



ON ISSUES IN ANTIPLATELET AND ANTITHROMBOTIC THERAPY • APRIL 2008

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LEARNING OBJECTIVES: After reading articles in this issue of *Onsiteinsight*[®], participants should be able to:

- ✦ Relate findings from clinical trials conducted with antiplatelet therapies in the setting of ACS and apply those findings to clinical practice
- ✦ Explain the problem of hyporesponse/resistance to antiplatelet therapy and its potential clinical implications for patients with ACS or in those who undergo PCI
- ✦ Describe methods to optimize the use of current antiplatelet strategies to prevent thrombotic events post-PCI
- ✦ Discuss emerging antiplatelet strategies under investigation for use in patients with ACS and undergoing PCI

TARGET AUDIENCE: Physicians and other healthcare professionals who treat patients with ACS

RELEASE/END DATES: 04/07/2008—04/07/2009

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Efficacy and Safety of Aggressive Platelet Inhibition: News from ACC/SCAI 2008 New Evidence on Prasugrel and Higher Clopidogrel Doses

Numerous studies and new data were presented at the ACC and SCAI Annual Scientific Sessions in Chicago, IL. This newsletter will cover highlights from many of these studies.

Stephen D. Wiviott, MD, presented data from a subanalysis of TRITON-TIMI 38 involving 12,844 patients with ACS, of whom 50% had BMS*, 45% had DES*, and 5% had both. In patients taking prasugrel†, a 52% reduction in definite or probable stent thrombosis (ST; 1.13% vs 2.35%; $P < 0.0001$) and a 58% reduction in definite ST (0.88% vs 2.03%; $P < 0.0001$) were seen.

*Not FDA approved for this indication

†Investigational agent; not yet FDA approved

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Suboptimal ASA Response in CAD

Patients with CAD who are resistant to aspirin (ASA) are at increased risk for recurrent cardiac events, yet the prevalence and predictors of a suboptimal response to ASA remain insufficiently defined.

Kassab and colleagues monitored platelet aggregation (PA) in 352 patients with stable CAD who have been on ASA for >1 month (37% with a history of prior MI, 32% with prior PCI, and 45% with prior CABG). Patients with ACS and those taking other antiplatelet drugs were excluded.

Overall, mean PA inhibition was $48 \pm 17\%$. Compared with patients with good ASA response ($57 \pm 12\%$), poor responders (32%; $n = 113$) had a mean PA inhibition of $29 \pm 8\%$ ($P < 0.001$). Increased age, lower BMI, male gender, and prior MI were associated with a suboptimal ASA response (See Table).

These results suggest that as many as one-third of patients may have a suboptimal ASA response. ✚

Predictors of Suboptimal Response to ASA

	Relative Risk (95% CI)	P
Male gender	2.2 (1.3–3.6)	<0.001
Age	1.03 (1.01–1.05)	0.007
BMI	0.9 (0.84–0.97)	0.008
Prior MI	1.3 (1.01–1.85)	0.04

Novel Clopidogrel Loading Doses

Aggressive platelet inhibition is crucial to reduce cardiac events. However, controversy exists as to whether clopidogrel loading doses (LD) >600 mg and maintenance doses (MD) >75 mg qd provide additional benefit. The PRINC and RELOAD studies addressed these issues.

PRINC enrolled 60 patients who received clopidogrel 600 mg at the start of PCI. Patients received a second 600-mg clopidogrel dose or matching placebo 2 hours later, and intra-arterial verapamil 5 mg to address possible microvascular dysfunction or placebo at the time of PCI. Platelet inhibition was measured at 2, 4, and 7 hours from the first LD. The next day, patients received a clopidogrel MD of 75 or 150 mg qd, with platelet function assessed after 1 week.

Platelet inhibition with clopidogrel was $42 \pm 27\%$ versus $24 \pm 22\%$ with placebo ($P = 0.0006$) 2 hours after the second clopidogrel dose. Five hours after the second dose, platelet inhibition was $49 \pm 30\%$ with clopidogrel versus $29 \pm 22\%$ with placebo ($P = 0.006$). A 150-mg clopidogrel MD for 1 week

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The data reported in this issue of *Onsiteinsight*[®] were presented during the American College of Cardiology (ACC) 57th Annual Scientific Session and The Society for Cardiovascular Angiography and Interventions (SCAI) Annual Scientific Sessions in Partnership with the ACC2 Summit from March 29–April 1, 2008 in Chicago, IL.

