ANTIPLATELETS THERAPY FOR ACUTE CORONARY SYNDROME

A Workshop Concentrating on the Long-term Care of the ACS Patient
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  Assistant Clinical Professor, McMaster University
  Corporate Chief of Cardiology & Medical Director
  Cardiovascular Health System, William Osler Health System

Relationships with commercial interests:
  ► Consulting Fees: Astra-Zeneca, Bayer
  ► Speakers’ Bureau: Astra-Zeneca, Bayer, Pfizer, BMS

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Mitigating Potential Bias

► All the recommendations involving clinical medicine are based on evidence that is accepted within the profession.
► All scientific research referred to, reported, or used is in the support or justification of patient care.
► Recommendations conform to the generally accepted standards.
► Independent content validation.
► The presentation will mitigate potential bias by ensuring that data and recommendations are presented in a fair and balanced way.
► Potential bias will be mitigated by presenting a full range of products that can be used in this therapeutic area.
► Information of the history, development, funding, and the sponsoring organizations of the disclosure presented will be discussed.
Learning Objectives

1. Overview the current guidelines on the duration of dual antiplatelet therapy in cardiac patients and the rational for these guidelines.

2. To discuss recent trials suggesting that more prolonged DAPT may be of benefit in select patients.

3. To discuss managing the complex patient requiring antiplatelet therapy who also having other comorbidities such as atrial fibrillation and bleeding.
Dual Antiplatelet Therapy in the Heart Patient

► DAPT (ASA plus clopidogrel or ticagrelor or prasugrel) has become the cornerstone in the management of ACS and PCI patients.

► Trials such as CURE, CREDO (performed in the 1995-2005 era) showed that the addition of clopidogrel to ASA alone was of incremental benefit in decreasing major CV events and mortality.

► The duration of DAPT had been standardized by guidelines based on RCT’s such as the CURE and CREDO trials.
Antiplatelet Therapy with ASA and Clopidogrel Improves Major Outcomes in NSTE ACS – CURE Trial

Primary Endpoint: MI/Stroke/CV Death

Cumulative Hazard Rate (%)

<table>
<thead>
<tr>
<th>Months of follow-up</th>
<th>Placebo + ASA (n=6303)</th>
<th>Clopidogrel + ASA (n=6259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>6</td>
<td>3.2</td>
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<tr>
<td>9</td>
<td>5.9</td>
<td>5.1</td>
</tr>
<tr>
<td>12</td>
<td>8.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

RR 0.80
95% CI 0.72–0.90
p<0.001

20% RRR

Placebo + ASA

Clopidogrel + ASA

All patients received ASA and UFH or LMWH

Major Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel + ASA</th>
<th>Placebo + ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (%)</td>
<td>3.7</td>
<td>2.7</td>
</tr>
<tr>
<td>RR</td>
<td>1.38</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>1.13–1.67</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>


UFH = unfractionated heparin; LMWH = low molecular weight heparin
BUT how did we actually determine the optimal duration of DAPT?

1. Trials comparing variable durations of DAPT?
2. Disease pathophysiology? Is atherosclerosis cured after a year?
3. Trial protocols which determined trial durations for largely non-clinical reasons?
Dual Antiplatelet Therapy in the Heart Patient: Points to Consider

- Is it clinically reasonable that we treat all ACS and PCI patients for the same duration of DAPT?
- ACS and PCI patients are a heterogeneous group of patients with highly variable risk of subsequent ischemic events and bleeding risk.
- Benefit/risk of DAPT duration may vary on patient profile, coronary pathology and the PCI procedure.
Should the duration of DAPT be tailored to the patients risk of future ischemic events and bleeding risk?

- Prior guidelines have recommended one year of DAPT for most ACS patients.
- But the risk of future CV events and the bleeding risks amongst ACS patients are highly variable.
- There is no pathophysiologic reason to believe that the patients risk of ischemic events is resolved after a year. In fact, data would indicate that most ACS patients will eventually have future ischemic events.
- PCI diminishes symptoms and future ischemic events attributed to the culprit lesion, but doesn’t change the patients propensity for ischemic events from disease progression elsewhere.
Should the duration of DAPT be tailored to the patients’ risk of future ischemic events and bleeding risk?

- In the past 2 years we have had several studies that address the question of optimal duration of DAPT in patients with ACS, PCI and chronic stable CAD.
- Guidelines are now incorporating these trials and moving from a standardized approach (e.g. all ACS patients get one year of DAPT) to a patient personalized strategy with the goal of maximizing the ischemic benefit while minimizing the bleeding risk of DAPT.
PEGASUS-TIMI 54

Is DAPT (ASA + ticagrelor) of greater benefit than ASA alone in patients with a history of myocardial infarction?
Patients aged ≥50 years with a history of spontaneous MI 1–3 years prior to enrolment AND at least one additional atherothrombosis risk factor* (N=21,162)

- Ticagrelor 90 mg bid + ASA 75–150 mg/day
- Ticagrelor 60 mg bid + ASA 75–150 mg/day
- Placebo + ASA 75–150 mg/day

Minimum of 12 months’ follow up:
Every 4 months in Year 1, then semi-annually

Primary efficacy endpoint: CV death, MI or stroke
Primary safety endpoint: TIMI-defined major bleeding

