What is the Right Dose, Timing and Duration of Clopidogrel Therapy when Used with Drug Eluting Stents?

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Summary of Efficacy and Safety of Antiplatelet Therapy

**Death, MI**
- Aspirin: -46%
- Clopidogrel: -19%
- GP IIb/IIIa: -9%

**Major Bleeding**
- Aspirin: +60%
- Clopidogrel: +38%
- GP IIb/IIIa: +62%

Efficacy-safety endpoint in CURE RR 0.84 (0.78-0.93) $P=0.001$.

Mehta. *J Am Coll Cardiol.* 2003;41:79S.
INR below 2.0 results in a higher risk of stroke.

The estimated odds ratio of subdural hemorrhage increased 7 fold as INR increased above 4.0.

Variability in Clopidogrel Response

Change in ADP-Induced Platelet Aggregation
75 mg chronic dosing

Maximal aggregation 5 μmol/L ADP (%) following 600 mg loading dose

N=544

N=1001


Hochholzer W et al., Circulation 2005.
Case Report: Stent Thrombosis

Patient J.V., 64 Years, Stable Angina, CCS III

Patient J.V., Angina at Rest, Positive Troponin

26th October, 2004

75mg clopidogrel once daily

11th November, 2004

75 mg clopidogrel twice daily
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<tr>
<th>Study</th>
<th>Results</th>
<th>Clinical Relevance</th>
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<td>1. Barragan et al.</td>
<td>▲ P2Y₁₂ reactivity ratio (VASP-P levels)</td>
<td>Stent Thrombosis</td>
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<td>(Catheter Cardiovasc Interv. 2003;59::295)</td>
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<td>2. Ajzenberg et al.</td>
<td>▲ Shear-Induced platelet aggregation</td>
<td>Stent Thrombosis</td>
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<td>(J Am Coll Cardiol. 2005;45:1753)</td>
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<td>3. Gurbel et al.</td>
<td>▲ P2Y₁₂ reactivity ratio, ▲ ADP-induced aggregation, ▲ Stimulated GPIIb/IIIa expression</td>
<td>Stent Thrombosis</td>
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<td>(CREST Study)</td>
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<td>(J Am Coll Cardiol. 2005;46:1827)</td>
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<td>4. Matzesky et al.</td>
<td>▲ ADP-Induced platelet aggregation</td>
<td>Recurrent Cardiac Events (4th quartile)</td>
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<td>(Circulation.2005;109:3171)</td>
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<td>5. Gurbel et al.</td>
<td>▲ Periprocedural platelet aggregation</td>
<td>Myonecrosis and Inflammation Marker Release</td>
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<td>(CLEAR PLATELETS and CLEAR PLATELETS Ib)</td>
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<td>(Circulation. 2005;111:1153, J Am Coll Cardiol;2006 (in press))</td>
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<td>7. Bliden et al.</td>
<td>▲ Platelet aggregation (pre-PCI) on chronic clopidogrel</td>
<td>1 yr Post -PCI Events</td>
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<td>(J Am Coll Cardiol. 2006; (in press))</td>
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<td>8. Cuisset et al.</td>
<td>▲ Platelet aggregation</td>
<td>30-day Post-PCI events</td>
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<td>(J Thromb Haemost. 2006;3:542-9)</td>
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<td>9. Lev et al.</td>
<td>Clopidogrel/Aspirin resistant patients</td>
<td>Post-PCI Myonecrosis</td>
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<td>(J Am Coll Cardiol. 2006;47:27)</td>
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<td>10. Cuisset et al.</td>
<td>▲ Platelet aggregation</td>
<td>30-day Post-PCI events 600mg- less events</td>
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<td>(J Am Coll Cardiol. 2006;48:1339-45)</td>
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<tr>
<td>11. Hochholzer et al.</td>
<td>▲ Platelet aggregation (Upper quartile)</td>
<td>30 day MACE</td>
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<td>(J Am Coll Cardiol 2006:48:1742-50)</td>
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Guidelines Suggest Measurement of Platelet Aggregation

Acc/Aha/Scai 2005 Guideline Update for Percutaneous Coronary Intervention
A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Acc/AHA/Scai Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention)

6.2. Antiplatelet and Antithrombotic Adjunctive Therapies for PCI
6.2.1. Oral Antiplatelet Therapy

Class Iib
In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main, or last patent coronary vessel), platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg per day if less than 50% inhibition of platelet aggregation is demonstrated. (Level of Evidence: C)
Point of Care Assay
Accumetrics VerifyNow

Insert assay device
Add blood sample
Read result in minutes
Scripps DES Real World Registry: Platelet Substudy

- Prospective registry of patients undergoing SES implantation at Scripps Clinic.
- Platelet function testing with VerifyNow is performed at baseline (prior to PCI) and again 12 hours post-procedure.
- Patients not already on clopidogrel receive a 600-mg load.
- Operators are blinded to the results of the platelet function tests (no management decisions are made based on them).
Stent Thrombosis at 30 day Follow-Up

Association with Stent Thrombosis:
- Clop NR: $p=0.046$
- High post-Rx reactivity: $p=0.06$
- Clop NR + high post-Rx reactivity: $p=0.02$

N=280

Price MJ et al, AHA 2006
Potential Approach to Platelet Function Screening Post-PCI

AT RISK PATIENT: overweight (> 100 kg), MI, DM, CHF
Clopidogrel Non-Responder/High Absolute Reactivity
(% inhibition < 10-15%, PRU > 240)

Increase clopidogrel to 75 mg twice daily (± re-load)

Recheck platelet function in 1-2 weeks
Effect of Increasing Dose on Platelet Inhibition

Clopidogrel Dose

150 mg/day 75 mg/day

Aggregometry (30 days)

120 100 80 60 40 20 0

ADP (5 µmol/L)-Induced Aggregation (%)

150 mg/day 75 mg/day

P < 0.001

Beckerath N et al., ESC 2006

Clopidogrel Dose
Aspirin Non-Responsiveness

N=464, 26.9% ASA non-responsive

Endpoint= CV Death, MI, CVA/TIA, Hosp UA

Chen et al. AHA Scientific Sessions 2005
Clinical Significance of Non-Response to ADP-Receptor Antagonists

The level of platelet inhibition at the time of PCI has a clinically relevant impact on outcome.

Even after appropriate loading or chronic administration with clopidogrel, platelet inhibition is suboptimal in a large proportion of patients.

Monitoring of platelet inhibition at the bedside is now possible for the first time.

Monitoring will help yield insights into the optimal dose, timing, and duration of antiplatelet therapy in conjunction with drug eluting stents.
Offset of Clopidogrel after discontinuation VerifyNow P$_2$Y$_{12}$ test

Price et al  AJC 2006
Frequency Distribution of Platelet Inhibition After Cessation of Daily Clopidogrel Therapy

The chart shows the frequency distribution of platelet inhibition across different days of recovery. The x-axis represents the day of recovery, and the y-axis represents the frequency (%) of different inhibition levels. Different levels of inhibition are indicated by different symbols:

- Black square: ≤ 20%
- Light gray square: 20% - 40%
- Dark gray square: 40% - 60%
- Light gray diagonal: 60% - 80%
- Dark gray diagonal: 80% - 100%

The chart indicates a significant increase in platelet inhibition towards Day 5, particularly in the higher inhibition categories.