Recurrent Stent Thrombosis: Clinical Outcomes

Using data from the Dutch Stent Thrombosis study, van Werkum and colleagues illustrated short- and long-term outcomes (27 months) of recurrent ST among 431 patients. Primary endpoint: incidence of death and definite recurrent ST; secondary endpoint: incidence of cardiac death, all-cause mortality, MI, and definite or probable recurrent ST. All patients (75% male) received PCI or balloon angioplasty. Of the recurrently thrombosed stents, 62% were BMS, 34% were DES, and 3.7% were both.

ST presentation was acute in 31.5% of patients, and late (30 days–1 yr) and very late (>1 yr) ST in 13.0% each. Eighty-seven percent of patients were on aspirin, and nearly 70% were on clopidogrel at the time of ST. At 3 years, mortality was 12.3%, and recurrent ST occurred in 18.8% of patients. Diabetes and impaired LVEF were predictors of recurrent ST. Patients who had an additional stent implanted during emergency treatment for the first episode of ST were >4 times as likely to experience a repeat episode of ST. Notably, the type of stent and timing of ST were not associated with differences in clinical outcome. ✚

More from SCAI on Dosing Strategies

Several posters addressed different clopidogrel dosing strategies. Guagliumi and colleagues reported on HORIZONS AMI, which evaluated a 300- or 600-mg loading dose of clopidogrel plus bivalirudin or GP IIb/IIIa inhibitors plus unfractionated heparin (UFH). Bivalirudin (vs UFH+GPI) yielded a 40% reduction in major bleeding, similar major adverse cardiac events (MACE), and a 24% reduction in net adverse clinical events. This effect was independent of the clopidogrel loading dose (interaction *P* values for the above three endpoints: 0.41, 0.75, and 0.48, respectively).

Chen and colleagues presented data from a randomized study assessing the effect of triple antiplatelet therapy (clopidogrel+aspirin+cilostazol) versus dual antiplatelet therapy (clopidogrel+ASA) in 4,892 patients with acute MI undergoing PCI. In triple antiplatelet therapy: early mortality and revascularization rates were lower for 1 month (2.7% vs 10.7%; *P*=0.046), and all MACE were significantly lower for 6 months (8.2% vs 10.7%; *P*=0.004). ✚

Effect of Bivalirudin Versus UFH on Major Bleeding

In the ISAR-REACT 3 trial, Kastrati and colleagues evaluated bivalirudin versus unfractionated heparin (UFH) in 4,570 patients taking clopidogrel and undergoing PCI. All patients received clopidogrel loading (600 mg) ≥2 hours pre-PCI, 325 mg of aspirin (ASA), and maintenance doses of ASA (80–325 mg qd indefinitely) and clopidogrel (75 mg qd for 6 mos). The bivalirudin group received 0.75 mg/kg, followed by 1.75 mg/kg/h. The UFH group received a 140-U/kg UFH bolus followed by a placebo infusion. Most patients (83%) had DES.

The primary endpoint (death, MI, urgent target vessel revascularization, or in-hospital major bleeding) was not significantly different between groups (8.3% bivalirudin vs 8.7% UFH; *P*=0.57). The secondary endpoint (death, MI, and urgent revascularization) was also similar between groups. Bleeding rates were 3.1% and 4.6% in the bivalirudin and UFH groups, respectively.

The authors concluded that bivalirudin provides no net clinical benefit compared with UFH, although it significantly reduces the risk of bleeding.

Commenting on the results, Harvey D. White, MB, CLB, DSc, cited a 50% reduction in TIMI major bleeding with bivalirudin (*P*=0.04), noting that bleeding is associated with long-term morbidity and mortality in these patients, and is thus an important outcome. ✚

Antiplatelet Therapies in Special Populations

The use of antiplatelet therapies in special patient populations was the topic of several studies.

