Double-Dose Clopidogrel in ACS: The CURRENT/OASIS-7 Trial

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Background

- Among patients with ACS, clopidogrel 300mg followed by 75 mg/d maintenance dose has been shown to improve short and long-term outcomes compared with ASA alone
- Many patients do not achieve sufficient platelet inhibition with standard dose clopidogrel
- Recent studies have shown that higher doses of clopidogrel lead to more rapid and higher levels of platelet inhibition
- Whether these pharmacodynamic findings translate into improved clinical outcomes is less certain

CURRENT Study Design, Flow and Compliance

25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

Planned Early (<24 h) Invasive Management with intended PCI</p>

✓ Ischemic ECG \triangle (80.8%) or \uparrow cardiac biomarker (42%)

Randomized to receive (2 X 2 factorial):

CLOPIDOGREL: <u>Double-dose</u> (600 mg then150 mg/d x 7d then 75 mg/d) vs <u>Standard dose</u> (300 mg then 75 mg/d)

ASA: <u>High Dose</u> (300-325 mg/d) vs <u>Low dose</u> (75-100 mg/d)



CURRENT ASA Dose Comparison Primary Outcome and Bleeding

	ASA	ASA	HR	95% CI	Р
	75-100 mg	300-325 mg			
CV Death/MI/Stroke					
PCI (2N=17,232)	4.2	4.1	0.98	0.84-1.13	0.76
No PCI (2N=7855)	4.7	4.4	0.92	0.75-1.14	0.44
Overall (2N=25,087)	4.4	4.2	0.96	0.85-1.08	0.47
Stent Thrombosis	2.1	1.9	0.91	0.73-1.12	0.37
TIMI Major Bleed	1.03	0.97	0.94	0.73-1.21	0.71
CURRENT Major Bleed	2.3	2.3	0.99	0.84-1.17	0.90
CURRENT Severe Bleed	1.7	1.7	1.00	0.83-1.21	1.00

GI Bleeds: 30 (0.24%) v 47 (0.38%), P=0.051

No other significant differences between ASA dose groups



2 Significant Interactions:
1. PCI v No PCI (P=0.016)
2. ASA dose (P=0.043)



Clopidogrel Dose vs. ASA Dose

CURRENT Clopidogrel Double-Dose vs. Single-Dose by ASA Factorial



ASA Dose Interaction: Is it real?

- Interaction statistically borderline (p=0.043)
- No biologic plausibility
- If there were an ASA interaction, might expect the benefit of clopidogrel would be greater in low-dose ASA→ but the opposite was observed
- If there were a true ASA interaction, would expect the interaction would be accentuated for the most platelet-specific endpoint (stent thrombosis)→ not seen in CURRENT



Definite Stent Thrombosis According to Clopidogrel and ASA Dose



ASA Dose Interaction: Is it real?

Conclusions

C vs. A interaction <u>unlikely</u> to be real

Implication

 Don't need to analyze clopidogrel dose separately by ASA dose



Clopidogrel Dose vs. PCI Strategy



Clopidogrel Double- vs. Single-Dose by PCI Attempted



PCI-Clodidogrel Dose Interaction: Is it real?

• Statistical interaction fairly strong (p=0.016)

Conclusions

C vs. PCI interaction is most likely a true effect

Implication

- Need to analyze clopidogrel dose separately by PCI strategy
 - Benefits of high-dose vs. low dose clopidogrel on biomarker release previously shown in PCI patients (ARMYDA-2 trial)



PCI Population (N = 17,232)



Clopidogrel: Double vs Standard Dose Major Efficacy Outcomes in PCI Patients

Day 30	Clopidogrel				
	Standard N=8684	Double N=8548	Hazard Ratio	95% CI	P value
	%	%			
Stent Thrombosis	2.3	1.6	0.71	0.57-0.89	0.002
Definite	1.2	0.7	0.58	0.42-0.79	0.001
MI	2.6	2.0	0.78	0.64-0.95	0.012
MI or stent thrombosis	3.7	3.0	0.80	0.68-0.94	0.008
CV Death	1.9	1.9	0.96	0.77-1.19	0.68
Stroke	0.4	0.4	0.88	0.55-1.41	0.59
CV Death/MI/Stroke	4.5	3.9	0.85	0.74-0.99	0.036

CURRENT Clopidogrel: Double vs Standard Dose Primary Outcome: PCI Patients

CV Death, MI or Stroke



Clopidogrel: Double vs Standard Dose Definite Stent Thrombosis



CURRENT

CURRENT PCI Subgroup: Definite Stent Thrombosis According to Stent Type

Bare Metal Stents



Drug-Eluting Stents



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Clopidogrel Double vs Standard Dose Bleeding PCI Population

	Clopid	logrel			
	Standard	Double	Hazard	95% CI	P
	N= 8684	N=8548	Ratio		
TIMI Major ¹	0.5	0.5	1.06	0.70-1.61	0.79
CURRENT Major ²	1.1	1.6	1.44	1.11-1.86	0.006
CURRENT Severe ³	0.8	1.1	1.39	1.02-1.90	0.034
Fatal	0.15	0.07	0.47	0.18-1.23	0.125
ICH	0.035	0.046	1.35	0.30-6.04	0.69
RBC transfusion \geq 2U	0.91	1.35	1.49	1.11-1.98	0.007
CABG-related Major	0.1	0.1	1.69	0.61-4.7	0.31

¹ICH, Hb drop \geq 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal ²Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units ³Fatal or \downarrow Hb \geq 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of \geq 4 units



- Double-dose clopidogrel significantly reduced stent thrombosis and major CV events (CV death, MI or stroke) in patients undergoing PCI
- 2. In patients not undergoing PCI, double dose clopidogrel was not significantly different from standard dose (70% had no significant CAD or stopped study drug early for CABG)
- 3. There was a modest excess in CURRENT-defined major bleeds but no difference in TIMI major bleeds, ICH, fatal bleeds or CABG-related bleeds



Conclusions ASA Dose Comparison

No significant difference in efficacy or bleeding between ASA 300-325 mg and ASA 75-100 mg.



Clinical Implications

- 1. For every 1,000 patients with ACS receiving PCI, using double-dose clopidogrel for 7 days instead of standard dose will prevent an additional 6 MI's and 7 stent thromboses with an excess of 3 severe bleeds and no increase in fatal, CABG-related or TIMI major bleeds.
- 2. Patients not undergoing PCI should continue to use the standard dose regimen of clopidogrel.