Optimal Duration and of Dual Antiplatelet Therapy after PCI

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Department of Internal Medicine,
Cardiovascular Center,
Seoul National University Hospital
1. Optimal Duration of DAPT

2. Optimal Combination of antiplatelet agents
How long do you maintain DAPT? (for patients receiving DES)

1. 6 months
2. 12 months
3. More than 12 months but not forever
4. Forever
5. Differs according to thrombosis risk
Should the default duration of DAPT be the same for 1\textsuperscript{st} vs 2\textsuperscript{nd} generation DES?

1. Yes

2. No
Background

1. DAPT is the backbone of medical therapy post-PCI.

2. Guidelines recommend the use of at least 12 months of DAPT for patients receiving DES.

3. Even longer use is common practice in the ‘real world’.
Questions raised

1. Are the guidelines based on robust randomized trial data?

2. Is the optimal duration of DAPT the same for all patients receiving DES (Does one size fit all)

3. What is the potential benefit of prolonged use of DAPT? Reduction in ST or reduction of global vascular risk

4. Does prolonged DAPT result in a risk reduction of very late ST large enough to negate the bleeding issue and economic costs of prolonged treatment?
The duration of P2Y12 inhibitor therapy after stent implantation should generally be as follows:

In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y12 inhibitor therapy should be given for at least 12 months.

In patients receiving a DES for a non–ACS indication, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding.

In patients receiving a BMS for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months.
If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of P2Y12 inhibitor therapy after stent implantation, earlier discontinuation (e.g., <12 months) of P2Y12 inhibitor therapy is reasonable.
Continuation of clopidogrel therapy beyond 1 year may be considered in patients undergoing DES placement.

(New Recommendation)
In patients receiving a stent (BMS or DES) during PCI for ACS, **clopidogrel 75 mg daily (B)** or prasugrel 10 mg daily (B) should be given for at least 12 months.

Continuation of **clopidogrel** or prasugrel beyond 15 months may be considered in patients undergoing DES placement (C).
Issues To Be Covered

1. Prolonged use of DAPT
   a. Data that don’t support prolonged DAPT
   b. Data that support prolonged DAPT

2. Same story for newer generation DES?

3. Which trials in the future could possibly give us the answers?
Issues To Be Covered

1. Prolonged use of DAPT
   a. Data that don’t support prolonged DAPT
   b. Data that support prolonged DAPT

2. Same story for newer generation DES?

3. Which trials in the future could possibly give us the answers?
Discontinuation of Thienopyridine and Risk of Stent Thrombosis: Milan-Siegburg Cohort Study

3,021 patients with 5,389 lesions treated with DES (2002-2004)

HR=13.7 4.0-47 P<0.001
HR=0.94 0.30-3.0 P=0.92

Patients on double antiplatelet therapy %

Thrombosis rate %

Event rates

No. of Patients
Discontinued thienopyridine 258 422 560 1128 1180 1680 2044 2138 2251
On thienopyridine 2750 2576 2411 1829 1771 1245 865 756 634
Discontinuation of Thienopyridine and Risk of Stent Thrombosis With Sirolimus-Eluting Stents


Landmark Analysis on Thienopyridine Use Beyond 6 Months

**A** Unadjusted

**B** Adjusted

**Death or Myocardial Infarction**

- On thienopyridine
- Off thienopyridine

- Log-rank p value 0.26
- p value 0.99
Discontinuation of Antiplatelet Therapy and Risk of Stent Thrombosis With DES

Eisenberg et al. *Circulation* 2009

161 cases of late/very late stent thrombosis
**Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stents**

: Park SJ et al. NEJM 2010

**REAL-LATE**

N=1,625
Broader population of patients who had received any DES

**ZEST-LATE**

N=1,357
Patients who had participated in ZEST trial

N=2,701
Patients who were free of MACCE with dual antiplatelet therapy for at least a 12 month after DES implantation

N=1,357
Clopidogrel + Aspirin

N=1,344
Aspirin Alone

From July 2007 through September 2008

Clinical follow-up every 6 months
Composite of MI or Death from cardiac causes

From July 2007 through September 2008

Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stents

: Park SJ et al. NEJM 2010
Primary End Point:
Cardiac Death or Myocardial Infarction

![Graph showing cumulative incidence of cardiac death or myocardial infarction over days after randomization.]

