STEMI and NSTEMI-ACS:
The Evolving Antithrombotic Agents and Combinations
The Challenge of a High Benefit / Bleeding Ratio

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Disclosures for Dr. Bhatt

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This presentation discusses off-label and/or investigational uses of various drugs and devices.
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.
OR and attributable risk for baseline factors associated with death by 12 months

**Myocardial infarction definitions and late mortality**

- Percentage attributable fraction
- Odds Ratio

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

DAPT: Design

12 mos. 18 mos.

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

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

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


www.daptstudy.org   www.clinicaltrials.gov – NCT00977938
Co-Primary Effectiveness End Point
Stent Thrombosis and MACCE

Mauri L, et al. NEJM 2014

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

Cumulative Incidence of Stent Thrombosis and MACCE

Thienopyridine vs Placebo

# At Risk

<table>
<thead>
<tr>
<th>Treatment Ends</th>
<th>Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
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<tr>
<td>Thienopyridine</td>
<td>4934</td>
</tr>
<tr>
<td>Placebo</td>
<td>4941</td>
</tr>
</tbody>
</table>

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

- Moderate or Severe: 0.001
- Moderate: 0.004
- Severe: 0.15
- BARC Type 2: <0.001
- BARC Type 3: <0.001
- BARC Type 5: 0.38

Thienopyridine (N=4710) vs Placebo (N=4649)
Trials of DAPT Duration

Ongoing trials in green

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)

Non-inferiority $P$-value = 0.002

PEGASUS – TIMI 54

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

N ~ 21,000

RANDOMIZE DOUBLE BLIND

Ticagrelor 90 mg bid

Ticagrelor 60 mg bid

Placebo

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

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

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
**THEMIS**

**Design and main eligibility criteria**

- **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

- **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=17 000)**

- **Low-dose ASA background therapy based on individual risk**

  * 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

http://www.clinicaltrials.gov/show/NCT01991795
Primary Outcome
CV Death, MI, Ischemic Stroke

Apixaban 279 (7.5%)
Placebo 293 (7.9%)
HR 0.95; 95% CI 0.80-1.11; p=0.509

Alexander et al. NEJM 2011.
TIMI Major Bleeding

Apixaban  48 (1.3%)
Placebo   18 (0.5%)
HR 2.59; 95% CI 1.50–4.46; p=0.001

Alexander et al. NEJM 2011.
Study Chairs: Drs. Harrington and Wallentin
## TIMI Major Bleeding
### Subgroups

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>n/N</th>
<th>Interaction P Value</th>
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<tbody>
<tr>
<td><strong>Antiplatelet therapy</strong></td>
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<tr>
<td>Dual</td>
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<tr>
<td>Single*</td>
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<td>STEMI</td>
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<td>UA*</td>
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<td>PCI</td>
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<td>CABG*</td>
<td>2/40</td>
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<td><strong>Apixaban dose (or matching placebo)</strong></td>
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<td>5 mg BID</td>
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<td>2.5 mg BID*</td>
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<td>&gt;75</td>
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<td><strong>Number of risk factors</strong></td>
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<td>&gt;2</td>
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<td>Yes</td>
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<td>0.24</td>
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</table>

*HR not calculated for subgroups with ≤10 events

Alexander et al. NEJM 2011.

Study Chairs: Drs. Harrington and Wallentin
Primary Efficacy Endpoint:
CV Death / MI / Stroke

Rivaroxaban (both doses)

Placebo

No. at Risk
Placebo    5113   4307   3470   2664   1831   1079   421
Rivaroxaban 10292  8502   6753   5137   3554   2084   831

Estimated Cumulative Incidence (%)  
Mega et al. NEJM 2011.
Stent Thrombosis
ARC Definite, Probable, Possible

Rivaroxaban (both doses)

HR 0.69 (0.51 - 0.93)
mITT p = 0.016
ITT p = 0.008

2 Yr KM Estimate
Placebo 2.9%
Rivaroxaban 2.3%

Estimated Cumulative incidence (%)

Gibson CM et al. JACC 2013
Efficacy Endpoints: Very Low Dose 2.5 mg BID
Patients Treated with ASA + Thienopyridine

- CV Death / MI / Stroke
  - Placebo: HR 0.85 (mITT p=0.04, ITT p=0.01)
  - Rivaroxaban: NNT = 71

- Cardiovascular Death
  - Placebo: HR 0.62 (mITT p<0.001, ITT p<0.001)
  - Rivaroxaban: NNT = 59

