Stent Thrombosis
Importance of
Pharmacotherapy

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Presenter Disclosure Information

**Speaker Honoraria:**
Sanofi-Aventis, BMS

**Discuss Off-Label Uses:** Yes
History of Stent Thrombosis

STARS Trial

Clinical Events @ 30 days
(Death, MI, Revasc, Angio-thrombus)

- ASA: 3.6%
- ASA + Warfarin: 2.7%
- ASA + Ticlopidine: 0.5%

p = 0.001

Leon et al. NEJM;339:1665, 1998
AMI <12 hours, any age, cardiogenic shock excluded
n=2,681 at 76 centers in N.A., S.A. and Europe

**Registry (n=599)**
- PTCA - 127 (5%)
- Stent - 142 (5%)
- CABG - 140 (5%)
- Med Rx - 190 (7%)

**Randomized:**
- 89% of all PCI
- 94% of all stent

Angiography

? met angiographic criteria

Yes → n=2,082 (78%)

Randomize

- Primary PTCA (n=518)
- Primary PTCA + Abciximab (n=528)
- MultiLink stent (n=512)
- MultiLink stent + Abciximab (n=524)
**CADILLAC: Subacute Thrombosis**

- **30 days -**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Event Rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCA</td>
<td>1.9%</td>
<td>P=0.05</td>
</tr>
<tr>
<td>PTCA + Abciximab</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>Stent</td>
<td>1.0%</td>
<td>P=0.03</td>
</tr>
<tr>
<td>Stent + Abciximab</td>
<td>0.0%</td>
<td></td>
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*Kaplan Meier estimates*
The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS)

Patients after successful stent placement
n = 1020

1º Endpoint: Major peripheral or bleeding complications, neutropenia, thrombopenia, or early discontinuation of study drug

- Clopidogrel 300/75 mg
  + ASA 325 mg
  (n = 345)

- Clopidogrel 75 mg
  + ASA 325 mg
  (n = 335)

- Ticlopidine 250 mg BID
  + ASA 325 mg
  (n = 340)

**CLASSICS**

Occurrence of Primary Endpoint*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Occurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticlopidine 250 mg BID</td>
<td>9.1</td>
</tr>
<tr>
<td>Clopidogrel 75 mg</td>
<td>6.3</td>
</tr>
<tr>
<td>Clopidogrel 300/75 mg</td>
<td>2.9</td>
</tr>
<tr>
<td>Clopidogrel Total</td>
<td>4.6</td>
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</tbody>
</table>

*p = 0.005

*p = 0.001

*p = NS

*Due to early discontinuance of drug because of skin disorder, GI disorder or allergy

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Bertrand et al. Circ;102:624, 2000
PCI-CURE (ACS pts) Study Design

N = 2,658 patients undergoing PCI

N = 1345

N = 1313

Pretreatment

Open-label thienopyridine

30 days post PCI

End of follow-up
Up to 12 months after randomization

CURE

PCI-CURE

PLACEBO + ASA *

CLOPIDOGREL + ASA *

R


* In addition to other standard therapies.
Overall Long-term Results

Composite of MI or cardiovascular death from randomization to end of follow-up

* In addition to other standard therapies.

**CREDO Study Design**

**Clopidogrel for the Reduction of Events During Observation**

*Planned or likely PCI (N=2,116)*

- Clopidogrel 300 mg and 325 mg ASA
- Placebo and 325 mg ASA

*Time of procedure to day 28**

- Clopidogrel 75 mg and 325 mg ASA daily
- Placebo and ASA 81-325 mg daily

**Day 28 to One Year**

- Clopidogrel 75 mg ASA 81-325 mg daily

**Study Chairman:** Eric J. Topol, MD  
**Principal Investigator:** Steven R. Steinhubl, MD
1 Year Primary Outcome

ASA+ Placebo
N=1063
11.5%

ASA+ Clopidogrel
N=1053
8.5%

27% RRR

p = 0.02
BMS era

- Profound decrease of SAT with combination antiplatelet therapy
- Clopidogrel safer than Ticlopidine
- Long-term benefit of dual Rx established post-ACS and post non-urgent stent implantation
  - “Long-term” studies were at a 6-12 month horizon
  - Beyond 1-year benefit unclear
    - Negative approach – Do not use because it was not studied
    - Positive approach – Go ahead because the event curves keep diverging
Safety of Long-Term Clopidogrel

