Keynote:
Top Studies of the American Heart Association and European Society of Cardiology from 2008

Chicago, IL
November 21, 2008
7:30 AM – 8:30 AM
Session 1: Keynote:
Top Studies of the American Heart Association and European Society of Cardiology from 2008

Learning Objectives

- Evaluate the latest developments in cardiology in 2008.
- Discuss the impact of these latest developments on patient care.

Faculty

Eugene Braunwald, MD, MACC
Distinguished Hersey Professor of Medicine
Harvard Medical School
Cambridge, Massachusetts

Chairman
TIMI Study Group
Brigham and Women’s Hospital
Boston, Massachusetts

Eugene Braunwald, MD, MACC, is the Distinguished Hersey Professor of Medicine at Harvard Medical School, and chairman of the TIMI Study Group at the Brigham and Women’s Hospital.

Dr Braunwald received his medical training at New York University and completed his medical residency at the Johns Hopkins Hospital. He served as the first chief of the cardiology branch and as clinical director of the National Heart, Lung and Blood Institute and founding chairman of the Department of Medicine at the University of California, San Diego. From 1972 to 1996 he was chairman of the Department of Medicine at the Brigham and Women’s Hospital. He was a founding trustee and chief academic officer of Partners HealthCare System.

Dr Braunwald’s first major paper was published in Circulation Research in July 1954, and he has been a major force in cardiology in the past half century. His early work focused on the control of ventricular function and he was the first to measure both left ventricular ejection fraction and left ventricular dp/dt in patients. His group showed the first neurohumoral defect in human heart failure, defined the pathophysiology of hypertrophic cardiomyopathy, and demonstrated salvage of ischemic myocardium following coronary occlusion. They defined myocardial stunning and ventricular modeling following myocardial infarction. For the past 21 years, as chairman of the TIMI Study Group, he and his colleagues demonstrated improved patient survival with a patent coronary artery which led to the widely accepted “open artery hypotheses.” They were the first to show the benefit of preventing adverse remodeling of the infarcted ventricle with angiotensin converting enzyme (ACE) inhibition. In the PROVE-IT TIMI 22 Trial, in 2004, they demonstrated the benefit of more intensive reduction of low-density lipoprotein (LDL) in high-risk coronary artery patients, which has already changed practice guidelines and will favorably affect the lives of millions.

Dr Braunwald is an editor of Harrison’s Principles of Internal Medicine, and the founding editor of Heart Disease, now in its 8th edition, the most influential textbooks in their fields.

Science Watch listed Dr Braunwald as the most frequently cited author in cardiology. Based on his contributions, Dr Braunwald has received numerous honors and awards including the Distinguished Scientist Award of the American College of Cardiology, Research Achievement, and Herrick Awards of the American Heart Association, the Gold Medal of the European Society of Cardiology and is the recipient of 14 honorary degrees from distinguished universities throughout the world. The living Nobel Prize winners in medicine voted Dr Braunwald as “the person who has contributed the most to cardiology in recent years.” Dr Braunwald was the first cardiologist elected to the National Academy of Sciences of the United States.

Faculty Financial Disclosure Statement

The presenting faculty reported the following:
Dr Braunwald reports that the TIMI Study Group, of which he is chairman, receives or has received grant support from AstraZeneca LP; Johnson & Johnson; Beckman Coulter, Inc.; Bristol-Myers Squibb Pharmaceutical Research Institute; CV Therapeutics; Daiichi Sankyo, Inc.; Eli Lilly and Company; Genentech; Integrated Therapeutics Group; Merck &
Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Roche Diagnostics Corp.; sanofi-aventis U.S.; and Schering-Plough Research Institute.

Dr Braunwald reports that he receives or has received research support from and that he provides occasional lectures (though not as part of an official speakers bureau) for Eli Lilly & Company; Merck & Co., Inc.; Schering-Plough Pharmaceuticals; and sanofi-aventis U.S.

**Drug List**
There are no drugs mentioned in this presentation

**Suggested Reading List**
There is no reading list for this presentation.
Important Recent Developments in Cardiology:
Late Breaking Clinical Trials
ESC 2008, AHA 2008

Eugene Braunwald, MD
Updates for Cardiologists
November 21, 2008

DISCLOSURES
Research Support for the TIMI Study Group

NATIONAL INSTITUTES OF HEALTH
AstraZeneca Pharmaceuticals LP
Johnson & Johnson
Beckman Coulter, Inc.
Bristol Myers Squibb Pharmaceutical Research Institute
CV Therapeutics
El Lilly
Genentech
Integrated Therapeutics Group
Merck & Co., Inc.
Novartis
Pfizer, Inc.
Roche Diagnostics Corp.
Sanofi Aventis
Schering Plough Research Institute

JUPITER
AHA November 9, 2008

A Randomized Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among 17,802 Apparently Healthy Men and Women With Elevated Levels of C-Reactive Protein (hsCRP): The JUPITER Trial


An Investigator Initiated Trial Funded by AstraZeneca, USA

* These authors have received research grant support and/or consultation fees from one or more statin manufacturers, including Astra-Zeneca. Dr Ridker is a co-inventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Dade-Behring and AstraZeneca.