*Age ≥65 years, diabetes mellitus, second prior MI, multivessel CAD or chronic non-end stage renal disease bid, twice daily; CAD, coronary artery disease; TIMI, Thrombolysis in Myocardial Infarction

PEGASUS-TIMI 54: Inclusion Criteria

- Age ≥50 years old
- History of a spontaneous MI 1–3 years prior to enrolment and one additional high-risk feature
  - Age ≥65 years old
  - Diabetes mellitus requiring medication
  - A second prior spontaneous MI
  - Angiographic evidence of multivessel CAD
  - Chronic, non-end-stage renal dysfunction (CrCl <60 mL/min)
- Prescribed and tolerating ASA at the time of enrolment
**PEGASUS-TIMI 54: Primary Endpoint**

**Composite of CV death, MI or stroke**

- **Placebo**
  - No. at risk: 90 mg bid
    - 7067
  - No. at risk: 60 mg bid
    - 7050
  - No. at risk: 6979
  - No. at risk: 6892
  - No. at risk: 6823
  - No. at risk: 6761
  - No. at risk: 6681
  - No. at risk: 6508
  - No. at risk: 6236
  - No. at risk: 5876
  - No. at risk: 5157
  - No. at risk: 4343
  - No. at risk: 3360
  - No. at risk: 2028

- **Ticagrelor 90 mg bid**
  - Event rate (%): 9.04%
  - No. at risk: 90 mg bid
    - 6979
  - No. at risk: 6892
  - No. at risk: 6823
  - No. at risk: 6761
  - No. at risk: 6681
  - No. at risk: 6508
  - No. at risk: 6236
  - No. at risk: 5876
  - No. at risk: 5157
  - No. at risk: 4343
  - No. at risk: 3360
  - No. at risk: 2028

- **Ticagrelor 60 mg bid**
  - Event rate (%): 7.77%
  - No. at risk: 60 mg bid
    - 6973
  - No. at risk: 6899
  - No. at risk: 6827
  - No. at risk: 6769
  - No. at risk: 6719
  - No. at risk: 6550
  - No. at risk: 6272
  - No. at risk: 5921
  - No. at risk: 5243
  - No. at risk: 4401
  - No. at risk: 3368
  - No. at risk: 2038

**Event rate (%)**

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

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

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PEGASUS-TIMI 54: EfficacyEndpoints

**Endpoint**

- **Primary – CV death, MI or stroke (1558 events)**
- **CV death (566 events)**
- **MI (898 events)**
- **Stroke (313 events)**

**3-year KM event rates (%)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>3-year KM event rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ticagrelor</td>
</tr>
<tr>
<td>Primary – CV death, MI or stroke (1558 events)</td>
<td>7.85</td>
</tr>
<tr>
<td></td>
<td>7.77</td>
</tr>
<tr>
<td></td>
<td>7.81</td>
</tr>
<tr>
<td>CV death (566 events)</td>
<td>2.94</td>
</tr>
<tr>
<td></td>
<td>2.86</td>
</tr>
<tr>
<td></td>
<td>2.90</td>
</tr>
<tr>
<td>MI (898 events)</td>
<td>4.40</td>
</tr>
<tr>
<td></td>
<td>4.53</td>
</tr>
<tr>
<td></td>
<td>4.47</td>
</tr>
<tr>
<td>Stroke (313 events)</td>
<td>1.61</td>
</tr>
<tr>
<td></td>
<td>1.47</td>
</tr>
<tr>
<td></td>
<td>1.54</td>
</tr>
</tbody>
</table>

*Indicates nominal P value; P<0.026 indicates statistical significance

PEGASUS-TIMI 54: Bleeding

Rates are presented as 3-year Kaplan-Meier estimates.

The PEGASUS-TIMI 54 study demonstrated that the addition of ticagrelor 60 mg bid or 90 mg bid to low-dose ASA in patients 1–3 years after a MI significantly reduced the risk of the primary endpoint of CV death, MI or stroke.

A directionally consistent effect was observed on all components of the primary endpoint, including CV death.

The reduction in ischemic events by ticagrelor was consistent among major clinical subgroups and by region and continued to accrue over time with a median of 33 months of follow-up.

The rate of the primary safety endpoint of TIMI major bleeding was significantly higher with both doses of ticagrelor compared with placebo.

The rate of fatal bleeding or non-fatal intracranial hemorrhage was low (<1% at 3 years) and did not significantly differ between treatment arms.

Dyspnea was more frequent with both doses of ticagrelor; however, the majority of episodes with either dose were characterised as either mild (58.1%) or moderate (36.9%) in severity.

- Dyspnoea leading to discontinuation occurred in 6.5%, 4.55% and 0.79% of patients in the ticagrelor 90 mg bid, ticagrelor 60 mg bid placebo arms, respectively.
PEGASUS-TIMI 54: Conclusions

► Patients who have had a MI remain at heightened risk for ischemic events over the long term\(^1\)–\(^3\)

► PEGASUS-TIMI 54 is the first prospective, randomized controlled clinical trial appropriately powered to assess the benefit of long-term DAPT in patients with prior MI

► The study therefore suggests that prolonged antiplatelet therapy with ticagrelor plus low-dose ASA may represent a new strategy to reduce atherothrombotic events in appropriately selected patients with prior MI

Dual Antiplatelet Therapy Beyond One Year after Drug-eluting PCI

Laura Mauri, Dean J. Kereiakes, Robert W. Yeh, Priscilla Driscoll-Shempp, Donald E. Cutlip, P. Gabriel Steg, Sharon-Lise T. Normand, Eugene Braunwald, Stephen Wiviott, David J. Cohen, David R. Holmes, Michael J. Rinaldi, Joseph M. Massaro, on behalf of the Dual Antiplatelet Therapy (DAPT) Study Investigators
Objective

- To determine whether DAPT beyond 12 months after PCI is associated with reduction in stent thrombosis and/or major adverse cardiovascular & cerebrovascular events.

