0.88 (0.75 - 1.02)</td>
<td></td>
</tr>
<tr>
<td>Combined [Random Effects Model]</td>
<td>0.81 (0.73 - 0.91)</td>
<td>p=&lt;0.0001</td>
</tr>
</tbody>
</table>

N=58,541

Heterogeneity p=0.13

Secondary Efficacy Outcomes

Risk Ratio (95% CI)

- **Ischemic Stroke**: 0.92 (0.83 - 1.02), p=0.10
- **Hemorrhagic Stroke**: 0.49 (0.38 - 0.64), p<0.0001
- **MI**: 0.97 (0.78 - 1.20), p=0.77
- **All-Cause Mortality**: 0.90 (0.85 - 0.95), p=0.0003

*Heterogeneity p=NS for all outcomes*

All NOACS: Major Bleeding

- **RE-LY** [150 mg]  
  Risk Ratio (95% CI) 0.94 (0.82 - 1.07)

- **ROCKET AF**  
  Risk Ratio (95% CI) 1.03 (0.90 - 1.18)

- **ARISTOTLE**  
  Risk Ratio (95% CI) 0.71 (0.61 - 0.81)

- **ENGAGE AF-TIMI 48** [60 mg]  
  Risk Ratio (95% CI) 0.80 (0.71 - 0.90)

- **Combined** [Random Effects Model]  
  N=58,498  
  Risk Ratio (95% CI) 0.86 (0.73 - 1.00)

Heterogeneity p=0.001

Secondary Safety Outcomes

- **ICH**
  - Risk Ratio (95% CI): 0.48 (0.39 - 0.59)
  - p-value: <0.0001

- **GI Bleeding**
  - Risk Ratio (95% CI): 1.25 (1.01 - 1.55)
  - p-value: 0.043

Heterogeneity
- ICH, p=0.22
- GI Bleeding, p=0.009

When is a Double Better Than a Triple?

Bhatt DL. JACC 2015.
Rivaroxaban Use in Patients With AF Undergoing PCI: PIONEER AF-PCI

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

• Primary endpoint: TIMI major, minor, and bleeding requiring medical attention
• Secondary endpoint: CV death, MI, stroke, and stent thrombosis

Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative P2Y₁₂ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d).
Paroxysmal, persistent or permanent NVAF
(PCI with stenting [BMS or DES] elective or ACS)

Screening

Worldwide Event Driven Trial

Dabigatran 110mg BID + P2Y12 inhibitor

Dabigatran 150mg BID + P2Y12 inhibitor

Warfarin (INR 2.0-3.0) + P2Y12 inhibitor + ASA

1° End Point
Thrombotic Event Rate
(Death + MI + Stroke/SE)

Plus
Clinically Relevant Bleeding Rate
(ISTH Major)

3M 6M 9M 12M 15M 18/24/30M or EOT
Apixaban Versus Warfarin in Patients with AF and ACS or PCI: The AUGUSTUS Trial

**Inclusion**
- AF (prior, persistent, and/or >6 hours duration)
- CHADS ≥ 1
- Physician decision that oral anticoag is indicated
- ACS or PCI with planned P2Y12 inhibitor for 6 months

**Randomize**

\[ n = 4,600 \]

**Patients**

**Exclusion**
- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, moderate/severe MS)

**Apixaban**
- ASA
- placebo

**Warfarin**
- ASA
- placebo

P2Y12 inhibitor for all patients x 6 months
Aspirin for all on the day of ACS or PCI
Aspirin versus placebo after randomization

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

**Secondary objective:** Death, MI, stroke, stent thrombosis
COMPASS

Rivaroxaban on top of aspirin and versus aspirin in patients with coronary and/or peripheral artery disease

Rivaroxaban 2.5 mg bid + Aspirin 100 mg od

Rivaroxaban 5 mg bid

Aspirin 100 mg od

Screening Period

Run-in period

Primary outcome: MI, Stroke, CV death (n=2,200)
Mean follow up: 3-4 years
Conclusions

• Dual antiplatelet therapy indicated for at least 1 year after ACS

• Likely benefit > 1 year in patients w/ prior MI – CHARISMA subgroup

• PEGASUS showed a significant reduction in CV death/MI/stroke

• PEGASUS also showed an increase in non-fatal bleeding

• Duration for elective 2\textsuperscript{nd} generation DES likely shorter, for ACS longer

• Cangrelor may be an option in patients not pretreated

• Unclear what to do with afib + ACS +/- PCI

• Important to individualize therapy based on ischemic/bleeding risks
Thank You!

