



2nd Annual

CARDIOLOGY FELLOWS FORUM OF EXCELLENCE

Highlights of Events from the American Heart Association's 2002 Annual Scientific Sessions

The materials contained in this newsletter are based on events that occurred November 16 through November 20, 2002 at the American Heart Association's Annual Scientific Sessions in Chicago, Illinois.

CHAIRMAN'S CORNER

The American Heart Association's (AHA) 2002 Annual Meeting marked the 75th year of Scientific Sessions. Each year there is an expanding wealth of scientific discoveries in heart disease. Indeed, we are in a very exciting time as the prevention and treatment of cardiovascular and related diseases are at their finest.

More importantly, there is certainty for continuing advances in the years to come.

I had the honor of chairing the Cardiology Fellows Forum of Excellence, this year being the 2nd Annual Forum, held on November 16, 2002 at the Chicago Omni Hotel. As the focus of this newsletter, this program deserves special mention because it is a highly competitive educational forum that enables some of our finest fellows training in cardiology to gather together and share their academic and professional research experience. In essence, these will be our future leaders who will pave the road to new discoveries in cardiovascular disease research and set the standards for its treatment.

Like last year, the 2nd Annual Cardiology Fellows Forum of Excellence was a huge success. We invited 179 institutions to participate and received more than 100 abstracts of original research or interesting case studies. Together with my co-chairs, Dr Robert Chilton, Associate Professor of Medicine, University of Texas Health Science Center, Division of Cardiology, Audie L. Murphy Memorial Veterans Hospital, San Antonio, Tex

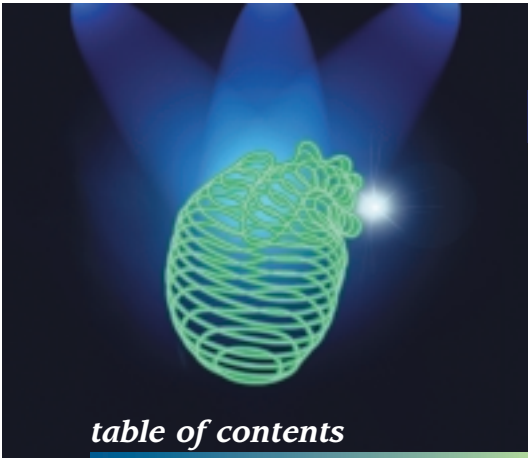


and Dr Gary Gibbons, Director, Cardiovascular Research Institute, Associate Professor of Medicine, Morehouse School of Medicine, Atlanta, Ga, we reviewed each abstract and selected the top 31. These fellows each received an educational grant that allowed them to attend the AHA meeting as well as the 2nd Annual Cardiology Fellows Forum of Excellence. Of the 31 abstracts accepted, four were chosen for Outstanding Recognition Awards: 2 in scientific research and 2 in clinical research. A brief biography and abstract of each of the 4 winners are included in this newsletter.

I would like again to congratulate all the fellows and thank them for making this year's program a huge success. As a final note, I would like to thank Bristol-Myers Squibb Company for their continued support and commitment to cardiovascular disease prevention and treatment.

John Banas, Jr., MD

Professor of Clinical Medicine
College of Physicians
and Surgeons
Columbia University, NY
The Dorothy and Lloyd Huck Chair
Chairman, Department of Cardiovascular Medicine
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Continuing Education Accreditation Information

Program Release Date: January 2003
 Program Expiration Date: January 2005

TARGET AUDIENCE

This activity is designed for physicians with an interest in cardiovascular disease.

EDUCATIONAL OBJECTIVES

Upon completion of this program, participants should be able to:

- Discuss the relationship between LDL-cholesterol lowering and clinical outcomes
- Describe the potential role of C-reactive protein for identifying and stratifying patients at high cardiovascular risk
- Discuss the principles and selection strategies of combination drug therapies for cardiovascular disease management and prevention
- Review results of the PROSPER study, including clinical implications of statin therapy in the elderly population

Program Completion Time: 1 hour

ACCREDITATION STATEMENT

MER Medical Education Resources is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

Medical Education Resources designates this educational activity for a maximum of 1 hour in category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This activity was planned and produced in accordance with the ACCME Essentials.

SUPPORTER

This educational activity is supported by an unrestricted educational grant from Bristol-Myers Squibb Company.

PROGRAM LOGISTICS

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John Banas has disclosed the following:

Grant Research/Support: none
 Consultant: Pharmacia, Bristol-Myers Squibb, Inc.

Speaker's Bureau: Bristol-Myers Squibb, Sanofi, Pfizer, Sankyo, Merck

Gary Gibbons has no financial relationships to disclose.

Robert Chilton has no financial relationships to disclose.