Log-rank, $P=0.17$

<table>
<thead>
<tr>
<th></th>
<th>Continuation group</th>
<th>Discontinuation group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin Alone</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Clopidogrel + Aspirin</td>
<td>1.2</td>
<td>1.8</td>
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No. at Risk

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<tr>
<th></th>
<th>1357</th>
<th>1344</th>
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<tbody>
<tr>
<td>Continuation group</td>
<td>1122</td>
<td>299</td>
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<tr>
<td>Discontinuation group</td>
<td>1100</td>
<td>301</td>
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</table>
Death, Myocardial Infarction, or Stroke

<table>
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<th>Discontinuation group</th>
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</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>1357</td>
<td>1344</td>
</tr>
<tr>
<td>Continuation</td>
<td>1119</td>
<td>1097</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>295</td>
<td>300</td>
</tr>
</tbody>
</table>

Log-rank, P=0.048
Definite Stent Thrombosis

Log-rank, P=0.76

For the graph:
- **Clopidogrel + Aspirin**
- **Aspirin Alone**

<table>
<thead>
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<th>No. at Risk</th>
<th>Continuation group</th>
<th>Discontinuation group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>1344</td>
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<td>1124</td>
<td>1102</td>
</tr>
<tr>
<td></td>
<td>301</td>
<td>303</td>
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</table>
Limitations of REAL- & ZEST-LATE

1. Interim analysis of two ongoing, underpowered studies.

2. Observed primary outcome event rate is less than 25% of that anticipated.

3. Higher thrombotic event rate in aspirin+clopidogrel group: not supported by any previous data and not scientifically feasible.

4. Many received cilostazol during the year prior to enrollment.

5. Major statistical assumption: 50% RRR in the DAT group: too generous of an assumption, no prior studies have shown 50% RRR with DAT.


Peter B. Berger. NEJM 2010
Antonio Colombo, Sanjay Kaul, theheart.org
Issues To Be Covered

1. Prolonged use of DAPT
   a. Data that don’t support prolonged DAPT
   b. Data that support prolonged DAPT

2. Same story for newer generation DES?

3. Which trials in the future could possibly give us the answers?
Old Historical Data

1. Long-term DAT appears to reduce adverse events in ACS pts:
   - managed medically (CURE)
   - after balloon angioplasty (PCI-CURE)
   - after BMS (CREDO, RACS, PCI-CURE)

2. Long-term DAT appears to reduce adverse events in post-PCI patients (BMS era)
   - CREDO

3. Long-term DAT appears to reduce adverse events in selected group of stable patients receiving medical therapy
   - CHARISMA vs. ‘CAPRIE like’ CHARISMA
CREDO: Study Design

Plus other standard therapies

* Both groups received clopidogrel 75 mg + ASA 325 mg at time of procedure

**CREDO:**
Long-Term Benefits of Clopidogrel in PCI Patients

**MI, Stroke, or Death – ITT Population**

- **Placebo**: 11.5%
- **Clopidogrel**: 8.5%

Combined Endpoint Occurrence

- **27% RRR**
- **P=0.02**

*Plus ASA and other standard therapies*

‘CAPRIE like’ CHARISMA

in Patients With Previous MI, IS, or PAD*

Primary Endpoint (MI/Stroke/CV Death)

N=9,478

- Placebo + ASA
- Clopidogrel + ASA

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

* Post hoc analysis.

Clopidogrel and long-term outcomes after stent implantation for acute coronary syndrome

P. Michael Ho, MD, PhD, FACC, a,b Stephan D. Fihn, MD, MPH, c,d,e Li Wang, MS, c,d Chris L. Bryson, MD, MS, d,e Elliott Lowy, PhD, c,d,e Charles Maynard, PhD, c,d,e David J. Magid, MD, MPH, b,f Eric D. Peterson, MD, MPH, FACC, g Robert L. Jesse, MD, PhD, FACC, h and John S. Rumsfeld, MD, PhD, FACC a,b Denver and Aurora, CO; Seattle, WA; Durham, NC; and Richmond, VA

Among patients who were event free at 6 months, similar trend as main results

Main results:

All cause mortality HR 2.40, 95% CI 1.61-3.58.

