American Academy of Dermatology Cardiovascular Research Technologies 2013 American College of Cardiology

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Key presentations are covered from three recent meetings: The American Academy of Dermatology (March 1–5, 2013, in Miami Beach, Florida), Cardiovascular Research Technologies (February 23–26, 2013, in Washington D.C.), and the American College of Cardiology (March 9–11, 2013, in San Francisco, California). Dermatology topics include psoriasis, hives, and infantile hemangiomas. For the latter two meetings, the focus is on newer anticoagulation agents used to treat acute coronary syndrome in cardiac catheter laboratories, where preventing ischemic events while controlling bleeding risk is a particular challenge.

Annual Meeting of the American Academy of Dermatology

Apremilast for Psoriasis: ESTEEM 1, Phase 3

• Kristian Reich, MD, PhD, SCIderm Research Institute and Dermatologikum Hamburg, Hamburg, Germany

Improvement in psoriasis plaques and, similarly, in specific locations (such as in the scalp and nails) and manifestations (e.g., pruritus) "indicates a rather broad usage for apremilast," said Dr. Reich in a late-breaking clinical trial presentation of results of ESTEEM 1. Patients enrolled in this randomized controlled phase 3 trial were assigned to receive placebo (n = 282) or apremilast (CC-10004, Celgene) 30 mg twice daily (n = 560) for 16 weeks. Apremilast is an investigational oral phospho-diesterase-4 (PDE_4) inhibitor.

Patients had significant comorbidities, a mean body mass index (BMI) of 31.2 (indicating obesity), longstanding disease (a mean duration of psoriasis for about 19 years), extensive prior therapies, and high scores (19.4) in the Psoriasis Area and Severity Index (PASI). About 53% had received systemic therapies (conventional with or without biologics), 29% had previous biologic therapy, and about 18% had prior treatment with tumor necrosis factor (TNF) blockers.

In the apremilast group, about 10% of patients (n = 59) discontinued treatment; 23 patients withdrew because of adverse drug events, and two withdrew because of a lack of efficacy. In the placebo group, 12% of patients (n = 33) discontinued treatment; five withdrew because of adverse drug events, and seven withdrew because of a lack of efficacy.

Significant improvements with apremilast were reported at 16 weeks for PASI 75 (a reduction of 75% or more in PASI scores) (33.1% vs. 5.3% for placebo; $P < 0.0001$), PASI 50 (58.7% vs. 17.0%, respectively; $P < 0.0001$) and for the static Physician's Global Assessment (sPGA 0-1) (21.7% vs. 3.9%, respectively; $P < 0.0001$).

Dr. Reich noted that even though PASI 75 benefits were greater in the patients who had received no previous systemic or biologic therapy (38.7% and 35.8%, respectively), about 27% of those who had not responded to TNF inhibitors had a PASI 75 response.

Importantly, onset of action was relatively fast (within 2 to 4 weeks), and after 16 weeks, responder rates continued to increase with apremilast. Improvements were observed in pruritus scores on the Visual Analogue Scale (VAS), in Dermatology Life Quality Index ((DLQI) scores, in Nail Psoriasis Severity Index (NAPSI-50) scores, and in scalp PGA (ScPGA 0–1) scores as well.

Intestinal intolerabilty, which is well known with PDE_4 inhibitors, was reported for apremilast, including diarrhea and nausea (18.8% and 15.7% for apremilast vs. 7.1% and 6.7% for placebo). Gastrointestinal (GI) adverse events occurred most often within the first 15 days of the first dose, and most events resolved within an additional 15 days. Fewer than 2% of patients withdrew because of these events, and more than 96% of patients had mild, moderate, or no adverse events. Severe adverse events were reported in 3.6% of apremilast patients and in 3.2% of placebo patients.

No cases of tuberculosis or lymphoma and no increases in cardiovascular risk or opportunistic infections were reported.

"What stands out so far is an extremely good safety profile and moderate efficacy," Dr. Reich said. If the price after approval is moderate, he continued, "it appears that we have here a new small molecule that we could use to treat psoriasis earlier and for more moderate cases."

Given apremilast's good safety profile, he added, higher doses might be explored.