DISCLAIMER

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Cardiology Fellows Forum of Excellence Winners

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***Fadi Alameddine, MD**
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Decatur, Ga

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Ochsner Clinic Foundation
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Kurt G. Barringhaus, MD
University of Virginia Health
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Charlottesville, Va

Su Min Chang, MD
Baylor College of Medicine
Houston, Tex

Neil C. Chi, MD, PhD
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San Francisco, Calif

Dion L. Franga, MD
Medical College of Georgia
Augusta, Ga

Jeffrey M. Friedel, MD
Allegheny General Hospital
Pittsburgh, Pa

Sanjay Gandhi, MD
University of Illinois at Chicago
Chicago, Ill

Ruchira Garg, MD
Columbus Children's Hospital
The Ohio State University
Columbus, Ohio

Swaminatha V. Gurudevan, MD
University of California
San Diego
San Diego, Calif

Xinqiang Han, MD, PhD
University of Minnesota
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Ravi Kanagala, MD
Mayo Clinic
Rochester, Minn

David A. Lin, MD
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***Jakirshan J. Khatri, MD**
Emory University
School of Medicine
Atlanta, Ga

Michelle S.C. Khoo, MB, BCh, BAO
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New York, NY

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Medical School
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Memphis, Tenn

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Boston University
School of Medicine
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University of North Carolina
at Chapel Hill
Chapel Hill, NC

David D. Spragg, MD
Johns Hopkins Hospital
Baltimore, Md

***W.H. Wilson Tang, MD**
Cleveland Clinic Foundation
Cleveland, Ohio

Ethan J. Weiss, MD
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San Francisco, Calif

Michael Yeh, MD
University of California
Los Angeles
Los Angeles, Calif

Frank J. Zidar, MD
Cleveland Clinic Foundation
Cleveland, Ohio

*Denotes fellows who received the
Outstanding Recognition Award.

Future Developments in Cardiovascular Risk Management:

What Does the Future Hold? *Highlights of a Satellite Symposium from the American Heart Association's 2002 Annual Scientific Sessions*

On November 16, 2002, an educational program on cardiovascular disease management and prevention was held at the Hilton Chicago. Here, leading experts in the field presented and discussed the latest developments in cardiovascular disease research. The symposium was chaired by Dr Antonio Gotto, Dean and Provost for Medical Affairs, Weill Medical College of Cornell University.

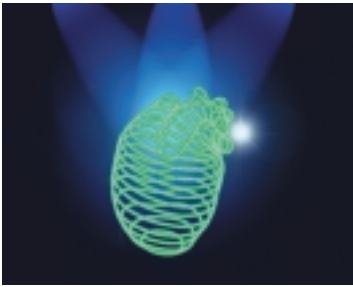
Professor James Shepherd, Head of the Department of Pathological Biochemistry, Royal Infirmary – University of Glasgow, provided the first presentation "**Cardiovascular Management of the Elderly: What Can We Expect to Learn from the PROSPER Trial?**" He indicated that atherosclerotic coronary occlusion is the leading cause of premature death and that its impact falls primarily on the elderly. In fact, more than 80% of those who die from coronary heart disease are older than 65 years of age. There is also an increasing risk of stroke with age that leads to cerebral degeneration and physical and mental disability. It is still unclear whether predictors of vascular risk among the middle-aged continued to apply to the aged. For example, cholesterol, which is a clear marker for premature death in middle-aged individuals, may not carry the same predictive power in the elderly. By extrapolation, there is uncertainty about the benefits of lowering cholesterol to reduce vascular dysfunction and cognitive decline in the elderly. Dr Shepherd, the principal investigator for PROSPER (PROspective Study of Pravastatin in the Elderly at Risk), also spoke about the rationale and design of this study in elderly subjects.

The next topic "**Pharmacologic Strategies in Coronary Prevention?**" was presented by Dr Thomas A. Pearson, Albert D. Kaiser Professor and Chair, Department of Community and Preventive Medicine, University of Rochester. Dr Pearson spoke about the use of combinations of pharmacologic agents, each of which has evidence for efficacy in single drug versus placebo studies. The AHA guide-

lines on secondary prevention recommend all of the following drugs in patients with cardiovascular disease: aspirin, ACE inhibitor, beta-blocker, and lipid-lowering agents. At least four issues should likely be considered when selecting a combination of drugs: drug interactions (efficacy and side effects), cost-effectiveness, compliance, and accuracy of dose and drug. Combinations of drugs have at least four possible scenarios of effects: additive ($1+1=2$); non-additive ($1+1=1$); antagonistic ($1+1<1$); and synergistic ($1+1>2$). Secondary prevention trials with pravastatin (N=14,617) included patients taking aspirin (80.4%) and not taking aspirin (19.6%). Multivariate modeling shows reduction of cardiovascular endpoints when taking both pravastatin and aspirin as compared to each taken separately. Further analyses provided statistically significant evidence for a synergistic effect. Similar kinds of data are needed to characterize safety. A second issue, often not investigated, is the cost-effectiveness of the combination of drugs. A synergistic effect may improve cost-effectiveness, whereas the addition of a second drug to a group of patients with risk significantly reduced by the first drug may not have the same cost-effectiveness as the use of either drug used alone. Combinations of drugs into a single tablet may have some benefits for compliance, especially in older patients already taking multiple medications. Finally, another advantage of combination tablets may be the assurance of the correct doses and drugs for the purposes prescribed. In summary, combinations of pharmaceuticals have become the norm in preventive cardiology. Definition of benefits and risks of these combinations is essential, if increasingly complex regimens are to have optimal efficacy, safety, cost-effectiveness, compliance, and adherence.