[Consistent among patients receiving BMS (HR 2.65, 95% CI 1.59-4.42) or DES (HR 2.00, 95% CI 1.06-3.75).]
In conclusion, the use of clopidogrel for >1 year after PCI was associated with lower mortality.
# Dutch Stent Thrombosis Registry

**Independent Risk Factors for ST, N=21,009**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel stop &lt;30 days</td>
<td>36.53</td>
<td>[7.96-167.77]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Undersizing</td>
<td>13.39</td>
<td>[5.27-34.04]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clopidogrel stop 180-365 days</td>
<td>5.87</td>
<td>[1.74-19.80]</td>
<td>0.0043</td>
</tr>
<tr>
<td>Clopidogrel stop 30-180 days</td>
<td>4.63</td>
<td>[1.40-15.35]</td>
<td>0.0122</td>
</tr>
<tr>
<td>Malignancy</td>
<td>4.50</td>
<td>[2.14-9.49]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAD &gt;50% proximal of culprit</td>
<td>4.40</td>
<td>[2.71-7.16]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMI flow post-PCI &lt;3</td>
<td>3.77</td>
<td>[2.09-6.80]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dissection</td>
<td>2.88</td>
<td>[1.67-5.00]</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>Bifurcation stenting</td>
<td>2.27</td>
<td>[1.48-3.47]</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>LVEF &lt;30%</td>
<td>2.27</td>
<td>[1.43-3.60]</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>PAD</td>
<td>2.13</td>
<td>[1.01-4.51]</td>
<td>0.0482</td>
</tr>
<tr>
<td>CAD &gt;50% distal of culprit</td>
<td>1.98</td>
<td>[1.32-2.95]</td>
<td>&lt;0.0009</td>
</tr>
<tr>
<td>No ASA</td>
<td>1.91</td>
<td>[1.01-3.88]</td>
<td>0.0487</td>
</tr>
<tr>
<td>any DES</td>
<td>1.88</td>
<td>[1.21-2.94]</td>
<td>0.0052</td>
</tr>
<tr>
<td>DM</td>
<td>0.80</td>
<td>[0.68-0.94]</td>
<td>&lt;0.0007</td>
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Adjusted Cumulative Mortality and MI Rates

Using the 6-Month Landmark Analysis

<table>
<thead>
<tr>
<th></th>
<th>DES w/ Clopidogrel</th>
<th>DES w/o Clopidogrel</th>
<th>BMS w/ Clopidogrel</th>
<th>BMS w/o Clopidogrel</th>
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<tr>
<td>No. at Risk</td>
<td>637</td>
<td>618</td>
<td>579</td>
<td>532</td>
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<tr>
<td>Months</td>
<td>6 12 18 24</td>
<td>6 12 18 24</td>
<td>6 12 18 24</td>
<td>6 12 18 24</td>
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<tr>
<td>Mortality</td>
<td></td>
<td></td>
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<tr>
<td>Cumulative Incidence, %</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Composite of Death or MI</td>
<td></td>
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<td></td>
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</tbody>
</table>

Adjusted Cumulative Mortality and MI Rates

Using the 12-Month Landmark Analysis

Mortality

Cumulative Incidence, %

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>DES w/ Clopidogrel</th>
<th>DES w/o Clopidogrel</th>
<th>BMS w/ Clopidogrel</th>
<th>BMS w/o Clopidogrel</th>
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<tbody>
<tr>
<td></td>
<td>252</td>
<td>237</td>
<td>230</td>
<td>252</td>
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<tr>
<td></td>
<td>276</td>
<td>258</td>
<td>244</td>
<td>276</td>
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<tr>
<td></td>
<td>346</td>
<td>339</td>
<td>331</td>
<td>346</td>
</tr>
<tr>
<td></td>
<td>1644</td>
<td>1627</td>
<td>1596</td>
<td>1644</td>
</tr>
</tbody>
</table>

Months

TYCOON Registry
Clinical outcome up to 4 yrs post-PCI

<table>
<thead>
<tr>
<th>Variable</th>
<th>DES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 mos (n = 173)</td>
</tr>
<tr>
<td></td>
<td>24 mos (n = 274)</td>
</tr>
<tr>
<td>Clinical events</td>
<td></td>
</tr>
<tr>
<td>Cardiac death</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>10 (6%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td></td>
</tr>
<tr>
<td>Acute thrombosis</td>
<td>0</td>
</tr>
<tr>
<td>Subacute thrombosis (1–30 d)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Late thrombosis (1–12 mos)</td>
<td>0%</td>
</tr>
<tr>
<td>Very late thrombosis (&gt;12 mos)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>All thromboses</td>
<td>5 (3%)</td>
</tr>
</tbody>
</table>

Cumulative Survival

P=0.02

Tanzilli G. et al. AJC 2009
Duration of DAT

Longer or shorter than 1 Yr for EVERYBODY??

