Oral Antiplatelet Therapy in PCI/ACS



Dominick J. Angiolillo, MD, PhD, FACC, FESC Director of Cardiovascular Research Assistant Professor of Medicine





Basic Concepts





Thrombus Formation

Two key elements: <u>cellular</u> (platelets) and <u>plasmatic</u> (coagulation factors)







ANTITHROMBOTIC DRUGS USED DURING PCI/ACS



Bivalirudin





Oral Antiplatelet Therapy in PCI/ACS

- 1. Which drugs should we use?
- 2. When to start and at which dose?
- 3. Length of therapy?





Oral Antiplatelet Therapy in PCI/ACS

1. Which drugs should we use?

2. When to start and at which dose?

3. Length of therapy?





Mechanisms of Action of Oral Antiplatelet Therapies



ADP = adenosine diphosphate, TXA_2 = thromboxane A_2 , COX = cyclooxygenase. Adapted from Schafer AI. *Am J Med*. 1996;101:199-209.





Long-term Efficacy of ASA in Reducing Death or MI in Patients with Unstable Angina



Benefit of Long-Term Aspirin After PCI: M-HEART II

660 patients randomized to placebo, daily ASA or the thromboxane A₂ receptor inhibitor sulotroban for 6 months following PTCA.



Ticlopidine during PCI with use of Coronary Stents



- Schomig et al, N Engl J Med 1996 - Urban et al, Circulation 1998 - Bertrand et al, Circulation 1998 - Leon et al, Circulation 1998



The Thienopyridine Family



P2Y₁₂ **ADP** receptor antagonism: antithrombotic treatment of choice for coronary stenting



Side effects: neutropenia, thrombocytopenia, rash, diarrhea, etc



Delayed time frame to achieve full antiplatelet effects

Solution to these problems:



Better Safety profile - Fewer side effects (CLASSICS trial. Bertrand NE *et al. Circulation* 2000; 102: 624–9).



Rapid onset of action with a loading dose (Cadroy Y *et al. Circulation.* 2000;101:2823-28).



Better clinical outcomes (Bhatt DL *et al. J Am Coll Cardiol* 2002; 39: 9–14.).

Synergistic Antithrombotic Effect of Clopidogrel Plus Aspirin in Humans



THROMBOSIS



Cadroy et al. Circulation. 2000;101:2823-2828.

Oral Antiplatelet Therapy in PCI/ACS

- 1. Which drugs should we use?
- 2. When to start and at which dose?
- 3. Length of therapy?





Aspirin





ACC/AHA/SCAI 2005 Guideline Update for PCI Oral Antiplatelet Adjunctive Therapies



Patients <u>already</u> taking daily chronic ASA therapy should take 75 mg to 325 mg ASA before the PCI procedure is performed

Patients <u>not already</u> taking daily chronic ASA therapy should be given 300 to 325 mg of aspirin at least 2 hours and preferably 24 hours before the PCI procedure is performed

Adapted from Smith SC Jr, et al. Available at: www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf





ACC/AHA/SCAI 2005 Guideline Update for PCI Oral Antiplatelet Adjunctive Therapies



After the PCI procedure, in patients with neither ASA resistance, allergy, nor increased risk of bleeding, ASA 325 mg daily should be given for at least 1 month after bare-metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxeleluting stent implantation, *after* which daily chronic ASA use should be continued indefinitely at a dose of 75 to 162 mg.

Adapted from Smith SC Jr, et al. Available at: www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf





What is the Correct Dose of Aspirin in the Peri-PCI Setting?

- Only one randomized trial has investigated different doses of aspirin peri-PTCA and clinical outcomes (No difference between 80mg and 1500mg QD among 495 patients. J Am Coll Cardial. 1988;11:236A)
- Almost all trials of percutaneous coronary intervention have either mandated or recommend a daily aspirin be given as 325mg daily.





Antithrombotic Trialists' Collaboration

Different Doses of Aspirin vs Control



Insights from CURE Aspirin Dose and Incidence of Major Bleedings



Clopidogrel





ACC/AHA/SCAI 2005 Guideline Update for PCI Oral Antiplatelet Adjunctive Therapies





A loading dose of clopidogrel should be administered before PCI is performed An oral loading dose of 300 mg, administered at least 6 hours before the procedure, has the best established evidence of efficacy. Continue with a maintenance dose of 75 mg daily.

Adapted from Smith SC Jr, et al. Available at: www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf







Mehta SR. et al for the CURE Trial Investigators. Lancet. 2001.

Steinhubl S, et al. JAMA. 2002; Vol 288, No 19:2411 2420.

CREDO Effect of Timing of Loading Dose: 28 Day Endpoint - Death, MI, UTVR



PT= Pretreatment

* Plus ASA and other standard therapies

Steinhubl S, Berger P, Tift Mann III J et al. JAMA. 2002;Vol 288,No 19:2411-2420.





Clopidogrel Loading Dose Timing and Risk of MACE



Steinhubl SR et al. J Am Coll Cardiol 2006; 47(5):939-43



CURE: CABG-Related Bleeding

clopidogrel + ASA ASA



CURE Trial N Engl J Med 2001





ACC/AHA/SCAI 2005 Guideline Update for PCI Oral Antiplatelet Adjunctive Therapies

l lla llb lll



If clopidogrel is given at the time of procedure, supplementation with GP IIb/IIIa receptor antagonists can be beneficial to facilitate earlier platelet inhibition than with clopidogrel alone.