Dr Frank Sacks, Professor of Cardiovascular Disease Prevention, Harvard School of Public Health, Attending Physician, Vascular Medicine Division, Brigham and Women's Hospital, Harvard Medical School, presented "**LDL Lowering and Cardiovascular Disease: Do We Know the True Relationship?**" Statins have proven to have benefits in reducing coronary heart disease and stroke in nearly all populations studied in large, randomized, controlled trials. Statins reduce coronary events across a broad range of patient subgroups, includ-

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Outstanding Basic Research Abstract #1

Fadi Alameddine, MD
Emory University Hospital
Decatur, Ga



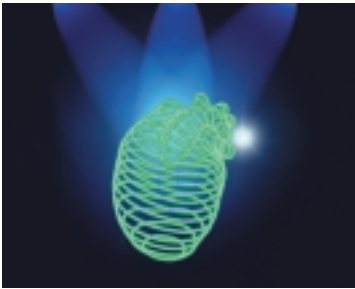
After obtaining the degrees of BS in Biology and Doctor of Medicine from the American University of Beirut in Lebanon in 1997, Dr Fadi Alameddine pursued an internal medicine residency and is currently pursuing a cardiology fellowship at Emory University Hospital in Atlanta. Dr Alameddine has a strong interest in vascular biology research and has worked on a research project studying hypertensive vascular wall hypertrophy during his internal medicine residency. Dr Alameddine's current basic science project during his cardiology fellowship is to investigate the role of osteopontin in mediating both ischemia-induced and inflammation-induced angiogenesis in mice. Both research projects have been orally presented at the 2002 AHA scientific sessions in Chicago 2002. Some of his honors/awards include Best PGY1 Resident from the Department of Internal Medicine at Emory (1999), Alpha Omega Alpha from Emory (2000) and Certificate of Excellence given by Emory Medical School Class of 2001. He has presented at the NAVBO (North American Vascular Biology Organization) meeting in San Francisco in 1998, at the SGIM (Society of General Internal Medicine) meeting in New Orleans in 2000 and at the ACP (American College of Physicians) meeting in Augusta, Ga in 2001. Dr Alameddine obtained the American Board in Internal Medicine in 2002 and is expecting to sit for his boards in general cardiology in 2004 and interventional cardiology in 2005. His long-term goal is to continue basic science research while practicing interventional cardiology in an academic setting.

OSTEOPONTIN PLAYS A CENTRAL ROLE IN ANGIOGENESIS

Fadi Alameddine, Craig Duvall, Galen Robertson, Lucy Liaw, Robert Guldberg, W. Robert Taylor

Osteopontin (OPN) is a multi-functional protein that is a survival factor for endothelial cells, and mediates macrophage and neutrophil migration. We therefore hypothesized that OPN may be functionally relevant in angiogenesis. To explore this possibility, we employed both the hindlimb ischemia model and the subcutaneous sponge model in wild-type and OPN-deficient mice. Sponges, ischemic and nonischemic hindlimb muscles were harvested 7 or 14 days post-surgery and paraffin-embedded. Ten microscopic fields were analyzed from sponges and from hindlimb muscles of each animal (3 per group). As compared to OPN-deficient mice, ischemic-to-nonischemic arteriolar density ratio and sponge capillary density were respectively 2.25±0.24-fold ($P<0.02$) and 2.19±0.10-fold ($P<0.01$) higher in wild-type mice where neutrophil and macrophage immunostaining was more prominent. To confirm the hemodynamic significance of the neo-vascularization, postmortem angiography was performed using high-resolution computed tomography. In hindlimbs at 7 days, the angiographic

score in wild-type mice was 1.42±0.30-fold higher than in OPN-deficient mice. Similarly, at 14 days, sponges implanted in wild-type animals had 11.55±1.04-fold ($P<0.01$) higher angiographic score compared to sponges implanted in OPN-deficient animals. When osmotic mini-pumps delivering 50 mcg/kg/d OPN into sponges were implanted in OPN-deficient mice, infused sponges had 6.75±1.46-fold ($P<0.04$) higher angiographic score than non-infused sponges in knockout mice, thus reconstituting 58.49%±9.56% of the angiographic score of 14-day wild-type sponges. In related in vitro experiments, preliminary data suggest that bone marrow-derived endothelial cells from OPN-deficient mice exhibited a reduced proliferative and migratory response following mechanical wounding compared to wild-type cells. In conclusion, we have shown that OPN is an absolute requirement for angiogenesis in two different murine models of angiogenesis. OPN may act through its effects on endothelial cell proliferation and migration and/or effects on inflammatory cell chemotaxis.