Clinical Trials

Dermatology

ASTERIA II: A Study to Evaluate the Efficacy, Response Duration and Safety of Xolair (Omalizumab) in Patients With Chronic Idiopathic Urticaria/Chronic Spontaneous Urticaria Who Remain Symptomatic Despite Antihistamine Treatment (H_1)

ESTEEM 1: Study to Evaluate Safety and Effectiveness of Oral Apremilast (CC-10004) in Patients With Moderate to Severe Plaque Psoriasis

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Monoclonal Antibody MK-3222 and Chronic Plaque Psoriasis: Phase 2b

• Kim Papp, MD, Probity Medical Research, Waterloo, Ontario, Canada

MK-3222, Merck's investigational anti-interleukin (IL)-23p19 highly humanized monoclonal antibody, was evaluated in a 355-patient phase 2b study presented in a late-breaking clinical trial session among patients with plaque psoriasis. Most patients were middle-aged, overweight Caucasian men (mean, about 45 years) who had psoriasis for about 10 years. The aim of the large dose-ranging study was to compare the efficacy and safety of MK-3222 5 mg, 25 mg, 100 mg, 200 mg, and placebo.

Patients received subcutaneous injections at weeks 0 and 4 and were evaluated at week 16. By that time, 16 patients (5%) had discontinued treatment; 2% of withdrawals were attributed to adverse events. The primary endpoint was a PASI 75 response.

Significant benefits were found for all active-treatment groups, with PASI 75 responses in 4.4% of patients receiving placebo, compared with 33.3%, 64.4%, 66.3%, and 74.4% of patients receiving 5 mg, 25 mg, 100 mg, and 200 mg, respectively. Differences from placebo were highly significant ($P = 0.001$) for the three higher doses. Response rates increased gradually over time but with a much more rapidly accelerated response for the 200-mg dose. The effect appeared to reach a plateau at about 16 weeks.

Significant improvements ($P \leq 0.001$) in Physician Global Assessment (PGA) responses followed a similar pattern for 2.2% receiving placebo, 33.3% receiving 5 mg, 57.8% receiving 25 mg, 61.8% receiving 100 mg, and 74.4% receiving 200 mg.

Most adverse events, according to Dr. Papp, were of a "nuisance" variety in "a scattergram across all the doses." Placebo adverse-event rates (69%) were similar to treatment-related adverse-event rates (60%–71%). Serious adverse events were reported in four patients, and one death was considered unrelated to treatment.

Dr. Papp commented, "What we see is a clear dose–response relationship for efficacy with MK-322, with the agent tolerated across all dosing arms. It deserves further exploration as a potential therapy for psoriasis," he concluded.

MK-3222 is currently in phase 3 development. Dr. Papp disclosed that he is both a consultant and an investigator for Merck.

Omalizumab (Xolair) for Urticaria: ASTERIA II, Phase 3

• Marcus Mauer, MD, Charité-Universitätsmedizin, Berlin, Germany

Histamine H_1 blockers, the only approved standard of care for chronic idiopathic urticaria (CIU), also known as spontaneous urticaria, are ineffective in about 50% of patients. Two-thirds of patients receiving 300 mg of omalizumab (Xolair, Genentech/Novartis) in ASTERIA II, the largest trial of urticaria on record, were responders, according to a late-breaking clinical trial presentation.[1] Omalizumab, a humanized antibody, is approved for the treatment of asthma.

CIU is defined as hives, angioedema, or both, occurring daily or almost daily for more than 6 weeks independent of external stimuli.

"These patients have very persistent symptoms, and their quality of life is massively impaired. They need better care," Dr. Maurer said. He noted further, "Itch is the most devastating symptom of CIU."

Current add-on treatments, which include leukotriene receptor antagonists, systemic steroids, cyclosporine, and methotrexate, are not approved by the FDA for this indication.

ASTERIA II, a global, multicenter, randomized, double-blind, placebo-controlled phase 3 trial, compared the efficacy and safety of omalizumab with placebo. The study was conducted at 55 centers in the U.S. and Europe and included 323 patients with moderate-to-severe refractory CIU. All patients were receiving antihistamines at approved doses.

The mean age was 41.5 years (12–75 years of age in the U.S., 18–75 years of age in Germany); 75.8% of the patients were women, and 84.5% were Caucasian. Mean body mass index (BMI) was 29.8, "on the heavy side," Dr. Maurer said.

Patients had experienced itching and hives for 8 or more consecutive weeks. They received placebo or omalizumab 300 mg, 150 mg, or 75 mg every 4 weeks, a total of three doses within a 12-week treatment period. The primary endpoint was the change in weekly scores on the Itch Severity Scale (ISS) at week 12.

