Incidence and Impact of Dual Antiplatelet Therapy (DAPT) Cessation on Adverse Events following Percutaneous Coronary Intervention (PCI):

Results from the Real-World PARIS Registry

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on behalf of PARIS Investigators
Conflict of Interest:

- Institutional Grant/Research Support:
  - Bristol-Myers Squibb/ Sanofi
  - Lilly/ DSI
  - The Medicines Company
  - BG Medicine

- Consulting Fees/Honoraria
  - Sanofi
  - Abbott Vascular
  - Astra Zeneca
  - Merck
  - Regado Biosciences
  - Janssen (J+J)
  - BSC
  - Covidien
  - CSL Behring
Background and Rationale

• Antiplatelet agents are the cornerstone of therapy in patients with ACS and in those undergoing PCI

• Current ACC/AHA guidelines\(^1\) recommend 30 days DAPT following placement of a BMS and 1 year following placement of a DES.

• In patients with ACS 12 months of DAPT is recommended regardless of stent type

DAPT Cessation and PCI: Existing Evidence

• Premature cessation of DAPT, within the first 6 months after PCI, has been associated with an increased risk of stent thrombosis.\textsuperscript{1}

• Sustained DAPT (one year or longer) has been associated with lower risk for adverse events in observational studies.\textsuperscript{2,3}

• Most studies involved select cohorts and limited by pre-specified or standard criteria to define DAPT status

\textsuperscript{1}Schulz et al., EHJ 2009; \textsuperscript{2}Ho et al., AHJ 2007; \textsuperscript{3}Park et al., AJ C 2006
DAPT Cessation and PCI: Unresolved Questions

• Does risk after DAPT cessation depend on the underlying context or clinical circumstances in which antiplatelet therapy is stopped (surgery vs. bleeding vs. physician-guidance)?

• How long does risk persist after antiplatelet therapy is withdrawn?

• What is the overall contribution of DAPT cessation on adverse events in the contemporary PCI era?
Study Design

• Multicenter, multinational, observational study

• 5,031 subjects were followed for approximately 24 months post stent implantation

• Included bare metal and drug-eluting stents

• All events, including all occurrences of DAPT cessation, were adjudicated by a blinded external clinical events committee
Modes of DAPT Cessation

- **Discontinuation**
  - patients had discontinued DAPT as per recommendation of their physician who felt the patient no longer needed therapy

- **Interruption**
  - patients had interrupted DAPT use on a voluntary basis and as guided by a physician due to (e.g. surgery)
  - DAPT was then reinstituted within 14 days

- **Disruption**
  - patients had disrupted DAPT use due to bleeding or non-compliance.
5,031 Patients with successful PCI with stenting enrolled at 15 sites in the US and Europe

Final Study Population – 5018 Patients

13 Patients excluded from analysis (1 died prior to discharge and 12 not discharged on DAPT)

Lost to follow-up (n=340)

Within 30 days Available Follow-up: 4972/5018 (99.1%)

Lost to follow-up (n=133)

Within 365 days Available Follow-up: 4885/5018 (97.3%)

Lost to follow-up (n=340)

Within 2 years Available Follow-up: 4678/5018 (93.2%)
2-Year Kaplan-Meier Plot of Any DAPT Cessation

Cumulative Incidence, %

Time From PCI, Months

30 Days (2.9%)

One Year (23.3%)

Two Years (57.3%)

Incidence rates calculated over entire study population. Patients censored at last known contact, death or study end.
2-Year Kaplan-Meier Plots of Any Discontinuation, Interruption and Disruption

Cumulative Incidence, %

- Discontinuation
- Disruption
- Interruption

Time From PCI, Months

Incidence rates calculated over entire study population. Patients censored at last known contact, death or study end.
Overall Event Rates Over 2 Years

Cumulative Incidence, %

- **MACE**: 11.6%, 7.4%, 0.5%
- **Spontaneous MI**: 7.4%, 3.8%, 0.5%
- **Stent Thrombosis (def/prob)**: 3.8%, 1.2%, 1.5%
- **Clinically indicated TLR**: 3.8%, 1.2%, 1.5%
- **Cardiac Death**: 3.8%, 1.2%, 1.5%

Incidence calculated as cumulative incidence from a Kaplan-Meier estimate of the time to the first occurrence of the adverse event.
Impact of DAPT Cessation on Adverse Events
**DAPT Cessation and MACE***

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

*Cardiac Death, Def/Prob ST, Spontaneous MI, Clinically Driven TLR.
All Cox Models adjusted for age, gender, region, ACS presentation, type of stent, number of stents implanted.
DAPT Cessation and Cardiac Death, Def/Prob ST, Spontaneous MI

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-DAPT</td>
<td>1.00 (Ref)</td>
<td></td>
<td>218</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>0.76 (0.50, 1.14)</td>
<td>0.181</td>
<td>31</td>
</tr>
<tr>
<td>Interruption</td>
<td>1.05 (0.58, 1.92)</td>
<td>0.864</td>
<td>12</td>
</tr>
<tr>
<td>Disruption</td>
<td>2.06 (1.49, 2.83)</td>
<td>&lt;0.001</td>
<td>54</td>
</tr>
<tr>
<td>0-7 Days</td>
<td>9.82 (4.57, 21.12)</td>
<td>&lt;0.001</td>
<td>7</td>
</tr>
<tr>
<td>8-30 days</td>
<td>2.96 (1.21, 7.24)</td>
<td>0.017</td>
<td>5</td>
</tr>
<tr>
<td>31+ days</td>
<td>1.71 (1.20, 2.44)</td>
<td>0.003</td>
<td>42</td>
</tr>
</tbody>
</table>

All Cox Models adjusted for age, gender, region, ACS presentation, type of stent, number of stents implanted.
# DAPT Cessation and Spontaneous MI

All Cox Models adjusted for age, gender, region, ACS presentation, type of stent, number of stents implanted.