Outstanding Basic Research Abstract #2



Jakirshan J. Khatri, MD

Emory University School of Medicine
Atlanta, Ga

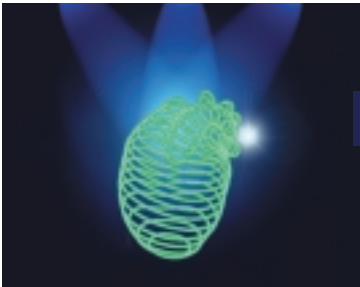
Dr Jakirshan Khatri received his medical degree from the Northeastern Ohio Universities College of Medicine (NEOUCOM) in Rootstown, Ohio and subsequently completed a residency in internal medicine at Case Western Reserve University (CWRU) in Cleveland, Ohio. During this time, Dr Khatri spent elective research rotations in the laboratory of Dr Steven A. Fisher in the Division of Cardiology, where he acquired experience in molecular biology techniques and began a project examining potential molecular determinants of smooth muscle sensitivity to nitric oxide-mediated relaxation. He received a Housestaff Research Award from the Department of Medicine. Subsequently, he received an AHA Ohio Valley Affiliate Postdoctoral Fellowship Award sponsored by Dr Fisher and Dr Frank V. Brozovich at CWRU. Presently, Dr Khatri is pursuing a cardiology fellowship at Emory University in Atlanta, Ga. Under the guidance of Dr Zorina S. Galis, he is studying potential mechanisms that promote angiogenesis in experimental atheroma. Our results support a new role for oxidative stress in triggering this known contributor to human plaque instability, the major cause of acute vascular events.

OXIDATIVE STRESS TRIGGERS ANGIOGENESIS IN EXPERIMENTAL ATHEROMA

Jakirshan J. Khatri, Sergey Dikalov, David G. Harrison, Zorina S. Galis

Intraplaque angiogenesis is a cause of plaque destabilization. We hypothesize that increased production of reactive oxygen species (ROS) in the atherosclerotic plaque may stimulate angiogenesis independently of hypoxia, a known stimulus of angiogenesis. To test this hypothesis we induced carotid artery lesion formation using the flow cessation model in a transgenic mouse strain with targeted smooth muscle overexpression of p22phox, a critical component of neutrophil and vascular NAD(P)H oxidase. Compared to wild type (WT) lesions, neointimal lesions in p22phox arteries demonstrated extensive intimal and medial angiogenesis at 14 to 28 days post-ligation (n=8 per time point). To examine production of ROS, vascular smooth muscle cells (VSMC) were isolated from the aortas of p22phox and WT mice and stained with ROS-sensitive fluorophores. Dihydroethidium (DHE) staining indicated that p22phox and WT VSMCs produced similar levels of superoxide (n=4). However, dichlorodihydrofluorescein diacetate (DCFDA) staining demonstrated that p22phox VSMCs produced 65%±14% greater H₂O₂ than WT

VSMCs (n=8, *P*<0.05). These results were confirmed in VSMC membrane fractions using an electron spin resonance spectroscopy (ESR) based assay. NAD(P)H oxidase derived H₂O₂ production was 72%±18% greater in p22phox than WT VSMCs (n=4, *P*<0.05). To investigate potential effects upon mediators of angiogenesis, we analyzed expression of vascular endothelial growth factor (VEGF) in VSMC-conditioned media. Media of p22phox VSMCs contained 36%±6% more VEGF than WT media (n=4, *P*<0.05). Hypoxia (5% O₂, 24 hours) also upregulated VEGF levels in WT media (24%±6%, n=4, *P*<0.05), but did not alter VEGF levels in p22phox media (n=4). Zymography indicated that p22phox over-expression increased VSMC gelatinolytic activity in culture media by 83%±19% compared to WT media (n=3, *P*<0.05). These data indicate that endogenous H₂O₂ stimulates angiogenesis in experimental atheroma by upregulating VEGF expression and gelatinolytic activity, suggesting a critical role of oxidative stress in modulation of intraplaque angiogenesis, likely contributing to plaque instability and rupture.