Deepak L. Bhatt, MD, MPH
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BWH Heart & Vascular Center
Professor of Medicine,
Harvard Medical School
1 (857) 307-1992
dlbhattmd@post.harvard.edu
Atherothrombosis: Clinical Manifestations

- Acute coronary syndromes
  - STEMI
  - NSTEMI
  - Unstable angina
- Stable CAD
- Atrial Fibrillation
- Angioplasty
- Bare metal stent
- Drug eluting stent
- CABG
- Abdominal aortic aneurysm (AAA)
- Stroke
- TIA
- Intracranial stenosis
- Carotid artery stenosis
- CEA
- Carotid stenting
- Renal artery stenosis
- Renal artery stenting
- Peripheral arterial disease
  - Acute limb ischemia
  - Claudication
  - Amputation
  - Endovascular stenting
  - Peripheral bypass
  - Abnormal ABI

Meadows TA, Bhatt DL. Circ Res. 2007;100:1261-1275.
OR and Attributable Risk for Baseline Factors Associated with Seath by 12 Months

Myocardial infarction definitions and late mortality

A

<table>
<thead>
<tr>
<th>Percentage attributable fraction</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 x ULN</td>
<td>2.0</td>
</tr>
<tr>
<td>&gt; 2 x ULN</td>
<td>2.8</td>
</tr>
<tr>
<td>&gt; 3 x ULN</td>
<td>3.5</td>
</tr>
<tr>
<td>&gt; 5 x ULN</td>
<td>5.3</td>
</tr>
<tr>
<td>&gt; 10 x ULN</td>
<td>7.6</td>
</tr>
</tbody>
</table>

B

Bleeding definitions and late mortality

<table>
<thead>
<tr>
<th>Percentage attributable fraction</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol major/minor bleed</td>
<td>1.6</td>
</tr>
<tr>
<td>Protocol major bleed</td>
<td>2.2</td>
</tr>
<tr>
<td>TIMI major/minor bleed</td>
<td>2.3</td>
</tr>
<tr>
<td>TIMI major bleed</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Odds ratio is represented by dotted lines; attributable risk by shaded area

Primary Endpoint (MI/Stroke/CV Death) in Patients With Previous MI, IS, or PAD*

“CAPRIE-like Cohort”

RRR: 17.1% (95% CI: 4.4%, 28.1%)  
\( P = 0.01 \)

* Post hoc analysis.

CHARISMA—CAD Without Prior MI

N=1,989

Primary Outcome Event Rate (%)

Months Since Randomization

HR=1.103 (95% CI (0.770–1.580])
P=0.593

# PEGASUS TIMI 54 – Other Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ticagrelor 90 mg bid (N=7050)</th>
<th>Ticagrelor 60 mg bid (N=7045)</th>
<th>Placebo (N=7067)</th>
<th>Ticagrelor 90 vs Placebo p-value</th>
<th>Ticagrelor 60 vs Placebo p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr KM rate (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Death, MI, or Stroke</td>
<td>7.0</td>
<td>7.1</td>
<td>8.3</td>
<td>HR 0.82 P=0.002</td>
<td>HR 0.83 P=0.003</td>
</tr>
<tr>
<td>Coronary Death or MI</td>
<td>5.6</td>
<td>5.8</td>
<td>6.7</td>
<td>HR 0.81 P=0.004</td>
<td>HR 0.84 P=0.01</td>
</tr>
<tr>
<td>Coronary Death</td>
<td>1.5</td>
<td>1.7</td>
<td>2.1</td>
<td>HR 0.73 P=0.02</td>
<td>HR 0.80 P=0.09</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>5.2</td>
<td>4.7</td>
<td>5.2</td>
<td>HR 1.00 P=0.99</td>
<td>HR 0.89 P=0.14</td>
</tr>
</tbody>
</table>

THEMIS
Design and main eligibility criteria

Type 2 diabetes; men and women ≥ 50 years
≥ 6 months glucose lowering drug treatment
At high risk for CV events*
No previous MI or stroke
No planned use of ADP receptor antagonist
or planned revascularisation

Ticagrelor

Placebo

Event driven study; 750 CV events required. 2 years mean follow-up. (n=19 000)

Primary endpoint: Composite of CV death, MI or stroke
Secondary endpoint: Composite of all-cause death, MI or stroke; CV death; All-cause death
Primary safety: TIMI Major bleeding

* At high risk of CV events defined as history of PCI or CABG or angiographic evidence of ≥ 50% lumen stenosis of at least 1 coronary artery

Low-dose ASA background therapy based on individual risk

http://www.clinicaltrials.gov/show/NCT01991795
Median Time of Late Stent Thrombosis

Desired Table: [DES/BMS] [SES/BMS] [PES/BMS]

- DES/BMS: [p = 0.0003]
- SES/BMS: [p = 0.0052]
- PES/BMS: [p = 0.04]
Major Bleeding Events and Safety

Event Rate (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Extended DAPT</th>
<th>Aspirin Alone</th>
<th>RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>1.9</td>
<td>1.1</td>
<td>1.73</td>
<td>0.004</td>
</tr>
<tr>
<td>ICH</td>
<td>0.4</td>
<td>0.3</td>
<td>1.05</td>
<td>NS</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>0.1</td>
<td>0.2</td>
<td>0.92</td>
<td>NS</td>
</tr>
<tr>
<td>Non-CV Death</td>
<td>1.7</td>
<td>1.6</td>
<td>0.92</td>
<td>NS</td>
</tr>
<tr>
<td>All-Cause Death</td>
<td>4.0</td>
<td>4.2</td>
<td>0.92</td>
<td>NS</td>
</tr>
</tbody>
</table>

Short- and Long-Term Outcomes With Drug-Eluting and Bare-Metal Coronary Stents

A Mixed-Treatment Comparison Analysis of 117,762 Patient-Years of Follow-Up From Randomized Trials

Sripal Bangalore, MD, MHA; Sunil Kumar, MD; Mario Fusaro, MD; Nicholas Amoroso, MD; Michael J. Attubato, MD; Frederick Feit, MD; Deepak L. Bhatt, MD, MPH; James Slater, MD

**Background**—Drug-eluting stents (DES) have been in clinical use for nearly a decade; however, the relative short- and long-term efficacy and safety of DES compared with bare-metal stents (BMS) and among the DES types are less well defined.