→ Not reasonable !!!

A Customized approach would be more reasonable.

Then, which patients need extended duration of DAT?
10 centers in Korea
Successful DES implantation
May 2003 ~ May 2007

Cases: 123 ST Pts
(124 ST cases, 128 ST lesions)
definite, possible and probable ST
in Korea Stent Thrombosis registry (KoST)

Controls: 2,192 control pts without ST for at least 6mo
in SNUH DES registry

Park KW, Kim HS et al. Circulation J 2011
Frequency of DES Stent Thrombosis
(From the KoST registry)

Entire treated patients: 14150 pts
ST incidence 0.87% (123/14150)

SES (Cypher™)
0.77%
69 patients developed ST
8933 pts received SES

PES (TAXUS™)
1.04%
54 patients developed ST
5217 pts received PES

Park KW, Kim HS et al. Circulation J 2011
# Independent Predictors of ST

## Both early and delayed ST

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>3.91 (2.66-5.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low EF</td>
<td>3.51 (2.01-6.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent diameter (per 1mm decrease)</td>
<td>2.71 (1.45-5.05)</td>
<td>0.002</td>
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<tr>
<td>DES ISR</td>
<td>4.75 (2.32-9.75)</td>
<td>&lt;0.001</td>
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## Only Early ST

<table>
<thead>
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<th>Predictor</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Bifurcation stenting</td>
<td>2.39 (1.27-4.52)</td>
<td>0.007</td>
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## Only Delayed ST (Late + VL)

<table>
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<th>Predictor</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Younger Age (per decade decrease)</td>
<td>1.8 (1.5-2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension / Anti-HT Med</td>
<td>0.50 (0.27-0.92)</td>
<td>0.025</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2.16 (1.05-6.31)</td>
<td>0.031</td>
</tr>
<tr>
<td>LAD PCI</td>
<td>2.47 (1.36-4.51)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Park KW, Kim HS et al. Circulation J 2011*
Message from the KoST registry

Attention to the overlapped risk factors

- Young AMI Patient with CHF and
- Insufficient Dilatation of
- Small-sized DES in
- Bifurcation Lesion for
- DES ISR lesion

Very High Risk for ST
ACS as Predictor of Stent Thrombosis

- OR=12.4 (1.7-89.7) (Park et al, Am J Card 2006)
- OR=2.3 (1.3-4.0) (Daemen et al, Lancet 2007)
- OR=1.8 (1.1-2.7) (Urban et al, Circulation 2006)
- HR=2.6 (1.3-4.9) (De la Torre et al, JACC 2008)
ACS Patients: Triton TIMI 38

- Prasugrel vs. Clopidogrel


Stent Thrombosis (ARC Definite + Probable)

Any Stent at Index PCI
N= 12,844

---

**Clopidogrel**

- HR 0.48
- P < 0.0001
- NNT= 77

**Prasugrel**

- 2.4 (142)
- 1.1 (68)

Days

Endpoint (%)
Impact of Thrombus Burden on Risk of Stent Thrombosis With DES in Patients With STEMI


Independent Predictors of ST

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>0.6</td>
<td>0.4-0.8</td>
</tr>
<tr>
<td>Index ST</td>
<td>6.2</td>
<td>2.1-18.9</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>4.1</td>
<td>1.6-10.0</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>0.1</td>
<td>0.01-0.8</td>
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<tr>
<td>Large thrombus</td>
<td>8.7</td>
<td>3.4-22.5</td>
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</tbody>
</table>
Overall Mortality in Diabetic Patients

Meta-Analysis of 3,853 Diabetic Patients


Impact of Dual Antiplatelet Therapy Duration

**SES vs. BMS**

- Clopidogrel <6 months
  - HR=2.37 (1.18-5.12)

- Clopidogrel ≥6 months
  - HR=0.89 (0.58-1.40)

P value for interaction = 0.02
Diabetic Patients: Triton TIMI 38

– Prasugrel vs. Clopidogrel


Diabetic Subgroup (N=3,146)

**Endpoint (%)**

- CV Death / MI / Stroke
- TIMI Major
- NonCABG Bleeds

- **Prasugrel**
  - CV Death / MI / Stroke: 12.2 (HR 0.70, P<0.001, NNT = 21)
  - TIMI Major: 2.5
  - NonCABG Bleeds: 2.6