Outstanding Clinical Research Abstract #1



Han W. Kim, MD
Weill Cornell Medical College
New York, NY

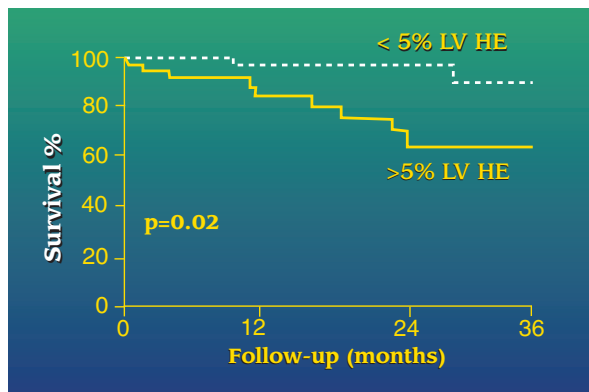
Dr Han Kim is currently a first year cardiology fellow at Weill Cornell Medical College in New York. He received his undergraduate degree from Stanford University, and subsequently attended Washington University, where he received his medical degree. He completed his training in Internal Medicine at Northwestern University Medical School. After completing his cardiology fellowship, Dr Kim plans to continue his training in cardiovascular MRI.

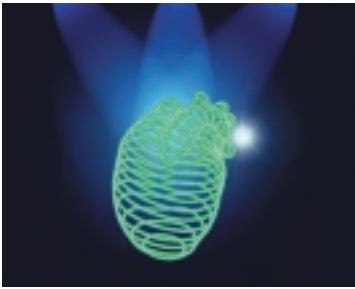
PROGNOSTIC SIGNIFICANCE OF UNRECOGNIZED MYOCARDIAL INFARCTION DETECTED BY CONTRAST ENHANCED MRI

Han W. Kim, Edwin Wu, Sheridan N. Meyers, Kelly M. Choi, Michele A. Parker, Francis J. Klocke, Robert O. Bonow, Robert M. Judd, Raymond J. Kim

Prior studies have shown that patients (pts) with unrecognized myocardial infarction (UMI) have a prognosis that is similar to those with recognized MI. Currently, the diagnosis of UMI is based on new Q waves on ECG. Contrast MRI (cMRI) detects both Q wave and non-Q wave MI with high sensitivity/specificity. However, the prognostic significance of UMI detected by cMRI is unknown. One hundred patients (mean age 63 ± 11 y, male 82%, avg risk factors [RF] 2.1, mean EF $53 \pm 19\%$) without history of MI, who were referred for coronary angiography, underwent cine and cMRI. Hyperenhancement (HE) on cMRI was considered to represent MI. Q waves were defined by Minnesota code. Pts were followed for a mean of 21 ± 13 months after MRI, during which 11 pts died. Cox regression was used to estimate risk of death associated with traditional RF, anginal and heart failure symptoms, Q waves, EF, angiographic severity of CAD, and presence/extent of HE. HE was present in 57% pts. The prevalence of HE was 3.9-fold higher than of Q waves (14%). Pts with UMI defined by cMRI and without Q waves had smaller infarcts than those with Q waves (15 ± 13 vs $29 \pm 13\%$ LV, $P=0.002$). The only significant univariate predictor of death (all cause) was

extent of HE ($P=0.02$), although presence of HE ($P=0.08$), female gender ($P=0.06$), extent of CAD ($P=0.07$), and diabetes ($P=0.08$) approached significance. Actuarial analysis demonstrated that pts with $>5\%$ LV HE had increased mortality compared to pts with $\leq 5\%$ ($P=0.02$). On multivariate analysis, extent of HE ($>5\%$ LV) was the only independent predictor of death ($P=0.02$) with the adjusted relative risk for extent of HE being 6.7 (95% CI: 1.4-31). The extent of UMI identified by contrast MRI is an independent predictor of death in patients referred for angiography.





Outstanding Clinical Research Abstract #2



W.H. Wilson Tang, MD
Cleveland Clinic Foundation
Cleveland, Ohio

Dr W.H. Wilson Tang is a third year cardiology fellow at the Cleveland Clinic Foundation. Dr Tang attended Harvard Medical School and continued his internship and residency training in internal medicine at Stanford University Medical Center. While he was at Stanford, he became interested in cardiomyopathy and heart failure, and worked as a postdoctoral research fellow with Dr Michael Fowler and Dr Bob Hu in the areas of: 1) pharmacologic reversal of cardiac remodeling (in both echocardiography and magnetic resonance imaging) and 2) neurohormonal responses to drug therapy in heart failure. He also collaborated with Dr Gerald Reaven to study the role of insulin resistance in patients with non-ischemic cardiomyopathy. At the Cleveland Clinic, Dr Tang began to investigate the use of natriuretic peptide as biomarkers in various clinical settings under the mentorship of Dr Gary Francis and Dr James Young. He plans to continue an academic career in clinical and translational research in heart failure, linking to his interests in neurohormones, insulin resistance, and cardiac imaging.