Background: I

- During the present decade, major developments in CABG (e.g. off-pump technique, less invasive approach, increased arterial revascularization and optimal perioperative care).
- In PCI (e.g. improved technique, stent design, guide wires, anti-platelet therapy, and drug-eluting stents) have made it important to reassess the respective values of the two revascularization techniques in an all-comers population as seen by the surgeon and the interventional cardiologist in their daily practice.

SYNTAX Eligible Patients

De novo disease

Limited Exclusion Criteria
Previous interventions
Acute MI with CK-MB >2x
Concomitant cardiac surgery

Left Main Disease
(isolated, +1, +2 or +3 vessels)
3 Vessel Disease
(revasc all 3 vascular territories)
SYNTAX Trial Design

- 62 EU Sites + 23 US Sites
- Heart Team (surgeon & interventionalist)
- Amenable for both treatment options
- Amenable for only one treatment approach
- Stratification: LM and Diabetes

Randomized Arms
N=1800
CABG  N=897  VS  TAXUS  N=903
DM  28.5%  Non DM  71.5%
Non DM  28.2%  NonDM  71.8%

Two Registry Arms
N=1275
CABG  N=1077  VS  PCI  N=198

SYNTAX Primary Endpoint
Randomized trial

The primary clinical endpoint is the 12 Month major Cardiovascular or Cerebrovascular event rate (MACCE *)

- MACCE is defined as:
  - All cause Death
  - Cerebrovascular Accident (CVA/Stroke)
  - Documented Myocardial Infarction (ARC definition)
  - Any Repeat Revascularization (PCI and/or CABG)
  - All events CEC Adjudicated

Procedural Characteristics
PCI Randomized Cohort

Patient-based
- Staged procedure, % 14.1
- Lesions treated/pt. mean + SD: 3.6 + 1.6
- No. stents implanted, mean + SD: 4.6 + 2.3
- Total length implanted, mm + SD: 86.1 + 47.9
- Range, mm: 8 - 324
- Long stenting (>100 mm), %: 33.2

Procedural Characteristics
CABG Randomized Cohort

- Off-pump surgery, %: 15.0
- Graft revascularization, %
  - At least one arterial graft: 97.3
  - Arterial graft to LAD: 95.6
  - LIMA-venous: 78.1
  - Double LIMA/RIMA: 27.6
  - Complete arterial revascularization: 18.9
  - Radial artery: 14.1
  - Venous graft only: 2.6
- Grafts per patient, mean + SD: 2.6 + 0.7
- Distal anastomoses/pt. mean + SD: 3.2 + 0.9

All-Cause Death to 12 Months

CABG (N=897)  VS  TAXUS (N=903)

Cumulative Event Rate (%)
0  10  20
0  6  12  Months Since Allocation

CVA to 12 Months

CABG (N=897)  VS  TAXUS (N=903)

Cumulative Event Rate (%)
0  10  20
0  6  12  Months Since Allocation
**Conclusions:**

- In the randomized SYNTAX cohort, there were comparable overall safety outcomes (Death, CVA, MI) in CABG and PCI patients at 12 months (7.7% vs. 7.6%).
- Per protocol rates of symptomatic graft occlusion and stent thrombosis were similar.
- There was a significantly higher rate of revascularization in the PCI group (13.7% vs. 5.9%), and a significantly higher rate of CVA in the CABG group (2.2% vs. 0.6%).
- Overall MACCE in the PCI group was higher (17.8% vs. 12.1%) due to an excess of redo revascularization compared with CABG.
- The SYNTAX score will help stratify patients for the appropriate revascularization option.
PI: Alan Maisel, San Diego / USA
Co-PI: Stefan D Anker, Berlin / GER

Richard Novak
Christian Müller
Mark Richards
Robert Christensen
Alan Riu
Martin Moerkel
Piotr Rokicki
Seán-Xavier Nealeh
Lori Daniels
Christophe Hagan
Frank Peacock
Inger Anned
Leong Ng
Salvatore Di Somma
Gerastas Filipatos
Judd Landsberg

**Background:**

What makes BACH so interesting?

- Does measuring of MR-proADM, a stable surrogate of adrenomedullin, provide strong prognostic information?
- Is this superior to BNP or NT-proBNP?
- Are MR-proADM results also better than & independent of Troponin values?

