Antiplatelet Therapy After PCI: How Much and How Long?

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Antiplatelet Therapy after PCI: How much and how long?

The simplest and extreme response:

Give the highest possible dose for life!!!

Safety concerns related to bleeding risk. No proven effectiveness.
Antiplatelet Therapy after PCI: How much and how long?

- Maintenance Dose
- Duration of Therapy
A Patient with Stent Thrombosis While on Clopidogrel Therapy
A Patient with Stent Thrombosis and Clopidogrel Resistance

Beckerath et al, Thromb Haemost 2005

Stent Thrombosis Patient

Control Individual

Beckerath et al, Thromb Haemost 2005
Does increased maintenance dose help?
Are 75 mg of Clopidogrel the Optimal Dose?

600 mg Loading in Pts on 75 mg Chronic Therapy

ADP (5μmol/L)-Induced Aggregation, %

Before loading

After loading

600 mg Clopidogrel

P<0.001

Kastrati et al, Circulation 2004
Are 75 mg of Clopidogrel the Optimal Dose?

- ISAR-CHOICE 2 -

60 Patients

150 mg

31

75 mg

29

No. of patients

0

600 mg clopidogrel

30 days

assessment of platelet function
(LT aggregometry, Point of care test: Verify Now)

ISAR-CHOICE 2, EHJ 2007
LT Aggregometry

VerifyNow™ P2Y12 Assay

$P < 0.001$

$P = 0.004$

ADP(5 μmol/L)-Induced Aggregation (%)

P2Y12 Reaction Units

150 mg/day  75 mg/day

Clopidogrel

ISAR-CHOICE 2, EHJ 2007
Patients with type 2 diabetes mellitus and coronary artery disease on standard aspirin plus clopidogrel therapy for > one-month

Study time point 1

Platelet function testing to define clopidogrel responsiveness

Suboptimal responders

Optimal responders

Randomization

Non eligible for randomization

150 mg clopidogrel/day for 30 days (n=20)

75 mg clopidogrel/day for 30 days (n=20)

Study time point 2

Platelet function testing

75 mg clopidogrel/day for 30 days

Study time point 3

Platelet function testing

OPTIMUS; Circ 2007
Fighting Low-Response by Increased Dose - OPTIMUS Trial -

OPTIMUS; Circ 2007
The clinical benefit of an increased maintenance dose of clopidogrel is not known and 75 mg still remain the standard dose for chronic therapy.
Duration of Therapy in PCI Patients
- PCI-CURE -

- No true PCI trial (only a subset)
- Pretreatment in the long-term arm
- Mean clopidogrel therapy duration 8 months

*In combination with standard therapy.
Duration of Therapy in PCI Patients - CRE DO -

1 year results (MI, Stroke, or Death)

- Pretreatment in the long-term arm
- 33 cases of ischemic complications prevented, but 22 cases of major bleeding added

CREDO, JAMA 2002
AHA/ACC/SCAI/ACS/ADA Science Advisory
(cardiologists, surgeons, dentists)

Abstract—Dual antiplatelet therapy with aspirin and a thienopyridine has been shown to reduce cardiac events after coronary stenting. However, many patients and healthcare providers prematurely discontinue dual antiplatelet therapy, which greatly increases the risk of stent thrombosis, myocardial infarction, and death. This advisory stresses the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent and educating the patient and healthcare providers about hazards of premature discontinuation. It also recommends postponing elective surgery for 1 year, and if surgery cannot be deferred, considering the continuation of aspirin during the perioperative period in high-risk patients with drug-eluting stents. (Circulation. 2007;115:813-818.)
From autopsies of 23 patients treated with DES > 30 days and 25 matched BMS-treated autopsies.