- All Cause Death
  - Placebo: HR 0.64 (mITT p<0.001, ITT p<0.001)
  - Rivaroxaban: NNT = 56

Mega et al. NEJM 2011.
TREATMENT-EMERGENT FATAL BLEEDS AND ICH

- Placebo
- 2.5 mg Rivaroxaban
- 5.0 mg Rivaroxaban

p=NS for Riva vs Placebo
p=NS for Riva 5 vs Placebo
p=NS for Riva 2.5 vs Placebo
p=0.044 for Riva 2.5 vs 5
p=0.009 for Riva vs Placebo
p= 0.005 Riva 5 vs Placebo
P=0.037 for Riva 2.5 vs Placebo
p=0.44 for Riva 2.5 vs 5

Mega et al. NEJM 2011.
All NOACS: Stroke or SEE

- RE-LY [150 mg]
  - Risk Ratio (95% CI): 0.66 (0.53 - 0.82)

- ROCKET AF
  - Risk Ratio (95% CI): 0.88 (0.75 - 1.03)

- ARISTOTLE
  - Risk Ratio (95% CI): 0.80 (0.67 - 0.95)

- ENGAGE AF-TIMI 48 [60 mg]
  - Risk Ratio (95% CI): 0.88 (0.75 - 1.02)

Combined [Random Effects Model]
- N=58,541
  - Risk Ratio (95% CI): 0.81 (0.73 - 0.91)
  - p=<0.0001

Heterogeneity p=0.13

Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke</td>
<td>0.92 (0.83 - 1.02)</td>
<td>p=0.10</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.49 (0.38 - 0.64)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>MI</td>
<td>0.97 (0.78 - 1.20)</td>
<td>p=0.77</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>0.90 (0.85 - 0.95)</td>
<td>p=0.0003</td>
</tr>
</tbody>
</table>

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]
  - Risk Ratio (95% CI): 0.86 (0.73 - 1.00)

*N=58,498*

Heterogeneity p=0.001

Secondary Safety Outcomes

Risk Ratio (95% CI)

ICH
- Risk Ratio: 0.48 (0.39 - 0.59)
- p-value: <0.0001

GI Bleeding
- Risk Ratio: 1.25 (1.01 - 1.55)
- p-value: 0.043

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

**Rivaroxaban Use in Patients With AF Undergoing PCI: PIioneer AF-PCI**

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

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

- **Randomize**
  - ≤72 hours after sheath removal

- **End of treatment at 12 months**

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- Rivaroxaban 15 mg qd* Clopidogrel 75 mg qd†
  - 1,6, or 12 months

- Rivaroxaban 2.5 mg bid Clopidogrel 75 mg qd† Aspirin 75-100 mg qd‡
  - 1,6, or 12 months

- VKA (target INR 2.0-3.0) Clopidogrel 75 mg qd† Aspirin 75-100 mg qd
  - 1,6, or 12 months

- VKA (target INR 2.0-3.0) Aspirin 75-100 mg qd

---

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 150mg BID + P2Y12 inhibitor

Dabigatran 110mg BID + P2Y12 inhibitor

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

3M 6M 9M 12M 15M 18/24/30M or EOT

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

Plus
Clinically Relevant Bleeding Rate
(ISTH Major)
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
Prior MI, CVA, or PAD

Standard care including oral antiplt rx

RANDOMIZE 1:1 DOUBLE BLIND

Vorapaxar 2.5 mg/d

Placebo

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

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  
$p < 0.001$

- **Placebo**
  - N = 26449  
  - Median f/u: 2.5 years  
  - 10.5% at 1080 days

- **Vorapaxar**
  - 9.3% at 1080 days

**Event Rate (%)**

<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>

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

3-yr KM rate (%)

- **Placebo**
  - TIMI Non-CABG Major: ARD 2.0%, HR 1.87, P<0.001
  - ICH: ARD 1.5%, HR 2.55, P<0.001
  - Fatal: ARD 0.2%, HR 1.48, P=0.46

- **Vorapaxar**
  - TIMI Non-CABG Major: ARD 0.2%, HR 1.55, P=0.049
  - ICH: ARD 0.2%, HR 1.44, P=0.30
  - Fatal: ARD 0.1%

**Prior Stroke**
- n = 5746

**No Hx of Stroke**
- n = 20699

Morrow DA et al. *NEJM* 2012;366:1404-13
Primary Efficacy Evaluation
Low Bleeding Risk Cohort* (N= 14,909)

