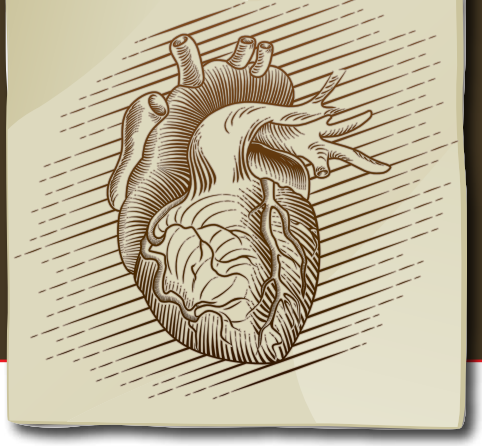

ABC Association of Black Cardiologists, Inc.

Cardiometabolic DIGEST

Edition 2, December 2009

A publication for cardiovascular specialists, specifically practicing clinicians and primary care providers
Providing an update on interesting and informative recent publications highlighting cardiometabolic diseases

Association of Black Cardiologists Chief Science Officer's Report from the American Heart Association Scientific Sessions: Cardiometabolic Highlights

The recent American Heart Association (AHA) 2009 Scientific Sessions were held in Orlando, Florida from November 14-18, 2009. Several interesting papers highlighted topics which may significantly impact clinical practice and lead to further research related to cardiometabolic diseases.

One of the trials reported extensively in the popular media and lay press tested the addition of extended-release niacin versus ezetimibe to statin therapy and their respective effects on carotid intima-media thickness (IMT). The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) was presented at the AHA conference and simultaneously was published online in the *New England Journal of Medicine*. The results of the study may have been over-interpreted by the lay press because of the potential political and economic ramifications of evidence demonstrating the benefits or harm of ezetimibe. Treatment with the niacin regimen was associated with significant regression from baseline in mean and maximal carotid IMT at eight months and fourteen months, whereas there was no significant change in IMT in patients treated with ezetimibe-statin therapy. The trial was relatively small and terminated early, based on efficacy, in a pre-specified analysis conducted after 208 patients had completed the trial. Paradoxically, greater reductions in the LDL cholesterol level in the ezetimibe cohort were significantly associated with an increase in the carotid intima–media thickness (R=–0.31, P<0.001). Furthermore, in this small population, the incidence of major cardiovascular events was lower in the niacin group than in the ezetimibe group , P=0.04 by the chi-square test..

Subsequently, in view of of the lack of benefit shown with ezetimibe, the lay public and many clinicians were concerned that this is another indication that lipid lowering with ezetimibe may not be as beneficial (or even potentially harmful) as that with statins alone or statins combined with niacin. Furthermore, although the study was not significantly powered to make definitive findings on clinical events, there appeared to have been more cardiovascular events in the ezetimibe versus the niacin cohort (9 events vs. 2 events; p = 0.04). The primary author, Dr. Allen Taylor of Medstar Research Institute in Washington, DC, suggested that this study could not confirm that ezetimibe was an acceptable alternative to niacin for cardiovascular benefit.

Despite these controversial findings, further research is needed, including future results of several large clinical outcome trials to confirm, or perhaps debunk, the harm or the value of the addition of ezetimibe to conventional statin therapy. Unfortunately, trials such as IMPROVE-IT (expected in 2012 or later), AIM-HIGH (2011) and HPS2-THRIVE (2013) will not have immediately available results, and clinicians must continue to assess their approaches to combination therapy without definitive scientific results.

