

The 1st Vulnerable Patient Satellite Symposium

Introducing a New Era in Preventive Cardiology

Annual Scientific Sessions of American Heart Association 2003, Orlando, FL



The VP Symposium to Go!

(A quick review of the speakers' presentation in bullet points)

Bullet Points from Dr. Fuster's Presentation:

- Diabetic patients are good example of vulnerable patients. The underlying pathology in diabetics and metabolic syndrome lead to the inflammatory pathways involved in atherosclerosis.
- We should pay more attention to the plaque adventitia instead of intima. Adventitia is where the problem originates. Dysfunctional vasa vasorum and breakdown of external elastic lamina may be more important in development of vulnerable / high-risk plaques.
- Macrophages are likely to come from the adventitia. There is a strong correlation between macrophage and vasa vasorum density. Vasa vasorum imaging may provide critical information about the underlying pathology of plaque. Similar to macrophage density, vasa vasorum density increases in rabbits on high fat diet and decreases with statin therapy.
- Virtual coronary endoscopy by fast CT is on the horizon. Soon, like virtual colonoscopy you will be able to see fly-through video imaging of coronary arteries.
- MR imaging is getting faster. Although it is not quite ready for coronary imaging, MR imaging of atherosclerosis in aorta, carotid, and peripheral arteries is available today and can measure the burden of the disease. Ruptured plaques that are clinically silent can be imaged by fibrin targeted antibody contrast enhanced MRI. Also PET-CT imaging that provides both morphology and activity information is promising.
- Increased blood thrombogenicity [vulnerable blood] in diabetic patients is directly resulted from high tissue factor activity in circulating monocytes. Increased apoptosis in plaque and also blood is detrimental. HDL based therapy is the best anti-apoptotic and anti-thrombotic therapy.

Bullet Points from Dr. Naghavi's Presentation:

- Vulnerable patients are subjects who have high likelihood (i.e. 10-15%) of developing an adverse cardiac event (acute coronary syndrome or sudden cardiac death) in the near future (i.e. 1-2 year).
- There are approximately 15 million asymptomatic vulnerable patients each year in the United States and much more worldwide. A large group of this population can be diagnosed before the event, based on today's technology. A stepwise cost-effective approach from the bottom to the top of the VP Pyramid is needed to save vulnerable patients.
- Major advancements in cardiovascular risk assessment including emerging serum markers and novel imaging techniques are providing us with new opportunities to establish an organized public screening program for prevention of heart attacks and out-of-hospital sudden cardiac death.

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- Tremendous improvements have been made in the past few years in the area of systemic and interventional therapies that promise rapid stabilization of vulnerable patients once diagnosed. The new therapeutic developments lend support to establishment of a cost-effective diagnostic screening program.
- Rupture-prone plaques are not the only type of vulnerable plaques. Other types of vulnerable plaques exist. And vulnerable plaques are not the only culprit factors in the development of acute coronary syndromes and sudden cardiac death. Vulnerable blood (prone to thrombosis) and vulnerable myocardium (prone to fatal arrhythmia) play an important role in the outcome of the atherosclerosis.
- A quantitative vulnerability score needs to be developed based on longitudinal follow-up studies. However, follow-up outcome studies like Framingham cohorts are hard to reproduce and may not be possible. Studying surrogate markers of outcome with imaging technologies offer many advantages. In the meantime, consensus statements based on the available evidence should be vigorously pursued to provide guidelines for public screening and risk stratification. A pyramid-based approach (VP Pyramid) seems to be most relevant.
- With the advent of genomic and proteomic research, numerous new serum markers will soon be available and can play a role in the first level of screening from the bottom of the VP Pyramid. However, for a most cost-effective risk stratification approach, it remains preferable to identify surrogate markers of atherosclerosis and serum markers of disease activity versus screening a long list of various risk factors that partially contribute to the long and complicated cascade of atherosclerosis.
- Noninvasive non-imaging tests and noninvasive imaging tests are becoming increasingly available and can link the bottom to the top of the Pyramid. Among these tests, endothelial function measurement and CT imaging can provide enormous information. CT imaging provides much more information than calcium score. Coronary angiography and plaque characterization along with several other non-cardiac measures of risk can be obtained by CT imaging.
- In interventional cardiology, despite many emerging intravascular diagnostic techniques, IVUS remains the most powerful and technique available to interventional cardiologists. The diagnostic value of IVUS significantly increases by addition of new technologies such as Virtual Histology, palpography, shear stress imaging,...
- Slow or reverse progress in prevention of sudden cardiovascular events in the past decade calls for new preventive strategies. Screening, diagnosis, and management of vulnerable patients introduce a new and promising era in preventive cardiology. Cardiovascular healthcare policy makers and regulatory agencies (i.e. NIH, FDA, CDC,...) along with the national organizations (i.e. AHA, ACC, ESC,...) are urged to seriously consider establishing a regular screening program for prevention of heart attacks much like the current screening strategies for prevention of advanced cancers.
- AEHA is leading the efforts to create the first draft of a consensus guideline for regular screening of population aged 35 and above, which will be presented in the 2nd Vulnerable Patient Satellite Symposium during the Annual Scientific Sessions of American College of Cardiology.