Joner, Virmani, JACC 2006
Overall stent thrombosis = 1.3% (N=2229)

- Unstable angina: 1.4%
- Thrombus: 2.0%
- Diabetes: 2.5%
- Unprotected left main: 3.3%
- Bifurcation: 3.6%
- Renal failure: 6.2%
- Prior brachy Rx: 8.7%
- Premature antiplatelet discont'd: 29.0%

Iakovou et al, JAMA 2005
Minimum Duration of Clopidogrel Therapy in DES Pivotal Randomized Trials

- SIRIUS (Cypher): 3 months
- TAXUS IV (Taxus): 6 months
- ISAR-TEST (ISAR I DES): 6 months
- ENDEAVOR II (Endeavor): 3 months
- SPIRIT III (Xience): 6 months
Is an excess of risk of stent thrombosis with DES vs. BMS?
DES vs BMS Thrombosis
The Truth in the Light of ARC Definition -

Mauri et al, NEJM 2007

Sirolimus Stent (ARC)

Paclitaxel Stent (ARC)

No. at risk
Sirolimus stent 878 863 848 823 788
Bare-metal stent 870 853 842 825 789

Days after initial procedure

Cumulative incidence (%)

P=.70
1.7%
1.5%
P=.52
1.8%
1.4%
Cypher vs BMS
Off-Label (13 Trials)

Death 0.97 (0.70-1.33)
Stent Thrombosis 0.88 (0.51-1.52)

Kastrati & Schömig, JACC 2007
Do We Need Dual Antiplatelet Therapy Beyond 6 Months After DES?

Discontinuation of thienopyridine therapy was the major determinant of ST within the first 6 months, but insufficient information is available to determine whether there is benefit in continuing a thienopyridine beyond 6 months.

Optimal Duration of Clopidogrel Therapy After DES

ISAR-SAFE
A Multi-Center, Randomized, Double-Blind Trial

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
Incidence of Death and Acute Myocardial Infarction Associated With Stopping Clopidogrel After Acute Coronary Syndrome

