Identifying the ‘Optimal’ Duration of DAPT
Less is More, More or Less…

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Stent thrombosis, irrespective of timing or stent type, is associated with considerable morbidity and mortality.

- **January 2006, December 2007**
  ACC/AHA/SCAI guidelines consensus-opinion based recommendations of 12 months DAPT following DES for pts without apparent contraindications.

- **December 2006**
  FDA Panel concern over annualized ST rates motivate FDA to mandate DES labeling incorporate 12 month DAPT recommendation.

- **December 2007**
  Inter-society Scientific Advisory reiterates 12 month guidelines.
‘Optimal’ DAPT Duration and DES Revascularization
A Less than ‘Optimal’ Evidence Basis

RCT and RCT substudies (CREDO, PCI-CURE)
- Pharma trials evaluating pretreatment and dosing strategies
- Follow-up limited to ≤12 months
- Majority of treatment effect within initial 30-90 days

Observational studies consistently demonstrate ‘premature’ thienopyridine discontinuation with increased risk of ST

No prospective, (randomized) data associating long-term DAPT with reductions in ST

- Duke Cardiovascular Database, Eisenstein et al. JAMA 2007
- Kaiser Permanente, Brar et al. J Am Coll Cardiol 2008

No estimate of bleeding risk
- CHARISMA Severe bleeding: 1.7% over ~2 year follow-up
- ‘Clopidogrel survivor’ theory reflects selection bias

Consensus opinion: Emotive, intuitive perception that extended DAPT could reduce ST events
Rate of ST in Patients On Dual-Anti-platelet Therapy and in Patients Who Discontinued Thienopyridine Therapy


* Aalen-Nelson estimate of cumulative hazard function

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Discontinued Thienopyridine</th>
<th>On Thienopyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>258  422  560  1,128  1,180  1,680  2,044  2,138  2,251</td>
<td>2,750  2,576  2,411  1,829  1,771  1,245  865  756  634</td>
</tr>
</tbody>
</table>

* Aalen-Nelson estimate of cumulative hazard function
Relationship Between Thienopyridine Discontinuation and ST

Median time from clopidogrel discontinuation and ST:
- ST within first 6 months: 13.5 days (IQR range, 5.2 to 25.7)
- ST after the first 6 months: 90 days (IQR, 30 to 365 days)

Temporal Trends in DAPT Compliance and Incidence of ST while On or Off Thienopyridine Therapy

Is Thienopyridine Discontinuation a Cause or Epiphenomenon?

Japan Cypher
2-Year Relationship Between ST Events and APT, N=10,778

## Japan Cypher

### 6-Month Landmark Analysis Based on Thienopyridine Use

\( N=9,875 \)

<table>
<thead>
<tr>
<th></th>
<th>ON Thienopyridine N=7,427</th>
<th>OFF Thienopyridine, N=2,628</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3.4</td>
<td>3.4</td>
<td>0.90</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.6</td>
<td>0.8</td>
<td>0.42</td>
</tr>
<tr>
<td>Death/ Myocardial Infarction</td>
<td>4.1</td>
<td>4.1</td>
<td>0.99</td>
</tr>
<tr>
<td>Death, MI or Stroke</td>
<td>4.0</td>
<td>4.1</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Korean Stent Thrombosis Registry
Multicenter Observational Cohort Study

- 7,221 PCI patients (48.3% DES)
- DES associated with significantly higher risk of ST beyond 1 year
- Adjusted risks of D, D/MI and TLR significantly lower with DES
- Despite increased risk of VLST with DES, thienopyridine continuation beyond 1 year not associated with reduced risk of D, D/MI or ST

Korean Stent Thrombosis Registry
Multicenter Observational Cohort Study

Aalen-Nelson Estimate Curves of Cumulative Hazard Function for Definite ST
ISAR
Relationship Between DAPT and ST over 4 year Follow-up, N=6,816

Cumulative incidence of stent thrombosis (%)