**Methods**

- Patients included who presented to ED with SCB not from trauma, or obvious MI, and not on dialysis.
- After consenting, MD assessment of probability of heart failure and/or pneumonia.
- Two independent cardiologists agreed on final diagnosis following discharge.
- Follow-up for 90 days for survival; Outcome “All cause mortality within 90 days”.

**Prognostic Accuracy**

MR-proADM 75.5% vs BNP 60.8% vs NT-proBNP 63.6% (p<0.001)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR-proADM</td>
<td>3.05</td>
<td>0.001</td>
</tr>
<tr>
<td>BNP</td>
<td>2.89</td>
<td>0.009</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>2.89</td>
<td>0.009</td>
</tr>
</tbody>
</table>

MR-proADM adds significantly to BNP or NT-proBNP, however neither BNP nor NT-proBNP add to MR-proADM.

**Summary**

- MR-proADM is a strong prognosticator in patients with AHF and in patients presenting with SCB.
- MR-proADM is superior to BNP or NT-proBNP for predicting 90-day mortality, both in AHF as well as in all ED pts with SCB.
- MR-proADM is particularly strong in predicting short-term prognosis within 4 weeks after assessment.
- All these results are unaffected by adjustment for Troponin.
- MR-proADM can significantly improve risk stratification over BNP or NT-proBNP.
- Assessment of MR-proADM can help to identify patients who should "move to the front of the line" of medical care.
Recent studies have demonstrated that the etiology of aortic valve disease has a similar pathophysiology to that of vascular atherosclerosis, and that the treatment of this disease could be similar to that of chronic vascular atherosclerosis.

The results of the prospective clinical trials testing the effects of statin therapy could change the paradigm for treating valvular heart disease.

### Primary Endpoint

**Major Cardiovascular Events (MCE):**
- Cardiovascular death
- Aortic valve replacement surgery (AVR)
- CHF as a result of progression of AS
- Non-fatal myocardial infarction
- CABG
- PCI
- Hospitalized unstable angina
- Non-hemorrhagic stroke

### Patient Definition

- Men and Women
- Age 45 - 85 years
- Asymptomatic
- Valvular AS:
  - Aortic valve thickening on echocardiographic evaluation
  - Doppler jet velocity ≥2.5 - ≤4.0 m/sec
- LDL-C < 6 mmol/L (or below local guidelines for lipid-lowering therapy)
- TG < 4.5 mmol/L
Baseline Characteristics: Echo

Mean values

Placebo | Simva + Ezetimibe
---|---
n = 929 | n = 944

Transaortic:

- Peak velocity (m/sec) 3.10 | 3.09
- Peak gradient (mmHg) 39.6 | 39.3
- Mean gradient (mmHg) 23.0 | 22.7
- Aortic valve area (cm²) 1.27 | 1.29
- Bicuspid valve 6.3% | 5.0%

LDL-Cholesterol

![Graph of LDL-Cholesterol values over time]

Aortic Valve Events

![Graph of aortic valve events over time]

Ischemic Cardiovascular Events

![Graph of ischemic cardiovascular events over time]

SUMMARY

The two hypothesis-testing trials (SHARP and IMPROVE-IT) contain about four times as many cancers as the SEAS trial.

They do not confirm the hypothesis raised by the SEAS trial that treatment increases the overall risk of developing cancer.

As there is no increase with time in the relative risk (active vs placebo) suggested by the cancer incidence and mortality from all 3 trials together (or just from the pair of hypothesis-testing trials), the SEAS, SHARP and IMPROVE-IT trials do not provide credible evidence of any adverse effect on cancer.

R. Peto, Press conference
July 21, 2008
Drug-Eluting and Bare Metal Stenting for Diabetes Mellitus: Results from the Mass-DAC Registry

Pallov Garg, Sharon-Lise T. Nomand, Tracy S. Silbaugh, Robert E. Wolf, Katya Zeflevsky, Ann Lovett, Manu Varma, Zheng Zhou, and Laura Mauri*

Brigham and Women’s Hospital, Harvard Medical School, Harvard School of Public Health all in Boston, Massachusetts

*presenting author

Drug-Eluting and Bare Metal Stenting for Diabetes Mellitus

Background

- Diabetic patients have a higher prevalence of ischemic heart disease than the general population.
- Percutaneous coronary intervention is associated with unique limitations in the diabetic population.
- Specifically, diabetic patients face a higher risk of restenosis, MI, and cardiac mortality after PCI.