FLUID RETENTION FOLLOWING INITIATION OF THIAZOLIDINEDIONE THERAPY IN PATIENTS WITH ESTABLISHED HEART FAILURE

W.H. Wilson Tang, Gary S. Francis, James B. Young

Fluid retention associated with the use of thiazolidinediones (TZDs) is often attributed to exacerbation of heart failure. However, the characteristics of fluid retention following TZD initiation (particularly in patients with underlying heart failure) are not well defined. We examined a total of 111 consecutive ambulatory patients with chronic systolic heart failure (NYHA I-III, LVEF \leq 45%) who were treated with TZDs between 1/99-6/01. Fluid retention following TZD initiation was arbitrarily defined as involuntary weight gain of over 10 pounds with clinical evidence of volume overload within 6 months of starting therapy. Signs and symptoms of fluid retention in TZD users were compared to those in a control group of diabetic, non-TZD users with heart failure who experienced fluid retention. Within the TZD users group, pre-TZD clinical and echocardiographic data were compared between patients with and without fluid retention (upper vs lower tertiles of weight gain). The overall mean change in weight over 6 months was 5.9 ± 8.3 pounds.

Nineteen patients (17.1%) developed refractory fluid retention following TZD initiation. The majority of TZD-induced fluid retention presented with peripheral edema that was reversible following TZD discontinuation. Only 2 patients had clinical evidence of worsening pulmonary edema and none had significant hepatotoxicity. Although more female patients and insulin users developed fluid retention following TZD initiation, the propensity to develop TZD-induced fluid retention was independent of the baseline severity of heart failure (NYHA class) or cardiac dysfunction (LVEF, LV end-diastolic dimension). We conclude that although fluid retention following TZD initiation in diabetic patients with systolic heart failure can mimic heart failure decompensation, the patterns of clinical presentation vary and can resolve following TZD discontinuation. No direct association can be made between the risk of fluid retention and the baseline severity of heart failure, arguing against a negative inotropic effect of TZDs.

PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)

The results of PROSPER were presented at the AHA this year in a plenary session on Sunday, November 17, 2002; and published in *Lancet*. 2002;360:1623-1630. PROSPER was the first trial specifically designed to determine the benefits of statin (pravastatin 40 mg) in men and women between the ages of 70 and 82 years. The PROSPER trial was conducted at three sites: Glasgow, Scotland; Cork, Ireland; and Leiden, Netherlands.

PROSPER was a randomized, double-blind, placebo-controlled study. A total of 5804 patients (age 70-82 years) were enrolled and randomized to either pravastatin 40 mg or placebo. About half of subjects had vascular disease and about half were at high risk of vascular disease. Patients were followed for an average of 3.2 years. The primary endpoint was a composite of coronary heart disease death, nonfatal myocardial infarction, and fatal or nonfatal stroke.

Pravastatin had a marked effect on lowering LDL-cholesterol. LDL levels were reduced by 34% (Figure 1), and overall, 82% of these patients reached their NCEP target goal. In addition, there was a 23.4% reduction in total cholesterol, a 13.3% reduction in triglycerides, and a 4.9% increase in HDL-cholesterol in patients taking pravastatin.

Table 1. Number Needed to Treat (NNT) to Prevent One Cardiac Event at 3.2 Years in Pravastatin Trials

Trial	NNT CHD Death + Nonfatal MI
PROSPER	48
LIPID	49
CARE	52
WOSCOPS	59

Based on Kaplan-Meier analyses, at 3.2 years, pravastatin reduced the risk of the primary endpoint by 15% ($P=0.014$) (Figure 2). The effect was achieved mainly by a reduction in coronary heart disease events rather than stroke. For the coronary endpoint of coronary heart disease death or nonfatal myocardial infarction, pravastatin resulted in a 19% relative risk reduction ($P=0.006$). Pravastatin also produced a significant 24% relative risk reduction in coronary heart disease death ($P=0.043$). In comparison with previous pravastatin trials, the results from PROSPER demonstrate a similar number need to treat (NNT) of 48 persons to prevent one cardiac event (Table 1). Fatal or nonfatal stroke was not significantly reduced with pravastatin compared with placebo over the 3.2-year study (4.7% vs 4.5%, respectively). The lack of effect might be

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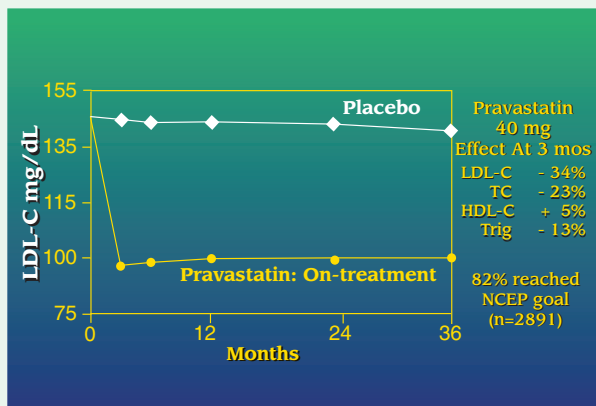


