

# Therapeutic challenges in the treatment of cardiovascular diseases: issues and answers

*(American Heart Association meeting, Orlando, Florida, November 2003)*

The satellite session devoted to the therapeutic challenges in the treatment of cardiovascular diseases was chaired by R.M. Califf (Durham, US) and E.J. Topol (Cleveland, US). This session was sponsored by an educational grant from the Bristol-Myers Squibb/Sanofi-Synthelabo partnership. The central theme of the session was atherothrombosis, a concept that encompasses both atherosclerosis and thrombosis. Atherothrombosis is characterised by a sudden (unpredictable) atherosclerotic plaque disruption (rupture or erosion) leading to platelet activation and thrombus formation. Atherothrombosis is a common pathological cause of all major clinical manifestations of vascular disease, such as myocardial infarction, ischaemic stroke, angina, transient ischaemic attack and peripheral arterial disease, and is a leading cause of death worldwide.

S.R. Mehta (Ontario, Canada) focussed on optimising long-term management strategies for atherothrombotic disease. The speaker discussed several recent clinical trials which show large patient benefits with combination antiplatelet therapy. In the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial, which compared aspirin with the combination of aspirin and clopidogrel, a 20% relative risk reduction with the combination therapy over aspirin alone ( $p < 0.0009$ ) was found in patients with unstable angina/non-ST-segment elevation myocardial infarction. Furthermore, patients undergoing coronary artery bypass

graft (CABG), who have a high risk of thrombosis, showed a 19% reduction in cardiovascular (CV) death/MI or stroke when undergoing early CABG surgery and there was a 11% relative risk reduction for all CABG patients. In PCI-CURE, a sub-study which evaluated patients undergoing percutaneous coronary intervention (PCI), who received clopidogrel for up to one year after having an angioplasty or stent, a 31% relative risk reduction of CV death/MI ( $p < 0.002$ ) with no significant increase in bleeding was observed. Economic analysis of administration of clopidogrel, based on CURE, showed a cost of \$6173 per life year gained, and based on PCI-CURE \$5910 per life year gained. These costs are roughly ten times less than the generally accepted cost-effectiveness ratio.

Next, C.P. Cannon (Boston, US) spoke on innovative directions in the future role of antiplatelet agents. According to the speaker, antiplatelet therapy is a cornerstone in management of atherothrombotic disease. Cannon stressed that atherothrombosis is a systemic disease, so that even in successfully treated PCI patients there are always multiple plaques not seen on angiogram. As these plaques will become the next event, long-term treatment is desirable. Several trials have been conducted for evaluating the long-term effects of aspirin in combination with clopidogrel: CURE, PCI-CURE and CREDO (Clopidogrel for the Reduction of Events During Observation), where patients re-

ceived clopidogrel before angioplasty or stenting procedures and up to one year afterwards. One of the conclusions from the data is that patients receiving aspirin at a low dose of 75 to 100 mg benefited from a maximum antithrombotic effect with the least side effects, such as major bleeding. Combining clopidogrel with aspirin slightly increased risk of major bleeding. However, a significant reduction in the incidence of CV death, MI, stroke and refractory angina over aspirin alone is observed, regardless of the aspirin dose. Other currently running major trials that should help to further document the clinical benefit of antiplatelet agents include stroke trials assessing the clinical use of aspirin and clopidogrel, such as MATCH (Management of ArteroThrombosis with Clopidogrel in High-risk patients with recent transient ischaemic attack or ischaemic stroke), and SPS-3 (Secondary Prevention of Small Subcortical Strokes). Ongoing cardiovascular trials include CLARITY (evaluation of the effectiveness of clopidogrel and aspirin in improving opening of a blocked artery in patients with an MI receiving a thrombolytic drug), ACTIVE (Atrial fibrillation Clopidogrel Trial with Irbesartan for the prevention of Vascular Events), CAMPER (Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularisation) and CHARISMA (Clopidogrel for High Arterothrombotic Risk and Ischaemic Stabilisation Management and Avoidance).