**Methods and Results**—PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized clinical trials, until March 2012, that compared any of the Food and Drug Administration–approved durable stent and polymer DES (sirolimus-eluting stent [SES], paclitaxel-eluting stent [PES], everolimus-eluting stent [EES], zotarolimus-eluting stent [ZES], and ZES-Resolute [ZES-R]) with each other or against BMS for de novo coronary lesions, enrolling at least 100 patients and with follow-up of at least 6 months. Short-term (<1 year) and long-term efficacy (target-vessel revascularization, target-lesion revascularization) and safety (death, myocardial infarction, stent thrombosis) outcomes were evaluated and trial-level data pooled by both mixed-treatment comparison and direct comparison analyses. From 76 randomized clinical trials with 117,762 patient-years of follow-up, compared with BMS, each DES reduced long-term target-vessel revascularization (39% to 61%), but the magnitude varied by DES type (EES > SES > ZES-R > PES > ZES > BMS), with a >42% probability that EES had the lowest target-vessel revascularization rate. There was no increase in the risk of any long-term safety outcomes, including stent thrombosis, with any DES (versus BMS). In addition, there was reduction in myocardial infarction (all DES except PES versus BMS) and stent thrombosis (with EES versus BMS: Rate ratio, 0.51; 95% credibility interval, 0.35–0.73). The safest DES appeared to be EES (>86% probability), with reduction in myocardial infarction and stent thrombosis compared with BMS. Short-term outcomes were similar to long-term outcomes, with SES, ZES-R, and everolimus-eluting stent being the most efficacious and EES being the safest stent.

**Conclusions**—DES are highly efficacious at reducing the risk of target-vessel revascularization without an increase in any safety outcomes, including stent thrombosis. However, among the DES types, there were considerable differences, such that EES, SES, and ZES-R were the most efficacious and EES was the safest stent. (*Circulation.* 2012;125:2873-2891.)

**Key Words:** drug-eluting stents • paclitaxel • pannus formation • sirolimus • everolimus • zotarolimus • stents

Drug-eluting stents (DES) are widely used for percutaneous coronary intervention in patients with coronary artery disease. These stents have the advantage of reducing the incidence of in-stent restenosis compared with bare-metal stents (BMS). However, DES are more expensive than BMS, and first-generation DES have been associated with an increased risk of late stent thrombosis when antiplatelet agents are withheld, and in some studies, very late stent thrombosis. Since the introduction of sirolimus-eluting stents (SES), followed by paclitaxel-eluting stents (PES), there has been considerable debate on the long-term efficacy and safety of these stents. Newer DES have been developed that have claimed to be safer and more efficacious; however, for safety outcomes, BMS is still considered the benchmark.

**Clinical Perspective on p 2891**

The relative efficacy and safety of the currently Food and Drug Administration (FDA)–approved DES (SES, PES,
Any Stent Thrombosis: Probability Best

% Probability of Lowest Any ST Rate

- ZES, 0.98
- ZES-R, 12.59
- BMS, 0.01
- PES, 0
- SES, 0.12
- EES, 86.32

DAPT: Design

DES n = 23,210
BMS n = 2,985
Completed Enrollment 2011

12 mos.

All patients on aspirin + open-label thienopyridine therapy for 12 months
1:1 Randomization at month 12

50% of patients receive aspirin + placebo

50% of patients continue on Dual Antiplatelet Therapy

18 mos.

Total 33 month patient evaluation including additional 3-month follow-up


Co-Primary Effectiveness End Point
Stent Thrombosis and MACCE

CVD/MI/Stroke
12-30 Months:
HR 0.71 (0.59-0.85)
4.3% vs. 5.9% P<0.001

ST 12-30 Months:
HR 0.29 (0.17-0.48)
0.4% vs. 1.4% P<0.001

Mauri L, et al. NEJM 2014
Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months

Mauri L, et al. NEJM 2014

Cumulative Incidence (%)
Co-Primary Effectiveness End Points & Components: 12-30 Months

Mauri L, et al. NEJM 2014

ST (Definite/Probable) | Definite ST | Probable ST | MACCE | Death | MI | Ischemic stroke | Hemorrhagic stroke
--- | --- | --- | --- | --- | --- | --- | ---
Thienopyridine (N=5020) | 0.4% | 1.4% | 0.1% | 5.9% | 2.0% | 0.5% | 0.3%
Placebo (N=4941) | 0.3% | 1.2% | 0.1% | <0.001 | 1.5% | 0.7% | 0.2%

Cumulative Incidence (%)