Figure 1. Effect of Pravastatin 40 mg on Lipid Profiles

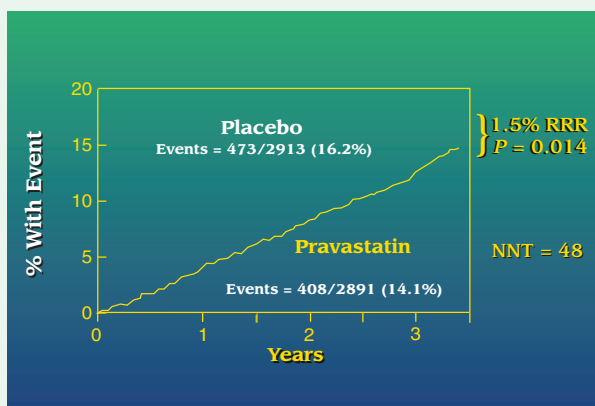


Figure 2. Primary Endpoint: CHD Death, Nonfatal MI, Fatal or Nonfatal Stroke

Future Developments in Cardiovascular Risk Management

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ing men, women, patients with diabetes, older and younger patients, smokers, those with average as well as high cholesterol, and across the population ranges of total cholesterol, HDL-cholesterol, and triglyceride concentrations. The question of what if any LDL-cholesterol level should be a treatment goal is not yet fully established. On the one hand, extrapolation of some epidemiological and clinical studies suggests that the risk of coronary heart disease decreases by 25% for every 40 mg/dL (1 mmol/L) decrease in LDL-cholesterol. On the other hand, findings within the statin trials, including the Heart Protection Study (HPS), have failed to show a continuous relationship between LDL levels or LDL changes during statin treatment and event reduction. This question should be answered by several ongoing trials of statin treatment that compare starting doses to highest approved doses.

The last presentation "*C-Reactive Protein and LDL-Cholesterol: What Are the Relative Relationships to Cardiovascular Risk?*" was given by Dr Paul M. Ridker, Professor of Medicine, Harvard Medical School and Director, Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital. C-reactive protein (CRP) is a key mediator of the innate immune response and appears to play a role

in both early atherogenesis and the conversion of stable plaque to unstable vulnerable plaque. Over the past 5 years, evidence has emerged suggesting that measurement of CRP levels may be a new method to determine risk of future myocardial infarction, stroke, sudden cardiac death, and incident peripheral arterial disease. These data are important as half of all future events occur among those with normal cholesterol levels and inflammation is now understood to be a critical process in atherothrombosis. In a very recent study, CRP, LDL- and HDL-cholesterol were measured at baseline in all 27,939 healthy American women participating in the Women's Health Study who were then followed over an 8-year period for first-ever cardiovascular events. In that study, 77% of all future vascular events occurred among those with LDL-cholesterol less than 160 mg/dL, and 45% among those with LDL less than 130 mg/dL, the respective intervention and treatment targets currently set by the NCEP. By contrast, baseline CRP levels proved to be a stronger predictor of risk than LDL-cholesterol, and added important prognostic information on risk at all levels of calculated Framingham 10-Year Risk. Further, CRP was found to add to the predictive value of the ATP III definition of the metabolic syndrome.

PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) *continued from pg.9*

due to low statistical power and/or the short duration of the trial. However, there was a 25% relative risk reduction in transient ischemic attacks following pravastatin versus placebo treatment ($P=0.051$), suggesting that pravastatin did not have an effect on cerebrovascular circulation in reducing ischemia.

A number of tertiary endpoints were evaluated in PROSPER, including all-cause mortality, heart failure requiring hospitalization, and revascularization procedures. Although there were positive trends for pravastatin in each of these clinical outcomes, the trial was not designed or powered to detect differences in these tertiary endpoints. In addition, in PROSPER, cognitive function declined at the same rate in the pravastatin and placebo treatment groups. It had been reported from observational studies that lowering cholesterol with statins might slow cognitive decline, but PROSPER expanded on the suggestion from the Heart Protection Study (HPS) that lowering cholesterol

does not prevent a decline in cognitive function. In HPS, there was no difference in cognitive function between patients treated with simvastatin or placebo for 5 years.

The treatment benefit of pravastatin was observed regardless of whether patients had cardiovascular disease or not, were male or female, smokers or non-smokers, or were hypertensive or not. Interestingly, there was no difference in benefit with respect to tertiles of LDL cholesterol (<132 mg/dL vs 132-<159 mg/dL vs ≥ 159 mg/dL; P for interaction=0.69). Thus, LDL cholesterol was not a good predictor of risk in PROSPER.

PROSPER shows that the benefit of pravastatin 40 mg observed in previous clinical trials of middle-aged people was also observed in this older population. Pravastatin treatment was also well-tolerated in these older patients. Therefore, it is important to treat at risk, older patients with pravastatin.