V. Fuster (New York, US) looked at the new imaging technologies for diagnosing and evaluating diffuse atherothrombotic disease. The speaker discussed four new techniques that can be used to determine the extent of atherosclerosis. Improvements in MRI technology allow differentiation between fibrous, thrombotic and calcified plaque components. Plaque composition is associated with risk of plaque rupture and using this technique the mechanisms of rupture and clotting can be studied. Computed tomography (CT) coronary calcium evaluation can be used to detect small calcium deposits in the coronary arterial wall. The amount of calcium deposits can be used to quantify the extent of plaques and add to the classic risk-factor profile. CT angiography (CTA) generates a virtual 3D image of blood vessels on which stenotic and calcified lesions can be identified noninvasively. Contrast-enhanced magnetic angiography (MRA) can also be used to detect arterial stenosis. A major benefit of these new imaging techniques is that they are completely noninvasive and thus will be ideal for use with high-risk patients.

E.J. Topol (Cleveland, US) focussed on the evolving science of atherothrombotic disease. In the majority of diseases, including atherothrombosis, patients are differently predisposed to the disease and exhibit individual variation in the response to therapy. For example, 10 to 20% of patients receiving antiplatelet therapy do not demonstrate full responsiveness. This can to some extent be attributed to the genetic variation between individuals. Various marker genes are known for inflammation, namely sCD40 ligand, hs-CRP and myeloperoxidase, which can be used to track the progression of athero-

thrombosis, but mutations in any single one of these genes do not account for the disease. We are only now discovering actual causal genes. For example, in one family, autosomal dominant coronary artery disease and myocardial infarction was ascribed to a deletion mutant of endothelial transcription factor. According to Topol, individualised therapy is needed to overcome the problem of variability in the response to medication. This requires screening of the individual genetic makeup of the patient, using such techniques as mass spectroscopy finger printing and gene chip expression arrays. These techniques enable genome-wide scanning for gene mutations, which is essential for the identification of complex diseases such as stroke that cannot be explained by single gene mutations.

Finally, R.M. Califf (Durham US) spoke on whether bridging quality care initiatives with improved patient outcomes was a leap of faith. Califf stressed that a major limitation of most current trials is that the patients who are enrolled for clinical trials differ from the average patient as seen by the clinician. They are more often older, female, diabetic and high-risk patients, while in practice the majority of patients will be lower-risk patients. New types of studies such as the REACH registry, may bring improvement in this situation. REACH (REduction of Atherothrombosis for Continued Health) is a worldwide registry of more than 50,000 patients from more than 35 countries, with a two-year follow-up. The large-scale set-up will allow determination of risk factors for specific patient groups. This is important because risk factors differ with age, sex and geography. First results from REACH are expected in one year. A second problem discussed by

Califf that is thought to play a role, especially in the lower quarter of American hospitals, is the insufficient application of evidence-based medicine. This means that new proven therapies hardly penetrate to the clinic, with a corresponding increased risk of death. Califf concludes by suggesting that in the immediate future the biggest gains in quality of care for patients can be obtained by improved education of and feedback to specialists and general practitioners.

### Conclusion

Atherothrombosis still constitutes a major cause of cardiovascular disease and death. New treatments including combination therapy with aspirin and clopidogrel are increasingly effective in preventing MI, stroke and death in patients who suffer from atherothrombosis. New imaging techniques allow more detailed study of the development and composition of the atherosclerotic lesions, potentially contributing to new therapeutic modalities. Individual tailoring of (drug) treatments through, for example, gene expression arrays may further improve outcome in patients with atherosclerotic disease; however these techniques require a lot of knowledge about the genetic basis of a disease, which will have to be built up first. Finally, lessons learned so far through evidence-based medicine should be applied more consequently to daily clinical practice to achieve optimal care for large patient groups. Professional guidelines and protocols can help to achieve these goals.

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