Keynote: The Changing Landscape of Cardiovascular Disease: The Implications for Practice Today and Tomorrow

Updates for Cardiologists
Chicago, Illinois
September 12, 2012

Content Collaborator
Session 1: Keynote: The Changing Landscape of Cardiovascular Disease: The Implications for Practice Today and Tomorrow

Learning Objectives

1. Apply evidence-based recommendations to the risk stratification of patients at risk for cardiovascular disease and for those experiencing acute thrombotic events in order to improve medication adherence, reduce hospital admissions, and improve patient outcomes.

2. Assess current controversies in cardiac risk stratification to include the use of newer therapeutic choices, potential drug interactions, the need for genetic or platelet response testing, as well as considerations for balancing risks and benefits.

Faculty

Peter Libby, MD, FACC
Chief, Cardiovascular Medicine
Brigham and Women’s Hospital
Mallinckrodt Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Dr Peter Libby is chief of cardiovascular medicine at the Brigham and Women’s Hospital (BWH) in Boston. He also serves as the Mallinckrodt Professor of Medicine at Harvard Medical School, where he directs the D. W. Reynolds Cardiovascular Clinical Research Center. His current research focus is the role of inflammation in vascular diseases such as atherosclerosis. His areas of clinical expertise include general and preventive cardiology.

An author and lecturer on cardiovascular medicine and atherosclerosis, Dr Libby has published extensively in medical journals, including Circulation, the Journal of Clinical Investigation, Proceedings of the National Academy of Sciences, the New England Journal of Medicine, and Nature. He is editor-in-chief of the new ninth edition of Braunwald’s Heart Disease. Dr Libby has also contributed the chapters on the pathogenesis, treatment, and prevention of atherosclerosis to Harrison’s Principles of Internal Medicine. He has frequently served as a consultant to the National Heart, Lung, and Blood Institute, including a five-year term on its Board of Scientific Councilors, and was the recipient of the organization’s MERIT Award. Dr Libby has held numerous visiting professorships and has been selected to deliver over 50 named or keynote lectures throughout the world.

Dr Libby’s professional memberships include the Association of American Physicians, the American Society for Clinical Investigation, and honorary membership in the British Atherosclerosis Society. The current president of the Association of University Cardiologists, Dr Libby has served in many roles as a volunteer for the American Heart Association, including chairman of several research committees and member of executive committee councils on arteriosclerosis, circulation, and basic science.

Dr Libby earned his medical degree at the University of California, San Diego, and completed his training in internal medicine and cardiology at the Peter Bent Brigham Hospital (now the BWH). He has received recognition and numerous awards for his research accomplishments, including the 2006 Distinguished Scientist Award of the American College of Cardiology. He also holds an honorary Master of Arts from Harvard University.

Faculty Financial Disclosure Statement

The presenting faculty reports the following:

Dr Libby is a scientific advisory board member for Athera Biotechnologies, BIND Biosciences, Carolus Therapeutics, and Interleukin Genetics. He also serves as an unpaid consultant and/or is involved in clinical trials with AstraZeneca Pharmaceuticals LP; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Pronova BioPharma; Sigma-Tau Pharmaceuticals, Inc.; and Merck & Co., Inc.
Suggested Reading List


The Changing Face of the Acute Coronary Syndromes

Peter Libby
Brigham & Women’s Hospital
Harvard Medical School

Keynote Talk
Pri-Med Updates for Cardiologists 2012

The Changing Face of the Acute Coronary Syndromes

♥ Changing demographics
♥ Younger patients
♥ More women
♥ More non-whites
♥ More diabetes and dysglycemia

Cardiovascular Risk ca. 1958

♥ Male
♥ Middle aged
♥ High cholesterol (LDL)
♥ Hypertensive
♥ Smoker
♥ Higher socioeconomic status

“Longevity is a vascular question, and has been well expressed in the axiom that ‘a man is only as old as his arteries’”
Sir Wm. Osler, 1892

The Changing Face of the Acute Coronary Syndromes

♥ The population at risk for cardiovascular disease is shifting - “democratization”
♥ The risk profile for cardiovascular disease is changing
Evolution of the coronary care unit: Clinical characteristics and temporal trends in healthcare delivery and outcomes

Jason N. Katz, MD; Bimal R. Shah, MD, MSA; Elizabeth M. Voic, MD; John R. Herdon, MD; Linda K. Sirun, MD, L. Kristy Manley, MD, MHS, FACC; Christopher B. Granger, MD, FACC; Daniel E. Mark, MD, MTH, FACC; Robert M. Califf, MD, FACC; Richard S. Becker, MD, FAVA

Objectives: To describe long-term temporal trends in patient characteristics, processes of care, and in-hospital outcomes among consecutive admissions within the interventional coronary care unit.

