Cardiovascular Update

More Tailored Treatments

BY LINDA HARDER
PHOTOGRAPHY BY TRACEY BROWN

Clopidogrel is Ineffective for 30% of Patients

In the process of helping to develop ticagrelor (Brilinta, Astra Zeneca), an oral antiplatelet medication that rivals clopidogrel bisulfate (Plavix, Sanofi, Bristol Myers Squibb), Paul A. Gurbel, M.D., director of the Sinai Center for Thrombosis Research at Sinai Hospital of Baltimore has learned just how long it can take to go from bench research to FDA approval of a new antiplatelet drug.

He began studying mechanisms of thrombosis while a cardiology fellow at Duke University in 1987. In the late 1990’s, his lab at Sinai Hospital discovered the pharmacodynamic limitations of clopidogrel when studying its effects on patients undergoing stenting. This groundbreaking research provided a major rationale for the development of antiplatelet agents with a more rapid, predictable and potent pharmacodynamic effect. The seminal observations of response variability and resistance to clopidogrel, the most widely used antiplatelet agent of its type worldwide, initiated the field of personalized antiplatelet therapy.

Although approved one year earlier in 28 countries, it took until July 2011 for the FDA to finally approve ticagrelor. Dr. Gurbel and his research team led the design and conduction of international pharmacodynamic and pharmacogenetic studies of ticagrelor that started in 2006. The data gathered from these studies demonstrated the superiority of ticagrelor’s antiplatelet effect as compared to clopidogrel. This key laboratory information was submitted to the FDA and other regulatory agencies around the world and was influential in the decision to approve ticagrelor for the treatment of patients with acute coronary syndromes. These data are now in the labeling of Brilinta.

Maryland Physician interviewed three cardiovascular specialists for the latest updates in antiplatelet medications, deep vein thrombosis and heart disease in women. In each case, patients benefit from medicine’s better understanding of individual responses to therapies.
Paul A. Gurbel, M.D., director of the Sinai Center for Thrombosis Research at Sinai Hospital of Baltimore
Clopidogrel’s Limitations

Clopidogrel is an inactive pro-drug that requires hepatic bioactivation via various enzymes, including cytochrome P450 (CYP)2C19. Therapy with clopidogrel reduces the likelihood of coronary artery thrombosis by specifically inhibiting the platelet ADP receptor, P2Y12.

However, a large proportion of the population (~25% of those of European ancestry, ~30% of African ancestry and ~50% of East Asian ancestry) has a variant of the CYP2C19 gene, termed a “loss-of-function allele” that results in non-functional gene product. These patients may therefore less effectively metabolize clopidogrel. Dr. Gurbel and his team first reported the relation of genotype to clopidogrel’s pharmacodynamic effect in a PCI (percutaneous coronary intervention) population. The FDA has now written a boxed warning regarding the influence of genotype on clopidogrel metabolism.

Dr. Gurbel recommends that, in high-risk patients undergoing stenting who are treated with clopidogrel, strong consideration be given to assuring that an adequate antiplatelet effect is present by testing platelet function. He says, “We call this, ‘personalizing therapy.’ If the effect is not desirable, then the patient can be switched to a new, more expensive and more pharmacodynamically potent and predictable agent such as ticagrelor or prasugrel.”

These recommendations for personalizing antiplatelet therapy are now addressed in American and European cardiology treatment guidelines. “Given that clopidogrel is one of the most commonly prescribed medications for patients with vascular disease, and that it became a generic drug in 2012, it is important for clinicians to identify those who should receive the more costly alternative treatments,” Dr. Gurbel remarks.

Finally, Dr. Gurbel emphasizes that, “Clopidogrel is pharmacodynamically effective in about two thirds of patients undergoing PCI; these patients do not have high platelet reactivity (HPR). Ischemic risk is much greater in patients with HPR. Therefore, selectively treating two thirds of patients with generic clopidogrel may provide significant cost savings. Unselected therapy with the new P2Y12 receptor blockers is associated with increased bleeding. We believe that clinicians should strive to find the
antiplatelet therapy that achieves the optimal level of platelet inhibition for the patient, regardless of cost. If generic clopidogrel is indeed pharmacodynamically effective in the patient, offering them this less expensive option appears to be a win/win scenario.”