CV Death, MI, or Stroke

CV Death

*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
4.0%

Vorapaxar
3.2%

HR 0.79
p = 0.003

Day 360 to 1080

CV Death / MI / Stroke (%)

Placebo
6.5%

Vorapaxar
5.5%

HR 0.82
p = 0.004

Bonaca et al. JACC 2014

Stent Thrombosis
By Randomized Treatment

ARC Definite Stent Thrombosis

**Placebo**
- Event Rate: 1.4%
- Hazard Ratio (HR): 0.71 (0.52 – 0.98)
- P-value: 0.04

**Vorapaxar**
- Event Rate: 1.1%

Days from randomization

Event Rate (%)
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

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

P<0.001
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

Events/1000 Patient/3 Years

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

Braunwald E. Source: US FDA website - 20140115 CRDAC-S1-03
Conclusions

- Delicate balance between preventing thrombosis and provoking bleeding – key is appropriate patient selection
- Prasugrel best used in ACS after the coronary anatomy is defined
- Ticagrelor of benefit across the full spectrum of ACS
- Vorapaxar of benefit in post-MI and PAD patients
- Several trials are ongoing which will affect care of ACS, PCI, Afib and provide insight into the optimal combinations/durations of single, double, and triple anti-thrombotic therapies
Thank You!

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Study population and design

- Documented evidence of STEMI
- Planned for angioplasty (PCI)
  - onset of ischaemic symptoms within 6 h
  - initially managed by ambulance physician/personnel; also concerning patients not pre-treated for STEMI in emergency rooms of non-PCI hospitals

**STE-ACS planned for PCI (N = 1862)**

- Randomised, double-blind
- Ticagrelor 180 mg loading dose
- Pre-hospital
- Placebo loading dose
- In-Hospital
- Ticagrelor 180 mg loading dose

**Primary Objectives**

- ≥ 70% ST-segment elevation resolution pre-PCI
- OR
- TIMI flow grade 3 of MI culprit vessel at initial angiography

- Ticagrelor 90 mg/bid 30 days

1st Co-primary endpoint
No ST-segment resolution (≥70%)

Montalescot G et al. NEJM 2014
2\textsuperscript{nd} Co-primary endpoint
No TIMI 3 flow in infarct-related artery

Montalescot G et al. NEJM 2014
Definite stent thrombosis up to 30 days

Montalescot G et al. NEJM 2014
TRITON – TIMI 38
CV Death, MI, Stroke

Primary Endpoint (%)

Prasugrel
HR 0.80
P=0.0003
HR 0.77
P=0.0001

Clopidogrel
HR 0.81
(0.73-0.90)
P=0.0004
NNT= 46

CV Death, MI, Stroke

ITT= 13,608
LTFU = 14 (0.1%)

Slide courtesy of Dr. Elliott Antman

TRITON-TIMI 38: Stent Thrombosis (ARC Definite + Probable)

Endpoint (%)

Any Stent at Index PCI
N = 12,844

Prasugrel
HR 0.48
P < 0.0001
NNT = 77

Clopidogrel
2.4 (142)


Slide courtesy of Dr. Elliott Antman
TRITON-TIMI 38: Bleeding Events

Safety Cohort

(N=13,457)

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>ICH in Pts w Prior Stroke/TIA (N=518)</th>
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<tbody>
<tr>
<td>TIMI Major Bleeds</td>
<td>1.8%</td>
<td>2.4%</td>
<td>Clop 0 (0) % Pras 6 (2.3)% (P=0.02)</td>
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<tr>
<td>ARD 0.6%</td>
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<td>HR 1.32</td>
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<td>NNH=167</td>
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<td>P=0.23</td>
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<tr>
<td>Fatal</td>
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<td>HR 1.52</td>
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<td>P=0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>ARD 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.74</td>
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</tr>
</tbody>
</table>

Slide courtesy of Dr. Elliott Antman

TRITON TIMI-38: Net Clinical Benefit

**Bleeding Risk Subgroups**

*Post-hoc analysis*

<table>
<thead>
<tr>
<th>Prior Stroke / TIA</th>
<th>Yes</th>
<th>No</th>
<th>Risk (%)</th>
<th>Risk (%)</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ 54</td>
<td>-16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P_{int} = 0.006</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&gt;=75</td>
<td></td>
<td>-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 75</td>
<td></td>
<td>+3</td>
<td>P_{int} = 0.18</td>
<td>-16</td>
</tr>
<tr>
<td>Wgt</td>
<td>&lt; 60 kg</td>
<td></td>
<td>+3</td>
<td>P_{int} = 0.36</td>
<td>-14</td>
</tr>
<tr>
<td></td>
<td>&gt;= 60 kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OVERALL

