



ON ISSUES IN ANTIPLATELET AND ANTITHROMBOTIC THERAPY • NOVEMBER 2008

INSTRUCTIONS FOR PARTICIPATION:

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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/antithrombotic therapies in the setting of ACS and apply those findings to clinical practice
- ◆ Explain the problem of hyporesponsiveness/resistance to antiplatelet/antithrombotic 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/antithrombotic strategies to prevent thrombotic events post-PCI
- ◆ Discuss emerging antiplatelet/antithrombotic 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/VALID THROUGH DATES:

11/20/2008–11/20/2009

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FACULTY: Stephen D. Wiviott, MD, Assistant Professor of Medicine, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, has indicated that he has received grant/research support from Daiichi Sankyo, Inc. and Eli Lilly and Company; consultant fees from ARENA Pharmaceuticals, Portola Pharmaceuticals Inc., and sanofi-aventis; and has participated as a CME speaker/writer for AstraZeneca, Daiichi Sankyo, Inc., and Eli Lilly and Company. Dr Wiviott has reviewed for accuracy and provided a commentary on articles containing data from the AHA Scientific Sessions only.

This activity is not part of the official AHA Scientific Sessions 2008.

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Relationship Between Access Site, Bleeding, and Outcomes

Several abstracts addressed the impact of MACE and/or major bleeding on mortality. Mehran et al presented data on mortality risk in 3,602 STEMI subjects undergoing PCI in HORIZONS-AMI. Subjects received UFH + GP IIb/IIIa inhibition or bivalirudin alone. At 30 days: 93 (2.6%) deaths following a MACE or major bleed. Non-CABG major bleeding (regardless of definition) was associated with a nearly 5-fold increased risk of 30-day mortality ($P<0.001$).

Dalby et al assessed the effect of access site on bleeding in 13,608 TRITON-TIMI 38 subjects. Femoral artery access (FAA) was used in 91.6% of subjects (31% arterial closure device), and radial artery access (RAA) was used in 8.4%. RAA was associated with a lower rate of TIMI major or minor non-CABG bleeding and blood transfusion. The use of a closure device in FAA did not impact bleeding.

Bertrand et al studied 1,348 ACS subjects undergoing transradial PCI who received clopidogrel (90% ≥ 12 hr pre-PCI) and abciximab prior to first balloon inflation in the EASY trial. Major bleeding occurred in just 1.4% of subjects. Baseline creatinine clearance <60 mL/min was associated with a 3.5-fold bleeding risk. Periprocedural independent predictors of bleeding included duration and sheath size. MACE incidence was higher at 30 days (37% vs 3%), 6 months (42% vs 8%), and 1 year (53% vs 12%) in subjects with major bleeding ($P<0.0001$ for all).

In AMI-Quebec, Allier et al assessed the impact of major bleeding on in-hospital mortality in STEMI subjects ($n=1,655$)—38% were treated with fibrinolysis, 51% primary PCI (65% femoral), and 12% no reperfusion therapy. TIMI major bleeding occurred in 7.3% of subjects. Overall in-hospital mortality was 11.6%. TIMI major bleeding and age were independent predictors of mortality. Identified predictors of TIMI major bleeding: femoral approach, female gender, and peak creatinine. TIMI major bleeding conferred a 4-fold increased annual risk of mortality. Use of the femoral approach for vascular access was the most powerful predictor of major bleeding. ◆

EASY=Early Discharge after Transradial Stenting of Coronary Arteries.

HORIZONS-AMI=Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction

DES Better for Diabetes

Drug-eluting stents reduced the risk of death, MI, and revascularization compared with bare metal stents in subjects with diabetes in the Mass-DAC Registry^a.