- **Clopidogrel**
  - CV Death / MI / Stroke: 17.0
  - TIMI Major: 2.6
  - NonCABG Bleeds: 2.5

NNT = 21
Long-term outcomes by clopidogrel duration: DM patients

A: Composite of death and myocardial infarction

B: Death

P < 0.001

All Patient Analysis

Brar et al. J Am Coll Cardiol 2008; 51:2220-7
Long-term outcomes by clopidogrel duration:

DM patients - 6-mo Landmark Analysis

Brar et al. J Am Coll Cardiol 2008; 51:2220-7
Issues To Be Covered

1. Prolonged use of DAPT
   a. Data that don’t support prolonged DAPT
   b. Data that support prolonged DAPT

2. Same story for newer generation DES?

3. Which trials in the future could possibly give us the answers?
SNUH Meta-analysis

- Study level meta-analysis
- Clinical studies comparing EES vs. SES
- Regardless of study design; RCT, cohort study
- Search; Pubmed, Cochrane central register of Controlled Trials, Clinicaltrials.org and internet-based sources
- Keywords; everolimus + sirolimus, Xience/Promus + Cypher

Shin DH, Park KW, Kim HS et al. unpublished data
## XienceV vs Cypher

<table>
<thead>
<tr>
<th>Release</th>
<th>Study</th>
<th>Design</th>
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<tbody>
<tr>
<td>TCT 2010</td>
<td>SORT-OUT4</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td>EXCELLENT-RCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ISAR-TEST4</td>
<td></td>
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<tr>
<td></td>
<td>ESSENCE-DM</td>
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<tr>
<td>AHA 2010</td>
<td>BASKET-PROVE</td>
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<tr>
<td>ESC 2011</td>
<td>RESET</td>
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<tr>
<td>ESC 2010</td>
<td>LESSON1</td>
<td>Cohort</td>
</tr>
<tr>
<td>AHA 2008 / JACC 2009</td>
<td>Xsearch</td>
<td>(historical control)</td>
</tr>
<tr>
<td>TCT 2009</td>
<td>Asian registry</td>
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</table>
Meta-analysis of 6 RCTs and 3 registries comparing EES vs SES

From SNUH
Cardiac death

- SORT-OUT4
- EXCELLENT
- ESSENCE-DM
- BASKET-PROVE
- RESET
- LESSON1
- Asian registry

Fixed effect model:
OR 0.94 (0.73~1.23)
p = 0.66

Random effects model:
OR 0.94 (0.72~1.23)
p = 0.67

I² = 0%
P heterogeneity = 0.74

Xience better
Cypher better
Myocardial infarction

- SORT-OUT4
- EXCELLENT
- ESSENCE-DM
- BASKET-PROVE
- RESET
- LESSON1
- Xsearch
- Asian registry

Fixed effect model
OR 0.75 (0.60~0.94)
p=0.013

Random effects model
OR 0.75 (0.57~1.00)
p=0.047

\[ I^2 = 16.2\% \]
\[ P_{\text{heterogeneity}} = 0.30 \]

Xience better
Cypher better
Stent thrombosis

- SORT-OUT4
- EXCELLENT
- ISAR-TEST4
- ESSENCE-DM
- BASKET-PROVE
- RESET
- LESSON1

Fixed effect model
OR 0.71 (0.52~0.98)  \( p=0.036 \)

Random effects model
OR 0.71 (0.52~0.98)  \( p=0.037 \)

\( I^2 = 0\% \)
\( P_{\text{heterogeneity}} = 0.92 \)

Xience better

Cypher better
EES vs. 1st gen DES: ST
(meta-analysis of 11 RCTs: 45% RR reduction)

