

Cardiovascular Gram

A NEWSLETTER TO PHYSICIANS FROM THE PAT AND JIM CALHOUN CARDIOLOGY CENTER AT UCONN HEALTH CENTER

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Carotid Angioplasty for the Management of Carotid Occlusive Disease

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Cerebrovascular disease is the third leading cause of death in the United States.¹ It is associated with 700,000 strokes per year resulting in huge morbidity and a significant economic burden to our society. Approximately 20-35 percent of these strokes are attributable to extracranial carotid occlusive disease.² Consequently, clinical management of carotid stenosis has been intensively studied for decades.

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Michael Azrin, M.D., Director of Intervention and Catheterization, treats acute myocardial infarction.

Currently, carotid endarterectomy (CEA) is the primary modality used to treat asymptomatic and symptomatic carotid stenosis. The efficacy of CEA in the management of carotid stenosis has been proven and its durability reaffirmed through prospective trials including the North American Symptomatic Carotid Endarterectomy Trial (NASCET),³ Asymptomatic Carotid Artery Stenosis Trial (ACAS),⁴ European Carotid Stenosis Trial (ECST)⁵ and Asymptomatic Carotid Stenosis Trial (ACST)⁶ trials. For example, the NASCET trial has demonstrated that the two-year ipsilateral stroke risk for symptomatic occlusive disease in the 70-99 percent range is 9 percent for patients undergoing carotid endarterectomy and 26 percent

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Director's Corner

Director of the Pat and Jim Calhoun Cardiology Center, Chief of Cardiology

Dr. Bruce Liang

Thanks to research and its translation into clinical practice, heart disease is no longer the leading cause of death for those under 85 in the U.S. While this is good news, the increased life expectancy and general prevalence of cardiovascular disease mean that it is still the number killer of Americans inclusive of all ages. This is particularly the case in women. Even as cardiovascular disease mortality has declined in men since about 1985, its mortality remains unchanged or is climbing in women. Women with coronary disease have symptoms different from men. The discomfort is often not localized to the chest but is felt as an ache in jaw, teeth, epigastric or abdominal area. Women often present with jaw or teeth pain, with fatigue or even no symptoms. It's important to remember that non-pharmacological therapies, medical as well as interventional treatments, are all effective in women as they are in men. Therefore, as we become better able to detect and diagnose heart disease in women, we will be able to bring about improved outcome.

In this context, I would like to bring your attention to the 2005 Cardiovascular

Symposium at UConn Health Center. This symposium is sponsored by the Calhoun Cardiology Center in collaboration with the Center for Interdisciplinary Research in Women's Health. The theme will be prevention, intervention, and gender differences. It will be held at the Keller Auditorium on October 19, 2005. For more information, please contact my assistant Lorraine Pandolfe at 860-679-7541.

We are particularly proud and pleased that we have scored the best in Connecticut and the U.S. on several core measures of cardiovascular performance that include evaluation of function and medical treatment of heart failure as well as heart attack. These two core measures represent the key indices annually surveyed by the Connecticut Hospital Association and the University Hospital Consortium, and were also recently reported at www.hospitalcompare.hhs.gov/Hospital/Search/Results.asp?MeasureCategory.

In this issue of "Cardiovascular Gram," we feature articles on two of our programs. One is on the current approach to patients with carotid arterial disease, written by Dr. Michael Dahn. The other article, written by

Dr. David Silverman, focuses on the diagnosis and treatment of lipid disorders.

We would like to welcome Dr. James Menzoian to the Cardiovascular Signature Program at the UCHC. Dr. Menzoian is a nationally recognized expert on vascular surgery. Dr. Menzoian comes to us after having been the Chief of Vascular Surgery at Boston University Medical Center. He specializes in surgeries for carotid blockage, abdominal aorta aneurysm, and peripheral arterial disease.

At the Calhoun Cardiology Center, clinical and research activities continue to expand. We are witnessing growth in extramural federal as well industry-sponsored research grants. Dialogue and scientific collaboration are occurring across departmental lines and overlap clinical/basic areas. The clinical researchers and the basic science investigators have much to teach one another.

Bruce T. Liang, M.D.

Ray Neag Distinguished Professor



Michael S. Dahn, M.D.