Primary prevention of cardiovascular events with statin therapy in women has thus far not been clearly demonstrated. One perhaps underreported positive trial was a new analysis of JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin). Females with elevated high-sensitivity C-reactive protein (hs-CRP) levels and low to average LDL-C levels treated with 20 mg rosuvastatin cut their risk of cardiovascular events in half, according to a new analysis resulting from JUPITER. Specifically, treating apparently healthy women was shown to be as beneficial in terms of the primary benefit as in men. The sex-specific analysis of JUPITER demonstrated a 46% reduction in the risk of cardiovascular events in women, which is consistent and similar to the results of the overall trial and the outcome of 42% benefit in men. Dr. Samia Mora of Brigham and Women's Hospital presented data on 6801 women of the primary end point--a composite of myocardial infarction, stroke, revascularization, hospitalization for unstable angina, and death from cardiovascular causes. The need for revascularization was reduced 76% compared with the placebo. This analysis is significant to clinicians because of the large number of women involved and the demonstration of an ability to reduce the cardiovascular endpoints with primary prevention.

Increasingly, clinicians and researchers have associated low levels of vitamin D with increasing risk of cardiovascular disease and death. In an observational study, Dr Tami L Bair of

Intermountain Medical Center, Murray, UT, reported on more than 27 000 people 50 years of age or older with no previous history of cardiovascular disease. Those persons with low levels of vitamin D (≤15 ng/mL) were 77% more likely to die, 45% more likely to develop coronary artery disease, and 78% more likely to have a stroke than those with normal levels (>30 ng/mL). It is also associated with the development of heart failure. Although this preliminary data does not prove a causal effect, Vitamin D deficiency appears to be an under-appreciated risk factor for cardiovascular morbidity and mortality.

Persons who are at increased risk of vitamin D deficiency include African Americans and people with darker skin, people residing in areas with high latitudes, and the elderly, who tend to spend less time outside and may be less efficient in converting vitamin D. Furthermore, persons who are obese, institutionalized, or pregnant and breast-feeding women are more commonly vitamin-D deficient. While clinicians await randomized trials, it is reasonable, especially in persons at risk for vitamin D deficiency, including Black Americans, to consider vitamin D replacement, and some studies have suggested African Americans commonly demonstrate blood levels in the deficiency range of 16-18 ng/mL.

During the AHA, ten-year morbidity and mortality data were presented from ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). ALLHAT had previously demonstrated that therapy with amlodipine, lisinopril and doxazosin were not superior to chlorthalidone-based treatments. This new report presented by William C. Cushman, MD from the Veterans Affairs Medical Center in Memphis, Tennessee, demonstrated that chlorthalidone was unsurpassed for cardiovascular mortality after ten years and many have had some benefits for some secondary endpoints: heart failure was almost 40% higher with amlodipine than chlorthalidone, and heart failure was 19% higher and strokes 15% higher with lisinopril vs. the diuretic. In the original ALLHAT report for Black patients, strokes were 40% higher with lisinopril than chlorthalidone. This analysis used the unique method of combining data from the National Death Index, the Social Security Administration, the Center for Medicare and Medicaid Services, and the U.S. Renal Data System. Overall there was no statistical benefit in mortality with amlodipine or lisinopril vs. chlorthalidone.

Table 1

Risk of Total and Cardiovascular Mortality with Amlodipine vs Chlorthalidone (A/C) and Lisinopril vs Chlorthalidone (L/C)

Comparison	Hazard Ratio (95% CI)	P Value
Mortality		
A/C	0.98 (0.94 – 1.03)	.43
L/C	0.97 (0.93 – 1.02)	.19
Cardiovascular mortality		
A/C	1.00 (0.93 – 1.06)	.89
L/C	0.97 (0.90 – 1.03)	.33

CI = confidence interval.

Furthermore, there was a risk of secondary endpoints with amlodipine vs chlorthalidone (A/C), lisinopril vs chlorthalidone (L/C), and doxazosin vs chlorthalidone (D/C).

Table 2

Comparison	Hazard Ratio (95% CI)	P Value
CHD		
A/C	1.00 (0.92 – 1.08)	.95
L/C	0.98 (0.90 – 1.06)	.64
Fatal heart failure in hospitalized patients		
A/C	1.12 (1.02 – 1.22)	.01
L/C	1.00 (0.91 – 1.09)	.94
D/C	1.07 (0.98 – 1.17)	.13
Fatal stroke in hospitalized patients		
A/C	0.99 (0.89 – 1.09)	.81
L/C	1.04 (0.94 – 1.15)	.41
D/C	1.02 (0.92 – 1.12)	.72

CHD = coronary heart disease; CI = confidence interval.