<table>
<thead>
<tr>
<th>YEAR</th>
<th>STUDY</th>
<th>EES</th>
<th>Control</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>SPIRIT II</td>
<td>2/223</td>
<td>2/77</td>
<td>0.35 (0.05, 2.41)</td>
</tr>
<tr>
<td>2009</td>
<td>SPIRIT III</td>
<td>8/669</td>
<td>5/332</td>
<td>0.79 (0.26, 2.41)</td>
</tr>
<tr>
<td>2010</td>
<td>BASKET-PROVE</td>
<td>5/774</td>
<td>6/775</td>
<td>0.83 (0.26, 2.72)</td>
</tr>
<tr>
<td>2010</td>
<td>COMPARE</td>
<td>8/897</td>
<td>35/903</td>
<td>0.23 (0.11, 0.49)</td>
</tr>
<tr>
<td>2010</td>
<td>ESSENCE DIABETES</td>
<td>1/149</td>
<td>1/151</td>
<td>1.01 (0.06, 16.05)</td>
</tr>
<tr>
<td>2010</td>
<td>EXCELLENT</td>
<td>4/1067</td>
<td>3/361</td>
<td>0.45 (0.10, 2.01)</td>
</tr>
<tr>
<td>2010</td>
<td>ISAR-TEST-4</td>
<td>9/652</td>
<td>12/652</td>
<td>0.75 (0.32, 1.77)</td>
</tr>
<tr>
<td>2010</td>
<td>Resolute All Comers</td>
<td>11/1152</td>
<td>21/1140</td>
<td>0.52 (0.25, 1.07)</td>
</tr>
<tr>
<td>2010</td>
<td>SORT OUT IV</td>
<td>13/1390</td>
<td>12/1384</td>
<td>1.08 (0.49, 2.36)</td>
</tr>
<tr>
<td>2010</td>
<td>SPIRIT IV</td>
<td>10/2458</td>
<td>15/1229</td>
<td>0.33 (0.15, 0.74)</td>
</tr>
<tr>
<td>2011</td>
<td>LONG-DES III</td>
<td>1/224</td>
<td>0/226</td>
<td>3.03 (0.12, 73.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.55 (0.38, 0.78)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Q=12.4, df=10, p=0.26, I²=19.4%
Test for overall effect: Z=3.32, p=0.001

Baber U, Kim HS, Dangas G et al. JACC 2011 in press
Seoul National University Hospital Cardiovascular Center
Risk reduction in ST
(meta-analysis of 11 RCTs)

Baber U, Kim HS, Dangas G et al. JACC 2011

R^2=0.89, p<0.001
EXCELLENT Trial Design

Investigator-initiated, multi-center, open label, prospective randomized trial

Patients Matching Enrollment Criteria

Percutaneous Coronary Intervention

Clinical

Angiographic

Primary clinical endpoint evaluation

Co-primary angiographic endpoint evaluation

1mo 3mo 9mo 12mo 2yr 3yr 4yr 5yr

DAT 6 months
N=722

DAT 12 months
N=721

2x2 factorial design

Stratified by Diabetes Long lesion

EES N=540

SES N=182

EES N=539

SES N=182

www.clinicaltrials.gov (NCT00698607)

Park KW, Kim HS et al. Am Heart J 2009
Park KW, Kim HS et al. J Am Coll Cardiol 2011
Gwon HC, Park KW, Kim HS et al. ACC 2011, LBCT

Seoul National University Hospital Cardiovascular Center
Study Flow

Enrolled and Randomized (n=1,443)

Allocated to 6-mo DAT (n=722)

Follow-up loss within 395 days n=6

Follow-up loss within 395 days n=9

Allocated to 12-mo DAT (n=721)

6-mo DAT with 12-mo FU (n=716)

12-mo DAT with 12-mo FU (n=712)

One-year clinical follow-up rate 99.0%
Target Vessel Failure

P = 0.708
HR = 1.10 (95% CI 0.68-1.79)

Cumulative incidence rate (%) vs Months after initial procedure

<table>
<thead>
<tr>
<th>Patient Number at Risk</th>
<th>6-month</th>
<th>12-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month</td>
<td>722</td>
<td>721</td>
</tr>
<tr>
<td>707</td>
<td>710</td>
<td></td>
</tr>
<tr>
<td>704</td>
<td>703</td>
<td></td>
</tr>
<tr>
<td>698</td>
<td>698</td>
<td></td>
</tr>
<tr>
<td>682</td>
<td>682</td>
<td></td>
</tr>
</tbody>
</table>