<table>
<thead>
<tr>
<th>HR</th>
<th>Prasugrel Better</th>
<th>Clopidogrel Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

ACCOAST: Primary Efficacy Endpoint (All Patients)

ACCOAST: Primary Safety Endpoint (All Patients)

PLATO: CV Death, MI, or Stroke

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>9,291</td>
<td>8,362</td>
<td>8,124</td>
</tr>
<tr>
<td>8,333</td>
<td>8,460</td>
<td>8,219</td>
</tr>
<tr>
<td>8,521</td>
<td>8,628</td>
<td>8,743</td>
</tr>
<tr>
<td>8,219</td>
<td>8,124</td>
<td>5,096</td>
</tr>
<tr>
<td>6,743</td>
<td>6,743</td>
<td>4,147</td>
</tr>
<tr>
<td>5,161</td>
<td>5,096</td>
<td></td>
</tr>
</tbody>
</table>

Days after randomisation

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>300</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>11.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>9.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Cumulative incidence (%)

HR 0.84 (95% CI 0.77–0.92), p=0.0003

Study Chairs: Drs. Harrington and Wallentin
**PLATO: Secondary Efficacy Endpoints**

**Myocardial infarction**

- Clopidogrel: 6.9%
- Ticagrelor: 5.8%

**Cumulative incidence (%)**

HR 0.84 (95% CI 0.75–0.95), p=0.005

**Cardiovascular death**

- Clopidogrel: 5.1%
- Ticagrelor: 4.0%

**Cumulative incidence (%)**

HR 0.79 (95% CI 0.69–0.91), p=0.001

---

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days</td>
<td>9,333</td>
<td>9,291</td>
</tr>
<tr>
<td>180 days</td>
<td>8,678</td>
<td>8,560</td>
</tr>
<tr>
<td>270 days</td>
<td>8,520</td>
<td>8,405</td>
</tr>
<tr>
<td>360 days</td>
<td>8,279</td>
<td>8,177</td>
</tr>
</tbody>
</table>

**Days after randomisation**

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days</td>
<td>6,703</td>
<td>6,703</td>
</tr>
<tr>
<td>180 days</td>
<td>6,796</td>
<td>6,796</td>
</tr>
<tr>
<td>270 days</td>
<td>6,796</td>
<td>6,796</td>
</tr>
<tr>
<td>360 days</td>
<td>6,796</td>
<td>6,796</td>
</tr>
</tbody>
</table>

---

*Study Chairs: Drs. Harrington and Wallentin*
PLATO: Stratification by Invasive vs Conservative Strategy

Number at risk

<table>
<thead>
<tr>
<th>Invasive</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>Non-invasive</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6732</td>
<td>6676</td>
<td>2601</td>
<td>2615</td>
<td>2392</td>
</tr>
<tr>
<td>60</td>
<td>6236</td>
<td>6129</td>
<td>2392</td>
<td>2392</td>
<td>2392</td>
</tr>
<tr>
<td>120</td>
<td>6134</td>
<td>6034</td>
<td>2326</td>
<td>2328</td>
<td>2328</td>
</tr>
<tr>
<td>180</td>
<td>5972</td>
<td>5881</td>
<td>2247</td>
<td>2243</td>
<td>2243</td>
</tr>
<tr>
<td>240</td>
<td>4889</td>
<td>4815</td>
<td>1854</td>
<td>1835</td>
<td>1835</td>
</tr>
<tr>
<td>300</td>
<td>3735</td>
<td>3680</td>
<td>1426</td>
<td>1416</td>
<td>1416</td>
</tr>
<tr>
<td>360</td>
<td>3048</td>
<td>2965</td>
<td>1099</td>
<td>1109</td>
<td>1109</td>
</tr>
</tbody>
</table>

**Invasive**

HR, 0.84, 95% CI: (0.75–0.94)

**Non-invasive**

HR, 0.85, 95% CI: (0.73–1.0)

James S et al. *BMJ* 2011;342:d3527
Major Bleeding: Non-CABG vs CABG

Study Chairs: Drs. Harrington and Wallentin

- **Non-CABG PLATO major bleeding**: 4.5% vs 3.8% (p=0.026)
- **Non-CABG TIMI major bleeding**: 2.8% vs 2.2% (p=0.025)
- **CABG PLATO major bleeding**: 7.4% vs 7.9% (NS)
- **CABG TIMI major bleeding**: 5.3% vs 5.8% (NS)