Methods: A comprehensive database that records both pre-hospital and in-hospital data was created from a single center, containing consecutive patients admitted to the interventional coronary care unit between January 1, 1988, and December 31, 2006. The database contained information on patient demographics, PCI, CABG, and hospital course. The patients were divided into 2 periods, 1989-1991 and 2004-2006. The database contained information on patient demographics, PCI, CABG, and hospital course. The patients were divided into 2 periods, 1989-1991 and 2004-2006.

The Changing Face of ACS: Shift in Ethnicity

Katz, Crit Care Med 2010; 38:375–381

The Changing Face of ACS: Shift in Sex

Katz, Crit Care Med 2010; 38:375–381

The Changing Face of ACS: Shift in Co-Morbidities

Katz, Crit Care Med 2010; 38:375–381
The Changing Face of the Acute Coronary Syndromes

♥ Changing disease
- More NSTEMI, fewer STEMI
- More MI, less “Unstable Angina”


The Changing Face of the Acute Coronary Syndromes

♥ Changing diagnosis
- LDH->CK->Tn->ultra Tn-> nano Tn
- Successive generations of troponins have lowered the detection threshold for myocardial injury: whither “unstable angina?”

Mills N et al. JAMA 2011; 305: 1210-1216

Impact of Implementation of a Sensitive Assay for Troponin

Emphasis on Diagnostic Value of using a Delta Troponin

The Changing Face of the Acute Coronary Syndromes

- Changing demographics
- Changing disease
- Changing diagnosis
- New pathophysiologic insights
- Changing treatments
- Advances in imaging

Traditional View of Human Atherogenesis

- Ischemic Heart Disease
- Cerebrovascular Disease
- Peripheral Vascular Disease

Atheromata that cause acute myocardial infarction often do not cause flow-limiting stenoses

- Post-thrombolysis angiography
- Serial angiographic studies
- Intravascular ultrasound studies

Ulcera.on and intraplaque dye penetration by CTA. A, Example of noncalcified plaque with ulceration, defined as contrast extending beyond the vessel lumen but contiguous with it, in a patient with acute chest pain and a coronary artery calcium score of zero. B, Two noncalcified plaques demonstrating intraplaque dye penetration, defined as a contrast pool within the plaque not contiguous with an overlying ulceration, in 2 patients with acute chest pain and coronary artery calcium scores of zero.

Computed Tomographic Angiography Characteristics of Atherosclerotic Plaques Subsequently Resulting in Acute Coronary Syndrome


Comcludions The patients demonstrating positive remodeling coronary segments with low-attenuation plaques on CT angiography were at a higher risk of ACS developing over time when compared with patients having lesions without these characteristics. (J Am Coll Cardiol 2013; 62:159-167) © 2013 by the American College of Cardiology Foundation

1,059 patients
Computed Tomographic Angiography Characteristics of Atherosclerotic Plaques Subsequently Resulting in Acute Coronary Syndrome Motoyama et al.

1,059 patients Months of follow-up

Angio w/ ACS 6 mos post CTA:

Time-to-Event Curves for Major Adverse Cardiovascular Events after Successful, Uncomplicated Percutaneous Coronary Intervention in 697 Patients with Acute Coronary Syndromes.

Traditional View of Human Atherogenesis

Four Mechanisms of Atherosclerotic Plaque Disruption

Characteristics of Plaques that have caused fatal acute MI

Love, macrophage rich

Thin fibrous caps

Paucity of SMC

Structural Integrity of the Plaque’s Fibrous Cap

- Depends on interstitial collagen fibrils (types I & III) synthesized by smooth muscle cells

Interstitial Collagenases
MMP-1, MMP-8, & MMP-13

Cleaved Collagen Colocalizes with MMP-1 & MMP-13 in Human Atheroma

GK Sukhova et al.

Dynamic Regulation of Plaque Collagen

Plaque rupture with thrombosis

Thrombus
Fibrous cap
Lipid core
Thrombosis on a disrupted atheroma, the cause of most acute coronary syndromes, results from:

- weakening of the fibrous cap
- thrombogenicity of the lipid core

CD40 and Tissue Factor in Atheroma


Molecular Biology of the High-Risk Plaque

After Libby P. Circulation 1995

The “New Biology” of Atherosclerosis

- Unstable coronary atheromata are often not the “tight” stenoses
- Stabilization of lesions, by medical therapy, provides a new therapeutic target beyond revascularization

Interventions that may “stabilize” atherosclerotic plaques

- Smoking Cessation
- Diet
- Physical activity
- HDL Raising?
- Lipid lowering

Plaque “Stabilization”: Plaques with a thick fibrous cap may have less tendency to rupture and cause thrombosis

“Unstable” plaque
- Fibrous cap
- Fewer inflammatory cells

“Stable” plaque
- Fibrous cap
- More inflammatory cells

How does lipid-lowering improve patient outcome?