Kim and colleagues evaluated the difference in clopidogrel responsiveness according to dose in patients with chronic renal failure (CRF) in whom increased DES use and stent thrombosis (ST) are common. The study enrolled 23 patients with normal renal function (NRF; clopidogrel 75 mg qd; Group 1) and 33 CRF subjects divided according to dose (Group 2: *n*=16, 75 mg qd; Group 3: *n*=17, 150 mg qd). All patients received clopidogrel for 4 weeks. No difference in % inhibition was seen between the groups, but there was a significant difference in residual platelet aggregation (measured by P2Y₁₂ reaction unit), with higher aggregation in the CRF versus NRF groups (*P*=0.016). In CRF patients, no significant difference was seen in platelet reaction units between clopidogrel 75 and 150 mg. These findings suggest that the degree of clopidogrel responsiveness is not affected by CRF, and this effect does not appear to be influenced by clopidogrel dose. However, platelets in patients with CRF are more activated at baseline and on treatment.

Geske and colleagues determined urinary 11dhTx_{B2} levels in 53 consecutive patients with type 2 diabetes (T2D) and 47 healthy controls to examine a link between platelet activation and T2D-related CVD events. High levels of 11dhTx_{B2} are linked with increased CVD event risk. Urinary creatinine levels were determined for normalization; final results were expressed as picograms (pg) of 11dhTx_{B2}/mg of creatinine. Patients with T2D had significantly higher average 11dhTx_{B2} levels than controls (*P*=0.005). Females with T2D had higher average 11dhTx_{B2} levels than control females (*P*=0.084) and males with T2D (*P*=0.012). Similarly, female controls had higher average 11dhTx_{B2} levels than male controls (*P*=0.029), but male patients with T2D and controls were not statistically different (*P*=0.577). ✚

New Evidence CONTINUED FROM COVER

When stratified according to stent type, DES patients taking prasugrel experienced a 64% reduction in ST risk ($P=0.0001$), regardless of the type of stent (sirolimus or paclitaxel). BMS patients taking prasugrel experienced a 48% reduction ($P=0.0009$)

Loading Doses

CONTINUED FROM COVER

yielded greater platelet inhibition than a 75-mg dose ($50\pm 28\%$ vs $29\pm 19\%$; $P=0.01$). Troponin levels were significantly lowered at 7 hours in responders versus nonresponders.

In RELOAD, Landivier A and colleagues evaluated 3 strategies of administration of a 900-mg clopidogrel LD in 166 patients already on chronic clopidogrel therapy. Patients with ACS, stable angina, or scheduled catheterization/PCI on a chronic MD clopidogrel 75 mg qd and aspirin 75 mg qd received 300, 600, or 900 mg of clopidogrel as an initial LD. Four hours later, a second dose (600, 300, or 0 mg, respectively) was administered to achieve a final LD of 900 mg in all patients. Platelet aggregation was evaluated at baseline, 4 hours post initial load (and prior to the second load), and 24 hours, and residual platelet activation (RPA) and percent inhibition of RPA (%IRPA) were determined.

There was a stepwise increase in %IRPA assessed at 4 hours in patients assigned to an initial load of 300 mg (30.7%) versus 600 mg (40.3%) versus 900 mg (64.0%) ($P=0.0008$). There was a significant difference between the 600- and 900-mg doses ($P=0.017$) and the 300- and 900-mg doses ($P=0.0008$). There was no difference among the 3 loading regimens at 24 hours. The rates of suboptimal response (%IRPA $<10\%$ at 4 hours) were significantly less with 900 (5.3%) versus 300 (23.6%) or 600 mg (20.4%) ($P=0.0036$).