The mean weekly score on the Urticaria Activity Scale (UAS7) was 30.7 (range, 0–42). The ISS score at baseline was 14.0. Angiodema was present in 40.7% of patients. The UAS is a composite score that patients record in a diary. The UAS7 is the sum of the daily average UAS for 7 days. Omalizumab produced significant improvements in weekly ISS scores at both higher doses compared with placebo, with a least squares mean treatment difference of –0.7 (95% CI [confidence interval], –2.5 to 1.2) for omalizumab 75 mg ($P = 0.46$), –3.0 (95% CI, –4.9 to –1.2) for omalizumab 150 mg ($P = 0.0011$) and –4.8 (95% CI, –6.5 to –3.1) for omalizumab 300 mg ($P < 0.0001$).

Onset of benefits was rapid with a clear dose response. After cessation of treatment at week 12, weekly ISS scores increased toward baseline values, indicating a return of symptoms.

A higher proportion of patients receiving the 150-mg and the 300-mg doses of omalizumab (42.7% and 65.8% vs. 19.0% for placebo; $P < 0.001$) experienced good symptom control (a UAS7 score of 6 or less), and a larger proportion of patients receiving the 300-mg dose were symptom-free (a UAS7 score of 0) by week 12 (44.3% vs. 5.1% for placebo, $P < 0.0001$). Higher doses of omalizumab also brought about significant improvements in quality of life, as reflected in DLQI scores. Only the 300-mg dose showed significant improvements over placebo in angioedema-free days ($P < 0.0001$).

In contrast to the known safety profile among allergic asthma patients, there were no new safety concerns with omalizumab. None of the nine serious adverse events were thought to be causes of withdrawal from treatment.

"Omalizumab is not a cure, but it is a very effective treatment," Dr. Mauer said, noting further that responses are almost immediate—among patients who "have been on all kinds of drugs that didn't work for years or decades."

When a physician in the audience asked, "How does the drug work?" Dr. Mauer responded: "We don't know. We are working on it."

He concluded, "This will revolutionize—or at least significantly change—the way we treat spontaneous chronic idiopathic urticaria patients."

Oral Propranolol in Infantile Hemangiomas: Phase 2/3

- Christine Léauté-Labrèze, MD, University of Bordeaux, France

Infantile hemangiomas, the most common pediatric vascular tumors, affect 5% of all newborns in the U.S. Among these infants, about 12% have complications leading to ulceration, impaired vision, or disfigurement, Dr. Léauté-Labrèze said in a late-breaking clinical trial session. Although she noted an initial review of propranolol for infantile hemangiomas from 5 years ago,[2] there remains a need for a pediatric formulation, approved treatment and dosages, and a randomized trial.

The study included 456 infants (1–5 months of age) who were randomly given a placebo or one of four active oral treatments with propranolol 1 or 3 mg/kg per day twice daily for 3 or 6 months. Dr. Léauté-Labrèze commented that the early age range was chosen to include infants with proliferative hemangiomas.

The primary endpoint was complete or nearly complete resolution based on independent assessments of week 24 photographs of target infantile hemangiomas compared with baseline photos. Success was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft-tissue swelling, or distortion of anatomical landmarks. The protocol called for an independent committee review at the end of the phase 2 portion to choose the most favorable dosing arm for the final analysis.

Although nearly half of the newborns receiving placebo were withdrawn because of a lack of efficacy by week 5, after 6 months, 86.3% receiving 3 mg/kg per day twice daily continued to receive therapy for 6 months. Shorter treatment, according to an interim analysis at week 24, was no better than placebo, with rates of complete or nearly complete resolution between 7.7% (with 3 mg/kg per day for 3 months) and 8.0 % (with placebo). Rates of complete or nearly complete resolution were 37.5% for propranolol 1 mg for 6 months and 62.8% for 3 mg for 6 months.

In the adaptive trial design, the best arm at the interim analysis chosen for the primary analysis was the 3 mg/day 6-month group of children. The rate in this arm was 60.4% complete or nearly complete resolution, compared with 3.6% for the placebo arm ($P < 0.0001$), surpassing the pre-trial hypothesis that rates would be 55% and 10%, respectively.

"Only two babies had complete remission in the placebo group, as compared with 61 in the propranolol 3-mg/kg per day twice-daily group," Dr. Léauté-Labrèze said.