- To determine the impact of DAPT beyond 12 months on moderate or severe bleeding.
**Design**

**Inclusion:** FDA-approved DES or BMS, candidates for thienopyridine

**Excluded:** Oral anticoagulant therapy; life expectancy < 3y

**Randomized:** Free from MI, stroke, repeat revascularization, moderate/severe bleeding, and adherent with therapy at 12 months


ClinicalTrials.gov number NCT00977938
Co-Primary Effectiveness End Points: 12-30 Months

Cumulative Incidence (%) for:
- ST (Definite/Probable)
- Definite ST
- Probable ST
- MACCE
- Death
- MI
- Ischemic stroke
- Hemorrhagic stroke

Thienopyridine (N=5020) vs Placebo (N=4941)

- ST (Definite/Probable): Thienopyridine 0.4%, Placebo 0.3%
- Definite ST: Thienopyridine 1.4%, Placebo 1.2%
- Probable ST: Thienopyridine 0.55%, Placebo 0.1%
- MACCE: Thienopyridine 5.9%, Placebo 4.3%
- Death: Thienopyridine 2.0%, Placebo 1.5%
- MI: Thienopyridine 4.1%, Placebo 2.1%
- Ischemic stroke: Thienopyridine 0.5%, Placebo 0.7%
- Hemorrhagic stroke: Thienopyridine 0.3%, Placebo 0.2%

Statistical Significance:
- ST (Definite/Probable): p < 0.001
- Definite ST: p < 0.001
- Probable ST: p < 0.001
- MACCE: p < 0.001
- Death: p = 0.052
- MI: p < 0.001
Myocardial Infarction: 12-30 Months

Cumulative Incidence of Myocardial Infarction

Primary Analysis Period

12-30 Months:
HR 0.47 (0.37-0.61)
2.1% vs. 4.1%
P<0.001

# At Risk

<table>
<thead>
<tr>
<th></th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>Study Drug Treatment Ends</th>
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</thead>
<tbody>
<tr>
<td>Thienopyridine</td>
<td>5020</td>
<td>4920</td>
<td>4849</td>
<td>4789</td>
<td>4717</td>
<td>4634</td>
<td>4580</td>
<td>3051</td>
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<tr>
<td>Placebo</td>
<td>4941</td>
<td>4804</td>
<td>4727</td>
<td>4653</td>
<td>4565</td>
<td>4501</td>
<td>4440</td>
<td>3012</td>
</tr>
</tbody>
</table>
Non-Stent Thrombosis MI: 12-30 Months

55% of the MI benefit is not related to stent thrombosis

12-30 Months:
HR 0.59 (0.45-0.78)
1.8% vs. 2.9%
P<0.001

<table>
<thead>
<tr>
<th>Months After Enrollment</th>
<th>Thienopyridine</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>12</td>
<td>4920</td>
<td>4820</td>
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<tr>
<td>15</td>
<td>4851</td>
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<td>18</td>
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<td>24</td>
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<td>27</td>
<td>4588</td>
<td>4491</td>
</tr>
<tr>
<td>30</td>
<td>3066</td>
<td>3052</td>
</tr>
</tbody>
</table>
Conclusions

• Following DES PCI continuation of DAPT beyond 12 months is associated with reduction in stent thrombosis and major adverse cardiovascular & cerebrovascular events compared to ASA alone.
  
  • Relative reduction of 71% for ST, 29% for MACCE and 53% for MI
  
  • Myocardial infarctions reduced both in the stent and in other locations.
  
  • Treatment benefit was consistent across drugs, stent types, and patients with higher or lower risk of events.
  
• The benefit of extended DAPT was tempered by an increase in bleeding events (2.5% vs 1.6%, P=0.001). Severe and/or fatal bleeding was uncommon.
Long-term Dual Antiplatelet Therapy for 2° Prevention of Cardiovascular Events in Patients with Previous Myocardial Infarction