Drug-Eluting and Bare Metal Stenting for Diabetes Mellitus

Procedure Characteristics after Match

<table>
<thead>
<tr>
<th></th>
<th>DES (n = 146)</th>
<th>BMS (n = 146)</th>
<th>%SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>17.8</td>
<td>17.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Unstable</td>
<td>26.6</td>
<td>29.3</td>
<td>-5.0</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>26.4</td>
<td>22.9</td>
<td>8.2</td>
</tr>
<tr>
<td>STEMI</td>
<td>17.9</td>
<td>15.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Procedure status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>35.7</td>
<td>41.5</td>
<td>-11.8</td>
</tr>
<tr>
<td>Urgent</td>
<td>45.4</td>
<td>41.7</td>
<td>7.4</td>
</tr>
<tr>
<td>Emergency/Salvage</td>
<td>18.9</td>
<td>16.6</td>
<td>-5.5</td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>1.8</td>
<td>1.9</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

*%SD = Percent Standardized Difference
Values <10% reflect well matched characteristics

Drug-Eluting and Bare Metal Stenting for Diabetes Mellitus

Matched Risk Differences at 3 years

C. Michael Gibson, Jessica L. Mega, Christopher J. Hammett, Vasil Hricak, Pascual Bordes, Adam Witkowski, Valentin Markov, Paul Burton, and Eugene Braunwald for the TIMI 46 Study Group

Funded by a Research Grant from Johnson and Johnson and Bayer to Brigham & Women’s Hospital. Dr. Gibson has received honoraria & consulting fees from J&J and Bayer

Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction 46 Trial

Funded by a Research Grant from Johnson and Johnson and Bayer to Brigham & Women’s Hospital. Dr. Gibson has received honoraria & consulting fees from J&J and Bayer
Rivaroxaban is a potent and selective oral direct factor Xa inhibitor which blocks initiation of the final common coagulation pathway.

**SUMMARY - SAFETY**

- There was increased bleeding associated with higher doses of rivaroxaban.
- Most bleeding was bleeding requiring medical attention, rather than TIMI major or TIMI minor bleeding.
- No evidence of drug induced liver injury.

**SUMMARY - EFFICACY**

1st Endpoint: 21% RRR (HR 0.79, p=0.10) in death, MI, stroke, or severe recurrent ischemia requiring revascularization

2nd Endpoint: 31% RRR in the risk of death, MI, or stroke (HR 0.69, p=0.028)
**ATLAS 1 Outcomes in Doses to be Taken Forward in Phase 3 Trial**

**Stratum 1: ASA Alone**
- Placebo
- Riva 2.5 & 5.0 mg BID
- Death, MI, Stroke
- TIMI Major Bleed
- 11.9% vs. 6.6%
- HR=0.54 (0.27-1.08)
- p=0.17

**Stratum 2: ASA + Clop.**
- Placebo
- Riva 2.5 & 5.0 mg BID
- Death, MI, Stroke
- TIMI Major Bleed
- 3.8% vs. 2.0%
- HR=0.55 (0.27-1.11)
- p=0.03

*If fewer than 5 events were present in a cell, raw event rates are reported and a Fisher’s exact test was used, otherwise Kaplan-Meier (KM) estimates and a Hazard Ratio (HR) with confidence interval are provided for 180 day period. Raw event rates were reported for TIMI Major Bleed. KM estimates of HR and rates of secondary efficacy endpoints are provided. Death=All Cause Death; MI=Myocardial Infarction*

**GISSI-HF: Rosuvastatin Study**

**Trial design:** Patients with chronic symptomatic HF were randomized to rosuvastatin 10 mg daily (n = 2,285) or placebo (n = 2,289). Median follow-up, 3.9 years.

**Results**
- All-cause mortality: 29% with rosuvastatin vs. 28% with placebo (p = 0.04)
- Death or hospital admission for cardiovascular reasons: 57% vs. 56% (p = 0.03), respectively
- Sudden cardiac death: 9.6% vs. 8.6% (p = 0.25), respectively

**Conclusions**
- Rosuvastatin 10 mg daily is not beneficial at reducing cardiac outcomes among patients with chronic symptomatic HF
- This study should not temper enthusiasm for statins in indicated situations like ACS

**CARESS-in-AMI**

**Trial design:** STEMI patients admitted to non-PCI hospitals and initially treated with heparin, half-dose reteplase, and abciximab were randomized to immediate transfer for urgent PCI (n = 299) or standard therapy with rescue PCI if needed (n = 301).

**Results**
- 86% of the immediate PCI group underwent PCI vs. 56% of the standard care group
- Death, MI, or refractory ischemia at 30 days (4.4% vs. 10.7%, p = 0.005)
- Refractory ischemia (3.4% vs. 2.3%, p = 0.003)

**Conclusions**
- STEMI patients treated with half-dose lytics and abciximab did better with immediate transfer for PCI
- This approach reduced death, MI, or refractory ischemia at 30 days
- Benefit driven by reduction in refractory ischemia