She concluded that the multinational trial findings of highly significant efficacy with satisfactory safety support up to 6 months of the beta-blocker propranolol given at 3 mg/day twice daily for proliferating infantile hemangiomas.

REFERENCES

1. Maurer M. Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;368:924–935.
2. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008;358(24):2649–2651.

Cardiovascular Research Technologies 2013

- Joshua P. Loh, MD, Washington Hospital Center, Washington D.C.
- Craig I. Coleman, PharmD, University of Connecticut, Storrs, Connecticut
- Dominick J. Angiolillo, MD, PhD, University of Florida–Jacksonville
- Paul Gurbel, MD, Johns Hopkins University School of Medicine, Baltimore, Maryland
- Ron Waksman, MD, Washington Hospital Center, Meeting Chairman and Session Moderator
- Steven Steinhubl, MD, Geisinger Health System, Danville, Pennsylvania

The Big Antiplatelet Debate: Prasugrel or Ticagrelor?

As in most major medical meeting debates, the combatants were assigned to a side— in this case either to "Why I prefer prasugrel over ticagrelor" or "Why I prefer ticagrelor over prasugrel." But somewhat atypically, here the speakers quickly disavowed their polar positions and acknowledged some merits, in specific circumstances, to their opponent's positions.

The context of the debate is noteworthy in itself. In patients with acute coronary syndrome (ACS) who were undergoing percutaneous coronary intervention (PCI), both ticagrelor (Brilinta, AstraZeneca) and prasugrel (Effient, Eli Lilly/Daiichi Sankyo) was superior to clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi), which is now available as a generic formulation; however, the adoption of these newer, more potent antiplatelet agents has been weak.

Aside from familiarity with clopidogrel use as an impediment to adopting ticagrelor or prasugrel, interventionists may well wonder whether or not the newer agents are cost-effective. Dr. Coleman compared a strategy of universal ticagrelor use with one in which only patients with high platelet reactivity (HPR) (above 230 on the VerifyNow assay (Accumetrics, San Diego), were given ticagrelor and the rest were given generic clopidogrel. Using a hybrid decision tree and Markov model with event rates from the CURE, PLATO, and TRITON–TIMI-38 trials and costs from TRITON–TIMI-38 and a handful of pharmacy chains, he conducted a cost-effectiveness analysis for an assumed cohort of 65-year-old ACS patients with a high platelet reactivity incidence of 32% at hospital discharge.

In an interview at his poster, Dr. Coleman said that the cost of the assay was about $30 (range, $14–$60), and the annual cost of clopidogrel was $639 (range, $48–$1,160), compared with $3,348 (range, $1,982–$4,014) for ticagrelor.

The incremental cost-effectiveness ratio (ICER) per quality of life-year (QALY) for ticagrelor was $68,182, well above the widely accepted $50,000 benchmark. Ticagrelor loses its cost-effectiveness, Dr. Coleman said, when its ICER surpasses

$2,800, and clopidogrel becomes non–cost-effective when its ICER exceeds $1,100. He commented further that a similar analysis for prasugrel found an estimated $80,000 ICER per QALY. He added that prasugrel is a bit cheaper, "but there's a slightly higher bleeding rate early on."

He concluded, "I believe it is cost-effective to use a VerifyNow platelet reactivity test to determine who should be receiving clopidogrel and who should be receiving one of the newer agents."

Pro Prasugrel

"The benefit of prasugrel is enhanced where we really need a new agent—in STEMI [ST-elevation MI] patients, in patients with diabetes, recurrent events, and stent thrombosis," Dr. Angiolillo said. He added, however, that he prefers clopidogrel because of lower bleeding rates in elderly and low-weight patients, regardless of management, particularly for long-term treatment. He prefers ticagrelor for patients who have had a previous transient ischemic attack or an ischemic stroke, in those undergoing primary PCI with STEMI, in diabetic patients with ACS, in those who have recurrent ACS while taking clopidogrel, and those with stent thrombosis. He also recommended ticagrelor for high-risk ACS patients being managed with medications.

Pro Ticagrelor

Dr. Gurbel noted that ticagrelor has a faster offset after maintenance dosing than prasugrel, which might be important for patients scheduled for surgery and might be related to less bleeding in coronary artery bypass graft (CABG) patients in the PLATO trial, compared with clopidogrel-treated patients (5.3% vs. 25.8%, respectively; P = not significant). In PLATO, non-CABG major bleeding was significantly higher with ticagrelor (2.8%) than with clopidogrel (2.2%) ($P = 0.03$).