CME POST-TEST AND EVALUATION FORM

Cardiology Fellows Forum of Excellence Newsletter

CME POST-TEST

If you desire CME credit for this activity, write the letter representing the single best answer to each of the following questions on the Answer Sheet and Evaluation Form. This activity is valid through January 1, 2005. No credit will be given after this date. Tear off along perforated edge and mail/fax the completed post-test and evaluation form to:

Medical Education Resources

- | | | |
|---|--|---|
| <p>1. What percentage of persons who die from coronary heart disease are older than 65 years of age?</p> <p>a. 20%</p> <p>b. 40%</p> <p>c. 60%</p> <p>d. 80%</p> | <p>3. In PROSPER, pravastatin significantly reduced the incidence of all of the following endpoints EXCEPT for:</p> <p>a. Nonfatal myocardial infarction</p> <p>b. Coronary heart disease death</p> <p>c. Fatal or nonfatal stroke</p> <p>d. None of the above</p> | <p>5. In PROSPER, the benefit of statin therapy was more apparent for which subgroup?</p> <p>a. Patients with preexisting cardiovascular disease</p> <p>b. Females</p> <p>c. Patients with higher baseline LDL levels</p> <p>d. There were no differences between subgroups</p> |
| <p>2. Of the following, which is the best predictor of risk for coronary disease?</p> <p>a. C-reactive protein</p> <p>b. HDL-C</p> <p>c. LDL-C</p> <p>d. Weight</p> | <p>4. Analyses of large clinical trials show that the effects of pravastatin and aspirin may be:</p> <p>a. Additive</p> <p>b. Non-additive</p> <p>c. Antagonistic</p> <p>d. Synergistic</p> | |

EVALUATION FORM

Medical Education Resources respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. Medical Education Resources will mail you a certificate 6 weeks from receipt of completed evaluation

PLEASE ANSWER THE FOLLOWING QUESTIONS BY CIRCLING THE APPROPRIATE RATING:

5= Outstanding 4= Good 3= Satisfactory 2= Fair 1= Poor

EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED OBJECTIVES

Upon completion of this activity, participants should be able to:

• Discuss the relationship between LDL-cholesterol lowering and clinical outcomes	5	4	3	2	1
• Describe the potential role of C-reactive protein for identifying and stratifying patients at high cardiovascular risk	5	4	3	2	1
• Discuss the principles and selection strategies of combination drug therapies for cardiovascular disease management and prevention	5	4	3	2	1
• Review results of the PROSPER study, including clinical implications of statin therapy in the elderly population	5	4	3	2	1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity	5	4	3	2	1
Related to my practice needs	5	4	3	2	1
Will influence how I practice	5	4	3	2	1
Will help me improve patient care	5	4	3	2	1
Stimulated my intellectual curiosity	5	4	3	2	1
Overall, the activity met my expectations	5	4	3	2	1

POST-TEST AND EVALUATION FORM

Cardiology Fellows Forum of Excellence Newsletter

Will the information presented cause you to make any changes in your practice? ___Yes___No
If Yes, please describe any change(s) you plan to make in your practice as a result of this activity.

How committed are you to making these changes? 5 (Very committed) 4 3 2 1 (Not at all committed)

Additional comments about this activity? _____

Do you feel future activities on this subject matter are necessary and/or important to your practice? ___Yes___No

Please list any other topics that would be of interest to you for future educational activities:

The program was educationally unbiased and not promotional: ___Yes___No

Degree: MD Other

IF YOU WISH TO RECEIVE CREDIT FOR THIS ACTIVITY, PLEASE FILL IN YOUR NAME AND/OR ADDRESS AND/OR MAIL/FAX BOTH SIDES TO:

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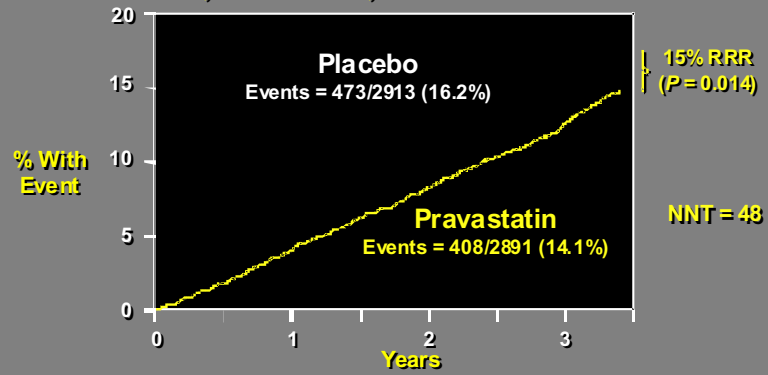
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Primary Endpoint

CHD death, Nonfatal MI, Fatal or Nonfatal Stroke



PROSPER Study Group. *Lancet*. 2002;360:1623-1630.

See important safety information and prescribing information