Mauri et al identified 5,051 subjects with diabetes who underwent PCI (66% received DES, 34% BMS). At 3 years, the unadjusted cumulative endpoint of death was 14.4% for DES vs 22.2% for BMS. The researchers then matched a subset of 2,952 subjects to control for baseline differences in the original population. This analysis at 3 years showed a risk-adjusted mortality rate of 17.5% for DES vs 20.7% for BMS ($P=0.02$); MI rate of 13.8% vs 16.9% ($P=0.02$); and target vessel revascularization rate of 18.4% vs 23.7%; $P<0.001$. ◆

^aData presented are observational and not derived from a randomized trial. As such, they are suggestive of, but not definitive evidence of, better outcomes in this population.

Predictors of Early Versus Late ST

Few data exist on the differences in factors of early vs late ST events. Jegar et al assessed baseline clinical and angiographic parameters, and 3-year follow-up data from BASKET ($n=826$ randomized 2:1 to DES vs BMS) in univariate and multivariate models with respect to ST (definite, probable, possible; ARC criteria). Early (DAT with ASA and clopidogrel in first 6 mos) and late (ASA only after first 6 mos) ST were assessed. Separate analyses were done for DES and BMS.

There was no significant difference in ST over 3 years for DES and BMS (9.3% vs 7.5%; $P=0.51$). In multivariate analysis, type C lesions, 3-vessel disease, statin dose, right coronary artery intervention, and use of GP IIb/IIIa inhibitors predicted early ST in DES ($n=16$). Age was the only predictor of early ST in BMS ($n=11$); saphenous vein graft intervention (SVGI) for late ST in DES ($n=35$); and SVGI and age for late ST in BMS. ◆

ARC=Academic Research Consortium
BASKET=Basel Kosten Effektivitäts Trial

The data reported in this issue of *Onsiteinsight*[®] were presented during the American Heart Association (AHA) Scientific Sessions 2008 from November 8–12, 2008 in New Orleans, Louisiana.

Promising Results for Factor Xa Inhibitor

Gibson et al presented phase II results from ATLAS ACS-TIMI-46 showing promise for rivaroxiban[†] for treatment of ACS. Nearly 4,000 subjects on ASA only or ASA plus clopidogrel were randomized to rivaroxiban (daily or twice daily doses) or placebo. Safety and efficacy were evaluated 6 months after therapy cessation. Results:

- Higher bleeding rates, most often mild, were seen with rivaroxiban vs placebo in a dose-dependent manner.
- Higher bleeding was also seen in those receiving DAT vs ASA alone; highest rates were in those with DAT and high-dose rivaroxiban.
- No evidence of drug-induced liver injury
- Although not designed or powered to show efficacy, study showed a 21% reduction in the primary efficacy endpoint (death/MI/stroke/recurrent ischemia requiring revascularization; $P=0.10$) and a 31% reduction in the secondary efficacy endpoint (death/MI/stroke; $P=0.029$) for rivaroxiban.

These data support the idea of the efficacy of post-ACS anticoagulation therapy, consistent with previous warfarin studies. An efficacy trial is needed to assess the magnitude of these results. ✚

[†]Investigational agent; not yet FDA approved; ATLAS ACS-TIMI-46=Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome – TIMI 46

Efficacy of Novel P2Y₁₂ Antagonist

Gurbel and colleagues evaluated the effect of the novel direct-acting, reversible P2Y₁₂ antagonist, PRT060128[†] on platelet reactivity in 20 subjects with hypo-response despite taking maintenance-dose clopidogrel therapy (75 mg/d) and ASA (81 mg/d) as mediated by high on-treatment platelet reactivity. At 7–14 days after screening, patients received a 60-mg dose of PRT060128 at 12–16 hours after the previous day's dose of clopidogrel. Platelet function was measured at 4, 6, and 24 hours with light transmittance aggregometry, Thrombelastography[®] PlateletMapping assay, VerifyNow[™] P2Y₁₂ assay, VASP, and perfusion chamber assay. PRT060128 rapidly and reversibly overcame high platelet reactivity. A good correlation was seen between peak plasma concentration of the drug and pharmacodynamic inhibition in all assays. ✚

[†]Investigational agent; not yet FDA approved

Renal Function and CVD Outcomes

Two studies focused on renal function and outcomes in CVD. Fox et al evaluated the effect of CKD (eGFR <60 mL/min/1.73m²) in 19,481 STEMI and 30,462 NSTEMI subjects from the ACTION registry. They found that 30.5% of STEMI and 42.9% of NSTEMI subjects had CKD Stage III or greater. Subjects with CKD and STEMI had a 2- to 7-fold higher in-hospital mortality risk, depending on disease severity, and 40–60% increased major bleeding. ASA, clopidogrel, and other CV medication use decreased as CKD severity increased.