Director of Endovascular Services

for patients undergoing the best medical therapy. Furthermore, peri-procedural adverse events such as stroke, myocardial infarction and death associated with each respective approach were similar (5.8 percent for endarterectomy and 3.3 percent for best medical management).

In contrast, observed morbidity and mortality rates for the application of carotid angioplasty to seriously ill patients had been reported to be in the range of 12-33 percent.^{7,8} Counsell, et al⁹ reported the early termination of a randomized trial comparing carotid endarterectomy with angioplasty because five of the first seven patients entered into the angioplasty arm suffered a stroke suggesting that this procedure was associated with excessive risk. Finally, Gollidge, et al¹⁰ reported that the risk of stroke and death associated with carotid angioplasty was almost twice (7.8 percent) that compared with carotid endarterectomy (4.0 percent). In view of these findings, one might question the value of pursuing this alternative technique for the management of carotid occlusive disease.

Carotid endarterectomy remains an effective treatment for carotid stenosis as established by evidenced based medicine whereas carotid angioplasty appears to exhibit considerable risk. However, despite the risks associated with carotid angioplasty, persistent and tenacious investigators have continued to improve angioplasty and carotid artery stenting (CAS). This has resulted in a variety of refinements to the procedure which make it a realistic alternative to surgical management of carotid artery stenosis.

Although early studies of carotid angioplasty have been associated with a higher stroke risk following angioplasty when compared to carotid endarterectomy, recent clinical trials have suggested the equivalency of carotid angioplasty with carotid endarterectomy as a consequence of refinements in carotid angioplasty technique.^{11, 12}

The SAPPHIRE trial has received the greatest attention in this regard.¹¹ This was an industry sponsored (Cordis, Inc.) prospective trial evaluating high-risk patients exhibiting carotid stenosis randomized to either carotid angioplasty

**Carotid
endarterectomy
is superior to
medical therapy for
carotid disease.**

with stent placement (CAS) or carotid endarterectomy. The outcome of this trial revealed a statistical benefit in the major adverse event rate (combined death, stroke and myocardial infarction rate) in favor of CAS (5.8 percent) when compared to carotid endarterectomy (12.6 percent) at 30 days. A number of additional CAS single arm trials have reported comparable major adverse event rates to the SAPPHIRE stenting arm. Although these additional trials show results consistent with SAPPHIRE, these studies rely upon historical surgical data with no concurrent comparators. The



▲ *Normal carotid arteries*

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CARESS trial, which was funded by the International Society of Endovascular Specialists, was a randomized trial, which does contain carotid endarterectomy as a comparator arm.¹³

This study demonstrated that there was no significant difference in the 30-day combined all-cause mortality and stroke rate between CEA (2 percent) and CAS (2 percent). This report concluded that the 30-day risk of stroke or death following CAS with

cerebral protection is equivalent to CEA. A recent update of this trial has indicated that there was no significant difference in the one-year combined all-cause mortality and stroke rate between CEA (13.6 percent) and CAS (10.0 percent). Significantly the CARESS trial included a patient population that was not limited to high risk patients. Inclusion of all patients as candidates for carotid artery angioplasty and stenting, not just high risk subjects, is the trend in this field.

The current CAS experience here at UConn is consistent with recent reports indicating the CAS can be accomplished with a low rate of adverse events. Our clinical experience observed a major event rate of 2.6 percent, which resulted from a single case of minor stroke. We attribute this low complication rate to several factors including careful attention to pre-procedure anti-platelet therapy, meticulous attention to procedure protocol and routine use of cerebral protection devices. This latter factor has been associated with a reduction of

procedure stroke rates by 50 percent when compared to non protected procedures.¹⁴

Several questions remain regarding the utility of the carotid angioplasty and stenting as a potential competitor or replacement therapy for carotid endarterectomy. The cost analysis of carotid artery stenting has not been reported to date and may significantly influence the utility of this procedure. Currently, the major high end cost factors involved in the stenting procedure

include dedicated self-expanding nitinol stents costing \$2,000 – \$2,500 per stent. This represents a doubling in the cost of non-dedicated nitinol stents used for other peripheral indications. At the time of this writing, one device (ACCULINK, Guidant Inc.) has been approved specifically for carotid indications by the FDA. It is likely that several additional devices will receive a similar indication within the next six months, which may reduce device costs. Furthermore, the current standard of care in this area requires the use of cerebral protection devices. Most commonly, these are filtration devices that are temporarily deployed in the distal internal carotid artery during the procedure in an effort to minimize cerebral embolization. The ACCUNET device manufactured by Guidant, Inc. has received FDA approval specifically for this application. The cost of this device ranges between \$1,500 – \$2,000. Thus, the addition of these two devices in the management of this disease will substantially alter the cost of