Gwon HC, Park KW, Kim HS et al. ACC 2011 LBCT
# Subgroup Analysis for TVF

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>6-mo DAT</th>
<th>12-mo DAT</th>
<th>X² p-value</th>
<th>Cox HR</th>
<th>Cox p-value</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>761</td>
<td>19 (5.0%)</td>
<td>12 (3.2%)</td>
<td>0.202</td>
<td></td>
<td>0.202</td>
<td>0.155</td>
</tr>
<tr>
<td>≥ 65</td>
<td>667</td>
<td>15 (4.5%)</td>
<td>19 (5.7%)</td>
<td>0.465</td>
<td></td>
<td>0.473</td>
<td></td>
</tr>
<tr>
<td><strong>ACS</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>694</td>
<td>21 (6.9%)</td>
<td>14 (4.1%)</td>
<td>0.252</td>
<td></td>
<td>0.243</td>
<td>0.186</td>
</tr>
<tr>
<td>Yes</td>
<td>734</td>
<td>13 (3.6%)</td>
<td>17 (4.6%)</td>
<td>0.474</td>
<td></td>
<td>0.471</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>884</td>
<td>10 (2.2%)</td>
<td>23 (5.3%)</td>
<td>0.018</td>
<td></td>
<td>0.022</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>544</td>
<td>24 (8.8%)</td>
<td>8 (2.9%)</td>
<td>0.003</td>
<td></td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>123</td>
<td>3 (3.0%)</td>
<td>4 (7.1%)</td>
<td>0.286</td>
<td></td>
<td>0.290</td>
<td>0.287</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>1086</td>
<td>26 (4.8%)</td>
<td>25 (4.6%)</td>
<td>0.833</td>
<td></td>
<td>0.808</td>
<td></td>
</tr>
<tr>
<td><strong>Bifurcation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>959</td>
<td>23 (4.7%)</td>
<td>20 (4.3%)</td>
<td>0.769</td>
<td></td>
<td>0.757</td>
<td>0.998</td>
</tr>
<tr>
<td>Yes</td>
<td>469</td>
<td>11 (4.9%)</td>
<td>11 (4.5%)</td>
<td>0.830</td>
<td></td>
<td>0.830</td>
<td></td>
</tr>
<tr>
<td><strong>Stent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EES</td>
<td>1067</td>
<td>25 (4.7%)</td>
<td>27 (5.1%)</td>
<td>0.739</td>
<td></td>
<td>0.764</td>
<td>0.168</td>
</tr>
<tr>
<td>SES</td>
<td>361</td>
<td>9 (5.0%)</td>
<td>4 (2.2%)</td>
<td>0.149</td>
<td></td>
<td>0.168</td>
<td></td>
</tr>
<tr>
<td><strong>Multi-stent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>854</td>
<td>14 (3.2%)</td>
<td>12 (2.9%)</td>
<td>0.819</td>
<td></td>
<td>0.816</td>
<td>0.871</td>
</tr>
<tr>
<td>Yes</td>
<td>563</td>
<td>20 (7.5%)</td>
<td>19 (6.4%)</td>
<td>0.601</td>
<td></td>
<td>0.585</td>
<td></td>
</tr>
</tbody>
</table>

*ACS = unstable angina, NSTEMI, or STEMI

Gwon HC, Park KW, Kim HS et al. ACC 2011 LBCT
PRODIGY

6 vs 24m DAPT after DES or BMS

2,013 Patients
randomly allocated to receive one of the four study stent types

499 randomized to and received EES
498 randomized to and received PES
500 randomized to and received ZES
502 randomized to and received BMS

(1497 DES)

1,970 DES and BMS randomized at 30 days

983 6 Months DAPT

984 2 year follow-up

987 24 Months DAPT

979 2 year follow-up

Valgimigli ESC 2011.
Primary Endpoint

Overall Death, MI or CVA

CEC adjudicated

Hazard Ratio: 0.98 (0.74-1.29)

P=0.91

No. at Risk
24-Month Clopidogrel 987
6-Month Clopidogrel 983

Valgimigli ESC 2011.
Type II, III or V BARC bleeding

CEC adjudicated

Hazard Ratio: 0.46 (0.1-0.69)