A Collaborative Meta-Analysis of Randomized Trials

Jacob A. Udell, MD, MPH, Marc P. Bonaca, MD, MPH, Jean-Philippe Collet, MD, PhD, A. Michael Lincoff, MD, Dean J. Kereiakes, MD, Francesco Costa, MD, Cheol Whan Lee, MD, Laura Mauri, MD, MSc, Marco Valgimigli, MD, PhD, Seung-Jung Park, MD, PhD, Gilles Montalescot, MD, PhD, Marc S. Sabatine, MD, MPH, Eugene Braunwald, MD, Deepak L. Bhatt, MD, MPH
# Trials Evaluating Prolonged DAPT following MI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subgroup /Population</th>
<th>N</th>
<th>Drug</th>
<th>Duration (months)</th>
<th>MACE Events</th>
<th>Bleeding EP</th>
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</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>Stable prior MI (mean 24 mo.)</td>
<td>3846</td>
<td>Clopi</td>
<td>28</td>
<td>287</td>
<td>GUSTO mod/severe</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>PCI for ACS</td>
<td>1465</td>
<td>Clopi</td>
<td>6 vs. 24</td>
<td>132</td>
<td>TIMI major</td>
</tr>
<tr>
<td>ARCTIC-</td>
<td>PCI for ACS (excluded STEMI)</td>
<td>323</td>
<td>Clopi or Pras</td>
<td>12 vs. 24</td>
<td>7</td>
<td>STEEPLE major</td>
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<tr>
<td>Interruption</td>
<td></td>
<td></td>
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<tr>
<td>DAPT</td>
<td>PCI for MI</td>
<td>3576</td>
<td>Clopi or Pras</td>
<td>12 vs. 30</td>
<td>167</td>
<td>GUSTO mod/severe</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>PCI for ACS</td>
<td>3063</td>
<td>Clopi</td>
<td>12 vs. 24</td>
<td>122</td>
<td>TIMI major</td>
</tr>
<tr>
<td>PEGASUS</td>
<td>Stable prior MI (median 20 mo.)</td>
<td>21162</td>
<td>Ticag</td>
<td>33</td>
<td>1558</td>
<td>TIMI major</td>
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<tr>
<td>TIMI-54</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>33435</strong></td>
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<td></td>
<td><strong>30</strong></td>
<td><strong>2273</strong></td>
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</tr>
</tbody>
</table>

Abbreviations: Clopi: clopidogrel; Pras: prasugrel; Ticag: ticagrelor
# 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>
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</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>
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<tr>
<td>PRODIGY</td>
<td>63</td>
<td>732</td>
<td>69</td>
<td>733</td>
<td>0.91 (0.65 - 1.28)</td>
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<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>
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<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>
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<tr>
<td>PEGASUS</td>
<td>980</td>
<td>14095</td>
<td>578</td>
<td>7067</td>
<td>0.84 (0.76 - 0.94)</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td>1286</td>
<td>20203</td>
<td>987</td>
<td>13232</td>
<td>0.78 (0.67 - 0.90)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Risk Ratio (95% CI)</th>
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</thead>
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<tr>
<td><strong>TOTAL</strong></td>
<td>1286</td>
<td>20203</td>
<td>987</td>
<td>13232</td>
<td>0.78 (0.67 - 0.90)</td>
</tr>
</tbody>
</table>

**P = 0.001**

**Primary Endpoint – CV Death, MI, or Stroke**

- CHARISMA
  - Events: 125
  - Total: 1903
  - Risk Ratio: 0.77 (0.61 - 0.98)

- PRODIGY
  - Events: 63
  - Total: 732
  - Risk Ratio: 0.91 (0.65 - 1.28)

- ARCTIC-Int’n
  - Events: 3
  - Total: 156
  - Risk Ratio: 0.79 (0.18 - 3.51)

- DAPT
  - Events: 59
  - Total: 1805
  - Risk Ratio: 0.52 (0.38 - 0.72)

- DES-LATE
  - Events: 56
  - Total: 1512
  - Risk Ratio: 0.85 (0.60 - 1.21)

- PEGASUS
  - Events: 980
  - Total: 14095
  - Risk Ratio: 0.84 (0.76 - 0.94)

- **TOTAL**
  - Events: 1286
  - Total: 20203
  - Risk Ratio: 0.78 (0.67 - 0.90)

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>
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<tr>
<td>PRODIGY</td>
<td>31</td>
<td>732</td>
<td>31</td>
<td>733</td>
<td>1.00 (0.61 - 1.64)</td>
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<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>
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<tr>
<td>DAPT</td>
<td>11</td>
<td>1805</td>
<td>16</td>
<td>1771</td>
<td>0.67 (0.31 - 1.44)</td>
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<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>
<tr>
<td></td>
<td>2.3%</td>
<td>2.6%</td>
<td></td>
<td></td>
<td>P = 0.03</td>
</tr>
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</table>

P = 0.03

# Major Bleeding

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Risk Ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>45</td>
<td>1903</td>
<td>39</td>
<td>1943</td>
<td>1.17 (0.76 - 1.79)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>9</td>
<td>732</td>
<td>6</td>
<td>733</td>
<td>1.50 (0.53 - 4.20)</td>
</tr>
<tr>
<td>ARCTIC-Int’n</td>
<td>2</td>
<td>156</td>
<td>0</td>
<td>167</td>
<td>5.35 (0.26 - 110.6)</td>
</tr>
<tr>
<td>DAPT</td>
<td>34</td>
<td>1805</td>
<td>14</td>
<td>1771</td>
<td>2.38 (1.27 - 4.43)</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>39</td>
<td>1512</td>
<td>31</td>
<td>1551</td>
<td>1.27 (0.79 - 2.03)</td>
</tr>
<tr>
<td>PEGASUS</td>
<td>242</td>
<td>13946</td>
<td>54</td>
<td>6996</td>
<td>2.50 (1.86 - 3.36)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>371</td>
<td>20054</td>
<td>144</td>
<td>13161</td>
<td>1.73 (1.19 - 2.50)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Extended DAPT Better