Percutaneous approach appears to be effective, alternative revascularization.

a therapeutic carotid intervention, which is currently one of the most commonly performed vascular surgical interventions in the United States today.

A second issue revolves around the durability of angioplasty in relationship to carotid endarterectomy. Currently, long-term studies assessing the degree of restenosis following intervention remain limited. Lai, et al¹⁵ has recently reported that the restenosis rate for carotid angioplasty is 6.4 percent at 60 months, which is comparable to the restenosis rate of carotid endarterectomy. However, additional long-term data will be required to fully assess this aspect of this procedure.

At the present time, the Center for Medicare Services has approved this procedure for reimbursement although

specific inclusion criteria remain limited to symptomatic patients exhibiting 70 percent or greater stenosis.^{16, 17} Nonetheless, numerous educational facilities are now offering training programs in carotid angioplasty and it is expected that there will be a major shift in the management of carotid stenosis. Currently, approximately 120,000 carotid endarterectomies are performed annually in the United States. In view of the greater applicability of this procedure to high-risk patients, it appears likely that the volume of carotid angioplasties will eventually exceed this number if this procedure is fully embraced by the medical community and reimbursement is extended to include the same patients who are eligible for carotid endarterectomy.

Carotid Stenosis



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Your Mother Was Right. It's Still Important to Get Plenty of Exercise and Eat your Vegetables.

As a heart disease specialist, I feel fortunate to practice in what can fairly be called cardiology's golden age. Less than 20 years ago a patient having a heart attack would be given pain medicine and not much else. Although we knew a blocked artery was cutting off the heart's blood supply, we were powerless to change the outcome. We would sit, and watch, and hope that things turned out alright. The major medicines we used, including nitroglycerine and morphine, had not changed in more than a century. How things have changed today! Now, a patient suffering a heart attack is whisked into the catheterization laboratory, where a dizzying array of clot busting medicines and special therapies such as angioplasty are used open the blockage, stop the heart attack before it causes major damage, and return that patient to normal health in a matter of days. Our success is reflected in the 25% decline in deaths from coronary artery disease in the last decade alone.

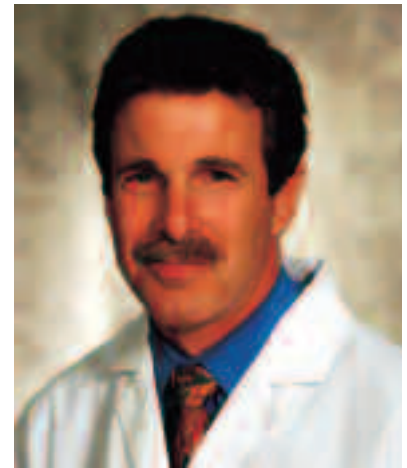
With all this high-tech success, however, comes the danger that the causes of heart attack and its related complications will be ignored. These marvelous treatments, one must remember, do not attack the root cause of the disease, which is the cholesterol-filled plaques that produced the blocked artery to begin with. The old-fashioned, and still quite effective, virtue of maintaining a healthy lifestyle is sometimes forgotten in the excitement over the medical advances

we have achieved. The wave of obesity now washing over us, and its companion public health disaster, diabetes, reinforces the importance of prevention and if we are to continue to make progress in combating the number one killer of Americans in the current era.

With the sole exception of family history, the other risk major factors for coronary artery disease can all be effectively reduced through a combination of medication and lifestyle intervention. For each of these factors, changing behavior, in addition to taking medicine, plays a crucial role that cannot be replaced by drugs alone. Numerous studies demonstrate the value of even modest amounts of exercise in controlling weight gain, reducing blood pressure, and lowering LDL or bad cholesterol. The effectiveness of cholesterol lowering drugs is markedly increased through simultaneous maintenance of a diet low in saturated fat. Reduced salt intake helps control high blood pressure even when medication is necessary. Finally, the irreplaceable value of smoking cessation is beyond question.