He said further, "Ticagrelor does a stellar job eliminating high platelet reactivity, whereas prasugrel is associated with a higher frequency of the high platelet reactivity [that is] associated with worse outcomes."

Later in an interview, Dr. Gurbel discredited the series of trials (GRAVITAS, TRIGGER, and ARCTIC) that showed no advantage for changing antiplatelet therapy based on platelet reactivity unit (PRU) testing. Those trials were under-powered, he said; one had protocol issues (ARCTIC); some trials used double-dose clopidogrel (GRAVITAS and ARCTIC), known to be a poor regimen for overcoming high platelet reactivity; and all of the trials included very-low-risk patients.

He said, "It would be a huge mistake to consider platelet function testing useless based on the evidence from these trials."

Clinical Trials

Cardiovascular Research Technologies

ARCTIC: Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation versus Continuation One Year after Stenting

CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events

GRAVITAS: Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety

PLATO: Platelet Inhibition and Patient Outcomes

TRIGGER-PCI: Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel

TRITON–TIMI-38: Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction

Mortality Advantage of Ticagrelor

Ticagrelor's significant cardiovascular mortality advantage (4.0%) over clopidogrel (5.1%) in PLATO ($P = 0.001$), Dr. Gurbel suggested, might be "the trump card for ticagrelor in acute coronary syndrome." Neither drug has been well vetted in ACS in terms of pharmacodynamics, he added.

So then, Dr. Waksman asked, why is penetration of both new drugs under 20%? Acknowledging that generic clopidogrel is a strong factor, Dr. Gurbel stated, "The clinical trial results say that we should be giving our patients either of these drugs because they are better than clopidogrel, which is essentially a placebo in up to 30% of patients. That's a very serious problem."

In the later interview, he further pointed out that TRITON–TIMI-38, the pivotal prasugrel trial, had excluded patients who were pretreated with clopidogrel. That, he said, is against guideline recommendations for a P_2Y_{12} inhibitor or a glycoprotein 2b/3a inhibitor on top of aspirin in patients with high-risk ACS. The fact that PLATO patients were pretreated with clopidogrel blunted the treatment effect of ticagrelor early, explaining the delayed separation of treatment curves with ticagrelor. The difference in the trials, he said, "makes it hard to come up with anything clear-cut, but still you have to use the data you have."

The Obvious Question

A practical consideration might be to give clopidogrel to all ACS patients, testing them quickly for high platelet reactivity, then switching nonresponders to the newer, more potent agents. To that suggestion, Dr. Gurbel responded, "You're preaching to the choir. That's what we do."

A trial to test such a strategy in high-risk ACS patients, he speculated, would need 7,500 or more patients and would be prohibitively expensive.

"Will we ever get past this quagmire?" he wondered aloud.

Yet Another View

During an interview at the meeting, Dr. Steinhubl commented with respect to ticagrelor's mortality benefit in PLATO:

"I have a very difficult time arguing that ticagrelor is not a better drug over the long term for everybody. Prasugrel is probably a very good drug, but TRITON did not reflect real-world practice, and I don't know how to implement its findings."

He also noted, "PRU is a great marker of patients' risk, but what's lacking is any evidence to show that treating high platelet reactivity with an antiplatelet therapy [affects] care. So using it or any measure of platelet function clinically is just not evidence-based."

What is the common practice at Dr. Steinhubl's institution?

Patients, especially those with STEMI, are given a loading dose of prasugrel and are discharged with clopidogrel. A poster

presentation (which was slated for the American College of Cardiology meeting in March, as discussed next), he said, would show that patients "do great on that switchover."

American College of Cardiology

Intravenous Cangrelor: CHAMPION PHOENIX, Phase 3

- Deepak L. Bhatt, MD, MPH, Veterans Affairs Boston Healthcare System, Boston, Massachusetts
- Harvey D. White, DSc, Auckland City Hospital, Auckland, New Zealand, Trial Co-Investigator

Cangrelor (The Medicines Company), an antiplatelet P_2Y_{12} inhibitor, may provide benefits for most patients needing percutaneous coronary intervention (PCI). Intravenous (IV) cangrelor is an investigational, rapid-acting, potent, and reversible adenosine diphosphate (ADP) receptor antagonist. In CHAMPION PHOENIX, cangrelor significantly reduced the composite endpoint of death, myocardial infarction (MI), ischemia-driven revascularization, or stent thrombosis at 48 hours compared with clopidogrel (Plavix).