<table>
<thead>
<tr>
<th>Discontinuation Mode</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-DAPT</td>
<td>1.00 (Ref)</td>
<td></td>
<td>116</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>0.92 (0.53, 1.58)</td>
<td>0.748</td>
<td>18</td>
</tr>
<tr>
<td>Interruption</td>
<td>1.20 (0.55, 2.63)</td>
<td>0.647</td>
<td>7</td>
</tr>
<tr>
<td>Disruption</td>
<td>2.95 (1.99, 4.38)</td>
<td>&lt;0.001</td>
<td>39</td>
</tr>
<tr>
<td>0-7 Days</td>
<td>18.25 (8.34, 39.95)</td>
<td>&lt;0.001</td>
<td>7</td>
</tr>
<tr>
<td>8-30 days</td>
<td>4.69 (1.71, 12.83)</td>
<td>0.003</td>
<td>4</td>
</tr>
<tr>
<td>31+ days</td>
<td>2.22 (1.42, 3.46)</td>
<td>&lt;0.001</td>
<td>28</td>
</tr>
</tbody>
</table>
DAPT Cessation and Def/Prob Stent Thrombosis

<table>
<thead>
<tr>
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<th>HR (95% CI)</th>
<th>P</th>
<th>Events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-DAPT</td>
<td>1.00 (Ref)</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>0.39 (0.11, 1.35)</td>
<td>0.137</td>
<td>3</td>
</tr>
<tr>
<td>Interruption</td>
<td>0.64 (0.09, 4.82)</td>
<td>0.664</td>
<td>1</td>
</tr>
<tr>
<td>Disruption</td>
<td>2.58 (1.22, 5.46)</td>
<td>0.013</td>
<td>10</td>
</tr>
<tr>
<td>0-7 Days</td>
<td>15.94 (5.57, 45.58)</td>
<td>&lt;0.001</td>
<td>4</td>
</tr>
<tr>
<td>8-30 days</td>
<td>2.68 (0.36, 19.68)</td>
<td>0.334</td>
<td>1</td>
</tr>
<tr>
<td>31+ days</td>
<td>1.35 (0.50, 3.64)</td>
<td>0.551</td>
<td>5</td>
</tr>
</tbody>
</table>

Hazard Ratio

All Cox Models adjusted for age, gender, region, ACS presentation, type of stent, number of stents implanted.
### DAPT Cessation and Cardiac Death

All Cox Models adjusted for age, gender, region, ACS presentation, type of stent, number of stents implanted.

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Events (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On-DAPT</strong></td>
<td>1.00 (Ref)</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td><strong>Discontinuation</strong></td>
<td>0.64 (0.36, 1.16)</td>
<td>0.141</td>
<td>15</td>
</tr>
<tr>
<td><strong>Interruption</strong></td>
<td>1.06 (0.48, 2.34)</td>
<td>0.885</td>
<td>7</td>
</tr>
<tr>
<td><strong>Disruption</strong></td>
<td>1.68 (1.05, 2.67)</td>
<td>0.029</td>
<td>26</td>
</tr>
</tbody>
</table>

**0-7 Days**
- Hazard Ratio: 5.73 (1.39, 23.62)  
- Events: 2

**8-30 days**
- Hazard Ratio: 3.44 (1.08, 10.98)  
- Events: 3

**31+ days**
- Hazard Ratio: 1.44 (0.87, 2.38)  
- Events: 21
Overall Contribution of DAPT Cessation on Adverse Events
*Out of 71 ST events at 2 years, 57 (80.3%) occurred while patients were ON DAPT. ST defined by the Academic Research Consortium (ARC) Criteria.
Number (%) of Cardiac Death events by DAPT Status*

*Out of 148 Cardiac Death events at 2 years, 100 (67.6%) occurred while patients were ON DAPT. Cardiac Death defined using ARC criteria.

*Recommended Discontinuation Interruption Disruption*
Conclusions

• The impact of DAPT cessation on cardiac risk after PCI is not uniform but varies substantially by underlying mode, a novel finding with important implications for future study design and clinical practice.

• Relative risk for MACE due to disruption is substantial, albeit short-lived, compared to those on DAPT.

• The overall impact of DAPT cessation on adverse events is modest and may have been mitigated with the introduction of safer stent platforms.

• Findings highlight the need for uniform approaches in classifying DAPT cessation, analogous to those currently used for bleeding and MI.
Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study