

## New Directions in Antithrombotic Therapy

### Strategies for Long-Term Antithrombotic Therapy

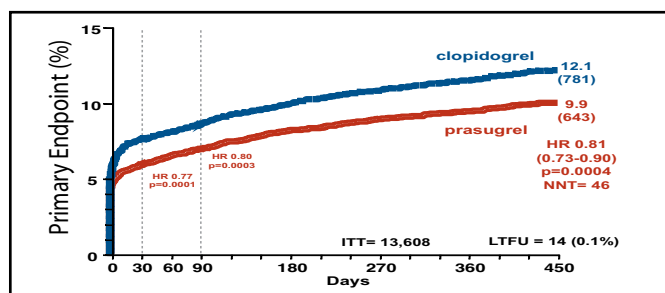
Aspirin therapy has consistently been shown to reduce the rate of cardiovascular events in secondary prevention following a cardiovascular event. However, aspirin alone is not sufficient to prevent ischemic events in patients at high risk, said Freek Verheugt, MD, PhD, Radboud University Nijmegen, The Netherlands. Prof. Verheugt provided an overview of evidence supporting the use of long-term antithrombotic therapy after acute coronary syndrome (ACS).

Dual antiplatelet therapy with clopidogrel and aspirin reduces ischemic events in patients with unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation MI (STEMI), as well as those undergoing percutaneous coronary intervention (PCI) and stenting [Bhatt DL et al. *NEJM* 2006; Mehta SR et al. *Lancet* 2001]. However, long-term treatment with clopidogrel is not necessarily appropriate in a broad population of patients at high risk for cardiovascular events. In the CHARISMA trial, the addition of clopidogrel to aspirin did not appear to reduce the combined risk of MI, stroke, or CV death compared with placebo in patients with multiple risk factors but no established disease (ie, primary prevention cohort) [Yusuf S et al. *NEJM* 2001].

A new generation of antiplatelet agents are currently under evaluation. For example, prasugrel provides more rapid, potent, and consistent inhibition of platelet function than clopidogrel. Compared with clopidogrel, prasugrel reduced the risk of CV death, MI, and stroke by 19% ( $p=0.0004$ ) and reduced the risk of stent thrombosis by 52% ( $p<0.0001$ ) in the TRITON-TIMI 38 trial. However, these gains came at the cost of excess major bleeding, including fatal bleeding (HR 1.32;  $p=0.03$ ; Figure 1) [Wiviott DS et al. *NEJM* 2007].

### Figure 1. Efficacy and Safety of Prasugrel vs Clopidogrel in Patients Scheduled for PCI.

Primary efficacy endpoint: CV death, MI, and Stroke. Safety Endpoint: TIMI Major Bleeding.



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Prof. Verheugt summarized his presentation by discussing the ideal duration of different therapies for different patient types. For example, he recommended the use of low-dose aspirin (<100 mg) for all patients, adding that the optimal duration of treatment is “forever”.

Prof. Verheugt advised that clopidogrel may be appropriate for 1 year in patients with NSTEMI who were treated with or without PCI, and for STEMI patients who were treated with PCI. For STEMI patients who did not undergo PCI, clopidogrel may be beneficial for approximately 1 month. For both NSTEMI and STEMI patients who were treated with drug-eluting stents, the optimal duration of clopidogrel therapy may be longer than 1 year.

### Balancing the Risks and Benefits of Antithrombotic Therapy

Bleeding and transfusion risk is high with current antithrombotic treatments, noted Frans Van de Werf, MD, University Hospital Gasthuisberg, Leuven, Belgium. Prof. Van de Werf suggested strategies for balancing the benefits and risks of long-term antithrombotic therapy for patients with NSTEMI or STEMI.

Approximately 15% of patients with NSTEMI require transfusions due to excess bleeding during their hospitalization [Yang J et al. *JACC* 2005]. Transfusions are associated with an increased risk in 30-day mortality in patients with NSTEMI (OR 3.94, 3.26-4.75) and in those with STEMI (OR 3.7;  $p<0.0001$ ) [Rao SV et al. *JAMA* 2004; The APEX-AMI Investigators. *JAMA* 2007], although a causal relationship is difficult to establish.

Prof. Van De Werf offered several recommendations for balancing benefit and risk in this patient population. For example, he recommended performing invasive procedures only when indicated, and suggested considering radial artery access in patients at high risk for bleeding. Coronary artery bypass grafting should be performed after stopping clopidogrel for at least 5 days.

