MD CONFERENCE EXPRESS

New Options for Improving DAPT and Stent Implantation

Written by Anne Jacobson

Stent thrombosis remains an important concern, following percutaneous revascularization in patients with obstructive coronary artery disease. Antonio Colombo, MD, San Raffaele Scientific Institute, Milan, Italy, described options for improving the safety of coronary stenting.

Dual Antiplatelet Therapy (DAPT)

Stent thrombosis is associated with several risk factors, including inadequate antiplatelet therapy and poor therapeutic response. Among 21,009 patients who were treated with either a bare-metal stent or drug-eluting stent (DES) in the Dutch Stent Thrombosis Registry, 437 (2.1%) presented with a definite stent thrombosis [van Werkum JW et al. *J Am Coll Cardiol* 2009]. This included 140 cases of acute stent thrombosis, 180 subacute cases, 58 late events, and 59 very late events. The strongest predictor of stent thrombosis was inadequate antiplatelet therapy, measured as less than 30 days of clopidogrel use following stent placement (HR, 36.5; 95% CI, 8.0 to 167.8; p<0.001).

Poor response to clopidogrel also increases the risk of early stent thrombosis. Approximately 15% to 20% of patients do not respond optimally to clopidogrel, Prof. Colombo said, and 3% to 5% do not respond at all [Mega JL et al. *N Engl J Med* 2009]. For some patients, genetic polymorphisms that are associated with clopidogrel metabolism result in poor therapeutic response to clopidogrel. Compared with patients with the CYP2C19*1/*1 allele, those who harbor the CYP2C19*2*2 allele are significantly more likely to experience stent thrombosis despite treatment with clopidogrel (p=0.002) [Sibbing D et al. *Eur Heart J* 2009; Mega JL et al. *N Engl J Med* 2009].

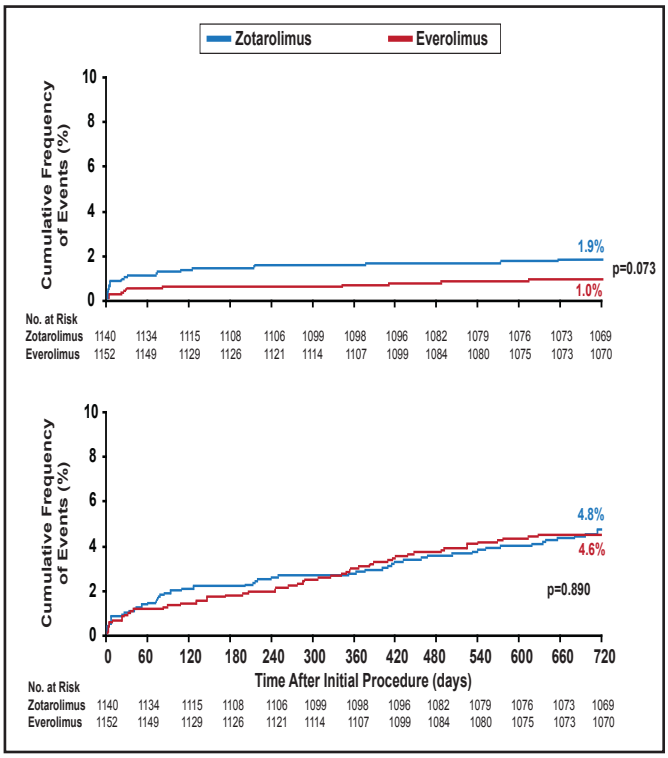
Point-of-care genetic testing may help to identify patients who will have an inadequate response to clopidogrel. For patients who are identified as having a genetic polymorphism that is associated with poor clopidogrel response, antiplatelet agents, such as prasugrel and ticagrelor, provide another route for thromboprophylaxis. To avoid issues that are related with poor clopidogrel response altogether, an alternative approach involves the preferential use of prasugrel or ticagrelor in all patients who require antiplatelet therapy.

New-Generation Stents

Certain features of stents themselves also increase the risk of stent thrombosis. In the Dutch Stent Thrombosis Registry, stent-related factors that were associated with thrombosis included undersizing (HR, 13.4; 95% CI, 5.3 to 34.0; p<0.0001) and dissection (HR, 2.88; 95% CI, 1.7 to 5.0; p=0.0002).

Second-generation DES include features, such as thin struts, thin polymers, and bioabsorbable polymers, that are designed to reduce the risk of restenosis and stent thrombosis. The RESOLUTE All Comers trial evaluated the zotarolimus-eluting stent (ZES), which uses the same base stent and the same drug coating as the everolimus-eluting stent (EES) but uses a different polymer that allows a more protracted release of zotarolimus [Silber S et al. *Lancet* 2011]. The cumulative risk of definite and probable stent thrombosis over 2 years was similar in the EES and ZES groups (1.0% vs 1.9%; p=0.07; Figure 1). Only 3 patients in each group (0.3%) had very late (>1 year) stent thrombosis. Patients in the EES and ZES groups were equally likely to meet the composite endpoint of definite or probable stent thrombosis and any death up to 2 years (4.8% vs 4.6%; p=0.89).

Figure 1. RESOLUTE All Comers Trial: 2-Year Safety Outcomes.