3 Placebo Controlled Trials

- **CURE**
  - N=12,563
  - 1 year FU
  - CURE major bleed
    - NEJM 2001;345;494-502

- **CREDO**
  - N=2,116
  - 1 year FU
  - TIMI major bleed
    - JAMA 2002;288:2411-20

- **CHARISMA**
  - N=15,603
  - 2.5 year FU
  - GUSTO major
    - NEJM 2006;354:1706-17

**Significant bleeding (%)**

- **CURE**
  - ASA + Clopidogrel: 3.7%
  - ASA + Placebo: 2.7%
  - P=0.001

- **CREDO**
  - ASA + Clopidogrel: 8.8%
  - ASA + Placebo: 6.7%
  - P=0.07

- **CHARISMA**
  - ASA + Clopidogrel: 3.8%
  - ASA + Placebo: 2.6%
  - P<0.001
BASKET Trial: 18 Month MACE
N=836 (All pts with 18 month FU)

Cardiac death MI TVR non MI related MACE

BMS DES

P=0.83 P=0.66 P=0.05 P=0.26

Kaiser C et al. ESC 2006.
STENT Registry (N=7,008): Nine Month Clinical Outcomes Comparing BMS and DES

Adjusted HR [95% CI] for death = 0.56 [0.40, 0.80]
DES vs. BMS: **Mortality** (completed 2 yr F/U)

- **HR [95% CI] = 2.0 [1.5-2.7], p=0.001**

**Freedom from death**

- **Mortality**
  - DES only (n=2,144)
  - BMS only (n=746)

**Time (days)**

- 0 100 200 300 400 500 600 700 800

- 5.9% (DES only)
- 11.4% (BMS only)

Chuck Simonton for the STENT Registry, March 2007
Duke Database Death/MI Analysis

Adjusted death/MI rates at 24 months in patients without events at 6 months

Clopidogrel status at 6 months
Overall P value = 0.07; P_{int} = 0.12

- **DES**
  - On clopidogrel: 3.1% (N=637)
  - Off clopidogrel: 7.2% (N=579)

- **BMS**
  - On clopidogrel: 5.5% (N=417)
  - Off clopidogrel: 6.0% (N=1976)

Clopidogrel status at 12 months
Overall P value <0.001; P_{int} = 0.003

- **DES**
  - On clopidogrel: 4.5% (N=252)
  - Off clopidogrel: 0.0% (N=276)

- **BMS**
  - On clopidogrel: 4.7% (N=346)
  - Off clopidogrel: 3.6% (N=1644)

Eisenstein EL et al. JAMA 2007;297: on line
Milan Stent Thrombosis Experience
2,160 consecutive pts with DES implanted

Aspirin + Clopidogrel
- 0-6 months: 0.4%
- 6-12 months: 0.3%
- 12-18 months: 0.4%

Aspirin only
- 0-6 months: 7.5%
- 6-12 months: 0.2%
- 12-18 months: 0.1%

Neither
- 0-6 months: 0%
- 6-12 months: 4%
- 12-18 months: 8%

Colombo A, TCT 2006
**Milan Stent Thrombosis Experience**

*Predictors of Stent Thrombosis (2160 consecutive pts)*

- No thieno* (0-6m): HR=11.7; 95%CI, 3.47-39.24, p<0.0001
- No thieno* (6-18m): HR=1.01; 95%CI, 0.30-3.46, p=0.98
- LVEF* ≤ 30%: HR=4.32; 95%CI, 1.61-11.60, p=0.004
- Prior Brachytherapy: HR=9.89; 95%CI, 3.56-27.46, p<0.0001
- RVD*: HR=0.16; 95%CI, 0.03-0.82, p=0.03
- Final atm: HR=0.41; 95%CI, 0.18-0.92, p=0.03
- Stent Length: HR=3.41; 95%CI, 1.94-5.97, p<0.0001
Clopidogrel Responsiveness at the Time of PCI and Stent Thrombosis After Cypher w/i 30 Days: \(N=280\)

**Price MJ et al, TCT 2006**

- Reactivity Post-Clopidogrel Treatment (PRUs)
- Inhibition by Clopidogrel (%)

**Association with Stent Thrombosis**
- Clop NR: \(p=0.046\)
- High post-Rx reactivity: \(p=0.06\)
- Clop NR + high post-Rx reactivity: \(p=0.02\)
The ADAPT DES Study