Prof. Van De Werf also suggested using fondaparinux or bivalirudin in patients at high risk for bleeding. Finally, limiting the use of upfront glycoprotein IIb/IIIa inhibitors to only high-risk NSTEMI patients may also reduce bleeding, although studies are conflicting regarding the potential loss in efficacy, and additional studies are ongoing [EARLY ACS – Giugliano. *AHJ* 2005;149:994-1002]. Antithrombotic agents should be dosed carefully, especially in elderly, female, or low-

weight patients, and in those with renal failure to avoid overdosing these patients who are at increased risk of bleeding. [Alexander. *JAMA* 2005;294:3108-16]. Lastly, Prof. Van De Werf reminded the audience that use of a proton pump inhibitor in patients with a history of gastrointestinal bleeding is now recommended by the updated nSTE-ACS guidelines [Anderson et al. *JACC* 2007].

## Advances in Cardiovascular Surgery Techniques

Cardiovascular surgery is becoming less invasive, more focused, and safer, according to speakers who presented new approaches to several traditional surgical procedures.

### Hybrid Revascularization for Coronary Artery Disease

Hybrid revascularization, which incorporates coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) in one intervention, offers clinical and cosmetic advantages over CABG alone, said Johannes Bonatti, FETCS, Medical University of Innsbruck, Innsbruck, Austria. Cumulative data from recent studies revealed 0% perioperative mortality, 2% stenosis of the left internal mammary artery, and 12% restenosis of PTCA/stent lesions. One comparative study (de Canniere D et al. *AHJ* 2001;142:563-70) found multiple advantages for the hybrid procedure versus CABG for double-vessel disease, including faster return-to-work time (22 vs 89 days).

Endoscopic robotics further enhances hybrid revascularization. Based on 51 cases (Table 1), Dr. Bonatti has found that the robotic approach offers better overview inside the chest, and produces a longer graft and a smaller scar than a full sternotomy. "This operation best preserves the patient's integrity," he observed.

**Table 1. Hybrid Revascularization Innsbruck (Robotics) 2001-2007.**

Intention to treat n=51		
MIDCAB (LIMA endoscopically)	2	4 %
AH-TECAB (LIMA-LAD)	38	74 %
BH-TECAB (LIMA-LAD)	4	8 %
AH-TECAB (RIMA-LAD/LIMA-Cx)	4	8 %
AH-TECAB (LIMA-Dg/LAD jump)	3	6 %
Endoscopic surgery first	33	65 %
PCI first	4	8 %
Simultaneous intervention	14	27 %

\*Significant stenosis was defined as more than 50% stenosis.

### Transapical Aortic Valve Replacement

A new technique has been introduced for aortic valve replacement. In this case, the valve is replaced using a transapical approach.

The transapical procedure involves a minithoracotomy, balloon valvuloplasty, and implantation of an investigational prosthesis. The lack of mortality and stroke was striking in a population of 89 elderly high-risk patients. Survival was >90% at 30 days and no new strokes occurred. Sixty-eight patients (76.4%) were operated off-pump, and perioperative conversion was required in only 4 (4.5%). Thirty-day mortality was 9%, predominantly from underlying disease.

Noting these results, Dr. Walther commented, "It is important that the elderly patients not just survive, but survive without strokes."

### Atrial Fibrillation Ablation

Finally, concomitant ablation of atrial fibrillation (AF) in patients undergoing cardiovascular surgery was discussed by Patrick M. McCarthy, MD, Northwestern University, Chicago, IL. Underlying AF raises the mortality risk in patients undergoing any cardiac surgery. In a study by Dr. McCarthy and colleagues (Quader MA et al. *Ann Thorac Surg* 2004;77:1514-1524) survival was significantly compromised in patients with AF undergoing CABG: 23% at 15 years (CABG-related?), vs 46% for patients without AF.

Concomitant ablation is therefore desirable to improve survival and to spare AF patients from additional ablation procedures. The goal of epicardial AF surgery is to reproduce the results achieved with the classic Cox-Maze procedure, using a minimally invasive technique and no cardiopulmonary bypass. In this procedure, surgeons can ablate the AF, close the left atrial appendage and ablate the ganglionated plexi.

In five prospective randomized trials of permanent AF ablation during mitral valve surgery, normal sinus rhythm was restored in 44-94% and the treatment arm was significantly improved over controls (p<0.001), he noted. During mitral valve repair, Dr. McCarthy uses bipolar radiofrequency ablation and cryoablation. During aortic valve replacement, CABG, and aneurysm, he uses pulmonary vein isolation and closes the left atrial appendage. Cryoablation is used during re-do mitral valve repair.