CLOPIDIGREL FOR ACS

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The big news from the American College of Cardiology 50th Annual Scientific Session in Orlando, FL, was the highly significant and clinically important benefits of the platelet–activating inhibitor clopidogrel (Plavix) plus aspirin (ASA) vs. ASA alone in patients with acute coronary syndrome (ACS). ACS patients are those with unstable angina pectoris (UAP) or those with non-ST-elevation (non-Q wave) myocardial infarction (MI).

The **C**lopidigrel in **U**nstable angina to prevent **R**ecurrent **E**vents (CURE) trial[1 2] revealed a 20% relative-risk reduction in the primary composite endpoint of CV death, MI or stroke and a similar reduction of the second co-primary endpoint of these events together with refractory ischemia. The CURE trial involved 12,502 patients with ACS, who were being treated with ASA, beta-blockers and the other drugs commonly used in these conditions:

46%…heparins
50%… low molecular weight heparin
78%… beta-blockers
36%… calcium blockers
50%… ACE inhibitors
47%… lipid –lowering drugs

Patients were randomized to clopidigrel (300 mg starting dose and 75 mg/day thereafter or matching placebo) and followed for 3-12 months (average 9 months). GIIb/IIIa inhibitors were not used in this trial.

The benefits started within hours on the first day of treatment and those on clopidigrel showed continued benefit throughout the course of the study. The early beneficial effects are thought to be secondary to the large clopidigrel dosage "soothing those angry platelets". There was a reduction in the number of patients in the clopidigrel group requiring percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). All subgroups (with or without cardiac injury markers) showed similar benefits, including those with prior PCI or CABG or those who underwent procedures after randomization. Twenty-five percent had elevated enzyme/troponin levels. The absolute benefit was greater in patients with higher baseline risk.

Table. CURE Trial: Main Results

	Aspirin (n = 6303)	**Aspirin plus clopidogrel (n = 6259)**	**Relative Risk**	***P* value**
CV death, MI, stroke (primary end point) (%)	11.47	9.28	0.80	.00005
CV death (%)	5.49	5.06	0.92	NR
MI (%)	6.68	5.19	0.77	< .001
Stroke (%)	1.4	1.2	0.85	NR
Major bleeding (%)	2.7	3.6	1.34	.003

Is Clopidigrel the "CURE"?

So far ASA is the only medication used for the long-term treatment of ACS to prevent recurrent coronary events. With the use of ASA, 10-15% of patients still will experience death or MI by one year and 20% of patients are readmitted to the hospital with unstable angina. ACS is the most common cause of admission to coronary care units and accounts for 1.5 million hospitalizations each year in the US. There is need for more help.

Lead investigator, Dr Salim Yusuf (McMaster University, Hamilton, ON) said the finding of an added benefit with clopidigrel "is one of the most significant advances for patients with ACS since aspirin." He added, "The widespread use of clopidigrel in addition to aspirin in ACS could prevent 50,000-100,000 heart attacks, strokes or deaths every year in North America." He said the global impact could be much greater with 250,000-500,000 major events prevented every year, even if only 20% of eligible patients are treated.

Expanded Usage:

Clopidigrel is currently approved for reduction of events in patients with atherosclerosis documented by a recent stroke, MI or established peripheral arterial disease (PAD) based on the CAPRIE trial.[3] This trial compared clopidigrel with ASA and showed a modest benefit of clopidigrel (8% relative reduction in events) over ASA out to 3 years. In subset analysis of CAPRIE this benefit appeared greater in post-CABG and PAD patients.

Because of cost most physicians felt that this modest benefit didn't justify exchanging it for ASA, and clopidigrel was only used in those intolerant to ASA. This drug is also used to prevent in–stent thrombosis for 4 weeks post procedure, replacing ticlopidine.

With the CURE trial results, which show a much larger benefit of clopidigrel on top of ASA, usage should expand to the CAPRIE indications. Post-stent treatment now should continue for at least one year. The dilemma will be how long to continue to treat. There is no data. This problem is not dissimilar to the beta-blocker question of how long to treat. Do the benefits continue? Most physicians use beta-blockers indefinitely in their patients.

Bitter Pill to Swallow:

There are no major safety problems with clopidigrel. No additional lab tests are required as with coumadin (also shown to be of greater benefit than ASA). The bleeding risk of clopidigrel (1% absolute increased risk in major bleeding) is considered acceptable considering the benefits.