So while we celebrate the advances that have brought such progress in treating heart disease, it's worthwhile to remind ourselves of another old saying. An ounce of prevention after all, really *is* worth a pound of cure.

In the spirit of the information age, I offer a series of "FAQs" addressing current controversies in clinical lipidology.



David Silverman, M.D.

Associate Professor
and Director of the
Echocardiography
Laboratory

What is the value of c-reactive protein (CRP) in assessing incremental risk for cardiovascular disease?

Since the initial finding that elevated CRP levels are associated with increased risk of heart attack, its potential usefulness as a screening test for risk of heart attack or other complications of atherosclerosis remains the subject of intense debate and ongoing research. Several lines of evidence argue that increased CRP levels are associated with a risk of heart attack over and above that described by cholesterol levels alone. Moreover, CRP levels decline when cholesterol is lowered through the use of statins. Whether or not CRP levels represent increased risk entirely outside the framework of traditional risk factors remains unknown. Finally, no specific therapy outside of those available for risk factor modification is available for elevated CRP levels.

Given these somewhat contradictory facts, a prudent course would be to restrict the use of CRP levels to those cases in which an elevated level might represent a “tie breaker” in the decision to initiate pharmacological lipid lowering therapy. For patients in whom the decision to initiate lipid lowering therapy has already been made, a CRP level will not alter management.

When is a homocysteine level of value?

There are no clear guidelines here. The clearest scenario in which such secondary risk factors may be useful presents itself as a patient with coronary artery disease and no obvious risk factors to explain its appearance. The classical risk factors explain only about two-thirds of patients with coronary disease, and improvement in homocysteine levels can be achieved through Vitamin B complex and folate supplementation. Whether all patients should be screened for homocysteinemia remains the subject of ongoing debate.

How do recent trials affect target LDL levels in patients with established coronary artery disease or at high risk for that disease?

A group of recent cholesterol lowering trials provides strong evidence that aggressive cholesterol lowering below levels though previously acceptable further reduces risk of future heart attack, bypass surgery, or angioplasty. The best available data suggest that for such patients, target for LDL cholesterol lowering should be 75 mg/dl or less. In addition to patients with established coronary disease, high risk patients include those with vascular disease elsewhere, diabetes, or the combination of factors that leads to the metabolic syndrome (central obesity, high blood pressure, elevated blood sugar, high triglycerides, or low HDL cholesterol).

Appendix (from <http://www.lipid.org/clinical/insights/1000002.php>)

Target LDL is <75 mg/dl for the following patients

- Identified coronary disease of any kind (angina, previous heart attack, bypass surgery or angioplasty).
- Multiple major risk factors (especially diabetes)
- Severe and poorly controlled risk factors (especially continued cigarette smoking)
- Multiple risk factors of the metabolic syndrome (especially high triglycerides >200 mg/dl, plus non-HDL-C >130 mg/dl with low HDL-C (<40 mg/dl).
- Vascular disease elsewhere (carotid disease, peripheral vascular disease)

Target LDL < 100 mg/dl for the following patients

- Advancing age
- >2 risk factors
- Severe risk factors (e.g. continued cigarette smoking, a strongly positive family history of premature CVD)
- High triglycerides (>200 mg/dl) plus elevated non-HDL-C (>130 mg/dl)
- Low HDL-C (<40 mg/dl)
- Metabolic syndrome
- Presence of emerging risk factors (e.g. high sensitivity CRP >3 mg/L, or coronary calcium >75th percentile for a person's age and sex)