Reproduced with permission from the *Lancet*. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. Silber S et al. Jan 1, 2011;377(9773):1241-1247.

"Stent thrombosis has almost been conquered," Prof. Colombo said. "Hopefully, late and very late thrombosis will be reduced by the new generation stents and possibly bioabsorbable stents," he concluded.

While late stent thrombosis is infrequent, it remains an important concern in patients who have received coronary stents. The combination of more potent and less variable antiplatelet agents and later-generation stents provides hope for continued reductions in the rates of stent thrombosis. The optimal duration of dual antiplatelet therapy, however, remains an open question, particularly in the setting of newer-generation and bioabsorbable stents.

Pitfalls in Troponin Evaluation

Written by Maria Vinall

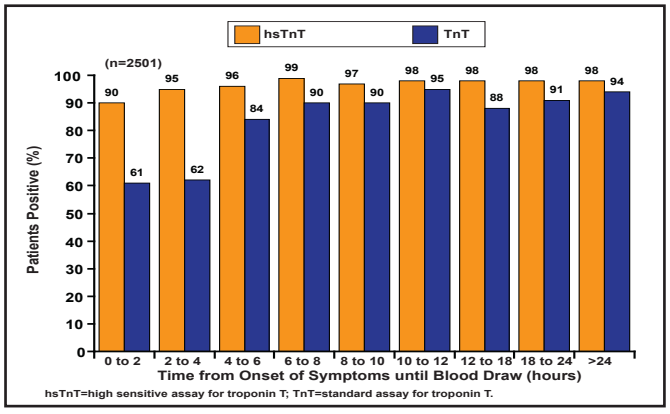
The Joint European Society of Cardiology/American College of Cardiology (ESC/ACC) Committee's 2007 consensus document for the redefinition of myocardial infarction (MI) places significant emphasis on the detection of troponin T and troponin I [Thygessen. *Eur Heart J* 2007]. Although the ability to measure cardiac troponin quickly and accurately has improved the cardiologist's ability to detect myocardial injury in the setting of acute coronary syndrome (ACS), there are a variety of noncoronary cardiac conditions that also lead to elevated troponin concentrations. Christian W. Hamm, MD, Kerckhoff Klinik, Bad Nauheim, Germany, discussed the implications of elevated troponin concentration in patients with noncoronary cardiopulmonary conditions, such as myocarditis, congestive heart failure, pulmonary embolism, and septic shock and in critically ill patients in whom there is myocardial necrosis but not necessarily ST or non-ST elevation myocardial infarction.

An elevated troponin concentration is relatively common in critically ill patients and is strongly predictive of adverse outcomes. Compared with patients who have ACS, critically ill patients without ACS but with an elevated troponin concentration have poorer outcomes [Alcalai R et al. *Arch Intern Med* 2007]. In patients with congestive heart failure, an elevated troponin concentration is correlated with the severity of symptoms and is more frequently detected in patients with NYHA class III or IV compared with class II symptoms (p=0.02). Patients with severe heart failure and elevated troponin have significantly worse outcomes than similar patients with no troponin elevation [Setsuta K et al. *Am J Med* 2002]. Similar findings have been reported for patients with myocarditis [Smith SC et al. *Circulation* 1997]. Troponin may also improve risk stratification in pulmonary embolism, as in-hospital death, prolonged hypotension, cardiogenic shock, and the need for resuscitation have been associated with elevated troponin concentration [Giannitsis E et al. *Circulation* 2000].

Low-level troponin elevations have been observed in patients with chronic renal failure. However, in this setting, the elevation is generally characterized not by a rise and fall (which is typical with ACS) but a constant elevation. Outcomes have been associated with the degree of elevation in this population, with a greater-than-7-fold increase in mortality risk when concentrations of cardiac troponin T reach levels >0.10 ng/mL [Dierkes J et al. *Circulation* 2000]. This prognostic ability of troponin T is retained, regardless of the creatinine clearance level, an indicator of kidney function [Aviles RJ et al. *N Engl J Med* 2002].

Improvements in the analytical performance of current-generation troponin assays have led to better prognostic assessment. The fourth- and fifth-generation assays are now 10 to 15 times more sensitive and are capable of detecting troponin within the first 2 hours of symptom onset in 90% of patients with MI compared with 61% of patients, using the older standard assays (Figure 1) [Weber M et al. *Am Heart J* 2011]. The ESC/ACC Consensus Document states the troponin assay performance must be in the 99th percentile of the reference control group and have a coefficient of variation ≤10% [Alpert JS. *Eur Heart J* 2000]. There are four assays, two each for troponin T and I, that satisfy this requirement.

Figure 1. High-Sensitivity Assay Troponin T in AMI.



hsTnT = high-sensitivity assay for troponin T; TnT = standard assay for troponin T; "Reprinted from the *American Heart Journal*, Weber M et al, Improved diagnostic and prognostic performance of a new high-sensitive troponin T assay in patients with acute coronary syndrome. July 2011;162(1):81-88, with permission from Elsevier.

Cardiac troponin remains the preferred biomarker of myocardial injury and a central component in the diagnosis of myocardial infarction. Troponin, even at low-level elevations, remains one of the most powerful