Aspirin Alone Better

Summary

- Compared with aspirin alone, extended DAPT >1 year among stabilized high-risk patients with previous MI:
  - Decreased the risk of MACE, MI, stroke alone & CV death alone
  - Increased risk of major bleeding, but not fatal bleeding or ICH
  - No excess of non-CV causes of death

- Effect of extended DAPT consistent irrespective of:
  - DAPT regimen, time from MI, ST-elevation, or PCI status

- Who were high-risk pts at low risk of bleeding that derived benefit from extended DAPT?
  - High Risk: ~1-3 years after an MI with additional CV risk factors
  - Low Bleeding Risk: Excluded patients with anticoagulation, recent bleeding, recent surgery, or any history of ICH
  - Caution: Very few patients studied had prior stroke/TIA

Conclusion

These findings indicate that in patients with prior MI who are at low risk of bleeding, continuation of dual antiplatelet therapy beyond a year offers a substantial reduction in important cardiovascular outcomes, including cardiovascular death.

How do we incorporate this new information on the benefits/risk of prolonged DAPT in individual patients?

Patient #2
85-Year-Old, Frail, Woman

Clinical Balance

Reduction in CV Events ↔ Increase in Bleeding

Death???
Parameters to consider in a personalized strategy to determine DAPT duration in individual patients?

**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
Decision-Making After the Mandatory DAPT Period

When a mandatory period of DAPT is completed, a careful evaluation of the patient’s ischemic risk and bleeding risk, and of the overall clinical profile should be undertaken.

Figure 5. Treatment Algorithm for Duration of P2Y\textsubscript{12} Inhibitor Therapy in Patient With Recent ACS (NSTE-ACS or STEMI)

- **Recent ACS (NSTE-ACS or STEMI)**
  - CABG
  - Medical Therapy
  - Lytic (STEMI)
  - PCI (BMS or DES)

- **0 mo**
  - Class I: After CABG, resume P2Y\textsubscript{12} inhibitor to complete 1 year of DAPT (clopidogrel, prasugrel, ticagrelor)

- **6 mo**
  - Class I: At least 12 mo (clopidogrel, ticagrelor)

- **12 mo**
  - Class I: At least 14 d and up to 12 mo (clopidogrel)
  - Class I: At least 12 mo (clopidogrel, prasugrel, ticagrelor)

- **Class IIb**: Discontinuation after 6 mo may be reasonable

- **No high risk of bleeding and no significant overt bleeding on DAPT**

- **Class IIb**: >12 mo may be reasonable

- **High bleeding risk* or significant overt bleeding**
Personalize Post-ACS DAPT Duration to Optimize Risk of future Ischemic Events and Bleeding Risk?

Case 1

- 55 yo robust appearing, cigarette smoking man, on no prior meds has a NSTEMI.
- Angiography shows an isolated RCA stenosis which is resolved with a 3.0 x 18mm DES. No significant disease elsewhere.
- Quits cigarette smoking and has no further cardiac symptoms.
- Returns to see you after 12 months for reassessment. He is doing well. Normal exam (128/82, 62 bpm)
- Atorvastatin 80mg/d, bisoprolol 2.5mg/d, Ramipril 5mg/d, ticagrelor 90mg BID, ASA 81mg/d
- Do I need to still take all these meds?
Personalize Post-ACS DAPT Duration to Optimize Risk of future Ischemic Events and Bleeding Risk?

Case 1

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- Angiography shows an isolated RCA stenosis which is resolved with a 3.0 x 18mm DES. No significant disease elsewhere.
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- Atorvastatin 80mg/d, bisoprolol 2.5mg/d, Ramipril 5mg/d, ticagrelor 90mg BID, ASA 81mg/d
- Do I need to still take all these meds?

What if he was diabetic and had multivessel CAD. He had a total of 5 drug-eluting stents deployed in the LAD, diagonal (bifurcation stents) and circumflex.
Personalize Post-ACS DAPT Duration to Optimize Risk of future Ischemic Events and Bleeding Risk
Personalize Post-ACS DAPT Duration to Optimize Risk of future Ischemic Events and Bleeding Risk

COMPETENCY IN MEDICAL KNOWLEDGE: Patients undergoing complex PCI are at higher risk of cardiac ischemic events, in a graded fashion with increase in procedural complexity. In patients who undergo complex PCI, compared with a short period of DAPT (3 or 6 months), longer DAPT (≥1 year) significantly reduced the risk of ischemic events. The magnitude of the benefit of prolonged DAPT seems to be greater as the degree of PCI complexity is higher.
Personalize Post-ACS DAPT Duration to Optimize Risk of future Ischemic Events and Bleeding Risk?

Case 2

- 74 yo hypertensive woman with history of NSTEMI 3 yrs ago which was managed conservatively without undergoing angiography.
- She had another NSTEMI 14 months ago while on ASA, atorvastatin and metoprolol.
- With second NSTEMI she had a 2.5 x 32mm DES PCI of culprit proximal-mid circumflex stenosis. Moderate diffuse LAD disease and chronically occluded RCA with collaterals from the LAD.
- Returns to see you after 14 months for reassessment. She is doing well. Normal exam except BP158/72, 62 bpm.
- Rosuvastatin 20mg/d, bisoprolol 2.5mg/d, Ramipril 10mg/d, ticagrelor 90mg BID, ASA 81mg/d
- Does she need any investigations, change in meds?
Personalize Post-ACS DAPT Duration to Optimize Risk of future Ischemic Events and Bleeding Risk?