The Future
Dr. Gurbel and his team are involved in many more studies. They are planning a large multicenter international investigation of personalized antiplatelet therapy in high-risk patients undergoing coronary artery stenting. They are currently investigating the antiplatelet effects of HDL by intravenously administering purified HDL to patients with coronary artery disease. Another investigation involves the first administration in humans of a novel intravenous antiplatelet agent that blocks the ability of thrombin to activate platelets.

Studying the effectiveness of ticagrelor in other patient populations is also underway. In July 2012, AstraZeneca announced that it plans to conduct EUCLID, a new global clinical trial of ticagrelor that will compare its efficacy to that of clopidogrel in reducing cardiovascular deaths, myocardial infarction or ischemic strokes in patients with peripheral arterial disease.

New Treatment for Acute Iliofemoral DVT
Deep vein thrombosis (DVT) affects 350,000 to 600,000 Americans (half of them women) each year, and these conditions may contribute to 100,000 deaths every year. Even when physicians can restore blood flow around the lower extremity clot, about half of patients show residual evidence of thrombus or stenosis one year later and the underlying valves are typically compromised. Patients with significant DVT are likely to experience post-thrombotic syndrome, a disorder characterized by lower extremity swelling, discomfort, eczema, pruritus, ulceration and cellulitis, venous stasis, venous reflux, and chronic edema.

Justin K. Nelms, M.D., a vascular surgeon at Baltimore Washington Medical Center (BWMC), has introduced percutaneous mechanical thrombectomy and thrombolysis, the newest treatment for acute iliofemoral DVT, to the hospital.

“This procedure significantly decreases the morbidity of post-thrombotic syndrome,” states Dr. Nelms. “However, it’s not indicated for femoral or popliteal DVT, only cases involving the iliofemoral veins.” Its greatest benefit is in situations where extensive thrombus burden is present. These tend to be DVTs that involve the iliac and femoral veins.

A committee of vascular experts, under the direction of the Society for Vascular Surgery and the American Venous Forum, developed evidence-based practice guidelines for early thrombus removal strategies. They recommend pharmaco-mechanical strategies over catheter-directed pharmacologic thrombolysis alone in a first episode of iliofemoral DVT of less than 14 days in duration, especially in patients with limb-threatening ischemia due to iliofemoral venous outflow obstruction.

Percutaneous Mechanical Thrombectomy Description
Dr. Nelms describes the procedure, “We introduce a catheter through the groin to the thrombus. A thrombolytic agent (diluted tissue plasminogen activator) is infused directly into the thrombus, softening it to facilitate its removal. We then use high-speed water jets in the catheter to create a vacuum that sucks in the thrombus, breaking it into minute fragments that are evacuated back through the catheter.”

He continues, “The procedure is performed in the endovascular suite and most patients have an overnight hospital stay. Intravenous ultrasound can be used to display the venous interior and cross sections in real time. With this technology, we can assess the adequacy of our intervention as well as identify any areas of narrowing. If the patient is found to have an underlying stenosis, angioplasty and possibly a stent may also be used.”

Percutaneous mechanical thrombectomy has a number of benefits, including:

- Rapid removal of the thrombus with restoration of blood flow
- Faster symptom resolution
- Shorter procedure time, shorter hospital stays and subsequent cost savings

In a small fraction of patients, the procedure may cause bleeding or result in hemolysis that damages the kidneys.

Dr. Nelms notes, “Patients also receive thrombolytic therapy to facilitate removal of the thrombus and preserve venous valve function. The main utility of percutaneous mechanical thrombectomy and thrombolysis lies in its ability to decrease the incidence and severity of post-thrombotic syndrome.”