Patients who discontinued clopidogrel therapy

Patients on clopidogrel therapy

Years after procedure

No. of patients
Discont. clopidogrel 0 1,277 3,934 2,539 1,373
On clopidogrel 6,816 5,181 1,074 398 116

ISAR

Relationship Between DAPT and ST over 4 year Follow-up, N=6,816

Dutch Stent Thrombosis Registry
Independent Risk Factors for ST, N=21,009

ENDEAVOR IV
ARC Definite/Probable VLST Δ1-2 years

[[Graph showing cumulative incidence of Def/Prob Thrombosis (ARC) over time.]]

Taxus, 6 events: 4 DAPT, 2 ASA only
Endeavor, 1 event: No ASA or thienopyridine

P values were calculated by log rank test

Leon et al. TCT 2008
What is the ‘optimal’ duration of DAPT? What is ‘premature’ discontinuation?

Is the ‘optimal’ duration same for all DES?

What are the consequences of brief DAPT interruption?

Is there a rebound phenomenon with thienopyridine discontinuation?

Will there be differences between different APT agents in real world practice?

Is there a role for platelet and/or genomic testing to individualize therapy?
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Group, N</th>
<th>DAPT Duration</th>
<th>DES Type</th>
<th>1° Endpoint</th>
<th>2° Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPT</td>
<td>20,645 12-month event free</td>
<td>12 vs 30 months</td>
<td>All DES</td>
<td>1. D/MI/Stroke at 33 mos</td>
<td>GUSTO Bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Def/prob ST at 33 mos</td>
<td></td>
</tr>
<tr>
<td>ISAR-SAFE</td>
<td>6,000 6-month event free</td>
<td>6 vs 12 months</td>
<td>All DES</td>
<td>D/MI/Stroke/TIMI major bleed at 15 mos</td>
<td>Individual component endpoints</td>
</tr>
<tr>
<td>REAL-LATE</td>
<td>2,000 12-month event free</td>
<td>12 vs 24 months</td>
<td>All DES</td>
<td>2-yr Cardiac D/MI</td>
<td>ARC ST, Bleeding</td>
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<tr>
<td>ZEST-LATE</td>
<td>2,000 12-month event free</td>
<td>12 vs 24 months</td>
<td>SES, PES, ZES</td>
<td>2-yr D/MI</td>
<td>ARC ST, Bleeding</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>3,120 non-STEMI</td>
<td>3 vs. 12 months</td>
<td>Endeavor ZES</td>
<td>1-yr D/MI/Stroke/TIMI major bleed</td>
<td>ARC ST</td>
</tr>
<tr>
<td>SEASIDE</td>
<td>900 non-ACS</td>
<td>6 months</td>
<td>Endeavor ZES</td>
<td>1-yr D/MI/Stroke</td>
<td>GUSTO Bleeding</td>
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<td>CYP2C19</td>
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Finding the ‘Optimal’ DAPT Duration

Summary

Given that ST is uniformly associated with MI and ~30% mortality, any measure that may reduce events is clinically meaningful but must be proven and without excessive risk!

• Role of DAPT in reducing early ST is firmly established

• Issue is not that thienopyridine should be discontinued for all pts at a predetermined timepoint but whether it is safe to discontinue (ST risk) and if there is acceptable benefit to maintain (D, MI, stroke)

• While extended DAPT may decrease late death or MI proportionate to risk, the benefit is most likely associated with reduction of events independent of stent territory

Available evidence consistently demonstrates that in all-comer, broad PCI populations, extended DAPT (eg, >6-12 months) does not reduce ST risk
Finding the ‘Optimal’ DAPT Duration

Summary

Studies are underway to identify the ‘optimal’ DAPT duration, but must consider:

- Variability in DAPT durations studied
- Potential differences in DES, thienopyridine therapy, individual patients
- Bleeding risk
- Intention to treat vs as treated, “clear” patients vs. those with events