Antithrombotic Therapy in Atherosclerosis

Where Are We in 2010?

Antiplatelet therapy with aspirin and/or clopidogrel remains a crucial treatment for patients with various forms of atherosclerosis. Neither therapy is ideal, however, because patients may be resistant to therapy and experience breakthrough events, said Jeffrey I. Weitz, MD, McMaster University, Ontario, Canada. This has been demonstrated more clearly for clopidogrel, for which the resistance is related, at least in part, to CYP2C19 loss-of-function mutations, which attenuate clopidogrel activation in the liver. These mutations appear to be associated with reduced clinical effect (cardiovascular [CV] death, myocardial infarction [MI], and stroke) in patients with acute coronary syndromes who undergo percutaneous coronary intervention (PCI), but they may be less important in patients who are managed medically [Mega JL et al. *N Engl J Med* 2009; Wallentin L et al. *Lancet* 2010; Paré G et al. *N Engl J Med* 2010].

One option for clopidogrel-resistant patients who undergo PCI is to increase the dose of clopidogrel. This hypothesis was tested in the CURRENT-OASIS 7 trial, which showed no benefit with double-dose versus standard-dose clopidogrel in patients with ACS (HR, 0.94; 95% CI, 0.83 to 1.06; p=0.30) [The CURRENT-OASIS 7 investigators. *NEJM* 2010]. However, in a subsequent post hoc subgroup analysis, double-dose clopidogrel was associated with reductions in the composite rate of CV death, MI, or stroke (HR, 0.86; 95% CI, 0.75 to 0.99; p=0.039) and in definite stent thrombosis (HR, 0.54; 95% CI, 0.39 to 0.74; p=0.0001) in patients who underwent PCI [Mehta SR et al. *Lancet* 2010].

A second option is to choose a more potent adenosine diphosphate (ADP) receptor antagonist, such as prasugrel and ticagrelor, both of which have shown significant benefits in reducing vascular events compared with clopidogrel [Wiviott SD et al. *N Engl J Med* 2007; Wallentin L et al. *N Engl J Med* 2009]. Although greater ADP receptor blockade improves outcomes, it also carries a higher risk of bleeding.

Additional approaches include genotyping and measuring platelet reactivity. Yet, the recently released results of the Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety (GRAVITAS) trial showed no significant benefit in cardiovascular outcomes when the clopidogrel dose was doubled in patients with high residual platelet activity after PCI [Price M et al. AHA 2010 Chicago].

Safer, more effective antiplatelet therapies are needed, Dr. Weitz concluded. Although several of the newer compounds that are under investigation are being evaluated as add-on therapy, he noted, it may be time to focus on a replacement approach instead of ascertaining whether agents, such as prasugrel, ticagrelor, and protease-activated receptor 1 (PAR-1) inhibitors, can replace existing agents without sacrificing safety.

Beyond 2010: The Future of Antithrombotic Therapy

Despite an extensive list of antithrombotic therapies that are available or under development, treating patients with acute and chronic coronary conditions that are related to thrombosis has become more challenging, said Robert A. Harrington, MD, Duke Clinical Research Institute, Durham, North Carolina, USA. Recent data from the ACTION Registry-Get With the Guidelines, for instance, showed that patients today are older and have more comorbidities (Table 1), making them an increasingly complex population to treat.

Table 1. Comorbidities Among Patients with CAD: Baseline Characteristics

Variable	STEMI (n=28,614)	NSTEMI (n=44,528)
Mean age ± SD (yrs)	60 ±14	67 ±14
Female gender	30%	38%
Diabetes mellitus	24%	36%
Prior MI	19%	29%
Prior CHF	5%	17%
Prior PCI	20%	26%
Prior CABG	7%	19%
Prior Stroke	5%	10%
Prior PAD	6%	12%

Rather than taking a one-size-fits-all approach to prevent thrombosis, Dr. Harrington said, clinicians will need to consider several factors when choosing antithrombotic therapy, including:

- Clinical setting
- Individual characteristics of each patient, including, importantly, whether or not a patient has adequate social support and financial means to be able to adhere to long-term therapy
- Use and timing of invasive strategy
- Anatomical complexities of revascularization, such as diffuse coronary artery disease and microvascular disease