<0.001 0.052 <0.001 0.16 0.68

Mauri L, et al. NEJM 2014
Treatment Effect According to ACS Status at 12-30 Months: Primary Endpoints All Randomized Subjects (N=11648)

Yeh R, et al. JACC 2015
Treatment Effect According to ACS Status at 12-30 Months – Secondary Endpoints All Randomized Subjects (N=11648)

Death

- Continued Thienopyridine
- Placebo

| ACS          | Continued Thienopyridine | Placebo | Interaction
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>1.4%</td>
<td>1.6%</td>
<td>P=0.61</td>
</tr>
<tr>
<td>No ACS</td>
<td>2.1%</td>
<td>1.1%</td>
<td>P=0.04</td>
</tr>
</tbody>
</table>

Interaction P=0.13

Yeh R, et al. JACC 2015
Trials of DAPT Duration

Ongoing trials in green

Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

<table>
<thead>
<tr>
<th>Study</th>
<th>MI</th>
<th>HR (95% CI)</th>
<th>Weight (%)</th>
<th>Events Group 1</th>
<th>Events Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTIC Interruption</td>
<td>1.04</td>
<td>0.41, 2.62</td>
<td>3.01</td>
<td>9/624</td>
<td>9/635</td>
</tr>
<tr>
<td>DAPT</td>
<td>1.94</td>
<td>1.55, 2.44</td>
<td>50.33</td>
<td>198/4941</td>
<td>99/5020</td>
</tr>
<tr>
<td>DES LATE</td>
<td>1.43</td>
<td>0.80, 2.58</td>
<td>7.56</td>
<td>27/2514</td>
<td>19/2531</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>1.86</td>
<td>0.74, 4.67</td>
<td>3.05</td>
<td>13/722</td>
<td>7/721</td>
</tr>
<tr>
<td>ISAR SAFE</td>
<td>0.93</td>
<td>0.44, 1.97</td>
<td>4.61</td>
<td>13/1997</td>
<td>14/2003</td>
</tr>
<tr>
<td>ITALIC</td>
<td>1.50</td>
<td>0.42, 5.32</td>
<td>1.61</td>
<td>6/912</td>
<td>4/910</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>1.17</td>
<td>0.77, 1.76</td>
<td>15.16</td>
<td>49/1563</td>
<td>42/1556</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>1.04</td>
<td>0.60, 1.79</td>
<td>8.67</td>
<td>26/751</td>
<td>25/750</td>
</tr>
<tr>
<td>RESET</td>
<td>0.50</td>
<td>0.91, 2.72</td>
<td>0.75</td>
<td>2/1059</td>
<td>1/1058</td>
</tr>
<tr>
<td>SECURITY</td>
<td>1.06</td>
<td>0.53, 2.16</td>
<td>5.25</td>
<td>16/682</td>
<td>15/717</td>
</tr>
<tr>
<td>I-V (I²=29.3%, p=0.17); p value for ES&lt;0.0001</td>
<td>1.51 (1.28, 1.77)</td>
<td>100.00</td>
<td>359/ 238/15901</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D+L: p value for ES=0.01</td>
<td>1.34 (1.07, 1.69)</td>
<td></td>
<td>15765</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

25% ↓ MI with prolonged DAPT (p=0.01)

ES=effect size

Palmerini T, ….Stone GW. Lancet 2015:on-line
Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

41% ↓ stent thrombosis with prolonged DAPT (p=0.06)

Definite/Probable ST

<table>
<thead>
<tr>
<th>Study</th>
<th>Definite/Probable ST</th>
<th>HR (95% CI)</th>
<th>Weight (%)</th>
<th>Events Group 1</th>
<th>Events Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPT</td>
<td></td>
<td>2.98 (1.95, 4.58)</td>
<td>55.53</td>
<td>65/4941</td>
<td>19/5020</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td></td>
<td>6.02 (0.72, 49.96)</td>
<td>2.25</td>
<td>6/722</td>
<td>1/721</td>
</tr>
<tr>
<td>ISAR SAFE</td>
<td></td>
<td>1.25 (0.33, 4.65)</td>
<td>5.79</td>
<td>5/1997</td>
<td>4/2003</td>
</tr>
<tr>
<td>ITALIC</td>
<td></td>
<td>7.38 (0.76, 71.00)</td>
<td>1.97</td>
<td>3/912</td>
<td>0/910</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td></td>
<td>1.08 (0.49, 2.36)</td>
<td>16.38</td>
<td>13/1563</td>
<td>12/1556</td>
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<tr>
<td>PRODIGY</td>
<td></td>
<td>1.24 (0.49, 3.14)</td>
<td>11.73</td>
<td>10/751</td>
<td>8/750</td>
</tr>
<tr>
<td>RESET</td>
<td></td>
<td>0.66 (0.11, 3.98)</td>
<td>3.14</td>
<td>2/1059</td>
<td>3/1058</td>
</tr>
<tr>
<td>SECURITY</td>
<td></td>
<td>0.67 (0.11, 3.86)</td>
<td>3.20</td>
<td>2/682</td>
<td>3/717</td>
</tr>
<tr>
<td>I-V (I²=43.7%, p=0.09); p value for ES&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td>2.04 (1.48, 2.80)</td>
<td>106/</td>
</tr>
<tr>
<td>D+L: p value for ES=0.06</td>
<td></td>
<td></td>
<td></td>
<td>1.68 (0.98, 2.87)</td>
<td>13251</td>
</tr>
</tbody>
</table>