Raggi et al assessed the effect of age (young <65 yrs; old 65–84 yrs; very old: ≥85 yrs) and eGFR on mortality after PCI in 169,826 subjects from the National Cardiovascular Data Registry. Worsening eGFR was associated with higher in-hospital mortality for young (OR: 7.58; 95% CI, 6.18–9.29) vs old (OR: 4.75; 95% CI, 4.14–5.45) or very old (OR: 3.50; 95% CI, 2.50–4.89) subjects. ✚

VASP-Guided Clopidogrel Therapy

Paganelli et al assessed the effect of clopidogrel on its target P2Y₁₂ receptor using vasodilator-associated phosphoprotein (VASP) phosphorylation. They tailored clopidogrel therapy in 1,122 subjects with nonemergent PCI according to VASP results. Subjects received ASA 250 mg + 600 mg clopidogrel loading*. After initial treatment, 429 subjects had a VASP ≥50% (low responders for randomization). The control group (n=215) received usual care of one more clopidogrel 600-mg dose. The test group (n=214) received up to 3 additional doses every 24 hours until reaching VASP <50%. Results:

- 8% of patients did not achieve target VASP despite multiple clopidogrel doses (up to 2,400 mg*).
- Tailored approach to clopidogrel administration significantly lowered the rate of early definite ST (primary endpoint): 0.5% in the test group vs 4.7% control ($P<0.01$).
- MACE rate (secondary endpoint) was also substantially lower: 0.5% vs 8.9% ($P<0.001$).
- No difference was seen for TIMI bleeding (other secondary endpoint; $P=0.8$). ✚

[†]Investigational agent; not yet FDA approved; *Not FDA approved for this use

Treating Clopidogrel Hypersensitivity Without Drug Interruption

Premature DAT discontinuation is a predictor of ST. Clopidogrel hypersensitivity often requires discontinuation. Current desensitization procedures can be of concern for subjects with recently implanted stents since therapy interruption carries significant ST risk.

Campbell et al assessed a strategy of clopidogrel hypersensitivity management using corticosteroids and/or antihistamines to allow for development of physiologic tolerance without the need for drug interruption. A retrospective analysis of 3 years' data on clopidogrel hypersensitivity following stent placement was performed in 20 subjects who underwent PCI and developed clopidogrel hypersensitivity at mean 6±2 days of therapy. Primary endpoint: response of hypersensitivity symptoms to treatment regimen.

Treatment was successful in 85% of subjects. Successful regimens included only corticosteroids (4 subjects) and only antihistamines (5), with combination therapy in 11. Median duration of corticosteroid and clopidogrel therapy: 6 days (range: 6–20 d) and 257±287 days (median: 151 d), respectively. Two subjects required a repeat course of corticosteroids for relapse, and three prematurely discontinued clopidogrel due to persistent symptoms. ✚ *Not FDA approved for this dose

Optimal Clopidogrel Doses Post-PCI

In this observational study, Lemesle et al assessed the impact of increased clopidogrel loading and maintenance doses (LD, MD) within the first 15 days after PCI on patient outcome among 2,954 subjects. The low-dose group (n=1,984) was pretreated with a 300-mg clopidogrel LD followed by a 75-mg/d MD after PCI. The high-dose group (n=970) was pretreated with a 600-mg LD* followed by a 150-mg/d MD* for the first 15 days and 75 mg/d thereafter.