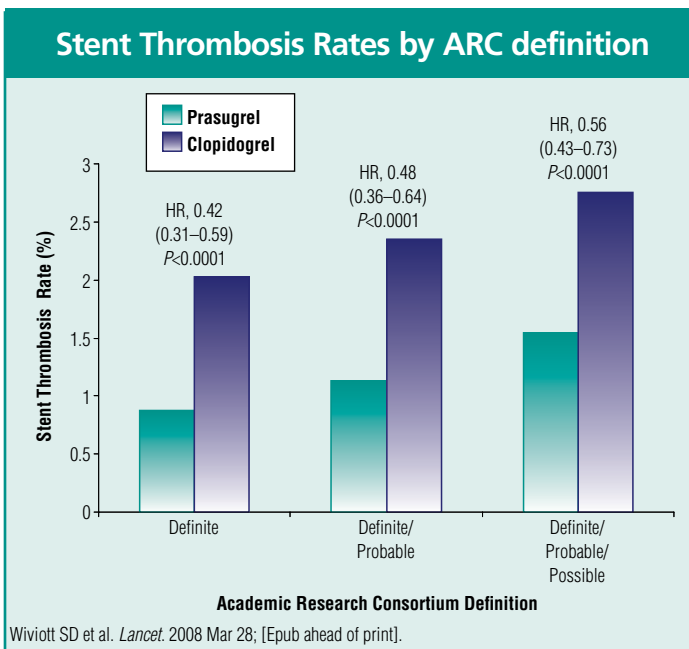
PRINC and RELOAD suggest a clinical benefit to using clopidogrel LD >600 mg. PRINC results also suggest that a 150-mg daily MD of clopidogrel provides superior platelet inhibition compared with a 75-mg daily dose; nonresponders have greater incidence of myonecrosis. RELOAD results indicate that reloading of patients already taking a clopidogrel 75-mg MD with 900 mg of clopidogrel is more effective than lesser amounts. \blackbox

in definite or probable ST. Overall, a 19% reduction in the primary endpoint (composite of CV death, nonfatal MI, or nonfatal stroke) was seen with prasugrel versus clopidogrel in patients who had a stent, regardless of stent type. Higher rates of non-CABG TIMI major bleeding (2.4% vs 1.9%; $P=0.06$), however, were seen

in the prasugrel group, although this difference was not significant.

Commenting on the study, George D. Dangas, MD, PhD, noted that it is the first of substantial size investigating the role of alternative antiplatelet therapy after off-label use of DES and BMS. He stated that prasugrel reduces platelet

inhibition by 70% to 85%, and early and late ST. Due to the bleeding risk with prasugrel, Dr Dangas asked whether it is possible to distinguish at-risk patients for ST from those who are at risk for bleeding, and treat them accordingly. He acknowledged that ST risk can be reduced by not eliminated. \blackbox



Clopidogrel Pretreatment Uncommon

Although clopidogrel pretreatment reduces the risk of peri- and post-procedural ischemic events in randomized trials, it is not clear what percentage of patients in clinical practice receive the drug pre-PCI. Several posters addressed this issue.

A study of 1,991 patients in the National Heart, Lung, and Blood Institute's Dynamic PCI Registry found that clopidogrel pretreatment (a 300- or 600-mg loading dose within 24 hrs pre-PCI) was given to 19.5% of patients. Pretreatment was more common in Asian (vs Caucasian) patients, those with prior PCI, those with MI, those who received heparin or bivalirudin pre-PCI, and stent implantation during more recent years in the registry. Pretreatment was less common among African-American (vs Caucasian) patients, those in cardiogenic shock, and in ad hoc procedures.

Another study by Aronow HD et al evaluated clopidogrel pretreatment in 80,062 patients and found that pretreatment with clopidogrel increased from 42.4% in 2003 to 51.3% in 2006. Significant predictors of receiving pretreatment included younger age (<65 years), female gender, hypertension, prior MI, prior PCI, prior CABG, and enrollment year after 2003.

Clopidogrel noncompliance after stent implantation was evaluated in 3,500 patients in the MATRIX registry—a study evaluating the outcomes of patients treated with sirolimus-eluting stents. Post-PCI, all patients were prescribed aspirin (ASA) 325 mg qd for 1 month and 81 mg qd indefinitely, plus clopidogrel 75 mg qd for 1 year and by physician discretion thereafter. At 6 months and 1 year, 22% and 26% of patients, respectively, stopped taking clopidogrel. One in five patients stopped clopidogrel therapy due to bleeding and the need to undergo noncardiac procedures. Patients who stopped therapy had slightly higher rates of death and MI, and there was a trend toward increased noncardiac mortality in patients whose physicians ordered them to stop taking clopidogrel; this trend was not significant when adjusted for patient comorbidities. Stent thrombosis occurred in 1% of the patients at 2 years. \blackbox