ES=effect size

Study

55.53
5.79
1.97
16.38
11.73
3.14
3.20
2/682
2.04 (1.48, 2.80)
1.68 (0.98, 2.87)

53/
106/
13251
13370

Shorter DAPT better
Longer DAPT better

Palmerini T, ....Stone GW. Lancet 2015:on-line
Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

Cardiac Death

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>Weight (%)</th>
<th>Events Group 1</th>
<th>Events Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPT</td>
<td>1.04 (0.70, 1.53)</td>
<td>35.40</td>
<td>52/4941</td>
<td>50/5020</td>
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<tr>
<td>DES LATE</td>
<td>0.68 (0.38, 1.23)</td>
<td>15.69</td>
<td>19/2514</td>
<td>28/2531</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>0.67 (0.11, 3.99)</td>
<td>1.68</td>
<td>2/722</td>
<td>3/721</td>
</tr>
<tr>
<td>ITALIC</td>
<td>1.67 (0.40, 6.97)</td>
<td>2.65</td>
<td>5/912</td>
<td>3/910</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>0.90 (0.55, 1.49)</td>
<td>21.79</td>
<td>29/1563</td>
<td>32/1556</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>0.92 (0.53, 1.58)</td>
<td>18.14</td>
<td>25/751</td>
<td>27/750</td>
</tr>
<tr>
<td>RESET</td>
<td>0.50 (0.91, 2.73)</td>
<td>1.86</td>
<td>2/1059</td>
<td>4/1058</td>
</tr>
<tr>
<td>SECURITY</td>
<td>1.64 (0.41, 6.59)</td>
<td>2.81</td>
<td>5/682</td>
<td>3/717</td>
</tr>
<tr>
<td>I-V (I²=0.0%, p=0.85); p value for ES=0.52</td>
<td>0.93 (0.73, 1.17)</td>
<td>100.00</td>
<td>139/</td>
<td>150/13263</td>
</tr>
<tr>
<td>D+L: p value for ES=0.52</td>
<td>0.93 (0.73, 1.17)</td>
<td>100.00</td>
<td>13144</td>
<td></td>
</tr>
</tbody>
</table>

8% ↑ cardiac mortality with prolonged DAPT (p=NS)

ES=effect size

Palmerini T, ....Stone GW. Lancet 2015:on-line
Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

Major Bleeding

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>Weight (%)</th>
<th>Events Group 1</th>
<th>Events Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTIC Interruption</td>
<td>0.15 (0.02, 1.20)</td>
<td>11.00</td>
<td>1/624</td>
<td>7/635</td>
</tr>
<tr>
<td>DAPT</td>
<td>0.57 (0.43, 0.75)</td>
<td>59.86</td>
<td>72/4941</td>
<td>129/5020</td>
</tr>
<tr>
<td>DES LATE</td>
<td>0.71 (0.42, 1.20)</td>
<td>16.81</td>
<td>24/2514</td>
<td>34/2531</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>0.50 (0.09, 2.73)</td>
<td>1.59</td>
<td>2/722</td>
<td>4/721</td>
</tr>
<tr>
<td>ISAR SAFE</td>
<td>0.80 (0.21, 2.98)</td>
<td>2.63</td>
<td>4/1997</td>
<td>5/2003</td>
</tr>
<tr>
<td>ITALIC</td>
<td>0.13 (0.01, 1.30)</td>
<td>0.78</td>
<td>0/912</td>
<td>3/910</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>0.71 (0.32, 1.60)</td>
<td>7.16</td>
<td>10/1563</td>
<td>12/1556</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>0.38 (0.14, 1.07)</td>
<td>4.48</td>
<td>5/751</td>
<td>6/750</td>
</tr>
<tr>
<td>RESET</td>
<td>0.75 (0.17, 3.35)</td>
<td>2.08</td>
<td>2/1059</td>
<td>6/1058</td>
</tr>
<tr>
<td>SECURITY</td>
<td>0.51 (0.16, 1.59)</td>
<td>3.51</td>
<td>4/682</td>
<td>8/717</td>
</tr>
<tr>
<td>I-V ($I^2=0.0.00, p=0.83$; p value for ES&lt;0.0001)</td>
<td>0.58 (0.47, 0.72)</td>
<td>100.00</td>
<td>124/221/15901</td>
<td></td>
</tr>
<tr>
<td>D+L: p value for ES&lt;0.0001</td>
<td>0.58 (0.47, 0.72)</td>
<td>15765</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

72% ↑ bleeding with prolonged DAPT ($p<0.0001$)