At 2 months, the incidence of death, MI, and ST (primary endpoint) was 7.6% in the whole population, 8.2% in the low-dose group, and 6.3% in the high-dose group ($P=0.04$). Multi-variate analysis revealed that the high clopidogrel dose was associated with a decrease in the composite primary endpoint (HR=0.69; $P=0.046$). Bleeding events were similar in the low- and high-dose groups (2.8% vs 3.4%; $P=0.379$).

The ongoing CURRENT-OASIS 7 trial will compare high- vs standard-dose clopidogrel in a large, randomized, blinded clinical trial; results are expected in 2009. ✚

*Not FDA approved for this dose

New Evidence on Novel Thienopyridine, Prasugrel

Numerous talks focused on use of the novel thienopyridine, prasugrel[†]. Frelinger et al measured VASP PRI in 125 subjects from TRITON-TIMI 38 to evaluate thienopyridine response. Hyporesponse was defined as PRI >50 and 10% PA decrease. At 1–2 hours and 30 days after loading, prasugrel subjects had lower PRI than those taking clopidogrel. The VASP PRI in clopidogrel subjects at 1–2 hours was unchanged. At 30 days, 77% of clopidogrel and 27% of prasugrel subjects had high mean PA. Hyporesponsiveness was less frequent in subjects treated with prasugrel.

Frelinger et al also measured the effects of prasugrel and high-dose clopidogrel on *in vivo* and *in vitro* platelet activation in 201 subjects in PRINCIPLE-TIMI 44. Although both drugs inhibited *in vivo* platelet activation, prasugrel inhibited these parameters to a greater extent.

Salazar et al also assessed the effect of exposure to the active metabolite of prasugrel and TIMI major/minor bleeding in 1,159 TRITON-TIMI 38 subjects. In the first 3 days from first dose, higher exposure to the active metabolite of prasugrel was not associated with a higher incidence of bleeding. However, after 3 days, significantly higher bleeding occurred ($P=0.007$). In subjects weighing <60 kg and those aged >75 years, exposure to active metabolite was higher than in those without these characteristics; bleeding seemed to be observed more frequently in those subjects with the highest exposure (upper two quartiles) ✚

[†]Investigational agent; not yet FDA approved

TIMACS: Early Vs Delayed Strategies in High-Risk Patients

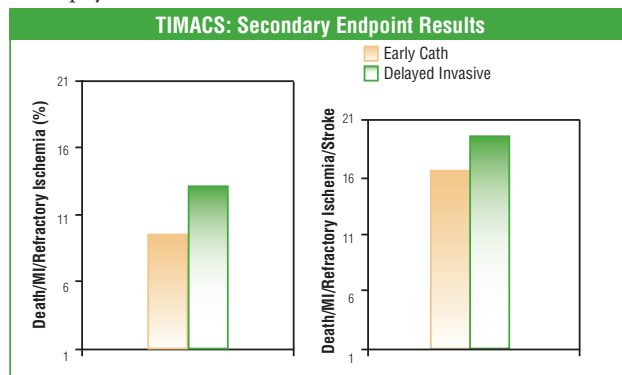
Mehta et al presented results of the TIMACS trial of early (catheterization as soon as possible) vs delayed invasive (>36 hrs after presentation) therapy in 3,031 low-, intermediate-, and high-risk subjects (NSTEMI-ACS); all received ASA and clopidogrel. Administration of GP IIb/IIIa inhibitors, fondaparinux*, enoxaparin, UFH, LMWH, or bivalirudin was at the discretion of the physician.