Case 3

- 74 yo hypertensive woman and prior TIA. She has chronic atrial fibrillation on warfarin, lisinopril, atenolol. No prior history of CAD.
- Admitted to hospital with an inferior STEMI.
- Undergoes primary PCI of occluded RCA with 2.75 x 20mm DES. Only mild-moderate disease elsewhere.
- Warfarin is held and started on ASA, ticagrelor.
- Also on rosuvastatin 20mg/d, bisoprolol 2.5mg/d, ramipril 10mg/d.
- What do we do about her anticoagulation?
Personalize Post-ACS DAPT Duration to Optimize Risk of future Ischemic Events and Bleeding Risk?

Case 3

The Patient with ACS and Atrial Fibrillation (Potential Nightmare)

What is the best management option?

- Warfarin, ASA, ticagrelor
- Warfarin, ASA, clopidogrel
- Apixaban 2.5mg BID, ASA, clopidogrel
- Apixaban 5mg BID, ASA, clopidogrel
- Rivaroxaban 15mg daily, ticagrelor 90mg BID
- Flip a coin!
Incidence of Atrial Fibrillation in ACS Patients

2 % to 21% of ACS Patients

Acute Coronary Syndrome

Atrial Fibrillation

ACS + Afib

Pathophysiological Basis for Dual Pathway Strategies
Thrombus formation involves both platelet activation and blood coagulation

Anticoagulants
- Rivaroxaban
- Apixaban
- Edoxaban
- Inflammation
  - Cellular proliferation
- Dabigatran

Antiplatelets
- ASA
- Clopidogrel
- Prasugrel
- Ticagrelor

Anticoagulants
- Coagulation cascade
  - Factor Xa
  - Thrombin
  - Fibrinogen
  - Fibrin
  - Clot

Platelets
- Thrombin
  - Activated platelet
  - Platelet aggregation

Inflammation
- Collagen + other mediators
- Thromboxane
- ADP

Platelets
- GPIIb/IIIa inhibitors

Mackman N. *Nature*, 2008
The new OAC agents are consistently associated with a numerically lower risk for all-cause mortality compared to warfarin.†

TRIAL | OAC Agent | Relative Risk (95% CI)
--- | --- | ---
RE-LY | Dabigatran 110mg b.i.d. |  
ROCKET-AF | Rivaroxaban 20mg o.d. |  
ARISTOTLE | Apixaban* 5mg b.i.d. |  

† Not intended as cross-trial comparison
*Not approved in Canada for stroke prevention in AF patients

Data obtained from intention-to-treat analysis

What if My Atrial Fibrillation Patient Had a Recent ACS?

Coronary risk of novel oral anticoagulants

<table>
<thead>
<tr>
<th>Risk of MI/ACS</th>
<th>N</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>43,902</td>
<td>0.94 (0.82-1.07)</td>
<td>0.333</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>36,767</td>
<td>1.30 (1.04-1.63)</td>
<td>0.021</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>44,110</td>
<td>0.78 (0.69-0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mixed treatment comparison meta-analysis

Bleeding Risk with Combination Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA alone</td>
<td>1.00</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Clopidogrel Alone</td>
<td>1.33</td>
<td>1.33</td>
<td>1.11-1.59</td>
</tr>
<tr>
<td>Warfarin Alone</td>
<td>1.23</td>
<td>1.23</td>
<td>0.94-1.61</td>
</tr>
<tr>
<td>ASA + clopidogrel</td>
<td>1.47</td>
<td>1.47</td>
<td>1.28-1.69</td>
</tr>
<tr>
<td>ASA + warfarin</td>
<td>1.84</td>
<td>1.84</td>
<td>1.51-2.23</td>
</tr>
<tr>
<td>Clopidogrel + warfarin</td>
<td>3.52</td>
<td>3.52</td>
<td>2.42-5.11</td>
</tr>
<tr>
<td>ASA + clopidogrel + warfarin</td>
<td>4.05</td>
<td>4.05</td>
<td>3.08-5.33</td>
</tr>
</tbody>
</table>

CI = Confidence Interval

P value not reported

Primary Endpoint: Any Bleeding

863 Pts undergoing PCI
Triple Rx - warfarin plus clopidogrel + ASA
Double Rx – warfarin plus clopidogrel

~25% had an ACS at baseline

Dewilde et al., Lancet 2013;381:1107-15
Secondary Endpoint: Death/MI/Stroke/Target Vessel Revascularization/Stent Thrombosis

Mortality:
Triple 6.3% vs. Double 2.5%
HR 0.39 (0.16-0.93);
p=0.027

No significant differences in other components but numerically lower MI (4.6% vs. 3.2%) stroke (2.8% vs. 1.1%), stent thrombosis (3.2% vs. 1.4%)
Primary Endpoint: Death, MI, Stent Thrombosis, Stroke, or TIMI Major Bleeding

614 pts (~32% ACS) with DES implantation and indication for OAC
All got ASA + warfarin
Randomized to 6-week vs. 6-month clopidogrel