Dr. Bhatt pointed out that although ADP receptor antagonism with oral agents reduces ischemic events during PCI, especially acute coronary syndromes (ACS), their relatively long duration of action and bioavailability can be a liability among patients needing urgent or emergent coronary artery bypass graft (CABG) surgery. With cangrelor, he said, normal platelet function returns within an hour.

CHAMPION PHOENIX, a randomized, double-blind, double-dummy phase 3 trial, was conducted at 153 sites in 12 countries. Nearly 10,900 patients ("all comers"; mean age, 64 years) were enrolled. Among these patients, 56% had stable angina, 25.5% with non–ST-segment MI (NSTEMI) and 18.5% had ST segment MI (STEMI). Patients with recent exposure to P_2Y_{12} inhibitors, glycoprotein 2b/3a inhibitors, or fibrinolytic drugs and those who were at a high risk of bleeding were excluded.

Patients received a cangrelor bolus of 30 mcg/kg plus an infusion of 4 mcg/kg per minute. This dose was followed by clopidogrel 600 mg or a loading dose of clopidogrel (600 mg or 300 mg oral, per physician choice) followed by oral placebo. Both arms were placebo-controlled.

For the primary composite endpoint of mortality rates, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours after randomization, cangrelor performed significantly better than clopidogrel (4.7% vs. 5.9%, respectively, for a 22% odds reduction; $P = 0.005$). Cangrelor also reduced stent thrombosis at 48 hours, the key secondary endpoint, by 38% ($P = 0.01$).

For the safety endpoint of GUSTO (severe bleeding at 48 hours), both treatment arms had low, statistically comparable incidence rates: 0.16% for cangrelor and 0.11% for clopidogrel ($P = 0.44$). There was no excess of severe bleeding or of the need for transfusions. Efficacy and safety results were consistent in all commonly reported subgroups.

Adverse events were low and similar for both groups, occurring in about 20% of patients, with low discontinuation rates (0.5% for cangrelor and 0.4% for clopidogrel; $P = 0.21$). Transient dyspnea occurred more frequently with cangrelor (1.2%) than with clopidogrel (0.3%) ($P < 0.001$).

Dr. Bhatt noted that the cangrelor benefits might have been attenuated if prasugrel or ticagrelor had been used in the control arm, but he pointed out also that the largest trial of pretreatment with prasugrel (ACCOAST) was terminated for a lack of efficacy and excess bleeding.

"Intravenous cangrelor may be an attractive option across the full spectrum of PCI, including stable angina, NSTEMI, and STEMI," Dr. Bhatt concluded.

Neither of two prior phase 3 PCI trials of cangrelor (CHAMPION PCI and CHAMPION PLATFORM) had met its primary endpoint, noted Dr. White, in an interview at the meeting. Impressed by the reduction in stent thrombosis in these trials, however, and convinced of the probable utility of the agent, investigators examined the earlier trials using the newer universal definition of MI. The revised definition requires PCI-associated MI biomarkers to be elevated to three times the 99th percentile upper limit of normal (ULN) and to be at stable pre-procedure levels for at least two samples taken 6 hours apart.

When that standard was applied to the two earlier trials, the cangrelor benefit for the primary endpoint of death, MI, or ischemia-driven revascularization (including stent thrombosis) at 48 hours became significant ($P = 0.037$).[1]

Dr. White concluded, "With the use of the universal definition of myocardial infarction, cangrelor was associated with a significant reduction in early ischemic events when compared with clopidogrel in patients with NSTEMI ACS undergoing PCI."

The universal definition of MI was used in CHAMPION PHOENIX.

Dr. Bhatt disclosed research grants from The Medicines Company, manufacturer of cangrelor and sponsor of CHAMPION PHOENIX.

Clinical Trials

American College of Cardiology

ACCOAST: A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction

CHAMPION PCI: Cangrelor Up Front Vs. Clopidogrel Up Front (2009)

CHAMPION PHOENIX: A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention (PCI) (2013)

CHAMPION PLATFORM: Cangrelor Up Front versus Delayed Clopidogrel (2009)

GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries

REFERENCE

1. White HD, Chew DP, Dauerman HL, et al. Reduced immediate ischemic events with cangrelor in PCI: A pooled analysis of the CHAMPION trials using the universal definition of myocardial infarction. *Am Heart J* 2012;163(2):182–190. ■