The results of ALLHAT appear to confirm that therapy based on a thiazide-type diuretic, specifically chlorthalidone, are beneficial in most patients, including those at increased cardiovascular risk. This, however, does not suggest that calcium channel blockers (CCBs) and angiotensin converting enzyme (ACE) inhibitors will not be beneficial in selected cases. Recent studies like the ACCOMPLISH Trial have confirmed that combination therapy, including CCBs and ACE inhibitors together as a first step, may be beneficial compared to ACE inhibitors and a thiazide diuretic.

The debate continues on the wisdom and utility of interventional approaches versus optimal medical care to reduce cardiovascular events in persons with diabetes. Cardiovascular specialists continue to examine the benefits and costs of intensive medical management vs. procedures, including percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG). Dr Mark Hlatky from Stanford University (Palo Alto, California) presented a cost-effective analysis from the BARI-2D trial. His findings suggested that in patients with diabetes, intensive medical management may be more cost effective than PCI in persons with less severe coronary disease and CABG may be more cost effective in patients with more severe disease. In an economic analysis of the BARI-2d trial with 2368 patients, the results showed that PCI, CABG, and optimal medical therapy demonstrated similar cardiovascular survival in patients with stable coronary heart disease and type 2 diabetes. Nevertheless, CABG reduced the risk of cardiovascular events, primarily non-fatal MI, more successfully than intensive medical management. The risks were similar in the cohort who underwent PCI or medical therapy alone.

The five-year analysis demonstrated that the cost of persons assigned to PCI was $46,890 compared with $33,354 for medical therapy alone. Patients treated with surgery had a two-year cost of approximately $55,900. The cost comparisons remained unchanged over the four years of follow-up.

Dr Bernard Chaitman (St Louis University, Missouri) presented additional Bari-2D data at the same AHA session and also published online in *Circulation*. The five-year cardiac mortality rates were similar for intensive medical therapy or revascularization (5.7% vs 5.9%). Nevertheless in the 763 patients with more severe disease MI and death (10%) or MI (21.1%) were less than that seen with medical therapy alone (17.6% and 29.2%, respectively). The results of BARI-2d appeared to build on the findings of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. However, a future study examining the benefits of intensive medical therapy vs. intervention in patients with demonstrated high levels of ischemic burden may further clarify which patients actually should be considered for intervention.

REFERENCES

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.

Chaitman, BR, et al. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease. Impact of treatment strategy on cardiac mortality and myocardial infarction. *Circulation* 2009;Nov 17:[Epub ahead of print].

Hlatky, MA, et al. Economic outcomes of treatment strategies for type 2 diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial. *Circulation*. 2009;Nov 17:[Epub ahead of print].

IMPROVE-IT: Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin. http://clinicaltrials.gov/ct2/show/NCT00202878

Mora, S "Rosuvastatin for the primary prevention of cardiovascular events in women with elevated hsCRP and Low LDLC: Sex-specific outcomes from the JUPITER Trial" *AHA* 2009; Abstract 1426.

Niacin Plus Statin to Prevent Vascular Events. http://clinicaltrials.gov/ct2/show/NCT00120289

Taylor, AJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *New England Journal of Medicine*. 209;361(22):2113-2122.

Treatment of HDL to Reduce the Incidence of Vascular Events HPS2-THRIVE. http://clinicaltrials.gov/ct2/show/NCT00461630

For further information or to post comments, please contact Keith C. Ferdinand, MD, FACC, FAHA, Clinical Professor of Cardiology, Cardiology Division, Emory University Chief Science Officer, Association of Black Cardiologists, Inc., 5355 Hunter Road, Atlanta, GA 30349, 404-201-6600, kferdinand@abcardio.org, www.abcardio.org.