Fiedler et al., J Am Coll Cardiol 2015;65:1619-29
Secondary Endpoints

Cardiac Death, MI, Stent Thrombosis or Stroke

BARC Bleeding (Landmark Analysis)
TIMI Major Bleeding

Fiedler et al., J Am Coll Cardiol 2015;65:1619-29
2016 CCS Atrial Fibrillation Guidelines: Patients with AF/ elective PCI

For patients with AF and recent elective PCI

Age < 65 and CHADS2 = 0
- ASA + Clopidogrel for 12 months
  - ASA alone after 12 months

Age ≥ 65 or CHADS2 ≥ 1
- OAC* + Clopidogrel for 12 months
  - OAC* alone after 12 months

* A NOAC is preferred over warfarin for non-valvular AF

Canadian Journal of Cardiology DOI: (10.1016/j.cjca.2016.07.591)
2016 CCS Atrial Fibrillation Guidelines: Patients with AF/ACS

For patients with AF in association with NSTEACS or STEMI

Age < 65 and CHADS² = 0

- No PCI
  - ASA + Ticagrelor or Clopidogrel for 12 months
  - ASA alone after 12 months

Age ≥ 65 or CHADS² ≥ 1

- PCI
  - ASA + Ticagrelor or Prasugrel or Clopidogrel for 12 months
  - ASA alone after 12 months

- No PCI
  - OAC* + Clopidogrel for 12 months
  - OAC* alone after 12 months

- PCI
  - OAC* + Clopidogrel + ASA for 3 to 6 months
  - OAC* + Clopidogrel through to 12 months

* A NOAC is preferred over warfarin for non-valvular AF
2016 ESC Atrial Fibrillation Guidelines: Patients with AF/ACS

AF patient in need of OAC after an ACS

- **Bleeding risk low** compared to risk for ACS or stent thrombosis
  - Time from ACS
    - 0
    - 1 month
    - 3 months
    - 6 months
    - 12 months
    - Lifelong
  - Triple therapy (IIaB)
  - Dual therapy (IIaC)
  - OAC monotherapy (IB)

- **Bleeding risk high** compared to risk for ACS or stent thrombosis
  - Triple therapy (IIaB)
  - Dual therapy (IIaC)
  - OAC monotherapy (IB)

DOIs: http://dx.doi.org/10.1093/eurheartj/ehw210  ehw210 First published online: 27 August 2016  www.escardio.org/guidelines
In an area of limited evidence, rivaroxaban is the *first* and currently *only* NOAC (versus VKA) to provide data from a dedicated RCT for patients with AF undergoing PCI.
Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI

- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

*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). ∆ Open label VKA


Gibson et al. AHA 2016
Both Rivaroxaban Strategies were Associated With Significantly Improved Safety

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); p<0.001
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); p<0.001

All subgroups analyzed were consistent with overall results

## Significantly Reduced Bleeding* with Rivaroxaban 15 mg Strategy Across Subgroups vs VKA plus DAPT

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>0.56</td>
<td>0.41–0.77</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥75 years</td>
<td>0.62</td>
<td>0.42–0.90</td>
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<td>0.011</td>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>0.63</td>
<td>0.47–0.84</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.51</td>
<td>0.32–0.80</td>
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<td>0.003</td>
</tr>
<tr>
<td><strong>Type of stent</strong></td>
<td></td>
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<tr>
<td>Drug-eluting</td>
<td>0.64</td>
<td>0.47–0.86</td>
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<tr>
<td>Bare metal</td>
<td>0.54</td>
<td>0.36–0.82</td>
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<tr>
<td>Both</td>
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<td>0.02–1.82</td>
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<tr>
<td><strong>Type of P2Y₁₂ inhibitor</strong></td>
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<td></td>
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<tr>
<td>Clopidogrel</td>
<td>0.59</td>
<td>0.46–0.76</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Prasugrel</td>
<td>1.16</td>
<td>0.22–6.03</td>
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<tr>
<td>Ticagrelor</td>
<td>0.33</td>
<td>0.11–1.01</td>
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</table>

*Composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention

Significantly Reduced Bleeding* with Rivaroxaban 2.5 mg Strategy Across Subgroups vs VKA plus DAPT

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>0.60</td>
<td>0.45–0.82</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>≥75 years</td>
<td>0.66</td>
<td>0.46–0.96</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.71</td>
<td>0.54–0.93</td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Female</td>
<td>0.47</td>
<td>0.29–0.76</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Intended DAPT duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>0.68</td>
<td>0.38–1.23</td>
<td></td>
<td>0.198</td>
</tr>
<tr>
<td>6 months</td>
<td>0.51</td>
<td>0.34–0.75</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>12 months</td>
<td>0.74</td>
<td>0.52–1.04</td>
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<td>0.081</td>
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<tr>
<td><strong>Type of stent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-eluting</td>
<td>0.76</td>
<td>0.57–1.01</td>
<td></td>
<td>0.057</td>
</tr>
<tr>
<td>Bare metal</td>
<td>0.45</td>
<td>0.29–0.70</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both</td>
<td>0.35</td>
<td>0.06–1.92</td>
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<td>0.207</td>
</tr>
<tr>
<td><strong>Type of P2Y₁₂ inhibitor</strong></td>
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<tr>
<td>Clopidogrel</td>
<td>0.62</td>
<td>0.48–0.79</td>
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<td>&lt;0.001</td>
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<tr>
<td>Prasugrel</td>
<td>0.88</td>
<td>0.16–4.81</td>
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<td>0.881</td>
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<tr>
<td>Ticagrelor</td>
<td>0.59</td>
<td>0.23–1.53</td>
<td></td>
<td>0.273</td>
</tr>
</tbody>
</table>

*Composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention


No significant p-value for interaction
Efficacy was Comparable Between All Three Treatment Strategies*

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); p=0.750
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); p=0.765

All subgroups analyzed were consistent with overall results

*Trial not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints

Time to All Cause Death or First Rehospitalization is Reduced in Both Rivaroxaban Treatment Arms

Gibson CM et al, Circulation 2016; doi:10.1161/CIRCULATIONAHA.116.025783
Summary

◆ A strategy of either rivaroxaban plus a P2Y$_{12}$ was associated with a reduction in clinically significant bleeding compared with conventional triple therapy of warfarin + DAPT (NNT = 11 or 12).

◆ CV death / MI / stroke were comparable among the groups.

◆ Rates of all cause death or hospitalization were reduced in the rivaroxaban arms (NNT = 10-15).
Clinical Implications of PIONEER AF-PCI Trial

In Patients with Atrial Fib who undergo PCI;

- Drop the ASA in all patients except for those with highest coronary ischemic risk.
- Maintain the patient on rivaroxaban 15 g daily plus clopidogrel or ticagrelor for up to 12 months.
- Subsequently drop the clopidogrel or ticagrelor and increase the rivaroxaban to 20mg daily (or one of other NOACS at recommended dose)
Management of Atrial Fib Patients with CAD

- Its going to be impossible to create a universal rule to apply to the wide spectrum of patients with CAD and atrial fibrillation.

Need to consider;

1. **Coronary ischemic risk** – chronic CAD vs NSTEMI vs STEMI, extent of CAD, number of stents, other technical interventional factors

2. **Stroke risk** – CHADS2 score

3. **Bleeding risk**

- There is not going to be a simple risk score to integrate all these continuous variables; we will have guiding principles.

- We will need to work as a team to determine the optimal combination of anticoagulant and anti-platelet agents for the individual patient and reassess the plan over time.
64 yo man with Hx of colonic angiodysplasia requiring prior blood transfusions.

Presents with unstable angina. Undergoes 3.5 x 18mm BMS PCI of 95% RCA stenosis. No significant disease elsewhere.

What antiplatelet therapy do you recommend?

How long do you maintain antiplatelet therapy?
What is in the future of patient management with DAPT?

GLOBAL LEADERS

Ticagrelor vs Standard Dual Antiplatelet Therapy

Randomized, open-label study
Estimated enrollment: 16,000

Inclusion Criteria:
- All-comers Undergoing PCI

Ticagrelor + Aspirin x 1 mo
Then Ticagrelor x 23 mo

Standard DAPT (Ticagrelor/Clopidogrel + Aspirin) x 12 mo
Then Aspirin indefinitely

Primary composite outcome: all-cause mortality or non-fatal new Q-wave MI up to 2 years post randomization
Secondary composite outcome: investigator-reported BARC3 or BARC5 bleeding up to 2 years post randomization

Clinicaltrials.gov.[20]
What is in the future of patient management with DAPT?

**TWILIGHT**

*Ticagrelor +/- Aspirin in High-Risk Patients After Coronary Intervention*

- **Randomized, double-blind, phase 4 study**
- **Enrollment:** Up to 9000 patients at the time of their index PCI
- **Duration:** Additional 12 months after ≥ 3 months DAPT

**Inclusion Criteria:**
- Adults ≥ 18 years of age
- High-risk patients after successful elective/urgent PCI with ≥ 1 DES; discharged on DAPT with aspirin and ticagrelor of ≥ 3 months intended duration

**Outcomes:**
- **Primary outcome:** time to first occurrence of clinically relevant bleeding (BARC Type 2, 3, or 5)
- **Secondary outcome:** time to first occurrence of confirmed CV death, non-fatal MI, ischemic stroke or ischemia-driven revascularization

*Clinicaltrials.gov*[19]
Take Home Points

1. The duration of DAPT therapy recommended by prior guidelines is based largely on the duration of RCT’s such as CURE and CREDO which were set for non-clinical reasons.

2. The standardized duration of DAPT recommended by guidelines ignores the large individual patient variability in ischemic benefit and bleeding risk.

3. Recent trials indicate a significant ischemic benefit of DAPT beyond a year at a modest cost of increased minor/moderate bleeding.

4. A personalized strategy is required to determine the optimal duration of DAPT. This requires a “heart team” approach involving the patient, PCP, cardiologist and others (e.g. GI, surgery).
5. Essentially all PCI and ACS patients will need a “mandatory” period of DAPT to prevent stent thrombosis and the very high likelihood of ischemic events. This period is likely 1-3 months in patients at very high risk of bleeding to 12 months in patients at low bleeding risk.

6. The duration of continued DAPT after this “mandatory” period has to be personalized and continuously reassessed dependent on patient and procedural parameters.

7. For patients with both atrial fibrillation and ACS a strategy of rivaroxaban 15mg/d plus clopidogrel or ticagrelor is safer that conventional triple therapy.

8. Ongoing trials will determine whether we can drop ASA from DAPT in order to limit bleeding risk while maintaining ischemic benefit.