The only barrier to treatment is cost. Plavix costs about $3 a pill and will be prescribed to a predominantly elderly population, many of whom already take three to five drugs just for their heart disease. This should not be a significant problem in the hospital. As outpatients, though, many of these people only have limited prescription coverage, if any, and limited incomes, which may put it beyond the reach of the patients who need it most.

This will be a dilemma for physicians also… "triage". Many clinicians have said they would treat their patients with clopidigrel indefinitely if costs allowed. Preliminary calculations suggest treatment would be cost saving for the first 6 months and cost-neutral if used for one year. Dr Yusuf is very aware of this issue and further analysis is pending.

Summary/ Recommendations:

Clopidigrel appears to have earned its nickname, "super aspirin." It is a single dose oral formulation that leads to an early and sustained long-term 20% reduction in major events in the ACS. Bleeding complications appear acceptable given the benefits. Statins and ACE inhibitors reduced relative risk by 20% over years. CURE showed quicker beneficial effects for clopidigrel.

The following **recommendations regarding** the clinical application of the CURE data to the **usage of clopidigrel in everyday practice** are based on a panel discussion at www.theHeart.org between Dr Valentin Fuster, Director, Cardiovascular Institute, Mount Sinai Medical Center, New York; Dr Christopher Cannon, Cardiologist, Brigham and Women's Hospital, Boston, MA; Dr Michael Weber, Dean for Research, State University of New York Health Sciences Center, Brooklyn, NY and Dr James Ferguson, Associate Director, Cardiology, St. Luke's Episcopal Hospital and Texas Heart Institute, Houston, TX.

1. Add clopidigrel – 300 mg loading and then 75 mg daily, to the armamentarium (ASA, beta-blockers, ACE inhibitors and statins) to all ACS patients (UAP or non-Q wave MI), on admission to the hospital, regardless of what is to be done afterwards, and continue for one year.
2. As for continuing treatment beyond 1 year and determining when to stop, there are no definitive answers. It is not much of an extrapolation to believe that what has been seen with CURE will superimpose on the results of CAPRIE (modest benefit of clopidigrel without ASA out to 3 years) and thus treat anyone with evidence of ongoing vascular disease. Identifying ***higher-risk patients (those with DM, extensive disease, multiple events or recurrent events despite ASA treatment),** who would benefit most, might make the treatment (Plavix 75mg) more cost-effective.
3. High-risk patients (positive enzymes) and those going for PCI should also get GIIb/IIIa inhibitors (not evaluated in this trial but safety shown in prior intervention trials). Patients with positive enzymes get 50%-70% risk reduction with GIIb/IIIa inhibitors.
4. PCI patients should get clopidigrel based on the stent trials.
5. In acute ST elevation (transmural Q wave) MI with thrombolytics, the advice now is to be cautious and wait until safety is proven. There is no data proving benefit, and there is 30% increased bleeding with the combo of thrombolytics and clopidigrel.
6. Avoid clopidigrel usage pre-CABG if possible (significant increased bleeding risk). The question of using it in the early stages post CABG needs to be evaluated with a trial. Hold for now (probable increased bleeding risk and no data regarding benefit).
7. The physicians agreed they would treat both post MI and post-CABG patients after discharge for 1 year based on the present data (CURE + CAPRIE). Most also said that the real problem would be to determine how long the benefit lasts and how long to continue therapy. The higher-risk patients (mentioned in 2nd recommendation*) could benefit from lifelong therapy.
8. Higher-risk* chronic stable angina patients could also be considered for treatment.
9. Treatment with clopidigrel for primary prevention should not be considered until there is a clinical trial to support it.
10. All were cautious about long-term clopidigrel therapy because of lack of data, the cost and possible bleeding risk. They recommended that usage be avoided in those at high risk for bleeding and to discontinue either ASA or clopidigrel or both pre-operatively.

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Heartbeats are available at www.newsrounds.com under “cardiology”.

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[1] The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rational, design and baseline characteristics. *Eur Heart J.* 2000; 21: 2033-41.

2 Yusif S. Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE). Late Breaking Clinical Trials I Program and abstracts of the American College of Cardiology 50th Annual Scientific Session; March 18-21, 2001; Orlando, Florida. Presentation #9, Session #405.

3 CAPRIE Steering Committee. Clopidogrel vs aspirin in patients at risk of ischemic events. *Lancet.* 1996: 1329-39.