Studies and Awards

selected examples

- Methods to protect against vascular insufficiency and skeletal muscle injury, Department of Defense: Drs. Bruce T. Liang (P.I.), Michael Azrin, Michael Dahn, David Silverman, George Mansoor, Ms. Jayne Schumacher et al (co-investigators).
- Studies on 24-hour blood pressure and vascular biomarkers in older people with white matter lesions of the brain, NIA, NIH, Dr. William B. White (co-PI; P.I.: Dr. Les Wolfson).
- Exercise testing for detection of stress induced pulmonary hypertension in patients with scleroderma, Drs. Naomi Rothfield, Raymond J. Foley, and David I. Silverman.
- Aspirin resistance in patients with coronary artery disease, Drs. Bruce T. Liang, Dave Hager, David Silverman, Mike Azrin, Peter Schulman, Ms. Jayne Schumacher (study coordinator).
- The ACUTY Trial: Angiomax vs. Lovenox in early invasive management for ACS, The Medicines Co., Dr. Michael Azrin.
- Disperse 2: AZD6140 vs. clopidogrel, AstraZeneca LP, Dr. Michael Azrin.
- Molecular correlates of atrial fibrillation, Drs. David I. Silverman, Richard Soucier, and Bruce T. Liang
- Follow-up serial infusions of natreacor for the management of patients with heart failure-FUSION II, Dr. David Hager, Ms. Marybeth Barry and Ms. Laura Kearney

Noteworthy Events

- Annual Cardiovascular Symposium "Current Management of Ischemic Heart and Vascular Diseases: Prevention, Intervention, and Gender Differences", co-sponsored with Center for Interdisciplinary Research in Women's Health, October 19th, 2005, Keller Auditorium, 7:30 am-5 pm.
Planning Committee: Azrin, Dahn, Liang, Reisine, Schulman
Faculty: Drs. Peter Deckers, Bruce T. Liang, Maurizio Tonetti, Julie Wagner, Peter Schulman, William White, David Silverman, Scott Solomon, Y. Joseph Woo, Jonathan Hammond, David Underhill, Paul Preissler, James J. Brakoniecki, James Menzoian.
To register, call Ms. Pandolfe at 860-679-7541.
- Cardiovascular Grand Rounds (8-9 am in Link Room):
 - Dr. Victor Ferrari, Cardiology, University of Pennsylvania Health System, title TBA, October 26th, 2005.
 - Dr. William Dec, Cardiac Unit, Massachusetts General Hospital/Harvard Medical School, title TBA, October 5th, 2005.
 - Dr. Gervasio Lamas, Cardiovascular Research and Academic Affairs Mount Sinai Medical Center- Miami Heart Institute, title TBA, June 15th, 2005
 - Dr. Bruce T. Liang, Calhoun Cardiology Center/Cardiovascular Signature Program, UCUH, Reverse remodeling in heart failure and link to translation, June 1, 2005
 - Dr. Stephen Vatner, Cardiovascular Institute, UMDNJ-New Jersey Medical School, Myocardial hibernation and stunning, May 18th, 2005
- Citywide conferences: Every 2nd Friday at 7:30 am, C2136, contact Ms. Barta 860-679-2771.

Physicians and Surgeons

- Cardiologists (679-3343 or 2626) and Interventionalists (679-2828)
 - Dr. Michael Azrin
 - Dr. David Hager
 - Dr. Matt Stoenescu
 - Dr. Bruce T. Liang
 - Dr. Peter Schulman
 - Dr. David Silverman
 - Dr. Moz Karimeddini
 - Ms. Gabriella Smith, PA
 - Ms. Marybeth Barry, APRN
 - Hypertension Specialists (679-3343)
 - Dr. William White
 - Dr. George Mansoor
 - Dr. Beatriz Tendler
 - CT Surgeons (679-3343 or 2626)
 - Dr. Jonathan Hammond
 - Dr. Paul Preissler
 - Dr. David Underhill
 - Ms. Heather Wilcox, APRN
 - Ms. Jill Desjardins, APRN
 - Vascular Surgeons
 - Dr. Michael Dahn (679-3540 or 4801)
 - Dr. James Menzoian (679-3540 or 4801)
 - Dr. David Underhill (679-3343)
 - Grove Hill Cardiologists (223-0220)
 - Dr. Alan Kudler
 - Dr. Jared Insel
 - Dr. Jan Paris
 - Dr. Morgan Werner
- ## Scientists
- Dr. Dipak Das
 - Dr. Kimberley Dodge
 - Dr. Bruce T. Liang
 - Dr. Nilanjana Maulik
 - Dr. Achilles Pappano
 - Dr. Jian-bing Shen
 - Dr. Lixia Yue

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