• Regression of fixed stenoses?

Regression of Human Atherogenesis?

Disproportionate reduction of coronary events and stenosis in lipid-lowering trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Δ Stenosis</th>
<th>Δ Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>FATS (niacin + resin)</td>
<td>- 0.9 %</td>
<td>- 80 %</td>
</tr>
<tr>
<td>FATS (statin + resin)</td>
<td>- 0.7 %</td>
<td>- 70 %</td>
</tr>
<tr>
<td>STARS (diet)</td>
<td>- 1.1 %</td>
<td>- 69 %</td>
</tr>
<tr>
<td>STARS (diet + resin)</td>
<td>- 1.9 %</td>
<td>- 89 %</td>
</tr>
</tbody>
</table>

After Brown BG.

What accounts for the disparity between degree of coronary artery stenosis and producing the acute coronary syndromes?

The functional state of the atheroma, not merely its size or the degree of luminal encroachment, determines the propensity for development of acute coronary syndromes.

How does lipid-lowering improve patient outcome?

Angiographic and intravascular ultrasound studies show only modest decreases in stenosis and plaque volume with lipid lowering

♥ Regression of fixed stenoses?

♥ Anti-inflammatory effect/ lesion “stabilization?”
Dietary lipid lowering reduces collagenase expression and increases collagen accumulation in atheromata of cholesterol-fed rabbits

Masanori Aikawa, Elena Rabkin, Yoshikatsu Okada, Sami Voglic, Steven Clinton, Constance Brinckerhoff, Galina Sukhova, Peter Libby
Circulation 1998; 97:2433-2444

Dietary lipid lowering reduces tissue factor expression in rabbit atheroma
Aikawa, Voglic, Sugiyama, Rabkin, Taubman, Fallon, Libby.
Circulation 100:1215; 1999

Dietary Lipid Lowering Reduces Inflammation in Atheromata
Lipid lowering by diet alone reduces ROS production, oxLDL accumulation, and VCAM-1 and MCP-1 expression in atheroma of cholesterol-fed rabbits.
Circulation 2002; 106:1390-1396

Plaque “stabilization” by lipid lowering: an anti-inflammatory therapy

In rabbits with diet-induced atherosclerosis, reduced cholesterol consumption:
♥ Limits inflammation in atheroma
♥ Improves features of plaques associated with stability
♥ Reduces plaque thrombogenicity
♥ Decreases oxidative stress and endothelial dysfunction
Clinical Evidence for Statin Treatment: Increasing Fibrous vs. Lipid Character of Atherosclerotic Plaques

Stabilization of Carotid Atheroma Assessed by Quantitative Ultrasound Analysis in Nonhypercholesterolemic Patients With Coronary Artery Disease

Watanabe M, JACC Cardiovasc Imaging 2009:2:1213

IBS = Integrated Back Scatter
IMT = Intima-Media Thickness

Statin Treatment Increases Fibrous Character of Atherosclerotic Plaques but not Intima Media Thickness

Four Mechanisms of Atherosclerotic Plaque Disruption

IMT = Intima-Media Thickness

How can we translate inflammation biology to the clinic?

F-4V PET: sensitive, quantitative, translatable

Nahrendorf M, JACC Cardiovasc Imaging 2008:1:1213
The Changing Face of the Acute Coronary Syndromes

♥ New pathophysiologic insights
♥ Mechanisms of plaque rupture and stabilization better understood
♥ Is superficial erosion on the rise and fibrous cap rupture less so in the stain era?

The Changing Face of the Acute Coronary Syndromes

♥ Changing demographics
♥ Changing disease
♥ Changing diagnosis
♥ New pathophysiologic insights
♥ Changing treatments
♥ Advances in imaging

The Changing Face of the Acute Coronary Syndromes

♥ Changing treatments
♥ Primary PCI
♥ DES
♥ Potent statins, higher use
♥ Novel anti-platelet and anti-coagulant agents

Novel Anti-Platelet Agents Cross-study Comparison

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Triton-TIMI 38*</th>
<th>PLATO†</th>
<th>CURRENT-OASIS 7†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death/MI/stroke</td>
<td>0.81</td>
<td>0.84</td>
<td>0.86</td>
</tr>
<tr>
<td>Stent Thrombosis*</td>
<td>0.48</td>
<td>0.75</td>
<td>0.69</td>
</tr>
<tr>
<td>Major Bleeding*</td>
<td>1.32</td>
<td>1.25</td>
<td>1.36</td>
</tr>
<tr>
<td>CV death</td>
<td>0.89</td>
<td>0.88</td>
<td>0.95</td>
</tr>
<tr>
<td>All cause death</td>
<td>0.95</td>
<td>0.97</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*TIMI major not related to CABG
†Definite or Probable