ES=effect size

Shorter DAPT better
Longer DAPT better

Palmerini T, ....Stone GW. Lancet 2015: on-line
Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-cardiac Death HR (95% CI)</th>
<th>Weight (%)</th>
<th>Events Group 1</th>
<th>Events Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPT</td>
<td>0.47 (0.29, 0.76)</td>
<td>34.27</td>
<td>22/4941</td>
<td>48/5020</td>
</tr>
<tr>
<td>DES LATE</td>
<td>0.68 (0.34, 1.37)</td>
<td>16.38</td>
<td>13/2514</td>
<td>19/2531</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>0.50 (0.09, 2.74)</td>
<td>2.73</td>
<td>2/722</td>
<td>4/721</td>
</tr>
<tr>
<td>ITALIC</td>
<td>0.75 (0.17, 3.30)</td>
<td>3.62</td>
<td>3/912</td>
<td>4/910</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>1.07 (0.50, 2.28)</td>
<td>13.82</td>
<td>14/1563</td>
<td>13/1556</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>0.90 (0.49, 1.65)</td>
<td>21.58</td>
<td>20/751</td>
<td>22/750</td>
</tr>
<tr>
<td>RESET</td>
<td>0.73 (0.16, 3.26)</td>
<td>3.50</td>
<td>3/1059</td>
<td>4/1058</td>
</tr>
<tr>
<td>SECURITY</td>
<td>0.60 (0.15, 2.42)</td>
<td>4.11</td>
<td>3/682</td>
<td>5/717</td>
</tr>
</tbody>
</table>

I² (I²=0.0%, p=0.71); p value for ES=0.006

D+L: p value for ES=0.006

ES=effect size

49% ↑ Non-cardiac mortality with prolonged DAPT (p=0.006)

Palmerini T, ....Stone GW. Lancet 2015:on-line
Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

22% ↑ mortality with prolonged DAPT (p=0.02)

All-cause Death

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>Weight (%)</th>
<th>Events Group 1</th>
<th>Events Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTIC Interruption</td>
<td>1.32 (0.49, 3.55)</td>
<td>3.03</td>
<td>9/624</td>
<td>7/635</td>
</tr>
<tr>
<td>DAPT</td>
<td>0.75 (0.56, 1.02)</td>
<td>33.00</td>
<td>74/4941</td>
<td>98/5020</td>
</tr>
<tr>
<td>DES LATE</td>
<td>0.71 (0.45, 1.10)</td>
<td>14.85</td>
<td>32/2514</td>
<td>46/251</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>0.57 (0.17, 1.95)</td>
<td>1.99</td>
<td>4/722</td>
<td>7/721</td>
</tr>
<tr>
<td>ISAR SAFE</td>
<td>0.66 (0.27, 1.63)</td>
<td>3.67</td>
<td>8/1997</td>
<td>12/2003</td>
</tr>
<tr>
<td>ITALIC</td>
<td>1.14 (0.41, 3.15)</td>
<td>2.85</td>
<td>8/912</td>
<td>7/910</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>0.95 (0.63, 1.45)</td>
<td>17.07</td>
<td>43/1563</td>
<td>45/1556</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>0.91 (0.61, 1.37)</td>
<td>18.12</td>
<td>45/751</td>
<td>49/750</td>
</tr>
<tr>
<td>RESET</td>
<td>0.62 (0.20, 1.88)</td>
<td>2.36</td>
<td>5/1059</td>
<td>8/1058</td>
</tr>
<tr>
<td>SECURITY</td>
<td>1.00 (0.37, 2.66)</td>
<td>3.05</td>
<td>8/682</td>
<td>8/717</td>
</tr>
<tr>
<td>I-V (I²=0.0%, p=0.93); p value for ES=0.02</td>
<td>0.82 (0.69, 0.98)</td>
<td>100.00</td>
<td>236/287</td>
<td>1590/1590</td>
</tr>
<tr>
<td>D+L: p value for ES=0.02</td>
<td>0.82 (0.69, 0.98)</td>
<td>100.00</td>
<td>15765</td>
<td></td>
</tr>
</tbody>
</table>

ES=effect size

Palmerini T, ....Stone GW. Lancet 2015: on-line
2012 ACCF/AHA Focused Update
Unstable Angina/NonSTEMI Guidelines

Class IIb Recommendations

1. Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on P2Y12 receptor inhibitor therapy may be considered if results of testing may alter management.  *(Level of Evidence: B)*

2. Genotyping for a *CYP2C19* loss of function variant in patients with UA/NSTEMI (or, after ACS and with PCI) on P2Y12 receptor inhibitor therapy might be considered if results of testing may alter management.  *(Level of Evidence: C)*

Nonadherence >> Resistance

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=8,667 mITT
SA / NSTE-ACS / STEMI
Placebo or clopidogrel before PCI

CHAMPION PLATFORM
n=5,301 mITT
SA / NSTE-ACS
P2Y₁₂ naïve
Placebo or clopidogrel after PCI

Cangrelor bolus then infusion

OR

Clopidogrel 600 mg or 300 mg oral

Clopidogrel 600 mg oral

OR

Clopidogrel 600 mg oral

Clopidogrel 600 mg oral

OR

Clopidogrel 600 mg oral

PCI ~30’

Harrington RA, et al. NEJM 2009
Bhatt DL, et al. NEJM 2009
Bhatt DL, et al. NEJM 2013
## Summary of Clinical Efficacy: Pooled Analysis