Crossover from delayed to early strategy occurred in 11% of subjects, and from early to delayed in 25%. There was no significant between-group difference in the primary endpoint (death/MI/stroke) at 180 days (9.7% early vs 11.4% delayed; $P=0.15$). The secondary endpoint (death/MI/refractory ischemia) occurred in 9.6% of the early group and 13.1% of

the delayed group, representing a 28% relative risk reduction ($P=0.002$). There was no bleeding difference between groups. In a secondary analysis, subjects were stratified by GRACE risk score. Those with low or intermediate scores (0–140) had similar outcomes regardless of strategy. Those with high scores (>140) had markedly improved outcomes when treated with early catheterization (14.1% vs 21.6% delayed; HR, 0.65; 95% CI, 0.48–0.88; $P=0.0097$). ✚

*Not FDA approved for this use

TIMACS=Timing of Intervention in Patients with Acute Coronary Syndromes



Socioeconomic, Insurance, Hospital Characteristics: Outcomes in MI

Several abstracts assessed novel mediators of outcomes in AMI. Jackevicius et al examined the impact of a change in Canadian government insurance program from a prior authorization (PA) to a limited use (LU) policy on access to clopidogrel in 6,161 subjects with AMI. The rate of clopidogrel use within 30 days of discharge increased from 35–88%. The 1-year rate of death, recurrent AMI, PCI, and CABG (primary endpoint) decreased by 4%; no difference in bleeding between PA and LU periods.

Casale et al presented data on socioeconomic and ethnic disparities, and the use of invasive cardiac procedures (ICP) such as catheterization, PCI, and CABG in 291,100 subjects with AMI. Those with heart failure, diabetes, or stroke, and those without private health insurance, were less likely to have ICP. African-Americans were less likely to undergo ICP; gap narrowed from 59% to 38% over time.

Nallamothu and colleagues compared hospitals that did and did not follow the “Get-With-the-Guidelines” goal of a door-to-balloon (D2B) time of <90 mins. At baseline, 54.6% and 53.1% of subjects ($n=5,801$) at D2B and non-D2B Alliance hospitals were treated within 90 mins; over time, this increased to 75.4% and 71.6% ($P<0.001$ for both). ✚

Do Proton Pump Inhibitors Impact Clopidogrel?

Two presentations explored the effect of PPIs on clopidogrel efficacy. Some have said that a drug-drug interaction may exist with PPIs and clopidogrel, resulting in reduced absorption and/or activation of clopidogrel, and leading to a decreased effect. Through a retrospective cohort study of stent subjects, Aubert et al compared 12-month incidence of MACE in 9,862 subjects who took only clopidogrel and 6,828 who took clopidogrel and a PPI. Results: use of PPI and clopidogrel was associated with a 50% increased MACE risk.

Dunn et al performed a retrospective study of PPI use CREDO (374 subjects were taking PPIs at baseline). At 28 days, death, MI, or urgent target vessel revascularization (primary endpoint) occurred in 10.2% of subjects on clopidogrel and PPI vs 5.4% on clopidogrel and no PPI (OR, 1.8; $P=0.051$). At 1 year, there was a significant difference in the rate of death, MI, or stroke in subjects on clopidogrel and PPI vs those on clopidogrel alone (13.2% vs 7.7%; $P=0.043$). Authors

noted that clopidogrel use was beneficial regardless of PPI use.

Some voiced concern about the viability of results from retrospective analyses that could be subject to confounding factors. Without a rigorous study comparing subjects with similar health profiles, “you cannot assume that the groups are balanced” and the results are real rather than a fluke, said Robert Harrington, MD, Duke University. ✚

CREDO=Clopidogrel for the Reduction of Events During Observation

This special feature of *OnsiteInsight*® highlights proceedings from two satellite symposia conducted during the AHA Scientific Sessions 2008 in New Orleans, Louisiana. PPS Editorial staff covered these industry-supported symposia, and the data are presented here for readers who were unable to attend these meetings. These symposia were not part of the official Scientific Sessions 2008 as planned by the AHA Committee on Scientific Sessions Programming.