P=0.00018

No. at Risk
24-Month Clopidogrel 987
6-Month Clopidogrel 983

Valgimigli ESC 2011.
Let’s Summarize up to now

1. All studies are underpowered.

2. All studies are confounded and biased and have statistical limitations

3. Only one RCT data
   : interim data analysis from a unplanned pooled analysis of two unfinished studies.

→ **inconclusive & causing confusion!!**
Issues To Be Covered

1. Prolonged use of DAPT
   a. Data that don’t support prolonged DAPT
   b. Data that support prolonged DAPT

2. Same story for newer generation DES?

3. Which trials in the future could possibly give us the answers?
## Randomized Antiplatelet Rx Duration Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Group, N</th>
<th>DAPT Duration</th>
<th>DES Type</th>
<th>1&lt;sup&gt;o&lt;/sup&gt; Endpoint</th>
<th>2&lt;sup&gt;o&lt;/sup&gt; Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>REAL+ZEST LATE</td>
<td>2701 12-month event free</td>
<td>~12 vs 24</td>
<td>All DES</td>
<td>2-year cardiac death/MI</td>
<td>Presented ACC 2010</td>
</tr>
<tr>
<td>EXCELLENT</td>
<td>1443 Non-STEMI</td>
<td>6 vs 12</td>
<td>SES or EES</td>
<td>1-year cardiac death/MI/TVR</td>
<td>Presented ACC 2011</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>1357 12-month event free</td>
<td>6 vs 24</td>
<td>DES and BMS</td>
<td>2-year death/MI</td>
<td>Presented ESC 2011</td>
</tr>
<tr>
<td>ITALIC</td>
<td>3200</td>
<td>6 vs 12</td>
<td>EES</td>
<td>1-year death/MI/revasc/stroke</td>
<td>Enrolling</td>
</tr>
<tr>
<td>ISAR-SAFE</td>
<td>6000 6-month event free</td>
<td>6 vs 12</td>
<td>All DES</td>
<td>Death/MI/stroke/TIMI major bleed at 15 months</td>
<td>Enrolling</td>
</tr>
<tr>
<td>OPTIMIZE</td>
<td>3120 non-STEMI</td>
<td>3 vs 12</td>
<td>ZES</td>
<td>1-year death/MI/stroke/bleed</td>
<td>Enrolling</td>
</tr>
<tr>
<td>DAPT</td>
<td>20,645 12-month event free</td>
<td>12 vs 30</td>
<td>1.DES</td>
<td>1. Death/MI/stroke at 33 months</td>
<td>Enrollment Complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.BMS</td>
<td>2. Def/prob ST at 33 months</td>
<td></td>
</tr>
</tbody>
</table>

PES = paclitaxel-eluting stent  
ZES = zotarolimus-eluting stent  
SES = sirolimus-eluting stent  
EES = everolimus-eluting stent

Presented ACC 2010  
Presented ACC 2011  
Presented ESC 2011  
Enrolling  
Enrollment Complete
Optimal Duration of Clopidogrel Therapy

**ISAR-SAFE**
A double-blind, placebo-controlled RCT

6000 DES Patients

- 6-month therapy
- 12-month therapy

Primary end point at 15 months
A composite of death, MI, stent thrombosis, stroke, major bleeding
Dual Antiplatelet Therapy (DAPT) Study

12 mos. 18 mos.

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

All patients on aspirin + open-label thienopyridine therapy for 12 months

1:1 Randomization at month 12

50% of patients continue on Dual Antiplatelet Therapy

50% of patients receive aspirin + placebo

DES n = 15,245
BMS n = 5,400

1:1 Randomization at month 12
Optimal duration of DAPT?

1. No study has adequately assessed prospectively whether long term DAPT would be clinically better than short term DAPT.

2. Several on-going studies will try to address this issue.

3. Until we have more evidence, it is too premature to say that 1 year of DAPT is enough, or less or greater than 1yr is ok for all patients post-PCI.

4. A ‘One size fits all’ strategy does not seem wise. Customized approach would be ideal!

   long-term DAPT: targeting high risk patient with previous ST, AMI, poor LV fxn, small vessel stenting, DM, CRF, and Bifurcation multi-stenting.
HOST-Duration: Trial Design

Prospective, open label, randomized multi-center trial

8500 Non-AMI Patients Receiving Single Type of 2nd generation DES

100 centers from Korea, China, Japan

6mo DAPT
N=4250

12mo DAPT
N=4250

Randomization
1:1

1mo 6mo 12mo 15mo 2yr 3yr

Clinical

Primary Endpoint
Net clinical outcome

Composite of
Any death, MI, Def/Prob ST, stroke, PLATO major bleeding
From 6mo-15months
Conclusions and Take Home Message

1. The optimal duration of DAPT may vary from patient to patient. The ‘One size fits all’ approach may not be appropriate.

2. The body of evidence is adding up suggesting that 2\textsuperscript{nd} gen DES may be safer than 1\textsuperscript{st} gen DES. → May need a dedicated trial to test a shorter duration of DAPT in pts receiving 2\textsuperscript{nd} gen DES
Thank you for your attention!!