For patients with an absolute contraindication to ASA, it is reasonable to give a 300-mg loading dose of clopidogrel, administered at least 6 hours before PCI, and/or GP IIb/IIIa antagonists, administered at the time of PCI.

Adapted from Smith SC Jr, et al. Available at: www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf





ACC/AHA/SCAI 2005 Guideline Update for PCI Oral Antiplatelet Adjunctive Therapies

l lla llb lll

C

C

When a loading dose of clopidogrel is administered, a regimen of greater than 300 mg is reasonable to achieve higher levels of antiplatelet activity more rapidly, but the efficacy and safety compared with a 300-mg loading dose are less established.

It is reasonable that patients undergoing brachytherapy be given daily clopidogrel 75 mg indefinitely and daily aspirin 75 to 325 mg indefinitely unless there is significant risk for bleeding.

Adapted from Smith SC Jr, et al. Available at: www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf





High Clopidogrel Loading Dose Regimen

Activated GP IIb/IIIa (ADP 2µM)



Angiolillo DJ, et al. Eur Heart Journal 2004;25:1903-10.

Cardiovascular Center

at SHANDS Jacksonville



ARMYDA-2 Trial: Primary endpoint

Primary Composite of death, MI, and TVR at 30 days

Clopidogrel pre-treatment 4-8 hrs before PCI





Patti G et al. Circulation 2005



ISAR REACT: Abciximab vs. Placebo in Low-Moderate Risk PCI

All patients pretreated with 600mg clopidogrel at least 2 hrs prior to PCI.



ISAR-SWEET: Abciximab vs. Placebo in DM Patients

701 patients with DM (29% on Insulin) undergoing elective PCI pretreated (>2 hrs) with 600 mg clopidogrel



Mehilli, J. Circulation 2004;110:3627-35





ISAR-REACT 2: Abciximab vs. Placebo in ACS

Troponin Level & Benefit of Abciximab



ACC/AHA/SCAI 2005 Guideline Update for PCI Oral Antiplatelet Adjunctive Therapies

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.

Only small size platelet function studies available

- OPTIMUS Angiolillo DJ et al. Circulation 2007
- ISAR-CHOICE 2 von Beckerath et al. Eur Heart J 2007

No safety/efficacy data

Adapted from Smith SC Jr, et al. Available at: www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf



lla llb lll

С



Triple versus Dual Antiplatelet Therapy

Role for cilostazol (PDE-III inhibitor) in adjunct to ASA & clopidogrel?

Stent thrombosis @ 30 days (Lee SW et al JACC 2006) Triple therapy vs dual therapy 9/1597 (0.5%) vs 1/1415 (0.1%) p=0.024

Cilostazol (Pletal): No PCI guideline recommendation FDA approval only for symptomatic relief of PAD





Oral Antiplatelet Therapy in PCI/ACS

- 1. Which drugs should we use?
- 2. When to start and at which dose?
- 3. Length of therapy?





Long Term Efficacy of Clopidogrel



MehtaSR. et al for the CURE Trial Investigators. *Lancet.* 2001.

Steinhubl S, et al. JAMA. 2002; Vol 288, No 19:2411 2420.

ACC/AHA/SCAI 2005 Guideline Update for PCI Oral Antiplatelet Adjunctive Therapies



B

Clopidogrel

In patients who have undergone PCI, clopidogrel 75 mg daily should be given for at least 1 month after bare-metal stent implantation (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks), 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, and ideally up to 12 months in patients who are not at high risk of bleeding.

Adapted from Smith SC Jr, et al. Available at: www.acc.org/clinical/guidelines/percutaneous/update/index_rev.pdf





Incidence, Predictors, and Outcome of Thrombosis After Successful Implantation of Drug-Eluding Stents

Univariate Predictors of Cumulative Stent Thrombosis



Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

Eugène P McFadden, Eugenio Stabile, Evelyn Regar, Edouard Cheneau, Andrew T L Ong, Timothy Kinnaird, William O Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pichard, Lowell F Satler, Ron Waksman, Patrick W Serruys

Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concern has arisen about the potential for late stent thromboses related to delayed endothelialisation of the stent struts. We report four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paxlitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.



Clopidogrel for >1-year?





Clopidogrel Use and Long-term Clinical Outcomes after DES - Duke Registry

Adjusted rates of death or MI starting at 12 months



Eisenstein EL, et al. JAMA. 2007;10;297(2):159-168.



- Adjusted outcomes were analyzed at 24 months
- Patients in the DES with clop. group had significantly lower rates of death or MI than did patients in the DES without clopidogrel group
- Among BMS patients, there were no differences in death or MI

CAPRIE-like cohort from CHARISMA – Prior MI



Bhatt DL, Flather MD, Hacke W, et al. JACC 2007; 49: 1982-8





Insights from CHARISMA: Timing of Severe or Moderate Bleeding



Bhatt DL, Flather MD, Hacke W, et al. JACC 2007; 49: 1982-8





Oral Antiplatelet Therapy in PCI/ACS

- 1. Which drugs should we use?
- 2. When to start and at which dose?

3. Length of therapy?

Emphasize with your DES treated patients one-year of dual antiplatelet therapy (*follow the guidelines*),..... afterwards evaluate on a patient-to-patient basis (*individualized treatment... no guidelines available*).