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Bullet Points from Dr. Serruys' Case Presentation:

- Rupture-prone vulnerable plaques are the most common type of vulnerable plaques and easier to detect. As for the other types of vulnerable plaque, we are in a vacuum of diagnostic techniques.
- IBIS trial (Integrated Biomarker and Imaging Study), a single center investigation by the Thorax Center, has recruited 95 vulnerable patients with non-flow-limiting vulnerable plaques who exhibited indications of vulnerability in a series of emerging diagnostic tests.
- The diagnostic tests in IBIS trial include the following:
 - (lipid profile, inflammatory markers, MMPs, ...)
 - Multi-slice CT scan
 - Endothelial and medial dysfunction test
 - IVUS (morphology, virtual histology, palpography, and shear stress imaging)
 - Thermography
 - Optical coherent tomography
- Vulnerable plaques in IBIS vulnerable patients were treated with drug-eluting stents.
- All patients in IBIS trial are being followed. In each 6 month or 12 month examinations the above diagnostics testes are repeated.
- Dr Serruys discussed a detailed presentation of a vulnerable patient with a 3-year history of NSTEMI (non-ST elevation MI) and repeated adverse events related to LAD. In this case presentation Dr Serruys walks the audience through his stepwise decision making process to stent a non-flow-limiting non-culprit lesion that is likely to be a vulnerable plaque.
- The patient was stented with Cypher stent and the procedure had no complications.
- In 6 months follow up the patient was completely symptom free. Angiography and IVUS with Virtual Histology, palpography, and shear stress imaging showed satisfactory results.

Bullet Points from Dr. Shah's Presentation:

(presented by his associate Dr. Kuang-Yuh Chyu)

- Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques. This study was evidenced by pathology examinations of carotid specimens after 3 months of statin therapy, indicating the significant role of systemic therapy in plaque stabilization.
- Low-HDL level is a major risk factor of coronary heart disease. In addition to stimulating reverse cholesterol transfer, HDL has many biological effects (such as antioxidant, anti-inflammatory, anti-apoptosis, and anti-thrombosis) which make HDL a great therapeutic target.
- Apo-A1 Milano is a mutant form of Apo-A1 that was found in people with low-HDL but no heart disease indicating a strong protective effect. In animals models, intravenous recombinant Apo-A1 Milano markedly inhibits atherosclerosis, halting its progression and even inducing regression of lesions within 5 weeks .. Furthermore it reduced lipid and macrophage content of plaques indicating a plaque stabilizing effect. Adeno

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associated virus mediated Apo A-I milano gene transfer also produces similar effects in mice.

- Even a single high-dose of recombinant Apo-A Milano significantly reduced lipid and macrophage content of plaques within 48 hours in a mouse model indicating a rapid plaque stabilizing action..
- The first double blind human clinical trial with 5 weekly injection of recombinant Apo-A1 Milano showed significant reduction in plaque volume evidenced by IVUS indication that Apo-A Milano induced rapid regression of atherosclerosis.
- HDL based therapy has a promising future in stabilization / regression of atherosclerosis in vulnerable patients.

Bullet Points from Dr. Stone's Presentation

- While detection of already-vulnerable plaques is critical, it is equally important to identify areas in the coronary arteries that will become vulnerable (prone to rupture, thrombosis, or progression).
- Although cardiovascular atherosclerotic disease is a systemic abnormality with major metabolic and immune components, it does not occur evenly through the total vascular bed of the body. Indeed a small portion of the total arterial tree and none of the venous bed develops significant atherosclerosis. This may vary in different people. The dynamic and pattern of blood flow (shear stress) seem to be responsible for the local manifestation of the disease.
- Change in shear stress directly affects the activity of endothelial cells. Increased or decreased shear stress beyond the physiological range impairs endothelial function and may result in expression of certain inflammatory adhesion molecules. It also affects the permeability of endothelial layer and other properties of endothelial surface (i.e. antithrombotic and antiproliferative effects). Also it has been shown that excess free radicals are created at the site of abnormal shear stress which may link the mechanical stress to biochemical oxidative stress and create the ground for development of atherosclerotic plaque.
- Therefore shear stress imaging may provide significant information to identify the trajectory of the natural history of atherosclerosis and to find the areas of the artery prone to development or progression of atherosclerosis. Normal physiological shear stress varies between 15-50 dyne/cm²
- Coronary shear stress can be visualized by combining coronary IVUS and angiography images using 3 D reconstruction of arterial segments and computational flow dynamic technology.
- Dr Stone's group has just completed the study of 10 patients in whom they measured baseline coronary shear stress and repeated the measurement at 6 month follow up. They discovered that areas with low shear stress developed outward remodeling to the areas with high shear stress developed inward remodeling to minimize the change in shear stress.

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- Therefore areas of low shear stress with substantial outward remodeling (~40% increase in EEA) may bear a high likelihood of complications and should be targeted for preemptive therapeutic interventions such as stenting.

Bullet Points from Dr. Koenig's Presentation

- The addition of CRP to Framingham risk prediction model results in a better fit of the model and can significantly improve the predictive value.
- This improvement is more enhanced for those at intermediate risk (10-20% risk of CHD over 10 years)
- Thus, CRP measurement modulates coronary risk and may therefore modify the physician's interpretation of the patient's risk status
- Calcium scoring also seems to improve Framingham risk prediction model. A combination of coronary calcium score and CRP along with Framingham score sounds quite reasonable.
- However, these findings have to be replicated in other populations.