10,000 consecutive pts receiving DES at up to 12 sites

Aspirin and Clopidogrel responsiveness evaluated (Accumetrics VerifyNow system)

Clinical FU for 2-5 years

Angiographic core lab assessment of all stent thromboses and 1:3 matching controls

PIs: Gregg W. Stone and Chuck Simonton
Sponsors: CRF and the Dickinson Inst.
Principal study group: STENT Registry investigators

Funded by grants from Boston Scientific (lead supporter), Accumetrics, Abbott Vascular, Cordis, and Medtronic
Coronary Stenting Summary

• ASA+Plavix for everyone up to 1 year (at least) based on the CREDO, CURE and PCI-CURE trials.
  - Probably for ever if no problems occurred?
• In case of warfarin therapy that cannot be interrupted, triple therapy with ASA 81mg, Plavix 75 QD and warfarin with target INR around 2.0 (a.fib).
DES + Long-term Clop + 30% IVUS

Overall All-Cause and Cardiac Mortality

Mortality (%)

Number at Risk

1522 1336 1005 652 515

All-cause: 3.3%
Cardiac: 1.0%

Dangas et al, i2/ACC-2007
DES + Long-term Clop + 30% IVUS

MATRIX

Overall MI and Q-wave MI

Number at Risk

1522 1292 974 629 494

0 0.5 1 1.5 2

0 2 4 6 8 10 12 14

MI (%)

Any MI

4.0%

Q-wave MI

0.4%

Dangas et al, i2/ACC-2007
Stent Thrombosis (K-M analysis)

* Stent thrombosis included the definite and probable thromboses by ARC

P=0.829
P=0.826
P=0.826
P=0.649

Columbia University Medical Center
MATRIX Registry

Cardiovascular Research Foundation
Duration of dual anti-platelet therapy should extend beyond the present product labels

- One year is reasonable compromise (esp. for “off-label” DES use)
- Must balance against the increased risk of bleeding with dual anti-platelet therapy
- Additional studies immediately required to better clarify optimal anti-platelet therapy
Assess patient factors which may preclude long-term (at least one year) dual AP therapy

• Planned or possible intercurrent surgery
• Bleeding Hx or tendencies
• Other concomitant medications (e.g. coumadin)
• Socio-economic factors which may affect Plavix compliance
Must-Do List

- Careful explanations and open communication with patients and families
  - Careful pre-treatment history
  - Discussion with EVERY pt re: risks and benefits of DES vs. alternative therapies
  - Ongoing (post-Rx) communication and careful FU re: dual AP compliance (instructions = NO Plavix discontinuation without MD approval)!
**Allergy Scenarios**

- **ASA allergy**
  - Desensitization
  - Plavix alone
  - Low threshold for GPIIb/IIIa inhibitor.
- **Plavix allergy**
  - Ticlopidine should be tried first, then all others options as above.
  - Plavix + prednisone has also been used in specifically high-risk patients.
  - Pletal is an alternative agent
Management After PCI with DES
Has been completed

Dangas G, Treatment with DES, In: Antman’s Cardiovascular Therapeutics, A Companion to Braunwald’s Heart Disease
Fig 7-8

First Month Management

- Clopidogrel 75mg po QD
  Consider BID for 1 month in exceptionally high-risk cases, STEMI, platelet resistance
- Ticlopidine 250mg po BID
  For clopidogrel Allergy
  Or
  Cilostazol 100mg po BID for A to both thienopyridines
- GPIIb/IIIa Inhibitor Infusion
  Continue for 12-18 hrs

plus

- Enteric-coated aspirin 325mg
- Enteric-coated aspirin 81mg

or

- Clopidogrel for 1 year
  Afterwards continue unless there are side-effects,
- Consider cilostazol for 1 year

After the first month

Elective non-cardiac surgery
Postpone after 6-12 months.
Discontinue (only if needed) either aspirin or clopidogrel 5 days pre-op and restart dual antiplatelet therapy ASAP

Urgent surgery
Stop both antiplatelets reluctantly and with understanding of possible stent thrombosis and a set-up to handle this complication. Post-op restart dual antiplatelet therapy ASAP

Non-urgent surgery
At 2-6 month window
Necessitating stopping both antiplatelet agents 5 days pre-op
Initiate Enoxaparin 1mg/kg SQ BID 5 days pre-op and restart dual antiplatelet therapy post-op ASAP