New Perspectives on Antiplatelet Therapy During PCI

Constant change in the science of platelet inhibition was captured during a satellite symposium featuring several experts in the field. An overview of presentations:

- In discussing the role and limitations of thienopyridines, George D. Dangas, MD, focused on evidence that thienopyridine-based combination antiplatelet therapy reduces coronary events after stenting and PCI. He pointed to the CREDO study, which showed a 26.9% 1-year relative risk reduction (RRR) in MI, stroke, or death in clopidogrel-treated patients. Similarly, from the CURE trial: an 18% RRR over 1 year. Dr Dangas also reviewed the results of the GP IIb/IIIa inhibitor trials, which showed mixed results on the efficacy of these drugs.
- Discussing TRITON-TIMI 38, Elliott M. Antman, MD, noted that its endpoint (CV death, MI, and stroke) was identical to that in the CURE trial, which established the value of clopidogrel. In TRITON-TIMI 38, patients in the prasugrel[†] group had a 34% reduction in urgent target vessel revascularization and a 52% reduction in stent thrombosis (ST). Overall, the prasugrel group had 23 fewer MIs, yet six more episodes of bleeding. Ways to prevent bleeding include use of a radial- rather than a femoral-artery approach for cardiac catheterization, administration of proton pump inhibitors, and nonuse of prasugrel in high-risk patients.
- Continuing the focus on novel agents, David J. Schneider, MD, reviewed the design of phase III trials CHAMPION-PCI (N=9,000) and CHAMPION-PLATFORM (N=6,400), involving cangrelor[†], a new rapid-acting, reversible, intravenous P2Y₁₂ inhibitor. Another Phase II trial comparing abciximab and cangrelor[†] in patients treated with unfractionated heparin has thus far shown similar rates of ischemia (5.7% and 5.4%), and a trend toward less bleeding with cangrelor (5.7% vs 7.9%).
- Peter B. Berger, MD, who reviewed antiplatelet drug resistance, noted that there are many methods used to assess platelet aggregation—yet no consistent definition of resistance. He pointed out that a patient with high baseline platelet reactivity may respond well to antiplatelet therapy but still have higher platelet reactivity than a patient with low

baseline reactivity who responds poorly to antiplatelet therapy (thus considered to have resistance). He reiterated that TRITON-TIMI 38 showed that prasugrel achieves greater inhibition of aggregation than clopidogrel, and that a reduction in thrombotic complications was linked to outcomes. The presentation also focused on the upcoming GRAVITAS study: it will screen up to 6,600 patients with DES who will undergo testing with the VerifyNow[®] P2Y₁₂ assay after PCI. Normal responders will continue receiving clopidogrel 75 mg qd; patients with high residual platelet aggregation will receive clopidogrel 75 or 150 mg qd. Primary endpoint: 6-month rate of CV death, nonfatal MI, and ST.

- Eric Topol, MD, looked to the future and focused on using genetics to personalize antiplatelet therapy, citing evidence that 25% of healthy patients have no response to clopidogrel due to a genetic variant. Further, he reiterated that platelets have RNA but no DNA, and many platelet receptors—PAR-1, IIB/IIIa, von Willebrand—can be new targets for therapies. GRAVITAS, ARCTIC, and EXCELSIOR trials will examine individualized antiplatelet therapy. 🚩

[†]Investigational agent; not yet FDA approved

Bleeding Risk of Dual Antiplatelet Therapy

Bleeding is a recognized complication of dual antiplatelet therapy (DAT). A study from Latib et al evaluated the bleeding risk in 2,355 patients on DAT after DES implantation; follow-up was 18 months. Median therapy duration was 209 days. The rate of overall, major, and minor bleeding occurred in 1.9%, 0.8%, and 1.1% of patients, respectively. Median time from stent implantation to any bleeding was 216 days. Independent predictors of bleeding included DAT ($P<0.001$) and age >65 years ($P=0.02$).

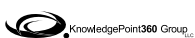
Bleeding risk remained constant during the 18-month follow-up. The incidence of any bleeding event between 30 days and 18 months was 2.57/100 person-years, and the incidence of major bleeding was 1.10/100 person-years. 🚩

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