Refer Patients with Iliofemoral DVT Early
“All patients with acute, symptomatic iliofemoral DVT who present to the ER should be referred to a vascular surgeon for evaluation,” Dr. Nelms advises. “The fresher the clot, the more likely the thrombolysis is to be effective. Within one week of symptom onset is ideal, though I advocate the procedure up to four weeks post event. A venous duplex study remains the gold standard for diagnosis.

“Many practitioners may not realize that you can or should do thrombolysis for this type of DVT,” concludes Dr. Nelms. “Percutaneous mechanical thrombectomy and thrombolysis has gained wide acceptance in academic centers and increasingly is available in community hospitals.”

Women’s Heart Disease: Shifting to Prevention
It’s still apparently a challenge for women and even some physicians to grasp that cardiovascular (CV) disease, not cancer, is the number one killer of women.

“Women should start thinking about CV disease in their 30s or 40s, when they can still prevent it,” says Shannon J. Winakur, M.D., cardiologist and medical director of the Women’s Heart Center at Saint Agnes Hospital.

“Age and family history are the only risk factors you can’t change,” she claims. “Yet, many women are not taking time to care for themselves or go to the doctor until they’re sick. Further, many practitioners still don’t take a family history of heart disease as seriously for women as for men.”

Dr. Winakur’s advice is underscored by data pooled from five studies that were presented at the American Heart Association Scientific Sessions in November 2012, indicating that healthy habits in middle age can extend longevity by as much as a decade.

Her comments are also supported by the preliminary results of a new European study presented as an abstract at the 2012 Acute Cardiac Care Congress meeting in
Turkey. The study found that, compared with men, women with ST-elevation myocardial infarction (MI) had a longer delay in calling for medical assistance and receiving reperfusion once at the hospital; perhaps as a result, they were more than twice as likely to die of MI (9% vs. 4.4% of men).

Women: Know Your Numbers
Dr. Winakur stresses that, “Women need to make sure they know their numbers. At our center, we offer a 60-minute screening with our certified cardiovascular nurse for $60. Women receive a blood pressure screening, BMI, an EKG and blood work that includes a lipid profile and hemoglobin A1c. These results, combined with responses to a questionnaire, create a personalized risk factor profile. Depending on the results, we then educate each woman about her cardiac risk factors and make personalized diet, exercise and smoking cessation recommendations as appropriate. We also make referrals for a full cardiology consultation if needed.

“This service supplements what a primary care physician can do,” she continues. “Being a primary care physician these days is so difficult—you have to do everything in 10 minutes. We’re here to help them.”

It’s especially critical that women stop smoking as early as possible. A recent prospective study of more than one million women in the UK, published online in The Lancet, showed that women who smoke triple their risk of early death and that smoking cessation in middle age can largely reverse that risk.

Dr. Winakur states, “Other CV risk factors include autoimmune diseases, radiation therapy and other cancer treatments. Survivors of childhood cancers need to be monitored throughout their lives because they’re at higher cardiovascular risk. Physical and sexual abuse survivors are also at greater risk of heart disease.

“I would love to see more women for cardiac prevention, before treatment of an event,” she adds. “I want to empower women to take control. Patients are sometimes sheepish—they worry that it might be a false alarm, but it’s never a waste of time to get checked out.”

The issue of different symptom presentation continues to stymie prompt attention to possible cardiac disease in women. According to Dr. Winakur, “Fatigue and shortness of breath are common symptoms. Of course, the woman’s physician needs to rule out thyroid disease, anemia and other causes of fatigue.”

Staying abreast of current research requires vigilance. Dr. Winakur notes that, “A new look at the EPIC trial suggests that dietary calcium is better than taking calcium supplements, which correlated with a doubling of MI risk in a study of 24,000 German women. Newer hormone replacement data also suggests that taking lower doses of HRT when women are in their 50s, closer to the onset of menopause, does not increase the risk of death and MI, and in some cases may lower the risk. This reinforces the importance of considering individual patient history when prescribing treatment.”

“My hope is that we can be as successful at increasing awareness of heart disease in women as Komen has been in getting attention to breast cancer,” she concludes.