<table>
<thead>
<tr>
<th></th>
<th>Death / MI / IDR / ST</th>
<th>Death / MI / IDR</th>
<th>Death / QMI / IDR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
<td>p for interaction</td>
</tr>
<tr>
<td>Platform</td>
<td>0.72 (0.53, 0.97)</td>
<td>0.0330</td>
<td>0.4681</td>
</tr>
<tr>
<td>PCI</td>
<td>0.90 (0.72, 1.14)</td>
<td>0.3859</td>
<td></td>
</tr>
<tr>
<td>PHOENIX</td>
<td>0.79 (0.67, 0.93)</td>
<td>0.0055</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>0.81 (0.71, 0.91)</td>
<td>0.0007</td>
<td>0.4537</td>
</tr>
<tr>
<td>ST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platform</td>
<td>0.31 (0.11, 0.85)</td>
<td>0.0157</td>
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</tr>
<tr>
<td>PCI</td>
<td>0.73 (0.33, 1.59)</td>
<td>0.4242</td>
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<tr>
<td>PHOENIX</td>
<td>0.62 (0.43, 0.90)</td>
<td>0.0101</td>
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</tr>
<tr>
<td>Pooled</td>
<td>0.59 (0.43, 0.80)</td>
<td>0.0008</td>
<td>0.3716</td>
</tr>
<tr>
<td>Death / MI / IDR</td>
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<tr>
<td>Platform</td>
<td>0.72 (0.53, 0.97)</td>
<td>0.0330</td>
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</tr>
<tr>
<td>PCI</td>
<td>0.90 (0.72, 1.14)</td>
<td>0.3859</td>
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</tr>
<tr>
<td>PHOENIX</td>
<td>0.80 (0.67, 0.95)</td>
<td>0.0115</td>
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<tr>
<td>Pooled</td>
<td>0.81 (0.71, 0.92)</td>
<td>0.0014</td>
<td>0.4681</td>
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<tr>
<td>Death / QMI / IDR</td>
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<td></td>
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</tr>
<tr>
<td>Platform</td>
<td>0.55 (0.33, 0.93)</td>
<td>0.0224</td>
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<td>PCI</td>
<td>0.66 (0.42, 1.05)</td>
<td>0.0779</td>
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</tr>
<tr>
<td>PHOENIX</td>
<td>0.76 (0.53, 1.11)</td>
<td>0.1558</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>0.68 (0.52, 0.87)</td>
<td>0.0022</td>
<td>0.6093</td>
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</tbody>
</table>

Cangrelor: a new CHAMPION for percutaneous coronary intervention
Pooled CHAMPION Trials
Overall and STEMI outcomes, 48 h

**Primary Endpoint**

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mITT* (N=24,910)</td>
<td>473/12,459 (3.8%)</td>
<td>579/12,422 (4.7%)</td>
<td>0.81 (0.71-0.91)</td>
</tr>
<tr>
<td>STEMI† (n=2884)</td>
<td>41/1407 (2.9%)</td>
<td>51/1477 (3.5%)</td>
<td>0.84 (0.55-1.27)</td>
</tr>
</tbody>
</table>

**Stent Thrombosis**

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mITT* (N=24,881)</td>
<td>62/12,459 (0.5%)</td>
<td>105/12,422 (0.8%)</td>
<td>0.59 (0.43-0.80)</td>
</tr>
<tr>
<td>STEMI (n=2,884)</td>
<td>16/1407 (1.1%)</td>
<td>24/1477 (1.6%)</td>
<td>0.70 (0.37-1.32)</td>
</tr>
</tbody>
</table>

**GUSTO sev/mod bleeding**

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor</th>
<th>Clopidogrel</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall safety* (N=25,107)</td>
<td>103 (0.8%)</td>
<td>79 (0.6%)</td>
<td>1.30 (0.97-1.75)</td>
</tr>
<tr>
<td>STEMI (n=3008)</td>
<td>17/1463 (1.2%)</td>
<td>15/1545 (1.0%)</td>
<td>1.20 (0.60-2.41)</td>
</tr>
</tbody>
</table>

* Overall population includes CHAMPION PHOENIX, PCI, and PLATFORM; †STEMI population from PHOENIX and PCI
Conclusions

- Dual antiplatelet therapy indicated for at least 1 year after ACS

- Likely benefit > 1 year in patients w/ prior MI – CHARISMA subgroup

- PEGASUS showed a significant reduction in CV death/MI/stroke

- PEGASUS also showed an increase in non-fatal bleeding

- DAPT data more nuanced, risks may outweigh benefits outside of ACS

- Duration for elective 2nd generation DES likely shorter, for ACS longer

- A year after ACS, in selected patients, 2 drugs are better than 1

- Important to individualize therapy based on ischemic/bleeding risks
Prior MI, CVA, or PAD

Randomize 1:1 Double Blind

Vorapaxar 2.5 mg/d

Stratified by:
1) Qualifying athero
2) Use of thienopyridine

Placebo

Follow up Visits:
Day 30, Mo 4, Mo 8, Mo 12 Q6 months

Final Visit

Key Inclusion:
1) Type 1 MI: 2 wks - 12 mo
2) Ischemic CVA: 2 wk - 12 mo
3) PAD: claudication + abnl ABI or prior revasc