ONSITEINSIGHT® Glossary

ACS	acute coronary syndrome
ASA	aspirin
BMS	bare metal stent
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CKD	chronic kidney disease
DAT	dual antiplatelet therapy
DES	drug-eluting stent
eGFR	estimated glomerular filtration rate
GP IIb/IIIa	glycoprotein IIb/IIIa
LMWH	low-molecular-weight heparin
MACE	major adverse coronary event
NSTEMI	non-ST-segment myocardial infarction
PA	platelet aggregation
PRI	platelet reactivity index
PCI	percutaneous coronary intervention
ST	stent thrombosis
STEMI	ST-segment elevation MI
UFH	unfractionated heparin

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Antiplatelet Therapy: More Questions than Answers^a

The risks and benefits of antiplatelet therapy were discussed during a satellite symposium featuring several experts in the field. An overview:

- Peter B. Berger, MD, cited publication bias as a limitation of current guidelines. For example, 2007 ACC/AHA guidelines recommend that ASA 165–325 mg/d should be given for 1 month after BMS placement despite evidence showing that lower doses (75–150 mg/d) are as effective and reduce bleeding risk.
- Phillippe G. Steg, MD, cited evidence from ACTION/CRUSADE that 78% of STEMI and 54% of NSTEMI subjects receive clopidogrel at discharge. According to REACH, 21.4% of subjects were not receiving clopidogrel. This is important because cessation of clopidogrel is associated with increased death risk.
- Harvey White, MD, and Daniel Simon, MD, debated the importance of bleeding as a prognostic indicator. Dr White noted that bleeding costs twice as much to treat as MI and can increase mortality by as much as 5-fold. Dr Simon countered that other mortality predictors are as likely as bleeding to cause death.
- Shamir R. Mehta, MD, concluded with data from CURE showing that long-term clopidogrel is beneficial in medically managed patients and in those treated with PCI and CABG. ✚

^aIndustry-supported satellite symposium (Daiichi Sankyo, Inc. and Eli Lilly and Company); [†]Investigational agent; not yet FDA approved

ACC/AHA=American College of Cardiology/American Heart Association

ACTION/CRUSADE=The AntiCoagulation Treatment Influence ON postoperative patients/Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines

CURE= Clopidogrel in Unstable Angina to Prevent Recurrent Events

REACH=REduction of Atherothrombosis for Continued Health Registry

New Perspectives on Prevention Post-PCI^a

Several experts offered perspectives on prevention of ischemic events after PCI in a satellite symposium chaired by Ted Feldman, MD. An overview:

- Deepak Bhatt, MD, discussed the fact that there is no mortality difference in BMS vs DES, suggesting that antiplatelet therapy can mitigate ST risk.
- Michael Farkouh, MD, called for diabetes to be viewed as a cardiovascular disease and mentioned that the management of patients with diabetes and cardiac conditions is more complex due to differences in biology, higher thrombosis rates, and the potential adverse effect of diabetes drugs. He discussed his group's FREEDOM trial, which will evaluate CABG vs PCI with DES in subjects with diabetes.
- James Hermiller, MD, reviewed data suggesting that premature antiplatelet discontinuation is the most potent predictor of ST, and called for a higher 600-mg loading dose of clopidogrel* for PCI. ✚

^aIndustry-supported satellite symposium (Daiichi Sankyo, Inc. and Eli Lilly and Company); *Not FDA approved for this dose; FREEDOM=Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease



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The 2008 American Heart Association Scientific Sessions provided new insights on the use of antiplatelet and antithrombotic therapies.

Hello, I am Dr Stephen Wiviott from Brigham and Women's Hospital in Boston, Massachusetts, and the TIMI Study Group. I have just returned from the American Heart Association Scientific Sessions 2008 in New Orleans and wanted to share some of my perspectives on the data presented and how they relate to issues of antiplatelet antithrombotic medications and strategies.

Clearly, the biggest news out of the AHA Scientific Sessions was the presentation and simultaneous publication in the *New England Journal of Medicine* of the results of the JUPITER study presented and first-authored by Dr Paul Ridker, also from Brigham and Women's Hospital. The JUPITER study demonstrated that the use of a potent statin in subjects without LDL-C levels previously thought to warrant lipid-lowering therapy, but with elevated high-sensitivity C-reactive protein (hs-CRP) levels, resulted in marked benefit in the reduction of ischemic events, and even a significant reduction in total mortality. This study will undoubtedly change the way we practice medicine, expanding the pool of patients who should receive lipid-lowering therapy. However, it also challenges the paradigms of how we assess the risk of our patients and how we should monitor the therapies we use.