ATLAS-2 TIMI-53: Primary Efficacy End Point


ACS Treatments Changing with Time

Jernberg, T. et al. JAMA 2011;305:1677-1684
The Changing Face of the Acute Coronary Syndromes

- Changing demographics
- Changing disease
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- Changing treatments
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The Vascular Biology of Atherosclerosis and Imaging Targets

Peter Libby, DiCarli, and Weisleder

The growing worldwide health challenge of atherosclerosis, together with advances in imaging technologies, has stimulated considerable interest in novel approaches to gauging this disease. The last several decades have witnessed a burgeoning in understanding of the molecular pathways involved in atherogenesis, lesion progression, and the mechanisms underlying the complications of human atherosclerotic plaques. The imaging of atherosclerosis is reaching beyond anatomy to encompass assessment of aspects of plaque biology related to the pathogenesis and complication of the disease. The harnessing of these biologic insights promises to provide a plethora of new targets for molecular imaging of atherosclerosis. The goals for the years to come must include translation of the experimental work to visualization of these appealing biologic targets in humans.
Near Infrared-Detecting Wire for Intra-arterial Use

Jaffer et al. Circulation 2008

Near Infrared Catheter Interrogation of Rabbit Atheroma in vivo

Jaffer et al. Circulation 2008

Two-Dimensional Intravascular Near-Infrared Fluorescence Molecular Imaging of Inflammation in Atherosclerosis and Stent-Induced Vascular Injury


Indocyanine Green Enables Near-Infrared Fluorescence Imaging of Lipid-Rich, Inflamed Atherosclerotic Plaques

Claudio Vinegoni, et al.
Sci Transl Med 3, 84ra45 (2011); DOI: 10.1126/scitranslmed.3001577

Two-Dimensional Intravascular Near-Infrared Fluorescence Molecular Imaging of Inflammation in Atherosclerosis and Stent-Induced Vascular Injury


Indocyanine green rapidly targets atheroma in rabbit arteries and provides NIRF signal enhancement.

Vinegoni C et al. Sci Transl Med 2011;3:84ra45-84ra45

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Editors' Summary

Gravity Your Arteries

Many have taken it upon themselves to "go green," perhaps by tuning down the thermostat, swapping out old lightbulbs, or even buying a hybrid car. But who would have thought that even your heart doctor can take part in this green initiative? As described by Jaffer et al., going green may be just what you and your arteries need to detect atherosclerotic plaques within them.

Indocyanine green rapidly targets atheroma in rabbit arteries and provides NIRF signal enhancement.

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Indocyanine green rapidly targets atheroma in rabbit arteries and provides NIRF signal enhancement.
In vivo intravascular near infrared guidewire sensing of indocyanine localized in atherosclerotic plaques in rabbits

Vinegoni C et al. Sci Transl Med 2011;3:84ra45-84ra45

Intra-arterial Protein-degrading Enzyme Imaging in Atherosclerotic Rabbits

White Light

Near infrared fluorescence

Conclusions

Novel imaging probes can detect protease activity in atheromata in vivo and may serve as a useful tool to visualize inflammation and to monitor changes during therapies.

The Changing Face of the Acute Coronary Syndromes

♥ Changing demographics
♥ Changing disease
♥ Changing diagnosis
♥ New pathophysiologic insights
♥ Changing treatments
♥ Advances in imaging

The Forgotten Majority: Residual Burden of Events in the Statin “Megatrials”

PROVE IT-TIMI 22: ACS Patients
Death/Major CV Events

The GOOD NEWS

Pravastatin 40mg
Median LDL-C 95 mg/dL
Event rate 26.3%

Atorvastatin 80mg
Median LDL-C 62 mg/dL
Event rate 22.4%

16% RRR
(p = 0.005)

% with Event
Months of Follow-up

PROVE IT-TIMI 22: ACS Patients
Death/Major CV Events

The BAD NEWS

Pravastatin 40mg
Median LDL-C 95 mg/dL
Event rate 26.3%

Atorvastatin 80mg
Event rate 22.4%

16% RRR
(p = 0.005)

% with Event
Months of Follow-up

Therapeutic Implications of Inflammation in Atherothrombosis

♥Despite advances in the standard of care, a considerable residual burden of atherothrombotic events persists

Yoshihiro Fukumoto
Jun-o Deguchi
Masanori Aikawa
Guo Ping Shi
Galina Sukhova
Farouc Jaffer
Matthias Nahrendorf
Thibaut Quillard
Ralph Weissleder