DSMB observed ↑ risk of ICH in Pts w/ stroke → Rec stopping study drug in Pts w/ any h/o stroke
Primary Efficacy Evaluation

CV Death, MI, or Stroke

Hazard Ratio 0.87; 95% CI 0.80 to 0.94
p < 0.001

N = 26449
Median f/u 2.5 years

Morrow DA et al. *NEJM* 2012;366:1404-13

<table>
<thead>
<tr>
<th>Event</th>
<th>Vora</th>
<th>Plac</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td>2.7</td>
<td>3.0</td>
<td>0.89</td>
<td>0.15</td>
</tr>
<tr>
<td>MI</td>
<td>5.2</td>
<td>6.1</td>
<td>0.83</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.8</td>
<td>2.8</td>
<td>0.97</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Major Bleeding Endpoints

3-yr KM rate (%)

Prior Stroke
n = 5746

No Hx of Stroke
n = 20699

TIMI Non-CABG Major

AR D 2.0%
HR 1.87
P <0.001

AR D 1.5%
HR 2.55
P <0.001

ICH

AR D 0.2%
HR 1.48
P =0.46

AR D 0.7%
HR 1.35
P =0.005

Fatal

TIMI Non-CABG Major

AR D 0.4%
HR 1.55
P =0.049

AR D 0.1%
HR 1.44
P =0.30

ICH

Morrow DA et al. NEJM 2012;366:1404-13
Primary Efficacy Evaluation

Low Bleeding Risk Cohort* (N= 14,909)

**CV Death, MI, or Stroke**

- **Placebo**: 8.6%
- **Vorapaxar**: 6.8%

**CV Death**

- **Placebo**: 2.0%
- **Vorapaxar**: 1.5%

**HR 0.75**  
*p < 0.0001*

**HR 0.73**  
*p = 0.02*

*Age <75 y, no h/o stroke/TIA, wt ≥60 kg*

Efficacy Early and Late
Prior MI Cohort

Days 0 to 360

CV Death / MI / Stroke (%)

Placebo

Vorapaxar

HR 0.79  
$p = 0.003$

Day 360 to 1080

CV Death / MI / Stroke (%)

Placebo

Vorapaxar

HR 0.82  
$p = 0.004$

Stent Thrombosis By Randomized Treatment

ARC Definite Stent Thrombosis

Placebo: 1.4%
Vorapaxar: 1.1%

HR 0.71 (0.52 – 0.98)
P=0.04

Bonaca et al.  JACC 2014
Vorapaxar and Limb Vascular Efficacy

Hospitalization for Acute Limb Ischemia

Pre-specified, adjudicated

N = 3767

Placebo: 3.9%
Vorapaxar: 2.3%

Hazard Ratio 0.58
95% CI 0.39 to 0.86
p = 0.006

Days from randomization

Peripheral Revascularization

Prespecified, Investigator

Placebo: 22.2%
Vorapaxar: 18.4%

Hazard Ratio 0.84
95% CI 0.73 to 0.97
p = 0.017

Incidence of New Ischemic Stroke

**Patients without history of Stroke/TIA**  
N = 20,170

- Ischemic stroke HR 0.57, p<0.001  
- Hemorrhagic stroke HR 2.78, p=0.049  
- *Overall stroke HR 0.68, p=0.005*

Bonaca MP et al.  *JACC* 2014
Patients with Prior MI and No Hx of Stroke or TIA

Risk Differences for 1000 Patients per 3 years - Vora vs. PBO

First Serious (Irreversible) Events

-25 CV Death
-14 MI
-6 Stroke
-5 CV Death
0 Fatal Bleeding
+1 Non-Fatal ICH

Braunwald E. Source: US FDA website - 20140115 CRDAC-S1-03
## Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

<table>
<thead>
<tr>
<th>Event</th>
<th>≤6-month vs 1-year DAPT HR (95% CrI)</th>
<th>6-month vs &gt;1-year DAPT HR (95% CrI)</th>
<th>1-year vs &gt;1-year DAPT HR (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause death</strong></td>
<td>0.95 (0.76-1.20)</td>
<td>0.78 (0.59-1.00)</td>
<td>0.82 (0.65-1.00)</td>
</tr>
<tr>
<td>- Cardiac</td>
<td>0.96 (0.68-1.40)</td>
<td>0.90 (0.62-1.30)</td>
<td>0.93 (0.69-1.20)</td>
</tr>
<tr>
<td>- Non-cardiac</td>
<td>1.00 (0.69-1.60)</td>
<td>0.65 (0.41-1.00)</td>
<td>0.61 (0.42-0.87)</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>1.00 (0.75-1.30)</td>
<td>1.70 (1.30-2.40)</td>
<td>1.70 (1.40-2.10)</td>
</tr>
<tr>
<td><strong>Def/prob stent thrombosis</strong></td>
<td>1.10 (0.66-1.70)</td>
<td>2.70 (1.50-5.00)</td>
<td>2.50 (1.70-4.00)</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td>0.59 (0.36-0.95)</td>
<td>0.34 (0.20-0.55)</td>
<td>0.58 (0.45-0.74)</td>
</tr>
</tbody>
</table>
Oral Pretreatment in STEMI

Oral Pretreatment in STEMI