These issues were also highlighted by several of the key presentations from the Scientific Sessions. First, The Home INR Study (THINRS) evaluated the use of a traditional anticoagulation clinic approach to warfarin monitoring compared with a home-based point-of-care device. This was presented by Dr Alan K Jacobsen from the Jerry L. Pettis Memorial Veterans Administration Medical Center, Loma Linda, California. The primary endpoint of death, major bleeding, or stroke

tended to be lower, but not statistically significantly different, with home monitoring. Although home monitoring did not reduce events, a greater proportion of subjects in the home-monitoring group had an international normalized ratio (INR) within therapeutic range; these subjects also reported a greater level of satisfaction. While these data do not mandate change, they do suggest that home monitoring may be a safe, viable, and reasonable alternative for some patients.

Although home monitoring of warfarin anticoagulation may improve satisfaction, few physicians or patients would argue that there is a desire to replace warfarin with medications that are safe and effective, but do not require the intensive monitoring that some may find so difficult with warfarin. To this end, one class of medications that is currently in development is the oral factor Xa inhibitors. At the Scientific Sessions, the results of a major, phase II study of the novel factor Xa inhibitor, rivaroxiban[†], in acute coronary syndrome (ACS)—the ATLAS ACS-TIMI-46 trial—were presented by Dr C. Michael Gibson of the TIMI Study Group. This study was a dose-ranging safety trial of differing doses of rivaroxiban in patients following ACS. As expected with use of an anticoagulant, there were increased rates of bleeding, though predominantly non-severe bleeding, with increasing doses of rivaroxiban. This was especially true when rivaroxiban was administered in combination with dual antiplatelet therapy. However, of interest was a trend toward a reduction in ischemic events: Death/MI/Stroke/urgent revascularization were reduced (HR 0.79, $P=0.10$), and there was a significant reduction in the triple endpoint of death/MI/stroke (HR 0.69, $P=0.03$). These encouraging data are consistent with previous studies such

as WARIS and WARIS II suggesting a role for longer-term anticoagulation in the setting of ACS. Whether the advantages in terms of efficiency of use and consistency of effect of these novel anticoagulants will allow for these agents to become part of the standard therapy for ACS will require the results of larger studies powered for clinical efficacy.

Finally, another monitoring strategy was employed by Dr Franck Paganelli (Marseille, France) and colleagues to address the issue of variability of response to clopidogrel. These investigators used an assay of vasodilator-associated stimulated phosphoprotein (VASP) phosphorylation, a measure of thienopyridine effect on the P2Y₁₂ receptor, their major target, to assess the effects of clopidogrel on platelets prior to PCI. The investigators compared a single loading dose of 600 mg of clopidogrel* without monitoring, to a VASP-guided approach of serial dosing of clopidogrel 600 mg until a specific threshold—a VASP of $\leq 50\%$ —was reached. To reach this threshold, some subjects had to receive up to 2,400 mg of clopidogrel* over a 4-day period. The VASP-guided subjects had lower rates of major adverse cardiac events (MACE), including significant reductions in stent thrombosis and myocardial infarction. These data suggest that there may be a clinical role for monitoring platelet reactivity following clopidogrel in some clinical settings. How these data may be affected by newer, more potent and consistent intravenous and oral antiplatelet agents in development is not known at this time.

In summary, the AHA Scientific Sessions was an exciting meeting with key data for cardiologists both related to and not related to antiplatelet and antithrombotic strategies. A theme has emerged that we need to critically reassess how we determine risk, choose therapies for specific patients, and how individual monitoring of medication effects can help us to tailor these therapies to individual patients. As we move forward, we may begin to rely more on biomarkers (such as hs-CRP), point-of-care tests (such as home-INR monitoring), laboratory testing (such as VASP), and genetic information to individualize care of our patients.

*Not FDA approved for this dose

[†]Investigational agent; not yet FDA approved