JAMA, February 6, 2008—Vol 299, No. 5

Design, Setting, and Patients  Retrospective cohort study of 3137 patients with ACS discharged from 127 Veterans Affairs hospitals between October 1, 2003, and March 31, 2005, with posthospital treatment with clopidogrel.
<table>
<thead>
<tr>
<th>Variables</th>
<th>All (n = 3137)</th>
<th>Medical Therapy (n = 1569)</th>
<th>PCI (n = 1569)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
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<tr>
<td>Age, y, Mean (SD)</td>
<td>66.0 (11.7)</td>
<td>68.5 (11.7)</td>
<td>63.5 (11.1)</td>
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<tr>
<td></td>
<td>Median (range)</td>
<td>65 (57-75)</td>
<td>70 (60-79)</td>
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<tr>
<td>Male sex, No. (%)</td>
<td>3080 (98.2)</td>
<td>1543 (98.4)</td>
<td>1537 (98.0)</td>
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<tr>
<td>White race, No. (%)</td>
<td>1669 (53.2)</td>
<td>853 (54.4)</td>
<td>816 (52.0)</td>
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<tr>
<td>Comorbidities, No. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heart failure</td>
<td>715 (22.8)</td>
<td>487 (31.1)</td>
<td>228 (14.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>669 (21.0)</td>
<td>376 (24.0)</td>
<td>293 (18.0)</td>
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<tr>
<td>Prior myocardial infarction</td>
<td>809 (25.8)</td>
<td>485 (30.9)</td>
<td>325 (20.7)</td>
</tr>
<tr>
<td>PCI within prior 6 mo</td>
<td>272 (8.7)</td>
<td>98 (6.2)</td>
<td>174 (11.1)</td>
</tr>
<tr>
<td>Prior CAEIG</td>
<td>710 (22.6)</td>
<td>449 (28.6)</td>
<td>261 (16.6)</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>228 (7.3)</td>
<td>153 (9.8)</td>
<td>75 (4.8)</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>805 (25.7)</td>
<td>518 (33.0)</td>
<td>287 (18.3)</td>
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<tr>
<td>Renal disease</td>
<td>504 (16.1)</td>
<td>338 (21.6)</td>
<td>166 (10.6)</td>
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<tr>
<td>COPD</td>
<td>472 (15.1)</td>
<td>200 (12.5)</td>
<td>182 (11.6)</td>
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<tr>
<td>Dementia</td>
<td>358 (11.4)</td>
<td>225 (14.4)</td>
<td>133 (8.5)</td>
</tr>
<tr>
<td>Cancer</td>
<td>202 (6.4)</td>
<td>123 (7.8)</td>
<td>79 (5.0)</td>
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<tr>
<td>Current smoker</td>
<td>1068 (34.0)</td>
<td>468 (29.9)</td>
<td>600 (38.2)</td>
</tr>
<tr>
<td>Medications, No. (%)</td>
<td></td>
<td></td>
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<tr>
<td>Prior clopidogrel use</td>
<td>620 (19.8)</td>
<td>452 (28.8)</td>
<td>168 (10.7)</td>
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<tr>
<td>Aspirin at discharge</td>
<td>2866 (91.4)</td>
<td>1381 (88.1)</td>
<td>1485 (94.7)</td>
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<td>β-Blocker at discharge</td>
<td>2007 (62.7)</td>
<td>1430 (91.8)</td>
<td>1468 (93.6)</td>
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<tr>
<td>ACE Inhibitor at discharge</td>
<td>2865 (75.4)</td>
<td>1111 (70.9)</td>
<td>1254 (79.9)</td>
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<tr>
<td>Statin at discharge</td>
<td>2540 (81.0)</td>
<td>1198 (75.4)</td>
<td>1342 (85.5)</td>
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<tr>
<td>ACS presentation factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI risk score, mean (SD)</td>
<td>3.2 (1.3)</td>
<td>3.2 (1.3)</td>
<td>3.2 (1.3)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;40%, No. (%)</td>
<td>786 (25.1)</td>
<td>441 (28.1)</td>
<td>345 (22.0)</td>
</tr>
<tr>
<td>Unstable angina, No. (%)</td>
<td>402 (12.8)</td>
<td>326 (20.8)</td>
<td>76 (4.8)</td>
</tr>
<tr>
<td>ACS treatment, No. (%)</td>
<td>1437 (45.8)</td>
<td>408 (26.0)</td>
<td>1029 (65.6)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa use</td>
<td></td>
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<tr>
<td>Duration receiving clopidogrel following hospital discharge, d</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>290 (161)</td>
<td>278 (160)</td>
<td>302 (151)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>298 (163-413)</td>
<td>281 (120-417)</td>
<td>310 (182-410)</td>
</tr>
</tbody>
</table>
The findings of this study, coupled with prior physiological studies, support the hypothesis of a possible clopidogrel rebound effect from rebound platelet activation following clopidogrel withdrawal.
ISAR-REBOUND

Intracoronary Stenting and Antithrombotic Regimen: REBOUND Platelet Aggregation After Discontinuation of Long-Term Clopidogrel Treatment
Protocol Overview

60 Patients

double-blinded treatment

weeks after randomization

Off group

Tapering group

1\textsuperscript{st} week: 1/0/1/0/1/0/1
2\textsuperscript{nd} week: 0/0/1/0/1/0/1
3\textsuperscript{rd} week: 0/1/0/0/0/1/0
4\textsuperscript{th} week: 0/0/1/0/0/0/1

60 Patients
... in discontinuing clopidogrel therapy
Optimal Duration of Clopidogrel Therapy After DES

ISAR-CAUTION
A Randomized, Double-Blind Trial

3000 DES Patients

- Tapering
- No tapering

Primary end point at 3 months
A composite of cardiac death, MI, stent thrombosis, stroke, major bleeding or rehospitalization for ACS
Randomization:
Tapered vs. abrupt interruption of clopidogrel therapy

PCI

Randomization

Clopidogrel
tapered

Clopidogrel
abrupt

Discont. of study drug

-6 -5 -4 -3 -2 -1 0 1 2 3

time (months)

30-day Follow-up

3-month Follow-up